Melanoom Hersenmetastasen

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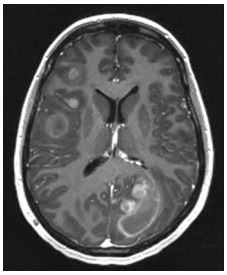
DISCLOSURES

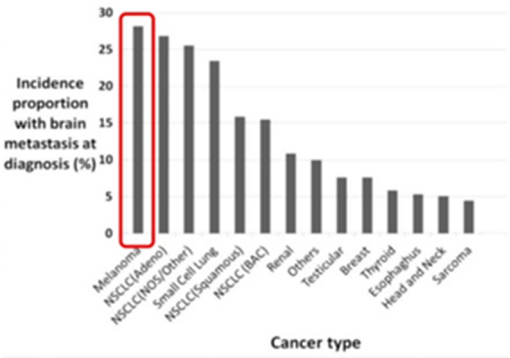
- Personal financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca, EtheRNA, CryoStorage for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to research projects conducted by my team from from Pfizer, Novartis, Roche, Merck-Serono

2

Epidemiology

- Melanoma = 1 out of 3 diagnoses of all brain metastases[1]
- 15-20% at initial diagnosis of stage IV melanoma
- Clinical diagnosis in 10-40% advanced melanoma
- 50-73% at autopsy[2]





[1]Carlino, MS et al. PHAMOUS Study, SMR 2010.
[2]de la Monte, SM et al. Cancer Res, 1983.
[3]Sampson, JH et al. J Neurosurg, 1998.

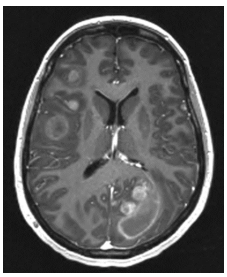
3

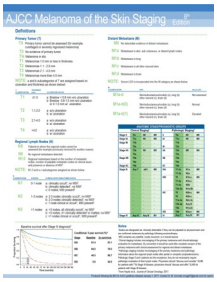
Natural Prognosis

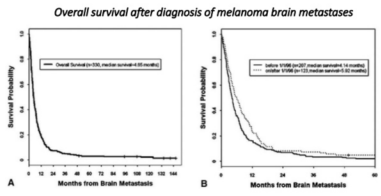
Median survival of 3-7 months[3]

Cause of death in 20-55% of advanced melanoma patients

Direct cause of death in 95% of cases diagnosed with MBM
(high risk for spontaneous hemorrhage)







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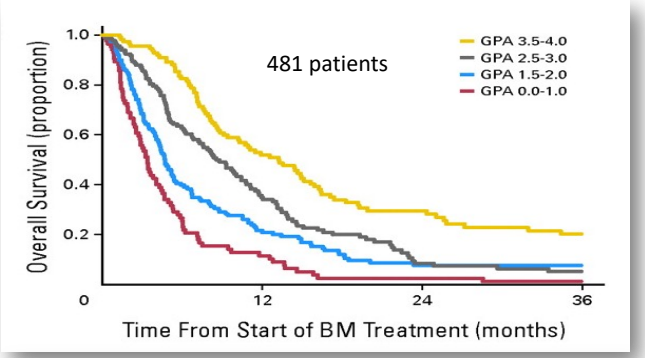
Kaplan-Meier curves for survival by graded prognostic assessment group for patients with melanoma brain metastases



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

Sperduto P W et al. JCO 2012;30:419-425 JOURNAL OF CLINICAL ONCOLOGY

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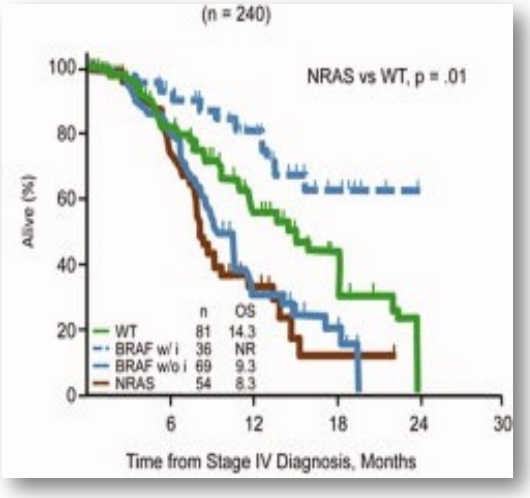
BRAF/NRAS-mutation status is an independent prognostic factor in metastatic melanoma

- ✓ **677 patients:**
  - 47% BRAF V600^{mut}
  - 20% NRAS Q61/G12/G13^{mut}
  - 32% BRAF^{wt} & NRAS^{wt}
  - 4% BRAF^{mut} & NRAS^{mut}
- ✓ **CNS metastasis at diagnosis:**
  - 24% BRAF V600^{mut}
  - 23% NRAS^{mut}
  - 12% BRAF^{wt} & NRAS^{wt}

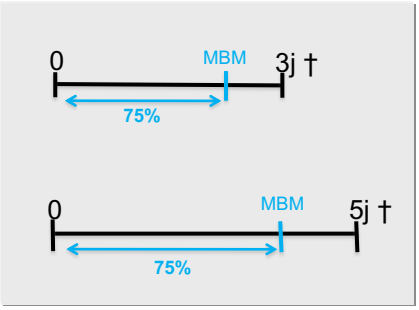


Jakob et al. Cancer. 2012 Aug 15;118(16):4014-23

6

Melanoma metastais to the brain
Is it a time dependent event?

- 159 pts recruited in immunotherapy studies at UZ Brussel
- Median follow-up: 40 months
- Incidence of MBM: 25% (41 pts)
- Patients already suffering from brain metastases at initiation of immunotherapy had a better OS than patients who developed brain metastases after immunotherapy

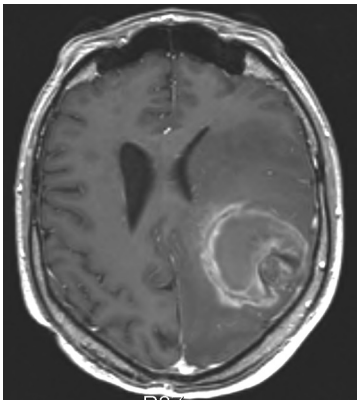


The development of brain metastases is an event that occurs relatively late in the natural course of the disease, most likely related to the emergence of a subclonal melanoma cell population with homing capacity to the brain

7

Loco(regional) Treatment for Melanoma Brain Metastases

- Neurosurgical resection
  - Immediate reduction of mass effect
  - Hematoma
- Radiosurgery/Stereotactic RT
  - Small, solitary- or small no. of MBM
  - Pancranial RT (e.g. 10x3 Gy)



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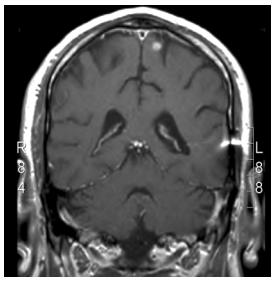
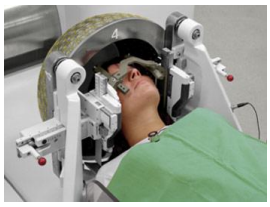
Loco(regional) Treatment for Melanoma Brain Metastases

- Neurosurgical resection
  - Immediate reduction of mass effect
- Radiosurgery/Stereotactic RT
  - Small, asymptomatic MBM
  - Solitary- or low (#?) no. of MBM
  - Radiosurgery (frame(less))
- Pancranial RT (e.g. 10x3 Gy)
  - Ineffective





9

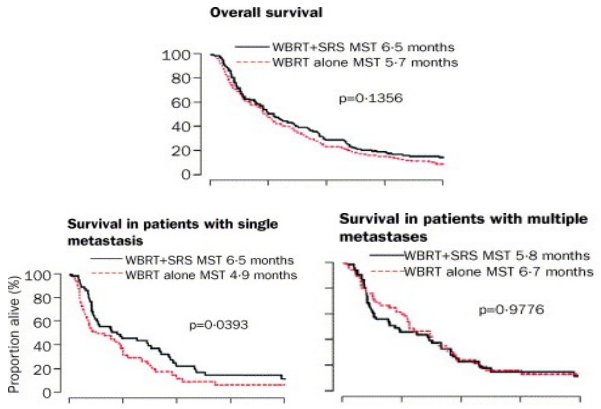
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

David W Andrews, Charles B Scott, Paul W Sperduto, Adam E Flanders, Laurie E Gaspar, Michael C Schell, Marla Werner-Wasik, William Demas, Janice Ryu, Jean-Paul Bahary, Luis Souhami, Marvin Rotman, Minesh P Mehta, Walter J Curran Jr

Lancet 2004; **363:** 1665–72

- 331 randomized (7+7 melanoma patients)

-WBRT and stRT boost improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis



10

original report

Adjuvant Whole-Brain Radiation Therapy Compared With Observation After Local Treatment of Melanoma Brain Metastases: A Multicenter, Randomized Phase III Trial

Angela M. Hong, MBBS, PhD[1,2]; Gerald B. Fogarty, MBBS, PhD[1,2]; Kari Dolven-Jacobsen, PhD[1]; Bryan H. Burmeister, MBBS[3,5]; Serigne N. Lo, PhD[1,4]; Lauren E. Haydu, PhD, MPH[1]; Janette L. Vardy, MD, PhD[1,6]; Anna K. Nowak, PhD[7]; Haryana M. Dhillon, PhD[1]; Tasnia Ahmed, MS[1]; Brindha Shivalingam, MBBS[1,2,10]; Georgina V. Long, MBBS, PhD[1,11]; Alexander M. Menzies, MBBS, PhD[1,11]; Geoge Hruby, MBChB[1,2,12]; Katharine J. Drummond, MD[2,13]; Catherine Mandel, MBBS[14]; Mark R. Middleton, PhD[15]; Claudius H. Reisse, MD[1]; Elizabeth J. Paton, MSc[1]; Victoria Steel, BSc[1]; Narelle C. Williams, MPH[1]; Richard A. Scolyer, MBBS, MD[1,10]; Rachael L. Morton, MSc, PhD[1]; and John F. Thompson, MBBS, MD[1,10]

CONCLUSION After local treatment of one to three melanoma brain metastases, adjuvant WBRT does not provide clinical benefit in terms of distant intracranial control, survival, or preservation of performance status.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

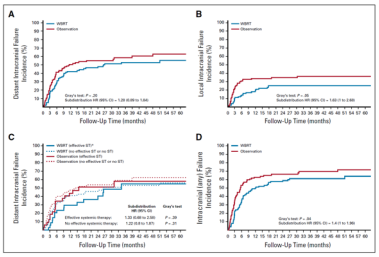


FIG 2. (A) Cumulative incidence of distant intracranial failure during follow- up. (B) Cumulative incidence of local intracranial failure during follow-up. (C) Cumulative incidence of distant intracranial failure during follow-up stratified by whether patients received systemic therapy (ST) before reaching primary end point. (D) Cumulative incidence of intracranial failure (distant and local) during follow-up. (*) Effective systemic therapy was BRAF-targeted therapy and/or immune checkpoint inhibitor. No effective therapy was cytotoxic chemotherapy or intralesional therapy. HR, hazard ratio; ST, systemic therapy; WBRT, whole-brain radiation therapy.

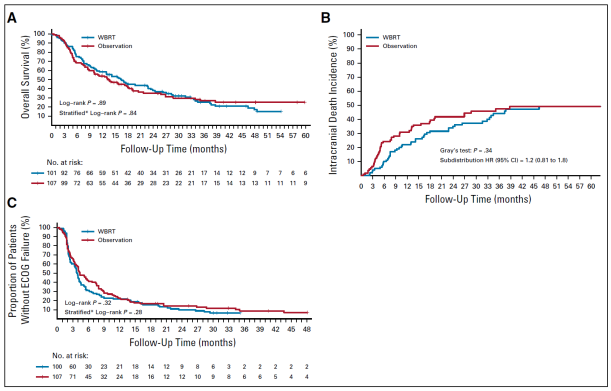


FIG 3. (A) Kaplan-Meier estimates of overall survival according to treatment group. One patient undergoing whole-brain radiation therapy (WBRT) was included in the overall survival analysis only as no baseline or intracranial follow-up data were collected. (B) Cumulative incidence of death as a result of intracranial disease during follow-up. (C) Time-to-deterioration in Eastern Cooperative Oncology Group (ECOG) performance status during follow-up. ECOG failure is defined as the time that elapsed between random assignment and the first recorded worsening in ECOG performance status.

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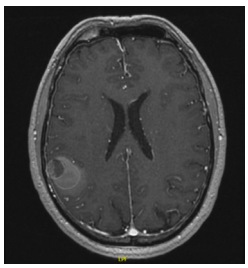
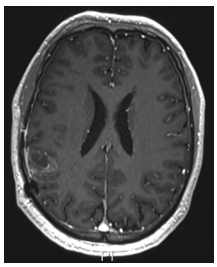
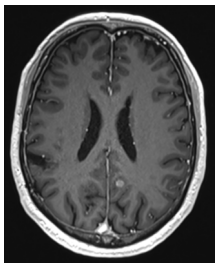
Case Illustration

Male patient °1963

2011: melanoma (trunk, Breslow 3,27 mm, N1a(sn-bilateral))
Bilateral axillary CLND (N0)
09/2016: resection solitary lung metastasis (BRAF V600mut)
10/2016: PET+ sc meta, start pembrolizumab
CR
2/2017: PD CNS; surgery, 4x ipilimumab
Resume anti-PD-1
3/2018: solitary new metastasis, frameless radiosurgery (1x 20Gy)
01/2020: PS 0, nivolumab continued


27/01/2017


22/03/2017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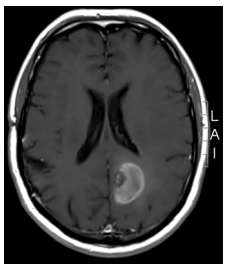
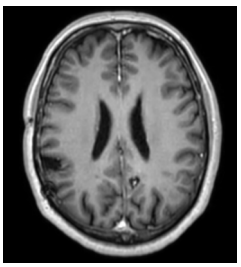


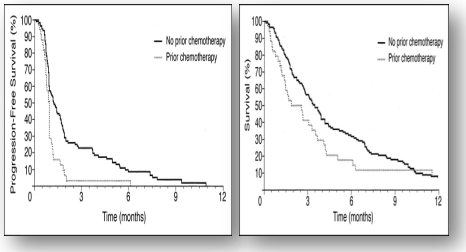
20/6/2018


04/01/2020

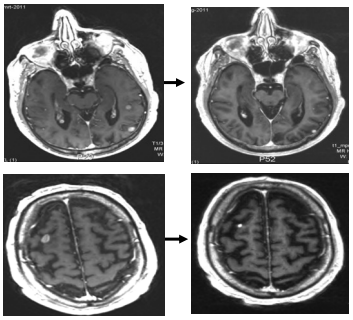
12

Temozolomide for MBM

- 7-9% BORR in pts with MBM [1,2]
- Median OS[2]
  - 3.5 mths (117 not previously treated)
  - 2.2 mths (34 previously treated)



78y male stIV-M1c



March `11 March`13

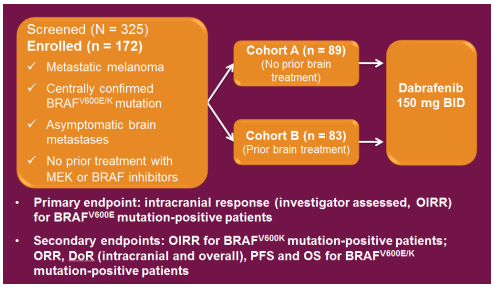
24 cycles Temozolomide

[1] Boogerd et al., Cancer 2007 ; [2] Agarwala S S et al. JCO 2004

13

Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

Georgina V Long, Uwe Trefzer, Michael A Davies, Richard F Kefford, Paolo A Ascierto, Paul B Chapman, Igor Puzanov, Axel Hauschild, Caroline Robert, Alain Algazi, Laurent Mortier, Hussein Tawbi, Tabea Wilhelm, Lisa Zimmer, Julie Switzky, Suzanne Swann, Anne-Marie Martin, Mary Guckert, Vicki Goodman, Michael Streit, John M Kirkwood, Dirk Schadendorf**



	Intracranial		Overall	
	Number of patients (%)		Number of patients (%)	
	No prior brain treatment (n=74)	Prior brain treatment (n=65)	No prior brain treatment (n=74)	Prior brain treatment (n=65)
OIRR (CR+PR)	29 (39)	20 (31)	28 (38)	20 (31)
Intracranial response				
CR	2 (3)	0	2 (3)	0
PR	27 (36)	20 (31)	27 (36)	20 (31)
SD	31 (42)	38 (58)	31 (42)	38 (58)
PD	9 (12)	5 (8)	9 (12)	5 (8)
Not evaluable	5 (7)	2 (3)	5 (7)	2 (3)
Intracranial disease control (CR+PR+SD)	60 (81)	58 (89)	59 (80)	54 (83)
Median duration of intracranial response (weeks)	20.1	28.1	27.6	20.1

Lancet Oncol 2012; 13: 879–86

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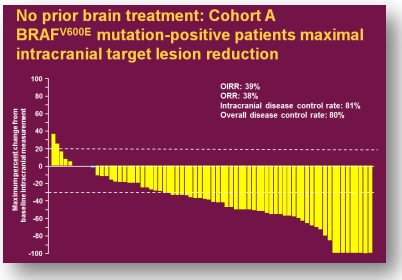
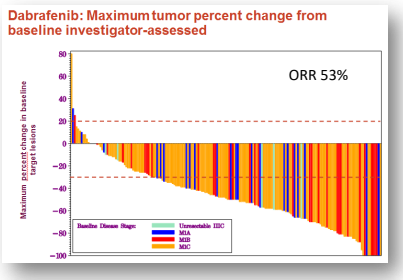
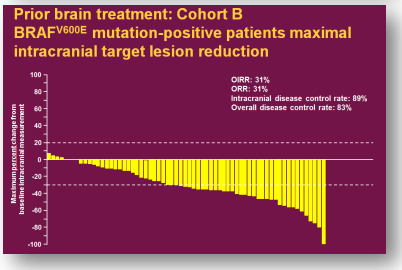
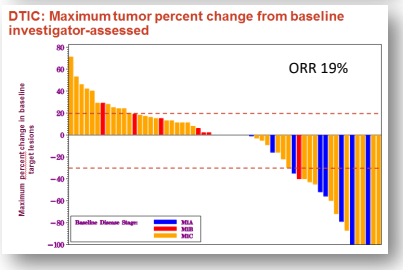
BOR in BREAK-MB and BREAK-3









Long Lancet Oncology 2012; Hauschild Lancet 2012

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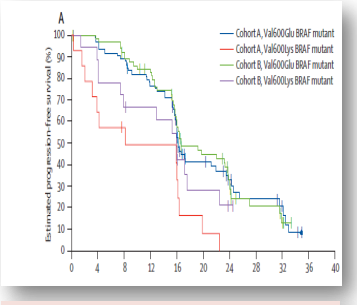
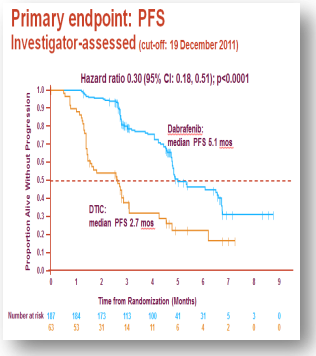
Survival in BREAK-MB and BREAK-3



	Cohort A	Cohort B
Val600Glu BRAF mutant	74 pt	65 pt
Intracranial duration of response*	20·1 (12·1–NR)	28·1 (20·1–28·1)
Progression-free survival	16·1 (15·7–21·9)	16·6 (15·9–23·7)
Overall survival	33·1 (25·6–NR)	31·4 (25·7–NR)
Val600Lys BRAF mutant	15 pt	18 pt
Intracranial duration of response*	12·4 (NR–NR)	16·6 (NR–NR)
Progression-free survival	8·1 (3·1–16·1)	15·9 (7·9–22·4)
Overall survival	16·3 (6·9–22·4)	21·9 (15·3–NR)

Data are median number of weeks (95% CI). NR=not reached. *Duration of response in those with an intracranial partial or complete response.



Long Lancet Oncology 2012; Hauschild Lancet 2012

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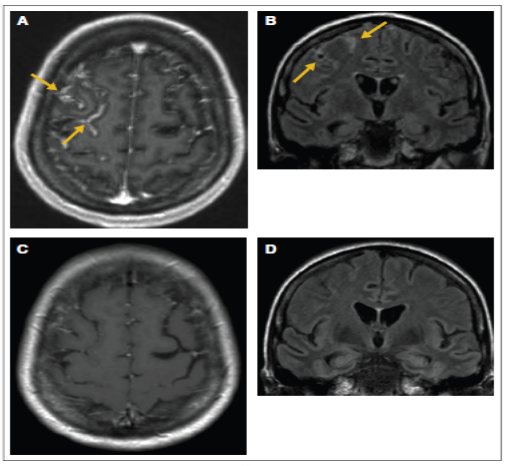

Table 1. CSF Analysis Before and 6 Weeks After the Initiation of Dabrafenib Treatment

	October 24, 2012	November 30, 2012	Normal Range
Cytology, per µL			
Red blood cells	353	751	< 2
Nucleated cells	24	9	0-5
Differential count, %			
Neutrophils	0.5	—	0-6
Basophils	0	—	0
Eosinophils	0	—	0
Lymphocytes	53.5	—	40-80
Monocytes	3	—	15-45
Atypical lymphocytes	2.0	—	0
Epithelial cells plus macrophages, %	41*	0	0
Chemical analysis			
Glucose, mg/dL	25	54	60%-70% of plasma measurement
Total protein, mg/dL	253	76	26-79
Lactate, mmol/L	5.0	1.4	< 1.7

*With presence of malignant cells.

Sofie Wilgenhof and Bart Neyns
Universitair Ziekenhuis Brussel, Brussels, Belgium
2013

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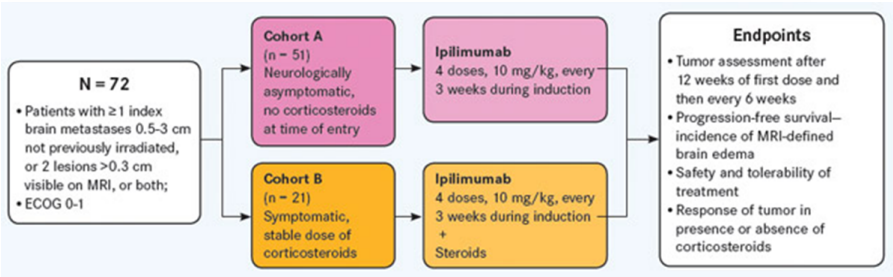
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi



- **Treatment: 4 doses of 10 mg/kg ipilimumab, q3 wks; q12w if no PD at 24w**
- **No unexpected ipilimumab related AE**

Lancet Oncol 2012; 13: 459-65

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Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
Global disease control	9 (18%, 8–31)	13 (25%, 14–40)	1 (5%, 0·1–24)	2 (10%, 1–30)
CNS disease control	12 (24%, 13–38)	13 (25%, 14–40)	2 (10%, 1–30)	2 (10%, 1–30)
Non-CNS disease control	14 (27%, 16–42)	17 (33%, 21–48)	1 (5%, 0·1–24)	2 (10%, 1–30)
Global objective response	5 (10%, 3–21)	5 (10%, 3–21)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
CNS objective response	8 (16%, 7–29)	8 (16%, 7–29)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
Non-CNS objective response	7 (14%, 6–26)	7 (14%, 6–26)	1 (5%, 0·1–24)	1 (5%, 0·1–24)

Data are n (%, 95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

Table 3: **Disease control and objective response after 12 weeks**

Lancet Oncol 2012; 13: 459–65

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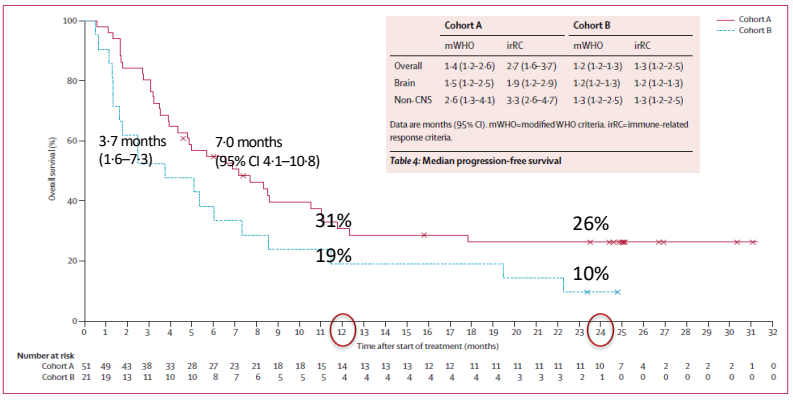
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi



	Cohort A		Cohort B	
	mWHO	irRC	mWHO	irRC
Overall	1·4 (1·2–2·6)	2·7 (1·6–3·7)	1·2 (1·2–1·3)	1·3 (1·2–2·5)
Brain	1·5 (1·2–2·5)	1·9 (1·2–2·9)	1·2 (1·2–1·3)	1·2 (1·2–1·3)
Non-CNS	2·6 (1·3–4·1)	3·3 (2·6–4·7)	1·3 (1·2–2·5)	1·3 (1·2–2·5)

Data are months (95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

Table 4: **Median progression-free survival**

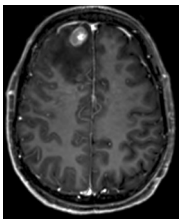
Figure: **Overall survival**
Crosses indicate censored patients.

Hodi et al NEJM 2010: mOS 10,0mths; 2yOS 23%

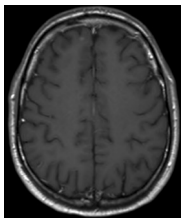
Lancet Oncol 2012; 13: 459–65

20

Case report : Post radiation necrosis of the brain during successful ipilimumab therapy

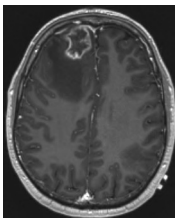


At first diagnosis (March 2009)



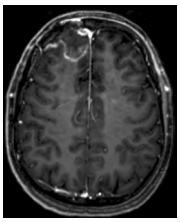
1 y post stRT (March 2010)

Initiation of ipilimumab

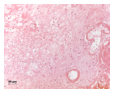


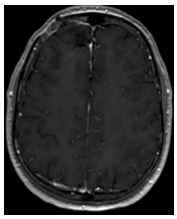
2 y post stRT

CR outside the CNS



Post-surgery = Necrosis



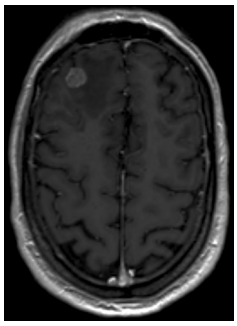


6 months post surgery

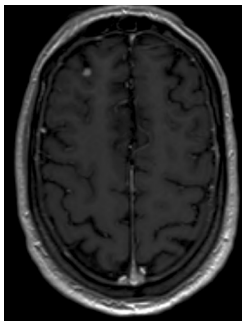
Du Four S et al. Eur J Cancer. 2012

21

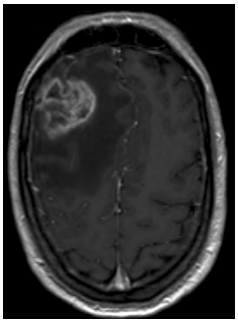
Case report : Post radiation necrosis of the brain during successful dabrafenib therapy



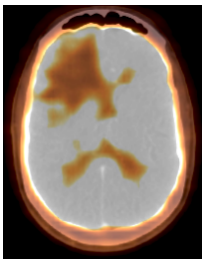
-February 2012
-Radiosurgery (20Gy)
- Start Dabrafenib for PD outside CNS



+ 6mths
CR outside CNS



+ 9mths
CR outside CNS



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Hindawi Publishing Corporation
Case Reports in Oncological Medicine
Volume 2014, Article ID 417913, 6 pages
http://dx.doi.org/10.1155/2014/417913

Hindawi

Case Report

Symptomatic Histologically Proven Necrosis of Brain following Stereotactic Radiation and Ipilimumab in Six Lesions in Four Melanoma Patients

Stephanie Du Four,[1,2] Angela Hong,[3] Matthew Chan,[4] Michail Charakidis,[5] Johnny Duerinck,[1] Sofie Wilgenhof,[2] Wei Wang,[6] Linda Feng,[7] Alex Michotte,[8] Meena Okera,[3] Brindha Shivalingam,[9] Gerald Fogarty,[10] Richard Kefford,[4] and Bart Neyns[2]

Cancer Medicine
Open Access

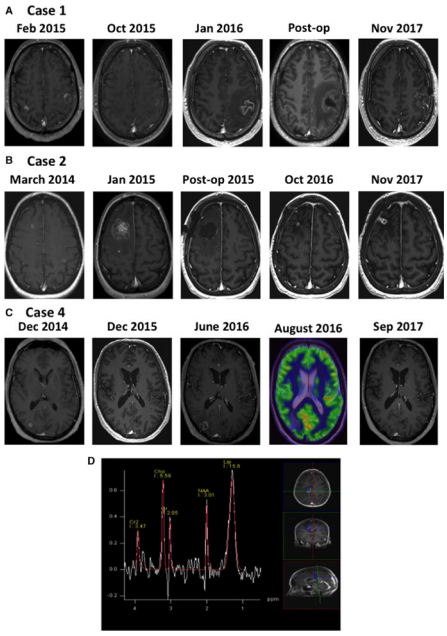
ORIGINAL RESEARCH | Open Access

Focal radiation necrosis of the brain in patients with melanoma brain metastases treated with pembrolizumab

Stephanie Du Four, Yanina Janssen, Alex Michotte, Anne-Marie Van Binst, Robbe Van den Begin, Johnny Duerinck, Bart Neyns

First published: 21 August 2018 | https://doi.org/10.1002/cam4.1726 | Citations: 7

Of the 142 patients, 43 (30.7%) patients had MBM at initiation pembrolizumab. Of these, 31 (72.1%) were treated with SRS, 8 (18.6%) with WBRT while 4 (9.3%) had no prior local therapy. Of patients treated with RT, 28 (71.1%) received RT before the initiation of pembrolizumab. 5 (12.8%) patients developed a new symptomatic pseudotumoral lesion at a median time of 11.15 months (range 8–46) after the RT. In all patients, the diagnosis of RNB was radiologically confirmed. The RNB was treated with corticosteroids in two patients, bevacizumab in two patients, and surgery in three symptomatic patients. The diagnosis was histologically confirmed in the patients treated with surgery.



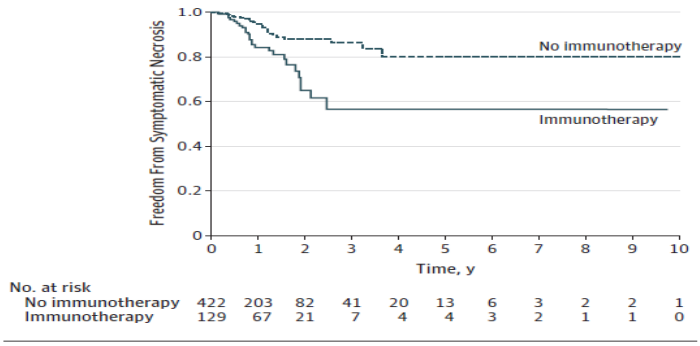
Cancer Medicine, Volume: 7, Issue: 10, Pages: 4870-4879, First published: 21 August 2018, DOI: (10.1002/cam4.1726)

23

RESEARCH LETTER

Immunotherapy and Symptomatic Radiation Necrosis in Patients With Brain Metastases Treated With Stereotactic Radiation

Figure. Kaplan-Meier Curves Displaying Freedom From Symptomatic Necrosis as Stratified by Receipt of Immunotherapy vs No Receipt of Immunotherapy



No. at risk

No immunotherapy	422	203	82	41	20	13	6	3	2	2	1
Immunotherapy	129	67	21	7	4	4	3	2	1	1	0

Log rank $P<.001$.

Table. Baseline Patient Characteristics at Time of Diagnosis of Brain Metastases in Patients Who Did or Did Not Receive Immunotherapy

Characteristic	No. (%) No Immuno-therapy (n = 365)	Immuno-therapy (n = 115)	*P* Value[a]
Age, mean (SD), y	62 (11)	61 (11)	.17
Sex			.13
Female	166 (45)	43 (37)	
Male	199 (55)	72 (63)	
Race			.04
White	313 (86)	109 (95)	
African American	17 (5)	0	
Hispanic	6 (2)	1 (1)	
Asian	15 (4)	1 (1)	
Other	1 (<1)	0	
Unknown	13 (4)	4 (3)	
Primary cancer			<.001
Melanoma	73 (20)	72 (63)	
NSCLC	256 (70)	38 (33)	
Renal cell carcinoma	36 (10)	5 (4)	
KPS, median (IQR)	90 (80-90)	90 (80-90)	.16
Size of largest metastasis, median (IQR), mm	14 (8-22)	12 (6-22)	.20
Neurologic symptoms	170 (47)	64 (57)	.07
Seizures	6 (2)	2 (2)	.99
Primary cancer controlled	172 (47)	62 (54)	.31
Extracranial disease	290 (79)	102 (89)	.03
Extracranial disease sites			
Lung	169 (46)	72 (63)	.003
Liver	35 (10)	24 (21)	.003
Bone	69 (19)	35 (30)	.01
Lymph nodes	110 (30)	47 (41)	.04
Soft tissue	47 (13)	34 (30)	<.001
Adrenal	37 (10)	9 (8)	.59
Type of initial radiation			.24
SRS	291 (80)	88 (77)	
SRT	55 (15)	16 (14)	
SRS and SRT	19 (5)	11 (10)	
Systemic therapy prior to SRS/SRT	106 (29)	41 (36)	.20
No. of prior systemic therapy regimens, median (IQR)	0 (0-1)	0 (0-1)	.29
Salvage whole brain radiation after initial SRS/SRT	95 (26)	33 (29)	.63
SRS/SRT after initial SRS/SRT	127 (35)	59 (51)	.002

Abbreviations: IQR, interquartile range; KPS, Karnsofsky performance status; NSCLC, non-small-cell lung cancer; SD, standard deviation; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy.
[a] Baseline patient characteristics in patients who received immunotherapy vs not were compared using the *t* test, Wilcoxon rank sum test, and Fisher exact test, as indicated.

JAMA Oncology August 2018 Volume 4, Number 8

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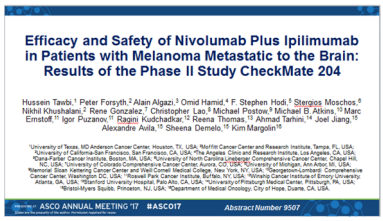
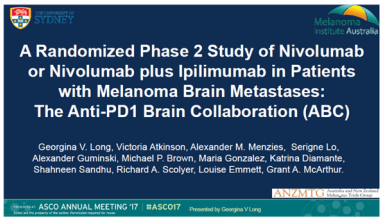
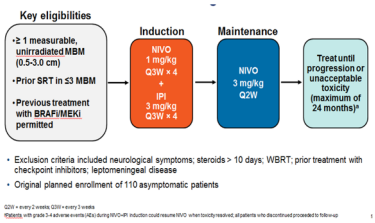
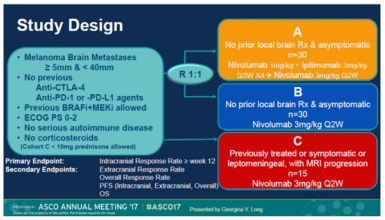
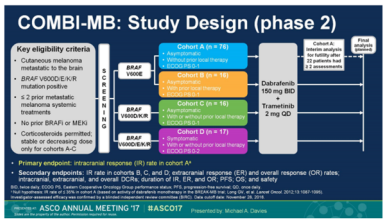
Prospective Phase II Clinical Trials on Melanoma Brain Metastases presented at the 2017 ASCO AM







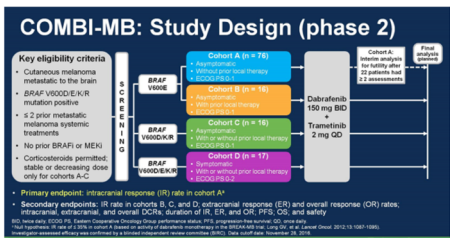




25

Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Michael A Davies, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang, Bijoyesh Mookerjee, Georgina V Long*



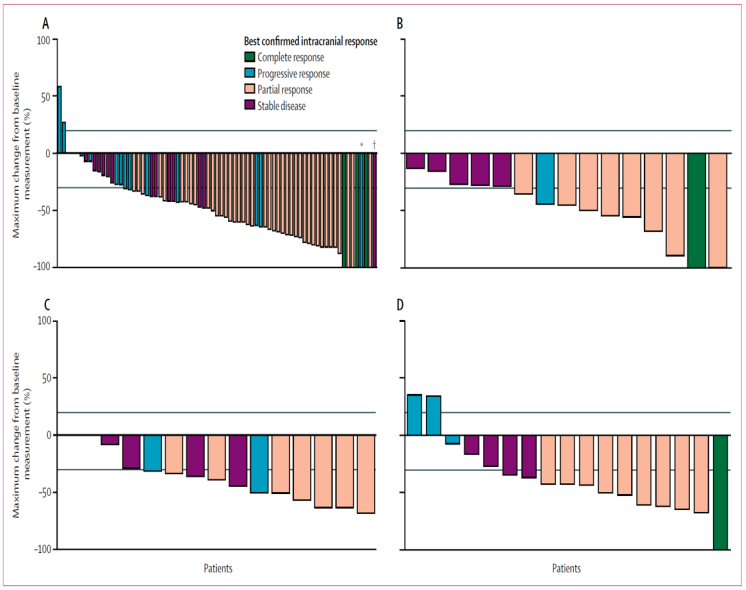


Figure 2: Confirmed maxiumum reduction in intracranial target lesion in cohort A (A), cohort B (B), cohort C (C), and cohort D (D)

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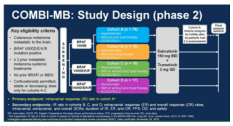
Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Michael A Davies, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang, Bijoyesh Mookerjee, Georgina V Long*



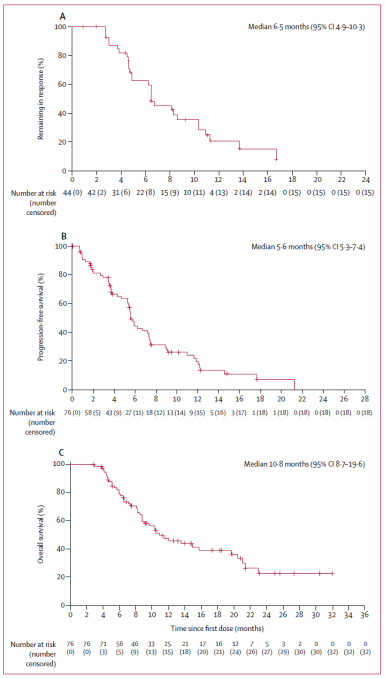


Figure 3: Investigator-assessed duration of intracranial response (A), progression-free survival (B), and preliminary overall survival (C) in cohort A

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The NEW ENGLAND JOURNAL of MEDICINE

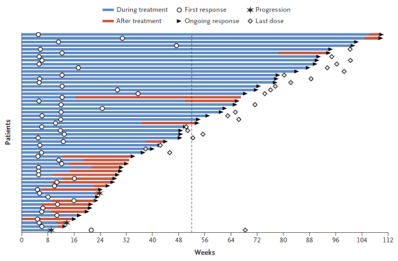
ORIGINAL ARTICLE

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.

METHODS

In this open-label, multicenter, phase 2 study, patients with metastatic melanoma and at least one measurable, non-irradiated brain metastasis (tumor diameter, 0.5 to 3 cm) and no neurologic symptoms received nivolumab (1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for up to four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks until progression or unacceptable toxic effects.



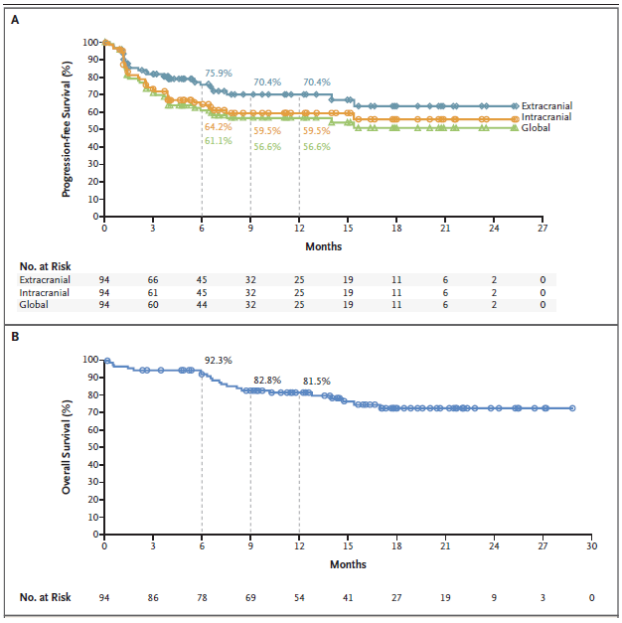


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Table 2. Response to Treatment.

Variable	Intracranial (N = 94)	Extracranial (N = 94)	Global (N = 94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

55 to 22% ORR

CheckMate 204

Response to Treatment – Symptomatic Patients

	Patients (n = 18)		
	Intracranial	Extracranial	Global
Best overall response, n (%)			
Complete response	2 (11)	0	0
Partial response	2 (11)	4 (22)	4 (22)
Stable disease ≥ 6 months	0	0	0
Progressive disease	10 (56)	6 (33)	8 (44)
Not evaluable	4 (22)	8 (44)[a]	6 (33)
Death prior to first on-study assessment	2	1	1
Early discontinuation due to toxicity	0	0	0
Stable disease < 6 months	2	4	2
Other	0	3	3
ORR, n/N (%) (95% CI)	4/18 (22) (6–48)	4/18 (22) (6–48)	4/18 (22) (6–48)
CBR,[b] n/N (%) (95% CI)	4/18 (22) (6–48)	4/18 (22) (6–48)	4/18 (22) (6–48)

[a] One of these patients did not have extracranial disease at baseline; [b] Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

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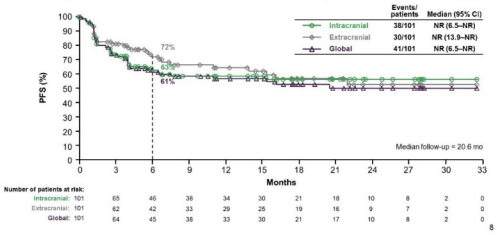
CheckMate 204

Progression-Free Survival – Asymptomatic Patients



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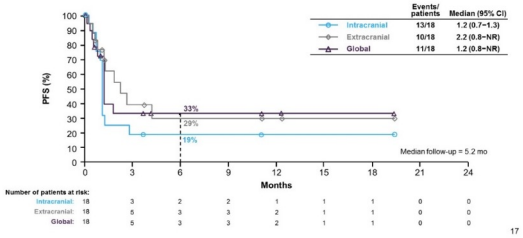
CheckMate 204

Progression-Free Survival – Symptomatic Patients



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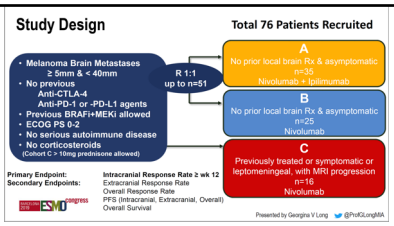
Long-term Outcomes from the Randomized Ph 2 Study of Nivolumab or Nivolumab + Ipilimumab in Patients With Melanoma Brain Metastases: Anti-PD1 Brain Collaboration (The ABC Trial)

Georgina V. Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Michael P. Brown, Maria Gonzalez, Alexander Guminski, Richard A. Scolyer, Louise Emmett, Alexander M. Menzies, Grant A. McArthur

esmo.org

Study Design



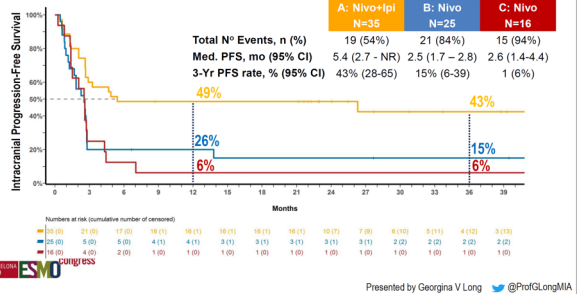
Best Intracranial RECIST Response

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo* N=16
Intracranial Response, n (%)	18 (51%)	5 (20%)	1 (6%)
CR	9 (26%)	4 (16%)	0 (0%)
PR	9 (26%)	1 (4%)	1 (6%)
SD	2 (6%)	0 (0%)	2 (13%)
PD	14 (40%)	19 (76%)	13 (81%)
NE*	1 (3%)	1 (4%)	0 (0%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*Pts who deceased prior to wk 12 = PD
†Leptomeningeal, previous local treatment or symptoms

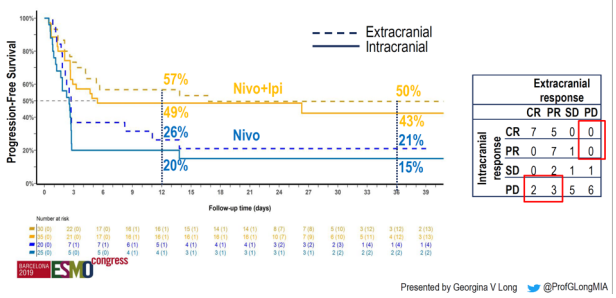
Intracranial Progression-Free Survival



Presented by Georgina V Long @ProfGLongMIA

Intracranial and Extracranial Concordance

All Patients Cohort A and B



Presented by Georgina V Long @ProfGLongMIA

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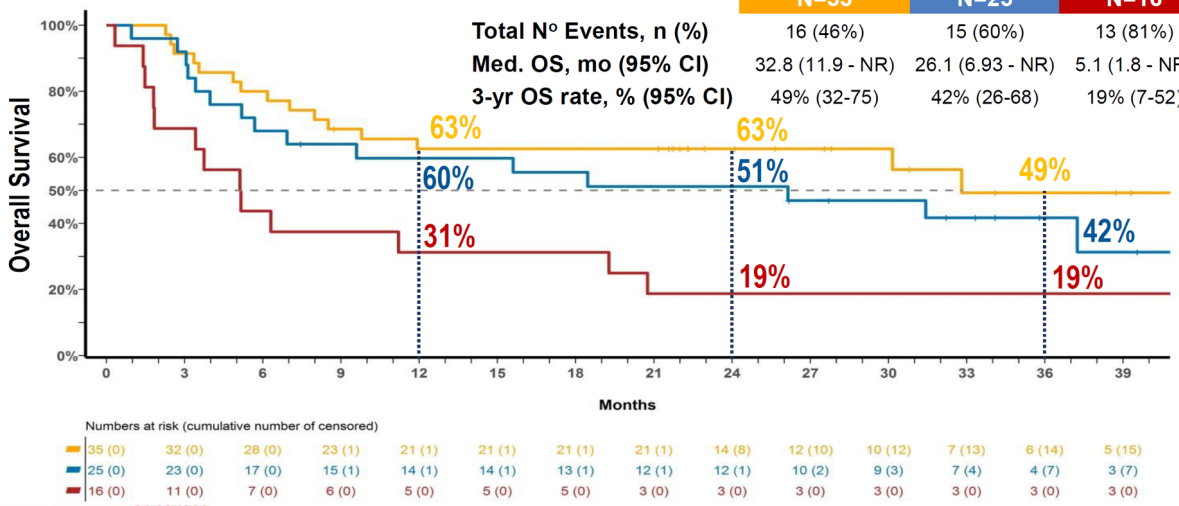
Overall Survival

Melanoma Institute Australia

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	16 (46%)	15 (60%)	13 (81%)
Med. OS, mo (95% CI)	32.8 (11.9 - NR)	26.1 (6.93 - NR)	5.1 (1.8 - NR)
3-yr OS rate, % (95% CI)	49% (32-75)	42% (26-68)	19% (7-52)



Numbers at risk (cumulative number of censored)

35 (0)	32 (0)	28 (0)	23 (1)	21 (1)	21 (1)	21 (1)	21 (1)	14 (8)	12 (10)	10 (12)	7 (13)	6 (14)	5 (15)
25 (0)	23 (0)	17 (0)	15 (1)	14 (1)	14 (1)	13 (1)	12 (1)	12 (1)	10 (2)	9 (3)	7 (4)	4 (7)	3 (7)
16 (0)	11 (0)	7 (0)	6 (0)	5 (0)	5 (0)	5 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)

BARCELONA 2019 ESMO congress

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Treatment-Related Adverse Events

Melanoma Institute Australia

	A: Ipi+Nivo N=35	B: Nivo N=25	C: Nivo† N=16
Treatment-related AEs, n (%)	34 (97%)	17 (68%)	8 (50%)
Grade 3/4 treatment-related AEs, n (%)	19 (54%)	5 (20%)	2 (13%)
Treatment-related SAE, n (%)	16 (46%)	1 (4%)	2 (13%)
Discontinuation due to AE*	5 (14%)	1 (4%)	0 (0%)

- No new or unexpected AEs
- 4/76 (5%) pts had neurological SAE: 1 radionecrosis^, 1 seizure, 2 headache
- No deaths due to treatment-related AE

SAE; Serious Adverse Event
*Pts with grade 3/4 treatment related AE in Cohort A were allowed to continue nivolumab monotherapy if recovered and deemed due to ipilimumab
^ Pt in cohort C, prior SRS

BARCELONA 2019 ESMO congress

Presented by Georgina V Long @ProfGLongMIA

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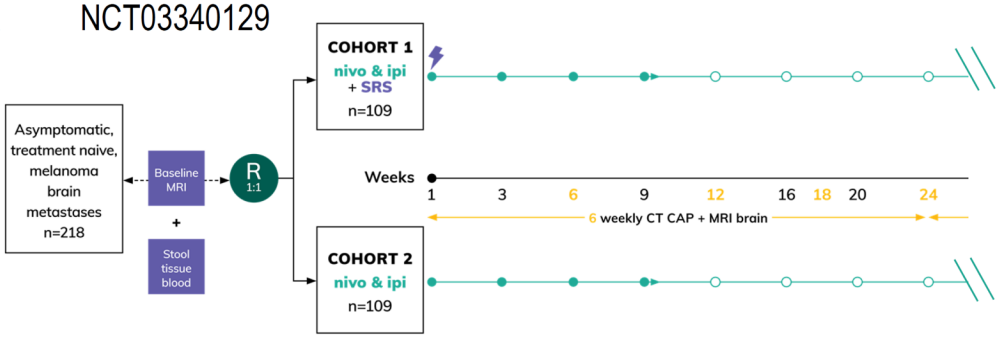
- ABC-X NCT03340129



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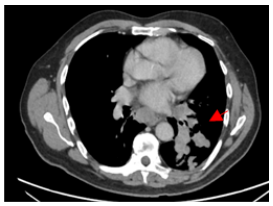
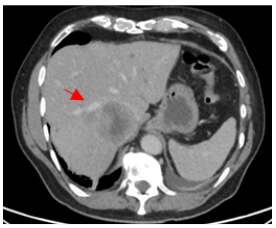
Case presentation

- 74-year-old male patient
- Prior history of BRAF V600mut primary melanoma on right shoulder
- Nov 2017: diagnosis stage IV-M1c melanoma (metastases to LLN, lung, liver and skeleton)
- *What to do?*





07DEC2017
CT Baseline

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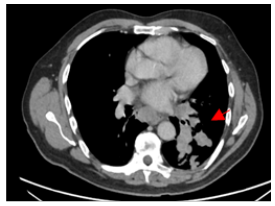
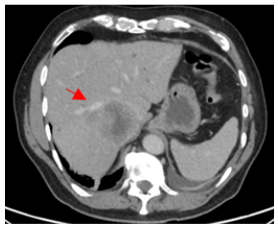
Case presentation

- Start nivolumab (3 mg/kg Q2w)
- Dec 2017: rapid increase of symptoms (pain, anorexia, weakness) during first 4w on nivolumab.
- Deterioration of blood values: LDH: 8966 U/L (ULN 618 U/L), CRP 76.4 mg/l (ULN 5 mg/l)
- *What to do?*





07DEC2017
CT Baseline

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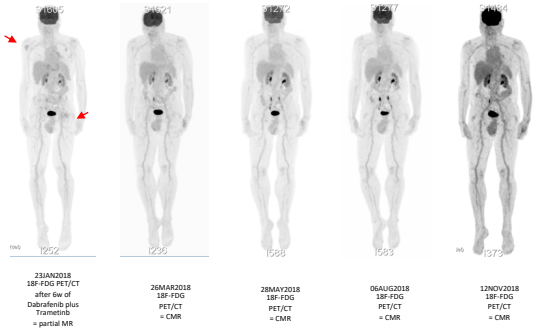
Case presentation

- **Switch to Dabrafenib/Trametinib**
- Symptom improvement after 4 days of therapy
- Stop pain medication after 1w of therapy
- Recovery of activity level, appetite
- One short episode of pyrexia (self-limited, 2 days of treatment interruption) after 3w of therapy
- Up to March 2019: uneventful evolution, dabrafenib/trametinib continued at full dose, full recovery of activity level



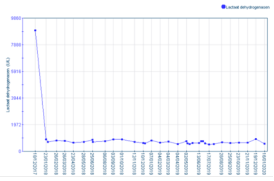
23JAN2018
18F-FDG PET/CT
after 6w of
Dabrafenib plus
Trametinib
= partial MR

26MAR2018
18F-FDG
PET/CT
= CMR

28MAY2018
18F-FDG
PET/CT
= CMR

06AUG2018
18F-FDG
PET/CT
= CMR

12NOV2018
18F-FDG
PET/CT
= CMR



Longitudinal LDH measurements

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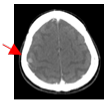
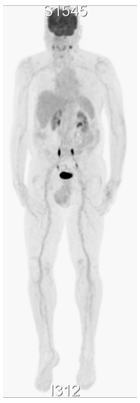
Case presentation

- Switch to Dabrafenib/Trametinib
- Symptom improvement after 4 days of therapy
- Stop pain medication after 1w of therapy
- Recovery of activity level, appetite
- One short episode of pyrexia (self-limited, 2 days of treatment interruption) after 3w of therapy
- Up to March 2019: uneventful evolution, dabrafenib/trametinib continued at full dose, full recovery of activity level
- March 2019: diagnosis of multiple (asymptomatic) brain metastases on whole body 18F-PET/CT
- *What to do?*





04MAR2019
18F-FDG
PET/CT
= brain
metastases

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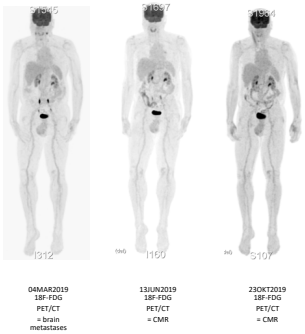
Case presentation

- **Start ipilimumab/nivolumab, Q3w x4**
- **Stereotactic radiation therapy** withTrue Beam system (single fraction of 20 Gy at 80 % isodose on 18 brain metastases, 3 days methylprednisolone following stRT)

- April 2019: transient problems reading/writing
- May 2019: silent hypophysitis with associated hypopituitarism. Hormone substitution therapy initiated (Hydrocortisone 20+10mg, levothyroxine 125µ/d). Spontaneous recovery of testosterone levels at follow-up
- May 2019: recovery of KPS 100%

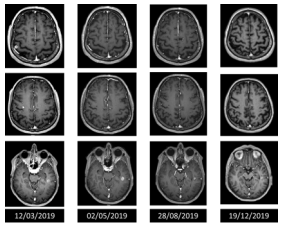
- Favorable evolution on MRI of the brain and CMR on whole-body 18F-FDG/PET
- June 2019: treatment continued with nivolumab 240mg iv Q2w
- August 2019: switch to nivolumab 480mg Q4w up to present
- Uneventful evolution up to latest follow-up (KPS 100%)



04MAR2019
18F-FDG
PET/CT
= brain
metastases

13JUN2019
18F-FDG
PET/CT
= CMR

23OKT2019
18F-FDG
PET/CT
= CMR



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Take Home Messages

- Treatment of patients with MBM
  - Requires a multidisciplinary approach (incl. neuro-radiologist, neurosurgeon, radiation- and medical oncology with expertise)
- New active medical treatment options have become available
  - BRAFi/MEKi in BRAF V600mut melanoma: high ORR, irrespective of tumor burden, suboptimal duration of response
  - PD-1/CTLA-4 inhibition: encouraging activity/durability in patients with low tumor burden CNS involvement
- Post (radiation) treatment necrosis of the brain

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