ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

- KATEDRA ZA ONKOLOGIJO
- SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO

Slovensko Zdravniško Društvo

#2

INTERNATIONAL SUMMER SCHOOL IN MEDICAL ONCOLOGY

ONKOLOŠKI INŠTITUT LJUBLJANA
7.-10. SEPTEMBER 2021

Uredniki zbornika:
Marko Boc, dr.med.
prof. dr. Janja Ocvirk, dr.med.
doc. dr. Tanja Mesti, dr.med.

Recezenti:
doc. dr. Tanja Mesti, dr.med.
doc. dr. Erika Matos, dr.med.

Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Zborniki šol o melanoma in ostale publikacije s strokovnih dogodkov so dosegljivi na spletnih straneh Onkološkega inštituta:
www.onko-i.si/publikacije-strokovnih-dogodkov-oi

Ljubljana, september 2021

Tuesday, September 7

08.50-09.10	Registration of participants
09.10-09.30	Satellite Symposium Abbott
	The importance of the palliativist and nutritionist (Moderators Mesti, Ocvirk)
09.30-10.00	The palliative care – is early too early? (Ebert)
10.00-10.30	The nutritional support – is fat bad? (Dobrila)
10.30-10.45	Discussion
10.45-11.15	Break
	Systemic treatment – the other side of the coin
11.15-11.45	Side effects of immunotherapy and the management (Hribernik) Our experience – interesting cases (Žižek, Hribernik)
11.45-12.15	Side effects of chemotherapy (including extravasation) and management (Ovčariček)
12.15-12.45	Side effects of TKI and Management (Bokal)
12.45-13.15	Car-T Neurological complications (Carpentier)
13.15-13.30	Discussion
13.30-13.50	Break
	Future perspectives – are we there yet
	Systemic treatment of the skin cancer – where we stand (Moderators Ocvirk, Mesti)
13.50-14.20	Adjuvant and neoadjuvant systemic treatment of melanoma (Schadendorf)
14.20-15.00	Systemic treatment for metastatic melanoma (Kandolf Sekulović) Our experience – interesting cases (Vid Čeplak Mencin, Mesti)
15.00-15.40	Systemic treatment of non melanoma (Ocvirk) Our experience – interesting cases (Sever, Ocvirk)
15.40-16.10	NGS - the new Superhero in Oncology (Mesti)
	Systemic treatment of the skin cancer – where we stand
16.10-17.00	Interesting interactive cases and discussion

Wednesday, September 8

08.40-9.00	Satellite Symposium Servier
	Future perspectives – are we there yet (Moderators Ocvirk, Mesti)
09.00-09.30	Systemic treatment of the gastric cancer – where we stand (Boc) Our experience – interesting cases (Erman, Mesti)
09.30-10.00	Systemic treatment of the biliary cancer – where we stand (Reberšek)
10.00-10.30	Systemic treatment for the pancreatic cancer – are we going forward (Pašič)
10.30-11.00	How to approach NET/NEC (Ignjatovič) Our experience – interesting cases (Leskovšek, Ocvirk)
11.00-11.30	HCC – lots has been going on (Ocvirk) Our experience – interesting cases (Stefanovski, Ocvirk)
11.30-12.00	Precision systemic treatment of colorectal cancer – can we understand the complexity (Pleština)
12.00-12.15	Discussion

12.15-12.40	**Break**
	Future perspectives – are we there yet (Moderator Matos)
12.40-13.00	**Enrichment of treatment at metastatic NSCLC with PD-L1 overexpression (PD-L1≥50) (Radisavljević)**
13.00-13.20	**Clinical choices at metastatic NSCLC without actionable oncogenic driver regardless of PD-L1 status (Jakopović)**
13.20-14.00	**Systemic treatment of head and neck cancer – what's new in the old (Grašič)** **Our experience – interesting cases (Plavc, Zupančič, Grašič)**
14.00-14.40	**Management of cancer of unknown primary in the molecular era (Matos)** **Our experience – interesting cases (Cankar, Matos)**
14.40-15.10	**Systemic treatment of Ewing sarcoma – where do we stand (Unk)** **Our experience – interesting cases (Sokolova, Unk)**
15.10-15.30	**Discussion and conclusion**
15.30-15.50	**Satellite Symposium Amgen**

Thursday, September 9

Future perspectives – are we there yet (Moderator Škrbinc)	
08.40-09.00	**Satellite Symposium BMS**
09.00-09.30	**Systemic treatment of prostate cancer – standards and prespectives (Belev)**
09.30-10.00	**Systemic treatment of RCC - standards and prespectives (Šeruga)**
10.00-10.30	**An approach to patient with cancer and kidney disease (Milanez)**
10.30-11.00	**The systemic treatment of the bladder cancer – is something new going on (Gnjidić)**
11.00-11.30	**Systemic treatment of germinal tumors – could it get better (Škrbinc)**
11.30-12.00	**Systemic treatment of gynecological tumors – standards and perspectives (Mandič)**
12.00-12.15	**Discussion**
12.15-12.45	**Break**
	Future perspectives – are we there yet (Moderator Borštnar)
12.45-13.15	**Early and locally advanced hormone dependant Breast cancer – where do we stand (Bešlija)**
13.15-13.45	**Metastatic breast cancer – standards and perspectives (Borštnar)**
13.45-14.00	**Discussion and conclusion**
14.00-14.20	**Satellite Symposium Pfizer**
14.20.14.40	**Satellite Symposium Eli Lilly**

Friday, September 10

Future perspectives – are we there yet (Moderators Jezeršek, Pahole, Rugelj)	
09.00-09.20	**Satellite Symposium Roche**
(09.20-13.00)	**Standards and perspectives in the systemic treatment of Lymphomas**
09.20-09.40	**Diffuse Large B cell Lymphoma (Jezeršek)**
09.40-10.00	**Marginal Zone Lymphoma (Miljković)**
10.00-10.20	**Follicular Lymphoma (Južnič Šetina)**
10.20-11.00	**Break**
11.00-11:20	**Mantle Cell Lymphoma (Jagodic)**

11.20-11.40	**T Cell Lymphomas (Pahole)**
11.40-12.00	**Hodgkin lymphoma (Rugelj)**
12.00-12.30	**Break**
12.30-13.00	**Principles of Radiotherapy in Lymphomas (Zadravec Zaletel)**
13.00-13.30	**Discussion and Conclusion**

KAZALO

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

2nd SUMMER SCHOOL IN MEDICAL ONCOLOGY

PALLIATIVE CARE
Is early too early?

Maja Ebert Moltara, MD
mebert@onko-i.si
Head of a Department for Acute Palliative Care
Department of Medical Oncology

ESMO Designated Centers of Integrated Oncology and Palliative Care

7 - 10 September 2021, Ljubljana, Slovenia

PALLIATIVE CARE
Is early too early?

EARLY PALLIATIVE CARE

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6 BASIC QUESTIONS:

WHAT?

For WHO?

WHO provides?

WHERE?

WHEN?

WHY?

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WHAT?

WHO definition of palliative care

Palliative care is an approach that improves

the quality of life

of patients and their families

facing the problem associated with life-threatening illness, through the prevention and relief of suffering

by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

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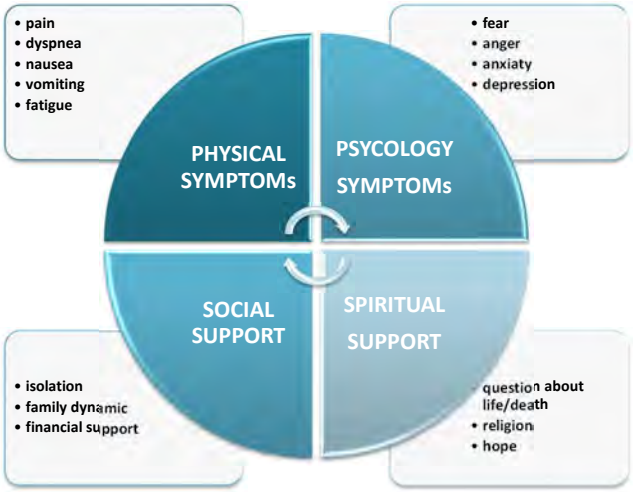
COMPREHENSIVE PALLIATIVE CARE

ONKOLOŠKI INŠTITUT LJUBLJANA INSTITUTE OF ONCOLOGY LJUBLJANA ESMO

COMPREHENSIVE PALLIATIVE CARE



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WHO provides and WHERE?

All medical and non-medical members of teams in institutions where incurable patients are treated.

Basic palliative care (80% patient):
All levels of health system
(hospitals, community health centre, at home, senior homes, hospicih...)
All.

Specialied palliative care (20%):
Does not substitute basic palliative care, but it upgrade it for the patients with the most difficult and complex problems
Specialized teams (acute palliative care departent, mobile PC team)

EAPC: White Paper on standards and norms for hospice and palliative care in Europe

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CONTINOUS PALLIATIVE CARE

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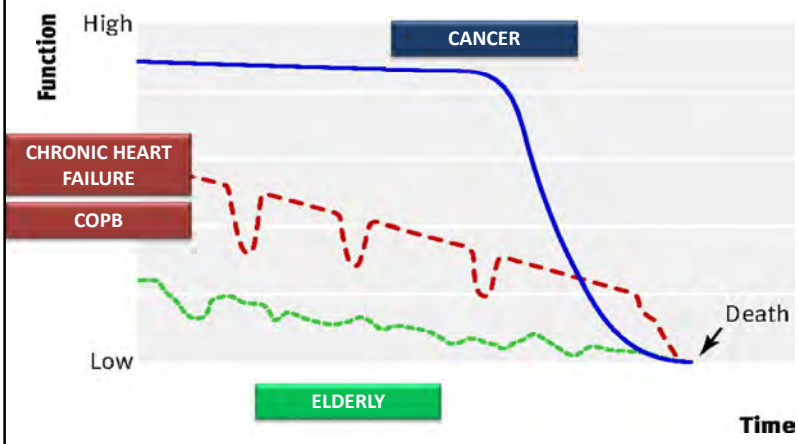
For WHO?



Murray, S. A et al. BMJ 2008;336:958-959

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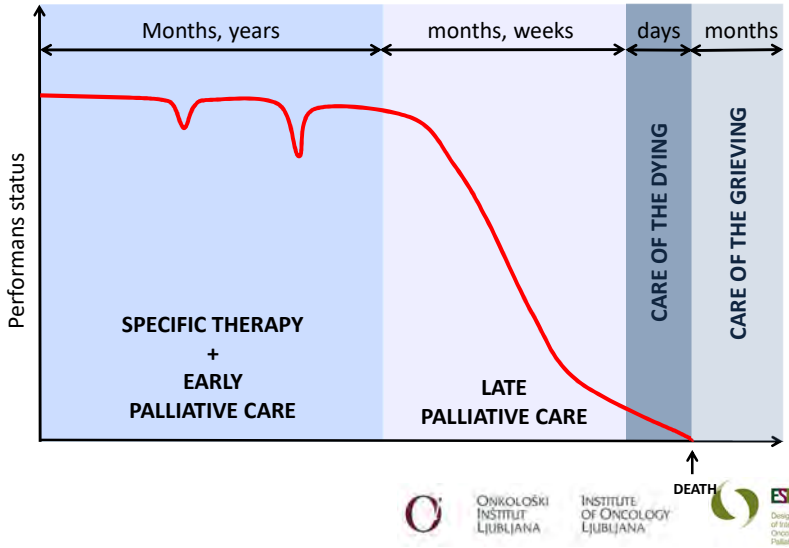
WHEN?



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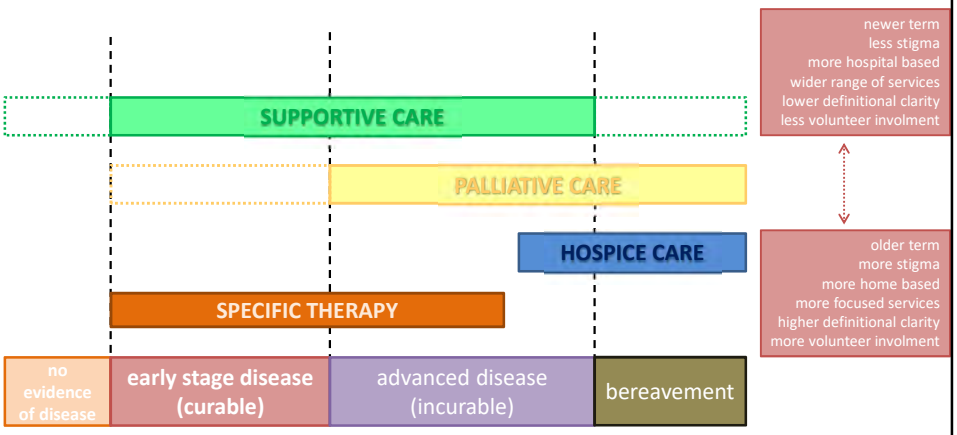
Conceptual framework



Hui, D. *et al.* Concepts and definitions for "supportive care," "best supportive care, " "palliative care, " and "hospice care" in the published literature, dictionaries, and textbooks. *Support. Care Cancer* 21, 659–685 (2013).

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WHEN?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

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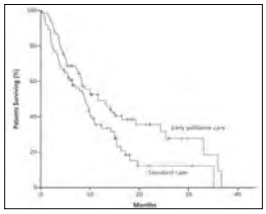
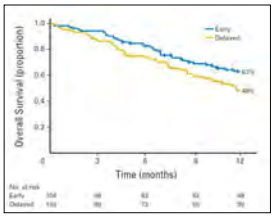
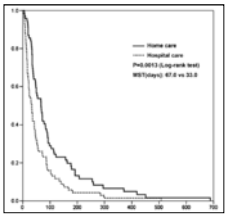
EARLY PALLIATIVE CARE



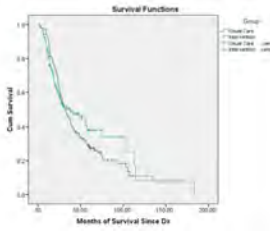
Temel, NEJM 2010



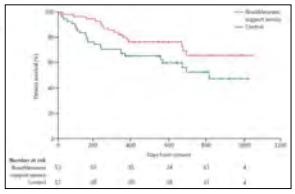
Bakitas, JCO 2015



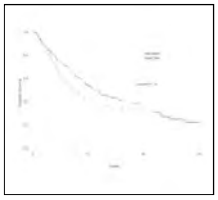
Murakami BMC Pall 2015



Ferell, J Pain Manag, 2015



Higginson 2015



Bakitas, JCO 2013

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PALLIATIVE CARE
Is early too early?

PALLIATIVE CARE

CAN NOT BE TOO EARLY

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1. DENIAL

2. PALLIPHOBIA

"He's our new Palliative Specialist!"

3. PALLILALIA

4. PALLIACTIVE

THANK YOU!!!

Top 10 Things Palliative Care Clinicians Wished Everyone Knew About Palliative Care

Jacob J. Strand, MD; Mihir M. Kamdar, MD; and Elise C. Carey, MD

2013 Mayo Foundation for Medical education an Research, Mayo Clin Proc. 2013; 88 (8):859865

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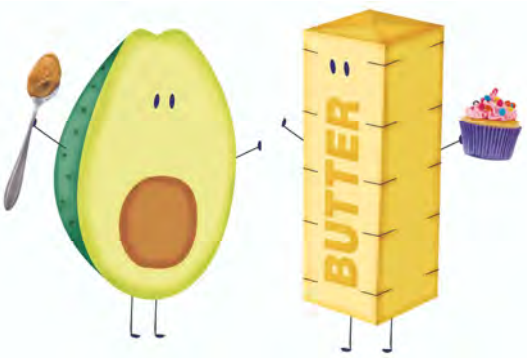
The nutritional support- is fat bad?



Prof. Renata Dobrila-Dintinjana, MD. PhD.

Damir Vučinić, MD.

Clinical Hospital Center Rijeka

School of Medicine, University of Rijeka, Croatia

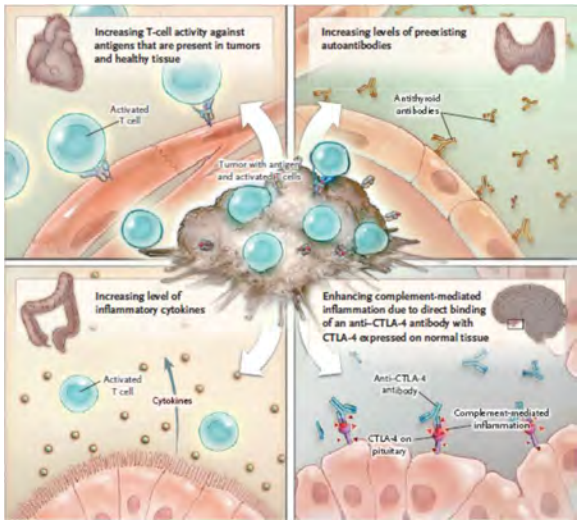
- *Monounsaturated fat, n-3 PUFA, and fat soluble vitamins may have a profound influence on the prevention and/or suppression of cancer, whereas saturated fat and n-6 PUFA may increase the risk of carcinogenesis*
- *Monounsaturated fat and n-3 fatty acids should be preferred over animal fats and other vegetable fats in the diet*
- *Malnutrition is an important issue in cancer patients, which should be appropriately managed by structured collaboration of MDT*
- *Pharmacological approach (EPA/MA) to the treatment of anorexia cachexia syndrome in cancer patients significantly improves QoL and probably prolongs OS*

IMMUNE-RELATED ADVERSE EVENTS OF IMMUNE CHECKPOINT INHIBITORS

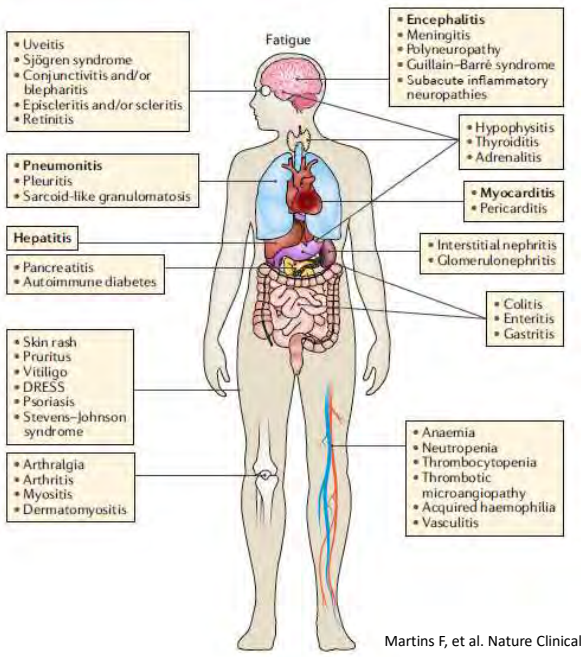
Nežka Hribernik, MD
Institute of Oncology Ljubljana

2nd Summer School in Medical Oncology
September 2021

Possible mechanisms underlying irAE



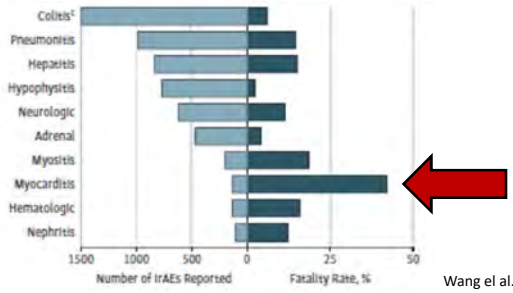
Postow MA, et al. NEJM 2018



Martins F, et al. Nature Clinical Oncology Reviews, 2019

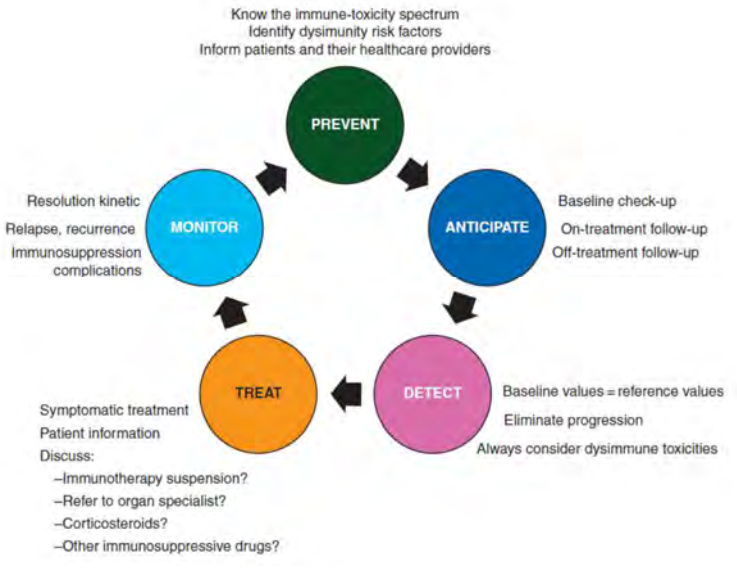
Fatal irAE (cont`d)

- Risk of fatality:
  - **Myocarditis 40%**
  - Hypophysitis, adrenal insufficiency, colitis **2 - 5%**
  - 10 – 17% for other irAEs
  - Older patients at higher risk (impared functional reserve, comorbidities)



Wang el al. JAMA ONCO 2018

Management of irAEs



Champiat S et al. Ann Oncol 2016

Special populations that are not presented in RCT

Rzeniewicz el al. Ann Oncol 2021

TAKE-HOME MESSAGES!

- MULTIDISCIPLINARY APPROACH
  - Baseline assessment
  - Ongoing assessment
  - PATIENT & PHYSICIAN EDUCATION
  - Management protocols
  - **Collaboration with emergency departments, GPs, specialists, visiting nurses!!**

Melanoma patient with multiple irAE - clinical case

Side effects of immunotherapy and the management

2nd International Summer school

Ana Žižek, dr.med

Nežka Hribernik, dr.med.

Female, 1960

- Family history: mother had skin cancer
- Comorbidities: arterial hypertension

- Year 2012: presented with skin lesion on her left thigh, changing in colour
  - June 2012 – excision: melanoma, Clark IV, Breslow 2,4 mm, no ulceration
  - September 2012 – reexcision of tumor bed + SLNB (Institute of Oncology LJ)
  - **pT3a N0 (0/1), R0, stage IIA**
  - FU

January 2021 progression of disease (DFI: 9 years)

- January 2021: palpable resistance in her left thigh, loss of 6 kg in 1 month, nausea, back pain, night sweats
- Diagnostic procedure:
  - Lab: LDH 2.66 ukat/L, S-100 1.250 ug/L, CRP 160 mg/L
  - Bx of resistance: **melanoma metastasis → BRAF V600E mutation**
  - PET/CT: high metabolic uptake in the liver, subcutaneous tissue of left thigh, bones (Th 4,5,8,11, L1,5, sacrum, pubis, scapula, 10th and 5th rib)
  - CT of the head: solitary metastasis in basal ganglia (1 cm) without edema; no neurological symptoms

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Systemic treatment

- February 2021: started with comboIT **ipilimumab 3 mg/kg + nivolumab 1 mg/kg**
  - Supportive treatment: Zoledronic acid, vitamin D, CaCO3
  - No radiotherapy (1 week after 1st infusion her back pain was gone)
- March 2021: increased appetite, no back pain, reduction in size of subcutaneous resistance in left thigh --> continues with 2nd infusion of nivo1/ipi3
  - Side effects: pruritus grade II (Th: antihistamine)
- April 2021 – early time-point PET/CT (study QTA): PMR in most localisations, S100 normalized
- April 2021: 3rd infusion of nivo1/ipi3

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Multiple irAE

- End od April 2021 - Regional hospital admission: hepatitis gr. III, diarrhoea gr. I, arthralgia gr.
  - Treatment: **steroids i.v. (2mg/kg/d)**+Pneumocystis prophylaxis, PPI
  - In one week no more liquid stools and no more pain in her joints
  - regular lab controls - liver transaminases decreased to gr. I
  - Tapering of dexamethasone
- End of May 2021: worsening of sympthoms - skin rash around waist, fatigue, transaminitis gr. III, diarrhoea gr. I → again **higher dose of steroids p.o. (2mg/kg/d)**
- After improvement of lab and sympthoms, **SLOW** tapering of dexametasone over 5 weeks
- ACTH test!
- Permanently completed IT due to irAE

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- June 2021: PET/CT: complete metabolic response of all metastatic localisations
- July 2021: normal AST/ALT, bili, S100, LDH, CRP
- August 2021: regular check-up, no signs of progression

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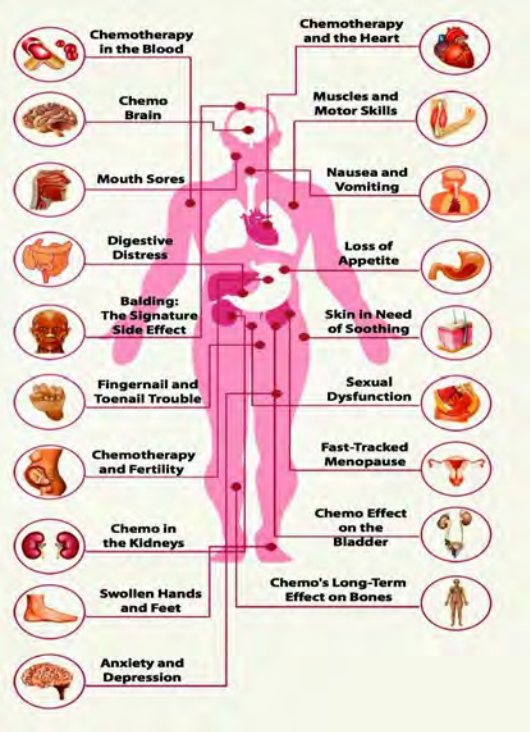
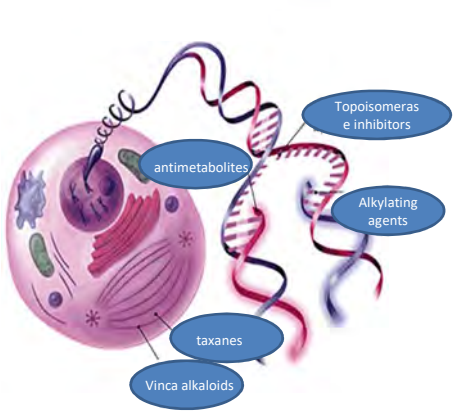
Side effects of chemotherapy and the management

Tanja Ovčariček
Oncology institute Ljubljana, 2021

Knowing side effects of certain treatment is basic knowledge every oncologist should have!

- a number of potential side effects
- Side effects and long term sequelae of chemotherapy major source of concern for patients
- Education of patients is important for adherence to cht treatment





- Gastrointestinal epithelial cells
- Bone marrow cells
- Hair follicles

Nurgali K, et al. Front.Pharmacol.2018

Timing of chemotherapy side effects

Acute (minutes to hours/first days)

During cht application:
- allergic/infusion reaction
- cardiac arrythmia
- exstravasation

Early (in hours after cht application):
- nausea/vomiting
- malaise
- tumor lysis syndrome
- phlebitis
- cystitis

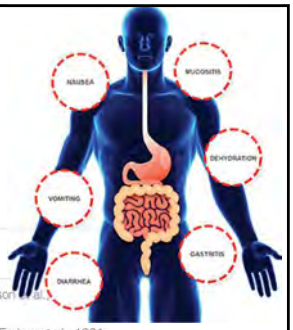
Subacute

After couple of days/week:
- stomatisis, gastroenteritis
- renal insufficiency
- myelosuppression
- peripheral neurotoxicity
- Fatigue
- alopecia

Late

After weeks, months, years
- nail changes
- organ failure (heart failure)
- infertility
- teratogeneticy and cancerogeneticy

GASTROINTESTINAL SIDE EFFECTS OF CHEMOTHERAPY



Mechanisms	Chemotherapeutic agents	Cancer type	GI side-effects
Alkylating Agents	Cisplatin	Lung, Breast, Stomach, Colorectal, Liver	Nausea, Vomiting, **Diarrhea, Constipation** (Ilson et al., Ardizzoni et al., 2007)
	Cyclophosphamide	Breast	Nausea, Vomiting, Abdominal Pain, **Diarrhea** (Fraiser et al., 1991; Boussios et al., 2012)
	Oxaliplatin	Colorectal, Breast, Stomach	Nausea, Vomiting, **Diarrhea**, **Constipation** (Extra et al., 1990; Kim et al., 2003)
Antimetabolites	5-Fluorouracil	Breast, Colorectal, Stomach, Liver	Nausea, Vomiting, Abdominal Pain, **Diarrhea** (Douillard et al., 2010; Boussios et al., 2012)
	Capecitabine	Colorectal, Breast, Stomach	Nausea, Vomiting, **Diarrhea** (Walko and Lindley, 2005; Stathopoulos et al., 2007; Boussios et al., 2012)
	Gemcitabine	Lung, Breast	Nausea, Vomiting, Abdominal Pain, **Constipation, Diarrhea** (Wolff et al., 2001; Mutch et al., 2007; Boussios et al., 2012)
	Methotrexate	Breast	Nausea, Vomiting, Abdominal Pain, **Diarrhea** (Boussios et al., 2012)
Anthracycline	Doxorubicin	Breast, Lung, Liver	Nausea, Vomiting, Abdominal pain, GI Ulceration, **Diarrhea** (Boussios et al., 2012; Tacar et al., 2013)
Immunomodulating agent	Thalidomide	Myeloma, Kidney	Nausea, Vomiting, **Diarrhea, Constipation** (Smith et al., 2008)
Mitotic inhibitors	Cabazitaxel	Prostate	Nausea, Vomiting, Abdominal pain, **Diarrhea** (Nightingale and Ryu, 2012; Dieras et al., 2013)
	Docetaxel	Prostate, Breast, Lung, Stomach	Nausea, Vomiting, **Diarrhea** (Boussios et al., 2012)
	Paclitaxel	Lung, Stomach, Prostate, Breast	Nausea, Vomiting, **Diarrhea** (Boussios et al., 2012)
	Vincristine	Breast, Lung	**Constipation**, Abdominal Pain (Holland et al., 1973)
Topoisomerase inhibitor	Irinotecan	Colorectal, Breast, Stomach, Lung	Nausea, Vomiting, Acute and Delayed **Diarrhea** (Hecht, 1998)

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

- the most common and feared side-effects among the patients
- compromise treatment outcomes

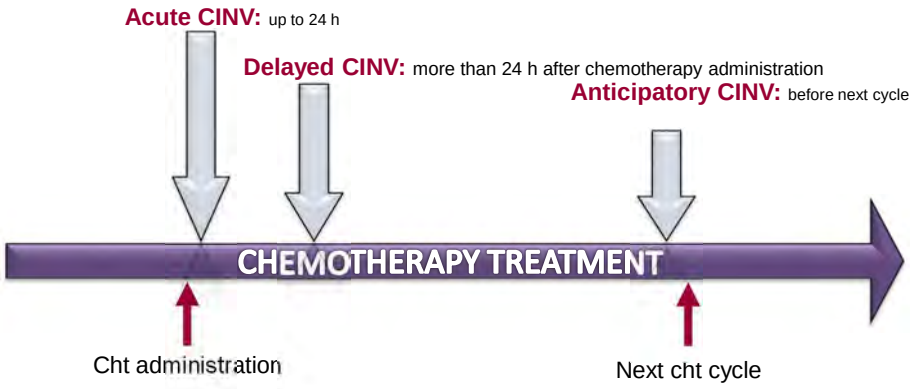
What should oncologist know about CINV?

- Timing of nausea
- Emetogenic potential of chemotherapy/individual risk
- Patophysiology of CINV and drugs used

Roila F et al, Ann Oncol 2016

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

- in two phases, the acute and the delayed phase:

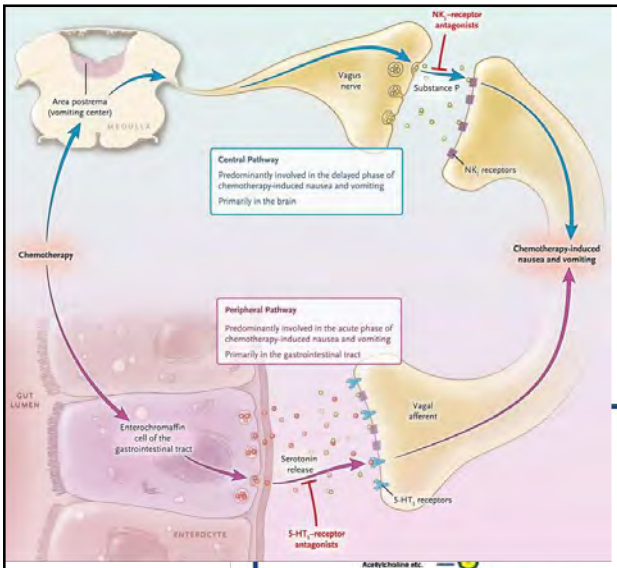


Roila F et al, Ann Oncol 2016

Emetic classification of chemotherapy agents

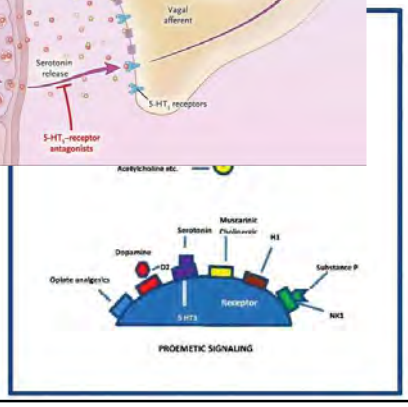
High risk (>90 % patients)	Moderate risk (30-90 % patients)	Low risk (10-30% patients)	Minimal risk (<10 % patients)
Anthracycline/cyclophosphamide combination[b]	Azacitidine	Cabazitaxel	Bleomycin
Carmustine	Bendamustine	Cytarabine ≤1000 mg/m^2	Busulfan
Cisplatin	Carboplatin	Docetaxel	2-Chlorodeoxyadenosine
Cyclophosphamide ≥1500 mg/m^2	Clofarabine	Eribulin	Cladribine
Dacarbazine	Cyclophosphamide <1500 mg/m^2	Etoposide	Fludarabine
Mechlorethamine	Cytarabine >1000 mg/m^2	5-Fluorouracil	Pixantrone
Streptozocin	Daunorubicin	Gemcitabine	Pralatrexate
	Doxorubicin	Ixabepilone	Vinblastine
	Epirubicin	Methotrexate	Vincristine
	Idarubicin	Mitomycin	Vinorelbine
	Ifosfamide	Mitoxantrone	
	Irinotecan	Nab-paclitaxel	
	Oxaliplatin	Paclitaxel	
	Romidepsin	Pemetrexed	
	Temozolomide[c]	Pegylated liposomal doxorubicin	
	Thiotepa[d]	Topotecan	
	Trabectedin	Trastuzumab-emtansine	
		Vinflunine	

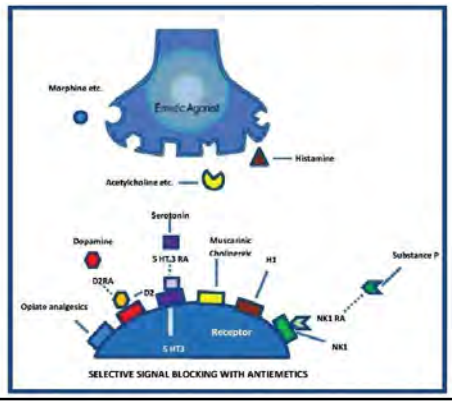
Roila et. Al. Ann Oncol 2016



Mechanism of antiemetic drugs:

1. 5HT3 RA acute CINV
2. NK1 RA delayed CINV
3. D2 RA
4. Multiple R
5. CB1
6. Other



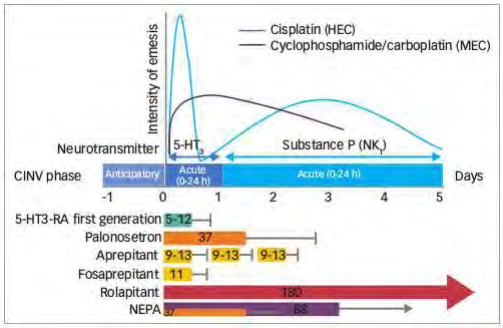


Navari RM, et al. NEJM 2016

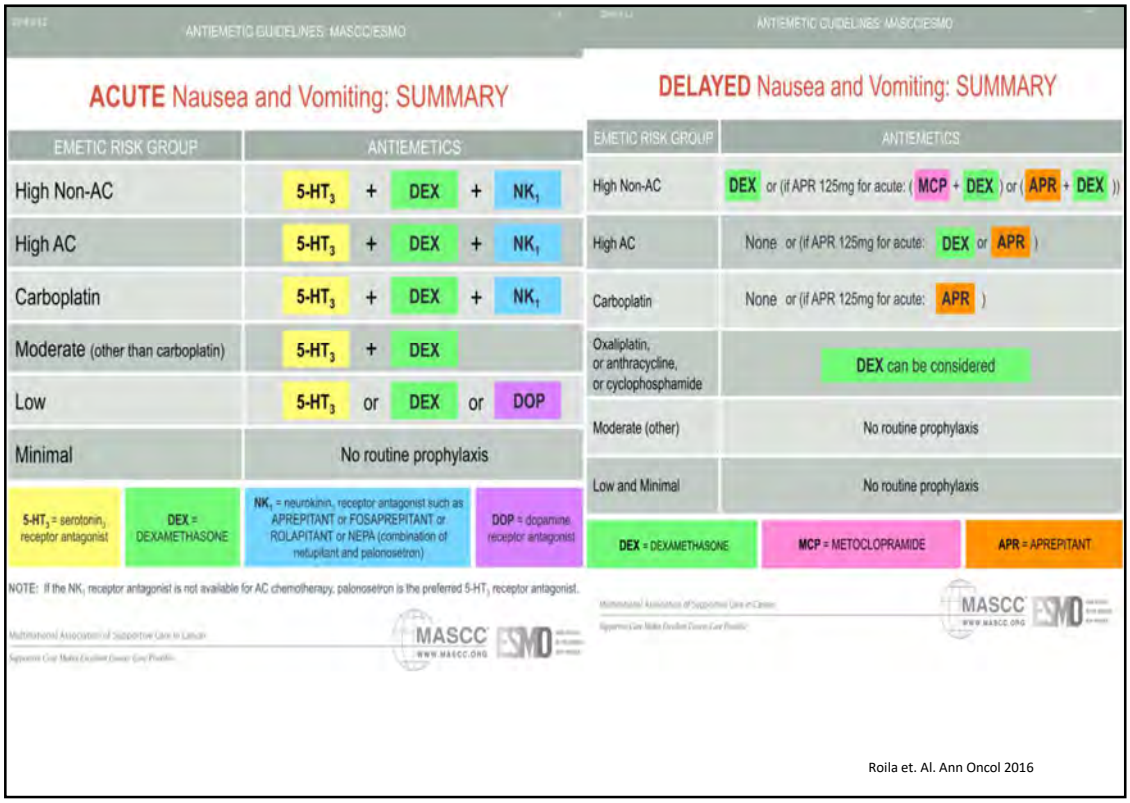
Antiemetic arsenal:

- 5HT3 RA: granisetron, palonosetron, ondasetron
- NK1 RA: aprepitant, fosaprepitant, netupitant
- D2 RA: metoklopramid
- Multiple R: deksamethasone, olanzepin
- CB1: canabinoids
- Other: benzodiazepines

NK-1 receptor antagonist	Day 1	Days 2–3
Aprepitant	Single oral 125-mg dose prior to chemotherapy	Oral dose of 80 mg once daily on days 2 and 3
Fosaprepitant	Single intravenous 150-mg dose prior to chemotherapy	-
Netupitant	Single oral 300 mg netupitant/0.5-mg palonosetron dose prior to chemotherapy	-
Rolapitant	Single oral 180-mg dose prior to chemotherapy	-



Navari RM, et al. NEJM 2016



Roila et. Al. Ann Oncol 2016

CLINICAL CASE

- 50 years old women with T3N0M0 urothelial bladder cancer, hematuria, no comorbidities
- Treatment plan: neoadjuvant cisplatin-based chemotherapy
- Worried about nausea and vomiting

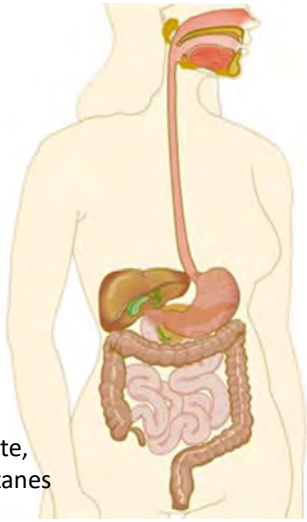
High risk
(>90 % patients)

- Acute CINV: NK1 RA (aprepitant 125 mg)+5HT3 RA (granisetron 1 mg)+deksamethason 12 mg
- Delayed CINV: aprepitant 80 mg 2.3 D+deksamethason 8 mg 2.-4. d

NK-1 receptor antagonist	Day 1	Days 2–3
Aprepitant	Single oral 125-mg dose prior to chemotherapy	Oral dose of 80 mg once daily on days 2 and 3
Fosaprepitant	Single intravenous 150-mg dose prior to chemotherapy	—
Netupitant	Single oral 300 mg netupitant/0.5-mg palonosetron dose prior to chemotherapy	—
Rolapitant	Single oral 180-mg dose prior to chemotherapy	—

- Persisting N/V: breakthrough CINV: antiemetics with different mechanism of action: metoclopramide/olanzapine

MUCOSITIS

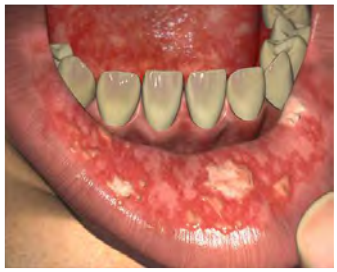


- inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract
- anatomical distribution: oral mucositis (OM), gastrointestinal mucositis (GIM, diarrhea), and proctitis
- the incidence of clinically significant mucositis has been reported to range from 40% (standard dose cht), 60–100% (high-dose cht)
- Predisposing factors:
  - various mucotoxicity for different cht agents: 5-FU,methotrexate, irinotecan, cyclophosphamide, cisplatin, anthracyclines and taxanes
  - bolus infusion tends to be more toxic
  - in general, if a patient develops mucositis in the first cycle of treatment, the probability of the condition recurring in a subsequent cycle is high

Stein et al, 2010, Kwon et al. 2016

ORAL MUCOSITIS

- erythema of the movable mucosa which progress to form painful ulcerations often covered by a pseudomembrane
- may be associated with microbial colonization that may remain localized or become disseminated, especially in patients with severe neutropenia-SEPSIS!!
- first signs appear shortly after administration and usually peak at about days 7–14, is usually self-limiting



Stein et al, 2010, Kwon et al. 2016, Peterson DE et al, Ann Oncol 2015

MASCC and ESMO have developed guidelines whith strategies for managing oral mucositis

- effective preventative and treatment strategies are lacking
- Preventative meassurements: Oral health at the start of and during chemotherapy: general hygiene standards, dental care, normal saline and baking soda-non-alcochol mouthwashes, regular tooth brush, dietary and behavioral measures

Intervention	Aim	Clinical setting	Authors' comment	Guidelines (grade of evidence)
Oral care protocols	Prevention	All cancer patients	General agreement on the value of oral care protocols	MASCC/ESMO (III) NCCN
Oral cryotherapy	Prevention	Bolus 5-FU chemotherapy	Safe, low cost, with some positive results	MASCC/ESMO (II) NCCN
		High-dose melphalan +/– TB-RT for HSCT	As above	MASCC/ESMO (III) NCCN
Palifermin	Prevention	High-dose CT and TB-RT for HSCT	Only approved agent for OM mitigation in a narrow patient population	MASCC/ESMO (II) NCCN ASCO
Low-laser therapy	Prevention	High-dose CT +/– TB-RT for HSCT	Data suggesting possible benefit	MASCC/ESMO (II)
		HN cancer patients receiving RT alone	Data suggests possible benefit, but potential tumor impact unresolved	MASCC/ESMO (III)
Benzydamine mouthwash	Prevention	HN cancer patients receiving moderate dose RT alone	Anti-inflammatory rinse with some data supporting its use in patients receiving radiation only	MASCC/ESMO (I)
0.2% morphine mouthwash	Pain treatment	HN cancer patients receiving CT-RT	Data suggests effective adjunct for topical pain control	MASCC/ESMO (III)
Doxepin mouthwash	Pain treatment	All cancer patients	Data suggests effective adjunct for topical pain control	MASCC/ESMO (IV)

CT, chemotherapy; RT, radiotherapy; TB-RT, total-body radiotherapy, HN, head and neck; HSCT, hematopoietic stem cell transplantation; MASCC, Multinational Association of Supportive Care in Cancer; ESMO, European Society for Medical Oncology.

Peterson DE et al, Ann Oncol 2015

CHEMOTHERAPY INDUCED DIARRHEA (CID)

- CID is potentially fatal (5%) due dehidration and electrolyte imbalances

- CHT regimens CID: 5-fluorouracil and irinotecan are associated with rates of CID of up to 80% with one third of patients experiencing severe (grade 3 or 4) diarrhea, taxanes
- CID:-uncomplicated (grade 1–2 with no complications) or complicated (grade 3–4 with one or more complicating signs or symptoms),
  - -early onset (<24 h after administration, irinotecan) or late onset (>24 h after administration)
  - -persistent (present for >4 weeks) or non-persistent (present for <4 weeks)

- **Treatment CID:**

1. Modification of diet and re-hydration
2. Loperamide
3. Ocreotide: loperamide refractory diarrhea (48 h), severe diarrhea
4. Tincture of opium: may be considered as a second-line therapy for persistent and uncomplicated diarrhea

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline.	Increase of 4–6 stools per day over baseline.	Increase of >7 stools per day over baseline. Incontinence. Hospitalization.	Life threatening consequences. Urgent intervention indicated.	Death

Peterson DE et al, Ann Oncol 2015, Stein et al. Ther Adv Med Oncol 2010

CLINICAL CASE

- 54 years old patient on adjuvant chemotherapy for T3N1M0 BC
- 4. cycle of adjuvant chemotherapy, 1. application of docetaxel 100 mg/m2, prior cht applications without meaningful AE
- Docetaxel was administreted with deksamethasone premedication according to standard scheme without acute toxic reaction

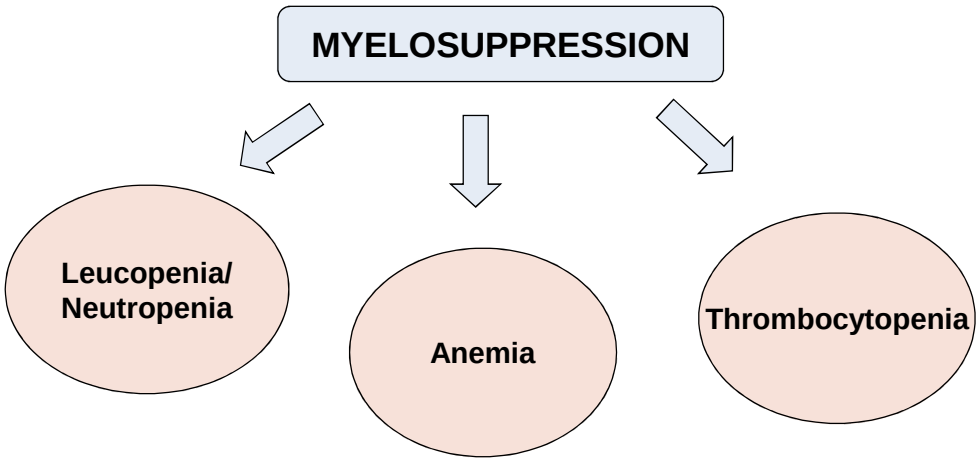
- D7: confusion, sleepiness, unable to answer questions; afebrile, RR 100/70, p: 100/min, normal ECG, without major neurologic deficit on examination, physical examination otherwise unrenarkabe

- Heteroanamnesis: profound diarrhea (6-10 stools per day 5 days, last 2 days vomiting) without fever
- Lab. Test: profound hyponatremia (Na: 115, K:2.1 mmol/l) elevated creatinin value and urea, CRP, PCT normal, no signs of myelosuppression

- X-ray abdomen and stool cultures: negative

- DIAGNOSIS: acute dehydration and hypovolemic hyponatriemia as a consequence of diarrhea, nausea and vomiting
- Treated with parenteral saline infusion, loperamide
- Adjuvant chemotherapy: weekly paclitaxel administration

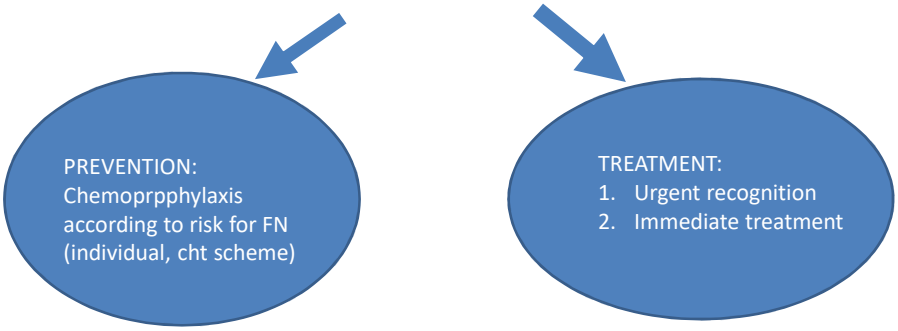
CHEMOTHERAPY INDUCED MYELOSUPPRESSION



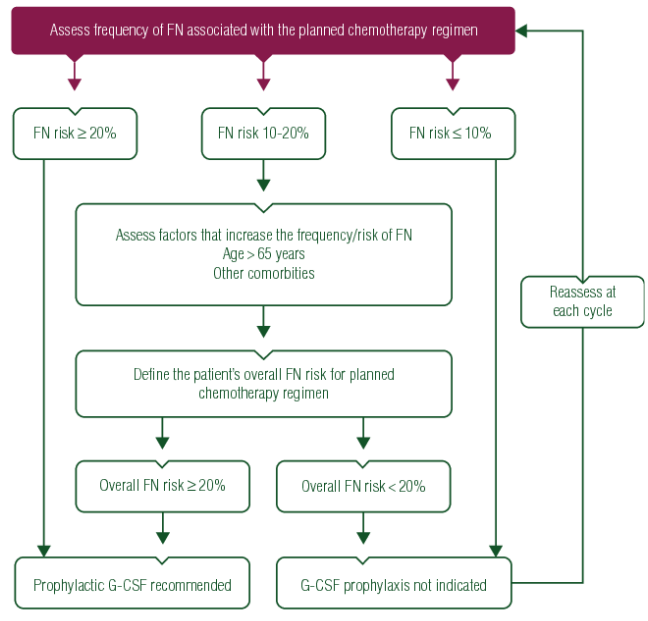
FEBRILE NEUTROPENIA

DEFINITION:an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of <0.5 × 109/l

- FN remains one of the most frequent and serious complications of cancer chemotherapy
- 20-30 % pts require hospitalisation, mortality 10%
- Predisposing factors: certain chemotherapeutics regimen-FN risk, age, advanced disease, prior FN, mucositis, low PS, CVS disease



Klastersky J et al, Ann Oncol 2016



Klastersky J et al, Ann Oncol 2016

FEVER AND SUSPECTED NEUTROPENIA

History, previous microbiology reports, physical examination- source of infection?

Lab test: blood counts, CRP, liver, kidney
Blood cultures: i.v.cathethers, peripheral vein
Urinanalysis
X-ray
Urin/sputum/other culture in case of suspicion

MASCC Score

Characteristic	Score
Burden of illness:[1]	
• No or mild symptoms	5
• Moderate symptoms	3
• Severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Out[illegible]nt at presentation	3
Age [illegible] years	2

≥21 Low risk

MONITORING!!!

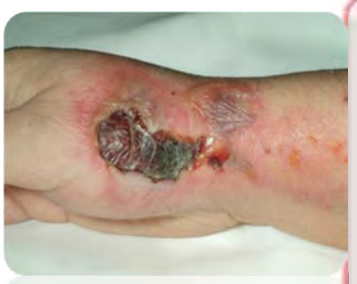
<21 High risk

No pneumonia, stable, no i.v. cathethers:
Po/iv antibiotics: amoksicillin plus clavulanic acid and quinolones

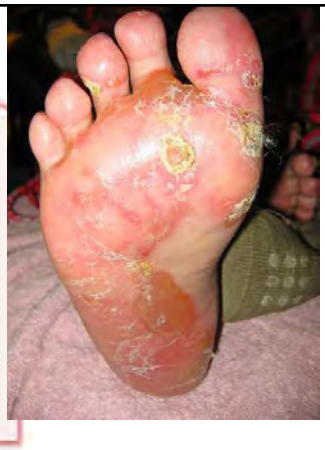
i.**v. broad spectrum antibiotics**

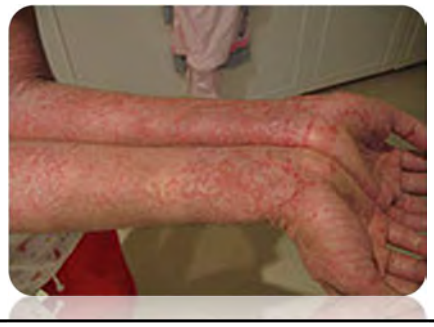
Early discharge?

Klastersky J, eta al. Ann Oncol 2016



- extravasation
- alopecia
- nail changes
- hand-foot syndrome (capecitabin, taxanes, 5-FU)
- dermatitis





- HFS:palmar-plantar erythrodysaesthesia syndrome: redness, marked discomfort, swelling and tingling in the palms of the hands or the soles of the feet (5-fluorouracil (5-FU), (6%-34%), capecitabine (50%-60%), doxorubicin (22%-29%), PEGylated liposomal doxorubicin (40%-50%), docetaxel [6%-58%; preventative mesures are important-10% urea cream significantly reduces the incidence of HFS
- Treatment of HFS: , skin inflammation: high-potency topical corticosteroids], while erosions and ulcerations: with antiseptic solutions (silver sulfadiazine 1%), analgesia on painful areas: lidocaine 5% patches
- Skin cooling (e.g. cold gloves or socks) significantly reduce of HFS for ChT given as an infusion(paclitaxel, docetaxel and liposomal doxorubicin)

Lacouture ME, et al, Ann Oncol 2020

EXTRAVASATION:inadvertent infiltration of chemotherapy into the tissues surrounding the intravenous site

- Extravasated drugs are classified according to their potential for causing damage as 'vesicant', 'irritant' and 'nonvesicant'

VESICANT: blisters/tissue destruction !!!!!
IRRITANTS: pain along the vein and inflammatory reaction

DNA-binding vesicant drugs	**Alkylating agents** **Anthracyclines** **Antitumor antibiotics**	Mechloretamine Doxorubicin, Daunorubicin, Epirubicin, Idarubicin Mitomycin, Dactinomycin, Mitoxantrone*
Non-DNA binding vesicant drugs	**Vinca alkaloids Taxane**	Vinblastine, Vincristine, Vinorelbine, Vindesine Paclitaxel, Docetaxel
Irritant drugs	Alkylating agents Platinum analogs Topoisomerase II inhibitors Anthracyclines Topoisomerase I inhibitors	Carmustine, Dacarbazine, Ifosfamide, Melphalan, Thiotepa, Carboplatin,° Cisplatin,# Oxaliplatin Teniposide, Etoposide Liposomal Doxorubicin, Liposomal Daunorubicin Irinotecan, Topotecan

Fidalgo JA, et al, Ann Oncol 2012

Extravasated vesicant	Antidote	Treatment
Anthracyclines	DMSO Dexrazoxane	Topical cooling
Docetaxel	Hyaluronidase	Topical cooling
Mytomicin	DMSO	Topical cooling
Mitoxantrone	DMSO	Topical cooling
Vinca alkaloids	Hyaluronidase	Topical warming

- DMSO (topical application): is a solvent capable of penetrating tissue, it neutralizes free-radical accumulation and encances systemic absorption of the extravasated drug.
- Dexrazosane (intravenously): is approved for anthracycline extravasation treatment, it binds to iron and prevents the formation of free radicals which induce extravasation-induced tissue necrosis.
- Hyaluronidase (subcutaneously) degrades hyaluronic acid, breaks down subcutaneous tissue bonds promoting drug diffusion and enhances the absorption of injected substances.

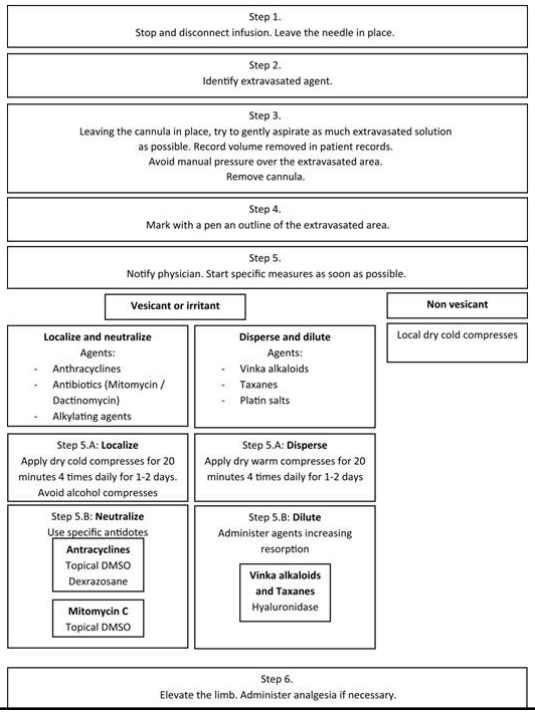
Signs and symptoms of vesicant extravasation:
swelling, redness and/or discomfort, resistance during drug administration, a slow and sluggish infusion, and lack or loss of a blood return from the i.v. cannula, implanted port or other central venous access device.

Fidalgo JA, et al, Ann Oncol 2012

It is essential to recognize that an extravasation has taken place as quickly as possible!!!

- 40 years BC patients develops sweeling and redness in the arm where the canula during doksorubicin infusion is inserted

WHAT WOULD YOU DO?



Fidalgo JA, et al, Ann Oncol 2012

CENTRAL AND PERIPHERAL CHEMOTHERAPY INDUCED NEUROTOXICITY (CIPN)

- chemotherapy-induced cognitive dysfunctions=„chemo-brain“, other: other types of acute encephalopathy: ifosfamide-induced acute encephalopathy, increased risk of trombemolic stroke
- incidence of CIPN approximately 38% (up to 90% with oxaliplatin)
- reduce functional capacity and quality of life, the long-term reversibility questionable, symptoms may last years after chemotherapy discontinuation
- CIPN: platinum-based agents (cisplatin, oxaliplatin), vinca alkaloids (vincristine, vinorelbine), taxanes (docetaxel, paklitaksel)
- **Oxaliplatin-Induced Peripheral Neuropathy:**
  - more than 90% of patients developed acute neuropathy (paresthesia, dysesthesia of the hands, feet and perioral area induced by cold stimuli in the hours and days) and 30–50% of patients developed chronic neuropathy (paresthesia, numbness, sensory ataxia)
- **Taxane, vinca alkaloids neuropathy:** sensory neuropathy with a stocking-and-glove distribution over the hands and feet

Kerckhove N, et al. F Phar 2017

Platinum-based anticancer drugs	
Oxaliplatin	Acute CIPN (>90% of patients): paresthesia, dysesthesia of the hands, feet and perioral area induced by cold stimuli
	Chronic CIPN (30–50% of patients): paresthesia, numbness, sensory ataxia, functional deficits, and pain
	No vegetative disturbances
	Coasting effect
	Maximum duration in the literature: 8 years
Cisplatin	Sensory neuropathy similar to oxaliplatin-induced chronic neuropathy (50% of patients)
	Maximum duration in the literature: 25 years (adult survivors of childhood extracranial solid tumors)
Taxanes	
Paclitaxel	80–97% of patients
Docetaxel	Acute and chronic sensory neuropathy associated with paresthesia, numbness, tingling and burning, and mechanical and cold allodynia
	Rare motor symptoms with mild distal weakness and myalgia
	Rare vegetative disturbances
	Coasting effect
	Maximum duration in the literature: 4.75 years
Vinca alkaloids	
Vinblastine	35–45% of patients
Vinorelbine	Sensory neuropathy in the hands and feet, leading to functional disability with fine motor tasks and walking, including numbness and tingling
Vindesine	Motor neuropathy with cramps and distal muscle weakness
Vincristine	Vegetative neuropathy associated with postural hypotension, bladder and bowel disturbance
	Coasting effect
	Maximum duration in the literature: 7 years (cancer survivors of childhood hematological malignancies)

Kerckhove N, et al. F Phar 2017

- no effective agent exists to prevent CIPN
- prevention of CIPN with cryotherapy can be considered according to ESMO, similar recommendation for medical exercise for cancer patients (low LoeE/GoR-IIC)
- Management of CIPN:- reducing or discontinuing chemotherapy when CIPN develops
  - treatment of the symptoms of neuropathic pain- only duloxetine was shown to help neuropathic pain in established CIPN; any other medications (gabapentin, topical preparations, etc.) are used in an off-label fashion

Jordan B, et al. Ann Oncol 2020

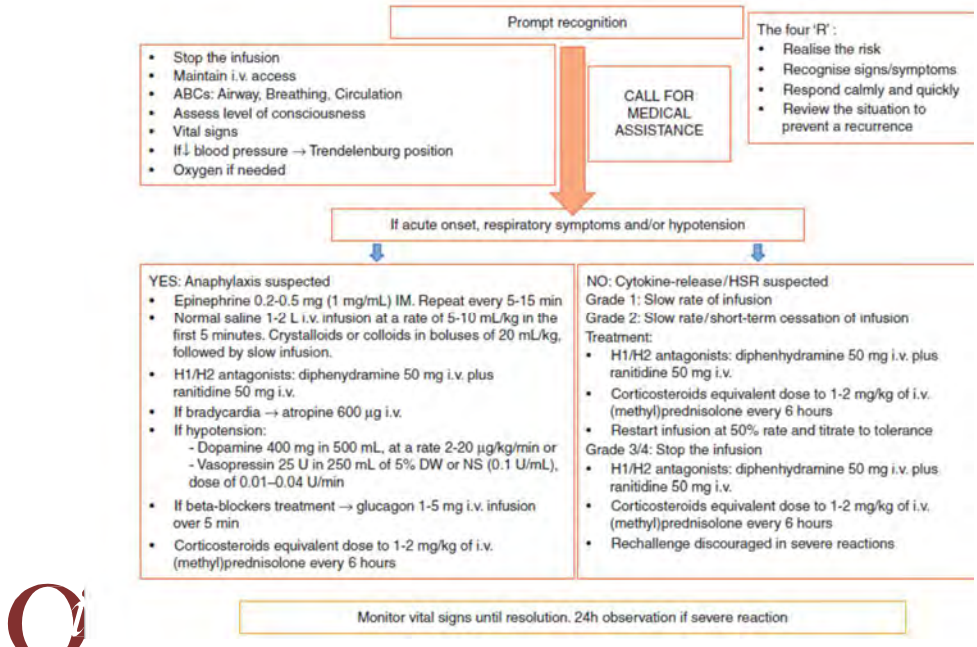
True allergic responses vs non-allergic responses

Table 2. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three sets of criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of skin/mucous membranes (e.g. hives, generalised itch/flush, swollen lips/tongue/uvula) and at least one of the following:
   a. Respiratory compromise (e.g. dyspnoea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence].
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of skin/mucous membranes (e.g. generalised hives, itch/flush, swollen lips/tongue/uvula).
   b. Respiratory compromise (e.g. dyspnoea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).
   c. Reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence].
   d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours). Adults: systolic blood pressure of < 90 mmHg or > 30% decrease from that person's baseline.

Rosello S, et al, Ann Oncol 2016



Rosello S, et al, Ann Oncol 2016

CARDIOTOXICITY

- **Arrythmias**: taxanes
- **Coronary artery spasem:**5-FU, capecitabin, cisplatin
- **Heart failure:** anthracyclines

- Use all the knowledge for preventative meassures!
- Educate the patient!

THANK YOU FOR YOUR ATTENTION!

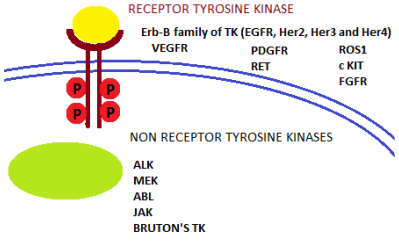
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Toxicity of tyrosine kinase inhibitors (TKI) and the management

Urška Bokal

2nd Summer School of Medical Oncology, 7/ 9/2021

Tyrosine kinase inhibitors



Tyrosine kinases:

- activate proteins/autoactivate by phosphorylation of tyrosine moiety - important for signal transduction and cell cycle regulation

Tyrosine kinase inhibitors:

- Small molecules, oral application
- act mostly by blocking ATP binding site, therefore inhibit phosphorylation
- bind reversibly or irreversibly

Other protein kinases:

B Raf (serine threonine kinase)

WHO Collaborating Centre for Drug Statistics Methodology

https://www.whocc.no/atc_ddd_index/?code=L01XE&showdescription=no

ATC classification system

L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01 ANTINEOPLASTIC AGENTS
L01X OTHER ANTINEOPLASTIC AGENTS
L01XE Protein kinase inhibitors

ATC code	Name
L01XE01	imatinib
L01XE02	gefitinib
L01XE03	erlotinib
L01XE04	sunitinib
L01XE05	sorafenib
L01XE06	dasatinib
L01XE07	lapatinib
L01XE08	nilotinib

On- and off- target toxicity

On-target:

- due to inhibition of the desired target (mechanism based)
- class effect: shared with all agents that inhibit specific target
- VEGFR TKI: hypertension
- EGFR TKI: rash

Off-target:

- due to inhibiton of other unintended targets
- „off targets“ share structures or residues with the intended targets
- sunitib: hematologic toxicity (FLT3 inhibition)

- toxicities can ovelap due to cross interaction of multiple pathways

TABLE. Examples of On-Target and Off-Target Adverse Effects

Drug Example	Main Target	On-Target Effects	Off-Target Effects
Erlotinib Afatinib Cetuximab	EGFR	Skin rash Diarrhea Stomatitis/mucositis	Anorexia
Bevacizumab Aflibercept	VEGF	Hypertension Poor wound healing GI perforation Cardiac toxicity	
Sunitinib Axitinib Sorafenib Pazopanib Cabozantinib	VEGFR-2	Hypertension Poor wound healing GI perforation Cardiac toxicity	Hypophosphatemia Neutropenia Hand-foot syndrome Hypoglycemia
Everolimus Temsirolimus	mTOR	Hyperglycemia Pneumonitis Stomatitis/mucositis Hypertriglyceridemia	
Trametinib	MEK	Retinal detachment Retinal vein occlusion Skin rash Decreased LVEF Increased creatine kinase	
Vemurafenib Dabrafenib	BRAF	Skin rash Arthralgia Keratoacanthomas, cutaneous squamous cell carcinomas	Hemolytic anemia in patients with G6PD deficiency (dabrafenib has sulfonamide moiety)
Dasatinib	BCR-ABL	BCR-ABL	Edema/effusions Pulmonary arterial hypertension

CA Cancer J Clin. 2013;63:249-79

https://www.targetedonc.com/publications/targeted-therapies-cancer/2013/december-2013/Toxicities-of-Targeted-Therapies-and-Their-Management

The good news: toxicity may correlate with response/better survival

- rash due to EGFR TKI in lung cancer
- hypertension and hypothyroidism due to VEGFR TKI in renal cell carcinoma

PLoS One. 2013;8(1):e55128. doi: 10.1371/journal.pone.0055128. Epub 2013 Jan 30.

Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis.

Liu HB[1], Wu Y, Lv TF, Yao YW, Xiao YY, Yuan DM, Song Y

J Natl Cancer Inst. 2011 May 4;103(9):763-73. doi: 10.1093/jnci/djr128. Epub 2011 Apr 28.

Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.

Cancer. 2011 Feb 1;117(3):534-44. doi: 10.1002/cncr.25422. Epub 2010 Sep 15.

Hypothyroidism in patients with renal cell carcinoma: blessing or curse?

Schmidinger M[1], Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A, Clodi M, Kramer G, Zielinski CC.

Liu S et al. Cancer Treat Rev. 2014; 40: 883-91

ErbB tyrosine kinase inhibitors

Compound	Target inhibition	Specific toxicity
erlotinib gefitinib	1st generation EGFR TKI (mutant EGFR, reversible)	skin related toxicity diarrhea stomatitis ocular toxicity interstitial pneumonitis
afatinib dacomitinib	2nd generation EGFR TKI (EGFR, Her2 and Her4, irreversible)	
osimertinib	3rd generation EGFR TKI (mutant EGFR including mutation T790M, irreversible)	
lapatinib	EGFR and Her2, reversible	diarrhea nausea, vomiting rash cardiomyopathy
neratinib	EGFR, Her2 and Her4, irreversible	

all agents: hepatotoxicity

Shah R et al. Drug Safety. 2019; 42:181-98

spc of selected drugs

ErbB TKI toxicity: management

Toxicity	Most frequent with	Treatment/ Comments
rash	afatinib, erlotinib, dacomitinib	sunscreen, moisturizing cream topical clindamycin 1% gel/ oral doxycycline 100 mg bid topical corticosteroid (e.g. hydrocortisone 2.5% cream) prophylaxis!!
diarrhea	afatinib neratinib dacomitinib erlotinib	dietary changes appropriate fluid and salt intake (ORS/infusions) antidiarrheal agents (loperamid, 4 mg then 2 mg every 4 h or after each loose stool until the desired effect)
interstitial lung disease	osimertinib dacomitinib gefitinib	risk factors: previous pulmonary fibrosis, male, smoking, prior EGFR TKI therapy usually no cross reactivity between agents discontinuation of TKI, corticosteroids
ocular (keratoconjunctivitis)	erlotinib dacomitinib	artificial tears, antibacterial ointment if superimposed infection ophthalmologic evaluation if keratitis is suspected (acute onset or worsening of eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) → withhold or discontinue the treatment
hepatoxicity	gefetinib dacomitinib	regular monitoring of liver enzymes

- drug interruption, lowering of the dose
- life threatening: discontinuation of treatment

Up to Date

Shah R et al. Drug Safety. 2019; 42:181-98

Lacouture M et al. Am J Clin Dermatol. 2018; 19: S31-9

VEGFR tyrosine kinase inhibitors

Compound	Specific toxicity
sunitinb pazopanib axitinib tivozanib cabozanitib sorafenib regorafenib lenvatinib	thyroid dysfunction, dysphonia, palmar-plantar erythrodysaesthesia syndrome thromboembolism, hypertension, cardiac failure, QT prolongation hemorrhages, GIT perforation/fistulas, impaired wound healing liver toxicity, proteinuria, fatigue, taste disorder

VEGFR TKI – management of cardiovascular toxicity

Toxicity	Recommendations
LVEF decrease/ heart failure	• evaluation of preexisting risk factors: uncontrolled hypertension, coronary artery disease → baseline and periodic assessment of LVEF • if symptomatic, LVEF declines to < 50 % or for ≥ 10 % from baseline, withhold treatment and introduce cardiac failure medications • discontinue therapy if: heart failure ≥ CTC G3, LVEF decline > 20 % from baseline or recurrent decline upon rechallenge
hypertension	• prior to start of the treatment blood pressure should be controlled • regular monitoring and introduction of antihypertensive therapy if needed; preferable ACE or angiotensin receptor inhibitors (↓ proteinuria, antitumor effect in renal cell carcinoma?) • interruption of treatment if severe hypertension, hypertensive urgency or persistent hypertension despite medications • discontinue therapy if: life threatening symptoms (reversible posterior leucoencephalopathy syndrome) or uncontrolled hypertension despite medications
venous TE	• withhold therapy and initiate standard anticoagulant treatment • may resume at initial dose after resolution of symptoms and achievement of therapeutic level of anticoagulation
arterial TE	• evaluate risk factors • avoid therapy in patients with history of the event in preceding 6-12 months

TE: thromboembolic events

CA Cancer J Clin. 2013;63:249-79

Up to Date

VEGFR TKI – management of toxicity

Toxicity	Recommendations
palmar plantar erythrodysesthesia	• preventive measures (callus removal, minimize friction and direct trauma by wearing well fitted, well-padded footwear) • avoid hot water and sun exposure • application of moistures containing salicylic acid or urea
hypothyroidism	• regular monitoring of thyroid function and introduction of thyroid replacement therapy if needed
fatigue	• modification of daily activities including rest periods • regular daily exercise if the patient is fit enough • consider other causes: anemia, hypothyroidism, depression, sleep disturbances • TKI dosing in the evening may reduce fatigue

CA Cancer J Clin. 2013;63:249-79

Rimassa L et al. Can Treat Rev 2019; 77: 20-8

ALK tyrosine kinase inhibitors

Compound	Target inhibition	The most common toxicity (incidence of all grades)	Other toxicity
crizotinib (+ ROS1, cMET)	1st generation ALK TKI	nausea, vomiting, diarrhea, constipation, edema, fatigue, ↓ appetite, neuropathy, dizziness hepatotoxicity, vision disorder, (≥ 25%)	neutropenia, QT prolongation, bradycardia, cardiac failure, GIT perforation, renal impairment
ceritinib (+ ROS1)	2nd generation ALK TKI	nausea, vomiting, diarrhea, constipation, fatigue, ↓ appetite, ↓ weight, abdominal pain, hepatotoxicity, ↑ creatinine, rash, anemia, esophageal disorder (≥ 10%)	QT prolongation, bradycardia, hyperglycemia, ↑ amylase and lipase
alectinib (+ RET)		constipation, edema, myalgia (≥ 20%)	hepatotoxicity, ↑ CPK, bradycardia, photosensitivity
brigatinib (+ ROS1)		↑ glucose, insulin, CPK, lipase, amylase, AP, aPTT, ↓ lymphocytes, phosphate, leucocytes, anemia, nausea, diarrhea, fatigue, cough, headache, rash, vomiting, dyspnea, hypertension, myalgia, peripheral neuropathy (≥ 25%)	bradycardia visual disturbance
lorlatinib (+ ROS1)	3rd generation ALK TKI	hyperlipidemia, peripheral neuropathy, cognitive effects, edema, fatigue, weight increase, diarrhea, arthralgia (≥ 20%)	↑ amylase, lipase, AV block, LVEF decrease

CPK – creatine phosphokinase
AP – alkaine phosphatase

GASTROINTESTINAL
NEUROLOGIC
MUSCULAR
METABOLIC
CARDIOVASCULAR

Kassem L et al. Crit Rev Oncol Hematol 2019; 134:56-64

smpc

ALK TKI – management of toxicity

Toxicity	Recommendations
QT prolongation	• monitor electrolytes and ECG regularly • if no arrhythmia and QT interval ≥ 500 ms or ≥ 60 ms from baseline: interrupt treatment and start at lower dose when QT < 480 ms • if concomitant signs of arrhythmia: discontinue the treatment
bradycardia	• if symptomatic (dizziness, angina, (pre)syncope, heart failure) interrupt treatment and start at lower dose when asymptomatic or heart rate > 60bpm • Check for concomitant medicines known to cause bradycardia, as well as anti-hypertensive medicines.
vision disorders (diplopia, photopsia, blurry/impaired vision, and vitreous floaters, poor light dark adaptation - crizotinib)	• Occurs soon after the beginning of the therapy; often improves with length of time on treatment. • Rarely require treatment interruption/cessation. Consider ophthalmological evaluation if vision disorder is severe, persists, or worsens in severity. • Patients experiencing vision disorders should be cautious when driving or operating machinery.

Kassem L et al. Crit Rev Oncol Hematol 2019; 134:56-64

smpc

http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Crizotinib_monograph_1Sep2014.pdf

MEK 1,2 inhibitors (+ B-RAF inhibitors)

Compound	The most common toxicity (incidence of all grades)
cobimetinib (+ vemurafenib)	diarrhoea, rash, nausea, pyrexia, photosensitivity reaction, hepatotoxicity, ↑ CK, vomiting (> 20%)
trametinb (+ dabrafenib)	pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash (> 20 %)
binimetinib (+ encorafenib)	fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, ↑CK, myalgia (> 25 %)

CK – creatine phosphokinase

MEK1,2 inhibitors:

- ↓ LVEF, hypertension,
- retinal pigment epithelial detachment/retinal vein occlusion,
- interstitial lung disease,

Kdaud A et al. The Oncologist 2017;22:823-33

smpc

B-RAF inhibitors:

- QT prolongation (vemurafenib, encorafenib),
- uveitis,
- cutaneus squamous cell carcinoma, keratoacantomas, hyperkeratosis,
- pyrexia

Ocular toxicity

Possible mechanism of MET TKI ocular toxicity:

- ERK activation is important for photoreceptor survival
- MEK inhibition results in apoptosis and loss of differentiation during photoreceptor development

Toxicity	Recommendations
uveitis	• local therapy • discontinue BRAF inhibitor if it is ineffective or uveitis grade 3 • and after resolution introduce it at lower dose
retinal vein occlusion	• discontinue treatment
retinal pigment epithelial detachment	• if G2-3: discontinue treatment and resume at lower dose when improved • most events resolve or improve to asymptomatic grade 1 following dose interruption or reduction

EGFR TKI: keratoconjunctivitis

crizotinib: poor light-dark adaptation

Kdaud A et al. The Oncologist 2017;22:823-33

smpc

Take home messages

- **Toxicity varies between patients.**
- **Beware of interactions with food and drugs!**
- **Multidisciplinary management: referral to doctors of other specialities.**
- **Chronic low grade toxicity influence the quality of life of patients.**

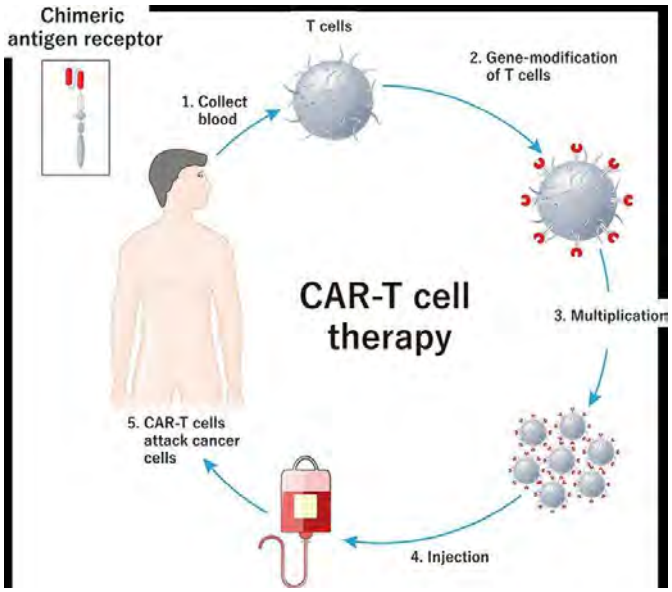
CAR T-cells and neurotoxicity

Pr Antoine Carpentier

Service de neurologie

Hôpital Saint-Louis AP-HP, Université de Paris

Chimeric antigen receptor (CAR) T-cell Therapy



https://www.noile-immune.com/en/Our_Science/prime_car-t.html

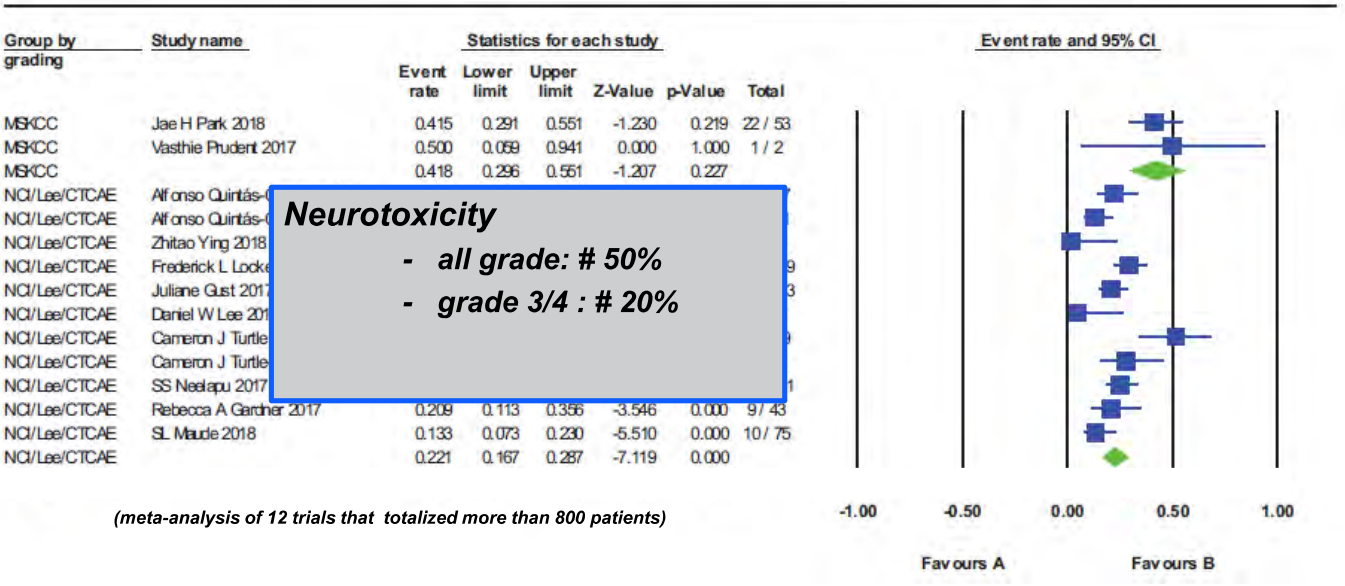
Main side effects:

Cytokine Release Syndrome (CRS)

Neurotoxicity

Potential anti-CD19 CAR T-cell sides effects: neurotoxicity

(=ICANS for « Immune effector Cell–Associated Neurotoxicity Syndrome)



Neurotoxicity

- ***all grade: # 50%***
- ***grade 3/4 : # 20%***

(meta-analysis of 12 trials that totalized more than 800 patients)

For MM patients treated with BCMA CAR T-cells: *all grade: <30%; grade 3/4: #15%*

Cao et al, Cytotherapy, 2020; Roex, J Hematol Oncol, 2020

Neurological signs	n	Categories	n
Aphasia	10	Cognitive signs	43
Executive syndrome	7		
Agraphia	5		
Cognitive slowness	5		
Confusional state	4		
Apraxia	2		
Disorientation	2		
Restlessness	2		
Attentional disorders	1		
Dysarthria	1		
Dyscalculia	1		
Hallucination	1		
Memory disorders	1		
Neglect syndrome	1		
Tremor	3	Movement disorders and cerebellar signs	16
Asterixis	1		
Cerebellar syndrome	7		
Dyskinesia	1		
Myoclonus	4		
Consciousness disorders	6	Consciousness disorders	5
Seizures	3	Seizures	3
Headaches	5	Miscellaneous	9
Others	4		

Clinical patterns of neurotoxicity

N=84 patients for B- cell lymphoma, treated with CAR T cells → 36 pts with neurotoxicity

No peripheral symptoms

Highly heterogeneous

Belin et al, Scientific reports, 2020

Neurological signs	n	Categories	n
Aphasia	10	Cognitive signs	43
Executive syndrome	7		
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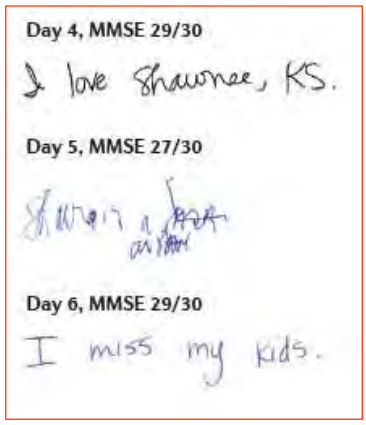
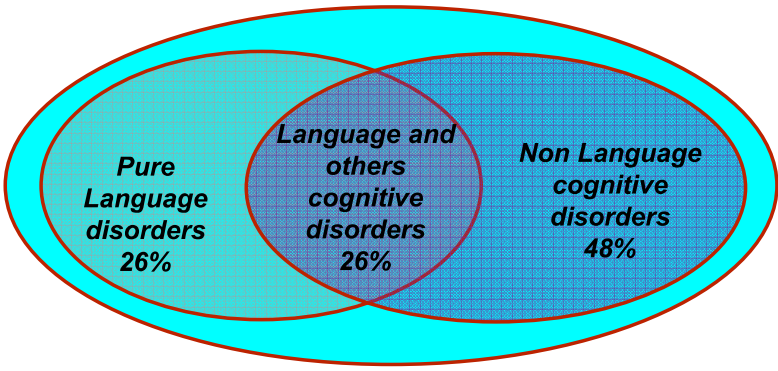


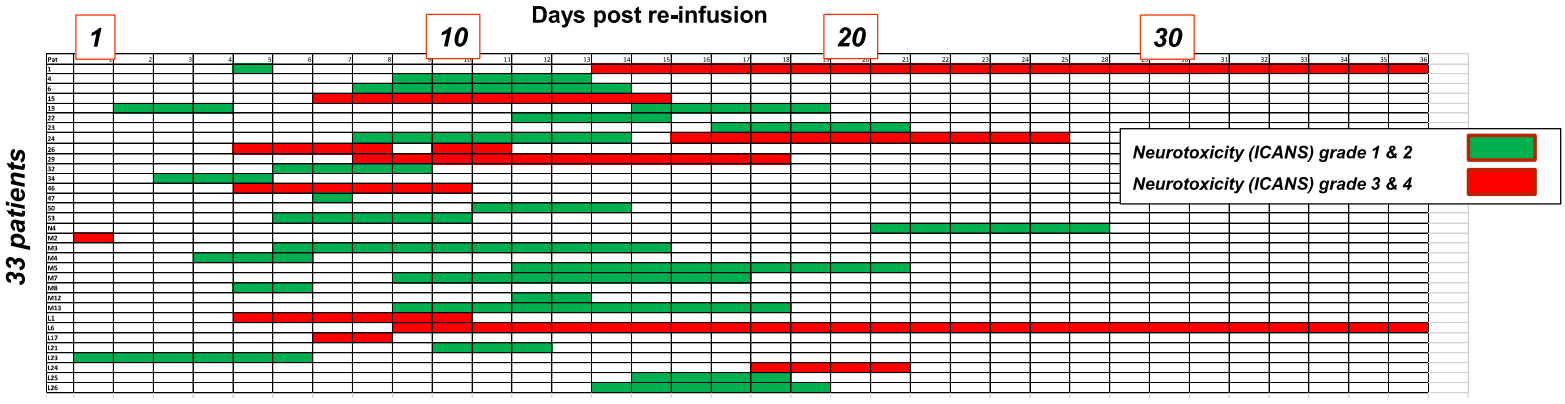
Language Disorders 52%

Non Language Cognitive Disorders 48%



Belin et al, Scientific reports, 2020

Evolution over time



- ***Median duration of neurological symptoms : <u>6 days</u>***
- ***almost all patients recovered within one month after CAR T-cells***
- ***Non severe in 2/3rd of the cases (1 possible neurological-related death)***

Evolution over time (6 to 12 months)

Neuro-Oncology

23(9), 1569–1575, 2021 | doi:10.1093/neuonc/noab077 | Advance Access date 2 April 2021

Evaluation of mid-term (6-12 months) neurotoxicity in B-cell lymphoma patients treated with CAR T cells: a prospective cohort study

(N= 56 patients)

Didier Maillet, Catherine Belin, Christine Moroni, Stefania Cuzzubbo, Renata Ursu, Lila Sirven-Villaros, Roberta Di Blasi, Catherine Thieblemont, and Antoine F. Carpentier

Service de Neurologie, Assistance Publique - Hôpitaux de Paris (AP-HP), Hôpital Saint-Louis, Paris, France (D.M., C.B., S.C., R.U., L.S.-V., A.F.C.); ULR 4072 - PSITEC - Psychologie: Interactions, Temps, Emotions, Cognition, Université de Lille, Lille, France (C.M.); Université de Paris, Paris Diderot, Paris, France (L.S.-V., R.D.B., C.T., A.F.C.); Service d'Hémato-Oncologie, Assistance Publique - Hôpitaux de Paris (AP-HP), Hôpital Saint-Louis, Paris, France (R.D.B., C.T.)

Conclusion. In this cohort of patients treated with CD19-targeted CART cells, we found no evidence for neurological or cognitive toxicity, 6-12 months after treatment.

How to diagnose ICANS?

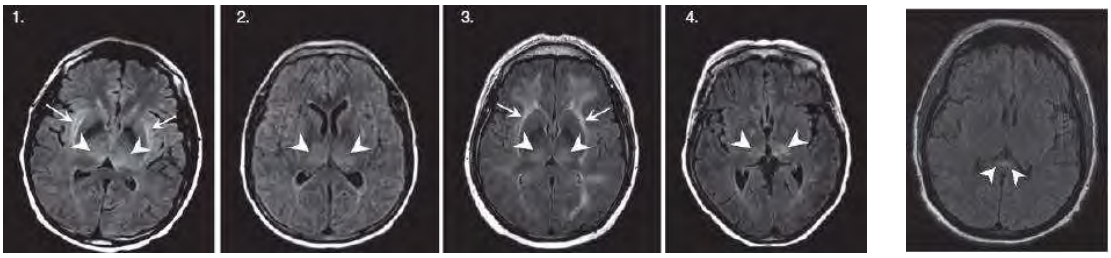
Differential diagnosis in these heavily-treated pts

- **Conditioning chemotherapy**
  - → thrombopenia : hemorrhage
  - → Coagulopathy: ischemia
  - → neutropenia & lymphopenia : opportunistic infections ++
- **Intra cerebral lymphoma progression**
- **<u>Iatrogenic complications</u>++**
  - Levetiracetam, benzodiazepine ….
  - 3rd gen Cephalosporins (Cefepim +++) can be neurotoxic (encephalopathy, myoclonus, seizures)

Brain MRI

- ***usually normal***

Some patients with severe neurotoxicity might develop bilateral T2/FLAIR hyperintensities (depending upon series: # 0% - 20% of the cases)



- ***Mainly useful for differential diagnosis***

Santomasso, Cancer Discovery, 2018
Gust et al , Cancer Discovery, 2017
Rubin, Brain, 2019;
Strati, Blood Adv, 2020

EEG

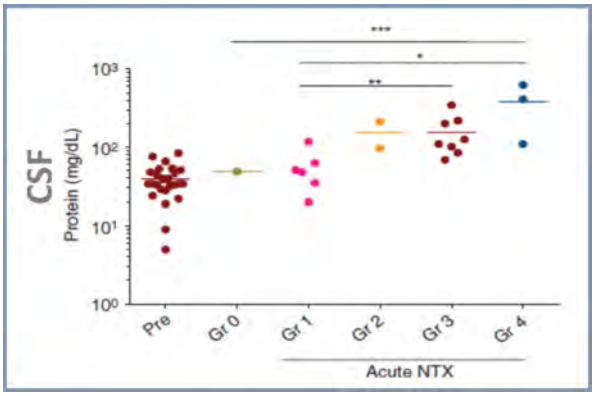
Almost always abnormal

- **Diffuse slowing in the theta-delta range with loss of the posterior dominant rhythm.**
- **Frontally predominant generalized rhythmic delta activity (RDA), with or without triphasic waves**
- **Only few patients exhibited epileptiform discharges (<10%)**

Gust, CNS Drugs, 2017; Santomasso, Cancer Discovery, 2018; Lee, BBMT, 2018; Rubin et al 2019

CSF studies

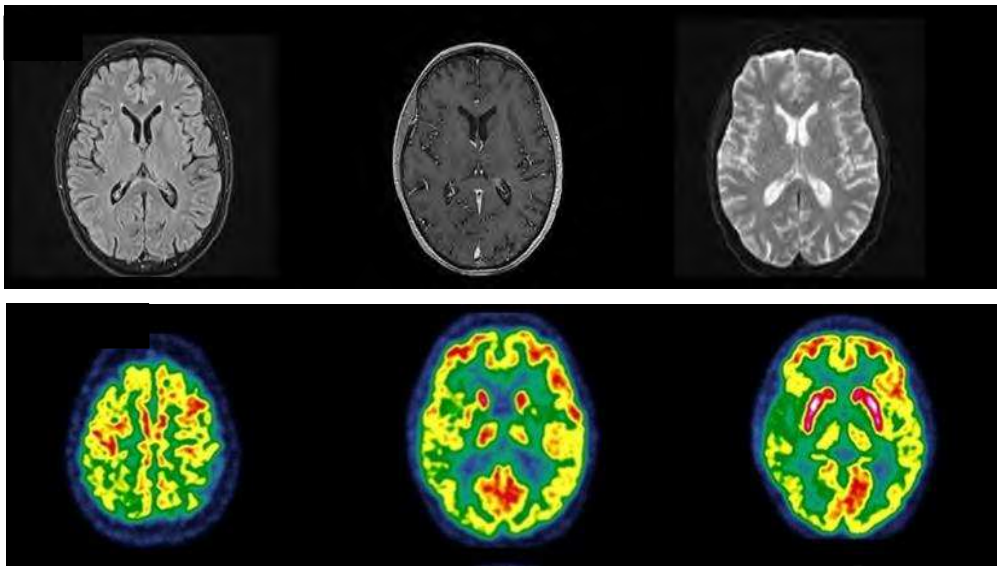
- **Rarely done because of thrombopenia**
- **When possible:**
  - Hyperproteinorachia (51 mg/dl, range 27 – 234)
  - Mild pleocytosis (3/µl, range 0–35)
  - CAR T cells detected in CSF in 19/21
- **Raised intracranial pressure (ICP): frequency?**



Gust, CNS Drugs, 2017; Neelapu, Nature Review, 2018; Santomasso, Cancer Discovery, 2018; Lee, BBMT, 2018

BRAIN ^{18}FDG-PET FOR NEUROTOXICITY?

66-yr old woman with refractory DBCL.
4 days after CAR T-cells infusion: Grade 3 ideational slowness, apraxia and ataxia



→ ***hypofixation of the cortex, mainly parietal and temporal lobes***

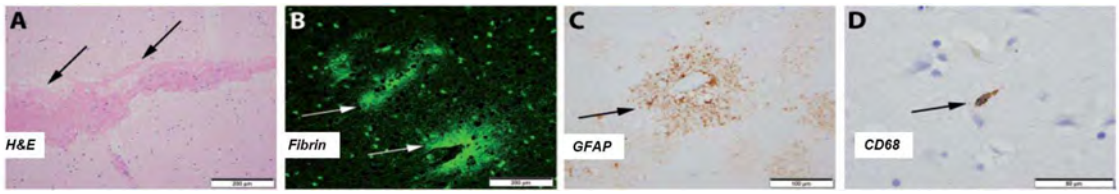
→ ***FDG-PET scanner allows an early mapping of cortical impairments***

Vernier et al, Revue Neurologique, 2021

Physiopathology ?

Neuropathologic studies after fatal neurotoxicity

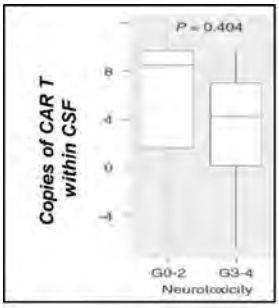
- ***Diffuse cerebral edema***
- ***microglial activation. Mild perivascular infiltration***



Schuster, NEJM,2017; Gust, Cancer Discov, 2017;
DeAngelo, J Immunother Cancer, 2017; Torre 2018; Rubin, Brain 2019
Taraseviciute et al, Cancer Discovery, 2018

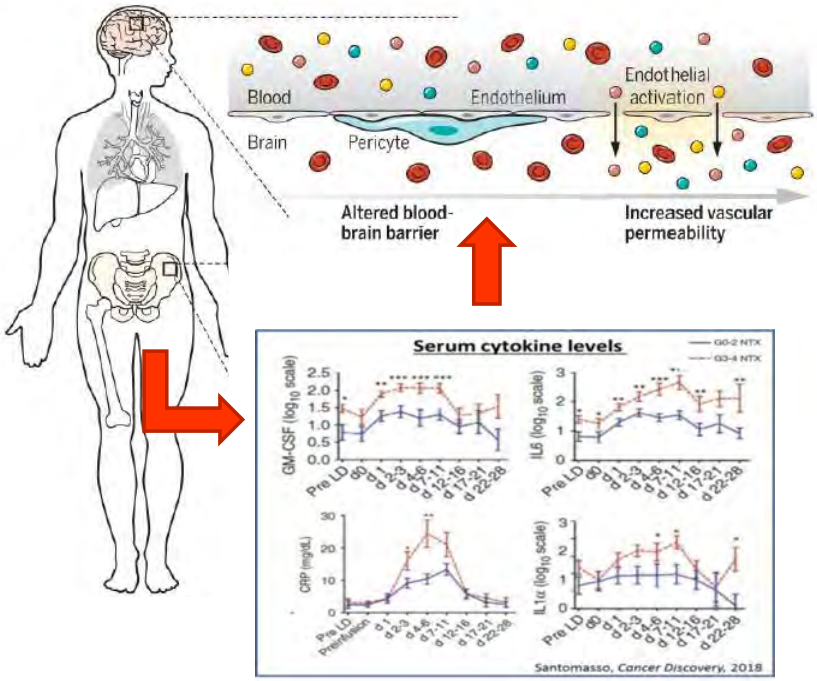
- ***CAR-T cells in brain tissue and CSF in some cases,***

but poor correlation with toxicity
→ bystanders or active players ?

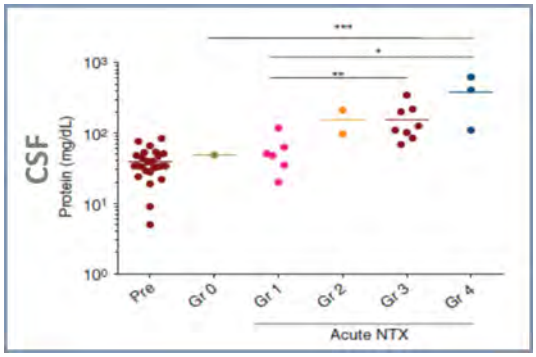


Santomasso, Cancer Discovery, 2018

Physiopathology



increased BBB permeability



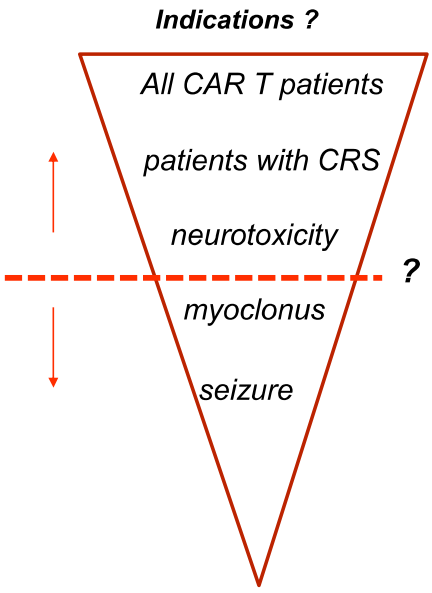
Jain and Litzow Blood Adv 2018; Santomasso, Cancer discovery, 2017;
June et al, Science, 2018

Managment of neurotoxicity

- *Standard of care difficult to define*
- *No controlled studies*

Anti-epileptic drugs

- **No consensus**
  - Some investigators start all patients on anti-seizure prophylaxis
  - some use it only for patients with CRS or neurotoxicity
  - others use it only for patients who had myoclonus/seizures



Gust, CNS Drugs, 2017; Neelapu, Nature Review, 2018; Santomasso, Cancer Discovery, 2018; Lee, BBMT, 2018

Steroids: largely prescribed

- Impact on CAR T-cells? short courses of moderate-dose corticosteroids (e.g. DXM 20 mg/d) do not appear to have a detrimental effect.

- Efficacy??

french series (retrospective analysis)		*Median duration of NTX*
22 patients with grade 1-2 NTX	*15 pts received no steroids:*	*5 days (1-9)*
	8 pts received steroids:	*8 days (3-17)*

Belin et al, Scientific Reports, 2020

- **anti IL-6 receptor Ab ?**

Largely prescribed for CRS… but does not decreased incidence or severity of neurotoxicity

In Santomasso,2018: **16 patients with severe neurotoxicity received Tocilizumab**

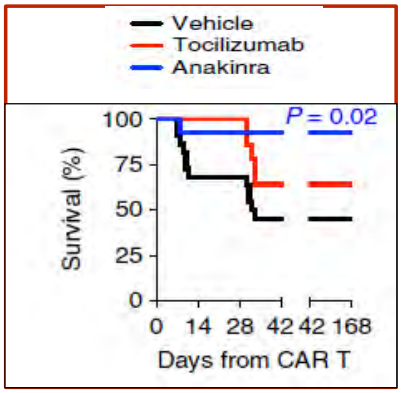
- **44% had peak neurotoxicity prior to or on the day of tocilizumab**
- **56% had peak neurotoxicity after the first dose of tocilizumab**

→ anti IL6 blockade only if associated CRS

- ***anti IL-1 receptor Ab?***

In a murine model of CAR T-cells:

- ***Monocytes are major sources of IL-1 and IL-6 during CRS. and IL1 is known to induce IL6& IL6R***
- ***Both anti IL-1R & anti IL-6R abolish CRS***
- ***anti IL-1R, but not anti IL-6R , abolishes neurotoxicity***



Norelli M, Nat Med. 2018;24(6):739–48

Locke et al, Blood. 2017; Park et al. NEJM 2018 ; Santomasso, 2018

Conclusions

- **Neurotoxicity is frequent (# 20 %) and usually has a good outcome**

- **Clinical presentation is heterogenous**
  - **Cognitive disorders, NOT LIMITED TO APHASIA , appeared as signature of severe neurotoxicity**
  - **Cerebellar and movements disorders are frequent but usually mild**

- **Optimal guidelines for treatment remain to be defined**
  - **Steroids? Prophylactic anti-epileptic drugs? Anti-IL6R: no. New options: anti-IL1?**
  - **Avoid other drugs with potential neurotoxicity +++ *"primum non nocere…."***

Systemic treatment for metastatic melanoma 2021

Prof. Lidija Kandolf Sekulovic MD, PhD
Faculty of Medicine, MMA
Belgrade, Serbia

2nd Summer School in medical oncology

Slovensko Zdravniško Društvo

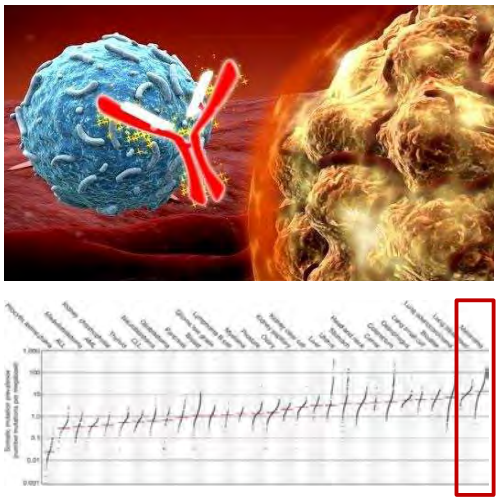
Metastatic melanoma: standard of care

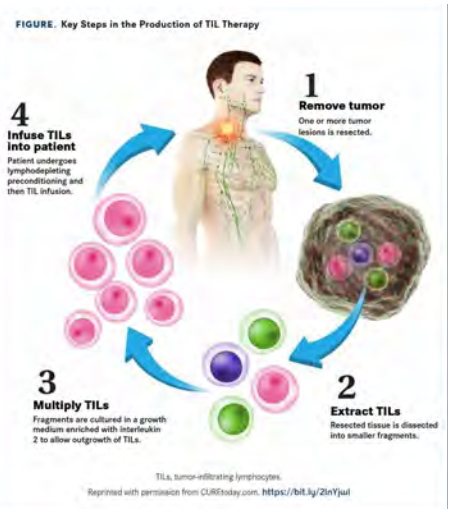
- **SURGERY:**
- For solitary metastases: PET-CT and brain MRI necessary before decision for surgery (+adjuvant therapy with anti-PD1)
- **SYSTEMIC THERAPY:**
  - Checkpoint inhibitor immunotherapy: anti-PD1 antibodies, anti-CTLA4 antibody
  - Targeted therapy: BRAF and MEK inhibitors
- **RADIOTHERAPY :**
- STEREOTACTIC RADIOTHERAPY AND GAMMA KNIFE SURGERY for CNS and other distant sites
- Palliative for bone metastases, lymph nodes and soft tissues, CNS metastases
- **SUPPORTIVE CARE**

Systemic treatment of metastatic melanoma 2021

BRAF gene mutation early event in oncogenesis

Targeted therapy effective in up to 60% of patients that are BRAFm





High mutational load = Immunotherapy effective
MoAb checkpoint inhibitors
Autologous TIL therapy

Targeted therapy

- Vemurafenib
- Cobimetinib
- Dabrafenib
- Trametinib
- Encorafenib
- Binimetinib

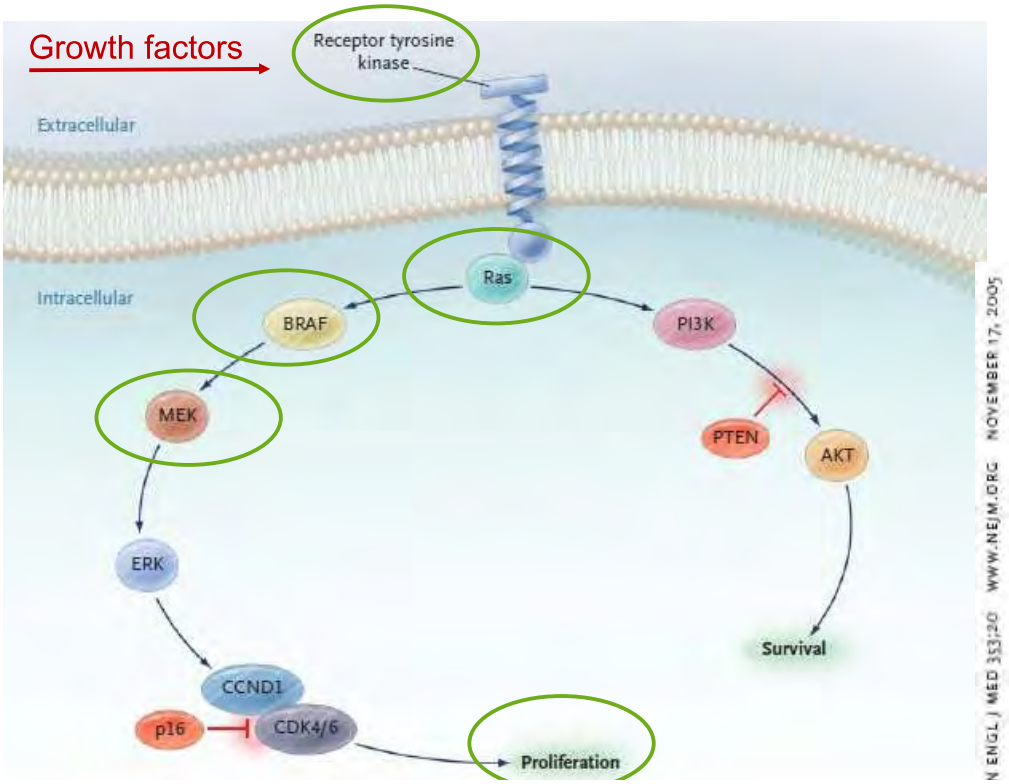
Checkpoint inhibitors

- Ipilimumab
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Avelumab
- Durvalumab

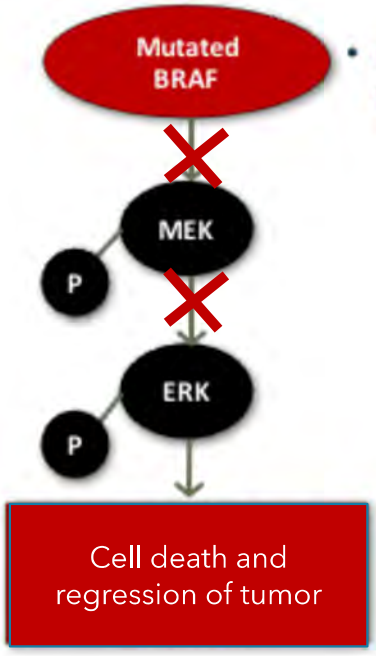
FDA APPROVED

EMA APPROVED

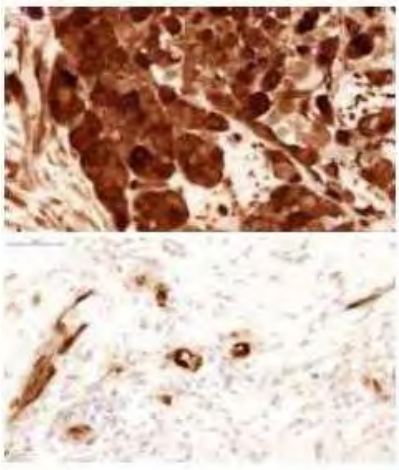
BRAF AND MEK in melanoma oncogenesis



BRAF+MEK INHIBITOR

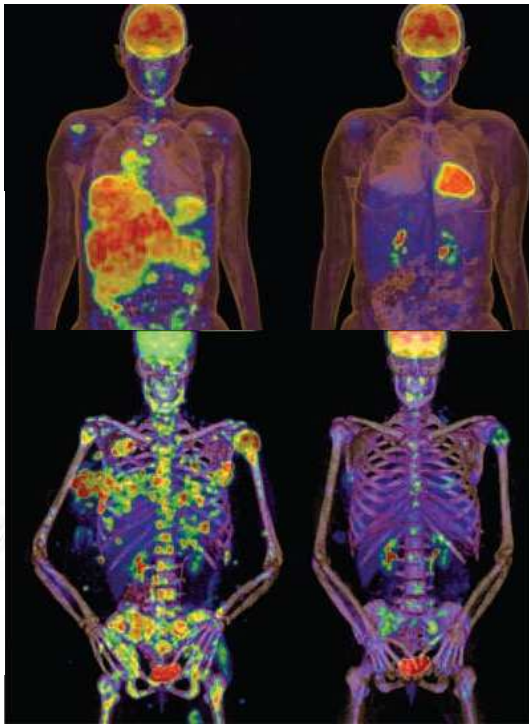


- Constant activation without control

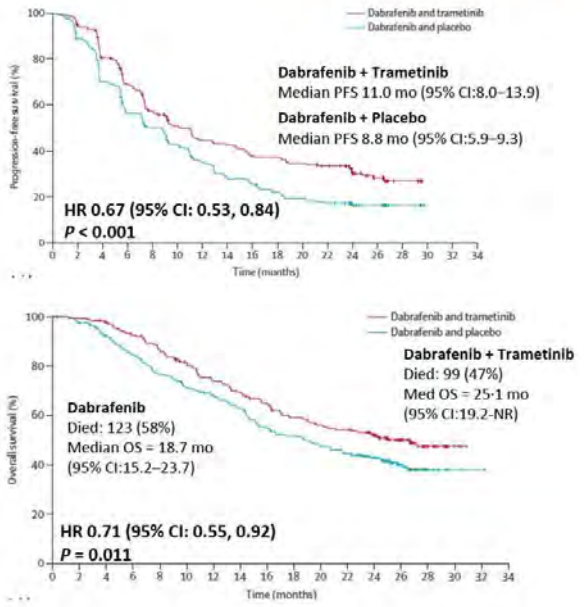


BL

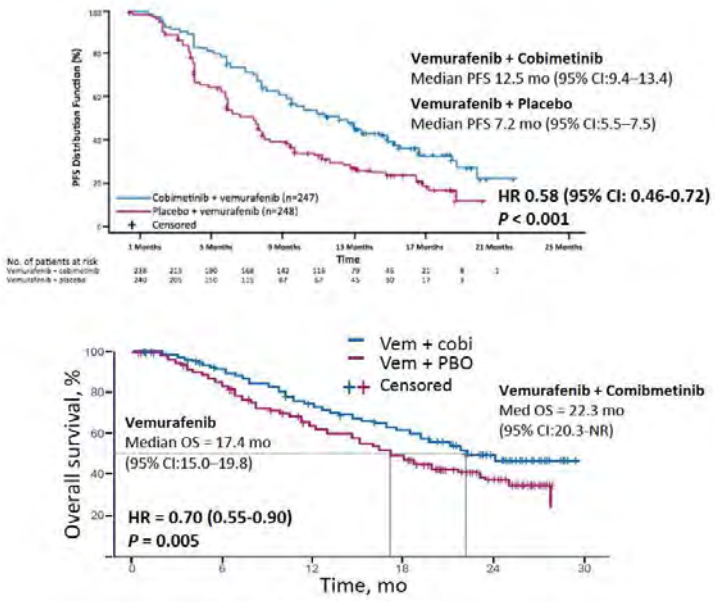
Day 15



Combined BRAFi+MEKi: standard of care

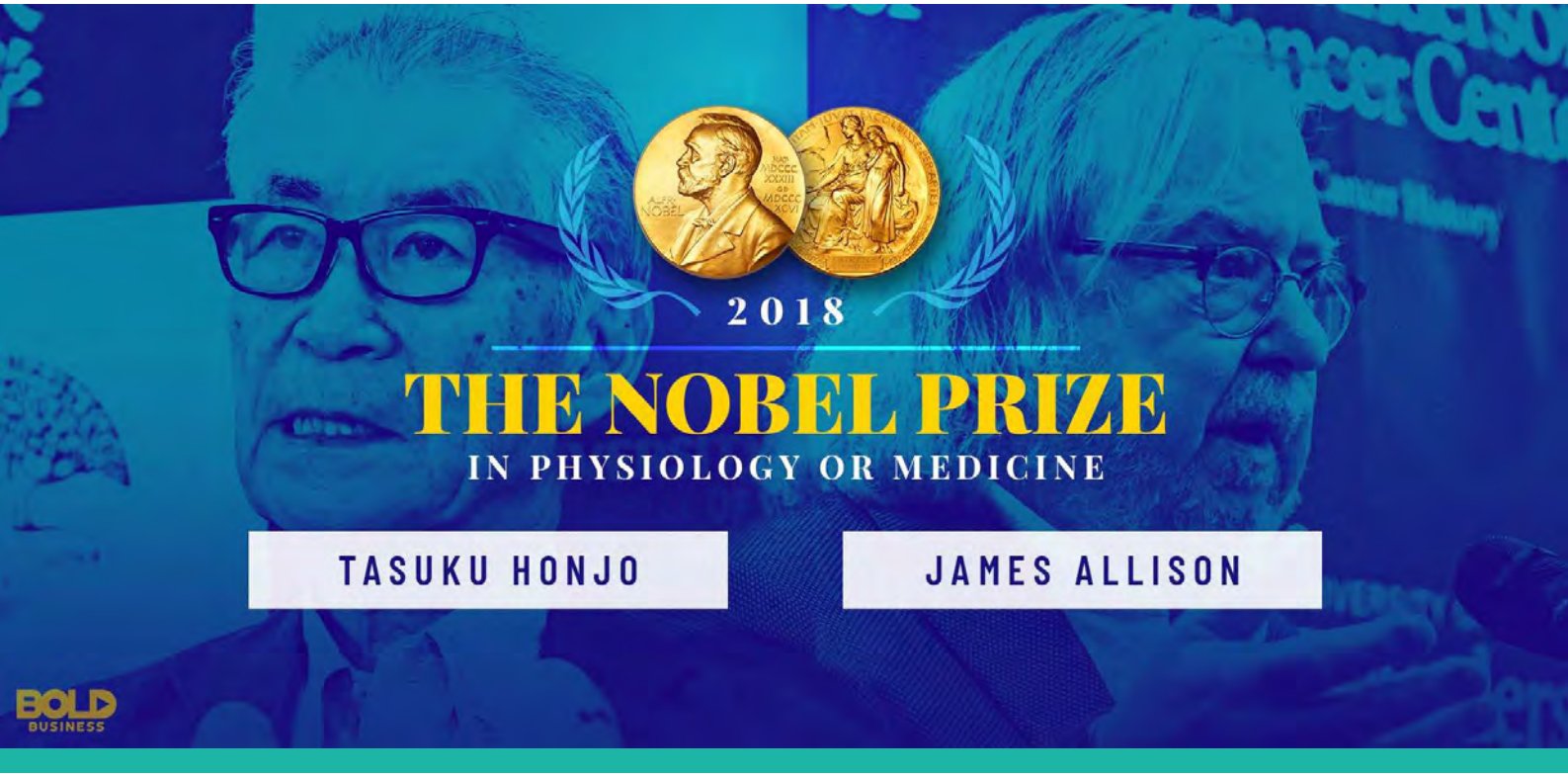


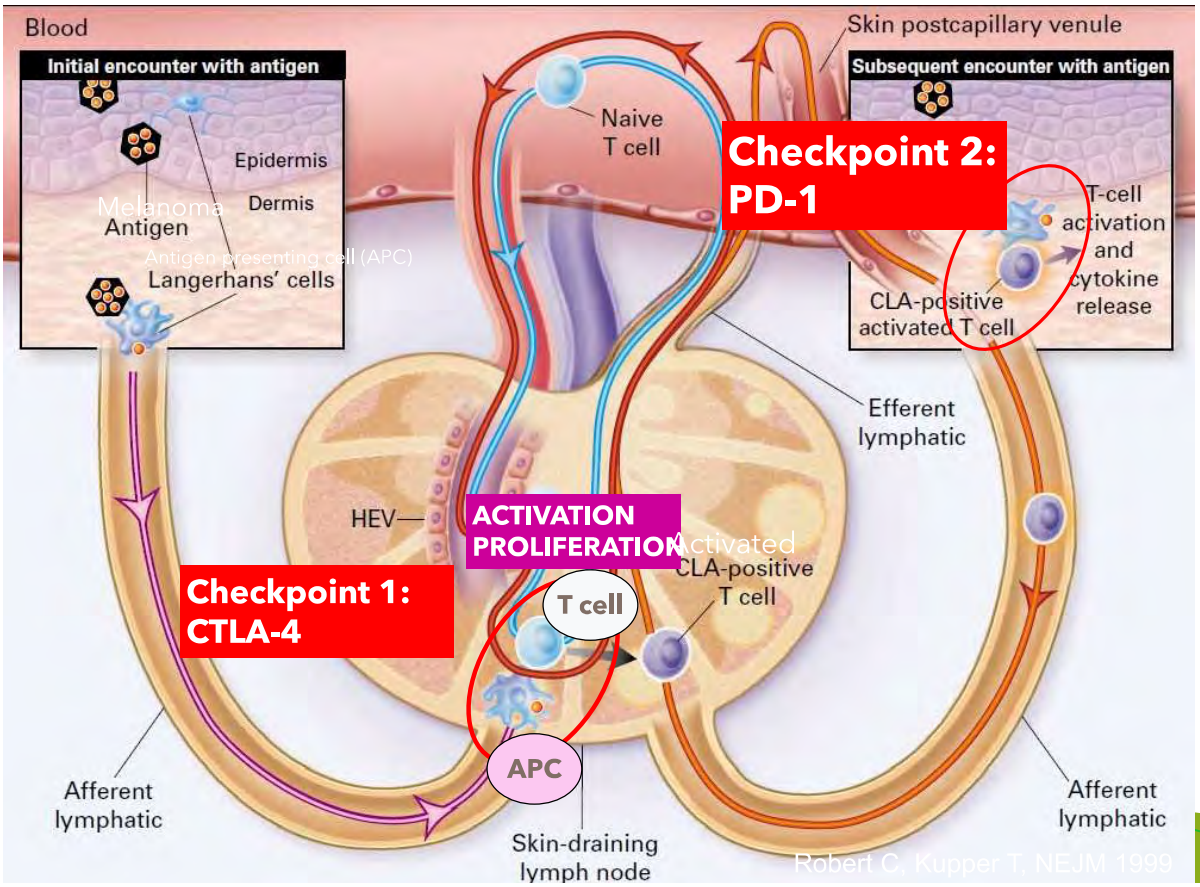
Long et al. NEJM 2014; Long et al. *Lancet* 2015.



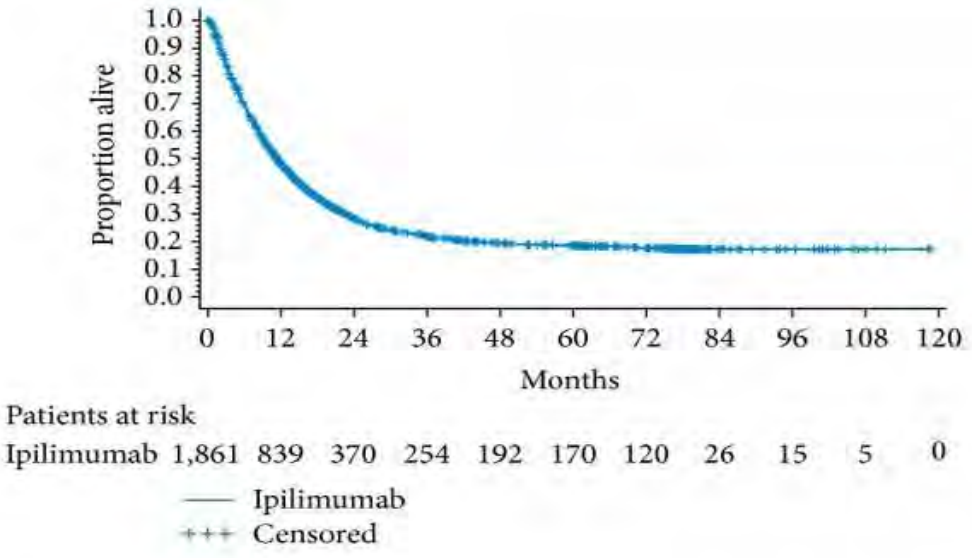
Larkin et al. NEJM 2015

Checkpoint inhibitor immunotherapy: anti-PD1 and anti-CTLA4





Anti-CTLA4 antibody: ipilimumab



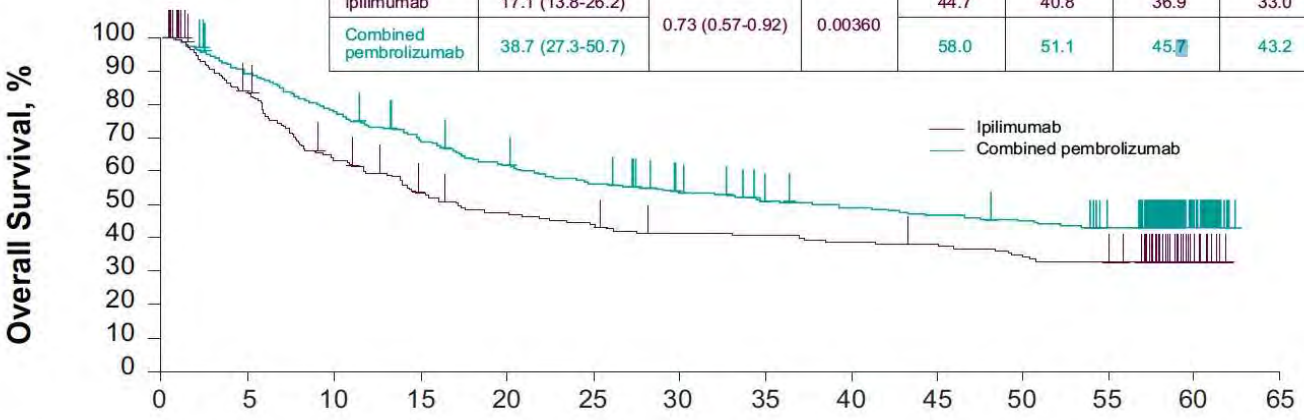
- Pooled analysis of 1,861 ipilimumab-treated patients from 12 clinical trials [3]. Median overall survival was 11.4 months (95% CI: 10.7–12.1 months) and 3-year overall survival was 22% (95% CI: 20–24%).

1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

Pembrolizumab (KN-006): 5-Year Survival vs. ipi

Robert C et al. Lancet 2019

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2



No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
ombined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

Combination immunotherapy: anti-PD1 plus anti CTLA4

anti-PD1+anti-CTLA4 (nivolumab+ipilimumab):

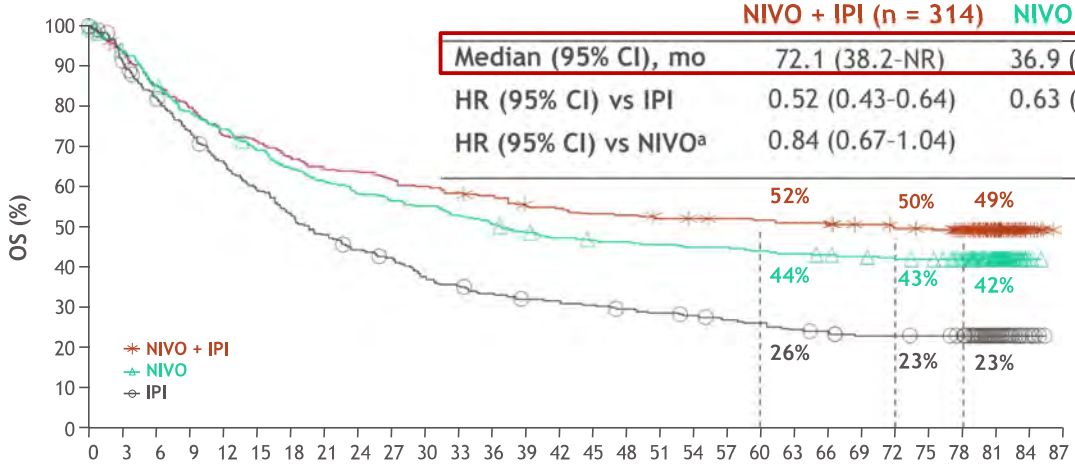
- Higher response rates
- Faster response
- Long-term responses
- More frequent and more severe side effects

Overall survival

2021 ASCO ANNUAL MEETING

Checkmate 067 6.5-year outcome in patients with advanced melanoma. Wolchok J et al.

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



No. at risk

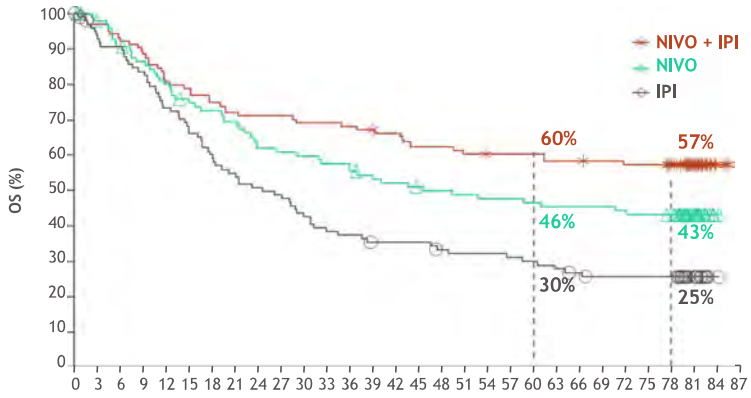
NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

[a]Descriptive analysis.

OS by *BRAF* mutation status[a]

BRAF mutant

	NIVO + IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median (95% CI), mo	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI HR	0.43 (0.30-0.60)	0.63 (0.44-0.90)	-
(95% CI) vs NIVO[b]	0.68 (0.46-1.0)	-	-

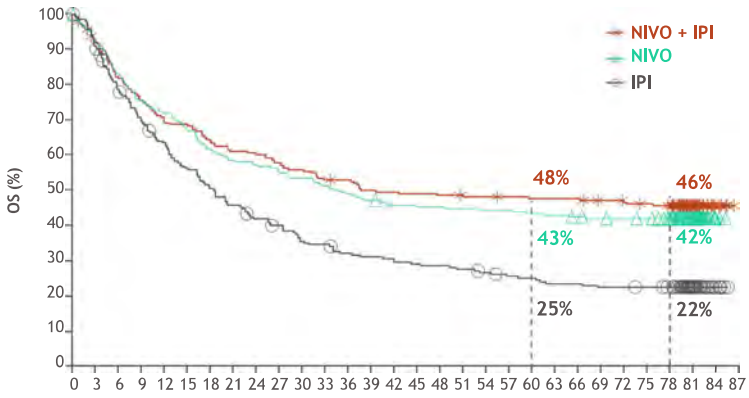


No. at risk

NIVO + IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	60	60	58	58	57	56	56	51	29	3	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	42	41	40	40	40	39	38	37	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	25	23	21	21	21	21	11	1	0

BRAF wild-type

	NIVO + IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median (95% CI), mo	39.1 (27.5-NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI HR	0.58 (0.45-0.74)	0.63 (0.50-0.80)	-
(95% CI) vs NIVO[b]	0.92 (0.71-1.18)	-	-

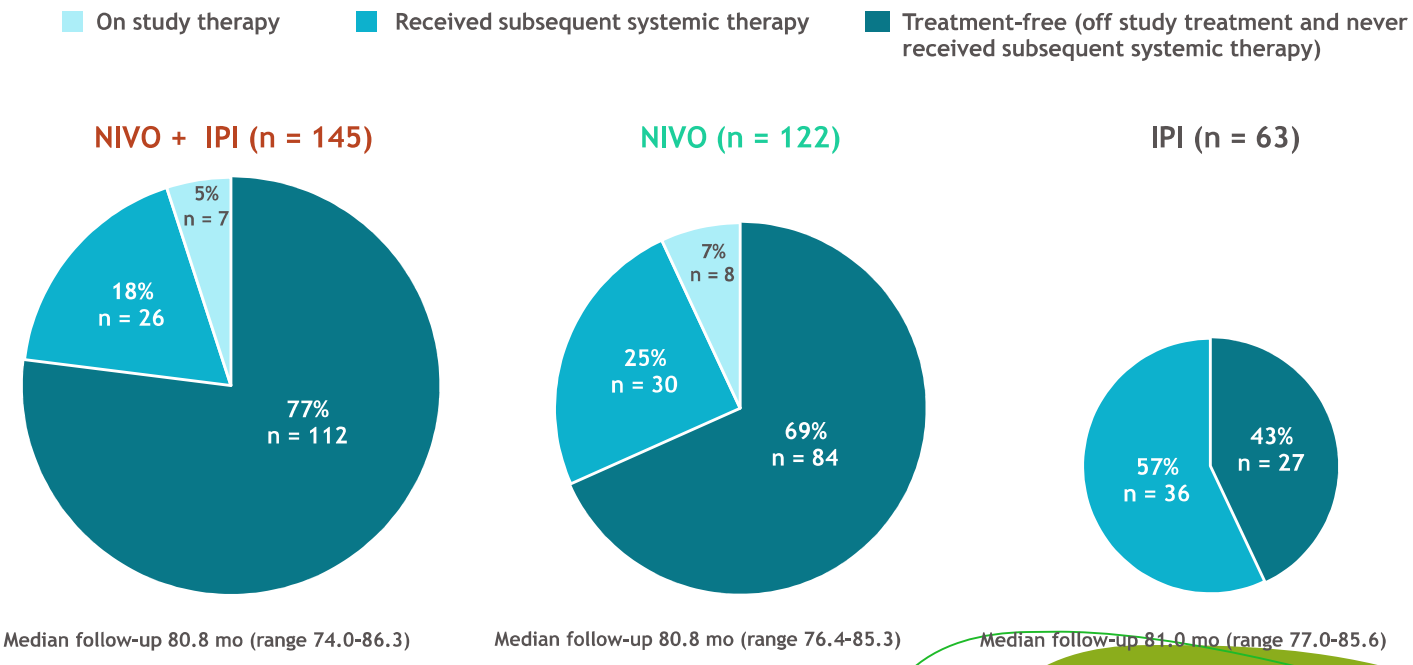


No. at risk

NIVO + IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	98	97	96	96	95	93	91	89	87	37	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	95	93	92	90	88	87	86	80	42	2	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	48	45	45	43	43	42	40	21	6	0

[a]Patients with *BRAF* status results were 314 for NIVO + IPI, 316 for NIVO, and 315 for IPI. [b]Descriptive analysis.

Patients alive and treatment-free at 6.5 years



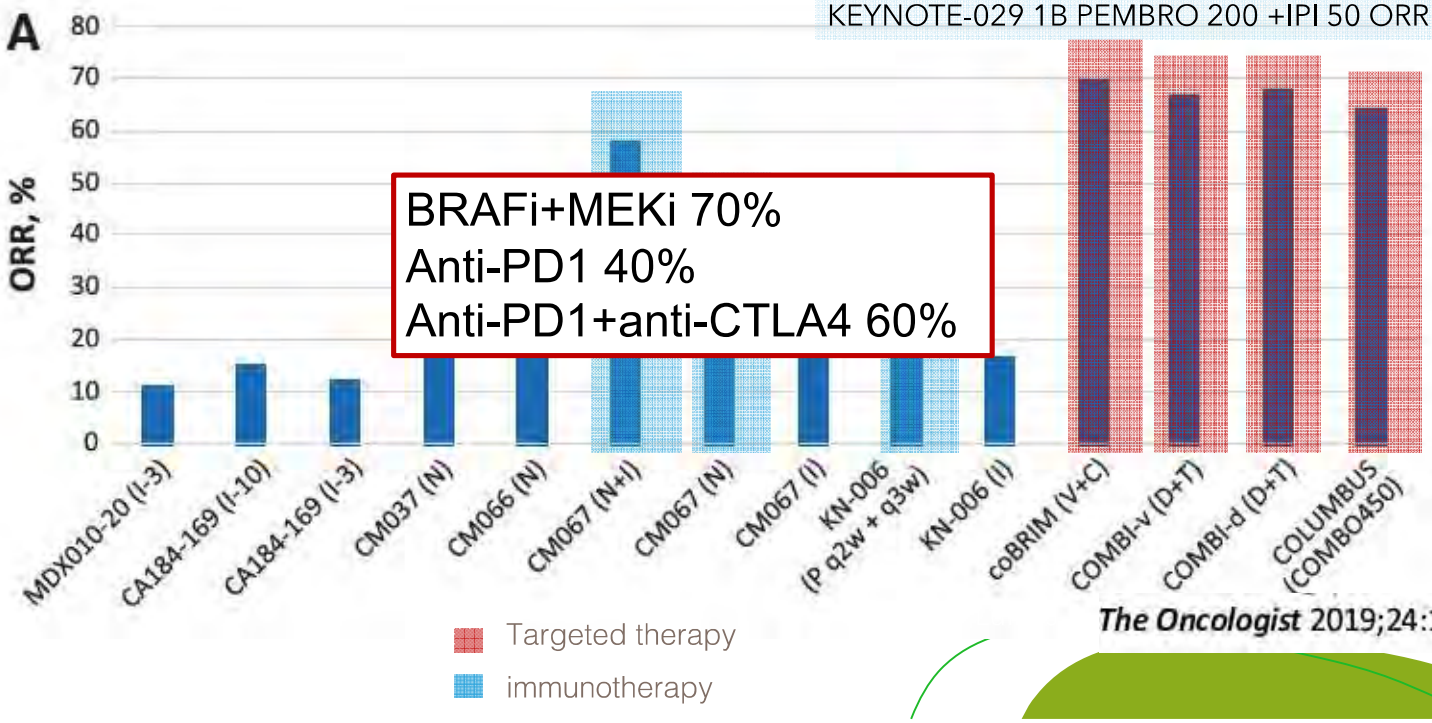
Median follow-up 80.8 mo (range 74.0-86.3)

Median follow-up 80.8 mo (range 76.4-85.3)

Median follow-up 81.0 mo (range 77.0-85.6)

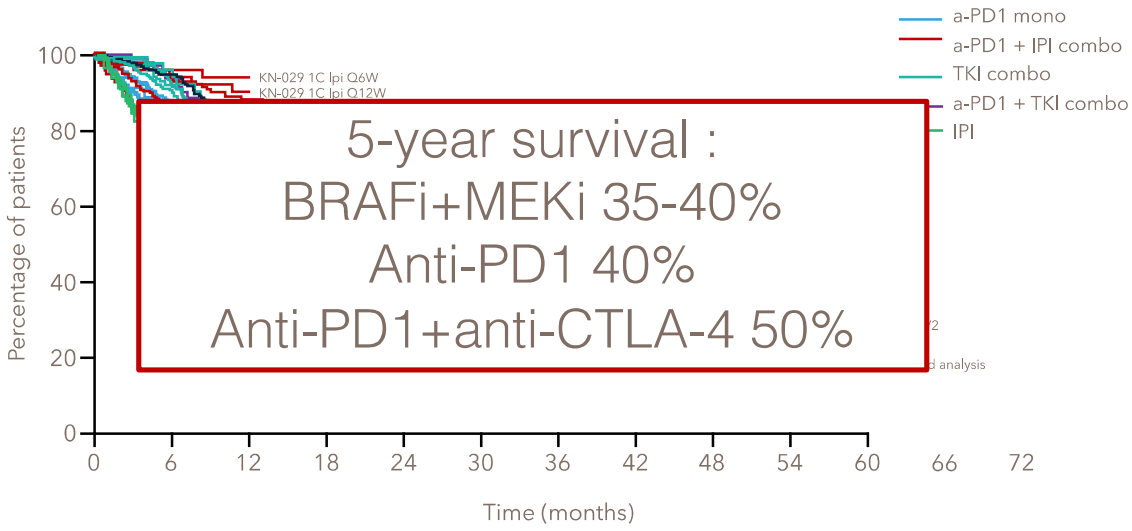
Metastatic melanoma 2021: ORR

KEYNOTE-029 1C PEMBRO 200 +IPI 100 ORR 61%
KEYNOTE-029 1B PEMBRO 200 +IPI 50 ORR 57%



The Oncologist 2019;24:1–15

Metastatic melanoma 2021 : OS



KN-006: Robert C et al. AACR 2019; abstract CT188
KN-001: Hamid O et al. ASCO 2018; abstract 9516
KN-022: Ascierto PA et al. ESMO 2018; abstract 1244O
KN-029 Cohort 1B: Long GV et al. SMR 2018*
KN-029 Cohort 1C: Long GV et al. ASCO 2019; abstract 9514
CM-066: Atkinson V et al. SMR 2015
CM-003: Hodi FS et al. AACR 2016; abstract CT001
CM-067: Hodi FS et al. Lancet Oncol 2018 [Epub ahead of print]
CM-069: Hodi FS et al. Lancet Oncol 2016; 17(11):1558–68

COLUMBUS: Liszkay G et al. ASCO 2019; abstract 9512
D+T 150/2: Long GV et al. J Clin Oncol 2018; 36(7): 667–73
COMBI-d: Long GV et al. Ann Oncol 2017; 28(7): 1631–39
COMBI-v: Long GV et al. Ann Oncol 2016; 27(6): 1–36
coBRIM: Dreno B et al. ASCO 2018; abstract 9522
IPI 002: Hodi FS et al. N Engl J Med 2010; 363(8): 711–23
IPI pooled: Schadendorf D et al. J Clin Oncol 2015; 33(17): 1889–94
IPI 3/10mg: Ascierto PA et al. Lancet Oncol 2017; 18(5): 611–22

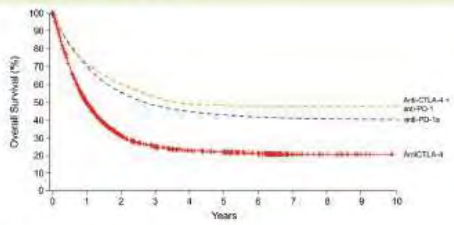
*13% of KN-029 (cohort 1b) population not in 1L

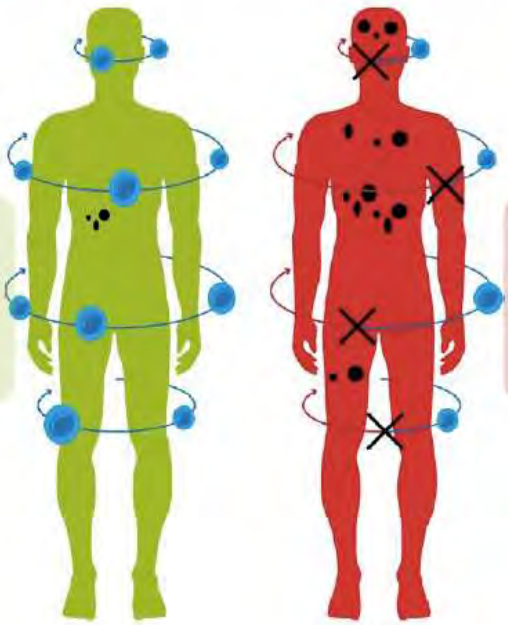
VIRTUAL 2020 ESMO congress

Long-term benefit, patient characteristics and immune surveillance

Active immune surveillance

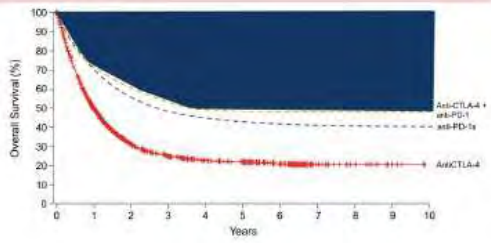
Long-term benefit patients
- ≤ 3 brain metastases (size < 2 cm)
- Low tumour burden (< 3 organ involved?)
- Normal LDH





Inactive immune surveillance

No long-term benefit patients
- Multiple (>3) brain metastases
- High tumour burden (>3 organ involved?)
- High LDH



LDH, lactate dehydrogenase

Ascierto P, Dummer R. Oncoimmunology. 2018; Ascierto P, Ed. Session ASCO. 2019

How to sequence treatment in BRAFm patients?

- Only retrospective data available
- Biased data due to the preference that for high tumor burden BRAFi+MEKi should be the 1st treatment option

VIRTUAL 2020 ESMO congress

First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study).

Ascierto PA,[1] Mandalà M,[2] Ferrucci PF,[3] Rutkowski P,[4] Guidoboni M,[5] Arance AM,[6] Ferraresi V[7], Maiello E,[8] Guida M,[9] Del Vecchio M,[10] Fierro MT,[11] Queirolo P,[3-12] Lebbé C,[13] Helgadottir H,[14] Melero I,[15] Palmieri G,[16] Giannarelli D,[17] Grimaldi AM,[1] Dummer R,[18*] Chiarion Sileni V,[19*].

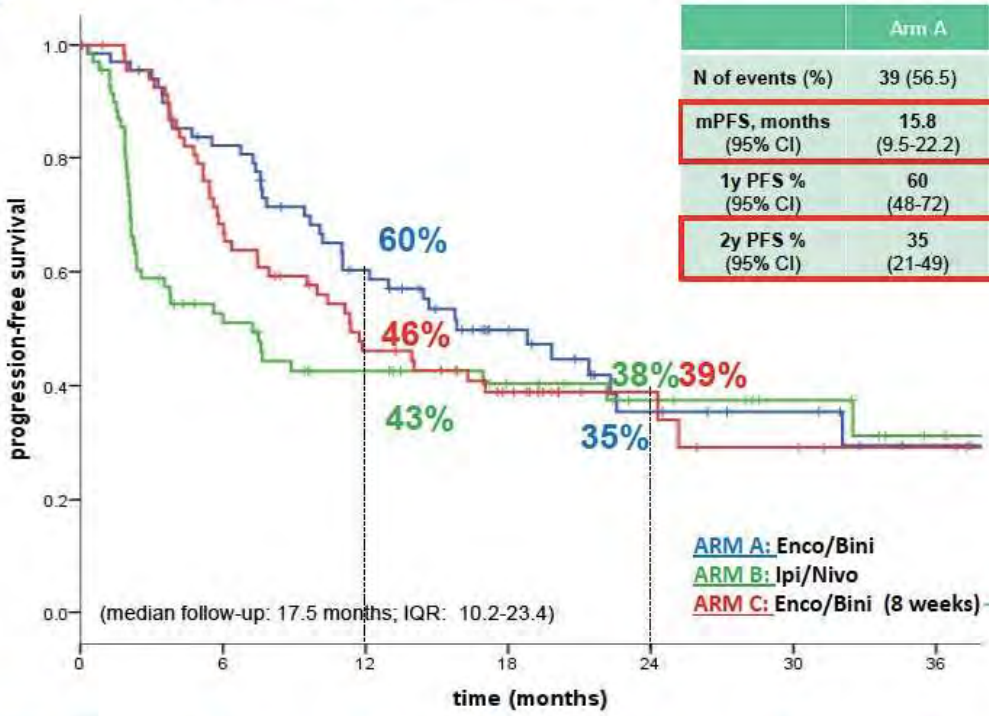
1-Department of Melanoma, Cancer Immunotherapy and Development Therapeutics. I.N.T. IRCCS Fondazione "G. Pascale" Napoli; 2-Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; 3- Unit of Oncology of Melanoma, European Institute of Oncology, 20141 - Milan/IT; 4-Department of Soft Tissue/Bone Sarcoma, Maria Sklodowska Curie National Research Institute of Oncology, 02-781 - Warsaw/PL; 5-Immunotherapy and Cell Therapy Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; 6-Department of Medical Oncology, Hospital Clínic Barcelona, 08036 - Barcelona/ES; 7-Department of Medical Oncology 1; 7-IRCCS Regina Elena National Cancer Institute, Rome, Italy; 8-Department of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy; 9-Medical Oncology Department, National Cancer Research Centre "Giovanni Paolo II", Bari, Italy; 10-Unit of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 11-Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy; 12-IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy; 13-Institut de Recherche Saint Louis (IRSL), Université de Paris, F-75010 Paris, France; 14-Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital Solna, Stockholm, Sweden; 15-Department of Immunology and Immunotherapy, Clínica Universidad de Navarra, Pamplona, Spain; 16-Unit of Cancer Genetics, CNR, Sassari, Italy; 17-Regina Elena National Cancer Institute, IRCCS - Biostatistical Unit, Rome, Italy; 18-Department of Dermatology, University and University Hospital Zurich, Zurich, Switzerland; 19-Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy.

*contributed equally to this study

Abstract Number LBA#3621

SECOMBIT: Progression Free Survival

	Arm A	Arm B	Arm C
N of events (%)	39 (56.5)	41 (57.7)	41 (59.4)
mPFS, months (95% CI)	15.8 (9.5-22.2)	7.2 (3.2-11.3)	11.4 (7.2-15.5)
1y PFS % (95% CI)	60 (48-72)	43 (31-55)	46 (34-58)
2y PFS % (95% CI)	35 (21-49)	38 (26-50)	39 (27-51)

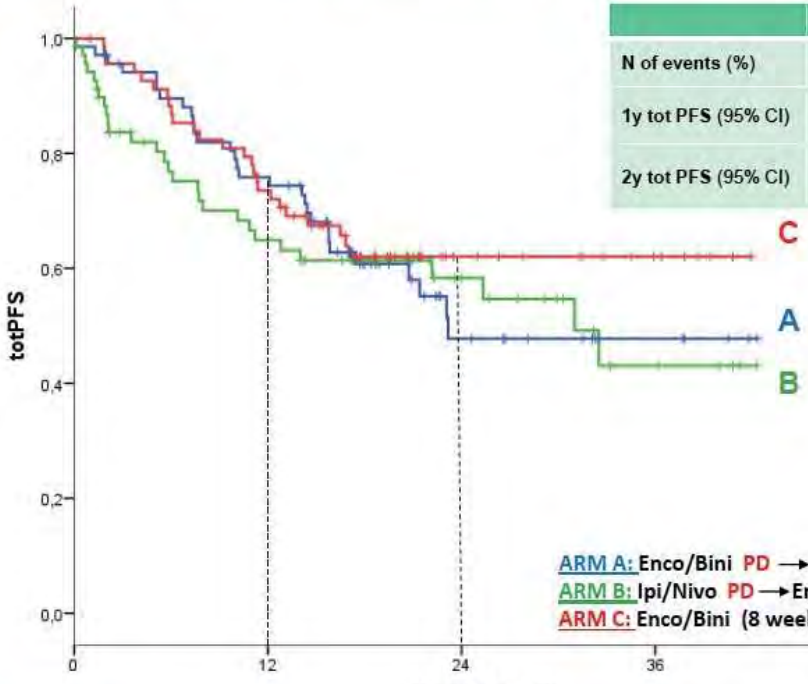


ARM A: Enco/Bini
ARM B: Ipi/Nivo
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo

ARM A:	69	54	37	21	11	8	3
ARM B:	71	32	23	16	11	7	2

SECOMBIT: Total Progression Free Survival – *preliminary report*

	Arm A	Arm B	Arm C
N of events (%)	29 (42.0)	28 (39.4)	25 (35.2)
1y tot PFS (95% CI)	76 (66-86)	65 (53-77)	73 (62-84)
2y tot PFS (95% CI)	48 (33-63)	58 (45-71)	62 (50-74)



ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

ARM A:	69	50	13	5
ARM B:	71	38	17	5
ARM C:	69	50	14	6

Total Progression Free Survival = time from randomization until the date of the second progression.

EORTC 1216: study design

Objective: to assess whether PFS can be improved with a sequential approach, using a 12-week induction of encorafenib + binimetinib, followed by combination nivolumab + ipilimumab, compared with nivolumab + ipilimumab alone, in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, two-arm, open-label, randomised comparative Phase 2 study

Key eligibility criteria
- Aged ≥18 years
- Treatment-naïve patients
- Presence of *BRAF*V600E or V600K mutation in tumour tissue prior to enrolment
- ECOG PS 0–1

Randomisation

- NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W for 4 doses then NIVO 480 mg IV Q4W → Progression → Investigator Choice until progression 2
- ENCO 450 mg PO QD + BINI 45 mg PO BID → After 12 weeks → NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W for 4 doses then NIVO 480 mg IV Q4W → Progression → ENCO 450 mg PO QD + BINI 45 mg PO BID until progression 2

Primary endpoint
- PFS

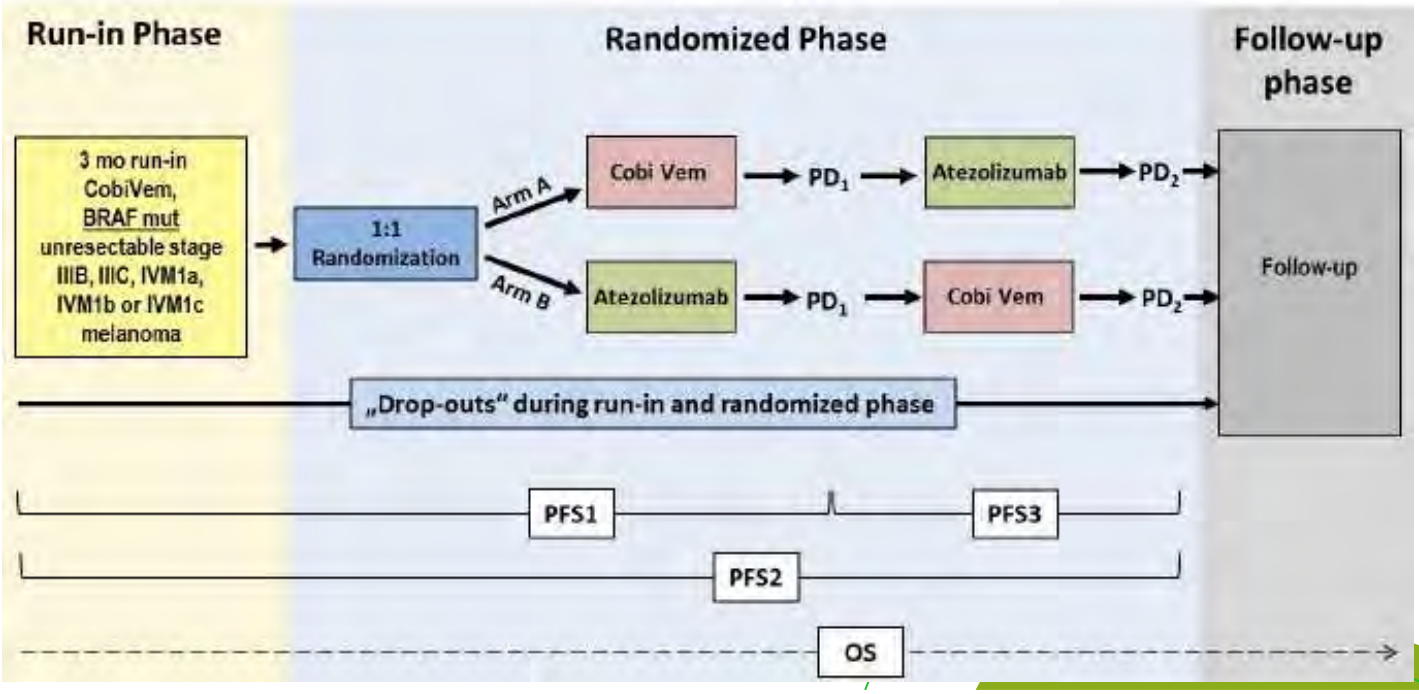
Secondary endpoints
- OS
- CR
- ORR
- PFS2*
- Safety

*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first

BID, twice daily; BINI, binimetinib; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENCO, encorafenib; IPI, ipilimumab; IV, intravenous; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily

ClinicalTrials.gov. NCT03235245. Available from: https://clinicaltrials.gov/(Accessed 15 October 2018)

ImmunoCobiVem



NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma

- ECOG PS 0 or 1
- Patients may have had prior systemic therapy in the adjuvant setting, however, this must not have included a CTLA-4 or PD-1 pathway blocking antibody or a BRAFi/MEKi

Primary endpoint:
- OS rate, defined as the proportion of patients alive after 2 years of follow-up time

Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

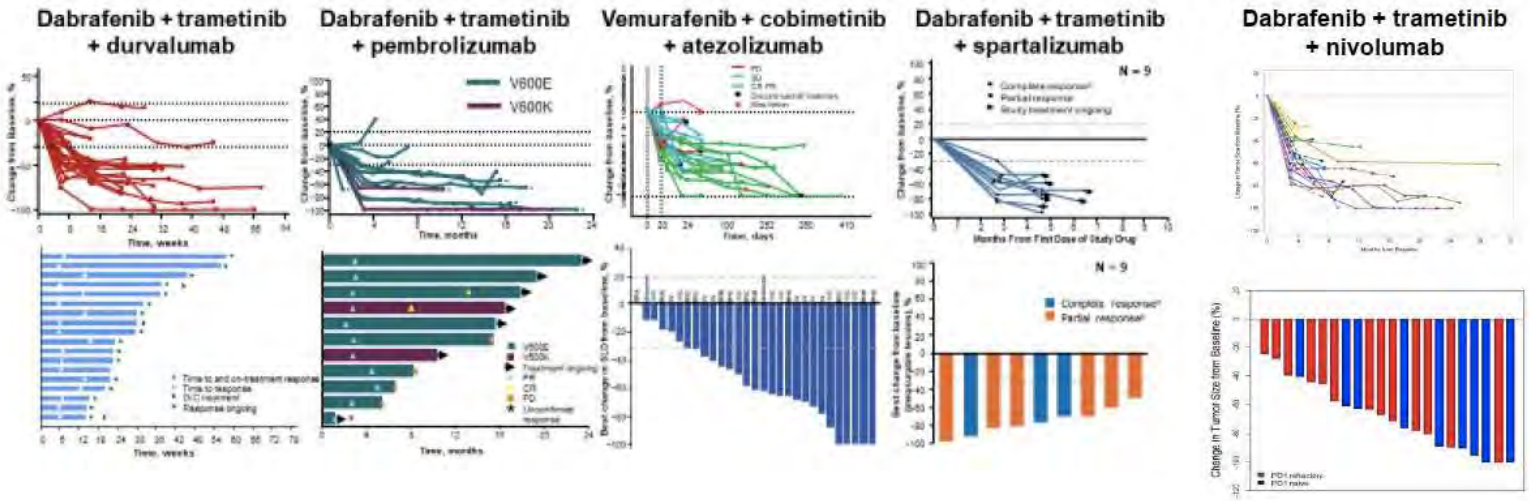
Objective:
Does the initial treatment with the dabrafenib-trametinib combination (and subsequent ipilimumab-nivolumab) or ipilimumab-nivolumab combination (and subsequent dabrafenib-trametinib combination) improve the 2-year OS significantly in patients with unresectable stage III or stage IV BRAFV600 mutant melanoma?

Actual Study Start Date : July 13, 20

Estimated Primary Completion Date : October 2, 2022

ECOG-PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free

Triple combinations: clinical trials



BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].; 5 Burton E. et al. ESMO 2019

VIRTUAL 2020 ESMO congress

Spartalizumab plus dabrafenib and trametinib in patients with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma: results from the randomized part 3 of the Phase III COMBI-i trial

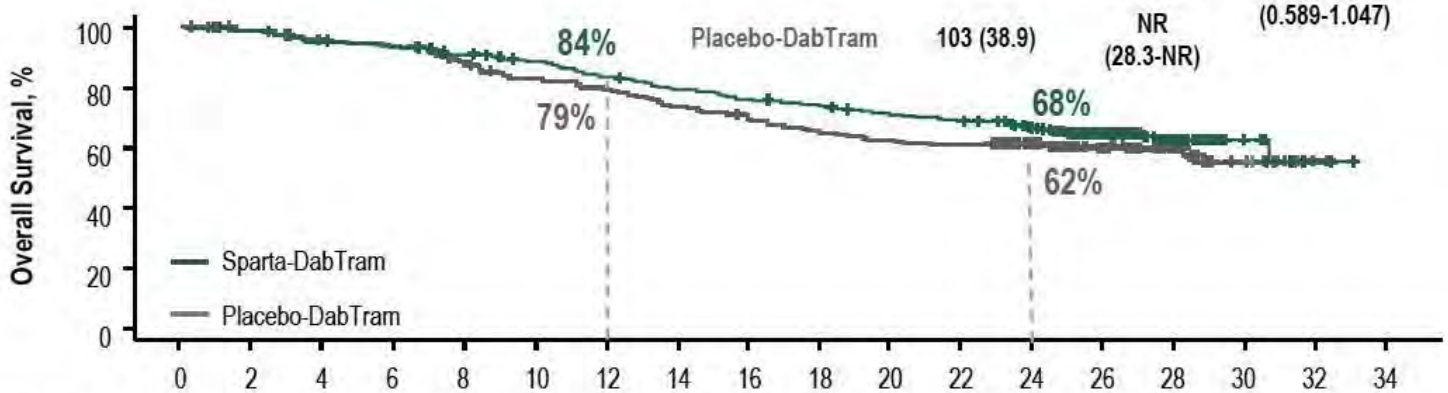
Paul D. Nathan,[1] Reinhard Dummer,[2] Georgina V. Long,[3] Paolo A. Ascierto,[4] Hussein A. Tawbi,[5] Caroline Robert,[6] Piotr Rutkowski,[7] Oleg Leonov,[8] Caroline Dutriaux,[9] Mario Mandalà,[10] Paul Lorigan,[11] Pier Francesco Ferrucci,[12] Keith T. Flaherty,[13] Jan C. Brase,[14] Steven Green,[15] Tomas Haas,[15] Aisha Masood,[16] Eduard Gasal,[16] Antoni Ribas,[17] Dirk Schadendorf[18]

[1]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK; [2]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; [3]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [4]Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS "G. Pascale," Napoli, Italy; [5]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Dermatology Service and Melanoma Research Unit, Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [7]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]Department of Medical Oncology, Clinical Oncological Dispensary, Omsk, Russian Federation; [9]Service de Dermatologie, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; [10]Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [11]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [12]Cancer Biotherapy Unit, Department of Experimental Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [13]Department of Medicine and Cancer Center, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [14]Precision Medicine, Novartis Pharma AG, Basel, Switzerland; [15]Clinical Development and Analytics, Novartis Pharma AG, Basel, Switzerland; [16]Oncology Clinical Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Department of Medicine, Division of Hematology-Oncology, University of California, Los Angeles, Los Angeles, CA, USA; [18]Department of Dermatology, Comprehensive Cancer Center (Westdeutsches Tumorzentrum), University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany

VIRTUAL 2020 ESMO congress

Overall Survival

	Events n (%)	Median (95% CI), mo	HR (95% CI)
Sparta-DabTram	90 (33.7)	NR (30.6-NR)	0.785 (0.589-1.047)
Placebo-DabTram	103 (38.9)	NR (28.3-NR)	



No. at risk																	
Sparta-DabTram	267	264	253	248	238	228	215	203	195	189	179	174	153	91	48	13	2	0
Placebo-DabTram	265	259	248	243	223	209	199	186	173	163	157	154	130	81	43	13	1	0

- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

NR, not reached.

Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

Ralf Gutzmer, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Georgy Moiseevich Manikhas, Yibing Yan, Kuan-Chieh Huang, Anne Uyei, Virginia McNally, Grant A McArthur, Paolo A Ascierto**

Overall survival estimates

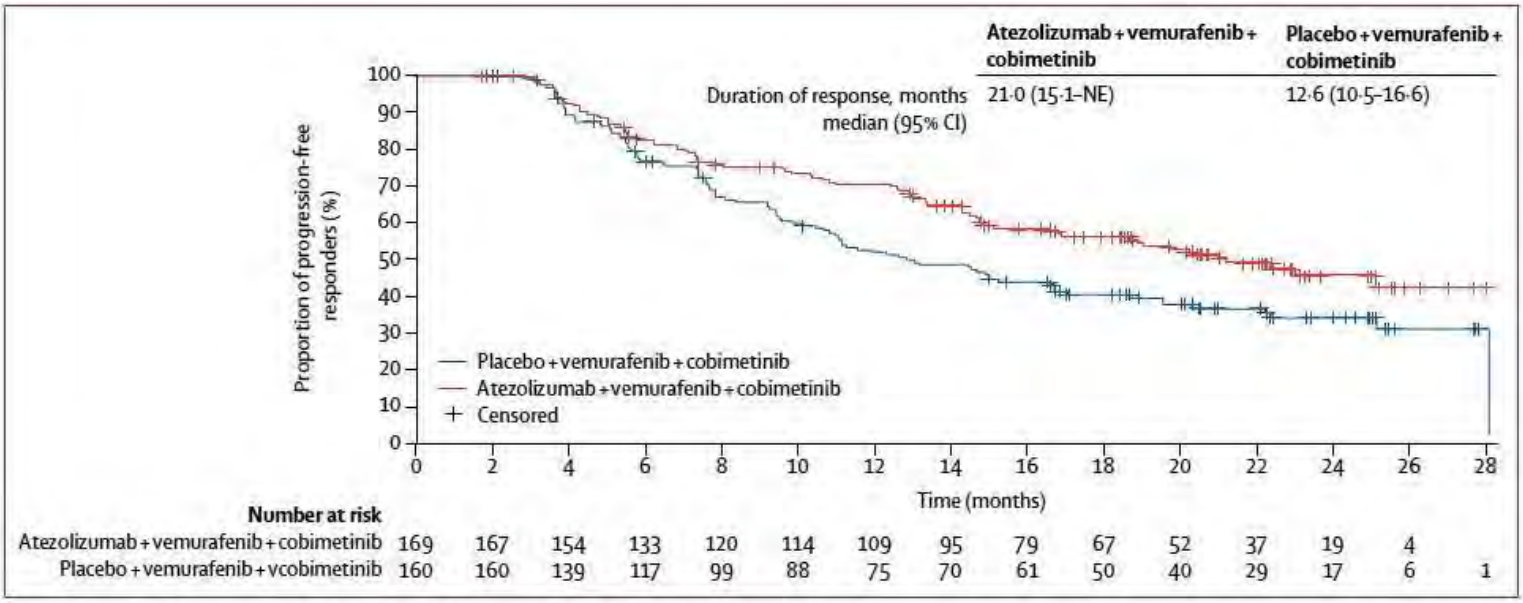


Figure 3: Kaplan-Meier estimate of duration of response in the intention-to-treat population
NE=not estimable.

Conclusion

- Data from triplet studies controversial, more data needed
- Impact of subsequent therapies
- Increased toxicity
- Patient subgroups that can benefit most?
  - High-tumor burden patients
  - Patients wit symptomatic brain mets

Brain metastases

- STAGE III: 10-13% of patients already have CNS mets (CT/MRI necessary in follow-up!)
- STAGE IV: 18-46%
- ON AUTOPSY 55-75%

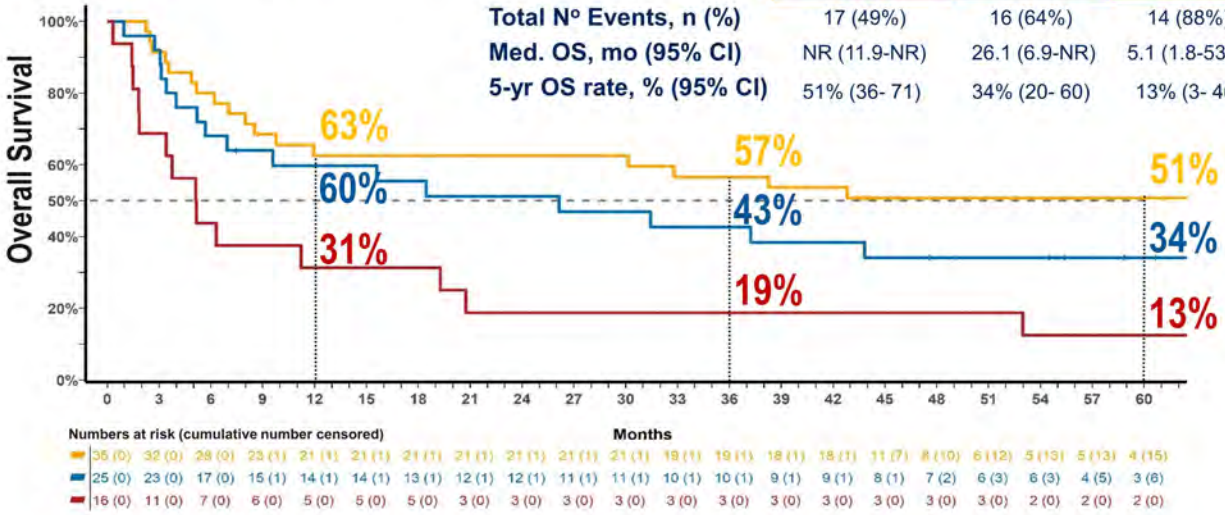
- Frequent relapses in patients with regression of internal organ metastases
- Overall survival: 4 months after diagnosis *(Fife et al, J Clin Oncol 2004)*

an JS, 2004; Harrison BE, Am J Clin

NIVOLUMAB+IPILIMUMAB IN MBM: ABC trial ASCO 2021

Overall Survival

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	17 (49%)	16 (64%)	14 (88%)
Med. OS, mo (95% CI)	NR (11.9-NR)	26.1 (6.9-NR)	5.1 (1.8-53.0)
5-yr OS rate, % (95% CI)	51% (36- 71)	34% (20- 60)	13% (3- 46)



- Death solely due to intracranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

Presented By: **Georgina V Long** @ProfGLongMIA #ASCO21 |

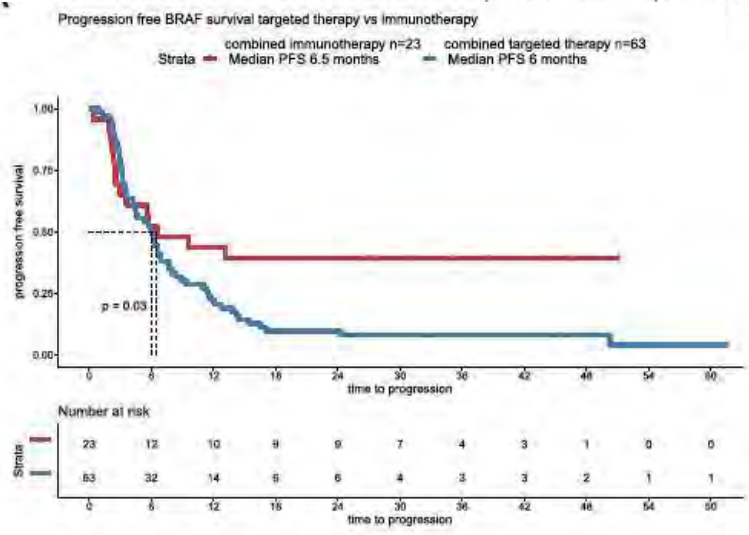
2021 ASCO ANNUAL MEETING

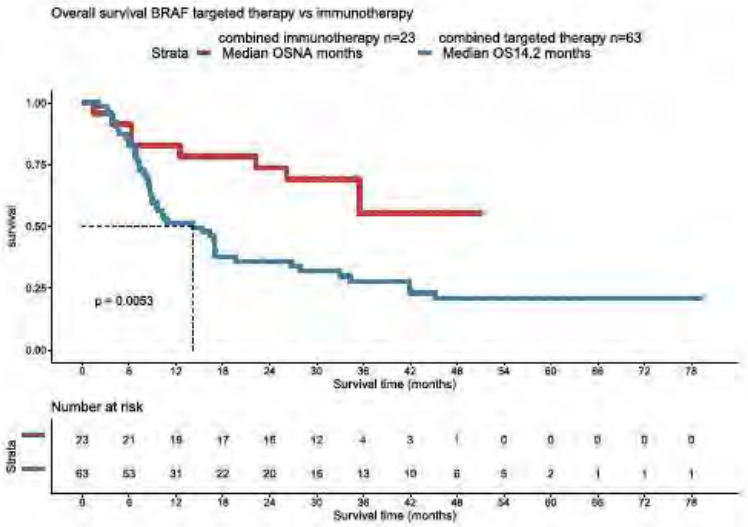
Real-life data for first-line combination immune-checkpoint inhibition and targeted therapy in patients with melanoma brain metastases

Marie-Luise Hilbers [a,1], Florentia Dimitriou [a,1], Peter Lau [b], Prachi Bhave [b], Grant A. McArthur [b], Lisa Zimmer [c], Ken Kudura [d], Camille L. Gérard [e], Mitchell P. Levesque [a], Olivier Michielin [e], Reinhard Dummer [a,1,*], Phil F. Cheng [a,1], Joanna Mangana [a,1]

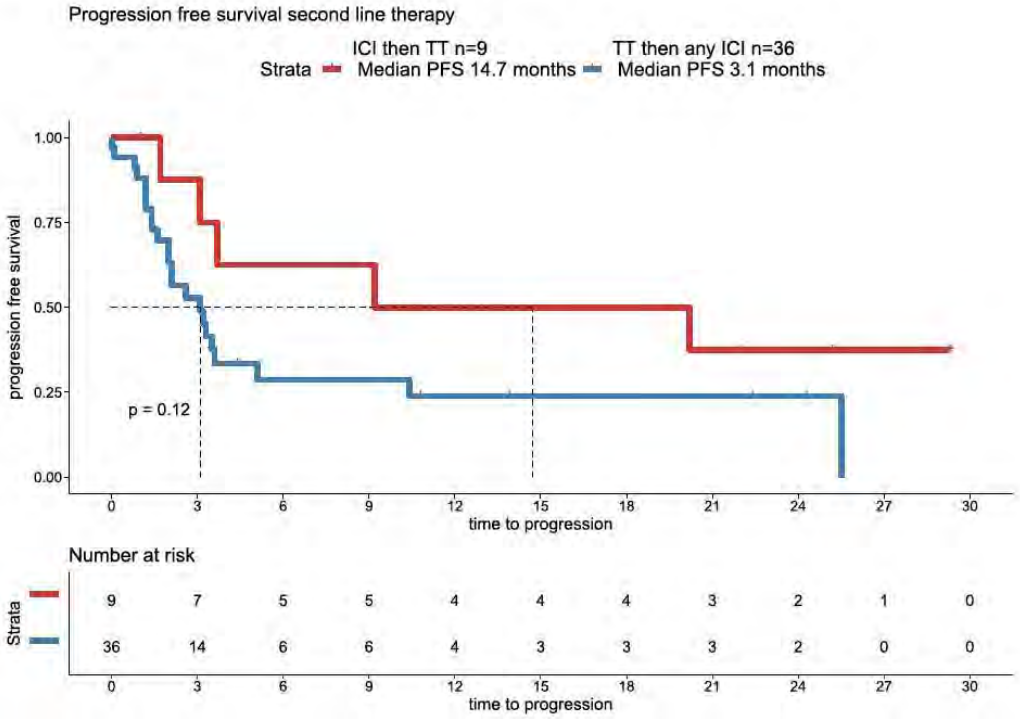
European Journal of Cancer 156 (2021) 149–163

- 53 patients received Combi-ICI, 32% had symptomatic MBM and 33.9% elevated LDH, 71.7% required local treatment
- 63 patients received Combi-TT, 55.6% of patients had symptomatic MBM, 57.2% of patients had elevated LDH and 68.3% of patients required local treatment

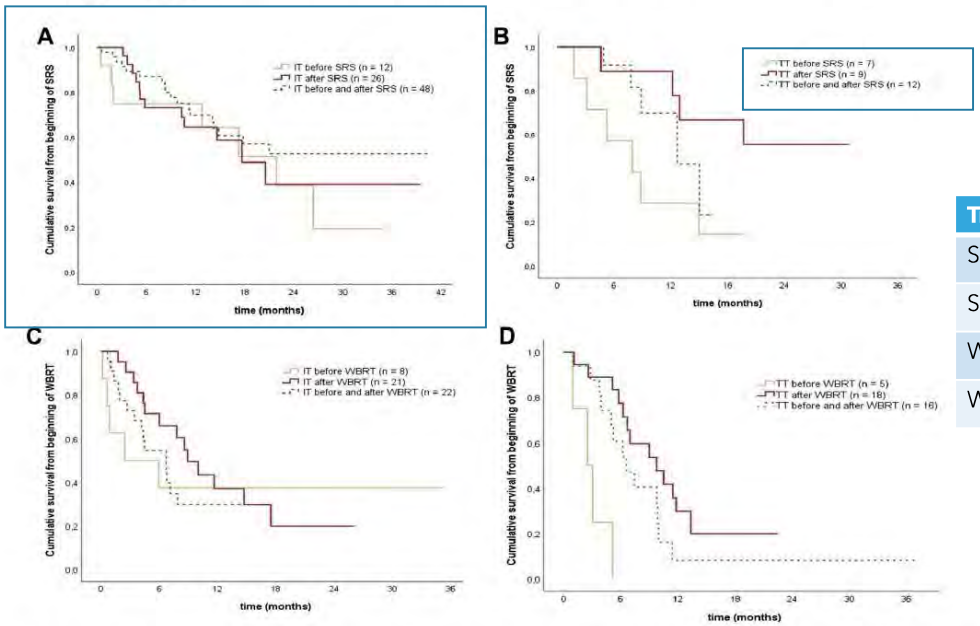




SECOND LINE THERAPY FOR MBM



Impact of radiation, systemic therapy and treatment sequencing on survival of patients with melanoma brain metastases



Treatment	1 year OS rates
SRS+Immunotherapy	69%
SRS+targeted therapy	65%
WBRT+immunotherapy	38%
WBRT+TT	18%

Fig. 1. Overall survival of 202 patients treated with A: IT and SRS (N = 86); B: TT and SRS (N = 26); C: IT and WBRT (N = 51); D: TT and WBRT (N = 39). IT, immunotherapy; TT, targeted therapy; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

R. Rauschenberg et al. / European Journal of Cancer 110 (2019) 11–20

Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review

Stephanie G.C. Kroeze [a,*], Corinna Fritz [a], Morten Hoyer [b], Simon S. Lo [c], Umberto Ricardi [d], Arjun Sahgal [e], Rolf Stahel [f], Roger Stupp [f], Matthias Guckenberger [a]

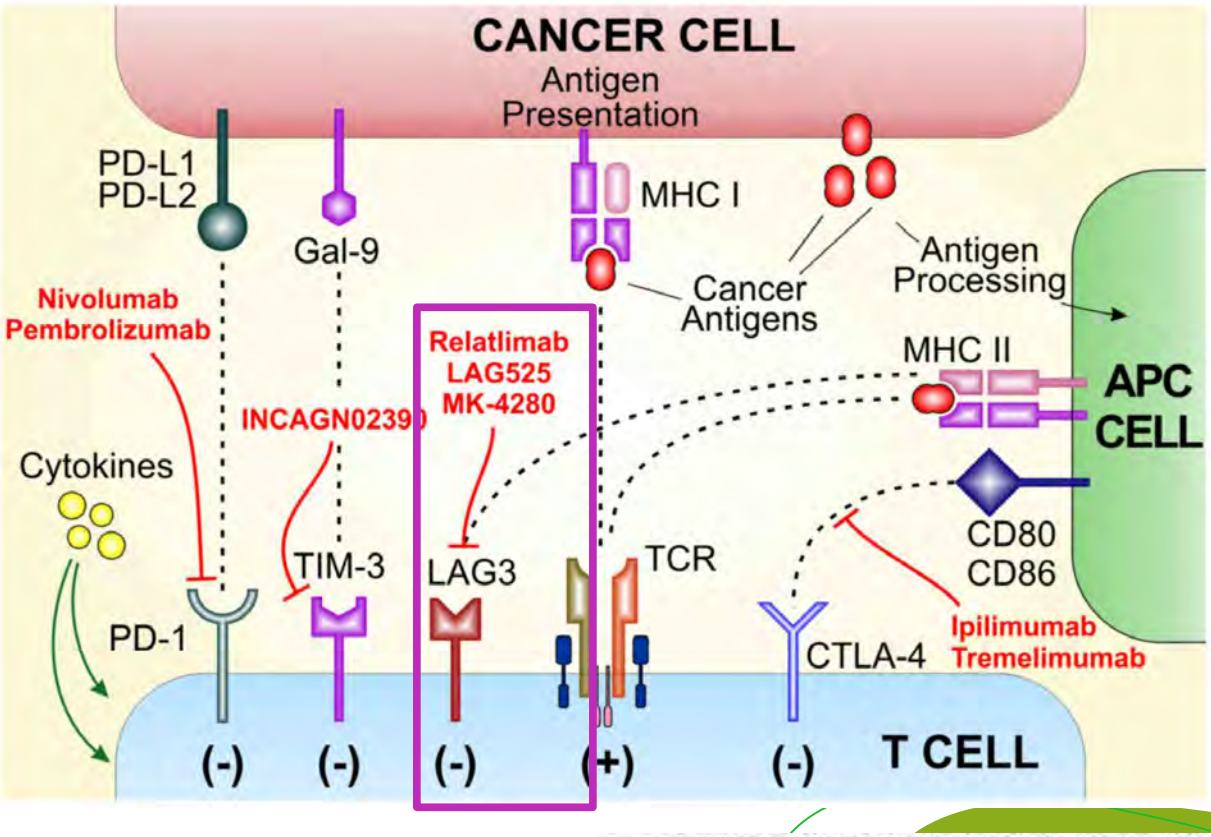
20/129 (15.5%) grade 3/4 - 1

Table 2
Toxicity as observed within the included articles.

Targeted therapy	Study	Patients (n)	Grade 3 (n)	Grade 4 (n)	Grade 5 (n)	Total toxicity (n)	Total toxicity within the irradiated volume (n)
Vemurafenib/ dabrafenib		129	19	1	0	20	20
	Ahmed et al. [54]	24	Haemorrhage (n = 1)	NR	NR	1	1
	Peuvrel et al. [60]	1	Headache (n = 1)	NR	NR	1	1
	Narayana et al. [57]	6	No intracranial bleeding and no ≥ Gr3 cutaneous toxicity observed				
	Ly et al. [56]	17	Increased haemorrhage risk associated with BRAF-inhibitors (61% vs 23%)				
	Lieboer et al. [59]	2	Headache (n = 1)	Cerebral oedema (n = 1)	NR	2	2
	Stefan et al. [61]	1	NR	NR	NR	0	0
	Gaudy et al. [55]	24	Cerebral oedema (n = 6); Haemorrhage (n = 10)	NR	NR	16	16
	Wolf et al. [53]	31	No significant difference in haemorrhage to RT alone (18% haemorrhage of unreported grading for concurrent therapy)				
	Hecht et al. [4]	19	NR	NR	NR	0	0
	Patel et al. [58]	4	No increased or unexpected neurologic nor cutaneous toxicity with administration of SRS				
Trametinib		4	0	0	0	0	0
	Patel et al. [58]	4	No increased or unexpected neurologic nor cutaneous toxicity with administration of SRS				
Nivolumab		27	2	1	0	3	3
	Alomari et al. [41]	1	NR	Cerebral oedema (n = 1)	NR	1	1
	Ahmed et al. [42]	26	Cerebral oedema (n = 2)	NR	NR	2	2

MELANOMA UPDATE 2021: treatment of stage IV disease

- Systemic therapy of stage IV melanoma:
  - *New front-line therapy option:*
    - Anti-PD1+anti-LAG3 Ab – nivolumab+relatlimab
  - *Updated results of combination therapies:*
    - anti-PD1+anti-CTLA4 Ab – nivolumab+ipilimumab Checkmate 067
    - anti-PD1+anti-CTLA4 Ab – nivolumab+ipilimumab ABC trial
    - BRAFi+MEKi – encorafenib+binimetinib 5 year OS
  - *Therapies for anti-PD1 refractory disease:*
    - Cell based therapy lifileucel
    - anti-PD1+anti-VEGF – pembrolizumab+lenvatinib
    - Anti-PD1+anti-LAG3 Ab – nivolumab+relatlimab



INTERNATIONAL JOURNAL OF ONCOLOGY 57: 609-618, 2020

2021 ASCO ANNUAL MEETING

Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from **RELA**TIVITY-047 (CA224-047)

Evan J. Lipson,[1] Hussein A. Tawbi,[2] Dirk Schadendorf,[3] Paolo A. Ascierto,[4] Luis Matamala,[5] Erika Castillo Gutiérrez,[6] Piotr Rutkowski,[7] Helen J. Gogas,[8] Christopher D. Lao,[9] Juliana Janoski De Menezes,[10] Stéphane Dalle,[11] Ana Arance,[12] Jean-Jacques Grob,[13] Shivani Srivastava,[14] Mena Abaskharoun,[14] Katy L. Simonsen,[14] Bin Li,[14] Georgina V. Long,[a,15] F. Stephen Hodi[a,16]

[1]Bloomberg Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]University Hospital Essen, Essen, Germany; [4]Istituto Nazionale Tumori Fondazione "G. Pascale", Napoli, Italy; [5]Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile; [6]FAICIC Clinical Research, Veracruz, Mexico; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]National and Kapodistrian University of Athens, Athens, Greece; [9]University of Michigan, Ann Arbor, MI, USA; [10]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [11]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [12]Hospital Clinic Barcelona, Barcelona, Spain; [13]Aix-Marseille University, CHU Timone, Marseille, France; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; [16]Dana-Farber Cancer Institute, Boston, MA, USA [a]Co-senior author

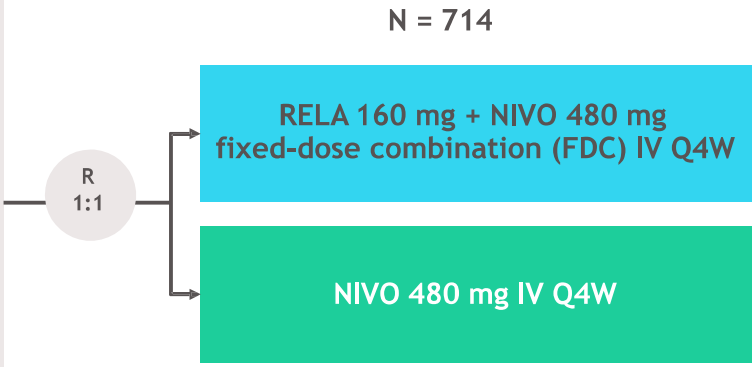
Presentation Number 9503

Study design

- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0-1

Stratification factors
- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



Primary endpoint
- PFS by BICR[d]

Secondary endpoints
- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

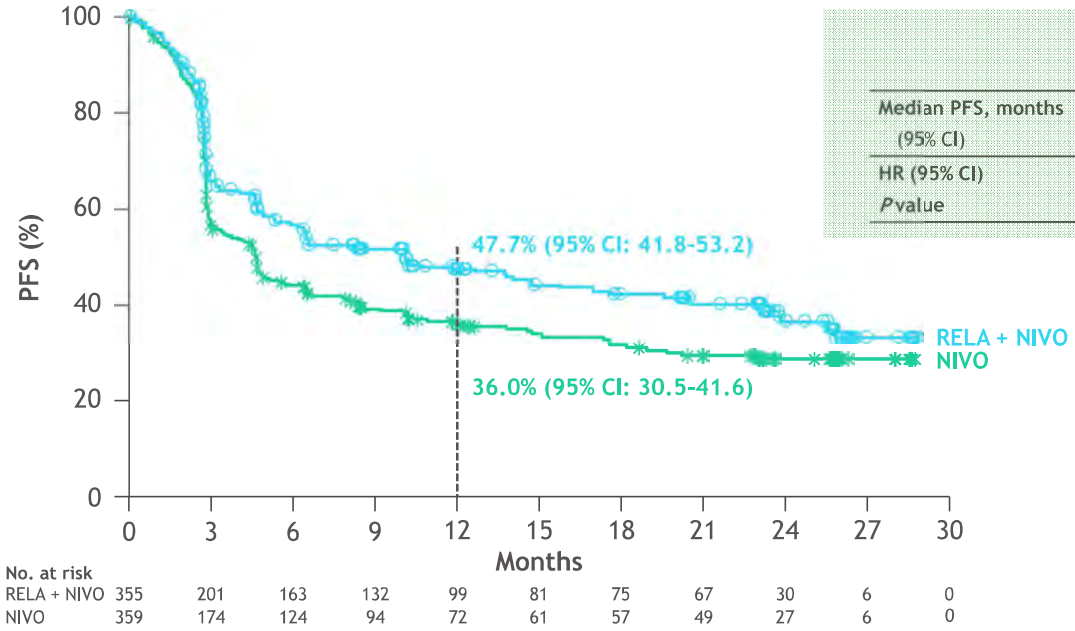
Baseline characteristics

Characteristic		RELA + NIVO (n = 355)	NIVO (n = 359)	Total (N = 714)
Median age, years		63	62	63
Female, n (%)		145 (40.8)	153 (42.6)	298 (41.7)
AJCC v8 M stage, n (%)	M1A	77 (21.7)	107 (29.8)	184 (25.8)
	M1B	85 (23.9)	88 (24.5)	173 (24.2)
	M1C	151 (42.5)	127 (35.4)	278 (38.9)
	M1D	6 (1.7)	11 (3.1)	17 (2.4)
ECOG PS, n (%)	0	236 (66.5)	242 (67.4)	478 (66.9)
	1	119 (33.5)	117 (32.6)	236 (33.1)
Serum LDH level, n (%)	> ULN	130 (36.6)	128 (35.7)	258 (36.1)
	> 2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Prior neoadjuvant/adjuvant[a], n (%)		33 (9.3)	27 (7.5)	60 (8.4)
Tumor burden[b], median (min.-max.), mm		59.0 (10-317)	54.5 (10-548)	
Stratification factor, n (%)				
LAG-3 expression	≥ 1%	268 (75.5)	269 (74.9)	537 (75.2)
	< 1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression	≥ 1%	146 (41.1)	147 (40.9)	293 (41.0)
	< 1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status	Mutant	136 (38.3)	139 (38.7)	275 (38.5)
	Wild-type	219 (61.7)	220 (61.3)	439 (61.5)
AJCC M stage	M0/M1any[0][c]	232 (65.4)	237 (66.0)	469 (65.7)
	M1any[1][d]	123 (34.6)	122 (34.0)	245 (34.3)

LDH, lactate dehydrogenase; ULN, upper limit of normal. [a]Most common therapy was interferon; [b]Sum of reference diameters of target lesions in mm; [c]AJCC M stage M0/M1any [LDH not elevated]; [d]AJCC M stage M1any [elevated LDH].

RELATIVITY-047

NIVO-RELA superior PFS benefit



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.12 (6.37-15.74)	4.63 (3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

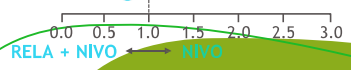
CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

RELATIVITY-047

PFS across prespecified subgroups and stratification factors

- RELA + NIVO FDC extended PFS regardless of prespecified subgroups and stratification factors

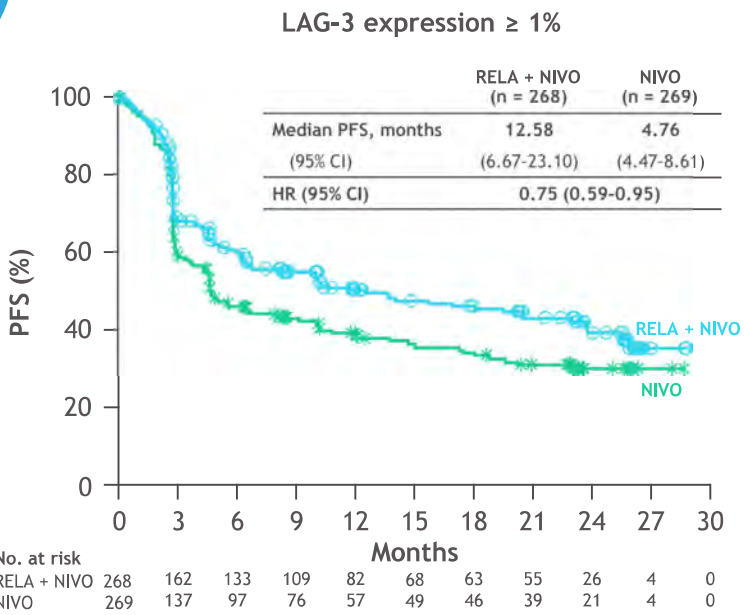
Subgroup		RELA + NIVO Events/no. of patients	NIVO Events/no. of patients	Unstratified HR for progression or death (95% CI)
Overall		180 (355)	211 (359)	0.76 (0.62-0.92)
Age categorization, years	≥ 18 and < 65	99 (187)	117 (196)	0.83 (0.64-1.09)
	≥ 65 and < 75	50 (102)	60 (103)	0.69 (0.47-1.00)
	≥ 65	81 (168)	94 (163)	0.69 (0.51-0.93)
	≥ 75	31 (66)	34 (60)	0.69 (0.42-1.13)
Sex	Male	98 (210)	123 (206)	0.68 (0.52-0.89)
	Female	82 (145)	88 (153)	0.88 (0.65-1.19)
LDH	≤ ULN	100 (224)	127 (231)	0.70 (0.54-0.91)
	> ULN	79 (130)	84 (128)	0.80 (0.59-1.09)
	≤ 2 × ULN	158 (322)	186 (328)	0.75 (0.60-0.92)
	> 2 × ULN	21 (32)	25 (31)	0.75 (0.42-1.35)
ECOG PS	0	108 (236)	136 (242)	0.74 (0.57-0.95)
	1	72 (119)	75 (117)	0.78 (0.56-1.07)
Tumor burden per BICR	< Q1	26 (74)	37 (83)	0.62 (0.37-1.03)
	Q1 to <Q3	84 (161)	96 (153)	0.80 (0.60-1.07)
	≥ Q3	53 (84)	53 (75)	0.72 (0.49-1.06)
BRAF mutation status	Mutant	67 (136)	83 (139)	0.74 (0.54-1.03)
	Wild-type	113 (219)	128 (220)	0.76 (0.59-0.98)
AJCC v8 M stage	M0/M1any[0] LDH not elevated	104 (232)	130 (237)	0.71 (0.55-0.92)
	M1any[1] elevated LDH level	76 (123)	81 (122)	0.79 (0.58-1.09)
PD-L1	≥ 1%	68 (146)	67 (147)	0.95 (0.68-1.33)
	< 1%/nonquantifiable	112 (209)	144 (212)	0.66 (0.51-0.84)
	≥ 5%	33 (88)	36 (86)	0.86 (0.54-1.38)
	< 5%/nonquantifiable	147 (267)	175 (273)	0.73 (0.58-0.90)
LAG-3	≥ 1%	131 (268)	151 (269)	0.75 (0.59-0.95)
	< 1%	49 (87)	60 (90)	0.78 (0.54-1.15)

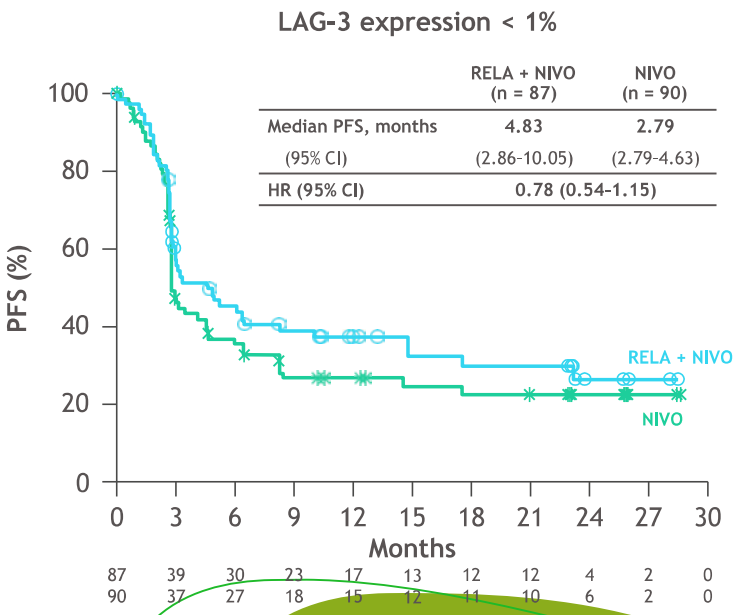


Exploratory/descriptive analyses.

PFS by LAG-3 expression

- PFS benefit favored RELA + NIVO FDC regardless of LAG-3 expression status





Statistical model for HR: unstratified Cox proportional hazard model.

Safety summary

- RELA + NIVO FDC was associated with a manageable safety profile and without unexpected safety signals

AE, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
TRAE ≥ 10%				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0

- Treatment-related deaths: RELA + NIVO (n = 3) - hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis; NIVO (n = 2) - sepsis and myocarditis, and worsening pneumonia

AE, adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3/4 TRAEs that were associated with any grade TRAEs occurring in <10% of patients not shown.

Immune-mediated adverse events

Immune-mediated AE category[a], n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hypothyroidism/thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea/colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

- Additional AE of interest: myocarditis (any grade) occurred in 5 (1.7%) patients with RELA + NIVO and 2 (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol

[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

Summary

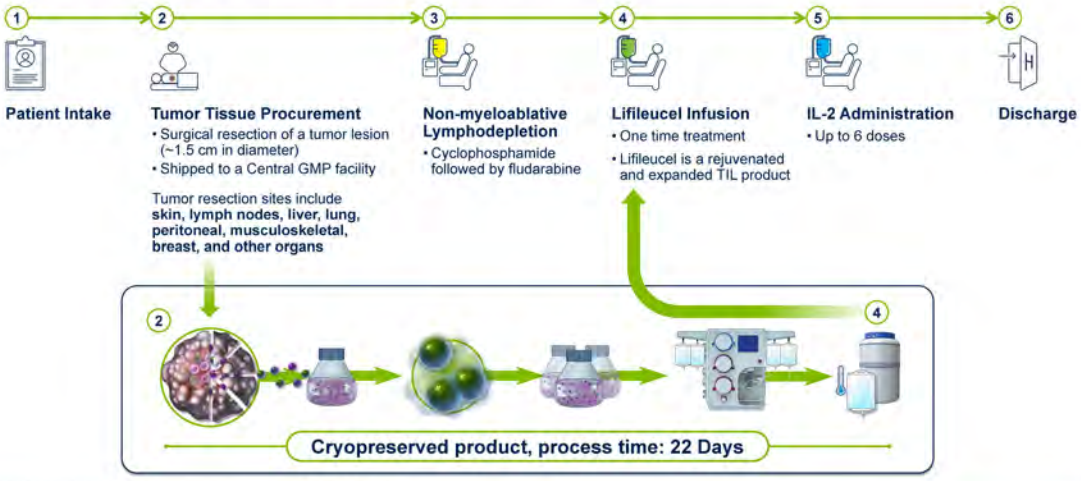
- In RELATIVITY-047, RELA + NIVO as a fixed-dose combination (FDC) demonstrated superior PFS by BICR, with more than a doubling of improvement in median PFS compared with NIVO alone
  - Median PFS 10.12 vs 4.63 months (HR [95% CI] vs NIVO: 0.75 [0.62–0.92]; P = 0.0055)
  - PFS favored RELA + NIVO FDC across key prespecified subgroups
  - OS and ORR remain blinded
- RELA + NIVO FDC demonstrated a manageable safety profile without unexpected safety signals
  - Grade 3/4 TRAEs occurred in 18.9% with RELA + NIVO FDC vs 9.7% with NIVO
- RELATIVITY-047 is the first phase 3 study to validate dual LAG-3 and PD-1 inhibition
- RELA + NIVO FDC is a potential new treatment option for patients with advanced melanoma, bringing the benefits of dual checkpoint inhibition to more patients

Autologous TIL for mM: lifileucel

- Standardized adoptive T-cell transfer

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Journey and TIL Manufacturing



GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes

4

C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Population

Unresectable or metastatic melanoma treated with ≥1 prior systemic therapy including a PD-1–blocking antibody and, if BRAF V600 mutation positive, a BRAFi ± MEKi

Cohort 1
Non-cryopreserved TIL product (Gen 1)
N=30
Closed to enrollment

Cohort 2
Cryopreserved TIL product (Gen 2)
N=60
Closed to enrollment

Cohort 4 (Pivotal)
Cryopreserved TIL product (Gen 2)
N=75
Closed to enrollment

Cohort 3
TIL re-treatment
N=10

Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria

- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

3

Objective Response Rate

Response, n (%)	N=66
Objective Response Rate	**24 (36.4)**
Complete response	3 (4.5)
Partial response	21 (31.8)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable*	4 (6.1)
Disease control rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, max (months)	2.2, 38.5+

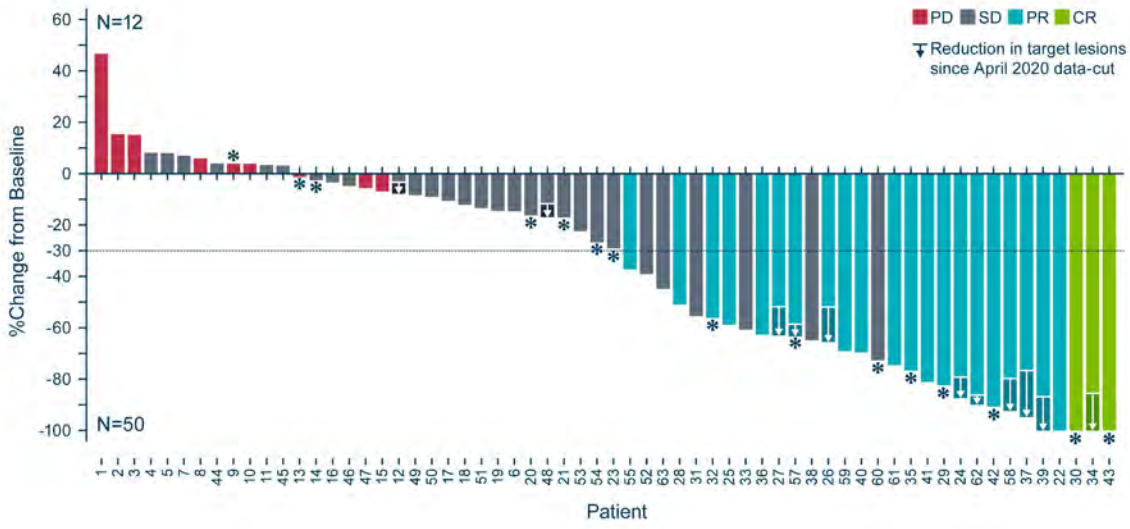
- Mean number of TIL cells infused: 27.3×10^9

- After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

*Not evaluable due to not reaching first assessment.
DOR, duration of response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes

Best Overall Response

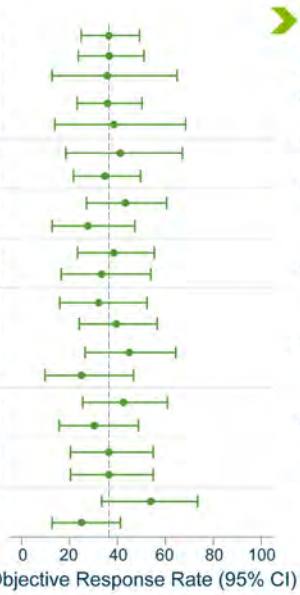
- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut



*Patients with BRAF V600 mutation. 3 patients had no post-TIL disease assessment due to early death, and 1 due to start of new anticancer therapy.
DOR, duration of response; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes

Univariable Analyses: ORR of Lifileucel

Subgroup		n/N	ORR	95% CI*
Overall		24/66	36.4	(24.9, 49.1)
Age Group	<65	19/52	36.5	(23.6, 51.0)
	≥65	5/14	35.7	(12.8, 64.9)
Prior CTLA-4 Use	Yes	19/53	35.8	(23.1, 50.2)
	No	5/13	38.5	(13.9, 68.4)
BRAF Mutation Status	Mutated (V600E or K)	7/17	41.2	(18.4, 67.1)
	Non-Mutated	17/49	34.7	(21.7, 49.6)
Baseline ECOG	0	16/37	43.2	(27.1, 60.5)
	≥1	8/29	27.6	(12.7, 47.2)
Baseline LDH	≤ULN	15/39	38.5	(23.4, 55.4)
	>ULN	9/27	33.3	(16.5, 54.0)
Baseline Brain/Liver Lesion	Yes	9/28	32.1	(15.9, 52.4)
	No	15/38	39.5	(24.0, 56.6)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10 mo)	13/29	44.8	(26.4, 64.3)
	>Median (2.10 mo)	6/24	25.0	(9.8, 46.7)
Cumulative Duration on Anti–PD-1/PD-L1	≤Median (5.06 mo)	14/33	42.4	(25.5, 60.8)
	>Median (5.06 mo)	10/33	30.3	(15.6, 48.7)
Time from Stop of Anti–PD-1 /PD-L1 to TIL infusion	≤Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
	>Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
Baseline Target Lesion SOD	<70 mm	14/26	53.8	(33.4, 73.4)
	≥70 mm	10/40	25.0	(12.7, 41.2)

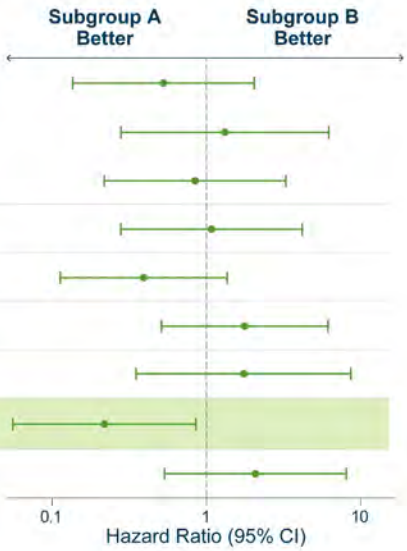


- ORR was not predicted by any patient or clinical characteristics analyzed, including:
  - Baseline LDH (≤ULN vs >ULN)
  - Baseline ECOG performance status (0 vs ≥1)
  - Baseline brain / liver lesions (yes vs no)
  - Cumulative duration on anti–CTLA-4 (≤median vs >median)
  - Cumulative duration on anti–PD-1 / anti–PD-L1 (≤median vs >median) in a post–PD-1 patient population

*95% CI is calculated using the Clopper-Pearson Exact test.
CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mo, months; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes; ULN, upper limit of normal.

Univariable Analyses*: DOR of Lifileucel

Parameter	Subgroup A vs B	N in Subgroup A	N in Subgroup B	HR (95% CI)
Age Group	<65 vs ≥65	19	5	0.527 (0.136, 2.046)
Prior CTLA-4 Use	Yes vs No	19	5	1.320 (0.280, 6.233)
BRAF Mutation Status	Yes vs No	7	17	0.845 (0.218, 3.278)
Baseline ECOG	0 vs ≥1	16	8	1.079 (0.279, 4.179)
Baseline LDH	≤ULN vs >ULN	15	9	0.393 (0.113, 1.364)
Baseline Brain/Liver Lesion	Yes vs No	9	15	1.776 (0.513, 6.154)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10m) vs >Median	13	6	1.743 (0.350, 8.664)
Cumulative Duration on Anti–PD-1/PD-L1	**≤Median (5.06m) vs >Median**	**14**	**10**	**0.218 (0.056, 0.854)**
Baseline Target Lesion SOD	<70mm vs ≥70mm	14	10	2.083 (0.537, 8.079)



- Although cumulative duration on prior anti–PD-1 / anti–PD-L1 was not associated with achieving a response to lifileucel (ORR), it was associated with DOR

*Univariable Cox proportional hazards regression model was used to estimate hazard ratios with 95% confidence intervals between subgroups on DOR.
CTLA-4, cytotoxic T-lymphocyte antigen-4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes; ULN, upper limit of normal.

Conclusions

- In heavily pretreated patients with advanced or metastatic melanoma who progressed on or after multiple prior therapies, including anti–PD-1 / anti–PD-L1 and BRAF/MEK inhibitors (if BRAF V600 mutant), lifileucel treatment resulted in:
  - 36.4% ORR
  - **Median DOR not reached at median 33.1 months of study follow-up**
- Responses deepened over time:
  - 11 patients (17.7%) demonstrated further reduction in SOD since April 2020 datacut
  - 1 patient converted from PR to CR at 24 months post lifileucel infusion
- Prior anti–PD-1 therapy:
  - Shorter duration of prior anti–PD-1 therapy maximizes DOR to lifileucel treatment
  - All newly diagnosed patients should be closely monitored for progression on anti–PD-1 therapy
  - **Early intervention with lifileucel at the time of initial progression on anti–PD-1 agents may maximize benefit**

CR, complete response; DOR, duration of response; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PR, partial response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

FIRST-LINE THERAPY IN METASTATIC MELANOMA?

OPTIONS:

1. anti-PD1
2. anti-PD1+anti-CTLA4
3. BRAFi+MEKi
4. BRAFi+MEKi+anti-PD1
5. anti-PD1+anti-LAG3 – increased PFS and favourable safety profile
6. Cell-based treatment of mM: lifileucel? Still not FDA approved

NEW STANDARD OF CARE FOR FIRST-LINE TREATMENT?

with longer follow-up and ORR results

more data in high tumor burden and MBM patients needed…

FIRST-LINE THERAPY IN METASTATIC MELANOMA?

OPTIONS:

1. anti-PD1
2. anti-PD1+anti-CTLA4
3. BRAFi+MEKi
4. BRAFi+MEKi+anti-PD1
5. anti-PD1+anti-LAG3
6. Lifileucel

Choosing the right upfront treatment
for the right patient: predictive biomarkers

TRIALS IN PROGRESS:

1. SEQUENCING BRAFi+MEKi and anti-PD1+anti-CTLA4
   A. SECOMBIT: ENCO-BINI vs IPI-NIVO
   B. DREAM-SEQ: DABRA-TRAME vs IPI-NIVO
2. NIVO-IPI vs. NIVO-RELA?
3. SUBGROUPS THAT MIGHT BENEFIT FROM BRAFi+MEKi+anti-PD1?

FUTURE?

- 1. Triple combination immunotherapy anti-PD1+anti-CTLA4+anti-LAG3?
  NIVO+RELA+IPI
- 2. Neoadjuvant treatment: NIVO+RELA

	PD1 mono N=35	PD1+CTLA4 N=103	PD1+LAG3 N=30
PD prior to surgery	11%	3%	3%
Efficacy			
pCR	20%	43%	59%
MPR	26%	61%	66%
No response	65%	25%	27%
Toxicity			
Grade 3+	0%^	20%*	26%

^ Huang et al Nat Med 2019
* Rozeman et al Lan Onc 2019 I1N3 dose

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- 3. CELL-BASED THERAPIES (TIL) – LIFILEUCEL

SURVIVAL ANALYSIS IN SLOVENIAN PATIENTS WITH METASTATIC MELANOMA AND IMMUNE RELATED ADVERSE EVENTS

Vid Čeplak Mencin
assist. prof. Tanja Mesti, MD, PhD
Summer School 2021
Institute of Oncology Ljubljana, sept. 2021

CONCLUSION

- irAE cohort: better treatment outcome, longer time to disease progression, better ORR
- ORR: irAE 57%, NirAE 37%
- PFS: irAE 301,6 days, NirAE 247,3 days
- SP: irAE 80%, NirAE 60%
  - Better SP in patients with elevated LDH and irAE M1a/b (TNM classification)
  - Worse SP for M1c/d – new type of melanoma?

Patient with BRAF mutated metastatic melanoma Sequencing, rechallenge, new therapies...

L.Simetic, K.Blazicevic and D. Herceg

On behalf of MDT for melanoma and skin cancers

UHC Zagreb, Croatia

HRVATSKI LIJEČNIČKI ZBOR
HDIO Hrvatsko društvo za internističku onkologiju

QUESTIONS

- Should we continue with BRAF MEK therapy or not? Patient was treated with 2 lines in metastatic setting so no other option, except Cht, is available in Croatia (by National regulatory agency for health insurance)
- Do we have „ a joker card" with previous response to ICI (lung mets regression) ? Rechallenge with mono PD-1 inhibitors or combo ICI?
- Clinical study/ compassionate use programe:: ICI+ lenvatinib or?
- Something new like Fecal Transplant therapy + ICI?
- Your comments are precious ☺

Multidisciplinary team for melanoma treatment
University hospital centre Zagreb; core members

- ✓ dermatologist, dermatooncologist: D. Štulhofer (chair), R.Čeović
- ✓ plastic surgeon: D. Mijatović, S. Smuđ Orehovec
- ✓ head and neck surgeon: M.Jurlina, J.Biloš, D. Leović
- ✓ ophthalmologist: N.Vukojević, M. Štanfel
- ✓ medical oncologist: D.Herceg, K.Blažičević, L.Simetić
- ✓ radiooncologist: F.Šantek
- ✓ pathologist: S.Dotlić, I.Ilić
- ✓ nuclear medicine specialist: G.Horvatić Herceg, S. Kusačić Kuna, M.Ciglar
- ✓ radiologist: M.Lušić, M.Kralik

lsimetic@kbc-zagreb.hr

Systemic treatment of nemelanomskih skin cancer

Prof. Janja Ocvirk

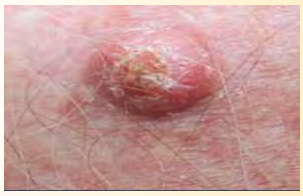
Ljubljana, 7.9.2021

Systemic treatment of non-melanoma skin cancers - immunotherapy?

Squamous cell carcinoma of the skin

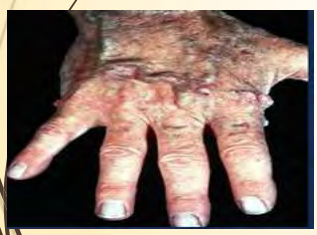
- The second most common NMSC (20%)
- The incidence has been growing over the last 30 years(50-200%)
- Head and neck 80-90%
- 90% has a good prognosis

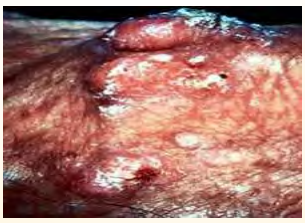
- **What about the rest 10%?**

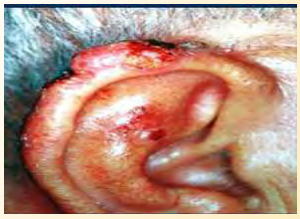


SCC in transplant patients

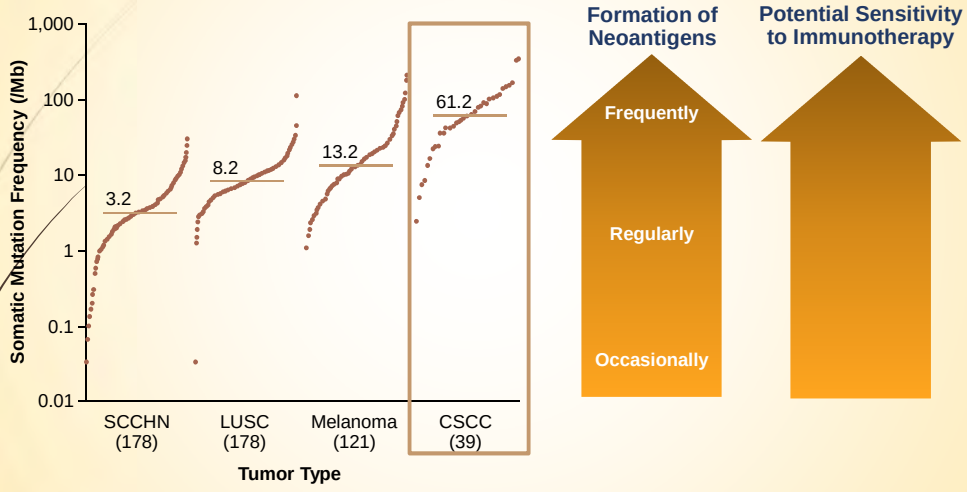
36 times higher incidence than usual(BCC: SCC 4: 1)
Aggressive course - poor prognosis







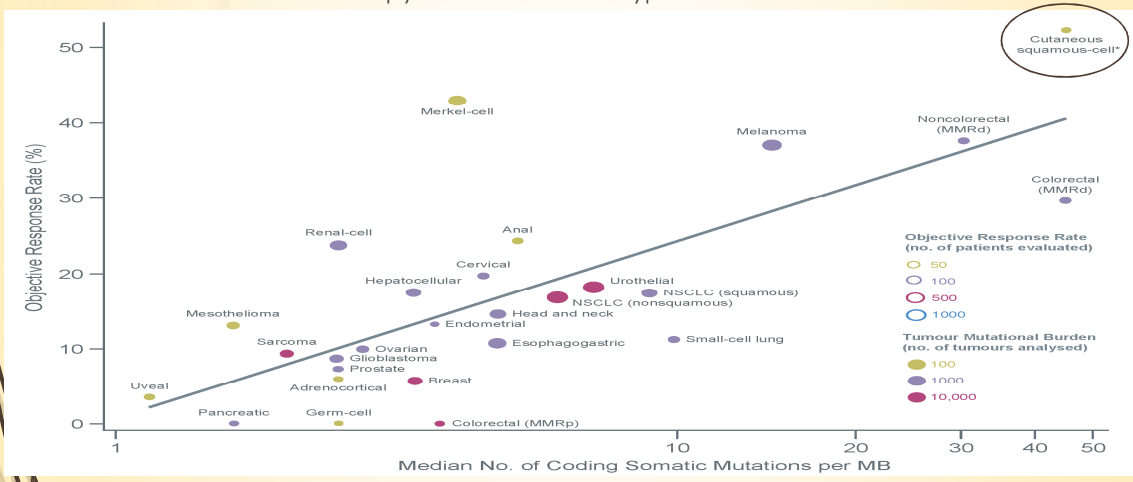
Tumor Mutational Burden in CSCC



Red horizontal line and associated number in figurer = median mutations per MB.
CSCC, cutaneous squamous cell carcinoma; LUSC, lung squamous cell carcinoma; Mb, megabase of DNA; SCCHN, Squamous cell carcinoma of the head and neck.
Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582–6592.

Tumour mutational burden & objective response rate

- Anti–PD-1 and anti–PD-L1 therapy across 27 tumour types[1]



1. Yarchoan M, et al. N Engl J Med. 2017; 377: 2500–01; 2. Papadopoulos K, et al. Presentation at 2017 American Society of Clinical Oncology, Chicago, IL. J Clin Oncol. 2017;35(15_suppl):9503; Adapted from Yarchoan et al, 2017

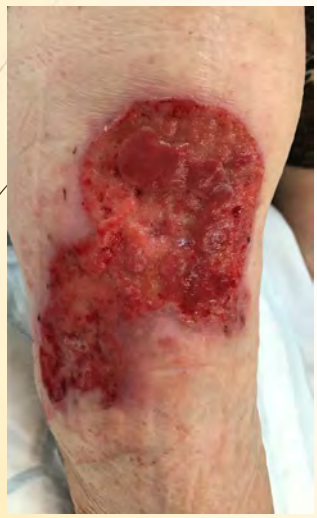
Reasons for immunotherapy in CSCC

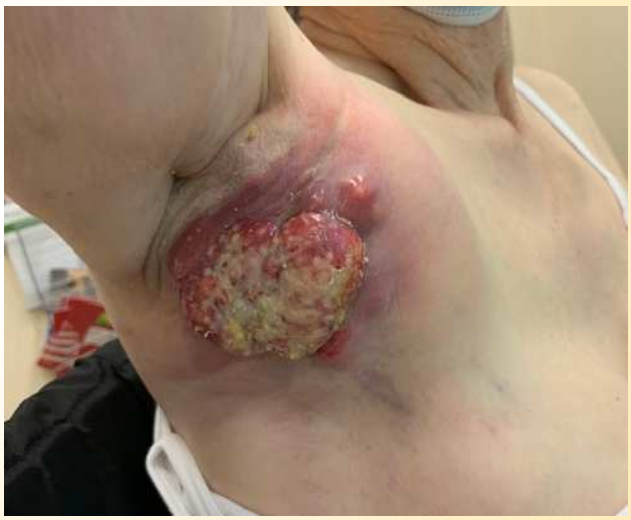
- High tumor mutation load (TMB) and immunogenic cancer
- High TMB may contribute to increased neoantigen production, which may increase tumor antigenicity [1]
- Immunosuppression is a well-described risk factor for CSCC (especially in organ transplant patients)[2]
- PD-L1 expression was detected in advanced CSCC[3]

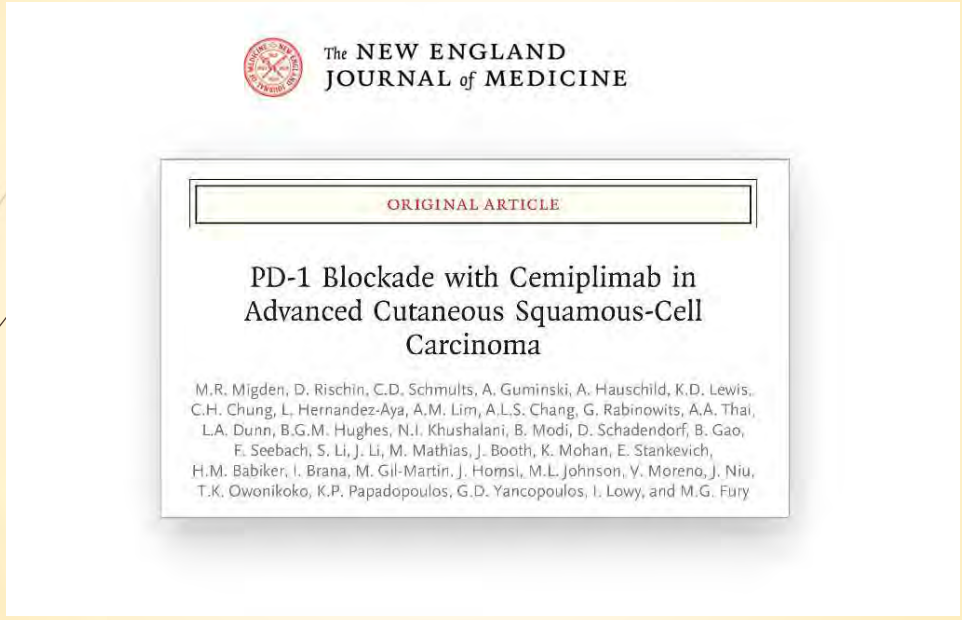
1. Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582-92; 2. Euvrard E, et al. *N Engl J Med*. 2003;348:1681-1691.
3. Slater NA, et al. *J Cutan Pathol*. 2016;43:663-70.

Candidates for immunotherapy in advanced CSCC

- Patients with advanced CSCC
- Locally advanced / metastatic disease
- Patients with recurrences after previous surgeries
- Patients who are not candidates for surgery due to morbidity / potential exhaustion or a low level of confidence within clear boundaries
- Patients who are not candidates for radiotherapy







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

Migden MR, et al. *N Engl J Med*. 2018;379:341-351.

EMPOWER-CSCC-1 study design

1	Metastatic CSCC (nodal and/or distant)	**Cemiplimab 3 mg/kg Q2W IV* for up to 96 weeks** (retreatment optional for patients with progression during follow-up†)	**Tumour imaging every 8 weeks** for the assessment of efficacy
2	Locally advanced CSCC		
3	Metastatic CSCC (nodal and/or distant)	**Cemiplimab 350 mg Q3W IV for up to 54 weeks**	**Tumour imaging every 9 weeks** for the assessment of efficacy

Tumour response assessment by ICR (RECIST 1.1 for scans: modified WHO criteria for photographs)

Key inclusion criteria
- ECOG performance status of 0 or 1
- Adequate organ function
- At least one lesion measurable by RECIST 1.1 criteria (for scans) or modified WHO criteria (for photos)
- CSCC lesion that is not amenable to surgery or radiation therapy per investigator assessment

Key exclusion criteria
- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- History of solid organ transplant, concurrent malignancies (unless indolent or not considered life threatening; for example, basal cell carcinoma), or haematologic malignancies

†To account for possible pseudoprogression, treatment could be continued beyond initial RECIST 1.1-defined progression informed by ir-related response criteria

***Cemiplimab is not licensed at this dose for the treatment of CSCC**

CSCC, cutaneous squamous-cell carcinoma; ECOG, Eastern Cooperative Oncology Group; ICR, independent central review; IV, intravenous; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; WHO, World Health Organisation.

Migden MR, et al. Presentation at 2019 American Society of Clinical Oncology, Chicago, IL. J Clin Oncol. 2019;37(15_suppl):6015

CSCC, cutaneous squamous cell carcinoma

11

EMPOWER-CSCC-1 treatment arms

- Phase II data supporting cemiplimab license (n=193)

	Group 1	Group 2	Group 3
CSCC	**Metastatic**	**Locally advanced**	**Metastatic**
Number of patients	59	78	56
Cemiplimab dosing	3 mg/kg Q2W	3 mg/kg Q2W	350 mg Q2W
Data cut-off	Sept 20 2018	Oct 10 2018	Sept 20 2018
Median follow-up (months)	16.5	9.3	8.1

Cemiplimab SmPC, available at https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_hr.pdf; accessed January 2020

EMPOWER-CSCC-1

- Response rates in three treatment groups

	Group 1	Group 2	Group 3
	Metastatic CSCC Cemiplimab 3 mg/kg Q2W* N=59	**Locally advanced CSCC** Cemiplimab 3 mg/kg Q2W* N=78	**Metastatic CSCC** Cemiplimab 350 mg Q3W N=56
Objective response rate 95% Confidence interval	**49.2%** 35.9, 62.5	**43.6%** 32.4, 55.3	**39.3%** 26.5, 53.2
Confirmed objective response			
Complete response†	16.9%	12.8%	3.6%
Partial response	32.2%	30.8%	35.7%
Stable disease	15.3%	35.9%	14.3%
Progressive disease	16.9%	11.5%	26.8%

*Cemiplimab is not licensed at this dose for the treatment of CSCC

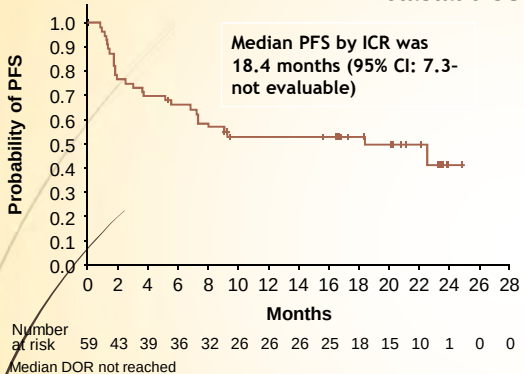
†Only patients with complete healing of prior cutaneous involvement; for locally advanced CSCC, biopsy required to confirm complete response

CSCC, cutaneous squamous-cell carcinoma; Q2W, every 2 weeks

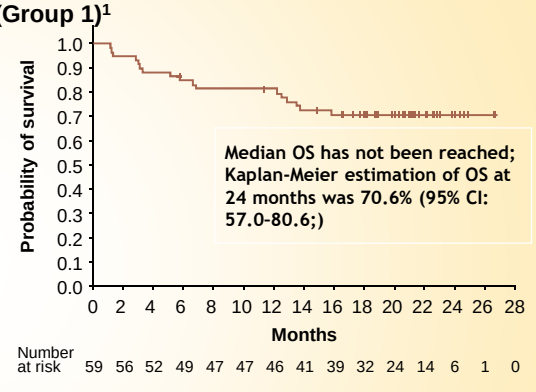
Cemiplimab SmPC, available at https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_hr.pdf; accessed January 2020

Kaplan–Meier Estimation Overall Survival, Progression-Free Survival, and Duration of Response in Advanced CSCC Patients

Metastatic CSCC (Group 1)[1]



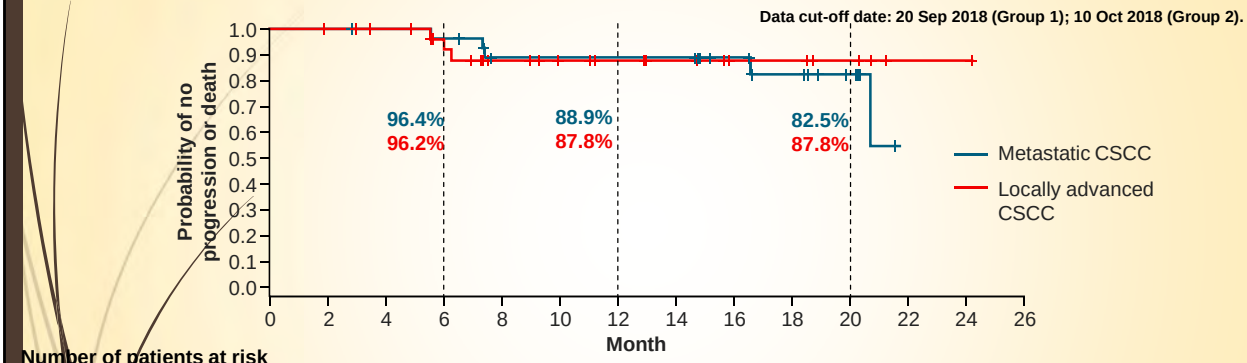
Median DOR not reached



	Locally Advanced CSCC (Group 2)[2]
Median PFS	NR
K-M Estimated PFS at 12 months	58.1% (95% CI: 43.7–70.0)
Median OS	NR
K-M Estimated OS at 12 months	93.2% (95% CI: 84.4–97.1)
Median DOR	NR

Group 1: Median duration of follow-up = 16.5 mos (range 1.1 – 26.6); Group 2: Median duration of follow-up = 9.3 mos (range 0.8 – 27.9)
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; OS, overall survival; PFS, progression-free survival; NR, not reached
1. Gurminski et al. J Clin Oncol. 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. J Clin Oncol. 2019:37 (suppl; abstr 6015) [poster presentation].

EMPOWER-CSCC-1:Duration of response K-M estimated event-free probability by ICR in responding patients



Number of patients at risk

Metastatic CSCC	29	29	28	27	22	22	22	22	15	11	7	0	0	0
Locally advanced CSCC	34	30	27	23	17	14	12	9	6	6	4	1	1	0

Median duration of response has not been reached.

CSCC, cutaneous squamous cell carcinoma; ICR, independent central review.

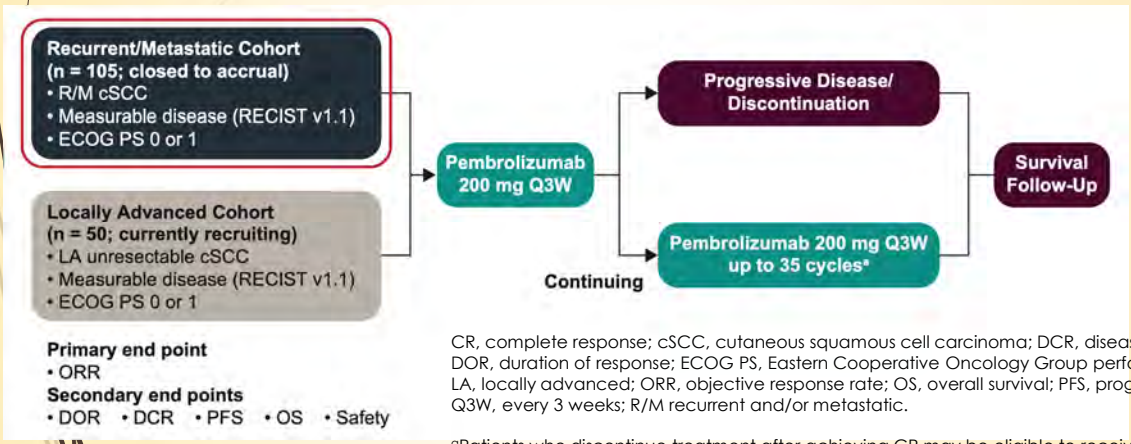
Cemiplimab adverse reaction profile

	Safety population N=591	Permanent discontinuation
Serious adverse events	8.6%	5.8%
Immune-related adverse reactions	20.1%	4.4%
≥Grade 3 irARs		
Grade 3	6.1%	
Grade 4	1.2%	
Grade 5	0.7%	
Most common irARs		
Hypothyroidism	7.1%	0
Pneumonitis	3.7%	1.9%
Immune-related skin ARs	2.0%	0.3%
Hyperthyroidism	1.9%	0
Hepatitis	1.9%	0.8%
Infusion-related reactions	9.1%	0.3%

Cemiplimab SmPC, available at https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_hr.pdf; accessed January 2020
irARs, immune-related adverse reactions

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From Phase 2 KEYNOTE-629 Study

Studiendesign



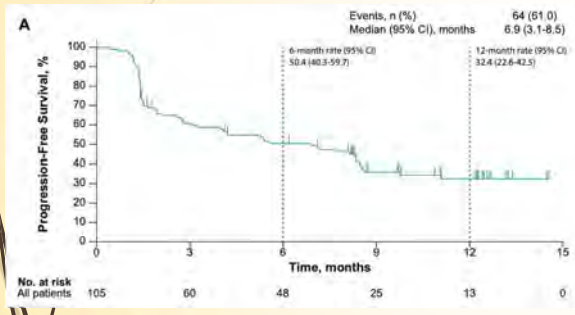
CR, complete response; cSCC, cutaneous squamous cell carcinoma; DCR, disease control rate DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance statu LA, locally advanced; ORR, objective response rate; OS, overall survival; PFS, progression-free su Q3W, every 3 weeks; R/M recurrent and/or metastatic.

[a]Patients who discontinue treatment after achieving CR may be eligible to receive an addition 17 cycles of pembrolizumab if disease progression occurs.

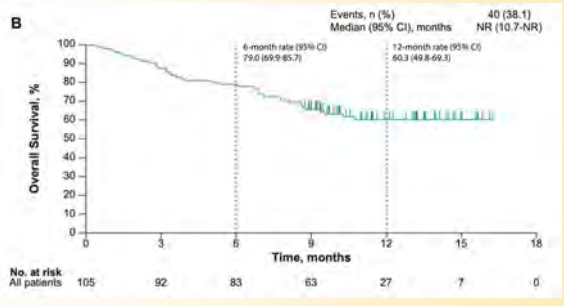
J.-J. Grobet al., KEYNOTE-629 Efficacy and Safety of pembrolizumab in patients with R/M cSCC, Poster presented at ESMO 2019

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From Phase 2 KEYNOTE-629 Study

PFS[a] in the R/M Cohort



OS[a] in the R/M Cohort



NR, not reached; OS, overall survival; PFS, progression-free survival; R/M, recurrent and/or metastatic.
[a]From product-limit (Kaplan-Meier) method for censored data.

J.-J. Grobet al., KEYNOTE-629 Efficacy and Safety of pembrolizumab in patients with R/M cSCC, Poster presented at ESMO 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR SQUAMOUS CELL SKIN CANCER

Local Disease Amenable to Surgery
- Systemic therapy is not recommended.

Locally Advanced Disease in Non-Surgical Candidates
- For potential use with RT: (See SCC-3)
  - Options for multidisciplinary team to consider for use in combination with RT for patients who have residual disease and further surgery is not feasible:
    - Clinical trial[1,2]
    - Chemotherapy
- Systemic therapy alone: (See SCC-3)
  - Options for multidisciplinary team to consider for complicated cases of locally advanced disease in which curative surgery and curative RT are not feasible:
    - Cemiplimab-rwlc[1,2] (preferred)
    - Clinical trial[1,2]

Regional Disease (See SCC-4)
- For most cases of fully resected regional disease, adjuvant systemic therapy is not recommended, unless within a clinical trial. (See SCC-4 and SCC-5)
- For patients with completely resected ECE or similar high-risk regional disease, consider RT ± systemic therapy in the context of a clinical trial.
- Options for patients with inoperable or incompletely resected regional disease:
  - For potential use with RT: (See SCC-4 and SCC-5)
    - Cisplatin[3] (category 3)
    - Cisplatin + 5-FU[3] (category 2B)
    - EGFR inhibitors (eg, cetuximab)[3]
    - Carboplatin[3] (category 3)
  - Systemic therapy alone, if curative RT not feasible: (See SCC-4)
    - Cemiplimab-rwlc[1,2] (preferred)
    - Clinical trial[1,2]
    - If ineligible for immune checkpoint inhibitors and clinical trials, consider:
      - Cisplatin[3] (category 2B)
      - Cisplatin + 5-FU[3]
      - EGFR inhibitors (eg, cetuximab)[3]
      - Carboplatin[3] (category 2B)

Regional Recurrence or Distant Metastatic Disease (See SCC-6)
- Cemiplimab-rwlc[1,2] (preferred) if curative surgery and curative RT are not feasible
- Clinical trial[1,2]
- If ineligible for immune checkpoint inhibitors and clinical trials, consider:
  - Cisplatin ± 5-FU[3]
  - EGFR inhibitors (eg, cetuximab)[3]
  - Carboplatin[3] (category 2B)

[1] Recently published phase I–II trial data have shown high response rates (approximately 50%) to cemiplimab-rwlc in patients with locally advanced or metastatic cutaneous squamous cell carcinoma. Preliminary data and the clinical experience of NCCN Panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting.
[2] In solid organ transplant recipients, potential benefit from immune checkpoint inhibitor therapy has to be weighed against a significant risk of organ rejection. For patients receiving immunosuppressive therapy, in consultation with their treating physician, consider dose reduction of the immunosuppressive agent(s) and/or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors where appropriate. Patients with underlying immunodeficiencies, including CLL, were excluded from the phase I–II cemiplimab-rwlc trial, so the efficacy of cemiplimab-rwlc in this population is unclear.
[3] These options have occasionally produced useful responses, but data supporting efficacy are limited.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

- Cemiplimab is indicated as monotherapy in adult patients with metastatic or locally advanced squamous cell carcinoma of the skin who are not candidates for curative surgery or curative first-line radiation.

Basal cell carcinoma of the skin

A major cause of BCC is exposure to UV radiation

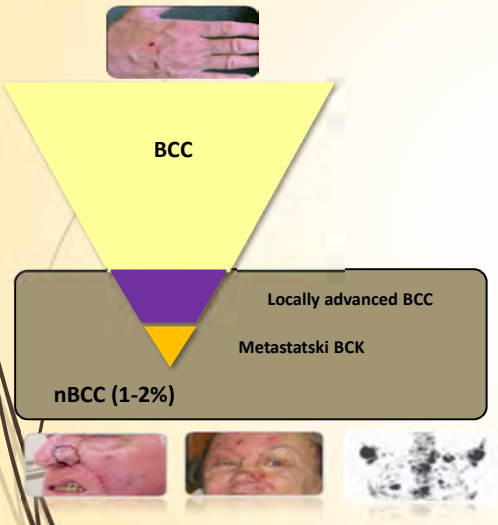
- A major cause of BCC is exposure to UV radiation, leading to cumulative DNA damage and gene mutations[1–5]
- Epidemiological data suggest the overall incidence of BCC is increasing significantly and show marked geographical variation[1,6–8]
- Australia has the highest incidence rate of BCC in the world, reporting a rate of 1–2% per year[1,6]

Most sporadic cases of BCC arise from chronic sun-exposure[1,2]

- 80% occur on the head and neck
- 15% occur on the trunk
- 5% occur on the arms, legs or other sites

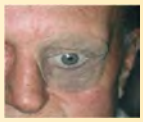
Rubin AI et al. N Engl J Med 2005;353:2262–9
Wong CSM et al. Br Med J 2003;327:794–8
Roewert-Huber J et al. Br J Dermatol 2007;157:47–51
4. Lear JT et al. J R Soc Med 1998;91:585–8
Caro I, Low JA. Clin Cancer Res 2010;16:3335–9
Diepgen TL, Mahler V. Br J Dermatol 2002;146(suppl):1–6
Ting PT et al. J Cutan Med Surg 2005;9:10–15
Rogers HW et al. Arch Dermatol 2010;146:283–7

Advanced basal cell carcinoma



Locally advanced basal cell carcinoma (lnBCC)

Aggressive disease with local tissue damage
Frequent recurrences after surgery
The operation would cause deformation



Metastatc BCC (mBCC)

Rare but serious form of BCK
It involves the presence of metastases (e.g., lymph nodes, bones, lungs, liver [1]
Weak outcome (median survival: 8-14 months[2-3]
5-year survival rate: 10% [3,4]

1. Ting PT et al. J Cutan Med Surg 2005;9:10–15
2. von Domarus H, Stevens PJ. J Am Acad Dermatol 1984;10:1043–60
3. Lo JS et al. J Am Acad Dermatol 1991;24:715–19
4. Wong CSM et al. Br Med J 2003;327:794–8

Treatment of basal cell carcinoma

- Curettage and cavertisation, cryosurgery
- Cream imiquimod

- Surgical excision
- Electrochemotherapy
- Radiotherapy
- Targeted therapy – HHI:Vismodegib, Sonidegib,
- Immunotherapy

nBCC

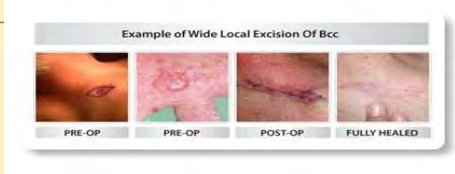


Table 1. Risk factors for recurrence[†].

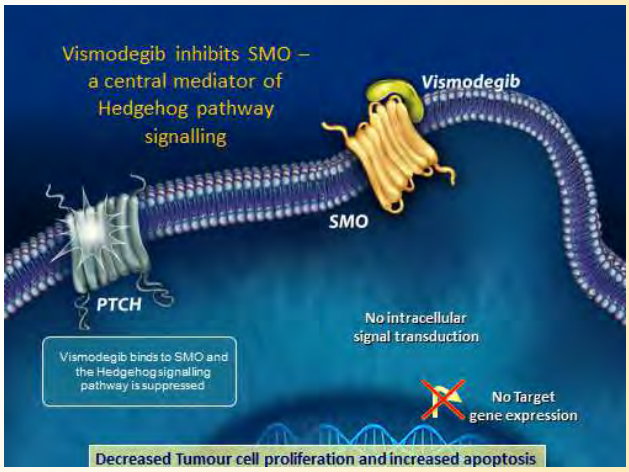
	Clinical	Histological
Location	Low risk: trunk and limbs Intermediate risk: forehead, cheek, chin, scalp and neck High risk: nose and periorificial areas on the head and neck	Aggressive subtype[‡]: – Morpheaform – Infiltrating – Basosquamous – Multifocal
Size (largest tumor diameter)	>1 cm for high-risk location >2 cm for low- or intermediate-risk location	
Clinical aspect	Ill-defined lesions or morpheaform subtypes	
Disease status	Recurrent	

[†]Level of evidence 3 (i.e., based on case–control studies).
[‡]When several subtypes are associated, global prognosis depends on the component with the poorest prognosis.
Adapted with permission from [26].

BCC and Hedgehog signal pathway

26

- The pathway of cell growth and differentiation that controls the formation of organs in embryonic development
- The Hedgehog signaling pathway is inactive in most of the tissue of the adult
- Abnormal activation (mutation) of the Hedgehog signal pathway plays an important role in pathogenesis BCC[1]
- Hedgehog signaling pathway inhibitors provide a new treatment option for advanced patients BCC (vismodegib, sonidegib)



Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunstfeld, Brigitte Dréno, Laurent Mortier, Paolo A Ascierto, Lisa Licitra, Caroline Dutriaux, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Guillot, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldo, Ioannis Xynos, Johan Hansson

Summary

Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal

Lancet Oncol 2015; 16: 729–36

	All patients (n=482*)	Patients with locally advanced basal cell carcinoma (n=453)	Patients with metastatic basal cell carcinoma (n=29)
Complete	155 (32%)	153 (34%)	2 (7%)
Partial	158 (33%)	149 (33%)	9 (31%)
Stable disease	128 (27%)	118 (26%)	10 (34%)
Progressive disease	15 (3%)	11 (2%)	4 (14%)
Missing/not evaluable	26 (5%)	22 (5%)	4 (14%)

Data are n (%). *Excludes patients without histologically confirmed disease (n=3) and without measurable disease (n=14).

Table 4: Best response to treatment

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunstfeld, Brigitte Dréno, Laurent Mortier, Paolo A Ascierto, Lisa Licitra, Caroline Dutriaux, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Guillot, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldo, Ioannis Xynos, Johan Hansson

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	All TEAEs		Grade 3–5 TEAEs	
	<12 months' exposure (n=314)	≥12 months' exposure (n=185)	<12 months' exposure (n=314)	≥12 months' exposure (n=185)
Any TEAE	307 (98%)	184 (99%)	130 (41%)	84 (45%)
Muscle spasms	169 (54%)	148 (80%)	21 (7%)	17 (9%)
Alopecia	154 (49%)	153 (83%)	1 (<1%)	1 (<1%)
Dysgeusia	139 (44%)	130 (70%)	8 (3%)	3 (2%)
Weight loss	80 (25%)	82 (44%)	4 (1%)	14 (8%)
Asthenia	76 (24%)	65 (35%)	9 (3%)	5 (3%)
Decreased appetite	74 (24%)	52 (28%)	7 (2%)	4 (2%)
Ageusia	75 (24%)	37 (20%)	6 (2%)	5 (3%)
Fatigue	50 (16%)	30 (16%)	9 (3%)	3 (2%)
Nausea	38 (12%)	42 (23%)	0	1 (<1%)
Diarrhoea	32 (10%)	51 (28%)	1 (<1%)	2 (1%)

Data are n (%). For the most common treatment-emergent adverse events (TEAEs) of any grade, event occurring in 10% or more of patients are reported. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version (version 4.0).

Table 3: Incidence of treatment-emergent adverse events according to duration of vismodegib exposure (≥12 months *vs* <12 months; n=499)

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

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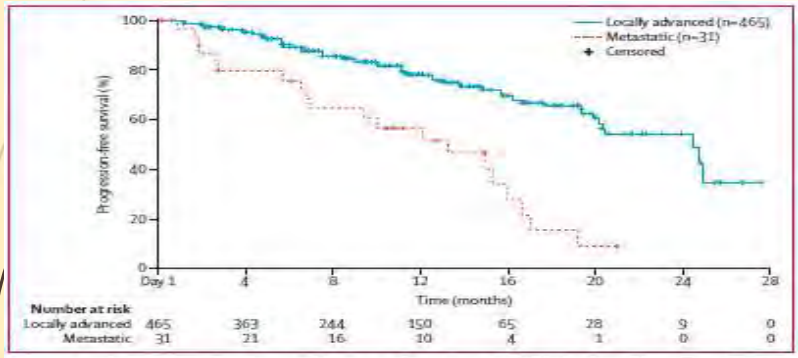
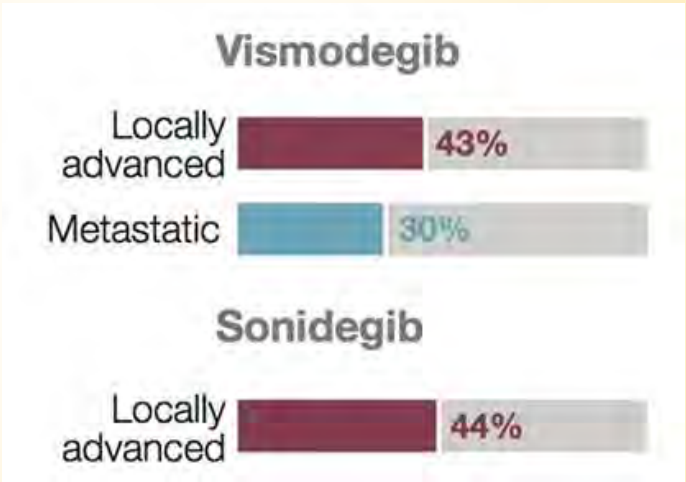


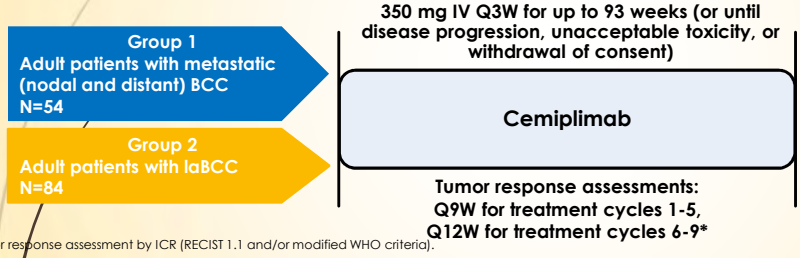
Figure 2: Kaplan-Meier plot of progression-free survival in patients who had histologically confirmed basal cell carcinoma

RR in 1st line treatment - HHI



Phase 2 Study of Cemiplimab in Advanced BCC (Study 1620) – NCT03132636[1-3]

An open-label, non-randomized Phase 2 study of cemiplimab in patients with advanced BCC who experienced progression on or intolerance to hedgehog pathway inhibitor therapy[1-4]



Primary endpoint

- ORR by ICR

Select secondary endpoint

- DOR, PFS, OS, complete response by ICR, ORR per investigator, and safety and tolerability

*Tumor response assessment by ICR (RECIST 1.1 and/or modified WHO criteria).

BCC=basal cell carcinoma; DOR=duration of response; ICR=independent central review; IV=intravenous; laBCC=locally advanced BCC; N=number of patients; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; WHO=World Health Organization.

1. ClinicalTrials.gov/NCT03132636. https://clinicaltrials.gov/ct2/show/NCT03132636. Accessed October 2020. 2. Stratigos AJ, et al. Poster presented at: European Society for Medical Oncology (ESMO) Virtual Congress; September 19–21, 2020:LBA47. 3. Lewis KD, et al. Poster presented at: Society for Immunotherapy of Cancer (SITC) Virtual Congress; November 9–14, 2020:Poster 428.

REGENERON

Patient Eligibility

Select Inclusion Criteria[1-3]

- Adults (≥18 years) with histologically confirmed diagnosis of invasive BCC
- Prior disease progression on HHI therapy, *or* intolerance to prior HHI therapy,* *or* no better than stable disease after 9 months on HHI therapy
- ≥1 measurable baseline lesion
- ECOG performance status ≤1
- Adequate organ function
- Must not be a candidate for radiation therapy or surgery

Select Exclusion Criteria[1-3]

- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- Active brain metastases
- Immunosuppressive doses of steroids (>10 mg prednisone daily or equivalent)
- Concurrent malignancy other than BCC and/or history of malignancy other than BCC within 3 years of date of first planned dose of cemiplimab, except for tumors with negligible risk of metastasis

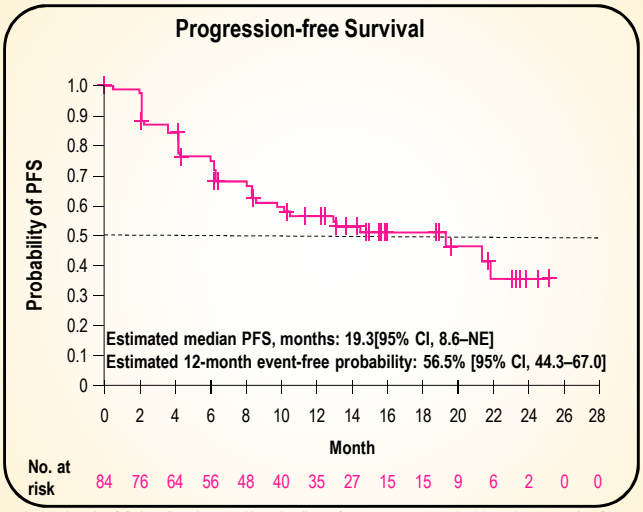
*Defined as any Grade 3/4 HHI-related AEs, or any of the following Grade 2 HHI-related AEs following ≥3 months of exposure: muscle spasms or myalgias, dysgeusia or anorexia (if accompanied by Grade ≥1 weight loss), nausea, or diarrhea (despite medical management).

BCC=basal cell carcinoma; ECOG=Eastern Cooperative Oncology Group; HHI=hedgehog inhibitor; PD-1=programmed cell death protein-1; PD-L1=programmed death-ligand 1.

1. ClinicalTrials.gov/NCT03132636. https://clinicaltrials.gov/ct2/show/NCT03132636. Accessed October 2020. 2. Stratigos AJ, et al. Poster presented at: European Society for Medical Oncology (ESMO) Virtual Congress; September 19–21, 2020:LBA47; 3. Lewis KD, et al. Poster presented at: Society for Immunotherapy of Cancer (SITC) Virtual Congress; November 9–14, 2020:Poster 428.

REGENERON

Kaplan-Meier Curve for PFS by ICR in Patients with laBCC



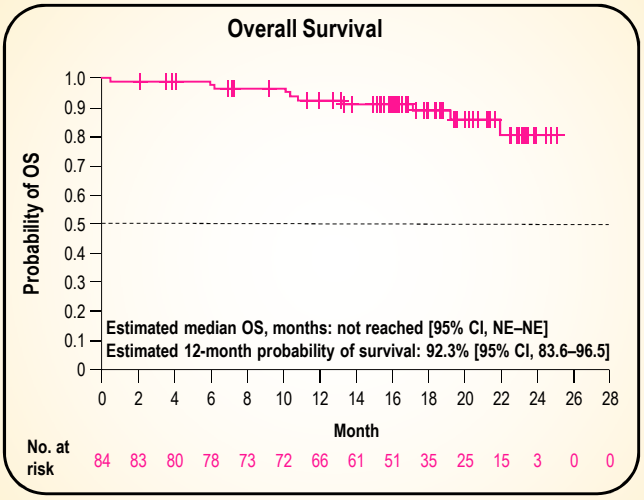
Data cut-off date: 17 February 2020.

CI=confidence interval; ICR=independent central review; laBCC=locally advanced basal cell carcinoma; NE=not evaluable; PFS=progression-free survival.

Stratigos AJ, et al. Poster presented at: European Society for Medical Oncology (ESMO) Virtual Congress; September 19–21, 2020:LBA47.

REGENERON

Kaplan-Meier Curve for OS by ICR in Patients with laBCC



Data cut-off date: 17 February 2020.

CI=confidence interval; ICR=independent central review; laBCC=locally advanced basal cell carcinoma; NE=not evaluable; OS=overall survival

Stratigos AJ, et al. Poster presented at: European Society for Medical Oncology (ESMO) Virtual Congress; September 19–21, 2020:LBA47.

REGENERON

- Cemiplimab is the first systemic treatment to show clinical benefit in patients with laBCC and mBCC after HHI therapy.
- 31% and 21% ORR The safety profile is acceptable for the patient population. Consistent with other PD-1 antibodies and previous reports of cemiplimab in other tumor types

Merkel cell carcinoma (MCC)

Merkel cell carcinoma (MCC) - Epidemiology

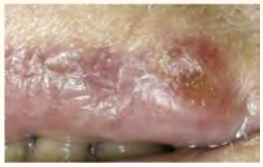
- Each year ~ 2,500 new cases diagnosed in the EU[1] and 1,500 in USA
- Increasing incidence over the past few decades[2]
  - Unclear whether this trend is due to an aging population or increased awareness and diagnosis
- The highest rates of MCC have been observed in Australia, with an incidence rate of 1.6 per 100,000 persons reported in Queensland[3,4]
- ~80% of MCCs are caused by MCV (Merkel cell polyomavirus)
- Each year approximately 1 in 3 patients with Merkel Cell Carcinoma will die from their disease

1. IMMOMEC (European Commission). Merkel cell carcinoma. Available at: www.immomec.eu/project/objectives/background/merkel-cell-carcinoma (accessed July 2017); 2. Saini AT, Miles BA. Onco Targets Ther 2015;8:2157–67; 3. Schadendorf D, et al. Eur J Cancer. 2017;71:53–69; 4. Youlden DR, et al. JAMA Dermatol 2014;150:864–72.

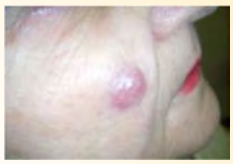
MCC – Signs, Symptoms and Risk Factors

Clinical Presentation

- Typical presentation
  - single painless lump on sun-exposed skin[1]



MCC on the lip



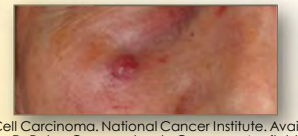
MCC on a cheek

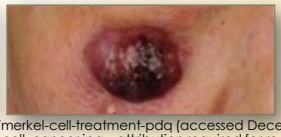
FEATURES OF MCC[4,5]
- Firm, red to purple papule/nodule
- **A**symptomatic/lack of tenderness
- Rapidly **E**xpanding
- Mets at an early stage

COMMONLY AFFECTED AREAS[6]
- Head and neck (~50%)
- Upper extremities (~16%)
- Lower extremities (~30%)
- Trunk (<5%)

RISK FACTORS[5]
- **I**mmune suppression
- Median age ~76 years – **O**lder age
- **U**V exposure
- Fair skin

A E I O U





1. Merkel Cell Carcinoma. National Cancer Institute. Available at: www.cancer.gov/types/skin/patient/merkel-cell-treatment-pdq (accessed December 20163. Image credit: Klaus D. Peter, Gummersbach, Germany. Available at: commons.wikimedia.org/wiki/File:Merkel_cell_cancer.jpg – attribution required for re-use; 4. Nutan FNU et al. Cutis 2014;94:E18–20; 5. Heath M et al. J Am Acad Dermatol 2008;58:375–81; 6. Hitchcock CL et al. Ann Surg 1988;207:201–7.

Merkel cell carcinoma

Where does MCC occur on the body?

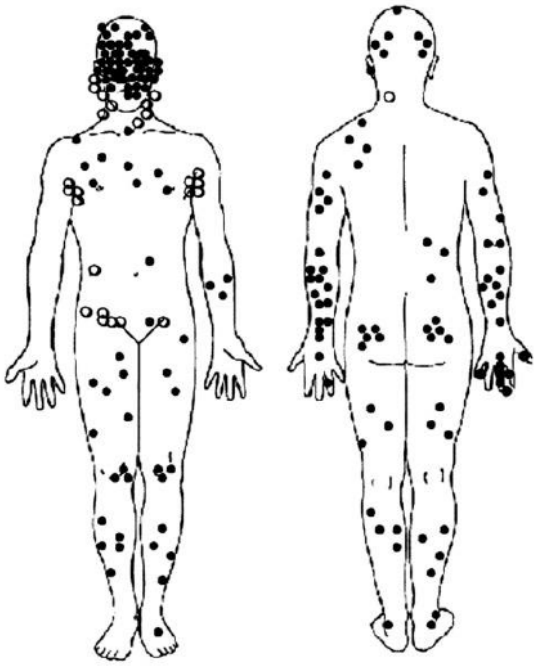
- MCC primarily occurs on highly sun-exposed skin, but it can occur anywhere on the body, including sun-protected areas such as the buttock or the scalp under hair.

Solid circles depict MCC tumors that arose on the skin:

86% of these cases.

Open circles indicate MCCs that presented in lymph nodes

without an associated "primary lesion" : 14% of cases



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Treatment

- Treatment is generally based on stage of the disease and many issues that are highly variable between patients.
- It is best to obtain care from a multi-disciplinary team of physicians with significant MCC experience who take into consideration many clinical factors.

Major treatments

1) surgical excision of the primary lesion or lymph node,

2) radiation therapy, and

3) systemic therapy including immunotherapy and chemotherapy.

Reason for use of immunotherapy in mMCC

- PD-L1 is expressed in MCC tumor cells and infiltrates of adjacent immune cells[1]
- Dysfunction of MCPyV-specific T cells[2]

  -Levels of CD8 T cells increase with a higher tumor load

  -Exhausted phenotype (PD-1 +, Tim-3 +)
- MCPyV-negative tumors have a higher burden on mutations and neoanthigens[3]

1. Lipson EJ, et al. *Cancer Immunol Res*. 2013;1(1):54-63; 2. Afanasiev O, et al. *Clin Cancer Res*. 2014;19(19):5351-60; 3. Goh G, et al. *Oncotarget*. 2016;7(3):3403-15.

JAVELIN MERKEL 200

N=200 (estimated) A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma

Patients with
- Histologically-proven mMCC
- ECOG PS 0–1

Part A: patients have received at least one line of chemotherapy (n=88)[2]

Part B: patients have not received any prior systemic treatment for mMCC (n=112)[1,2]

Tumor assessments every 6 weeks (RECIST v1.1; IERC)

Avelumab 10 mg/kg IV (1-h infusion) every 2 weeks until disease progression, clinical deterioration, unacceptable toxicity or other criterion for withdrawal

Part A:
PRIMARY ENDPOINT:
- Best Overall Response

SECONDARY ENDPOINTS:
- DoR, PFS, OS, safety, anti-drug antibodies, PK

Part B:
PRIMARY ENDPOINT:
- Durable response

SECONDARY ENDPOINTS:
- BOR, DoR, PFS, OS, safety, anti-drug antibodies, PK

42

1. NCT02155647. Available at ClinicalTrials.gov (accessed Oct 2017). 2. Kaufman HL et al. Lancet Oncol 2016;17:1374–85.

Part A cohort, mMCC 2L+: design[1]

n=88 (estimated)

A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma

Key Inclusion Criteria
- Histologically-proven Stage IV MCC
- ECOG PS 0–1
- Patients received at least one line of chemotherapy

Avelumab 10 mg/kg IV (1-h infusion) every 2 weeks until disease progression, clinical deterioration, unacceptable toxicity or other criterion for withdrawal

Tumor assessments every 6 weeks (RECIST v1.1; IERC)

Part A:

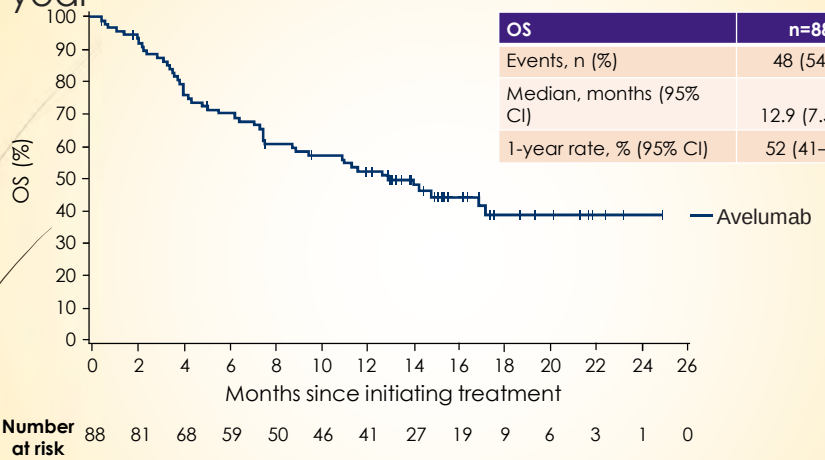
PRIMARY ENDPOINT:
- **Best Overall Response**

SECONDARY ENDPOINTS:
- **DoR, PFS, OS, safety, anti-drug antibodies, PK**

****Best Overall Response is defined as complete response, partial response, stable disease, or progressive disease, according to RECIST version 1.1 and assessed by an independent review committee.**

1. NCT02155647. Available at ClinicalTrials.gov (accessed Oct 2017.

In previously treated patients who received avelumab 52% are still alive at 1 year[1]



OS	n=88
Events, n (%)	48 (54.5)
Median, months (95% CI)	12.9 (7.5, –)
1-year rate, % (95% CI)	52 (41–62)

1. Kaufman HL et al. AACR 2017. Abstract CT079 (presentation). – ≥ 12 month follow-up

Part B cohort, mMCC –Treatment naïve - 1L: design[1]

n=112[1,2] (estimated)

A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma

Key Inclusion Criteria
- Histologically-proven Stage IV MCC
- ECOG PS 0–1
- Not received any prior systemic treatment for mMCC

Avelumab 10 mg/kg IV (1-h infusion) every 2 weeks until disease progression, clinical deterioration, unacceptable toxicity or other criterion for withdrawal

Tumor assessments every 6 weeks (RECIST v1.1; IERC)

PRIMARY ENDPOINT:
- **Durable response***

KEY SECONDARY ENDPOINTS:
- **BOR, DoR, PFS, OS, safety, anti-drug antibodies, PK**

Estimated primary completion date: September 2019

* By Kaplan Meier Method

Durable response is defined as proportion of patients of the total ITT population with objective response (CR or PR) according to RECIST v1.1, with a duration of at least 6 months.

45

1. NCT02155647. Available at ClinicalTrials.gov (accessed Oct 2017). 2. Kaufman HL et al. Lancet Oncol 2016;17:1374–85.

Avelumab in 1L mMCC:

High ORR 62.1% and >80% on-going for at least 6 months CR in 4 patients

Preliminary Efficacy Data – Treatment naïve – 1L[1]

Response	Confirmed response in patients with ≥3 months of follow-up (n=29)	Confirmed response in patients with ≥6 months of follow-up (n=14)
ORR (95% CI), %	62.1 (42.3–79.3)	71.4 (41.9–91.6)
BOR, n (%)		
Complete response	4 (13.8)	4 (28.6)
Partial response	14 (48.3)	6 (42.9)
Stable disease	3 (10.3)	1 (7.1)
Progressive disease	7 (24.1)	2 (14.3)
Non-evaluable*	1 (3.4)	1 (7.1)
Response durability	**n=18**	**n=10**
Median DOR (95% CI), months	NE (4.0–NE)	NE (4.0–NE)
Responses with ≥3 months' duration (95% CI), %	93 (61–99)	100 (NE–NE)
Responses with ≥6 months' duration (95% CI), %	83 (46–96)	89 (43–98)

1. D'Angelo SP, et al. Efficacy and Safety of First-lineAvelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysisof a Clinical Trial. JAMA Oncol 2018 Sep 1;4(9):e180077;

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Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

Paul Nghiem, MD, PhD[1]; Shailender Bhatia, MD[1]; Evan J. Lipson, MD[2]; William H. Sharfman, MD[2]; Ragini R. Kudchadkar, MD[3]; Andrew S. Brohl, MD[4]; Phillip A. Friedlander, MD[5]; Adil Daud, MD[6]; Harriet M. Kluger, MD[7]; Sunil A. Reddy, MD[8]; Brian C. Boulmay, MD[9]; Adam I. Riker, MD[9]; Melissa A. Burgess, MD[10]; Brent A. Hanks, MD, PhD[11]; Thomas Olencki, DO[12]; Kim Margolin, MD[13]; Lisa M. Lundgren, MS[14]; Abha Soni, DO[2]; Nirasha Ramchurren, PhD[14]; Candice Church, PhD[15]; Song Y. Park, MD[15]; Michi M. Shinohara, MD[15]; Bob Salim, PhD[16]; Janis M. Taube, MD[2]; Steven R. Bird, MS[17]; Nageatte Ibrahim, MD[17]; Steven P. Fling, PhD[14]; Blanca Homet Moreno, MD, PhD[17]; Elad Sharon, MD, MPH[15]; Martin A. Cheever, MD[14]; and Suzanne L. Topalian, MD[2]

In this multicenter phase II trial (Cancer Immunotherapy Trials Network-09/Keynote- 017), 50 adults na¨ive to systemic therapy for aMCC received pembrolizumab (2 mg/kg every 3 weeks) for up to 2 years. Radiographic responses were assessed centrally per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

J Clin Oncol 37:693-702. 2019

- ORR to pembrolizumab was 56% (complete response [24%] plus partial response [32%]; 95% CI, 41.3% to 70.0%), with ORRs of 59% in virus-positive and 53% in virus-negative tumors.
- Median follow-up time was 14.9 months (range, 0.4 to 36.4+ months).
- Among 28 responders, median response duration was not reached (range, 5.9 to 34.5+ months).
- The 24-month PFS rate was 48.3%, and median PFS time was 16.8 months (95% CI, 4.6 months to not estimable).
- The 24-month OS rate was 68.7%, and median OS time was not reached.
- Although tumor viral status did not correlate with ORR, PFS, or OS, there was a trend toward improved PFS and OS in patients with programmed death ligand-1–positive tumors.
- Grade 3 or greater treatment-related adverse events occurred in 14 (28%) of 50 patients and led to treatment discontinuation in seven (14%) of 50 patients, including one treatment-related death.

J Clin Oncol 37:693-702. 2019

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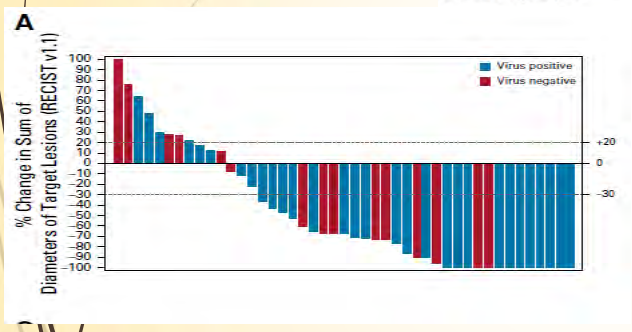
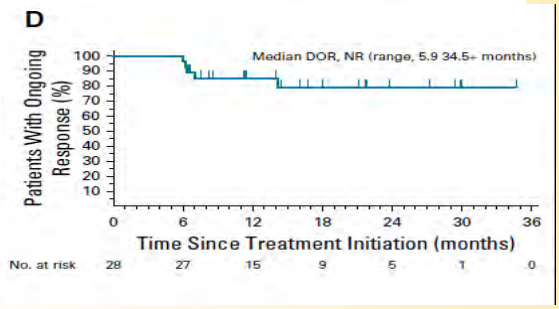




J Clin Oncol 37:693-702. 2019

In patients with aMCC receiving first-line anti– programmed cell death-1 therapy - Pembrolizumab demonstrated durable tumor control, a generally manageable safety profile, and favorable OS compared with historical data from patients treated with first-line chemotherapy.

J Clin Oncol 37:693-702. 2019

Nivolumab trial: CheckMate358 (NCT02488759)

N=500

Non-comparative, two-cohort, single-arm, open-label, Phase I/II study of nivolumab (BMS-936558) in subjects with virus-positive and virus-negative solid tumors

Tumor types: MCC, gastric or GEJ carcinoma, nasopharyngeal carcinoma, SCC of cervix, vagina or vulva, SCCHN

NEOADJUVANT COHORT
Nivolumab

METASTATIC COHORT
Nivolumab

PRIMARY ENDPOINT
Safety and tolerability, ORR in metastatic patients, surgery delay rate

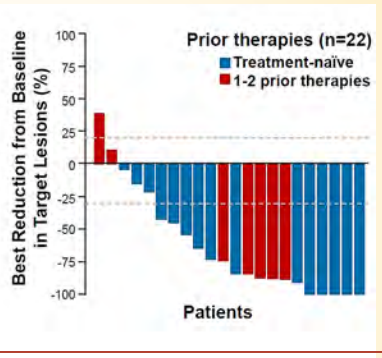
SECONDARY ENDPOINTS
Change in immune cells of viral-specific T-cells; change in immune activation/inhibitory molecules of viral-specific T-cells; PFS; OS

- NCT02488759. Available at: ClinicalTrials.gov (accessed December 2016).[51]

Nivolumab in 1L advanced MCC - Efficacy

RESPONSE*	(n=15)
ORR, % (95% CI)	**73 (45–92)**
CR, n (%)	7 (47)
PR, n (%)	4 (27)

*By RECIST v1.1, investigator assessed



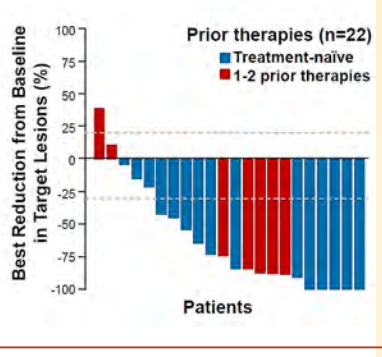
1. Topalian SL et al. AACR 2017. Abstract CT074 (presentation).

[52]

Nivolumab* in 2L+ - Efficacy

RESPONSE*	(n=10)
ORR, % (95% CI)	**50 (19–81)**
CR, n (%) PR, n (%)	10 (1) 40 (4)

*By RECIST v1.1, investigator assessed



1. Topalian SL et al. AACR 2017. Abstract CT074 (presentation).

Immunotherapy

- Phase II of the **JAVELIN Merkel 200** trial studied **Avelumab** in patients with **metastatic MCC** either as 1st line therapy[1] or in chemotherapy-refractory MCC[2-3]. In patients with no prior systemic therapy, after a median follow-up of 5.1 months (range 0.3-11.3 months), the overall response rate was 62.1%, and 83% of patients had a duration of response of at least 6 months[1]. In patients treated with avelumab after progression on chemotherapy, the overall response rate was 33.0% after a minimum follow up of 12 months. At the time of data cut-off, 72.4% of responses were ongoing[3]
- A different phase II trial studied patients with advanced MCC treated with pembrolizumab[4];

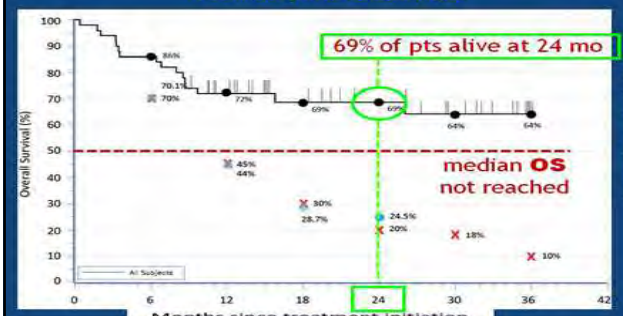
- after a median follow up of 33 weeks (range 7-53 weeks) the overall response rate was 56%, with a response duration ranging from 2.2-9.7 months.

- The ongoing **CHECKMATE 358** phase I/II trial is studying **nivolumab** in patients **with resectable MCC[5]**. In pts treated with nivolumab prior to surgery, 80% had tumour regression and 65% had a major pathologic response including 8 CR.

1.D'Angelo SP, et al. Efficacy and Safety of First-lineAvelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysisof a Clinical Trial. JAMA Oncol 2018 Sep 1;4(9):e180077; 2.Kaufman HL, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma:a multicentre, single-group, open-label, phase 2 trial.Lancet Oncol 2016 Oct;17(10):1374-1385; 3. Kaufman HL, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >/=1 year of follow-up: JAVELIN Merkel200, a phase 2 clinical trial. J Immunother Cancer 2018 Jan 17;6(1):x. 4.Nghiem PT, et al. PD-1 Blockade withPembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med 2016 Jun 30;374(26):2542-2552. 5.Topalian SL, Bhatia S, Kudchadkar RR, Amin A, Sharfman WH, Lebbe C, et al. Nivolumab (Nivo) as neoadjuvanttherapy in patients with resectable Merkel cell

Anti-PD-1/PD-L1 in advanced MCC: first-line or second-line (chemo-naïve or chemo-pretreated) ?

1st line (pembrolizumab)



Abstract #9506 (Paul Nghiem et al)

2nd line (avelumab) after previous chemo

Abstract #9507 (Paul Nghiem et al)

Anti PD-1/PD-L1 in advanced MCC

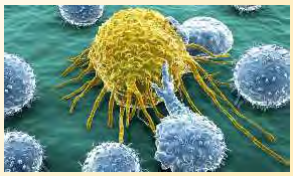
- **ORR** 1st line 56-73%
  2nd line 33-50%
- **PFS** 1st line 17 mo (median)
  2nd line 3 mo (median)
- **OS** 1st line median not reached
  2nd line 13 mo (median)

Summary MCC

- NMSC - the most common cancer
- Incidence is rising
- Numerous mutations in UV-induced cancer
- Surgery is a standard therapy for non-complicated cases
- Limited role of radiotherapy despite radiosensitivity in MCC
- anti-PD-1/PD-L1 should be applied as first-line treatment
- ChT should be postponed to 2nd line
- Previous ChT impairs outcome of anti-PD-1/PD-L1

Summary NMSC

- There is no clear benefit of chemotherapy
- Targeted therapy in BCC patched / SMOi is effective (RR 58%, CR 20-30%)
- Imunoterapies (PD-1 and PD-L1 antibodies) are effective in MCC and SCC, they also promise a great deal of potential for BCC



Our experience & interesting cases

Maša Sever, Janja Ocvirk

Onkološki inštitut
Institute of Oncology
Ljubljana

Vismodegib in Routine Clinical Practice in Slovenia

- Although basal cell carcinoma (BCC) is the most common malignancy among Caucasians, the incidence of advanced forms is relatively rare and therefore there is little data in the literature on treatment of locally advanced BCC (laBCC) or metastatic BCC (mBCC) by systemic therapy. Vismodegib is a Hh signaling pathway inhibitor and was approved by the European Medicines Agency for the treatment of adults with mBCC, or with laBCC inappropriate for surgery or radiotherapy.
- A retrospective analysis was conducted to provide vismodegib long-term efficacy and safety data in a real-world setting in Slovenia.

Methods

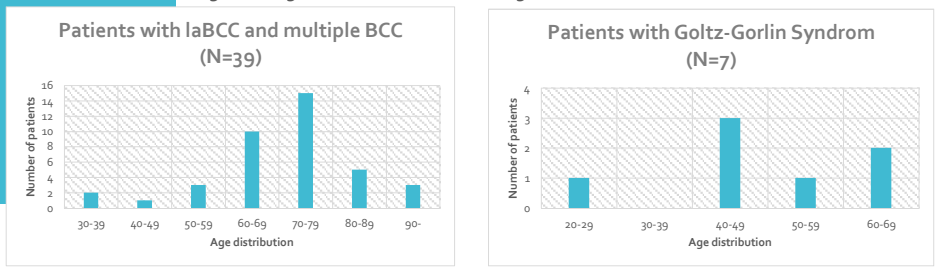
- Evaluation of efficacy and safety of vismodegib (V) was done in a retrospective analysis of patients (pts) with laBCC or multiple BCC and pts with Goltz-Gorlin Syndrom (G-G Syn) in routine clinical practice.
- Baseline characteristics, efficacy data and treatment-related adverse events (AEs) were collected from pts who were treated with V from November 2012 to January 2021.
- Efficacy was assessed by objective response rate - ORR (CR + PR), disease control rate - DCR (CR + PR + SD) and duration of vismodegib treatment – DoT. Reasons for treatment discontinuation were analyzed.

Results

Baseline characteristics

During the 100-month period, 46 pts were diagnosed with laBCC (26 pts), multiple BCC (13 pts) or G-G Syn (7 pts), all inappropriate for surgery or radiotherapy. Baseline characteristics: median age was 72.8 years in laBCC + multiple BCC pts group and 47.4 years in the G-G Syn pts group (Fig.1). Fifty-six percent of pts in laBCC +multiple BCC group were females; the majority (67%) of pts were previously treated by surgery and/or radiotherapy; 51% of pts had one lesion with predominant localization in the central face area (eyes, nose, lips, or ears in 76% of pts), 18% had 2-3 lesions, and 31% more than 3 lesions. Fifty-seven percent of pts in G-G Syn group were males; 86% of pts were previously treated with surgery and/or radiotherapy.

Figure 1. Age distribution at vismodegib treatment initiation



Efficacy results

- At the time of analysis in laBCC or multiple BCC group treatment has been interrupted during the treatment course in 23% of pts [in 8 out of 9 pts due to adverse events (AEs)], 31% of pts are still on treatment. In G-G Syn group treatment has been interrupted in 57% of pts (in most cases due to adverse events), 43% of pts are still on treatment. Efficacy data are presented in Table 1.

Table 1. Response to vismodegib treatment

Efficacy variable	laBCC + multiple BCC group (N=39)	G-G Syn group (N=7)
Investigator-assessed objective response rate (CR+PR); n, %	31 (80%)	6 (86%)
Investigator-assessed disease control rate (CR+PR+SD); n, %	37 (95%)	7 (100%)
Duration of treatment (months); median (range)	9.9 (1.5-43.1)	19.5 (3.6-94.1)

Safety results

- Serious adverse events were reported in 6 out of 46 patients (13.0%): two cases of squamous cell cancer, one case of angiosarcoma, melanoma, cholangiocarcinoma and intracerebral hemorrhage each, while one patient died due to other reasons than cancer. AEs of any grade were reported in 82% of pts in laBCC or multiple BCC group and 71% in G-G Syn group.
- The majority of AEs in laBCC or multiple BCC group were grade 1 or 2 (96%) and only 4% of AEs were grade 3: muscle cramps in 3 pts, respiratory infection, vomiting and anemia in 1 patient each. The majority of AEs in G-G Syn group were also grade 1 or 2 (87%), while 13% of AEs were grade 3: muscle cramps in 2 pts, weight loss and diarrhea in 1 patient each. No grade 4 or 5 vismodegib related AEs were reported.

Conclusion

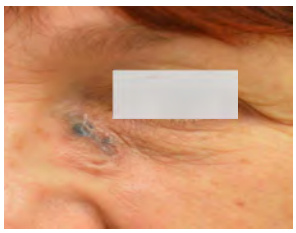
Vismodegib has shown meaningful long-term efficacy with manageable safety profile in pts with laBCC or multiple BCC as well as in pts with G-G Syn in real-world setting.

Clinical cases

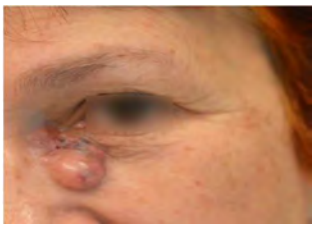
BCC

Case from OIL

19. 12. 2013



23. 9. 2013

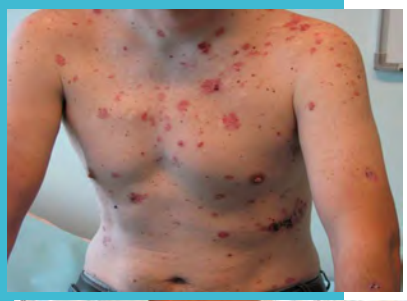


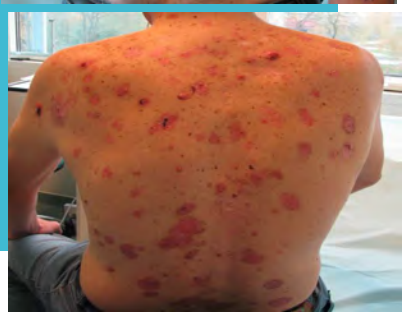
31. 7. 2014

Quick response to high-dose treatment
Side effects: alopecia gr. 2 after one year of treatment, increased CPK gr.1, muscle cramps gr.1

11

- 8. 11. 2012

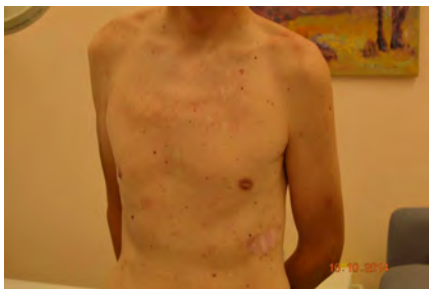


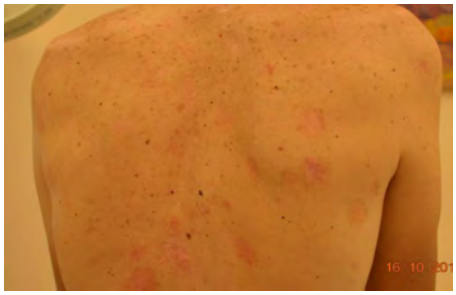


Patient with Gorlin syndrome (multiple BCC)

Side effects: alopecia gr.1 weight loss gr.2 increased CPK gr.1-3

- 16. 10. 2014



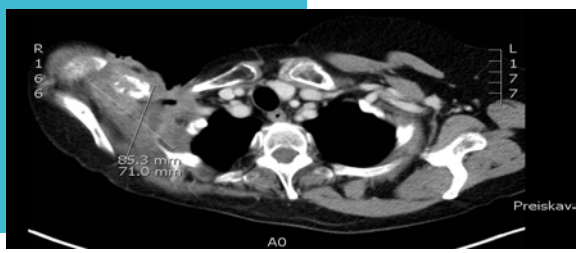


12

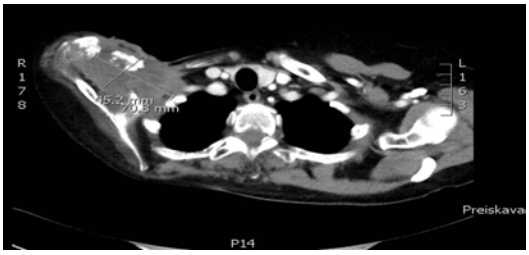
Case from OIL

Side effects: alopecia gr. 2, muscle spasms gr.2, change in taste gr.1

21.11.2013



25.9.2014



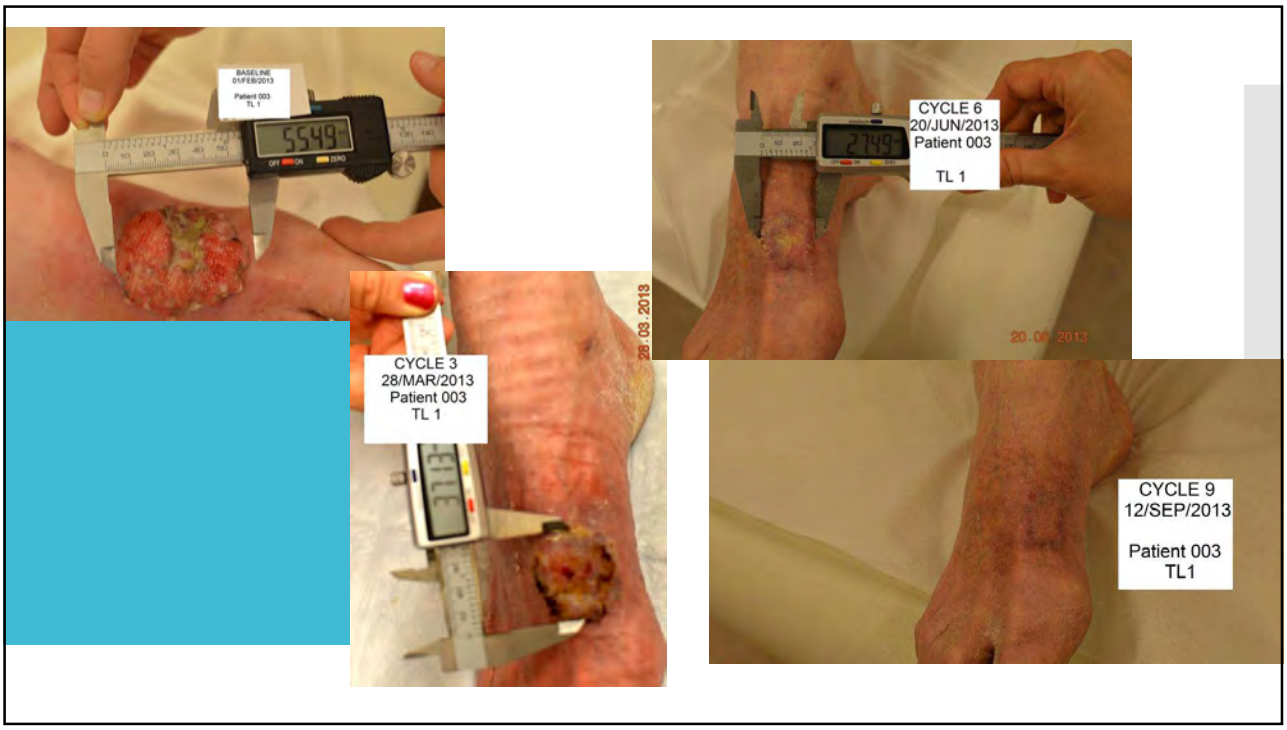
13

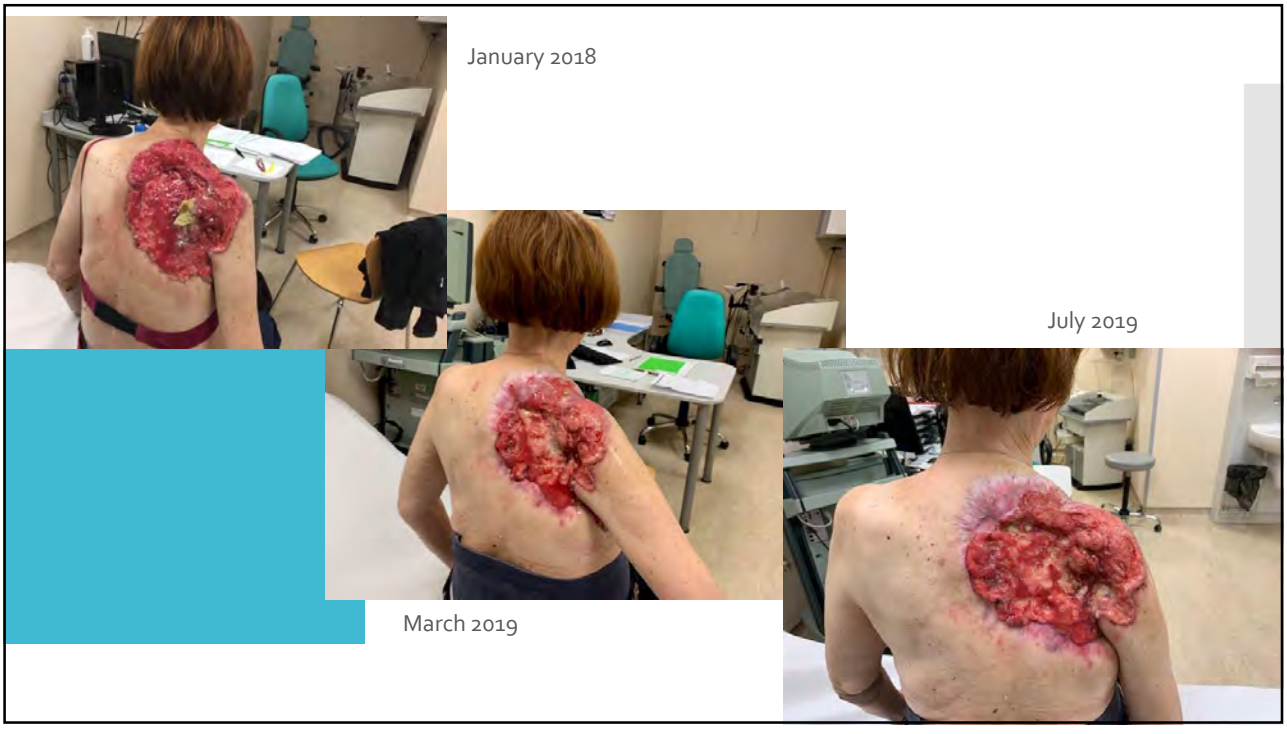
Man, 87 years old

History:
2001 – Multipl epiteliomas left leg
2001 – Malignant melanoma left leg/excision
2011 – BCC/SCC left leg/
excision, RT → ulcus
BCC right leg →
Not suitable for RT or excision

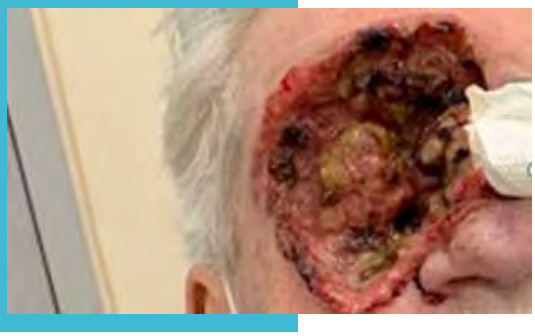
Others:
2003 – Nefrectomy
2006 – Deep vein thrombosis
2012 – Deep vein thrombosis
2012 – hypertension
therapy: varfarin and trandolapril since 2012

14

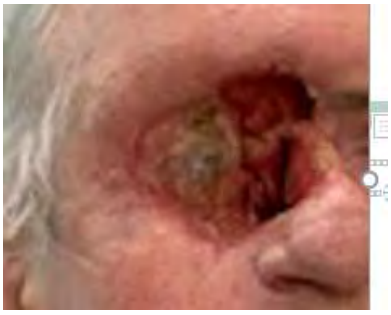

BASELINE
01/FEB/2013
Patient 003
TL 1
CYCLE 6
20/JUN/2013
Patient 003
TL 1
CYCLE 3
28/MAR/2013
Patient 003
TL 1
CYCLE 9
12/SEP/2013
Patient 003
TL1


January 2018
March 2019
July 2019

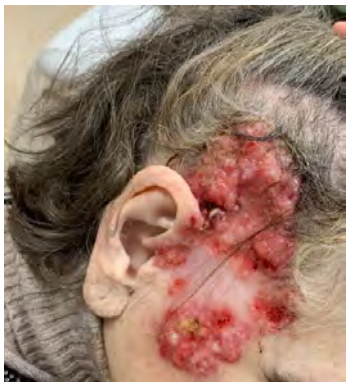
August 2020



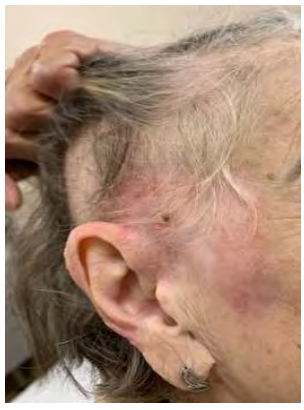
October 2020



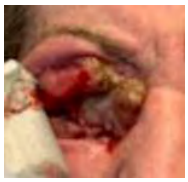
January 2020



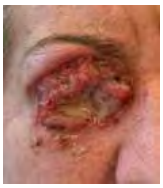
May 2020



BCC – 2 lines of treatment



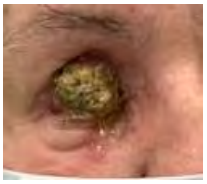
La BCC



After 3 m vismodegib

Progres on vismodegib, Start of immunotherapy

After 6 w of immunotherapy



After 3 m of immunotherapy

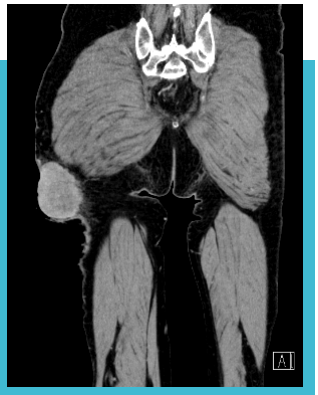
MCC Case October 2018

- October 2018
- Male 68-year-old, presented with bleeding tumor on right thigh, invasions in inguinal lymph nodes, obturator lymph nodes, right iliac lymph nodes
- Biopsy - MCC
- TMB decision: immunotherapy- avelumab

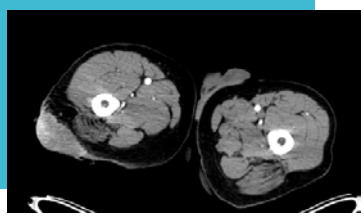
- before starting immunotherapy
- marked pain occurred
- bleeding from the tumor
- the surgeons decided for resection of a bleeding tumor on the thigh
- complication of treatment for sepsis, wound dehiscence
- he was recovering from complications of surgical treatment in January 2019

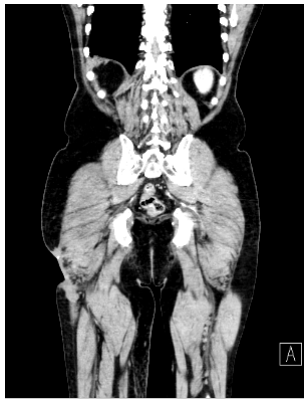
January 2019

- referred to medical oncologist
- the patient also has rheumatoid arthritis on methotrexate therapy
- highly motivated for immunotherapy treatment
- he began with immunotherapy (Avalumab) in January 2019
- CT scan in April 2019 - PRCT
- scan in July 2019 – further response
- CT scan in october 2019 - borderline enlarged lymph node left inguinal, no other evident residum of the disease
- Stop immunotherapy due to AE in March 2020

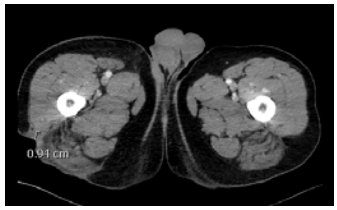


16.10.2018



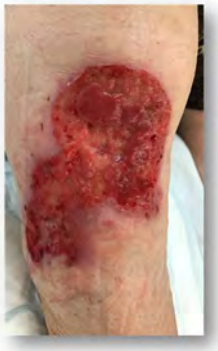


27.8.2019



SCC

11.10.2020

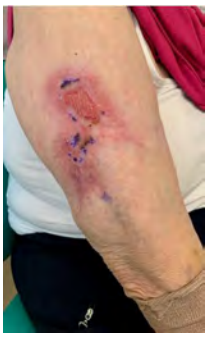


Start treatment with cemiplimab

2.11.2020

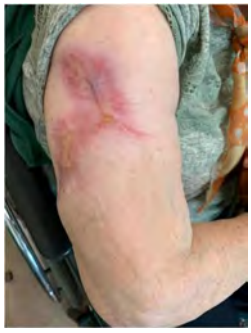
After 1 application

22.2.2021



After 2 appl and post COVID pneumonia

7.6.2021



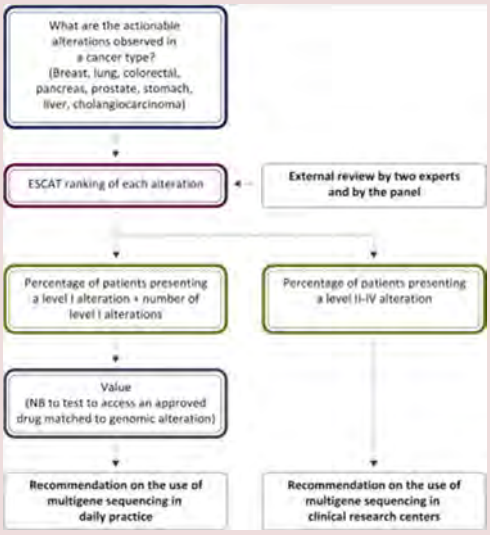
CR confirmed with biopsy

Thank you for your attention

NEXT-GENERATION SEQUENCING

Assist. Prof. Tanja Mesti, MD., PhD
2nd Summer school
7 September 2021

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group



- ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)
- Advanced lung carcinoma
- Metastatic prostate cancer
- Metastatic ovarian cancer
- Metastatic cholangiocarcinoma

*cancer types without clear standard-of-care options, such as carcinoma of unknown primary and other rare tumors

Annals of Oncology 2020 311491-1505DOI: (10.1016/j.annonc.2020.07.014)

CONCLUSION

- ESMO Guidelines
- NGS consilium - subgroup of patients with advanced cancer and no standard therapeutic options.

Systemic treatment of gastric carcinoma

Marko Boc, MD
Department for Medical Oncology
Institute of Oncology Ljubljana

Ljubljana, 08.09.2021

LOCALLY ADVANCED GASTRIC CARCINOMA

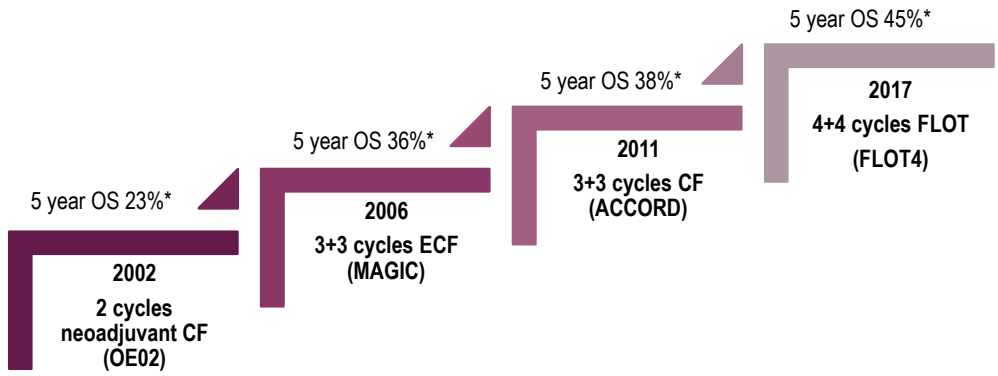
NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY

- Downstage the tumour
- Increase R0 resection rate
- Treat micrometastatic disease
- Improve overall survival

Neoadjuvant and perioperative chemotherapy is more commonly used in non-Asian countries where tumours are frequently locally advanced and require downstaging prior to successful resection

LOCALLY ADVANCED GASTRIC CARCINOMA

NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY



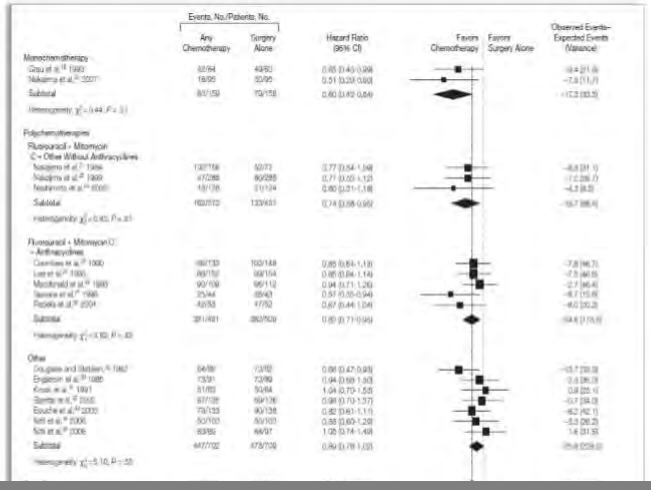
*chemotherapy patients; CF, cisplatin + 5-fluourouracil; ECF epirubicin + CF; FLOT. 5-fluororuraci, leucovorin, oxaliplatin, docetaxel

1. OE02 Trial Group, Lancet 2002.
2. Cunningham D, *et al.* N Engl J Med 2006.
3. Ychou M, *et al.* J Clin Oncol. 2011.
4. Al-Batran S, *et al.* Lancet 2019.

LOCALLY ADVANCED GASTRIC CARCINOMA

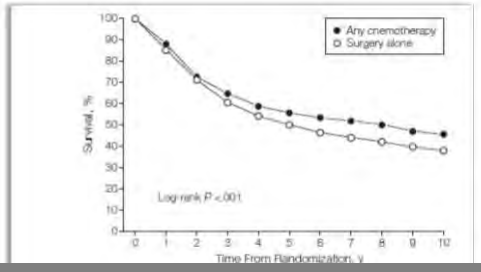
ADJUVANT CHEMOTHERAPY FOR NON-ASIAN PATIENTS

ADJUVANT CHEMOTHERAPY



Neoadjuvant or peri-operative chemotherapy is preferred due to the downstaging effects associated with this.

The GASTRIC group meta-analysis suggests a 5.8% absolute OS benefit at 5 years (55.3% to 49.6%) for patients treated with adjuvant chemotherapy .



Although non-Asian adjuvant gastric cancer trials have not shown a survival benefit, this metanalysis can be used to justify use of adjuvant chemotherapy in non-Asian patients

Paolettiet al, JAMA. 2010 May 5;303(17):1729-37.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab[a] should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma
  (See Principles of Pathologic Review and Biomarker Testing [GAST-B])
  - Combination with fluoropyrimidine and platinum (category 1 in combination with cisplatin;[11] category 2A in combination with other platinum agents)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[12-14]
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and cisplatin[12, 15-17]

Other Recommended Regimens
- Fluorouracil[c,f] and irinotecan[18]
- Paclitaxel with cisplatin or carboplatin[19-21]
- Docetaxel with cisplatin[22,23]
- Fluoropyrimidine[16,24,25] (fluorouracil[c] or capecitabine)
- Docetaxel[26,27]
- Paclitaxel[28,29]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[c,30]
  - Docetaxel, oxaliplatin, and fluorouracil[31]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[32]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]
- ECF modifications (category 2B)[34,35]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

mOS: 8-11m
mPFS: 4.8-6.2m

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[36]
- Docetaxel (category 1)[26,27]
- Paclitaxel (category 1)[28,29,37]
- Irinotecan (category 1)[37-40]
- Trifluridine and tipiracil (category 1)[41]
  - For third-line or subsequent therapy
- Fluorouracil[c,f] and irinotecan[38,42,43]
- Pembrolizumab[g]
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[44,45]
  - For third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1[h,46]

Other Recommended Regimens
- Ramucirumab (category 1)[47]
- Irinotecan and cisplatin[13,48]
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Docetaxel and irinotecan (category 2B)[51]

Useful in Certain Circumstances
- Fluorouracil and irinotecan + ramucirumab (category 2B)[c,f,52]

2nd Summer School in medical oncology – Precision oncology – Are we there yet

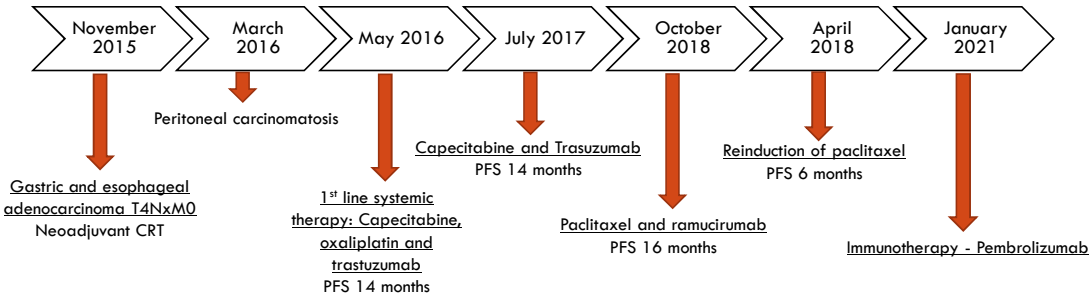
CLINICAL CASE

GASTRIC CANCER

Ana Erman, dr. med.
Mentor: doc. dr. Tanja Mesti, dr. med.

Ljubljana, 8.9.2021

SUMMARY



SUMMARY

- HER2, MSI and NTRK testing
- If sufficient tissue: NGS
- Pembrolizumab for MSI-H/dMMR tumors or TMB-high (≥10 mutations/megabase) tumors

Systemic treatment of the Biliary tract cancer (BTC)– where we stand

Summer School, 8th September 2021

assist.prof. Martina Reberšek, MD, PhD

Current recommendations for systemic treatment of metastatic disease

Systemic chemotherapy:

- 1st line: gemcitabine + cisplatin (PS ECOG 0-1), gemcitabine mono (PS ECOG 2)
- 2nd line: mFOLFOX or new standard option Nal-IRI+5FU/LV

Immunotherapy:

- 1st line: MSI-H/dMMR → pembrolizumab
- 2nd line: nivolumab, MSI-H/dMMR/TMB-H → pembrolizumab

Targeted therapy

- 1st line: positive *NTRK* fusion gene →larotrectinib, entrectinib
- 2nd line:

→positive *NTRK* fusion gene → larotrectinib, entrectinib

→ mt *BRAF* V600 → dabrafenib+trametinib

→ mt *IDH1* → ivosidenib

→*FGFR2* fusions or rearrangements → pemigatinib

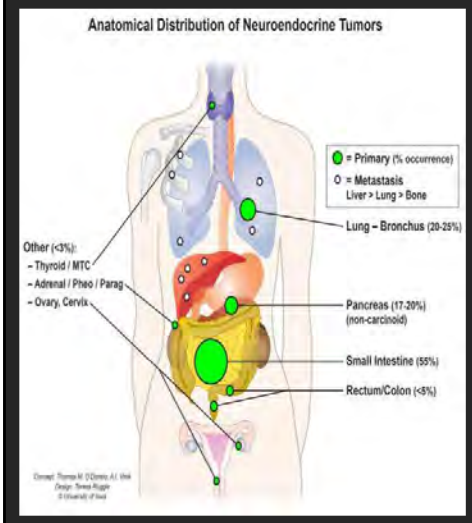
How to approach GEP NET & NEC

MARIJA IGNJATOVIĆ.

2ND SUMMER SCHOOL IN MEDICAL ONCOLOGY

08.09.2021

NEUROENDOCRINE NEOPLASMS (NENs)



- Heterogeneous group of malignancies ► **arise from neuroendocrine cells** ► release of catecholamines and hormones
- **Rare malignancies**
  - Less then 0.5% of all malignancies, only 1%-2% of gastrointestinal malignancies
  - **Growing incidence**, especially of localized and regional NENs
  - **EUR 1.33 – 2.33/100.000**; USA: 3.56/100.00
  - **men > women**, men have adverse outcome
- **Sporadic**/hereditary
  - Younger then < 40 with gastrinoma
  - Multiple neuroendocrine neoplasia (MEN)
  - Family history of NENs

CLASSIFICATION OF GASTROENTEROPANCREATIC NEOPLASMS (GEP-NENs)

FIRST MORPHOLOGY
Well-differentiated & poorly-differentiated

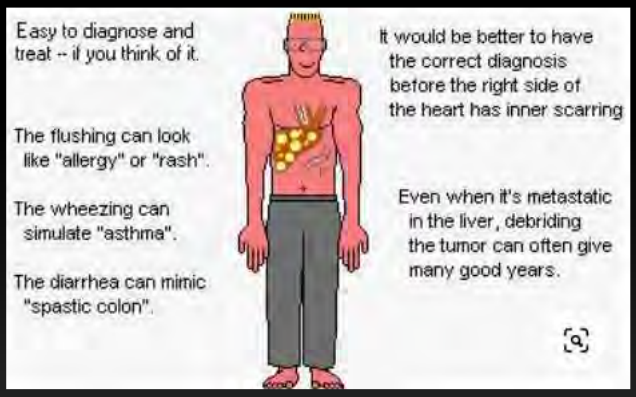
THEN KI67
Grade1/2/3

WHO 2019				
MORPHOLOGY	GRADE	MITOTIC INDEX (2 mm²)	KI 67 (%)	
WELL DIFFERENTIATED	G1	<2	<3	*Neuroendocrine tumors (NET)*
	G2	2-20	3-30	
	G3	>20	>20	
POORLY DIFFERENTIATED	G3	>20	>20	*Neuroendocrine carcinomas (NEC)*
				MiNEN

GASTROENTEROPANCREATIC NEOPLASMS (GEP-NENs)

GEP-NET ► 80% - 90%

GEP-NEC ► 10% - 20%



YOUR PATIENTS MIGHT BE
(A)SYMPTOMATIC

DIAGNOSIS

HYSTOPATHOLOGY
- *Morphology*
- *Grade*
- *IHC*

STAGING

PET CT with GALLIUM 68/SRS
FDE-PETCT
MRI
CT

MANAGEMENT OF PATIENTS WITH LOCAL & LOCOREGIONAL GEP NETs

SURGERY

MANAGEMENT OF PATIENTS WITH LOCAL & LOCOREGIONAL GEP NECs

The role of surgery for localised Pan-NEC G3 is still controversial, as upfront surgery may not have a clear benefit in terms of survival.[37]

Adjuvant therapy

There are no data to support adjuvant therapy in NET G1/G2, as data from prospective randomised clinical trials (RCTs) are lacking [IV, A]. However, in aggressive NENs (NEC G3), adjuvant therapy with platinum-based chemotherapy (ChT) can be considered [V, C]. Prospective clinical trials are warranted.

MANAGEMENT OF PATIENTS WITH METASTATIC GEP NET

SURGERY

SYSTEMIC TREATMENT

Systemic treatment and mGEP-NETs

- CONTROL OF HORMONAL OVERPRODUCTION
- CONTROL OF TUMOUR GROWTH

MENAGMENT OF PATIENTS WITH mGEP NEC

- *SYSTEMIC TREATMENT*

How to approach NET/NEC

Our experience – clinical case

Katja Leskovšek, dr. med.
prof. dr. Janja Ocvirk, dr. med.

Institute of Oncology Ljubljana,
08.09.2021

D.N., female, 54y

- **On presentation, Nov 2005**
  - 6 months of diarrhoea, loss of weight (10 kg).
    - Family history: positive.
    - Past medical history: asthma (2003), discus hernia L4-5 op. (1999).
    - PS ECOG 1.
    - Therapy: Symbicort.
    - Alergies: ketoprofen.
  - US: 3 liver metastases ⟶ Core needle biopsy: **NEC** metastases; origo ignota.
  - Laparotomy (Sept 2005): tumor of distal pancreas, invading spleen
    - Distal pancreatectomy and splenectomy, resection of IV. and V. liver segment, cholecystectomy.

D.N., female, 54y

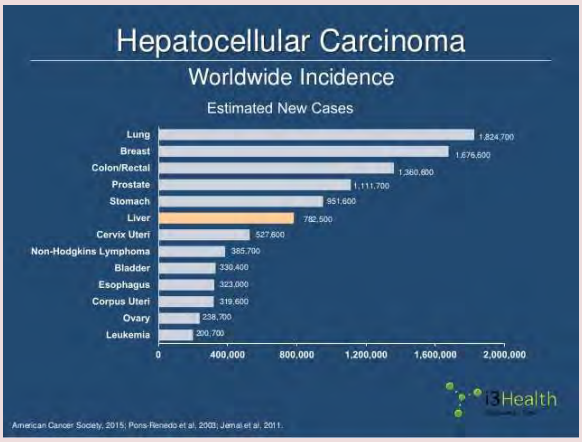
- Histopathology report: **NEC of pancreas**, invading retroperitoneal fat, hilum of spleen, vascular, peri- and intraneural invasion, lymphangiosis carcinomatosa; lymph node status 3/5.
- R1 resection.
- Somatostatin: 10 %.
- Partial liver resection: metastasis of endocrine carcinoma.

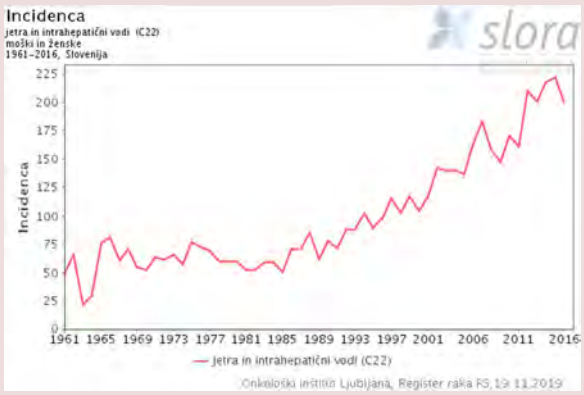
Discussion

- NEC of pancreas, liver metastasis, R1.
- On treatment for 15 years.
- Systemic therapy:
  - I. line ChT: etoposide + cisplatin;
  - II. line ChT: 5-FU + dacarbazine + epidoxorubicin;
  - 3 x partial liver resection/metastasectomy (12', 13', 13');
  - III. line: lanreotide;
  - IV. line: lanreotide + everolimus;
  - V. line: octreotide + sunitinib;
  - 6 x TACE (19', 20', 21');
- PRRT ?

HCC – LOTS HAS BEEN GOING ON

Janja Ocvirk





HCC

The **fourth most common** cause of cancer-related death worldwide[1]

HCC accounts for **>80% of primary liver cancers** worldwide[1]

Chronic HBV and HCV infection are the most important causes of HCC and account for 80% of HCC cases globally[1]

It is estimated that **72% of cases occur in Asia** (more than 50% in China)[2]

Staging of HCC is important to determine outcome and planning of optimal therapy. While there are a number staging systems used, the **BCLC is currently commonly used to compare clinical outcomes**:[3]

- BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; TACE, transarterial chemoembolisation

1. Yang JD, et al. Nat Rev Gastroenterol Hepatol. 2019;16:589-604
2. Singal AG, et al. J Hepatol. 2020;72:250-61
3. Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019;16:617-30

BCLC Staging System

BCLC Staging

BCLC Stage		ECOG PS	Tumor Size/Number, Vascular Involvement, Etc	Child-Pugh Score
0	Very early	0	Solitary <2 cm nodule	A
A	Early	0	Solitary <5 cm nodule or up to 3 nodules each ≤3 cm	A - B
B	Intermediate	0	Large/multinodular	A - B
C	Advanced	1-2	Portal venous invasion and/or extrahepatic spread (N+ or M+)	A - B
D	Terminal	>2	Any of the above	C

BCLC – Barcelona Clinic Liver Cancer; ECOG PS – Eastern Cooperative Oncology Group performance status.
Llovet et al. 1999.

i3Health

Table 2. Child Pugh Turcotte (CTP) Score

Parameters	Points 1	2	3
Serum Bilirubin(mg/dl)	2.0	2-3	>3.0
Serum Albumin(g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin Time (Prolongation (s))	1-4	5-6	>6
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	None	Slight	Moderate

One and two year survival based on CTP Score

Class	1 yr	2 yr
A (5-6 points)	100 %	85 %
B (7-9 points)	80%	60%
C (10-15 points)	45%	35%

Data from Child CG, Turcotte JG.Surgery and portal hypertension. In: Child CG. The liver and portal hypertension. Philadelphia: Saunders; 1964.p.50-64

HCC

	BCLC staging	Survival rate with current therapy	Standard of care treatment
Early and intermediate HCC	Stage 0-A	>5 years	Ablation, resection, transplantation
	Stage B	>2.5 years	Chemoembolisation (TACE)
Advanced HCC	Stage C	>1 year	Systemic therapy
	Stage D	3 months	Best supportive care

- BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; TACE, transarterial chemoembolisation

1. Yang JD, et al. Nat Rev Gastroenterol Hepatol. 2019;16:589-604
2. Singal AG, et al. J Hepatol. 2020;72:250-61
3. Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019;16:617-30

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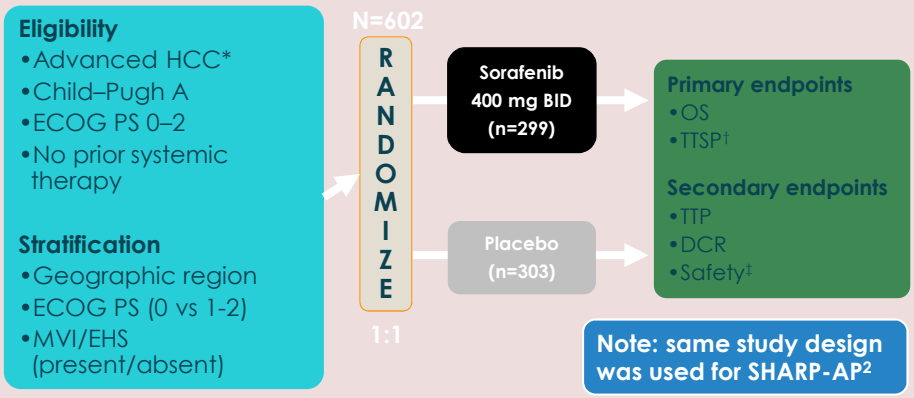
1L FOR ADVANCED HCC PATIENTS

Phase 3 SHARP trial of sorafenib vs placebo: study design[1]



*Not eligible for, or had disease progression after surgical or locoregional therapies.
†Assessed by the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8 (FSHI-8).
‡Assessed using version 3.0 of the USA National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).
BID, twice daily; DCR, disease control rate; EHS, extrahepatic spread; MVI , macroscopic vascular invasion; OS, overall survival; TTP, time to treatment progression; TTSP, time to symptomatic progression.
1. Llovet JM et al. N Engl J Med. 2008;359(4):378-390; 2. Cheng A et al. Lancet Oncol 2009;10:25–34.

SHARP: Baseline Patient Characteristics

Characteristic	Sorafenib (n = 299)	Placebo (n = 303)
Median age, yrs	65	66
Male, %	87	87
Etiology, %		
▪ HBV	19	18
▪ HCV	29	27
▪ Alcohol only	26	26
▪ Other	9	10
Previous therapies, %		
▪ Surgical resection	19	21
▪ Locoregional therapies	29	30

BCLC stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%) in sorafenib and placebo respective

SHARP - efficacy data

Efficacy parameter	Sorafenib (n=299)	Placebo (n=303)	P-value	HR (95% CI)
Median OS, months (95% CI)	10.7 (9.4-13.3)	7.9 (6.8-9.1)	0.00058	0.69 (0.55-0.87)
Median TTP, months (95% CI)	5.5 (4.1-6.9)	2.8 (2.7-3.9)	0.000007	0.58 (0.45-0.74)

1. Llovet JM et al. N Engl J Med. 2008;359(4):378-390;

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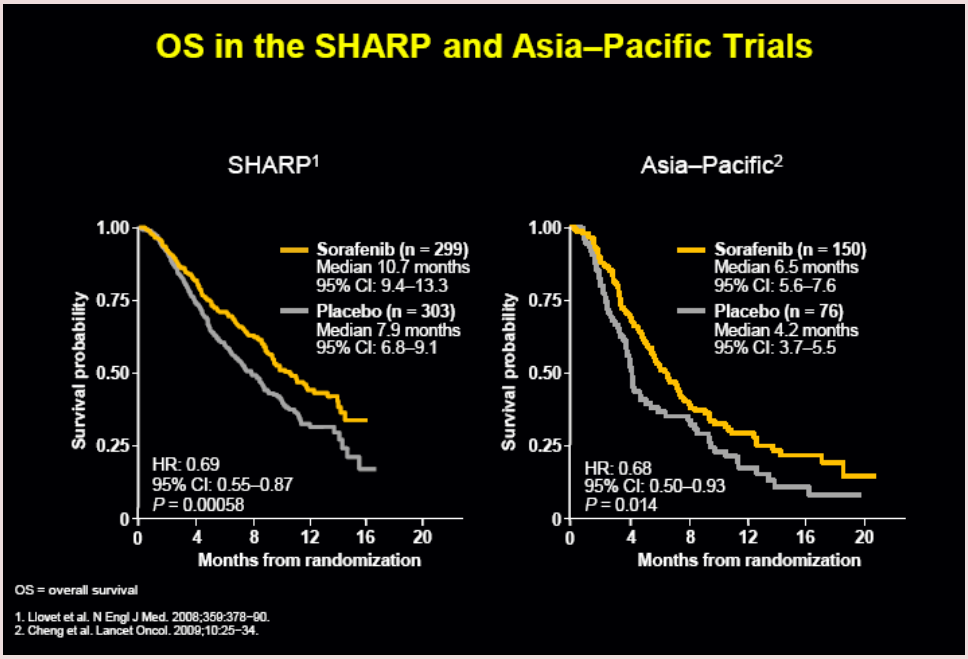
SHARP: sorafenib is generally well tolerated in advanced HCC

Adverse event*	Incidence by grade (%) (N=297)	
	Any grade	Grade 3/4
Diarrhoea	39	8†
Fatigue	22	4
HFSR	21	8†
Rash/desquamation	16	1†
Anorexia	14	<1†
Abdominal pain	8	2†
Liver dysfunction	<1	<1†
Nausea	11	<1†
Vomiting	5	1†
Weight loss	9	2†
Hypertension	5	2†

*Defined by NCI CTC (version 3.0) that occurred in at least 5% of patients; †No grade 4 events reported.
HFSR, hand–foot skin reaction.
Llovet JM et al. N Engl J Med 2008;359:378–90; EASL–EORTC Clinical Practice: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–43; Verslype C et al. ESMO guidelines. Ann Oncol 2012;23(Suppl 7):vii41–8.



Data from SHARP and real-world practice support use of sorafenib in intermediate HCC

SHARP[1] BCLC-B subgroup	• **Increased OS and TTP with sorafenib (n=54) vs placebo (n=51)** – Median OS: 14.5 vs 11.4 months (HR: 0.72; 95% CI: 0.38–1.38) – Median TTP: 6.9 vs 4.4 months (HR: 0.47; 95% CI: 0.23–0.96)
SHARP[1] previous TACE subgroup	• **Increased OS and TTP with sorafenib (n=86) vs placebo (n=90)** – Median OS: 11.9 vs 9.9 months (HR: 0.75; 95% CI: 0.49–1.14) – Median TTP: 5.8 vs 4.0 months (HR: 0.57; 95% CI: 0.36–0.91)
SOFIA[2]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 20.6 vs 8.4 months
INSIGHT[3]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 19.6 vs 14.5 months
GIDEON interim analysis[4]	• **Similar safety profile for sorafenib across BCLC stages**

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; TTP, time to progression

1. Bruix J et al. J Hepatol. 2012;57:821–9; 2. Iavarone M et al. Hepatology 2011;54:2055–63; 3. Ganten TM et al. EMSO 2012;poster 77;
4. Lencioni R et al. Eur J Cancer 2011;47 (Suppl 1):abstract 6500

Lenvatinib - REFLECT

REFLECT (NCT01761266): phase 3, international, multicentre, open-label, randomised study in 954 patients with hepatocellular carcinoma

Non inferiority assessment of lenvatinib vs. sorafenib for OS

Primary endpoint: OS

Secondary endpoints: PFS, ORR (mRECIST and RECIST v1.1)

Population enrolled: BCLC stage B: 20%; stage C: 80%

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; mRECIST, modified RECIST;
ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours
Sources: lenvatinib summary of product characteristics dated June 2020; lenvatinib US prescribing information dated February 2020

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Efficacy parameters	Lenvatinib N=478	Sorafenib N=476
Overall survival		
Number of deaths (%)	351 (73)	350 (74)
Median OS in months (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)
Hazard ratio (95% CI)	0.92 (0.79-1.06)	
Progression-free survival (mRECIST)		
Number of events (%)	311 (65)	323 (68)
Median PFS in months (95% CI)	7.3 (5.6-7.5)	3.6 (3.6-3.7)
Hazard ratio (95% CI) and P-value	0.64 (0.55-0.75); <0.001	
Objective response rate (mRECIST)		
Objective response rate	41%	12%
Complete responses, n (%)	10 (2.1)	4 (0.8)
Partial responses, n (%)	184 (38.5)	55 (11.6)
95% CI	(36-45)	(10-16)
P-value	<0.001	
Progression-free survival (RECIST 1.1)		
Number of events (%)	307 (64)	320 (67)
Median PFS in months (95% CI)	7.3 (5.6-7.5)	3.6 (3.6-3.9)
Hazard ratio (95% CI)	0.65 (0.56-0.77)	
Objective response rate (RECIST 1.1)		
Objective response rate	19%	7%
Complete responses, n (%)	2 (0.4)	1 (0.2)
Partial responses, n (%)	88 (18.4)	30 (6.3)
95% CI	(15-22)	(4-9)

- BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; mRECIST, modified RECIST;
  ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours
- Sources: lenvatinib summary of product characteristics dated June 2020; lenvatinib US prescribing information dated February 2020

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Sorafenib and lenvatinib safety data in HCC patients

Most common adverse reactions (≥20%)	
sorafenib-treated patients in SHARP trial	Diarrhoea – fatigue – hand-foot skin reaction – weight loss – anorexia – nausea – abdominal pain
lenvatinib-treated patients in REFLECT trial	Hypertension – fatigue – diarrhoea – decreased appetite – arthralgia/myalgia – decreased weight – abdominal pain – palmar-plantar erythrodysesthesia syndrome – proteinuria – dysphonia – haemorrhagic events – hypothyroidism – nausea

- Sources: sorafenib SmPC; lenvatinib SmPC

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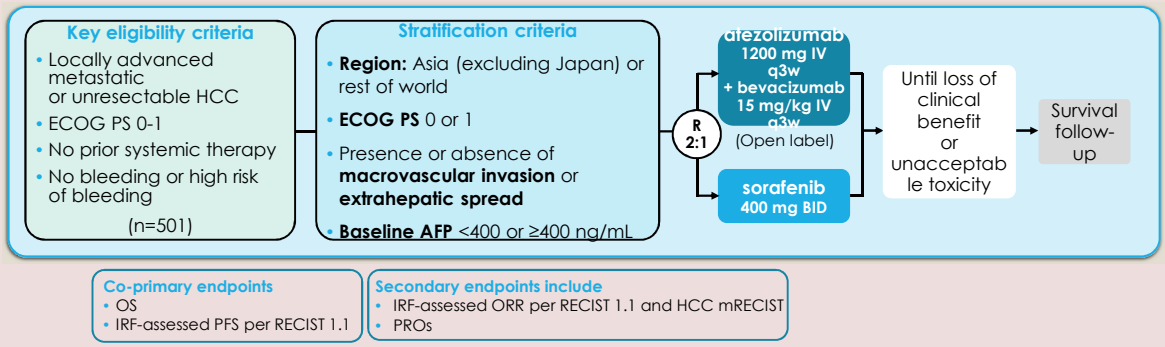
IMbrave150 clinical trial



AFP, alpha-fetoprotein; BID, twice a day; ECOG PS; Eastern Cooperative Oncology Group performance status; HCC; hepatocellular carcinoma; IRF, independent review facility; IV, intravenous; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumours; VEGF, vascular endothelial growth factor

Finn RS, et al. N Engl J Med. 2020;382:1894-905

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IMbrave150 clinical trial
Efficacy results: primary endpoints

	atezolizumab + bevacizumab (n=336)	sorafenib (n=165)
Median OS (95% CI), months	NE	13.2 (10.4–NE)
OS, HR (95% CI)	0.58 (0.42–0.79)	
P-value	<0.001	
Median PFS (95% CI) per IRF RECIST v1.1, months	6.8 (5.7–8.3)	4.3 (4.0–5.6)
PFS, HR (95% CI)	0.59 (0.47–0.76)	
P-value	<0.001	

- Finn RS, et al. N Engl J Med. 2020;382:1894-905

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IMbrave150 clinical trial
Efficacy results: secondary endpoints

	atezolizumab + bevacizumab (n=326)	sorafenib (n=159)
Confirmed ORR per IRF RECIST v1.1, % (95% CI)	27.3 (22.5–32.5)	11.9 (7.4–18.0)
P-value	<0.001	

	atezolizumab + bevacizumab (n=325)	sorafenib (n=158)
Confirmed ORR per HCC specific mRECIST, % (95% CI)	33.2 (28.1–38.6)	13.3 (8.4–19.6)
P-value	<0.001	

- Finn RS, et al. N Engl J Med. 2020;382:1894-905

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IMbrave150 clinical trial - safety results

Variables, n (%)	atezolizumab + bevacizumab (n=329)	sorafenib (n=156)
Patients with an AE from any cause	323 (98.2)	154 (98.7)
Grade 3-4 AEs (numbers represents the highest grades assigned)	186 (56.5)	86 (55.1)
Grade 5 AEs	15* (4.6)	9** (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
AEs leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
AEs leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	–	58 (37.2)

*Grade 5 events in the atezolizumab–bevacizumab group: gastrointestinal haemorrhage (in 3 patients), pneumonia (in 2 patients), empyema, gastric ulcer perforation, abnormal hepatic function, liver injury, multiple-organ dysfunction syndrome, oesophageal varices haemorrhage, subarachnoid haemorrhage, respiratory distress, sepsis, and cardiac arrest (in 1 patient each)

**Grade 5 events in the sorafenib group: death (in 2 patients), hepatic cirrhosis (in 2 patients), cardiac arrest, cardiac failure, general physical health deterioration, hepatitis E, and peritoneal haemorrhage (in 1 patient each)

- AEs, adverse events
- Finn RS, et al. N Engl J Med. 2020;382:1894-905

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IMbrave150 clinical trial - conclusion

- IMbrave150 demonstrated a **statistically significant improvement in OS and PFS with atezolizumab + bevacizumab versus sorafenib** in the first-line setting in patients with advanced HCC
- Times to response were similar in the combination and sorafenib arms
- **Response rates were significantly higher** in the combination arm
- The trial was conducted in a patient population that had preserved liver function (Child–Pugh class A) and a decreased risk of variceal bleeding. **The safety** of the combination in a **broader population warrants further study**

Finn RS, et al. N Engl J Med. 2020;382:1894-905

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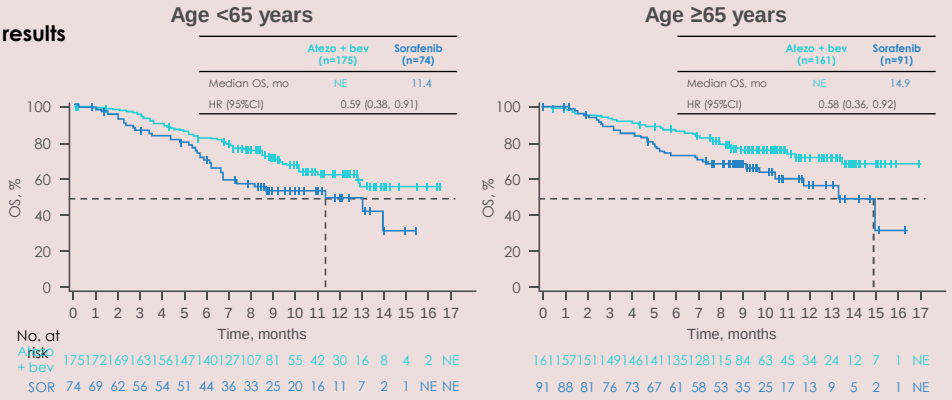
Atezolizumab + bevacizumab vs sorafenib for unresectable hepatocellular carcinoma (HCC): Results from older adults enrolled in IMbrave150

Key results

Overall survival



Li D, et al. Ann Oncol 2020;31(suppl):abstr O-8

Atezolizumab + bevacizumab vs sorafenib for unresectable hepatocellular carcinoma (HCC): Results from older adults enrolled in IMbrave150

AEs occurring in ≥15% of patients treated with atezolizumab + bevacizumab, n (%)	<65 years (n=171)	≥65 years (n=158)
Hypertension	47 (27)	51 (32)
Fatigue	24 (14)	43 (27)
Diarrhoea	28 (16)	34 (22)
Appetite decreased	26 (15)	32 (20)
Pyrexia	29 (17)	30 (19)
Pruritus	35 (20)	29 (18)
Proteinuria	39 (23)	27 (17)
AST increased	39 (23)	25 (16)

Conclusions

- **In older patients (≥65 years) with unresectable HCC, atezolizumab + bevacizumab demonstrated clinically meaningful benefits with no significant additional toxicities**

Li D, et al. Ann Oncol 2020;31(suppl):abstr O-8

CheckMate 459: long-term efficacy outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma – Sangro B, et al

Study objective

- To evaluate the long-term efficacy and safety of nivolumab as a 1L treatment for patients with advanced HCC

Key patient inclusion criteria

- Advanced HCC
- Ineligible for surgery and/or for loco-regional therapy or PD after surgery and/or loco-regional therapy
- Child-Pugh class A
- Systemic therapy naïve
- ECOG PS 0–1

(n=743)

R 1:1

Nivolumab 240 mg iv q2w (n=371) → PD/ toxicity

Sorafenib 400 mg po bid (n=372) → PD/ toxicity

Stratification

- Aetiology (HCV vs. non-HCV)
- Vascular invasion and/or extrahepatic spread (present vs. absent)
- Geography (Asia vs. non-Asia)

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- ORR, PFS, efficacy by PD-L1 status, safety

Sangro B, et al. Ann Oncol 2020;31(suppl):abstr LBA-3

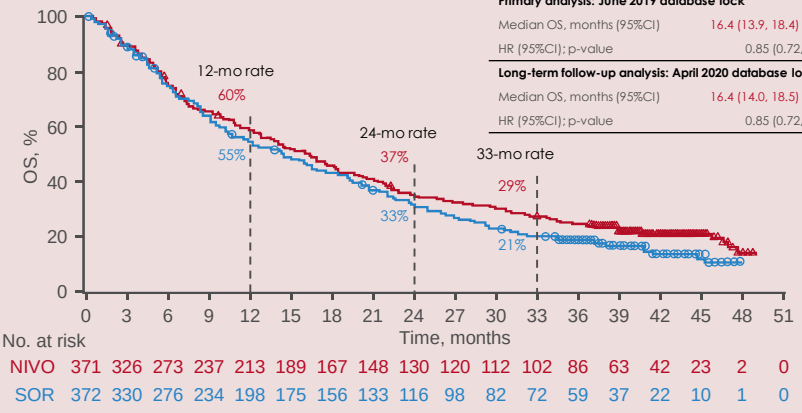
This talk was presented at the 22nd ESMO WCGC on 1 July 2020 at 18:20

CheckMate 459: long-term efficacy outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma – Sangro B, et al

Overall survival

Key results

	Nivolumab (n=371)	Sorafenib (n=372)
Primary analysis: June 2019 database lock		
Median OS, months (95%CI)	16.4 (13.9, 18.4)	14.7 (11.9, 17.2)
HR (95%CI); p-value	0.85 (0.72, 1.02); 0.0752	
Long-term follow-up analysis: April 2020 database lock		
Median OS, months (95%CI)	16.4 (14.0, 18.5)	14.8 (12.1, 17.3)
HR (95%CI); p-value	0.85 (0.72, 1.00); 0.0522	



No. at risk

NIVO	371	326	273	237	213	189	167	148	130	120	112	102	86	63	42	23	2	0
SOR	372	330	276	234	198	175	156	133	116	98	82	72	59	37	22	10	1	0

Sangro B, et al. Ann Oncol 2020;31(suppl):abstr LBA-3

CheckMate 459: long-term efficacy outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma – Sangro B, et al

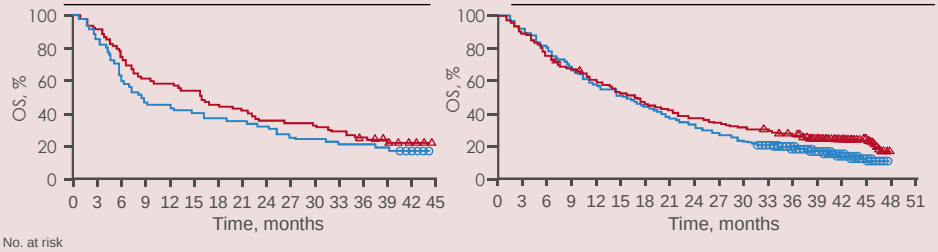
Overall survival by PD-L1 expression

Key results (cont.) **Tumour-cell PD-L1 expression ≥1%**

	Nivolumab (n=71)	Sorafenib (n=64)
Median OS, mo (95%CI)	16.1 (8.4, 22.3)	8.6 (5.7, 16.3)
HR (95%CI)	0.80 (0.54, 1.17)	

Tumour-cell PD-L1 expression <1%

	Nivolumab (n=295)	Sorafenib (n=300)
Median OS, mo (95%CI)	16.7 (13.9, 19.4)	15.2 (12.7, 18.1)
HR (95%CI)	0.84 (0.70, 1.01)	



No. at risk

NIVO	71	64	53	43	41	38	32	29	25	24	23	20	16	12	8	0	295	257	216	190	169	148	133	117	104	95	88	81	69	50	34	23	2	0
SOR	64	53	37	29	28	25	23	22	20	17	15	14	13	12	7	0	300	271	233	199	165	145	128	106	93	78	65	56	45	25	15	10	1	0

Sangro B, et al. Ann Oncol 2020;31(suppl):abstr LBA-3

CheckMate 459: long-term efficacy outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma – Sangro B, et al

Overall survival by aetiology

Key results (cont.)

HCV[a]

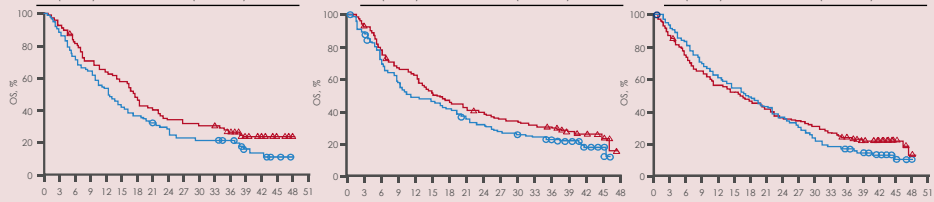
	Nivolumab (n=87)	Sorafenib (n=86)
Median OS, mo (95%CI)	17.5 (13.9, 21.9)	12.7 (9.9, 16.2)
HR (95%CI)	0.72 (0.51, 1.02)	

HBV[a]

	Nivolumab (n=116)	Sorafenib (n=117)
Median OS, mo (95%CI)	16.1 (12.5, 21.3)	10.4 (8.5, 17.3)
HR (95%CI)	0.79 (0.59, 1.07)	

Uninfected

	Nivolumab (n=168)	Sorafenib (n=168)
Median OS, mo (95%CI)	16.0 (10.8, 20.2)	17.4 (13.7, 21.3)
HR (95%CI)	0.91 (0.72, 1.16)	



No. at risk

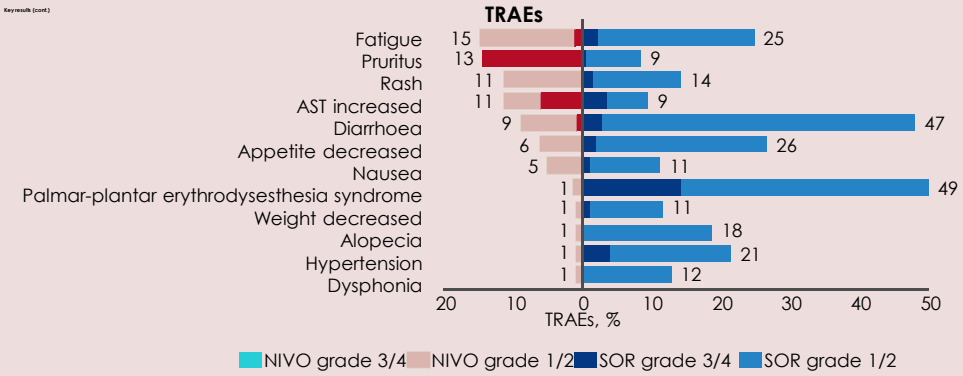
NIVO	87	77	67	58	53	48	40	34	29	27	26	25	20	13	8	4	1	0	116	106	86	72	68	56	51	46	42	37	36	33	31	21	14	9	0
SOR	87	74	61	54	43	34	30	25	22	18	17	17	14	7	5	2	0	0	117	101	77	63	53	50	45	37	33	29	27	24	21	17	8	4	0

NIVO	168	143	120	107	92	85	76	68	59	56	50	44	35	29	20	10	1	0										
SOR	168	154	137	116	101	90	80	70	60	50	37	30	23	13	9	4	1	0										

[a]Patients could have had active or resolved HBV or HCV infection as a risk factor for HCC

Sangro B, et al. Ann Oncol 2020;31(suppl):abstr LBA-3

CheckMate 459: long-term efficacy outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma – Sangro B, et al



Conclusions

- **In patients with advanced HCC, 1L nivolumab continued to demonstrate improvements in OS regardless of PD-L1 status or viral aetiology and had a manageable safety profile**

Sangro B, et al. Ann Oncol 2020;31(suppl):abstr LBA-3

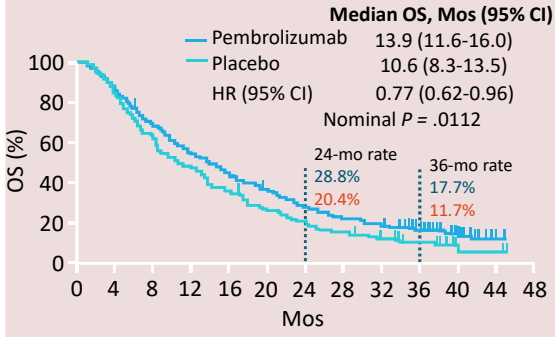
SECOND-LINE SYSTEMIC THERAPY

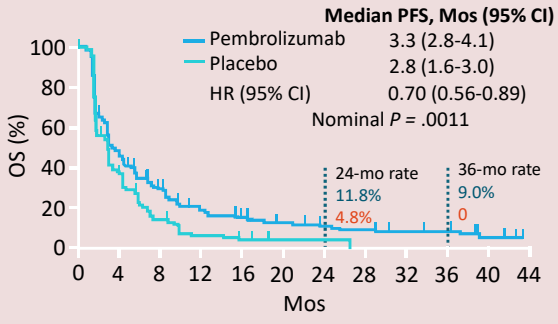
Second-Line Systemic Therapy

- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab
- Pembrolizumab
- Nivolumab + ipilimumab

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

- Randomized, double-blind phase III trial of pembrolizumab vs placebo (both with BSC) for pts with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A (N = 413)
- Failed to reach prespecified level of statistical significance for OS, PFS in primary analysis (prespecified *P* = .0174 [OS] and *P* = .002 [PFS] required) (median f/u 10.6-13.8 mos); updated analysis with additional 18 mos f/u





- ORR: pembrolizumab, 18.3%; placebo 4.4%

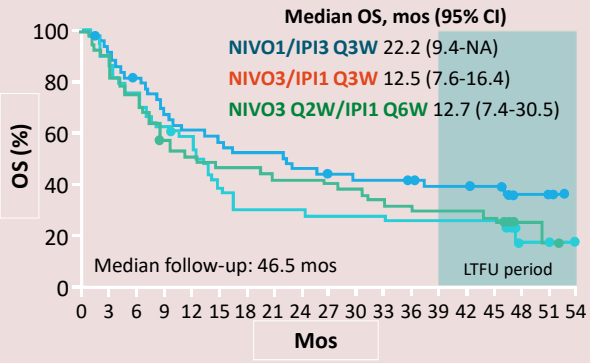
Finn. JCO. 2020;38:193. Merle. ASCO GI 2021. Abstr 268.

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; Child-Pugh score A5-A6; ECOG PS 0/1
- Dosing:
  - **NIVO1/IPI3 Q3W**: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (4 doses)
  - **NIVO3/IPI1 Q3W**: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), each followed by nivolumab 240 mg Q2W
  - **NIVO3 Q2W/IPI1 Q6W**: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

	NIVO1/IPI3 Q3W (n = 50)	NIVO3/IPI1 Q3W (n = 49)	NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, % (95% CI)	32 (20-47)	31 (18-45)	31 (18-45)

OS



Yau. JAMA Oncol. 2020;6:e204564. El-Khoueiry. ASCO GI 2021. Abstr 269.

Efficacy and safety of nivolumab + ipilimumab in Asian patients with advanced hepatocellular carcinoma: subanalysis of the CheckMate 040 study

Study objective

- To evaluate the efficacy and safety of nivolumab + ipilimumab in Asian patients with advanced HCC

Key patient inclusion criteria
- Advanced HCC
- Sorafenib naïve or progression after or intolerant to sorafenib
- Child-Pugh A5 or A6
- HBV, HCV or non-viral HCC
- ECOG PS 0–1

(n=71)

R 1:1:1

Arm A
Nivolumab 1 mg + ipilimumab 3 mg q3w x4 (n=50; 34 Asian)

Arm B
Nivolumab 3 mg + ipilimumab 1 mg q3w x4 (n=49; 27 Asian)

Arm C
Nivolumab 3 mg q2w + ipilimumab 1 mg q6w (n=49; 29 Asian)

Nivolumab 240 mg iv q2w flat dose

PD/toxicity

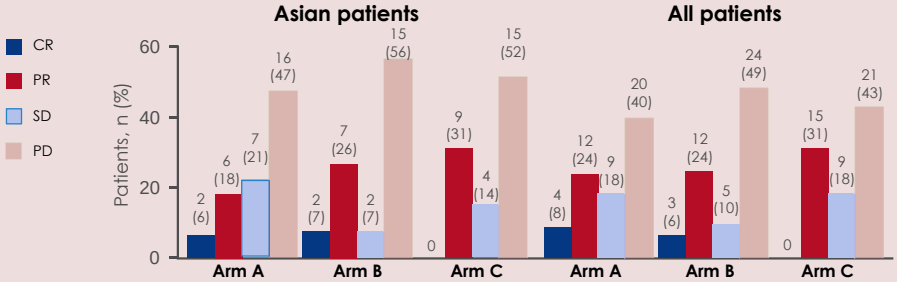
PRIMARY ENDPOINTS
- Safety, ORR (RECIST v1.1, investigator assessed), DoR

SECONDARY ENDPOINTS
- DCR, TTR, TTP, PFS, OS

Yao T, et al. Ann Oncol 2020;31(suppl):abstr O-5

This talk was presented at the 22nd ESMO WCGC on 1 July 2020 at 18:29

Efficacy and safety of nivolumab + ipilimumab in Asian patients with advanced hepatocellular carcinoma: subanalysis of the CheckMate 040 study



	Arm A NIVO1 + IPI3 q3w (n=34)	Arm B NIVO3 + IPI1 q3w (n=27)	Arm C NIVO3 q2w + IPI1 q6w (n=29)	Arm A NIVO1 + IPI3 q3w (n=50)	Arm B NIVO3 + IPI1 q3w (n=49)	Arm C NIVO3 q2w + IPI1 q6w (n=49)
ORR, n (%)	8 (24)	9 (33)	9 (31)	16 (32)	15 (31)	15 (31)
DCR, n (%)	17 (50)	11 (41)	13 (45)	27 (54)	21 (43)	24 (49)
Median DoR, mo (95%CI)	9.8 (7.0, NR)	15.2 (4.2, NR)	11.1 (4.2, NR)	17.5 (8.3, NR)	22.2 (4.4, NR)	16.6 (4.3, NR)
Median OS, mo (95%CI)	16.4 (8.6, NR)	11.8 (6.1, 16.4)	11.2 (6.1, NR)	22.8 (9.4, NE)	12.5 (7.6, 16.4)	12.7 (7.4, 33.0)

Yao T, et al. Ann Oncol 2020;31(suppl):abstr O-5

Efficacy and safety of nivolumab + ipilimumab in Asian patients with advanced hepatocellular carcinoma: subanalysis of the CheckMate 040 study

Key results (cont.)

Grade 3/4 TRAEs, n (%)	Asian patients			All patients		
	Arm A NIVO1 + IPI3 q3w (n=33)	Arm B NIVO3 + IPI1 q3w (n=27)	Arm C NIVO3 q2w + IPI1 q6w (n=29)	Arm A NIVO1 + IPI3 q3w (n=49)	Arm B NIVO3 + IPI1 q3w (n=49)	Arm C NIVO3 q2w + IPI1 q6w (n=48)
Any	17 (52)	7 (26)	8 (28)	26 (53)	14 (29)	15 (31)
Pruritus	1 (3)	0	0	2 (4)	0	0
Rash	1 (3)	1 (4)	0	2 (4)	2 (4)	0
Diarrhoea	1 (3)	0	0	2 (4)	1 (2)	1 (2)
AST increased	5 (15)	3 (11)	2 (7)	8 (16)	4 (8)	2 (4)
Fatigue	0	0	0	1 (2)	0	0
ALT increased	3 (9)	2 (7)	0	4 (8)	3 (6)	0

Conclusions

- **In Asian patients with advanced HCC, nivolumab + ipilimumab demonstrated clinically meaningful responses, particularly in the nivolumab 1 + ipilimumab 3 arm**
- **The safety profile was manageable with no new safety signals observed**

Yao T, et al. Ann Oncol 2020;31(suppl):abstr O-5

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

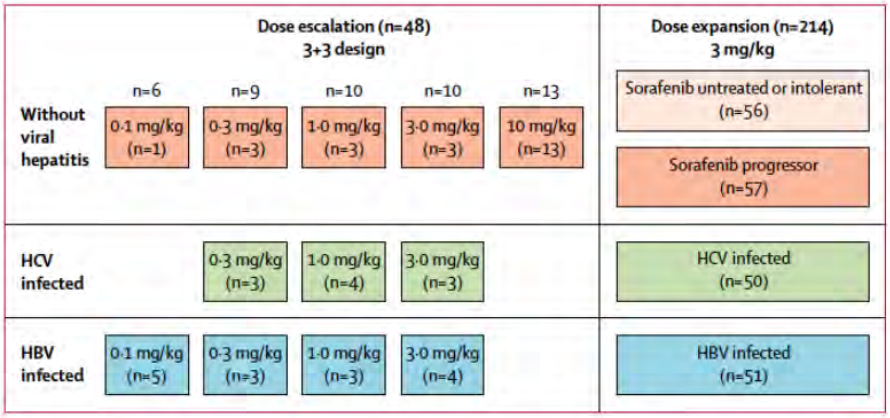
- Phase 1 / 2 using nivolumab 3 mg/kg every 2 weeks in patients with advanced HCC progressor or intolerant to sorafenib
- Primary endpoint: objective response rate

Inclusion criteria
Child Pugh A patient
Advanced HCC
Progression after 1 prior line of systemic therapy or intolerant to sorafenib

Exclusion criteria
Any history of hepatic encephalopathy
Prior or current clinically significant ascites

El Khoueiry AB, et al. Lancet 2017

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

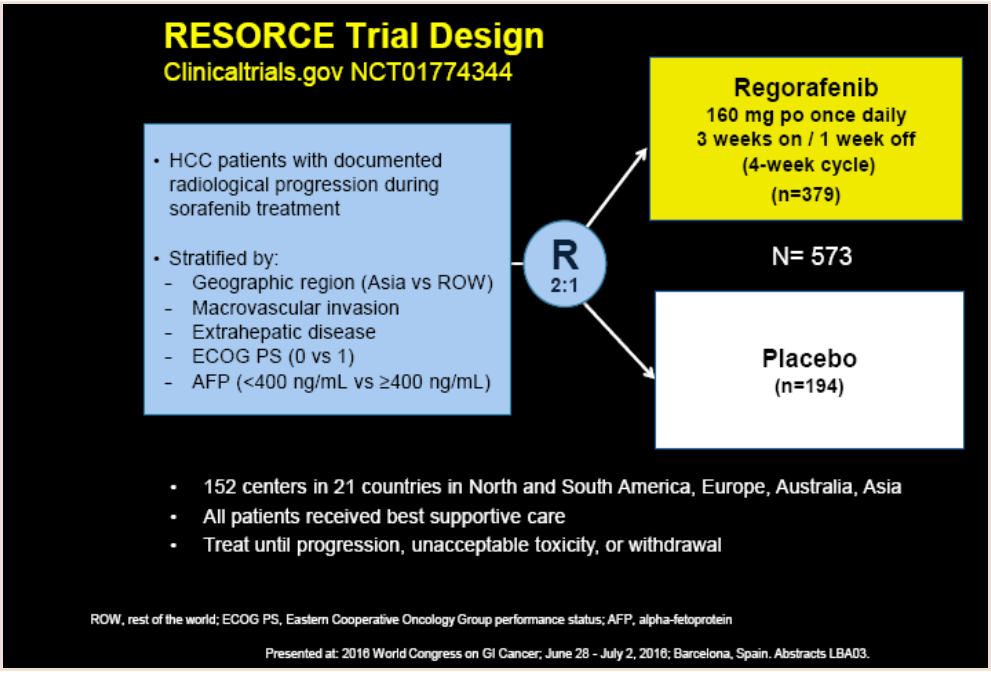


El Khoueiry AB, et al. Lancet 2017

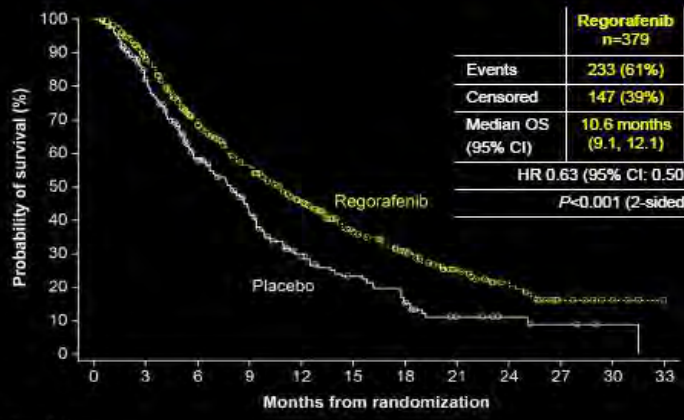
Checkmate 040 : nivolumab in advanced hepatocellular carcinoma

- Nivolumab 3 mg/kg lead to objective response in 16% of the patients using RECIST 1.1 (15% of PR and 1% of CR)
- Disease control rate of 68%
- Median overall survival of 15 months
- Acceptable safety profile
- Randomized controlled trial phase 3 comparing sorafenib to ivolumab in advanced HCC (Checkmate 459)

El Khoueiry AB, et al. Lancet 2017



Regorafenib vs Placebo in Second Line Overall Survival (OS)



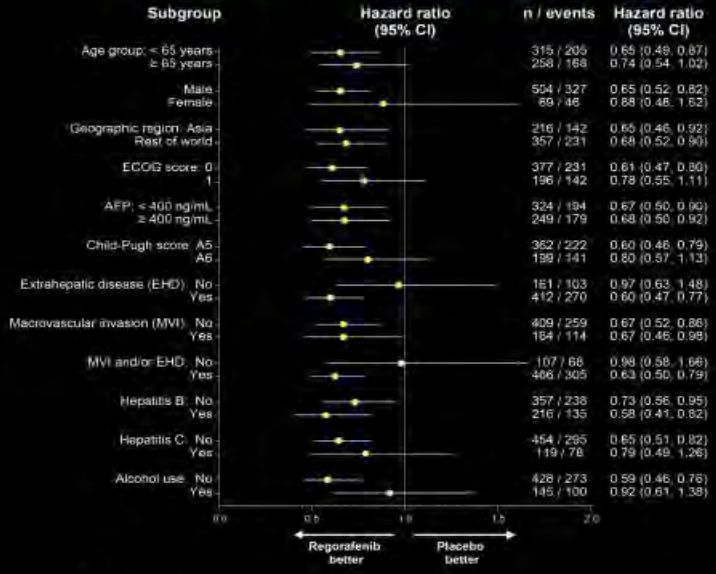
	Regorafenib n=379	Placebo n=194
Events	233 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.63 (95% CI: 0.50, 0.79)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.

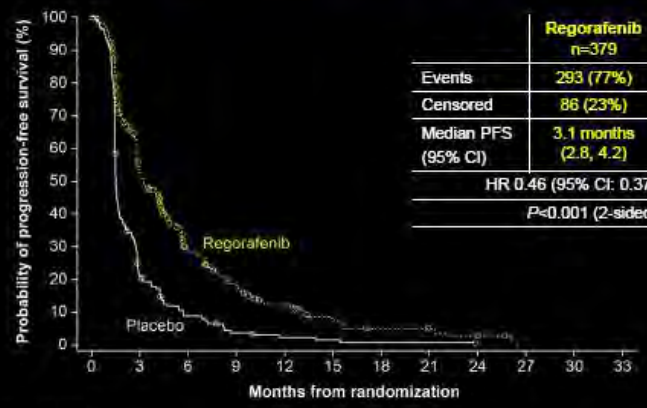
Subgroup Analysis of OS



AFP, alpha-fetoprotein

Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Progression-free Survival (PFS)



	Regorafenib n=379	Placebo n=194
Events	293 (77%)	181 (93%)
Censored	86 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	166	76	43	27	14	8	7	4	0	0	0
Placebo	194	37	15	6	3	2	1	1	0	0	0	0

Based on mRECIST

Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Outcomes for patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh B liver function in the phase 3 CELESTIAL study of cabozantinib vs placebo

Study objective

- To evaluate the efficacy and safety of cabozantinib in the subgroup of patients with advanced HCC whose liver function had deteriorated to Child-Pugh B by Week 8

Key patient inclusion criteria
- Advanced HCC
- Child-Pugh score A
- Received prior sorafenib
- Progressed after ≥1 prior systemic treatment for HCC
- Received ≤2 prior systemic regimens for advanced HCC
- ECOG PS 0–1

(n=707)

R 2:1

Cabozantinib 60 mg/day (n=470) → Loss of clinical benefit / toxicity

Stratification
- Disease aetiology (HBV, HCV, other)
- Geographic region (Asia, other)
- Presence of extrahepatic spread and/or macrovascular invasion (EHS/MVI)

Placebo (n=237) → Loss of clinical benefit / toxicity

PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- PFS, ORR, safety

El-Khoueiry A, et al. Ann Oncol 2020;31(suppl):abstr SO-9

This talk was presented at the 22nd ESMO WCGC on 1 July 2020 at 19:32

Outcomes for patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh B liver function in the phase 3 CELESTIAL study of cabozantinib vs placebo

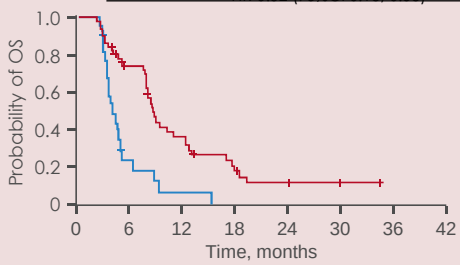
Overall survival

Key results

Child-Pugh B subgroup

	Median OS, mo (95%CI)	No. of deaths
Cabozantinib (n=51)	8.5 (7.7, 12.2)	37
Placebo (n=22)	3.8 (3.3, 4.8)	20

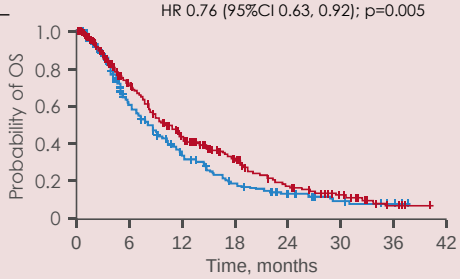
HR 0.32 (95%CI 0.18, 0.58)



Overall

	Median OS, mo (95%CI)	No. of deaths
Cabozantinib (n=470)	10.2 (9.1, 12.0)	317
Placebo (n=237)	8.0 (6.8, 9.4)	167

HR 0.76 (95%CI 0.63, 0.92); p=0.005



El-Khoueiry A, et al. Ann Oncol 2020;31(suppl):abstr SO-9

Outcomes for patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh B liver function in the phase 3 CELESTIAL study of cabozantinib vs placebo

Key results (cont.)

Grade 3/4 AEs, %	Child-Pugh B subgroup (n=51)	Overall population (n=467)
Any	71	68
Fatigue	20	10
Ascites	14	4
AST increased	14	12
Thrombocytopenia	12	3
Palmar-plantar erythrodysesthesia	8	17
Hypertension	8	16

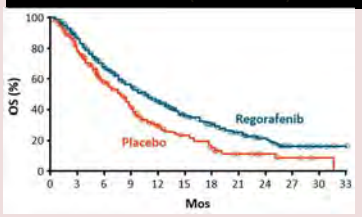
Conclusions

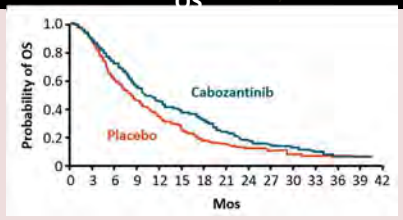
- **In patients with advanced HCC and Child-Pugh B liver function by Week 8, cabozantinib demonstrated similar outcomes to those of the overall population and had a manageable safety profile**

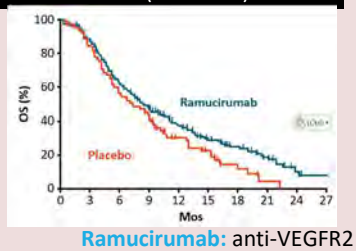
El-Khoueiry A, et al. Ann Oncol 2020;31(suppl):abstr SO-9

Multiple VEGF-Targeted Therapies Have Activity After Sorafenib: Phase III Data

RESORCE	CELESTIAL	REACH-2
Regorafenib vs placebo	Cabozantinib vs placebo (N = 707)	Ramucirumab vs placebo
2L, sorafenib-tolerating pts only (N = 573)	2L or 3L (N = 707)	2L, AFP ≥ 400 ng/mL (N = 292)
Median OS: 10.6 vs 8.0 mos	Median OS: 10.2 vs 8.0 mos	Median OS: 8.5 vs 7.3 mos
HR: 0.63 (*P* < .0001)	HR: 0.76 (*P* = .005)	HR: 0.71 (P = .0199)







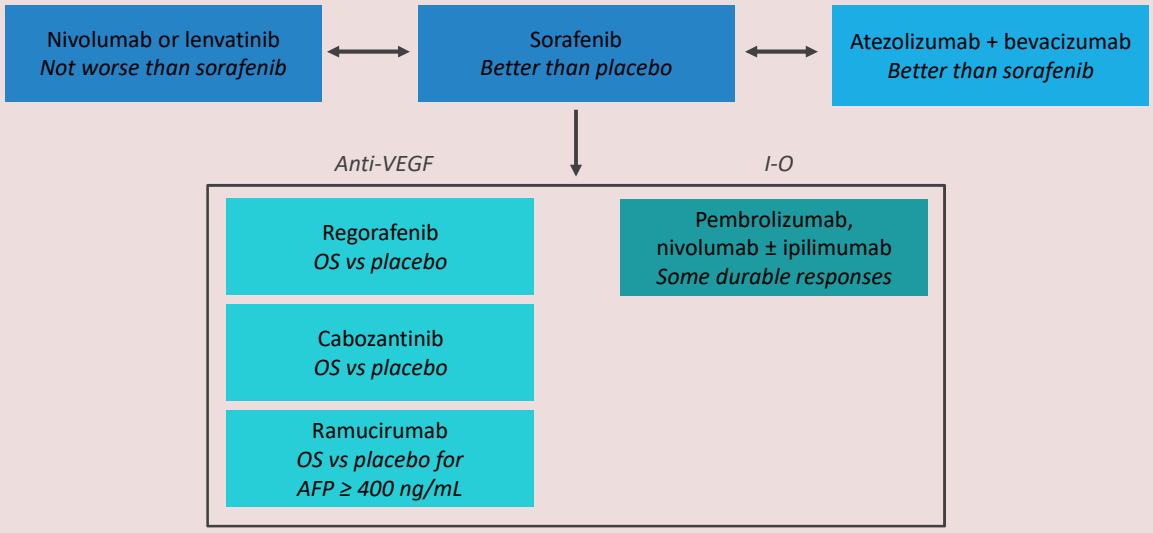
Regorafenib: multitargeted TKI

Cabozantinib multitargeted TKI

Ramucirumab: anti-VEGFR2 Ab

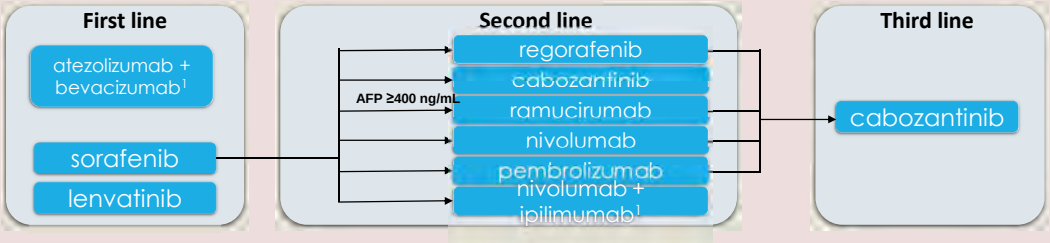
Bruix. Lancet. 2017;389:56. Abou-Alfa. NEJM. 2018;379:54. Zhu. Lancet Oncol. 2019;20:282.

Evolving Landscape of HCC



Systemic treatment sequencing for BCLC Stage C advanced HCC

- **Targeted first-line therapies**
  - Combination: **atezolizumab** (PD-L1 inhibitor) **+ bevacizumab*** (VEGF inhibitor) **(US only)**
  - Oral multikinase inhibitors: **sorafenib** and **lenvatinib**
- **Targeted second-line therapies**
  - Multikinase inhibitor: **regorafenib**
  - Multikinase inhibitor: **cabozantinib**
  - Anti-VEGFR (AFP ≥400 ng/mL) antibody: **ramucirumab**
  - PD-1 inhibitors: **nivolumab, pembrolizumab**
  - Immune therapy Combination: **nivolumab + ipilimumab**



Bruix J, et al. Nat Rev Gastroenterol Hepatol. 2019;16:617-30

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

First-Line Systemic Therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]	• Sorafenib (Child-Pugh Class A) [category 1] or B7)[d,e,2,3] • Lenvatinib (Child-Pugh Class A only)[4,5] (category 1)	• Nivolumab[b,6] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B) • FOLFOX (category 2B)[f]

Subsequent-Line Therapy[g] if Disease Progression[h] Options	Other Recommended Regimens	Useful in Certain Circumstances
• Regorafenib (Child-Pugh Class A only) (category 1)[i,7] • Cabozantinib (Child-Pugh Class A only) (category 1)[i,8] • Ramucirumab (AFP ≥400 ng/mL only) (category 1)[i,9] • Lenvatinib (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7)[d,e]	• Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13] • Pembrolizumab (Child-Pugh Class A only)[b,j,k,14] (category 2B)	• Nivolumab (Child-Pugh Class B only)[b,j,10-12] (category 2B)

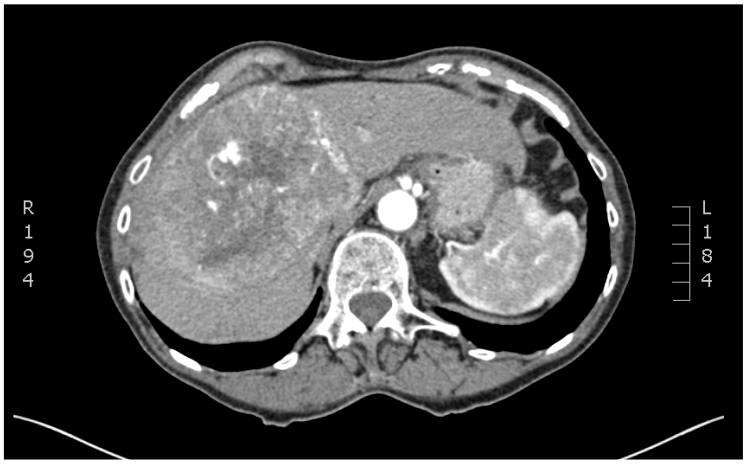
ADVERSE EFFECTS OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA
- case presentation -

Dimitar Stefanovski, dr.med.
Prof. dr. Janja Ocvirk, dr. med.
2nd International Summer school

OCTOBER 2019

- 83 years old female patient;
- former smoker, no history of alcohol consumption;
- y. 2010 - excision of the submandibular gland (adenoca.), osteoporosis GERD, AMD;
- PS WHO 1
- pain under the right costal arch;
- abdominal US: tumour formation in the liver;
- moderately differentiated, pseudo glandular HCC.

- CT thorax + abdomen: hypervascular tumour in the right liver lobe with A – V fistulas, invasion of the middle hepatic vein, without cirrhosis, no signs of distant metastasis.



NOVEMBER 2019

- 1st line treatment with Sorafenib
- After 1st application: skin toxicity - erythematous skin with macular rash
- Continuing the treatment with dose reduced Sorafenib
- pain in the palms and soles of the feet, macular rash.

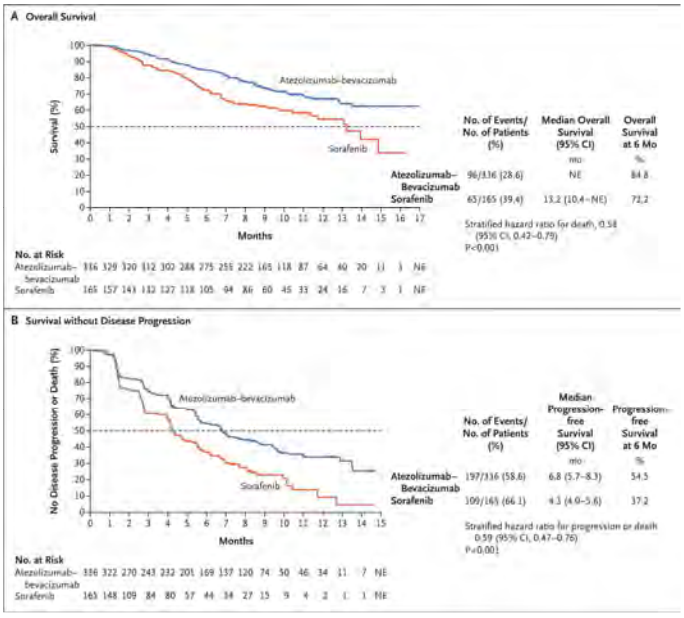
DECEMBER 2019

- Sorafenib therapy was terminated prematurely due to side effects.

NEXT OPTION?

- EMBOLIZATION not possible due to the vascular shunt.

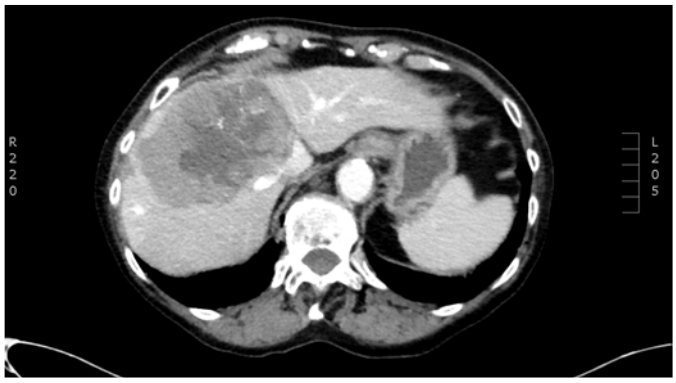
- **IMbrave 150 tiral** results: Patients with unresectable hepatocellular carcinoma have better survival with the combination of atezolizumab and bevacizumab than with sorafenib as first line treatment.



JANUARY 2020

- Systemic therapy with Atezolizumab + Bevacizumab.

- CT scans showing stable disease.



JUNE 2021

- oral mucositis (grade 2)
- petechiae, somewhere ulcerated skin with bleeding (grade 1)
- productive cough, non purulent sputum (grade 1)

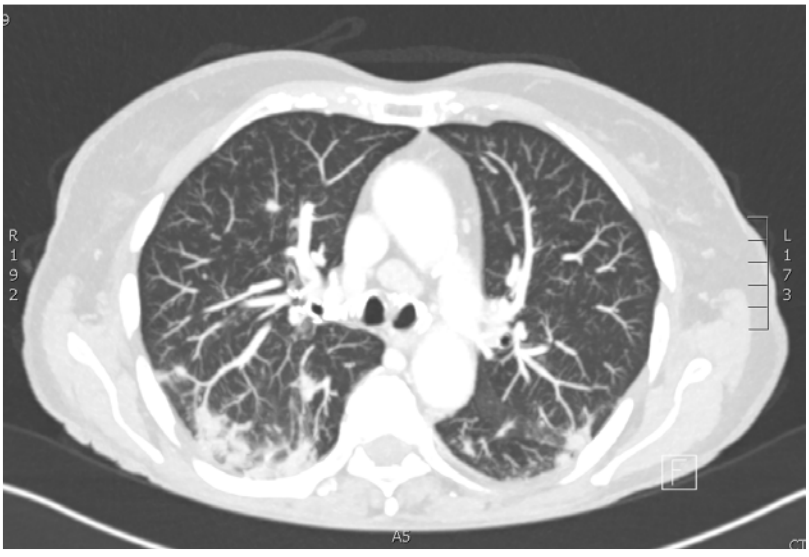
- temporarily suspended bevacizumab, continuation with atezolizumab

JULY 2021 - HOSPITALIZATION

- feeling extremely unwell
- cough (grade 2)
- bloody diarrhea (grade 2)
- ecchymosis, somewhere superficially ulcerated skin with bleeding (grade 1)

- negative microbiological analyses

- CT scan: PNEUMONITIS



TREATMENT

- i.v. corticosteroids in high doses 1 mg/kg BW
- i.v. Vit K

- after 1 week of hospitalization, discharged in stable condition

- continuation of corticosteroids therapy p.o. at home

THANK YOU FOR YOUR ATTENTION

Enrichment of treatment at metastatic NSCLC with PD-L1 overexpression (PD-L1≥50%)

Davorin Radosavljevic

Institute for Oncology and Radiology
of Serbia Belgrade

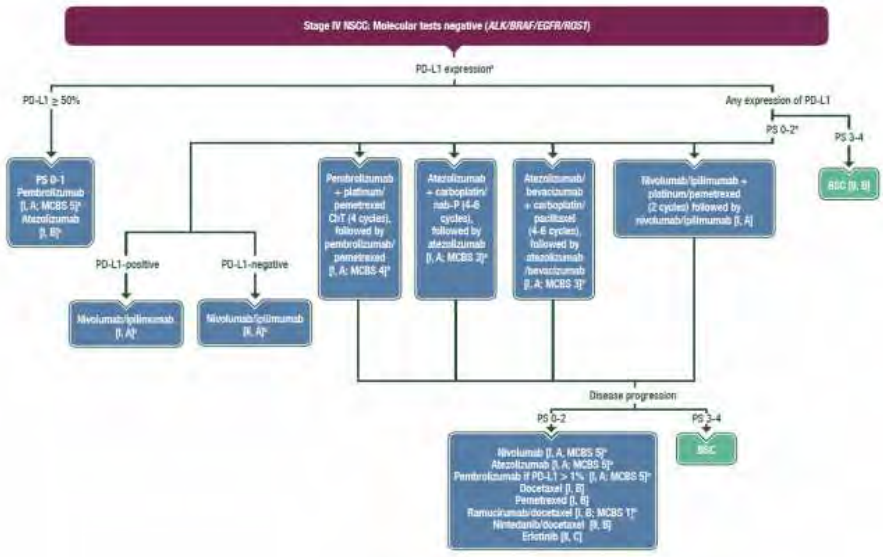
2nd International Summer School of Oncology
Onkološki Inštitut Ljubljana, 08.09.2021.

Advent of immunotherapy supstantially changed initial treatment of advanced NSCLC

Factors in choosing initial therapy:

- ✓ Level of PD-L1(≥50%)
- ✓ Presence or absence of a driven mutation (EGFR, ALK, ROS1, BRAF,etc)
- ✓ The extent of disease (number and sites of metastases, symptoms)
- ✓ Squamous vs nonsquamous histology

Treatment algorithm for stage IV NSCC, molecular tests negative (ALK/BRAF/EGFR/ROS1), ESMO 2020



Check-point inhibitors, specially targeting PD-1 or PD-L1 have became the cornerstone of 1st line therapy

- ✓ Monotherapy
- ✓ Chemotherapy-immunotherapy combinations
- ✓ Immunotherapy-exclusive regimens

Decision-making in this space is complex:

- ➢ **the absence of head-to-head prospective comparisons**

Paramount for patient selection:

- ➢ **tumor cell PD-L1 expression and histology**

Immunotherapy today

MONOTHERAPY[1–6]

- **CheckMate 026** — Nivolumab monotherapy
- **KEYNOTE-024** — Pembrolizumab monotherapy
- **KEYNOTE-042** — Pembrolizumab monotherapy
- **MYSTIC** — Durvalumab monotherapy
- **IMpower110** — Atezolizumab monotherapy
- **B-FAST*** — Atezolizumab monotherapy
- **IPSOS*** — Atezolizumab monotherapy
- **EMPOWER-lung 1** — Cemiplimab monotherapy

*Data not yet made public

CHEMOTHERAPY COMBINATIONS[7–13]

- **KEYNOTE-189** — Pembrolizumab + cisplatin/carboplatin + pemetrexed
- **KEYNOTE-407** — Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel
- **IMpower131** — Atezolizumab + carboplatin + paclitaxel/nab-paclitaxel
- **IMpower130** — Atezolizumab + carboplatin + nab-paclitaxel
- **IMpower132** — Atezolizumab + cisplatin/carboplatin + pemetrexed
- **IMpower150** — Atezolizumab + bevacizumab + carboplatin + paclitaxel
- **CheckMate 9LA** — Nivolumab + ipilimumab + chemotherapy
- **CheckMate 227** — Nivolumab + chemotherapy
- **POSEIDON*** — Durvalumab + tremelimumab + chemotherapy
- **EMPOWER-lung 3** — Cemiplimab + platinum doublet chemotherapy

CIT + CIT COMBINATIONS[4,14]

- **CheckMate 227** — Nivolumab + ipilimumab
- **MYSTIC** — Durvalumab + tremelimumab

1. Carbone, et al. N Engl J Med 2017; 2. Reck, et al. N Engl J Med 2016; 3. Mok, et al. Lancet 2019
4. Rizvi, et al. JAMA Oncol 2020; 5. Spigel, et al. ESMO 2019 (Abs LBA78)
6. Regeneron press release (5 November 2019); 7. Gandhi, et al. N Engl J Med 2018
8. Socinski, et al. N Engl J Med 2018; 9. West, et al. Lancet Oncol 2019
10. Papadimitrakopoulou, et al. WCLC 2018 (Abs OA05.07); 11. Paz-Ares, et al. ESMO IO 2019 (Abs LBA3)
12. Reck, et al. ASCO 2020 (Abs 9501; 13. AstraZeneca press release (28 October 2019)
14. Hellmann, et al. N Engl J Med 2018

5

Tumor PD-L1 expression ≥ 50%: **Initial systemic treatment (driven mutation absent or unknown) for patients with squamous or non-squamous NSCLC**

- ✓ Pembrolizumab superior in OS over platinum doublet (KN024)
- ✓ Atezolizumab superior in OS over platinum doublet (IMpower 110)
- ✓ Cemiplimab superior in OS over platinum doublet (EMPOWER-Lung1)

- ✓ An exception, combination doublet chemotherapy with concurrent pembrolizumab : high tumor burden or rapidly progressive disease in which early PD might preclude the option of chemotherapy in 2nd line setting, due to functional decline
- ✓ Contraindication for immunotherapy (a histology-appropriate platinum doublet): allograft recipiens, myastenia gravis, severe IBD or vasculitis

Cochrane Meta-analysis 2020: data from 7 clinical trials comparing the efficacy of PD-L1/PD1 inhibitors to that of chemotherapy in patients with advanced NCSLC (n=5893)
Ferrara et al. Cochrane Database Syst.Rev 12. CD13257 (2020)

- ✓ Anti PD1/PD-L1 antibodies improved OS in patients with tumor cell PD-L1≥50% (n=2111) compred with chemotherapy (HR 0.68, 95%CI 0.60-0.76) with a moderate level of certainty
- ✓ Among never-smokers with PD-L1 expression ≥50%, N=179, no stat.significant difference in OS between PD1/PD-L1 Abs and chemotherapy; current or former smokers had OS advantage with immunotherapy over chemotherapy
- ✓ No statistically significant difference in OS in PD-L1<1% or ≥1%

Response rate and Survival at Key Timepoints With PD-L1 Blockade vs Chemotherapy in PD-L1 Subgroups: Meta-analysis of Metastatic NSCLC trials
J.Man et al. JNCI Cancer Spectrum(2021)5(3):pkabo012

- ✓ 9810 pts in 27 studies, retrospective analysis, systematic research of MEDLINE/EMBASE
- ✓ **In treatment naive patients** benefits with PD-L1 blockade over CT were seen in
  ORR in pts having PD-L1 ≥50%,
  2yrOS for PD-L1 ≥1%,
  1-yrPFS, 2-yrPFS and 3-yrOS in unselected pts
- ✓ **First-line PD-L1 blockade compared with CT:**
  Higher ORR, 2-yrPFS and 3-yrOS if PD-L1 was 50% or greater
  Lower ORR, higher 2-yrPFS and similar 3-yrOS if PD-L1 was 1-49%
  Lower ORR, similar 1-yrPFS and lower 2-yrOS if PD-L1 was less than 1%
- ✓ **In previously treated patients, PD-L1 blockade demonstrated similar or superior outcomes in all PD-L1 subgroups**

Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression

Aguilar EJ. Et al. Ann Oncol 2019.

Multicentric retrospective analysis 187 patients,
ORR 44.4%, mPFS 6.5mo, mOS NR

- ✓ *PD-L1 50-89% N=107pts*, ORR 32.7%, mPFS 4.1mo, OS 15.9mo
- ✓ *PD-L1 90-100%* N=80pts, ORR 60%, mPFS 14.5mo, OS NR

Implication: **treatment selection, clinical trial intepretation and design**

Does immuno-chemotherapy and imuno-immunotherapy provide additional benefit beyond that of pembrolizumab or atezolizumab monotherapy in PD-L1≥50% population?

24 months OS:
50% pembrolizumab mono in KEYNOTE 024 trial
52% pembrolizumab+chemotherapy in PD-L1≥50% subgroup of KEYNOTE189
48% with nivolumab+ipilimumab in CheckMate227 trial.

Immuno-chemo and immuno-immuno **combination** are associated with predictable but higher risk of toxicities, while mono anti-PD1/PD-L1 provide impressive levels of tolerability compared to chemotherapy

AntiPD1/PD-L1 antibodies as monotherapy for most patients

Whom we should offer **combo immuno-chemotherapy** in **PD-L1≥50%** population?

Imminent need for cytoreduction:

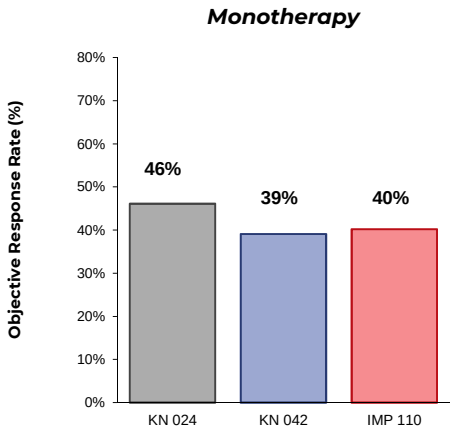
- ✓substantial tumor burden,
- ✓rapidly progressive disease and/or
- ✓severe disease related symptoms

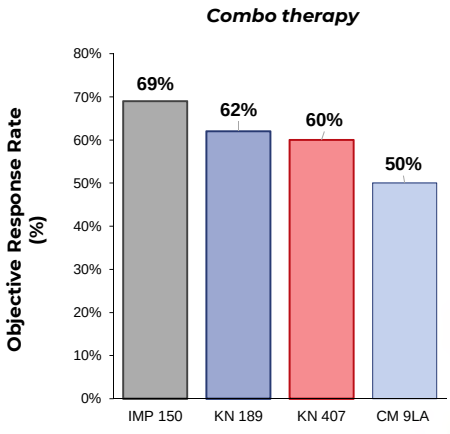
Numerically higher ORR than PD-1/PD-L1 monotherapy

Rapid cytoreduction produced by combo might also attenuate the early decrements in OS seen in patients receiving monotherapies

Only 51% of patients with PD on pembrolizumab in KN024 and 38% in experimental arm of KN042 received subsequent therapy

Mono vs combo approach
ORR in patients with PD-L1 expression > 50%





Brahmer et al ESMO 2020 KEYNOTE-024 5 year OS update, Gray et al WCLC 2020 KEYNOTE-189 4 year OS update, Cho et al WCLC 2020 KEYNOTE-042 3 year OS update, Herbst, et al. WCLC 2020 Abs FP13.03, Reck et al ASCO 2021 (Abs 9000), Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med 2018;379:2040-51. DOI: 10.1056/NEJMoa1810865

Addition of chemo to immunotherapy <u>does not add benefit</u> in <u>nonsquamous</u> mNSCLC with high expression of PD-L1 (except in patients with no smoking history) ***S.Peters et al. ESMO Virtual Pnenary, April 8, 2020.***

Observational study, Flatitron Health database, 520 pts, PS 0-2, PD-L1≥50%, pembrolizumab mono (N=351) or plus paclitaxel-carboplatin (N=169)

Mono arm: higher proportion of poor prognostic baseline characteristics (age, extent of disease)

Median OS 22.1mo vs 21.0mo p=0.63 HR 1.03, PFS 11.5 vs 10.8mo

No smoking population: combo reduced risk by 75%, P=0.02 and 60%,P=0.04

Liver and brain metastases: outcomes were similar

Invited discutant F.Cappuzzo, ESMO 2020.

About 30% of patients in phase III clinical trials have better survival outcome with chemotherapy than with single-agent CPI.

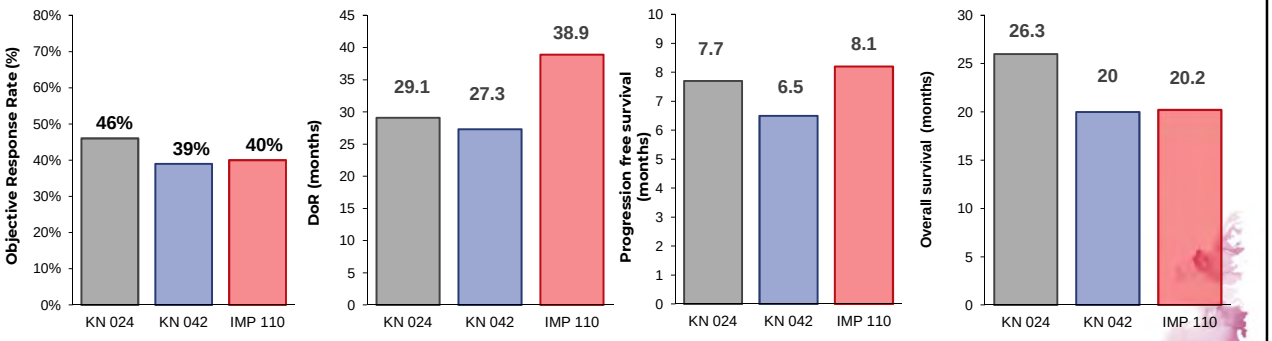
In most relevant trials mOS with single-agent was less than two years, but more than two years in combo approach, ORR were also higher

Cost: toxicity – grade 3-5 in appr. 60% with combo, compared to 20% treated with single agents

Combo certainly in never-smokers

Not all patients with PD-L1 are equall (Pts with≥90% are extremly sensitive to immunotherapy)

Mono imunotherapy options in 1L NSCLC
ORR,DoR, PFS, OS in PD-L1 >50% population



Brahmer et al ESMO 2020 KEYNOTE-024 5 year OS update, Cho et al WCLC 2020 KEYNOTE-042 3 year OS update, Herbst, et al. WCLC 2020 Abs FP13.03, Herbst, et al. N England J Med 2020

Combo and hyperprogression

A subset of patients have a paradoxical acceleration in tumor growth and clinical deterioration upon initiation of therapy

The incidence of hyperprogression in previously treated NSCLC ranges from 8 to 21%

In treatment-naive NSCLC receiving anti-PD1/PD-L1 as monotherapy the incidence was **16%**

This effect can largely be avoided using first-line chemo-immunotherapy combinations

Therapy duration

Up to 2 years in KEYNOTE and CheckMate 227 trials

Indefinite maintenance in IMpower119, IMpower 130 and IMpower150

Results of KN158 randomized study favored longer duration than a 1 year fixed dose (small sample, lack of alternative fixed dose, such as 2 years)

In KEYNOTE 024 39 of 154 pts (25%) completed 2 years of pembrolizumab, and 3-year landmark OS from completion was 81%

These data suggest that most patients completing 2 years of treatment continue to derive long-term benefit, despite therapy cessation

The decision to discontinue maintenance in the absence of substantial toxicities or disease progression should be individualized: whether therapy beyond 2 years improves outcome remains largely unclear

Post-progression outcome of NSCLC patients with PD-L1 expression ≥50% receiving first-line single-agent pembrolizumab in a large multicentre real-world study
Cortellini A. et al, Eur J Cancer 2021.

974 patients were included, median follow-up 22.7months

Median OS 15.8 months (95% CI:13.5-17.5; 548 events)

55.9% had not received any further treatment, 52.9% died

Patients who did not receive post-PD therapies were: older (p=0.0011), with a worse PS (p<0.0001) and were on corticosteroids prior to pembrolizumab (p=0.0024);

At disease progression, 29.2% received a switched approach, 14.9% received pembrolizumab beyond PD, either alone (9.4%) or in combo with local ablative treatments (5.5%): OS 13.9 vs 7.8mo (p=0.0179)

35.5% received second-line systemic treatment (sign.higher proportion of age under 70, poorer PS, having CNS and liver mets)

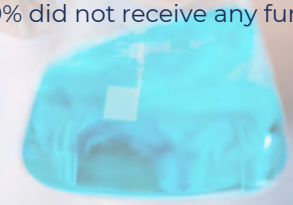
Real-world study (Cortellini 2021) and KN024: Pts with PDL1≥50%

Median OS 15.8mo vs 26.3mo

Not unsuprising: higher proportion of patients with adverse prognostic factors (PS ≥2, receiving corticosteroids, older than 70years)

Patients in clinical studies are highly selected for lower co-morbidity burden

Inferior outcome: patients with poor baseline PS, particulary if related to disease burden; 55.9% did not receive any further treatment;

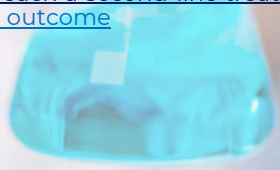


Real-world study (Cortellini 2021) and KN024: Pts with PDL1≥50%

Older pts, PS ≥ 2, receiving systemic corticosteroids are at higher risk of life-thretening progressive disease – thus, treatment sequencing approach ICI-CT doublet is unlikely to be completed

Oligoprogression and pembrolizumab beyond PD: the best post-PD outcome: pembrolizuimab beyond PD + local ablative treatment

Among patients who reach a second-line treatment, PS still remains th major determinent of clinical outcome



Take home messages – mNSCLC with PD-L1≥50%

Decision-making in this space is complex: the absence of head-to-head prospective comparisons

Paramount for patient selection: tumor cell PD-L1 expression and histology

AntiPD1/PD-L1 antibodies as monotherapy for most patients

Not all patients with PD-L1 are equall: patients with ≥ 90% are extremly sensitive to immunotherapy, non-smokers are for combo approach or chemotherapy

Take home messages – mNSCLC with PD-L1≥50%

The decision to discontinue maintenance in the absence of substantial toxicities or disease progression should be individualized: whether therapy beyond 2 years improves outcome remains largely unclear

Hyperprogression can largely be avoided using first-line chemo-immunotherapy combinations

Toxicity – grade 3-5 in appr. 60% with combo, compared to 20% treated with single agents

Clinical choices in metastatic NSCLC without actionable oncogenic driver mutations regardless of PD-L1 status

Marko Jakopović, MD, PhD
Associate Professor
Zagreb Medical School
Department of Respiratory Medicine
University Hospital Centre Zagreb

Disclosures

Speakers fees: AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Berlin Chemie, Sandoz, Novartis, MSD, Novartis Oncology, Abbott

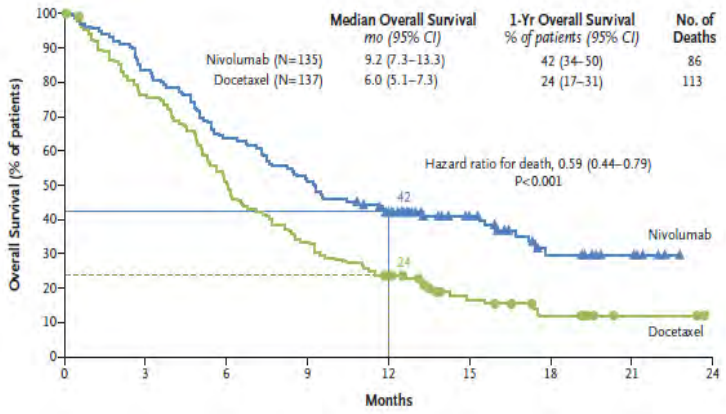
Advisory boards: AstraZeneca, Roche, BoehringerIngelheim, Eli Lilly, MSD, Novartis Oncology

Overview

How to choose treatment options in metastatic NSCLC in patients without driver mutation?

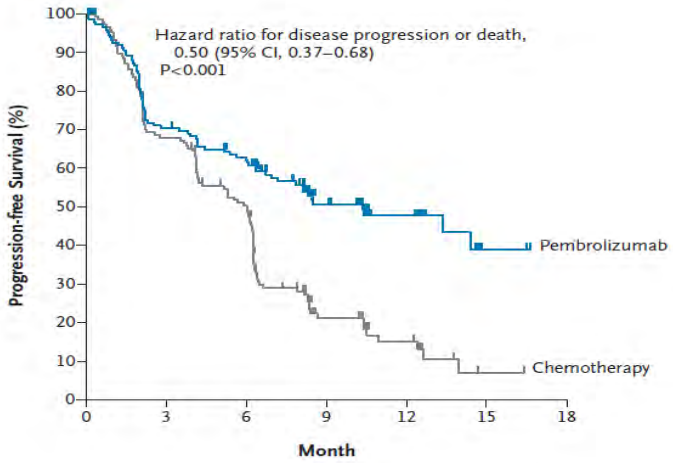
- Immunotherapy vs chemotherapy?

Nivolumab vs docetaxel in previously treated squamous NSCLC



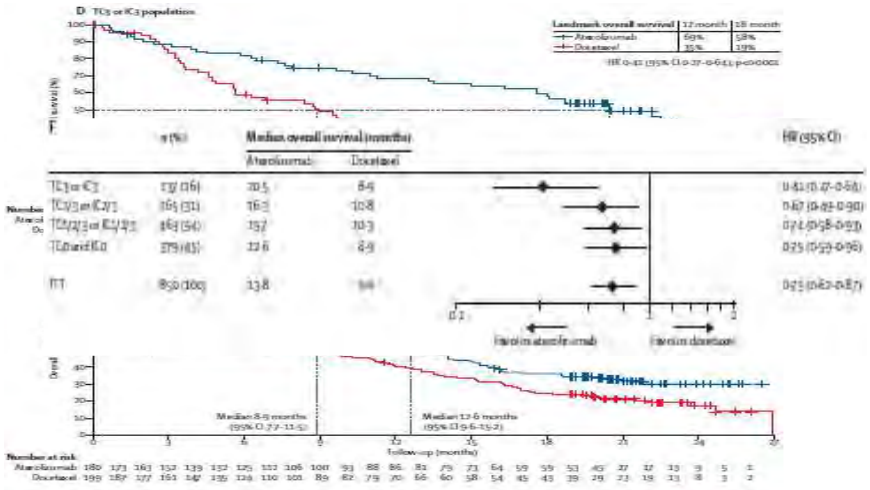
Brahmer J et al. N Engl J Med 2015;373:123-135.

Pembrolizumab in treatment-naive highly positive PD-L1 NSCLC patients



Reck M et al. N Engl J Med 2016; 375:1823-1833.

Atezolizumab was superior to docetaxel regardless of PD-L1 expression in NSCLC



Rittmeyer et al. Lancet 2016.

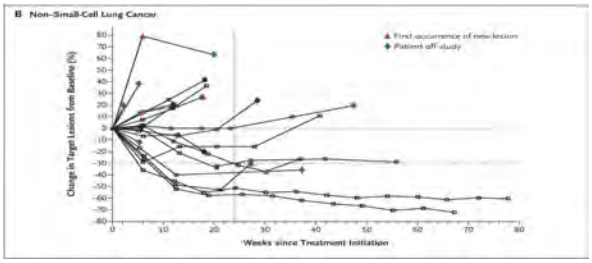
Overview

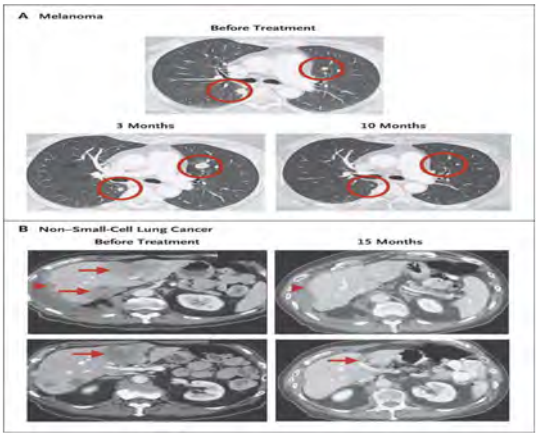
How to choose treatment options in metastatic NSCLC in patients without driver mutations?

- Immunotherapy vs chemotherapy? The winner is immunotherapy!!!!!
- Line of treatment of immunotherapy?
- Monotherapy vs combination therapy (CT+IO, IO+IO)?
- Does histology matter?
- Open questions
- Conclusions

Line of treatment of immunotherapy?

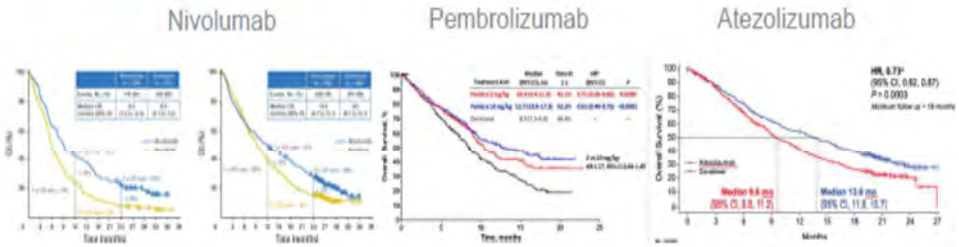
Nivolumab in heavily preatreated patients





Brahmer JR et al. N Engl J Med 2012;366:2455-2465.

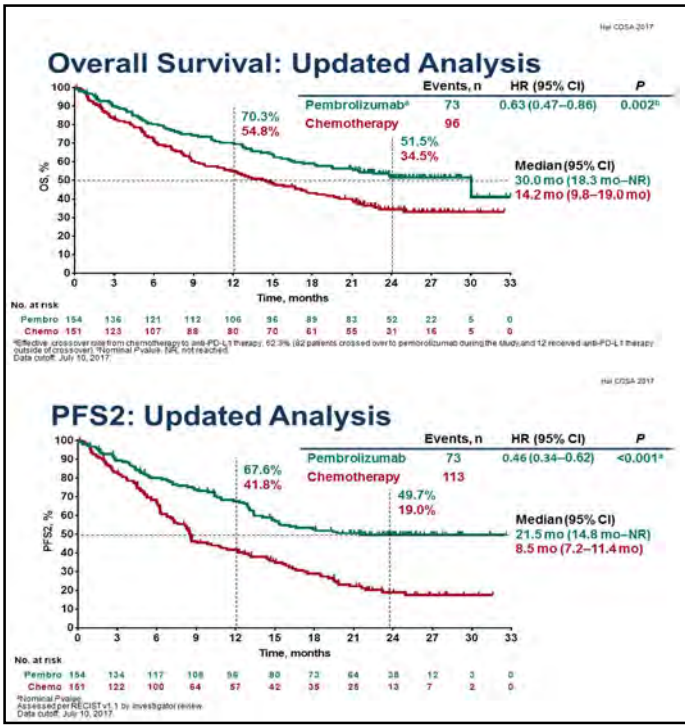
Second-line immunotherapy in NSCLC



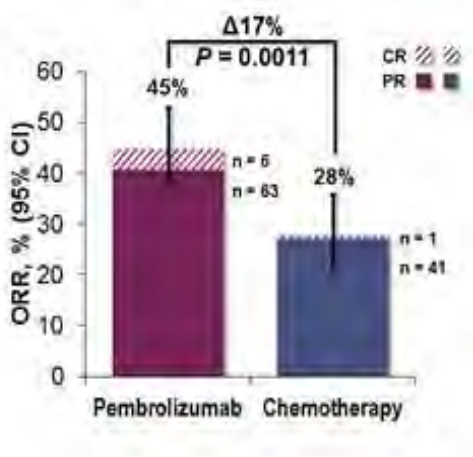
Bramer, NEJM 2015; Borghai, NEJM 2015; Horn, JCO 2017

Herbst, Lancet 2016

Rittmeyer, Lancet 2017



KeyNote-024: First-line pembrolizumab in PD-L1 highly positive patients



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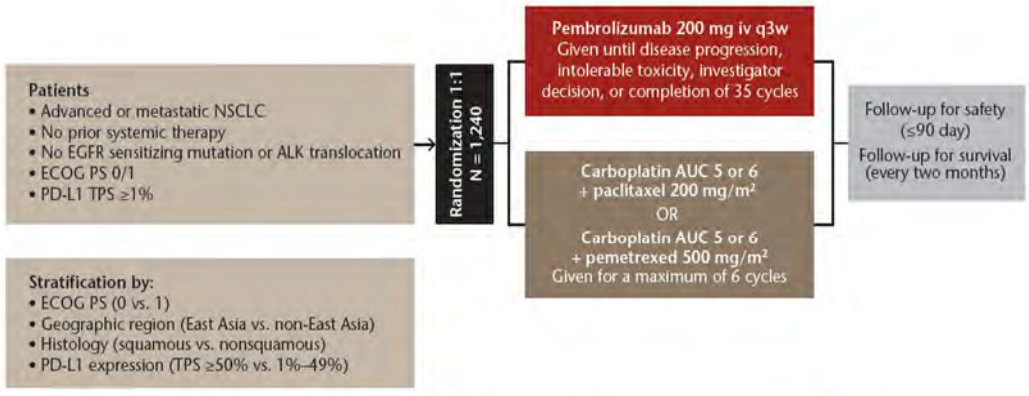
Monotherapy vs combination therapy (CT+IO, IO+IO)?

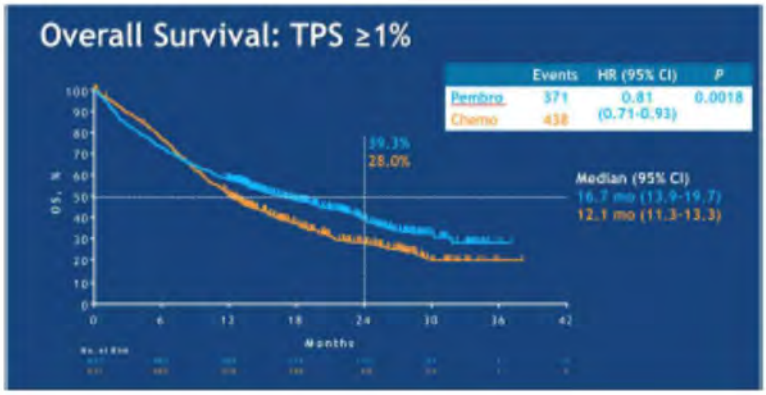
Keynote-042: Pembrolizumab vs Chemotherapy in PD-L1 positive NSCLC

Study design



ALK = anaplastic lymphoma kinase; AUC = area under concentration-time curve; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; iv = intravenous; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; q3w = every three weeks; TPS = tumour proportion score

Keynote-042: Overall survival in ITT population



Mok TS et al. Lancet 2019

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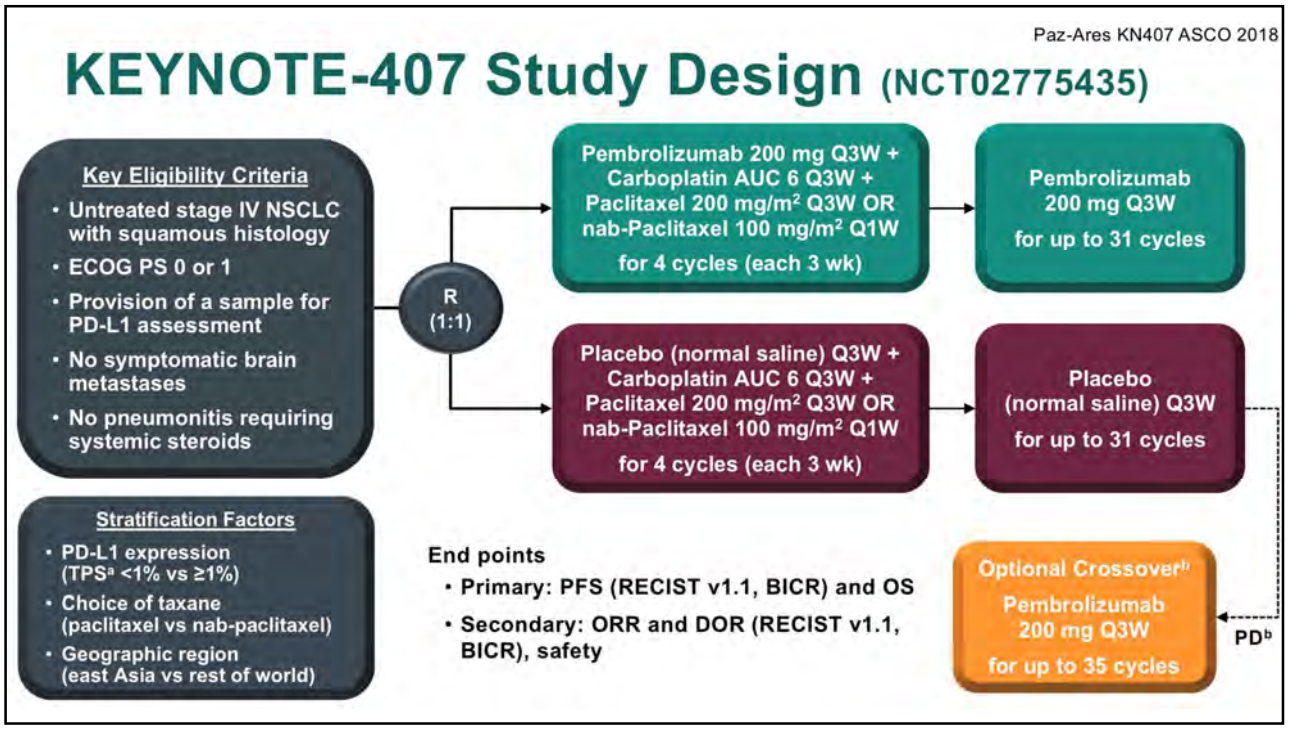
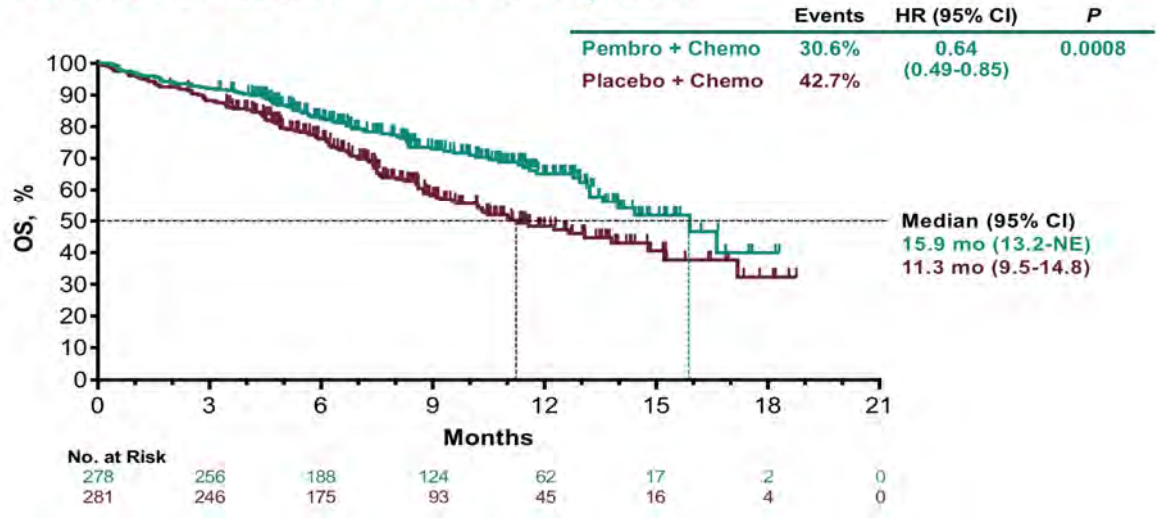
Does histology matter?

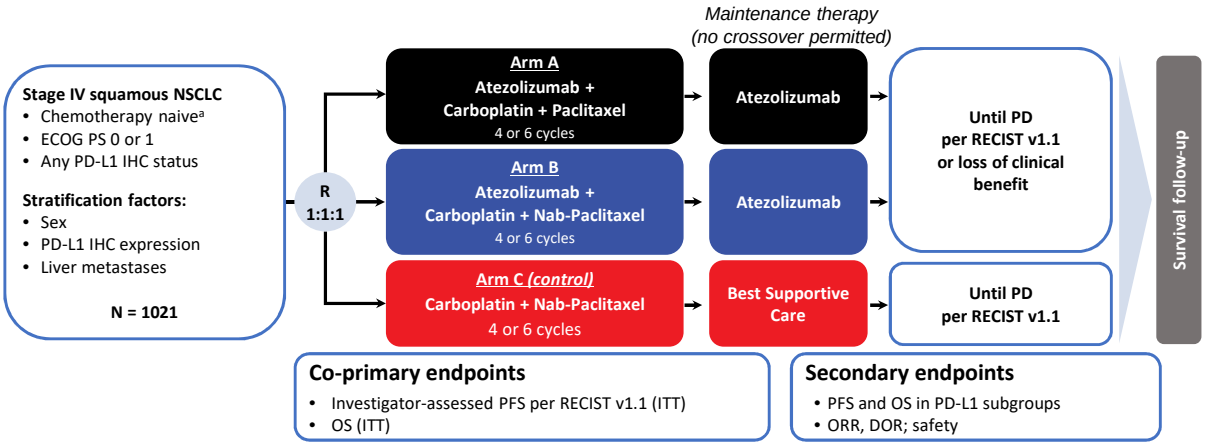


Paz-Ares KN407 ASCO 2018

Overall Survival at IA2, ITT



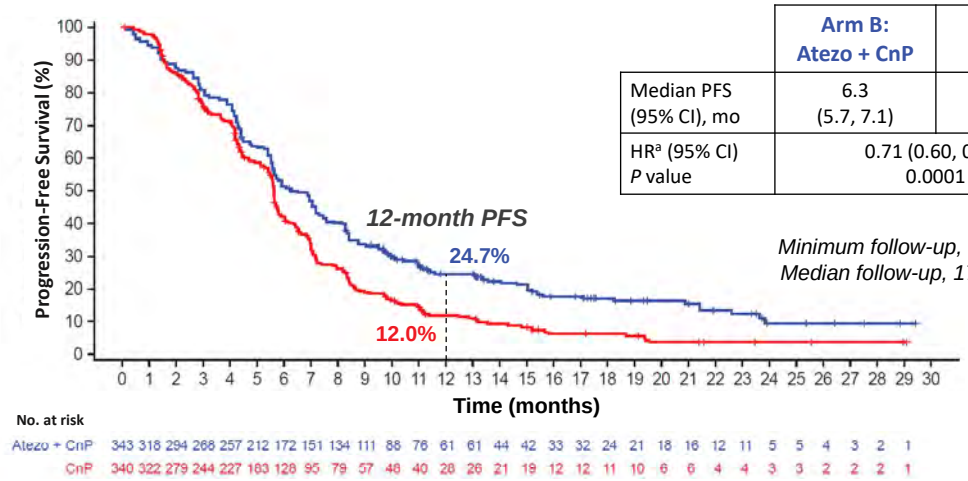
IMower131: Study Design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

Jotte R, et al. IMpower131 PFS Analysis. https://bit.ly/2snPEzb

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	

Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

Jotte R, et al. IMpower131 PFS Analysis.

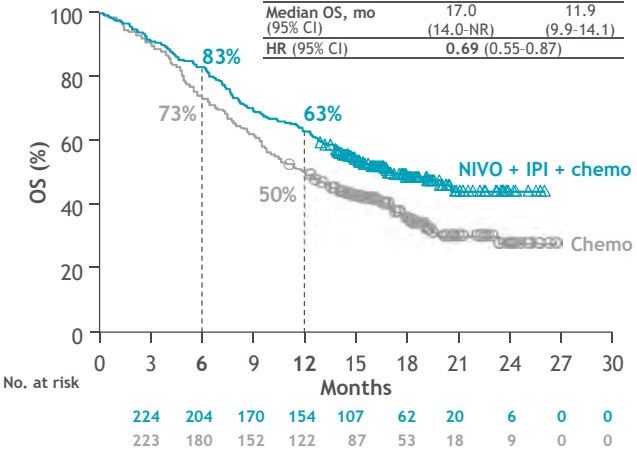
https://bit.ly/2snPEzb

CheckMate 9LA: NIVO + IPI + 2 cycles of chemo in 1L NSCLC

Overall survival by histology

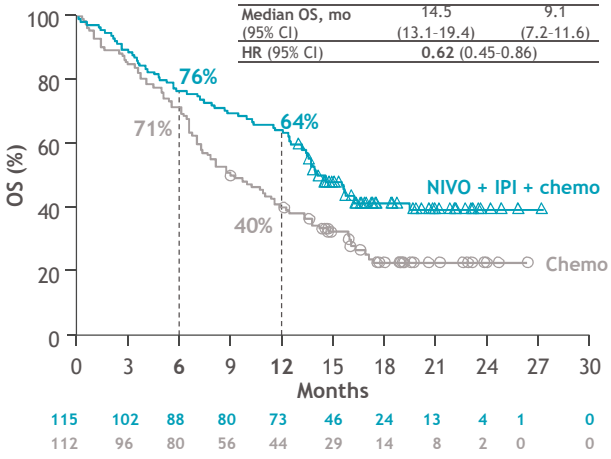
NSQ NSCLC[a]

	NIVO + IPI + chemo (n = 246)	Chemo (n = 246)
Median OS, mo (95% CI)	17.0 (14.0-NR)	11.9 (9.9-14.1)
HR (95% CI)	**0.69** (0.55-0.87)	



SQ NSCLC[b]

	NIVO + IPI + chemo (n = 115)	Chemo (n = 112)
Median OS, mo (95% CI)	14.5 (13.1-19.4)	9.1 (7.2-11.6)
HR (95% CI)	**0.62** (0.45-0.86)	



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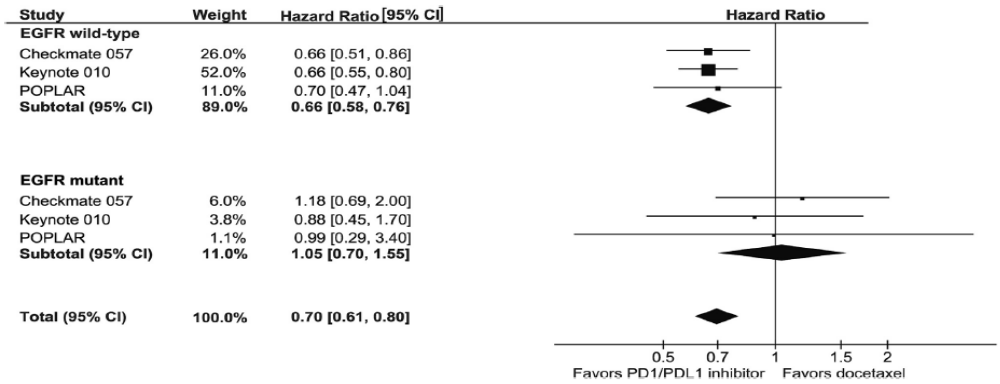
- Does histology matter? Combination treatment is superior to chemotherapy alone regardless of histology subtype!!!!
- Open questions
- Conclusions

Sorry….

I still have to talk about patients wit metastatic NSCLC and driver mutations

Check-point inhibitors in EGFR mutated lung cancer

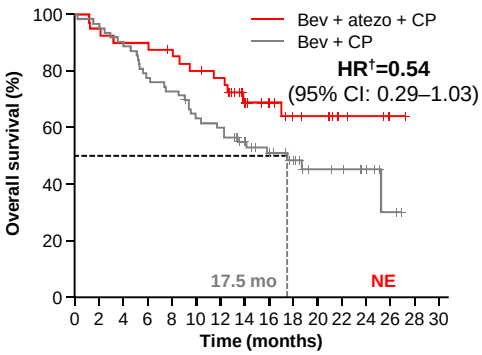


Lee CK et al. J Thorac Oncol 2016; in press

In *EGFR/ALK*+ NSCLC patients, OS benefit seen with combination of bevacizumab + atezolizumab + chemotherapy

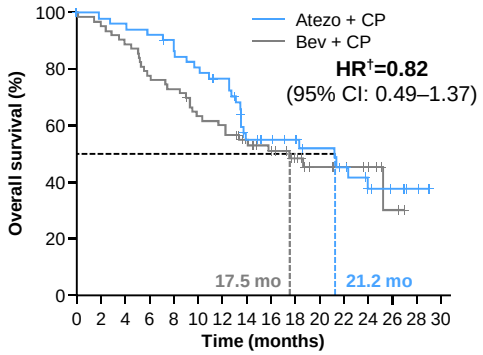
EGFR/ALK+

Bev + atezo + CP* vs Bev + CP



EGFR/ALK+

Atezo + CP vs Bev + CP



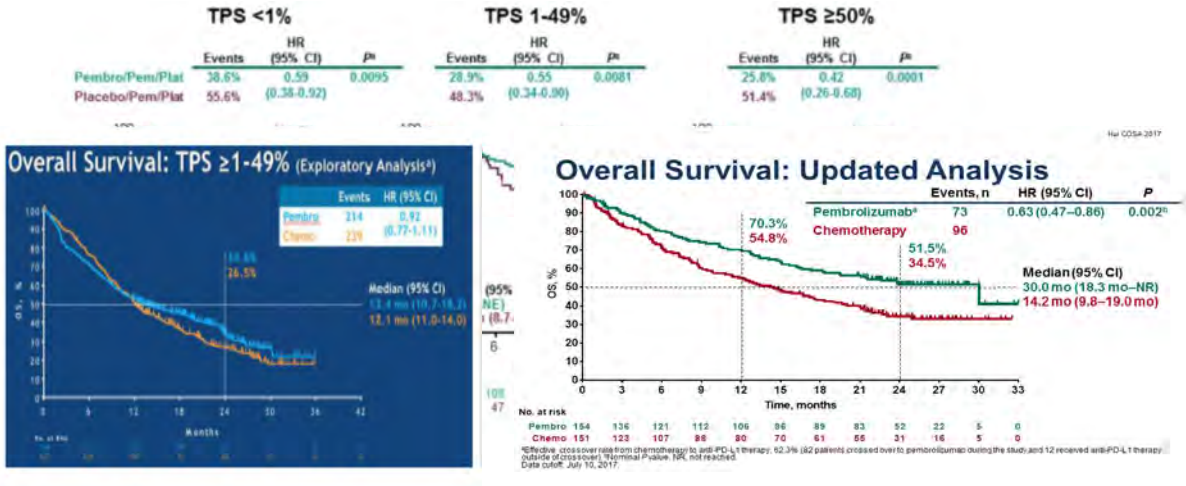
OS benefit in *EGFR/ALK*+ patients was observed despite lower PD-L1 expression in these patients

*One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab;
†Unstratified HR; Data cut-off: 22 January 2018

Socinski, et al. ASCO 2018 (Abstract 9002); Kowanetz, et al. AACR 2018 (Abstract CT076)

Mono-immunotherapy vs combination therapy?

Mono vs combination of IO plus chemotherapy – what to choose?



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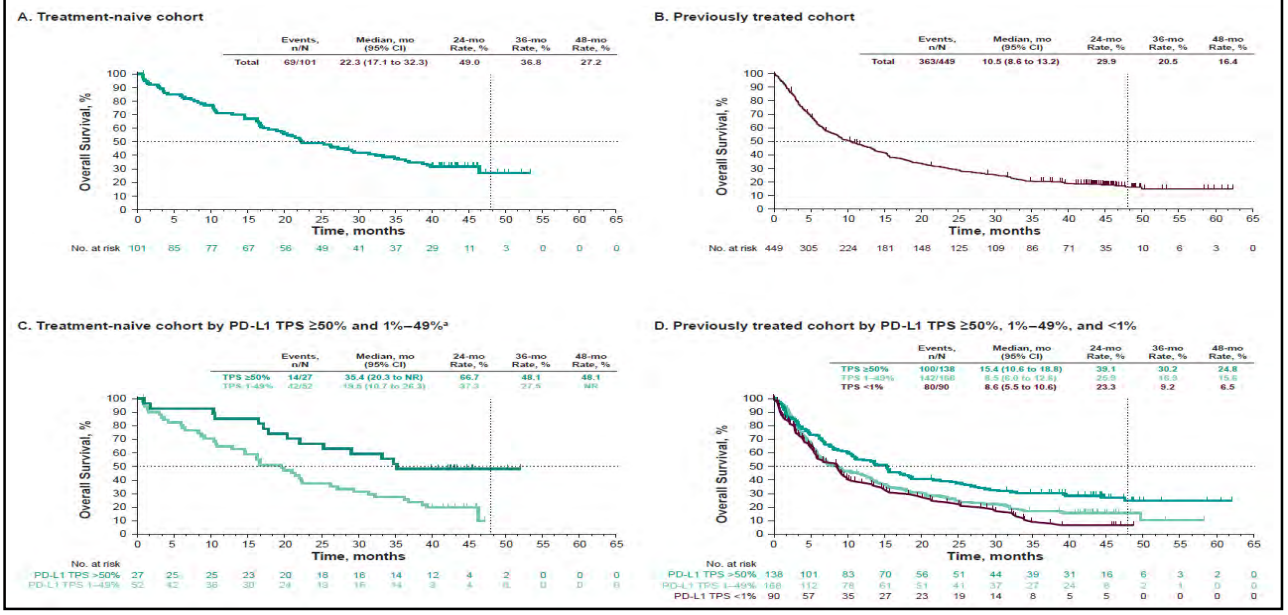
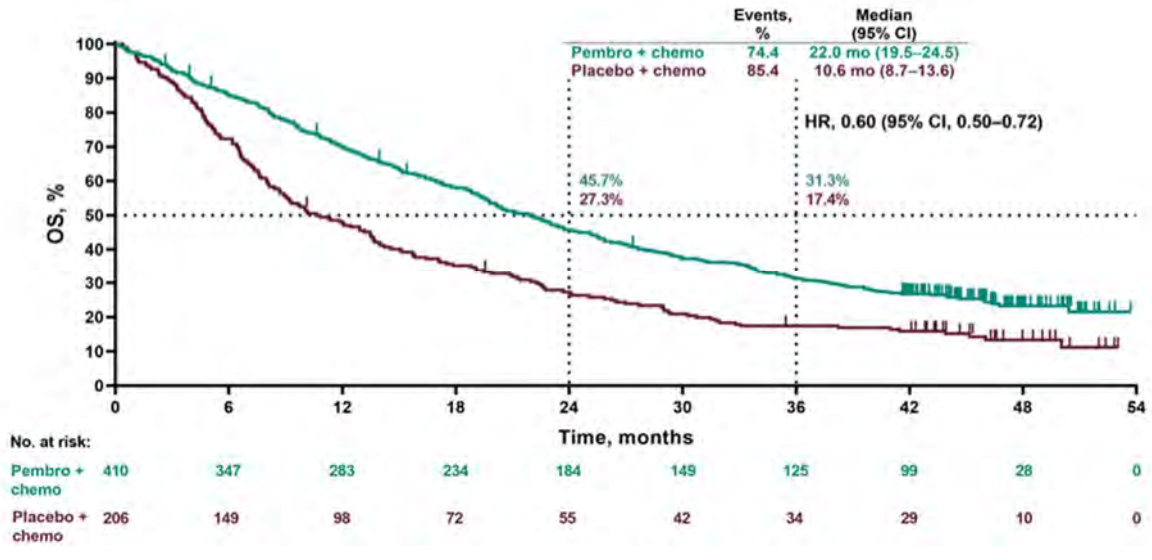
  In patients with PD-L1 expression <50% the winner is combination therapy!!!!
- Does histology matter?
  Combination treatment is superior to chemotherapy alone regardless of histology subtype!!!!
- Open questions? In patients with driver mutations combination of IO+bevacizumab+CT is an option!!!!
  In patients with PD-L1<50% combination therapy is better option!!!!
  Some questions open in PD-L1≥50% about monoIO vs combination!!!!
- Conclusions

Instead of conclusions

Long-term survival with mono-immunotherapy



Long-term survival with combination therapy



Systemic treatment of head and neck cancer – what's new in the old

Assist. Professor Cvetka Grašič Kuhar, MD, PhD
Institute of Oncology Ljubljana, Slovenia

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group

Radiotherapy and Oncology 156 (2021) 281–293

Main question: comparing curative locoregional treatment (LRT) with LRT+Cht

Chemotherapy and radiotherapy in locally advanced head and neck cancer: an individual patient data network meta-analysis

*Claire Petit, Benjamin Lacas, Jean-Pierre Pignon, Quynh Thu Le, Vincent Grégoire, Cai Grau, Allan Hackshaw, Björn Zackrisson, Mahesh K B Parmar, . on behalf of the MACH-NC and MARCH Collaborative Groups**

Lancet Oncol 2021
Published Online
April 13, 2021

Which treatment is the most effective?

Conclusions regarding systemic treatment in SCHNC

- Treatment of stage III/IV disease
- Cisplatin based CRT remained the standard of care in cisplatin-fit patients
  - There is evidence from 2 phase III trials that weekly cisplatin could be delivered instead of high dose cisplatin, efficacy is similar, treatment is less toxic
  - Addition of cetuximab or ICI does not improve outcome
  - Replacing cisplatin with cetuximab or ICI is less effective (less locoregional control)
  - Xevinepant may further increase treatment efficacy
- Recurrent/metastatic disease
- Cisplatin sensitive:
- ICI (Immune checkpoint inhibitor pembrolizumab) in I. line of SCHNC
  - with Chemotherapy (CPS≥1) or as monotherapy (CPS ≥ 1/, >20)
- Extreme regimen: CPS<1 or contraindication for ICI
- Cisplatin resistant : ICI monotherapy, mono-chemotherapy

Updated results of patients with recurrent or metastatic head and neck cancer treated with nivolumab between January 2018 and March 2020 in Slovenia

In total, 27 patients with head and neck cancers were treated with nivolumab in this period. The cohort consisted almost entirely of male patients (96%) and the median age was 59 years. Most of these patients were smokers (89%), and their performance status was 0-1 in 88.9%.

The majority had pharyngeal cancer (63%) of which 3 were HPV positive. Almost a third of patients were heavily pre-treated, having received three or more lines of systemic therapy. Cetuximab was a part of this treatment in 44% of patients.

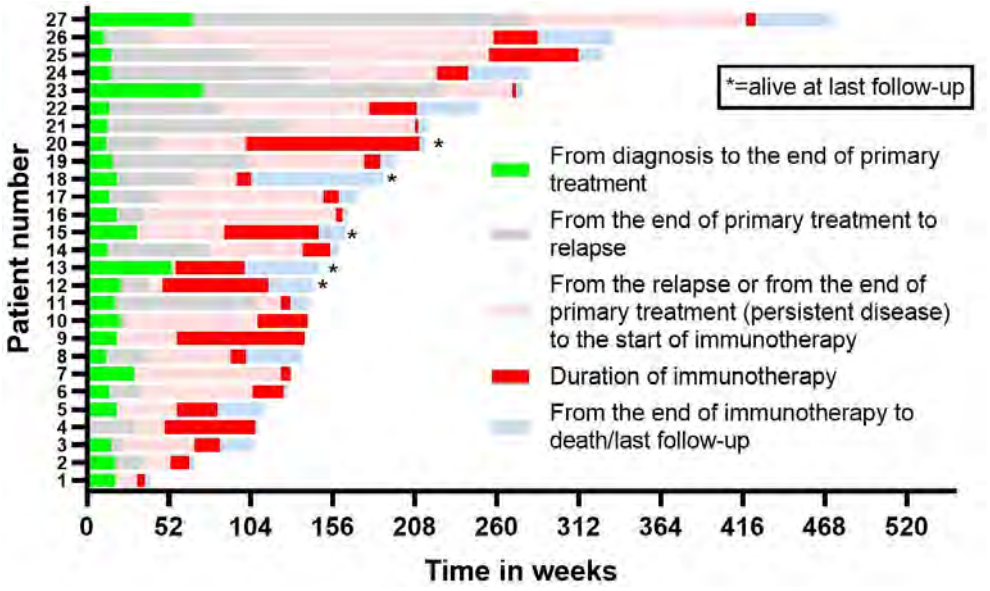
There were in total 14 immune-related adverse events occurring in 8 patients in total, of which there was only one case of grade 2-3 event (bullous pemphigoid), while other 13 events were all grade 1. Only one patient received concurrent radiotherapy (60Gy to parastomal recurrence).

At the end of the updated observation period there were 22 deaths in total. Median overall survival from the first nivolumab application was 10.7 months (95% CI 1.7-19.7) which is comparable to the CheckMate 141 results.[1] One-year overall survival rate was 48.1% (95%CI 29.3-66.9).

Univariate analyses of possible predictive variables with log-rank test, namely the impact of presence of distant metastases, immune-related adverse events, neutrophil to lymphocyte ratio, and impact of concurrent antibiotics treatment on overall survival, found no statistically significant correlation. Individual patients' timelines from diagnosis to death or to last follow up are presented in figure 1.

Overall, we can conclude that treatment with nivolumab has been shown to be safe also in Slovenian patients with recurrent or metastatic head and neck cancer. Due to the small number of patients, it is difficult to align the outcomes with the results of previous studies, but in general results are comparable.

Figure 1. Individual patients' timelines from diagnosis to death or to last follow up



References

1. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375(19):1856–67.

Outcome of patients with recurrent/metastatic squamous cell head and neck cancer treated with platinum-based chemotherapy with or without cetuximab in real-world practice

Tina Zupančič, prof.dr. Branko Zakotnik, doc.dr. Cvetka Grašič Kuhar

- A retrospective analysis of patients with R/M SCHNC treated at the Institute of Oncology Ljubljana between April 2008 and May 2018.
- A total of 67 patients: 34 patients received the PF (platinum, 5-FU), 33 the PFE (PF + cetuximab).
- Inclusion criteria for the PF and PFE protocols: First-line therapy for R/M SCHNC, PS 0-2, adequate haematologic, renal and liver function, approved reimbursement for cetuximab (for PFE only).
- Exclusion criteria for the PE and PFE protocols: Patients with nasopharyngeal carcinoma, PS >2.
- Exclusion criteria for PFE only: Infusion reaction to cetuximab grade >2, prior treatment with cetuximab, known allergy to bee or wasp venom grade >2,bulky tumour in the oropharynx or larynx.
- The primary aim: to compare the PSF and OS in the routine clinical setting with outcomes in a randomized trial and to identify possible prognostic factors for PFS and OS.
- The secondary aim: to assess the tolerability.

Conclusions

- PFE regimen has improved OS (but not PFS) when compared to the PF regimen (median PFS 7.1 vs 6.6; median OS 11.5 vs 9.6 months).
- Objective response to therapy, good nutritional status and possible further treatment after progression have better prognosis (prognostic factors for OS).
- Our results regarding OS are comparable to the EXTREME study.
- Similar median PFS and OS with PFE were reported by other real-world studies.
- OS of our patients is better than real-world global OS.
- No differences in diarrhoea, hypomagnesaemia, infections and febrile neutropenia.
- High mortality (13.4%).
- PFE still represents the optimal 1st line therapy for fit patients with PD-L1 negative R/M SCHNC (20-30%) or with contraindication for anti-PD-L1 inhibitors and as 2nd line therapy.

Management of cancer of unknown primary in the molecular era

2nd Summer School in medical oncology, September 8th

Erika MATOS,MD, PhD
Kaja CANKAR, MD

Definition

- CUP is biopsy-proven malignancy for which the anatomic origin at the time of presentation remains unidentified in spite of a detailed history, physical examination and a thorough diagnostic work-up.
- CUP is a heterogeneous group of metastatic tumors, which share some common features:
  - the ability of an early dissemination,
  - clinical absence of the primary site,
  - aggressive behaviour,
  - unpredictable metastatic pattern,
  - poor response to conventional systemic cytotoxic therapy.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Basic diagnostic-work-up in CUP (ESMO guidelines)

- Patient's history
  - history of previous biopsies, spontaneously regressing lesions and family history
- Physical examination
  - Including rectal and breast examination.
- Good quality tissue sample (ESENTIAL!):
  - meticulous immunohistochemistry.
- Basic blood and biochemical analyses.
- CT of the chest, abdomen and pelvis.
- Mammography in women.

Diagnostic strategy should take in account the natural behaviour of the disease and the expected duration of survival based on extent of the disease and PS.
Difficult and time-consuming diagnostic studies should not compromise patients' quality of life.

Ann Oncol 2015; 26(Suppl 5): v133-138.

Additional diagnostic-work-up in CUP (1)

- Additional procedures should be sign-, symptom-, lab. abnormalities guided.
- Breast MRI: in patients with isolated axillary lymph node metastases and suspected occult primary breast carcinoma after negative mammography and sonography results.
- Broader use of MRI in CUP diagnostics is questionable.
- Endoscopy: if the patient has symptoms or relevant signs.
- FDG-PET imaging in CUP diagnostics:
  - in patients with cervical lymphadenopathy of primarily squamous histological subtype.
  - PET-CT is useful (not been prospectively studied):
    - Patients presenting with solitary metastatic disease who are candidates for curative loco-regional treatment in purpose to exclude occult metastases before extensive surgery,
    - Patients with known severe iodine dye allergy
    - Patients with predominant bone disease who would otherwise require either multiple MRIs or bone scans to evaluate response to therapy.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Additional diagnostic-work-up in CUP (2)

- **Serum tumour markers have no proven prognostic, predictive or diagnostic assistance.**
- Increased values of some tumour markers may help in guiding further diagnostics:
  - Beta human chorionic gonadotropin (beta-HCG) and alpha-fetoprotein (AFP):
    - in patients with midline tumour masses with undifferentiated histology.
  - Prostate Specific Antigen (PSA):
    - in men with adenocarcinoma and predominantly bone disease.

Unfortunately, most tumour markers (CEA, CA125, CA19-9 and CA15-3) are not specific and thus are not helpful in searching for the site of primary tumour.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Clinical presentation of patients with CUP?

- There is no unique clinical picture.
- The majority of patients presents with symptoms and signs of metastatic disease.
- There are patients with only or manly liver metastases, with lymph node metastases in mediastinal or retroperitoneal region, with axillary lymph nodes, with cervical lymph nodes, with peritoneal disease, with malignant ascites, with lung disease only or pleural effusion only, bone only disease or metastases to CNS only, although more often as a part of disseminated disease.
- Clinical presentation depends on number of metastatic lesions and their distribution.
- The majority of patients has metastatic disease in more than one organ, the most often in liver, lung, bone and lymph nodes.

Ann Oncol 2015; 26(Suppl 5): v133-138.

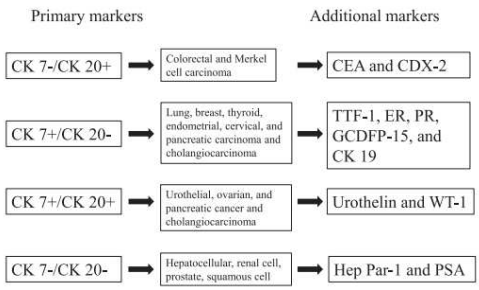
How can pathologist help? (1)

- Challenging work! Direct communication between clinician and pathologist is crucial.
- The trend across all cancer types is personalized medicine (CUP seem ideal candidate).
- Core biopsy is preferred over fine needle aspirate specimen.
- Light microscopy (LM): the tissue specimen (paraffin sections stained with eosin and haematoxylin)
  - Based on established cytological criteria, the pathologist usually can classify the tumors into broad groups:
    - Carcinoma (5% SSC)OR adenocarcinoma (60%),
    - Sarcoma,
    - Lymphoma.
  - Some specimens will lack any cytological distinguishing features:
    - undifferentiated malignancy (35%).

Ann Oncol 2015; 26(Suppl 5): v133-138.

How can pathologist help? (2)

- IHC: significant role in the workup of CUP
  - Define tumour lineage by using peroxidase-labelled antibodies against specific tumour antigens.
  - Have to be directed in terms of clinical and radiological patient's data.
  - Random use of large numbers of tissue markers is rarely helpful.
  - Staining for different CK (components of cytoskeleton of epithelial tissue) may be very helpful.
    - Commonly used staining for CK7, 20, 5 and 6.
    - From the pattern of theirs' expression, the most likely site of origin can be identified.



The method has limitations:

- the majority of tissue markers are not specific for one organ
- no pattern is 100% specific,
- the absence of markers does not exclude the origin in certain organ/tissue.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

How can pathologist help? (3)

- The value of some antibodies, such as AFP, beta-HCG, PSA is well established.
- Some stainings are organ/tissue specific, such as ER, leukocyte common antigen.
- The absence of certain marker does not exclude the origin in that organ/tissue.
- The majority of tissue markers are not specific for one organ.

Table 1. Immunohistochemical work-up in patients with cancers of unknown primary site (CUPs)

	Cytokeratins	PSA	ER, PgR	CDX2+, CK20+, CK7−	TTF1, NapsinA, CK7+	Thyroglobulin, calcitonin	NSE, chromogranin, synaptophysin	AFP, OCT4, hCG, PLAP	LCA	S100, HMB45	Vimentin, desmin
Undifferentiated carcinoma	+	−	±	−	−	−	−	−	−	−	±
Prostate cancer	+	+	−	−	−	−	−	−	−	−	−
Breast cancer	+	−	±	−	−	−	−	−	−	−	±
Colorectal cancer	+	−	−	±	−	−	−	−	−	−	−
Lung adenocarcinoma	+	−	−	−	+	−	−	−	−	−	−
Thyroid cancer	+	−	−	−	±	±	±	−	−	−	−
Neuroendocrine	+	−	−	−	±	±	+	−	−	−	−
Germ-cell cancer	+	−	−	−	−	−	−	+	−	−	±
Lymphoma	−	−	−	−	−	−	−	−	+	−	−
Melanoma	−	−	−	−	−	−	−	−	−	+	±
Sarcoma	−	−	−	−	−	−	−	−	−	±	+

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin
Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with NapsinA.
PSA, prostate specific antigen; ER, oestrogen receptor; PgR, progesterone receptor; CK, cytokeratin; TTF1, thyroid transcription factor 1; NSE, neuron-specific enolase; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; LCA, leukocyte common antigen.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

How can pathologist help? (4)

- Novel molecular approaches in CUP evaluation:
  - Gene expression profiling tests (GEP) to identify the tissue of origin (ToO)
  - Comprehensive genomic profiling tests (CGP) to find treatable (clinically relevant) genomic aberrations (GA)

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Gene expression profiling

- Methodology: RT-PCR or microarrays evaluating the expression od different genes
- Several assays on the market (evaluating from 10 to 92 and more genes)
- Tested in a randomized phase III trial (GEFCAPI 04)

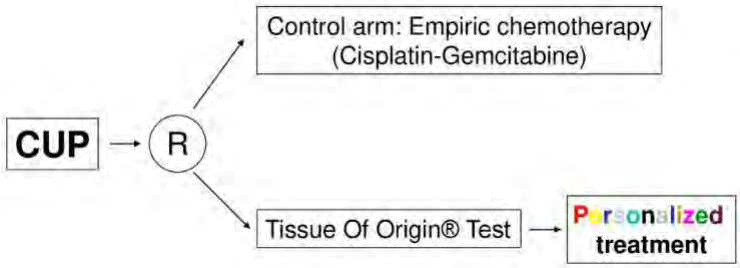
Gene expression tests

- Are molecular cancer classifiers that help identify the site of origin for cancers with indeterminate, uncertain, or differential diagnoses.
  - CancerTYPE ID® uses real-time RT-PCR to measure the expression of 92 genes in the patient's tumor and classifies the tumor by matching the gene expression pattern of the patient's tumor to a database of known tumor types and subtypes, encompassing 50 tumor types (not FDA approved).
  - Tissue of Origin Test® is based on Affymetrix microarray. It compares the expression for 2000 genes in a patient's tumor with a panel of 15 know tumor types that were diagnosed according to current clinical and pathological practice (FDA approved in June 2010).

GEFCAPI 04 (Study description)

- Phase III trial of empiric chemotherapy with cisplatin and gemcitabine (GC) or systemic treatment tailored by molecular gene expression analysis in patients with carcinomas of an unknown primary (CUP) site
- TOO (Pathwork; n=21) or CancerTYPE ID (Biotheranostics; n=222); N=243
- Primary endpoint: PFS
- Secondary endpoints:
  - OS
  - PFS in patients with cancers likely insensitive to GC

Stratification: PS, LDH level



Ann Oncol30; 2019 (Suppl 5): v851–v934.

GEFCAPI 04 (Results)

- Primary cancers most often reported: pancreatico-biliary (19%), SCC (11%), kidney cancer (8%), lung cancer (8%)
- 91/123 (arm B): tailored treatment
- PFS: 5.3 mos (arm A) vs 4.6 mos (arm B); HR 0.95 (0.72-1.25); p=0.7
- OS: 10.0 mos (arm A) vs 10.7 mos (mos) (arm B); HR 0.92 (0.69-1.23)
- 60 pts with suspected cancers likely insensitive to GC

Conclusion:

In GEFCAPI 04, using a molecular test followed by tailored systemic treatment did not improve outcomes of pts with CUP.

Ann Oncol30 (Suppl 5); 2019: v851–v934.

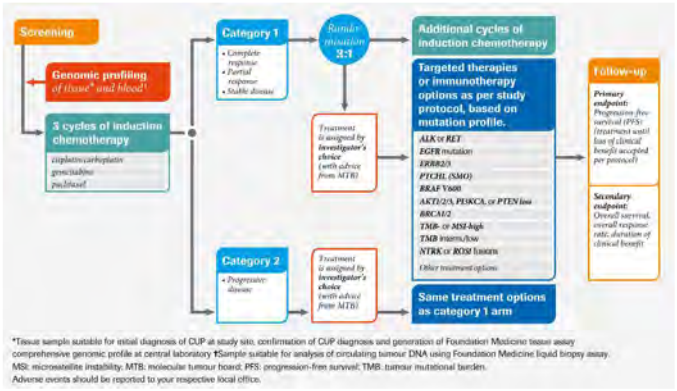
Comprehensive genomic profiling

- Methodology: NGS
- Ongoing CUPISCO trial: A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site (NCT03498521)

https://clinicaltrials.gov/ct2/show/NCT03498521.
Ross JS et al. The Oncologist 2021;26:e394–e402.

CUPISCO (Study description)

- Aim: to determine the efficacy and safety of targeted therapies and cancer immunotherapies for patients with a subset of CUP syndrome.
- The selection of therapies is based on results from CGP (FMT*)
- N=790; F II, global, 162 sites participate
- After 3 cycles of induction platinum-based ChT doublets the responders are randomized to experimental arm (targeted therapy tailored to the molecular profile) or continue with standard ChT. The non-responders go directly to molecular guided therapy.



- The primary endpoint: PFS or death from any cause.
- The secondary endpoints: OS, RR, CBR, safety….
- Estimated date of competition: 2023.

https://cup-syndrome.com/en/home/cupisco-study.html
*FMT: Foundation Medicine tissue or liquid Test

Do we (currently) have effective drugs for CUP patients?

a responsive subset:

favourable prognostic subset

- About 20% of CUP patients
- Have histopathology, biomarkers and clinical presentation consistent with specific tissue of origin
- Should be treated with primary-specific therapy corresponding to most likely primary site

an unresponsive subset:

poor prognostic subset

- About 80% of CUP patients
- No type of ChT prolonged survival in these patients

Int J Cancer 2014; 135, 2475–81.
Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Favourable prognostic subset

- Traditionally defined favourable subset:
  - women with isolated axillary adenopathy,
  - women with serous papillary peritoneal carcinomatosis,
  - squamous cell carcinoma involving mid-high cervical lymph nodes,
  - poorly as well as well-differentiated neuroendocrine carcinoma,
  - poorly differentiated and undifferentiated carcinoma (extra gonadal germ cell cancers),
  - men with blastic bone metastases and elevated PSA
  - patients with single, small and potentially resectable tumours
- Newly identified favourable CUP subset:
  - patients who look like CRC (CK 20 pos, CK 7 neg, CDX pos), should be treated as patients with advanced CRC (expected RR around 50% and mOS up to 3 years)

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Unfavourable prognostic subset (1)

- Sensitivity to chemotherapy is modest.
- Include the patient in clinical trial (if an option).
- Do the CGP to identify potentially treatable, clinically relevant GA and treat accordingly.
    - In many countries expensive molecular assays are not available or not covered by insurance.
    - Targeted drugs and check point inhibitors are not covered by insurance.
    - At the time being we have no prove that such approach really influence patients' survival. Data from well designed clinical trials are necessary (are ongoing).

Unfavourable prognostic subset (2)

- The majority of patients from this subset have poor prognosis.
- At presentation, two-thirds of patients have metastatic lesions in two or more visceral sites (most often liver, lung, lymph nodes and/or peritoneum).
- Patients are often in poor performance status.
    - For many of these patients BSC is the best option.
    - For selected patients empiric chemotherapy is justified.
    - Cisplatin or taxane-based doublets have been used, with little impact on survival.
    - Patients and relatives have to be informed that expected RR to ChT is only 20% to 30% and expected mOS not more than 9 to 11 mos. This might influence theirs' decision about treatment.

NCCN guidelines

Burning questions

- 1. Does site-specific therapy determined by GEP improves outcome in patients with CUP?
  - According to the result of GEFCAPI 04 study: NO
    - The study has limitations!
- 2. If genomic profiling identifies a targetable mutation in a tissue sample of CUP and the patients receives targeted therapy, is the outcome improved compared to standard chemotherapy?
  - It seems logical, but it is not necessary.
  - A good lesion in terms of this is BRAF mutation. It can be effectively treated if CUP has metastasized from melanoma but not from colon cancer.
    - The study is underway.

Summary and assessment algorithm (1)

- Does molecular profiling assay increases accuracy of identifying the primary site?
  - **Most probably yes.**
- Does molecular profiling (CGP) help us in directing effective targeted treatment?
  - **We are not certain yet. Studies are ongoing.**
- Does identification of primary site based on molecular assays (GEP tests) and accordingly directed therapy improves patient survival?
  - **According to the results we have: NO.**
- How to proceed knowing all these in current clinical practice?

Summary and assessment algorithm (2)

- Try to search for primary site: clinically, by IHC, imaging, endoscopy studies.
- Rule out potentially treatable or curable tumours (breast cancer, germ cell tumour, lymphoma)
- Select, which clinic-pathological entity the patient belongs to:
  - If to favourable prognostic subset:
    - treat accordingly
  - If to poor prognostic subset:
    - Have a profound discussion with the patient and relatives about the disease
    - Evaluate patient performance, bear in mind patient's condition and preferences
    - Choose either empirical ChT or BSC
    - Do CGP, look at targetable, clinically relevant GA and treat the patient on the bases of the results of this test. **Of note: without big evidence so far that this approach is beneficial**.
    - The best option: include the patient in a clinical study if available.

Conclusions

- CUP is a heterogeneous disease with poor prognosis.
- It is mandatory to establish to which prognostic group the patient belongs to.
- In patients belonging to a favourable prognostic subset long-term survival can be achieved with appropriate treatment.
- Patients classified to unfavourable prognostic subset have to be informed about benefits and disadvantages of empiric therapy. For many patients with widespread disease on first presentation and poor PS BSC is the best option.
- Novel approaches (searching for clinically relevant GA) are promising, present a fundamental shift in the paradigm of treatment of cancer patients from tissue-specific to individual, patient/tumour customized treatment, directed according to tumour specific GAs.

2nd Summer School in Medical Oncology
Precision oncology- Are we there yet?
7. - 10. September 2021

Systemic treatment of Ewing sarcoma Where do we stand?

Mojca Unk, MD,MS
Institute of Oncology Ljubljana
Department of medical oncology

James Stephen Ewing
1866- 1943
American pathologist
the first Professor of pathology at Cornell University
1921: discovery of a form of bone cancer later named Ewing's sarcoma

Introduction

Translocation	Fusion	Frequency in ESFT
t(11;22)(q24;q12)	EWSR1–FLI1	~85%–90% of cases
t(21;22)(q22;q12)	EWSR1–ERG	~10% of cases
t(7;22)(p22;q12)	EWSR1–ETV1	Rare
t(17;22)(q12;q12)	EWSR1–ETV4	Rare
t(2;22)(q35;q12)	EWSR1–FEV	Rare
t(16;21)(p11;q22)	FUS–ERG	Rare
t(2;16)(q35;p11)	FUS–FEV	Rare

- a small, blue, round cell sarcoma (RCS)
  gene fusion involving a member of
  the **FET** family and a member of the **ETS** family
  of transcription factors (definitive diagnosis)
- the 3rd most common bone sarcoma (incidence: ~0.1/100,000/year)
- children and adolescents (rarely adults)
- median age at diagnosis: 15 y
- male predominance
- extremity bones (50%), pelvis, ribs and vertebra (any bone, soft tissue)

Rizk et al. Pharmgenomics Pers Med. 2019

Outcome

- historical series: 5-year survival <10 % (micrometastatic disease)
- current recommended multimodal approaches:
  - Localised disease 5-year survival is ~60 % - 75 %
  - Metastatic disease 5-y survival ~20 % - 40 % (metastatic sites, tumour burden)

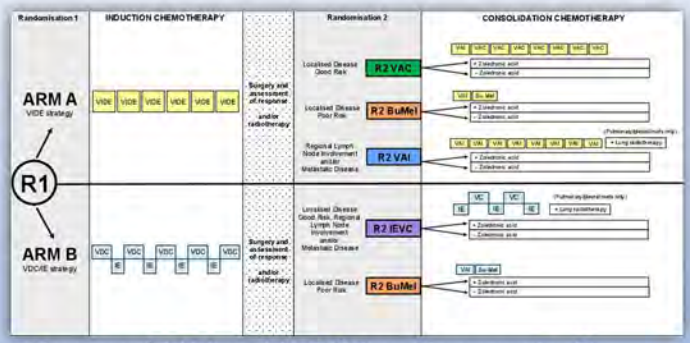
Schuck et al. Int J Radiat Oncol Biol Phys 2003; Womer et al. J Clin Oncol 2012; Le Deley et al J Clin Oncol 2014.

Initial systemic treatment

- Intensive chemotherapy: reported long term survival 60-70 %
- No novel agents available
- Different chemotherapy regimens standard in Europe and USA
- Multi-agent regimen:
  - vincristine (V),
  - doxorubicin (D),
  - actinomycin D (DTIC)
  - cyclophosphamide (C)/ifosfamide (I)
  - etoposide (E).

Schuck et al. Int J Radiat Oncol Biol Phys 2003; Womer et al. J Clin Oncol 2012; Le Deley et al J Clin Oncol 2014.

Comparison of two chemotherapy regimens in Ewing sarcoma (ES):
Euro Ewing 2012 randomized trial (EE2012)

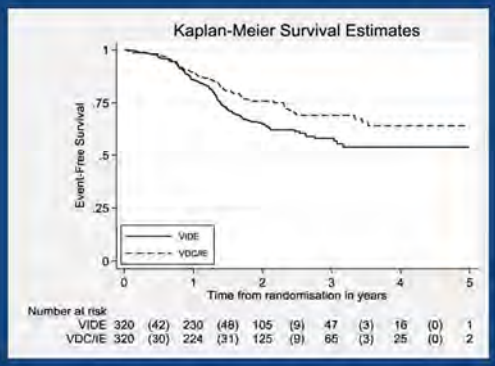


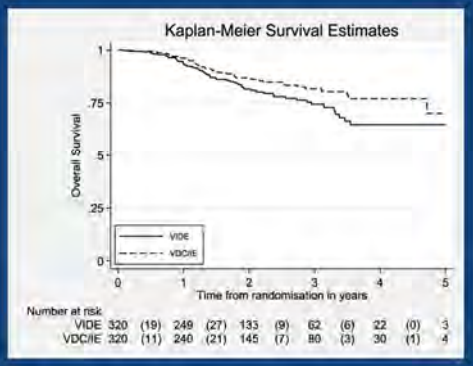
- randomised study
- localised or metastatic ES
- patients aged 5-50 years
- European regimen of VIDE induction and VAI or VAC (V, actinomycin D and I or C) consolidation
- USA regimen of compressed VDC/IE induction and IE/VC consolidation

Brennan et al. J Clin Oncol 2020

Results

Event-free survival (left) and overall survival (right)





Brennan et al. J Clin Oncol 2020

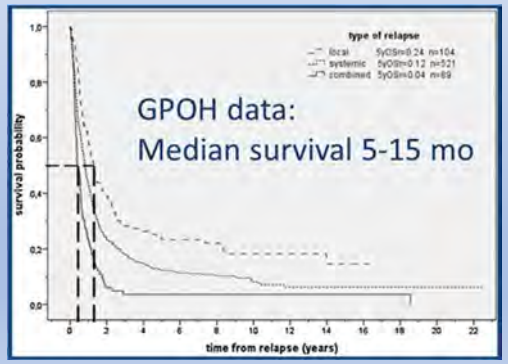
Conclusion

- The interval-compressed VDC/IE regimen is currently the preferred first-line treatment in ES
  - up to nine cycles of induction ChT
  - local therapy
  - consolidation chemotherapy
- The optimal timing for local control:
  - primary site,
  - size,
  - response,
  - anticipated morbidity from surgery
  - tolerability.
- Primary metastatic disease
  - the same treatment approach
  - worse prognosis
  - local treatment with responding metastatic disease; outcome improvement

Bone sarcomas: ESMO–EURACAN–GENTURIS–ERNPaedCan: Ann Oncol 2021

Relapsed ES

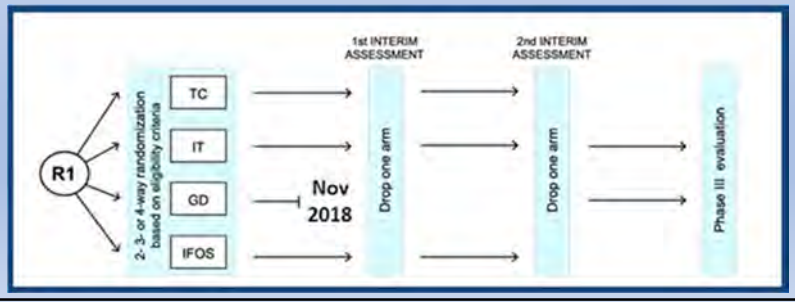
- fatal
- prognostic factor: time to relapse (>2 years from initial diagnosis)
- no standard of care
- multiple regimens used at progression
- little prospective evidence



Stahl et al. Pediatr Blood Cancer 2011; Ferrari et al. Pediatr Blood Cancer 2009; Hunold et al. Pediatr Blood Cancer 2006

rEECur study

- first randomised controlled trial in this setting
- drug regimens:
  - Topotecan/cyclophosphamide (TC)
  - Irinotecan/temozolamid (TEMIRI)
  - HD ifosfamide
  - Gemcitabine/docetaxel (GD)

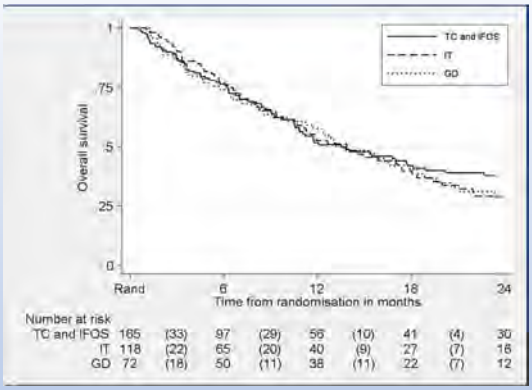


McCabe et al. J Clin Oncol 2020

Results

Treatment Overall Response	GD	IT	TC or IFOS	Overall
Complete response	1	4	2	7 (2%)
Partial response	6	14	27	47 (15%)
Stable disease	16	27	29	72 (23%)
Progressive disease	4	14	11	29 (9%)
Discontinued before cycle 4	36	28	53	117 (38%)
Not evaluable	1	1	4	3 (1%)
Missing	1	16	15	35 (11%)
Total	65	**104**	**141**	**310 (100%)**

Treatment Overall Response	GD	IT	TC or IFOS	Overall
Non responder	[illegible]	70 (80%)	97 (77%)	224 (81%)
Responder	7 (11%)	18 (20%)	29 (23%)	54 (19%)
Total	[illegible]	**88**	**126**	**278**



Irinotecan&temozolamid is less effective than topotecan/cyclophosphamide and HD ifosfamide in

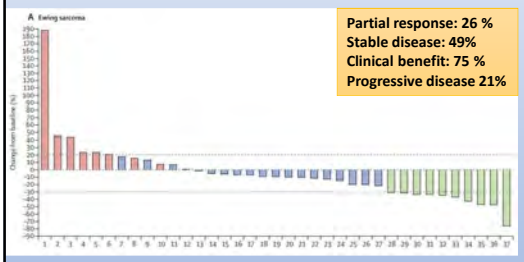
response rate
progression free survival
overall survival

McCabe et al. J Clin Oncol 2020

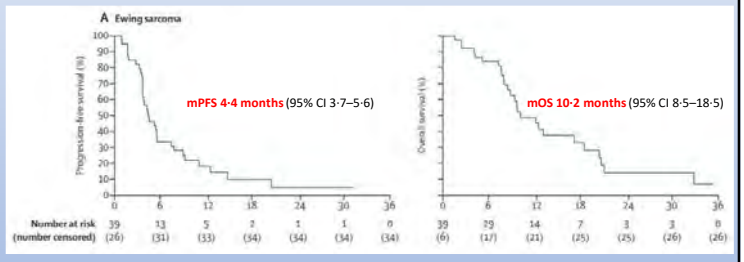
Targeted therapy

Cabozanitib: CABONE study

Multicentre, single arm, phase II



Partial response: 26 %
Stable disease: 49%
Clinical benefit: 75 %
Progressive disease 21%



*2 pts NA

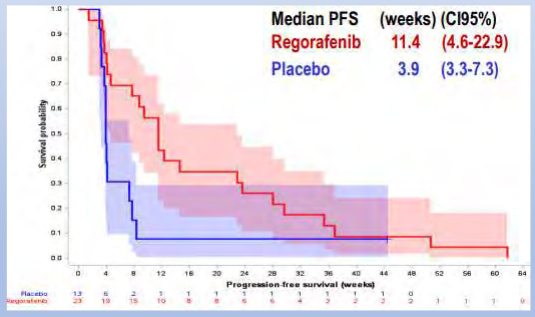
Cabozantinib produced high tumour shrinkage.
MET expression in Ewing sarcoma (negative prognostic factor).
MET inhibition might contribute to the clinical activity of cabozantinib.

Italiano et al. Lancet Oncol. 2020; DuBois et al. Cancer 2010

Regorafenib: REGOBONE study

- randomized, placebo -controlled phase II study
- efficacy and safety of regorafenib (REG) in pts with Ewing sarcoma

Median Follow-up: 25.9 months [11.6 – 51]		Placebo N=13	Regorafenib N=23
Non-progressive rate at 8 weeks (%)		1 (7.7%)	13 (56.5%)
One–sided Confidence Interval (CI95%)		[0.4 – [	[37.5 – [
Response at 8 weeks, n (%)	PR	0 (0)	2 (8.7)
	SD	1 (7.7)	11 (47.8)
	PD	12 (93.3)	10 (43.5)
Best responses	PR*	1 (7.7)	**5 (21.7)**
	SD	3 (23.1)	11 (47.8)
	PD	9 (69.2)	6 (26.1)
Median PFS (CI 95%), (weeks)		**3.9 (3.3-7.3)**	**11.4 (4.6-22.9)**
PFS rate at 24 weeks (CI95%)		**8% (0-29)**	**26% (11-45)**



Regorafenib delays disease progression
Only modest activity- combination therapy???

Duffaud et al. ESMO 2020

Conclusion

- Ewing sarcoma a rare curable cancer
- Treatment in experienced reference centres
- Treatment of primary tumour complex and individualised
- Long term consequences of treatment very significant
- Recurrence remains frequently fatal
- Active new agents emerging
- Testing new strategies requires coordinated international collaboration
- Many improvements still needed

Institute of Oncology Ljubljana
a member of EURACAN

Thank you for your attention!

2nd Summer School in Medical Oncology
Institute of Oncology Ljubljana
September 7-10, 2021

Presentation of Two Patients with Localised Ewing Sarcoma

Aleksandra Sokolova

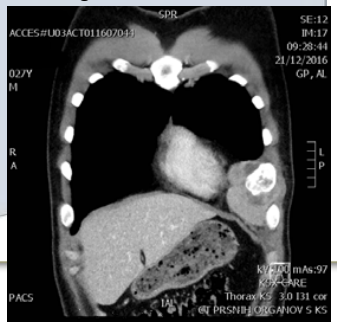
Patient 1, December 2016: male, 27 years

First visit 6/1/17

- no previous diseases
- **3 weeks lump above the left lower ribs, slightly painful, growing**
- no other symptoms
- examination: 6x5 cm palpable lump above lower left ribs
- CRP 35; LDH, AF - normal

US: tumour in left hemithorax

chest CT 21/12/16: 6x7 cm tumour arising from destructed anterior part of the **6th left rib**, infiltrating surrounding soft tissues



US guided fine needle aspiration biopsy 21/12/16

citology: Ewing sarcoma (FISH positive for EWS gene translocation)

bone scintigraphy 4/1/17: no other bone lesions

PET/CT 5/1/17: 8 cm tumour of the 6th left rib (SUV 17.3), infiltration of surrounding soft tissues, **no metastases/pathologic lymph nodes**

Multidisciplinary sarcoma tumour board

Dec/16: male, 27 years, localised Ewing sarcoma of 6th left rib

January 2017 – October 2017: protocol INT-0091

neoadjuvant ChT

- **4 cycles VACA/IE at 3-week intervals** (vincristine, doxorubicin (dactinomycin), cyclophosphamide, alternating with ifosfamide, etoposide)
  - after 2nd cycle the tumour no more palpable
- **CT (Feb/2017)**: good partial regression, no new lesions

surgery

- **tumour excision** (Apr/2017) - resection of tumour with anterior parts of 6th and 7th left ribs
- histology: <5% residual Ewing sarcoma, **R0 resection**, narrow margins

adjuvant ChT + adjuvant RT

- **8 cycles VACA/IE at 3-week intervals** (5th-12th cycle)
  - after 9th and 10th cycle febrile neutropenia gr. 4 and anemia gr. 3
  - 11th and 12th cycle 75% dose
- **concomitant RT to the site of the surgery** (May-Jul/2017, TD 50 Gy)

Dec/16: male, 27 years, localised Ewing sarcoma of 6th left rib

INT-0091: ChT + surgery + RT (Jan-Oct/17)

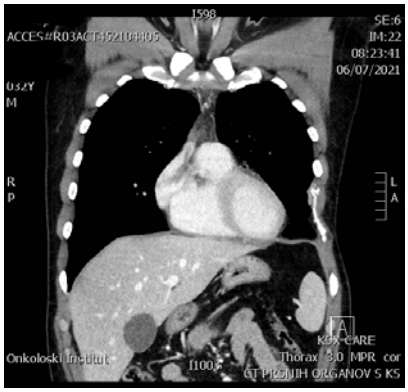
October 2017 ⇢ today:

Regular checkups (+ lab. + chest X-ray) every 3 months for the first 2 years, later every 6 months

Chest CT and bone scintigraphy once a year

After almost 4 years no recurrence of the disease

last chest CT from 2 months ago →



Dec/16: male, 27 years, localised Ewing sarcoma of 6th left rib

INT-0091: ChT + surgery + RT (Jan-Oct/17)

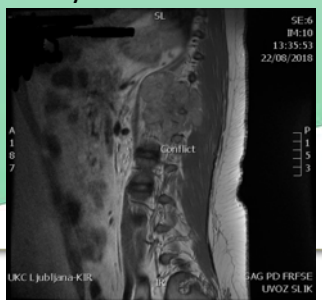
Follow-up Oct/17 ⇢ today: no recurrence

Patient 2, August 2018: male, 23 years

first visit 11/9/18

- previous conditions: psoriasis
- symptoms:
  - 9 months pain in left lumbar region and left lower ribs
  - progressing to both legs with tingling, difficulty walking
  - Aug/2018: **acute paraparesis and urine retention**
- CRP, LDH, AF – all normal

MRI 22/8/18
9x7x6 cm left **paravertebral tumour** (Th11-Th12) **arising from** posterior part of the **12th left rib**, **spreading intraspinally cousing compression of medullary cone**



Urgent surgery 22/8/18 hemilaminectomy of Th11 and Th12 and **removal of intraspinal part of the tumor** -> after surgery residual mild left lumbar pain and still some weakness in legs with tingling

Histology: **Ewing sarcoma** (fusion EWSR1-FLI1)

CT thorax & abdomen and PET/CT – **no distant metastases**

Multidisciplinary sarcoma tumour board

Aug/18: male, 23 years, localised Ewing sarcoma of 12th left rib

September 2018 – June 2019: protocol INT-0091

neoadjuvant ChT

- **4 cycles VACA/IE at 3-week intervals** (vincristine, doxorubicin, cyclophosphamide, dactinomycin alternating with ifosfamide, etoposide)
  - - after 2nd cycle complete resolution of symptoms
- **MRI (Oct/2018)**: good partial regression (9 cm -> 5 cm), no new lesions

surgery

- **tumour excision** (Dec/2018) - posterior spine mobilisation with pediculotomy at Th12 and spine fixation at Th10-L1, and resection of tumour with left diaphragm and 12th rib and posterior parts of 9-11th ribs
- histology: residual Ewing sarcoma with 40-50% tumour necrosis, max diameter 5 cm, **R1 resection**

adjuvant ChT + adjuvant RT

- **8 cycles VACA/IE at 3-week intervals** (5th-12th cycle)
- **concomitant RT to the site of first and second surgery** (Feb-Mar/2019, TD 58 Gy)

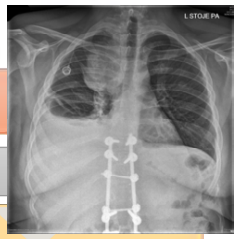
June 2019 ⇢
regular checkups (+ lab. + chest X-ray) every 3 months, chest CT every 6 months

Aug/18: male, 23 years, localised Ewing sarcoma of 12th left rib

INT-0091: ChT + surgery + RT (Sep/18-Jun/19)

June 2020: deterioration

dyspnea, cough, right pleuritic chest pain – right pleural effusion, pneumonia;
↑CRP 200 mg/L, ↑LDH 7 ukat/L, AF norm.

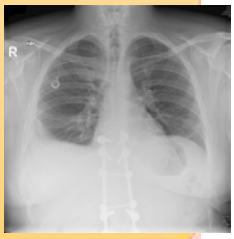


Chest x-ray and CT – metastases (lungs, pleura, mediastinum)

June 2020: metastatic disease
→ 2nd line ChT: gemcitabine and docetaxel
(gemcitabine day 1 and 8, docetaxel day 8, at 3-week intervals)

- after 1st cycle – no more symptoms
- chest X-ray after 3rd cycle: regression
- total 7 cycles (Jun-Nov/2019)

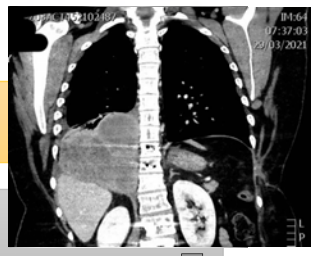
•**PET/CT** (Dec/2020): almost complete response, **only one metabolically active residual mass in right upper mediastinum** behind right brachiocephalic vein (2 cm, SUV 6.4) ➔ **RT** (Jan-Feb/2021, TD 58.8 Gy)



Aug/18: male, 23 years, localised Ewing sarcoma of 12th left rib | **INT-0091: ChT + surgery + RT (Sep/18-Jun/19)** | **Jun/20: metastatic 2nd line ChT (Jun-Nov/20) + RT mediastinum (Feb/21)**

March 2021: regular checkup

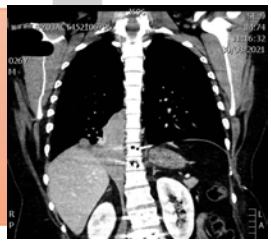
Follow-up chest X-ray 15/3/2021: progression (lungs, pleura)
mild stabbing pain in right chest and right shoulder, PS 0-1



CT 29/3/2021: progression – large tumour mass on right pleura infiltrating right diaphragm and liver + bone metastasis in left iliac bone

3rd line ChT: topotecan and cyclophosphamide
(day 1-5 at 3-week intervals)

- •at initiation of therapy (Apr/2021): right chest pain spreading to right shoulder and legs, fatigue, no dyspnea or caugh; ↑CRP 200 mg/L, ↑LDH 22 ukat/L, ↑AF 3 ukat/L
- •after 1st cycle – disappearance of all symptoms
- •April/2021 ⇢ today: 6 cycles, 2-6th cycle 60% dose (3/5 days, fever on day 3)
- •CT (Aug/2021): good partial regression



Aug/18: male, 23 years, localised Ewing sarcoma of 12th left rib | **INT-0091: ChT + surgery + RT (Sep/18-Jun/19)** | **Jun/20: metastatic 2nd line ChT (Jun-Nov/20) + RT mediastinum (Feb/21)** | **3rd line ChT (Mar/21 ⇢ today)**

Conclusion

Patient 1: male, 27 years, localised Ewing sarcoma of 6th left rib	Patient 2: male, 23 years, localised Ewing sarcoma of 12th left rib
1. biopsy in sarcoma reference center 2. neoadjuvant ChT 3. surgery (R0) 4. adjuvant RT + ChT 5. follow-up – after 4 years no recurrence	1. urgent surgery due to spine compression 2. dignosis from resected part of the tumour 3. neoadjuvant ChT 4. second surgery (R1) 5. adjuvant RT + ChT 6. early recurrence 1 year after completment of treatment, currently on 3rd line of ChT

Best survival with **neoadjuvant ChT** followed by **surgery/RT** if not resectable and **adjuvant ChT +/- RT.**

All patients with **radiological signs of sarcoma** should be **referred to the reference centre for bone sarcomas**.

Biopsy and further treatment should be descussed at multidisciplinary sarcoma tumour board and carried out **in sarcoma reference center.**

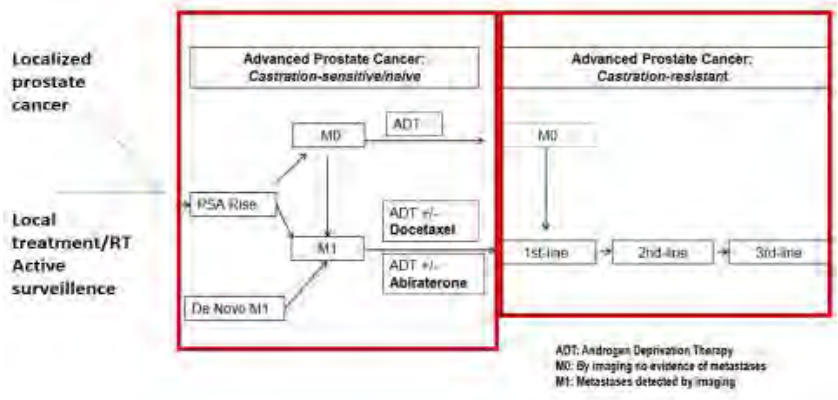
We should **monitor cured patients for long term toxicities and secondary malignancies** >10 years after treatment.

Systemic treatment of prostate cancer – standards and perspectives

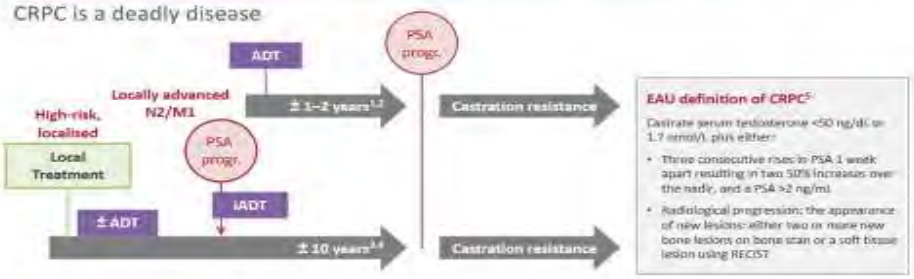
Borislav Belev

Dpt of Medical Oncology
Clinic of Oncology
Clinical Hospital Center Zagreb

Prostate cancer – possible scenarios

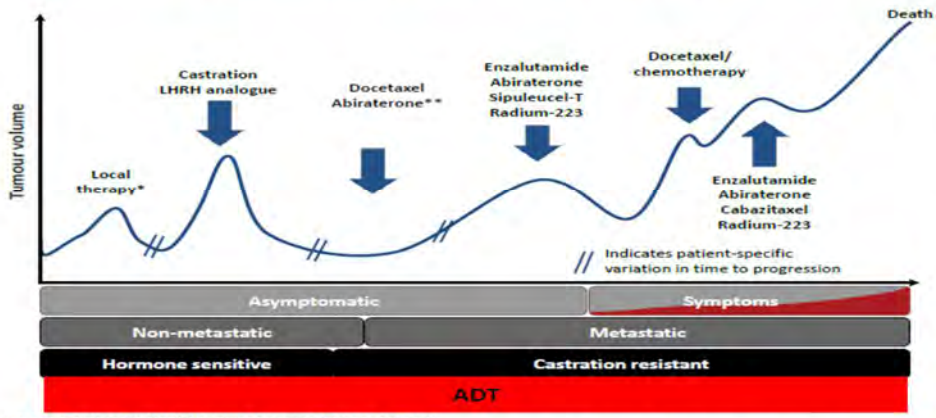


One-third of patients with PCa treated with ADT for a PSA recurrence after local treatment will develop CRPC



ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; EAU, European Association of Urology; IADT, intermittent ADT; M1, distant metastasis of cancer; N2, cancer in lymph nodes; PCa, prostate cancer; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.
1. James ND *Eur Urol* 2015;67:1028–1038; 2. Aly A *et al. Curr Opin Oncol* 2015;27:209–216; 3. Crook JM *et al. N Engl J Med* 2012;367:895–903; 4. Crook JM *et al. N Engl J Med* 2012;367:895–903 (supplementary appendices); 5. Mottet N et al. EAU guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer (accessed October 2018).

ADT remains backbone in CRPC

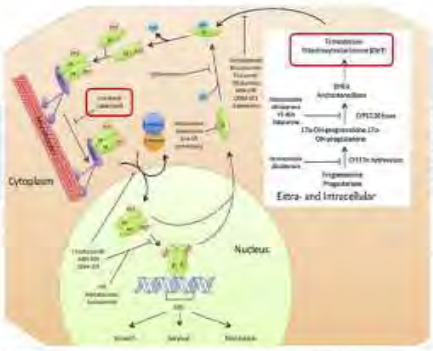


*For example surgery, radiotherapy. LHRH=luteinising hormone-releasing hormone.
**Proposed treatment option are in line with ESMO 2017 guidelines. Abiraterone and docetaxel are not registered for treating patients with HSPC in Romania.
Adapted from George D. *Urology – The Gold Journal* 2013; Available at: http://education.goldjournal.net/path.php?1396:0:Media:title:bxvc:bxvcs. Last accessed February 2016.

Prostate cancer –systemic treatment mechanisms

Chemotherapy

- Docetaxel
- Cabazitaxel



novel generation of antiandrogens

- Enzalutamide
- Abiraterone
- Apalutamide
- Darolutamide
- ...

Pharmacological Research 114 (2016) 162–182

Definition of nonmetastatic-CRPC

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

- a minimum PSA level of 1.0 ng/mL,
- a rising PSA that is at least 2 ng/ml. higher than the nadir PSA
- this rise being at least 25% over the nadir PSA,
- castrate levels of testosterone (<50 ng/mL),
- no radiographic evidence of metastases

CRPC is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:

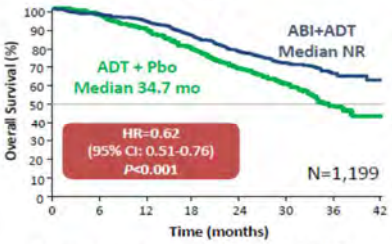
- biochemical progression: Three consecutive rises in PSA 1 wk apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml
- radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft lesion using the Response Evaluation Criteria in Solid Tumours

J Clin Oncol 36:1602-1614. 2016. J Urol 2001;165:1146–51. EUROPEAN UROLOGY 71 (2017) 630–643

ABI+ADT in HPSC

LATITUDE (M1)

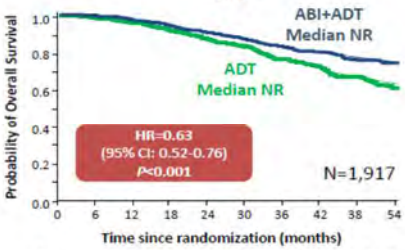
OS



Phase III randomized trial in M1 HSPC
(100% newly diagnosed M1)
Co-primary endpoints: OS and rPFS

STAMPEDE (M0/M1)

OS



Phase III randomized trial in M0/M1 HSPC
(49% newly diagnosed M1)
Primary endpoint: OS

ABI: abiraterone acetate; NR: not reached; rPFS: radiographic progression-free survival

Fizazi K et al. N Eng J Med 2017;377:352-60; James ND et al. N Engl J Med 2017;377:338-51

FDA-Approved Agents for mCRPC

- Dates are for initial approvals

Abiraterone PI, Enzalutamide PI, Docetaxel PI, Cabazitaxel PI, Mitoxantrone PI, Estramustine PI, Sipuleucel-T PI, Pembrolizumab PI, Radium-223 PI, Olaparib PI, Rucaparib PI

VISION: Study Design

- Randomized, open-label phase III study

Stratified by ECOG (0/1 vs 2), LDH (high vs low), liver mets (yes vs no), androgen receptor pathway inhibitors in SoC (yes vs no)

Patients with PSMA+ mCRPC* previously treated with both ≥1 androgen receptor pathway inhibitor and 1-2 taxane regimens, ECOG PS 0-2, life expectancy >6 mo (N = 831)

2:1

^{177}Lu-PSMA-617 7.4 GBq (200 mCi) Q6W for 4 cycles, can be increased to 6 cycles + **Protocol-permitted SoC†** (n = 551)

Protocol-permitted SoC† (n = 280)

CT/MRI/bone scans by BICR:
- *Q8W during treatment*
- *Q12W during follow-up*

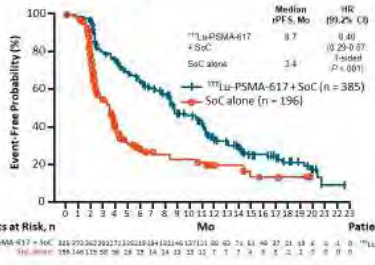
- **Alternate primary endpoints:** radiographic PFS per PCWG3, OS
- **Key secondary endpoints:** ORR and DCR per RECIST v1.1 by BICR, time to first symptomatic skeletal event; **other secondary endpoints:** safety and tolerability, biomarkers including PSA, HRQoL
- 2 analysis sets: OS analysis in full randomized population, radiographic PFS in subset after dropout reduction measures implemented

*≥1 PSMA-positive metastatic lesion with ^{68}Ga uptake >liver and no PSMA-negative lesions in bone with soft tissue component ≥1 cm, lymph nodes ≥2.5 cm, or solid organ ≥1 cm. †Protocol-permitted SoC excludes chemotherapy, immunotherapy, radium-223, and investigational drugs.

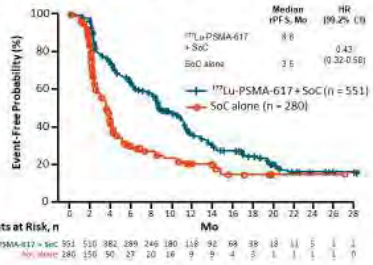
Morris, ASCO 2021; Abstr LBA4; Sartor, NEJM 2021;[Epub]

VISION: Radiographic PFS (Coprimary Endpoint)

Primary Analysis of rPFS (n = 581)



rPFS in OS Analysis Set: All Randomized Patients (N = 831)



Morris, ASCO 2021; Abstr LBA4; Sartor, NEJM 2021;[Epub]

TITAN: Study Design

- International, randomized, double-blind, placebo-controlled phase III trial

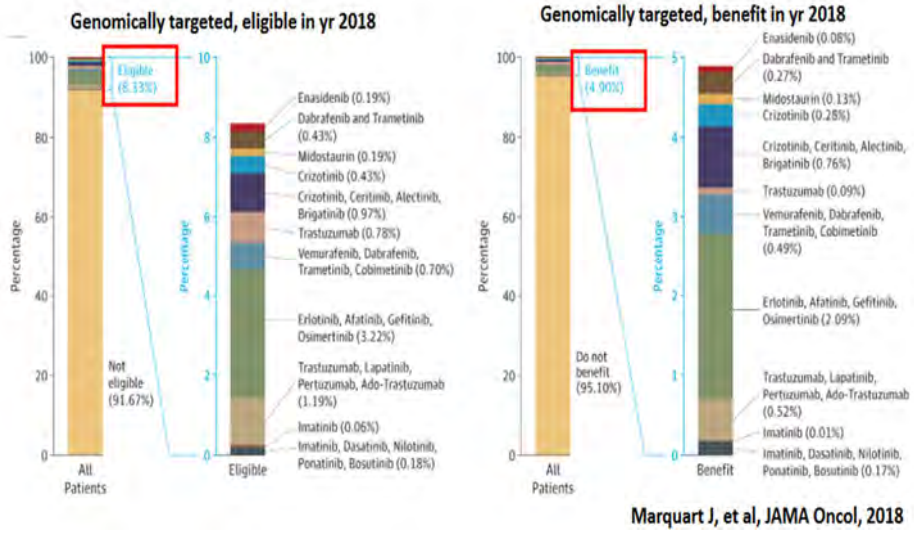
Patients with metastatic castration-sensitive prostate cancer; ECOG PS 0/1; prior ADT ≤ 6 mos for mCSPC or ≤ 3 yrs for local disease (N = 1052)

Apalutamide 240 mg QD + ADT (n = 525)

Placebo + ADT (n = 527)

- Primary endpoints: OS, radiographic PFS
- Secondary endpoints: time to pain progression, time to SRE, time to chronic opioid use, time to cytotoxic chemotherapy
- Exploratory endpoints including: time to PSA progression, PFS2

Chi. ASCO 2015; Abstr 5006. Chi. NEJM. 2015[Epub].



Marquart J, et al, JAMA Oncol, 2018

Conclusion

- 2 main trends in prostate cancer treatment:
  - Tendency to earlier systemic aproach
  - Genetic profiling being more important
- New treatment options should prolong OS in prostate cancer
- Personalized treatment more important and dictate optimal treatment

Univerza v Ljubljani

Advances in Systemic Treatment of Renal Cell Carcinoma (RCC)

Onkološki inštitut Ljubljana

Boštjan Šeruga, MD, PhD

Division of Medical Oncology

Institute of Oncology Ljubljana and University in Ljubljana

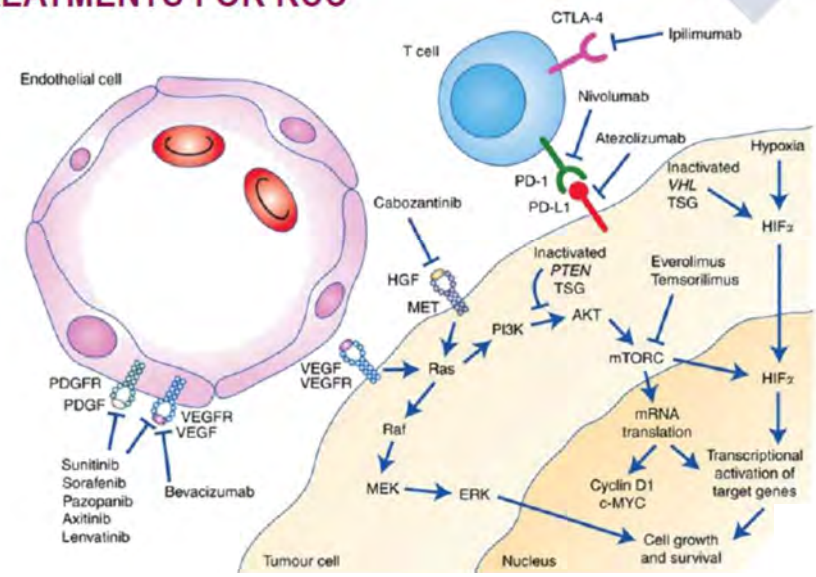
2nd Summer School in Medical Oncology

Ljubljana, September 9, 2021

Topics

- **Adjuvant systemic therapy in RCC**
  - **Anti-VEGF agents**
  - **Immune checkpoint inhibitors (ICIs)**
- **Combined 1st line systemic therapy for advanced RCC**

MECHANISM OF ACTION OF TREATMENTS FOR RCC



Adjuvant phase III trials in RCC

	n	Risk Groups	Patients with clear cell histology	Dosing Intended starting dose	Proportion of patients receiving intended starting dose	Duration of treatment
ASSURE[1]	1943	pT1bN0/NxM0 g 3-4 pT2-4NxM0 any g pT(any)N+M0 any g	79%	Sunitinib 50 mg/d Sorafenib 400 mg BID	Sunitinib:69.6% Sorafenib: 69.8%	Median cycle of treatment sunitinib/sorafenib: 8 Cycles (IQR:2-9) Placebo: 9 Cycles (IQR:7-9)
S-TRAC[2]	615	pT3-4NxM0 any g pT(any)N+M0 any g	>99%	Sunitinib 50 mg/d	Sunitinib: 100%	Median (range, months Sunitinib: 12.4 (0.1-14.9) Placebo: 12.4 (0.03-13/7)
PROTECT[3]	1540	pT2N0/NxM0 g3-4 pT3-4N0/NxM0 any g pT(any)N+M0 any g	>99%	Pazopanib 800 mg/d	Pazopanib: 25%	Median, months Pazopanib 600 mg: 10.6 Pazopanib 800 mg: 10.2
SORCE[4]	1656	Intermediate-or-high-risk (Leibovich score, 3-11)	Predominantly	Sorafenib 400 mg BID	NA	NA
ATLAS[5]	700	pT2-4N0M0 pTxN1M0	Predominantly	Axitinib 5 mg BID	NA	NA

1. Haas NB, et al. Lancet 2016; 387: 2008–16
2. Ravaud, A, et al. New Engl J Med 2016 Dec 8;375(23):2246-2254
3. Motzer RJ, et al. J Clin Oncol. 2017 Dec 10;35(35):3916-3923
4. NCT00492258
5. NCT01599754

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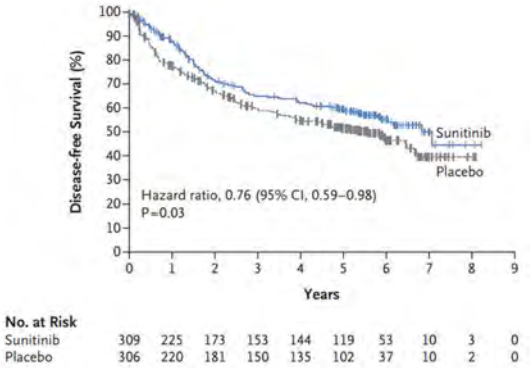
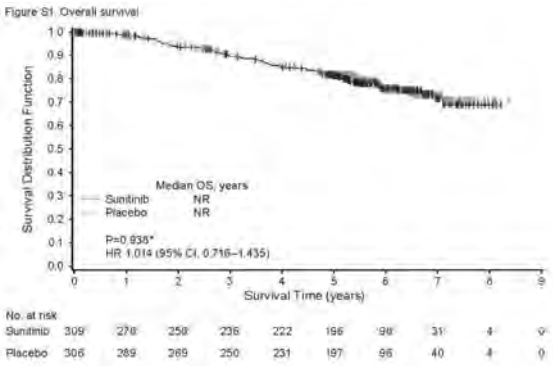
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel,





NEJM 2016

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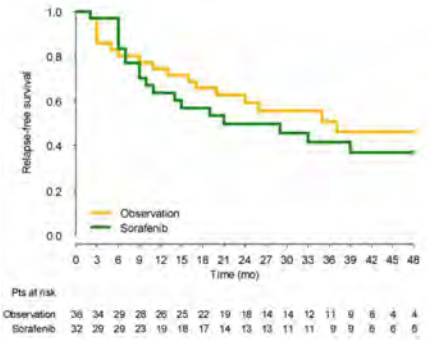
There is no role of adjuvant anti VEGF therapy

1. Haas NB, et al. Lancet 2016; 387: 2008–16
2. Ravaud, A, et al. New Engl J Med 2016 Dec 8;375(23):2246-2254
3. Motzer RJ, et al. J Clin Oncol. 2017 Dec 10;35(35):3916-3923
4. NCT00492258
5. NCT01599754

Sorafenib Versus Observation Following Radical Metastasectomy for Clear-cell Renal Cell Carcinoma: Results from the Phase 2 Randomized Open-label RESORT Study

Giuseppe Procopio [a,], Giulia Apollonio [a], Francesco Cognetti [b], Rosalba Miceli [c], Michele Milella [b],*



Similar results in ECOG-ACRIN E2810 study, which evaluated pazopanib in this setting

There is no role of anti VEGF therapy after radical metastasectomy

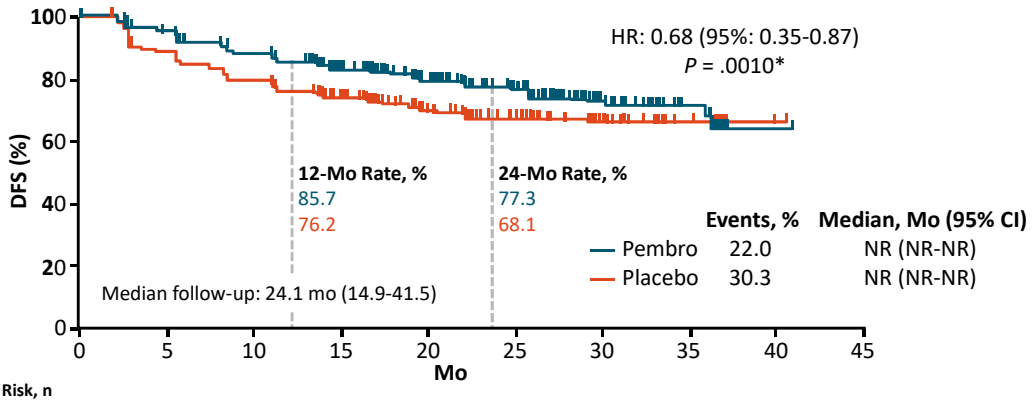
Eur Urol Oncol 2019

Phase III Adjuvant Trials with Immunotherapy

Parameter	IMmotion010[1] (NCT03024996)	PROSPER[2] (NCT03055013)	KEYNOTE-564[3] (NCT03142334)	CheckMate 914[4] (NCT03138512)
Drug	Atezolizumab	Nivolumab	Pembrolizumab	Nivolumab + ipilimumab
Histology	Clear-cell ± sarcomatoid histology	RCC of any histology	Clear-cell ± sarcomatoid features	Clear-cell ± sarcomatoid features
Dose duration	1 yr	2 doses prior to surgery and adjuvant nivolumab for 9 mos	1 yr	6 mos
Risk classification	T2 grade 4, T3a grade 3/4, T3b/c any grade, T4 any grade, or TxN+ any grade	Clinical stage ≥ T2 or any N+	pT2, grade 4; pT3/4, any grade; N+ M0; M1 NED	pT2aN0, grade 3-4; pT2b-T4; N+
Primary endpoint	DFS	RFS at 5 yrs	DFS	DFS
BICR	Yes	Yes	Yes	Yes

1. Uzzo. ASCO 2017. Abstr TPS4598. 2. Harshman. ASCO 2018. Abstr TPS4597.
3. Choueiri. ASCO 2018. Abstr TPS4599. 4. Bex. ESMO 2018. Abstr 927TiP.

KEYNOTE-564: DFS (Primary Endpoint)



Patients at Risk, n										
Pembro	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

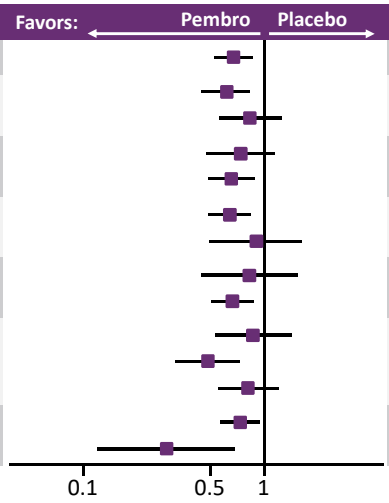
*Crossed *P* value boundary for statistical significance of .0114.

Choueiri. ASCO 2021. Abstr LBA5. Reproduced with permission.

Slide credit: clinicaloptions.com

KEYNOTE-564: DFS by Subgroup (ITT)

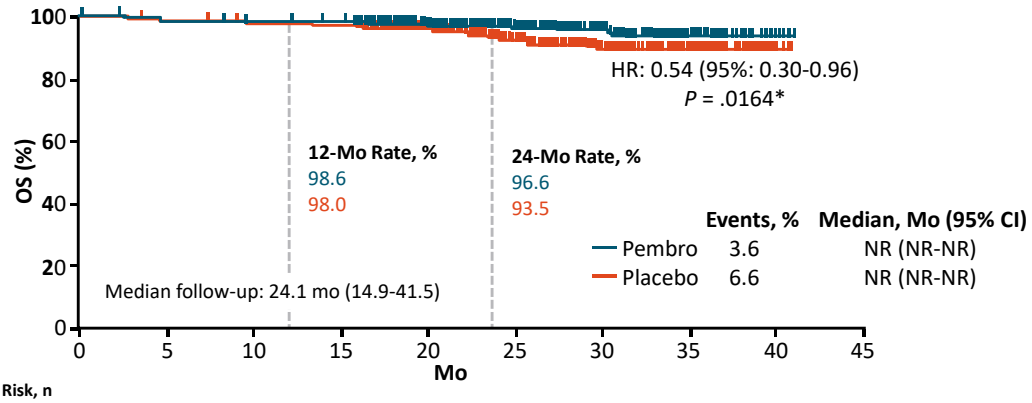
Subgroup		Events/Patients, n/N	HR (95% CI)
Overall		260/994	0.68 (0.53-0.87)
Age	▪ <65 yr	166/664	0.62 (0.45-0.84)
	▪ ≥65 yr	94/330	0.84 (0.56-1.26)
Sex	▪ Male	79/288	0.75 (0.48-1.16)
	▪ Female	181/706	0.66 (0.49-0.89)
ECOG PS	▪ 0	215/847	0.65 (0.49-0.85)
	▪ 1	45/147	0.91 (0.50-1.63)
PD-L1 status	▪ CPS <1	42/237	0.83 (0.45-1.51)
	▪ CPS ≥1	215/748	0.67 (0.51-0.88)
Region	▪ North America	65/258	0.87 (0.53-1.41)
	▪ European Union	97/375	0.49 (0.32-0.74)
	▪ Rest of world	98/361	0.81 (0.55-1.21)
Metastatic staging	▪ M0	234/936	0.74 (0.57-0.96)
	▪ M1 NED	26/58	0.29 (0.12-0.69)



Choueiri. ASCO 2021. Abstr LBA5. Reproduced with permission.

Slide credit: clinicaloptions.com

KEYNOTE-564: Interim OS



Patients at Risk, n										
Pembro	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

*Did not cross *P* value boundary for statistical significance of .0000093 for 51 OS events; final OS analysis to occur after ~200 OS events.

Choueiri. ASCO 2021. Abstr LBA5. Reproduced with permission.

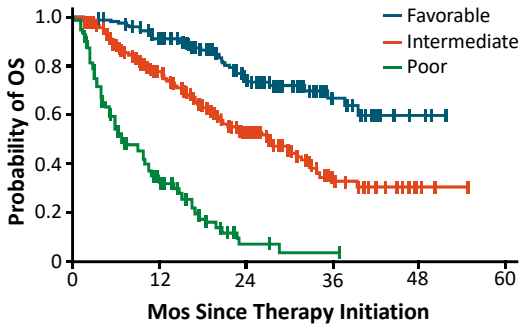
Slide credit: clinicaloptions.com

Take home message (adjuvant therapy)

- **No role of anti-VEGF adjuvant therapy in locoregional RCC after nephrectomy and after "radical" metastasectomy**
  - **Conflicting results for DFS, does not improve OS,**
  - **Toxic treatment, deterioration of QoL**
- **ICIs promising new adjuvant therapy in RCC**

IMDC (Heng) Prognostic Criteria

- **Clinical**
  - **KPS < 80% (*P* < .0001)**
  - **Time from diagnosis to tx < 1 yr (*P* = .01)**
- **Laboratory**
  - **Hemoglobin < LLN (*P* < .0001)**
  - **Calcium > ULN (*P* = .0006)**
  - **Neutrophil count > ULN (*P* < .0001)**
  - **Platelet count > ULN (*P* = .01)**



No. of Events/No. at Risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Favorable: 0 risk factors; intermediate: 1-2 risk factors; poor: 3+ risk factors

Heng. JCO. 2009;27:5794.

IMDC (Heng) Prognostic Criteria

- **Clinical**
  - **KPS < 80% (*P* < .0001)**
  - **Time from diagnosis to tx < 1 yr (*P* = .01)**
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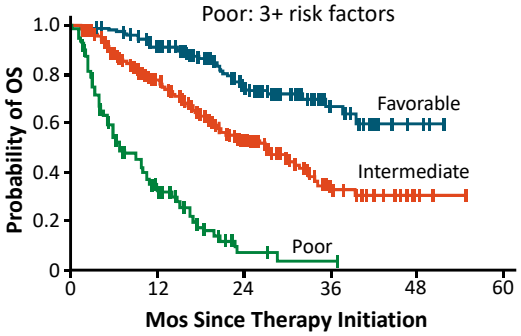
Favorable: 0 risk factors; Intermediate: 1-2 risk factors; Poor: 3+ risk factors

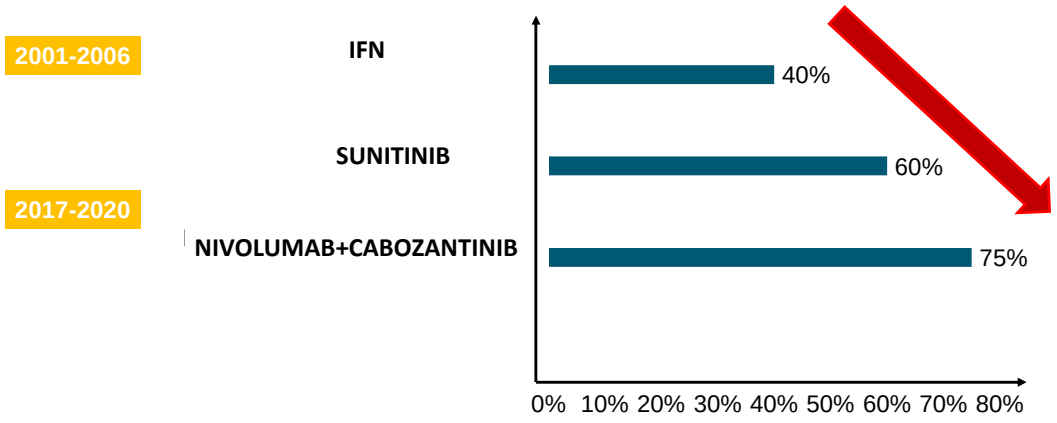


75% to 80% of patients with mRCC have ≥ 1 of these risk factors (intermediate or poor risk)

Heng. JCO. 2009;27:5794.

Progress in the treatment of patients with advanced RCC

2-year OS of all patients (all prognostic groups)



Choueiri T, Check Mate 9ER,ESMO 2020; Gore ME, Lancet 2010

Phase III clinical trials in the 1st line therapy

Trial	Comparison	Primary endpoint (s)
CheckMate 214 Motzer et al, NEJM, 2018	Ipilimumab+Nivolumab vs. Sunitinib	OS, ORR, PFS in patients with intermediate and poor prognosis
Keynote 426 Rini et al, NEJM, 2019	Pembrolizumab+Axitinib vs. Sunitinib	OS in PFS in the ITT populations (all-comers)
Javelin Renal 101 Motzer et al, NEJM, 2018	Avelumab+Axitinib vs. Sunitinib	OS in PFS in PD-L1+ patients
Immotion 151 Rini et al, Lancet, 2019	Atezolizumab+Bevacizumab vs. Sunitinib	PFS in PD-L1+ OS in the ITT population
CheckMate 9ER Choueiri et al, ESMO 2020	Nivolumab+Cabozantinib vs. Sunitinib	PFS in the ITT population
Clear Motzer et al, NEJM 2021	Pembrolizumab+Lenvatinib vs. Lenvatinib+Everolimus vs. Sunitinib	PFS in the ITT population

Results of phase III trials in the 1st line

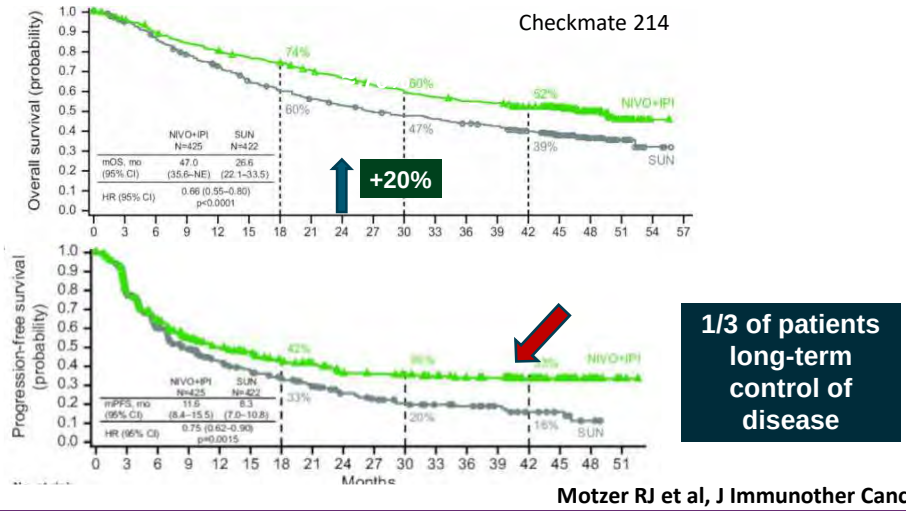
Trial	Comparison	Results
CheckMate 214 Motzer et al, NEJM, 2018	Ipilimumab+Nivolumab vs. Sunitinib	ORR: 42% vs. 27%, PFS: 11.6 vs 8.4 mo (HR 0.82-ns), OS: at 4 yrs HR 0.65
Keynote 426 Rini et al, NEJM, 2019	Pembrolizumab+Axitinib vs. Sunitinib	PFS: 15.1 vs. 11.1. mo (HR 0.69), at OS: 2 yrs 74% vs 66% (HR 0.68)
Javelin Renal 101 Motzer et al, NEJM, 2018	Avelumab+Axitinib vs. Sunitinib	PFS (PD-L1+): 13.8 vs 7.2 mo (HR 0.61). OS: HR 0.82 (ns-immature)
Immotion 151 Rini et al, Lancet, 2019	Atezolizumab+Bevacizumab vs. Sunitinib	PFS (PD-L1+): 11.2 vs 7.7 mo (HR 0.74) OS (ITT): HR 0.93 -ns
CheckMate 9ER Choueiri et al, ESMO 2020	Nivolumab+Cabozantinib vs. Sunitinib	PFS (ITT): 16.6 vs. 8.3 mo (HR 0.51) OS (ITT) @ 12 mo: 85.7% vs 75.6%
Clear Motzer et al, NEJM 2021	Pembrolizumab+Lenvatinib vs. Lenvatinib+Everolimus vs. Sunitinib	PFS (ITT): 23.9 vs. 9.2 mo (HR 0.39) for P+L, OS (ITT): HR 0.66 for P+L

Phase III clinical trials in the 1st line therapy

Trial	Comparison	ORR (CR) (%)
CheckMate 214 Motzer et al, NEJM, 2018	Ipilimumab+Nivolumab vs. Sunitinib	42% vs. 27% (9% vs 1%)
Keynote 426 Rini et al, NEJM, 2019	Pembrolizumab+Axitinib vs. Sunitinib	59.3% vs. 35.7% (5.8% vs. 1.9%)
Javelin Renal 101 Motzer et al, NEJM, 2018	Avelumab+Axitinib vs. Sunitinib	51.4% vs. 25.7% (3.4% vs. 1.8%)
Immotion 151 Rini et al, Lancet, 2019	Atezolizumab+Bevacizumab vs. Sunitinib	37% vs. 33% (5% vs. 2%)
CheckMate 9ER Choueiri et al, ESMO 2020	Nivolumab+Kabozantinib vs. Sunitinib	55.7% vs. 27.1% (8% vs. 4.6%)
Clear Motzer et al, NEJM 2021	Pembrolizumab+Lenvatinib vs. Lenvatinib+Everolimus vs. Sunitinib	71% vs. 53.5% vs. 36.1% (16.8% vs. 9.8 vs. 4.2%)

Long-term control of disease with ICIs

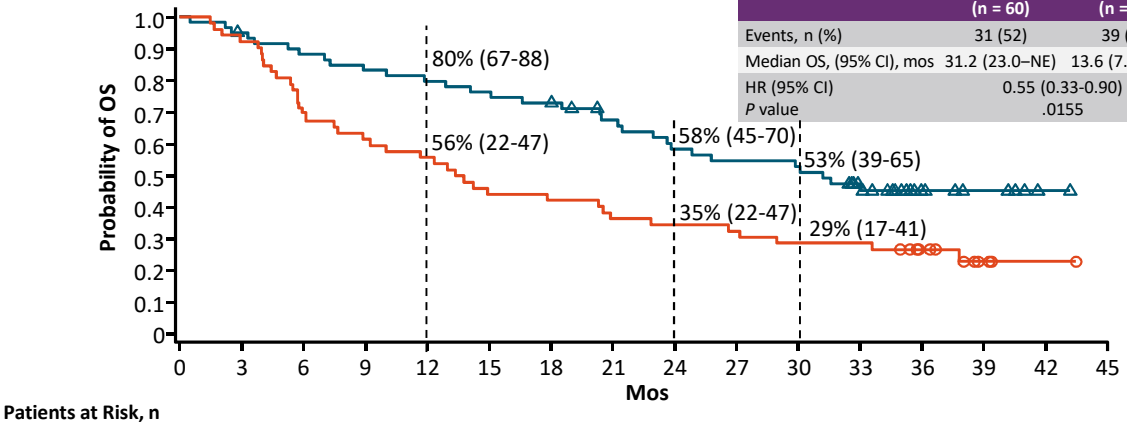
Patients with intermediate and poor prognosis



1/3 of patients long-term control of disease

Motzer RJ et al, J Immunother Cancer, 2020

OS with Nivo + Ipi vs Sunitinib in CheckMate 214: Intermediate/Poor-Risk Sarcomatoid Patients



	Nivo + Ipi (n = 60)	Sun (n = 52)
Events, n (%)	31 (52)	39 (75)
Median OS, (95% CI), mos	31.2 (23.0–NE)	13.6 (7.7–20.9)
HR (95% CI)	0.55 (0.33-0.90)	
P value	.0155	

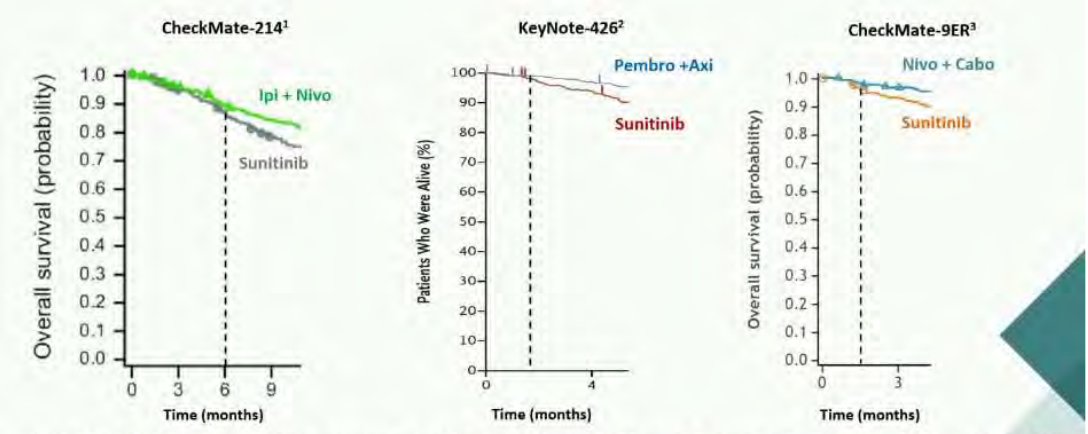
Patients at Risk, n

Nivo + ipi	60	56	52	49	47	45	43	37	32	30	29	22	10	5	1	0
Sun	52	48	36	32	29	23	22	19	18	17	15	15	9	3	1	0

McDermott. KCA 2018.

Slide credit: clinicaloptions.com

Which combination works earlier?



In the CM-214 trial, curves started separating at 6 months (i.e. at the second disease assessment), while in both the KN-426, as well as in the CM-9ER, curves' separation appears to be anticipated by almost 4 months

1. Motzer RJ, et al. *J Immunother Cancer* 2020;8:e000891; 2. Rini BI, et al. *N Engl J Med* 2019:380:1116-27; 3. Choueiri TK, et al. *ESMO* 2020 (abs. 6960); 4. Porta C & Rizzo M. *Nat Rev Nephrol* 2019;15:324-5.

KEYNOTE 426
Absolute benefits of combined therapy

Subgroup	12-mo survival		
	Pembrolizumab+ Axitinib	Sunitinib	
Prognostic group			
Favourable	95%	94%	Δ 1%
Intermediate	91%	77%	Δ 14%
Poor	70%	45%	Δ 25%
PD-L1 CPS			
≥ 1%	90%	78%	Δ 12%
< 1%	92%	78%	Δ 14%

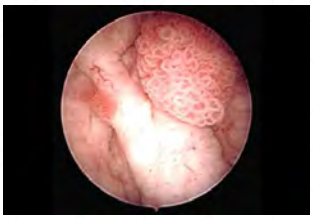
IMDC denotes International Metastatic Renal Cell Carcinoma Database Consortium

Rini et al, NEJM, 2019

Take-home Messages (advanced disease)

- **Combined therapy which involves ICIs is a new 1st line standard of treatment in patients with advanced RCC (for all?)**
- **With combination therapy durable remission can be achieved also in patients with poor prognosis disease**
- **Combination of ICI and anti VEGF preferable 1st line therapy in patients with symptomatic disease**


Be curious, ask questions and share what you learn.
ASK. LEARN. SHARE.
mike-taylor.org



Bladder cancer systemic treatment

Is something new going on?

Milena Gnjidić, UHC Zagreb, Croatia

9.2021

Is something new going on ?

~ 3% of all new cancer
~ 550 000 new cases per year worldwide
~ 200 000 death annually (2018)

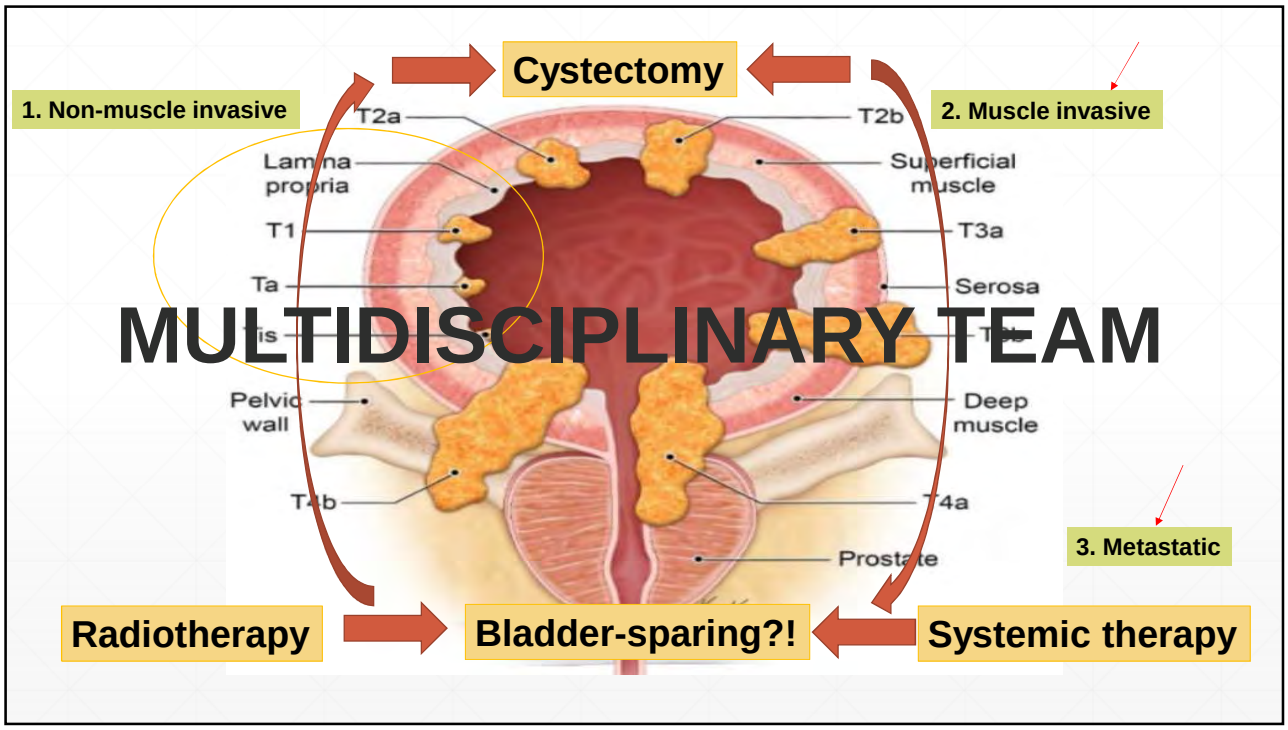
HAVE YOU EVER HEARD ABOUT BLADDER CANCER?

#BladderCancerAware

Bladder Cancer Awareness Month
Digital World Tour
May 2021

~ Until the advent of immunotherapy 2015. there was no new treatment options for decades

Bray F at al. GLOBOCAN. CA Cancer J Clin. 2018.

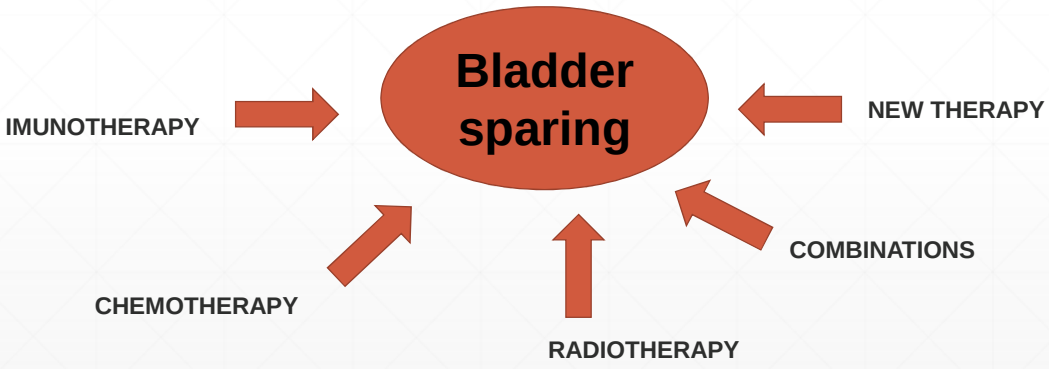


Local disease

Is something new going on ?

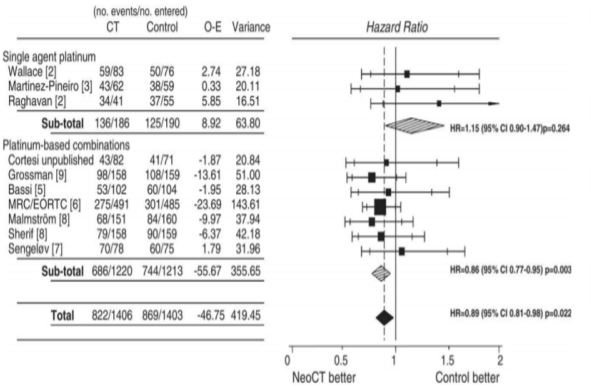
Dream of every bladder-cancer patient: NO cystectomy !

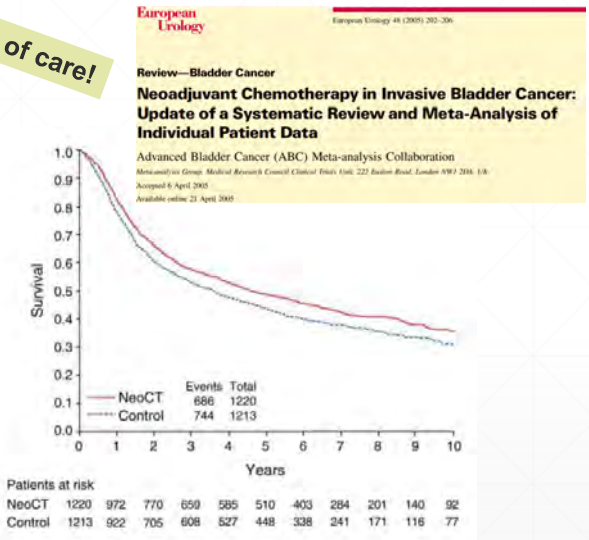
Early diagnosis



Neoadjuvant chemotherapy

Standard of care!





Cisplatin-combinations better than mono Cis

ABC meta analysis. Eur Urol. 2005

Neoadjuvant chemotherapy

	SWOG-8710 [6]	BA06 30894 [8]	Choueiri et al. [13] (NCT00808639)	Plimack et al. [14] (NCT01031420)	Dash et al. [18]	MSK [20]
N	317	976	39	40	42	154
Phase	3	3	2	2	R	R
Regimen	MVAC	CMV	ddMVAC	aaMVAC	GC	GC
Duration of NAC, weeks	14	NA	8	6	12	12
Median time to definitive treatment after randomization, weeks	16	NA	14	9.7	19	17
Planned surgery rates, %	82	NA	97	98	NA	NA
pCR (pT0N0) rates, %	38	NA	26	38	26	21
Downstaging (<pT2) to non-muscle invasive disease, %	44	NA	49	53	36	46

R: retrospective; NA: not available.

Kim I et al. Int J Mol Sci. 2021.

Neoadjuvant immunotherapy

Trial	Agent	Phase	Population	Cisplatin Eligibility	Upper-Tract Disease Included
Signle-Agent therapy					
NCT02662309 (ABACUS)	Atezolizumab	2	cT2-T4N0	N	N
NCT02451423	Atezolizumab	2	cTa-T4N0	N	N
NCT03577132	Atezolizumab	2	cT2-T4N0-1	Y	N
NCT03498196 (BL-AIR)	Avelumab	1/2	cT2-T4aN0	N	N
NCT03406650 (SAKK 06/17)	Durvalumab	2	cT2-T4N0-1	Y	Y
NCT02736266 (PURE-01)	Pembrolizumab	2	cT2-T4N0	Y	N
NCT03212651 (PANDORE)	Pembrolizumab	2	cT2-T4N0	N	N
NCT03319745	Pembrolizumab	2	cT2-T4N0	Y	N
CPI with other immunotherapy					
NCT02812420	Durvalumab + Tremelimumab	1	cT2-3aN0	Y	Y
NCT03472274 (DUTRENEO)	Durvalumab + Tremelimumab	2	cT2-T4N0-1	Y	N
NCT03234153 (NITIMIB)	Durvalumab + Tremelimumab	2	cTa-T4anyN	N	N
NCT02845323	Nivolumab + Urelumab	2	cTa-T4N0	N	N
NCT03387761 (NABUCCO)	Nivolumab + Ipilimumab	1b	cTa-T4anyN	Y	N
NCT03520491 (CA209-9DJ)	Nivolumab + Ipilimumab	2	cT2-4aN0	N	N
NCT03532451 (PrE0807)	Nivolumab + Lirilumab	1b	cT2-T4aN0-1	Y	N
NCT04209114 (CA045-009)	Nivolumab + Bempeg	3	cT2-T4N0	N	N
NCT03832673 (PECULIAR)	Pembrolizumab + Epacadostat	2	cT2-T3N0	Y	N
NCT04586244 (Optimus)	Retifanlimab + Epacadostat	2	cT2-T3bN0	N	N
NCT04430036	Zalifrelimab + Balstilimab	2	cT2-T4N0-1	Y	N

Kim I et al. Int J Mol Sci. 2021.

Neoadjuvant therapy

CPI with chemotherapy					
NCT02989584	Atezolizumab + GC	2	cT2-T4aN0	Y	N
NCT03674424 (AURA)	Avelumab + Chemotherapy	2	cT2-T4anyN	Y	N
NCT03732677 (NIAGARA)	Durvalumab + GC	3	cT2-T4aN0	Y	N
NCT03549715 (NEMIO)	Durvalumab + Tremelimumab + ddMVAC	1/2	cT2-T4N0-1	Y	N
NCT03912818	Durvalumab + Chemotherapy	2	cT2-T4N0-1	Y	N
NCT03661320 (ENERGIZE)	Nivolumab + BMS-986205 + GC	3	cT2-T4N0	Y	N
NCT03294304 (BLASST-1)	Nivolumab + GC	2	cT2-T4N0-1	Y	N
NCT03558087	Nivolumab + GC	2	cTa-T4N0	Y	N
NCT04506554	Nivolumab + aaMVAC	2	cT2-T3N0	Y	N
NCT04383743	Pembrolizumab + MVAC	2	cT2-T4N0-1	Y	N
NCT02690558	Pembrolizumab + GC	2	cT2-T4N0	Y	N
NCT02365766 (HCRN GU14-188)	Pembrolizumab + GC	2	cT2-T4N0	Y/N (two cohorts)	Y
NCT03924856 (KEYNOTE-866)	Pembrolizumab + GC	3	cT2-T4N0-1	Y	N
NCT04861584 (GZZJU-2021NB)	Teriprizumab + GC	2	cT2-T4N0-1	Y	N
NCT04730219	Tislelizumab + Nab-paclitaxel	2	cT2-T4aN0	Y	N
NCT04553939	Toripalimab + Gemcitabine	2	cT2-T4anyN	N	N
NCT04099589	Toripalimab + GC	2	cT2-T4aN0	Y	Y

Kim I et al. Int J Mol Sci. 2021.

Neoadjuvant therapy

CPI with other agents					
NCT04289779 (ABATE)	Atezolizumab + Cabozantinib	2	cT2-T4anyN	N	N
NCT03534492 (NEODURVARIB)	Durvalumab + Olaparib	2	cT2-T4aN0	Y	N
NCT03773666 (BLASST-2)	Durvalumab + Oleclumab	1	cT2-T4aN0	N	N
NCT04610671	Nivolumab + CG0070	1	cT2-T4aN0	N	N
NCT03518320	Nivolumab + TAR-200	1	cT2-T3N0-1	N	N
NCT04700124 (KEYNOTE-B15/EV-304)	Pembrolizumab + Enfortumab vedotin	3	cT2-T4N0-1	Y	N
NCT03924895 (KEYNOTE-905/EV-303)	Pembrolizumab + Enfortumab vedotin	3	cT2-T4N0-1	N	N
NCT03978624	Pembrolizumab + Entinostat	2	cT2-T4aN0	N	N
NA (SURE)	Pembrolizumab + Sacituzumab govitecan	2	cT2-T4N0	N	N
NCT04813107	Tislelizumab + APL-1202	1/2	cT2-T4aN0	N	N
CPI with radiation					
NCT04543110 (RADIANT)	Durvalumab + Radiation	2	cT2-T4aN0	N	N
NCT04779489 (CIRTiN-BC)	CPIs + Radiation	2	anyTN+	N	N
NCT03529890 (RACE IT)	Nivolumab + Radiation	2	cT3-T4anyN	N	N

Kim I et al. Int J Mol Sci. 2021.

Neoadjuvant therapy

Is something new going on ?

Could neoadj CPIs replace neoadj chemo?

	Pure-01 [38,41]	ABACUS [39,42]	NABUCCO [50]	DUTRENEO [51]	BLASST-1 [55]	HCRN GU14-188 [56,57]		SWOG8710 [6]	GETUG/AFU [21]	
	PEM	ATEZO	IPI/NIVO	DU/TREME	NIVO + GC	Cohort 1: PEM + GC	Cohort 2: PEM + GEM	MVAC	Arm A: ddM-VAC	ARM B: GC
N	143	88	24	23	41	43	37	317	248	245
pCR (%)	39	31	46	35	49	44	45	38	42	36
Downstaging (<pT2) (%)	56	39	58	57	66	61	52	NA	63	49

Combinations?
New combinations?

CPIs = checkpoint inhibitors

Kim I et al. Int J Mol Sci. 2021.

Adjuvant chemotherapy

	EORTC 30994, 2015 [22] (NCT00028756)	SOGUG, 2010 [24]	Cognetti et al., 2012 [23]
N	284	142	194
Phase	3	3	3
Regimen	GC, high-dose MVAC, MVAC	PGC	GC
DFS	5-year DFS rates: 47.6% (AC) vs. 31.8% (control)	NA	5-year DFS rates: 37.2% (AC) vs. 42.3% (control)
OS	5-year OS rates: 53.6% (AC) vs. 47.7% (control)	5-year OS rates: 60% (AC) vs. 31% (control)	5-year OS rates: 43.4% (AC) vs. 53.7% (control)

PGC: Paclitaxel/gemcitabine/cisplatin; NA, not available.

Kim I et al. Int J Mol Sci. 2021.

Adjuvant immunotherapy

Trial	Phase	Agent	Control	N	Primary Endpoint	Upper Tract	Cisplatin-Based NAC
NCT03244384 [76] (AMBASSADOR)	3	Pembrolizumab	Observation	739	OS, DFS	Included	Included
NCT02632409 [75] (CheckMate 274)	3	Nivolumab	Placebo	700	DFS	Included	Included
NCT02450331 [74] (IMvigor010)	3	Atezolizumab	Observation	809	DFS	Included	Included

negative

Kim I et al. Int J Mol Sci. 2021.

Adjuvant immunotherapy

Is something new going on ?

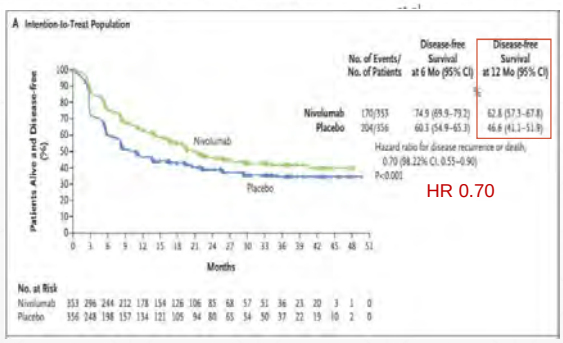
The NEW ENGLAND JOURNAL of MEDICINE June 3, 2021

CheckMate 274

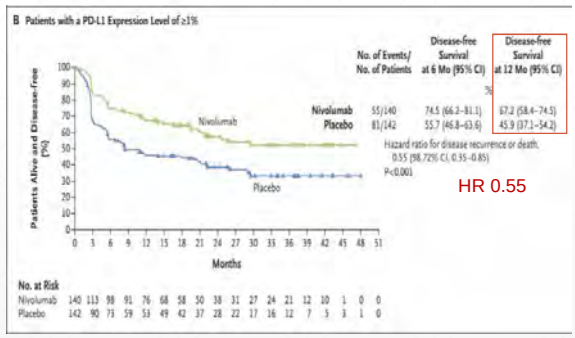
Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

Dean F. Bajorin, M.D., J. Alfred Witjes, M.D., Jürgen E. Gschwend, M.D., Michael Schenker, M.D., Begoña P. Valderrama, M.D., Yoshihiko Tomita, M.D., Ph.D., Aristotelis Bamias, M.D., Thierry Lebret, M.D., Shahrokh F. Shariat, M.D., Se Hoon Park, M.D., Dingwei Ye, M.D., Mads Agerbaek, M.D.,

8.2021 FDA approved!



HR 0.70



HR 0.55

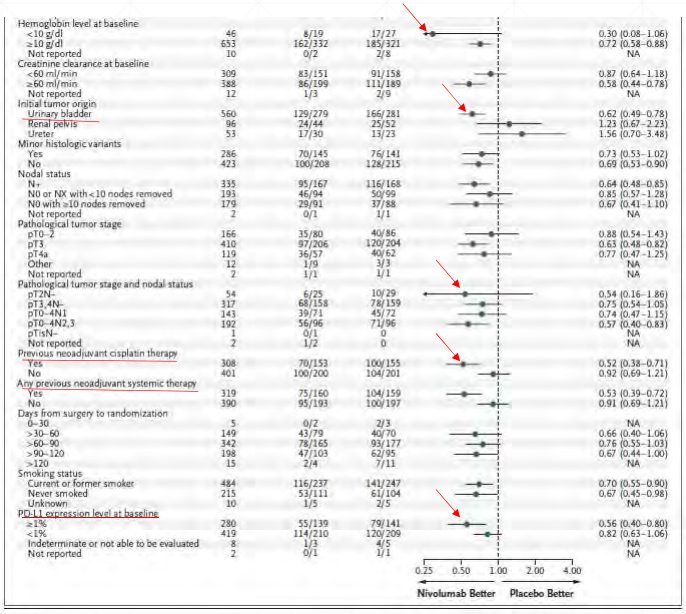
DFS 20.8 ~ 10.8mo

Adjuvant Nivolumab

CheckMate 274

Subgroup analysis

1. **PD-L1 expression > 1% !**
2. **Neoadjuvant chemotherapy !**
3. **Urinary bladder !**



Overall survival ?!
Follow-up 20 mo disease recurrence = 48.2% ~ 57.3%

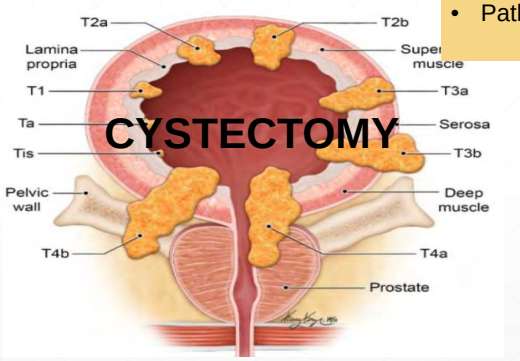
Bajorin DF et al. N Engl J Med. 2021.

Neoadjuvant vs adjuvant therapy?

pro

- Better tolerance
- Less extensive surgery
- Response monitoring
- Primary tumor=more antigens

- Not delaying currative cystectomy
- Pathohistology



neoadjuvant

adjuvant

contra

- Delaying cystectomy
- Refractoriness to chemoth or immunoth

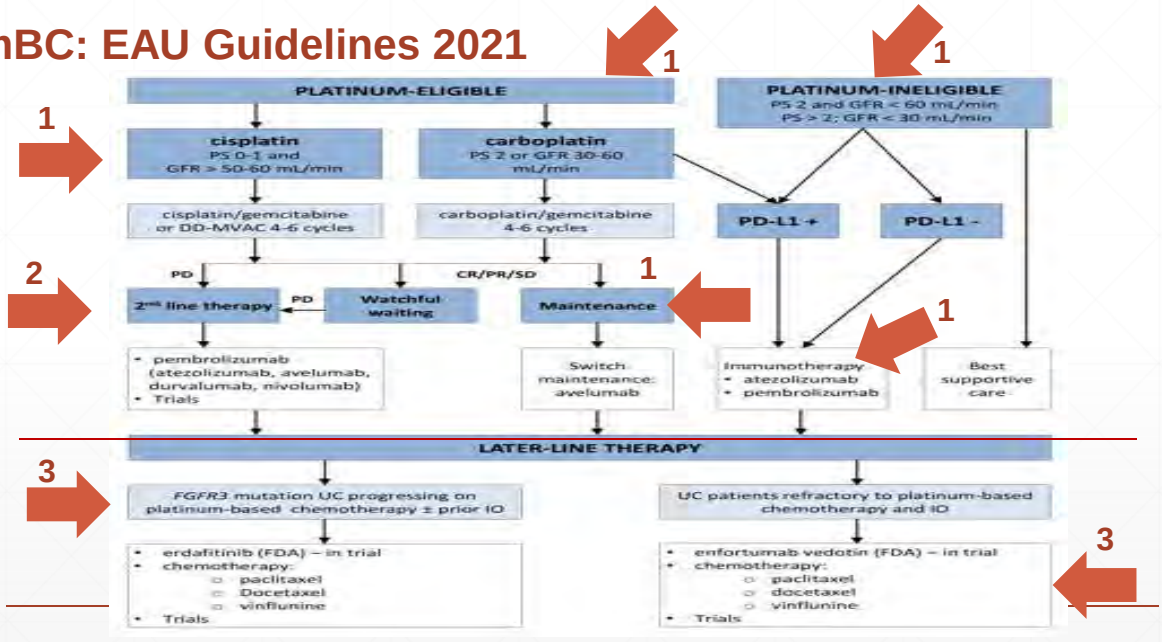
Biomarkers !?

Advanced disease

Is something new going on ?

Dream of every metastatic bladder-cancer patient: NO mets !

mBC: EAU Guidelines 2021



17

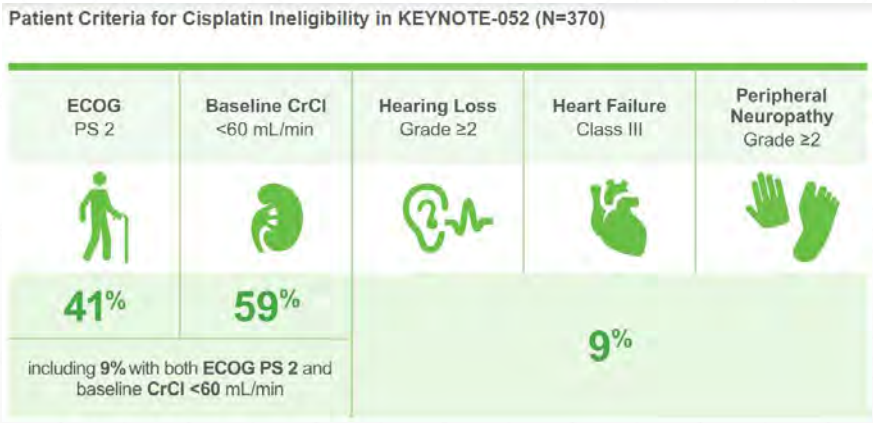
mBC: First line - chemotherapy

	Setting	Regimen	ORR	mOS
First line	Cisplatin eligible	MVAC[1] Gemcitabine+cisplatin[2] PGC[3]	40-50%	12-15 months
First line	Cisplatin ineligible	Gemcitabine+ Carboplatin[4-6]	36-56%	7-9 months
Second line	Single agent chemotherapy[7-9]	Single agent chemotherapy[7-9]	~10%	5-8 months

1.Loehrerer JCO 1992, 2. Van der Masse JCO 2000, 3. Bellmunt JCO 2012, 4. De Santis JCO 2012. 5. Linardou Urology 2004, 6. Nogue-Aliguer Cancer 2003, 7. Bellmunt NEJM 2017, 8.Bellmunt JCO 2009. 9. Petrilac JCO 2015.

mBC: First line - Chemotherpy

50% patients cisplatin ineligible



mBC: First line - Immunotherapy

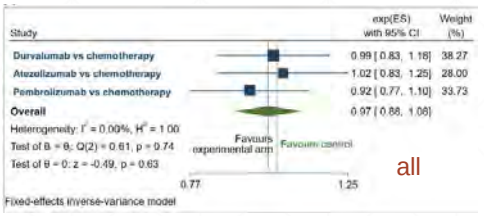
OS

only PDL1+

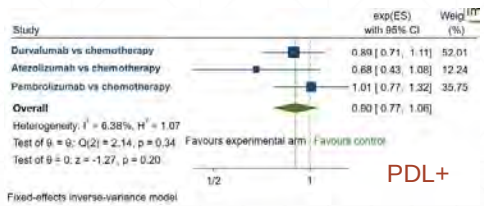
- **Pembrolizumab**
- **Atezolizumab**

Chemotherapy is still standard of care!

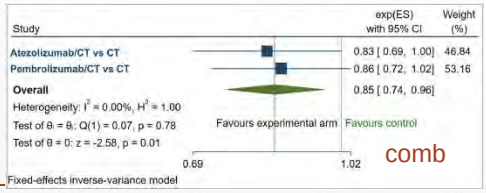
Combinations are still pending!



all



PDL+



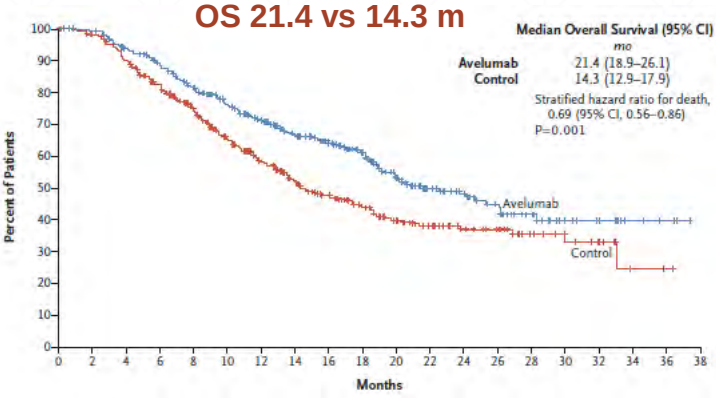
comb

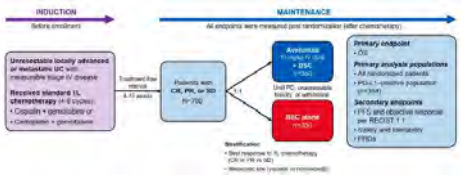
Szabados B, et al. Eur Urol Oncol. 2021.

mBC: First line - Maintenance

JAVELIN Bladder 100

AVELUMAB
OS 21.4 vs 14.3 m





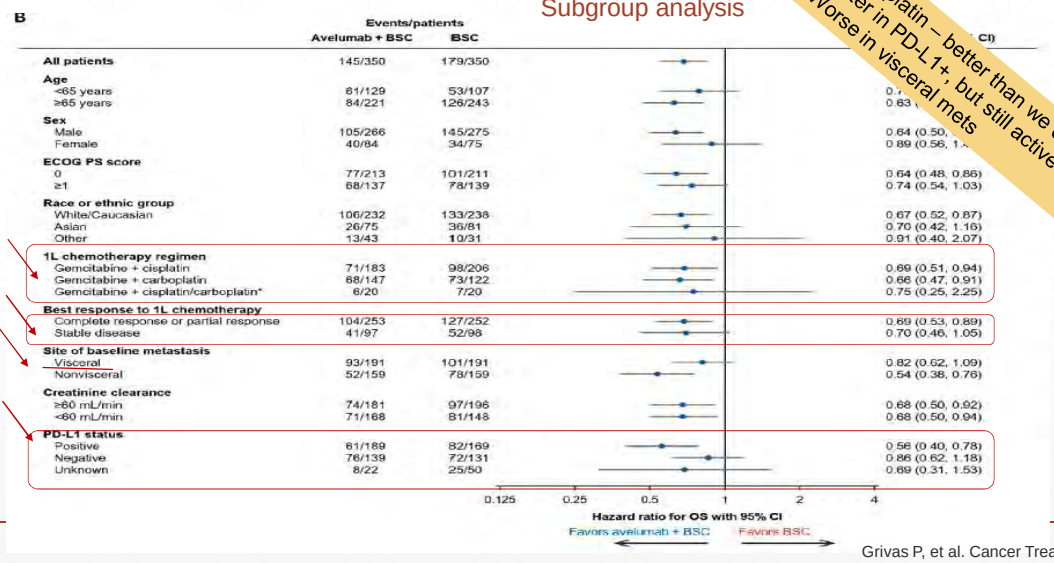
9.2020

EMA approved 10.2020

mBC: First line - Maintenance AVELUMAB

Subgroup analysis

Carboplatin – better than we expect
Better in PD-L1+, but still active in PD-L1-
Worse in visceral mets



Grivas P, et al. Cancer Treat Rev. 2021.

mBC: Second line - immunotherapy

EMA+

- **Pembrolizumab** – OS
- **Atezolizumab**
- **Nivolumab**
- Avelumab
- Durvalumab

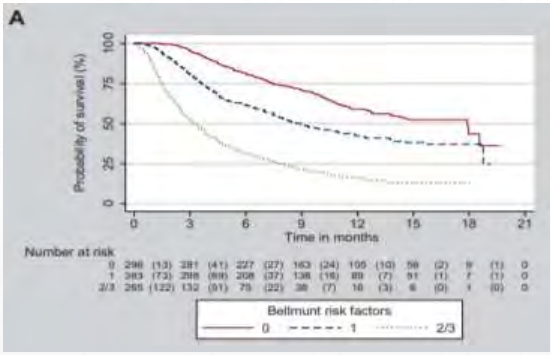
Advantages:
- longer duration - PFS
- better tolerability

ESMO OPEN | CANCER HORIZONS

SAUL, a single-arm study of atezolizumab for chemotherapy-pretreated locally advanced or metastatic carcinoma of the urinary tract: outcomes by key baseline factors, PD-L1 expression and prior platinum therapy

A. Bamias[1*], A. S. Merseburger[2], Y. Loriot[3], N. James[4], E. Choy[5], D. Castellano[6], F. Lopez-Rios[7], F. Calabrò[8], M. Kramer[9], G. de Velasco[9], R. Zakopoulou[9], K. Tzannis[1] & C. N. Sternberg[10]

5.2021



mBC: Second line - chemotherapy

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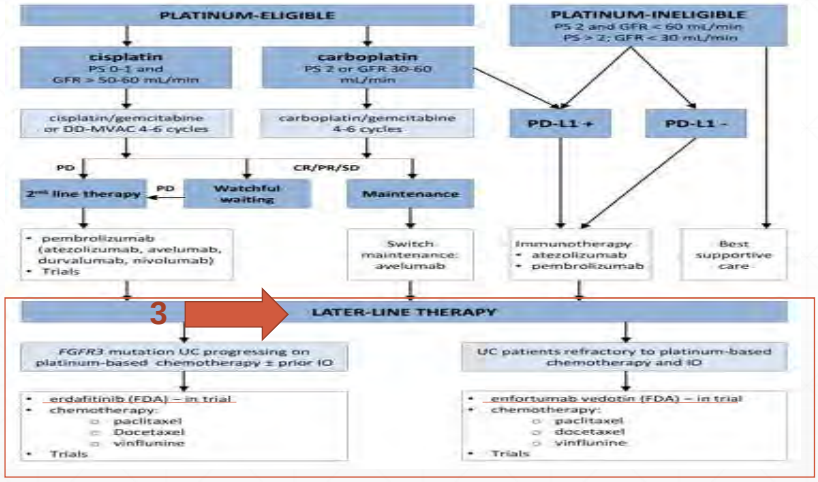
TAXANS

VINFLUNINE

1.Loehrerer JCO 1992, 2. Van der Masse JCO 2000, 3. Bellmunt JCO 2012, 4. De Santis JCO 2012. 5. Linardou Urology 2004, 6. Nogue-Aliguer Cancer 2003, 7. Bellmunt NEJM 2017, 8.Bellmunt JCO 2009. 9. Petrilac JCO 2015.

mBC: Second line and beyond

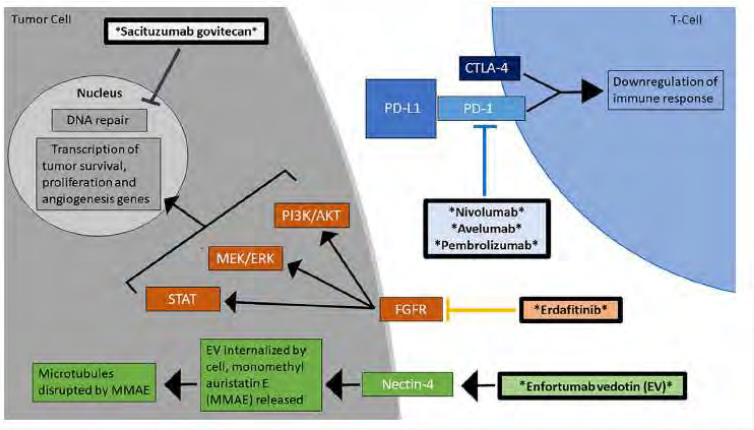


ERDAFITINIB (antiFGFR1-4)

ENFORTUMAB VEDOTIN (ADC)
Sacituzumab govitecan (ADC)

Targeted therapy in mBC – today and tomorrow

Is something new going on ?



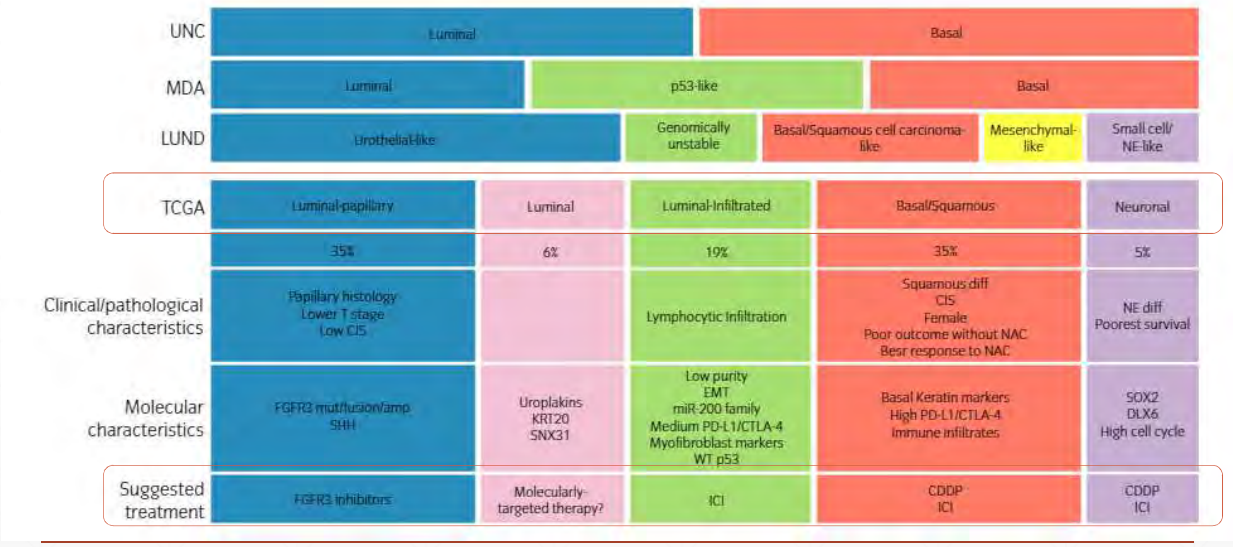
New therapies:

- New immunotherapy
- New anti-FGFR
- New antibody-drug conjugates
- Anti EGFR, HER
- Anti VEGF
- New chemotherapy
- Vaccines
- CAR-T cell therapy

- Combinations

Nelson BE et al. Front Oncol. 2021.

Biomarkers



Yoshida T. In J Urol. 2019.

Predictive biomarkers for immunotherapy

Is something new going on ?

	Biomarker	Predictive capacity
	PD-L1	Increased = improved response
	TMB - tumor mutational burden	Increased = improved response
	STING – stimulator of interferon genes	Deficient = reduced response
	ASC - apoptosis-associated speck-like protein containing CARD	Gene methylation = worse survival
tissue	**TME** - tumor microenvironment	High CD4+, CD8+, CD45RO+ T cells = better survival
blood	**PBMCs** – peripheral blood mononuclear cells	High CD4+, CD8+ T cells = better response
	ctDNA – ciculating tumor DNA	Increased = worse survival
	Exsomes – extracellular vesicles	Increased = better response
	Cytokines	Predict irAEs
	Metal chelators	Cooper chelating drugs = increase CD8+, NK
	sPD-L1/sPD-1 – soluble PD-L1/PD-1	Low level = better survival
	CTCs – circulating tumor cells	Presence = poor response
	Microbiome	Some species = better response

Adam T et al. Cancers. 2021

Is something new going on ?

Conclusions

- Immunotherapy in the earlier stages is at the door
- Perioperative therapy is required; neoadjuvant > adjuvant
- Bladder-sparing approach is increasingly being on the mind
- Trials with new targeted therapy or combinations are ongoing
- Urgent need for better biomarkers to guide the optimal choice of therapy

Systemic treatment of germ cell tumors – could it get better

BREDA ŠKRBINC

INSTITUTE OF ONCOLOGY LJUBLJANA

2ND SUMMER SCHOOL IN MEDICAL ONCOLOGY

7-10 SEPTEMBER 2021

FACTS ABOUT GERM-CELL TUMORS (GCT)

- GCT the most common cancer in men aged 18-35 years
  - Testicular cancer accounts for ~1% of newly diagnosed cancer in men worldwide

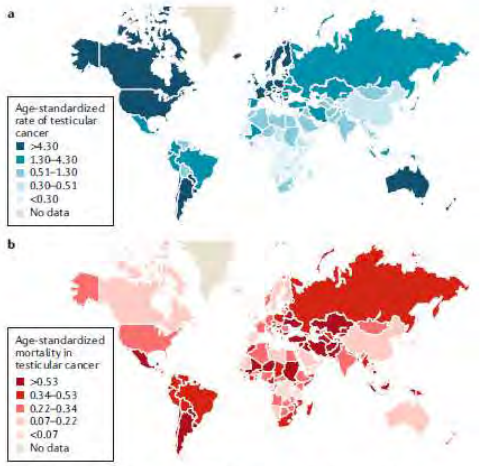


Fig. 3 | Rates of testicular cancer. a | Global age-standardized rate of testicular cancer per 100,000 male individuals. b | Global age-standardized mortality values from testicular cancer per 100,000 male individuals. The incidence of testicular cancer is increasing worldwide, but the reasons for this increase have not been well documented. In the United States, testicular cancer is more common in white individuals than in African Americans. Data from REF.[4].

Testicular cancer - NATURE REVIEWS | DISEASE PRIMERS 2018

FACTS ABOUT GERM-CELL TUMORS (GCT)

- GCT the most common cancer in men aged 18-35 years
  - Testicular cancer accounts for ~1% of newly diagnosed cancer in men worldwide
- Highly curable disease
  - Since 1975 with platinum based chemotherapy - the most curable metastatic solid cancer in males
  - Histology
    - 50%seminoma, 40% NSGCT, 10% combined GCT
  - Stage of the disease
    - 60% of patients present with lokalised disease (stage I)
  - Primary tumor location
    - Testicular, retroperitoneal, mediastinal, intracranial
  - Level of serum tumor markers AFP, β-hCG, LDH determine the treatment choice
  - IGCCCG classification PROGNOSTIC CLASSIFICATION (y 1997 + updates)
    - Good prognostic group
    - Intermediate prognostic group
    - Poor prognostic group

FACTS ABOUT GERM-CELL TUMORS (GCT)

Table 2 | **The International Germ Cell Cancer Collaborative Group prognostic grouping**

Prognosis grouping (risk status)		Nonpulmonary visceral metastases or mediastinal primary metastases	Serum markers[a]			5-year progression-free survival (%)	5-year overall survival (%)
			AFP (ng/ml)	βHCG (IU/l)	LDH		
Good	NSGCT	No	<1,000	<5,000	<1.5 × ULN	89[b] (90[c])	92[b] (95[c])
	Seminoma	No	Normal	Any	Any	82[b] (87[c])	86[b] (93[c])
Intermediate	NSGCT	No	1,000–10,000	5,000–50,000	1.5–10.0 × ULN	75[b] (76[c])	80[b] (85[c])
	Seminoma	Yes	Normal	Any	Any	67[d]	72[d]
Poor	NSGCT	Yes	>10,000	>50,000	>10 × ULN	41[b] (55[c])	48[b] (64[c])
	Seminoma[e]	NA	NA	NA	NA	NA	NA

AFP, α-fetoprotein; βHCG, β-subunit of human chorionic gonadotropin; IU, international units; LDH, lactate dehydrogenase; NA, not applicable; NSGCT, nonseminomatous germ cell tumour; ULN, upper limit of normal. [a]Markers used for risk classification after orchiectomy. [b]Based on data in REF.[23]. [c]Based on data from a population-based study in REF.[28]. [d]Based on only a few patients. [e]No seminoma cases classified as poor prognosis.

Testicular cancer - NATURE REVIEWS | DISEASE PRIMERS 2018

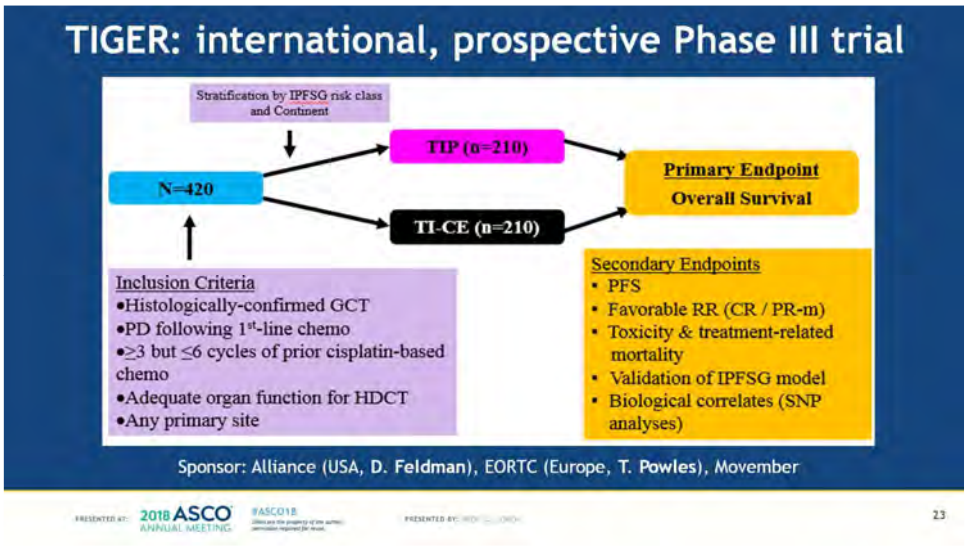
FACTS ABOUT GERM-CELL TUMORS (GCT)

Multidisciplinary treatment

FACTS ABOUT GERM-CELL TUMORS (GCT)

- Recidivant disease still curable (probability for cure signifficantly reduced)
  - more efficient treatment modalities are needed for this group of GCT patients

Testicular cancer - NATURE REVIEWS | DISEASE PRIMERS 2018



Presented By Anja Lorch at 2018 ASCO Annual Meeting

Phase I / II studies			
Kollmansberger C	trastuzumab	HER2/neu expressing GCT	...nn Oncol 1999
Rick O	talidomid	platinum refrac...	Eur J Cancer 2006
Feldman DR	sunitinib	relapse... ...actory GCT	Invest New Drugs 2010
Feldman DR	tivantinib	...ed or refractory	Invest New Drugs 2013
Einhorn LH	imatinibmesil...	CTX refractory GCT expressing KIT	J Clin Oncol 2006
Necchi A	pazor...	relapsed or refractory GCT	Ann Oncol 2017
Fenner M	...limus	multiply relapsed GCT	Journal of Cancer Research and Clinical Oncology, 2018
Adra N	pembrolizumab	multiply relapsed GCT, no other treatment option	Annals of Oncology, 2018

negative results

RESEARCH

CANCER BIOMARKERS

Mismatch repair deficie… predicts response of … tumors to PD-1 blockade

Le et al., Science 357 … 13 (2017)

the gen… of cancers deficient in MMR contain exceptionally high numbers of som… utations
… nsitivity to immune checkpoint blockade

The overall rate of mutations per megabase in cisplatin resistan GCT is low (< 1 mutation/ MB) *J Clin Oncol.* 2016, 33:4000-4007
⟶ low sensitivity to immune checkpoint blokade

FACTS ABOUT GERM-CELL TUMORS (GCT)

- Long term survivals
  - risk for 2nd CA
  - neuropathy / hearing loss
  - nefropathy
  - risk for cardiovascular events
  - fertility impairment
  - cognitive impairment
  - suicidal tendencies

Testicular cancer - NATURE REVIEWS | DISEASE PRIMERS 2018

GCT SURVIVALS

original reports

Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort

Ragnhild Heilenes, MD[1,2]; Tor Åge Myklebust, PhD[3,4]; Sophie D. Fosså, MD, PhD[1,4,5]; Roy M. Bremnes, MD, PhD[1,4]; Åsa Karlsdottir, MD, PhD[1]; Øivind Kvammen, MD, PhD[6]; Torgrim Tandstad, MD, PhD[4,7,8]; Tom Wilsgaard, PhD[11]; Helene F. S. Negaard, MD, PhD[1]; and Hege S. Haugnes, MD, PhD[1,2]

How does treatment with platinum-based chemotherapy or radiotherapy influence the non–testicular cancer mortality and causes of death in GTC survivors?

Investigation of cause specific non-GCT mortality with impact on previous treatment with platinum-based chemotherapy or radiotherapy

The aim of the study was to assess non-TC mortality and causes of death in relation to TC treatment, including the impact of number of cisplatin based chemotherapy cycles, in a population-based cohort with complete information on TC treatment burden.

10.1200/JCO.21.00637 Journal of Clinical Oncology 2021

Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort

METHODS

- Overall, 5,707 men identified by the Cancer Registry of Norway diagnosed with TC from 1980 to 2009 were included in this population-based cohort study.
- By linking data with the Norwegian Cause of Death Registry, **standardized mortality ratios (SMRs)**, **absolute excess risks (AERs;** [(observed number of deaths – expected number of deaths)/person-years of observation] x 10,000), and **adjusted hazard ratios (HRs)** were calculated

5707 GCT patients diagnosed with GCT Jan 1st 1980-Dec 31st 2009 identified by the Cancer Registry of Norway

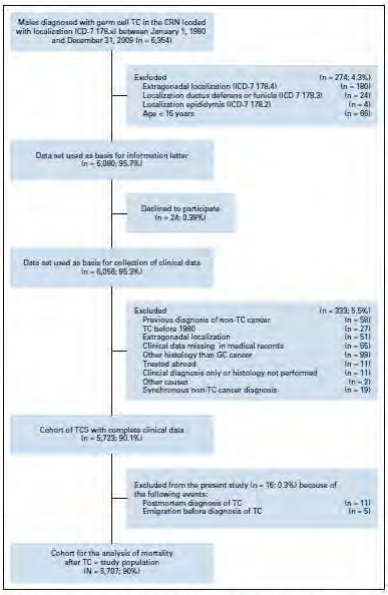
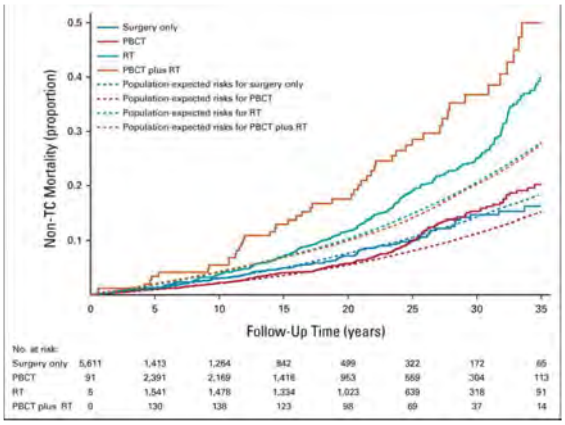


FIG A1. Flowchart presenting the study cohort. CRN, the Cancer Registry of Norway; GC, germ cell; ICD-7, International Classification of Diseases version 7; TC, testicular cancer; TCS, testicular cancer survivors.

Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort



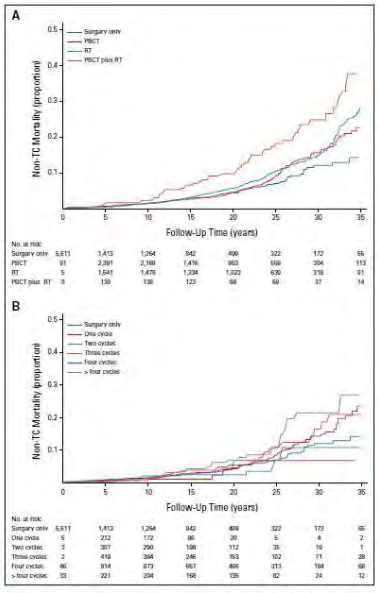


FIG 1. Non-TC mortality by follow-up time adjusted for age centered on mean. (A) stratified by treatment group and (B) stratified by number of cisplatin-based chemotherapy cycles. The risk tables present the crude number of individuals by follow-up time. PBCT, platinum-based chemotherapy; RT, radiotherapy; TC, testicular cancer.

10.1200/JCO.21.00637 Journal of Clinical Oncology 2021

Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort

Results

- **Median follow-up was 18.7 years**, during which ***non-TC death was registered*** for 665 ***(12%) men***.
- ***Overall excess non-TC mortality 23% (SMR, 1.23*** - **AER, 11.14)** compared with the general population,
- **Increased risks after PBCT (SMR, 1.23 - AER, 7.68**)
- **Compared with surgery**, **increased non-TC mortality appeared after 3, 4, and more than 4 cisplatin-based chemotherapy cycles after > 10 years of follow-up**
- ***Increased risk after RT (SMR, 1.28*** - **AER, 19.55**).
- **The highest non-TC mortality** was ***in those < 20 years at TC diagnosis (SMR, 2.27*** - **AER, 14.42)**.
- ***The most important cause of death*** *was* ***non-TC second cancer with an overall SMR of 1.53 -*** **AER, 7.94),** with ***increased risks after PBCT and RT***.
- ***Overall noncancer mortality*** *was* ***increased by 15% (SMR 1.15*** - **AER, 4.71**).
- ***Excess suicides*** *appeared* ***after PBCT (SMR 1.65*** - **AER, 1.39).**

10.1200/JCO.21.00637 Journal of Clinical Oncology 2021

Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort

Conclusions

- GCT surviviors treated with platinum based CTX or RT suffer increased mortality rates compared with the general population.
- The most notable excess mortality was caused by **seconnd cancers**,
  - measures to avoid delayed SC diagnosis are essential (extende follow up)
- **Citotoxic treatment (CTX / RT)** seems to be the main risk factor for increased mortality.
- The increased mortality risk might be reduced by lifestyle improvements, which should be recommended following GTC treatment.
- It is crucial that GCT surviviors and health personnel involved in the follow-up should be aware of the increased premature mortality risk.

RISK ADAPTED TREATMENT

10.1200/JCO.21.00637 Journal of Clinical Oncology 2021

original reports

Predicting Outcomes in Men With Metastatic Nonseminomatous Germ Cell Tumors (NSGCT): Results From the IGCCCG Update Consortium

Silke Gillessen, MD[1,2,3]; Nicolas Sauvé, MSc[4]; Laurence Collette, PhD[4]; Gedske Daugaard, MD[5]; Ronald de Wit, MD[6]; Costantine Albany, MD[7]; Alexey Tyakin, MD[8,9]; Karim Fizazi, MD[10]; Olof Stahl, MD[11]; Jourik A. Gietema, MD[12]; Ugo De Giorgi, MD[13]; Fay H. Cafferty, PhD[14]; Aaron R. Hansen, MD[15]; Torgrim Tandstad, MD[16]; Robert A. Huddart, MD[17]; Andrea Necchi, MD[18]; Christopher J. Sweeney, DM[19]; Xavier Garcia-Del-Muro, MD[20]; Daniel Y. C. Heng, MD[21]; Anja Lorch, DM[22,23]; Michal Chovanec, MD[24]; Eric Winquist, MD[25]; Peter Grimison, MD[26]; Darren R. Feldman, MD[27,28]; Angelika Terbuch, MD[29]; Marcus Hentrich, MD[30]; Carsten Bokemeyer, MD[31]; Helene Negaard, MD[32]; Christian Fankhauser, MD[33]; Jonathan Shamash, MD[34]; David J. Vaughn, MD[35]; Cora N. Sternberg, MD[36]; Axel Heidenreich, MD[37]; and Jörg Beyer, MD[38]; for the International Germ Cell Cancer Classification Update Consortium

- **Validation of the 1997 prognostic classification and update of the survival probabilities in a modern cohort**
- **Identification of additional prognostic factors to refine the IGCCCG prognostic classification**

J Clin Oncol 39:1563-1574. 2021

- 30 Institutions
- Complete patients database 1980-2013

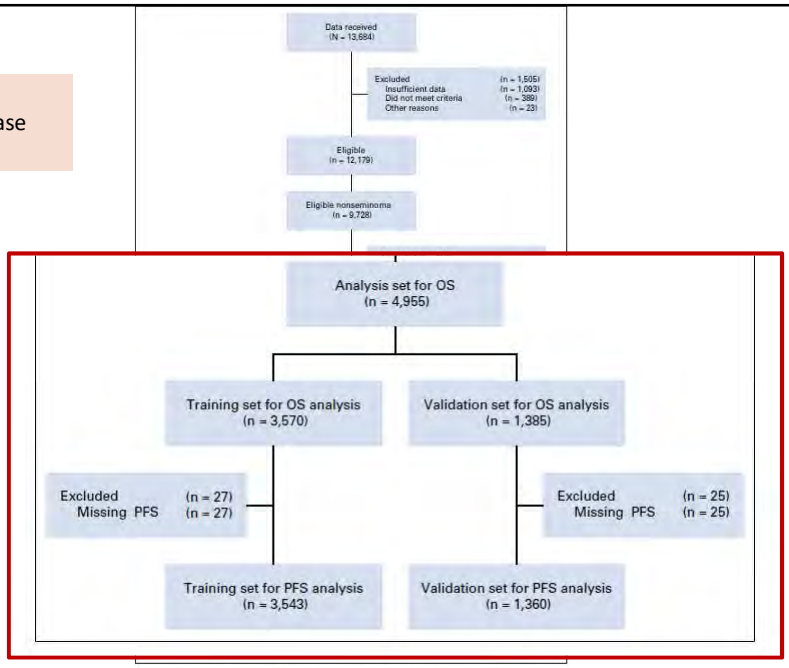


FIG 1. CONSORT diagram. IGCCCG, International Germ Cell Cancer Collaborative Group; OS, overall survival; PFS, progression-free survival.

J Clin Oncol 39:1563-1574. 2021

TABLE 2. Update of IGCCCG Survival Probabilities

Original IGCCCG Prognostic Groups	Original IGCCCG Survival Estimates (1997)		Updated Estimates Based on Patients With Nonseminoma With Prechemotherapy IGCCCG Prognostic Groups Available	
	5-Year PFS (95% CI)	5-Year OS (95% CI)	5-Year PFS (95% CI)	5-Year OS (95% CI)
Good	89 (87 to 91)	92 (90 to 94)	90 (89 to 91)	96 (95 to 96)
Intermediate	75 (71 to 79)	80 (76 to 84)	78 (76 to 80)	89 (88 to 91)
Poor	41 (35 to 47)	48 (42 to 54)	54 (52 to 56)	67 (65 to 69)

Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group; OS, overall survival; PFS, progression-free survival.

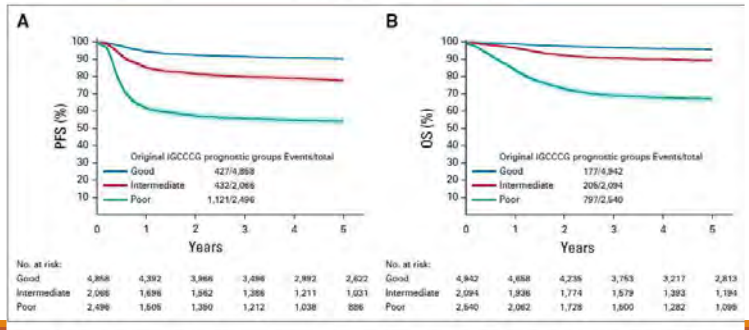


FIG 2. Survival probabilities and 95% CI according to original IGCCCG prognostic groups for (A) PFS and (B) OS. IGCCCG, International Germ Cell Cancer Collaborative Group; OS, overall survival; PFS, progression-free survival.

J Clin Oncol 39:1563-1574. 2021

TABLE 3. Hazard Ratios of the Final Prognostic Model

Variables	Values of Interacting Variables Used for Computation	Hazard Ratio	95% CI
Age (10 years increase)		1.25	1.15 to 1.36
Mediastinal primary		2.68	2.04 to 3.53
Presence of lung metastases		1.62	1.36 to 1.92
Presence of NPVM	AFP levels ≤ 30 ng/mL	6.61	4.62 to 9.46
	HCG levels ≤ 5 U/L		
	LDH ≤ 2.5× ULN		
LDH > 2.5× ULN	Absence of NPVM	1.46	1.18 to 1.81
	Presence of NPVM	1.01	0.74 to 1.36
Doubling of AFP levels (for values > 30 ng/mL)	Absence of NPVM	1.12	1.09 to 1.16
	Presence of NPVM	1.02	0.98 to 1.06
Doubling of HCG levels (for values > 5 U/L)	Absence of NPVM	1.07	1.05 to 1.09
	Presence of NPVM	1.02	0.99 to 1.04

Abbreviations: AFP, alpha-fetoprotein, HCG, human chorionic gonadotropin, LDH, lactate dehydrogenase, NPVM, nonpulmonary visceral metastases; ULN, upper limit of normal.

J Clin Oncol 39:1563-1574. 2021

Nomograms of the final prognostic model for patients

Without nonpulmonary visceral metastases

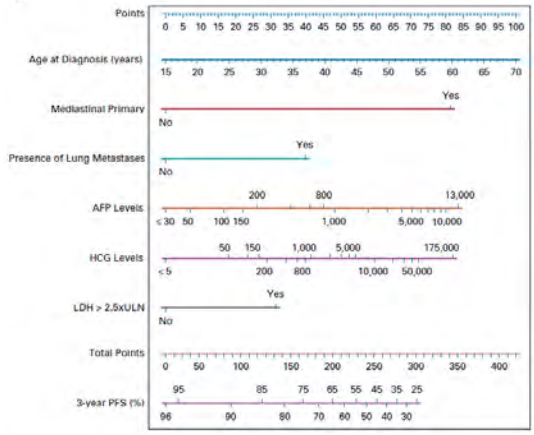


FIG 3. Nomograms of the final prognostic model for patients (A) without NPVM and (B) with NPVM. The extreme values of AFP and HCG markers on the nomograms were truncated to the rounded 95% percentile of the training set (13,000 ng/mL for AFP, 175,000 U/L for HCG). Predicted 3-year PFS below 25% are not shown, as it corresponds to a combination of baseline prognostic factors rarely seen in the training set. AFP, alpha-fetoprotein, HCG, human chorionic gonadotropin, LDH, lactate dehydrogenase, NPVM, nonpulmonary visceral metastases; PFS, progression-free survival; ULN, upper limit of normal.

J Clin Oncol 39:1563-1574. 2021

Nomograms of the final prognostic model for patients

With nonpulmonary visceral metastases

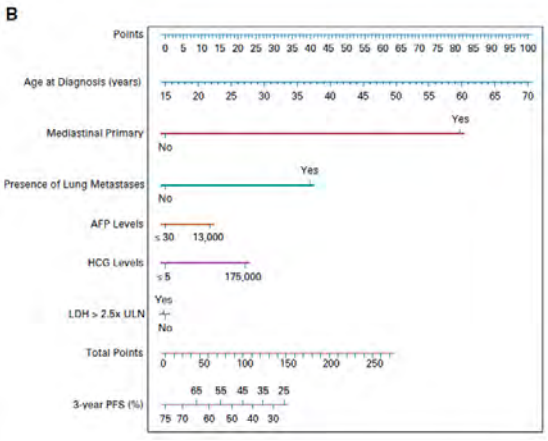
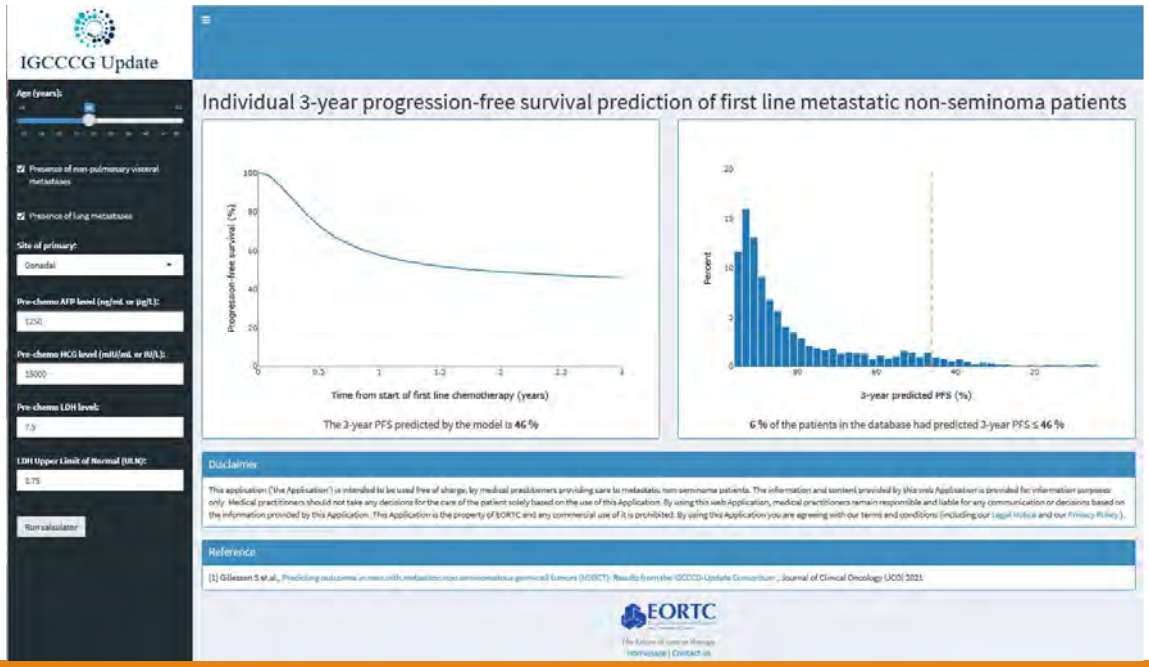


FIG 3. Nomograms of the final prognostic model for patients (A) without NPVM and (B) with NPVM. The extreme values of AFP and HCG markers on the nomograms were truncated to the rounded 95% percentile of the training set (13,000 ng/mL for AFP, 175,000 U/L for HCG). Predicted 3-year PFS below 25% are not shown, as it corresponds to a combination of baseline prognostic factors rarely seen in the training set. AFP, alpha-fetoprotein, HCG, human chorionic gonadotropin, LDH, lactate dehydrogenase, NPVM, nonpulmonary visceral metastases; PFS, progression-free survival; ULN, upper limit of normal.

J Clin Oncol 39:1563-1574. 2021



https://eortc.shinyapps.io/IGCCCG-Update/

- IGCCCG database is the largest dataset on metastatic NSGCT worldwide
- ***Improved treatment outcomes***
  - stage migration because of earlier diagnosis and better diagnostic tools,
  - improved supportive care,
  - superiority of cisplatin- and etoposide-based first-line treatment over other combinations,
  - use of upfront dose-intensified regimens,
  - more stringent use and higher quality of postchemotherapy surgery,
  - better salvage strategies in nonresponding or relapsing patients,
  - more stringent guideline adherence,
  - centralization of care at experienced expert centers,
    - a combination of these factors

J Clin Oncol 39:1563-1574. 2021

- In future **trials,** patients with a particularly favorable prognosis in the nomogram may be subjected to de-escalation strategies to further reduce treatment burden in patients likely to be cured.
- In contrast, trials evaluating dose-escalation strategies should be pursued in patients with the worst prognosis according to the new IGCCCG update model

J Clin Oncol 39:1563-1574. 2021

Survival and New Prognosticators in Metastati Seminoma: Results From the IGCCCG-Update Consortium

Jörg Beyer, MD[1]; Laurence Collette, PhD[2]; Nicolas Sauvé, MSc[2]; Gedske Daugaard, MD[3]; Darren R. Feldman, MD[4,5]; Torgrim Tandstad, MD[6]; Alexey Tryakin, MD[7,8]; Olof Stahl, MD[9]; Enrique Gonzalez-Billalabeitia, MD[10,11]; Ugo De Giorgi, MD[12]; Stéphane Culine, MD[13]; Ronald de Wit, MD[14]; Aaron R. Hansen, MD[15]; Marko Bebek, MD[16]; Angelika Terbuch, MD[17]; Costantine Albany, MD[18]; Marcus Hentrich, MD[19]; Jourik A. Gietema, MD[20]; Helene Negaard, MD[21]; Robert A. Huddart, MD[22]; Anja Lorch, MD[23,24]; Fay H. Cafferty, PhD[25]; Daniel Y. C. Heng, MD[26]; Christopher J. Sweeney, MD[27]; Eric Winquist, MD[28]; Michal Chovanec, MD[29]; Christian Fankhauser, MD[30]; Daniel Stark, MD[31]; Peter Grimison, MD[32]; Andrea Necchi, MD[33]; Ben Tran, MD[34]; Axel Heidenreich, MD[35]; Jonathan Shamash, MD[36]; Cora N. Sternberg, MD[37]; David J. Vaughn, MD[38]; Ignacio Duran, MD[39]; Carsten Bokemeyer, MD[40]; Anna Patrikidou, MD[41]; Richard Cathomas, MD[42]; Samson Assele, MSc[2]; and Silke Gillessen, MD[43,44,45] for the International Germ Cell Cancer Classification Update Consortium

The classification of the International Germ-Cell Cancer Collaborative Group (IGCCCG) has been a major advance in the management of germ-cell tumors, but relies on data of only *660 patients with seminoma* treated between 1975 and 1990.

- **To reassess the original International Germ-Cell Cancer Collaborative Group (IGCCCG) classification for seminoma with modern treatment data and to screen for additional prognostic variables**

J Clin Oncol 39:1553-1562.2021

Survival and New Prognosticators in Metastati
Seminoma: Results From the IGCCCG-Update
Consortium

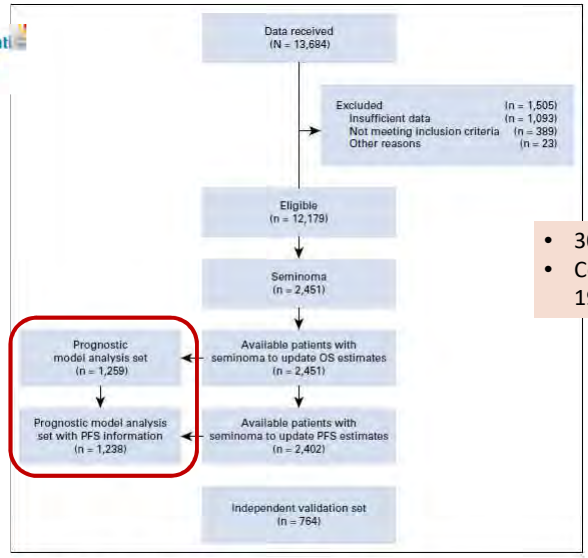


FIG 1. CONSORT diagram. OS, overall survival; PFS, progression-free survival.

- 30 Institutions
- Complete patients database 1980-2013

J Clin Oncol 39:1553-1562.2021

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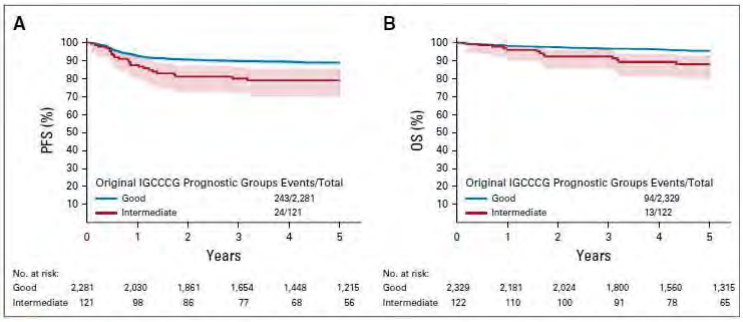

FIG 2. Survival probabilities and 95% CI according to original IGCCCG prognostic groups for (A) PFS and (B) OS. IGCCCG, International Germ-Cell

J Clin Oncol 39:1553-1562.2021

Survival and New Prognosticators in Metastati
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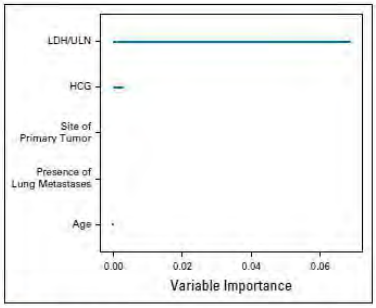
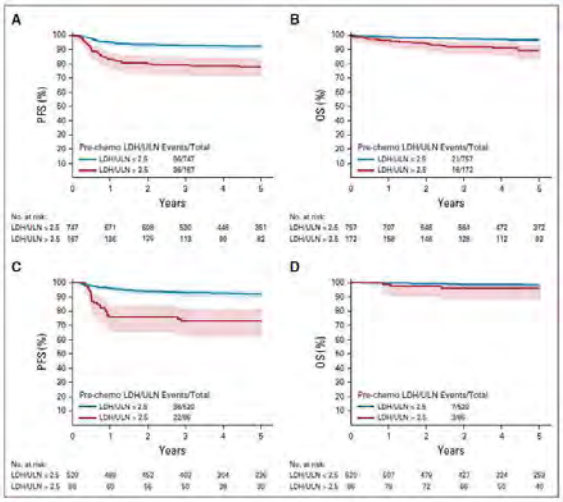


FIG A2. Variable importance of all candidate variables on PFS in the prognostic model analysis set. HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limit of normal.



J Clin Oncol 39:1553-1562.2021

- LDH above 2.5 x ULN levels before chemotherapy an additional adverse prognostic factor that allowed splitting the good prognostic group further.
- Good prognosis patients with an elevated LDH above 2.5 x ULN before chemotherapy experienced significantly worse outcomes.

- Other variables such as age, extragonadal primary tumor, elevated levels of β-hCG, or the presence of lung metastases did not add significant prognostic information in good prognosis patients once LDH elevations were considered

Until the availability of prospective trials results of this analysis do not allow to recommend using intensified CTX schemes instead of three cycles BEP in good (according to the original classification) prognosis patients who have an LDH level above 2.5 x ULN

J Clin Oncol 39:1553-1562.2021

Given **5-year PFS and OS survival probabilities of 88% (95% CI, 87 to 89) and 95% (95% CI, 94 to 96)**, respectively, across all prognostic groups,

metastatic seminoma represents the most curable metastatic cancer in males

J Clin Oncol 39:1553-1562.2021

numerous challenges and pitfalls in testis cancer care that need to be addressed

Testicular Cancer Biomarkers

- **Clinical management greatly relies on sTM measurements**
- **AFP, β-hCG, LDH** – specific cellular proteins secreted into the bloodstream,
  - conventional panel of serum tumor markers of GCT (sTMs)
  - standard in GCT diagnosis and treatment monitoring
    - ***Special S stage in the TNM sistem***
- **Poor specificity and sensitivity** of clasical sTM (https://doi.org/10.1155/2019/5030349)
  - Elevated in seminomas: bhCG 28% and LDH 29.1% , (AFP never)
  - Elevated in NSGCT: bhCG 53%, AFP 60.1%, and LDH 37.8%
  - sTMs may be elevated ***nonspecifically*** by processes other than GCT and may be ***normal*** in the setting of radiographically and serologically occult metastatic disease
  - Need for novel biomarkers with superior performance characteristics compared to conventional sTMs

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Testicular Cancer

NCCN Guidelines Index
Table of Contents
Discussion

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Testis Cancer 8th ed., 2017

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

	M Distant Metastasis
M0	No distant metastases
M1	Distant metastases
M1a	Non-retroperitoneal nodal or pulmonary metastases
M1b	Non-pulmonary visceral metastases

	S Serum Markers
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 x N* and hCG (mIU/mL) <5,000 *and* AFP (ng/mL) <1,000
S2	LDH 1.5–10 x N* or hCG (mIU/mL) 5,000–50,000 *or* AFP (ng/mL) 1,000–10,000
S3	LDH >10 x N* or hCG (mIU/mL) >50,000 *or* AFP (ng/mL) >10,000

Table 2 | **The International Germ Cell Cancer Collaborative Group prognostic grouping**

Prognosis grouping (risk status)		Nonpulmonary visceral metastases or mediastinal primary metastases	Serum markers[a]			5-year progression-free survival (%)	5-year overall survival (%)
			AFP (ng/ml)	βHCG (IU/l)	LDH		
Good	NSGCT	No	<1,000	<5,000	<1.5 x ULN	89[b] (90[c])	92[b] (95[c])
	Seminoma	No	Normal	Any	Any	82[d] (87[c])	86[b] (93[c])
Intermediate	NSGCT	No	1,000–10,000	5,000–50,000	1.5–10.0 x ULN	75[d] (76[c])	80[d] (85[c])
	Seminoma	Yes	Normal	Any	Any	67[d]	72[d]
Poor	NSGCT	Yes	>10,000	>50,000	>10 x ULN	41[d] (55[c])	48[d] (64[c])
	Seminoma[e]	NA	NA	NA	NA	NA	NA

AFP, α-fetoprotein; βHCG, β-subunit of human chorionic gonadotropin; IU, international units; LDH, lactate dehydrogenase; NA, not applicable; NSGCT, nonseminomatous germ cell tumour; ULN, upper limit of normal. [a]Markers used for risk classification after orchiectomy. [b]Based on data in REF. [c]. [d]Based on data from a population-based study in REF. [28]. [e]Based on only a few patients. [e]No seminoma cases classified as poor prognosis.

https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf

on horizon there is an important change in the field of GCT sTMs

- In the past decade, nucleic acid–based markers, specifically **microRNAs (miRNAs),** have garnered attention

- miRNAs - small noncoding RNA molecules of approximately 22 nucleotides
  - involved in epigenetic regulation of mRNA translation by direct interaction with the larger messenger RNA molecules regulating the level of gene expression on a post-transcriptional level
  - influencing cellular differentiation and other physiological processes

  as well as

  - carcinogenesis, for which they can operate as oncogenes or tumor suppressors

Nat Rev Clin Oncol 2011;8:467–77 https://doi.org/10.1016/j.eururo.2021.06.006

- Serum miRNA - the most exciting discovery in the GCT field
- Emerged as promising biomarkers in diagnosing and monitoring of patients with GCT

- Several clusters of miRNA that are expressed in testicular cancer tissue and measurable in the serum have been identified on historical samples / retrospective studies
  - **miR-371a-3p** specifically exhibited greater accuracy than traditional sTMs in GCT

https://doi.org/10.1016/j.eururo.2021.06.006

original report

Serum Levels of MicroRNA-371a-3p (M371 Test) as a New Biomarker of Testicular Germ Cell Tumors: Results of a Prospective Multicentric Study

Klaus-Peter Dieckmann, Prof[1,2]; Arlo Radtke, PhD[3]; Lajos Geczi, MD, PhD[4]; Cord Matthies, MD[5]; Petra Anheuser, MD[5]; Ulrike Eckardt, MD[6]; Jörg Sommer, MD[7]; Friedemann Zengerling, MD[8]; Emanuela Trenti, MD[9]; Renate Pichler, PhD[10]; Hanjo Belz, MD[11]; Stefan Zastrow, MD[12]; Alexander Winter, MD[13]; Sebastian Melchior, Prof[14]; Johannes Hammel, MD[14]; Jennifer Kranz, MD[15]; Marius Bolten, MD[16]; Susanne Krege, Prof[17]; Björn Haben, MD[18]; Wolfgang Loidl, MD[19]; Christian Guido Ruf, MD[20]; Julia Heinzelbecker, MD[21]; Axel Heidenreich, Prof[22]; Jann Frederik Cremers, MD[23]; Christoph Oing, MD[24]; Thomas Hermanns, MD[25]; Christian Daniel Fankhauser, MD[26]; Silke Gillessen, MD[27]; Hermann Reichegger, MD[28]; Richard Cathomas, MD[27]; Martin Pichler, Prof[29]; Marcus Hentrich, MD[30]; Klaus Eredics, MD[30]; Anja Lorch, Prof[31]; Christian Wülfing, Prof[1]; Sven Peine, MD[32]; Werner Wosniok, PhD[3]; Carsten Bokemeyer, Prof[32]; and Gazanfer Belge, PhD[3]

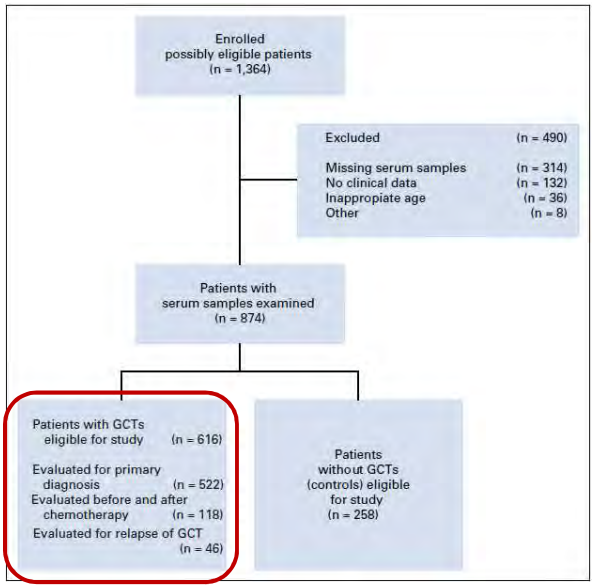
- to prospectively evaluate the utility of the M371 test in a large and representative patient population enrolled from a large number of European institutions
- to involve various histologies and clinical stages

and in particular

- to evaluate the diagnostic sensitivity and specificity of the test for the primary diagnosis of GCT
- to assess its usefulness for monitoring GCT treatment

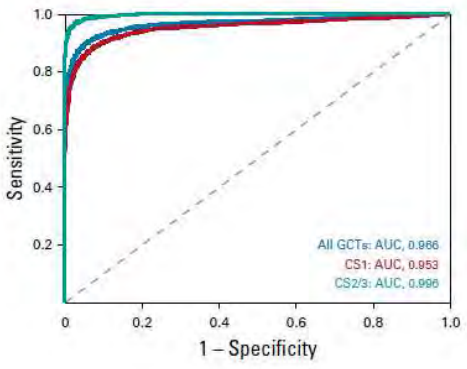
J Clin Oncol 37:1412-1423; 2019

FIG 1. Study profile. The diagram shows the selection process of patient enrollment. GCT, germ cell tumor.



J Clin Oncol 37:1412-1423; 2019

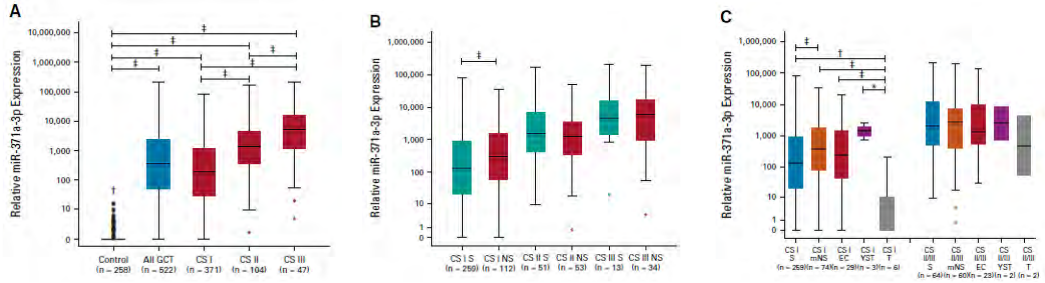
Receiver operating characteristic curves that discriminate *controls* from all *patients with germ cell tumors*, clinical stage (CS) I only or CS II/III only



ROC = the measure of the usefulness of any test
(a greater AUC area means a more useful test)

J Clin Oncol 37:1412-1423; 2019

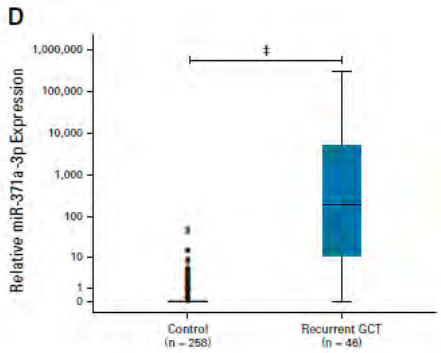
- The median expression of miR-371a-3p was significantly higher in the entire GCT group and in all the CS subgroups compared with the controls
- Patients with CS greater than I had a higher serum level than those with CS I (all P < 0.001) (fig A)



- Seminoma was found to have significantly lower miR-371a-3p values than nonseminoma (fig B)
  - difference only detectable in CS I patients
- Teratoma had the lowest expression values of all subtypes (fig C)

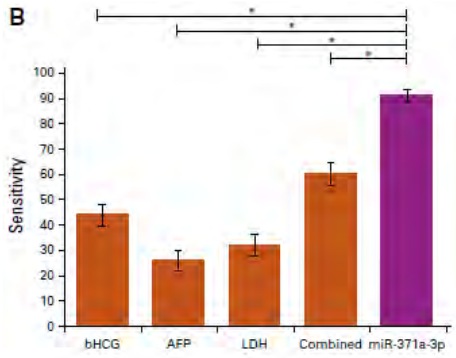
J Clin Oncol 37:1412-1423; 2019

Expression of miR-371a-3p in controls and patients with GCT recurrence.



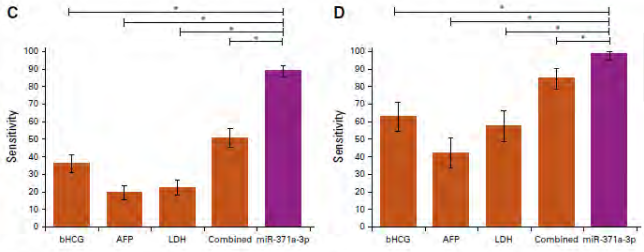
J Clin Oncol 37:1412-1423; 2019

Sensitivity of miR-371a-3p in all GCTs compared with the classic GCT markers b-human chorionic gonadotropin (bHCG), a-fetoprotein (AFP), and lactate dehydrogenase (LDH) and all three classic markers combined



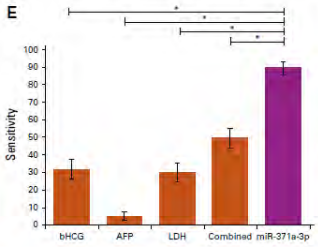
J Clin Oncol 37:1412-1423; 2019

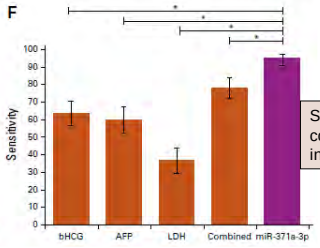
Sensitivity of miR-371a-3p compared with the classic GCT markers in **all GCTs CS I**



Sensitivity of miR-371a-3p compared with the classic GCT markers in **all GCTs CS II / III**

Sensitivity of miR-371a-3p compared with the classic GCT markers in **NSGCTs CS II / III**



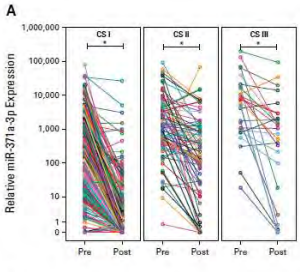


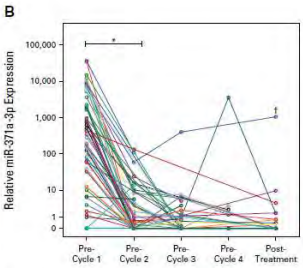
Sensitivity of miR-371a-3p compared with the classic GCT markers in **seminoma GCTs CS II / III**

J Clin Oncol 37:1412-1423; 2019

Post-treatment decrease of microRNA (miR)-371a-3p

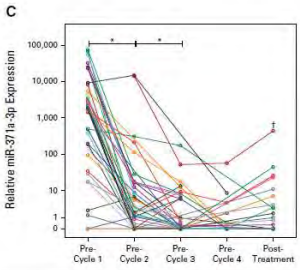
Decrease of miR-371a-3p expression after surgical removal of the primary tumor
in clinical stage (CS) I , CS II, and CS III

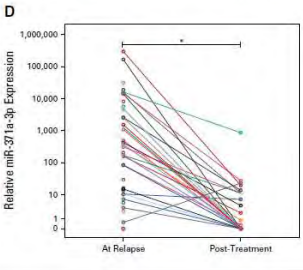




Decrease of miR-371a-3p serum levels over the course of chemotherapy
in CS II patients

Decreas of miR-371a-3p serum levels over the course of chemotherapy
in CS III patients





Decrease of miR-371a-3p expression
in recurrent germ cell tumors (GCTs) after treatment

J Clin Oncol 37:1412-1423; 2019

This study provides a considerable body of evidence that supports the usefulness of miR-371a-3p serum levels as a new biomarker of GCTs.

<u>Five features of the M371 test are noteworthy</u>:

- the test has a 90.1% sensitivity and a 94.0% specificity for establishing the primary diagnosis of GCT;
- it is relevant for the two main histologic subgroups of GCT;
- miR serum levels correlate with primary tumor size, local stage, and CSs;
- miR levels mirror treatment-related disease changes;
- miR levels are elevated in recurrences

- the study strongly confirmed previous data regarding to the usefulness of the M371 test as a new serum biomarker of GCT that is informative in both seminoma and nonseminoma;

- because of its high sensitivity and specificity, M371 test involves the potential of simplifying clinical pathways of the management of GCT
- further validation in an independent cohort is needed

J Clin Oncol 37:1412-1423; 2019

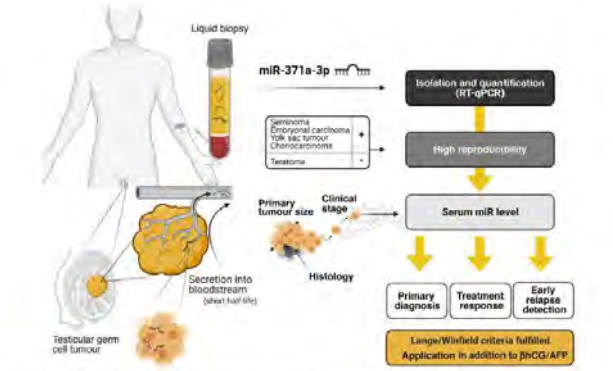


Fig. 2 – Serum miR-371a-3p in testicular germ cell tumours: Biology, detection, and clinical application as a blood-based biomarker in compliance with the Lange-Winfield criteria for biomarkers. (1) The candidate substance is produced only by the malignancy itself. (2) It is secreted into body fluids. (3) It can be measured in reproducible fashion. (4) Levels in body fluids correlate with the amount of tumour present. (5) The substance can be detected even in early disease. (6) Measured levels correlate with response to treatment. (7) The half-life of the substance is short. Created in Biorender (www.biorender.com). CSI = clinical stage I; CSIIA = clinical stage IIA; RPLND = retroperitoneal pelvic lymph-node dissection.

The Lange-Winfild criteria for biomarkers

The ideal TM is a substance that

(1) is produced only by the malignancy itself;
(2) is secreted into body fluids in such a way that it can easily be measured in a reproducible fashion;
(3) correlates well with the amount of tumor present;
(4) can be detected at an early stage of the disease;
(5) has a half-life which is short enough so as not to accumulate in body tissues and result in false-positive results;
(6) correlates with the response of the tumor to treatment

- M371 test has the potential of simplifying clinical pathways of the management of GCT
- further validation in an independent cohort is needed

https://doi.org/10.1016/j.eururo.2021.06.006 Cancer 60:464-472. 1987

Systemic treatment of germ cell tumors – could it get any better?

Yes it cann

and

it should still get better

Provided that

- **GCT patients are treated strictly according the international guidelines on diagnosis and treatment of GCT**
- **The patients are treated by expirienced physicians dedicated to the treatment of GCT patients**
- **GCT poor prognostic group patients are treated by multidisciplinary teams dedicated to the treatment of GCT patients**

A new era in the treatment of endometrial cancer integrated with Molecular Classification of Endometrial Cancer-advance and reccurent disease

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in high income countries, and the second most common in low income countries (1). In Serbia it is the fourth most common cancer in the female population – behind breast, lung and colorectal cancer (2). The molecular classification of EC introduced by the Cancer Genome Atlas (TCGA) (3) has ushered in a change in the way we view and classify EC. This project used genomic, transcriptomic, and proteomic analyses to characterize over 370 ECs. Four molecular subgroups and several predictive biomarkers have been defined based on based the genetic architecture of tumor cells. The Cancer Genome Atlas (TCGA) Research Network suggested 4 genomic classifications for endometrial cancers:

a) polymerase ε (POLE) ultramutated,
b) microsatellite instability hypermutated (MSI-H),
c) copy-number low,
d) and copy-number high.

POLE ultra-mutated cancers are relatively rare (5% to 10% of endometrial cancers), highly immunogenic, and typically have a favorable prognosis.(3) MSI-H tumors have high rates of genomic mutations related to altered or defective DNA repair, including dysfunction in mismatch repair (dMMR).(3,4) Approximately 20% to 30% of endometrial cancers exhibit an MSI-H phenotype or loss of MMR. Alterations in PI3K/AKT/mTOR signaling are also common.Copy-number low tumors, or microsatellite stable (MSS) tumors, represent the majority of low-grade endometrioid cancers and have an intermediate prognosis.(3,4) These tumors have low mutation rates with few TP53 mutations, but often have mutations in PTEN, CTNNB1, PIK3CA, ARID1A, or KRAS.Copy-number high or serous-like tumors are generally high-grade with low estrogen and progesterone receptor expression and low mutation rates.(3,4) As the name suggests, these malignancies have extensive copy number variations and frequent mutation of TP53.

These groups display distinct prognostic outcomes, clinical and pathological features.

Although prognosis is favorable for patients with early stage disease, outcomes are poor for patients with recurrent or advanced disease. Numerous therapeutic options are available for

patients with recurrent or metastatic endometrial cancer, primarily focused on platinum-based regimens. Carboplatin in combination with paclitaxel is the option of choice (5).

Recent years have witnessed the emergence of newer options for progressive disease, including bevacizumab, pembrolizumab, lenvatinib, and everolimus/letrozole. These expanded options have the potential to improve patient outcomes and provide more individualized care for patients with advanced or recurrent endometrial cancer.

Patients with HER2-positive uterine serous carcinoma should be considered for the addition of trastuzumab to platinum-based doublet chemotherapy, while those with low-grade endometrioid histology may benefit from the use of hormone therapies.

Targeted Therapy

Antiangiogenic Therapies.

In patients with advanced endometrial cancers early research indicated that there is a role for bevacizumab in certain subsets of patients, leading to phase 2 trials such as GOG-86P and MITO END-2 with the goal of testing the effectiveness of bevacizumab in combination with carboplatin/paclitaxel. (6,7). The GOG-86P trial, which also evaluated combinations with temsirolimus, did not show a significant PFS benefit for the addition of bevacizumab to platinum-doublet chemotherapy.(8). However, the ORR was 60% and median OS was significantly increased compared with historical controls from the GOG209 study (HR 0.71; P < .039). PFS was not significantly increased in any experimental arm compared to historical controls.The MITO END-2 trial failed to demonstrate a significant PFS or OS benefit for bevacizumab plus chemotherapy, although the rate of 6-month disease control was significantly higher (91% vs 70%).(7) Current NCCN Guidelines® list bevacizumab alone as an option after progression on chemotherapy or in combination with platinum-based chemotherapy for advanced disease.(5). The multi-targeted tyrosine kinase inhibitors (TKIs) lenvatinib and cediranib have also demonstrated efficacy in patients with advanced endometrial cancers.(9,10).

Inhibitors of HER2 and mTOR.

Uterine serous carcinomas are an aggressive variant of endometrial cancer and often have dysregulated HER2 signaling, leading to investigation of trastuzumab in combination with carboplatin/paclitaxel in this patient subset. A randomized phase 2 trial showed a 4.6-month improvement in median PFS with the addition of trastuzumab to chemotherapy (HR 0.44; P = .005) in patients with HER2-positive uterine serous carcinomas. The PFS benefit was consistent in both treatment-naive and pretreated patients, and the combination was well tolerated.(11). The phase 2 GOG-3007 trial compared hormone therapy alone with everolimus (an mTOR inhibitor) plus letrozole in patients with advanced endometrial cancer and showed an improvement in median PFS from 3.8 to 6.3 months.(12)

PFS benefit from everolimus/letrozole was particularly evident in patients who had received no prior chemotherapy (median PFS: 21.6 months). This combination was well tolerated, although

rates of grade 3/4 anemia and hyperglycemia were increased compared with hormone therapy alone.

Immunotherapy

Several checkpoint inhibitors have demonstrated some efficacy in patients with advanced endometrial cancers.(13-20). Pembrolizumab has a tumor-agnostic approval for patients with MSI-H or dMMR advanced solid tumors and is listed in current NCCN Guidelines® as an option for advanced endometrial cancers. (5,21)

Another PD-1 inhibitor, dostarlimab (TSR-042), was evaluated in the phase 2 GARNET trial, in advanced endometrial cancer. The ORR was 29.6% overall, but reached 48.8% in patients with MSI-H tumors (compared with 20.3% for those with MSS tumors). A total of 85% of patients with MSI-H endometrial cancer experienced a reduction in total tumor burden of over 50%. The DCR was 63% for MSI-H tumors vs 46.8% for those with MSS tumors.(15) Responses were durable in both cohorts, with 50% of responders remaining on therapy longer than 1 year. Dostarlimab had a manageable safety profile and was most commonly associated with fatigue, diarrhea, and nausea. Grade 3 or higher immune-mediated AEs only occurred in 5.6% of patients and included increases in alanine aminotransferase and aspartate aminotransferase, hyperglycemia, autoimmune hemolytic anemia, colitis, and infusion-related reaction.

A phase 2 study evaluated avelumab in patients with dMMR and those with proficient MMR proteins.(22) The MMR-proficient cohort was closed early due to futility, while the dMMR subgroup demonstrated an ORR of 26.7%. PFS at 6 months was 40%, and responses were observed independent of PD-L1 expression. The most frequent any-grade treatment-related AEs were fatigue, nausea, hypothyroidism, neutropenia, anemia, and diarrhea. Grade 3 AEs included anemia and diarrhea, and no grade 4 toxicities were reported.

A phase 1b trial recently reported data on the activity of atezolizumab in patients with advanced solid tumors, including 15 patients with recurrent or metastatic endometrial cancers. Benefit was modest, with an ORR of 13%, median PFS of 1.4 months, and median OS of 9.6 months. Benefit was more substantial in patients with high PD-L1 expression (n = 5), with an ORR of 40% and median PFS and OS of 4.2 and 38.2 months, respectively.(23)

Combination regimens. Potential synergy between targeted agents and immunotherapies continues to be explored based on the hypothesis that the action of targeted therapies may prime the immune system, thus increasing the anti-immune response elicited by immunotherapies.[44] Targeted agents may enhance immunotherapy activity by improving the function or activation of immune cells, creating neoantigens, or eliciting immune cell infiltration of the tumor microenvironment.

The KEYNOTE-146 trial investigated the co-inhibition of VEGF and PD-1 signaling by combining these 2 agents, lenvantinib and pembrolizumab.(25) Lenvatinib plus pembrolizumab had an ORR of 40% and a DCR of 87%. Responses were durable, with 65% having a response lasting at least 12 months. The most common any-grade AEs were fatigue, hypothyroidism, diarrhea, hypertension, decreased appetite, nausea, and stomatitis. The most frequent grade 3/4

side effects included hypertension, palmar-plantar erythrodysesthesia syndrome, and fatigue. Based on these data, lenvatinib combined with pembrolizumab recently received accelerated FDA approval for the treatment of patients with previously treated advanced endometrial carcinoma that is not MSI-H or dMMR.(21) Also concidering AE patients should be monitored regularly and educated regarding the potential for AEs to protect patient quality of life (QoL) and avoid unnecessary treatment delays or interruptions.

Some others ongoing clinical trials continue to investigate immunotherapeutic combination approaches for endometrial cancer, including combinations with chemotherapy such as phase 2 trial is evaluating pembrolizumab with carboplatin/paclitaxel in patients with advanced endometrial carcinoma.(26) The phase 3 RUBY trial is directly comparing carboplatin/paclitaxel with placebo or dostarlimab in patients with recurrent or primary advanced endometrial cancer.(27) The phase 3 AtTEnd trial is evaluating atezolizumab plus carboplatin/paclitaxel in patients with advanced or recurrent endometrial cancer.(28)

Another area of interest is the potential efficacy of combining immune checkpoint inhibitors with inhibitors of poly(ADP-ribose) polymerase (PARP). Ongoing phase 2 trials are investigating combinations such as olaparib/durvalumab (DOMEC trial), rucaparib/atezolizumab/bevacizumab (EndoBARR trial), and niraparib/dostarlimab in patients with recurrent or metastatic endometrial cancers.(29-31)

Highlights

Given the molecular subtypes of endometrial cancer outlined by TCGA, optimal patient selection for emerging therapies is going to be paramount to ensuring patients receive the most effective therapy without compromising safety and QoL.

Despite randomized phase II trials suggesting that adding bevacizumab to chemotherapy carboplatin and paclitaxel in frontline endometrial cancer was feasible and may result in some benefit, no randomized phase III trials have been conducted to confirm those results

Immune checkpoint inhibitors have shown efficacy in patients with recurrent MSI-H/dMMR solid tumors, including endometrial cancers, with a prolonged duration of response in those who respond

Single-agent immunotherapy with anti–PD-1 monoclonal antibodies, either dostarlimab or pembrolizumab, is approved for patients with recurrent endometrial cancer with MSI-H/dMMR.

Still, experts suggest that adding lenvatinib to pembrolizumab monotherapy in patients with MSI-H tumors is likely to result in added toxicity, but not meaningfully improve response

Response with single-agent pembrolizumab in MSI-H endometrial cancer in KEYNOTE-158 is comparable to that of the combination of lenvatinib plus pembrolizumab in MSI-H/dMMR endometrial cancers from KEYNOTE-146 (57.1% vs 63.6%)

Single-agent checkpoint inhibitor is the preferred choice in MSI-H/dMMR endometrial cancer

Also have to notice that many of the currently available therapies are associated with AEs that can negatively affect patient QoL and lead to early treatment discontinuation. Unique targets continue to be identified, and ongoing clinical trials will hopefully elucidate promising therapies to improve survival and QoL for patients with advanced disease.

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The Early and locally advanced hormone dependant Breast cancer – where do we stand?

Semir Beslija

Oncology Division
KCUS

EARLY BREAST CANCER: WHO NEEDS ADJUVANT ET?

- **(almost) All ER+ EARLY BREAST CANCER patients!**

Identifying Patients at Biological High Risk for Recurrence

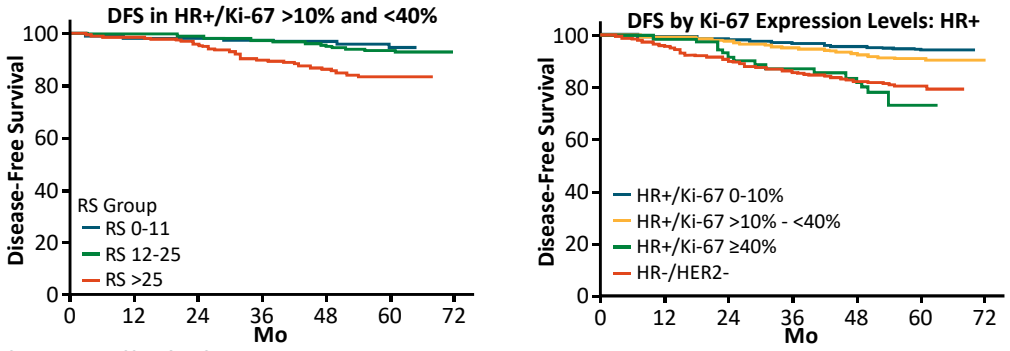
Genomic features

- Gene expression assays
  - 21-gene (Oncotype DX)
  - 70-gene (MammaPrint)

Proliferation features

- Ki-67 by immunohistochemistry
  - Cutoff values of High vs Low

WSG PlanB Trial: DFS by Oncotype RS and Ki-67



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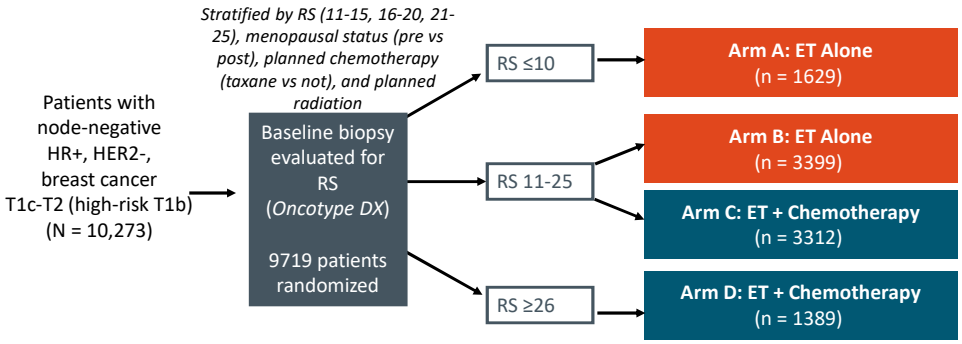
TAILORx: Treatment Assignment and Randomization

- Randomized, parallel-assignment phase III study



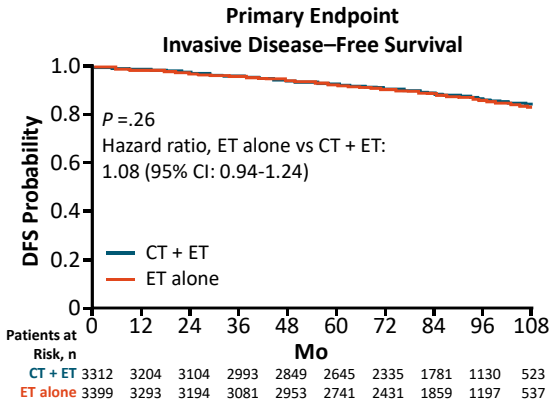
Statistical Design
Noninferiority - iDFS
Hazard Ratio: 1.332
(90 vs. 87% 5-yr DFS)
Type I 10%, type II 5%
Full info: 835 iDFS events

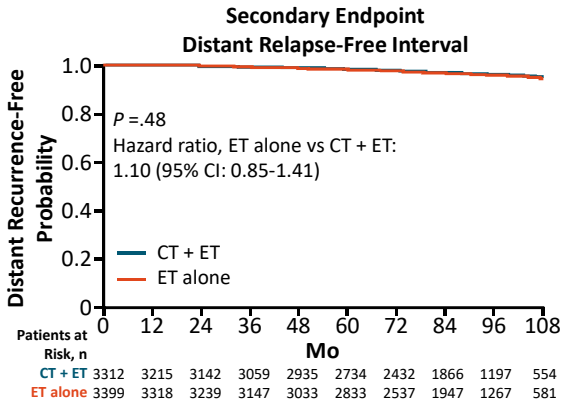
- Primary endpoint: iDFS, secondary primary cancer, or death
- Key secondary endpoints: freedom from breast cancer recurrence at distant site, freedom from breast cancer recurrence at distant or local-regional site, OS

NCT00310180. Sparano. NEJM. 2018;379:111

TAILORx: ITT Population—RS 11-25 (Arms B & C)

- 836 iDFS events (after median of 7.5 yr), including 338 (40.4%) with recurrence as first event, of which 199 (23.8%) were distant





Sparano. NEJM. 2018;379:111.

RxPONDER: Adjuvant ET ± Chemotherapy in HR+/HER2- EBC With 1-3 Positive Lymph Nodes and RS ≤25

- Randomized phase III trial

Stratified by RS (0-13 vs 14-25), menopausal status (pre vs post), axillary surgery (ALND vs SLNB)

Adults with HR+/HER2- EBC and 1-3 positive LN without distant mets*; able to receive adjuvant taxane and/or anthracycline-based CT†; axillary staging by SLNB or ALND; RS 0-25‡ (N = 5015)

→ **Chemotherapy Followed by ET** (n = 2509)

→ **ET Alone** (n = 2506)

→ *Baseline characteristics generally well balanced between treatment arms*

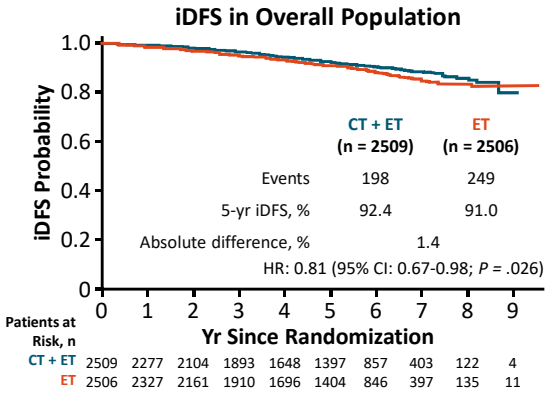
*Protocol amended to exclude patients with pN1mic as only nodal disease after 2493 patients randomized. †Approved CT regimens: TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T); AC alone or CMF not allowed. ‡Patients with RS > 25 recommended to be treated with CT followed ET off study.

- Primary endpoint: iDFS
- Key secondary endpoints: OS, distant DFS, local DFI, toxicity, QoL

Kalinsky. SABCS 2020. Abstr GS3-00.

RxPONDER: iDFS (Primary Endpoint)

- In this population of node positive, hormone receptor–positive BC with RS 0-25, RS did not predict relative CT benefit for iDFS
  - HR: 1.02 (95% CI: 0.98-1.06; *P* = .30)
- CT use and RS independently prognostic for iDFS
  - iDFS events **less likely** among patients who received CT
    - HR: 0.81 (95% CI: 0.67-0.96; *P* = .026)
  - iDFS events **more likely** among patients with higher RS
    - HR: 1.06 (95% CI: 1.04-1.07; *P* <.001)



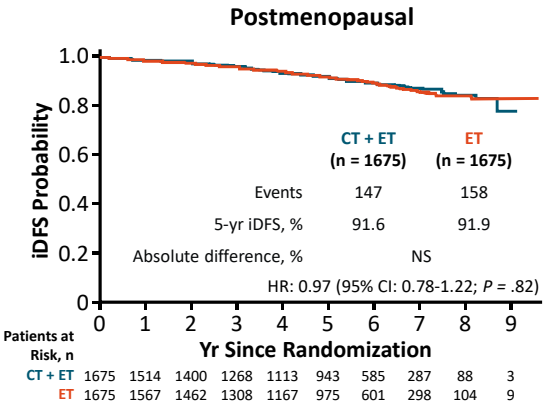
Patients at Risk, n

CT + ET	2509	2277	2104	1893	1648	1397	857	403	122	4
ET	2506	2327	2161	1910	1696	1404	846	397	135	11

- At median follow-up of 5.1 yr, 447 iDFS events were observed (54% of expected at final analysis)

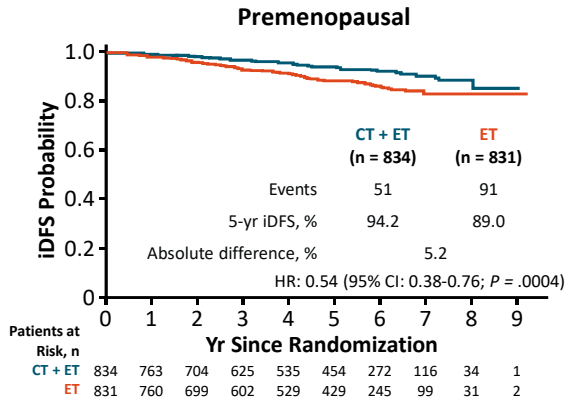
Kalinsky. SABCS 2020. Abstr GS3-00.

RxPONDER: iDFS by Menopausal Status



Patients at Risk, n

CT + ET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9



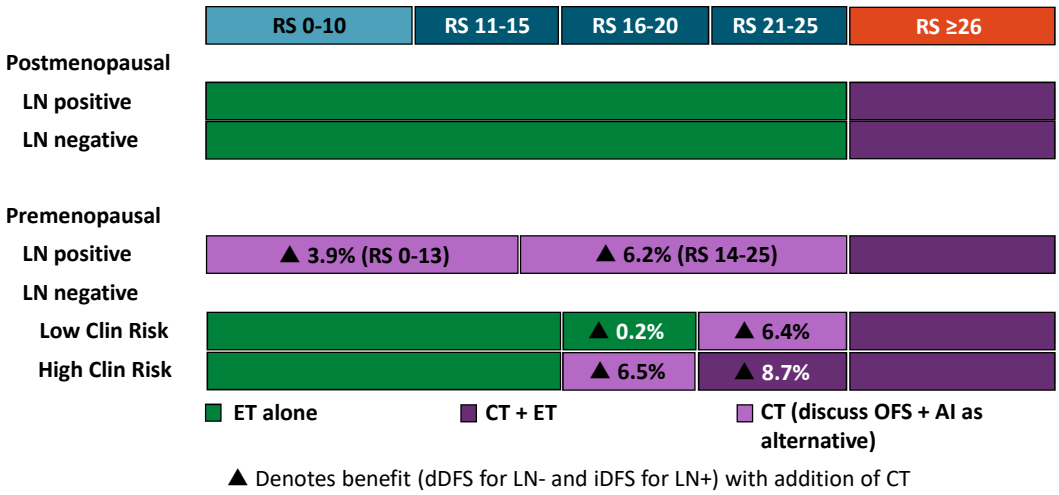
Patients at Risk, n

CT + ET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

- Absolute difference in distant recurrence as first site: 0.3% (2.3% CT + ET vs 2.6% ET)
- Absolute difference in distant recurrence as first site: 2.9% (3.1% CT + ET vs 6.0% ET)

Kalinsky. SABCS 2020. Abstr GS3-00.

Chemotherapy for ER+/HER2- BC With 0-3 LN



▲ Denotes benefit (dDFS for LN- and iDFS for LN+) with addition of CT

Kalinsky. SABCS 2020. Abstr GS3-00. Sparano. **NEJM**. 2019;380:2395.

ADAPT HR+/HER2-: Adjuvant ET ± Chemotherapy in Intermediate/High-Risk, HR+/HER2- Luminal EBC

- 2-part, prospective phase III trial
  - Part 1: Current analysis evaluated prognostic impact of RS <26 and Ki-67 decrease after short-course of preoperative ET in the ET alone arm and is not a randomized comparison

Adult patients with HR+/HER2- unilateral luminal EBC; cT1-4c, cN0-3; candidates for adjuvant CT by conventional prognostic criteria* (N = 4691)

→ Baseline biopsy evaluated for RS (*Oncotype DX*) and Ki-67 expression; surgical specimen evaluated for Ki-67 expression† after short ET run-in

- pN2-3
- pN0-1/RS >25
- pN0-1/RS 12-25/ $Ki\text{-}67_{post}$ > 10%

→ **CT Followed by ET** (n = 2335)

- pN0-1/RS 12-25/ $Ki\text{-}67_{post}$ ≤10%
- pN0-1/RS 0-11

→ **ET Alone** (n = 2356)

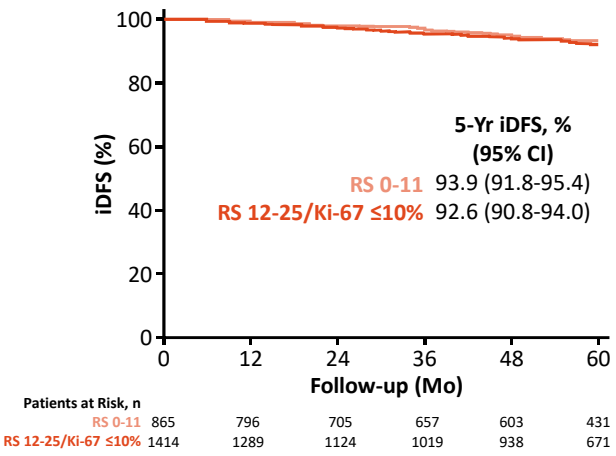
*cT2 or G3 or Ki-67 ≥15% or <35 yr old or cN+.
†$Ki\text{-}67_{post}$ ≤10% = ET response.

- **Primary endpoint: 5-yr iDFS**
  - **Part 1: NI* for pN0-1/RS 12-25/$Ki\text{-}67_{post}$ ≤10% vs pN0-1/RS 0-11**
- Key secondary endpoints: dDFS, OS, translational research

*NI defined as ≤3.3% 1-sided 95% CL of 5-yr iDFS difference (α = .05, 80% power; 5% dropouts)

Harbeck. SABCS 2020. Abstr GS4-04.

ADAPT HR+/HER2-: 5-Yr iDFS (Primary Endpoint)



- Primary endpoint met
  - 5-yr iDFS difference: -1.3% (95% CI: -3.3% to 0.6%)
  - 95% lower confidence limit of -3.3% met prespecified criterion for noninferiority of pN0-1/RS 12-25/ Ki-67$_{post}$ ≤10% vs pN0-1/RS 0-11 (*P* = .05)
- 5-yr OS rate
  - 97.3% for pN0-1/RS 12-25/Ki-67 ≤10% vs 98.0% for pN0-1/RS 0-11 (*P* = .160)

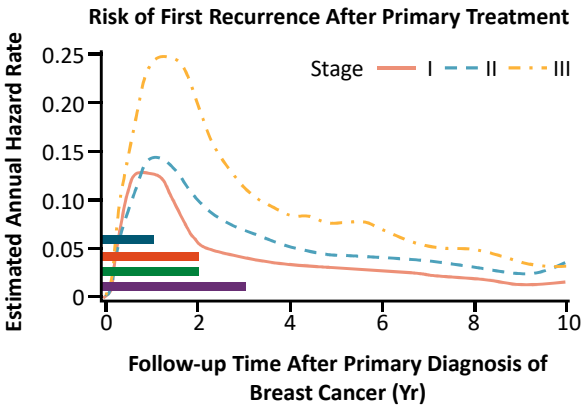
Harbeck. SABCS 2020. Abstr GS4-04.

Treatment De-Escalation Strategies in HR+/HER2- EBC: Summary

- **TAILOR-x :**In LN-negative breast cancer:
  - Age >50 yr: RS ≤25 have no chemotherapy benefit
  - Age ≤50 yr: RS 16-25 may derive chemotherapy benefit
- **RxPONDER:** analysis of adj CT for HR+/HER2- EBC with 1-3 positive nodes and RS ≤25, postmenopausal women did not benefit, whereas premenopausal women did[1]
  - Premenopausal patients experienced a 46% decrease in iDFS events and a 53% decrease in deaths, leading to a 5-yr OS absolute improvement of 1.3%
- **ADAPT HR+/HER2-:** primary endpoint reached: patients with luminal EBC and 0-3 positive nodes, RS 12-25 and endocrine response (Ki-67$_{post}$ ≤10%)[2] after short preoperative ET had a 5-yr iDFS (92.6%) comparable to those with 0-3 LN and RS 0-11 (93.9%)
  - Outcome was excellent in both groups with adj ET alone: 5-yr dDFS (95.6% vs 96.3%) and 5-yr OS (97.3% vs 98.0%)

1. Kalinsky. SABCS 2020. Abstr GS3-00. 2. Harbeck. SABCS 2020. Abstr GS4-04.

Is There a Role for CDK4/6 Inhibition for Early-Stage HR+ Disease?



PENELOPE-B
palbociclib
After neoadjuvant, high risk

monarchE
abemaciclib
High-risk CPR factors, Ki-67

PALLAS
palbociclib
Stage II, III

NATALEE
ribociclib
Stage II, III

Cheng. Cancer Epidemiol Biomarkers Prev. 2012;21:800.

PALLAS: Phase III Open-Label Study of Adjuvant Palbociclib + Endocrine Therapy

- Multicenter, open-label, randomized phase III trial

Stratified by stage (IIA vs IIB/III), chemotherapy (yes vs no), age (≤50 vs >50 yr), geographic region (N America vs Europe vs other)

Patients with stage II-III HR+/HER2- breast cancer; completion of prior surgery, ± CT, RT within 12 mo of diagnosis or within 6 mo of starting adjuvant endocrine treatment; FFPE tumor block submitted (N = 5760)

→ **Palbociclib** x 2 yr*+ **Endocrine therapy**† (n = 2883)

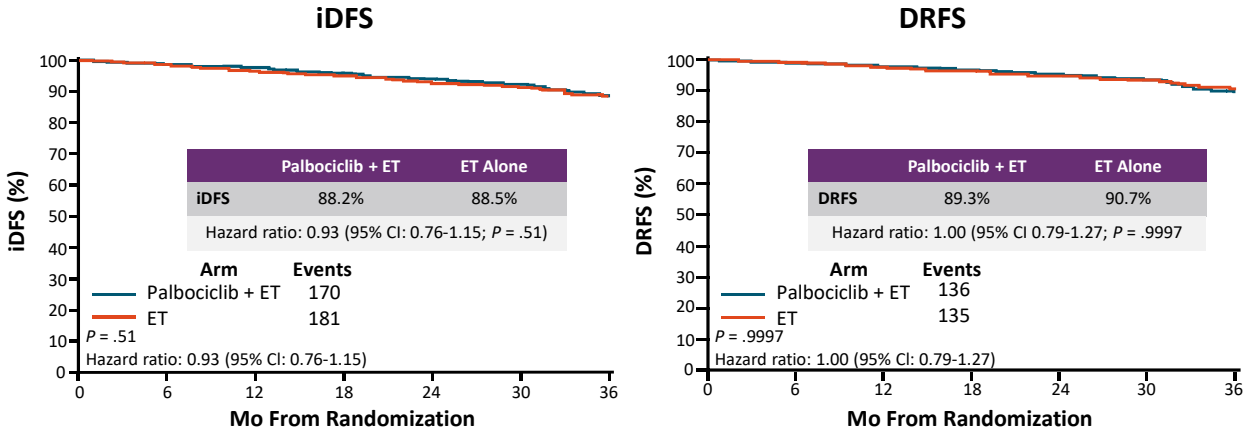
→ **Endocrine therapy**† (n = 2877)

*125 mg QD, 3 wk on/1 wk off †Aromatase inhibitor or tamoxifen ± LHRH agonist.

- **Primary endpoint:** invasive disease–free survival

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021;22:212.

PALLAS: Primary Endpoint iDFS



- At a median follow-up of 23.7 mo, no significant difference in either 3-yr iDFS or DRFS was observed

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021; 22:212.

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial

Women or men with high-risk, node-positive, HR+/HER2- EBC; prior (neo)adjuvant CT permitted; pre- or postmenopausal no distant metastasis; ≤16 mo from surgery to randomization; ≤12 wk of ET after last non-ET (N = 5637)

ITT Population (Cohorts 1 + 2)

Cohort 1
≥4 positive ALN *or* 1-3 positive ALN plus histologic grade 3 and/or tumor ≥5 cm

Cohort 2
1-3 positive ALN, Ki-67 ≥20% per central testing, not grade 3, tumor size <5 cm

Stratified by prior CT, menopausal status, region

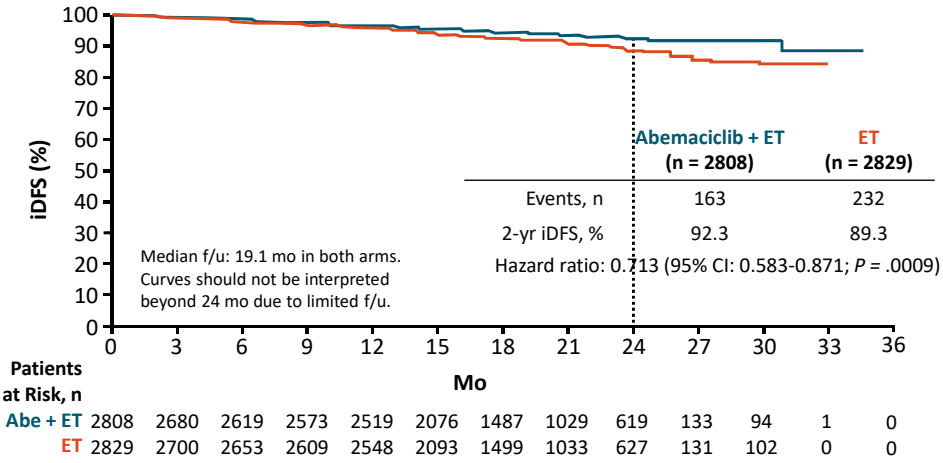
Abemaciclib 150 mg BID up to 2 yr + **ET** per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2808)

ET per standard of care of physician's choice for 5-10 yr as clinically indicated (n = 2829)

- Primary endpoint: iDFS
  - Planned for after ~390 iDFS events (~85% power, assumed iDFS hazard ratio of 0.73, cumulative 2-sided α = 0.05)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

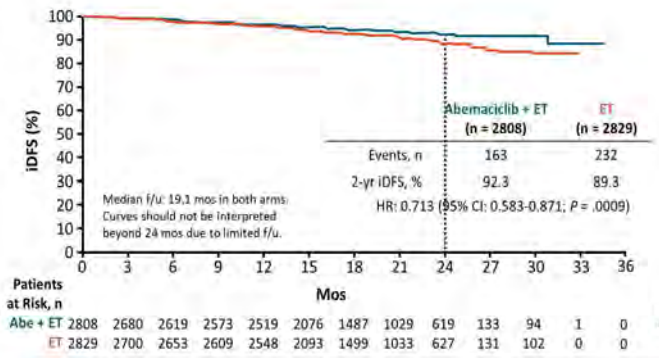
monarchE: iDFS (Primary Endpoint)



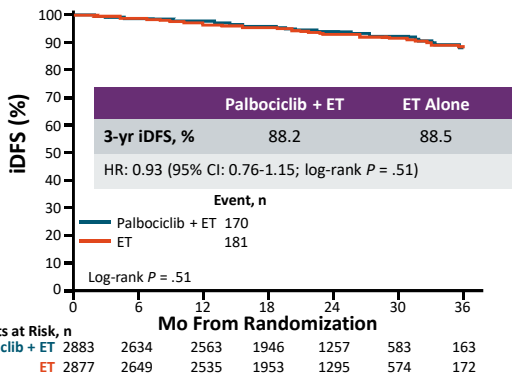
Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

Why Did MonarchE Succeed Where PALLAS Failed?

MonarchE iDFS



PALLAS iDFS



Differences between the drugs themselves/drug exposure and discontinuations/ level of risk within patient populations?

Johnston. JCO. 2020;38:3987. Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021;22:212.

monarchE NAC Subgroup Analysis: Prior NAC Regimen

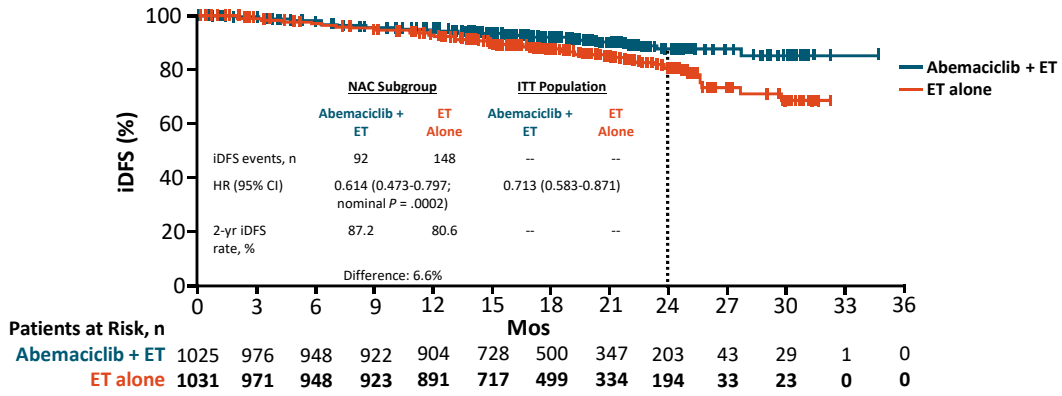
Prior NAC Regimen, n (%)	Abemaciclib + ET (n = 1025)	ET Alone (n = 1031)
Anthracycline + taxane	903 (88.1)	931 (90.3)
Anthracycline without taxane	71 (6.9)	59 (5.7)
Taxane + cyclophosphamide	28 (2.7)	23 (2.2)
Other*	23 (2.2)	18 (1.7)

*Includes taxane only, cyclophosphamide only, other CT.

- NAC subgroup comprised 36% of ITT population
- Most patients received standard NAC regimen of anthracycline + taxane
  - Use of standard NAC regimen was consistent between treatment arms

Martin. ASCO 2021. Abstr 517.

monarchE NAC Subgroup Analysis: iDFS (Primary Endpoint)



- In the NAC subgroup, abemaciclib + ET demonstrated a clinically meaningful 38.6% reduction in risk of an iDFS event vs ET alone
- The 2-yr iDFS rate was higher with abemaciclib + ET vs ET alone in the NAC subgroup (87.2% vs 80.6%; difference: 6.6%)

Martin. ASCO 2021. Abstr 517. Reproduced with permission.

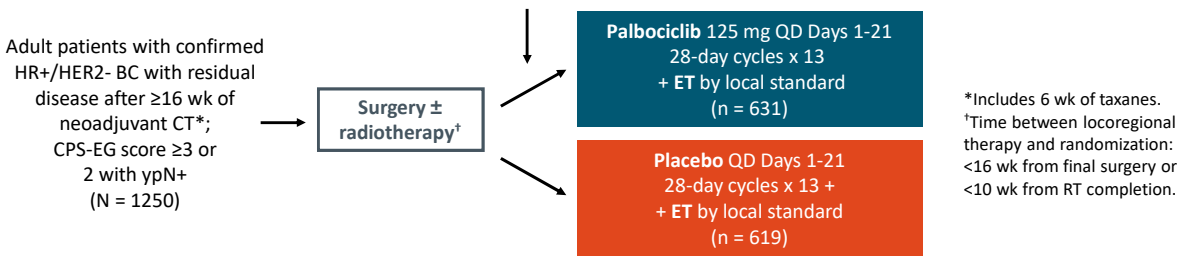
monarchE NAC Subgroup Analysis: Conclusions

- In this preplanned subgroup analysis of the monarchE trial, abemaciclib + adjuvant ET demonstrated clinically meaningful improvements in iDFS and distant RFS vs ET alone in patients with high-risk HR+/HER2- EBC who received prior NAC[1]
  - Reduction in risk: iDFS, 38.6%; distant RFS, 39.1%
  - Benefits were numerically greater than those observed in ITT population and were maintained independent of tumor size at diagnosis and surgery
- Among those treated with ET alone, the NAC subgroup exhibited a lower 2-yr iDFS rate vs the ITT population consistent with a higher risk of recurrence[1-3]
  - 2-yr iDFS rate comparable to that reported in control arm of phase III PENELOPE-B trial, which compared palbociclib + ET vs placebo + ET in women with high-risk HR+/HER2- EBC after NAC[4]
- Safety profile in this population consistent with prior reports for abemaciclib[1]

1. Martin. ASCO 2021. Abstr 517. 2. Rastogi. SABCS 2020. Abstr GS1-01. 3. Johnston. JCO. 2020;38:3987.
4. Loibl. JCO. 2021;39:1518.

PENELOPE-B: Palbociclib + ET in HR+/HER2- BC at High Risk of Relapse After Neoadjuvant Chemotherapy

- Randomized, double-blind, placebo-controlled phase III trial

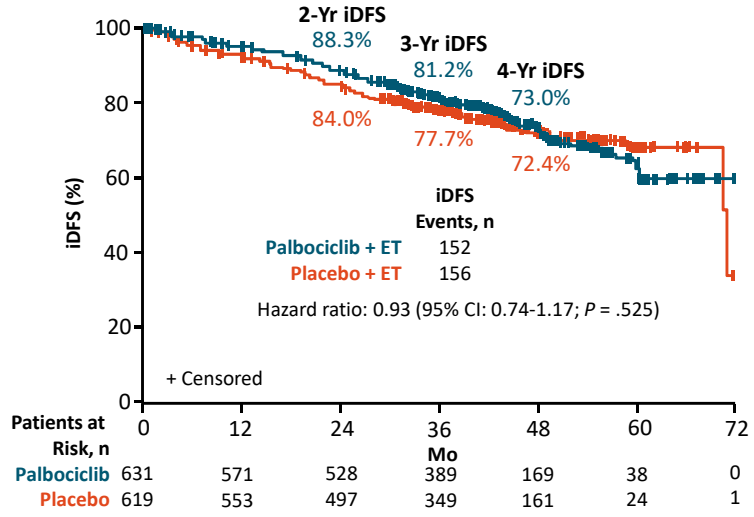


*Includes 6 wk of taxanes.
†Time between locoregional therapy and randomization: <16 wk from final surgery or <10 wk from RT completion.

- Primary endpoint: iDFS
- Secondary endpoints include: iDFS excluding second primary invasive non-breast cancers, distant DFS, locoregional RFS, OS, safety, compliance, QoL

Loibl. JCO 2021;10:1200.

PENELOPE-B: iDFS (Primary Endpoint)



Loibl. JCO 2021;10:1200.

- Median f/u: 42.8 mo
- Types of iDFS events
  - 74% distant recurrences
    - 116 with palbociclib, 111 with placebo
  - 16% invasive locoregional recurrences
    - 21 with palbociclib, 27 with placebo

CDK4/6 Inhibition in High-Risk HR+/HER2- EBC: Summary

- **monarchE:** In a preplanned interim analysis, adj abemaciclib + ET continued to demonstrate improved iDFS vs ET alone for HR+/HER2- EBC at high risk of relapse after locoregional tx and/or (neo)adj CT (hazard ratio: 0.75; 95% CI: 0.60-0.93; *P* = .01)[1,2]
  - 2-yr iDFS rates: 92.2% with abemaciclib + ET vs 88.7% with ET
  - Significant iDFS improvement observed in Ki-67 high (≥20%) tumors
  - Distant RFS also improved (hazard ratio: 0.72; 95% CI: 0.56-0.92; *P* = .01), with 2-yr distant RFS rates of 93.6% vs 90.3%, respectively
- **PENELOPE-B:** In the first interim analysis, the addition of 1 yr of adjuvant palbociclib to ET in the curative setting failed to demonstrate a benefit in patients with higher-risk HR+/HER2- EBC after locoregional tx and neoadjuvant CT[3]

1. Johnston. JCO. 2020;38:3987. 2. Rastogi. SABCS 2020. Abstr GS1-01. 3. Loibl. SABCS 2020. Abstr GS1-02.

Why Different Outcomes Across These Trials (or Are There)?

- Different definitions of high risk?
  - Was there more luminal B (high proliferation) in monarchE than in PALLAS or PENELOPE-B?
- Differences in therapy adherence?
  - May explain PALLAS results but adherence much higher in PENELOPE-B (though shorter duration of therapy with only 1 yr)
- Is abemaciclib a more effective CDK inhibitor?
  - Possible, although not supported by metastatic first-line trials that have remarkably similar hazard ratios (continuous dosing, more potent inhibition of CDK4, monotherapy activity)
- Durations of CDK inhibitor therapy?
  - Possible PENELOPE-B would have been positive if palbociclib had been given for longer
  - Await NATALEE results with 3 yr of ribociclib

O'Regan. SABCS 2020. Abstr GS1-03.

Why Should Neoadjuvant Endocrine Therapy Be Given?

- Down-stage tumor prior to surgery
  - NET and chemotherapy have similar rates of clinical response, radiographic response, and rates of BCS, but lower rates of toxicity
  - AI superior to tamoxifen in terms of clinical response, radiographic response, and rates of BCS
  - Longer duration of NEC allows for higher rates of BCS and pCR
- Identify HR+ tumors that may not require chemotherapy
- Gain insights into the biology of the tumors
  - Biomarkers response/resistance to treatment
  - Predict phase III trial results

Barchiesi. Int J Mol Sci. 2020;21:3528.

No Significant Improvement in ORR/BCS With Neoadjuvant Chemotherapy vs Endocrine Therapy

Trial	Treatment Arm	Duration	Primary Endpoint	Objective Response	Breast Cancer Survival
Semiglazov et al.	A: CT (n = 118) (dox + paclitaxel) B: ET (total n = 121) Ana (n = 60) + Exe (n = 61)	3 mo	Objective response by clinical palpation	A: 63% B: 64%	A: 24% B: 33% *P* = .058 (statistically significant)
GEICAM 2006-03	A: CT (EC -> doxetaxel) B: Exe (+ goserelin if premenopausal)	--	Response rate by MRI	A: 66% B: 48%	A: 47% B: 56%
NEO CENT	A: CT (n = 22) B: Letrozole (n = 22)	18-23 wk	Recruitment feasibility and tissue collection	A: 54% B: 59%	--
UNICANCER-NEO Pal	A: CT (n = 53) B: Letrozole/ palbociclib (n = 53)	20 wk	Residual cancer burden index	A: 76% B: 75%	A: 69% B: 69%

Reinert. Curr Treat Options Oncol. 2018;19:23.

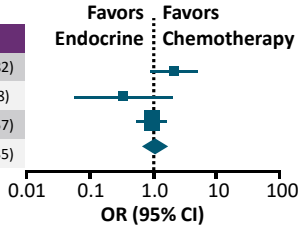
Neoadjuvant ET vs CT: Systematic Review/ Meta-analysis of 20 RCTs Through 2015 (N = 3490)

- AIs showed significantly higher rates of clinical response, radiologic response, and BCS vs tamoxifen; radiologic response rate higher with CT + ET vs ET

Clinical Response

Source	OR (95% CI)
Alba 2012	2.11 (0.92-4.82)
Palmieri 2014	0.34 (0.6-1.98)
Semiglazov 2007	0.93 (0.55-1.57)
Total	1.08 (0.50-2.35)

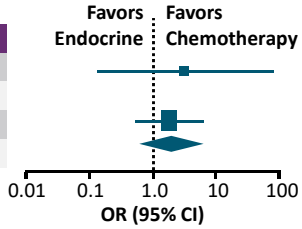
Heterogeneity: $x^2_2 = 4.47$ ($P = .11$), $I^2 = 55\%$.
Test for overall effect: $z = 0.19$ ($P = .85$).



Pathologic CR

Source	OR (95% CI)
Alba 2012	3.13 (0.12-78.77)
Palmieri 2014	Not estimated
Semiglazov 2007	1.84 (0.53-6.47)
Total	1.99 (0.62-6.39)

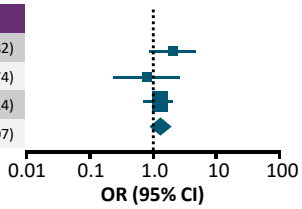
Heterogeneity: $x^2_2 = 0.09$ ($P = .76$), $I^2 = 0\%$.
Test for overall effect: $z = 1.16$ ($P = .25$).



Radiologic Response

Source	OR (95% CI)
Alba 2012	2.11 (0.92-4.82)
Palmieri 2014	0.83 (0.25-2.74)
Semiglazov 2007	1.28 (0.77-2.14)
Total	1.38 (0.92-2.07)

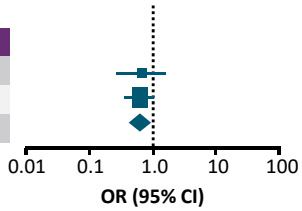
Heterogeneity: $x^2_2 = 1.77$ ($P = .41$), $I^2 = 0\%$
Test for overall effect: $z = 1.54$ ($P = .12$)



Breast Conservation Response

Source	OR (95% CI)
Alba 2012	0.68 (0.30-1.54)
Semiglazov 2007	0.63 (0.36-1.11)
Total	0.65 (0.41-1.03)

Heterogeneity: $x^2_2 = 0.03$ ($P = .87$), $I^2 = 0\%$
Test for overall effect: $z = 1.83$ ($P = .07$)



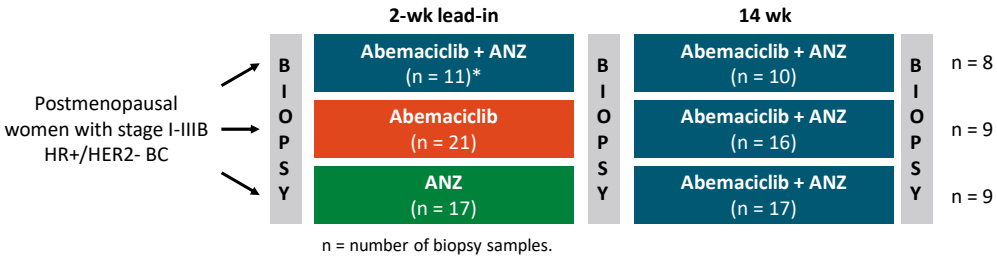
Spring. JAMA Oncol. 2016;2:1477.

Summary of Endocrine Therapy Alone

- Neoadjuvant endocrine therapy yields similar ORR response to chemotherapy
  - AI > tamoxifen in terms of ORR and BCS
- Endpoints of trials in ER+ breast cancer challenging
  - Achievement of pCR rare (<5%)
  - Use of Ki67 and PEPI may correlate with long-term outcome and may allow triage of patients with no drop in Ki67 to chemotherapy
    - ALTERNATE: fulvestrant = AI = AI + fulvestrant in terms of Ki67 response, PEPI; long-term outcomes are awaited

neoMONARCH: Neoadjuvant Abemaciclib, Anastrozole, and Abemaciclib + Anastrozole in HR+/HER2- BC

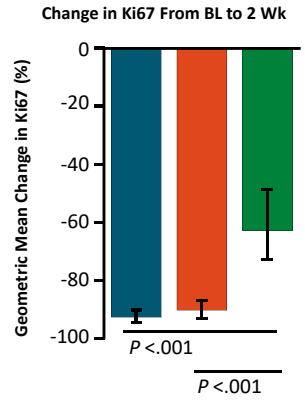
- RNAseq analysis of biopsy samples from multicenter, randomized, open-label phase II trial

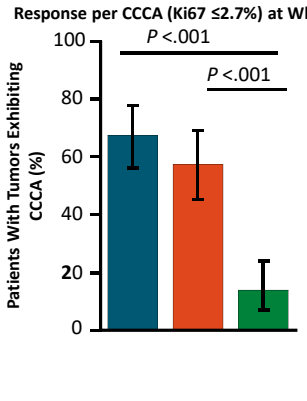


- **Primary endpoint:** percent change in Ki67 from baseline to 2 wk of treatment
- **Secondary endpoints:** pCR, OR, radiologic response

Hurvitz. Clin Cancer Res. 2020;26:566.

neoMONARCH: Antiproliferative Effects of Abemaciclib, Anastrozole, and Combination Tx on HR+/HER2- BC





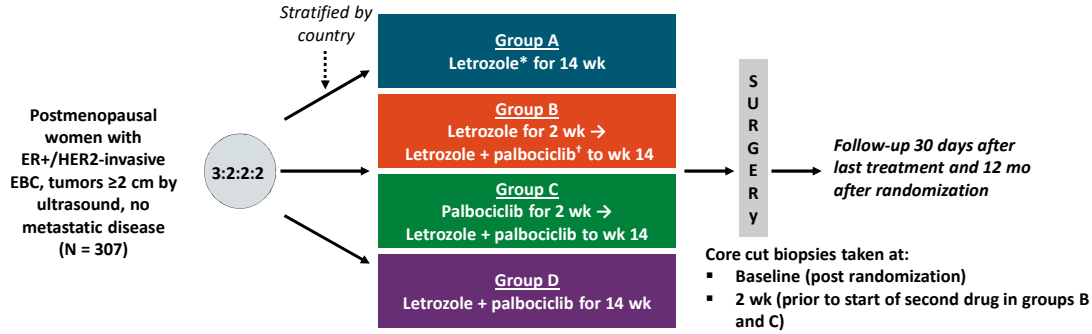
Outcome, %	Abema + ANZ	Abema	ANZ
Geometric mean change in Ki67 at 2 wk	-93	-91	-63
CCCA	68	58	14

- ORR: 46% (5% CR, 42% PR)
- pCR: 4%

Hurvitz. Clin Cancer Res. 2020;26:566.

PALLET: Palbociclib + Neoadjuvant Letrozole in ER+/HER2- EBC

- Randomized phase II trial (parallel protocols in North America and UK)



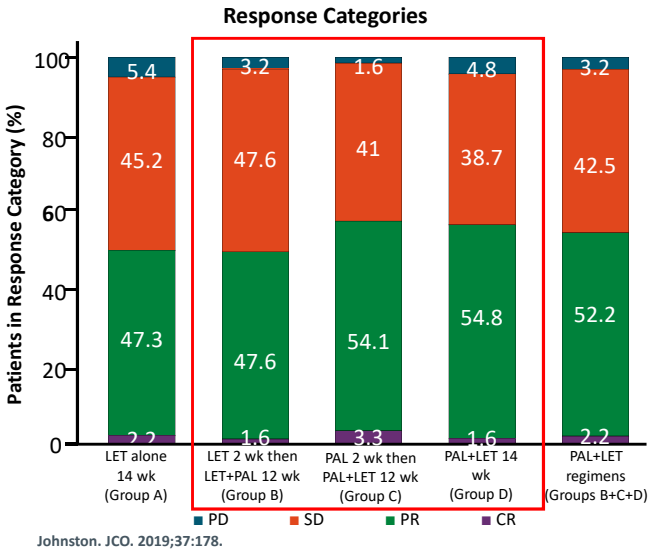
*Letrozole 2.5mb/day PO. †**Palbociclib 125 mg/day PO** (3 wk on, 1 wk off). Dose reduction to 100 mg and 75 mg available.

Core cut biopsies taken at:
- **Baseline (post randomization)**
- **2 wk (prior to start of second drug in groups B and C)**
- **14 wk or at discontinuation treatment (within 48 hr of last dose)**

- **Coprimary endpoints (for group A vs B + C + D): change in Ki67 (protein between baseline and 14 wk and clinical response (ordinal and ultrasound) after 14 wk**
- **Secondary endpoint: pCR**

Johnston. JCO. 2019;37:178.

PALLET: Clinical Response (Coprimary Endpoint)



- No significant difference in ORR with letrozole (Group A) vs letrozole + palbociclib (Groups B + C + D)
  - ORR: 49.5% vs 54.4%; *P* = .20 per Mann-Whitney test (ordinal)

Johnston. JCO. 2019;37:178.

PALLET Summary

- Compared to letrozole, palbociclib + letrozole:
  - Enhanced Ki67 suppression (*P* <.001)
  - Increased CCCA rate (58.5% to 90.4%; *P* <.001)
  - Did not improve ORR (49.5% to 54.4%; *P* = .2)
  - pCR rate: 1%

Johnston. JCO. 2019;37:178.

FELINE: Neoadjuvant Ribociclib + Letrozole vs Placebo + Letrozole in ER+/HER2- Breast Cancer

- Randomized, open-label phase II trial (patients accrued Feb 2016 to Aug 2018)

Postmenopausal women with HER2- breast cancer, stage II/III, primary >2 cm; ER+ >66% (N = 120)

→ **Ribociclib** 400 mg/day PO, continuously + **Letrozole** 2.5 mg PO QD (n = 41)

→ **Ribociclib** 600 mg/day PO, 3 wk on/off + **Letrozole** 2.5 mg PO QD (n = 41)

→ **Letrozole** 2.5 mg PO QD + **Placebo** (n = 38)

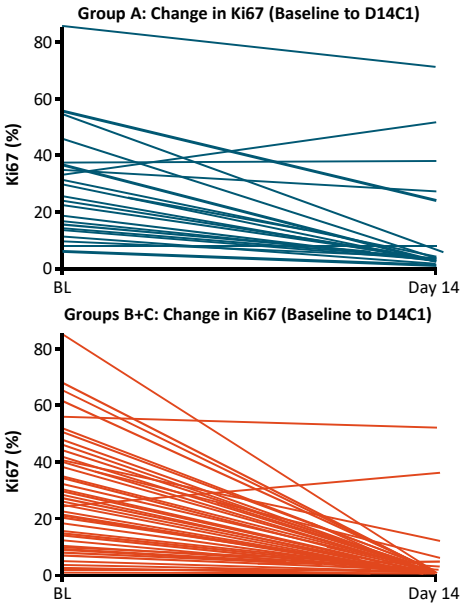
- 6 28-day cycles
- Surgery between D8-21 of cycle 6
- Treatment continued until day before surgery
- Clinical response measurement: ultrasound, MRI
- Tissue samples: baseline, Day 14 of cycle 1, and at surgery
- If Ki-67 > 10% at Day 14 of cycle 1, patient removed from trial

- **Primary endpoint:** Proportion reaching PEPI score 0 at surgery (ie, removing need for adjuvant chemo)
  - PEPI 0: tumor ≤5 cm, node negative, Ki-67 ≤2.7%, Allred ER score 3-8
- **Secondary endpoints:** complete cell-cycle arrest, responses (RECIST), safety

Khan. ASCO 2020. Abstr 505.

FELINE: Ki67 Change Between Baseline and Day 14 of Cycle 1

Parameter	Group A Placebo + Letrozole	Groups B+C	*P* Value	Group B Ribociclib Intermittent + Letrozole	Group C Ribociclib Continuous + Letrozole
Baseline Ki67, median %	15.8	21.4	.9129	16.5	24.7
Day 14 Ki67 > 10%, % (n/N)	17.24 (5/29)	4.05 (3/74)	.025	2.86 (1/35)	5.13 (2/39)
Mean change Ki67% (baseline to D14C1)	-15.7	-23.3	.047	-20.6	-25.7
CCCA at Day 14, % (n/N)	51.7 (15/29)	91.9 (68/74)	<.0001	97.1 (34/35)	87.2 (34/39)



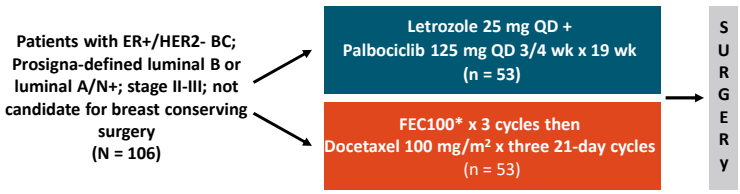
Khan. ASCO 2020. Abstr 505.

FELINE: Summary

- Adding ribociclib to letrozole **did not**
  - Increase number of patients with PEPI = 0
  - Improve ORR
- Adding ribociclib to letrozole **did**
  - Improve complete cell cycle arrest at C1D14
    - But this was not maintained at surgery (acquired resistance?)

NeoPal: Neoadjuvant Letrozole + Palbociclib vs CT

- Randomized, parallel, non-comparative phase II trial



*FEC100: 5-FU 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m².

Final Analysis

Outcome, n (%)	LET + PAL (n = 52)	CT (n = 51)
RCB 0-I	4 (7.7)	8 (15.7)
RCB II-III	48 (92.3)	43 (84.3)
pCR	2 (3.8)	3 (5.9)

- **Primary endpoint: rate of RCB 0-I**
- **Secondary endpoints: clinical response, proliferation-based markers, safety**
- **Sample size: null hypothesis (p0) was RCB 0-I in 20% of cases; alternative hypothesis was 40%, type I error of 0.045, type II error of 0.042 (power: 95.8%); required sample size n = 60/arm**

Cottu. Ann Oncol. 2018;29:2334.

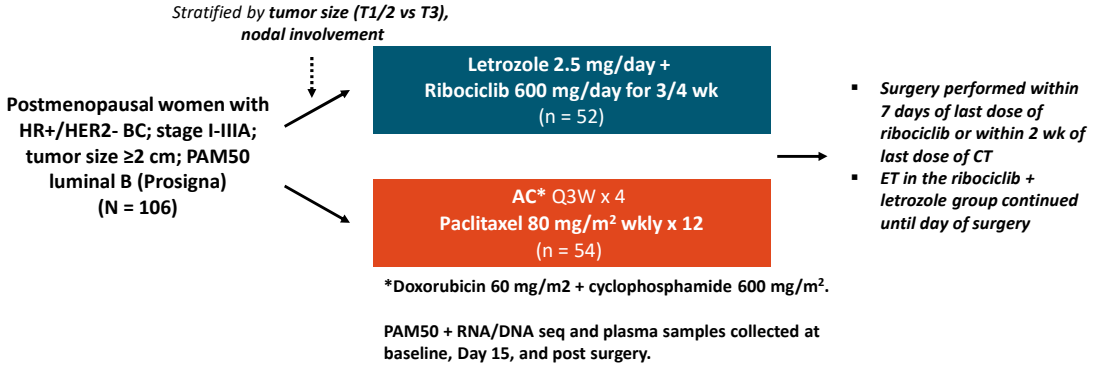
NeoPal Conclusion

- Neoadjuvant LET + PAL or CT was associated with poor pathologic response for Prosigna-defined high-risk luminal breast cancer
  - RCB 0-1 rate: 7.7% with LET + PAL; 15.7% with CT
  - pCR rate: 3.8% with LET + PAL; 5.9%% with CT
- Neoadjuvant LET + PAL or CT led to similar rates of clinical or radiologic response and BCS
- PEPI = 0 was numerically higher with LET + PAL (17.6% vs 8.0% with CT)

Cottu. Ann Oncol. 2018;29:2334.

CORALLEEN: Neoadjuvant Letrozole + Ribociclib vs CT

- Multicenter, randomized, open-label phase II trial



- **At baseline, ~40% of patients had node-positive disease, median Ki67 expression was 30-35, median ROR score was 70-77, and ≥85% had ROR high-risk disease**

Prat. Lancet Oncol. 2020;21:33.

CORALEEN: Primary Endpoint

ROR	Ribociclib + Letrozole (n = 49)		Chemotherapy (n = 52)	
	n (%)	95% CI	n (%)	95% CI
Low	23 (46.9)	32.5-61.7	24 (46.1)	32.9-61.5
Intermediate	15 (30.6)	18.2-45.4	13 (30.8)	19.1-45.9
High	11 (22.5)	11.8-36.7	11 (21.2)	11.2-35.2
Missing	NA	NA	1 (1.9)	NA

Prat. Lancet Oncol. 2020;21:33.

Summary: Neoadjuvant CDK4/6 Inhibitors

- Addition of CDK4/6 inhibitors to ET shows biologic activity (potent reduction in Ki67 at 2 wk)
- Addition of CDK4/6 inhibitors to ET does not appear to improve ORR or pathologic response vs ET alone or CT, with low rates of pCR or RCB 0-1
- Cross-trial comparisons suggest similar level of benefit across the 3 CDK4/6 inhibitors; however, there was no head-to-head comparison
- The optimum endpoint is unknown; it has not been firmly established that increasing the rate of pCR and RCB 0-1 improves long-term outcomes for luminal cancers
- *Without long-term outcomes, neoadjuvant CDK4/6 inhibitors remain investigational*

Summary

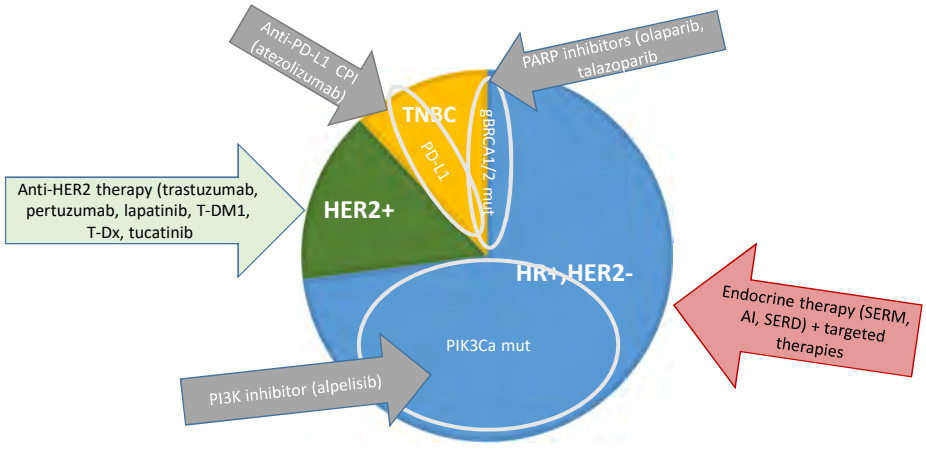
- Use of genomic assays in the preoperative setting may help us best select patients who may benefit from preoperative endocrine therapy vs chemotherapy
- Assessing endpoint to assess response to endocrine therapy + CDK4/6 inhibition not clearly established

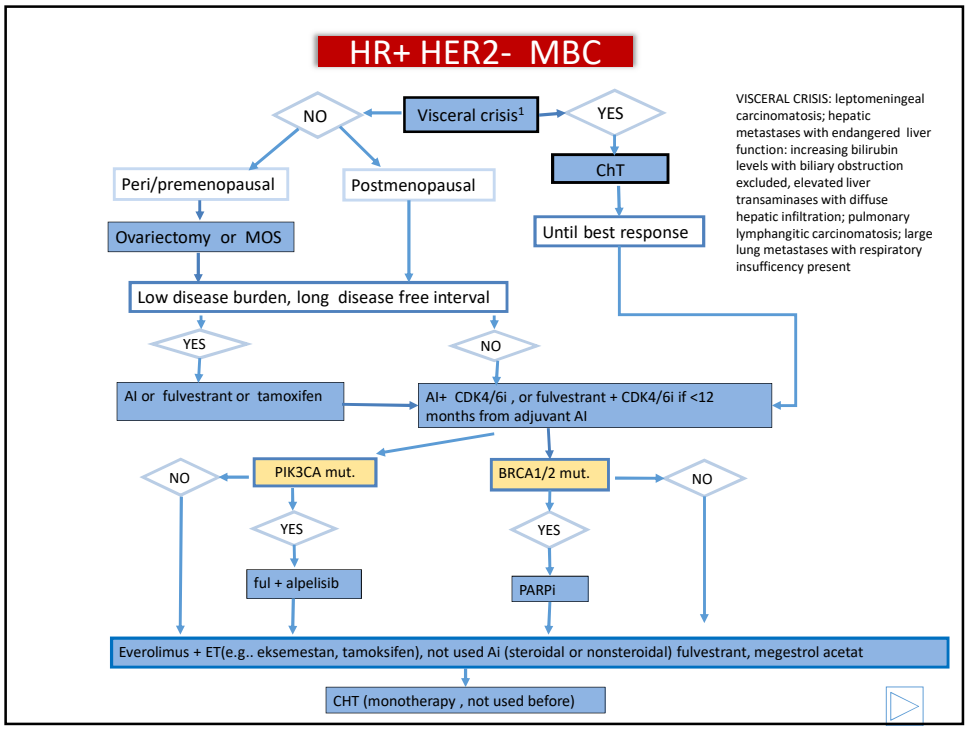
Metastatic breast cancer– standards and perspectives

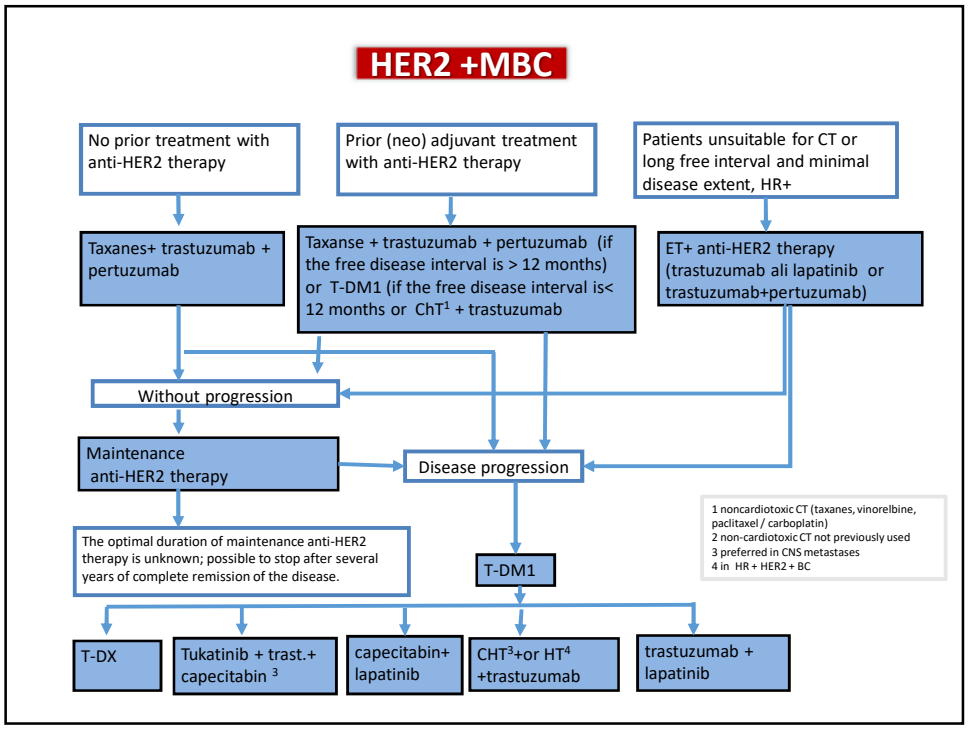
Simona Borštnar
Division of Medical Oncology
Institute of oncology Ljubljana

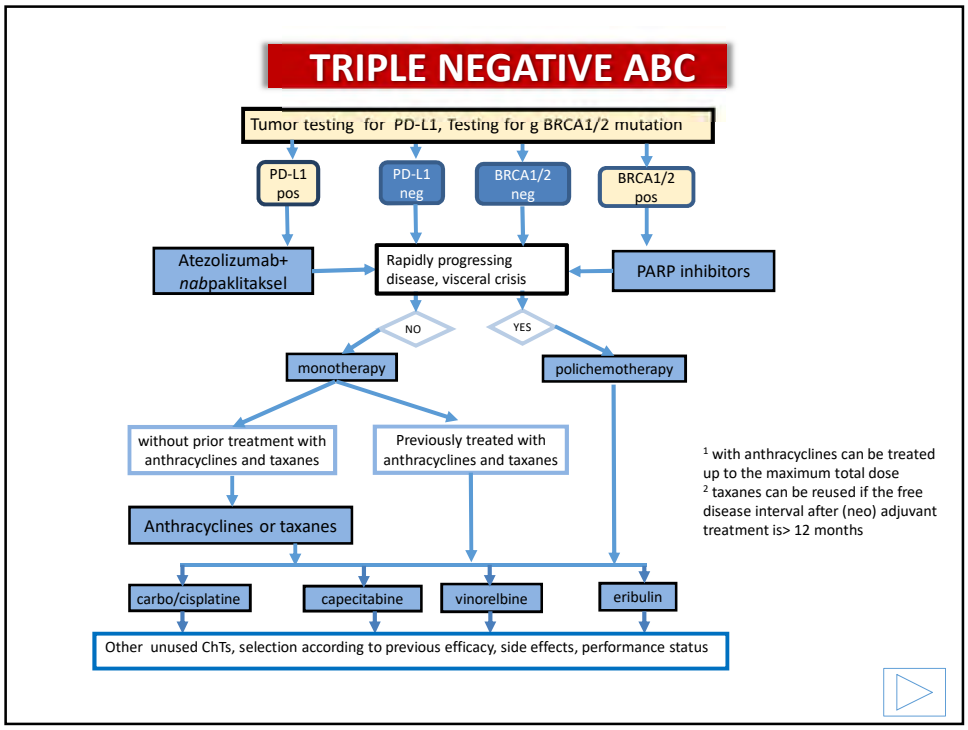
2nd Summer School in medical oncology
September 2021

Targeted treatment in MBC




HR+ HER2- MBC
Visceral crisis[1]
NO
YES
ChT
Until best response
Peri/premenopausal
Postmenopausal
Ovariectomy or MOS
Low disease burden, long disease free interval
YES
NO
AI or fulvestrant or tamoxifen
AI+ CDK4/6i , or fulvestrant + CDK4/6i if <12 months from adjuvant AI
PIK3CA mut.
BRCA1/2 mut.
NO
YES
NO
YES
ful + alpelisib
PARPi
Everolimus + ET(e.g.. eksemestan, tamoksifen), not used Ai (steroidal or nonsteroidal) fulvestrant, megestrol acetat
CHT (monotherapy , not used before)
VISCERAL CRISIS: leptomeningeal carcinomatosis; hepatic metastases with endangered liver function: increasing bilirubin levels with biliary obstruction excluded, elevated liver transaminases with diffuse hepatic infiltration; pulmonary lymphangitic carcinomatosis; large lung metastases with respiratory insufficency present


HER2 +MBC
No prior treatment with anti-HER2 therapy
Prior (neo) adjuvant treatment with anti-HER2 therapy
Patients unsuitable for CT or long free interval and minimal disease extent, HR+
Taxanes+ trastuzumab + pertuzumab
Taxanse + trastuzumab + pertuzumab (if the free disease interval is > 12 months) or T-DM1 (if the free disease interval is< 12 months or ChT[1] + trastuzumab
ET+ anti-HER2 therapy (trastuzumab ali lapatinib or trastuzumab+pertuzumab)
Without progression
Maintenance anti-HER2 therapy
Disease progression
The optimal duration of maintenance anti-HER2 therapy is unknown; possible to stop after several years of complete remission of the disease.
T-DM1
T-DX
Tukatinib + trast.+ capecitabin [3]
capecitabin+ lapatinib
CHT[3]+or HT[4] +trastuzumab
trastuzumab + lapatinib
1 noncardiotoxic CT (taxanes, vinorelbine, paclitaxel / carboplatin)
2 non-cardiotoxic CT not previously used
3 preferred in CNS metastases
4 in HR + HER2 + BC



Conclusion

- Approximately 20% to 30% of woman initially diagnosed with early stage disease will develop metastatic breast cancer.
- The goals of treatment are: maximizing the quality of life, prevention and palliation of symptoms, and prolongation of survival. Treatment is lifelong, characterized by remissions and relapses.
- When choosing a treatment, it is necessary to know the tumor characteristics and identify molecular targets.
- Targeted drugs such are anti-HER2 therapies in HER2 positive subtype, CDK4/6, mTOR and PIK3CA inhibitors in HR+/HER2- subtype and immune check point inhibitors in TNBC have significantly improved disease control.
- New promising drugs are under way, however we need clinical trials and continued basic and translational research to make new breakthroughs.

The diffuse large B cell lymphoma – recommendations and current knowledge

Barbara Jezeršek Novaković
Onkološki inštitut Ljubljana

Conclusion

LBCL are a heterogeneous group of diseases with different clinical and biological features – for an adequate treatment, histopathological evaluation of an extirpated lymph node is a prerequisite.

Conclusion

With current treatment, only 50 to 60% of patients will be cured. In relapsed disease, salvage chemotherapy results in long term disease free survival in a small minority of patients. Additional curative option is offered through high dose therapy and autologous SCT. Multiply relapsed lymphomas can be treated with CAR T cell therapy and allogeneic SCT, other treatments are predominately palliative.

And results…

Oncol Lett. 2018 Mar; 15(3): 3602–3609.
Published online 2018 Jan 11. doi: 10.3892/ol.2018.7774
PMCID: PMC5796369

Diffuse large B-cell lymphoma: 10 years' real-world clinical experience with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone

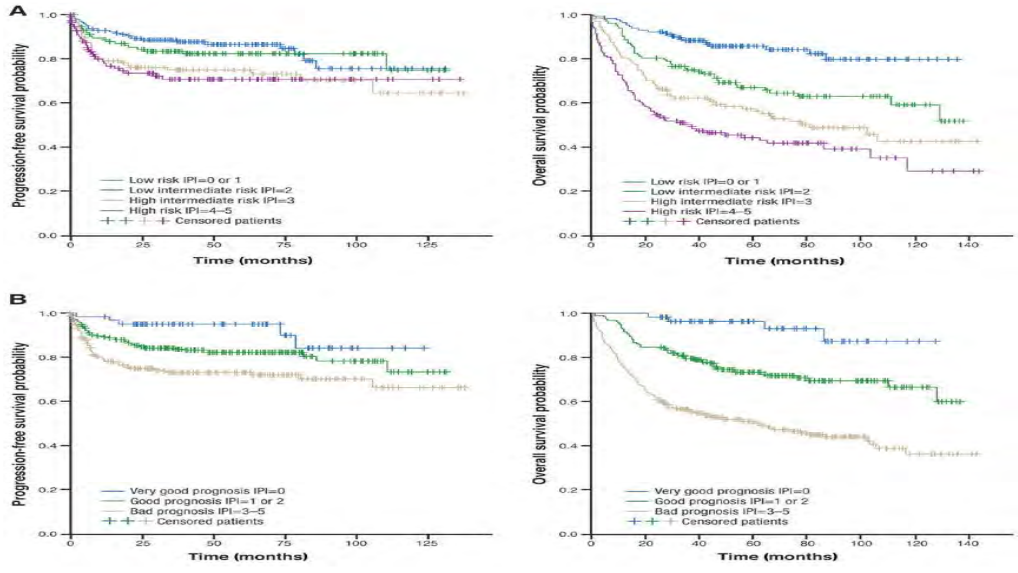
Matej Horvat,[1] Vesna Zadnik,[2] Tanja Južnič Šetina,[1] Lučka Boltežar,[1] Jana Pahole Goličnik,[1] Srdjan Novaković,[3] and Barbara Jezeršek Novaković[1]

And results…

Table I. Patient clinical and demographic characteristics at the start of treatment (n=624).

Sex	Male 297 (48%)	Female 327 (52%)
Median age	67.0 (19-89)	<60 years, 208 (33%)
ECOG performance status	0: 299 (48%)	1: 183 (29%)
	2: 90 (14%)	3: 33 (5%)
	4: 19 (3%)	
Disease stage	I: 73 (12%)	II: 178 (29%)
	III: 111 (18%)	IV: 245 (39%)
Elevated LDH level	311 (50%)	
Extranodal involvement	439 (70%)	
Treatment regimen	Rituximab + CHOP 575 (92%)	
	Rituximab + other chemotherapy 32 (5%)	
	Chemotherapy alone 17 (3%)	
IPI score	0: 63 (10%)	1: 122 (20%)
	2: 143 (23%)	3: 141 (23%)
	4: 108 (17%)	5: 44 (7%)

And results…

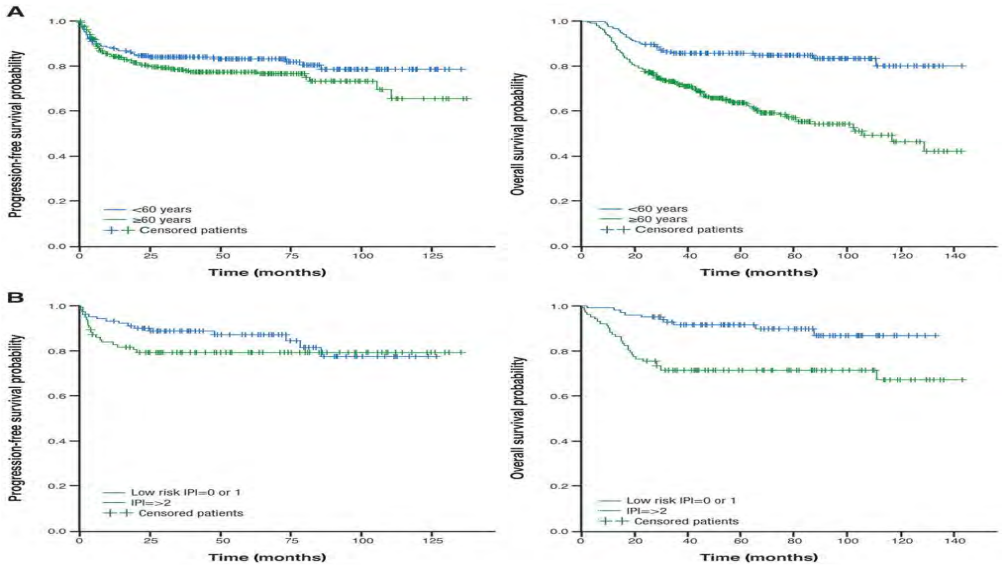


And results…

Survival rate (%)

Outcome	1-year	2-year	3-year	5-year	10-year	Median survival (months)
Progression-free survival						
Age, <60 years	88	85	84	83	79	NR
Age. ≥60 years	84	80	79	78	70	NR
Age, <60 years, IPI 0 or 1	93	90	89	87	77	NR
Age, <60, IPI ≥2	83	79	79	79	79	NR
Overall survival						
Age, <60 years	93	85	81	81	76	NR
Age, ≥60 years	82	70	64	56	41	80.1
Age, <60 years, IPI 0 or 1	98	95	91	91	87	NR
Age, <60, IPI ≥2	87	76	71	71	67	NR

And results…



Marginal zone lymphoma (MZL)

Summer school 2021
Oncology institute of Ljubljana
Milica Miljković, medical oncologist

Introduction

- Indolent (slow growing) Non – Hodgkin B cell lymphomas
- 5-15% of Non-Hodgkin lymphomas
- Average age at diagnosis is 60 years
- Slightly more common in women

WHO classification

- Clonal B-cell lymphocytosis of marginal zone origin (CBL-MZ)
- Nodal marginal zone lymphoma (NMZL)
- Splenic marginal zone lymphoma (SMZL)
- Extranodal marginal zone lymphoma (EMZL) or Mucosa –Associated Lymphoid Tissue (MALT) : The stomach is the most common site, followed by ocular adnexa, lung and salivary glands.

Treatment of EMZL, NMZL, SMZL

- Treat just symptomatic systemic disease
- It means:

-B simptomps: fewer, night sweats and weight loss

-Bulky disese

-Symptomatic splenomegaly and/ or any progressive cytopaenias

- Hb < 100 g/L
- Platelets < 80x10/L
- Neutrophils < 1 x10/L

Treatment of EMZL, NMZL, SMZL

- Stage I and II: surgery +/- RT (25,2GY)
- Stage III and IV and with B simptoms:

6-8 x R-LP (rituximab,chlorambucil, prednisolone)

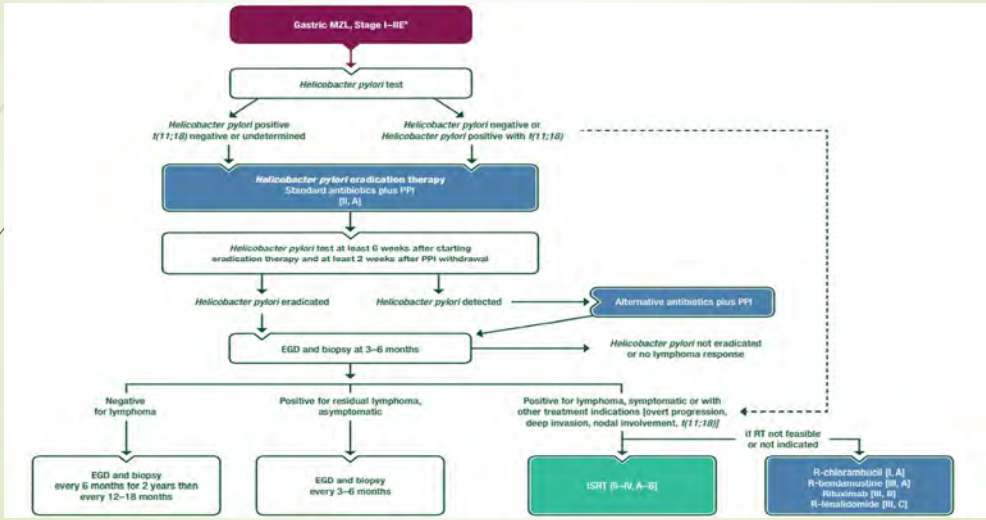
4-6 x R-Bendamustine

6-8 x R-Lenalidomide

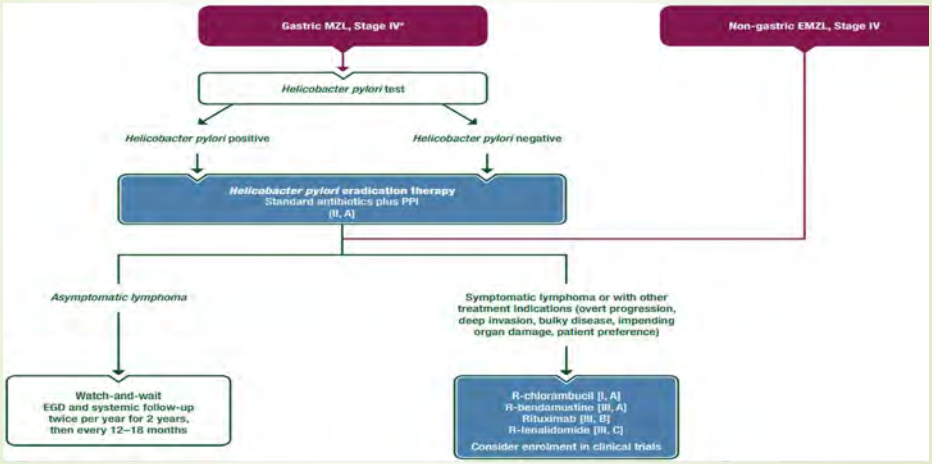
4 x Rituksimab + RT for old and unfit patients

6-8 x R-CHOP for aggressive disease (rituximab,ciklofosfamid,doxorubicin,vincristine,prednisolone)

Treatment algorithm for localised gastric MZL



Treatment algorithm for advanced gastric MZL



Sekcija internistične onkologije pri SZD, Onkološki inštitut Ljubljana in Katedra za onkologijo
2nd Summer School in medical oncology –
Precision oncology – Are we there yet
7-10 September 2021
Institute of Oncology Ljubljana, Zaloška 2, Ljubljana

Standards and perspectives in the systemic treatment of Lymphomas – Follicular lymphoma

dr. Tanja Južnič Šetina, dr.med
Institute of Oncology, Ljubljana

Follicular lymphoma

- Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma
- It accounts for 20% of all NHL cases and around 70 % of indolent lymphomas
- The clinical presentation is usually characterized by asymptomatic peripheral lymphadenopathy in cervical, axillary, inguinal and femoral regions. Most patients are diagnosed with advanced stage disease. Bone marrow involvement is present in more than >80%.
- The course of FL is quite variable. The disease is usually characterized by an indolent clinical course and response to initial therapy, but relapses are common.
- The prognosis of FL is good. The median survival of FL is over 15 years but considering it`s indolent nature, survival can often be measured in decades.
- Histologic transformation of FL to a DLBCL has been reported in up to 70 percent of patients over time, and is associated often with a poor prognosis.

Risk Assessment

The Follicular Lymphoma International Prognostic Index (FLIPI)

	FLIPI 1[a]	FLIPI 2[b]
Nodal site	• > 4 LN regions	• Long diameter of largest LN > 6 cm
Age	• > 60 years	• > 60 years
Serum marker	• LDH increased	• β2-microglobulin increased
Stage	• III-IV (Ann Arbor)	• Bone marrow involvement
Hemoglobin	• < 12 g/dL	• < 12 g/dL

PRIMA – PI

- B2M increased
- Bone marrow involvement

Low risk	Intermediate risk	High risk
Number of factors	Number of factors	Number of factors
FLIPI1: 0-1	FLIPI1: 2	FLIPI1: 3-5
FLIPI2: 0	FLIPI2: 1-2	FLIPI2: 3-5

- **low risk**: B2M normal and bone marrow not involved
- **intermediate risk**: B2M normal and bone marrow involved
- **high risk**: B2M elevated

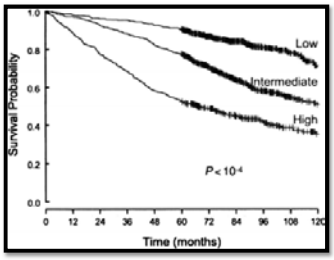
a. Solal-Céligny P, et al. *Blood.* 2004;104:1258-1265; b. Federico M, et al. *J Clin Oncol.* 2009;27:4555-4562.

FLIPI - outcome according to risk group

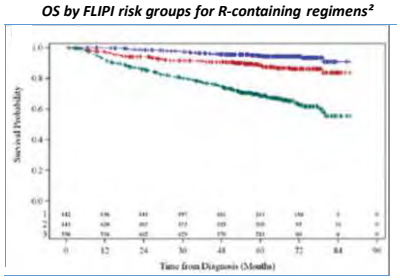
Risk group	score	5 year OS %	10-year OS %
Low	0 to 1	91	71
Intermediate	2	78	51
High	> 3	52	36

FLIPI score applied to patients in the rituximab era (68% received R, n=2192)			
score	2- yr OS %	2-yr PFS %	mPFS (months)
0 to 1	98	84	84
2	94	72	70
> 3	87	65	42

OS by FLIPI risk groups[1]



OS by FLIPI risk groups for R-containing regimens[2]



1. Solal-Celigny, P, Roy, P, Colombat, P, et al. Follicular lymphoma international prognostic index. Blood 2004; 104:1258
2. Nooka AK, Nabhan C, Zhou X, et al.. Ann Oncol 2013; 24:441.

Initial treatment of stage I to IV follicular lymphoma

- treatment of FL depends on the stage of disease at presentation
- introduction of anti-CD20 monoclonal antibody rituksimab into first line FL treatment or relapsed disease significantly improved the outcome of FL patients

Stage I/II

- 10-20% of FL patients present with limited stage I/II disease
  - radiotherapy (24-30 Gy) is generally the treatment of choice for limited stage FL, and results in 10-year OS rates of 60% to 80%;
  - 2 x 2 Gy schedule is less durable but might be used in special situations to minimize side-effects (e.g. lacrimal gland, parotid glands)
  - In selected cases (e.g. limited life expectancy, large abdominal fields), observation or rituximab monotherapy may be considered

Stage III/IV

- Initial observation ("watch and wait") is the standard approach in asymptomatic, stable patients with stage II (high tumor burden), III, or IV
- Immunotherapy-based treatment (rituximab, obinutuzumab and chemotherapy)
- Radioimmunotherapy
- lenalidomide-rituximab
- rituximab monotherapy or R in combination with chlorambucil

Indications for treatment

- local symptoms due to progressive or bulky nodal disease
- vital organ compression
- presence of systemic B symptoms (fevers >38°C, weight loss, night sweats)
- presence of symptomatic extranodal disease, such as effusions
- cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism
- rapid lymphoma progression

First-line therapy

- Preferred regimens
  - R – bendamustin, R-CHOP or R-CVP
  - Obinutuzumab / bendamustin, CHOP or CVP
  - Rituximab+ lenalidomide
- Less preferred
  - Rituximab – monotherapy (4 weekly doses)
  - Rituximab+chlorambucil
  - Radioimmunotherapy

- Rituximab maintenance (every 8 weeks for 2 years) - improves PFS and OS
- Obinutuzumab maintenance (every 8 weeks, 12 doses)

Randomized trials in first-line FL treatment (R-chemotherapy)

Study	Treatment, n	Median FU, months	ORR, %	PFS %	Median TTP/ TTF/ EFS, mo	OS, %
Marcus et al. 2006	CVP, 159 R-CVP, 162	53	57 81		15 34 p<0.0001	77(4-y) 83 (4-y) p = 0.029
Hiddemann et al. 2005	CHOP-IFN, 205 R-CHOP-IFN, 223	18	90 96		29 NR p<0.001	90(2-y) 95 (2-y) p = 0.016
Herold et al. 2006	MCP-IFN, 96 R-MCP-IFN, 105	47	75 92	71	26 NR p<0.0001	74 (4-y) 87 (4-y) p = 0.009
Salles et al.2008	CHVP-IFN, 183 R-CHVP-IFN, 175	60	73 84	37 53	33 p<0.0004 67	79(5-y) p = 0.07 84 (5-y)
Schulz H, 2007 metaanalysis	**PFS:** R-ChT vs ChT (HR 0,62, CI 0,55-0,71, p<0,001) **OS**: R-ChT vs ChT, 1480 (1.line+relapses) (HR 0,63; 95 % CI 0,51-0,79, p<0,001)					
Rummel et al. 2009	R-Bendamustine, 279 R- CHOP, 275	45	92,7		69 31 p<0.0001,HR 0.58	70 (10-y) 66 (10-y)
Morschhauser et al. 2018	R-CHOP/BR + R maint., 517 R-lenalidomide + R maint., 513	38 38	84 89		PFS 78% (3y) 77% (3y)	94 (3 y) 94 (3 y)

- With the introduction of R, survival of FL has improved.
- The improvement was established in at least four prospective first-line trials and a systematic meta-analysis.

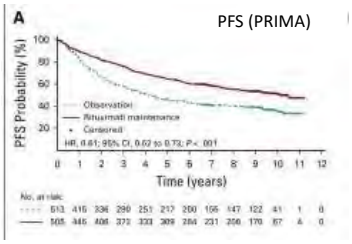
Maintenance treatment with rituximab (PRIMA study)

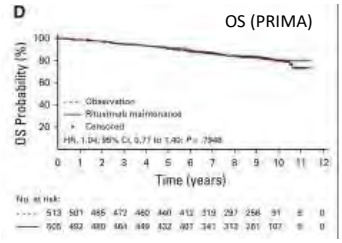
1. Long-Term Results of the PRIMA Study (9y FU)

Study	FU, n	Treatment	Median PFS	OS
PRIMA, 2011 First-line FL	9y of FU 1018 pts	R-ChT+observation vs R-ChT+mainten R	4.1y 10.5y p<0,001	>80 (10-y) >80 (10-y) p= NS

CONCLUSION (PRIMA)

- rituximab maintenance after induction immunochemotherapy provides a significant PFS benefit over observation
- no OS benefit





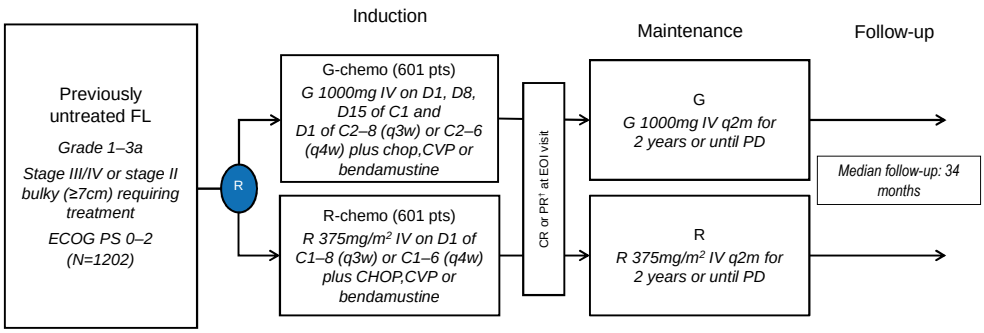
2. ***Meta-analysis*** (Vidal et al, 2017); seven trials including PRIMA, 2315 pts with FL evaluating rituximab maintenance on OS

CONCLUSION: Maintenance rituximab improved PFS (HR 0.57; 95% CI 0.51-0.64) and OS (HR 0.79; 95% CI 0.66-0.96)

1. Bachy E, et al. J Clin Oncol. 2019;37(31):2815-2824. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study.
2. Vidal L, Gafter-Gvili A, Salles G, et al. Eur J Cancer. 2017;76:216

GALLIUM Study

(randomised phase III study in previously untreated FL patients)

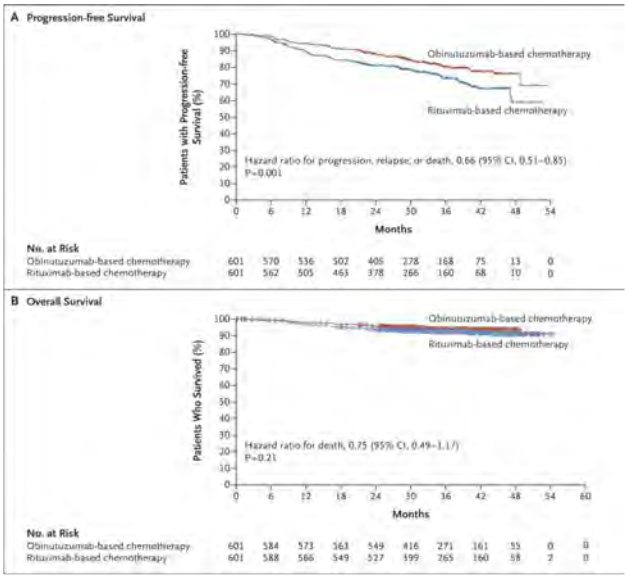


Primary endpoint

- *PFS*

Marcus, et al NEJM 2017; 377(14):1331-1344

GALLIUM study results : PFS and OS in patients with FL (first-line)



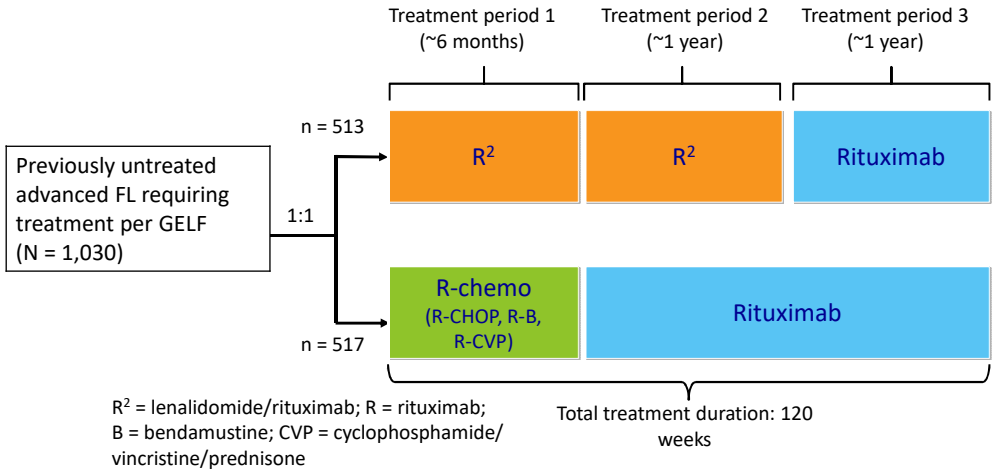
	R-ChT, n=601	G-ChT, n=601
3-y PFS,% (95% CI) HR (95% CI), =p=0.001	73,3 (68.8-77.2)	80,0 (75.9-83.6)
3-y OS HR 0.75, P=0,21	92	94

Conclusion:

- Obinutuzumab/chemo + maintenance is superior to similar R-based regimens with improvement of PFS
- no difference in OS

Marcus, et al NEJM 2017; 377(14):1331-1344

RELEVANCE: Phase III Trial Design (previously untreated FL patients)

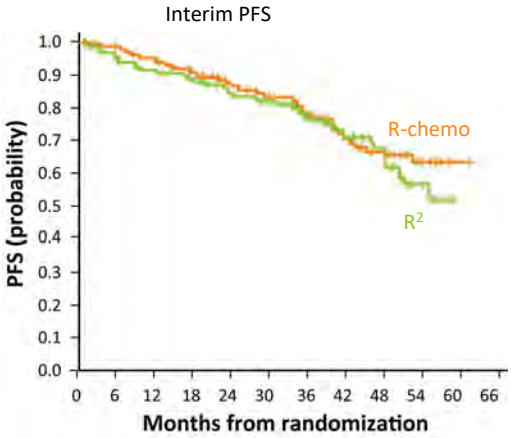


R^2 = lenalidomide/rituximab; R = rituximab; B = bendamustine; CVP = cyclophosphamide/ vincristine/prednisone

Primary endpoints: CR/CRu at 120 weeks and PFS

Morschhauser F, Fowler NH, et al. N Engl J Med. 2018;379(10):934

RELEVANCE: Interim PFS (first-line FL patients)



	R² (n = 513)	R-chemo (n = 517)
3-year PFS	77%	78%
HR	1.10	
p-value	0.48	

Conclusions

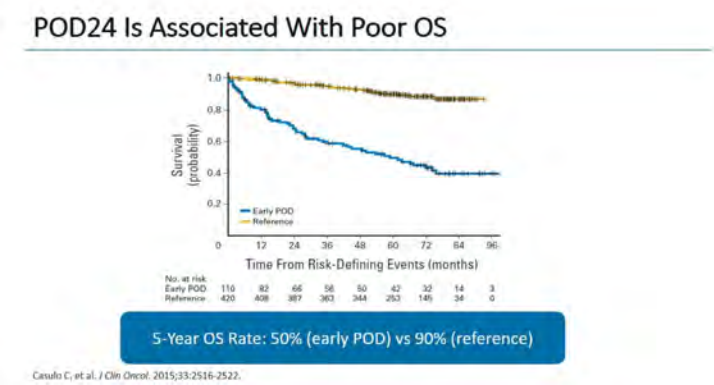
- similar rates of CR (48% in R² vs 53 % in R chemo)
- similar 3-y PFS (77% vs 78 %, HR 1.10, 95% CI 0.85-1.43)
- similar OS (94 vs 94 %, HR 1.16, 95% CI 0.72-1.86)
- more rash, diarrhea and tumor flare, less neutropenia in the R²

- At median follow-up of 37.9 mo, interim PFS was similar in both arms
- 3-y OS = 94% (R²) vs 94% (R-chemo), HR 1.16

Morschhauser F, Fowler NH, et al. N Engl J Med. 2018;379(10):934.

Treatment of R/R FL

- 20 to 30 % of patients with FL relapse after first- line therapy
- rule out histologic transformation
- patients who progress within 24 months have significantly worse OS than those who do not
- asymptomatic recurrent FL do not necessarily require immediate treatment



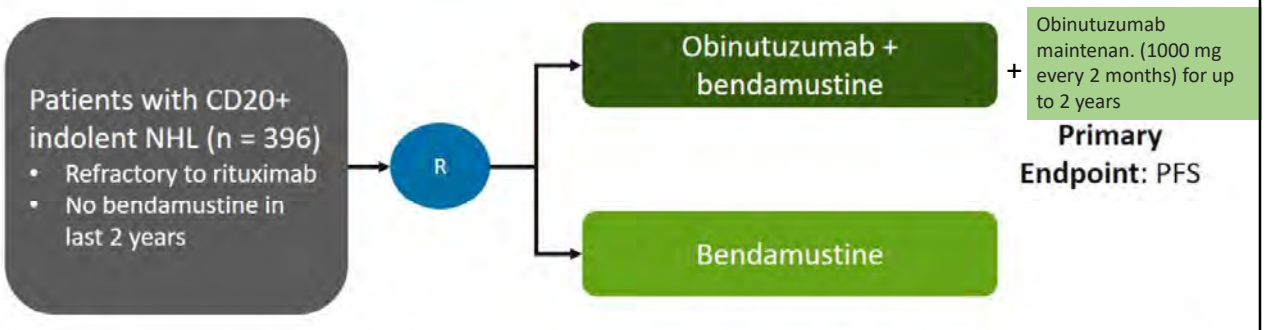
Treatment regimens for R/R FL

- Preferred regimens
  - Bendamustin + rituximab or obinutuzumab
  - CHOP or R-CVP + obinutuzumab or rituximab
  - Lenalidomide + rituximab or obinutuzumab
  - PI3K inhibitors (after 2 prior therapies)
- Less preferred (eldery, frail pts)
  - Rituximab alone (4 weekly doses)
  - Chlorambucil +/- R
  - Cyclophosphamide +/- R
  - Radioimmunotherapy
- **Rituximab maintenance** (every 3 months for 2 years)
- **Obinutuzumab maintenance for R-refractory** (every 8 weeks, 12 doses)
- Other
  - High dose therapy with ASCT, allogeneic transplant for selected patients
- Novel treatments (CAR-T-cell therapy, tazemetostat – EZH2 mut posit after 2 prior therapies or EZH2 WT in pts with no other alternative), mosunetuzumab

R, rituximab

GADOLIN *Study Design*

Randomised phase III study for R/R FL patients

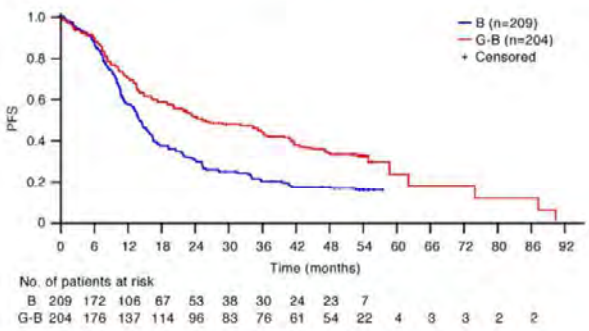


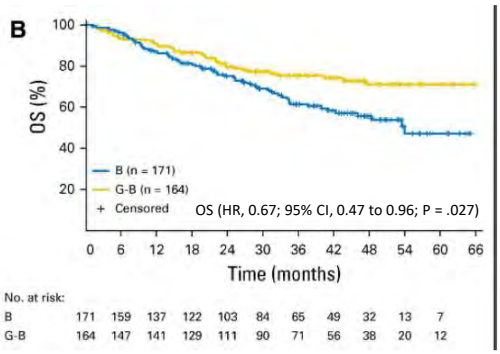
Dosing: Obinutuzumab 1000 mg IV on days 1, 8, 15 (cycle 1) and day 1 (cycles 2-6) + bendamustine 90 mg/m² IV on days 1 and 2 (cycles 1-6)

Dosing: Bendamustine alone, 120 mg/m² IV on days 1 and 2 (cycles 1-6)

Sehn LH, et al. *Lancet Oncol*. 2016;17:1081-1093.

GADOLIN
Final Efficacy and Safety Results





median follow-up 31,8 months
Median PFS 25.8 vs 14.1 months
Hazard ratio 0.57 (95% CI: 0.45, 0.73); *P* < .0001

Conclusion: the addition of obinutuzumab improves PFS and OS. Toxicity was similar in both treatments.

Adding obinutuzumab to bendamustine led to:
- Higher rates of AEs, including neutropenia, infusion reaction
- Lower rates of thrombocytopenia, anemia
- Similar rates of infection and second malignancy

Cheson BD. J Clin Oncol. 2018;36(22):2259.

AUGMENT
Study Design

AUGMENT: R^2 versus Rituximab/Placebo for R/R FL or Marginal Zone Lymphoma - randomised phase III study

Patients with FL or MZL requiring treatment (n = 358)
- ≥ 1 prior regimen and ≥ 2 prior doses of rituximab
- Relapsed, refractory, or progressive disease (not rituximab-refractory)
- No grade > 1 neuropathy

R

- Lenalidomide + rituximab
- Placebo + rituximab

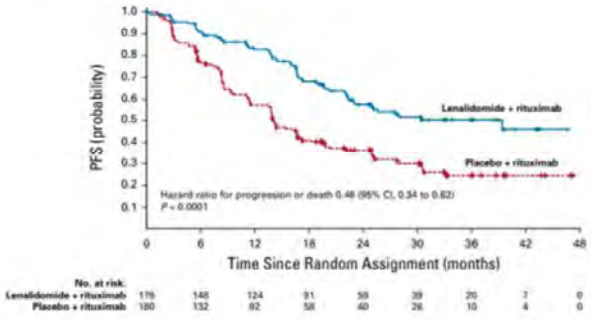
Primary Endpoint: PFS

Dosing:
- Lenalidomide 20 mg/d orally on days 1 to 21 of each 28-day cycle × 12 cycles
- Rituximab 375 mg/m² IV on days 1, 8, 15, 22 (cycle 1) and day 1 (cycles 2-5)

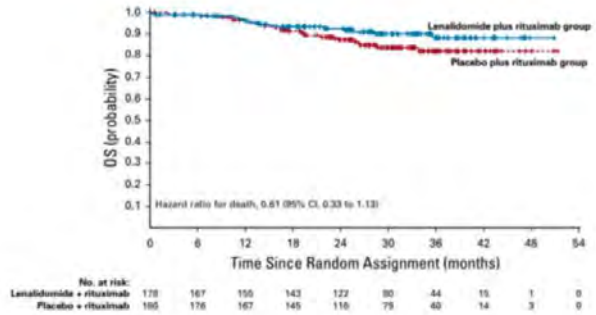
Leonard JP, et al. *J Clin Oncol.* 2019;37:1188-1199.

AUGMENT PFS and OS by IRC in ITT Population

PFS



OS



Conclusions:

- improved PFS with R^2 vs R alone (39 mo vs 14 mo)
- 2-year OS was 95% for R^2 and 86% for R/placebo
- similar efficacy to chemoimmunotherapy

Leonard JP, et al. *J Clin Oncol.* 2019;37:1188-1199.

Idelalisib

- oral PI3K inhibitor that has shown therapeutic activity in initial studies of patients with multiple relapsed FL
- approved by EMA and FDA as a single agent for the treatment of patients with relapsed FL who have received at least two prior systemic therapies
- approval based on a phase 2 study of idelalisib (n=72) in patients with FL who have received at least 2 prior lines of therapy[1]
  - ORR was 57 % with a median duration of response of 12.5 months
  - The starting dose is 150 mg twice daily
- toxicity:
  - diarrhea – 14%
  - cytopenias – 28%
  - infections – 21%
  - pneumonitis - 4%
  - hepatotoxicity – 18%
  - hypertriglyceridemia, hyperglycemia
- anti-infectious prophylaxis

1.Gopal AK, et al. N Engl J Med. 2014

Avtologous, allogeneic transplantation

- an appropriate consolidative therapy for patients in second or third remission
- may have the greatest benefit in patients with early treatment failure, refractory FL and those with histologic transformation to a more aggressive histology
- there is a plateau in the survival curves between 10 and 15 years after autologous HCT, suggesting that this procedure may be curative for one-quarter to one-third of transplanted patients[1,2]
- allogeneic transplantation can be considered in highly selected patients (lower rates of relapse vs autoHCT, high TRM up to 20%)

1. Metzner B, et al. Ann Oncol. 2013
2. Casulo C, et al. Biol Blood Marrow Transplant. 2018

Conclusions

- FL is a chronic, incurable disease with a long natural history
- a small subgroup of patients presenting with limited stage disease may be cured with radiation
- observation is the first approach in asymptomatic patients
- for those who require therapy : multiple treatment regimens, anti-CD20 +/- chemotherapy and chemotherapy-free alternatives, novel agents,…
  - antiCD20 +/- chemotherapy
  - lenalidomide +/- rituximab
  - PI3K inhibitors
  - autologous and allogeneic stem cell transplantation
  - novel agents (tazemetostat - EZH2 inhibitor, mosunetuzumab - bispecific antibody ,…)
  - CAR-T cell therapy - may dramatically alter the prognosis for heavily pretreated patients (ZUMA-5 study with high ORR more than 90%, median PFS at 2 years 78%, CR rate 80 %,..)
- disease can still be fatal in patients with histologic transformation

MANTLE CELL LYMPHOMA

Monika Jagodic, MD, PhD

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

SUMMARY: Mantle cell lymphoma (MCL)

Histology: the image is of mantle zone cells surrounding normal germinal centre follicles

Biology: the translocation **t (11;14) (q13; q32)** leading to cyclin-D1 overexpression is **typical**

Prognosis: Clinical and biological prognosticators (**combined mantle cell lymphoma International Prognostic Index, MIPI-c**) should be used routinely to estimate clinical behaviour) including **age, ECOG, LDH, WBC count, Ki-67 index.** Other prognosticators: **SOX-11 expression**, **TP 53 mutations**

Initial treatment approach: a short course of **watch-wait** under close observation is recommended for suspected **indolent cases** with **low tumour burden** and **asymptomatic disease** at diagnosis.

When **starting of treatment** is required (symptoms, high tumour burden) **initial treatment** is conventional **chemoterapy** (ChT) with **rituximab** (Rx) +/-consolidation RT. In **younger patients** are used **aggresive regimens** by **autologous stem-cell transplantation (SCT)** as **1st line.**

In **older patients** are used **conventional ChT** combinations **and less intense immunoChT** or **low- toxicity single agent targeted therapy** in **frail patients.**

Maintenance with **rituximab significantly improves progression-free survival** and **overall survival.**

Relapse disease treatment: salvage therapy: in early relapses (<12-24 months) a **non-cross resistant scheme** after R-CHOP or vice versa is **recommended**, with Rx maintenance.

Molecular targeted substances (ibrutinib, lenalidomide) should be considered in **refractory disease.** Additional options: temsirolimus, bortezomid.

AlloSCT transplantation should be considered in **younger patients** as potentially curative treatment in **early relapse and refractory disease.**

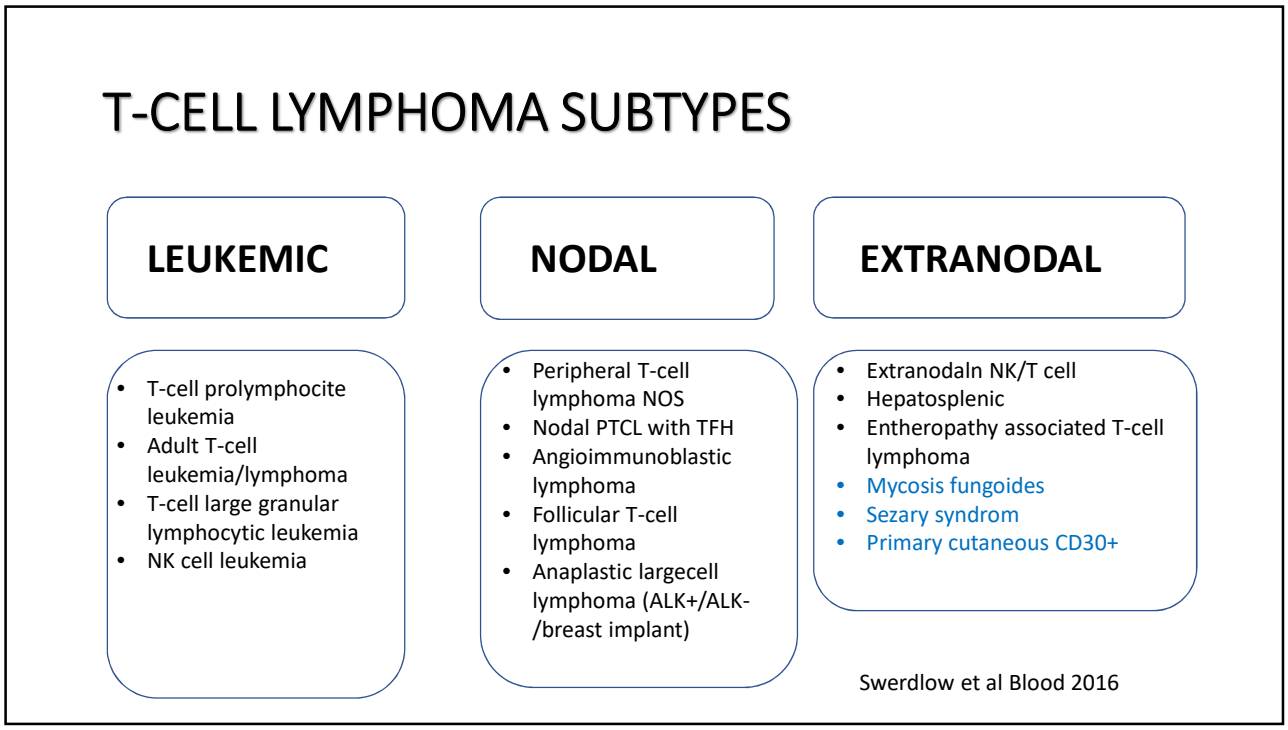
T-CELL LYMPHOMA

Jana Pahole MD
Institute of Oncology Ljubljana
10/09/2021

T-CELL LYMPHOMA – short facts

- 7-10% of all NHL
- Most are clinically aggressive
- Heterogenous in their presentation, features and prognosis
- Lack of efficient treatment
- Most can be healed not cured
- Outcomes are poor
  - Low response rates
  - 5-year OS ~32%
  - 5-year failure-free survival ~20%
  - Most patients relapse within 2-3 years

T-CELL LYMPHOMA SUBTYPES



Swerdlow et al Blood 2016

2nd Summer School in medical oncology

Standards and perspectives in the systemic treatment of Hodgkin lymphoma

Urska Rugelj, MD

Ljubljana, 10.9.2021

Conclusions

- Incidence in EU 2.3/100.000, most often affects young adults
- Multiple signaling pathways/transcription factors deregulated activities in RS cells involved in pathogenesis
- 5-FDG PET-CT scan an important part of diagnostic and treatment modifying decisions
- Type of treatment depends on clinical stage and risk factors
- Combined approach of treatment in early stages, chemotherapy-based treatment for advance disease
- Overall >80% achieve long remission – are cured
- Standard care of relapse in young fit patient is high-dose ChT + AutoSCT
- In relapse settings already approved use of some novel drugs as antibody-drug conjugates, anti PD-1 antibodies, others as small molecule inhibitors, cellular therapies in study settings

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PRINCIPLES OF RADIOTHERAPY IN LYMPHOMAS

Assist. Prof. PhD Lorna Zadravec Zaletel, MD

2nd Summer School in medical oncology, 2021

Conclusions

- malignant lymphomas are radiosensitive.
- RT may be a stand-alone treatment for some indolent NHL and for low stage HL- type lymphocyte predominance .
- in indolent NHL of higher stages, RT is reserved for treating the rest of the disease after CT or low-dose RT of larger infiltrates in order to delay CT.
- in aggressive lymphomas, radiation is always associated with systemic treatment.
- life-long follow-up of late sequelae of treatment is of vital importance.

ZAUSTAVITE NAPREDOVANJE BOLEZNI IN PODALJŠAJTE PREŽIVETJE

Pri bolnikih z mHSPC, zdravljenje samo z ADT ni dovolj.

ZDRAVILO ERLEADA® JE SEDAJ ODOBRENO TUDI ZA ZDRAVLJENJE BOLNIKOV S HORMONSKO OBČUTLJIVIM, METASTATSKIM RAKOM PROSTATE (mHSPC).[1]

Zgodnja uporaba zdravila ERLEADA+ADT v primerjavi z ADT pomembno podaljša preživetje bolnikov in zmanjša tveganje za napredovanje bolezni, hkrati pa prihrani druge oblike zdravljenja za kasnejše stadije bolezni.[1-3]

Skrajšan povzetek glavnih značilnosti zdravila ERLEADA®

▽ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih. **Ime zdravila:** Erleada 60 mg filmsko obložene tablete. **Kakovostna in količinska sestava:** 60 mg apalutamida; pomožne snovi: brezvodni koloidni silicijev dioksid, premreženi natrijev karmelozat, hipromeloza acetat sukcinat, magnezijev stearat, mikrokristalna celuloza, mikrokristalna celuloza (silicifirana), črni in rumeni železov dioksid, makrogol, polivinilalkohol (delno hidroliziran), smukec, titanov dioksid. **Indikacije:** Zdravljenje odraslih moških z nemetastatskim, na kastracijo odpornim rakom prostate (nmCRPC), pri katerih obstaja veliko tveganje za razvoj metastatske bolezni. Za zdravljenje odraslih moških s hormonsko občutljivim metastatskim rakom prostate (mHSCP) v kombinaciji z zdravljenjem z odtegnitvijo androgenov. **Odmerjanje in način uporabe:** Priporočeni odmerek je 240 mg (štiri 60-miligramske tablete) v enkratnem peroralnem odmerku na dan. Med zdravljenjem je treba pri bolnikih, ki niso bili kirurško kastrirani, nadaljevati medicinsko kastracijo z analogom gonadoliberina. V primeru izpuščenega odmerka je treba zdravilo vzeti čimprej še isti dan, naslednji dan pa naj odmerjanje nadaljuje po običajnem razporedu. Dodatnih tablet za nadomestitev pozabljenega odmerka se ne sme vzeti. Če se pri bolniku pojavijo toksični učinki ≥ 3. stopnje ali nesprejemljivi neželeni učinki, je treba uporabo zdravila prekiniti začasno in ne dokončno, dokler se simptomi ne izboljšajo na ≤ 1. stopnjo oziroma na začetno stopnjo, nato pa z zdravljenjem nadaljevati z enakim ali manjšim odmerkom (180 mg ali 120 mg), če je potrebno. Starejšim bolnikom, bolnikom z blago do zmerno okvaro ledvic ali jeter odmerka ni treba prilagajati. Pri bolnikih s hudo okvaro ledvic je potrebna previdnost, pri bolnikih s hudo okvaro jeter pa uporaba ni priporočljiva. Tablete je treba pogoltniti cele in se jih lahko jemlje s hrano ali brez nje. Apalutamid ni namenjen za uporabo pri pediatrični populaciji. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov, nosečnice in ženske, ki bi lahko zanosile. **Posebna opozorila in previdnostni ukrepi:** Uporaba zdravila ni priporočljiva pri bolnikih z anamnezo konvulzij ali drugimi predispozicijskimi dejavniki, med drugim tudi pri bolnikih s poškodbo možganov, nedavno kapjo (v zadnjem letu), pri bolnikih s primarnimi možganskimi tumorji ali metastazami v možganih. Pri bolnikih, ki so prejemali apalutamid je prišlo do padcev in zlomov, zato je treba pred uvedbo zdravljenja pri bolnikih oceniti tveganje za zlome in padce, bolnike pa spremljati po ustaljenih smernicah in premisliti o uporabi učinkovin, ki delujejo na kosti. Bolnike je treba spremljati tudi glede znakov in simptomov ishemične bolezni srca in ishemičnih možganskožilnih bolezni ter optimatizirati obvladovanje dejavnikov tveganja, kot so hipertenzija, diabetes ali dislipidemija, skladno s standardno oskrbo. Sočasni uporabi apalutamida z zdravili, ki so občutljivi substrati več presnovnih encimov ali prenašalcev, se je načeloma treba izogibati, če je terapevtski učinek teh zdravil za bolnika zelo pomemben in njihovega odmerjanja ni mogoče enostavno prilagajati na osnovi spremljanja učinkovitosti ali koncentracij v plazmi. Sočasni uporabi z varfarinom ali kumarinskimi antikoagulansi se je treba izogibati. Če se predpiše apalutamid, je treba pri bolnikih s klinično pomembnimi boleznimi srca in ožilja spremljati dejavnike tveganja kot so hiperholesterolemija, hipertrigliceridemija ali druge srčno presnovne bolezni. Zdravljenje z odtegnitvijo androgenov lahko podaljša interval QT. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Apalutamid je induktor encimov in prenašalcev in lahko povzroči povečan obseg odstranjevanja številnih pogosto uporabljanih zdravil. Pri sočasnem odmerjanju tega zdravila s katerim od močnih zaviralcev CYP2C8 ali močnih zaviralcev CYP3A4 začetnega odmerka ni treba prilagajati, premisliti pa velja o zmanjšanju odmerka zdravila Erleada na osnovi prenašanja zdravila. Ni pričakovati, da bi induktorji CYP3A4 ali CYP2C8 klinično pomembno vplivali na farmakokinetiko apalutamida in aktivnih frakcij. . Pri sočasni uporabi s substrati CYP2B6 je treba spremljati neželene učinke in oceniti izgubo učinka substrata ter za zagotovitev optimalnih plazemskih koncentracij morda prilagoditi odmerek substrata. Sočasna uporaba z zdravili, ki se primarno presnavljajo s CYP3A4 (kot so darunavir, felodipin, midazolam in simvastatin), s CYP2C19 (kot sta diazepam in omeprazol) ali s CYP2C9 (kot sta varfarin in fenitoin), lahko povzroči zmanjšanje izpostavljenosti tem zdravilom. Pri sočasni uporabi s substrati UDP-glukuronil transferaze je potrebna previdnost. Pri sočasni uporabi s substrati P-gp, BCRP ali OATP1B1 je potrebna ocena obsega zmanjšanja učinka ter za zagotovitev optimalnih plazemskih koncentracij morda prilagoditi odmerek substrata. Ni mogoče izključiti možnosti, da apalutamid in njegov N-desmetil presnovek zavirata prenašalce OCT2,OAT3 in MATE. Pri preiskovancih z mHSPC, ki so prejemali levprorelinijev acetat (analog GnRH), sočasna uporaba apalutamida ni bistveno vplivala na izpostavljenost leuprolidu v stanju dinamičnega ravnovesja. Skrbna presoja je potrebna tudi pri sočasni uporabi z zdravili, za katera je ugotovljeno, da podaljšujejo interval QT, oziroma z zdravili, ki lahko izzovejo Torsades de pointes. Plodnost, n**osečnost in dojenje:** Ni znano, ali so apalutamid ali njegovi presnovki prisotni v spermi, zato lahko to zdravilo škoduje plodu v razvoju. Bolniki, ki imajo spolne odnose z žensko v rodni dobi, morajo med zdravljenjem in še 3 mesece po zadnjem odmerku zdravila Erleada uporabljati kondome skupaj s še katero od drugih visoko učinkovitih metod kontracepcije. Zdravilo je kontraindicirano pri nosečnicah in ženskah , ki bi lahko zanosile in se ne sme uporabljati med dojenjem. **Neželeni učinki:** Hipotiroidizem, zmanjšan apetit, hiperholesterolemija, hipertrigliceridemija, disgevzija, ishemične možganskožilne bolezni, konvulzije, ishemična bolezen srca, podaljšanje intervala QT, vročinski oblivi, hipertenzija, driska, kožni izpuščaj, srbenje, alopecija, TEN, zlomi, artralgija, mišični krči, utrujenost, zmanjšanje telesne mase, padci. Za popoln seznam neželenih učinkov glejte Povzetek glavnih značilnosti zdravila. **Imetnik DzP:** Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgija **Predstavnik imetnika DzP v Sloveniji**: Johnson & Johnson d.o.o., Šmartinska cesta 53, Ljubljana.
Režim izdajanja zdravila: Rp/Spec. **Datum zadnje revizije besedila:** 10. junij 2021
Povzetek glavnih značilnosti zdravila s podrobnejšimi informacijami o zdravilu je dostopen pri predstavniku imetnika dovoljenja za promet.

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CP-198062/020921

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Erleada® ▼
(apalutamid) tablete

Prevzemite nadzor nad KLL, MCL in WM z zdravilom IMBRUVICA®[1-6]

ENA **TABLETA** ENKRAT NA **DAN DOMA**

Dolgotrajno izboljšanje preživetja po 8 letih spremljanja.[2-3]
Poznan in obvladljiv varnostni profil.[2-6]
Enostavno, enkrat dnevno jemanje zdravila na domu.[1]

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pharmacyclics®
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imbruvica®
(ibrutinib) tablete
Izkušnje, na katere se lahko zanesete

KLL=kronična limfocitna levkemija; MCL=limfom plaščnih celic; WM=Waldenströmova makroglobulinemija.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Ime zdravila: IMBRUVICA 140 mg/280 mg/420 mg/560 mg filmsko obložene tablete
Kakovostna in količinska sestava: 140/280/420 ali 560 mg ibrutiniba, brezvodni koloidni silicijev dioksid, premrežen natrijev karmelozat, laktoza monohidrat, magnezijev stearat, mikrokristalna celuloza, natrijev lavrilsulfat (E487), povidon; filmska obloga: makrogol, polivinilalkohol, smukec, titanov dioksid (E171), črni železov oksid (E172), rumeni železov oksid (E172 - 140, 420 in 560 mg), rdeči železov oksid (E172 - 280 in 560 mg) **Indikacije:** *Kot samostojno zdravilo*: zdravljenje odraslih bolnikov s ponovitvijo limfoma plaščnih celic (MCL) ali z na zdravljenje neodzivno obliko te bolezni, zdravljenje odraslih bolnikov z Waldenstromovo makroglobulinemijo (WM - Waldenström's macroglobulinaemia), ki so predhodno prejeli vsaj eno vrsto zdravljenja oziroma v prvi liniji pri bolnikih, ki niso primerni za kemoimunoterapijo. *Kot samostojno zdravilo ali v kombinaciji* z obinutuzumabom za zdravljenje odraslih bolnikov s predhodno neozdravljivo kronično limfocitno levkemijo (KLL)/z bendamustinom in rituksimabom za zdravljenje odraslih bolnikov s KLL, ki so predhodno prejeli vsaj eno vrsto zdravljenja; samostojno zdravilo indicirano. *V kombinaciji* z rituksimabom za zdravljenje odraslih bolnikov z WM. **Odmerjanje:** Zdravilo je treba jemati peroralno enkrat na dan s kozarcem vode, in sicer vsak dan ob približno istem času. Tablete je treba pogoltniti cele z vodo. Tablet se ne sme drobiti ali žvečiti. Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo onkoloških zdravil. MCL: priporočeni odmerek je 560 mg enkrat na dan. KLL (samostojno ali v kombinaciji) in WM: priporočeni odmerek je 420 mg enkrat na dan. Z zdravljenjem je treba nadaljevati do napredovanja bolezni oz. dokler bolnik zdravilo prenaša. Pri odmerjanju tega zdravila v kombinaciji z zdravilom, ki je usmerjeno proti CD20, je priporočljivo vzeti ibrutinib pred zdravilom, ki je usmerjeno proti CD20, kadar ju je treba vzeti na isti dan. Podrobna navodila za odmerjanje pri posebnih skupinah bolnikov in za prilagajanje odmerkov v primeru sočasne uporabe z zmernimi in močnimi zaviralci CYP3A4 in ob pojavu hematološke toksičnosti so navedena v Povzetku glavnih značilnosti zdravila. Če bolnik izpusti odmerek, ga lahko vzame čimprej istega dne, naslednjega dne pa spet začne z odmerjanjem po običajnem razporedu. Bolnik naj ne jemlje dodatnih tablet, da bi nadomestil pozabljeni odmerek. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov, sočasna uporaba pripravkov rastlinskega izvora s šentanževko (*Hypericum perforatum*). **Posebna opozorila in previdnostni ukrepi:** Poročali so o krvavitvah s trombocitopenijo ali brez nje (vključno z manjšimi hemoragičnimi dogodki (podplutbe, krvavitev iz nosu, petehije) ter večjimi krvavitvami (gastrointestinalna in intrakranialna krvavitev, hematurija)). Sočasno se ne sme jemati varfarina in drugih antagonistov vitamina K. Izogibati se je treba prehranskim dopolnilom (npr. pripravki ribjega olja ali vitamina E). Pri sočasnem zdravljenju z antikoagulanti je potrebna posebna previdnost. Zdravila se ne sme jemati najmanj 3 do 7 dni (odvisno od vrste kirurškega posega in tveganja za krvavitev) pred kirurškim posegom in po njem. Poročali so o primerih levkostaze. Po prekinitvi zdravljenja z ibrutinibom so poročali o primerih rupture vranice. Veliko število cirkulirajočih limfocitov (> 400.000/mikroliter) lahko pomeni povečano tveganje; treba je razmisliti o začasni prekinitvi jemanja zdravila, bolnika skrbno spremljati in po potrebi uvesti podporne ukrepe vključno s hidracijo in/ali citoredukcijo. Opažali so okužbe; bolnike je treba spremljati glede morebitnega pojava zvišane telesne temperature, nenormalnih izvidov preiskav delovanja jeter, nevtropenije in okužbe ter po potrebi uvesti ustrezno antimikrobno zdravljenje. Pri bolnikih s povečanim tveganjem za oportunistične okužbe razmislite o standardnih ukrepih za njihovo preprečevanje. Po uporabi ibrutiniba so poročali so o primerih invazivnih glivičnih okužb, vključno s primeri aspergiloze, kriptokokoze in okužbe s Pneumocystis jiroveci. Pri uporabi ibrutiniba ob predhodni ali sočasni uporabi imunosupresivnega zdravljenja so poročali o PML, vključno s smrtnimi primeri. PML je treba upoštevati v diferencialni diagnozi pri bolnikih z novimi ali s poslabšanjem obstoječih nevroloških, kognitivnih ali vedenjskih znakov ali simptomov. Če obstaja sum za PML, je treba opraviti diagnostične preiskave in zdravljenje prekiniti dokler ni izključena. Pri bolnikih, zdravljenih z ibrutinibom so se pojavili primeri hepatotoksičnosti, reaktivacije virusa hepatitisa B in primeri hepatitisa E, ki so lahko kronične narave, prišlo je tudi do odpovedi jeter, vključno s smrtnimi izidi. Pred uvedbo zdravila je treba preveriti delovanje jeter in prisotnost virusa hepatitisa. Poročali so tudi o citopenijah, zato je treba enkrat mesečno določati celotno krvno sliko. Pri bolnikih, ki so jemali ibrutinib so poročali tudi o primerih atrijske fibrilacije, atrijske undulacije, ventrikularne tahiaritmije in srčnega popuščanja. Zaradi možnosti pojava srčnih bolezni, vključno s srčnimi aritmijami in srčnim popuščanjem je treba vse bolnike občasno klinično pregledati. Pri bolnikih, pri katerih so se pojavili simptomi in/ali znaki ventrikularne tahiaritmije je treba zdravljenje s tem zdravilom začasno prekiniti, pred ponovno uvedbo je treba temeljito oceniti klinično razmerje med koristjo in tveganjem. Bolnike, pri katerih se pojavijo simptomi aritmije ali se na novo pojavi zadihanost, omotica ali omedlevica, je treba klinično pregledati in jim po potrebi posneti EKG. Pri bolnikih z obstoječo atrijsko fibrilacijo, ki potrebujejo zdravljenje z antikoagulanti, je treba razmisliti o drugih možnostih zdravljenja. Če se atrijska fibrilacija pojavi med zdravljenjem, je treba temeljito oceniti tveganje za trombembolične bolezni. Pri bolnikih z velikim tveganjem in kadar druge možnosti zdravljenja niso primerne, je treba razmisliti o skrbno nadzorovanem zdravljenju z antikoagulanti Bolnike je treba med zdravljenjem skrbno spremljati glede znakov in simptomov srčnega popuščanja. Pri bolnikih, ki so jemali to zdravilo so poročali o primerih ILD. Bolnike spremljajte glede pljučnih simptomov ILD. Če se simptomi pojavijo, je treba zdravljenje prekiniti in ILD ustrezno zdraviti. Če simptomi vztrajajo je treba oceniti tveganje in korist zdravljenja in upoštevati smernice za prilagoditev odmerjanja. Pri bolnikih, ki so prejemali ibrutinib so poročali o primerih cerebrovaskularnega insulta, prehodnega ishemičnega napada in ishemične možganske kapi s sočasno atrijsko fibrilacijo in/ali hipertenzijo ali brez njiju. Med primeri, ki so bili poročani z zakasnitvijo, je od začetka zdravljenja do pojava ishemičnih žilnih bolezni osrednjega živčevja večinoma minilo nekaj mesecev. Bolnike z večjo maso tumorja pred začetkom zdravljenja je treba skrbno spremljati zaradi večjega tveganja za pojav sindroma razpada tumorja. Med zdravljenjem je treba bolnike spremljati glede morebitnega pojava nemelanomskega kožnega raka. Bolnikom, ki prejemajo ibrutinib, je treba med celotnim potekom zdravljenja redno meriti krvni tlak in jim po potrebi uvesti ali prilagoditi odmerjanje antihipertenzivnih zdravil. Poročali so tudi o primerih hemofagocitne limfohistiocitoze, vključno s smrtnimi primeri. Pri sočasni uporabi z zmernimi/močnimi zaviralci CYP3A4 lahko pride do povečane izpostavljenosti ibrutinibu in večjega tveganja za pojav toksičnosti, pri sočasni uporabi z indukdorji CYP3A4 pa do zmanjšane izpostavljenosti in tveganja za pomanjkanje učinkovitosti. Zato se je treba sočasni uporabi z močnimi zaviralci CYP3A4 in močnimi ali zmernimi induktorji CYP3A4 izogibati. O sočasni uporabi lahko razmislite samo, kadar pričakovane koristi nedvoumno presegajo morebitno tveganje. Pri bolnikih, ki morajo jemati zaviralce CYP3A4, je treba skrbno spremljati morebitne znake toksičnega delovanja zdravila; pri tistih, ki jemljejo induktorje CYP3A4 pa znake pomanjkanja učinkovitosti. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. Ena filmsko obložena tableta vsebuje manj kot 1 mmol natrija (23 mg) kar v bistvu pomeni 'brez natrija'. **Interakcije**: Sočasna uporaba z zdravili, ki močno/zmerno zavirajo CYP3A4, lahko poveča izpostavljenost ibrutinibu, zato se je treba uporabi močnih zaviralcev CYP3A4 izogibati. Če mora bolnik jemati katerega od močnih/zmernih zaviralcev CYP3A4, je treba odmerek zdravila Imbruvica prilagoditi (glejte Povzetek glavnih značilnosti zdravila), bolnike pa skrbno spremljati. V kombinaciji s šibkimi zaviralci prilagajanje odmerjanja ni potrebno. Bolnike je treba skrbno spremljati in po potrebi upoštevati smernice za prilagajanje odmerka. Med zdravljenjem se je treba izogibati uživanju grenivk in seviljskih pomaranč, ker vsebujejo zmerne zaviralce CYP3A4. Sočasna uporaba zdravila Imbruvica z induktorji CYP3A4 lahko zmanjša koncentracijo ibrutiniba v plazmi. Razmisliti velja o uporabi drugih učinkovin, ki v manjši meri inducirajo CYP3A4. Če je potrebna uporaba močnega ali zmernega induktorja CYP3A4 in pričakovana korist presega morebitno tveganje, je treba bolnika skrbno spremljati glede znakov pomanjkanja učinkovitosti. Zdravilo se lahko sočasno uporablja z blagimi induktorji, vendar je treba bolnike skrbno spremljati glede znakov pomanjkanja učinkovitosti. Topnost ibrutiniba je odvisna od pH, zato lahko zdravila, ki zvečajo pH v želodcu (npr. zaviralci protonske črpalke), zmanjšajo izpostavljenost ibrutinibu. *In vitro* ibrutinib zavira P-glikoprotein in BCRP, zato je treba substrate P-glikoproteina in BCRP, ki imajo ozko peroralno terapevtsko okno (npr. digoksin, metotreksat) jemati najmanj 6 ur pred oz. najmanj 6 ur po odmerjanju zdravila Imbruvica. Ibrutinib lahko zavira tudi BCRP v jetrih in zveča izpostavljenost zdravilom, katerih izločanje skozi jetra je povezano z BCRP (rosuvastatin). V študiji medsebojnega delovanja z drugimi zdravili pri bolnikih z malignomi celic B, ibrutinib v enkratnem, 560 mg odmerku ni klinično pomembno vplival na izpostavljenost substratu CYP3A4 midazolamu. V isti študiji, 2 tedensko zdravljenje z ibrutinibom v odmerku 560 mg na dan, ni klinično pomembno vplivalo na farmakokinetiko oralnih kontraceptivov (etiniletradiol in levonorgestrel), substrata CYP3A4 midazolama ali substrata CYP2B6 bupropiona. **Nosečnost, dojenje in plodnost:** Ženske v rodni dobi morajo med zdravljenjem in še tri mesece po zaključku zdravljenja uporabljati zelo učinkovito metodo kontracepcije. Zdravila ne smete uporabljati pri nosečnicah. Med zdravljenjem je treba prenehati z dojenjem. Podatkov o vplivu ibrutiniba na plodnost pri ljudeh ni na voljo. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo ima blag vpliv na sposobnost vožnje in upravljanja strojev. Pri nekaterih bolnikih so poročali o utrujenosti, omotičnosti in asteniji, kar je treba upoštevati pri presoji bolnikove sposobnosti za vožnjo in upravljanje strojev. **Neželeni učinki**: pljučnica, okužba zgornjih dihal, sinusitis, sepsa, kriptokokna/pnevmocistična okužba, okužba z aspergilusom, reaktivacija hepatitisa B, nemelanomski kožni raki, okužba sečil, okužba kože, nevtropenija, trombocitopenija, limfocitoza, anemija, febrilna nevtropenija, levkocitoza, sindrom levkostaze, ILD, dehidracija, hiperurikemija, sindrom razpada tumorja, omotičnost, glavobol, periferna nevropatija, cerebrovaskularni insult, prehodni ishemični napad, ishemična možganska kap, zamegljen vid, očesna krvavitev, srčno popuščanje, atrijska fibrilacija, ventrikularna tahiaritmija, krvavitev, podplutba,petehije, subduralni hematom, krvavitev iz nosu, diareja, bruhanje, stomatitis, navzea, obstipacija, suha usta, odpoved jeter, izpuščaj, angioedem, panikulitis, nevtrofilne dermatoze, urtikarija, eritem, lomljenje nohtov, Stevens-Johnsonov sindrom, artralgija, mišičnoskeletne bolečine, zvišana telesna temperatura, periferni edem, zvišanje kreatinina v krvi (vsi NU so opisani v povzetku glavnih značilnosti zdravila) **Način in režim izdajanja zdravila:** Rp/Spec. **Imetnik DzP**: Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgija **Predstavnik imetnika DzP v Sloveniji**: Johnson & Johnson d.o.o., Šmartinska cesta 53, 1000 Ljubljana
Datum zadnje revizije besedila: 20. 08. 2021

Povzetek glavnih značilnosti zdravila s podrobnejšimi informacijami o zdravilu je dostopen pri predstavniku imetnika dovoljenja za promet.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!

Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab. **Terapevtske indikacije:** Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih in pediatričnih bolnikov, starih 3 leta ali več, s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) ni bila uspešna, ali po najmanj dveh predhodnih zdravljenjih kadar ASCT ne pride v poštev kot možnost zdravljenja; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino in za prvo linijo zdravljenja metastatskega kolorektalnega raka z visoko mikrosatelitsko nestabilnostjo (MSI-H – microsatellite instability-high) ali s pomanjkljivim popravljanjem neujemanja pri podvojevanju DNA (dMMR - mismatch repair deficient) pri odraslih. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih; v kombinaciji s kemoterapijo s platino in fluoropirimidinom indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10. **Odmerjanje in način uporabe:** Testiranje PD-L1: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi izraženosti PD-L1 tumorja potrditi z validirano preiskavo. Testiranje MSI-H/dMMR pri bolnikih s CRC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje MSI-H/dMMR statusa tumorja z validirano preiskavo, da se izbere bolnike s CRC. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje pri pediatričnih bolnikih s cHL, starih 3 leta ali več, je 2 mg/kg telesne mase (do največ 200 mg) na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. Odložitev odmerka ali ukinitev zdravljenja: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov:** Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati. Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 6.185 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom, HNSCC ali CRC s štirimi odmerki (2 mg/kg telesne mase na 3 tedne, 200 mg na 3 tedne in 10 mg/kg telesne mase na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,6 mesece (v razponu od 1 dneva do 47 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (21 %) in diareja (21 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.437 bolnikih NSCLC, HNSCC ali rakom požiralnika, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg telesne mase ali 10 mg/kg telesne mase na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: navzea (55 %), anemija (51 %), utrujenost (39 %), zaprtost (37 %), zmanjšanje apetita (34 %), diareja (33 %), nevtropenija (29 %) in bruhanje (28 %). Pojavnost neželenih učinkov 3. do 5. stopnje je pri bolnikih z NSCLC pri kombiniranem zdravljenju s pembrolizumabom znašala 67 % in pri zdravljenju samo s kemoterapijo 66 %, pri bolnikih s HNSCC pri kombiniranem zdravljenju s pembrolizumabom 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %, ter pri bolnikih z rakom požiralnika pri kombiniranem zdravljenju s pembrolizumabom 86 % in pri zdravljenju samo s kemoterapijo 83 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Način in režim izdaje zdravila:** H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD **Merck Sharp & Dohme inovativna zdravila d.o.o.,**
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tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50;
Pripravljeno v Sloveniji, julij 2021; SI-KEY-00304 EXP: 07/2023

Samo za strokovno javnost.

H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

KEYTRUDA®
(pembrolizumab, MSD)

Zdravilo KEYTRUDA®

OMOGOČA VEČ ČASA

Q6W - samo 9 infuzij letno*

ODMERJANJE NA 6 TEDNOV: MANJ INFUZIJ ZA VAŠE BOLNIKE, VEČ ČASA ZA VAS!

* Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah.

Q3W = vsake 3 tedne; Q6W = vsakih 6 tednov. Referenca: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!
Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab. **Terapevtske indikacije:** Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih in pediatričnih bolnikov, starih 3 leta ali več, s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) ni bila uspešna, ali po najmanj dveh predhodnih zdravljenjih kadar ASCT ne pride v poštev kot možnost zdravljenja; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino in za prvo linijo zdravljenja metastatskega kolorektalnega raka z visoko mikrosatelitsko nestabilnostjo (MSI-H – microsatellite instability-high) ali s pomanjkljivim popravljanjem neujemanja pri podvojevanju DNA (dMMR - mismatch repair deficient) pri odraslih. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih; v kombinaciji s kemoterapijo s platino in fluoropirimidinom indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10. **Odmerjanje in način uporabe:** Testiranje PD-L1: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi izraženosti PD-L1 tumorja potrditi z validirano preiskavo. Testiranje MSI-H/dMMR pri bolnikih s CRC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje MSI-H/dMMR statusa tumorja z validirano preiskavo, da se izbere bolnike s CRC. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje pri pediatričnih bolnikih s cHL, starih 3 leta ali več, je 2 mg/kg telesne mase (do največ 200 mg) na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. Odložitev odmerka ali ukinitev zdravljenja: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov:** Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati. Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 6.185 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom, HNSCC ali CRC s štirimi odmerki (2 mg/kg telesne mase na 3 tedne, 200 mg na 3 tedne in 10 mg/kg telesne mase na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,6 mesece (v razponu od 1 dneva do 47 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (21 %) in diareja (21 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.437 bolnikih NSCLC, HNSCC ali rakom požiralnika, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg telesne mase ali 10 mg/kg telesne mase na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: navzea (55 %), anemija (51 %), utrujenost (39 %), zaprtost (37 %), zmanjšanje apetita (34 %), diareja (33 %), nevtropenija (29 %) in bruhanje (28 %). Pojavnost neželenih učinkov 3. do 5. stopnje je pri bolnikih z NSCLC pri kombiniranem zdravljenju s pembrolizumabom znašala 67 % in pri zdravljenju samo s kemoterapijo 66 %, pri bolnikih s HNSCC pri kombiniranem zdravljenju s pembrolizumabom 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %, ter pri bolnikih z rakom požiralnika pri kombiniranem zdravljenju s pembrolizumabom 86 % in pri zdravljenju samo s kemoterapijo 83 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Način in režim izdaje zdravila:** H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD
Merck Sharp & Dohme inovativna zdravila d.o.o.,
Ameriška ulica 2, 1000 Ljubljana,
tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50;
Pripravljeno v Sloveniji, julij 2021; SI-KEY-00305 EXP: 07/2023

Samo za strokovno javnost.
H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

CILJI ZDRAVLJENJA bolnic z napredovalim HR+/HER2- rakom dojk

ESMO-MCBS 5† TOČK[5]

RAZLIKA JE!

NAJDALJŠE CELOKUPNO PREŽIVETJE[1,2*] in IZBOLJŠANA ALI OHRANJENA KVALITETA ŽIVLJENJA[3,4]

ASCO 2021

KISQALI + zaviralec aromataze + goserelin, 1. red zdravljenja: mOS = **58,7** meseca*

KISQALI + fulvestrant, 1. in 2. red zdravljenja: mOS = **53,7** meseca#

KISQALI je edini zaviralec CDK4/6, ki dokazano podaljša življenje v različnih kombinacijah (zaviralec aromataze ali fulvestrant) in redih zdravljenja ter hkrati izboljša ali ohranja kvaliteto življenja[1-6]

HR+ hormonsko odvisen rak dojk, **HER2-** rak dojk, negativen na receptorje humanega epidermalnega rastnega faktorja 2, **Overall Survival, OS** Celokupno preživetje, **mediani OS, mOS** mediana celokupnega preživetja. **ESMO-MCBS**, European Society for Medical Oncology Magnitude of Clinical Benefit Scale: ESMO lestvica obsega klinične koristi.† Zdravilo KISQALI je po ESMO-MCBS lestvici za študijo MONALEESA-7 prejelo največje možno število točk (5 točk)[5].

* MONALEESA-7 je bila randomizirana, dvojno slepa, s placebom nadzorovana multicentrična klinična študija faze III zdravljenja premenopavznih in perimenopavznih žensk z napredovalim HR+ HER2- rakom dojk, ki so poleg endokrinega zdravljenja prejemale še zdravilo Kisqali ali placebo. V raziskavo je bilo vključenih 672 bolnic, zdravilo Kisqali. je prejemalo 335 bolnic. V študiji je bil dosežen sekundarni cilj, dokazana je bila statistično značilna razlika med obema skupinama v dolžini preživetja bolnic[1,6,7] Relativno znižanje tveganja za smrt je bilo 24% (razmerje ogroženosti = 0,76: 95% IZ [0,608; 0,956])[1]. V skupini bolnic, ki so prejemale kombinacijo zdravila KISQALI + zaviralec aromataze je bilo doseženo najdaljše mediano celokupno preživetje med vsemi raziskavami faze III v katere so bile vključene bolnice s HR+ HER2- napredovalim rakom dojk: 58,7 meseca[1].

MONALEESA- 3 je bila randomizirana, dvojno slepa, s placebom nadzorovana multicentrična klinična študija faze III zdravljenja pomenopavznih žensk z napredovalim HR+ HER2- rakom dojk, ki so poleg fulvestranta prejemale še zdravilo Kisqali ali placebo v prvi ali drugi liniji zdravljenja. V študijo je bilo vključenih 726 bolnic, zdravilo Kisqali je prejemalo 484 bolnic. V študiji je bil dosežen sekundarni cilj, dokazana je bila statistično značilna razlika med obema skupinama v dolžini preživetja bolnic[2,6,8]. Relativno znižanje tveganja za smrt je bilo 28% (razmerje ogroženosti = 0,72: 95% IZ [0,568; 0,924])[6] Podatki do presečnega datuma 30. oktober 2020 za skupino bolnic, ki so prejemale kombinacijo zdravila Kisqali in fulvestranta kažejo mediano celokupno preživetje, 53,7 meseca (razmerje ogroženosti 0,73: 95% IZ [0,59; 0,90]).[2]

Reference: 1. Tripathy D, Im S-A, Colleoni M, in sod. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2–) advanced breast cancer (ABC) treated with endocrine therapy (ET) +/- ribociclib. Predstavljeno na: San Antonio Breast Cancer Symposium; 8-12. december 2020, 2020; San Antonio, Texas. Poster PD2-04. **2.** Slamon D, Neven P, Chia S, in sod. Updated overall survival (OS) results from the phase III MONALEESA-3 trial of post-menopausal patients (pts) with HR+/HER2- advanced breast cancer (ABC) treated with fulvestrant ± placebo. Predstavljeno na kongresu American Society of Clinical Oncology (ASCO) 2021, 4-8. junij 2021, virtualni kongres. **3.** Harbeck N, Vazquez RV, Franke F, in sod. Ribociclib+ tamoxifen or a non-steroidal aromatase inhibitor in premenopausal patients with hormone receptor-positive, HER2-negative advanced breast cancer: MONALEESA-7 patient-reported outcomes. Predstavljeno na: European Society for Medical Oncology Congress; 19- 23 oktober 2018; Munchen, Nemčija. **4.** Fasching PA, Esteva FJ, Pivot X, in sod. Patient-reported outcomes in advanced breast cancer treated with ribociclib + fulvestrant: results from MONALEESA-3. Predstavljeno na: European Society for Medical Oncology Congress; 19-23. oktober, Munchen, Nemčija. **5.** Cardoso F, Paluch-Shimon S, Senkus E, in sod. 5th ESOESMO international consensus guidelines for advanced breast cancer (ABC5) 2020; 31 (12): 1623-1649. **6.** Povzetek glavnih značilnosti zdravila Kisqali. Oktober 2020. **7.** Im SA, Lu YS, Bardia A, in sod. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med 2019; 381:307-16. **8.** Slamon DJ, Neven P, Chia S, in sod. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med 2020; 382:514-524.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA KISQALI®

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih.

Ime zdravila: Kisqali 200 mg filmsko obložene tablete. **Sestava:** Ena tableta vsebuje ribociklibijev sukcinat v količini, ki ustreza 200 mg ribocikliba. **Indikacija:** Zdravilo Kisqali je v kombinaciji z zaviralcem aromataze ali fulvestrantom indicirano za zdravljenje žensk z lokalno napredovalim ali metastatskim rakom dojk, ki je hormonsko odvisen (HR pozitiven) in negativen na receptorje humanega epidermalnega rastnega faktorja 2 (HER2 negativen), in sicer kot začetno hormonsko zdravljenje ali pri ženskah, ki so predhodno že prejemale hormonsko zdravljenje. Pri ženskah pred menopavzo ali v perimenopavzi je treba hormonsko zdravljenje uporabljati skupaj z agonistom gonadoliberina (LHRH-luteinizing hormone releasing hormone). **Odmerjanje in način uporabe:** Zdravljenje mora uvesti zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Priporočeni odmerek je 600 mg (tri 200-miligramske tablete) ribocikliba 1x/dan 21 dni zaporedoma, čemur sledi 7 dni brez zdravljenja, tako da celotni ciklus traja 28 dni. Zdravljenje je treba nadaljevati, dokler ima bolnik od zdravljenja klinično korist oz. do pojava nesprejemljivih toksičnih učinkov. Kisqali je treba uporabljati skupaj z 2,5 mg letrozola ali drugim zaviralcem aromataze ali s 500 mg fulvestranta. Zaviralec aromataze je treba jemati peroralno 1x/dan neprekinjeno vseh 28 dni ciklusa. Fulvestrant je treba odmerjati intramuskularno 1., 15. in 29. dan ciklusa, nato pa 1x/mesec. Za več podatkov glejte povzetek glavnih značilnosti zdravila za zaviralec aromataze oz. fulvestrant. Ženske pred menopavzo ali v perimenopavzi morajo prejemati tudi katerega od agonistov gonadoliberina v skladu z lokalno klinično prakso. Kisqali je treba jemati peroralno 1x/dan skupaj s hrano ali brez nje. Bolniki naj vzamejo odmerek zdravila vsak dan ob približno istem času, najbolje zjutraj. Tablete je treba pogoltniti cele in se jih pred zaužitjem ne sme gristi, drobiti ali lomiti. Tablet, ki so razlomljene, zdrobljene ali kako drugače poškodovane, se ne sme zaužiti. Če bolnik po zaužitju odmerka bruha ali pozabi vzeti odmerek, na ta dan ne sme vzeti dodatnega odmerka. Naslednji predpisani odmerek mora vzeti ob običajnem času. *Prilagajanje odmerkov:* Obvladovanje hudih ali nesprejemljivih neželenih dogodkov zdravila lahko vključuje prekinitev jemanja zdravila, znižanje odmerka ali ukinitev zdravila Kisqali. Ob prvem zmanjšanju odmerek zmanjšamo na 400 mg/dan (dve 200-miligramski tableti), ob drugem zmanjšanju pa na 200 mg/dan (ena 200-miligramska tableta). Če bi bilo treba odmerek zmanjšati na manj kot 200 mg/dan, je treba zdravljenje ukiniti. Za priporočila glede prekinitve jemanja zdravila, zmanjšanje odmerka ali ukinitev zdravljenja v primerih, ko je to potrebno za obvladovanje določenih neželenih dogodkov zdravila, prosimo glejte povzetek glavnih značilnosti zdravila. Za prilagajanje odmerkov in druge pomembne podatke v primeru toksičnega delovanja glejte povzetek glavnih značilnosti zdravila za sočasno uporabljeni zaviralec aromataze, fulvestrant oz. agonist gonadoliberina. *Okvara ledvic:* Pri bolnikih z blago ali zmerno okvaro ledvic prilagajanje odmerka ni potrebno. Pri bolnikih s hudo okvaro ledvic (aGFR 15 do < 30 ml/min) je priporočen začetni odmerek 200 mg. *Okvara jeter:* Bolnikom z blago okvaro jeter (Child-Pugh razreda A) odmerka ni potrebno prilagajati. Pri bolnikih z zmerno (Child-Pugh razreda B) ali hudo okvaro jeter (Child-Pugh razreda C) je priporočeni začetni odmerek zdravila Kisqali 400 mg 1x/dan. *Pediatrična populacija:* Varnost in učinkovitost zdravila pri otrocih in mladostnikih, starih manj kot 18 let, nista bili dokazani. *Starostniki:* Pri bolnikih, ki so stari več kot 65 let, prilagajanje odmerka ni potrebno. **Kontraindikacije:** Preobčutljivost na učinkovino, arašide, sojo ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Kritična visceralna bolezen: Učinkovitosti in varnosti ribocikliba pri bolnikih s kritično visceralno boleznijo niso proučevali. Nevtropenija in hepatobiliarna toksičnost: Pregled celotne krvne slike in vrednosti jetrnih testov je treba opraviti pred začetkom zdravljenja, nato v prvih 2 ciklusih vsaka 2 tedna, v naslednjih 4 ciklusih na začetku vsakega ciklusa, nato pa kot je klinično indicirano. Če pride do nenormalnih vrednosti jetrnih testov stopnje ≥ 2, so priporočene pogostejše meritve jetrnih testov. Za bolnike z zvišanjem vrednosti AST/ALT stopnje ≥3 ob izhodišču priporočila za odmerjanje niso dognana. Glede na to, kako močno je izražena nevtropenija ali zvišane vrednosti aminotransferaz, je morda treba odmerjanje zdravila Kisqali prekiniti, zmanjšati odmerek ali zdravljenje ukiniti. Podaljšanje intervala QT: Pred začetkom zdravljenja je treba posneti EKG. Zdravljenje je mogoče začeti samo pri bolnikih s trajanjem intervala QTcF manj kot 450 ms. EKG je treba ponovno posneti približno 14. dan prvega ciklusa in na začetku drugega ciklusa, nato pa kot je klinično indicirano. V primeru, da v času zdravljenja pride do podaljšanja intervala QTcF, je priporočeno pogostejše snemanje EKG. Ustrezno spremljanje koncentracij elektrolitov v serumu (vključno s koncentracijami kalija, kalcija, fosforja in magnezija) je treba izvajati pred začetkom zdravljenja, nato na začetku prvih 6 ciklusov in kasneje kot je klinično indicirano. Kakršnekoli nepravilnosti je treba odpraviti pred začetkom oz. med potekom zdravljenja z zdravilom Kisqali. Uporabi zdravila Kisqali se je treba izogibati pri bolnikih s prisotnim podaljšanjem intervala QTc ali s povečanim tveganjem za podaljšanje intervala QTc. To vključuje bolnike s sindromom podaljšanega intervala QT, z neurejenim ali pomembnim srčnim obolenjem, kar vključuje nedaven miokardni infarkt, kongestivno popuščanje srca, nestabilno angino pektoris in bradiaritmije ter bolnike z elektrolitskimi nepravilnostmi. Izogibati se je treba sočasni uporabi zdravila Kisqali z zdravili, za katera je znano, da lahko podaljšajo interval QT, kot so antiaritmiki (med drugim amiodaron, dizopiramid, prokainamid, kinidin in sotalol) ter druga zdravila, za katera je znano, da podaljšujejo interval QT (med drugim klorokin, halofantrin, klaritromicin, ciprofloksacin, levofloksacin, azitromicin, haloperidol, metadon, moksifloksacin, bepridil, pimozid in intravenski ondansetron). Zdravila Kisqali prav tako ni priporočeno uporabljati v kombinaciji s tamoksifenom. Če se zdravljenju z močnim zaviralcem CYP3A4 ni mogoče izogniti, je treba odmerek zdravila Kisqali zmanjšati na 400 mg 1x/dan. Glede na izmerjeno podaljšanje intervala QT v času zdravljenja je morda treba odmerjanje zdravila Kisqali prekiniti, zmanjšati odmerek ali zdravljenje ukiniti. Hude kožne reakcije: Poročali so o pojavu toksične epidermalne nekrolize (TEN). Če se pojavijo znaki in simptomi, ki lahko pomenijo, da gre za hudo kožno reakcijo (na primer progresiven generaliziran kožni izpuščaj, pogosto z mehurji, ali lezijami sluznice), je treba zdravljenje takoj prekiniti. Intersticijska pljučna bolezen/pnevmonitis: Glede na izraženost intersticijske pljučne bolezni/pnevmonitisa, ki se lahko končata tudi s smrtjo bolnika, bo v skladu s priporočilom v povzetku glavnih značilnosti zdravila morda potrebno odmerjanje zdravila Kisqali prekiniti, zmanjšati odmerek ali zdravljenje ukiniti. Bolnike je treba spremljati glede pljučnih simptomov, ki bi lahko nakazovali na intersticijsko pljučno bolezen/pnevmonitis, in lahko vključujejo hipoksijo, kašelj in dispnejo. Zvišanje kreatinina: Če v času zdravljenja pride do zvišanja vrednosti kreatinina v krvi, je priporočeno izvesti dodatno oceno ledvične funkcije za izključitev okvare ledvic. Okvara ledvic: Pri začetnem odmerku 200 mg pri bolnikih s hudo okvaro ledvic so ocenili, da je izpostavljenost za približno 45 % nižja kot pri standardnem začetnem odmerku pri bolnikih z normalnim delovanjem ledvic. Učinkovitosti pri tem začetnem odmerku niso preučevali. Pri bolnikih s hudo okvaro ledvic je potrebna previdnost s skrbnim spremljanjem glede znakov toksičnega delovanja. Sojin lecitin: Zdravilo vsebuje sojin lecitin. Bolniki s preobčutljivostjo na arašide ali sojo ne smejo jemati zdravila Kisqali. **Plodnost, nosečnost in dojenje:** Pred začetkom zdravljenja je treba preveriti status nosečnosti. Ženskam v rodni dobi je treba svetovati, naj v času zdravljenja z zdravilom Kisqali in še najmanj 21 dni po prejemu zadnjega odmerka uporabljajo učinkovito kontracepcijsko metodo. Bolnice, ki jemljejo zdravilo Kisqali, ne smejo dojiti še najmanj 21 dni po prejemu zadnjega odmerka. Glede na ugotovitve študij pri živalih lahko zdravilo Kisqali zmanjša plodnost pri reproduktivno sposobnih moških. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo ima lahko blag vpliv na sposobnost vožnje in upravljanja strojev. Bolnike je treba opozoriti, naj bodo pri vožnji in upravljanju strojev previdni, če imajo v času zdravljenja težave z utrujenostjo, omotičnostjo ali vrtoglavico. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Snovi, ki lahko zvišajo koncentracijo ribocikliba v plazmi: Izogibati se je treba sočasni uporabi močnih zaviralcev CYP3A4, med drugim klaritromicinu, indinavirju, itrakonazolu, ketokonazolu, lopinavirju, ritonavirju, nefazodonu, nelfinavirju, posakonazolu, sakvinavirju, telaprevirju, telitromicinu, verapamilu in vorikonazolu. Za sočasno uporabo je treba razmisliti o izbiri drugih zdravil z manjšim potencialom za zaviranje CYP3A4, bolnike pa je treba spremljati glede neželenih dogodkov v povezavi z ribociklibom. Če mora bolnik sočasno z ribociklibom prejemati močan zaviralec CYP3A4, je treba odmerek zdravila Kisqali zmanjšati na 400 mg 1x/dan. Pri bolnikih, pri katerih je odmerek že zmanjšan na 400 mg/dan, je treba odmerek zmanjšati na 200 mg, pri bolnikih, pri katerih je odmerek ribocikliba že zmanjšan na 200 mg dnevno, pa je treba zdravljenje z zdravilom Kisqali prekiniti. Zaradi interindividualne variabilnosti priporočeno prilagajanje odmerjanja morda ni najboljše za vse bolnike, zato je priporočeno skrbno spremljanje bolnikov glede znakov toksičnega delovanja. Če bolnik preneha jemati zdravilo, ki je močan zaviralec, je treba odmerek zdravila Kisqali prilagoditi in po najmanj 5 razpolovnih dobah močnega zaviralca CYP3A4 spet začeti z odmerkom zdravila Kisqali, ki ga je bolnik prejemal pred začetkom uporabe močnega zaviralca CYP3A4. Po začetku sočasne uporabe šibkih ali zmernih zaviralcev CYP3A4 odmerka ribocikliba ni treba prilagajati, priporočeno pa je spremljanje bolnikov glede neželenih dogodkov v povezavi z ribociklibom. Bolnikom je treba naročiti, naj se izogibajo uživanju grenivk in njihovega soka, ker lahko povečajo izpostavljenost ribociklibu. Snovi, ki lahko znižajo koncentracijo ribocikliba v plazmi: Sočasna uporaba močnih induktorjev CYP3A4 lahko zmanjša izpostavljenost zdravilu, to pa lahko predstavlja tveganje za manjšo učinkovitost zdravila. Izogibati se je treba sočasni uporabi močnih induktorjev CYP3A4, med drugim fenitoina, rifampicina, karbamazepina in šentjanževke *(Hypericum perforatum).* Za sočasno uporabo je treba razmisliti o izbiri drugega zdravila, ki ne inducira oziroma ima manjši potencial za indukcijo CYP3A4. Učinka zmernega induktorja CYP3A4 na izpostavljenost ribociklibu niso proučevali. Sočasna uporaba zmernega induktorja CYP3A4 lahko privede do zmanjšane izpostavljenosti ribociklibu, to pa lahko predstavlja tveganje za manjšo učinkovitost, še posebej pri bolnikih, ki se zdravijo z ribociklibom v odmerku 400 mg ali 200 mg 1x/dan. Snovi, na katerih koncentracijo v plazmi lahko vpliva zdravilo Kisqali: Ribociklib je zmeren do močan zaviralec CYP3A4, zato lahko pride do interakcij z zdravili, ki so substrati oz. jih presnavlja CYP3A4, kar lahko povzroči zvišanje koncentracij sočasno uporabljenih zdravil v serumu. Pri sočasnem odmerjanju ribocikliba z drugimi zdravili je praviloma treba pregledati povzetek glavnih značilnosti drugega zdravila in poiskati priporočila za sočasno odmerjanje z zaviralci CYP3A4. Pri sočasni uporabi z občutljivimi substrati CYP3A4, ki imajo nizek terapevtski indeks, je priporočena previdnost. Pri teh substratih, med drugim pri alfentanilu, ciklosporinu, everolimusu, fentanilu, sirolimusu in takrolimusu, je v nekaterih primerih treba zmanjšati njihov odmerek, saj ribociklib lahko poveča izpostavljenost tem snovem. Izogibati se je treba sočasni uporabi ribocikliba v odmerku 600 mg skupaj z naslednjimi substrati CYP3A4: alfuzosin, amiodaron, cisaprid, pimozid, kinidin, ergotamin, dihidroergotamin, kvetiapin, lovastatin, simvastatin, sildenafil, midazolam in triazolam. Pri uporabi klinično ustreznega odmerka 600 mg je mogoče pričakovati le šibak zaviralni učinek ribociklibla na substrate CYP1A2 (< 2-kratno povečanje AUC). Snovi, ki so substrati prenašalcev: Vrednotenje podatkov *in vitro* raziskav kaže, da ima ribociklib potencial za zaviranje aktivnosti prenašalcev P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 in BSEP. Pri sočasnem zdravljenju s snovmi, ki so občutljivi substrati teh prenašalcev in imajo nizek terapevtski indeks, med drugim z digoksinom, pitavastatinom, pravastatinom, rosuvastatinom in metforminom, je priporočena previdnost in spremljanje bolnikov glede toksičnega delovanja. Zdravila, ki zvišujejo pH v želodcu: Pri populacijski farmakokinetični analizi in nekompartmentalni farmakokinetični analizi pri sočasni uporabi niso opažali sprememb v absorpciji ribociklibla. Medsebojno delovanje med ribociklibom in letrozolom oz. anastrozolom oz. fulvestrantom oz. tamoksifenom: Med ribociklibom in letrozolom oz. med ribociklibom in anastrozolom ne prihaja do medsebojnega delovanja pri sočasnem odmerjanju obeh zdravil. Po podatkih iz klinične študije fulvestrant nima klinično pomembnega vpliva na izpostavljenost ribociklibu pri sočasnem odmerjanju, po sočasnem odmerjanju ribociklibla in tamoksifena pa se je izpostavljenost tamoksifenu povečala na približno 2-kratno vrednost. **Neželeni učinki:** *Zelo pogosti* (≥ 1/10): okužbe, nevtropenija, levkopenija, anemija, limfopenija, zmanjšan apetit, glavobol, omotičnost, dispneja, kašelj, navzea, diareja, bruhanje, obstipacija, stomatitis, bolečine v trebuhu, dispepsija, alopecija, izpuščaj, pruritus, bolečine v hrbtu, utrujenost, periferni edemi, astenija, zvišana telesna temperatura, nenormalne vrednosti jetrnih testov. *Pogosti* (≥ 1/100 do < 1/10): trombocitopenija, febrilna nevtropenija, hipokalciemija, hipokaliemija, hipofosfatemija, vrtoglavica, močnejše solzenje, suhe oči, sinkopa, motnje okušanja, hepatotoksičnost, eritem, suha koža, vitiligo, suha usta, orofaringealna bolečina, zvišana vrednost kreatinina v krvi, podaljšan interval QT v elektrokardiogramu. *Neznana pogostnost:* toksična epidermalna nekroliza (TEN). **Imetnik dovoljenja za promet z zdravilom:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Irska. **Dodatne informacije in literatura:** Novartis Pharma Services Inc., Podružnica v Sloveniji, Verovškova ulica 57, 1000 Ljubljana. **Način/režim izdajanja zdravila:** Rp/Spec. **Pred predpisovanjem natančno preberite zadnji odobreni povzetek glavnih značilnosti zdravila. Datum zadnje revizije skrajšanega povzetka glavnih značilnosti zdravila**: november 2020.

NOVARTIS

Novartis Pharma Services Inc., Podružnica v Sloveniji
Verovškova ulica 57, 1000 Ljubljana, tel.: 01 300 75 50

Datum priprave materiala: junij 2021

Samo za strokovno javnost.

SI-2021-KIS-099

KISQALI® ribociklib

LIBTAYO®
(cemiplimab)

Prva terapija za zdravljenje odraslih bolnikov z metastatskim ali lokalno napredovalim ploščatoceličnim karcinomom kože (PCKK), ki niso kandidati za kurativni kirurški poseg ali kurativno obsevanje. [1,2]

Zaviralec PD-1: spodbuja bolnikov imunski protitumorski odziv za izboljšanje rezultatov zdravljenja [3]

PD-1, receptor programirane celične smrti 1

Pred predpisovanjem prosimo preberite celoten povzetek glavnih značilnosti zdravila.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.
Ime zdravila: LIBTAYO 350 mg koncentrat za raztopino za infundiranje. **Sestava:** En mililiter koncentrata vsebuje 50 mg cemiplimaba. Ena viala vsebuje 350 mg cemiplimaba v 7 ml raztopine. **Terapevtske indikacije:** Ploščatocelični karcinom kože: Zdravilo LIBTAYO je kot samostojno zdravljenje (monoterapija) indicirano za zdravljenje odraslih bolnikov z metastatskim ali lokalno napredovalim ploščatoceličnim karcinomom kože (mPCKK ali lnPCKK), ki niso kandidati za kurativni kirurški poseg ali kurativno obsevanje. Bazalnocelični karcinom: Zdravilo LIBTAYO je kot samostojno zdravljenje (monoterapija) indicirano za zdravljenje odraslih bolnikov z lokalno napredovalim ali metastatskim bazalnoceličnim karcinomom (1aBCK ali mBCK), pri katerih je bolezen napredovala kljub uporabi zaviralca signalne poti Hedgehog (HHI) ali ga ne prenašajo. Nedrobnocelični pljučni rak: Zdravilo LIBTAYO je kot samostojno zdravljenje (monoterapija) indicirano za prvo linijo zdravljenja odraslih bolnikov z nedrobnoceličnim pljučnim rakom (NSCLC – Non-Small Cell Lung Cancer), katerih tumorji izražajo PD-L1 (v ≥ 50 % tumorskih celic) brez aberacij EGFR, ALK ali ROSI z: lokalno napredovalim NSCLC, ki niso primerni za definitivno kemoradiacijo, ali metastatskim NSCLC. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, izkušen na področju zdravljenja raka. Testiranje PD-L1 pri bolnikih z NSCLC: Za zdravljenje s cemiplimabom kot monoterapijo je treba bolnike izbrati na podlagi validiranega testa izražanja PD-L1 v tumorju. *Priporočeni odmerek:* Priporočeni odmerek cemiplimaba je 350 mg na 3 tedne v 30 minutni intravenski infuziji. Zdravljenje se sme nadaljevati do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. *Prilagoditve odmerka:* Zmanjšanja odmerka niso priporočena. Glede na varnost in prenašanje pri posameznem bolniku je lahko potrebna odložitev odmerka ali prenehanje uporabe. Za priporočene prilagoditve za obvladovanje neželenih učinkov glejte celoten Povzetek glavnih značilnosti zdravila. *Posebne populacije: Pediatrična populacija:* Varnost in učinkovitost zdravila LIBTAYO pri otrocih in mladostnikih, mlajših od 18 let, nista ugotovljeni. *Starejše osebe, okvara ledvic, okvara jeter:* odmerka ni treba prilagoditi. Način uporabe: Zdravilo LIBTAYO je namenjeno intravenski uporabi. Daje se v intravenski infuziji v obdobju 30 minut po intravenski liniji, ki vsebuje sterilen, nepirogen filter (v sami liniji ali kot dodatek), ki malo veže beljakovine (velikost por od 0,2 do 5 mikronov). Po isti infuzijski liniji se ne sme istočasno dajati drugih zdravil. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila. Imunsko pogojeni neželeni učinki: Med uporabo cemiplimaba so opažali hude imunsko pogojene neželene učinke, tudi s smrtnim izidom. Pri bolnikih, zdravljenih s cemiplimabom ali drugimi zaviralci PD-1/PD-L1, se lahko sočasno pojavijo imunski neželeni učinki, ki vplivajo na več telesnih sistemov, na primer miozitis in miokarditis ali miastenija gravis. Za obvladanje imunsko pogojenih neželenih učinkov je treba prilagoditi odmerek cemiplimaba, nadomestno hormonsko zdravljenje (če je klinično indicirano) in kortkosteroide. Odvisno od izrazitosti neželenega učinka je treba uporabo cemiplimaba začasno prekiniti ali za stalno prenehati. *Imunsko pogojeni pnevmonitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni pnevmonitis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije, vključno s primeri s smrtnim izidom. *Imunsko pogojeni kolitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeno drisko ali kolitis, opredeljena s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije. *Imunsko pogojeni hepatitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni hepatitis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije, vključno s primeri s smrtnim izidom. *Imunsko pogojene endokrinopatije:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojene endokrinopatije, opredeljene kot med zdravljenjem nastale endokrinopatije brez jasne alternativne etiologije. *Motnje v delovanju ščitnice (hipotiroidizem/hipertiroidizem/tiroiditis):* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojene motnje v delovanju ščitnice. Tiroiditis se lahko pojavi s spremembo testov delovanja ščitnice ali brez nje. *Hipertiroidizmu lahko sledi hipotiroidizem. Hipofizitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni hipofizitis. *Nadledvična insuficienca:* Pri bolnikih, ki so prejemali cemiplimab, so opažali nadledvično insuficienco. *Sladkorna bolezen tipa 1:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeno sladkorno bolezen tipa 1, vključno z diabetično ketoacidozo. *Imunsko pogojeni neželeni učinki na kožo:* Med zdravljenjem s cemiplimabom so poročali o imunsko pogojenih neželenih učinkih na kožo, opredeljenih s potrebo po uporabi sistemskih kortikosteroidov in brez jasne alternativne etiologije; med njimi so bili hudi neželeni učinki na kožo, na primer Stevens-Johnsonov sindrom (SJS) in toksična epidermalna nekroliza (TEN) (v nekaterih primerih s smrtnim izidom), in druge kožne reakcije, na primer izpuščaj, multiformni eritem in pemfigoid. *Imunsko pogojeni nefritis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni nefritis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije. Drugi imunsko pogojeni neželeni učinki: Pri bolnikih, ki so prejemali cemiplimab, so opažali še druge življenjsko nevarne in smrtne imunsko pogojene neželene učinke, med njimi paraneoplastični encefalomielitis, meningitis in miozitis. Zdravljenje s cemiplimabom lahko pri prejemnikih presadkov parenhimskih organov poveča tveganje za zavrnitev. V obdobju po prihodu na trg so pri bolnikih, ki so prejemali druge zaviralce PD-1/PD-L1 obenem z alogensko presaditvijo hematopoetskih matičnih celic, poročali o primerih bolezni presadka proti gostitelju. Z infundiranjem povezane reakcije: Cemiplimab lahko povzroči resne ali življenjsko nevarne z infundiranjem povezane reakcije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo cemiplimaba se je treba izogibati, razen fizioloških odmerkov sistemskih kortikosteroidov (≤ 10 mg/dan prednizolona ali enakovredno), ker lahko motijo farmakodinamično aktivnost in učinkovitost cemiplimaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti po začetku zdravljenja s cemiplimabom za zdravljenje imunsko pogojenih neželenih učinkov. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi morajo med zdravljenjem s cemiplimabom in vsaj še 4 mesece po zadnjem odmerku cemiplimaba uporabljati učinkovito kontracepcijo. Cemiplimab ni priporočljiv med nosečnostjo in za ženske v rodni dobi, ki ne uporabljajo učinkovite kontracepcije, razen če klinična korist odtehta možno tveganje. Če se ženska odloči za zdravljenje s cemiplimabom, ji je treba svetovati, da med zdravljenjem s cemiplimabom in vsaj še 4 mesece po zadnjem odmerku ne sme dojiti. **Vpliv na sposobnost vožnje in upravljanja strojev:** Po zdravljenju s cemiplimabom so poročali o utrujenosti. **Neželeni učinki:** Zelo pogosti: okužba zgornjih dihal, anemija, zmanjšan apetit, kašelj, slabost, driska, zaprtje, izpuščaj, pruritus, mišično-skeletna bolečina, utrujenost. Pogosti: okužba sečil, z infundiranjem povezane reakcije, hipotiroidizem, hipertiroidizem, glavobol, periferna nevropatija, hipertenzija, dispneja, pnevmonitis, bolečina v trebuhu, bruhanje, stomatitis, kolitis, hepatitis, artritis, nefritis, zvišana aspartat-aminotransferaza, zvišana alanin-aminotransferaza, zvišana alkalna fosfataza v krvi, zvišan kreatinin v krvi. Občasni: sjögrenov sindrom, imunsko pogojena trombocitopenična purpura, nadledvična insuficienca, tiroiditis, sladkorna bolezen tipa 1, hipofizitis, meningitis, encefalitis, miastenija gravis, praneoplastični encefalomielitis, kronična vnetna demielinizirajoča poliradikulonevropatija, keratitis, miokarditis, perikarditis, šibkost mišic, miozitis, revmatska polimialgija, zvišan ščitnični hormon v krvi, zvišane transaminase, zvišan bilirubin v krvi, znižan ščitnični hormon v krvi. **Preveliko odmerjanje:** V primeru prevelikega odmerjanja naj se bolnike natančno kontrolira glede znakov in simptomov neželenih učinkov in uvede ustrezno simptomatsko zdravljenje. **Način in režim izdaje zdravila:** H-Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** Regeneron Ireland Designated Activity Company (DAC), One Warrington Place, Dublin 2, D02 HH27, Irska. **Datum zadnje revizije besedila:** 21.06.2021

SAMO ZA STROKOVNO JAVNOST

REGENERON | SANOFI GENZYME

Sanofi and Regeneron are collaborating in the global development and commercialization for LIBTAYO (cemiplimab).

MAT-SI-2000079-5.0-09/2021

1. Libtayo (cemiplimab) Povzetek glavnih značilnosti zdravila, www.ema.europa.com, datum zadnjega podaljšanja 08.03.2021
2. www.nice.org.uk, technology appraisal guidance TA592. dostop 07.08.2019. 3. www.cancer.gov/publications/dictionaries/cancer-terms/def/pd-1, dostop 07.08.2019

ZAUPANJE, ZGRAJENO NA MOČI

Za zdravljenje lokalno napredovalega ali metastatskega HR+/HER2- raka dojk:

- v kombinaciji z zaviralcem aromataze,
- v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje.

Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina (*LHRH – Luteinizing Hormone–Releasing Hormone*).

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

IIBRANCE 75 mg, 100 mg, 125 mg trde kapsule[1]
IBRANCE 75 mg, 100 mg, 125 mg filmsko obložene tablete[2]
Sestava in oblika zdravila: (1) Ena trda kapsula vsebuje 75 mg, 100 mg ali 125 mg palbociklība in 56 mg, 74 mg ali 93 mg laktoze (v obliki monohidrata). (2) Ena filmsko obložena tableta vsebuje 75 mg, 100 mg ali 125 mg palbociklība. **Indikacije:** Zdravljenje lokalno napredovalega ali metastatskega na hormonske receptorje (HR – *Hormone Receptors*) pozitivnega in na receptorje humanega epidermalnega rastnega faktorja 2 (HER2 – *Human Epidermal growth factor Receptor 2*) negativnega raka dojk: v kombinaciji z zaviralcem aromataze ali v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje. Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek je 125 mg enkrat na dan 21 zaporednih dni, sledi 7 dni brez zdravljenja (shema 3/1), celotni cikel traja 28 dni. Zdravljenje je treba nadaljevati, dokler ima bolnik od zdravljenja klinično korist ali dokler se ne pojavi nesprejemljiva toksičnost. Pri sočasnem dajanju s palbociklibom je treba zaviralec aromataze dajati v skladu s shemo odmerjanja, ki je navedena v Povzetku glavnih značilnosti zdravila (PGZZ). Pri sočasnem dajanju s palbociklibom je priporočeni odmerek fulvestranta 500 mg intramuskularno 1., 15. in 29. dan ter nato enkrat na mesec, glejte PGZZ za fulvestrant. Prilagajanja odmerkov: Za prilagajanja odmerkov zaradi hematološke toksičnosti glejte preglednico 2, zaradi nehematološke toksičnosti pa preglednico 3 v PGZZ-ju. Pri bolnikih s hudo intersticijsko boleznijo pljuč (ILD)/pnevmonitisom je treba zdravljenje trajno prekiniti. Posebne skupine bolnikov: *Starejši:* Prilagajanje odmerka ni potrebno. *Okvara jeter ali ledvic*: Pri bolnikih z blago ali zmerno okvaro jeter ali blago, zmerno ali hudo okvaro ledvic prilagajanje odmerka ni potrebno. Pri bolnikih s hudo okvaro jeter je priporočeni odmerek 75 mg enkrat na dan po shemi 3/1. *Pediatrična populacija*: Varnost in učinkovitost pri otrocih in mladostnikih, starih < 18 let, nista bili dokazani. Način uporabe: Peroralna uporaba. (1) Jemanje s hrano, priporočljivo z obrokom. (2) Tablete se lahko jemlje s hrano ali brez nje. (1, 2) Ne smemo jemati z grenivko ali grenivkinim sokom. Kapsule oz. tablete zdravila je treba pogoltniti cele. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. Uporaba pripravkov s šentjanževko. **Posebna opozorila in previdnostni ukrepi:** Ženske v pred- in perimenopavzi: Kadar zdravilo uporabljamo v kombinaciji z zaviralcem aromataze je obvezna ovarijska ablacija ali supresija z agonistom gonadoliberina. Hematološke bolezni: Pri nevtropeniji stopnje 3 ali 4 je priporočljiva prekinitev odmerjanja, zmanjšanje odmerka ali odložitev začetka ciklov zdravljenja, bolnike pa je treba ustrezno spremljati. ILD/pnevmonitis: Pri bolnikih se lahko pojavita huda, življenjsko ogrožajoča ali smrtna ILD in/ali pnevmonitis, kadar zdravilo jemljejo v kombinaciji z endokrinim zdravljenjem. Bolnike je treba spremljati glede pljučnih simptomov, ki kažejo na ILD/pnevmonitis (npr. hipoksija, kašelj, dispneja), in pri pojavu novih ali poslabšanju respiratornih simptomov oz. sumu na ILD/pnevmonitis zdravljenje prekiniti. Okužbe: Zdravilo lahko poveča nagnjenost k okužbam, zato je bolnike treba spremljati glede znakov in simptomov okužbe ter jih ustrezno zdraviti. Okvara jeter ali ledvic: Pri bolnikih z zmerno ali hudo okvaro jeter ali ledvic je treba zdravilo uporabljati previdno in skrbno spremljati znake toksičnosti. (1) Laktoza: Vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze-galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Učinki drugih zdravil na farmakokinetiko palbociklība: *Zaviralci CYP3A:* Sočasni uporabi močnih zaviralcev CYP3A, med drugim klaritromicina, indinavirja, itrakonazola, ketokonazola, lopinavirja/ritonavirja, nefazodona, nelfinavirja, posakonazola, sakvinavirja, telaprevirja, telitromicina, vorikonazola in grenivke ali grenivkinega soka, se je treba izogibati. *Induktorji CYP3A:* Sočasni uporabi močnih induktorjev CYP3A, med drugim karbamazepina, enzalutamida, fenitoina, rifampicina in šentjanževke, se je treba izogibati. Učinek zdravil za zmanjševanje kisline: (1) Če palbociklib zaužijemo s hrano, klinično pomembnega učinka na izpostavljenost palbociklibu ni pričakovati. (2) Klinično pomembnega učinka na izpostavljenost palbociklibu ni pričakovati. Učinki palbociklība na farmakokinetiko drugih zdravil: Pri sočasni uporabi bo morda treba zmanjšati odmerek občutljivih substratov CYP3A z ozkim terapevtskim indeksom (npr. alfentanil, ciklosporin, dihidroergotamin, ergotamin, everolimus, fentanil, pimozid, kinidin, sirolimus in takrolimus), saj IBRANCE lahko poveča izpostavljenost tem zdravilom. Študije *in vitro* s prenašalci: Palbociklib lahko zavira prenos, posredovan s P-gp v prebavilih in beljakovino odpornosti pri raku dojk (BCRP). Uporaba palbociklība z zdravili, ki so substrati P-gp (npr. digoksin, dabigatran, kolhicin) ali BCRP (npr. pravastatin, rosuvastatin, sulfasalazin) lahko poveča njihov terapevtski učinek in neželene učinke. Palbociklib lahko zavira privzemni prenašalec organskih kationov OCT1. **Plodnost, nosečnost in dojenje:** Med zdravljenjem in vsaj 3 tedne (ženske) oziroma 14 tednov (moški) po koncu zdravljenja je treba uporabljati ustrezne kontracepcijske metode. Zdravila ne uporabljajte pri nosečnicah in ženskah v rodni dobi, ki ne uporabljajo kontracepcije. Bolnice, ki prejemajo palbociklib, ne smejo dojiti. Zdravljenje s palbociklibom lahko ogrozi plodnost pri moških. Pred začetkom zdravljenja naj moški zato razmislijo o hrambi sperme. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Ima blag vpliv na sposobnost vožnje in upravljanja strojev. Potrebna je previdnost. **Neželeni učinki:** Zelo pogosti: okužbe, nevtropenija, levkopenija, anemija, trombocitopenija, pomanjkanje teka, stomatitis, navzea, diareja, bruhanje, izpuščaj, alopecija, suha koža, utrujenost, astenija, pireksija, povečane vrednosti ALT/AST. **Način in režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 16.07.2021

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

PP-IBR-EEP-0236 Datum priprave: avgust 2021. Samo za strokovno javnost.
HR+/HER2- = pozitiven na hormonske receptorje in negativen na receptorje humanega epidermalnega rastnega faktorja 2.
Literatura: Povzetek glavnih značilnosti zdravila Ibrance, 16.7.2021.

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Pfizer, podružnica Ljubljana, Letališka cesta 29a, Ljubljana

IBRANCE® palbociklib

Revolucije

zahtevajo strast.

Več kot stoletje postavljamo nove standarde v diagnostiki in zdravljenju številnih bolezni. Danes nam novi viri podatkov in napredna analitika omogočajo, da zagotovimo pravo zdravljenje za pravega bolnika ob pravem času. Zato se povezujemo s tistimi, ki stremijo k istemu cilju in razumejo, da nova znanja služijo ne samo znanosti, temveč predvsem človeštvu.

M-SI-00000051(v2.0)

Informacija pripravljena: september 2020.
DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Stegne 13g, 1000 Ljubljana.

Tafinlar® (dabrafenib) + Mekinist® (trametinib)

KO PRI VAŠIH BOLNIKIH Z MELANOMOM STADIJA III ALI IV UGOTOVITE PRISOTNOST MUTACIJE BRAF

ODGOVORITE S PREIZKUŠENIM OROŽJEM

Dosežite podaljšano preživetje pri bolnikih z BRAF+ melanomom stadija IV ali možnost ozdravitve pri bolnikih s stadijem III s kombinacijo zdravil TAFINLAR + MEKINIST.[3,4*#†]

* V študiji COMBI-AD je bila po medianem času spremljanja 60 mesecev (dabrafenib in trametinib), oz. 58 mesecev (placebo) ocenjena stopnja ozdravitve 52 % (95-% IZ, 48 %-58 %; dabrafenib in trametinib), in 36 % (95-% IZ, 32 %-41 %; placebo).

V združeni populaciji bolnikov iz študij COMBI-d in COMBI-v je bila stopnja celokupnega preživetja bolnikov v skupini zdravljeni s kombinacijo zdravil dabrafenib in trametinib po 5 letih 34 % (95-% IZ, 30 %-38 %) v primerjavi s 27% (dabrafenib+placebo) in 23 % (vemurafenib).

† Zdravili TAFINLAR in MEKINIST sta v kombinaciji indicirani za zdravljenje odraslih bolnikov z inoperabilnim ali metastatskim melanomom z mutacijo BRAF V600 in adjuvantno zdravljenje odraslih bolnikov po totalni resekciji melanoma stadija III z mutacijo BRAF V600.[1,2]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA ZA ZDRAVILI TAFINLAR IN MEKINIST

Imena zdravil: Tafinlar 50 mg trde kapsule, Tafinlar 75 mg trde kapsule, Mekinist 0,5 mg filmsko obložene tablete, Mekinist 2 mg filmsko obložene tablete. **Sestava:** Ena trda kapsula zdravila Tafinlar vsebuje dabrafenibijev mesilat, ki ustreza 50 mg dabrafeniba ali 75 mg dabrafeniba. Ena filmsko obložena tableta zdravila Mekinist vsebuje 0,5 mg trametiniba ali 2 mg trametiniba v obliki trametinibijevega dimetilsulfoksida. **Indikacija: Melanom: Dabrafenib in trametinib sta v kombinaciji indicirana za zdravljenje odraslih bolnikov z inoperabilnim ali metastatskim melanomom z mutacijo BRAF V600.** Dabrafenib in trametinib sta oba tudi v monoterapiji indicirana za zdravljenje odraslih bolnikov z inoperabilnim ali metastatskim melanomom z mutacijo BRAF V600. Trametinib v monoterapiji ni izkazal klinične aktivnosti pri bolnikih, ki jim je bolezen napredovala med predhodnim zdravljenjem z zaviralcem BRAF. **Adjuvantno zdravljenje melanoma: Dabrafenib in trametinib sta v kombinaciji indicirana za adjuvantno zdravljenje odraslih bolnikov po totalni resekciji melanoma stadija III z mutacijo BRAF V600. Nedrobnocelični pljučni rak (NDCPR): Dabrafenib in trametinib sta v kombinaciji indicirana za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim pljučnim rakom z mutacijo BRAF V600. Odmerjanje:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Pred uporabo dabrafeniba in/ali trametiniba mora biti z validirano preiskavo potrjeno, da ima bolnik mutacijo BRAF V600. Kombinirano zdravljenje: 150 mg dabrafeniba 2x/dan in 2 mg trametiniba 1x/dan. Dabrafenib v monoterapiji (melanom): 150 mg dabrafeniba 2x/dan. Trametinib v monoterapiji (melanom): 2 mg trametiniba 1x/dan. Če bolnik pozabi vzeti odmerek trametiniba, naj ga vzame samo, če je do naslednjega rednega odmerka več kot 12 ur, pozabljenega odmerka dabrafeniba ne sme vzeti, če je do naslednjega odmerka po razporedu manj kot 6 ur. Zdravljenje je priporočljivo nadaljevati, dokler bolniku koristi oz. do pojava nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba bolnike zdraviti 12 mesecev, razen če pride do ponovitve bolezni ali nesprejemljivih toksičnih učinkov. Obvladovanje neželenih učinkov lahko zahteva znižanje odmerka, prekinitev zdravljenja ali prenehanje zdravljenja. Prilagoditve odmerka ali prekinitve zdravljenja niso priporočljive v primeru neželenih učinkov ploščatoceličnega karcinoma kože ali novega primarnega melanoma. Če pri uporabi kombinacije dabrafeniba in trametiniba pride do toksičnih učinkov zdravljenja, je treba sočasno znižati odmerek obeh zdravil oz. sočasno začasno prekiniti ali dokončno ukiniti obe zdravljenji. Izjeme, pri katerih je treba odmerek prilagajati samo pri enem od obeh zdravil, so pojav zvišane telesne temperature (dabrafenib), uveitisa (dabrafenib), nekožnih malignomov z mutacijo RAS (dabrafenib), zmanjšanja iztisnega deleža levega prekata (LVEF) (trametinib), zapore mrežnične vene (RVO) ali odstopa mrežničnega pigmentnega epitelija (RPED) (trametinib) in intersticijske bolezni pljuč (IBP)/pnevmonitisa (trametinib). Za natančnejša navodila glede prilagajanja odmerkov glejte povzetka glavnih značilnosti zdravil Tafinlar in Mekinist. Bolnikom z blago ali zmerno okvaro ledvic ali z blago okvaro jeter odmerkov dabrafeniba in trametiniba ni treba prilagoditi. Pri bolnikih s hudo okvaro ledvic ali z zmerno ali hudo okvaro jeter je treba dabrafenib in trametinib, bodisi v monoterapiji ali v kombinaciji, uporabljati previdno. Bolnikom, starim > 65 let, začetnega odmerka dabrafeniba in trametiniba ni treba prilagoditi, je pa pri teh bolnikih lahko potrebno pogostejše prilagajanje odmerka trametiniba. Pri bolnikih azijske rase ni potrebno prilagajati odmerkov dabrafeniba. Varnost in učinkovitost trametiniba nista ugotovljeni pri bolnikih, ki niso belci. Varnost in učinkovitost dabrafeniba in trametiniba pri otrocih in mladostnikih (< 18 let) nista bili dokazani. **Način uporabe: Zdravilo Tafinlar**: Kapsule je treba zaužiti cele z vodo najmanj 1 uro pred jedjo oz. najmanj 2 uri po jedi. Ne sme se jih zgristi ali odpreti. Če bolnik po zaužitju dabrafeniba ali trametiniba bruha, odmerka ne sme vzeti ponovno, temveč mora vzeti naslednji odmerek ob običajnem času. **Zdravilo Mekinist**: Tablete je treba zaužiti s polnim kozarcem vode vsaj 1 uro pred jedjo ali vsaj 2 uri po jedi. Ne sme se jih gristi ali drobiti. **Kontraindikacije**: Preobčutljivost na učinkovini ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi**: Dabrafeniba se ne sme uporabljati pri bolnikih z melanomom in pri bolnikih z NDCPR z divjim tipom BRAF. O uporabi kombinacije dabrafeniba in trametiniba pri bolnikih z melanomom, pri katerih je bolezen napredovala med predhodnim zdravljenjem z zaviralcem BRAF, je na voljo malo podatkov, ki pa kažejo, da je učinkovitost kombinacije pri teh bolnikih manjša. *Ploščatocelični karcinom kože (dabrafenib ali kombinirano zdravljenje):* Opisani so primeri ploščatoceličnega karcinoma kože. Priporočljivo je opraviti pregled kože pred uvedbo dabrafeniba, vsak mesec med zdravljenjem in še do 6 mesecev po zdravljenju ploščatoceličnega karcinoma kože. Bolnika se mora spremljati še 6 mesecev po prenehanju zdravljenja z dabrafenibom ali do uvedbe drugega antineoplastičnega zdravljenja. Primere ploščatoceličnega karcinoma kože je treba zdraviti z dermatološko ekscizijo, z dabrafenibom oz. kombinacijo pa nadaljevati brez prilagoditve odmerka. Bolnikom je treba naročiti, naj nemudoma obvestijo zdravnika, če se jim pojavi kakšna nova sprememba. *Nov primarni melanom (dabrafenib ali kombinirano zdravljenje):* Bolnika je mogoče zdraviti z ekscizijo, spremembe v zdravljenju niso potrebne. Nadzor kot pri ploščatoceličnem karcinomu kože. *Nekožni malignomi (dabrafenib ali kombinirano zdravljenje):* Dabrafenib lahko poveča tveganje za razvoj nekožnih malignomov, če so prisotne mutacije RAS. Bolnikom je treba pred uvedbo zdravljenja pregledati glavo in vrat (najmanj ogled ustne sluznice in palpacijo bezgavk), opraviti morajo CT prsnega koša/trebuha. Med zdravljenjem jih je treba nadzirati, kot je klinično primerno; to lahko vključuje pregled glave in vratu na 3 mesece in CT prsnega koša/trebuha na 6 mesecev. Pred zdravljenjem in na koncu zdravljenja (ter kadar koli je klinično indicirano) sta priporočljiva analni in ginekološki pregled. Opraviti je treba pregled celotne krvne slike in biokemične preiskave krvi, kot je klinično indicirano. *Krvavitev (trametinib ali kombinirano zdravljenje):* Prihajalo je do krvavitev, med katerimi so bile tudi večje krvavitve in krvavitve, zaradi katerih so bolniki umrli. Tveganje se lahko poveča v primeru sočasne uporabe antiagregacijskih ali antikoagulantnih zdravil. Če pride do krvavitve, je treba bolnika zdraviti v skladu s kliničnimi indikacijami. *LVEF (trametinib ali kombinirano zdravljenje):* Poročali so, da trametinib zmanjša LVEF. Vsem bolnikom je treba LVEF oceniti pred uvedbo trametiniba, 1 mesec po uvedbi in nato na približno 3 mesece med zdravljenjem. Pri jemanju trametiniba v kombinaciji z dabrafenibom, so poročali o akutni hudi disfunkciji levega prekata zaradi miokarditisa. Zdravniki naj bodo pozorni na možnost miokarditisa pri bolnikih, pri katerih se znaki ali simptomi težav s srcem pojavijo na novo oziroma se poslabšajo. *Zvišana telesna temperatura (dabrafenib, trametinib ali kombinirano zdravljenje):* Poročali so o zvišanju telesne temperature. Pri kombiniranem zdravljenju sta pogostnost in izraženost večji. Zdravljenje z dabrafenibom je treba prekiniti, če je bolnikova telesna temperatura ≥ 38,5 °C in bolnike oceniti glede znakov in simptomov okužbe. Ko mine, je mogoče zdravljenje z dabrafenibom znova začeti ob ustrezni profilaksi z uporabo nesteroidnih protivnetnih zdravil ali paracetamola. Če antipiretiki ne zadoščajo, je treba razmisliti o uporabi peroralnih kortikosteroidov. Če je zvišana telesna temperatura povezana z drugimi hudimi znaki ali simptomi, je treba zdravljenje z dabrafenibom znova začeti z nižjim odmerkom, ko zvišana telesna temperatura mine in kot je klinično primerno. *Hipertenzija (trametinib ali kombinirano zdravljenje):* Opisana so zvišanja krvnega tlaka tako pri bolnikih, ki so že prej imeli hipertenzijo, kot pri tistih, ki je prej niso imeli. Krvni tlak je treba izmeriti izhodiščno in med zdravljenjem; hipertenzijo je treba obvladovati s standardnim zdravljenjem. *IBP (trametinib ali kombinirano zdravljenje):* V primeru suma na IBP ali pnevmonitis je treba zdravljenje s trametinibom prekiniti; tudi pri bolnikih z novonastalimi ali napredujočimi pljučnimi simptomi ali izvidi, vključno s kašljem, dispnejo, hipoksijo, plevralnim izlivom ali infiltrati, dokler niso opravljene klinične preiskave. Pri bolnikih, ki imajo diagnosticirano z zdravljenjem povezano IBP ali pnevmonitis, je treba zdravljenje s trametinibom trajno končati. *Okvara vida (trametinib ali kombinirano zdravljenje):* Lahko pride do težav, povezanih z motnjami vida, vključno z RPED in RVO. Uporaba trametiniba ni priporočljiva pri bolnikih, ki so v preteklosti že imeli RVO. Če se pojavijo novonastale motnje vida, npr. poslabšanje centralnega vida, zamegljen vid ali izguba vida, je priporočljiva takojšnja oftalmološka ocena. Pri bolnikih z diagnozo RVO, je treba trametinib trajno ukiniti. *Okvara vida (dabrafenib ali kombinirano zdravljenje):* Opisovali so oftalmološke reakcije, vključno z uveitisom, iridociklitisom in/ali iritisom. Bolnike je treba redno kontrolirati glede znakov in simptomov s strani vida (npr. sprememb vida, fotofobije in bolečin v očesu). Prilagajanje odmerka ni potrebno, dokler je očesno vnetje mogoče obvladati z učinkovitimi lokalnimi zdravili. Če se uveitis ne odziva na lokalna očesna zdravila, je treba zdravljenje z dabrafenibom prekiniti, dokler očesno vnetje ni odpravljeno, nato pa ga ponovno uvesti v odmerku, ki je za eno odmerno raven nižji. *Odpoved ledvic (dabrafenib ali kombinirano zdravljenje):* Med zdravljenjem je treba rutinsko določati vrednost kreatinina v serumu. Če se vrednost zviša, je morda treba začasno prekiniti uporabo dabrafeniba, če je to klinično primerno. Uporabe dabrafeniba niso preučili pri bolnikih z insuficienco ledvic (kreatinin > 1,5 x ZMN), zato ga je treba v takšnih okoliščinah uporabljati previdno. *Pankreatitis (dabrafenib ali kombinirano zdravljenje):* Poročali so o primerih pankreatitisa. Nepojasnjene bolečine v trebuhu je treba nemudoma raziskati, vključno z meritvijo amilaze in lipaze v serumu. Ob ponovnem začetku uporabe dabrafeniba po pankreatitisu je treba bolnike skrbno kontrolirati. *Jetrni dogodki (trametinib ali kombinirano zdravljenje):* Prvih 6 mesecev po začetku zdravljenja s trametinibom je delovanje jeter priporočljivo kontrolirati na 4 tedne in nato kot je klinično indicirano. *Globoka venska tromboza/pljučna embolija (trametinib ali kombinirano zdravljenje):* Če se pri bolniku pojavijo znaki pljučne embolije ali globoke venske tromboze, kot so zadihanost, bolečine v prsnem košu ali zatekanje rok ali nog, mora takoj poiskati zdravniško pomoč. Če gre za življenjsko nevarno pljučno embolijo, je treba bolniku dokončno ukiniti zdravljenje s trametinibom in dabrafenibom. *Hude kožne neželene reakcije:* Pred uvedbo zdravljenja je treba bolnike opozoriti na znake in simptome kožnih reakcij in jih skrbno spremljati. Če se pojavijo znaki in simptomi, ki lahko pomenijo, da gre za hudo kožno neželeno reakcijo, mora bolnik prekiniti zdravljenje z dabrafenibom in trametinibom. *Bolezni prebavil (trametinib ali kombinirano zdravljenje):* Poročali so o kolitisu in perforaciji prebavil, vključno s primeri, ki so se končali s smrtjo. Previdnost je potrebna pri uporabi trametiniba pri bolnikih z dejavniki tveganja za perforacijo prebavil, kot so divertikulitis v anamnezi, metastaze v prebavnem traktu ali sočasna uporaba zdravil z znanim tveganjem za perforacijo prebavil. *Sarkoidoza:* Ob diagnozi sarkoidoze je treba razmisliti o ustreznem zdravljenju. Pomembno je, da se sarkoidoza ne interpretira kot napredovanje bolezni. *Plodnost, nosečnost in dojenje:* Ženske v rodni dobi morajo uporabljati učinkovite kontracepcijske metode med zdravljenjem in še 2 tedna po prenehanju zdravljenja z dabrafenibom ter še 16 tednov po zadnjem odmerku trametiniba. Dabrafenib lahko zmanjša učinkovitost peroralnih oz. katerihkoli hormonskih kontraceptivov, zato je treba uporabiti drug učinkovit način kontracepcije. Trenutno ni znano, ali trametinib vpliva na hormonske kontraceptive. Za preprečitev nosečnosti se bolnicam, ki jemljejo hormonske kontraceptive svetuje, da uporabijo dodaten ali drug način kontracepcije med zdravljenjem in še 16 tednov po prekinitvi zdravljenja s trametinibom. Nosečnice in doječe matere ne smejo dobivati trametiniba. Nosečnice naj ne bi prejemale dabrafeniba, razen če možna korist za mater odtehta možno tveganje za plod. Odločiti se je treba bodisi za prenehanje dojenja bodisi za prenehanje zdravljenja z dabrafenibom, upoštevaje koristi dojenja za otroka in koristi zdravljenja za žensko. Dabrafenib in trametinib lahko prizadeneta plodnost moških in žensk. Moške bolnike, ki jemljejo dabrafenib in/ali trametinib, je treba seznaniti z možnim tveganjem za motnje spermatogeneze, ki so lahko ireverzibilne. Dabrafenib in trametinib imata blag vpliv na sposobnost vožnje in upravljanja strojev. Bolnika je treba seznaniti z možnostjo za utrujenost, omotico in težave z očmi, ki lahko vplivajo na takšne dejavnosti. **Medsebojno delovanje z drugimi zdravili: Zdravilo Tafinlar:** Verjetno je, da zdravila, ki močno zavirajo ali inducirajo CYP2C8 ali CYP3A4, povečajo oz. zmanjšajo koncentracijo dabrafeniba. Če je mogoče, je treba med uporabo dabrafeniba uporabiti druga zdravila. V primeru uporabe dabrafeniba z močnimi zaviralci (npr. ketokonazolom, gemfibrozilom, nefazodonom, klaritromicinom, ritonavirjem, sakvinavirjem, telitromicinom, itrakonazolom, vorikonazolom, posakonazolom, atazanavirjem) je potrebna previdnost. Izogibajte se sočasni uporabi dabrafeniba z močnimi induktorji (npr. rifampicinom, fenitoinom, karbamazepinom, fenobarbitalom ali šentjanževko (Hypericum perforatum)) CYP2C8 ali CYP3A4. Ne pričakuje se, da bi zdravila, ki spreminjajo pH zgornjega gastrointestinalnega trakta (npr. zaviralci protonske črpalke, antagonisti histaminskih receptorjev H_2, antacidi), zmanjšala biološko uporabnost dabrafeniba. Dabrafenib je induktor encimov in poveča sintezo encimov, ki presnavljajo zdravila. Posledica je manjša plazemska koncentracija zdravil, ki se presnavljajo s temi encimi, kar lahko povzroči izgubo ali zmanjšanje kliničnega učinka teh zdravil. Pričakovati je mogoče medsebojna delovanja s številnimi zdravili, ki se izločajo s presnavljanjem ali aktivnim transportom, a velikost medsebojnega delovanja se razlikuje. To lahko velja za, vendar ni omejeno na naštete skupine zdravil: analgetiki (npr. fentanil, metadon), antibiotiki (npr. klaritromicin, doksiciklin), zdravila proti raku (npr. kabazitaksel), antikoagulansi (npr. acenokumarol, varfarin), antiepileptiki (npr. karbamazepin, fenitoin, primidon, valprojska kislina), antipsihotiki (npr. haloperidol), zaviralci kalcijevih kanalčkov (npr. diltiazem, felodipin, nikardipin, nifedipin, verapamil), srčni glikozidi (npr. digoksin), kortikosteroidi (npr. deksametazon, metilprednizolon), protivirusna zdravila proti HIV (npr. amprenavir, atazanavir, darunavir, delavirdin, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, sakvinavir, tipranavir), hormonski kontraceptivi, hipnotiki (npr. diazepam, midazolam, zolpidem), imunosupresivi (npr. ciklosporin, takrolimus, sirolimus), statini, ki se presnavljajo s CYP3A4 (npr. atorvastatin, simvastatin). Če je njihov terapevtski učinek za bolnika zelo pomemben in če odmerka ni mogoče zlahka prilagoditi glede na kontrolo učinkovitosti ali koncentracije v plazmi, se je tem zdravilom treba izogniti ali jih je treba uporabljati previdno. Tveganje za okvaro jeter po uporabi paracetamola je domnevno večje pri bolnikih, ki sočasno prejemajo induktorje encimov. Pojav indukcije je verjeten po 3 dneh ponavljajočega se odmerjanja dabrafeniba. Po prenehanju uporabe dabrafeniba indukcija mine postopoma. Bolnike je treba spremljati glede toksičnih učinkov; potrebna je lahko prilagoditev odmerjanja navedenih zdravil. **Zdravilo Mekinist**: Zaradi možnosti zvišanja koncentracije trametiniba, je priporočena previdnost pri sočasnem odmerjanju trametiniba in zdravil, ki so močni zaviralci P-gp (na primer verapamila, ciklosporina, ritonavirja, kinidina, itrakonazola). Trametinib lahko povzroči prehodno zavrtje substratov BCRP (npr. pitavastatina) v črevesu; to je mogoče omejiti na najmanjšo mero tako, da se ta zdravila in trametinib uporablja z medsebojnim zamikom (zamik 2 ur). **Neželeni učinki:** Dabrafenib v monoterapiji: *Zelo pogosti* (≥ 1/10): papilom, zmanjšan apetit, glavobol, kašelj, navzea, bruhanje, driska, hiperkeratoza, alopecija, izpuščaj, sindrom palmarno-plantarne eritrodisestezije, artralgija, mialgija, bolečine v okončini, pireksija, utrujenost, mrzlica, astenija. *Pogosti* (≥ 1/100 do < 1/10): ploščatocelični karcinom kože, seboroična keratoza, akrohordon (kožni izrastki), bazalnocelični karcinom, hipofosfatemija, hiperglikemija, zaprtost, suha koža, srbenje, aktinična keratoza, kožne lezije, eritem, fotosenzitivnost, gripi podobna bolezen. *Občasni* (≥ 1/1.000 do < 1/100): nov primarni melanom, preobčutljivost, uveitis, pankreatitis, panikulitis, odpoved ledvic, akutna odpoved ledvic, nefritis. Trametinib v monoterapiji: *Zelo pogosti*: hipertenzija, krvavitev, kašelj, dispneja, driska, navzea, bruhanje, zaprtost, bolečine v trebuhu, suha usta, izpuščaj, akneiformni dermatitis, suha koža, srbenje, alopecija, utrujenost, periferni edemi, zvišana telesna temperatura, zvišana aspartat-aminotransferaza. *Pogosti*: folikulitis, paronihija, celulitis, pustulozen izpuščaj, anemija, preobčutljivost, dehidracija, zameglјen vid, periorbitalni edem, okvara vida, disfunkcija levega prekata, zmanjšanje iztisnega deleža, bradikardija, limfedem, pnevmonitis, stomatitis, eritem, sindrom palmarno-plantarne eritrodisestezije, fisure na koži, razpokana koža, edem obraza, vnetje sluznice, astenija, zvišana alanin-aminotransferaza, zvišana alkalna fosfataza v krvi, zvišana kreatin-fosfokinaza v krvi. *Občasni*: horioretinopatija, papiledem, odstop mrežnice, zapora mrežnične vene, srčno popuščanje, intersticijska bolezen pljuč, perforacija prebavil, kolitis, rabdomioliza. Kombinirano zdravljenje z dabrafenibom in trametinibom: *Zelo pogosti*:nazofaringitis, zmanjšan apetit, glavobol, omotica, hipertenzija, krvavitev, kašelj, bolečine v trebuhu, zaprtost, diareja, navzea, bruhanje, suha koža, srbenje, izpuščaj, eritem, artralgija, mialgija, bolečine v okončini, mišični krči, utrujenost, mrzlica, astenija, periferni edemi, zvišana telesna temperatura, gripi podobna bolezen, zvišana vrednost alanin aminotransferaze, zvišana vrednost aspartat aminotransferaze. *Pogosti:* okužba sečil, celulitis, folikulitis, paronihija, pustulozen izpuščaj, ploščatocelični karcinom kože, papilom, seboroična keratoza, nevtropenija, anemija, trombocitopenija, levkopenija, dehidracija, hiponatriemija, hipofosfatemija, hiperglikemija, zameglјen vid, okvara vida, uveitis, zmanjšanje iztisnega deleža, limfedem, hipotenzija, dispneja, suha usta, stomatitis, akneiformni dermatitis, aktinična keratoza, nočno znojenje, hiperkeratoza, alopecija, sindrom palmarno-plantarne eritrodisestezije, kožne spremembe, čezmerno znojenje, panikulitis, fisure na koži, fotosenzitivnost, vnetje sluznice, edem obraza, zvišana vrednost alkalne fosfataze v krvi, zvišana vrednost gama-glutamiltransferaze, zvišana vrednost kreatin-fosfokinaze v krvi. *Občasni:* nov primarni melanom, akrohordon (peciјati fibrom), preobčutljivost, sarkoidoza, horioretinopatija, odstop mrežnice, periorbitalni edem, bradikardija, pnevmonitis, pankreatitis, kolitis, odpoved ledvic, nefritis. *Redki:* perforacija prebavil. *Neznana pogostnost:* miokarditis, Stevens-Johnsonov sindrom, reakcija na zdravilo z eozinofilijo in sistemskimi simptomi (DRESS sindrom), generaliziran eksfoliativni dermatitis. **Imetnik dovoljenja za promet z zdravilom:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Irska **Dodatne informacije in literatura:** Novartis Pharma Services Inc., Podružnica v Sloveniji, Verovškova ulica 57, 1000 Ljubljana. **Način/režim izdajanja zdravil Tafinlar in Mekinist:** Rp/Spec. **Pred predpisovanjem natančno preberite zadnji odobreni povzetek glavnih značilnosti zdravila. Datum zadnje revizije skrajšanega povzetka glavnih značilnosti zdravila**: januar 2021.

Viri in literatura: 1. Povzetek glavnih značilnosti zdravila Tafinlar. Januar 2021. **2.** Povzetek glavnih značilnosti zdravila Mekinist. Januar 2021. **3.** Dummer R, Hauschild A, Santinami M, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med 2020;383:1139-48. **4.** Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med 2019;381:626-36.

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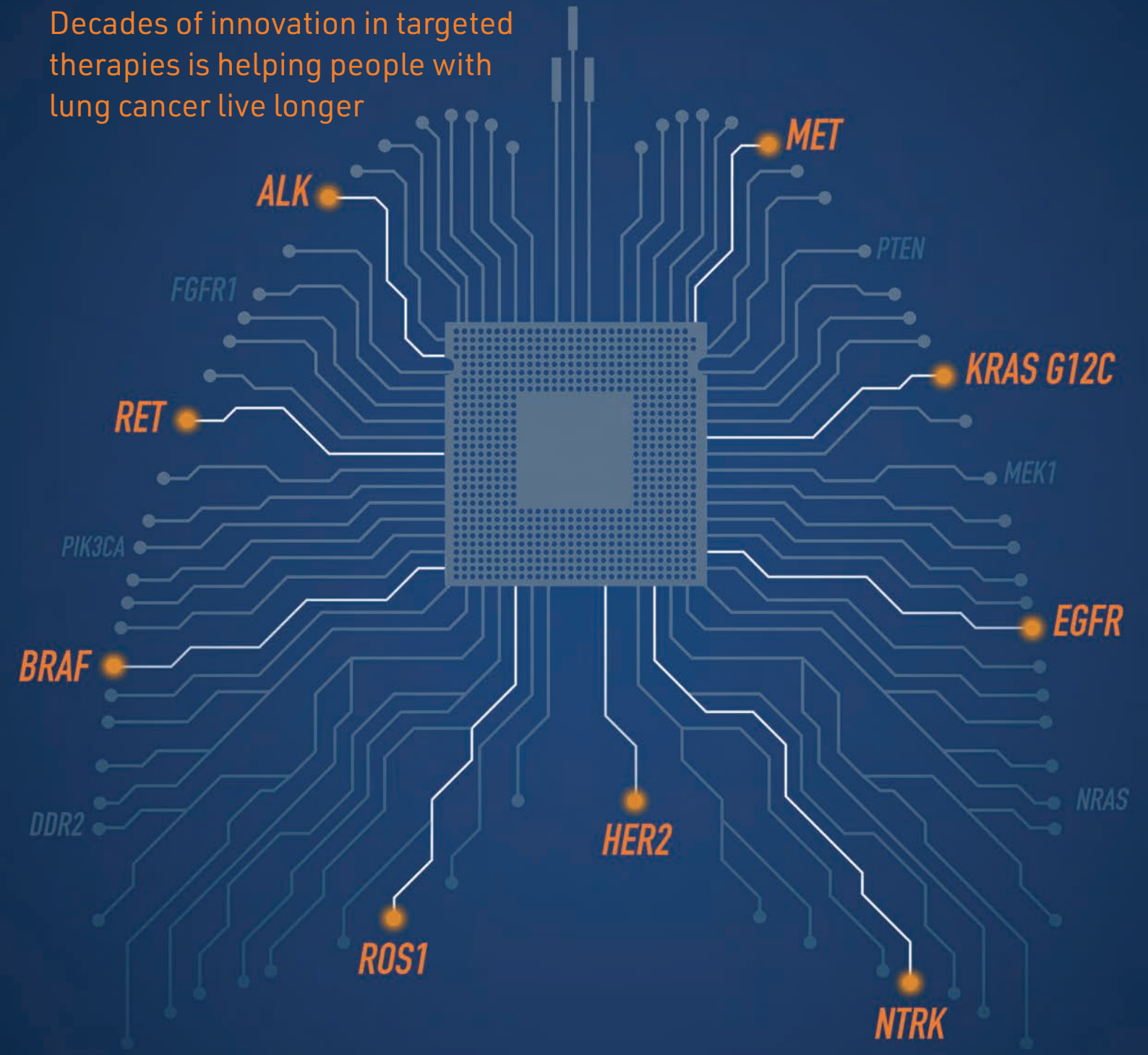
Datum priprave materiala: februar 2021 Samo za strokovno javnost SI-2021-MEK-014

POWERING TARGETED THERAPY

Decades of innovation in targeted therapies is helping people with lung cancer live longer



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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.
IME ZDRAVILA: Verzenios 50 mg/100 mg/150 mg filmsko obložene tablete **KAKOVOSTNA IN KOLIČINSKA SESTAVA:** Ena filmsko obložena tableta vsebuje 50 mg/100 mg/150 mg abemaciklib. Ena filmsko obložena tableta vsebuje 14 mg/28 mg/42 mg laktoze (v obliki monohidrata). **Terapevtske indikacije:** Zdravilo Verzenios je indicirano za zdravljenje žensk z lokalno napredovalim ali metastatskim, na hormonske receptorje (HR – *Hormone Receptor*) pozitivnim in na receptorje humanega epidermalnega rastnega faktorja 2 (HER2 – *Human Epidermal Growth Factor Receptor 2*) negativnim rakom dojk v kombinaciji z zaviralcem aromataze ali s fulvestrantom kot začetnim endokrinim zdravljenjem ali pri ženskah, ki so prejele predhodno endokrino zdravljenje. Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina (LHRH – *Luteinizing Hormone–Releasing Hormone*). **Odmerjanje in način uporabe:** Zdravljenje z zdravilom Verzenios mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. *Zdravilo Verzenios v kombinaciji z endokrinim zdravljenjem:* Priporočeni odmerek abemaciklība je 150 mg dvakrat na dan, kadar se uporablja v kombinaciji z endokrinim zdravljenjem. Zdravilo Verzenios je treba jemati, dokler ima bolnica od zdravljenja klinično korist ali do pojava nesprejemljive toksičnosti. Če bolnica bruha ali izpusti odmerek zdravila Verzenios, ji je treba naročiti, da naj naslednji odmerek vzame ob predvidenem času; dodatnega odmerka ne sme vzeti. Obvladovanje nekaterih neželenih učinkov lahko zahteva prekinitev in/ali zmanjšanje odmerka. Zdravljenje z abemaciklibom prekinite v primeru povišanja vrednosti AST in/ali ALT >3 x ZMN SKUPAJ s celokupnim bilirubinom > 2,0 x ZMN v odsotnosti holestaze ter pri bolnicah z intersticijsko pljučno boleznijo (ILD)/pnevmonitis stopnje 3 ali 4. Sočasni uporabi močnih zaviralcev CYP3A4 se je treba izogibati. Če se uporabi močnih zaviralcev CYP3A4 ni mogoče izogniti, je treba odmerek abemaciklība znižati na 100 mg dvakrat na dan. Pri bolnicah, pri katerih je bil odmerek znižan na 100 mg abemaciklība dvakrat na dan in pri katerih se sočasnemu dajanju močnega zaviralca CYP3A4 ni mogoče izogniti, je treba odmerek abemaciklība dodatno znižati na 50 mg dvakrat na dan. Pri bolnicah, pri katerih je bil odmerek znižan na 50 mg abemaciklība dvakrat na dan in pri katerih se sočasnemu dajanju močnega zaviralca CYP3A4 ni mogoče izogniti, je mogoče z odmerkom abemaciklība nadaljevati ob natančnem spremljanju znakov toksičnosti. Alternativno je mogoče odmerek abemaciklība znižati na 50 mg enkrat na dan ali prekiniti dajanje abemaciklība. Če je uporaba zaviralca CYP3A4 prekinjena, je treba odmerek abemaciklība povečati na odmerek, kakršen je bil pred uvedbo zaviralca CYP3A4 (po 3–5 razpolovnih časih zaviralca CYP3A4). Prilagajanje odmerka glede na starost in pri bolnicah z blago ali zmerno ledvično okvaro ter z blago (Child Pugh A) ali zmerno (Child Pugh B) jetrno okvaro ni potrebno. Pri dajanju abemaciklība bolnicam s hudo ledvično okvaro sta potrebna previdnost in skrbno spremljanje glede znakov toksičnosti. Način uporabe: Zdravilo Verzenios je namenjeno za peroralno uporabo. Odmerek se lahko vzame s hrano ali brez nje. Zdravilo se ne sme jemati z grenivko ali grenivkinim sokom. Bolnice naj odmerke vzamejo vsak dan ob približno istem času. Tableto je treba zaužiti celo (bolnice je pred zaužitjem ne smejo gristi, drobiti ali deliti). **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri bolnicah, ki so prejemale abemaciklib, so poročali o nevtropeniji, o večji pogostnosti okužb kot pri bolnicah, zdravljenih s placebom in endokrinim zdravljenjem, o povečanih vrednostih ALT in AST. Pri bolnicah, pri katerih se pojavi nevtropenija stopnje 3 ali 4, je priporočljivo prilagoditi odmerek. Bolnice je treba spremljati za znake in simptome globoke venske tromboze in pljučne embolije ter jih zdraviti, kot je medicinsko utemeljeno. Glede na povečanje vrednosti ALT ali AST je mogoče potrebna prilagoditev odmerka. Driska je najpogostejši neželeni učinek. Bolnice je treba ob prvem znaku tekočega blata začeti zdraviti z antidiaroiki, kot je loperamid, povečati vnos peroralnih tekočin in obvestiti zdravnika. Sočasni uporabi induktorjev CYP3A4 se je treba izogibati zaradi tveganja za zmanjšano učinkovitost abemaciklība. Bolnice z redkimi dednimi motnjami, kot so intoleranca za galaktozo, popolno pomanjkanje laktaze ali malapsorpcija glukoze/galaktoze, tega zdravila ne smejo jemati. Bolnice spremljajte glede pljučnih simptomov, ki kažejo na ILD/pnevmonitis, in jih ustrezno zdravite. Glede na stopnjo ILD/pnevmonitisa je morda potrebno prilagajanje odmerka abemaciklība. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Abemaciklib se primarno presnavlja s CYP3A4. Sočasna uporaba abemaciklība in zaviralcev CYP3A4 lahko poveča plazemsko koncentracijo abemaciklība. Uporabi močnih zaviralcev CYP3A4 sočasno z abemaciklibom se je treba izogibati. Če je močne zaviralce CYP3A4 treba dajati sočasno, je treba odmerek abemaciklība zmanjšati, nato pa bolnico skrbno spremljati glede toksičnosti. Pri bolnicah, zdravljenih z zmernimi ali šibkimi zaviralci CYP3A4, ni potrebno prilagajanje odmerka, vendar jih je treba skrbno spremljati za znake toksičnosti. Sočasni uporabi močnih induktorjev CYP3A4 (vključno, vendar ne omejeno na: karbamazepin, fenitoin, rifampicin in šentjanževko) se je treba izogibati zaradi tveganja za zmanjšano učinkovitost abemaciklība. Abemaciklib in njegovi glavni aktivni presnovki zavirajo prenašalce v ledvicah, in sicer kationski organski prenašalec 2 (OCT2) ter prenašalca MATE1. *In vivo* lahko pride do medsebojnega delovanja abemaciklība in klinično pomembnih substratov teh prenašalcev, kot je dofelitid ali kreatinin. Trenutno ni znano, ali lahko abemaciklib zmanjša učinkovitost sistemskih hormonskih kontraceptivov, zato se ženskam, ki uporabljajo sistemske hormonske kontraceptive, svetuje, da hkrati uporabljajo tudi mehansko metodo. **Neželeni učinki:** Najpogostejši neželeni učinki so driska, okužbe, nevtropenija, anemija, utrujenost, navzea, bruhanje in zmanjšanje apetita. *Zelo pogosti:* okužbe, nevtropenija, levkopenija, anemija, trombocitopenija, driska, bruhanje, navzea, zmanjšanje apetita, disgevzija, omotica, alopecija, pruritus, izpuščaj, utrujenost, pireksija, povečana vrednost alanin-aminotransferaze, povečana vrednost aspartat-aminotransferaze *Pogosti:* limfopenija, povečano solzenje, venska trombembolija, intersticijska pljučna bolezen (ILD)/pnevmonitis, suha koža, mišična šibkost *Občasni:* febrilna nevtropenija **Rok uporabnosti:** 3 leta **Posebna navodila za shranjevanje:** Za shranjevanje zdravila niso potrebna posebna navodila. **Imetnik dovoljenja za promet z zdravilom**: Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ, Utrecht, Nizozemska. Datum prve odobritve dovoljenja za promet: 27. september 2018 **Datum zadnje revizije besedila**: 19.7.2021 **Režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika.

Reference:
1. Povzetek glavnih značilnosti zdravila Verzenios. Datum zadnje revizije besedila: 19.7.2021. **2.** Povzetek glavnih značilnosti zdravila Ibrance. Dostop preverjen 10.4.2020. **3.** Povzetek glavnih značilnosti zdravila Kisqali. Dostop preverjen 10.4.2020.

Pomembno: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. Pred predpisovanjem zdravila Verzenios si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu

Eli Lilly farmacevtska družba, d.o.o., Dunajska cesta 167, 1000 Ljubljana, telefon 01 / 580 00 10, faks 01 / 569 17 05

PP-AL-SI-0110, 23.8.2021, Samo za strokovno javnost.

Emmanuel, 54
Nigerija
policist
Crohnova bolezen

Peter, 42
Slovenija
električar
rak

Bolniki morajo imeti
dostop do zdravil,
ki jih potrebujejo.

podobna biološka zdravila brez meja

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