Treatment options for ALK-TKI resistance

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elcc

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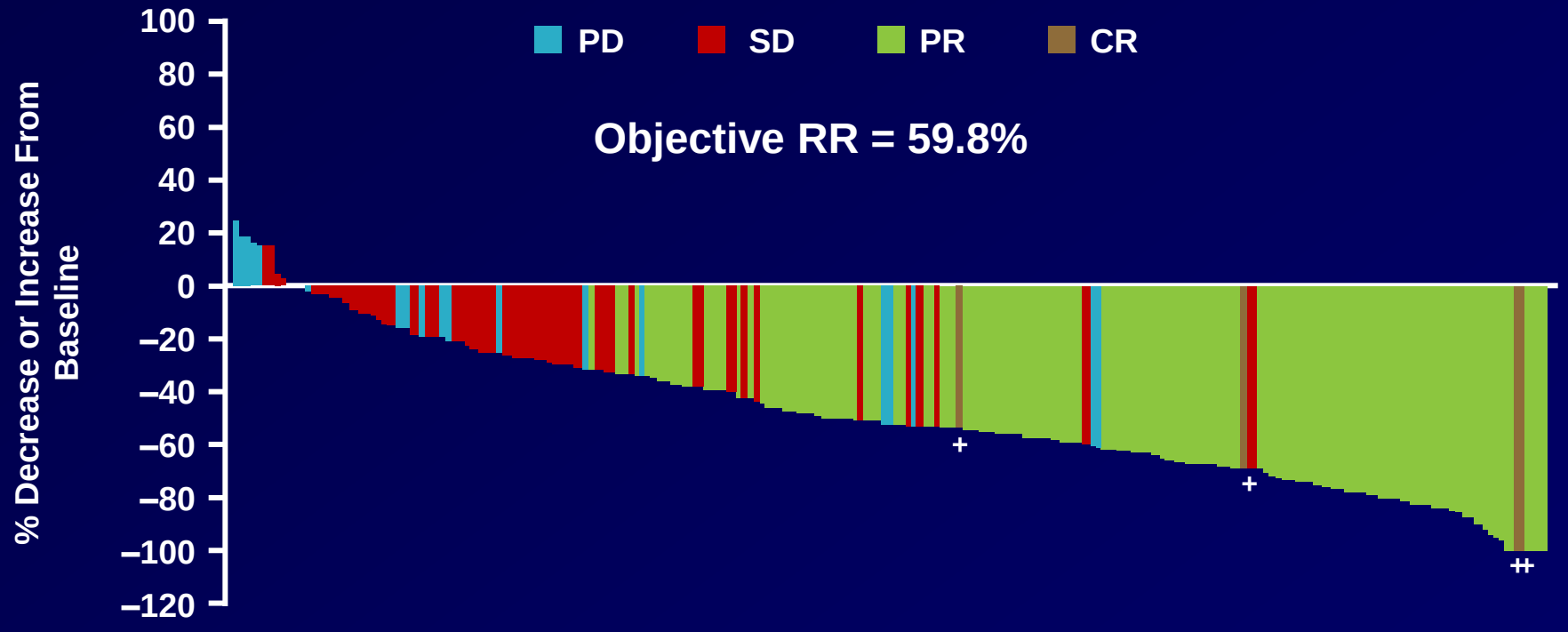
Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop

Disclosure

- I have no financial interest to disclose.

Crizotinib Phase II Study (PROFILE 1005) in ALK-positive NSCLC

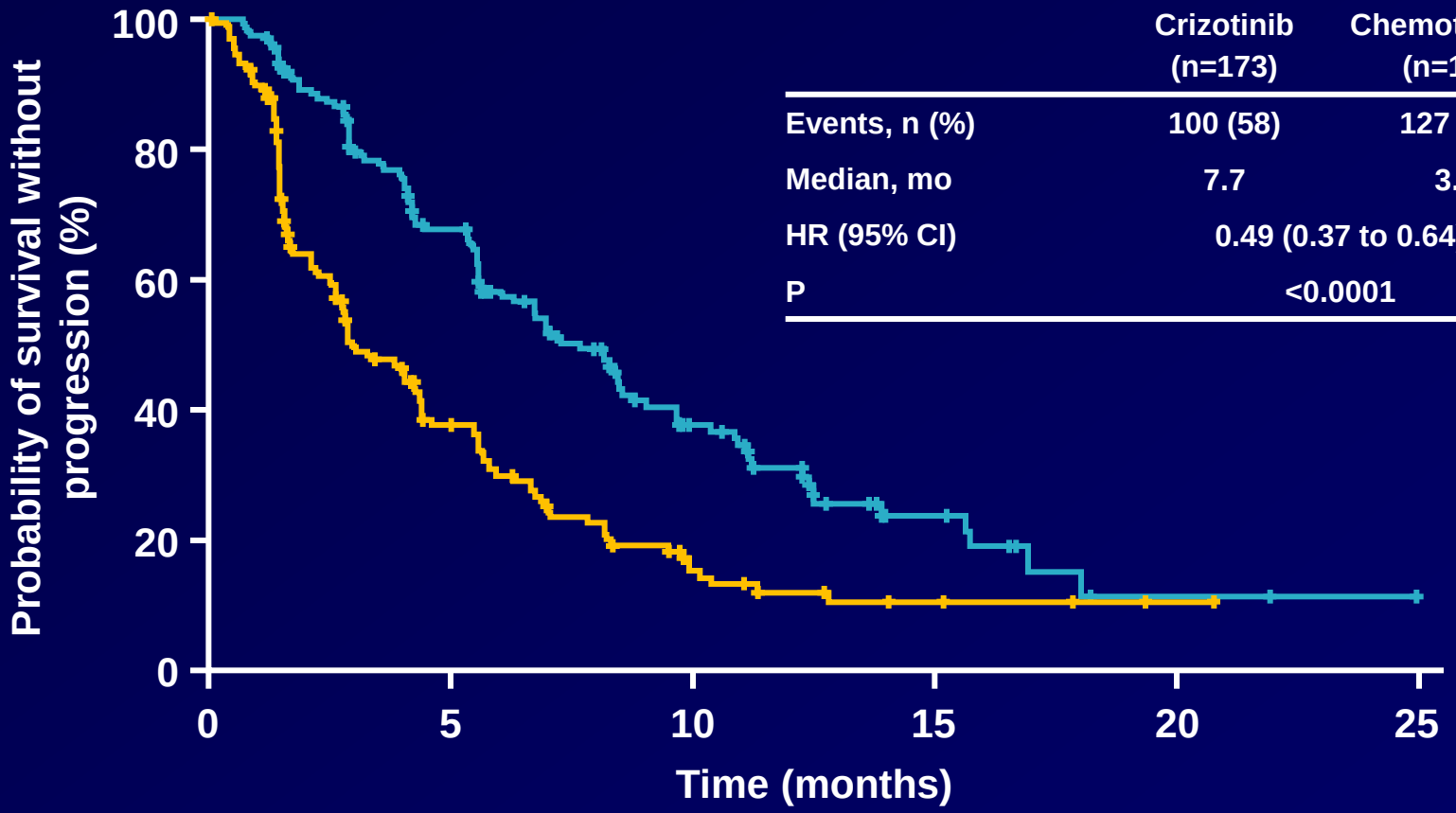


*N=240 response-evaluable patients from the mature population, and excludes patients with early death, indeterminate response and non-measurable disease

+Per RECIST 1.1, percent change from baseline for subjects with best overall response of CR can be less than 100% when lymph nodes are included as target lesions.

Kim DW, *et al*. ASCO 2012

Crizotinib 2nd line Phase III Study (PROFILE 1007)
- PFS analysis -

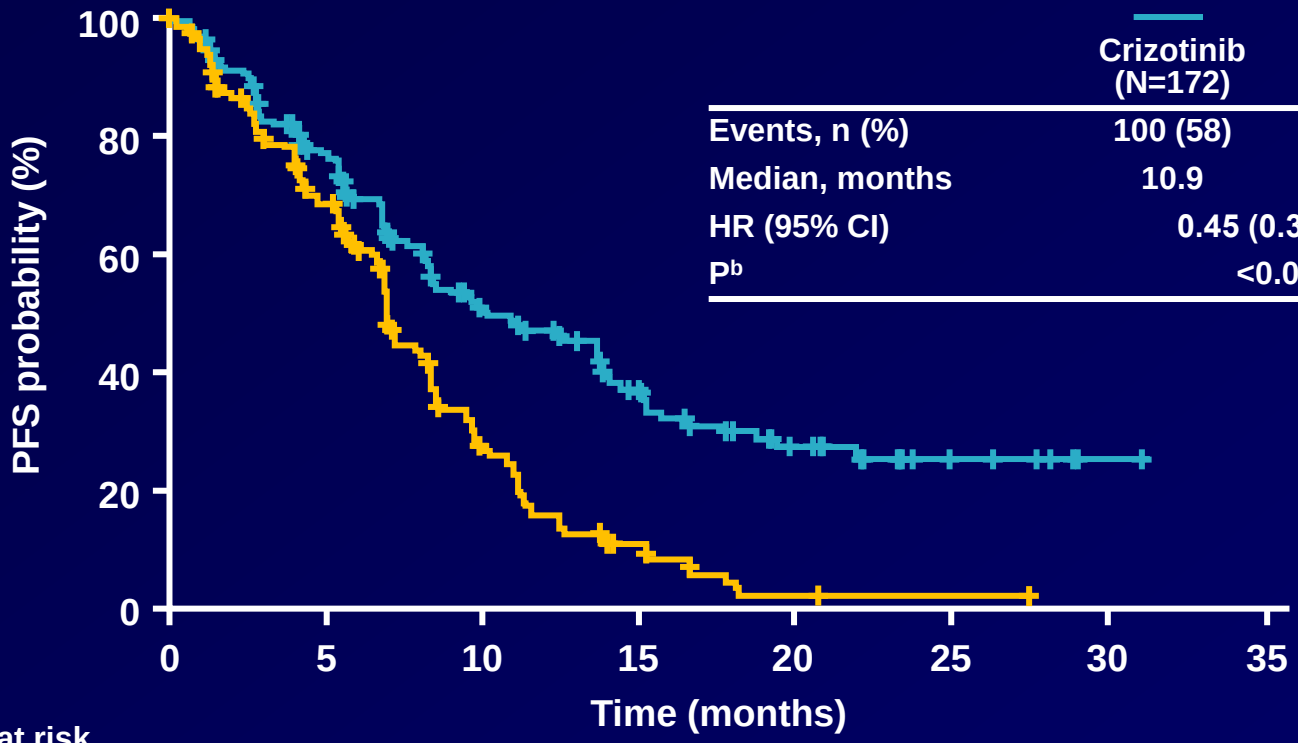


	Crizotinib (n=173)	Chemotherapy (n=174)
Events, n (%)	100 (58)	127 (73)
Median, mo	7.7	3.0
HR (95% CI)	0.49 (0.37 to 0.64)	
P	<0.0001	

No. at risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Shaw AT, Kim DW, *et al*. N Engl J Med 2013

Crizotinib 1st line Phase III Study (PROFILE 1014)
- PFS analysis -



	Crizotinib (N=172)	Chemotherapy (N=171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0[a]
HR (95% CI)	0.45 (0.35−0.60)	
P[b]	<0.0001	

No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

- Median duration of treatment: crizotinib, 10.9 months; chemotherapy, 4.1 months

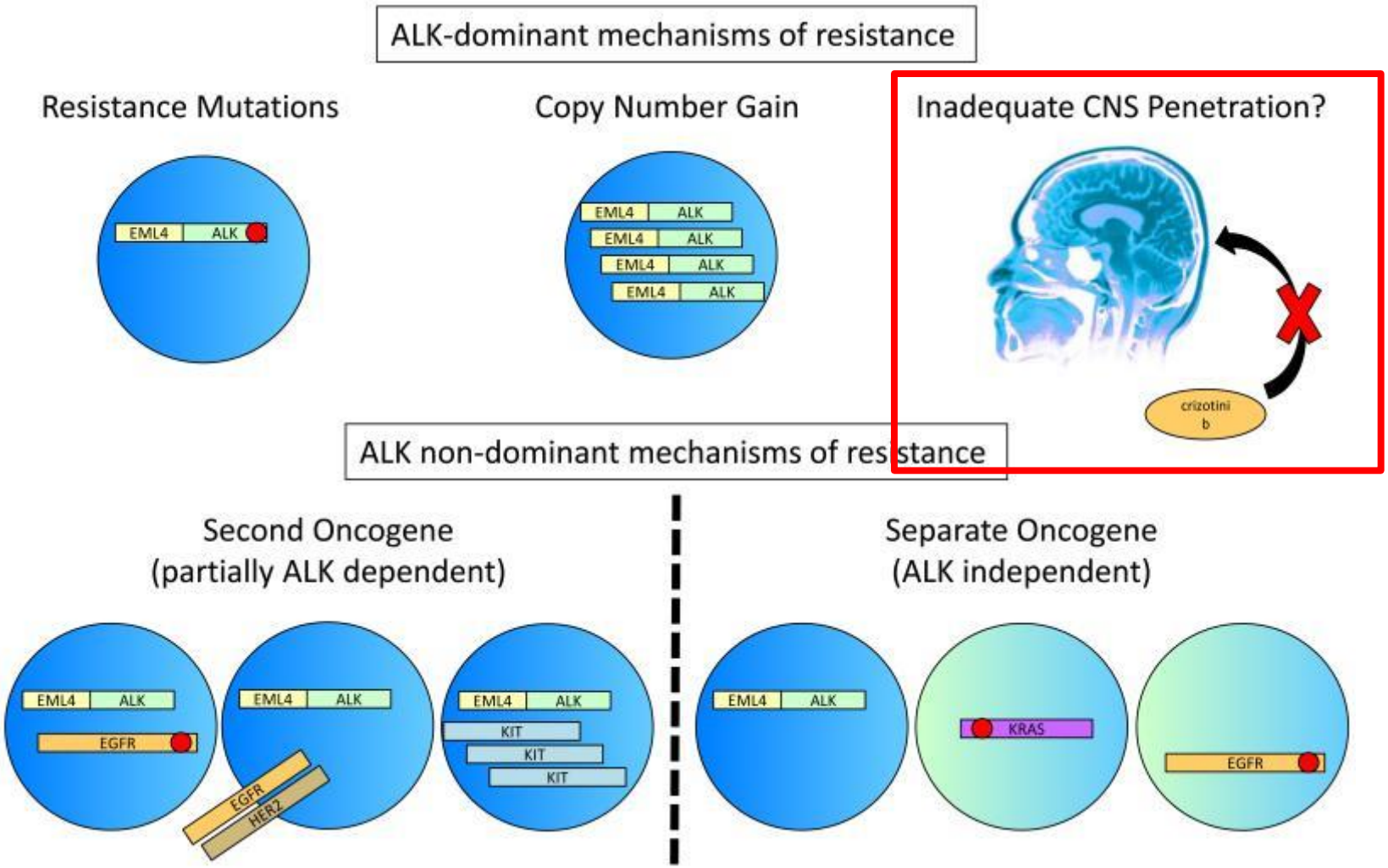
Data cutoff: November 30, 2013

[a]As-treated population: pemetrexed−cisplatin, 6.9 months (n=91; HR: 0.49; P<0.0001); pemetrexed−carboplatin, 7.0 months (n=78; HR: 0.45; P<0.0001)

[b]2-sided stratified log-rank test

Solomon BJ, Mok T, *et al*. N Engl J Med 2014

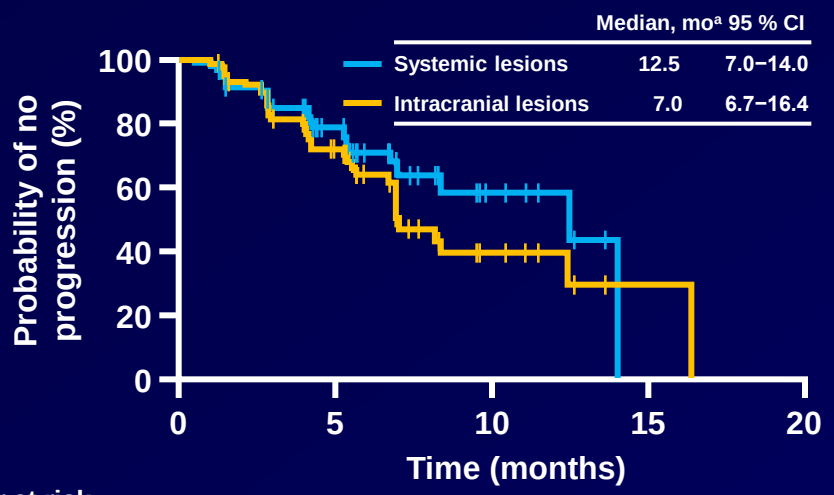
Crizotinib Resistance Mechanism



Camidge DR, *et al.* Nat Rev Clin Oncol 2012

Crizotinib: Systemic and Intracranial TTP in Patients with Baseline Brain Metastases

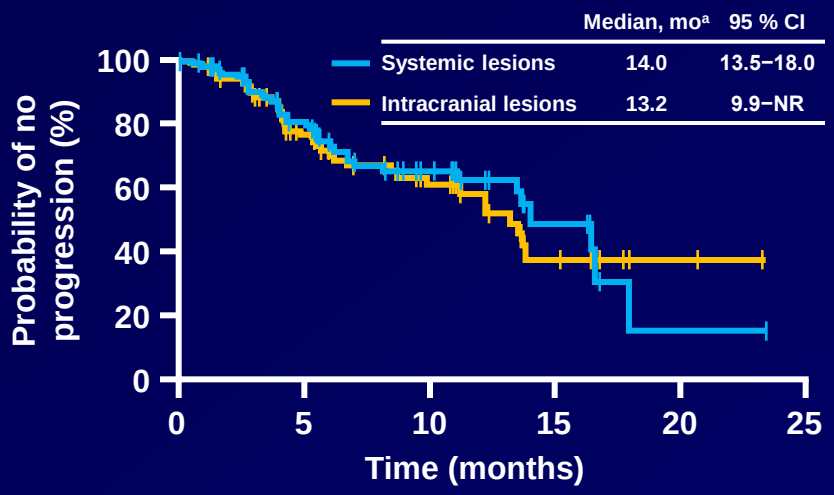
Previously untreated brain metastases



Number at risk

Systemic lesions	109	43	7	0		
Intracranial lesions	109	40	8	1	0	

Previously treated brain metastases



Systemic lesions	166	70	30	8	1	0
Intracranial lesions	166	70	28	8	2	0

- Of patients with non-target or new lesions as PD, the CNS was the most common site of progression, occurring in:
  - 70% of patients (30/43) with previously untreated brain metastases
  - 72% of patients (39/54) with previously treated brain metastases

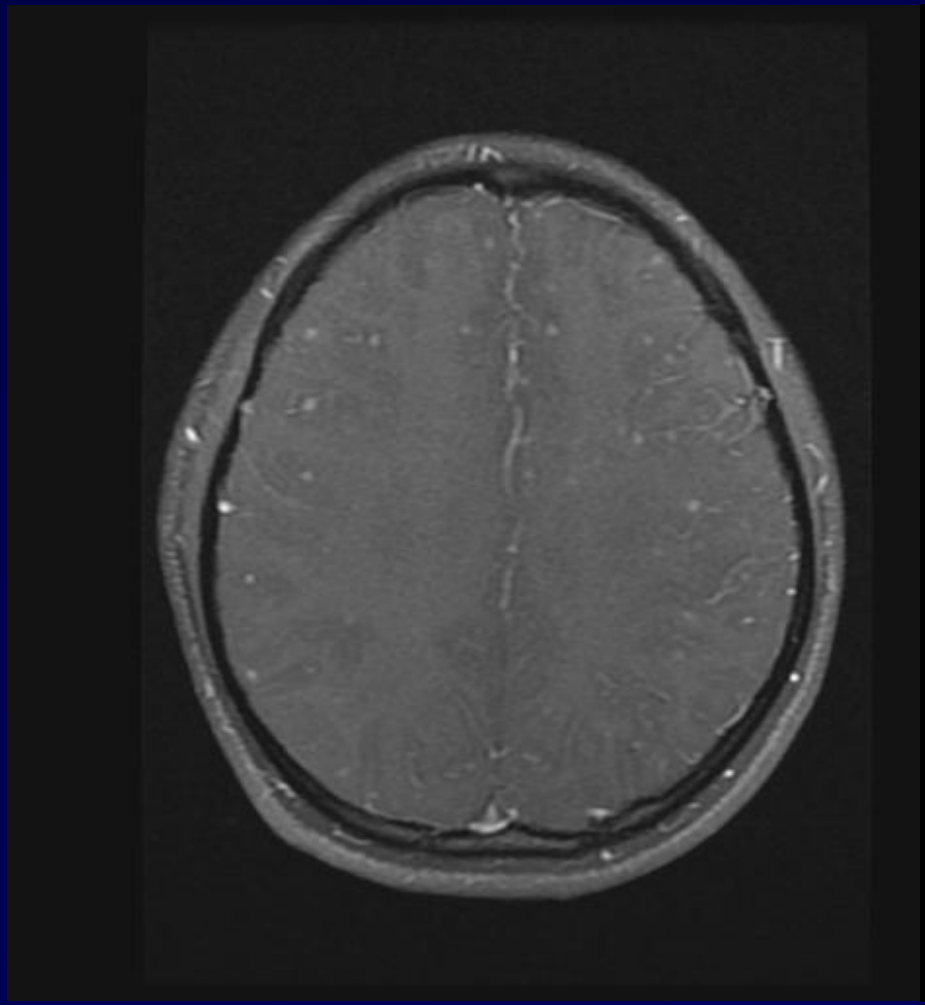
Costa DB, *et al*. J Clin Oncol 2015

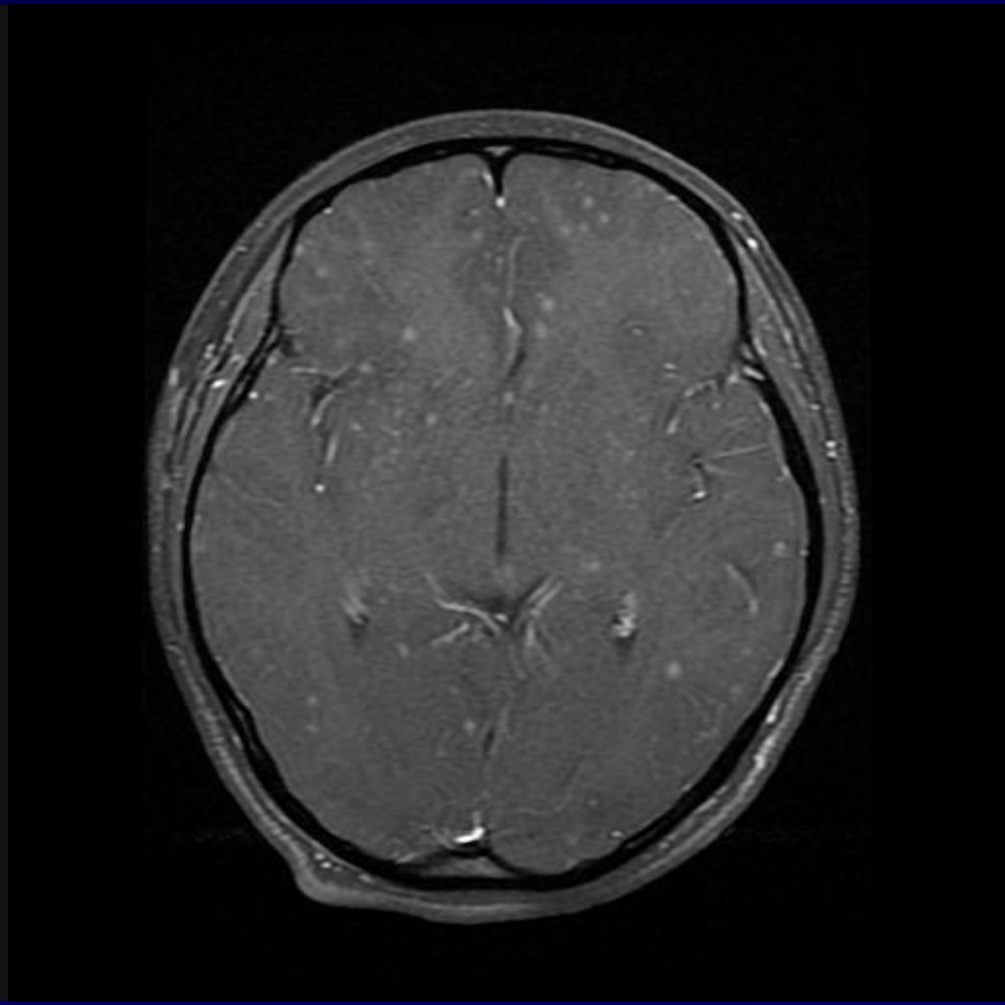
Crizotinib: TTP and Progression in Patients without Baseline Brain Metastases

- For patients without evidence of brain metastases at initiation of crizotinib treatment, median overall TTP was 9.8 months (95% CI, 8.4–11.7)
  - Progression occurred in 41% of these patients (253/613) while receiving crizotinib
  - Brain metastases developed in 20% of these patients (51/253)
  - The median time to detection of brain metastases in these 51 patients was 29.9 weeks (range, 2.6–79.0)

Costa DB, *et al*. J Clin Oncol 2015

A case: Headache after 2 years of crizotinib treatment

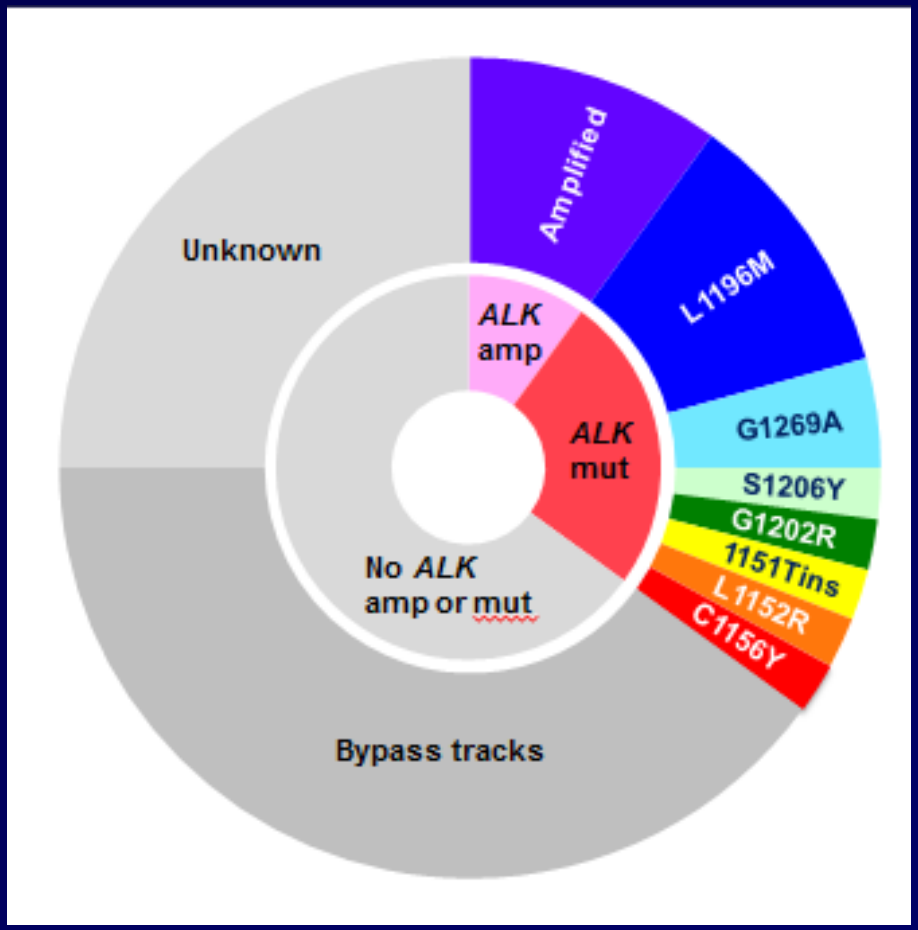




- No extra-CNS progression
- Under crizotinib for 2 years after whole brain RT

Acquired Resistance in ALK+ NSCLC

- *ALK*-rearranged (ALK+) NSCLC is sensitive to crizotinib[1–3]
  - ORR 60%
  - Median PFS 8–10 months
- Most patients develop resistance to crizotinib[4,5]
  - Usually within 1–2 years
  - CNS relapses are common[6]
- Mechanisms of resistance are diverse[4,5]
  - ALK resistance mutations
  - Alternative signaling pathways



1. Camidge DR, *et al. Lancet Oncol* 2012;13:1011–1019; 2. Kim D-W, *et al. ESMO* 2012 (Abstr 1230PD);
3. Shaw AT, *et al. ESMO* 2012 (Abstr LBA1_PR); 4. Katayama R, *et al. Sci Transl Med 2012;*4:120ra17;
5. Doebele RC, *et al. Clin Cancer Res* 2012;18:1472–1482; 6. Takeda M, *et al. J Thorac Oncol* 2013;8:654–657.

Shaw AT, et al. ASCO 2013

Expectations on 2nd generation ALK inhibitors

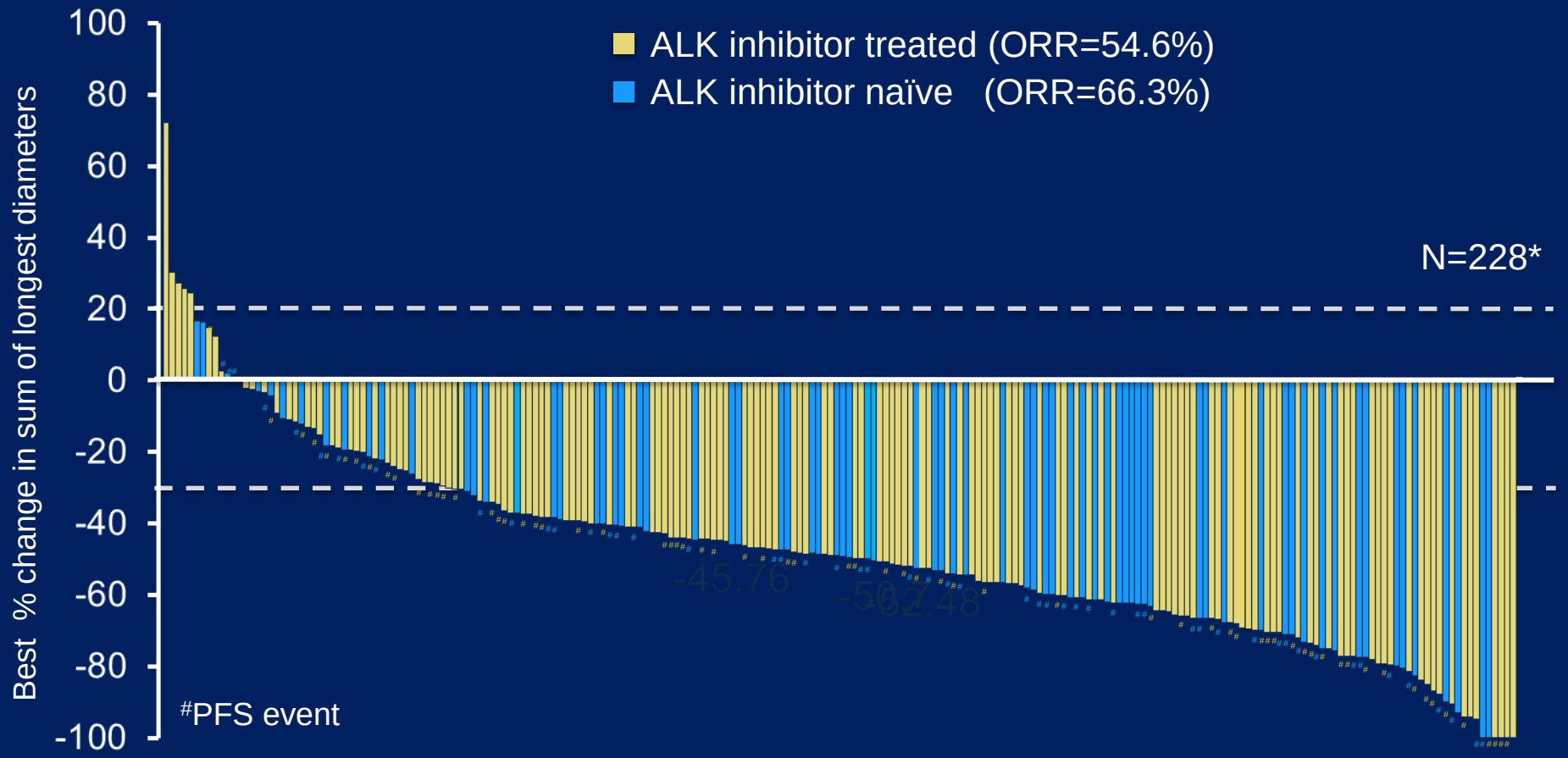
- To overcome ALK resistance mutations
- To have CNS activity

2nd generation ALK inhibitors

Mutations	Ceritinib	Alectinib	AP26113	ASP3026	TSR-011	PF-6463922	X-396
L1196M	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C1156Y	No	Yes	?	?	?	Yes	Yes
L1152R	No	Yes	?	?	?	Yes	?
F1174L	No	Yes	Yes	?	?	Yes	?
G1269A	Yes	Yes	Yes	?	?	Yes	?
G1202R	No	No	?	?	?	Yes	?
S1206Y	Yes	?	No	?	?	Yes	?
1151T	No	Yes	?	?	?	Yes	?
I1171T	Yes	?	?	?	?	?	?

Pall G. Curr Opin Oncol 2015

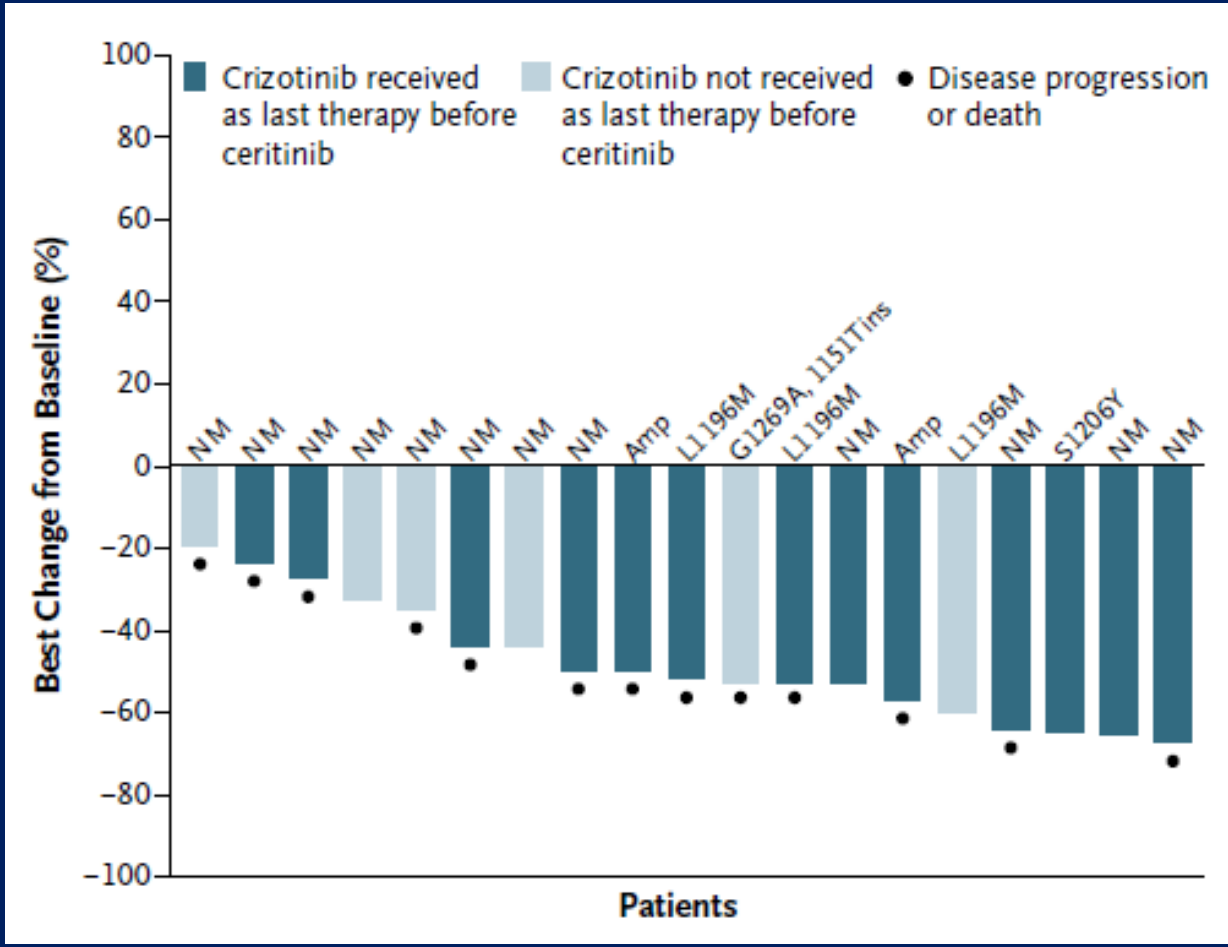
Ceritinib: Best Percentage Change from Baseline (ASCEND-1)



*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

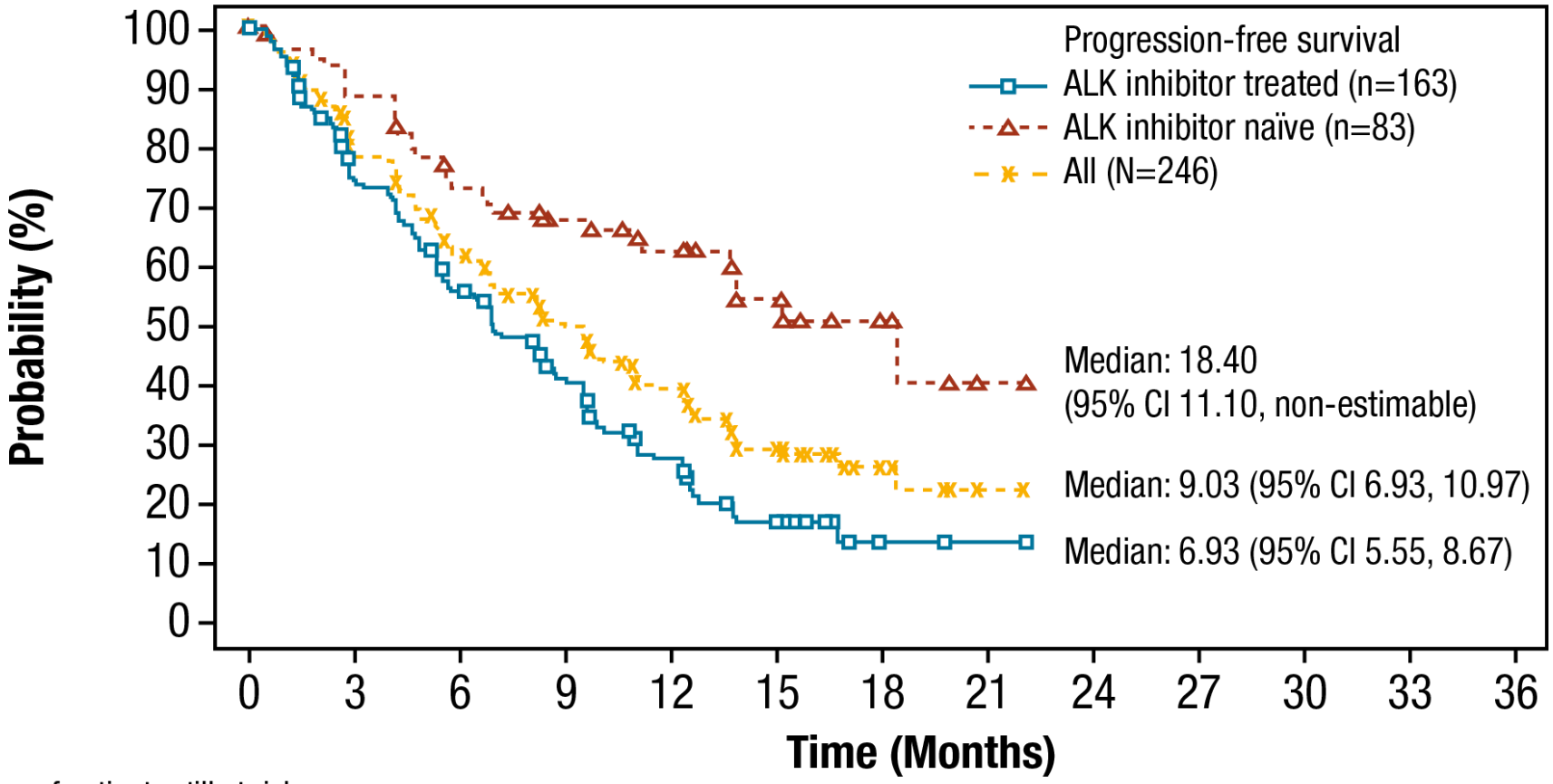
Kim DW, *et al*. ASCO 2014

Correlation of Response to Ceritinib with ALK Gene Alteration



Shaw AT, *et al*. N Engl J Med 2014

Progression-free Survival for ALK+ NSCLC Treated with Ceritinib 750 mg/day



Number of patients still at risk

NSCLC with prior ALKi	163	108	79	52	29	13	2	1	0	0	0	0	0
NSCLC ALKi naïve	83	69	55	43	32	17	6	2	0	0	0	0	0
All NSCLC	246	177	134	95	61	30	8	3	0	0	0	0	0

Felip E, et al. ECCO/ESMO 2014

Intracranial Response of Measurable Baseline Brain Metastases to Ceritinib Assessed by MRI/CT‡

Endpoint	NSCLC with Prior ALK Inhibitor (n=28)	NSCLC ALK Inhibitor Naïve (n=8)
Complete response [CR], n (%)	0 (0)	0 (0)
Partial response [PR], n (%)	10 (36)	5 (63)
Stable disease [SD], n (%)	7 (25)	0 (0)
Progressive disease [PD], n (%)	6 (21)	0 (0)
Unknown, n (%)	5 (18)	3 (38)
OIRR (CR + PR), n (%) [95% CI]	**10 (36) [19, 56]**	**5 (63) [25, 92]**
IDCR* (CR + PR + SD), n (%) [95% CI]	17 (61) [41, 79]	5 (63) [25, 92]

*Limited data on prior radiotherapy to brain available
CI, confidence interval; NA, not available; NSCLC, non-small cell lung cancer; IDCR, intracranial disease control rate; OIRR, overall intracranial response rate; NE, non-estimable; DOR, duration of response. ‡RECIST 1.1.

Mehra et al, SNO 2014

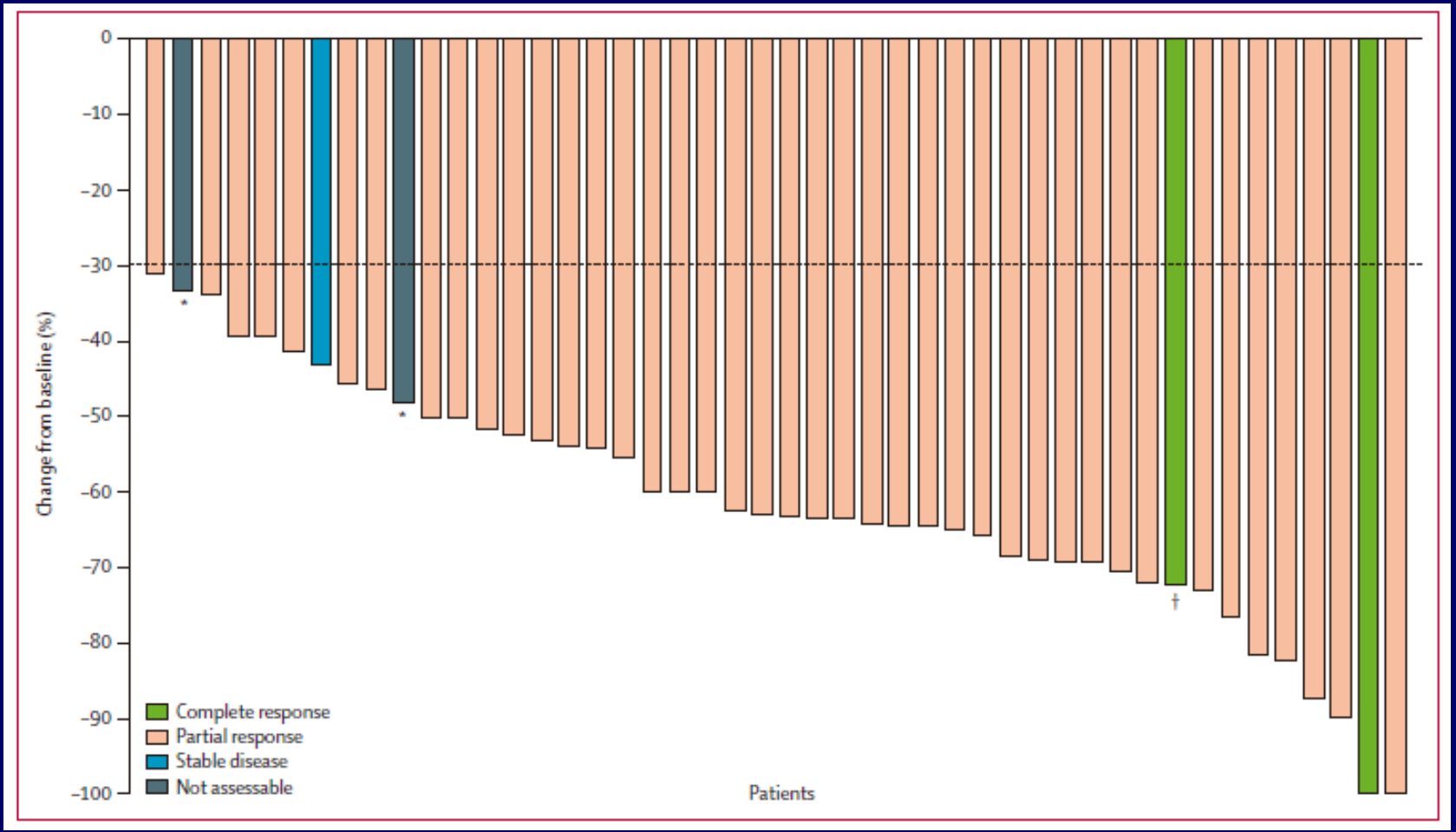
Summary of Adverse Events for all Patients with ALK+ Disease Treated at Recommended Dose

All patients treated with 750 mg (N=255; Includes nine non-NSCLC patients)		
Adverse Events	**All Grades,* n (%)**	**Grade 3/4,* n (%)**
Diarrhoea	221 (86.7)	15 (5.9)
Nausea	211 (82.7)	15 (5.9)
Vomiting	157 (61.6)	12 (4.7)
Fatigue	109 (42.7)	13 (5.1)
Abdominal pain	98 (38.4)	3 (1.2)
Decreased appetite	95 (37.3)	4 (1.6)
Constipation	79 (31.0)	0 (0.0)
Cough	73 (28.6)	0 (0.0)
Dyspnoea	63 (24.7)	11 (4.3)
Abdominal pain, upper	60 (23.5)	2 (0.8)
Weight decreased	46 (18.0)	5 (2.0)
Anaemia	31 (12.2)	13 (5.1)
Pneumonia	25 (9.8)	12 (4.7)
Convulsion	15 (5.9)	8 (3.1)

*AEs shown for >20% for all grades or ≥2% for grades 3/4

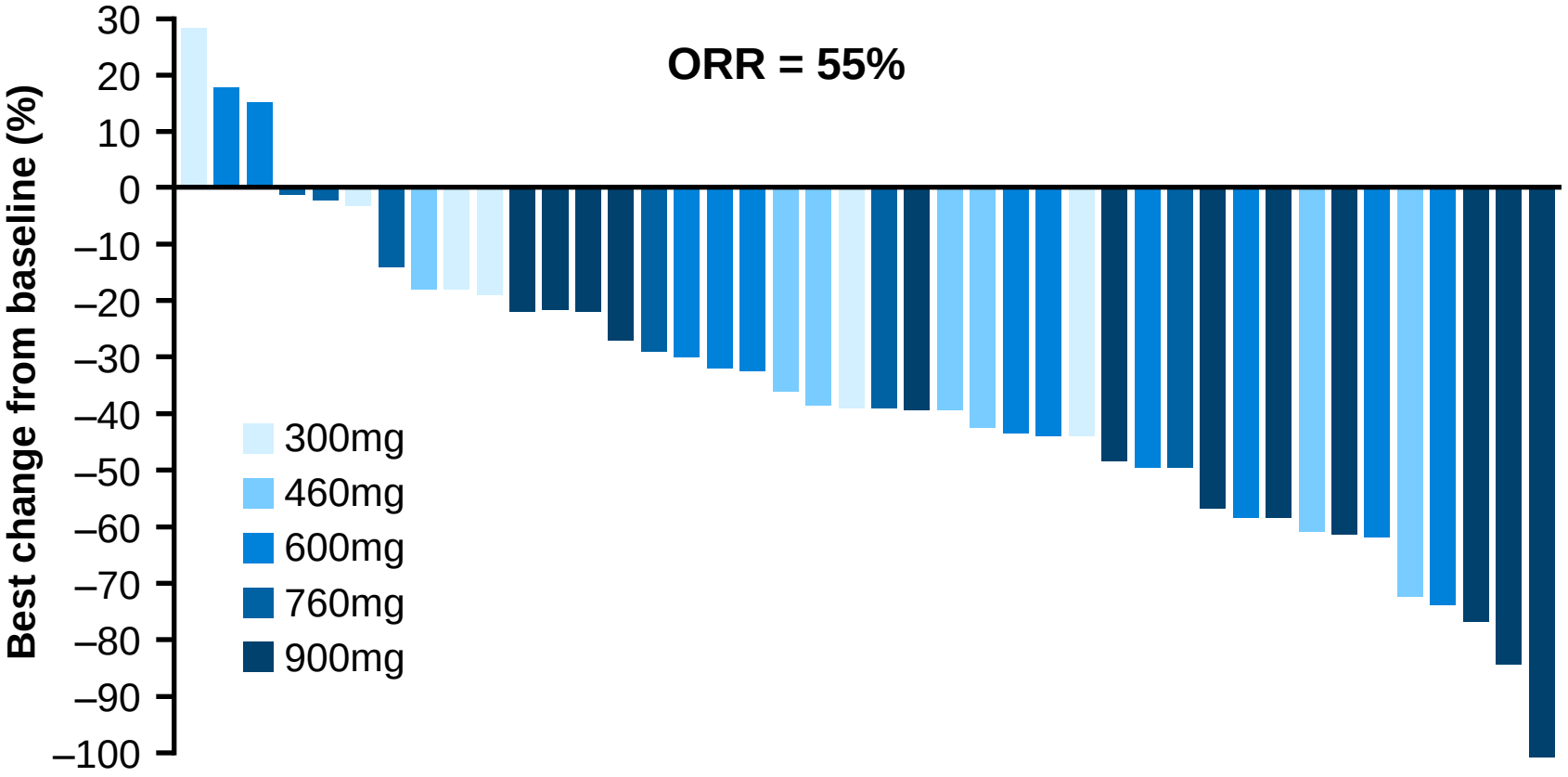
Felip E, *et al.* ECCO/ESMO 2014

Alectinib in ALK inhibitor naïve NSCLC (AF-001JP)



Seto T, et al. Lancet Oncol 2013

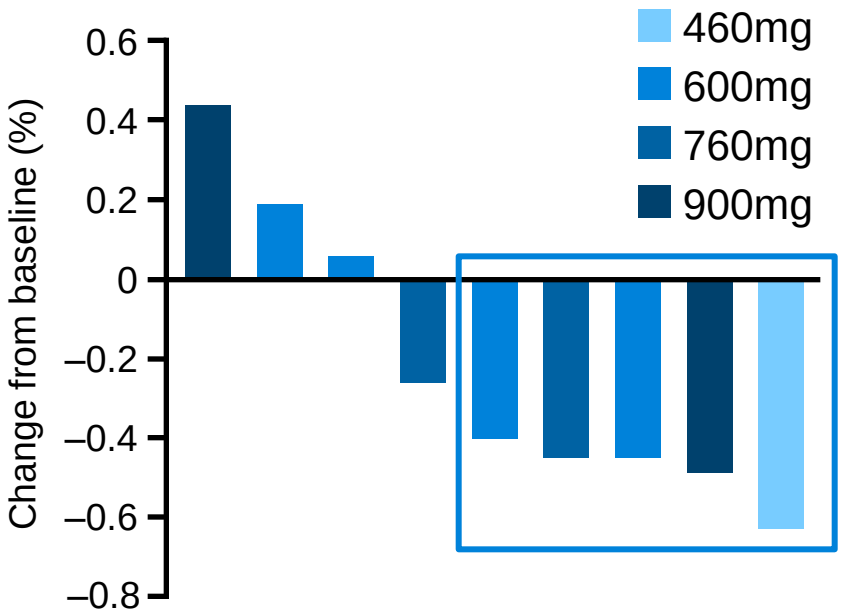
Alectinib activity in patients previously treated with crizotinib (Phase 1/2 trial: AF-002JG)



Gadgeel SM, *et al.* Lancet Oncol 2014

Alectinib activity against brain metastases (AF-002JG)

Patients with measurable brain metastases at baseline (n=9)

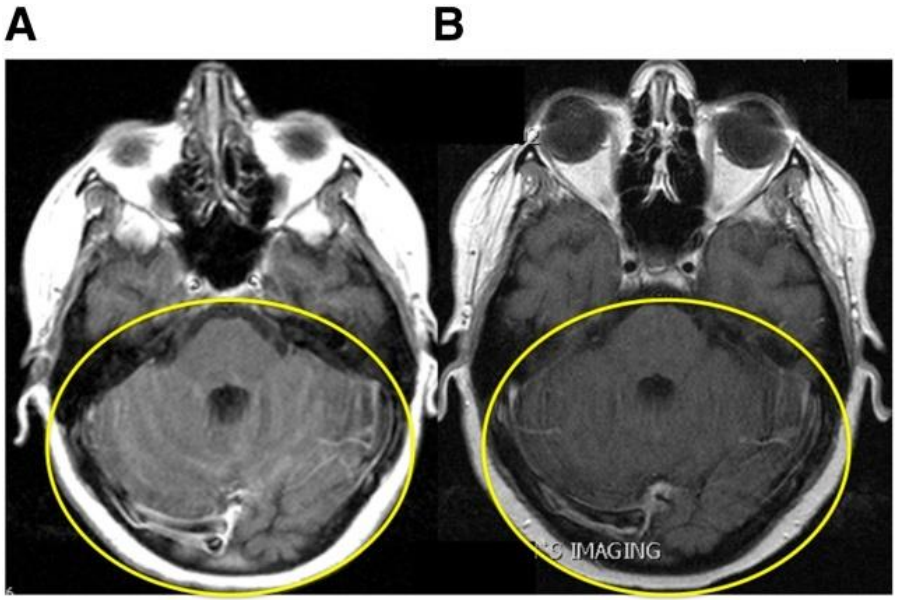


Best intracranial response, %	
OIRR	52
CR	29
PR	24
SD	38
PD	10

Patients with brain metastases at baseline (n=21)

Gadgeel SM, *et al.* Lancet Oncol 2014

A case of improved leptomeningeal carcinomatosis with alectinib



Ou SI, *et al.* Oncologist 2015

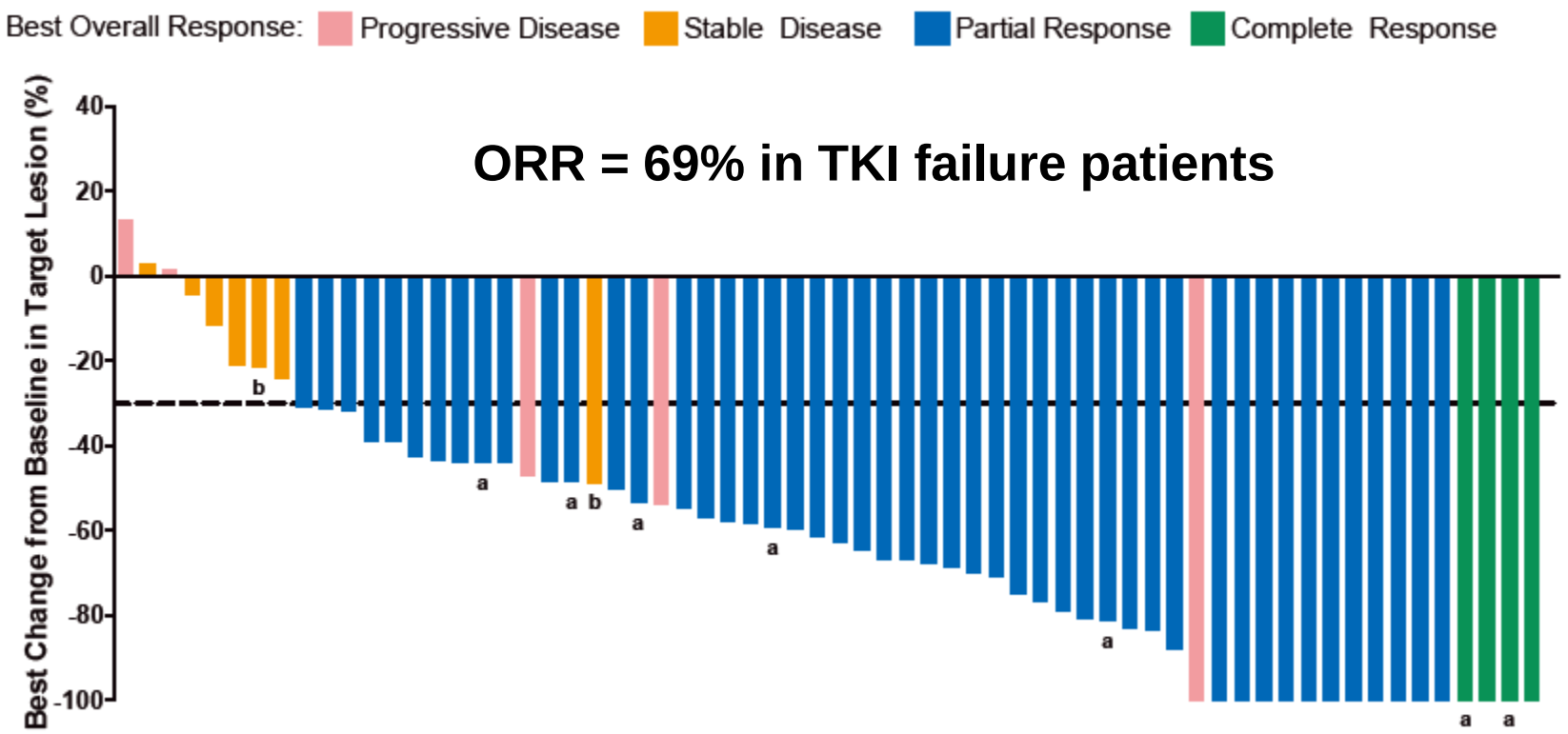
AF-002JG: summary of adverse events

Phase I portion of the study (dose-escalation)

	300–900mg BID (n=47)		
Selected AEs (>10%), %	**Gr 1–2**	**Gr 3**	**Gr 4**
Fatigue	**30**	**0**	**0**
Myalgia	**17**	**0**	**0**
Peripheral oedema	**15**	**2**	**0**
Increased blood CPK	**15**	**0**	**0**
Nausea	**15**	**0**	**0**
Increased ALT	**13**	**0**	**0**
Photosensitivity	**13**	**0**	**0**
Constipation	**11**	**0**	**0**
Rash	**9**	**2**	**0**

Gadgeel SM*, et al.* Lancet Oncol 2014

AP26113 in ALK+ NSCLC (N=64)

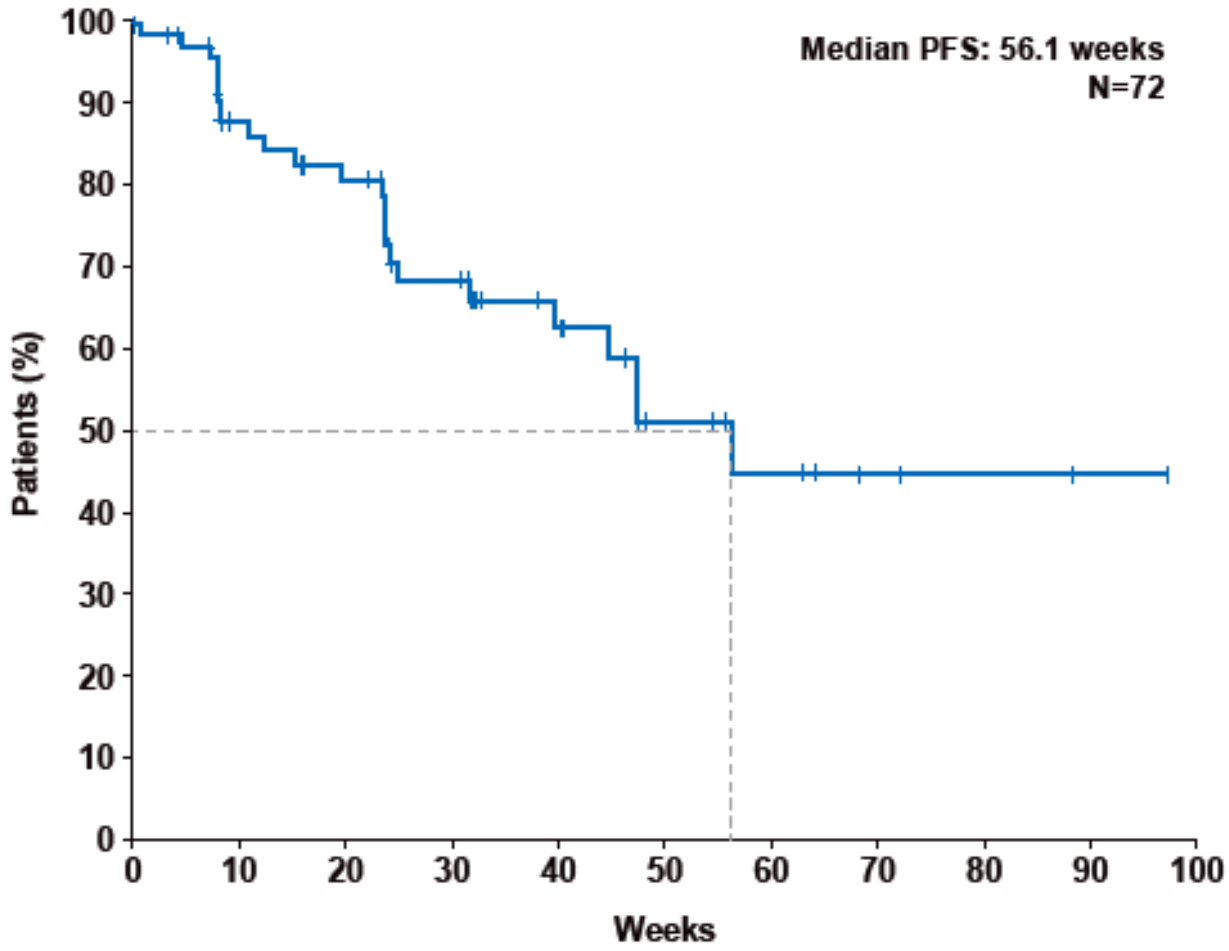


All patients received prior crizotinib unless indicated; Dose ranged from 30-360 mg/d

a. TKI-naïve, b. Received prior crizotinib and ceritinib

Gettinger *et al*. ESMO 2014

AP26113, PFS in ALK+ NSCLC



Gettinger *et al*. ESMO 2014

Questions to be answered

- Optimal sequencing of ALK inhibitors

  Crizotinib followed by 2nd generation ALK inhibitors *vs.*

  Upfront 2nd generation ALK inhibitors

- More comprehensive CNS efficacy data of 2nd generation ALK inhibitors

- Combination with other classes of drugs
  - Anti-PD-1/L1 inhibitors
  - HSP90 inhibitors, EGFR inhibitors, etc.

Thank you for your attention !