CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on Targeted Treatment of Metastatic Non-Small Cell Lung Cancer

March 16, 2017
6:30 PM – 8:00 PM

Faculty

Ramaswamy Govindan, MD
Joel W Neal, MD, PhD
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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Disclosures for Dr Govindan

Advisory Committee	AbbVie Inc, Ariad Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, INC Research, Roche Laboratories Inc
Consulting Agreements	AbbVie Inc, Ariad Pharmaceuticals Inc, Astellas Pharma Global Development Inc, Baxalta Inc, Bristol-Myers Squibb Company, Genentech BioOncology, INC Research
Contracted Research and Speakers Bureau	AbbVie Inc, Ariad Pharmaceuticals Inc, Baxalta Inc, INC Research

Disclosures for Dr Neal

Consulting Agreements	Ariad Pharmaceuticals Inc, ARMO BioSciences, Boehringer Ingelheim Pharmaceuticals Inc, CARET/Physicians Resource Management, Clovis Oncology, Nektar
Contracted Research	Ariad Pharmaceuticals Inc, ArQule Inc, Boehringer Ingelheim Pharmaceuticals Inc, Exelixis Inc, Genentech BioOncology, Merck, Nektar, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc

Disclosures for Dr Riely

Consulting Agreement	Genentech BioOncology
Contracted Research	Ariad Pharmaceuticals Inc, Astellas Pharma Global Development Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc

Disclosures for Moderator Neil Love, MD

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Module 2: Treatment of Patients with ALK and ROS1 Tumor Alterations

What would be your preferred first-line systemic therapy recommendation for a younger, otherwise healthy patient with metastatic nonsquamous NSCLC and a TPS of 10% who is demonstrated to have an ALK translocation? A TPS of 60%?

	TPS 10%	TPS 60%
 RAMASWAMY GOVINDAN, MD	Crizotinib	Crizotinib
 JOEL W NEAL, MD, PHD	Crizotinib	Crizotinib
 GREGORY J RIELY, MD, PHD	Crizotinib	Crizotinib
 JULIE R BRAHMER, MD	Crizotinib	Crizotinib
 COREY J LANGER, MD	Alectinib	Crizotinib
 HEATHER WAKELEE, MD	Crizotinib or ceritinib	Crizotinib

Cost and reimbursement issues aside, for a patient with untreated ALK-rearranged, widely metastatic nonsquamous cancer with multiple bilateral asymptomatic brain metastases that would require whole brain radiation therapy, do you generally start with a TKI and hold the radiation therapy?

 RAMASWAMY GOVINDAN, MD	Yes, alectinib
 JOEL W NEAL, MD, PHD	Yes, ceritinib or alectinib
 GREGORY J RIELY, MD, PHD	Yes, alectinib or crizotinib if necessary
 JULIE R BRAHMER, MD	Yes, alectinib
 COREY J LANGER, MD	Yes, alectinib if possible
 HEATHER WAKELEE, MD	Yes, ceritinib or alectinib

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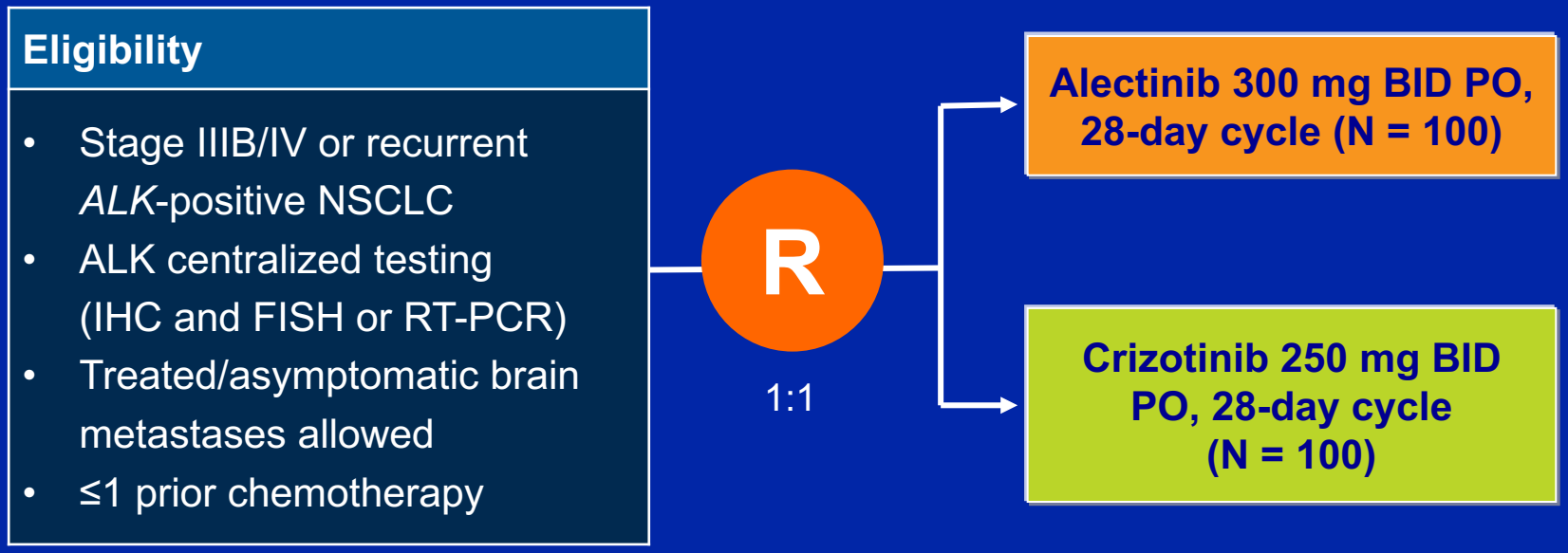
ALK Inhibitors: Comparison of Activity

	Crizotinib	Ceritinib	Alectinib	Brigatinib
Indication	ALK+ NSCLC	ALK resistance	ALK resistance	(Not yet approved)
Highly active	Yes	Yes	Yes	Yes
Tolerability	Good	Moderate	Good	Good
CNS activity	Some	Good	Good	Good
Potency against resistance	Poor	Moderate	Moderate	Good

Courtesy of Geoffrey R Oxnard, MD

Kwak et al. *NEJM* 2010; Awad et al. *Clin Adv Hematol Oncol* 2014; Kodama et al. *MCT* 2014; Solomon et al. *JCO* 2016.

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

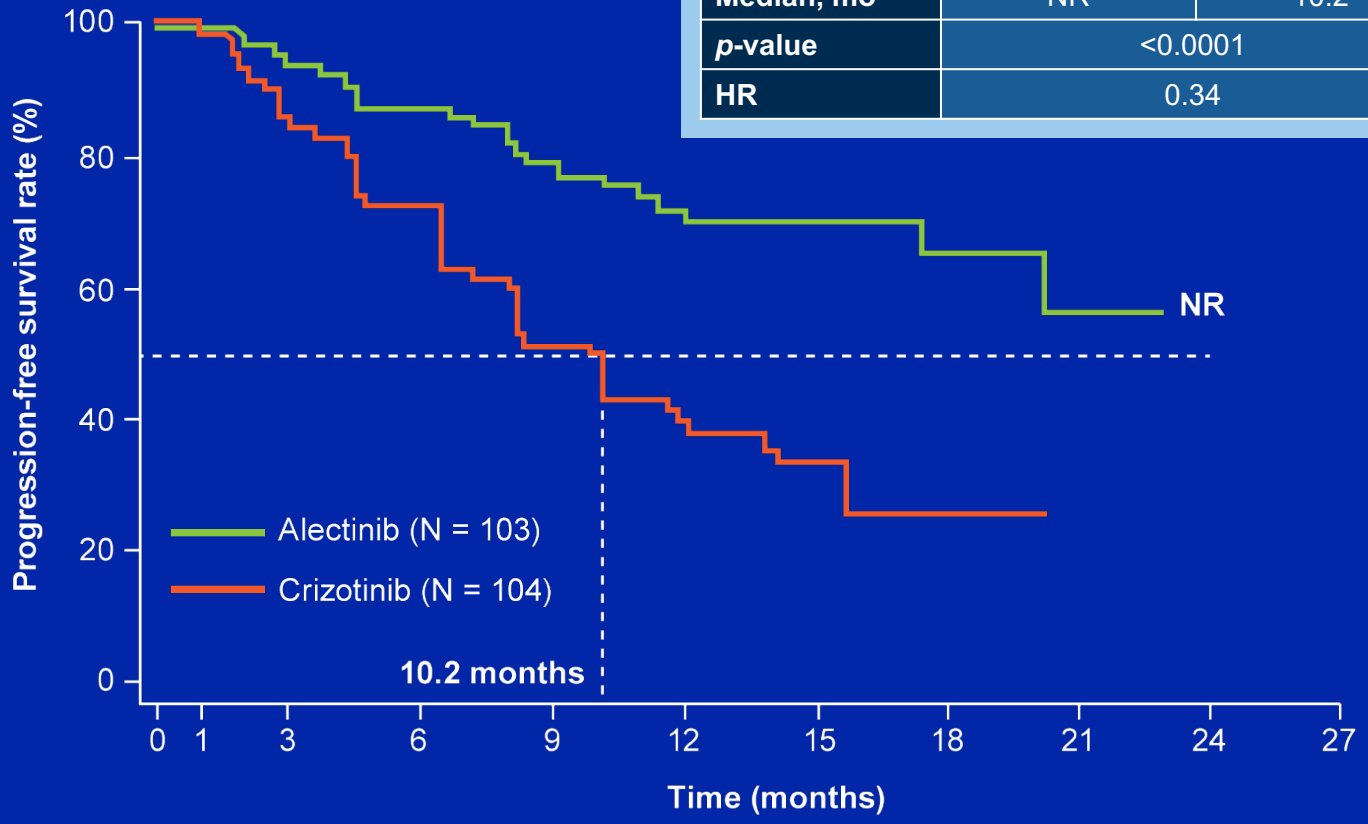


Primary Endpoint: PFS assessed by independent review facility

Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

J-ALEX Study: Progression-Free Survival (ITT)

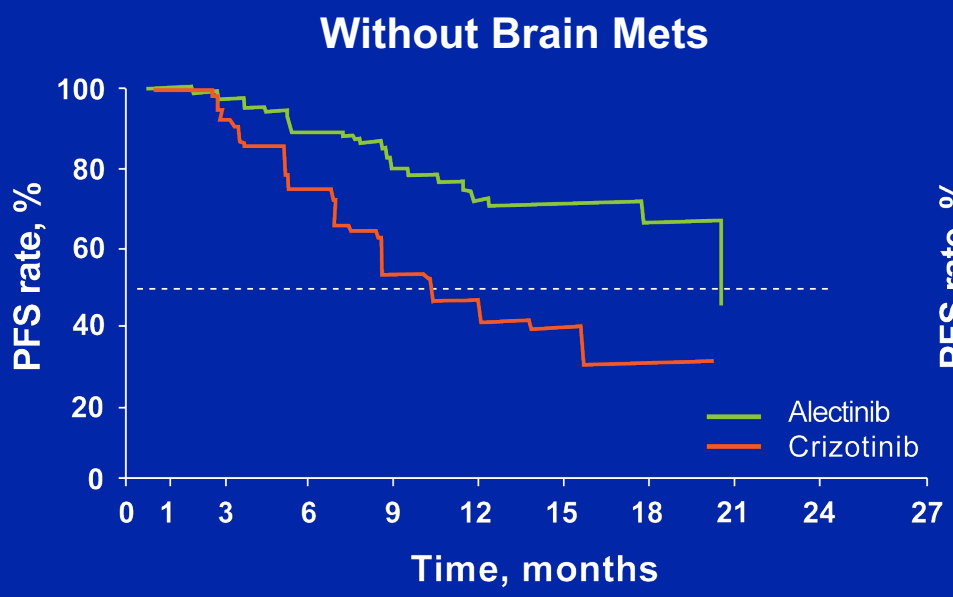
	Alectinib	Crizotinib
Events, n (%)	25 (24.3%)	58 (55.8%)
Median, mo	NR	10.2
***p*-value**	<0.0001	
HR	0.34	

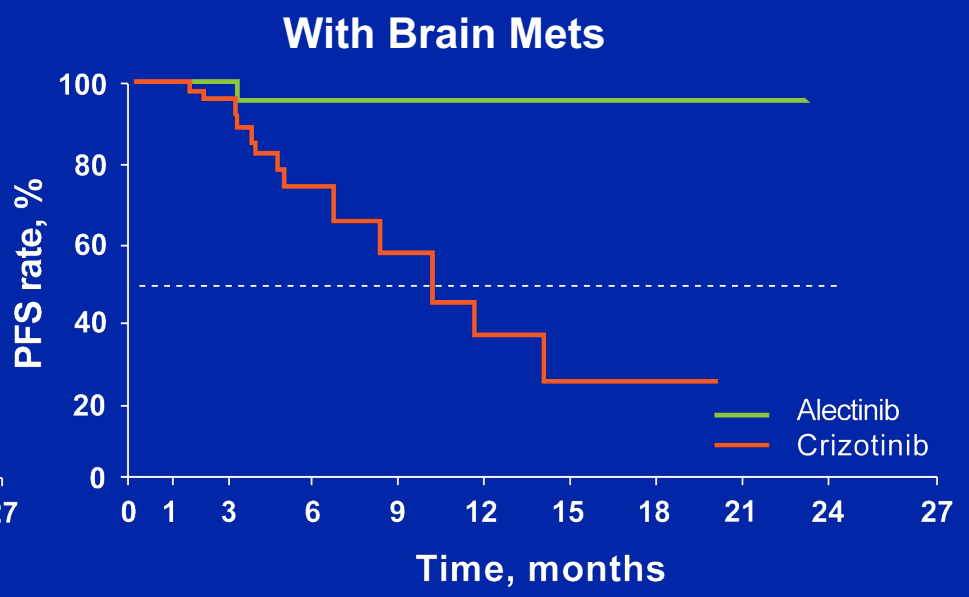


- Consistent benefit observed with alectinib in all subgroups
- Patients with brain metastases: HR 0.08 favoring alectinib

Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

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





	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]	

	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.

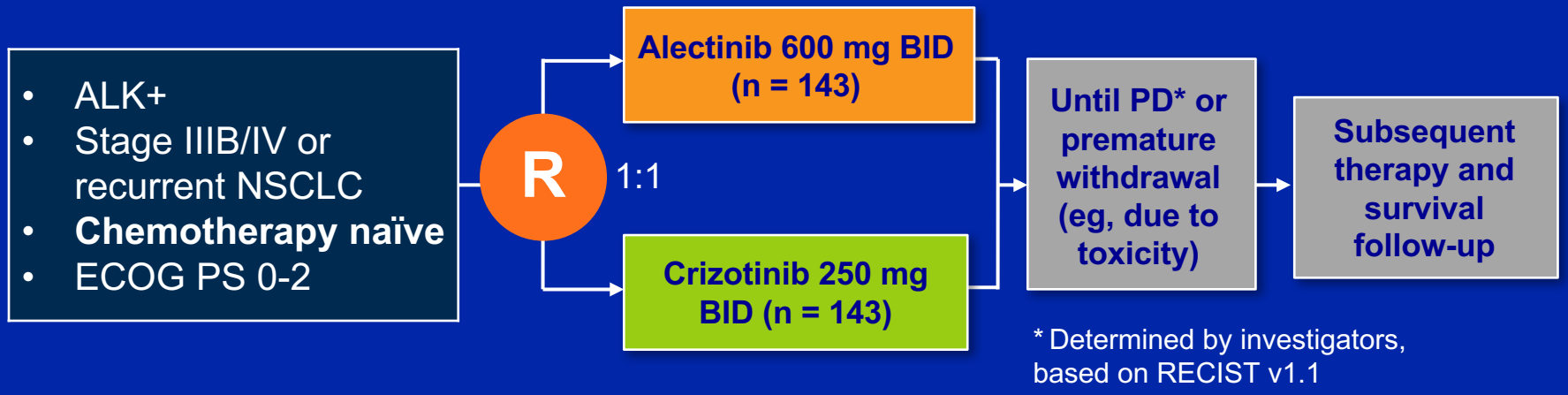
J-ALEX: Select Adverse Events

Adverse event	Alectinib (n = 103)		Crizotinib (n = 104)	
	All grades	Grade 3/4	All grades	Grade 3/4
Constipation	35.0%	1.0%	44.2%	1.0%
Nausea	10.7%	0%	74.0%	1.9%
Diarrhea	8.7%	0%	73.1%	1.9%
Vomiting	5.8%	0%	57.7%	1.9%
Elevated AST level	10.7%	1.0%	30.8%	4.8%
Elevated ALT level	8.7%	1.0%	31.7%	12.5%
Visual disturbance	1.0%	0%	54.8%	0%
Dysgeusia	18.4%	0%	51.9%	0%

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

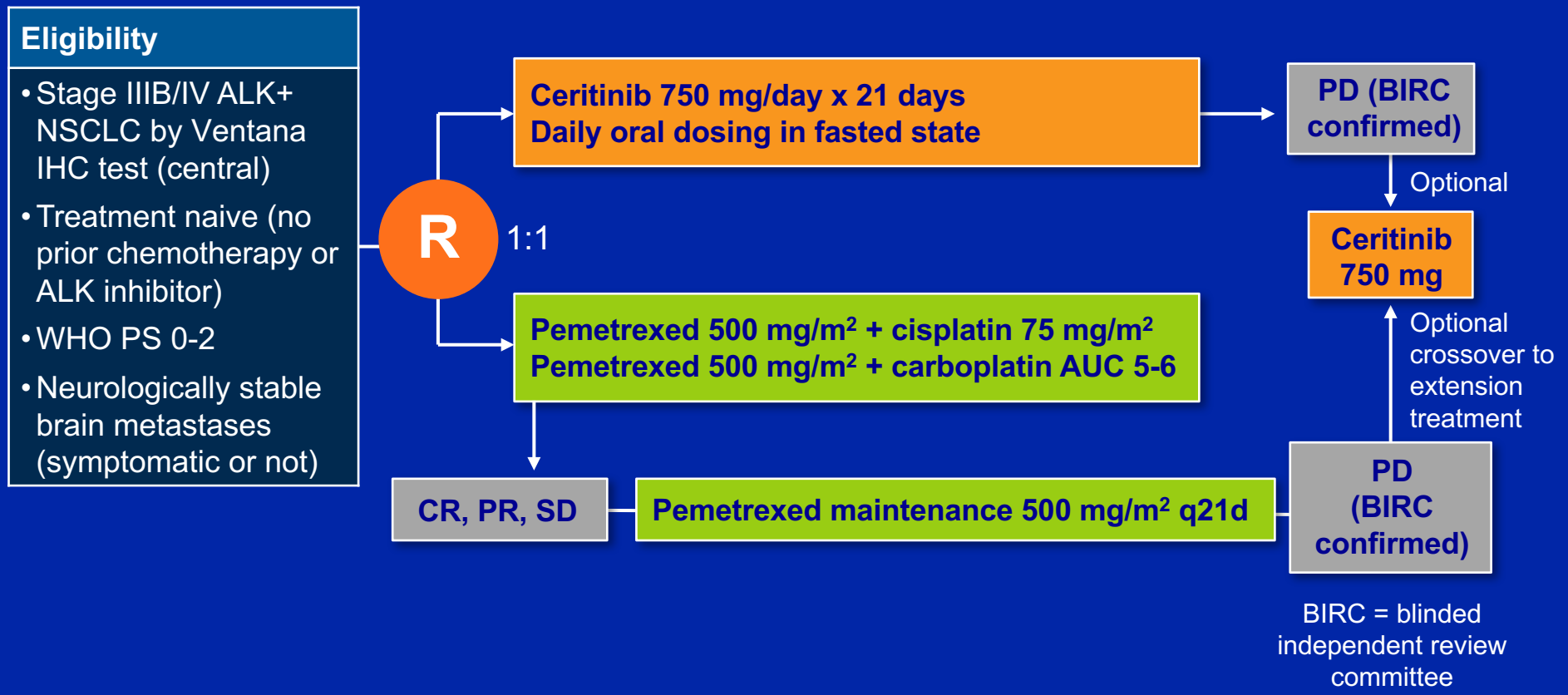
ALEX Phase III Study Design



In comparison to crizotinib, alectinib demonstrated statistically significant improvement in PFS in the Japanese Phase III parallel trial J-ALEX (HR = 0.34, $p < 0.0001$).

Ou SHI et al. *Proc ASCO* 2015;Abstract 8008; Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

ASCEND-4: Randomized Phase III Study Comparing First-Line Ceritinib with Chemotherapy



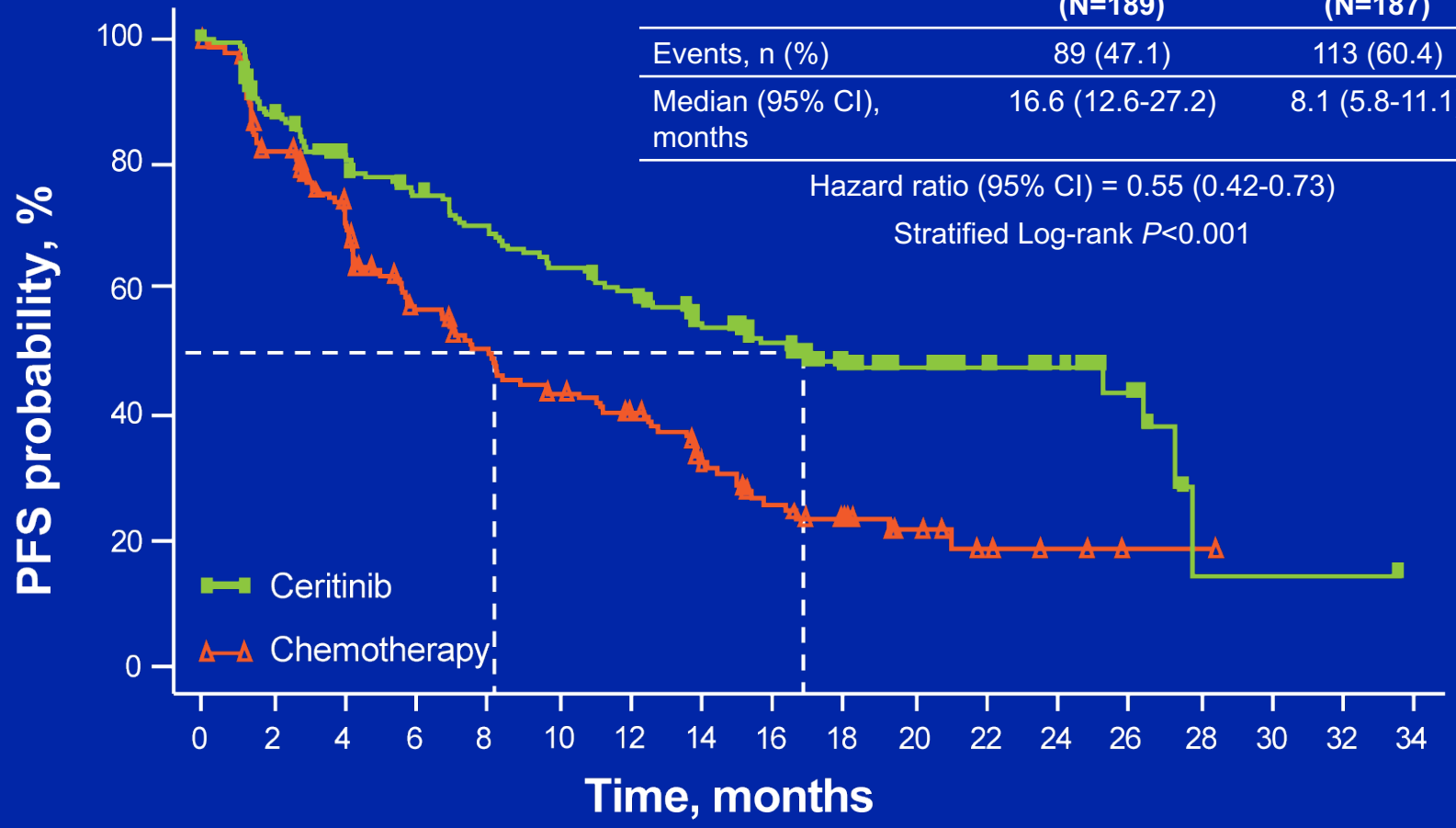
De Castro G et al. *Proc WCLC* 2016;Abstract PL03.07.

ASCEND-4 Primary Endpoint: PFS by BIRC

	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



Ceritinib demonstrated an estimated 45% risk reduction vs chemotherapy

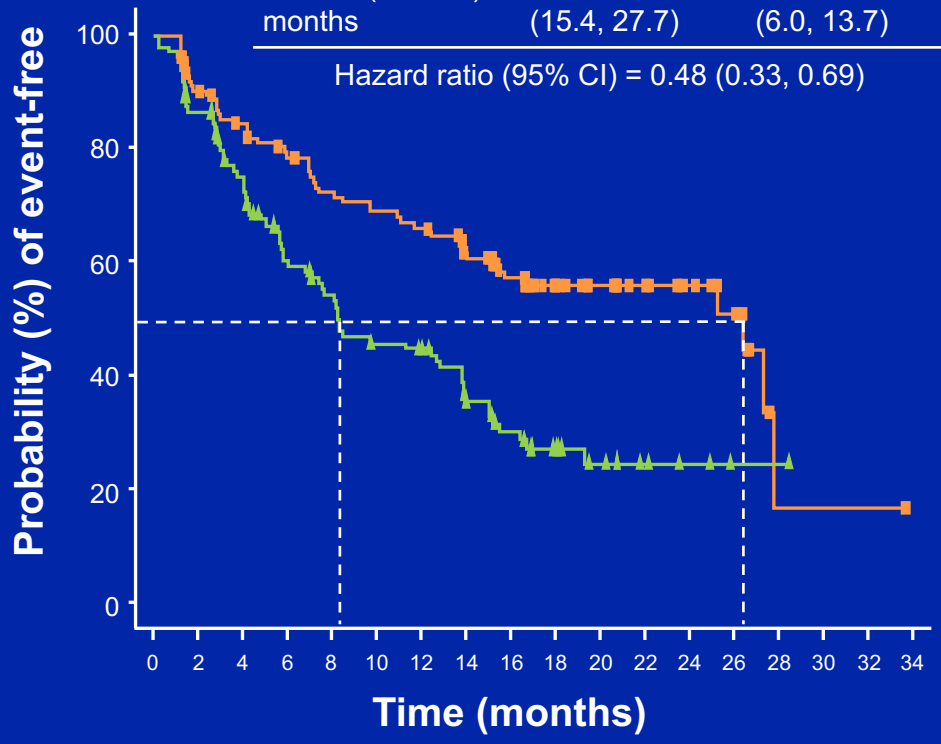
De Castro G et al. *Proc WCLC* 2016;Abstract PL03.07.

ASCEND-4: PFS for Patients With or Without Brain Metastases

Brain metastases at baseline: No

	Ceritinib (N = 130)	Chemotherapy (N = 125)
Events, n (%)	54 (41.5)	72 (57.6)
Median (95% CI), months	26.3 (15.4, 27.7)	8.3 (6.0, 13.7)

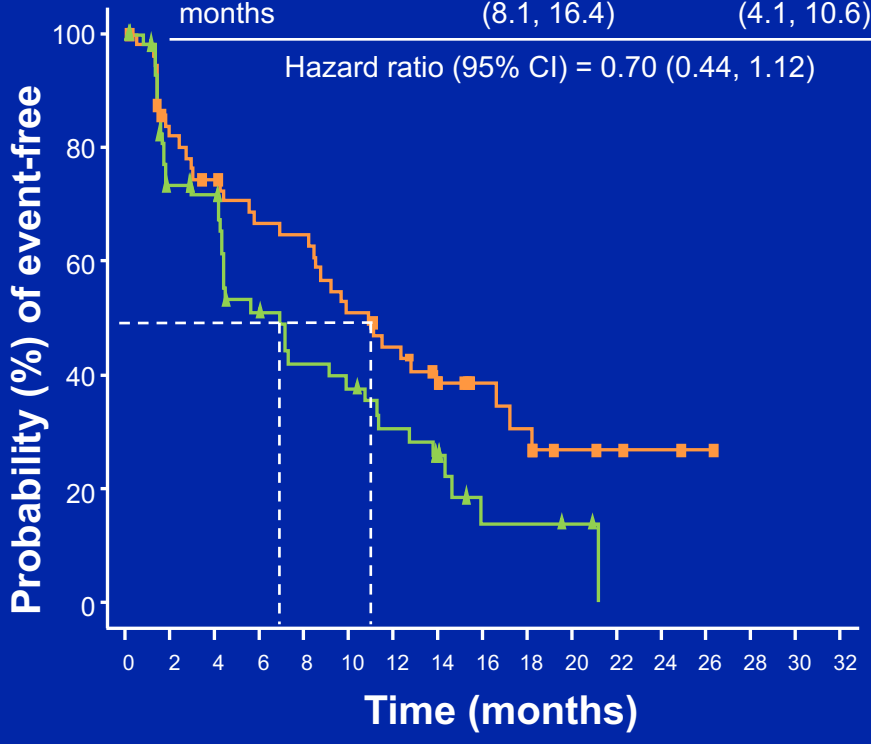
Hazard ratio (95% CI) = 0.48 (0.33, 0.69)



Brain metastases at baseline: Yes

	Ceritinib (N = 59)	Chemotherapy (N = 62)
Events, n (%)	35 (59.3)	41 (66.1)
Median (95% CI), months	10.7 (8.1, 16.4)	6.7 (4.1, 10.6)

Hazard ratio (95% CI) = 0.70 (0.44, 1.12)



De Castro G et al. *Proc WCLC* 2016;Abstract PL03.07.

ASCEND-4: Select Adverse Events

	Ceritinib (N = 189)		Chemotherapy (N = 175)	
	All grades (%)	Grade 3/4* (%)	All grades (%)	Grade 3/4* (%)
Diarrhea	84.7%	5.3%	10.9%	1.1%
ALT increased	60.3%	30.7%	21.7%	2.9%
AST increased	52.9%	16.9%	19.4%	1.7%
GGT increased	37.0%	28.6%	10.3%	1.7%
Asthenia	17.5%	2.6%	20.6%	3.4%
Dyspnea	15.3%	2.1%	20.0%	6.3%
Anemia	14.8%	2.1%	35.4%	7.4%
Neutropenia	4.8%	0.5%	21.7%	10.9%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl-transferase

* Grade 3/4 AEs in 148 (78.3%) patients in ceritinib and 108 (61.7%) in chemotherapy

De Castro G et al. *Proc WCLC* 2016;Abstract PL03.07.

In general, what is your usual starting dose of ceritinib? A 75-year-old patient with ALK-rearranged NSCLC that progressed on crizotinib is started on ceritinib at 750 mg qd leading to a rapid complete response but Grade 3 diarrhea, which abates upon cessation of treatment. Would you restart ceritinib, and if so, at what dose?

	STARTING DOSE	RESTART CERITINIB?
 RAMASWAMY GOVINDAN, MD	600 mg daily	Restart at 600 mg daily
 JOEL W NEAL, MD, PHD	600 mg daily	Restart at 600 mg daily
 GREGORY J RIELY, MD, PHD	450 mg daily	Restart at 450 mg daily
 JULIE R BRAHMER, MD	450 mg daily	Restart at 450 mg daily
 COREY J LANGER, MD	450 mg daily	Restart at 600 mg daily
 HEATHER WAKELEE, MD	450 mg daily with food	Restart at 450 mg daily with food

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In general, what would be your preferred choice of second-line therapy for a patient with ALK-rearranged metastatic nonsquamous cell cancer of the lung and a TPS of 60% who experiences disease progression on crizotinib?

 RAMASWAMY GOVINDAN, MD	Alectinib
 JOEL W NEAL, MD, PHD	Ceritinib or alectinib
 GREGORY J RIELY, MD, PHD	Alectinib
 JULIE R BRAHMER, MD	Alectinib
 COREY J LANGER, MD	Alectinib
 HEATHER WAKELEE, MD	Ceritinib or alectinib

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In general, what would be your preferred choice of second-line therapy for a patient with ALK-rearranged metastatic nonsquamous cell cancer of the lung and a TPS of 60% who experiences disease progression on alectinib?

 RAMASWAMY GOVINDAN, MD	Carboplatin/pemetrexed +/- bev
 JOEL W NEAL, MD, PHD	Carboplatin/pemetrexed +/- bev
 GREGORY J RIELY, MD, PHD	Carboplatin/pemetrexed/bev
 JULIE R BRAHMER, MD	Brigatinib*
 COREY J LANGER, MD	Carboplatin/pemetrexed/bev
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed +/- bev

* Depends also on mutations at time of resistance

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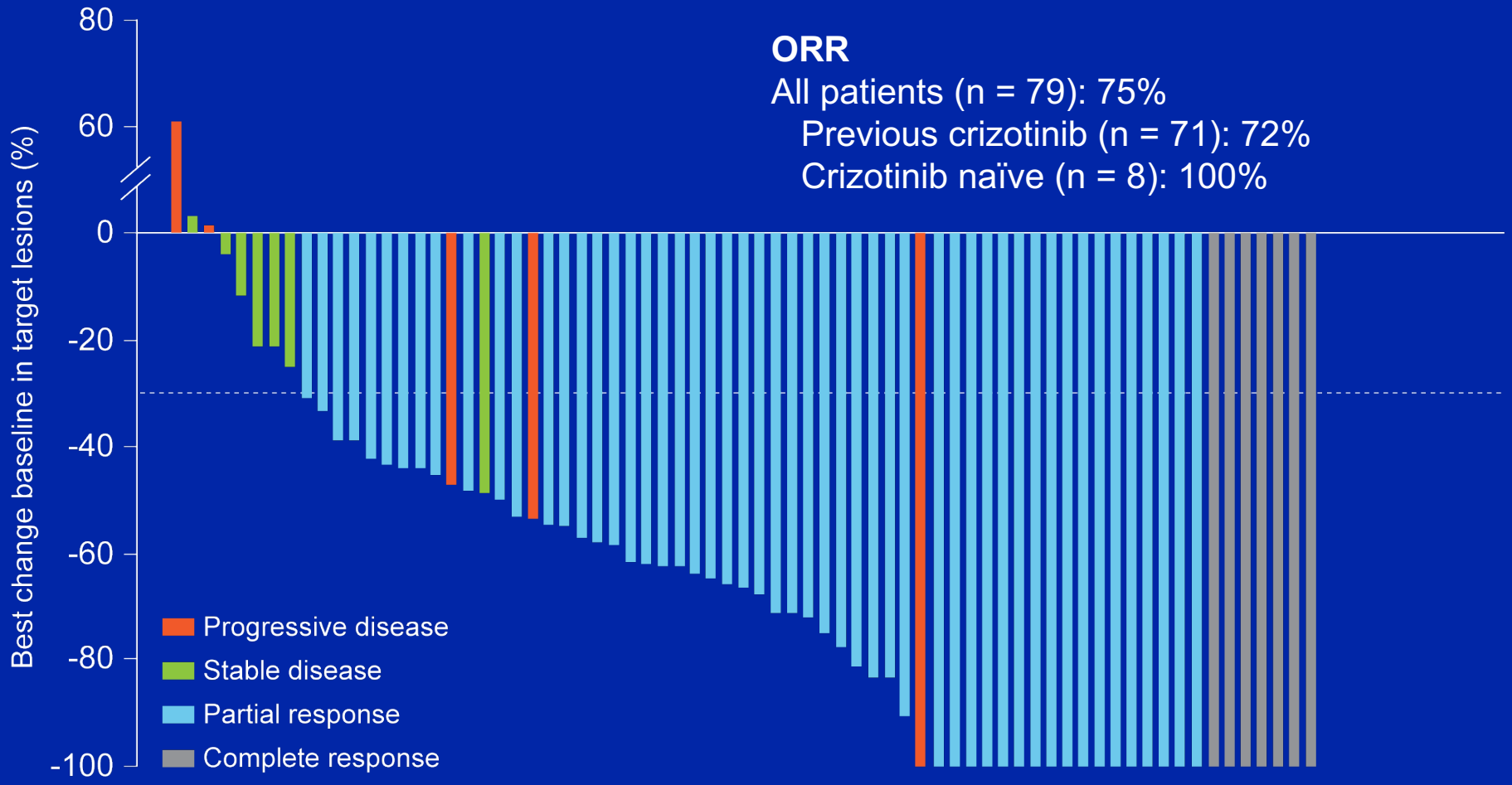
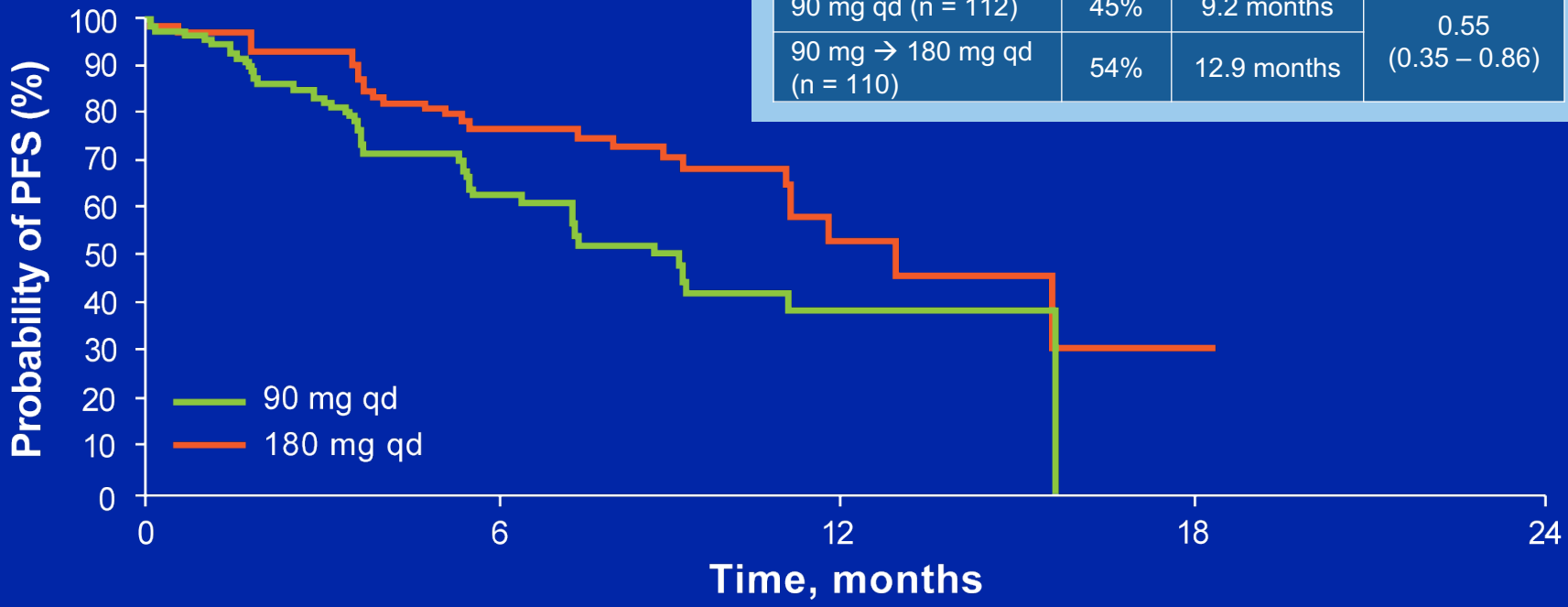
Brigatinib: Response in Phase I/II Trial in ALK-Rearranged NSCLC



Gettinger SN et al. *Lancet Oncol* 2016;17(12):1683-96.

ALTA: A Phase II Trial of Brigatinib in Crizotinib-Refractory ALK-Rearranged NSCLC

	ORR	Median PFS	PFS HR
90 mg qd (n = 112)	45%	9.2 months	0.55 (0.35 – 0.86)
90 mg → 180 mg qd (n = 110)	54%	12.9 months	



Broad activity against a range of resistance mutations

Kim D-W et al. *Proc ASCO* 2016;Abstract 9007.

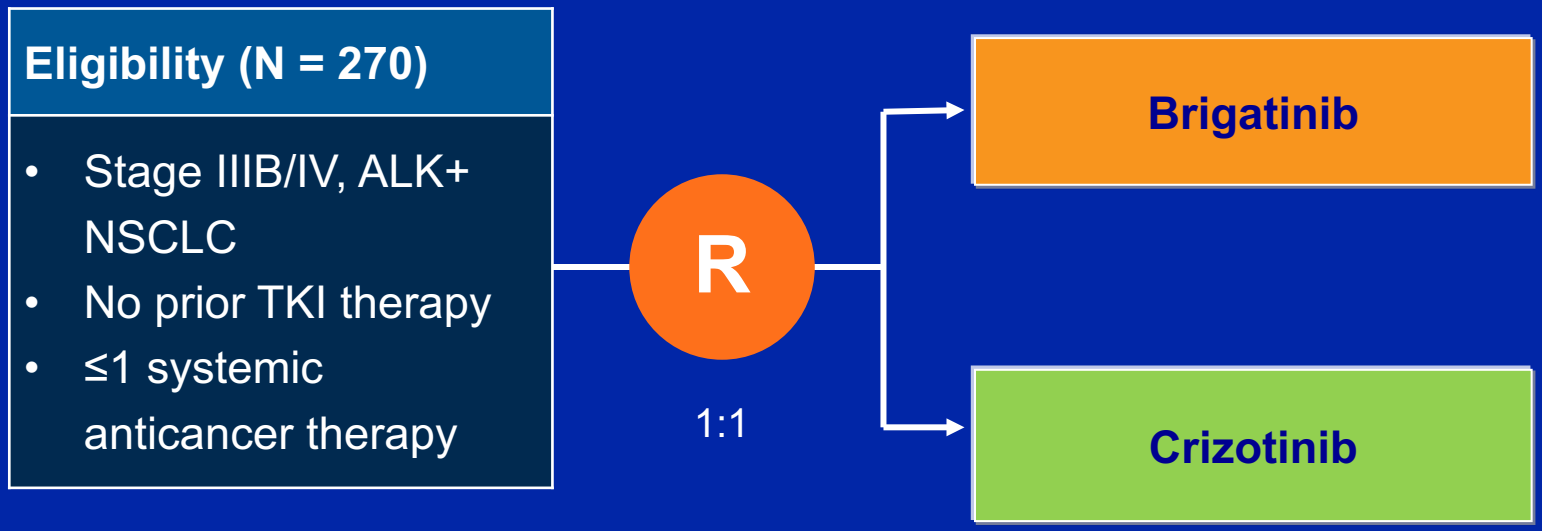
ALTA: Select Adverse Events

Any grade AE (≥10% of patients)	Brigatinib 90 mg qd (n = 109)	Brigatinib 180 mg qd (n = 110)
Nausea	33%	40%
Diarrhea	19%	38%
Cough	18%	34%
Dyspnea	21%	21%
Hypertension	11%	21%

A subset of pulmonary AEs with early onset (including dyspnea, hypoxia, cough, pneumonia, pneumonitis) occurred in 14 (6%) of patients, before dose escalation to 180 mg

Kim D-W et al. *Proc ASCO* 2016;Abstract 9007.

ALTA-1L: A Phase III Trial of First-Line Brigatinib Versus Crizotinib in ALK-Rearranged NSCLC



Primary Endpoint: Progression-free survival
Key Secondary Endpoints: Objective response rate, overall survival, safety, intracranial PFS

www.clinicaltrials.gov. NCT02737501

A 56-year-old woman with metastatic adenocarcinoma of the lung with a PD-L1 TPS of 60% and a known ROS1 rearrangement experiences a 1-year response to crizotinib but now develops disease relapse in the brain and lung. In addition to local therapy to the brain, what would be your most likely next systemic treatment?

 RAMASWAMY GOVINDAN, MD	Carboplatin/pemetrexed +/- bev
 JOEL W NEAL, MD, PHD	Carboplatin/pemetrexed +/- bev
 GREGORY J RIELY, MD, PHD	Platinum/pemetrexed/bev
 JULIE R BRAHMER, MD	Cabozantinib or pemetrexed/carboplatin
 COREY J LANGER, MD	Carboplatin/pemetrexed/bev
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed +/- bev

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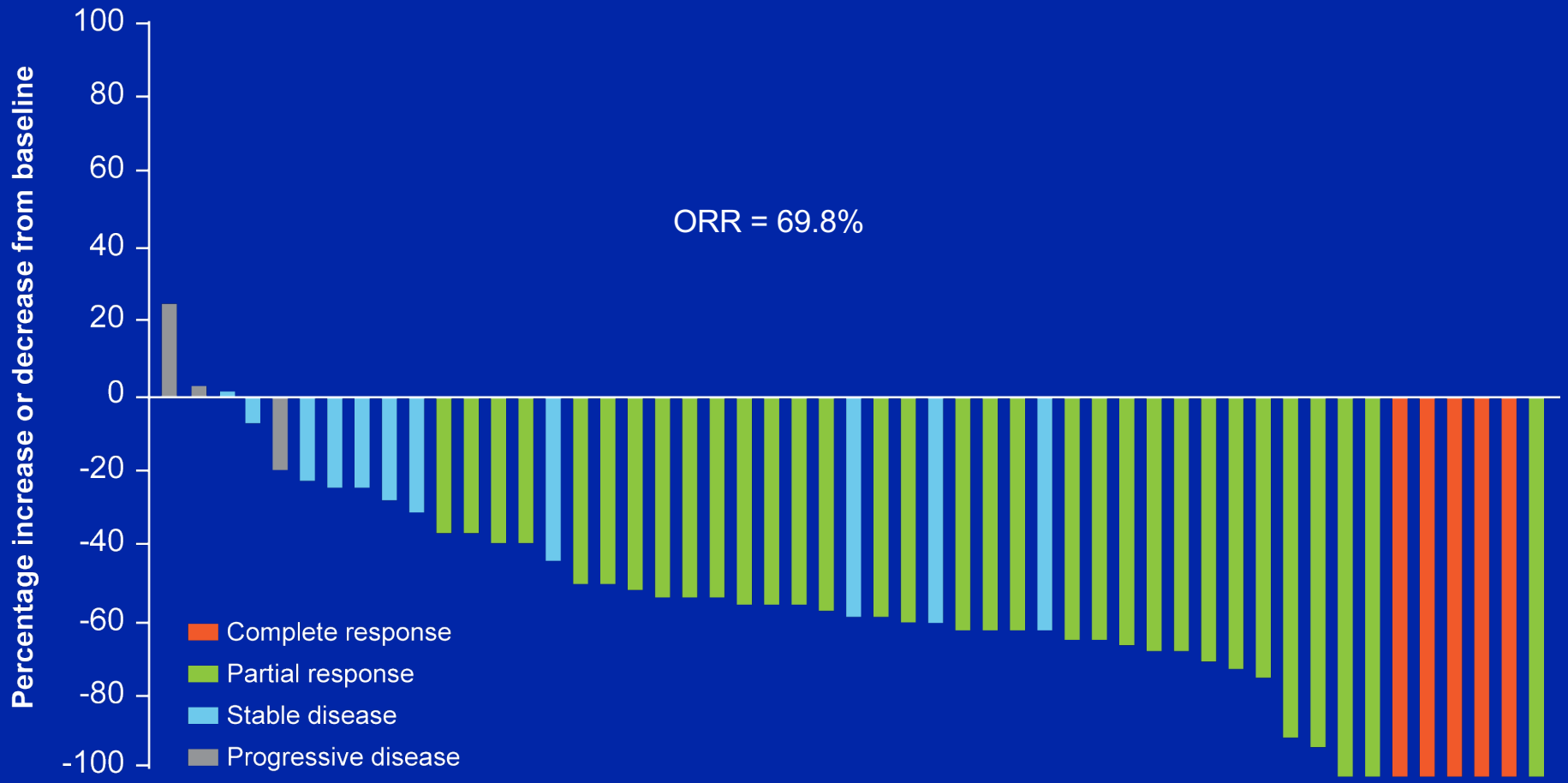
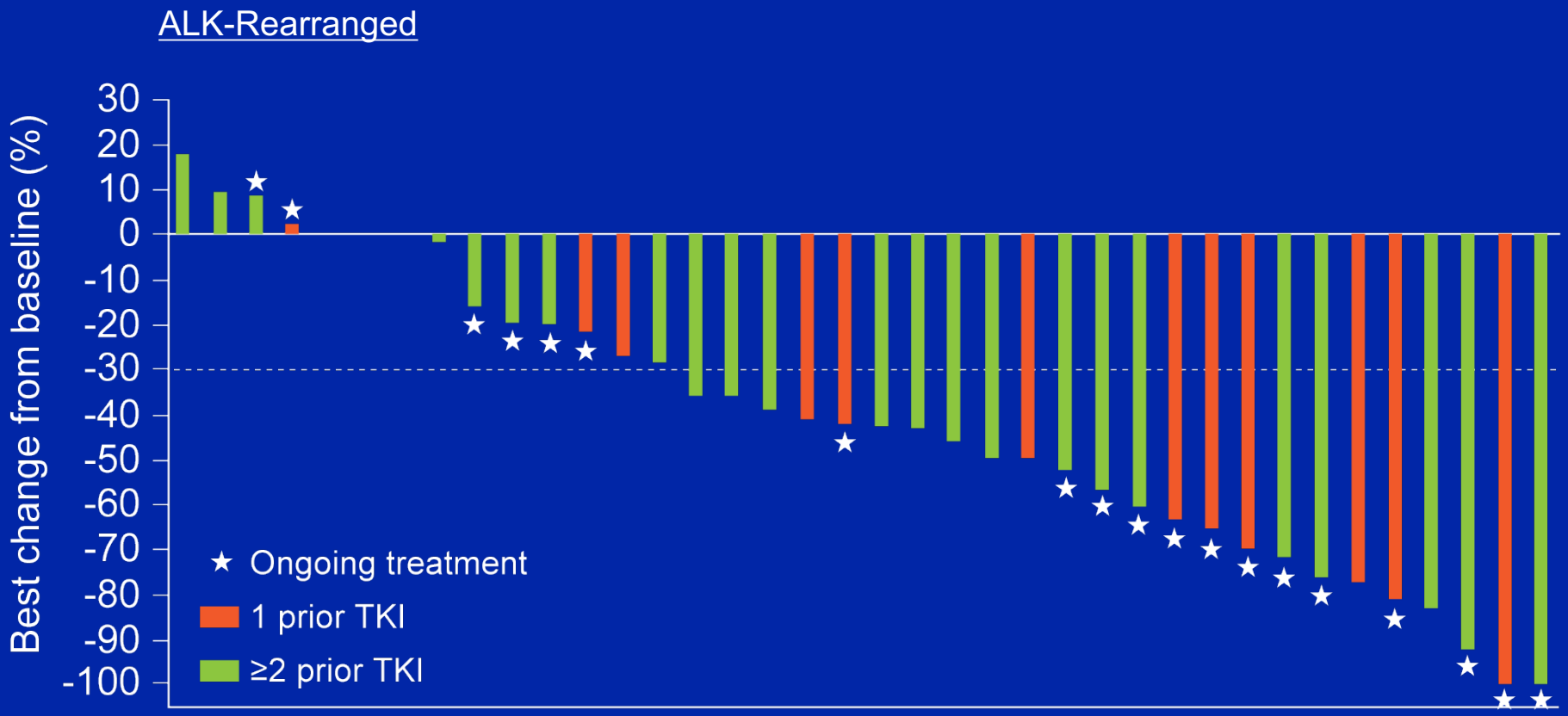
PROFILE 1001 Updated Results: Antitumor Activity and Response to Crizotinib in ROS1-Rearranged NSCLC



Shaw AT et al. *Proc ESMO* 2016;Abstract 1206PD.

Phase I Study of Lorlatinib in ALK- or ROS1-Rearranged NSCLC



- Robust clinical activity in patients with ALK- or ROS1-rearranged NSCLC
- Most patients had brain metastases and had received ≥1 prior ALK TKI

Solomon BJ et al. *Proc ASCO* 2016;Abstract 9009.

Other ROS1-Targeted Agents Under Clinical Investigation in Advanced NSCLC

Therapeutic agent	Trial identifier	Phase	Study population
Lorlatinib	NCT02927340 (Open)	II	• Treatment-naïve or ≥1 ROS1 inhibitor • CNS metastases without measurable extracranial lesions
Cabozantinib	NCT01639508 (Open)	II	• Group C: Metastatic or unresectable NSCLC with ROS1 fusion
Ceritinib	SIGNATURE: NCT02186821 (Completed)	II	• ≥1 treatment for recurrent, metastatic and/or locally advanced disease and for whom no standard therapy options are available

www.clinicaltrials.gov. Accessed March 2017.