Biomarker driven treatment of selected NSCLC: ALK

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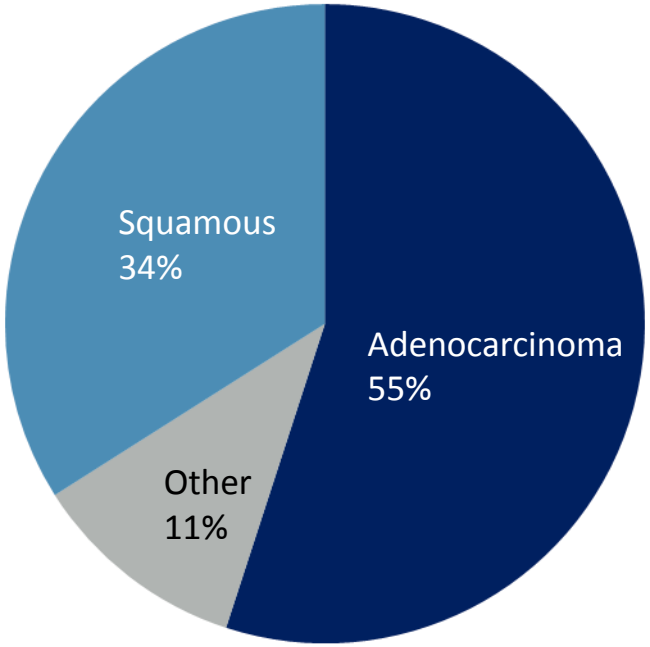
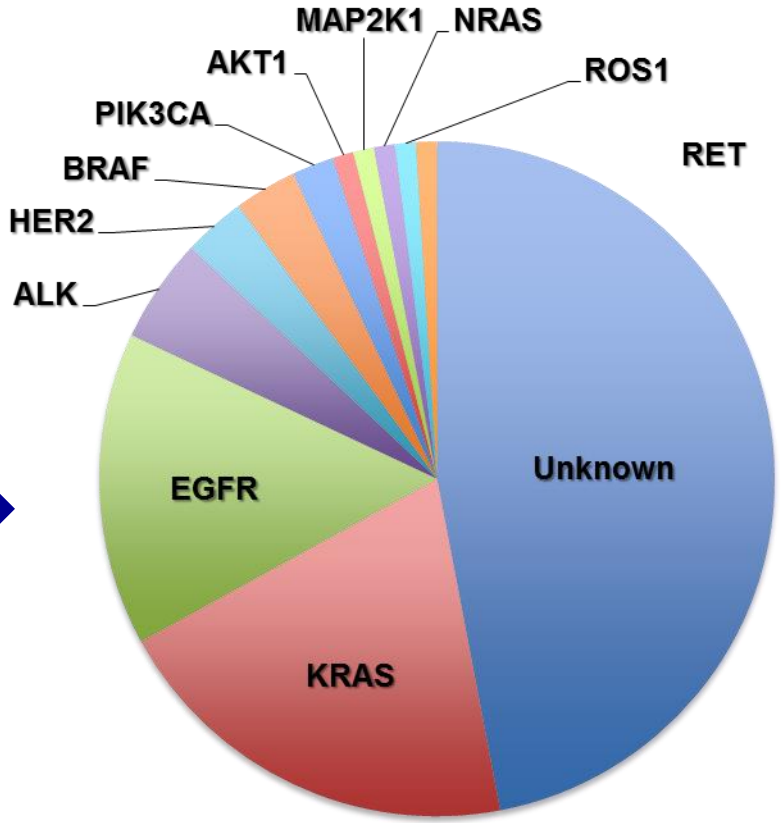
ALK as an oncogenic driver in NSCLC

Histology-based subtyping in NSCLC



Adenocarcinoma



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Li T et al. *J Clin Oncol*. 2013;31:1039-1049.

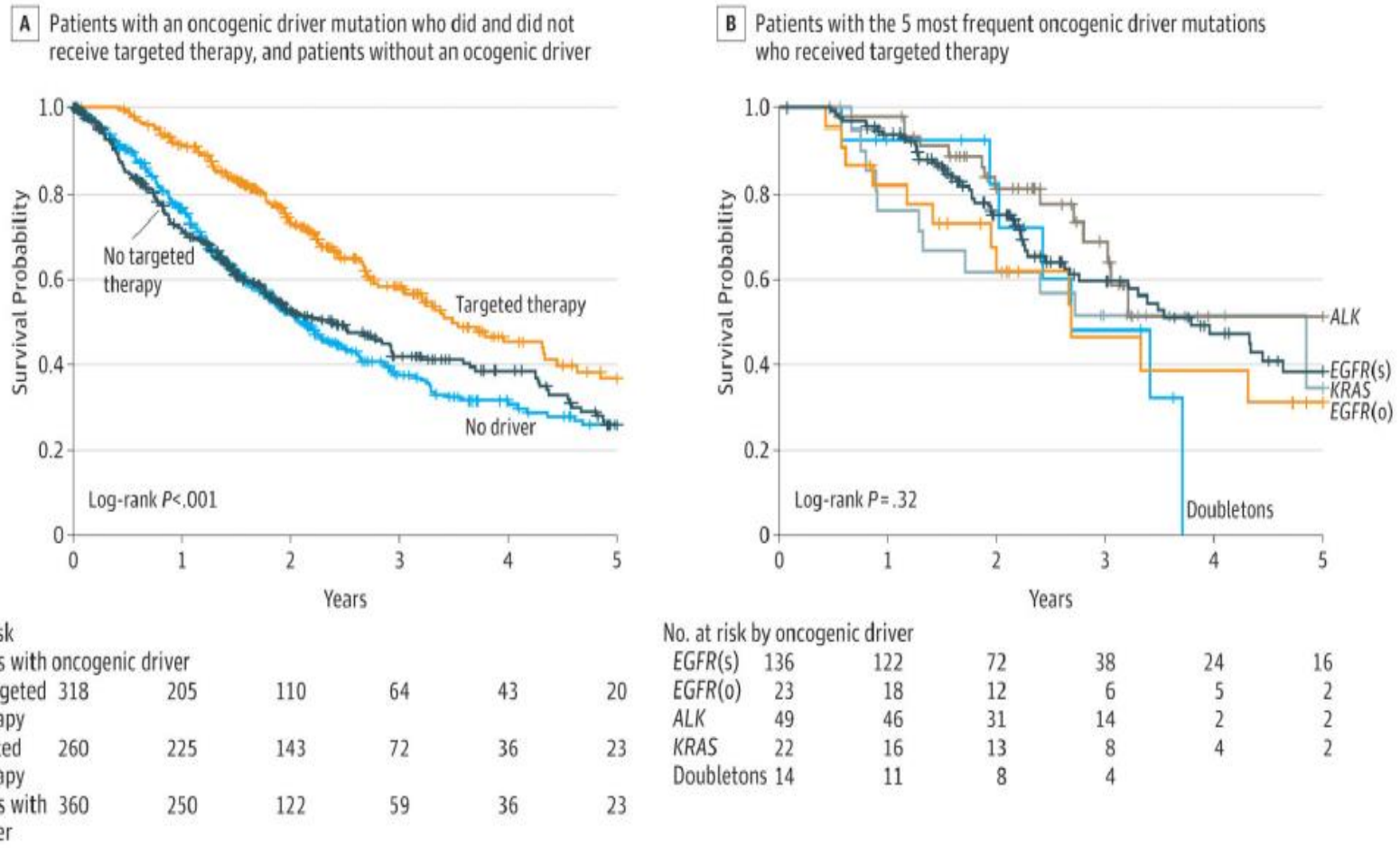
Epidemiology

- 2–7% of NSCLC patients exhibit rearrangements of the *ALK* gene

- Higher prevalence in patients who have the following characteristics:
  - Adenocarcinoma histology
  - Never/light smoking history
  - Younger age than ALK-negative NSCLC patients

- Brain metastases, common

Survival by oncogenic driver in NSCLC



Kris MG et al. *JAMA*. 2014; 311(19): 1998–2006.

Biomarker driven treatment of selected NSCLC: ALK

Outline

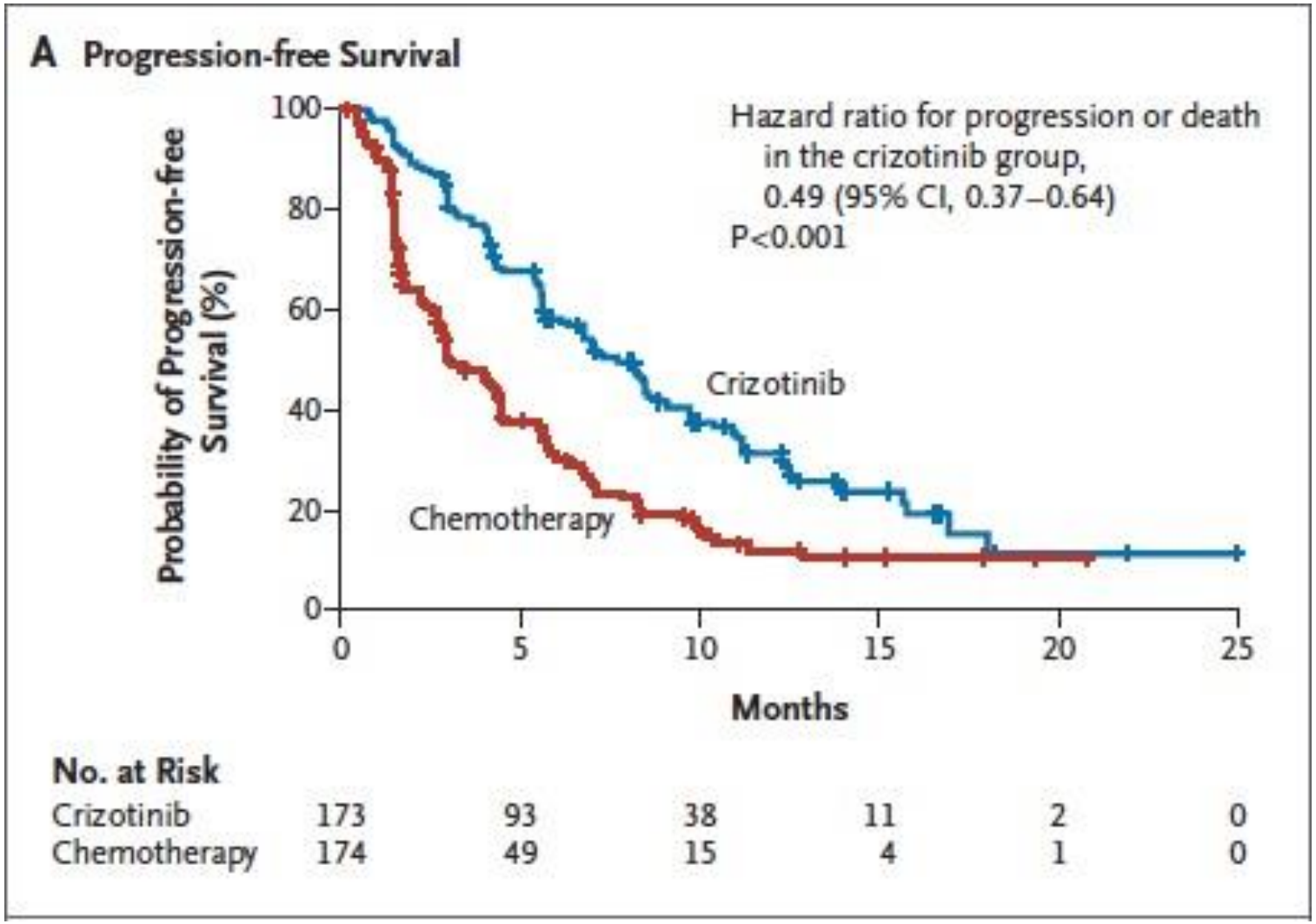
- Crizotinib
- Mechanisms of resistance
- Brain metastases
- Ceritinib
- Alectinib
- Brigatinib
- PF-06463922
- Optimal sequence

Crizotinib

Crizotinib in ALK+ NSCLC

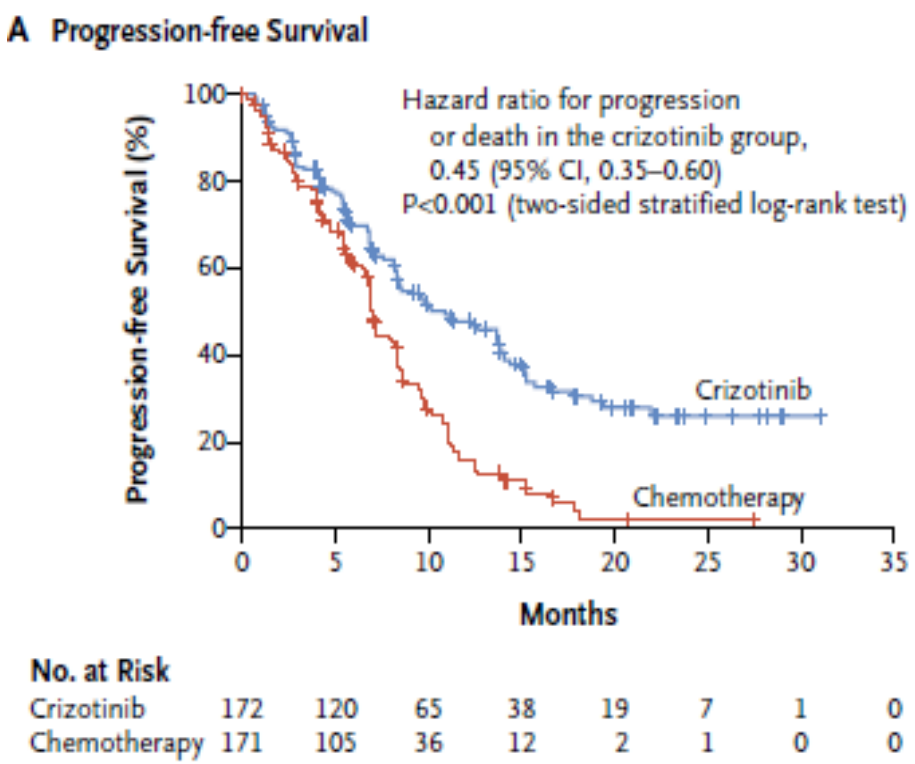
- PROFILE 1001 – expanded cohort of ALK+ NSCLC patients (NCT00585195)
- PROFILE 1005 – Ph II pretreated (NCT00932451)
- PROFILE 1007 – Ph III 2nd-line (NCT00932893)
- PROFILE 1014 – Ph III 1st-line (NCT01154140)

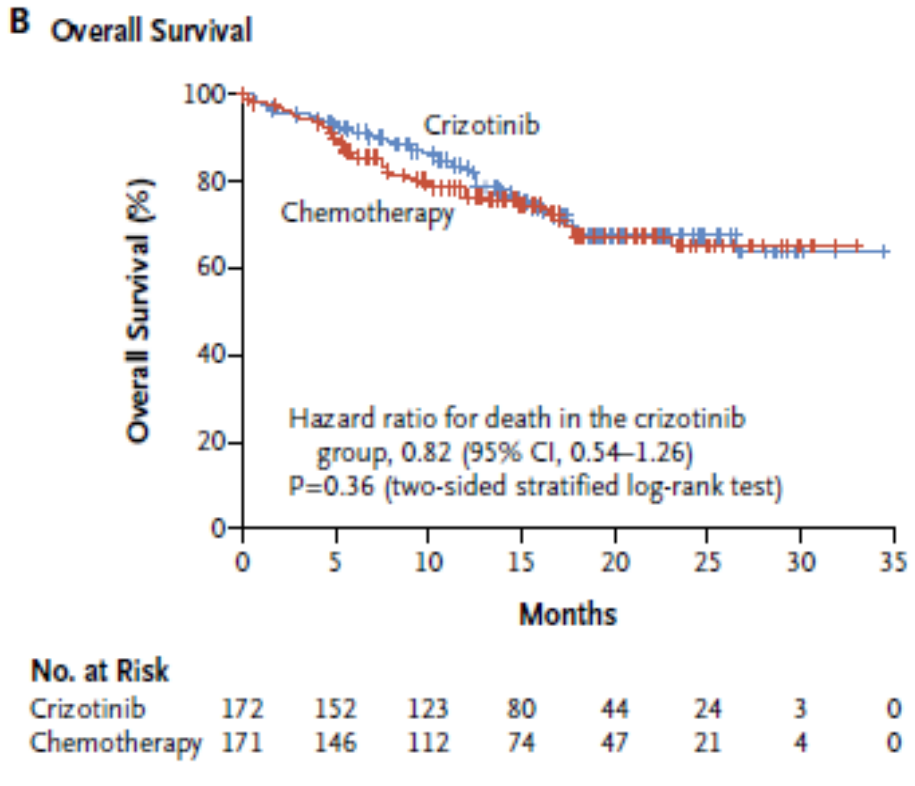
Crizotinib 2nd-line: PFS in PROFILE 1007



Shaw AT, et al. *N Engl J Med.* 2013;368:2385-94.

Crizotinib in 1st-line: PFS in PROFILE 1014





Solomon BJ, et al. *N Engl J Med.* 2014;371:2167-77.

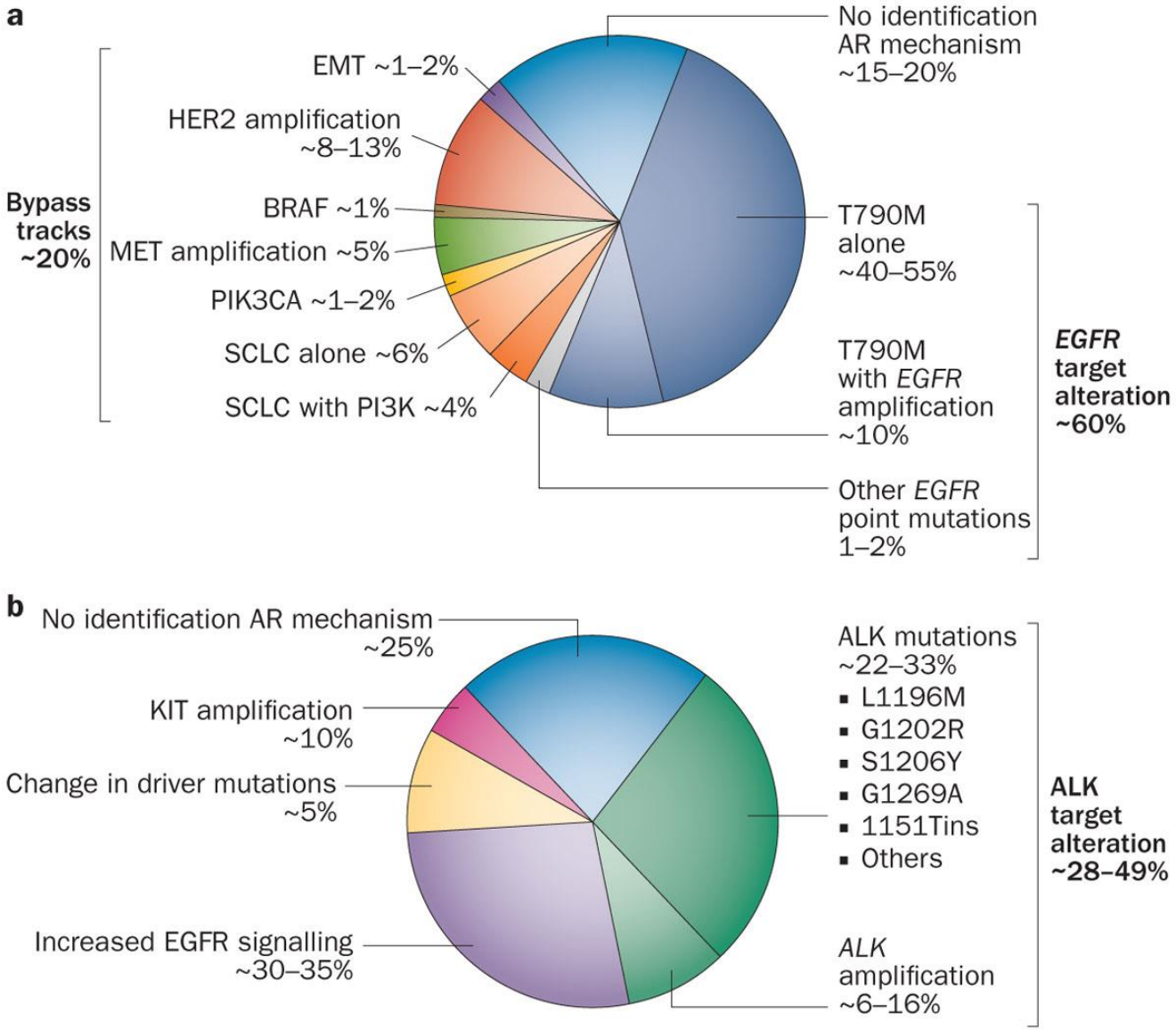
Mechanisms of resistance

Mechanisms of resistance to ALK inhibition, an heterogeneous phenomenon

- Target gene modification, including ALK amplification and ALK mutation within the ALK kinase domain
  - ✓25-30% of patients with crizotinib resistance harbor an ALK kinase domain mutation (most common: L1196M, G1269A; several described)

- Activation of alternative signaling pathways
  - Increased EGFR, IGF-1R phosphorylation
  - Src activation
  - KRAS mutation

Mechanisms of biological acquired resistance in NSCLC

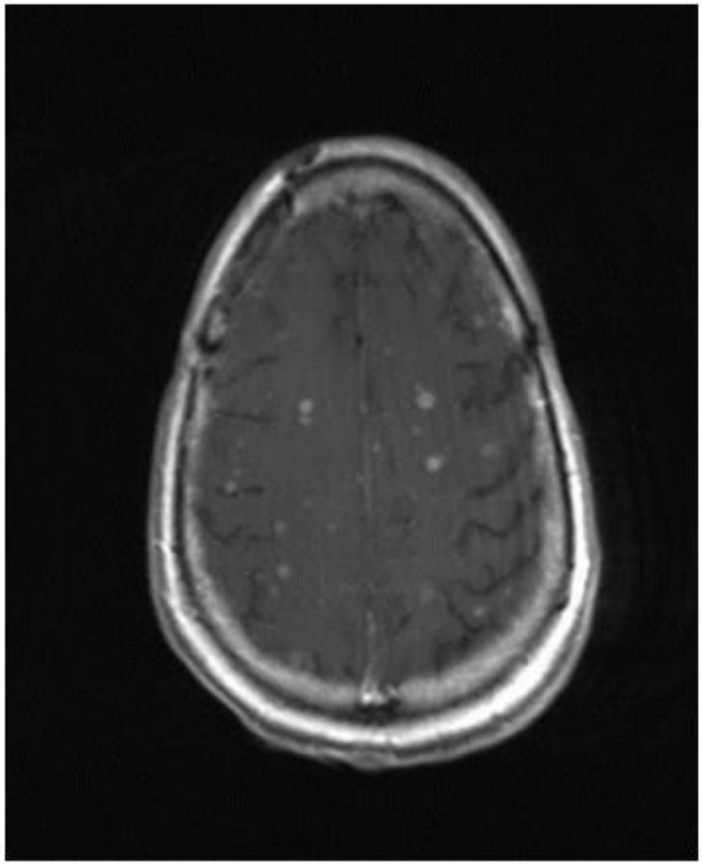


Camidge DR, et al. Nat Rev Clin Oncol 11:473-481, 2014

Brain metastases

CNS Metastases in ALK+ NSCLC

- 26% of ALK+ patients have CNS metastases at initial diagnosis.
- CNS is among the most common sites of relapse on crizotinib.
- Among crizotinib-resistant patients entering trials of next-generation ALK inhibitors, rates of CNS metastases approach 60%.



Treatment of BM: a challenge in ALK+ patients

- A common metastatic site

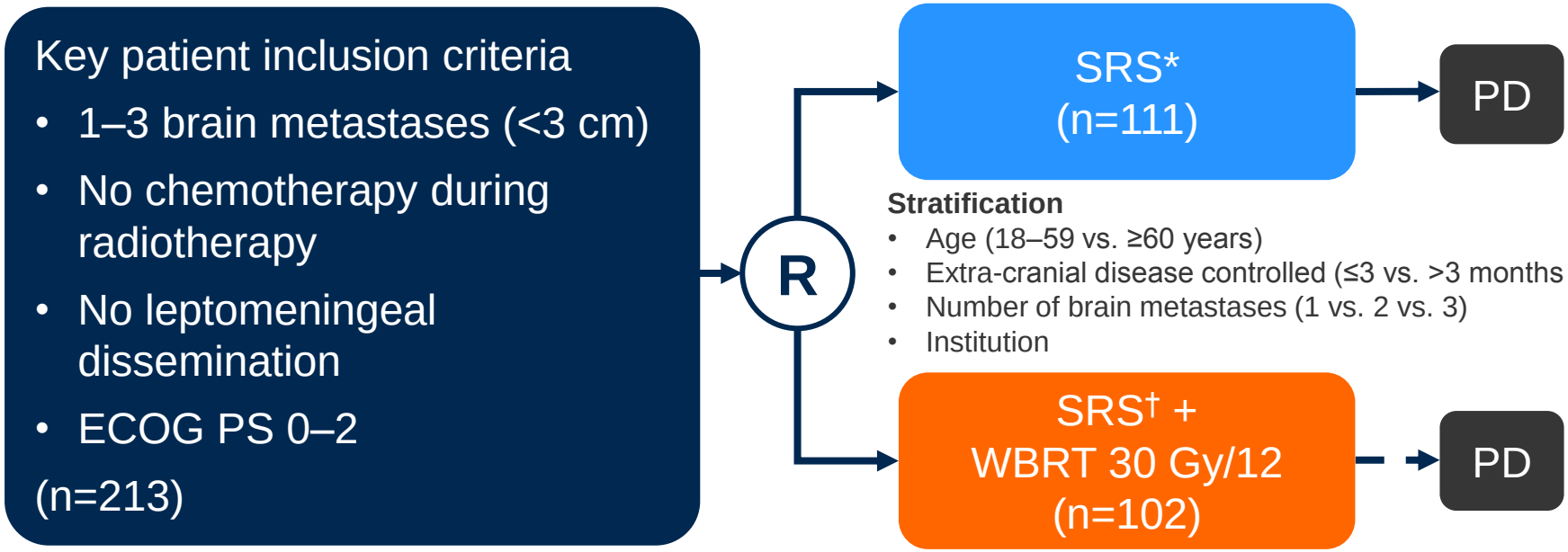
- Factors to consider when deciding treatment of BM
  - present at diagnosis *vs* diagnosed during disease evolution
  - symptomatic *vs* asymptomatic
  - potentially treatable by stereotactic RT *vs* WBRT
  - PD only in the brain *vs* PD outside the brain

- ALK+ patients: young population with long survival
  - Concerns about long-term toxicity associated with WBRT

LBA4: NCCTG N0574 (Alliance): A phase III randomized trial of WBRT in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases

Study objective

- To investigate the effectiveness and safety of using WBRT with SRS compared with SRS alone in patients with brain metastases



Primary endpoint

- Cognitive progression (defined as drop in 1 SD in one cognitive test

Secondary endpoints

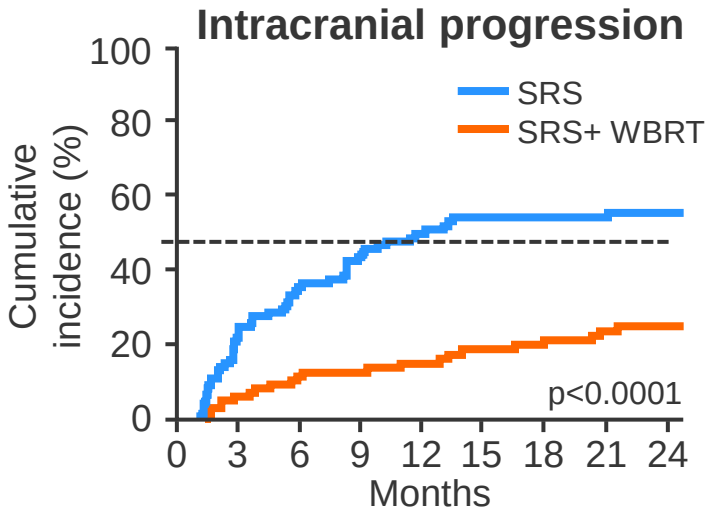
- OS, safety, QoL

*Lesions <2.0 cm 24 Gy; lesions 2–2.9 cm 20 Gy;
†Lesions <2.0 cm 22 Gy; lesions 2–2.9 cm 18 Gy

Brown et al. J Clin Oncol 2015; 33 (suppl): abstr LBA4

LBA4: NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases

- **Key results**
  - Cognitive decline more frequent with SRS + WBRT than SRS alone (91.7% vs. 63.5%; p=0.0007), which remained at 6 months (97.9% vs. 77.8%; p=0.032)
  - Significant deterioration at 3 months for SRS + WBRT compared with SRS in the cognitive domains of HVLT total recall (p=0.0043), HVLT delayed recall (p=0.009) and COWA (p=0.009)
  - Four times as many CNS failures following SRS at 3 months



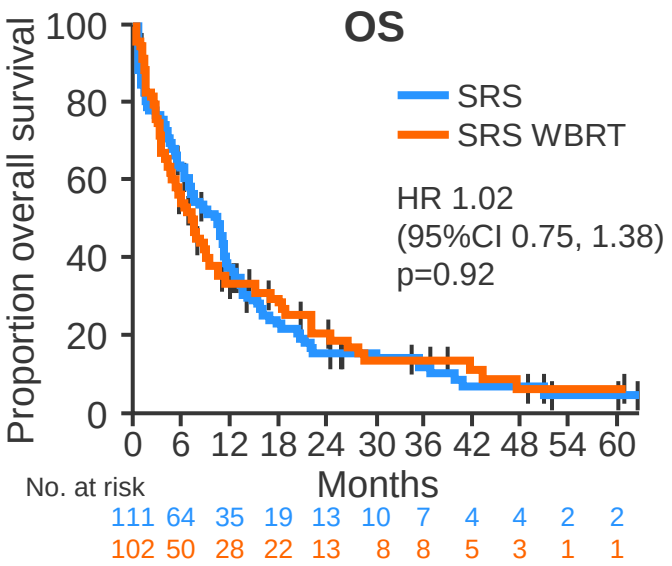
CNS failure, %	SRS + WBRT	SRS
At 3 months	6.3	24.7
At 6 months	11.6	35.4

  - Alopecia (p=0.01) and dermatitis (p=0.06) significantly more common at 6 weeks with SRS + WBRT than with SRS
  - No difference in late radiation side effects (CNS necrosis) between SRS + WBRT vs. SRS alone (4.3% vs. 6.8%; p=0.72)

Brown et al. J Clin Oncol 2015; 33 (suppl): abstr LBA4

LBA4: NCCTG N0574 (Alliance): A phase III randomized trial of WBRT in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases

- **Key results (cont.)**
  - Median OS was 7.4 vs. 10.4 months for SRS + WBRT vs. SRS alone



QoL test/subtest at 3 months*	SRS + WBRT	SRS	p-value
Physical wellbeing	-4	-18	0.053
Social/family wellbeing	1	-3	0.369
Emotional wellbeing	13	5	0.129
Functional wellbeing	**3**	**-22**	**0.006**
FACT general	**0**	**-12**	**0.001**
FACT brain specific	**-1**	**-9**	**0.029**
FACT-BR total	**-1**	**-11**	**0.002**

  - Similar results were observed in the small number of long-term survivors
- **Conclusions**
  - Patients receiving SRS with WBRT had a more frequent decline in cognitive function (early evaluation) including immediate recall, memory and verbal fluency, than those receiving SRS alone
  - Adjuvant WBRT had no impact on OS and worsened QoL, but did improve brain control by four times over SRS alone
  - SRS alone with close monitoring is recommended for patients with 1–3 newly diagnosed brain metastases to better preserve cognitive function and QoL

*Mean change from baseline with minimally clinically significant difference = 10 points

Brown et al. J Clin Oncol 2015; 33 (suppl): abstr LBA4

CSF concentration of the ALK inhibitor crizotinib

Drug	Dose	Serum concentrations (µmol/L)	CSF* concentrations (µmol/L)
Topotecan	10 mg/m^2	0.27-0.45	0.07 (30%)
Gefitinib	250 mg/d	0.5	< 0.01
Erlotinib	150 mg/d	> 2	< 0.01
Crizotinib	250 mg/12h	0.53	0.0014

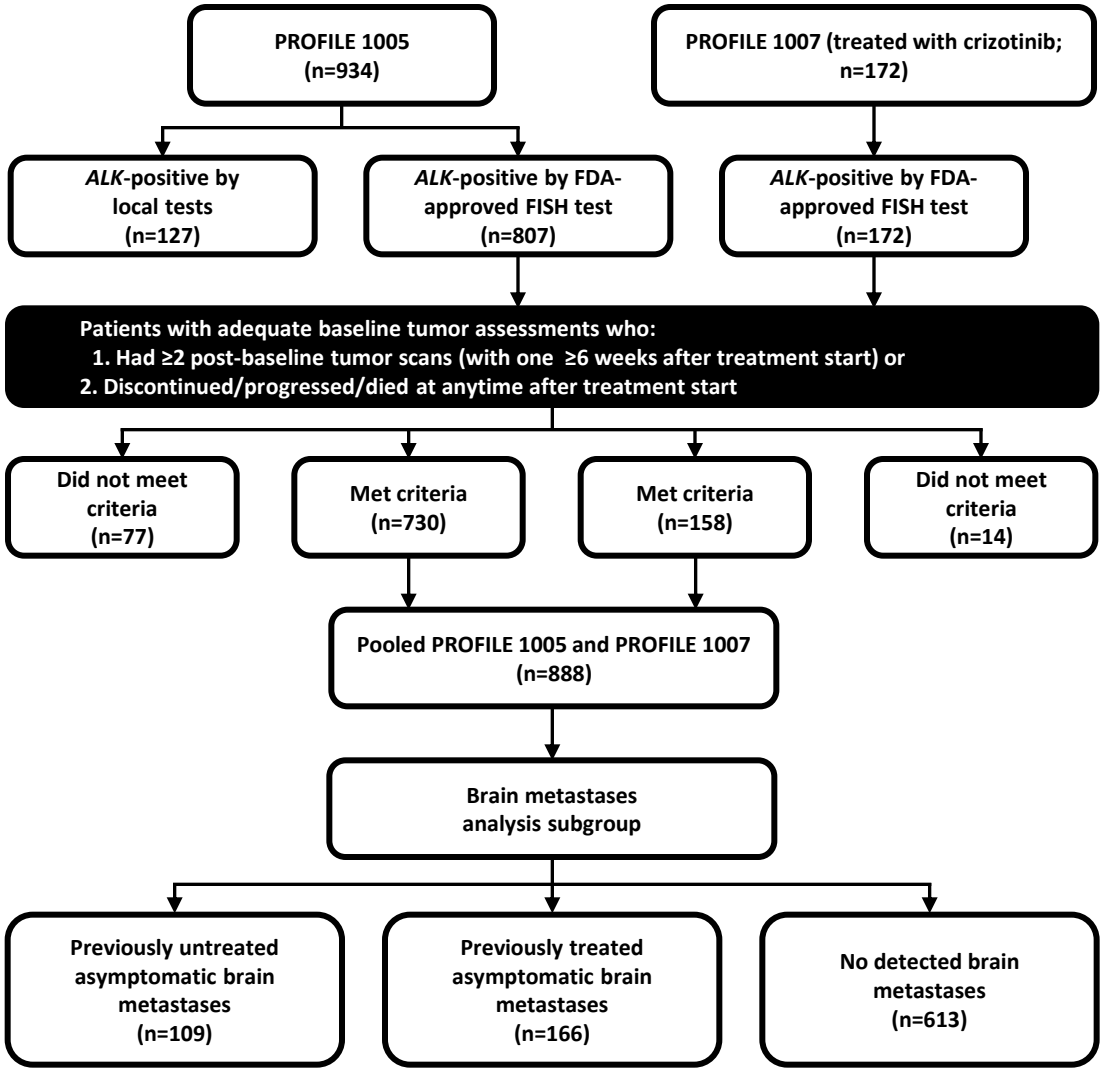
Crizotinib penetrates the blood brain barrier poorly, hindering the anticancer effect of this drug in metastatic brain tumors

* CSF: CerebroSpinal Fluid

Costa DB, JCO 2011

Crizotinib in patients with advanced ALK+ NSCLC and brain metastases

- 888 patients were pooled from PROFILE 1005 and 1007 as shown
- Three patient groups were defined:
  - Previously untreated (no prior RT) asymptomatic brain metastases (12%)
  - Previously treated (with intracranial RT) asymptomatic brain metastases (19%)
  - No detectable brain metastases at baseline (69%)



Costa DB, et al. J Clin Oncol 2015

Crizotinib antitumor activity

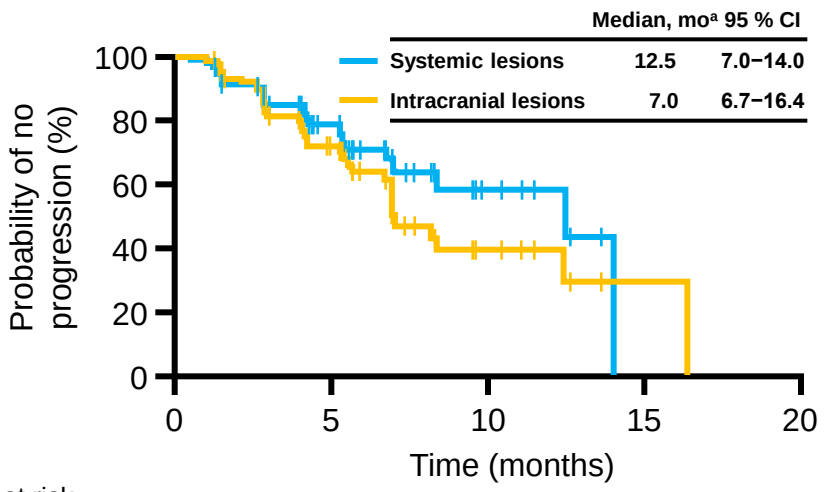
- Patients with previously treated or untreated BMs and systemic disease control at 12 weeks were also likely to experience IC disease control at 12 weeks and vice versa (correlation coefficient, 0.7652; P<0.001)

	Previously untreated for BMs (n=109)		Previously treated for BMs (n=166)		No BMs detected (n=613)	
	n	Outcome	n	Outcome	n	Outcome
DCR at 12 weeks (95% CI), %						
IC	109	56 (46–66)	166	62 (54–70)	NA	NA
Systemic	109	63 (54–72)	166	65 (57–72)	613	71 (68–75)
ORR (95% CI), %						
IC (TL BMs)	22	18 (5–40)	18	33 (13–59)	NA	NA
Systemic	109	53 (43–63)	166	46 (39–54)	613	55 (51–59)

Costa DB, et al. J Clin Oncol 2015

Systemic and IC TTP in patients with baseline BM

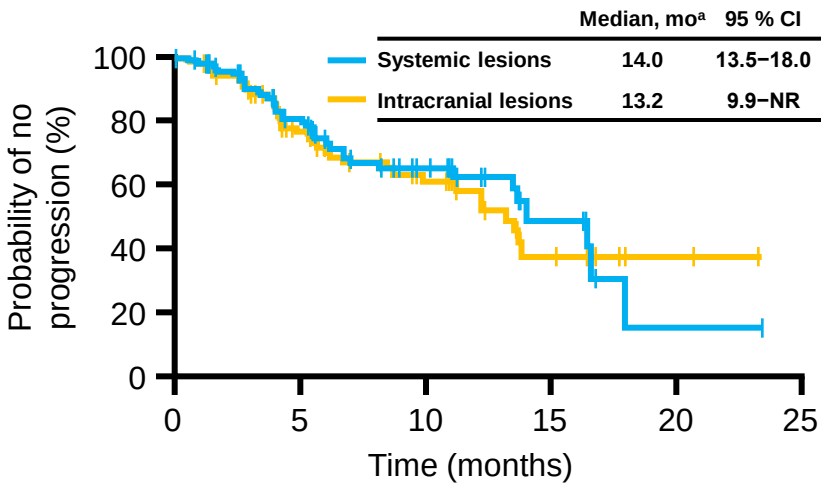
Previously untreated brain metastases



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 baseline BM with PD, the CNS was the most common site of progression, occurring in:
  - 70% of patients (30/43) with previously untreated BM
  - 72% of patients (39/54) with previously treated BM
- 20% of patients without baseline BM progressed in brain

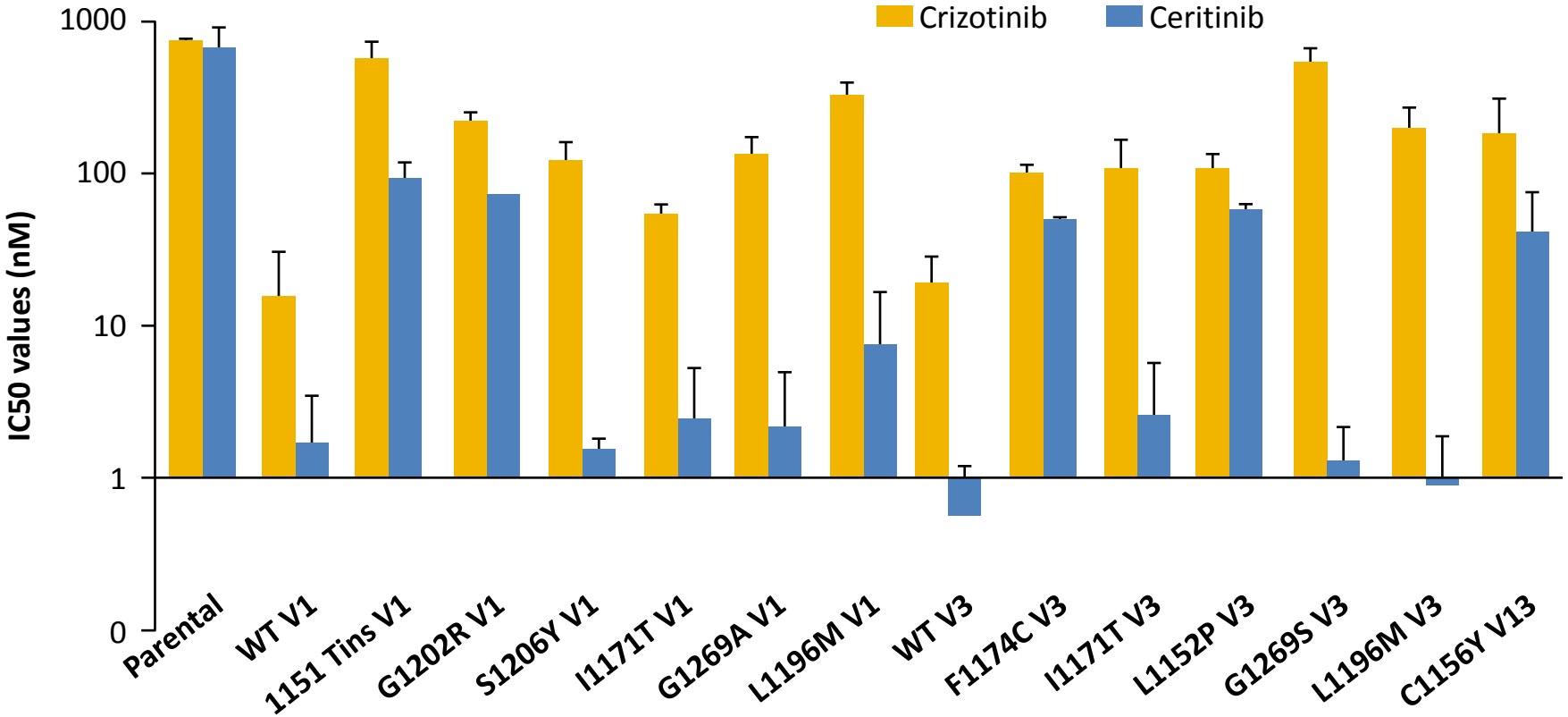
Costa DB, et al. J Clin Oncol 2015

ALK 2nd generation TKIs

- Better affinity for ALK
- Better affinity for crizotinib resistant second-site mutated ALK
- Improvement in pharmacokinetics to brain tissue and CSF

Ceritinib

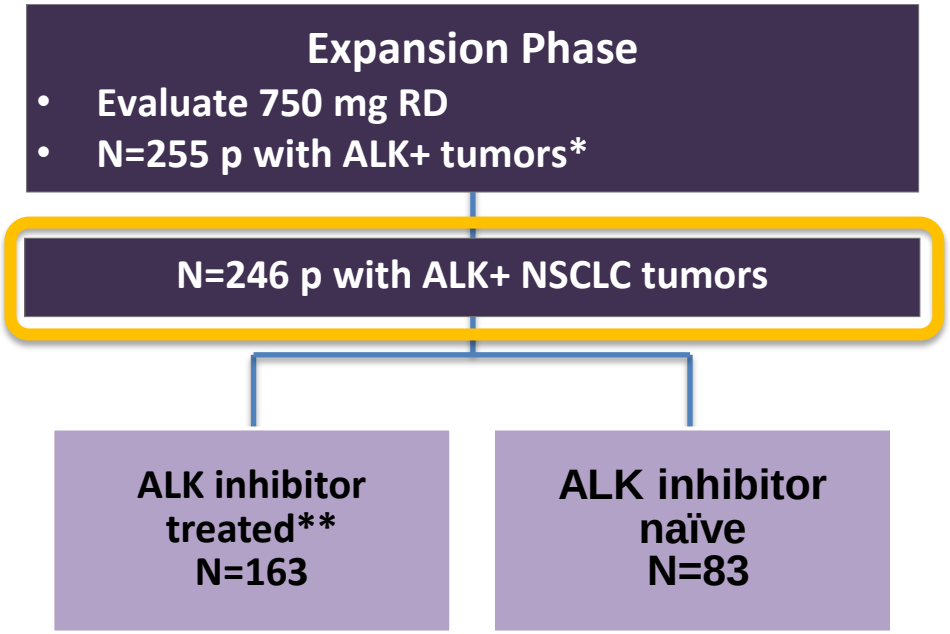
Common crizotinib-resistance mutations, sensitive to ceritinib



Friboulet L et al. Cancer Discov. 2014;4:662-73.
Takeda M et al. J Thoracic Oncol. 2013;8:654-7.

ASCEND-1 study

Global pivotal phase 1 trial including 20 centers across 11 countries



Recruitment closed July 2013

- 31 October 2013 data cut-off used for current analysis

*9 ALK+ p had cancers other than NSCLC

**All received crizotinib and 5 also received alectinib

Key Objectives: to determine anti-tumour efficacy and safety of ceritinib

Baseline demographics for p with ALK+ NSCLC

The majority of ALK+ NSCLC p were never/ex-smokers and had an ECOG PS ≤1

No notable differences in p demographics found between ALK-inhibitor naive p and those ALK inhibitor pre-treated

Characteristics	NSCLC with prior ALK inhibitor n=163	NSCLC ALK inhibitor naive n=83	All NSCLC n=246
Age (median), years (range)	52 (24–80)	55 (22–80)	53 (22–80)
Sex (female; n [%])	88 (54.0)	44 (53.0)	132 (53.7)
WHO/ECOG PS, n (%)			
0	38 (23.3)	25 (30.1)	63 (25.6)
1	104 (63.8)	51 (61.4)	155 (63.0)
2	20 (12.3)	7 (8.4)	27 (11.0)
>2	1 (0.6)	0	1 (0.4)
Smoking history			
Never /Ex-smoker	158 (96.9%)	82 (98.8%)	240 (97.6%)
Current smoker	5 (3.1%)	1 (1.2%)	6 (2.4%)

Baseline disease characteristics for p with ALK+ NSCLC

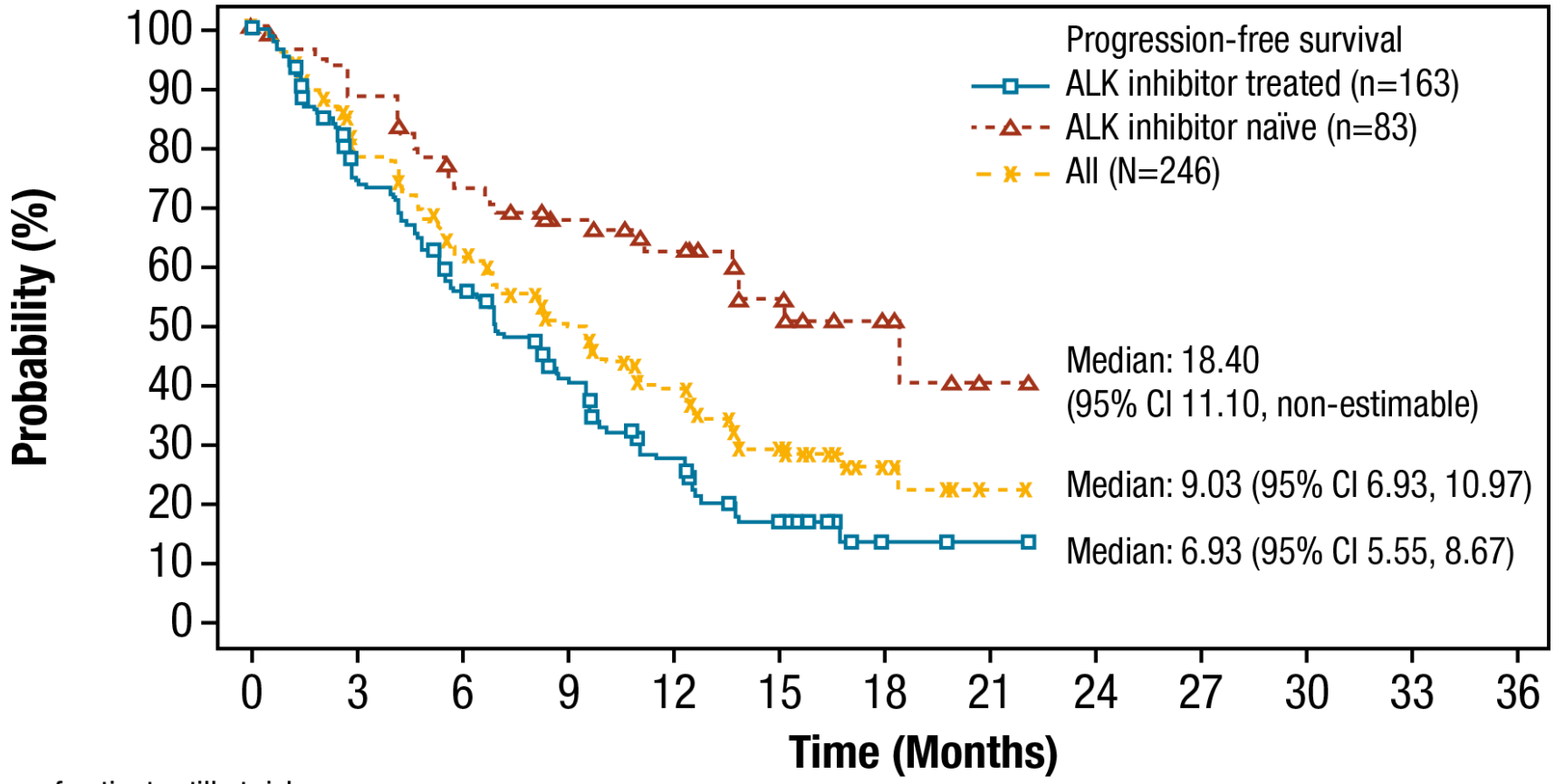
Characteristics	NSCLC with prior ALK inhibitor n=163	NSCLC ALK inhibitor naive n=83	All NSCLC n=246
Tumor histology N (%)			
ADC	152 (93.3)	76 (91.6)	228 (92.7)
Other	11 (6.7)	7 (8.4)	18 (7.3)
No. of prior regimens, N(%)			
0	0	16 (19.3)	16 (6.5)
1	26 (16.0)	38 (45.8)	64 (26.0)
2	45 (27.6)	16 (19.3)	61 (24.8)
3	35 (21.5)	7 (8.4)	42 (17.1)
>3	57 (35.0)	6 (7.2)	63 (25.6)
Median time from initial diagnosis to first dose, mo (range)	21.2 (2.4–174.2)	8.1 (1.0–109.3)	18.0 (1.0–174.2)

Number of prior regimens was higher in p previously treated with an ALK inhibitor than in ALK inhibitor naïve p

Investigator-assessed efficacy outcomes for p with ALK+ NSCLC

Efficacy Parameter	NSCLC with prior ALK inhibitor n=163	NSCLC ALK inhibitor naïve n=83	All NSCLC n=246
CR, n (%)	3 (1.8)	1 (1.2)	4 (1.6)
PR, n (%)	89 (54.6)	59 (71.1)	148 (60.2)
SD, n (%)	29 (17.8)	14 (16.9)	43 (17.5)
PD, n (%)	16 (9.8)	0	16 (6.5)
Unknown, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
ORR, n (%) [95% CI]	92 (56.4) [48.5, 64.2]	60 (72.3) [61.4, 81.6]	152 (61.8) [55.4, 67.9]

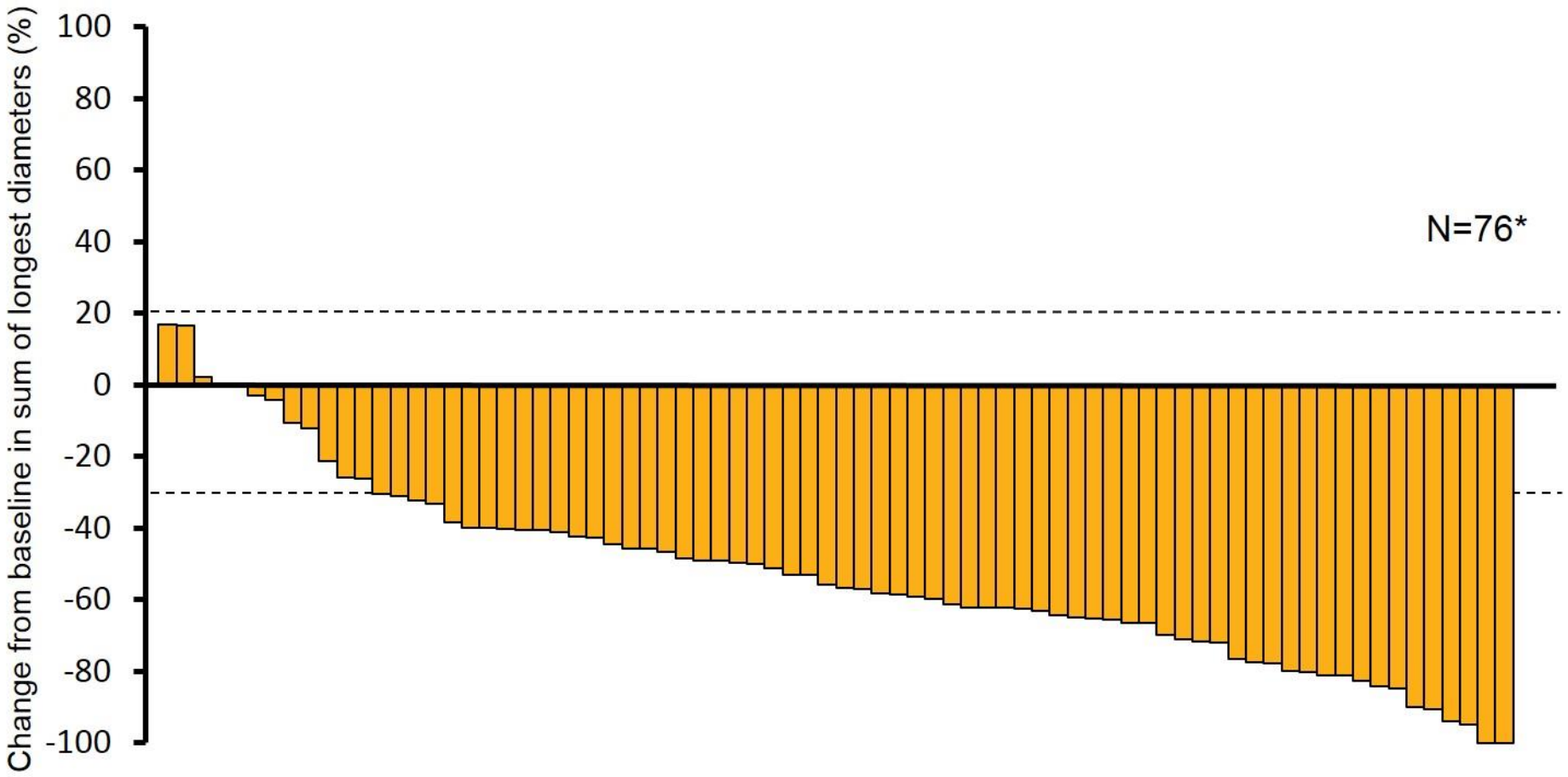
PFS for ALK+ NSCLC p treated with ceritinib 750 mg/day



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

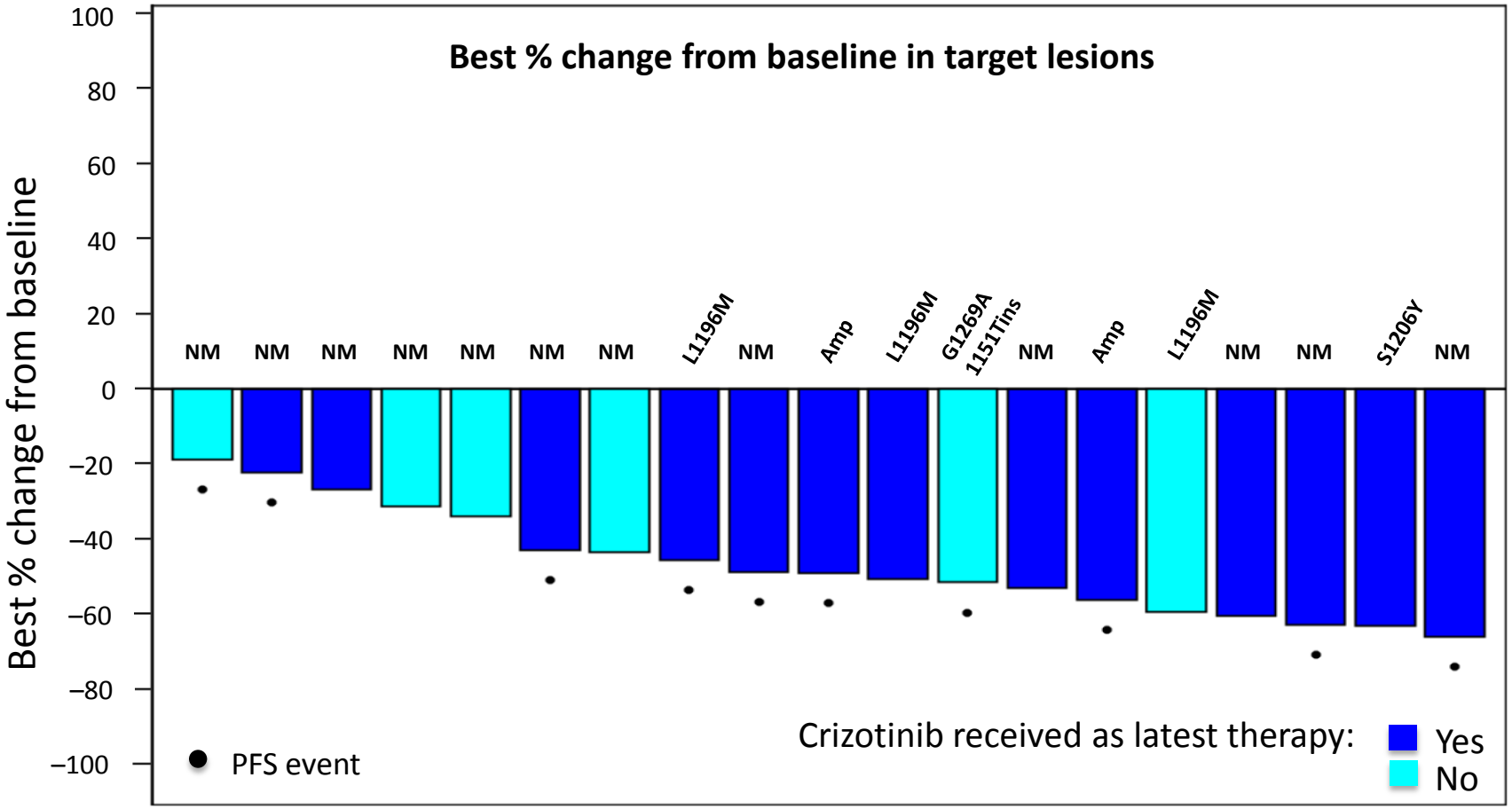
Best percentage change from baseline for ALK inhibitor-naïve p with ALK+ NSCLC



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

Ceritinib response in molecularly-defined, crizotinib-resistant tumors

19 crizotinib-resistant ALK+ NSCLC p underwent tumor biopsy prior to study enrollment



Shaw A *et al. NEJM* 2014;370(13):1189–1197

STUDY DESIGN

ASCEND-2 (NCT01685060) single-arm, open-label, multicenter, phase 2 study

Advanced or metastatic ALK + NSCLC

- Progression on standard therapy and crizotinib
- 1-3 lines of chemotherapy
- WHO PS 0-2

Ceritinib at 750 mg/d

- Continuous oral dosing
- Once daily
- 28-day cycle
- Treatment continued until unacceptable toxicity, discontinuation of treatment at the discretion of the investigator or patient, initiation of new anticancer therapy and/or death

- Primary objective: Determination of ORR per RECIST (investigator assessed)
- Secondary objectives: Determination of DOR, DCR, TTR, OIRR by investigator and BIRC assessment; ORR by BIRC assessment; safety; PFS; OS; and patient reported outcomes

BIRC, Blinded Independent Review Committee; DCR, disease control rate; DOR, duration of response; OIRR, overall intracranial response rate; ORR, objective response rate; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to response; PFS, progression-free survival

Baseline Characteristics

Table 2. Patient Demographics and Disease Characteristics at Baseline

	N = 140
Age (median), years (range)	51 (29-80)
Age category, n (%)	
< 65 years	122 (87.1)
Sex, n (%)	
Female	70 (50.0)
Race, n (%)	
Caucasian	84 (60.0)
Black	0
Asian	53 (37.9)
Other	3 (2.1)
WHO performance status, n (%)	
0	42 (30.0)
1	78 (55.7)
2	20 (14.3)
Tumor histology/cytology, n (%)	
Adenocarcinoma	129 (92.1)
Other	11 (7.9)
Stage at study entry, n (%)	
IV	140 (100.0)

Baseline Characteristics

Table 2. Patient Demographics and Disease Characteristics at Baseline...*Contd*.

	N = 140
Site of metastases, n (%)	
Adrenal	14 (10.0)
Bone	81 (57.9)
Brain	100 (71.4)
Patients with prior radiotherapy to the brain, n (%)	72/100 (72.0)
Time elapsed from prior radiotherapy to the brain to first dose of ceritinib	
Months, median (range)	6.2 (0.5-54.0)
≤ 3 months prior, n (%)	21 (29.2)
> 3 months prior, n (%)	51 (70.8)
Kidney	9 (6.4)
Liver	52 (37.1)
Lung	47 (33.6)
Pleura	52 (37.1)
Soft tissue	3 (2.1)
Lymph nodes	73 (52.1)
Other	37 (26.4)
Number of target lesions at baseline (investigator)	
1	60 (42.9)
≥ 2	80 (57.1)
Number of target lesions at baseline (BIRC)	
0	26 (18.6)
1	37 (26.4)
≥ 2	75 (53.6)
Missing baseline	2 (1.4)
Time since most recent relapse/progression (months), median (range)	1.2 (0.2-15.9)

Results

Table 3. Best Overall Response

	Investigator Review (FAS) N = 140
Best overall response, n (%)	
Complete response (CR)	4 (2.9)
Partial response (PR)	50 (35.7)
Stable disease (SD)	54 (38.6)
Non-CR/non-progressive disease (PD)*	-
PD	19 (13.6)
Unknown	13 (9.3)
ORR, n (%) (95% CI)	54 (38.6) (30.5, 47.2)
DCR (CR + PR + SD), n (%) (95% CI)	108 (77.1) (69.3, 83.8)

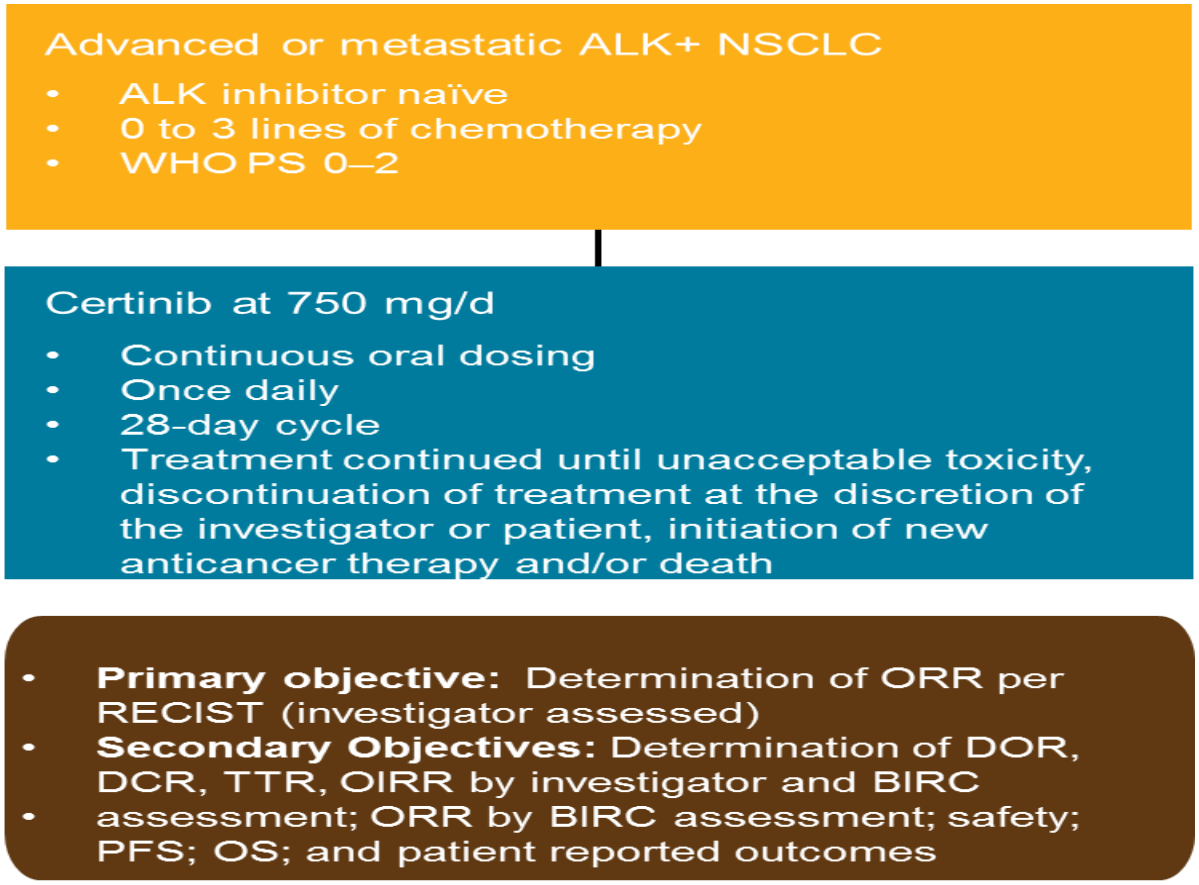
Table 4. Whole-Body Response to Ceritinib in Patients with BM at Baseline

	Investigator Review (FAS) N = 100
ORR, n (%) (95% CI)	33 (33.0) (23.9, 43.1)
DCR, n (%) (95% CI)	74 (74.0) (64.3, 82.3)
Median DOR Months (95% CI)	9.2 (5.5, 11.1)
Median PFS Months (95% CI)	5.4 (4.7, 7.2)

FAS, full analysis set; PPS, per-protocol set. *Includes patients who do not have target lesions at baseline per BIRC assessment and who do not qualify for CR (non-target non-nodal lesions all absent post-baseline and all non-target nodal lesions returned to normal size - < 10mm) and do not qualify for PD (eg no new lesions and the non-target lesions did not progress). #Includes those patients who had no major protocol deviations (i.e. patients were excluded if they had no post-baseline tumor assessment [n=9], no local documentation of ALK positive status using the FDA-approved FISH test [n=3], no valid baseline assessment [n=2 for BIRC only, one without local ALK documentation as well], or no baseline target lesions [n=24 for BIRC only, one with no post-baseline assessment as well]).

STUDY DESIGN ASCEND 3

single-arm, open-label, multicenter, phase 2 study of ceritinib in ALK inhibitor-naïve adult patients with ALK+ NSCLC



– Intracranial responses were calculated in patients with brain metastases selected as the target lesion at baseline by the investigator. All brain metastases target lesions were confirmed, to ensure patients with prior radiotherapy and without progression were not included in the analyses.

BIRC, Blinded Independent Review Committee; DCR, disease control rate; DOR, duration of response; OIRR, overall intracranial response rate; ORR, objective response rate; OS, overall survival, RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to response; PFS, progression-free survival; WHO, World Health Organisation.

Results

- Baseline characteristics

Table 2. Patient Demographics and Disease Characteristics at Baseline

	N = 124
Age (median), years (range)	56 (27-82)
Age category, n (%) < 65 years	 94 (75.8)
Sex, n (%) Female	 74 (59.7)
Race, n (%) Caucasian Black Asian Other	 48 (38.7) 1 (0.8) 74 (59.7) 1 (0.8)
WHO performance status, n (%) 0 1 2	 46 (37.1) 69 (55.6) 9 (7.3)
Tumor histology/cytology, n (%) Adenocarcinoma Other	 120 (96.8) 4 (3.2)
Stage at study entry, n (%) IV	 124 (100.0)

Results

Table 2. Patient Demographics and Disease Characteristics at Baseline...*Contd*.

	N = 124
Site of metastases, n (%)	
Adrenal	15 (12.1)
Bone	55 (44.4)
Brain	50 (40.3)
Patients with prior radiotherapy to the brain, n (%)	27/50 (54.0)
Time elapsed from prior radiotherapy to the brain to first dose of ceritinib	
Months, median (range)	2.7 (0.5-31.9)
≤ 3 months prior, n (%)	14 (51.9)
3 months prior, n (%)	13 (48.1)
Kidney	3 (2.4)
Liver	33 (26.6)
Lung	123 (99.2)
Pleura	50 (40.3)
Soft tissue	4 (3.2)
Lymph nodes	78 (62.9)
Other	30 (24.2)
Number of target lesions at baseline (investigator)	
0	1 (0.8)
1	45 (36.3)
≥ 2	78 (62.9)
Number of target lesions at baseline (BIRC)	
0	11 (8.9)
1	35 (28.2)
≥ 2	78 (62.9)
Time since most recent relapse/progression (months), median (range)	1.7 (0.1-8.1)

Results

Table 3. Best Overall Response

	Investigator Review (FAS) N = 124
Best overall response, n (%)	
Complete response (CR)	-
Partial response (PR)	79 (63.7)
Stable disease (SD)	32 (25.8)
Non-CR/non-progressive disease (PD)*	1 (0.8)
PD	5 (4.0)
Unknown	7 (5.6)
ORR, n (%) (95% CI)	79 (63.7) (54.6, 72.2)
DCR (CR + PR + SD), n (%) (95% CI)	111 (89.5) (82.7, 94.3)

Table 4. Whole-Body Response to Ceritinib in Patients with BM at Baseline

	Investigator Review (FAS) N = 50
ORR, n (%) (95% CI)	29 (58.0) (43.2, 71.8)
DCR, n (%) (95% CI)	43 (86.0) (73.3, 94.2)
Median DOR Months (95% CI)	9.1 (7.5, NE)
Median PFS Months (95% CI)	10.8 (7.3, NE)

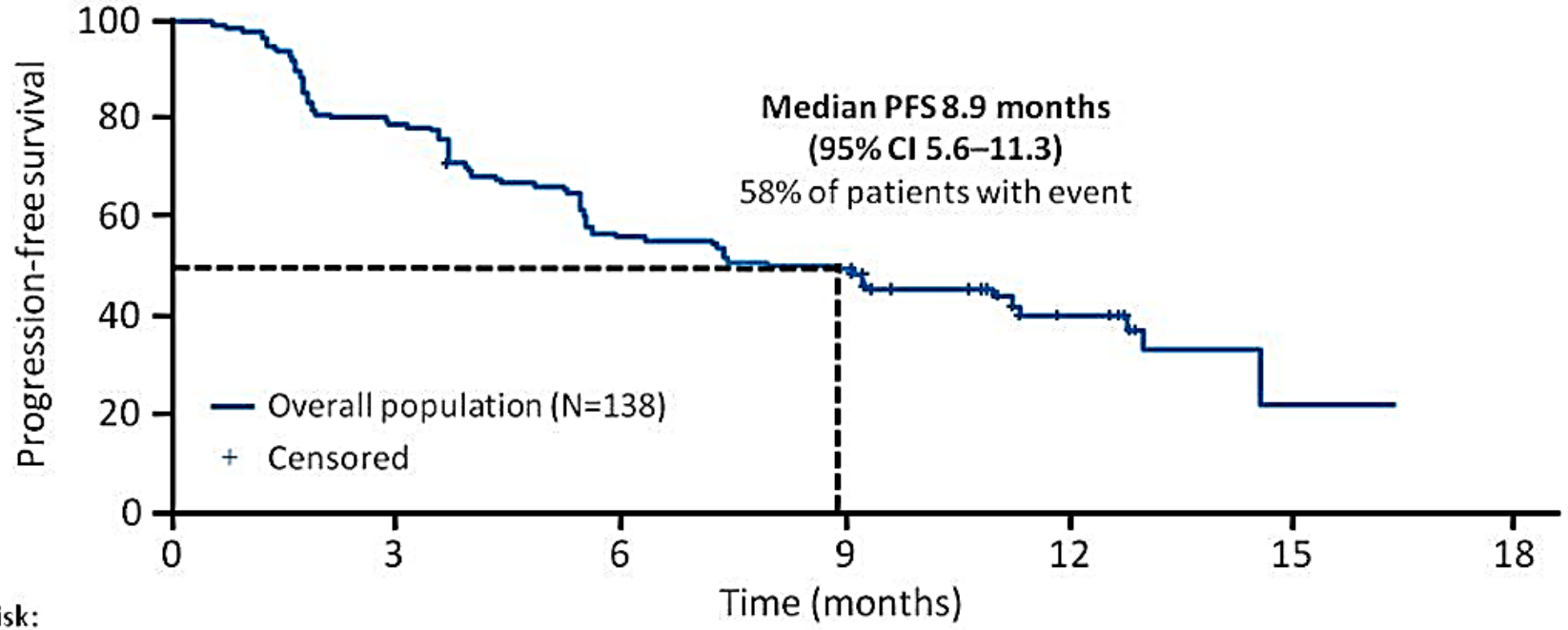
Alectinib

Response rates to alectinib in patients with crizotinib-resistant ALK+ NSCLC in NP28673

	RE population* (N=122)	Prior chemo* (N=96)	Chemo-naïve* (N=26)
Responders (ORR %)	**61 (50.0)**	**43 (44.8)**	**18 (69.2)**
[95% CI]	[40.8; 59.1]	[34.6; 55.3]	[48.2; 85.7]
Complete response	0 (0)	0 (0)	0 (0)
Partial response	61 (50.0)	43 (44.8)	18 (69.2)
Stable disease	35 (28.7)	31 (32.3)	4 (15.4)
Progressive disease	22 (18.0)	18 (18.8)	4 (15.4)
Missing / unevaluable	4 (3.3)	4 (3.3)	0 (0)
Disease control rate (%)	**96 (78.7)**	**74 (77.1)**	**22 (84.6)**
[95% CI]	[70.6; 85.6]	[67.4; 85.0]	[65.1; 95.6]

Ou et al. ASCO 2015 Abstract 8008

Median progression-free survival in crizotinib-resistant ALK+ NSCLC treated with alectinib



No. at risk:						
Overall population	138	109	76	65	17	1	–

Updated analysis cut-off 8 Jan 2015

Response and DCR rates with alectinib in ALK+ NSCLC with CNS metastases

	Patients with measurable CNS metastases (N=35)	All patients with CNS metastases* (N=84)
CNS response by IRC, n (%)		
Responder (ORR %)	**20 (57.1)**	**36 (42.9)**
[95% CI]	[39.4; 73.7]	[32.1; 54.1]
Complete response	**7 (20.0)**	**23 (27.4)**
Partial response	13 (37.1)	13 (15.5)
Stable disease	10 (28.6)	34 (40.5)
Progressive disease	3 (8.6)	7 (8.3)
Missing/unevaluable	2 (5.7)	7 (8.3)
Disease control rate (%)	**85.7%**	**83.3%**
[95% CI]	[69.7; 95.2]	[73.6; 90.6]

Ou et al. ASCO 2015 Abstract 8008

Efficacy of alectinib in crizotinib-resistant ALK+ NSCLC from the Phase 2 NP28761 in N.America

	Alectinib 600 mg BID (N=52)
Responders, n	20
ORR, % (95% CI)	38.5 (25.3-53.0)
Best overall CNS response, n (%) Complete response Non-complete response/non-progressive disease* Progressive disease Missing/unevaluable	 11 (21.2) 35 (67.3) 5 (9.6) 1 (1.9)
CNS DCR	46 (88.5)

Gandhi et al, ASCO 2015

Brigatinib

Latest data on brigatinib from NCT01449461

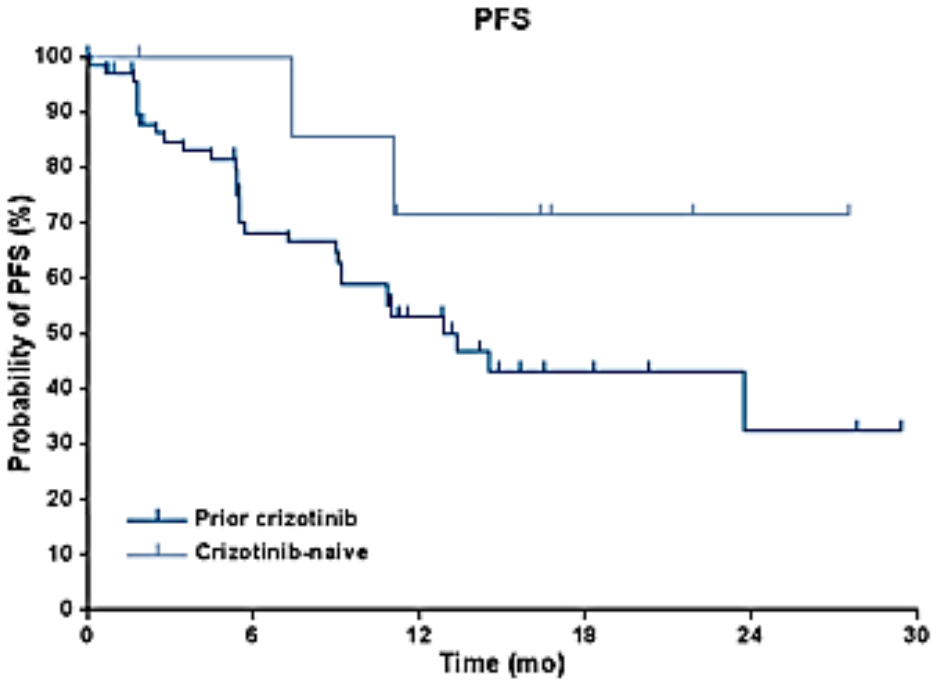
Endpoint	All Evaluable ALK+ NSCLC N=78[a]	With prior crizotinib N=70	Crizotinib-naïve N=8
ORR (CR + PR), n (%)	58 (74)[b]	50 (71)[c]	8 (100)[d]
[95% CI]	[63-84]	[59-82]	[63-100]
CR, n (%)	7 (9)	4 (6)	3 (38)
PR, n (%)	51 (65)	46 (66)	5 (63)
SD, n (%)	11 (14)[e]	11 (16)	0
PD, n (%)	6 (8)	6 (9)	0
Discontinued prior to scan, n (%)	3 (4)	3 (4)	0

Camidge, et al. ASCO 2015 Abstract 8062.

PFS in ALK+ NSCLC patients treated with brigatinib

- For patients with a follow-up scan, median (KM estimate) PFS was 13.4 months for patients treated with prior crizotinib (n=70) and not reached for crizotinib-naïve patients (N=8).

- For patients with a follow-up scan, median (KM estimate) PFS was 10.9 months for patients treated with 90 mg (N=14) and 13.4 months for patients treated with 90 mg for 7 days and then escalated to 180 mg (N=27); the difference was not significant.



Camidge, et al. ASCO 2015 Abstract 8062.

Brigatinib in ALK+ NSCLC with intracranial CNS metastases

	Patients with measurable intracranial CNS metastases N=15	Patients with only non-measurable intracranial CNS metastases N=33
ORR, n (%)	8 (53)	11 (33)
CR, n (%)	1 (7)	11 (33)
PR, n (%)	7 (47)	NA
SD or non-CR/non-PD, n (%)	5 (33)	18 (55)
PD, n (%)	2 (13)	4 (12)

Camidge, et al. ASCO

PF-06463922

PF-06463922 Is Active Against All Known ALK and ROS1 Resistance Mutations

Mutation Status	Cell Line	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
		PF-06463922	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1151Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	4.0	150	161	26

Target/ Cell Line (engineered)	Cellular ROS1 Phosphorylation Mean IC_{50} (nM)		
	PF-06463922	Crizotinib	Ceritinib (LDK-378)
CD74-ROS1(s) NIH3T3	0.23	11	51*
CD74-ROS1(s) BaF3	0.11	3.9	
CD74-ROS1(s) G2032R BaF3	186	2033	2666

- IC_{50} < 100 nM
- IC_{50} ≥ 100 < 200 nM
- IC_{50} ≥ 200 nM

* Based on results in BaF3 cell line

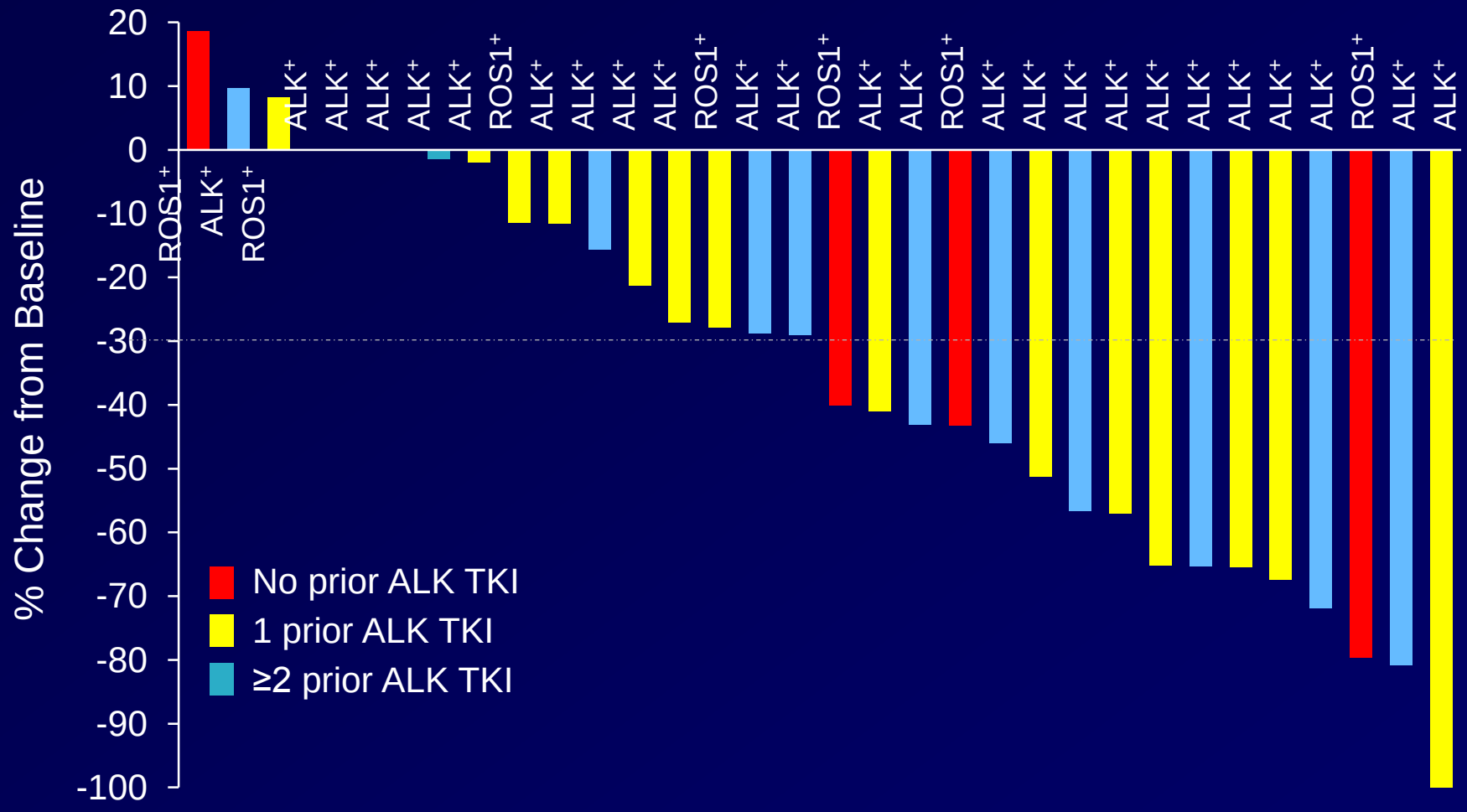
Baseline Patient Characteristics

Characteristic		PF-06463922 (N=44)
Age, years	Mean (SD)	52.5 (±12.8)
Sex, n (%)	Male Female	18 (41) 26 (59)
Race, n (%)	White Black Asian	34 (77) 4 (9) 6 (14)
Brain metastases, n (%)	Present	31 (70)
ALK/ROS1 status, n (%)	ALK^+ $ROS1^+$	33 (75) 11 (25)
Prior ALK TKI,* n (%)	0 1 ≥2	7 (16) 18 (41) 19 (43)

Clinical Activity: Best Overall Tumor Response

		PF-06463922 (n=34)*
Best overall response, n (%)	Complete response	1 (3)
	Confirmed partial response	10 (29)
	Unconfirmed partial response	4 (12)
	Stable disease	6 (18)
	Progressive disease	12 (35)
	Indeterminate	1 (3)
Overall ORR,† n (%)		15 (44)
95% CI‡		(27–62)

Clinical Activity: Maximum Percentage Change in Target Lesion Size*



ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

Clinical Activity: Intracranial Response

		PF-06463922 (n=25)*
Best overall response,† n (%)	Complete response	4 (16)
	Confirmed partial response	3 (12)
	Unconfirmed partial response	2 (8)
	Stable disease	9 (36)
	Progressive disease	6 (24)
	Indeterminate	1 (4)
Overall ORR,‡ n (%)		9 (36)
95% CI§		(18–58)

Optimal sequence

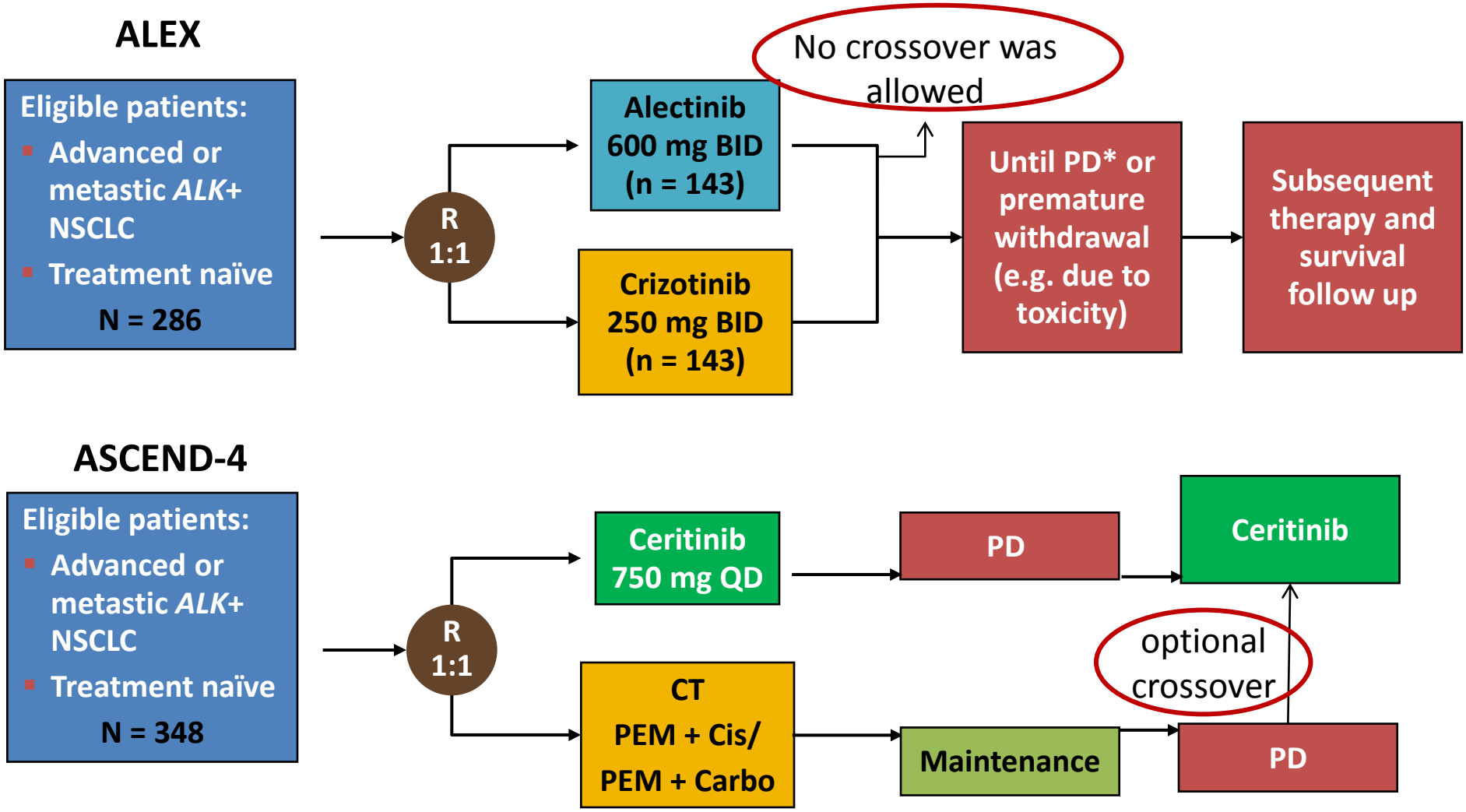
How to setup the most potent treatment strategy?

- Management of solid tumours is historically based on the sequential addition of treatments

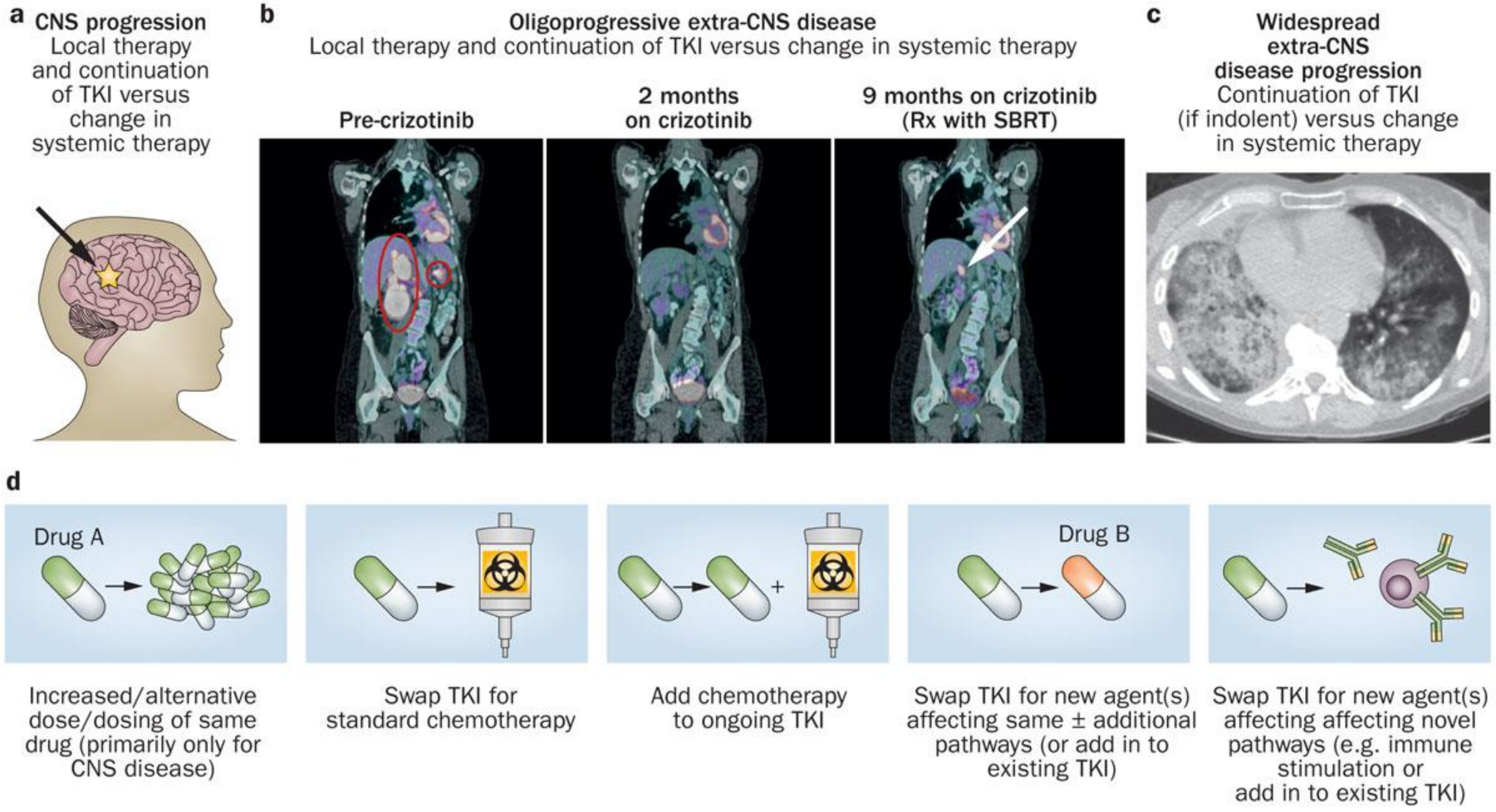
- No results of studies comparing starting crizotinib and then 2nd generation ALKi *vs* starting first with 2nd generation ALKi

- Efficacy of most of the sequences regarding ALKi is unknown
  - crizotinib after ceritinib?
  - intercalation of chemotherapy?
  - Anti-PD1 / anti-PDL1 strategies?

Phase 3 trial of next generation TKIs in first-line



Acquired resistance situation, clinically heterogeneous, different approaches



Camidge DR, et al. Nat Rev Clin Oncol 11:473-481, 2014

Not all patients with PD will receive further treatment
PROFILE 1014: 2nd line therapies

Therapy	Crizotinib (n=89)	Chemotherapy (n=132)
	no. of patients (%)	
Any systemic therapy	38 (43)	118 (89)†
Alectinib	1 (1)	3 (2)
Bevacizumab	2 (2)	0
Carboplatin	15 (17)	3 (2)
Ceritinib	6 (7)	2 (2)
Cisplatin	13 (15)	1 (1)
Crizotinib	1 (1)	114 (86)†
Cyclophosphamide	0	1 (1)
Denosumab	0	1 (1)
Docetaxel	3 (3)	6 (5)
Doxorubicin	0	1 (1)
Gefitinib	1 (1)	1 (1)
Gemcitabine	6 (7)	1 (1)
Icotinib	1 (1)	0
Investigational drug (unspecified)	3 (3)	3 (2)
Paclitaxel	1 (1)	2 (2)
Pemetrexed	25 (28)	3 (2)
Tegafur/gimeracil/oteracil	1 (1)	0
Vinblastine	0	1 (1)
Vinorelbine	3 (3)	0
Other therapeutic products	1 (1)	0

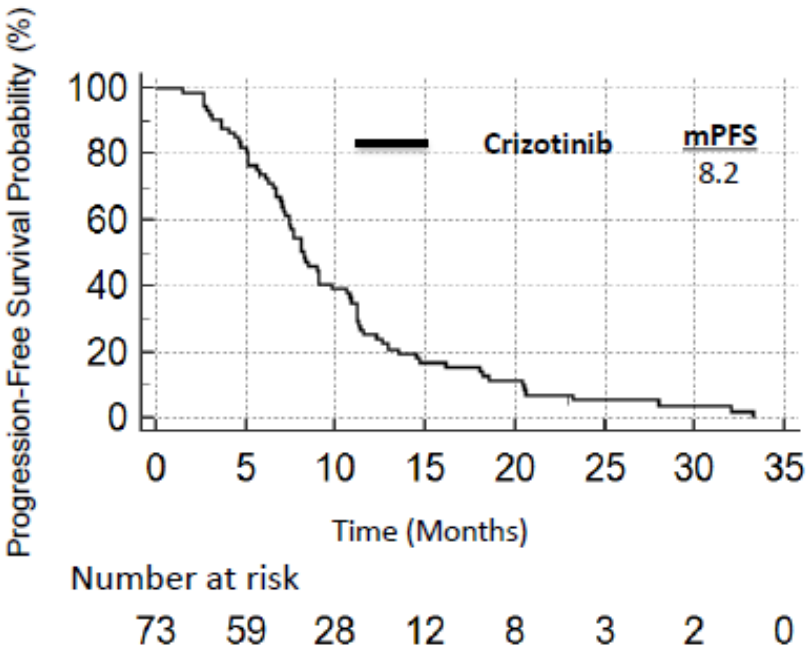
Solomon BJ, et al. *N Engl J Med.* 2014;371:2167-77.

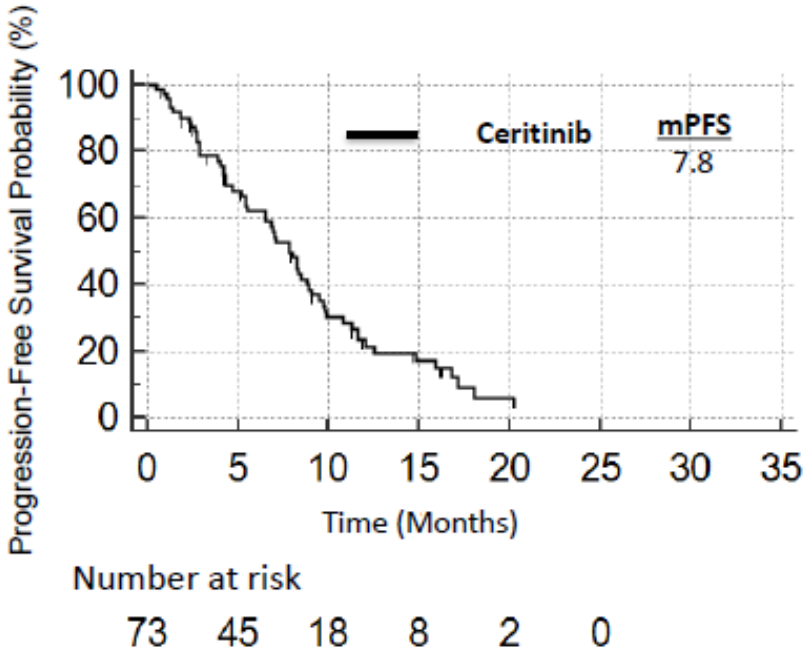
Sequential crizotinib and ceritinib in NSCLC

Characteristic	All Patients (N=73)
Age at Diagnosis	
Median	50
Range	22-72
Sex – no. (%)	
Male	38 (52)
Female	35 (48)
Ethnicity – no. (%)	
Caucasian	54 (74)
Asian	17 (23)
Other	2 (3)
Smoking History – no. (%)	
Never	57 (78)
Light (≤10 pack years)	10 (14)
Heavy (>10 pack years)	6 (8)
Histology – no. (%)	
Adenocarcinoma	69 (95)
Squamous	3 (4)
Adenosquamous	1 (1)
Stage at Diagnosis – no. (%)	
Stage I-II	2 (3)
Stage III-IV	71 (97)
Lines of Therapy Prior to Crizotinib[a]	
0	10 (14)
1	32 (44)
2	16 (22)
3	7 (10)
4-8	8 (11)
Brain Metastases Prior to Crizotinib – no. (%)[b]	
Present	25 (35)
Absent	47 (65)

Gainor JF, et al. Clin Cancer Res 2015

Sequential crizotinib and ceritinib in NSCLC





The median combined PFS for sequential treatment with crizotinib and ceritinib was 17.4 mo

Gainor JF, et al. Clin Cancer Res, 2015

Summary

- ALK+ patients, clear molecular subgroup with specific treatment options
- In ALKi-naïve patients, 1st-line crizotinib, standard treatment
- Brain metastasis, common
  - Treatment, a challenge
- A number of 2nd generation ALKi now available / in development
- No studies establishing optimal sequence
  - Difficult to design such studies, no control over further lines of therapy

Thanks!!

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