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Brain metastases: future developments

Emilie Le Rhun

Lille, France

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Disclosures

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Brain metastases: future developments

- Lung cancer
- Melanoma
- Breast cancer
- Challenges for brain metastases patients

Clinical challenge

Neuro-Oncology
19(11), 1511–1521, 2017 | doi:10.1093/neuonc/nox077 | Advance Access date 30 May 2017

Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study

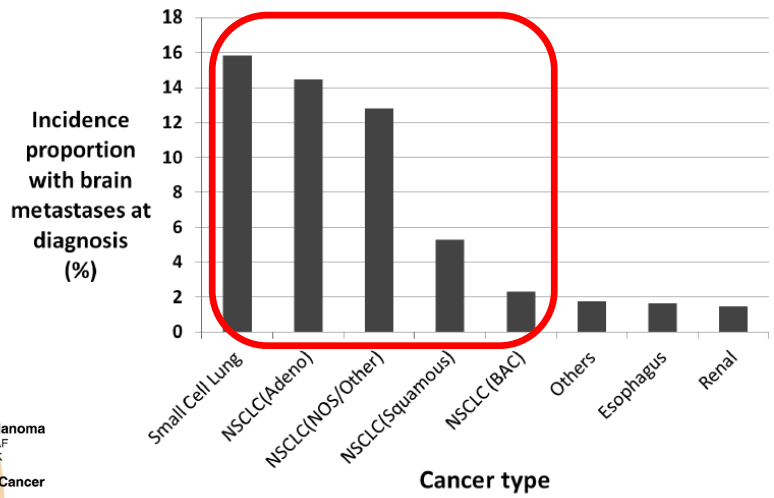
Daniel N. Cagney,* Allison M. Martin,* Paul J. Catalano, Amanda J. Redig, Nancy U. Lin, Eudocia Q. Lee, Patrick Y. Wen, Ian F. Dunn, Wenya Linda Bi, Stephanie E. Weiss, Daphne A. Haas-Kogan, Brian M. Alexander, and Ayal A. Aizer

cohort of 1 302 166 patients with diagnoses of non-hematologic malignancies originating outside of the CNS between 2010-2013

26 430 patients with brain metastases at diagnosis of cancer (2%)

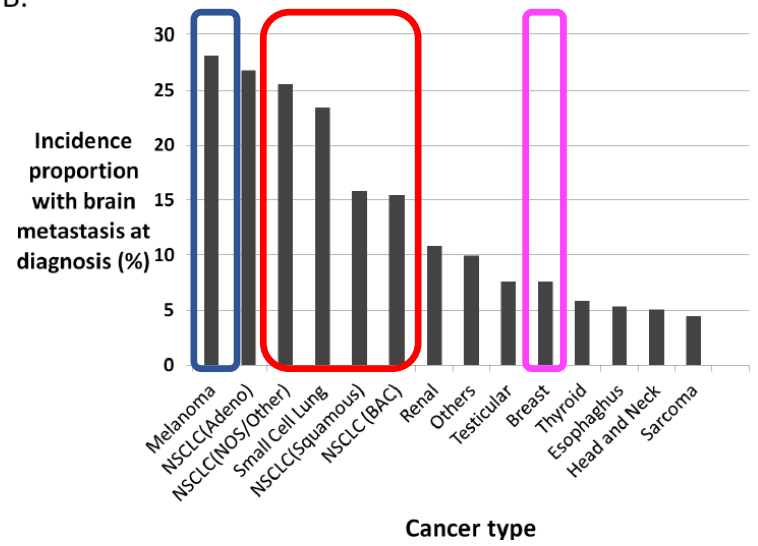
among the entire cohort (2% of the whole population)

A.



amonth the subset with metastatic disease (12.1% of the whole population)

B.



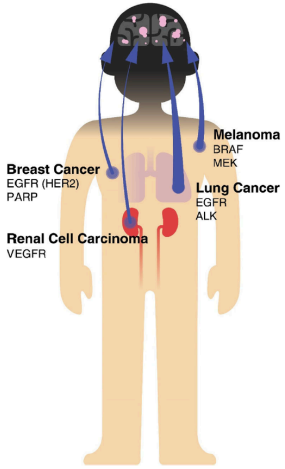


Fig. 2 Primary tumors that preferentially metastasize to the brain and the occurrence of brain metastases from each of these primary tumors. Examples of key tumor driving oncogenes are represented for each tumor type.

Kim et al., 2018

European Journal of Cancer 96 (2018) 64–72
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
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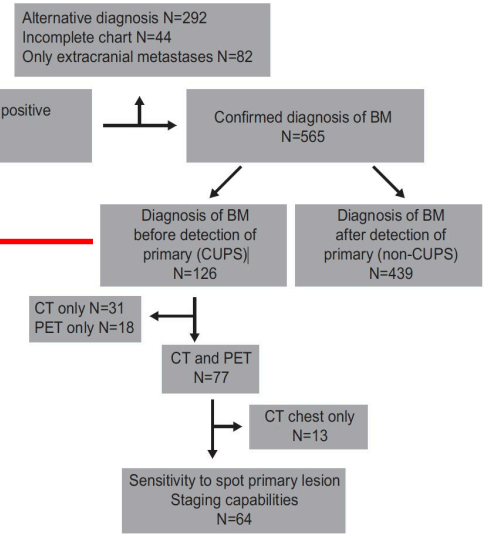
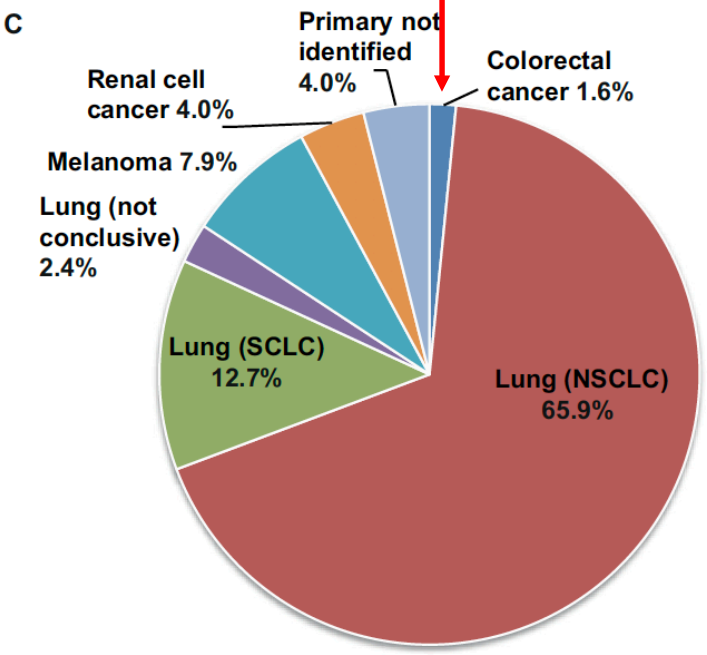
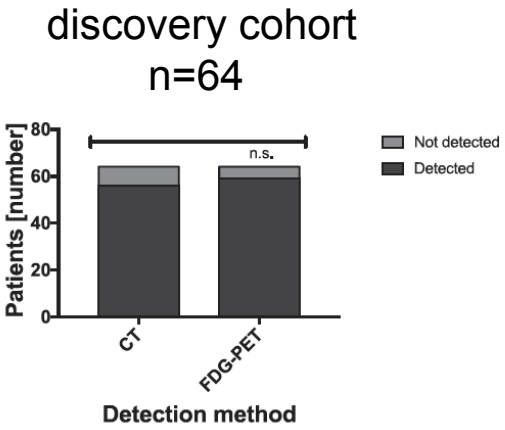
Original Research

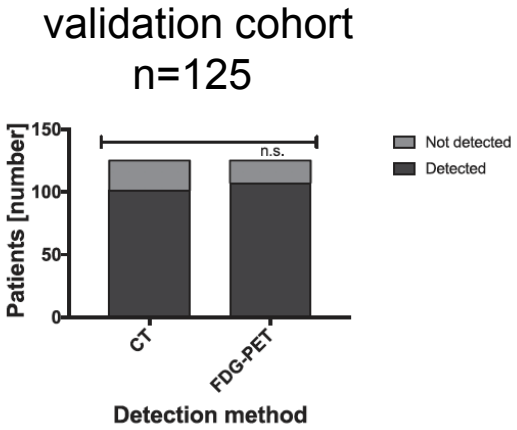
Diagnostic value of ^{18}F-fluordesoxyglucose positron emission tomography for patients with brain metastasis from unknown primary site

Fabian Wolpert [a,*], Michael Weller [a], Anna Sophie Berghoff [b], Elisabeth Rushing [c], Lisa Michaela Füreder [b], Gregory Petyt [d], Henning Leske [e], Nicolaus Andratschke [e], Luca Regli [f], Marian Christoph Neidert [f], Roger Stupp [g], Rolf Stahel [g], Reinhard Dummer [h], Thomas Frauenfelder [i], Patrick Roth [a], Nicolas Reyns [j], Philipp Antonio Kaufmann [k], Matthias Preusser [b], Emilie Le Rhun [a,l,m,n]









Overall sensitivities of diagnostic methods shown by stacked columns, showing the respective method and number of patients in which the primary tumour was detected (dark grey) or not detected (light grey)

FDG-PET/CT was not superior to chest/abdomen CT in localising the primary lesion

- In a meta-analysis of 413 NSCLC clinical trials

- 31% of the industry sponsored

- 16% of university/investigator-sponsored trials

allowed inclusion of patients with known brain metastases

- For cancer other than NSCLC, the majority of oncology clinical trials have excluded patients with brain metastases.

BRIEF REPORT

A Brief Report of the Status of Central Nervous System Metastasis Enrollment Criteria for Advanced Non-Small Cell Lung Cancer Clinical Trials: A Review of the ClinicalTrials.gov Trial Registry

Caroline E. McCoach, MD, PhD,[a,*] Eamon M. Berge, MD,[a] Xian Lu, MS,[b] Anna E. Barón, PhD,[b] D. Ross Camidge, MD, PhD[a]

[a]Division of Medical Oncology, University of Colorado, Denver, CO, USA
[b]Department of Biostatistics and Informatics, Colorado School of Public Health, Denver, CO, USA

Received 17 July 2015; revised 25 October 2015; accepted 30 October 2015

Table 3. Univariate Analysis of Trial Characteristics by CNS Inclusion/Exclusion

	Strict Exclusion	Allowed[a]	Total	Fisher's Exact Test
Sponsor (81)[b]				$p = 0.1020$
Industry	31	119	150	
University/ investigator	16	120	136	
NCI	3	11	14	
Cooperative group	8	24	32	
Phase (81)[b]				$p = 0.0853$
Phase I	15	83	98	
Phase I/II	4	36	40	
Phase II	27	119	146	
Phase III	13	28	41	
Phase IV	0	7	7	
Industry (79)[b]				$p = 0.3554$
Small pharma	21	74	95	
Large pharma	10	45	55	
Not industry sponsored	28	156	184	
Location (80)[b]				$p = 0.2488$
United States only	20	110	130	
International only	36	141	177	
United States and elsewhere	2	24	26	
Chemotherapy (79)[b]				$p = 1$
No	31	147	178	
Yes	28	128	156	
Targeted treatment (79)[b]				$p = 0.0063$
No	29	83	112	
Yes	30	192	222	
Immunotherapy (79)[b]				$p = 0.0413$
No	45	240	285	
Yes	14	35	49	
Antiangiogenic treatment (79)[b]				$p = 0.8267$
No	51	242	293	
Yes	8	33	41	

Suboptimal drug concentration in the brain metastases

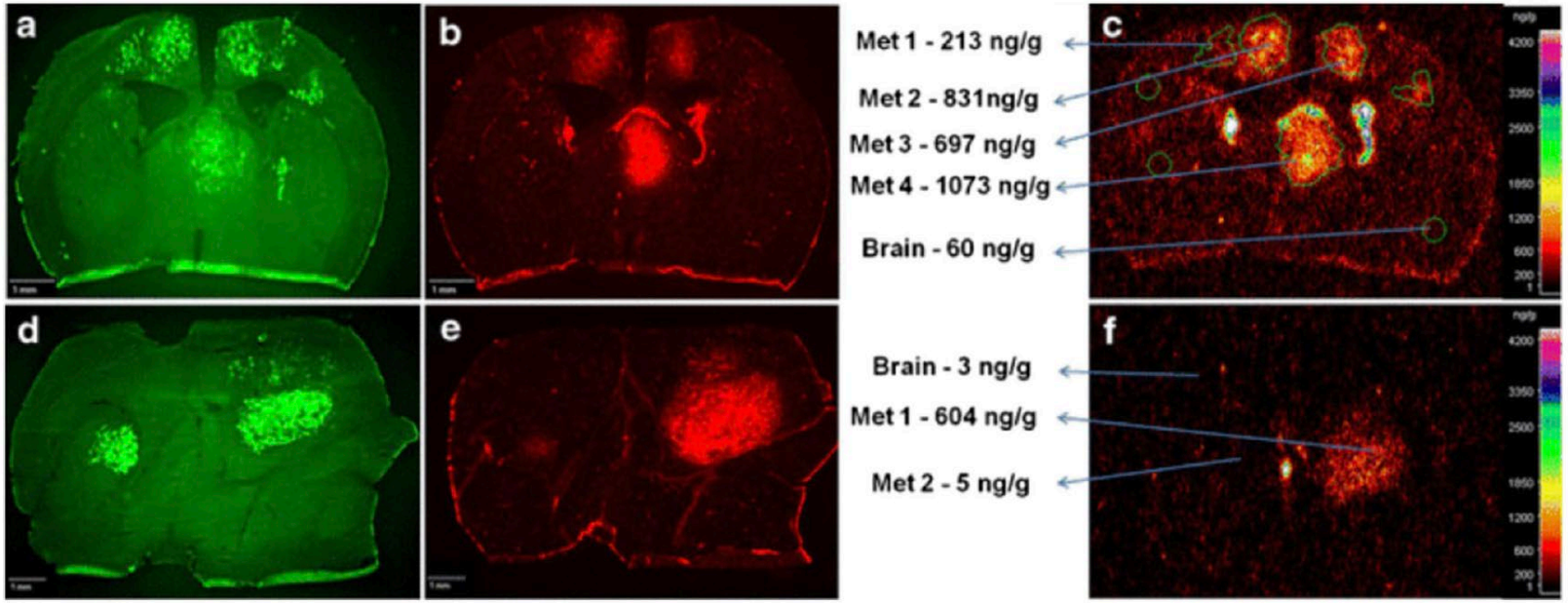
EGPF
(metastatic cells)

Texas Red dextran
(integrity of the BBB)

Lapatinib
(drug concentration)

2 hours after oral administration of 100 mg/kg 14C-lapatinib

12 hours after oral administration of 100 mg/kg 14C-lapatinib



Heterogeneity of BBB disruption and drug concentration in the experimental model (mice) of breast cancer brain metastases (Taskar et al., 2012)

14C-lapatinib measured in normal brain and different brain metastases by quantitative autoradiography

Pharm Res (2018) 35: 177
https://doi.org/10.1007/s11095-018-2455-9

EXPERT REVIEW

Barriers to Effective Drug Treatment for Brain Metastases: A Multifactorial Problem in the Delivery of Precision Medicine

Minjee Kim[1] • Sani H. Kizilbash[2] • Janice K. Laramy[1] • Gautham Gampa[1] • Karen E. Parrish[1] • Jann N. Sarkaria[2] • William F. Elmquist[1]

Blood brain barrier
Blood tumor barrier

Table II Brain and Transporter Related Features of Molecularly Targeted Therapy for Lung Cancer

Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-dinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Gefitinib	EGFR-TKI	750–1000	1.07–3.58	27	27%	P-gp substrate	(109,192)
Erlotinib	EGFR-TKI	150	2.77–5.1	13.7	82.4% (EGFR mutation)	P-gp and Bcrp substrate	(93,108,193)
Afatinib	EGFR-TKI	50	0.7	ND	35%	P-gp substrate	(114,194)
Osimertinib	EGFR-TKI	80	NA	180	ND	P-gp and Bcrp substrate	(115)
AZD3759	EGFR-TKI	100–1000	111	282	83%	ND	(117)
Crizotinib	ALK-TKI	500	0.26	23	18–33%	P-gp substrate but not Bcrp	(100)
Alectinib	ALK-TKI	1200	0.3	63–94	52%	Not a P-gp substrate	(127–129)
Ceritinib	ALK-TKI	400	ND	15	34.5–58.8%	P-gp and Bcrp substrate	(132,195,196)
Brigatinib	ALK and EGFR TKI	300	ND	ND	53%	ND	(197)
Lorlatinib (PF-06463922)	ALK-TKI	100	ND	64	ND	Not a P-gp substrate	(133)
Entrectinib	ALK-TKI	ND	ND	43	ND	ND	(134,198)

(ND, not determined; NA, not available)
*Total drug concentrations are reported

Table III Brain and Transporter Related Features of Molecularly Targeted Therapy for Melanoma

Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-dinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Vemurafenib	BRAF inhibitor	960 (b.i.d.)	0.98	0.012	NA	P-gp and Bcrp substrate	(144,199)
Dabrafenib	BRAF inhibitor	150 × 2 (b.i.d.)	ND	4.4	71–78	P-gp and Bcrp substrate	(70,149)
Cobimetinib	MEK inhibitor	60	ND	8	Under investigation (NCT02537600)	P-gp substrate (Not Bcrp)	(154)
Trametinib	MEK inhibitor	2	ND	0.28	NA	P-gp substrate, but not Bcrp	(71)
E6201	MEK inhibitor		ND	270	NA	Minimal effect with P-gp and Bcrp	(200)

(ND, not determined; NA, not available)
*Total drug concentrations are reported

Table IV Brain and Transporter Related Features of Molecularly Targeted Therapy for Breast Cancer and Renal Cancer Cell

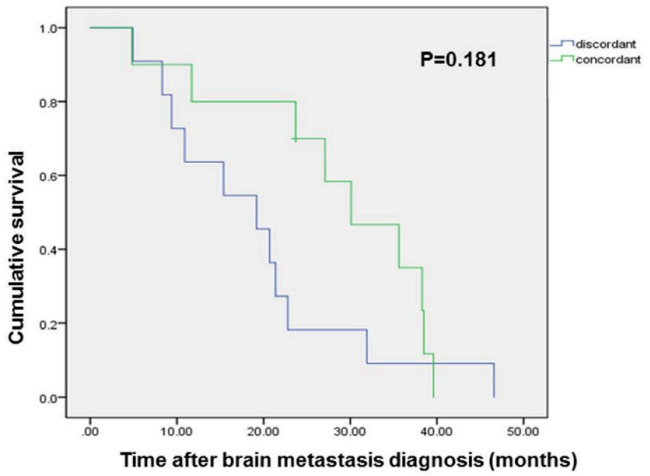
Compound	Molecular target	Dose in patients (mg/day)	Brain penetration (% of CSF to plasma levels) in patient*	Brain penetration (% of brain to plasma ratio) in pre-clinical model*	Response rate in BM patients (%)	Transporter effect	Reference
Lapatinib	EGFR and HER2	1250	0.11	3	6%	P-gp and Bcrp substrate	(99,167,171)
Trastuzumab	HER2	NA	0.24	ND	0.5	NA	(201)
Rucaparib	PARP inhibitor	40	ND	11	ND	P-gp and Bcrp substrate	(97)
Olaparib	PARP inhibitor	400 × 2 (b.i.d.)	ND	1.1#	ND	P-gp substrate	(202)
Veliparib (ABT-888)	PARP inhibitor	400 × 2 (b.i.d.)	ND	less than 5%	ND	P-gp and Bcrp substrate	(95)
Talazoparib (BMN-673)	PARP inhibitor	1	ND	2	ND	P-gp substrate, but not Bcrp	(203)
Niraparib	PARP inhibitor	300	10–52+	85–99	ND	NA	(173)
Vorinostat	HDAC inhibitor	360	ND	4	ND	P-gp and Bcrp substrate	(176)
Sunitinib	TKI	50	ND	42	12	P-gp and Bcrp substrate	(96,182)
Sorafenib	Multi-kinase inhibitor	400 × 2 (b.i.d.)	0.02–3.4+	9.4	ND	P-gp and Bcrp substrate	(204)
Axitinib	VEGFR inhibitor	5 mg × 2 (b.i.d.)	ND	Less than 10%	ND	P-gp and Bcrp substrate	(205)

(ND, not determined; NA, not available)
*Total drug concentrations are reported
Unpublished data
+ in non-human primate

Table 2 ER, PR, and HER2 expression profiles in patients with primary breast cancer and brain metastasis

Brain metastasis	Primary breast cancer		Total
	–	+	
ER status			
–	10 (47.6%)	1 (4.8%)	11 (52.4%)
+	1 (4.8%)	9 (42.9%)	10 (47.6%)
PR status			
–	10 (47.6%)	2 (9.5%)	12 (57.1%)
+	6 (28.6%)	3 (14.3%)	9 (42.9%)
HER2 status			
–	10 (47.6%)	3 (14.3%)	13 (61.9%)
+	2 (9.5%)	6 (28.6%)	8 (38.1%)

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2



	Median Survival (months)	1 year Survival Estimates	2 year Survival Estimates	Log-rank test
Discordant (n=11)	19.20	0.64	0.18	P=0.181
Concordant (n=10)	31.10	0.80	0.60	

Fig. 2 Overall survival comparison between the discordant and concordant groups

Journal of Neuro-Oncology (2018) 137:295–302
https://doi.org/10.1007/s11060-017-2717-0

CLINICAL STUDY

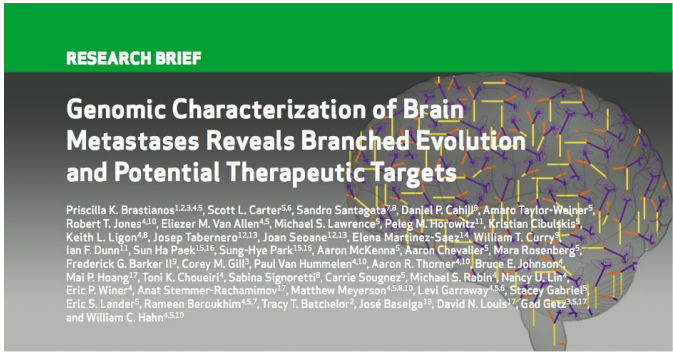
Discordances in ER, PR, and HER2 between primary breast cancer and brain metastasis

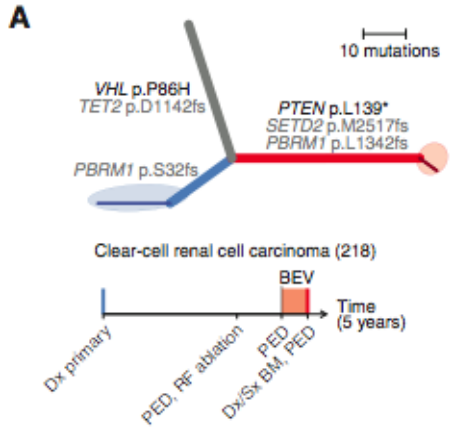
Jaehag Jung[1] · Seung Hoon Lee[2,4] · Mira Park[3] · Ji Hye Youn[4] · Sang Hoon Shin[4] · Ho Shin Gwak[4] · Heon Yoo[4]

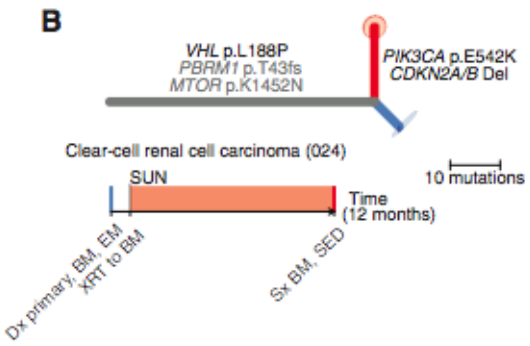
	Markers	No. of cases	Positive conversion	Negative conversion	Total
Gaedcke et al. [16]	ER	23	2	4	6 (26.1%)
	PR	23	2	3	5 (21.7%)
	HER2	23	2	1	1 (4.2%)
Yonomori et al. [17]	ER	24	2	2	4 (16.7%)
	PR	24	0	1	1 (4.2%)
	HER2	24	1	2	3 (12.5%)
Omoto et al. [9]	ER	21	2	2	4 (19.0%)
	PR	21	1	3	4 (19.0%)
	HER2	21	3	1	4 (19.0%)
Hoefnage et al. [7]	ER	44	NA	NA	6 (13.6%)
	PR	44	NA	NA	16 (36.4%)
	HER2	44	NA	NA	1 (2.3%)
Shao et al. [18]	ER	18	0	1	6 (16.2%)
	PR	18	4	4	8 (44.4%)
	HER2	18	1	0	1 (5.6%)
Brogi et al. [4]	ER	37	NA	NA	6 (16.2%)
	PR	39	NA	NA	8 (20.5%)
	HER2	40	0	2	2 (5.0%)
Duchnowska et al. [10]	ER	120	13	22	35 (29.2%)
	PR	119	11	18	29 (24.4%)
	HER2	119	10	7	17 (14.3%)
Total	ER	287			62 (21.6%)
	PR	288			71 (26.7%)
	HER2	289			31 (10.7%)

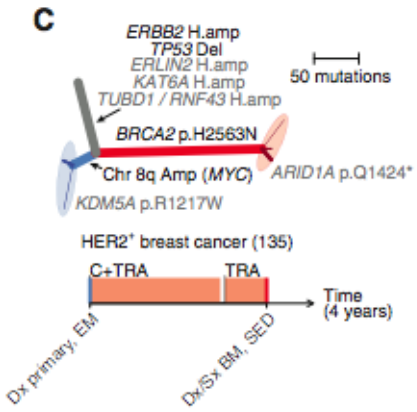
ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *NA* not applicable

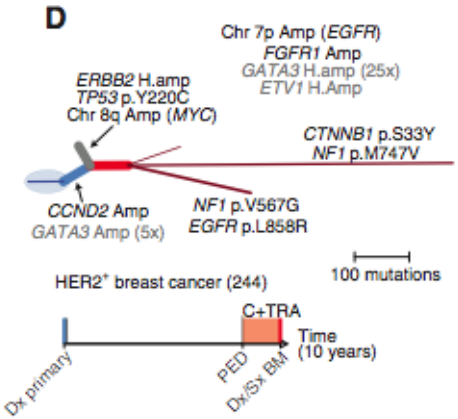
Heterogeneity of the brain metastases

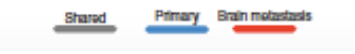












Brain metastases: future developments

- **Lung cancer**
- Melanoma
- Breast cancer
- Challenges for brain metastases patients

J. Remon[1*] and Benjamin Besse[2,3*]

REVIEW
published: 11 April 2018

TABLE 1 | Efficacy of EGFR tyrosine kinase inhibitors (TKIs) in *EGFR*-mutant non-small cell lung cancer (NSCLC) patients and brain metastases (BM).

Drug	Trial	*N*	icRR (%)	icDOR (months)	icPFS (months)
Erlotinib	Retrospective (29)	17	82	NA	11.7
	Ph II (30)	8	58.4	NA	10.1
Gefitinib	Ph II (32)	41	88	NA	14.5
	Retrospective (34)	14	43	7.7	9.1
Afatinib	Pooled analysis (37)	81	21[a]	NA	8.2[a]
Icotinib[b]	Ph III (38)	85	65	NA	10.0
AZD3759	Ph I (28)	18	83	NA	NA
Osimertinib	AURA + AURA2 (49, 50)	128	54[c]	NR	1 year: 56%
	AURA3 (51)	116	70[d]	8.9[d]	11.7
	FLAURA (17)	128	66	NA	NR

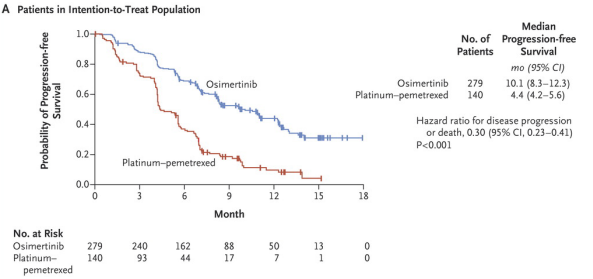
icDOR, intracranial duration of response; icRR, intracranial response rate; icPFS, intracranial progression-free survival; NA, not available; NR, not reached.

[a]*Systemic RR and progression-free survival (PFS).*

[b]*Patients should have at least 3 metastatic brain lesions.*

[c]*In 50 evaluable patients.*

[d]*In 30 evaluable patients with osimertinib.*



Mok, NEJM 2017

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

Yi-Long Wu, Myung-Ju Ahn, Marina Chiara Garassino, Ji-Youn Han, Nobuyuki Katakami, Hye Ryun Kim, Rachel Hodge, Paramjit Kaur, Andrew P. Brown, Dana Ghiorghiu, Vassiliki A. Papadimitrakopoulou, and Tony S.K. Mok

AURA 3

AZD9291 Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer: a phase III study in patients with **EGFR T790M–positive advanced NSCLC who experience disease progression with prior EGFR–TKI**

preplanned CNS analysis: CNS objective response rate

patients with asymptomatic stable CNS metastases

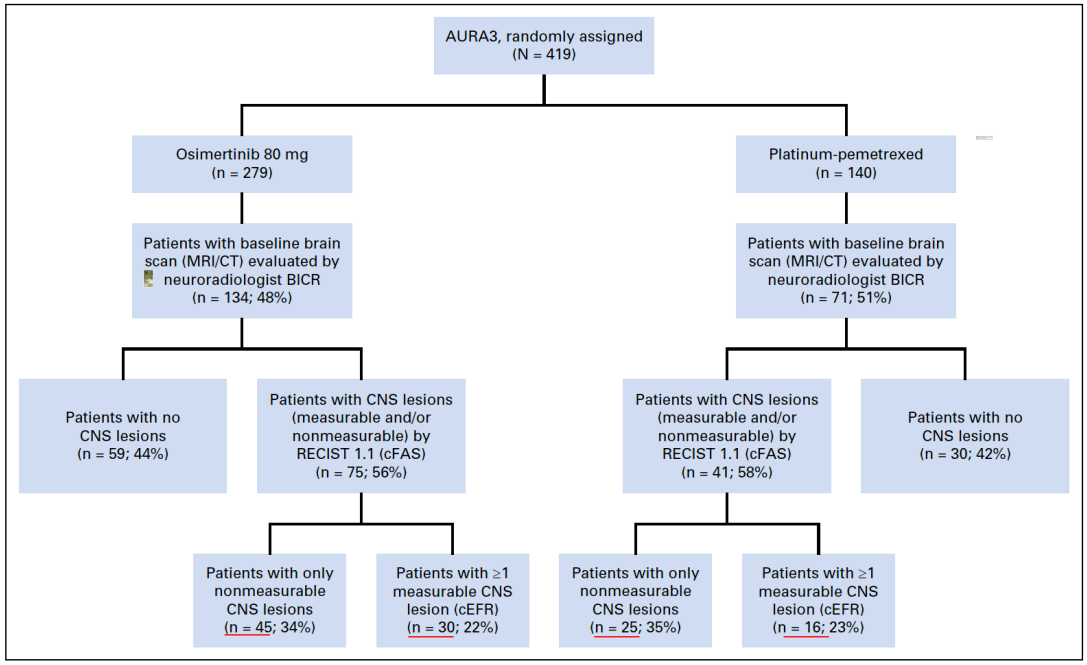


Fig 1. CONSORT diagram. BICR, blinded independent central review; cEFR, CNS evaluable for response set; cFAS, CNS full analysis set; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline brain scans by MRI or computed tomography were mandatory only in those patients with known or suspected CNS metastases at study entry.

Submitted baseline brain scans were assessed for CNS metastases by neuroradiological BICR; for patients with evidence of CNS metastases, follow-up brain scans were performed every 6 weeks until objective systemic disease progression. Brain scans could be performed on study in patients with no baseline brain scans if clinically indicated.

Patients with nonmeasurable and/or measurable CNS lesions on baseline brain scan by BICR were included in the CNS full analysis set, referred to herein as cFAS. The CNS evaluable for response set included only patients with ≥ 1 measurable CNS lesion (≥ 10 mm in the longest diameter), referred to herein as cEFR.

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018
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AURA 3

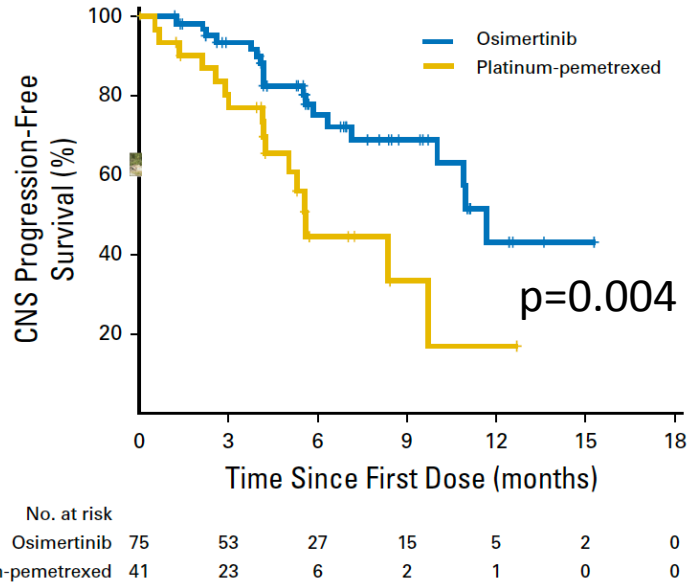
AZD9291 Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer: a phase III study in patients with EGFR T790M–positive advanced NSCLC who experience disease progression with prior EGFR–TKI

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)
Yi-Long Wu, Myung-Ju Ahn, Marina Chiara Garassino, Ji-Youn Han, Nobuyuki Katakami, Hye Ryun Kim, Rachel Hodge, Paramjit Kaur, Andrew P. Brown, Dana Ghiorghiu, Vassilki A. Papadimitrakopoulou, and Tony S.K. Mok

Table 2. Central Nervous System Response to Osimertinib, Compared With Platinum-Pemetrexed

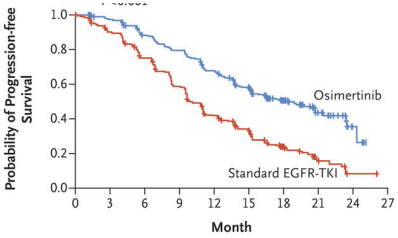
Analysis Set/Response	cFAS		cEFR	
	Osimertinib (n = 75)	Platinum-Pemetrexed (n = 41)	Osimertinib (n = 30)	Platinum-Pemetrexed (n = 16)
CNS ORR, No. (%)*†	30 (40)	7 (17)	21 (70)	5 (31)
CR	11 (15)	3 (7)	2 (7)	1 (6)
PR	19 (25)	4 (10)	19 (63)	4 (25)
Stable disease ≥ 6 weeks	35 (47)	21 (51)	7 (23)	5 (31)
PD	1 (1)	2 (5)	1 (3)	0
Not evaluable‡	8 (11)	9 (22)	1 (3)	5 (31)
CNS DCR, % (95% CI)	87 (77 to 93)	68 (52 to 82)	93 (78 to 99)	63 (35 to 85)
CNS DoR*§‖				
Median, months (95% CI)	8.9 (4.3 to NC)	5.7 (4.4 to 5.7)	8.9 (4.3 to NC)	5.7 (NC to NC)
Estimated % remaining in response (95% CI)‖				
At 3 months	88 (66 to 96)	100 (100 to 100)	88 (59 to 97)	100 (100 to 100)
At 6 months	67 (38 to 84)	0 (NC to NC)	70 (37 to 88)	0 (NC to NC)
At 9 months	45 (9 to 76)	0 (NC to NC)	47 (9 to 79)	0 (NC to NC)
Time to onset of response				
Median, (weeks, interquartile range)	9.1 (5.4-13.9)	6.1 (5.3-25.4)	6.1 (5.4-12.1)	6.1 (6.0-17.4)
≤ 6 weeks, No. (%)	15 (50)	4 (57)	13 (62)	3 (60)

Abbreviations: cEFR, CNS evaluable for response set; cFAS, CNS full analysis set; CR, complete response; DCR, disease control rate; DoR, duration of response; NC, not calculable; ORR, objective response rate; PD, progressive disease; PR, partial response.
*Responses did not require confirmation, per RECIST 1.1 guidance on randomized studies.
†For patients with nontarget lesions only, response could be classed as CR; non-CR, non-PD; PD or not evaluable, but not PR. Stable disease listed in the table includes non-CR, non-PD in patients with nontarget lesions only.
‡Due to no evaluable follow-up assessments.
§Duration of response is time from first documentation of CR/PR until date of progression or death in the absence of progression.
‖Calculated using Kaplan-Meier technique.



Full set of patients, median CNS PFS
- osimertinib: 11.7 months (95% CI, 10 months to NC)
- platinum pemetrexed :5.6 months (95% CI 4.2 to 9.7 months)
(HR, 0.32; 95% CI, 0.15 to 0.69; P = .004)

Osimertinib median PFS 18.9 months



No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard	277	239	197	152	107	78	37	10	2	0

Soria, NEJM 2018

preplanned CNS analysis: CNS PFS by neuroradiologic BICR.

FLAURA

Phase III, Double-Blind, Randomised Study to Assess the **Efficacy and Safety of AZD9291 versus a SOC EGFR as First-Line Treatment** in Patients with **EGFR Mutation Positive**, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste

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Exclusion criteria

5. Spinal cord compression, symptomatic and unstable brain metastases, requiring steroids over the last 4 weeks prior to randomisation in this study (asymptomatic or symptomatic brain metastases stable for at least 4 weeks and off steroids are allowed).

Specifically, patients with known or suspected brain metastases at screening should have a CT/MRI of the brain at baseline. Patients with confirmed brain metastases at baseline should be followed up on study with repeated CT/MRI assessment using the same frequency as the other RECIST assessments. The same modality for CT/MRI should be used for a patient throughout the study. Brain metastases will be assessed as non-target lesions.

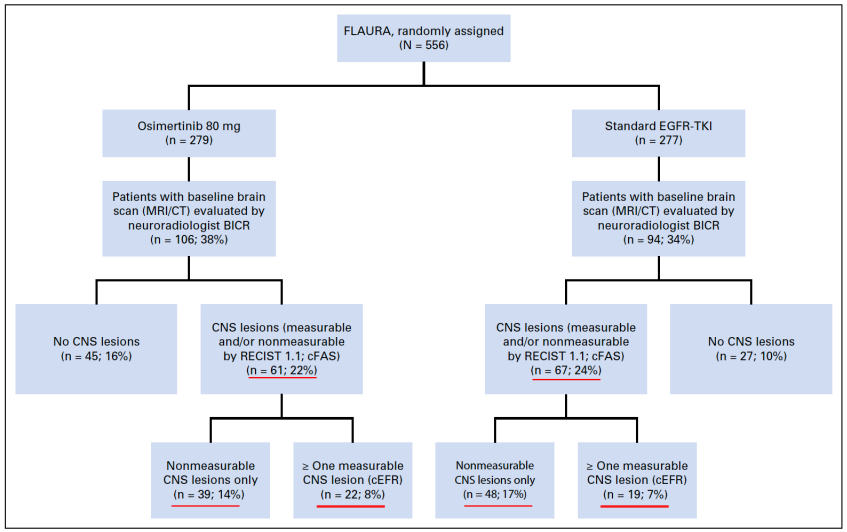

Fig 1. CONSORT diagram. Patient disposition. BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full-analysis set; CT, computed tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; TKI, tyrosine kinase inhibitor.

CNS efficacy was assessed according to RECIST (version 1.1).

CNS metastases identified on MRI and/or CT scans that were ≥ 10 mm in longest diameter or ≥ two times the slice thickness or reconstruction interval were considered measurable lesions and could be selected as target lesions (TLs; up to a maximum of five).

All other lesions, including suspected LMs, were considered NTLs. Patients with measurable and/or nonmeasurable CNS metastases on available baseline brain scans were included in the CNS full-analysis set (cFAS). The CNS evaluable-for-response set (cEFR) included only patients with ≥ one measurable CNS lesion.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

FLAURA

Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a SOC EGFR as First-Line Treatment in Patients with EGFR Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alexandra Bertolini, Sabine Bohnet, Gaicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste

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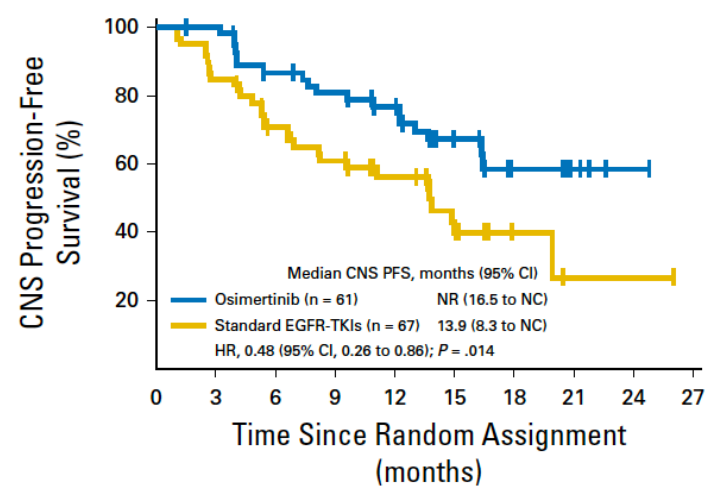
Table 3. CNS Response to Osimertinib Versus Standard EGFR-TKIs

Response	cFAS (n = 128) Osimertinib (n = 61)	cFAS (n = 128) Standard EGFR-TKIs (n = 67)	cEFR (n = 41) Osimertinib (n = 22)	cEFR (n = 41) Standard EGFR-TKIs (n = 19)
CNS ORR, No. (%)*	40 (66)	29 (43)	20 (91)	13 (68)
CR	25 (41)	16 (24)	5 (23)	0
PR	15 (25)	13 (19)	15 (68)	13 (68)
SD ≥ 6 weeks†	15 (25)	27 (40)	1 (5)	4 (21)
PD	0	5 (7)	0	2 (11)
Not evaluable	6 (10)	6 (9)	1 (5)	0
CNS DCR, No. (%)	55 (90)	56 (84)	21 (95)	17 (89)
95% CI‡	80 to 96	73 to 92	77 to 100	67 to 99
OR§	1.8		2.5	
95% CI	0.6 to 5.5		0.2 to 55.8	
P¶	.269		.462	
Median time to response, weeks (interquartile range)	6 (6-12)	12 (6-18)	6 (6-6)	6 (6-12)
Median CNS DoR, months (95% CI)	NR (11.9 to NC)	14.4 (7.0 to 18.7)	15.2 (4.1 to NC)	18.7 (4.2 to 18.7)
Estimated % remaining in response (95% CI)*‖				
At 3 months	92 (77 to 97)	89 (71 to 97)	85 (60 to 95)	85 (51 to 96)
At 6 months	86 (70 to 94)	76 (55 to 89)	75 (50 to 89)	65 (30 to 85)
At 9 months	80 (63 to 90)	67 (43 to 82)	65 (40 to 81)	54 (21 to 78)
At 12 months	65 (46 to 79)	67 (43 to 82)	58 (33 to 77)	54 (21 to 78)



No. at risk:

Osimertinib	61	54	44	40	34	21	8	4	1	0
Standard EGFR-TKIs	67	50	37	31	21	13	4	1	1	0

VOLUME 35 · NUMBER 10 · APRIL 1, 2017
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

William J. Magnuson, Nataniel H. Lester-Coll, Abraham J. Wu, T. Jonathan Yang, Natalie A. Lockney, Naamit K. Gerber, Kathryn Beal, Arya Amini, Tejas Patil, Brian D. Kavanagh, D. Ross Camidge, Steven E. Braunstein, Lauren C. Boreta, Suresh K. Balasubramanian, Manmeet S. Ahluwalia, Niteshkumar G. Rana, Albert Attia, Scott N. Gettinger, Joseph N. Contessa, James B. Yu, and Veronica L. Chiang

patients with EGFR mutant lung adenocarcinoma who developed brain metastases
351 patients:

- 131 (37%) received EGFR-TKI followed by SRS or WBRT at intracranial progression
- 120 (34%) were treated with WBRT followed by EGFR-TKI
- 100 (29%) received SRS followed by EGFR-TKI

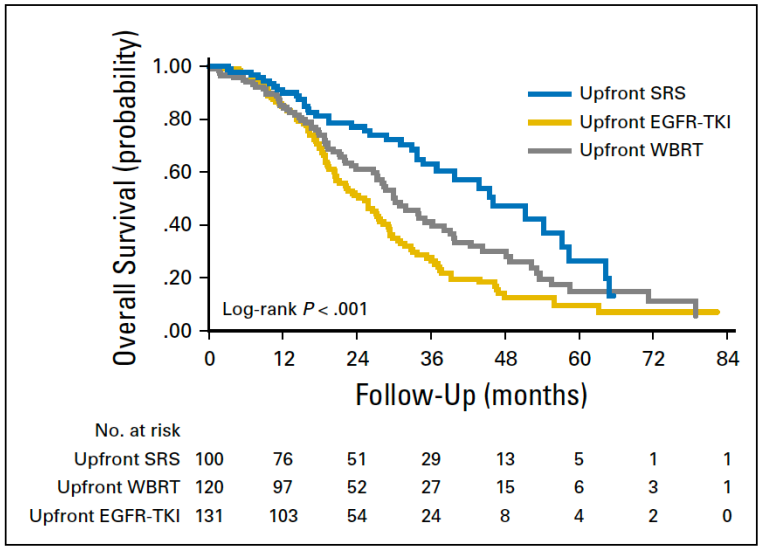


Fig 1. Kaplan-Meier analysis comparing overall survival in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI).

median OS for the
entire cohort: 30 months
SRS group (n = 100): 46 months
WBRT group (n = 120): 30 months
EGFK-TKI group (n = 131): 25 months
(p<0.001).

« SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT. A prospective, multi-institutional randomized trial of SRS followed by EGFR-TKI versus EGFR-TKI followed by SRS at intracranial progression is urgently needed. »

J. Remon[1]* and Benjamin Besse[2,3]*

TABLE 2 | Efficacy of ALK tyrosine kinase inhibitor (TKIs) in patients with baseline brain metastases (BM).

Drug	Trial (reference)	Brain M1	Measurable Brain M1	icRR (%)	icTTP (months)	s/ic PFS (months)	icDOR (monthss)
Crizotinib	PROFILE 1005 + 1007 pooled. ALK-naïve (previous CT) (68)	275	22/18[b]	18/33[b]	7.0/13.2	NA	26.4,/NR[b]
	PROFILE 1014. Ph III ALK-naïve (70)	79	79	85[c]	15.7	sPFS: 9	NA
Ceritinib	ASCEND 5. Ph III Crizotinib + CT resistant (76)	133	17	35 72.7	NA	sPFS: 4.4	6.9 16.6
	ASCEND 4. Ph III ALK-naïve (64)	121	22	62	NA	sPFS: 10.7	NA
	ASCEND 3. Ph II ALK TKI-naïve[a] (75)	49	13	39.4	NA	sPFS: 10.8	9.2
	ASCEND 2. Ph II Crizotinib-resistant (74)	100	33	63	NA	sPFS: 5.4	8.2,
	ASCEND 1. Ph I Naïve and pretreated (73)	94	36	61[d]	NA	NA	11.1[d]
Alectinib	Pooled analysis of ph II. Crizotinib resistant (85)	136	50	64	9.2	NA	10.8
	ALUR ph II. Crizotinib and CT resistant (86, 87)	76	40	54	NA	sPFS: 9.6	17.3
	ALEX. Ph III. ALK TKI-naïve (65, 72)	122	21	81	NA	sPFS: 25.7	
Lorlatinib	Ph I in *ALK*-positive (11% crizotinib-naïve) (90)	41	19	42	NA	sPFS: 9.6	12.4
	Ph I in *ROS1*-positive (90)	12	5	60	NA	sPFS: 7.0	12.0
	Ph II in *ALK/ROS1*-positive (91)						
	ALK TKI treatment-naïve	8	8	75	NA	NR	NA
	Prior crizotinib only and crizotinib ± 1-2 CT	37	37	68	NA	NR	NA
	No-crizotinib TKI ± CT	12	12	42	NA	sPFS: 5.5	NA
	2-3 ALK TKI ± CT	83	83	48	NA	sPFS: 6.9	NA
	ROS1-positive any prior line	25	25	56	NA	sPFS:9.6	NA
Brigatinib	Ph I ALK-naïve and crizotinib resistant (93)	46	15	53	NA	icPFS: 15.6	18.9
	ALTA. Ph II in crizotinib-resistant (94, 95)	153	18	67[e]	NA	icPFS: 18.4[e]	NR[e]

icRR, intracranial response rate; icTTP, intracranial time to progression; s/icPFS, systemic/intracranial progression-free survival (PFS); icDOR, intracranial duration of response; CT, chemotherapy; NA, not available; NR, not reached.

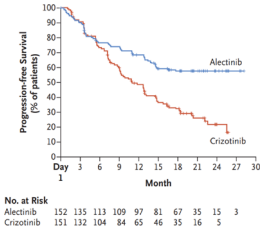
[a]*ALK TKI naive and chemotherapy-naïve or up to three lines of chemotherapy with progression during or after the last chemotherapy regimen.*

[b]*Data reported for previously untreated BM/previously treated BM.*

[c]*12-week intracranial disease control rate.*

[d]*Results expressed as ALK inhibitor-naïve patients, ALK inhibitor-pretreated patients.*

[e]*Patients receiving 180 mg/day.*



Peters et al. 2017

A Study Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants NCT02075840

Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (*ALK*+) non-small-cell lung cancer: CNS efficacy results from the ALEX study

S. Gadgeel[1*], S. Peters[2], T. Mok[3], A. T. Shaw[4], D. W. Kim[5], S. I. Ou[6], M. Pérol[7], A. Wrona[8], S. Novello[9], R. Rosell[10], A. Zeaiter[11†], T. Liu[11], E. Nüesch[11], B. Balas[11] & D. R. Camidge[12]

Received 14 January 2018; revised 1 July 2018; accepted 2 July 2018
Available online - 5 July 2018

Patients with asymptomatic brain or leptomeningeal metastases were eligible; previous CNS radiotherapy was allowed if completed at least 14 days before enrollment.

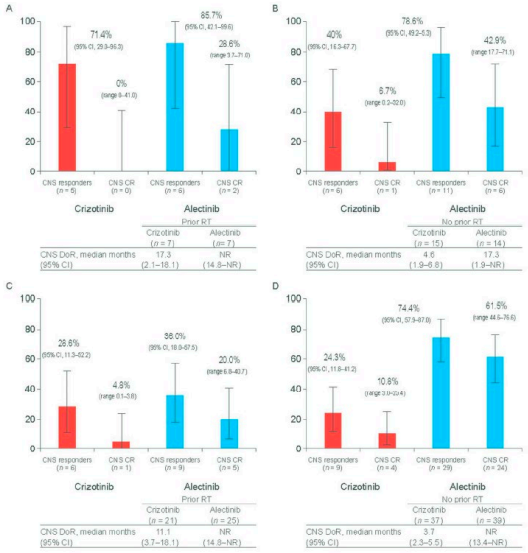
Brain imaging at baseline and every 8 weeks.

Analyse per subgroup:
- patients with/without baseline CNS metastases
- patients with/without prior RT

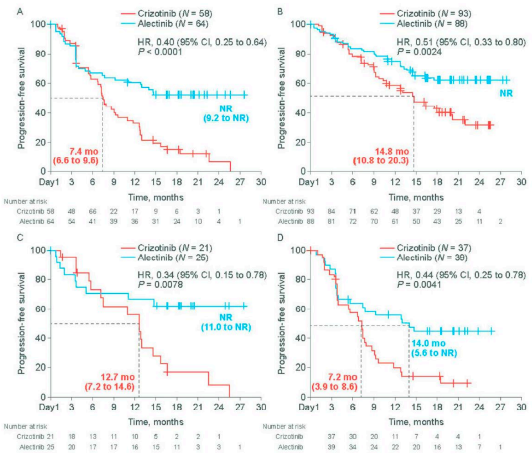
- PFS, CNS objective response rate, time to CNS progression

- 122 patients (alectinib n=84, including 21 with measurable lesions, crizotinib n=58, including 22 with measurable lesions)
- prior RT: alectinib, n=25; crizotinib, n=21

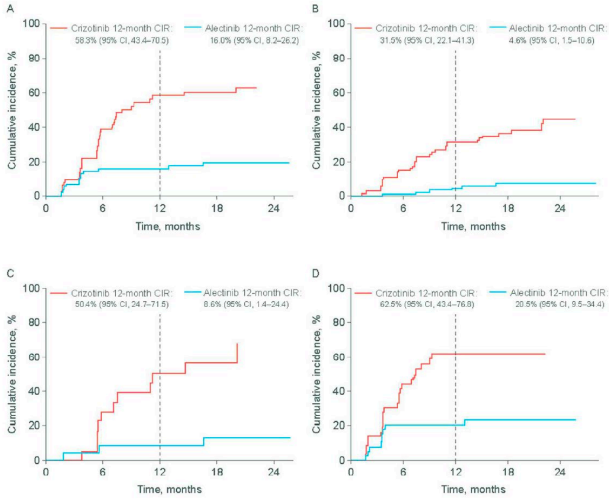
CNS response



PFS according to CNS metastatic status

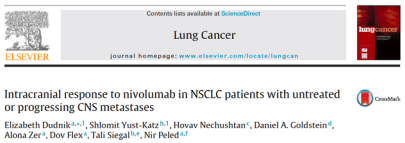


Cumulative incidence rate of CNS progression



(A) patients with CNS metastases at baseline, (B) patients without CNS metastases at baseline, (C) patients with CNS metastases at baseline who had received prior radiotherapy, and (D) patients with CNS metastases at baseline who had not received prior radiotherapy.

Immunotherapy and brain metastasis

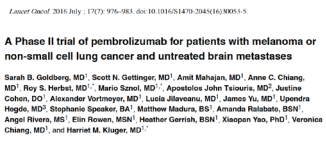

Contents lists available at ScienceDirect

Lung Cancer

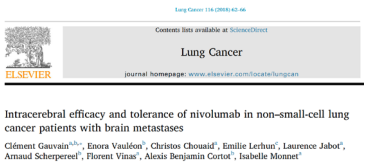
journal homepage: www.elsevier.com/locate/lungcan

Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases

Elizabeth Dudnik[a,*,1], Shlomit Yust-Katz[b,1], Hovav Nechushtan[c], Daniel A. Goldstein[d], Alona Zer[a], Dov Flex[a], Tali Siegal[b,e], Nir Peled[a,f]


A Phase II trial of pembrolizumab for patients with melanoma or non-small cell lung cancer and untreated brain metastases

Sarah B. Goldberg, MD[1], Scott N. Gettinger, MD[1], Amit Mahajan, MD[1], Anne C. Chiang, MD[1], Roy S. Herbst, MD[1,*], Mario Sznol, MD[1,*], Apostolos John Tsiouris, MD[2], Justine Cohen, DO[1], Alexander Vortmeyer, MD[1], Lucia Jilaveanu, MD[1], James Yu, MD[1], Upendra Hegde, MD[3], Stephanie Speaker, BA[1], Matthew Madura, BS[1], Amanda Ralabate, BSN[1], Angel Rivera, MS[1], Elin Rowen, MSN[1], Heather Gerrish, BSN[1], Xiaopan Yao, PhD[1], Veronica Chiang, MD[1], and Harriet M. Kluger, MD[1,*]


Contents lists available at ScienceDirect

Lung Cancer

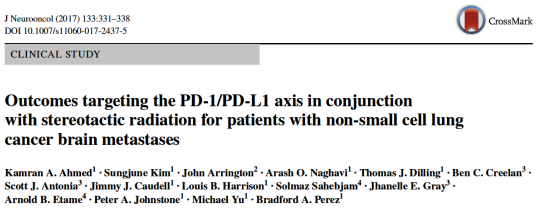
journal homepage: www.elsevier.com/locate/lungcan

Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases

Clément Gauvain[a,b,*], Enora Vauléon[b], Christos Chouaid[b], Emilie Lerhun[c], Laurence Jabot[a], Arnaud Scherpereel[b], Florent Vinas[c], Alexis Benjamin Cortot[b], Isabelle Monnet[c]

NSCLC	Dudnick et al., 2016	Goldberg et al., 2016	Gauvain et al., 2018
Agent	nivolumab	pembrolizumab	nivolumab
Type of study	retrospective cohort	prospective cohort	retrospective cohort
Nb of patients	5 (PD-L1 status not assessed)	18 (all PD-L1 posistive, with a cut-off =1%)	43 (n=30 assessable for CNS response) (PDL1 overexpression: 12%)
Brain metastasis characteristics	3 patients with brain metastases 2 patients with brain and meningeal metastases asymptomatic patients, no steroids, no prior brain focal treat prior to IT	at least one asymptomatic lesion, 5-20 mm, not treated or progressing, local treatment allowed for brain mets with a diameter of at least 20 mm or in eloquent areas	BMs had to be present either on brain magnetic resonance imaging or brain computed-tomography (CT) scans obtained before the first nivolumab dose.
Local treatment prior to IT	WBRT: 1 SRS: 2	none: 44% surgery: 11% WBRT: 33% SRS: 28%	BMs were locally pretreated in 34 (79%) patients and active in 16 (37%) patients.
Intracranial response rate	**40%**	**33%**	**51%**
Duration of response	**21 - 23 weeks +**	**3 - 7 months**	**3.9 months**
Overall survival	NR	NR	7.5 (95% CI: 5.6–not reached) months
Safety	No treatment-related or CNS metastases-related grade ≥ 3 AE	6 grade 3/4 AE serious neurological AE included cognitive dysfunction (n=1) and seizures (n=3)	5 neurological AE (including 1 grade-4 transient ischemic attack of uncertain imputability and 1 grade-3 neurological deficit)

Immunotherapy and SRS/FSRT and brain metastasis



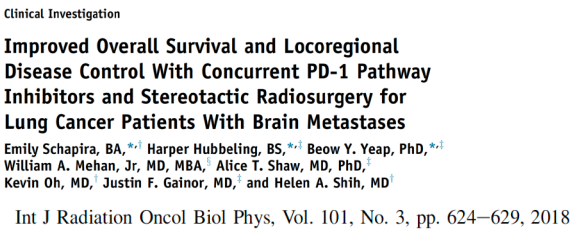
J Neurooncol (2017) 133:331–338
DOI 10.1007/s11060-017-2437-5

CrossMark

CLINICAL STUDY

Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases

Kamran A. Ahmed[1] · Sungjune Kim[1] · John Arrington[2] · Arash O. Naghavi[1] · Thomas J. Dilling[1] · Ben C. Creelan[3] · Scott J. Antonia[3] · Jimmy J. Caudell[1] · Louis B. Harrison[1] · Solmaz Sahebjam[4] · Jhanelle E. Gray[3] · Arnold B. Etame[4] · Peter A. Johnstone[1] · Michael Yu[1] · Bradford A. Perez[1]



Clinical Investigation

Improved Overall Survival and Locoregional Disease Control With Concurrent PD-1 Pathway Inhibitors and Stereotactic Radiosurgery for Lung Cancer Patients With Brain Metastases

Emily Schapira, BA,*,† Harper Hubbeling, BS,*,‡ Beow Y. Yeap, PhD,*,‡ William A. Mehan, Jr, MD, MBA,§ Alice T. Shaw, MD, PhD,† Kevin Oh, MD,† Justin F. Gainor, MD,‡ and Helen A. Shih, MD†

Int J Radiation Oncol Biol Phys, Vol. 101, No. 3, pp. 624–629, 2018

NSCLC	Ahmed et al., 2017	Schapira et al., 2018
Number of patients	17	37
Type of study	retrospective cohort (median FU after cranial met dg: 8.7 months)	retrospective cohort (median FU after SRS 14.3 months)
IT	nivolumab (anti-PD1) or durvalumab (anti-PDL1)	nivolumab (n=31), pembrolizumab (n=2), atezolizumab (n=4)
RT	SRS or FSRT	SRS before IT (n=24) SRS concurrent (n=8) SRS after (n=5)
Local brain control	96%	1-year LC: 100% (SRS concurrent or after IT) vs 72.3% (SRS before IT)
Distant brain control	48% at 6 months RT before or during IT: 57% RT after IT: 0% (n=29% of BM)	
Radionecrosis	non surgery for RN	? 10.8% of patients required steroids for SRS toxicity

Brain metastases: future developments

- Lung cancer
- **Melanoma**
- Breast cancer
- Challenges for brain metastases patients

Patients with BRAFV600 mutated melanoma with BM were enrolled into

- cohort 1 (previously untreated BM)
- cohort 2 (previously treated BM)

Table 2. Intracranial BORR assessed by IRC and investigator

	Cohort 1 (*n*=90)	Cohort 2 (*n*=56)	Total (*n*=146)
IRC assessment			
Complete response	2 (2%)	0	2 (1%)
Partial response	14 (16%)	10 (18%)	24 (16%)
Stable disease	39 (43%)	23 (41%)	62 (43%)
Progressive disease	29 (32%)	19 (34%)	48 (33%)
Not evaluable	6 (7%)	4 (7%)	10 (7%)
Number of responders	16 (18%)	10 (18%)	26 (18%)
[95% CI]	[11–27]	[9–30]	[12–25]
Investigator assessment			
Complete response	2 (2%)	0	2 (1%)
Partial response	24 (27%)	13 (23%)	37 (25%)
Stable disease	36 (40%)	30 (54%)	66 (45%)
Progressive disease	25 (28%)	11 (20%)	36 (25%)
Not evaluable	3 (3%)	2 (4%)	5 (3%)
Number of responders	26 (29%)	13 (23%)	39 (27%)
[95% CI]	[20–39]	[13–36]	[20–35]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 634–641, 2017
doi:10.1093/annonc/mdw641
Published online 19 December 2016

ORIGINAL ARTICLE

Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study

G. A. McArthur[1*], M. Maio[2], A. Arance[3], P. Nathan[4], C. Blank[5], M.-F. Avril[6], C. Garbe[7], A. Hauschild[8], D. Schadendorf[9], O. Hamid[10], M. Fluck[11], M. Thebeau[12], J. Schachter[13], R. Kefford[14], M. Chamberlain[15], M. Makrutzki[16], S. Robson[16], R. Gonzalez[17] & K. Margolin[18]

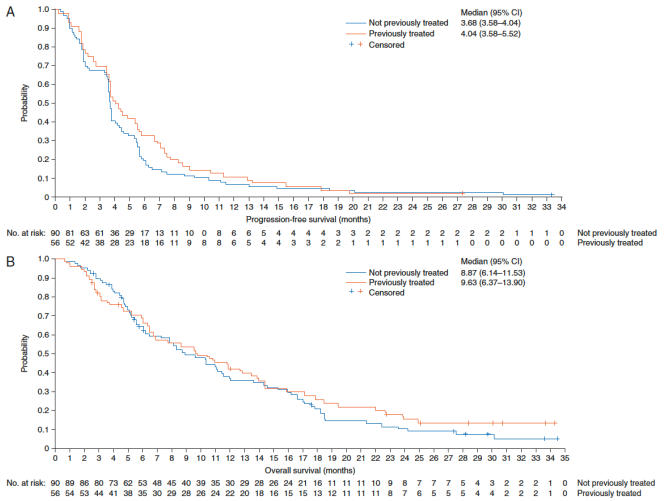


Figure 3. (A) Kaplan–Meier plot of PFS as assessed by the investigator (brain only). (B) Kaplan–Meier plot of OS.

multicentre, open-label, phase 2 trial

Val600Glu or Val600Lys BRAF-mutant melanoma and at least one asymptomatic brain metastasis (≥5 mm and ≤40 mm in diameter). ECOG PS 0-1

- cohort A: no previous local treatment for brain metastases
- cohort B had progressive brain metastases after previous local treatments.

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***

Lancet Oncol 2012; 13: 1087–95

	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%)

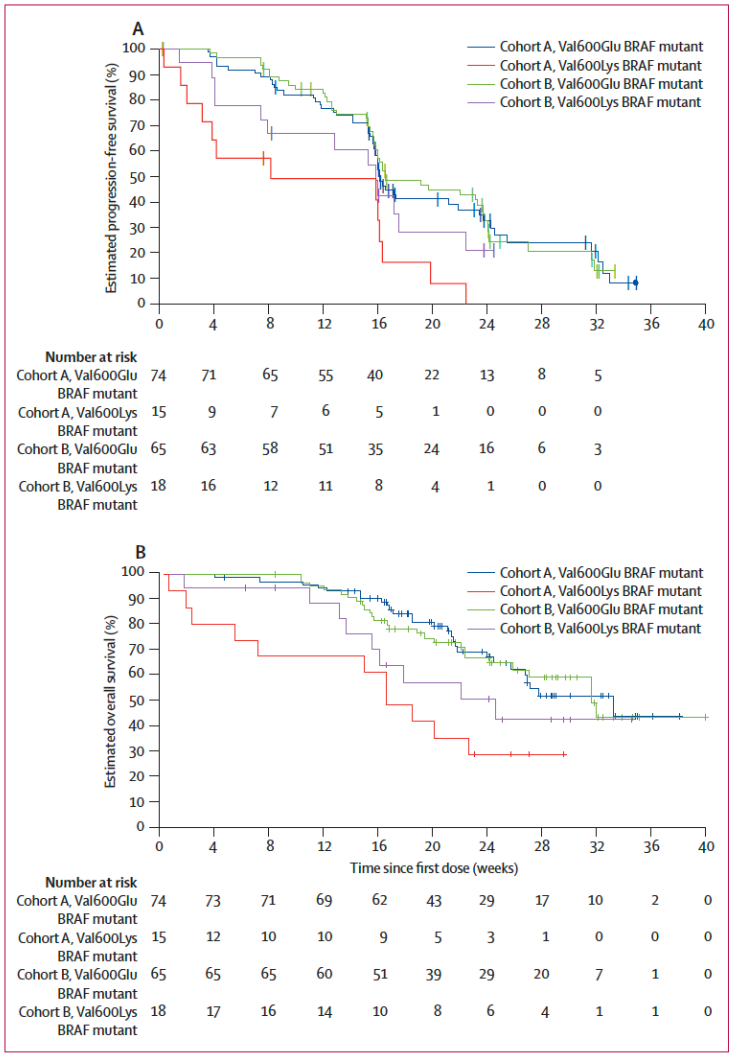


Figure 3: Confirmed progression-free survival (A) and overall survival (B) by cohort and BRAF mutation subtype

multicentre, multicohort, open-label, phase 2 study evaluated oral dabrafenib + oral trametinib in four patient cohorts with melanoma brain :

(A) BRAFV600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, ECOG PS: 0-1,
(B) BRAFV600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOGPS: 0-1
(C) BRAFV600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOGPS: 0-1,
(D) BRAFV600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOGPS: 0-2.

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*

Lancet Oncol 2017; 18: 863–73

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
Intracranial response				
Overall intracranial response (CR+PR)	44 (58%; 46–69)	9 (56%; 30–80)	7 (44%; 20–70)	10 (59%; 33–82)
Intracranial disease control (CR+PR+SD)	59 (78%)	14 (88%)	12 (75%)	14 (82%)
Intracranial CR	3 (4%)	1 (6%)	0	1 (6%)
Intracranial PR	41 (54%)	8 (50%)	7 (44%)	9 (53%)
Intracranial SD	15 (20%)	5 (31%)	5 (31%)	4 (24%)
Intracranial PD	14 (18%)	1 (6%)	4 (25%)	3 (18%)
Not evaluable	3 (4%)	1 (6%)	0	0
Intracranial duration of response				
Events	29/44 (66%)	6/9 (67%)	4/7 (57%)	8/10 (80%)
Median (95% CI; months)	6·5 (4·9–10·3)	7·3 (3·6–12·6)	8·3 (1·3–15·0)	4·5 (2·8–5·9)
Response at 6 months	63% (45–76)	73% (28–93)	67% (19–90)	13% (1–43)

Ipilimumab

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

Lancet Oncol 2012; 13: 459–65

	Margolin et al., 2012	Margolin et al., 2012	Queirolo et al., 2014	Konstantinou et al., 2014
Number of patients	51 (cohort A)	21 (cohort B)	146	38
Study	phase 2	phase 2	retrospective cohort	retrospective cohort
Patients with symptomatic disease	0	21 (100)	0	8 (21)
Brain control Complete response Partial response Stability	12 (24 [13-38]) 0 8 (16) 4 (8)	2 (10 [1-30]) 1 (5) 0 1 (5)	39 (27) 4 (3) 13 (9) 22 (15)	8 (15.8) 0 2 (5.3) 4 (10.5)
Brain PFS	1.5 (1.2-2.5)	1.2 (1.2-1.3)	UK	UK
Overall survival	7 (IC 95 4.1-10.8)	3.7 (IC 95 1.6-7.3)	4.3 (IC 95 3.4-5.2)	3.3 (IC 95 1.7-5)
Grade 3/4, n(%)	Diarrhea 6 (12) Rash 1 (2)	Hépatitie 2 (10) Rash 1 (5)	9 (6)	UK

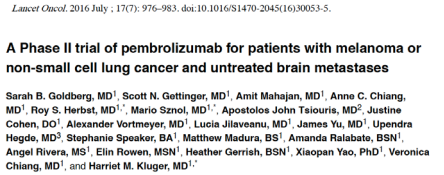
PD1 checkpoint inhibitor monotherapy

BJC

FULL PAPER

British Journal of Cancer

Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases


Lancet Oncol. 2016 July ; 17(7): 976–983. doi:10.1016/S1470-2045(16)30053-5.

A Phase II trial of pembrolizumab for patients with melanoma or non-small cell lung cancer and untreated brain metastases

Sarah B. Goldberg, MD[1], Scott N. Gettinger, MD[1], Amit Mahajan, MD[1], Anne C. Chiang, MD[1], Roy S. Herbst, MD[1,*], Mario Sznol, MD[1,*], Apostolos John Tsiouris, MD[2], Justine Cohen, DO[1], Alexander Vortmeyer, MD[1], Lucia Jilaveanu, MD[1], James Yu, MD[1], Upendra Hegde, MD[3], Stephanie Speaker, BA[1], Matthew Madura, BS[1], Amanda Ralabate, BSN[1], Angel Rivera, MS[1], Elin Rowen, MSN[1], Heather Gerrish, BSN[1], Xiaopan Yao, PhD[1], Veronica Chiang, MD[1], and Harriet M. Kluger, MD[1,*]

	Parakh et al., 2017	Goldberg et al., 2016
	nivolumab (n=6)/pembrolizumab (n=60)	pembrolizumab
Type of cohort	retrospective	prospective
Nb of patients	66	18
Patients with asymptomatic disease	20 (30)	UK
Brain control Complete response Partial response Stable disease	37 (56%) UK UK UK	6 (33%) 0 4 (22% [7-48]) 2 (11%)
Brain PFS	5.3 (3.3-8.2)	UK
Overall survival	9.9 (6.9-17.7)	UK
Grade 3/4, n(%)	UK	1 (6) (Hepatitis)

at least one measurable, nonirradiated brain metastasis (tumor diameter, 0.5 to 3 cm) and no neurologic symptoms

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.

N ENGL J MED 379;8 NEJM.ORG AUGUST 23, 2018

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)

Table 3. Adverse Events.*

Event	Any Grade (N=94)	Grade 3 or 4 (N=94)
	no. of patients (%)	
Any adverse event	91 (97)	56 (60)
Treatment-related adverse event	90 (96)	52 (55)
Fatigue	45 (48)	4 (4)
Increased ALT level	35 (37)	15 (16)
Maculopapular rash	34 (36)	7 (7)
Diarrhea	33 (35)	6 (6)
Increased AST level	32 (34)	14 (15)
Nausea	26 (28)	2 (2)
Headache	21 (22)	3 (3)
Hypothyroidism	20 (21)	1 (1)
Decreased appetite	16 (17)	1 (1)
Increased lipase level	14 (15)	8 (9)
Hyperthyroidism	12 (13)	3 (3)
Vomiting	12 (13)	2 (2)
Increased amylase level	11 (12)	6 (6)
Hypophysitis	11 (12)	5 (5)
Pneumonitis	8 (9)	2 (2)
Rash	8 (9)	2 (2)
Anemia	8 (9)	1 (1)
Colitis	7 (7)	7 (7)
Abdominal pain	7 (7)	1 (1)
Adrenal insufficiency	6 (6)	1 (1)
Increased blood bilirubin level	6 (6)	1 (1)
Hyponatremia	5 (5)	1 (1)
Treatment-related adverse event leading to discontinuation of treatment	25 (27)	19 (20)

Treatment-related grade 3 or 4 adverse events were reported in 55% of patients, including events involving the CNS in 7%.

- multicentre open-label randomised phase 2 trial
- Patients with asymptomatic brain metastases with no previous local brain therapy were randomly assigned to cohort A (nivolumab plus ipilimumab) or cohort B (nivolumab).
- Patients with brain metastases in whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease were enrolled in non-randomised cohort C (nivolumab)

nivolumab plus ipilimumab nivolumab

	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%; 95% CI)	15 (56%; 35–75)	16 (46%; 29–63)	4 (21%; 6–46)	5 (20%; 7–41)	1 (6%; 0–30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0
Extracranial response†					
Overall (%; 95% CI)	15 (63%; 41–81)	17 (57%; 37–75)	5 (29%; 10–56)	6 (29%; 11–52)	3 (25%)
Complete response	0	1 (3%)	1 (6%)	2 (10%)	1 (8%)
Partial response	15 (63%)	16 (53%)	4 (24%)	4 (19%)	2 (17%)
Stable disease	3 (13%)	4 (13%)	2 (12%)	2 (10%)	1 (8%)
Progressive disease	5 (21%)	8 (27%)	9 (53%)	11 (52%)	7 (58%)
Non-evaluable	1 (4%)	1 (3%)	1 (6%)	2 (10%)	1 (8%)
Intracranial progression-free survival					
Number of patients with disease progression	10 (37%)	16 (46%)	15 (79%)	20 (80%)	15 (94%)
Median duration, months (95% CI)	NR (4·7–NR)	NR (2·9–NR)	2·6 (1·8–NR)	2·5 (1·7–2·8)	2·3 (1·4–4·3)
At 6 months (95% CI)‡	60% (44–83)	53% (38–73)	21% (9–50)	20% (9–44)	13% (3–46)
Extracranial progression-free survival†					
Number of patients with disease progression	11 (46%)	15 (50%)	14 (82%)	16 (76%)	9 (75%)
Median duration, months (95% CI)	13·8 (5·3–NR)	13·8 (4·9–NR)	2·5 (1·8–NR)	2·6 (1·8–13·8)	2·6 (2·1–13·6)
At 6 months (95% CI)‡	56% (38–83)	51% (35–76)	35% (19–67)	35% (19–64)	19% (5–65)
Overall survival					
Number of patients with disease progression	8 (30%)	13 (37%)	8 (42%)	12 (48%)	13 (81%)
Median duration, months (95% CI)	NR (11·9–NR)	NR (8·5–NR)	NR (6·9–NR)	18·5 (6·9–NR)	5·1 (1·8–NR)
At 6 months (95% CI)‡	80% (65–98)	78% (65–94)	73% (56–96)	68% (52–89)	44% (25–76)

Data are n (%) unless otherwise stated. NR=not reached. *Drug naive refers to combined MEK and BRAF inhibitor therapy-naive patients. †Denominators for percentages are total patients with extracranial metastases, in cohort A drug-naive patients (24) and total cohort (30), cohort B drug-naive patients (17) and total cohort (21), and cohort C (12). ‡Rate estimated from Kaplan-Meier analysis.

Table 2: **Patient outcomes at data cutoff**

Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

Georgina V Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Alexander D Guminski, Michael P Brown, James S Wilmott, Jarem Edwards, Maria Gonzalez, Richard A Scolyer, Alexander M Menzies*, Grant A McArthur*

Lancet Oncol 2018; 19: 672–81

	Cohort A (n=35)			Cohort B (n=25)		Cohort C (n=16)	
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Total number of patients with at least one adverse event	32 (91%)	19 (54%)	3 (9%)†	16 (64%)	4 (16%)	7 (44%)	2 (13%)
Skin	25 (71%)	4 (11%)	0	6 (24%)	0	2 (13%)	0
Rash	20 (57%)	4 (11%)	0	5 (20%)	0	1 (6%)	0
Pruritus	13 (37%)	0	0	2 (8%)	0	2 (13%)	0
Vitiligo	4 (11%)	0	0	2 (8%)	0	1 (6%)	0
Gastrointestinal	24 (69%)	14 (40%)	1 (3%)	11 (44%)	4 (16%)	1 (6%)	0
Diarrhoea or colitis	15 (43%)	7 (20%)	0	5 (20%)	0	1 (6%)	0
Nausea or vomiting	12 (34%)	1 (3%)	0	5 (20%)	0	1 (6%)	0
Hepatitis	10 (29%)	6 (17%)	1 (3%)	4 (16%)	2 (8%)	0	0
Xerostomia	6 (17%)	0	0	1 (4%)	0	0	0
Increased alanine aminotransferase or aspartate aminotransferase	4 (11%)	2 (6%)	0	1 (4%)	0	0	0
Increased amylase	4 (11%)	1 (3%)	0	1 (4%)	0	0	0
Increased lipase	3 (9%)	2 (6%)	0	0	1 (4%)	0	0
Increased alkaline phosphatase or γ-glutamyl transferase	1 (3%)	1 (3%)	0	1 (4%)	1 (4%)	0	0
Fatigue	20 (57%)	1 (3%)	0	9 (36%)	0	1 (6%)	0
Endocrine	11 (31%)	1 (3%)	1 (3%)	1 (4%)	0	1 (6%)	0
Hypophysitis or hypopituitarism	7 (20%)	1 (3%)	1 (3%)	0	0	0	0
Hyperthyroid or thyroiditis	6 (17%)	0	0	1 (4%)	0	1 (6%)	0
Musculoskeletal	12 (34%)	0	0	4 (16%)	0	4 (25%)	0
Arthralgia	7 (20%)	0	0	4 (16%)	0	4 (25%)	0
Myalgia or muscle weakness	6 (17%)	0	0	0	0	0	0
Nervous system	7 (20%)	2 (6%)	0	5 (20%)	0	1 (6%)	2 (13%)
Headache	4 (11%)	0	0	5 (20%)	0	0	1 (6%)
Peripheral neuropathy	3 (9%)	0	0	0	0	1 (6%)	0
Diaphragmatic weakness	0	1 (3%)	0	0	0	0	0
Seizure	0	1 (3%)	0	0	0	0	0
Radionecrosis	0	0	0	0	0	0	1 (6%)
Respiratory	6 (17%)	1 (3%)	1 (3%)	1 (4%)	0	1 (6%)	0
Pneumonitis	4 (11%)	1 (3%)	0	1 (4%)	0	1 (6%)	0
Cough	2 (6%)	0	0	0	0	0	0
Pulmonary oedema	0	0	1 (3%)	0	0	0	0
Other							
Nephritis	2 (6%)	1 (3%)	0	0	0	0	0
Increased creatine phosphokinase	1 (3%)	1 (3%)	0	1 (4%)	0	0	0
Decreased neutrophil	1 (3%)	1 (3%)	0	0	0	0	0

No grade 4 events were reported in cohort B or C and no treatment-related adverse event deaths were reported in any patients. *Some patients had more than one event. †The three patients with grade 4 events also had separate grade 3 events.

Table 3: **Treatment-related adverse events in at least 10% of patients and all grade 3 or 4 events***

Treatment-related adverse events occurred in 34 (97%) of 35 patients in cohort A, 17 (68%) of 25 in cohort B, and eight (50%) of 16 in cohort C. Grade 3 or 4 treatment-related adverse events occurred in 19 (54%) patients in cohort A, four (16%) in cohort B, and two (13%) in cohort C. No treatment-related deaths occurred.

Annals of Oncology 27: 2288–2294, 2016
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Published online 15 September 2016

Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy

K. A. Ahmed[1], Y. A. Abuodeh[1], M. I. Echevarria[1], J. A. Arrington[2], D. G. Stallworth[2], C. Hogue[3], A. O. Naghavi[1], S. Kim[1], Y. Kim[4], B. G. Patel[5], S. Sarangkasiri[1], P. A. S. Johnstone[1], S. Sahebjam[6], N. I. Khushalani[7], P. A. Forsyth[6], L. B. Harrison[1], M. Yu[1], A. B. Etame[6] & J. J. Caudell[1*]

Departments of [1]Radiation Oncology, [2]Radiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [3]School of Medicine, University of Louisville, Louisville; [4]Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [5]Morsani College of Medicine, University of South Florida, Tampa; [6]Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [7]Cutaneous-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA

Anderson *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:76
DOI 10.1186/s40425-017-0282-x

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment

Erik S. Anderson[1], Michael A. Postow[2], Jedd D. Wolchok[2], Robert J. Young[3], Åse Ballangrud[1], Timothy A. Chan[1], Yoshiya Yamada[1] and Kathryn Beal[1*]

Tolerance and outcomes of stereotactic radiosurgery combined with anti-programmed cell death-1 (pembrolizumab) for melanoma brain metastases

Charlee Nardin[a], Christine Mateus[a], Mathieu Texier[b], Emilie Lanoy[b], Salima Hibat-Allah[c], Samy Ammari[c], Caroline Robert[a] and Frederic Dhermain[d]

Melanoma Research 2018, 28:111–119

Journal of Neuro-Oncology (2018) 138:299–306
https://doi.org/10.1007/s11060-018-2795-7

CLINICAL STUDY

The impact of timing of immunotherapy with cranial irradiation in melanoma patients with brain metastases: intracranial progression, survival and toxicity

Rifaquat Rahman[1] · Alfonso Cortes[2] · Andrzej Niemierko[1] · Kevin S. Oh[1] · Keith T. Flaherty[3] · Donald P. Lawrence[3] · Ryan J. Sullivan[3] · Helen A. Shih[1]

Brain metastases: future developments

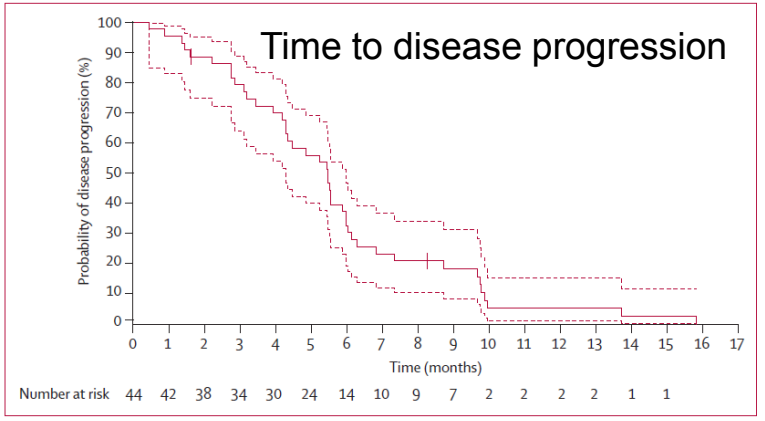
- Lung cancer
- Melanoma
- **Breast cancer**
- Challenges for brain metastases patients

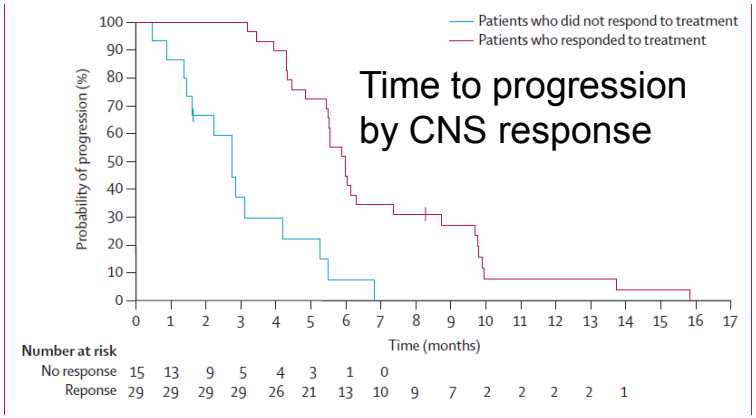
Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

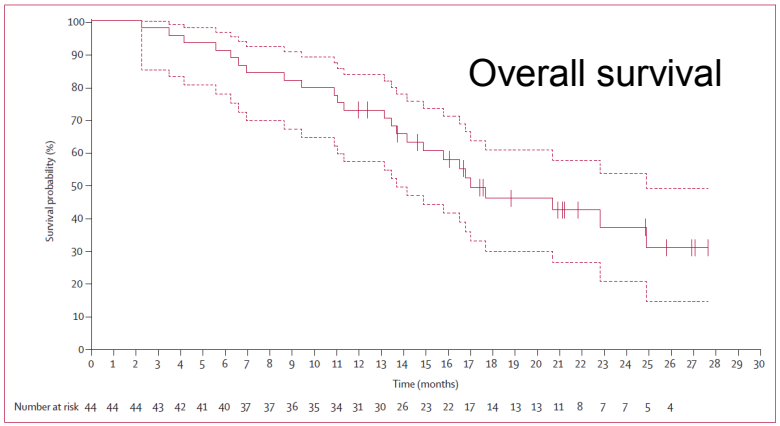
Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers

45 patients; 29/45 PR= 66%

CNS Volumetric change	n = 44	(%)
≥ 80% Reduction	9	(20)
50- <80% Reduction	20	(45)
20- <50% Reduction	6	(14)
> 0- <20% Reduction	2	(5)
Progression*	7	(16)







Breast Cancer Res Treat (2017) 165:329–341
DOI 10.1007/s10549-017-4304-7

CLINICAL TRIAL

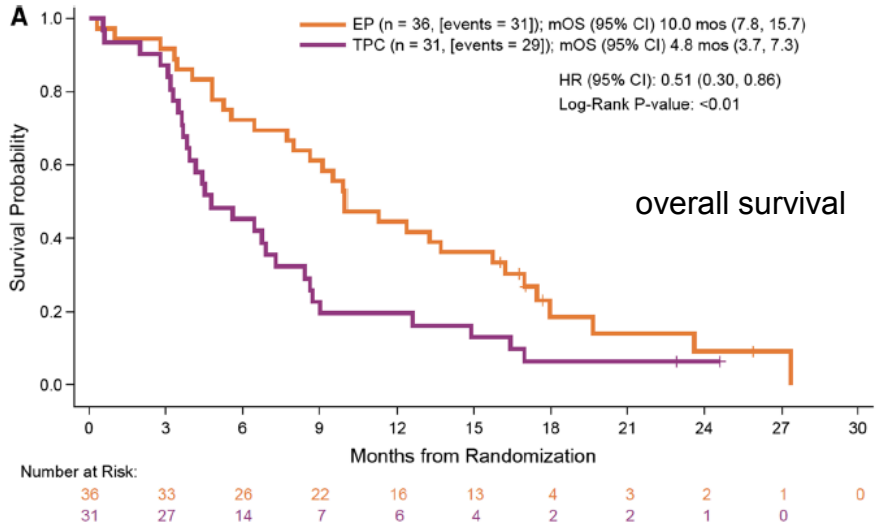
Prolonged survival in patients with breast cancer and a history of brain metastases: results of a preplanned subgroup analysis from the randomized phase III BEACON trial

Javier Cortés[1] · Hope S. Rugo[2] · Ahmad Awada[3] · Chris Twelves[4] · Edith A. Perez[5] · Seock-Ah Im[6] · Patricia Gómez-Pardo[7] · Lee S. Schwartzberg[8] · Veronique Diéras[9] · Denise A. Yardley[10] · David A. Potter[11] · Audrey Mailliez[12] · Alvaro Moreno-Aspitia[1] · Jin-Seok Ahn[13] · Carol Zhao[14] · Ute Hoch[14] · Mary Tagliaferri[14] · Alison L. Hannah[15] · Joyce O'Shaughnessy[16]

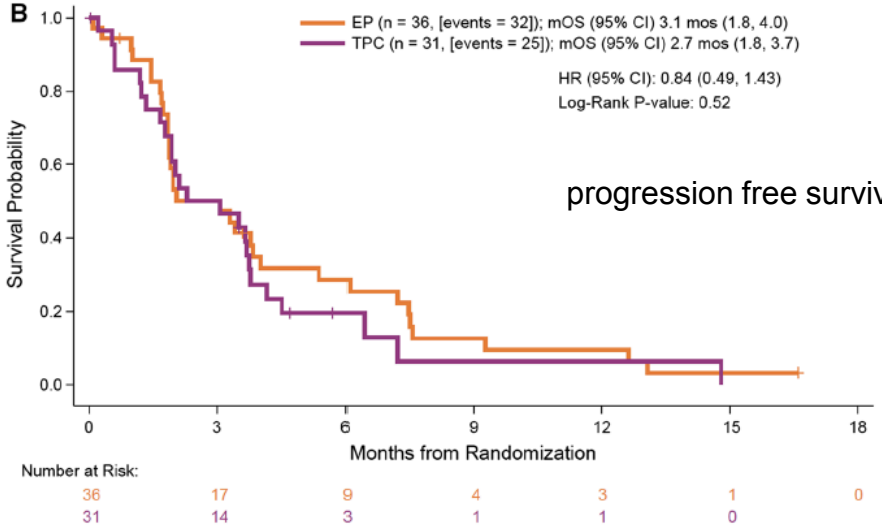
Etirinotecan pegol (EP)
long-acting topoisomerase-1 inhibitor

Patients with a history of BM were eligible provided their BM were symptomatically and radiologically stable, local therapy (surgery, whole brain or stereotactic radiation) had been completed, and corticosteroids for this indication had been discontinued > 3 weeks prior to randomization. Signs and/or symptoms of BM had to have been stable for > 28 days prior to randomization.

Radiologic assessment of the brain at screening was required in patients with focal neurological signs or known BM.
Patients with symptomatic or radiologic progression (according to RECIST v1.1) of BM at screening, leptomeningeal disease, or meningeal carcinomatosis were excluded.



overall survival



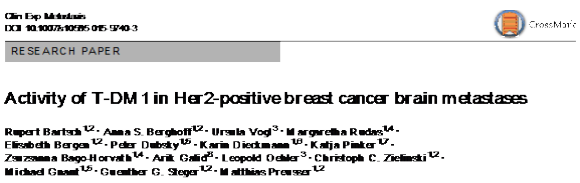
progression free survival

HER 2 positive tumors

Study	Agent	Nb pt	prior CT	prior WBRT	Response criteria	CNS ORR	TTP/PFS	OS
Lin 2008*	Lapatinib	39	64 % with > 2 chimio + T	95 %	RECIST	2,6 %	3,0 mo	NR
Lin 2009	Lapatinib	242	81 % with 2 chimio + T	100 %	composite criteria	6 %	2,4 mo	6,4 mo
Toi 2009	Lapatinib	10	> 80 % with > 3 différent regimen	NR	RECIST?	2 PR	NR	NR

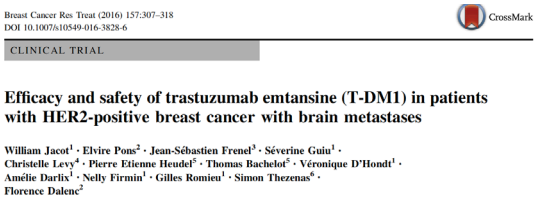
Study	Regimen	N	Prior chemo	Prior RT	Response criteria	CNS ORR	TTP/PFS	OS
Lin et al, 2009	L + cape	50	81% with ≥2 T+chemo; PD on lapatinib monotherapy	100%	50% vol NSS, steroids, lack of non-CNS PD	**20 %**	**3.6 mo**	NR
Boccardo et al, 2008	L + cape	138	Prior T required	NR	Investigator-assessed on survey	**18 %**	Median time on study 2.8 mo	NR
Sutherland et al, 2010 (LEAP)	L + cape	34	82% with ≥2 chemo for MBC; prior T required	94 %	RECIST	**21 %**	**5.1 mo**	NR
Metro et al, 2011	L + cape	22	Median of 2 prior T-based tx for MBC	86 %	WHO	**32 %**	**5.1 mo**	27.9 mo
Lin et al, 2011	L+ cape	13	Prior T required	100 %	50% vol, NSS, steroids, lack of non-CNS PD	**38 %**	NR	NR
Lin et al., J 2011	L+ Topotecan	9	Prior T required	100 %	50% vol, NSS, steroids, lack of non-CNS PD	**0 %**	NR	NR
De Azambuka et al.,2011	L+ TMZ	13	100 % prior T	65 % WBRT 42 % SRS	NR	**0 %**	2,8 mo	10,9 mo

T-DM1



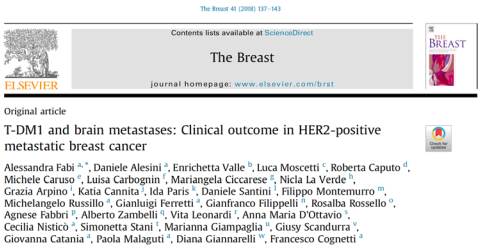
RESEARCH PAPER

Activity of T-DM1 in Her2-positive breast cancer brain metastases



CLINICAL TRIAL

Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases



Original article

T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer

Best intracranial response	Bartsch et al.,	Jacot et al., 2016	Fabi et al., 2016
complete response	0%	0%	3.8%
partial response	30%	44%	20.7%
stable disease	40%	15%	24.5%
progression	30%	41%	45.3%

VOLUME 34 · NUMBER 9 · MARCH 20, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Translational Breast Cancer Research Consortium (TBCRC) 022: A Phase II Trial of Neratinib for Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases

Rachel A. Freedman, Rebecca S. Gelman, Jeffrey S. Wefel, Michelle E. Melisko, Kenneth R. Hess, Roisin M. Connolly, Catherine H. Van Poznak, Polly A. Niravath, Shannon L. Puhalla, Nuhad Ibrahim, Kimberly L. Blackwell, Beverly Moy, Christina Herold, Minetta C. Liu, Alarice Lowe, Nathalie Y.R. Agar, Nicole Ryabin, Sarah Farooq, Elizabeth Lawler, Mothaffar F. Rimawi, Ian E. Krop, Antonio C. Wolff, Eric P. Winer, and Nancy U. Lin

Table 2. Best CNS Response According to Composite Criteria

Best Response	Cohort 1 (N = 40)
CR	0 (0)
PR	3* (8; 95% CI, 2% to 22%)
SD six or more cycles	4 (10)
SD less than six cycles	12 (30)
PD	
PD in CNS only	10 (25)
Symptomatic deterioration/clinical progression (CNS or non-CNS)	7 (18)
PD in CNS and non-CNS	2 (5)
Off treatment before restaging for toxicity	2 (5)

Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial

Javier Cortés, Véronique Dieras, Jungsil Ro, Jérôme Barriere, Thomas Bachelot, Sara Hurvitz, Emilie Le Rhun, Marc Espié, Sung-Bae Kim, Andreas Schneeweiss, Joo Hyuk Sohn, Jean-Marc Nabholtz, Pirkko-Liisa Kellokumpu-Lehtinen, Julie Taguchi, Federico Piacentini, Eva Ciruelos, Petri Bono, Mahmoud Ould-Kaci, Flavien Roux, Heikki Joensuu

Lancet Oncol 2015; 16: 1700–10

	Afatinib alone n=40	Afatinib plus vinorelbine n=38	Investigator's choice n=43
Patient benefit at 12 weeks (primary outcome)			
Number of patients	12 (30·0%; 16·6–46·5)	13 (34·2%; 19·6–51·4)	18 (41·9%; 27·0–57·9)
Difference (95% CI) versus investigator's choice group, p value	−11·9 (−32·9 to 9·7), 0·37	−7·6 (−28·9 to 14·2), 0·63	..
Progression-free survival			
Duration (weeks)	11·9 (6·3–18·7)	12·3 (7·4–17·3)	18·4 (11·1–21·1)
HR (95% CI)* versus investigator's choice group , p value	1·18 (0·72–1·93), 0·51	0·94 (0·57–1·54), 0·78	..
Overall survival			
Duration (weeks)	57·7 (39·3–68·1)	37·3 (25·3–57·3)	52·1 (39·3–80·4)
HR (95% CI)* versus investigator's choice group, p value	1·27 (0·72–2·21), 0·41	1·60 (0·93–2·76), 0·09	..
Proportion of patients with an objective response†			
CNS lesions‡	0	3 (8%)	6 (14%)
Median (IQR) duration of response (days)	..	46 (13–70)	192 (135–247)
Extra-CNS lesions§	0	3 (8%)	2 (5%)
Median (IQR) duration of response (days)	..	192 (108–235)	170 (108–232)
Disease control¶			
CNS lesions‡	27 (68%)	27 (71%)	31 (72%)
Extra-CNS lesions§	17 (43%)	19 (50%)	26 (61%)

Data are n (%; 95% CI), n (%), or median (95% CI) unless otherwise stated. ··=not applicable. HR=hazard ratio. *From Cox proportional hazards regression model, stratified by Eastern Cooperative Oncology Group performance score at baseline, number of brain metastases at screening, and previous treatment with lapatinib. †Complete or partial response. ‡Tumour response was not assessed in four patients in the afatinib alone group, four patients in the afatinib plus vinorelbine group, and five patients in the investigator's choice group. ¶Complete response, partial response, or stable disease for at least 6 weeks. §Tumour response was not assessed in 13 patients in the afatinib group, 16 patients in the afatinib plus vinorelbine group, and 13 patients in the investigator's choice group.

Table 2: **Patient benefit, survival outcomes, and tumour response**

2 exploratory expansion cohorts of patients with untreated brain metastases or treated progressive metastases not requiring immediate CNS-directed therapy were evaluated after establishing the recommended phase 2 dose in the escalation cohorts

Brain metastases were measurable in 29 patients treated at the recommended phase 2 dose: 11 patients with treated progressive brain metastases and one patient with untreated asymptomatic brain metastases.

PR: 5 (42%)
SD: 5 (42%)
PD: 1
NE: 1

Median PFS was 6.7 months (95% CI 1.4–12.5)

Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study

Rashmi Murthy, Virginia F Borges, Alison Conlin, Jorge Chaves, Marc Chamberlain, Todd Gray, Alex Vo, Erika Hamilton

Lancet Oncol 2018; 19: 880–88

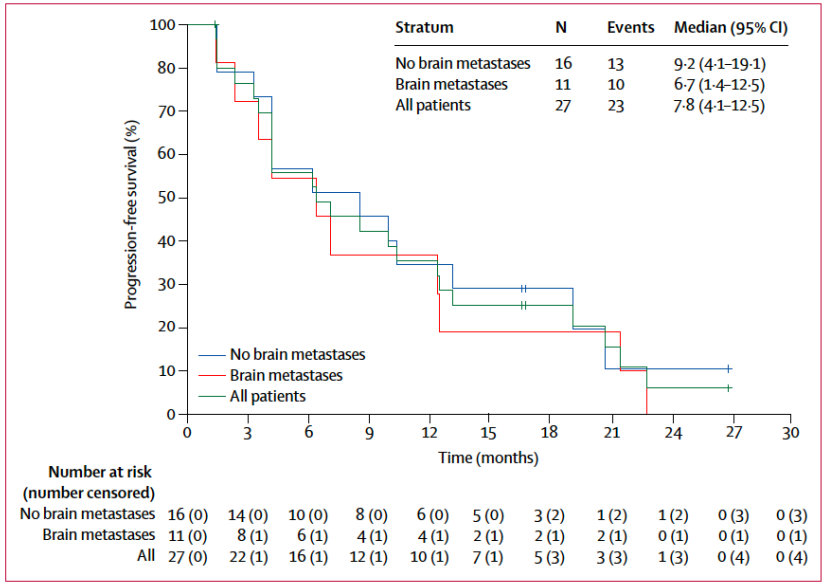


Figure 2: **Kaplan-Meier plot of progression-free survival in tucatinib plus capecitabine and trastuzumab group**
Crosses indicate censored patients.

Future development

- mTOR inhibitors?
- CDK4/6 inhibitors?
- PARP inhibitors?

Brain metastases: future developments

- Lung cancer
- Melanoma
- Breast cancer
- **Challenges for brain metastases patients**

Supportive care in brain tumors patients

Complications of disease and its treatment:

- Headache, intracranial hypertension
- Epilepsy
- Venous thrombo-embolism
- Fatigue
- Cognition
- Mood and behavioral disorders
- Radionecrosis
- End of life

Multidisciplinary approach

European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma

Andrea Pace, Linda Dirven, Johan A F Koekkoek, Heidrun Golla, Jane Fleming, Roberta Rudà, Christine Marosi, Emilie Le Rhun, Robin Grant, Kathy Oliver, Ingela Oberg, Helen J Bulbeck, Alasdair G Rooney, Roger Henriksson, H Roeline W Pasman, Stefan Oberndorfer, Michael Weller, Martin J B Taphoorn, for the European Association of Neuro-Oncology palliative care task force

Lancet Oncol 2017; 18: e330–40

EANO EUROPEAN ASSOCIATION OF NEURO-ONCOLOGY

ESMO

Neurological and vascular complications of primary and secondary brain tumors: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up

Patrick Roth (EANO coordinator), Matthias Preusser (ESMO coordinator)

Special needs for trials in brain metastases: which endpoint?

- target inhibition
- safety
- tolerability

- (compartmental) response?
- (compartmental) time to event (progression)?
- survival?
- survival specified for quality?
- clinical benefit?

Special needs for trials in brain metastases: which tools?

- Neurological evaluation: NANO scale, seizures control, steroids use
- Living in independence: IADL scale
- Cognition: HTLV-R, TMT A/B, COWA, MoCA….
- Quality of life: QLQ C30, BN20

- Brain MRI evaluation: RANO, iRANO, RECIST, iRECIST?

Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group

Nancy U Lin, Jeffrey S Wefel, Eudocia Q Lee, David Schiff, Martin J van den Bent, Riccardo Soffietti, John H Suh, Michael A Vogelbaum, Minesh P Mehta, Janet Dancey, Mark E Linskey, D Ross Camidge, Hidefumi Aoyama, Paul D Brown, Susan M Chang, Steven N Kalkanis, Igor J Barani, Brigitta G Baumert, Laurie E Gaspar, F Stephen Hodi, David R Macdonald, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Lancet Oncol 2013; 14: e407–16

Conclusion

Multidisciplinary approach

Need of trial dedicated to brain metastases in organ-specific disease:

- with active BM
- adapted endpoints
- validated response assessment criteria
- adapted tools for the evaluation of QOL and cognition