ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

Slovensko Zdravniško Društvo
Sekcija za internistično onkologijo

KATEDRA ZA ONKOLOGIJO

IMUNOTERAPIJA V ONKOLOGIJI

ONKOLOŠKI INŠTITUT LJUBLJANA
28. SEPTEMBER 2017

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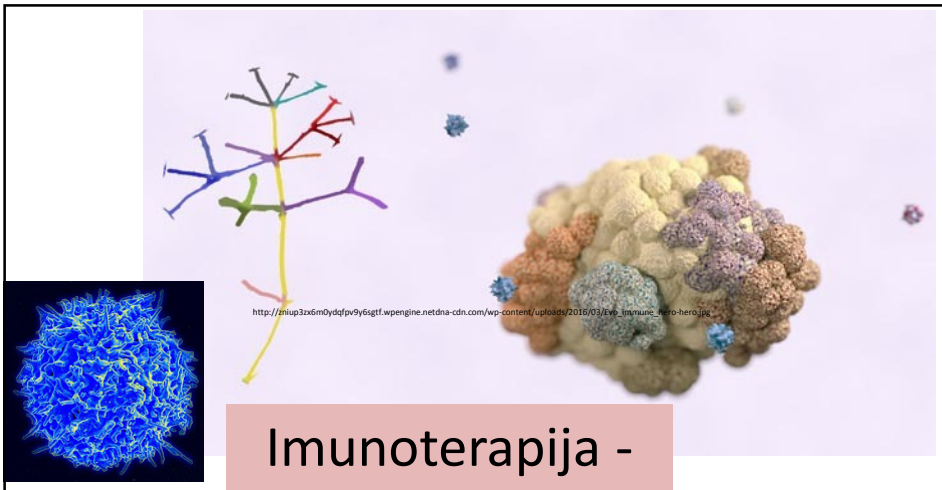
Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, september 2017

VSEBINA:

PROGRAM SREČANJA: **ČETRTEK, 28.09.2017**

07.30-09.00	**REGISTRACIJA UDELEŽENCEV**
Moderator:	**dr. Erika Matos, dr.med.,**
09.00-09.30	*Grašič Kuhar C.:* Uvodno pregledno predavanje
09.30-09.50	*Reberšek M.:* Interferoni: uporaba, delovanje, neželjeni učinki
09.50-10.05	*Knez Arbeiter J., Reberšek M.:* Predstavitev bolnika z malignim melanomom na zdravljenju z interferonom
10.05-10.25	*Boc M.:* antiCTLA-4 protitelesa: uporaba, delovanje, neželjeni učinki
10.25-10.40	*Ignjatović M., Ocvirk J.:* Predstavitev bolnika z malignim melanomom na zdravljenju z antiCTLA-4 protitelesi
10.40-11.20	**ODMOR**
11.20-11.50	**SATELITNO PREDAVANJE 1**
Moderator:	**dr. Simona Borštnar, dr.med., doc.dr. Boštjan Šeruga, dr.med., dr. Erika Matos, dr.med., dr. Rotar-Pavlič, dr.med.**
11.50-12.10	*Ocvirk J.:* antiPD-1 protitelesa: uporaba, delovanje, neželeni učinki
12.10-12.25	*Mencinger M.:* Predstavitev bolnika z malignomom GUT na zdravljenju z antiPD-L1 prostitelesi
12.25-12.55	*Škrbinc B.:* antiPD-L1 protitelesa: uporaba, delovanje, neželeni učinki
12.55-13.10	*Unk M.:* Predstavitev bolnika z rakom pljuč na zdravljenju z antiPD-1 protitelesi
13.10-14.10	**SATELITNO PREDAVANJE 2**
14.10-14.25	**ZAKLJUČKI SREČANJA**

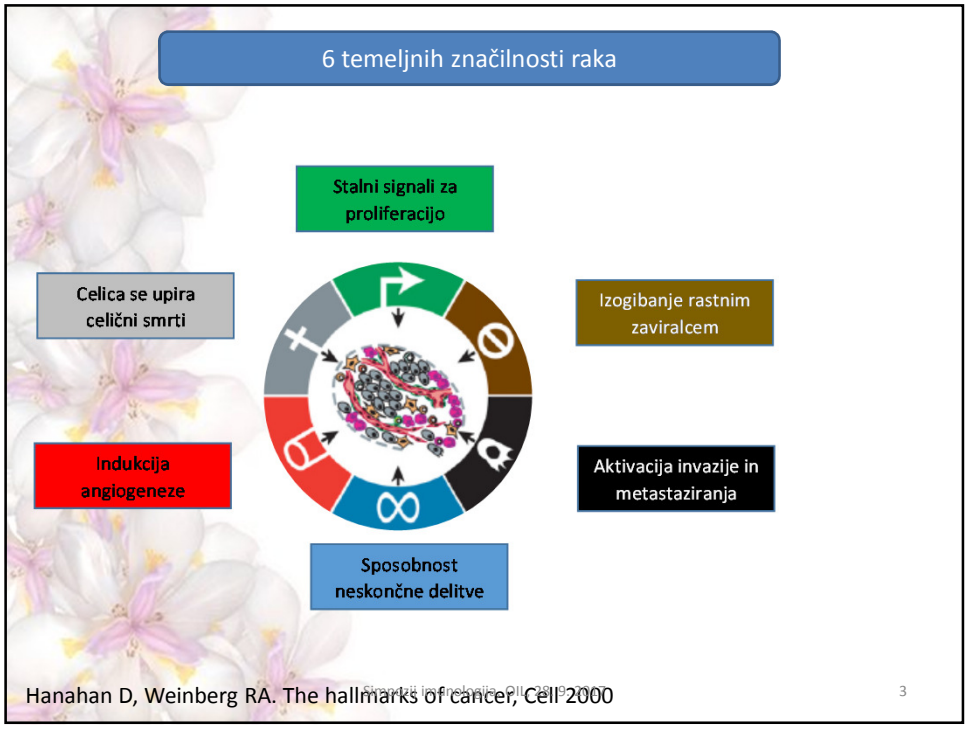


Imunoterapija - *pregled področja*

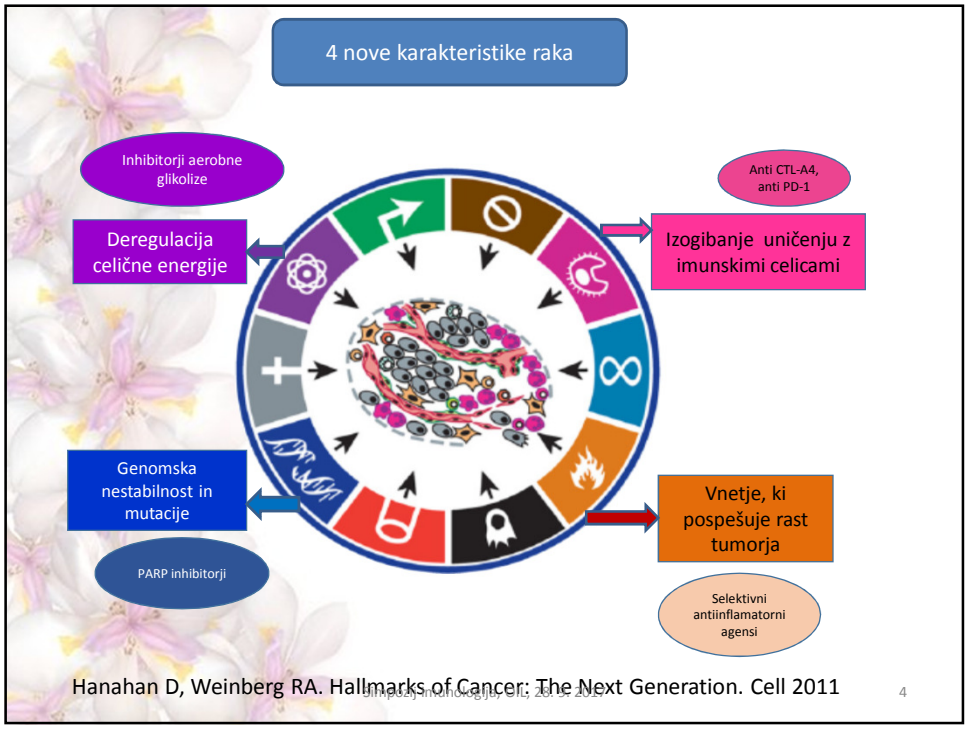
Doc. dr. Cvetka Grašič Kuhar, dr. med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana

Zasnova predavanja

- Temeljne značilnosti raka – ena od teh je tudi izogibanje imunskemu sistemu
- Zgodovina imunoterapije
- Imunski cikel pri raku
- Vloga koinhibitornih in kostimulativnih dejavnikov
- Implementacija imunoterapije pri nekaterih solidnih rakih in limfomih
- Prva odobritev imunoterapije ne glede na tip raka
- Neželeni učinki imunoterapije in obvladovanje le-teh



Hanahan D, Weinberg RA. The hallmarks of cancer, Cell 2000



Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011

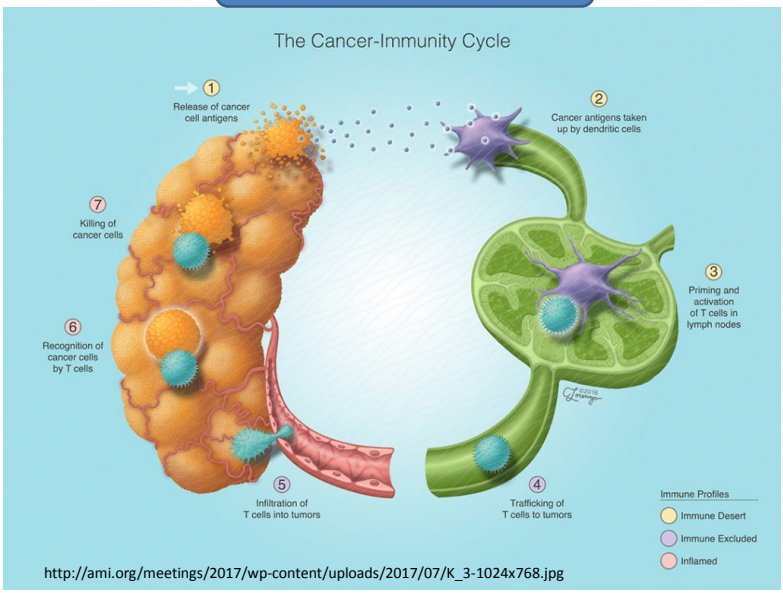
Mejniki v razvoju imunoterapije

Cancer Immunotherapy, Part 1: Current Strategies and Agents

C. Lee Ventola, MS

1893	Dr. William B. Coley izumi Coleyev toksin
1899	Parke-Davis & Company proizvaja Coleyev toksin
1915	Memorial Hospital (sedaj MSK) prepove Coleyev toksin, preferira RADIOTERAPIJO
1943	Pričetek uporabe KEMOTERAPIJE pri zdravljenju raka
1953	Helen Coley Nauts (hči dr. Coleya) objavi očetove izsledke in ustanovi Cancer Research Institute v New Yorku
1957	Dr. E. Donnall uspešno zdravi bolnika z levkemijo z alogeno transplantacijo
1971	Predsednik Nixon objavi vojno proti raku
1986	FDA odobri rekombinantni IFN-α za lasastocelično levkemijo
1988	Dr. Rosenberg poroča o ozdravitvi melanoma z aktiviranimi imunskimi celicami in citokini
1992	FDA odobri rekomb. humani IL-2 za rak ledvic
1996	FDA odobri prvo monoklon. protitelo za B-celične limfome
2010	FDA odobri vakcino za rak prostate (na bazi dendritičnih celic)
2011	FDA odobri prvo anti-CTLA-4 zdravilo (blokator imunskih stikal) za metastaski maligni melanom
2014	FDA odobri prvo anti-PD-1 zdravilo (blokator imunskih stikal) za maligni melanom
2017	FDA odobri anti PD-1 zdravilo za Msi-high tumorje, ne glede na lokacijo raka

Protitumorski imunski cikel



http://ami.org/meetings/2017/wp-content/uploads/2017/07/K_3-1024x768.jpg

Open Access Educational video

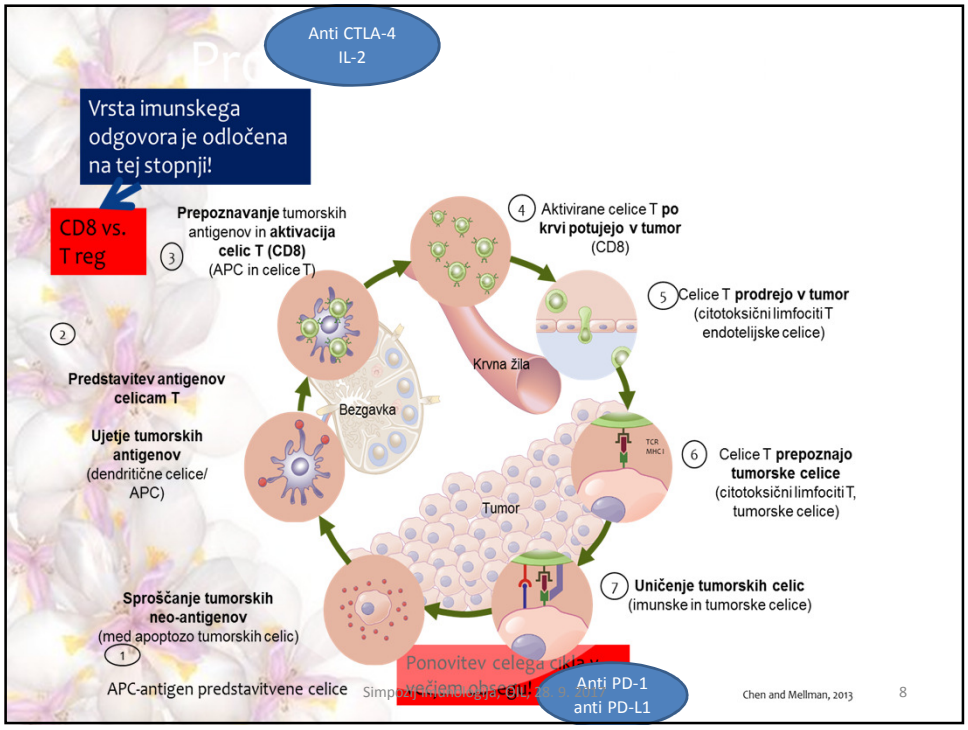
ESMO Open Cancer Horizons

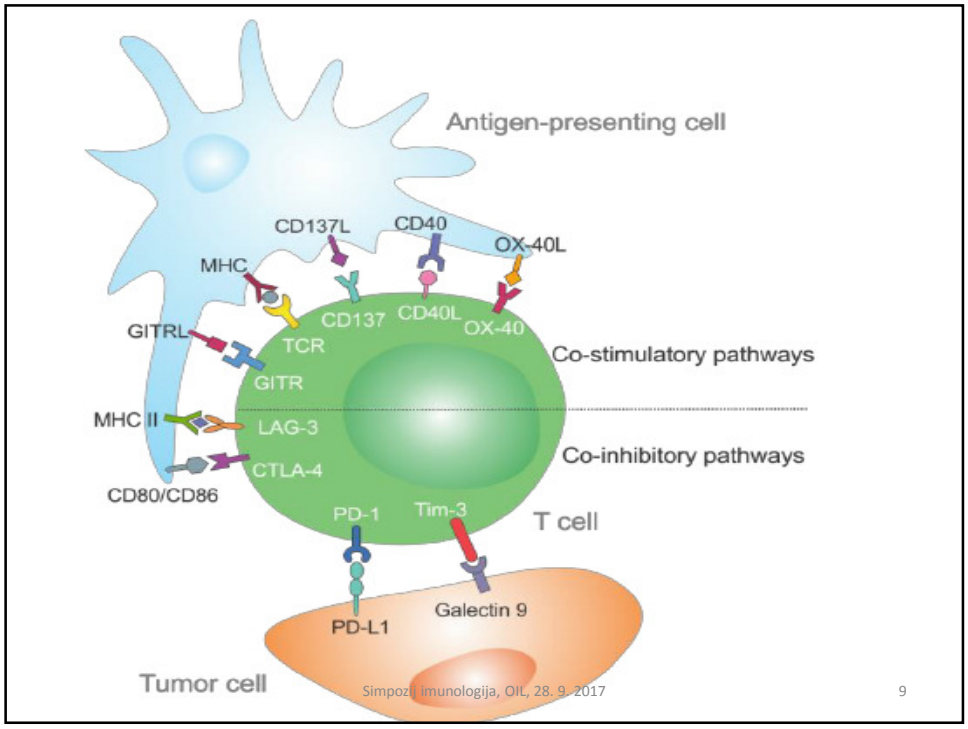
CrossMark

Cancer immune cycle: a video introduction to the interaction between cancer and the immune system

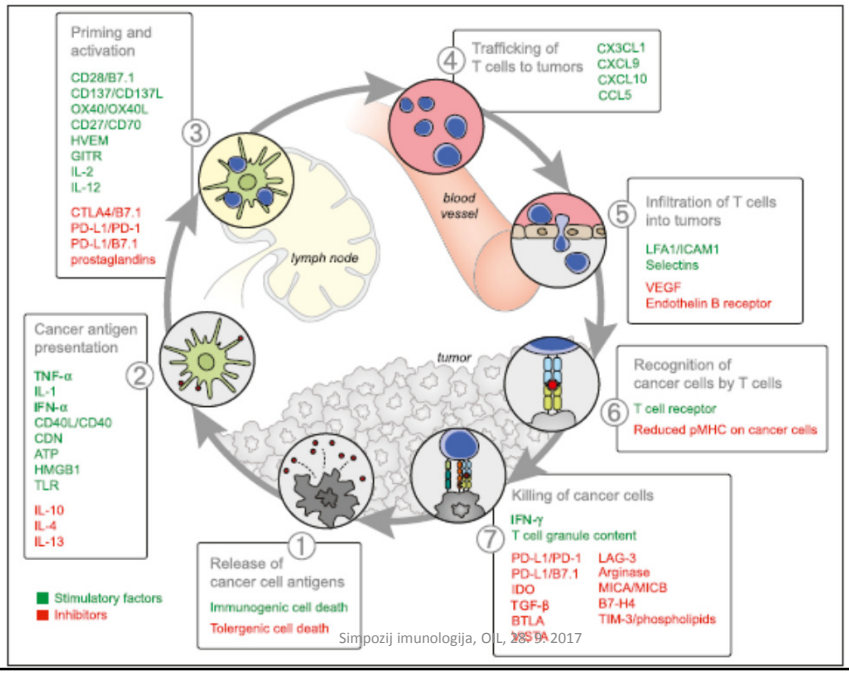
Matthias Preusser, Anna S Berghoff, Christiane Thallinger, Christoph C Zielinski

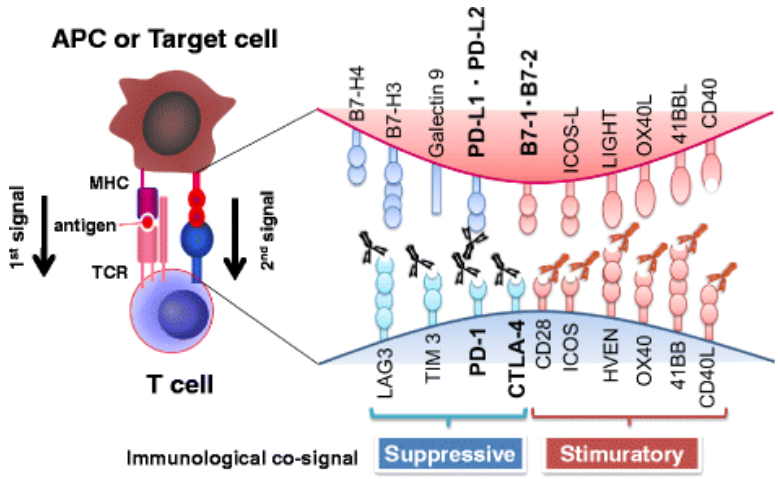
http://players.brightcove.net/2696240571001/default_default/index.html?videoId=4805669863001





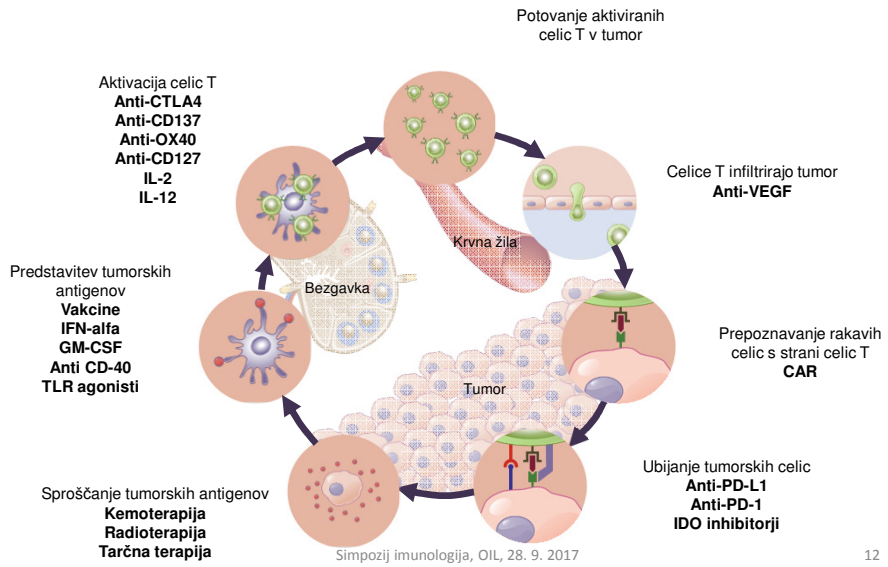
IMUNSKI CIKEL- STIMULATORNI in INHIBITORNI FAKTORJI

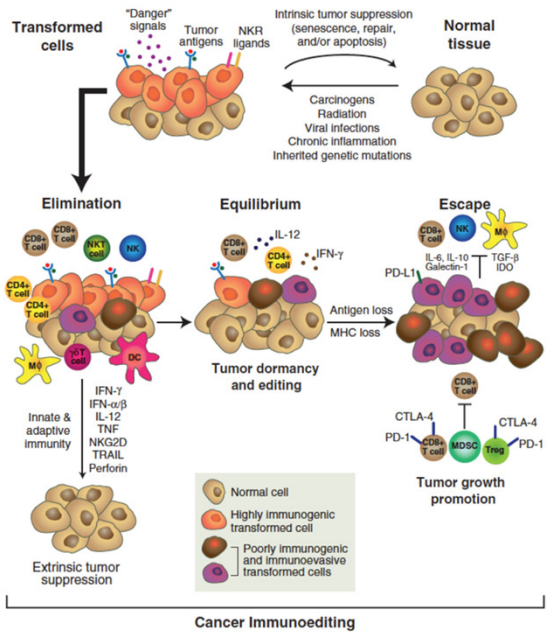




http://media.springernature.com/full/springer-static/image/art%3A10.1186%2Fs12929-017-0329-9/MediaObjects/12929_2017_329_Fig1_HTML.gif

Terapije, ki lahko vplivajo na protitumorski imunski cikel





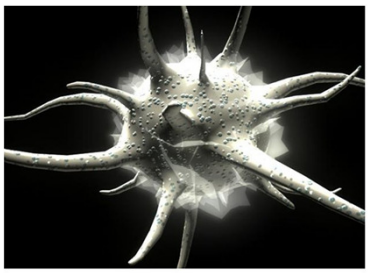
CILJ IMUNOTERAPIJE pri zdravljenju raka

- Pričeti ali ponovno vzpodbuditi samovzdrževalni imunski cikel pri raku
- Pospešiti ali ojačiti imunski cikel, vendar ne toliko, da bi vzpodbudil avtoimunske odgovore

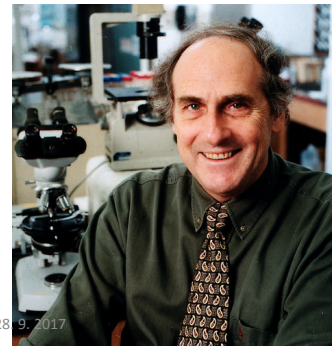
- Pospešitev celotnega cikla imunosti povzroča stranske učinke na normalna tkiva
- Najbolj učinkovito bi bilo selektivno vplivati na najšibkejši člen pri določenem bolniku
- Najšibkejši člen je trenutno imunosupresija v tumorskem mikrookolju

Dendritične celice

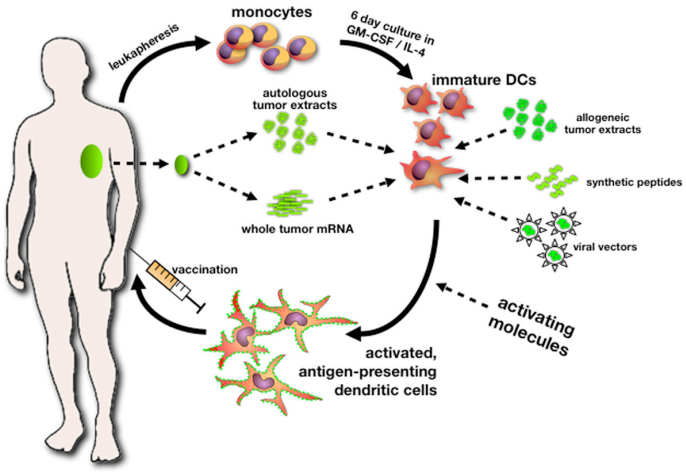
- Zbolel je za rakom prostate, živel je 4,5 let
- Prejel je vso konvencionalno th. in 8-9 odmerkov vakcin z lastnimi dendritičnimi celicami
- 2011: Nobelova nagrada iz imunologije



Ralph.M.Steinman, 1973

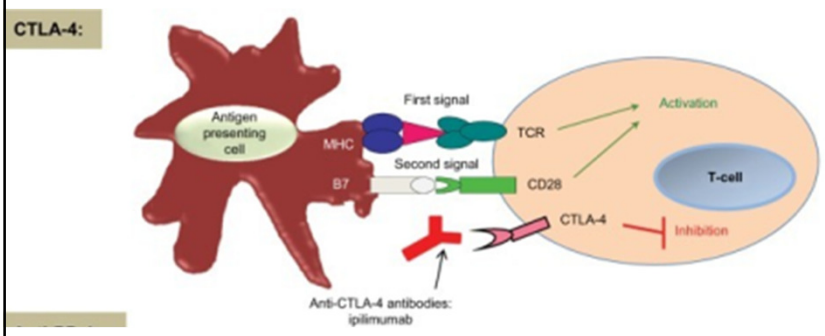


Vakcine z dendritičnimi celicami



http://www.frontiersin.org/files/Articles/12154/fonc-01-00022-r2/image_m/fonc-01-00022-g002.jpg

Princip delovanja anti-CTLA-4 protiteles



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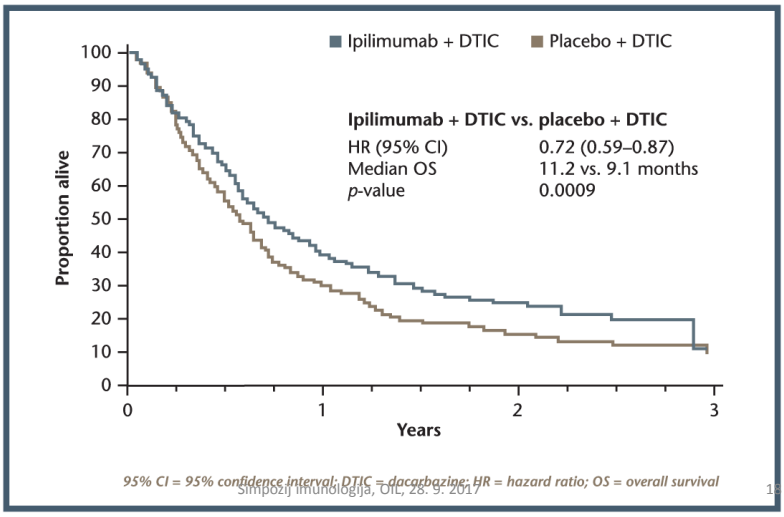
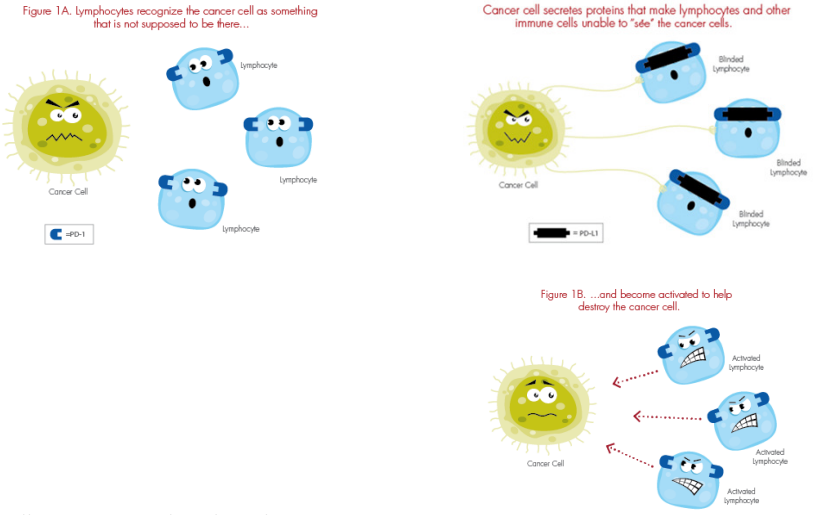
Ipililumab pri malignem melanomu

Figure 1. Overall survival

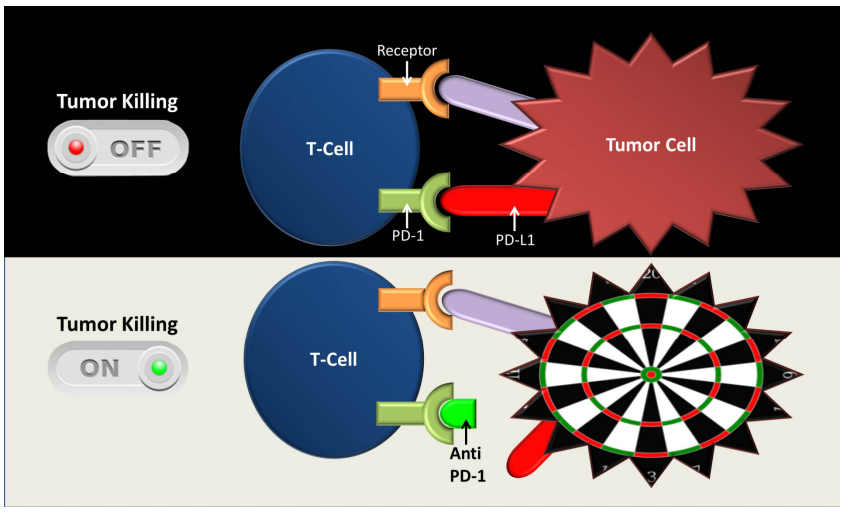


95% CI = 95% confidence interval; DTIC = dacarbazine; HR = hazard ratio; OS = overall survival

IMUNOTERAPIJA proti PD-1

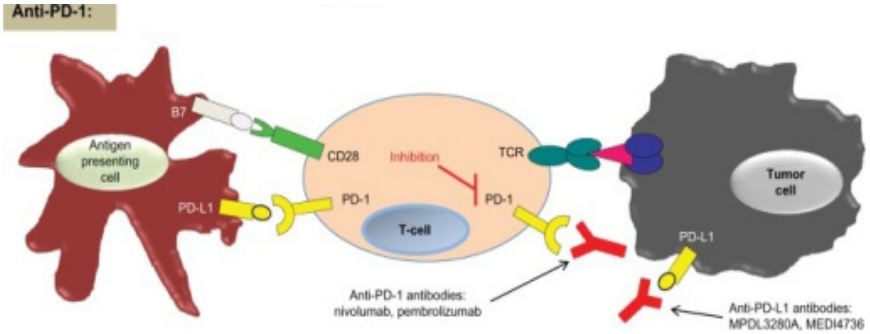


http://www.freetobreathe.org/images/uploads/immunotherapy-figure1.png



https://nihdirectorsblog.files.wordpress.com/2015/06/pd-1-pathway.jpg

Princip delovanja anti-PD-, anti PD-L1 protiteles



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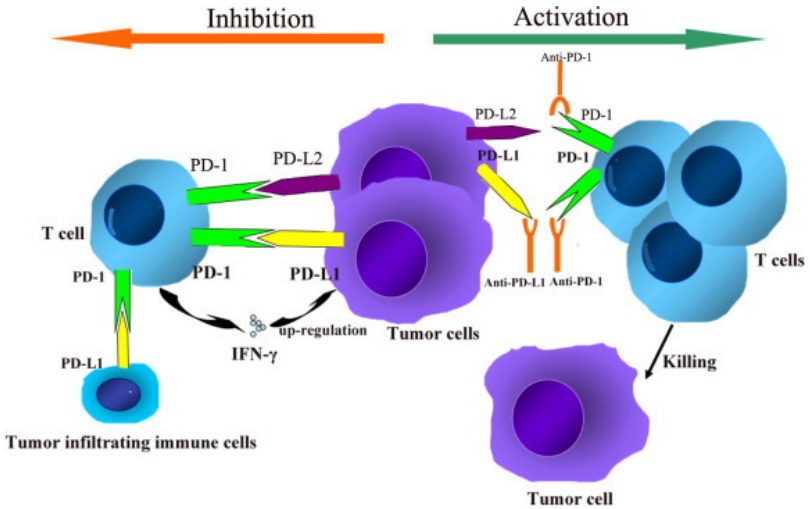
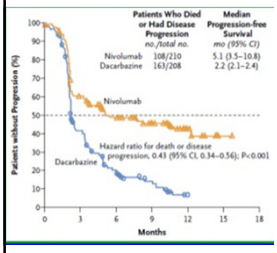


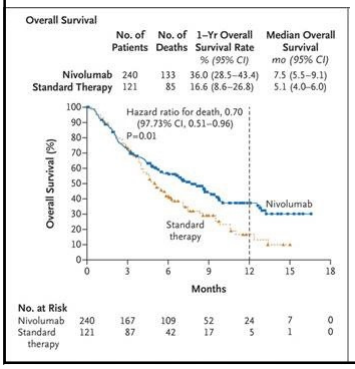
Programmed cell death protein 1, also known as PD-1 and CD279 (cluster of differentiation 279), is a cell surface receptor that plays an important role in down-regulating the immune system and promoting self tolerance by suppressing T cell inflammatory activity. PD-1 is an immune checkpoint and guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (anti-inflammatory, suppressive T cells).[5][6]

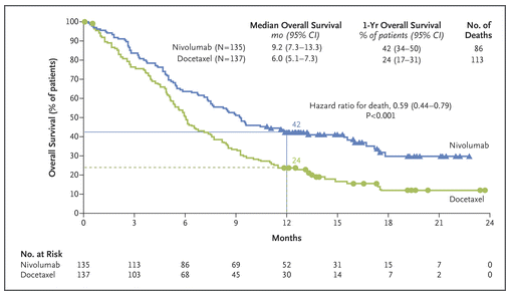
So PD-1 inhibits the immune system. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells.

http://ars.els-cdn.com/content/image/1-s2.0-S0305737215001966-gr1.jpg

Nivolumab (anti PD-1) pri malignem melanomu, raku glave in vratu ter raku pljuč





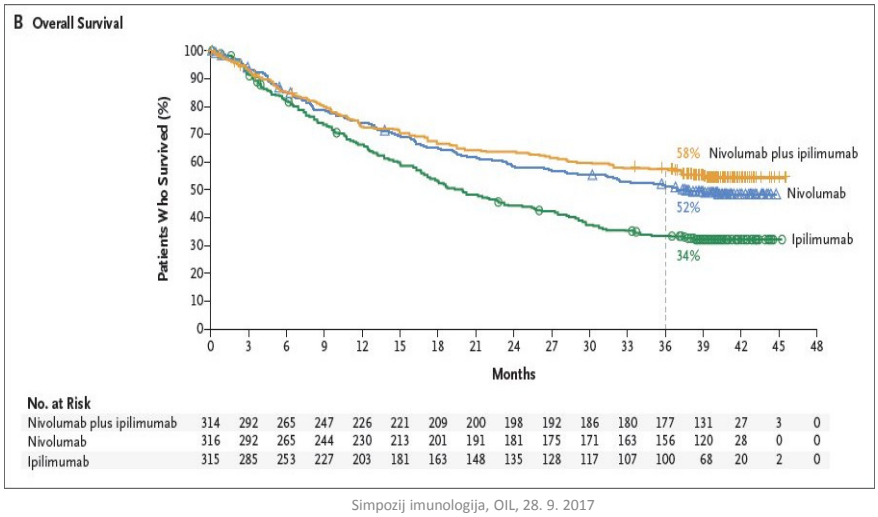


http://blogs.nejm.org/now/wp-content/uploads/sites/6/2016/10/nivolumab.jpg

https://image.slidesharecdn.com/ascorev6132015a-share-150713203745-lva1-app6891/95/asco-2015-melanoma-immunotherapy-30-638.jpg?cb=1436820441

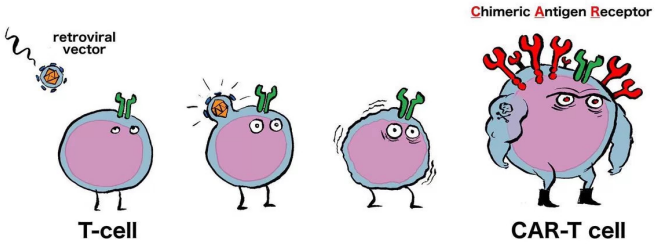
http://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2015/nejm_2015.373.issue-2/nejmoa1504627/20161115/images/medium/nejmoa1504627_f1.gif

Napredovali maligni melanom Kombinirano zdravljenje, ESMO 2017



https://pbs.twimg.com/media/DJbom06UEAAQejo.jpg

Generating super-soldiers
the production of CAR-T cells



https://i2.wp.com/www.sciwri.club/wp-content/uploads/2017/04/C9sPrnTXUAAtTP5.jpg?fit=1200%2C665

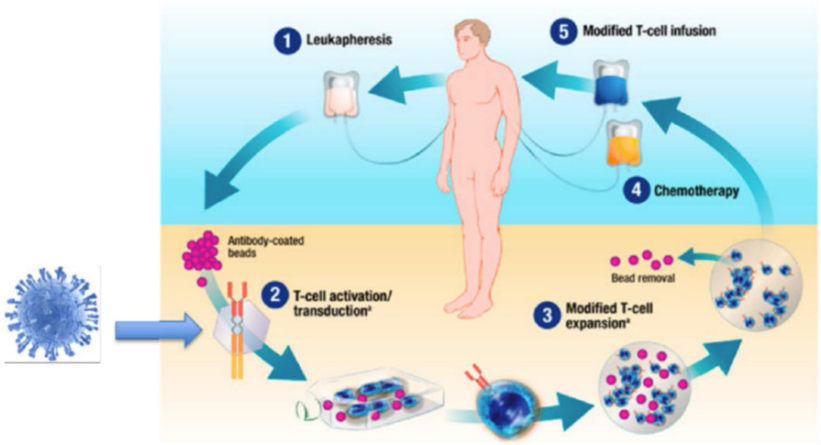


Figure 1. Overview of CAR T cell manufacturing process.
Modified from (Levine, 2015)

https://endpts.com/wp-content/uploads/2017/07/cartmanfda-1024x636.png

tisagenlecleucel

- Za ponovitev/refraktarno B-ALL (3.-25. let)
- Akutna toksičnost: sidrom sproščanja citokinov, odpoved ledvic, nevrotoksičnost, koagulopatije, možganski edem. Bolniki potrebujejo intenzivno nego, pogosto umetno ventilaciji in hemodializo.
- Tveganje za varnost (pozne posledice): Zaradi inkorporacije lentivirusa (ali retrovirusa pri drugih CAR T celicah) v genom, obstaja tveganje, da bo vstavljen virus pridobil sposobnost replikacije, da bo povzročil insercijsko mutagenost (sekundarni raki) in genotoksičnost (prenos genskih okvar na potomce).
- Spremljanje v raziskavi je kratkotrajno (mFU<1 leto)

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

U.S. FOOD & DRUG ADMINISTRATION

BLA 125646

Tisagenlecleucel

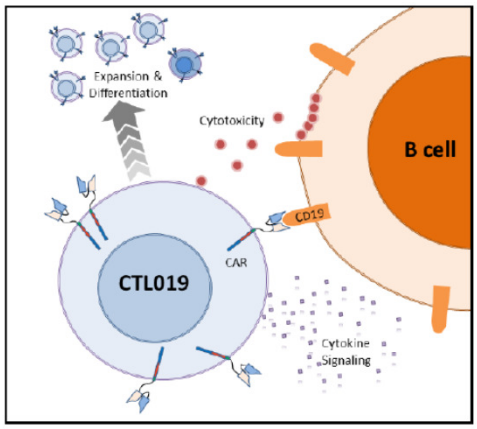


Figure 2. Schematic representation of tisagenlecleucel mechanisms of action.
Upon CAR engagement with CD19 on the surface of a B cell, tisagenlecleucel may produce cytokines for autocrine and paracrine effects necessary for CAR T cell expansion, differentiation, and release of cytotoxic granules.

tisagenlecleucel

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

Figure 8. Analysis of Duration of Response (DOR)

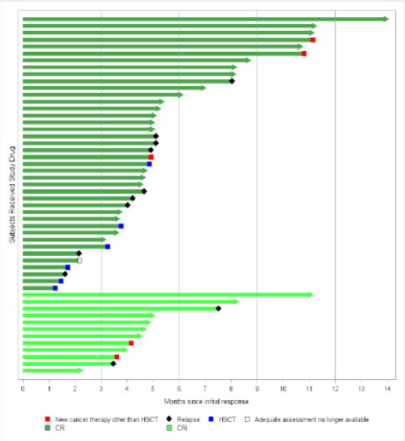
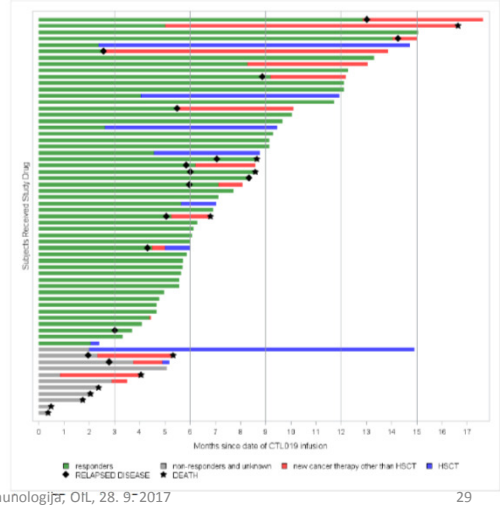


Figure 9. Overall Survival for Study B2202



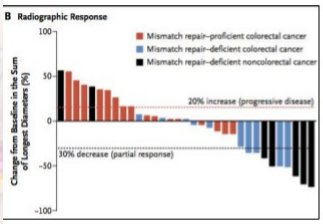
ORR 52/63 (82,5%)
CR 40/63; 29 of them were still in remission
mFU< 1 year

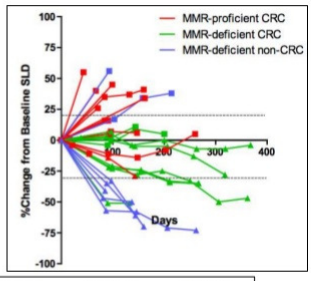
Table 1. Approved indications for KPIs

Drug	Indications	EMA/FDA approval
Ipilimumab	Metastatic melanoma	EMA + FDA
	Adjuvant therapy stage III melanoma	FDA
Nivolumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC	EMA + FDA
	2nd line metastatic RCC	EMA + FDA
	Classical Hodgkin's disease[a]	EMA + FDA
	Recurrent or metastatic SCCHN[b]	EMA + FDA
	Locally advanced or metastatic UCC[c]	EMA + FDA
Pembrolizumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC (PD-L1 ≥ 1%)	EMA + FDA
	1st line metastatic NSCLC (PD-L1 ≥ 50%)	EMA + FDA
	1st line metastatic NSCLC in combination with pemetrexed + carboplatin	FDA
	Classical Hodgkin's disease	EMA[a] + FDA[d]
	Locally advanced or metastatic UCC[c]	FDA
	MSI-H or MMR deficient metastatic malignancies[e]	FDA
Atezolizumab	Locally advanced or metastatic UCC[c]	FDA
	2nd line metastatic NSCLC	FDA
Avelumab	Locally advanced or metastatic UCC[c]	FDA
	Metastatic Merkel cell carcinoma	FDA
Durvalumab	Locally advanced or metastatic UCC[c]	FDA
Ipilimumab + nivolumab	Metastatic melanoma	EMA + FDA

Prva odobritev imunoterapije ne glede na tip raka

Pembrolizumab: Response Rate

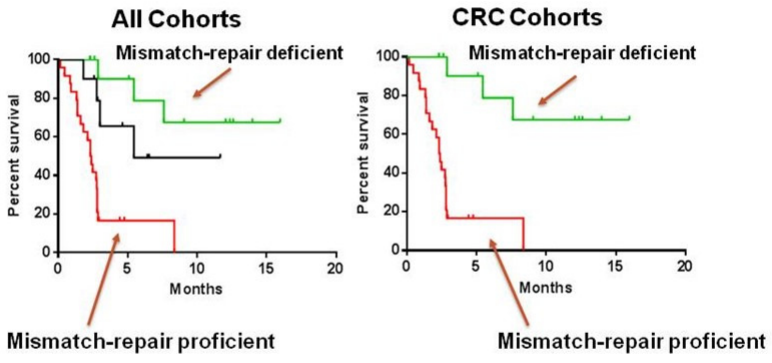




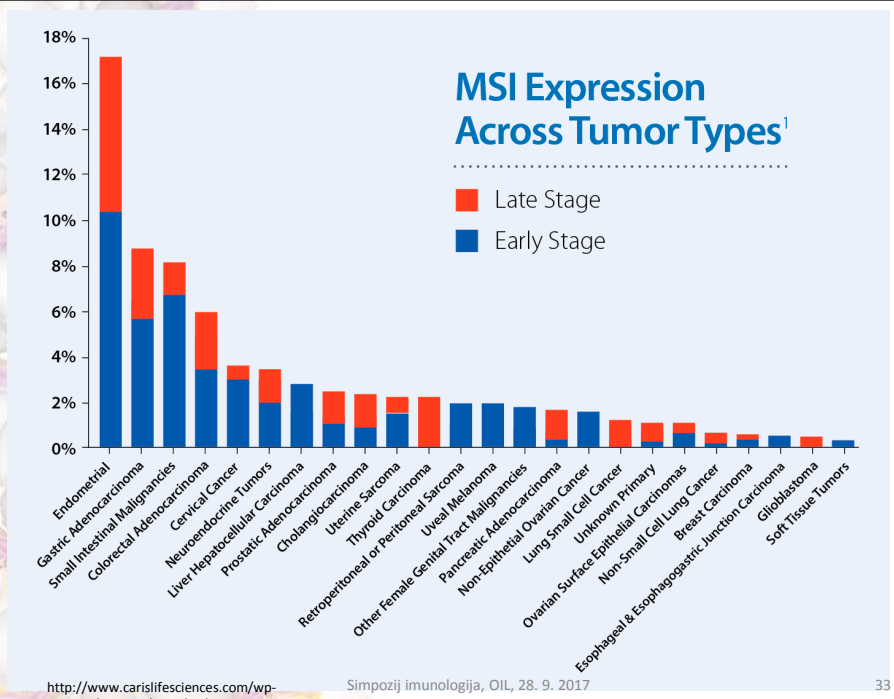
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)

https://image.slidesharecdn.com/ue0obckrkctdjkznxe9d-signature-00f4c4d096b7bd6e1bb05b55f88850f9ce0ca6124b2323f2bd00ddd507b81dc2-poli-150905153635-lva1-app6891/95/immunotherapy-for-colorectal-cancer-17-638.jpg?cb=1441468045

Progression-Free Survival



Presented By Dung Le at 2015 ASCO Annual Meeting



http://www.carislifesciences.com/wp-content/uploads/2017/06/MSI_Chart.png

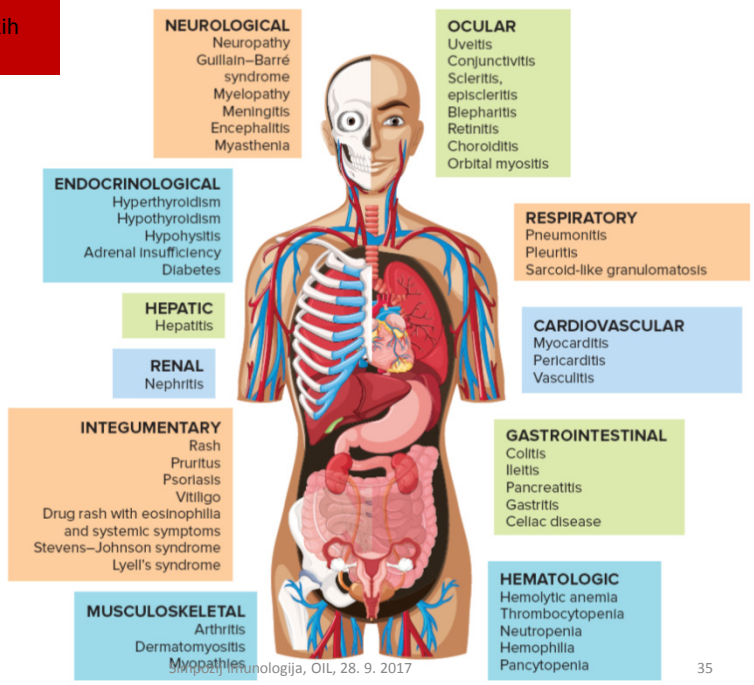
ESMO

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Neželeni učinki blokatorjev imunskih stikal



Čas do nastopa toksičnosti

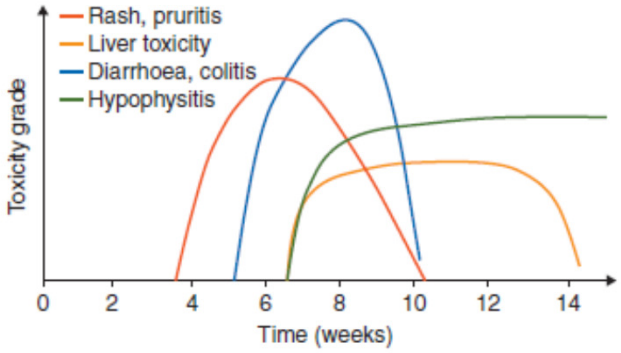
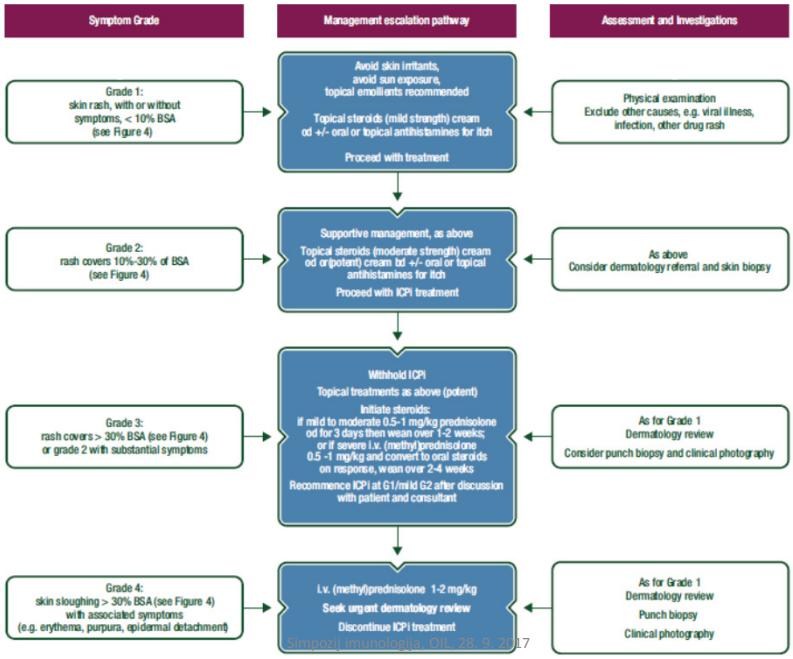


Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.

Primer: Obravnava kožne toksičnosti



Zaključek

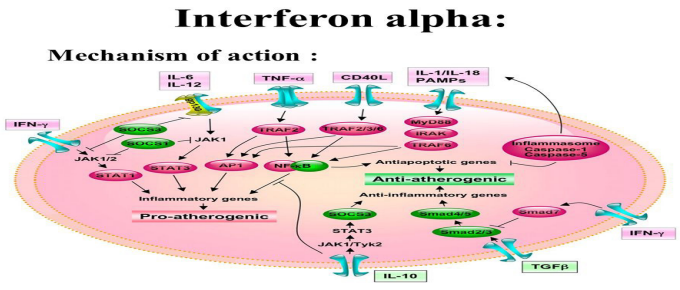
- Pomen imunskega sistema pri poteku rakave bolezni se je nakazoval že dolgo (spontane remisije…)
- Protitumorski imunski cikel - osnova za razumevanje delovanja
- Neželeni učinki
- Nevarnosti pri vnosu virusnega vektorja (CAR-T celice)

INTERFERONI V SISTEMSKEM ONKOLOŠKEM ZDRAVLJENJU 28.9.2017

Asist.dr.Martina Reberšek, dr.med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana

Definicija interferonov

- Interferoni so majhni proteinski in glikoproteinski citokini, ki jih izločajo limfociti T, fibroblasti in druge gostiteljeve celice kot odgovor na virusno okužbo, okužbe z bakterijami in paraziti, ter drugimi stimulusi kot so npr. tumorske celice
- Zavirajo virusno proliferacijo, spodbujajo fagocitno aktivnost makrofagov, aktivirajo naravne celice ubijalke, povečajo citotoksičnot limfocitov T



Funkcija interferonov

- Dve glavni skupini:
- delujejo protivirusno
- modulirajo delovanje imunskega sistema

- V humani medicini jih predpisujemo za zdravljenje virusnih okužb (hepatitis B in C), multiple skleroze in raka
- V onkologiji: zdravljenje levkemij, limfomov, Kaposi sarkoma in malignega melanoma

Vloga delovanja interferonov

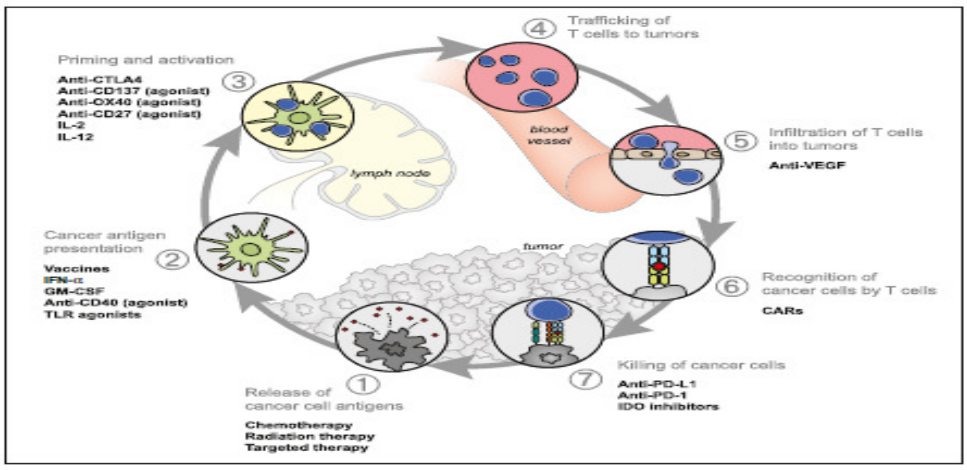


Figure 3. Therapies that Might Affect the Cancer-Immunity Cycle

Chen DS, Mellman I. Oncology Meets Immunology:TheCancer-Immunity Cycle. Immunity 39, July 25, 2013 ª2013 Elsevier Inc

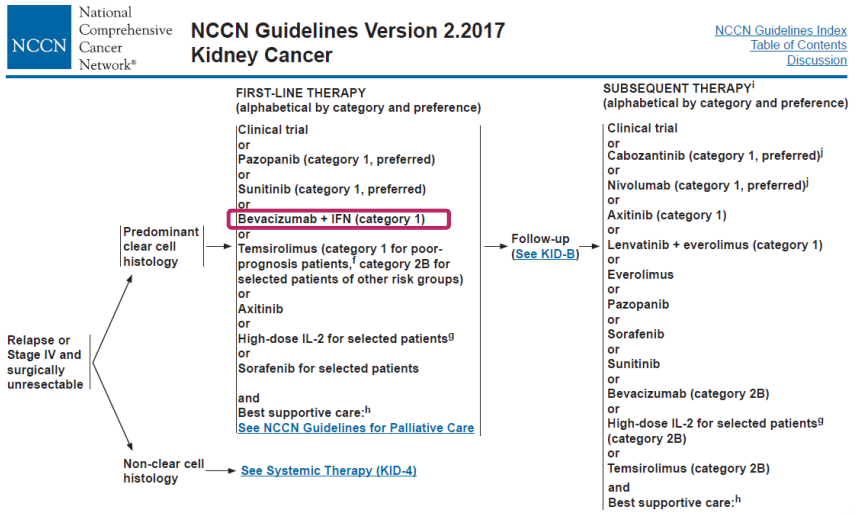
Farmacevtske oblike interferonov

- interferon α2a in α2b
- humani levkocitni interferon α
- interferon β1a in β1b
- pegilirane oblike interferonov

TERAPEVTSKE INDIKACIJE V ONKOLOGIJI

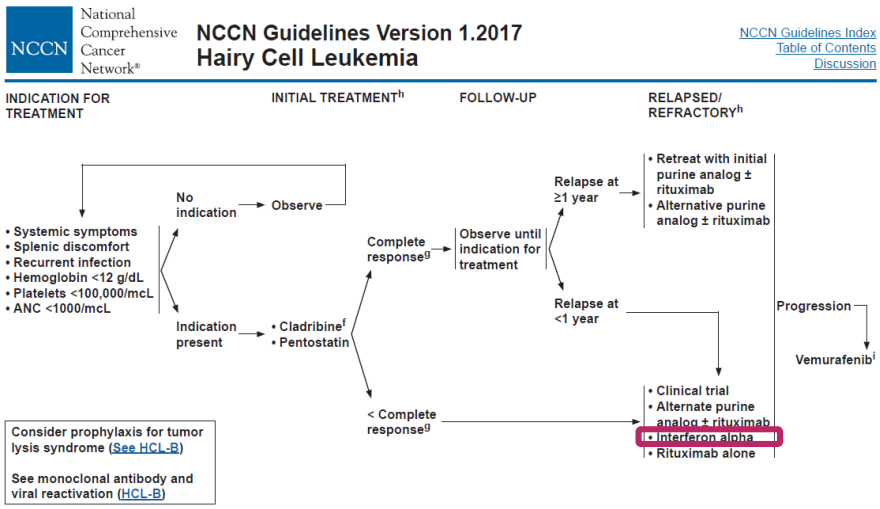
- Limfomi, levkemije (nodularni limfom, dlakastocelična levkemija, T- celični limfom kože)
- Kaposi sarkom
- Metastatski ledvični karcinom
- Melanom (adjuvantno zdravljenje)

Metastatski ledvični karcinom



IFN 9 MIU 3x/teden s.c..

Dlakasto-celična levkemija



ADJUVANTNO SISTEMSKO ZDRAVLJENJE MELANOMA

- IFN-α2b v visokih odmerkih se je v kliničnih raziskavah edini izkazal za učinkovitega v adjuvantnem zdravljenju bolnikov z melanomom z visokih tveganjem za ponovitev bolezni (stadij II, III)
- Podaljša celokupno preživetje in čas do ponovitve bolezni

Klinične raziskave- visokodozni IFN

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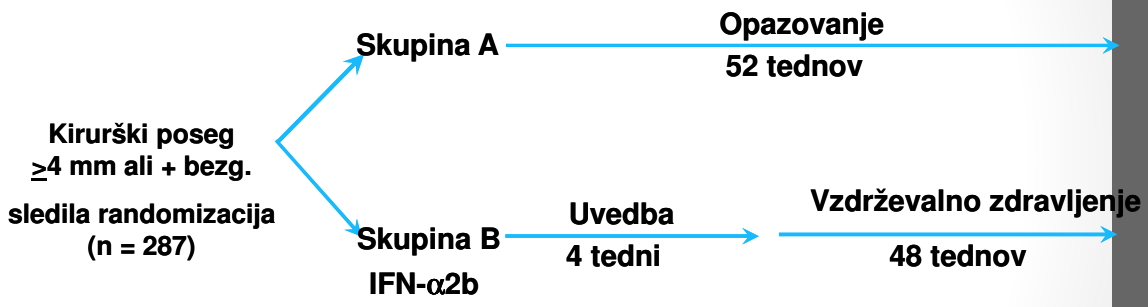
Table 6. High-Dose Interferon[a]

Trial[b]	References	IFN type	Patients, n		Median Follow-up	Statistically Significant Impact of IFN	
			IFN	Obs		Relapse-free Survival[c]	Survival[d]
ECOG 1684	Kirkwood 1996[378] Kirkwood 2004[366]	2b	143	137	6.9 y 12.6 y	Yes; $P = .0023$ Yes; $P = .02$	Yes; $P = .0237$ No
ECOG 1690	Kirkwood 2000[365] Kirkwood 2004[366]	2b	215	212	4.3 y 6.6 y	Yes; $P = .05$ Trend; $P = .09$	No No
ECOG 1694	Kirkwood 2001[379] Kirkwood 2004[366]	2b	440	440[e]	1.3 y 2.1 y	Yes; $P = .0027$ Yes; $P = .006$	Yes; $P = .0147$ Yes; $P = .04$
ECOG E2696	Kirkwood 2001[379] Kirkwood 2004[366]	2b	72[f]	35[f]	1.9 y 2.8 y	Yes; $P = .03$ No	No No
Sunbelt Trial	McMasters 2016[380]	2b	112	106	5.9 y	No	No

IFN, interferon; NR, not reported; Obs, observation
[a]High-dose IFN regimen: 20 MU/m²/d IV for 5 d/wk for 4 weeks, then 10 MU/m²/d SC for 3 d/wk for 48 weeks.
[b]All prospective, randomized, multicenter studies comparing adjuvant interferon with observation in patients with fully resected cutaneus non-metastatic melanoma at high risk for recurrence.
[c]Relapse-free survival for ECOG trials, disease-free survival for Sunbelt Trial.
[d]Overall survival or melanoma-specific survival.
[e]Control was GM2-KLH21 vaccine (GMK) instead of observation.
[f]Treatment arms: A, GMK + High-dose IFN alfa-2b (n = 36); B: GMK alone; then GMK + high-dose IFN alfa-2b (n = 36); C: GMK alone (n = 35); $P = .03$ for relapse-free survival from B versus C using Cox regression analysis.

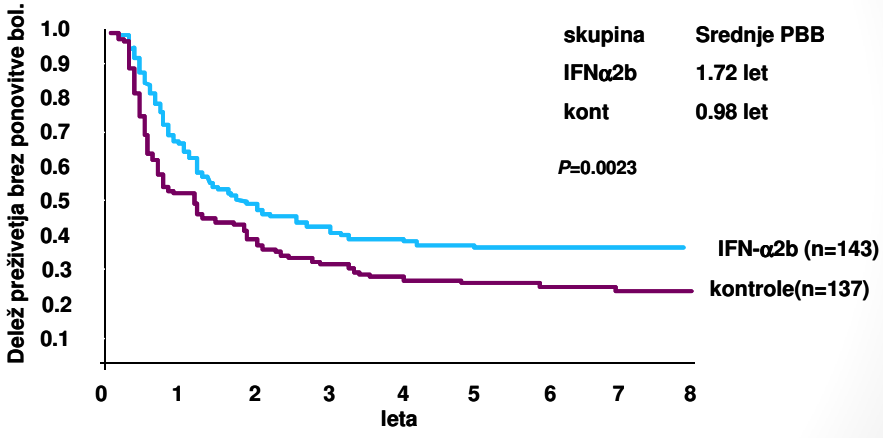
KLINIČNA RAZISKAVA E1684:



Uvedba: 20 MIU/m² i.v. 5x tedensko x 4 tedni
Vzdrževalno zdravljenje: 10 MIU/m² s.c. 3x tedensko x 48 tednov

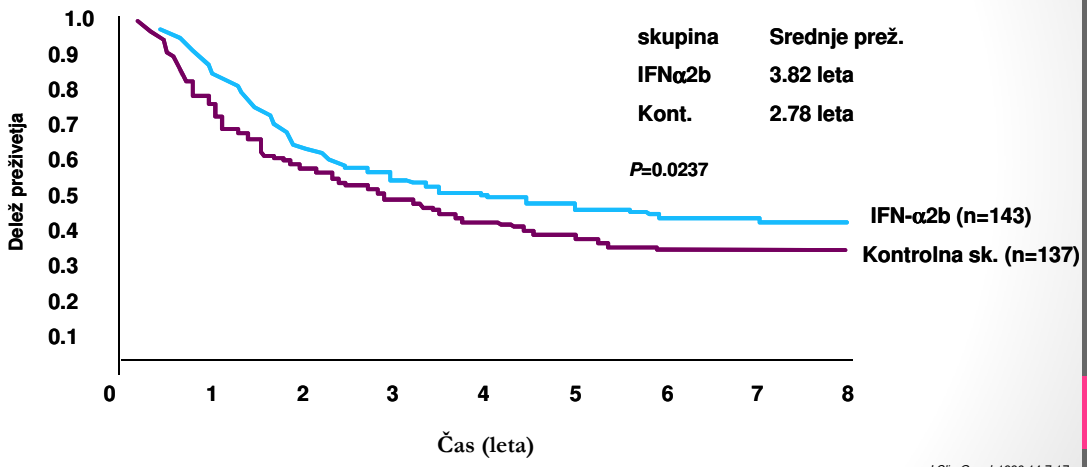
J Clin Oncol. 1996;14:7-17.

E1684:
PREŽIVETJE BREZ PONOVITVE BOLEZNI



J Clin Oncol. 1996;14:7-17.

E1684:
CELOKUPNO PREŽIVETJE



J Clin Oncol. 1996;14:7-17.

TNM klasifikacija

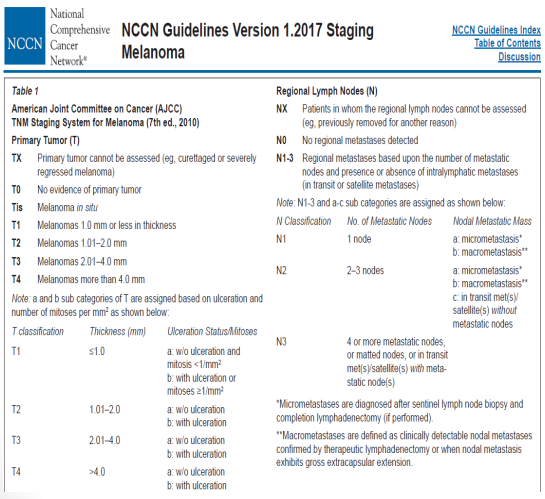


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Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
T1	Melanomas 1.0 mm or less in thickness
T2	Melanomas 1.01–2.0 mm
T3	Melanomas 2.01–4.0 mm
T4	Melanomas more than 4.0 mm

Note: a and b sub categories of T are assigned based on ulceration and number of mitoses per mm² as shown below:

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

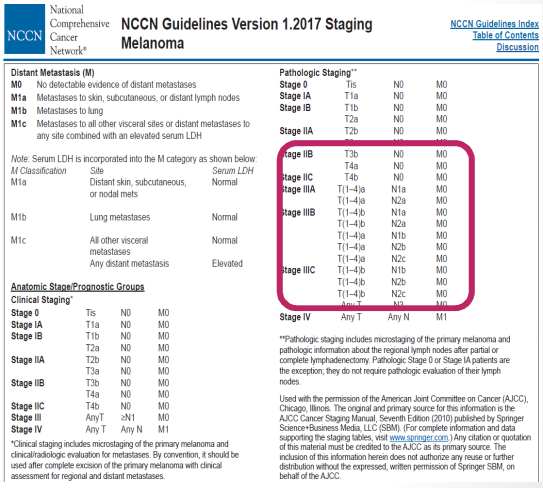
NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2–3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* metastatic node(s)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.



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Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic Stage/Prognostic Groups
Clinical Staging*

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	AnyT	≥N1	M0
Stage IV	Any T	Any N	M1

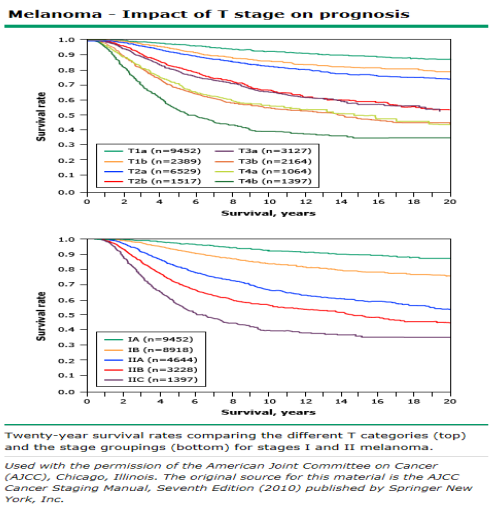
*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

Pathologic Staging**

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T(1–4)a	N1a	M0
	T(1–4)a	N2a	M0
Stage IIIB	T(1–4)b	N1a	M0
	T(1–4)b	N2a	M0
	T(1–4)a	N1b	M0
	T(1–4)a	N2b	M0
	T(1–4)a	N2c	M0
Stage IIIC	T(1–4)b	N1b	M0
	T(1–4)b	N2b	M0
	T(1–4)b	N2c	M0
Stage IV	Any T	Any N	M1

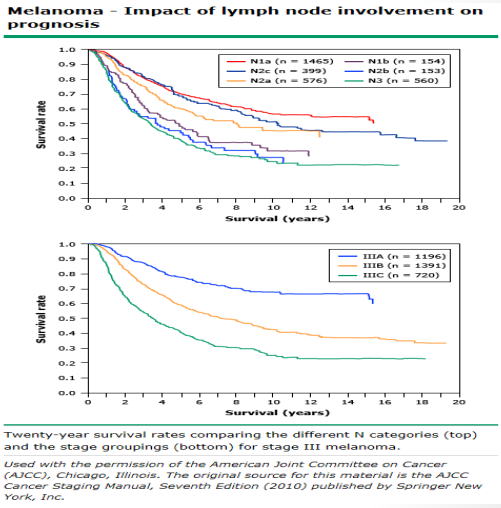
**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Vpliv T and N stadija na prognozo



Twenty-year survival rates comparing the different T categories (top) and the stage groupings (bottom) for stages I and II melanoma.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.



Twenty-year survival rates comparing the different N categories (top) and the stage groupings (bottom) for stage III melanoma.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

SHEMA PREJEMANJA IFN-α2b

UVEDBA

20 milijonov IE/m² na dan, i.v. , 20 min infuzija

5 x na teden, 4 tedni

kontrola enkrat na teden (KKS, DKS, hepatogram)

VZDRŽEVALNO ZDRAVLJENJE

10 milijonov IE/m² na dan, s.c.

3 x na teden (vsak drugi dan), 48 tednov

kontrola dvakrat mesečno, izmenično osebni zdravnik (KKS, DKS, hepatogram) in internist onkolog (tudi ostalo)

RELATIVNE KONTRAINDIKACIJE

- Srčnožilne in pljučne bolezni (KOPB)
- Huda ledvična in jeterna insuficienca
- Metabolne bolezni
- Psihiatrične bolezni, epilepsija
- Neurejena sladkorna bolezen
- Bolezni ščitnice
- Avtoimune bolezni
- Imunosupresija po transplantaciji
- Starost > 70 let ?

NEŽELENI UČINKI ZDRAVLJENJA (1)

- Splošni simptomi: **zvišana telesna temperatura, gripozni sindrom, utrujenost, mialgija, artralgije, splošno slabše počutje**
- Presnovne in prehranske motnje: **anoreksija, hujšanje**, dehidracija, žeja, ↓Ca, ↑urat, hipertrigliceridemija
- Zavora kostnega mozga: **levkopenija**, trombocitopenija,…
- Motnje delovanja jeter: **↑AST/ALT**, hepatomegalija
- Bolezni živčevja: **omotica, glavobol, zmanjšana koncentracija, tremor,…**
- Večja dojemljivost za infekcijske bolezni: virusne okužbe, …

NEŽELENI UČINKI ZDRAVLJENJA (2)

- Psihiatrične motnje: **čustvena labilnost, razdražljivost, nespečnost, depresija,** agresivnost , samomorilne misli …

  (Psihiatrična obravnava, simptomi tudi 6 mesecev po koncu terapije)
- Pojav avtoprotiteles (aTG, ANA, ACL) in avtoimunskih bolezni: sarkoidoza oz. poslabšanje sarkoidoze, SLE, vaskulitisi, pojav RA oz. poslabšanje RA

  Hiper/hipotiroidizem
- Akutne preobčutljivostne reakcije

  Redko, zaradi prehodnega izpuščaja ni potrebna prekinitev
- Sladkorna bolezen oz. poslabšanje

NEŽELENI UČINKI ZDRAVLJENJA (3)

- Koža: **alopecija, srbež, suha koža, potenje**, pojav psoriaze oz. poslabšanje, eritematozni ali makulopapulozni izpuščaj,…
- GIT: **navzea, bruhanje, driska, stomatitis, dispepsija**, abdominalne bolečine, zaprtje/vodeno blato
- Pljučne bolezni: **suh kašelj**, pljučni infiltrati, pnevmonitis, pljučnice
- Očesne bolezni: **zamegljen vid**, konjunktivitis, bolečine
- CŽS: otopelost, koma, encefalopatija (starostniki)
- KVS: palpitacije, tahikardija, hipertenzija, obstoječe motnje ritma

NEŽELENI UČINKI ZDRAVLJENJA

Delež neželenih učinkov glede na stopnjo

Toxicity profile of high-dose interferon-alfa in patients with melanoma

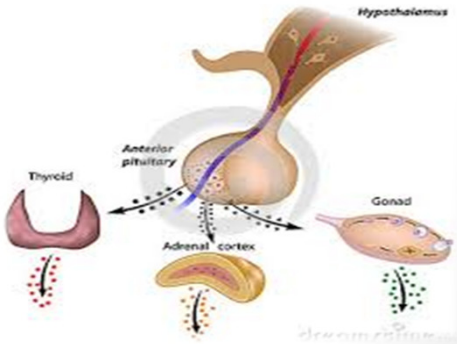
Adverse event	Patients, percent	
	All grades* (n = 143)	Grade 3/4• (range)
Fatigue	96	21-24
Fever	81	18
Myalgia	75	4-17
Nausea	66	5-9
Vomiting	66	5
Myelosuppression	92	26-60
Increased AST	63	14-29
Depression/neuropsychiatric/neuropsychologic	40	2-10

AST: aspartate aminotransferase.
* Based upon data from 143 patients treated with high-dose interferon-alfa in ECOG trial 1684.
• Based upon combined data from ECOG 1684, 1690, and 1694.
Reproduced with permission from: Kirkwood, JM, Bender, C, Agarwala, S, et al. Mechanisms and management of toxicities associated with high-dose interferon of alfa-2b therapy. J Clin Oncol 2002; 20:3703. Copyright ©2002 American Society of Clinical Oncology.

NEŽELENI UČINKI ZDRAVLJENJA

Citokini v povezavi s toksičnostjo IFN

- Citokini vplivajo na hipotalamusno – hipofizno - ščitnično/adrenalno/gonadalno os
- Vpliv na nivo dopamina in serotonina v CŽS



Mechanisms of INF-a2b Associated Toxicities

Administration of exogenous IFN-a initiates the release of a cascade of cytokines, including TNF-a, IL-1, IL-2, IL-6, IFN-gamma, and IFN-inducible protein-10

IL-1	Anorexia, Cognitive dysfunction, Fatigue, Fever, Hematologic toxicities, Depression
IL-2	Hypotension, Fatigue, Confusion, Neurotoxicity, Depression?
IL-6	Fever, Headache, Chills, Depression, Anorexia
IL-10	Anorexia,, Hematologic toxicities
TNF-a	Fatigue, Anorexia, Fever, Depression?

Effects of IFN-a2b on cytochrome P450 isoenzymes

- Inhibition of CYPIA2 was highly correlated with neurologic toxicity
- Inhibition of CYP2D6 was highly correlated with fever and anemia
- Inhibition of both CYPIA2 and CYP2D6 correlated with fatigue

- Prediction patients are more likely to have adverse events based on their CYP450 isoenzyme profile
- Proactive management of IFN-a-associated toxicities
- Consideration of drug catabolism is required when coadministering IFN-a with drugs that are metabolized by CYPIA2, CYP2D6 or CYP2C19

OBVLADOVANJE NEŽELENIH UČINKOV i.v. aplikacije

- Paracetamol (30 minut pred in 2-4 ure po infuziji)
- Antiemetiki
- Dobra hidracija (do 3l/dan)
- NSAID pri glavobolu in bolečinah v mišicah in sklepih
- Pomen zdravega načina prehranjevanja
- Pravilna nega suhe kože
- Zgodnja detekcija depresije

OBVLADOVANJE NEŽELENIH UČINKOV s.c. aplikacije (1)

- Podkožna aplikacija zvečer pred spanjem
- Paracetamol 1 uro pred aplikacijo
- NSAID ob bolečinah v mišicah in sklepih
- Glavobol kot posledica dehidracije ali s histaminom pogojen odgovor:
  - hidracija
  - nesedativni antihistaminik (loratadin)
- Depresija:
  - zgodnje odkrivanje, antidepresivi (SSRI's)

OBVLADOVANJE NEŽELENIH UČINKOV s.c. aplikacije (2)

- **Utrujenost**

Prepoznava

Drugi vzroki: dehidracija, anemija, depresija, nazadostna prehrana, hormonske motnje, druga zdravila, motnje spanja, stres, nezadostna fizična aktivnost, izguba telesne teže

Telesna aktivnost 20 – 30 min dnevno, 3x tedensko

Medikamentozna terapija

Sprostitvene tehnike

PRILAGAJANJE ODMERKA IFN-α2b

- Hudi neželeni učinki – 3. stopnja toksičnosti

N≤ 500/mm³, ALT/AST naraste na ≥ 5x zg. mejo normale

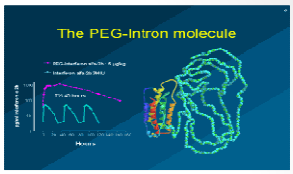
Začasna prekinitev IFN-α2b , ponovna uvedba v 50% odmerku

- Trdovratna intoleranca po prilagoditvi odmerka, N≤250/mm³, ALT/AST naraste na ≥ 10x zg. mejo normale

Motnje v delovanju ščitnice, hipofize, depresija, samomorilnost

Trajna prekinitev terapije IFN-α2b

PEG Interferon alfa -2b



- PEG-interferon alpha-2b- delovanje preko JAK- STAT signalne poti
- Brez razlike in OS, 7-letno preživetje brez ponovitve bolezni statistično značilno daljše v PEG IFN skupini vs. placebo (FDA, stadij IIIA)
- Alternativa standardni terapiji z visokodoznim IFN za stadij III

Eggermont AM, et al. Long term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa- 2b versussobservation in resected stage III melanoma. J Clin Oncol 2012;30.3810

U.S. Food and Drug Administration Approval: Peginterferon-alfa-2b for the Adjuvant Treatment of Patients with Melanoma (**Herndon TM,*The Oncologist*** 2012;17:1323–1328)

Table 2. Independent review committee–determined RFS results in the intent-to-treat population

RFS result	PEG-IFN (n = 627)	Observation (n = 629)
n (%) of patients with RFS event	328 (52.3)	368 (58.5)
n (%) of patients without RFS event	299 (47.7)	261 (41.5)
Median duration of RFS (95% CI), mos	34.8 (26.1–47.4)	25.5 (19.6–30.8)
Hazard ratio[a] (95% CI)	0.82 (0.71–0.96)	
Nominal p-value (unadjusted log-rank test)	.011	

Data cutoff date was March 31, 2006.
[a]The hazard ratio was estimated using a Cox proportional hazards regression model with treatment arm as the only covariate. A hazard ratio <1 indicates that treatment with PEG-IFN is associated with a lower risk for recurrence or death than observation.
Abbreviations: CI, confidence interval; PEG-IFN, peginterferon-alfa-2b; RFS, relapse-free survival.

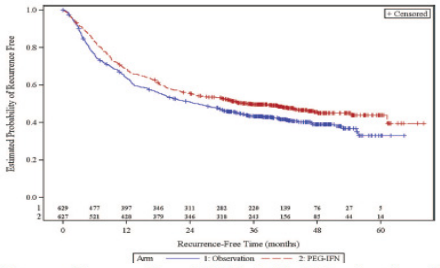
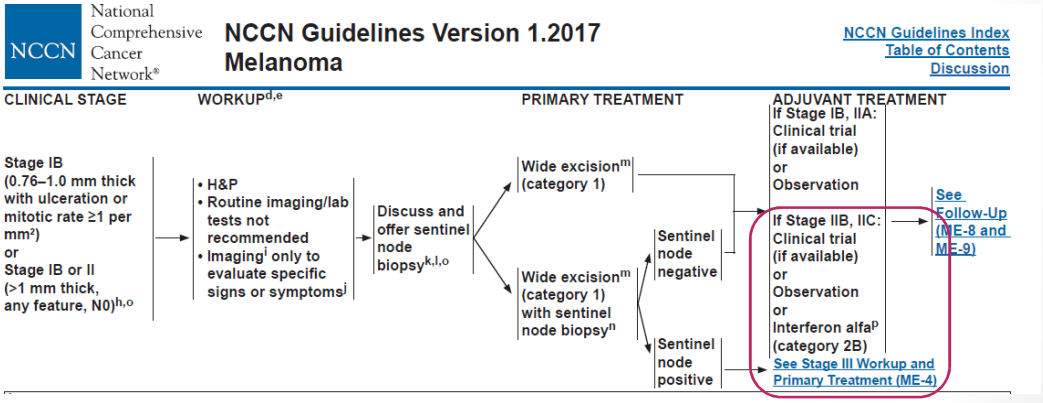
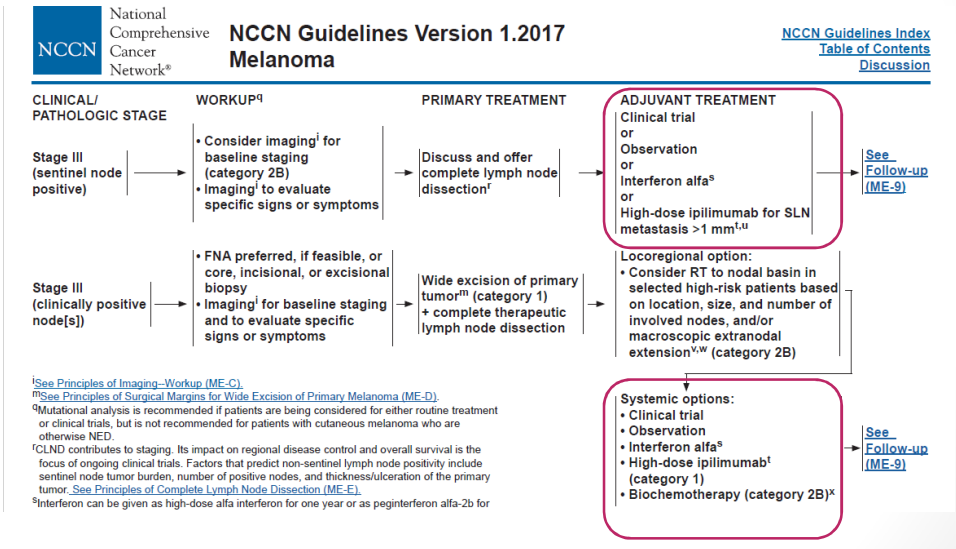


Figure 1. Kaplan–Meier curves of the recurrence-free survival (RFS) probability. The log-rank p-value was .011 based on 696 RFS events determined by the independent review committee at the data cutoff date of March 31, 2006.

NCCN smernice za adjuvantno zdravljenje stadija II



NCCN smernice za adjuvantno zdravljenje stadija III



ZAKLJUČKI O ADJUVANTNEM ZDRAVLJENJU

- Zdravljenje bolnikov z melanomom z visokim tveganjem za ponovitev bolezni z IFN-α2b v visokih odmerkih po operaciji podaljša celokupno preživetje in čas do ponovitve bolezni.
- Glede na rezultate E1684 je bilo zdravljenje z IFN-α2b registrirano v ZDA in v Evropi.
- IFN-α2b v visokih odmerkih je priporočeno adjuvantno zdravljenje v stadiju IIB, IIC in stadiju III- Evropa (IIB, IIC in stadij IIIA (N1a- <1mm velik zasevek v bezgavki- ZDA)
- PEG Intron- alternativa standardni terapiji z visokodoznim IFN za stadij III
- Številni neželeni učinki so obvladljivi z navodili in dobrim sodelovanjem bolnika

HVALA ZA POZORNOST

ADJUVANTNO ZDRAVLJENJE MALIGNEGA MELANOMA Z IFN-α2b in OBVLADOVANJE NEŽELENIH UČINKOV

PRIKAZ KLINIČNEGA PRIMERA

Imunoterapija v onkologiji

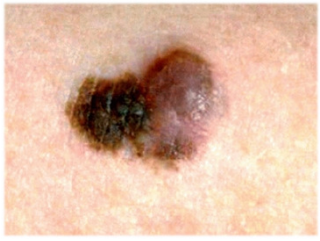
Jasna K. Arbeiter, dr.med., Nežka Hribernik, dr.med.,
Asist.dr.Martina Reberšek, dr.med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana

28.9.2017

KLINIČNI PRIMER – zdravljenje z interferonom

45 – letna bolnica, st. po op. melanoma kože desno lumbalno

- 27.2.2013 operacija,
- 10.4.2013 reekscizija in biopsija varovalne bezgavke (oboje negativno) ➡
  primarno stadij IIB



KLINIČNI PRIMER – zdravljenje z interferonom

- 27.5.2013 začetek aplikacij IFN-α2b v visokih odmerkih i.v.
  - Vrednosti S-100 in LDH v mejah normale, transaminaze mejno zvišane (AST 0.54 ukat/L, ALT 0.67 ukat/L), CRP 8 mg/L.

Po prvih 5 aplikacijah i.v.

Povišana telesna temperatura do 39.5°C,
mrzlica,
utrujenost,
bolečine v mišicah in kosteh.
Dnevno zaužila do 4 tbl. Lekadola.

L 2.37x 10^9/L
T 115x 10^9/L
Hb 148 g/L
N 0.74x 10^9/L
AST 0.84 ukat/L
ALT 0.76 ukat/L

KLINIČNI PRIMER – zdravljenje z interferonom

Po 10 aplikacijah i.v.

V ospredju predvsem utrujenost.
Dnevno zaužila do 4 tbl. Lekadola.

L 2.16x 10^9/L
T 214x 10^9/L
Hb 150 g/L
N 0.63x 10^9/L
AST 2.64 ukat/L
ALT 3.24 ukat/L

Prekinitev terapije z interferonom za 7 dni.

KLINIČNI PRIMER – zdravljenje z interferonom

- 14.6.2017 nadaljevanje aplikacij IFN-α2b v visokih odmerkih i.v.
  - Normalizacija krvne slike, AST 0.98ukat/L, ALT 1.73ukat/L

Po 15 aplikacijah i.v.

Utrujenost,
bolečine v sklepih in kosteh,
slabši apetit,
suha usta.
Dnevno zaužila do 4 tbl. Lekadola.

L 2.15x 10^9/L
T 176x 10^9/L
Hb 150 g/L
N 0.62x 10^9/L
AST 1.26 ukat/L
ALT 1.55 ukat/L

KLINIČNI PRIMER – zdravljenje z interferonom

Po 20 aplikacijah i.v.

Utrujenost,
bolečine v sklepih in kosteh,
glavobol,
slabši apetit.
Dnevno zaužila do 4 tbl. Lekadola.

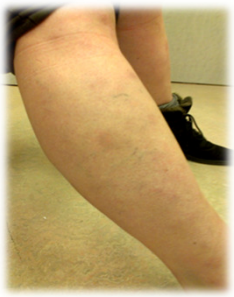
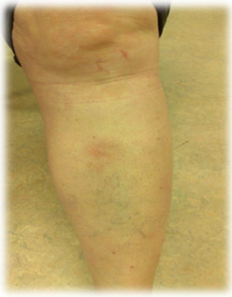
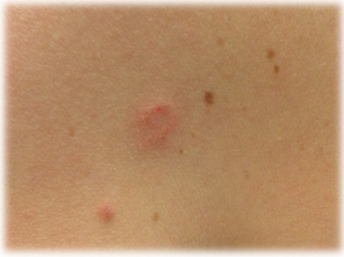
L 2.68x 10^9/L
T 170x 10^9/L
Hb 144 g/L
N 1.24x 10^9/L
AST 1.17 ukat/L
ALT 1.31 ukat/L

KLINIČNI PRIMER – zdravljenje z interferonom

- 1.7.2017 pričetek z aplikacijami IFN-α2b v polovičnem odmerku s.c. 3x tedensko.
  - Kontrole v ambulanti 1x/mesec, izmenjaje s kontrolami pri izbranem osebnem zdravniku.
- 25.11.2013 ↑ AST (2.15 ukat/L) / ALT (2.33 ukat/L) in izrazita utrujenost ⟹ znižanje odmerka s.c. aplikacij IFN-α2b (75%).
- 16.12.2013 prehodna prekinitev zaradi ↑ AST (2.86 ukat/L) / ALT (3.87 ukat/L) in tireotoksičnosti (TSH 28.47 mU/L).

KLINIČNI PRIMER – zdravljenje z interferonom

- 27.1.2014 po 5 tednih premora zaključek zdravljenja z IFN-α2b zaradi vztrajajočih povišanih vrednosti TSH (14.28 mU/L), (AST 0.54 ukat/L, ALT 0.71 ukat/L).
  - Prisoten kožni izpuščaj obeh goleni (pordelo, boleče, srbeče, trdo).

KLINIČNI PRIMER – zdravljenje z interferonom

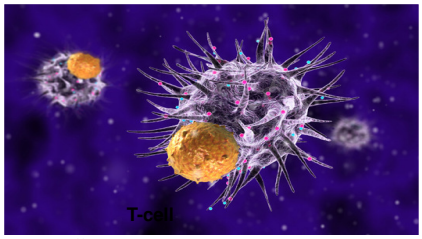
- 20.5.2014 zadnja kontrola v ambulanti internističnega onkologa.
- Vrednosti transaminaz AST 0.49 ukat/L, ALT 0.56 ukat/L
- Vrednost TSH 5.7 mU/L
- Izpuščaj na golenih popolnoma izzvenel
- Nadaljuje kontrole pri lečečem kirurgu na OI.

ANTI-CTLA-4 PROTITELESA: UPORABA, DELOVANJE, NEŽELENI UČINKI

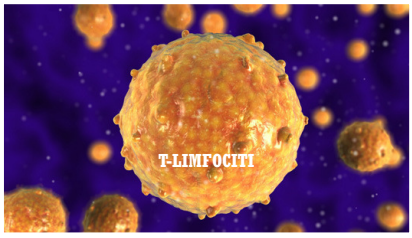
MARKO BOC, DR.MED.
SEKTOR INTERNISTIČNE ONKOLOGIJE
ONKOLOŠKI INŠTITUT LJUBLJANA

IMUNOTERAPIJA V ONKOLOGIJI
LJUBLJANA, 28. SEPTEMBER 2017.

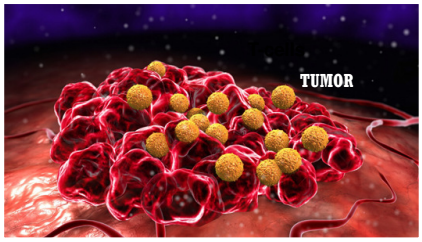
ŽELENI T-CELIČNI ODGOVOR NA TUMOR



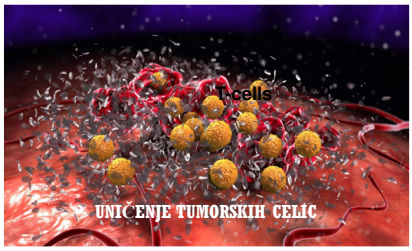
1 - T-CELIČNA AKTIVACIJA



2 - T-CELIČNA PROLIFERACIJA



3 - INFILTRACIJA TUMORJA



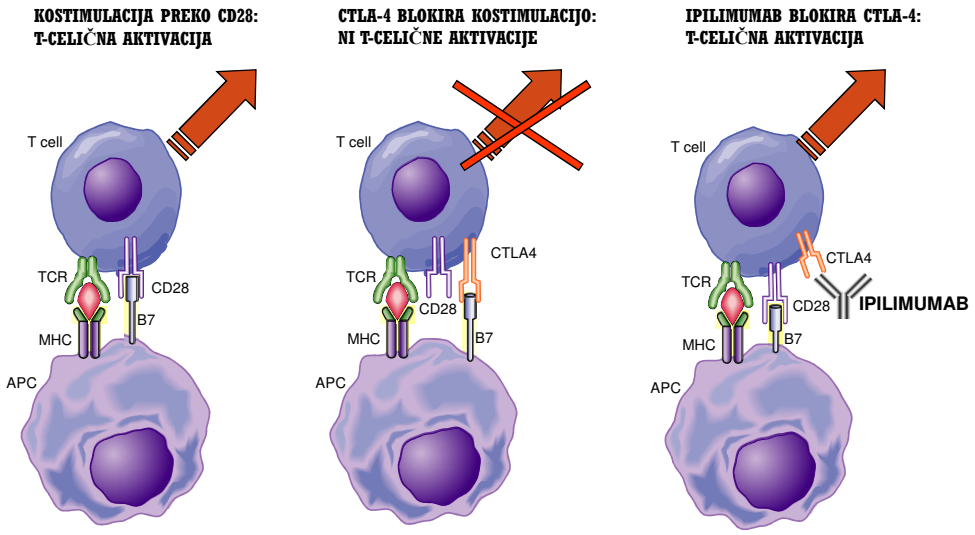
4 – DESTRUKCIJA TUMORSKIH CELIC

TUMORJI IMAJO SPOSOBNOST, DA ZAOBIDEJO IMUNSKI SISTEM IN T-CELIČNO ACTIVACIJO.

STRATEGIJA IMUNOTHERAPIJE JE OJAČANJE NARAVNEGA ODGOVORA.

N Engl J Med 2006; 355(10): 973-5.
Proc Natl Acad Sci USA 2002; 99(25): 15840-2.

IPILIMUMAB BLOKIRA NEGATIVNI SIGNAL CTLA-4



Immunology, 7th ed. Mosby Elsevier, 2006.
Immunology a short course 5th ed Wiley-Liss, 2003.
Am J Respir Crit Care Med 2000;162(4 Pt 2):S164-8

IPILIMUMAB – RAZISKAVE FAZE II – 2. LINIJA ZDRAVLJENJA

- CA184-022: N=217
  - RANDOMIZIRANA, DVOJNO SLEPA RAZISKAVA
  - *3 ROKE: 10 mg/kg, 3 mg/kg and 0.3 mg/kg*
  - PROGRES OZ. INTOLERANCA NA PREDHODNO TERAPIJO
  - IZKLJUČENI BOLNIKI Z mCŽS
- CA184-008: N=155
  - *ENA ROKA; 10 mg/kg*
  - PROGRES NA ALI PO STANDARDNI TERAPIJI
  - IZKLJUČENI BOLNIKI Z mCŽS
- CA184-007: N=115
  - *10 mg/kg + placebo vs. 10 mg/kg + PROFILAKTIČNI BUDENOSID*
  - NETRETIRANI ALI V PROGRESU PO PREDHODNI TERAPIJI
  - BUDENOSID PROFILAKTIČNO ➔ PREVENCIJA TOKSIČNIH SOPOJAVOV
- PRIMARNI CILJ: ODGOVOR NA ZDRAVLJENJE

IPILIMUMAB - PREŽIVETJE V RAZISKAVAH FAZE II

	CA184-022[2,5] (N=217)	CA184-008[3,5] (N=155)	CA184-007[4,5] (N=115)	
Dose	10 mg/kg pretreated N=72	10 mg/kg pretreated N=155	10 mg/kg + budesonide Untreated + pretreated N=58	10 mg/kg + placebo Untreated + pretreated N=57
1 year survival rate (%, 95%CI)	48.6 (36.8 – 60.4)	47.2 (39.5 – 55.1)	55.9 (42.7 – 68.8)	62.4 (49.4 – 75.1)
2 year survival rate (%, 95%CI)	29.8 (19.1 – 41.1)	32.8 (25.4 – 40.5)	40.5 (27.1 – 54.4)	41.7 (28.3 – 55.5)
3 year survival rate (%, 95%CI)	25.4 (15.4–36.3)	23.3 (16.7–30.4)	38.7 (25.2–52.4)	34.4 (21.1–48.2)

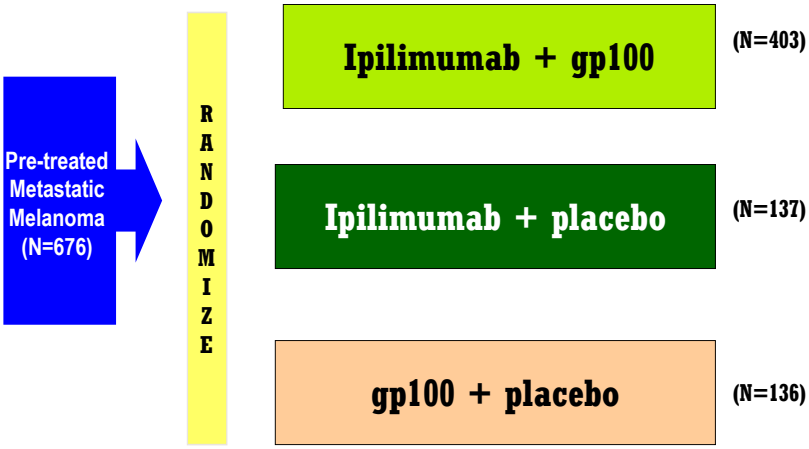
1. Kom EL, et al. J Clin Oncol 2008;26(4):527-534.
2. Wolchok JD, et al. Lancet Oncol 2010;11(2):155-164.
3. O'Day SJ, et al. Ann Oncol 2010; 21(8):1712-1717 .
4. Weber J, et al. Clin Cancer Res 2009;15(17):5591-5598
5. Maio M et al. Presented at Perspectives in Melanoma XIV; Poster -0020:2010

A PHASE III, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY COMPARING MONOTHERAPY WITH IPILIMUMAB OR GP100 PEPTIDE VACCINE AND THE COMBINATION IN PATIENTS WITH PREVIOUSLY TREATED, UNRESECTABLE STAGE III OR IV MELANOMA
STUDY MDX010-20

Steven O'Day, F. Stephen Hodi, David McDermott, Robert Weber, Jeffrey Sosman, John Haanen, Xiaoping Zhu, Michael Yellin, Axel Hoos, Walter J. Urba

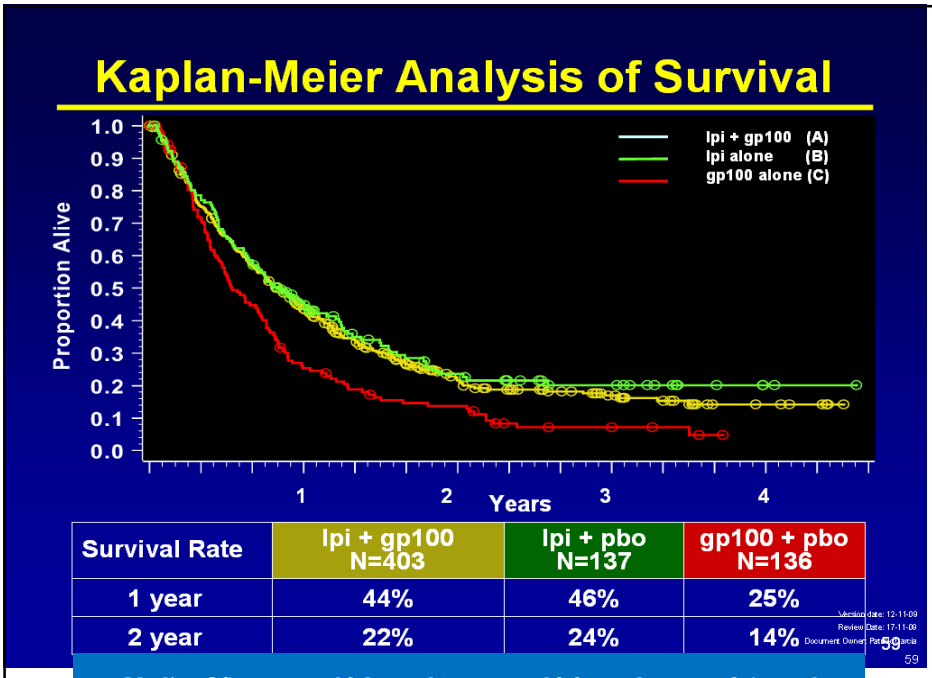
N Engl J Med 2010; 363:711-723

MDX010-20



N Engl J Med 2010; 363:711-723

MDX010-20 PREŽIVETJE



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%
Median OS	10.1 month	10.0 month	6.4 month

N Engl J Med 2010; 363:711-723

MDX010-20
RR

Ipilimumab Improves Best Objective Response Rate (BORR)

	Arm A Ipi + gp100 N=403	Arm B Ipi + pbo N=137	Arm C gp100 + pbo N=136
BORR, %	5.7	10.9	1.5
P-value: A vs C	0.0433		
P-value: B vs C	0.0012		
DCR‡, %	20.1	28.5	11.0
P-value: A vs C	0.0179		
P-value: B vs C	0.0002		

N Engl J Med 2010; 363:711-723

IPILIMUMAB – IMUNSKO POGOJENI NEŽELENI UČINKI (IPNU)

- IPNU SE LAHKO POJAVIJO V KATEREMKOLI ORGANSKEM SISTEMU
- GRE ZA NEŽELENE UČINKE, KI JIH LAHKO PRIPIŠEMO ZDRAVILU, KI GA APLICIRAMO IN SO POSLEDICA IMUNSKIH MEHANIZMOV POGOJENIH Z SAMIM ZDRAVILOM. PRED TEM MORAMO IZKLJUČITI VSE OSTALE VZROKE (PROGRES BOLEZNI, INFEKTIVNI, METABOLNI VZROKI, ITD.)
- V VEČINI PRIMEROV SO PODOBNIH KARAKTERISTIK KOT ZNANE AVTOIMUNE BOLEZNI
- POJAVIJO SE PRI 80 % BOLNIKOV

IPILIMUMAB – IMUNSKO POGOJENI NEŽELENI UČINKI (IPNU)

IPNU POVZROČENI Z IPILIMUMABOM	ZNANE AVTOIMUNE BOLEZNI
KOLITIS IN DRISKA	MB. CHRON, ULCEROZNI KOLITIS
TIROIDITIS	HASHIMOTO TIROIDITIS
HEPATITIS/HEPATOPATIJA	AI HEPATITIS
PANKREATITIS	AI PANKREATITIS
UVEITIS	UVEITIS KOT POSLEDICA REVMATIČNIH OBOLENJ
HIPOFIZITIS	ANTERIORNA HIPOFIZNA INSUFICIENCA
NEUROPATIJA	SINDROM GIULLAIN-BARRE
TROMBOCITOPENIJA	ITP – IDIOPATSKA TROMBOCITOPENIJA
SRBEČICA, URTIKA	AI KOŽNE REAKCIJE

MDX010-20 TOKSIČNOST

Summary of Safety Events

% of Patients	Ipi + gp100 N=380	Ipi + pbo N=131	gp100 + pbo N=132
Any adverse event (AE)	98.4	96.9	97.0
Treatment - related Any AE	88.9	80.2	78.8
Treatment - related Grade 3/4 AE	17.4	22.9	11.4
Treatment - related Deaths	2.1	3.1	1.5

Version date: 12-11-09
Review Date: 17-11-09
Document Owner: Patricia
IPI-066-2009 62

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MDX010-20: IPNU

	%		%
DERMATOLOŠKI	57	SRBEŽ	24.4
		IZPUŠČAJ	19.1
GASTROINTESTINALNI	38	DRISKA	27.5
		KOLITIS	7.6
ENDOKRINI	10	HIPOTIROIDIZM	1.5
JETRNI	5	POVIŠAN ALT	1.5

N Engl J Med 2010; 363:711-723

Most Common Immune-Related Adverse Events* (Grades 3, 4 & 5)

MDX010-20 IPNU

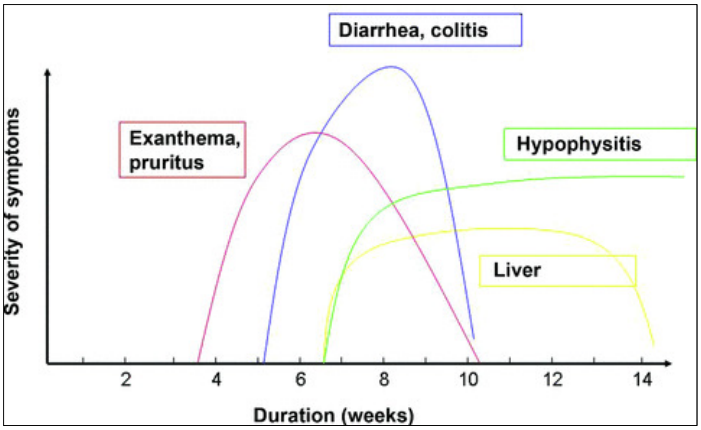
	% of Patients					
irAE	Ipi + gp100 N=380		Ipi + pbo N=131		gp100 + pbo N=132	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	9.7	0.5	12.2	2.3	3.0	0
Dermatologic	2.1	0.3	1.5	0	0	0
GI	5.3	0.5	7.6	0	0.8	0
Endocrine	1.1	0	2.3	1.5	0	0
Hepatic	1.1	0	0	0	2.3	0
Death due to irAE	1.3		1.5		0	

*Across entire study duration

Version date: 12-11-09
Review Date: 17-11-09
Document Owner: Patricia
IPI-066-2009 64

N Engl J Med 2010; 363:711-723

IPILIMUMAB – IMUNSKO POGOJENI NEŽELENI UČINKI (IPNU)



TIP IPNU	ČAS DO NASTANKA (TEDNI) (N=131) GRADUS 2-5
KOŽA, mediani (n , 95% CI)	3.1 (24, 1.9 - 6.1)
GI, mediani (n, 95% CI)	8.6 (18, 7.0 - 10.9)
JETRA (n=3) min-max	3.4 - 9.0
ENDOKRINI (n=8) min-max	7.1 – 19.3

N Engl J Med 2010; 363:711-723

IPILIMUMAB – IMUNSKO POGOJENI NEŽELENI UČINKI (IPNU)

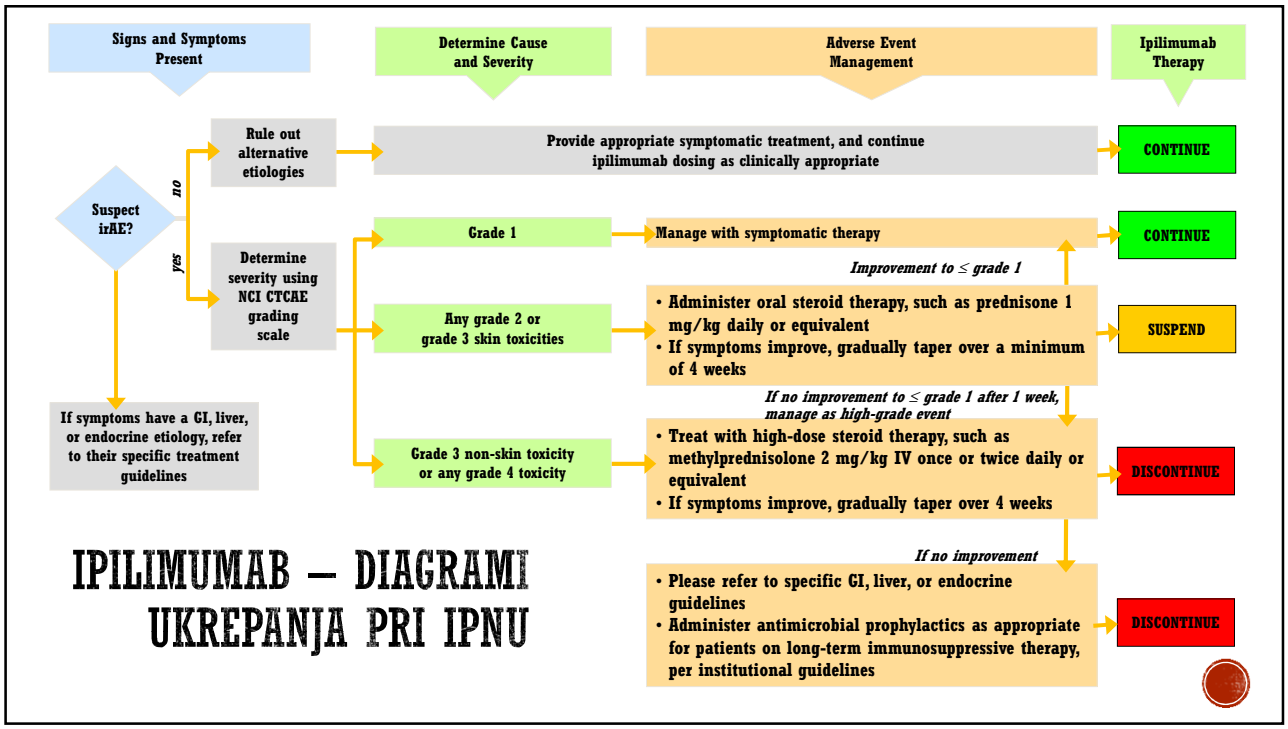
KOŽA	ČAS DO IZBOLJŠANJA (TEDNI)
Gr2-4, št.b.	24
št. izboljšanj	21
Mediana, tedni	5.2
(95% CI)	(2.6 – 7.9)

GI	ČAS DO IZBOLJŠANJA (TEDNI)
Gr2-4, št.b.	18
št. izboljšanj	16
Mediana, tedni	4.1
(95% CI)	(2.0 – 5.4)

JETRA	ČAS DO IZBOLJŠANJA (TEDNI)
Gr2-4, št.b.	2
št. izboljšanj	2
Min-Max, tedni	0.7 – 2.1

ENDOKRINI	ČAS DO IZBOLJŠANJA (TEDNI)
Gr2-4, št.b.	8
št. izboljšanj	3
Min-Max, tedni	2.0 – 9.1+

N Engl J Med 2010; 363:711-723



IPILIMUMAB – DIAGRAMI UKREPANJA PRI IPNU

ZAKLJUČKI

- POMEMBNA JE EDUKACIJA BOLNIKOV ZA ZGODNJE SPOZNAVANJE IMUNSKO POGOJENIH NEŽELENIH UČINKOV (IPNU)
- POZORNOST, ZGODNJE ODKRIVANJE IN ZDRAVLJENJE IPNU!!!
- POMAGAMO SI Z ALGORITMI OBRAVNAVE, KI NAM POMAGAJO SPOZNAVATI IN ZDRAVITI IPNU
- IPNU NIZKIH GRADUSOV
  - USTREZNA SIMPTOMATSKA TERAPIJA IN/ALI ORALNI KORTIKOSTEROID
- IPNU SREDNJIH IN VISOKIH GRADUSOV
  - ZDRAVLJENJE PO SMERNICAH USTREZNIH AVTOIMUNIH BOLEZNI
    - VEČINA ODREAGIRA NA VISOKODOZNI KS
    - REDKO - ZDRAVLJENJE Z IMUNOSUPRESIVI
- NESPECIFIČNE TEŽAVE LAHKO POMENIJO ENDOKRINO AI - RECIMO HIPOFOZITIS

METASTATSKI MELANOM ZDRAVLJENJE Z ANTICTLA 4 PROTITELESOM

(CASE REPORT)

Marija Ignjatović, dr. med.
Izredni prof. dr. Janja Ocvirk, dr. med.

PG (1957, ♂): ANAMNEZA

- DA: negativna
- DB: po operaciji BCC levo temporalno

PG (1957, ♂): SEDANJA BOLEZEN

Avgust 2013, NEVROLOG

- Tiščoč, stalno prisoten glavobol
- Latentna LS hemipareza, osebnostna spremenjenost

PG(1957, ♂): DIAGNOSTIKA

- CT glave → 4 x 6 cm cističen tumor D frontalno
  - okolni edem
  - utesnitev desnega stranskega ventrikula
  - hernijacija v levo in delno v tentorialno odprtino
- MRI glave: ?
- RTG PC → zgostitev v L spodnjem pljučnem reženju
- CT prsnih organov → spremembe
  - L spodnji pljučni režanj bazalno (3,0 cm)
  - L spodnji pljučni režanj apikalno (0,5 cm)
  - D zgornji pljučni režanj blizu hilusa (2,5 cm)
- Bronhoskopija: vzorec ni uporaben
- UZ trebuha: bp

PG(1957, ♂): KONZILIJ

OPERATIVNA ODSTRANITEV EKSPANIZIVNEGA PROCESA

PG(1957, ♂): NEVROKIRURG

Septemeber 2013

- Osteoplastična trepanacija frontalno desno
- Tumor makroskopski v celoti odstranjen
- Pooperativni nevrološki status → bp

- ***PH: metastaza MM***

PG(1957, ♂): MELANOMSKI KONZILIJ

1. DERMATOLOG → ni ležišča primarnega melanoma
2. RADIOTERAPEVT → WBRT +/- RT ležišča tumorja
3. ONKOLOG → sistemska terapija

PG(1957, ♂): PET CT

- Jasno patološko kopičenje radiofarmaka
  - L sp.pljučni režanj - medialno, 4 cm (max SUV 20.6)
  - D zg.pljučni režanj, 3 cm (max SUV 24.4)
- Nakazano povišano kopičenje radiofarmaka
  - L sp.pljučni režanj – apikalno, 0.5 cm (max SUV 1.8)

PG(1957, ♂): ONKOLOG

- 56 letni bolnik
- V odlični kondiciji
- MM z metastazami v pljučih in solitarnim zasevkom v CŽS, ki je reseciran
- B raf WT ≠ B raf inhibitorji

ST → Temozolamid

Kontrolni CT ″trojček″ po 4. ciklusu KT → progres bolezni v pljučih

- L sp.pljučni režanj medialno 5.5 cm (prej 4 cm)
- L sp.pljučni režanj apikalno 0.3 cm (prej 0.5 cm)
- D zg.pljučni režanj – 4 cm (prej 3 cm)

PG(1957, ♂): ONKOLOG

ST 2. REDA Z AntiCTLA 4 → IPILIMUMAB

Melanomski konzilij

PG (1957, ♂): ONKOLOG

MAREC 2014

- Začetek zdravljenja z ipilimumabom
- Prejel je vse 4 aplikacije
- Neželjeni učinki:
  - Utrujenost
  - Občasno slabši apetit
  - Driska po 3 in 4 ciklusu

JULIJ 2014

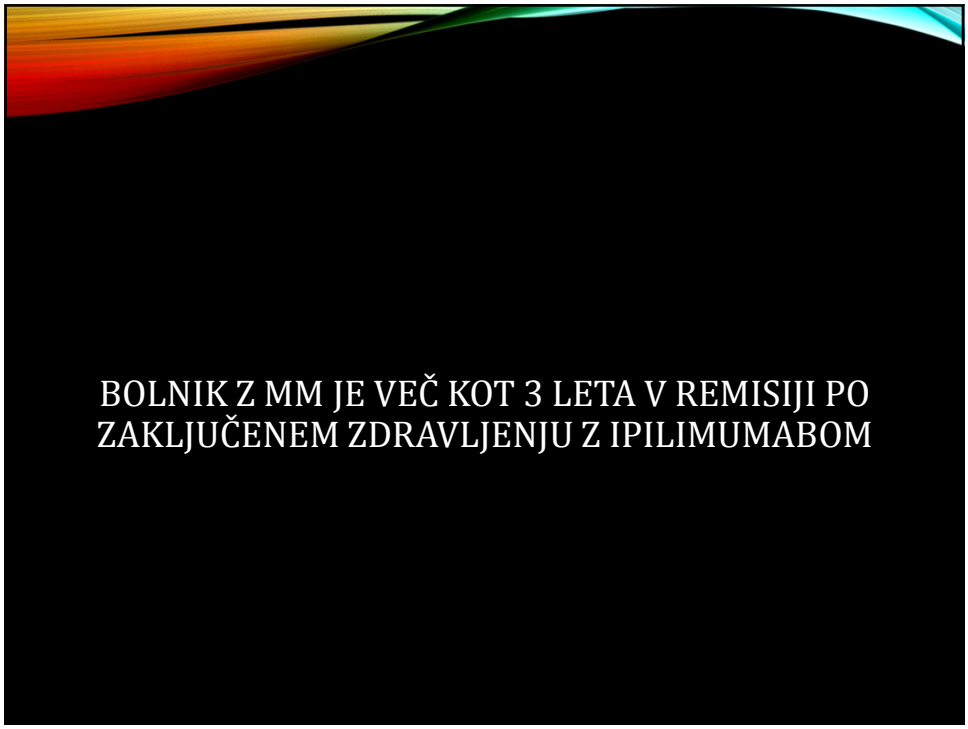
Kontrolni CT ″trojček″ → dalni regres pljučnih zasevkov

- L sp.pljučni režanj medialno 2,6 cm (prej 5,5 cm)
- L sp.pljučni režanj apikalno 0.1 cm (prej 0.3 cm)
- D zg.pljučni režanj – 2,7 cm (prej 4 cm)

PG (1957, ♂): ONKOLOG

REDNI KONTROLNI PREGLEDI NA 3 MESECE

- Asimptomatski
- CT ″trojček″ (oktober 2014 in januar 2015) → stagnacija
- PET CT maj 2015 → izrazit regres glede na izhodišni iz oktobra 2013
- Ostali kontrolni PET CT → nevitalni zasevki v pljučih

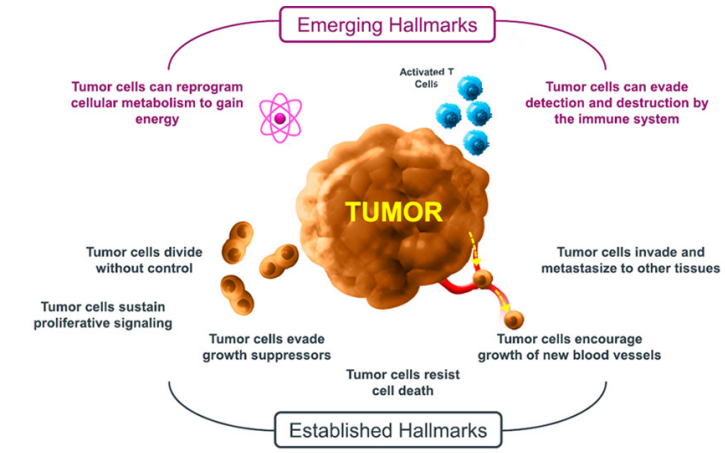

BOLNIK Z MM JE VEČ KOT 3 LETA V REMISIJI PO ZAKLJUČENEM ZDRAVLJENJU Z IPILIMUMABOM

Anti PD 1

Prof.dr. Janja Ocvirk, dr.med.
Onkološki inštitut Ljubljana

Ljubljana, 28.9.2017

Odpoved imunskega sistema – nastajajoča značilnost raka

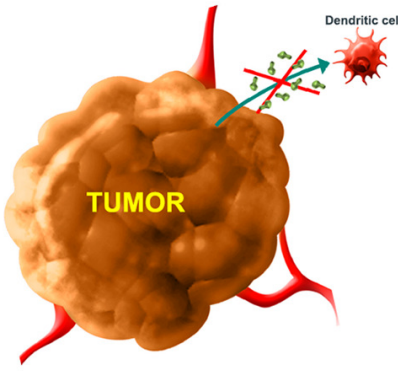


1. Hanahan D et al, *Cell*, 2011;144:646–674.

Tumorske celice lahko zaobidejo imunski sistem na več načinov:

- Izguba exspresije antigenov
- Sekrecija imunosupresivnih citokinov in zaposlovanje imunosupresivnih celic
- Izkoriščanje imunskih preglednih mest poti, kot so PD-1 pot

Izguba ekspresije antigena

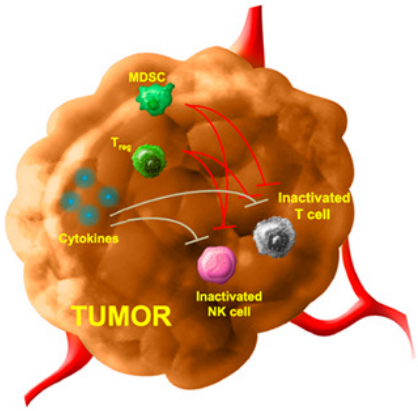


- In the adaptive immune response, the first step of tumor cell detection is antigen capture and presentation by dendritic cells[1]
- Tumors can escape detection by decreasing or completely shutting down antigen expression[2]

1. Pinzon-Charry A et al. *Immunol Cell Biol*. 2005;83:451–461.
2. Ahmad M et al. *Cancer Immunol Immunother*. 2004;53:844–854.

Sekrecija imunosupresivnih citokinov in zaposlovanje imunosupresivnih celic

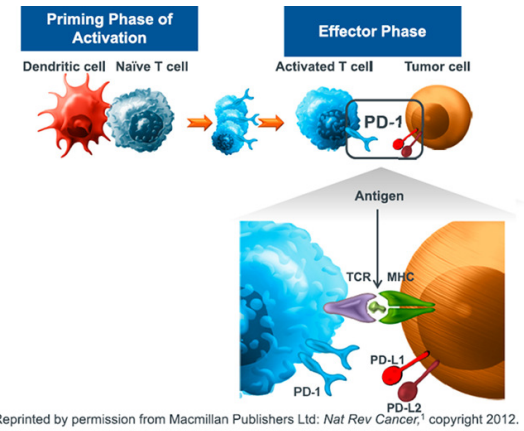
- Tumor cells can secrete cytokines (TGF-β, IL-10, VEGF) that have an inhibitory effect on T and NK cell function[1]
- Tumor cells can be infiltrated by immunosuppressive cells that can inhibit T cell function[2]:
  - T_{reg} cells
  - MDSCs



TGF-[] = transforming growth factor []; IL-10 = interleukin10; VEGF = vascular endothelial growth factor; NK = natural killer; T_{reg} = T regulatory; MDSCs = myeloid-derived suppressor cells.

1. Zou W. *Nat Rev Immunol*. 2006;6:295–307; 2. Finn OJ. *N Engl J Med*. 2008;358:2704–2715.

Izkoriščanje imunskih preglednih mest poti, kot so PD-1 pot



- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

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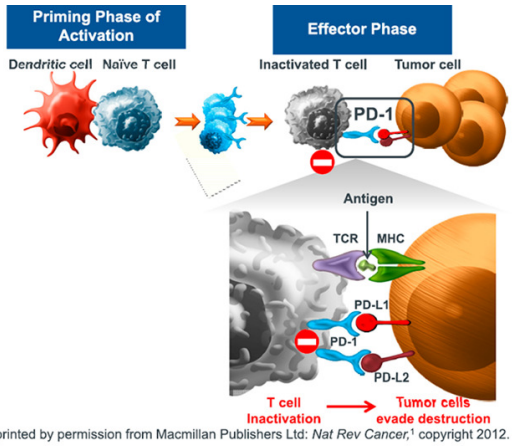
PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

Izkoriščanje imunskih preglednih mest poti, kot so PD-1 pot

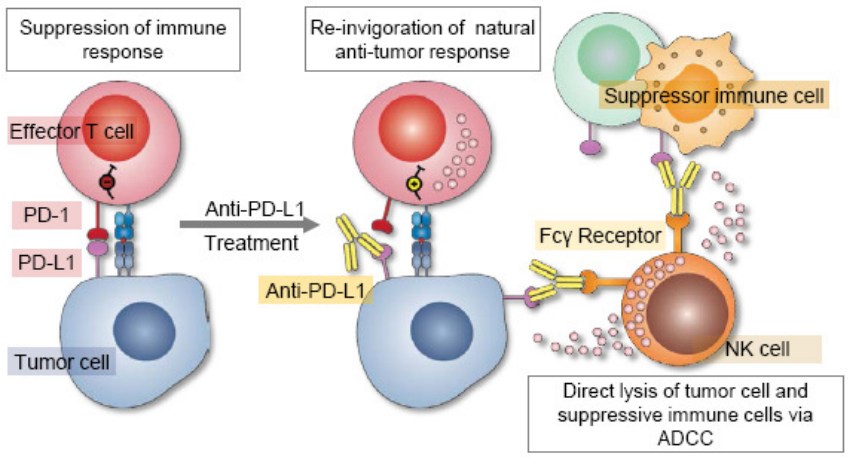


- PD-1 is upregulated on activated T cells during the effector phase of the immune response
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells to downregulate T-cell activity in the effector phase

Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer*,[1] copyright 2012.
PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.
1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

PD-L1 in PD-l2 so lahko izraženi na nekaterih tumorskih celicah

- Ekspresija PD-L1 v nekaterih tumorjih lahko z vezavo na PD-1 zmanjša delovanje Tumorsko specifičnih T celic
- PD-L2 ima pomembno vlogo pri tem, da se zaobide imunski sistem
- Imonologija pri raku, ki zajema tudi PD 1 in njegova liganda PD-L1 in PD-L2, je v fazi intenzivnih raziskav



PD-1 inhibitorji

- **Pembrolizumab (Keytruda)**
- **Nivolumab (Opdivo)**
- Ta zdravila so pokazala, da so koristna pri zdravljenju več vrst raka, vključno z melanomom, nedrobnoceličnim pljučnim rakom, rakom ledvic, rakom mehurja, rakom glave in vratu ter Hodgkinovim limfomom. Raziskujejo tudi uporabo pri številnih drugih vrstah raka.

Neželeni sopojavi

- PD-1 inhibitorji imajo ugoden toksični profil
- Najpogostejši sopojavi terapije so: utrujenost, srbež, izguba apetita in diareja
- Imunsko pogojeni neželeni sopojavi so redki, a se lahko pojavljajo v obliki dermatitisa, pneumonitisa, hepatitisa, kolitisa ali hipofizitisa
- Običajna intenziteta sopojavov blaga in obvladljiva s standardnimi ukrepi, resne neželene sopojave gradusa 3-4 razvije 10-15% bolnikov

Sunshine J. Curr Opin Pharmacol 2015;23:32-8; (11) Weber J S, 2015, J Clin Oncol;33:2092-99

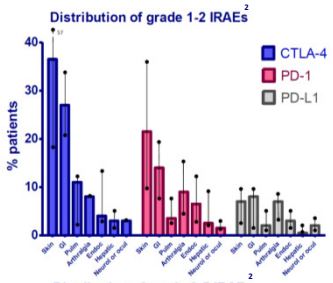
Neželeni sopojavi

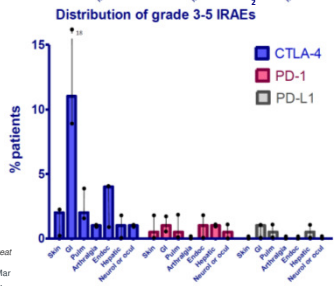
- V primeru imunsko pogojenih sopojavov uporaba imunosupresivov (kortikosteroidi, infliksimab, mikofenolat) in ustrezno nadomeščanje hormonov pri endokrinopatijah
- Potek le-teh predvidljiv
  - prva se pojavi kožna toksičnost
  - sledi pojav kolitisa po okoli 6 tednih od začetka zdravljenja.
  - hepatitis in endokrinopatije se pojavijo med 12 in 24 tednov zdravljenja.
  - po 24 tednih je pojav novih imunsko pogojenih sopojavov redek

Sunshine J. Curr Opin Pharmacol 2015;23:32-8; (11) Weber J S, 2015, J Clin Oncol;33:2092-99

Onset, Frequency, and Severity of irAEs Widely Varies by Organ System and by Type of Checkpoint Blockade[1–3]

- irAEs may occur at any time during treatment[1]
  - Time to irAE onset can range from within the first few weeks or months to up to a year after treatment initiation[2,4]
  - Most irAEs will occur during the first few doses[5]
  - The pattern of onset may vary by organ system[5]
- Incidence of all-grade irAEs is approximately 58% with CTLA-4 inhibition[6] and approximately 35% with PD-1 inhibition[7-8]
  - The majority of irAEs with PD-1 or CTLA-4 monotherapy blockade are grade 1-2, most frequently occurring in skin or GI tract[2]
  - Grade 3–5 events in the GI tract occur in ≥10% of patients receiving CTLA-4 inhibition[2]
  - Grade 3-5 events occur in <5% of patients in all organ systems during monotherapy with PD-1 and PD-L1 blocakde[2]
- Risk of irAEs appears to be dose-dependent for anti-CTLA-4 but not for anti-PD-1 agents[2,9]
- Combination therapy with anti-CTLA-4 + anti-PD-1 increases the incidence and severity of irAEs but does not modify the pattern of organ involvement[4]





CTLA-4 = cytotoxic T-lymphocyte–associated protein-4; GI = gastrointestinal; irAE = immune-related adverse event; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.
1. Champiat S et al. *Ann Oncol.* 2016;27(4):559–574. **2.** Michot JM et al. *Eur J Cancer.* 2016;54:139–148. **3.** Eigentler TK et al. *Cancer Treat Rev.* 2016;45:7–18. **4.** Boutros C et al. *Nat Rev Clin Oncol.* 2016;13(8):473–486. **5.** KEYTRUDA [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 10/2016. **6.** Hodi FS et al. *N Engl J Med* 2010; 363:711-723. **7.** Yamazaki N et al. *Cancer Chemother Pharmacol.* 2017 Mar 11 [Epub ahead of print]. **8.** Topalian SL et al. *N Engl J Med* 2012; 366:2443-2454. **9.** Wu J et al. Sci Rep. 7:44173 doi:10.1038/srep44173.

Table 1. Immunotherapy Toxicity

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Checkpoint protein inhibition: PD-1	Fevers, chills, and lethargy[68-72]	Maculopapular[68-72]	Diarrhea and colitis with ulceration: uncommon[68-72]	Elevated LFTs uncommon[68-72]	Hypophysitis, thyroiditis more common, adrenal insufficiency[68-72]	Pneumonitis not common; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[68-72]
Checkpoint protein inhibition: PD-L1	Fevers, chills, and lethargy[81,82]	Maculopapular[81,82]	Diarrhea and colitis with ulceration: rare[81,82]	Elevated LFTs rare[81,82]	Hypophysitis, thyroiditis more common, adrenal insufficiency[81,82]	Pneumonitis rare; anemia rare[81,82]

Sunshine J. Curr Opin Pharmacol 2015;23:32-8; (11) Weber J S, 2015, J Clin Oncol;33:2092-99

PN001 Part B1:
Drug-Related Adverse Events (N = 135)[1]

Adverse Event	All Grades, n (%)	Grade 3-4, n (%)
Any	107 (79)	17 (13)
Fatigue	41 (30)	2 (1)
Rash	28 (21)	3 (2)
Pruritus	28 (21)	1 (1)
Diarrhea	27 (20)	1 (1)
Myalgia	16 (12)	0
Headache	14 (10)	0
Increased AST	13 (10)	2 (1)
Asthenia	13 (10)	0
Nausea	13 (10)	0
Vitiligo	12 (9)	0
Hypothyroidism	11 (8)	1 (1)
Increased ALT	11 (8)	0
Cough	11 (8)	0
Pyrexia	10 (7)	0
Chills	9 (7)	0
Abdominal pain	7 (5)	1 (1)

1. Hamid O et al. *N Engl J Med.* 2013;369:134–144.

Table 3. Adverse Events.*

Event	Nivolumab (N = 206)	
	Any Grade	Grade 3 or 4
	no. of patients with	
Any adverse event	192 (93.2)	70 (34.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)
Fatigue	41 (19.9)	0
Pruritus	35 (17.0)	1 (0.5)
Nausea	34 (16.5)	0
Diarrhea	33 (16.0)	2 (1.0)
Rash	31 (15.0)	1 (0.5)
Vitiligo	22 (10.7)	0
Constipation	22 (10.7)	0
Asthenia	21 (10.2)	0
Vomiting	13 (6.3)	1 (0.5)
Neutropenia	0	0
Thrombocytopenia	0	0
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)
Serious adverse event		
Any event	64 (31.1)	43 (20.9)
Treatment-related event	19 (9.2)	12 (5.8)

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

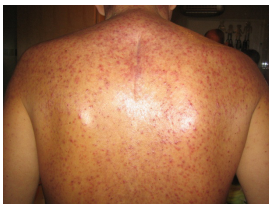
*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

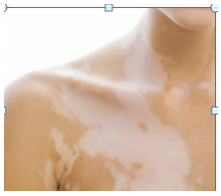
†Approved by the ESMO Guidelines Committee: May 2017.

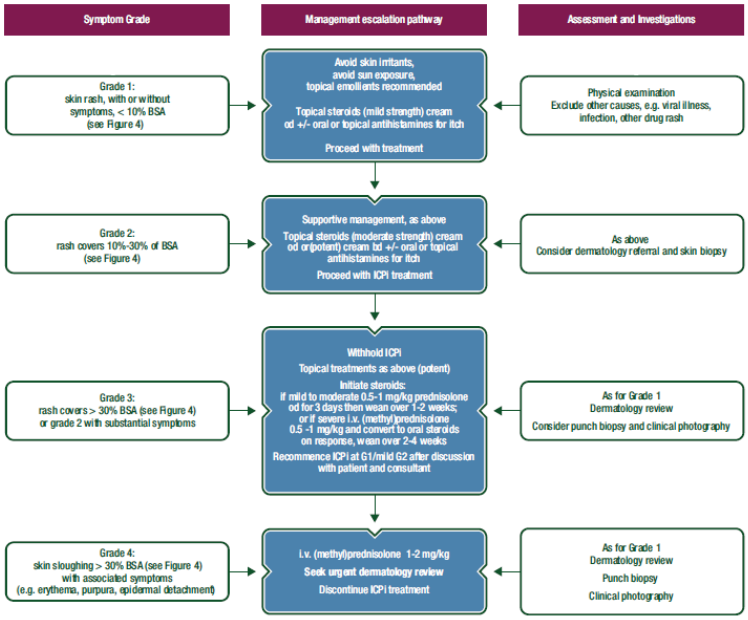
Nivolumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC	EMA + FDA
	2nd line metastatic RCC	EMA + FDA
	Classical Hodgkin's disease[a]	EMA + FDA
	Recurrent or metastatic SCCHN[b]	EMA + FDA
	Locally advanced or metastatic UCC[c]	EMA + FDA
Pembrolizumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC (PD-L1 $\geq$ 1%)	EMA + FDA
	1st line metastatic NSCLC (PD-L1 $\geq$ 50%)	EMA + FDA
	1st line metastatic NSCLC in combination with pemetrexed + carboplatin	FDA
	Classical Hodgkin's disease	EMA[a] + FDA[d]
	Locally advanced or metastatic UCC[c]	FDA
	MSI-H or MMR deficient metastatic malignancies[e]	FDA

Kožni neželeni učinki

- Rash
- Pruritus
- Vitiligo





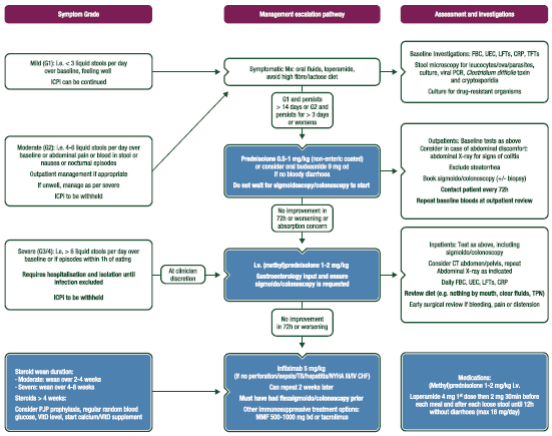


Hannen, Ann of Oncol, 2017

Kolitis

- Pri anti PD 1 je G3,4 zelo redek, samo 1-2%

- kortikosteroidi (prednizolon 1mg/kg/dan)
- Odgovori 87,5% bolnikov

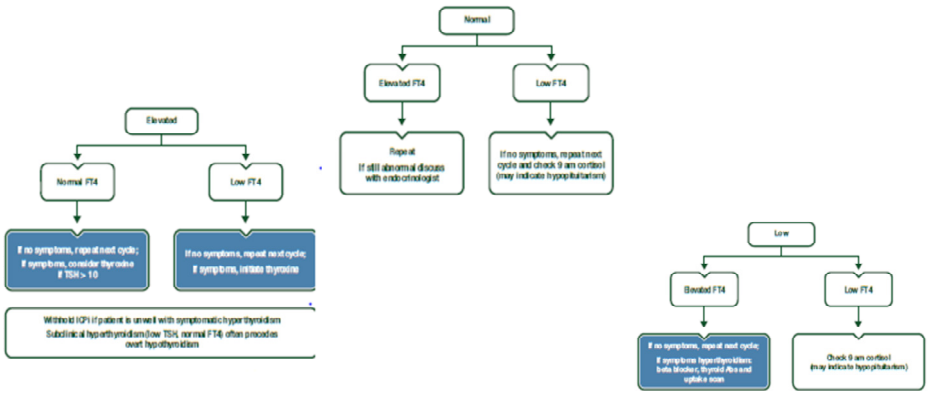


Motnje v delovanju ščitnice

- Merjenje TSH, T3, T4

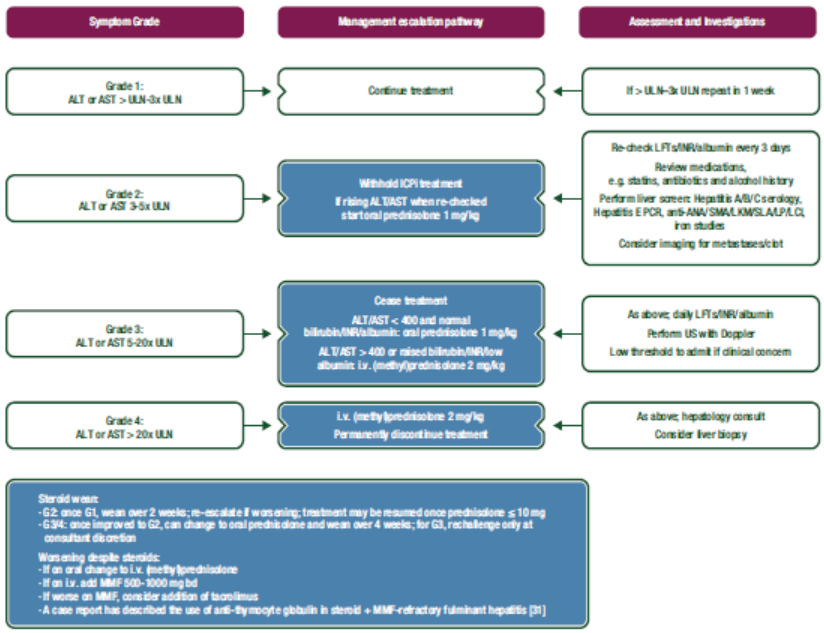
- Pred zdarvljenejem in v spremljevi vsak 3 cikel.
- Ob nepravilnostih ob vsakem ciklu imunoterapije

TSH

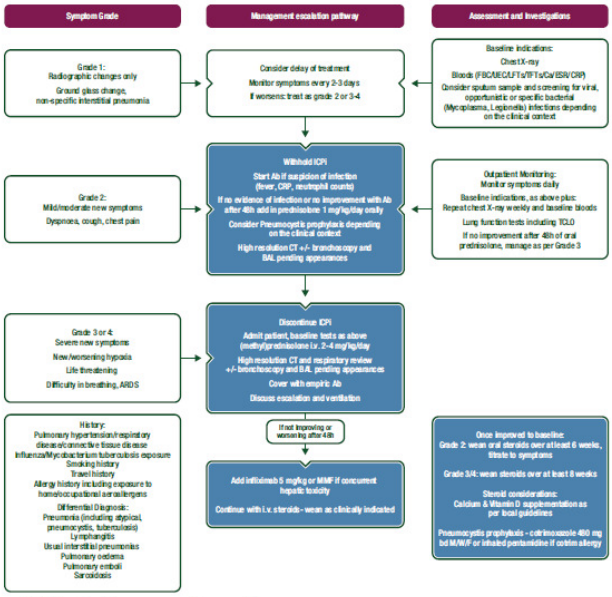


Hepatitis

- Pojavi se pri 5-10% bolnikov
- G2 – začasna prekinitev z imunoterapijo, do znižanja na G1. Če vztraja daj kot 2 tedna, kortikosteroidi (prednizolon 1mg/kg/dan)
- G3,4 – ukinitev imunoterapije in kortikosteroidi (prednizolon 1mg/kg/dan), če ni odgovora biopsija jeter in konzultacija s hepatologom



Pneumonitis



Zaključki

- PD-1 inhibitorji so učinkovita imunoterapija, ki jo že uporabljamo v zdravljenju melanoma, pljučneag raka, raka ledvic, raka mehurja, raka glave in vratu ter Hodgkinovega limfoma.
- Neželeni učinki so utrujenost, srbež, izguba apetita in diareja, lahko tudi pneumonitisa, hepatitisa ali hipofizitis.
- Neželeni učinki so običajno blagi in dobro obvladljivi.

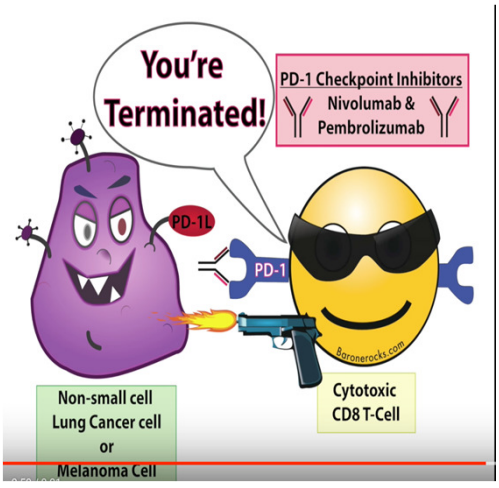
Zdravljenje bolnika z met. svetloceličnim karcinomom ledvice s PD-1 zaviralcem - nivolumabom

Dr. Marina Mencinger dr. med.
Onkološki Inštitut, Ljubljana,
Sept 2017, Imunoterapija v onkologiji

Nivolumab: Zaviralec PD-1 imunskih stikal

Receptor PD-1 na T celicah zavira imunski sistem.
To preprečuje avtoimune bolezni, a prepreči delovanje imunskega sistema proti tumorskim celicam.

Nivolumab je humano monoklonsko IgG4 protitelo, ki se veže ne PD-1 receptor ter deblokira zavrt imunski sistem.



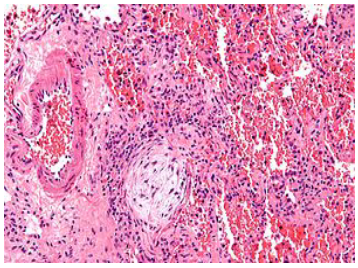
https://www.youtube.com/watch?v=50cFleeWgZA

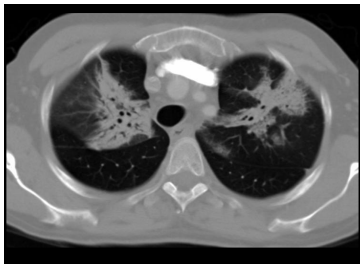
Kaj je intersticijski pnevmonitis?

Simptomi /znaki:(dispnea, kašelj, bolečina v prsih, utrujenost, izguba teže, vročina)

Diagnostika:
HR-CT
BAL, pljučna biopsija
pljučne funkcije (znižana DLCO)

Histologija





Pnevmonitis je “star znanec”….pri sistemskem onkološkem zdravljenju ter obsevanju

Onkološka zdravila, ki povzročajo pneumonitis:

Citostatiki-docetaxel, bleomicin, gentamicin

Tarčna zdravila: zaviralci EGFR-cetuximab, transtuzumab, erlotinib, gefitinib, lapatinib

mTOR inhibitorji: temsirolimus, everolimus

OBSEVANJE

1-Topalian ST, NEJM 2012

Pogostost intersticijskega pnevmonitisa z nivolumabom (smpc)

Pnevmonitis, dispnea kašej: : pogosti (≥ 1/100 do < 1/10)

Nivolumab v monoterapiji: pojavnost pnevmonitisa, vključno z boleznijo pljučnega intersticija in s pljučnimi infiltrati, znašala 3,0 % (67/2.227).
Resnost večine primerov je bila stopnje 1 ali 2.
O primerih stopnje 3 so poročali pri 0,7 % (16/2.227) bolnikov, o primerih stopnje 4 pa pri < 0,1 % bolnikov (1/2.227).

Mediani čas do pojava je znašal 3,3 meseca (razpon: 0,0-19,6).
Do izboljšanja je prišlo pri 52 bolnikih (78 %), mediani čas do izboljšanja pa je znašal 5,6 tedna (razpon: 0,1+-53,1);.

Moški, 60 let,

Živi z ženo, dva otroka

Hipertonik od 2009, operacija hernija disci, trebušne kila, Dupytrenova kontraktura,
Zdravila:, Prenessa 4, Coupet 1 tbl., Aspirin 100, Omnic ocas 1 tbl, Codein, Doreta pp, Loram zv,

2009 hematurija, tu desne ledvice, D nefrektomija, DG: svetlocelični ca

2015 sept: bolečina aksilarno, shujšal 10 kg, se hitro zadiha, tipna zadebelitev ob rebrih aksilarno 10 cm
Lab: Hb 129, Ca 3.2, CRP 57,

1. red zdravljenja

RTG, CT: zasevki v torakalni steni (plevra, rebra), mediast bezg,
Biopsija zasevka v 8. rebru: potrdi zasevek svetlocelični ca

Dec 2015:
1. Pazopanib 400 mg (polovični odmerek), ki smo ga v 1 m dvignili na 800 mg

2. Hiperkalciemija
Hidracija, Zoledronska kislina 4mg/mesec iv.

Opusti naj statin.

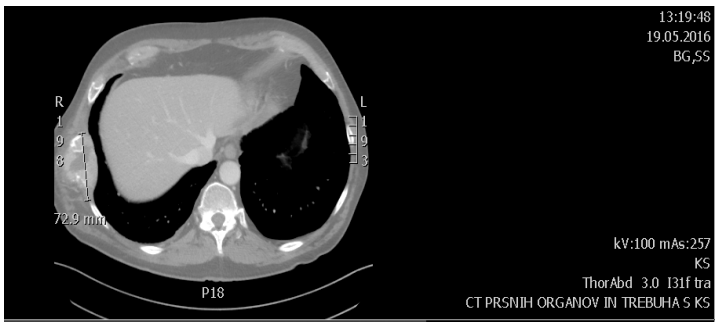
Stranski učinki pazopaniba

JAN 2016

1. Splošno počutje boljše, izboljšan apetit, krvavitev iz nosu 2x po 30 min
2. Hemogram : levko, nevtropenija 1.0x 10 9, Hb 128, Tr N, CRP 142, jetrni testi normalni
3. Krvni pritisk 160/80

4. Prehodna ukinitev pazopaniba.
5. Napotitev k ORL specialistu-lasersko požgal krvavečo žilico.
6. Ureditev krvnega pritiska z antihipertenzivi

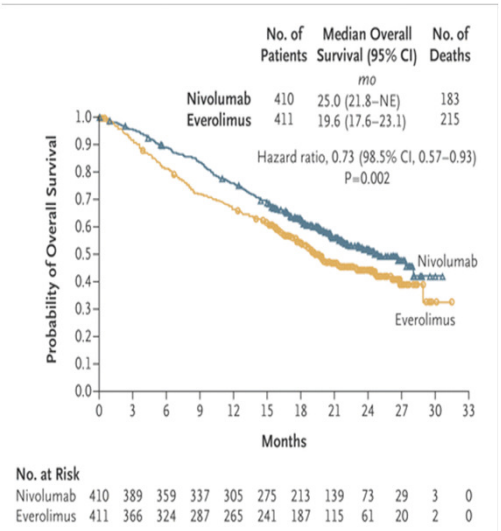
Učinkovitost pazopaniba: progres večje lezije, mešan odgovor



CT maj 2017, primerjava s 24.11.2016:
V poteku VIII. rebra desno lateralno je videti mehkotkivno formacijo z destrukcijo rebra premera cca 73 mm (predhodno 43 mm).
Plevra desno je mestoma nodularno zadebeljena - nekoliko manj kot pri predhodni preiskavi, zadebelitve je videti tudi v interlobiju

Učinkovitost nivolumaba pri karcinomu ledvic

Podaljšano preživetje pri bolnikih z metastatskim svetloceličnim karcinomom ledvice v primerjavi z everolimusom pri bolnikih, ki so predhodno prejemali enega od tirozin kinaznih inhibitorjev (sunitinib ali pazopanib).



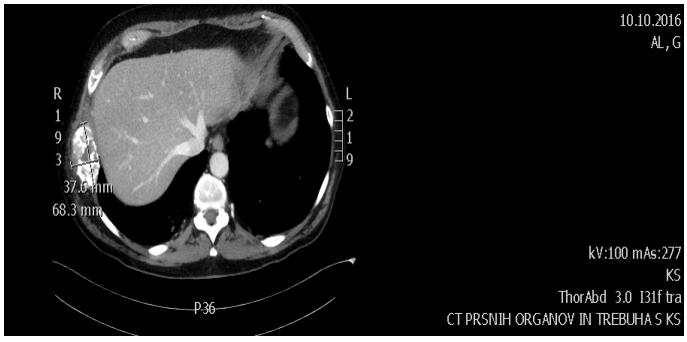
NEJM, Motzer et al, 2015

Klinično stanje pred uvedbo nivolumaba

Ob pregledu: brez težav s strani dihanja, splošno počutje dobro, apetit izboljšan, bolečina aksilarno

Lab.: CRP 27, Hb 117, Ca 2,76

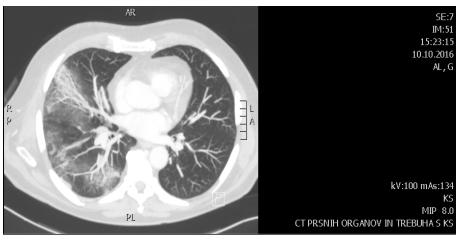
Učinkovitost nivolumaba-regres



CT 10.10.2016: Zasevki v bezgavkah mediastinuma, plevri, pljučih in skeletu reber desno so se glede predhodnega CT 19.05.2016 zmanjšali, posamezni že v regresu.

VENDAR……

Organizirajoča pljučnica ob nivolumabu



CT 10.10.2016: Na novo so vidni obsežnejši intersticijski infiltrati v desnem pljučnem krilu, mestoma alveolarni- CT lahko pnevmonični ali medikamentozni ? glede na obliko manj verjetno postobsevalne narave

Pulmolog: bronhoskopija s TBB, pljučne funkcije

DG: **kriptogena organizirajoča pljučnica**,
Medrol 32 mg, pulmolog svetuje nadaljevanje z nivolumabom

Pnevmonitis se največkrat pojavi v prvih 6 mesecih..

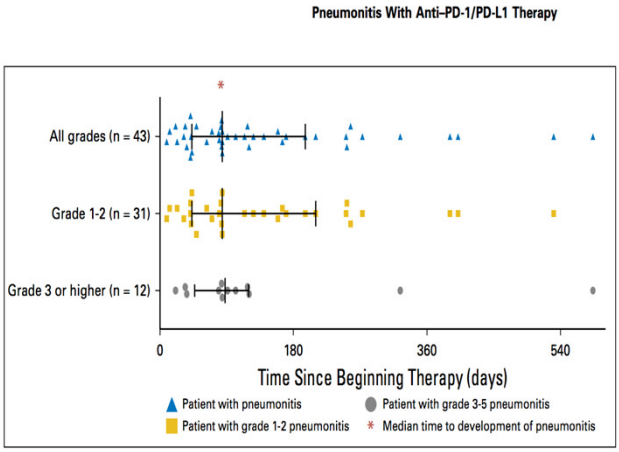
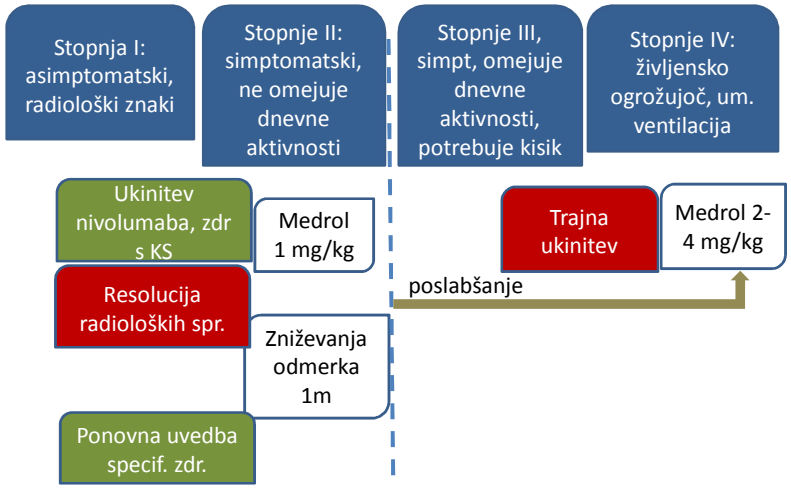


Fig 1. Time from first dose of anti–programmed death-1/programmed death ligand 1 therapy to date of pneumonitis event stratified by grade, with interquartile range and median values shown.

Naidoo, JCO, 2017

Ukrepi ob pnevmonitisu (SMPC-nivolumab)



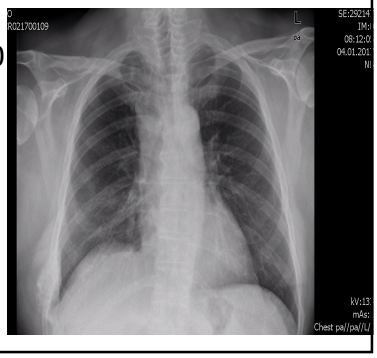
Klinično spremljanje

V **nov 2016**, Kontrola pri pulmologu, RTG izboljšanje, pljučne funkcije brez dinamike.
Zniževanje Medrola.

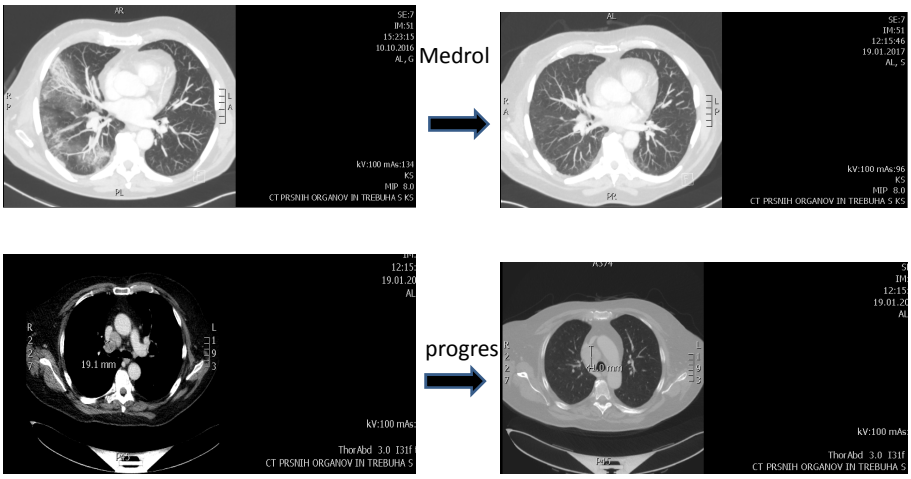
Dec 2016 navaja dispneo**,** ukinjen nivolumab za en mesec, nadaljuje z Medrolom v odmerku 24 mg

Konec dec 2016 povišana TT do 39, CRP 200
Uvede se antibiotik Amoksiklav,

Jan 2017:
Še kašlja. Klinično slabši.
Lab: CRP 50,
RTG pc regres IT sprememb,
nujni CT



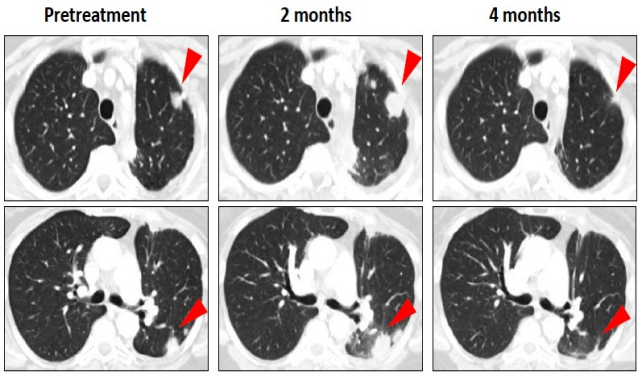
Resolucija intersticijskih sprememb na pljučih, vendar...



19.1.2017: Progres zasevkov v mediastinalnih bezgavkah. Regres zgostitev na plevri D. Ostale lezije v stagnaciji.

Progres zaradi ukinitve zdravljenja?
Progres zaradi prejemanja kortikosteroidov?
Pseudoprogres?
Rezistenca na nivolumab?

Pseudoprogres

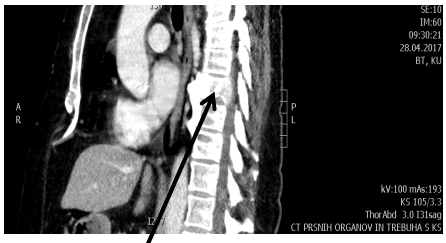


- Ni pogost.
- V klinični raziskavi CheckMate 057, 16/71 bolnikov ki je prejelo zdravljenje po progresu (22%), ali 16/292 bolnikov, ki je prejelo nivolumab (5%)

Topalian S et al. *NEJM* 2012;

Nadaljevanje z nivolumabom po progresu v mediastinumu...

Klinično se stanje počasi izboljšuje. Manj kašlja. Še vedno se hitro zadi

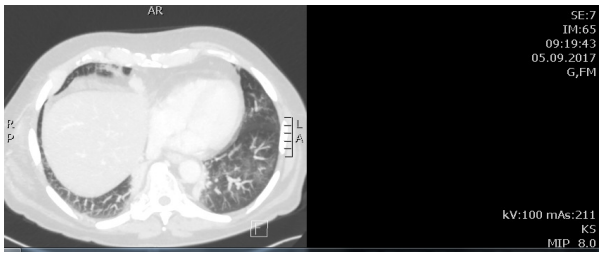


CT 28.4. 2017: Stanje po patološki frakturi korpusa TH8, mehkotkivna komponenta zasevka nekoliko utesnjuje spinalni kanal ter levi i.v. foramen nivoja TH8/9. Stagnacija oz regres ostalih lezij.

Nadaljuje z nivolumabom ter lokalno zdravljenje frakture-obsevanje T

Ponoven zagon intersticijskega pnevmonitisa?, okužba?, progres?

Avg 2017: več kašlja, po 100 m se zadiha, ➡ Ukinitev nivolumaba



CT 5.9. 2017 V pljučih obojestransko mediobazalnih segmentih so vidne alveolarne zgostitve z zračnim bronhogramom, desno premera 46x19, levo 43 x 12 mm - lahko gre za vnetne infiltrate. Zadebeljen intersticij obojestransko posterobazalno - fibrozne spremembe? Ostale lezije v stagnaciji.

Torej ponoven zagon pnevmonitisa?....

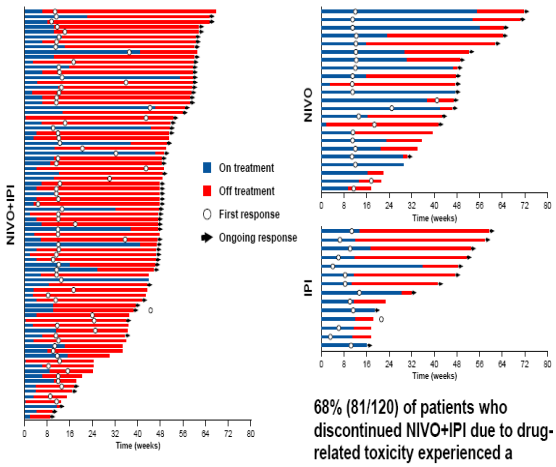
Trenutno v diagnostiki na KOPA Golnik

Pljučne funkcije:

Bronhoskopija s TBB:

Time to and Durability of Response in Patients Who Discontinued Due to Toxicity

- A total of 38% (120/314) of patients who received NIVO+IPI discontinued due to toxicity



68% (81/120) of patients who discontinued NIVO+IPI due to drug-related toxicity experienced a complete or partial response

Larkin, ECC, 2015

Priporočila proizvajalca glede stranskih učinkov

Bolnike je treba neprestano nadzirati (**še vsaj do 5 mesecev po aplikaciji zadnjega odmerka**), saj se neželeni učinki nivolumaba ali nivolumaba v kombinaciji z ipilimumabom lahko pojavijo v katerem koli času med zdravljenjem ali po ukinitvi zdravljenja.

Kaj ste prejemali v zadnji polovici leta?

Ob kombinaciji zaviralcev stikalnih točk, je p pogosteje težje stopnje

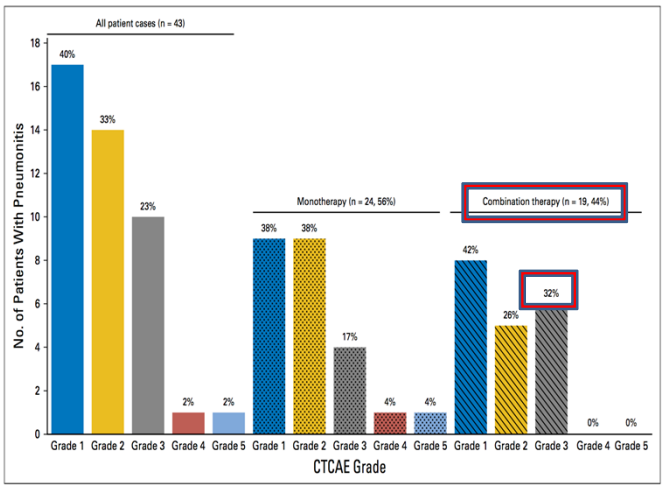


Fig 2. Patients in whom pneumonitis developed stratified by highest Common Terminology Criteria for Adverse Events (version 4.0; CTCAE) grade, including whether patients received anti–programmed death-1/programmed death ligand 1 monotherapy versus in combination with anti–cytotoxic T-cell lymphocyte associated antigen-4 monoclonal antibody.

Št vseh pacientov 915

Naidoo, JCO, 2017

Zaključek

- Pri bolnikih, ki prejemajo zaviralce stikalnih točk ali kombinacije z njimi je potrebno pomisliti na možne avtoimune bolezni.
- Pomembno je tesno sodelovanje med specialisti različnih ved.
- Toksičnost lahko zaustavimo s kortikosteroidi ali drugimi imunosupresivnimi zdravili.
- Toksičnost/učinkovitost zdravljenja se lahko pojavi po prenehanju zdravljenja oz ob ponovni uvedbi zdravljenja.

AntiPDL1 – uporaba, delovanje, neželeni učinki

Breda Škrbinc

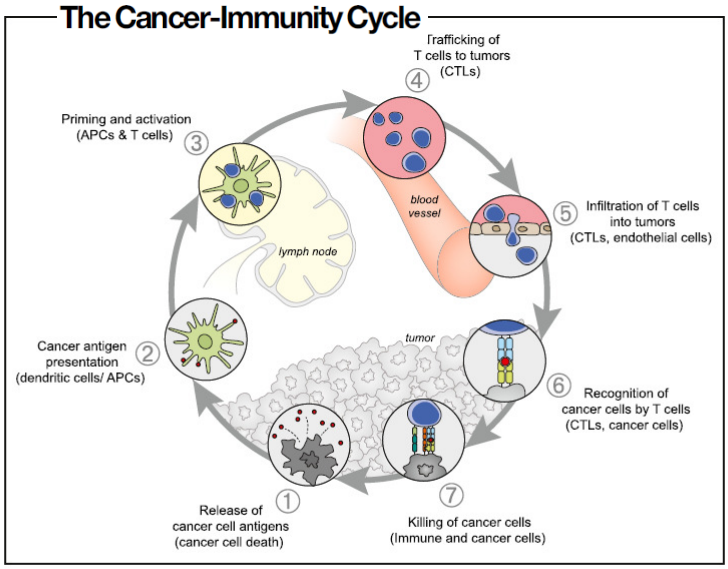
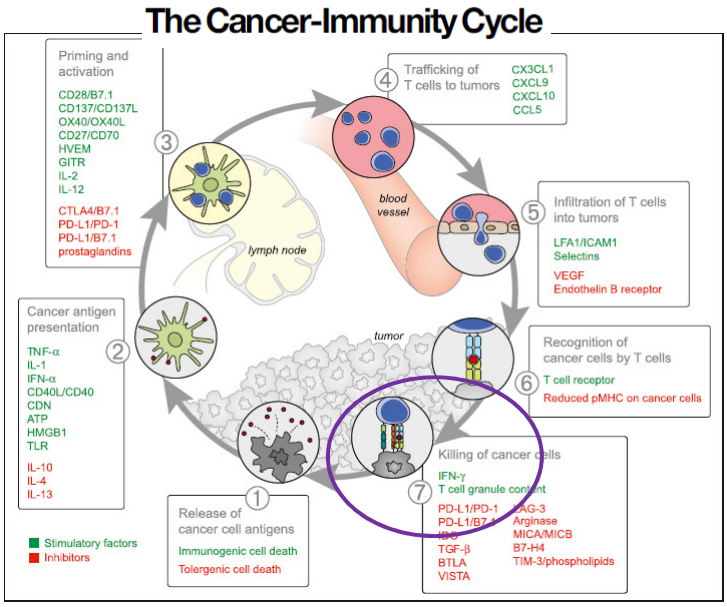


Figure 1. The Cancer-Immunity Cycle

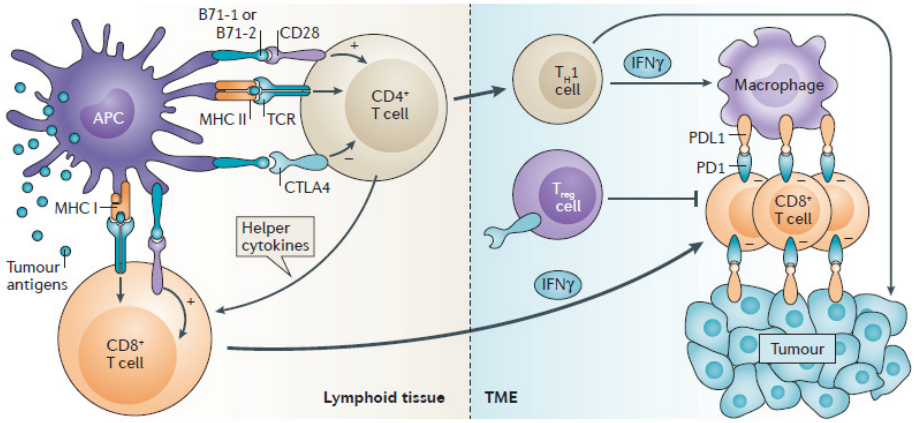
The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and the anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells; CTLs, cytotoxic T lymphocytes.

Immunity 39, July 25, 2013 ©2013 Elsevier Inc.



Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle

Immunity 39, July 25, 2013 ©2013 Elsevier Inc.



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"PDLOMAS" ACTIVITY IN 2015

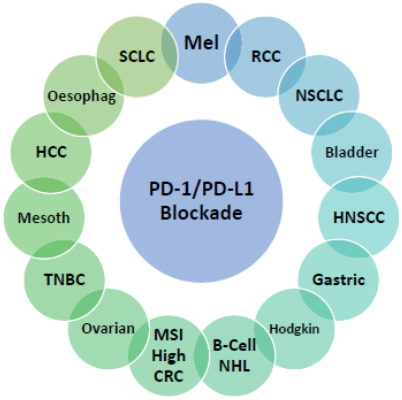
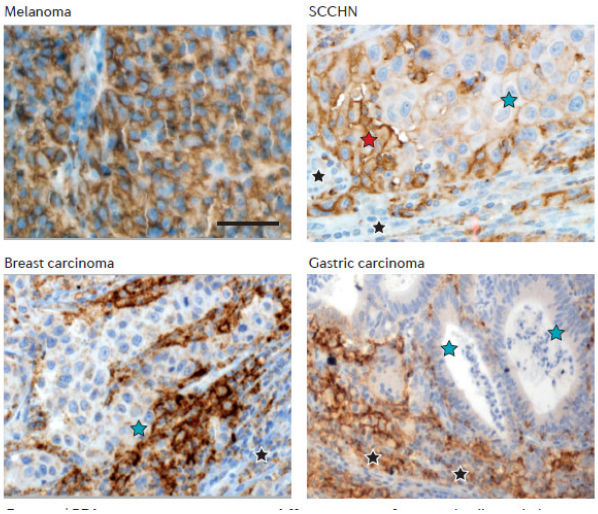


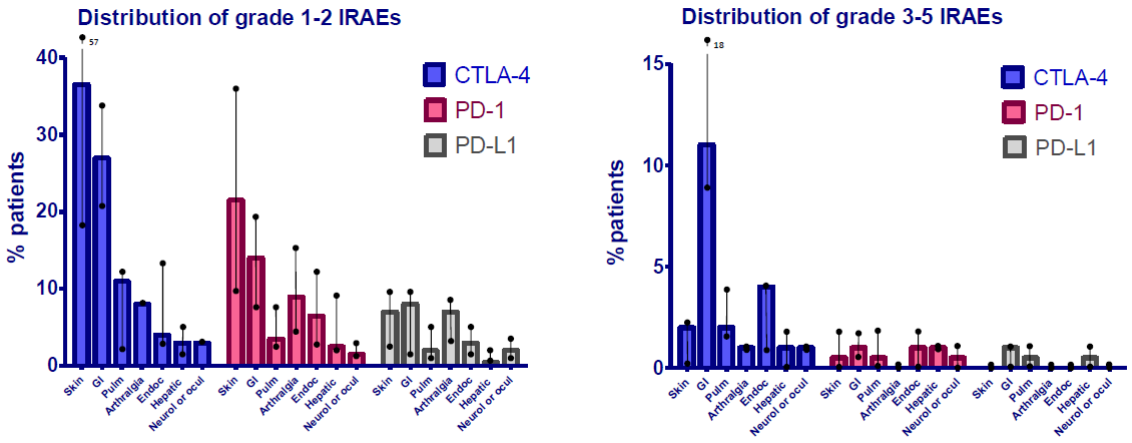
Fig. 1. The spectrum of activity of PD-1 and PD-L1 antibodies in many types of cancer defines the 'PDLoma' concept. PD-1: programmed cell death protein; Mel: melanoma; RCC: renal cell carcinoma; NSCLC: non-small cell lung cancer; HNSCC: head and neck squamous cell carcinoma; NHL: non-Hodgkin lymphoma; MSI high CRC: microsatellite instability colorectal carcinoma; TNBC: triple-negative breast cancer; Mesoth: mesothelioma; HCC: hepatocellular carcinoma; oesophag: oesophageal cancer; SCLC: small cell lung cancer.

J.M. Michot et al. / European Journal of Cancer 54 (2016) 139–148

PDL1 expression patterns in different types of cancer



NATURE REVIEWS | CANCER VOLUME 16 | MAY 2016 | 275



Distribution of grade IeII and grade IIIeV IRAEs for all tumour types in the main clinical trials with anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies as single therapies.

The values quoted are the median (range) IRAE rates for the set of clinical trials as a whole. IRAEs: immune-related adverse events; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; PD-1: programmed cell death protein; GI: Gastro-Intestinal.

J.M. Michot et al. / European Journal of Cancer 54 (2016) 139–148

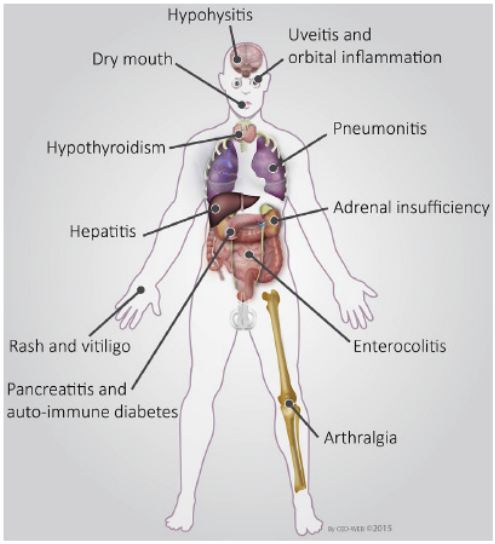


Fig. 3. The clinical spectrum of IRAEs. IRAEs: immune-related adverse events.

J.M. Michot et al. / European Journal of Cancer 54 (2016) 139–148

The overall management approach and actions to be implemented for IRAEs associated with immune checkpoint blockade, according to the Common Terminology Criteria for Adverse Events (CTCAE) severity grade.

Severity CTCAE grade	Type of patient care	Steroids	Other immunosuppressive drugs	Immunotherapy and subsequent approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or systemic steroids oral 0.5−1 mg/kg/d	Not recommended	Suspend** temporarily
3	Hospitalisation	Systemic steroids oral or IV 1−2 mg/kg/d for 3 d then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3−5 d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalisation consider the intensive care unit	Systemic steroids IV methylprednisolone 1−2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3−5 d of steroid course Organ specialist advised	Discontinue permanently

** Outside skin or endocrine disorders, where immunotherapy can be maintained.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECENTRIQ safely and effectively. See full prescribing information for TECENTRIQ.

Indications and Usage (1.1) 10/2016
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6) 10/2016

INDICATIONS AND USAGE

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for cisplatin-containing chemotherapy, or
  - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. (1.1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

- Metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ. (1.2)

DOSAGE AND ADMINISTRATION

- Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Related Pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-Related Hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.2)
- Immune-Related Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.3)
- Immune-Related Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold for symptomatic thyroid disease.
  - Adrenal Insufficiency: Withhold for symptomatic adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold for ≥ Grade 3 hyperglycemia.
- Immune-Related Myasthenic Syndrome/Myasthenia Gravis, Guillain-Barré or Meningoencephalitis: Permanently discontinue for any grade. (5.5)
- Ocular Inflammatory Toxicity: Withhold for moderate and permanently discontinue for severe ocular inflammatory toxicity. (5.5)
- Immune-Related Pancreatitis: Withhold for moderate or severe, and permanently discontinue for life-threatening pancreatitis, or any grade of recurring pancreatitis. (5.5)
- Infection: Withhold for severe or life-threatening infection. (5.6)
- Infusion Reaction: Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions. (5.7)
- Embryo-Fetal Toxicity: TECENTRIQ can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 25%) in patients with locally advanced or metastatic urothelial carcinoma were fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, and pyrexia. (6.1)

Most common adverse reactions (≥ 20%) in patients with metastatic non-small cell lung cancer were fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAVENCIO safely and effectively. See full prescribing information for BAVENCIO.

----------INDICATIONS AND USAGE----------

BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). (1)

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)
- Premedicate with acetaminophen and an antihistamine for the first 4 infusions and subsequently as needed. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Immune-mediated pneumonitis: Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis. (5.2)
- Immune-mediated colitis: Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis. (5.3)
- Immune-mediated endocrinopathies: Withhold for severe or life-threatening endocrinopathies (5.4)
- Immune-mediated nephritis and renal dysfunction: Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction. (5.5)
- Infusion-related reactions: Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions. (5.7)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (reported in ≥ 20% of patients) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMFINZI safely and effectively. See full prescribing information for IMFINZI.

---------- INDICATIONS AND USAGE ----------

IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy. (1)
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 500 mg/10mL (50 mg/mL) solution in a single-dose vial. (3)
- Injection: 120 mg/2.4mL (50 mg/mL) solution in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Immune-Mediated Pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (2.2, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (2.2, 5.2)
- Immune-Mediated Colitis: Withhold for moderate and permanently discontinue for severe or life-threatening colitis. (2.2, 5.3)
- Immune-Mediated Endocrinopathies:
  - Adrenal Insufficiency, Hypophysitis, or Type 1 Diabetes Mellitus: Withhold for moderate, severe or life-threatening. (2.2, 5.4)
- Immune-Mediated Nephritis: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening nephritis. (2.2, 5.5)
- Infection: Withhold for severe or life-threatening infection. (2.2, 5.6)
- Infusion-Related Reactions: Interrupt infusion or slow the rate of infusion for mild or moderate and permanently discontinue for severe or life-threatening infusion-related reactions. (2.2, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

Most common adverse events (reported in ≥15% of patients) were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

IMUNOTERAPIJA V ONKOLOGIJI
Ljubljana, 28.9.2017

Predstavitev bolnika z malignomom pljuč na zdravljenju z antiPDL1

Mag. M. Unk, dr. med.
Onkološki inštitut Ljubljana

- 69 letni bolnik
- DB: arterijska hipertenzija, hiperlipidemija, generalizirana ateroskleroza (periferna arterijska obliterativna in koronarna boleznen, aortobifemoralni obvod in TEA ACI sin. (2007), žilna opornica v RCA (2011 in 2012) in v ACI dex. (2013),
- V predoperativni obravnavi januarja 2013 opravljen RTG p/c – lezija v levem zgornjem pljučnem režnju
- Slikovna in invazivna pulmološka diagnostika (bronhoskopija): LZR nedrobnocelični karcinom

- 21. 2. 2013:
  leva zgornja lobektomija
- Dokončen pato-histološki izvid:
  pT1b N0 R0
  pT1b: velikocelični karcinom 30×20 mm
  pN0: bezgavke (subaortne 0/8, hilusne 0/2, interlobarne 0/2)
- Brez dopolnilnega zdravljenja

- Februarja 2014: RTG p/c
  ovalna sprememba v preostanku levega pljučnega krila
- Februar 2014: CT prsnega koša
  sumljiva zgostitev v levem spodnjem pljučnem režnju (LSpR), velikosti 2,5 x 3 cm, sumljivo za vraščanje v visceralno plevro. Brez znakov razsoja v prsnem košu
- Marec 2014: PET/CT
  primarni pljučni tumor v apikalnem delu levega spodnjega pljučnega režnja z zasevkoma v levem jetrnem režnju

- April 2016:

  prvič na OI

  dispneja ob zmerni telesni obremenitvi (PS po WHO 1)

  v kliničnem statusu brez večjih odstopanj

  laboratorijski izvidi brez pomembnejših odstopanj

  Redna terapija: Aspirin P 100 mg, Plavix 75 mg, Nebilet 5 mg, Tertensif SR 1tbl., Bioprexanil 5 mg, Preductal MR 2x1 tbl., Sinvacor 40 mg, NLG p.p.

- RTG p/c (april 2014):

  tumorska formacija v apikalnem segmentu LSpR, velikosti 62x32 mm (feb 2014 na CT 25x30 mm)

- CT glave:

  brez znakov za razsoj

- Citološka verifikacija lezije v levem jetrnem režnju (april 2014):

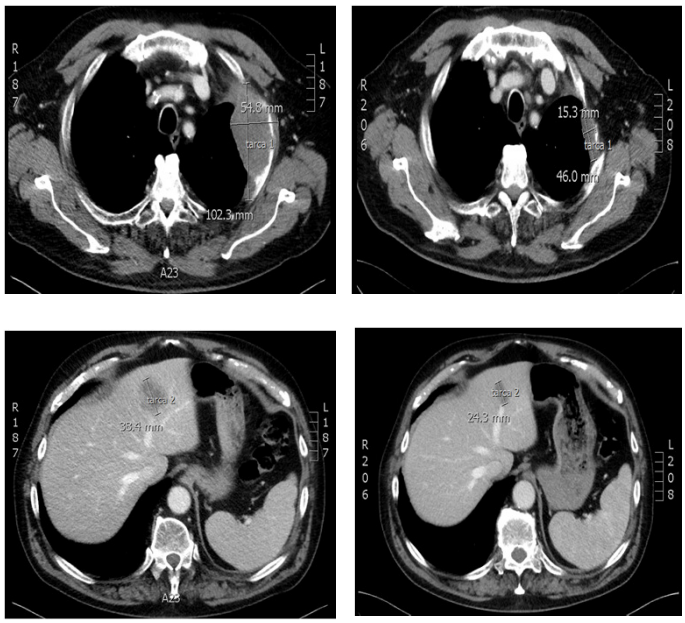
  zasevek slabo diferenciranega velikoceličnega karcinoma; EGFR negativen

- iz vzorcev pridobljenih med operativnim posegom leve zgornje lobektomije pljuč: ALK negativen in PD-L1pozitiven (BIRCH)

- VENDAR: hitro napredovanje bolezni (povečanje obeh zasevkov v jetrih za več kot 50% v 2 mesecih)
  Ni časa za čakanje na začetek klinične raziskave!
- Aprila 2014: pemetreksed/karboplatin → progres po 2 ciklusih v jetrih in pljučih, retroperitonealnih bezgavkah in skeletu
- V klinični sliki pojav in stopnjevanje kašlja ter tope tiščoče bolečine v levem hemitoraksu, pojav hemoptiz
- Junija 2014: atezolizumab (anti PD L1) v sklopu klinične raziskave

- Že po 1. aplikaciji kliničen odgovor
  (zmanjšanje intenzivnosti in pogostosti napadov kašlja, bolečin v levem hemitoraksu ter prenehanje hemoptiz; stomatitis II. stopnje po drugi in tretji aplikaciji)
- CT prsnega koša in trebuha v avgustu 2014: regres bolezni
  (v pljučih, v jetrih, stagnacija v abdominalnih bezgavkah ter kosteh (modificirani iRECIST kriteriji))

20.6.2014 15.9.2014



- januar 2015:

  po 10 aplikacijah atezolizumaba porast vrednosti serumskega kreatinina (razlog?)

  DD: kontrast?, statin in rabdomioliza?

  imunoterapija začasno prekinjena

  kontrolni CT prsnega koša in trebuha: delni odgovor, ki vztraja

- februar 2015: dobro splošno počutje, blage bolečine v stegnih, brez večjih odstopanj v kliničnem statusu, v laboratorijskih izvidih nadaljnje višanje vrednosti kreatinina in encimov skeletno-mišičnega razpada, blag porast telesne teže, in blaga bradikardija (beta blokator?)

  DD: avtoimuno? s statini povzročena avtoimuna miopatija? toksična miopatija? paraneoplastično?....

- februar 2015:

  laboratorijsko hipotiroza

  tirolog: kronični limfocitni tiroiditis; nadomestno hormonsko zdravljenje → upad vrednosti serumskega kreatinina in encimov skeletno mišičnega razpada (do popolne normalizacije)

- marec 2015 (8 tednov po zadnji aplikaciji)

  CT prsnega koša in trebuha: še vedno regres oz stagnacija glede na izhodiščne CT preiskave

- april 2015:

  po 3 mesečnem premoru nadaljevanje imunoterapije

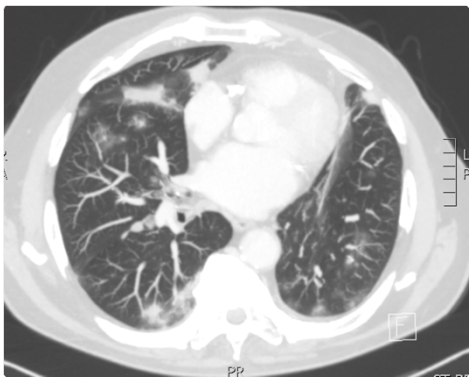
- oktober 2015:

  klinično in radiološko stabilno stanje, nadaljuje z zdravljenjem do CT prsnega koša in trebuha (1.10.2015): pojav številnih manjših zgostitev tipa „mlečnega stekla“ v spodnjih predelih obeh pljučnih kril, stagnacija tarčnih lezij

  klinična slika: brez respiratorne simptomatike, v statusu pojav zgodnjih inspiratornih pokov obojestransko bazalno

  začasna prekinitev imunoterapije → invazivna pulmološka diagnostika v drugi ustanovi

  histološka analiza bronhoskopskih odvzemkov iz predela lezij tipa „mlečnega stekla“ (TBB): organizirajoča pljučnica



Hipersenzitivni pneumonitis

1.10.2015

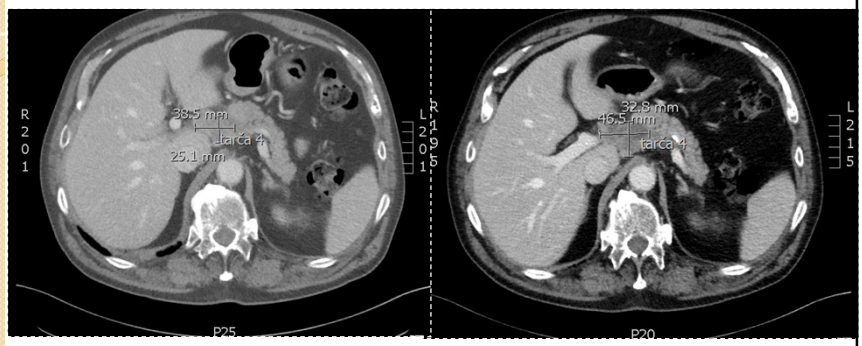
- december 2015:

  CT prsnega koša in trebuha:

  stagnacija zgostitev tipa „mlečnega stekla“ v pljučih in večine tarčnih lezij z izjemo konglomerata bezgavk med jetri in trebušno slinavko, ki je v progresu glede na iRECIST kriterije

  Hipersenzitivni pneumonitis povsem asimptomatski, pulmološki konzilij OI oceni, da je smiselno nadaljevanje imunoterapije po 2,5 mesečnem premoru kljub “fokalnemu” progresu

1.10.2015 3.12.2015



Napredovanje "fokalno"

- september 2016:

  brez subjektivnih težav, PS po WHO 0

  kontrolne CT preiskave:

  stagnacijo tarčnih lezij kot tudi zgostitev tipa „mlečnega stekla" v pljučih

  preiskave pljučne funkcije: blaga restrikcija, brez dinamike od decembra 2015

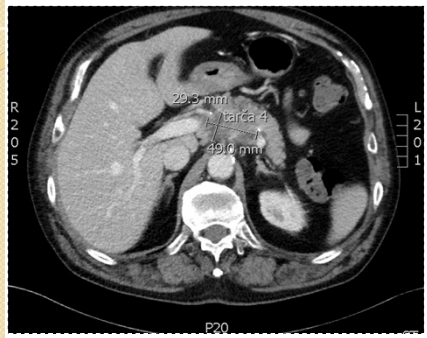
- oktober 2016:

  CT prsnega koša in trebuha:

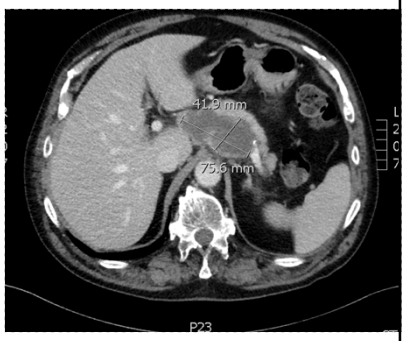
  izrazit progres konglomerata bezgavke med jetri in trebušno slinavko (vraščanje), pojav manjših nodularnih lezij v pljučih in mehkih tkivih (podkožje), stagnacija preostalih tarčnih lezij in zgostitev tipa „mlečnega stekla“ v pljučih

  Pulmološki konzilij: začasni premor imunoterapije, obsevanje konglomerata bezgavk med jetri in trebušno slinavko,

4.8.2016

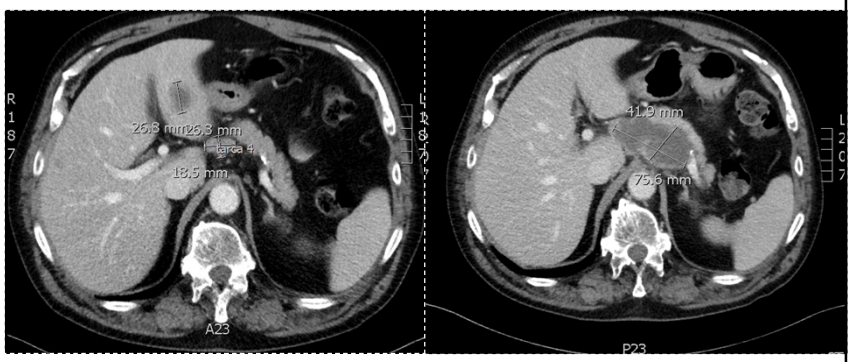


6.10.2016



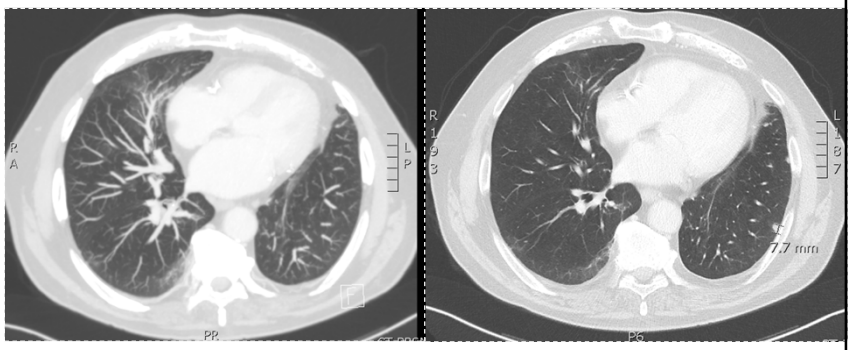
napredovanje v 2 mesecih

20.6.2014 6.10.2016



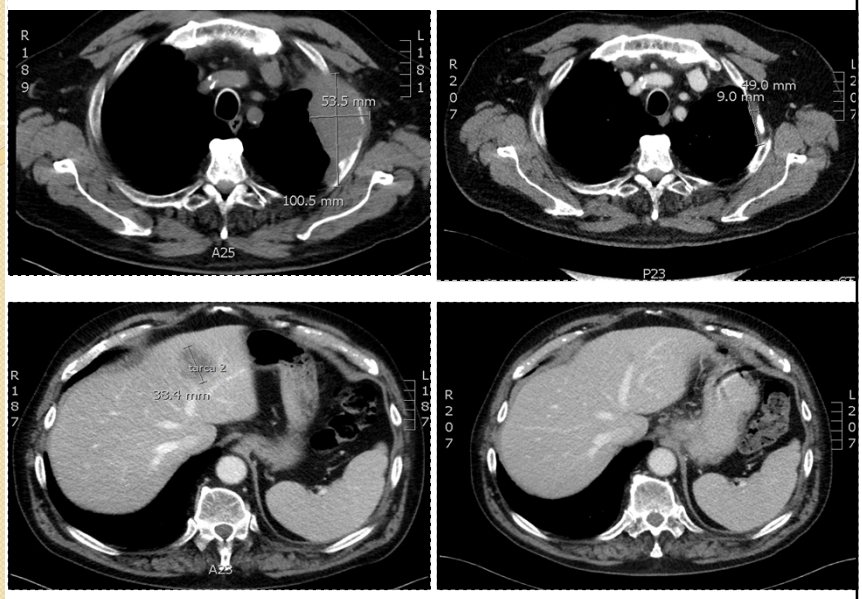
napredovanje v 2 letih

4.8.2016 6.10.2016



napredovanje v pljučih

20.6.2014 6.10.2016



vendar,..

- November 2016
  nadaljuje z atezolizumabom
- September 2017
  še vedno na zdravljenju z atezolizumabom
  asimptomatski, PS po WHO 0

POUDARKI

- Kljub metastaski bolezni dolgo preživetje
- Specifični sopojavi, obvladljivi, predvidljivi, a je potrebno pomisliti nanje
- Zdravljenje v sklopu klinične raziskave, če se le da, pri vseh bolnikih z rakom
- Multidisciplinarno sodelovanje večih ustanov

- hvala za pozornost

SIMPOZIJ SO PODPRLE NASLEDNJE DRUŽBE:

SERVIER

ELI LILLY

MSD

AMICUS

ROCHE

AMGEN

TEVA

JANSSEN

PFIZER

ABBOTT

ASTRA ZENECA