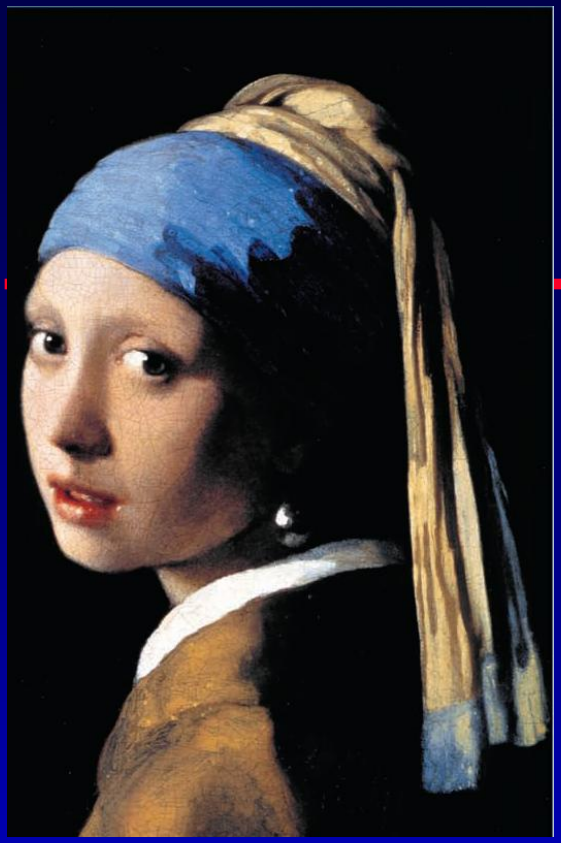


ONCOLOGIA AL FEMMINILE
Verona 18/19 Settembre 2015

Le metastasi cerebrali nei pazienti con NSCLC e traslocazione di ALK

Rita Chiari
Oncologia Medica
Azienda Ospedaliero-Universitaria di Perugia

NSCLC ALK + and Brain mets: Outline

1. Incidence of brain mets in *ALK*+ NSCLCs
2. Management of *ALK*+ NSCLCs with brain mets : CRIZOTINIB
3. Activity of next-generation ALK-TKI against brain mets
4. Future therapeutic algorithm for the treatment of *ALK*+ NSCLC…and our experience

NSCLC ALK + and Brain mets: Incidence

- Lung cancer (expecially ADK) is the most common solid tumor metastasizing to brain
- At diagnosis Brain Mets in 20-25% of NSCLC pts whereas during the course of disease CNS mets in 40% and spinal cord and/or leptomeningeal disese in 5%
- The reported lifetime incidence of Brain mets in ALK+ NSCLC is approximately 35-50%

NSCLC ALK + and Brain mets: Incidence

		Crizotinib (n=173)	Chemotherapy (n=174)
Age, years	Median (range)	51 (22–81)	49 (24–85)
Sex, n (%)	Male	75 (43)	78 (45)
	Female	98 (57)	96 (55)
Race, n (%)	Caucasian	90 (52)	91 (52)
	Asian	79 (46)	78 (45)
	Other	4 (2)	5 (3)
Smoking, n (%)	Never smoker	108 (62)	11 (64)
	Ex-smoker	59 (34)	54 (31)
	Current smoker	5 (3)	9 (5)
Histology, n (%)	Adenocarcinoma	163 (94)	160 (92)
	Other	9 (5)	14 (8)
ECOG PS, n (%)	0	72 (42)	65 (37)
	1	84 (49)	95 (55)
	2	16 (9)	14 (8)
Brain metastases, n (%)	Present	60 (35)	60 (35)
	Absent	113 (65)	114 (66)

Shaw et al, NEJM 2013;370(26):2537-9

NSCLC ALK + and Brain mets: Incidence

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

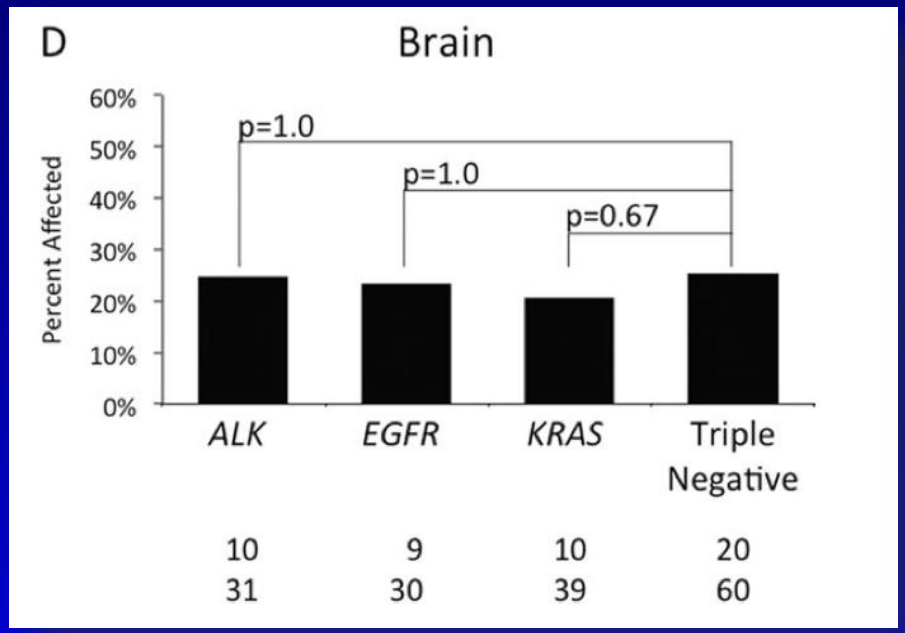
Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

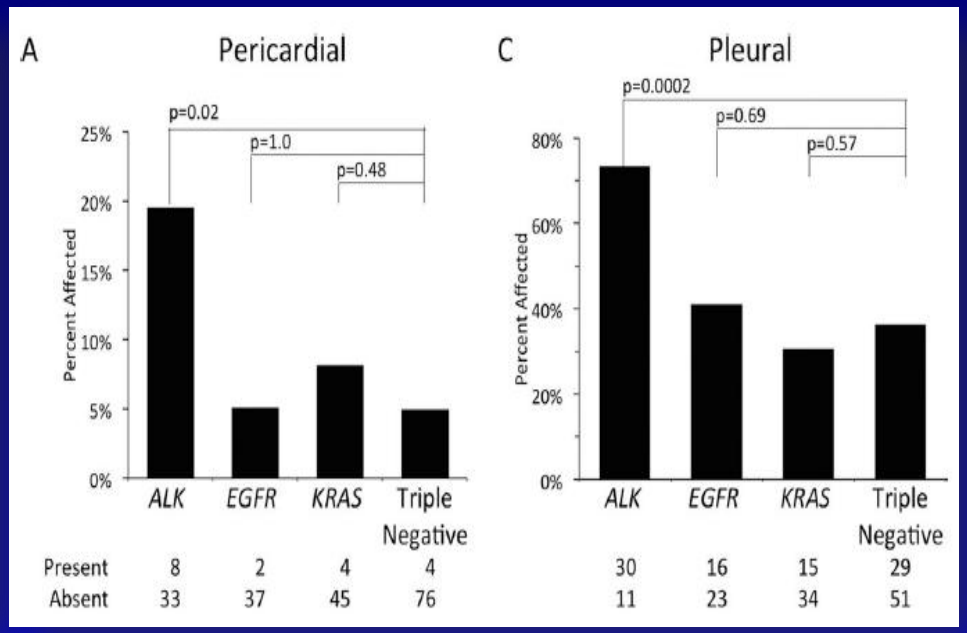
Select sites of metastases — no. (%)	
Lung	101 (78)
Thoracic lymph nodes	73 (56)
Brain	64 (49)
Liver	51 (39)
Bone	49 (38)
Meninges	1 (1)
Prior crizotinib therapy for non–small-cell lung cancer — no./total no. (%)	
Yes	83/122 (68)
No	39/122 (32)

Shaw et al, NEJM 2014;370(26):2537-9

NSCLC ALK + and Brain mts:

Incidence compared with other genotypes?





Doebele et al, Cancer 2012;118(18):4502-11.ca

NSCLC ALK + and Brain mets: Outcome compared with other genotypes?

Table 3. Median overall survival in months

	EGFR	*ALK*	*KRAS*	WT	*P* value[a]
Median OS	13.6	26.3	5.7	5.5	.001

[a]For log-rank test.

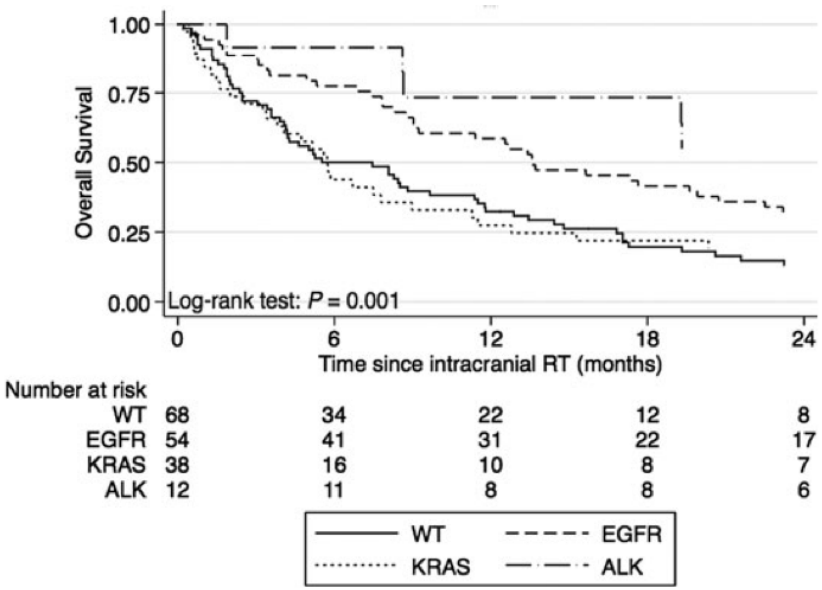


Fig. 1. Kaplan-Meier curves for overall survival.

Table 4. Multivariate Cox proportional hazards model

Covariate	OS	
	HR (95% CI)	*P* value
EGFR	0.71 (0.37–1.38)	.3
ALK	**0.37 (0.15–0.92)**	**.03**
KRAS	0.93 (0.59–1.47)	.8
Targeted therapy	**0.32 (0.17–0.59)**	**<.001**
Chemotherapy	**0.39 (0.27–0.58)**	**<.001**
Number of brain metastases	**1.13 (1.04–1.25)**	**.007**
Extracranial metastases	**3.20 (2.02–5.07)**	**<.001**
Age	**1.02 (1.00–1.04)**	**.02**
ECOG Performance Status	**1.54 (1.07–2.23)**	**.02**

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Mak KS et al, Neuro Oncol. 2015 Feb;17(2):296-302

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Crizotinib and Brain mets: more certainties than doubts! (1)

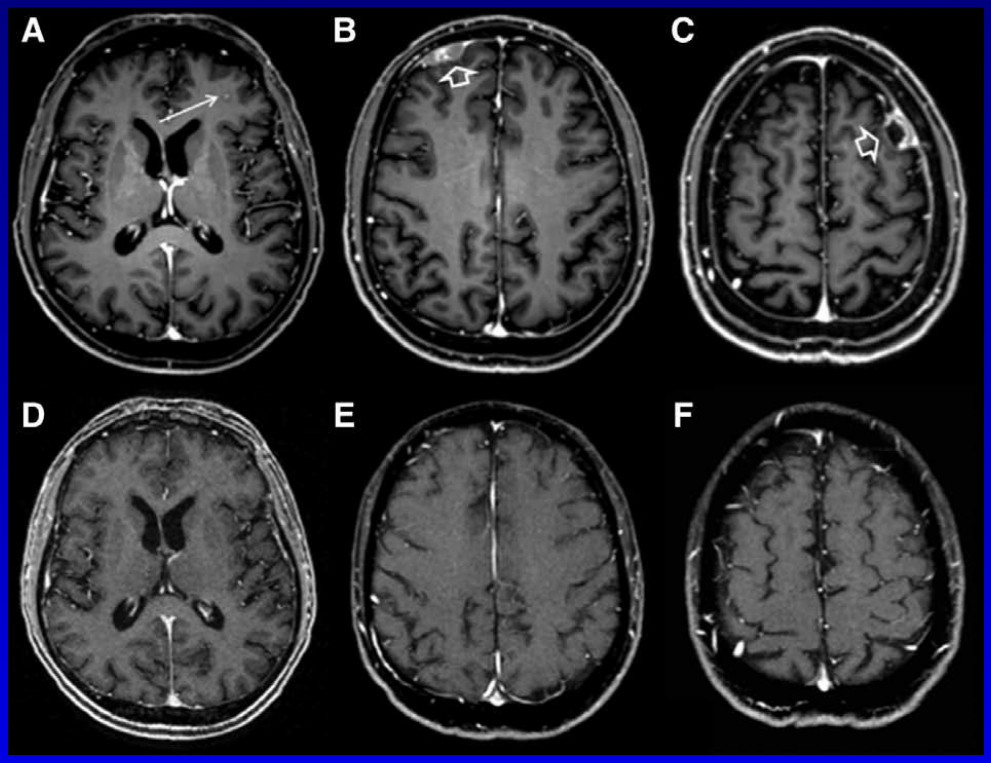
- Crizotinib, has a very poor penetration rate to the CSF of 0.06-0.26% [1,2]

- However, crizotinib has a well documented clinical activity against BMs (retrospective analysis of PROFILE 1005 and PROFILE 1007) [3] as well as data from PROFILE 1014 [4]

[1]Costa, et al. JCO 2011
[2]Metro et al, JTO 2015
[3]Costa et al, JCO2015
[4]Solomon et al, NEJM 2014

Crizotinib active against brain mets despite very low CSF concentrations

1. WBRT-naive pt with meningeal carcinomatosis and a CSF-to-serum ratio 1:1677
2. WBRT pretreated pt without meningeal carcinomatosis and a CSF-to-serum ratio 1:1000



Metro G, et al. J Thorac Oncol 2015;10:e26-7

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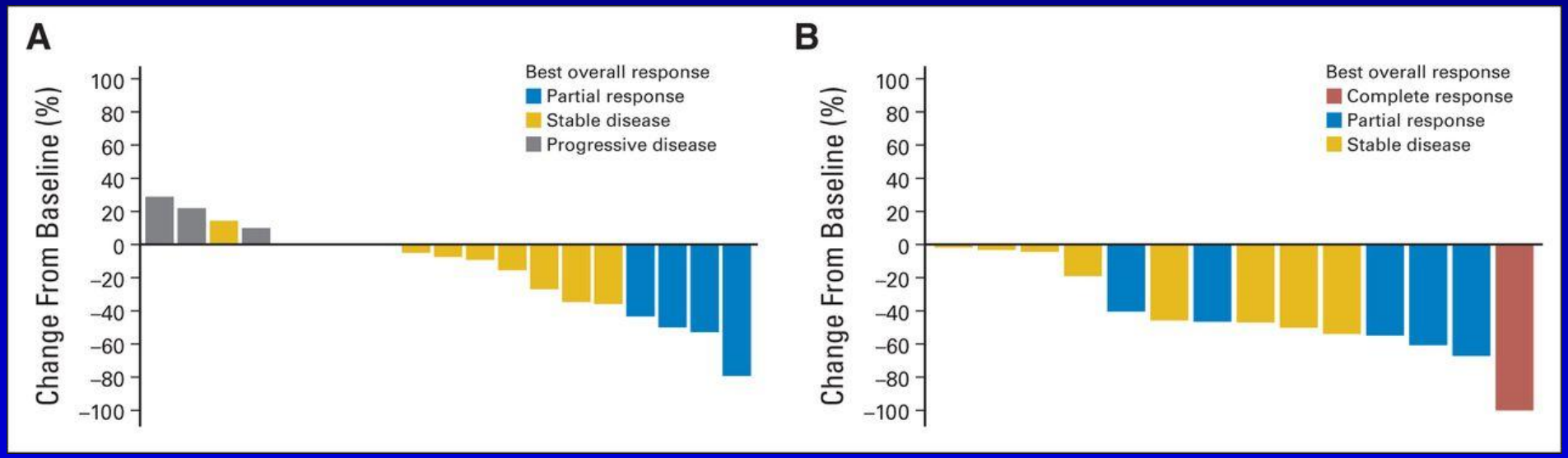
Crizotinib and Brain mets in PROFILE 1005 and 1007

Waterfall plots of best % change in intracranial target lesions for patients with ≥ one intracranial target lesion at baseline.

A: Untreated brain mets

B: Treated brain mets



OIDCR at 12 wks of 56%

OIDCR at 12 wks of 62%

OIRR at 12 wks of 18%

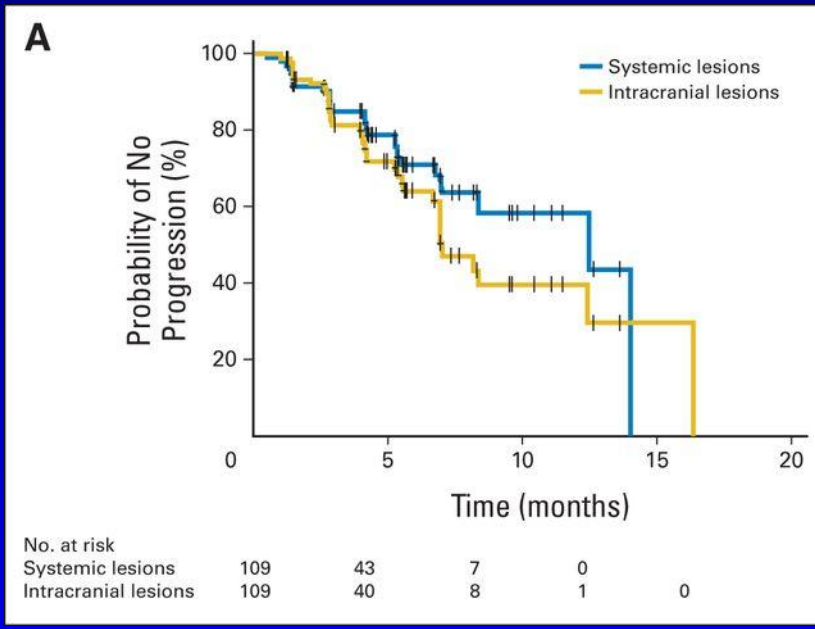
OIRR at 12 wks of 33%

Daniel B. Costa et al. JCO 2015;33:1881-1888

Crizotinib and Brain mets in PROFILE 1005 and 1007

Systemic and intracranial time to progression

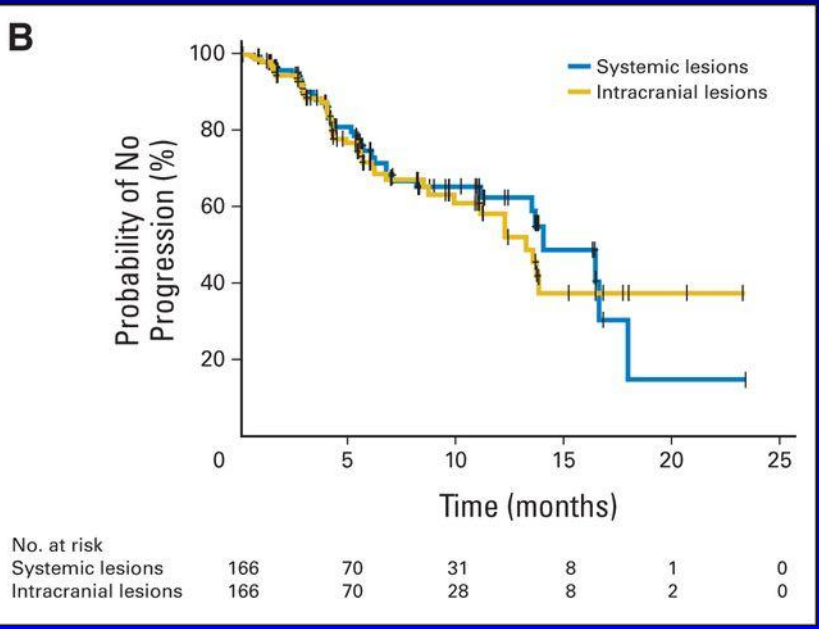
A: Untreated brain mets



intracranial TTP 7 mos

systemic TTP 12.5 mos

B: Treated brain mets



intracranial TTP 13.2 mos

systemic TTP 14 mos

Daniel B. Costa et al. JCO 2015;33:1881-1888

Table 2. Crizotinib Antitumor Activity in Patients With and Without BM at Baseline

Activity	Previously Untreated for BM (n = 109)			Previously Treated for BM (n = 166)			No BM Detected (n = 613)		
	No. of Patients	Outcome	95% CI	No. of Patients	Outcome	95% CI	No. of Patients	Outcome	95% CI
DCR at 12 weeks, %									
IC	109	56	46 to 66	166	62	54 to 70		NA	
Systemic	109	63	54 to 72	166	65	57 to 72	613	71	68 to 75
ORR, %									
IC (target lesion BM)	22	18	5 to 40	18	33	13 to 59		NA	
Systemic	109	53	43 to 63	166	46	39 to 54	613	55	51 to 59
Time to tumor response, weeks									
IC	8			12					
Median		6.0			6.4			NA	
Range*		4.9-12.4			5.9-17.7			NA	
Systemic	58			77			336		
Median		6.1			6.1			6.1	
Range*		2.0-31.4			3.1-35.3			3.0-49.1	
Duration of response, weeks									
IC	8			12					
Median†		26.4			NR			NA	
Range*		6.1-59.3			6.0-59.9			NA	
Systemic	58			77			336		
Median†		47.9			55.6			49.0	
Range*		5.3-55.0			4.4-95.3			4.1-96.1	
Median PFS, months†									
Overall	109	5.9	4.2 to 6.9	166	6.0	4.3 to 9.9	613	8.8	7.9 to 9.9
Systemic	109	8.3	6.7 to 14.0	166	13.5	6.2 to 16.5	613	9.9	8.8 to 12.2
Median TTP, months†									
IC	109	7.0	6.7 to 16.4	166	13.2	9.9 to NR		NA	
Systemic	109	12.5	7.0 to 14.0	166	14.0	13.5 to 18.0		NA	

Abbreviations: BM, brain metastases; DCR, disease control rate; IC, intracranial; NA, not applicable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression.

*In patients with respective type of objective response.

†Kaplan-Meier method.

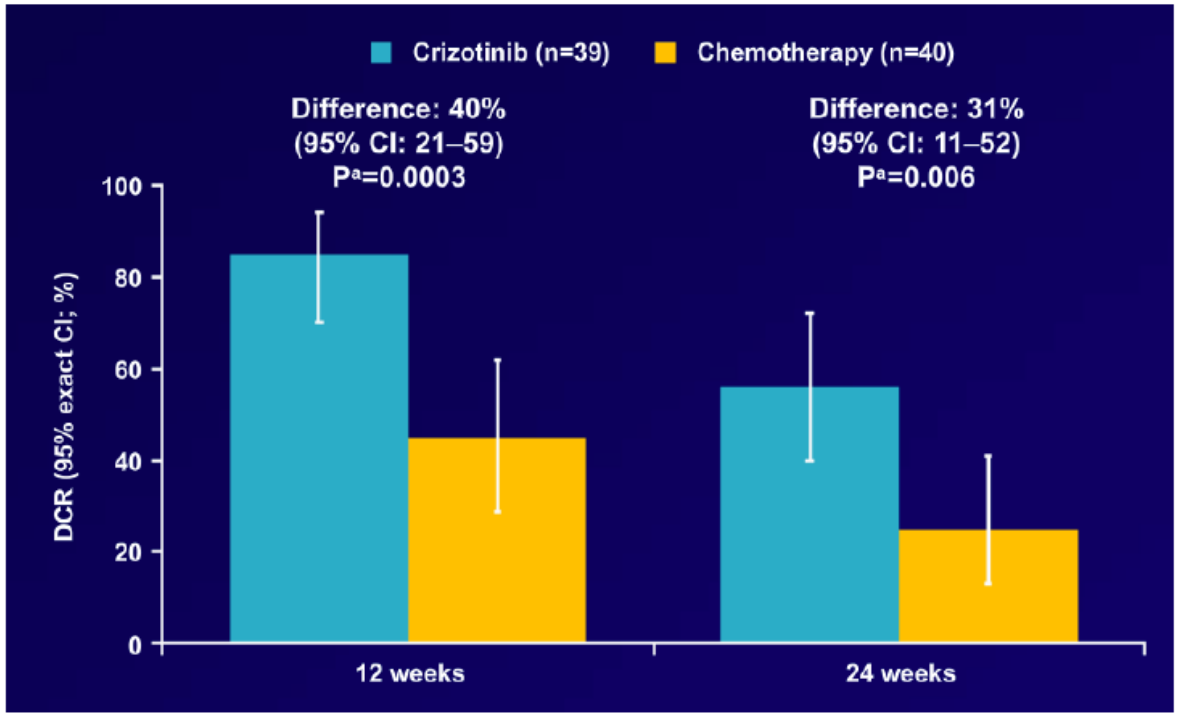
Daniel B. Costa et al. JCO 2015;33:1881-1888

Crizotinib and Brain mets in PROFILE 1014 (first line)

MADRID 2014 ESMO congress

Solomon - Abstract 1225O

Intracranial disease control in patients with treated CNS mets at baseline



26-30 September 2014, Madrid, Spain

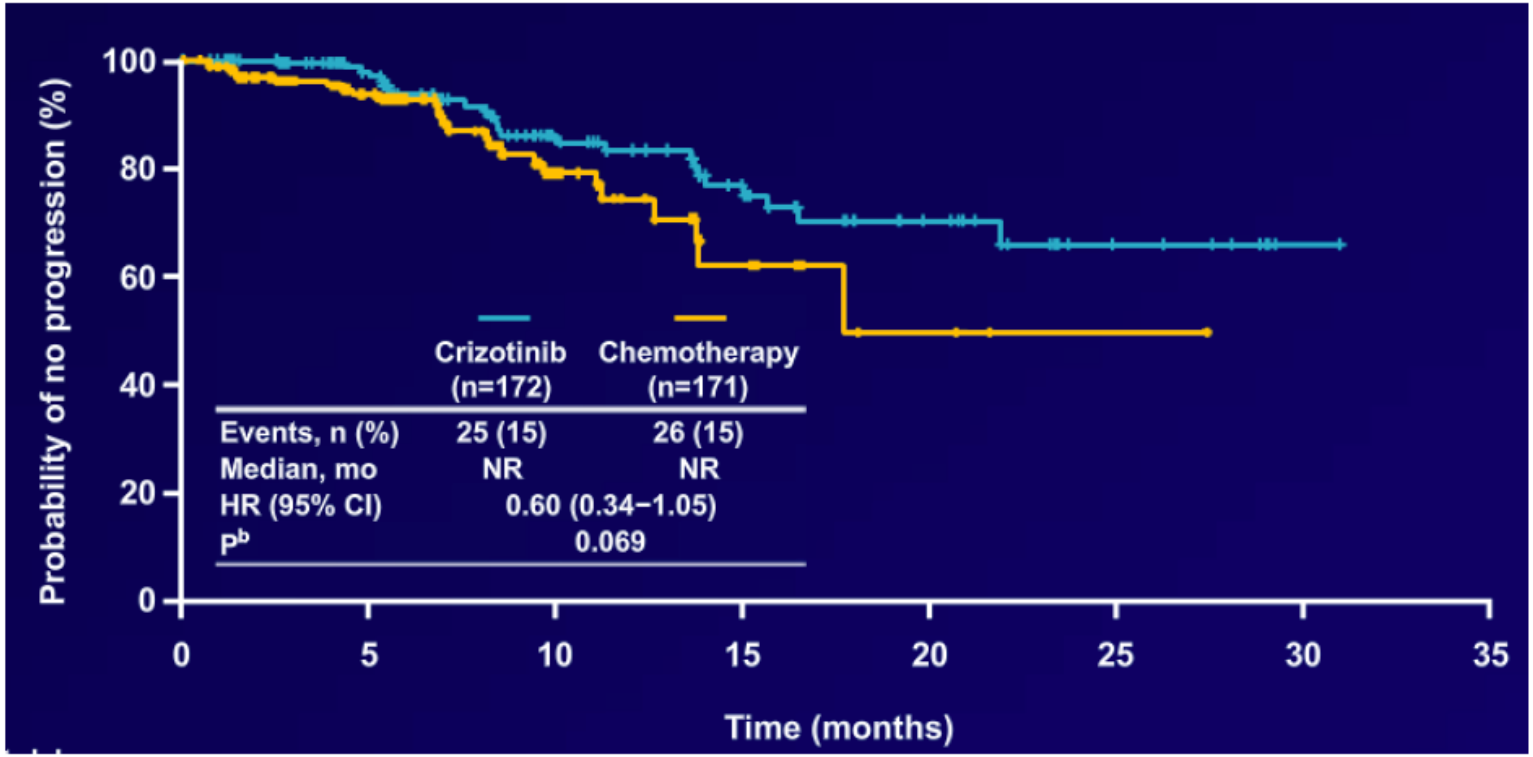
esmo.org

Crizotinib and Brain mets in PROFILE 1014 (first line)

MADRID 2014 ESMO congress

Solomon - Abstract 1225O

Time to intracranial progression in PROFILE 1014 patients with CNS mets



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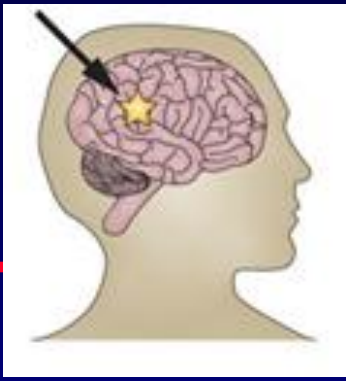
esmo.org

Crizotinib and Brain mets: more certainties than doubts! (2)



- ***"The CNS is a sanctuary site in ALK positive NSCLC on crizotinib"*** being the first site of progression in 46% of cases, 85% of which lacked coincident systemic progression[1]
- **More frequent intramedullary spinal cord metastasis and leptomeningeal carcinomatosis[2]**
- **High-dose crizotinib for brain mts refractory to standard-dose (500 mg single adm[3]; 600 mg/day[4]; 1000 mg/day[5])**

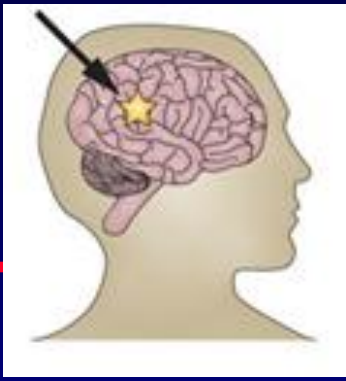
[1]Weickhardt et al, JTO 2012
[2]Gainor et al, JTO 2013
[3]Peled et al, JTO 2013
[4]Gandhi et al, JTO 2013
[5]Kim et al, JTO 2013

CNS is the most common site of PD on crizotinib in patients with and without CNS metastases at baseline

	Previously untreated for BM (n=109)		Previously treated for BM (n=166)		No BM detected (n=613)	
	n	Outcome	n	Outcome	n	Outcome
Target lesions only, n (%)	4	9%	8	13%	52	21%
Non-Target lesions or New lesions	(n=43)		(n=54)		(n=201)	
Intracranial (IC)/Brain, n (%)	30	70%	39	72%	51	25%
Lung, n (%)	3	7%	6	11%	25	12%
Bone, n (%)	4	9%	8	15%	25	12%
Liver, n (%)	2	5%	3	6%	47	23%
Other sites not included in this table						

Daniel B. Costa et al. JCO 2015;33:1881-1888

Crizotinib and Brain mets: more certainties than doubts! (2)



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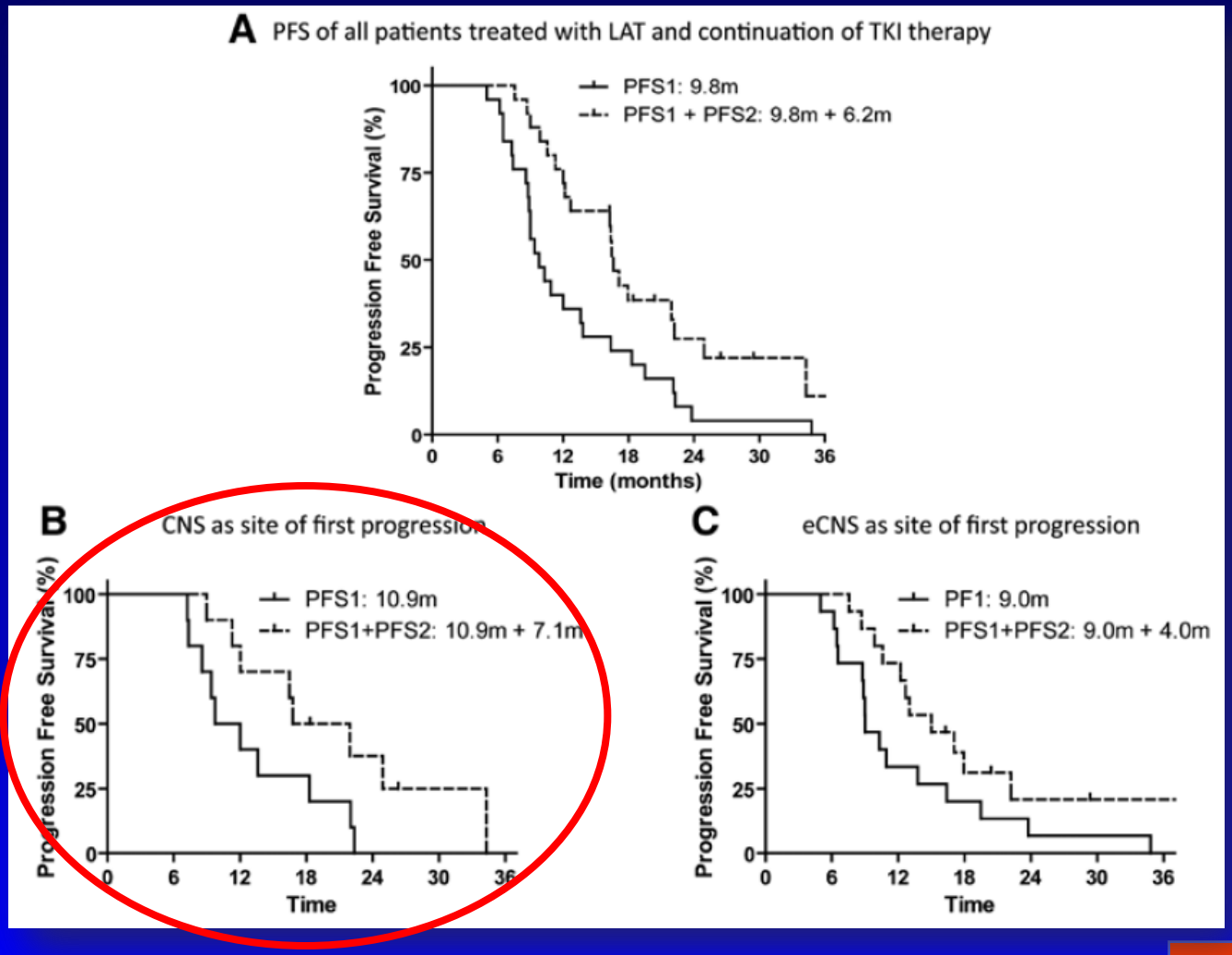
[4]Gandhi et al, JTO 2013
[5]Kim et al, JTO 2013

Options at CNS progression on Crizotinib: 1) post-progression crizotinib + RT



Weickhardt et al, JTO 2012

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Activity of 2nd generation ALK-TKIs in CNS disease: CERITINIB

ALK-TKI	Prior ALK-TKI	OIRR	Pts with target lesions[1] in the CNS, OIRR, N (%)	Independent review
Ceritinib [1]	Allowed	67/124 (54%)	7/14 (50%)	Yes
Ceritinib [2]	Mandatory (Crizotinib)	Not reported	13/33 (39.3%)	Yes
Ceritinib [3]	Not allowed	Not reported	10/17 (58.8%)	Yes

1. Kim DW, JCO 2014;32(suppl 5): 8003
2. Mok T, JCO 2015;33(suppl):8059
3. Felip E, JCO 2015;33(suppl):8060

ASCEND-3: CERITINIB in ALKI-naive CHT pre-treated ALK+ NSCLC

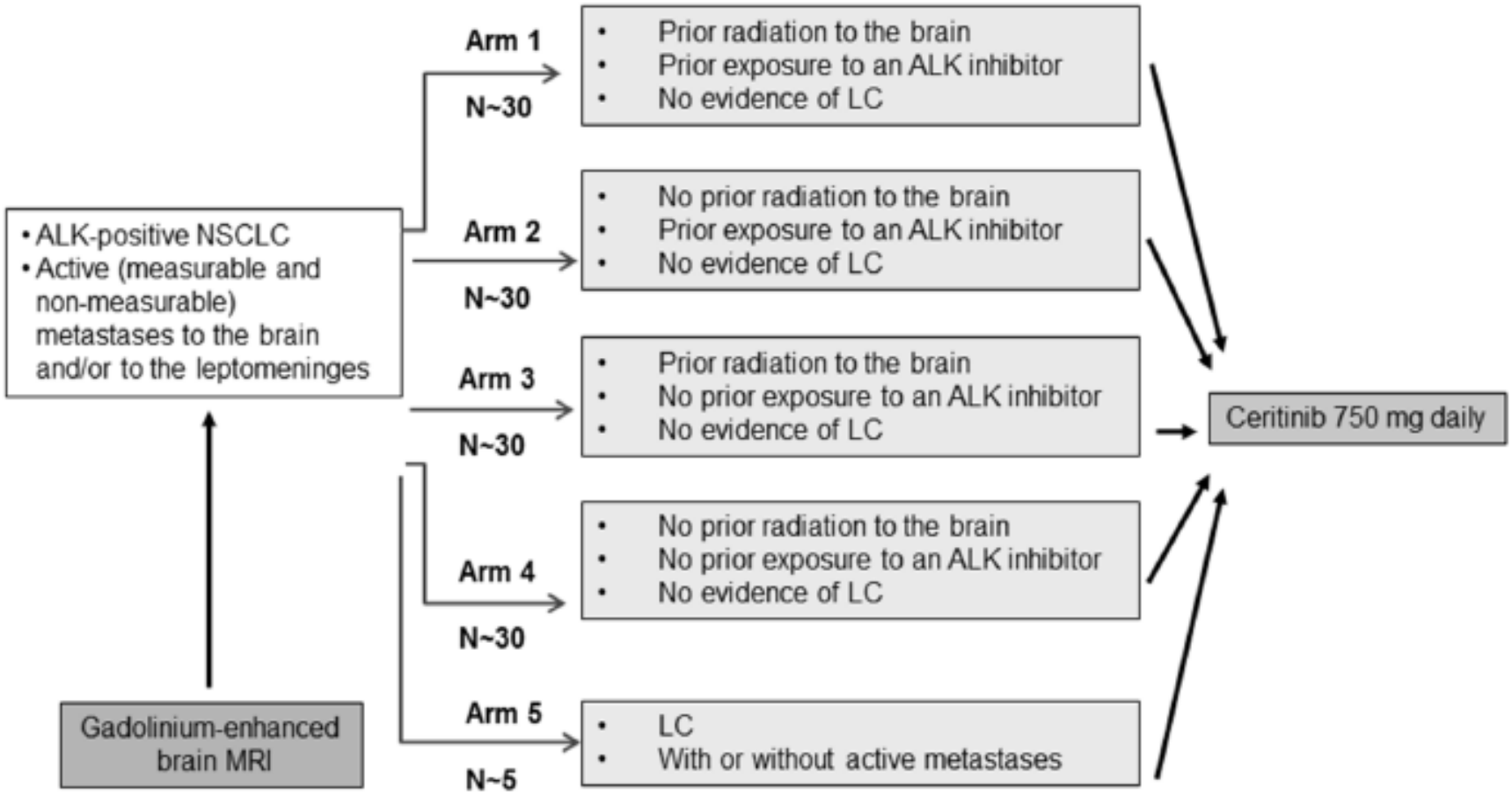
Table 5. Intracranial Response Rate in NSCLC Patients with Target Lesions in the Brain

	Investigator Review (FAS)	BIRC (FAS)
Patients with target lesions in the brain	N = 10	N = 17
Best overall response, n (%)		
CR	-	1 (5.9)
PR	2 (20.0)	9 (52.9)
SD	6 (60.0)	4 (23.5)
PD	1 (10.0)	-
Unknown	1 (10.0)	3 (17.6)
OIRR, n (%) (95% CI)	2 (20.0) (2.5, 55.6)	10 (58.8) (32.9, 81.6)
IDCR, n (%) (95% CI)	8 (80.0) (44.4, 97.5)	14 (82.4) (56.6, 96.2)

Felip E.,ASCO 2015

A phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of ceritinib in pts with ALK+ NSCLC metastatic to the brain and/or to leptomeninges : ASCEND-7 (LDL378A2205)

Figure 4-1 Study design

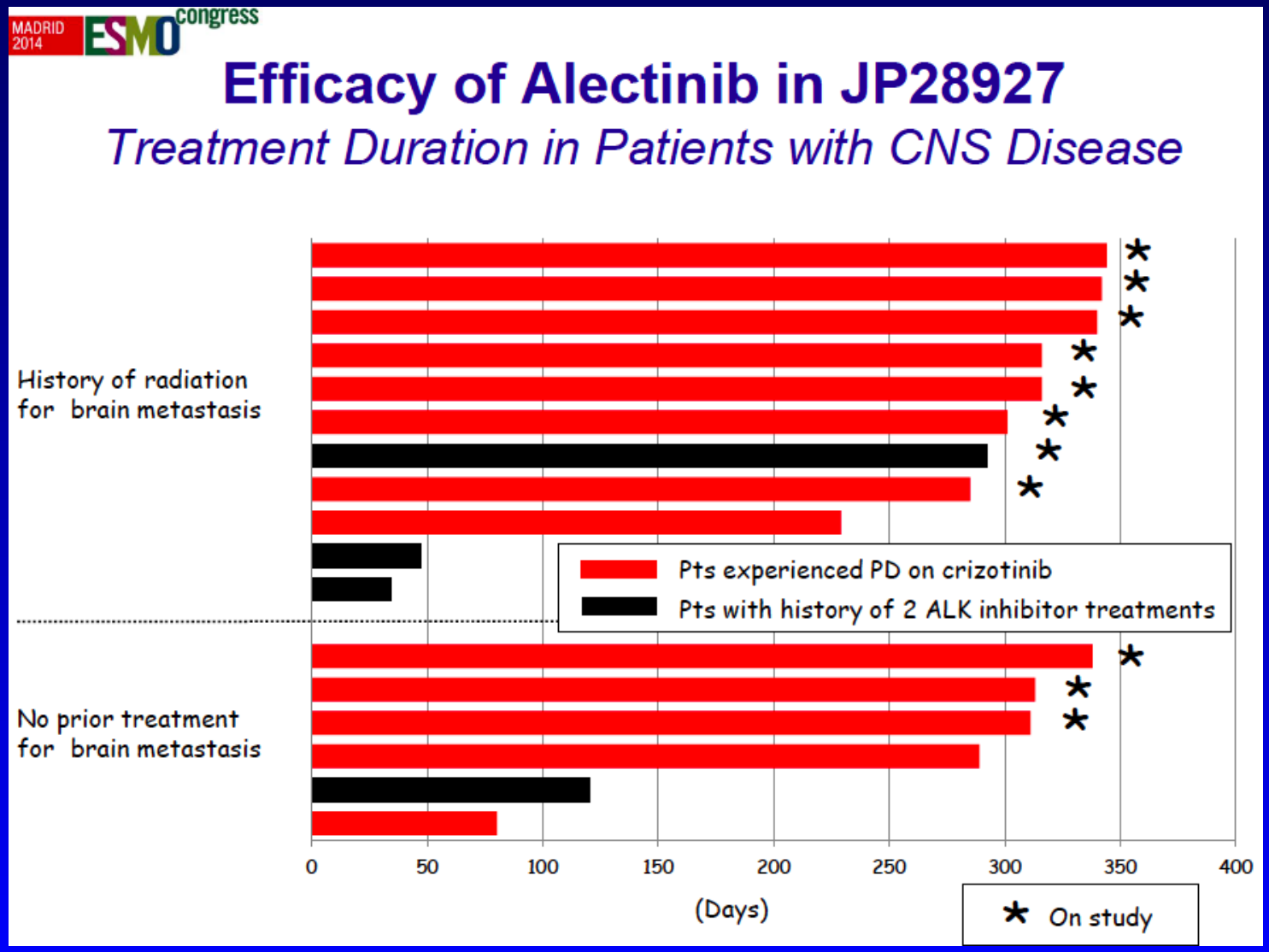


Activity of 2nd generation ALK-TKIs in CNS disease: ALECTINIB and the others

ALK-TKI	Prior ALK-TKI	OIRR	Pts with target lesions[1] in the CNS, OIRR, N (%)	Independent review
Alectinib [4]	Mandatory (Criz) (Crizotinib)	11/21 (52.5%)	5/9 (55.5%)	Yes
Alectinib [5]	Mandatory (Crizotinib)	20/52 (38.5%)	11/16 (68.8%)	Yes
Alectinib [6]	Mandatory (Crizotinib)	36/84 (42.9%)	20/35 (57.1%)	Yes

4. Gadgel SM, Lancet Oncol 2014;15:1119-28
5. Gandhi L, JCO 2015;33 (suppl): 8019
6.Ou SH, JCO 2015;33(suppl): 8008

Alectinib and brain mets

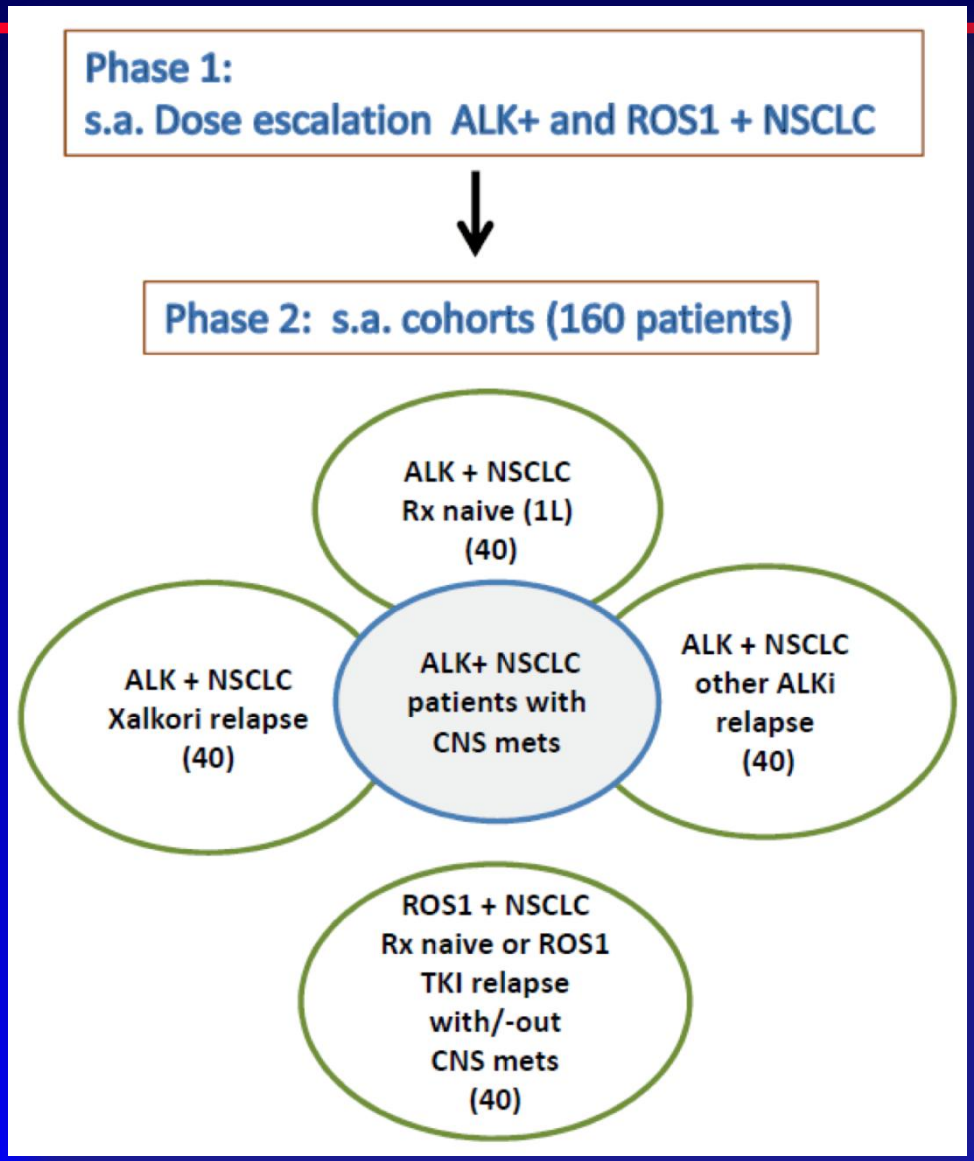


Activity of 2nd generation ALK-TKIs in CNS disease: ….. and the others

ALK-TKI	Prior ALK-TKI	OIRR	Pts with target lesions[1] in the CNS, OIRR, N (%)	Independent review
Brigatinib [7]	Allowed	19/48 (39.5%)	8/15 (53%)	Yes
PF-06463922[8]	Allowed	9/25 (36%)[2]	Not reported	Not specified

7.Camidge DR, JCO 2015;33(suppl): 8062
8.Shaw AT, JCO 2015;33(suppl)): 8018

Phase 1/2 study of PF-06463922 (an ALK/ROS1 tyrosine kinase inhibitor) in patients with advanced NSCLC harboring specific molecular alterations



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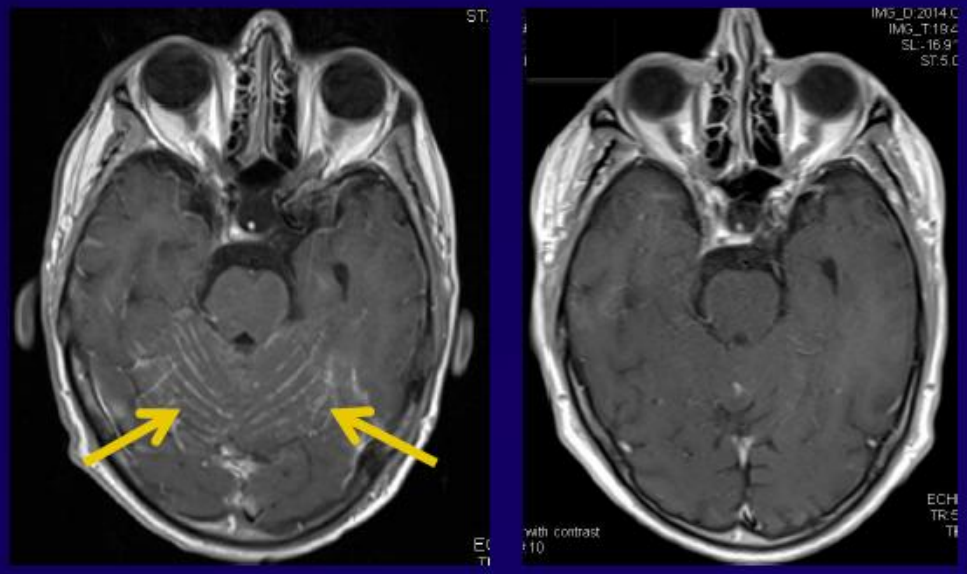
NSCLC ALK + and Brain mets: Future therapeutic algorithm?

Role for Multiple Sequential ALK Inhibitors

CNS Disease

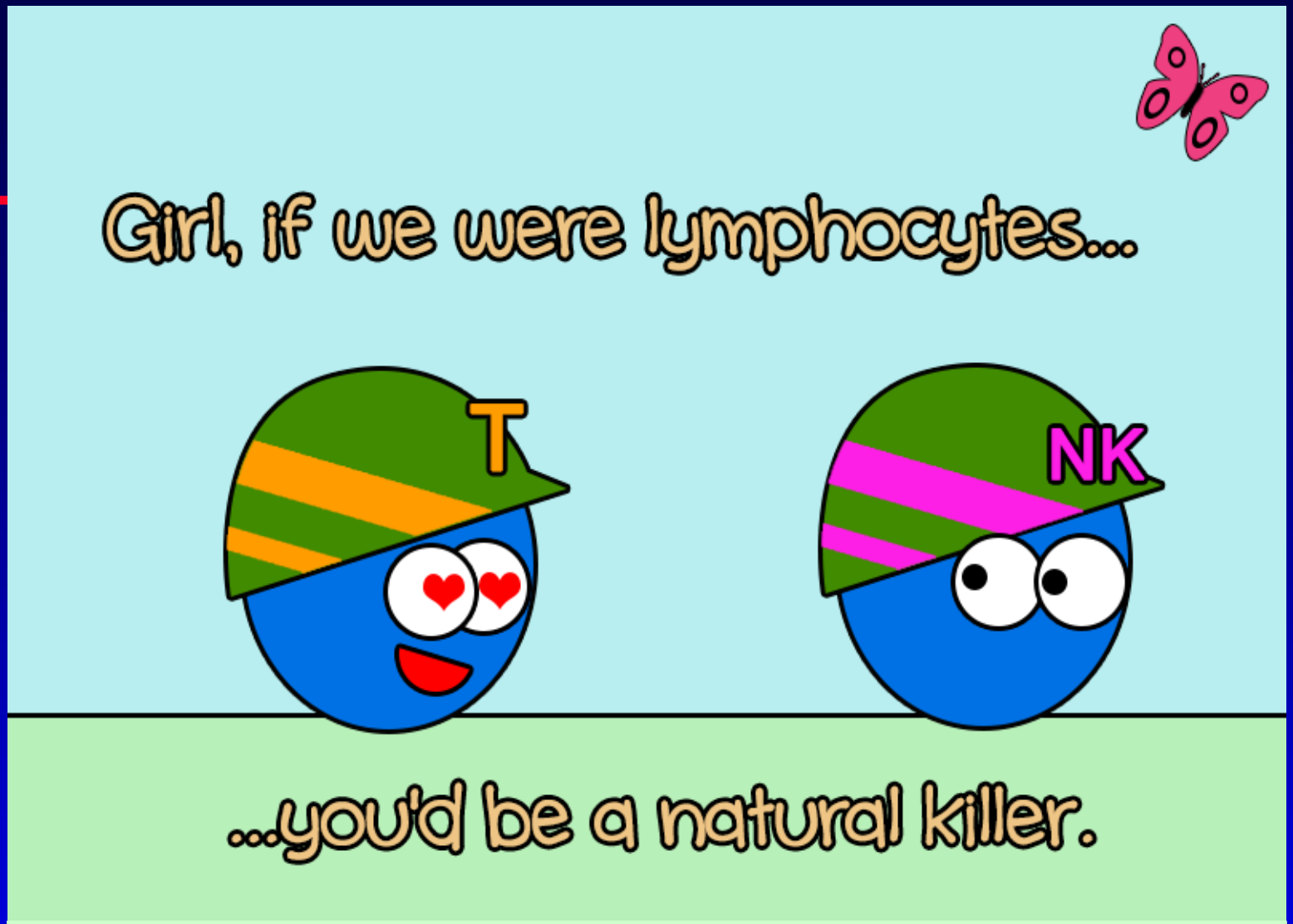
1L	2L	3L
Crizotinib	Ceritinib *CNS*	Alectinib



Shaw
ESMO 2014

NSCLC ALK + and Brain mets: conclusions

- Incidence of CNS mts in *ALK*+ NSCLC is 35-50%
- *ALK*+ NSCLCs with CNS mts live longer than differently genotyped NSCLC pts
- CNS is the most common site of progression on crizotinib in pts with and without CNS mts
- Crizotinib has modest activity in the CNS
- Novel ALK-TKIs may improve prognosis of *ALK*+ NSCLC
- Based on our experience, the use of ALK-TKIs for BMs' treatment in the first-line setting, might be a reasonable option for asymptomatic pts, for whom WBRT may be postponed at a later stage of disease→ trials ongoing to answer this question



Thank you for your attention!!

ritachiar@gmail.com