De aanpak van hersenmetastasen van het melanoom anno 2024

Prof. dr. Jeroen Mebis
Jessa Ziekenhuis Hasselt

MELANOOM STUDIEDAG 2024

10 JAAR HOOP

Melanoompunt is een volledig onafhankelijke patiëntenvereniging voor en door melanoompatiënten en hun naastbetrokkenen. Met de gewaardeerde steun van :

Met steun van Kom op tegen Kanker
ichting tegen Kanker
Pierre Fabre
MSD
Bristol Myers Squibb
NOVARTIS
Eau Thermale Avène Laboratoire Dermatologique
sanofi

Hersenmetastasen bij het maligne melanoom

JEROEN MEBIS

MEDISCH ONCOLOOG

JESSAZIEKENHUIS,UHASSELT

LIMBURGS ONCOLOGISCH CENTRUM

Hersenmetastasen bij het maligne melanoom

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Disclosures

Scientific grants: Pierre Fabre, Astra Zeneca, Gilead, Sanofi, MSD, GSK

Consultancy fees: Seagen, Amgen, BMS, Ocare Pharma

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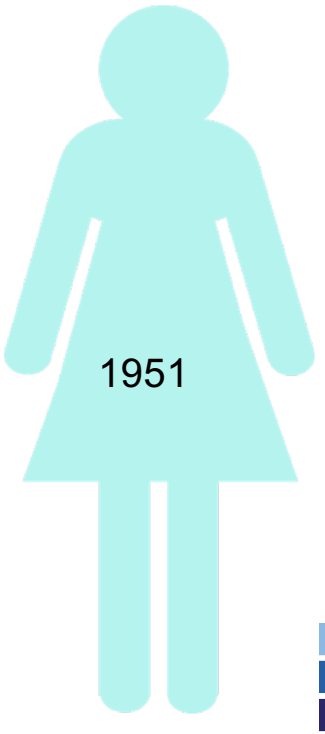
Casus

Initially presented in 11/2012

- SSM left leg: Breslow 1.2mm, Clark IV
- Broad excision with negative sentinel node



Medical history

- Arthrosis hip
- Nefrolithiasis

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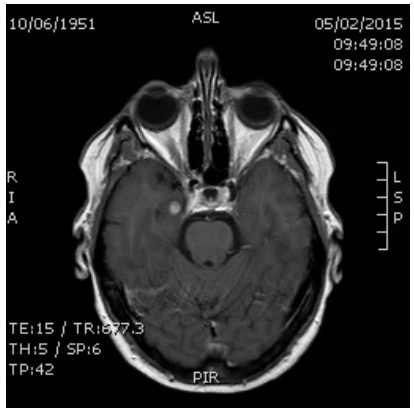
10/2013 Relapse locally in skin transplant

- Broad excision 7.5 cm x 4,8 cm x 1 cm
- NGS: BRAF wild type, NRAS mutation

07/2014 Metastatic lymph node left groin

- groin complete lymph node extirpation
- 3/13 lymph nodes metastatic involvement

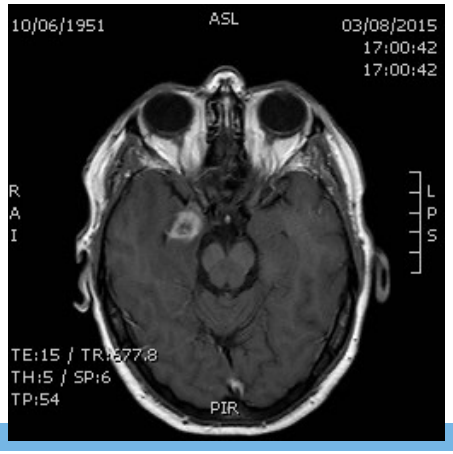


02/2015 vomiting and headache: Solitary brain metastasis parasellair right

LIMBURGS ONCOLOGISCH CENTRUM

Stereotactic radiosurgery 18 Gray

08/2015 new brain met left frontal: refusal of surgery or RT



ONCOLOGISCH CENTRUM

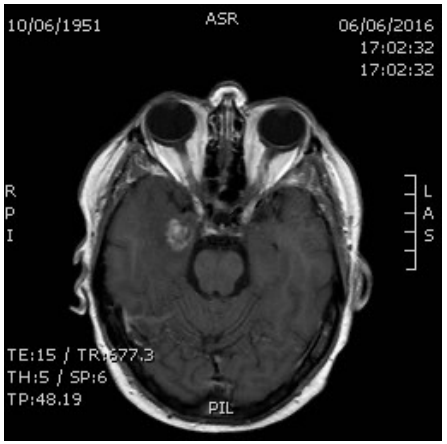
11/2015 brain metastasis frontal left progressive and more symptoms

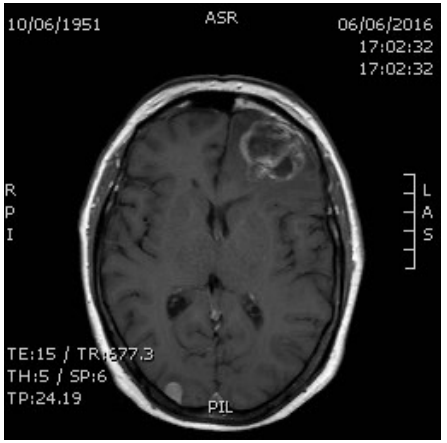
Refusal surgery, Stereotactic radiosurgery 16 Gray

03/2016: bleeding in meta left frontal: start Medrol

LIMBURGS ONCOLOGISCH CENTRUM

06/2016 new asymptomatic metastatic brain lesion right occiput: SRS 20 Gray





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09/2016 progression frontal left metastasis with edema and dysarthria, with right occipital progressive disease

- Resection frontal metastasis: pathology metastatic melanoma, NRAS mutation

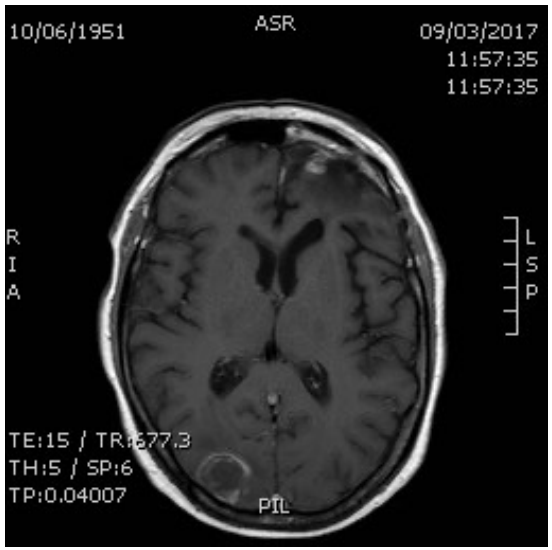
10/2016: stable disease

- Partial adrenal insufficiency: start Medrol, intolerance hydrocortisone

12/2016: relapse in operation zone with dural thickening and progression of metastasis right occiput

LIMBURGS ONCOLOGISCH CENTRUM

Symptomatic brain mets: start Nivolumab/ipilimumab in 1/2017



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Patient developed 3 months after initiation of treatment

- Vomiting, confusion, fever and anorexia
- Brain imaging : response of brain mets
- Hyponatremia
- Adrenal insufficiency
  - Start Hydrocortison
  - Solucortef once IV
- Asymptomatic hyperthyroidism

- Evaluation 5/2017: central response, no new lesions on pet
- Evaluation 8/2017: stable disease

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Het probleem: HM bij melanoma

Frequentie: 5000-7000 ptn/jaar

10% van alle hersenmeta's

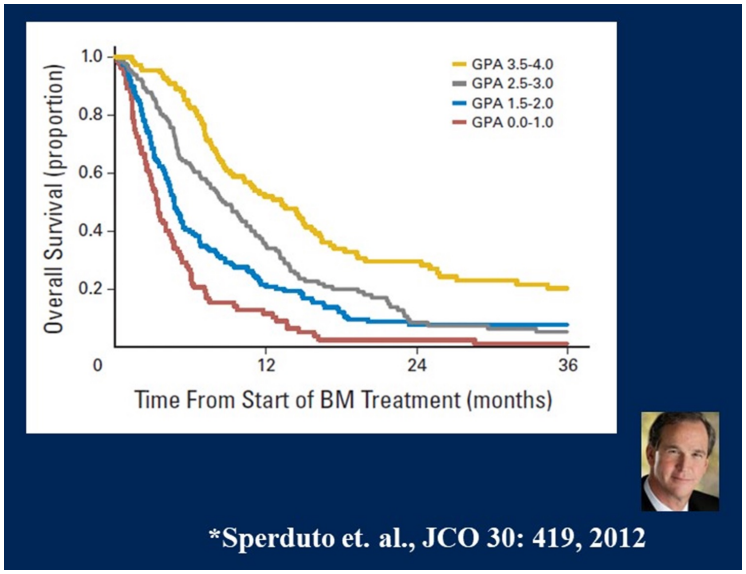
70% bij autopsie; 1/3 alle nieuwe stadia IV

Incidentie lijkt af te nemen: effect IO?

Prognose:

- Leeftijd, KPS, extracraniale ziekte, aantal mets
- EG 3-12 maanden in melanoom ptn

Enkel een 840 pts in klinische studies in MBM



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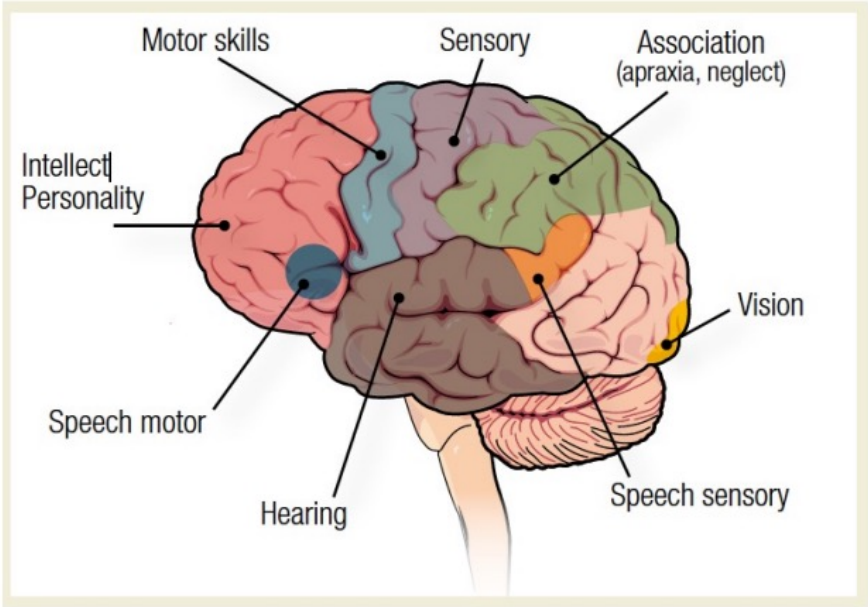
CLINICAL PRESENTATION

Clinical presentation is highly variable, depends on the tumour localisation and size

- Symptoms of increased intracranial pressure
- Seizures
- Focal neurological signs
  - Aphasia
  - Paraesthesia
  - Hemiparesis
  - Visual disturbances
- Mood and personality changes



Symptomatisch: zelden herstel normale neurologische functie

LIMBURGS ONCOLOGISCH CENTRUM

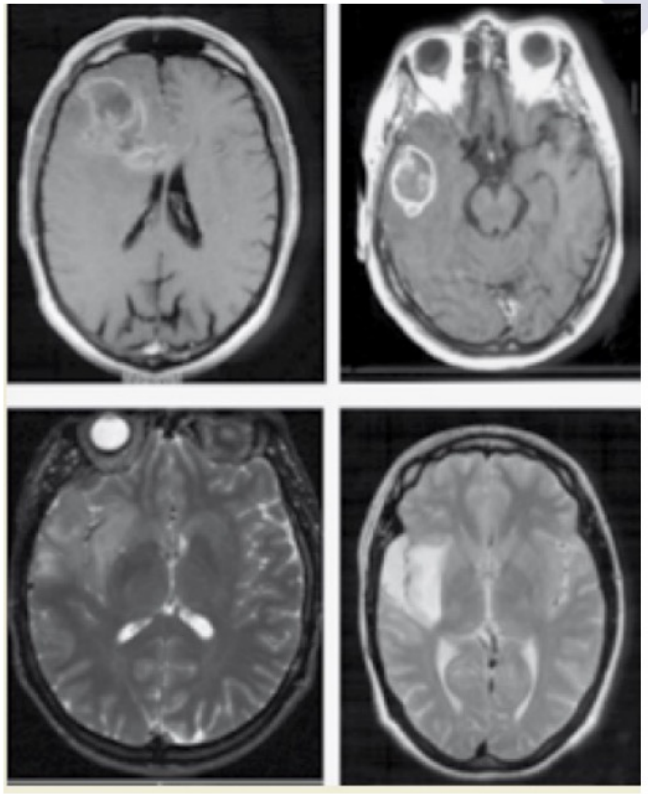
DIAGNOSIS

MAGNETIC RESONANGE IMAGING (MRI)

Brain MRI, including:

- T2- weighted,
- T2- weighted fluid-attenuated inversion recovery (FLAIR) sequences and
- 3D T1-weighted sequence

before and after application of a gadolinium-based contrast agent, is the **diagnostic gold standard** to detect a brain tumour



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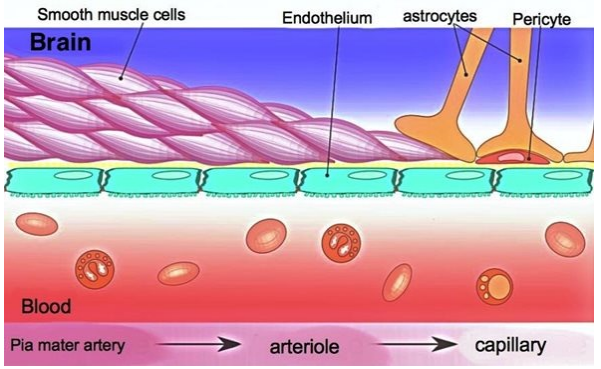
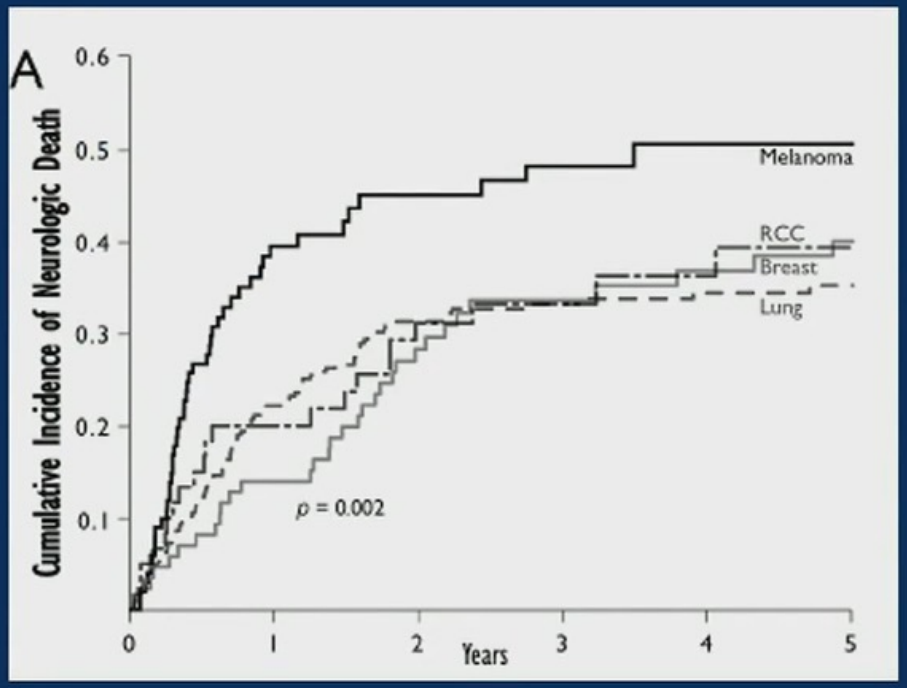
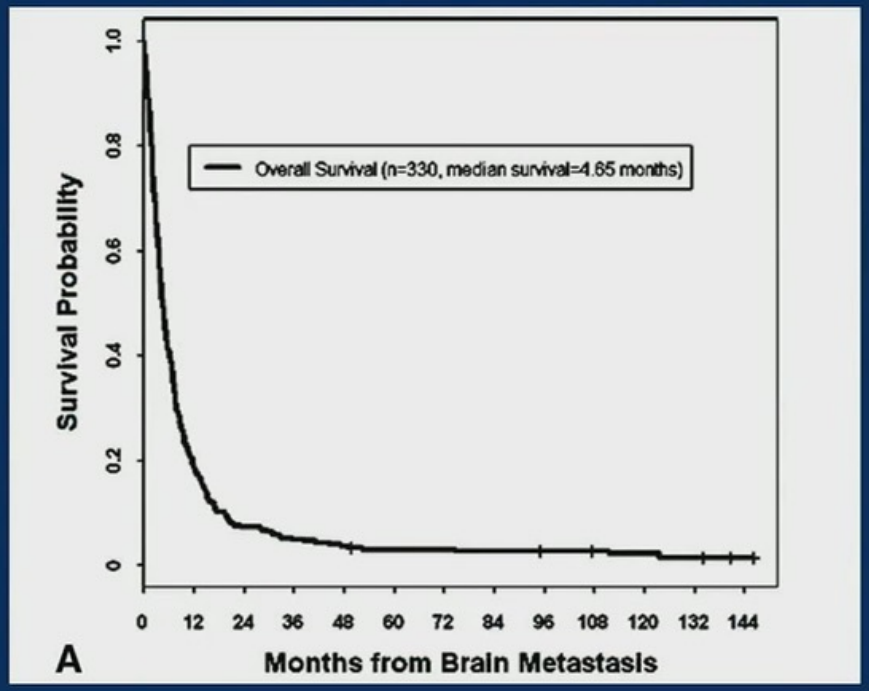
Risicofactoren HM

- Man, >60 jaar
- Melanomen op romp, HeN, scalp
- Invasiediepte en ulceratie
- Acraal, lentigineus, nodulair
- >3 LN+
- Verhoogd LDH
- Viscerale meta's
- BRAFmt-NRASmt



Brain Metastases in Melanoma





1. Cohen JV, Tawbi, HA. *et al. PCMR* 2016: 29: 627-642. 2. Jakob JA *et al., Cancer* 2012: 118: 4014-4023. 3. Davies M *et al. Cancer* 2011: 117:1687–96.
4. McTyre ER et al., Neuro-Oncol, 2017: 19(4),558-566.

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Prognose bepaling hersenmetas

Table 3

Survival of patients grouped by the VTS score

VTS score	*n* = 110	median OS (months)	logrank pairwise
0–1	46	5.1	**vs. 1.5: 0.001**
			vs. 2: 0.0001
1.5	36	18.9	**vs. 2: 0.03**
2	28	34.5	

Open in a separate window

Abbreviations: *VTS* Volume-timing-systemic therapy, *OS* Overall survival

Table 4

Awarded points for VTS score

	0 points	0.5 points	1 point
Cumulative brain metastases volume	> 1.5 cc	< 1.5 cc	
Timing	synchronous	metachronous	
Systemic treatment	targeted therapy		immunotherapy

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Behandelingen:

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Behandelingen:

Steeds multidisciplinair!

Factoren te bekijken:

- Kenmerken hersenmets: aantal, locatie, klachten
- Uitgebreidheid extra-craniële ziekte
- WHO, co-morbiditeiten
- BRAF status
- Blootstelling aan intracraniële therapie en efficiëntie

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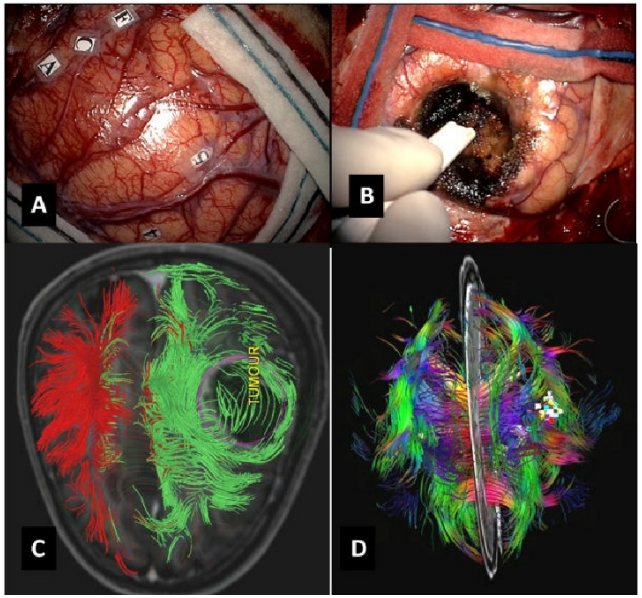
Heelkunde

Pt selectie: Goede PS, minimale comorbiditeiten, beperkt aantal mets in niet-eloquente regio, of >3cm lesies met oedeem of herniatie

Vaak + post-op SRS



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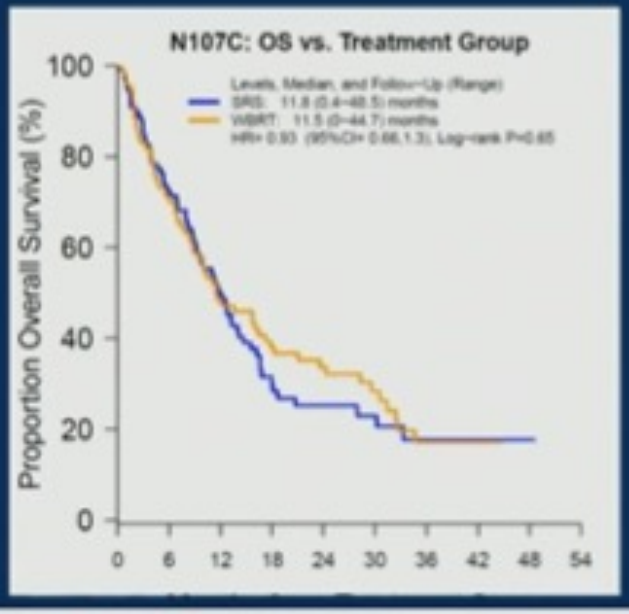
Postoperative radiotherapy: WBRT or SRS?

With limited intracranial mets, postop single-fraction SRS offers similar OS but improved cognitive outcomes vs. conventional WBRT



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Brown Lancet Oncol 2017

ASCO KNOWLEDGE CONQUERS CANCER

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Heelkunde

- Snelste optie voor herstel neurologische functies
- Beste optie voor controle E
- Toegang tot weefsel
- HK als een brug naar immunotherapie

Risico's van craniotomie en narcose

7-28% risico op downstream LMS

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Radiotherapie

SRS: single-fraction vs hypofractionated SRS

- <5lesies; <3cm
- CCR 90-95%; rr 55 %
- Locale controle op 12 mnd: 68%
- Nadelen: laattijdige cognitieve problemen, radionecrose
- Combinatie met IO: sequentieel-concurrent?
- Geen combinatie met BRAF-MEKi : stop tot 3 d vooraf en tot 1 d na SRS

- WBRT: zelden nog gezien sequelae en invloed op QOL

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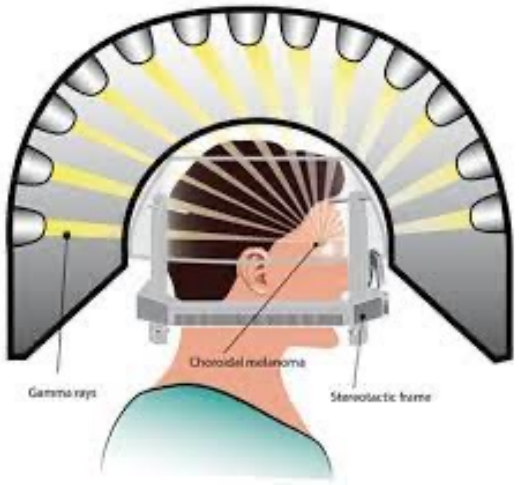
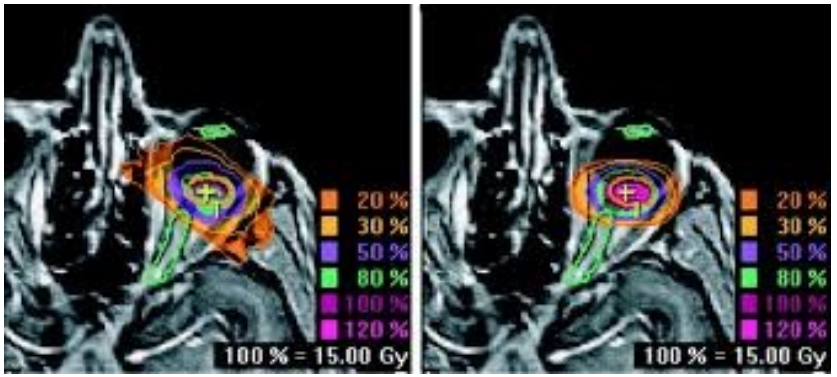
Radiotherapie





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Systeemtherapie

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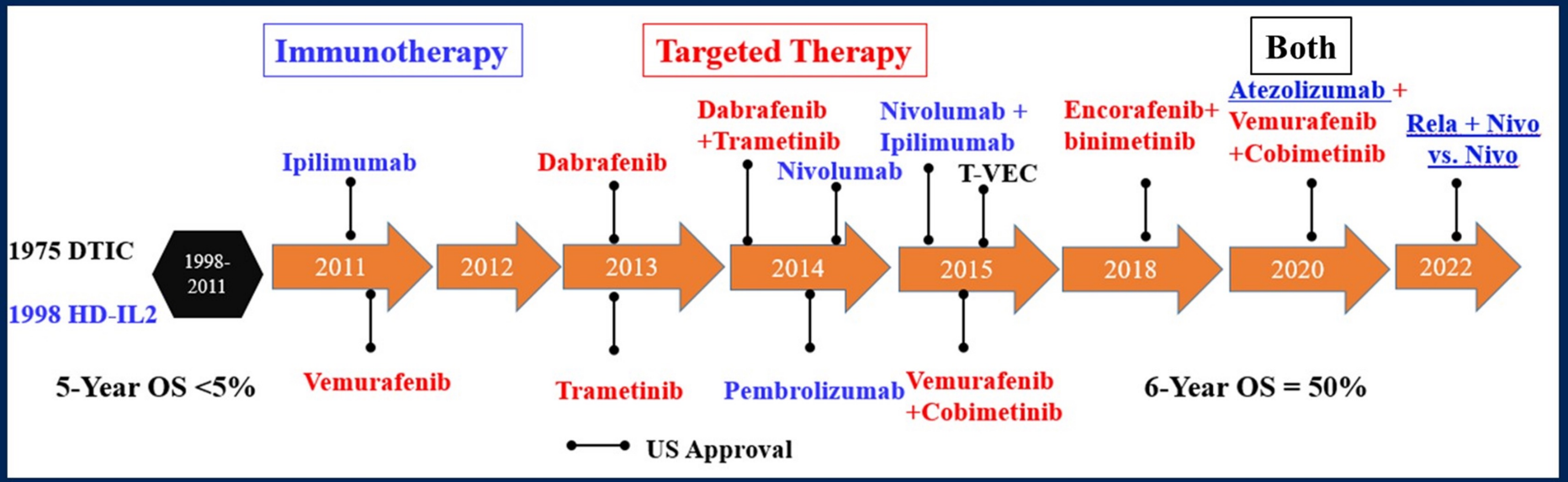
Approved Agents for Stage IV Melanoma



Pre-1998	Approvals w/o (+) randomized trials
1998-2011	No approvals
2011-2020	12 approvals

Slide modified, courtesy of Dr. Hussein Tawbi

Need to Treat More Patients with MBMs on Trials!

Pivotal Phase 3 Trials

Ipi+gp100	676
Ipi + DTIC	502
BRIM-3	645
BREAK-3	250
COMBI-v	704
COMBI-d	423
coBRIM	495
KEYNOTE-002	540
KEYNOTE-006	834
CheckMate-037	631
CheckMate-067	945
COLUMBUS	577
IMspire150	514
RELATIVITY-047	714
TOTAL	7,939

Phase 2 Trials in MBM

BREAK-MB	172
Vemurafenib	146
COMBI-MB	125
Ipi- CWG	72
NIBIT-M1	20
Pembro	18
CheckMate-204	119
ABC Collaboration	76
NIBIT-M2	27
Pembro + Bevacizumab	i.p.
Atez + Cobi + Vemu	65
TOTAL	840 (10.5%)

Slide modified from Dr. Hussein Tawbi: i.p. = in progress

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Immunotherapie

Ipilimumab

Activity in melanoma patients without brain mets
- → Response rate ~15%, 5 year OS ~20%

Melanoma patients with brain mets: Phase II trial
- Cohort A: Asymptomatic (n=51)
- Cohort B: Symptomatic, receiving corticosteroids on study initiation (n=21)

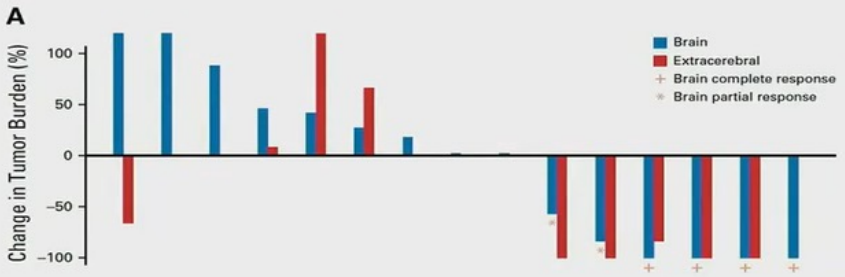
Outcome n (%)	Cohort A (n=51)	Cohort B (n=21)
CNS ORR	9 (18)	1 (5)
CNS disease control	12 (24)	2 (10%)
Median (OS)	7.0 mos	3.7 mos

Margolin K, et al. *Lancet Oncol.* 2012;13:459-465.

Pembrolizumab

Activity in melanoma patients without brain mets
- → Response rate ~40%, most responses > 2yrs

Phase II trial – melanoma & lung pts with brain mets:
- 18 melanoma patients
- ORR 22% (4 PR, 3 SD, and 7 PD)
- At medium f/u 38 months, median OS 17 months



Kluger, HM, et al. *J Clin Oncol.* 2019 Jan 1;37(1):52-60.

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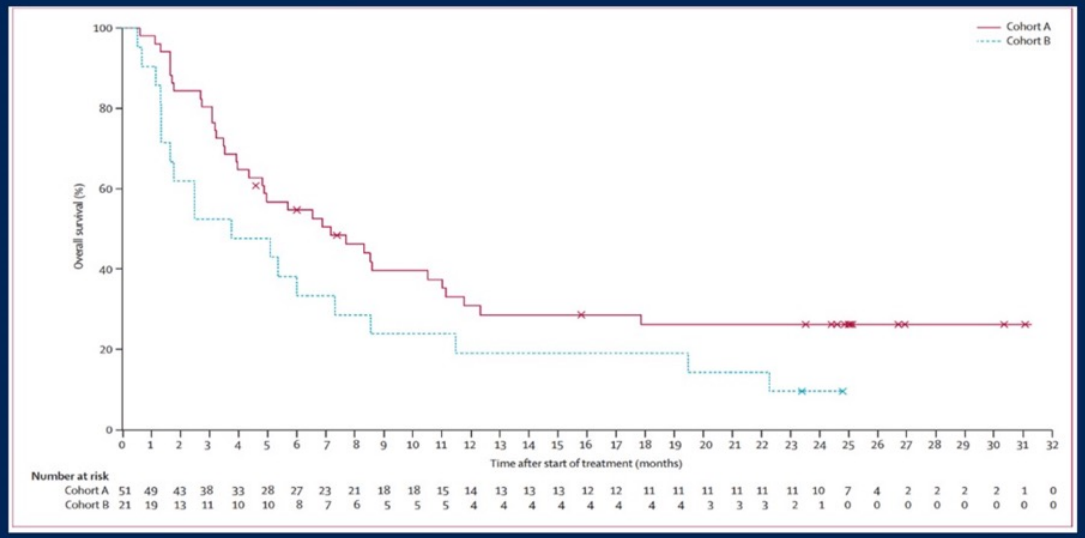
Phase 2 Study of Ipilumab (Ipi) in MBMs Prolongs Survival & Has Long Term Survivors



Outcome n (%) [95% CI]	Cohort A (n=51)	Cohort B (n=21)
CNS objective response	9 (18) [8–31]	1 (5) [0.1–24]
CNS disease control	12 (24) [13–38]	2 (10%) [1–30]
Median Overall Survival (OS)	7.0 mos	3.7 mos

- In melanoma pts without MBMs:
  - Response Rate ~ 15%
  - 5 yr. Survival ~ 20%
- Phase 2 MBM trial:
  - Cohort A: Asymptomatic, no corticosteroids (n=51)
  - Cohort B: Symptomatic and receiving corticosteroids (n=21)

Margolin K, et al. Lancet Oncol. 13:459, 2012

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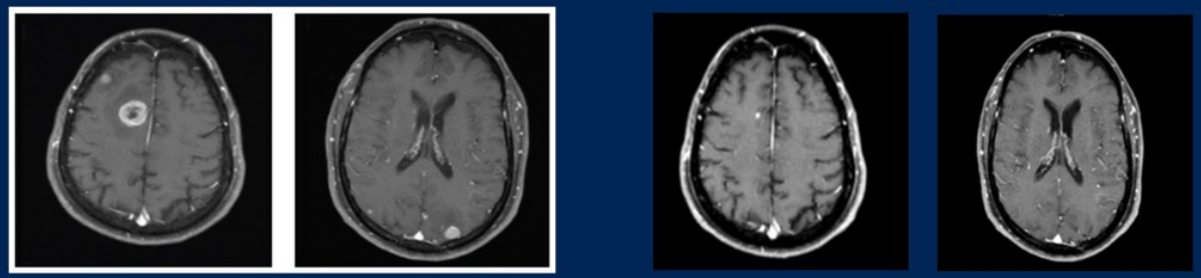
Checkpoint Inhibition with Ipilumumab & Nivolumab in Melanoma Brain Mets: ?Defer WBRT

Baseline **1 year**



Response to Treatment – All Patients (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

[a]Confirmed and unconfirmed progressive disease
[b]Includes unconfirmed responses
[c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.

Tawbi HA, Forsyth PA…Hodi S…Reardon DA et al., NEJM August 2018

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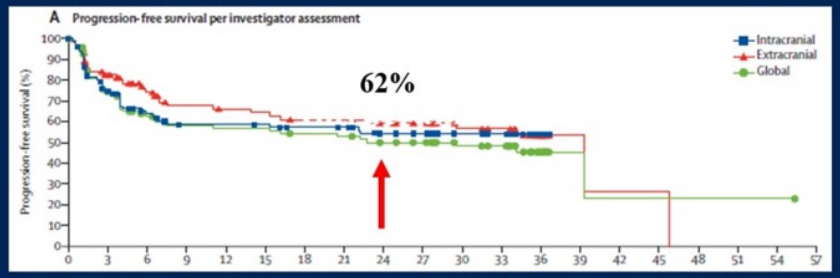
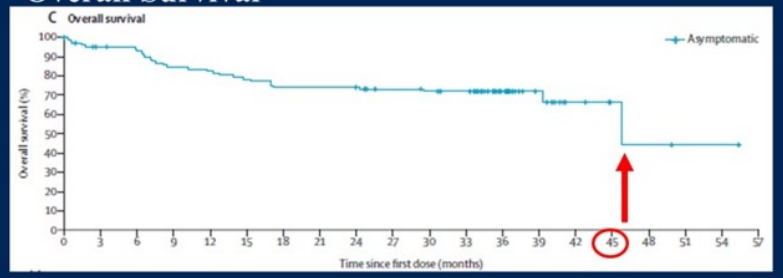
Asymptomatic Patients

Intracranial PFS



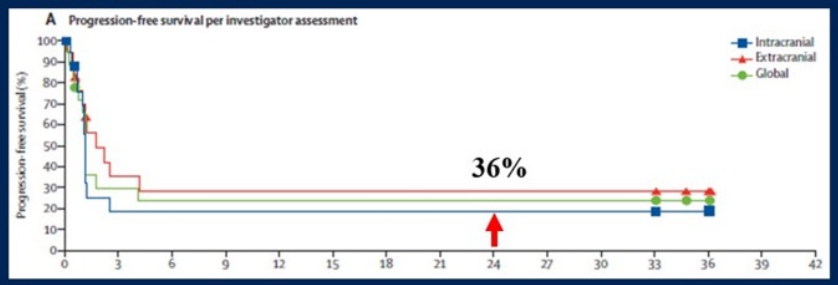
Overall Survival



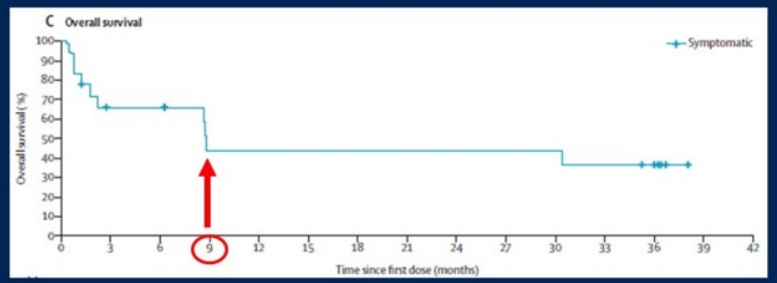
- PFS rates for extracranial and global disease were similar
  - Extracranial 24-month rates were 59% and 62% (BICR); 36-month rates were 53% and 62%
  - Global 24-month rates were 50% (INV) and 48% (BICR); 36-month rates were 45% and 48%

Symptomatic Patients

Intracranial PFS



Overall Survival



- PFS rates for extracranial and global disease were similar
  - Extracranial 24- and 36-month rates were 28% (INV) and 36% (BICR)
  - Global 24- and 36-month rates were 24% (INV) and 26% (BICR)

Tawbi HA et al., Lancet Oncology, 2021

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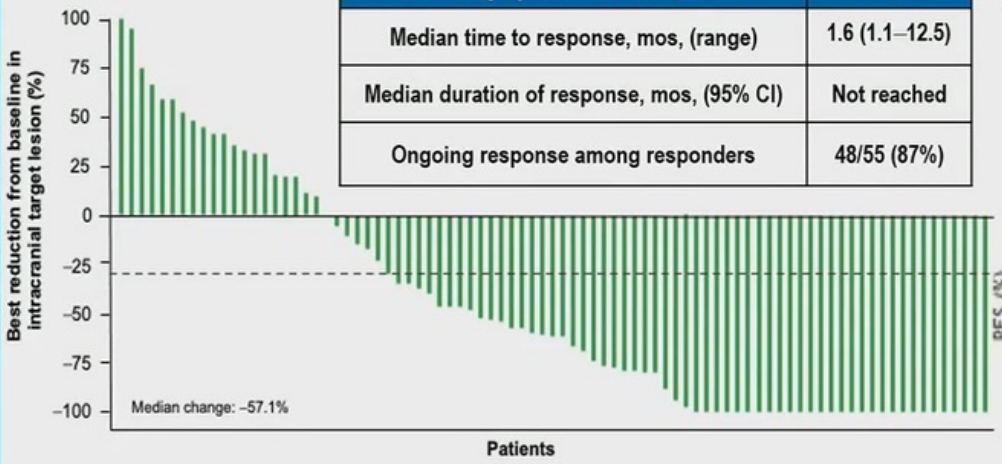
Combination Checkpoint Blockade in Melanoma Brain Mets

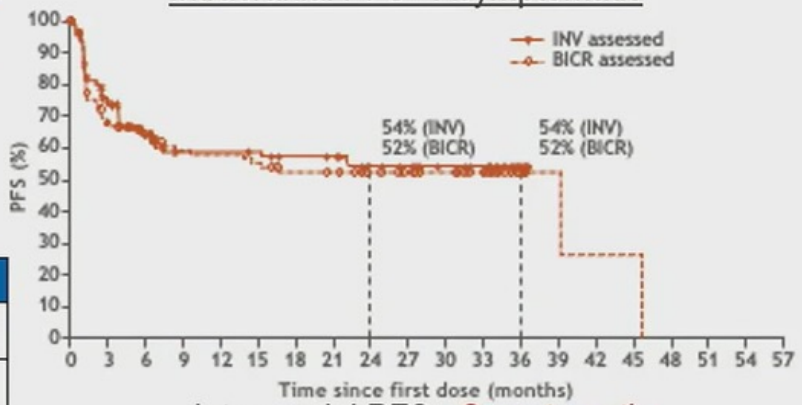
Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study

Hussein A Tawbi, Peter A Forsyth, F Stephen Hodi, Alain P Algazi, Omid Hamid, Christopher D Lao, Stergios J Moschos, Michael B Atkins, Karl Lewis, Michael A Postow, Reena P Thomas, John Glaspy, Sekwon Jang, Nikhil I Khushalani, Anna C Pavlick, Marc S Ernstoff, David A Reardon, Ragini Kudchadkar, Ahmad Tarhini, Caroline Chung, Corey Ritchings, Piyush Durani, Margarita Askelson, Igor Puzanov, Kim A Margolin

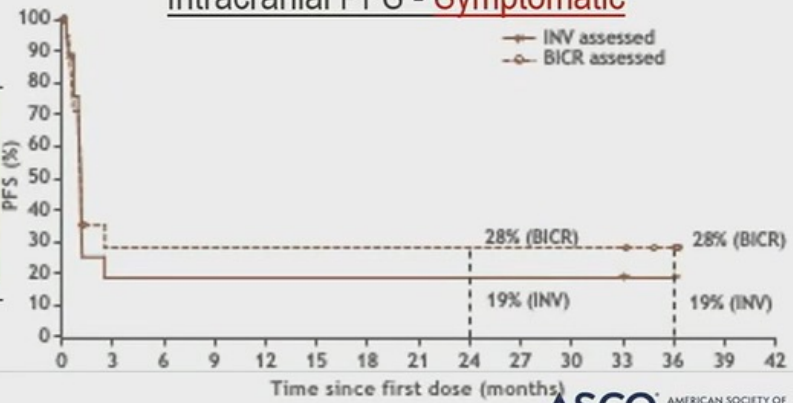
Asymptomatic Patients	N = 101
Median time to response, mos, (range)	1.6 (1.1–12.5)
Median duration of response, mos, (95% CI)	Not reached
Ongoing response among responders	48/55 (87%)



Intracranial PFS - Asymptomatic



Intracranial PFS - Symptomatic



Tawbi HA, et al. NEJM, 2018 Aug 23; Tawbi, H. et al, *Lancet Oncology, Nov 10, 2021.*

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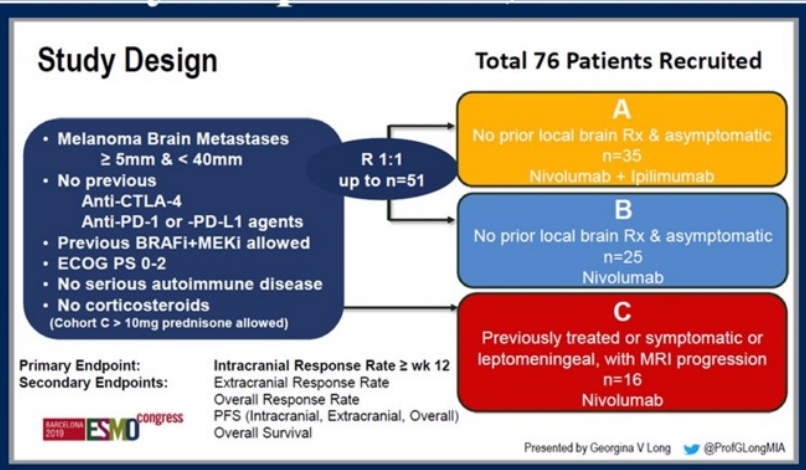
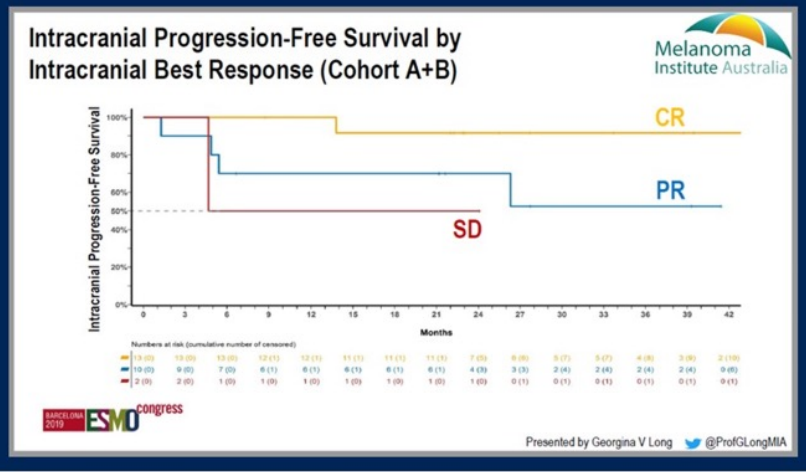
ABC Study of Ipi + Nivo; Similar Results



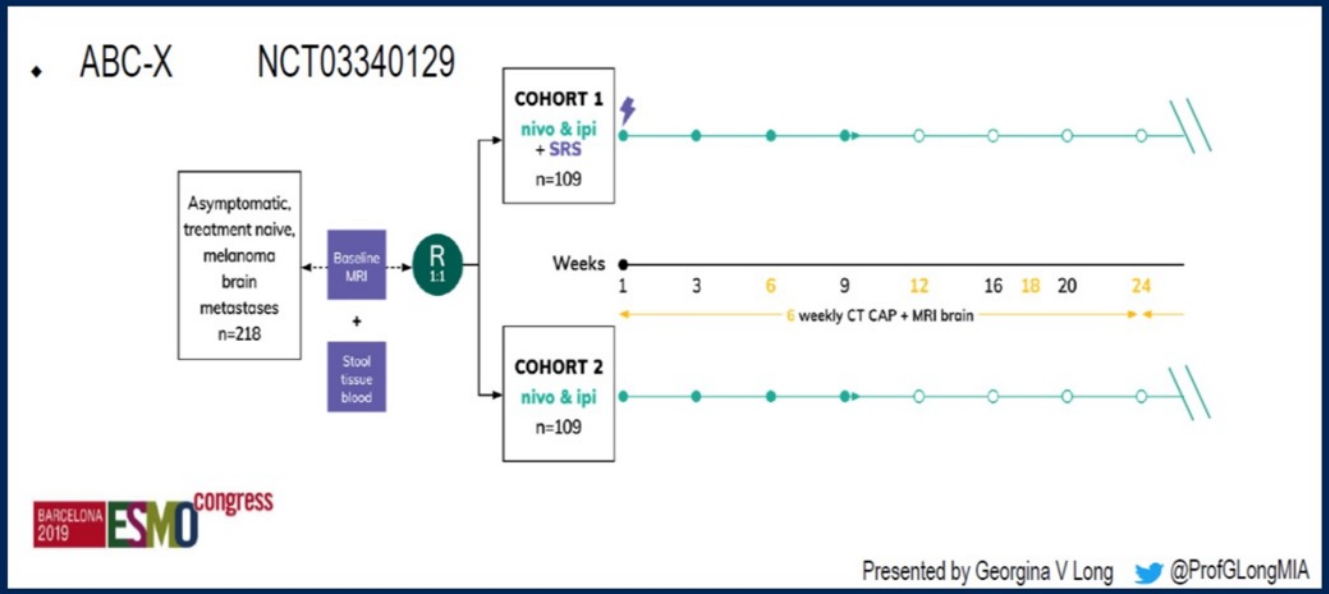


Courtesy Georgina V. Long et al.

LIMBURGS ONCOLOGISCH CENTRUM

Immunotherapy in MBMs: Still Not Good Enough!

- Ipi Nivo +/- SRS in progress in Australia (Dr. Georgina Long, PI)



Courtesy Georgina V. Long et al.

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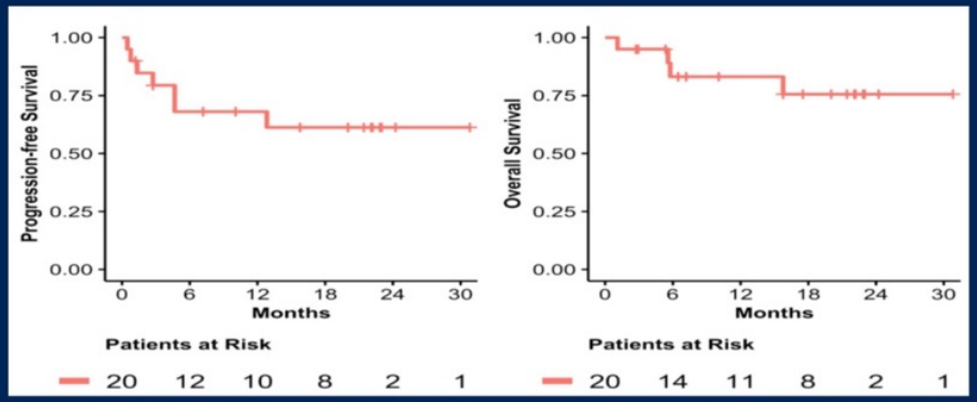
Phase 2 of Pembro + Avastin in Asymptomatic MBMs



Overall and Progression-free Survival of MBMs

- Prelim. response rate ?similar to Ipi + Nivo (N=20)
- Still accruing!

PIs: Harriet Kluger/Sarah Goldberg at Yale Intra-SPORE SNO abstract

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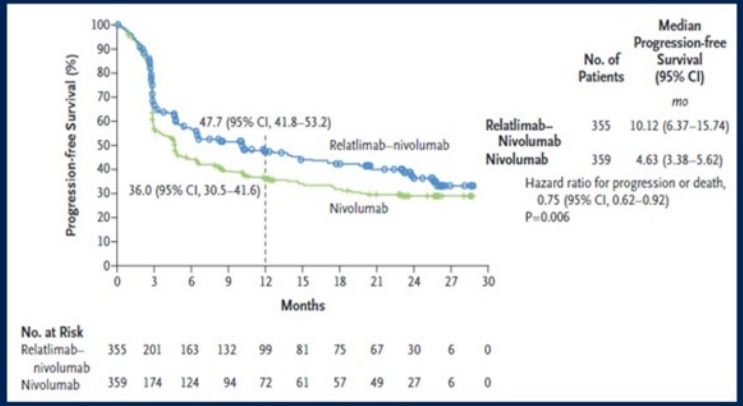
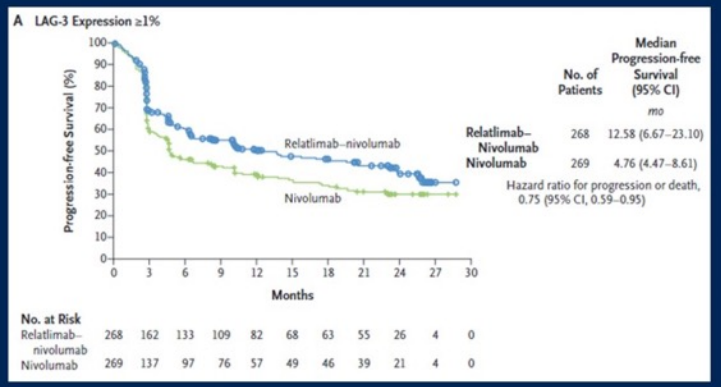
? New Immune Checkpoint Inhibitors for MBMs

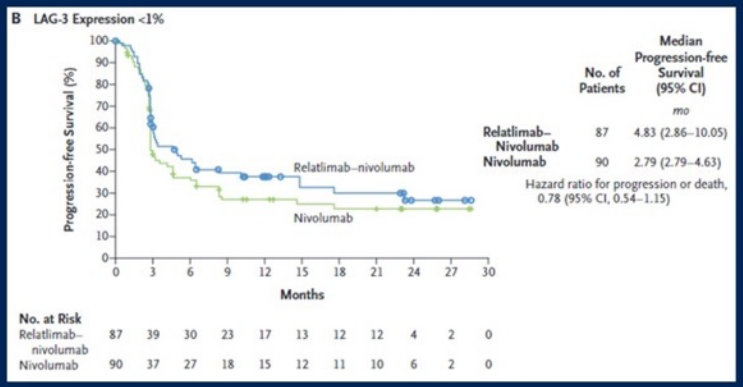
ORIGINAL ARTICLE

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Hussein A. Tawbi, M.D., Ph.D., Dirk Schadendorf, M.D., Evan J. Lipson, M.D., Paolo A. Ascierto, M.D., Luis Matamala, M.D., Erika Castillo Gutiérrez, M.D., Piotr Rutkowski, M.D., Ph.D., Helen J. Gogas, M.D., Christopher D. Lao, M.D., M.P.H., Juliana Janoski De Menezes, M.D., Stéphane Dalle, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean-Jacques Grob, M.D., Shivani Srivastava, M.D., Mena Abaskharoun, Pharm.D., Melissa Hamilton, M.P.H., Sarah Keidel, M.B., Ch.B., Katy L. Simonsen, Ph.D., Anne Marie Sobiesk, Ph.D., Bin Li, Ph.D., F. Stephen Hodi, M.D., and Georgina V. Long, M.D., Ph.D., for the RELATIVITY-047 Investigators*







? Triplets in MBMs

Tawbi HA et al., NEJM 2022

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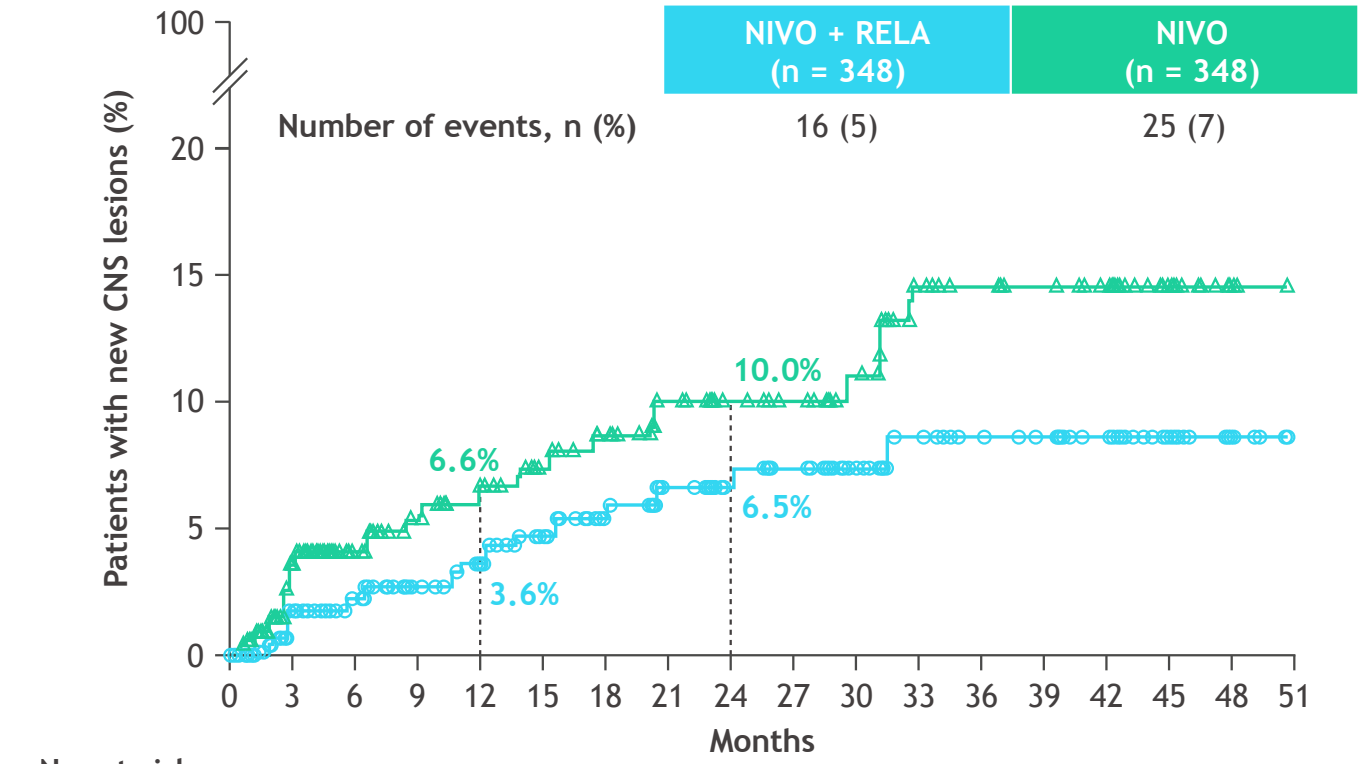
Time to the development of new CNS lesions per BICR in patients without CNS lesions at baseline



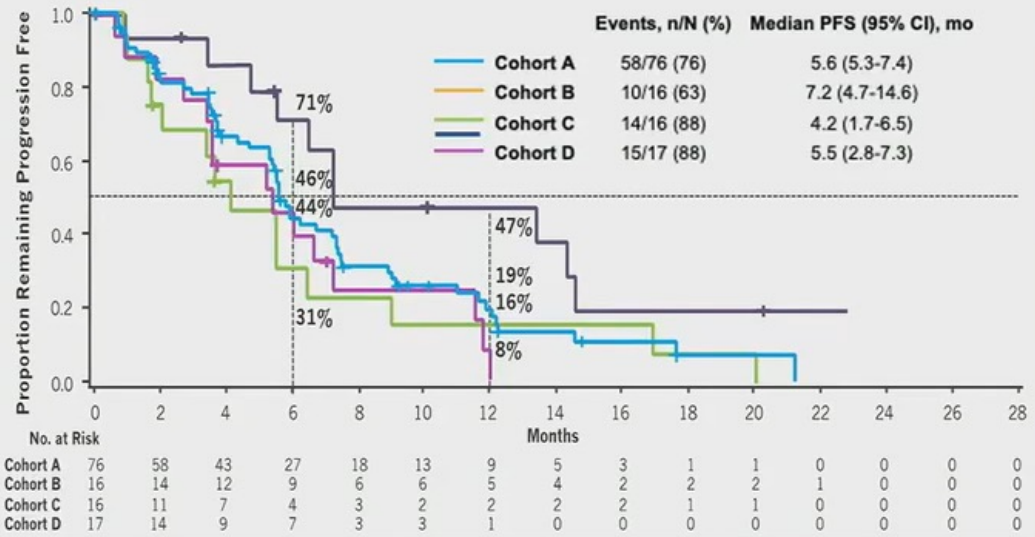
Analysis did not include scans beyond BICR-assessed progression. Patients who experienced extracranial progression were censored on the date of progression per RECIST v1.1.

COMBI- MB: Dabrafenib + Trametinib – Melanoma Brain Mets

	Intracranial ORR	Intracranial DCR
Cohort A (n=78)	58%	78%
Cohort B (n=16)	56%	88%
Cohort C (n=16)	44%	75%
Cohort D (n=17)	59%	82%

short duration of response across all cohorts

Frequent & rapid intracranial responses in patient with BRAF mutated melanoma brain metastases



Davies MA, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 9506.

LIMBURGS ONCOLOGISCH CENTRUM

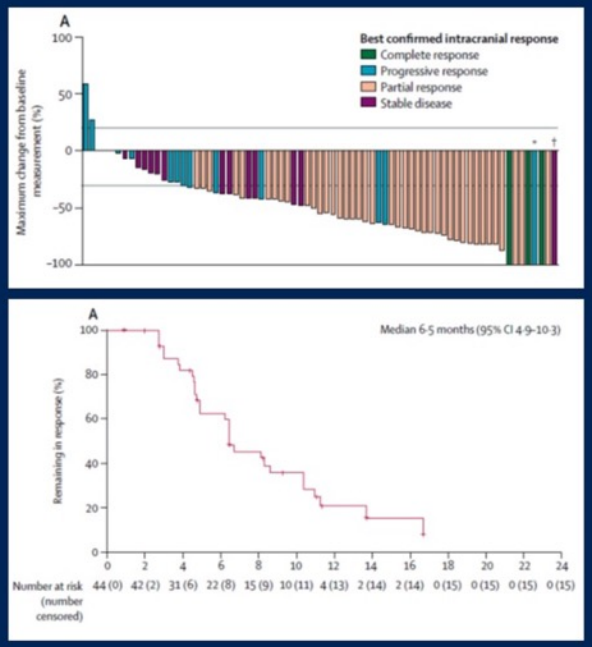
Phase 2 Trial (COMBI-MB) with Dabrafenib + Trametinib in BRAFmt MBMs

Prospective Phase 2 Trial

- Response rates high ~ 58%
- Rapid responses
- Duration of response ~ 6.5 months

Implications

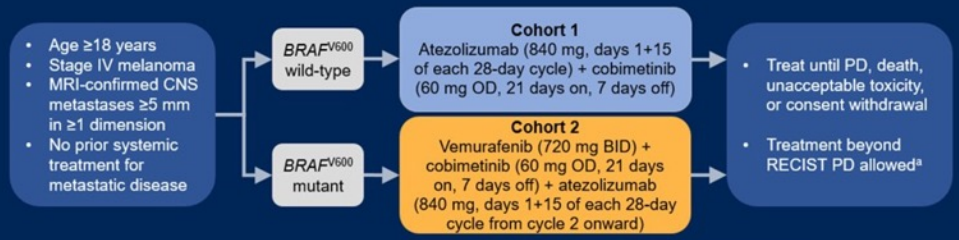
- ?Brain penetrant Braf+MEKi
- ?Sequencing of Immunotherapies + Braf + MEK inhibitors
- Murine data show Immunotherapy then Targeted (Phadke M…Smalley KSM, CIR 2021) BUT see Dr. Reihard Dummer's ASCO talk!



Davies MA,…Long VG. HA, et al., Lancet Oncol. 2017

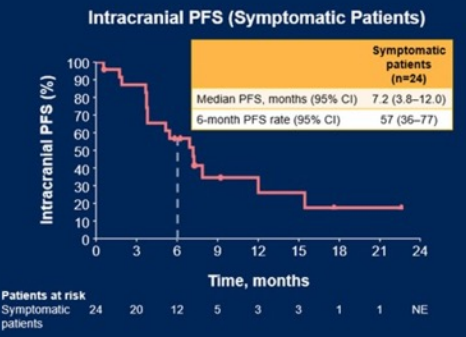
LIMBURGS ONCOLOGISCH CENTRUM

Phase 2 Study of Atezolizumab + Cobimetinib + Vemurafenib in BRAF V600 mt Melanoma Brain Mets - ASCO Abstract



Median SLD of target intracranial lesions, mm (range)	20.0 (5.0–91.0)
Receiving corticosteroids and/or symptomatic, n (%)	24 (37)[b]

Outcome	Intracranial (IRC)
ORR, % (95% CI)	42 (29–54)
Objective response, n (%)	27 (42)
CR	4 (6)
PR	23 (35)
SD	18 (28)
Non-CR/non-PD	3 (5)
PD	13 (20)
Not evaluable	1 (2)
Missing	3 (5)
Median DOR, months (95% CI)	7.4 (5.7–11.0)



Vemurafenib + cobimetinib run-in may reduce need for corticosteroid use, thereby increasing benefit from subsequent addition of atezolizumab

Courtesy R. Dummer, MD, 2022 ASCO abstract #9515

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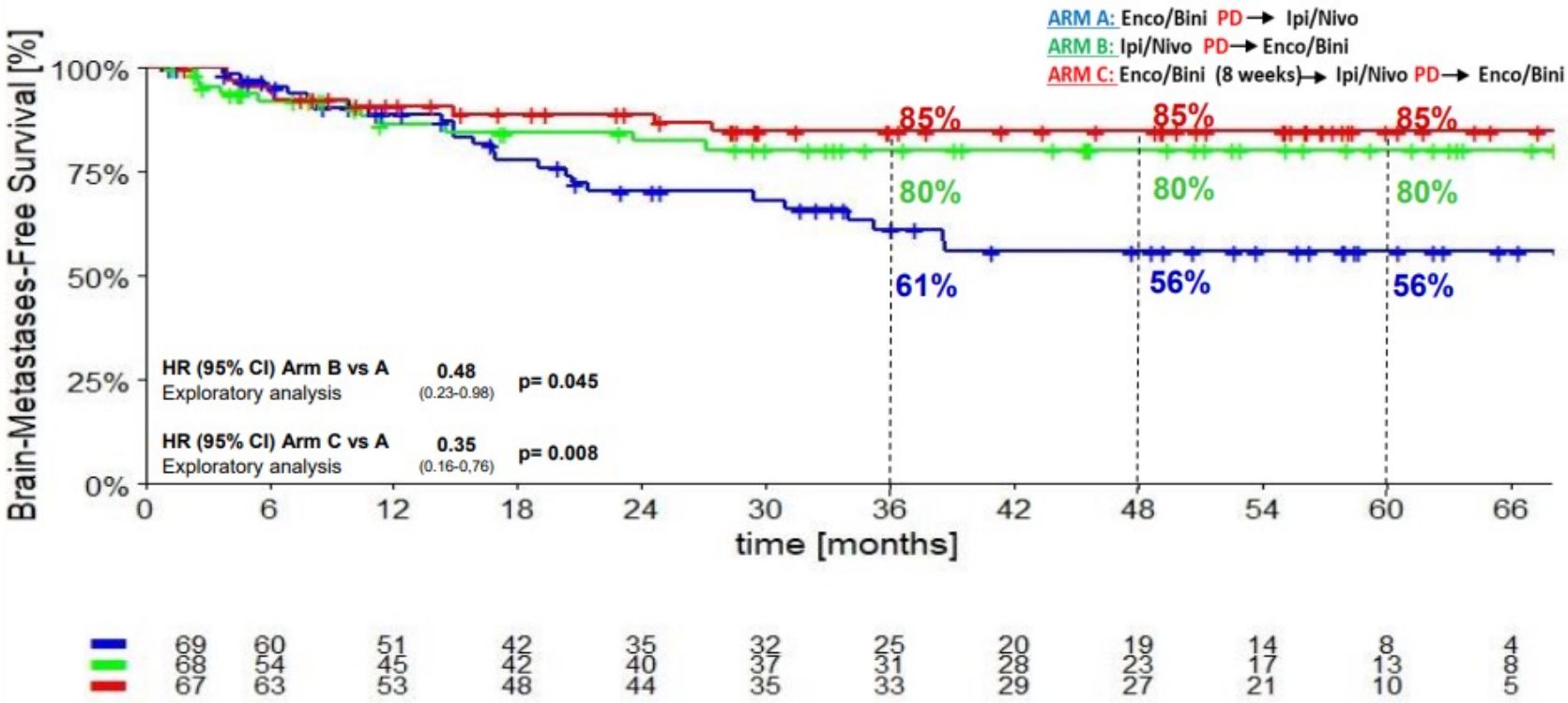
SECOMBIT STUDY: Brain Metastasis Free Survival (BMFS)



Brain metastasis free survival (BMFS) is the time from baseline to the discovery of brain metastases during the observation period of the trial.

MADRID 2023 ESMO congress

Paolo Antonio Ascierto

LIMBURGS ONCOLOGISCH CENTRUM

Regorafenib combined with BRAF-/MEK-inhibitors for the treatment of refractory melanoma brain metastases

J. Dirven, A.-S. Vander Mijnsbrugge, J. Tijtgat, M. Vounckx, B. Neyns

Department of Medical Oncology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Jette, Belgium

MADRID 2023 ESMO congress

FPN: 1136P

INTRODUCTION

- **Melanoma brain metastases** (MBM; AJCC stage IV-M1d) are associated with a poor prognosis and remain a major cause of morbidity and mortality
- **Regorafenib** (REGO, Stivarga®) is an oral multikinase inhibitor targeting angiogenic, stromal and oncogenic kinases (e.g. VEGFR1-3, RAF, KIT, CSF-1R)[1]
- REGO is also a **class II dimer-RAF inhibitor**
- REGO has **activity in pretreated melanoma**[2]

Effect of REGO (dimer selective RAFi) + monomer selective BRAFi + MEKi on MAPK-pathway (adapted from Adamopoulos et al.)[3]

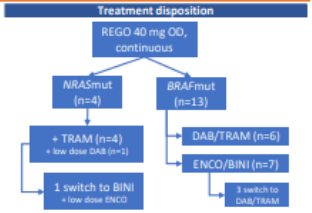
METHODS

- Single center retrospective case series
- 18 prospectively identified patients with MBM refractory to ICI and BRAF/MEKi if applicable
- 1 patient excluded from analysis due to concomitant active CLL
- Treated on compassionate use basis with "triple targeted therapy":
  - ***BRAF*-mutant: REGO+BRAF/MEKi**
  - ***NRAS*-mutant: REGO+MEKi** (+low dose BRAFi to mitigate MEKi associated skin toxicity[4])

RESULTS

Baseline characteristics	n=17
Median Age, Years (range)	54 (33-75)
Female sex, n (%)	8 (47)
ECOG Performance status, n (%)	
ECOG 0	3 (18)
ECOG 1	6 (35)
ECOG 2	6 (35)
ECOG 3	2 (12)
Progression MBM at initiation triple therapy, n (%)	
Yes	15 (88)
No	2 (12)
Steroids at initiation triple therapy, n (%)	
No steroids	9 (53)
< 32 mg methylprednisone daily	2 (12)
≥ 32 mg methylprednisone daily	6 (35)
Oncogenic driver mutation, n (%)	
BRAF^{V600E}mut	12 (71)
BRAF fusion	1 (6)
NRAS^{Q61}mut	4 (23)
Prior lines of systemic therapy, n (%)	
Anti-PD-1 and anti-CTLA-4	17 (100)
BRAF/MEKi	16 (94)
Chemotherapy	4 (23)
T-VEC	2 (12)
Prior treatment MBM, n (%)	
None	4 (23)
Surgery	5 (29)
SRT/SRS	12 (71)
WBRT	2 (12)

Treatment disposition



- **REGO** was successfully **increased** to 40/80 mg alternating OD (n=5) or 80 mg OD (n=5)
- **Combination** was either **upfront** (n=14) or **sequentially** (n=3)
- Median time on
  REGO + BRAF/MEKi was 13 weeks [range 3-62 weeks]
  REGO + MEKi was 27,5 weeks [3-56 weeks]
- Treatment ongoing in 3 patients (9-62 weeks after initiation)

Treatment beyond first progression

Treatment beyond progression* was allowed if there was clear evidence of clinical benefit

***BRAF*-mutant patients: 8 out of 12 patients**
***NRAS*-mutant patients: 2 out of 4 patients**

For an additional 3-48 weeks (median 7 weeks)

* Based on observations of rapid deterioration and disease progression upon treatment interruption (cfr. Case 1)

RESULTS

Adverse events

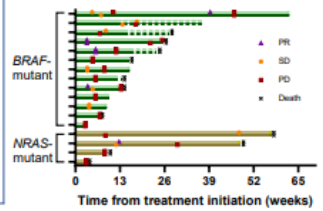
Treatment related adverse events; n (%)	All grades	Grade 1-2	Grade 3
Arterial hypertension	3 (18)		3 (18) *
Maculopapular rash	4 (24)	2 (12)	2 (12)
Diarrhea	9 (53)	8 (47)	1 (6)
Anemia	4 (24)	3 (18)	1 (6)
Hepatotoxicity	4 (24)	3 (18)	1 (6) **
Anorexia	3 (18)	2 (12)	1 (6)
Colonic hemorrhage	1 (6)		1 (6)
Duodenal perforation	1 (6)		1 (6) ***
Abdominal pain	8 (47)	8 (47)	
Fatigue	7 (41)	7 (41)	
Folliculitis	6 (35)	6 (35)	
Fever	4 (24)	4 (24)	
Alopecia	3 (18)	3 (18)	
Constipation	3 (18)	3 (18)	
Dry skin	3 (18)	3 (18)	
Nausea	3 (18)	3 (18)	
Hand-foot syndrome	3 (18)	3 (18)	
Low platelets	3 (18)	3 (18)	
Skin ulceration	3 (18)	3 (18)	

No grade ≥ 4 treatment related adverse events
* Treated medically
** flair-up of ir-hepatitis treated with steroids
*** Treated conservatively

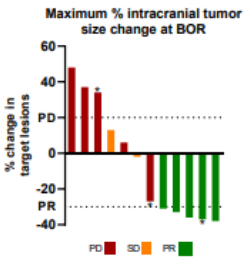
Response assessment (cont.)

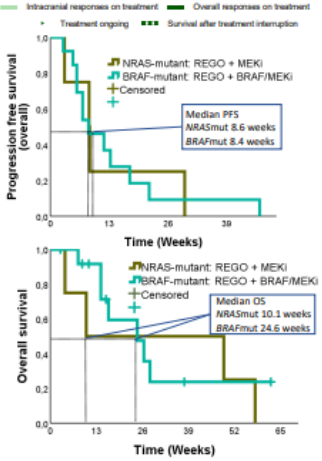
	BRAF-mutant, n=13 (%)			*NRAS*-mutant, n=4 (%)		
	PR	SD	PD	PR	SD	PD
Intracranial BOR	4 (31)	4 (31)	5 (38)	1 (25)	1 (25)	2 (25)
Extracranial BOR*	2 (15)	6 (46)	3 (23)		2 (50)	1 (25)
Overall BOR	2 (15)	5 (38)	6 (46)		1 (25)	3 (75)

BOR = Best objective response
* In 3 patients imaging of extracranial lesions was not performed



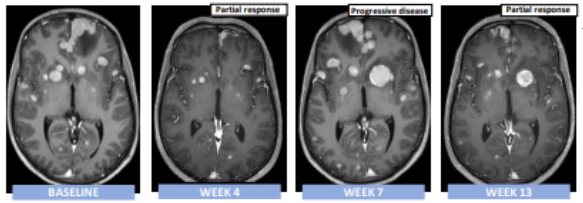
Response assessment





CASE ILLUSTRATIONS

1 32y, M, stage IV-M1d, *BRAF*^{V600E}mut melanoma
Progressive following Nivolumab, Dabrafenib/Trametinib and Ipilimumab/Nivolumab

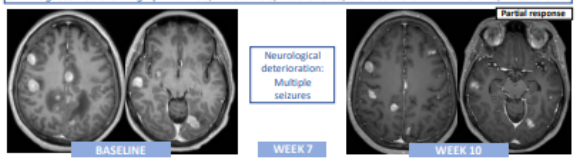


START
REGO 40 MG OD
DABRAFENIB 150 MG BID
TRAMETINIB 2 MG OD

Week 5:
stop due to flare-up immune-related hepatitis

Week 7: seizures
START REGO 40 MG OD
DABRAFENIB 150 MG BID
TRAMETINIB 2 MG OD

2 52y, F, stage IV-M1d *BRAF*^{V600E}mut melanoma
Progressive following Ipilimumab/Nivolumab, Dabrafenib/Trametinib and Binimetinib/Encorafenib



Neurological deterioration: Multiple seizures

No more seizures
Decreased perilesional edema

START
REGO 40 MG OD
BINIMETINIB 15 MG BID

ASSOCIATION
ENCORAFENIB 300 MG OD

She continued "triple targeted therapy" beyond first progression in week 29.
She died due to progressive disease in week 33.

CONCLUSION

- **In heavily pretreated patients with refractory MBM, REGO combined with BRAF/MEKi demonstrated promising anti-tumor activity (: 62% intracranial disease control rate in *BRAF*mut melanoma).**
- **Treatment beyond first progression may prevent rapid clinical deterioration associated with treatment discontinuation and offer clinically meaningful palliative benefit.**
- **Further investigation in a prospective clinical trial is ongoing (clinicaltrials.gov ID: NCT05370807).**

Abbreviations: MBM: melanoma brain metastases; REGO: regorafenib; BRAFi: BRAF-inhibitor; MEKi: MEK-inhibitor; BRAF/MEKi: BRAF/MEK-inhibitor combination; ICI: immune checkpoint inhibitor; SRT: stereotactic radiotherapy; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy; *NRAS*mut: *NRAS*-mutant; *BRAF*mut: *BRAF*-mutant; DAB: Dabrafenib; TRAM: trametinib; ENCO: encorafenib; BINI: binimetinib; OD: once daily; BID: twice a day; BOR: best objective response; PR: partial response; SD: stable disease; PD: progressive disease.

References: 1 . Wilhelm et al. Int J Cancer. 2011 2. VD Mijnsbrugge et al. SMR congress. 2022 3. Adamopoulos et al. Cancer discovery. 2021 4. Awada et al. Cancers. 2021

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Acknowledgments: drug-only support (Stivarga ®) was obtained from Bayer
DOI: the presenting author does not have any conflicts of interest

LIMBURGS ONCOLOGISCH CENTRUM

Conclusies

- Belangrijke vooruitgang geboekt!
- Systeemtherapie kan soms lokale behandelingen vervangen
- Combinatie IO +/- SRS standaard bij asymptomatische patiënten
- Symptomatische patiënten: ?
  - Evtl cytoreductie gevolgd door combinatie IO?

LIMBURGS ONCOLOGISCH CENTRUM

Dank voor Uw aandacht!

LIMBURGS ONCOLOGISCH CENTRUM

Melanoompunt

MELANOOM STUDIEDAG 2024

10 JAAR HOOP

www.melanoompunt.be

Facebook besloten groep voor patiënten en naastbetrokkenen

informeren, ontmoeten, ondersteunen

Melanoompunt is een volledig onafhankelijke patiëntenvereniging voor en door melanoompatiënten en hun naastbetrokkenen. Met de gewaardeerde steun van :

Met steun van Kom op tegen Kanker

ichting tegen Kanker

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MSD

Bristol Myers Squibb

NOVARTIS

Eau Thermale Avène Laboratoire Dermatologique

sanofi