Targeted Therapies and Immunotherapies For Brain Metastases

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DISCLOSURES

Research Support

- Agios, Astra Zeneca, Beigene, Eli Lily, Genentech/Roche, Kadmon, Karyopharm, Kazia, Merck, Novartis, Oncoceutics, Sanofi-Aventis, VBI Vaccines

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Speaker

- Merck

DSMB

- Monteris, Tocagen

Editor

- UpToDate, Elsevier

Outline

- Overview and Challenges
- Targeted Therapies
  - Melanoma
  - NSCLC
  - Breast Cancer
- Immunotherapies
  - Melanoma
  - NSCLC
- Future Strategies

Incidence of Brain Metastases

Primary site	Incidence Rates
Lung (overall)	16.3–19.9%
SCLC*	29.7% (at 5 years)
NSCLC*	12.6% (at 5 years)
Breast	10–15%
HER2 positive	25–50%
Triple negative	20%
Melanoma	6.9–7.4%
Renal	6.5–9.8%
Colorectal	3.0%

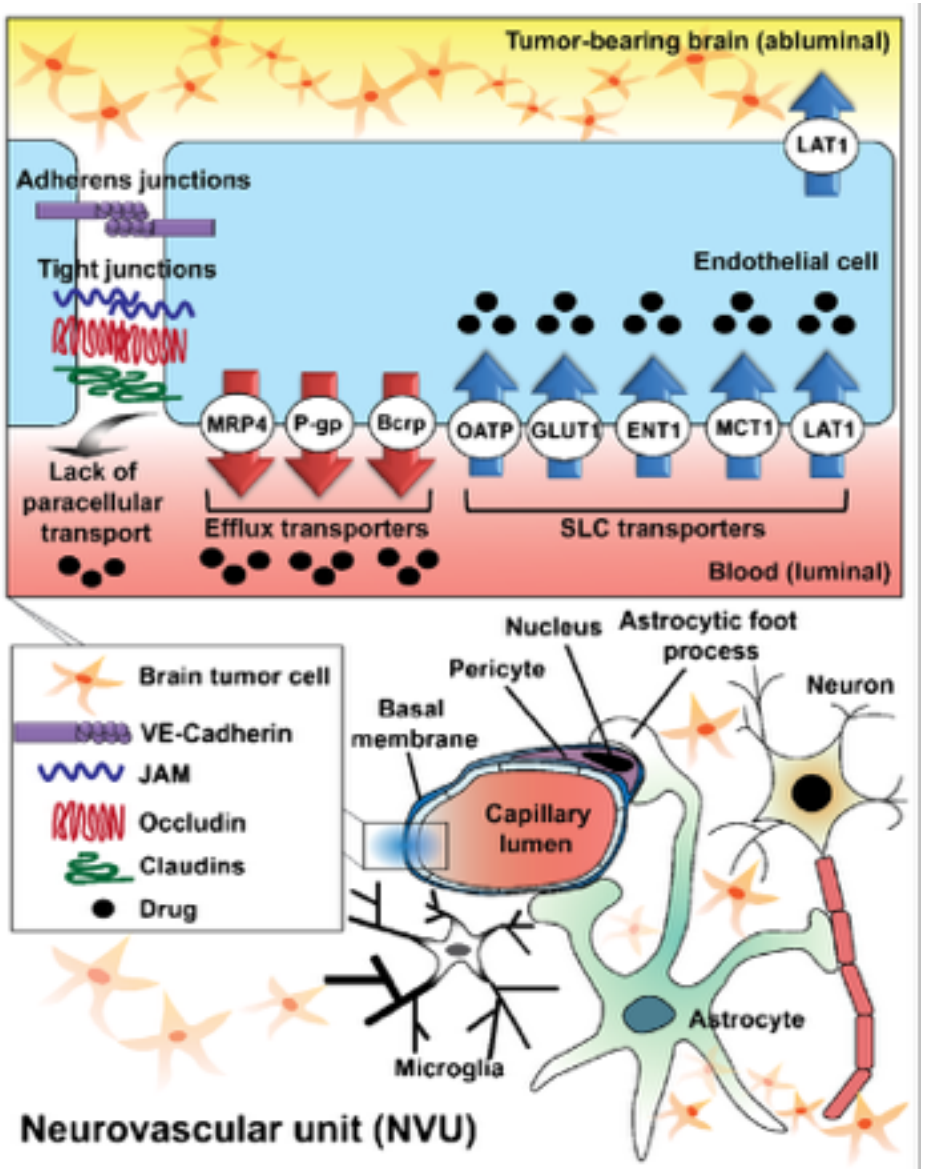
*can be up to 50–60% depending on study and disease duration

Glitza Oliva et al. Ann Oncol 2018;29: 1509–1520
Barnholtz-Sloan et al. J. Clin Oncol. 2004;22(14):2865–72
Schouten et al. Cancer. 2002;94(10):2698–705
Chamberalin et al. Neuro-Oncology. 2017;19(1):i1–i24

Challenges

- Blood-brain barrier
- Genetic Heterogeneity
- Tumor Microenvironment
- Exclusion from Clinical Trials

Kim et al., Pharm Res 2018;35:177



Blood-Brain Barrier

- Importance controversial
- Less intact than GBM
- Nonetheless not completely open
- Heterogenous drug distribution

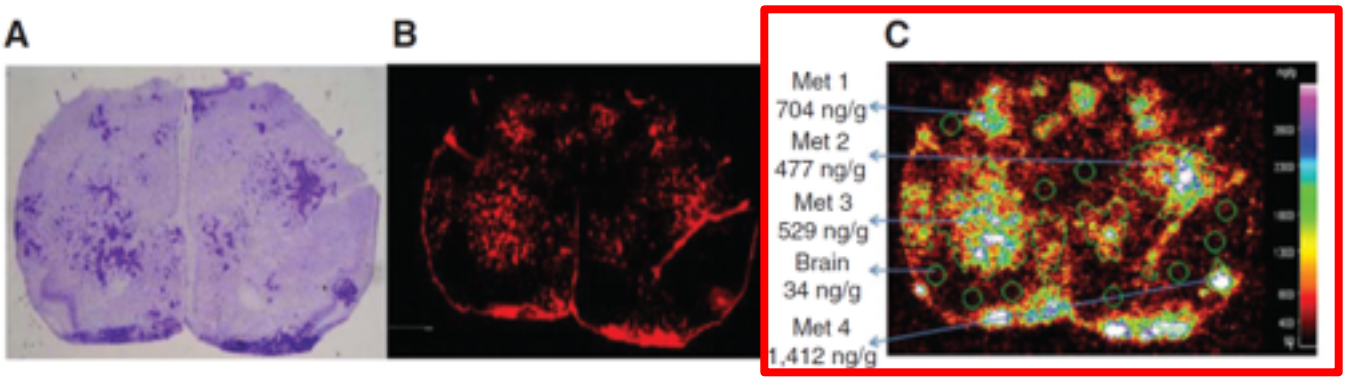
Cancer Therapy: Preclinical
See commentary p. 5605

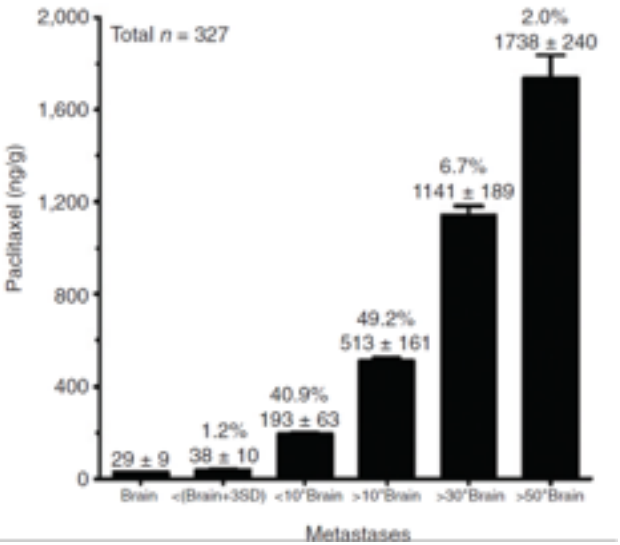
Clinical Cancer Research

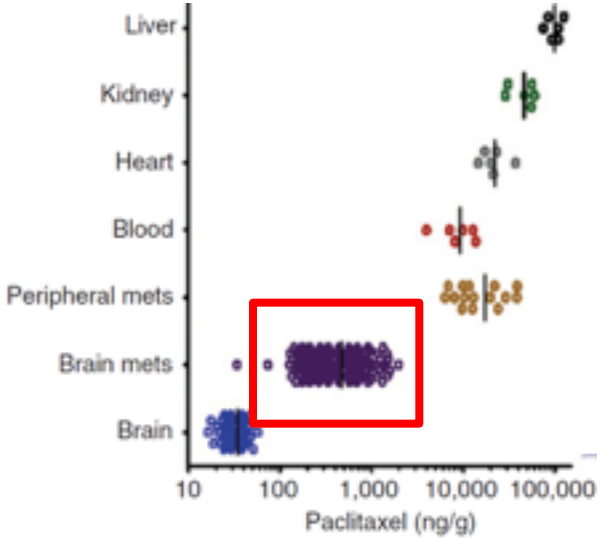
2010;16:5664-78

Heterogeneous Blood–Tumor Barrier Permeability Determines Drug Efficacy in Experimental Brain Metastases of Breast Cancer

Paul R. Lockman[1], Rajendar K. Mittapalli[1], Kunal S. Taskar[1], Vinay Rudraraju[1], Brunilde Gril[2], Kaci A. Bohn[1], Chris E. Adkins[1], Amanda Roberts[1], Helen R. Thorsheim[1], Julie A. Gaasch[3], Suyun Huang[4], Diane Palmieri[2], Patricia S. Steeg[2], and Quentin R. Smith[1]

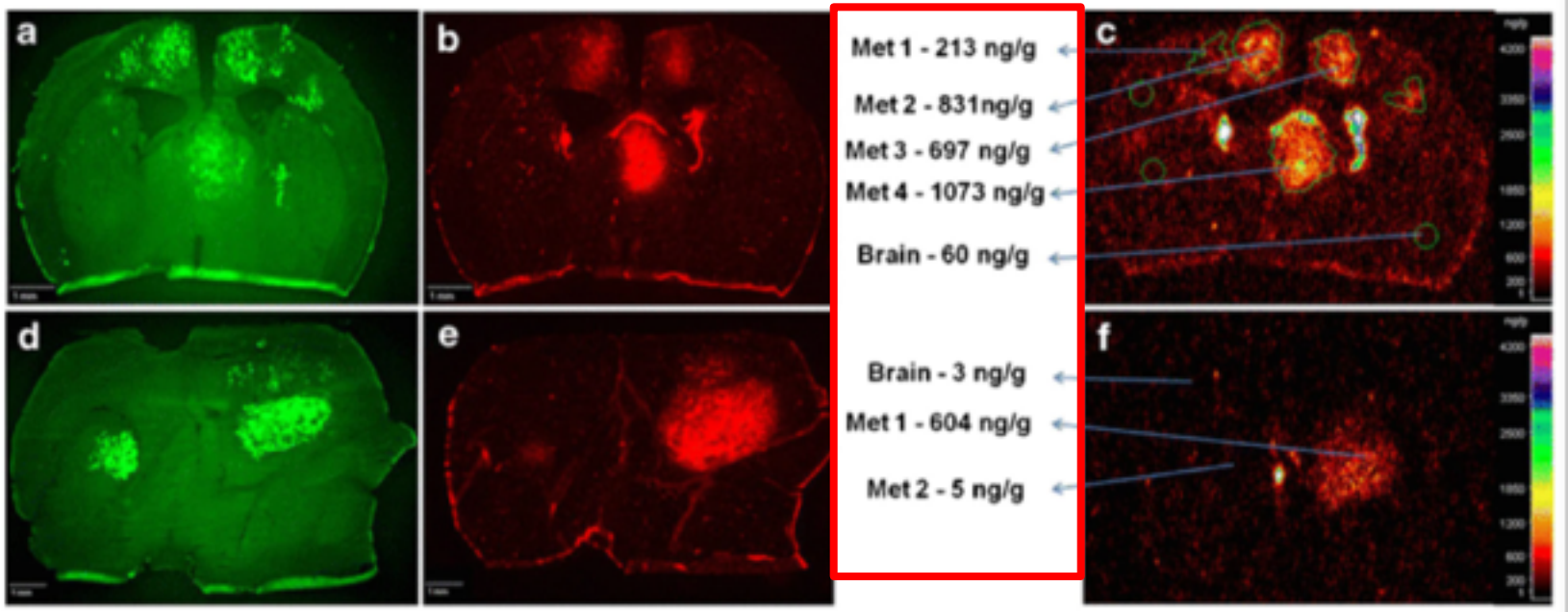






Lapatinib

Heterogeneity of BBB disruption and lapatinib concentration in mouse model of breast cancer



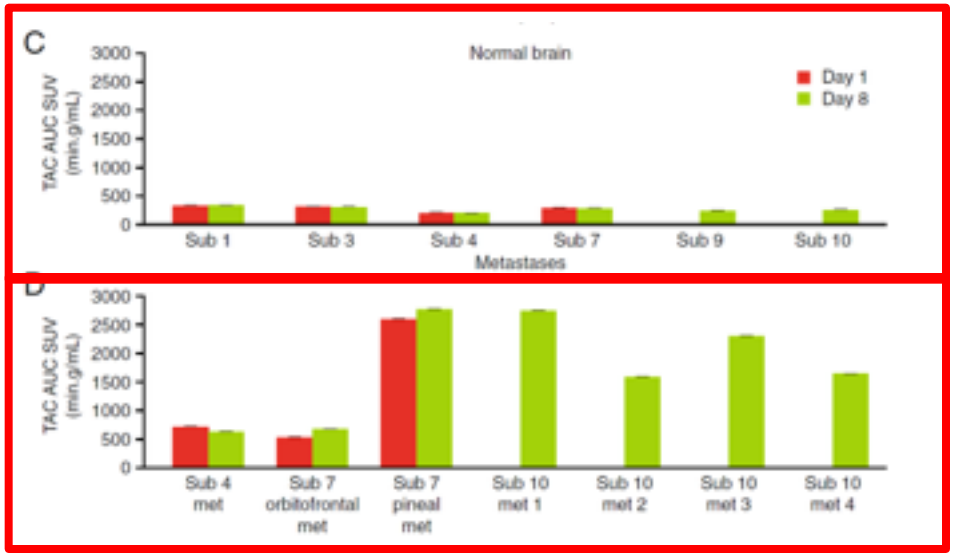
Taskar et al. Pharm Res. 2012;29(3):770–81

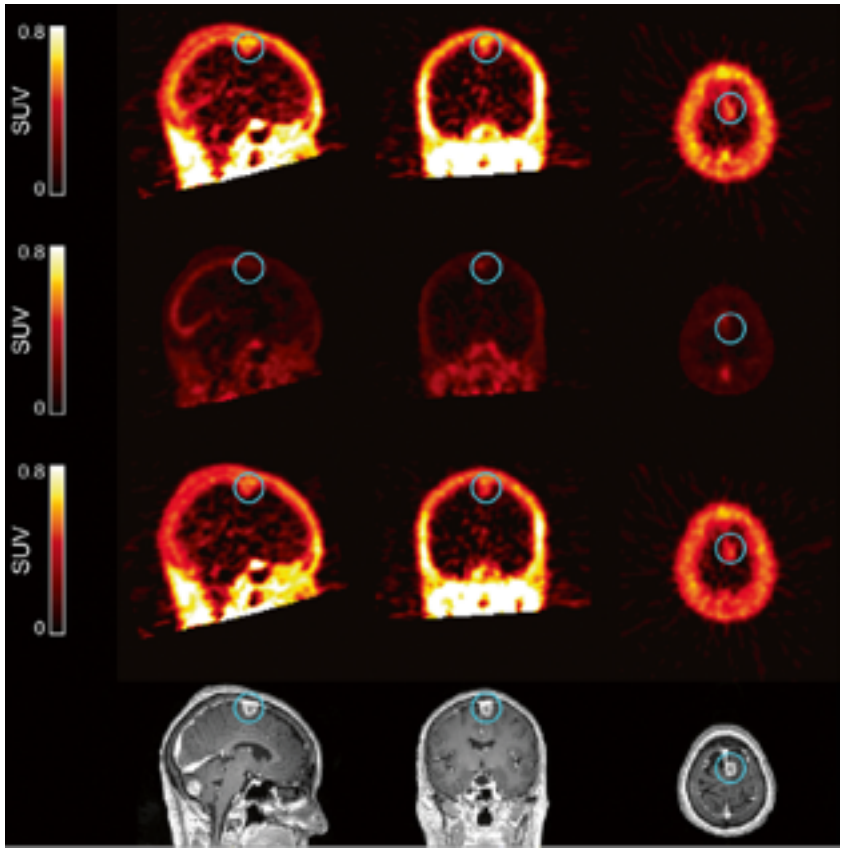
Lapatinib access into normal brain and brain metastases in patients with Her-2 overexpressing breast cancer

EJNMMI Research
2015;5:30

Azeem Saleem[1*], Graham E Searle[1], Laura M Kenny[2], Mickael Huiban[1], Kasia Kozlowski[2], Adam D Waldman[3], Laura Woodley[4], Carlo Palmieri[5], Charles Lowdell[6], Tomomi Kaneko[7], Philip S Murphy[8], Mike R Lau[8], Eric O Aboagye[2] and Raoul C Coombes[2]

Uptake of 11C-Lapatinib





Neuro-Oncology

Neuro-Oncology 17(2), 289–295, 2015

Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study

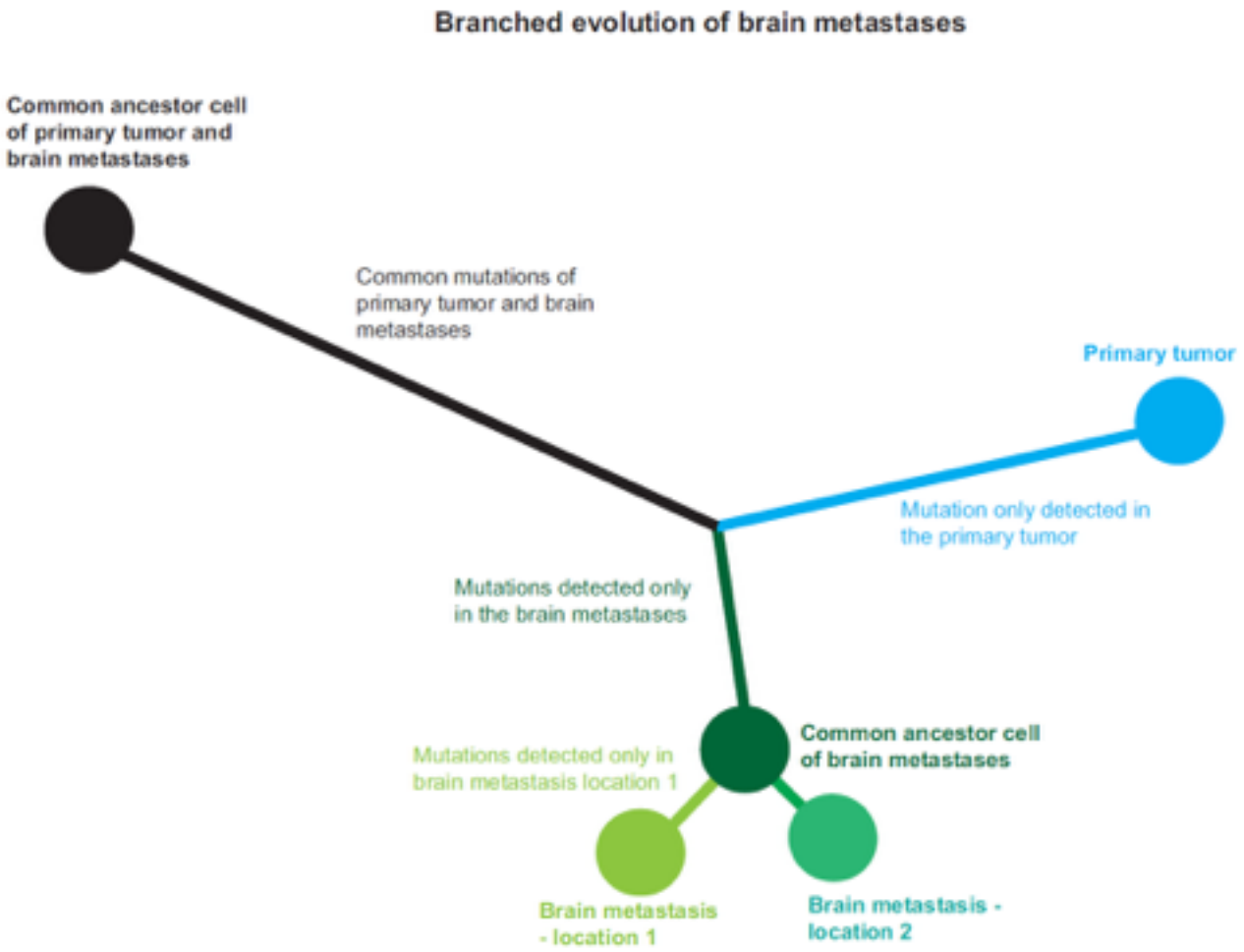
Aki Morikawa, David M. Peereboom, Helen R. Thorsheim, Ramakrishna Samala, Rajiv Balyan, Conleth G. Murphy, Paul R. Lockman, Ahkeem Simmons, Robert J. Weil, Viviane Tabar, Patricia S. Steeg, Quentin R. Smith, and Andrew D. Seidman

Table 3. Lapatinib concentrations at time of BCBM resection and BCBM-to-serum ratio[a]

Patient	No. Preop Doses	BCBM Avg Concentration (range), μM[a]	Serum 4 Concentration,[b] μM	BCBM/ Serum 4
L1	5	63.6 (43.9–77.2)	6.5	9.8
L2	3	14.6 (11.7–22.2)	2.4	6.0
L3	3	18.6 (11.3–31.0)	3.5	5.3
L4	2	1.0 (0.7–1.5)	5.3	0.19

[a]BCBM average concentrations were calculated from multiple samples of a single collected lesion.
[b]Serum 4 is taken at the time the BCBM is identified.

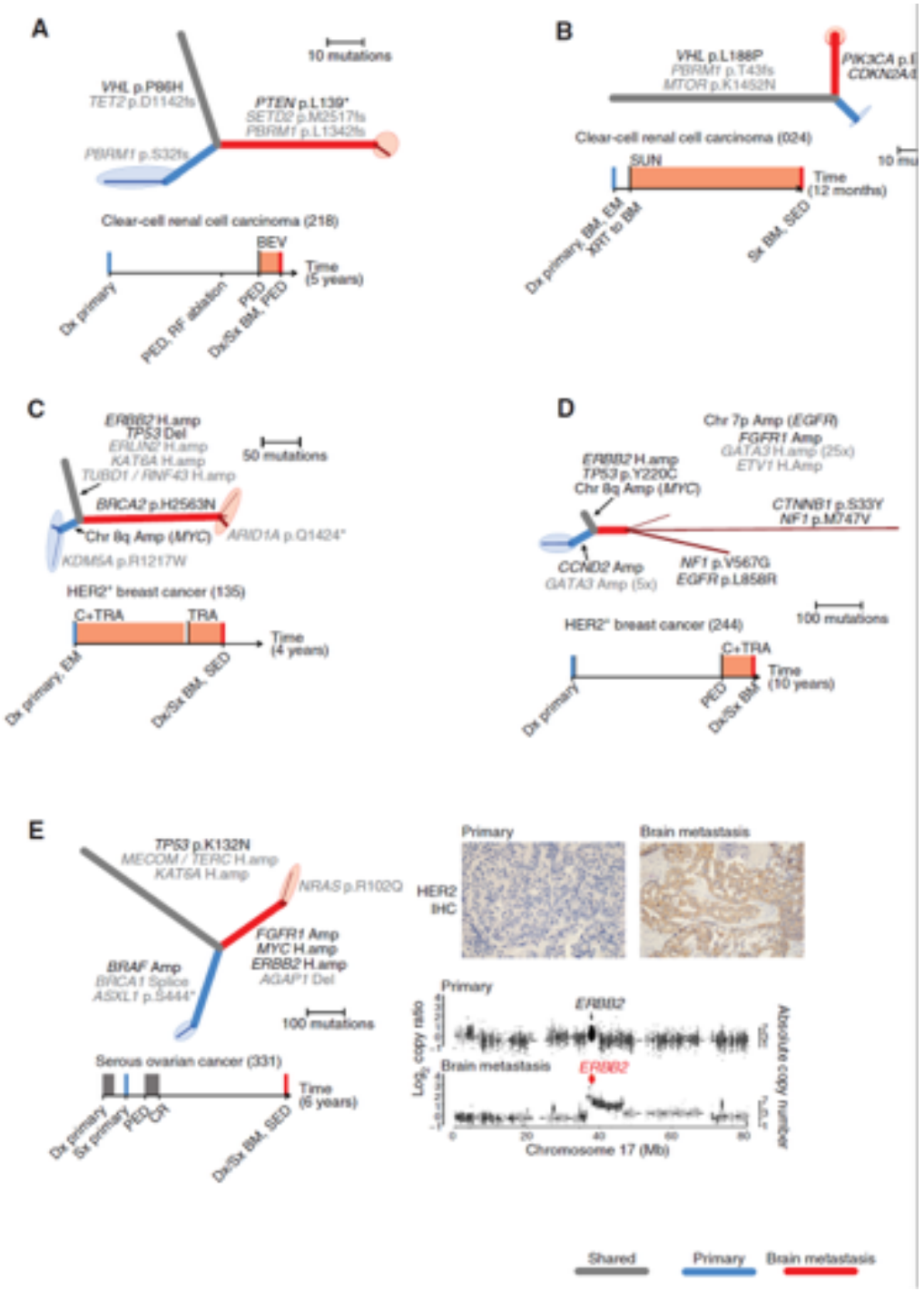
Genetic Heterogeneity in Brain Metastases



Bergoff and Brastianos Seminar Neurol 2018;35:95-103

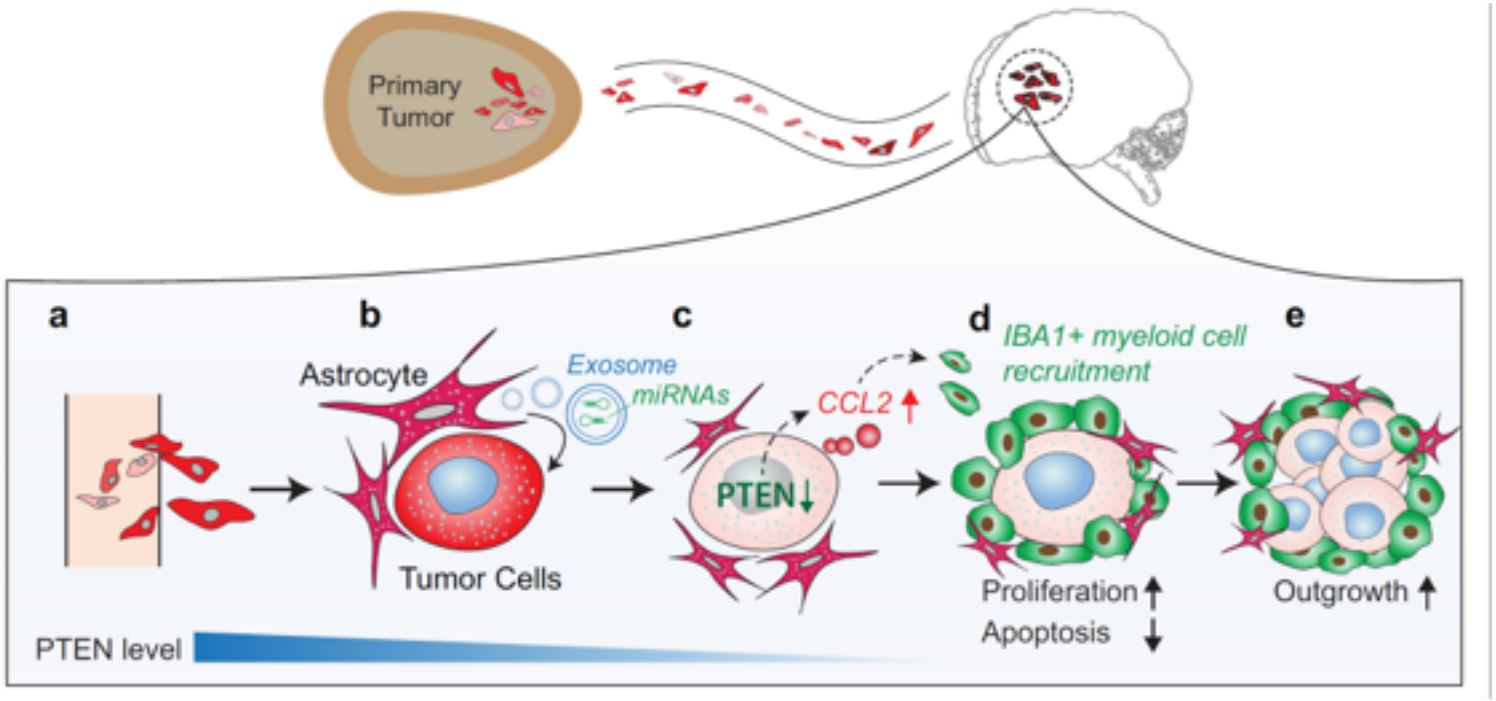
Cancer Discovery 2015

- **53% of brain metastases have genetically distinct molecular drivers compared to primary tumor**
- Little intralesional heterogeneity
- Molecular drivers in different metastases in the same patient are relatively similar
- Evidence of upregulation of PI3Kinase and CDK pathways



Brain-Specific Microenvironment

PTEN loss induced by astrocyte-derived exosomal microRNA primes brain metastasis outgrowth via functional cross-talk between disseminated tumour cells and brain metastatic microenvironment



Zhang et al. Nature 2015; 527(7576): 100–104

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

2017

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group

Nancy U. Lin, Tatiana Prowell, Antoinette R. Tan, Marina Kozak, Oliver Rosen, Laleh Amiri-Kordestani, Julia White, Joohee Sul, Louise Perkins, Katherine Beal, Richard Gaynor, and Edward S. Kim

- **Pts with treated or stable brain mets**
  - Pts with treated or stable brain mets who are stable for 4 weeks are eligible for all phases of clinical trials
- **Pts with active brain mets**
  - Pts with active brain mets should be considered early in clinical development if there is a strong scientific rationale for likelihood of benefit based on molecular pathway, histology or preclinical data
  - For therapies with less robust preclinical data, inclusion of brain met pts should still be considered esp if BM common in the intended population. Consider brain met specific cohort.
- **Leptomeningeal Disease**
  - Inclusion of LMD cohort encouraged in early phase trials if CNS activity expected and when relevant in specific disease type under study
  - CSF PK measurement encouraged
  - Consider LMD cohort in later phase trials

THE LANCET Oncology

Clinical trial design for systemic agents in patients with brain metastases from solid tumours: a guideline by the Response Assessment in Neuro-Oncology Brain Metastases working group

D Ross Camidge, Eudocia Q Lee, Nancy U Lin, Kim Margolin, Manmeet S Ahluwalia, Martin Bendszus, Susan M Chang, Janet Dancey, Elisabeth G E de Vries, Gordon J Harris, F Stephen Hodi, Andrew B Lassman, David R Macdonald, David M Peereboom, David Schiff, Ricardo Soffietti, Martin J van den Bent, Jeffrey S Wefel, Patrick Y Wen

2018;19:e20

Targeted Molecular Therapies

"The wife made it. Why?"

Melanoma

- **Columbino et al. J Clin Oncol 2012; 30(20): 2522–2529**
  - Paired tissue samples from primary tumors and metastases showed an 80% genetic concordance (lower than that between the primary tumor and metastases to the draining lymph node (93%) and visceral organs (96%).
  - More MBM than primary tumors harbored BRAF (48% versus 43%) or NRAS (23% versus 15%) mutations.
- **Chen et al. Clin Cancer Res 2014;20(21): 5537–5546**
  - Extracranial metastases and found that all 16 sample pairs were concordant for BRAF and NRAS mutations and other genetic alterations
- **Zhang et al. Nature 2015; 527(7576): 100–104**
  - Loss of PTEN, upregulation of pAKT

Glitza Oliva et al. Ann Oncol 29: 1509–1520, 2018

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-clinical 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

Kim et al. Pharm Res 2018;35:177

Melanoma

Table 1. Completed clinical trials of targeted therapies for the treatment of MBM

Study	Therapy	Cohort	*N*	Key inclusion criteria	Median PFS (months)	Median OS (months)
NCT01781026 [110]	Vemurafenib	–	2	≥1 lesion unamenable to SRS or surgical resection	Measurement of CSF levels of vemurafenib	N/A
NCT01378975 [37]	Vemurafenib	–		*BRAF* V600; ≥1 measurable MBM		
			90	Previously untreated	3.7	8.9
			56	Previously treated	4.0	9.6
NCT01253564 [111]	Vemurafenib	–	24	Unresectable MBM; prior failed MBM treatment	3.9	5.3

BRAF, serine/threonine-protein kinase B-Raf; CSF, cerebrospinal fluid; MBM, melanoma brain metastases; N/A, not applicable; OS, overall survival; PFS, progression-free survival; SRS, stereotactic radiosurgery.

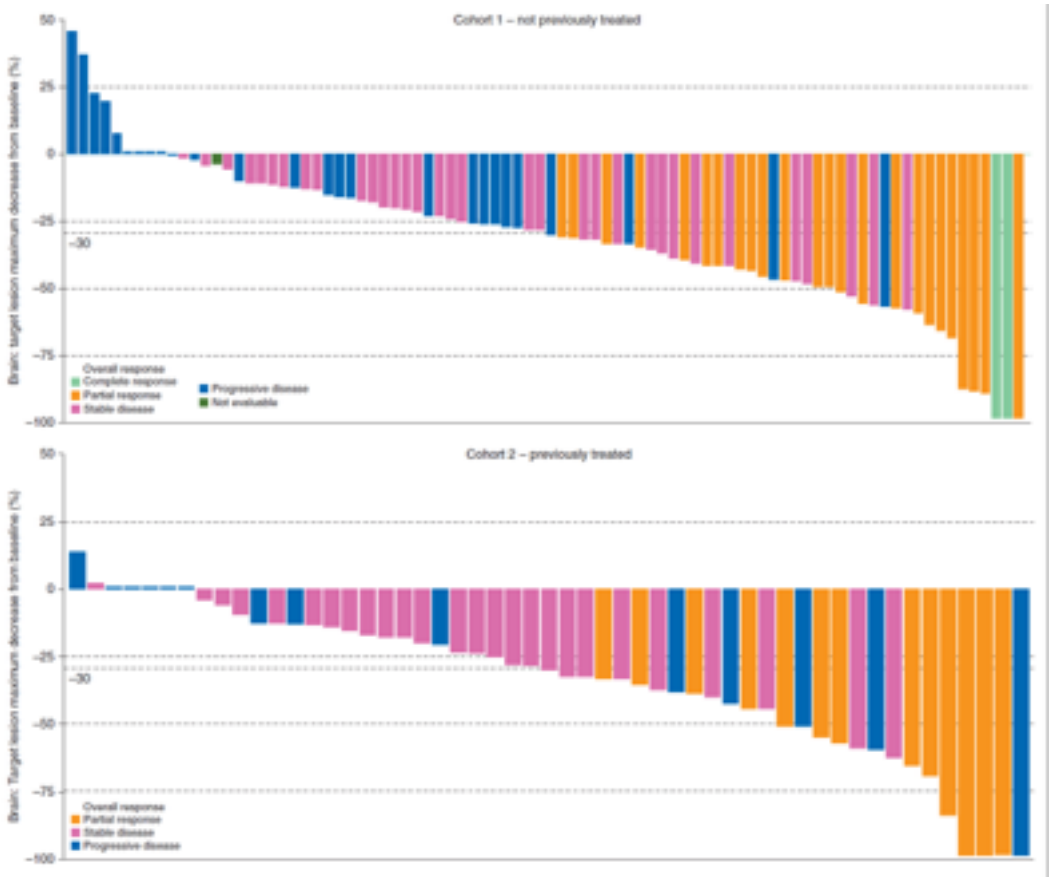
Glitza Oliva et al. Ann Oncol 29: 1509–1520, 2018

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 634–641, 2017

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]



- 146 patients were treated
  - Cohort 1 (untreated)-90
  - Cohort 2 (previously treated)-56
- **Intracranial BORR:**
  - Cohort 1 by IRC was **18% (2 CRs, 14 PRs)**
- **Median PFS** (brain only, investigator-assessed) was 3.7 months in cohort 1 and 4.0 months in cohort 2
- **Median OS** was 8.9 months in cohort 1 and 9.6 months in cohort 2

Melanoma

Table 2. Ongoing or recruiting clinical trials of targeted therapies for the treatment of MBM

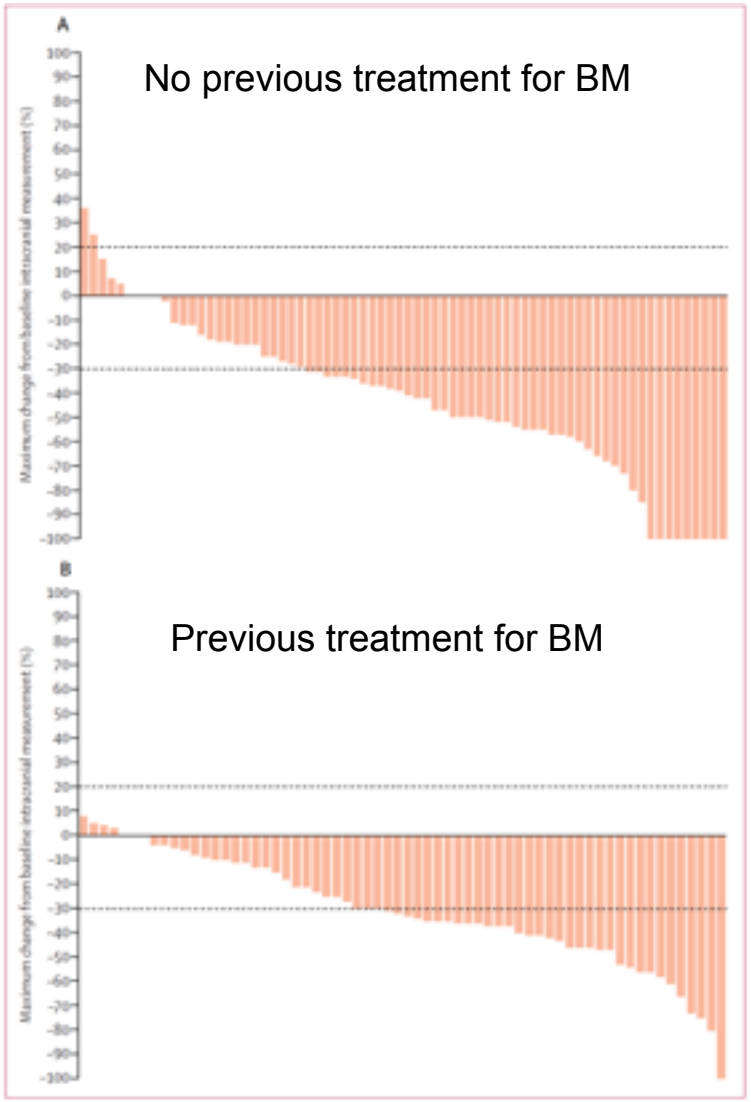
Study	Therapy	Cohort	*N*	Key inclusion criteria	Planned primary and secondary outcome measures
NCT02038348 [112]	Vemurafenib	–	5	*BRAF* mutation	Value of ^{18}F-DOPA-PET imaging in assessment of tumor
NCT02537600 (CONVERCE) [113]	Vemurafenib and cobimetinib	A B C	137 (total)	Neurologically asymptomatic; without (A) or with (B) prior local treatment Neurologically symptomatic; without or with prior local treatment	CR or PR intracranial RR; CSF-to-plasma ratio of vemurafenib and cobimetinib
NCT02039947 (COMBI-MB) [38]	Dabrafenib and trametinib	A B C D	76 16 16 17	*BRAF* V600E; asymptomatic; without (A) or with (B) prior local therapy *BRAF* V600D/K/R; asymptomatic *BRAF* V600D/E/K/R; symptomatic	Intracranial RR of cohort A; intracranial RR of cohorts B, C, and D; extracranial RR, PFS, OS, safety
NCT01978236[a] [114]	Dabrafenib before surgery Dabrafenib and trametinib before surgery	A B	15 15	*BRAF* V600E or V600K extracranial lesions+MBM	Concentration of drug and metabolites in tumor and surrounding tissue
NCT02452294 (BUMPER) [115]	Buparlisib	–	22	WT *BRAF* and *BRAF* V600E/K; failed therapy with BRAFi±MEKi (*BRAF* V600E) and anti-PD-1 and/or anti-CTLA-4 (*BRAF* WT)	Intracranial DCR

Glitza Oliva et al. Ann Oncol 29: 1509–1520, 2018

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

Lancet Oncol 2012; 13: 1087–95

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**



	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%)

Response rate in BRAFV600K mutations 15%

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

Lancet Oncol 2017; 18: 863–73

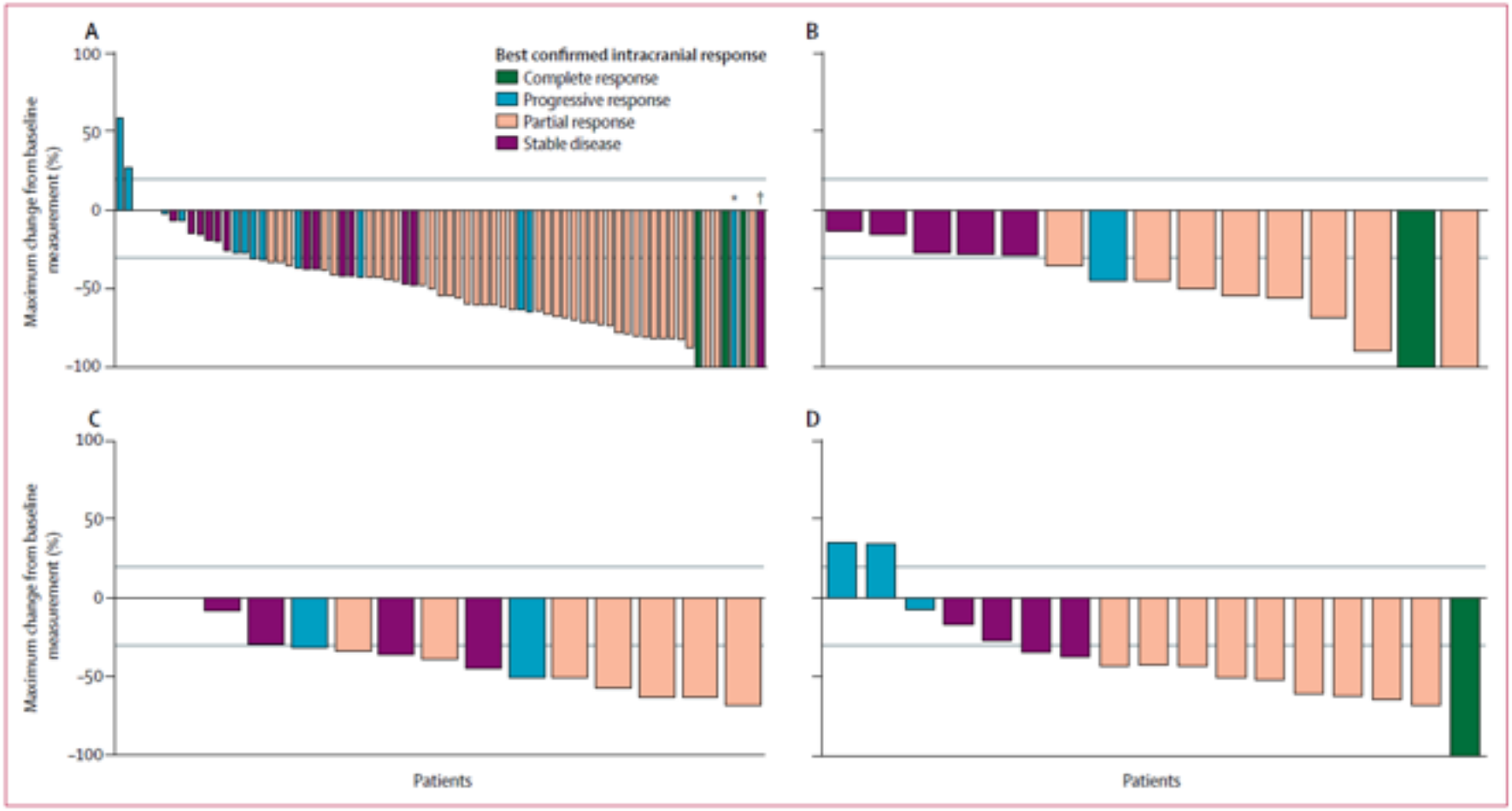
Michael A Davies, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang,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

- Multicenter, multicohort, open-label phase II study
- Dabrafenib 150mg bid and trematinib 2mg qd
  - Group A (76pt) : BRAFv600E +ve, asymptomatic melanoma BM, no previous local brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=58%)**
  - Group B (16 pt): BRAFv600E +ve, asymptomatic melanoma BM, previous local brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=56%)**
  - Group C (16 pt): BRAFv600D/K/R +ve, asymptomatic melanoma BM, with or without previous brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=44%)**
  - Group D (17 pt): BRAFv600D/E/K/R +ve, symptomatic melanoma BM, with or without previous brain therapy, ECOG 0,1 or 2
    - **Overall intracranial response (CR+PR=59%)**

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

Lancet Oncol 2017; 18: 863–73

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*



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

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	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
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)
Extracranial duration of response				
Events	16/42 (38%)	0/7	6/12 (50%)	4/7 (57%)
Median (95% CI; months)	10·2 (5·8–NE)	NE (NE–NE)	4·9 (3·0–NE)	5·9 (1·8–NE)
Response at 6 months	69% (50–82)	100% (100–100)†	40% (10–70)	48% (8–81)

- Intracranial response appears to be shorter than extracranial response
- ? Upregulation of PI3K pathway
- Potentially combinations of MAPKi and PI3Ki maybe beneficial

Lung Cancer

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-clinical model*	Response rate in BM patients (%)	Transporter effect
Gefitinib	EGFR-TKI	750–1000	1.07–3.58	27	27%	P-gp substrate
Erlotinib	EGFR-TKI	150	2.77–5.1	13.7	82.4% (EGFR mutation)	P-gp and Bcrp substrate
Afatinib	EGFR-TKI	50	0.7	ND	35%	P-gp substrate
Osimertinib	EGFR-TKI	80	NA	180	ND	P-gp and Bcrp substrate
AZD3759	EGFR-TKI	100–1000	111	282	83%	ND
Crizotinib	ALK-TKI	500	0.26	23	18–33%	P-gp substrate but not Bcrp
Alectinib	ALK-TKI	1200	0.3	63–94	52%	Not a P-gp substrate
Ceritinib	ALK-TKI	400	ND	15	34.5–58.8%	P-gp and Bcrp substrate
Brigatinib	ALK and EGFR TKI	300	ND	ND	53%	ND
Lorlatinib (PF-06463922)	ALK-TKI	100	ND	64	ND	Not a P-gp substrate
Entrectinib	ALK-TKI	ND	ND	43	ND	ND

(ND, not determined; NA, not available)

*Total drug concentrations are reported

Kim et al. Pharm Res 2018;35:177

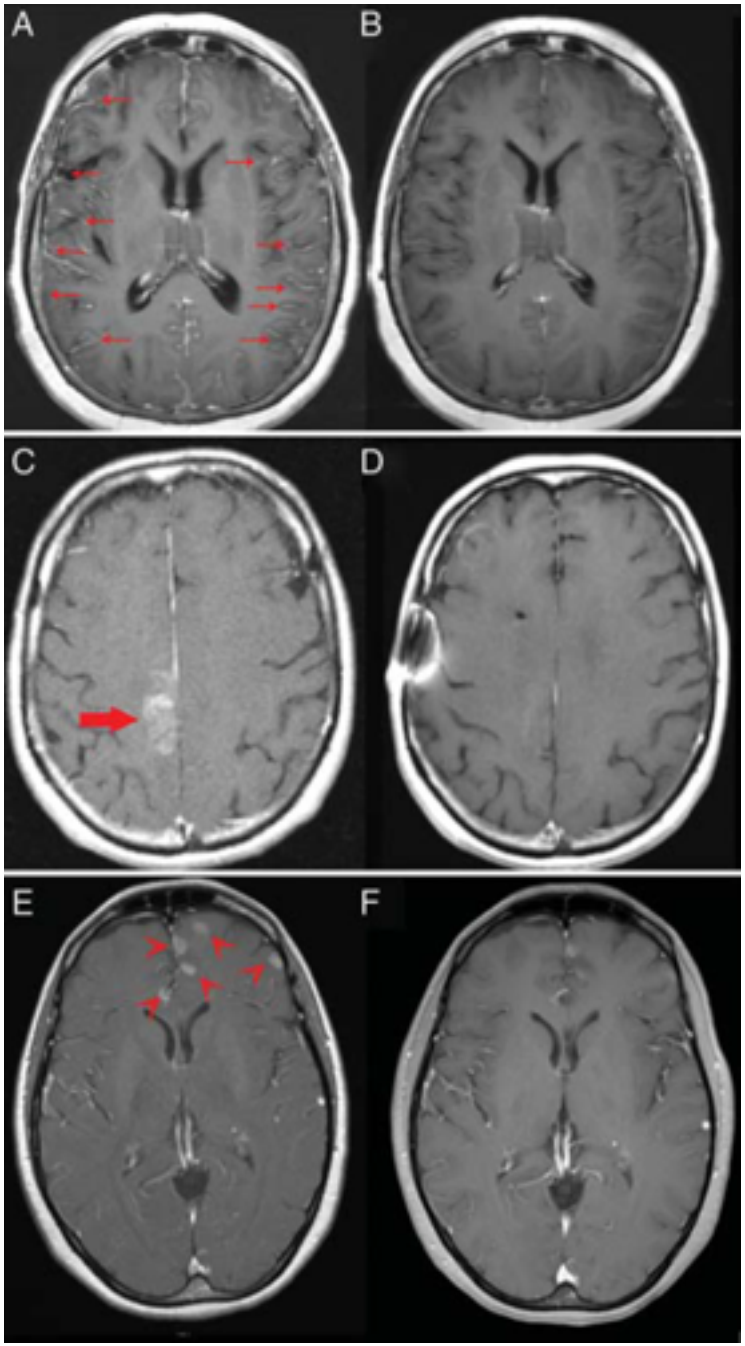
NSCLC (EGFR mutated)

Table 2. Intracranial response rates in patients treated with TKI with brain metastasis

Reference	Drug	Study	Line of treatment	Number of patients with brain metastases	Response rate %	Survival months
Kim et al. (2009)	Gefitinib or Erlotinib	Case series	First line	23	70	OS = 18.8
Hotta et al. (200[illegible])	Gefitinib	Case series	Prior chemotherapy exposure	14	43	
Porta et al. (201[illegible])	Erlotinib	Case series	Some patients had prior WBRT exposure	69	82	OS = 12.9
Park et al. (2012)	Gefitinib or Erlotinib	Phase II	Some patients had prior chemotherapy exposure	28	83	OS = 15.9
Wu et al. (2013)	Erlotinib	Phase II	Prior chemotherapy exposure	48	58	PFS = 15.2
Iuchi et al. (2013)	Gefitinib followed by sequential Erlotinib	Phase II	First line	41	88	OS = 21.9
Hoffknecht et al. (2015)	Afatinib	Efficacy from compassionate usage program	Prior chemotherapy and TKI exposure	100	35	–
Mok et al. (2017)	Osimertinib	Subgroup analysis from RCT	Prior TKI exposure	93	–	PFS = 8.5
Yang et al. (2017)	Icotinib	Phase III	First-line comparison of WBRT and chemo versus Icotinib	85	65	PFS = 10
	Dacomitinib	To date, to our knowledge, there are no data with regards to intracranial efficacy. Recent phase III trials have not reported intracranial outcomes or have excluded patients with brain metastasis in their design. ARCHER 1009/1050.				

TKI, tyrosine kinase inhibitor; OS, overall survival; WBRT, whole brain radiotherapy; PFS, progression-free survival; RCT, randomized controlled trial.

Ulahannan et al. Ann Oncol 28: 2923–2931, 2017



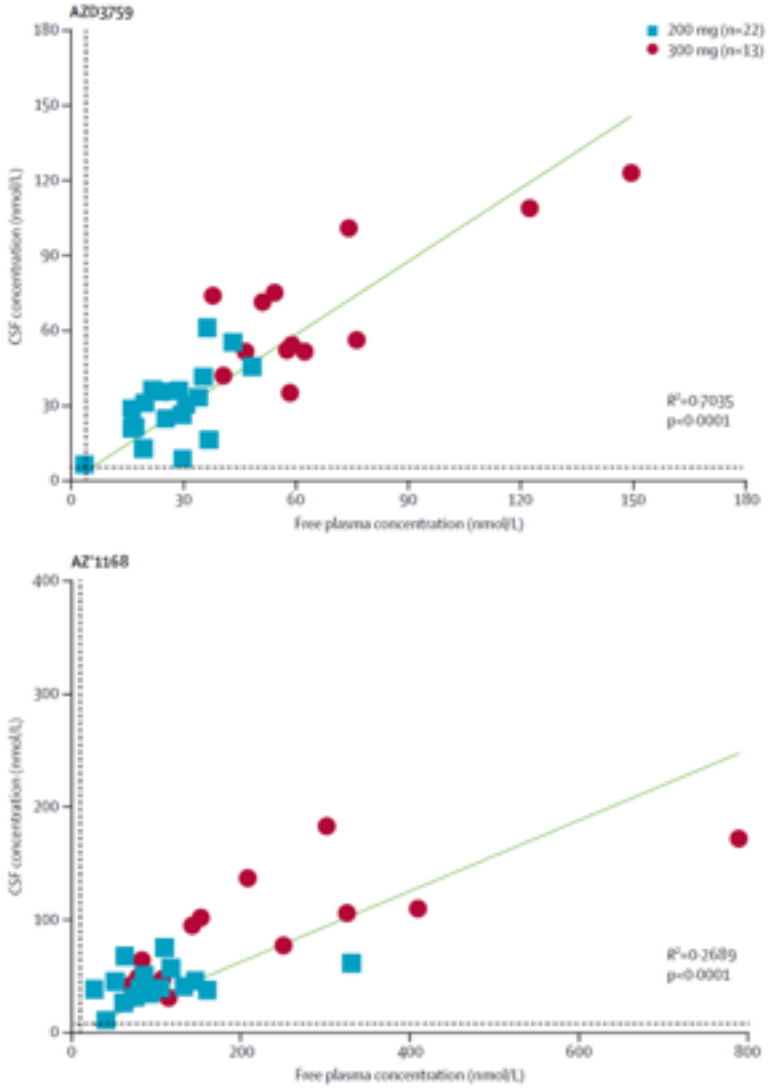
- Pulsatile erlotinib (1500mg 1x/week)

Grommes et al. Neuro-Oncol 2011;13:1364–1369

Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study

Myung-Ju Ahn, Dong-Wan Kim, Byoung Chol Cho, Sang-We Kim, Jong Seok Lee, Jin-Seok Ahn, Tae Min Kim, Chia-Chi Lin, Hye Ryun Kim, Thomas John, Steven Kao, Jonathan W Goldman, Wu-Chou Su, Ronald Natale, Sarit Rabbie, Bryony Horrop, Philip Overend, Zhenjian Yang, James Chih-Hsin Yang

Lancet Resp Med 2017;5:891



AZD3759 (EGFR mutant kinase inhibitor) has high passive permeability and is not a P-gp or BCRP transporter substrate

Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study

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Lancet Resp Med 2017;5:891

Pretreated with EGFRi

Not Pretreated with EGFRi

- 15/18 (83%) BM pts who had not received prior EGFRi had a response
- ¼ LM pts had a response

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT 2018;36:2702-2709

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

- Osimertinib is a EGFR-TKI selective for both EGFR-TKI–sensitizing and EGFR T790M–resistance mutations with good BBB penetration.
- Patients with asymptomatic, stable CNS metastases were randomly assigned 2:1 to osimertinib 80 mg once daily or platinum-pemetrexed.
- Preplanned sub-group analysis was conducted in patients with measurable and/or nonmeasurable CNS lesions on baseline brain scan by blinded independent central neuroradiological review.
- Primary objective for this analysis was CNS objective response rate (ORR).
- Of 116/419 patients had CNS lesions, including 46 patients with measurable CNS lesions.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT 2018;36:2702-2709

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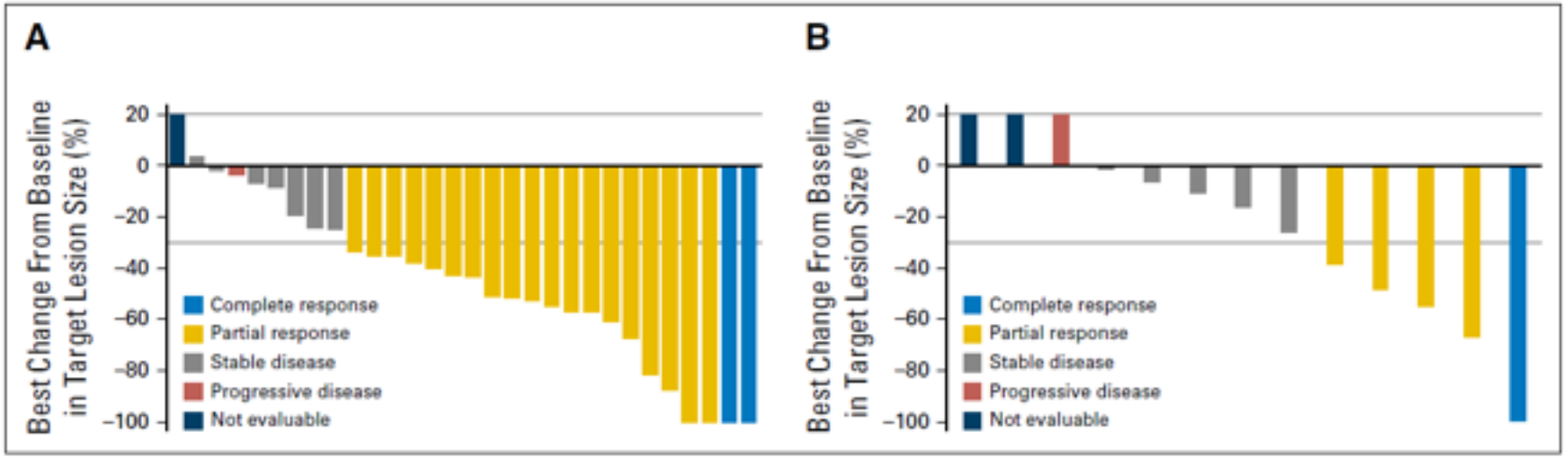
- Pt with measurable lesions:
  - CNS ORR was:
    - 70% with osimertinib
    - 31% with platinum-pemetrexed
    - (odds ratio, 5.13; 95% CI, 1.44 to 20.64; P = .015)



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT 2018;36:2702-2709

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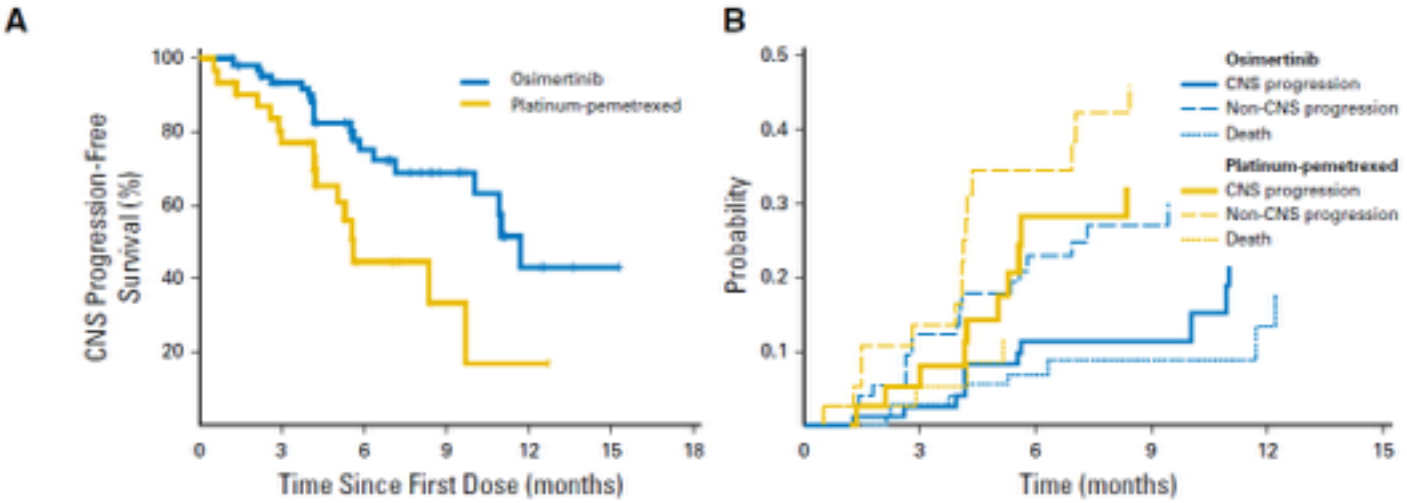
- Median CNS duration of response in patients with measurable and/or nonmeasurable CNS lesions was:
  - 8.9 months for osimertinib
  - 5.7 months for platinum-pemetrexed
- Median CNS progression-free survival was:
  - 11.7 months for osimertinib
  - 5.6 months for platinum-premetrexed (HR, 0.32; 95% CI, 0.15 to 0.69; P = .004)



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

2018 (epub)

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

- 556 pts randomly assigned to osimertinib or standard EGFR-TKIs (gefitinib or erlotinib)
- Patients with asymptomatic or stable CNS metastases were included.
- Preplanned subgroup analysis with CNS progression-free survival as primary objective was conducted in patients with measurable and/or non-measurable CNS lesions (IRR)
- 200 patients with available brain scans at baseline, 128 (osimertinib, n = 61; standard EGFR-TKIs, n = 67) had measurable and/or nonmeasurable CNS lesions
- 41 patients (osimertinib, n = 22; standard EGFR-TKIs, n = 19) with ≥ one measurable CNS lesion.

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

2018 (epub)

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

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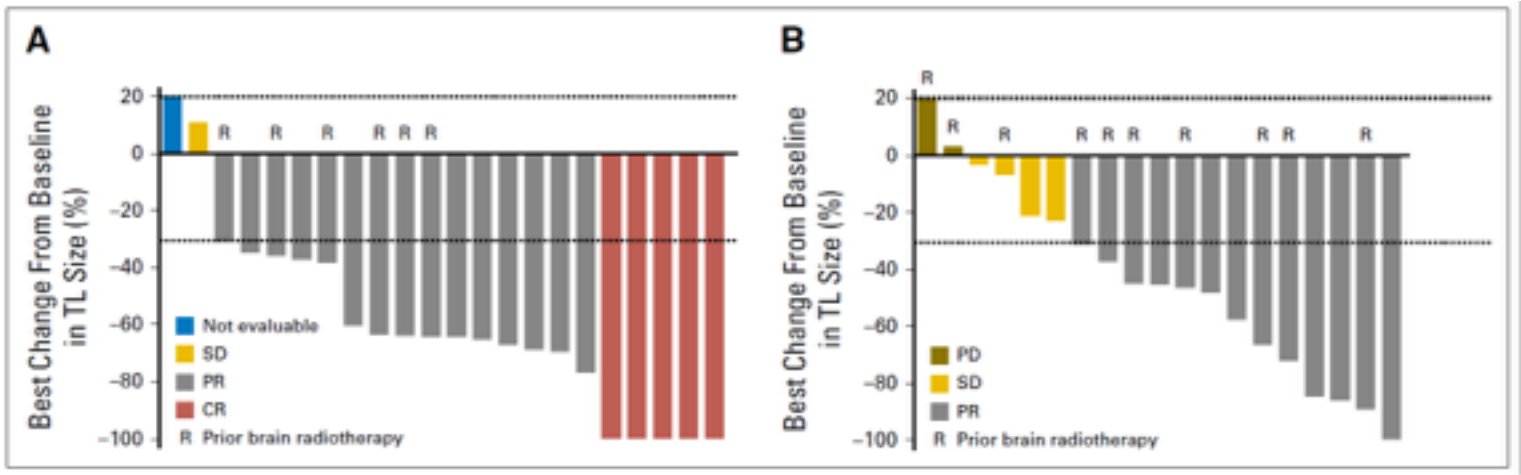
- **CNS ORR were 91% with osimertinib** and **68%with EGFR-TKI** in patients with ≥ one measurable CNS lesion (odds ratio, 4.6; 95% CI, 0.9 to 34.9; P = .066)
- CNS ORR was 66% for osimertinib and 43% for EGFR-TKI in patients with measurable and/or nonmeasurable CNS lesions (OR, 2.5; 95% CI, 1.2 to 5.2; P = .011) treated with osimertinib and standard EGFR-TKIs, respectively.



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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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

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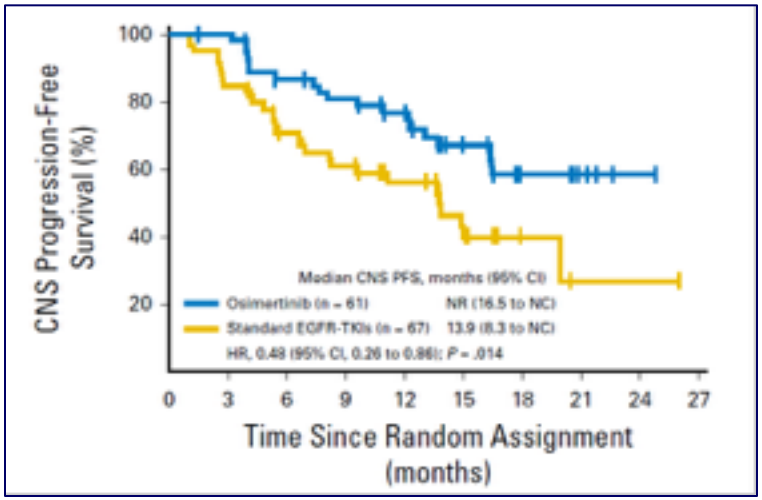
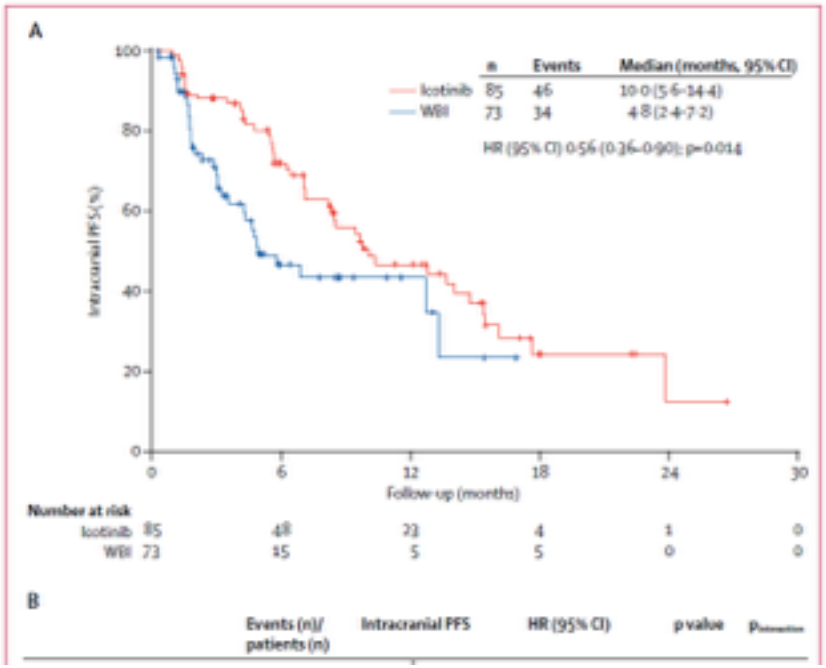
- Median CNS progression-free survival in patients with measurable and/or nonmeasurable CNS lesions was not reached with osimertinib (95% CI, 16.5 months to not calculable) and 13.9 months (95% CI, 8.3 months to not calculable) with standard EGFR-TKIs (HR, 0.48; 95% CI, 0.26 to 0.86; P = .014.
- Probability of experiencing a CNS progression event was consistently lower with osimertinib versus standard EGFR-TKIs.

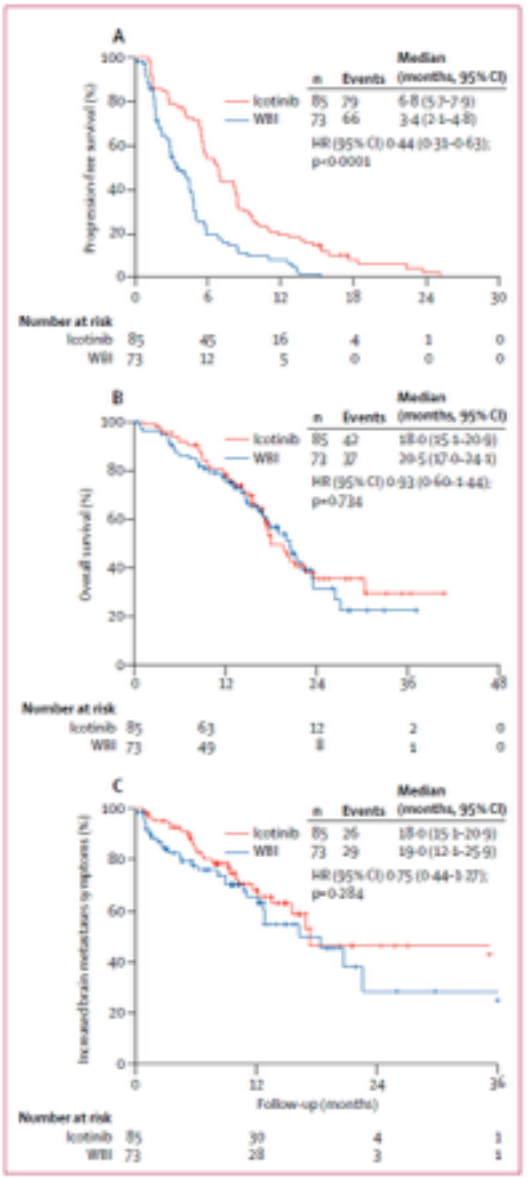


Icotinib versus whole-brain irradiation in patients with *EGFR*-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial

Jin-Ji Yang, Caicun Zhou, Yisheng Huang, Jifeng Feng, Sun Lu, Yong Song, Cheng Huang, Gang Wu, Li Zhang, Ying Cheng, Chengping Hu, Gongyan Chen, Li Zhang, Xiaoqing Liu, Hong Hong Yan, Fen Lai Tan, Wenzhao Zhong, Yi-Long Wu

Lancet Resp Med 2017



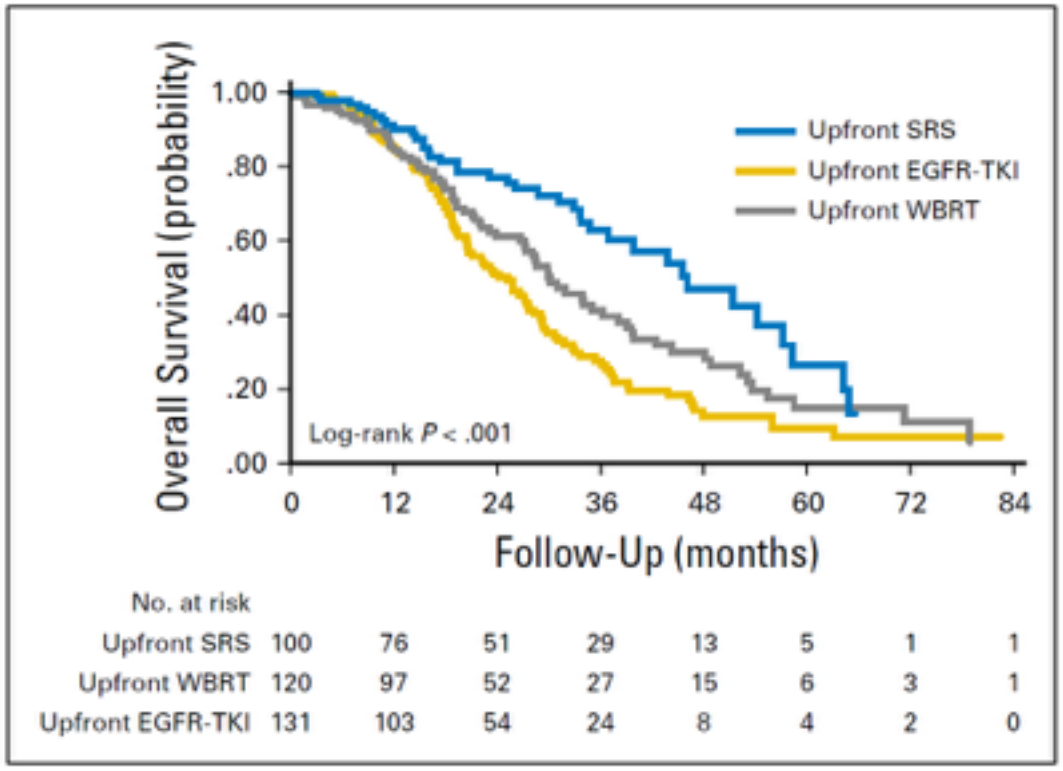


VOLUME 35 · NUMBER 10 · APRIL 1, 2017

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



Median OS:

- SRS = 46 mo
- WBRT = 30 mo
- EGFR-TKI = 25 mo

NSCLC (ALK+)

Table 3. Intracranial outcomes in brain metastases with ALK inhibitor

Reference	Drug	Study	Line of treatment	Number of patients with brain metastases	Outcome
Costa et al. (2015)	Crizotinib	Pooled retrospec-	Previous chemotherapy	275	Intracranial disease control rate at 12 weeks 56% in asymptomatic brain metastasis
Ou et al. (2015)	Alectinib				Intracranial RR = 57%
Soria et al. (2017)	Ceritinib				Intracranial RR = 73%
Hida et al. (2017)	(J-ALEX) versus			; > 29	HR = 0.16 for time to progression of brain metastatic lesion favouring alectinib
Peters et al. (2017)	(Global A versus			; > 22	Intracranial RR: alectinib = 81%; Crizotinib = 50%
Gettinger et al. (2017)	Brigatinib	Pooled analysis Phase 1/2	Mixed population	154	Intracranial RR = 53%
Felip et al. (2017)	Lorlatinib	Phase I/II	Previous ALK inhibitor exposure	39	Intracranial RR = 44%

RR, response rate; HR, hazard ratio.

Intracranial Resonse Rates

Alectinib: 81%

Ceritinib: 73%

Crizotinib: 50-57%

Brigatinib: 53%

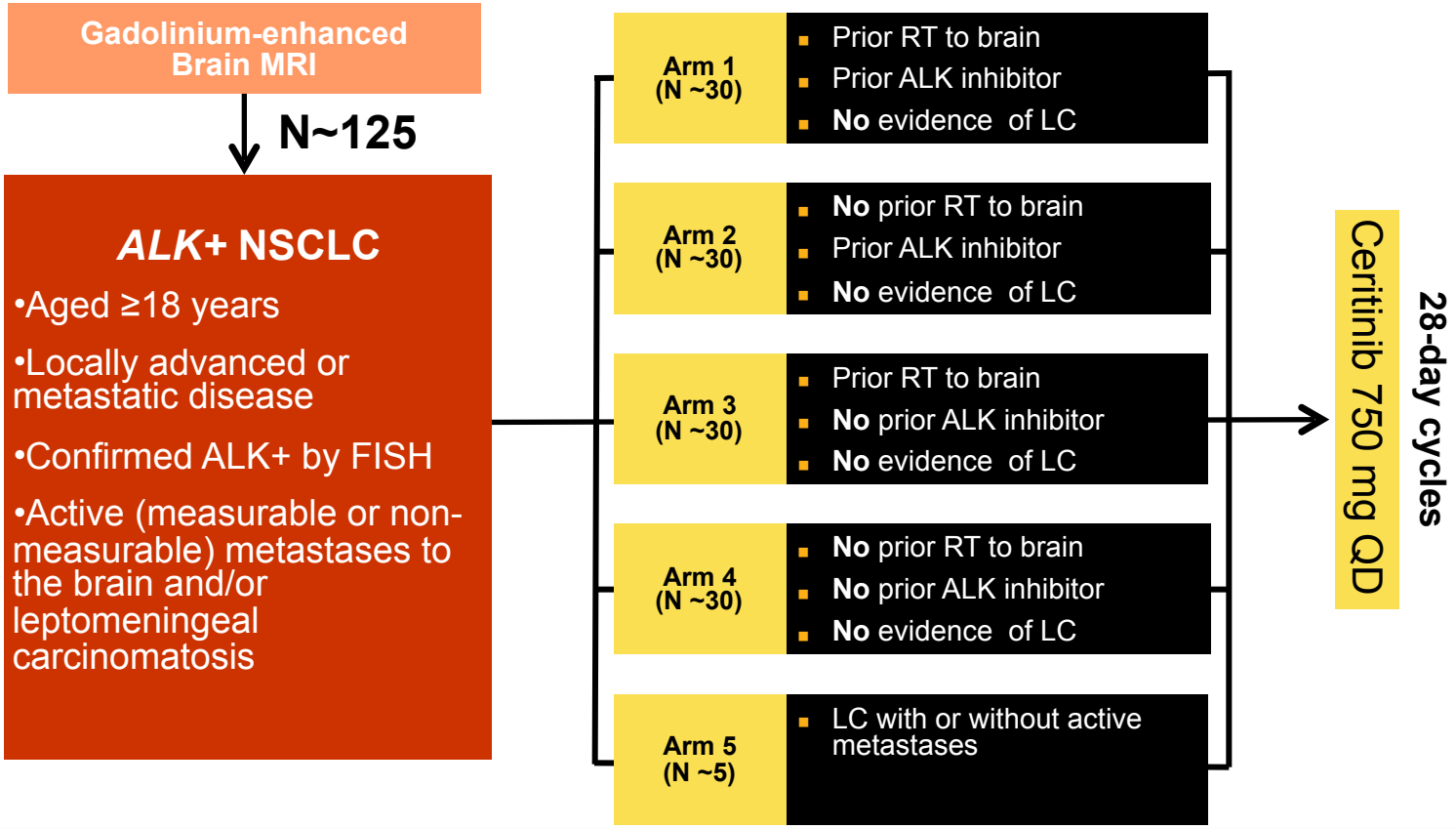
Lorlatinib: 44%

Ulahannan et al. Ann Oncol 28: 2923–2931, 2017

ENROLLING

ASCEND-7

Phase 2 Study in Patients with NSCLC Brain Metastases: CLDK378A2205



- ***Primary endpoint*** Whole body ORR
- ***Secondary endpoints*** *Whole body Disease Control Rate (DCR), intracranial ORR, DCR, Time To Response, and Duration Of Response;*
  Whole body TTR, Duration Of Response, and PFS; OS, safety, PK

LC, leptomeningeal carcinomatosis.

Clinical Trial Protocol CLDK378A2205. EUDRACT 2014-000578-20; 29 Jul 2014.

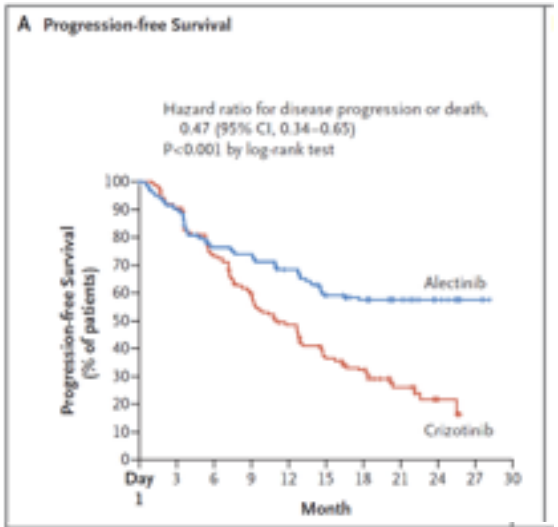
Clinicaltrials.gov identifier: NCT02336451

The NEW ENGLAND JOURNAL of MEDICINE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D., Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D., for the ALEX Trial Investigators*

2017;377:829-38



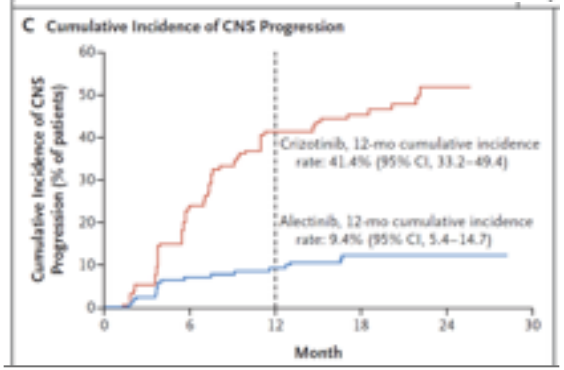


Table 2. Objective Response Rates in the Intention-to-Treat Population and among Patients with CNS Lesions at Baseline.*

Variable	Crizotinib	Alectinib
Intention-to-treat population		
No. of patients	151	152
Response		
No. of patients	114	126
% (95% CI)	75.5 (67.8–82.1)	82.9 (76.0–88.5)†
Complete response — no. (%)	2 (1)	6 (4)
Partial response — no. (%)	112 (74)	120 (79)
Stable disease — no. (%)	24 (16)	9 (6)
Median duration of response (95% CI) — mo	11.1 (7.9–13.0)	NE (NE)
Patients with measurable CNS lesions at baseline		
No. of patients	22	21
CNS response		
No. of patients	11	17
% (95% CI)	50 (28–72)	81 (58–95)
CNS complete response — no. (%)	1 (5)	8 (38)
Median duration of response (95% CI) — mo	5.5 (2.1–17.3)	17.3 (14.8–NE)

Breast Cancer

Neuro-Oncology
XX(XX), 1–11, 2018 | doi:10.1093/neuonc/noy044 | Advance Access date 16 March 2018

Breast cancer brain metastasis: molecular mechanisms and directions for treatment

Rute M. S. M. Pedrosa, Dana A. Mustafa, Riccardo Soffietti, and Johan M. Kros

Table 2 Overview of actionable targets and clinical studies on targeted therapies in established brain metastasis

Target	Targeted Agent	Pretreatment with Radiotherapy	Response Rate	Progression-free Survival (mo)	Overall Survival	Type of Trial	Reference or Clinicaltrials.Gov
HER2, EGFR	Lapatinib	Yes	6%	2.4	6.4	Phase II	[81]
	Lapatinib + Capecitabine	No	66%	5.5	~70% (1 y)	Phase II	[83]
Her2	Neratinib	Yes	8%	1.9	8.7	Phase II	[94]
	Neratinib + Capecitabine	Yes	49%	NA	63% (1 y)	Phase II	[95] (preliminary results)
	Tucatinib (ONT-380) + (TDM1)	Yes	33%	6.5	NA	Phase I	[97]
PARP	Iniparib [c]	Yes	27%	2.14	NA	Phase II	[102]
HER2	Pertuzumab + High-dose Trastuzumab (intravenous)	Yes	NA	NA	NA	Phase II	NCT02536339
	Pertuzumab + Trastuzumab (intrathecal)	No	NA	NA	NA	Phase I	NCT02598427
	Tucatinib (ONT-380) + Trastuzumab	Yes	NA	NA	NA	Phase I	NCT019221335
CDK4/6	Abemaciclib	Yes	NA	NA	NA	Phase II	NCT02774681
	Palbociclib	No	NA	NA	NA	Phase II	NCT02308020
P13K/Akt	Everolimus	Yes	NA	NA	NA	Phase II	NCT01305941 [a] NCT01783756 [b]
PARP	Veliparib	Yes (in association)	NA	NA	NA	Phase II	NCT00649207

TDM1, trastuzumab emtansine; CDK4/6, cyclin-dependent kinase 4 and 6; Akt, protein kinase B; NA, not available.
[a]In association with trastuzumab and vinorelbine. [b]In association with lapatinib and capecitabine. [c]In association with irinotecan.

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)

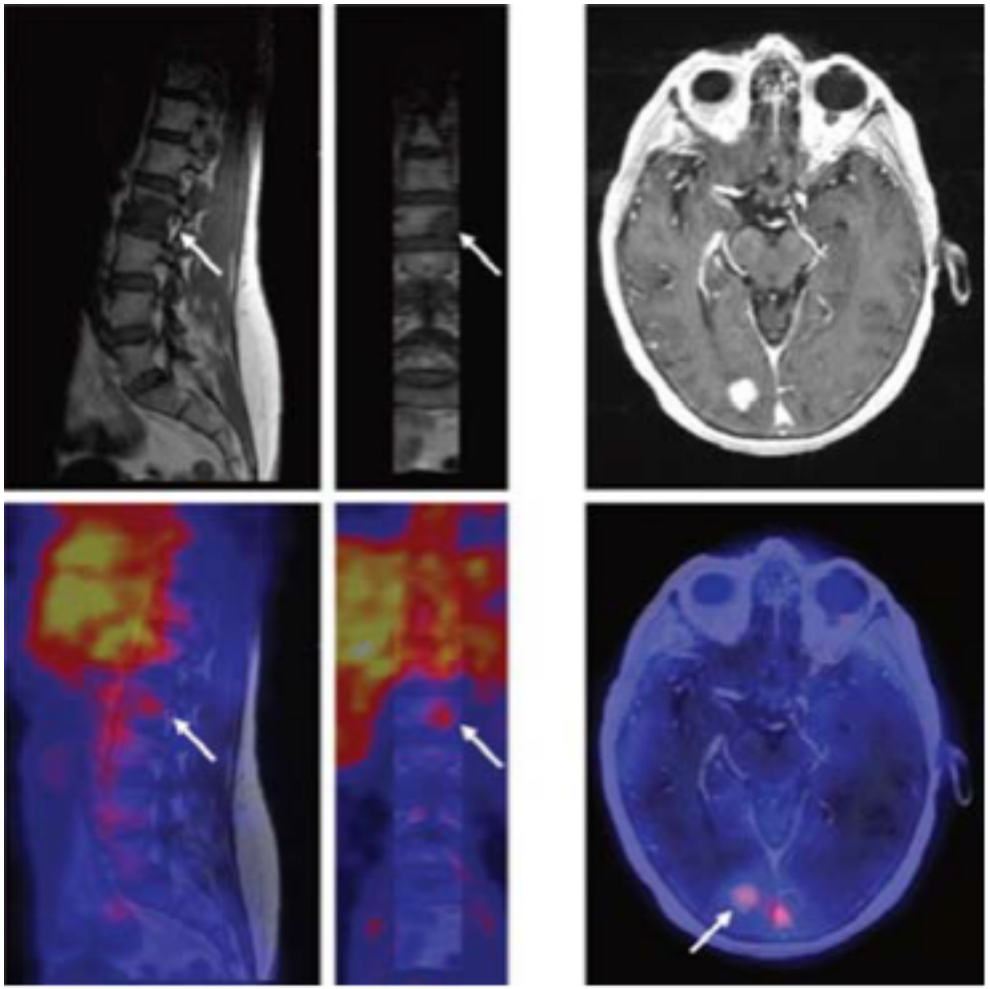
*Total drug concentrations are reported

Unpublished data

+ in non-human primate

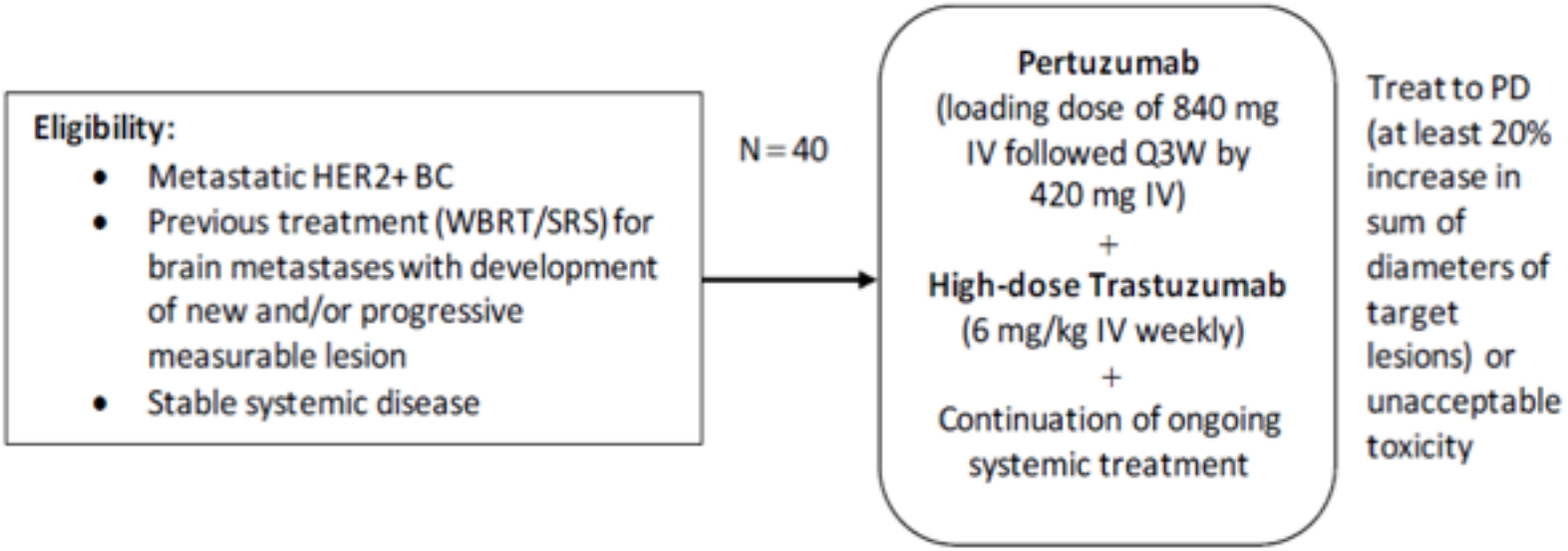
Kim et al. Pharm Res 2018;35:177

Biodistribution of 89Zr-trastuzumab and PET Imaging of HER-2-Positive Lesions in Patients With Metastatic Breast Cancer



Dijkers, et al Clin Pharmacol & Ther 2010

Lin et al (ASCO 2017, Abstr 2074): PATRICIA TRIAL



- **Primary efficacy endpoint:** ORR in the CNS
- **Secondary efficacy endpoint:** DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS
- **Safety endpoint:** Safety of pertuzumab and trastuzumab for the treatment of HER2-positive MBC with CNS progression post-radiotherapy

Trastuzumab-Emtansine (TDM1)

- **Bartsch et al (Clin Exp Metastasis 2015)**
  - 10 pt; 3PR (**30%**), 2SD > 6 mo
  - Median intracranial PFS 5 mo
- **Jacot et al (Breast Ca Res Treat 2016)**
  - Retrospective review of 39 pt (CNS ORR **44%**)
  - Median PFS 6.1 mo

Lapatinib For Brain Metastases

Study	Regimen	N	Prior chemo	Prior RT	CNS ORR	TTP/PFS
Lin et al JCO 2008*	Lapatinib	39	64% with ≥2 T+chemo	95%	2.6%	3.0 mo
Lin et al CCR 2009*	Lapatinib	237	81% with ≥2 T+chemo	100%	6%	2.4 mo
Toi et al Br J Cancer 2009	Lapatinib	10	>80% with ≥3 prior regimens	NR	2 PR	NR

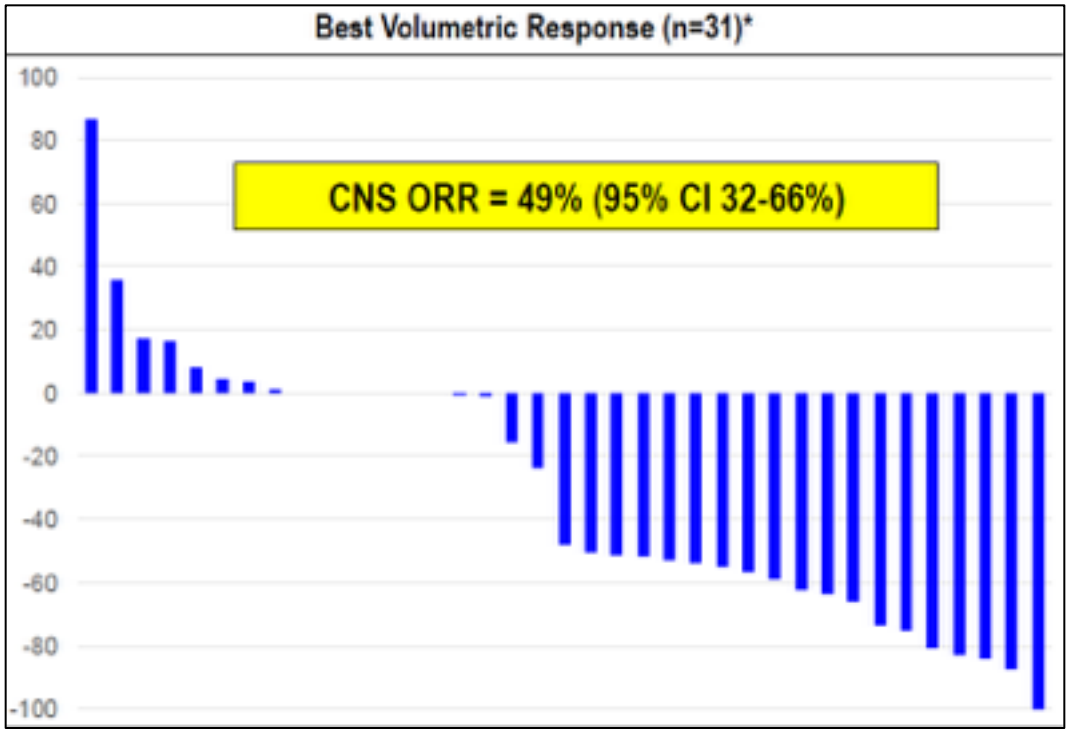
Lapatinib and Capecitabine For Brain Metastases

Study	N	Prior RT	CNS ORR	TTP/PFS
Lin et al CCR 2009	50	100%	20%	3.6 mo
Boccardo et al, ASCO 2008 (LEAP)	138	NR	18%	Median time on study 2.8 mo
Sutherland et al, Br J Ca 2010 (LEAP)	34	94%	21%	5.1 mo
Metro et al, Ann Oncol 2011	22	86%	32%	5.1 mo
Lin et al, J Neuro-Oncol 2011	13	100%	38%	NR
Bachelot et al, Lancet Oncol 2013	45	0%	66%	5.5 mo

Neratinib

- Oral, irreversible-binding inhibitor of the erbB TKI
- **Single agent activity** in brain metastases: **ORR 8%** in patients pretreated with WBRT or SRS (Freedman et al, J Clin Oncol 2016)
- **Neratinib + capecitabine** (Friedman et al (ASCO 2017): **CNS ORR 49%**

% reduction in volume of CNS lesion



- **Median time to CNS progression = 5.5 mo**
- **6M-PFS= 38%**

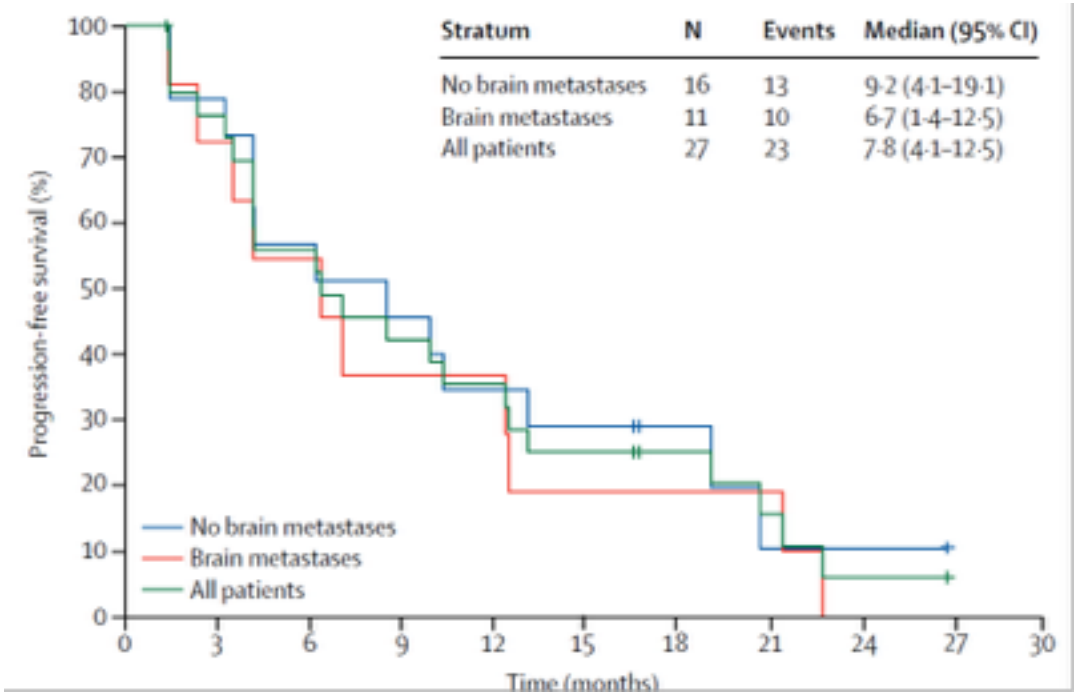
JAMA Oncology | Original Investigation

Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced *ERBB2/HER2*-Positive Metastatic Breast Cancer
A Phase 1b Clinical Trial

2018;4(9):1214-1220

Virginia F. Borges, MD, MMSc; Cristiano Ferrario, MD; Nathalie Aucoin, MD; Carla Falkson, MD; Qamar Khan, MD; Ian Krop, MD, PhD; Stephen Welch, MD; Alison Conlin, MD; Jorge Chaves, MD; Philippe L. Bedard, MD; Marc Chamberlain, MD; Todd Gray, MD; Alex Vo, MD; Erika Hamilton, MD

- Tucatinib (ONT-380), HER2 inhibitor with good BBB penetration
- 12 patients treated at the recommended phase 2 dose had measurable brain mets
- **5 (42%) of these patients achieved brain-specific objective response**

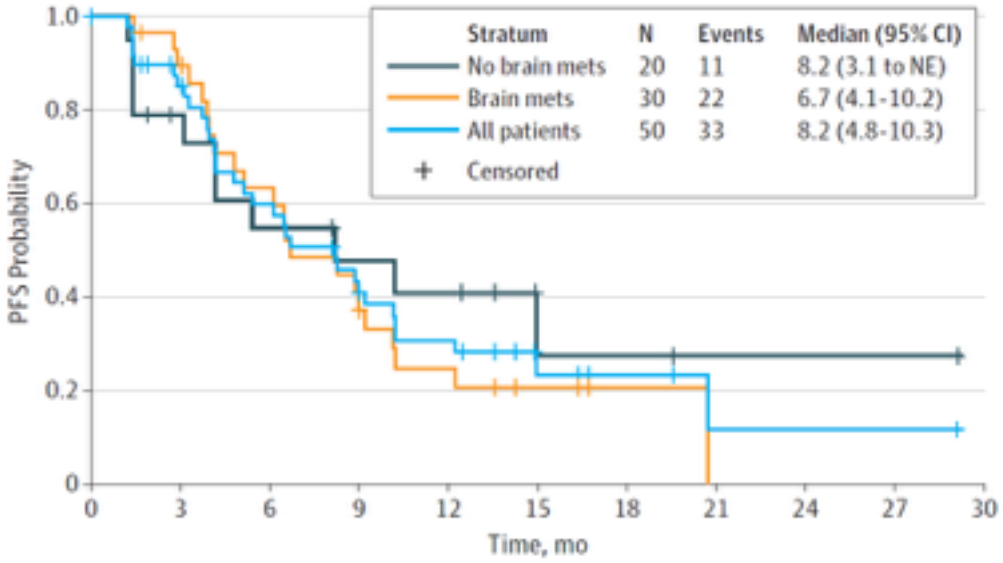


Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study

Lancet Oncol 2018

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

- MTD 300mg bid
- 50 pt with brain met
  - Median PFS was 6.7 months (95% CI, 4.1-10.2 months)
- 14/30 pt with measurable brain met
  - **Brain-specific objective response rate was 36%** (2 CR, 3 PR, 7 SD, and 2 nonevaluable).

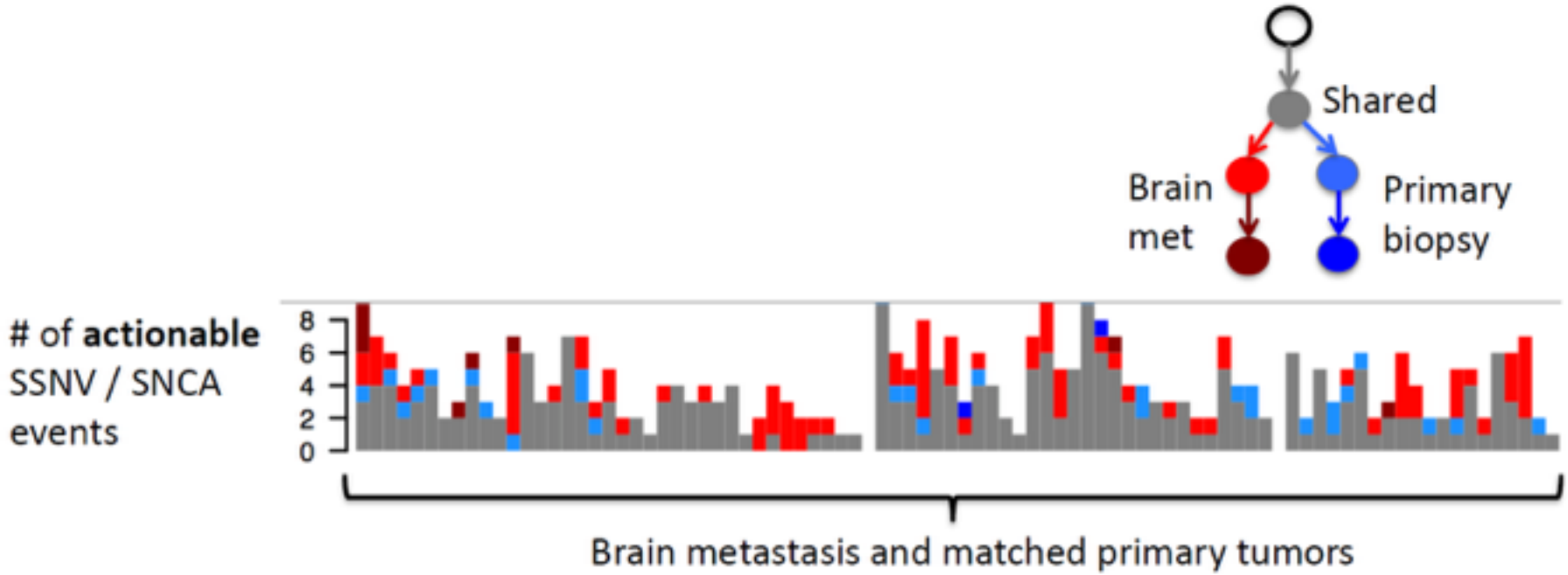


Ongoing HER2 TKI Trials

Ongoing key clinical trials of TKI in HER2-positive advanced breast cancer with brain metastases.

Clinical trial	Phase	N	Treatment and comparator (if any)	Primary endpoints	Expected study completion
NCT01622868 (BM present)	2	143	WBRT (15 fractions) or SRS vs. WBRT or SRS and lapatinib ditosylate PO QD for 6 weeks	CR in the measurable BM at 12 weeks after WBRT or SRS; brain response after 12 weeks RECIST v. 1.1	February 2018
NCT01494662 (BM present)	2	96	Cohort 1: HKI-272 (neratinib) 340 mg PO QD Cohort 2: HKI-272 (neratinib) 340 mg PO QD → surgical resection Cohort 3a: no prior lapatinib → neratinib 240 mg PO QD and 750 mg/m^2 capecitabine BID, 14 days, followed by 7 days rest Cohort 3b: prior lapatinib → neratinib 240 mg PO QD and 750 mg/m^2 capecitabine BID, 14 days, followed by 7 days rest	Cohort 1: ORR in the CNS by composite response criteria Cohort 2: neratinib concentrations from craniotomy specimen, CSF, plasma Cohort 3a, 3b: ORR	December 2018
NCT00777101 (BM absent or present)	2	233	Neratinib 240 mg PO OQ until PD or unacceptable toxicity vs. lapatinib 1250 mg PO QD and capecitabine 1000 mg/m^2 BID 14 days followed by 7 days rest. Given until PD or unacceptable toxicity	PFS (secondary endpoint: frequency and time to CNS metastases)	December 2018
NCT02614794 HER2CLIMB (BM absent or stable)	2	480	Tucatinib 300 mg or placebo PO BID and capecitabine 1000 mg/m^2 PO BID 14 followed by 7 days rest, and trastuzumab at a loading dose 8 mg/kg IV followed by 6 mg/kg once every 21 days	PFS; OS; PFS in the subgroup of patients with baseline BM; according to RECIST v. 1.1	January 2021
NCT03054363 TULiP (BM absent or stable)	1b/2	20/20	Tucatinib 300 mg or placebo PO BID in combination with palbociclib 125 mg PO QD for 3 weeks, followed by 7 days off and letrozol 2.5 mg PO QD	Phase 1b: safety and tolerability (any AE) Phase 2: PFS according to RECIST v.1.1.	January 2019
NCT02260531 (BM present)	2	40	Cabozantinib 60 mg PO QD of each 21 day cycle and trastuzumab IV on day 1 of each 21 day cycle	ORR in CNS	February 2022

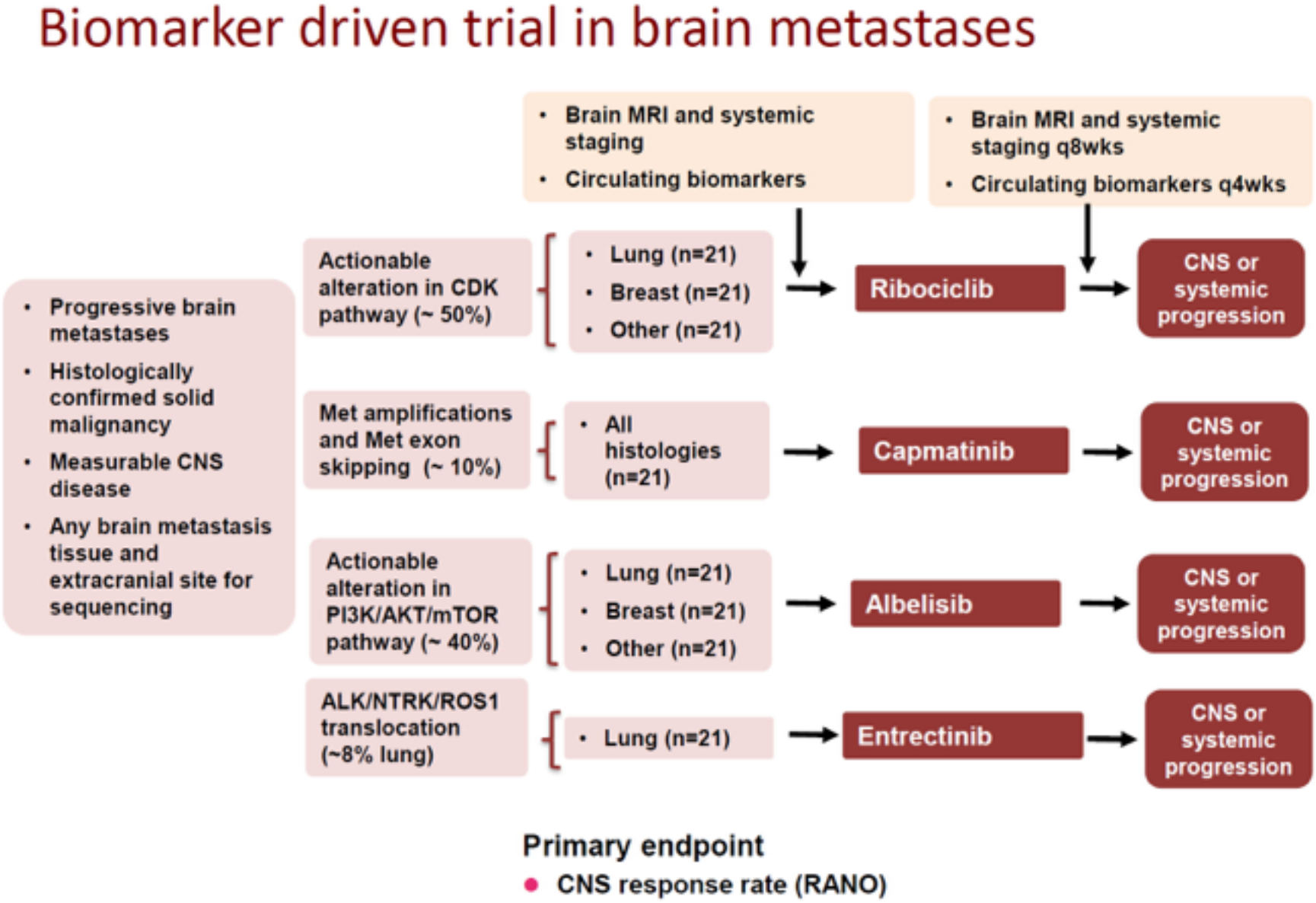
Primary tumors and brain metastases are often genetically distinct



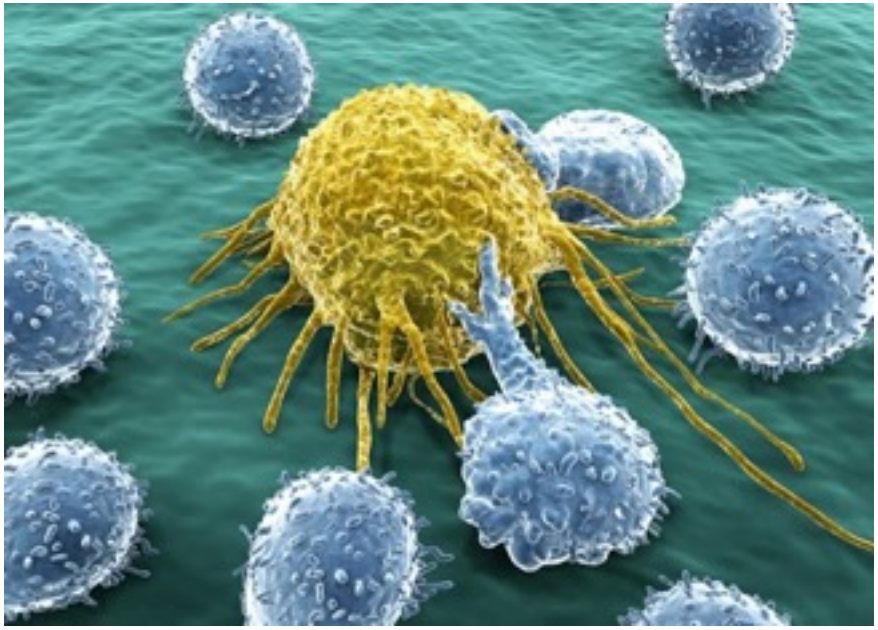
Targeted treatments that are appropriate for the primary tumor may not be appropriate for the brain metastasis.

Brastianos, Carter et al., *Cancer Discovery 2015*

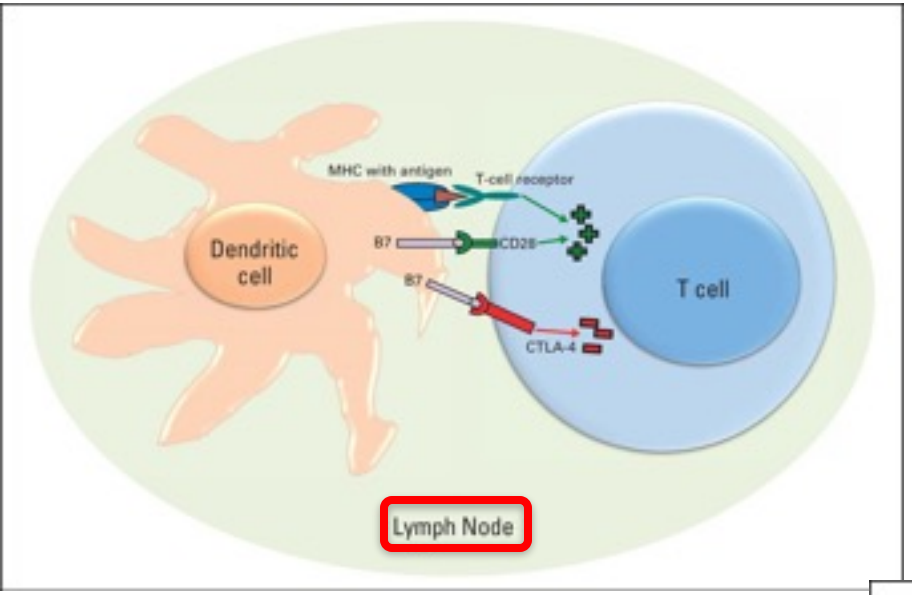
AO71701 (Brastianos et al)



Immunotherapy



Immune Checkpoint Blockade

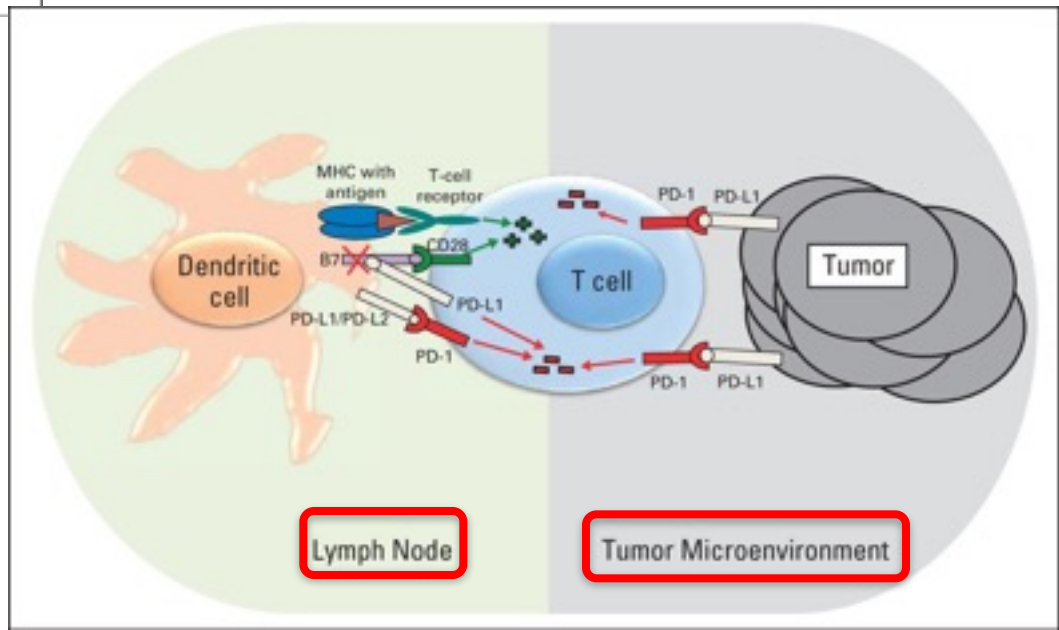


Cytotoxic T Lymphocyte Antigen – 4 (CTLA-4)

Initial T cell activation

Programmed Death – 1 (PD-1/PD-L1)

Later/after T cell activation



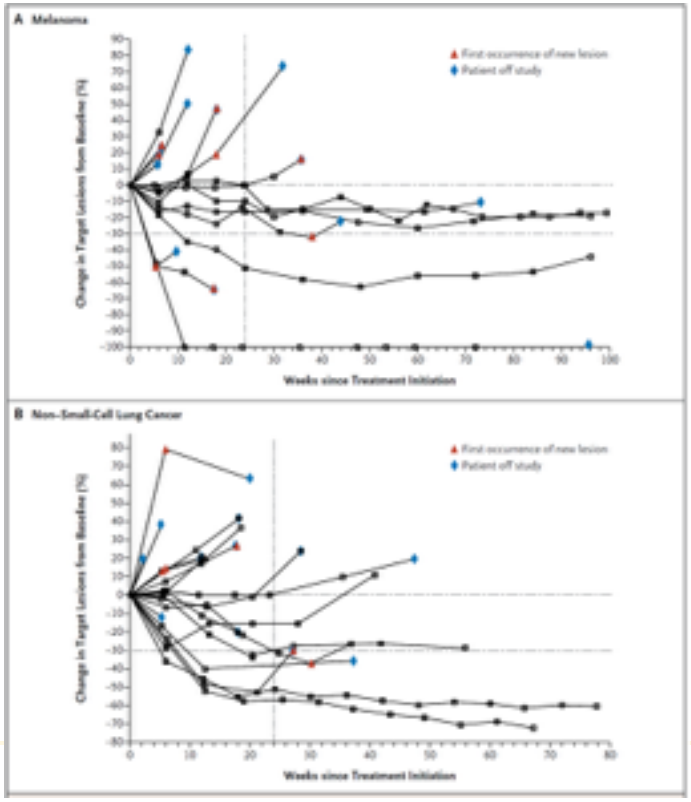
Postow et al. J Clin Oncol 33:1974, 2015

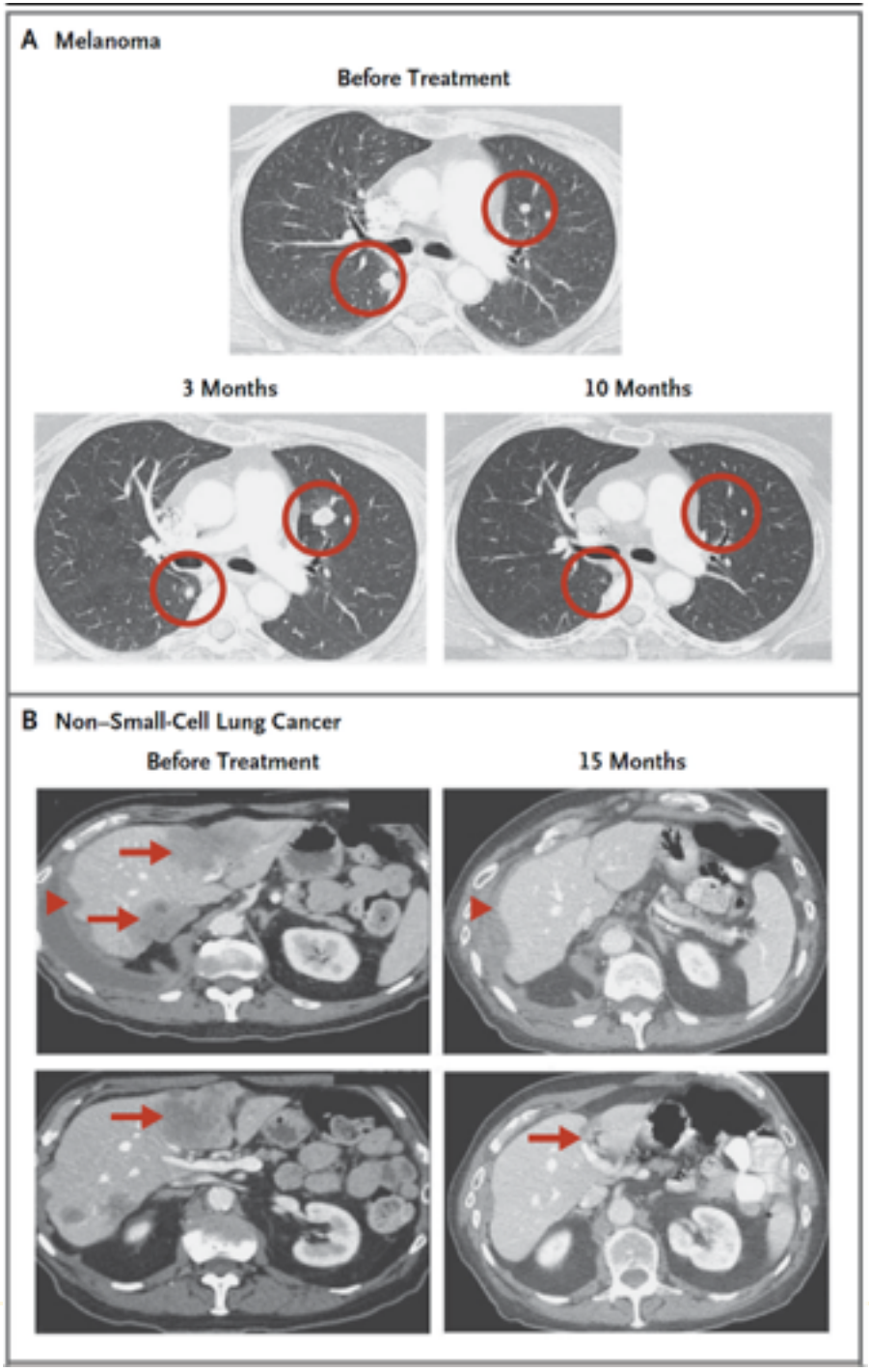
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

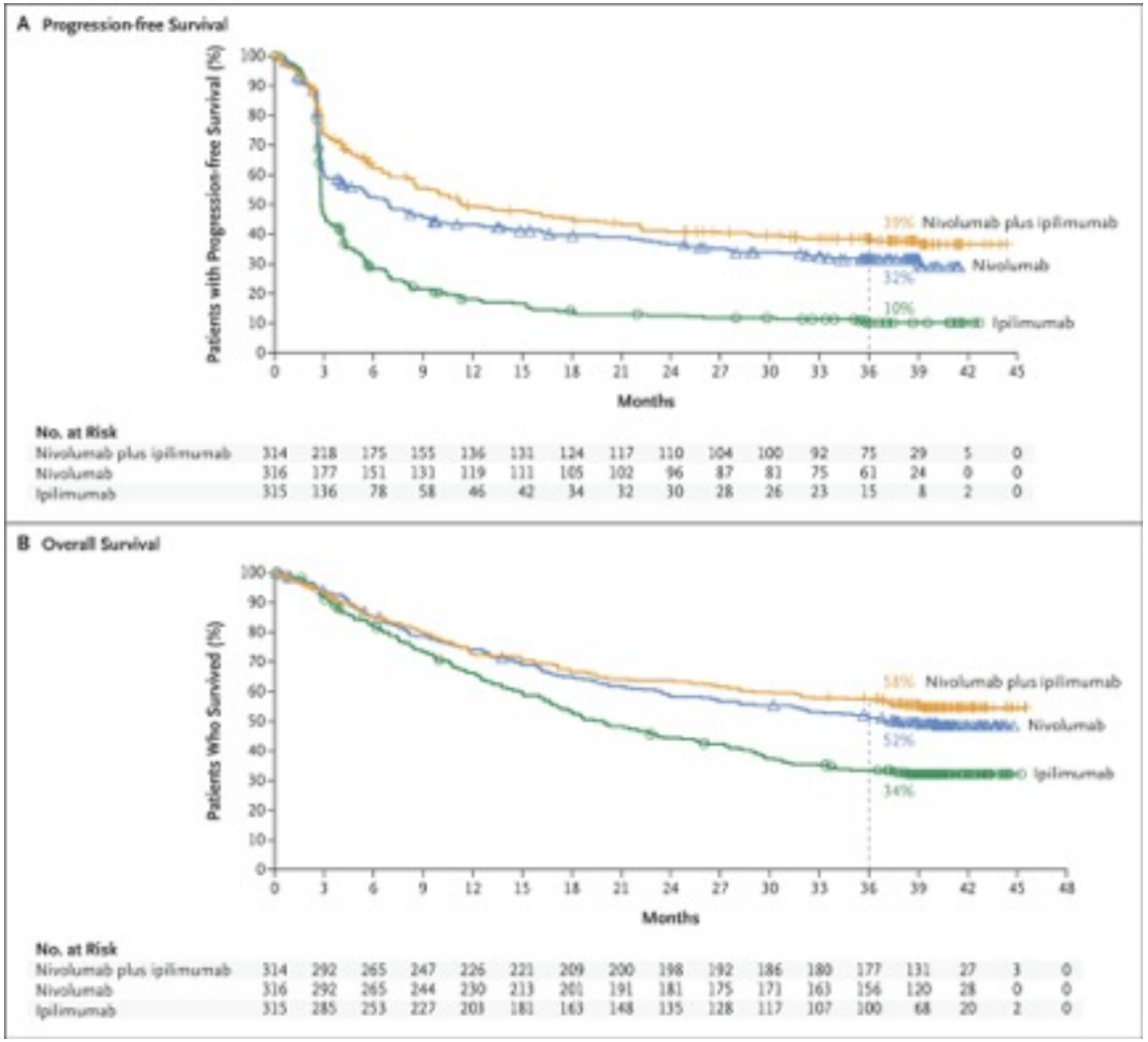
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.





Kaplan–Meier Estimates of Survival.



Wolchok JD et al. N Engl J Med 2017;377:1345-1356

The NEW ENGLAND JOURNAL of MEDICINE

Table 3. Completed clinical trials of immunotherapies for the treatment of MBM

Study	Therapy	Cohort	*N*	Key inclusion criteria	PFS (months)	OS (months)
NCT00623766 [59]	Ipilimumab	A	51	Neurologically asymptomatic; no steroids	1.5[a] 1.9[b]	7.0
		B	21	Neurologically symptomatic; steroids	1.2[a] 1.2[b]	3.7
NCT01654692 (NIBIT-M1) [60]	Ipilimumab and fotemustine		86	All patients	4.5	12.9
	Ipilimumab and fotemustine		20	Patients with asymptomatic MBM	3.4	12.7

[a]Brain-specific PFS per modified World Health Organization criteria.
[b]Brain-specific PFS per immune-related response criteria.
MBM, melanoma brain metastases; OS, overall survival; PFS, progression-free survival.

Table 4. Ongoing or recruiting clinical trials of immunotherapies for the treatment of MBM

Study	Therapy	Cohort	*N*	Key inclusion criteria	Planned primary and secondary outcome measures
NCT02107755 [116]	Ipilimumab and SRS	–	8	1–3 melanoma metastases to visceral organs[a] targetable with SRS	PFS; 6-month PFS, SAEs, ORR, local control, OS
NCT02085070 [62]	Pembrolizumab	A	18	Melanoma; ≥1 untreated MBM	ORR; MBM response per modified RECIST v1.1 criteria, safety
		B	18	Non-small cell lung cancer; ≥1 brain lesion, PD-L1 positive	
NCT02115139 (GRAY-B) [117]	Ipilimumab and WBRT	–	58	First radiologic evidence of MBM	1-year survival; PFS, intra- and extracranial PFS, OS, RR, AEs, biomarker correlation with PFS
NCT02320058 (CheckMate-204) [63]	Nivolumab and ipilimumab	–	75	≥1 measurable, unirradiated MBM (0.5–3.0 cm), prior SRT in ≤3 MBM, no neurological symptoms, no prior WBRT	Intracranial CBR; extracranial CBR, global CBR, OS, AEs and SAEs, systemic CBR
NCT02374242 (ABC) [64]	Nivolumab and ipilimumab (A) versus nivolumab (B)	A	35	No prior local brain therapy; asymptomatic MBM; no prior anti-CTLA-4, anti-PD-1, or anti-PD-L1; lesion size ≥5 and <40 mm	Intracranial RR from week 12 per modified RECIST v1.1; extracranial RR, ORR, intra- and extracranial PFS, overall PFS, OS, AEs, SAEs, irRC RR, biomarkers of progression
		B	25		
	Nivolumab	C	16	Prior treatment, symptomatic MBM, and LMD allowed	
NCT02460068 (NIBIT-M2) [61]	Fotemustine	A	168	Asymptomatic MBM	OS, AEs, PFS, ORR, TTR, DOR, intracranial PFS
	Fotemustine and ipilimumab	B			
	Ipilimumab and nivolumab	C			

Melanoma BM immunotherapy trials

Glitza Oliva et al. Ann Oncol 29: 1509–1520, 2018

THE LANCET Oncology 2012;13:459

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

- 72 patients with melanoma and brain metastases enrolled into 2 cohorts:
  - **Cohort A** (51 pt) were **neurologically asymptomatic and not receiving corticosteroid** treatment at study entry
  - **Cohort B** (21 pt) were **symptomatic and on a stable dose of corticosteroids**.
- Patients were to receive four doses of 10 mg/kg intravenous ipilimumab, one every 3 weeks.
- Individuals who were clinically stable at week 24 were eligible to receive 10 mg/kg intravenous ipilimumab every12 weeks
- Primary endpoint was the proportion of patients with disease control, defined as CR, PR or SD after 12 weeks

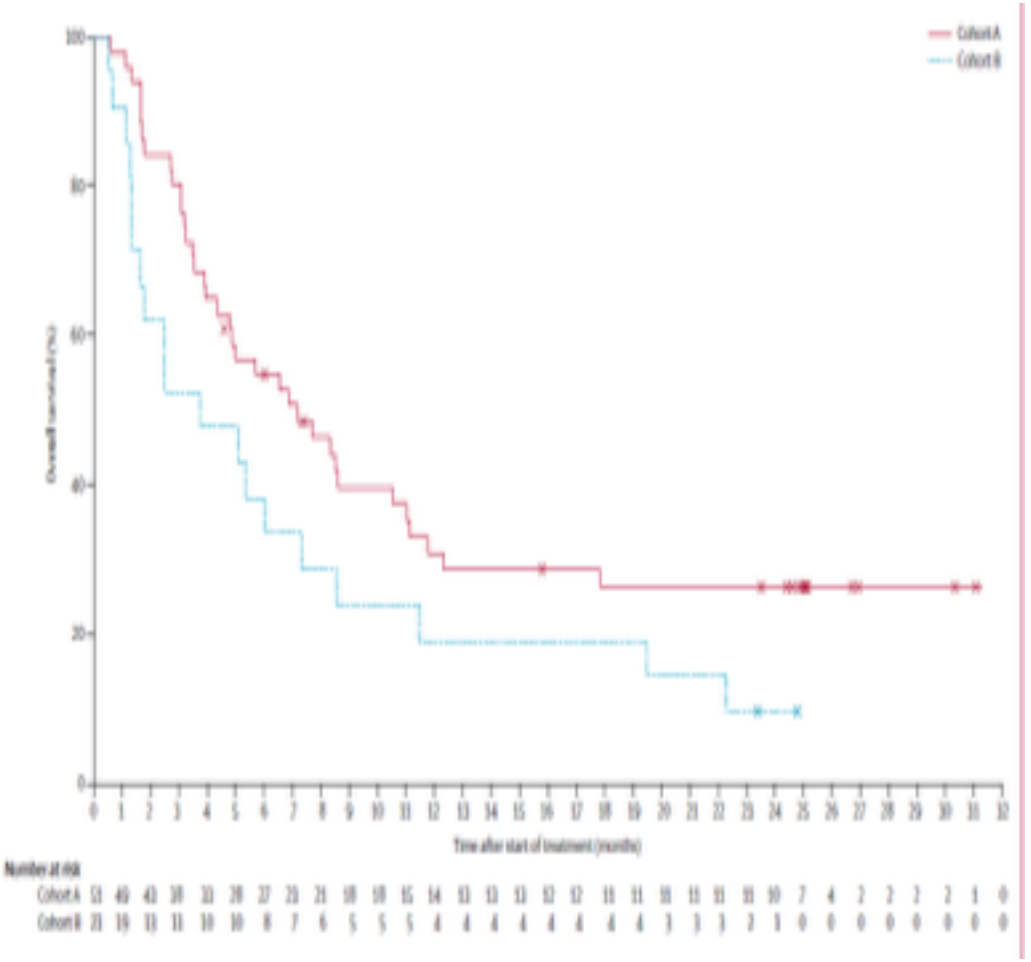
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
CNS				
CR	0	0	1 (5%)	1 (5%)
PR	8 (16%)	8 (16%)	0	0
SD	4 (8%)	5 (10%)	1 (5%)	1 (5%)
PD†	39 (76%)	38 (75%)	19 (90%)	19 (90%)
Unknown	0	0	0	0

	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



Margolin K. Lancet Oncol. 2012 May;13(5):459-65

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

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
CNS				
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PR	8 (16%)	8 (16%)	0	0
SD	4 (8%)	5 (10%)	1 (5%)	1 (5%)
PD†	39 (76%)	38 (75%)	19 (90%)	19 (90%)
Unknown	0	0	0	0

	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.

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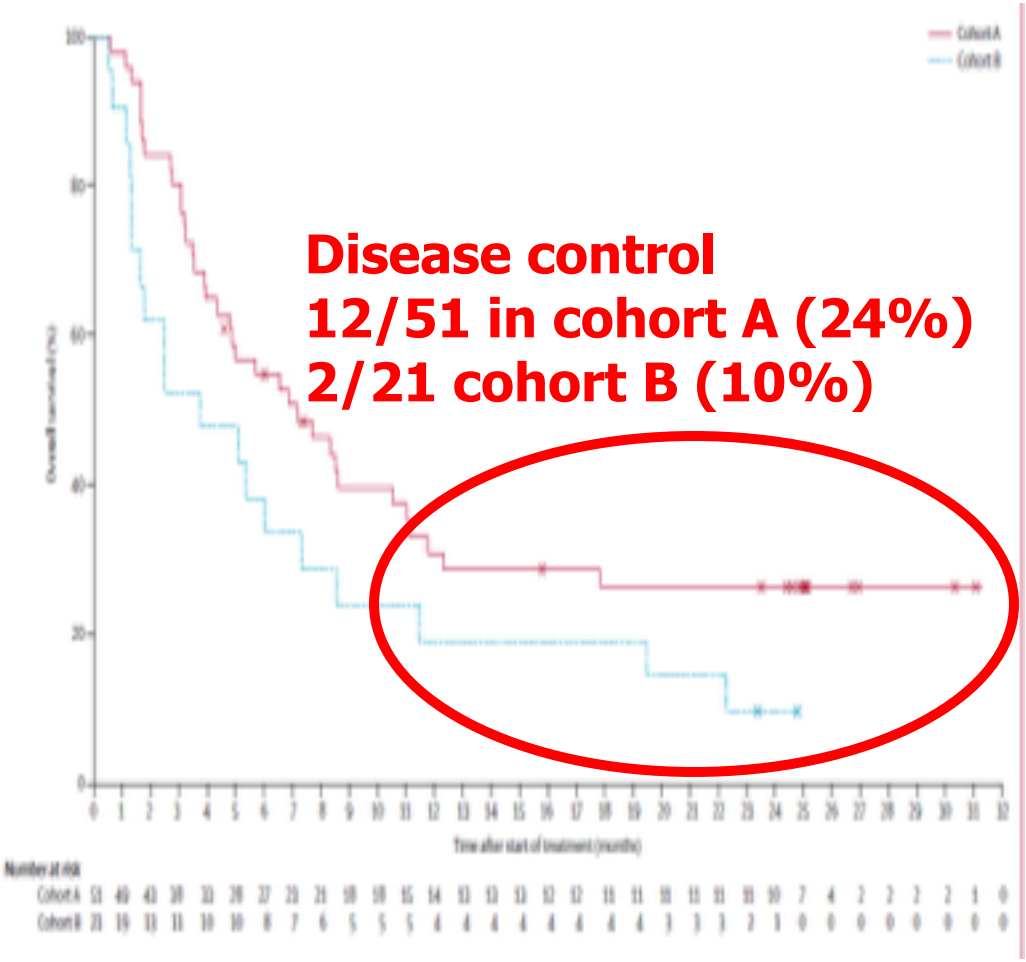


Margolin K. Lancet Oncol. 2012 May;13(5):459-65

THE LANCET Oncology 2016;17:976

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Ralabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger

Key eligibility:

- Advanced NSCLC or melanoma
- At least one untreated or progressive brain metastasis 5–20 mm
- No neurologic symptoms or steroid requirement
- PS 0–1
- PD-L1 expression from tumor biopsy after most recent systemic therapy

→ Pembrolizumab 10 mg/kg q2w

→ Brain metastasis PD → Consider radiation or surgery to progressing lesions

→ Brain metastasis CR, PR, or SD → Continue pembrolizumab if systemic control achieved

Safety evaluation at 4 weeks:

- Brain MRI

Response evaluation every 8 weeks:

- Brain MRI
- CT chest/abdomen/pelvis

Primary endpoint:
brain metastasis response rate

Secondary endpoints:
overall response rate, safety, PFS, OS

CT, computed tomography; PD-L-1, programmed cell death ligand-1; PS, performance status; q2w, every 2 weeks; SD, standard deviation.

Courtesy: Harriet Kluger.

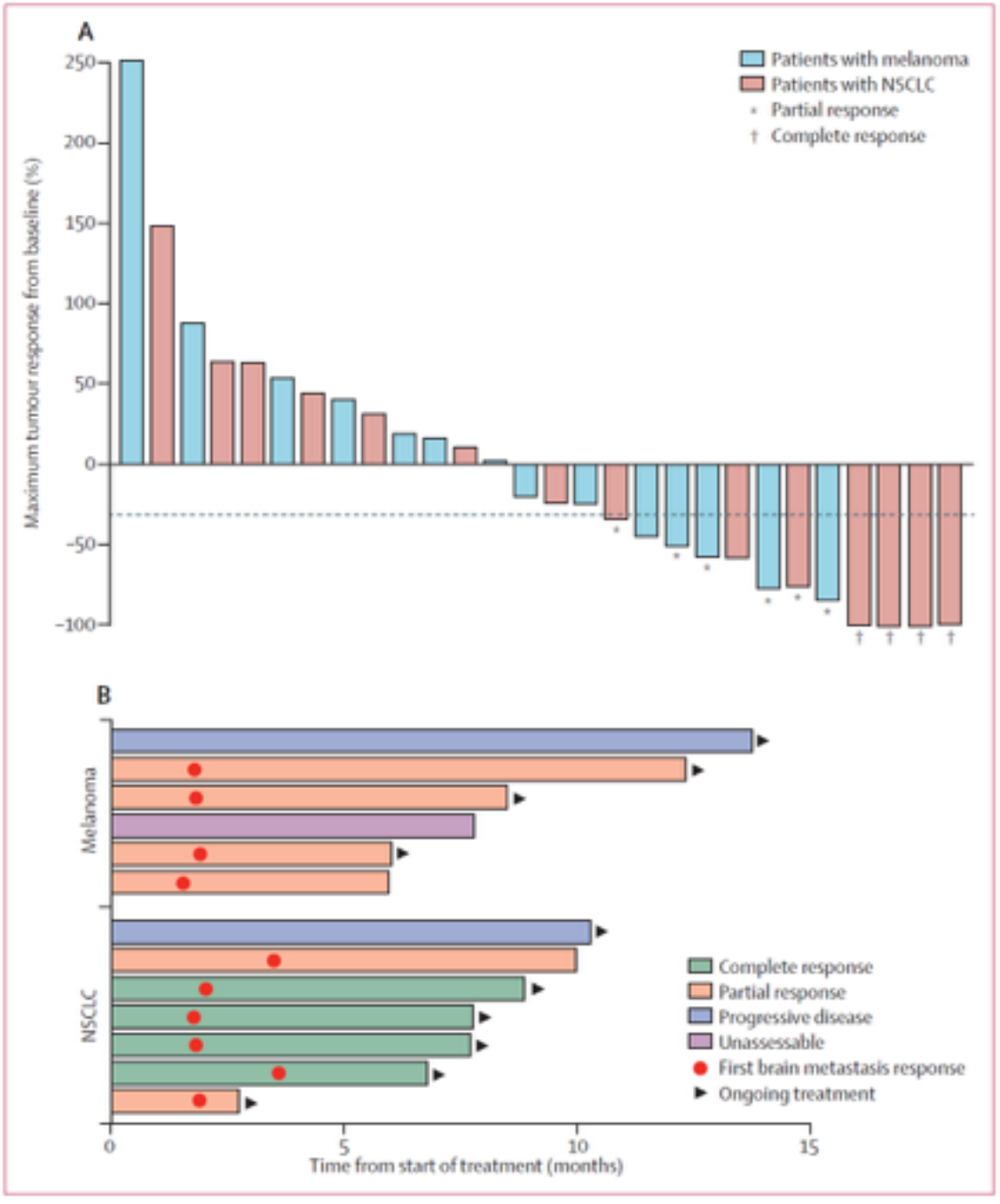
	Melanoma (n=18)			NSCLC (n=18)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neurological*						
Cognitive dysfunction	0	1 (6%)	0	1 (6%)	0	0
Headache	3 (17%)	0	0	4 (22%)	0	0
Dizziness	1 (6%)	0	0	2 (11%)	0	0
Stroke	0	0	0	1 (6%)	0	0
Seizure	3 (17%)	0	0	0	0	0
Treatment-related non-neurological						
Colitis or diarrhoea	0	0	0	3 (17%)	1 (6%)	0
Pneumonitis	0	0	0	0	1 (6%)	0
Acute kidney injury	0	0	0	1 (6%)	0	0
Fatigue	8 (44%)	0	0	5 (28%)	1 (6%)	0
Anorexia	1 (6%)	0	0	2 (11%)	0	0
Dermatological	6 (33%)	0	0	4 (22%)	0	0
Arthralgias	2 (11%)	0	0	1 (6%)	0	0
Endocrine	1 (6%)	0	0	5 (28%)	0	0
Hyperkalemia	0	0	0	0	0	1 (6%)
Haematological	0	0	0	2 (11%)	0	0
Elevated aminotransferases	0	1 (6%)	0	0	0	0

NSCLC=non-small-cell lung cancer. There were no treatment-related deaths. *Irrespective of attribution to study drug.

***Table 3*: Neurological adverse events and treatment-related non-neurological adverse events in all treated patients with melanoma or NSCLC**

Generally well-tolerated

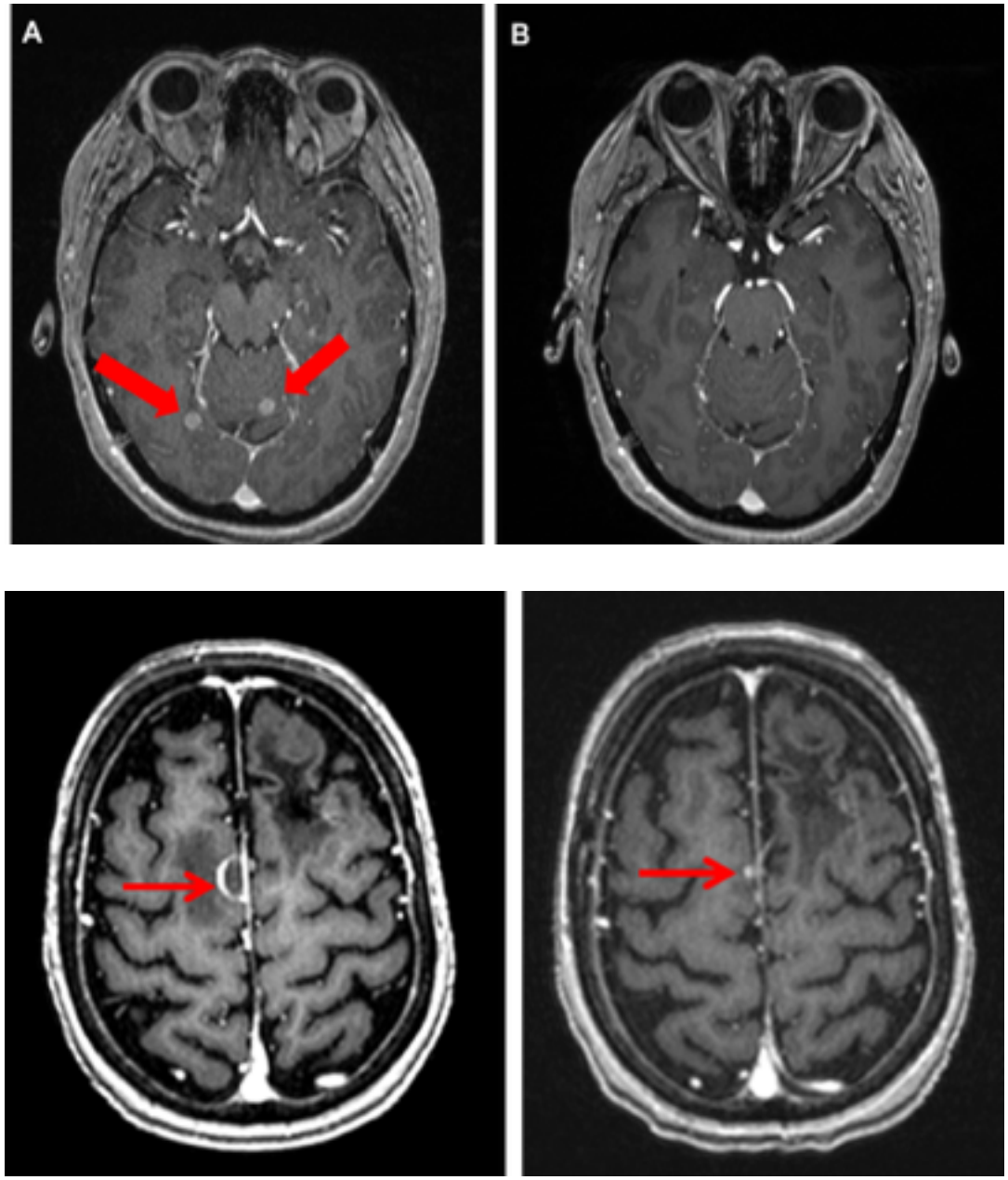
Goldberg Lancet Oncol 2016



Response was achieved in:

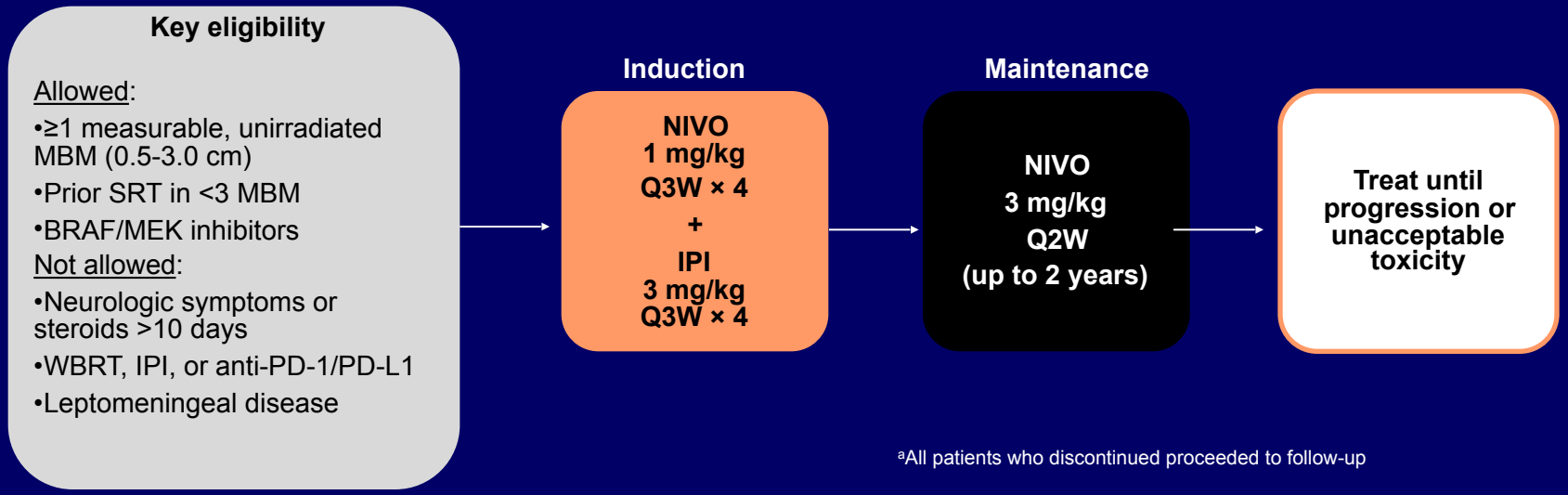
- **4 (22%) of 18 patients with melanoma**
- **6 (33%) of 18 patients with NSCLC**
- Responses were durable

Goldberg Lancet Oncol 2016



Courtesy: Sarah Goldberg.

Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Melanoma Metastatic to the Brain: Results of the Phase II Study CheckMate 204



[a]All patients who discontinued proceeded to follow-up

- Original planned enrollment of 110 asymptomatic patients; amended to include 20 symptomatic patients
- Patients with grade 3-4 AEs during NIVO+IPI induction could resume NIVO when toxicity resolved

Tawbi H et. al Abstract 9507, ASCO Annual Meeting 2017

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The NEW ENGLAND JOURNAL of MEDICINE

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.

2018;379:722-730

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)

- Open label single arm phase II study (94 pts)
- At least one measurable, non-radiated BM, no neurologic symptoms
- 26% CR, 30% PR, SD for at least 6 months 2%
- 57% intracranial benefit
- Extracranial clinical benefit 56%
- 55% Gr ¾ adverse events; 7% CNS

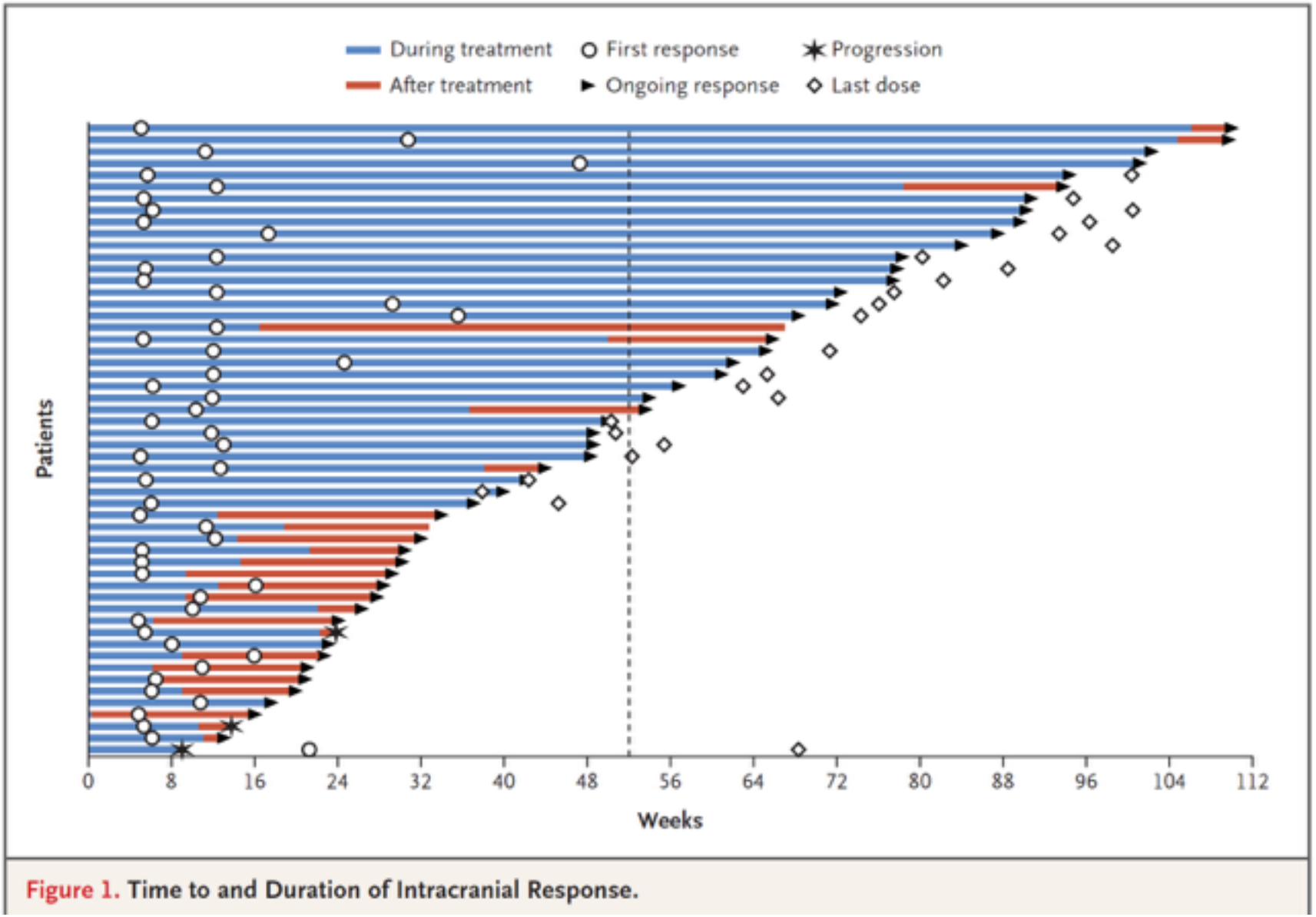

Figure 1. Time to and Duration of Intracranial Response.

Tawbi et al. NEJM 2018;379:722-730

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

Lancet Oncol 2018

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*

- Asymptomatic brain metastases with no previous local brain therapy were randomly assigned to:
  - **Cohort A (nivolumab plus ipilimumab)**
  - **Cohort B (nivolumab)**
- Patients with brain metastases in whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease
  - **Cohort C : (nivolumab)**
- Patients in cohort A received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks
- Patients in cohort B or cohort C received intravenous nivolumab 3 mg/kg every 2 weeks.
- Primary endpoint was intracranial response from week 12

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

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	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%)

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

Lancet Oncol 2018

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*

	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
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)

Treatment-related grade 3/4 AEs occurred in **54% (combination)** and **15% (nivolumab)** of patients, and 26% and 5% of patients, respectively, discontinued due to an AE.

Summary of Results of Immune Checkpoint Blockade for Melanoma

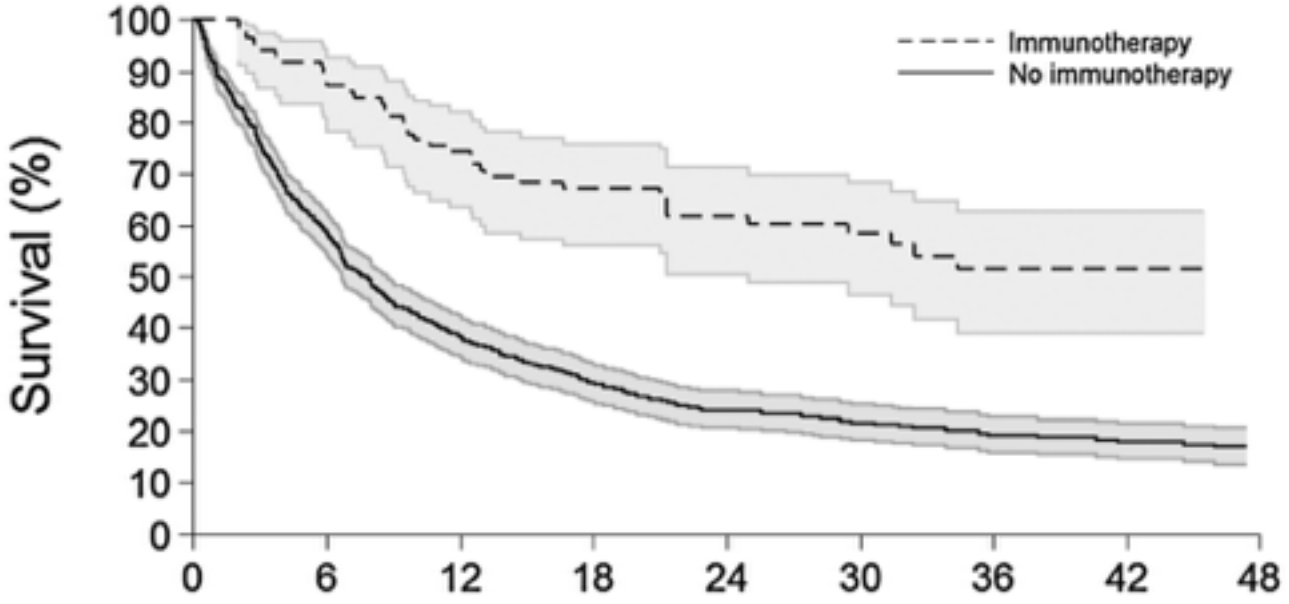
Checkpoint inhibitor	ORR
Ipilimumab	**16%** (Margolin, Lancet Oncol 2012)
Pembrolizumab	**22%** (Goldberg, Lancet Oncol 2016)
Nivolumab	**20%** (Long; Lancet Oncol 2018)
Nivolumab + Ipilimumab	**56%** (Tawbi; NEJM 2018) **46-56%** (Long; Lancet Oncol 2018)

Improved Risk-Adjusted Survival for Melanoma Brain Metastases in the Era of Checkpoint Blockade Immunotherapies: Results from a National Cohort

J. Bryan Iorgulescu[1,2,3], Maya Harary[2,3], Cheryl K. Zogg[4,5], Keith L. Ligon[1,2,6], David A. Reardon[2,7], F. Stephen Hodi[2,8], Ayal A. Aizer[2,9], and Timothy R. Smith[2,3]

Cancer Immunology Research

2018



Number at risk

Immunotherapy									
Yes	86	77	63	52	42	31	19	14	12
No	590	338	215	161	122	86	62	41	28

Future Studies

- **Combination of TKI + immunotherapy**
  - Atezolizumab combined with cobimetinib and vemurafenib
  - Ipilimumab with or without dabrafenib, trametinib, and/or nivolumab
  - Pembrolizumab plus dabrafenib and trametinib
  - Nivolumab in combination with dabrafenib and/or trametinib
- **Immunotherapy + RT**

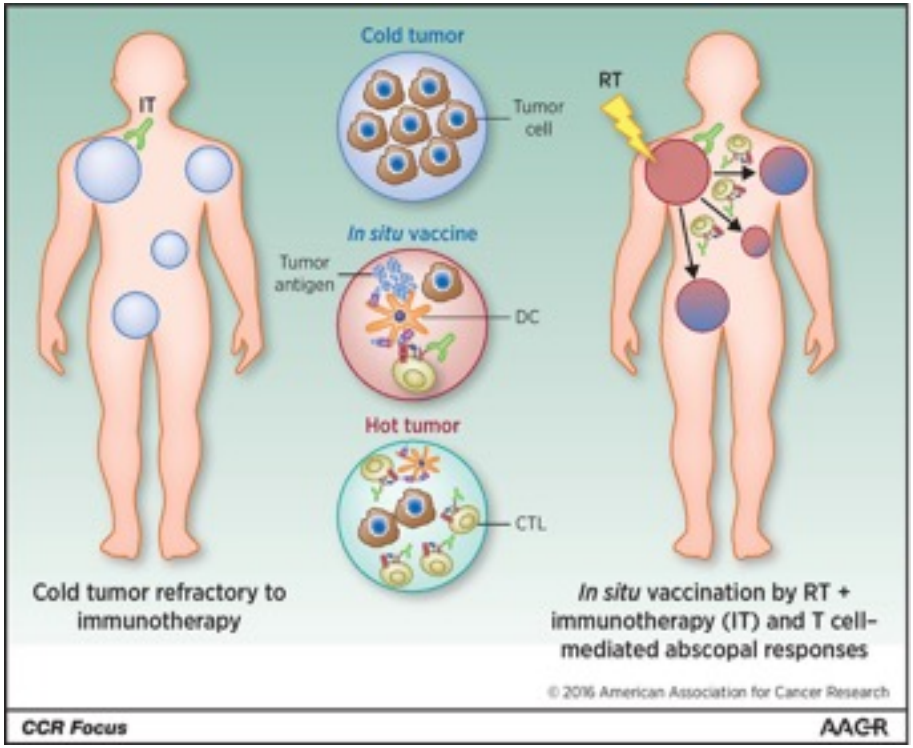
Selected Ongoing Immunotherapy Trials in Brain Metastases

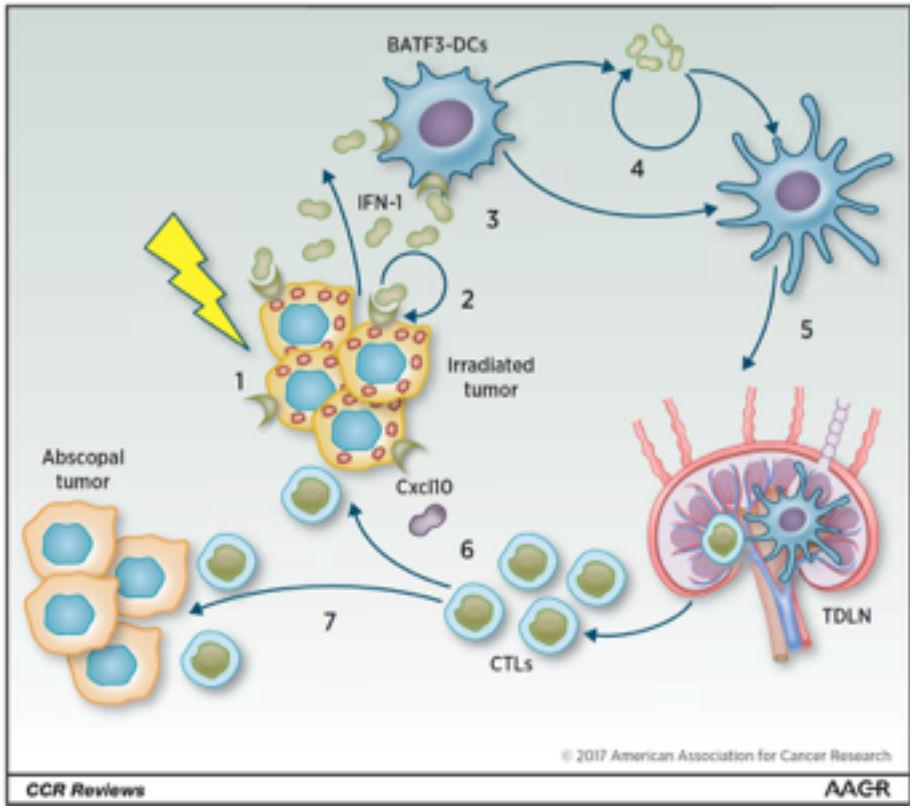
NTC number	Status	Phase	Checkpoint inhibitor	Tumor type	*N*	Treatment groups
02662725	Completed	II	Ipilimumab	Melanoma	73	Ipilimumab plus SRS
01454102	Active, not recruiting	I	Nivolumab	NSCLC	NA	One arm containing patients with brain metastases treated with nivolumab monotherapy
02027961	Active, not recruiting	I	Durvalumab	Melanoma	NA	Durvalumab with either dabrafenib, trametinib, or both
02107755	Active, not recruiting	II	Ipilimumab	Melanoma	8	Ipilimumab plus SRS
02115139	Active, not recruiting	II	Ipilimumab	Melanoma	58	Ipilimumab plus WBRT
02596035	Active, not recruiting	IV	Nivolumab	RCC	150[a]	Nivolumab
02460068	Recruiting	III	Ipilimumab and nivolumab	Melanoma	168[a]	Fotemustine Fotemustine plus ipilimumab Ipilimumab plus nivolumab
02621515	Recruiting	II	Nivolumab	Melanoma	70[a]	Nivolumab
02681549	Recruiting	II	Pembrolizumab	Melanoma and NSCLCL	53[a]	Pembrolizumab plus bevacizumab
02696993	Recruiting	I and II	Ipilimumab and nivolumab	NSCLC	80[a]	Nivolumab plus SRS, nivolumab plus WBRT, nivolumab plus ipilimumab plus SRS, nivolumab plus ipilimumab plus WBRT
02858869	Recruiting	I	Pembrolizumab	Melanoma and NSCLC	30[a]	Three cohorts with pembrolizumab and three different doses of SRS
02599402	Recruiting	III	Ipilimumab and nivolumab	Melanoma	615[a]	Nivolumab plus ipilimumab, nivolumab alone
02978404	Recruiting	II	Nivolumab	NSCLC and RCC	60[a]	Nivolumab plus SRS
03297463	Recruiting	I and II	Ipilimumab	Melanoma	40[a]	Ipilimumab plus interleukin-2
02886585	Recruiting	II	Pembrolizumab	Multiple	102[a]	Untreated brain metastases, progressive, neoplastic meningitis, metastasis from melanoma
03340129	Not yet recruiting	II	Ipilimumab and nivolumab	Melanoma	155[a]	Nivolumab plus ipilimumab followed by nivolumab alone, two additional cohorts with same immunotherapy, one with SRS, the other with WBRT

[a] Estimated enrollment

Lauko et al. Curr Neurol Neuroscience Rep 2018;18:70

Radiotherapy + PD1 Blockade



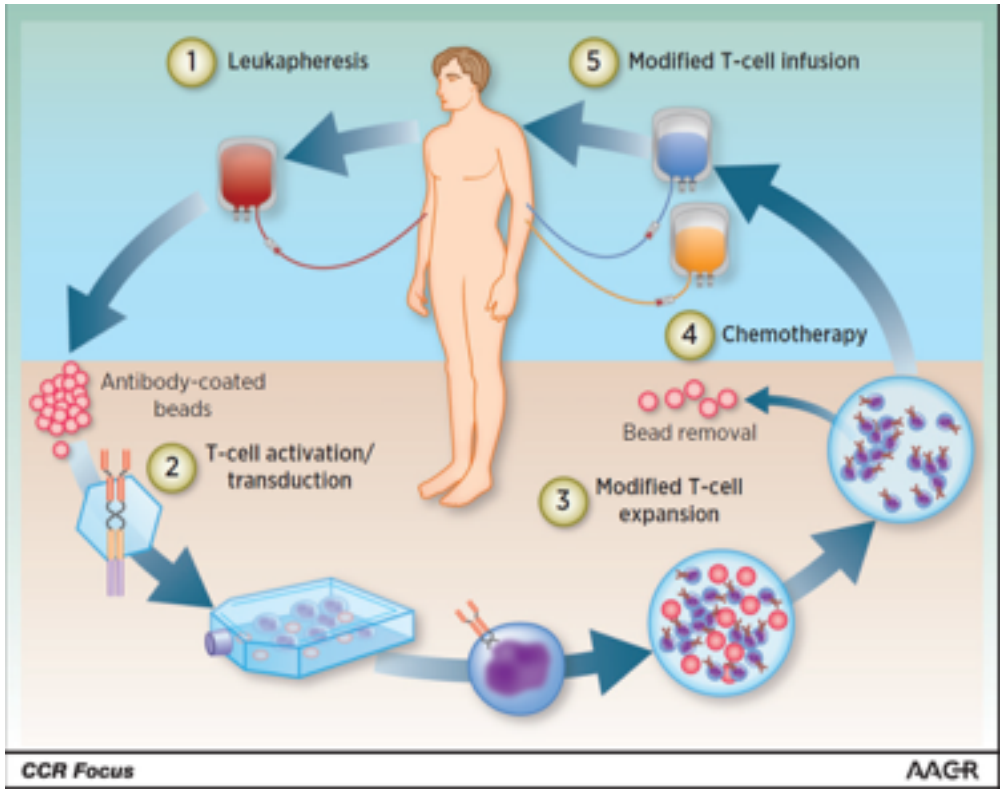


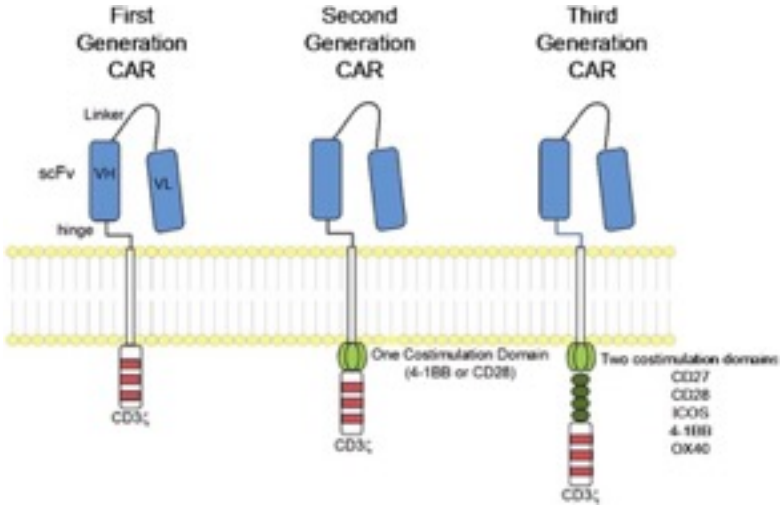
Vanpouille-Box et al. CCR 2017

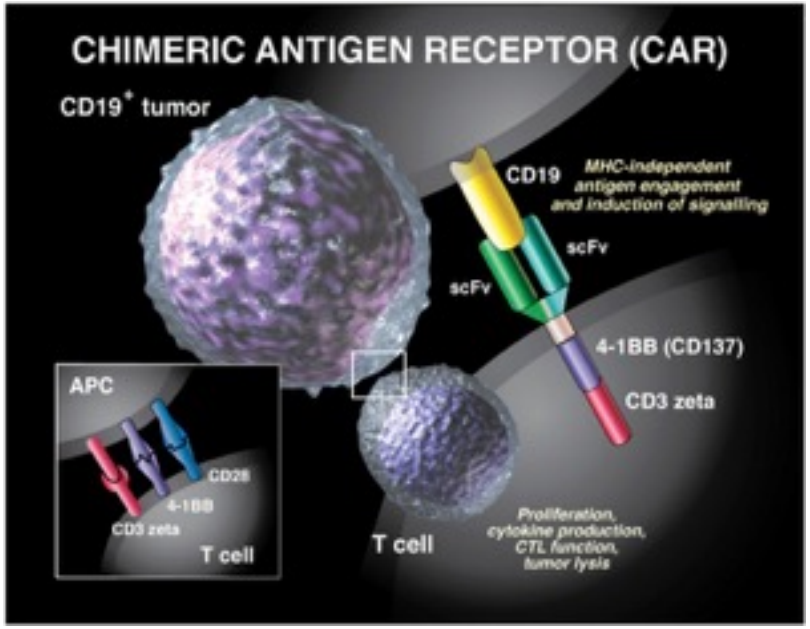
Radiation and Immunotherapy

- RT can augment the immune response through a variety of mechanisms
  - RT can cause inflammatory cell death, priming the immune system to tumor derived antigens, converting tumor into an *in situ* vaccine
  - RT can modulate tumor vasculature and enhance T-cell extravasation, increasing the number of tumor infiltrating lymphocytes
  - RT improves recognition and killing of tumor cells by CD8+ cytotoxic T cells by increasing in a dose dependent manner the number of MHC molecules on tumor cell surface, by upregulating death receptors, and promoting exposure of NK cell-activating ligands

Sahebjam J Neuro-Ocol 2017;134:531
Vanpouille-Box CCR 2017

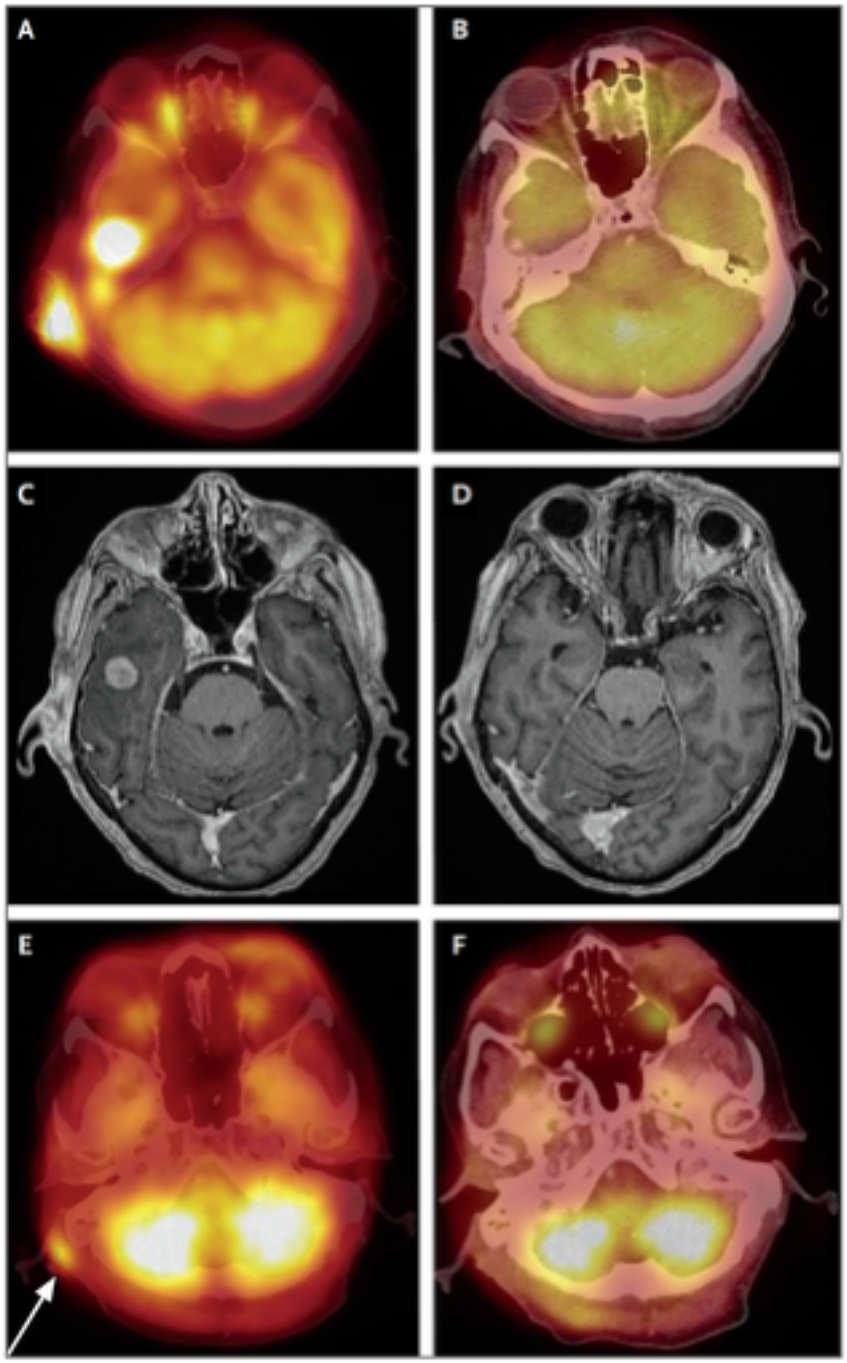






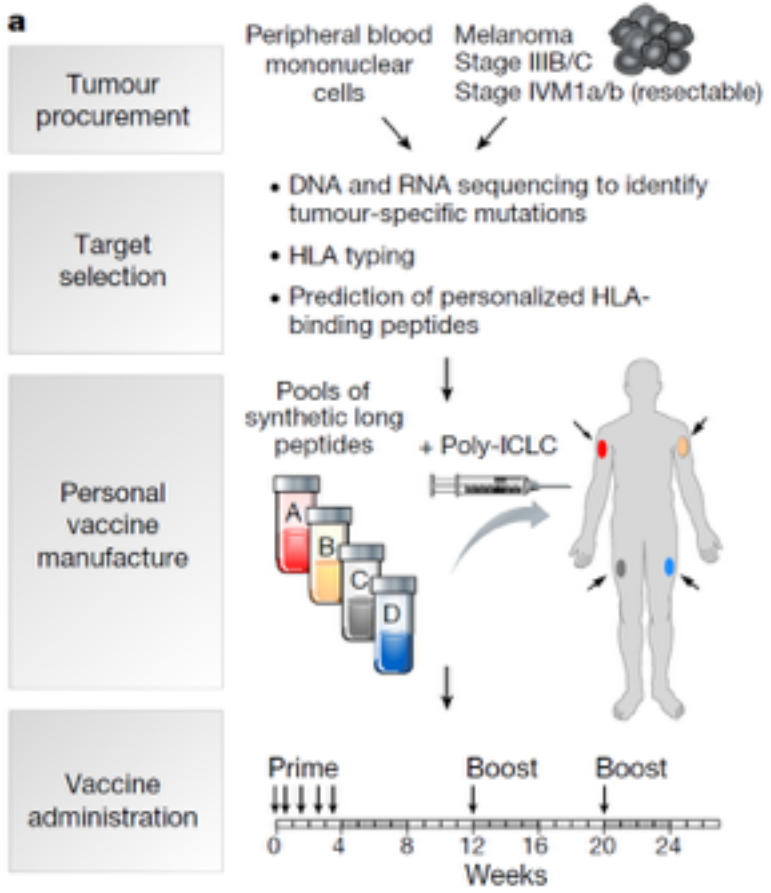
FDA Approved of tisagenlecleucel-T (Kymriah) for leukemia and axicabtagene ciloleucel (Yescarta) for lymphoma in 2017

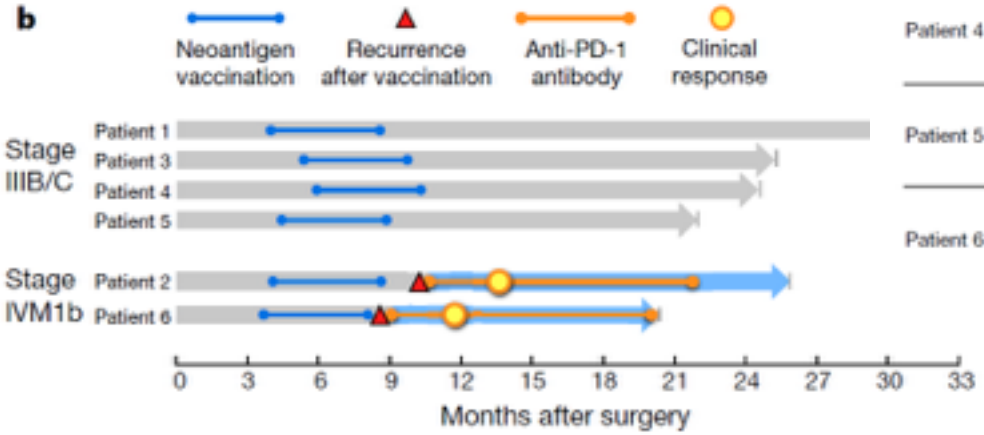
Maude et al. Blood 2015
Maus and June CCR 2016



DLBCL refractory to multiple therapies showing response to CD19 CAR-T-Cell therapy

Abramson et al. NEJM 2017;377;8





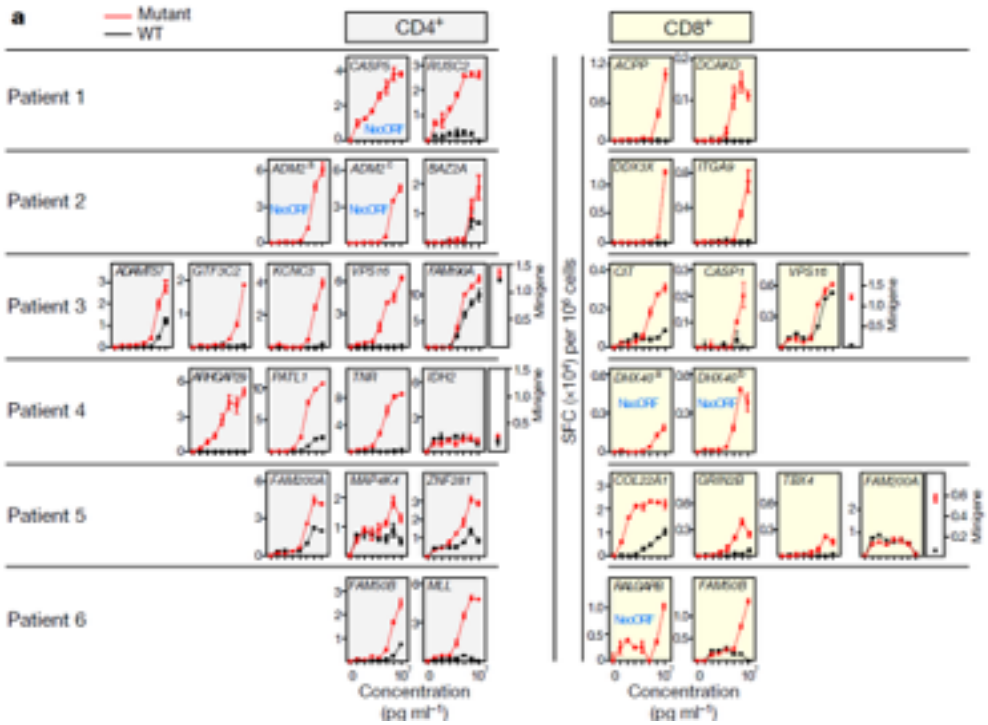
LETTER

2017

doi:10.1038/nature22991

An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3]*, Zhuting Hu[1]*, Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[1], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[1,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[5,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[3,4]†, Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]



LETTER

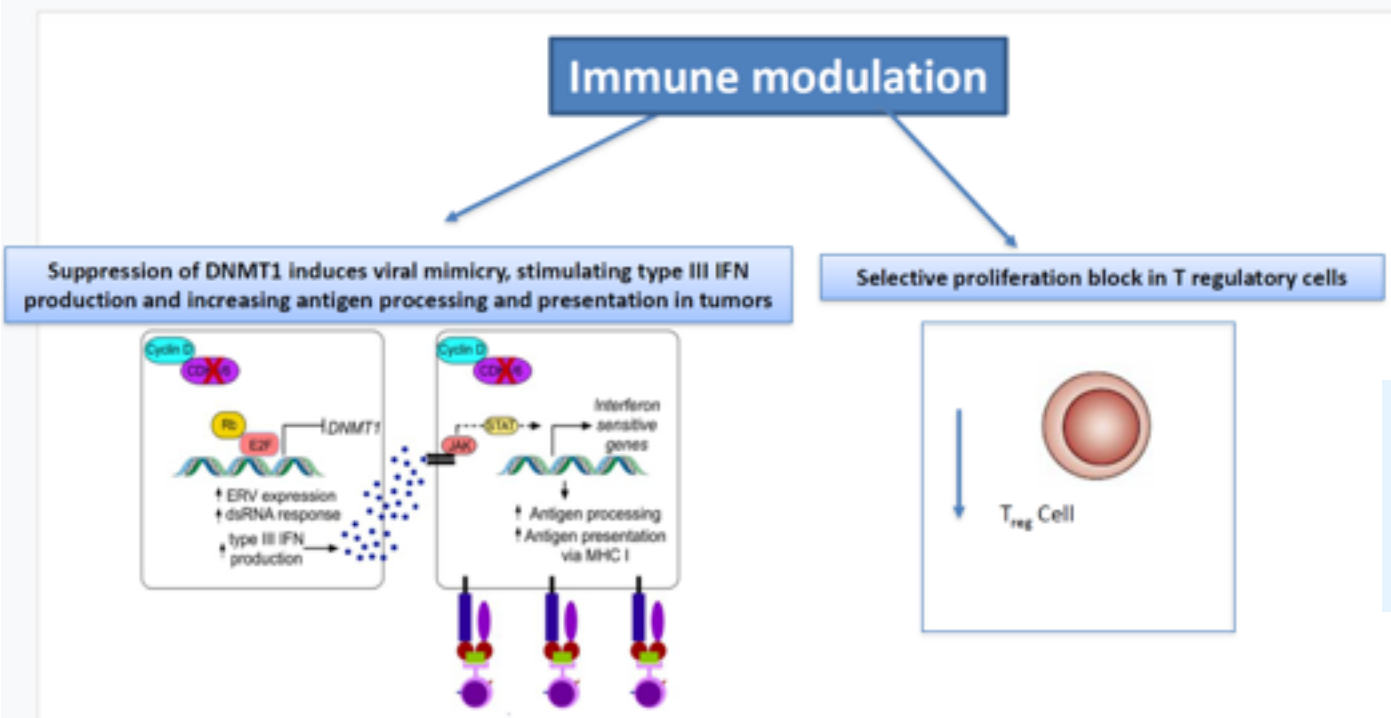
doi:10.1038/nature23465

Nature 2017

CDK4/6 inhibition triggers anti-tumour immunity

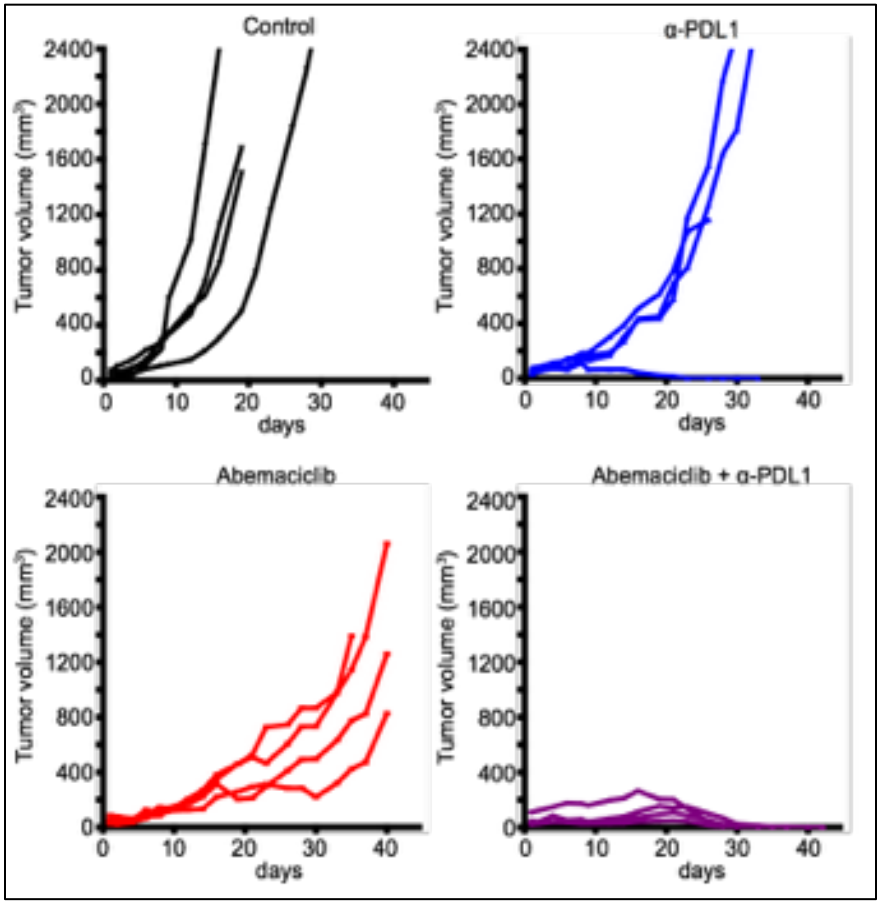
Shom Goel[1,2]*, Molly J. DeCristo[3,4]*, April C. Watt[3], Haley BrinJones[3], Jaclyn Sceneay[3,4], Ben B. Li[1], Naveed Khan[3], Jessalyn M. Ubellacker[3,4], Shaozhen Xie[1], Otto Metzger-Filho[2], Jeremy Hoog[5], Matthew J. Ellis[6], Cynthia X. Ma[5], Susanne Ramm[7,8], Ian E. Krop[2], Eric P. Winer[2], Thomas M. Roberts[1], Hye-Jung Kim[9,10]§, Sandra S. McAllister[3,4,11,12]§ & Jean J. Zhao[1,12,13]§

- CDK4/6 inhibitors stimulates production of type III interferons and hence enhances tumour antigen presentation
- CDK4/6 inhibitors markedly suppress the proliferation of regulatory T cells
- Synergy with PD1 inhibitors



Example of immunotherapy using combination of targeted molecular agent and PD1 antibody

Combination of CDK4/6i and PD1 blockade



CT26 model

Combination of CDK4/6 inhibitor abemaciclib and PD1 antibody produces complete tumor regression

Goel and DeCristo et al, Nature 2017

LETTER

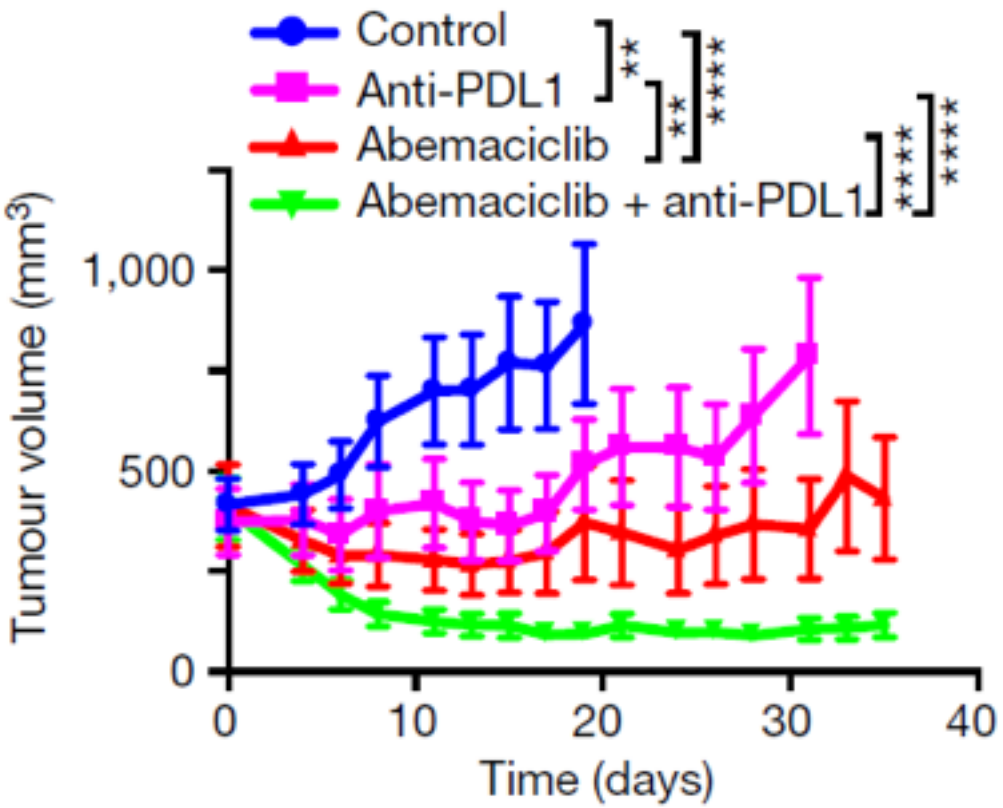
doi:10.1038/nature23465

CDK4/6 inhibition triggers anti-tumour immunity

Shom Goel[1,2*], Molly J. DeCristo[3,4*], April C. Watt[1], Haley BrinJones[1], Jaclyn Sceneay[3,4], Ben B. Li[1], Naveed Khan[1], Jessalyn M. Ubellacker[3,4], Shaozhen Xie[1], Otto Metzger-Filho[2], Jeremy Hoog[5], Matthew J. Ellis[6], Cynthia X. Ma[5], Susanne Ramm[7,8], Ian E. Krop[2], Eric P. Winer[2], Thomas M. Roberts[1], Hye-Jung Kim[9,10]§, Sandra S. McAllister[3,4,11,12]§ & Jean J. Zhao[1,12,13]§

- Synergistic antitumor activity with PD1 blockade for breast cancer brain metastases

Targeting CDK4/6 potentially integrates targeted molecular therapy and immunotherapy



Summary

- Growing evidence of therapeutic benefit of targeted therapies and immunotherapies for brain metastases, especially for melanoma. EGFR mutated NSCLC, and HER2+ breast cancer
- Optimal combinations of targeted agents and immunotherapies, and with RT remained to be defined
- Need for more randomized trials focused on brain metastases



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Thank You!

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Bourbon

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

2016;34:4079-4085

Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With *ALK*-Positive Non–Small-Cell Lung Cancer

Shirish M. Gadgeel, Alice T. Shaw, Ramaswamy Govindan, Leena Gandhi, Mark A. Socinski, D. Ross Camidge, Luigi De Petris, Dong-Wan Kim, Alberto Chiappori, Denis L. Moro-Sibilot, Michael Duruisseaux, Lucio Crino, Tommaso De Pas, Eric Dansin, Antje Tessmer, James Chih-Hsin Yang, Ji-Youn Han, Walter Bordogna, Sophie Golding, Ali Zeaiter, and Sai-Hong Ignatius Ou

Table 2. Pooled Analysis of IRC CORR and CDCR for Patients With CNS Disease at Baseline

Response	Measurable Baseline CNS Disease (n = 50)	Measurable and/or Nonmeasurable Baseline CNS Disease (n = 136)
CNS response rate		
Responders, No.	32	58
CORR, % (95% CI)	64.0 (49.2 to 77.1)	42.6 (34.2 to 51.4)
Best overall response, No. (%)		
Complete response	11 (22.0)	37 (27.2)
Partial response	21 (42.0)	21 (15.4)
Stable disease	13 (26.0)	58 (42.6)
Progressive disease	3 (6.0)	12 (8.8)
Missing or unevaluable	2 (4.0)	8 (5.9)
CDCR		
No.	45	116
% (95% CI)	90.0 (78.2 to 96.7)	85.3 (78.2 to 90.8)
Median CDOR, months (95% CI)	10.8 (7.6 to 14.1)	11.1 (10.3 to NE)
Patients included in analysis, No. (%)	32 (100.0)	58 (100.0)
Patients with event, No. (%)	18 (56.3)	26 (44.8)

NOTE. Responses evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Data cutoff for both NP28673 and NP28761 was April 27, 2015.
Abbreviations: CDCR, CNS disease control rate; CDOR, CNS duration of response; CORR, CNS objective response rate; IRC, independent review committee; NE, not evaluable.

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