ONKOLOŠKI INŠTITUT LJUBLJANA

INSTITUTE OF ONCOLOGY LJUBLJANA

Slovensko Zdravniško Društvo

Sekcija za internistično onkologijo

KATEDRA ZA ONKOLOGIJO

14. ŠOLA MALIGNEGA MELANOMA

ONKOLOŠKI INŠTITUT LJUBLJANA

09. MAREC 2018

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ga. Lidija Kristan

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

Ljubljana, marec. 2018

VSEBINA 14. ŠOLE MALIGNEGA MELANOMA:

PROGRAM SREČANJA:

PETEK, 09.03.2018

07.00-08.30 **REGISTRACIJA UDELEŽENCEV**

Moderator: dr. Barbara Perić, dr.med., Aleksandra Dugonik, dr.med., dr. Mesti Tanja, dr.med.

08.30-08.50 *B.Perić:* Epidemiologija in genetika melanoma
08.50-09.20 *T. Mesti, J. Ocvirk:* Vloga biomarkerjev v sistemskem zdravljenju melanoma
09.20-09.50 *A.Dugonik:* Obravnava bolnika s sumom na melanom
09.50-10.20 *M. Marolt Mušič:* Slikovne preiskave pri bolnikih z melanomom
10.20-10.50 *B. Luzar:* Vloga patologa v diagnostiki malignega melanoma
10.50-11.00 **RAZPRAVA**

11.00-11.15 **ODMOR**

Moderator: prof. dr. Marko Hočevar, dr.med., asist. dr. Martina Reberšek, dr.med.

11.15-11.45 *M. Hočevar:* Kirurško zdravljenje melanoma
11.45-12.10 *J. Ocvirk:* Sistemsko dopolnilno zdravljenje melanoma
J. Knez, M. Reberšek: Primer bolnika
12.10-12.25 *M. Reberšek:* Sistemsko zdravljenje razsejanega malignega melanoma-kemoterapija
12.25-12.40 **RAZPRAVA**
12.40-13.10 *J. Ocvirk:* Sistemsko zdravljenje razsejanega melanoma - imunoterapija
M. Ignjatović, *M. Pernek, J. Ocvirk:* Primer bolnika

13.10-14.00 **ODMOR (KOSILO)**

Moderator: prof. dr. Primož Strojan, dr.med., izr. prof. dr. Janja Ocvirk, dr.med.

14.00-14.30 *M. Boc:* Sistemsko zdravljenje razsejanega melanoma – tarčno zdravljenje
N. Fokter, M. Boc: Primer bolnika
14.30-14.45 *P. Jaki:* Retinopatija ob zdravljenju z MEK inhibitorji
14.45-15.15 **SATELITSKI SIMPOZIJ**
15.15-15.35 *P. Strojan:* Mesto radioterapije v zdravljenju melanoma
15.35-15.55 *U. Smrdel:* Stereotaksija
15.55-16.10 **RAZPRAVA**

16.10-16.20 **ODMOR**

Moderator: prof. dr. Marko Hočevar, dr.med.

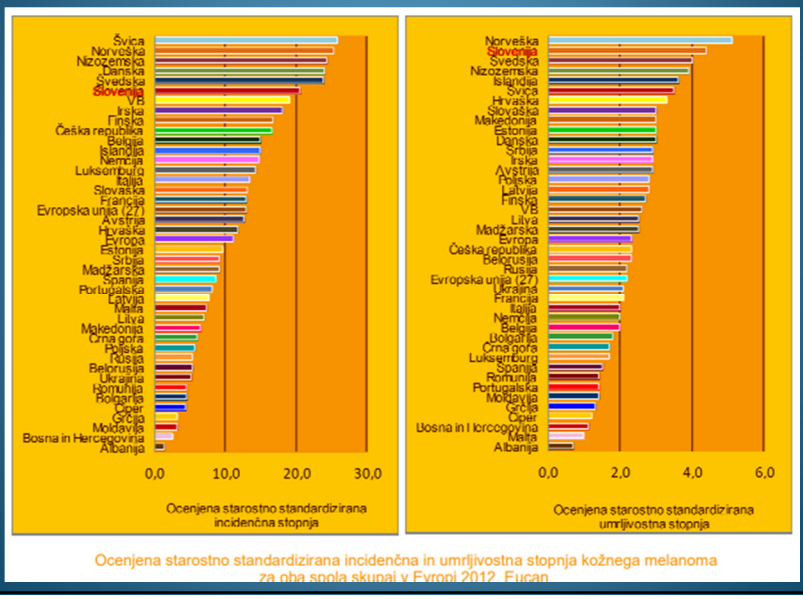
16.20-17.05 PREDSTAVITEV KLINIČNIH PRIMEROV BOLNIKOV
Z VIDIKA DERMATOLOGA (30 min)
K. Šmuc Bergar: Primer 1
T. Bremec: Primer 2
T. Planinšek Ručigaj: Primer 3
PRIMER ELEKTROKEMOTERAPIJE (30 min)
N. Glumac, G. Serša: Primer 4
17.05-17.20 *V. Zadnik:* Klinični register melanoma
17.20-17.40 *M. Hočevar, J. Ocvirk:* Klinična pot obravnave bolnika z melanomom in multidisciplinarni pristop k zdravljenju
17.40-18.00 **RAZPRAVA IN ZAKLJUČKI**

ŠTIRINAJSTA ŠOLA O MELANOMU

Epidemiologija in genetika melanoma

asist.dr. Barbara Perić, dr. med.
Oddelek za kirurško onkologijo

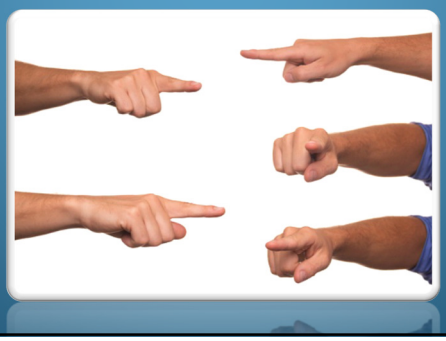
Breme KM v svetu



Ocenjena starostno standardizirana incidenčna in umrljivostna stopnja kožnega melanoma za oba spola skupaj v Evropi 2012, Eucan

Incidenca

- KM 232.000 v svetu zboli
- 55.000 umre
- KM 0.6% letno pri < 50 let
- EU 13/100.000 vs. SLO 20.6/100.00

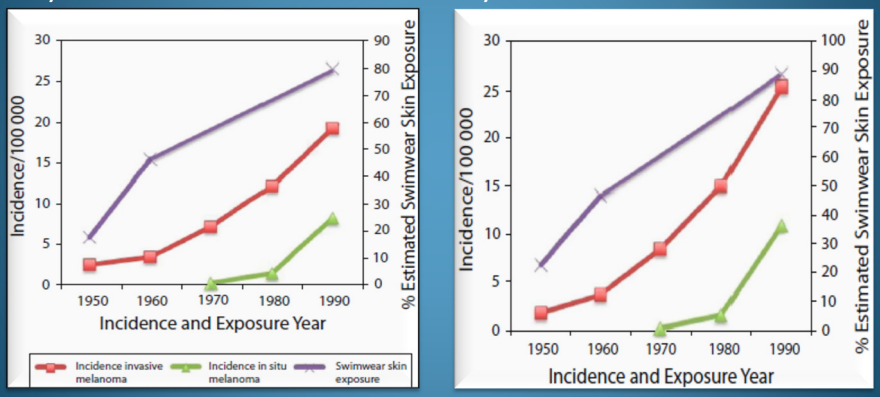


Spremembe

More skin, more sun, more tan, more melanoma.Chang C, Murzaku EC, Penn L, et al.Am J Public Health. 2014, Voda, zrak in svetloba - Arnold Rikli (1823-1906) - ob 190-letnici rojstva.Toplak C, Zupanič SZ.. *Isis*. ISSN 1318-0193. jan. 2014

Posledice

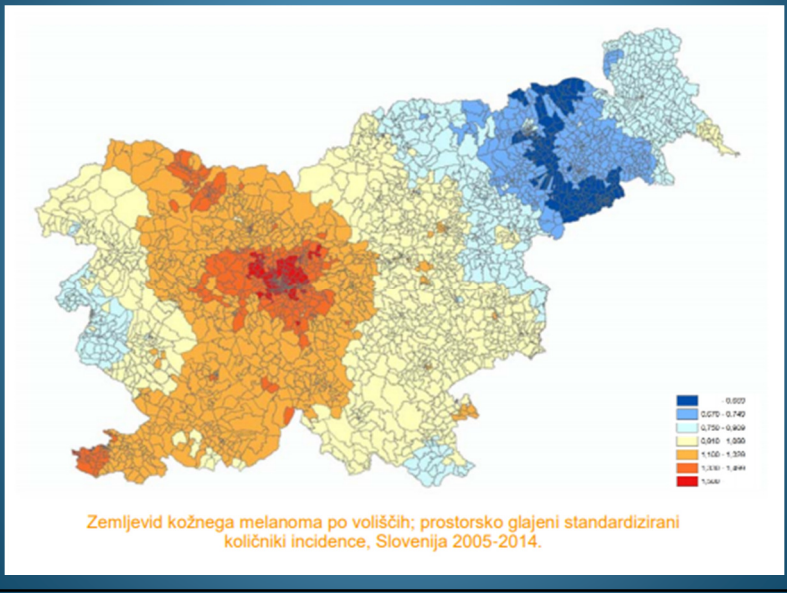
a) ženske **b) moški**



Starostno standardizirana incidenca melanoma glede na količino v kopalnih oblačilih izpostavljene kože

More skin, more sun, more tan, more melanoma:Chang C, Murzaku EC, Penn L, et al.Am J Public Health. 2014

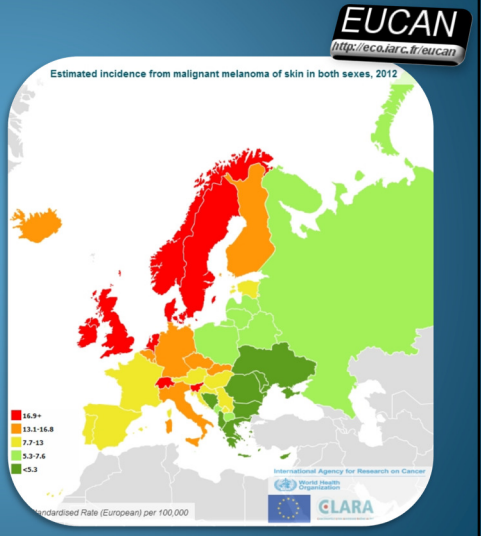
Socialno-ekonomski vpliv



Zemljevid kožnega melanoma po voliščih; prostorsko glajeni standardizirani količniki incidence, Slovenija 2005-2014.

Incidenca

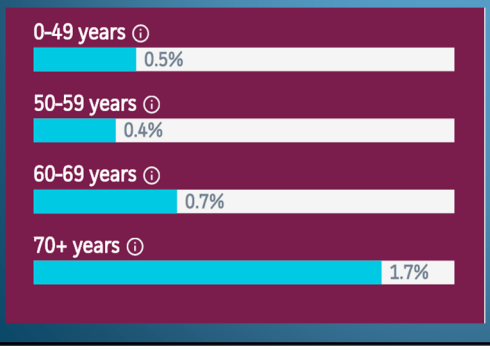
- ‘‘suggest that the melanoma epidemic is real and not simply an artefact of increased detection pressure of earlier-stage T1/T2 lesions’’



Skin Cancer: Epidemiology, Disease Burden, Pathophysiology, Diagnosis, and Therapeutic Approaches. **Apalla** Z, Nashan D, Weller RB, Castellsagué X. Dermatol Ther (Heidelb). 2017 Jan;7(Suppl 1):5-19.

Tveganje

- svetlopolti → 1 izmed 40 (**2.5%**)
- temnopolti → 1 izmed 1000 (**0.1%**)
- ↑ starostjo, ≈ **63 let**



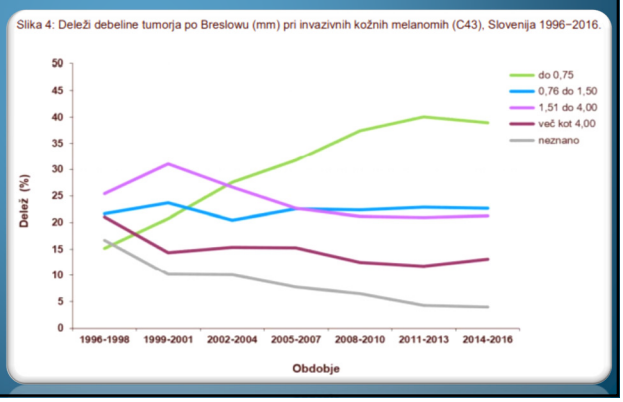
Odrasli 20 -39

- dojka
- limfom (non-Hodgk & Hodgk)
- **melanom**
- sarcoma
- GIN (cerviks in ovarij)
- ščitnica
- testis
- kolorektalni
- leukemija
- CŽS

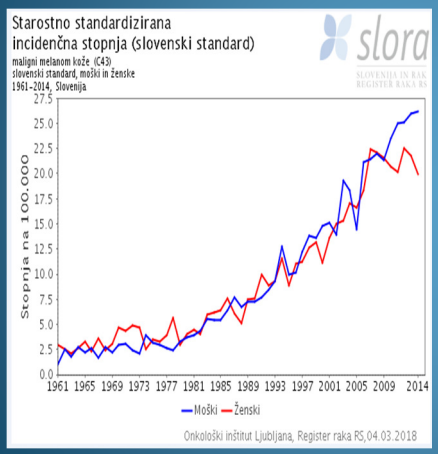
Slovenija

5.612 bolnikov leta 2014

- 62.3% Breslow < 1.5mm
- 12.5% Breslow > 4mm
- 11.3% stadij III



Incidenca

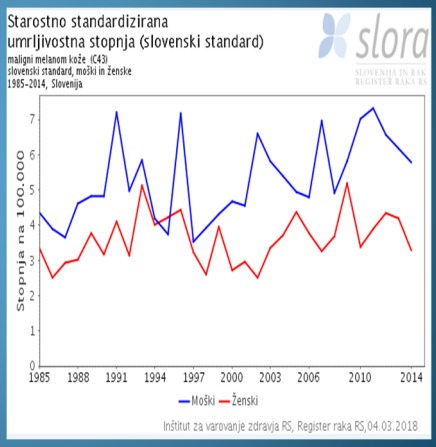


- 9/teden
- 3.8% vseh rakov
- 6.mesto
- tveganje 1.6% do 75 leta
- 24.8/100.000
- delež letne spremembe grobe inc.st. 4.0%

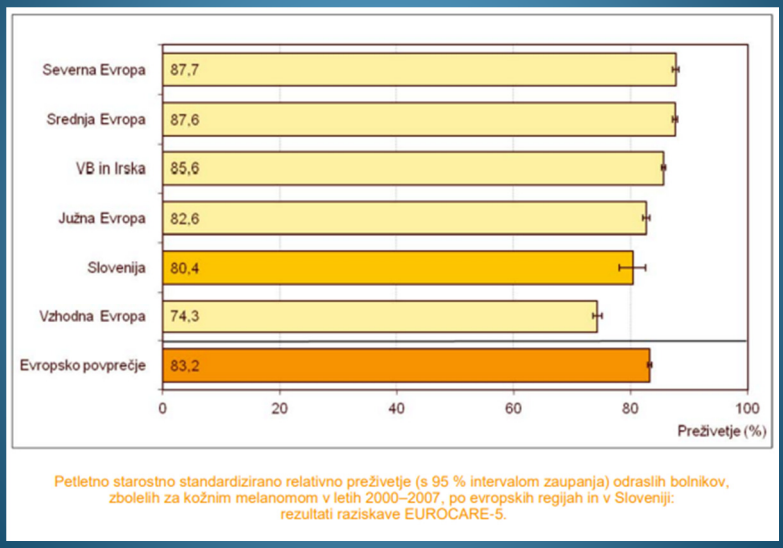
Umrljivost

UMRLJIVOST

- 2/teden
- med vsemi raki 2.1%
- tveganje do 75 leta 0.3%
- 2.9/100.000

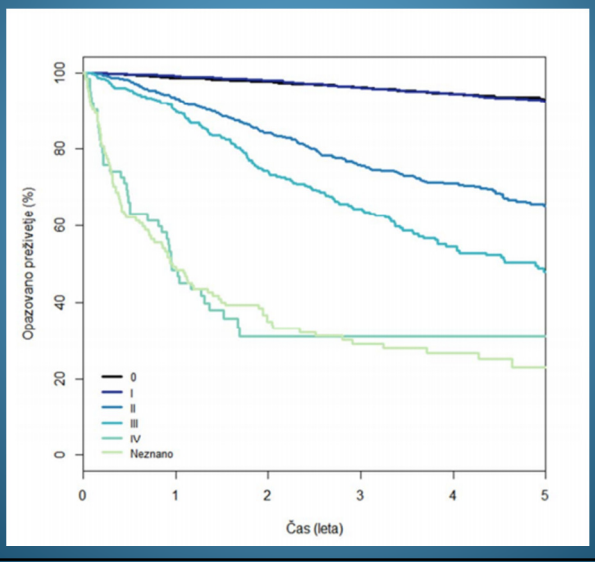


Preživetje



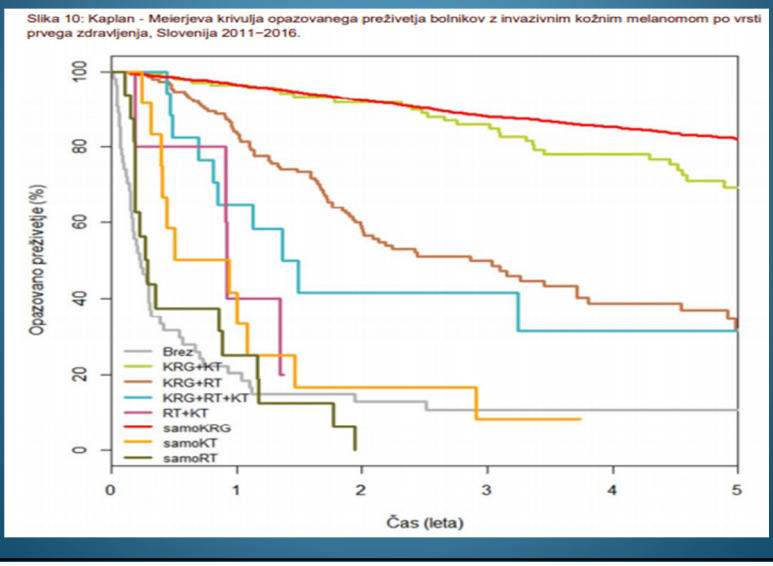
Petletno starostno standardizirano relativno preživetje (s 95 % intervalom zaupanja) odraslih bolnikov, zbolelih za kožnim melanomom v letih 2000–2007, po evropskih regijah in v Sloveniji: rezultati raziskave EUROCARE-5.

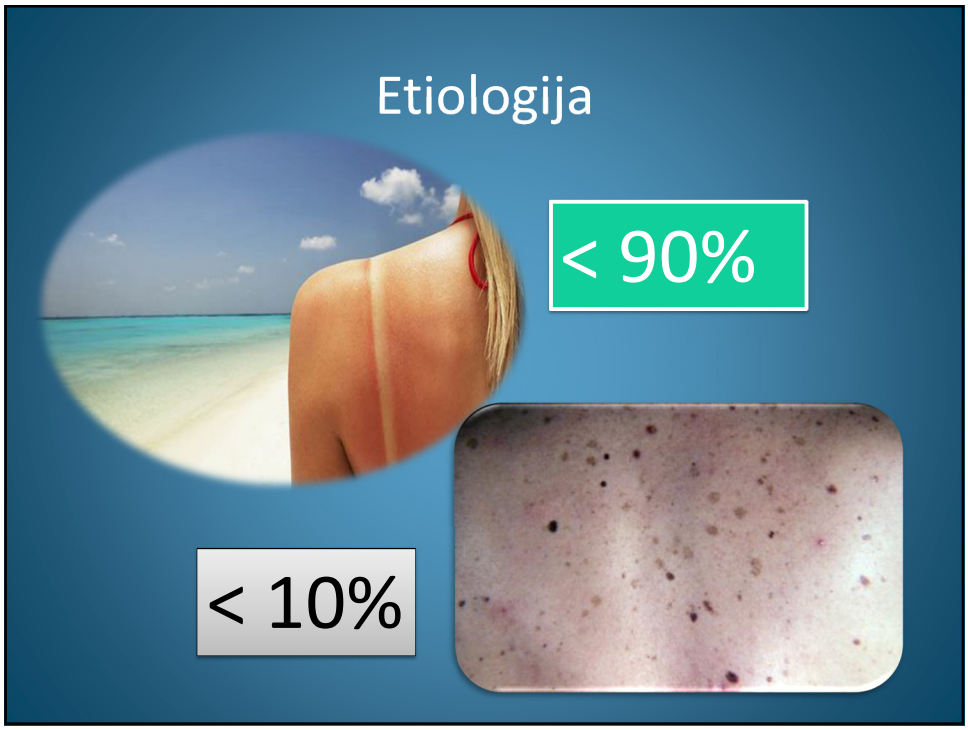
Preživetje po stadiju
Slovenija 2011-2016

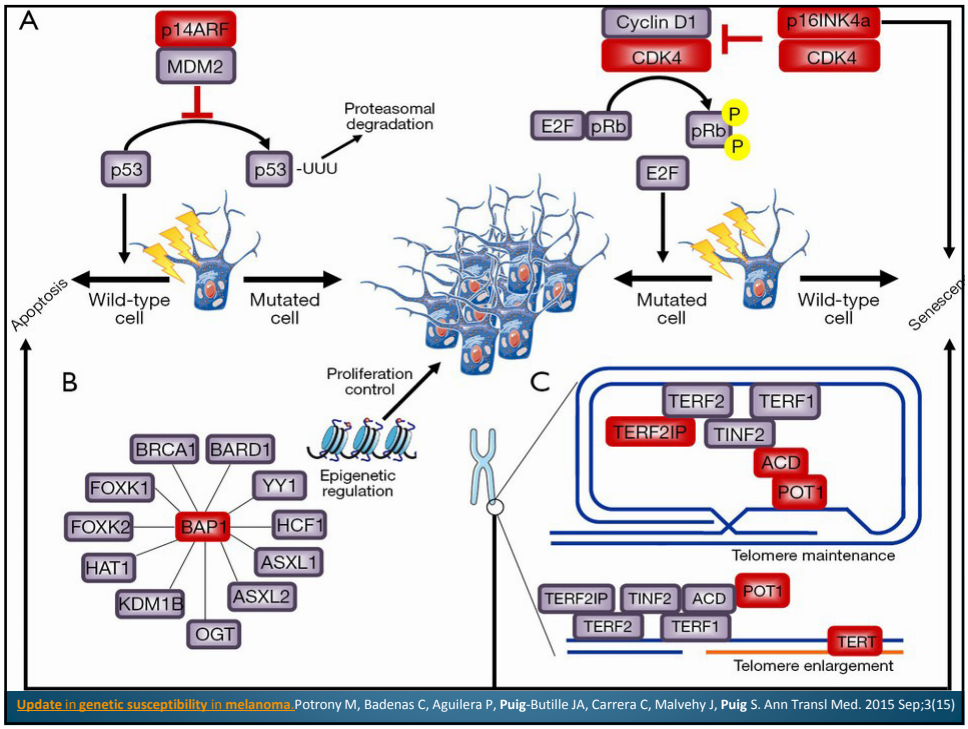


Preživetje
po vrsti prvega zdravljenja

Slika 10: Kaplan - Meierjeva krivulja opazovanega preživetja bolnikov z invazivnim kožnim melanomom po vrsti prvega zdravljenja, Slovenija 2011–2016.

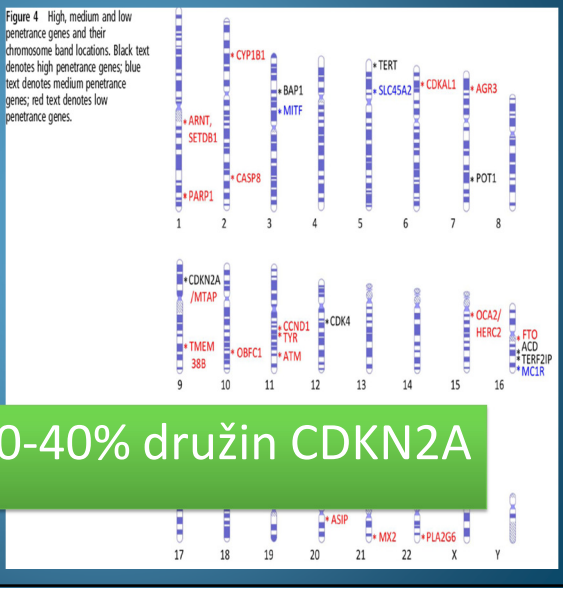



Etiologija
< 90%
< 10%


A
p14ARF
MDM2
p53
p53 -UUU
Proteasomal degradation
Apoptosis
Wild-type cell
Mutated cell
Cyclin D1
CDK4
p16INK4a
CDK4
E2F
pRb
P
P
E2F
Mutated cell
Wild-type cell
Senescen
B
Proliferation control
Epigenetic regulation
BRCA1
BARD1
FOXK1
YY1
FOXK2
BAP1
HCF1
HAT1
ASXL1
KDM1B
ASXL2
OGT
C
TERF2
TERF1
TERF2IP
TINF2
ACD
POT1
Telomere maintenance
TERF2IP
TINF2
ACD
POT1
TERF2
TERF1
TERT
Telomere enlargement
Update in genetic susceptibility in melanoma. Potrony M, Badenas C, Aguilera P, Puig-Butille JA, Carrera C, Malvehy J, Puig S. Ann Transl Med. 2015 Sep;3(15)

Genska predispozicija

- 10% družinska anamneza
- penetranca genov
- 50% pozitivne družinske NE
- drugi raki?
  - pankreas
  - mezoteljom
  - ledvični
  - glioblastom

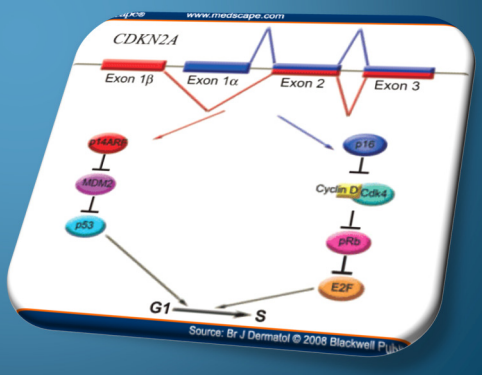


20-40% družin CDKN2A

CDKN2A

- tumor supresor
- p16 in p14ARF
- penetranca ↔ geografska lega

Značilnosti:
- multipli primarni
- > 3 družinski člani,
- pankreas
- zgodnje obolevanje
- Breslow > 0.4 mm



Gensko svetovanje in testiranje

- *„the results influence clinical decisions and treatment can be implemented to prevent or improve clinical outcomes“*
- **! samopregledovanje, zaščita pred soncem, pogostejši pregledi, osveščenost**

Melanoma genetics Read J, Wadt KA, **Hayward** NK. J Med Genet. 2016 Jan;53(1):1-14.

Indikacija

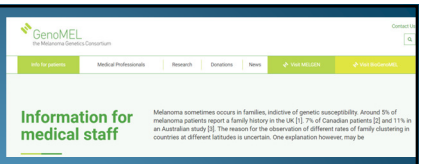
SVETOVANJE	ODVZEM KRVI
• KM 2 sorodnika v prvem kolenu • 2 s KM v družini, če je eden od bolnikov zbolel z več primarnimi KM ali ima sindrom atipičnih nevusov • družina s ≥ 3 sorodniki z KM	• posameznik s ≥ 3 KM • 3 s KM v prvem ali drugem kolenu sorodstva • 2 s KM in bolnik z rakom trebušne slinavke v prvem ali drugem kolenu sorodstva • s KM in 2 bolnika z rakom trebušne slinavke v prvem ali drugem kolenu sorodstva

OI svetovanje in testiranje

- sekvenciranje druge generacije (NGS, Illumina MiSeq DX, panel TruSight Cancer Panel)
- sekvenciranjem po Sangerju
- CDKN2A, CDK4, BAP1, DDB2, ERCC2-5, RB1, WRN, XPA, XPC
- SNPs; MITF, TERT, MC1R

- 2001 – 2017
- 253 pts
- 30 pts CDKN2A
- Gly101Trp → Italija → Kelti
- IVS1-1G>A !!!
- 9 VUS Ala148Thr
- MC1R

Svetovanje



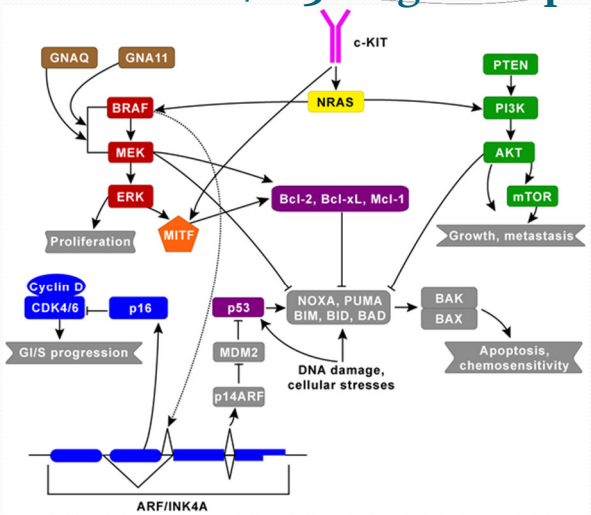
- obisk pri dermatologu (pregled kože skalpa, oralne mukoze, nohtov, genitalij);
  - več kot 50 nevusov, številni atipični nevusi – prvič v 3 mesecih po svetovanju, nato na 6 mesecev
  - več kot 50 nevusov, nesumljivi – na 6 mesecev, če nizko tveganje obiski 1x letno
  - maloštevilni nevusi – prvič po 6 mesecih, nato 1x letno
- 1x mesečno samopregledovanje kože z upoštevanje ABCDE kriterijev, ob odkritju sumljivega znamenja posvet z osebnim zdravnikom
- preprečiti nastanek sončnih opeklin
- v primeru visokega UV indeksa uporabiti zaščitna oblačila
- uporaba zaščitnih krem na delih telesa, katere ne moremo zaščititi z oblačili. Priporočene so tiste z SPF 30 ali več ter UVA in UVB zaščito. Nanašati jih je potrebno vsaki 2 uri, v primeru kopanja pa pogosteje.
- poskrbite za ustrezen vnos vitamina D (200 IU, 5mcg, po 50 letu starosti 400 IU, 10mcg vit D dnevno)

HVALA !

VLOGA BIOMARKERJEV V SISTEMSKEM ZDRAVLJENJU MALIGNEGA MELANOMA

Tanja Mesti

MAPK in AKT/PI3K signalne poti



Vidwans SJ, Flaherty KT, Fisher DE, Tenenbaum JM, Travers MD, et al. (2011) A Melanoma Molecular Disease Model. PLOS ONE 6(3): e18257. doi:10.1371/journal.pone.0018257
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0018257

PLOS ONE TENTH ANNIVERSARY

Molekularni Model Melanoma

Detailed subtypes	Pathway(s)	Key gene / biomarker(s)	Diagnostic technologies	Potentially relevant therapeutics
1.1	MAPK	BRAF	Targeted sequencing	BRAF inhibitors, MEK inhibitors, Hsp90 inhibitors
1.2		BRAF/PTEN	Targeted sequencing & IHC	(BRAF inhibitors) AND (PI3K inhibitors, AKT inhibitors or mTOR inhibitors)
1.3		BRAF/AKT	Targeted sequencing & copy number	(BRAF inhibitors) AND (AKT inhibitors or mTOR inhibitors)
1.4		BRAF/CDK4	Targeted sequencing & copy number/CGH	BRAF inhibitors AND CDK inhibitors
2.1	c-KIT	c-KIT	Targeted sequencing	Gleevec & other c-KIT inhibitors
3.1	GNAQ GNA11	GNAQ	Targeted sequencing	MEK inhibitors
3.2		GNA11	Targeted sequencing	MEK inhibitors
4.1	NRAS	NRAS	Targeted sequencing	MAPK & PI3K pathway inhibitors; Farnesyl transferase inhibitors
5.1	MITF	MITF	Copy number	HDAC inhibitors

Primarni molekularni subtipi

doi:10.1371/journal.pone.0018257.t001

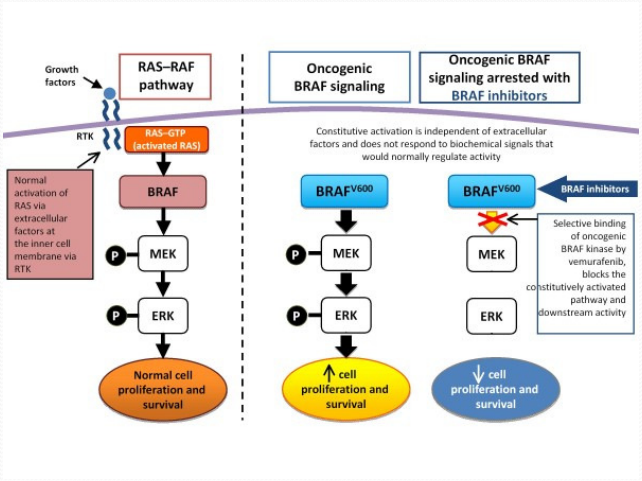
Detailed subtypes	Pathway(s)	Key gene / biomarker(s)	Diagnostic technologies	Potentially relevant therapeutics
6.1	AKT/PI3K	PTEN	IHC	PI3K inhibitors, AKT inhibitors or mTOR inhibitors
6.2		AKT	Copy number	AKT inhibitors or mTOR inhibitors
6.3		PI3K	IHC	PI3K inhibitors, AKT inhibitors or mTOR inhibitors
7.1	CDK	ARF/INK4A	Targeted sequencing / CGH	CDK inhibitors
7.2		CDK4	Copy number / CGH	CDK inhibitors
7.3		CCND1 / Cyclin D1	Copy number / CGH	CDK inhibitors
8.1	P53 / BCL	Bcl-2	IHC	TBD
8.2		P53	Targeted sequencing	TBD

Sekundarni molekularni subtipi

doi:10.1371/journal.pone.0018257.t002

S. J. Vidwans. "A melanoma molecular disease model," PLoS ONE, vol. 6, no. 3, Article ID e18257, 2011

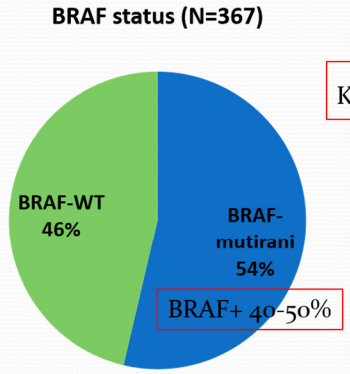
BRAF Signalna Pot



Ascierto et al. Journal of Translational Medicine 2012, 10:85

BRAF testiranje v Sloveniji

Obdobje: april 2013 – december 2017 (367 bolnikov)



Kozni MM UVØ

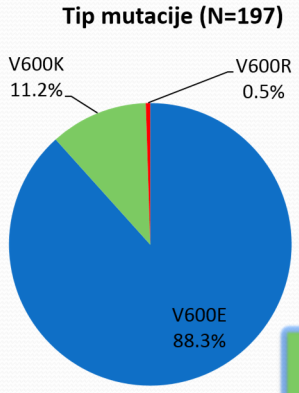
BRAF+ 40-50%

Približno polovica bolnikov z metastatskim melanomom ima tumor z BRAF mutacijo.

Podatki Onkološkega inštituta Ljubljana, marec 2018

Tip BRAF mutacije

Obdobje: april 2013 – december 2017 (197 BRAF+ bolnikov)



Najbolj pogosta je mutacija BRAF V600E.

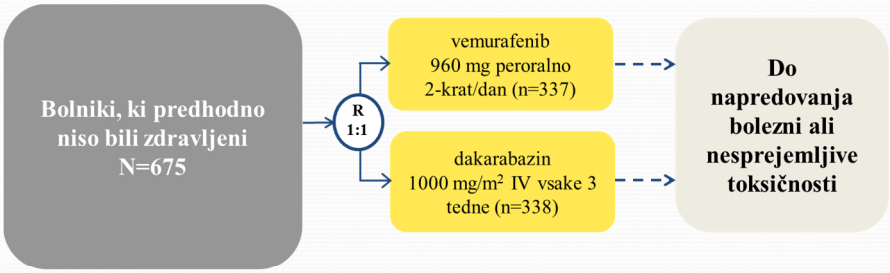
Izidi zdravljenja pri mutaciji BRAF V600K so nekoliko boljši v primerjavi z mutacijo V600E.

V600E: Val/Glu
V600K: Val/Liz
V600R: Val/Arg

Podatki Onkološkega inštituta Ljubljana, marec 2018

McArthur GA, et al. *Lancet Oncol* 2014;15(3):323–32.

BRIM3: registracijska raziskava faze III pri bolnikih z metastatskim melanomom, s potrjeno mutacijo BRAF V600



Primarni opazovani dogodek:

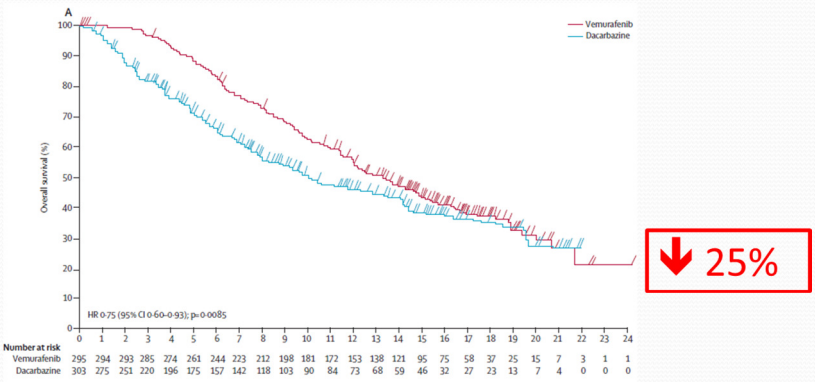
- preživetje brez napredovanja bolezni,
- celokupno preživetje.

Sekundarni opazovani dogodki:

- potrjen odziv na zdravljenje,
- trajanje odziva,
- čas do odziva,
- varnost.

Chapman PB, et al. *N Engl J Med* 2011;364:2507–16.
McArthur GA, et al. *Lancet Oncol* 2014;15(3):323–32.

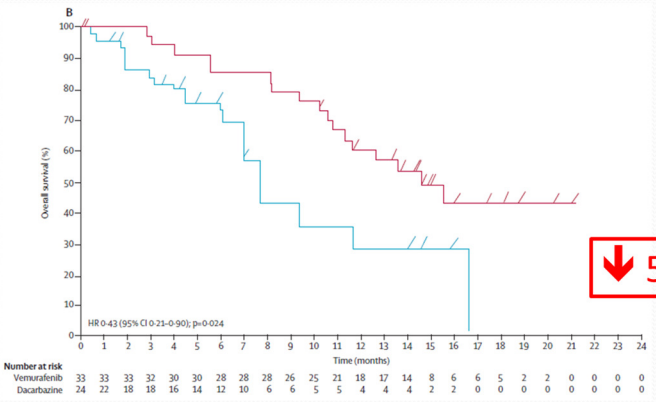
OS – v podskupini BRAF V600E v raziskavi BRIM-3



	BRAF^{V600E}	
	dakarbazin (n=303)	vemurafenib (n=295)
mediana OS (meseci)	10,0	**13,3**
Razmerje ogroženosti HR (95% IZ)	0,75 (0,60–0,93) p=0,0085	

McArthur GA, et al. *Lancet Oncol* 2014;15(3):323–32.

OS – v podskupini BRAF V600K v raziskavi BRIM-3



57%

	BRAF^{V600K}	
	dakarbazin (n=24)	**vemurafenib (n=33)**
mediana OS (meseci)	7,6	**14,5**
Razmerje ogroženosti HR (95% IZ)	0,43 (0,21–0,90) p=0,024	

McArthur GA, et al. *Lancet Oncol* 2014;15(3):323–32.

coBRIM (GO28141): vemurafenib + kobimetinib v primerjavi s samostojnim zdravljenjem z vemurafenibom pri BRAF V600-mutiranem metastatskem melanomu

- neresektabilni ali metastatski melanom (n = 495)
- *BRAF*^{V600} mutacija (cobas® 4800)
- brez predhodne sistemske terapije za napredovalo bolezen
- ECOG PS 0/1

1:1 ®

vemurafenib 960 mg 2x/dan × 28 dni (dnevi 1-28) + **kobimetinib** 60 mg 1x/dan × 21 dni (dnevi 1-21)

Stratifikacija:
- geografska regija,
- obseg bolezni (M1c / ostalo).

vemurafenib 960 mg 2x/dan × 28 dni (dnevi 1-28) + **placebo**

Napredovanje bolezni, nesprejemljiva toksičnost ali umik soglasja

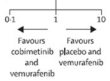
Primarni opazovani dogodek:
Preživetje brez napredovanja bolezni po oceni raziskovalcev

Sekundarni opazovani dogodki:
Celokupno preživetje, celokupni odziv, trajanje odziva, preživetje brez napredovanja bolezni po oceni neodvisne komisije, prenosljivost, farmakokinetika, kakovost življenja (QLQ-C30 and EQ-5D)

ECOG - Eastern Cooperative Oncology Group; PS - performance status (stanje zmogljivosti);
QLQ - quality-of-life questionnaire; ® - randomizacija.
Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

coBRIM: PFS – analiza podskupin

	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)		Hazard ratio (95% CI)
	Events (n)/ total (N)	Median progression-free survival, months (95% CI)	Events (n)/ total (N)	Median progression-free survival, months (95% CI)	
Disease stage IIIC/M1a/M1b, or M1c					
M1c	128/153	5·5 (3·9–5·8)	94/146	9·5 (7·9–12·9)	0·52 (0·40–0·68)
Unresectable stage IIIC/M1a/M1b	52/95	11·0 (7·8–15·0)	49/101	13·4 (11·2–NE)	0·73 (0·49–1·08)
Age group (years)					
<65	128/179	7·2 (5·7–7·6)	107/183	12·6 (9·3–14·7)	0·61 (0·47–0·79)
≥65	52/69	5·6 (3·9–9·4)	36/64	11·2 (8·6–16·5)	0·52 (0·34–0·80)
Sex					
Women	72/108	7·5 (5·7–9·2)	52/101	12·9 (10·0–18·4)	0·57 (0·40–0·82)
Men	108/140	5·7 (5·5–7·4)	91/146	11·1 (9·0–13·0)	0·58 (0·44–0·77)
Geographical region					
Australia/New Zealand/Israel	26/38	7·4 (3·7–12·0)	20/40	13·3 (10·0–18·7)	0·57 (0·32–1·03)
Europe	138/184	6·0 (5·6–7·5)	107/182	11·2 (9·2–14·8)	0·58 (0·45–0·75)
North America	16/26	7·5 (6·0–11·0)	16/25	11·2 (5·5–14·9)	0·57 (0·28–1·17)
ECOG performance status					
0	110/164	7·6 (7·0–9·3)	100/184	12·9 (9·7–15·0)	0·65 (0·49–0·85)
1	66/80	5·5 (4·1–6·0)	41/58	10·6 (7·8–13·6)	0·53 (0·35–0·78)
Lactate dehydrogenase concentration					
Raised	85/104	5·4 (3·9–5·8)	78/112	8·2 (7·3–10·6)	0·57 (0·42–0·78)
Normal	90/138	7·8 (7·3–10·9)	65/130	13·4 (12·0–16·5)	0·59 (0·43–0·81)
Previous adjuvant therapy					
Yes	16/24	7·2 (4·8–16·7)	12/24	16·5 (8·2–NE)	0·60 (0·28–1·27)
No	164/224	7·2 (5·6–7·6)	131/223	11·2 (9·3–13·4)	0·59 (0·47–0·74)
***BRAF*^{V600} mutation status**					
V600E	126/174	7·2 (5·6–7·7)	102/170	10·6 (9·0–13·0)	0·64 (0·49–0·83)
V600K	24/32	6·0 (3·8–9·5)	14/24	12·4 (9·0–NE)	0·52 (0·27–1·02)
Overall*	**180/248**	**7·2 (5·6–7·5)**	**143/247**	**12·3 (9·5–13·4)**	**0·59 (0·47–0·73)**



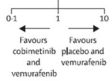
36% V600E

48% V600K

PFS – preživetje brez napredovanja bolezni (progression free survival); HR – razmerje ogroženosti (hazard ratio); CI – interval zaupanja (confidence interval)
Ascierto PA et al. *Lancet Oncol* 2016; 17:1248-1260.

coBRIM: OS – analiza podskupin

	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)		Hazard ratio (95% CI)
	Events (n)/ total (N)	Median overall survival, months (95% CI)	Events (n)/ total (N)	Median overall survival, months (95% CI)	
Disease stage IIIC/M1a/M1b, or M1c					
M1c	106/153	14·8 (11·3–17·0)	80/146	18·9 (16·2–22·3)	0·65 (0·48–0·87)
Unresectable stage IIIC/M1a/M1b	35/95	NE (23·3–NE)	34/101	NE (24·1–NE)	0·83 (0·52–1·33)
Age group (years)					
<65	99/179	18·3 (16·1–23·2)	85/183	22·1 (19·4–NE)	0·75 (0·56–1·01)
≥65	42/69	14·7 (10·1–18·4)	29/64	24·1 (17·6–NE)	0·56 (0·35–0·91)
Sex					
Women	54/108	22·7 (17·4–NE)	40/101	NE (21·7–NE)	0·72 (0·48–1·08)
Men	87/140	15·0 (12·3–17·5)	74/146	21·1 (17·6–NE)	0·66 (0·48–0·90)
Geographical region					
Australia/New Zealand/Israel	16/38	23·0 (16·7–27·8)	13/40	NE (20·7–NE)	0·71 (0·34–1·48)
Europe	111/184	16·1 (12·6–18·4)	87/182	22·8 (19·1–NE)	0·67 (0·51–0·89)
North America	14/26	22·7 (15·9–24·9)	14/25	19·2 (12·1–NE)	0·95 (0·45–2·00)
ECOG performance status					
0	83/164	19·8 (17·4–27·8)	83/184	23·8 (20·3–NE)	0·80 (0·59–1·09)
1	56/80	11·7 (9·1–15·9)	28/58	21·8 (13·3–NE)	0·53 (0·34–0·84)
Lactate dehydrogenase concentration					
Raised	70/104	11·2 (7·9–16·1)	73/112	14·8 (11·3–18·6)	0·77 (0·56–1·07)
Normal	66/138	23·3 (18·3–NE)	41/130	NE (NE–NE)	0·59 (0·40–0·87)
Previous adjuvant therapy					
Yes	13/24	19·1 (16·1–NE)	10/24	NE (12·3–NE)	0·76 (0·33–1·75)
No	128/224	17·4 (14·1–19·8)	104/223	22·3 (19·4–NE)	0·69 (0·53–0·89)
***BRAF*^{V600} mutation status**					
V600E	101/174	17·5 (14·7–20·5)	82/170	21·9 (18·1–NE)	0·73 (0·55–0·98)
V600K	17/32	16·7 (11·7–NE)	11/24	24·1 (12·6–NE)	0·79 (0·37–1·69)
Overall*	**141/248**	**17·4 (15·0–19·8)**	**114/247**	**22·3 (20·3–NE)**	**0·70 (0·54–0·89)**



27% V600E

21% V600K

OS – celokupno preživetje (overall survival); HR – razmerje ogroženosti (hazard ratio); CI – interval zaupanja (confidence interval)
Ascierto PA et al. *Lancet Oncol* 2016; 17:1248-1260.

OS – ni povezave med OS in biološkimi označevalci ob izhodišču (Ki67, pERK, pS6)

	Placebo and vemurafenib (n=248)		Cobimetinib and vemurafenib (n=247)	
Ki67				
>20%	66/140 (47%)	14·9 (9·5–19·1)	79/150 (53%)	21·6 (17·0–NE)
≤20%	74/140 (53%)	19·8 (13·3–NE)	71/150 (47%)	21·5 (18·1–NE)
HR of high vs low	NA	1·45 (0·94–2·25)	NA	0·95 (0·60–1·49)
pERK				
H-score >40	78/154 (51%)	14·9 (11·9–22·7)	81/165 (49%)	NE (18·3–NE)
H-score ≤40	76/154 (49%)	17·1 (12·6–24·9)	84/165 (51%)	21·1 (15·3–NE)
HR of high vs low H-score	NA	1·09 (0·72–1·66)	NA	0·75 (0·48–1·17)
pS6				
H-score >71	82/158 (52%)	19·1 (12·6–24·9)	80/167 (48%)	19·2 (16·2–NE)
H-score ≤71	76/158 (48%)	15·4 (11·9–20·5)	87/167 (52%)	24·1 (18·3–NE)
HR of high vs low H-score	NA	0·80 (0·53–1·21)	NA	1·14 (0·74–1·76)

Data are n/N (%), median overall survival in months (95% CI) or HR (95% CI). NE=not estimable. HR=hazard ratio. NA=not applicable. *Biomarker status is based on population median.

Table 4: **Overall survival by baseline biomarker status* (data cutoff Aug 28, 2015)**

OS – celokupno preživetje (overall survival); HR – razmerje ogroženosti (hazard ratio); CI – interval zaupanja (confidence interval)
Ascierto PA et al. *Lancet Oncol* 2016; 17:1248-1260.

COMBI-d: dizajn

- *BRAF* V600E/K
- Unresectable stage IIIC/IV
- Treatment naive
- ECOG PS 0/1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification
- *BRAF*-mutant (V600E vs K)
- LDH (> ULN vs ≤ ULN)

Primary Analysis (PFS) [213 events] Aug 2013

Final Analysis (OS) [222 deaths] Jan 2015

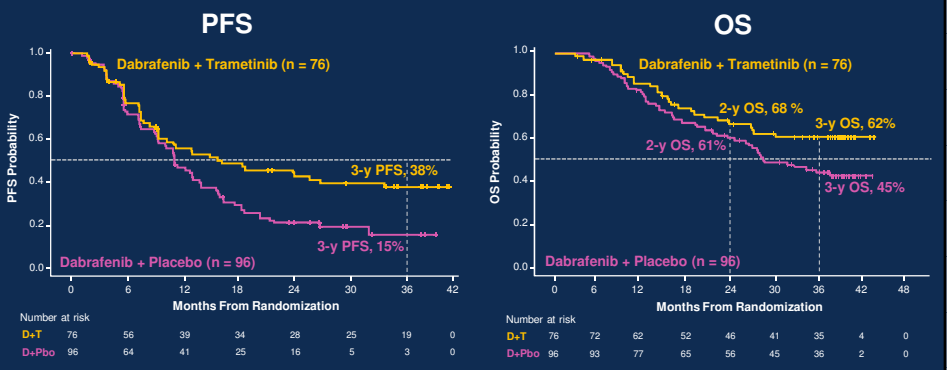
Dabrafenib + trametinib
150 mg BID + 2 mg QD
n = 211

Dabrafenib + placebo
150 mg BID + placebo QD
n = 212

Pre-planned interim OS [95 events]

Presented by: Keith T. Flaherty, MD

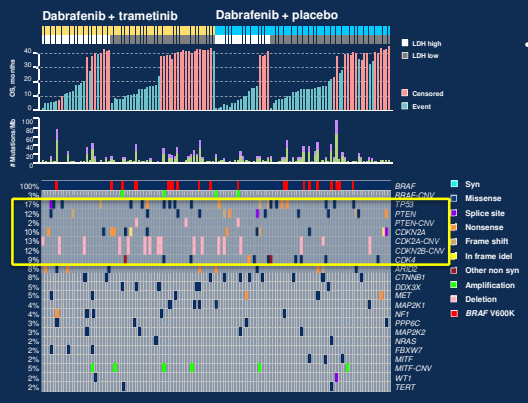
COMBI-d: Normalen LDH in < 3 metastatskih lokacij



PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Keith T. Flaherty, MD

COMBI-d: Genomski podpis

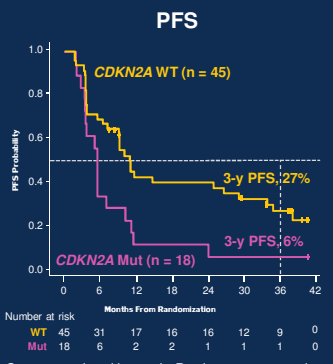


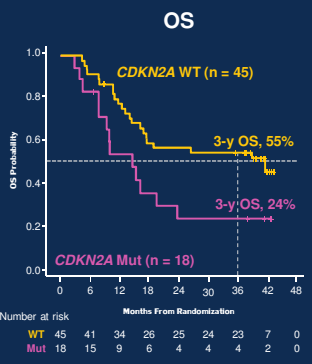
- Genomic landscape showed alterations in:
  - Previously identified recurrently mutated melanoma genes (*TP53, PTEN, CDKN2A, CTNNB1*)
  - MAPK-pathway inhibition resistance genes (*MAP2K1, MAP2K2, NF1, MITF*)

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Keith T. Flaherty, MD

COMBI-d: *CDKN2A* delecija v Dabrafenib + Trametinib roki





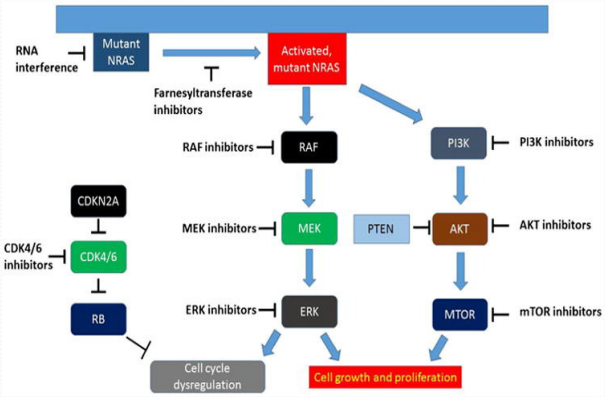
[a] Cox proportional hazards *P* value; +, censored.

- *CDKN2A* mutation and deletion were significantly associated with poorer OS ($P = 0.027$[a]) and PFS ($P < 0.001$[a])
- Preclinical data suggest that combination with CDK4/6 inhibitors could be a beneficial strategy
- Higher overall mutation rate[a] was associated with longer OS in the dabrafenib + trametinib arm ($P = 0.06$,[b] $P = 0.01$[c])
- No significant association with PFS was detected ($P = 0.3$)

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Keith T. Flaherty, MD

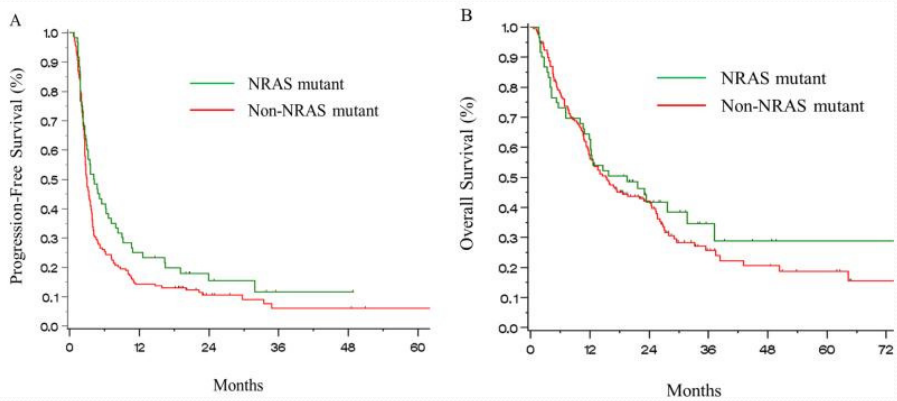
NRAS



- Kožni MM UV + 15 – 20%
- NRAS Ø BRAF

Johnson DB et al. Cancer Immunol Res. 2015 Mar; 3(3): 288–295

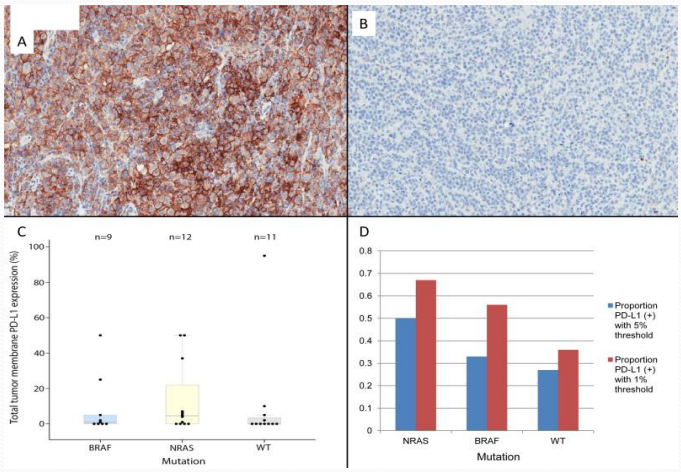
NRAS/Imunoterapija



Kaplan-Meier krivulje (A) Čas do progresa in (B) Celotno preživetje ob imunoterapiji v prvem redu zdravljena za NRAS-mutirane in NRAS-nemutirane skupine

Johnson DB et al. Cancer Immunol Res. 2015 Mar; 3(3): 288–295

Ekspresija PD-L1 glede na prisotnost BRAF, NRAS mutacij



Panel A shows an NRAS-mutant melanoma sample with strongly positive expression (~50% of cells); Panel B shows a WT melanoma with <1% of cells with PDL1 expression. Panel C shows the distribution of PD-L1 staining by genotype. Panel D shows number of samples evaluated by genotype and whether they were positive for PD-L1 expression (≥5%) or negative (<5%).

Johnson DB et al. Cancer Immunol Res. 2015 Mar; 3(3): 288–295

NRAS/MEK162 zaviralec

	Full analysis set		Analysis set for response rate*	
	NRAS 45 mg (n=30)	*BRAF* 45 mg (n=41)	*NRAS* 45 mg (n=28)	*BRAF* 45 mg (n=35)
CR	0	0	0	0
Total PR	6 (20%)	8 (20%)	6 (21%)	8 (23%)
Confirmed PR	3 (10%)	2 (5%)	3 (11%)	2 (6%)
Unconfirmed PR	3 (10%)†	6 (15%)‡	3 (11%)†	6 (17%)‡
Overall response rate (CR or confirmed PR)	3 (10%)	2 (5%)	3 (11%)	2 (6%)
Stable disease	13 (43%)	13 (32%)	13 (46%)	13 (37%)
Progressive disease	9 (30%)	12 (29%)	9 (32%)	12 (34%)
Unknown§	2 (7%)	8 (20%)	0 (0%)	2 (6%)
Disease control rate (CR, PR, or SD)	19 (63%)	21 (51%)	19 (68%)	21 (60%)

Data are n (%). CR=complete response. PR=partial response. SD=stable disease. *Includes only patients who had two CT scans available for assessment of response; we excluded two patients in the *NRAS* group who were not enrolled for enough time to assess efficacy and were in follow-up at time of data cutoff (at the next available CT scan after data cutoff, one of these patients had SD and one had PD); six patients in the *BRAF* group were excluded because of death (two patients), discontinuation due to an adverse event (three), and withdrawn consent (one). †One patient had progressive disease, one had an adverse event, and one was too early to confirm (PR was confirmed at the next available CT scan after data cutoff). ‡Three patients had PD and three had an adverse event. §Unknown response in non-target lesion or because target lesions were not measured.

Table 4: Clinical activity

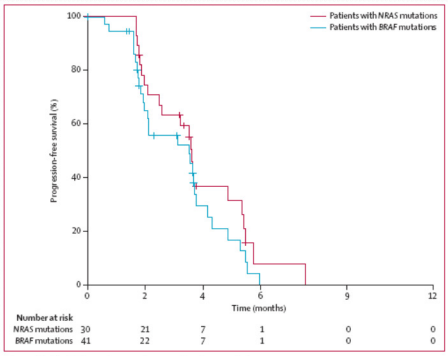


Figure 2: Kaplan-Meier estimates of progression-free survival
22 patients had documented events in the *NRAS*-mutation group; 26 patients had documented events in the *BRAF*-mutation group. 20 patients were censored (12 patients in the *BRAF* group and eight patients in the *NRAS* group) because either consent was withdrawn (two patients in the *BRAF* group), the patient started new treatment (nine patients in the *BRAF* group and one in the *NRAS* group), analysis was ongoing at the time of data cutoff (six patients in the *NRAS* group), or no follow-up data were available (one patient in the *BRAF* group and one patient in the *NRAS* group).

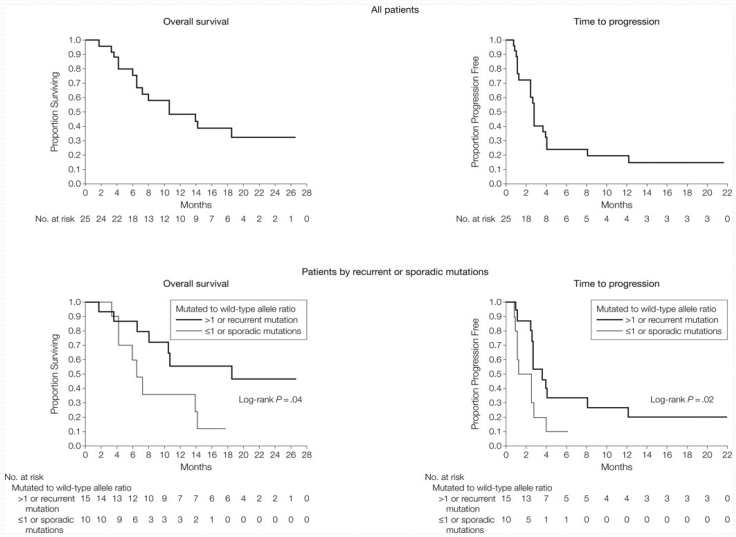
Ascierto PA et al. Lancet Oncol 2013; 14: 249–56

cKit

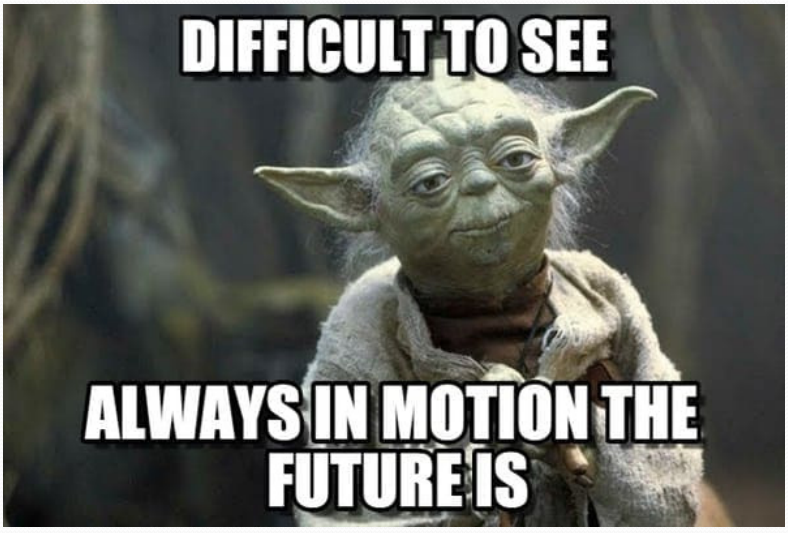
- 3% MM:
  - mukoznih
  - akralnih
  - kožni MM UV Ø

Carvajal RD et al. JAMA. 2011 Jun 8; 305(22): 2327–2334.

Imatinib



Carvajal RD et al. JAMA. 2011 Jun 8; 305(22): 2327–2334.



Slikovne preiskave pri bolnikih z malignim melanomom

asist dr. Maja Mušič, spec. radiologije

Oddelek za radiologijo, OI

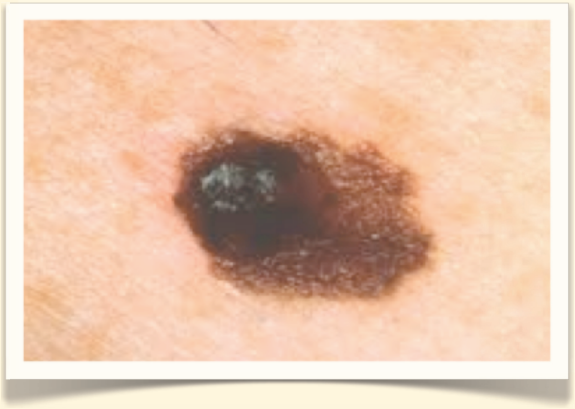
marec 2018

Slikovne preiskave pri MM

1. Preiskave pri zamejitvi bolezni
2. Slikovne metode pri sumu na progres
3. Sledenje , ocena učinka terapije

Klinično jasni MM

- Diagnostična ekscizija pigmentne lezije z varnostnim robom 2- 5 mm + biosija varovalne bezgavke



- Radikalna ekscizija +/- disekcija bezgavčne lože

Hočevar in sod. Klinična pot.. OI, 2010

Pomen UZ preiskave

- Zamejitev bolezni ob odkritju

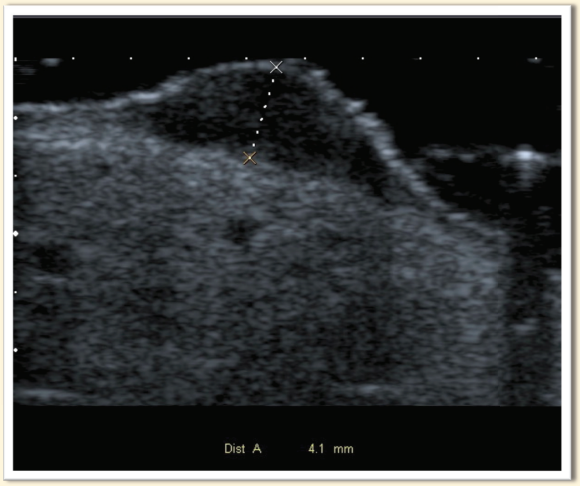
  UZ preiskava primarne lezije

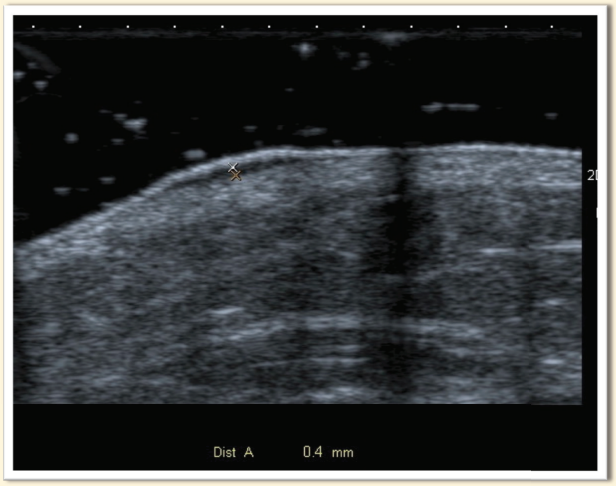
  UZ preiskava regionalne bezgavčne lože

- Follow – up
- Ponovitev bolezni

Harland C.C. et all., Br J Dermatol, 2000.
Binder M., et al., Eur J Cancer, 1997

UZ – primarni MM

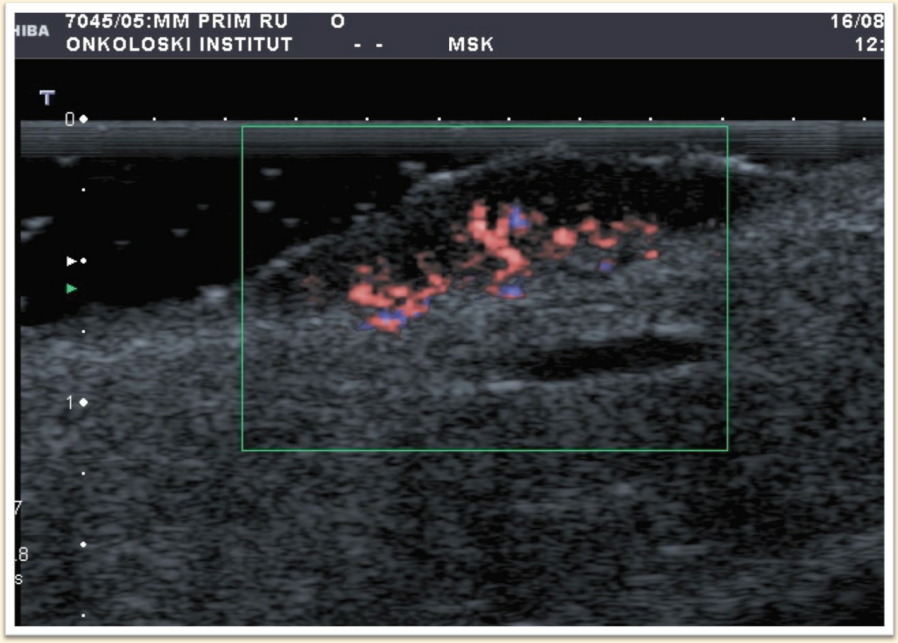




4 mm 0.4 mm

UZ izgled MM

Primarni MM - prekrvavitev



UZ- primarni MM

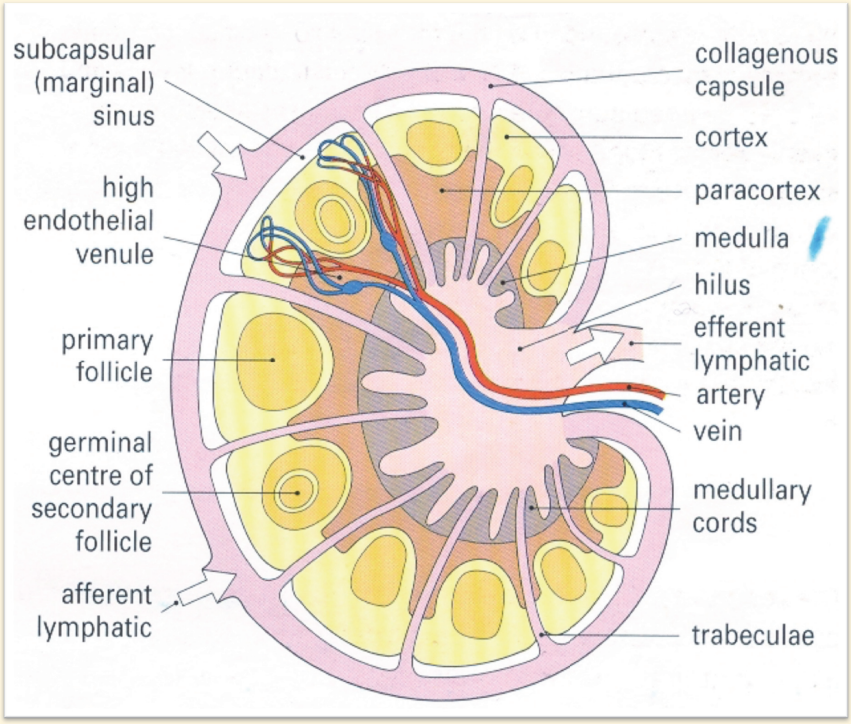
- UZ-preiskava primarne pigmentne lezije ne more nadomestiti kliničnega pregleda.
- Na UZ-preiskavo naj bodo napoteni le bolniki, ki imajo po dermoskopskem pregledu PKL, sumljivo za MM
- UZ-izmera debeline primarnega MM je objektivna metoda z visoko ponovljivostjo med različnimi preiskovalci.
- **Dermoskopija in UZ nista metodi, s katerima lahko vedno razlikujemo benigne pigmentne lezije od MM.**

Mušič M; Pomen UZ preiskave…, Doktorska disert. 2010

UZ bezgavčne lože

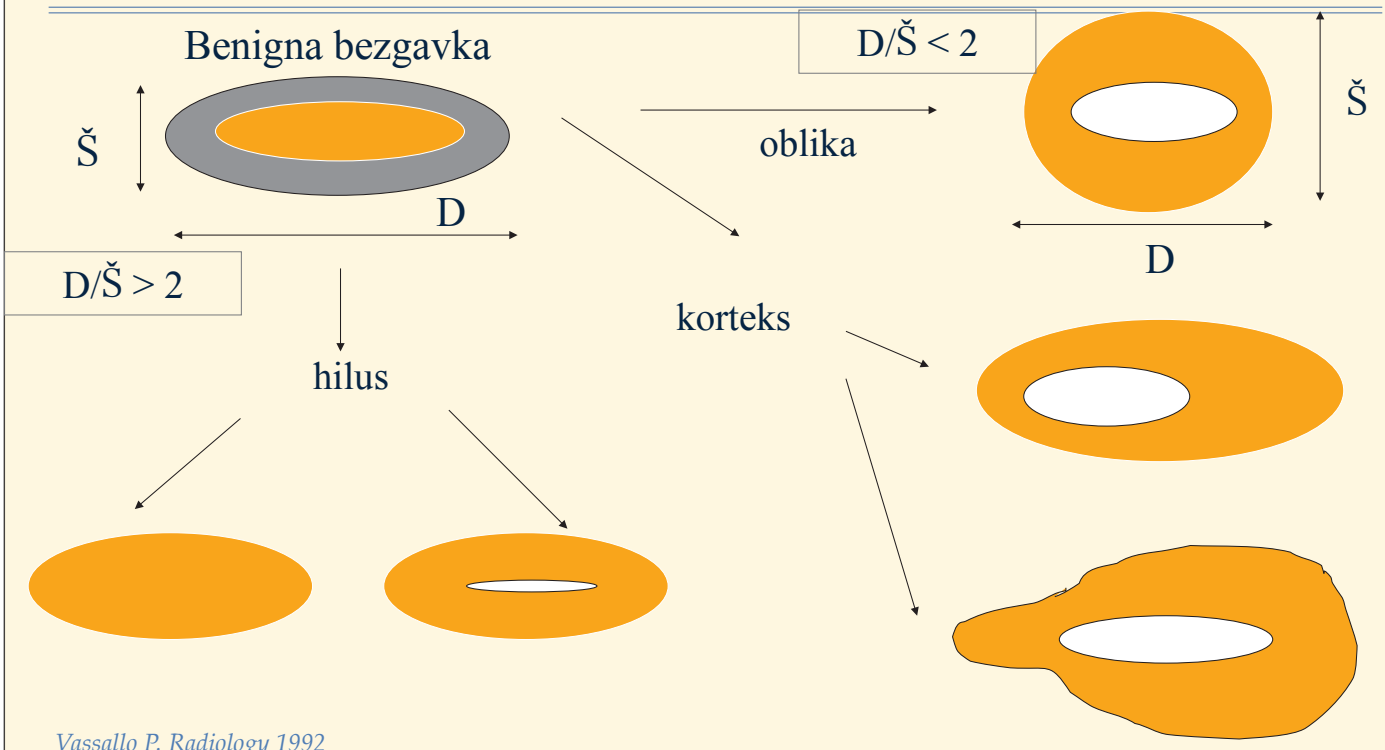
- Neinvazivna metoda
- Relativno poceni
- Dostopna
- Izmerimo največji premer bezgavke
- Odvisna od izvajalca

Reaktivna bezgavka



Roit: Immunology 2000

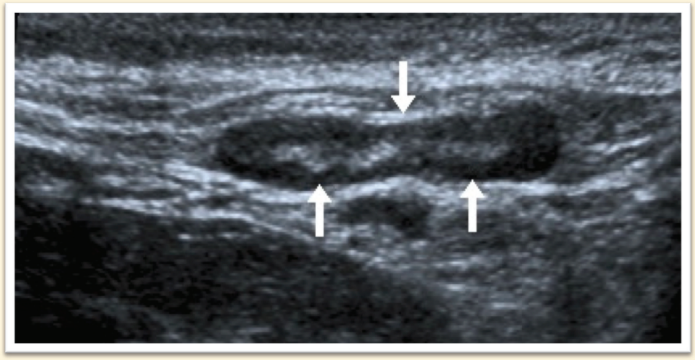
Spremembe v bezgavkah

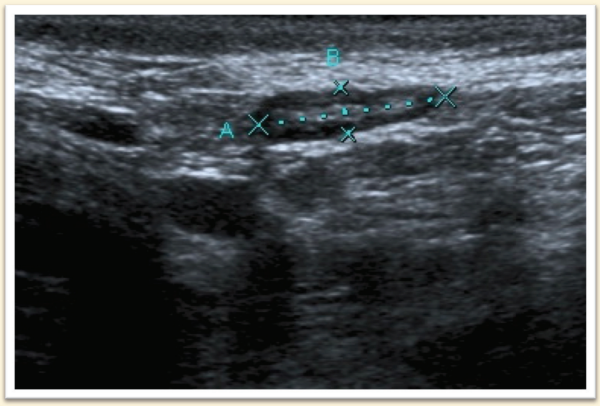


Vassallo P. Radiology 1992

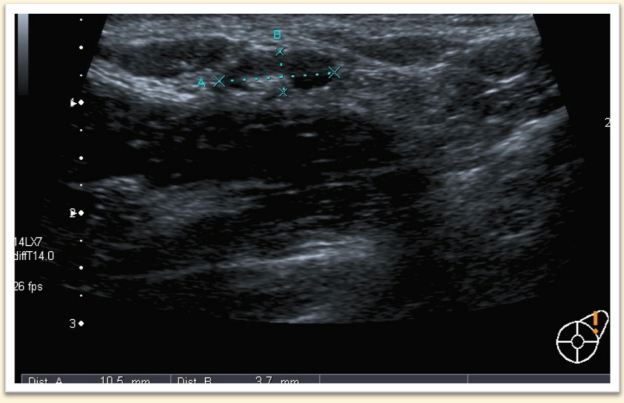
UZ- Benigna bezgavka

- Razmerje dolžina / širina > 2
- Hiperehogen hilus
- Hilusni tip prekrvavitve

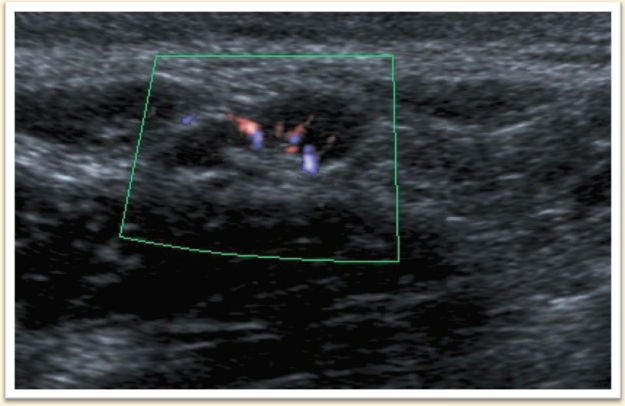




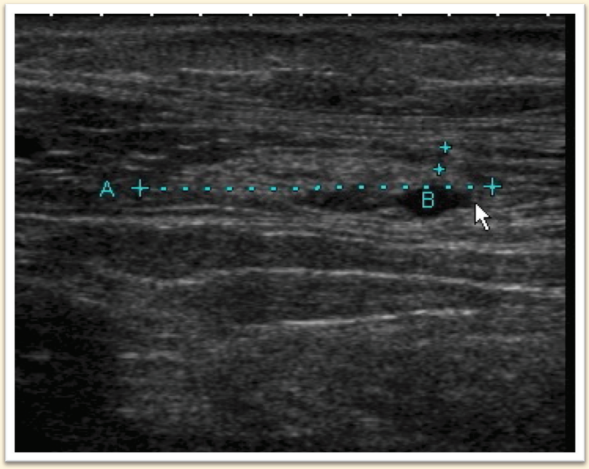
Benigna bezgavka - UZ

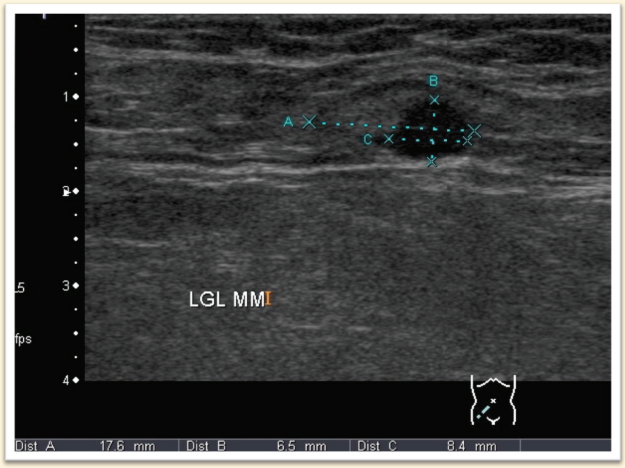


Hilusni tip prekrvavitve

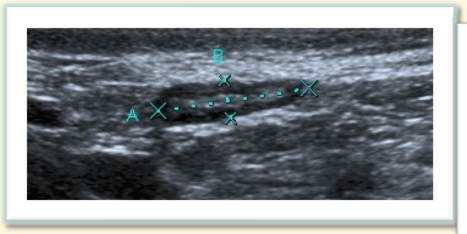


Maligna bezgavka

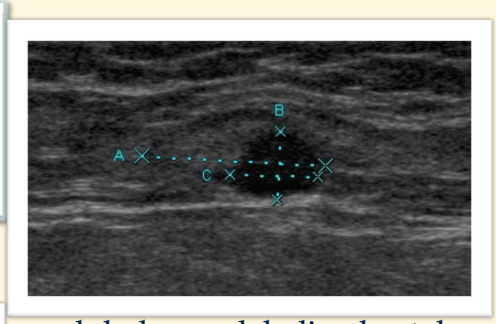




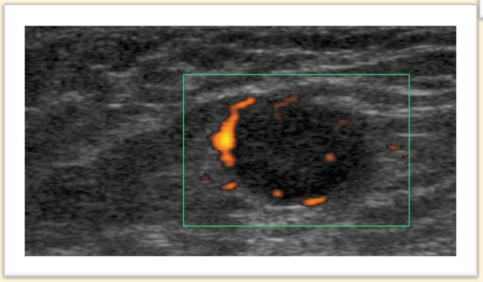
Maligna bezgavka



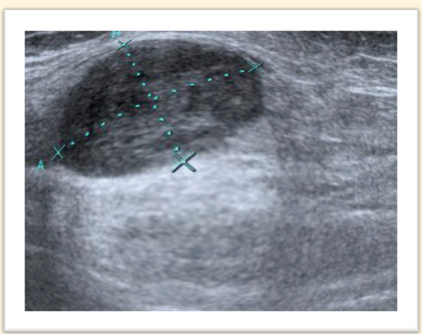
reaktivna bezgavka



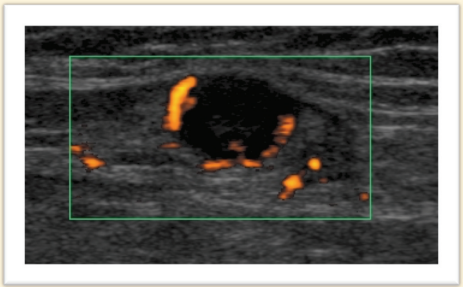
lokalno zadebeljen korteks



asimetričen hilus



spremenjeno razmerje D/Š



periferna prekrvavitev

UZ- bezgavčna loža

- **Občutljivost UZ preiskave**, da prepozna zasevke v VB je 24%
- **Specifičnost** 88%
- Pozitivna napovedna vrednost 45%
- Negativna napovedna vrednost 76%

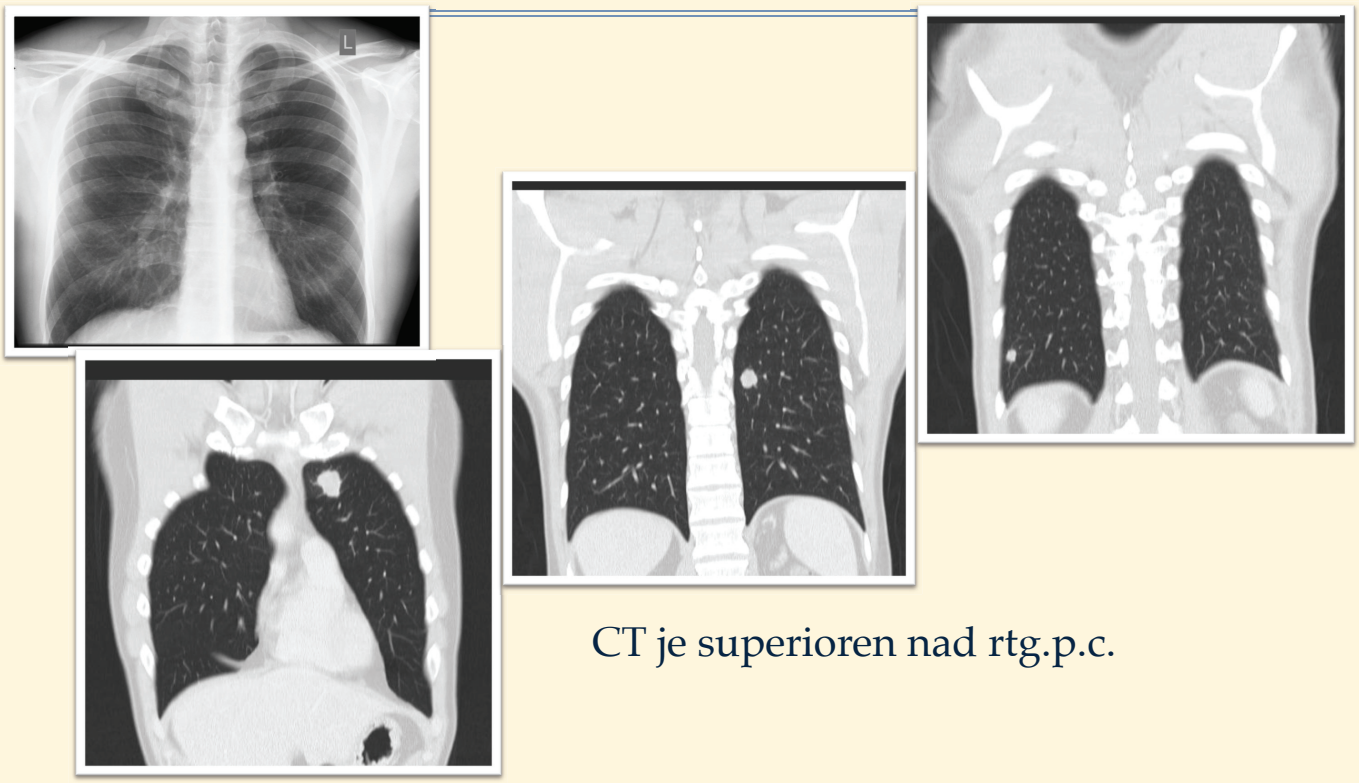
- **Občutljivost UZ- TIAB, da v UZ spremenjeni bezgavki** prepozna zasevek je 58%
- Specifičnost 100%
- Pozitivna napovedna vrednost 100%
- Negativna napovedna vrednost 78%

1.Slikovne preiskave za zamejitev MM

STADIJ	Preiskave za zamejitev bolezni
stadij 0, IA IB, IIA, IIB	zamejitvene preiskave niso potrebne rtg, UZ (bezgavčne lože, trebuha), c.p opravimo samo ob simptomih
II C (MM > 4mm, N0)	UZ bezgavčne lože in trebuha, rtg p.c.
IIIA (N1..)	rtg p.c., UZ/ CT trebuha
IIIB, C	CT prsnega koša + trebuha ali PET/CT
IV (brez možganskih zasevkov)	CT prsnega koša + trebuha ali PET/CT

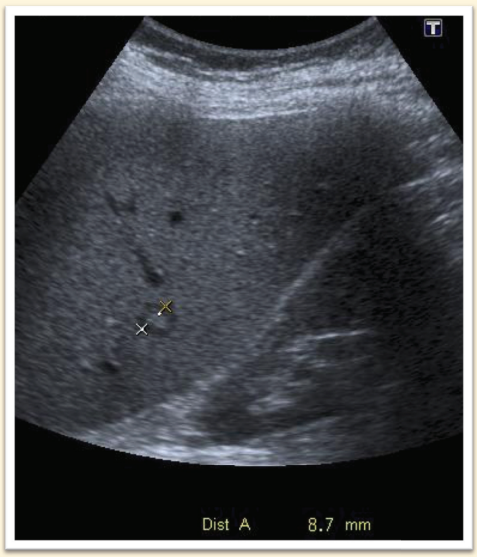
Hočevar M, in sod : Smernice in klin. pot…., 2010

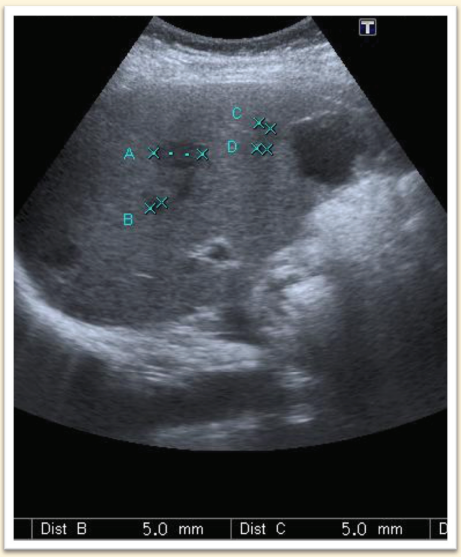
Pljuča



CT je superioren nad rtg.p.c.

UZ preiskava trebuha - MM

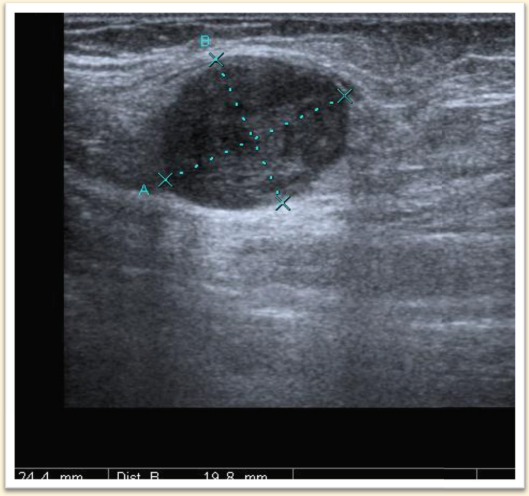




UZ – jetrne metastaze

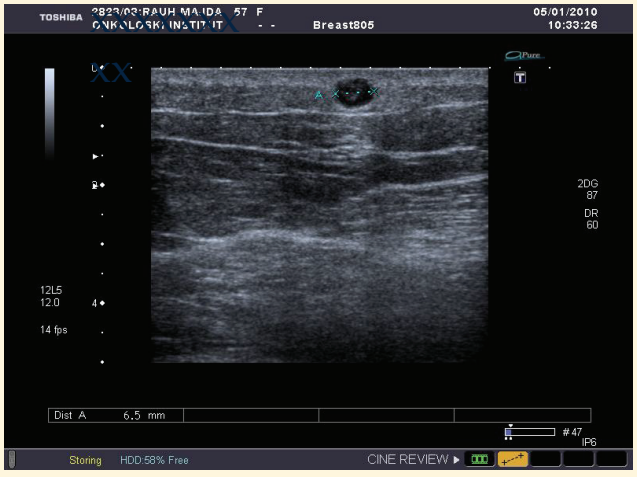
UZ region. bezgavčne lože- follow up

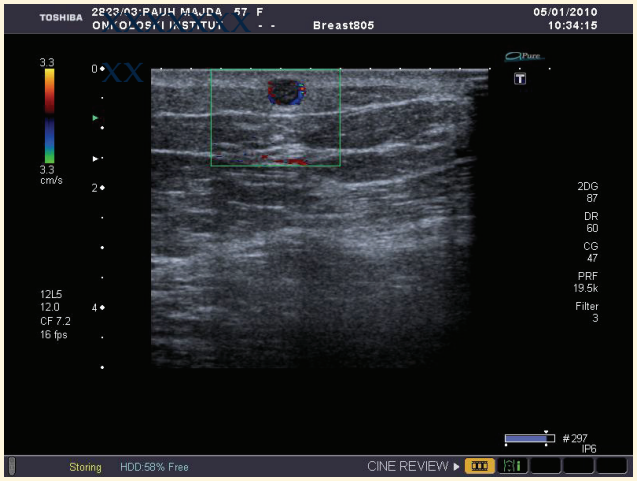
- UZ preiskava regionalne bezgavčne lože je visoko občutljiva
- Bolj občutljiva od palpacije
- + TIAB : dokončna dg
- Podaljšuje preživetje
- Različna senzitivnost, specifičnost



Blum A., et al. Cancer 2000
Voit: Sem in Onc 2002

In-transit metastaza



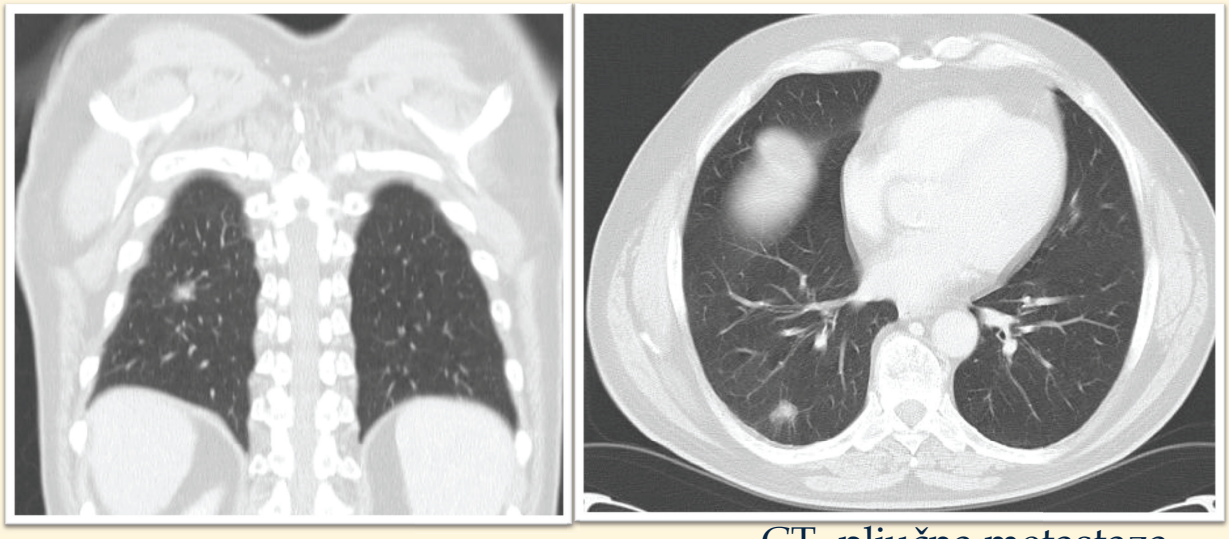


Razsoj MM

- pljuča
- jetra
- CŽS
- skelet
- GI trakt …..

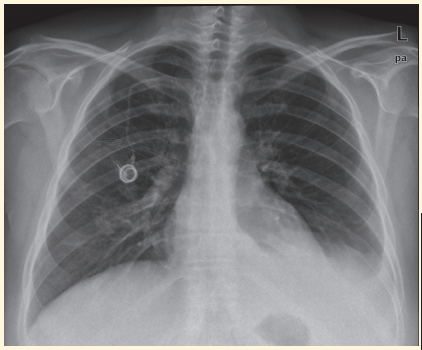
Ponovitev bolezni- CT

MM najpogosteje zaseva v pljuča

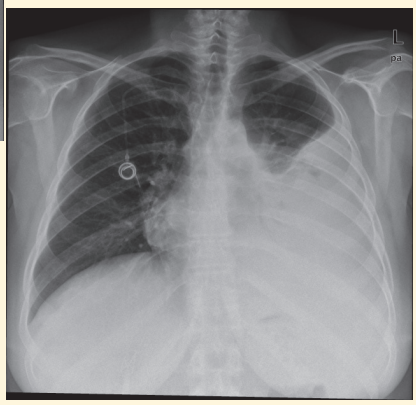


CT- pljučna metastaza

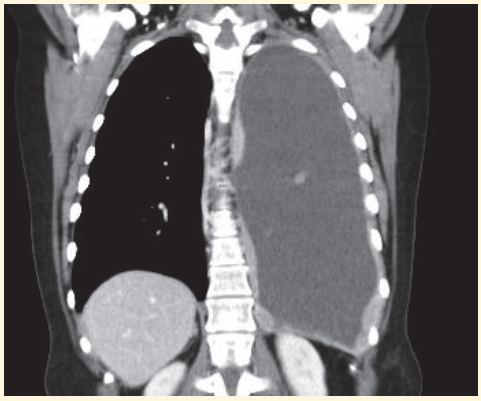
MM- plevra



September 13

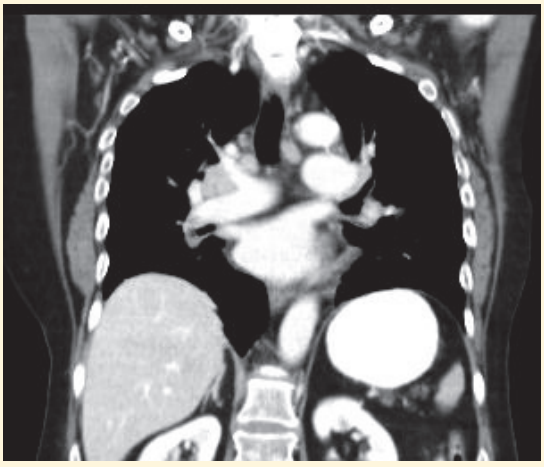


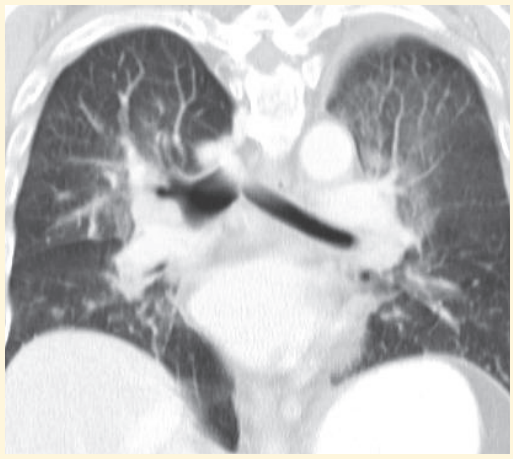
November 13



November 13

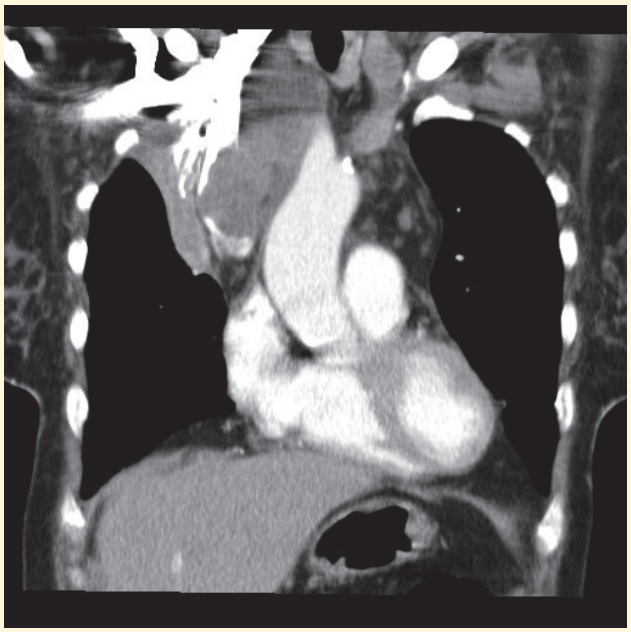
Razsoj mediastinum

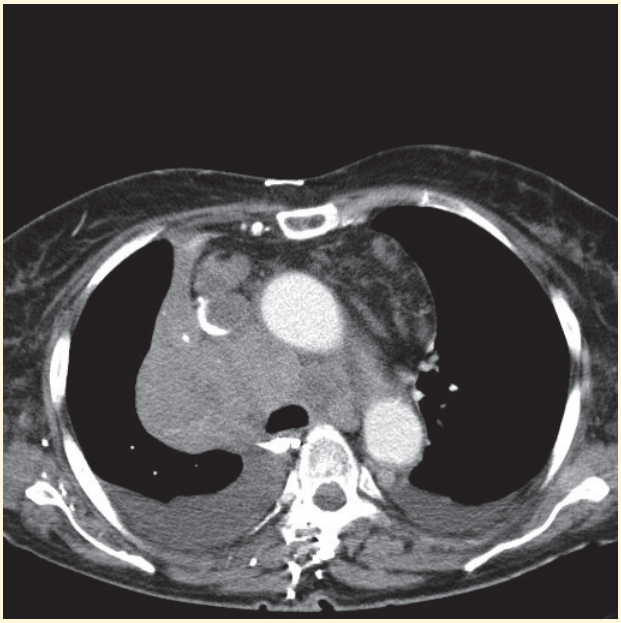




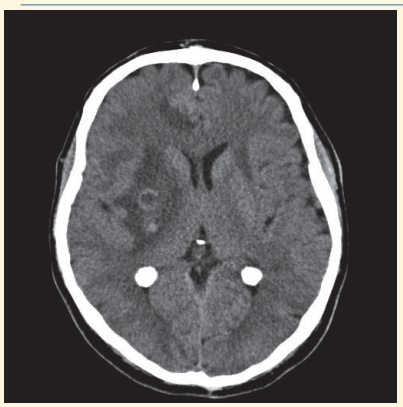
mediastinalne bezgavke in posledična obstrukcija

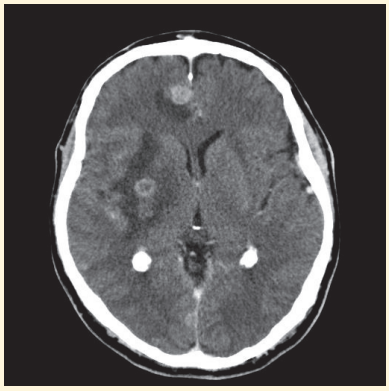
Sindrom zgornje vene cave

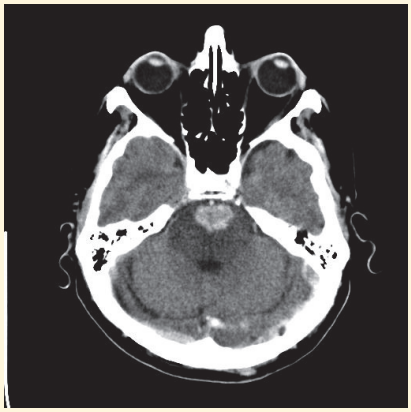




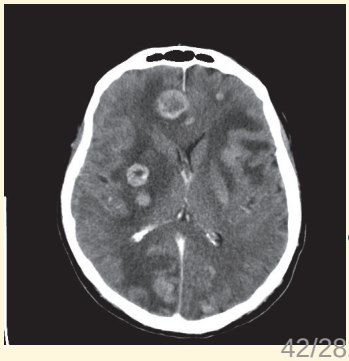
MM- progres v CŽŠ





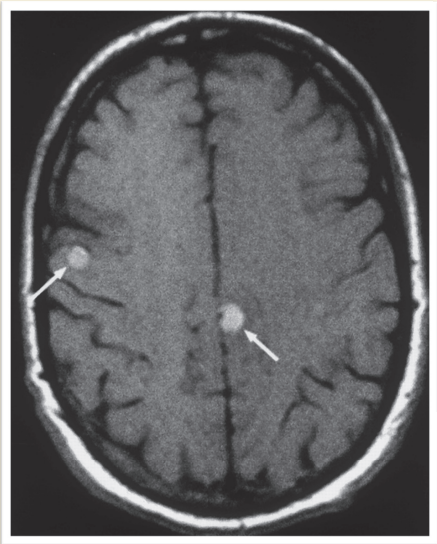


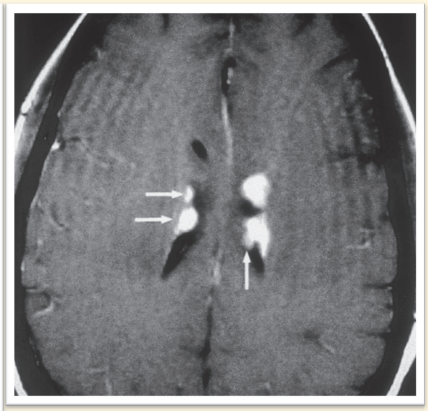
maj 2010

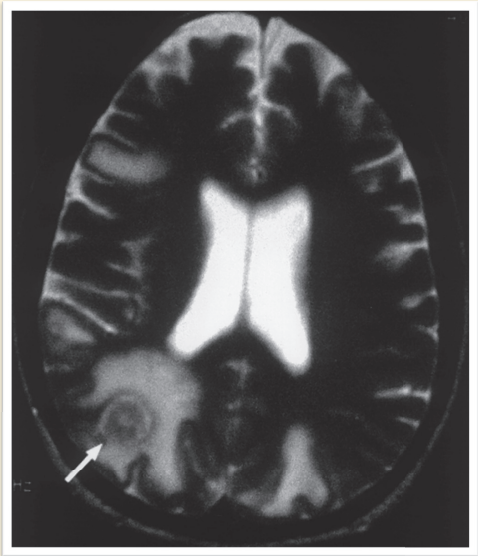


avgust 2010

MM- možganske metastaze

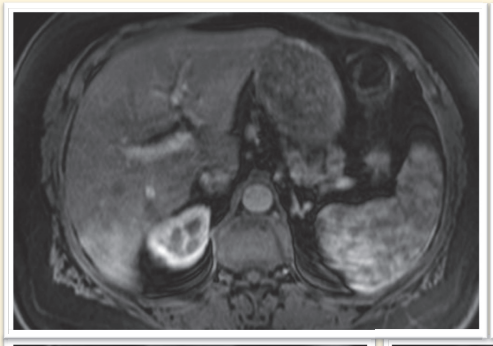


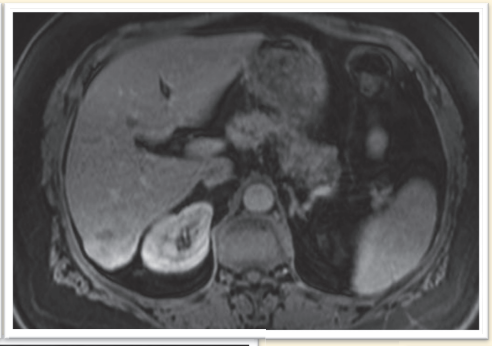




Metastaze v CŽS
49-73%

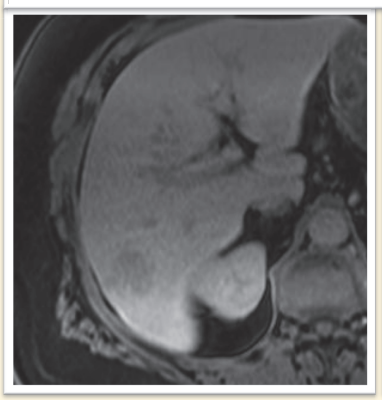
MM – ponovitev bolezni

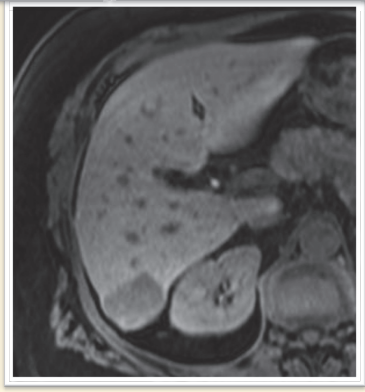




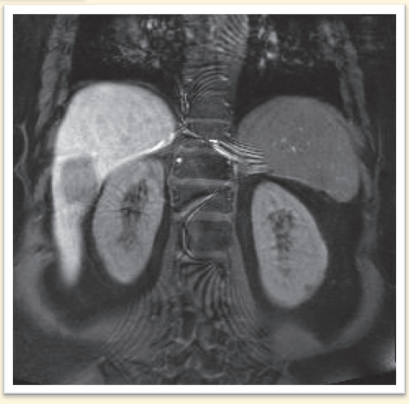
Dinamični
MRI

20s, 50s

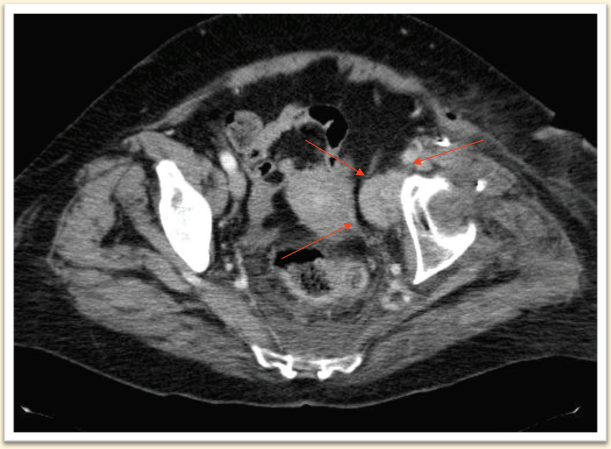


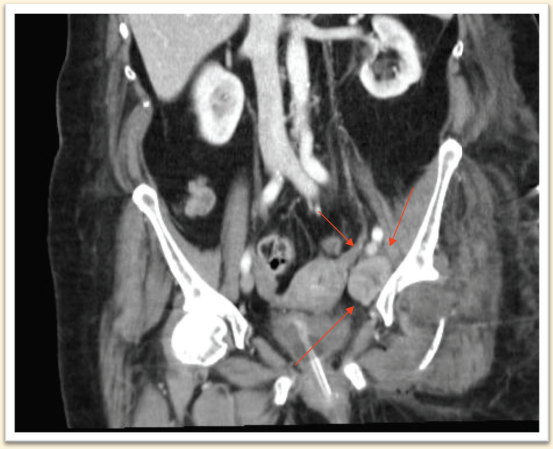


5min,
20min



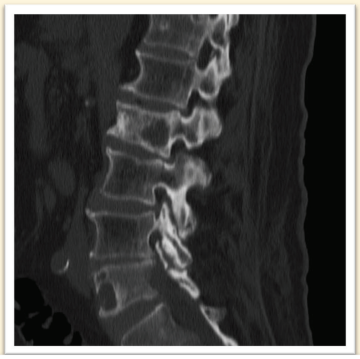
Ponovitev bolezni - CT

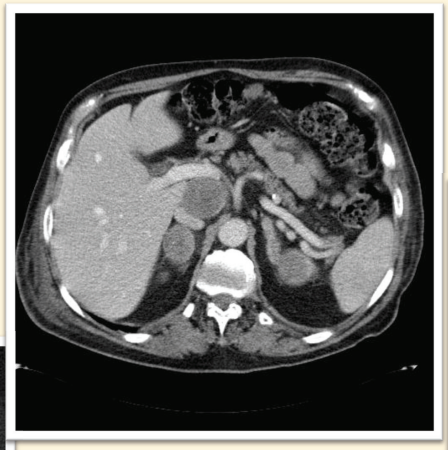


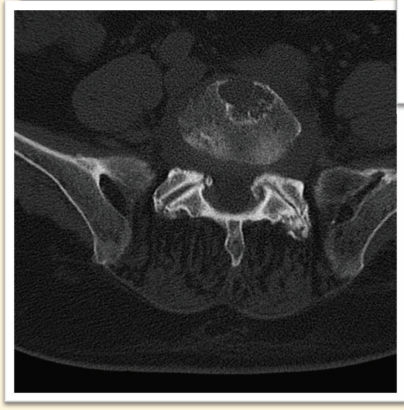


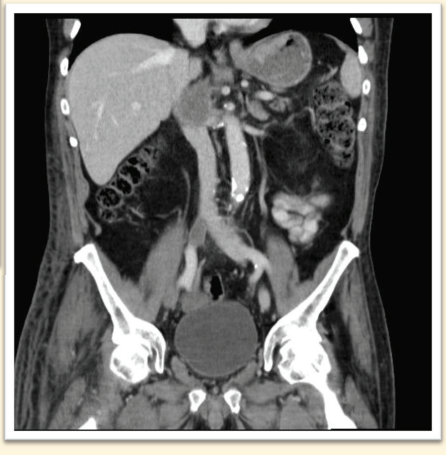
Metastaza L ingvinalno

Ponovitev bolezni









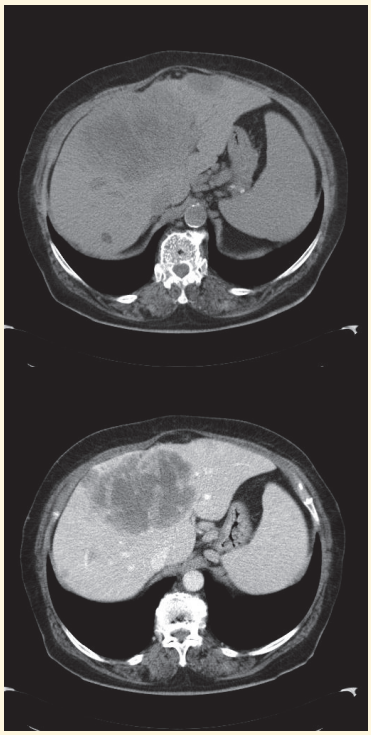
tromb v D iliak.veni

Zakaj potrebujemo kriterije za oceno odgovora (response evaluation)

- **Ocena učinka zdravljenja v klinični praksi**
  - Odgovor na zdravljenje
  - Obdobje brez bolezni
  - Čas do progresa
  - …drugo ?
- **Ocena učinkovitosti zdravljenja**
  - Faza II. in III. Kliničnih študij
  - Posamezen bolnik(zanesljivost, standardizacija)
  - Primerjava preživetja

RECIST - response evaluation criteria in solid tumors

- Za evaluacijo vedno ista slikovna preiskava
- Najbolj primeren CT (debelina reza > 5 mm)
- Uporaba i.v. KS (portalna faza), razen HCC in NET
- Meritve v aksialni ravnini, opis lege
- MR
- UZ ni primeren
- Tu markerji (v pomoč)



RECIST- osnovna preiskava

Tarčne lezije

- 5 lezij (vsota največiih premerov)
- največ 2 /organ
- reproducibilnost

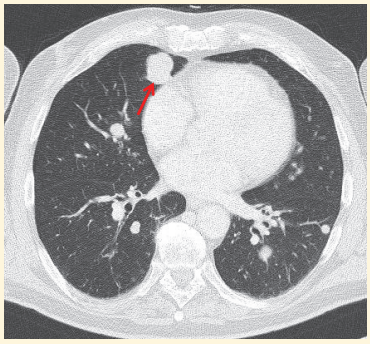
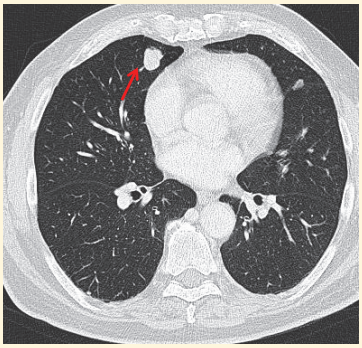
Ne-tarčne lezije

- opišemo v izvidu

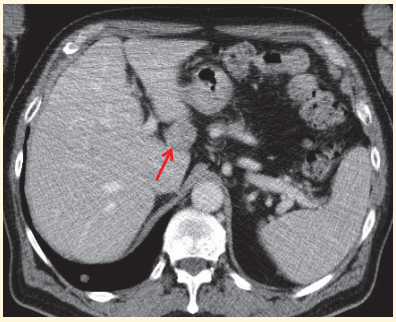
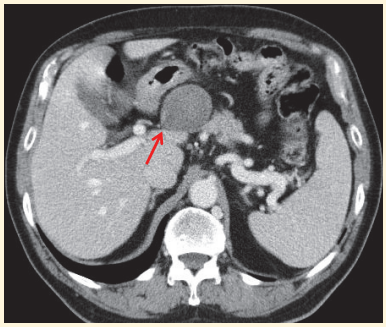
Ocena odgovora na zdravljenje

RECIST KRITERIJI	
POPOLN ODGOVOR (complete response) - CR	vse tarčne lezije so izginile vse bezgavke so prečno ≤ 10 mm
REGRES	zmanjšanje vsote maksimalnih premerov > 30 %
PROGRES	povečanje vsote maksimalnih premerov > 20% Absolutno povečanje > 5 mm Nastanek vsake nove lezije
STAGNACIJA	Spremembe ne zadoščajo kriterijem za progres ali regres

Ocena odgovora na terapijo

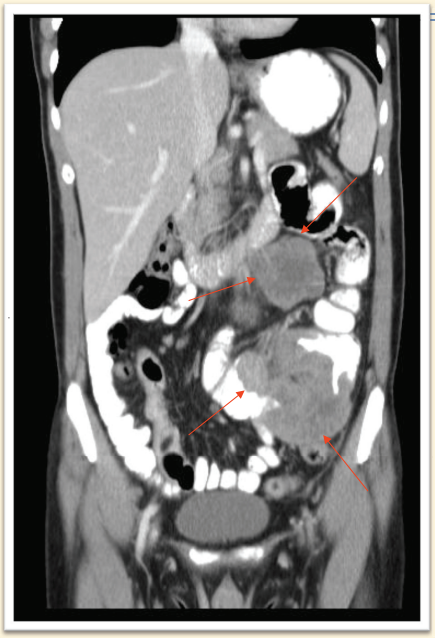
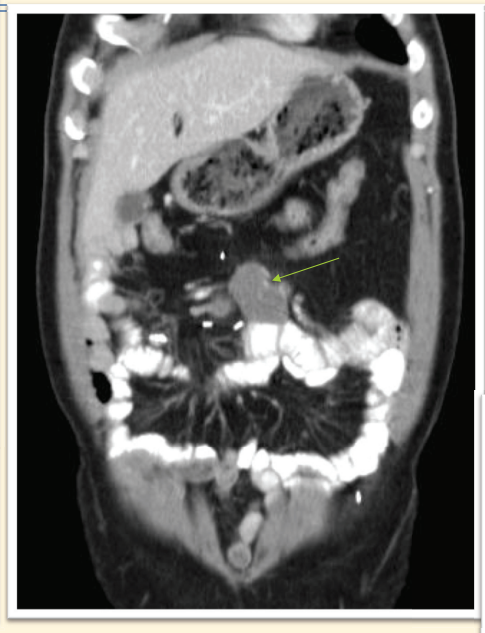
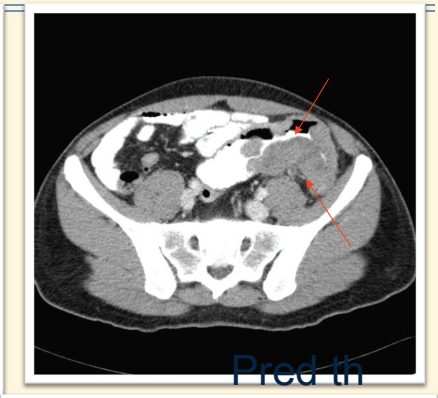



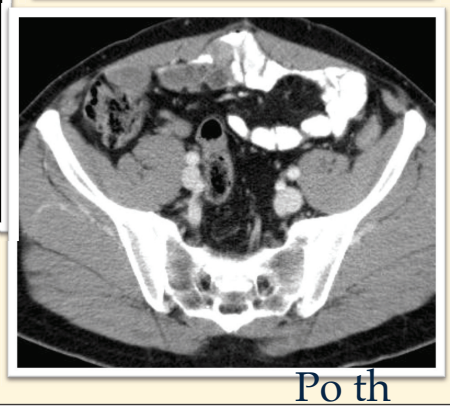
regres

progres

RECIST - regres

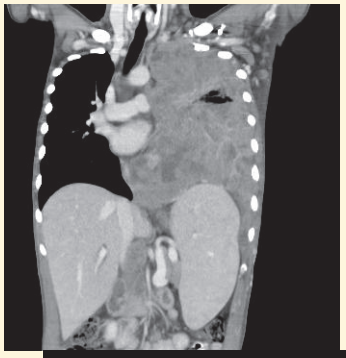






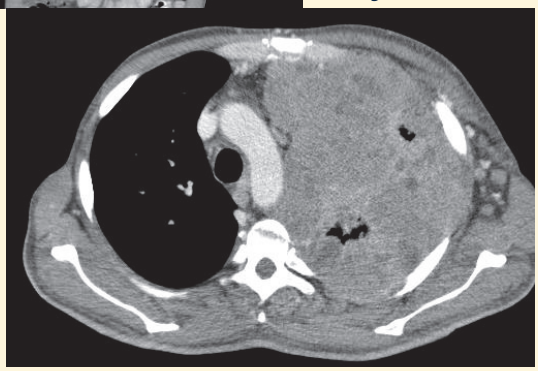
pred

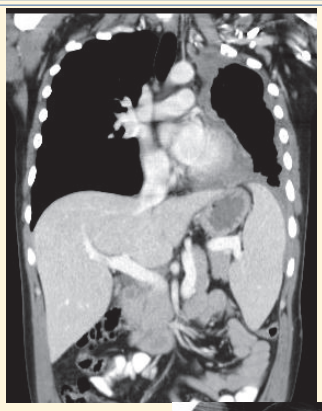
po terapiji

Odgovor na zdravljenje – biološko zdravilo



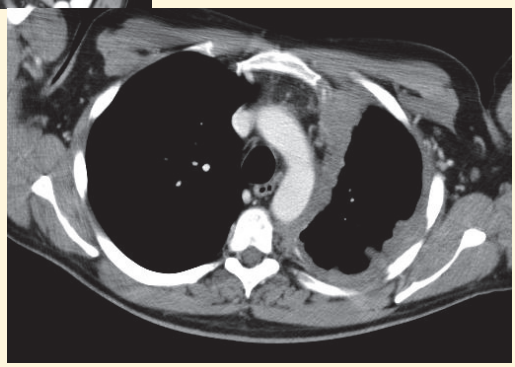
maj 2011





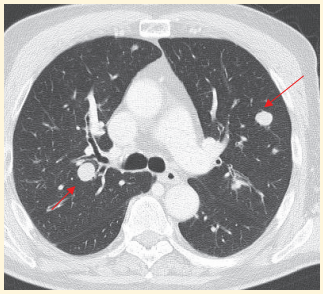
M, 37 let

avgust 2011



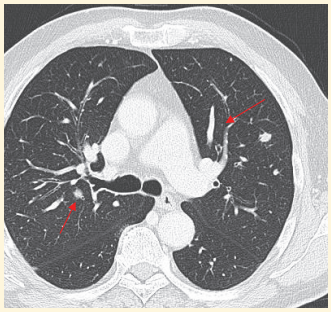
Odgovor na zdravljenje – biološka zdravila

18 mm



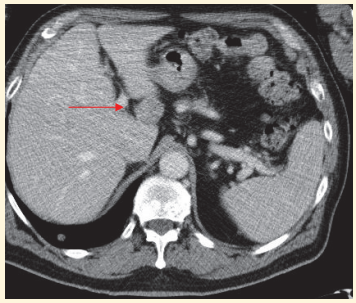
16 mm

12mm



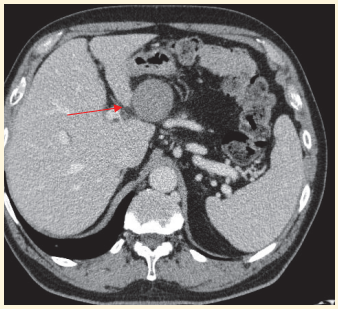
12 mm

26 mm



avgust 2011

45 mm



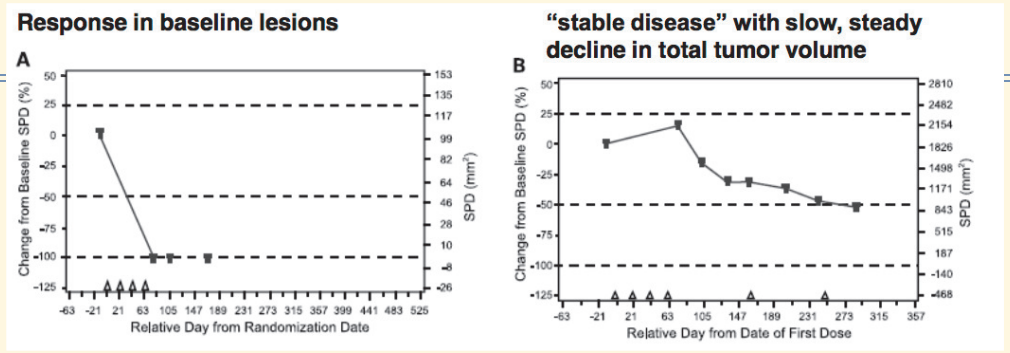
oktober 2011

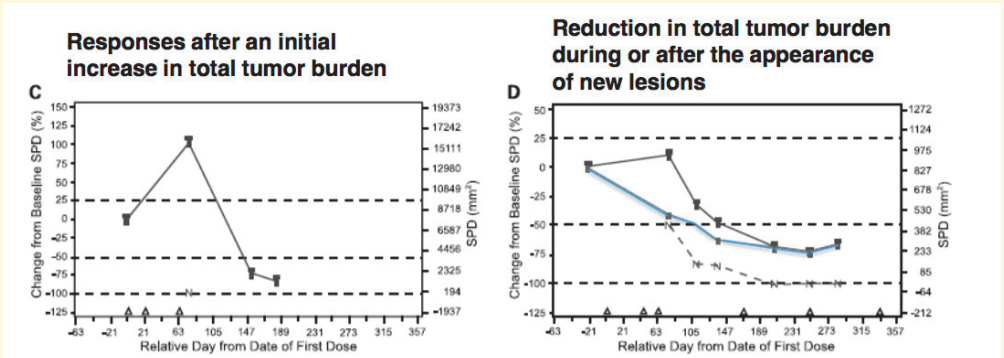
Imunoterapija

- Povzroči specifičen imunski odgovor
- S spremembo naravnega imun. odgovora
- 487 p, z razsejanim melanomom, zdravljenih z ipilimumabom
- 3 multicentrične študije faza II

- 4 različične vrste odgovora:
  - Regres vseh lezij/ brez novih
  - Stagnacija , z počasnim zmanševanjem
  - Odgovor po začetnem porastu lezij
  - Zmanjšanje obstoječih lezij/ nastanek novih
- irRECIST (Nichino et all, 2014)

Wolchok J., Clin Ca Res, 2009





Wolchok, Jur of Clin Ca Res, 2009

Imunoterapija - razlogi

- Razkorak med začetkom aplikacije zdravila in časom preiskave rast tu v vmesnem
- imunska reakcija na tu mikro okolje
- T-celična infiltracija:
  - Pseudoprogres
  - Detekcija novih, predhodno okultnih lezij

Henze J., Curr Radiol Rep, 2016

	RECIST	irRECIST
Nova lezija	Vedno progres	Premer lezije dodamo k vsoti (do 5 lezij- celokupno breme) 2 leziji/organ)
		Vse nove lezije se označijo kot ne-tarčne lezije
Progres	> 20% porast vsote vseh lezij Vsaka nova lezija	>20% porast TMTB Potrditi po >4 tednih Klinično progres

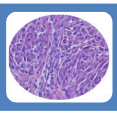
Henze J., Curr Radiol Rep, 2016

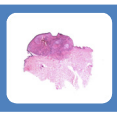
HVALA ZA POZORNOST

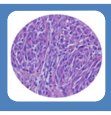
VLOGA PATOLOGA V DIAGNOSTIKI MELANOMA

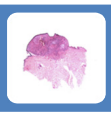
Boštjan Luzar
Inštitut za patologijo
Medicinska fakulteta Ljubljnana
Slovenija

VLOGA PATOLOGA V DIAGNOSTIKI MELANOMA
- *PREGLED PREDAVANJA-*


ZAKAJ JE HISTOLOŠKA ANALIZA MELANOCITNIH LEZIJ LAHKO PROBLEMATIČNA


HISTOLOŠKI KRITERIJI ZA MELANOM


HISTOLOŠKE RAZLIČICE MELANOMA

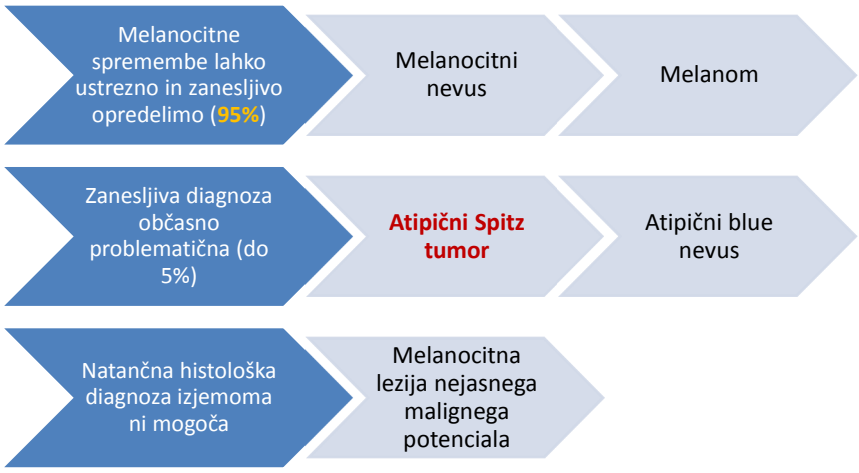

STANDARDIZIRANI HISTOLOŠKI IZVID

Nekaj dejstev o melanocitnih lezijah

- 15% vseh medicinsko-pravnih zahtevkov
- Napačna diagnoza patologa

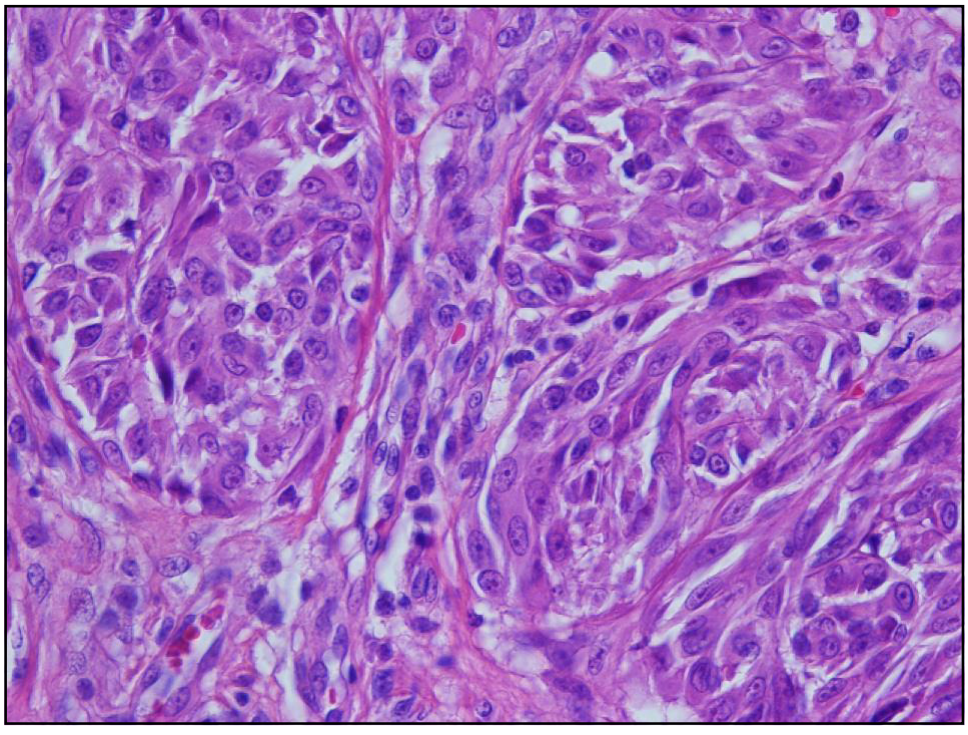
Maligna lezija, opredeljena kot benigna	• Dezmoplastični/nevrotropni melanom • Nevoidni melanom • Spizoidni melanom
Benigna lezija, opredeljena kot maligna	• Rekurentni melanocitni nevus • Pagetoidni Spitz nevus • Spitz nevus (izven obdobja adolescence)

Nekaj dejstev o melanocitnih lezijah



SPEKTER SPITZOIDNIH LEZIJ

SPITZ NEVUS → **ATIPIČNI SPITZ TUMOR** → SPITZOIDNI MELANOM



Histomorphologic Assessment and Interobserver Diagnostic Reproducibility of Atypical Spitzoid Melanocytic Neoplasms With Long-term Follow-up

Pedram Gerami, MD,† Klaus Busam, MD,‡ Alistair Cochran, MD,§ Martin G. Cook, MD,‖ Lyn M. Duncan, MD,¶ David E. Elder, MB, ChB, FRCPA,# Douglas R. Fullen, MD,**†† Joan Guitart, MD,*† Philip E. LeBoit, MD,‡‡ Martin C. Mihm, Jr, MD,¶ Victor G. Prieto, MD, PhD,§§‖‖ Michael S. Rabkin, MD, PhD,¶¶ Richard A. Scolyer, MD,## Xiaowei Xu, MD, PhD,# Sook Jung Yun, MD, PhD,*** Roxana Obregon, BA,* Pedram Yazdan, MD,* Chelsea Cooper, BA,* Bing Bing Weitner, MS,††† Alfred Rademaker, PhD,††† and Raymond L. Barnhill, MD§*

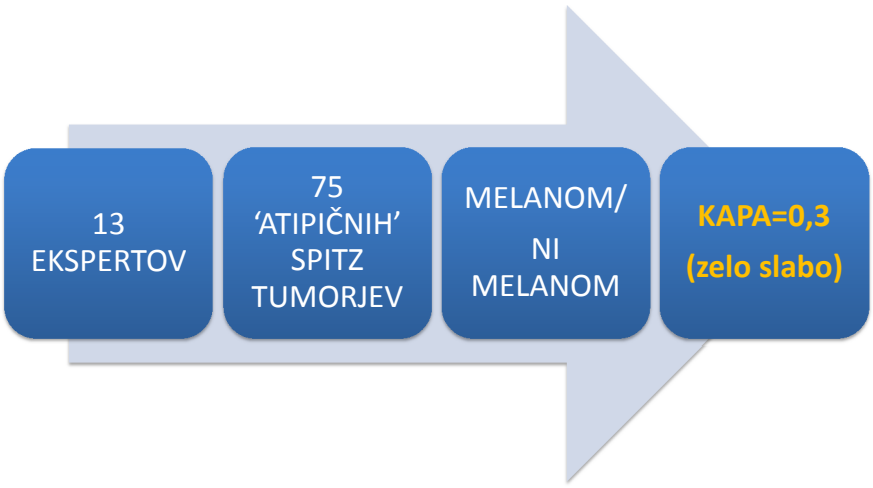
Abstract: Predicting clinical behavior of atypical Spitz tumors remains problematic. In this study, we assessed interobserver agreement of diagnosis by 13 expert dermatopathologists for atypical Spitz tumors (n = 75). We determined which histomorphologic features were most heavily weighted for their diagnostic significance by the experts and also which histomorphologic features had a statistically significant correlation with clinical outcome. There was a low interobserver agreement among the experts in categorizing lesions as malignant versus nonmalignant (κ = 0.30). The histomorphologic features that were given the most diagnostic significance by the experts were: consumption of the epidermis, atypical mitoses, high-grade cytologic atypia, and mitotic rate. Conversely, the histomorphologic features that most correlated with disease progression were: frequent mitoses, deep mitoses, asymmetry, high-grade cytologic atypia, and ulceration. The presence and/or pattern of pagetoid spread, consumption of the epidermis, and lymphoid aggregates demonstrated no association with clinical behavior. The results support the assertion that there is a lack of consensus in the assessment of atypical Spitz tumors by expert dermatopathologists. Importantly, many features used to distinguish conventional melanoma from nevi were not useful in predicting the behavior of atypical Spitz tumors. This study may provide some guidance regarding histologic assessment of these enigmatic tumors.

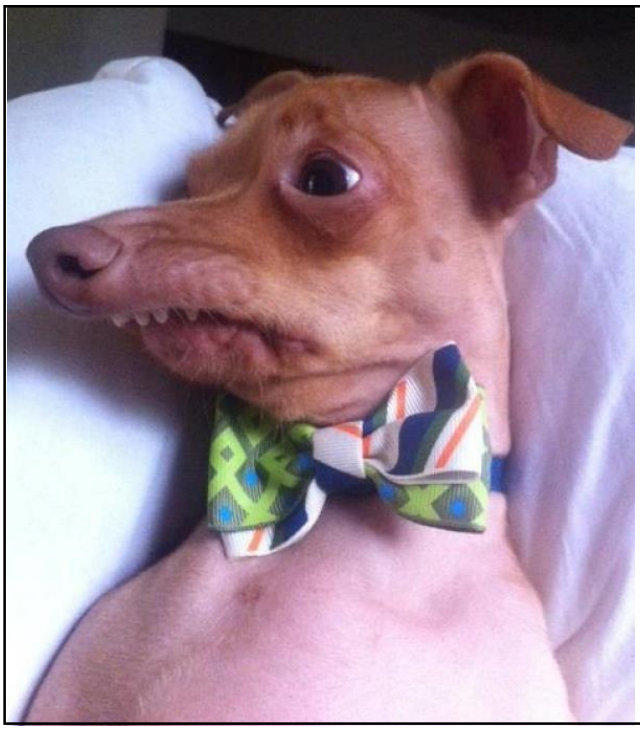
From the *Department of Dermatology; †Robert H. Lurie Cancer Center; †††Department of Preventive Medicine and the Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; ‡Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY; §Department of Pathology and Laboratory Medicine, Dermatopathology, UCLA Medical Center, Los Angeles; ‡‡Departments of

Key Words: melanoma, atypical Spitz tumor, Spitz tumor, Spitz nevus, spitzoid melanoma, interobserver

(*Am J Surg Pathol* 2014;38:934–940)

ATYPICAL SPITZ TUMOR
- Konceptualni problem -

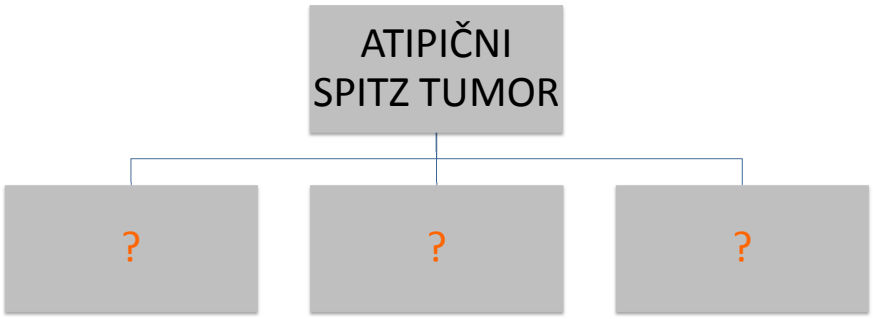




UPS!
I DID IT,
AGAIN!

- PAGETOIDNA PROLIFERACIJA
- PORABA EPIDERMISA
- MATURACIJA
- LIMFATIČNI AGREGATI

NIMAJO NAPOVEDNE VREDNOSTI



*

ATIPIČNI SPITZ NEVUS

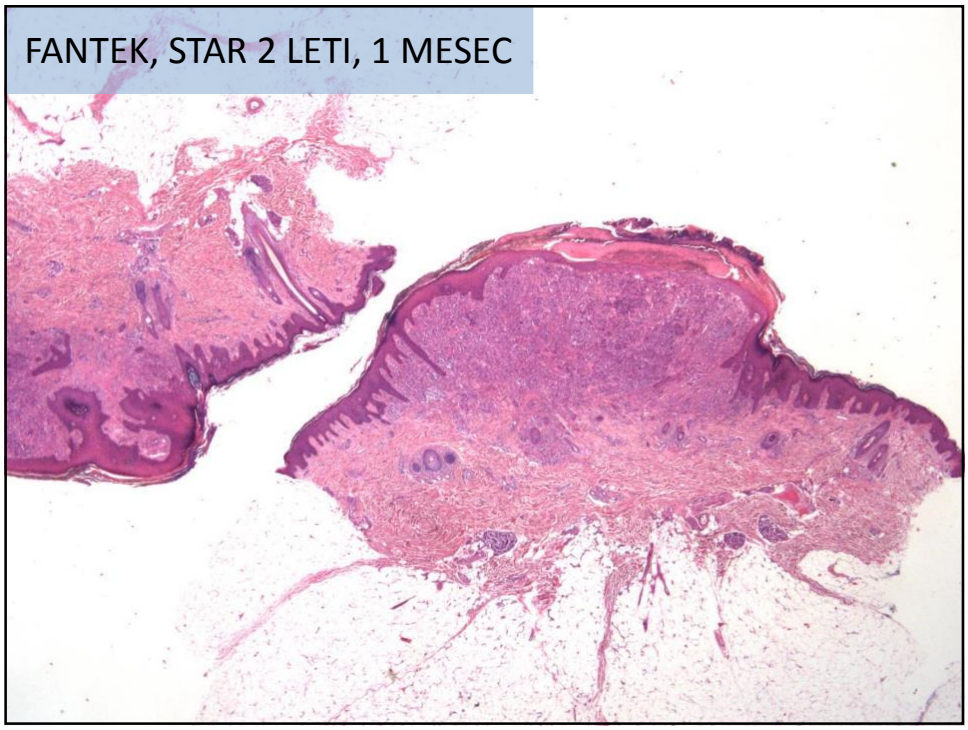
JE

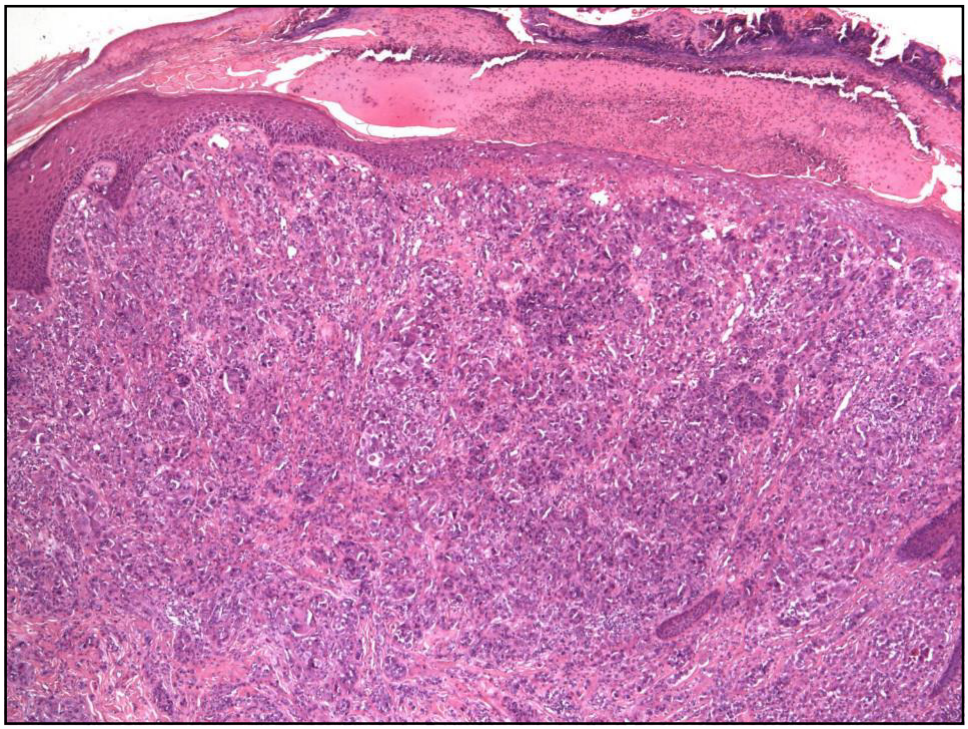
GENETSKO

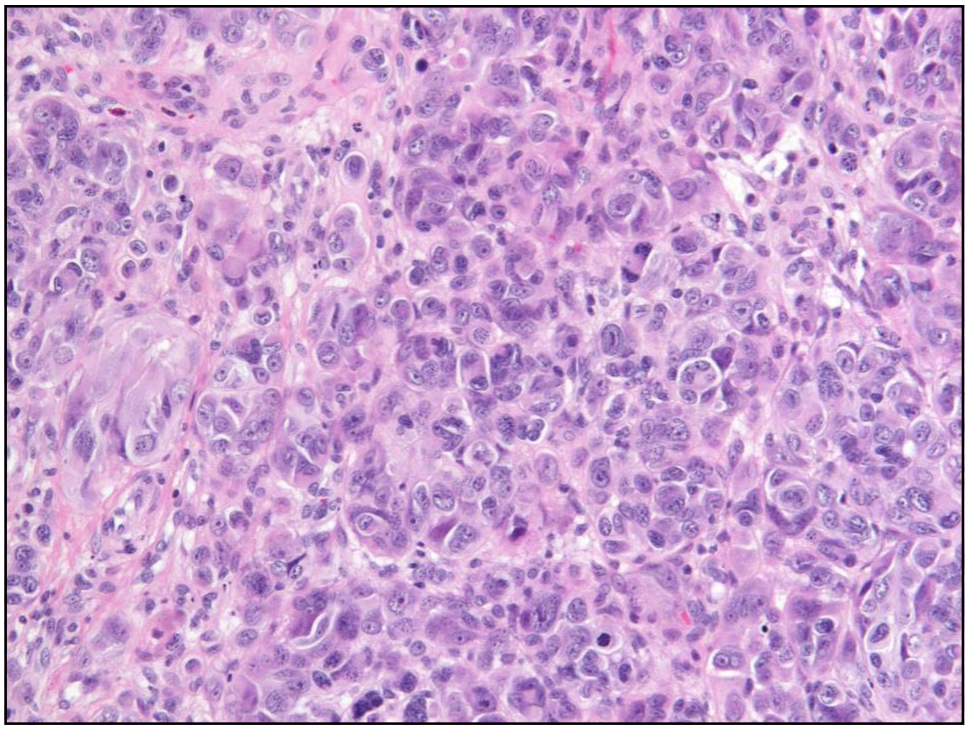
HETEROGENA SKUPINA

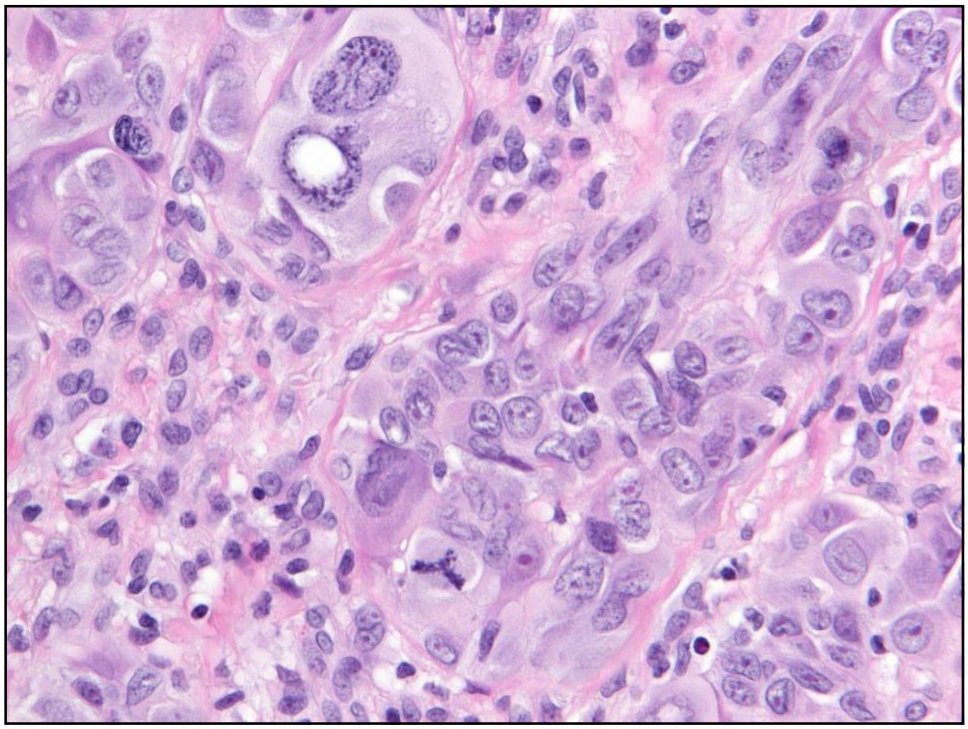
MELANOCITNIH PROLIFERACIJ

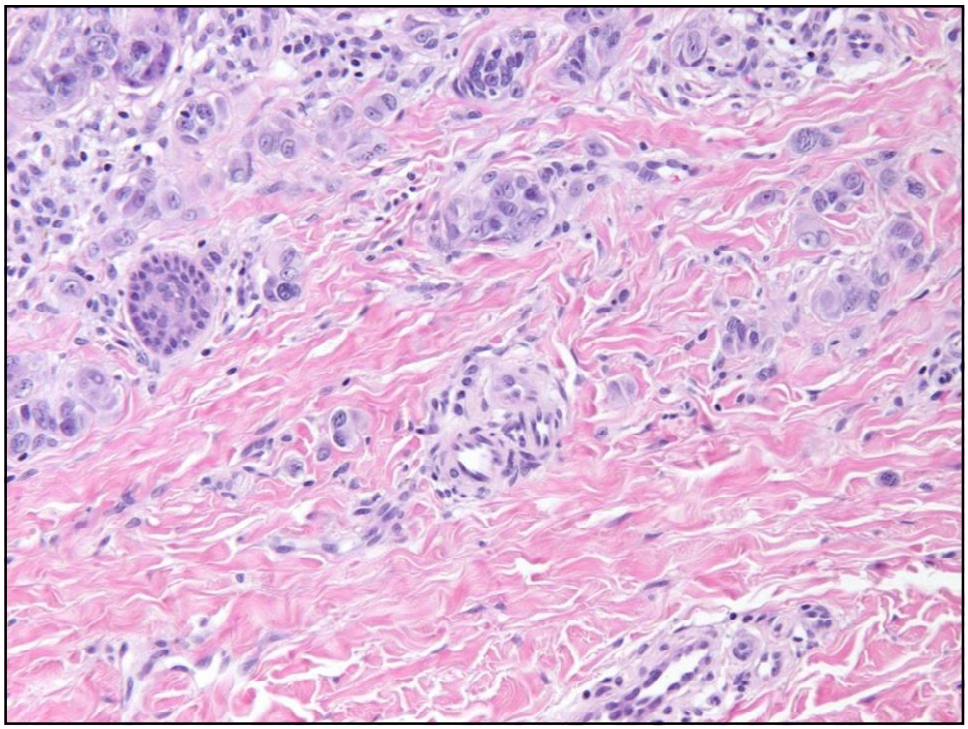
!

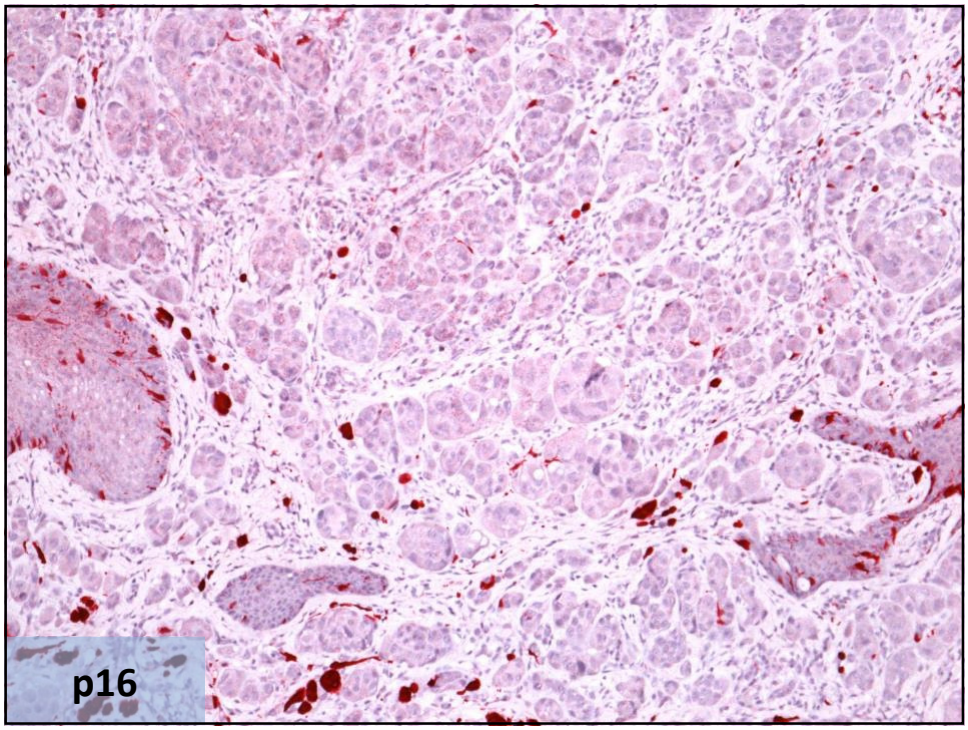

FANTEK, STAR 2 LETI, 1 MESEC










p16

Enhanced Detection of Spitzoid Melanomas Using Fluorescence In Situ Hybridization With 9p21 as an Adjunctive Probe

Bryan Gammon, MD, Beth Beilfuss, BS, Joan Guitart, MD, and Pedram Gerami, MD

Abstract: The use of molecular diagnostic methods such as fluorescence in situ hybridization (FISH) for challenging melanocytic neoplasms is becoming more widespread. In light of the diagnostic difficulty they pose, spitzoid melanocytic neoplasms constitute an area of greatest potential utilization. In this study we wished to evaluate the sensitivity of the currently used melanoma FISH probe assay in a group of unambiguous spitzoid melanomas. On the basis of comparative genomic hybridization data, copy number losses at chromosome 9 have long been recognized as a complementary to the standard melanoma FISH assay. Hence, in this study, we validated the efficacy of 9p21/Cep9 as a diagnostic FISH assay in melanoma, and demonstrated its complementary effect to the standard FISH assay. 9p21 may be particularly helpful in lesions with spitzoid morphology.

Key Words: spitzoid melanoma, FISH, 9p21

(*Am J Surg Pathol* 2012;36:81–88)

HOMOZIGOTNA DELECIJA 9p21

OMOGOČA RAZLIKOVANJE MED

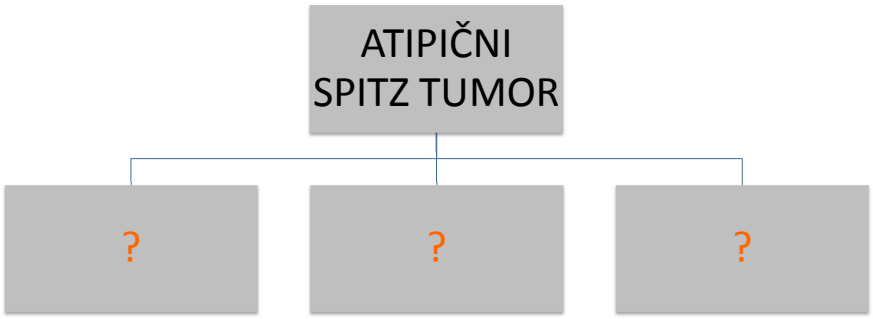
SPITZOIDNIM MELANOMOM

IN

SPITZOIDNIMI PROLIFERACIJAMI Z BENIGNIM POTEKOM

ATIPIČNI SPITZ TUMOR KLINIČNI POTEK	HETEROZIGOTNA DELECIJA 9p21 (N=16)	HOMOZIGOTNA DELECIJA 9p21 (N=22)
BREZ BOLEZNI	75%	23%
BREZ BOLEZNI & NEG SENTINEL BEZG.	6%	27%
BREZ BOLEZNI & POZ SENTINEL BEZG.	19%	9%
PREKO SENTINEL BEZG.	**0**	22%
ODDALJENI ZASEVKI	**0**	9%
SMRT	**0**	9%

Yazdan et al. Am J Surg Pathol 2014; 38: 638-645.

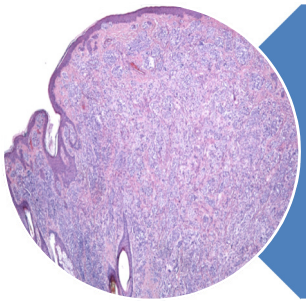


ATIPIČNI SPITZ TUMOR

DELECIJA 9p21

?

?



WIESNERJEV NEVUS (BAP-om)

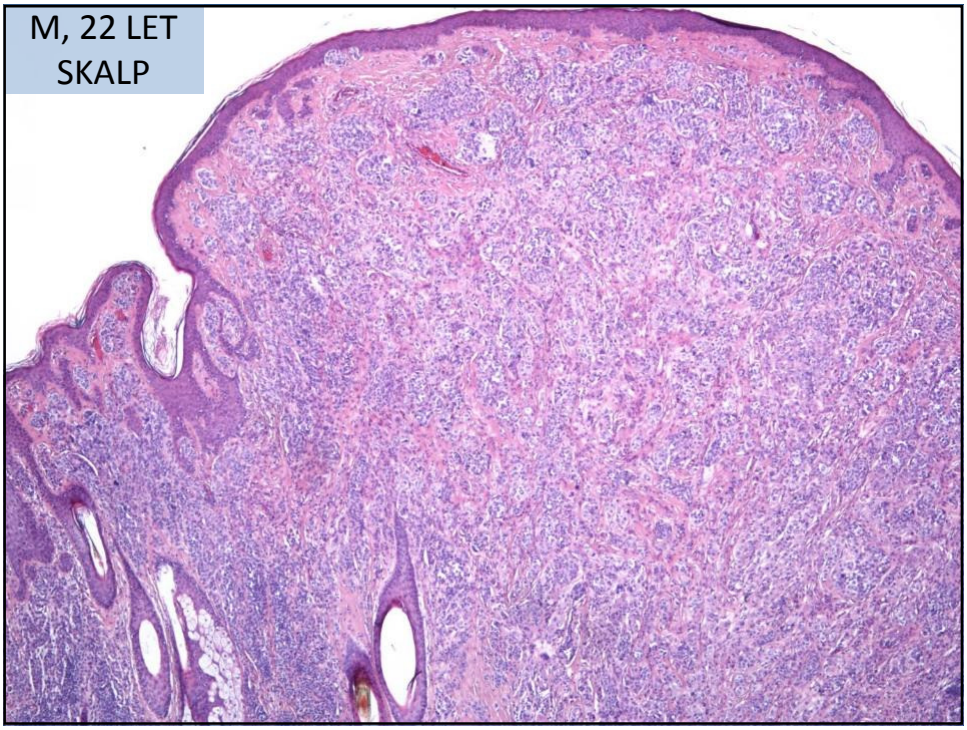
WIESNERJEV MELANOCITNI NEVUS

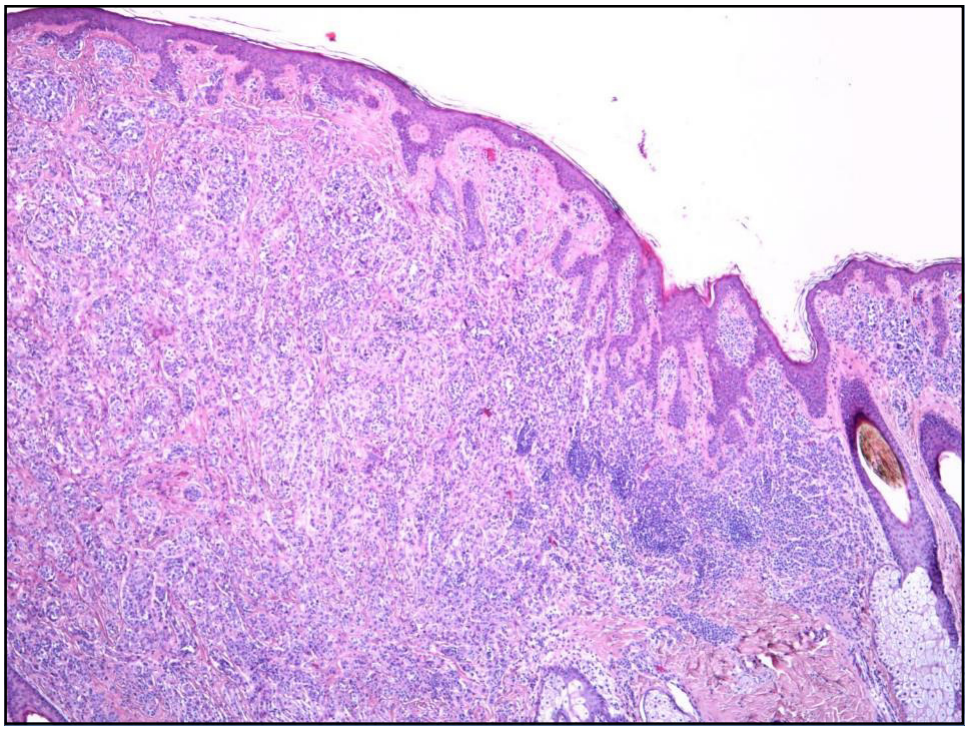
DVE NEODVISNI DRUŽINI

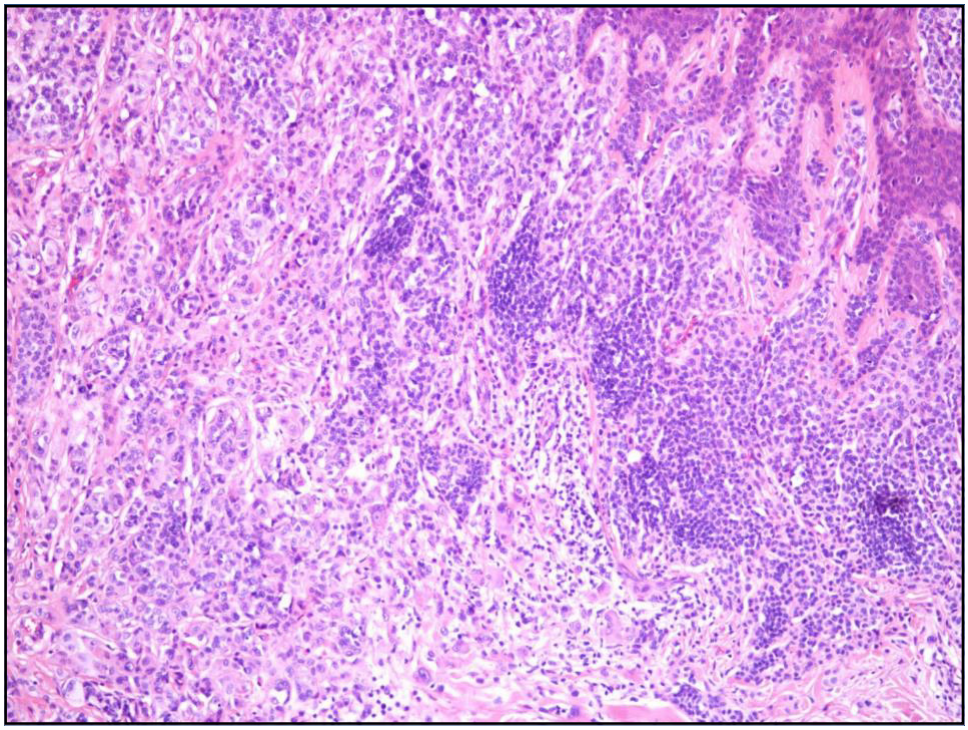
1.	2.	3.	4.
MULTIPLE KOŽNE SPREMEMBE	EPITELIOIDNA SPITZOIDNA MORFOLOGIJA	DRUGA DEKADA ŽIVLJENJA	POVEČANO TVEGANJE ZA MELANOM: KOŽA, OČESNO OZADJE

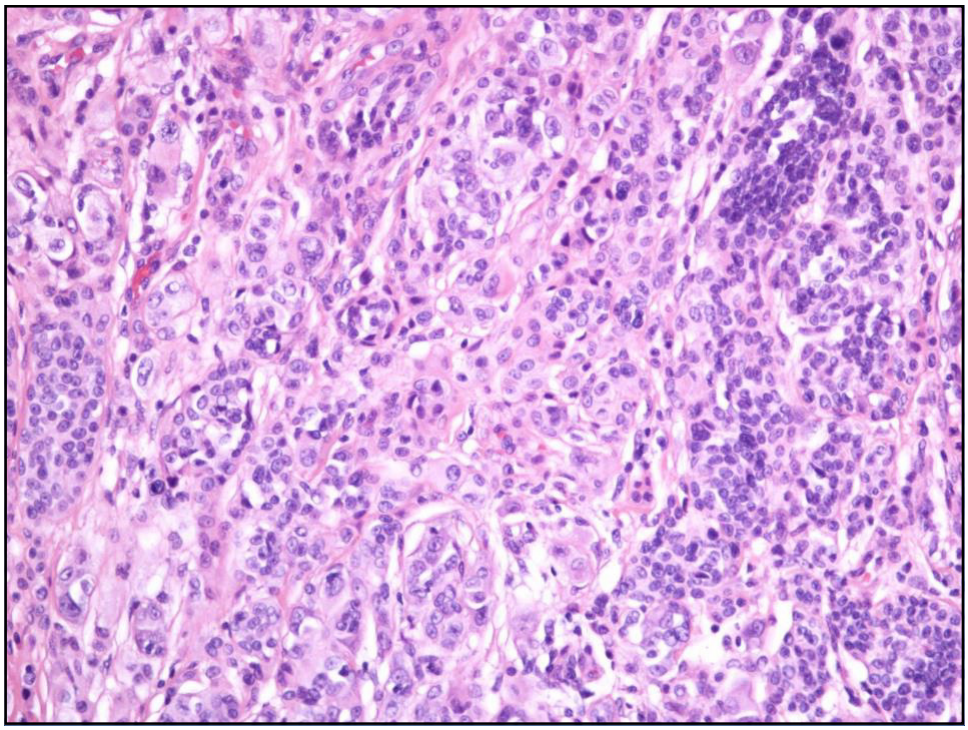
Wiesner T et al. Nat Genet 2011; 43: 1018-1021.

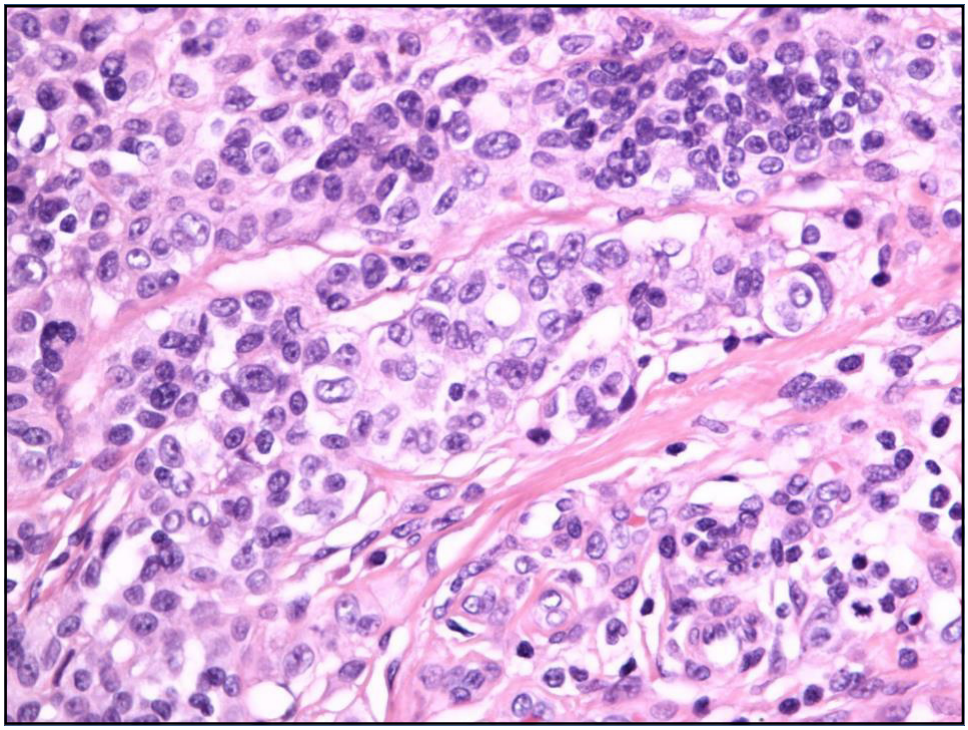
M, 22 LET
SKALP

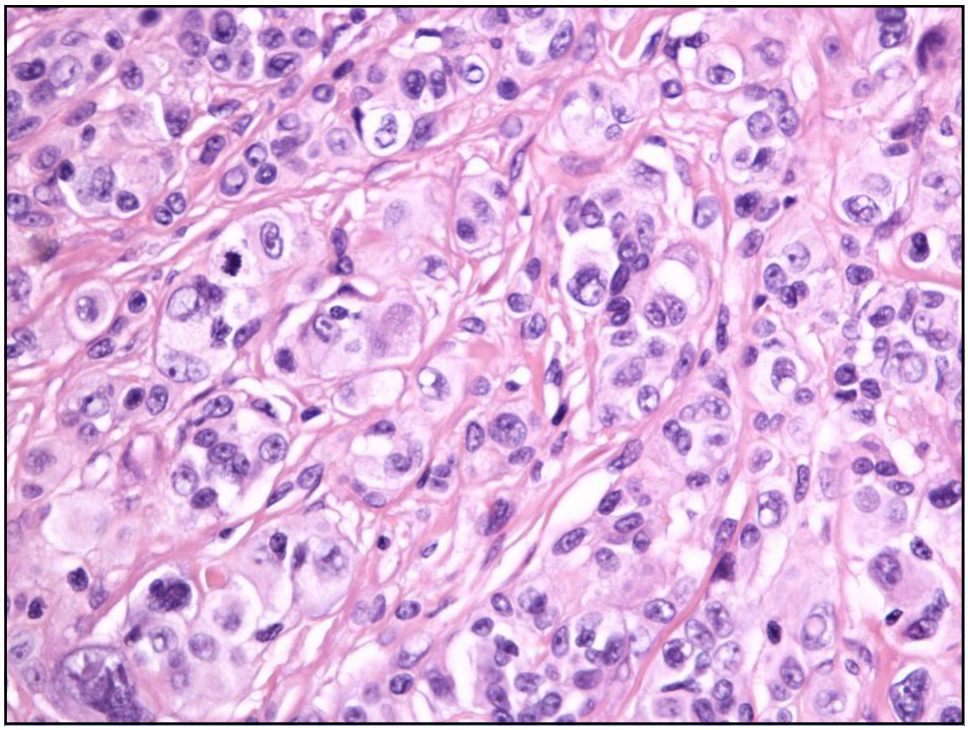


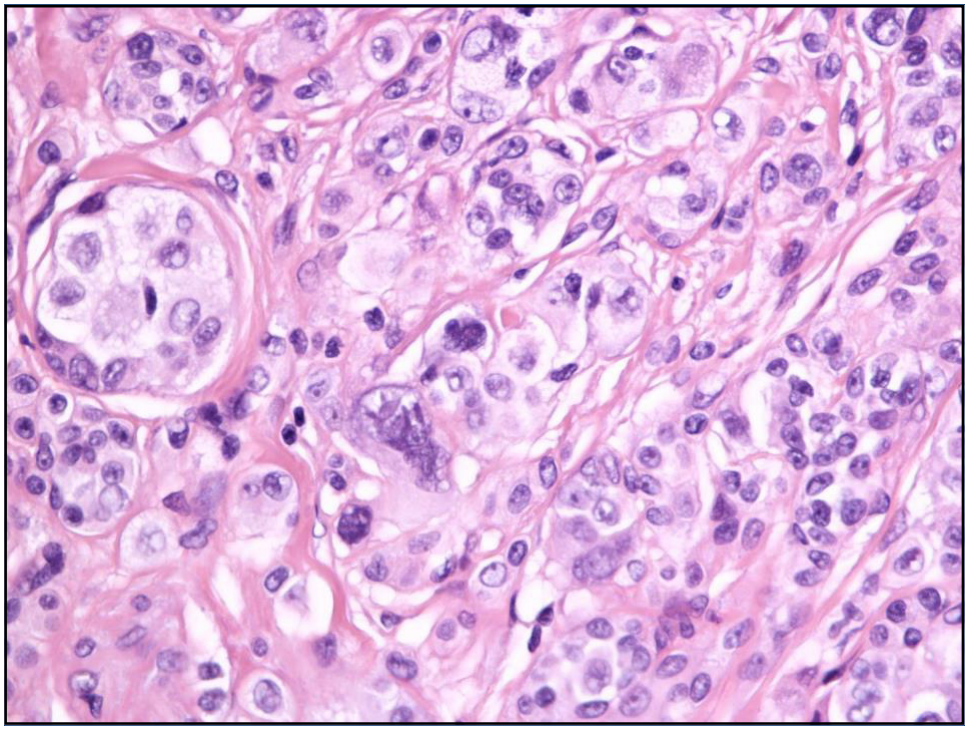


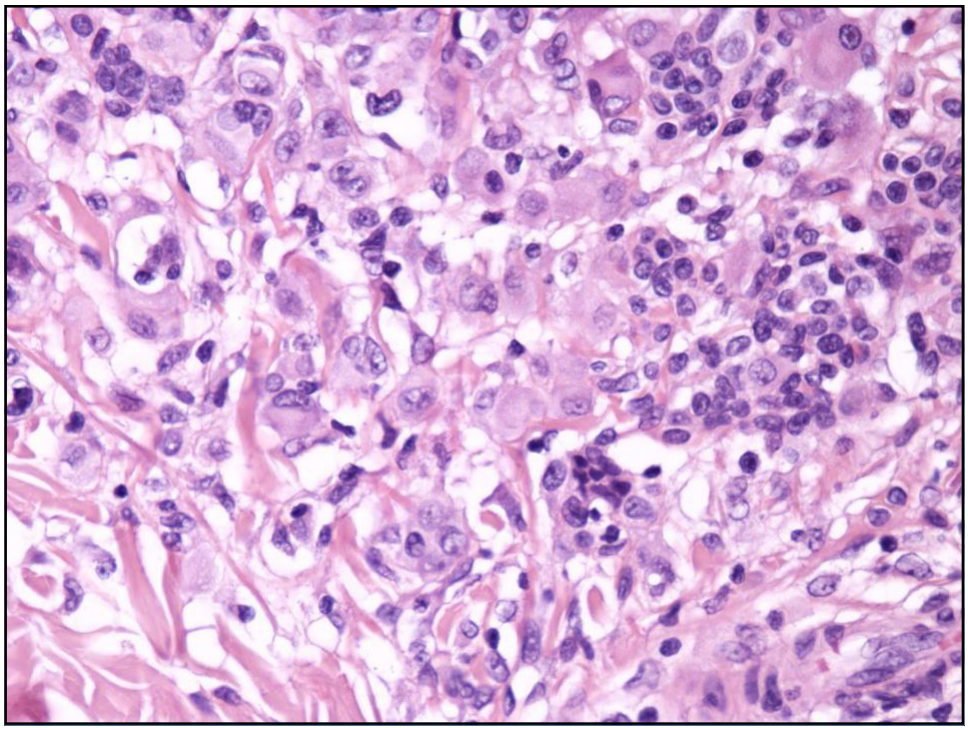


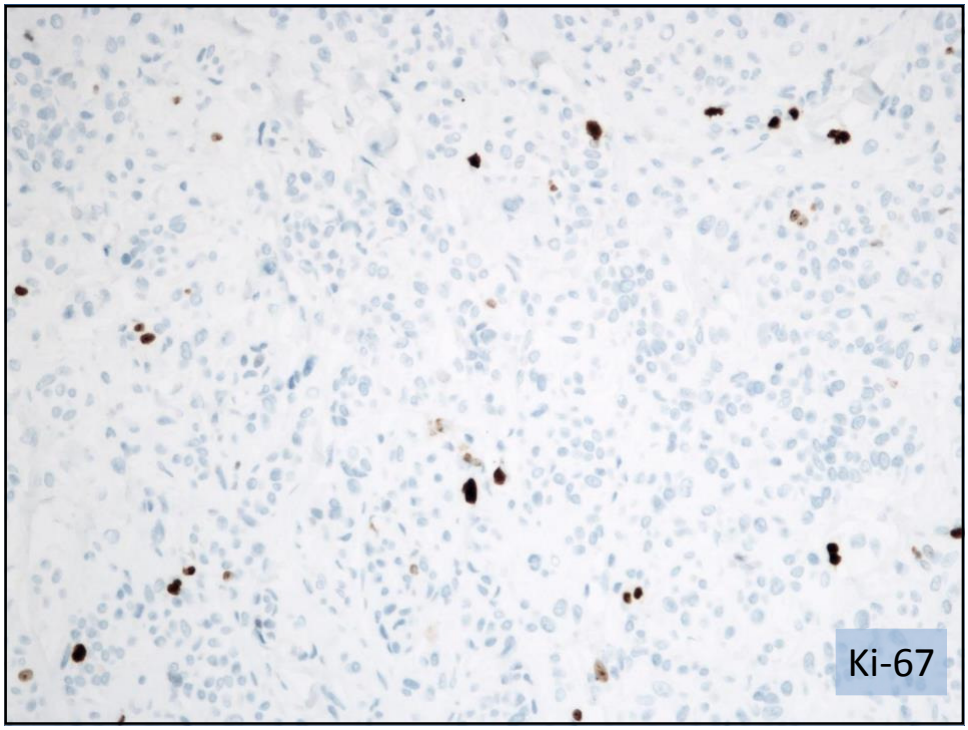


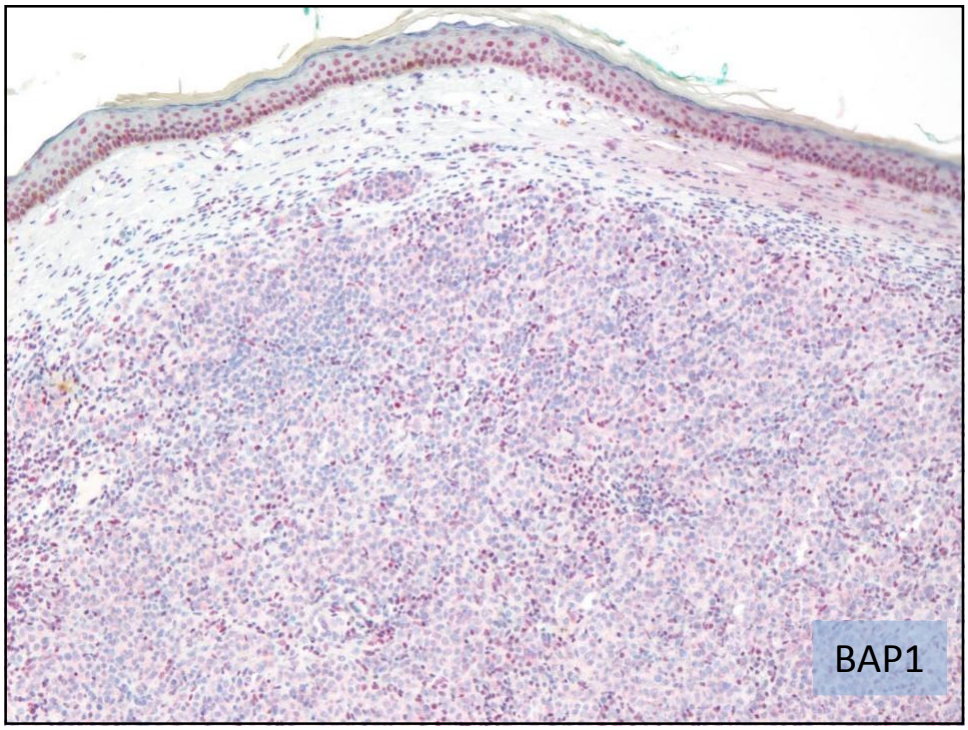


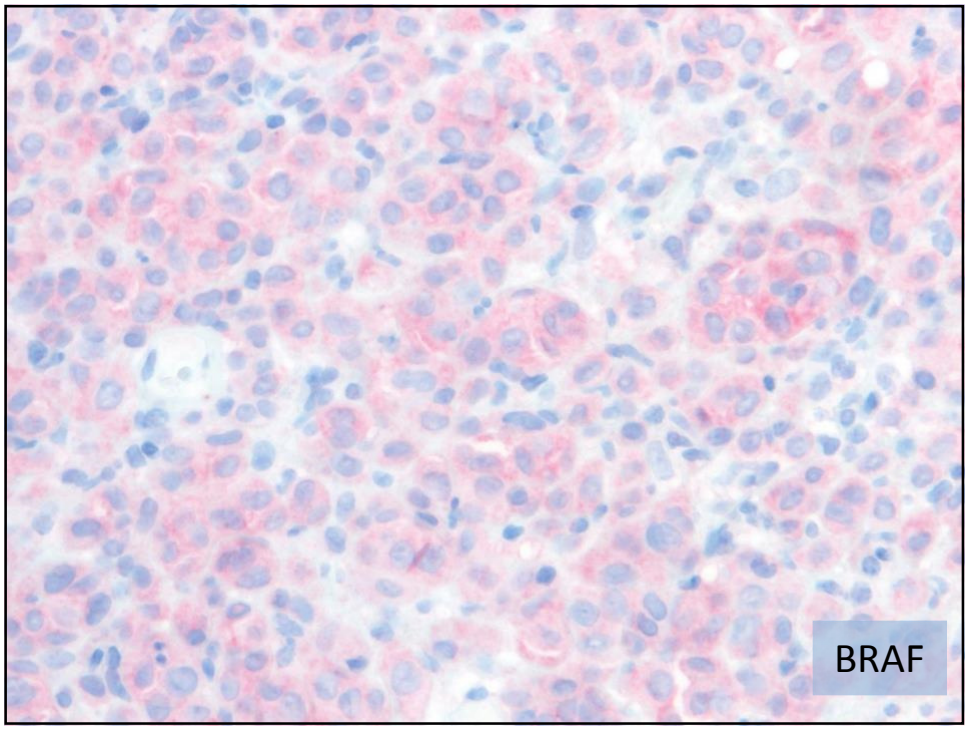







Ki-67


BAP1


BRAF

WIESNERJEV MELANOCITNI NEVUS

AUTOSOMNO DOMINANTNO DEDOVANJE

‘Germline’ *BAP1* MUTACIJE

BRAF MUTACIJE

Wiesner T et al. Nat Genet 2011; 43: 1018-1021.

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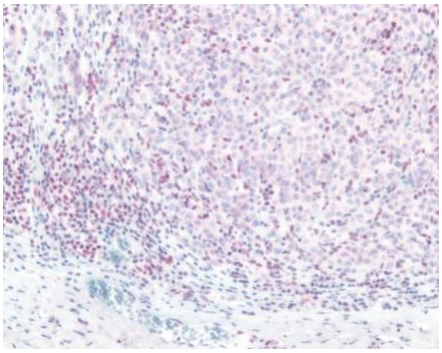
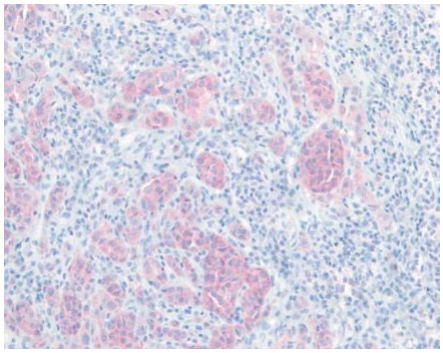
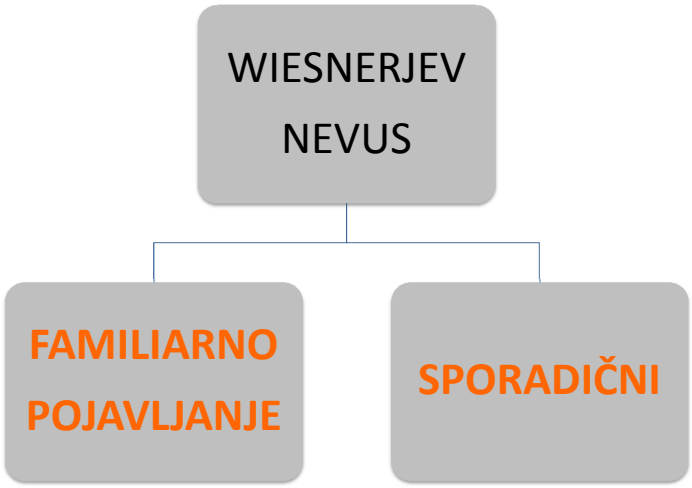
WIESNERJEV MELAOCITNI NEVUS
- Molekularna genetika -

- Mutacija *BAP1* gena
  - izguba ekspresije BAP1 proteina
- Mutacija *BRAF* gena
  - BRAF V600E





WIESNERJEV MELANOCITNI NEVUS



Wiesner T et al. Am J Surg Pathol 2012; 36: 818-830.

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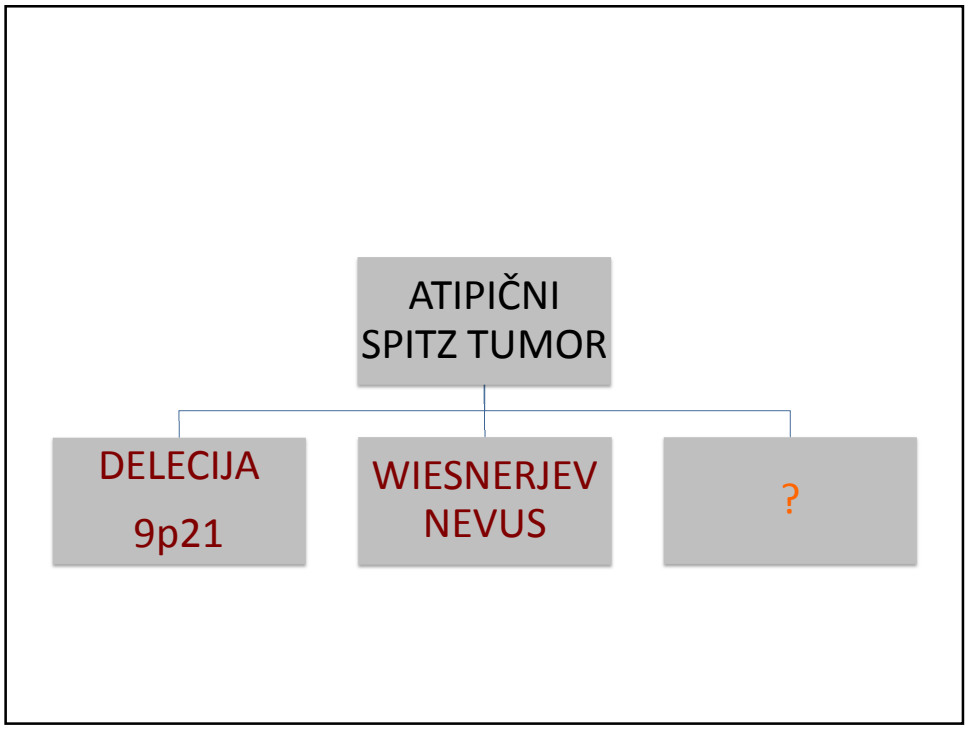
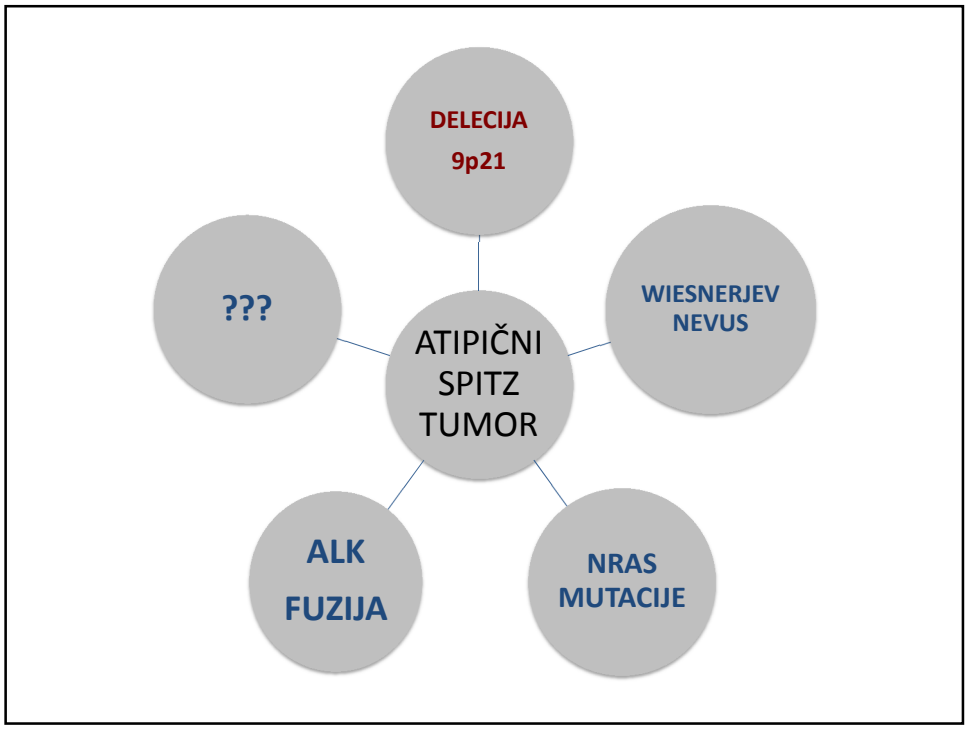
MELANOCITNI IN OSTALI TUMORJI Z MUTACIJO *BAP1*

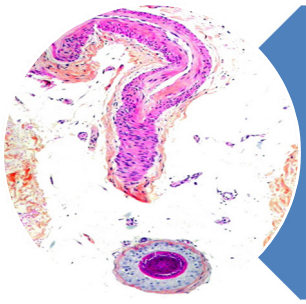
- MELANOM OČESNEGA OZADJA 50%
- MEZOTELIOM (PERITONEJ>PLEVRA) 20%
- KUTANI MELANOM 5%
- KARCINOM LEDVICE, SVETLOCELIČNI 8%
- MENINGIOM
- ADENOKARCINOM PLJUČ

Wiesner T et al. J Clin Oncol 2012; 30: 337-340.


ATIPIČNI SPITZ TUMOR
DELECIJA 9p21
WIESNERJEV NEVUS
?

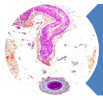

DELECIJA 9p21
???
WIESNERJEV NEVUS
ATIPIČNI SPITZ TUMOR
ALK FUZIJA
NRAS MUTACIJE

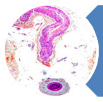
ATIPIČNI SPITZ TUMOR

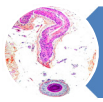


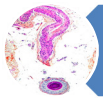
NAJPOGOSTEJŠI VZROKI NEUSTREZNIH DIAGNOZ

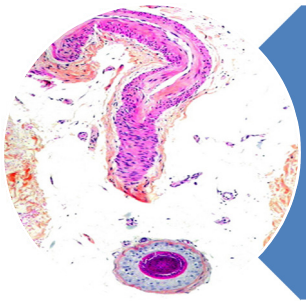
Najpogostejši vzroki neustreznih diagnoz


Neustrezen vzorec za histološko preiskavo

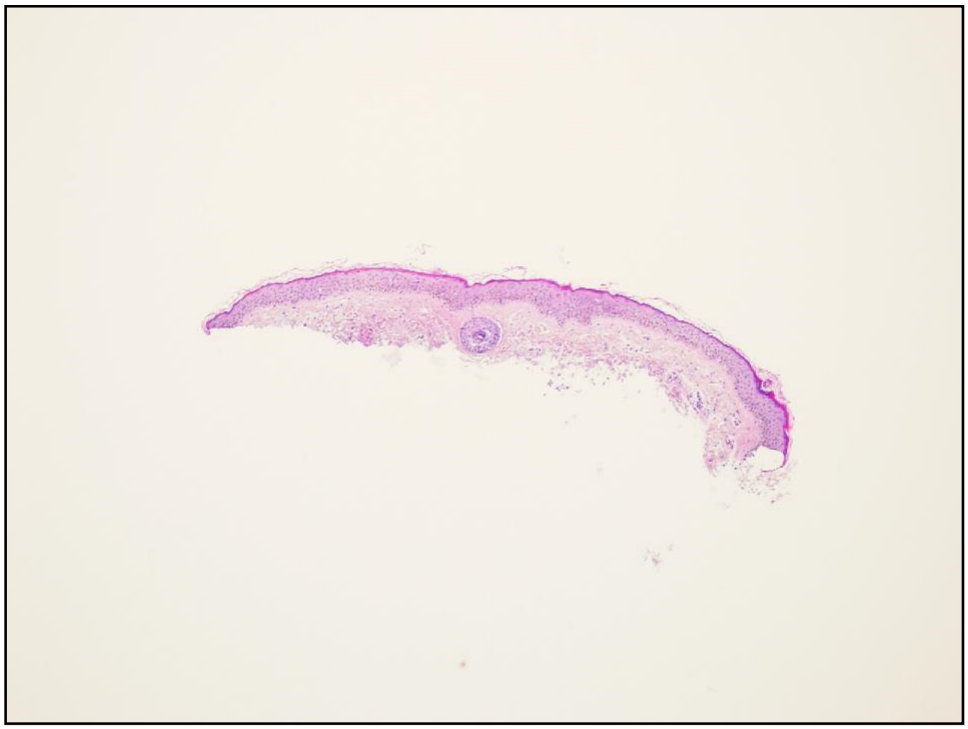

Neustrezni klinični podatki


Pomanjkanje izkušenj patologa


Subjektivnost histoloških parametrov za oceno melanocitnih sprememb

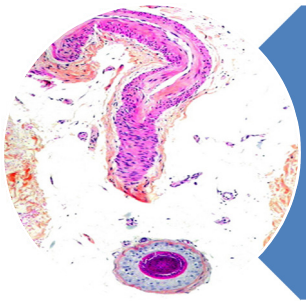


NEUSTREZEN VZOREC



DELNE EKSCIZIJA/BIOPSIJA

- **Ne omogočijo natančne ocene celotne lezije in zvečujejo možnost napačne interpretacije!!!**



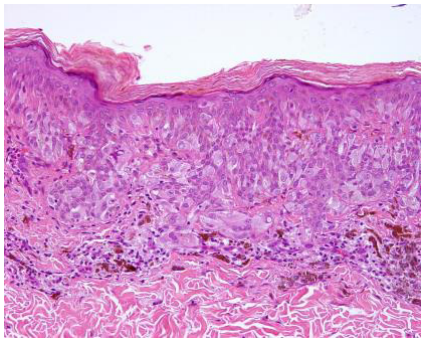
KLINIČNI PODATKI

KLINIČNI PODATKI

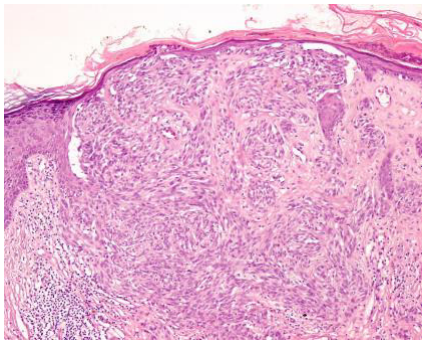
- LOKALIZACIJA
- STAROST
- ANAMNEZA
  - koliko časa
  - kako hitro
  - predhodni posegi
  - ...

ZAKAJ JE POMEMBNA STAROST BOLNIKA?

5 let



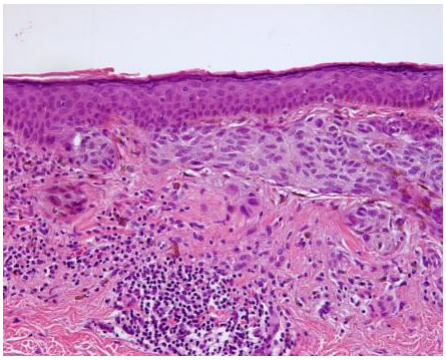
68 let



Spitz nevus / Spitzoidni melanom

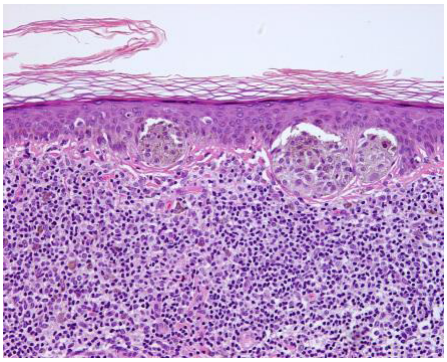
ZAKAJ JE POMEMBEN PODATEK O PREDHODNEM POSEGU?

55 let



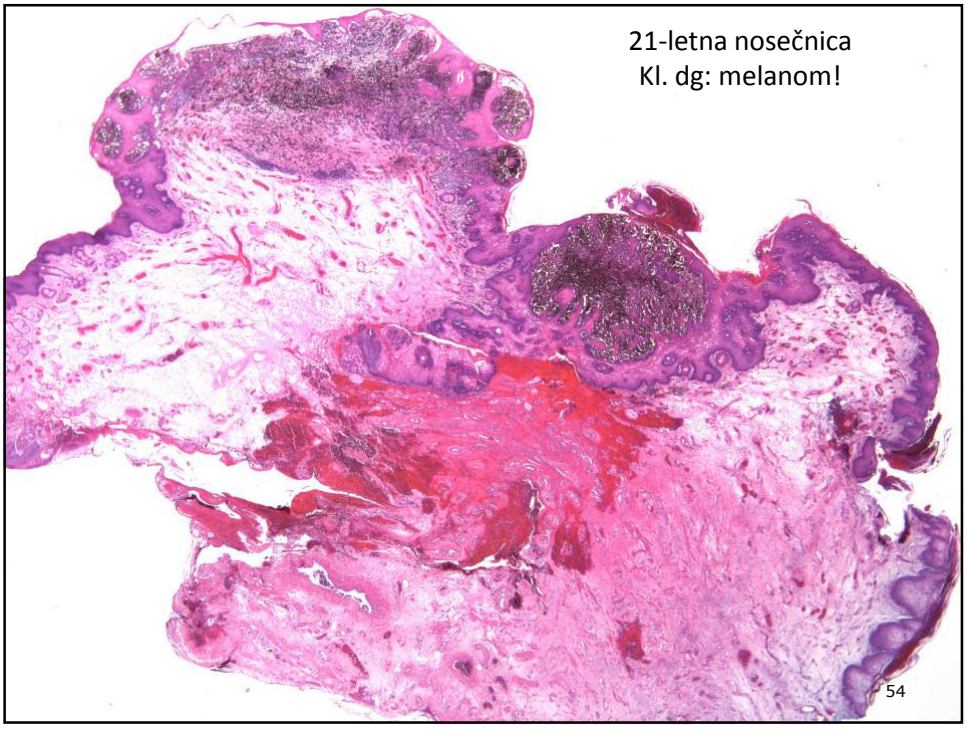
Melanom

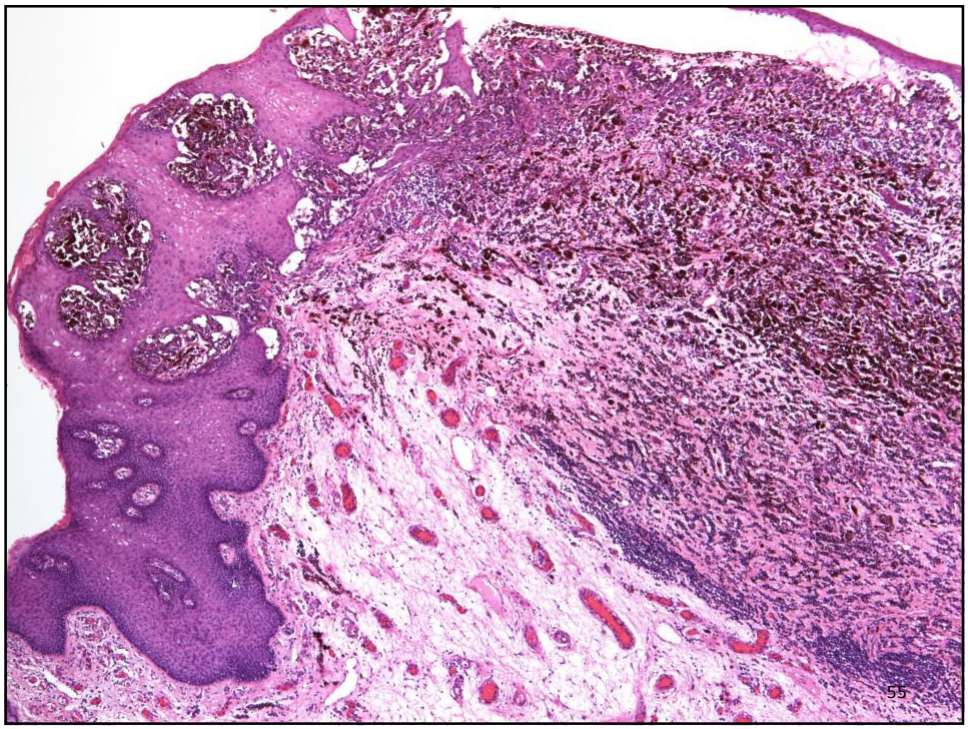
15 let



Rekurentni nevus

ZAKAJ JE POMEMBEN PODATEK O LOKALIZACIJI?

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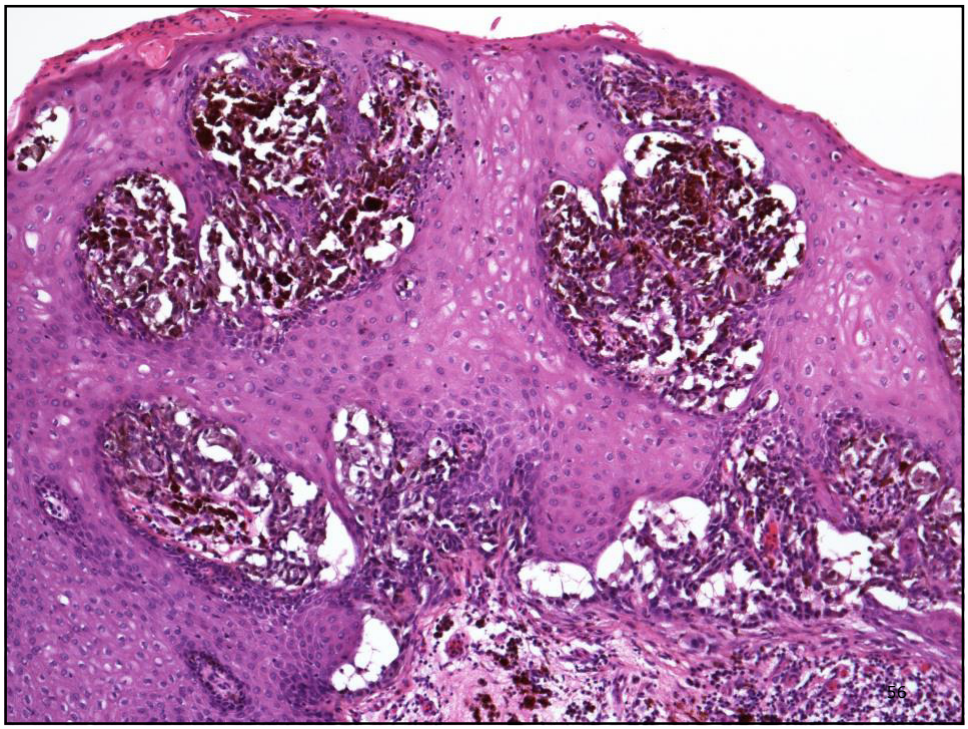
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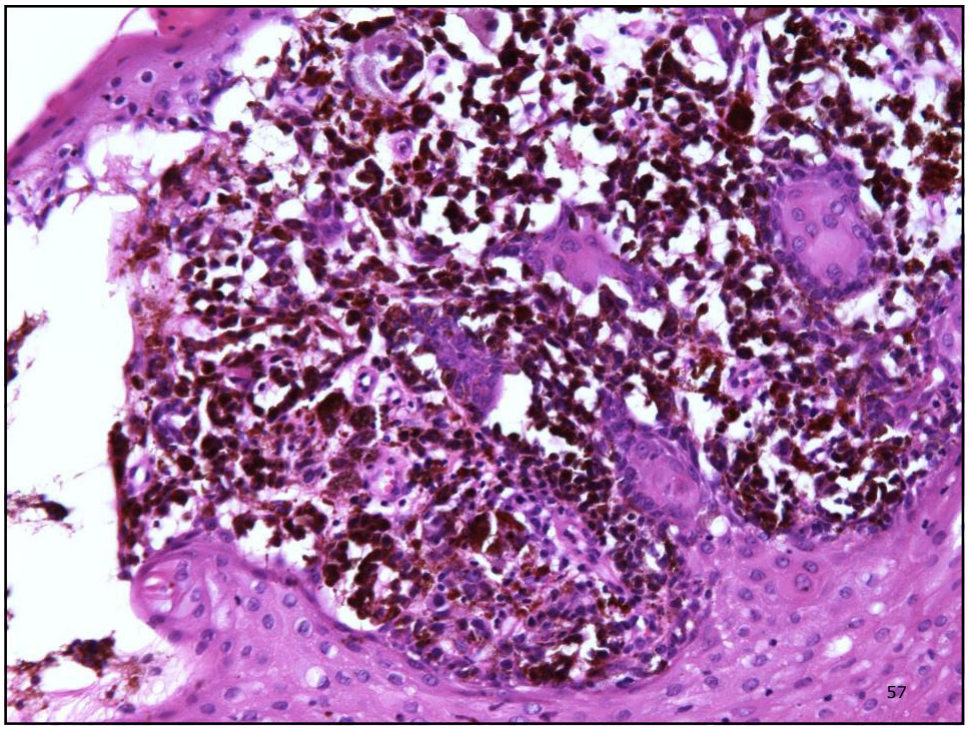
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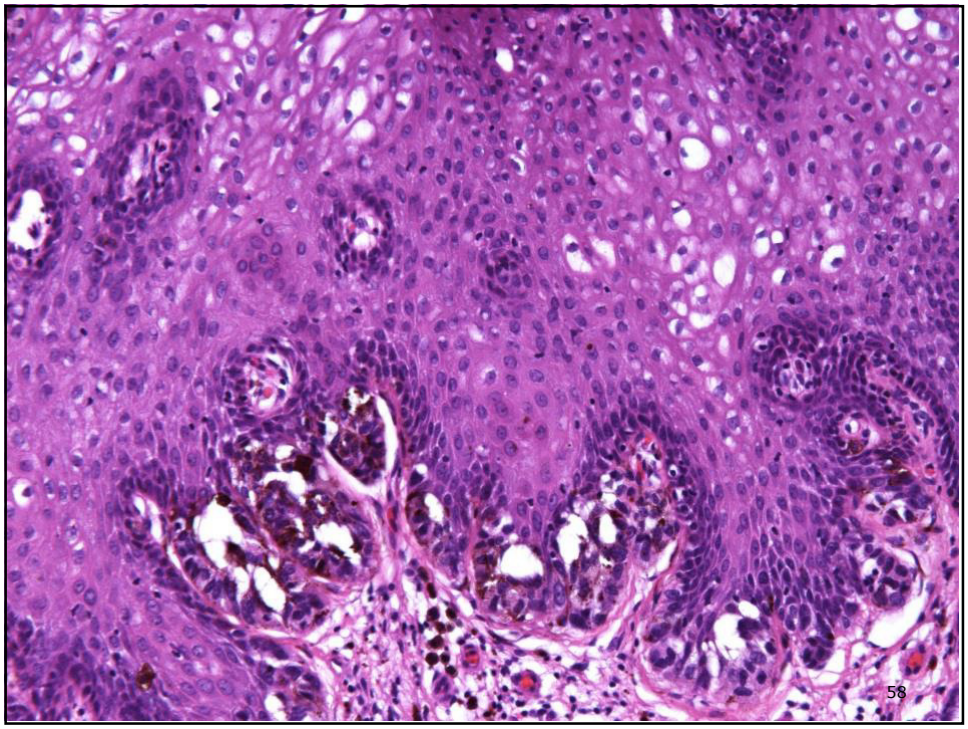
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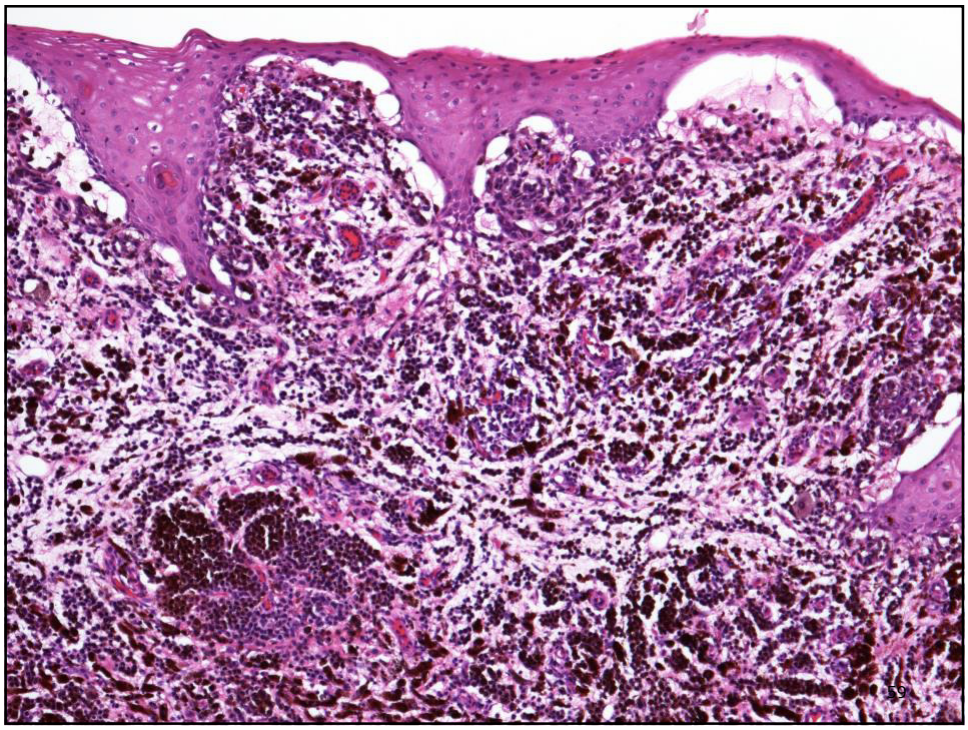
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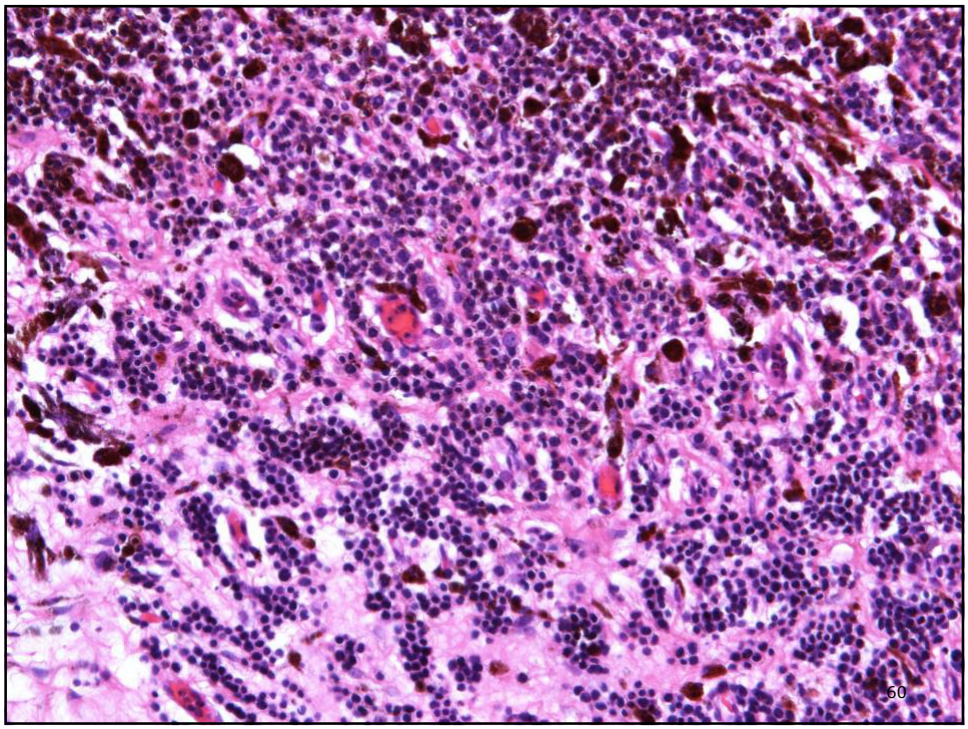
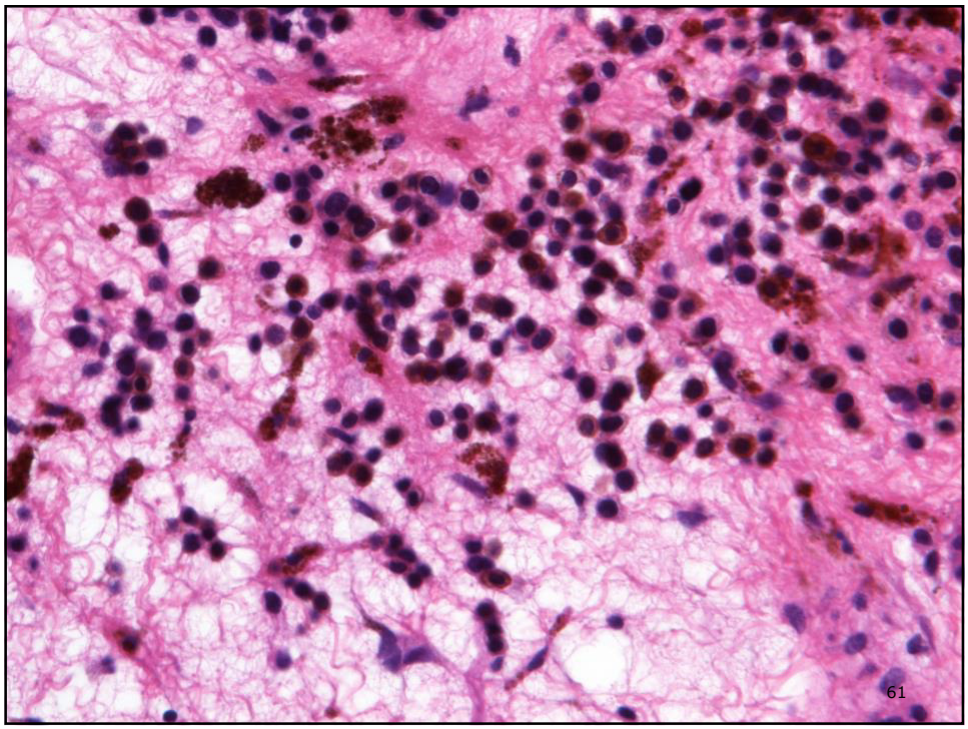

60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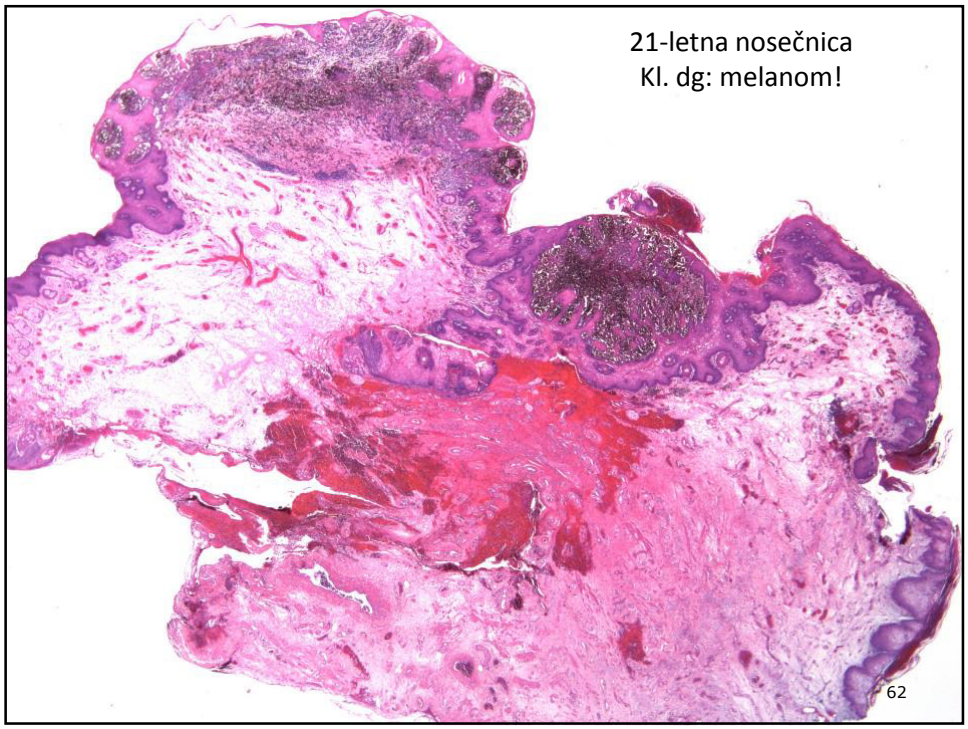
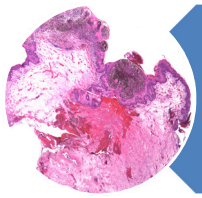
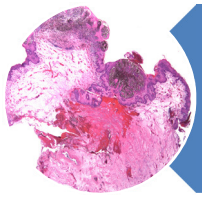

21-letna nosečnica
Kl. dg: melanom!
62

MELANOCITNI NEVUS VULVE

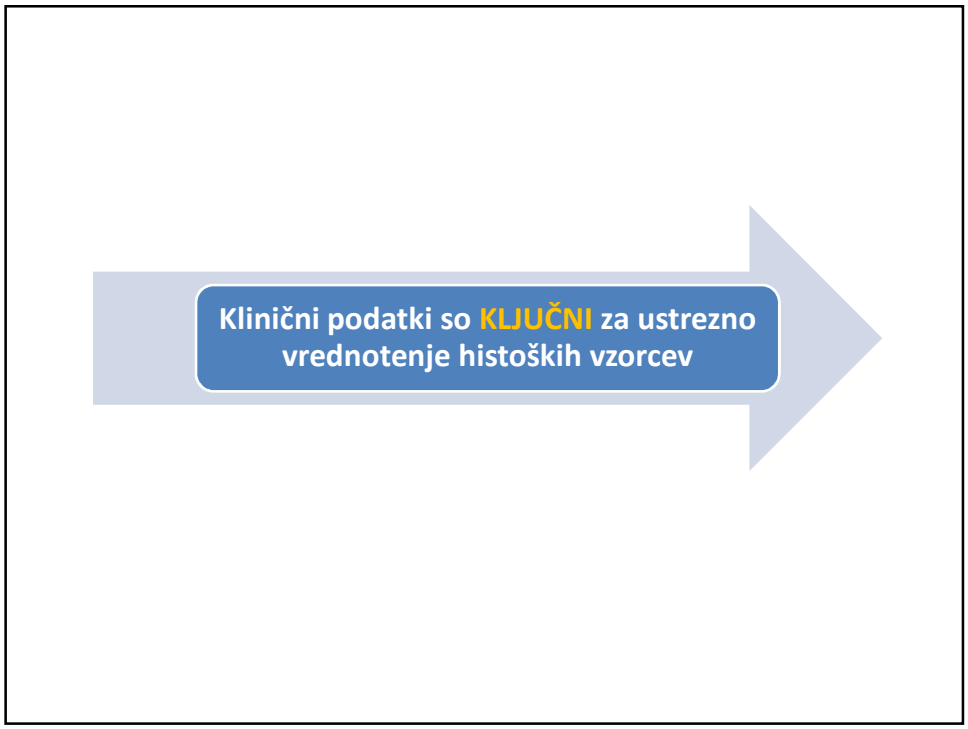
Melanocitni nevusi na posebnih mestih

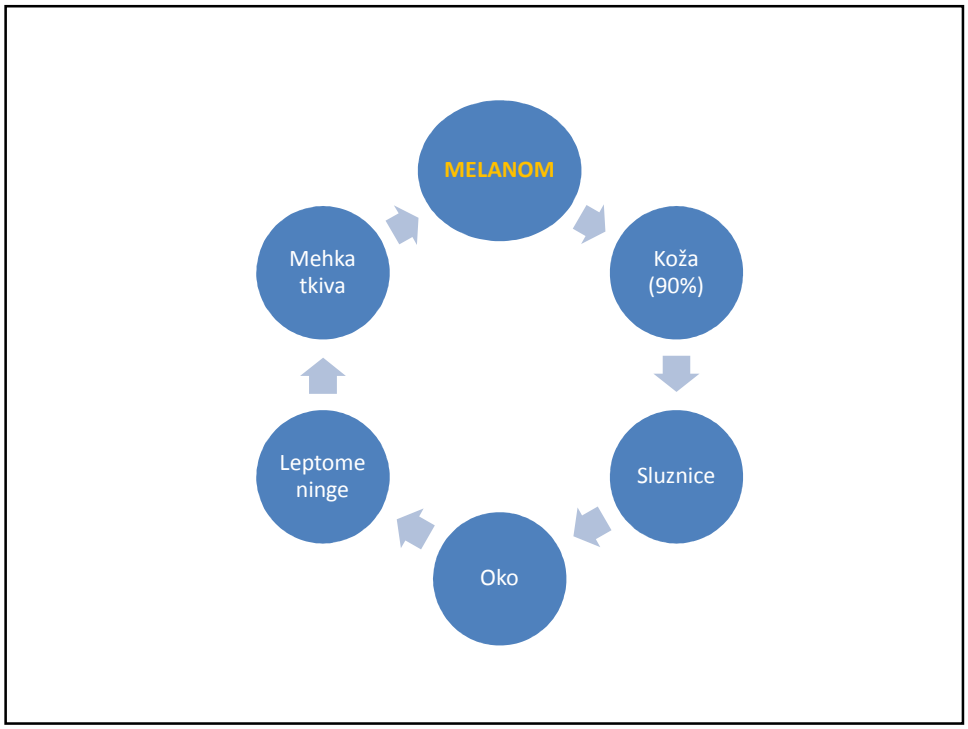


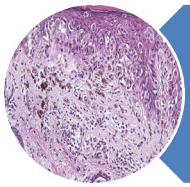
Arhitekturne in citološke posebnosti,



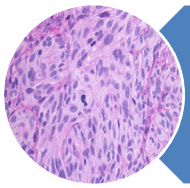
ki na običajnih mestih niso prisotne!


Klinični podatki so KLJUČNI za ustrezno vrednotenje histoških vzorcev


MELANOM
Koža (90%)
Sluznice
Oko
Leptomeninge
Mehka tkiva



Melanom praviloma vznikne znotraj epidermisa.

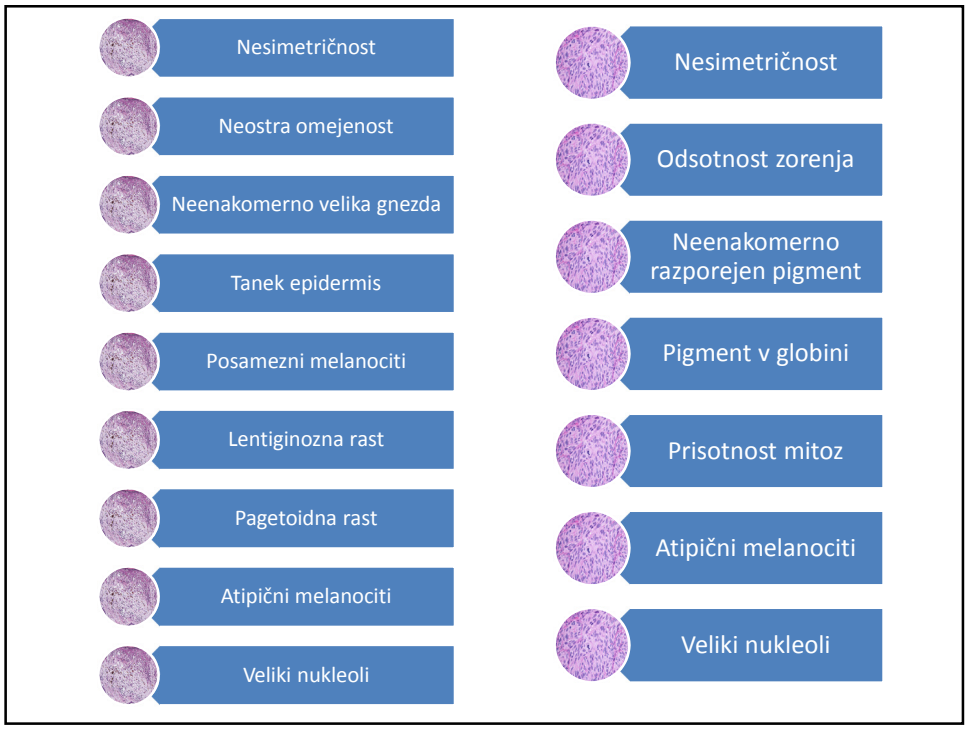


Primarni intradermalni melanomi so izjemno redki

Histološki kriteriji za melanom

Arhitekturni

Citološki



Histološke različice melanoma

- Nevoidni melanom
- Spitzoidni melanom
- **Dezmoplastični / nevrotropni melanom**
- Pigment sintetizirajoči melanom
- Blue-nevus-u podoben melanom
- Pečatnocelični melanom
- Rabdoidni melanom
- Melanom, ki tvori rozete
- ....

Histološke različice melanoma

- Nevoidni melanom
- Spitzoidni melanom
- **Dezmoplastični / nevrotropni melanom**
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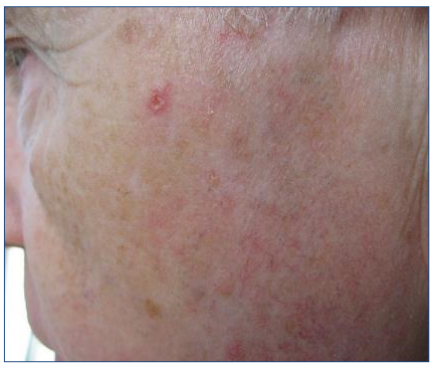
- Blue-nevus-u podoben melanom
- Pečatnocelični melanom
- Rabdoidni melanom
- Melanom, ki tvori rozete
- ....

Desmoplastični melanom

- Starejši (60 let in več)
- M:Ž=2:1
- Soncu izpostavljena koža predela glave in vratu
- Ulceriran eritematozen plak, vozlič
- Pogosto amelanotičen



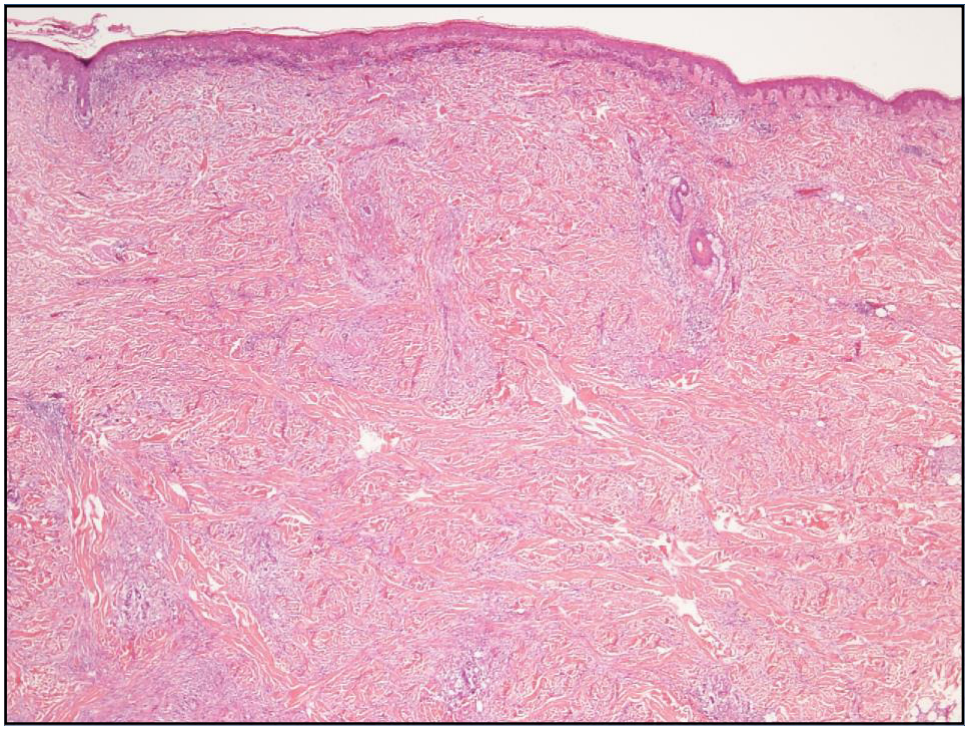
Klinična diagnoza pogosto neznačilna!

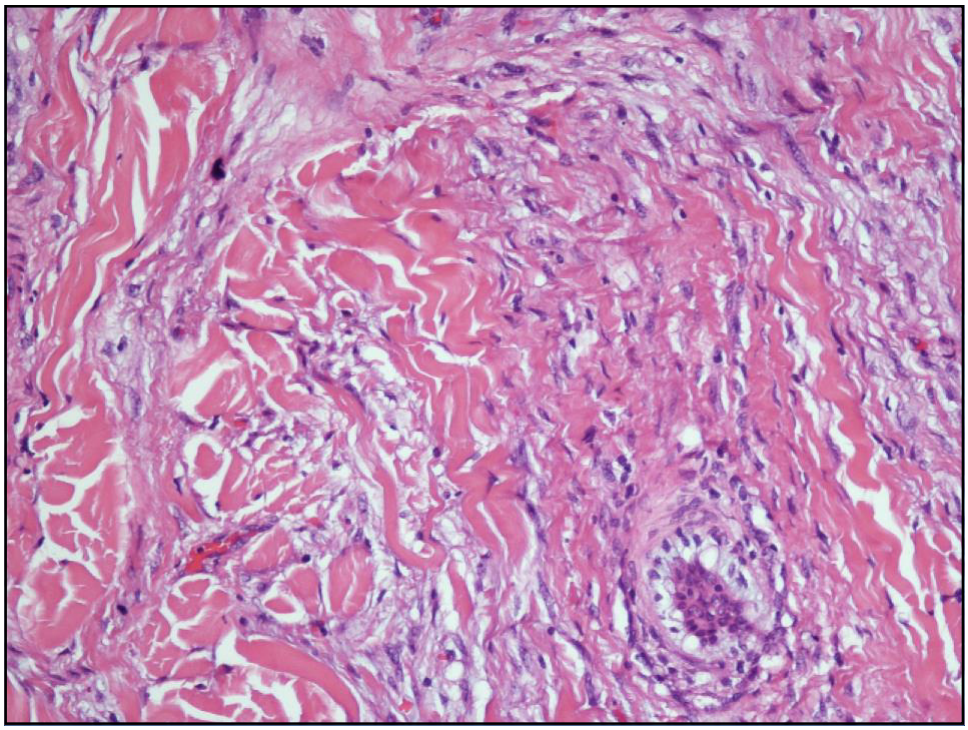
DESMOPLASTIC MALIGNANT MELANOMA (A RARE VARIANT OF SPINDLE CELL MELANOMA)

JOHN CONLEY, MD, RAFFAELE LATTES, MD, AND WILLIAM ORR, MD

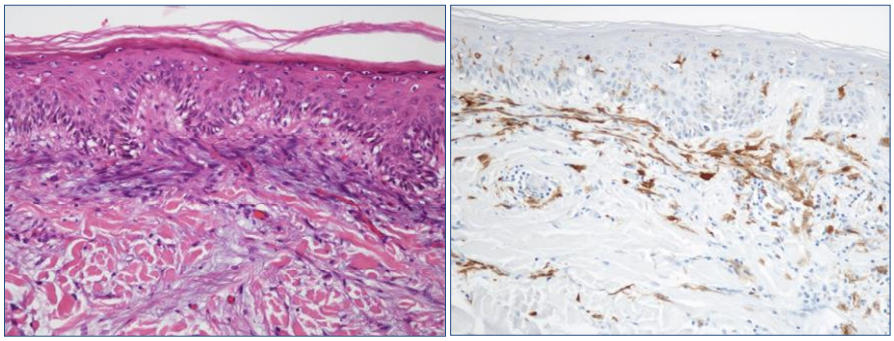
This is a detailed report of seven cases presenting a peculiar sequence of events which, starting from inconspicuous superficial melanotic lesions, generally located in the head and neck regions leads to the production of bulky subcutaneous tumefactions. These have the clinical and histologic appearance of locally invasive fibrous tumors. However, the elongated neoplastic cells are cytologically different from neoplastic fibroblasts, and these tumors behave as highly malignant stubbornly recurring and often metastasizing neoplasms. Some of the recurrences, as well as some of the metastases, are histologically acceptable as malignant melanoma of the more usual type. This appears to be a hitherto undescribed clinicopathologic entity, for which we suggest the term "desmoplastic malignant melanoma."

Cancer 1971; 28: 914-936



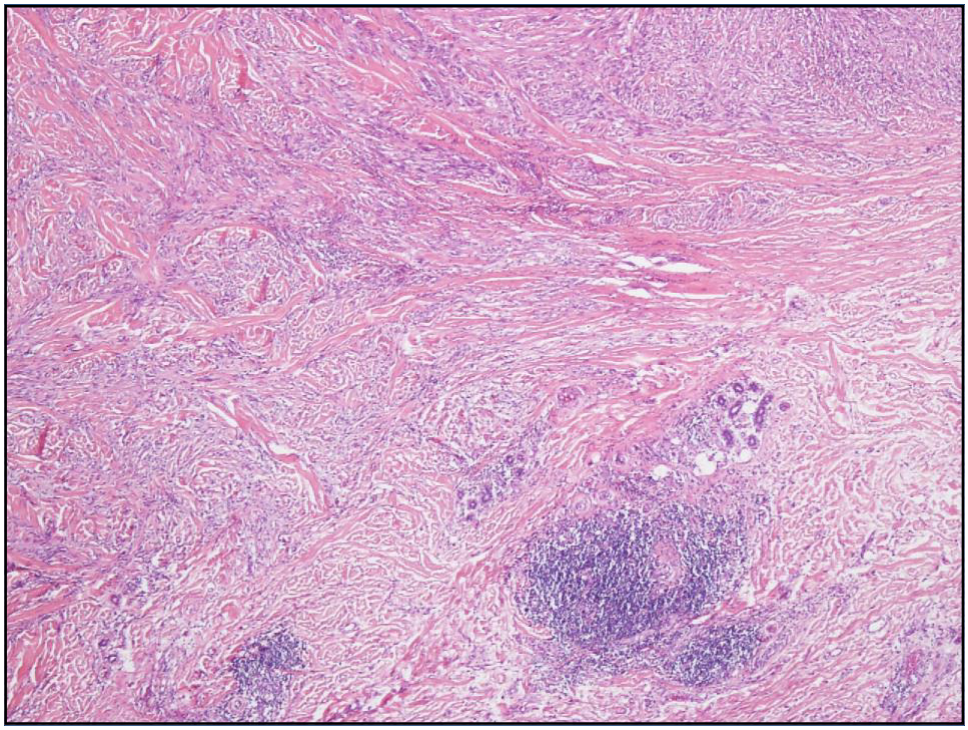


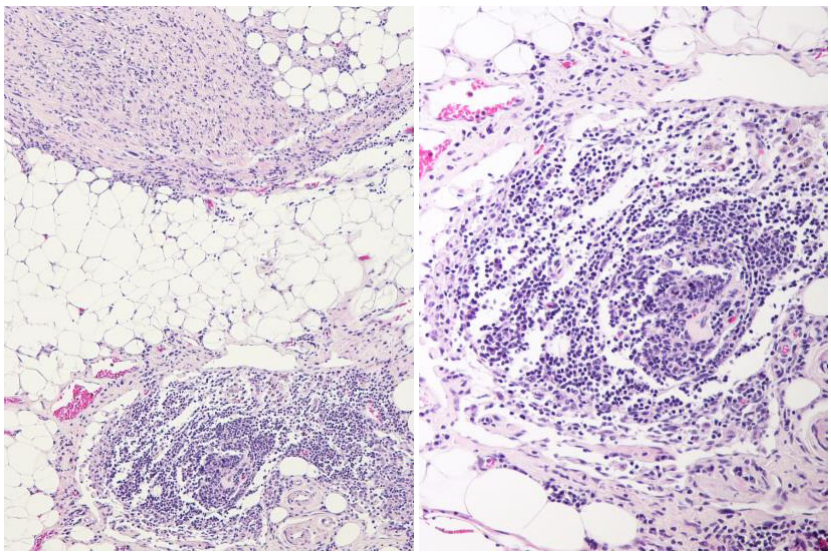
Velik delež dezmoplastičnih melanomov nima epidermalne melanocitne komponente



Uporabni histološki parameter:

Limfatični agregati oziroma folikli
so pogosto prisotni
na obrobju lezije





Richard J. Reed, M.D.

Donald D. Leonard, M.D.

Neurotropic melanoma

A variant of desmoplastic melanoma

ABSTRACT We report a group of neuroid, cutaneous tumors that are usually associated with, or preceded by a melanocytic dysplasia. For this clinicopathologic entity we have chosen the term neurotropic melanoma.

The neurotropic melanoma is a cutaneous fibrous tumor whose clinical course is characterized by local infiltration, multiple recurrences, and commonly by metastases. Its microscopic picture is characterized by atypical "neuroma-like" patterns, by poorly defined margins, and by neurotropism. Its early or precursory melanocytic dysplasias include lentigo maligna (actinic or lentigo maligna variant), and a melanoma with borderline cytologic characteristics (minimal deviation variant). A third type is not preceded by a recognizable melanocytic dysplasia: it has "neuroma-like" qualities at its inception (*de novo* variant).

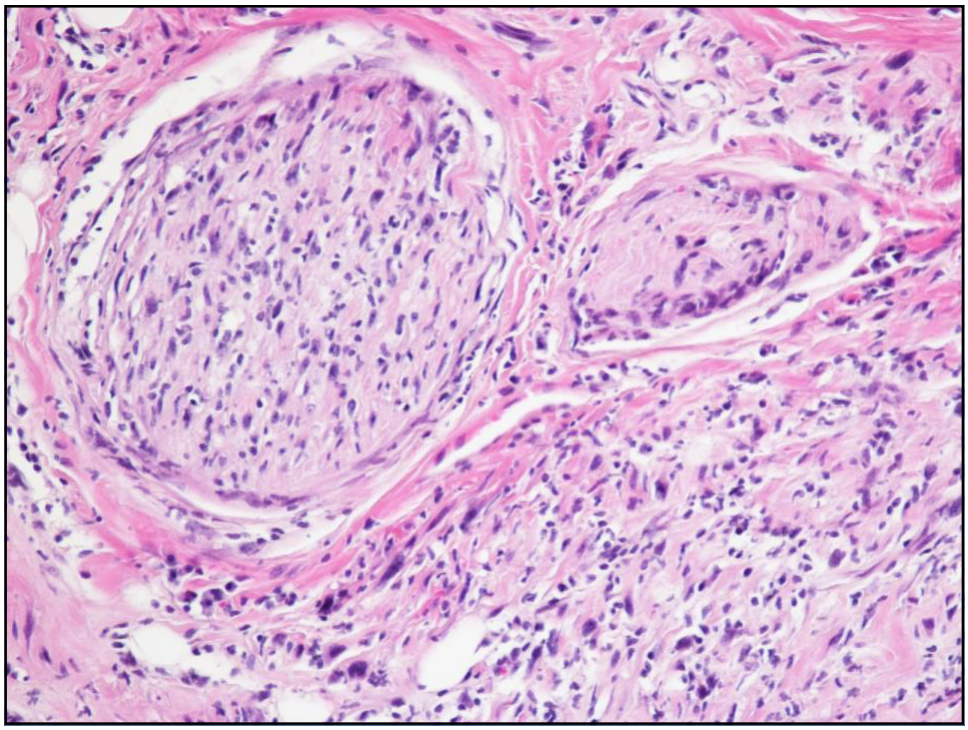
In our 22 cases, the preponderant sites were the head, neck, and lip. The patients were fair-faced, and 18 of the patients were over 40 years old. Seventeen patients had one or more recurrences. Of 16 patients with follow-up, nine died with evidence of disease, five are alive with active disease, and seven are apparently free of disease.

Am J Surg Pathol 3: 301–311, 1979.

INTRODUCTION

Primary spindle cell tumors of the skin and mucous membranes are histogenetically heterogeneous. They comprise a problem category which includes spindle cell carcinomas, and mesenchymal tumors. Melanomas, with the features of desmoplasia, neuroid or Schwann cell differentiation, and minimal or absent melanogenesis, are included in the problem category.[2,6] If melanogenesis is not a feature of a problem spindle-cell melanoma, the choice between a melanocyte and a Schwann cell, as a cell origin, is often arbitrary.

Desmoplastic melanomas are uncommon fibrous tumors whose individual spindle cells are isolated in a dense fibrous matrix.[6,14,25] Desmoplasia is most commonly associated with a lentiginous radial component and a spindle cell vertical component in acral lentiginous melanomas and lentigo maligna melanomas. Neuroid qualities are not emphasized in descriptions of desmoplastic melanomas but are evident in some of the published photomicrographs.[6]



Cutaneous Desmoplastic Melanoma

Reappraisal of Morphologic Heterogeneity and Prognostic Factors

Klaus J. Busam, MD, Urvi Mujumdar, MPH,† Amanda J. Hummer, MS,† Jennifer Nobrega, BA,* William G. Hawkins, MD,‡ Daniel G. Coit, MD,‡ and Mary S. Brady, MD‡*

Abstract: Desmoplastic melanoma (DM) is a variant of melanoma, which may be confused with nonmelanocytic benign or malignant spindle cell proliferations. The histologic hallmark of DM is the presence of fusiform melanocytes dispersed in a prominent collagenous stroma. Phenotypic heterogeneity of DM is underrecognized. Desmoplasia may be prominent throughout the entire tumor ("pure" DM) or represent a portion of an otherwise nondesmoplastic melanoma ("combined" DM). We reviewed melanomas with desmoplasia from 92 patients seen at a single institution between 1980 and 2002. Fifty-five of the tumors were pure DM. Thirty-seven were classified as combined. Mean follow-up of patients was 46 months for those alive at the last follow-up. Univariate analysis of clinical and pathologic parameters revealed four significant variables for disease-free survival: Clark level (IV vs. V; $P = 0.005$), DM subtype (pure vs. combined; $P = 0.01$), tumor mitotic rate (<1, 1–4, >4 mitoses/mm^2; $P = 0.01$), and tumor thickness (<1 mm, 1–4 mm, >4 mm; $P = 0.02$). Only histologic subtype ($P = 0.02$) and Clark level ($P = 0.05$) were independently significant by Cox regression analysis. Our results indicate that distinguishing pure from combined forms of DM is clinically relevant for prognosis (pure forms being associated with longer disease-specific survival). Failure to make this distinction may account for conflicting reports in the literature on the biologic behavior and prognosis of DM.

Key Words: desmoplastic, melanoma, prognostic factors

(*Am J Surg Pathol* 2004;28:1518–1525)

"fibrous tumors whose individual spindle cells are isolated in a dense fibrous matrix."[20] They termed a related variant of spindle cell melanoma with "neuroma-like" features "neurotropic melanoma."[20]

DM may be confused with a variety of benign or malignant nonmelanocytic spindle cell proliferations, such as dermal scar, dermatofibroma, sarcomas, especially fibrosarcoma, atypical fibroxanthoma, nerve sheath tumors, and even sarcomatoid carcinomas.[2,15,23,26] The misdiagnosis of DM is a recurring issue of malpractice claims related to melanoma.[27] The various types of misdiagnoses suggest a broad range in the histologic appearances of DM.

Heterogeneity among tumors classified as DM is apparent in the literature, which describes a spectrum of spindle cell neoplasm from fibrous to neural/schwannian features. Some DMs display a uniform appearance, while others are reported to have arisen in association with a "conventional" melanoma. Our review of tumors from patients referred to our institution with a diagnosis of DM is further testament to this heterogeneity. Some pathologists use the term "desmoplastic melanoma" quite liberally for any spindle cell melanoma with or without neurotropism, even if desmoplasia is only a focal and minor feature. Others reserve the term for melanomas with prominent fibrosis throughout the entire invasive tumor component. In this review, we describe our experience with 92

Desmoplastic melanoma: čisti *vs.* mešani

- čisti
  - >90% dezmoplazije
- mešani
  - 10-90% dezmoplazije

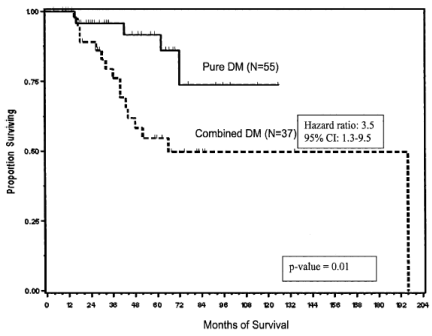
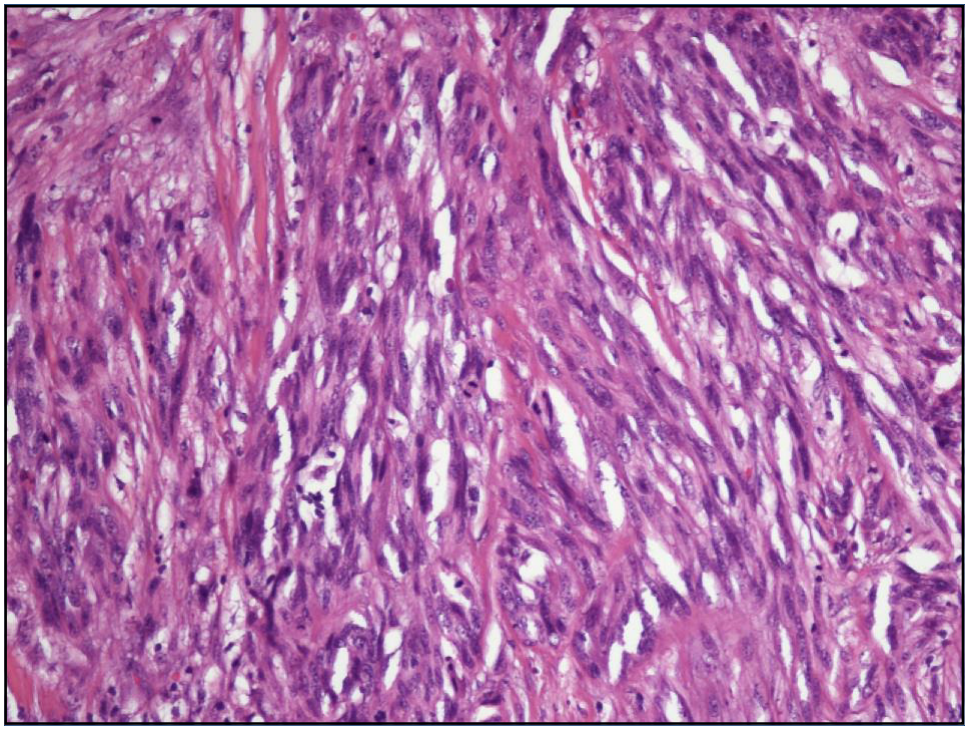


FIGURE 5. Association of histologic subtype (pure vs. combined DM) with disease-free survival for individuals with DM.



J Cutan Pathol 2009: 36: 425–432
doi: 10.1111/j.1600-0560.2008.01058.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Continuing Medical Education Article

Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis

Background: There is disagreement about the behavior and optimal management of desmoplastic melanoma (DM), particularly regarding the incidence of lymph node (LN) involvement. Recently, investigators have noted the frequently heterogenous histologic composition of DM and have found significant differences between pure desmoplastic melanoma (PDM) (≥90% comprised of histologically typical DM) and mixed desmoplastic melanoma (MDM) [≥10% DM and >10% conventional melanoma (CM)].
Method: We reviewed 87 cases of DM comparing the histologic and clinical features of PDM (n = 44) to MDM (n = 43).
Results: At surgical staging, there were LN metastases in 5 of 23 (22%) MDM patients, whereas all 17 PDM patients had negative LN biopsies (0%) (p = 0.04). PDM was less often clinically pigmented (36% vs. 67%) and had a lower mean mitotic index (1.3 vs. 3.0).
Conclusions: There are differences between PDM and MDM, the most important of which is the incidence of LN involvement. Our findings support the clinical utility of classifying DM into pure and mixed subtypes because the negligible rate of nodal involvement in PDM does not support the routine performance of sentinel LN biopsy in this subgroup of melanoma patients. In contrast, the incidence of LN involvement in MDM is comparable to that of CM.

George E, McClain SE, Slingluff CL, Polissar NL, Patterson JW. Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis. J Cutan Pathol 2009; 36: 425–432. © 2008 Blackwell Munksgaard.

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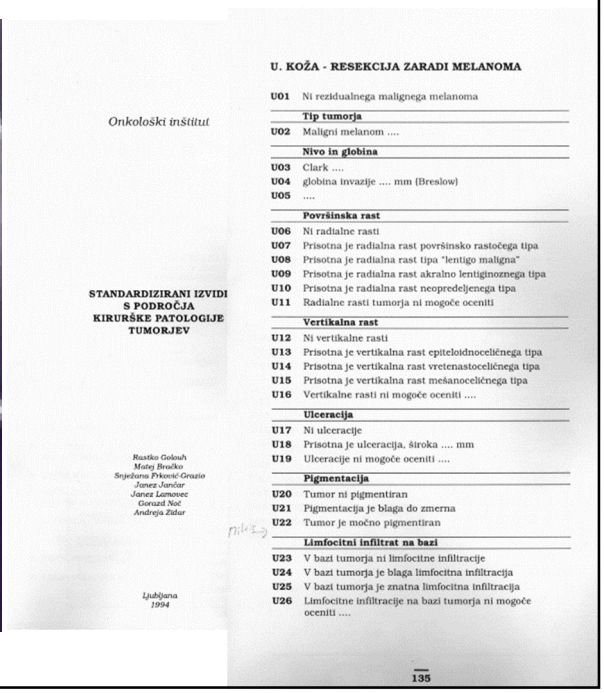
Table 5. Compiled regional LN surgical staging data for clinically node-negative PDM and MDM patients

Author	Number of PDM patients	Number and percentage of PDM patients with +RLN	Number of MDM patients	Number and percentage of MDM patients with +RLN
*Hawkins et al. (MSK)[15]	92	1 (1%)	39	7 (18%)
†Pawlik et al. (MDA)[16]	46	1 (2%)	19	3 (16%)
‡George et al. (UVA) (this study)	17	0	23	5 (22%)
Total	155	2 (1.4%)	81	15 (18.5%)

MDA, M. D. Anderson Cancer Center; MDM, mixed desmoplastic melanoma; MSK, New York Memorial Sloan-Kettering Cancer Center; PDM, pure desmoplastic melanoma; +RLN, regional lymph nodes positive for metastatic melanoma at the time of initial surgical staging; SLN, sentinel lymph node; UVA, University of Virginia Health System.
*The number of patients who were staged by SLN biopsy is not indicated.
†All patients in this study were staged by SLN biopsy.
‡SLN biopsy was the initial surgical staging procedure in greater than 80% of surgically staged patients.

George et al. J Cutan Pathol 2009; 36: 425-432.

Katere podatke vsebuje histopatološki izvid pri melanomu?



Onkološki inštitut

STANDARDIZIRANI IZVIDI S PODROČJA KIRURŠKE PATOLOGIJE TUMORJEV

Rastko Golouh
Matej Brecko
Snježana Pyković-Grazio
Janez Jančar
Janez Lamovec
Gorazd Noč
Andreja Židar

Ljubljana
1994

U. KOŽA - RESEKCIJA ZARADI MELANOMA

U01	Ni rezidualnega malignega melanoma
	Tip tumorja
U02	Maligni melanom ....
	Nivo in globina
U03	Clark ....
U04	globina invazije .... mm (Breslow)
U05	....
	Površinska rast
U06	Ni radialne rasti
U07	Prisotna je radialna rast površinsko rastočega tipa
U08	Prisotna je radialna rast tipa "lentigo maligna"
U09	Prisotna je radialna rast akralno lentiginoznega tipa
U10	Prisotna je radialna rast neopredeljenega tipa
U11	Radialne rasti tumorja ni mogoče oceniti
	Vertikalna rast
U12	Ni vertikalne rasti
U13	Prisotna je vertikalna rast epiteloidnoceličnega tipa
U14	Prisotna je vertikalna rast vretenastoceličnega tipa
U15	Prisotna je vertikalna rast mešanoceličnega tipa
U16	Vertikalne rasti ni mogoče oceniti ....
	Ulceracija
U17	Ni ulceracije
U18	Prisotna je ulceracija, široka .... mm
U19	Ulceracije ni mogoče oceniti ....
	Pigmentacija
U20	Tumor ni pigmentiran
U21	Pigmentacija je blaga do zmerna
U22	Tumor je močno pigmentiran
	Limfocitni infiltrat na bazi
U23	V bazi tumorja ni limfocitne infiltracije
U24	V bazi tumorja je blaga limfocitna infiltracija
U25	V bazi tumorja je znatna limfocitna infiltracija
U26	Limfocitne infiltracije na bazi tumorja ni mogoče oceniti ....

135

Koža, lokacija: Melanom

- Nivo in globina invazije
  - Clark
  - **Breslow**
- Radialna rast
- Vertikalna rast
- **Mitoze**
- **Ulceracija**
- Pigmentacija

- Limfocitna infiltracija
- Regresija
- Spremljajoč melanocitni nevus
- Vaskularna invazija
- Satelitski infiltrati
- Kirurški robovi
- Koža zunaj tumorja

NEODVISNI HISTOLOŠKI NAPOVEDNI DEJAVNIKI

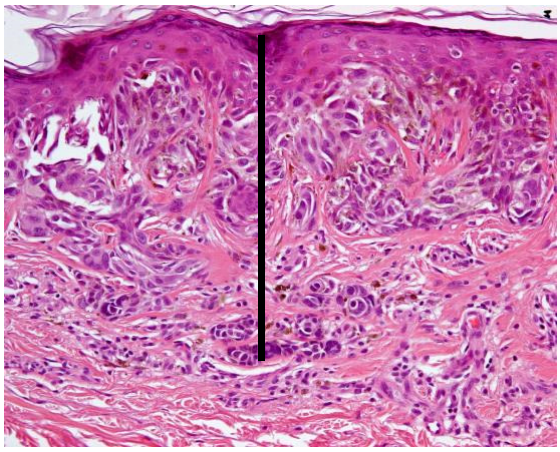
- DEBELINA INVAZIJE (BRESLOW)
- ULCERACIJA
- MITOZE V INVAZIVNI KOMPONENTI

Debelina melanoma (Breslow)

Najpomembnejši neodvisni napovedni dejavnik

Osnova za določanje stadija T

Merimo v milimetrih, na eno decimalno mesto



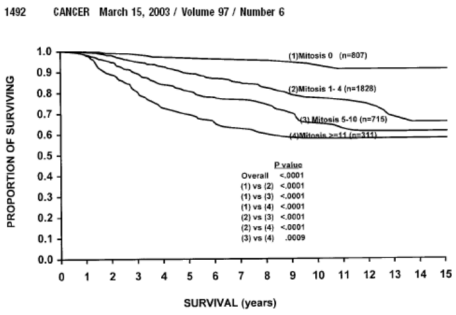
Princip merjenja:

- od zgornjega dela granularnega sloja do naglobje ležečega malignega melanocita
- od dna ulceracije do najglobje ležečega malignega melanocita

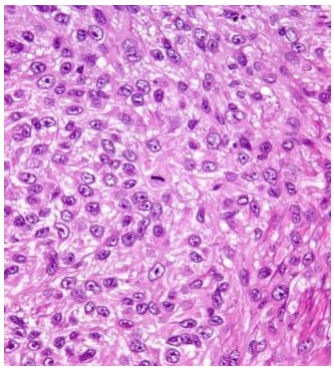
Število mitoz

(za melanome v vertikalni fazi rasti)

- Število na 1 mm^2
- Zelo pomemben neodvisni napovedni dejavnik

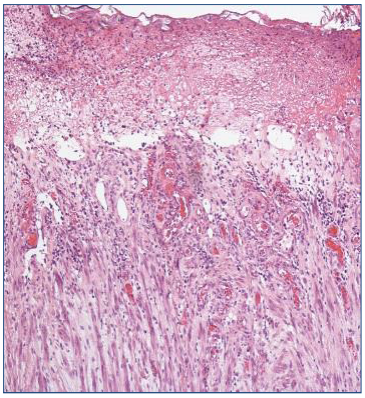


Azzola MF et al, 2003



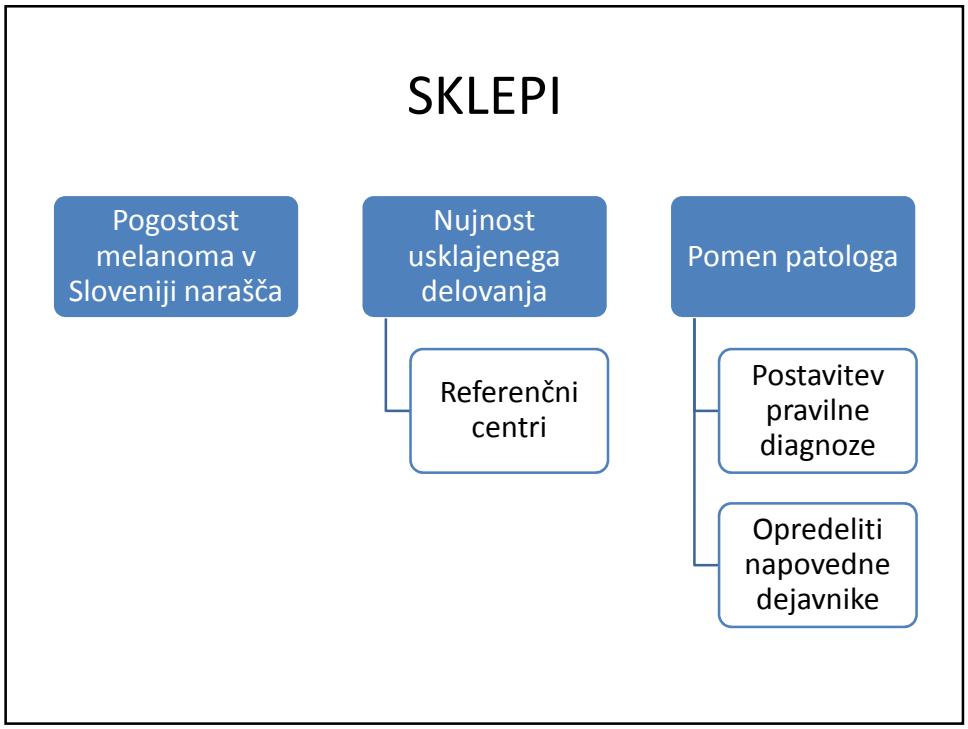
ULCERACIJA

•ODSOTNOST EPIDERMISA NAD TUMORJEM



2017 AJCC, 8 izdaja

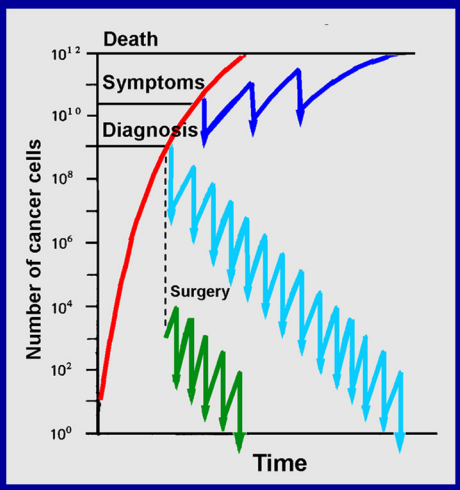
- T1a ≤ 0.8 mm, brez ulceracije
- T1b ≤ 0.8 mm, z ulceracijo
  0.8-1.0 mm, z/brez ulceracijo


SKLEPI
Pogostost melanoma v Sloveniji narašča
Nujnost usklajenega delovanja
Referenčni centri
Pomen patologa
Postavitev pravilne diagnoze
Opredeliti napovedne dejavnike

Maligni melanom – kirurško zdravljenje

Marko Hočevar
Onkološki inštitut

Zdravljenje raka



Melanom - kirurgija

- Primarna lezija
- Regionalne bezgavke
- In transit metastaze
- Oddaljene metastaze

Primarna lezija

- Ekscizijska biopsija
  - Varnostni rob 2-5 mm
- Incizijska biopsija/punch biopsija
  - Celotna debelina najbolj suspektnega dela
- Ablacija nohta (subungualni melanom)

Primarna lezija - histologija

- Benigno
- In situ melanom

} 2-5 mm

- Invazivni melanom ⟶ ≥1 cm

Primarna lezija - radikalna ekscizija

- Veronesi U N Engl J Med. 1988 ;318(18):1159-62.
  - <2 mm 1-3 cm
- Balch CM Ann Surg Oncol. 2001 ;8(2):101-8.
  - 1-4 mm 2-4 cm
- Ringborg U Cancer. 1996 ;77(9):1809-14.
  - 0,8-2 mm 2-5 cm
- Thomas JM N Engl J Med. 2004 ;350(8):757-66.
  - > 2 mm 1-3 cm
- Haigh PI Can J Surg. 2003 Dec; 46(6): 419-26.
- Zitelli JA J Am Acad Dermatol. 1997 ;37(3):422-9.
  - Večina <1,5 mm
    - 6 mm (83%)
    - 9 mm (95%)
    - 12 mm (97%)

Primarna lezija - radikalna ekscizija

- Melanom in situ 5 mm
- Melanom < 1 mm 1 cm
- Melanom 1-4 mm 1-2 cm
- Melanom > 4 mm ≥2 cm

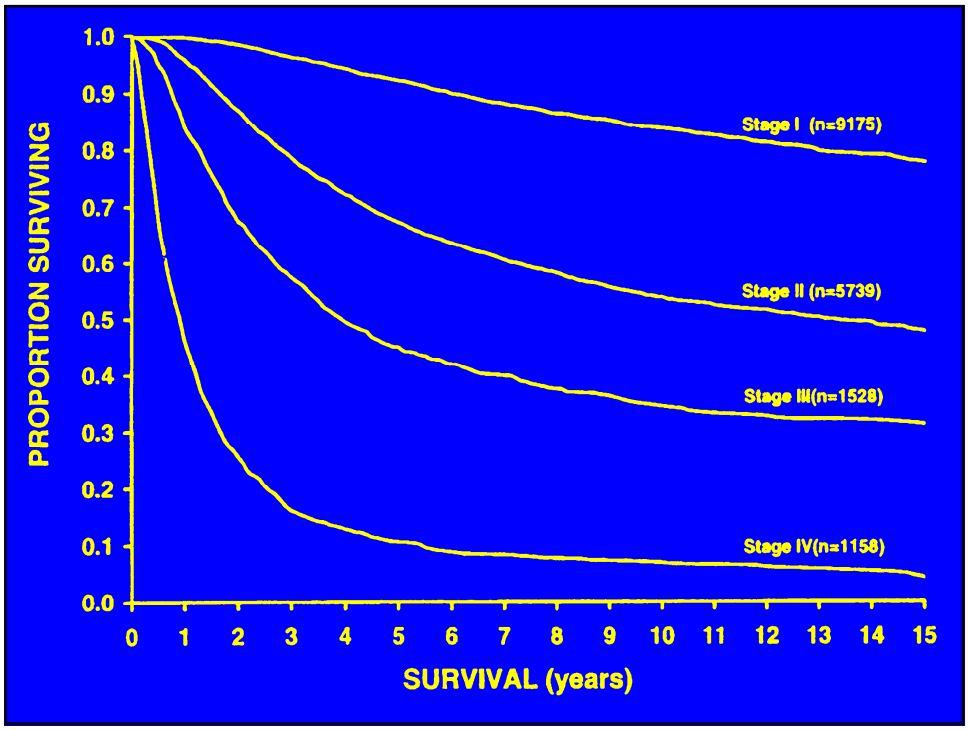
Melanom - kirurgija

- Primarna lezija
- Regionalne bezgavke
- In transit metastaze
- Oddaljene metastaze

Melanom – regionalne metastaze

- Najpomembnejši prognostični dejavnik
- 65% bolnikov → sistemski razsoj

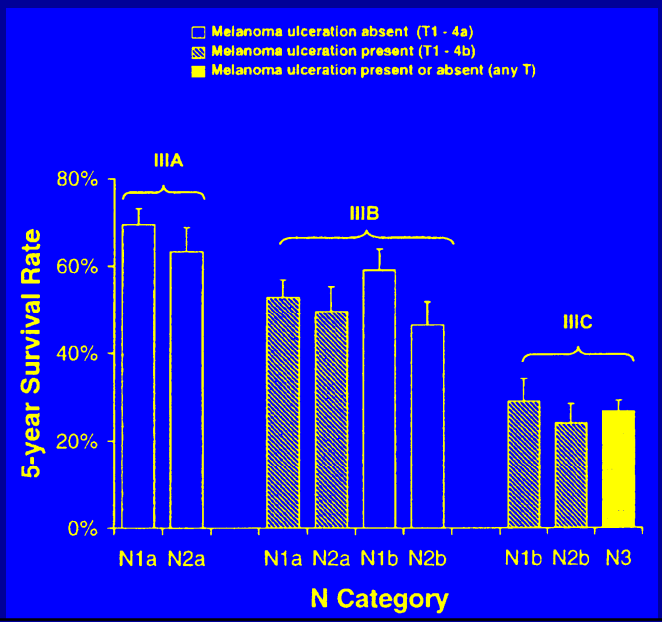
Shaw HM. Pathology 1985; 17: 271-274



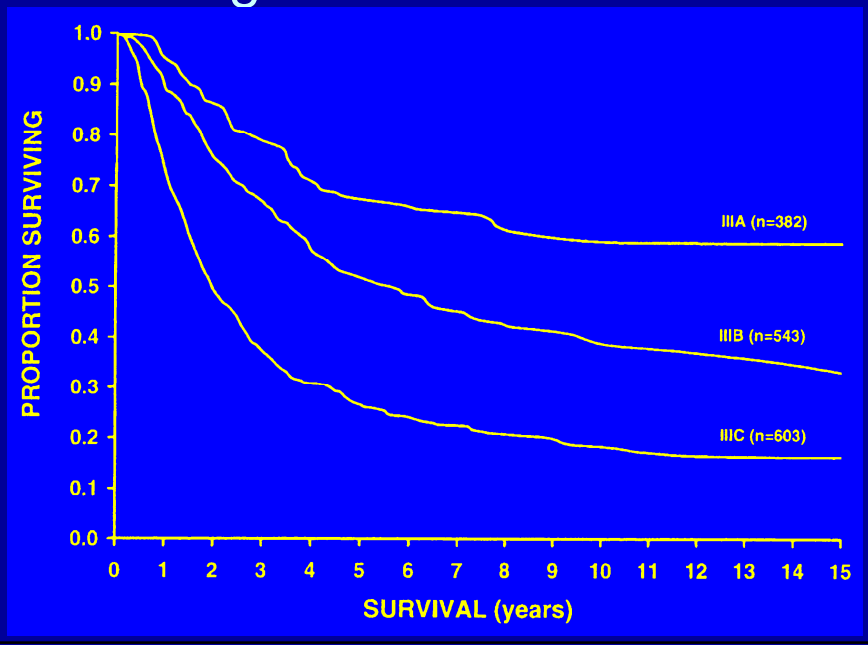
Regionalne metastaze TNM

N1	1 bezgavka	a:klinično okultna metastaza b:klinično odkrita metastaza c:in transit metastaza, mikrosatelit/satelit
N2	2-3 bezgavke	a:klinično okultne metastaze b:klinično odkrite metastaze c:okultne/klinično odkrite metastaze v 1 bezgavki + in transit metastaza, mikrosatelit/satelit
N3	≥ 4	a:klinično okultne metastaze b:klinično odkrite metastaze ali zraščene bezgavke c:okultne/klinično odkrite metastaze v ≥2 bezgavkah ali zraščene bezgavke + in transit metastaza mikrosatelit/satelit

Regionalne metastaze



Regionalne metastaze



Regionalne metastaze

Klinično ugotovljene

- Radikalna limfadenektomija
  - En-block odstranitev celotne bezgavčne lože

Klinično okultne

- SLNB (biopsija sentinel bezgavke)

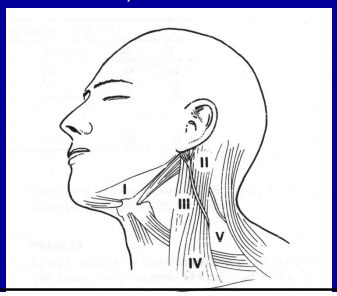
Radikalna limfadenektomija

- Vrat (≥15LN)
- Aksila (≥10LN)
- Ingvine (≥5LN)

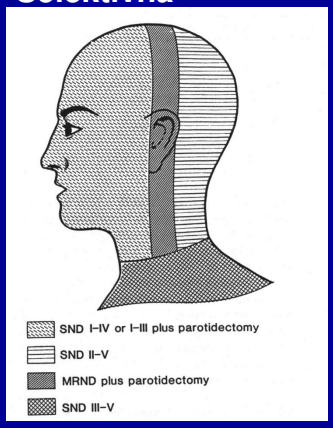
Vratna limfadenektomija

Kompletna

- RND
- mRND
  - I (XI.nerve)
  - II (XI. nerve, SCM)
  - III (XI.nerve, SCM, jugular vein)

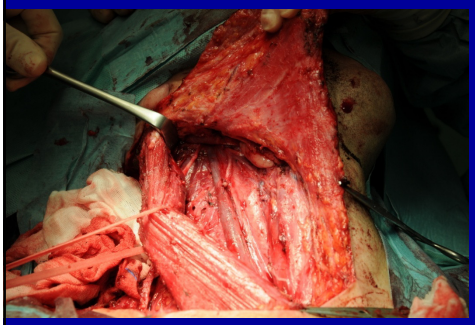


Selektivna

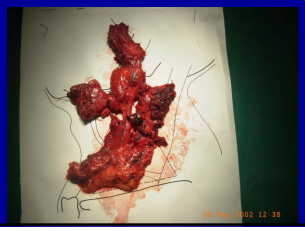


O'Brien CJ. Head&Neck 1995; 17: 232-241.
Shah JP. Am J Surg 1991; 162: 320-323.

Vratna limfadenektomija



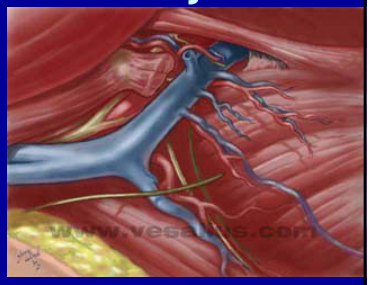
- Nivoji I-III

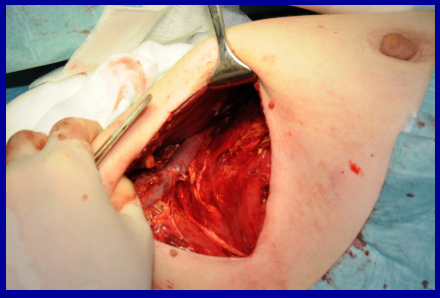


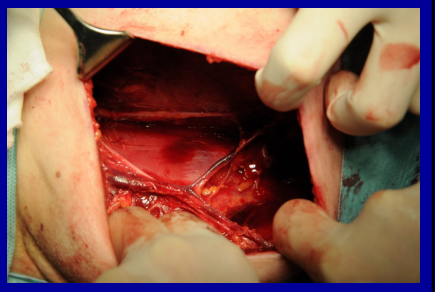
- Nivoja V, V

Aksilarna limfadenektomija

- Kompletna
  - Nivoji I-III





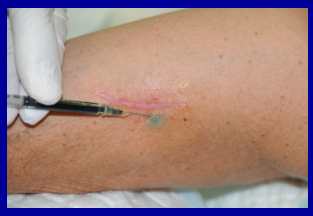


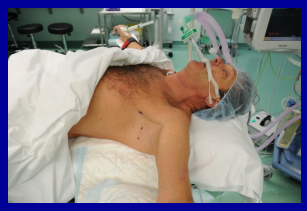
Ingvinalna limfadenektomija

- Superficialna (ingvinalna)
- Globoka (ingvinoiliakalna)

Biopsija sentinel bezgavke

- Nuklearna medicina
- Kirurgija
- Patologija
- Bolnik



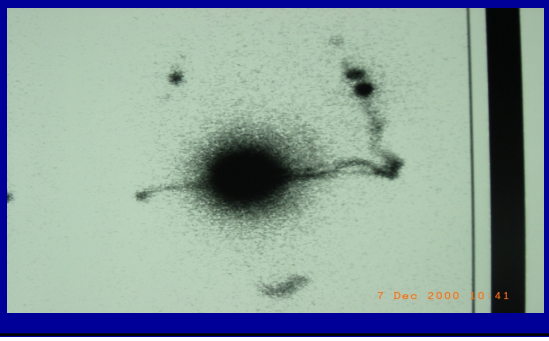


Biopsija sentinel bezgavke

Nuklearna medicina

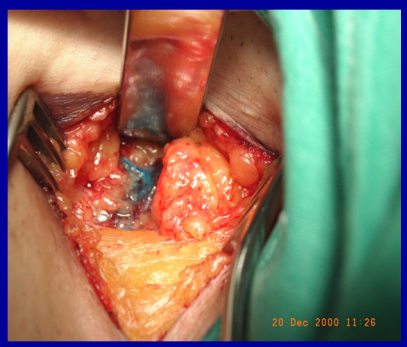
↓

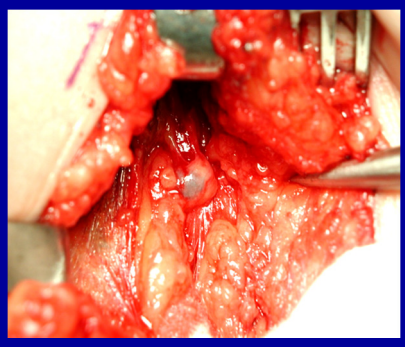
limfoscintigrafija



Biopsija sentinel bezgavke

kirurgija





Biopsija sentinel bezgavke

patologija

serijsko rezanje
imunohistokemija
RT-PCR

Biopsija sentinel bezgavke

Bolnik

⇓

individualni pristop
minimalno invaziven
↑ histopatologška občutljivost

Biopsija sentinel bezgavke

- Verjetnost regionalnih metastaz ≥ 10%
  - (T1b melanomi)?
  - ≥T2 melanomi
- Prednosti
  - najpomembnejša prognostična informacija
  - najnatančnejša zamejitev bolezni
- Neželjene posledice
  - 5-10% možnost infekta, seroma, limfedema,
  - krvavitve, tromboze, zapleti splošne anestezije

Pozitivna biopsija sentinel bezgavke

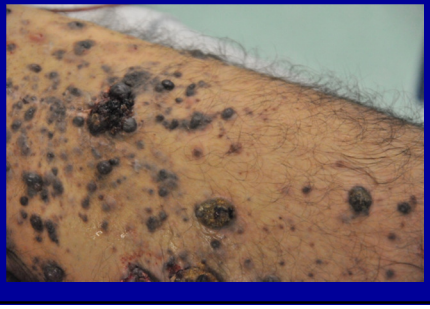
- Kompletna radikalna limfadenektomija
- Aktivno spremljanje
  - UZ regionalnih bezgavk na 3-12 mesecev
- Prednosti
  - najpomembnejša prognostična informacija
  - ↓ regionalnih ponovitev
- Neželjene posledice
  - Limfedem!

Melanom - kirurgija

- Primarna lezija
- Regionalne bezgavke
- In transit metastaze
- Oddaljene metastaze

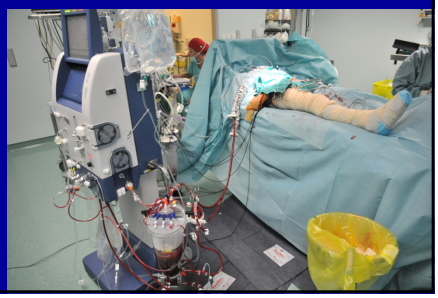
In transit metastaze

- Multifokalne kožne ali podkožne metastaze, ki se širijo po limfatičnem sistemu med mestom primarnega tumorja in regionalno bezgavčno ložo



In transit metastaze

- ↓ število majhnih in-transit metastaz (< 5)
  - kirurška ekscizija z minimalnim negativnim robom
- številne in/ali velike in-transit metastaz na udih
  - Isolated limb perfusion (ILP)
    - Hipertermija (40-41°C)
    - Melfalan (phenylalanine mustard) +/-TNF
    - EKC (perfuzor, oksigenator)
    - transfuzija
  - Isolated limb infusion (ILI)
    - Hipertermija (40-41°C)
    - Melfalan, D actinomicin
    - Interventni radiolog
    - Ni transfuzije



Melanom - kirurgija

- Primarna lezija
- Regionalne bezgavke
- In transit metastaze
- Oddaljene metastaze

Metastazektomija

- Solitarne metastaze
  - CŽS
  - pljuča
  - jetra
  - vranica
  - mehka tkiva
- Ileus

Zaključki

- Kirurgija je osnovno in najpomembnejše zdravljenje melanoma
- Edini kurativen način zdravljenja
- Omogoči uporabo specifičnih zdravil, ki so sistemsko preveč toksična za klinično uporabo

Adjuvantno zdravljenje

Prof.dr.Janja Ocvirk, dr.med.

ADJUVANTNO ZDRAVLJENJE

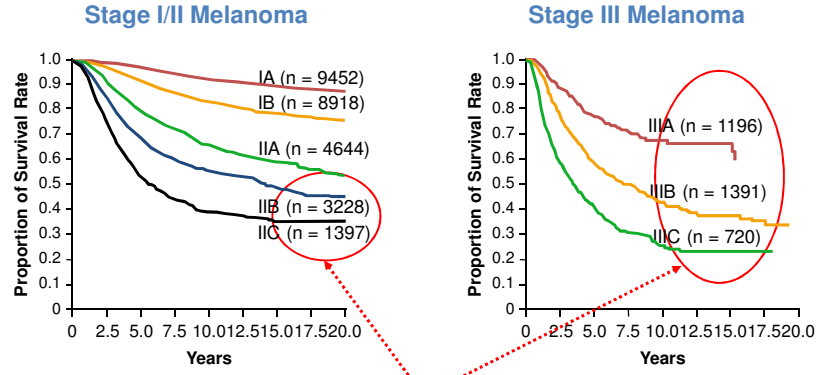
- Je dodatno zdravljenje po uspešni operaciji z namenom, da bi povečali možnost ozdravitve. Uporabljamo ga, ko obstaja veliko tveganje za metastatsko bolezen, vendar brez evidentnih znakov metastaz. Adjuvantno zdravljenje je lahko kemoterapija, radioterapija, hormonska ali biološka terapija.
- Pri bolnikih z melanomom uporabljamo biološko terapijo in radioterapijo.

Cilji adjuvantne terapije in morebitni cilji adjuvantnih preskušanj

- Izboljšanje OS?
  Težko ga je prikazati
  Potencial za ozdravljenje
- Izboljšanj RFS?
  Pacientom je pomemben čas brez bolezni
  "Most" za boljše zdravljenje

OS = celokupno preživetje; RFS = preživetje brez ponovitve.
Prilagojeno po Lorigan P. Predstavljen na ASCO 2016

Kdo potrebuje adjuvantno zdarvljenje?



High-risk patients: higher recurrence rate and relatively poor survival

Adapted from Balch CM et al. *J Clin Oncol.* 2009;27:6199-6206.

Opcije adjuvantnega zdravljenja[1-4]

IFN-α
High-dose IFN-α (preferred in USA)
Low-dose IFN-α (preferred in EU)
PEG–IFN-α
- Some RFS improvement
- Marginal OS improvement
- Toxicity concerns

Ipilimumab (10 mg/kg)
-approved for patients with LN mets > 1 mm
- RFS improvement
- OS improvement
- Toxicity concerns

Clinical Trial

Observation

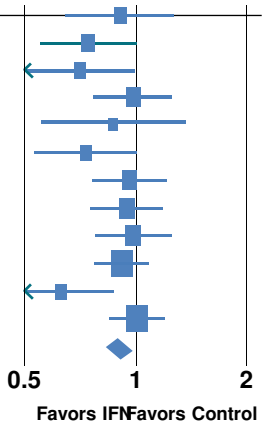
IFN = interferon; LN = lymph node; mets = metastases; PEG = pegylated.

1. Garbe C et al. *Eur J Cancer.* 2016;63:201-217. 2. NCCN Guidelines®: Melanoma. Version 3.2016. https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf. Accessed September 2016. 3. McArthur GA. *J Clin Oncol.* 2014;32:171-173. 4. Eggermont AM et al. *New Engl J Med* 2016 Oct 7.

Adjuvantni IFN-α – Kaj vemo?

OS Hazard Ratios

	HR	LL	UL	SE	Patients	Events (IFN/Control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
F1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.98	0.04		



Mocellin S et al, *J Natl Cancer Inst.* 2010;102:493-501.

RELATIVNE KONTRAINDIKACIJE za IFN

- Kardiovaskularne bolezni
- Pulmonarne bolezni
- Jetrna disfunkcija
- Metabolne bolezni
- Psihiatrična stanja
- Slabo nadzorovana sladkorna bolezen
- Nepravilnosti delovanja ščitnice
- Autoimune bolezni

NAJPOGOSTEJŠI NEŽELENI UČINKI ZDRAVLJENJA z IFN-α2b

Simptomi		**Znaki**
Fatigue		Neutopenija/
Mialgija		↑AST/ALT
Glavobol	Gripozni	Alopecija
↑ TT	sindrom	
Mrzlica		
Nausea/Vomiting		
Diareja		
Spr. volje/depresija		
Anoreksija		

Obvladovanje neželenih učinkov

- Uporaba paracetamola, antiemetikov
- Dobra hidracija
- Nesteroidni antirevmatiki pri glavobolu in mialgiji
- Pomen prehrane in prehranjevanja
- Zgodnja detekcija depresije
- Pravilne nega suhe kože

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

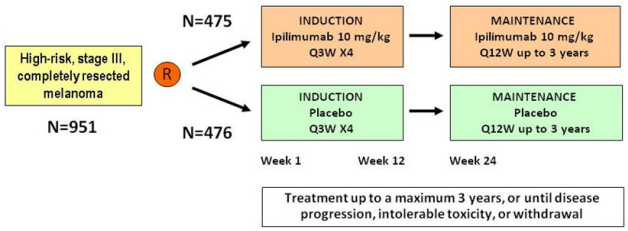
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

Eggermont AM et al. *New Engl J Med* 2016 Oct 7.

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial (Eggerrmont AMM, et al, *Lancet Oncol* 2015; 16: 522–30)- 1

EORTC 18071/CA184-029: Study Design

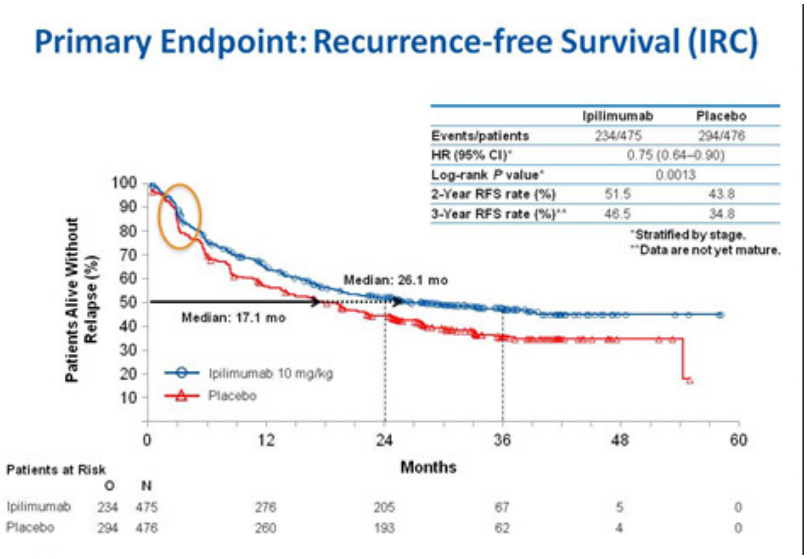


Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Eggerrmont AMM, et al, *Lancet Oncol* 2015; 16: 522–30)- 2

Primary Endpoint: Recurrence-free Survival (IRC)



Eggerrmont AMM, et al, *Lancet Oncol* 2015; 16: 522–30)- 2

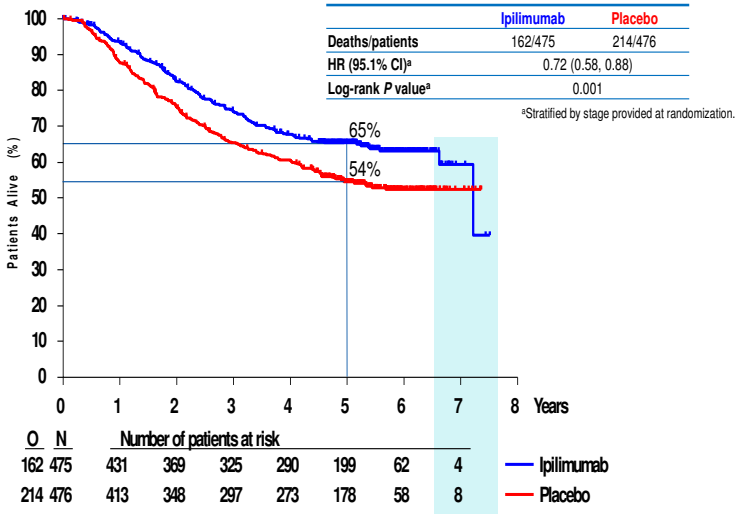
Resolution of Grade 2-4 irAEs

	Ipilimumab (n=471)	Placebo (n=474)
Skin irAE		
N with event	129	14
Resolved, n (%)	115 (89.1)	13 (92.9)
Median, wks (95% CI)	5.5 (4.1–8.1)	2.6 (0.1–39.7)
Gastrointestinal irAE		
N with event	144	18
Resolved, n (%)	135 (93.8)	17 (94.4)
Median, wks (95% CI)	4.0 (2.7–5.1)	0.9 (0.4–1.9)
Hepatic irAE		
N with event	77	5
Resolved, n (%)	73 (94.8)	4 (80.0)
Median, wks (95% CI)	5.0 (3.7–8.4)	12.0 (1.1–NR)
Endocrine irAE		
N with event	134	5
Resolved, n (%)	75 (56.0)	4 (80.0)
Median, wks (95% CI)	31.0 (13.9–186.0)	12.6 (3.4–NR)

NR=not reached.

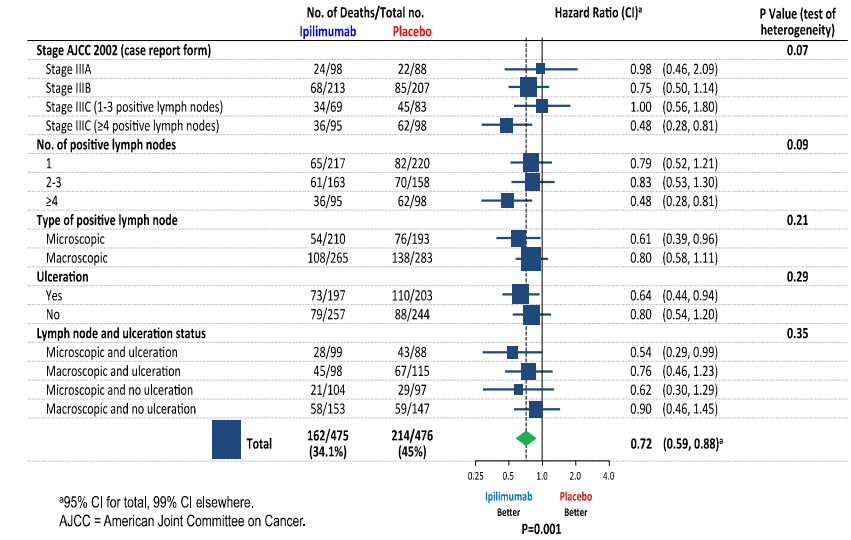
Eggerrmont AMM, et al, *Lancet Oncol* 2015; 16: 522–30)- 2

OS



Eggermont AM et al. Presented at ESMO 2016; abstract LBA 3070.

OS: Forrest Plot



Eggermont AM et al. Presented at ESMO 2016; abstract LBA 3070.

Adjuvantni ipilimumab v primerjavi s placebom po popolni resekciji visoko rizičnega melanoma stadija III (EORTC 18071): randomizirano, dvojno slepoto preiskušanje 3. faze (Eggerrmont AMM, et al, Lancet Oncol 2015; 16: 522-30) - 1

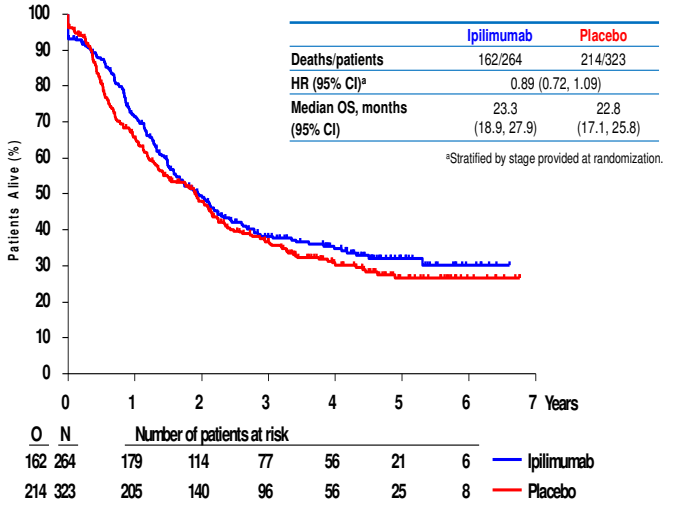
- 951 bolnikov, pri katerih je bila opravljena popolna resekcija kožnega melanoma stadija III (brez metastaze brez limfnih vozlov ≤ 1 mm ali samo v tranzitnih metastazah), stadij IIIA / IIIB / IIIC (42% ulceriranih primarnih in 58% makroskopskih bezgavk) , stratificiran po stadiju in regiji, od 1: 1 do 10 mg / kg (n = 475) ali PBO (n = 476) q3w za 4 odmerke, nato vsake 3 mesece do tri leta do zaključka, ponovitve bolezni ali nesprejemljivega toksičnosti. Primarni cilj je bil RFS, sekundarni cilji vključujejo DFS, OS in varnost.
  Median FU 2,74 let
  Mediana RFS: ipilimumab vs placebo: 26,1 meseca vs 17,1 meseca (HR 0,75; 95% CI 0,64-0,90; p = 0,0013)
  3-letni RFS: ipilimumab vs placebo: 46,55 vs 34,8%
  Toksičnost G3-G4: prebavila (16% vs 4%), jetrna (11% vs <1%), endokrine (8% vs 0%)

Zdravljenej po relapsu (%)[a]

	Patients with an RFS event	
	Ipilimumab (n = 264)	Placebo (n = 323)
Any antitumoral therapy	73.5	77.4
Chemotherapy	15.2	16.1
Radiotherapy	7.2	5.9
Surgery	15.5	9.6
Chemoradiotherapy	0.4	1.2
Other	12.5	11.1
Ipilimumab	9.1	23.5
Anti–PD-1 agent	9.1	9.3
BRAF inhibitor	23.9	27.2

[a]Patients could receive more than 1 subsequent antitumoral therapy.
Eggermont AM et al. Presented at ESMO 2016; abstract LBA 3070.

OS po ponovitvi bolezni je bil podoben



	Ipilimumab	Placebo
Deaths/patients	162/264	214/323
HR (95% CI)[a]	0.89 (0.72, 1.09)	
Median OS, months (95% CI)	23.3 (18.9, 27.9)	22.8 (17.1, 25.8)

[a]Stratified by stage provided at randomization.

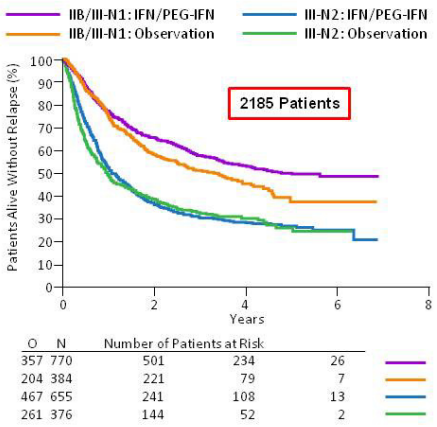
Eggermont AM et al. Presented at ESMO 2016; abstract LBA 3070.

- Učinkovitost ipilimumaba 10 mg / kg vs placebo
- Podaljšani OS, DMFS in RFS
  28-odstotno zmanjšanje tveganja smrti;
  24-odstotno zmanjšanje tveganja za DMFS in RFS
- Povečane 5-letne vrednosti
  OS: 65% vs 54%;
  DMFS: 48% proti 39%;
  RFS: 41% proti 30%

Varnostni rezultati kažejo pomembno stopnjo AE, povezano z imunskim sistemom
Trenutno je adjuvant ipilimumab pomembna možnost zdravljenja pri bolnikih z visokim tveganjem stopnje III melanom

Subgroup Analyses of RFS: Microscopic (N1) vs Clinically Palpable (N2) Lymph Nodes

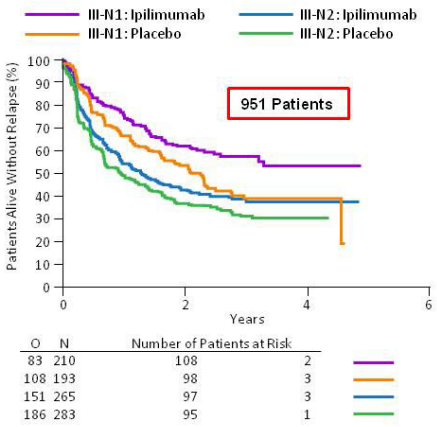
Interferon (IFN)/PEG-IFN
EORTC 18952/EORTC 18991[1]



O	N	Number of Patients at Risk			
357	770	501	234	26	
204	384	221	79	7	
467	655	241	108	13	
261	376	144	52	2	

Stage IIB/III-N1: HR 0.78 (99% CI: 0.61–0.99)
Stage III-N2: HR 0.91 (99% CI: 0.74–1.12)

Ipilimumab
EORTC 18071



O	N	Number of Patients at Risk			
83	210	108	2		
108	193	98	3		
151	265	97	3		
186	283	95	1		

Stage III-N1: HR 0.68 (99% CI: 0.47–0.99)
Stage III-N2: HR 0.83 (99% CI: 0.63–1.10)

[1]Eggermont AM, et al. *Eur J Cancer* 2012;48:218–25.

EORTC 16 *The future of cancer therapy*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

ABSTRACT

MADRID 2017 ESMO congress

Combi-AD: Study design

Key eligibility criteria
- Completely resected, high-risk stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- Surgically free of disease ≤ 12 weeks before randomization
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy

Stratification
- ***BRAF* mutation status (V600E, V600K)**
- **Disease stage (IIIA, IIIB, IIIC)**

RANDOMIZATION

N = 870

1:1

Treatment: 12 months[a]

Dabrafenib 150 mg BID + trametinib 2 mg QD

(n = 438)

2 matched placebos

(n = 432)

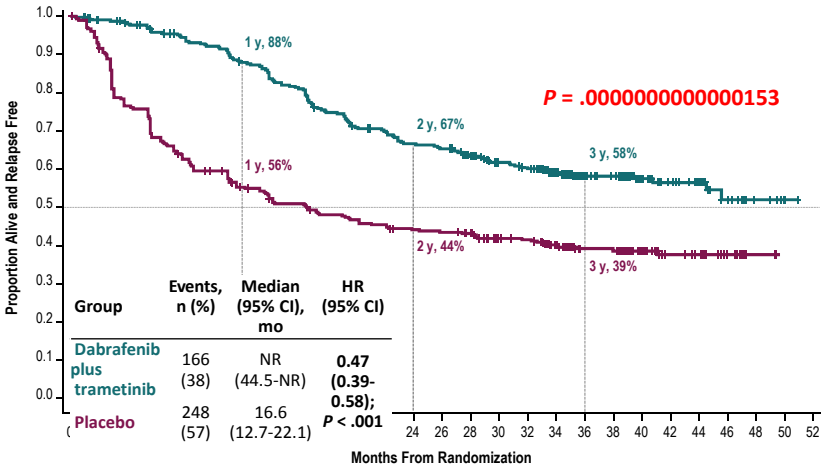
Follow-up[b] until end of study[c]

- **Primary endpoint: RFS[d]**
- **Secondary endpoints: OS, DMFS, FFR, safety**

BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival. [a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b] Patients were followed for disease recurrence until the first recurrence and thereafter for survival;
[c] The study will be considered complete and final OS analysis will occur when ≈ 70% of randomized patients have died or are lost to follow-up; [d] New primary melanoma considered as an event.

Hauschild A, presented at ESMO 2017

Relapse-free survival (primary endpoint)

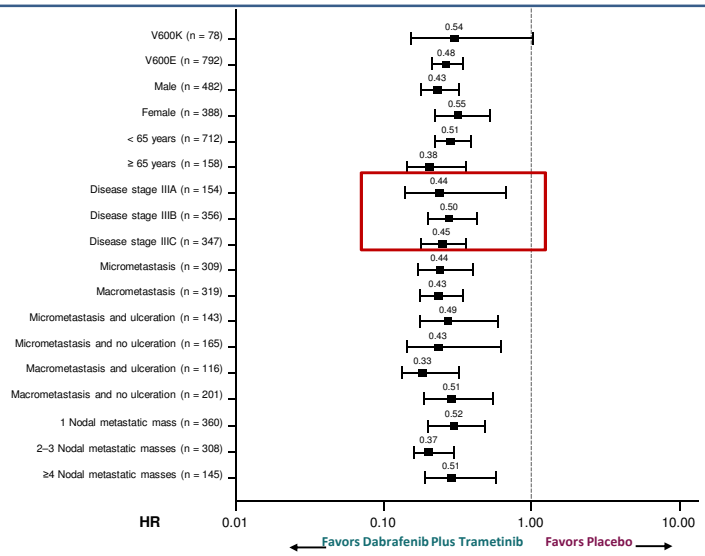


No. at Risk																									
Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

NR, not reached.

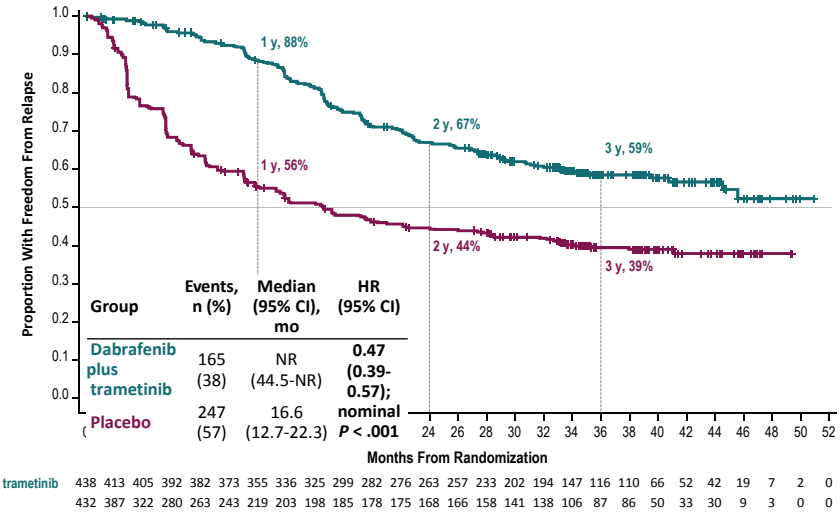
Long GV, NEJM 2017

Relapse-free survival by Subgroup



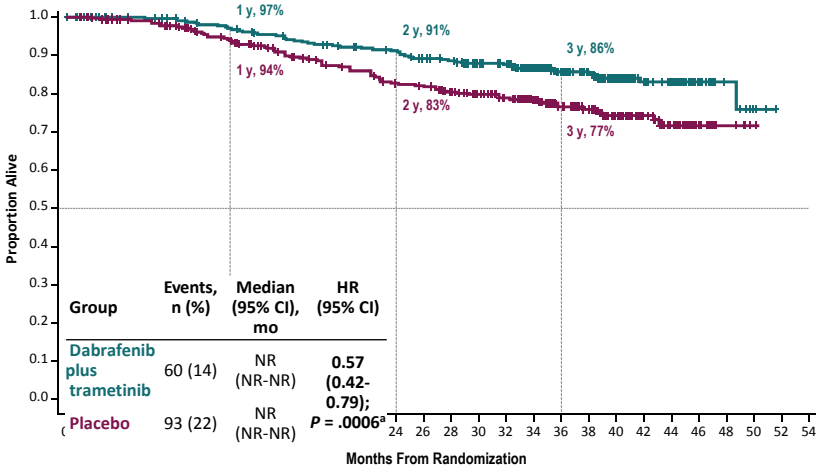
Long GV, NEJM 2017

Freedom from relapse



No. at Risk																									
Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

Overall survival (first interim analysis)



No. at Risk																											
Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

[a] Prespecified significance boundary (P = .000019).

Hauschild A, presented at ESMO 2017

Safety summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Any grade 3/4 AE	180 (41)	61 (14)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal AEs related to study drug	0	0
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	12 (3)

Hauschild A, presented at ESMO 2017

Common adverse events

	Dabrafenib Plus Trametinib (n = 435)		Placebo (n = 432)	
AEs, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Any AE (> 20% with dabrafenib plus trametinib)[a]	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (< 1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (< 1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhoea	144 (33)	4 (1)	65 (15)	1 (< 1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (< 1)

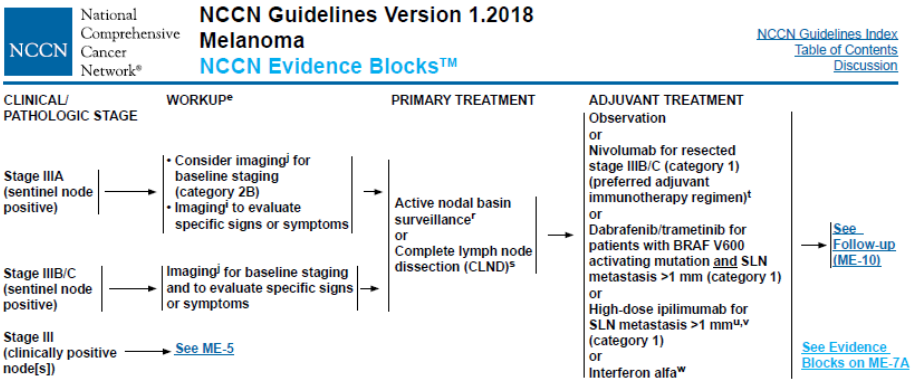
[a] Eleven patients (3%) in the treatment arm and 10 patients (2%) in the placebo arm had new primary melanomas; 8 (2%) and 7 (2%), respectively, had cutaneous squamous cell carcinoma/keratoacanthoma; 19 (4%) and 14 (3%), respectively, had basal cell carcinoma; and 10 (2%) and 4 (1%), respectively, had noncutaneous malignancies.

Hauschild A, presented at ESMO 2017

- Prva randomizirana študija kombinacija BRAF in MEK inhibitorjev v adjuvantnem zdr. Melanoma
- Dabrafenib plus trametinib je pomembno zmanjšal tveganje ponovitve bolezni v primerjavi s placebom pri bolnikih z reseciranim melanomom z BRAF V600E / K mutiranim, stadija III (RFS HR, 0,47 [95% IZ, 0,39-0,58], P <.001)
- Ocenjene 1-, 2- in 3-letne stopnje RFS z dabrafenibom in trametinibom so bile 88%, 67% in 58%

Long GV, NEJM 2017

- Poleg RFS je bil dokazano tudi izboljšanje OS z dabrafenibom in trametinibom (HR, 0,57 [95% IZ, 0,42-0,79])
- Dabrafenib plus trametinib bo nova možnost adjuvantnega zdravljenja za bolnike z BRAF V600-mutiranimi melanomi, ko bo uvrščeno na listo zdravil



Slovenska priporočila

- Prenova slovenskih priporočil – temelji na mednarodnih priporočilih
- predstavitev kasneje v programu

Učinkovito zdravljenje

je mogoče le z:

- Edukacijo bolnikov, podporo, motivacijo
- Sodelovanje bolnikov → večja dobrobit zdravljenja
- Zaupanje

ADJUVANTNO ZDRAVLJENJE MALIGNEGA MELANOMA Z IFN-α2B IN OBVLADOVANJE NEŽELENIH UČINKOV

PRIKAZ KLINIČNEGA PRIMERA

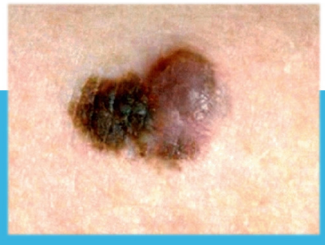
14.ŠOLA MALIGNEGA MELANOMA, 9.MAREC 2018

JASNA K. ARBEITER, DR.MED., NEŽKA HRIBERNIK, DR.MED.,
ASIST.DR.MARTINA REBERŠEK, DR.MED.
SEKTOR INTERNISTIČNE ONKOLOGIJE
ONKOLOŠKI INŠTITUT LJUBLJANA

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

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

- 2/2013 operacija,
- 4/2013 reekscizija in biopsija varovalne bezgavke (oboje negativno) ⟹ primarno stadij IIB



KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

- **5/2013 začetek aplikacij IFN-α2b v visokih odmerkih i.v.**
- Vrednosti S-100 in LDH v mejah normale, transaminaze mejno zvišane (AST 0.54 ukat/L, ALT 0.67 ukat/L), CRP 8 mg/L.

Po prvih 5 aplikacijah i.v.

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

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

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

Po 10 aplikacijah i.v.

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

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

Prekinitev terapije z interferonom za 7 dni.

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

- **6/2013 nadaljevanje aplikacij IFN-α2b v visokih odmerkih i.v.**
- Normalizacija krvne slike, AST 0.98ukat/L, ALT 1.73ukat/L

Po 15 aplikacijah i.v.

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

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

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

Po 20 aplikacijah i.v.

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

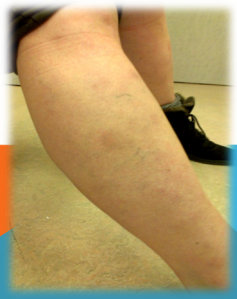
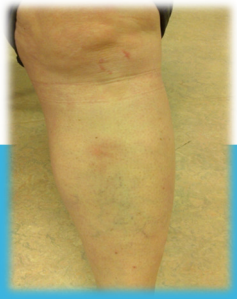
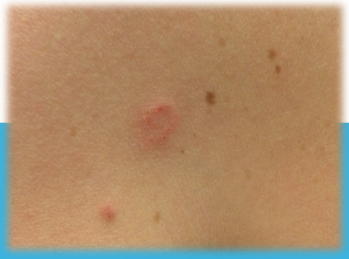
- L 2.68x 10^9/L
- T 170x 10^9/L
- Hb 144 g/L
- N 1.24x 10^9/L
- AST 1.17 ukat/L
- ALT 1.31 ukat/L

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

- 7/2013 pričetek z aplikacijami IFN-α2b v polovičnem odmerku s.c. 3x tedensko.
- Kontrole v ambulanti 1x/mesec, izmenjaje s kontrolami pri izbranem osebnem zdravniku.
- 11/2013 ↑ AST (2.15 ukat/L) / ALT (2.33 ukat/L) in izrazita utrujenost ⟹ znižanje odmerka s.c. aplikacij IFN-α2b (75%).
- 12/2013 prehodna prekinitev zaradi ↑ AST (2.86 ukat/L) / ALT (3.87 ukat/L) in tireotoksičnosti (TSH 28.47 mU/L).

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

- 1/2014 po 5 tednih premora zaključek zdravljenja z IFN-α2b zaradi vztrajajočih povišanih vrednosti TSH (14.28 mU/L), (AST 0.54 ukat/L, ALT 0.71 ukat/L).
- Prisoten kožni izpuščaj obeh goleni (pordelo, boleče, srbeče, trdo).

KLINIČNI PRIMER – ZDRAVLJENJE Z INTERFERONOM

- 5/2014 zadnja kontrola v ambulanti internističnega onkologa.
- Vrednosti transaminaz AST 0.49 ukat/L, ALT 0.56 ukat/L.
- Vrednost TSH 5.7 mU/L.
- Izpuščaj na golenih popolnoma izzvenel.
- Nadaljuje kontrole pri lečečem kirurgu na OI.

VPRAŠANJA in KOMENTARJI

HVALA ZA POZORNOST

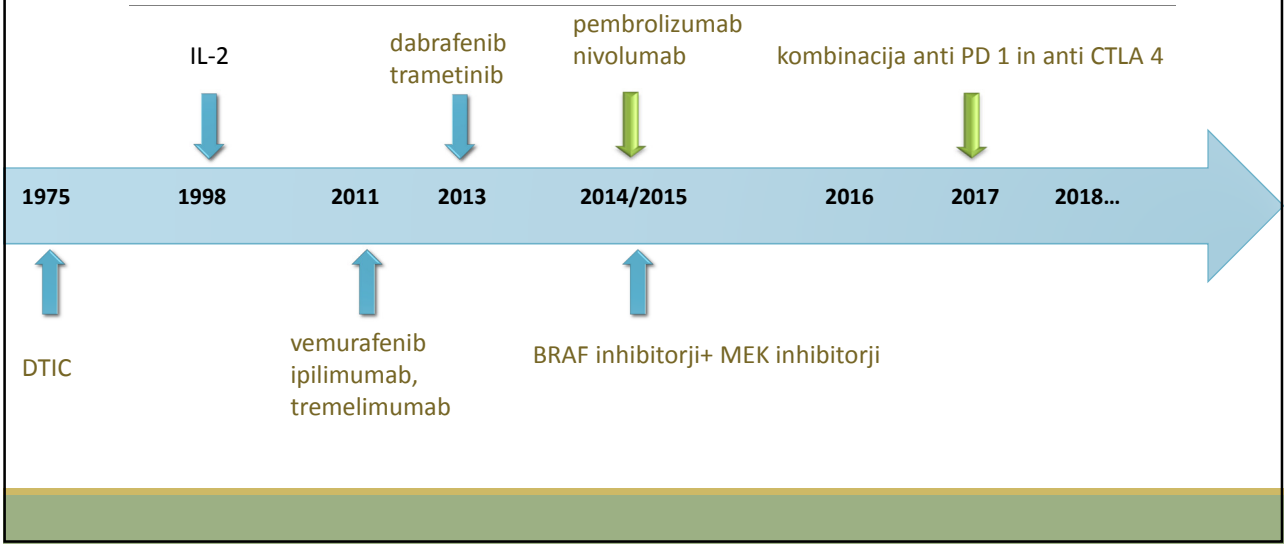
SISTEMSKO ZDRAVLJENJE NAPREDOVALEGA MELANOMA – KEMOTERAPIJA

14.šola melanoma

9.marec 2018

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

Razvoj sistemske terapije metastatskega melanoma



SISTEMSKO ZDRAVLJENJE METASTATSKEGA MELANOMA

Neozdravljiva bolezen

Slaba prognoza

Srednje preživetje z metastatsko boleznijo ~ 7- 9 mesecev

5- letno preživetje < 4 %

Najpogostejše lokalizacije:

- koža, podkožje,bezgavke v 50%
- CŽS v 40%
- pljuča v 18- 36%
- jetra
- kosti

TNM klasifikacija

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

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AJCC PROGNOSTIC STAGE GROUPS

Clinical Staging (cTNM)*

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

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

Pathological Staging (pTNM)†

	T	N	M
Stage 0††	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a/b,T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

†Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.
††Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.

The AJCC 8th Edition Cancer Staging System will be implemented on January 1, 2018. For the AJCC 7th Edition Staging Manual, visit www.springer.com.

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ST-4

NCCN Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

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Definition of Distant Metastasis (M)

	M Criteria	
M Category	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

- **Serum lactate dehydrogenase (LDH)**
- **Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.**
- **No suffix is used if LDH is not recorded or is unspecified.**

The AJCC 8th Edition Cancer Staging System will be implemented on January 1, 2018.

TNM kriteriji

Podskupine M glede na mesto zasevanja in vrednost LDH

- M1a → koža, podkožje, oddaljene bezgavke
- M1b → pljuča
- M1c → drugi visceralni organi ali več kot ena metastatska lokalizacija ali povišana LDH neodvisno od mesta zasevanja
- **M1d →CŽS z ali brez M1a, M1b, M1c, z ali brez ↑ LDH**

ZNAČILNOSTI MELANOMA STADIJA IV

Srednja starost ob diagnozi 40- 50 let

Srednje preživetje ~ 9 mesecev:

- Nevisceralne metastaze ~ 14 mesecev (M1a) in ~ 16 mesecev (M1b- pljuča)
- Visceralne metastaze ~ 7 mesecev (M1c)
- CŽS ~ 3 mesece

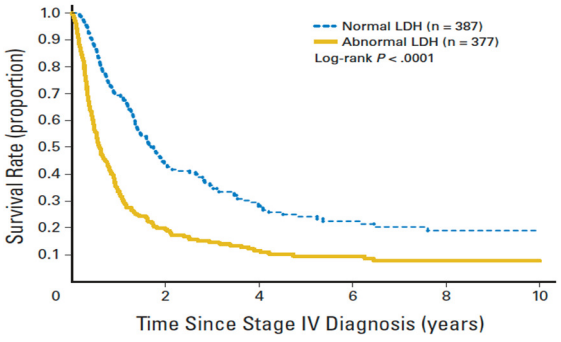
Preživetje odvisno od:

- mesta prvega razsoja
- števila metastatskih lokalizacij
- odgovora na zdravljenje na predhodno terapijo

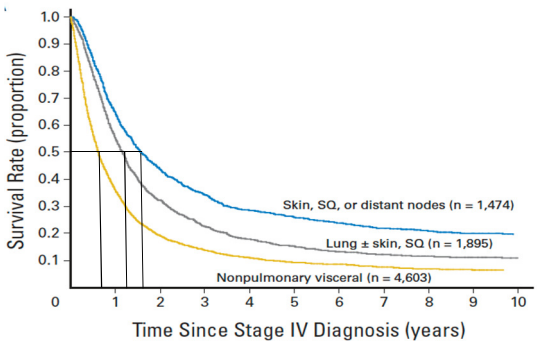
Historically poor survival prognosis in Stage IV melanoma

Survival of patients with stage IV melanoma

Survival by LDH status



Survival by site of metastatic disease



LDH=lactate dehydrogenase; SQ=subcutaneous

Balch CM, et al. J Clin Oncol 2009;27:6199–6206.

ZDRAVLJENJE METASTATSKE BOLEZNI

Sistemska kemoterapija

Imunoterapija

Tarčna zdravila

NCCN smernice za sistemsko kemoterapijo in imunoterapijo napredovalega in metastatskega melanoma

NCCN Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Melanoma

OTHER SYSTEMIC THERAPIES

Cytotoxic Regimens for Metastatic Disease[1]
- Dacarbazine
- Temozolomide
- Paclitaxel
- Albumin-bound paclitaxel
- Carboplatin/paclitaxel

Biochemotherapy for Adjuvant Treatment of High-Risk Disease
- Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)

SISTEMSKA MONOKEMOTERAPIJA

- Dakarbazin, temozolomid
- Analogi platine
- Analogi nitrozaureje
- Vinka alkaloidi
- Taksani

DAKARBAZIN (DTIC)

objektivni odgovor na zdravljenje v 8- 20 %

~ 5% popolnih odgovorov

srednje trajanje odgovorov 4-6 mesecev

< 2% bolnikov preživi 6 let

- nobena klinična raziskava faze III ni pokazala pomembno daljšega preživetja z zdravljenjem z DTIC vs BSC

- dolgoletno edini odobren citostatik za zdravljenje metastatskega melanoma

obvladljivi neželeni učinki

TEMOZOLOMID

analog dakarbazina

v obliki tbl

prehaja skozi krvno- možgansko bariero

podobno učinkovit kot DTIC

manj ponovitev bolezni z napredovanjem v CŽS

ne izboljša pomembno preživetja in odgovora na zdravljenje v primerjavi z DTIC

SISTEMSKA MONOKEMOTERAPIJA (2)

Analogi platine:

- cisplatin, karboplatin učinkovita v 15- 20%, nekajmesečno trajanje odgovora
- oksaliplatin neučinkovit

Analogi nitrozaureje: karmustin, lomustin, semustin, fotemustin

fotemustin: najučinkovitejši,odgovor v 20-25%, popolni odgovor v 15 %

Vinka alkaloidi: odgovor v 14%

Taksani: odgovor v 16-17% (nab-paklitaksel v 22-26%)

KOMBINIRANA SISTEMSKA KEMOTERAPIJA IN IMUNOTERAPIJA

Polikemoterapija

CVD (cisplatin,vinblastin,DTIC) vs DTIC:

- odgovor v 19% vs 14% , brez razlike v trajanju odgovorov in preživetju bolnikov med obema skupinama

Dortmouthov režim (cisplatin,karmustin,DTIC)

- v kombinaciji s tamoksifenom vs polikemoterapija,odgovor v 30% vs 21%, v kombinaciji s tamoksifenom vs DTIC, odgovor 18.5% vs 10.2%

CVD (cisplatin,vinblastin,DTIC) vs **CVD+ IL- 2+ IFN alfa:** odgovor 25% vs 48%, srednje preživetje mesecev 9.2 vs 11.9 mesecev

Polikemoterapija v kombinaciji s hormonsko terapijo ali kombinaciji z imunoterapijo:

META- ANALIZA 6 randomiziranih kliničnih raziskav

- kemoterapija vs kemoterapija z imunoterapijo s ali brez tamoksifena → brez razlike v preživetju in učinkovitosti zdravljenja med skupinami

KOMBINIRANA SISTEMSKA TERAPIJA

Klinična raziskava faze II BEAM:

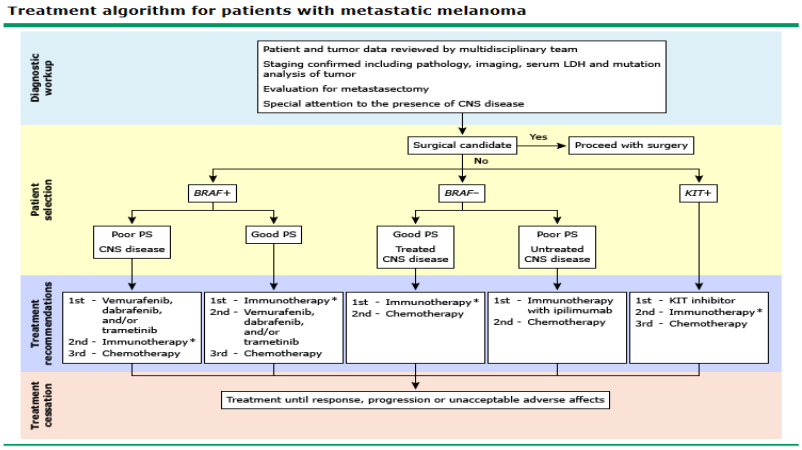
- paklitaksel+karboplatin (PK) vs paklitaksel+karboplatin +**bevacizumab** (PKB)
- vključenih 214 bolnikov
- **OS**: PK 8.6 mesecev vs PKB 12.3 mesecev (HR 0.67)
- **ORR:** PK 16.4% vs PKB 25.5%
- OS ↑ pri bolnikih z M1c in ↑LDH na terapiji PKB

Sistemska kemoterapija	Odgovor na zdravljenje (%)	Srednje trajanje odgovora (meseci)
DTIC/temozolomid	**8-20**	**4-6**
CCV(cisplatin, CCNU, vinblastin)	**~20**	**~3**
Paklitaxel/karboplatin	**~20**	**~3**

ODGOVOR (%)

Terapija	popolni	celokupni
monokemoterapija	< 5	10- 20
imunoterapija	< 5	10- 20
kombinirana kemoterapija	~ 5	20- 40
kemoimunoterapija	10- 20	40- 60

Algoritem zdravljenja metastatskega melanoma



Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology. Kaufman HL, Kirkwood JM, Hodi FS, et al. The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. Nat Rev Clin Oncol 2013; 10:588. Copyright © 2013. www.nature.com/nrclinonc.

ZAKLJUČKI O SISTEMSKI KEMOTERAPIJI METASTATSKEGA MELANOMA

- Sistemsko zdravljenje s kemoterapijo je malo učinkovito
- Sistemsko kombinirano zdravljenje s kemoterapijo ne podaljša pomembno preživetja v primerjavi s kemoterapijo v monoterapiji, več je neželenih učinkov
- <u>Paliativno sistemsko zdravljenje v 2. ali 3.redu:</u>
  - M1c, ↑LDH: paklitaksel+karboplatin+ bevacizumab (“Kategorija 2C”)

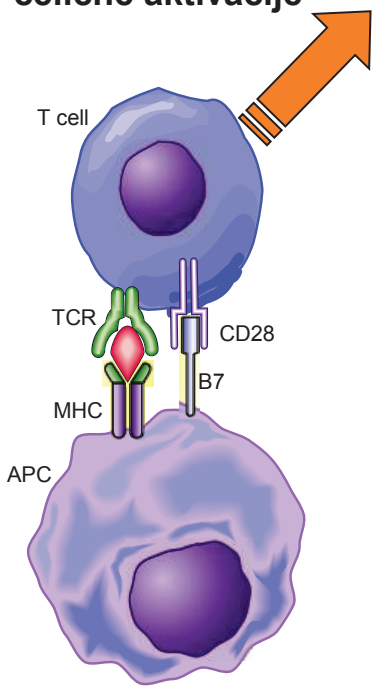
HVALA ZA POZORNOST

IMUNOTERAPIJA V ZDARVLJENJU MELANOMA

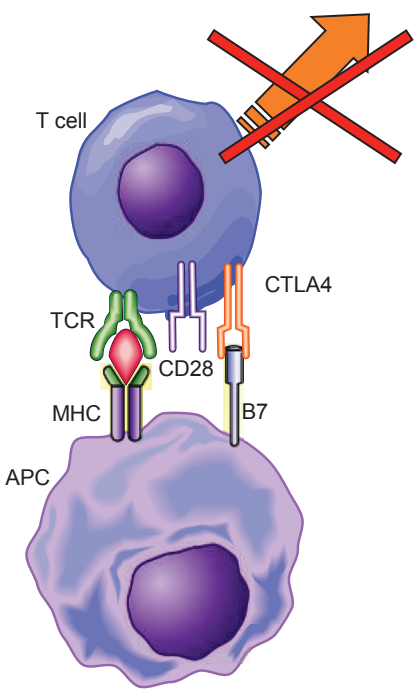
Prof.dr. Janja Ocvirk, dr.med.

IPILIMUMAB BLOKIRA NEGATIVNI SIGNAL CTLA4

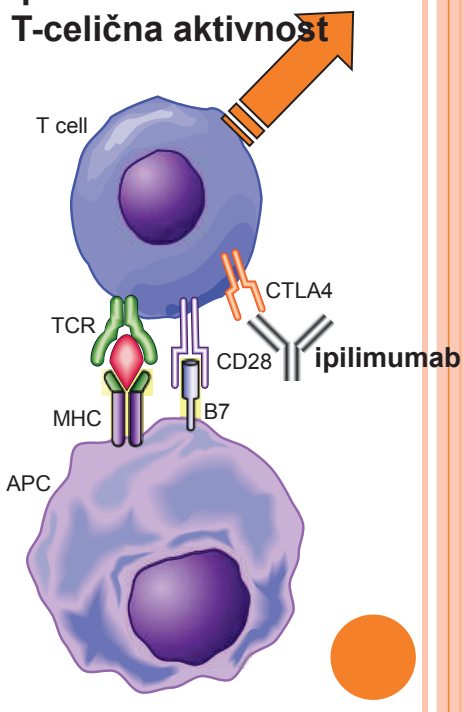
ko-stimulacija preko CD28: T-celične aktivacije



CTLA-4 blokira ko-stimulacijo: Ni T-celične activnosti



Ipilimumab blokira CTLA-4: T-celična aktivnost

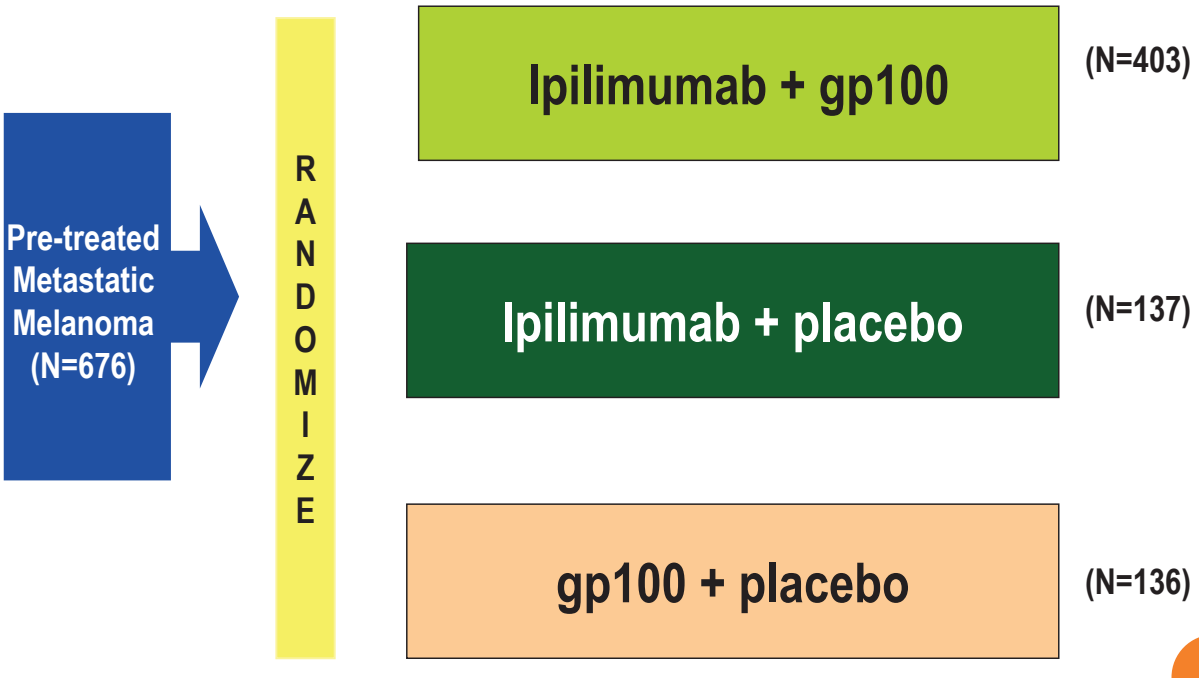


Adapted from Lebbé et al. ESMO 2008

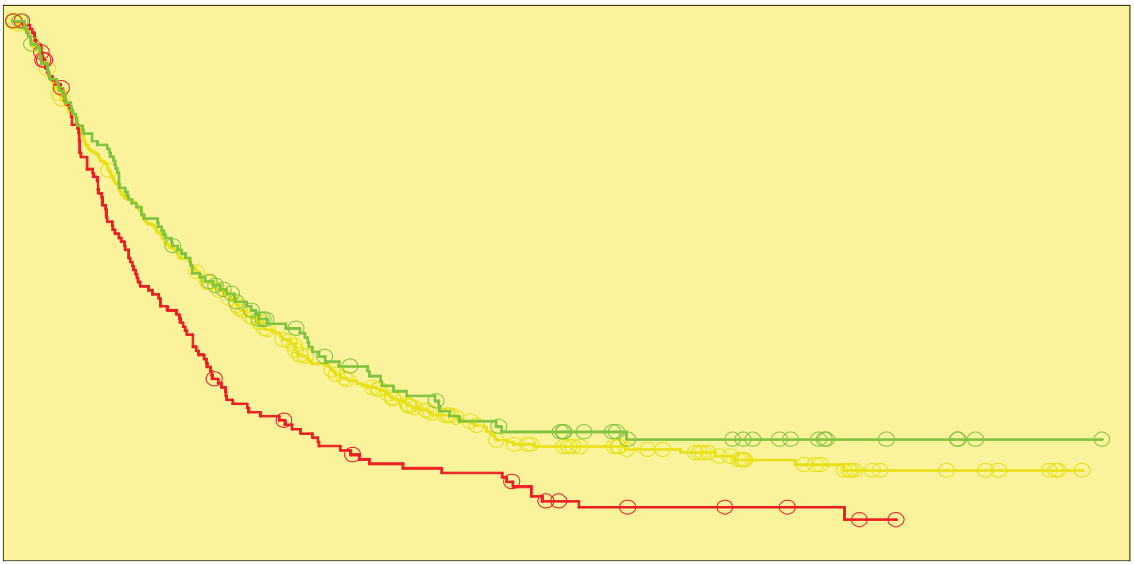
IPILIMUMAB

- Protitelo proti CTLA- 4
- Klinična raziskava faze III:
- Ipilimumab+ gp 100 vs. Ipilimumab vs. Gp 100
- Dobrobit na preživetje (44% vs 46% vs 25%)., odgovor na zdravljenje, kontrolo bolezni (20,1% vs. 28,5% vs. 11%)

MDX010-20: STUDY DESIGN



KAPLAN-MEIER ANALIZA PREŽIVETJA



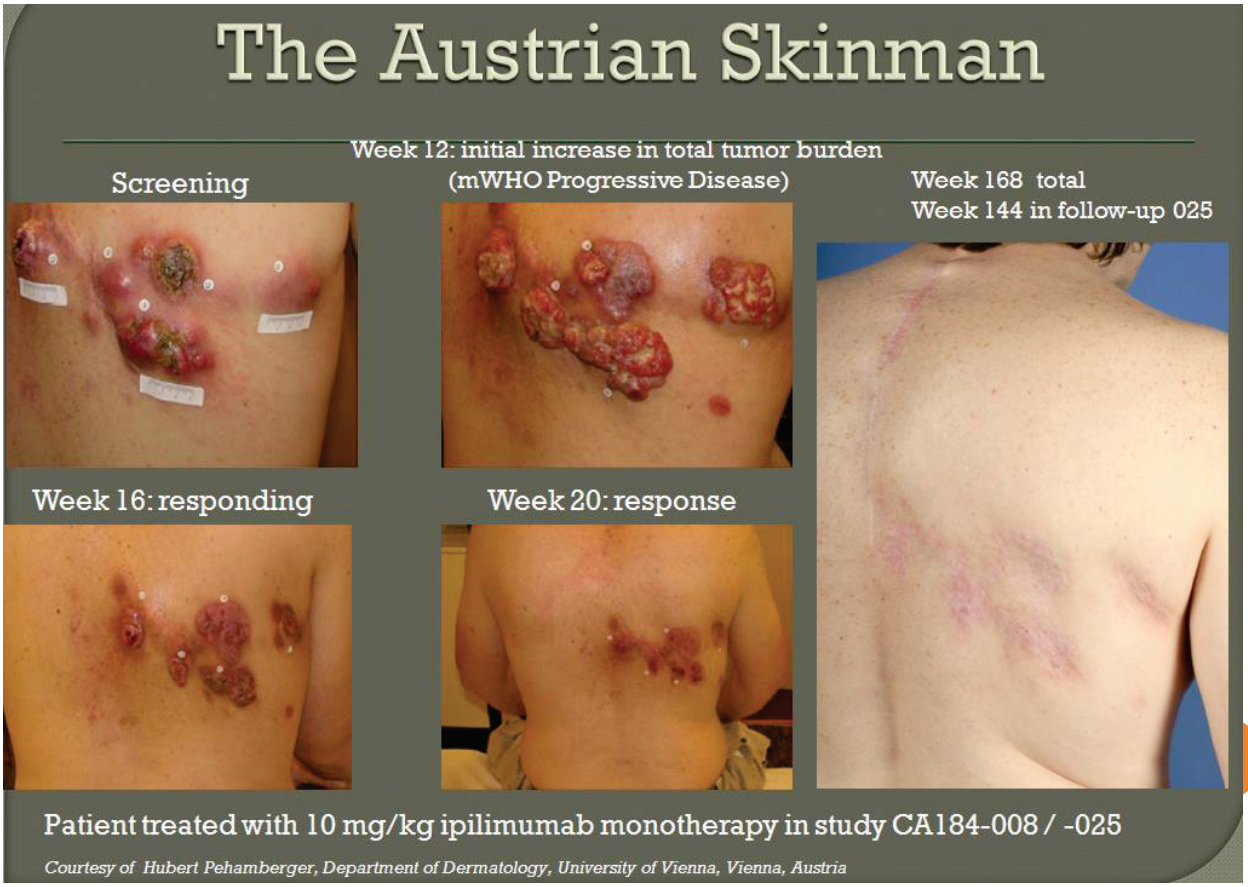
Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

5

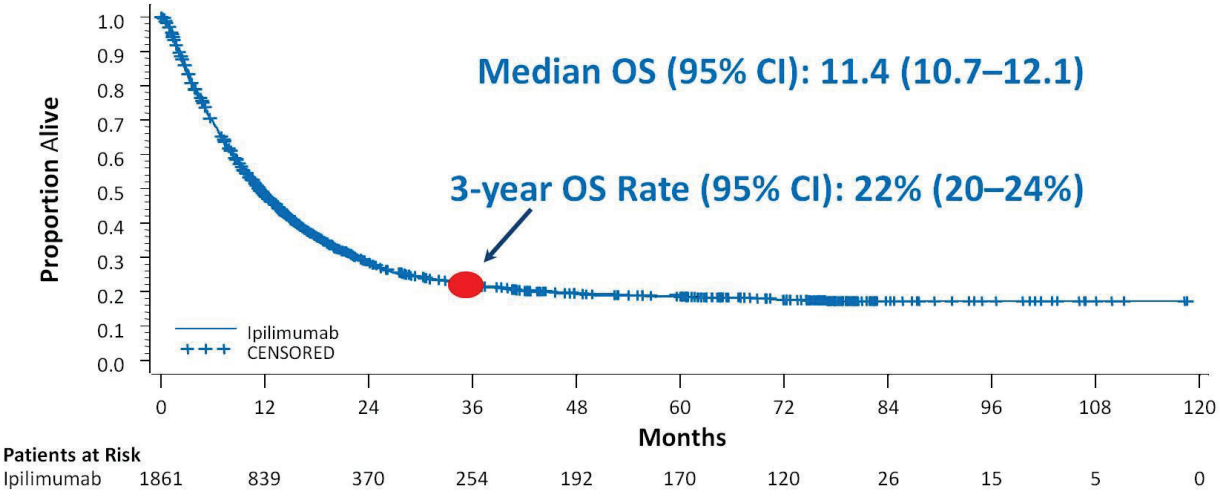
NEŽELENI UČINKI IPILIMUMABA

Večinoma nastajajo zaradi imunskega odgovora:

- Gastrointestinalni- driska, kolitis
- Kožni – srbečica, urtika
- Endokrini – hipotiroidizem, hipopituitarizem



Primary Analysis of Pooled OS Data: 1861 Patients



Hodi ECCO 2013

IPILIMUMAB + DTIC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

- Klinična raziskava faze III v 1. liniji metastatskega melanoma ne glede na BRAF mutacijo
- Ipilimumab + DTIC vs DTIC
- Kombinirano zdravljenje podaljša celokupno preživetje – HR 0,72, p=0,0009
- Trajanja odgovora na zdravvljenje 19,3 meseca vs. 8,1 meseca

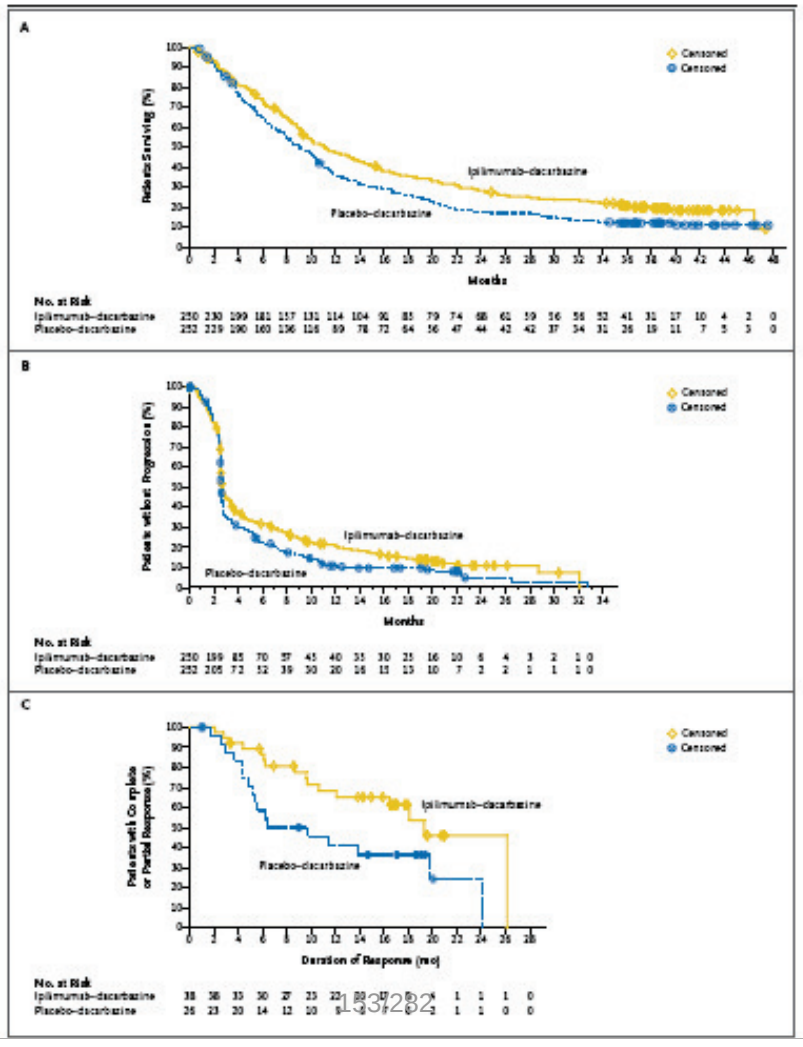


Table 2. Adverse Events and Immune-Related Adverse Events.*

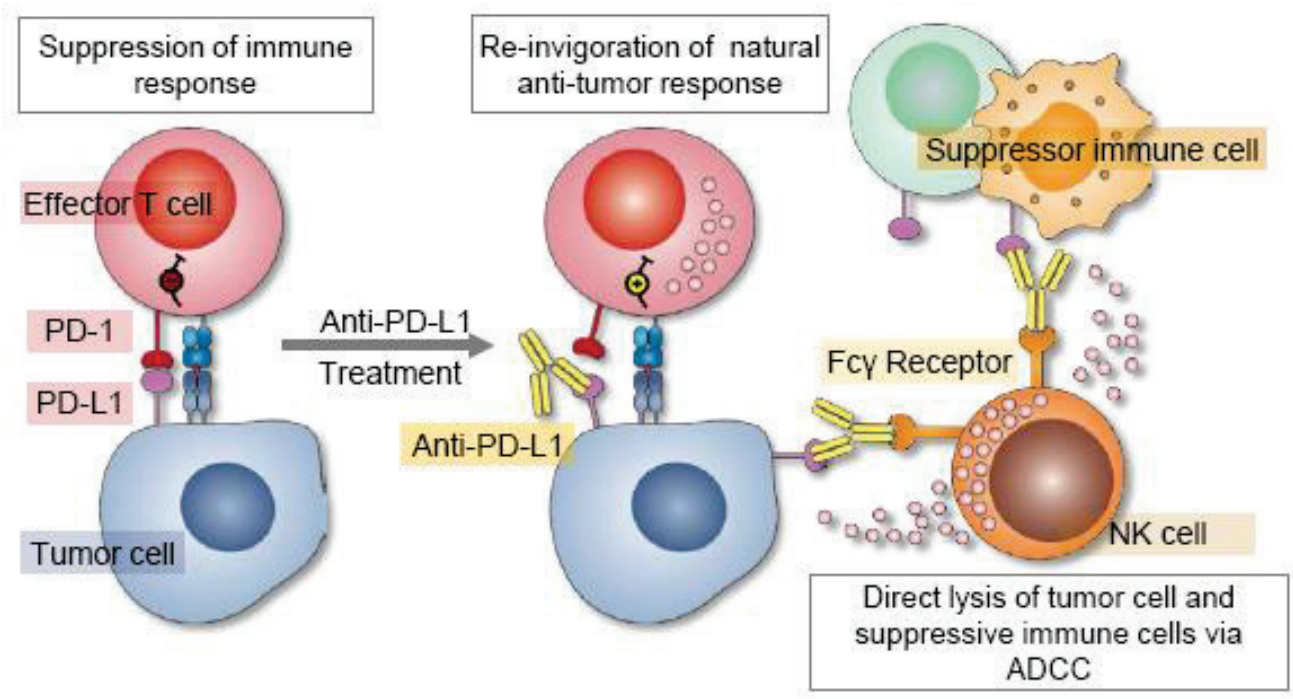
Adverse Event	Ipilimumab plus Dacarbazine (N = 247)			Placebo plus Dacarbazine (N = 251)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
All adverse events, regardless of cause†						
Any event	244 (98.8)	99 (40.1)	40 (16.2)	236 (94.0)	45 (17.9)	24 (9.6)
Gastrointestinal: diarrhea	90 (36.4)	10 (4.0)	0	62 (24.7)	0	0
Dermatologic						
Pruritus	73 (29.6)	5 (2.0)	0	22 (8.8)	0	0
Rash	61 (24.7)	3 (1.2)	0	17 (6.8)	0	0
Hepatic						
Increase in alanine aminotransferase	82 (33.2)	40 (16.2)	14 (5.7)	14 (5.6)	2 (0.8)	0
Increase in aspartate aminotransferase	72 (29.1)	36 (14.6)	9 (3.6)	14 (5.6)	3 (1.2)	0
Other						
Pyrexia	91 (36.8)	0	0	23 (9.2)	0	0
Chills	28 (11.3)	0	0	10 (4.0)	0	0
Weight loss	27 (10.9)	1 (0.4)	0	13 (5.2)	1 (0.4)	0
Immune-related adverse events						
Any event	192 (77.7)	78 (31.6)	25 (10.1)	96 (38.2)	8 (3.2)	7 (2.8)
Dermatologic						
Pruritus	66 (26.7)	5 (2.0)	0	15 (6.0)	0	0
Rash	55 (22.3)	3 (1.2)	0	12 (4.8)	0	0
Gastrointestinal						
Diarrhea	81 (32.8)	10 (4.0)	0	40 (15.9)	0	0
Colitis	11 (4.5)	4 (1.6)	1 (0.4)	0	0	0
Hepatic‡						
Increase in alanine aminotransferase	72 (29.1)	37 (15.0)	14 (5.7)	11 (4.4)	2 (0.8)	0
Increase in aspartate aminotransferase	66 (26.7)	34 (13.8)	9 (3.6)	8 (3.2)	1 (0.4)	0
Hepatitis	4 (1.6)	3 (1.2)	0	0	0	0

* The safety analysis included all patients who underwent randomization and received at least one dose of study drug (498 patients). Adverse events and immune-related adverse events were prospectively defined: the *Medical Dictionary for Regulatory Activities* [MedDRA], version 23.0, was used for the reporting of adverse events, and a list of events prespecified in the protocol was used to capture immune-related adverse events, which were a subgroup of the reported adverse events. The categories are not mutually exclusive (i.e., one patient could have events in multiple categories).
† A complete list of adverse events that occurred in at least 10% of patients is available in the Supplementary Appendix.
‡ Terms used in the category of hepatic immune-related adverse events are MedDRA preferred terms, as listed by the investigator in case-report forms.

PD-L1 IN PD-L2 SO LAHKO IZRAŽENI NA NEKATERIH TUMORSKIH CELICAH

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

- Anti PD-1
  - nivolumab
  - pembrolizumab
- Anti PD-L1(v fazi kliničnih preizkušanj)
  - atezolizumab
  - BMS-936559



CHECKMATE 066

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

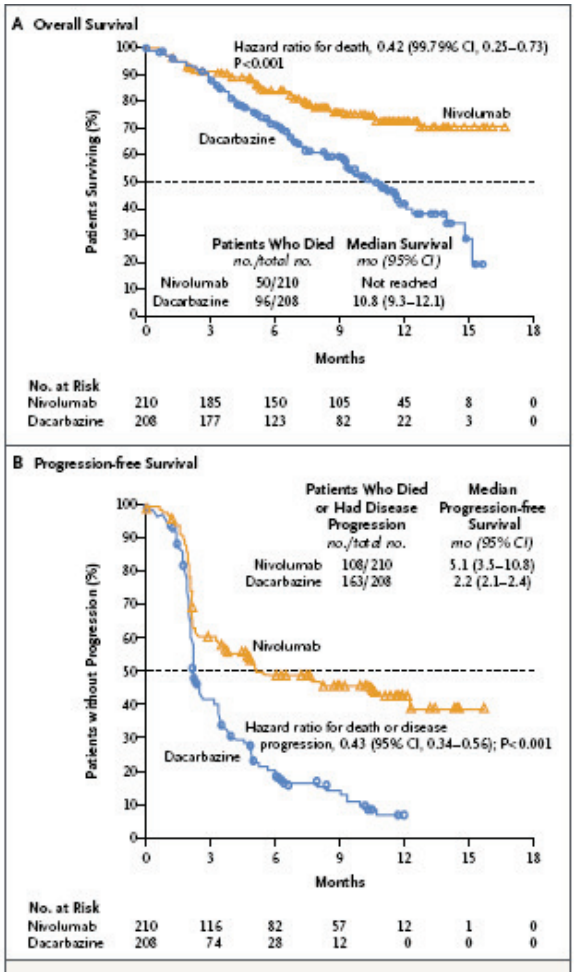


Table 2. Response to Treatment.*

Response	Nivolumab (N=210)	Dacarbazine (N=208)
Best overall response — no. (%)†		
Complete response	16 (7.6)	2 (1.0)
Partial response	68 (32.4)	27 (13.0)
Stable disease	35 (16.7)	46 (22.1)
Progressive disease	69 (32.9)	101 (48.6)
Could not be determined	22 (10.5)	32 (15.4)
Objective response‡		
No. of patients (% [95% CI])	84 (40.0 [33.3–47.0])	29 (13.9 [9.5–19.4])
Difference — percentage points (95% CI)	26.1 (18.0–34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52–6.54)	
P value	<0.001	
Time to objective response — mo		
Median	2.1	2.1
Range	1.2–7.6	1.8–3.6
Mean	2.6±1.3	2.5±0.7
Duration of response — mo§		
Median (95% CI)	Not reached	6.0 (3.0–not reached)
Range	0.0–12.3	1.1–10.0

* Plus–minus values are means ±SD.
† The best overall response was assessed by the investigator with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1.[18]
‡ Data include patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. The estimate of the difference (the rate in the nivolumab group minus the rate in the dacarbazine group) was based on the Cochran–Mantel–Haenszel method of weighting, with adjustment for PD-L1 status and metastasis stage as entered into the interactive voice-response system. The odds ratio and two-sided P value for an objective response with nivolumab as compared with dacarbazine were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to PD-L1 status and metastasis stage.
§ The median was calculated with the use of the Kaplan–Meier method. Data were censored for the range values because the observations are ongoing. The cutoff date for clinical data was August 5, 2014, with a range of follow-up from 5.2 to 16.7 months.

Table 3. Adverse Events.*

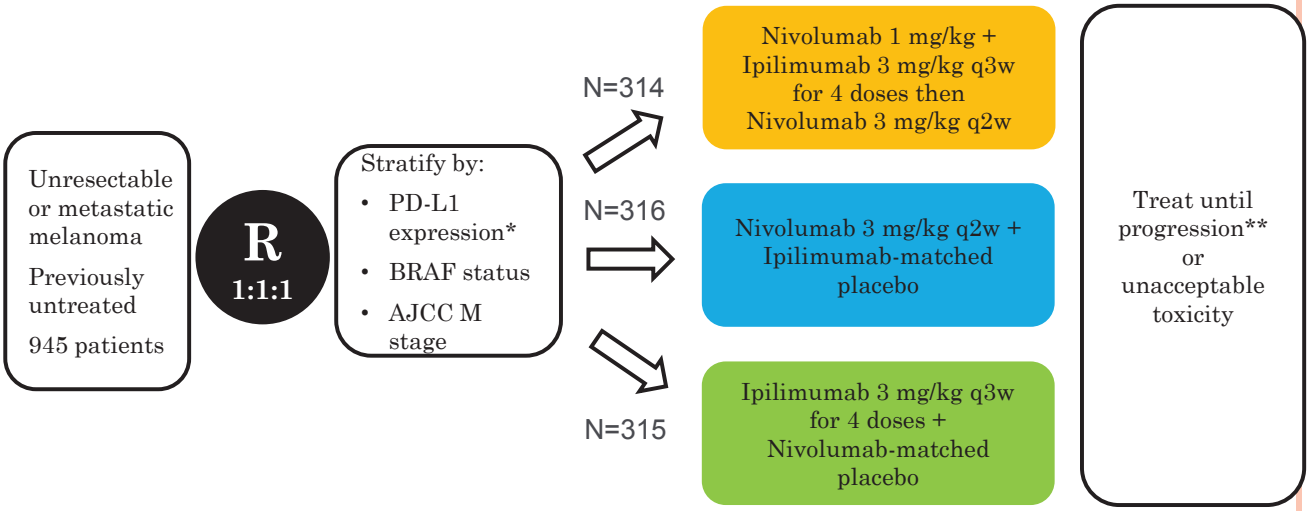
Event	Nivolumab (N=206)		Dacarbazine (N=205)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients with event (%)			
Any adverse event	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)
Fatigue	42 (20.9)	0	30 (14.6)	2 (1.0)
Pruritus	35 (17.0)	1 (0.5)	11 (5.4)	0
Nausea	34 (16.5)	0	85 (41.5)	0
Diarrhea	33 (16.0)	2 (1.0)	32 (15.6)	1 (0.5)
Rash	31 (15.0)	1 (0.5)	6 (2.9)	0
Vitiligo	22 (10.7)	0	1 (0.5)	0
Constipation	22 (10.7)	0	25 (12.2)	0
Asthenia	21 (10.2)	0	25 (12.2)	1 (0.5)
Vomiting	13 (6.3)	1 (0.5)	43 (21.0)	1 (0.5)
Neutropenia	0	0	23 (11.2)	9 (4.4)
Thrombocytopenia	0	0	21 (10.2)	10 (4.9)
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)
Serious adverse event				
Any event	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)
Treatment-related event	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)

* The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[30]
† The treatment-related adverse events listed here were reported in at least 10% of the patients in either study group.

CheckMate 067

STUDY DESIGN

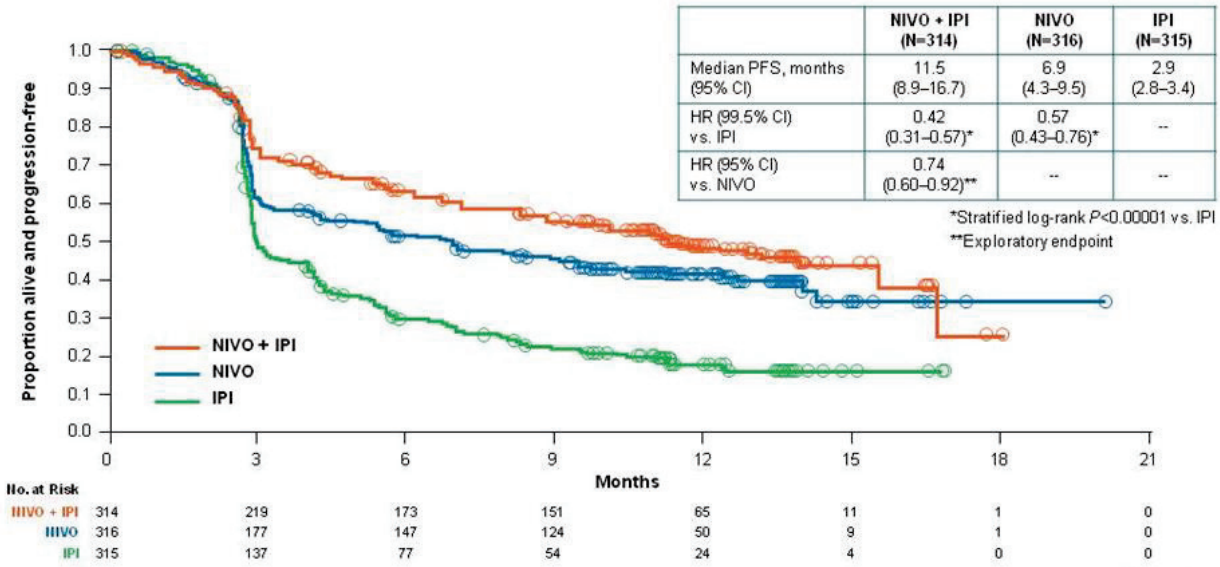
Randomized, double-blind, phase III study to compare nivolumab + ipilimumab or nivolumab alone to ipilimumab alone:



*Verified PD-L1 assay with 5% expression level was used for stratification of patients; validated PD-L1 assay was used for efficacy analyses
**Patients could have been treated beyond progression under protocol-defined circumstances

Larkin et al. Nejm 2015

PFS (Intent-to-Treat)



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI
**Exploratory endpoint

Larkin et al. Nejm 2015

Response to Treatment

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1, NR)	NR (11.7, NR)	NR (6.9, NR)

*By RECIST v1.1.
NR, not reached.

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Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

12

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Most Common Treatment-related Select AEs

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

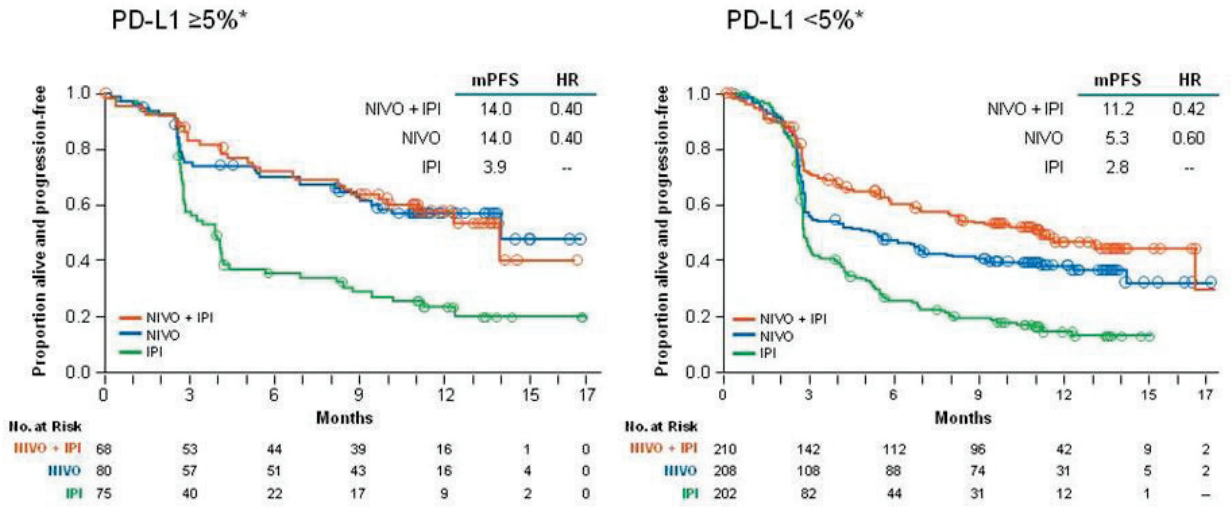
- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

Database lock Nov 2015

13

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

PFS by PD-L1 Expression Level (5%)



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

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- bolniki z izrazom PDL1> 5% enako dobro odzivajo na kombinacijo in na sam Nivo. Vendar so se pri bolnikih s PDL1 <5% bolniki bolje odzvali na kombinacijo kot samo zdravilo Nivo.

KEYNOTE-001: 655 Patients With Melanoma

11	2012												2013								
D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S

Nonrandomized
Ipi Naive and Ipi Treated
2 Q3W, 10 Q3W, 10 Q2W
N = 135

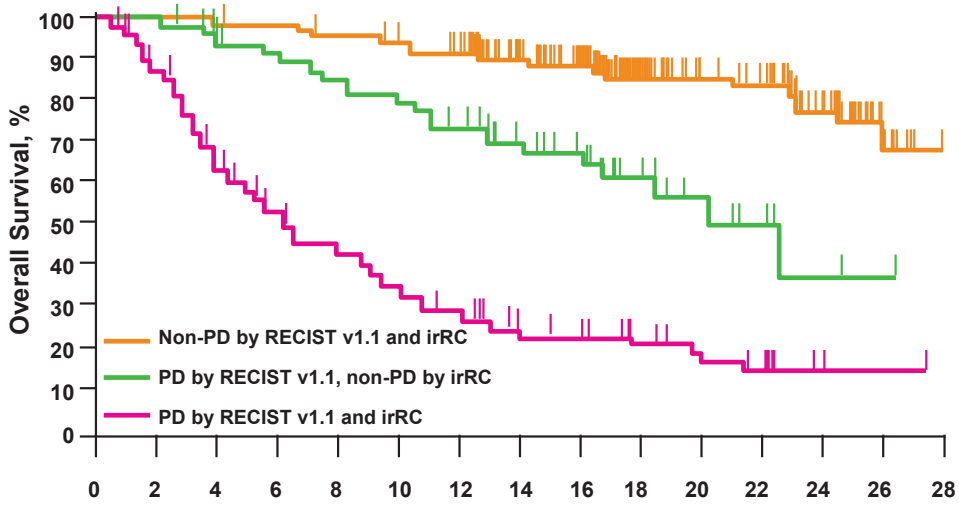
Randomized
Ipi Treated
2 Q3W vs 10 Q3W
N = 173

Randomized
Ipi Naive and Treated
10 Q3W vs 10 Q2W
N = 244

Randomized
Ipi Naive
2 Q3W vs 10 Q3W
N = 103

- Ipi-T defined as unequivocal PD within 6 mo of first IPI dose
- BRAF inhibitor not required for *BRAF*-mutant melanoma
- Ipi-T defined as confirmed PD within 24 wk of last Ipi dose; ≥2 IPI doses required
- BRAF inhibitor required for Ipi-T, but not Ipi-N, *BRAF*-mutant melanoma

KAPLAN-MEIER ESTIMATES OF OS BASED ON RESPONSE PER RECIST V1.1 AND IRRC[A]



	Median, mo	95% CI	Rate, 24 mo
Non-PD by RECIST v1.1 and irRC	NR	25.9-NR	78%
PD by RECIST v1.1, non-PD by irRC	20.2	15.9-NR	37%
PD by RECIST v1.1 and irRC	6.4	5.1-8.4	14%

215	215	213	210	206	197	192	159	136	79	60	55	31	8	0
57	56	50	46	44	41	37	28	22	13	9	6	3	2	1
139	116	84	66	54	42	33	23	20	15	10	8	1	1	0

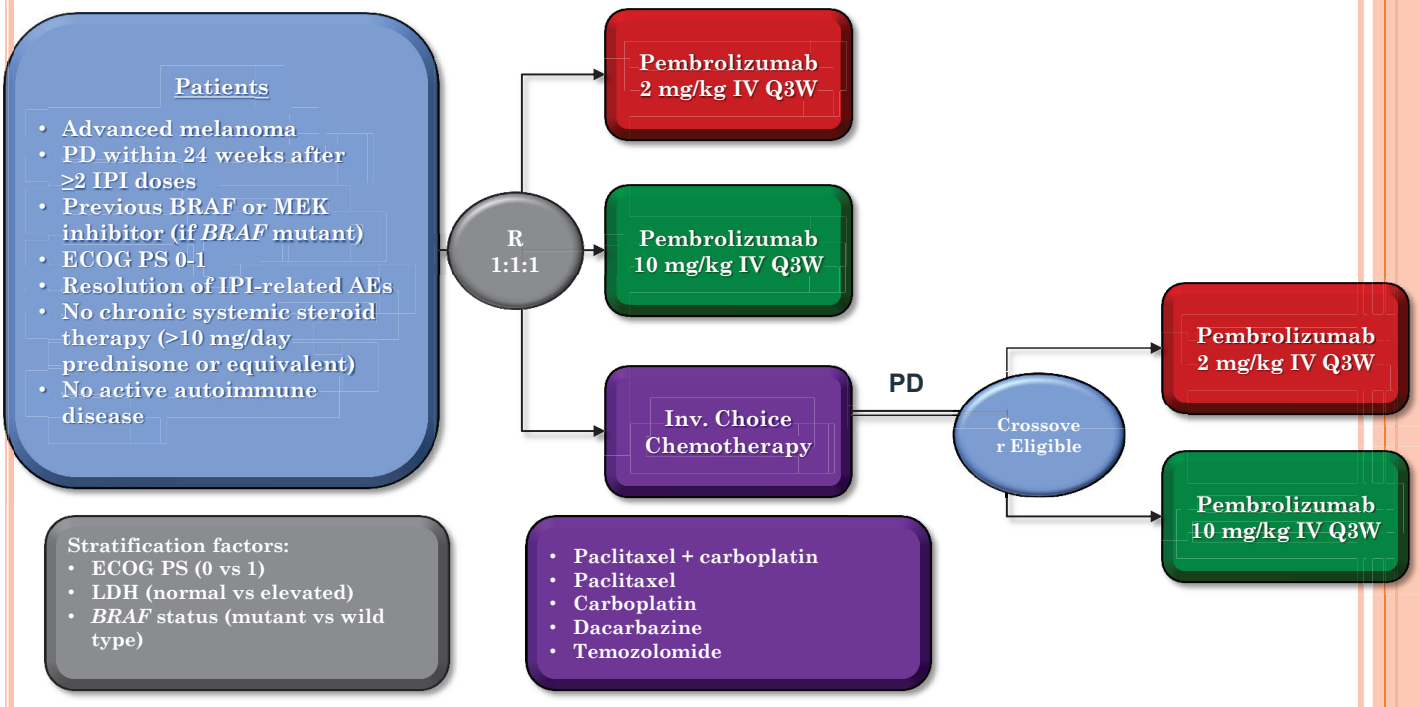
[a]Assessed per central review.
Analysis cut-off date: April 18, 2014.
Hodi FS et al. Presented at: SITC 29th Annual Meeting & Associated Programs; November 6-9, 2014; National Harbor, MD, USA.

Long term outcomes from Pembrolizumab Keynote 001: 3 year survival

- Time on treatment:
  - ~37% of subjects treated ≥ 12 months
  - Mean exposure 11.4 months
- OS by dose, schedule, & prior ipilimumab Rx:
  - No apparent difference: 3 yr OS for all groups 38-41%
- PFS
  - Rx Naïve vs. total: Median 5 mo vs. 4.9
    3yr PFS 30% vs. 21%
- ORR
  - 33% with disease control in an additional 51%
  - Median duration of response not reached and continued at 3 yr in 57% of subjects
  - CR in 15%, 13% (85% of CR) ongoing with 81% off of treatment
  - 61 (64%) on surveillance median time on RX is 23 months (8-44mo); median time to CR 13 months, 2 with progression.

C Robert ASCO 2016

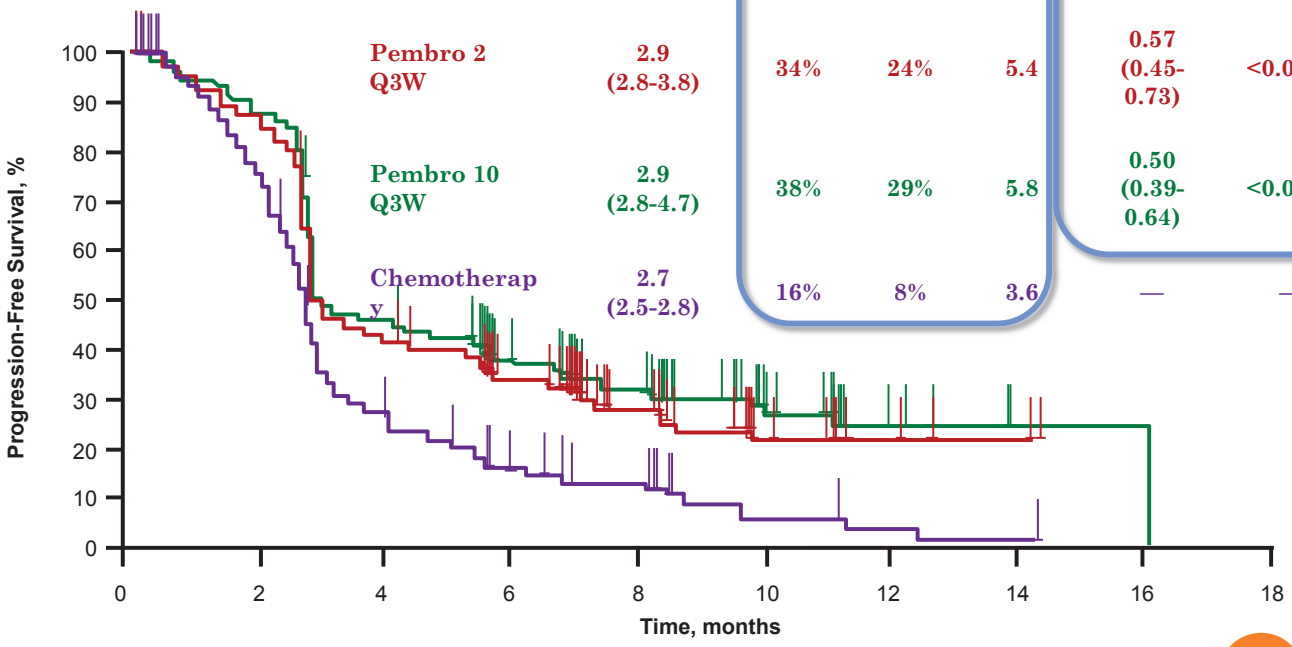
KEYNOTE-002 (NCT01704287): INTERNATIONAL, RANDOMIZED, PIVOTAL STUDY



- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety
- Prespecified exploratory end point: health-related quality of life at week 12 (HRQoL)

Primary End Point: PFS (RECIST v1.1, Central Review)

Arm	Median (95% CI), mo	Rate at 6 mo	Rate at 9 mo	Mean[a] mo	HR (95% CI)	*P*
Pembro 2 Q3W	2.9 (2.8-3.8)	34%	24%	5.4	0.57 (0.45-0.73)	<0.0001
Pembro 10 Q3W	2.9 (2.8-4.7)	38%	29%	5.8	0.50 (0.39-0.64)	<0.0001
Chemotherapy	2.7 (2.5-2.8)	16%	8%	3.6	—	—

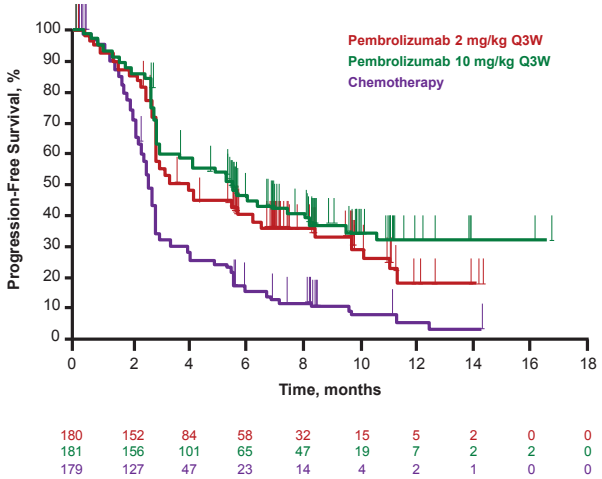


180	153	74	53	26	9	4	2	0	0
181	158	82	55	39	15	5	1	1	0
179	128	43	22	15	4	2	1	0	0

[a]Restricted mean PFS time based on 12 months of follow-up.
Analysis cut-off date: May 12, 2014.

PFS Assessed by Investigator Review

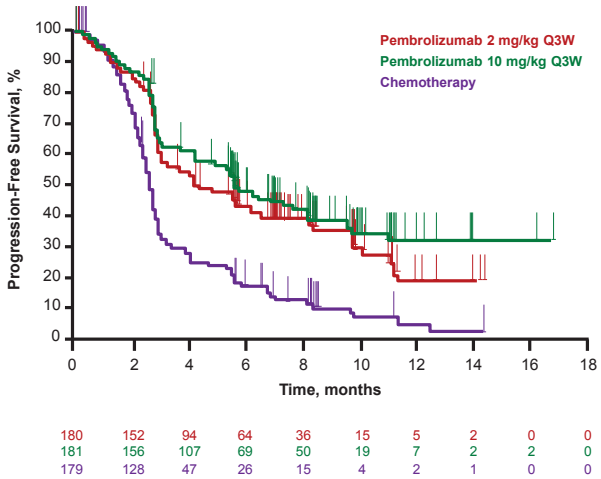
RECIST v1.1



180	152	84	58	32	15	5	2	0	0
181	156	101	65	47	19	7	2	2	0
179	127	47	23	14	4	2	1	0	0

Arm	Median (95% CI), mo	Rate at 6 mo	HR	*P*
Pembro 2 Q3W	3.7 (2.9-5.4)	39%	0.49	<0.0001
Pembro 10 Q3W	5.4 (3.8-6.8)	45%	0.41	<0.0001
Chemotherapy	2.6 (2.4-2.8)	15%	—	—

Modified RECIST v1.1
(requires confirmation of PD)



180	152	94	64	36	15	5	2	0	0
181	156	107	69	50	19	7	2	2	0
179	128	47	26	15	4	2	1	0	0

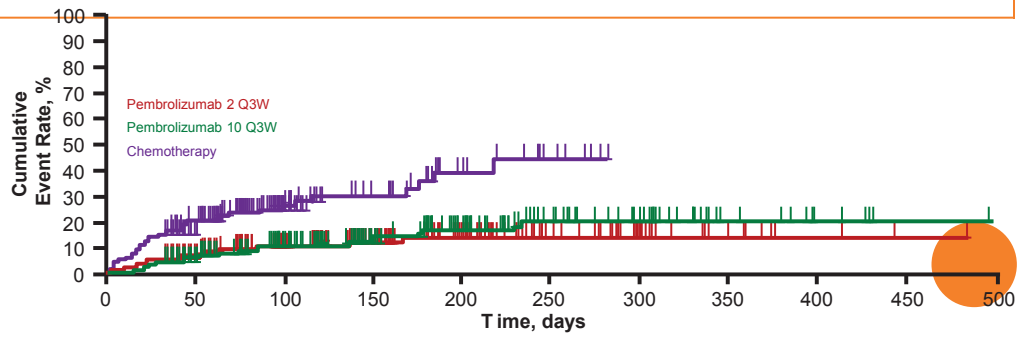
Arm	Median (95% CI), mo	Rate at 6 mo	HR	*P*
Pembro 2 Q3W	4.2 (3.1-6.2)	43%	0.45	<0.0001
Pembro 10 Q3W	5.6 (4.2-7.7)	48%	0.39	<0.0001
Chemotherapy	2.6 (2.5-2.8)	17%	—	—

Analysis cut-off date: May 12, 2014.

Summary of Exposure and Treatment-Related AEs

	Pembrolizumab 2 Q3W n = 178	Pembrolizumab 10 Q3W n = 179	Chemotherapy n = 171
Exposure, days			
Median (range)	112.5 (1-499)	145 (1-505)	61 (1-335)
Mean (SD)	144.2 (107.7)	157.0 (115.1)	75.5 (66.4)
Any grade AE	121 (68%)	133 (74%)	138 (81%)
Grade 3-5 AE	20 (11%)	25 (14%)	45 (26%)
Serious AE	14 (8%)	20 (11%)	17 (10%)
AE leading to death	1 (<1%)	0 (0%)	0 (0%)
AE leading to discontinuation	5 (3%)	12 (7%)	10 (6%)

Time to First Treatment-Related Grade 3-5 AE



178	154	117	83	58	35	19	9	4	2	1
179	156	121	89	67	42	29	12	6	2	1
171	121	44	29	13	6	0	0	0	0	0

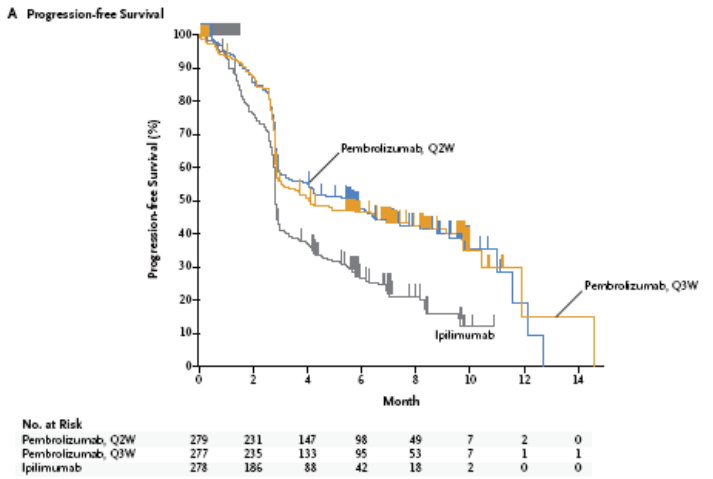
Analysis cut-off date: May 12, 2014.

The NEW ENGLAND JOURNAL of MEDICINE

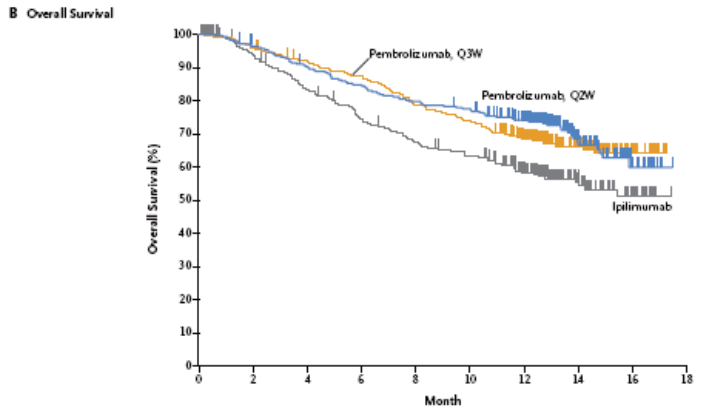
ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Carolina Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christina Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*



No. at Risk								
Pembrolizumab, Q2W	279	231	147	98	49	7	2	0
Pembrolizumab, Q3W	277	235	133	95	53	7	1	1
Ipilimumab	278	186	88	42	18	2	0	0



No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

KEYNOTE 006

Table 2. Adverse Events in the As-Treated Population.

Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)		Ipilimumab (N=256)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)					
Related to treatment*						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in ≥10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest†						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

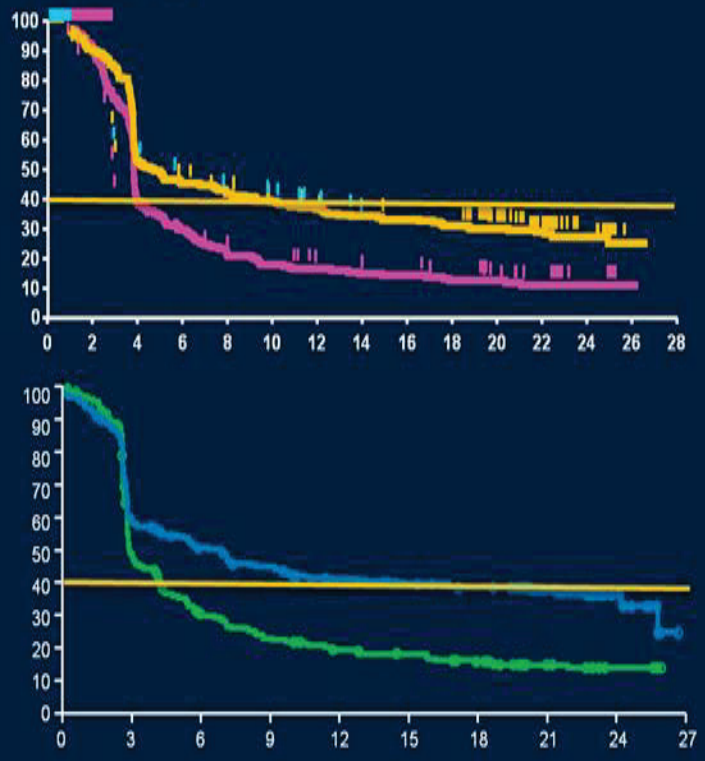
* The relationship between an adverse event and a study drug was attributed by the investigator. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks, except for hypothyroidism, hyperthyroidism, and colitis, which are reported as adverse events of special interest.
† The listed adverse events of special interest include related terms and are provided regardless of attribution to a study drug. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks.

DOBROBIT ANTI PD1

- Dolgoročni izidi pembrolizumaba kažejo, da povečajo preživetje v primerjavi z ipilimumabom za približno 18% z 22 na 40% pri treh letih
- Randomizirane študije (Keynote 006 in Checkmate 067) potrjujejo to opazovanje

Singe agent Anti-PD1 vs Anti-CTLA4

PFS curves



Keynote 06
P q3w vs. I

Checkmate 067
N vs. I

Marc Ernstoff at 2016 ASCO

Single Agent Anti-PD1 vs. Anti-CTLA4

- Keynote -006 (P vs. I)
  - OS 55% vs. 43% at 24 mo
  - PFS ~30% vs. 14% at 24 mo
  - ORR ~37% vs. 13%
  - CR ~13% vs. 5%
  - Median duration of response not met for all groups
- Checkmate 067 (N vs. I)
  - OS not reported
  - PFS ~35% vs. ~14% at 24 mo
  - ORR ~44% vs. 19%
  - CR ~12% vs. 2%
  - Median duration of response not reported

No studies compare P to N

The slight differences in observations between N & P suggest no major differences in outcomes.

Outcomes between anti-PD1 and anti-CTLA4 remarkably consistent across studies

Marc Ernstoff at 2016 ASCO

G V Long et al. SMR 2015.

KEYNOTE-029: Study Design

Dose Run-In (Part 1A)

Patients
- Advanced melanoma, any number of prior therapies OR
- Advanced clear cell RCC, ≥1 prior therapy
- No prior anti-CTLA4 or anti-PD1/PDL1
- ECOG PS 0 or 1

→ Pembro 2 mg/kg Q3W up to 24 months + Ipi 1 mg/kg Q3W x 4 doses → Tolerable Based on DLT Rate

Yes → **Dose Expansion (Part 1B)**

Patients
- Advanced melanoma
- Any number of prior therapies
- No prior anti-CTLA4 or anti-PD1/PDL1
- ECOG PS 0 or 1

No → Stop development of pembro + ipi

Primary end point:
Dose-limiting toxicity (DLT) rate

Primary end point:
Safety

Secondary end points:
ORR, DOR, and PFS (per RECIST v1.1) and OS

ClinicalTrials.gov identifier NCT02089685.

G V Long et al. SMR 2015.

KEYNOTE-029: Patients

Dose Run-In (Part 1A; N = 22)
- Advanced melanoma, any no. of prior therapies
- Advanced clear cell RCC, ≥1 prior therapy
- ECOG PS 0 or 1

Dose Expansion (Part 1B; N = 153)
- Advanced or metastatic melanoma
- Any number of prior therapies
- No prior anti-CTLA4 or anti-PD1/PDL1
- ECOG PS 0 or 1

Pembrolizumab 2 mg/kg Q3W up to 24 months + Ipilimumab 1 mg/kg Q3W x 4 doses

Current analysis: N = 72
- Melanoma pts enrolled as of April 28, 2015
  n = 12 (part 1A) + n = 60 (part 1B)
- Follow-up duration: ≥18 weeks for all patients (range 18 - 63 weeks)

ClinicalTrials.gov identifier NCT02089685.

Treatment-related Adverse Events (1/3)

Event	N=153 Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any	78 (51)	59 (39)	10 (7)
Fatigue	74 (48)	0	0
Rash	60 (39)	4 (3)	0
Pruritus	63 (41)	0	0
Diarrhoea	39 (25)	1 (1)	0
Lipase concentration increased	7 (5)	17 (11)	8 (5)
Vitiligo	30 (20)	0	0
Nausea	26 (17)	0	0
Amylase concentration increased	19 (12)	5 (3)	1 (1)
Dry mouth	25 (16)	0	0
Hypothyroidism	24 (16)	0	0
Arthralgia	19 (12)	1 (1)	0
Maculopapular rash	18 (12)	1 (1)	0
ALT increased	15 (10)	3 (2)	0
AST increased	17 (11)	0	0
Hyperthyroidism	14 (9)	2 (1)	0
Headache	15 (10)	1 (1)	0

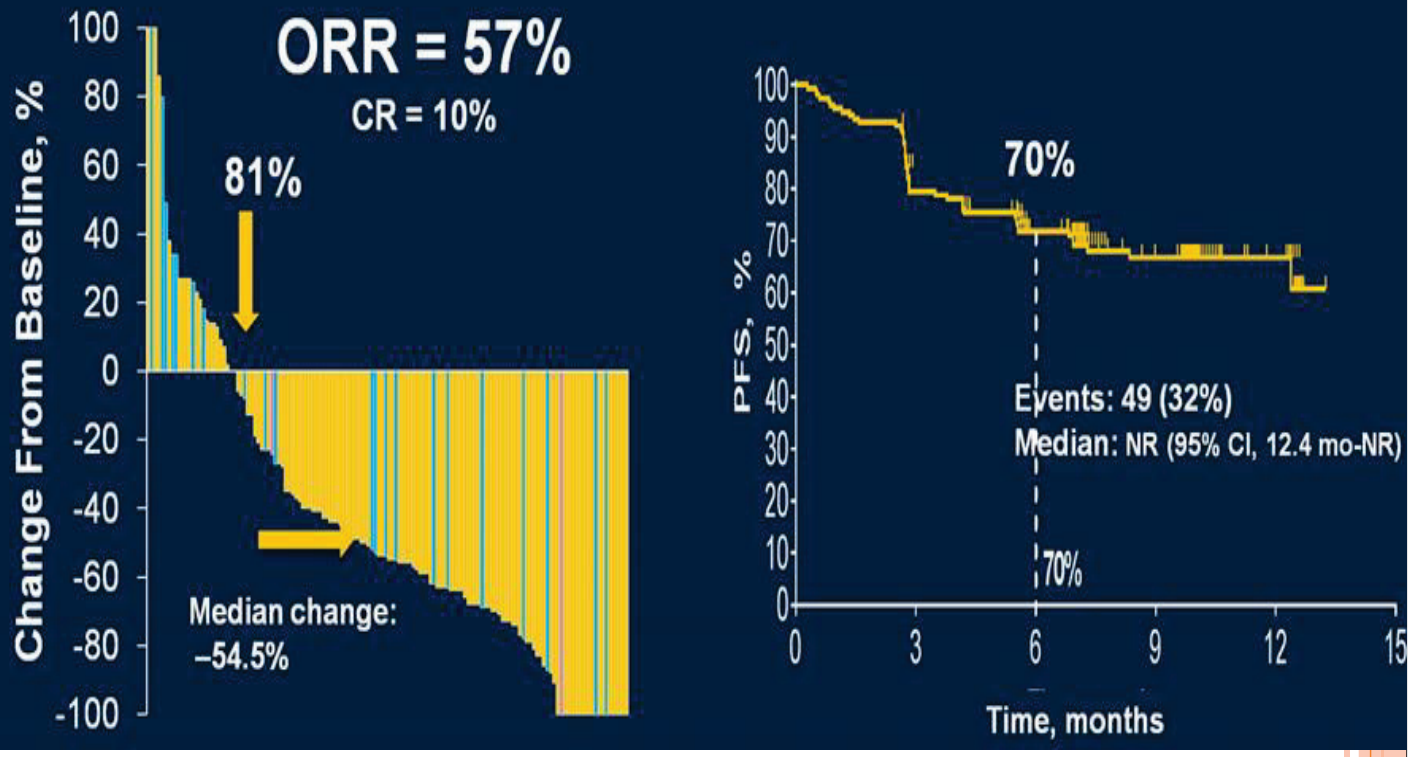
G.Long, ASCO 2016

Immune-mediated Adverse Events

	N=153 Grade 1-2	Grade 3	Grade 4
Hypothyroidism	25 (16)	0	0
Hyperthyroidism	15 (10)	2 (1)	0
Hypophysitis	13 (8)	3 (2)	0
Pneumonitis	13 (8)	3 (2)	0
Hepatitis	6 (4)	9 (6)	0
Colitis	3 (2)	11 (7)	0
Skin reactions	1 (1)	12 (8)	0
Thyroiditis	8 (5)	0	0
Infusion reactions	5 (3)	1 (1)	0
Adrenal insufficiency	4 (3)	1 (1)	0
Pancreatitis	4 (3)	1 (1)	0
Uveitis	4 (3)	0	0
Nephritis	1 (1)	2 (1)	0
Type 1 diabetes	0	2 (1)	1 (1)
Myositis	1 (1)	0	0

G.Long, ASCO 2016

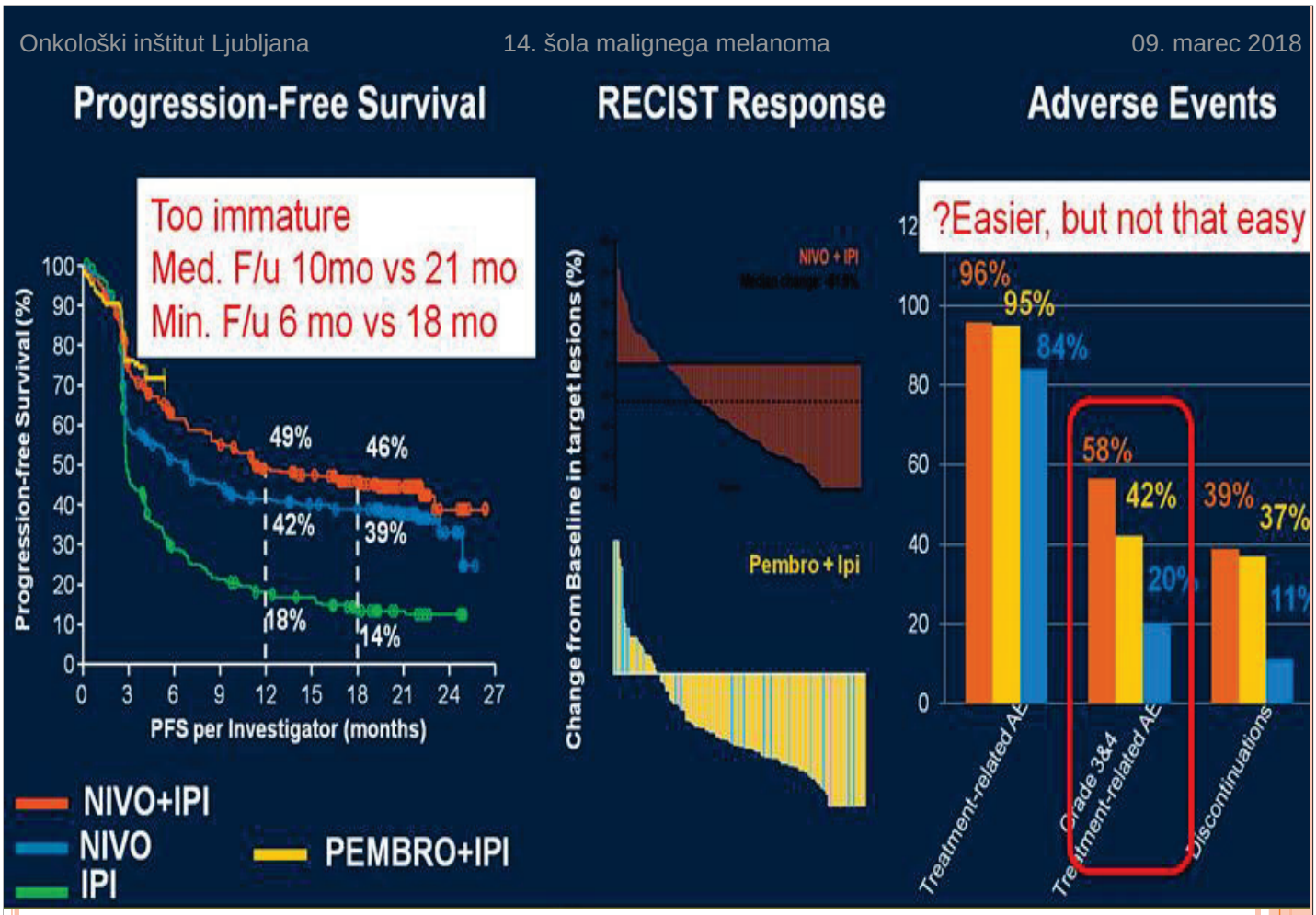
KEYNOTE-029: Pembrolizumab + Ipilimumab (1mg/kg) (n=153)



G.Long, ASCO 2016

Responses to Anti-PD1 + Anti-CTLA4 (With x-Study comparison)

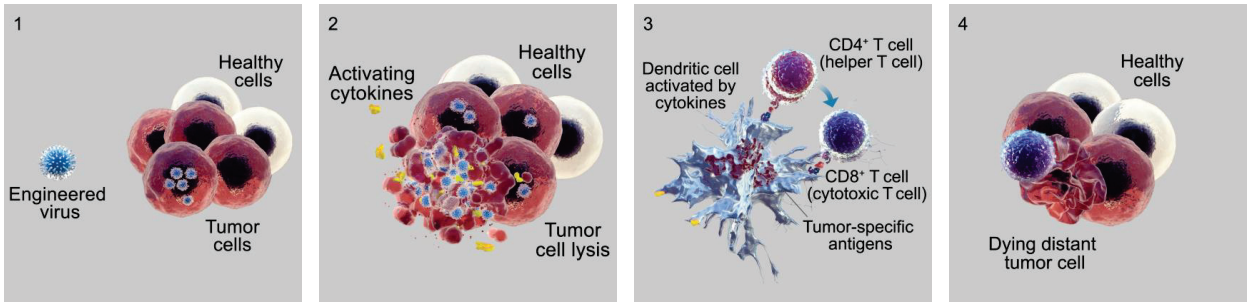
Checkmate 067	N+I	N	I
ORR %	57.6	43.7	19
CR %	12.1	9.8	2.2
MEDIAN DURATION OF RESPONSE (M)	NR	22.3	14.4
ONGOING RESPONSE IN RESPONDER %	72.5	72.4	51.7
Keynote 029	**P + I**		
ORR %	57		
CR %	15		
COMBI-d	**D+T**	**D**	
CR %	18	15	
ORR %	69	55	



G.Long, ASCO 2016

T-VEC – AN HSV-1-DERIVED ONCOLYTIC IMMUNOTHERAPY DESIGNED TO PRODUCE LOCAL AND SYSTEMIC EFFECTS

Local effect: virus-induced tumour-cell lysis ← → **Systemic effect: tumour-specific immune response**



Selective viral replication in tumour tissue[1,2]

Tumour cells rupture for an oncolytic effect[1–3]

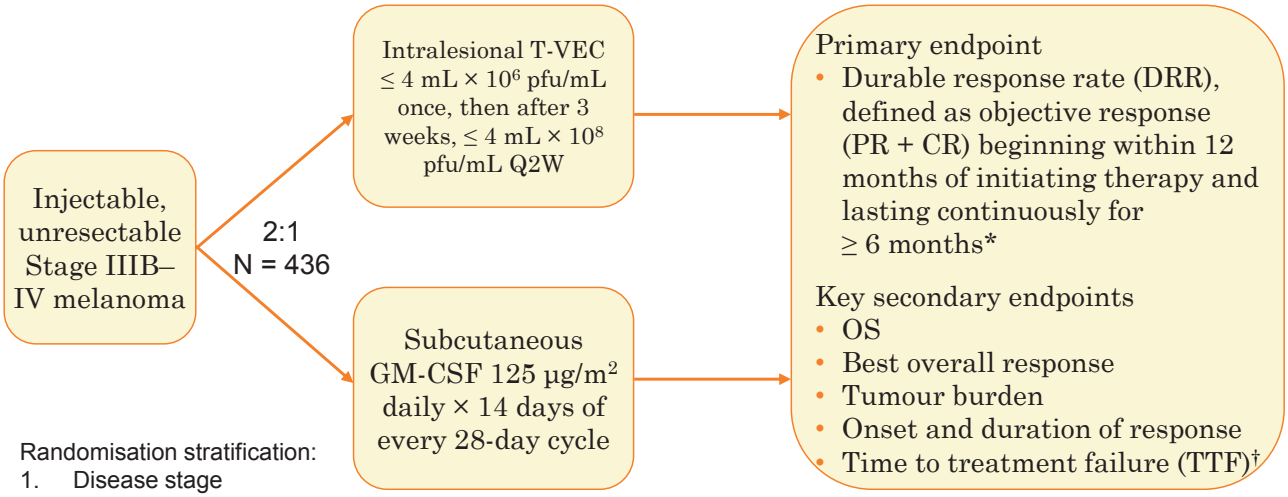
Systemic tumour-specific immune response[4,5]

Death of distant cancer cells[4–6]

Proposed mechanism of action for T-VEC.

1. Hawkins LK, et al. Lancet Oncol 2002;3:17–26; 2. Fukuhara H, Todo T. Curr Cancer Drug Targets 2007;7:149–155;
3. Pol JG, et al. Virus Adapt Treat 2012;4:1–21; 4. Melcher A, et al. Mol Ther 2011;19:1008–16;
5. Dranoff G. Oncogene 2003;22:3188–92; 6. Liu BL, et al. Gene Ther 2003;10:292–303.

STUDY DESIGN AND ENDPOINTS



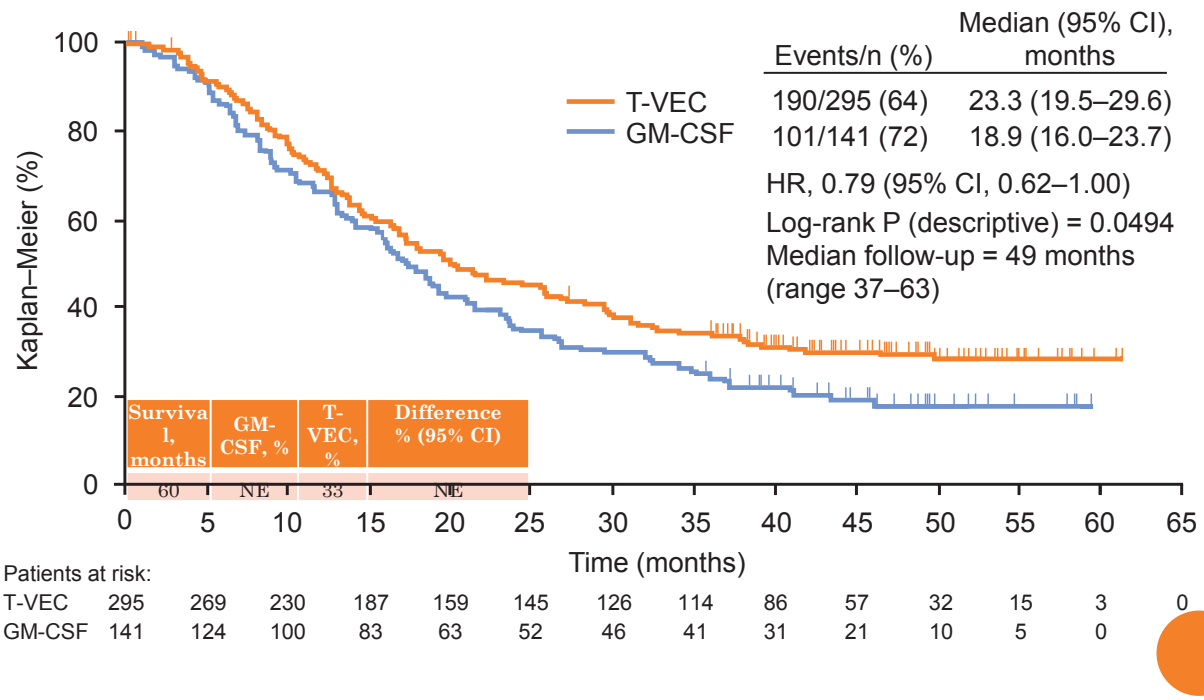
Randomisation stratification:
1. Disease stage
2. Prior non-adjuvant systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

Patients enrolled between May 2009 and July 2011. Discontinuation of treatment because of progressive disease per response assessment criteria was not required before 24 weeks unless alternate therapy was clinically indicated.

*Responses were determined using modified WHO criteria by a blinded EAC;
†TTF was defined as time from baseline to first clinically relevant disease progression for which no objective response was subsequently achieved or until death.
EAC, endpoint assessment committee; OPTiM, OncoVEX^{GM-CSF} Pivotal Trial in Melanoma.

Andtbacka RHI, et al. J Clin Oncol 2015 [Epub ahead of print].

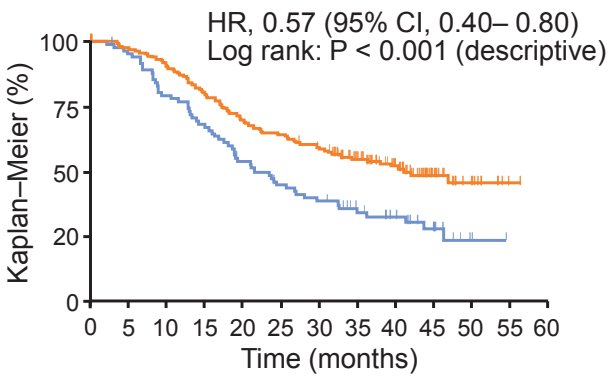
CLINICALLY MEANINGFUL IMPROVEMENT IN FINAL OVERALL SURVIVAL ANALYSIS WITH T-VEC VS GM-CSF



Andtbacka RHI, et al. SITC 2014: Abstract P263.

Exploratory subgroup analysis of OS by disease stage

Stage IIIB/C, IV M1a

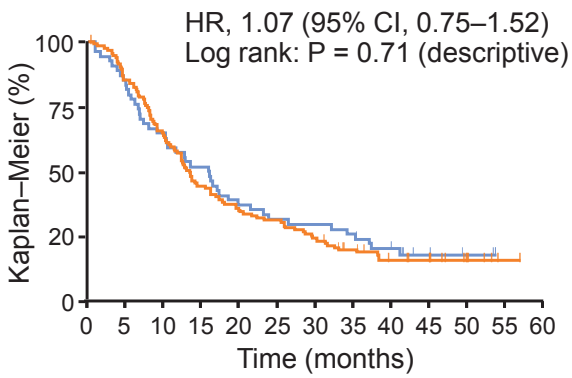


Risk set, n

T-VEC	163	157	146	129	113	104	93	73	51	23	10	1	0
GM-CSF	86	78	65	55	43	35	30	22	17	10	2	0	0

	Events/n, %	Median (95% CI), months
T-VEC	80/163 (49)	41.1 (30.6–NE)
GM-CSF	57/86 (66)	21.5 (17.4–29.6)

Stage IV M1b/c



Risk set, n

T-VEC	131	112	84	58	46	41	32	22	15	13	6	1	0
GM-CSF	55	46	35	28	20	17	16	14	10	5	3	0	0

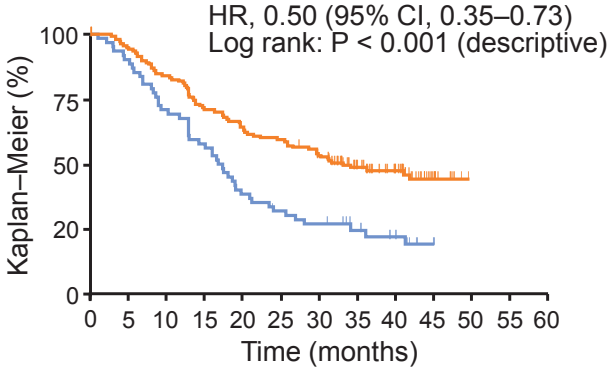
	Events/n, %	Median (95% CI), months
T-VEC	109/131 (83)	13.4 (11.4–16.2)
GM-CSF	44/55 (80)	15.9 (10.2–19.7)

NE, not evaluable.

Andtbacka RHI, et al. J Clin Oncol 2015 [Epub ahead of print].

Exploratory subgroup analysis of OS by treatment line

First-line therapy

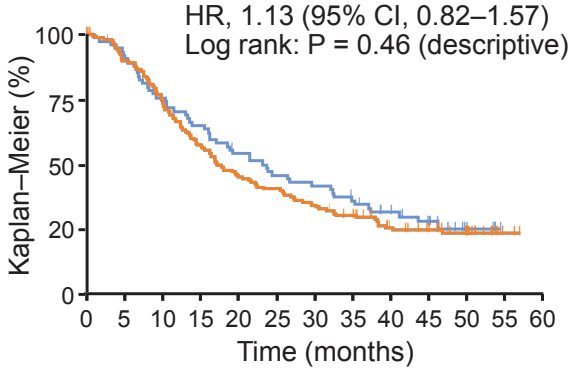


Risk set, n

T-VEC	138	130	116	98	89	82	72	50	37	12	0
GM-CSF	65	56	44	35	24	19	16	11	8	2	0

	Events/n, %	Median (95% CI), months
T-VEC	73/138 (53)	33.1 (25.9–NE)
GM-CSF	48/65 (74)	17.0 (12.8–20.9)

≥ second-line therapy



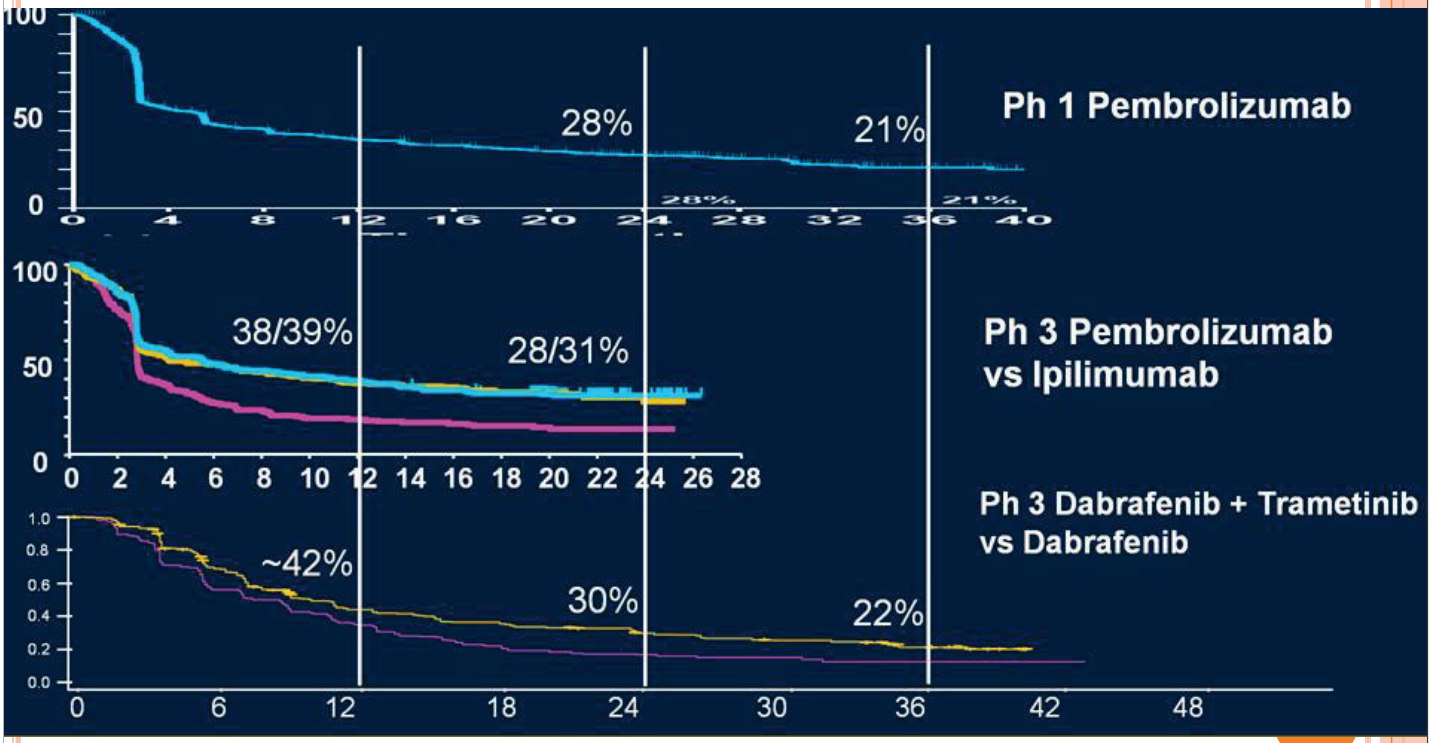
Risk set, n

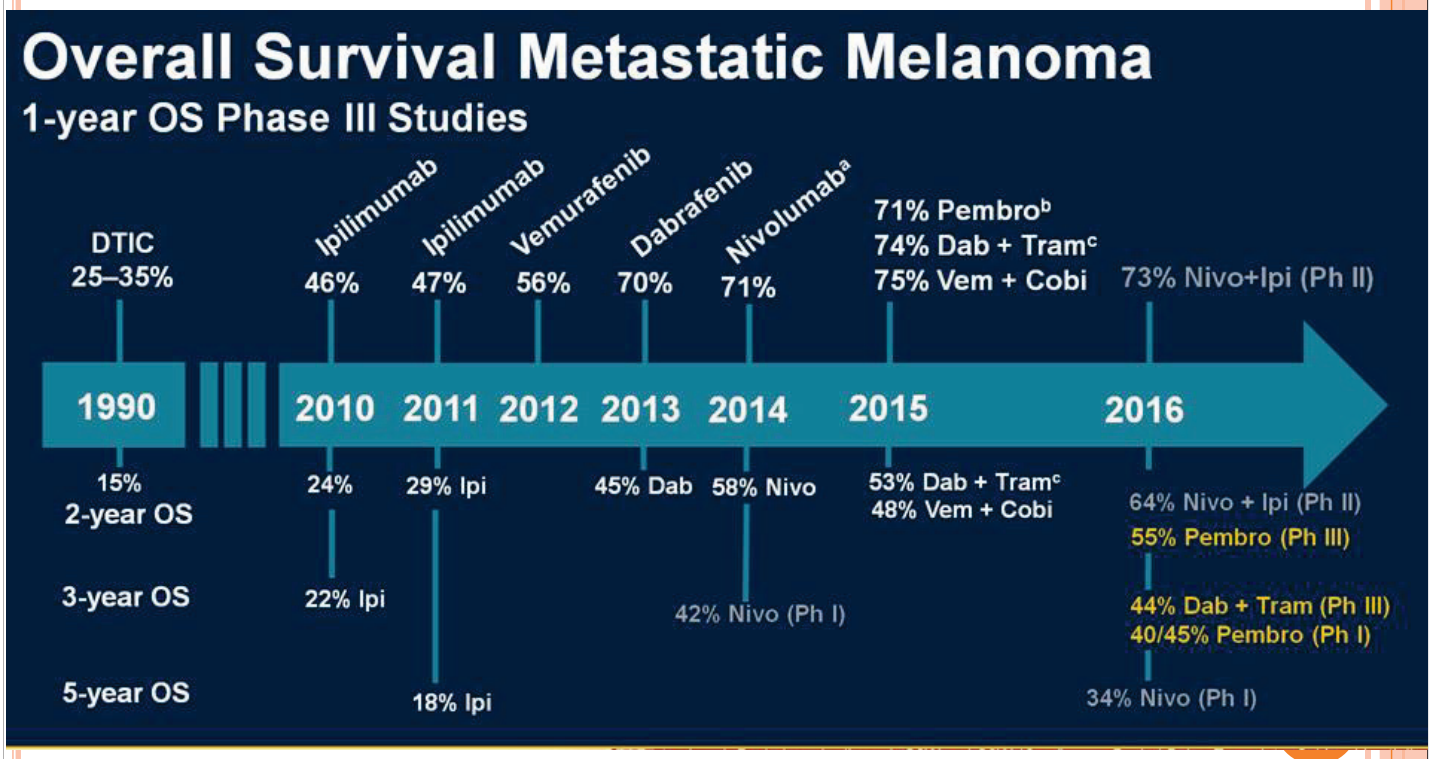
T-VEC	157	139	114	89	70	63	53	45	29	24	16	2	0
GM-CSF	76	68	56	48	39	33	30	25	19	13	5	0	0

	Events/n, %	Median (95% CI), months
T-VEC	116/157 (74)	17.1 (14.3–22.3)
GM-CSF	53/76 (70)	23.2 (16.2–32.4)

Andtbacka RHI, et al. J Clin Oncol 2015 [Epub ahead of print].

PFS UPDATE


Ph 1 Pembrolizumab
28%
21%
Ph 3 Pembrolizumab vs Ipilimumab
38/39%
28/31%
Ph 3 Dabrafenib + Trametinib vs Dabrafenib
~42%
30%
22%


Overall Survival Metastatic Melanoma
1-year OS Phase III Studies
DTIC 25–35%
Ipilimumab 46%
Ipilimumab 47%
Vemurafenib 56%
Dabrafenib 70%
Nivolumab[a] 71%
71% Pembro[b]
74% Dab + Tram[c]
75% Vem + Cobi
73% Nivo+Ipi (Ph II)
1990
2010
2011
2012
2013
2014
2015
2016
15% 2-year OS
3-year OS
5-year OS
24%
22% Ipi
29% Ipi
18% Ipi
45% Dab
58% Nivo
42% Nivo (Ph I)
53% Dab + Tram[c]
48% Vem + Cobi
64% Nivo + Ipi (Ph II)
55% Pembro (Ph III)
44% Dab + Tram (Ph III)
40/45% Pembro (Ph I)
34% Nivo (Ph I)

- Anti-CTLA- 4 terapija je bolj učinkovita kot KT
- Anti-PD-1 terapija ja bolj učinkovita kot KT
- Anti-PD-1 terapija je bolj učinkovita kot anti-CTLA-4 terapija

- Kombinacija imunoterapije je bolj učinkovita, vendar tudi bolj toksična
- Anti CTLA 4 pt lahko vplivajo na expresijo PD-L1
- Imunoterapija je učinkovita pri BRAF WT in mutiranih bolnikih z napredovalim melanomom

METASTATSKI MELANOM

Prikaz primera 1 & 2

Marija Ignjatović, dr. med.
Matej Pernek, dr. med.
Izr. prof. dr. Janja Ocvirk, dr. med.

PRIKAZ PRIMERA 1

50 let, ♂

- FA: negativna
- Brez pridruženih obolenj
- Brez redne terapije
- Dolgoletni kadilec, 40 cigaret/dan

Maj 2017: odstranitev kožne spremembe hrbta

- Histologija: epiteloidnocelični tumor nejasne histiogeneze, S-100 +, melan A -, HMB 45 –
- Konzultacija s patologom iz tujine: melanom-primarni tumor ali metastaza

Julij 2017

- Paket bezgavk v levi aksili
  - 3.5 x 4.5 x 5.5 cm, nekaj satelitskih lezij premera do 12 mm
- CT toraksa in abdomna – brez razsoja
- ABTI
  - Zasevek melanom

Aksilarna limfadenektomija

- Zasevki melanoma (11/27 bezgavk)

Konzilij

- Pooperativna RT

Pooperativna RT

- RT 28 x 2 Gy (TD 56 Gy) (22/8 – 29/9/17)
- Bezgavka SCL levo 2.5 x 2 cm
- ABTI
  - Zasevek melanoma
- PET CT
  - Zasevki v bezgavkah na vratu l. v regiji V in subpektoralno

Konzilij

- Molekularno testiranje → Sistemka terapija

Sistemska terapija

- Molekularno testiranje
  - B-RAF muticija

→ Tarčna terapija – BRAFi + MEKi

→ Imunoterapija – antiPD-1

?

Imunoterapija

- Pembrolizumab (2 mg/kg/3 tedne)

Pembrolizumab

- 1. aplikacija (3/10/17)

Odgovor na zdravljenje

- Po 2. apikaciji bezgavke več niso tipno povečane
- PET CT (po 5. aplikaciji – 9/1/18) CR!

- Stranski učinki
  - Po 6. aplikaciji papulozni izpuščaj v predelu leve aksile
  - Topikalni KS, antihistaminik

PRIKAZ PRIMERA 2

P.B.1947: **več suspektnih lezij po telesu**

2009 Ekscizija spremembe v D poplitealni regiji

- Histološka ***Dg: maligni melanom in situ***
- Reekscizija

2010 Ekscizija spremembe na hrbtu

- Histološka ***Dg: maligni melanom T1a***
- Reekscizija
- Follow up na 6 mesecev 5 let, dermatolog (SB Celje/kirurg (OI)

2016 **Povečane bezgavke na vratu**

- UZ vratu + citološka punkcija bezgavke L supraklavikularno
- Citološka ***Dg: zasevek malignega melanoma***

Maj 2016, OI

KLINIČNI PREGLED

- „na vratu L tipnih več pomičnih bezgavk od 2. do 5. nivoja“
- PS po WHO 0

LAB.IZVIDI

- ↑ LDH (9.61 L)
- ↑ S100 (0.711)

PET CT

Patološko povišana metabolna aktivnost v bezgavkah levo na vratu, levo retrofaringealno ob požiralniku, desno retrokruralno v nivoju TH12, v bezgavki v mezenteriju, v bezgavkah interaortokavalno, prekavalno, retro- in parakavalno ter v bezgavkah paraaortalno in retroaortalno - metastaze.

68-letni bolnik v odlični fizični kondiciji z MM in metastazami v bezgavkah L na vratu ter paraaortralno

TH:
- Disekcija bezgavk L na vratu in v trebuhu

HIST.IZVID:
- Metastatske bazgavke
- Vrat: **20,** s preraščanjem kapsule in obsežno vaskularno invazijo
- Abdomen: **34**

MOL.DIAGNOSTIKA:
- B-Raf mutiran (V600E)

B-Raf mutiran tumor, vendar mali obseg bolezni → IMUNOTERAPIJA!

PEMBROLIZUMAB
- Junij-oktober 2016, 7 aplikacij
- Brez večjih stranskih učinkov

MED ZDRAVLJENJEM
- Ponovno tipne povečane bezgavke na vratu → težave s požiranjem, hripavost
- Ponovni porast tumorskih markerjev, ki so bili po op. v upadanju → LDH 26.97 (po op. 3.88), S100 2.14 (po op. 0.184)

KONTROLNI PET CT

V primerjavi s prejšnjo preiskavo z dne 19.05.2016 so kopičenja obsežnejša, številna nova ter intenzivneje kopičijo radiofarmak - jasen progres metastaz.

BRAF mutiran tumor → TARČNO KOMBINIRANO ZDRAVLJENJE (braf + mek inhibitorji)

VEMURAFENIB + COBIMETINIB *UZ srca: bp, razen blago povečanega L atrija*

- November 2016-april 2017, 6 ciklusov

PO 1. CIKLLUSU Pomembno klinično in biokemično izboljšanje

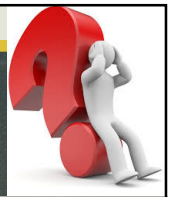
- Paket patoloških bezgavk pred zamenjavo th.7x7 cm, sedaj 3 cm v najdaljšem promeru
- LDH 7.11 (pred zamenjavo th. 22.34), S100 0.236 (pred zamenjavo th. 1.220)

MED 6.CIKLUSOM *Kontrolni UZ srca po 3.ciklusu v mejah normale*

- PAF (EK → sinusni ritem) in srčno popuščanje
- Respiratorni infekt (azitromicin)
- Srčna tampondana

cardiac	atrial fibrillation (2%)
	cardiac failure (<1%)
	QTc prolongation, may require treatment interruption and dose modification; see paragraph following **Side Effects** table

Srčna tamponda → perikardiocenteza → hemoragičen izliv (cito,izvid:***brez mlg celic***; MB izvid: (an)aerobna kultura ***negativno***



Causes of pericardial disease

Idiopathic (presumed to be viral, postviral, or immune-mediated)
In most case series, the majority of patients are not found to have an identifiable cause of pericardial disease. Frequently such cases are presumed to have a viral or autoimmune etiology.
Infectious
Viral - Coxsackievirus, echovirus, adenovirus, Epstein-Barr virus, cytomegalovirus, influenza, varicella, rubella, HIV, hepatitis B, mumps, parvovirus B19, vaccina (smallpox vaccine)
Bacterial - *Mycobacterium tuberculosis* (most common cause in countries where tuberculosis is endemic), *Staphylococcus, Streptococcus, Haemophilus, Neisseria (N. gonorrhoeae or N. meningitidis), Chlamydia (C. psittaci or C. trachomatis), Legionella, Salmonella, Borrelia burgdorferi* (the cause of Lyme disease), *Mycoplasma, Actinomyces, Nocardia, Tropheryma whipplei, Treponema, Rickettsia*
Fungal - *Histoplasma, Aspergillus, Blastomyces, Coccidioides, Candida*
Parasitic - *Echinococcus*, amebic, *Toxoplasma*
Infective endocarditis with valve ring abscess
Noninfectious
Autoimmune and autoinflammatory
Systemic inflammatory diseases, especially lupus, rheumatoid arthritis, scleroderma, Sjögren syndrome, vasculitis, mixed connective disease
Autoinflammatory diseases (especially familial Mediterranean fever and tumor necrosis factor associated periodic syndrome [TRAPS], IgD4-related disease)
Postcardiac injury syndromes (immune-mediated after cardiac trauma in predisposed individuals)
Other - Granulomatosis with polyangiitis (Wegener's), polyarteritis nodosa, sarcoidosis, inflammatory bowel disease (Crohn's, ulcerative colitis), Whipple's, giant cell arteritis, Behçet's disease, rheumatic fever
Neoplasm
Metastatic - Lung or breast cancer, Hodgkin's disease, leukemia, melanoma
Primary - Rhabdomyosarcoma, teratoma, fibroma, lipoma, leiomyoma, angioma
Paraneoplastic

Cardiac
Early infarction pericarditis
Late postcardiac injury syndrome (Dressler's syndrome), also seen in other settings (eg, post-myocardial infarction and post-cardiac surgery)
Myocarditis
Dissecting aortic aneurysm
Trauma
Blunt
Penetrating
Iatrogenic - Catheter and pacemaker perforations, cardiopulmonary resuscitation, post-thoracic surgery
Metabolic
Hypothyroidism - Primarily pericardial effusion
Uremia
Ovarian hyperstimulation syndrome
Radiation
Drugs (rare)
Procainamide, isoniazid, or hydralazine as part of drug-induced lupus
Other - Cromolyn sodium, dantrolene, methysergide, anticoagulants, thrombolytics, phenytoin, penicillin, phenylbutazone, doxorubicin

Azithromycin and Cardiac tamponade - from FDA reports

Summary

Cardiac tamponade is found among people who take Azithromycin, especially for people who are male, 60+ old , have been taking the drug for < 1 month, also take medication Dapsone, and have Atrial fibrillation/flutter. This review analyzes which people have Cardiac tamponade with Azithromycin. It is created by eHealthMe based on reports of 17,288 people who have side effects when taking Azithromycin from FDA , and is updated regularly.

P.B.1947

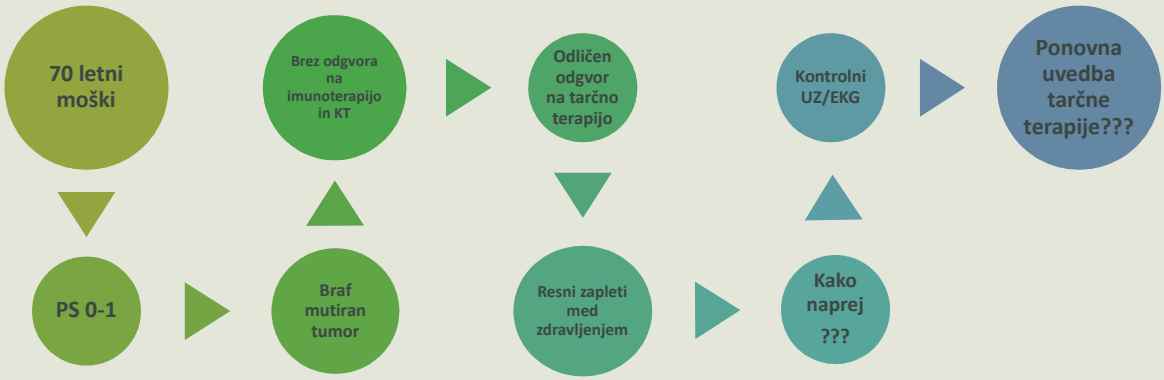
- Tipne povečane bezgvke na vratu (2 meseca po vkinitvi tarčenga zdravljenja)
- BK progres
- PET CT → progres bolezni

KT Paklitaksel + karboplatin

- Junij-oktober 2017, 5 ciklusov
- Slabost, nevtropenija gr.2

PROGRES

- Klinično - ponovno tipne bezgvke na vratu
- BK - porast LDH in s100
- CT trojček - nadaljni progres bolezni v bezgavkah. Srce normalne velikosti, *brez perikardialnega izliva*. Pljučna embolija



UZ srca popolnoma v mejah normale
EKG sinusni ritem

DABRAFENIB + TRAMETINIB 100% odmerek

- November 2017 →
- Povišena TT, mrzlica

PO 2. CIKLUSU

- Klinično: bezgavke na vratu so komaj tipne
- Tumorski markeji v upadnju

KONTROLNI CT V KRATKEM …

HVALA ZA POZORNOST!

TARČNO ZDRAVLJENJE METASTATSKEGA MALIGNEGA MELANOMA

MARKO BOC, DR.MED., SEKTOR ZA INTERNISTIČNO ONKOLOGIJO
ONKOLOŠKI INŠTITUT LJUBLJANA

14. ŠOLA MALIGNEGA MELANOMA
09.03.2018

METASTATSKI MALIGNI MELANOM
SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

- monoklonska protitelesa
  - ipilimumab (anti CTLA-4)
  - tremelimumab (anti CTLA-4)
  - pembrolizumab (anti PD-1)
  - nivolumab (anti PD-1)
  - anti PD-L1

IMUNOMODULATORNO ZDRAVLJENJE

- tirozin-kinazni inhibitorji (male molekule)
  - vemurafenib (BRAFi)
  - dabrafenib (BRAFi)
  - trametinib (MEKi)
  - BRAFi + MEKi

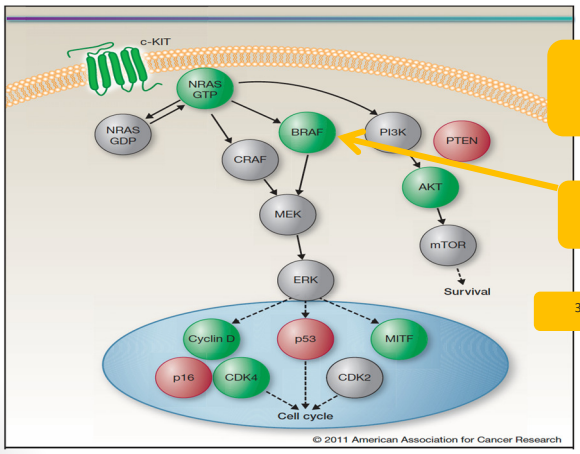
PD-1 - "anti-programmed-death-receptor-1"
PD-L1- „programmed-death-ligand-1"
CTLA-4 - cytotoxic T-lymphocyte-associated protein 4-receptor

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

BRAF INHIBITORJI

Signalne poti pri melanomu[1]:



BRAF-MAPK celična pot

~ 50% bolnikov ima prisotno $BRAF^{V600}$ mutacijo[2] (exon 15)

[3]80-90% $BRAF^{V600E}$

$BRAF^{V600K}$

1. Flaherty KT, Fisher DE. Clin Cancer Res 2011;17:4922–4928.
2. Jakob JA, et al. Cancer 2012;118:4014–4023.
3. Lovly et al. PLoS One. 2012; 7(4): e35309.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

BRAF INHIBITORJI - monoterapija

VEMURAFENIB[1] (BRIM 3)

- mPFS: 6.9 vs 1.6 meseca, HR = 0.38, *P*<.0001
- mOS: 13.6 vs 9.7 meseca, HR = 0.70, *P* = .0008
- ORR: 57%

DABRAFENIB[2] (BREAK-3)

- mPFS: 6.9 vs 2.7 meseca; HR 0.37; p<0.0001
- mOS: 18.2 vs. 15.6 meseca; HR 0.76; p=NS
- ORR: 53%[3]

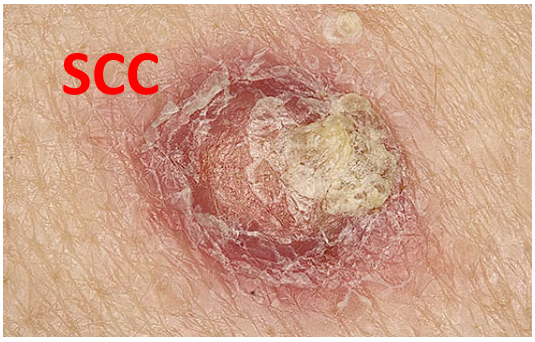
mPFS – srednje preživetje brez progresa
mOS – srednje celokupno preživetje
ORR – objektivni odgovor (CR+PR)

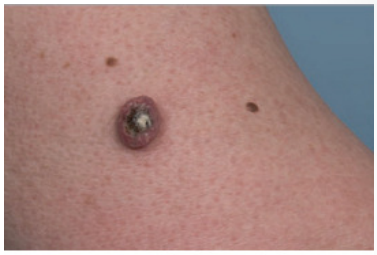
1. McArthur GA, et al. Lancet Oncol 2014; 15: 323-32.
2. Latimer NR, et al. TheOncologist 2015;20:798–805.
3. Hauschild A, et al. Lancet 2012; 380: 358-65.

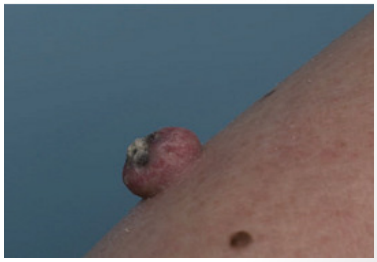
METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

***BRAF INHIBITORJI** – KOŽNA TOKSIČNOST 1/3*





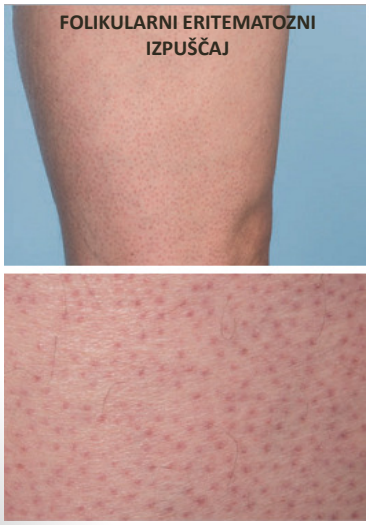


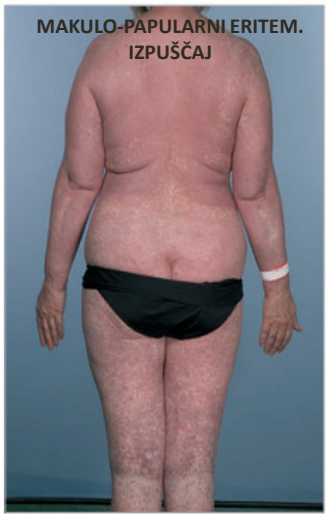
- Najbolj pogosto v prvih 7-8 tednih zdravljenja
- Dobro diferencirana neoplazma z majhno možnostjo zasevanja
- Terapija ➔ **EKSCIZIJA**

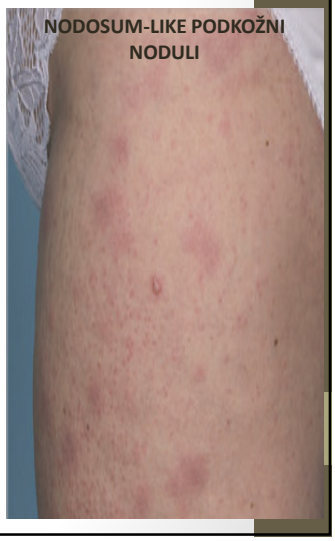
METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

***BRAF INHIBITORJI** – KOŽNA TOKSIČNOST 2/3*







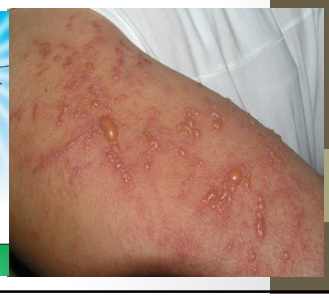
METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

***BRAF INHIBITORJI** – KOŽNA TOKSIČNOST 3/3*

FOTOSENZITIVNOST

ŽE V **PRVEM TEDNU** ZDRAVLJENJA OB IZPOSTAVLJENOSTI SONCU



METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

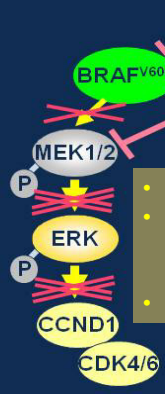
***BRAF INHIBITORJI** – NEŽELJENI UČINKI*

	VEMURAFENIB[1]	DABRAFENIB[2,3]
• Izpuščaj	+++	+
• Fotosenzitivnost	+++	+
• SCC, keratoakantomi	+++	+
• Jetrna toksičnost	+++	+
• Pireksija	+	+++
• Mrzlica	+	+++
• Slabost	+	+
• Bruhanje	+	+
• Driska	+	+
• Bolečine v mišicah in sklepih	++	++
• Utrujenost	+++	++

1. McArthur GA, et al. Lancet Oncol 2014; 15: 323-32.
2. Hauschild A, et al. Poster presentation at ASCO 2014, Abstract 1092PD.
3. Hauschild A, *et al.* Poster presentation at ASCO 2013.

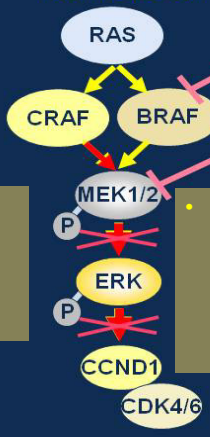
DVOJNA INHIBICIJA ONKOGENE POTI PRI MM

$BRAF^{V600}$
Mutirane melanomske celice



- Izboljšan ORR
- Preprečitev rezistence (daljše trajanje odgovora in daljši PFS)
- Daljši OS

$BRAF^{V600}$
Wild-type (normalne)celice



- Manj kožne toksičnosti, ki je posledica paradoksalne aktivacije MAPK poti

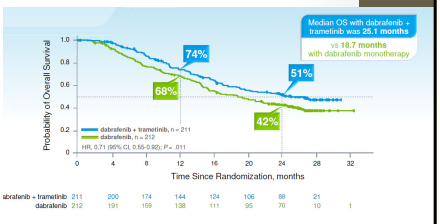
Presented by: Antoni Ribas at 2014 ASCO Annual Meeting PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

METASTATSKI MALIGNI MELANOM

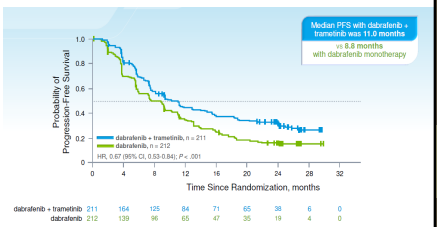
SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

UČINKOVITOST KOMBINIRANEGA ZDRAVLJENJA

- DABRAFENIB+TRAMETINIB (COMBI-d, COMBI-v)[1,2]
  - mOS: 25,1-25,6 mesecev
  - tveganje za smrt manjše za 29-34%
  - (HR 0.71, HR 0.66)
  - mPFS: 11,0-12,6 mesecev
  - tveganje za progres manjše za 33-39%
  - (HR 0.67, HR 0.61)
  - objektivni odgovor na zdravljenje: 66-69%
  - kontrola bolezni: preko 90%



- More than half of all patients (51%) treated with dabrafenib + trametinib were alive at 2 years



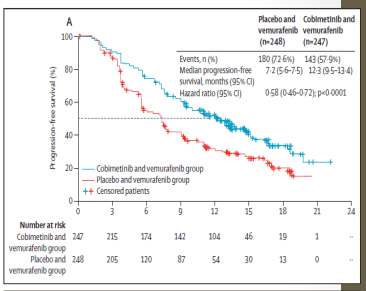
1. Robert C, et al. *Ann Oncol.* 2015;26(suppl 6) [abstract 3301].
2. Long GV, et al. *Lancet.* 2015;386(9992):444-451.

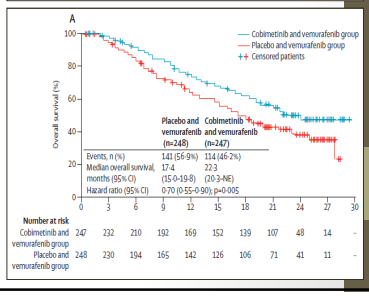
METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

UČINKOVITOST KOMBINIRANEGA ZDRAVLJENJA

- VEMURAFENIB + KOBIMETINIB (co-BRIM)[1]
  - mOS: 22,3 meseca
  - tveganje za smrt manjše za 30% (HR 0.70)
  - mPFS: 12,3 meseca
  - tveganje za progres manjše za 42% (HR 0.58)
  - objektivni odgovor na zdravljenje: 70%



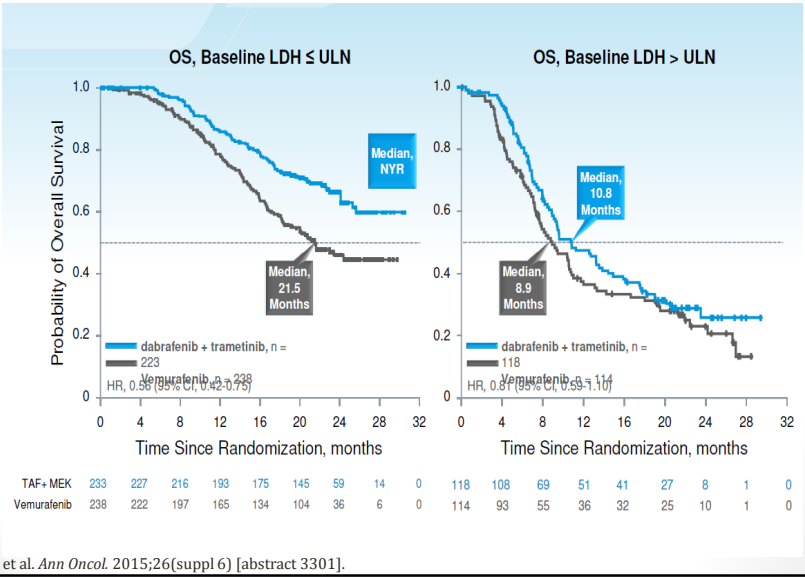


1. Lancet Oncol. 2016 Sep;17(9):1248-1260. Epub 2016 Jul 30.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

CELOKUPNO PREŽIVETJE & LDH (COMBI-v)

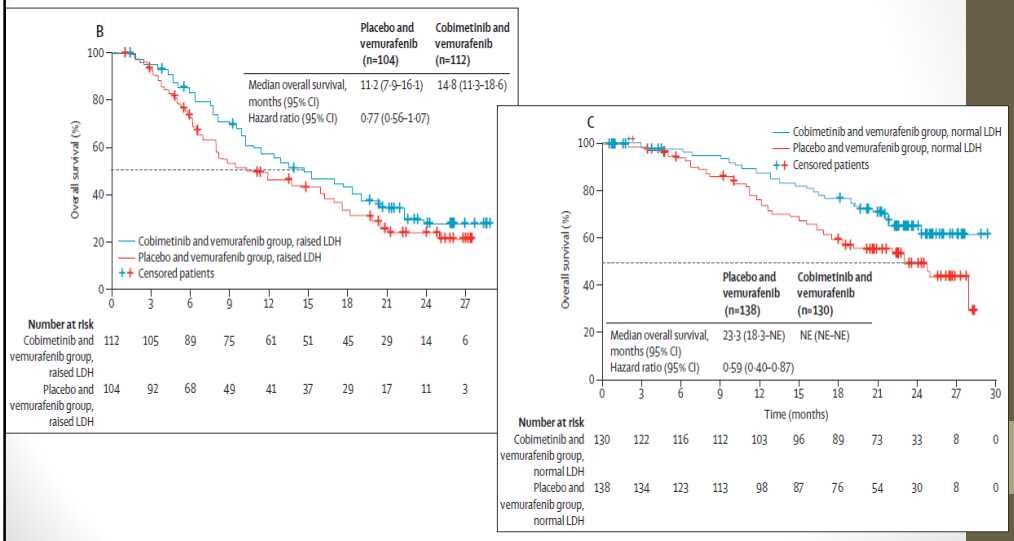


Robert C, et al. *Ann Oncol.* 2015;26(suppl 6) [abstract 3301].

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

CELOKUPNO PREŽIVETJE & LDH (co-BRIM)

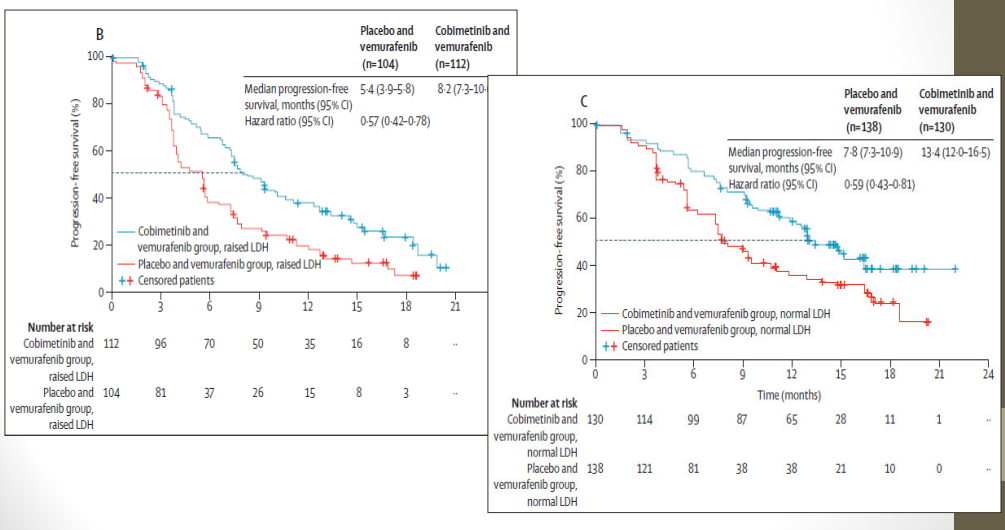


Lancet Oncol 2016: Published online July 29, 2016.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

PREŽIVETJE BREZ PROGRESA & LDH (co-BRIM)



Lancet Oncol 2016: Published online July 29, 2016.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

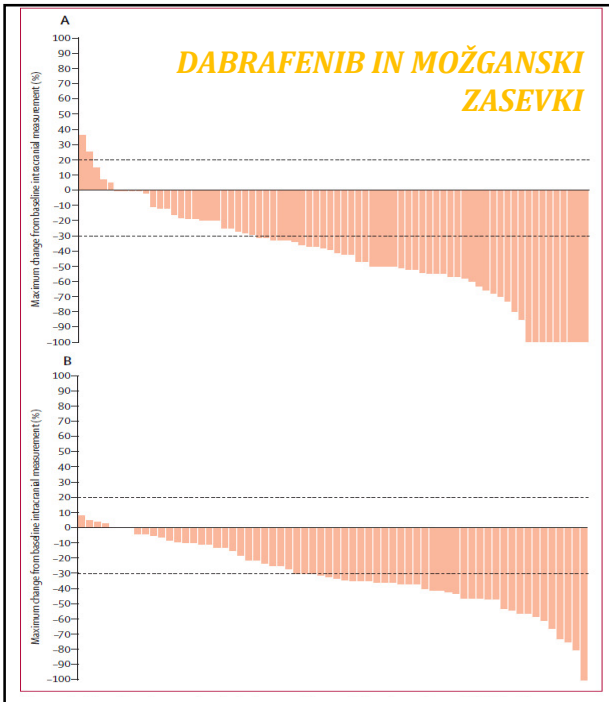
VEMURAFENIB IN MOŽGANSKI ZASEVKI

Table 4. Treatment Response (CR/PR) and Disease Progression

	N = 283	
Best response while on vemurafenib , n (%)	Intracranial	Extracranial
CR or PR	136 (48.1)	129 (45.6)
CR: disappearance of all target lesions	40 (14.1)	32 (11.3)
PR: decreased size in majority of target lesions, with no new lesions	96 (33.9)	97 (34.3)
PD	49 (17.3)	53 (18.7)
Enlargement of existing lesions	35 (12.4)	39 (13.8)
Appearance of new lesions	19 (6.7)	26 (9.2)
Other clinical evidence of progressive disease	1 (0.4)	0 (0.0)
SD: none of the above	54 (19.1)	57 (20.1)
Unknown	44 (15.5)	44 (15.5)
Patients who experienced progression while on vemurafenib, n (%)	78 (27.6)	101 (35.7)

Presented at the 2014 ESMO Congress; Poster 1104P.

DABRAFENIB IN MOŽGANSKI ZASEVKI



	Cohort A	Cohort B
Val600Glu BRAF mutant	74	65
Overall intracranial response (CR+PR)	29 (39·2%, 28·0–51·2%)	20 (30·8%, 19·9–43·4%)
Intracranial disease control (CR+PR+SD)*	60 (81·1%, 70·3–89·3%)	58 (89·2%, 79·1–95·6%)
Intracranial CR	2 (3%)	0
Intracranial PR	27 (36%)	20 (31%)
Intracranial SD	31 (42%)	38 (58%)
Intracranial PD	9 (12%)	5 (8%)
Not assessable	5 (7%)†	2 (3%)‡
Overall response (CR+PR)§	28 (37·8%, 26·8–49·9%)	20 (30·8%, 19·9–43·5%)
Overall disease control (CR+PR+SD)	59 (79·7%, 68·8–88·2%)	54 (83·1%, 71·7–91·2%)
6-month survival estimate (%)	61% (46·7–73·2%)	61% (46·3–72·7%)
Val600Lys BRAF mutant	15	18
Overall intracranial response (CR+PR)	1 (6·7%, 0–31·9%)	4 (22·2%, 6·4–47·6%)
Intracranial disease control (CR+PR+SD)*	5 (33·3%, 11·8–61·6%)	9 (50·0%, 26·0–74·0%)
Intracranial CR	0	0
Intracranial PR	1 (7%)	4 (22%)
Intracranial SD	4 (27%)	5 (28%)
Intracranial PD	6 (40%)	6 (33%)
Not assessable	4 (27%)¶	3 (17%)‖
Overall response (CR+PR)§	0 (0%, 0–21·8%)	5 (27·8%, 9·7–53·5)
Overall disease control (CR+PR+SD)	7 (46·7%, 21·3–73·4%)	9 (50·0%, 26·0–74·0%)
6-month survival estimate (%)	27% (8·3–49·6%)	41% (16·5–64·0%)

Data are n, n (%, 95% CI), or n (%). CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *SD as best response at or after week 8 assessment. †Two patients with no disease assessments after baseline, two patients with only week 4 assessments of SD, and one patient with only a week 4 assessment of PR. ‡One patient started new anticancer treatment 2 days after first dose of study treatment, and one patient with only a week 4 assessment of PR. §Overall response was defined as the proportion of patients with a best response of CR or PR when all disease (both extracranial and intracranial) was assessed. ¶Four patients with no disease assessments after baseline. ‖One patient with clinical progression at week 1, two with only week 4 assessments of SD.

Table 2: **Disease response**

Georgina VL, et al. Lancet Oncol 2012; 13: 1087-95.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

NEŽELJENI UČINKI KOMBINIRANEGA ZDRAVLJENJA (co-BRIM)

	Placebo and vemurafenib (n=246)		Cobimetinib and vemurafenib (n=247)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common adverse events (occurring in ≥20% of patients in either group)				
Rash*	166 (68%)	40 (16%)	179 (73%)	42 (17%)
Arthralgia	103 (42%)	12 (5%)	94 (38%)	6 (3%)
Diarrhoea	82 (33%)	2 (1%)	150 (61%)	16 (7%)
Fatigue	82 (33%)	7 (3%)	91 (37%)	11 (5%)
Alopecia	75 (31%)	1 (<1%)	41 (17%)	1 (<1%)
Hyperkeratosis	67 (27%)	6 (3%)	25 (10%)	1 (<1%)
Nausea	64 (26%)	2 (1%)	105 (43%)	3 (1%)
Pyrexia	59 (24%)	0	71 (29%)	3 (1%)
Decreased appetite	50 (20%)	1 (<1%)	50 (20%)	0
Photosensitivity reaction	48 (20%)	0	84 (34%)	8 (3%)
Alanine aminotransferase concentration increase	44 (18%)	15 (6%)	65 (26%)	28 (11%)
γ-glutamyltransferase concentration increase	44 (18%)	25 (10%)	54 (22%)	36 (15%)
Vomiting	34 (14%)	2 (1%)	63 (26%)	4 (2%)
Aspartate aminotransferase concentration increase	31 (13%)	5 (2%)	60 (24%)	22 (9%)
Serous retinopathy†	9 (4%)	0	67 (27%)	7 (3%)
Blood creatine phosphokinase level increase	7 (3%)	1 (<1%)	87 (35%)	30 (12%)
Other selected adverse events (selected based upon known association with BRAF or MEK inhibition)				
Cutaneous squamous cell carcinoma	31 (13%)	31 (13%)	10 (4%)	9 (4%)
Keratoacanthoma	23 (9%)	21 (9%)	4 (2%)	3 (1%)
Decreased ejection fraction	13 (5%)	3 (1%)	29 (12%)	5 (2%)
QT prolongation	13 (5%)	3 (1%)	11 (5%)	3 (1%)

Lancet Oncol 2016; 17: 1248–60

Prenehanje terapije zaradi NU v 14%.

METASTATSKI MALIGNI MELANOM

SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE

NEŽELJENI UČINKI KOMBINIRANEGA ZDRAVLJENJA (COMBI-v, COMBI-d)

	COMBI-d[1]		COMBI-v[2]	
	dabrafenib + trametinib (n = 209)	dabrafenib (n = 211)	dabrafenib + trametinib (n = 350)	Vemurafenib (n = 349)
Any AE, %	87	90	98	99
Pyrexia	52	25	53	21
Chills	28	14	31	8
Fatigue	27	28	29	33
Nausea	20	15	35	36
Vomiting	14	9	29	15
Diarrhea	18	9	32	38
Headache	19	17	29	—
Peripheral edema	11	2	—	—
Cough	—	—	—	—
Arthralgia	16	23	24	51
Rash	24	20	22	43

- The most common dabrafenib + trametinib adverse reactions (≥ 20%) were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, arthralgia, hypertension, vomiting, and cough[3]
- The rate of dabrafenib + trametinib discontinuations due to AEs was 11% in COMBI-d and 13% in COMBI-v[1,2]

1. Long GV, et al. *Lancet.* 2015;386(9992):444-451.
2. Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.
3. dabrafenib (dabrafenib) [summary of product characteristics]. West Sussex, UK: Novartis Europharm Limited; 2015.

METASTATSKI MALIGNI MELANOM
SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE
ZAKLJUČKI

- Za zdravljenje z BRAF-inh v monoterapiji ali v kombinaciji z MEK-inh je potrebna pristotnost $BRAF^{V600}$ mutacije (prediktivni dejavnik)
- BRAF inhibitorji v monoterapiji v primerjavi z kemoterapijo signifikantno podaljšajo celokupno preživetje in preživetje brez progresa
- Kombinacija BRAF in MEK-inh omogoča objektivni odgovor na zdravljenje in kontrolo bolezni v najvišjih odstotkih (cca. 70% in > 90%), v primerjavi z ostalimi vrstami sistemskih zdravljenj, ki so trenutno na voljo
- V primerjavi z imunoterapijo je srednji čas do odgovora na zdravljenje in izboljšanja simptomov krajši ➔simptomatski bolniki z velikim bremenom bolezni
- Možganski zasevki niso kontraindikacija za zdravljenje z BRAF-inh

METASTATSKI MALIGNI MELANOM
SISTEMSKA TERAPIJA – TARČNO ZDRAVLJENJE
ZAKLJUČKI

- Profil neželjenih učinkov različnih BRAF-inh in njihovih kombinacij z MEK-inh se razlikuje
- Večina neželjenih učinkov je ob ustreznih podpornih ukrepih in ustrezni informiranosti bolnikov obvladljiva
- Bolniki z normalnim LDH in z zasevki v manj kot treh organskih sistemih imajo veliko boljšo prognozo (daljše celokupno preživetje, daljši čas do progresa)

Tarčno zdravljenje napredovalega melanoma

Prikaz primera

Nina Fokter Dovnik
Marko Boc

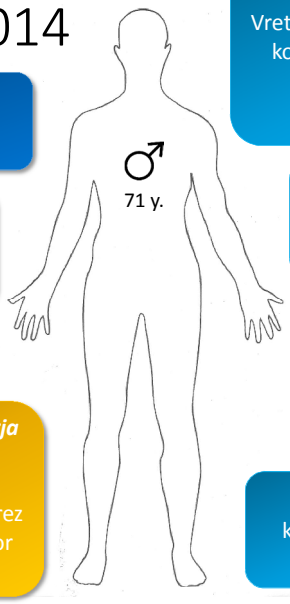
Prvi pregled: april 2014

Arterijska hipertenzija
Hiperplazija prostate
Hiperlipidemija

5 let zatrdlina v lasišču okcipitalno desno, pred 3 leti lasersko odstranjena, ponovno zrasla, opravljena ekscizija

7 let zatrdlina na vratu levo

Histologija ekscidiranega tumorja v lasišču:
maligni melanom, Breslow 6.3, brez ulceracije, 10 mitoz/mm^2, brez satelitskih mikroinfiltratov, tumor vrašča v globoki in stranski rob



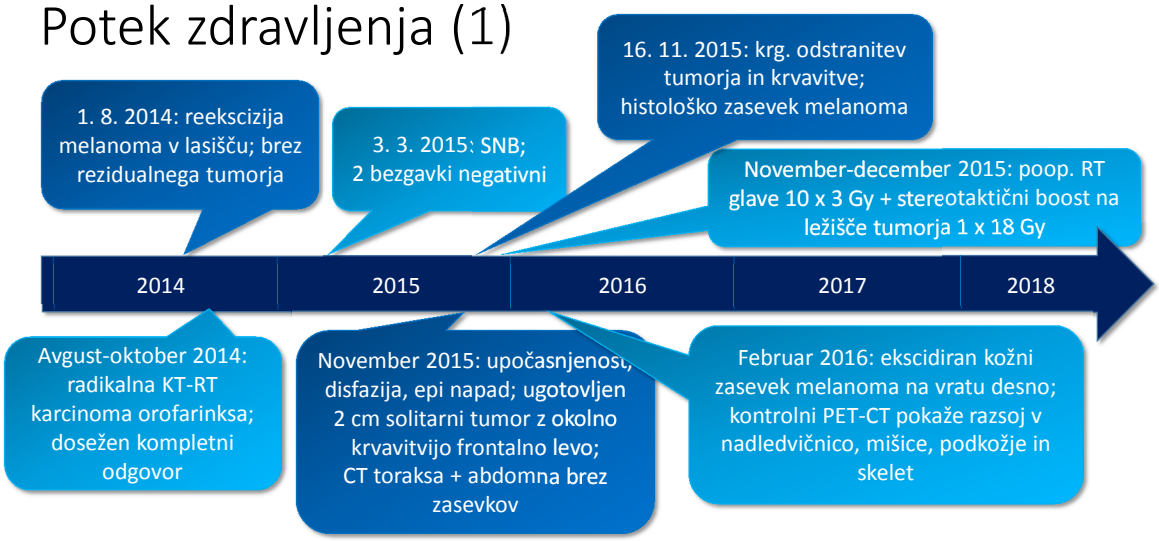
PET-CT:
Vretenasta formacija na vratu levo ne kopiči FDG – najverjetneje lipom; sumljivo za maligno raščo v sublingvalni žlezi desno

Citologija spremembe na vratu levo:
intramuskularni lipom

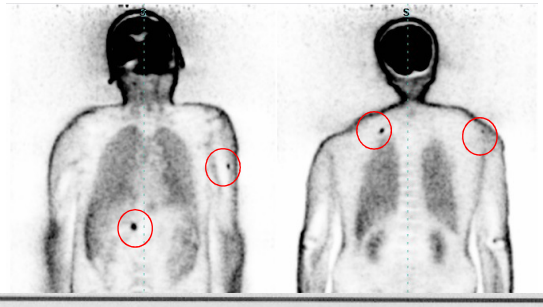
Citologija spremembe v ustnem dnu desno:
ploščatocelični karcinom

Direktoskopija:
karcinom orofarinksa T3N1

Potek zdravljenja (1)



Sistemski razsoj: marec 2016



Rezultati:

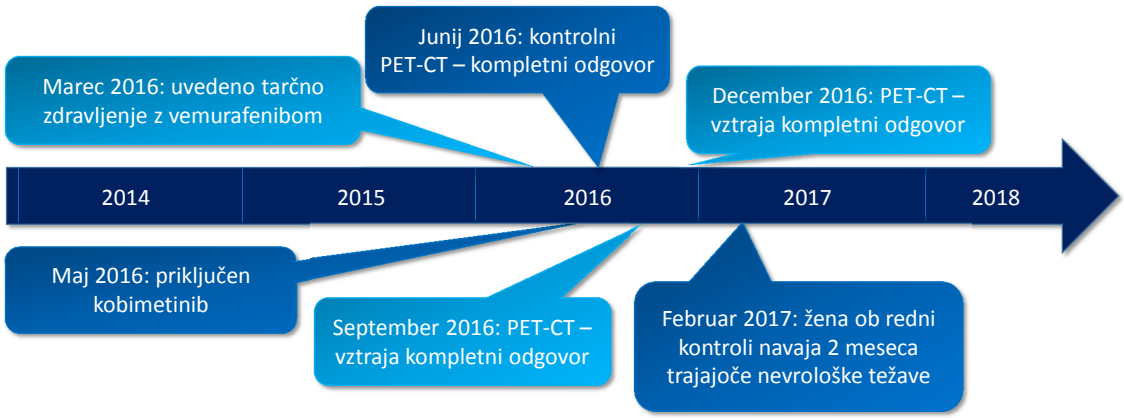
☑ **BRAF - mutiran** **vrsta mutacije: p.Val600Glu (c.1799T>A)** ☐ **BRAF - nemutiran** ☐ **Genotipizacija ni mogoča**

Aktivacijske mutacije p.Val600Glu (V600E), p.Val600Lys (V600K) in p.Val600Asp (V600D) v genu BRAF zvišajo aktivnost proteina BRAF. Mutacije na kodonu 600 v genu BRAF so prisotne pri različnih vrstah raka, vključno z melanomom. Zdravljenje s tarčnimi zdravili, ki se vežejo na mutiran protein, je uspešno le v primeru, ko je mutacija prisotna.

Uvedba tarčne terapije

- Marec 2016: vemurafenib 960 mg/12 h
- Maj 2016: priključen kobimetinib 60 mg/24 h 3 tedne, 1 teden pavze (v okviru programa razširjene dostopnosti)
- Neželeni učinki
  - otekanje obraza ob 1. ciklu vemurafeniba
  - rdečina kože in občasno izpuščaj po izpostavljenosti soncu
  - utrujenost
  - nihanje vida, oftalmološko brez jasnega vzroka
  - angioedem/šen obraza po > 1 letu terapije, zdravljenje prehodno prekinjeno, nato ob normalizaciji stanja uveden znižan odmerek zdravil
- S-100 se normalizira po 1. ciklu vemurafeniba, LDH ob uvedbi normalen

Potek zdravljenja (2)



Nevrološke težave

- Stopnjujoča epizodična pozabljivost, težave z govorom, motnje ravnotežja, otežena hoja
- Poskus s kortikosteroidi brez vpliva na simptome
- MR: izključen progres v možganih, izražene pooperativne in poobsevalne spremembe
- Nevrolog: depresija in blaga kognitivna motnja s psihomotorično upočasnjenostjo, lahko posledica obsevanja; predpiše escitalopram, piracetam in vitamin B12
- Zaradi neželenih učinkov (zaspanosti) zavrača zdravljenje z antidepresivi
- Na kontrolnih slikovnih preiskavah vztraja kompletni odgovor

Potek zdravljenja – povzetek

Retinopatija, ki jo povzroča inhibitor MEK

Polona Jaki Mekjavić
Očesna klinika, UKC Ljubljana

14. šola o melanomu, 9.3.2018

Financial disclosures

- Bayer: C, L
- Novartis: C, L
- Allergan: C, L
- Roche: L

MEKAR

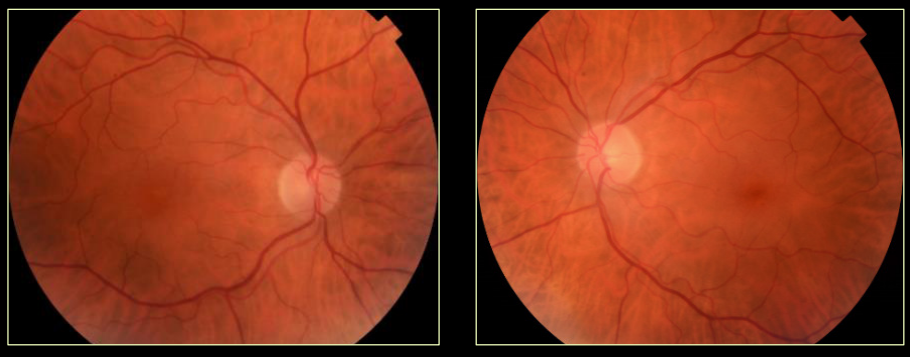
- MEKAR – MEK-inhibitor associated retinopathy
- samoomejujoči se serozni odstopi nevrosenzorne mrežnice na zadajšnjem polu obeh oči

odvisni od časa (najbolj izrazite prve 4 ure po aplikaciji zdravila in prvih nekaj tednov od začetka zdravljenja)

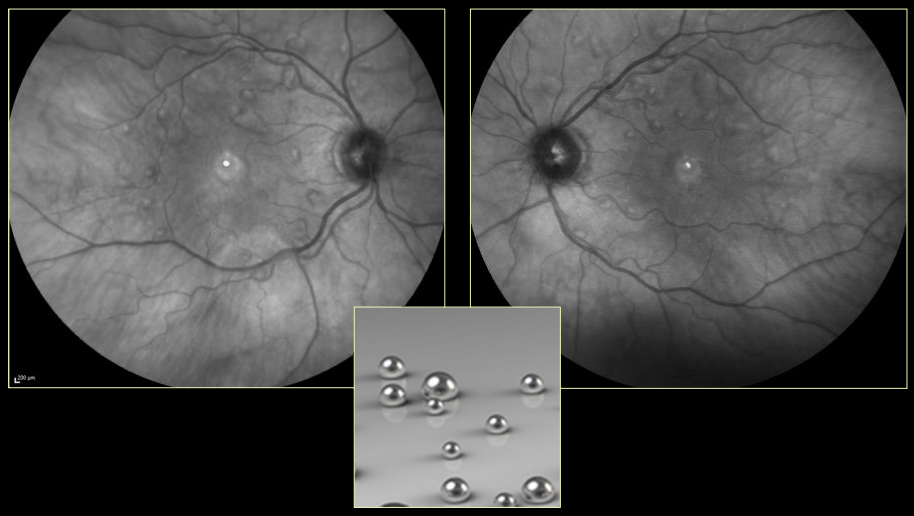
po končanem zdravljenju (do 2 leti) izzvenijo simptomi in ni vidnih morfoloških sprememb

Urner-Bloch, Eur J Canser 2016.

MEKAR



MEKAR

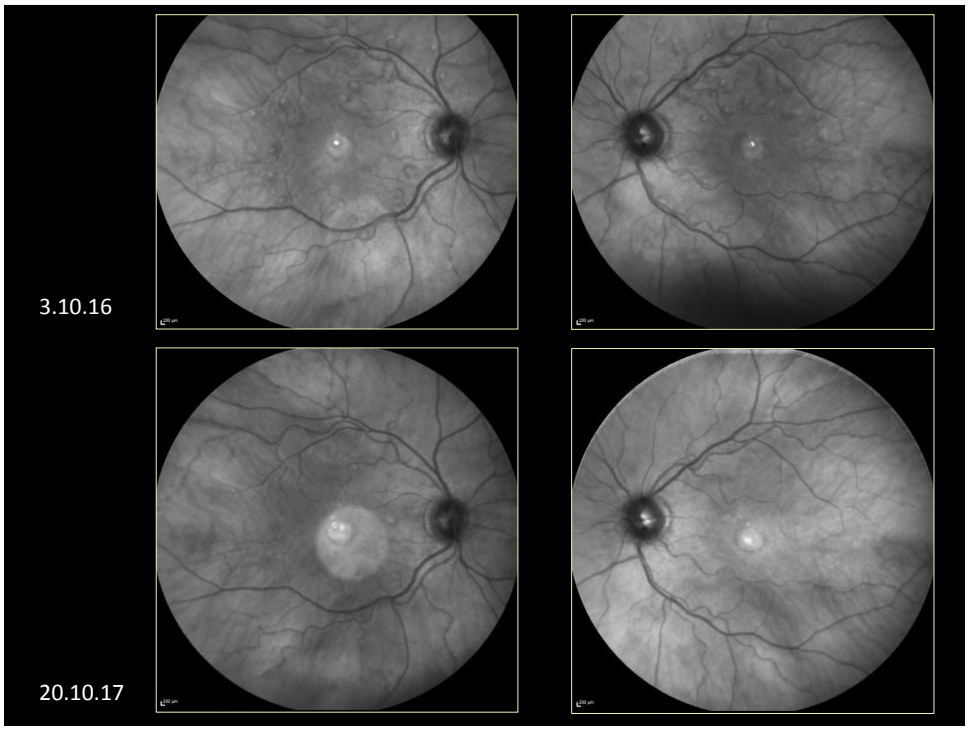


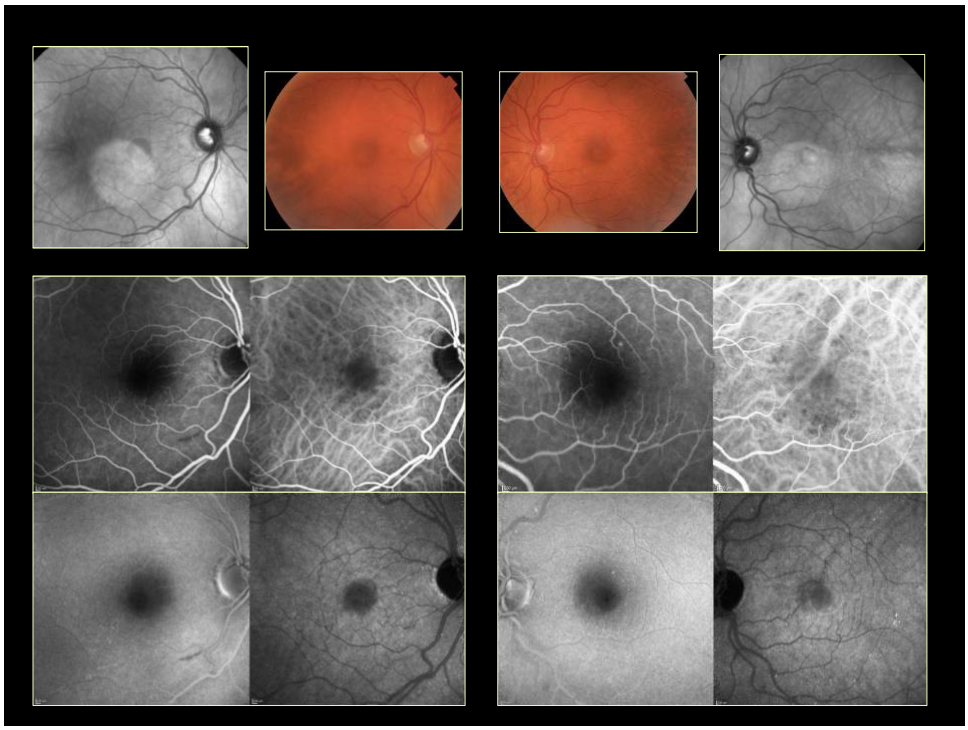
Klinično vidne spremembe na očesnem ozadju pri MEKAR

- rumeno-sivkaste prozorne izboklinice (viteliformne lezije) zaradi plitve subretinalne tekočine
- okrogle (živosrebrove kapljice)
- unifokalne ali multiple
- velike povprečno ½ premera papile
- pogosto binokularno, relativno simetrično
- pogosto vsaj ena lezija v foveji

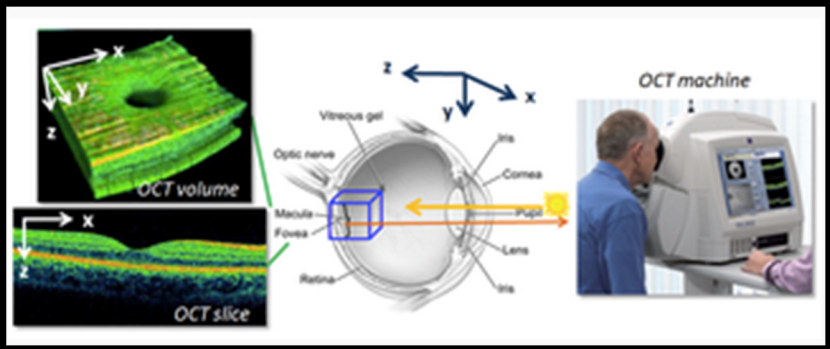
Simptomi pri MEKAR

- moten vid, mehurček (temen krogec) v centru, oranžen sijaj okrog predmetov
- le pri približno ¼ bolnikov z retinopatijo MEK
- pojavijo se nekaj ur do nekaj tednov po uvedbi terapije
- običajno izzvenijo po enem tednu

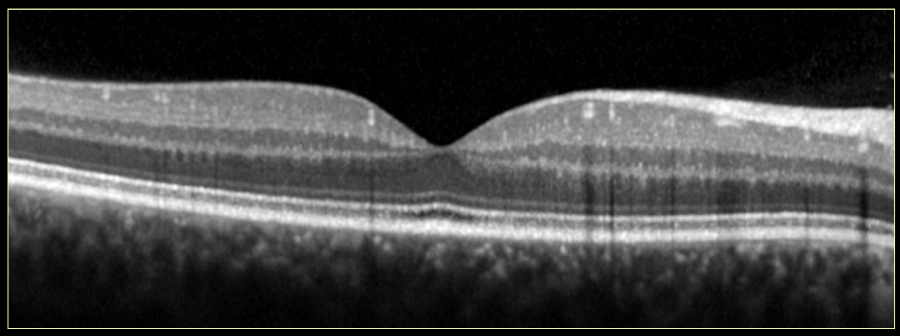


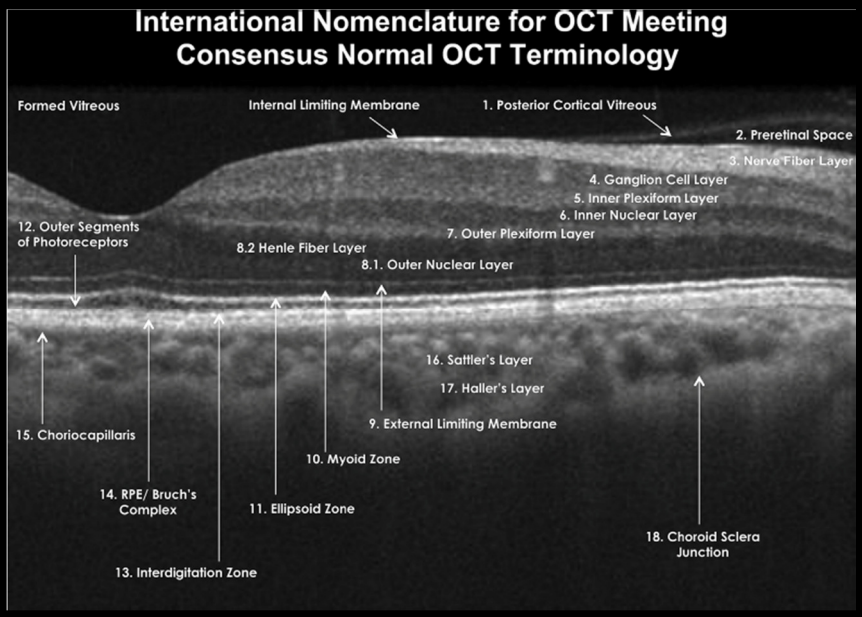


OCT – optična koherenčna tomografija

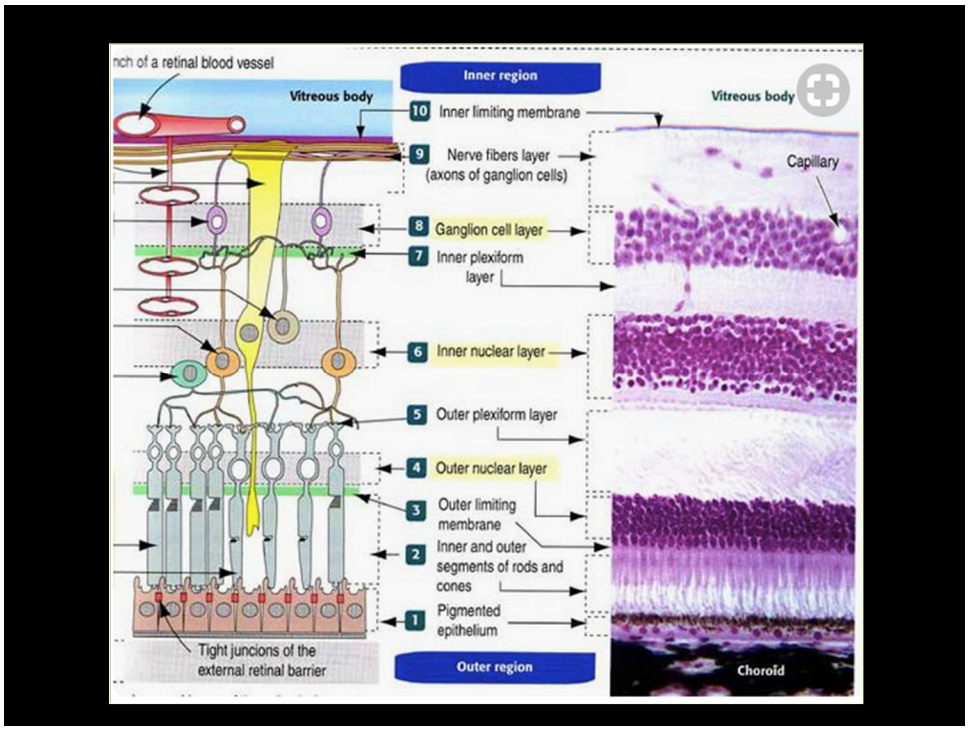


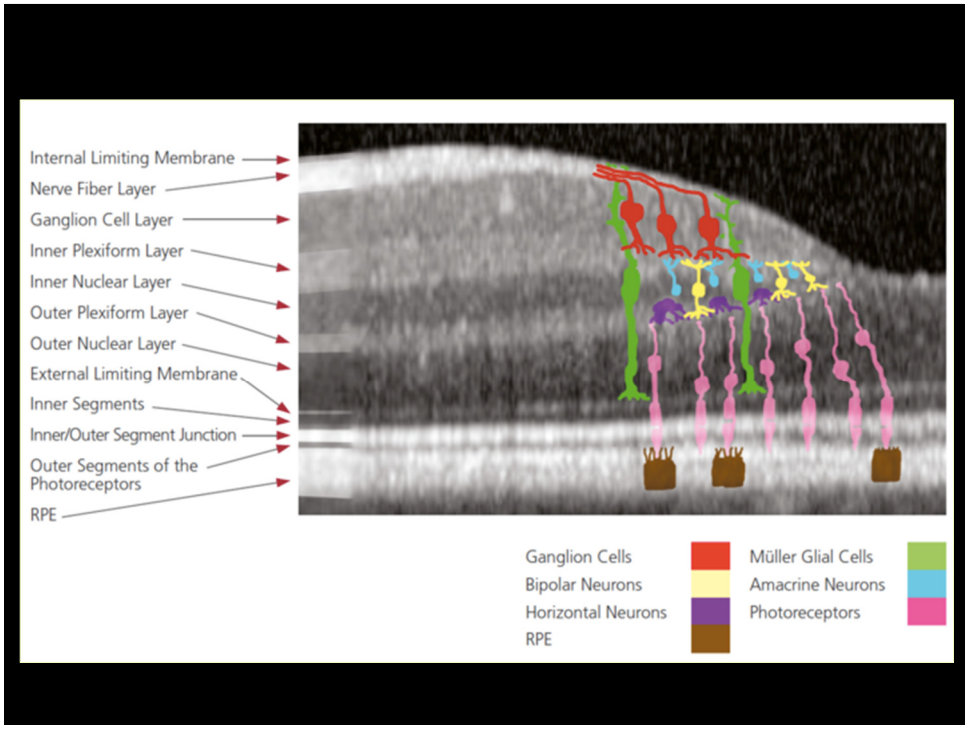
OCT – optična koherenčna tomografija



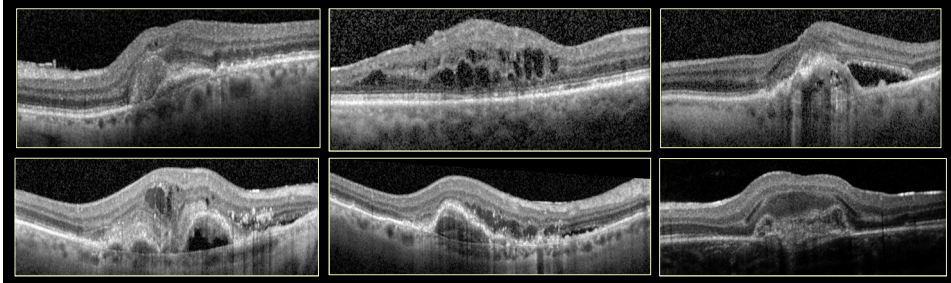


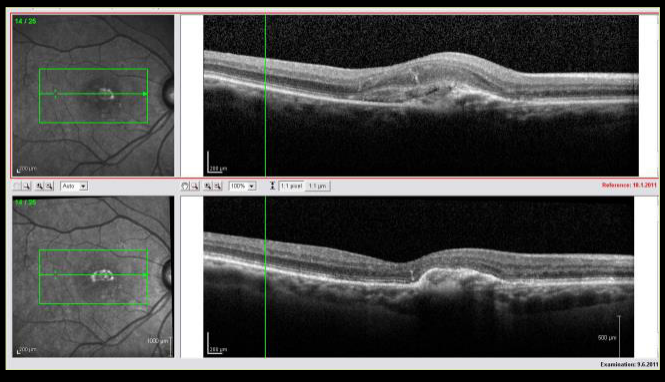
Staurenghi et al. Ophthalmology 2014


nch of a retinal blood vessel
Vitreous body
Inner region
10 Inner limiting membrane
9 Nerve fibers layer (axons of ganglion cells)
8 Ganglion cell layer
7 Inner plexiform layer
6 Inner nuclear layer
5 Outer plexiform layer
4 Outer nuclear layer
3 Outer limiting membrane
2 Inner and outer segments of rods and cones
1 Pigmented epithelium
Tight juncions of the external retinal barrier
Outer region
Vitreous body
Capillary
Choroid


Internal Limiting Membrane
Nerve Fiber Layer
Ganglion Cell Layer
Inner Plexiform Layer
Inner Nuclear Layer
Outer Plexiform Layer
Outer Nuclear Layer
External Limiting Membrane
Inner Segments
Inner/Outer Segment Junction
Outer Segments of the Photoreceptors
RPE
Ganglion Cells
Bipolar Neurons
Horizontal Neurons
RPE
Müller Glial Cells
Amacrine Neurons
Photoreceptors

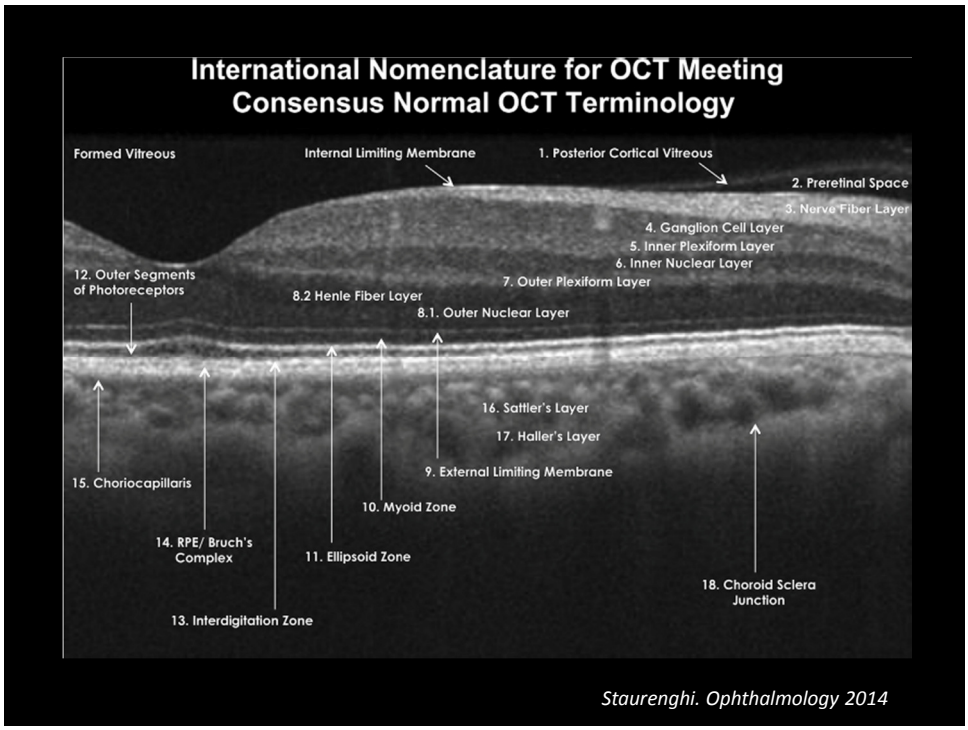
OCT – optična koherenčna tomografija

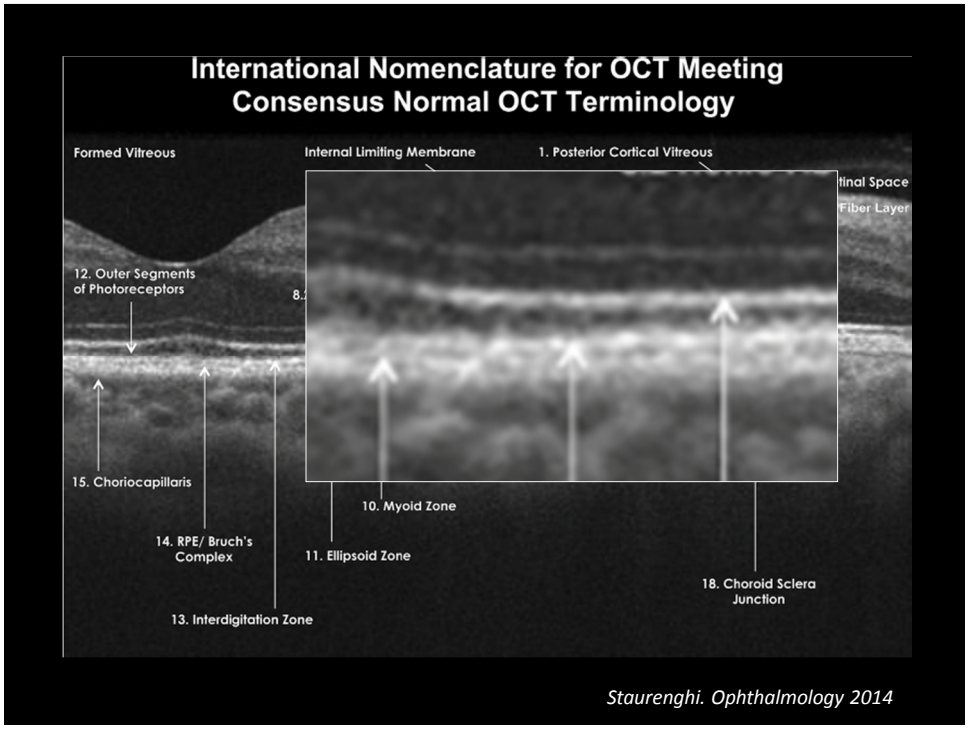




18.1.2011

9.6.2011


International Nomenclature for OCT Meeting
Consensus Normal OCT Terminology
Formed Vitreous
Internal Limiting Membrane
1. Posterior Cortical Vitreous
2. Preretinal Space
3. Nerve Fiber Layer
4. Ganglion Cell Layer
5. Inner Plexiform Layer
6. Inner Nuclear Layer
7. Outer Plexiform Layer
8.2 Henle Fiber Layer
8.1. Outer Nuclear Layer
12. Outer Segments of Photoreceptors
16. Sattler's Layer
17. Haller's Layer
9. External Limiting Membrane
15. Choriocapillaris
10. Myoid Zone
14. RPE/ Bruch's Complex
11. Ellipsoid Zone
18. Choroid Sclera Junction
13. Interdigitation Zone
Staurenghi. Ophthalmology 2014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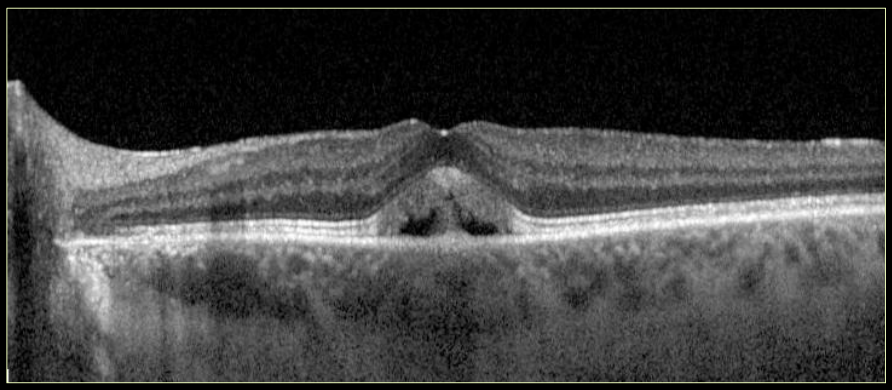
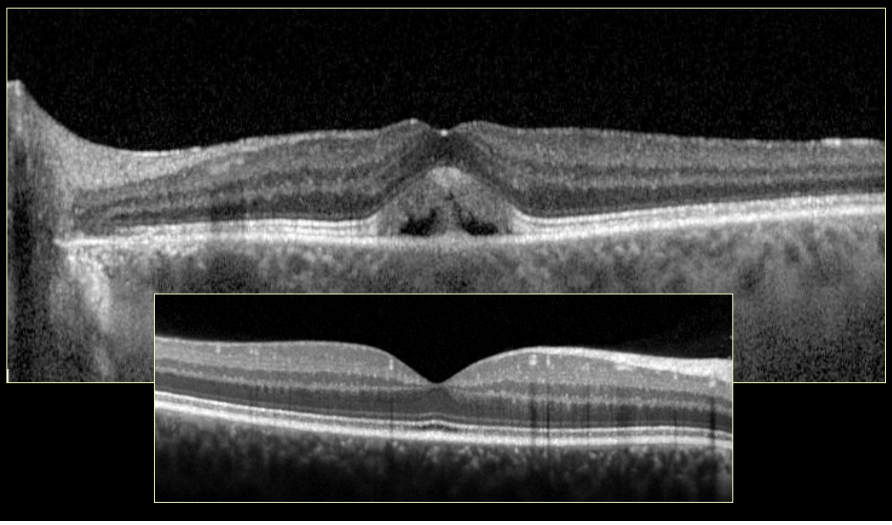
Staurenghi. Ophthalmology 2014

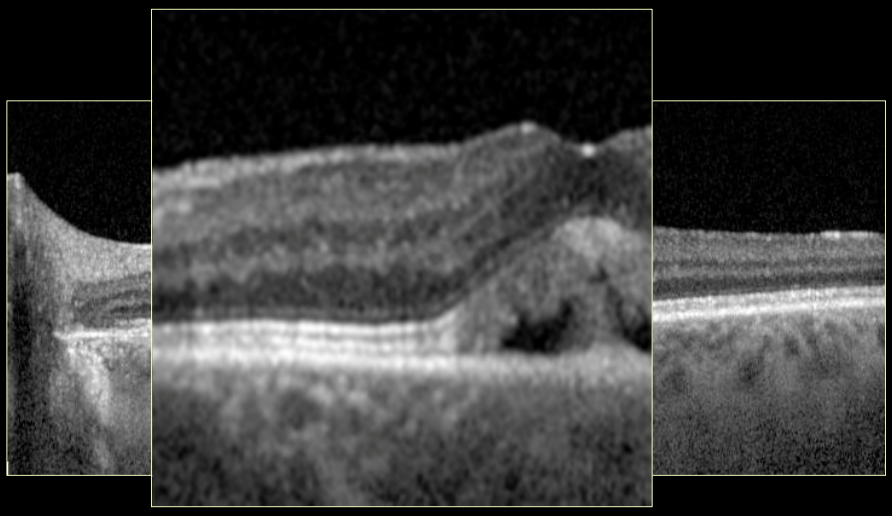
MEKAR



MEKAR

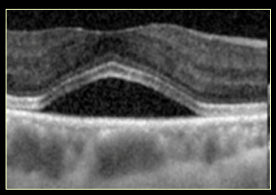


MEKAR

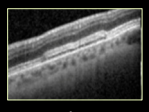


Značilnosti MEKAR na OCT

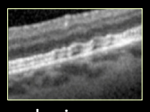
Hiporeflektiven prostor med RPE in IZ – zunanji segmenti fotoreceptorjev (in zunanjimi sloji mrežnice)



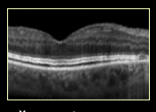
kupola



gosenica

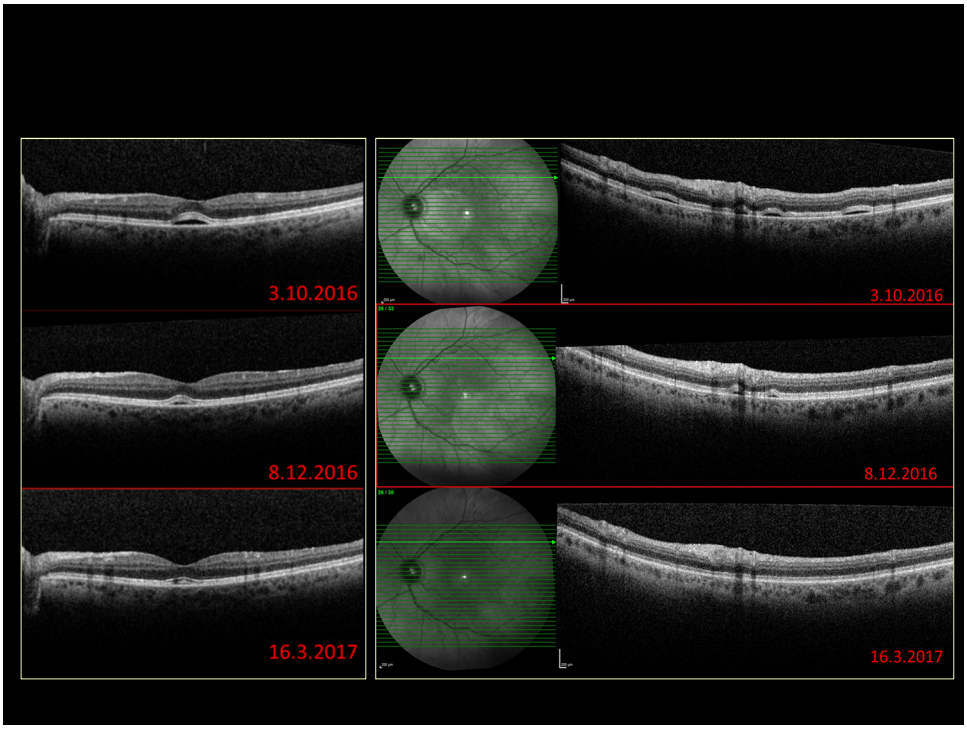


valovi



špranja

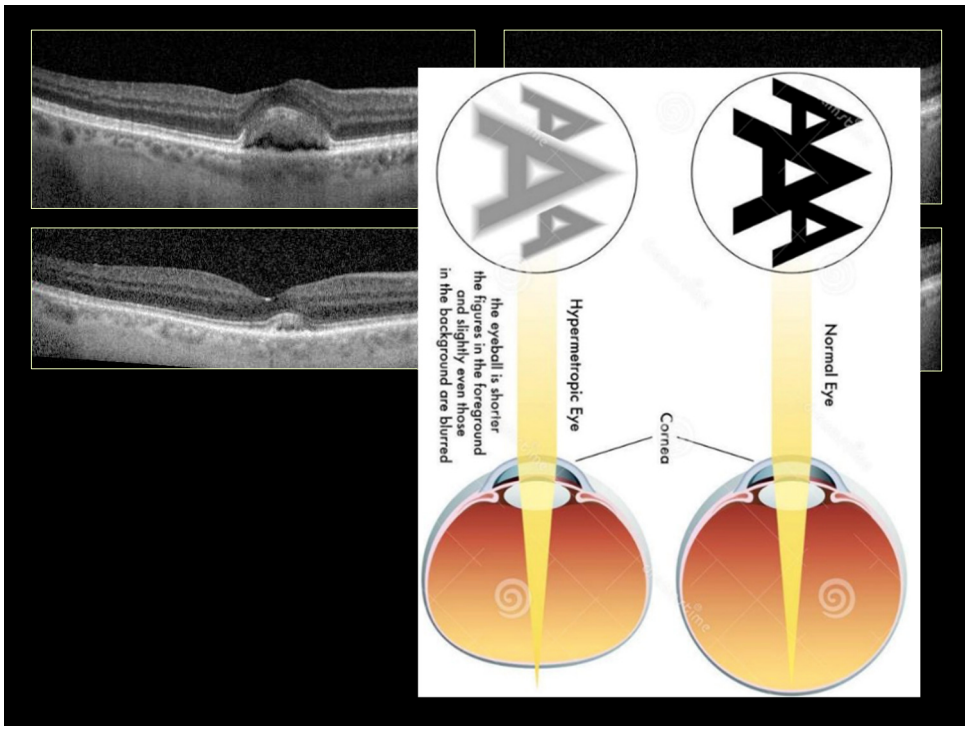
Različne stopnje akumulacije tekočine?



Simptomi pri MEKAR

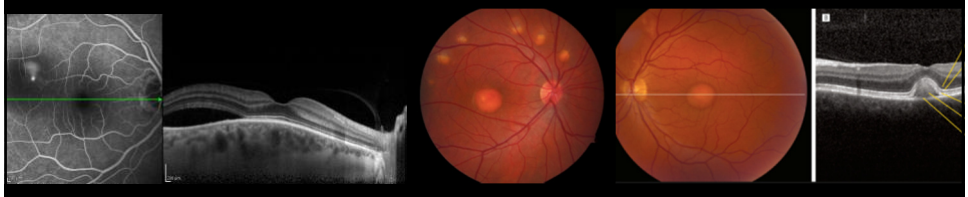
- moten vid, mehurček (temen krogec) v centru, oranžen sijaj okrog predmetov
- le pri približno ¼ bolnikov z retinopatijo MEK
- pojavijo se nekaj ur do nekaj tednov po uvedbi terapije
- običajno izzvenijo po enem tednu

- vidna ostrina normalna ali nekoliko znižana – meglen vid (do 0,4 cc)
  do 2 vrstici po Snellenu glede na VO pred zdravljenjem
- VO se po resorbciji tekočine izboljša ali celo vrne na izhodno
- VO se spreminja



Diferencialne diagnoze
MEKAR

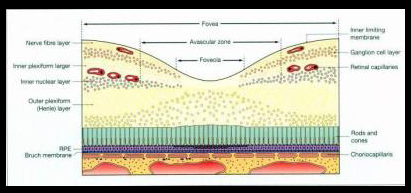
- Centralna serozna horioretinopatija (CSC)
- Bestova viteliformna distrofija, Bestova distrofija z začetkom v odrasli dobi
- multifokalni horioretinitis, post. skleritis, diseminirana intravask. koagulopatije, nefritis (TINU), viteliformna SDM, POHS…



Patogeneza MEKAR

- ni poznana
- vpliv za funkcijo RPE (tesni stiki, transportni kanalčki za vodo)

  (nenormalno Ardenovo razmerje na EOG):
  - preko protiteles?[1]
  - direkten toksični učinek?[2]



1. Koreen, Arch Ophthalmol 2011. 2.vanDijk, Ophthalmology 2015.

MEKAR

- bolniki imajo vid le blago poslabšan, ponavadi ostane dovolj dober za vožnjo
- vpliv na vid je običajno prehoden
- če je vid preslab, si lahko pomagajo s hipermetropimi očali (+ Dsph)

- serozne lezije na mrežnici najbolje prikažemo z OCT in IR
- morfološke spremembe običajno izzvenijo kljub nadaljevanju zdravljenja

research article

Ocular changes in metastatic melanoma patients treated with MEK inhibitor cobimetinib and BRAF inhibitor vemurafenib

Ana Ursula Gavric[1], Janja Ocvirk[2,3], Polona Jaki Mekjavic[1,3]

[1] Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[3] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Radiol Oncol

Received 4 October 2017
Accepted 20 November 2017

Patient N°	1	2	3	4	5	6	7
Sex	M	M	F	M	M	M	M
Age (years)	41	58	64	74	71	45	55
Nº of cycles at first eye exam	2	11	15	3	3	3	6
Nº of cycles at last eye exam	3	13	24	8	5	4	7
Change in dosage	yes*	no	no	no	no	no	no
BCVA RE	1.0	1.0	1.0	0.7 – 0.9	0.8	1.0	1.0
BCVA LE	1.0	1.0	1.0	0.7 – 0.9	0.7	1.0	1.0
Symptoms	circle centrally	blurred vision	no	blurred vision	floaters in LE, blurred vision	circle centrally	no
Occurrence of symptoms after starting the therapy	1 week	1 week	-	1 week	1 month	1 week	-
Fluctuations of symptoms	spontan. resolution	no	-	different spectacles needed	better after topical therapy	spontan. resolution	needs spectacles
OCT changes in the fovea	elongation of IZ	SRF	SRF	SRF	elongation of IZ in RE, SRF in LE	SRF	SRF
Extrafoveal SRF	multiple bilateral	multiple bilateral	multiple bilateral	multiple bilateral	no	no	multiple bilateral
Other ocular findings	-	-	-	incipient senile cataract ou	uveitis in LE; incipient cataract ou	-	dilatated conjuctival vessels in the RE

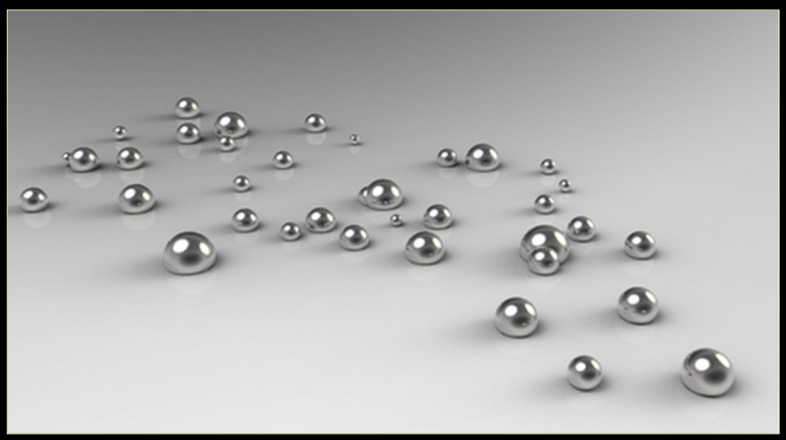
Gavric et al. Radiol Oncol 2018

Patient N°	1	2	3	4	5	6	7
Sex	M	M	F	M	M	M	M
Age (years)	41	58	64	74	71	45	55
Nº of cycles at first eye exam	2	11	15	3	3	3	6
Nº of cycles at last eye exam	3	13	24	8	5	4	7
Cha		no	no	no	no	no	no
BCV		1.0	1.0	0.7 – 0.9	0.8	1.0	1.0
BCV.		1.0	1.0	0.7 – 0.9	0.7	1.0	1.0
Symptoms	circle centrally	blurred vision	no	blurred vision	floaters in LE, blurred vision	circle centrally	no
Fluctuations of symptoms	resolution	no	-	spectacles needed	topical therapy	resolution	needs spectacles
OCT changes in the fovea	elongation of IZ	SRF	SRF	SRF	elongation of IZ in RE, SRF in LE	SRF	SRF
Extrafoveal SRF	multiple bilateral	multiple bilateral	multiple bilateral	multiple bilateral	no	no	multiple bilateral
Other ocular findings	-	-	-	incipient senile cataract ou	uveitis in LE; incipient cataract ou	-	dilatated conjuctival vessels in the RE

Symptoms

circle centrally blurred vision no blurred vision floaters in LE, blurred vision circle centrally no

Gavric et al. Radiol Oncol 2018



ZDRAVLJENJE MELANOMA Z OBSEVANJEM

Primož Strojan

Sektor radioterapije
Onkološki inštitut Ljubljana

9.3.2018

UVOD

RT DANES:

- **učinkovit ne-kirurški način zdravljenja melanoma**
- **lokoregionalno zdravljenje**

→ **INTEGRALNI DEL MULTIDISCIPLINARNE OBRAVNAVE BOLNIKOV Z MELANOMOM**

INDIKACIJE ZA RT

1) RT KOT PRIMARNO ZDRAVLJENJE
2) ADJUVANTNA/POOPERATIVNA RT
3) PALIATIVA RT

1

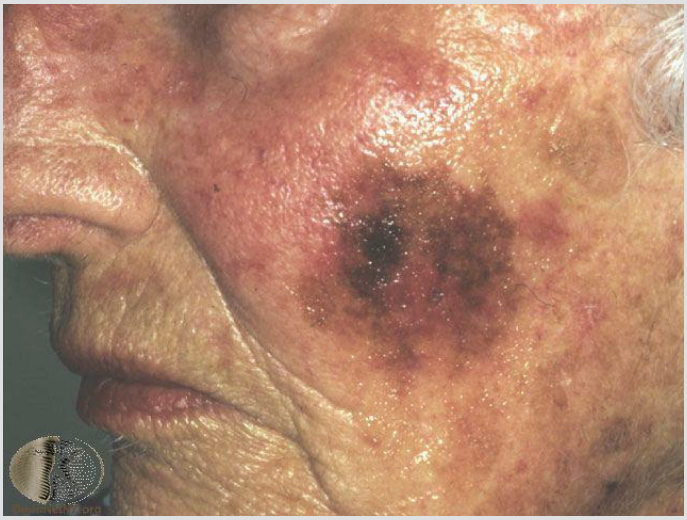
INDIKACIJE
RT KOT PRIMARNO ZDRAVLJENJE

REDKO:

- bolniki v slabem splošnem stanju
- bolniki ki so odklonili predlagano operacijo
- obsežen *lentigo maligna* melanom kože obraza

1

LENTIGO MALIGNA MELANOM



Harwood AR. Int J Radiat Oncol Biol Phys 1983; 9: 1019-21.
Schmid-Wendtner MH et al. J Am Acad Dermatol 2000; 43: 477-82.
Farshad A et al. Br J Dermatol 2002; 146: 1042-6.

RT LMM JE UČINKOVIT NAČIN ZDRAVLJENJA S KURATIVNIM POTENCIALOM

ALTERNATIVA KIRURGIJI, KADAR BI TA POVZROČILA POMEMBNO FUNKCIONALNO IN/ALI KOZMETIČNO OKVARO

2

INDIKACIJE

ADJUVANTNA/POOPERATIVNA RT

Po operaciji:

- **primarnega tumorja**
- **področnih metastaz**

INDIKACIJE
ADJUVANTNA/POOPERATIVNA RT

Po operaciji primarnega tumorja:
visoko tveganje za lokalno ponovitev po sami KRG

- **bližnji/pozitiven resekcijski rob**
  (re-operacija ni možna)
- **obsežna satelitoza**
- **(zgodnji ali multipli lokalni recidivi)**

Johanson CR et al. Cancer 1983; 51: 226-32.
Kelly JW et al. Ann Surg 1984; 200: 759-63.
Leon P et al. Arch Surg 1991; 126: 1461-8.
Stevens G et al. Cancer 2000; 88: 88-94.
Cooper JS et al. Cancer J 2001; 7: 498-502

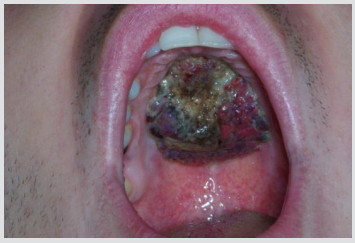
- ***desmoplastični* primarni Tu G&V**

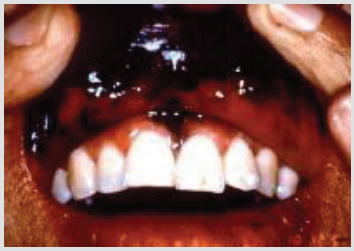
Randomizirana raziskava faze III: TROG 08.09 & ANZMTG 01.09
Smithers BM et al. World J Surg 1992; 16: 186-90.
Quinn MJ et al. Cancer 1998; 83: 1128-35.

- ***mukozni* melanom G&V**

2

MUKOZNI MELANOM





<0.5% vseh primerov melanoma
≅50% se jih nahaja v področju G&V

Ballo M, Ang KK. Surg Clin N Am 2003: 323-42.
Mendenhall WM et al. Am J Clin Oncol 2005; 58: 626-30.
Krengli M et al. Crit Rev Oncol Hematol 2008; 65: 121-8.

Mucosal melanoma of the head and neck: a population-based study from Slovenia, 1985-2013
Radiation Oncology (2016) 11:137
Gaber Plavc[1], Jasna But-Hadžić[1], Aleksandar Aničin[2], Boštjan Lanišnik[3], Vojislav Didanović[4] and Primož Strojan[1,5*]

Terapija izbora: KIRURGIJA
→ LRR ≅50%

RT:
- **verjetno izboljaša LK**
  še posebej po neradikalni resekciji
  ±
  - **veliki primarni Tu**
  - **perinevralna invazija**
  - **primarni Tu v nosni votlini/obnosnih sinusih**
- **najbolj učinkovit način zdravljenja obsežne/neresektabilne bolezni**
- **vloga elektivne RT vratu = ?**
  (tumorji ustne votline, ustnega žrela)
- **brez vpliva na preživetje!**

INDIKACIJE
ADJUVANTNA/POOPERATIVNA RT

Po operaciji
področnih zasevkov v bezgavkah

- neradikalna operacija
- ekstrakapsularno širjenje Tu
- premer prizadete bezgavke ≥3→4 cm
- multiple prizadete bezgavke ≥1→3
- (recidiv po predhodni operaciji)

} RR ≤60%

2

Surgery			Surgery plus radiotherapy		
Author, year[Ref.]	No. of pts.	Nodal basin recurrence (%)	Author, year[Ref.]	No. of pts.	Nodal basin recurrence (%)
Parotid & neck			*Parotid & neck*		
Bayers, 1986[54]	28	50	Ang et al., 1994[62]	95	8
Calabro et al. 1989[45]	287	15	O'Brian et al., 1997[47]	45	7
O'Brian et al., 1997[47]	107	19	Shen et al., 2000[51]	21	14
Shen et al., 2000[51]	196	14	Ballo et al., 2002[63]	160	8
Pidhorecky et al., 2001[52]	44	43	Strojan et al., 2010[22]	45	18
Strojan et al., 2010[22]	42	40	*Total*	*366*	*10*
Total	*704*	*20*			
Axilla			*Axilla*		
Bowsher et al., 1986[53]	22	14	Ballo et al, 2002[64]	89	10
Calabro et al. 1989[45]	438	15	Beadle et al., 2009[65]	200	10
Pidhorecky et al., 2001[52]	116	30	*Total*	*289*	*10*
Kretschmer, et al., 2001[55]	63	10			
Total	*639*	*17*			
Groin			*Groin*		
Bowsher et al., 1986[53]	36	8	Ballo et al., 2004[66]	40	23
Kissin et al., 1987[56]	44	34	Gojkovič-Horvat et al., 2012	36	14
Calabro et al. 1989[45]	276	17			
Hughes et al., 2000[57]	132	19			
Pidhorecky et al., 2001[52]	93	19			
Kretschmer et al., 2001[58]	104	34			
Allan et al., 2008[59]	72	8			
Total	*757*	*20*			
All sites			*All sites*		
Bowsher et al., 1986[53]	66	15	Burmeister et al., 1995[67]	26	12
Calabro et al. 1989[45]	1001	16	Corry et al., 1999[23]	42	21
Miller et al., 1992[49]	55	18	Stevens et al., 2000[68]	174[1]	11
Monsour et al., 1993[48]	48	52	Cooper et al., 2001[41]	40[1]	8
Pidhorecky et al., 2001[52]	253	28	Fuhrmann et al., 2001[69]	58	16
Mayer et al., 2002[60]	140	34	Chang et al., 2006[21]	54	12
Henderson et al., 2009[44]	108	31	Burmeister et al., 2006[24]	234	7
Agrawal et al., 2009[61]	106	41	Ballo et al., 2006[70]	466	9
Total	*1777*	*23*	Henderson et al., 2009[44]	123	18
			Agrawal et al., 2009[61]	509	10
			Total	*1726*	*11*

Strojan P, Radiol Oncol 2010.

INDIKACIJE
ADJUVANTNA/POOPERATIVNA RT

Henderson MA, Burmeister B, Thompson JF, Di Iulio J, Fisher R, Hong A, et al.
Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: results of an intergroup randomized trial (ANZMTG 01.02/TROG 02.01).
Lancet Oncol 2012; 13: 589-97 *in* Lancet Oncol 2015; 16: 1049-60

Stadij III, Visoko tveganje za RR

KRG

Št. N+:
- **parotis ≥1**
- **vrat/aksila ≥2**
- **dimlje ≥3**

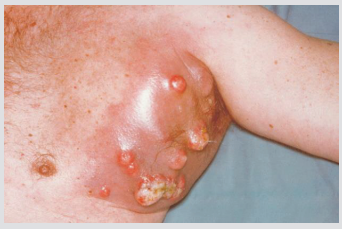
PBK+
Naj. premer:
- **vrat/aksila ≥3 cm**
- **dimlje ≥ 4 cm**

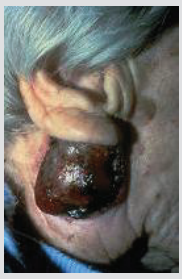
OBS

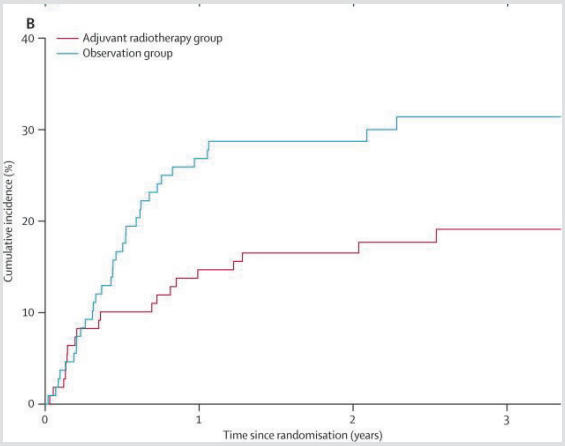
RT

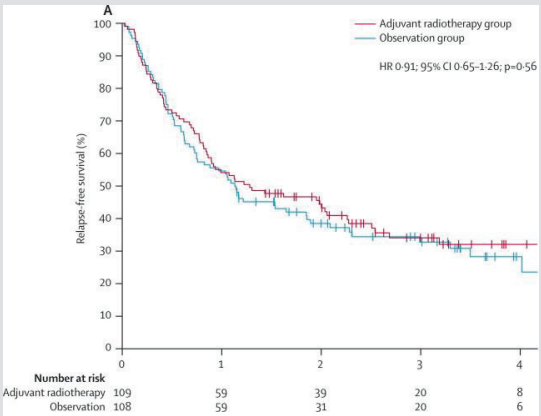
2

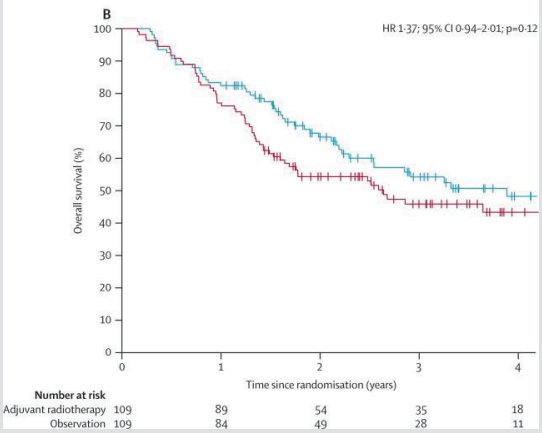
- **pri 50-60% se bodo pojavile oddaljeni zasevki**
- **ni izboljšanja preživetja**











$FUP_{mediana}$ = 40 mes

INDIKACIJE
ADJUVANTNA/POOPERATIVNA RT

ZDRAVLJENJE REZIDUALNE BOLEZNI:

- **po BVB_+**
  (Bonnen et al, Cancer 2004; Ballo et al, Head Neck 2005)

- **po tehnično neustrezni operaciji**
  (ekscizija klinično evidentne bezgačne metastaze)

  → **potrebna je dodatna, bolj obsežna operacija, ki pa ni izvedljiva ali nanjo bolnik ne pristane**
  (Ballo et al, Head Neck 2005)

INDIKACIJE
RT KOT DEL PALIATIVNEGA ZDRAVLJENJA

KDAJ?

- **kirurgija:**
  - **ni možna** (neoperabilni zasevki, slabo splošno stanje bolnika)
  - **ni smiselna** (multipli zasevki, multiorganska prizadetost)

KAJ?

- **vse vrste zasevkov** (kožni, bezgavčni, kostni, visceralni...)

ZAKAJ?

→ **Zmanjšati znake & simptome, ki jih povzroča bolezen**

INDIKACIJE
PALIATIVNA RT

- **KOSTNI ZASEVKI**
  - odprava bolečine pri 60% Chow E et al. J Clin Oncol 2007;25:1423-36.
  - pooperativna RT (po kirurški fiksaciji zlomljene kosti)

- **ZASEVKI KI POVZROČAJO KOMPRESIJO HRBTENJAČE**
  - samo RT + kortikosteroidi
  - pooperativna RT (po laminektomiji)
    - → zadrži lokalno razrast tumorja
    - → podaljša interval brez simptomov

- **KOŽNI – LIMFATIČNI ZASEVKI**
  - ≤1 cm → >85% PO Overgaard J et al, R&O 1986;5:183-92. Bentzen SM et al. R&O 1989:16:169-82.
  - >5 cm → <30% PO

INDIKACIJE
PALIATIVNA RT

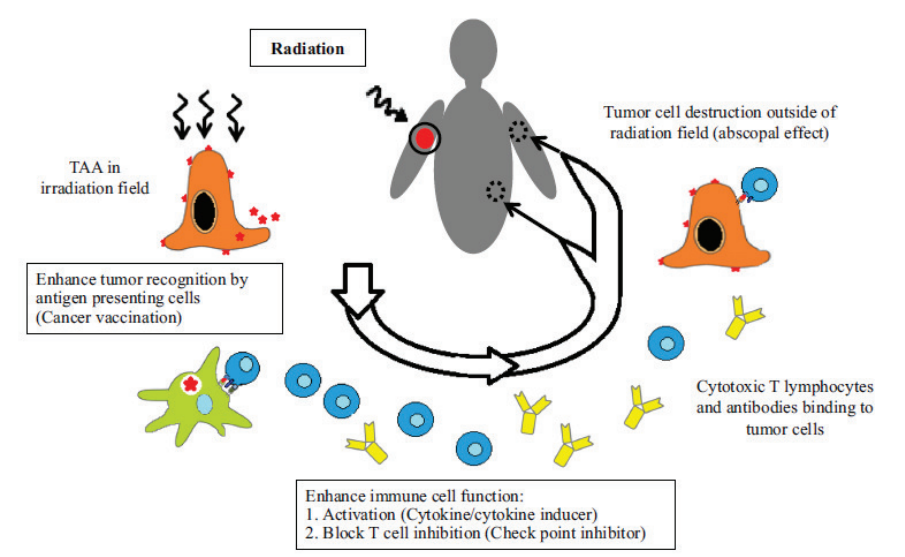
- **MOŽGANSKI ZASEVKI** (40-60% M+ bolnikov; avtopsija – 80%)
  - solitarni 40-50%
    multipli 50-60%
  - prognoza: v preteklosti <6 mes
    danes → leta (izbrani bolniki)

- multipli: RT možgan + kortikosteroidi Cohen JV et al. Pigm Cell Mel Res 2016;29:627-42.
  - → podaljšanje srednjega preživetja za 1-2 mes (3.4:2.1 mes)
  - → merljivo ↑ stanja zmogljivosti pri 60-70% bolnikih
- 1-3 zasevki, 2r <3 cm: stereotaktična RT + RT možgan
  - → lokalna kontrola ≥80%
  - → glavni vzrok smrti: zasevki izven CŽS
  - → sporadični primeri daljšega preživetja

Gaudy-Marqueste C et al. IJROBP 2006;65:809-16.

NOVI TRENDI
RT + IMUNOTERAPIJA

- **sinergistični učinek**
- **abskopalni učinek (Lat. *ab* – izven & *scopus* – tarča)**



Ishihara et al., Cancer Immunol Immunother 2016

ZAKLJUČKI

1) **KIRURGIJA**
2) **neradikalna KRG in/ali neugodni prognostični dejavniki → ADJUVANTNO zdravljenje**
3) **RT = učinkovita (kurativna, paliativna)**
   varna

NEPOGREŠLJIV DEL
MULTIDISCIPLINARNE OBRAVNAVE
BOLNIKOV Z MELANOMOM

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

STEREOTKTIČNA RADIOKIRURGIJA PRI MELANOMU

Uroš Smrdel
10.3.2016

STEREOTAKTIČNA RADIOKIRURGIJA (SRS)

- Stereotaksija - iz grščine στερεος in τακτική, kar pomeni prostorska dispozicija
- Radiokirurgija – obsevanje z enim samim visokim odmerkom
- Lars Leksel 1951, 1962 Gamma knife, 1982 linearni pospeševalnik
- Prostorsko načrtovanje in obsevanje
- Hiter padec odmerka izven obsevanega volumna
- Metastaze, nekateri primarni tumorji, žilne malformacije, nekatera funkcionalna stanja

SRS pri možganskih metastazah

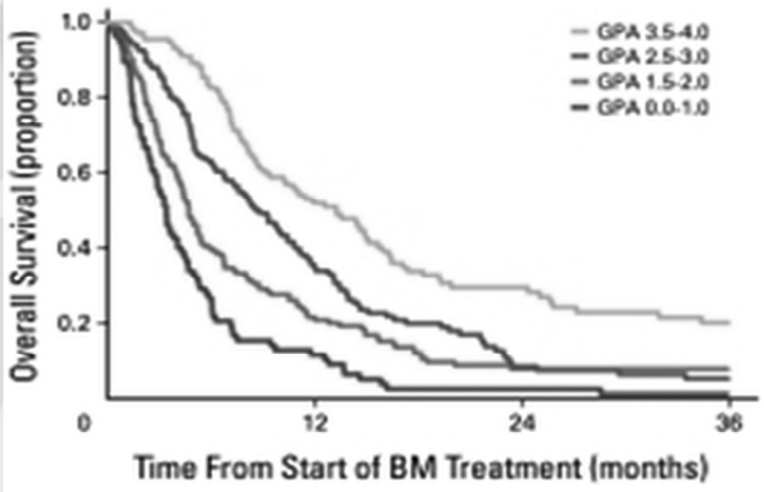
- Pogosto dojka, pljuča, ledvica, maligni melanom
- **Omejeno število dobro omejenih lezij**
- Rekurzivna particijska analiza (RPA) za oceno primernosti bolnika za postopek
- Občasno hipofrakcionirana stereotaktična radioterapija (velikost in lokalizacija lezij)
- Uporaba stereotaktičnega okvirja ali pa slikovno vodena

KOGA ZDRAVITI S SRS

- samo del bolnikov ima korist od zdravljenja
- popolnoma zanesljivega orodja za določitev prognoze ni
- pomagamo si lahko z nekaj orodji
  - REKURZIVNA PARTICIJSKA ANALIZA
  - STOPENJSKA PROGNOSTIČNA OCENA

REKURZIVNA PARTICIJSKA ANALIZA

- enostavno orodje za določitev prognoze
- ni odvisna od tipa tumorja
  - stanje zmogljivosti (KPS - >70 vs <70)
  - kontrola bolezni izven CŽS
- RPA 1: KPS > 70, ni bolezni izven CŽS
  - bolnik bo imel korist od zdravljenja
- RPA 2: KPS < 70, bolezen izven CŽS
  - bolnik ima lahko korist od zdravljenja
- RPA 3: KPS < 70
  - bolnik ne bo imel koristi od zdravljenja



GRADED PROGNOSTIC ASSESSMENT Sperduto et al. J Clin Oncol. 2012

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

SRS v Sloveniji

- Od sredine 2007
- Do konca leta 2010 s stereotaktičnim okvirjem, od sredine 2011 samo še slikovno vodena
- 142 stereotaktičnih procedur do konca 2012, 63 SRS, ostalo frakcionirano
- 7 bolnikov z malignim melanomom, vsi SRS

SRS pri možganskih metastazah malignega melanoma

- Srednja starost 56,5 let (47 -62)
- 4 – m, 3 – ž
- Število metastaz 4- 1, 2- 2, 1- 3
- RPA razred 6- 2, 1- 1
- WBRT 30 Gy pred SRS- 3, ne- 2, pred več meseci po op 2
- 2 bolnika operacija pred časom, 1 metastaza v meduli oblongati,

Rezultati

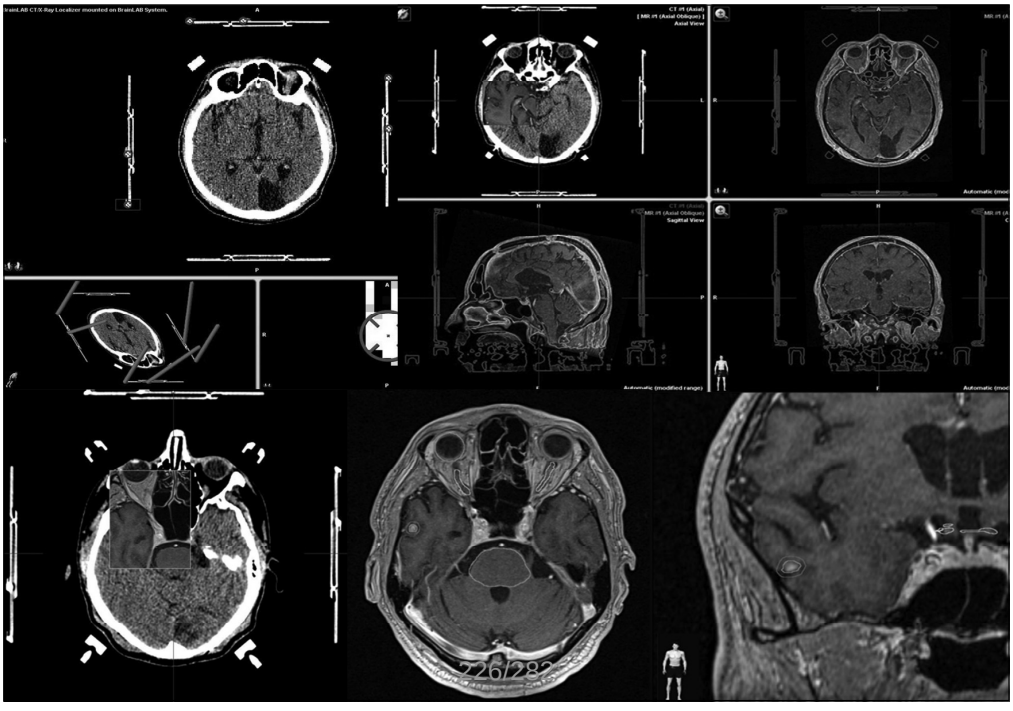
- Srednje preživetje 6,85 mesecev (SD 2,89)
- Učinek 2 x CR, 3 x SD, 2x ni evaluacije
- Progres v CŽS 1x - medula oblongata, 1 x izven področja SRS, 1x progres lezije po 1 letu

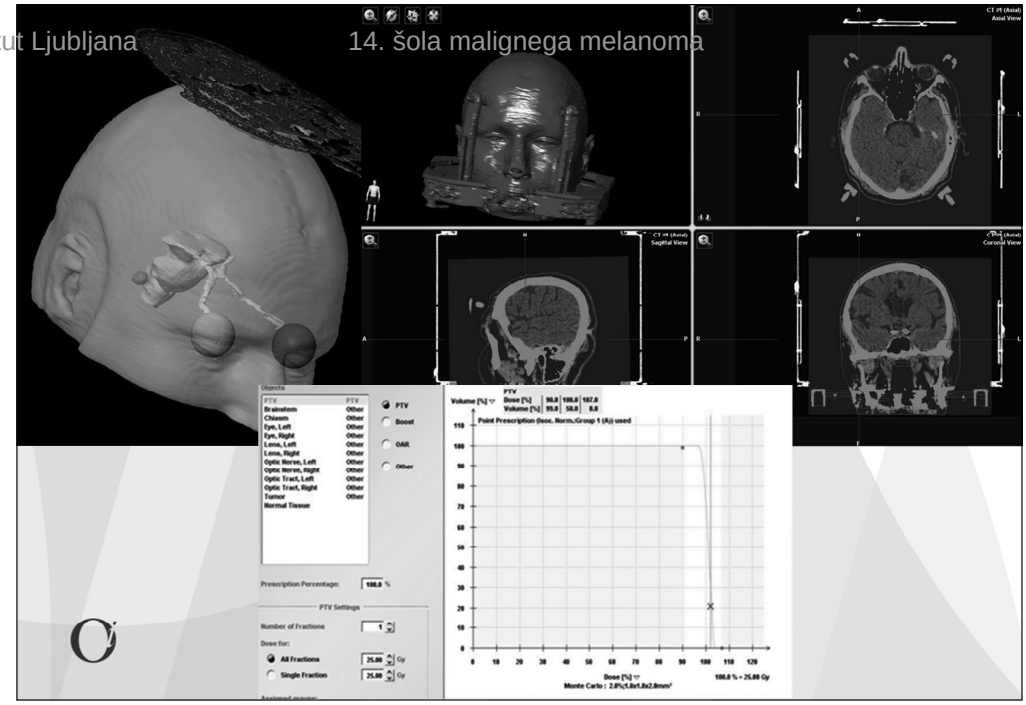
Primer 1

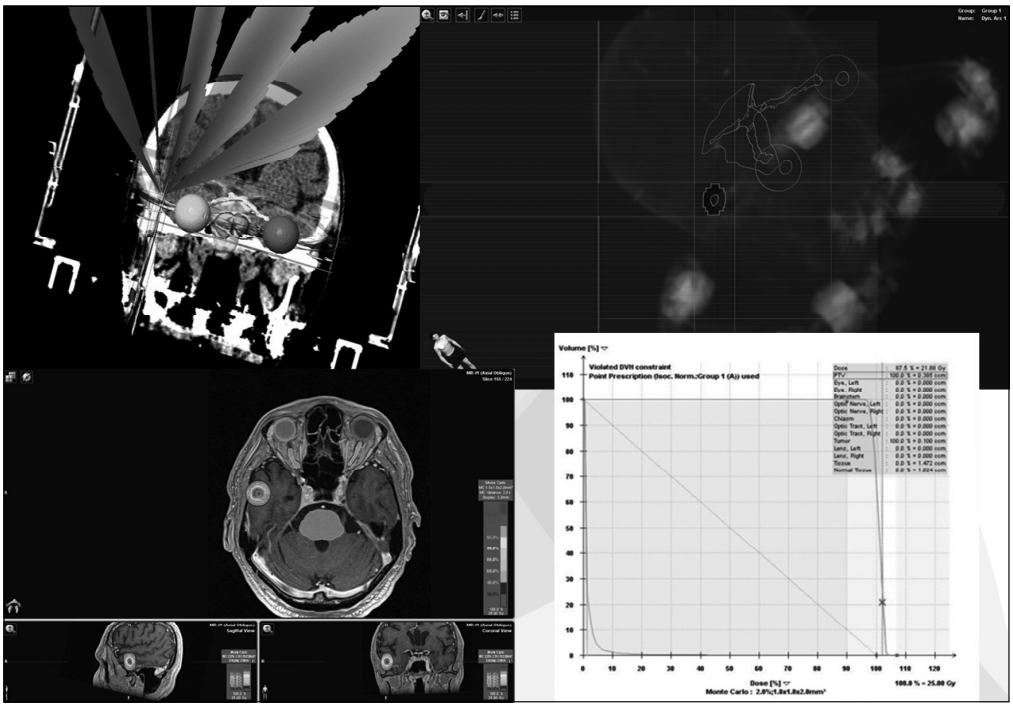
- 47 letni bolnik
- Neznana primarna lezija
- Disekcija ingvinalnih bezgavk, brez pooperativnega zdravljenja (2008)
- 5 cm zasevek okcipitalno, 3 mm sumljiva lezija d temporalno
- Operacija okcipitalno, WBRT 30 Gy #10 frakcij (10/2010)
- Temozolomid
- Progres lezije d temporalno (03/2011)

Primer 1

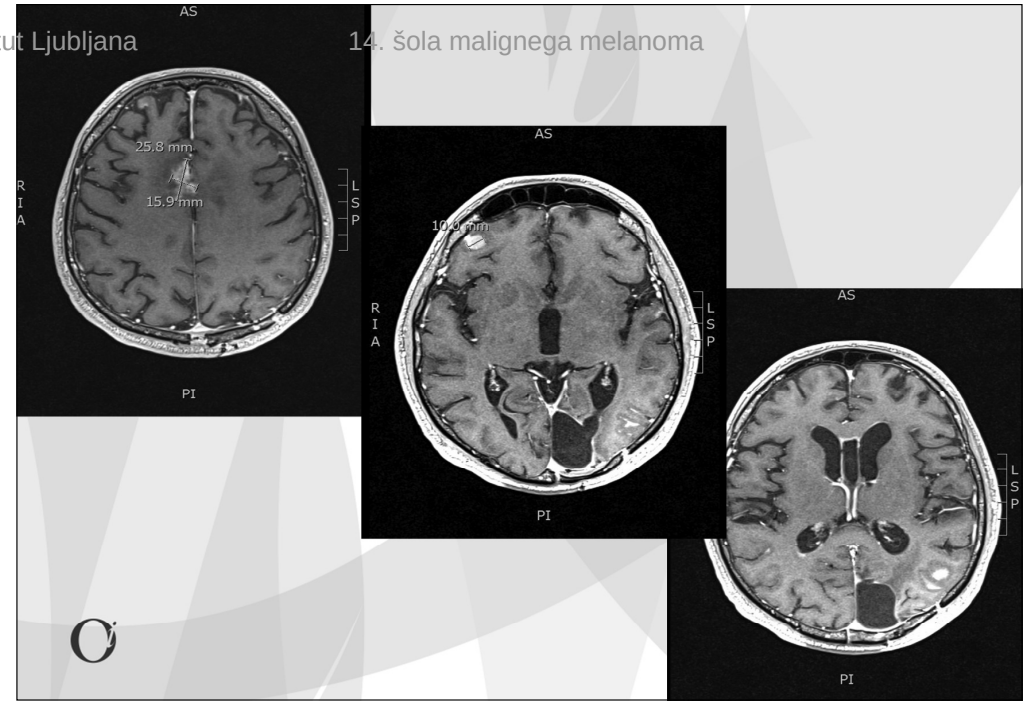
- 3.5.2011 SRS, 25 Gy # 1 frakcija
- 10.8.2011 MRI CR
- 16.11.2011 MRI progres izven obsevanega področja, infiltracija mening
- 12/2011 paliativna RT 24 Gy # 8 frakcij
- Asimptomatski, KT FOLFIRI, bevacizumab 3 ciklusi
- Bolnik spomladi 2012 umrl




Point Prescription (Isoc. Norm.;Group 1 (A)) used
Prescription Percentage:
PTV Settings
Number of Fractions
Dose for:
All Fractions
Single Fraction
Monte Carlo : 2.8%/1.8x1.8x2.8mm³


Violated DVH constraint
Point Prescription (Isoc. Norm.;Group 1 (A)) used
Monte Carlo : 2.8%/1.8x1.8x2.8mm³


AS
St. Preiskave:233725A450793
Datum Rojstva:06.05.1965
Spol:M
4.2 mm
5.6 mm
Komentar:
TE:3.63
TR:12.6
DFOV:
Razmak med rezi: sp
Flip Angle:15
Lokacija reza:25.49
Rez:0.8thk/
CONTRAST:GADOVIST
Inziner:GP
Datum Preiskave:02.03.2011
ONKOLOSKI INSTITUT, MR
W 920 : L 420
PI



Primer 2

- 55 letni bolnik
- 2005 znamenje v predelu d. rame, mm- Clark IV, Breslow 1,9; rob 6 mm od tumorja; varovalna bezgavka: mikrozasevek pod desno ključnico, aksila, vrat negativno
- pazdušna in vratna disekcija bezgavk
- reekscizija prim brazgotine
  - histološko ni bezgavke 0/50
  - brazgotina ni rezidualnega tumorskega tkiva

Primer 2

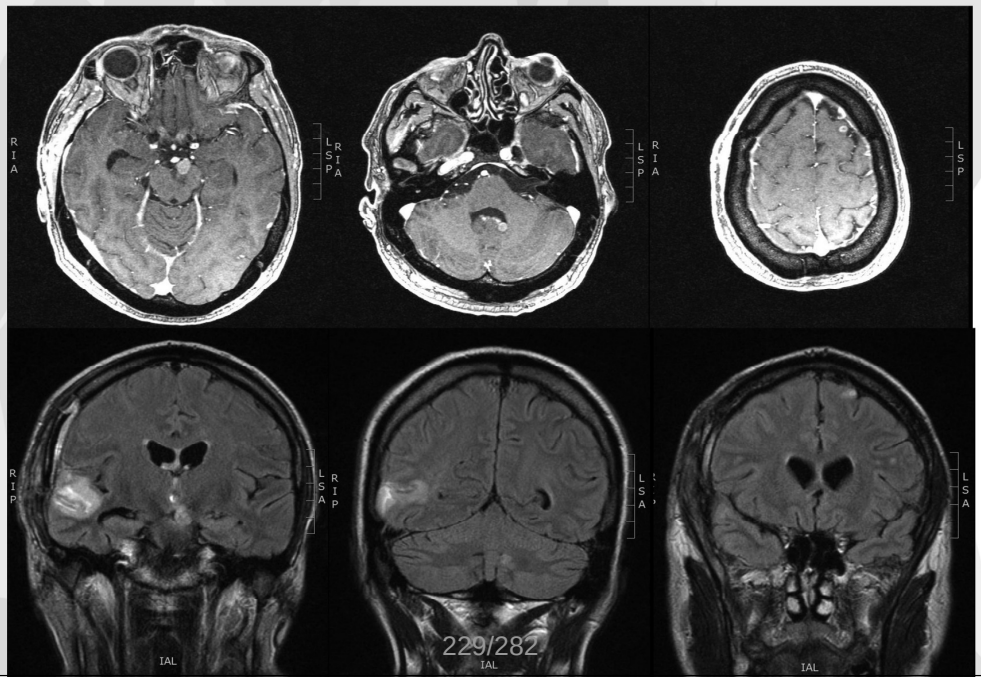
- stadij III A; Interferon 40000000 I.E. 5x tedensko, Interferon 20000000 I.E. 3x tedensko
- 09/2006: recidiv d. Infraklavikularno, 10/2006 resekcija recidiva; metastatski mm; 6 bezgavk, mikroskopske metastaze v podkožnem maščevju
- pooperativna radioterapija 52,5 Gy #21fr, do 09/2006
- 04/2008 zasevki v vranici; splenektomija; spremljanje

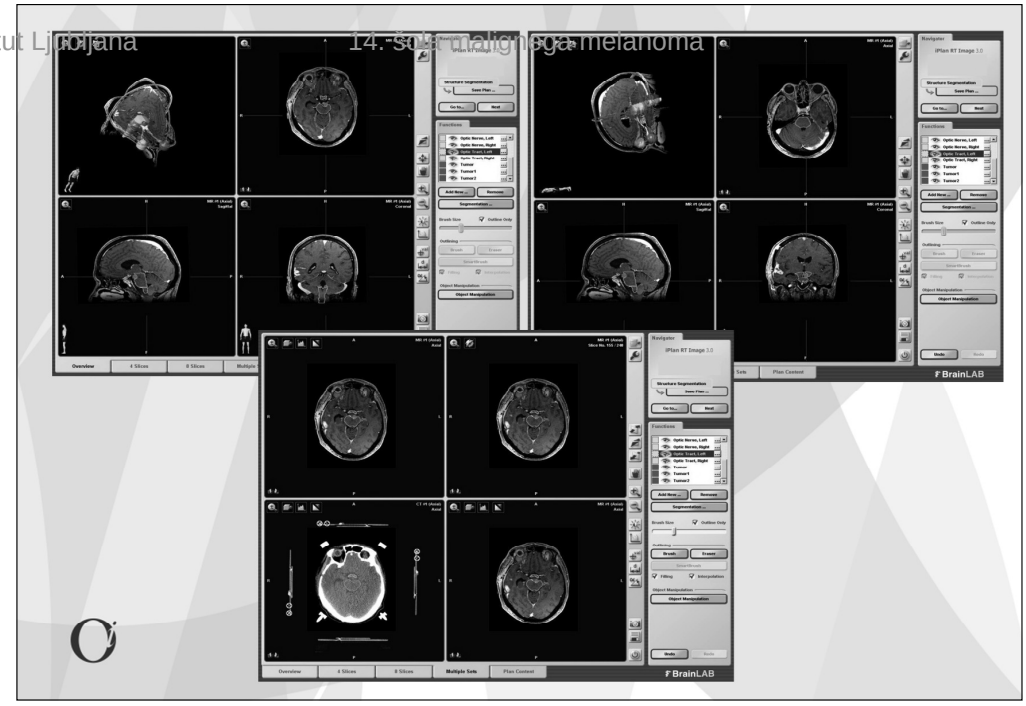
Primer 2

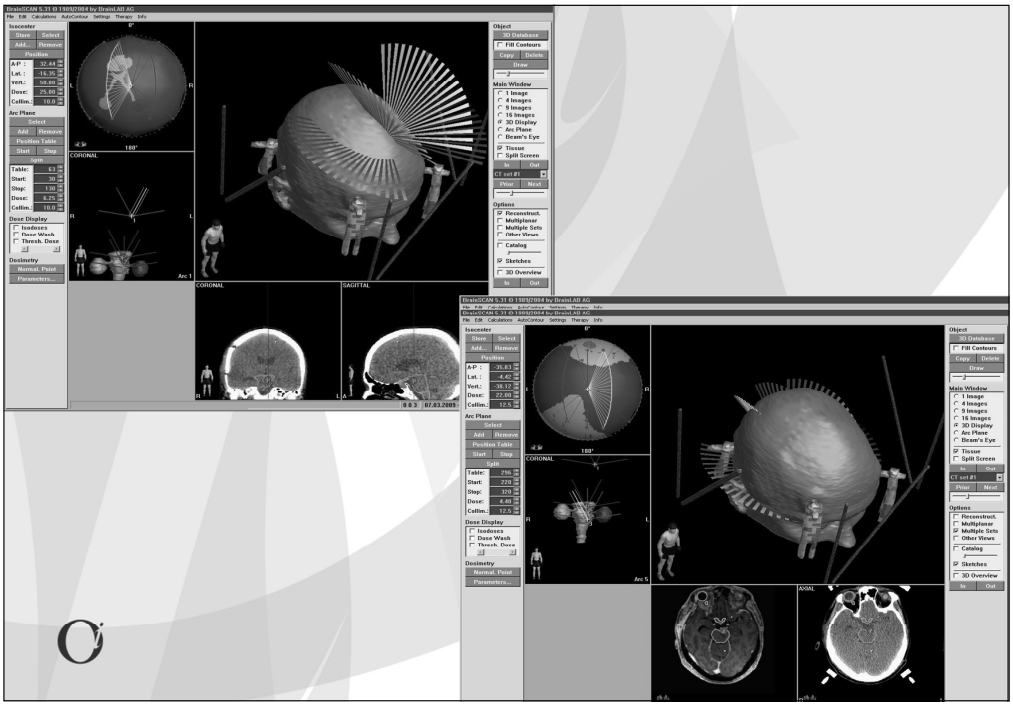
- 01/2009 metastaza temporoparietalno desno 3x2 cm, manjša v levi polovici ponsa
- PET-CT: meta. tik za levim m. rectus abdominis, L3, d temporoparietalno
- operacija zasevka d temporoparietalno; WBRT TD 30 Gy #10 frakcij
- Načrtovana SRS: MRI za načrtovanje: T1, KS, 0,8 mm
  - poleg odstranjene metastaze in metastaze v ponsu še 2 metastazi, 6 mm l frontalno, 7 mm medialno v l cerebelarni hemisferi

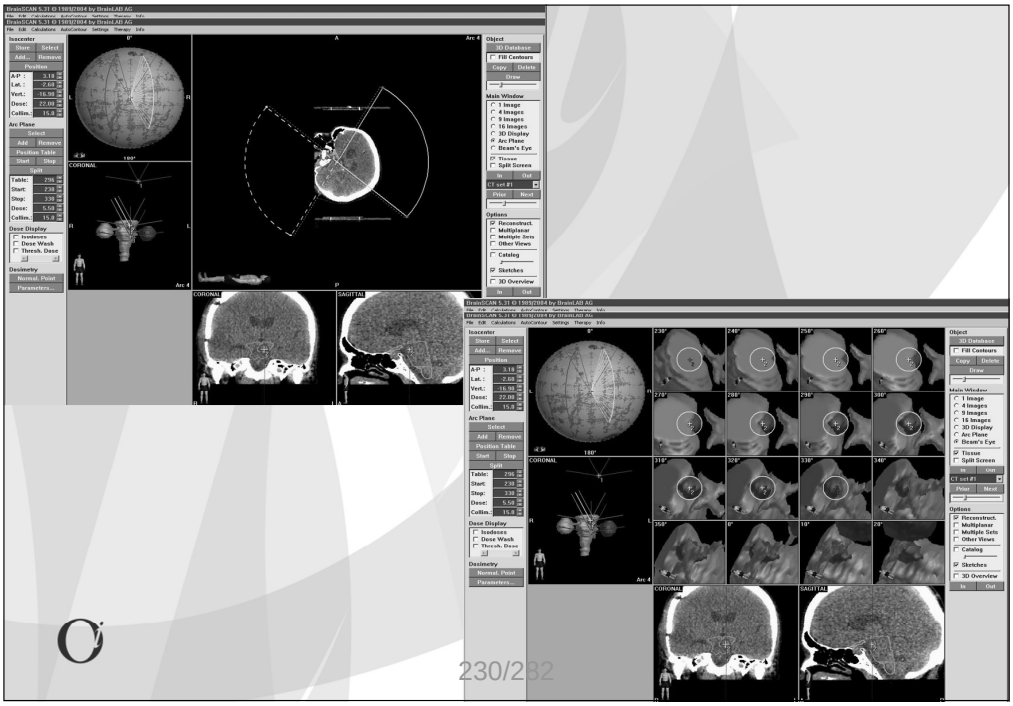
Primer 2

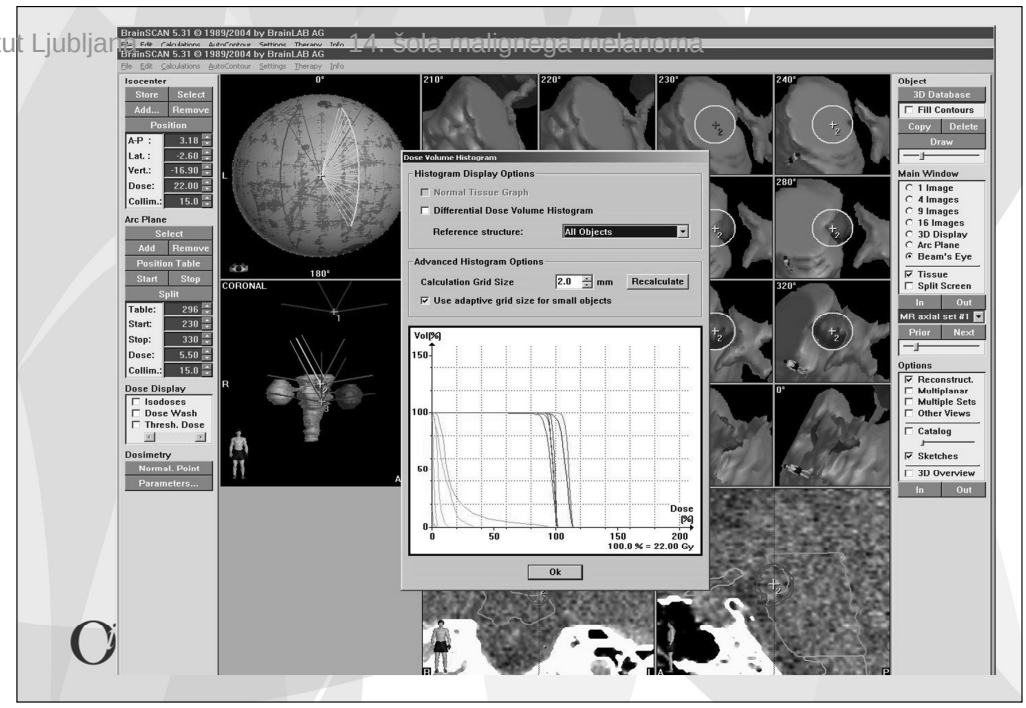
- SRS vseh treh rezidualnih lezij
  - l. frontalno 20 Gy; l. cerebralni pedunkel 18 Gy; l. cerebelarna hemisfera 18 Gy
- 06/2009; MRI:tumorske formacije v področju operativniga področja skoraj ni več videti, vidni le še ostanji. Tudi metastaze ob 4. ventriklu cerebelarno levo kot tudi ob levem cerebralnem pedunklu so manjše. Novih lezij intrakranialno ni videti.

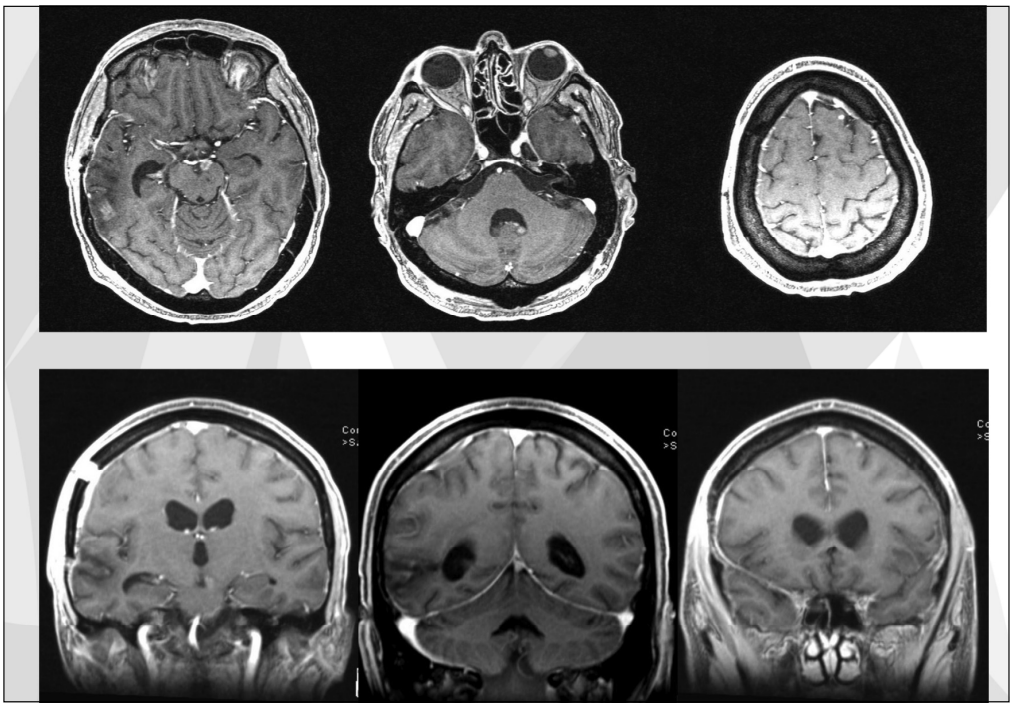


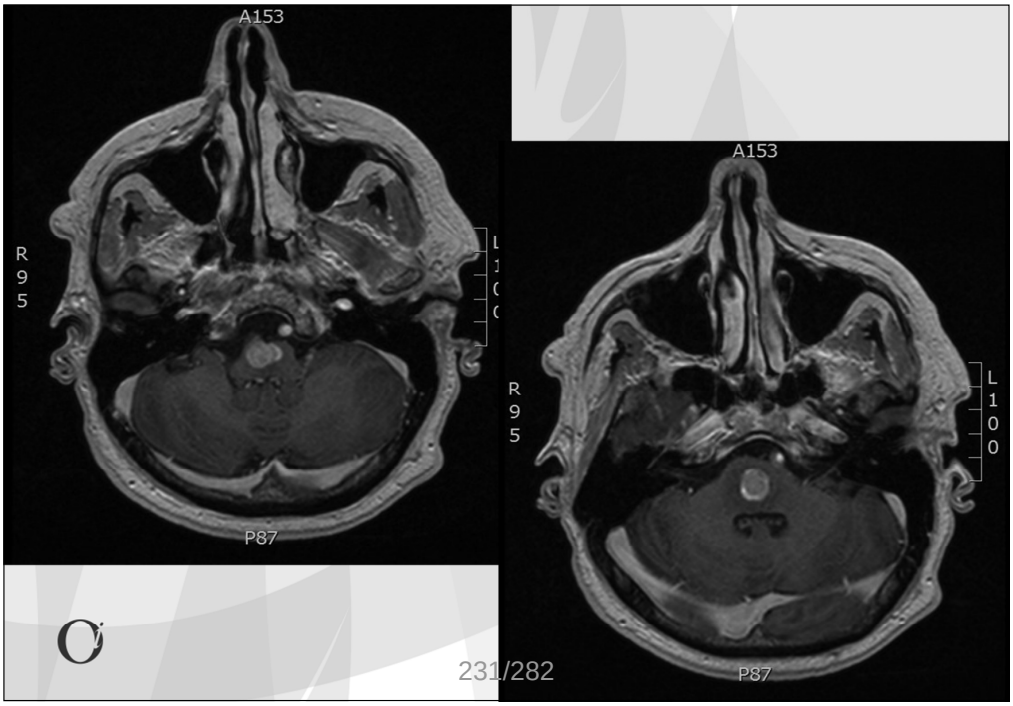

BrainLAB





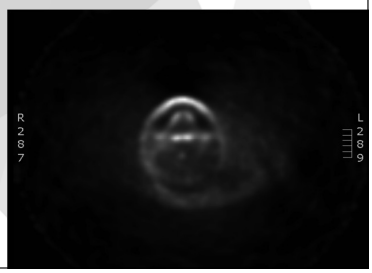

BrainSCAN 5.31 © 1989/2004 by BrainLAB AG
Isocenter
Store
Select
Add...
Remove
Position
A-P :
Lat. :
Vert.:
Dose:
Collim.:
Arc Plane
Select
Add
Remove
Position Table
Start
Stop
Split
Table:
Start:
Stop:
Dose:
Collim.:
Dose Display
Isodoses
Dose Wash
Thresh. Dose
Dosimetry
Normal. Point
Parameters...
CORONAL
Dose Volume Histogram
Histogram Display Options
Normal Tissue Graph
Differential Dose Volume Histogram
Reference structure:
All Objects
Advanced Histogram Options
Calculation Grid Size
mm
Recalculate
Use adaptive grid size for small objects
Vol[%]
Dose [%]
100.0 % = 22.00 Gy
Ok
Object
3D Database
Fill Contours
Copy
Delete
Draw
Main Window
1 Image
4 Images
9 Images
16 Images
3D Display
Arc Plane
Beam's Eye
Tissue
Split Screen
In
Out
MR axial set #1
Prior
Next
Options
Reconstruct.
Multiplanar
Multiple Sets
Other Views
Catalog
Sketches
3D Overview




A153
R 9 5
P87
A153
R 9 5
L 1 0 0
P87

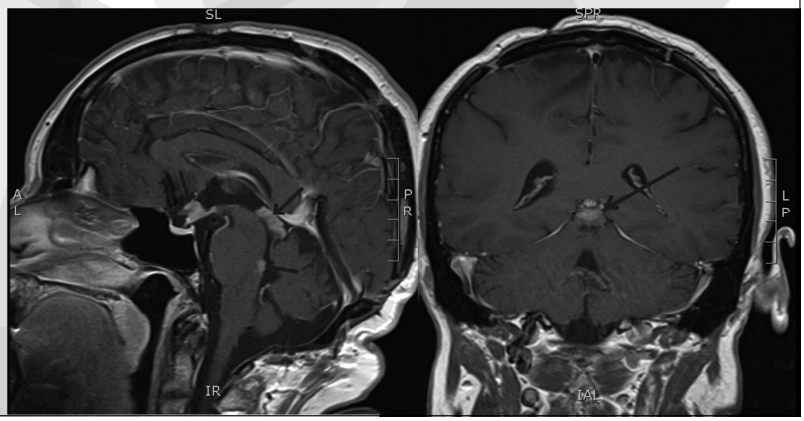
Primer 3

Bolnica 55 let
2010 operacija tumorja v pinealni regiji
makroskopsko v zdravo v enem kosu
ni drugih lezij na koži ali povečanih bezgavk
PET-CT hipermetabolne bezgavke na vratu reaktivne
konzilij: spremljanje pri operaterju
2013 adnoca pljuč pT3N0M0
lobektomija
adjuvantna terapija



Primer 3

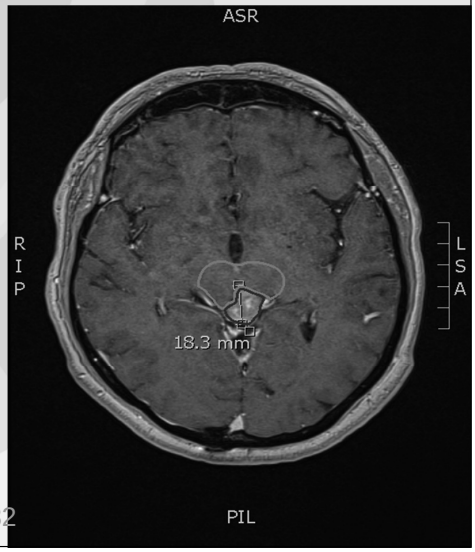
11.3.2015 MR sum na ponovitev melanoma v CŽS
nevrokirurg: spremembe niso operabilne



Primer 3

možgansko deblo v neposredni bližini tumorja

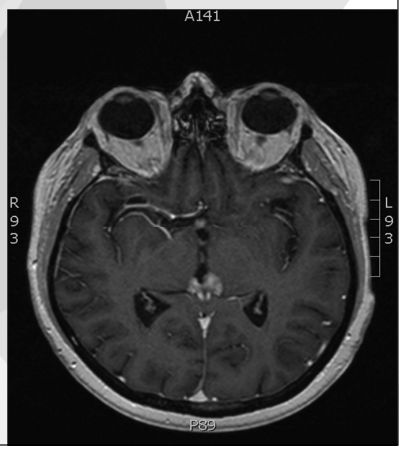
SRS omejitev
možgansko deblo:
<1ccm 12 Gy



Primer 3

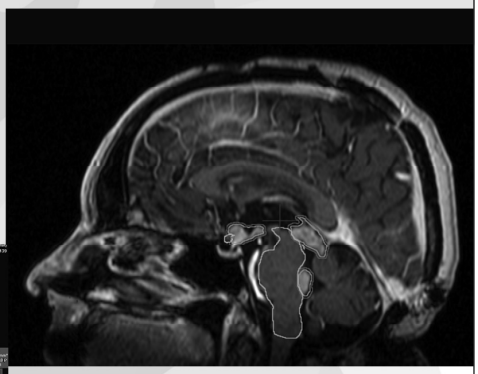
obsevanje ventrikularnega sistema
36 Gy # 12 frakcij po 3 Gy
CT 11. 11. 2015 regres

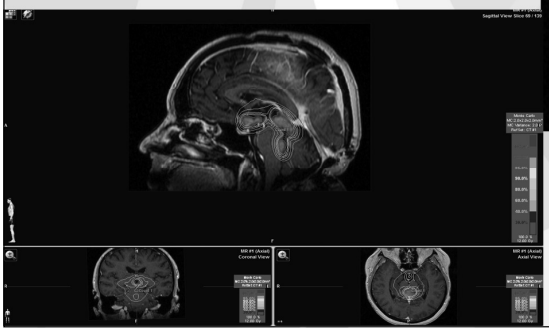
še stereotaktični boost



Primer 3

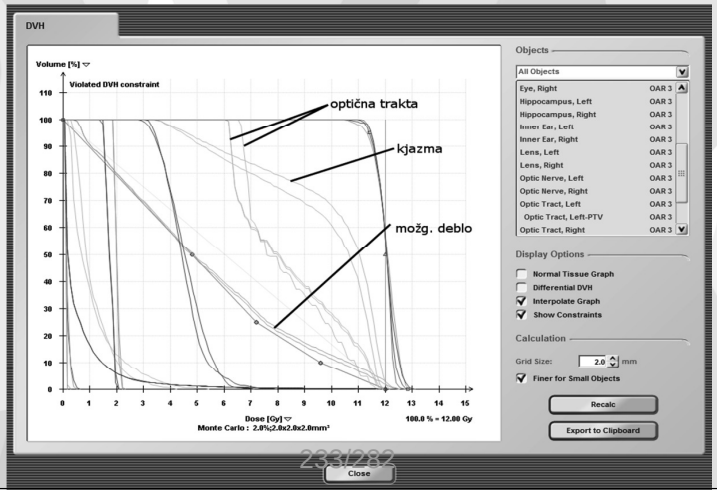
dodatek:
12 Gy # 3 frakcije
po 4 Gy





Primer 3

omejitve za radiokirurgijo presežene, možna SRT



Primer 3

Tumorji kontrolirani 10 mesecev nato progres

V vmesnem času zdravljena še s tarčno terapijo zaradi karcinoma pljuč

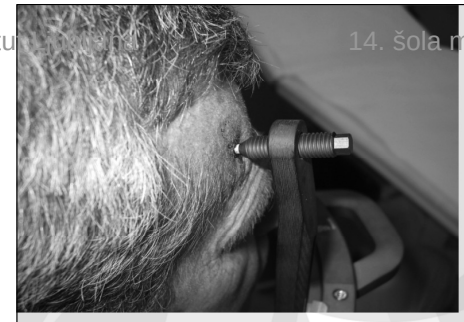
SRS

- SRS je lahko učinkovita kot reševalna terapija po operaciji
- SRS ne more odpraviti učinka mase, ki ga povzroča tumor
- SRS ne zmanjša edema
- Večinoma so progresi izven obsevanega področja (lokalna terapija)
- Možno je frakcionirano obsevanje (npr. Možgansko deblo)
- Ob uporabi maske je udobje bolnika večje
- Bolniki, ki so **RPA razred 3 niso** kandidati za SRS, saj le ta ne doda k preživetju

OMEJITVE SRS

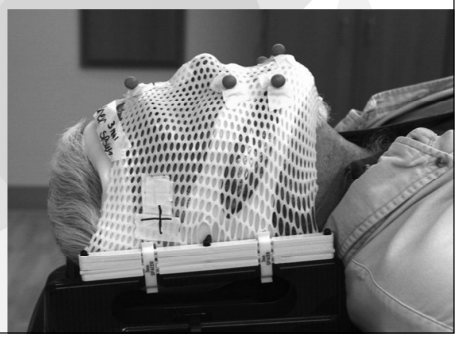
- ni primerna za tumorje, kjer težave povzroča učinek mase
- možgansko deblo: v 1 frakciji največ 1 ml 12 Gy
- radionekroza odvisna od volumna in odmerka

- SRT (lokalna RT visoke natančnosti)
  - primerna za večje lezije, za lezije v predelih, kjer bi s SRS povzročili nove izpade
  - ker je frakcionirana je potrebna še bolj natančna izbira bolnikov



fiksacija s stereotaktičnim okvirjem
dobra fiksacija
ni slikovno vodeno
ni za več frakcij
nevrokirurg

fiksacija z masko
fiksacija slabša
IGRT
možna frakcionacija
enostavna



Zaključki

- Stereotaktična radiokirurgija je učinkovito orodje za paliacijo omejenega števila možganskih zasevkov
  - postopek je enakovreden operativnemu zdravljenju
  - ni invaziven
  - ambulanten
- GLEDE NA KLINIČNE REZULTATE NI RAZLIK V USPEHU ZDRAVLJENJA GLEDE NA TEHNIKO
  - NovalisTx vs Cyber knife vs Gamma knife
- multiple lezije ? (<5 vs 5-10)

ZAKLJUČKI

- postopek izvajamo pri zasevkih v centralnem živčevju
- stereotaktično zdravljenje zasevkov drugod po telesu (pljuča, hrbtenica)
- v pripravi tudi jetra

ZAKLJUČKI

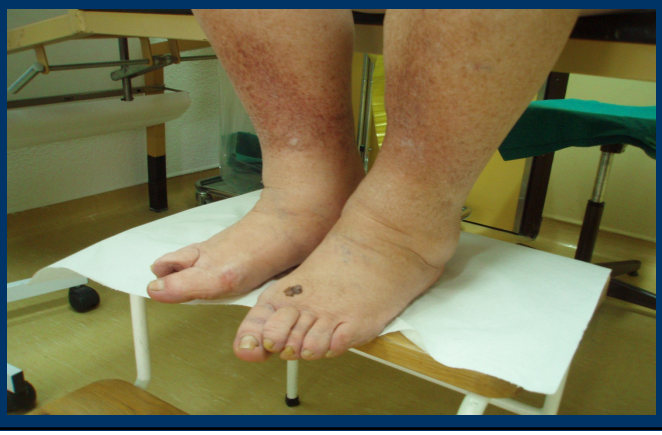
- v letu 2010 na OI pričel obratovati NovalisTX
- 2016 pričetek ekstrakranialne stereotaksije
  - pljuča
  - solitarne lezije v hrbtenici (prve izkušnje v pripravi protokol)
  - jetra (v pripravi)
  - prostata (v pripravi, potreba?)
  - ....

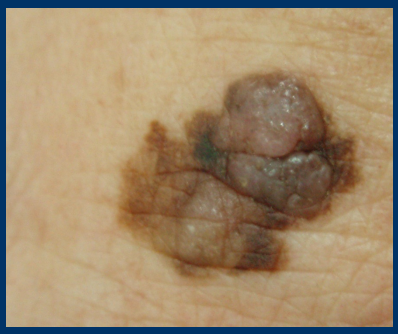
Katere bolnike obravnavamo?

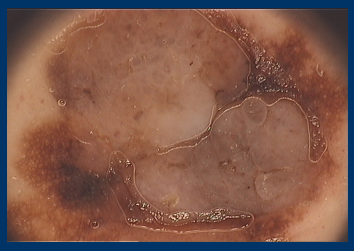
- Z novonastalimi /sumljivimi pigmentnimi spremembami
- S številnimi pigmentnimi spremembami
- Spremljanje bolnikov po odkritem melanomu
- S pozitivno družinsko anamnezo
- Iščemo možen izvor metastaz
- Izrežemo sumljive spremembe

Primer 1: G.A. , ♀, 67 let

- Hipostatski dermatitis, onihomikoza
- Lokalna terapija?







Anamneza:

-Znamenje že od mladosti

-Spreminja se zadnje leto

-Upala, da bo kdo opazil/ sama ni opozorila

Obravnava :

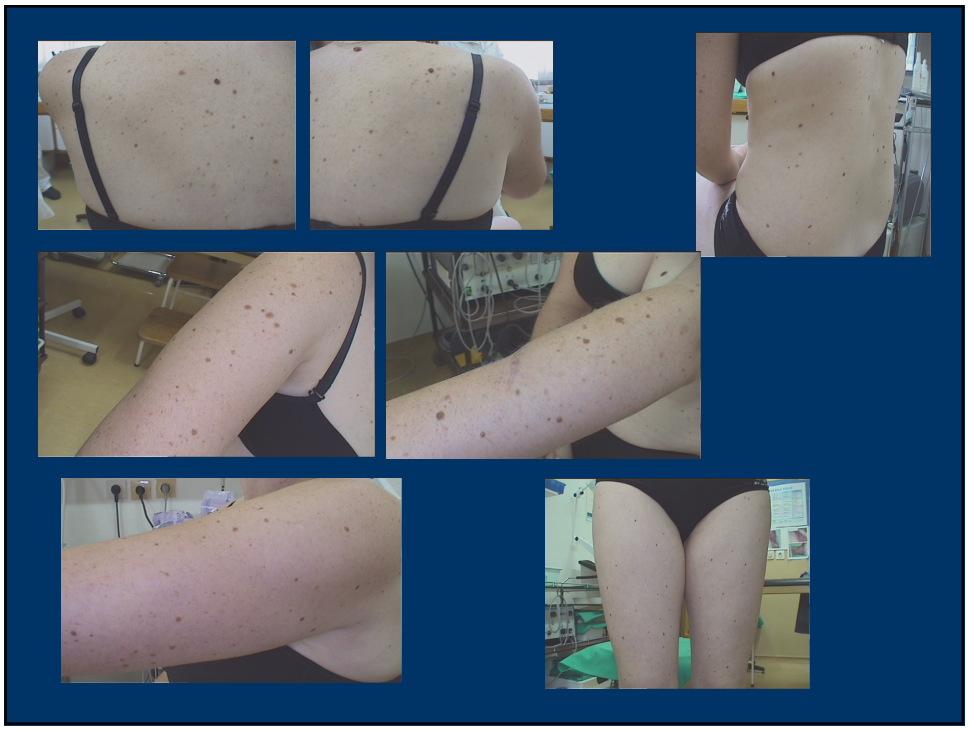
- Ekscizija
- Maligni melanom, Clark III., Breslow 1,6, 2 mitozi/mm², v melanocitnem nevusu
- Dodatne lab. in slikovne preiskave
- Napotitev na OI, BVB neg.

- Kontrole na OI in v dermatološki ambulanti

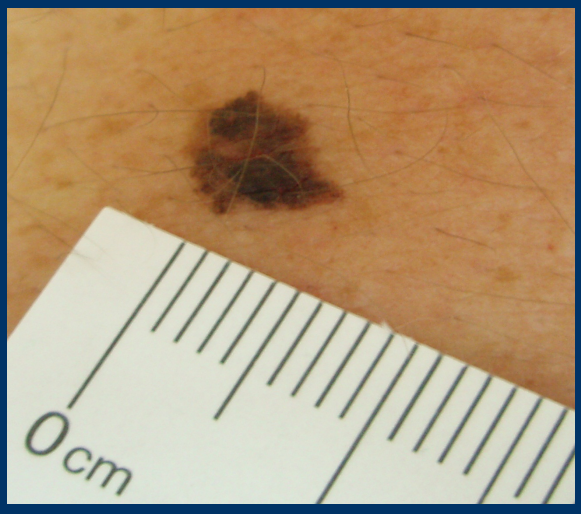
S.V., ♀, 32 let

- Eno leto spremenjeno znamenje
- V otroštvu sončne opekline
- Številna znamenja
- Družinska anamneza negativna

- Dobila info material o melanomu!



Leva podlaht

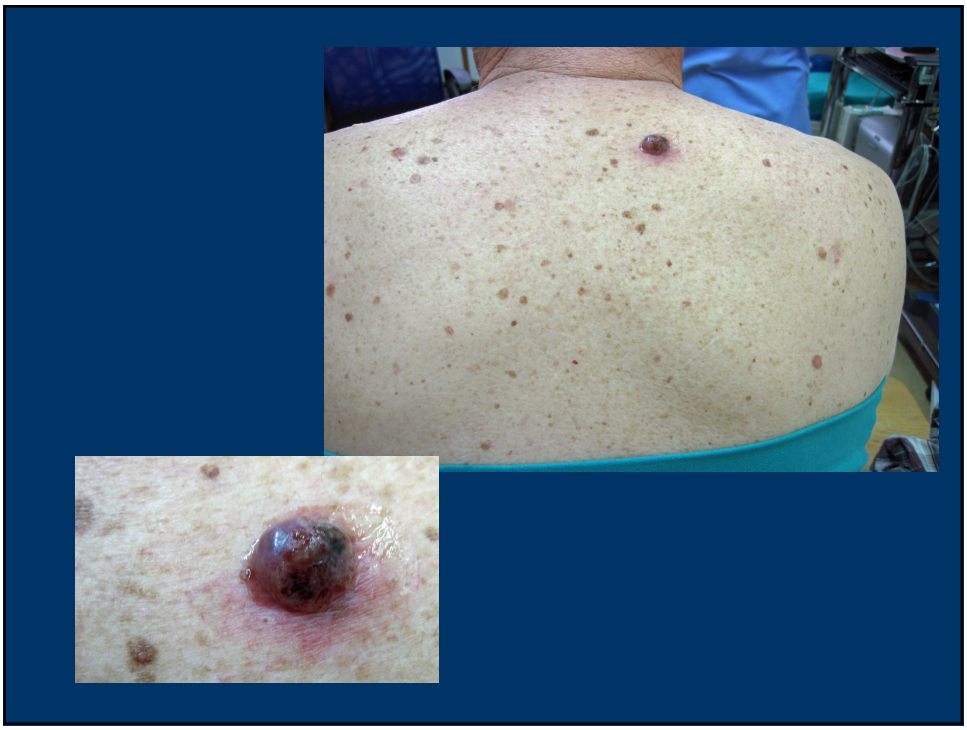


Obravnava :

- Ekscizija
- Maligni melanom in situ v preeksistenčnem melanocitnem nevusu
- Reekscizija
- Observacija, zaščita pred UV žarki

P.A., ♂, 65 let

- Pribl. 1 mesec krvaveča tvorba na hrbtu
- Poškodba?
- v preteklosti dosti izpostavljen UV žarkom, delal na prostem, večkrat opečen
- Družinska anamneza negativna

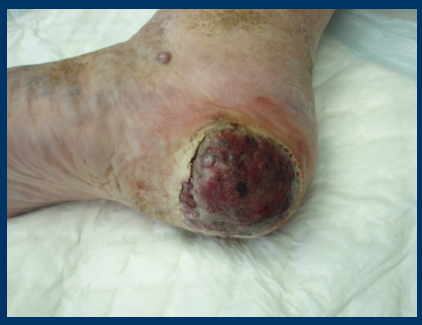


Obravnava:

- Ekscizija
- Maligni melanom, nodularni tip, Clark III., Breslow 5 mm, do 8 mitoz/mm², blago pigmentiran
- Lab. in slikovne preiskave
- Napotitev na O.I.
- Kontrole onkolog, dermatovenerolog

Š.M. , ♀ , 78, let

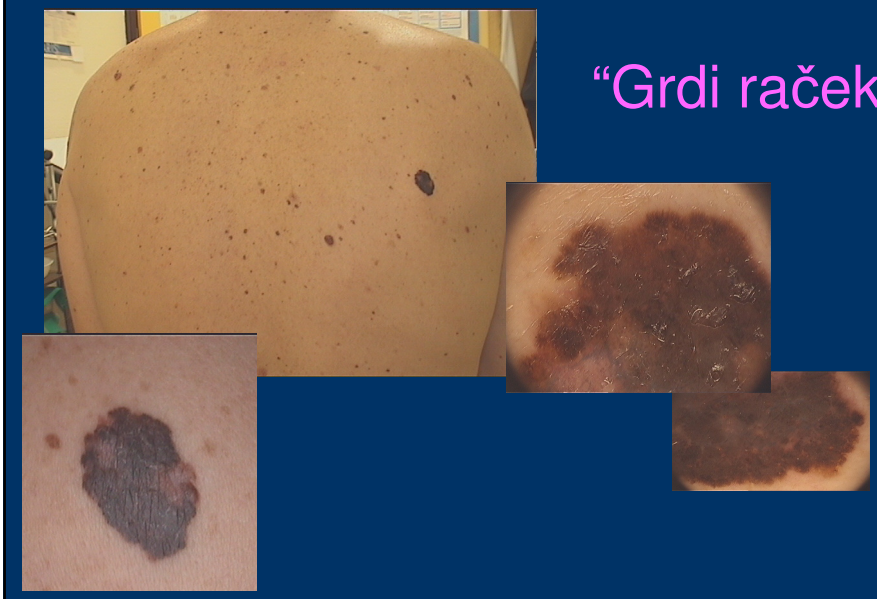
- Razjeda na peti, več mesecev
- Preveze s strani sorodnice
- Sprememba se širi
- Gospa ne more več stopiti na nogo



Ni vsaka razjeda na stopalu žilne etiologije!

M.B., ♂, 44 ,let

- Ob avskultaciji opažena sprememba na hrbtu
- Sam ne ve nič
- Dosti izpostavljen UV žarkom
- Številni nevusi
- Družinska anamneza negativna



“Grdi raček”

Scope A et al. Arch Dermatol 2008; 58-64.

Obravnava:

- Ekscizija
- Maligni melanom pretežno in situ, fokalno invaziven do Breslow 0.25 mm, Clark II, ni ostankov nevusa
- Reekscizija
- Kontrole v dermatološki ambulanti
- Samoopazovanje, zaščita pred UV žarki

- Bolnike spodbujajmo k samoopazovanju!
- Poglejmo kožo !

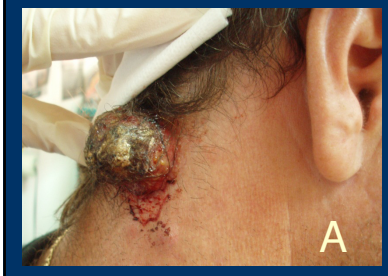
Zaključek-vprašanja

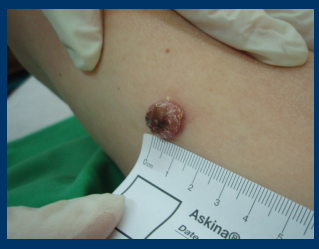
Katerega bolnika napotimo k dermatologu?

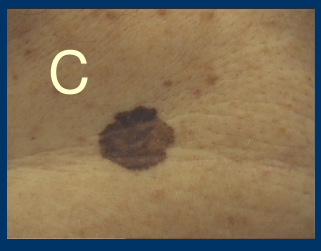
1. S spremembo sumljivo za melanom 0%
2. Po odstranitvi melanoma 0%
3. S številnimi melanocitnimi pigmentnimi nevusi 0%
4. Vse zgoraj našteto 0%

10

Melanom?







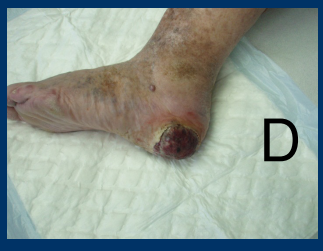
Odgovori

1 : A+C

2: A+B+C

3: A+B+C+D

4: C



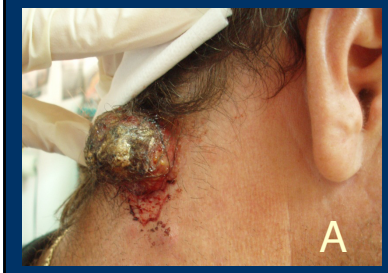
Melanom?

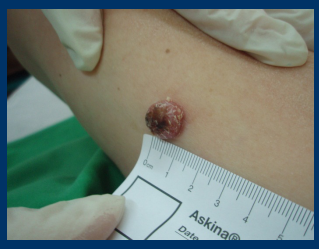
1. A in C 0%
2. A, B in C 0%
3. A, B, C in D 0%
4. C 0%

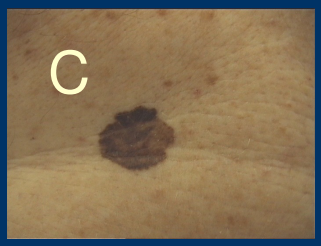
Pravilni odgovori: vsi (A+B+C+D)

- A: maligni melanom, Breslow 25 mm
- B: maligni melanom, Breslow 8 mm
- C: maligni melanom, in situ
- D: maligni melanom

Melanom? Vsi!







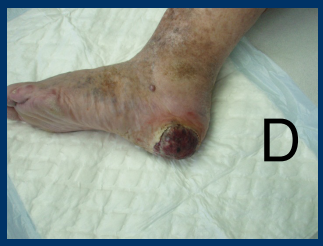
Odgovori

1 : A+C

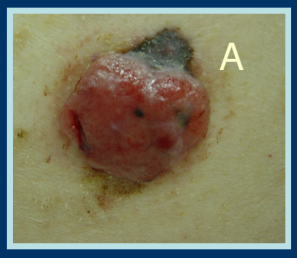
2: A+B+C

3: A+B+C+D

4: C



Melanom?



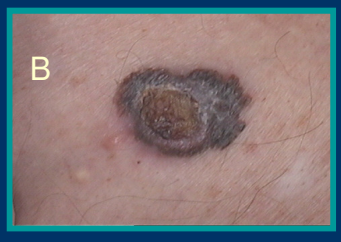
Odgovori :

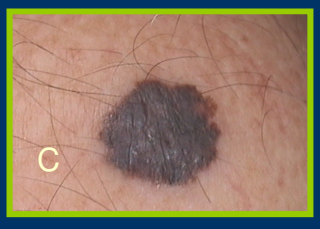
1: B+C

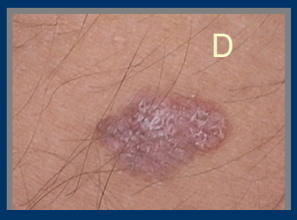
2: A+B+C

3: A+B+C+D

4: C





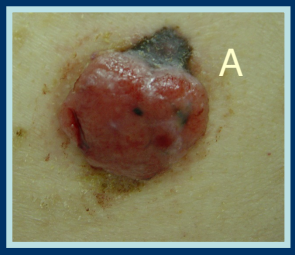


Melanom?

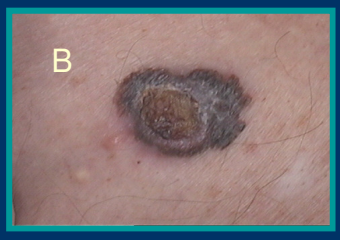
1. B in C 0%
2. A, B in C 0%
3. A, B, C in D 0%
4. C 0%

10

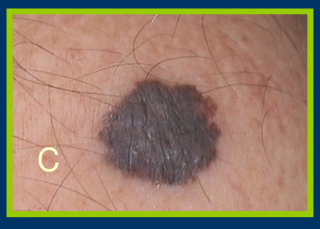
Pravilni odgovor: 3: A+B+C+D



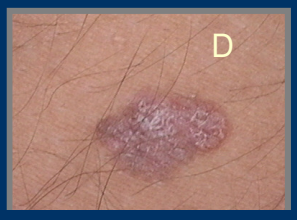
Nodularni, Breslow 6.6, Clark IV, ulceracija



Površinsko rastoči, Breslow 4, Clark V, ulceracija

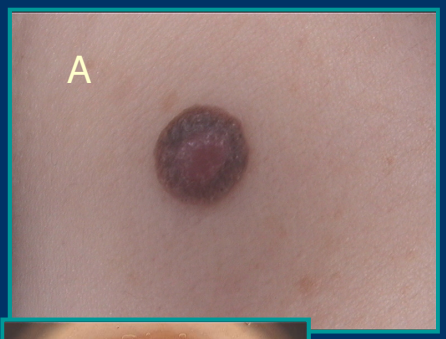


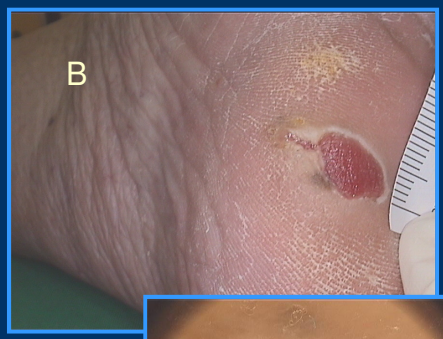
Površinsko rastoči, Breslow 0.4, Clark II

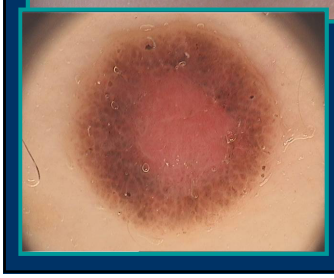


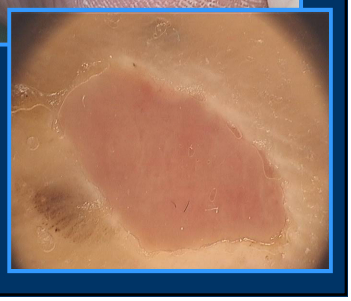
Površinsko rastoči, Breslow 0.4, Clark II, nepigmentiran

Melanom?









Odgovori :

1: A

2: B

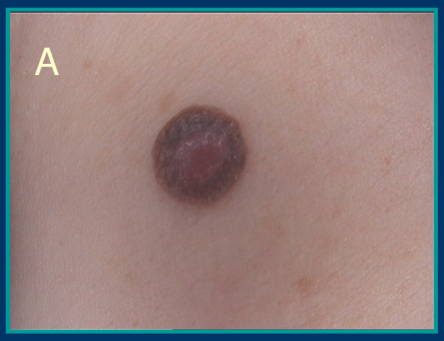
3: A+B

4: noben

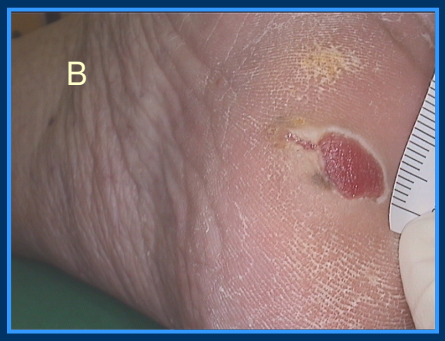
Melanom?

1. A 0%
2. B 0%
3. A + B 0%
4. noben 0%

Pravilni odgovor: 3: A+B



Maligni melanom, Breslow 2mm, Clark III, brez ulceracije



Biopsija potrdi maligni melanom

14. ŠOLA O MELANOMU

Predstavitev kliničnih primerov bolnikov z melanomom z vidika dermatologa

Tomi Bremec
Dermatovenerološka klinika, UKC Ljubljana

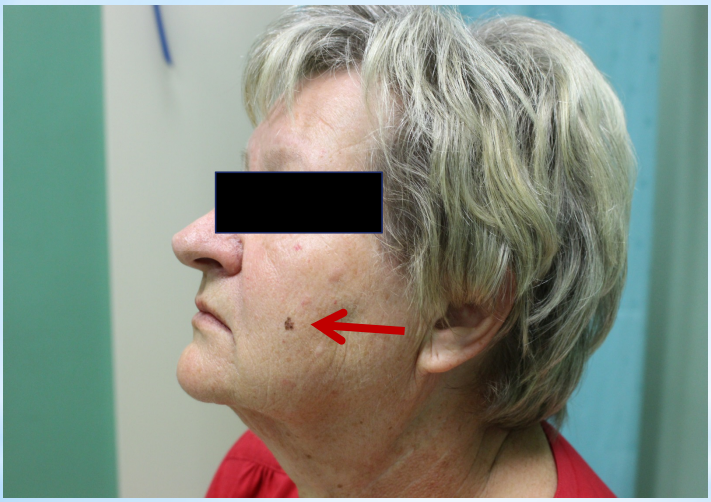
*PRIMER 1

Anamneza:

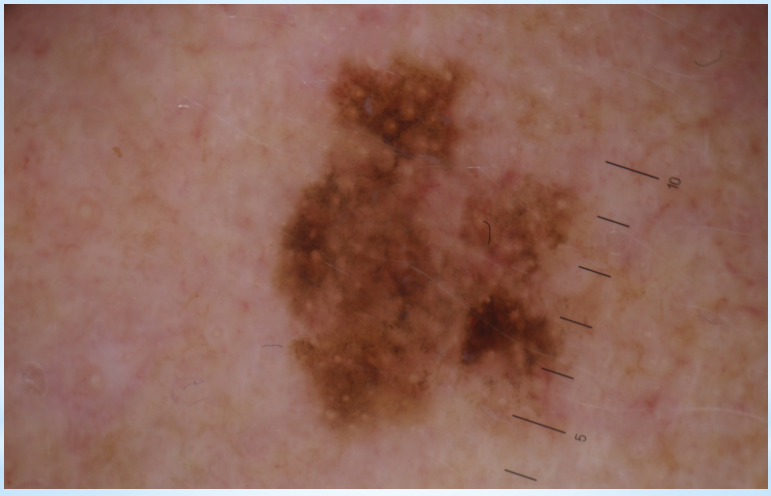
- 68-letna gospa B.E. prihaja na pregled pigmentnih znamenj
- opaža znamenje na levem licu, ki se povečuje
- družinska anamneza glede kožnega raka je negativna

Dermatološki status:

- na levem licu temno pigmentirana makula, dermatoskopsko suspektna za melanom
- drugje na koži melanocitni nevusi, seboroične keratoze in hemangiomi



Klinična slika



Dermatoskopska slika

Terapija:

- gospa prejme napotnico pod nujno za kirurga plastika za ekscizijo suspektne lezije v celoti

Patohistološki izvid:

A) Koža in podkožje levega lica, ekscizija

Maligni melanom, nivo po Clarku II, globina tumorja po Breslowu 0,20 mm. Prisotna je radialna rast površinsko rastočega tipa. Prisotna je vertikalna rast epiteloidnoceličnega tipa. Ni ulceracije. V invazivnii komponenti tumorja ni mitoz (0/1 mm2). Pigmentacija je zmerna. V bazi tumorja je znatna limocitna infiltracija. Prisotni so znaki regresije tumorja. Prisoten je spremljajoči melanocitni intradermalni kongenitalni nevus. Ni vaskularne invazije. Ni satelitskih mikroinifltratov. Stranski kirurški robovi niso tumorsko iniltrirani. Tumor je 3 mm oddaljen od stranskega kirurškega roba. Kirurški rob v globini ni tumorsko infiltriran. Tumor je 5 mm oddaljen od kirurškega roba v globini. Na koži zunaj tumorja je solarna elastoza.

- pri gospe je bil opravljen ponovni izrez ležišča primarnega melanoma (reekscizija) z 1 cm varnostnim robom

Patohistološki izvid:

A) Koža levega lica, reekscizija

Brazgotinsko tkivo in intradermalni melanocitni nevus.

Brazgotina leži centralno v vzorcu, sega preko celotnega dermisa, deloma v subkutano maščevje. Ob robu ekscizata izven brazgotinskega tkiva je dermalni melanocitni nevus, ki raste preko vse debeline dermisa. V povrhnjem dermisu so dobro razmejeni otočki izaziteje epiteloidnih melanocitov z zmerno stopnjo displazije, z globino melanociti dozorevajo, urejajo se v ˝prolieracijske noduse˝. Koža izven tumorja kaže intenzivno solarno elastozo.

KOMENTAR

Ni rezidualnega melanoma.

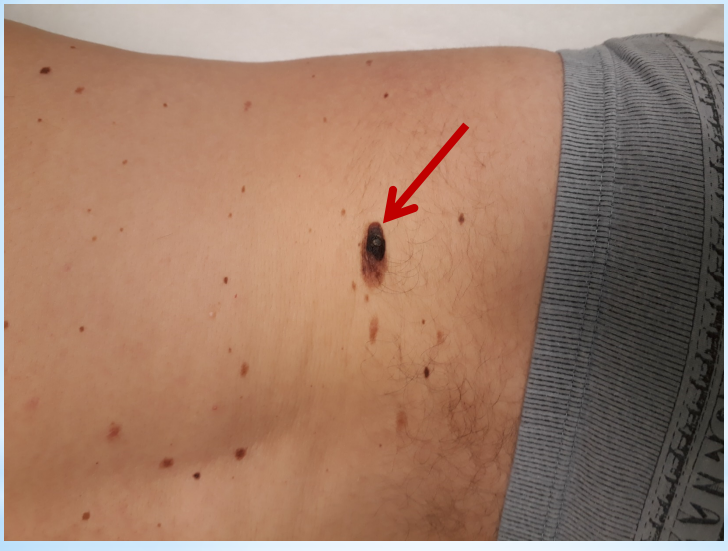
*PRIMER 2

Anamneza:

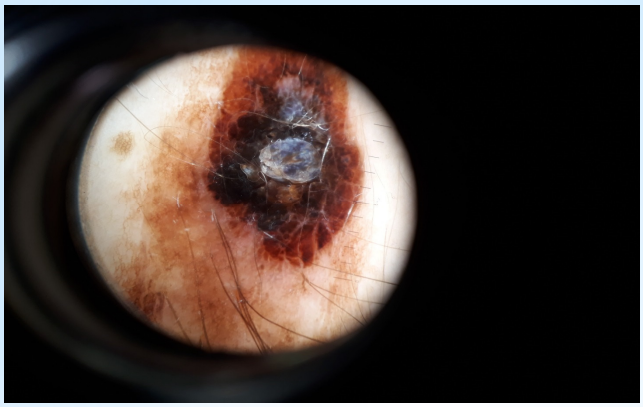
- 38-letni gospod S.R. prihaja na pregled zaradi spreminjanja pigmentnega znamenja na hrbtu ledveno
- družinska anamneza glede kožnega raka je negativna

Dermatološki status:

- desno ledveno lezija suspektna za melanom
- drugje na koži melanocitni nevusi in solarni lentigi, klinično in dermatoskopsko nesuspektno
- regionalne bezgavke niso tipno povečane



Klinična slika



Dermatoskopska slika

Terapija:

- gospoda pod nujno napotimo napotimo h kirurgu plastiku za ekscizijo suspektne lezije

- Povzetek patohistološkega izvida:
- maligni melanom desno ledveno
- debelina po Breslowu 1,71 mm
- 2 mitozi/mm2
- brez ulceracije

- gospod je bil napoten na OI za nadaljnje zdravljenje (biopsijo varovalne bezgavke (BVB) in sočasno reekscizijo)
- Izvid BVB: negativen

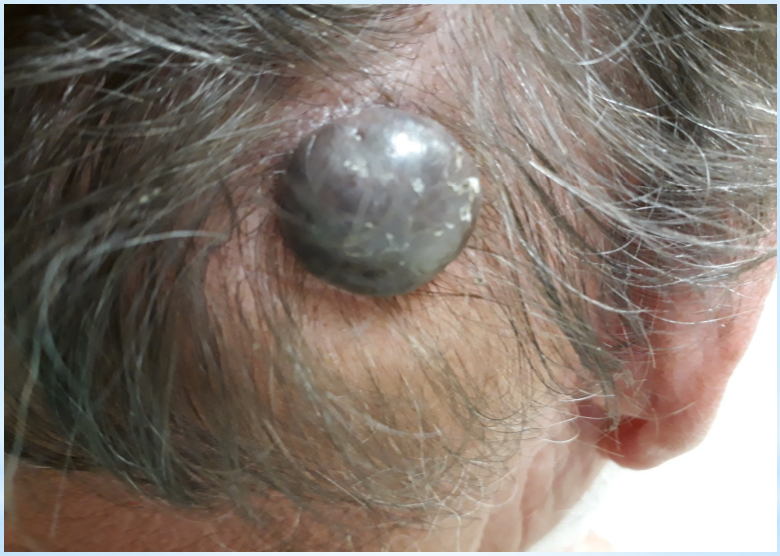
*PRIMER 3

Anamneza

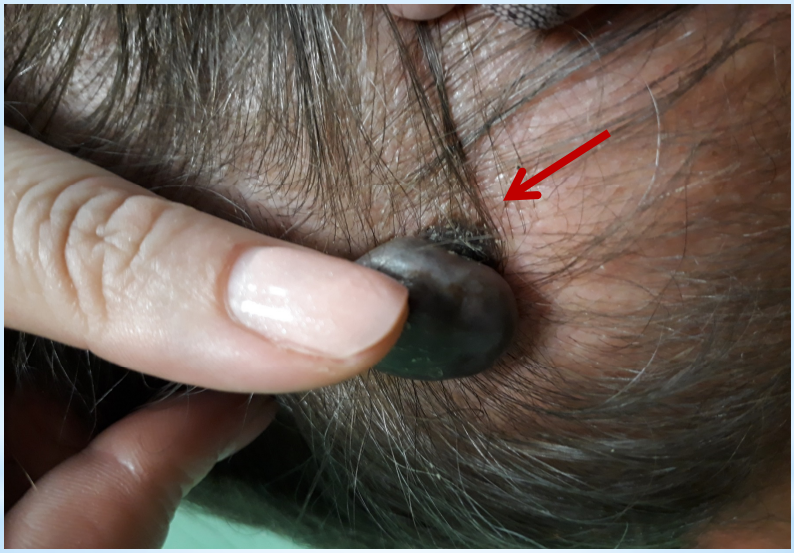
- 67-letni gospod B.A. prihaja na pregled zaradi lezije v zatilju desno, ki jo opaža od otroštva
- omenjena lezija se je bistveno povečala v zadnje pol leta
- družinska anamneza glede kožnega raka je negativna

Dermatološki status

- okcipitalno desno melanom
- regionalne bezgavke niso tipno povečane
- po telesu melanocitni nevusi in solarni lentigi, klinično in dermatoskopsko nesuspektni



Klinična slika



Klinična slika

Terapija

- gospoda pod nujno napotimo za izrez suspektne lezije h kirurgu plastiku

- Patohistološki izvid

A) Koža okcipitalno, ekscizija:

Melanom, Clark IV, globina invazije 13,5 mm (Breslow)

Prisotna je radialna rast površinsko rastočega tipa. Prisotna je vertikalna rast mešanoceličnega tipa. Ni ulceracije. Število mitoz 4/mm2. Tumor je blago do zmerno pigmentiran. V tumorju je blaga limocitna vnetna infiltracija. Ni znakov regresije tumorja. Ni spremljajočega melanocitnega nevusa. Priostna je melanomska limfangioza. V dermisu in podkožju ob in pod melanomom je več satelitskih mikroinfiltratov, ki merijo v največjem premeru do 1,5 mm. Stranski kirurški robovi niso tumorsko infiltrirani, od stranskega kirurškega roba je invazivni melanom (eden od satelitskih mikroinfiltratov) oddaljen 1 mm. Globoki kirurški rob ni tumorsko infiltriran, od globokega kirurškega roba je invazivni melanom (eden od staelitskih mikroinfiltratov) oddaljen 0,8 mm.

KOMENTAR: Glede na globino invazije in satelitske mikroinfiltrate bomo napravili molekularno-genetsko preiskavo za dokaz mutacije gena BRAF in drugih relevantnih genov.

- gospoda z izvidom histopatološke preiskave napotimo na melanomski konzilij na OI za nadaljnje zdravljenje

Kontrolni pregled pri dermatologu (6 mesecev po odkritju melanoma):

- pri gospodu z melanomom okcipitalno desno (Breslow 13,5 mm, brez ulceracije, 4 mitoze/mm2) je bila biopsija varovalne bezgavke pozitivna
- opravljena je bila cervikalna limfadenektomija desno
- gospod je bil pooperativno zdravljen z radioterapijo

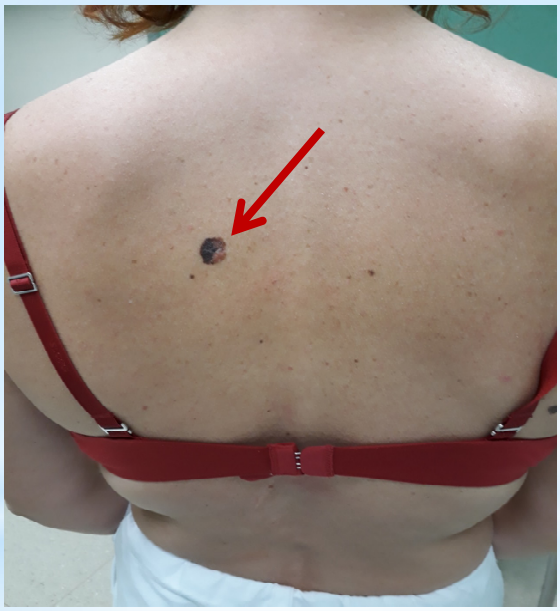
*PRIMER 4

Anamneza

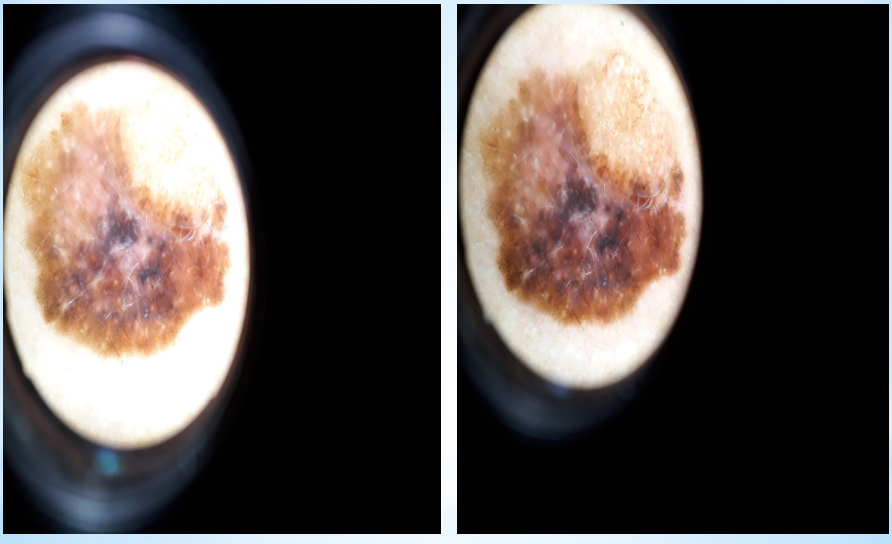
- 39-letna gospa D.T. prihaja na pregled zaradi lezije ob levi lopatici, ki jo opaža približno 4 leta
- melanoma v družini ni

Dermatološki status

- paravertebralno torakalno levo lezija suspektna za melanom
- drugje na koži brez suspektnih lezij
- regionalne bezgavke niso tipno povečane



Klinična slika



Dermatoskopski sliki

Terapija

- gospo z nujno napotnico napotimo h kirurgu plastiku za ekscizijo suspektne lezije

Povzetek patohistološkega izvida

- maligni melanom
- Breslow 0,6 mm
- brez ulceracije
- brez mitoz

- pri gospe je bila opravljena reekscizija (ponovni izrez) ležišča primarnega melanoma z 1 cm varnostnim robom

Hvala za pozornost!

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

PRIMER ZDRAVLJENJA Z ELEKTROKEMOTERAPIJO

N. Glumac, M. Snoj, G. Serša

13. šola melanoma

Ljubljana, 10.3.2017

POVZETEK II.

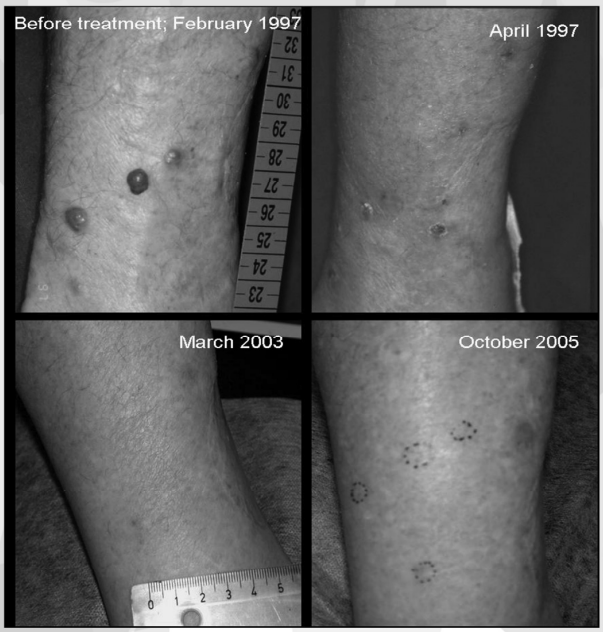
- Zdravljenje multiplih kožnih in podkožnih metastaz melanoma
- Pri majhnem številu metastaz na dostopnih mestih je kirurška ekscizija še vedno najprimernejši način zdravljenja
- Alternative:
  - A. Izolirana (infuzija) perfuzija uda
  - B. Radioterapija
  - C. Laserska evaporacija
  - D. Elektrokemoterapija

ELEKTROKEMOTERAPIJA

- Intratumorska ali iv. injekcija cisplatina (Platinol,1 mg/100 mm^3)
- Interval med injekcijo cisplatina in aplikacijo električnih impulzov je med 1 in 8 minutami
- Električni impulzi dolžine 100 µs, amplitude 910 V in frekvence 1 Hz – preko 2 kovinskih elektrod z medsebojno razdaljo 7 mm
- Vozliči večji od 7 mm so tretirani večkrat, tako da je zajeta celotna površina tumorja

ELEKTROKEMOTERAPIJA

- Metastaze – razvoj sprememb po zdravljenju
  - Eritem in edem metastaz do 2. tedna
  - Površinska krusta, ki odpade po 4. do 8. tednih
  - Rahlo depigmentirana koža z minimalno retrakcijo
  - S časom tudi slednje spremembe izginejo



ELEKTROKEMOTERAPIJA

- FILM

KOKIC NE STREŽEMO

PRIMER BOLNICE

- 57 letna bolnica, zdrava
- 1992: široka ekscizija melanoma, Breslow 1,3 mm na sprednji strani desnega gležnja
- Brez dodatnega zdravljenja

PRIMER BOLNICE

- Januar 1997
- Multipli kožni in podkožni vozliči (16) na desni goleni, velikosti od 4 do 18 mm
- Citološka punkcija: metastaze melanoma
- UZ abdomna in RTG pc: brez znakov razsoja

ELEKTROKEMOTERAPIJA

- Februar - Maj 1997
- 5 ciklusov elektrokemoterapije na 1-2 tedna
- Vključno z zdravljenjem dodatne 16 mm metastaze na stegnu, ki se je pojavila pred 5 ciklusom
- Splošna anestezija

ELEKTROKEMOTERAPIJA

- Avgust 1997
- Dosežen popoln odgovor metastaz
- Razen tumorja v predelu gležnja, ki se je povečal na 6 cm in ekzulceriral
- Odstranjen kirurško z ekscizijo in krioterapijo baze, defekt zaceljen per secundam

ELEKTROKEMOTERAPIJA

- Avgust 2005
- 2 podkožni metastazi na desni nogi pod (7 mm) in nad (13 mm) kolenom
- Obe sta bili tretirani z elektrokemoterapijo s cisplatinom z enakimi parametri kot pri prvem zdravljenju
- Odgovor na zdravljenje je bil enak – popoln

POVZETEK I.

- Zdravljenje multiplih kožnih in podkožnih metastaz melanoma z elektrokemoterapijo s cisplatinom je dalo popoln odgovor za dobo 8 let
- Smiselna ponovitev zdravljenja
- Multiple kožne in podkožne metastaze naj bi nastale z intralimfatičnim širjenjem tumorskih celic, zato je dolgotrajen popoln odgovor težko doseči

POVZETEK II.

- Pri majhnem številu metastaz na dostopnih mestih je kirurška ekscizija še vedno najprimernejši način zdravljenja
- Alternative:
  - Izolirana infuzija/perfuzija uda
  - Radioterapija
  - Laserska evaporacija
  - Elektrokemoterapija

13. šola melanoma

THE END

13. šola melanoma

THE END

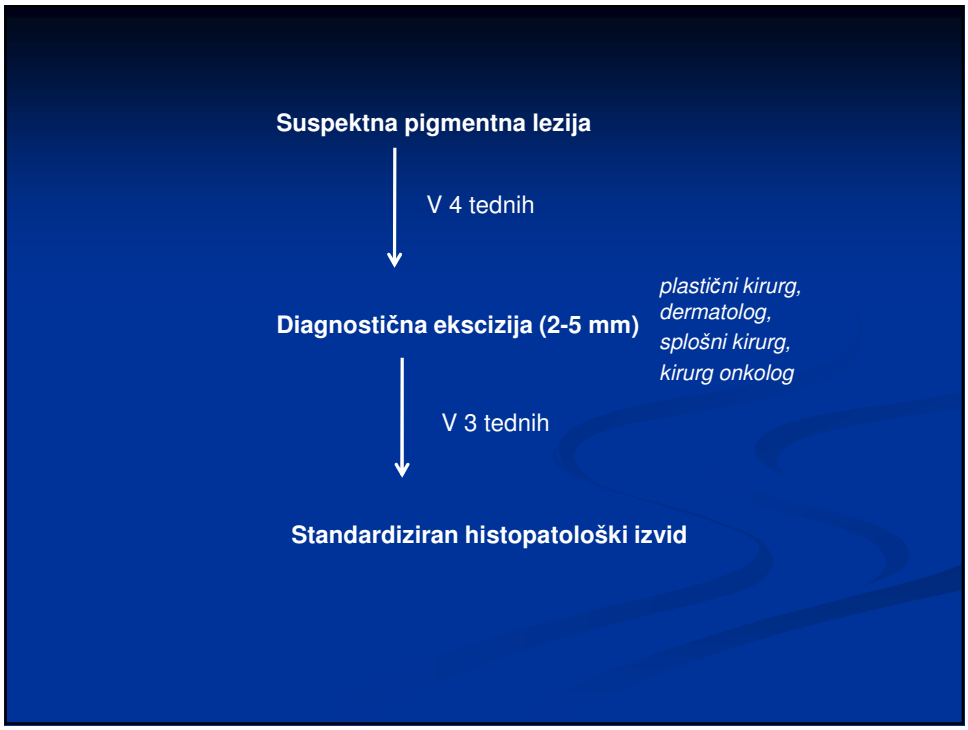
☺

Melanom klinična pot

Marko Hočevar, Janja Ocvirk, Primož Strojan, Tomi Bremec, Tanja Ručigaj, Barbara Perić, Boštjan Luzar, Martina Reberšek, Marko Boc, Jože Pižem, Katarina Karner

Klinična pot – zakaj?

- definiramo optimalno zdravljenje
  - Kaj je potrebno narediti?
  - Kdo naj naredi?
  - Kako hitro?
- spremljamo primernost posamičnih postopkov zdravljenja
- merimo rezultate zdravljenja



Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
0	In situ melanom	Kompletni pregled kože *Dermatolog (ob prvi kontroli)*	Široka ekscizija (5mm) v 3 mesecih *Plastični kirurg, dermatolog, splošni kirurg, kirurg onkolog*	Ni potrebno	Lokoregionalno *kirurg* 1x po eksciziji v 1. mesecu Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	>95%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
IA	T1a < 0,8 mm brez ulceracije	Kompletni pregled kože *Dermatolog (ob prvi kontroli)* Klinični pregled regionalnih bezgavk *Plastični kirurg, dermatolog, splošni kirurg, kirurg onkolog* Ob simptomih in znakih: rtg pc UZ: bezgavčne lože trebuha Citološka punkcija	Široka ekscizija (1 cm) v 3 mescih *Plastični kirurg, dermatolog, splošni kirurg, kirurg onkolog*	Ni potrebno	Lokoregionalno *kirurg* 1x po eksciziji v 1. mesecu Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	95%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
IB	T1b 0,8-1,0 mm brez ulceracije < 0,8 mm ulceracija ali T2a >1,0–2,0 mm brez ulceracije	Kompletni pregled kože *Dermatolog (ob prvi kontroli)* Klinični pregled regionalnih bezgavk *Kirurg onkolog* Ob simptomih in znakih: rtg pc UZ: bezgavčne lože trebuha Citološka punkcija	Široka ekscizija (1-2 cm) SLNB v 3 mesecih po diagnozi *Kirurg onkolog* Pozitivna SLNB glej Stadij III	Ni potrebno	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *Kirurg onkolog (prvo leto)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	89-91%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
IIA	T2b >1,0–2,0 mm ulceracija T3a >2,0-4,0 mm brez ulceracije	Kompletni pregled kože *Dermatolog (ob prvi kontroli)* Klinični pregled regionalnih bezgavk *Kirurg onkolog* Ob simptomih in znakih: rtg pc UZ: bezgavčne lože trebuha Citološka punkcija	Široka ekscizija (2 cm) SLNB v 3 mesecih po diagnozi *Kirurg onkolog* Pozitivna SLNB glej Stadij III	Ni potrebno	Lokoregionalno 3-4 mesece prvi 2 leti, 6 mesecev 3.-5. leto *Kirurg onkolog (prvi dve leti)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	77-78%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
IIB	T3b >2,0-4,0 mm ulceracija T4a > 4,0 mm brez ulceracije	Kompletni pregled kože *Dermatolog (ob prvi kontroli)* Klinični pregled regionalnih bezgavk *Kirurg onkolog* Ob simptomih in znakih: rtg pc UZ: bezgavčne lože trebuha Citološka punkcija	Široka ekscizija (2 cm) SLNB v 3 mesecih po diagnozi *Kirurg onkolog* Pozitivna SLNB glej Stadij III	Ni potrebno ali IFN v 2 mesecih *internist onkolog*	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *kirurg onkolog (5 let)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	63-67%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
IIC	T > 4,0 mm ulceracija	Kompletni pregled kože *Dermatolog (ob prvi kontroli)* Klinični pregled regionalnih bezgavk *Kirurg onkolog* Ob simptomih in znakih: rtg pc UZ: bezgavčne lože trebuha Citološka punkcija	Široka ekscizija (2 cm) SLNB v 3 mesecih po diagnozi *Kirurg onkolog* Pozitivna SLNB glej Stadij III	Ni potrebno ali IFN v 2 mesecih *internist onkolog*	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *kirurg onkolog (5 let)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	45%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
III A	T1a/b-T2a N1a/2a	Razmislimo o PET-CT Določitev BRAF statusa iz metastaze (primernega tumorja)	Radikalna limfadenektomia v 2-4 tednih *ali* *aktivno spremljanje (UZ regionalnih bezgavk na 3-12 mesecev)* *Kirurg onkolog*	↓ rizični (<1mm) IFN/nič *↑ rizični (>1mm) BRAF mutirani BRAF+MEK inhibitor.* *BRAF nemutirani ↑dozni Ipilimumab 3 leta** *Nivolumab 1 leto** v 2 mesecih *internist onkolog*	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *kirurg onkolog (5 let)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	69%

* Po razvrstitvi na listo zdravil

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
III B	T1a/b-T2a N1b/c ali N2b T2b-3a N1a-2b	PET-CT z/brez MR možganov Namesto PET-CT lahko CT toraksa, abdomna in medenice s kontrastom V 4 tednih do začetka zdravljenja Določitev BRAF statusa iz metastaze (primernega tumorja)	Radikalna limfadenektomia ali ILP ali radikalna ekscizija *Kirurg onkolog* *Obsevanje* *Radioterapevt* *Sistemsko zdravljenje* *Internist onkolog*	Obsevanje v 6 tednih: +multiple bezgavke (≥1-3) Velikost bezgavk ≥3-4 cm Perikapsularna/invazija v sosednji organ Regionalni re-relaps *Radioterapevt* *BRAF mutirani* *BRAF+MEK inhibitor** *BRAF nemutirani* *↑dozni Ipilimumab 3 leta** *Nivolumab 1 leto* v 2 *mesecih *internist*	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *kirurg onkolog (5 let)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	45%

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Adjuvantno zdravljenje	Kontrolni pregledi	5-letno preživetje
III C III D	T1a-T3a N2c/N3a/b/c T3b/4a N≥1 T4b N1a-2c T4b N3a/b/c	PET-CT z/brez MR možganov Namesto PET-CT lahko CT toraksa, abdomna in medenice s kontrastom V 4 tednih do začetka zdravljenja Določitev BRAF statusa iz metastaze (primernega tumorja)	Radikalna limfadenektomia ali ILP ali radikalna ekscizija *Kirurg onkolog* *Obsevanje* *Radioterapevt* *Sistemsko zdravljenje* *Internist onkolog*	*BRAF mutirani* *BRAF+MEK inhibitor** *BRAF nemutirani* *↑dozni Ipilimumab* 3 leta* *Nivolumab ali pembrolizumab* v 2 mesecih *internist onkolog*	Lokoregionalno 3-4 mesece prvi 2leti, 6 mesecev 3.-5. leto *kirurg onkolog (5 let)* Ostala koža *dermatolog* 2x letno prvih 5 let, nato 1x letno do konca življenja 1. obravnava 3-6 mesecev po eksciziji	30 %

* Po razvrstitvi na listo zdravil

Stadij	Opis	Diagnostična obdelava	Zdravljenje	Kontrolni pregledi	5-letno preživetje
IV	Katerikoli T Katerikoli N M1	Citološka punkcija PET-CT z/brez MR možganov Namesto PET-CT lahko CT toraksa, abdomna in medenice s kontrastom Določitev BRAF statusa iz metastaze (primernega tumorja)	Sistemsko zdravljenje Kemoterapija Imunoterapija (pembrolizuma ali nivolumab ali ipilimumab) Tarčno zdravljenje (BRAF * MEK inh) Obsevanje Kirurgija ali Simptomatsko zdravljenje	Ob simptomih in znakih	<5 %

KLINIČNI REGISTER KOŽNEGA MELANOMA
Register raka Republike Slovenije

izr. prof. dr. Vesna ZADNIK, dr. med., spec.

Onkološki inštitut Ljubljana
Epidemiologija in register raka
www.slora.si
vzadnik@onko-i.si

Register raka Republike Slovenije

Služba za zbiranje in obdelavo podatkov o vseh novih primerih raka (incidenci) in o preživetju bolnikov z rakom.

- Na Onkološkem inštitutu Ljubljana: Ur. l. RS, št. 47/15
- Prijavnice, ki jih pošiljajo iz bolnišnic in diagnostičnih centrov, izjemoma iz ambulant osnovnega zdravstvenega varstva
- Podatki o osebi, bolezni in zdravljenju

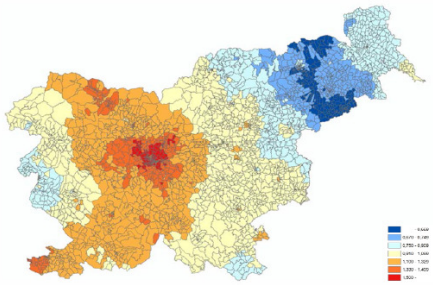
MELANOM

- Lokacija telesa
- Histološke različice
- TNM, Breslow, Clark
- KRG (varovalna b., rob, ustanova)
- Sistemsko (KT, biološka - da/ne)
- RT (da/ne)
- Datumi (incidenca, preživetje)

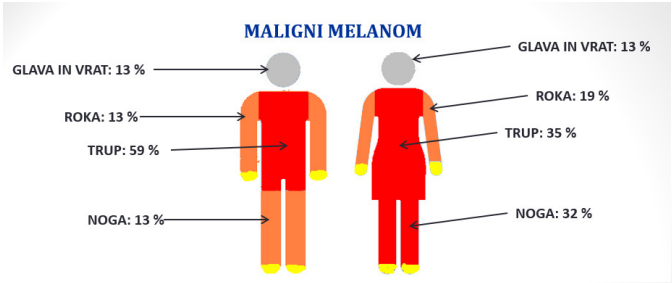
Državni program obvladovanja raka: SPREMLJANJE BREMENA RAKA

VZPOSTAVITEV KLINIČNIH REGISTROV
za izbrane vrste rakov se razširi nabor podatkov, ki jih spremlja Register raka Republike Slovenije, tako, da le-ti omogočajo pripravo kazalnikov za vrednotenje kakovosti obravnave onkološkega bolnika:

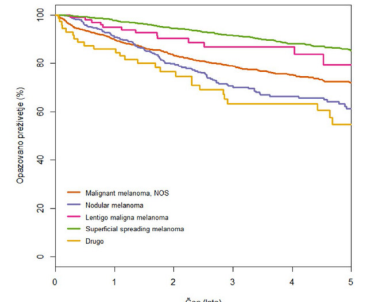
- 5 lokacij … MELANOM!
- Aktivno zbiranje podatkov
- Sprotni podatki (zamik do 1. leta)

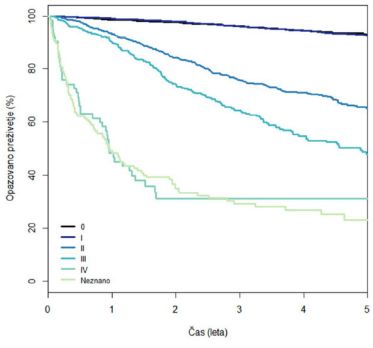


Zemljevid kožnega melanoma po voliščih; prostorsko glajeni standardizirani količniki incidence, Slovenija 2005-2014.

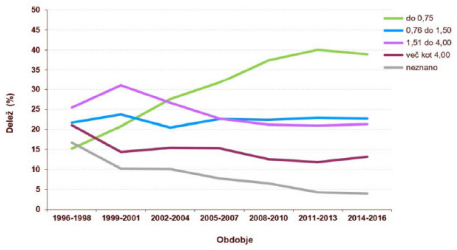


Slika 7: Kaplan - Meierjeva krivulja opazovanega preživetja bolnikov z invazivnim kožnim melanomom po histološki vrsti, Slovenija 2011–2016.

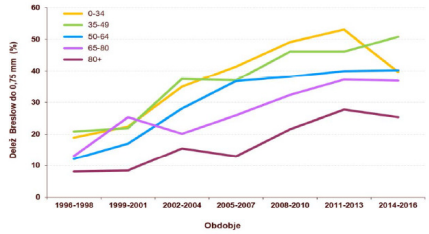




Slika 4: Deleži debeline tumorja po Breslowu (mm) pri invazivnih kožnih melanomih (C43), Slovenija 1996–2016.



Slika 5: Deleži debeline tumorja po Breslowu do 0,75 mm pri invazivnih kožnih melanomih (C43) po 15-letnih starostnih skupinah, Slovenija 1996–2016.



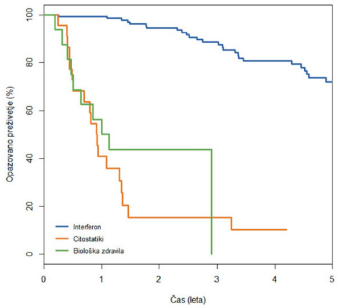
Bolnica ugotovitve	2011–2016	
	Št.	%
Splošna bolnišnica Celje	430	9,66
Splošna bolnišnica Jesenice	302	6,78
Univerzitetni klinični center Ljubljana	1413	31,74
Onkološki inštitut Ljubljana	166	3,73
Univerzitetni klinični center Maribor	393	8,83
Splošna bolnišnica Murska Sobota	129	2,90
Splošna bolnišnica Novo mesto	203	4,56
Sanatorij Rožna dolina	31	0,70
AKD D.O.O.	119	2,67
DERMATOLOGIJA BARTENJEV - ROGL D.O.O.	230	5,17
VOK MARKO-DERMATOVENEROLOŠKA ORDINACIJA	131	2,94
Estetika Fabijan	64	1,44
Zdravlišče Rogaška - Zdravstvo d.o.o.	58	1,30
JANEŽIČ TOMAŽ,DR.MED.	41	0,92
ARSDERMA D.O.O.	41	0,92
Ostale zasebne ordinacije	158	3,55
Zdravstveni dom	104	2,34
Ostale ustanove**	439	9,86
SKUPAJ	4452	100,00

Vrsta 1. zdravljenja	2011–2016	
	Št.	%
Brez zdravljenja	60	1,9
Kirurgija in sistemska terapija	141	4,3
Kirurgija in radioterapija	150	4,6
Kirurgija, radioterapija in sistemska terapija	17	0,5
Radioterapija in sistemska terapija	5	0,2
Kirurgija (izključno)	2842	87,6
Sistemska terapija (izključno)	12	0,4
Radioterapija (izključno)	16	0,5
Skupaj	3243	100

Tabela 10a: Število in deleži bolnikov z invazivnim kožnim melanomom po vrsti sistemske terapije v okviru prvega zdravljenja, Slovenija 2011–2016.

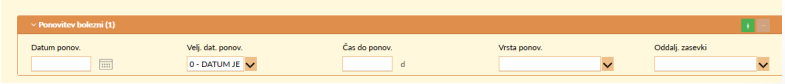
Vrsta sistemske terapije v okviru prvega zdravljenja	2011		2012		2013		2014		2015		2016		2011–2016	
	Št.	%	Št.	%	Št.	%	Št.	%	Št.	%	Št.	%	Št.	%
Interferon	31	75,6	24	82,8	20	74,1	18	81,8	20	83,3	24	75,0	137	78,3
Citostatiki	10	24,4	5	17,2	4	14,8	2	9,1	0	0,0	1	3,1	22	12,6
Biološka zdravila	0	0	0	0	3	11,1	2	9,1	4	16,7	7	21,9	16	9,1
Skupaj sistemska terapija	41	100	29	100	27	100	22	100	24	100	32	100	175	100

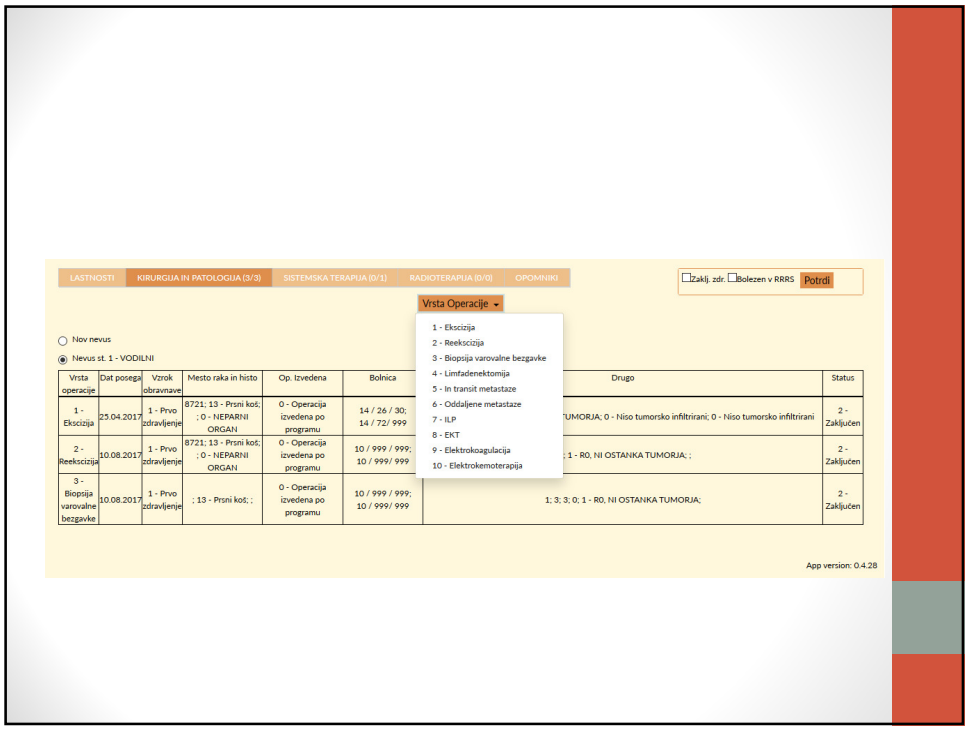
Slika 11: Kaplan - Meierjeva krivulja opazovanega preživetja bolnikov z invazivnim kožnim melanomom po vrsti sistemske terapije, Slovenija 2011–2016.

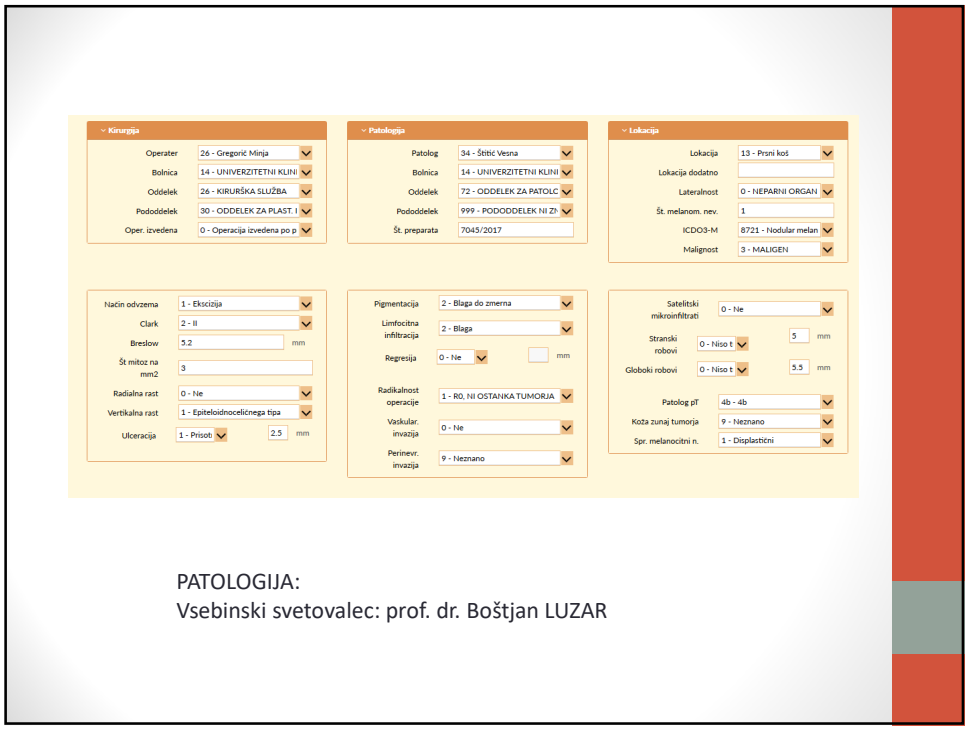


RRRS-KRMel:
KLINIČNI REGISTER MELANOM
Register raka Republike Slovenije

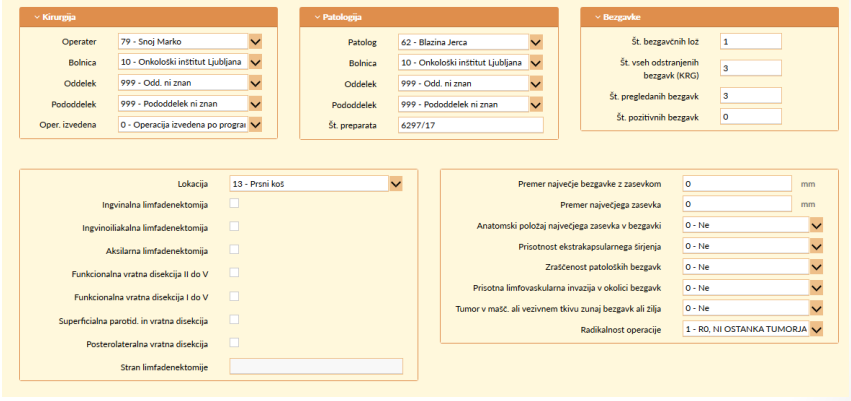
- Razširjen nabor podatkov:
  - HISTOLOŠKE ZNAČILNOSTI
  - ZAMEJITEV, BRAF
  - KIRURGIJA – re-ekscizije, operaterji
  - SISTEMSKA TERAPIJA – vrsta, doze, odziv



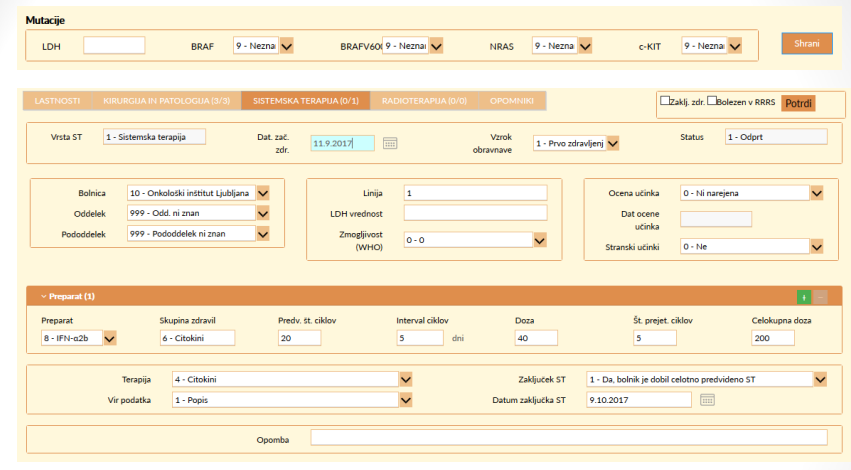




PATOLOGIJA:
Vsebinski svetovalec: prof. dr. Boštjan LUZAR



KIRURGIJA:
Vsebinska svetovalca: prof. dr. Marko HOČEVAR, dr. Barbara PERIČ



SISTEMSKO ZDRAVLJENJE:
Vsebinski svetovalec: prof. dr. Janja OCVIRK

RRRS-KRMel:
KLINIČNI REGISTER MELANOM
Registra raka Republike Slovenije

- Testni primer kliničnega registra
- Vzpostavljen v okviru OIL projekta na RRRS leta 2017
- Podatki za leto 2016 in naprej
- Aktivna registracija: deljeno papirno-elektronsko zbiranje podatkov
- Kazalniki obravnave na voljo 1 leto po diagnozi in naprej

14. ŠOLO MELANOMA SO PODPRLE NASLEDNJE DRUŽBE:

NOVARTIS

ROCHE

MSD

SANOFI GENZYME

SERVIER

AMGEN

EWOPHARMA

ELI LILLY

PFIZER

TEVA