A Teaching Affiliate of Harvard Medical School

Optimal Approach to ALK-Positive NSCLC

- first-line therapy -

Alice T. Shaw, MD, PhD

February 11, 2017

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

CANCER CENTER

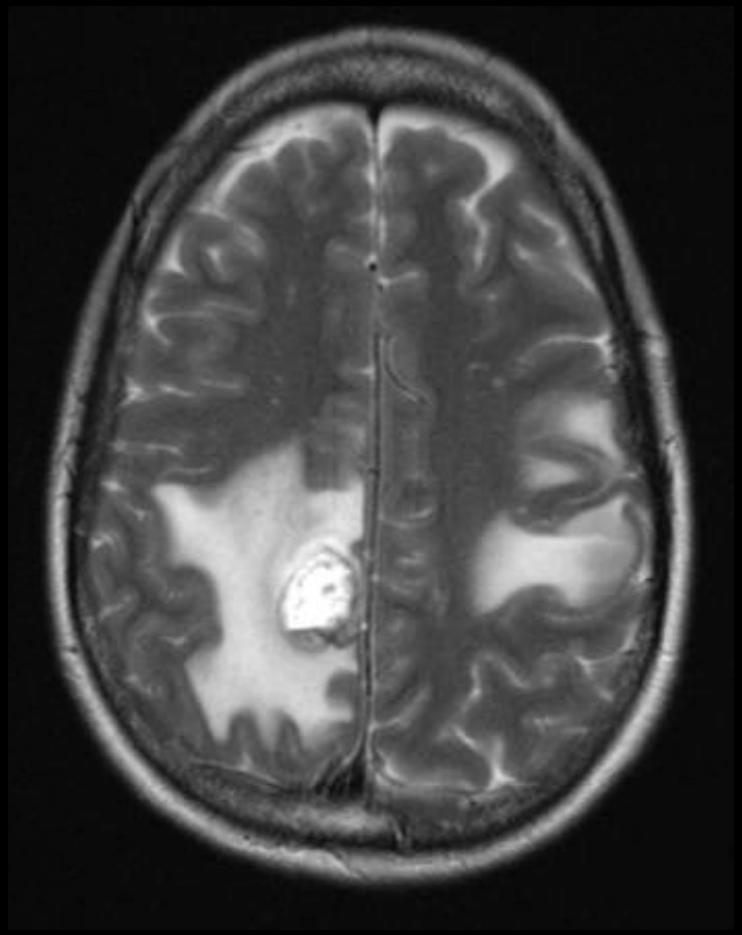
Case

- 41 yo F neversmoker with no past medical history who was incidentally found to have a 3.7-cm LLL mass.
- Workup revealed stage 3A NSCLC, adenocarcinoma histology. Brain MRI was negative.
- She underwent induction chemoRT, VATS LLL resection, and 4 cycles of consolidation chemotherapy.
- One year after completing chemotherapy, she developed headaches and neck pain.
- Brain MRI with multiple lesions, measuring up to 1.9 cm.

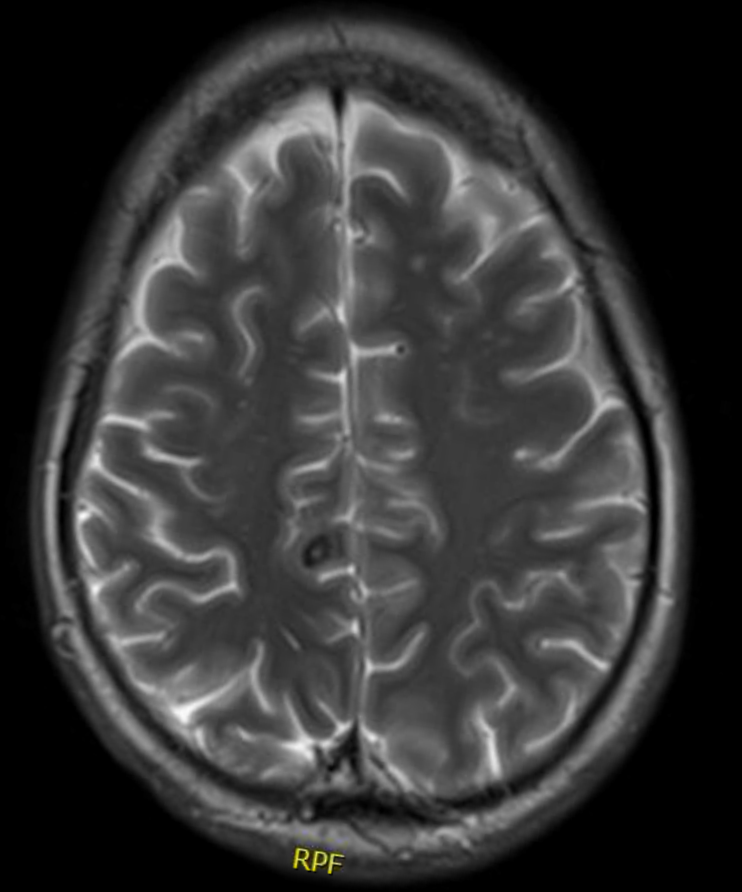
Case

- She was started on steroids
- PET-CT with FDG: avid L hilar and mediastinal lymphadenopathy
- Molecular testing was performed on her previous diagnostic biopsy
- EGFR wild type, ALK IHC positive, ROS1 FISH negative
- NGS confirmed a HIP1-ALK rearrangement
- WBRT and/or SRS was recommended, followed by crizotinib
- We recommended initiation of first-line alectinib

Case



Baseline



After 3 months of alectinib

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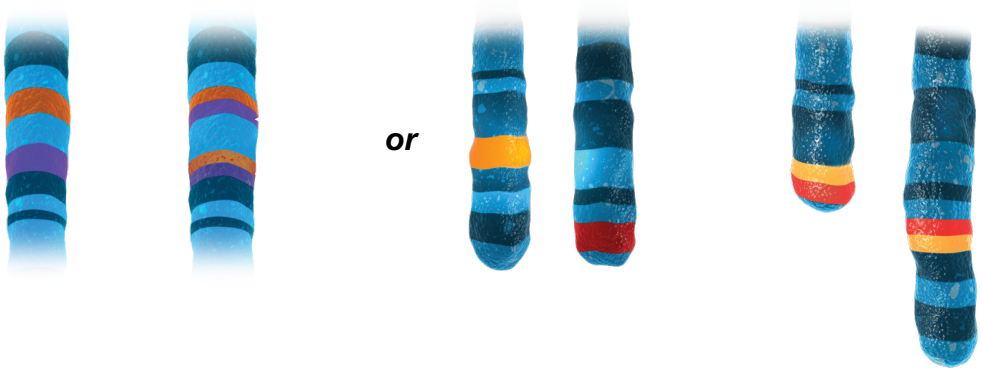
Disclosures

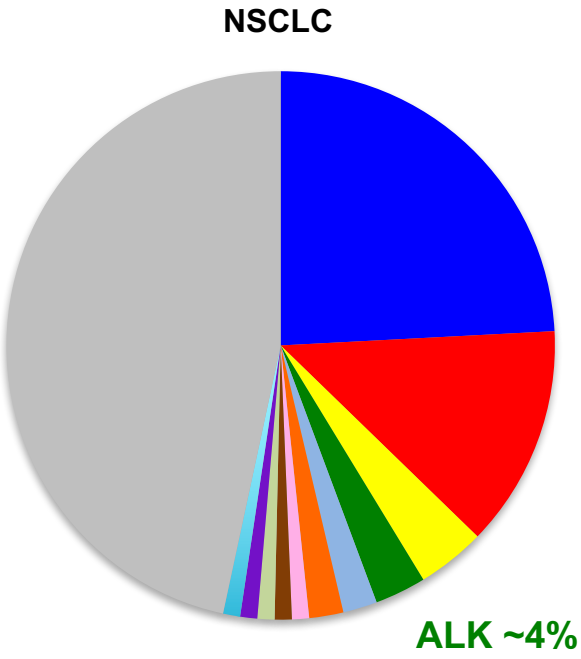
Advisory Committee	EMD Serono Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc
Consulting Agreements	Blueprint Medicines, Daiichi Sankyo Inc, EMD Serono Inc, Ignyta Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Taiho Oncology Inc

ALK-Rearranged NSCLC

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda, Young Lim Choi, Munehiro Enomoto, Shuji Takada, Yoshihiro Yamashita, Shunpei Ishikawa, Shin-ichiro Fujiwara, Hideki Watanabe, Kentaro Kurashina, Hisashi Hatanaka, Masashi Bando, Shoji Ohno, Yuichi Ishikawa, Hiroyuki Aburatani, Toshiro Niki, Yasunori Sohara, Yukihiko Sugiyama & Hiroyuki Mano





Common features:
Younger age
Neversmoking history
Adenocarcinoma
CNS metastasis
Sensitivity to ALK TKis

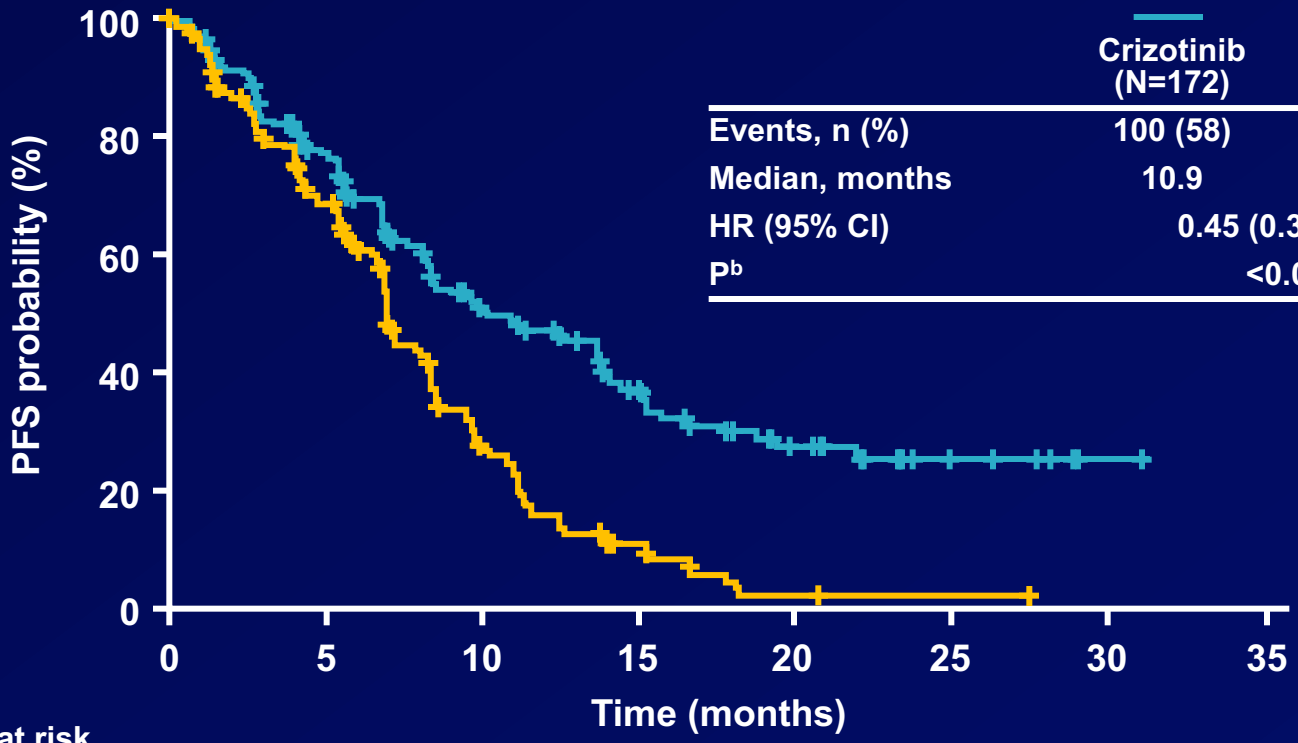
Soda et al., Nature 448: 561-7, 2007

Crizotinib Is a Standard Therapy for Patients with Metastatic ALK+ NSCLC

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
Phase	1	2	3	3
Line of therapy	Any line	2nd line and beyond	2nd line	1st line
Response rate	61%	60%	65%	74%
PFS, median (mos)	9.7	8.1	7.7	10.9
Survival probability at 12 mos	75%	NA	70%	84%

[1]Camidge et al., Lancet Oncol 13(10): 1011-9, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Solomon et al., NEJM 371(23): 2167-77, 2014

Crizotinib Is Superior to Platinum Combination Chemotherapy in First-Line ALK+ NSCLC



	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]	<0.001	

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

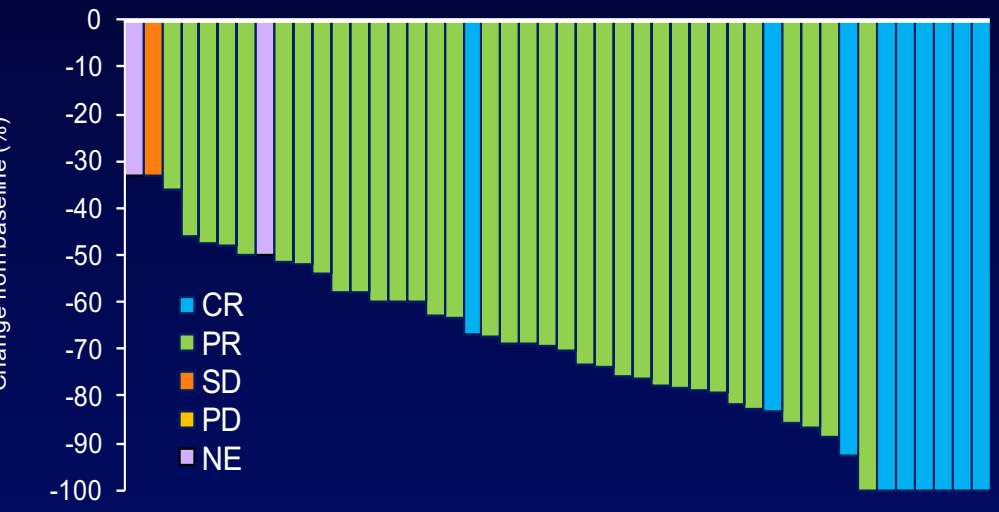
[a]As-treated population: pemetrexed−cisplatin, 6.9 months (n=91; HR: 0.49; P<0.0001); pemetrexed−carboplatin, 7.0 months (n=78; HR: 0.45; P<0.0001)

[b]2-sided stratified log-rank test

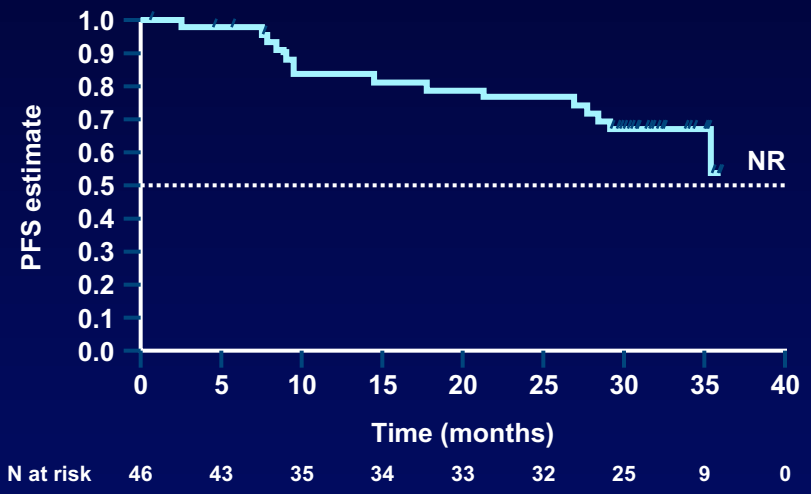
Solomon et al., NEJM 371(23): 2167-77, 2014

Alectinib in TKI-Naïve ALK+ NSCLC (AF-001JP Phase I/II Study)

ORR: 93.5% (95% CI: 82.1 - 98.6)

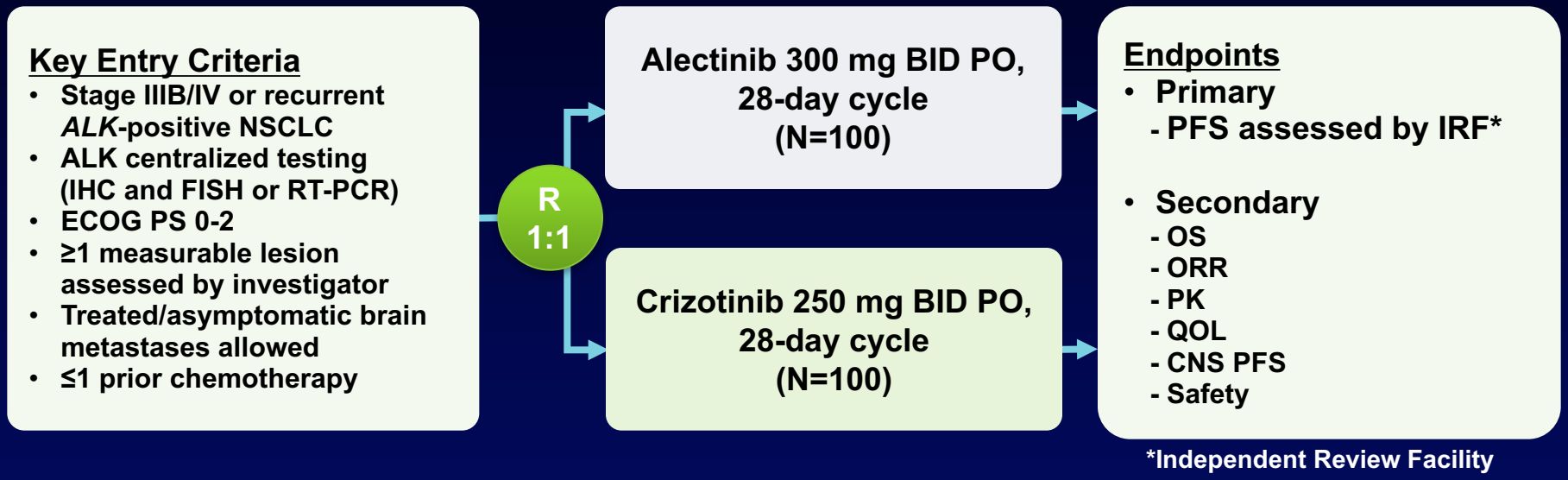


Median PFS: Longer than 29 months



1. Kozuki T et al. JSMO 2015 2. Takeuchi K et al. *Ann Oncol* 27:185-92, 2016

J-ALEX: Phase III Study Comparing Alectinib to Crizotinib in Japanese TKI-Naïve Patients



*Independent Review Facility

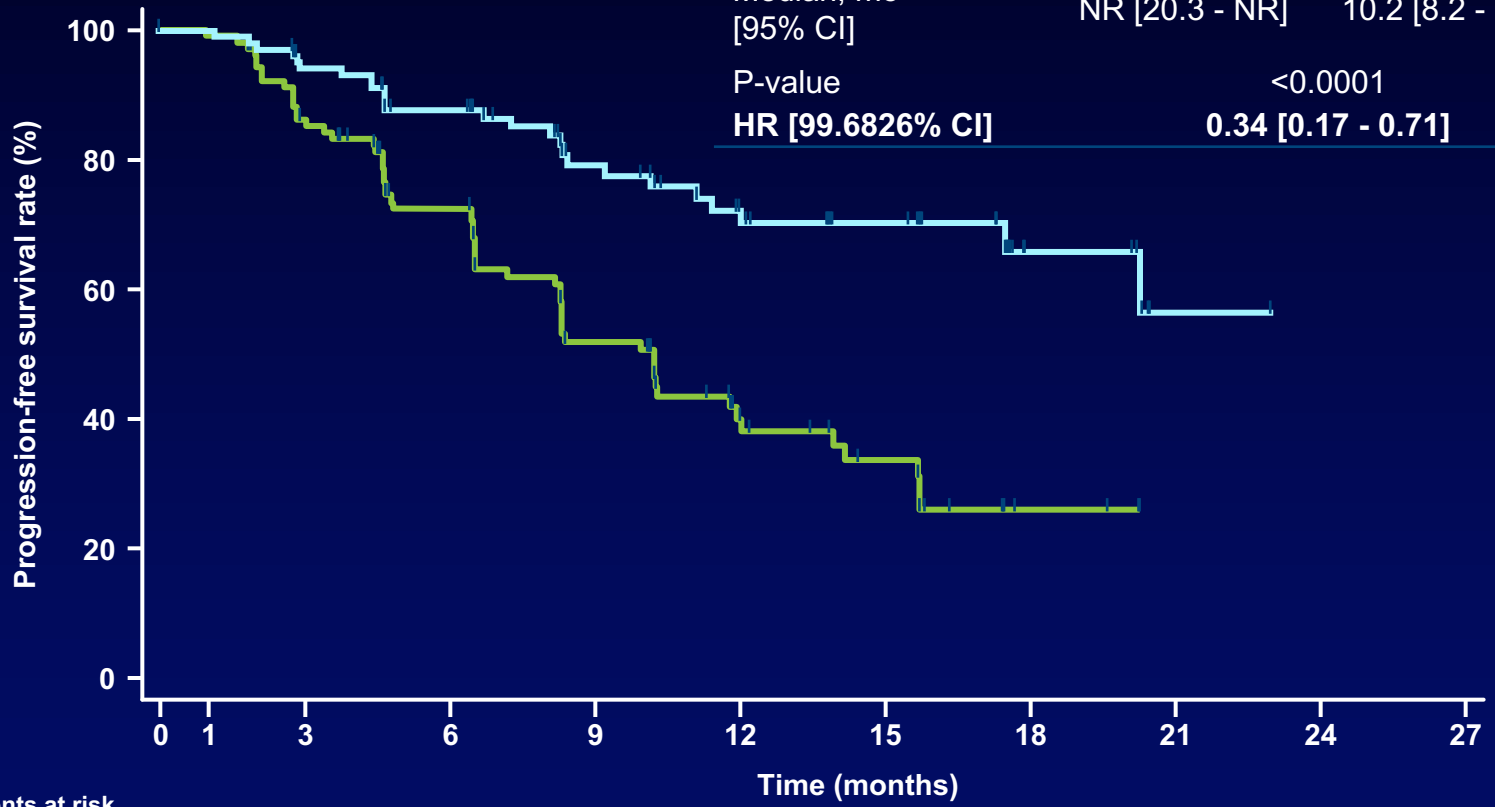
Stratification factors:
Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

Statistical considerations:
Targeted HR for PFS = 0.643
Assumed mPFS 14 vs 9 months
Two-sided significance level: 0.05, power: 80%

Nokihara et al., ASCO 2016

Primary Endpoint: PFS by IRF (ITT Population)

	Alectinib (N=103)	Crizotinib (N=104)
Events, n (%)	25 (24.3%)	58 (55.8%)
Median, mo [95% CI]	NR [20.3 - NR]	10.2 [8.2 - 12.0]
P-value	<0.0001	
HR [99.6826% CI]	**0.34 [0.17 - 0.71]**	



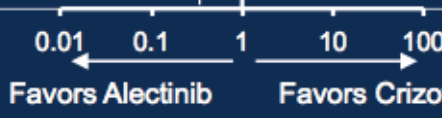
No. of patients at risk

Alectinib	103	103	93	76	49	36	27	9	1
Crizotinib	104	102	86	65	40	21	14	4	

Nokihara et al., ASCO 2016

Subgroup Analysis of PFS by IRF

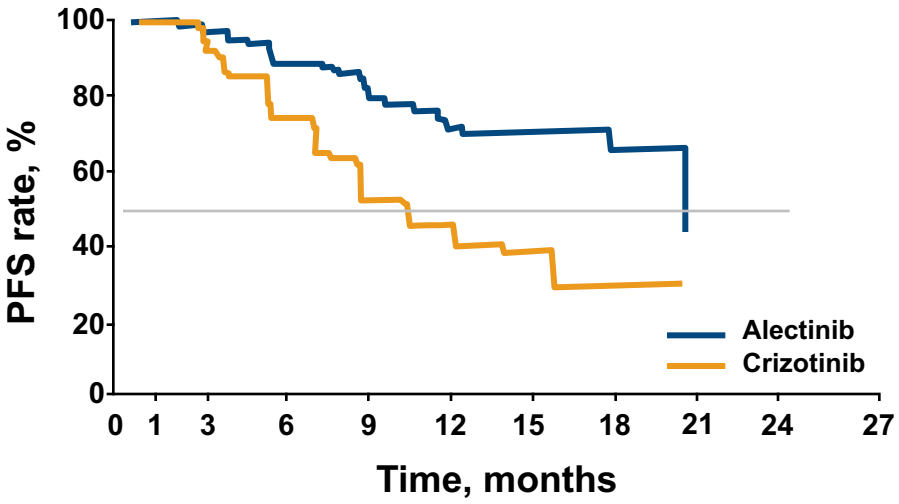
Subgroup		Alectinib (N=103) n	Alectinib (N=103) Events	Crizotinib (N=104) n	Crizotinib (N=104) Events	HR [95% CI]
Overall		103	25	104	58	0.34 [0.21 - 0.54]
ECOG performance status	0/1	101	24	102	57	0.33 [0.20 - 0.53]
	2	2	1	2	1	1.41 [0.08 - 23.57]
Prior chemotherapy	0	66	15	67	35	0.30 [0.17 - 0.56]
	1	37	10	37	23	0.39 [0.18 - 0.83]
Clinical stage	Postoperative recurrence	24	6	26	13	0.49 [0.18 - 1.30]
	Stage IIIB/IV	79	19	78	45	0.31 [0.18 - 0.52]
Age group	≥75	12	3	10	5	0.28 [0.06 - 1.19]
	<75	91	22	94	53	0.34 [0.21 - 0.56]
Smoking status	Never smoker	56	18	61	33	0.50 [0.28 - 0.89]
	Past or Current smoker	47	7	43	25	0.18 [0.08 - 0.42]
Brain metastases at baseline	Yes	14	1	29	16	0.08 [0.01 - 0.61]
	No	89	24	75	42	0.39 [0.23 - 0.64]
ALK testing method	IHC and FISH	96	21	94	52	0.30 [0.18 - 0.50]
	RT-PCR	7	4	10	6	0.80 [0.22 - 2.90]
Sex	Female	62	16	63	37	0.31 [0.17 - 0.57]
	Male	41	9	41	21	0.35 [0.16 - 0.77]



Nokihara et al., ASCO 2016

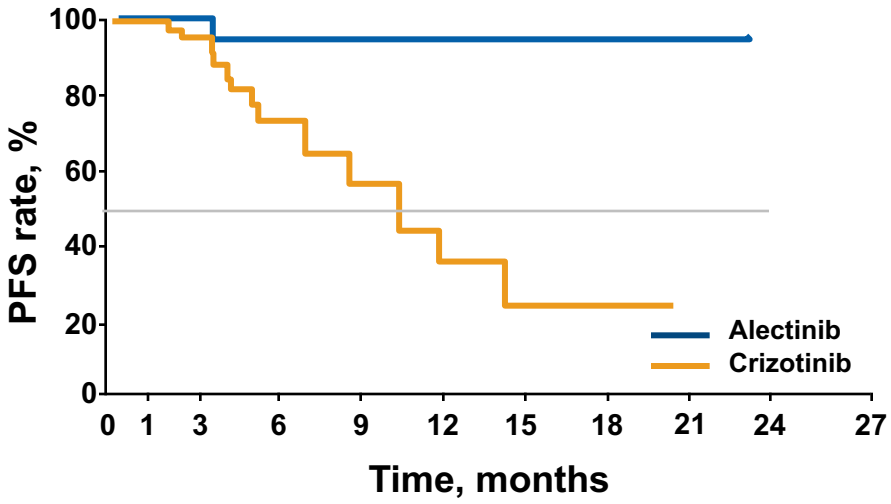
J-ALEX: PFS With or Without Brain Mets at Baseline

WITHOUT BRAIN METS



	Alectinib (N=89)	Crizotinib (N=75)
Event	24 (27.0%)	42 (55.2%)
Median [95% CI]	20.3 [17.5, —]	10.2 [6.5, 14.2]
P-value	0.0001	
HR [95% CI]	0.37 [0.22, 0.62]	

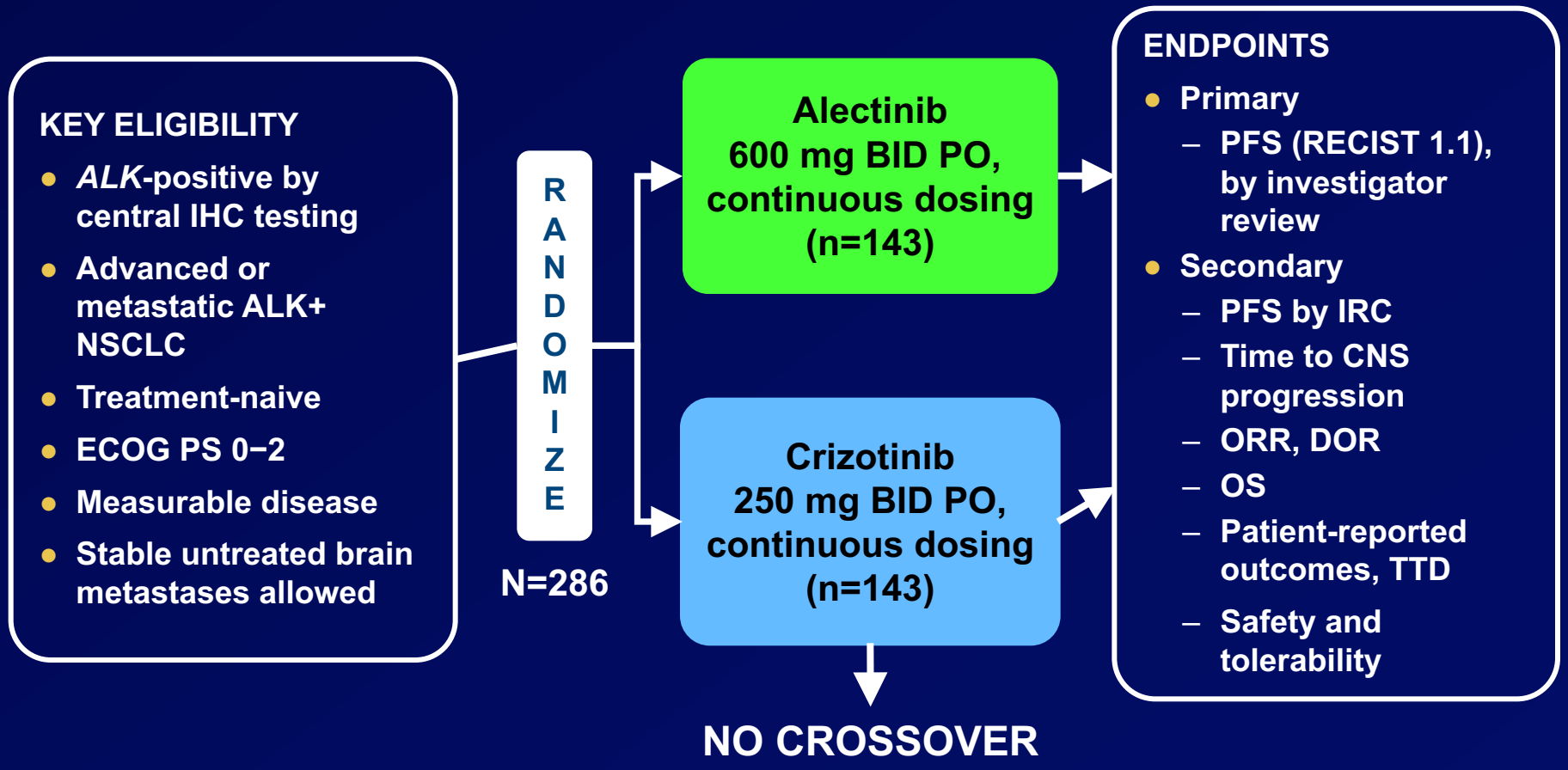
WITH BRAIN METS



	Alectinib (N=14)	Crizotinib (N=29)
Event	1 (7.1%)	16 (55.2%)
Median [95% CI]	— [—, —]	10.2 [6.5, 14.2]
P-value	0.0002	
HR [95% CI]	0.09 [0.1, 0.74]	

Kim YH, et al. WCLC 2016. Abstract 5597

ALEX: Global Randomized First-Line Study of Alectinib vs Crizotinib



Ceritinib as First ALK TKI in Advanced ALK+ NSCLC

	ASCEND-1[a] (FAS, N=83, by investigator)	ASCEND-3[b] (FAS, N=124, by BIRC)
ORR (95% CI), %	72 (61-82)	63.7 (54.6-72.2)
Median DOR (95% CI), months	17.0 (11.3-NE)	23.9 (16.6-NE)
DCR (95% CI), %	74 (67-81)	86.3 (79.0-91.8)
Median PFS (95% CI), months	18.4 (11.1-NE)	18.4 (10.9-26.3)
Median OS (95% CI), months	Not reached (19.6 – NE)	NE

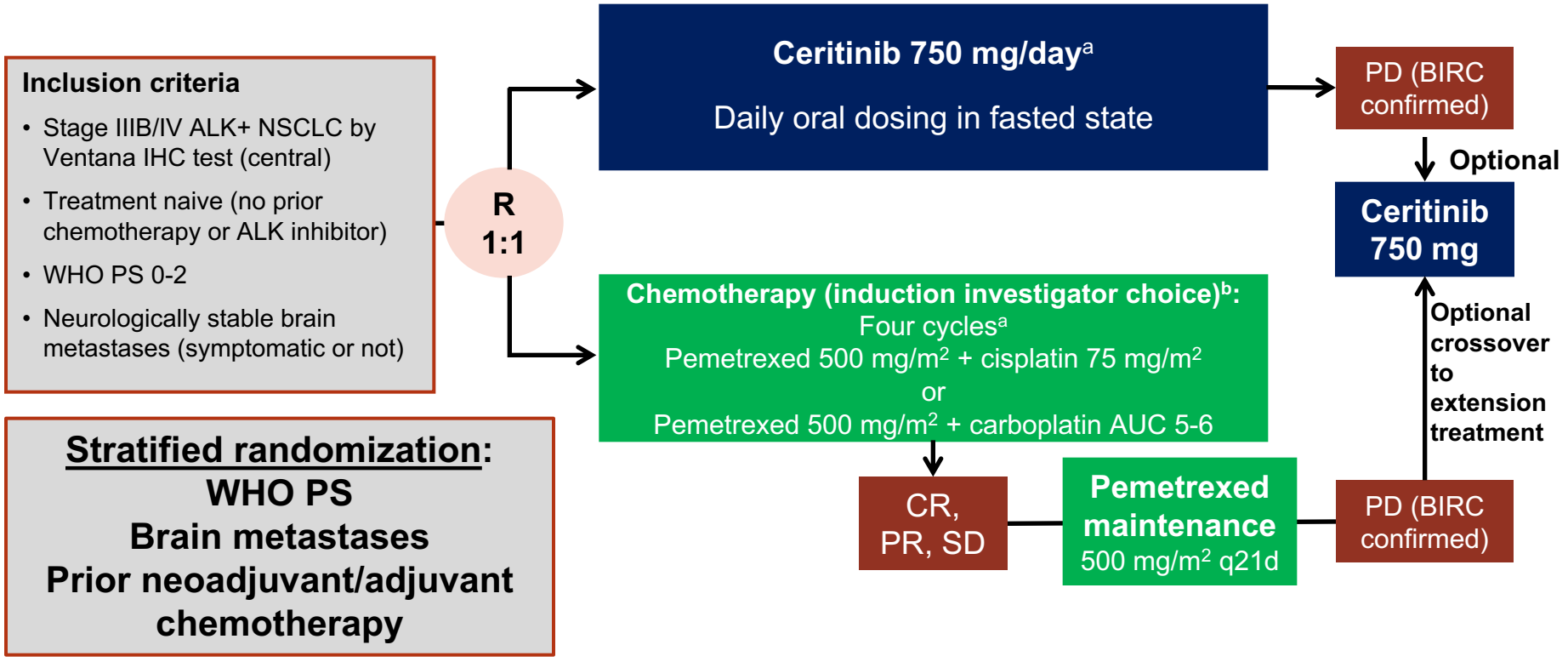
BIRC, Blinded Independent Review Committee; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]81% of patients had at least 1 prior line of chemotherapy.

[b]98.4% of patients had at least 1 prior line of chemotherapy.

Kim DW et al. *Lancet Oncol* 2016;17(4):452-463; Felip E et al. Presented at: European Society for Medical Oncology Annual Meeting October 7-11, 2016, Copenhagen, Denmark [abstract 1208O].

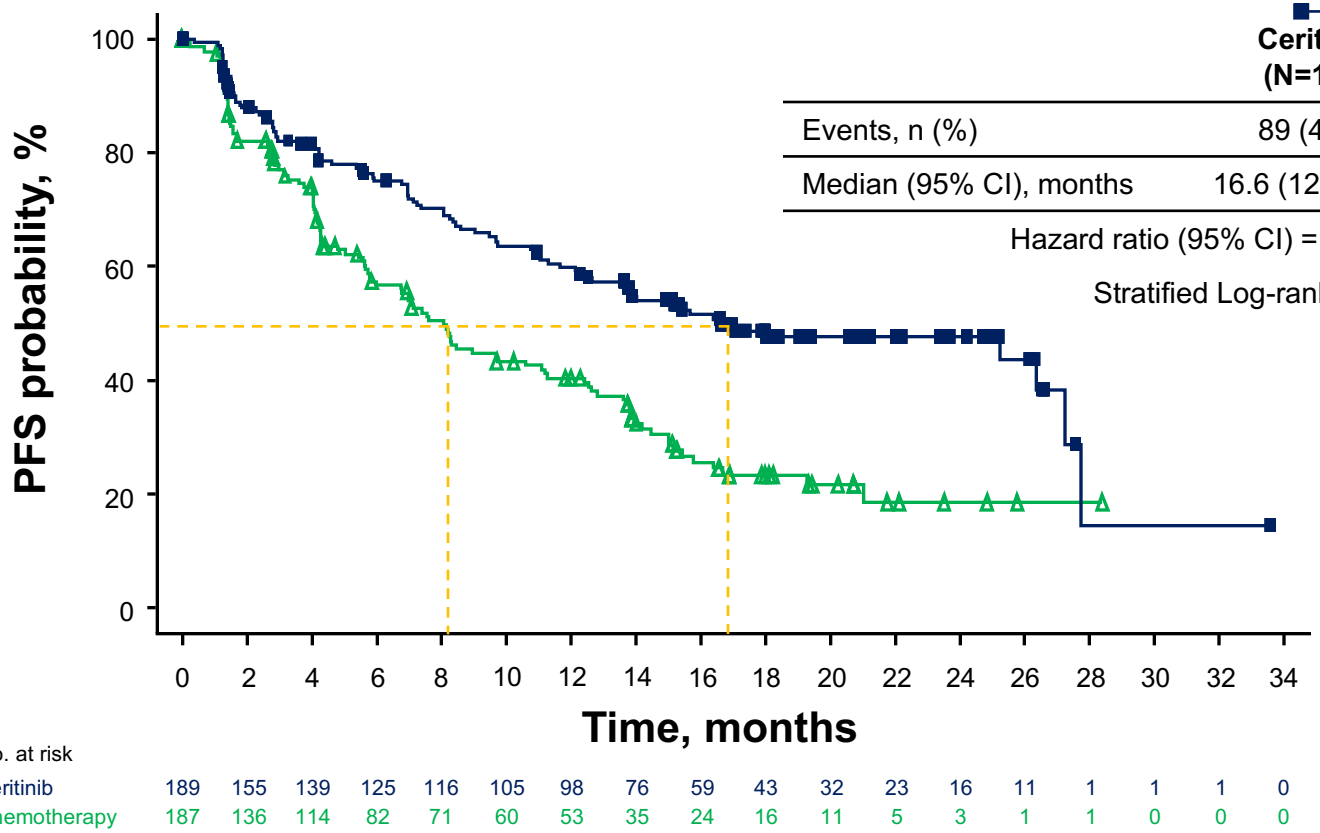
ASCEND-4: Randomized Phase 3 Study Comparing First-Line Ceritinib with Chemo



IHC, immunohistochemistry; PD, progressive disease; PS, performance status; WHO, World Health Organization.
[a]One cycle = 21 days.
[b]At the time when ASCEND-4 was designed and initiated, pemetrexed-platinum chemotherapy followed by pemetrexed maintenance was the standard of care in patients with non-squamous advanced NSCLC.
de Castro G, et al. Presented at WCLC 2016.

Primary Endpoint: PFS by BIRC

Ceritinib demonstrated an estimated 45% risk reduction vs chemotherapy



	Ceritinib (N=189)	Chemotherapy (N=187)
Events, n (%)	89 (47.1)	113 (60.4)
Median (95% CI), months	16.6 (12.6-27.2)	8.1 (5.8-11.1)

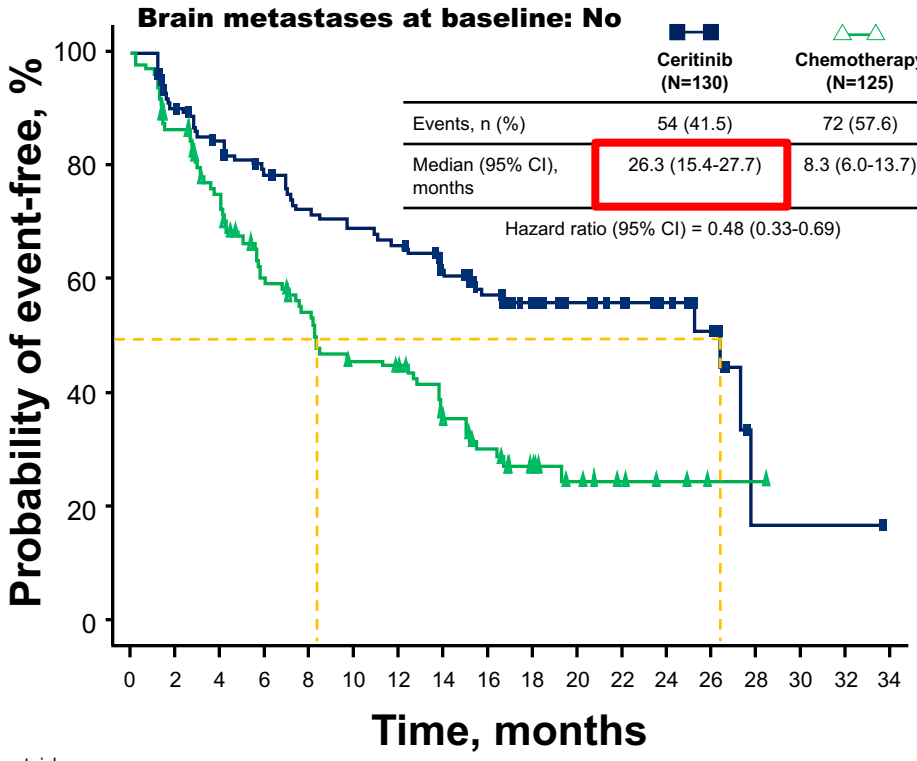
Hazard ratio (95% CI) = 0.55 (0.42-0.73)

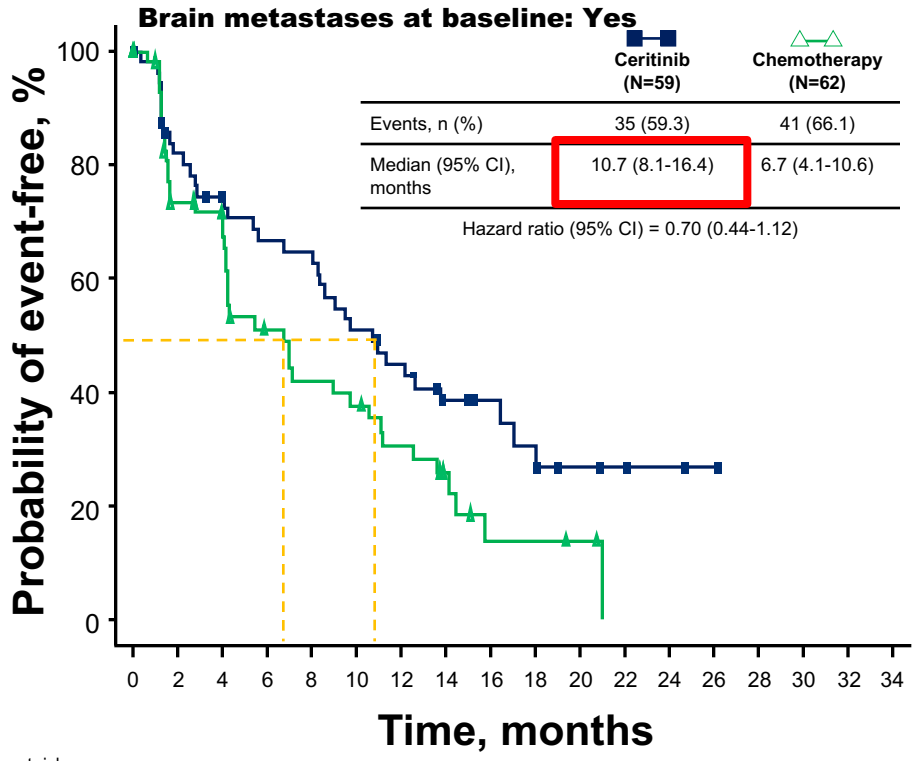
Stratified Log-rank *P*<0.001

de Castro G, et al. Presented at WCLC 2016

PFS by BIRC in Patients Without and With Brain Metastases

Ceritinib achieved better PFS in patients without and with brain metastases





de Castro G, et al. Presented at WCLC 2016

Summary

- Crizotinib is the current first-line therapy for patients with newly diagnosed, metastatic ALK+ NSCLC
- Second-generation ALK inhibitors are approved for patients who previously received crizotinib
- Second-generation ALK TKIs are highly effective in the first-line setting
  - Alectinib: mPFS NR (vs crizotinib)
  - Ceritinib: mPFS 16.6 mos (vs chemo)
- Alectinib is particularly active in the CNS
- Side effect profiles will impact selection of first-line ALK inhibitor