II SIMPOSIO INTERNACIONAL DE RADIOCIRUGIA ESTEREOTACTICA

30 de Junio de 2017

Fundación Marie Curie

Terapia biológica para metástasis cerebrales

Dr José Llugdar
Oncología Clinica
Clinica Reina Fabiola

METASTASIS CEREBRALES:

- Complicación Neurológica **mas frecuente e invalidante** en pacientes con cáncer avanzado

- AUMENTO de **Incidencia**:

  > Uso de neuro-imágenes

  Mejoría en control Sistemico extra-craneal del Cancer

- Cáncer más frecuente: **Pulmón, Mama y Melanoma**

OBJETIVOS del TRATAMIENTO:

* Control Sistémico

* Control Cerebral

* Preservar función neurológica

* Preservar Calidad de Vida

LIMITANTE paso BHE: Favorecido SI:

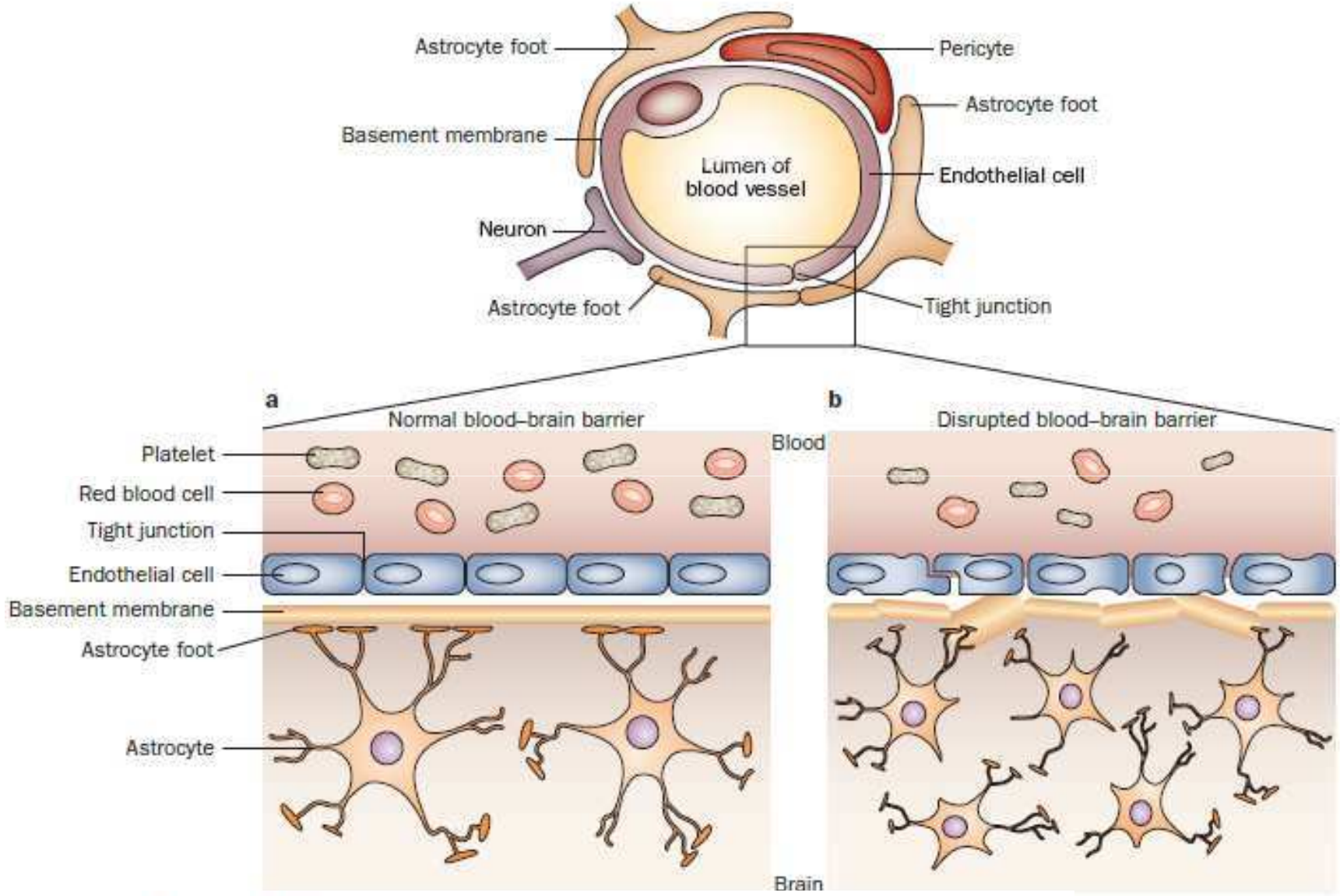
Bajo Peso Molecular

Liposolubles

Baja afinidad a proteínas plasmáticas

+

DISRUPCION BHE → REALCE DEL CONTRASTE



Gerstner, E. R. et al. Nat. Rev. Clin. Oncol. 6, 229–236 (2009); doi:10.1038/nrclinonc.2009.14

Cancer. 1999 Apr 1;85(7):1599-605.

Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study.

Franciosi V[1], Cocconi G, Michiara M, Di Costanzo F, Fosser V, Tonato M, Carlini P, Boni C, Di Sarra S.

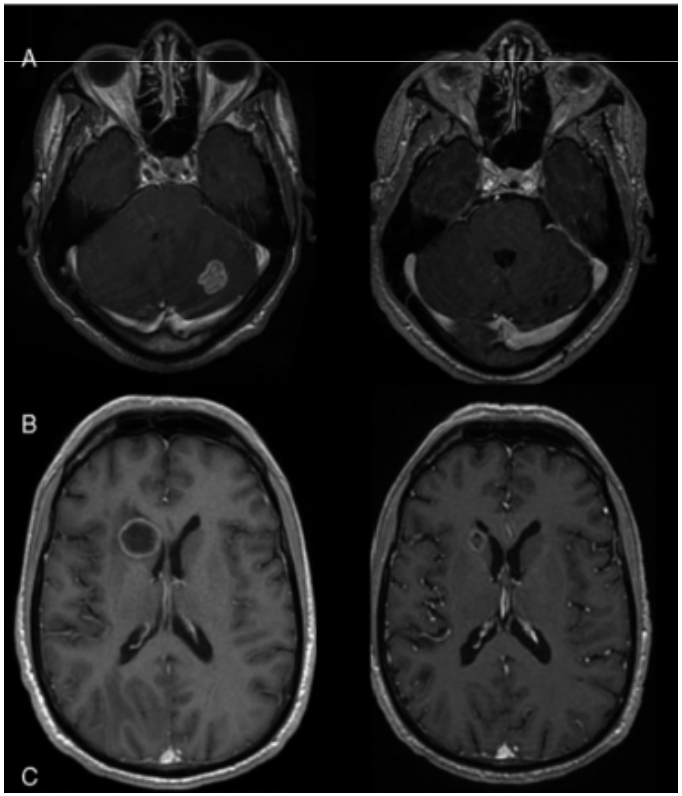
RESULTS: Among the 56 patients with BC, 7 achieved complete response (CR) (13%), 14 achieved partial response (PR), 12 had no change (NC), 15 had progressive disease (PD), and 8 had insufficient treatment or response was not assessed. The CR plus rate was 38%. Among the 43 patients with NSCLC, 3 achieved CR (7%), 10 achieved PR, 15 had SD, 7 had PD, and 8 had insufficient treatment or response was not assessed. The CR plus PR rate was 30%.

Neuro Oncol. 2012 Apr; 14(4): 491–495.
Published online 2012 Feb 22. doi: 10.1093/neuonc/nos004
PMCID: PMC3309855

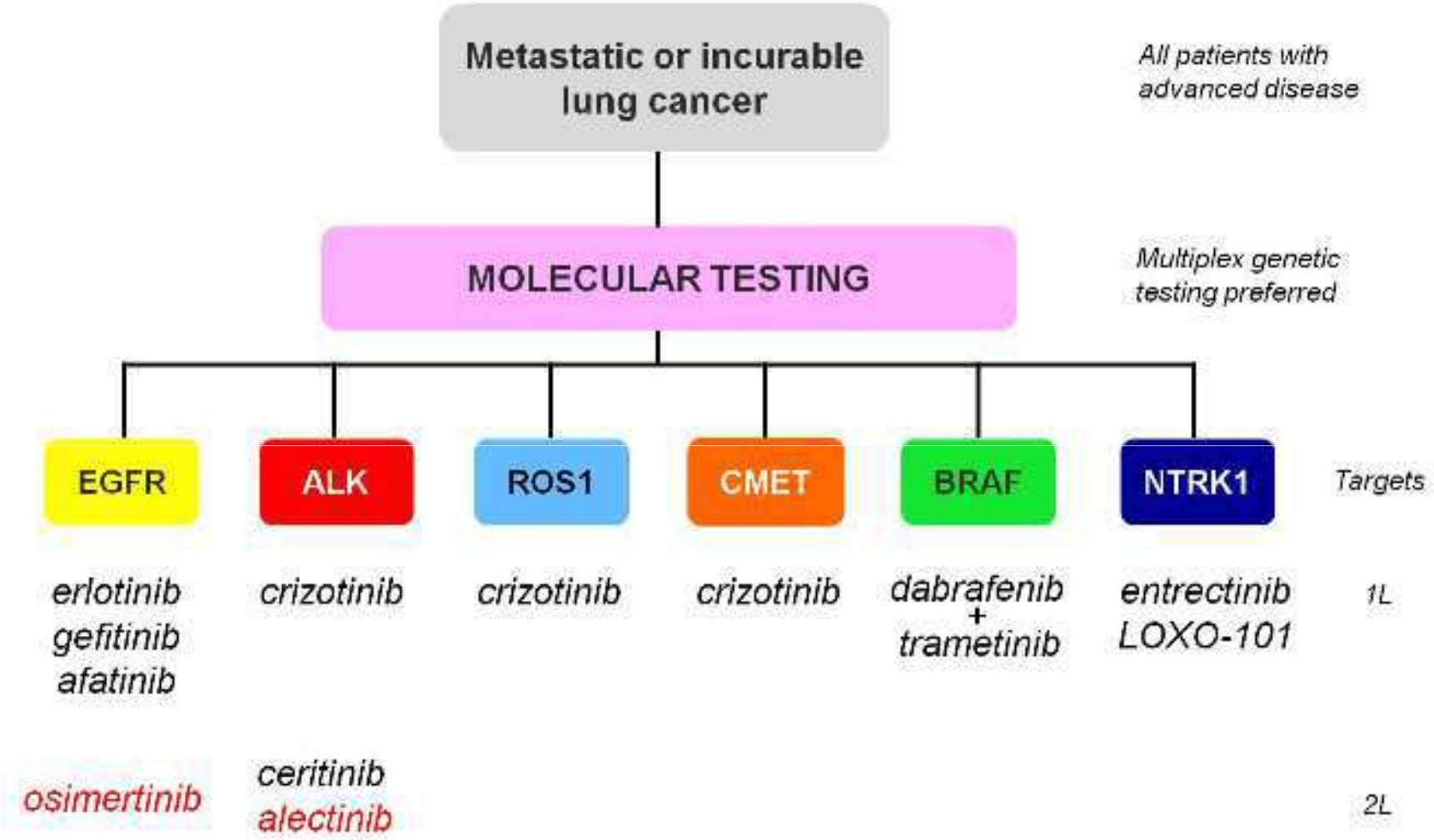
Upfront association of carboplatin plus pemetrexed in patients with brain metastases of lung adenocarcinoma

Olivier Bailon, Kader Chouahnia, Alexandre Augier, Thierry Bouillet, Ségolène Billot, Irène Coman, Rénata Ursu, Catherine Belin, Laurent Zelek, Gaëtan Des Guetz, Christine Levy, Antoine F. Carpentier, and Jean-François Morere

1 cm) had a complete response. The overall cerebral response rate was therefore 40% in the intent-to-treat population. In the 12 responder patients, the median time to best tumor response was 9.8 weeks after onset of chemotherapy. Although the radiologic responses



CANCER DE PULMÓN



Presented By Alice Shaw at 2016 ASCO Annual Meeting

Eficacia de AntiEGFR con/sin WBRT

Table 1. Published Data About Efficacy of EGFR-TKIs Alone or Combined With WBRT in Patients With *EGFR*-Mutated NSCLC With BMs

First Author	Trial Phase	No. of Patients	TKIs	iRR (%)	iPFS (months)	OS (months)
EGFR-TKIs alone						
Wu[2]	II	48	Erlotinib	58.3	10.1	18.9
Iuchi[3]	II	41	Gefitinib	87.8	14.5	21.9
Porta[4]	II	69	Erlotinib	82.4	11.7	12.9
Park[5]	II	23	Gefitinib/erlotinib	83	6.6	15.9
Jiang[6]	Retrospective	230	Gefitinib/erlotinib/icotinib	52.6	7.4	26.4
Gerber[7]	Retrospective	63	Erlotinib	NR	16	26
EGFR-TKIs combined with WBRT						
Zhou[16]	I	15	Icotinib	80	18.9	20.8
Welsh[20]	II	40	Erlotinib	89	12.3	19.1
Jiang[6]	Retrospective	230	Gefitinib/erlotinib/icotinib	52.9	6.9	21.6

Abbreviations: BMs, brain metastases; EGFR, epidermal growth factor receptor; iPFS, intracranial progression-free survival; iRR, intracranial response rate; iPFS, intracranial disease progression-free survival; NR, not reported; NSCLC, non–small-cell lung cancer; OS, overall survival; TKIs, tyrosine kinase inhibitors; WBRT, whole-brain radiotherapy.

DOI: 10.1200/JCO.2016.71.5706; published at jco.org on January 23, 2017.

Se puede demorar RT en pacientes con MTTS cerebrales EGFR Mutados ?

VOLUME 35 · NUMBER 10 · APRIL 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

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

N=351 – 6 centros academicos US – 2008-2014

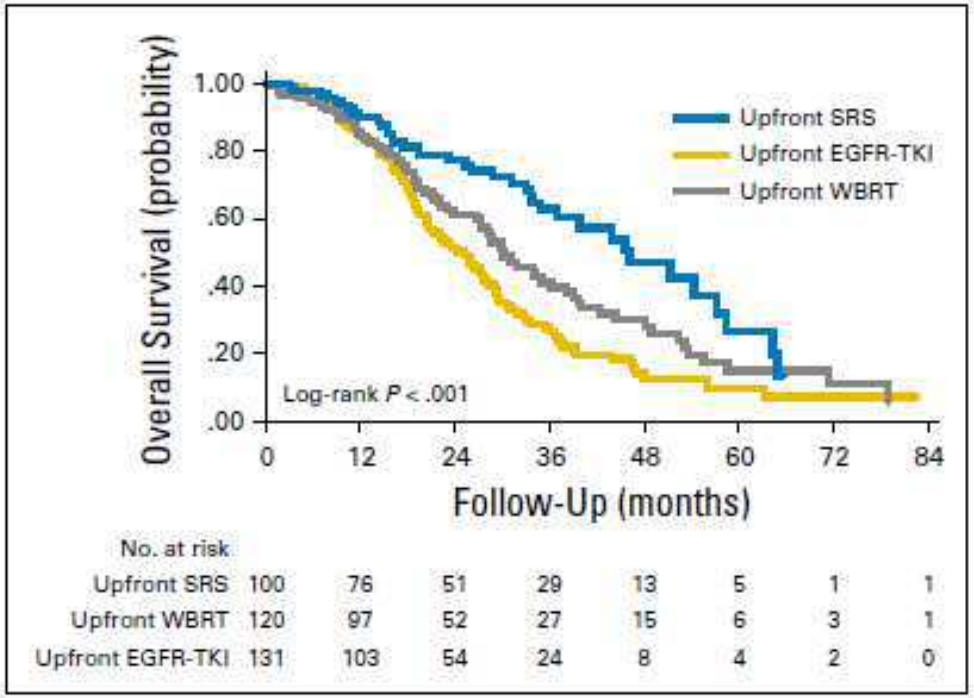
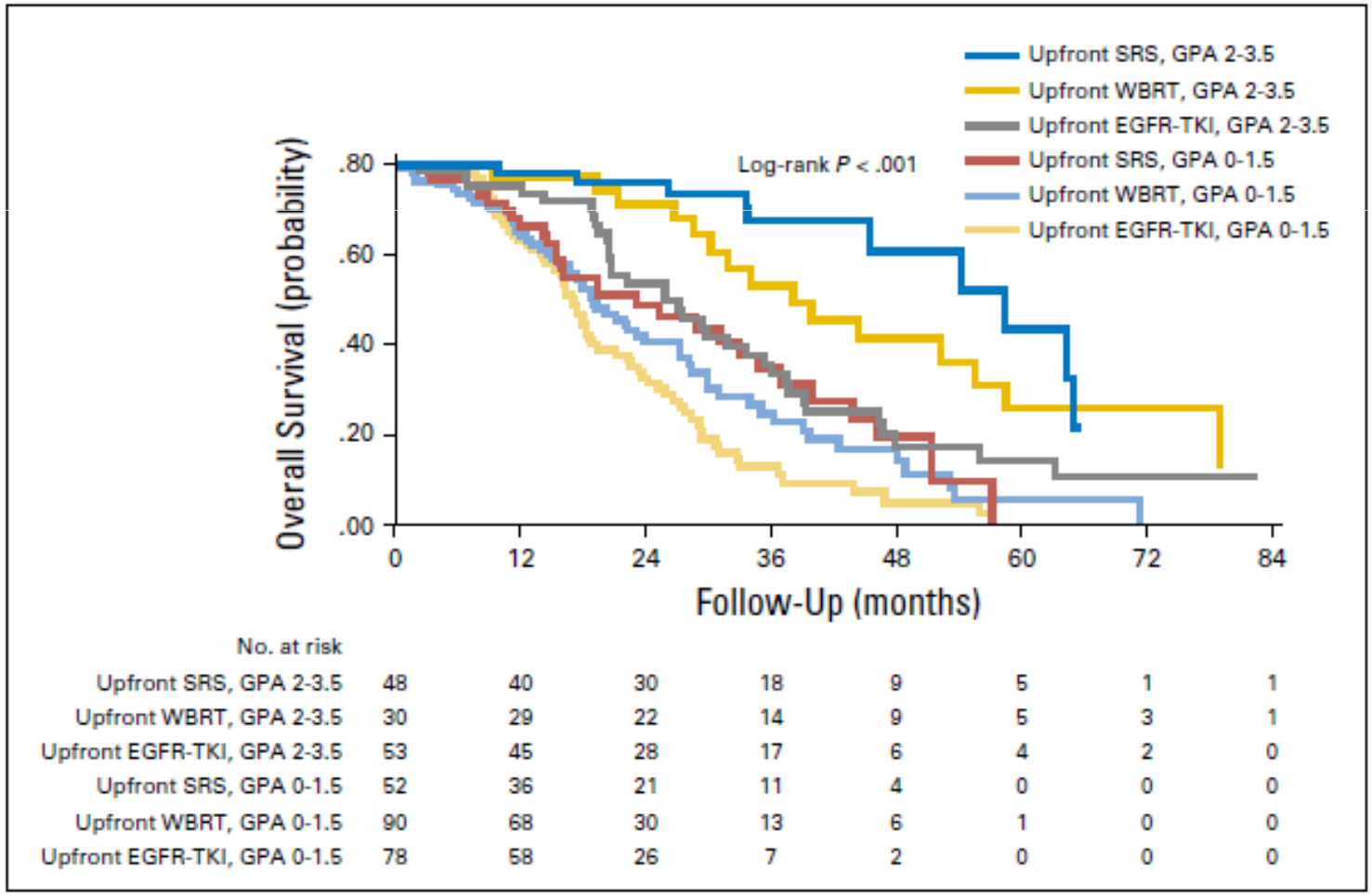
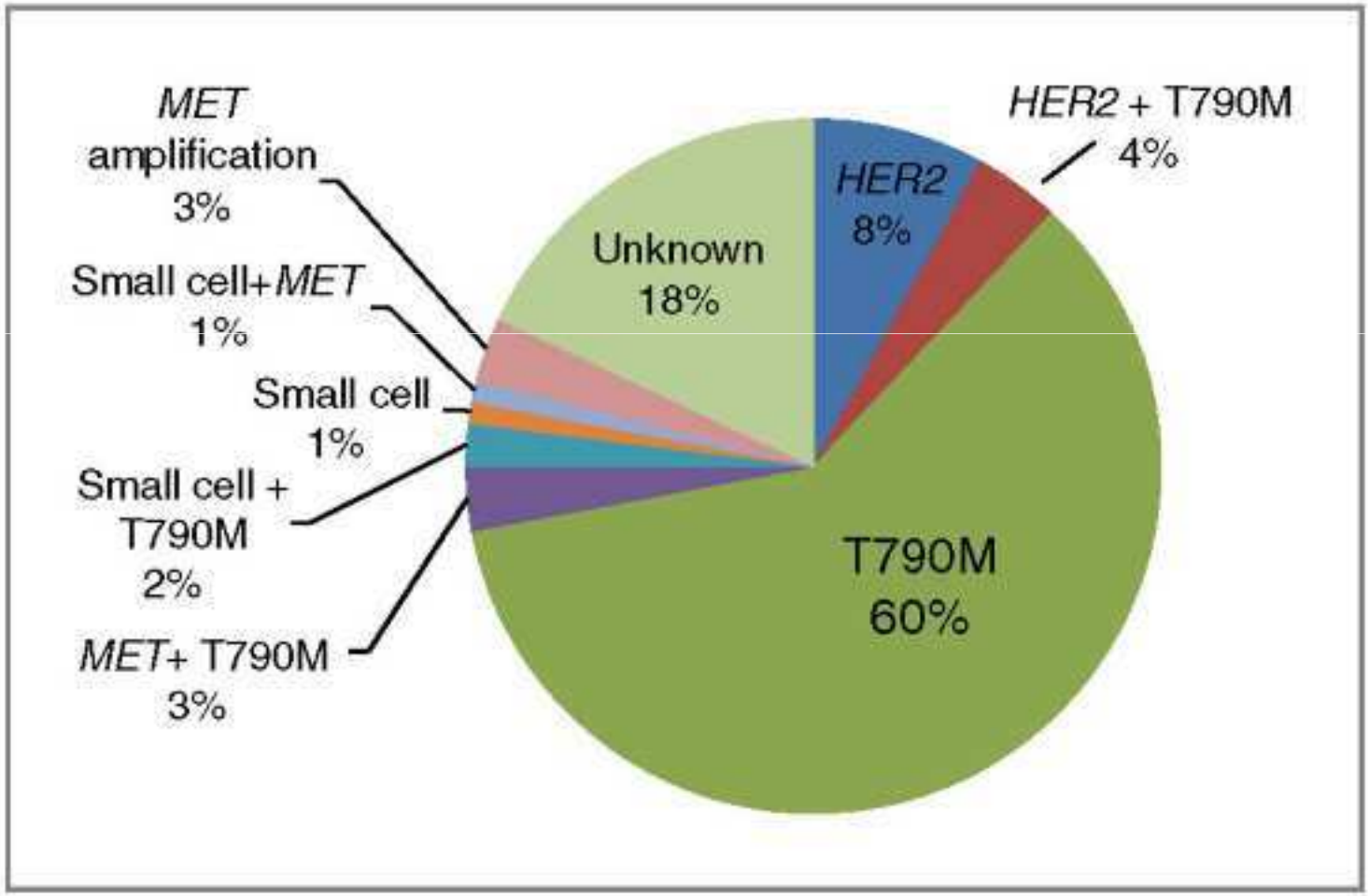


Table 2. Univariable and Multivariable Analyses of Covariables Associated With OS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Upfront WBRT *v* upfront EGFR-TKI	0.72	0.53 to 0.98	.039	0.70	0.50 to 0.98	.039
Upfront SRS *v* upfront EGFR-TKI	0.45	0.31 to 0.66	< .001	0.39	0.26 to 0.58	< .001



Mechanisms of Resistance to 1st Generatio EGFR Inhibitors



Yu H A et al. Clin Cancer Res 19:2240-2247, 2013

CNS response to osimertinib in patients with T790M-positive advanced NSCLC: data from a randomized Phase III trial (AURA3)

Tony Mok[1], Myung-Ju Ahn[2], Ji-Youn Han[3], Jin-Hyoung Kang[4], Nobuyuki Katakami[5], Hye Ryun Kim[6], Rachel Hodge[7], Dana Ghiorghiu[7], Mireille Cantarini[8*], Yi-Long Wu[9], Vassiliki A Papadimitrakopoulou[10], Marina Chiara Garassino[11]

PRESENTED AT: ASCO ANNUAL MEETING '17

AURA3 subset analysis

Key eligibility criteria:

- Locally advanced or metastatic NSCLC
- Disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumor EGFR T790M mutation after first-line EGFR-TKI
- No more than 1 prior line of treatment for advanced NSCLC
- **Stable* asymptomatic CNS metastases allowed**

R 2:1

Osimertinib 80 mg orally once daily **n=279**

Platinum-pemetrexed n=140

N = 419

CNS full analysis set (cFAS) Pts with measurable and/or non-measurable CNS metastases†

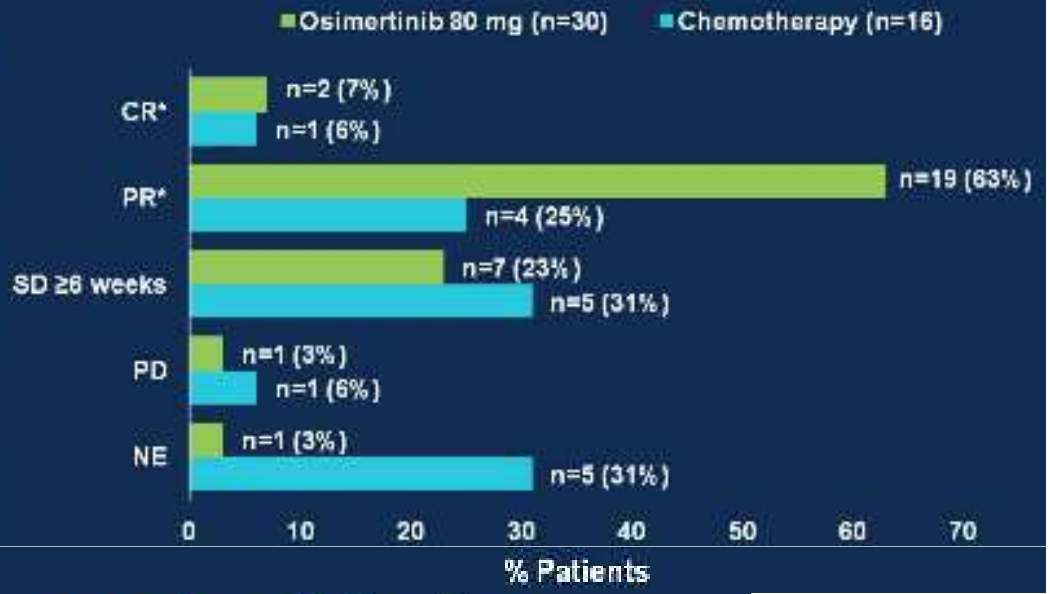
CNS metastases n=75 (27%)

CNS metastases n=41 (29%)

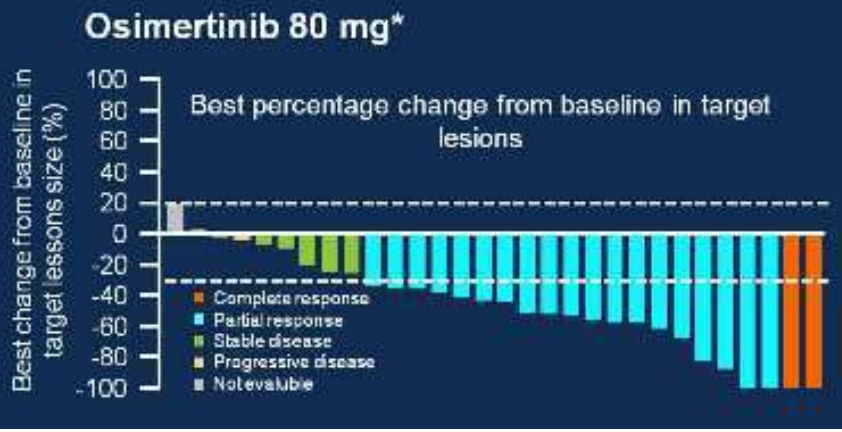
Total 28%

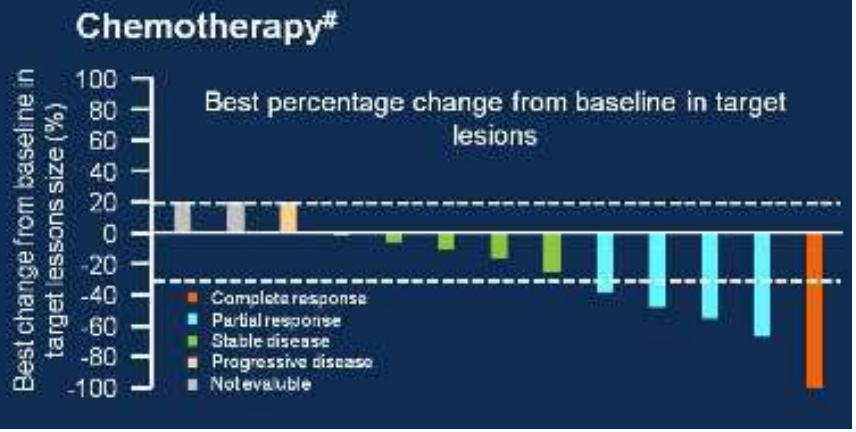
CNS overall response – evaluable for response set

	Osimertinib 80 mg n=30	Chemotherapy n=16
CNS ORR (95% CI)	70% (51, 85)	31% (11, 59)
Odds ratio (95% CI)	5.13 (1.44, 20.64); p=0.015	
Median time to response, weeks	6.1	6.1
Median DoR, months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)

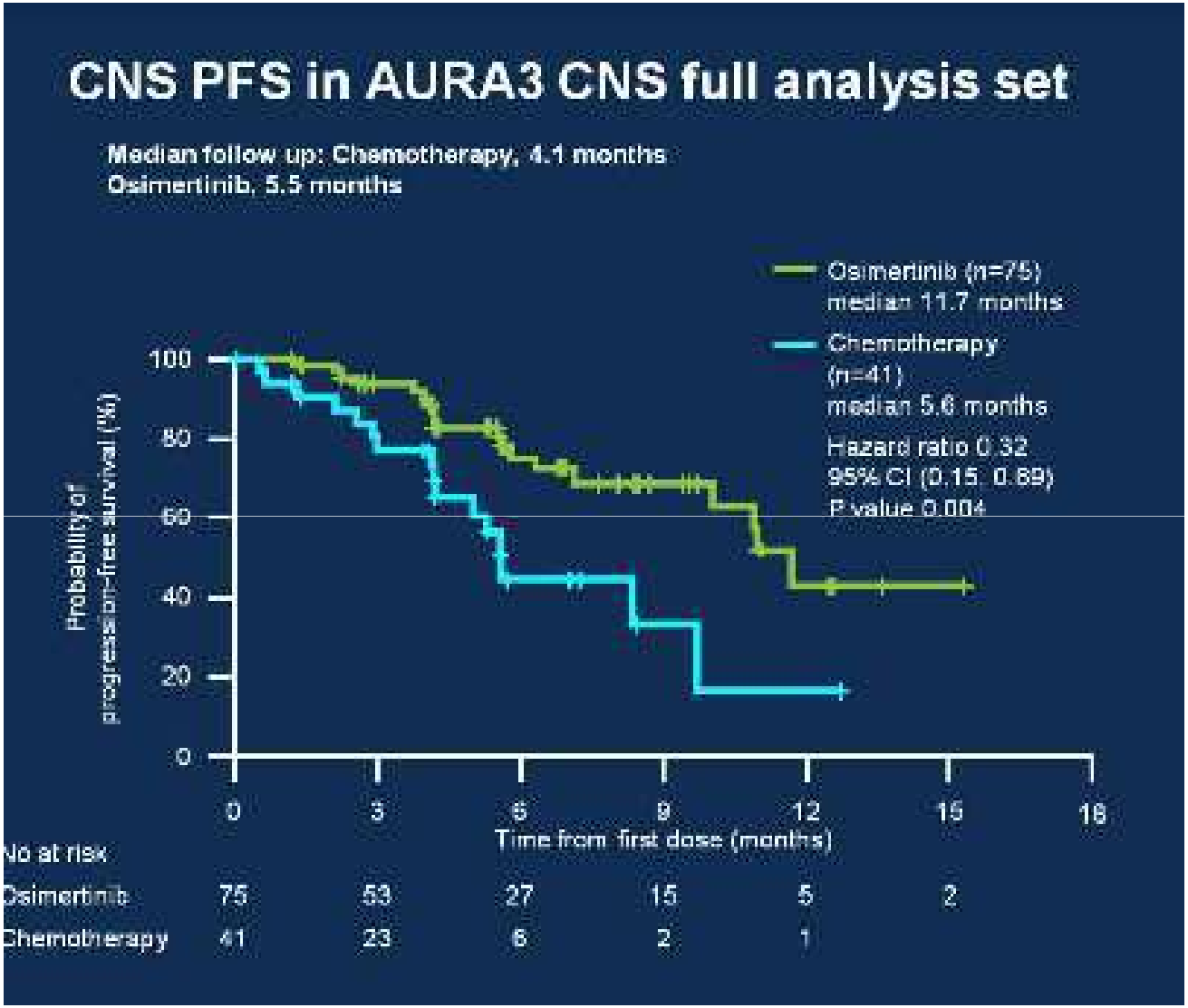


Tumor response in CNS – evaluable for response set





CNS PFS in AURA3 CNS full analysis set



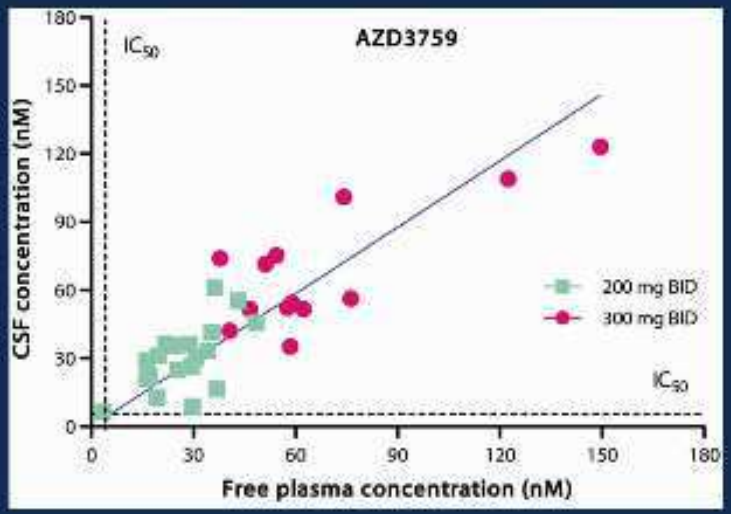
Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in TKI naïve EGFRm NSCLC patients with CNS metastases

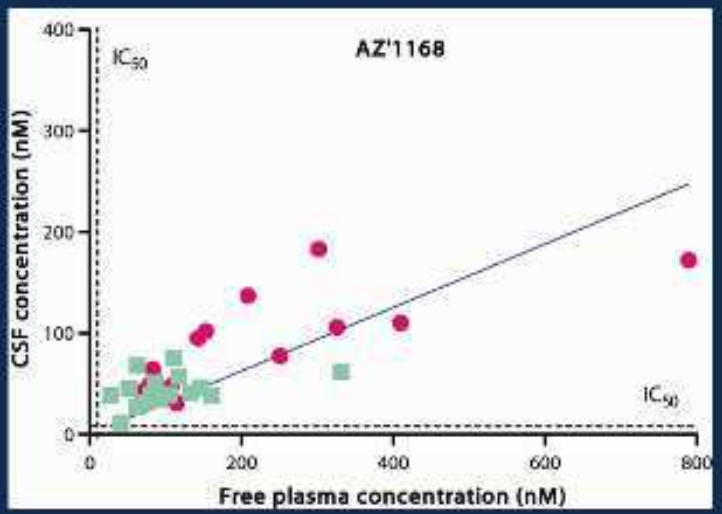
#ASCO17

Myung-Ju AHN[1], Dong-Wan KIM[2], Byoung Chul CHO[3], Sang-We KIM[4], Jong Seok LEE[5], Jin-Seok AHN[1], Tae Min KIM[2], Chia-Chi LIN[6], Hye Ryun KIM[3], Tom JOHN[7], Steven KAO[8], Jonathan W. GOLDMAN[9], Wu-Chou SU[10], Ronald NATALE[11], Philip OVEREND[12], Zhenfan YANG[13], James Chih-Hsin YANG[6]

Both AZD3759 and metabolite (AZ'1168)* effectively cross BBB

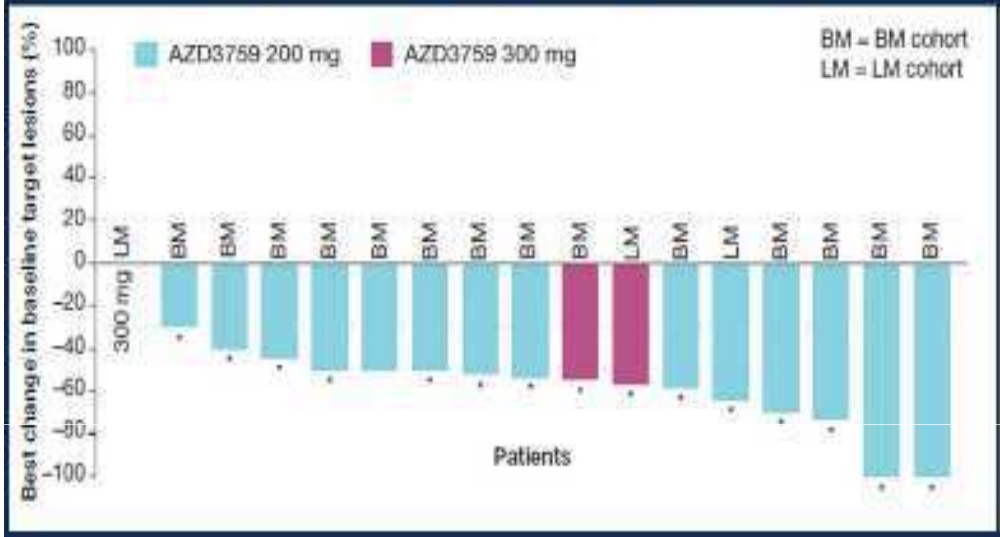
- Excellent CSF penetration of AZD3759 at a ratio of 1:1 to plasma and 0.5:1 for AZ'1168
- At both 200 and 300 mg BID, trough concentrations of both AZD3759 and AZ'1168 in CSF ≥ IC50 (PC-9 cell line)



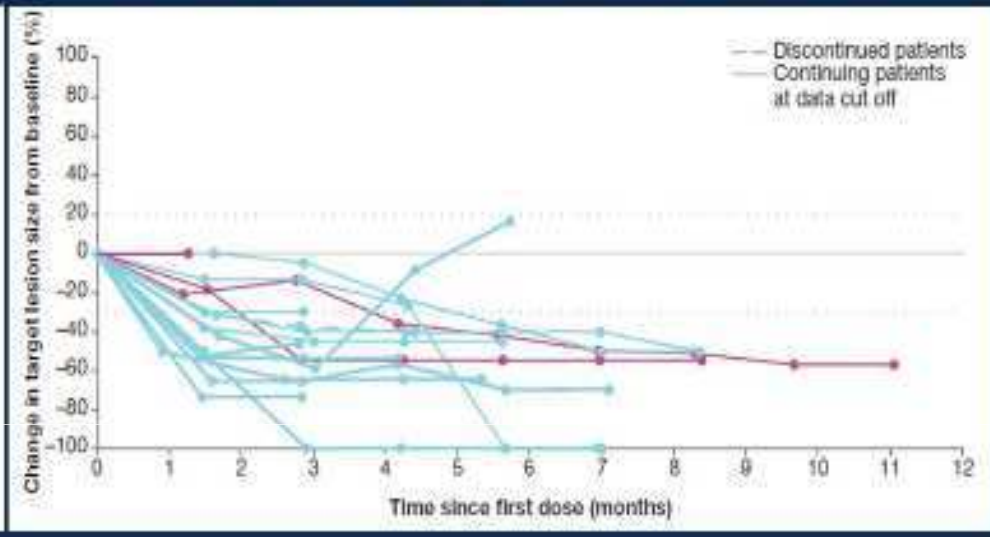


Promising intracranial anti-tumor efficacy

Best % change of BM target lesions



% change of BM target lesion size with time



Patients with BM target lesions at baseline and at least one mRECIST assessment were included. *: confirmed response

Investigator Assessed

- 15 out of 18 (83%) patients with measurable BM lesions at baseline had confirmed objective response, 14 PRs and 1 CR.
- Median best % change of intracranial target lesions was -54% (ranging -100% to 0)
- 16 patients were still on AZD3759 treatment at data cut-off on December 12th, 2016.

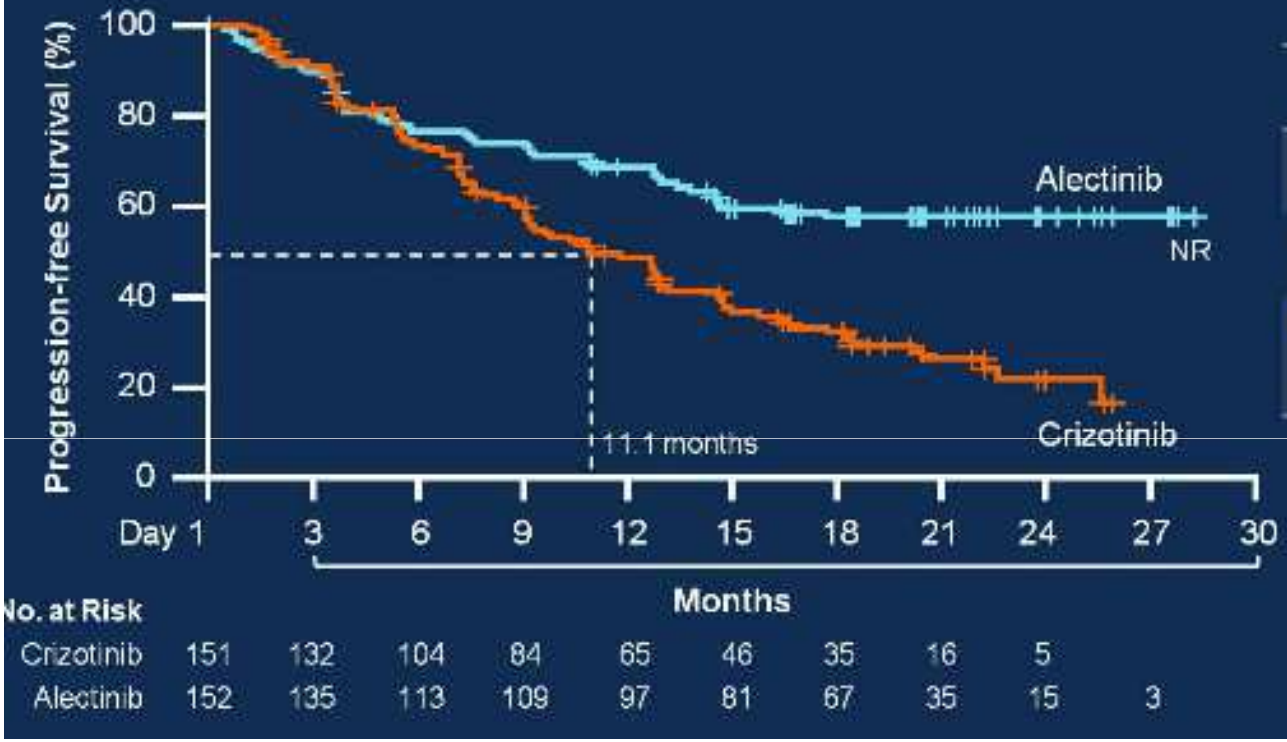
Alectinib vs crizotinib in treatment-naïve advanced *ALK*+ NSCLC: primary results of the global phase III ALEX study (LBA9008)

Alice Shaw[1], Solange Peters[2], Tony Mok[3], Shirish M. Gadgeel[4], Jin Seok Ahn[5], Sai-Hong Ignatius Ou[6], Maurice Perol[7], Rafal Dziadziuszko[8], Dong-Wan Kim[9], Rafael Rosell[10], Ali Zeaiter[11], Ting Liu[11], Sophie Golding[11], Bogdana Balas[11], Johannes Noe[11], Peter N. Morcos[12], and D. Ross Camidge[13] on behalf of the ALEX investigators

#ASCO17

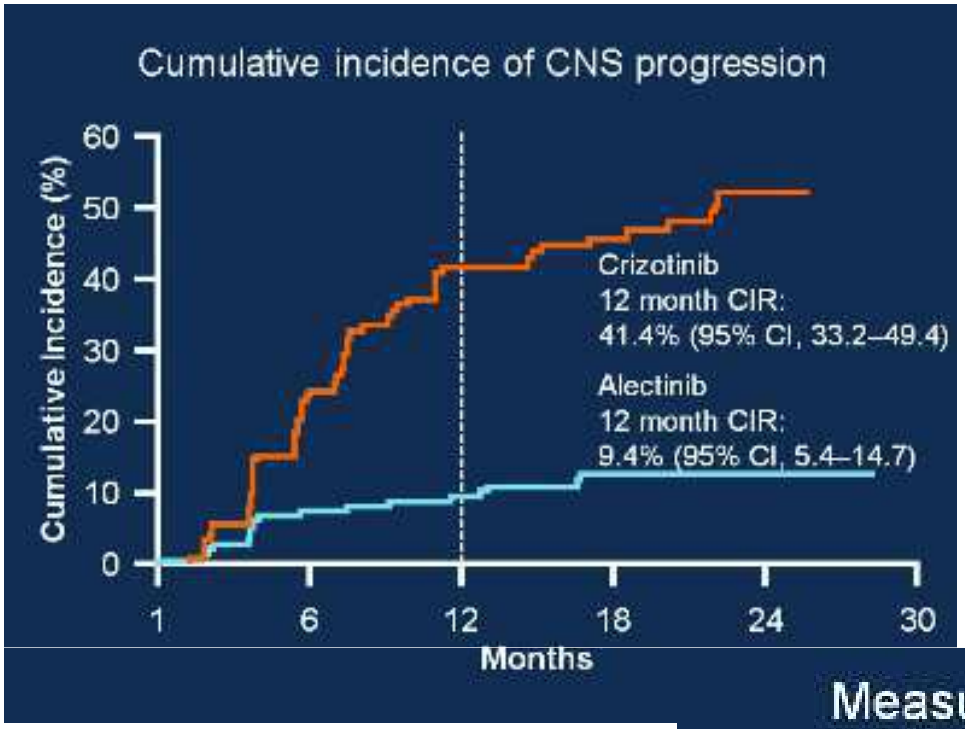
- The current standard of care for patients with newly diagnosed, advanced *ALK*+ NSCLC is the first generation ALK inhibitor crizotinib[3]
  - Objective response rate (ORR) 74%, median progression-free survival (PFS) 10.9 months (PROFILE 1014)
- Patients often experience disease progression on crizotinib within the first year of treatment; the central nervous system (CNS) is a common site of relapse[4,5]

Primary endpoint: PFS, investigator-assessed



No. at Risk										
Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	102 (68)	62 (41)
Median PFS, months (95% CI)	**11.1** (9.1–13.1)	**NR** (17.7–NR)
HR (95% CI)	**0.47** (0.34–0.65)	
P-value (log-rank test)	P<0.0001	



Measurable CNS lesions at baseline

	Crizotinib (N=22)	Alectinib (N=21)
CNS responders, n (%)	11 (50)	17 (81)
(95% CI)	(28–72)	(58–95)
CNS complete response, n (%)	1 (5)	8 (38)
Median DOR in the CNS, months	5.5	17.3
(95% CI)	(2.1–17.3)	(14.8–NR)

CANCER DE MAMA

- 10 - 30 % p MTTS Cerebrales

- Her2: Tropismo por SNC

-Terapias Anti Her2:

Trastuzumab, Pertuzumab, TDM1, Lapatinib, Neratinib

Overexpression or amplification of HER2/neu is associated with high risk of brain metastasis

Study		Incidence
Bendell et al	Cancer 2003	34%
Weitzen et al	ASCO 2002	29%
Heinrich et al	ASCO 2003	43%
Clayton et al	Br J Cancer 2004	39%
Altaha et al	ASCO 2004	33%
Stemmler et al	SABCS 2004	31%

Presented By Michelle Melisko at 2015 ASCO Annual Meeting

Survival after CNS diagnosis by subtype

Study	HER2+*	TN
Bendell et al, 2003	13 mo	
Gori et al, 2007	23 mo	
Eichler et al, 2008	17.1 mo	4.0 mo
Nam et al, 2008		3.4 mo
Park et al, 2009	14.9 mo	
Dawood et al, 2008	11.6 mo	
Lin et al, 2008		4.9 mo
Melisko et al, 2008	23.1 mo	
Hines et al, 2008		7 mo
Niwinska et al, 2009	10-13 mo	3-4 mo
Anders et al, 2011	13-14 mo	3 mo

*trastuzumab-treated pts

Presented By Michelle Melisko at 2015 ASCO Annual Meeting

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

www.thelancet.com/oncology Vol 14 January 2013

	Patients (n=44)
≥80% reduction	9 (20%)
50–<80% reduction	20 (45%)
20–<50% reduction	6 (14%)
0–<20% reduction	2 (5%)
Progression*	7 (16%)

*Two patients had progression outside of the CNS.

Table 3: Objective CNS response in assessable patients

Clin Exp Metastasis
DOI 10.1007/s10585-015-9740-3

RESEARCH PAPER

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

Rupert Bartsch[1,2] · Anna S. Berghoff[1,2] · Ursula Vogl[3] · Margaretha Rudas[1,4] · Elisabeth Bergen[1,2] · Peter Dubsky[1,5] · Karin Dieckmann[1,6] · Katja Pinker[1,7] · Zsuzsanna Bago-Horvath[1,4] · Arik Galid[8] · Leopold Oehler[3] · Christoph C. Zielinski[1,2] · Michael Gnant[1,5] · Guenther G. Steger[1,2] · Matthias Preusser[1,2]

Activity of T-DM1

	N = 10	
	N	%
Best intracranial response		
CR	0	0.0
PR	3	30.0
SD	4	40.0
PD	3	30.0
Cranial Clinical Benefit Rate (CBR)	5	50.0
Best extracranial response		
PR	4	40.0
SD	4	40.0
PD	0	0.0
Not available	1	10.0

Phase II trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer Brain Metastases

[1]Dana-Farber Cancer Institute, [2]University of California at San Francisco, [3]University of North Carolina, [4]Massachusetts General Hospital, [5]Duke University, [6]Johns Hopkins University, [7]Houston Methodist Hospital [8]University of Michigan, [9]University of Pittsburgh, [10]Mayo Clinic, [11]Baylor College of Medicine, [12]Beth Israel Deaconess Medical Center

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: Rachel A Freedman, MD, MPH

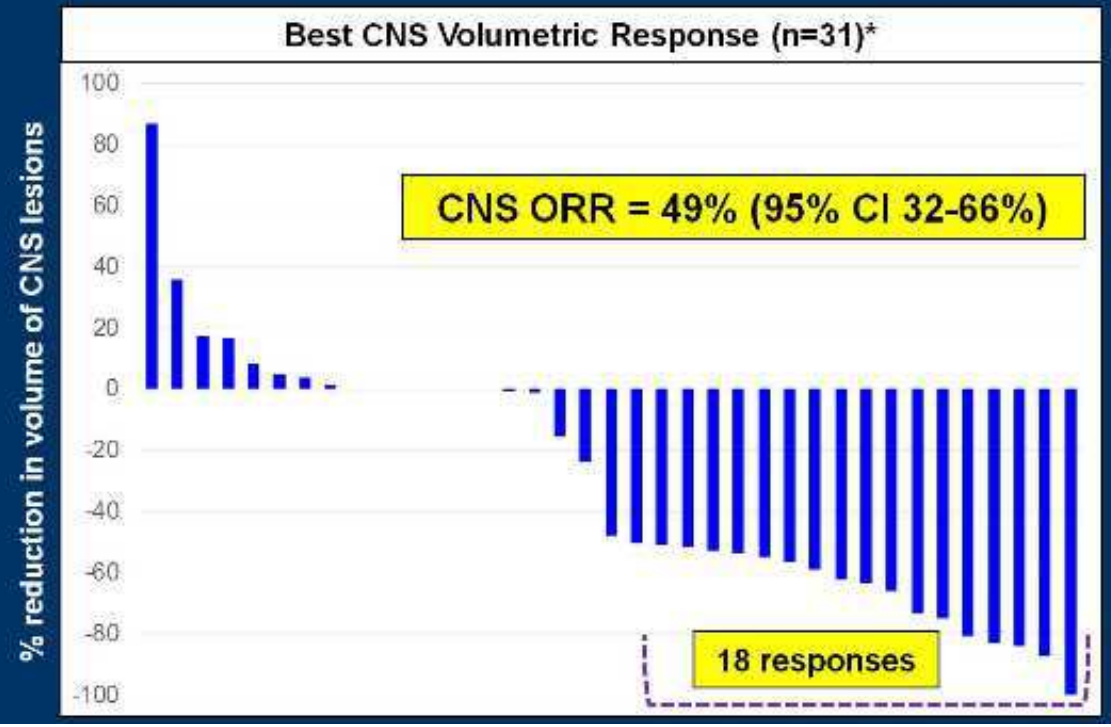
Neratinib

- Potent, oral, irreversible-binding inhibitor of the erbB family of receptor tyrosine kinases
  - Inhibits signal transduction through EGFR, HER2, HER4

Inclusion Criteria

- HER2+ metastatic breast cancer[1]
- CNS progression (new or previously treated site) after ≥1 line of local CNS therapy
- Measurable disease: ≥ 1 CNS lesion ≥ 10 mm
- ECOG PS 0-2
- Adequate end-organ function
- Normal ejection fraction

Primary Endpoint – CNS Volumetric Response



NALA Trial

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting (NALA)

This study is currently recruiting participants.

See Contacts and Locations

ClinicalTrials.gov Identifier:
NCT01808573

MELANOMA

- Hasta 40% desarrollan MTTS Cerebrales

TERAPIAS DISPONIBLES:

-Ac Anti PD1: Nivolumab y Pembrolizumab

-Ac Anti CTLA4: Ipilimumab

-BRAFi: Vemurafenib y Dabrafenib

-MEKi: Trametinib y Cobimetinib

COMBI-MB

A Phase 2 Study of Combination Dabrafenib and Trametinib in Patients With *BRAF* V600–Mutant Melanoma Brain Metastases

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

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Cohort A (n = 76)
- Asymptomatic
- Without prior local therapy
- ECOG PS 0-1

Cohort B (n = 16)
- Asymptomatic
- With prior local therapy
- ECOG PS 0-1

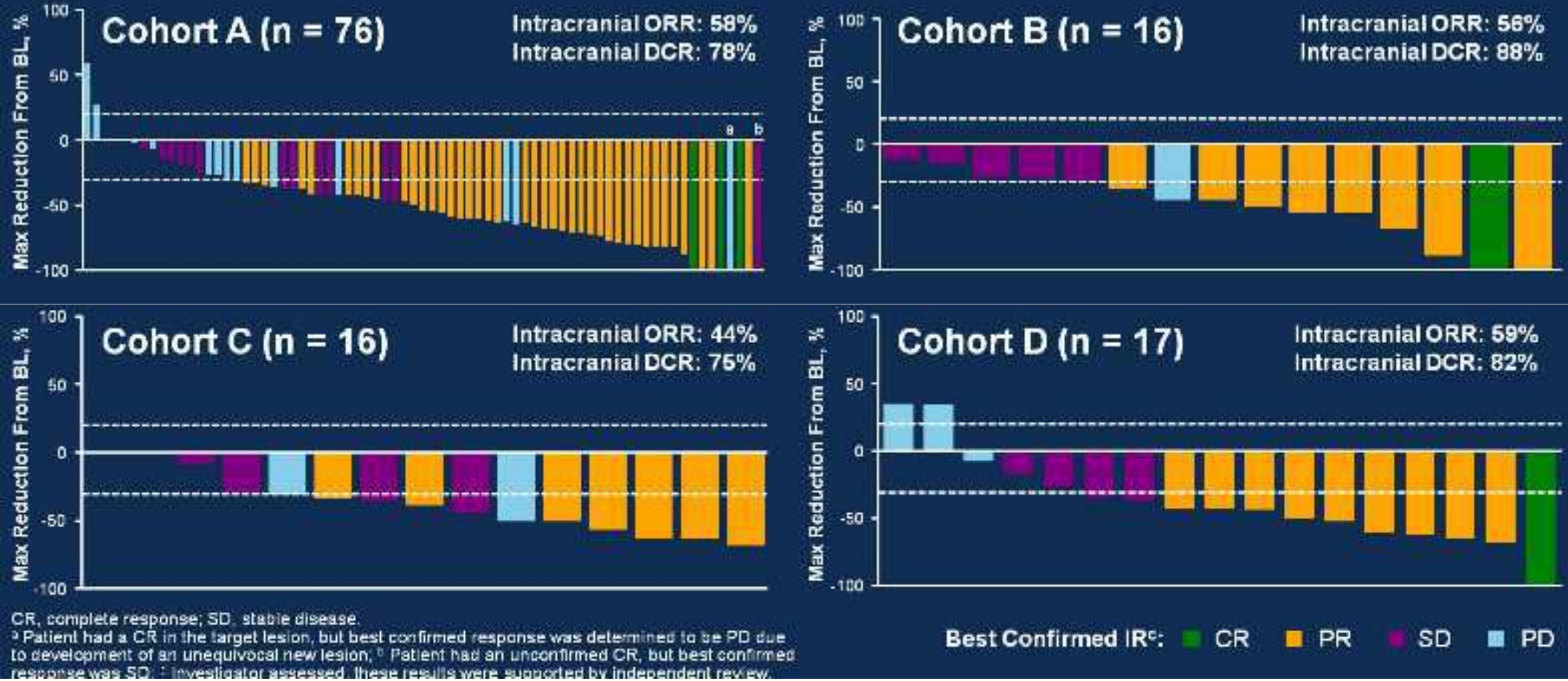
Cohort C (n = 16)
- Asymptomatic
- With or without prior local therapy
- ECOG PS 0-1

Cohort D (n = 17)
- Symptomatic
- With or without prior local therapy
- ECOG PS 0-2

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

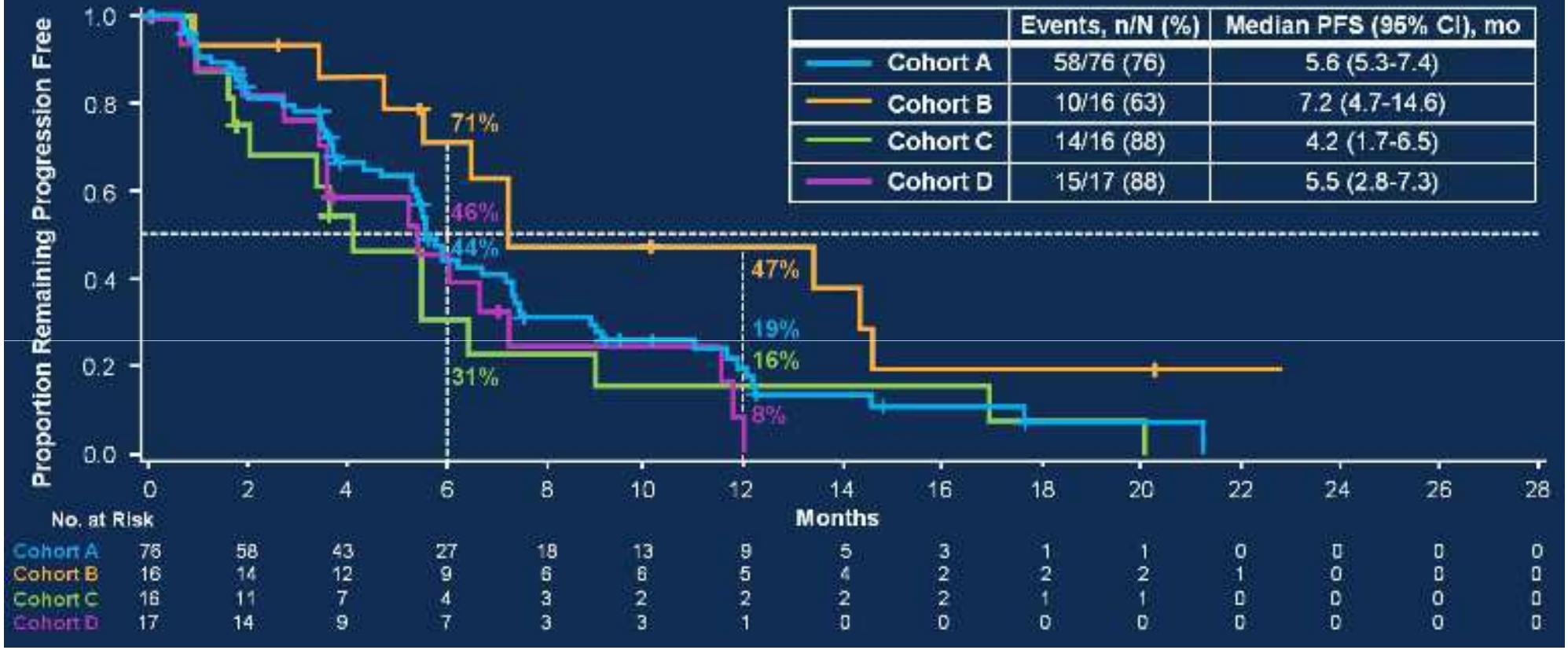
www.thelancet.com/oncology Vol 18 July 2017

Intracranial Response



CR, complete response; SD, stable disease.
[a] Patient had a CR in the target lesion, but best confirmed response was determined to be PD due to development of an unequivocal new lesion; [b] Patient had an unconfirmed CR, but best confirmed response was SD. [c] Investigator assessed. These results were supported by independent review.

Progression-Free Survival



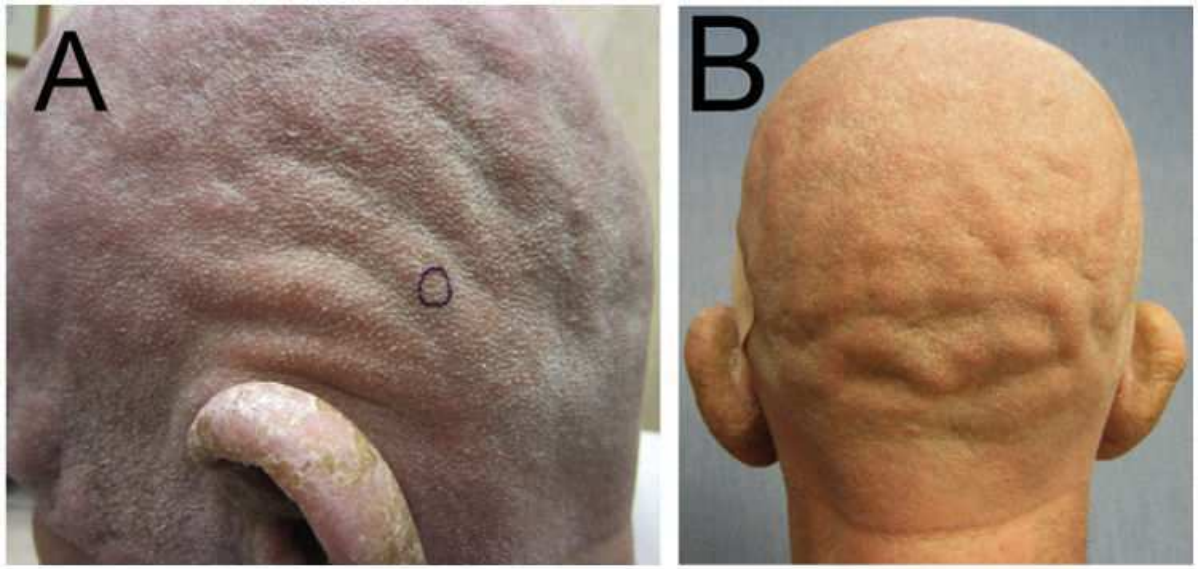
	Events, n/N (%)	Median PFS (95% CI), mo
Cohort A	58/76 (76)	5.6 (5.3-7.4)
Cohort B	10/16 (63)	7.2 (4.7-14.6)
Cohort C	14/16 (88)	4.2 (1.7-6.5)
Cohort D	15/17 (88)	5.5 (2.8-7.3)

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2016 June 1; 95(2): 632–646. doi:10.1016/j.ijrobp.2016.01.038.

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)

BRAFi and MEKi recommendations (eg, vemurafenib/dabrafenib and trametinib/cobimetinib)

- Hold ≥3 days before and after fractionated RT.
- Hold ≥1 day before and after SRS.



cutis verticis gyrata

✓ Tasas de Radionecrosis y Hemorragia con BRAFi + SRS/WBRT concurrente o secuencial parecen no aumentar

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

Lancet Oncol 2016; 17: 976–83

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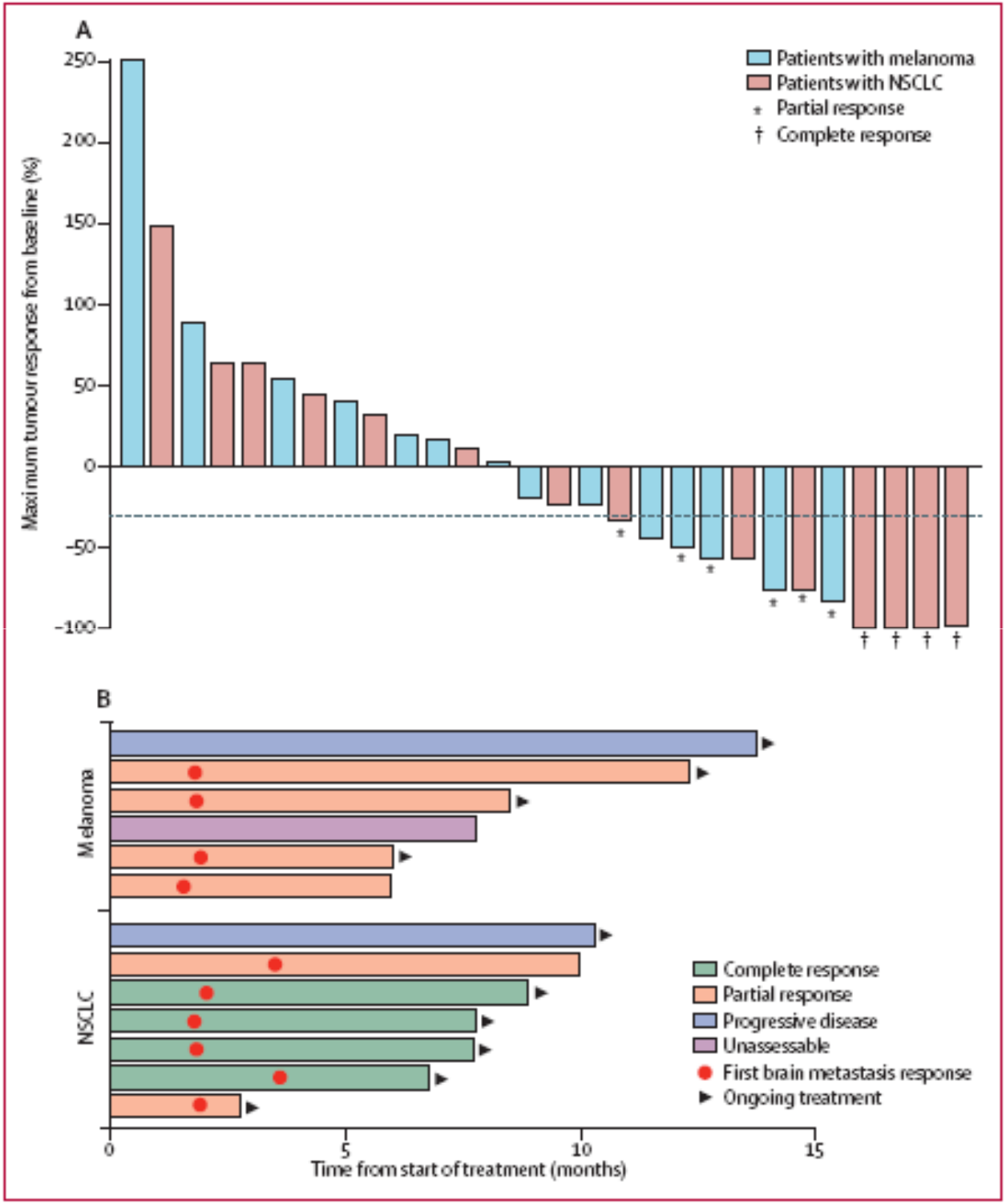
N = 18 Melanoma + 18 CPNCP

TR: 22% Melanoma y 33% CPNCP

	Melanoma	CPNCP
Previous ipilimumab	11 (61%)	NA
Previous CNS therapy†		
None	6 (33%)	8 (44%)
Surgical resection	8 (44%)	2 (11%)
Whole brain radiotherapy	3 (17%)	6 (33%)
Stereotactic radiosurgery	9 (50%)	5 (28%)


A
Maximum tumour response from base line (%)
250
200
150
100
50
0
−50
−100
Patients with melanoma
Patients with NSCLC
* Partial response
† Complete response
B
Melanoma
NSCLC
Complete response
Partial response
Progressive disease
Unassessable
First brain metastasis response
Ongoing treatment
0
5
10
15
Time from start of treatment (months)

A Randomized Phase 2 Study of Nivolumab or Nivolumab plus Ipilimumab in Patients with Melanoma Brain Metastases: The Anti-PD1 Brain Collaboration (ABC)

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

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by Georgina V Long

Patient Characteristics

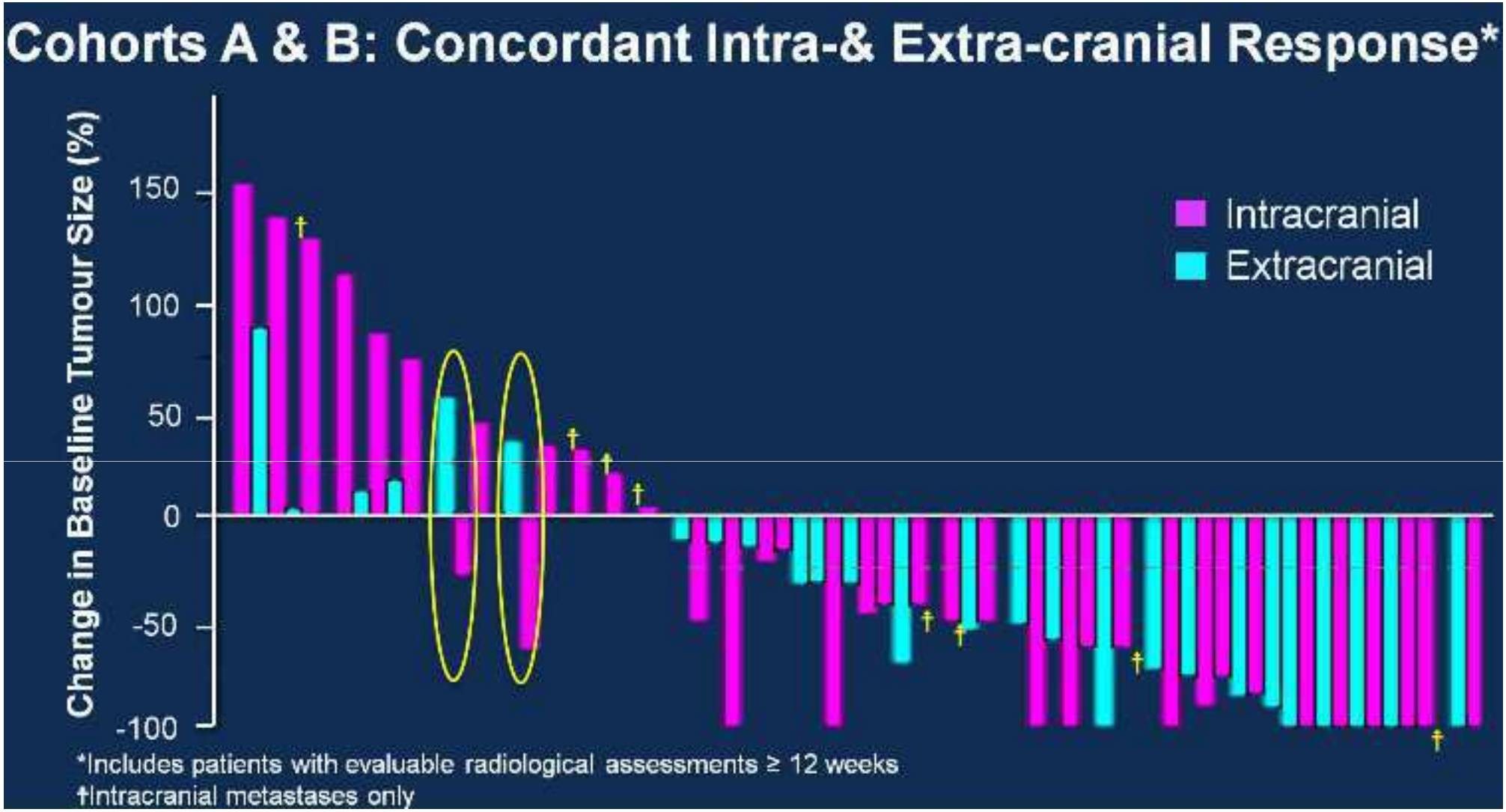
	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Age, median (range)	61 (29-76)	62 (31-86)	54 (28-73)
Sex, male n (%)	22 (85%)	19 (76%)	11 (69%)
ECOG performance status, n (%)			
1	6 (23%)	9 (36%)	7 (44%)
2	1 (4%)	0	1 (6%)
LDH > ULN, n (%)	11 (42%)	14 (58%)	6 (38%)
V600 BRAF mutation-positive, n (%)	12 (46%)	14 (56%)	13 (81%)
Target brain metastases, n (%)			
1	5 (19%)	5 (20%)	1 (6%)
2-4	9 (35%)	15 (60%)	7 (44%)
>4	12 (46%)	5 (20%)	8 (50%)
Extracranial metastases, n(%)	21 (81%)	20 (80%)	12 (75%)
Prior BRAFi+MEKi	6 (23%)	6 (24%)	12 (75%)
Prior local brain therapy	0	0	16 (100%)

†Leptomeningeal, previous local treatment or symptoms

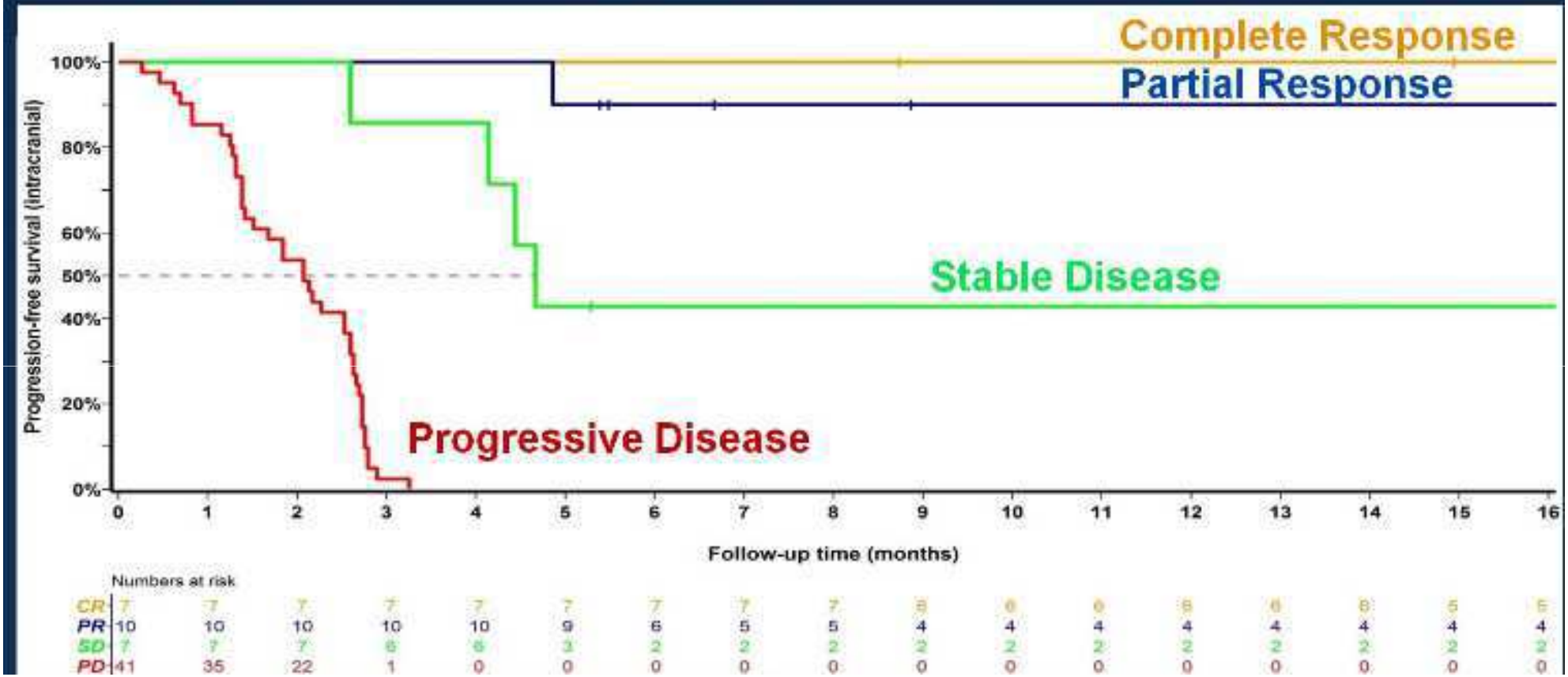
Best Intracranial RECIST Response

	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**11 (42%)**	**5 (20%)**	**1 (6%)**
CR	4 (15%)	3 (12%)	0
PR	7 (27%)	2 (8%)	1 (6%)
SD	2 (8%)	1 (4%)	4 (25%)
PD	12 (46%)	18 (72%)	11 (69%)
NE*	1 (4%)	1 (4%)	0

- Median duration of intracranial response not reached in any arm


Cohorts A & B: Concordant Intra-& Extra-cranial Response*
Change in Baseline Tumour Size (%)
150
100
50
0
-50
-100
Intracranial
Extracranial
*Includes patients with evaluable radiological assessments ≥ 12 weeks
†Intracranial metastases only

Intracranial Progression-Free Survival: Intracranial Best Response All Patients (Cohorts A+B+C)



- Nivolumab combined with ipilimumab or nivolumab alone have activity in active, asymptomatic melanoma brain metastases, without prior local therapy
  - Nivo+Ipi Intracranial: Response Rate = 42%; 6-month PFS 46%
  - Nivo alone Intracranial: Response Rate = 20%; 6-month PFS 29%
- Activity is **high** when nivo+ipi given upfront
  - Nivo+Ipi: Intracranial Response Rate = 50%
- Intracranial and extracranial responses were mostly concordant

Activity is **low** following BRAFi+MEKi

- Nivo+Ipi: Intracranial Response Rate = 16%
- Nivo alone: Intracranial Response Rate = 16%

CONCLUSIONES

- NOVEDADES recientes en tratamiento SISTEMICO de metastasis en SNC

- CPNCP EGFR mutado: TKI 1er y 2da Generacion + SRS

- CPNCP EGFR mutado T790M: Osimertinib → Optimo control en SNC

- CPNCP EGFR mutado: AZD3759: amplia distribución en SNC

- ALK translocado: superioridad de Alectinib sobre Crizotinib Sistemico y SNC

- Ca Mama Her2: Capecitabina + Lapatinib (Neratinib)

- Melanoma BRAF mutado: Dabrafenib + Trametinib

- Melanoma BRAF mutado/WT: Nivolumab + Ipilimumab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