ALK-translocation and specific inhibition

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12 March 2014, Negrar

Recent advances in cancer biology

- **The genomic map are redesigning the tumor taxonomy by moving from a histology to a genetic based level**
- **Somatic genetic alterations are legitimate targets for therapy**
- **Tumor specific DNA alterations represent highly sensitive biomarkers for disease detection and monitoring**
- **Tumor genotyping allows to individualize treatments by matching patients with the best treatment for their tumors**

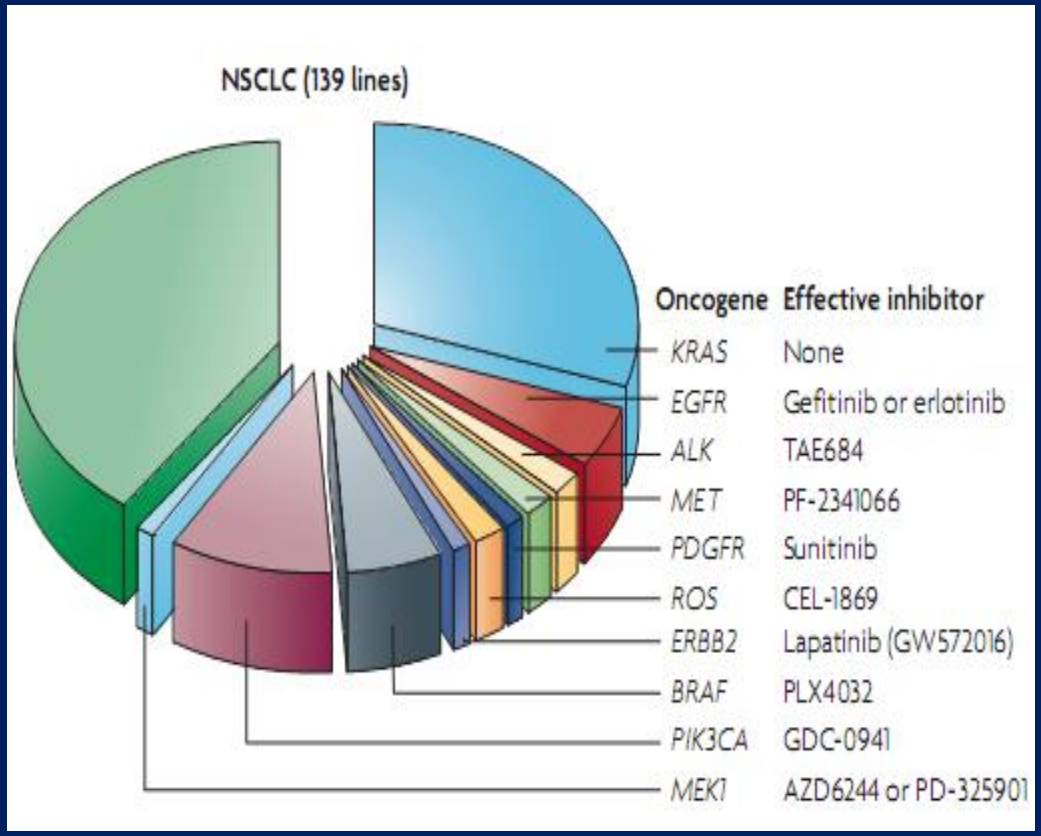
ONCOGENE ADDICTION

Some cancers that contain multiple genetic, epigenetic and chromosomal abnormalities are dependent to one or a few genes for both maintenance of the malignant phenotype and cell survival

- **ERB-B2 in breast cancer**
- **EGFR in NSCLC**
- **EML4-ALK in NSCLC**
- **ROS1 in NSCLC**
- **BRAF in NSCLC and melanoma-KIT in GIST**
- **RET in medullary thyroid cancer**
- **RET in NSCLC**
- **HIF/VEGF in renal cancer**

Weinstein Science, 2002

Molecular changes in NSCLC Cell Lines: Models for drug discovery



Sharma et al, 2010

Gene	Oncogenic activation	Frequency	
		Patients	Cell lines
EGFR	Deletion (ΔE746-A750), point mutation (L858R) and amplification	10–40%	5%
ALK	Translocation (EML4–ALK)	3–7%	2%
MET	Amplification	11%	2%
PDGFR	Amplification	13%	1%
ROS	Translocation (CD74–ROS)	1%	2%
ERBB2	Insertion	2–4%	1%
BRAF	Point mutation (exon 11)	3%	6%
PIK3CA	Point mutation	2%	10%
MEK1	Point mutation	0.50%	1%

Identification of Aberrant Forms of the Anaplastic Lymphoma Kinase

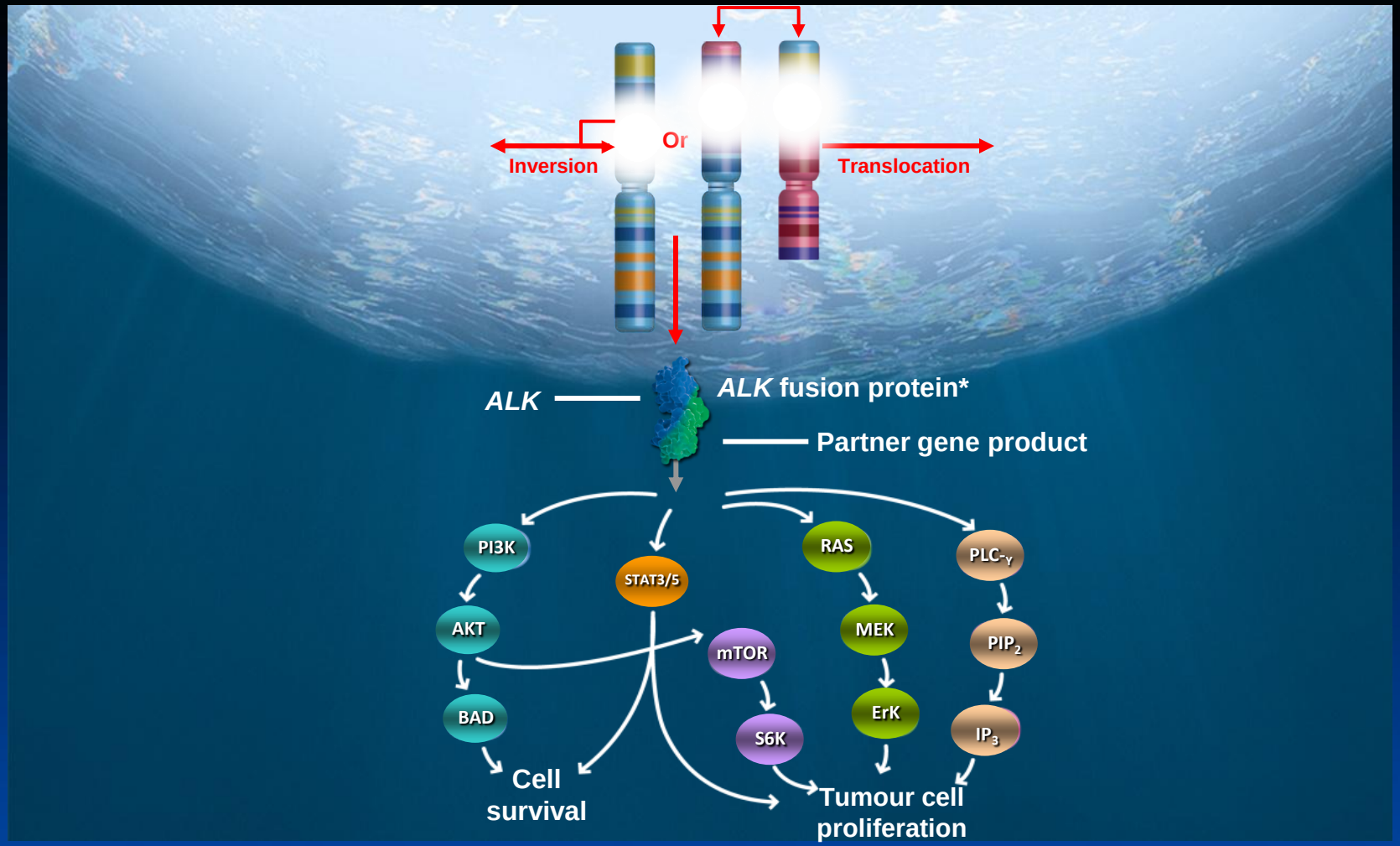
- Expressed in ALCL with t(2;5) chromosome rearrangement resulting in a fusion protein of two genes: the novel tyrosine kinase gene (*ALK*) and *NPM*[1]
- Other chromosome translocations involving the *ALK* locus have also been identified in several different human cancers [2,3,4]

Detection of phosphoprotein in an ALCL cell line in SCID mice compared with controls[1]

ALCL, anaplastic large-cell lymphoma; NPM, nucleophosmin; SCID, severe combined immunodeficiency.

[1]Shiota M & Mori S. *Leuk Lymphoma.* 1996;23:25–32. [2]Pulford K, et al. *J Cell Physiol.* 2004;199:330–58. [3]Palmer, et al. *Biochem J*. 2009;420:345–61. [4]Mano. *Cancer Sci.* 2008;99:2349–55.

ALK Pathway



*Subcellular localisation of the *ALK* fusion gene, while likely to occur in the cytoplasm, is not confirmed.[1,2]

BAD, BCL2-associated agonist of death; STAT3, signal transducer and activator of transcription 3; S6K, ribosome protein S6 kinase; ERK, extracellular signal-regulated kinase.

[1]Inamura K, et al. *J Thorac Oncol.* 2008;3:13–17. [2]Soda M, et al. *Proc Natl Acad Sci. U S A.* 2008;105:19893–97.
Figure based on: Chiarle R, et al. *Nat Rev Cancer.* 2008;8(1):11–23. Mossé YP, et al. *Clin Cancer Res.* 2009;15(18):5609–14; and Pfizer Inc, data on file.

Clinical Features of NSCLC Patients with EML4/ALK Fusion*

EML4/ALK+	Med. Age	Male	Female	Never** Smoker	Smoker†	Adeno‡	Non-Adeno
129/3933 (3.3%)	59 (29-79)	56/1451 3.9%	51/1017 5.0%	83/762 10.8%	36/1534 2.3%	118/2168 5.4%	8/870 0.9%

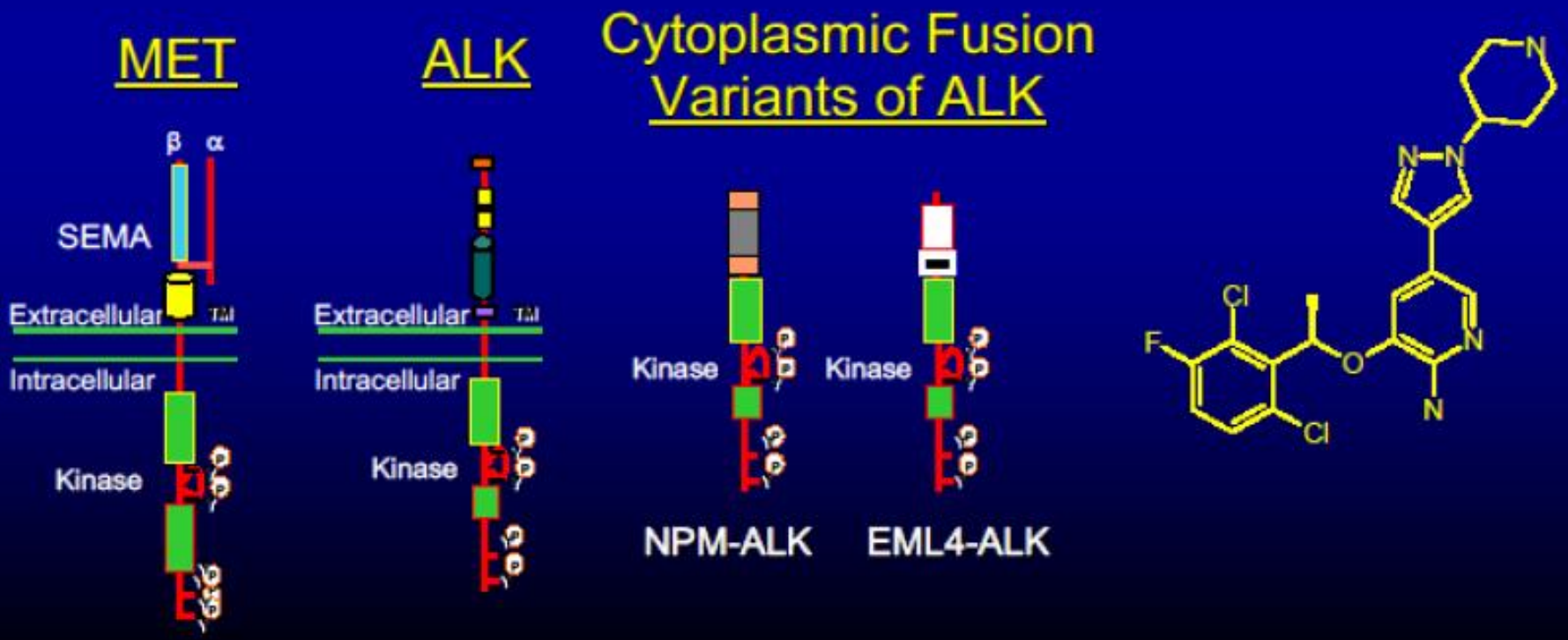
*From 14 literature studies. **includes never and light smokers. †includes current and former smokers. ‡includes all subtypes and adenosquamous

Conclusions:

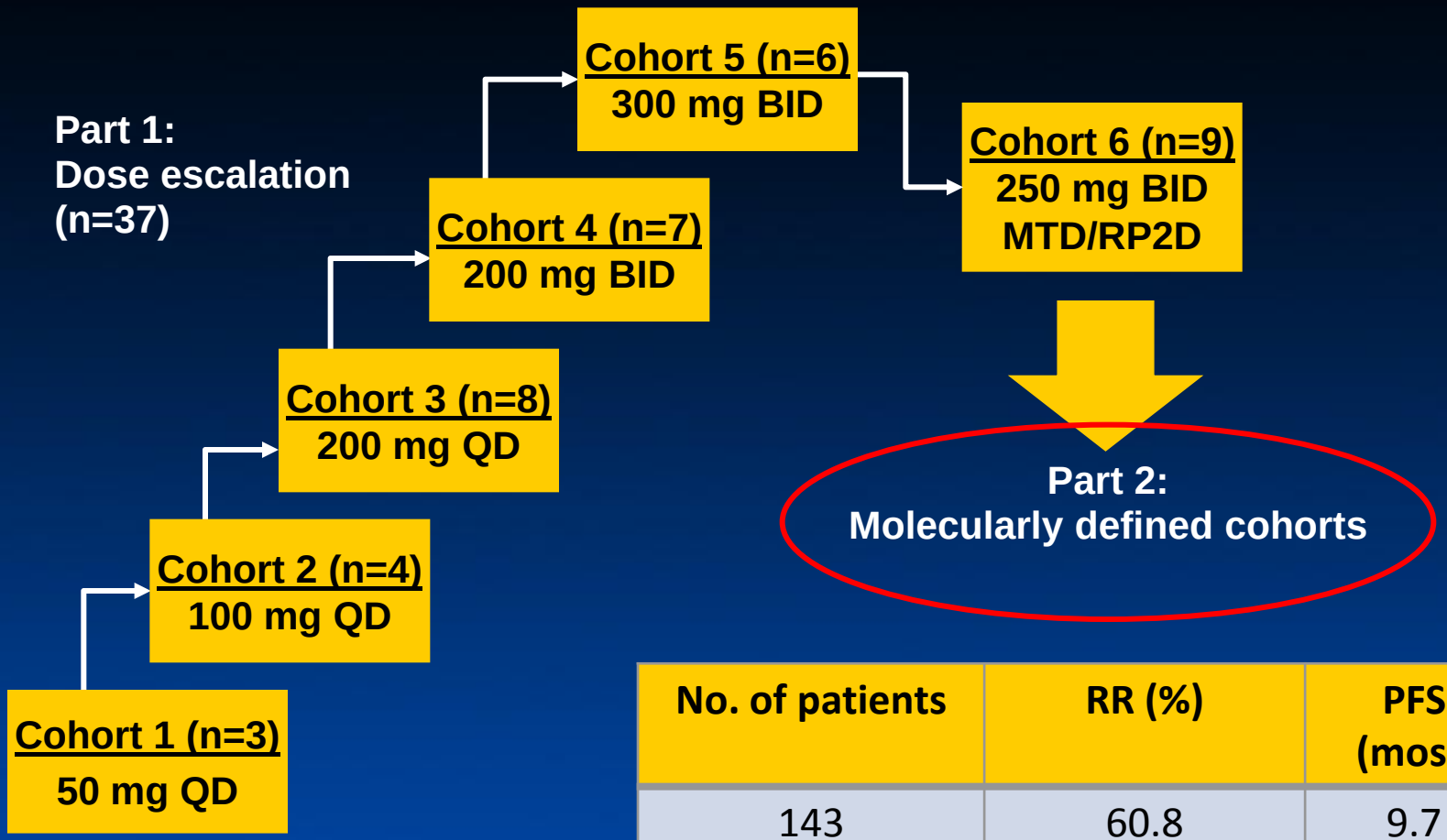
- Median age is low but cannot order based on age.
- Frequency equivalent by sex, ethnicity and stage.
- More common in adenocarcinoma histology but occurs in squamous.
- More common in never/light smokers but may occur in smokers.

Crizotinib, PF-02341066

Potent & selective ATP competitive oral inhibitor of MET and ALK kinases and their oncogenic variants



Crizotinib: First-in-human/Patient Trial (A8081001)



No. of patients	RR (%)	PFS (mos.)
143	60.8	9.7

BID, twice daily; QD, once daily; MTD, maximum tolerated dose; RP2D, randomised phase 2 dose.

Modified from: Tan, et al. *J Clin Oncol*. 2010;28:15S. Abstract 2596.

Phase II/III clinical development of Crizotinib for ALK+ NSCLC

Study	Phase (planned accrual)	Histology	Line of therapy	Study design	Primary endpoint
PROFILE 1014	III (334 pts)	Non-squamous	1st	Platinum*-Pemetrexed vs Crizotinib	PFS≠
PROFILE 1007	III (318 pts)	NSCLC	2nd	2nd line chemo** vs Crizotinib	PFS
PROFILE 1005	II (400 pts)	NSCLC	3rd or more∞	Crizotinib monotherapy	ORR

ORR = overall response rate; PFS = progression-free survival; pts = patients

*Cisplatin or carboplatin according to investigator's choice
≠Cross-over to crizotinib allowed at PD in the standard arm
**Pemetrexed or docetaxel; prior chemo must have been platinum-based chemotherapy
∞May have received Pemetrexed or Docetaxel from previous phase III PROFILE 1007 trial and discontinued treatment due to RECIST-defined progression

PROFILE 1005: patients characteristics

Characteristic	Crizotinib 250 mg (mature population) (n = 261)	Crizotinib 250 mg (overall population) (n = 901)
Age, years		
Median (range)	52.0 (24.0-82.0)	53.0 (>18-83.0)
Gender, n (%)		
Female	142 (54.4)	514 (57.0)
Ethnicity, n (%)		
Caucasian	154 (59.0)	485 (53.8)
Black	8 (3.1)	18 (2.0)
Asian	94 (36.0)	379 (42.1)
Other	5 (1.9)	19 (2.1)
Baseline ECOG PS, n (%)		
0	68 (26.1)	225 (25.0)
1	148 (56.7)	511 (56.7)
2	42 (16.1)	134 (14.9)
3	3 (1.1)	31 (3.4)
Histology, n (%)		
Adenocarcinoma	245 (93.9)	826 (91.7)
Smoking classification, n (%)		
Never smoker	176 (67.4)	592 (65.7)
Former smoker	73 (28.0)	271 (30.1)
Smoker	12 (4.6)	38 (4.2)
Prior therapy for locally advanced/metastatic disease, n (%)		
0	0 (0)	3 (<1.0) *
1	32 (12.3)	248 (27.5)
2	91 (34.9)	299 (33.2)
≥3	138 (52.8	351 (39.0)

*Three patients not eligible due to prior adjuvant treatment only

Kim, et al. ASCO 2012

PROFILE 1005: updated activity results

Variable	Crizotinib (N=259)[a] n (%)
ORR (95% CI)	**155 (59.8) (53.6, 65.9)**
CR	4 (1.5)
PR	151 (58.3)
SD	69 (26.6)
Duration of response, weeks median (95%CI)[b]	45.6 (35.3-53.6)
Time to response, weeks median (range)	6.1 (4.9-49.1)
Stable disease duration, months 0-<3 3-<6 6-<9 9-<12 ≥12	 12 (17.4) 29 (42.0) 11 (15.9) 7 (10.1) 10 (14.5)
PFS, median (95%CI)[b,c]	**8.1 month (6.8-9.7)**

[a]Response-evaluable population (2 pts were not evaluable due to inadequate baseline assessment); [b]Kaplan-Meier estimate; [c]PFS mature population includes 261 patients

Kim, et al. ASCO 2012

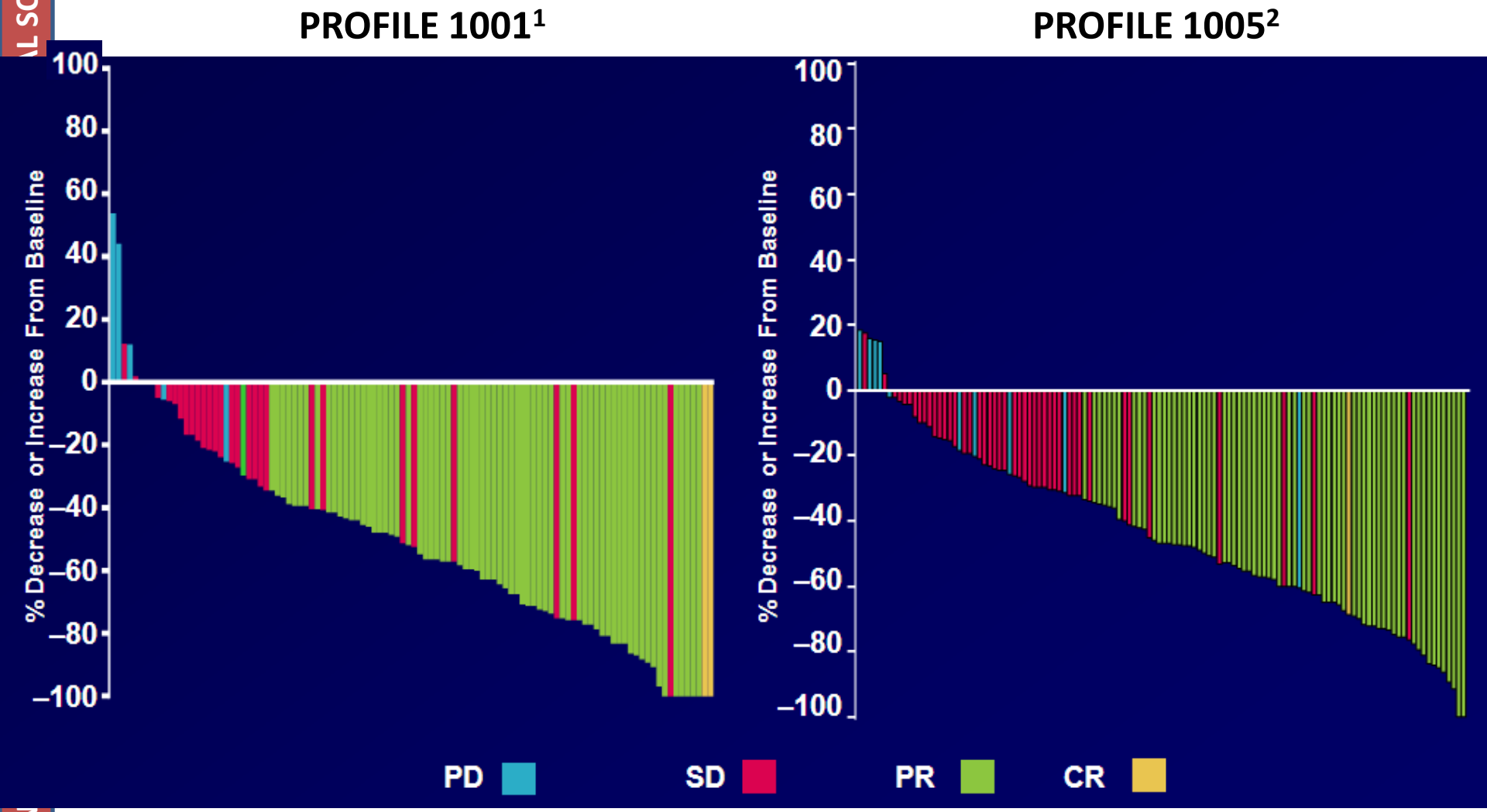
PROFILE 1005: treatment-related AEs in ≥ 10% of patients

	Crizotinib 250 mg (mature population) (n = 261) N (%)		Crizotinib 250 mg (overall population) (n = 901) N (%)	
Adverse event	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**
Any AE	245 (93.9)	76 (29.0)	827 (91.8)	41 (4.5)
Nausea	148 (56.7)	1 (0.4)	423 (46.9)	7 (0.8)
Vomiting	116 (44.4)	2 (0.8)	352 (39.1)	7 (0.8)
Vision disorder*	154 (59.0)	0 (0)	468 (51.9)	1 (0.1)
Diarrhea	106 (40.6)	2 (0.8)	369 (41.0)	9 (1.0)
Constipation	86 (33.0)	0 (0)	249 (27.6)	1 (0.1)
Peripheral edema	72 (27.6)	0 (0)	211 (23.4)	3 (0.3)
Fatigue	64 (24.5)	4 (1.5)	163 (18.1)	18 (1.9)
Decreased appetite	59 (22.6)	0 (0)	167 (18.5)	2 (0.2)
Alanine aminotransf. increased	45 (17.2)	19 (7.2)	146 (16.2)	36 (3.9)
Dysgeusia	43 (16.5)	0 (0)	149 (16.5)	0 (0)
Dizziness	40 (15.3)	0 (0)	95 (10.5)	0 (0)
Neutropenia	36 (13.8)	22 (8.4)	84 (9.3)	50 (5.5)
Aspartate aminotransf. increased	33 (12.6)	5 (1.9)	106 (11.8)	12 (1.3)

*Includes visual impairment, photopsia, vision blurred, vitreous floaters, photophobia and diplopia

Kim, et al. ASCO 2012

Tumor responses to crizotinib by patient



1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

Crizotinib beyond disease progression

Table 2. Clinical and treatment experience in patients with PD.

	All PD (n=229)	Crizotinib beyond PD (n=138)
Best response to crizotinib before PD, n (%)		
CR	3 (1)	3 (2)
PR	136 (59)	93 (67)
SD	66 (29)	36 (26)
PD	24 (10)	6 (4)
Not evaluable	0	0
Early death/indeterminate	0	0
Time to objective response,[a] n (%)[b]		
≤8 weeks	97 (70)	63 (66)
>8 weeks	42 (30)	33 (34)
Duration of crizotinib treatment after PD (weeks), median (95% CI)	–	20 (17–29)
Crizotinib as 1st-line treatment (n=6)	–	55 (37–70)
Crizotinib as 2nd-line treatment (n=28)	–	21 (11–31)
Crizotinib as ≥3rd-line treatment (n=104)	–	19 (15–24)

[a]CR or PR.

[b]Based on number of responders.

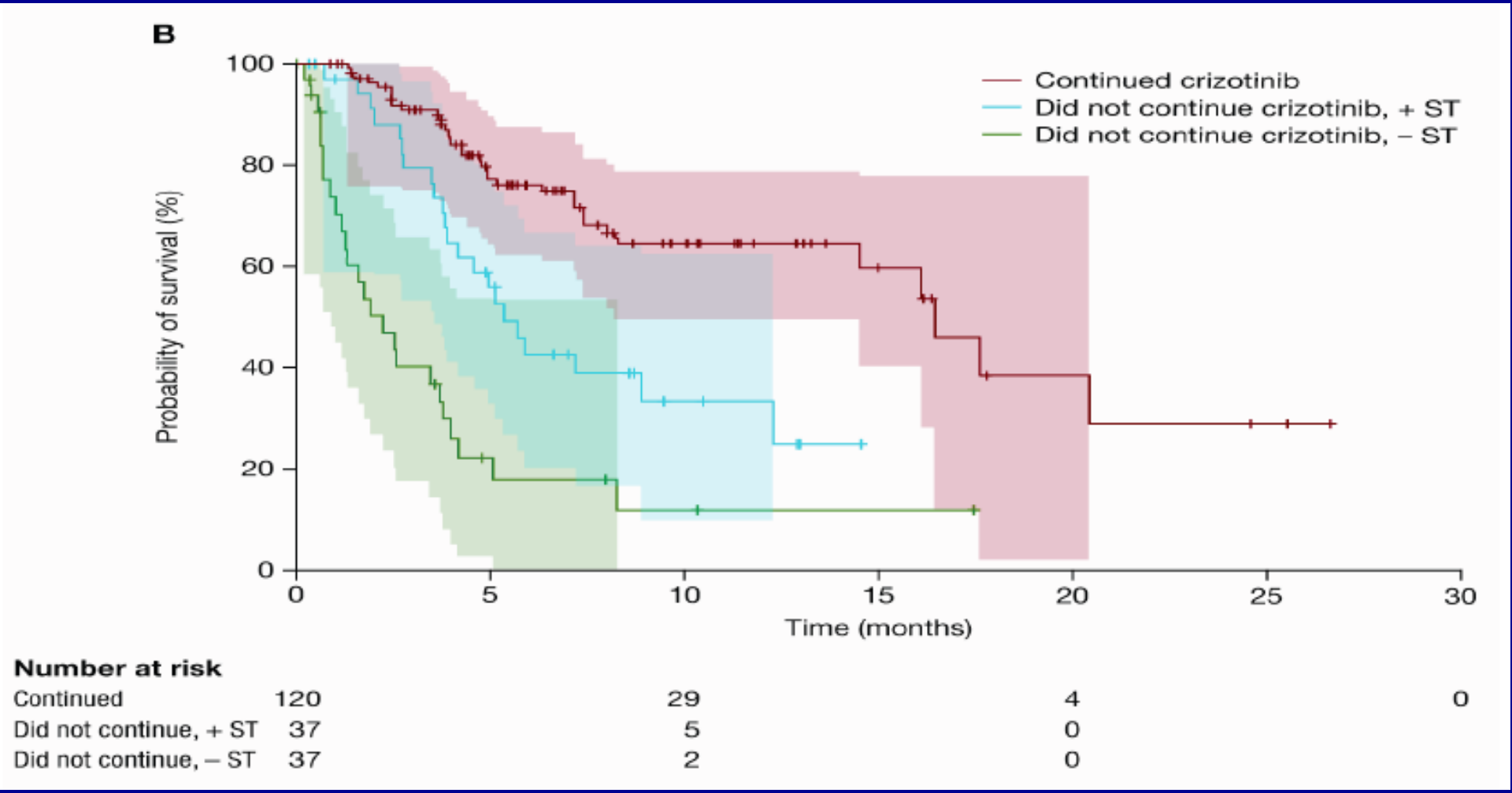
Most common sites of PD in patients continuing crizotinib beyond PD

Organ sites in which new lesions developed and/or non-target lesions progressed in the Crizotinib-Beyond-PD group	
Organ	Patients with new lesions and/or non-target lesions (n=115) No. of patients (%)[a]
Brain	53 (46)
Liver	30 (26)
Lung	23 (20)
Bone	20 (17)
Pleural effusion	16 (14)
Lymph node	12 (10)
Adrenal	1 (1)
Chest wall	1 (1)
Pelvis	1 (1)
Soft tissue	1 (1)
Spine	1 (1)
Other	21 (18)

[a]Excluding patients with target lesions only: patients could be counted more than once across organ sites

Otterson, et al. ASCO 2012

Crizotinib beyond progression



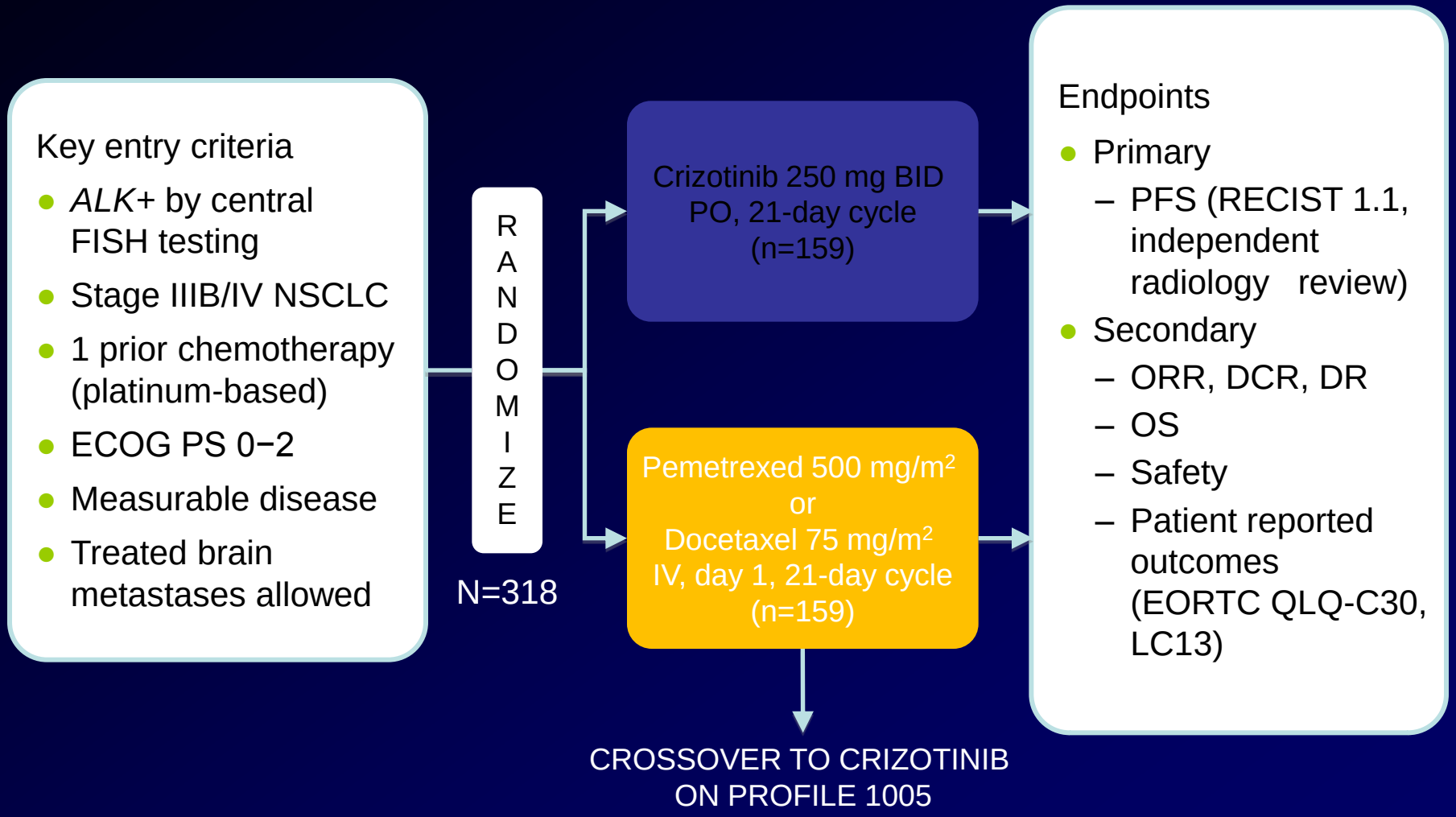
Ou, et al. IASLC 2013

Abstract 2862

Phase III Study of Crizotinib vs Pemetrexed or Docetaxel Chemotherapy in Patients with Advanced *ALK*-Positive NSCLC (PROFILE 1007)

Alice T. Shaw, Dong-Wan Kim, Kazuhiko Nakagawa, Takashi Seto, Lucio Crinó, Myung-Ju Ahn, Tommaso de Pas, Benjamin Besse, Benjamin J. Solomon, Fiona Blackhall, Yi-Long Wu, Michael Thomas, Kenneth J. O'Byrne, Denis Moro-Sibilot, D. Ross Camidge, Vera Hirsh, Tony Mok, Vanessa Tassell, Anna Polli, Pasi Jänne on behalf of all PROFILE 1007 investigators

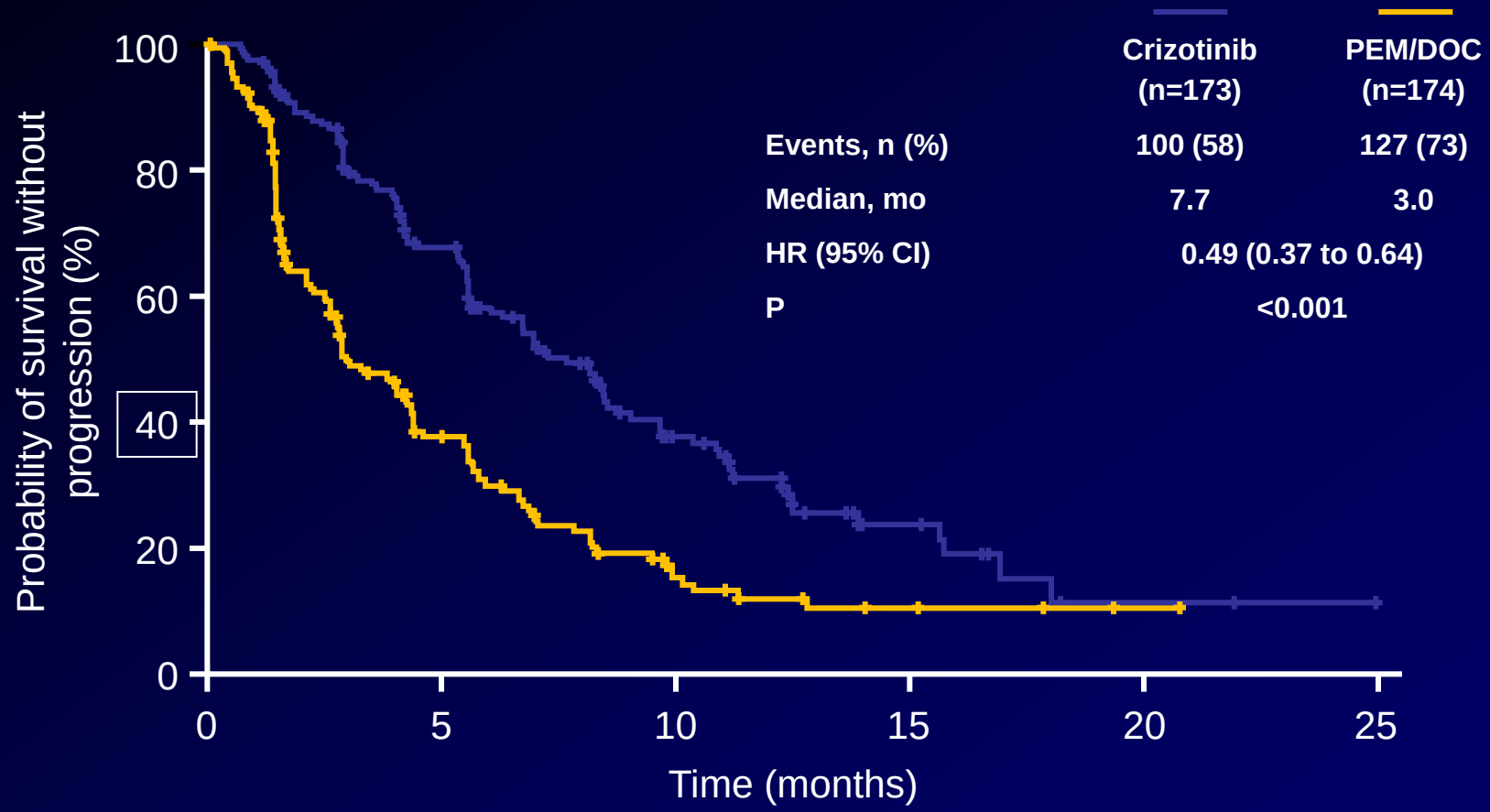
Study Design



[a]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

PROFILE 1007: NCT00932893

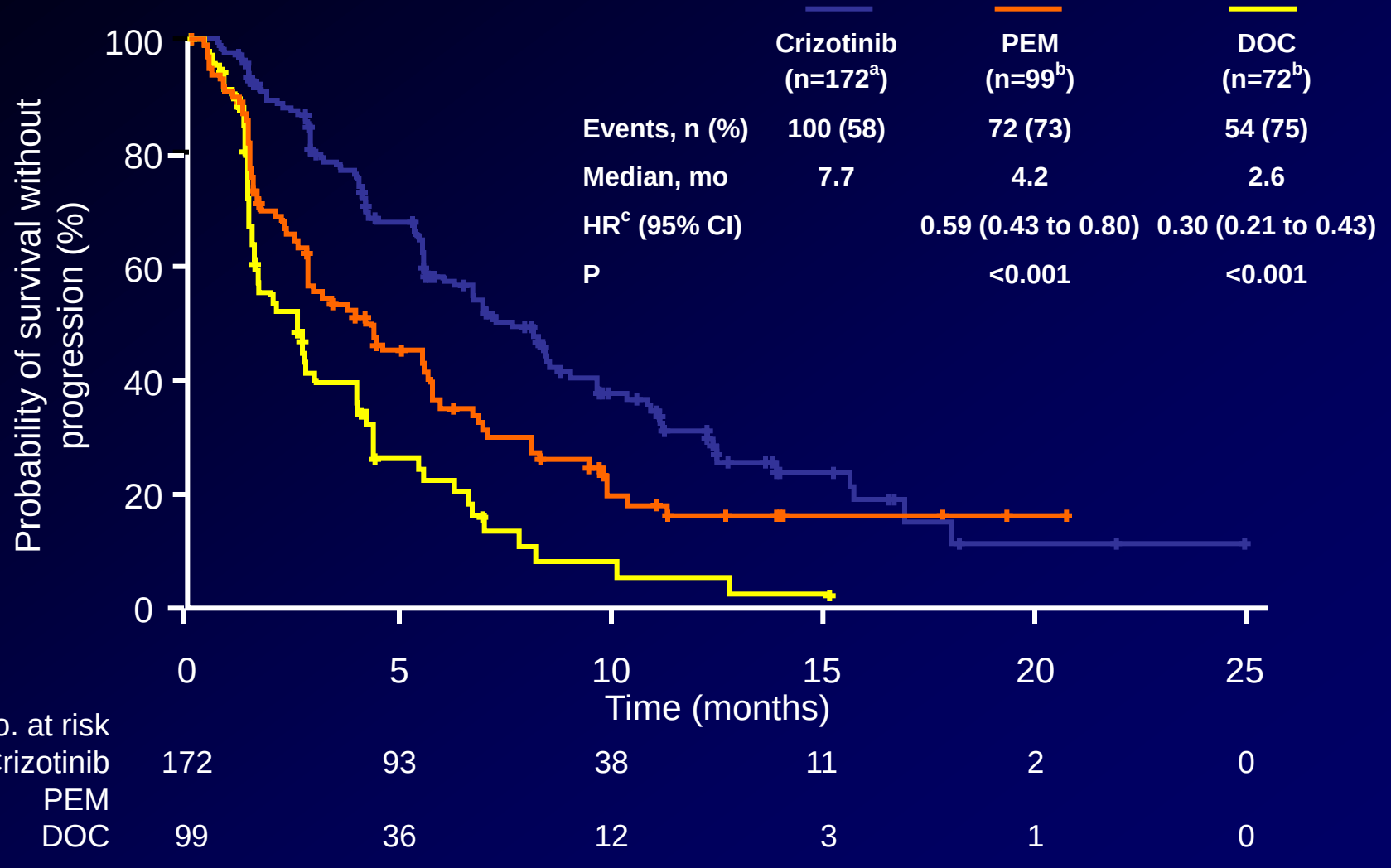
Primary Endpoint: PFS by Independent Radiologic Review (ITT Population)



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

PEM/DOC, pemetrexed/docetaxel

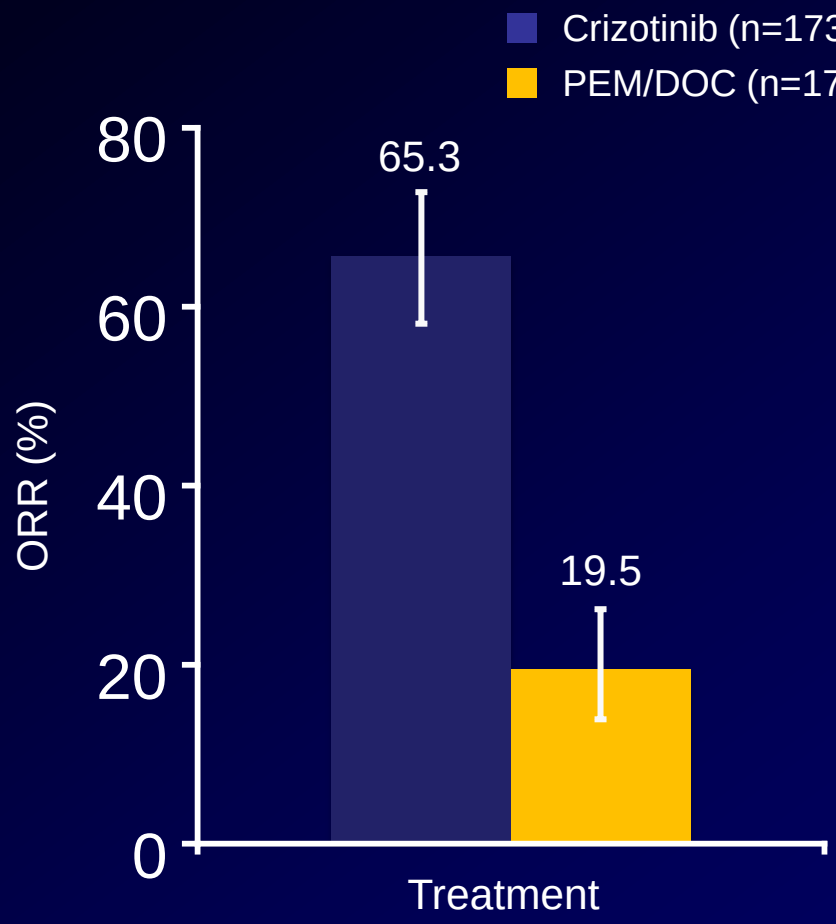
PFS of Crizotinib vs Pemetrexed or Docetaxel

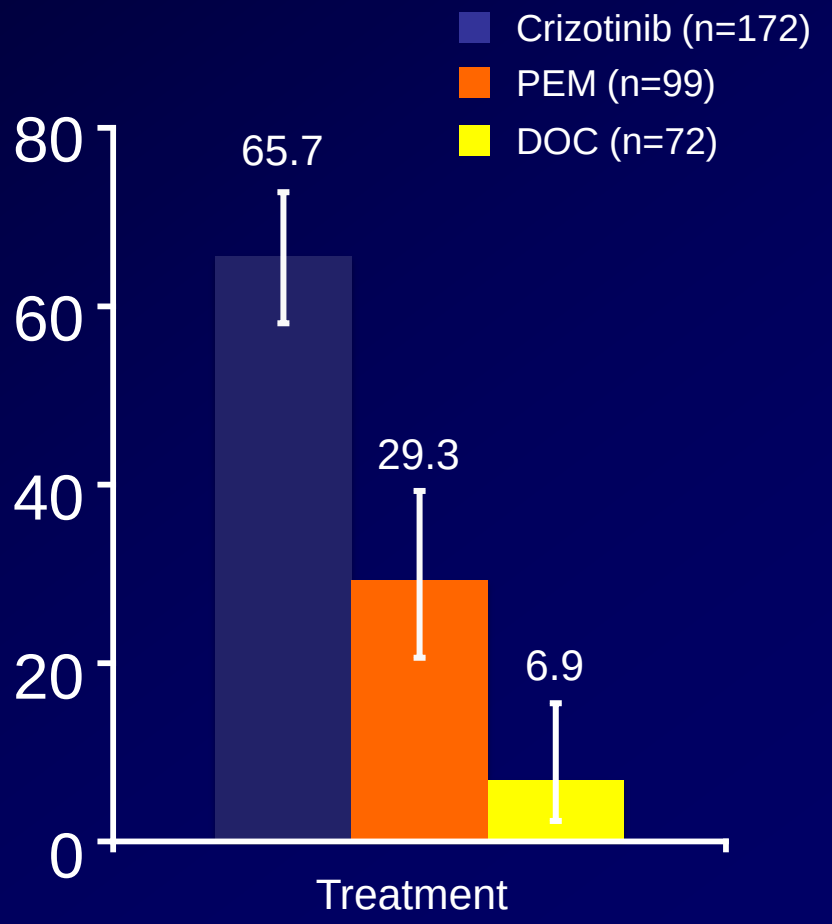


[a]Excludes 1 patient who did not receive study treatment; [b]excludes 3 patients in chemotherapy arm who did not receive study treatment; [c]vs crizotinib

ORR[a] by Independent Radiologic Review

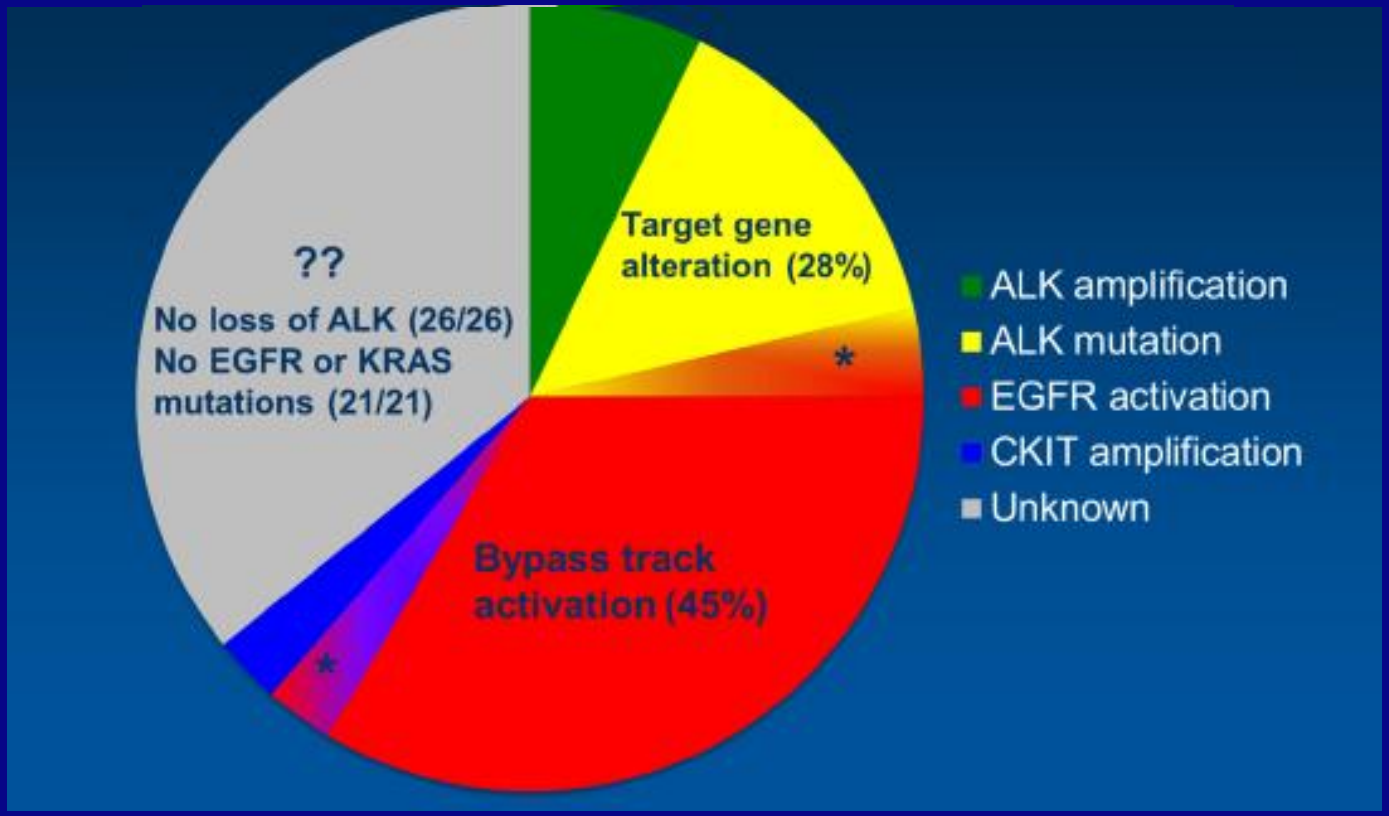
ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.001





[a]RECIST v1.1

Mechanisms of crizotinib resistance



2nd generation ALK-inhibitors in clinical development

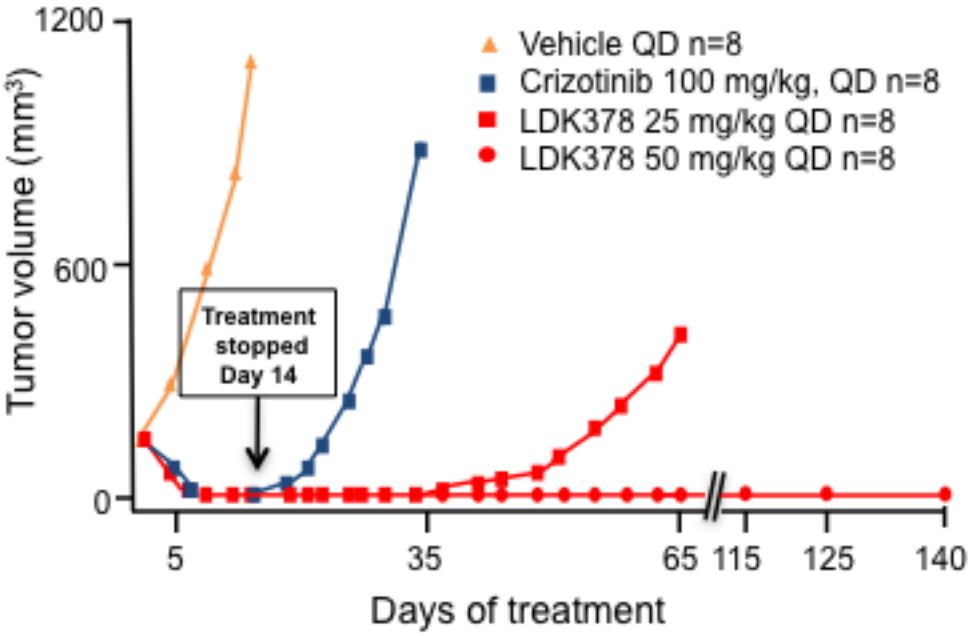
Drug	Inhibition of secondary L1196M 'gatekeeper' mutation	Company	Clinical stage
AP-26113	Yes	Ariad Pharmaceuticals	Phase I/II
LDK378	Yes	Novartis	Phase II/III
Alectinib	Yes	Chugai Pharmaceuticals	Phase I/II
TSR-011	Yes	Tesaro	Phase I
NMS-E628	Yes	Nerviano Medical	Phase I
ASP-3026	Yes	Astellas	Phase I
X-376 and -396	Yes	Xcovery	Phase I
CEP-28122	Yes	Cephalon	Preclinical

Beyond crizotinib: LDK378

- LDK378 is a potent and selective ALK inhibitor
- Potent activity in enzymatic and cell based assays

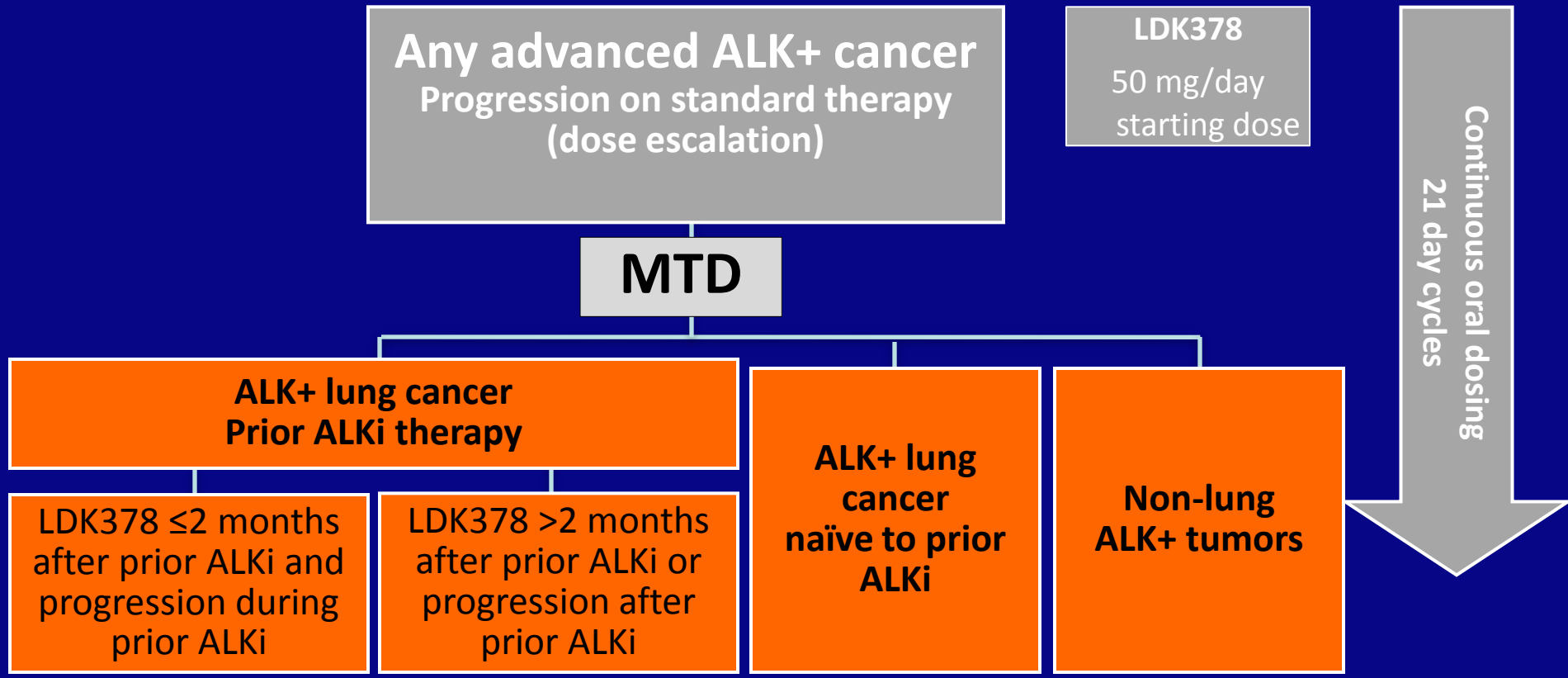
Assay	LDK378 IC_{50} (μM)	Crizotinib IC_{50} (μM)
Enzymatic		
ALK	0.00015	0.003
IGF1R	0.008	0.4
MET	3.2	0.008
Cell-based		
ALK	0.027	0.11
MET	1.3	0.028

- LDK378 provides durable responses in EML4-ALK xenografts, including those expressing a crizotinib-resistant mutation (C1156Y)



Shaw, et al. ESMO 2012

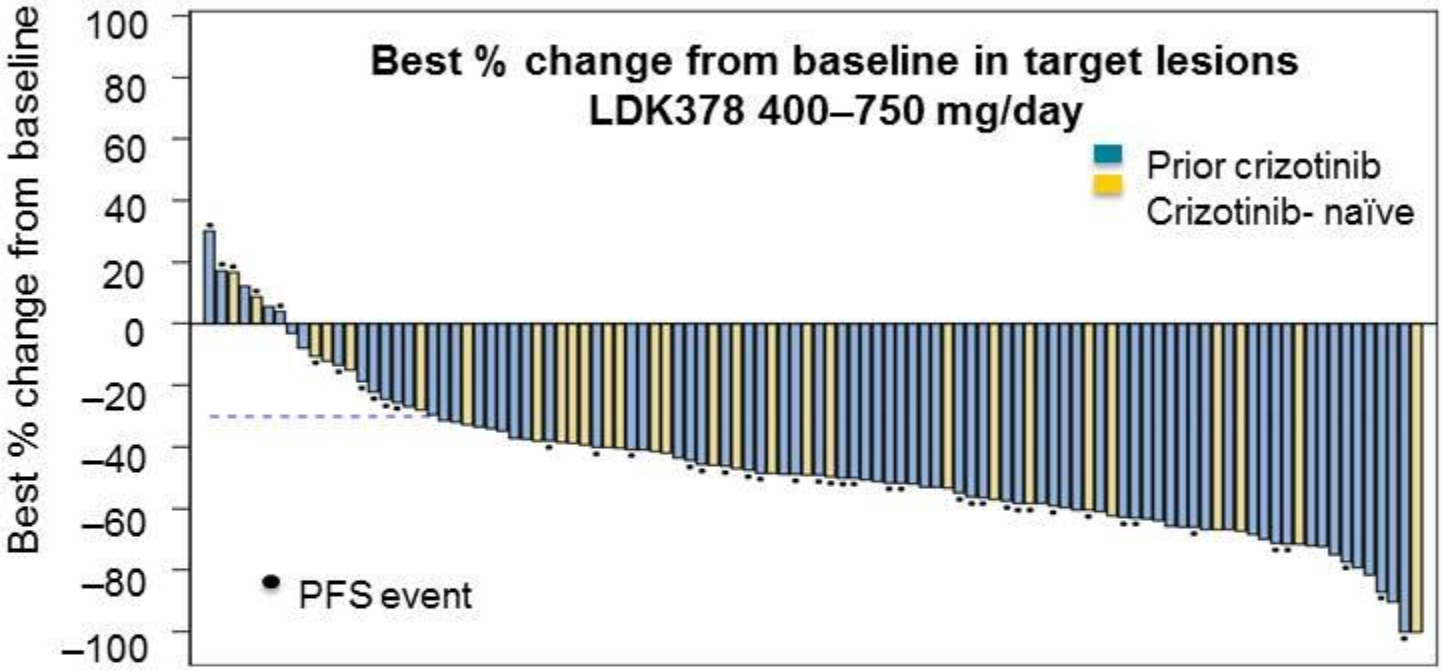
Phase I study of LDK378 in advanced malignancies



- **Primary objective**: determination of MTD
- **Secondary objectives**: safety, pharmacokinetics and preliminary antitumor activity

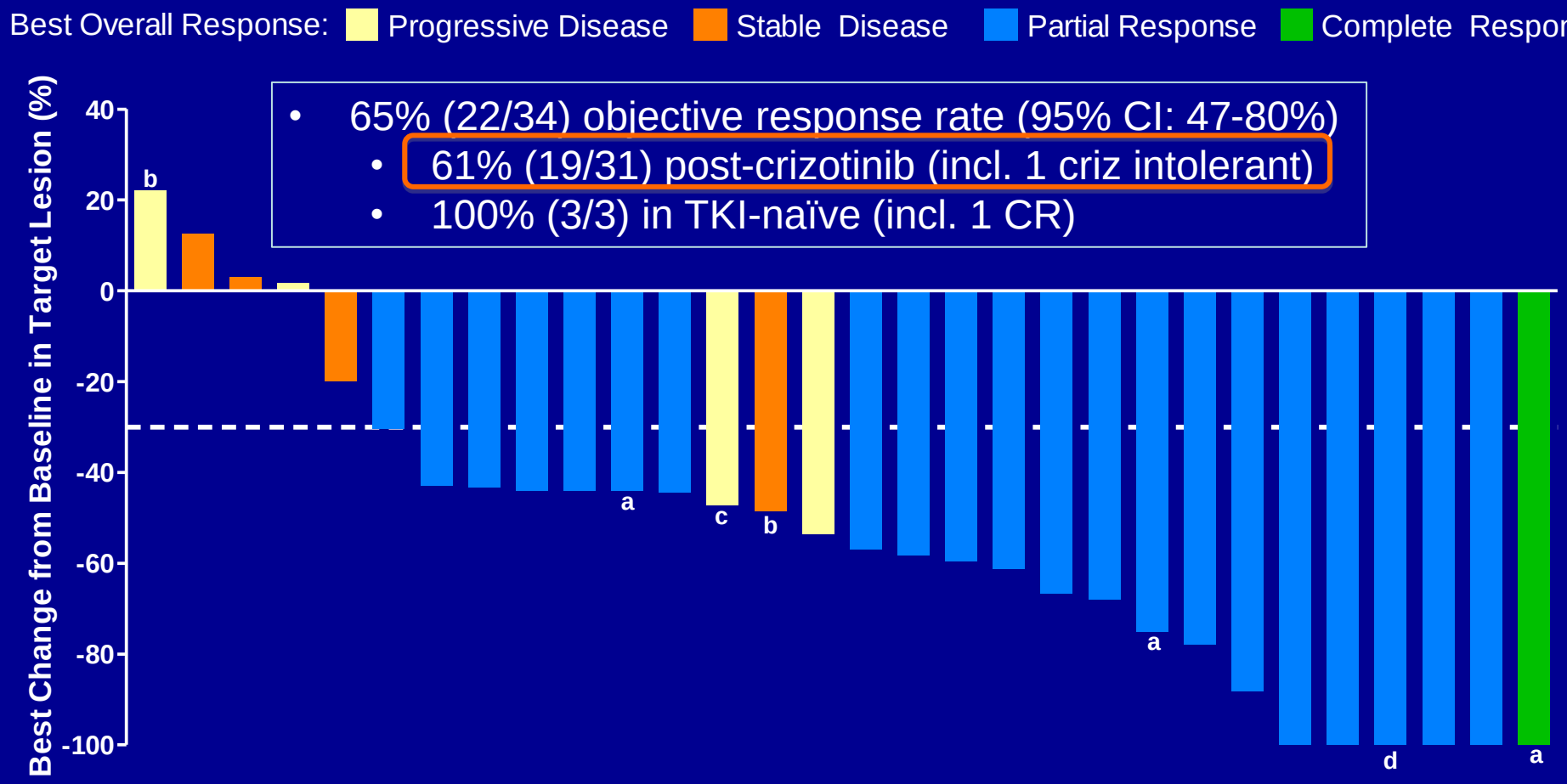
Shaw, et al. ESMO 2012

Tumor responses to the ALK inhibitor, LDK378, in ALK+ lung cancer



ORR 57% in crizotinib-treated patients
ORR 60% in crizotinib-naïve patients
Median PFS 8.6 months (95% CI 5.7–9.9)

AP26113 in ALK+ NSCLCs (N=34)



- 65% (22/34) objective response rate (95% CI: 47-80%)
  - 61% (19/31) post-crizotinib (incl. 1 criz intolerant)
  - 100% (3/3) in TKI-naïve (incl. 1 CR)

- Response duration 8+ to 40+ weeks
  - 14 confirmed, 4 awaiting confirmation, 4 not confirmed

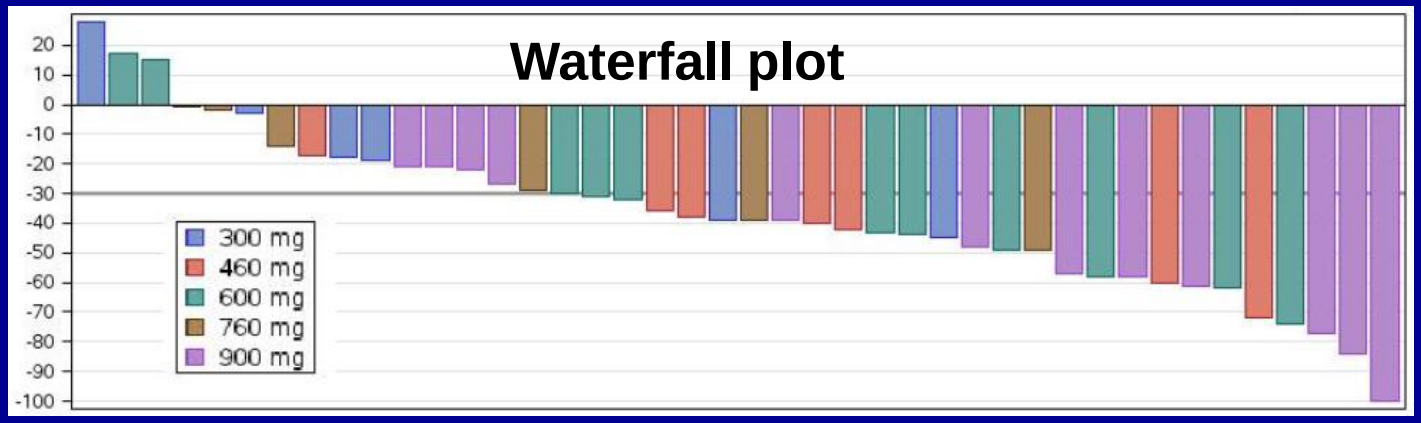
All patients received prior crizotinib unless otherwise indicated; Doses ranged from 60-240 mg/d (23 pts ≥180mg/d); [a]TKI-naïve; [b]Received prior crizotinib and LDK378; [c]PD by RECIST 1.1 due to 2nd primary tumor of melanoma; [d]Crizotinib-intolerant

Camidge, et al. IASLC 2013

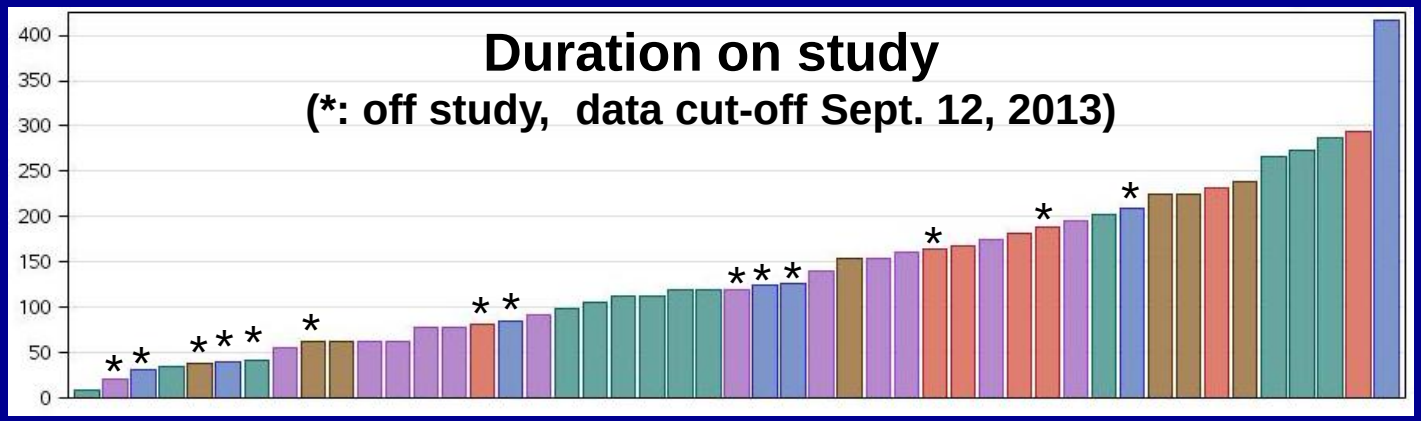
Alectinib in crizotinib-refractory patients

Overall RR 54.5% across all cohorts for all patients

% tumor shrinkage



Days on study



Overall RR 59.5% for cohorts of 460 mg dose or higher

24 of the 47 patients received the drug for 120 days or longer

Gadgeel, et al. IASLC 2013

RR with 2nd generation ALK-inhibitors in Crizotinib-naïve patients

Author	Drug	No. of pts	RR (%)
Camidge (ECCO 2013)	AP26113*	3	100
Shaw (ASCO 2013)	LDK378**	35	60
Seto (Lancet Oncol 2013)	Alectinib***	46	93.5

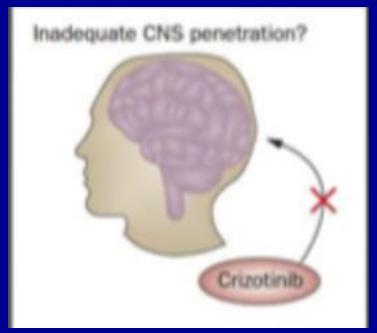
*60-300 mg/d
**400-750 mg/d
***300 mg x 2/d; Asiatic (Japanese) patients

The problem of CNS progression to Crizotinib in ALK+ patients

- 13/28 (46%) patients at U. of Colorado with first progression in CNS

  - 2/13 had synchronous systemic progression

  Weickardt et al. JTO 2013

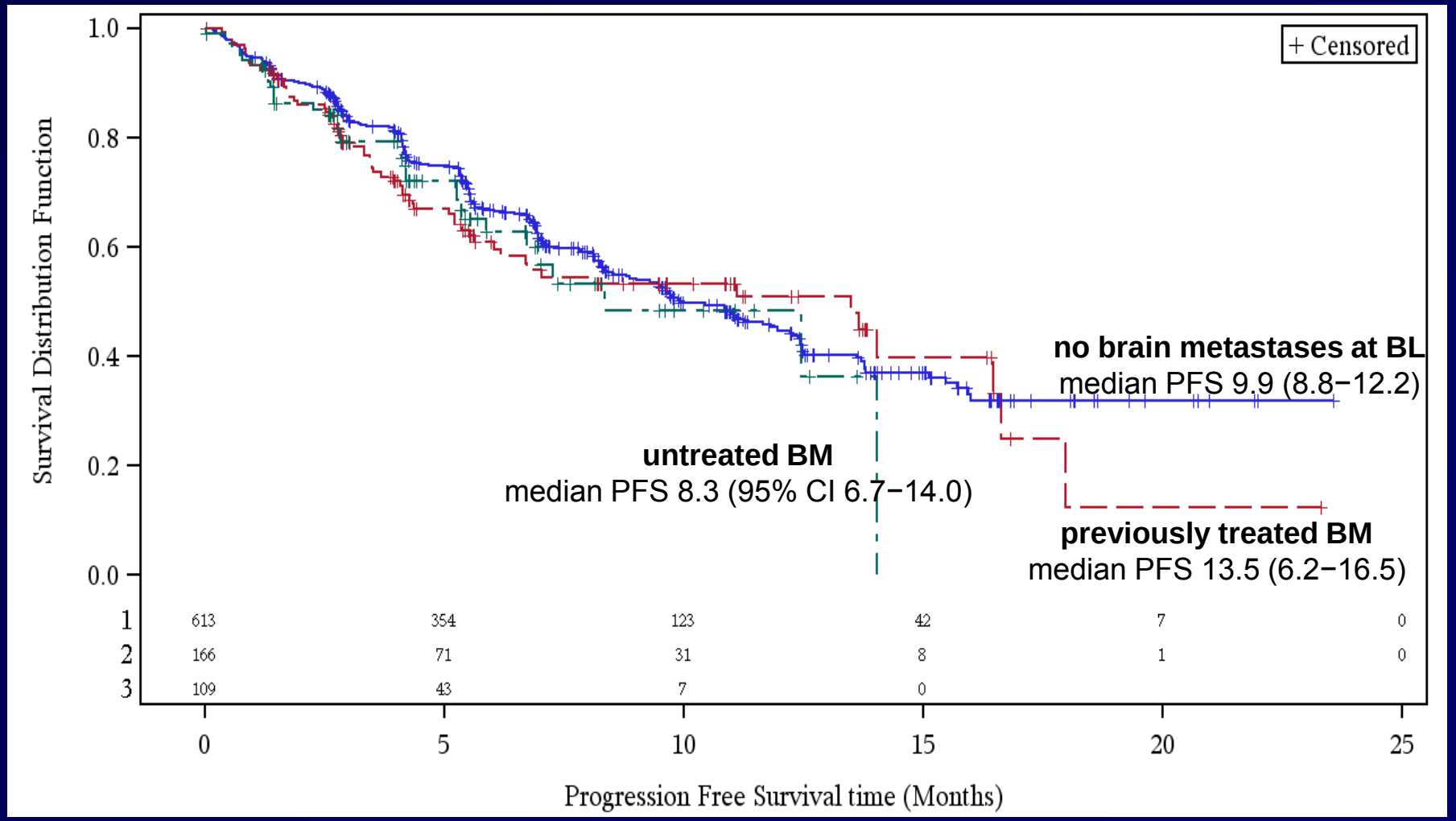


- Decreased CSF:plasma (0.0026) ratio suggestive of pharmacological failure of Crizotinib

  Costa et al. JCO 2011

Systemic progression-free survival by presence or absence of brain metastases (BM) at baseline (BL)

The presence of BM at BL does not significantly affect systemic response to crizotinib

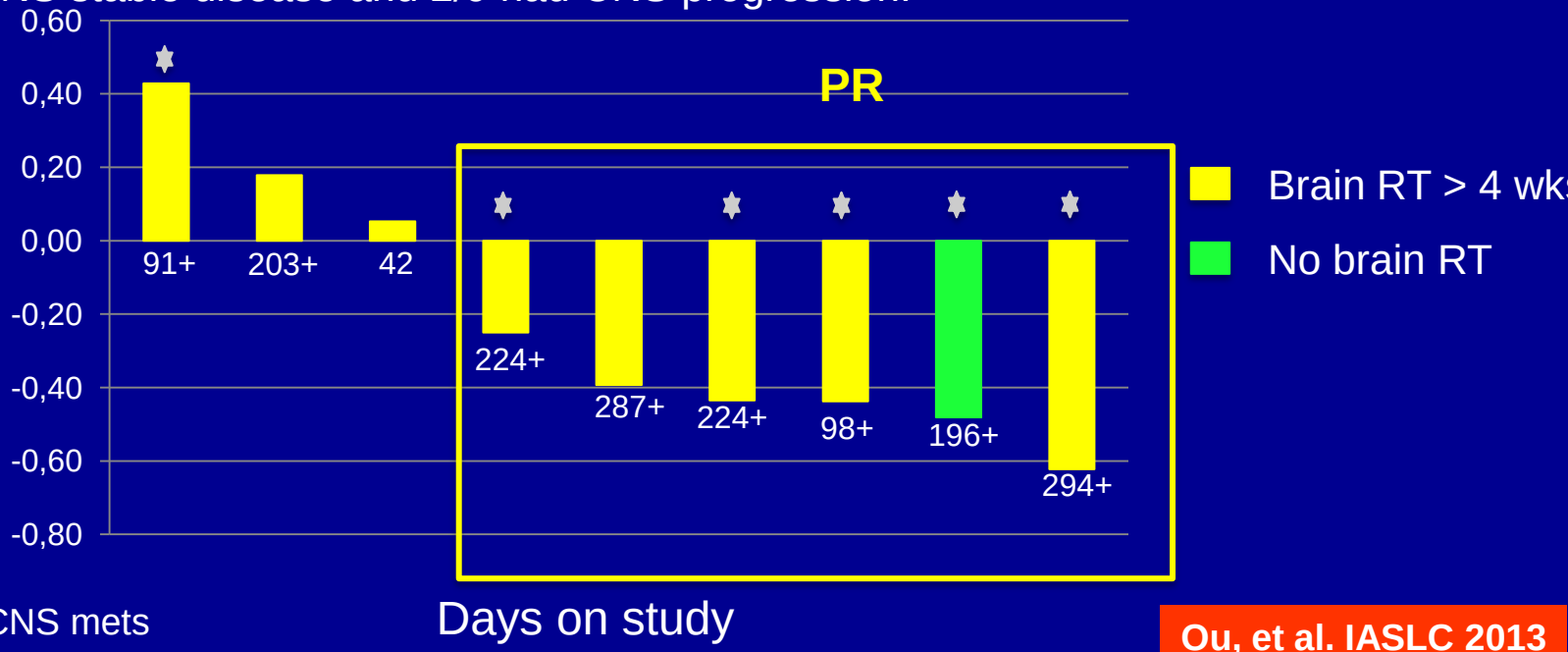


CNS activity of alectinib

- ORR of the 21 patients as determined by central image review

	CR	PR	SD	PD
Total N=21	6	5	8	2
%	29%	24%	38%	10%

- 9/21 patients with baseline CNS metastasis had measurable CNS lesions and received no prior radiation within 4 weeks from first dose of alectinib
  - No CR. 5/9 achieved CNS PR (≥ 30% reduction in sum of largest dimension). 2/9 had CNS stable disease and 2/9 had CNS progression.



Ou, et al. IASLC 2013

ROS1 Rearrangements in NSCLC

- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

CRIZOTINIB EXPERIENCE AT PERUGIA MEDICAL ONCOLOGY SINCE 2011

MUT	N PTS	PR	SD	PD
ALK+	31	18 (57%)	7 (23%)	6 (20%)
ROS+	4	3 (75%)	-	1 (25%)

TREATMENT WITH CRIZOTINIB BEYOND PROGRESSION IN ALK+ PTS

AGE AT DIAGNOSIS	BEST RESPONSE	RESPONSE DURATION (months)	SITE OF PROGRESSION	DURATION OF POST-PD CRIZOTINIB TREATMENT (months)	II ALK INHIBITOR	BEST RESPONSE	RESPONSE DURATION (months)
42	PR	36+	-		-	-	-
56	PR	12	LUNG, BONE	11	LDK 378	PR	7+
42	SD	4	BONE †	-	-		
65	SD	7	BRAIN, BONE	10	LDK 378	PR	6+
46	PR	9	LUNG	3	LDK 378	PR	3+
38	PR	26+	-	-			
34	PD	2	BRAIN, LYMPH		LDK 378	PR	4+
41	PR	20	BRAIN, BONE †	3	-	-	-
37	SD	7	BONE †	-	-	-	-
60	PR	8	LUNG	5	LDK 378	PR	7+
59	SD	24+	-	-	-	-	-
64	PR	6+	-	-	-	-	-
39	PR	8+	-	-	-	-	-
24	PR	5+	-	-	-	-	-

TREATMENT WITH CRIZOTINIB BEYOND PROGRESSION IN ALK+ PTS

AGE AT DIAGNOSIS	BEST RESPONSE	RESPONSE DURATION (months)	SITE OF PROGRESSION	DURATION OF POST-PD CRIZOTINIB TREATMENT (months)	II ALK INHIBITOR	BEST RESPONSE	RESPONSE DURATION (months)
47	SD	29+	-	-	-	-	-
57	PR	33+	-	-	-	-	-
59	PR	17	BRAIN	6	LDK 378	PR	6+
48	PR	20	BRAIN, LUNG	9	LDK 378	PR	4+
30	PR	9	LUNG	-	LDK 378	PR	7+
55	PR	19+	-	-	-	-	-
47	SD	18	LUNG, ADRENAL GLAND	3	LDK 378	SD	6+
56	PR	4	LIVER	6	LDK 378	SD	2+
46	PD	3	†	-	-	-	-
55	PR	5	BRAIN †	2	-	-	-
49	PD	<1	†	-	-	-	-
49	PD	2,5	LUNG †	-	-	-	-
34	PR	12	BRAIN	13	LDK 378	PR	6+
55	SD	5,5	BRAIN †	-	-	-	-

ROS+ PTS TREATED WITH CRIZOTINIB

AGE AT DIAGNOSIS	BEST RESPONSE	RESPONSE DURATION (months)	SITE OF PROGRESSION	DURATION OF POST-PD CRIZOTINIB TREATMENT (months)	II ALK INHIBITOR	BEST RESPONSE	RESPONSE DURATION (months)
71	PR	2+	-	-	-	-	-
45	RC	15+	-	-	-	-	-
50	RP	3	BONE †	4	-	-	-
51	PR	1	BRAIN	2+	-	-	-

CONCLUSIONS

- **Crizotinib** is the first in class ALK-TKI inhibitor fully developed and worldwide registered
- **Crizotinib** has shown in phase I-II and III trials relevant long lasting clinical activity in a heavy pretreated multimetastatic patient's population with NSCLC EML4-ALK translocation positive
- In most of the patients significant symptoms relief and a durable improvement in quality of life have been observed
- Resistance occurs with several different mechanisms but brain metastasis seems to be the most frequent reason for failure of **crizotinib** treatment

Thanks for your attention

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