ONKOLOŠKI INŠTITUT LJUBLJANA

INSTITUTE OF ONCOLOGY LJUBLJANA

Slovensko zdravniško društvo

Sekcija za internistično onkologijo

KATEDRA ZA ONKOLOGIJO

13. DAN INTERNISTIČNE ONKOLOGIJE

Novosti v sistemskem zdravljenju redkejših solidnih rakov

ONKOLOŠKI INŠTITUT LJUBLJANA

17. NOVEMBER 2017

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

Ljubljana, november 2017

VSEBINA:

PROGRAM SREČANJA: **PETEK, 17.11.2017**

07.00-08.30 **REGISTRACIJA UDELEŽENCEV**

08.30-09.15 **SATELITNO PREDAVANJE 1 (ELI LILLY)**
09.15-09.20 *Matos E.:* Uvod
Moderator: dr. Erika Matos, dr.med., mag. Zvezdana Hlebanja, dr.med.
09.20-09.30 *Zakotnik B.:* Obravnava redkih rakov – projekt »Rare Care Net«
09.30-10.15 *Grašič-Kuhar C.:* Sistemsko zdravljenje raka ščitnice
Azarija J., Grašič-Kuhar C.: Predstavitev primera
10.15-11.00 *Unk M.:* Sistemsko zdravljenje GIST-ov
Čakš M., Unk M.: Predstavitev primera

11.00-11.15 **ODMOR S KAVO**

Moderator: dr. Erika Matos, dr.med., mag. Zvezdana Hlebanja, dr.med.
11.15-12.00 *Čufer T.:* Sistemsko zdravljenje timičnega raka
Janžič U., Čufer T.: Predstavitev primera
12.00-12.45 *Reberšek M.:* Sistemsko zdravljenje raka žolčnika in žolčnih vodov
Fokter-Dovnik N., Boc M.: Predstavitev primera
12.45-13.15 **SATELITNO PREDAVANJE 2 (ROCHE)**

13.15-14.15 **KOSILO**

Moderator: dr. Simona Borštnar, dr.med., Marko Boc, dr.med.
14.15-15.00 *Škrbinc B.:* Sistemsko zdravljenje nekaterih redkih uroloških rakov (rak penisa, urahus)
Pavlova-Bojadžiski M., Škrbinc B.: Predstavitev primera
15.00-15.50 *Ocvirk J.:* Sistemsko zdravljenje redkih kožnih rakov (karcinom Merklovih celic, razsejan BCC)
Ignjatović M., Ocvirk J.: Predstavitev primera

15.50-16.00 **ZAKLJUČEK (Matos E.)**

16.00-16.15 **ODMOR**
16.15-16.45 **SKUPŠČINA SEKCIJE ZA INTERNISTIČNO ONKOLOGIJO**

Redki raki

B. Zakotnik

Dan internistične onkologije 17.11.2017

Vsebina

1. Definicija
2. Incidenca
3. Preživetje
4. Diagnostični problemi
5. Zdravljenje
6. Zaključek

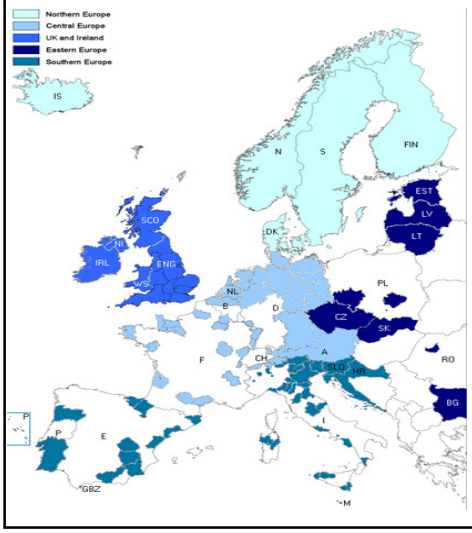
1. Definicija

- Redki raki (v sklopu redkih bolezni) izpostavljeni kot posebna entiteta v EU!
- Pri raku prevalenca ni najprimernejše merilo za breme bolezni, odvisna od incidence in preživetja
- **Definicija:** groba **incidenčna** stopnja

< 6/100.000 prebivalcev

(zelo redki <1/100.000)

RARECARE (Surveillance of rare cancer in Europe)



- Trajanje projekta 2007-2010
- Seznam 186 redkih entitet (so pripravili strokovnjaki kliniki, epidemiologi, patologi, hematologi, predstavniki strokovnih organizacij in organizacij bolnikov)
- Breme redkih rakov v Evropi (podatki iz EUROCARE-4, obdobje 1995-2002 (ocena za 2008), 21 držav, 89 populacijskih registrov raka)

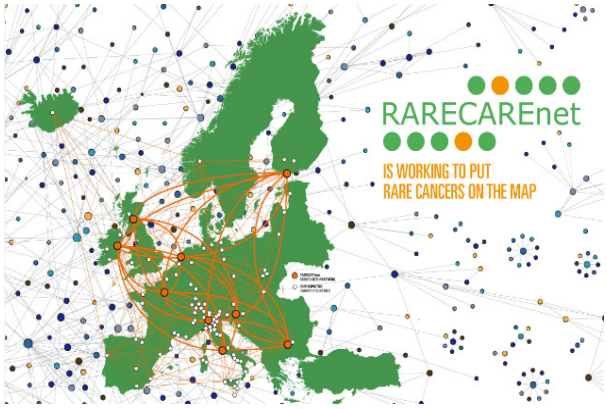
RARECARENet

Co-funded by the Health Programme of the European Union

European Commission

Information network on rare cancers (2012-2015)
http://www.rarecarenet.eu/

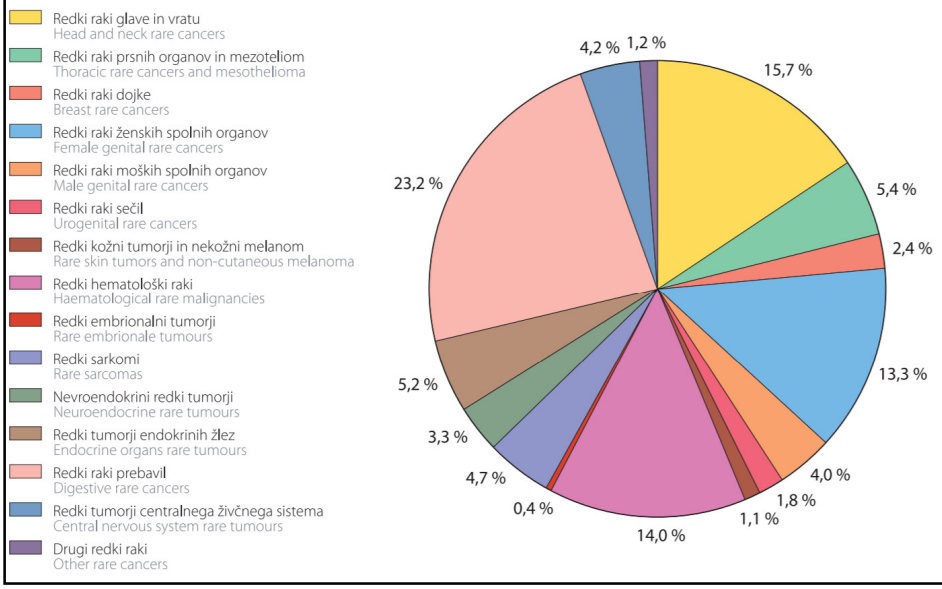
- analiza kliničnih poti
- obravnava redkih rakov v referenčnih centrih



Pilotni projekt s katerim so

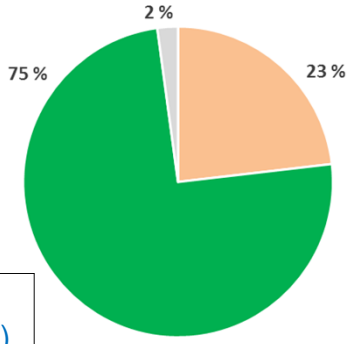
- Preučili zdravljenja
- Določili stopnjo centralizacije
- Ocenili povezavo s izzidom zdravljenja (preživetje)

Redki raki razporejeni v 15 družin, Slovenija 2004–2013



2. Incidenca

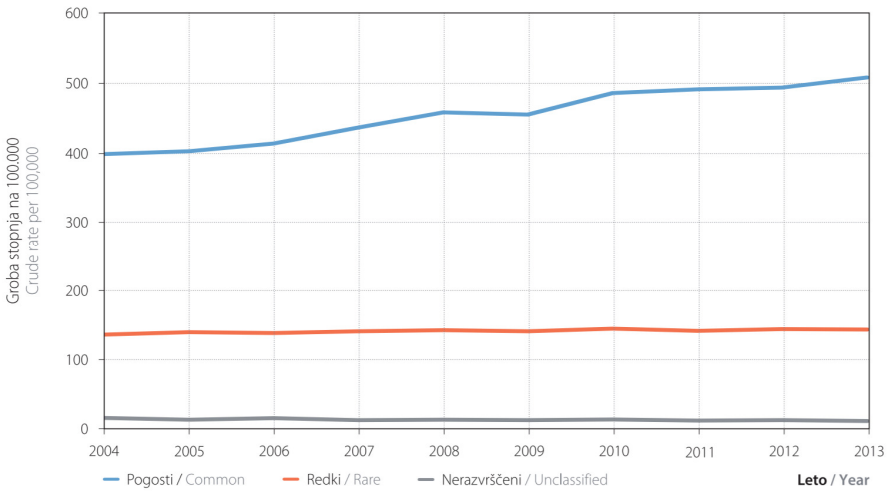
Incidenca, Slovenija 2004-2013



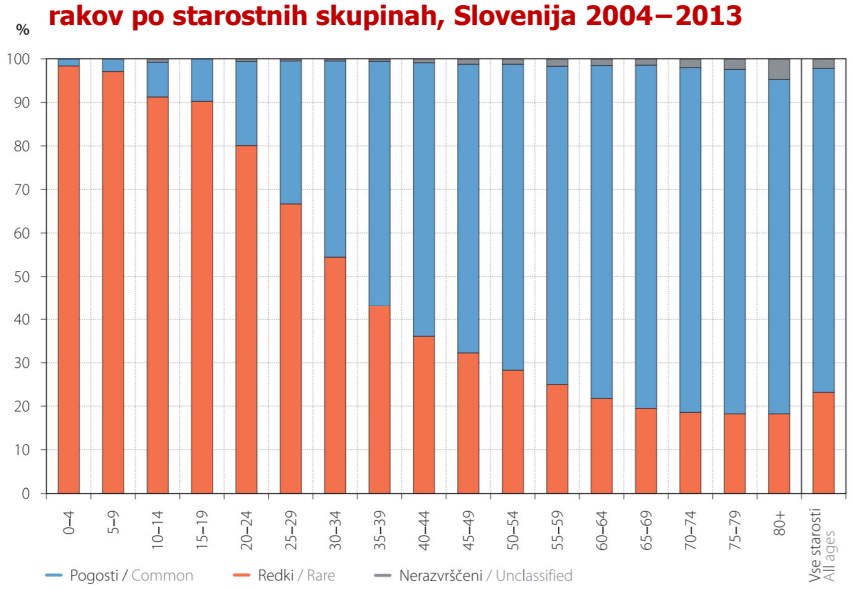
RareCare : 22 % (EU 27)

Primarna lokacija	Število novih primerov	Delež (%)
Redki raki	28768	23,2
Pogosti raki	92799	74,7
Nerazvrščeni raki	2665	2,1

Groba letna incidenčna stopnja redkih, pogostih in nerazvrščenih rakov, Slovenija 2004–2013

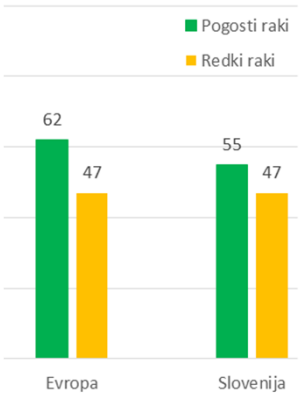


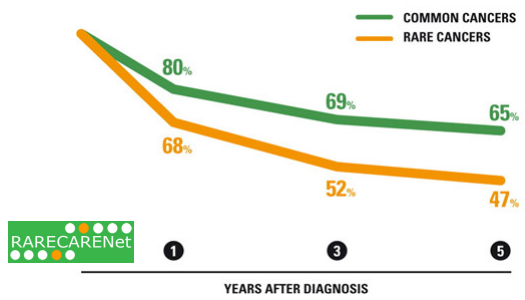
Odstotni delež redkih, pogostih in nerazvrščenih rakov po starostnih skupinah, Slovenija 2004–2013



3. Preživetje (1)

- Relativno preživetje oseb, ki so zbolele za redko vrsto raka je nižje od preživetja oseb, ki so zbolele za pogosto vrsto raka
- Pri mlajših so razlike v preživetju majhne





3. Preživetje (2)

- 5-letno relativno preživetje SLO (2007-2011)
  - Rak mod: 98%
  - Rak ščitnice: 95%
  - Otroški raki: 83% (0-19 let)
  - Rak grla: 69%
  - Kostni sarkomi: 68%
  - Sarkomi mehkih tkiv: 51%
  - Rak žrela: 29%

4. Diagnostični problemi

- Klinično se redki raki ne razlikujejo od pogostih, zato so problemi podobni (napotitve, čakalne dobe, odločitve o kiruškem zdravljenju brez predhodne diagnoze, stadija,....)
- **Prvo zdravljenje ni planirano na multidisciplinarnem konziliju (še bolj pomembno za redke rake!)**
- **Histološka diagnoza (konzultacije, dodatni testi, vzorci)**

čas do diagnoze in zdravljenja ponavadi daljši

5. Zdravljenje

- Plan prvega zdravljenja na multidisciplinarem konziliju (redosled zdravljenj)
  - Kirurgija: enak princip kot pri drugih rakih (radikalnost), ki lahko pedstavlja problem pri določenih lokacijah (baza lobanje, hrbtenica, ...)
  - Obsevanje (indikacija, posebne lokacije)
  - Sistemsko zdravljenje
    - zaradi redkosti velikokrat ni podprto z dokazi
    - investiranje farmacevtske industrije v redke rake (zdravila sirote)
    - klinične raziskave lahko le multicentrične (globalne), z razvojem molekularne biologije (t.i. Basket trials) boljši izgledi
- Ni še utečenih poti (centrov) za drugo mnenje za zelo redke rake (EurocareNet)

5. Zaključek

- Obravnava redkih rakov zahteva izkušen multidisciplinarni tim (diagnoza, pravilno zaporedje zdravljenja)
- Zaradi svoje redkosti velikokrat odločitve temeljijo na posameznih primerih
- Principi diagnostike in zdravljenja se bodo v bodoče z novimi dognanji molekularne biologije ter globalnimi raziskavami na tem področju bistveno spremenili

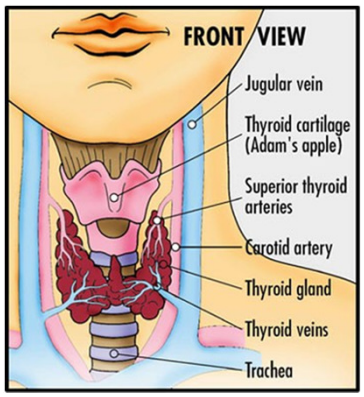
Redki raki – pot naprej

- Posodabljanje podatkov o incidenci redkih rakov na www.rarecarenet.eu
- JARC (Joint Action on Rare Cancers)
- ERN (European Reference Networks)
- EUCERD (European Committee of Experts on Rare Diseases), priporočila glede referenčnih centrov
- Multicentrične, t.i. Basket raziskave

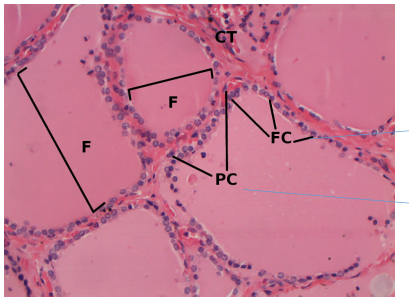
Viri informacij:
http://www.rarecarenet.eu/
http://www.slora.si
http://www.onko-i.si/rrs
http://www.onko-i.si
http://www.dpor.si

Sistemsko zdravljenje raka ščitnice

Doc. dr. Cvetka Grašič Kuhar, dr. med.
Onkološki inštitut Ljubljana

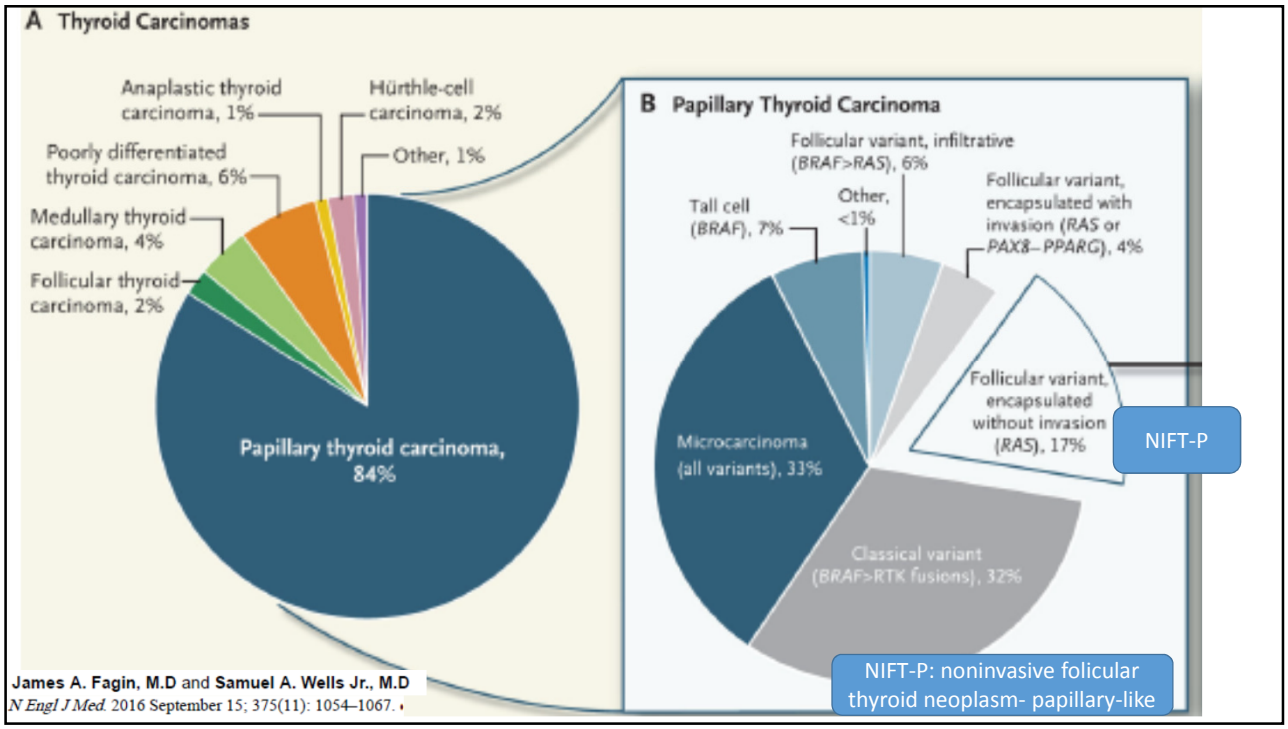


Rak ščitnice

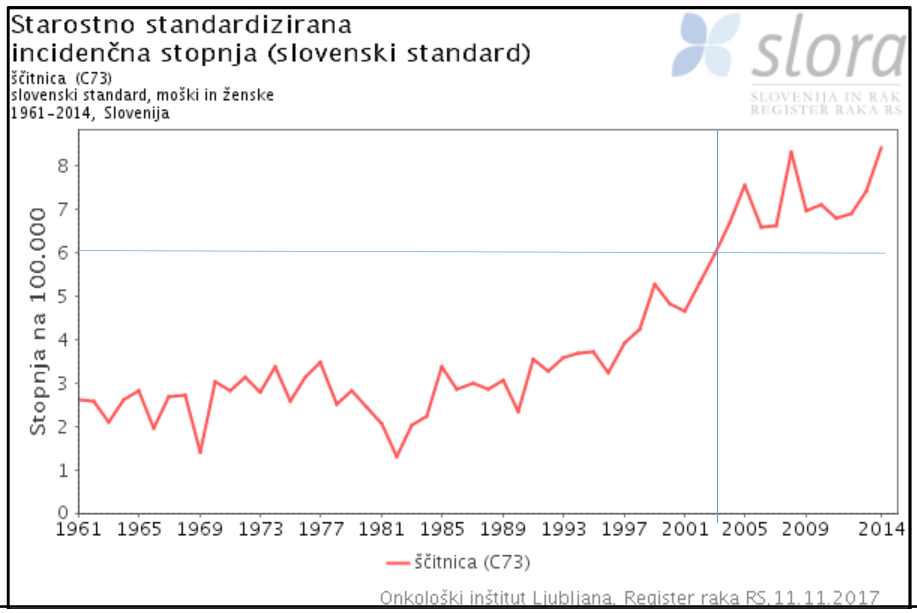


- FOLIKULARNE CELICE
  - PAPILARNI (>80 %)
  - FOLIKULARNI (6 %)
  - CA. HURTLOVIH CELIC (3 %)
  - Slabo diferenciran ca. (6 %)
  - ANAPLASTIČNI CA. (1-2%)
- PARAFOLIKULARNE CELICE (C celice)
  - MEDULARNI CA. (5-9%)

DIFERENCIRAN RAK ŠČITNICE

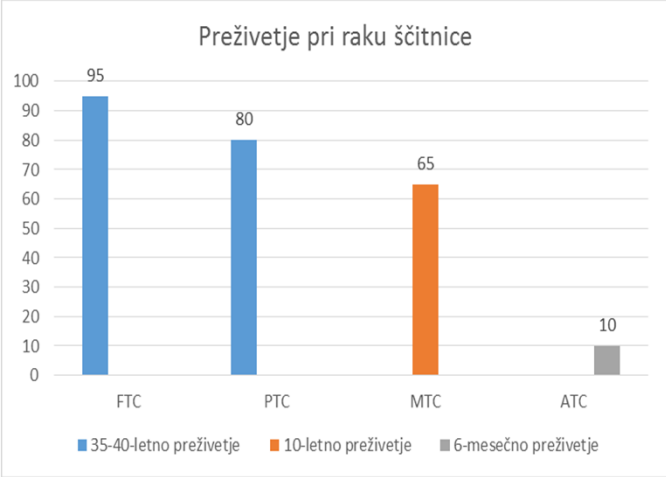


Rak ščitnice je do leta 2003 spadal med redke rake



Incidenca

- V ZDA se je incidenca povečala 3x (iz 4,9/100.000 na 14,3/100.000 letno)
- Ob tem je smrtnost ostala enaka: 0,5/100.000 letno
- Incidenca se je povečala na račun papilarnega ca. ščitnice (večinoma mikropapilarnega: T<1 cm; 40 %); na avtopsiji najdejo papil. ca ščitnice v 11,5 % (4-36)
- Ostalim entitetam se incidenca ni povečala



Zdravljenje diferenciranega raka ščitnice (DTC) v omejenem stadiju

- Primarno **kirurško zdravljenje**: totalna tiroidektomija in limfadenektomija
- Visoko rizični: adjuvantna terapija z **radiojodom** (131I)
- Nadomestna terapija z levotiroksinom; višji – supresijski - odmerek pri visoko rizičnih (TSH<0,1mU/L), Ca 1200 mg/d, ViD 1000IE/d

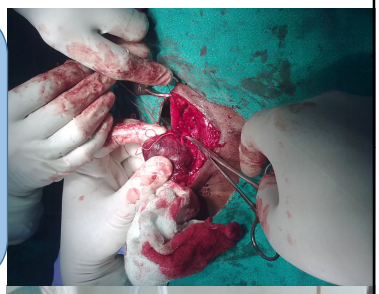
Spremljanje bolnikov (detekcija rezidualne bolezni ali ponovitve):

-serumski tiroglobulin (po 6-12 mes) in UZ vratu

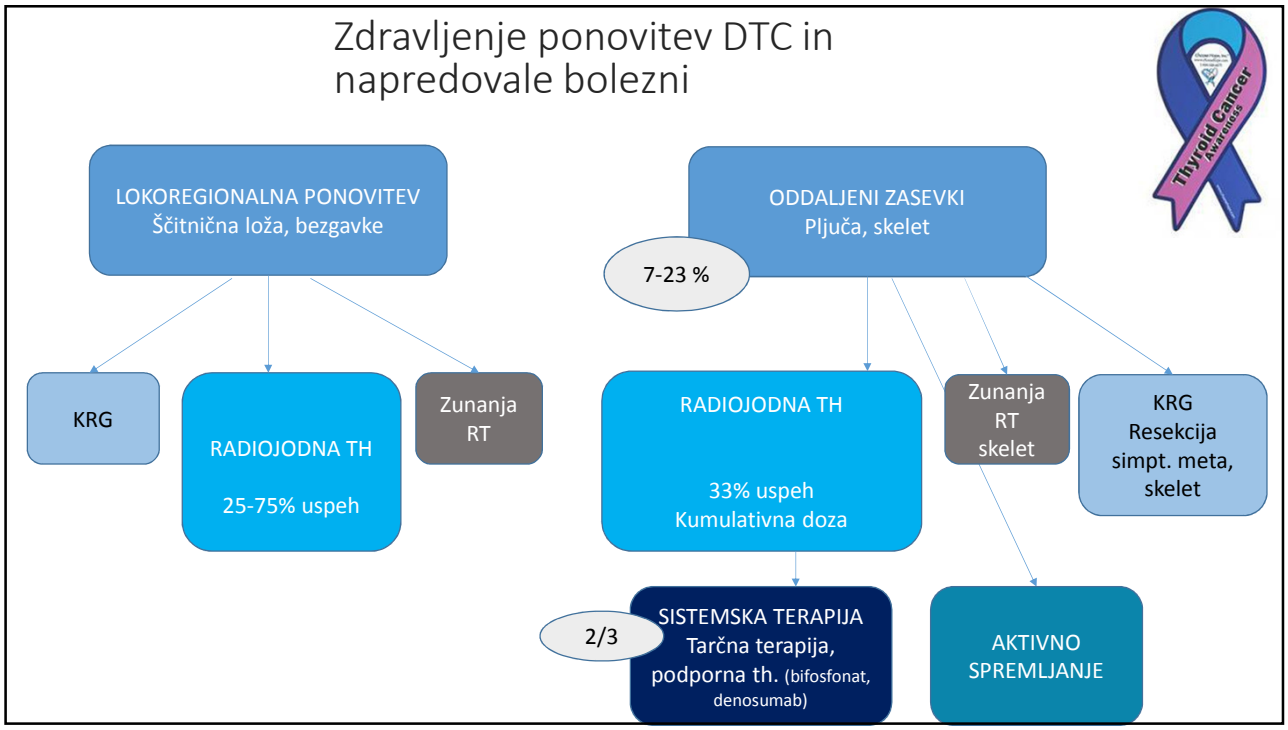
-rhTIROTROPIN; ČE PORASTE >2 ng/ml

KRG

RADIO JODNA TH

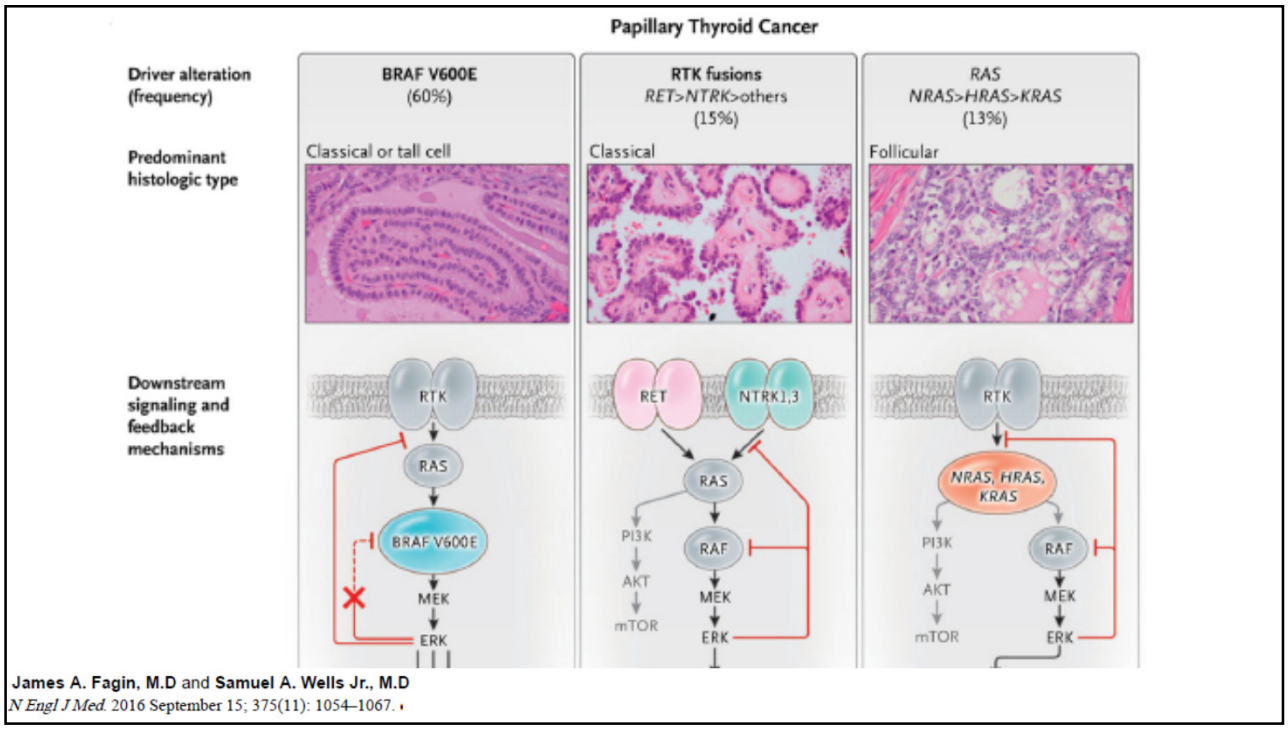


http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

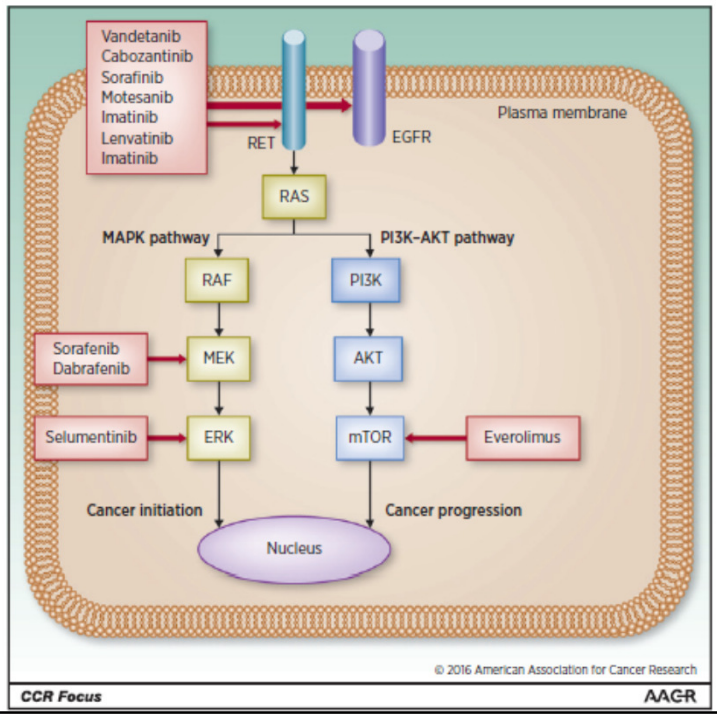


Sistemska terapija pri DTC

- Na radiojod rezistentna bolezen ali dosežena kumulativna doza radiojoda
- simptomatska, progresivna metastatska bolezen
- lokalizirana bolezen, ki ogroža vitalne strukture, kjer lokalna terapija ni možna
- Neresektabilna lokalna bolezen: paliativna RT+nizkodozna KT



James A. Fagin, M.D and **Samuel A. Wells Jr., M.D**
N Engl J Med. 2016 September 15; 375(11): 1054–1067.



Clin Cancer Res; 22(20) October 15, 2016

Raziskave faze III na področju tarčne terapije pri DTC

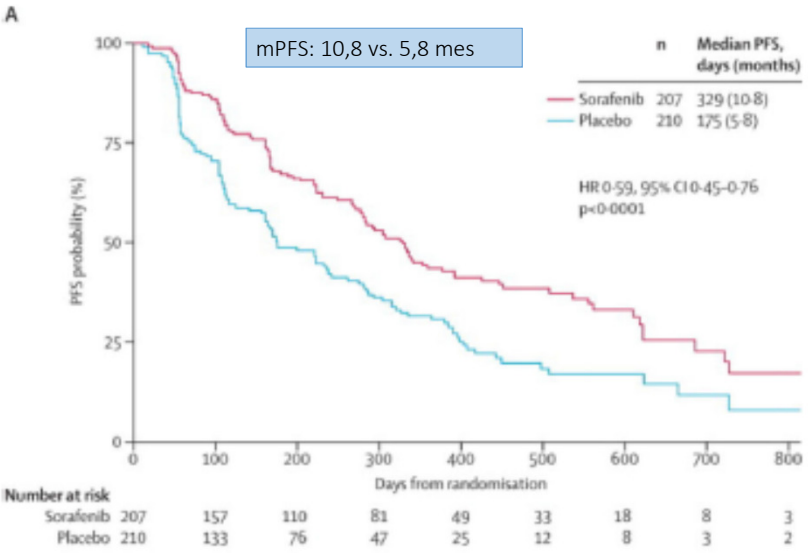
ŠTUDIJA	DECISION	SELECT
VRSTA ŠTUDIJE	Randomizirana, faza III, dvojno slepa, multicentrična	Randomizirana, faza III, dvojno slepa, multicentrična
ŠTUDIJSKE ROKE	Sorafenib (2x400 mg) vs. placebo	Lenvatinib 1x 24 mg vs. placebo
Randomizacija	1:1	2:1
Število bolnikov	417	392
Vključitveni kriteriji	RAI refraktorni bolniki: lokalno napredovali, metastaski (96,4%) Progres po RECIST kriterijih v zadnjih 14 mesecih	RAI refraktorni bolniki s progresivno boleznijo Progres po RECIST kriterijih v zadnjih 13 mesecih
Stanje zmogljivosti bolnika po ECOG	PS 0-1 (PS 2: 3%)	PS 0-3 PS 2-3: 5%/1,5%
Primarni cilj	PFS	PFS
Farmacevtska firma	Bayer	Eisai

Primerjava raziskav DECISION in SELECT

ZDRAVILO	SORAFENIB	LENVATINIB
TARČE	VEGF 1, 2, 3, RAF (vključno z BRAFV600E,) PDGFR β, RET (RET/PTC)	VEGFR 1, 2, 3, FGFR 1-4, PDGFR α, RET, KIT
Izključitveni kriteriji	Prej KT, talidomid ali TKI	Lahko prej 1 TKI (25/21%)
Čas od diagnoze	66 mes	
Analiza biomarkerjev	Serumski tiroglobulin BRAF in RAS (NRAS, HRAS, in KRAS) mutacije	 *BRAF* in *RAS* mutacije
Srednji čas opazovanja (median FU)	16,2 mes	17,1 mes
Cross-over	Da (71%)	Da (95,6%)
Nadaljnji red th	20/9 %	15,7% L

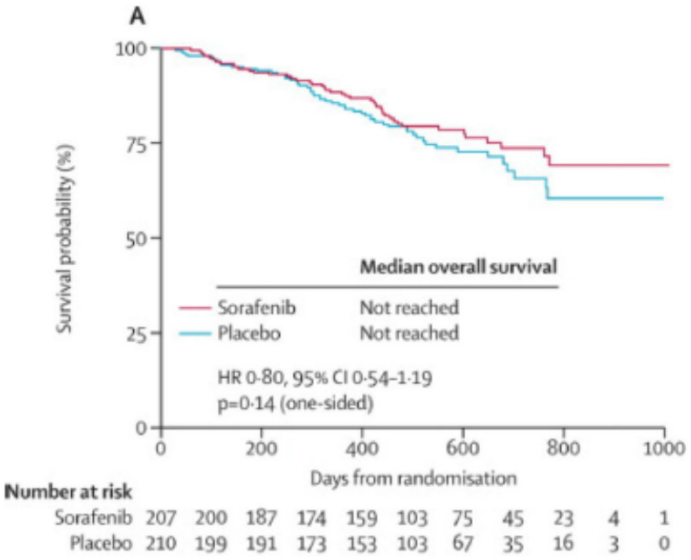
Raziskava DECISION (sorafenib) - PFS

BRAF in RAS mutaciji nista neodvisni prognostični faktor za PFS

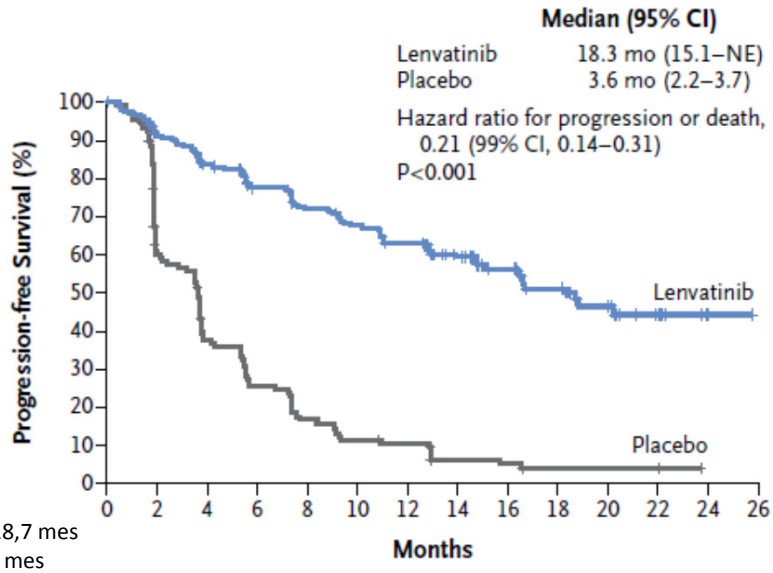


Lancet. 2014 July 26; 384(9940): 319–328.

Raziskava DECISION (sorafenib) – celotno preživetje



Raziskava SELECT – lenvatinib - PFS

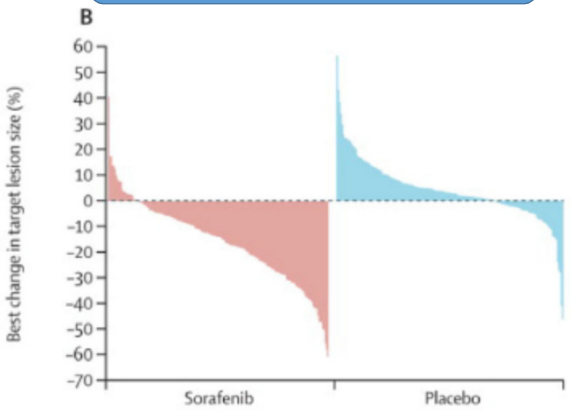


No prior TKI: PFS L 18,7 mes
Prior TKI: PFS L 15,1 mes
PFS neodvisen od BRAF, RAS mutacij!

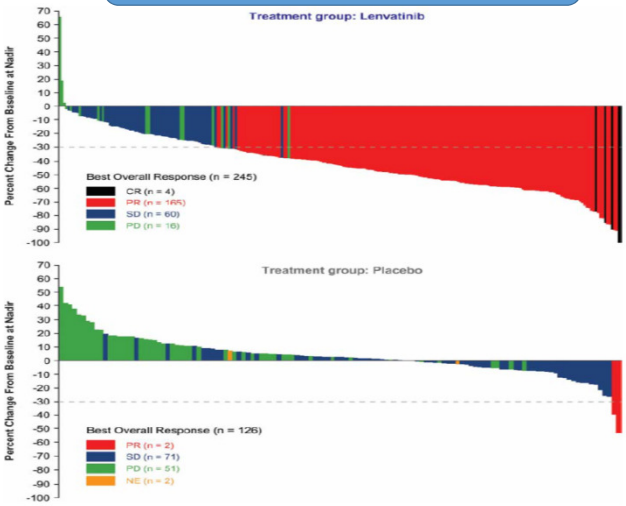
N Engl J Med 2015;372:621-30.

Prikaz zmanjšanja tarčnih lezij – ‚waterfall plot'

Raziskava DECISION– sorafenib



Raziskava SELECT – lenvatinib



Primerjava učinkovitosti in kompliance v testni roki

	Sorafenib vs. placebo	Lenvatinib vs. placebo
CR	0%	1,5%
PR	12,2 vs. 0,5%	63,2 vs. 1,5%
SD	SD>6 mes 41,8 vs. 33,2%	23% SD>23 tednov 15,3 vs. 30%
PD	?	6,9 vs. 39,7%
Evaluacija ni možna	?	5,5%
Srednje trajanje odgovora pri PR	10,2 mes.	
Srednje trajanje zdravljenja	10,6 vs. 6,5 mes	13,8 vs. 3,9 mes
Srednja dnevna doza zdravila	651 mg vs. 793 mg	17,2 mg (82% dose interruption , 67% dose reduction)

Medularni rak ščitnice

- Sporadični (75-80 %)
- Familiarni (20-25 %); MEN 2A, 2B, FMTC

- Tvori kalcitonin
- Etiologija:
- vsi familiarni: 'germline' RET mutacija
- Sporadični:
  - v 50-60 % somatska RET mutacija
  - RAS mutacija
  - Prekomerna izraženost VEGFR1, 2

Zdravljenje MTC

- KRG: totalna tiroidektomija + bilateralna disekcija bezgavk na vratu (T> 1cm, bezgavke bilateralno, familiarni rak)
- Genska okvara: profilaktična tiroidektomija (priporočljiva starost odvisno od rizičnosti kodona RET mutacije)
- Ev. dopolnilna RT, če R1, R2 resekcija, visok N stadij, ECE, če grozi obstrukcija dihal
- 3 mesece po KRG: CEA, kalcitonin (če > 150pg/ml)
  - Če nista zvišana: ozdravljen bolnik; kontrole 1x letno (CEA, kalcitonin, fizikalni pregled, UZ vratu)
  - Če zvišana po KRG: slikovna diagnostika: KRG rezidualne bolezni, če INOP.: RT, če KRG, RT in možna in simptomatska bolezen: TKI
  - Če asimptomatska: spremljanje CEA, kalcitonina na 3-6 mes. (podvojitveni čas; kalkulator)

Sistemsko zdravljenje medularnega raka ščitnice (MTC)

- V poštev pride v primeru:
  - inoperabilna lokalna ponovitev bolezni in/ali inoperabilne metastatske bolezni
  - primarno metastatska ali lokalno napredovala bolezen (sporadični MTC)
- Srednje preživetje bolnika z metastasko boleznijo je 3 leta, indolenten potek
- Kdaj začeti zdravljenje:
  - Ob dg.? (asimptomatski bolniki)
  - Ob simptomih?
  - Ob dokazanem radiološkem progresu?

Metastaze velikosti vsaj 1-2 cm
Rast vsaj 20 % letno

Multiple metastaze s simptomi, ki jih ne moremo zdraviti z OP, RT

Indikacije za sistemsko zdravljenje

- Klinično pomemben progres bolezni v zadnjih 12-14 mesecih
- Simptomatsko tumorsko breme, ki ga ne moremo obvladati z lokalizirano terapijo
- Prizadetost vitalnih organov ali funkcij zaradi tumorja
- Huda neznosna diareja

Metastaze velikosti vsaj 1-2 cm
Rast vsaj 20 % letno

Multiple metastaze s simptomi, ki jih ne moremo zdraviti z OP, RT

Samo porast tumorskih markerjev ni indikacija za uvedbo sistemske terapije!

Sistemsko zdravljenje

- Podporna (na simptome orientirana) terapija
- Tarčna terapija
- Sistemska kemoterapija

TARČNA TERAPIJA

- VANDETANIB
- CABOZANTINIB
- SUNITINIB
- SORAFENIB
- Klinične raziskave
  - PAZOPANIB...
  - per os th., male molekule

Raziskava ZETA

- Multicentrična raziskava faze III (2006-07), dvojno slepa, kontrolirana s placebom
- vandetanib 300 mg vs. placebo (2:1); n=331
- Lokalno napredovala neresektabilna bolezen/ metastatska bolezen
  - hereditarni in sporadični
- I. cilj: PFS

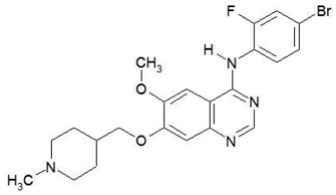
Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

Samuel A. Wells Jr, Bruce G. Robinson, Robert F. Gagel, Henning Dralle, James A. Fagin, Massimo Santoro, Eric Baudin, Rossella Elisei, Barbara Jarzab, James R. Vasselli, Jessica Read, Peter Langmuir, Anderson J. Ryan, and Martin J. Schlumberger

J Clin Oncol 30:134-141. © 2011.

Vandetanib

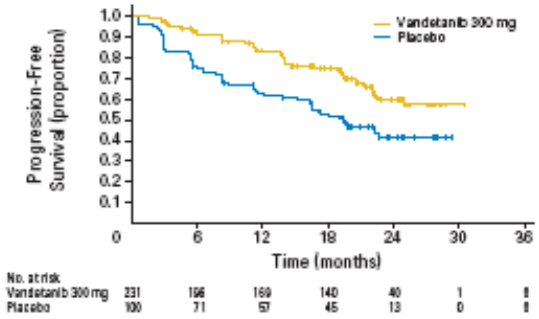
- Mala molekula



- Multi-kinazni inhibitor (RET, EGRF)
- Antiangiogeno delovanje (VEGFR-1, VEGFR-2)

RET: Rearranged during Transfection

Primarni cilj raziskave ZETA



J Clin Oncol 30:134-141. © 2011.

HR 0,46 (95% IZ 0,31-0.69), p<0.001

Srednji PFS: 30,5 mes. vs. 19,3 mes.

Mediano trajanje zdravljenja: 90 vs. 40 tednov

Sekundarni cilji raziskave ZETA

Sekundarni cilj	vandetanib	placebo	OR	p
Objektivni odgovor (CR+PR)	45%	13%	5,48	<0,001
Klinična kontrola bolezni (CR+PR+SD)	87%	71%	2,64	0,001
Biokemični odgovor: kalcitonin	69%	3%	72,9	<0,001
Biokemični odgovor: CEA	52%	2%	52	<0,001

J Clin Oncol 30:134-141. © 2011.

Neželeni učinki zdravljenja

Vandetanib:

- GIT: diareja; že simptom MTC (hiperkalcitonin.), nauzea...
- Kožni: izpuščaj (rash), akne, suha koža...
- Inapetenca, slabo počutje
- Podaljšanje QT dobe ($t_{1/2}$= 19 dni!) (imeti pri sebi kartico z opozorilom!), torsades de pointes
- G3: diareja 11%, art. hipertenzija 9%, pod. QTc 8%, fatigue 6%
- Znižanje doze: 35% vs. 3%
- Prekinitev zdravljenja: 12% vs. 3%
- Vandetanib: 5 smrti

Table 4. Common Adverse Events (safety population)

Adverse Event	Vandetanib (300 mg) (n = 231) No.	%	Placebo (n = 99) No.	%
Any grade occurring with an incidence ≥ 10% overall				
Diarrhea	130	56	26	26
Rash	104	45	11	11
Nausea	77	33	16	16
Hypertension	73	32	5	5
Fatigue	55	24	23	23
Headache	59	26	9	9
Decreased appetite	49	21	12	12
Acne	46	20	5	5
Asthenia	34	14	11	11
Vomiting	34	14	7	7
Back pain	21	9	20	20
Dry skin	35	15	5	5
Insomnia	30	13	10	10
Abdominal pain	33	14	5	5
Dermatitis acneiform	35	15	2	2
Cough	25	10	10	10
Nasopharyngitis	26	11	9	9
ECG QT prolonged*	33	14	1	1
Weight decreased	24	10	9	9

J Clin Oncol 30:134-141. © 2011.

Celotno preživetje – ni razlike

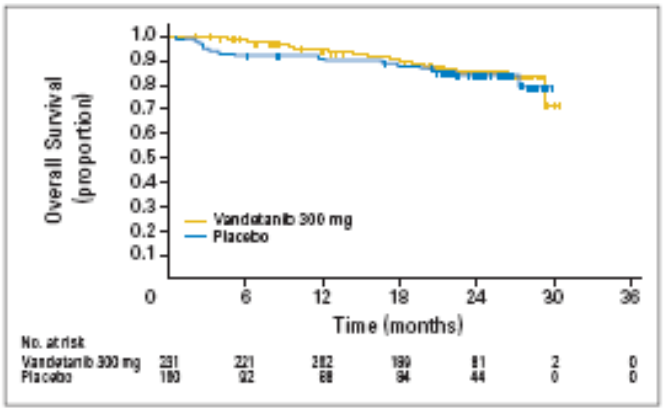


Fig 3. Kaplan-Meier curve of overall survival (intention-to-treat population; all randomly assigned patients).

Ob progresu so možen cross-over na vandetanib (93%)!

J Clin Oncol 30:134-141. © 2011.

Raziskava EXAM

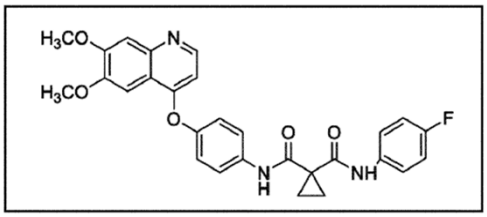
- Multicentrična raziskava faze III (2008-2011), dvojno slepa, kontrolirana s placebom
- Cabozantinib 140 mg vs. placebo (2:1); n=330
- Lokalno napredovala neresektabilna bolezen/ metastatska bolezen
- Radiološki PROGRES BOLEZNI po RECIST-u (v zadnjih 14. mes)
- I. cilj: PFS Ob progresu ni bil dovoljen cross-over!

Elisei J et al. J Clin Oncol 2013; 31: 3639-46.

Cabozantinib

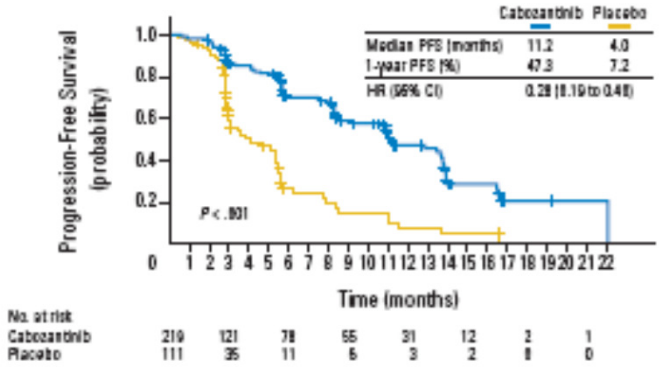
COMETRIQ (cabozantinib)

- Mala molekula



- Multi-kinazni inhibitor (RET, MET)
- Antiangiogeno delovanje (VEGFR-2)

Primarni cilj raziskave EXAM



Objektivni RR:
27% vs. 0%

HR 0,28 (95% IZ 0,19-0.40), p<0.001;
-srednji PFS: 11,2 mes. vs. 4,0 mes.;
-1-letni PFS (%): 47,3% vs. 7,2%
-mediano trajanje odgovora 14,6 mes
-mediano trajanje zdravljenja: 204 vs. 105 dni
Učinek neodvisen od RET mutacije!

Elisei J et al. J Clin Oncol 2013; 31: 3639-46.

Neželeni učinki

Povezani s kinaznim delovanjem

- Kožni: palmarno-plantarna eritrodizestezija
- Diareja
- splošna oslabelost (fatigue)
- vpliv na krvno sliko: nevtropenija, trombopenija
- elektrolitne motnje: K, Na, Mg, P, Ca,
- patološki jetrni testi!

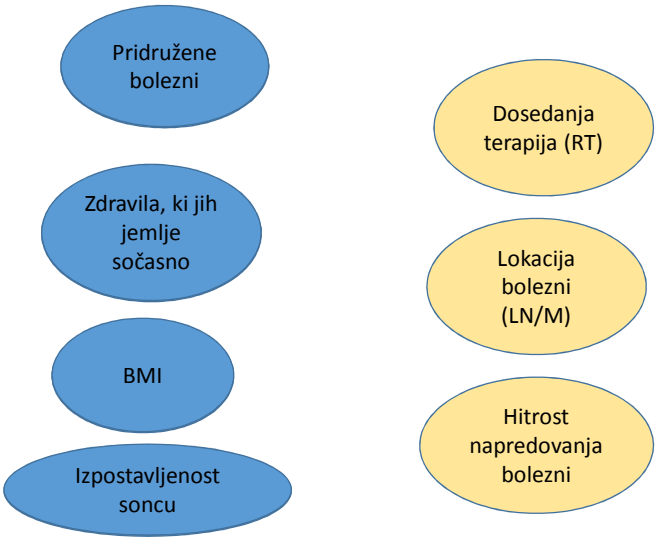
Povezani z antiangiogenim delovanjem

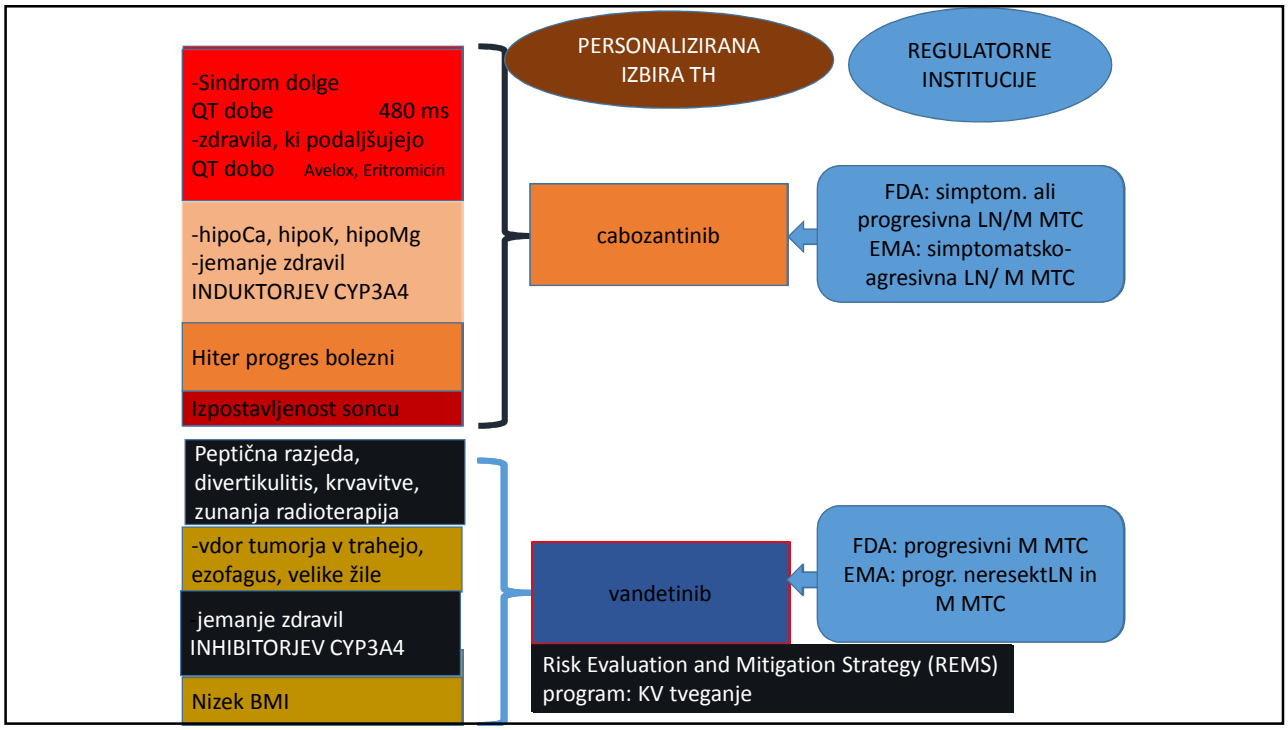
- fistule, perforacije GIT
- hude krvavitve
- venska tromboza
- arterijska hipertenzija

- AE G3/4: 69% vs 33%
- SEA: 42% vs. 23%
- ↓ doze: 79%!!!

Elisei J et al. J Clin Oncol 2013; 31: 3639-46.

Odločitev o izbiri tarčne terapije





Best Supportive Care from the Conservative/ Non-Surgical Perspective and Its Costs in the Treatment of Patients with Advanced Medullary Thyroid Cancer: Results of a Delphi Panel

Michael C. Kreissl[a,b] Christian Jacob[c] Dagmar Führer[d] Wolfram Karges[e]
Markus Luster[f] Michael P. Lux[g] Klaus Mann[d] Thomas Mittendorf[c]
Matthias Schott[h] Christine Spitzweg[i] Hans-Joachim Schmoll[k]

Oncol Res Treat 2014;37:316–322

Table 2. Costs of BSC in advanced MTC

Medications/BSC measures	Percentage of use	Weighted cost			
		Based on DDD (€)	Per day, €	Per month (30 days), €	Per year (365 days), €
Medications					
Antidiarrheals	56.67	2.30	1.30	39.10	475.74
Analgesics (excluding opiates)	39.44	1.45	0.57	17.16	208.74
Opiates	31.11	3.06	0.95	28.58	347.68
Bisphosphonates	27.78	12.97	3.60	108.10	1,315.19
Antiemetics	21.67	1.68	0.36	10.89	132.50
Antithrombotics	21.11	0.68	0.14	4.32	52.51
Other medications targeting functional gastrointestinal disorders	17.22	0.49	0.08	2.51	30.56
Antidepressants	9.44	0.69	0.07	1.95	23.77
Sedatives	8.11	0.67	0.05	1.63	19.84
Diuretics	5.63	0.20	0.01	0.33	4.01
Laxatives	5.56	0.76	0.04	1.27	15.45
Antiepileptics	4.22	2.58	0.11	3.26	39.70
Neuroleptics	3.11	3.82	0.12	3.56	43.35
Immunostimulants	0.89	66.33	0.59	17.71	215.48
Other services					
Physiotherapy	29.22	3.94	1.15	34.54	420.21
Palliative radiotherapy	28.75	3.65	1.05	31.48	383.02
Enteral nutrition	16.11	66.57	10.72	321.73	3,914.42
Occupational therapy	15.33	5.00	0.77	23.00	279.77
Psychotherapy	11.11	2.41	0.27	8.02	97.56
Palliative surgery	10.33	21.56	2.23	66.80	812.76
Oxygen support	2.78	41.02	1.14	34.21	416.23
Total costs, €			25.32	760.15	9,248.49

BSC = Best supportive care, DDD = defined daily dose.

Somatostatinski analogi za kontrolo diareje!

Kdaj sistemska KT

- Po progresu na vandetanib, cabozantinib: sunitinib ali sorafenib (raziskave faze II, n= 15-20) ali klinična raziskava

- Kemoterapija: po progresu na tarčno terapijo (NCCN)
- MTC spada med nevroendokrine tumorje, ki secernirajo kalcitonin, CEA…
- Dakarbazin (monoterapija ali kombinacija);
- Odgovor na th: <20%

Zaključki

- LN/M medularni rak ščitnice je lahko dolgo indolentna bolezen
- Zdravljenje s tarčnimi zdravili je indicirano ob simptomatskem radiološko dokazanem progresu
- individualizirana izbira tarčne terapije glede na dosedanje bolezni, lokacijo bolezni, sočasno jemanje drugih zdravil
- Pri nas vandetanib in cabozantinib nista na voljo; v tem primeru glede na mnenje konzilija indiciramo sunitinib ali sorafenib; KT

Primer bolnika z rakom ščitnice

Jelena Azarija

J.B., l. 1955, ♂

Februar 1995: pregled pri tireologu zaradi rezistence levo na vratu

Klinični pregled: tipen nodus v levem ščitničnem lobusu, ki je fiksiran na trahejo in premičen pri požiranju; brez tipno povečanih bezgavk na vratu

UZ ščitnice: povečan levi ščitnični reženj, v spodnjem delu je neostro omejeno nehomogeno hipoehogeno področje

Punkcija gomolja - citološki izvid: suspektno za folikularni maligni proces

Laboratorij: Tg 1.5, TSH 0.93, aTG in aTPO negativna

J.B., l. 1955, ♂

Marec 1995: pregledan na Onkološkem inštitutu

Punkcija gomolja - citološki izvid: posamezne skupine celic sumljive za papilarni karcinom, vendar procesa ni možno zanesljivo opredeliti

Scintigrafija ščitnice s ^{99m}Tc: hladen nodus v levem lobusu ščitnice

RTG p/c: bp

Laboratorij: bp

Primarno zdravljenje

Maj 1995: totalna tiroidektomija

Histološki izvid: **folikularni karcinom** v levem ščitničnem režnju, **multicentričen** (velikost?), **slabo diferenciran**, z blago do zmerno mitotsko aktivnostjo, **vrašča v ovojnico**, vendar se **ne širi izven** ščitnice, prisotna **obsežna vaskularna invazija**, nahaja se **v medialnem resekcijskem robu**.
D lobus, obščitnice, LNN (0/1): brez malignih celic.

Junij 1995: ablacija z ^{131}I (100 mCi) + ščitnični hormoni v supresijskem odmerku

Julij 1995: obsevanje predela ščitnice in zgornjega mediastinuma (TD 45 Gy)

Papilarni ali folikularni rak - Mlajši od 45 let			
Stadij I	katerikoli T	katerikoli N	M0
Stadij II	katerikoli T	katerikoli N	M1
Papilarni ali folikularni rak – 45 let ali starejši			
Stadij I	T1	N0	M0
Stadij II	T2	N0	M0
Stadij III	T3	N0	M0
	T1, T2, T3	N1a	M0
Stadij IV-A	T1, T2, T3	N1b	M0
	T4a	N0, N1	M0
Stadij IV-B	T4b	katerikoli N	M0
Stadij IV-C	katerikoli T	katerikoli N	M1

7. izdaja TNM klasifikacij

pT2/T3 N0 M0

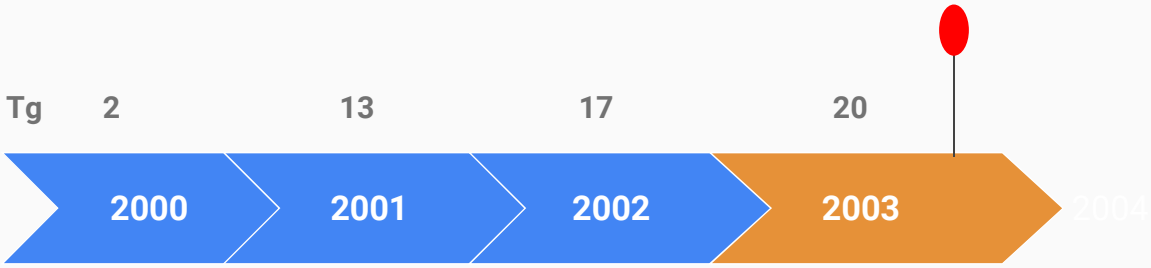
stadij I

Sledenje

Tg	0.01	NA	NA	NA	4
	1995	1996	1997	1998	1999

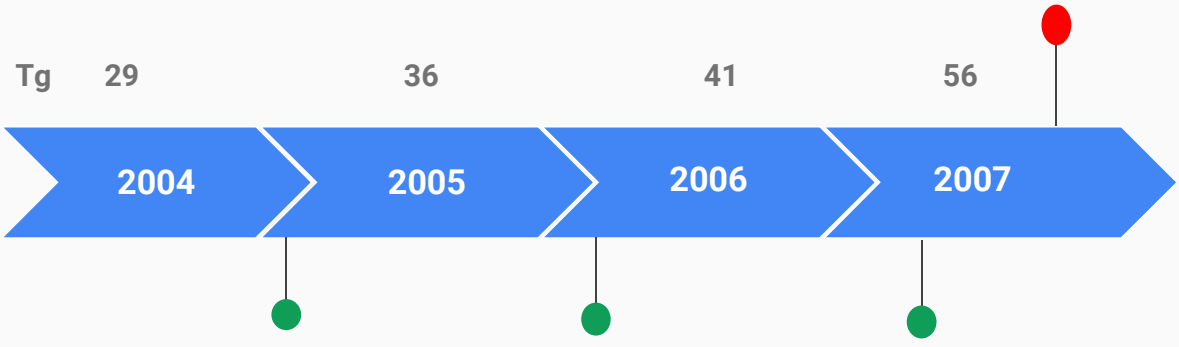
- asimptomatski
- laboratorijski izvidi: bp, TSH v supresijskem območju
- RTG p/c: bp

Terapija z ^{131}I (145,7 mCi)
Ni povišanega kopičenja ^{131}I v telesu.



- asimptomatski
- laboratorijski izvidi: bp, TSH v supresijskem območju
- RTG p/c: bp

Test z ^{131}I ob rTSH: neg.



SKEN telesa z MIBI: bp

UZ trebuha in vratu: bp

RTG p/c: bp

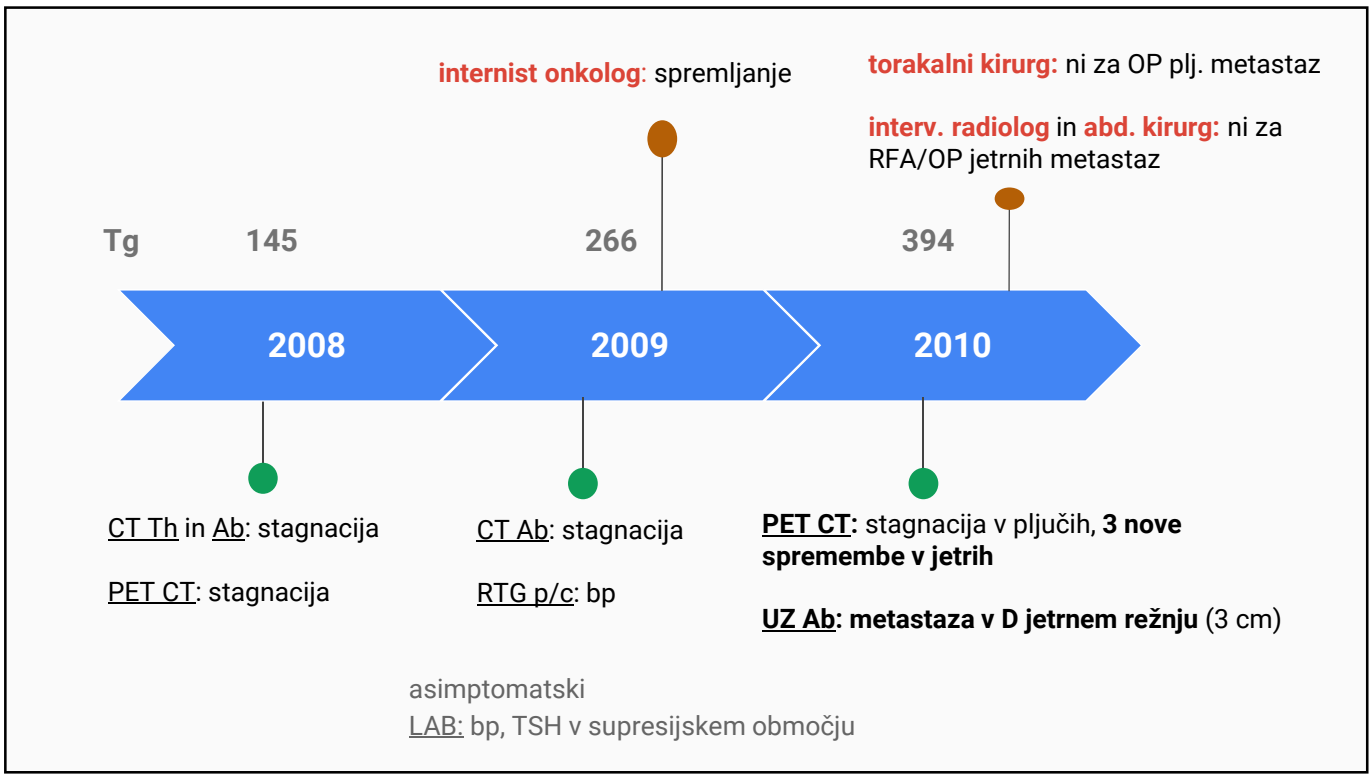
CT Th: več manjših (mm) nodularnih sprememb v pljučih

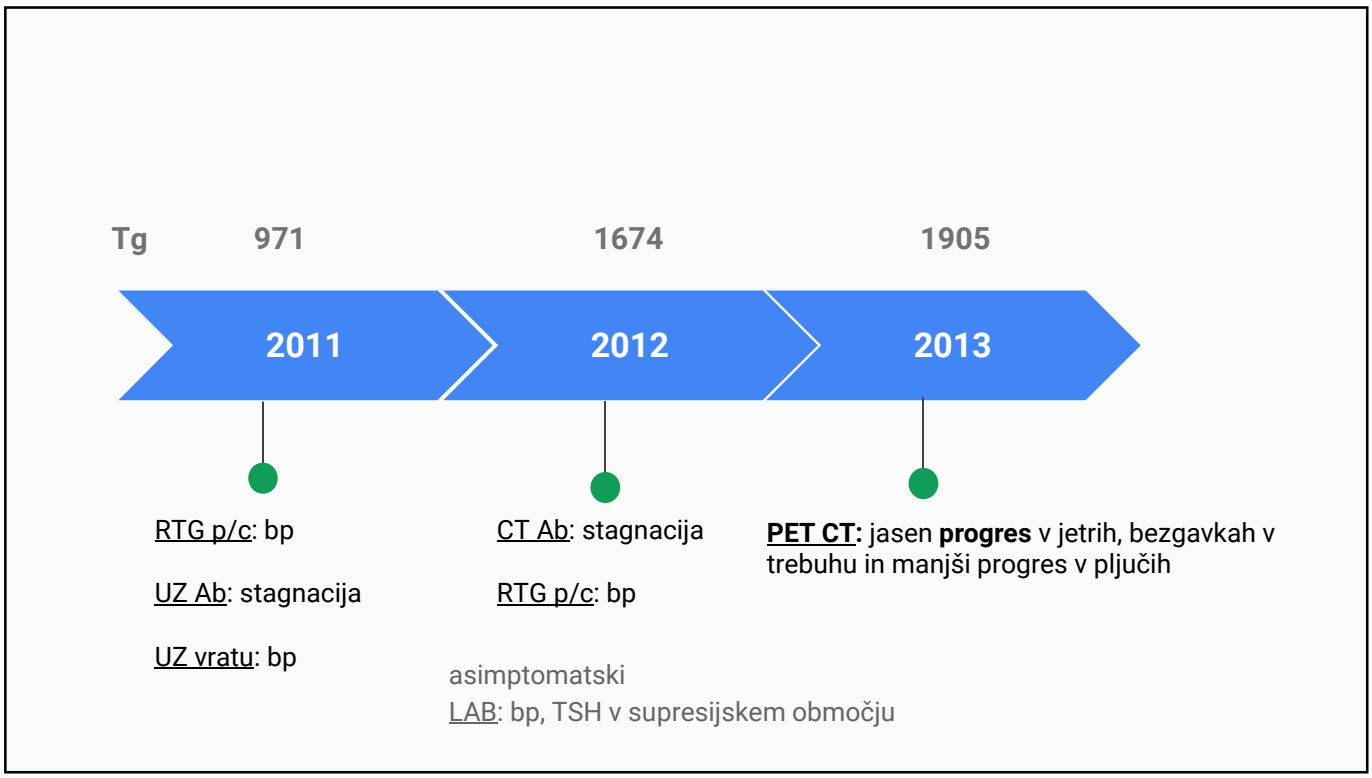
asimptomatski
LAB: bp, TSH v supresijskem območju

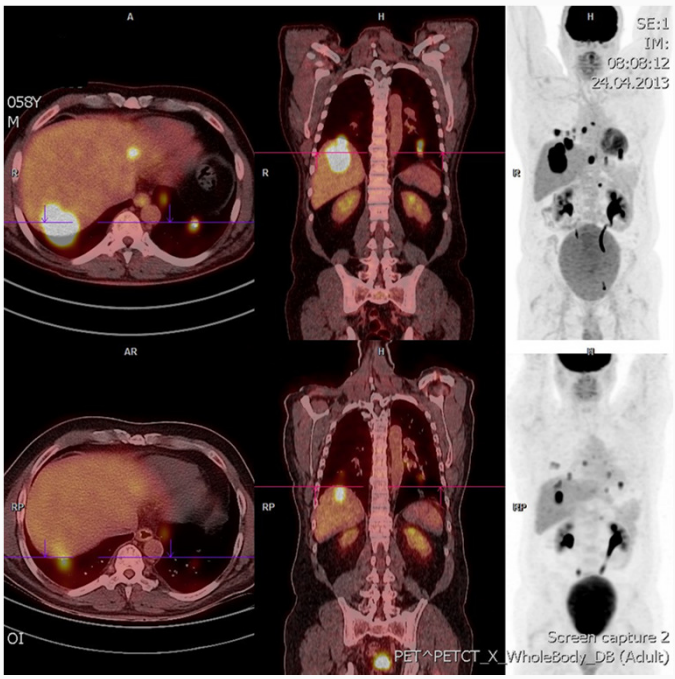
CT Th: stagnacija pljučnih zasevkov, **nova sprememba pod levo diafragmo**

UZ trebuha in vratu: bp

PET-CT: kopičenje v pljučih in pod levo diafragmo


internist onkolog: spremljanje
torakalni kirurg: ni za OP plj. metastaz
interv. radiolog in abd. kirurg: ni za RFA/OP jetrnih metastaz
Tg
145
266
394
2008
2009
2010
CT Th in Ab: stagnacija
PET CT: stagnacija
CT Ab: stagnacija
RTG p/c: bp
PET CT: stagnacija v pljučih, 3 nove spremembe v jetrih
UZ Ab: metastaza v D jetrnem režnju (3 cm)
asimptomatski
LAB: bp, TSH v supresijskem območju


Tg
971
1674
1905
2011
2012
2013
RTG p/c: bp
UZ Ab: stagnacija
UZ vratu: bp
CT Ab: stagnacija
RTG p/c: bp
PET CT: jasen progres v jetrih, bezgavkah v trebuhu in manjši progres v pljučih
asimptomatski
LAB: bp, TSH v supresijskem območju



Konzilij za ščitnične bolezni

sistemsko zdravljenje

Sistemsko zdravljenje

Maj 2013: pregled pri internistu onkologu

Anamneza:

- en mesec trajajoča nepojasnjena nevrološka simptomatika (težave z L okončinama - hemipareza, nevrogeni mehur), v obravnavi pri **nevrologu**

  (CT glave, MRI glave in Th-L hrbtenice, EMG, LP, onkonevronalna Ig: bp)

- drugih težav ne navaja

Klinični pregled: v mejah normale

Laboratorij: **Tg 1905**, preostali izvidi bp

1. linija zdravljenja

sorafenib 2 x 400 mg → **200 mg + 400 mg**

Tg	1905	693	540	676	759	830
	maj 2013	junij	avgust	oktober	december	februar 2014

- stomatitis
- rdečica obraza
- mehkejše blato

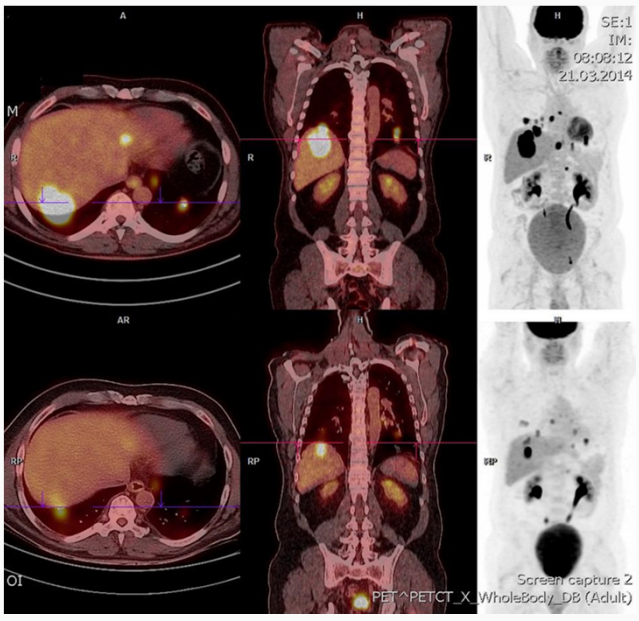
- utrujenost
- driska, Gr. 2
(Loperamid)

- **driska, Gr. 3**
(14 dni ni jemal terapije)

UZ Ab: stagnacija zasevkov v jetrih

- utrujenost
- mehkejše blato

Progres bolezni



PET-CT (marec 2014):

➤ **progres v jetrih in pljučih**

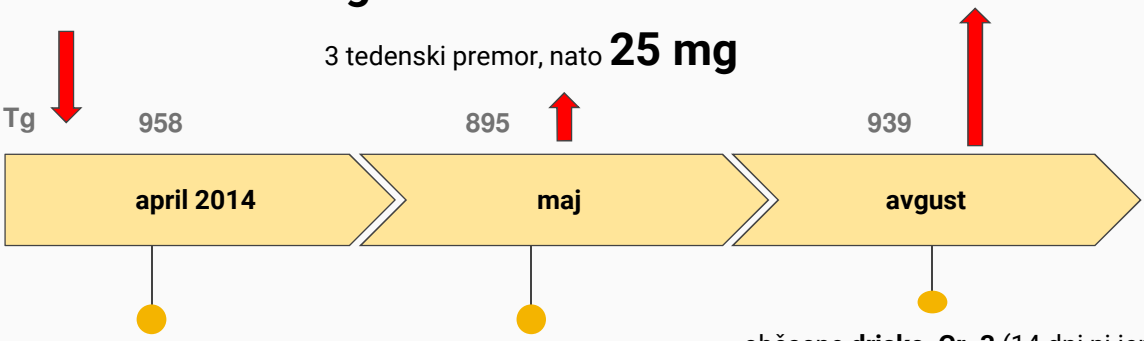
➤ **nove patološke bezgavke v Ab**

2. linija zdravljenja

sunitinib 37.5 mg

25 mg 4 tedne - 1 teden pavze

3 tedenski premor, nato **25 mg**



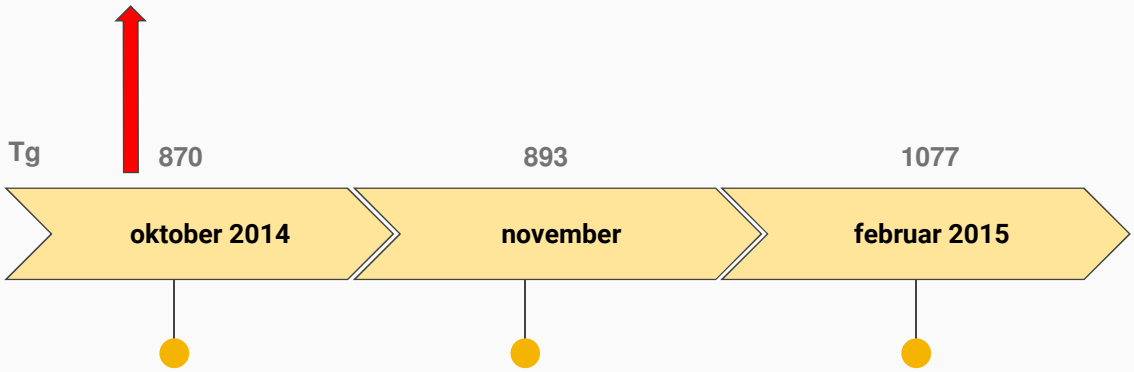
asimptomatski

- stopnjujoče **driske, Gr. 3**
- slabši apetit
- hujšanje

- občasne **driske, Gr. 3** (14 dni ni jemal terapije)
- vročinski oblivi
- suha koža, sprememba barve las

UZ Ab: stagnacija zasevkov v jetrih
RTG p/c: bp

sunitinib 25 mg 3 tedne - 12.5 mg 1 teden - 1 teden pavze



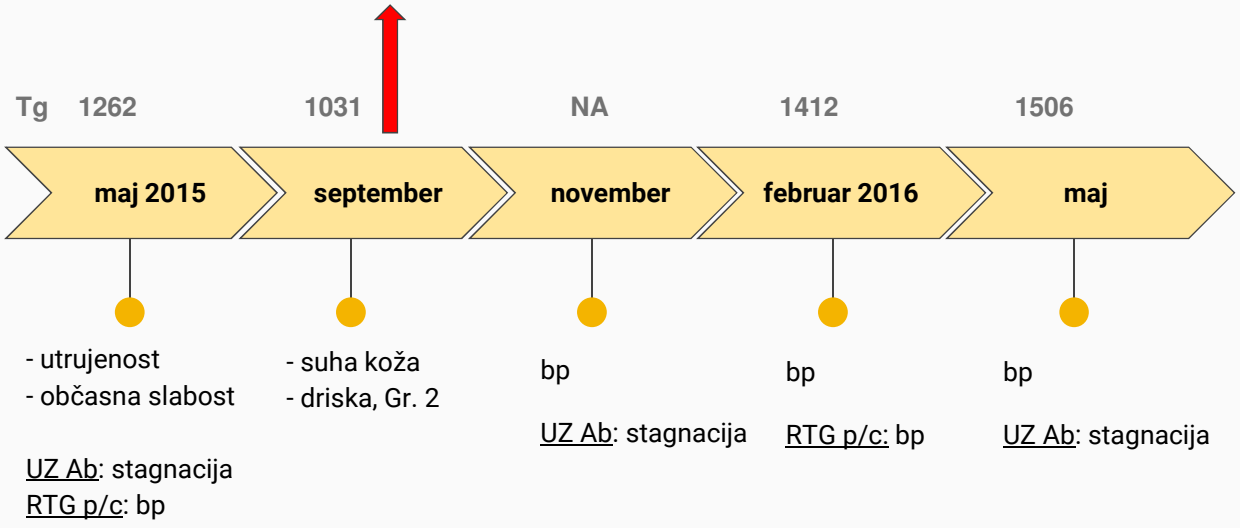
- suha koža
- utrujenost
- driske so izzvenele

bp

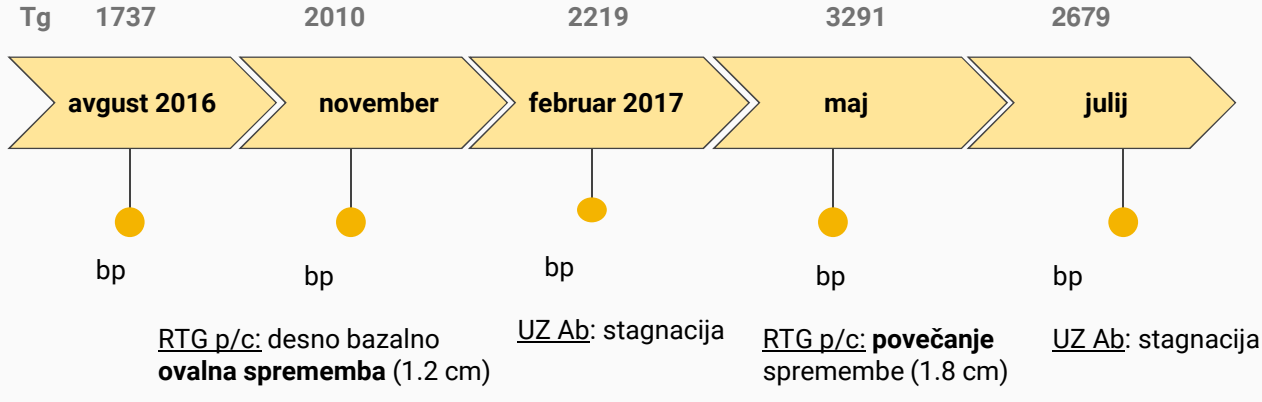
bp

UZ Ab: stagnacija zasevkov v jetrih

sunitinib 25 mg 1 teden - 12.5 mg 1 teden - še 1 x ponovit shemo - 3 tedni pavze



sunitinib 25 mg 1 teden - 12.5 mg 1 teden - še 1 x ponovit shemo - 3 tedni pavze



Oktober 2017

Anamneza: 1 teden trajajoča dispneja, občasna bolečina za prsnico, suh kašelj, huda utrujenost

Status: blažje prizadet, dispnoičen v mirovanju, FR_D 17/min, SaO2 97 %, RR 150/110 mmHg, FR_S 70/min. Preostali status bp.

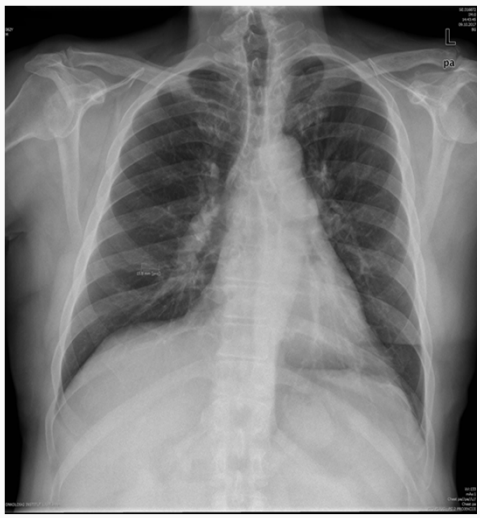
Laboratorij: **Tg 2889**, **LDH 5.57,** preostali izvidi bp.

↓

pljučna embolija / a. ishemija miokarda?

EKG: inverzni T valovi in ST denivelacije v V1-V3

RTG p/c: povečana oba pljučna hilusa, nodularna sprememba v pljučih v stagnaciji



↓

napoten na Internistično prvo pomoč

Dg: **obsežna pljučna embolija** z jahajočim trombom na odcepišču obeh glavnih pljučnih arterij (brez znakov za obremenitev desnega srca) ob **GVT D goleni**

Zadnji pregled: 6.11.2017

Anamneza: Okreva po pljučni emboliji, je na terapevtskih odmerkih NMH.
Počutje je zadovoljivo, nima večjih sopojavov zdravljenja s sunitinibom.

Status: v mejah normale

Laboratorij: **Tg 2935, AST 0.97, ALT 1.91,** preostali izvidi bp

↓

Nadaljuje z ustaljeno shemo sunitiniba.

Ob naslednji kontroli: UZ Ab, RTG p/c. → **Zamenjava terapije?**

Hvala za pozornost!

13. dan internistične onkologije
NOVOSTI V SISTEMSKEM ZDRAVLJENJU REDKEJŠIH SOLIDNIH RAKOV

SISTEMSKO ZDRAVLJENJE GASTROINTESTINALNIH STROMALNIH TUMORJEV (GIST)

Mag. M. Unk, dr.med.

Onkološki inštitut Ljubljana, 17.11.2017

Uvod

- Mazur in Clarck 1983
- Mezenhimalni tumor
- Mezoderm prebavnega trakta
- Pod 1% vseh tumorjev prebavil
- Hirota et al 1998: KIT mutacija
- Cajalove intersticijske celice (? prekurzor)

Epidemiologija

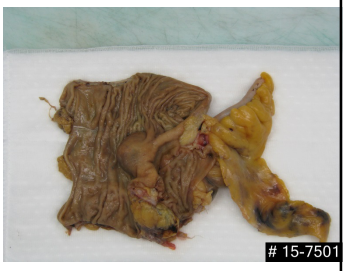
- Incidenca 1/100000/leto (klinično pomembni, >1 cm)
- moški > ženske
- Starost 40-80 let (srednja ~ 60 let)
- Večina sporadični
- V sklopu sindromov (Carneyeva triada, Carney Stratakis sindrom, nevrofibromatoza I)
- Familialno (AD mut KIT)

Eisenberg et al. Ann Surg Oncol 2004; Gold et al. Ann Surg 2006; DeMateo et al. Ann Surg 2000; Takazawa et al. Am J Surg Pathol 2005.

Lokacija

- Želodec: 50%
- Požiralnik: 5%
- Tanko črevo: 25%
- Debelo črevo in rektum: 10%
- Ekstraintestinalno: 10%

Rubin et al, Clin Can cer Res 2003

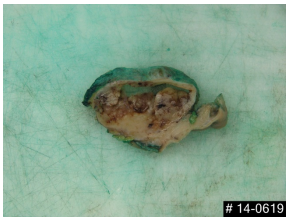


Z dovoljenjem: A. Kleviišar, OI

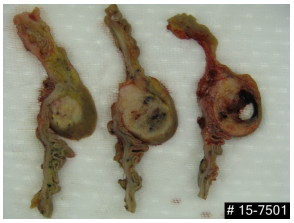
Klinična slika

- Nespecifična
- Odvisna od mesta
- V prebavilih: krvavitev
- Ostalo:
  - masa v trebuhu
  - bolečina
  - distenzija
  - obstrukcija
- Asimptomatski: 30%

Miettinen et al. Hum Pathol 1999.



Z dovoljenjem: O. Blatnik, OI



Z dovoljenjem: A. Klevišar, OI

Diagnoza

- Klinične, radiološke in patohistološke značilnosti
- CT s kontrastom (slikovna preiskava izbora)
- Endo UZ za manjše tumorje
- MRI: rektalni GIST
- PET CT

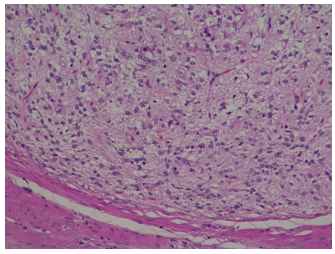
Naključno odkrita subepitelijska sprememba:
-Ni jasnih priporočil
-Na endoUZ pod 2 cm, ponovi čez 3 mesece; dinamika
-če izrašča iz mišičnine in je nad 3 cm; verjetno GIST; op
-Če izrašča iz mišičnine; ABTI in cKIT
-? Mase med 2 in 3 cm
-Rektum, vagina

- Predoperativna biposija:
  - ponavadi ne („seeding“, krvavitev)
  - endoskopska biopsija: potrditev dg, manj krvavitev

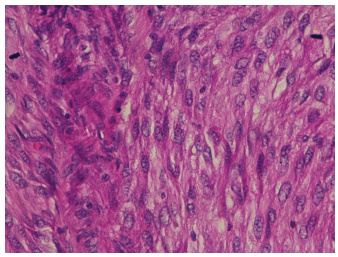
Blay et al. Ann Oncol 2005

Patohistologija

- Makroskopska slika: dobro omejen, belkasto siva, slaninasta površina, ulceracija v 50%
- Diagnoza: morfologija in imunohistokemija
  - Vretenaste celice
  - IHC: CD117 (5% je neg), DOG1
  - Molekularna analiza gena cKIT, PDGFRα, bRAF



Z dovoljenjem: O. Blatnik, OI



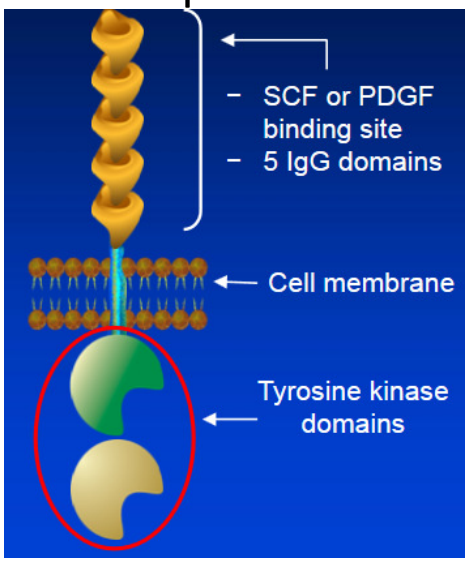
Z dovoljenjem: A. Klevišar, OI

Genetska osnova GIST: KIT – PDGFRα receptor

Tirozinska kinaza tipa 3

- Vezava liganda na KIT ali PDGFRα sproži kaskado reakcij...
  - proliferacija
  - antiapoptoza
- Ekstracelularna domena
  - SCF za KIT
  - PDGF za PDGFRα
- Intracelularna domena
  - dve tirozin kinazi
  - več avtofosforilitičnih mest

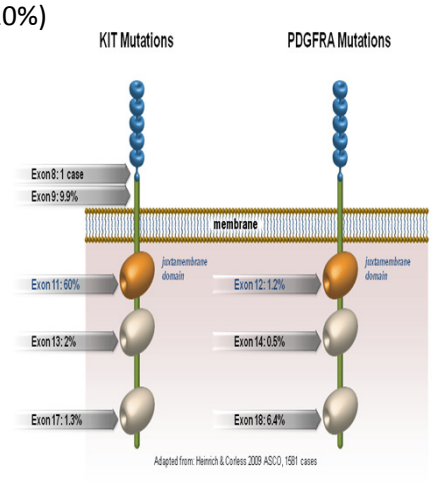
SCF: steam cell factor
Taylor et al. Haematol Oncol Clin North Am 2000; Corless et al. Annu Rev Pathol 2008.



Molekularni podtipi GIST

- KIT mutacija
  - 80% (exon 11- 70%, ekson 9- 10%)
- PDGFR mutacija – 10 %
- SDH-B pomanjkanje
- Raf V600E
- NF1
- Ras
- PI3K
- Prekomerno izražanje IGF-1R
- Wild type

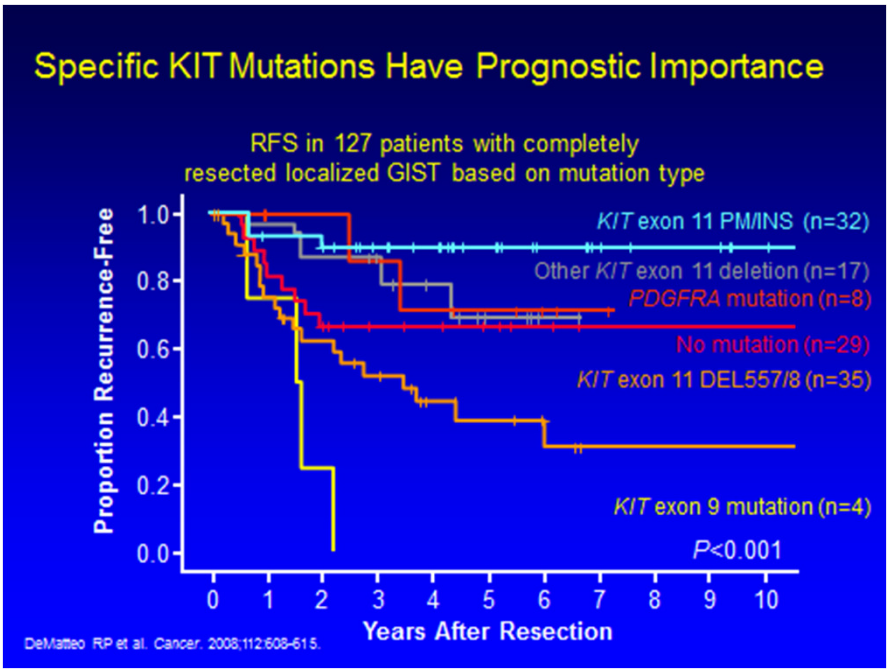
Blay et al. Discover Med 2012



Maligni potencial

- Ocena malignega potenciala: izziv
- Morfologija vpliva na maligni potencial:
  - mitoze
  - lokacija
  - velikost
- Vpliv rupture tumorja ob operaciji
- Tip mutacije prediktivni dejavnik za odgovor na zdravljenje metastatske bolezni (? Adj)

Fletcher et al. Hum Pathol. 2002; Demetri et al. J Natl Compr Cancer Netw. 2007; Miettinen et al.Ach Pathol Lab Med. 2006; Debiec-Rychter et al. Eur J Cancer. 2006; Heinrich MC et al. J Clin Oncol. 2003;21:4342-4349.



Vloga sistemskega zdravljenja

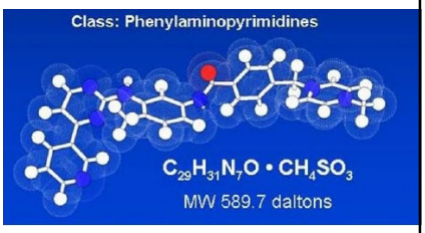
- Omejena bolezen:
  - Adjuvantno
  - Neoadjuvantno
- Metastatska bolezen:
  - 1. red
  - 2. red
  - 3. red

Statistično pomembno tveganje za ponovitev bolezni 50% (nomogrami)

Velikost
Mitoze
Lokacija
Molekularna analiza

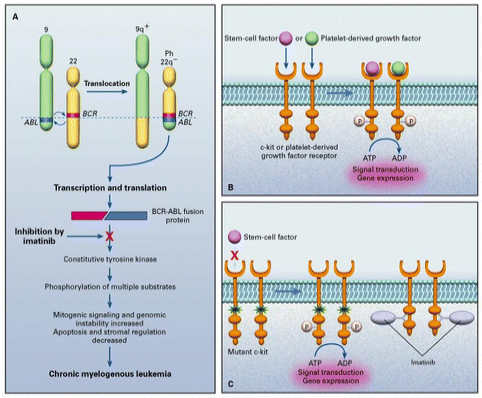
Mietinnen et al. Arch Pathol Lab Med 2006

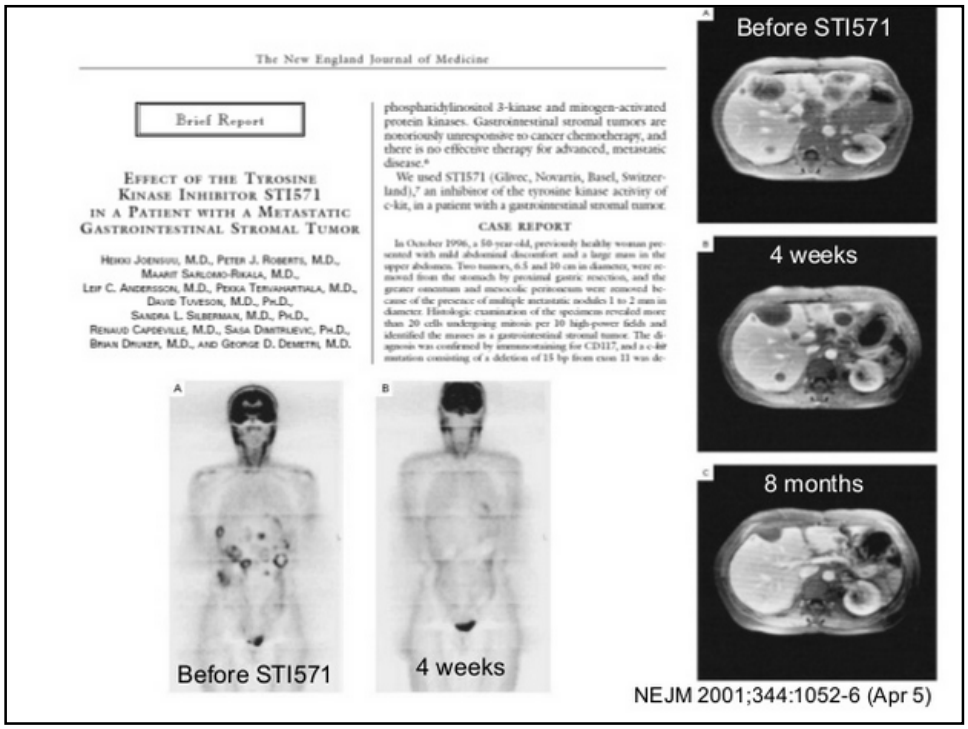
Imatinib

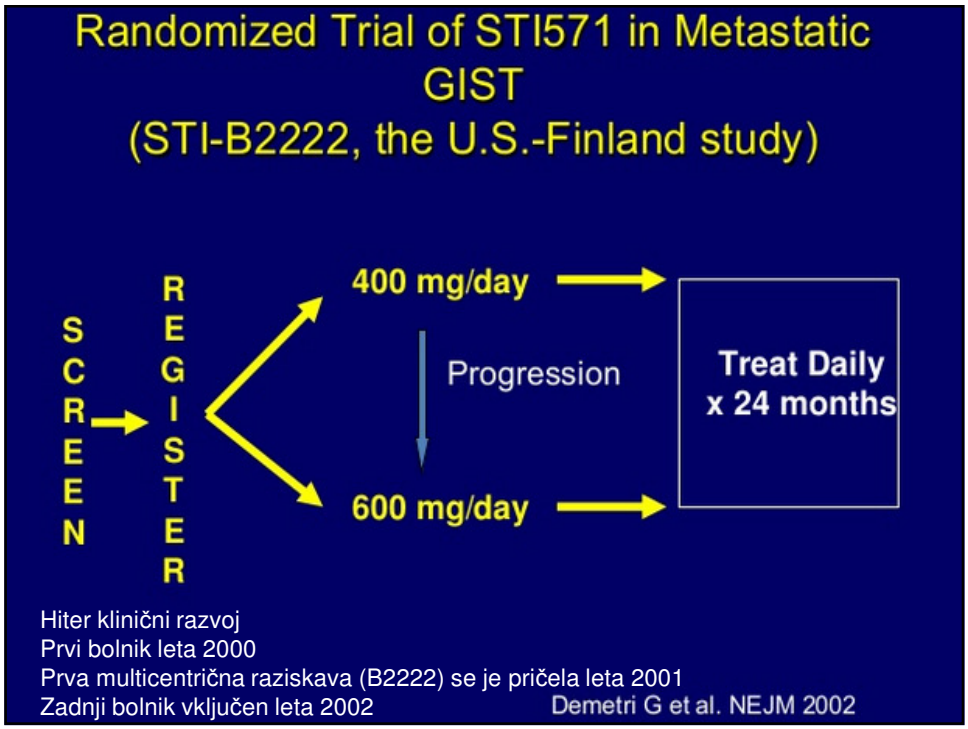


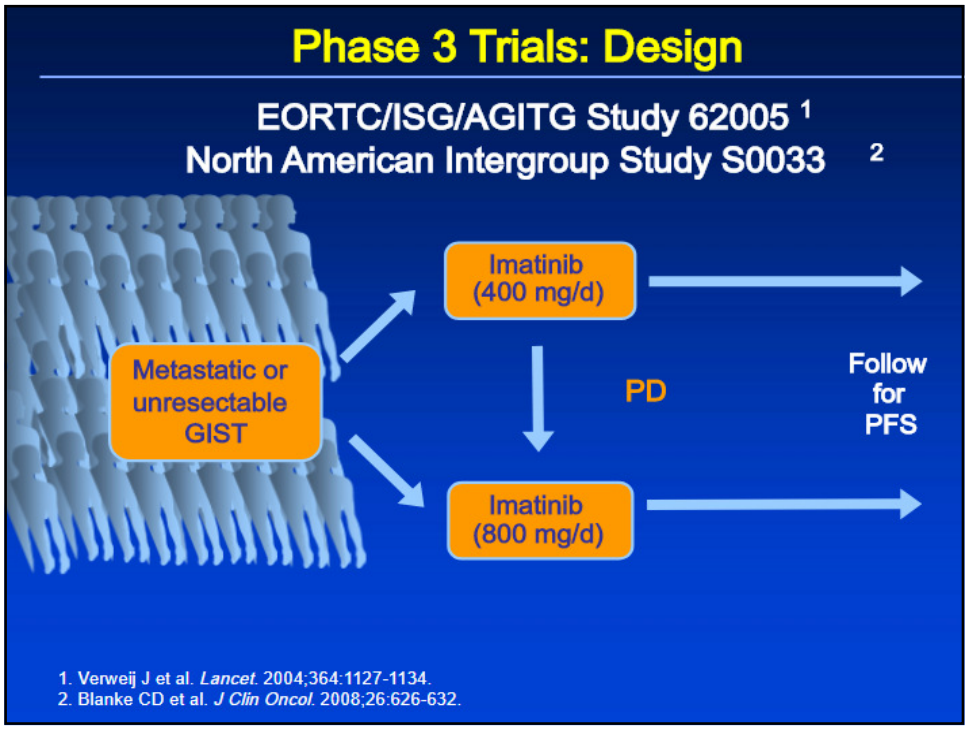
- Specifični inhibitor tirozin kinazne aktivnosti *abl* (Abelson proto-onkogen), c-kit PDGF-R (platelet derived growth factor receptor)
- Vezava na isto mesto kot ATP

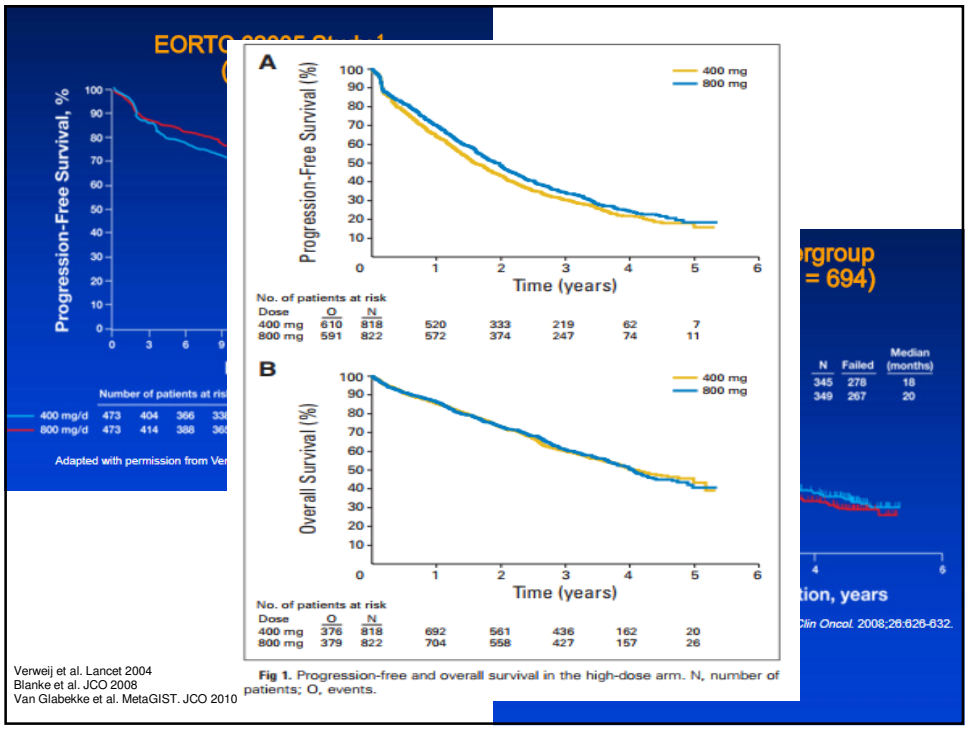
Hantsghel et al. Leukemia Lymphoma 2008.
Maley et al. EJC 2002; Savage et al. NEJM 2002.






Randomized Trial of STI571 in Metastatic GIST
(STI-B2222, the U.S.-Finland study)
SCREEN
REGISTER
400 mg/day
Progression
600 mg/day
Treat Daily
x 24 months
Hiter klinični razvoj
Prvi bolnik leta 2000
Prva multicentrična raziskava (B2222) se je pričela leta 2001
Zadnji bolnik vključen leta 2002
Demetri G et al. NEJM 2002


Phase 3 Trials: Design
EORTC/ISG/AGITG Study 62005 1
North American Intergroup Study S0033 2
Metastatic or unresectable GIST
Imatinib (400 mg/d)
PD
Imatinib (800 mg/d)
Follow for PFS
1. Verweij J et al. Lancet. 2004;364:1127-1134.
2. Blanke CD et al. J Clin Oncol. 2008;26:626-632.



Verweij et al. Lancet 2004
Blanke et al. JCO 2008
Van Glabekke et al. MetaGIST. JCO 2010

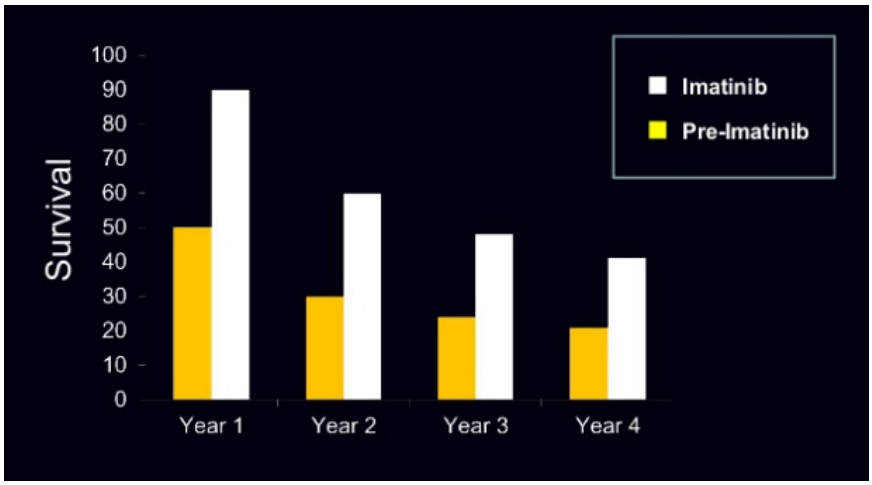
Fig 1. Progression-free and overall survival in the high-dose arm. N, number of patients; O, events.

Metastatski GIST in odgovor na imatinib

raziskava	odgovor (CR, PR, SD)	progres (P)	neocenljivo
B2222	123 (84%)	17 (12%)	7 (5%)
EORTC	794 (84%)	103 (11%)	49 (5%)
S0033	375 (69%)	79 (15%)	86 (16%)
skupaj	1292 (79%)	199 (12%)	142(9%)

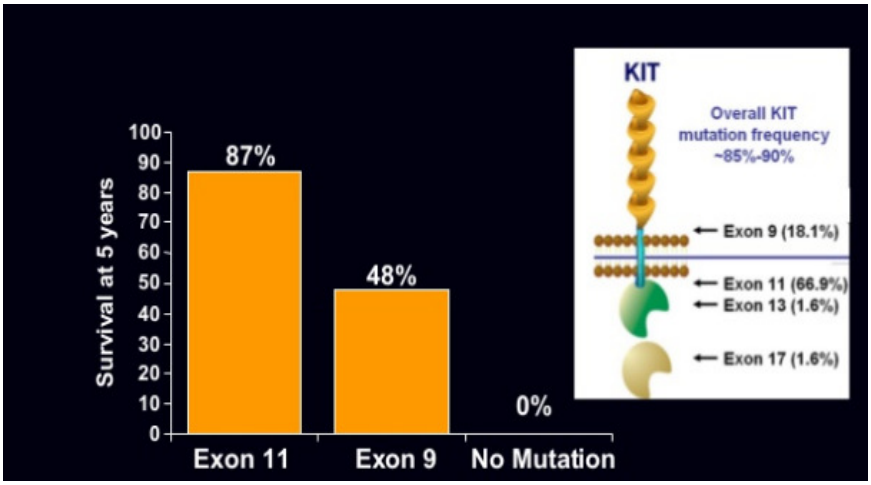
Demetri et al. NEJM 2002; Blanke et al. JCO 2008; Verweij et al. Lancet 2005;

Preživetje metastatskega GIST pred in po imatinibu



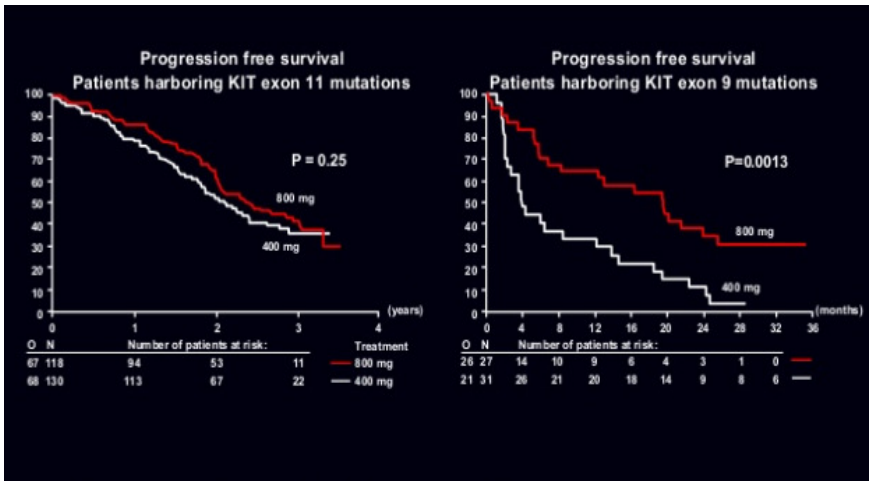
Artinyan and Ellenhorn. Cancer Epidemiol Biomarkers Prev 17:2194

Imatinib pri napredovalem GIST



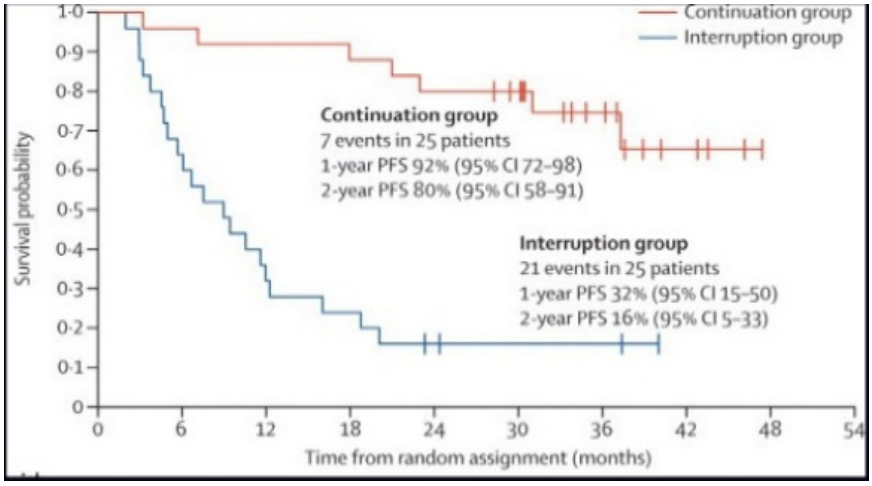
Blanke et al. Proc Am Soc Clin Oncol 2007

Vpliv odmerka imatiniba na čas do napredovanja bolezni



Debiec-Rychter et al. Eu J Cancer 2006

Trajanje zdravljenja z imatinibom pri metatstatski bolezni



Le Cesne et al. Lancet Oncol 2010

NAPREDOVANJE BOLEZNI

lokalno
kirurgija
RFA
kemoembolizacija
RT (požiralnik in rektum)

difuzno
sunitinib
regorafenib
re-callenge

ESMO Guidelines 2014

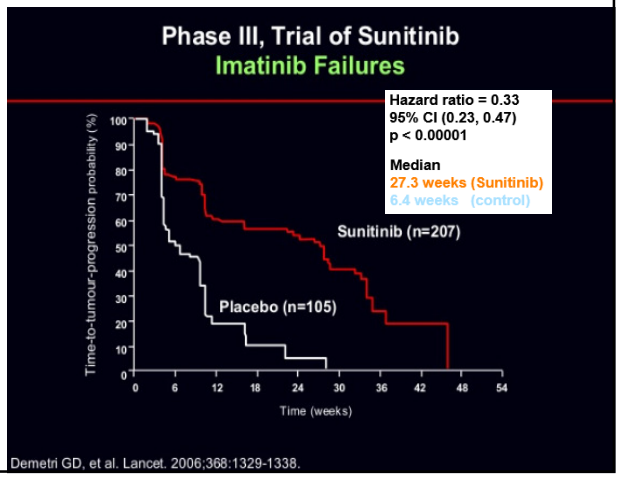
Na imatinib odporen metastatski GIST

Odobren za zdravljenje bolnikov z GIST, katerim je bolezen napredovala tekom zdravljenja z imatinibom ali pa imatiniba ne prenašajo

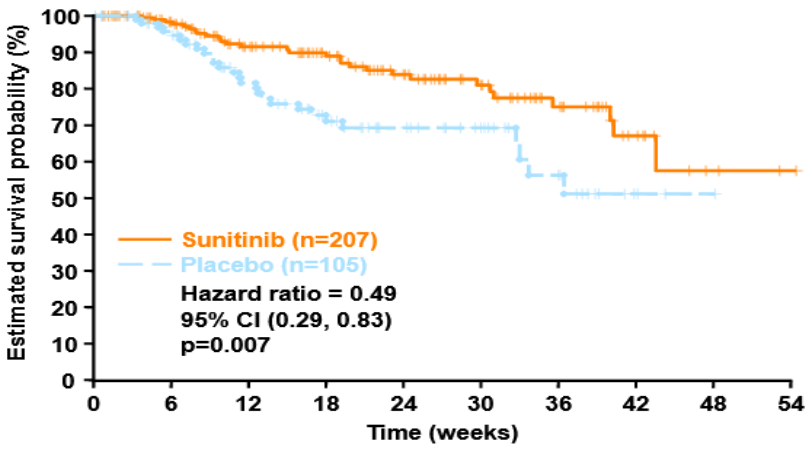
SUNITINIB

Zaviralec različnih receptorskih tirozinskih kinaz

Antitumorsko in antiangiogeno delovanje

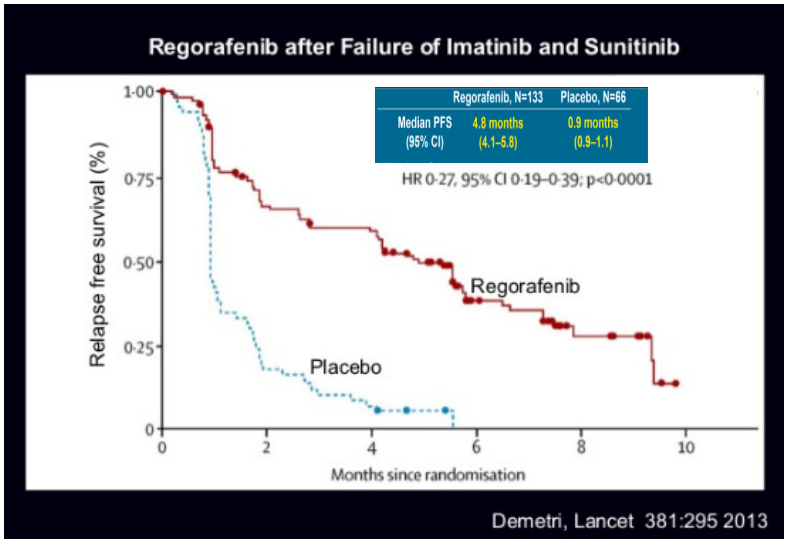


Preživetje

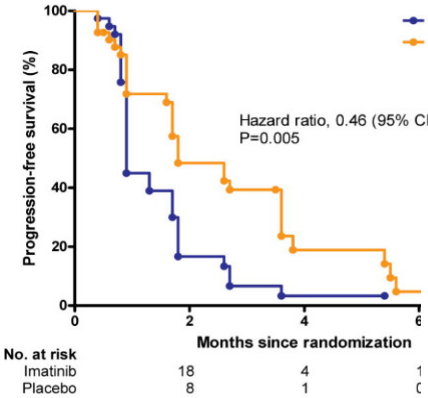


Demetri et al. Lancet.2006.

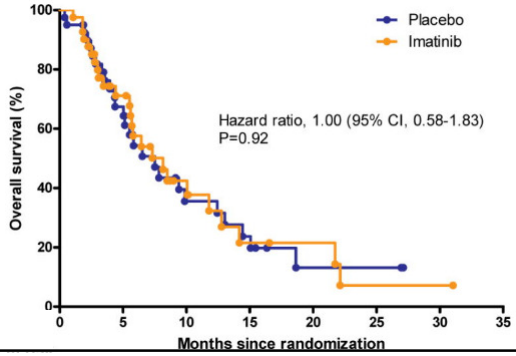
Napredovanje po imatinibu in sunitinibu- GRID



Re-challenge imatinib



po regorafenibu, sunitinibu, dovitinibu, nilotinibu



Kontinuirano zdravljenje z antiTKI upočasni napredovanje bolezni!

Kang et al.Lancet Oncol 2013.

Dopolnilno sistemsko zdravljenje

ACOSOGZ9001

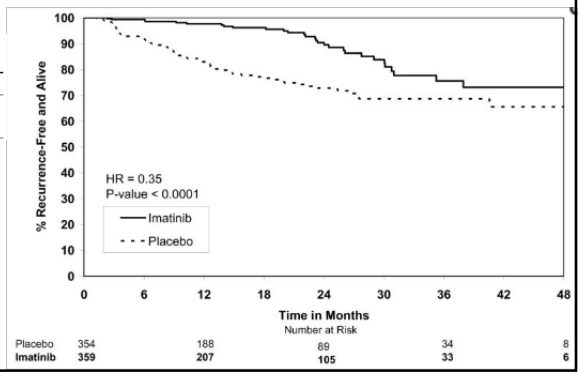
- 713 bolnikov, CD117 pozitivnih, GIST ≥ 3 cm
- Imatinib 400mg/dan vs placebo
- Izboljšanje PFS po srednjem spremljanju 20 mesecev
- Brez razlik v preživetju

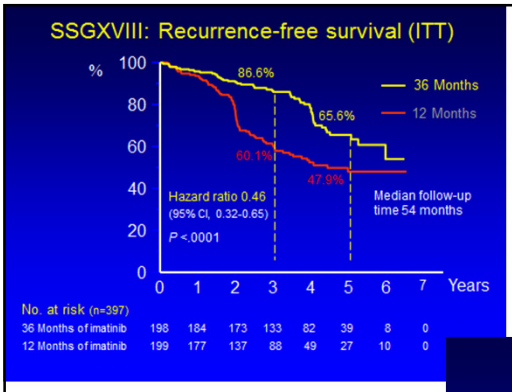
Summary of RFS and OS results.

Outcome	No. of pts	No. of events	HR (95% CI)	p-value
RFS (primary)	713	100 (14.0%)	0.35 (0.22 to 0.53)	< 0.0001
OS (secondary)	713	13 (1.8%)	0.66 (0.22 to 2.03)	0.4714

dobrobit PFS je največja pri velikih tumorjih (nad 10 cm), saj imajo ti bolniki več kot 50% tveganje za ponovitev bolezni v 2 letih

Dimateo et al. Lancet 2009.

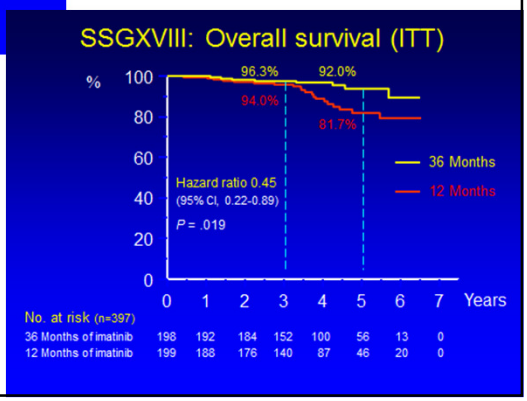




SSGXVIII[1]

785 bolnikov z velikim tveganjem za ponovitev[2]
36 proti 12 mesecev imatiniba
Izboljšanje časa do ponovitve bolezni
Izboljšanje preživetja
Varno zdravljenje

Kateri bolniki so najbolj primerni?
MUTACIJE!



1. Joensuu et al. JAMA 2012.
2. Fletcher et al. Hum pathol 2002

Neoadjuvantni imatinib

- Kdaj?
  - Inoperabilni ali mejno operabilni
  - Operacija bi imela veliko posledic (multivisceralna)
  - Eventuelno resektabilna metastatska bolezen

RTOG0132/ACRIN6665

faza II; ali tumor nad 5 cm (A) ali primarno M1 (B) in do 2 cm velik tumor

	Group A	Group B
Response to pre-operative therapy (RECIST)	7% PR, 83% SD, 10% unknown	4.5% PR, 91% SD, PD 4.5%
Estimated 2-year PFS	82.7%	77.3%
Estimated 5-year PFS	57%	30%
Estimated 2-year OS	93.3%	90.9%
Estimated 5-year OS	77%	68%
Type of resection	R0 77% R1 15% R2 8%	R0 58% R1 5% R2 32% Unspecified 5%

Eisenberg et al. J Surg Oncol 2009; Wang et al. ASCO 2011.

Klinični primer: metastatski GIST

DNEVI INTERNISTIČNE ONKOLOGIJE 2017

Pripravila: Marina Čakš, dr. med
Mentorica: mag. Mojca Unk, dr. med

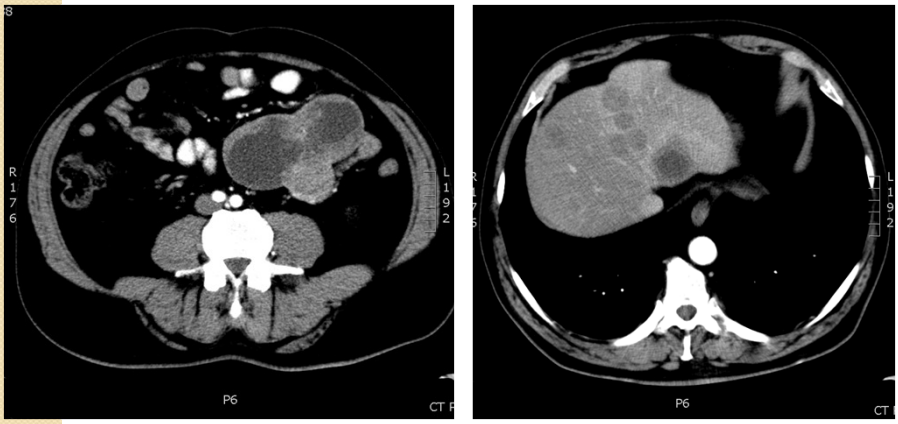
Predstavitev bolnika

- 62-letni bolnik
- Brez spremljajočih bolezni
- Nekadilec
- V družini rak na debelem črevesju pri teti

- Simptomi in znaki: slabost, melena, anemija

Diagnostika

- CT trebuha: TU v predelu tankega črevesja, zasevki v jetrih



Diagnostika

- Operacija zaradi krvavitve iz tumorja (11.9.2012): eksplorativna laparotomija, ekstirpacija tumorja, resekcija dela jejunuma.
- DG: GIST, 10x8,5x6 cm, 40 mitoz/10 polj velike povečave, CD117+; citološka punkcija spremembe v jetrih: metastaza GISTa
- Naknadna določitev mutacij iz primarnega tumorja: prisotna cKIT mutacija na exonu 11

1. VPRAŠANJE: Za kakšno zdravljenje bi se odločili?

- imatinib 400 mg/d
- imatinib 800 mg/d
- sunitinib
- študijsko zdravljenje
- KT

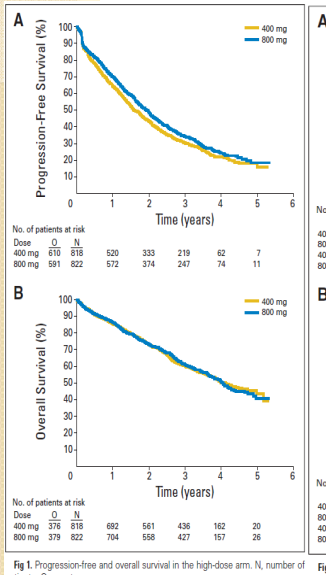


Fig 1. Progression-free and overall survival in the high-dose arm. N, number of patients; O, events.

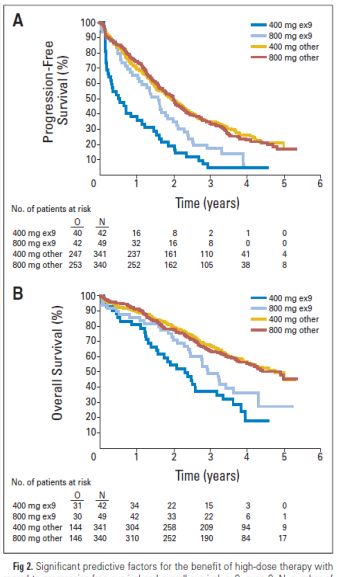


Fig 2. Significant predictive factors for the benefit of high-dose therapy with regard to progression-free survival and overall survival. ex9, exon 9; N, number of patients; O, events.

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). J Clin Oncol 2010; 28: 1247–1253.

standard dose of imatinib is 400 mg daily [I, A]. However, data have shown that patients with *KIT* exon 9 mutations fare better in terms of progression-free survival (PFS) on a higher dose level, i.e. 800 mg daily, which is therefore the standard treatment in this subgroup [27] [III, A]. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines.

Sistemsko zdravljenje 1. reda

- **Imatinib** 400 mg/d
- Po 9 mesecih zdravljenja delna remisija bolezni
- NU imatiniba: krči v mišicah, mialgije G1 diareja G1, edem G1 (periorbitalni), utrujenost oz. oslabelost G1
- Po 21 mesecih difuzen progres bolezni v jetrih, PS 1

2. vprašanje: Kaj bi naredili zdaj?

- imatinib 800 mg/d
- sunitinib 37,5 mg/d
- sunitinib 50 mg (4t on+2t off)
- klinična raziskava
- RFA

Povišanje odmerka imatiniba

EORTC 62005[1]

- 133 bolnikov, crossover na 800 mg
- odgovor: 2% PR, 27% SD
- mPFS: 81 dni

SOO33[2]

- 77 bolnikov, crossover na 800 mg
- odgovor: 3% PR, 28% SD
- mPFS: 5m

Možna razlaga:

- exon 9 mutacija
- nezadostna koncentracija zdravila v krvi [3]

[1]Zalcberg et al., Eur J Cancer 2005; 41(11): 1751-1757.
[2]Blanke et al., J Clin Oncol 2008; 26(4): 626-632.
[3] Demetri et al., J Clin Oncol 2009; 27(19): 3141-3147

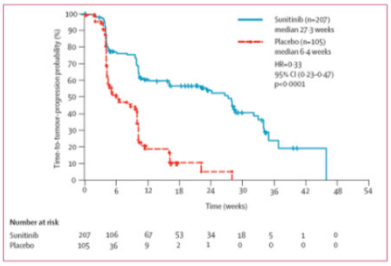
Sistemsko zdravljenje

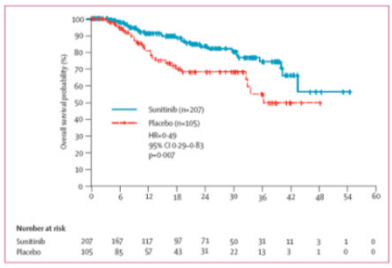
- **Imatinib 800 mg/d**
- Najboljši odgovor stagnacija bolezni
- NU: mialgije G1, edem G1 (periorbitalni)

- Po 6 mesecih zdravljenja difuzen progres bolezni v jetrih, pojav anemije, PS 1

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali





Demetri GD et al., Lancet. 2006;3681329-1338.

3. vprašanje: Za kakšen odmerek sunitiniba bi se odločili?

- sunitinib 50 mg; 4 t on+ 2 t off
- sunitinib 37,5 mg/d

In the case of confirmed progression or rare intolerance on imatinib (after attempts to manage side-effects also through expert advice, also exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is another tyrosine kinase inhibitor, sunitinib [34] [I, B]. The drug was proved effective in terms of PFS following a '4 weeks on–2 weeks off' regimen. Data have been provided that a continuously dosed daily oral regimen with a lower daily dose (37.5 mg) is effective and well tolerated, although no formal comparison has been carried out within a randomised clinical trial. This schedule can therefore be considered an alternative on an individualised basis [35] [III, B].

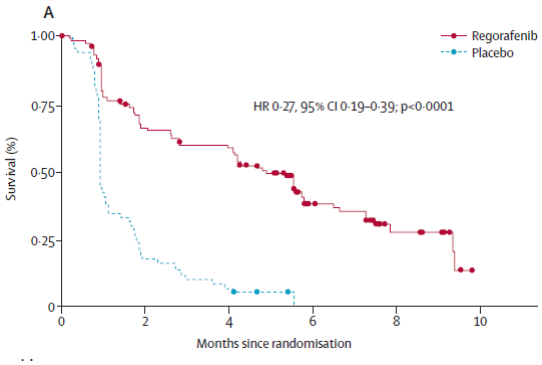
Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines

Sistemsko zdravljenje 2. reda

- **Sunitinib** 37,5 mg/d
- Po dveh mesecih zdravljenja dosežena delna remisija bolezni
- NU: diareja G2, sprememba barve kože, HFS G1, hipotiroidizem, trombocitopenija G1, AH
- Po 18 mesecih zdravljenja difuzen progres bolezni v jetrih, PS 1

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schöffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshirou Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paolo G Casali, on behalf of all GRID study investigators*



Sistemsko zdravljenje 3. reda

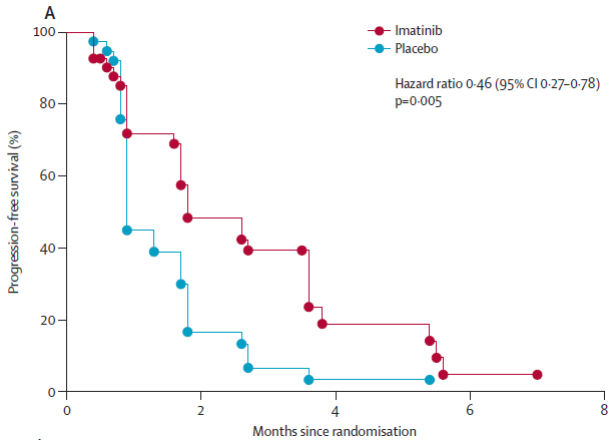
- **Regorafenib** 160 mg/d (3+1), zaradi NU doza po 3 mesecih znižana na 120 mg/d (3+1)
- Po 2 mescih stagnacija bolezni
- NU: Diareja G3, HFS G1, utrujenost oz. oslabelost, AH, sprememba glasu
- Bolečine v trebuhu ob pavzi: modifikacija sheme jemanja (krajša pavza)
- Po 15 mesecih zdravljenja progres bolezni v jetrih

4. vprašanje: Za kakšno zdravljenje bi se odločili zdaj?

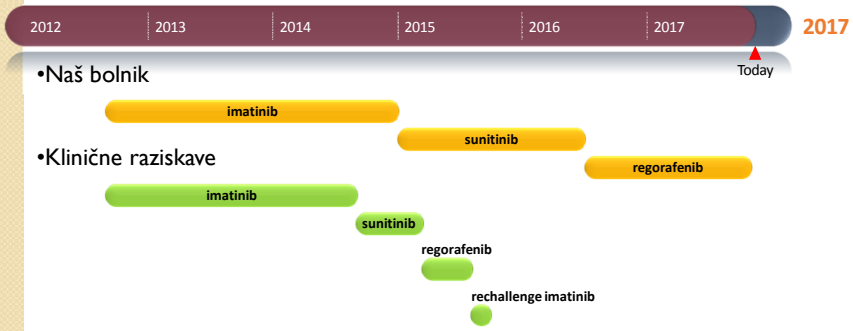
- ponovno povišanje odmerka regorafeniba
- ponovna uvedba imatiniba
- klinična raziskava
- BSC

Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial

Yoon-Koo Kang, Min-Hee Ryu, Changhoon Yoo, Baek-Yeol Ryoo, Hyun Jin Kim, Jong Jin Lee, Byung-Ho Nam, Nikhil Ramaiya, Jyothi Jagannathan, George D Demetri



Zaključek


2012
2013
2014
2015
2016
2017
2017
Today
•Naš bolnik
imatinib
sunitinib
regorafenib
•Klinične raziskave
imatinib
sunitinib
regorafenib
rechallenge imatinib

Sistemsko zdravljenje timičnih rakov (TR)

prof.dr. Tanja Čufer, dr.med
Urška Janžič, dr. med
Univerzitetna klinika Golnik
Medicinska Fakulteta, Univerza Ljubljana

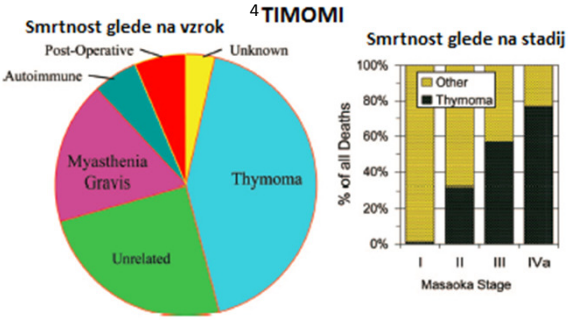
13. Dnevi Internistične onkologije, Ljubljana, 2017

Epidemiologija

- Incidenca timičnih rakov (TR):
  - [1]IACR: 1-5/1.000.000
  - [2]SLO (2010 – 2014) 26 primerov (5.2/leto) = 0.28/100.000
  - [3]UK Golnik (2010 – 2016) 26 primerov (3.7/leto)
- [5]5-letno preživetje:
  - Timomi 90%
  - Timični karcinomi 55%

ESMO definicija redkih rakov < 3 / 100.000

[4]TIMOMI



1 https://www.iacr.com.; 2 https://www.onko-i.si/rrs/.;
3 http://www.klinika-golnik.si/dejavnost-bolnisnice/klinicna-dejavnost/onkoloska-dejavnost/register-raka-pljuc.php
4 Huang L, et al. JTO. 2010.; 5 Strobel P, et al. JCO 2004.

Klinična slika

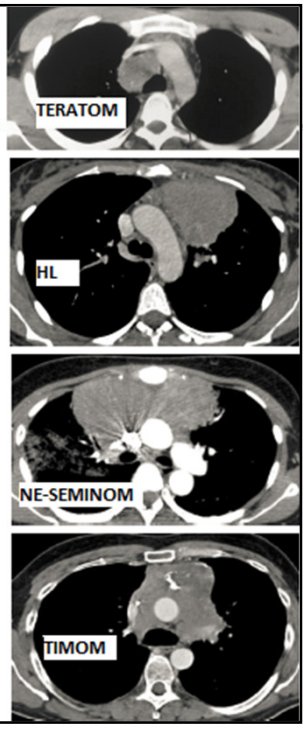
- Starost najpogosteje 50 – 60 let
- Blago tiščanje, težka sapa, kašelj, bolečina v prsnem košu, SVC
- Okoli 30% bolnikov s timomi ima paraneoplastični sindrom, najpogostejši je miastenija gravis (10-15% bolnikov z miastenijo gravis ima TR)

Organski sistem	Paraneoplastični sindrom	Preiskave
Živčnomišični	**Miastenija gravis** Periferna nevropatija Polimiozitis	**Acetiloholinska protitelesa** **ANA, ANCA**
Hematološki	**Aplazija eritrocitov** Pancitopenija Hemolitična anemija	KKS, DKS, retikulociti
Avtoimuni	SLE RA Sjogrenov sindrom	ANA, ANCA
Endokrini	Multiple endokrine neoplazme Cushingov sindrom.	Hormoni (kortizol, ACTH, LH, FSH, TSH, T3, T4)
Motnje imunske pomanjkljivosti	**Hipogamaglobulinemija** Sy. pomanjkanja T-celic	Elektroforeza, imunoelektroforeza
Koža	Pemfigus Lichen planus	

Diagnostični postopki

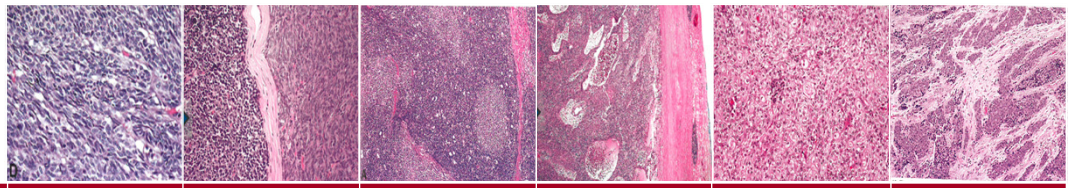
- CT prsnega koša s kontrastom (MRI, za opredelitev vraščanja v perikard, plevro)
- Krvne preiskave (KKS, DKS, LDH, AFP, beta-HCG, acetilholinska protitelesa in nuklearna protitelesa, ostalo glede na paraneoplastično simptomatiko)
- Pridobitev tkiva:
  - Debeloigelna biopsija (izogibati se plevri)
  - Če je tumor dobro omejen in je predvidena radikalna resekcija predhodna biopsija ni potrebna
- PET-CT samo izjemoma, pri timičnem karcinomu za iskanje oddaljenih metastaz

Najpogostejši vzrok mase v sprednjem mediastinumu po 40. letu je timična neoplazma!



Girard N, et al. Ann Oncol 2015.
https://www.nccn.org/professionals/physician_gls/default.aspx

Patolomorfološke značilke in prognoza



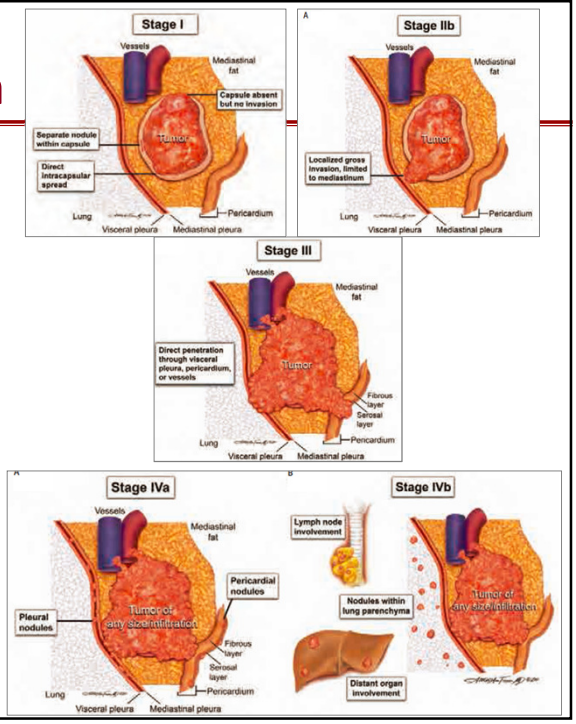
	TIMOM A	TIMOM AB	TIMOM B1	TIMOM B2	TIMOM B3	TIMIČNI KARCINOM
Značilnosti	Ovalne / vretenaste tumorske celice, malo limfocitov	Del tumorja z vretenastimi celicami, del bogat z limfociti	Podobnost z normalnim timusom; bogat z limfociti	Tumor z veliko limfociti in poligonalnimi tumorskimi celicami	Predominantno epitelijske celice, ki rastejo v plahtah, vmes posamični T limfociti	Porušena normalna arhitektura, skoraj nič limfocitov, najpogosteje SCC tip
Možnost ponovitve v 5-L po RO resekciji	5%	3%	11%	14%	23%	38%
Možnost ponovitve v 10-L po RO resekciji	9%	3%	14%	32%	29%	28%
5-L OS	90%	90%	96%	NR	89%	57-65%

Travis DW, et al. WHO 2015.

Stadij: Masaoka-Koga sistem

Temelji na KIRURGIJI =
pooperativni / patološki stadij

STADIJ	Značilnosti
I	V celoti enkapsuliran tumor
IIa	Mikroskopska transkapsularna invazija
IIb	Makroskopska invazija v timično in okolno maščevje ali v stiku (brez preraščanja) z mediastinalno plevro ali perikardom
III	Makroskopska invazija v sosednji organ (perikard, velike žile, pljuča)
IVa	Plevralni ali perikardialni zasevki
IVb	Limfogeni ali hematogeni zasevki



Detterbeck F, et al. JTO 2014.

Stadiji: IASLC – ITMIG

Osnova v 8. klasifikaciji TNM,
v povezavi z izidi zdravljenja pri bolnikih.

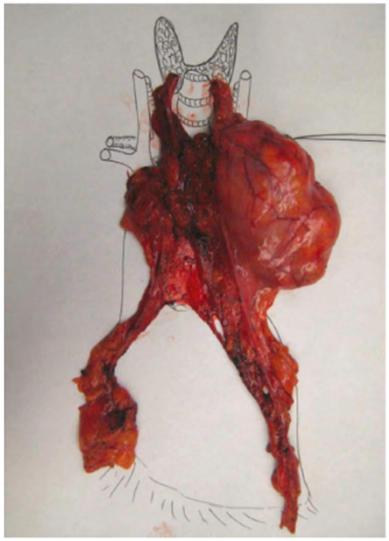
STADIJ	TNM	Odgovarjajoči Masaoka-Koga stadij
I	T1a 1b N0M0	I, IIA, IIB, III
II	T2N0M0	III
IIIA	T3N0M0	III
IIIB	T4N0M0	III
IVA	T any N0-1 M0-1a	IVA, IVB
IVB	T any N0-2 M0-1b	IVB

Carter BW, et al. Radio Graphics 2017.

T (tumor)	
T1a	Enkapsuliran ali ne-enkapsuliran tumor z ali brez vraščanja v okolno maščevje
T1b	Invazija v mediastinalno plevro
T2	Vraščanje v perikard
T3	Vraščanje v pljuča, prsno steno, frenični živec, brahiocefalno veno, v.cave sup., ali hilarne (ekstraperikardilane) pljučne žile
T4	Vraščanje v toraklano aorto, žile loka, glavno pljučno arterijo, trahejo, požiralnik, miokard
N (bezgavke)	
N0	Brez zasevkov v bezgavkah
N1	Zasevki v sprednjih (peritimičnih) bezgavkah
N2	Zasevki v globokih intratorakalnih ali cervikalnih bezgavkah
M (zasevki)	
M0	Brez zasevkov
M1a	Plevralni ali perikardialni zasevki
M1b	Zasevki v pljučih ali drugih solidnih organih

Kirurško zdravljenje

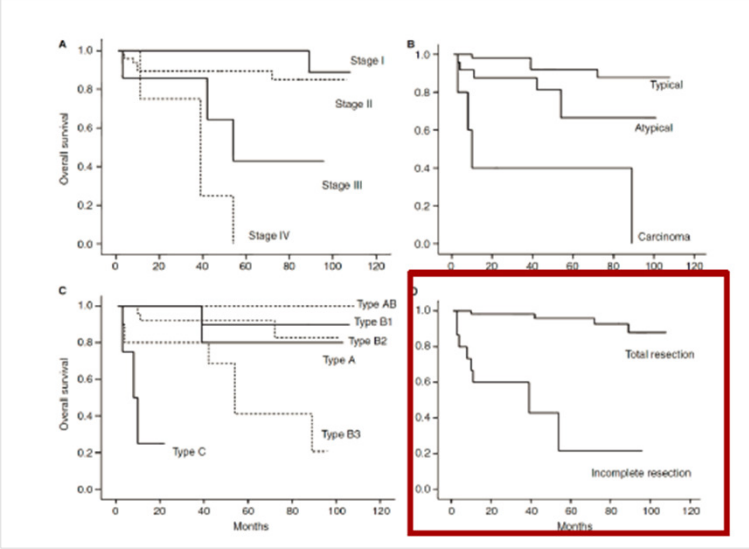
- Kirurško zdravljenje je temeljno zdravljenje vseh timičnih rakov, razen stadija IV
- Mediana sternotomija, minimalno invazivna krg samo za stadij I
- **Kompletna timektomija** (cel timus + okolno maščevje)
- Če je tumor **infiltrativen v okolico – en bloc odstranitev** vseh prizadetih struktur (žile, živci, perikard, plevra)
- Kjer je sum na ostanek, se položijo krg. sponke (za vodenje RT)
- Zmrzli rezi niso potrebni



Girard N, et al. Ann Oncol 2015.; Detterbeck F, et al. JTO 2011.; https://www.nccn.org/professionals/physician_gls/default.aspx

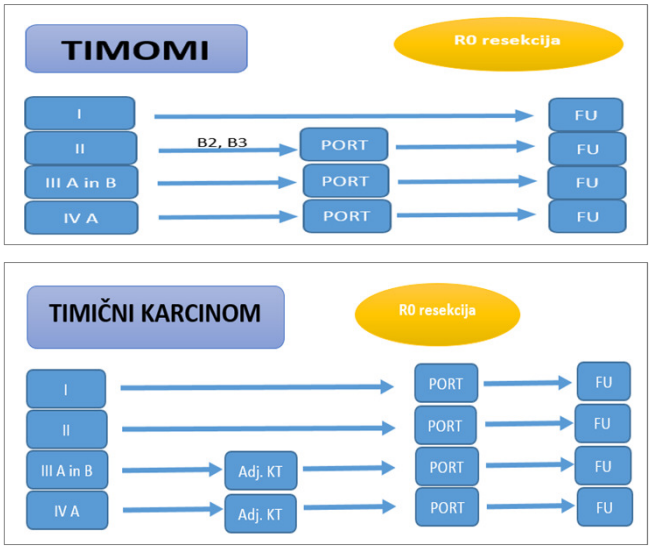
Prognostični dejavniki

- Starost
- Histologija
- Stadij
- R0 operacija = najpomembnejši prognostični dejavnik!!!



Rossi G, et al. Histopathology 2008.

Pooperativno zdravljenje

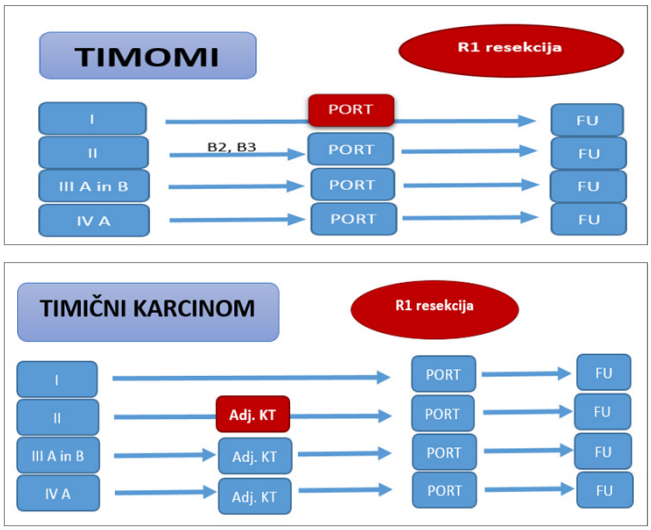


Sledenje:

- Klinični pregled na 3 mesece,
- CT toraksa
  - vsake 6-12 mesecev prve 2 leti
  - nato 1x letno do dopolnjenih 5 let za TC in 10 let za timom

Girard N, et al. Ann Oncol 2015.; https://www.nccn.org/professionals/physician_gls/default.aspx

Pooperativno zdravljenje



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Girard N. et al. Ann Oncol 2015.; https://www.nccn.org/professionals/physician_gls/default.aspx

Vloga pooperativne RT

- Zmanjšanje lokalnih ponovitev iz 30% na < 5%
- Največja dobrobit pri stadiju II-III
- Podatki so iz retrospektivnih študij velikih med-institucijskih baz

	Št. pacientov	Histologija	Stadij	PORT	Rezultat
[1]Jackson	3031 1025	T TC	I - IV	47% 54%	HR OS T: 0.8 HR OS TC: 0.79
[2]Rimner	1263	T	II - III	55%	5-L OS: 95% vs. 90% 10-L OS: 90% vs. 79%
[3]Boothe	1156	T + TC	II - III	42%	5-L OS: 83% vs. 79%
[4]Omasa	1100 155	T TC	II - III	52% 30%	5-L OS T st.II: 96% vs 96% 5-L OS T st. III: 93% vs 90% 5-L OS TC st.II: 91% vs 87% 5-L OS TC st.III: 65% vs 64%

T – timom; TC – timični karcinom; PORT – pooperativna radioterapija

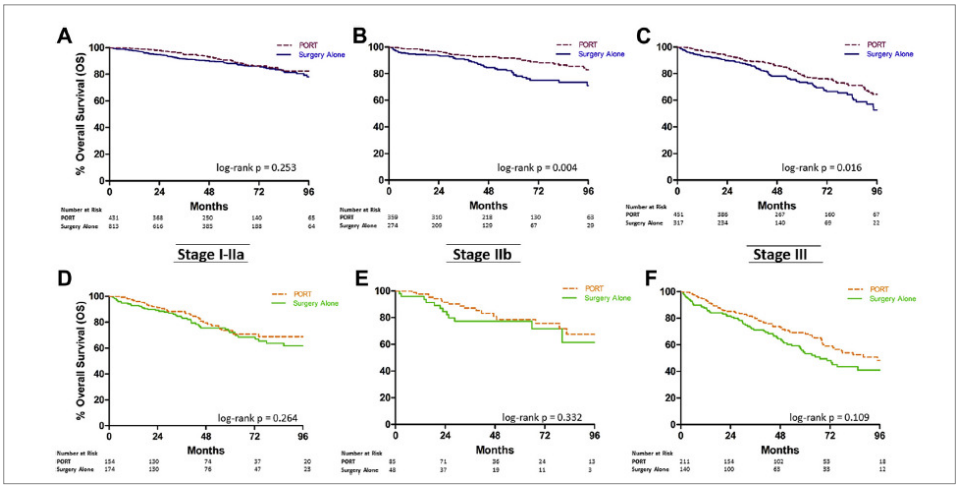
1 Jackson MW, et al. JTO 2017.; 2 Rimner A, et al. JTO 2016.; 3 Boothe D, et al. JTO 2016.; 4 Omasa M, et al. Cancer 2015.

Učinkovitost PORT glede na histološki tip in stadij

Velika ameriška observacijska raziskava, 3013 bolnikov s timomom in 1025 bolnikov s timičnim karcinomom

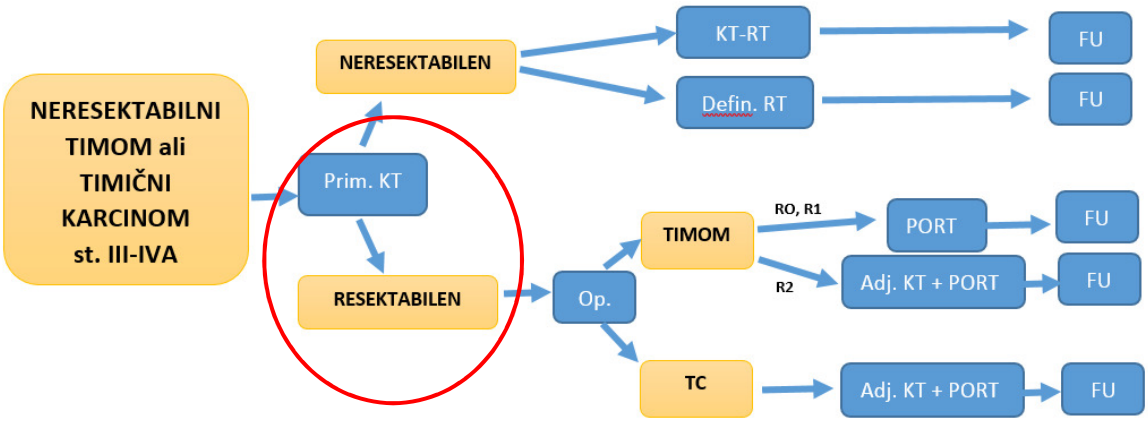
Timom

Timični karcinom



Jackson MW, et al. JTO 2017.

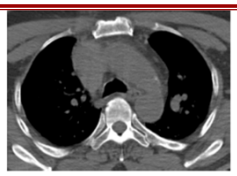
Zdravljenje inoperabilnih timičnih rakov



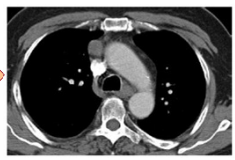
Girard N, et al. Ann Oncol 2015.; https://www.nccn.org/professionals/physician_gls/default.aspx

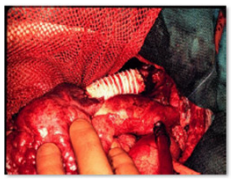
Primarna / indukcijska KT

	Primary chemo-therapy regimen	Subjects n	Tumour		Design	Response rate
			Type	Stage		
Chemotherapy						
Macchiarini [78]	CEE	7	T/TC	III	Phase II	100
Berruti [79]	ADOC	6	T	III–IVA	Phase II	83
Rea [80]	ADOC	16	T	III–IVA	Retrosp	100
Berruti [81]	ADOC	16	T	III–IVA	Phase II	81
Venuta [82]	CEE	15	T/TC	III	Retrosp	66
Bretti [83]	ADOC/PE	25	T/TC	III–IVA	Retrosp	72
Kim [74]	CAPP	22	T	III/IVA	Phase II	77
Lucchi [84]	CEE	36	T/TC	III–IVA	Retrosp	67
Jacot [85]	CAP	5	T/TC	III–IVA	Retrosp	75
Yokoi [86]	CAMP	14	T/TC	III, IV	Retrosp	93
Kunitoh [87]	CODE	21	T	III	Phase II	62
Park [88]	DDP-Docetaxel	27	T/TC	II/IV	Phase II	63
Chemoradiation						
Loehrer [72]	CAP/54 Gy	23	T/TC	III–IVA	Phase II	70
Wright [37]	PE, ADOC, CAP, CEE/45–60 Gy	10	T/TC	III–IVA	Retrosp	40



RR 80% → operacija

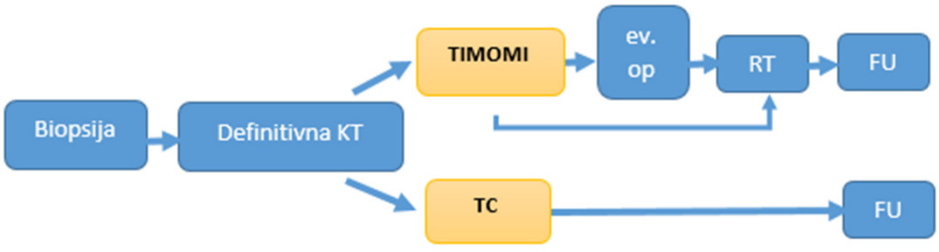




Delež kompletnih resekcij 14% – 78%

Girard N, et al. Eur Resp Rev 2013.

Zdravljenje metastatskih timičnih rakov, stadij IVB



Girard N, et al. Ann Oncol 2015.; https://www.nccn.org/professionals/physician_gls/default.aspx

Definitivna KT za metastatske timične rake

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1993[27]	21	4	T/TC	Phase II	Cisplatin		50 mg/m²/3 weeks	10
Highley et al 1999[28]	15	12	T/TC	Retrosp	Ifosfamide		1.5g/m² × 5 days/3 weeks	46
Loehrer et al 2006[29]	27	1	T/TC	Phase II	Pemetrexed		500 mg/m²/3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990[30]	32	11	T	Retrosp	ADOC	Doxorubicin Cisplatin Vincristin	40 mg/m²/3 weeks 50 mg/m²/3 weeks 0.6 mg/m²/3 weeks	91
Loehrer et al 1994[31]	30	9	T/TC	Phase II	CAP	Cyclophosphamide Cisplatin Doxorubicin	700 mg/m²/3 weeks 50 mg/m²/3 weeks 50 mg/m²/3 weeks	51
Giaccone et al 1996[32]	16	6	T	Phase II	PE	Cyclophosphamide Cisplatin Etoposide	500 mg/m²/3 weeks 60 mg/m²/3 weeks 120 mg/m² × 3/3 weeks	56
Loehrer et al 2001[33]	34	2	T/TC	Phase II	VIP	Etoposide Ifosfamide Cisplatin	75 mg/m² × 4 days/3 weeks 1.2 g/m² × 4 days/3 weeks 20 mg/m² × 4 days/3 weeks	32
Lemma et al 2011[34]	46	7	T/TC	Phase II	Carbo-Px	Carboplatin Paclitaxel	AUC 5/3 weeks 225 mg/m²/3 weeks	43
Palmieri et al 2011[35]	15	3	T/TC	Phase II	CAP-GEM	Capecitabine Gemcitabine	650 mg/m² bid × 14 days/3 weeks 1000 mg/m² × 2 days/3 weeks	40
Okuma et al 2011[36]	9	8	TC	Retrosp	Cisplatin-Irinotecan	Cisplatin Irinotecan	80 mg/m²/4 weeks 60 mg/m² × 3 days/4 weeks	56

KT z antraciklini:
ORR 50-90%
mOS 37-48 mes

KT brez antraciklinov:
ORR 30-50%
mOS 31-51 mes

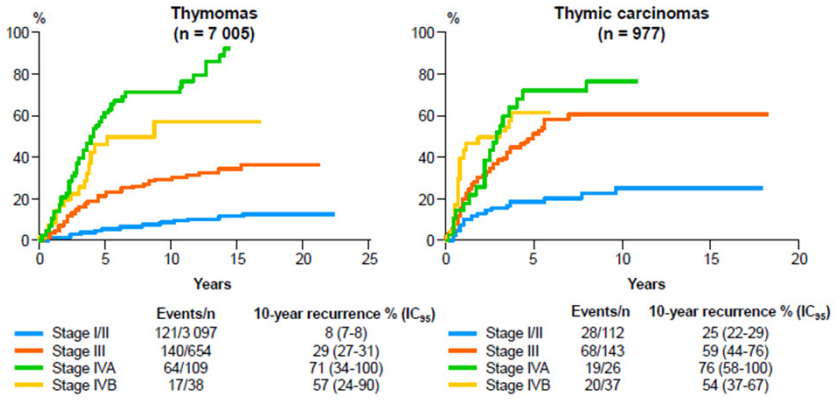
KT za TC:
karboplatin-paclitaxel
ORR 36%, mPFS 7.5 mes
(Hirai F.et al, Ann Oncol 2014)

Povzeto po Girard N, ASCO Educational Book, 2012.

Ukrepanje ob ponovitvi bolezni

ITMIG retrospective database

Cumulative incidence of recurrences in Masaoka-Koga groups



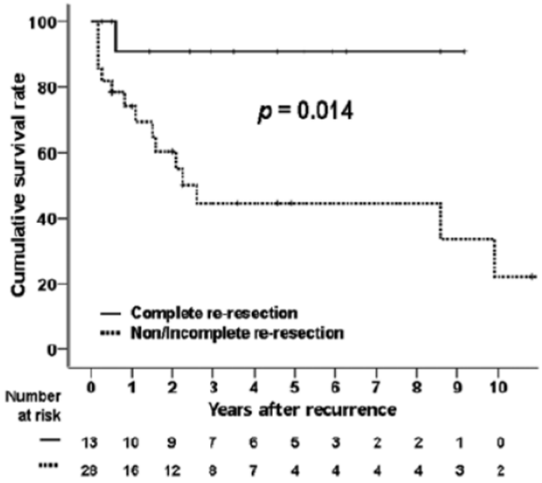
	Events/n	10-year recurrence % (IC_{95})
Stage I/II	121/3 097	8 (7-8)
Stage III	140/654	29 (27-31)
Stage IVA	64/109	71 (34-100)
Stage IVB	17/38	57 (24-90)

	Events/n	10-year recurrence % (IC_{95})
Stage I/II	28/112	25 (22-29)
Stage III	68/143	59 (44-76)
Stage IVA	19/26	76 (58-100)
Stage IVB	20/37	54 (37-67)

Detterbeck, et al. WCLC 2013..

Operativni poseg

- DA, v kolikor je možna KOMPLETNA RESEKCIJA
- Sicer je preživetje enako (slabo) kot če ne bi bilo kirurške intervencije
- Kompletna vs. nekompletna res.: 5-L OS: 91% vs. 45% (P=0.014)



Bae E, et al. JTO 2012.

Druga linija KT

KT ali shema	Študija	Histologija	Št. pacientov	ORR	mPFS (m)	mOS (m)
[1] Pemetrexed	Faza II	T TC	16 11	0% 17%	1.2 11.2	NR 29
[2] Amrubicin	Faza II	T TC	14 19	18% 11%	8.7 8.5	NR 18.1
[3] Kapecitabin + Gemcitabin	Faza II	T TC	8 22	40% 38%	11 6	1-yr OS 90% 2-yr OS 66%
[4] Pemetrexed	Retrospektiva	T TC	6 10	17% 10%	13.8 6.5	20.1 12.7
[5] Etopozid p.o.	Retrospektiva	T TC	5 8	15% 13%	53 4	98 22

[1] Loehrer PJ, et al. ASCO 2006.; [2] Wakelee H, et al. ASCO 2015.; [3] Palmieri G, et al. Future Onc 2014.; [4] Liang Y, et al. Lung Cancer 2015.; [5] Boutros CF, et al. Lung Cancer 2013.

Tarčna terapija

- **Sunitinib**
- **Sorafenib**
- **Imatinib**
- **Everolimus**
- Dasatinib
- Lucitanib
- Erlotinib
- Selumetinib
- CDK 4/6 inhibitorji
- Belinostat
- …

Schirosi L, et al. Ann Oncol 2012.

- Prekomerna ekspresija KIT (izražanje proteina CD117):
  - 2% T
  - 87% TC
- C-KIT mutacije:
  - 12% TC
- Boljši odgovor na:
  - Imatinib
  - Sunitinib
  - Sorafenib

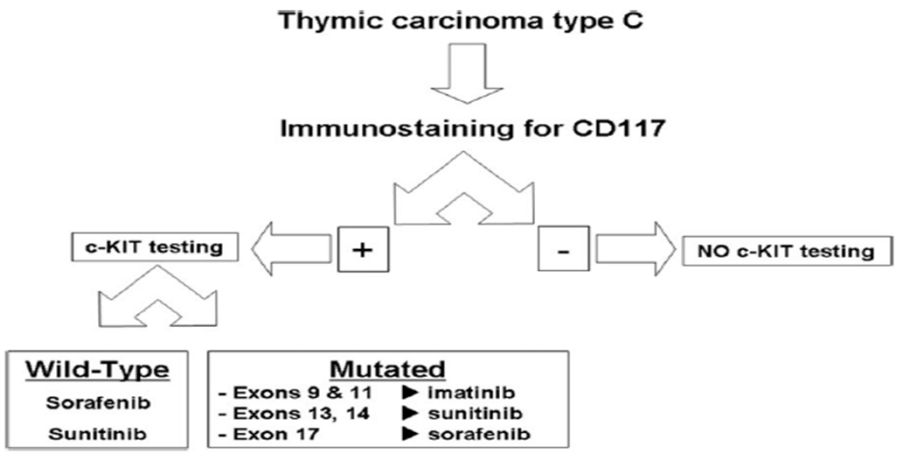
Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17

MOLECULAR AND CLINICAL ONCOLOGY, 2016

***c-Kit* mutation-positive advanced thymic carcinoma successfully treated as a mediastinal gastrointestinal stromal tumor: A case report**

FUMIHIKO HIRAI, MAKOTO EDAGAWA, SHINICHIRO SHIMAMATSU, RYO TOYOZAWA, GOUJI TOYOKAWA, KANAME NOSAKI, MASAFUMI YAMAGUCHI, TAKASHI SETO, MITSUHIRO TWAKENOYAMA and YUKITO ICHINOSE

Algoritem zdravljenja TC s tarčnimi zdravili



Povzeto po Schirosi L, et al. Ann Oncol 2012.

Tarčna terapija - OKTREOTID

- 50% timomov izraža visok nivo somatostatinskih receptorjev na OctreoScan-u
- Dodatno so pri timomih v 83% prisotni tudi steroidni receptorji → s steroidi je mogoče doseči „timolitični efekt“ = uničenje limfocitne populacije (NU: okužbe, ↑tveganje za miastenijo gravis)

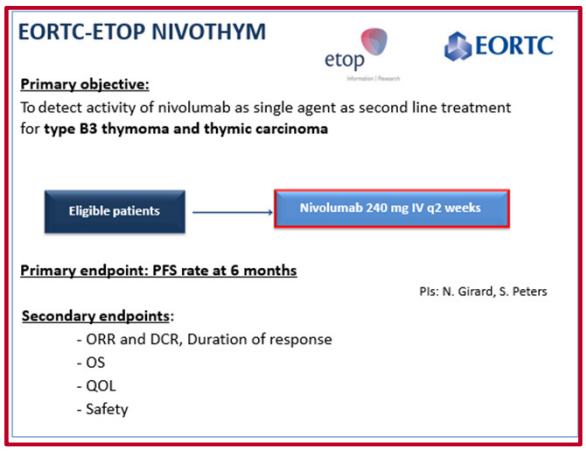
		TIMOMI			TIMIČNI KARCINOMI		
	GKK	n	CR+PR (%)	SD (%)	n	CR+PR (%)	SD (%)
1 Palmieri	+	10	40	40	3	33	33
2 Loehrer	+/-	32	38	34	5	0	60
3 Schalke	+	17	88	0	0	NA	NA

[1] Palmieri I, et al. Cancer 2002.; [2] Loehrer P, et al. JCO 2004.; [3] Schalke A, et al. ASCO 2012.

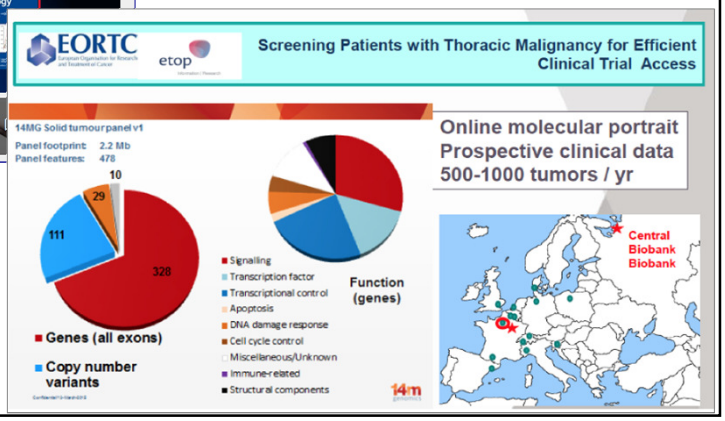
Imunoterapija: Pembrolizumab pri bolnikih s ponovitvijo timičnega karcinoma, faza II

Timični karcinomi, N = 40	
Odgovor	
CR	1/40 (2.5%)
PR	8/40 (20%)
SD	21/40 (52%)
PD	10/40 (25%)
mPFS	4.2 mes
mOS	24.9 mes
NU G 3/4	6/40 (15%)

Giaccone G, et al. Abstract 8573. ASCO 2017.



Pomembno je sodelovanje v kliničnih registrih in raziskavah!



KLINIČNI PRIMER: Kontinuirano vodenje in zdravljenje pacienta s timičnim karcinomom

Dnevi internistične onkologije 2017

Pripravila: Urška Janžič, dr.med.
Mentorica: prof. dr. Tanja Čufer, dr.med.

klinika GOLNIK

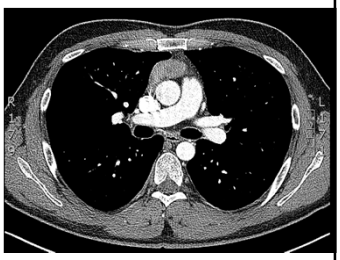
KLINIČNI PRIMER

- 29-letni moški
- Podiplomski študent, fizično aktiven, nekadilec
- Sicer zdrav, brez redne terapije
- Družinska anamneza negativna za rakava obolenja
- Simptomi: 4 mesece trajajoč suh kašelj
- Klinični pregled brez posebnosti
- PS po WHO 1

KLINIČNI PRIMER - nadaljevanje

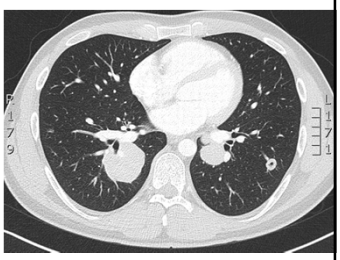
SLIKOVNA DIAGNOSTIKA:

- **Na RTG pc vidna masa v sprednjem mediastinumu**
- **CT prsnega koša:** tumorska masa v zg. mediastinumu brez vraščanja v okolno maščevje, perikard ali plevro in več okroglih lezij po pljučih obojestransko
- **CT abdomna in CŽS** brez posebnosti
- B-HCG < 0.1; AFP = 1.5



PATOHISTOLOŠKA DG:

- Timični karcinom
- IHC: CD5+, CD117+, AE1/AE3+ EMA+, vimentin -, LCA-, S100-



Anatomski stadij T1aN0M1b po IASLC-ITMIG klas.

Klinični stadij IVb

Klinični stadij timičnih neoplazem – nova IASLC / ITMIG klasifikacija

T1aN0M1b

Category	Description
T1a	Encapsulated or unencapsulated tumor, with or without extension into mediastinal fat
T1b	Invasion of mediastinal pleura
T2	Invasion of pericardium
T3	Involvement of lung, chest wall, phrenic nerve, brachiocephalic vein, SVC, or hilar (extrapericardial) pulmonary vessels
T4	Invasion of thoracic aorta, arch vessels, main pulmonary artery, trachea, esophagus, or myocardium

Category	Description
N0	No lymph node metastasis
N1	Involvement of anterior (perithymic) lymph nodes
N2	Involvement of deep intrathoracic or cervical lymph nodes

Category	Description
M0	No metastasis
M1a	Pleural or pericardial metastatic nodule(s)
M1b	Pulmonary intraparenchymal metastatic nodule or distant-organ metastasis

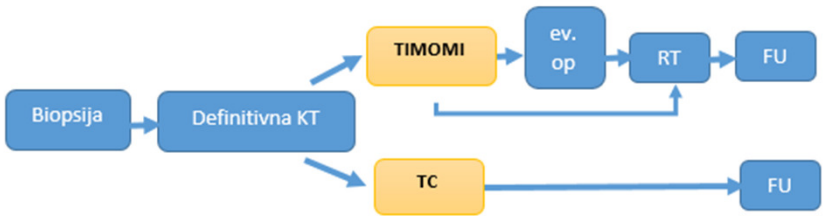
Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	T any T any	N1 N0, N1	M0 M1a
IVB	T any T any	N2 N any	M0, M1a M1b

Carter BW, at al. RadioGraphics. 2017

VPRAŠANJE 1:
Kakšno vrsto zdravljenja bi predlagali mlademu pacientu z metastatskim timičnim karcinomom?

1. Preoperativna KT + operacija + RT
2. Definitivna kemoterapija
3. Kemo-radioterapija
4. Operacija + radioterapija

Principi zdravljenja metastatskega timičnega karcinoma



Girard N, et al. Ann of Oncol. 2015

KT sheme za 1. linijo zdravljenja timičnih neoplazem

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1993[27]	21	4	T/TC	Phase II	Cisplatin		50 mg/m²/3 weeks	10
Highley et al 1999[28]	15	12	T/TC	Retrosp	Ifosfamide		1.5g/m² × 5 days/3 weeks	46
Loehrer et al 2006[29]	27	1	T/TC	Phase II	Pemetrexed		500 mg/m²/3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990[30]	32	11	T	Retrosp	ADOC	Doxorubicin	40 mg/m²/3 weeks	91
						Cisplatin	50 mg/m²/3 weeks	
						Vincristin	0.6 mg/m²/3 weeks	
Loehrer et al 1994[31]	30	9	T/TC	Phase II	CAP	Cyclophosphamide	700 mg/m²/3 weeks	51
						Cisplatin	50 mg/m²/3 weeks	
						Doxorubicin	50 mg/m²/3 weeks	
Giaccone et al 1996[32]	16	6	T	Phase II	PE	Cyclophosphamide	500 mg/m²/3 weeks	56
						Cisplatin	60 mg/m²/3 weeks	
						Etoposide	120 mg/m² × 3/3 weeks	
Loehrer et al 2001[33]	34	2	T/TC	Phase II	VIP	Etoposide	75 mg/m² × 4 days/3 weeks	32
						Ifosfamide	1.2 g/m² × 4 days/3 weeks	
						Cisplatin	20 mg/m² × 4 days/3 weeks	
Lemma et al 2011[34]	46	7	T/TC	Phase II	Carbo-Px	Carboplatin	AUC 5/3 weeks	43
						Paclitaxel	225 mg/m²/3 weeks	
Palmieri et al 2011[35]	15	3	T/TC	Phase II	CAP-GEM	Capecitabine	650 mg/m² bid × 14 days/3 weeks	40
						Gemcitabine	1000 mg/m² × 2 days/3 weeks	
Okuma et al 2011[36]	9	8	TC	Retrosp	Cisplatin-Irinotecan	Cisplatin	80 mg/m²/4 weeks	56
						Irinotecan	60 mg/m² × 3 days/4 weeks	

KT za TC: karboplatin-paclitaxel CR+PR: 36% + SD: 59%, mPFS 7.5 mes (Hirai F.et al, Ann Oncol 2014)

KT z antraciklini: ORR 50-90% mOS 37-48 mes

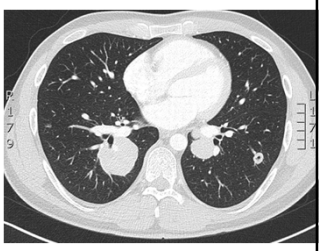
KT brez antraciklinov: ORR 30-50% mOS 31-51 mes

Povzeto po Girard N, ASCO Educational Book, 2012.

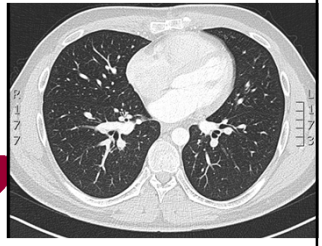
KLINIČNI PRIMER - nadaljevanje

- FEBRUAR 2013: prične s KT po shemi karboplatin - paclitaxel (7 ciklov)
- Klinično: prenehanje kašlja
- Radiološki učinek - CT toraksa: zmanjšanje primarnega tumorja in izginotje pljučnih metastaz
- Operativna odstranitev edine preostale tumorske mase – (timektomija)
- Patohistološki izvid: brez vitalnih tumorskih celic – dosežena pCR

Pred pričetkom KT



Ob zaključku KT



VPRAŠANJE 2:
Ali bi pacientu z metastatskim timičnim karcinomom po doseženi patološki kompletni remisiji in odstranitvi primarnega tumorja priporočali RT?

1. Da
2. Ne

Vloga pooperativne RT (PORT) pri timičnih karcinomih (retrospektivne analize)

	Št. pacientov	mFU (meseci)	Stadij*	Op + PORT (%)	5-letno preživetje PORT vs. No PORT
[1] SEER databaza	187	39	I – IV	56	57% vs. 54%
[1] Fu	329	36	I – IV	68	**75% vs. 44%**
[1] Mao	54	72	I – III	46	79% vs. 66%
[1] Omasa	155	57	I – III	52	91% vs. 87% st. II **65% vs 64% st. III**
[1] Song	76	44	I – IVa	64	70% vs. 57%
[1] Ruffini	137	68	I – IVb	66	60% vs. 50 % s KT 69% vs. 61% brez KT
[1] Weissferdt	65	50	I - IV	51	66% vs. 70%
[2] Ahmad ITMIG group	1042	53	I - IV	48	NR **HR 0.454**
[3] Jackson	1025	57	I - IV	54	NR **HR 0.79**

Večina vključenih pacientov je imela zgodnejši stadij bolezni (I – III)
Signifikantni rezultati so odebeljeni

[1] Hamaji M, et al. J Thor Surg. 2016
[2] Ahmad U, et al. Gen Thor Surg. 2015.
[3] Jackson MW, et al. JTO. 2017.

KLINIČNI PRIMER - nadaljevanje

- Pacient po doseženi pCR v rednem sledenju (klin. pregled na 3 mesece in CT na 6 mesecev)
- Po 16 mesečnem prostem intervalu
  - Klinično: utrujenost
  - Radiološko CT toraksa: pljučni zasevki
- Še vedno fizično dobro zmogljiv, PS 1, brez pridruženih bolezni ali redne terapije

VPRAŠANJE 3:
Kaj je najprimernejši naslednji korak?

1. Rebiopsija in dodatno molekularno testiranje
2. 2. linija KT
3. Tarčno zdravljenje
4. Vključitev v klinično študijo

Možnosti zdravljenja timičnega karcinoma v 2. liniji

ESMO smernice (2015)

Recurrences

- Recurrences of thymic epithelial tumours should be managed according to the same strategy as newly diagnosed tumours [IV, A].
- Complete resection of recurrent lesions, when achievable, is recommended.
- Several consecutive lines of chemotherapy may be administered when the patient presents with tumour progression. The re-administration of a previously effective regimen should be considered [IV, B].
- Preferred regimens for second-line treatment include carboplatin plus paclitaxel, and platin plus etoposide [III, B]; capecitabine plus gemcitabine is an option [III, B].
- Options for subsequent lines include pemetrexed [III, B] and oral etoposide.
- In patients with octreoscan-positive thymoma not eligible to receive additional chemotherapy, octreotide alone or with prednisone may represent a valuable option [III, B].

Targeted agents

- *KIT* sequencing (exons 9–17) is an option for refractory thymic carcinomas in the setting of potential access to specific inhibitors, particularly in the context of clinical trials [IV, B].
- It is not recommended to administer imatinib in the absence of a *KIT*-sensitising mutation [III, E].
- Sunitinib is an option as second-line treatment of thymic carcinomas independently from *KIT* status [III, A].
- Everolimus may represent an option for refractory tumours [III, B].

NCCN smernice 2017

SECOND-LINE CHEMOTHERAPY
Sunitinib (Thymic carcinomas only)[7]
Pemetrexed[8]
Everolimus[9]
Paclitaxel[10-11]
Octreotide (including LAR) +/- prednisone[12]
Gemcitabine[13]
5-FU and leucovorin[14]
Etoposide[4]
Ifosfamide[15]

Girard N, et al. Ann of Oncol. 2015
https://www.nccn.org

KT za 2. linijo zdravljenja timičnih karcinomov

Ponoviti KT za 1.linijo:

- CAP[6]
- Karboplatin + paclitaxel
- Cisplatin - etopozid

2.linija KT za timične karcinome

KT ali shema	Študija	Št. pacientov	ORR	mPFS (m)	mOS (m)
[1] Pemetrexed	Faza II	11	17%	11.2	29
[2] Amrubicin	Faza II	19	11% (+68% SD)	8.5	18.1
[3] Kapecitabin + Gemcitabin	Faza II	8	38%	6	1-yr OS 90% 2-yr OS 66%
[4] Pemetrexed	Retrospektiva	16	10% (+50% SD)	6.5	12.7
[5] Etopozid p.o.	Retrospektiva	13	13% (+63% SD)	9	22

[1] Loehrer PJ, et al. Abstract 7079. ASCO 2006
[2] Wakelee H, et al. Abstract 7580. ASCO 2015.
[3] Palmieri G, et. Al. Future Onc. 2014.
[4] Liang Y, et al. Lung Cancer. 2015.
[5] Boutros CF, Et al. Lung Cancer. 2013
[6] Lara PN, et al. Chest. 1996

Tarčna terapija za ≥ 2. linijo zdravljenja timičnih karcinomov

- **Sunitinib**
- **Sorafenib**
- **Imatinib**
- **Everolimus**
- Dasatinib
- Lucitanib
- Erlotinib
- Selumetinib
- CDK 4/6 inhibitorji
- Belinostat
- …

Schirosi L, et al. Ann Oncol 2012.

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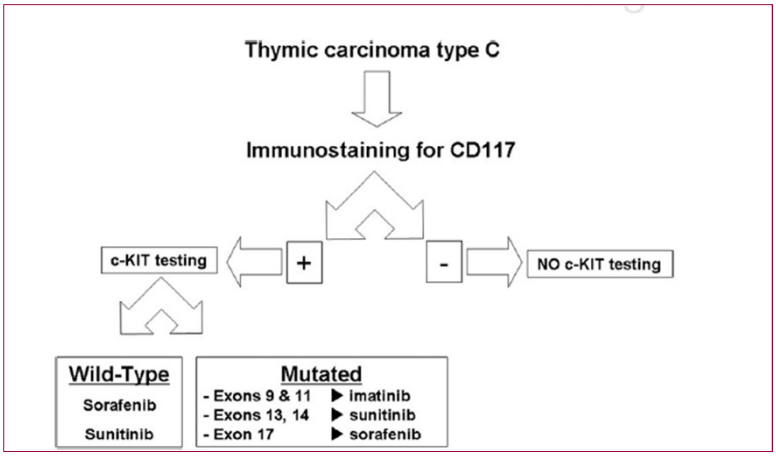
FUMIHIKO HIRAI, MAKOTO EDAGAWA, SHINICHIRO SHIMAMATSU, RYO TOYOZAWA, GOUJI TOYOKAWA, KANAME NOSAKI, MASAFUMI YAMAGUCHI, TAKASHI SETO, MITSUHIRO TWAKENOYAMA AND YUKITO ICHINOSE

CD117 ekspresija, c-KIT mutacije

PREDLAGAN ALGORITEM ZDRAVLJENJA TC S TARČNIMI ZDRAVILI:



Schirosi L, et al. Ann Oncol. 2012

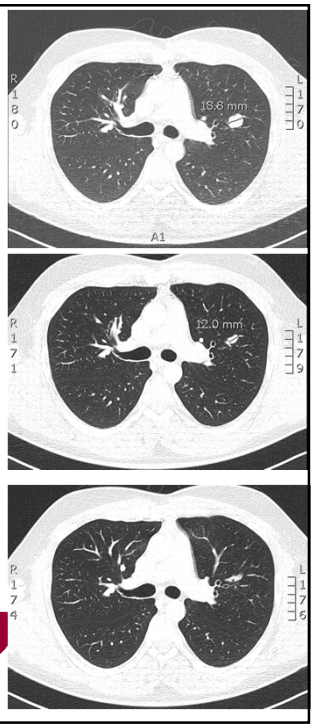
KLINIČNI PRIMER - nadaljevanje

- Dodatna molekularna analiza: CD117 +, vendar cKIT mutacije negativne (z IHC in PCR)
- JUNIJ 2014: prične z 2.linijo KT po shemi CAP (7 ciklov)
- Klinično: izboljšanje simptomatike
- Radiološko: izginotje vseh lezij, razen ene v LZR (celokupno PR)
- Radikalno obsevanje lezije v LZR s 54 Gy
- Sledenje

Pred pričetkom 2. linije KT

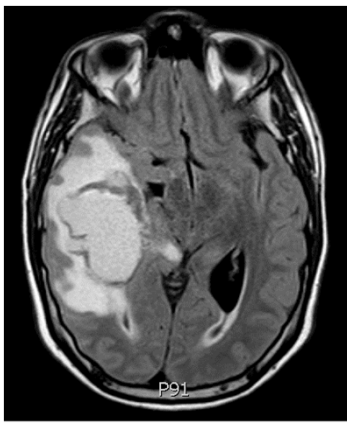
PR

Po RT edine preostale metastaze



KLINIČNI PRIMER - nadaljevanje

- Po PFS 18 mesecev hud glavobol, ki ne mine
- CT in MRI CŽS: solitarna metastaza desno z edemom
- CT prsnega koša in abdomna: brez znakov progresa bolezni izven CŽS
- FEBRUAR 2016: operativna odstranitev tumorja v CŽS + obsevanje na ležišče tumorja s 45 Gy
- Dodatna patohistološka analiza možg. zasevka: timični karcinom
  → Z NGS najdene c-KIT mutacije (mutacija Y553N na exonu 11)



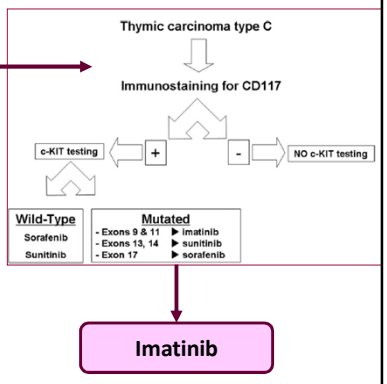
KLINIČNI PRIMER - nadaljevanje

- Od maja 2016 do danes je pacient v sledenju
- Na MRI prsnega koša je vidna počasna rast zgolj ene lezije v pljučih v DZR (12 mm v 30 mesecih)
- Kljub dvema progresoma bolezni je pacient v obravnavi že več kot **55 mesecev**, trenutno v zelo dobri psihofizični kondiciji, polno zaposlen in aktiven
- Vprašanje, ki se poraja: Kako ukrepati ob naslednjem sistemskem progresu bolezni?

CD117 ekspresija, c-KIT mutacije

- Prekomerna ekspresija KIT (izražanje proteina CD117):
  - 2% T
  - 87% TC
- C-KIT mutacije:
  - 12% TC
- Boljši odgovor na:
  - Imatinib
  - Sunitinib
  - Sorafenib

Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17



Schirosi L, et al. Ann Oncol. 2012;

CD117 ekspresija, c-KIT mutacije

Reference	Age/sex	Histologic type	c-KIT mutation	Stage	Therapy	Drug	Clinical response
Strobel et al. [7]	54/M	TC, squamous cell, G3	V560del ex11	Metastatic	None	Imatinib	SD (6 months)
Bisagni et al. [10]	46/M	TC, squamous cell, G3	D820E ex17	pT3, N2, M1	S + CT + RT	Sorafenib	PR (>15 months)
Disel et al. [13]	47/F	TC, squamous cell, G3	del577-578-579 ex11	IVA	CT + RT	Sorafenib	SD
Buti et al. [14]	48/M	TC, squamous cell, G3	Y553N	IV	CT	Imatinib	PR (>8 months)
Li et al. [19]	46/M	TC, squamous cell, G3	ND	IV	CT	Sorafenib	SD (>9 months)
Chuah et al. [20]	NA	Type-B2	ND	I	Imatinib + CT	Dasatinib	LR
Hamada et al. [21]	Case 1: 62/M	Atypical carcinoid	None	Invasive	CT	Imatinib	Good clinical response
	Case 2: 58/M	Atypical carcinoid	ND	Invasive	S + RT	Nessuno	Recurrence and metastasis
Giaccone et al. [22]	Case 1: 36/M	TC	ND	IVB	CT	Imatinib	PD
	Case 2: 67/M	Type-B3	None	IVA	S + RT + CT	Imatinib	SD
	Case 3: 47/M	Type-B2/3	ND	IVA	CT	Imatinib	SD
	Case 4: 76/M	TC	ND	IVB	None	Imatinib	PD
	Case 5: 36/M	TC	ND	IVB	CT	Imatinib	PD
	Case 6: 71/M	TC	None	IVB	None	Imatinib	PD
	Case 7: 69/F	TC, squamous cell type	None	IVB	None	Imatinib	PD
Strobel et al. [23]	Case 1: 35/M	TC, squamous cell type	None	IVB	CT + imatinib	Sunitinib	PR
	Case 2: 69/M	TC, squamous cell type	None	IVA	S + RT + CT	Sunitinib	PR
	Case 3: 77/M	TC, squamous cell type	None	II	S	Sunitinib	PR
	Case 4: 28/F	TC, undifferentiated	None	IVB	CT + RT	Sunitinib	PR (2 months)
Palmieri et al. [24]	15 cases	4 type B2	None	NA	NA	Imatinib	PD
		2 type B2/B3	None	NA	NA	Imatinib	PD
		6 type B3	None	NA	NA	Imatinib	1 SD
		3 TC	None	NA	NA	Imatinib	PD

Schirosi L, et al. Ann Oncol. 2012

Kaj pa imunoterapija?

Pembrolizumab in Patients with Recurrent Thymic Carcinoma: Results of a Phase II Study

ASCO Abstract #8573

Giuseppe Giaccone, Jillian Thompson, Colleen McGuire, Maria Manning, Bhaskar Kallakury, Joeffrey Chahine, Deepa S. Subramaniam, Stephen V. Liu, Geoffrey Gibney, Chul Kim, Justine N. McCutcheon
Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC USA

Responses (n=40 eligible)

Complete response	1
Partial response	8
Stable disease	21 (1 unconfirmed PR)
Progressive disease	10
Response rate	22.5% (95%CI 9.6% - 35.4%)

PFS, OS, DOR

- Median PFS: 4.2 months
- Median survival: 24.9 months
- Median duration of response (from first measurement): 22.7 months
- Median duration of stable disease (from start): 6.8 months

POZOR!!!
Avtoimuni neželeni učinki

Adverse Events

- Median 6 cycles (1-35)
- Mostly mild AEs
- 6 patients had severe irAEs
- Female gender more commonly associated with autoimmune disorders (4/6, P=.026)
- 3 patients interrupted treatment because of irAEs (all responders) and 3 because of progression around the time of the irAE
- 5 patients developed hypothyroidism and 1 hyperthyroidism

Giaccone G, et al. Abstract 8573. ASCO 2017.

NIVOTHYM: Nivolumab for patients with advanced type B3 thymoma and thymic carcinoma

= EORTC academic group trial - starts recrouting in Jan 2018

Sistemsko zdravljenje karcinoma žolčnika in žolčevodov

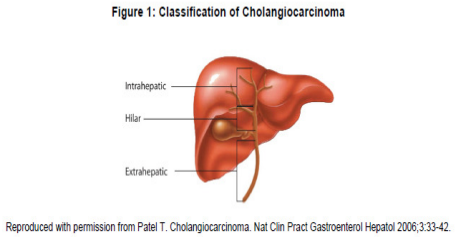
DIO 2017

ASIST.DR.MARTINA REBERŠEK, DR.MED.
SEKTOR INTERNISTIČNE ONKOLOGIJE
ONKOLOŠKI INŠTITUT LJUBLJANA
17.11.2017

Klasifikacija

Razdelitev:

- **Karcinom žolčnika**
- **Intrahepatični holangiokarcinom**
- **Perihilarni holangiokarcinom (Klatskinov tumor)**
- **Distalni (ekstrahepatični) holangiokarcinom**



Reproduced with permission from Patel T. Cholangiocarcinoma. Nat Clin Pract Gastroenterol Hepatol 2006;3:33-42.

- **≈2% vseh GIT tumorjev**
- **Karcinom žolčnega epitelija, ki lahko vznikne kjerkoli v žolčnem vejevju**
- **HISTOLOŠKO: 90% adenoCa, 10% SCC**

Epidemiologija (1)

Tabela 8: Incidenca raka (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti) po stadiju, lokaciji in spolu, Slovenija 2014.

Table 8: Cancer incidence (without cases registered from death certificates only) by stage, by site and by sex, Slovenia 2014.

Šifra MKB ICD code	Primarna lokacija Primary site	Spol Sex	Število novih primerov Number of new cases	Stadij							
				Omejen		Razširjen		Razsejan		Neznan	
				Število	%*	Število	%*	Število	%*	Število	%*
				Stage							
				Localized		Regional		Distant		Unknown	
				Number	%*	Number	%*	Number	%*	Number	%*
C22	Jetra in intrahepatični vodi	M	141	57	40,4	40	28,4	37	26,2	7	5,0
	Liver and intrahepatic bile ducts	Ž	67	20	29,9	13	19,4	33	49,3	1	1,5
C23	Žolčnik	M	22	8	36,4	5	22,7	9	40,9	0	0
	Gallbladder	Ž	46	12	26,1	12	26,1	22	47,8	0	0
C24	Drugi in neopredeljeni deli biliarnega trakta	M	74	17	23,0	35	47,3	19	25,7	3	4,1
	Biliary tract, other and unspecified parts	Ž	67	11	16,4	36	53,7	19	28,4	1	1,5

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

Epidemiologija (2)

Tabela 11a: Število in deleži bolnikov (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti), v Sloveniji zbolelih leta 2014, ki so bili v okviru prvega kurativnega zdravljenja operirani, zdravljeni s sistemskim zdravljenjem ali obsevani.

Table 11a: Number of patients (without cases registered from death certificates only) diagnosed in Slovenia in 2014, that were treated by primary curative surgery, systemic therapy or radiotherapy during their first treatment.

Šifra MKB ICD code	Primarna lokacija Primary site	Število novih primerov Number of new cases	Število kakorkoli zdravljenih* Number of all treated*		Število operiranih Number of treated by surgery		Število zdravljenih s sistemskim zdravljenjem Number of treated sistemic therapy		Število obsevanih Number of treated by radiotherapy	
			Število Number	%**	Število Number	%**	Število Number	%**	Število Number	%**
C00–C96	Vse lokacije All sites	13728	11109	80,9	8514	62,0	3994	29,1	3102	22,6
C00–C14	Usta in žrelo Mouth and pharynx	352	328	93,2	190	54,0	21	6,0	256	72,7
C15	Požiralnik Oesophagus	111	73	65,8	20	18,0	32	28,8	52	46,8
C16	Želodec Stomach	452	284	62,8	216	47,8	149	33,0	79	17,5
C18	Debelo črevo Colon	809	708	87,5	687	84,9	185	22,9	9	–
C19–C20	Rektum in rektosigmoidna zveza	592	517	87,3	472	79,7	193	32,6	199	33,6
C22	Jetra in intrahepatični vodi Liver and intrahepatic bile ducts	208	64	30,8	31	14,9	33	15,9	3	–
C23–C24	Žolčnik in žolčevodi Gallbladder and biliary tract	209	86	41,1	79	37,8	12	–	3	–
C25	Pancreas	392	140	35,7	76	19,4	87	22,2	13	–

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

KLINIČNA SLIKA

SIMPTOMI

Pruritus (66%)

Bolečina pod DRL (30-50%)

Hujšanje (30-50%)

Povišana tel. T(20%)

Temen urin, belo blato

Redko holangitis

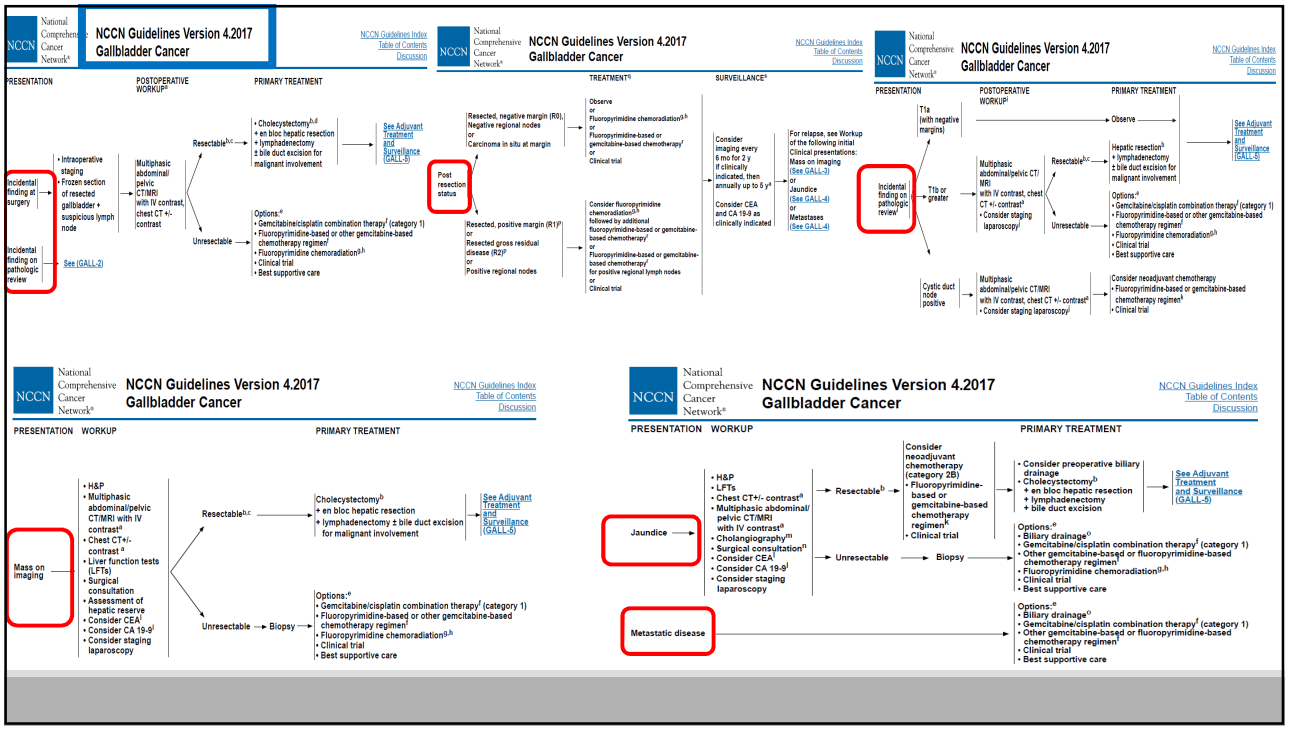
ZNAKI

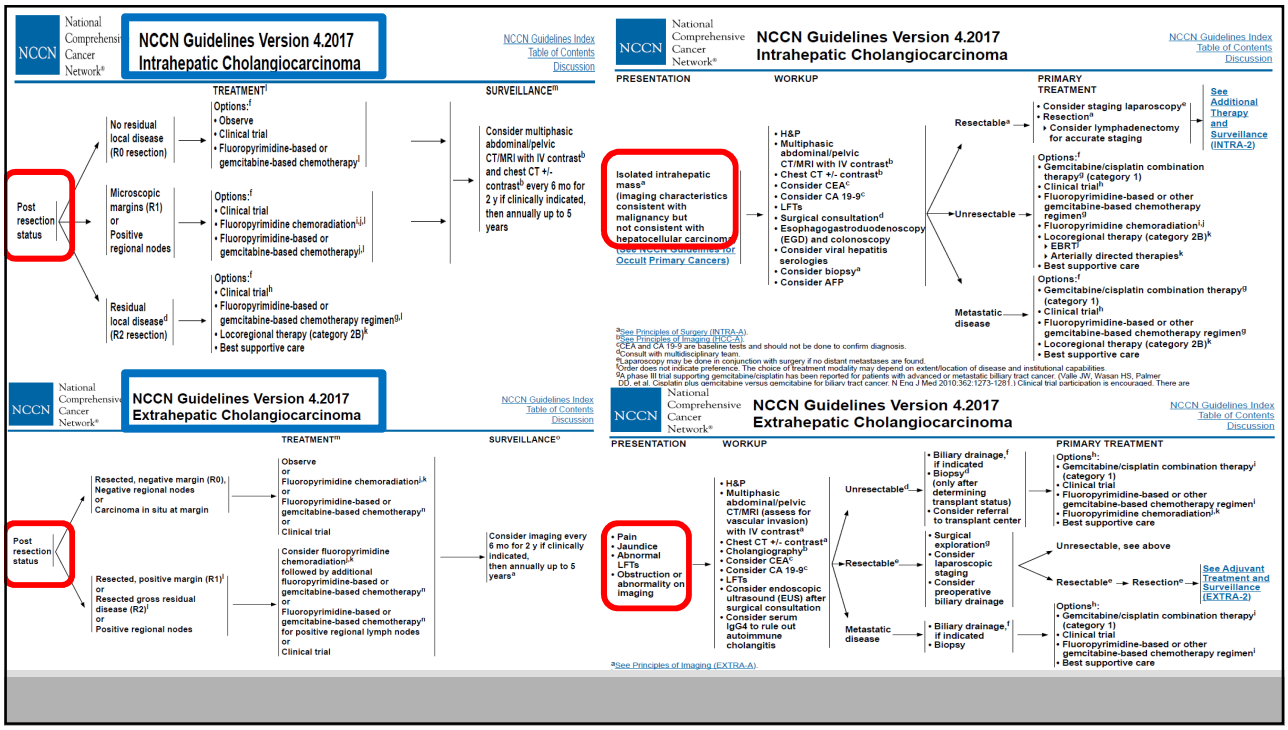
Zlatenica (90%)

Hepatomegalija (25-40%)

Masa pod DRL (10%)

Courvoisier-jev znak (redko)





J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up- TNM AJCC

Table 1. *Continued*

Cholangiocarcinoma – intrahepatic Primary tumour (T)				Cholangiocarcinoma – perihilar Primary tumour (T)				Cholangiocarcinoma – distal Primary tumour (T)				Gallbladder cancer Primary tumour (T)			
Stage grouping			Distant metastasis present	Stage grouping				Stage grouping				Stage grouping			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0	M0	Stage I	T1	N0	M0	Stage IA	T1	N0	M0	Stage I	T1	N0	M0
Stage II	T2	N0	M0	Stage II	T2a–b	N0	M0	Stage IB	T2	N0	M0	Stage II	T2	N0	M0
Stage III	T3	N0	M0	Stage IIIA	T3	N0	M0	Stage IIA	T3	N0	M0	Stage IIIA	T3	N0	M0
Stage IVA	T4	N0	M0	Stage IIIB	T1–3	N1	M0	Stage IIB	T1	N1	M0	Stage IIIB	T1–3	N1	M0
	Any T	N1	M0	Stage IVA	T4	N0–1	M0		T2	N1	M0	Stage IVA	T4	N0–1	M0
Stage IVB	Any T	Any N	M1	Stage IVB	Any T	N2	M0		T3	N1	M0	Stage IVB	Any T	N2	M0
					Any T	Any N	M1	Stage III	T4	Any N	M0		Any T	Any N	M1
								Stage IV	Any T	Any N	M1				

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.
Edge et al. [20]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324

Onkološko specifično zdravljenje

- kirurško
- radioterapija
- **sistemska terapija**:
  - adjuvantno sistemsko zdravljenje
  - sistemsko zdravljenje metastatske bolezni

Adjuvantna sistemska terapija (1)

- redki raki
- podatki iz retrospektivnih analiz, kliničnih primerov in klin.raziskav faze II

Only Older Randomized Adjuvant Therapy Trial

- Japanese study, randomly assigned patients with: extrahepatic biliary cancer, gallbladder cancer, periampullary cancer or pancreas cancer to chemotherapy post-op vs surgery alone
  - Chemotherapy was 5FU and MMC x 1 dose then oral 5FU
  - Only gallbladder came out positive
  - Problem: were these 5 trials or 5 subset analyses?

Adjuvantna sistemska terapija (2)

Adjuvantna kemoterapija:

- BILCAP faza III: kapecitabin vs. kontrola
- Prodige-12 faza III: GEMOX vs. kontrola
- ACTICCA-1 faza III: gem/cis vs. kontrola

Adjuvantna kemoradioterapija lahko izboljša preživetje (drenaža žolča)[1]

- mOS 9m vs. 3 m
- Rezultati retrospektivnih analiz

1.Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012; 30: 1934–1940.

Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study

Primrose JN, Fox RP, Palmer D, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Wasan H, Ross P, Wall L, Wadsley J, Evans J, Stocken D, Praseedom R, Cunningham D, Garden OJ, Stubbs C, Valle JW and Bridgewater J on behalf of the BILCAP investigators

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

1

CANCER RESEARCH UK

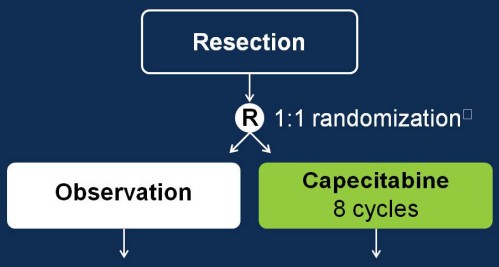
Study overview

BILCAP

- Two arm, open label, randomized, controlled clinical trial

Interventions
- Observation
- Capecitabine (1250mg/m²) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

Outcome measures
- Primary; overall survival (OS)
- Secondary;
  - Relapse free survival (RFS)
  - Toxicity
  - Quality of life*
  - Health economics



Primary analysis after a minimum 2 year follow-up

*EORTC QLQ-C30 & LMC-21 (latter for patients with colorectal liver metastasis)
□Minimized on surgical centre, tumour site, type of resection (RO/RI) & performance status (ECOG PS 0-2)

CANCER RESEARCH UK

Baseline characteristics

BILCAP

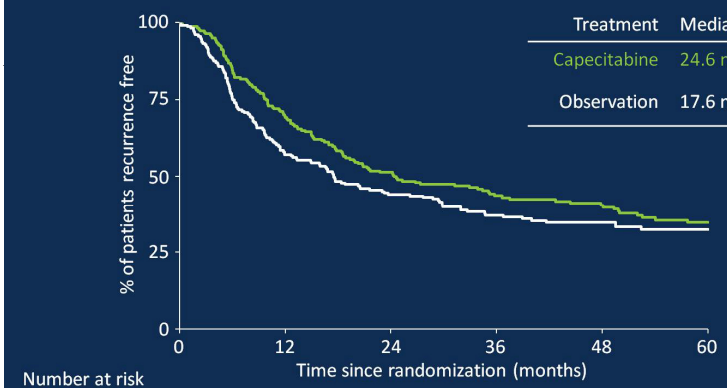
		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
Tumour site	Intrahepatic CC	41 (18%)	43 (19%)
	Hilar CC	63 (28%)	65 (29%)
	Muscle invasive gall bladder carcinoma	40 (18%)	39 (17%)
	Lower common bile duct CC	80 (36%)	76 (34%)
Resection status	R0	140 (63%)	139 (62%)
	R1	84 (38%)	84 (38%)
ECOG performance status	0	101 (45%)	100 (45%)
	1	116 (52%)	116 (52%)
	2	7 (3%)	7 (3%)
Tumour size	Median mm (inter-quartile range)	25 (20-44)	25 (19-45)
Lymph node status	N0	108 (48%)	100 (45%)
	N1	102 (46%)	108 (48%)
	NX	14 (6%)	15 (7%)

Values shown are n (%) for categorical data, and median (IQR) for continuous measures

CANCER RESEARCH UK

RFS in the ITT population

BILCAP



Treatment	Median RFS (95% CI)	HR (95% CI)
Capecitabine	24.6 months (18.9-36.7)	0.76 (0.58-0.99) p=0.039
Observation	17.6 months (12.8-27.6)	

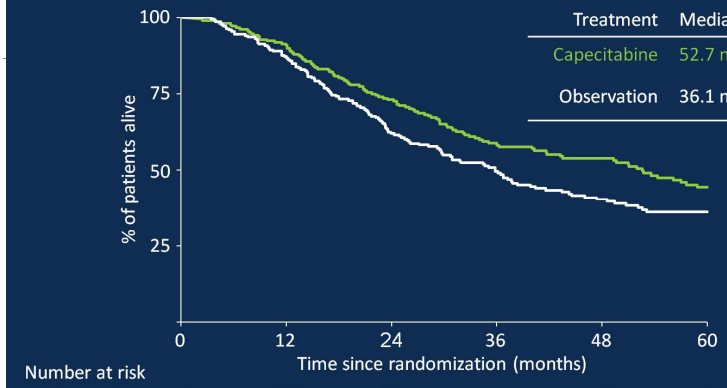
Number at risk						
observation	224	126	92	67	52	37
capecitabine	223	148	108	78	62	43

12

CANCER RESEARCH UK

OS in the PP population

BILCAP



Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	52.7 months (40.3-NR)	0.75 (0.58-0.97) p=0.028
Observation	36.1 months (29.6-44.2)	

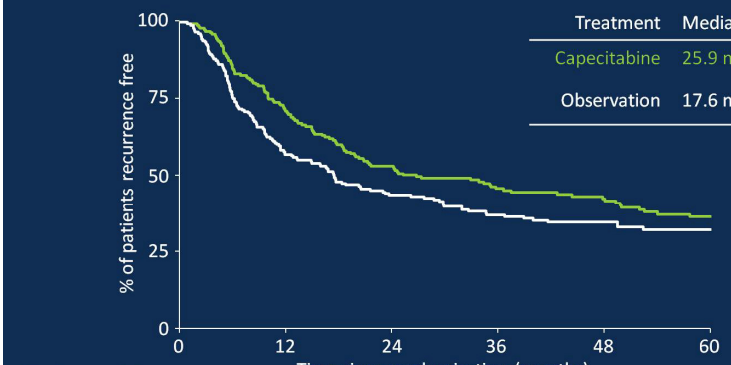
Number at risk						
observation	220	190	134	92	64	44
capecitabine	210	190	152	105	83	56

11

CANCER RESEARCH UK

RFS in the PP population

BILCAP



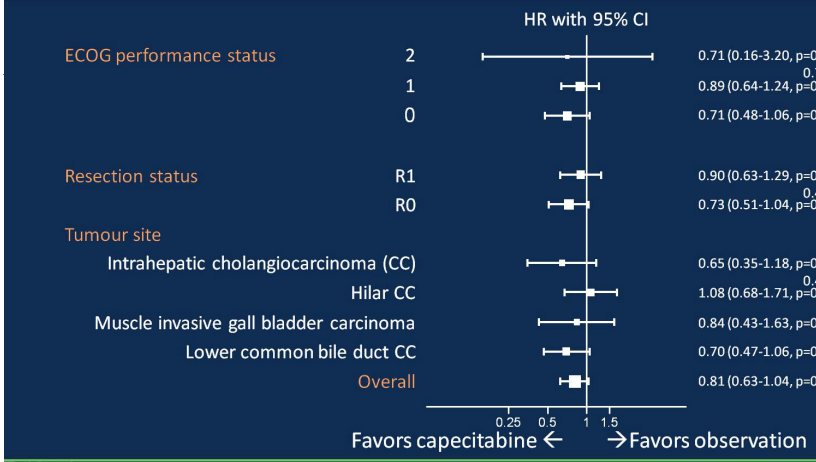
Treatment	Median RFS (95% CI)	HR (95% CI)
Capecitabine	25.9 months (19.8-46.3)	0.71 (0.54-0.92) p=0.011
Observation	17.6 months (12.0-23.8)	

Number at risk						
observation	220	123	89	65	50	35
capecitabine	210	145	107	78	62	43

CANCER RESEARCH UK

Sub-group analyses; OS

BILCAP



Toxicity

The safety population was conditional on receiving capecitabine (n=213)

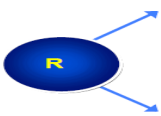
There were no deaths related to chemotherapy

Toxicity type	Grade 3/4
Fatigue	16 (7.5 %)
Plantar palmar erythrema	44 (20.7 %)
Diarrhea	16 (7.5 %)
Nausea	2 (0.9 %)
Mucositis/stomatitis	2 (0.9 %)
Vomiting	1 (0.5 %)
Neutropenia	4 (1.9 %)
Bilirubin	3 (1.4 %)
Thrombocytopenia	1 (0.5 %)
Alopecia	0

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: Professor John Primrose

Adjuvant GEMOX: Study Design

Prodige 12- Accord 18 (UNICANCER GI)



Observation

GEM-OX
Gemcitabine 1,000 mg/m2 day 1
Oxaliplatin 85Mg/m2 day2, both every other week x 12

Randomized phase III design

Edeline, J, et al. ASCO GI, 2017, abstract 225

AIM: whether GEMOX would improve RFS vs surveillance while maintaining health-related quality of life.

One hundred and ninety-six patients were enrolled; median follow-up was 44.3 months. Relapse events occurred in 54 patients with GEMOX and in 64 patients under surveillance. Median RFS was 30.4 months with GEMOX vs 22 months with surveillance; 4-year RFS rates were 39.3% and 33.2%, respectively. The differences were not significant.

Edeline J, Bonnetain F, Phelip JM, et al. Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol*. 2017;35(suppl):4S. Abstract 225.

Baseline Characteristics

Characteristic	GEMOX N= 94	Surveillance N = 99
M:F	59.6%/40.4%	50.5%/49.5%
ECOG PS: 0 1 2	53.2% 39.4% 5.3%	63.6% 31.3% 2.0%
IHC Perihilar Extrahepatic Gallbladder	43.6% 10.6% 27.7% 18.1%	45.5% 5.1% 28.3% 21.2%
Pre-op Tx: Portal vein Embo Biliary drain	20.2% 11.7%	23.2% 9.1%
Tumor characteristics: Node + R1 Perineural invasion	37.2% 13.8% 54.3%	36.4% 12.1% 45.5%
Vascular Emboli	26.6%	29.3%

Edeline, J, et al. ASCO GI, 2017, abstract 225

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Outcomes

- Primary endpoint, RFS
  - HR 0.83, p = 0.31
  - Median Gem-OX 30.4 months vs 22.0 Months for surveillance
  - 4-year RFS: 39.3% vs 33.2%
  - Forrest Plot
    - All subsets to left of 1 except Extrahepatic cholangiocarcinoma which was wildly to the right

Edeline, J, et al. ASCO GI, 2017, abstract 225

Vanderbilt-Ingram Cancer Center

- Health-related quality of life scores did not differ at 1-year and 2-year time points.
- Grade 4 adverse events occurred among 17% of patients receiving GEMOX and 9.1% of patients under surveillance. One patient died from each group.

Edeline J, Bonnetain F, Phelip JM, et al. Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol*. 2017;35(suppl):4S. Abstract 225.

Sistemsko zdravljenje metastatske bolezni (1)

Gemcitabine

Reference	Schedule	# of patients	Response Rate	TTP	Overall Survival
Penz, et al	2200/m2 Q o week	32	22%	5.6 mos	11.5 mos
Valencak, et al	1200/m2 Qw x3	24	4%	3.5 mos	6.8 mos
Kubicka, et al	1000/m2 qw x3	23	30%	4.4 mos	N/A
Arroyo, et al	1000/m2 qw x3	39	36%	N/A	6.5 mos

These and other trials are all summarized in Scheitauer W. Semin Oncol 29:6 (suppl 20), 40-45, 2002

Sistemsko zdravljenje metastatske bolezni (2)

Gemcitabine + 5-FU

Reference	Gemcitabine +_____	# of pts	Response Rate	TTP or PFS	Overall Survival
Murad (Am J Clin Oncol 26: 151-4, 2003	Bolus 5-FU	9 pts	33%	TTP	9 months
Jacobson D ASCO 2003	Bolus 5-FU with LV	42 pts	9.5%	3.8 months	6.8 months
Hsu C, et al ASCO 2003	Bolus 5-FU	26 pts	19%	4.2 months	7.3 months
Knox J, et al GI Symposium, 2004	Capecitabine	35 pts	26%	6.8 months	10.3 months

2nd study of gem-cape in 57 pts, RR18%, OS 7 months

Vanderbilt-Ingram Cancer Center

Sistemsko zdravljenje metastatske bolezni (3)

Gemcitabine + platinums

Reference	Type of platinum	# of pts	RR	Survival
Thengprasert, et al GI ASCO	Cisplatin	24	33%	13 mos
Reyes-Vidal, et al GI ASCO (GOCCHI trial)	Cisplatin	42	48%	7 mos
ASCO 2003	Carboplatin	13	30%	N/A
EORTC	Oxaliplatin	33 (1st line)	36%	14.3 months

Sistemsko zdravljenje metastatske bolezni (4)

Sistemska terapija:

- **Faza III UK ABC-02**: cisplatin/gemcitabine vs. gemcitab- mOS: 11.7 mesecev cisplatin/

Gemcitabin vs. 8.1 mesecev gemcitabin (95% CI: 0.53-0.79; P<0.001)

- **Meta-analiza** [1]: kombinacija kemoterapije učinkovitejša od monokemoterapije neodvisno od starosti (<65 vs≥65 let), spola, mesta primarnega tumorja (intrahepatični vs ekstrahepatični vs karcinom žolčnika), stadija bolezni (lokoregionalni vs metastatski) in predhodne terapije (operacija vs stent), razen v primeru PS ECOG 2 vs 0,1→ gemcitabin monoterapija, v primeru led.insuficience oksaliplatin

Kemoradioterapija

- **Nerandomizirane klinične raziskave: mOS 9- 14 mesecev**

- **Faza III FFCD 9902:** KT (5-FU, cis)RT (50 Gy) vs KT (GEMOX): DFS 5.8 m vs 11 m; OS 13.5 m vs 20 m

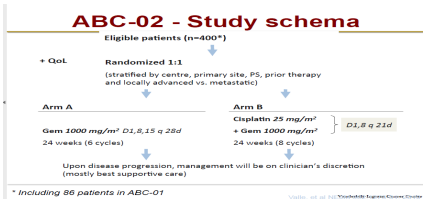
[1] Valle JW, Furuse J, Jitlal M et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014; 25: 391–398.

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*

ABC-02 - Study schema



ABC-02 statistical methods

Primary endpoint:	**OVERALL SURVIVAL:** ITT analysis (pre-planned ABC-01 and ABC-02)
Secondary endpoints:	• Progression-free survival • Toxicity • Quality of life (EORTC QLQ C-30)
Sample size:	• Powered to detect increase in median survival from 8 to 11 months • n=354 patients (315 OS events), n=400 to allow for drop-out • Log-rank test with 80% power and two-sided α 5% level

Valle, et al NEJM 362:1273-81, 2010

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Variable	Gemcitabine (N = 206)	Cisplatin plus Gemcitabine (N = 204)	P Value
Age — yr			
Median	63.2	63.9	0.88
Range	23.4–84.8	32.8–81.9	
Sex — no. (%)			
Female	108 (52.4)	108 (52.9)	0.92
Male	98 (47.6)	96 (47.1)	
Extent of disease — no. (%)			
Locally advanced	49 (23.8)	55 (27.0)	0.46
Metastatic	157 (76.2)	149 (73.0)	
Primary tumor site — no. (%)			
Gallbladder	76 (36.9)	73 (35.8)	0.87
Bile duct	119 (57.8)	122 (59.8)	
Ampulla	11 (5.3)	9 (4.4)	
Type of tumor — no. (%)			
Adenocarcinoma	191 (92.7)	186 (91.2)	0.27
Carcinoma, type not specified	12 (5.8)	17 (8.3)	
Adenosquamous carcinoma	2 (1.0)	0	
Squamous-cell carcinoma	1 (0.5)	0	
Carcinosarcoma	0	1 (0.5)	
ECOG performance-status score — no. (%)			
0	64 (31.1)	66 (32.4)	0.72
1	117 (56.8)	111 (54.4)	
2	24 (11.7)	27 (13.2)	
Unknown	1 (0.5)	0	
Previous therapy — no. (%)			
No	50 (24.3)	50 (24.5)	0.96
Yes	156 (75.7)	154 (75.5)	
Type of previous therapy — no. (%)			
Curative surgery	48 (23.3)	37 (18.1)	0.20
Palliative surgery	40 (19.4)	37 (18.1)	0.74
Laparotomy	49 (23.8)	48 (23.5)	0.95
Biliary stenting	92 (44.7)	93 (45.6)	0.85
Radiotherapy	5 (2.4)	3 (1.5)	0.48
Adjuvant chemotherapy	5 (2.4)	3 (1.5)	0.74
Photodynamic therapy	1 (0.5)	1 (0.5)	1.00
Other therapy	81 (39.3)	76 (37.3)	0.14

* ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

N Engl J Med 2010;362:1273-81.

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OS, PFS

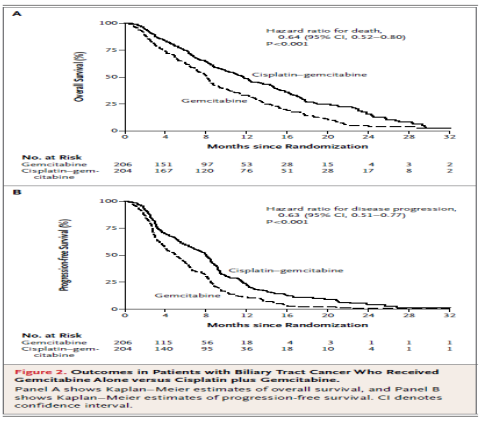

Figure 2. Outcomes in Patients with Biliary Tract Cancer Who Received Gemcitabine Alone versus Cisplatin plus Gemcitabine.
Panel A shows Kaplan–Meier estimates of overall survival, and Panel B shows Kaplan–Meier estimates of progression-free survival. CI denotes confidence interval.

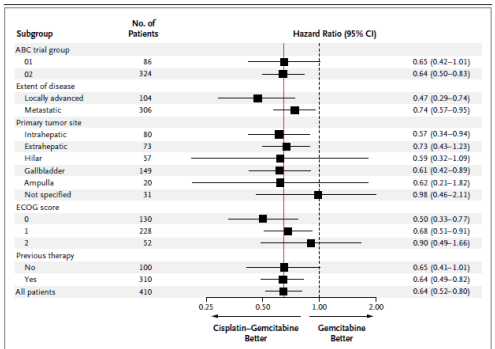

Figure 3. Hazard Ratio, According to Trial and Prespecified Baseline Factors.
ABC denotes Advanced Biliary Cancer, and ECOG Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning. The red line indicates the hazard ratio for death (0.64) in the intention-to-treat population.

N Engl J Med 2010;362:1273-81.

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

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NEŽELENI UČINKI

Table 2. Grade 3 or 4 Toxic Effects during Treatment, According to Treatment Group.

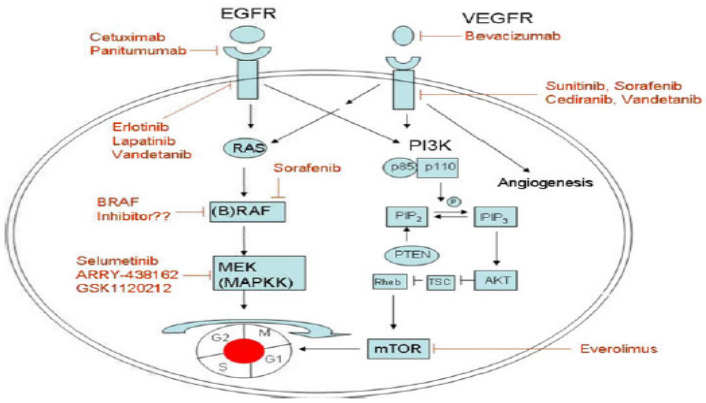
Variable	Gemcitabine (N=199)	Cisplatin plus Gemcitabine (N=198)	P Value
	number (percent)		
Hematologic toxic effects			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
Liver function			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01
Nonhematologic toxic effects			
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
Infection			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20
Other	62 (31.2)	66 (33.3)	0.64
Any	100 (50.3)	108 (54.5)	0.39
Any grade 3 or 4 toxic effect	137 (68.8)	140 (70.7)	0.69

N Engl J Med 2010;362:1273-81.

NOVOSTI v sistemskem zdravljenju

- Tarčna zdravila ?
- Imunoterapija ?

Signalne poti in tarčne terapije pri rakih biliarnega trakta



Faris JE, et al.Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

Tarčna zdravila (1)

Table 1 Clinical trials with targeted therapies in advanced biliary tract cancers

Agent	Trial design	Line	#Pts	CR (%)	PR (%)	ORR (%)	PFS	OS
EGFR								
Erlotinib monotherapy [31]	Single-arm PII	1st/2nd	43	0	8	8	TTP 2.6 months	7.5 months
GEMOX ± erlotinib [32]	Randomized PIII	1st	135/133	NR	NR	NR	5.8 vs. 4.2 months	9.5 vs. 9.5 months
GEMOX ± cetuximab [36]	Randomized PII	1st	36	NR	NR	NR	4 months: 61 vs. 44%	NR
GEMOX/cetuximab [35]	Single-arm PII	1st	30	10	53	63	8.8 months	15.2 months
GEMOX/capecitabine/ panitumumab [39]	Single-arm PII	Any	42	2.4	31	33	8.3 months	9.8 months
HER2								
Lapatanib monotherapy [45]	Single-arm PII	1st/2nd	17	0	0	0	1.8 months	5.2 months
VEGF								
GEMOX/bevacizumab [51]	Single-arm PII	1st	35	0	40	40	7 months	12.7 months
Sorafenib monotherapy [52]	Single-arm PII	Any	46	0	2.2	2.2	2.3 months	4.4 months
Sorafenib monotherapy [53]	Single-arm PII	First	31	0	0	0	3 months	9 months
Gemcitabine ± sorafenib [54]	Randomized PII	First	62	0	7	7	2.9 months	9.4 months
Sunitinib monotherapy [55]	Single-arm PII	Previously treated	56	0	8.9	8.9	1.7 months	4.8 months
MEK								
Selumetinib monotherapy [61]	Single-arm PII	Any	28	0	12	12	3.7 months	9.8 months
Combination								
Erlotinib/bevacizumab [33]	Single-arm PII	First	49	0	18.4	18.4	TTP 4.4 months	9.9 months

EGFR epidermal growth factor receptor, *GEMOX* gemcitabine and oxaliplatin, *HER2* human epidermal growth factor receptor 2, *VEGF* vascular endothelial growth factor, *MEK* mitogen-activated protein kinase/extracellular-signal regulated kinase

Faris JE, et al.Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

Tarčna zdravila (2)

Table 2 Planned or ongoing clinical trials using targeted agents

Agents	Trial type	Line of therapy	Country	Target #Pts	NCT#
EGFR					
GEMOX ± cetuximab	Randomized PII	1st line	Taiwan	120	01267344
GEMOX ± erlotinib	Randomized PIII	1st line	Korea	180	01149122
GEMOX + erlotinib	PIb	1st line	USA	22	00987766
GEMOX + panitumumab	Single-arm PII	1st line	USA	30	01308840
GEMOX/capecitabine ± panitumumab	Two arm PII based on KRAS	Any	Denmark	70	00779454
GEMOX ± panitumumab	Randomized PII	1st line	Italy	18	01389414
Gemcitabine/irinotecan + panitumumab	Single-arm PII	1st line	USA	45	00948935
Gemcitabine/cisplatin ± panitumumab	Randomized PII	1st line	Germany	92	01320254
MEK					
ARRY-438162	PI	2nd/subsequent	USA	95	00959127
GSK1120212, GSK1120212 + gemcitabine	PI	Any line	Japan	21	01324258
Gemcitabine/cisplatin/selumetinib	PI/II	Any line	UK	18	01242605
mTOR					
Everolimus	Single-arm PII	1st line	Australia	27	00973713
VEGF					
mFOLFOX6 + bevacizumab	PII	1st line	USA	24	00881504
Gemcitabine/capecitabine/bevacizumab	Single-arm PII	1st line	USA	50	01007552
mFOLFOX6 + cediranib	Single-arm PII	1st line	USA	25	01229111
Gemcitabine/cisplatin ± cediranib	Randomized PII	1st line	UK	136	00939848
GEMOX/sorafenib	Single-arm PI/II	Any line for PI 1st line for PII	USA	58	00955721
Gemcitabine ± vandetanib, vandetanib	Randomized PII	1st line	Italy	174	00753675
Gemcitabine/capecitabine/vandetanib	Phase I	Any line	USA	28	00551096

EGFR epidermal growth factor receptor, *GEMOX* gemcitabine and oxaliplatin, *MEK* mitogen-activated protein kinase/extracellular-signal regulated kinase, *mTOR* mammalian target of rapamycin, *VEGF* vascular endothelial growth factor, *mFOLFOX6* 5-fluorouracil, oxaliplatin, leucovorin

Faris JE, et al.Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

Tarčna zdravila (3)

Table 4. Completed EGFR inhibitor trials in BTC/GEMOX

Treatment	Phase	No. of subjects	ORR	mPFS (m)	mOS (m)	Reference
GEMOX GEMOX + erlotinib	III	268	16% 30%	4.2 5.8	9.5 9.5	Lee *et al*, 2012
GEMOX GEMOX + cetuximab	II	150	29% 23%	5.5 6.1	12.4 11	Malka *et al*, 2012
GEMOX GEMOX + cetuximab	II	122	17% 27%	4.1 6.7	9.8 10.6	Chen *et al*, 2013
GEMOX Panitumumab	II	31	45%	10.6	20.3	Hezel *et al*, 2010
GEMOX Cetuximab	II	30	63%	8.8	15.2	Gruenberger *et al*, 2010
Gemcitabine Capecitabine Cetuximab	II	34	18%	7.8	14.5	Rubovszky *et al*, 2013
GEMOX Capecitabine Panitumumab	II	46	33%	8.3	10	Jensen *et al*, 2012
Gemcitabine Irinotecan Panitumumab	II	31	31%	9.7	12.7	Sohal *et al*, 2013
Erlotinib (2nd line)	II	42	8%	2.6	7.5	Philip *et al*, 2006

Abbreviations: BTC = biliary tract cancer; EGFR = epidermal growth factor receptor; GEMOX = in combination with gemcitabine and oxaliplatin; mOS = median overall survival; mPFS = median progression free survival; ORR = objective response rate.

British Journal of Cancer (2014) 111, 430–436 | doi: 10.1038/bjc.2014.343

O-019
Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (1)

- Ramucirumab 8 mg/kg i.v. 1. in 8. dan

- Pembrolizumab 200 mg i.v. 1.dan/3 tedne

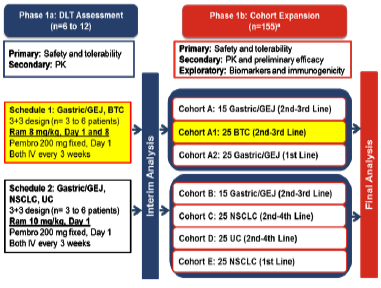
"The primary objective was to assess the safety and tolerability of ramucirumab plus pembrolizumab; preliminary efficacy will be examined. "

O-019
Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (2)

METHODS

JVDF (NCT02443324) Phase 1a/b Study Design (n=164)



*Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason.
DLT=dose-limiting toxicity; PK=pharmacokinetics; Ram=ramucirumab; Pembro=pembrolizumab

RESULTS

Baseline Demographics

		Cohort A1 n=26
Age	Median, yr (range)	63 (36-78)
	≤65 yr	16 (62)
Race, n (%)	White	23 (88)
Sex, n (%)	Female	18 (69)
ECOG PS, n (%)	1	14 (54)
Prior systemic therapy, n (%)	2 prior lines	9 (35)
Disease Stage	Metastatic	21 (81)
Site of primary tumor, n (%)	Intrahepatic CC	11 (42)
	Extrahepatic CC	8 (31)
	Gallbladder	4 (15)
	Ampulla of Vater	1 (4)
	Other	2 (8)
Histological grade, n (%)	Low	3 (12)
	Intermediate	10 (38)
	High	4 (15)
	Unknown[a]	9 (35)
PD-L1 status, n (%)	Positive	12 (46)
	Negative	11 (42)
	Pending	2 (8)
	Not available	1 (4)

[a]Unknown included patients with non-evaluable tissue, not yet evaluated, or missing tissue sample at time of data cut.

CC=cholangiocarcinoma

O-019
Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (3)

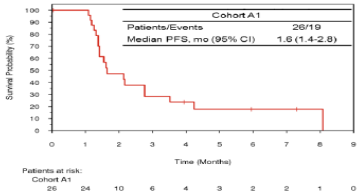
Treatment Exposure

	Cohort A1 n=26
Median follow-up duration, mo (95% CI)	5.3 (2.6-6.2)
Ramucirumab	
Median duration of therapy, months (IQR)	2.1 (1.4-3.8)
Median number of cycles, n (IQR)	3 (2-5)
Patients completing ≥ 3 cycles, n (%)	15 (58)
Pembrolizumab	
Median duration of therapy, months (IQR)	2.1 (1.4-4.1)
Median number of cycles, n (IQR)	3 (2-6)
Patients completing ≥ 3 cycles, n (%)	16 (62)

One treatment cycle is equal to 3 weeks. *IQR=interquartile range*

All treated patients	Cohort A1 n=26
Best overall response, n (%)	
Complete response	-
Partial response	1 (4)
Stable disease	9 (35)
Progressive disease	12 (46)
Not Evaluable	4 (15)
Objective response rate	4%
Disease control rate	38%
Duration of stable disease, mo (95% CI)	3.9 (2.2-8.1)

Progression-free Survival



O-019
Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (4)

Overview of Adverse Events

Number of patients, n (%)	Cohort A1 n=26 TEAE	TRAE
Any Grade	26 (100)	22 (85)
Grade ≥3	17 (65)	11 (42)
SAE	14 (54)	6 (23)
Discontinued due to AE/SAE	1 (4)[a]	1 (4)[a]
AE leading to death on study treatment	-	-
AE leading to death within 30 days of discontinuation from study treatment	-	-

[a]*Transaminases increased (grade 3)* *TEAE=treatment-emergent adverse event. TRAE=treatment-related adverse event.*

CONCLUSIONS

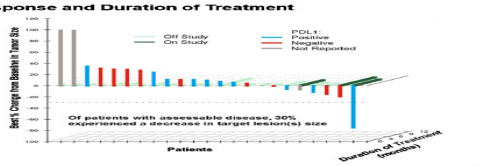
- At this interim evaluation, the combination of ramucirumab with pembrolizumab did not reveal any unexpected safety signals in patients with advanced or metastatic biliary tract cancer.
- In this heavily pretreated patient population with advanced or metastatic biliary tract cancer, limited antitumor activity was observed with the studied regimen.
- Additional overall survival follow-up and biomarker data will guide the future development of this combination in advanced or metastatic biliary tract cancer.

Treatment-related Adverse Events (≥2 patients)

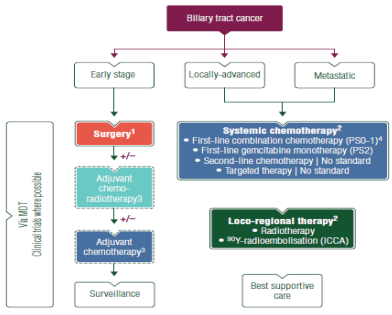
Treatment-related AE, pts (%)	Cohort A1, n=26 Any Grade	Grade 3/4
Any	22 (85)	11 (42)
Serious	6 (23)	6 (23)
Occurring in ≥ 2 patients		
Fatigue[a]	10 (38)	-
Nausea	7 (27)	-
Decreased appetite	3 (12)	-
Stomatitis	3 (12)	-
Pyrexia	3 (12)	-
Vomiting	2 (8)	-
Treatment-related AE of interest[b], pts (%)	**Any Grade**	**Grade 3/4**
Occurring in ≥ 2 patients		
Hypertension	8 (31)	5 (19)
Bleeding/hemorrhage event[c]	5 (19)	1 (4)
Endocrine disorder[d]	4 (15)	-
Diarrhea	4 (15)	-
Infusion related reaction	3 (12)	-
Transaminases increased[e]	3 (12)	2 (8)
Pruritus	2 (8)	-

[a]*consolidated category (fatigue and asthenia)*
[b]*independently pre-identified for ramucirumab and pembrolizumab*
[c]*consolidated category (epistaxis, gingival bleeding, rectal hemorrhage, hematemesis, [blood] and hematuria)*
[d]*consolidated category (hypothyroidism and hyperthyroidism)*
[e]*consolidated category (AST increased, ALT increased, and transaminases increased)*

Response and Duration of Treatment



J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

Figure 1. Algorithm for the management of patients with biliary tract cancer. MDT, multidisciplinary team; PS, performance status; iCCA, intrahepatic cholangiocarcinoma.

Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324

J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Treatment

Curative

- Radical surgery (with lymphadenectomy) is the only curative treatment of BTC; the exact nature and extent of surgery will depend on tumour subtype/location and should be agreed at a specialist hepatobiliary multidisciplinary tumour board
- Surgery involving hepatic resection will need to take into account the future liver remnant and may require portal vein embolisation
- For patients with incidentally diagnosed GBC (post-cholecystectomy), reoperation with radical intent should be considered for stage T1b and above (± resection of port sites)
- Adjuvant therapy (radiotherapy, chemoradiotherapy or chemotherapy alone) may be offered to patients on the understanding that the evidence base is weak and only after risk–benefit assessment; participation in clinical trials should be encouraged
- Neoadjuvant therapy and liver transplant (Mayo Clinic protocol) in early-stage hilar CCA remains investigational; participation in clinical trials should be encouraged
- Patients with initially inoperable, non-metastatic disease should be rediscussed at the multidisciplinary tumour board with a view to salvage surgery in the event of a good response to systemic and/or locoregional treatment, including participation in clinical trials

Palliative

- Systemic chemotherapy is the treatment of choice for patients with locally advanced or inoperable disease; combination chemotherapy for PS 0-1 patients and monotherapy for PS 2 patients
- Cisplatin/gemcitabine is the reference chemotherapy regimen for good PS (0-1) patients; oxaliplatin may be substituted for cisplatin where there is a concern about renal function
- Gemcitabine monotherapy may be considered for PS 2 patients
- There is no established second-line chemotherapy regimen; patients should be encouraged to participate in clinical trials
- There is no established evidence to support the use of targeted therapies; patients should be encouraged to participate in clinical trials
- Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy; patients should be encouraged to participate in clinical trials
- Radioembolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials

Zaključki (1)

- slaba prognoza
- pomen diagnostike
- prvo zdravljenje kiruško

Zaključki (2)- vloga sistemske terapije

• **Adjuvantno zdravljenje:**

- kapecitabin novo standardno sistemsko zdravljenje

- vloga radioterapije v kombinaciji s sistemsko kemoterapijo- prospektivne klin.raziskave

• **Metastatska bolezen:**

- 1.red: gemcitabin+cisplatin (PS0-1), gemcitabin mono (PS 2)

- 2.red: ni standardne terapije

- tarčno zdravljenje: ni standardne terapije

• **Imunoterapija:** prve klinične raziskave v poteku

HVALA ZA POZORNOST

Rak žolčnega voda

Predstavitev primera

Nina Fokter Dovnik,dr.med.
Marko Boc, dr.med.

13. dan internistične onkologije, Onkološki inštitut, 17. 11. 2017

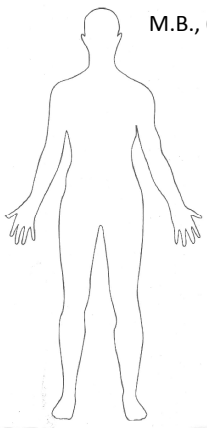
Anamneza

Družinska anamneza: bp.

Brez pridruženih bolezni

Brez redne terapije, brez alergij

Bivši kadilec, prekomerno uživa alkohol



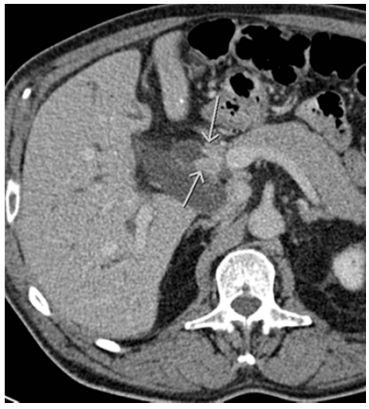
M.B., 67 let

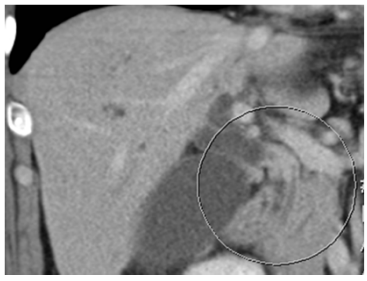
Ikterus
Hujšanje

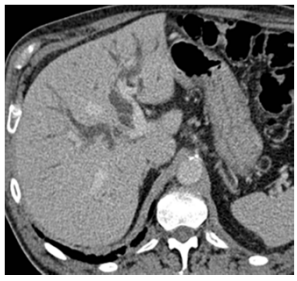
Rezistenca pod DRL

Diagnostične preiskave

Laboratorij	CT trebuha	ERCP + krtačenje
• Bilirubin cel. 184.3 µmol/L • GGT 15,02 µkat/L • AF 6,06 µkat/L • ALT 2,66 µkat/L • AST 1,87 µkat/L • CA 19-9 525,7 KU/L	• Povečan žolčnik • Razširjeni intrahepatalni žolčni vodi • Zadebeljena stena holedohusa v srednjem delu z zoženim lumnom	• Stenoza holedohusa v višini izstopišča cistikusa • Razširjeni proksimalni žolčni vodi • Citološki izvid: adenokarcinom







Vprašanje 1

Kakšno zdravljenje bi priporočili bolniku v tem trenutku?

A. Neoadjuvantno kemoterapijo
B. Neoadjuvantno kemoradioterapijo
C. Operacijo
D. Definitivno kemoradioterapijo
E. Paliativno sistemsko zdravljenje

Operacija in histološki izvid

- 15. 9. 2017: pankreatikoduodenektomija po Whipplu
- Pooperativni potek brez pomembnih zapletov
- Histološki izvid:
  - invazivni žlezni karcinom žolčnega voda, biliarni tip, večinoma G2, mestoma G3
  - tumor 1,8 cm, plitvo infiltrira preko stene žolčnega voda v tkivo pankreasa
  - obsežna peri- in intranevralna invazija, invazija v limfne žile
  - žarišča BilIN visoke stopnje
  - 1/28 bezgavk pozitivnih
  - izrezano v zdravo (R0)
  - pT3N1

Vprašanje 2

Bi po operaciji priporočili še kakšno zdravljenje?

A. Dopolnilno kemoterapijo
B. Dopolnilno radioterapijo
C. Dopolnilno kemoradioterapijo
D. Opazovanje

Dopolnilno sistemsko zdravljenje

Kapecitabin 1250 mg/m^2
1.-14. dan, vsakih 21 dni
8 ciklov

Vprašanje 3

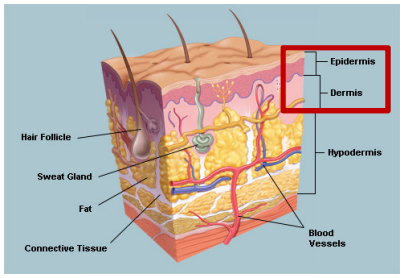
Kakšna je bila razlika v srednjem celokupnem preživetju bolnikov v ITT analizi raziskave BilCap?

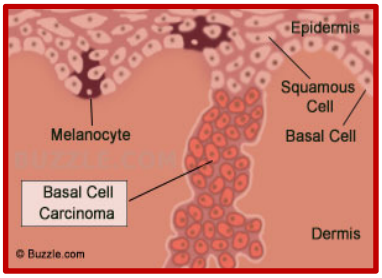
A. 14 dni
B. 2 meseca
C. 6 mesecev
D. 16 mesecev
E. 24 mesecev

Sistemsko zdravljenje nemelanomskih kožnih rakov

Janja Ocvirk

UVOD – anatomija kože in kožni rak





Melanom

Nemelanomski rak kože

- **Bazalnocelični – 80%**
- Ploščatocelični – 16%
- Ostalo – 4%

2

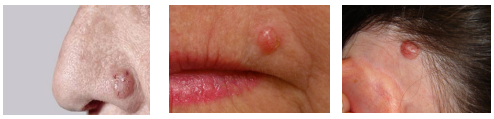
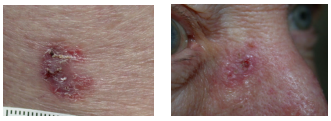
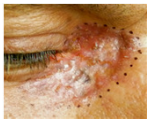
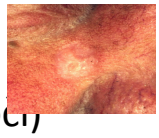
Bazalnocelični karcinom

- Bazalnocelični karcinom (BCK) raste iz bazalne plasti povrhnjice in je najpogosteje diagnosticiran maligni tumor ter najpogostejša oblika kožnega raka pri beli populaciji[1–4]
- Tveganje za pojav BCK pri beli populaciji je 30%[1,2]
- Slabo poročanje v registrih
- Glavni vzrok za pojav BCK je izpostavljenost UV sevanju, ki vodi do kumulativnih poškodb DNK in mutacije genov[1–5]

1. Rubin AI et al. N Engl J Med 2005;353:2262–9
2. Wong CSM et al. Br Med J 2003;327:794–8
3. Roewert-Huber J et al. Br J Dermatol 2007;157:47–51
4. Lear JT et al. J R Soc Med 1998;91:585–8
5. Caro I, Low JA. Clin Cancer Res 2010;16:3335–9

Bazalnocelični karcinom – *histološki podtipi*

- nodularni (**60%**)
- površinski (30%)
- infiltrirajoči
- morfeoformni (sklerozirajoči)

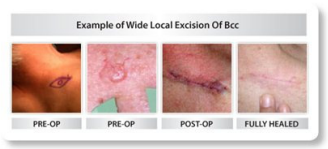
Update of the Guideline on Basal Cell Carcinoma. European Dermatology Forum.
http://www.eurodern.org/images/stories/guidelines/guideline_Basal_Cell_Carcinoma-update2012%20.pdf

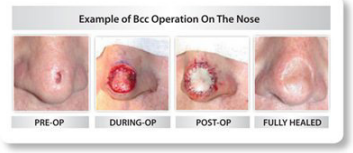
Zdravljenje bazalnoceličnega karcinoma

- Kiretaža in kavterizacija, kriokirurgija
- Krema imiquimod (Aldara®)

- **Kirurška ekscizija**
- **Elektrokemoterapija**
- **Obsevanje**
- **Tarčno zdravilo Erivedge®**

nBCK





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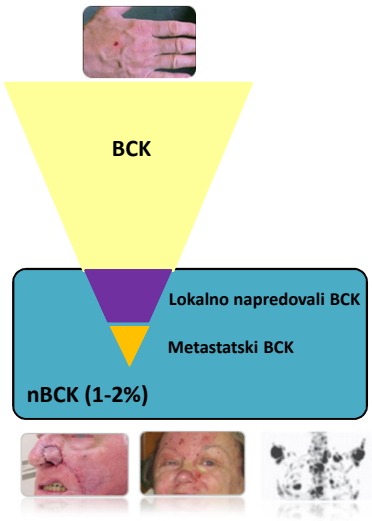
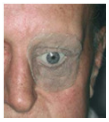
Napredovali bazalnocelični karcinom



Lokalno napredovali BCK (lnBCK)

- **Agresivna** oblika bolezni s **poškodbo lokalnih** tkiv
- Pogoste **ponovitve** po operaciji
- Operacija bi povzročila **deformacijo**



Metastatski BCK (mBCK)

- **Redka, a resna** oblika BCK
- Vključuje prisotnost **metastaz** (npr. bezgavke, kosti, pljuča, jetra)[1]
- **Slab izid** (mediana preživetja: 8–14 mesecev[2,3]; 5-letna stopnja preživetja: 10%[3,4])

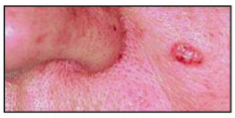
1. Ting PT et al. J Cutan Med Surg 2005;9:10–15
2. von Domarus H, Stevens PJ. J Am Acad Dermatol 1984;10:1043–60
3. Lo JS et al. J Am Acad Dermatol 1991;24:715–19
4. Wong CSM et al. Br Med J 2003;327:794–8

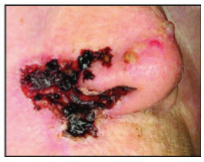
6

Kriteriji za opredelitev napredovale oblike BCK

- Velikost lezije ≥ 10 mm
- Vraščanje tumorja v okolna tkiva in strukture
- Kirurško zdravljenje/obsevanje je kontraindicirano zaradi lege tumorja ali bi vodilo v znatno obolevnost/ deformacijo/izgubo funkcije
- Dve ali več ponovitev lezije na enakem mestu

1



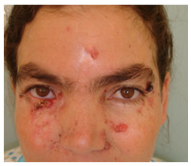


1. Basset-Seguin N. et al. Mol Cancer Ther 2015; 1–9

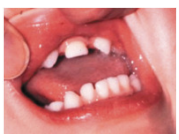
7

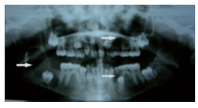
Sy. bazalnoceličnega nevusa (Gorlin Goltz)

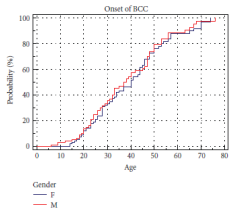
- Redka AD dedna bolezen kože in drugih organov
  (1:19,000, M=Ž, mutacija PTCH gena)[1]
- <u>Od otroštva pojav</u>:
  BCK (lahko več tisoč)
  palmoplantarne diskeratoze
  pogostejši meduloblastom CŽS, ovarijski fibrosarkom
- <u>Druge spremembe</u>:
  keratociste v čeljusti, spina bifida, kifoskolioza
  - ŽIVČNI SISTEM alteracije v EKG-ju, kalcifikacija dure
  - OČI povečan razmik med očmi, katarakta



- KOSTI







1. Jones E.A et al. Journal of Skin Cancer Volume 2011, Article ID 217378

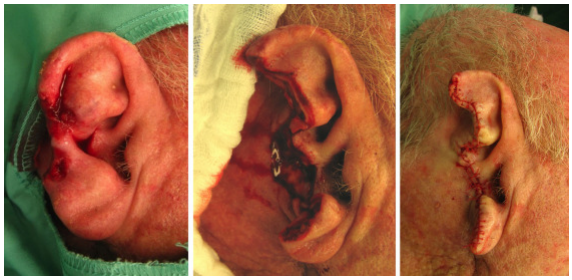
8

Tveganje za lokalno ponovitev

Tveganje za lokalno ponovitev	Majhno	Veliko
Trup, okončine	<20 mm	≥20mm
Lica, čelo, skalp, vrat	<10 mm	≥10mm
Centralni del obraza, veke, obrvi, periorbitalno, nos, ustnice, brada, mandibularno, uhlji in okrog uhljev, temporalno, spolovilo, roke, stopala	<6 mm	≥6mm
Klinična omejenost	Dobra	Slaba
Primarni vs. rekurentni	Primarni	Rekurentni
Predhodna radioterapija	Ne	Da
Imunosupresija	Ne	Da
Histološki podtip	Nodularni, superficialni	Mikronodularni, morfeiformni, infiltrativni
Perinevralna invazija	Ne	Da
Metoda zdravljenja	Kirurška (popolna ekscizija)	Lokalne destruktivne metode, nepopolna ekscizija

9

Kaj preostane bolniku, ko so vse možnosti zdravljenja izčrpane?

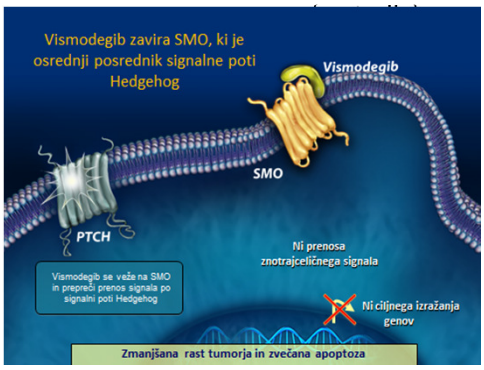


Puig S. Clin Transl Oncol DOI 10.1007/s12094-014-1272-9

10

BCK in signalna pot Hedgehog

- Pot celične rasti in diferenciacije, ki nadzira tvorbo organov v embrionalnem razvoju[1]
- Signalna pot Hedgehog je v večini tkiv odraslega neaktivna
- Nenormalna aktivacija signalne poti pomembno BCK[1]
- Zaviralci signalne poti Hedgehog omogočajo novo možnost zdravljenja za bolnike z napredovalim



1. Epstein EH. Nat Rev Cancer 2008;8:743–54

11

Raziskava ERIVANCE BCC - učinkovitost

Izidi	(30-mesečna analiza) mBCK (n=33)	lnBCK (n=63)	Total (n=96)
Mediana trajanja odgovora, meseci 95%CI	14,8 5,6 – 17,0 (n=16)	26,2 9,0 - 37,6 (n=38)	16,1 9,5 – 26,2 (n=54)
Objektivni odgovor, n (%) 95% CI	16 **(48,5)** 30,8 – 66,2	38 **(60,3)** 47,2 – 71,7	54 (56,3) 45,7 – 66,4
Popolni odgovor	0	20	20
Delni odgovor	16	18	34
Stabilna bolezen	14	15	29
Napredovanje bolezni	2	6	8

12

Sekulic A, Poster presentation ASCO 2014

Raziskava ERIVANCE BCC - varnost

Neželeni dogodek[a]	NCI CTCAE Stopnja (n = 104)				
n (%)	Total	1	2	3	4
Mišični krči	74 (71,2)	45 (43,3)	23 (22,1)	6 (5,8)	0 (0)
Alopecija	69 (66,3)	49 (47,1)	20 (19,2)	NA	NA
Sprememba okusa	58 (55,8)	32 (30,8)	26 (25,0)	NA	NA
Izguba teže	54 (51,9)	29 (27,9)	16 (15,4)	9 (8,7)	0 (0)
Utrujenost	45 (43,3)	33 (31,7)	7 (6,7)	4 (3,8)	1 (1,0)
Slabost	34 (32,7)	25 (24,0)	9 (8,7)	0 (0)	0 (0)
Zmanjšan apetit	29 (27,9)	19 (18,3)	7 (6,7)	3 (2,9)	0 (0)

[a] NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
Neželeni učinki se po intenzivnosti razvrščajo od stopnje 1 do stopnje 5, kjer pomeni stopnja 1 blage neželene učinke, stopnja 2,3,4 po intenzivnosti rastejo vse do stopnje 5, ki pomeni smrt zaradi neželenega učinka zdravila.
Sekulic A, Poster presentation ASCO 2014

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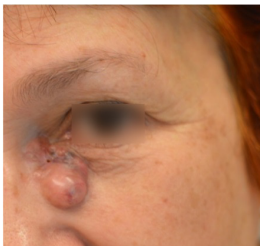
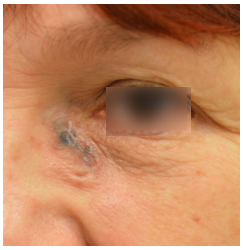
primer z Onkološkega inštituta

23. 9. 2013



19. 12. 2013



31. 7. 2014

- Hitri odgovor na zdravljenje
- Neželeni učinki: alopecia gr. 2 po enem letu zdravljenja, zvišan CPK gr.1, mišični krči gr.1

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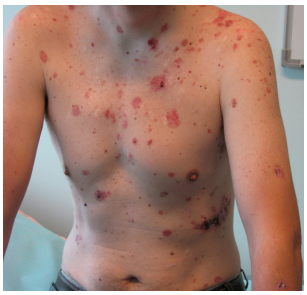
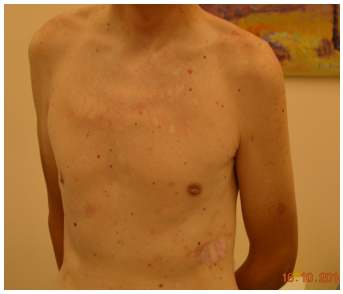
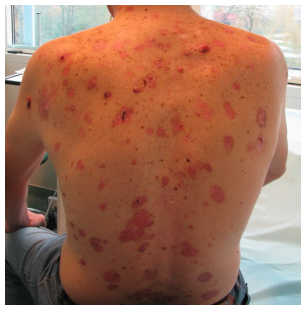
primer z Onkološkega inštituta



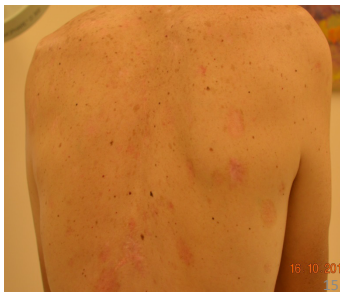
Bolnik z Gorlinovim sindromom (multipli BCK)



8. 11. 2012 **16. 10. 2014**



Neželeni učinki:
alopecia gr.1
izguba teže gr.2
zvišan CPK gr.1-3



Rak Merklovih celic

- Rak Merklovih celic (MCC) je redek, agresiven in pogosto smrten nevroendokrini kožni karcinom.
- Naraščajoča incidence (v ZDA se je od 1986 do 2001 potrojila).
- Možna povezava z nedavno odkritim poliomavirusom (80 % celic MCC).
- Pogosto se pojavlja na soncu izpostavljenih predelih kože.

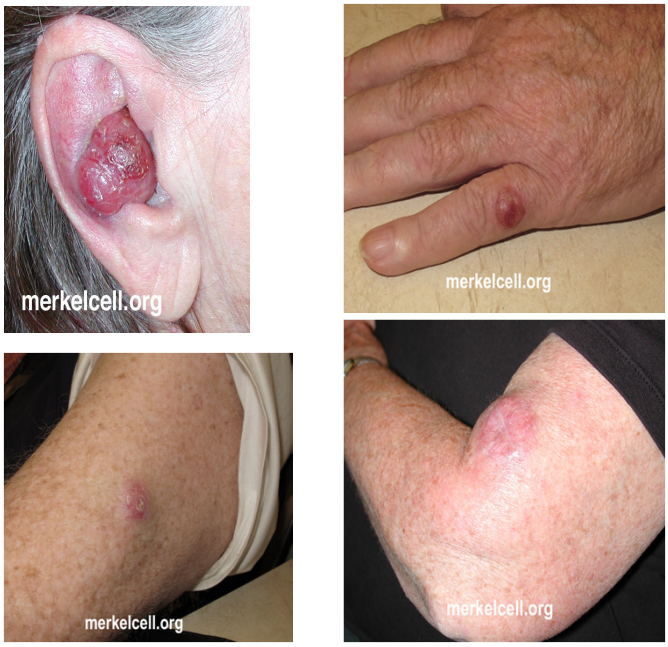
INCIDENCA

- Stopnja incidence karcinoma Merklovih celic se razlikuje glede na geografsko področje in varira med 0.2-1.6 primerov na 100.000 prebivalcev
- Najvišjo incidenco beležijo na Novi Zelandiji in Avstraliji (1.6/100.000), v Združenih državah Amerike je nekoliko nižja (0.8/100.000), v Evropi pa le 0.2-0.4 primerov na 100.000 prebivalcev.
- Incidenca je močno povečana pri starostnikih (srednja starost ob diagnozi je 75 let)
- Večja je tudi pri moških kot pri ženskah.
- Večja pri bolnikih na imunosupresivni terapiji (HIV, transplantacija...)

ETIOLOGIJA IN NASTANEK BOLEZNI

Poznamo dva vzroka za nastanek KMC:

- Preko onkoproteinov enkodiranih z polioma virusom Merklovih celic (MCPyV)
- Akumulacija mutacij povzročenih z UV sevanjem. Pogosteje pri imunosupresiranih bolnikih


merkelcell.org
merkelcell.org
merkelcell.org
merkelcell.org

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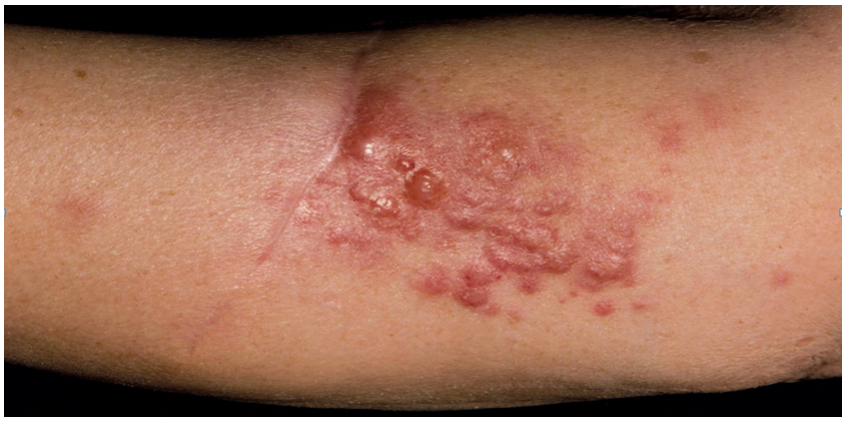


National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Merkel Cell Carcinoma

Staging continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Merkel Cell Carcinoma
(8th ed., 2016)

AJCC Prognostic Stage Groups

Clinical (cTNM)

Tis	N0	M0	0
T1	N0	M0	I
T2–3	N0	M0	IIA
T4	N0	M0	IIB
T0–4	N1–3	M0	III
T0–4	Any N	M1	IV

Pathological (pTNM)

Tis	N0	M0	0
T1	N0	M0	I
T2–3	N0	M0	IIA
T4	N0	M0	IIB
T1–4	N1a(sn) or N1a	M0	IIIA
T0	N1b	M0	IIIA
T1–4	N1b–3	M0	IIIB
T0–4	Any N	M1	IV

PRINCIPLES OF SYSTEMIC THERAPY[1]

Local Disease:
- Adjuvant chemotherapy not recommended

Regional Disease:
- Clinical trial (preferred)
- Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
  - Cisplatin ± etoposide
  - Carboplatin ± etoposide

Disseminated Disease:
- Clinical trial (preferred)
- Avelumab[2]
- Pembrolizumab[2]
- Nivolumab[2]
- As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  - Cisplatin ± etoposide
  - Carboplatin ± etoposide
  - Topotecan
  - (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

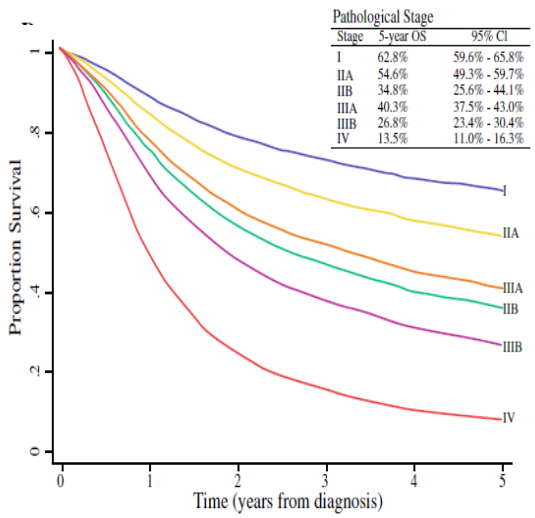
[1] When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

[2] Preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.

ZDRAVLJENJE

- Problem predstavlja visoka stopnja ponovitve bolezni, ki je celo pri bolnikih z lokalno ali regionalno boleznijo 48 %.
- Raziskave so pokazale, da je med bolniki s ponovitvijo bolezni, čas med diagnozo in ponovitvijo le 9 mesecev

PREŽIVETJE



Pathological Stage

Stage	5-year OS	95% CI
I	62.8%	59.6% - 65.8%
IIA	54.6%	49.3% - 59.7%
IIB	34.8%	25.6% - 44.1%
IIIA	40.3%	37.5% - 43.0%
IIIB	26.8%	23.4% - 30.4%
IV	13.5%	11.0% - 16.3%

Harms KL et al. Annals of Surgical Onc. 2016:23: 3564-71

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Role of chemo for metastatic MCC

Becker et al, ESMO 2016

Treatment results in pre-treated pts.:

- CR;PR;SD: 0%, 8,8%, 8,8%
- DOR (median): 1.9 mon
- PFS (median): 3.0 mon
- OS (median): 5.3 mon
- PFS and OS (at 1 year): 0% (!)
- No PRs/SDs in immunocompromised patients!

Razlog za uporabo imunoterapije pri mMCC

- PD-L1 se izraža v MCC tumorskih celicah in infiltratih sosednih imunskih celic[1]
- Disfunkcija MCPyV-specifičnih T celic[2]
  - Nivoji CD8 T celic se zvišajo z večjim tumorskim bremenom
  - Exhausted fenotip (PD-1$^+$, Tim-3$^+$)
- MCPyV-negativni tumorji imajo večje breme mutacij in neoantigenov[3]

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

Avelumab for metastatic MCCs

Kaufman et al, Lancet Oncol; 17: 1374-85 (2016)

- Multicentric phase 2 study (JAVELIN 200) on the use of a PD-L1 antibody, avelumab (10mg/kg; 2-weekly)
- 88 MCC patients (stage IV; chemo-resistent)
- Mean age: 72.5 years
- 66% PD-L1-positive; 52% MCPv-positive
- Median follow-up time: 10.4 months
- Primary trial endpoint: Response rate (RECIST criteria)

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Avelumab for metastatic MCC

Kaufman et al, Lancet Oncol; 17: 1374-85 (2016)

Outcome of JAVELIN 200 trial (second-line)

- CR; PR; SD: 9%; 23%; 10%
- Not evaluable: 20%
- 23/28 patients presented ongoing remissions
- Median PFS//OS: 2.8 mon//11.3 mon
- ORR (PD-L1-pos. vs. neg.): 34.5% vs. 18.8%
- ORR (MCPv-pos. vs. neg.): 35.5% vs. 26.1%
- Toxicity: CTC grade 3 only in 4/88 patients (5%)

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First-line avelumab treatment in patients with metastatic Merkel cell carcinoma (mMCC): preliminary data from an ongoing study

S. P. D'Angelo[1], J. S. Russell[2], J. Hassel[3], C. Lebbé[4], B. Chmielowski[5], G. Rabinowits[6], P. Terheyden[7], I. Brownell[8], I. Zwiener[9], M. Bajars[10], M. Hennessy[11], H. L. Kaufman[12]

[1]Memorial Sloan Kettering Cancer Center & Weill Cornell Medical College, New York, New York, USA; [2]H. Lee Moffitt Cancer Center, Tampa, Florida, USA; [3]Universitaetsklinikum Heidelberg, Heidelberg, Germany; [4]Saint Louis Hospital, Paris, France; [5]UCLA Medical Center, Los Angeles, California, USA; [6]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [7]University of Lübeck, Lübeck, Germany; [8]National Cancer Institute, Bethesda, Maryland, USA; [9]Merck KGaA, Darmstadt, Germany; [10]Merck Serono SIA, Riga, Latvia; [11]EMD Serono, Inc, Billerica, Massachusetts, USA; [12]Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA

Poster presentation at the 53rd ASCO Annual Meeting, June 2-6, 2017; Chicago, IL, USA.

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Table 2. BOR by RECIST v1.1 per IERC

	Patients with ≥13 weeks of follow-up, confirmed* BOR (n=16)	Patients with ≥6 weeks of follow-up, unconfirmed BOR (n=25)
BOR, n (%)		
CR	3 (18.8)	3 (12.0)
PR	7 (43.8)	14 (56.0)
Stable disease	2 (12.5)	2 (8.0)
Progressive disease	3 (18.8)	5 (20.0)
Non-evaluable	1 (6.3)†	1 (4.0)†
ORR, %	62.5	68.0
95% CI	(35.4-84.8)	(46.5-85.1)

* Response criteria met again in repeat assessment performed ≥5 weeks after initial documentation of CR or PR.
† Died prior to tumor assessment.

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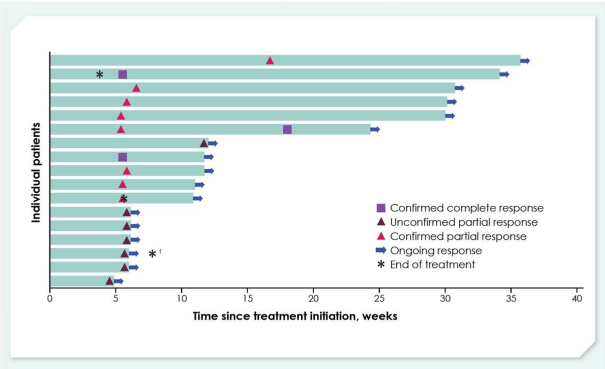
Figure 3. Time to and duration of response in patients with ≥6 weeks of follow-up



† Patient started a new treatment after discontinuing avelumab for an adverse event and is therefore nonevaluable for further study assessment; response cannot be confirmed.

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Merkel Cell Carcinoma: Pembrolizumab

Nghiem et al, N Engl J Med 2016

- Multicentric US phase-2 trial in MCC on Pembrolizumab (2mg/kg; 3-weekly)
- First-line therapy in 26 metastatic MCC pts (92% with stage IV)
- Mean age: 70.5 years; 62% males
- 17/26 pts (65%) were MCPyV-positive

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Merkel Cell Carcinoma: Pembrolizumab

Nghiem et al, N Engl J Med 2016

- 14/25 ORR (56%), "confirmed responses"
- 4 CR (16%), 10 PR (40%); 12/14 responses ongoing after 33 weeks of follow-up
- 4/26 pts (15%) with CTC-grade 3/4 adverse events
- 2/26 pts with grade 4 (1x myocarditis + 1x liver enzyme elevation), but ongoing PR/CR despite discontinuation
- Median PFS: 9 mon, Median OS: not reached

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Primerjava rezultatov študij: avelumab, pembrolizumab in nivolumab

	Avelumab - JAVELIN	Pembrolizumab	Nivolumab
	Stage IV - ALL	**Stage IIIB** (N=2) **Stage IV** (N=24)	**Unresectable local or Stage IV**
TARGET POPULATION	**Total N=200** **1L N=112** 2L N=52 3L N=26 4L+ N=10	**Total N=26** **1L N=26** (now increasing to 50)	**Total N=25** **1L N=15** 2L N=7 3L N=3
STUDY DESIGN	Phase 2 single arm **Global including Europe**	Phase 2 single arm, **US only**	Phase 2 single arm **Global including Europe**
CLINICAL ASSESSMENT	**6 week** intervals	**12 week** intervals after starting therapy 9 week intervals thereafter	**8 week** intervals
RESPONSE ASSESSMENT	**All responses** were assessed by an **independent review committee**	**Only patients who had a response** were assessed by **a central radiologic review**	By **Investigator assessment**
STRENGTH OF TRIAL	**Largest Study in MCC** **Pivotal study** with **longer follow-up intended for regulatory submission worldwide**	**Signal finding** study with **small data set** **Increase in cohort to 50 patients** **Approval in US likely** **Approval in Europe UNLIKELY**	**Signal finding** MCC cohort part of a large muti-tumour cohort study **Strategy** is in **adjuvant setting**

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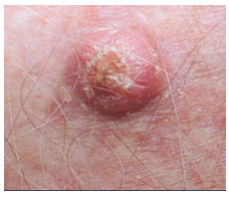
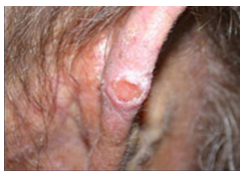
ZAKLJUČEK

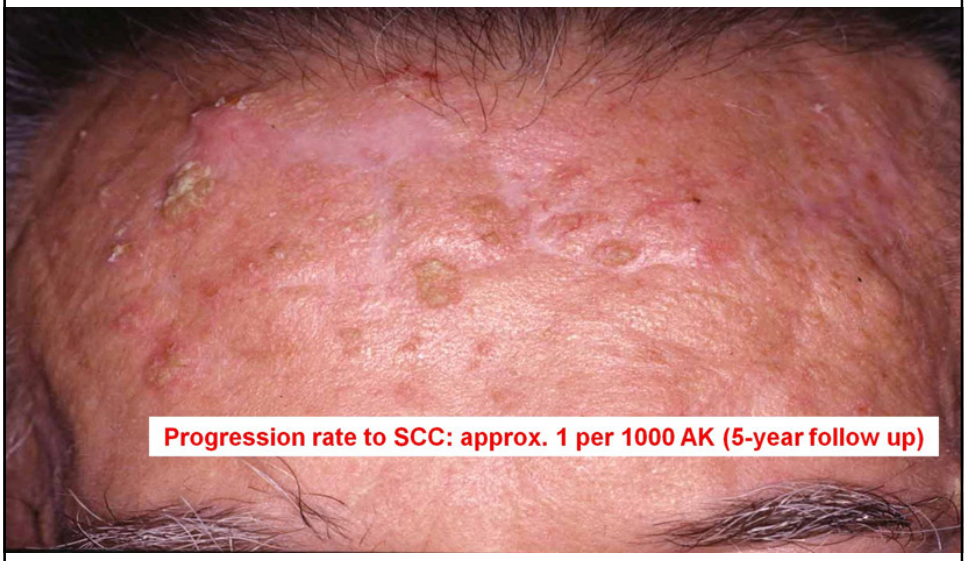
- Tudi pri MCC se je imunoterapija izkazala kot zelo učinkovita terapija.
- Učinkovitost imunoterapije je bila dokazana pri MCPyV pozitivnih in MCPyV negativnih tumorjih.
- Preizkušana je bila v prvem, drugem in poznejših redih zdravljenja napredovalega KMC.
- Zaenkrat je za zdravljenje razsejanega MCC z imunoterapijo, s strani FDA (ZDA) ter s strani Evropske agencije za zdravila, odobreno le zdravilo avelumab.

SCC

- Drugi najbolj pogost NMKR (20%)
- Incidenca v zadnjih 30 letih narašča (50-200%)
- Večina na glavi in vratu 80-90%
- Večinoma vznikne iz prekurzorskih lezij , a tudi na novo
- 90% jih ima odlično prognozo

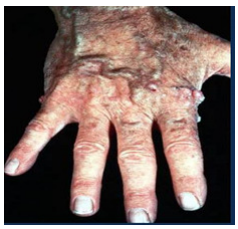
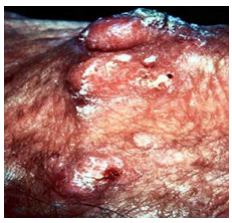
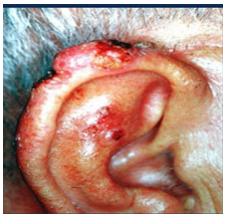




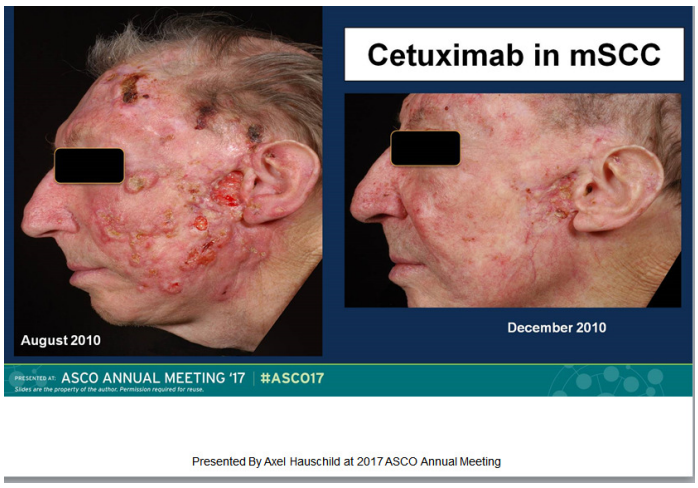


SCC pri transplantiranih bolnikih

36 x višje incidenca kot običajno (BCC:SCC 4:1)
Agresivno obnašanje – slaba priognoza

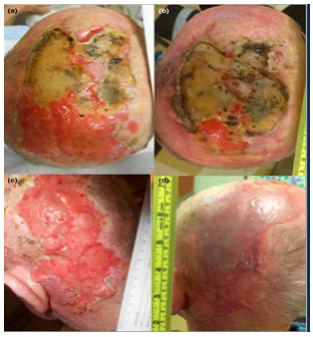




- Omejena bolezen – kirurgija, elektrokemoterapija
- Radioterapija
- Napredovala bolezen - lokalno in sistemsko
- Kemoterapija na osnovi cisplatina – ni standardnih shem, kratko trajanje remisij – 3 mesece
- Tarčna terapija: cetuximab (RR 21%), Panitumumab (31%)



PD 1 protitelesa pri SCC

Pred zdarvljenjem



Po zdravljenju

Boradori et al. Br J Dermatol, 2016. 175: 1382-6

REGN2810, a Fully Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy

Kyriakos Papadopoulos,[1] Taofeek Owonikoko,[2] Melissa Johnson,[3] Irene Braña,[4] Marta Gil Martin,[5] Raymond Perez,[6] Victor Moreno,[7] April Salama,[8] Emiliano Calvo,[9] Nelson Yee,[10] Howard Safran,[11] Antonio Gonzalez Martin,[12] Raid Aljumaily,[13] Daruka Mahadevan,[14] Kosalai Mohan,[15] Chetachi Emeremni,[15] Elizabeth Stankevich,[15] Israel Lowy,[15] Matthew Fury,[15] Jade Homsi[16]

[1]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; [2]Emory Winship Cancer Institute, Atlanta, GA, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Vall D'Hebron Institute of Oncology, Barcelona, Spain; [5]Institut Català d'Oncologia, Barcelona, Spain; [6]Unversity of Kansas, Fairway, KS, USA; [7]START Madrid Fundacion Jimenez Diaz, Madrid, Spain; [8]Duke University Medical Center, Durham, NC, USA; [9]START Madrid, Hospital Madrid Norte Sanchinarro, Madrid, Spain; [10]Penn State Cancer Institute, Hershey, PA, USA; [11]Miriam Hospital, Providence, RI, USA; [12]MD Anderson Cancer Center, Madrid, Spain; [13]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [14]University of Arizona Cancer Center, Tucson, AZ, USA; [15]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [16]Banner MD Anderson Cancer, Gilbert, AZ, USA.

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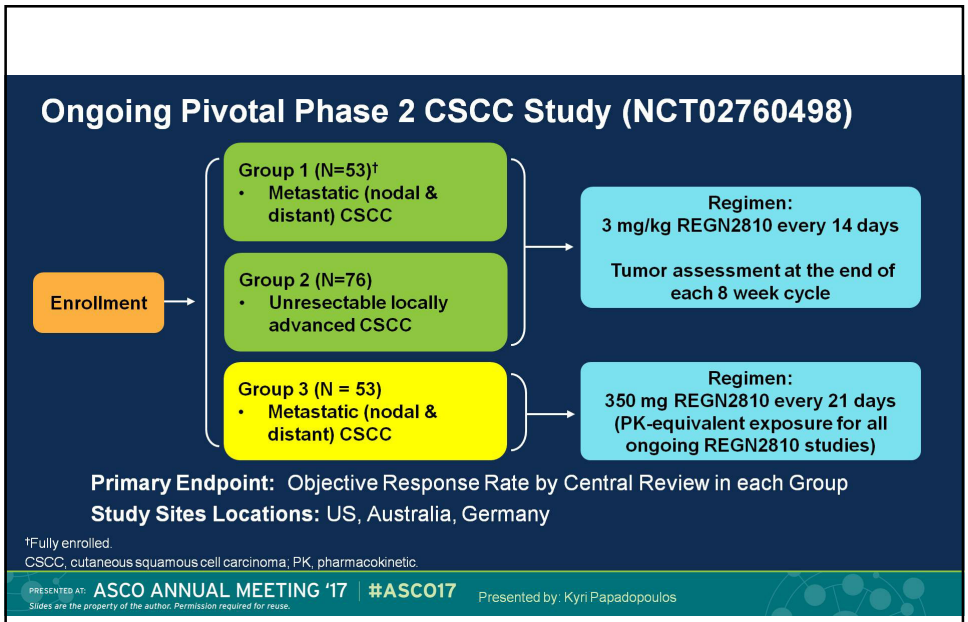

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Investigator Assessed Preliminary Response Rate by RECIST 1.1 (Intention-To-Treat Population) is 46.2%

Investigator assessment	Cohort 7 (N=10), n (%)	Cohort 8 (N=16), n (%)	Overall (N=26), n (%)
Complete response	0	2 (12.5)	2 (7.7)
Partial response	6 (60.0)†	4 (25.0)	10 (38.5)
Stable disease	1 (10.0)	5 (31.3)	6 (23.1)
Progressive disease	2 (20.0)	4 (25.0)	6 (23.1)
Not evaluated	1 (10.0)	1 (6.3)	2 (7.7)

ORR (CR + PR + one unconfirmed PR) = 46.2% (12/26 patients; 95% CI:26.6–66.6)
DCR (ORR + SD) = 69.2% (18/26 patients; 95% CI: 48.2–85.7)

†Includes 5 confirmed partial responses and 1 unconfirmed partial response.
CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria In Solid Tumors.

Data cut-off date: 27 April 2017

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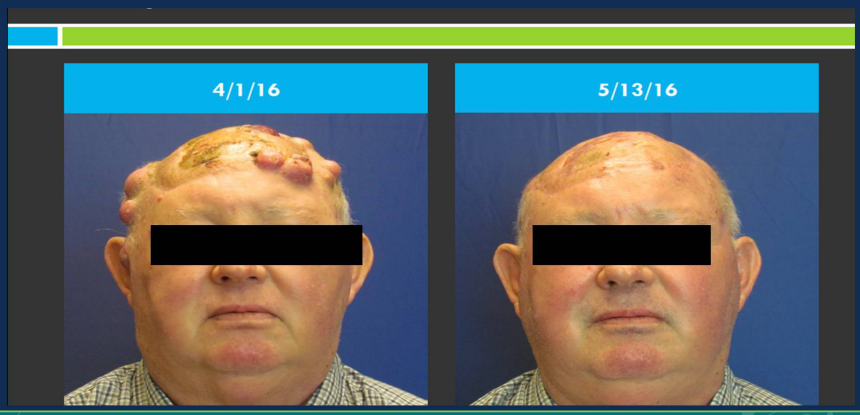
CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810



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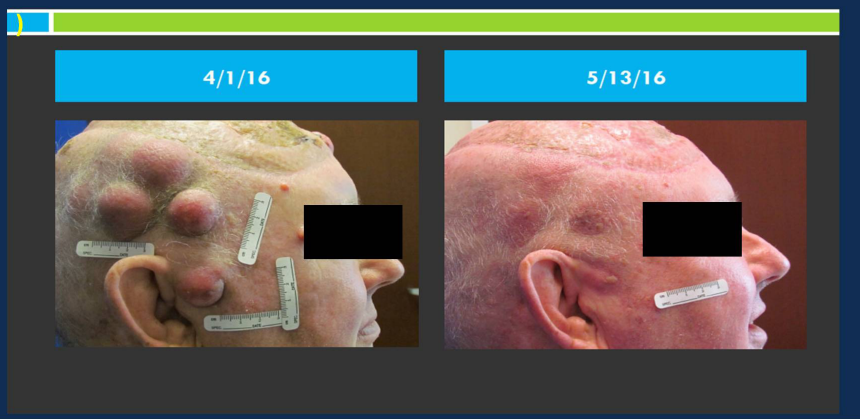
CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810



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Zaključki

- NMKR – so najbolj pogosti raki
- Incidenca raste
- Številne mutacije pri UV induciranih rakih
- Kirurgija ej standardno zdarvljenje pri nezahtevnih primerih
- Omejena vloga radioterapije kljub radiosenzitivnosti pri KMC

- Ni jasnega dobrobita kemoterapije
- Tarčna terapija glede na mutacije (SCC EGFRi in panHERi; BCC patched/SMOi) je učinkovita (RR 58%, CR 20-30%)
- Imunoterapija (PD-1 in PD-L1 protitelesa) so učinkovita pri KMC in veliko obetajo tudi pri SCC in BCC

LOKALNO NAPREDOVALI BCC
(CASE REPORT)

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

ANAMNEZA

- Maj 2017: 92 letni bolnik
- Dosedanje bolezni
  - Po prebolelem AMI (2008)
  - AH
  - Putika
- Nekdanji dolgoletni kadilec
- Poklic???

SEDANJA BOLEZEN

- Plastična kirurgija → operiran zaradi BCC desnega nosnega krila (kdaj???)
- ORL
  - Julij 2012 → (verjetno recidiv) BCC desnega nosnega krila → operacija s kritjem defekta
  - Oktober 2014 → eksofitičen recidiv BCC med korenom nosu in desnim medialnim očesnim kotom, vel.15x15 mm → operacija s kritjem defekta
  - Julij 2015 → ponovni recidiv BCC, adherenten na kost, vel.20mm, ektropij spodnje desne veke, epifora

ORL KONZILIJ

- Ponovna operacija?
- EKT?
- RT?

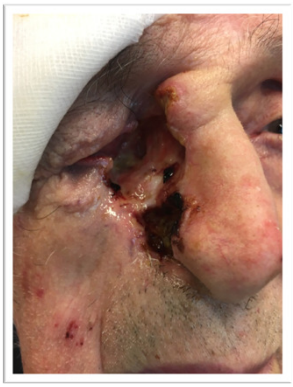
RT

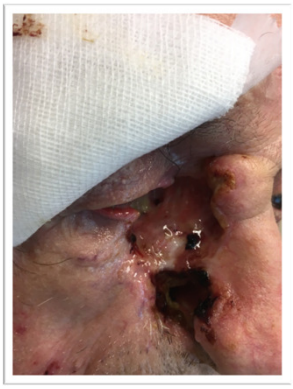
- 10x4 Gy (5.8-18.8.2015)
- 1.kontrola po zaključenem obsevanju → *ni rezidualnega tumorja*
- Zadnja kontrola s strani radioterapevta → defekt brez okolnega infiltrata
- Nadaljne kontrole…

APRIL 2017: PONOVNI RECIDIV BCC

- ORL konzilij
  - Operacija ≠ mutilantna
  - RT ≠ že bil obsevan
  - **ST = vismodegib**

MAJ 2017: INT. ONKOLOG



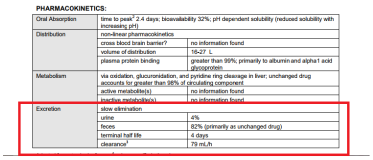


MAJ 2017: INT. ONKOLOG

- PS po WHO 2, blago dehidriran, brez evidentnih znakov srčnega popuščanja
- Laboratorij:
  - Kreatinin 278
  - Sečnina 21.4
  - Kalij 5.3
- Lasix 40 mg/dan → ex
- Hidracija

MAJ 2017: INT. ONKOLOG

- Kontrolni laboratorij čez 1 teden:
  - Kreatinin 235
  - Sečnina 14.9
- Vismodegib 150 mg/dan
- Kontrola na 4 tedne



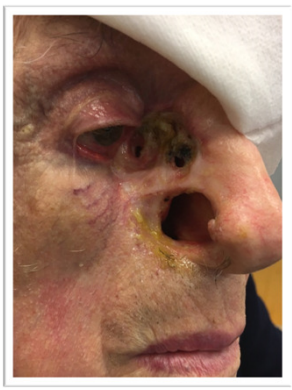
PHARMACOKINETICS:

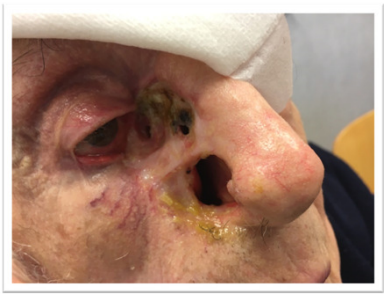
Oral Absorption	time to peak[1] 2.4 days; bioavailability 32%; pH dependent solubility (reduced solubility with increasing pH)	
Distribution	non-linear pharmacokinetics	
	cross blood brain barrier?	no information found
	volume of distribution	18-27 L
	plasma protein binding	greater than 99%; primarily to albumin and alpha1 acid glycoprotein
Metabolism	via oxidation, glucuronidation, and pyridine ring cleavage in liver; unchanged drug accounts for greater than 98% of circulating component	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	slow elimination	
	urine	4%
	feces	82% (primarily as unchanged drug)
	terminal half life	4 days
	clearance[1]	79 mL/h

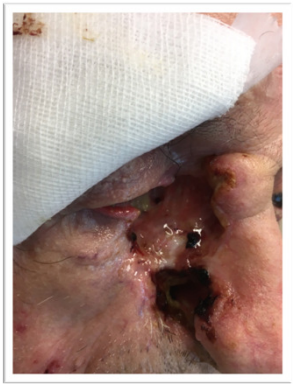
VISMODEGIB (NAJPOGOSTEJŠI STRANSKI UČINKI)

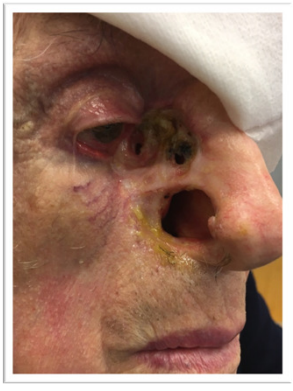
- Utrujenost
- Izguba okusa ✓
- Izguba apetita ✓
- Izguba TT ✓
- Mišični krči
- Alopecija
- Hepatopatija

OKTOBER 2017 → KONTROLNI PREGLED 5 MESECEV PO ZAČETKU ZDRAVLJENJA









PRED ZAČETKOM ZDRAVLJENJA

5 MESECEV KASNEJE


HVLA ZA
POZORNOST!

SIMPOZIJ SO PODPRLE NASLEDNJE DRUŽBE:

ROCHE

ELI LILLY

MERCK

NOVARTIS

MSD

SERVIER

BAYER

BOEHRINGER INGELHEIM

EWOPHARMA

PFIZER

AMGEN

PHARMASWISS

TAKEDE