Next-generation ALK inhibitors for ALK-positive NSCLC

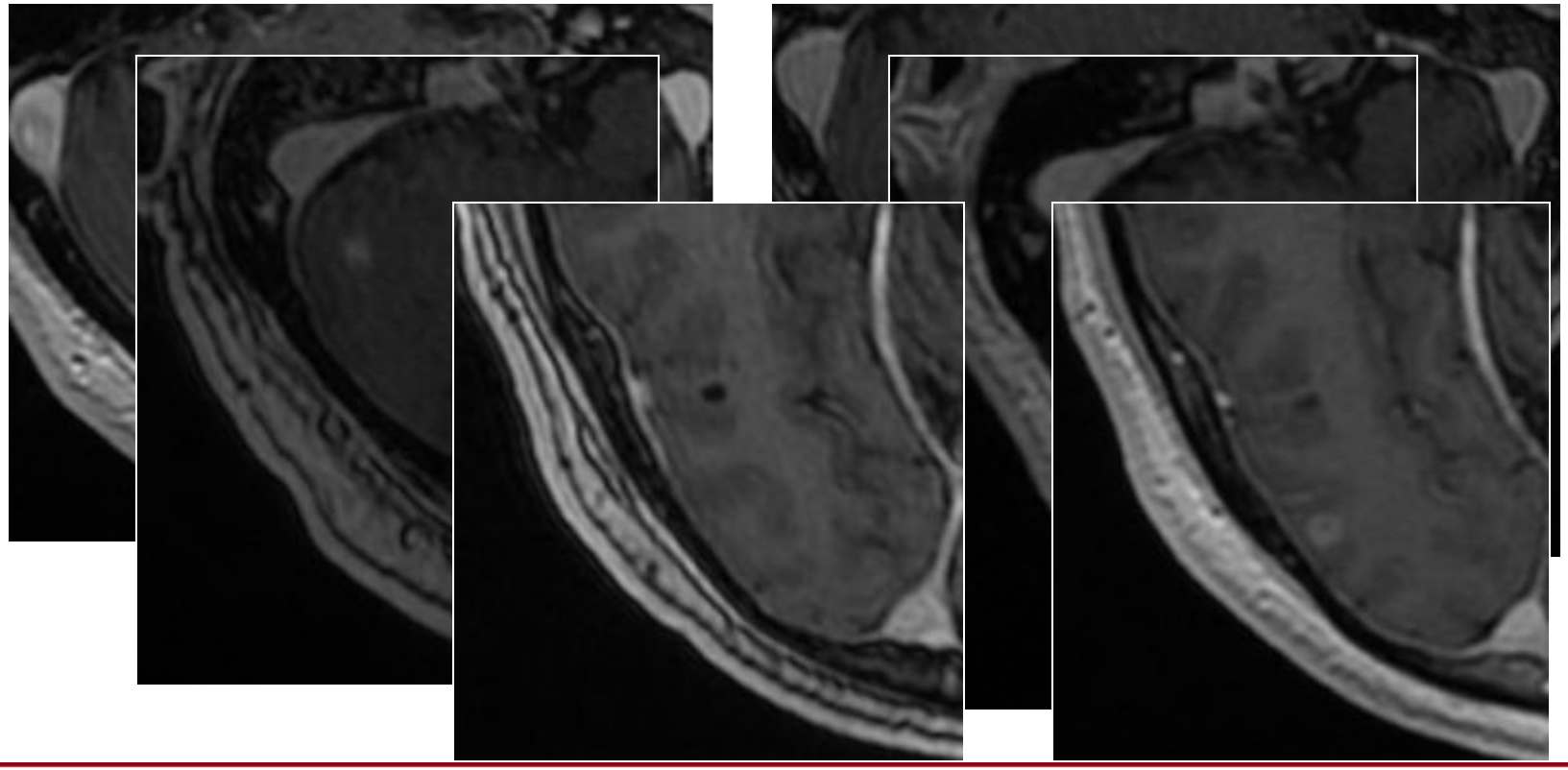
Geoffrey R. Oxnard, MD
Damon Runyon-Gordon Family Clinical Investigator
Assistant Professor of Medicine
Dana-Farber Cancer Institute

Case

- A 60-year-old never smoker presents with NSCLC metastatic to brain
  - First presented a year ago after resection of cerebellar mass showing adenocarcinoma
  - Received SRS to surgical bed and 2nd site
  - ALK FISH+, initiated crizotinib, well tolerated with systemic response
  - He is divorced, lives with one of his two children, works full time and travels a lot

Case

- A 60-year-old never smoker with ALK+ NSCLC on crizotinib
  - Brain MRI after 8 months shows progression



Case

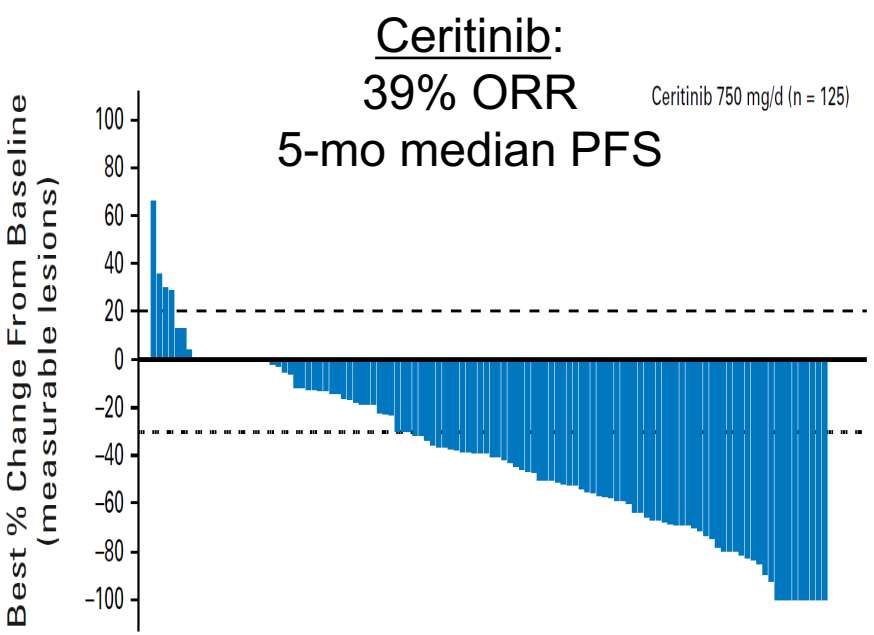
- A 60-year-old never smoker with ALK+ NSCLC and CNS progression on crizotinib
  - What would you recommend?
- Started ceritinib 750 mg QD
  - Stable brain mets, complained of GI toxicity
- Switched to alectinib 600 mg BID
  - Stable brain mets for 2 years

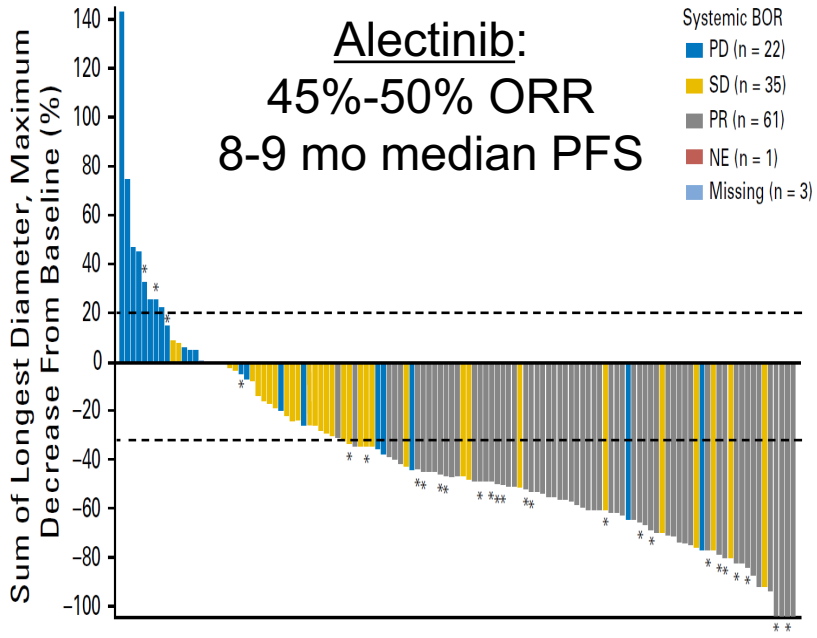
Next-generation ALK inhibitors for ALK-positive NSCLC

Geoffrey R. Oxnard, MD
Damon Runyon-Gordon Family Clinical Investigator
Assistant Professor of Medicine
Dana-Farber Cancer Institute

Second-generation ALK TKI

- **Ceritinib and alectinib both FDA approved after failure of crizotinib**
  - **39%-50% ORR, 5-9 mo median PFS, CNS activity**





Crino et al. JCO 2016;
Shaw et al. Lancet Oncol 2016; Ou et al. JCO 2016.

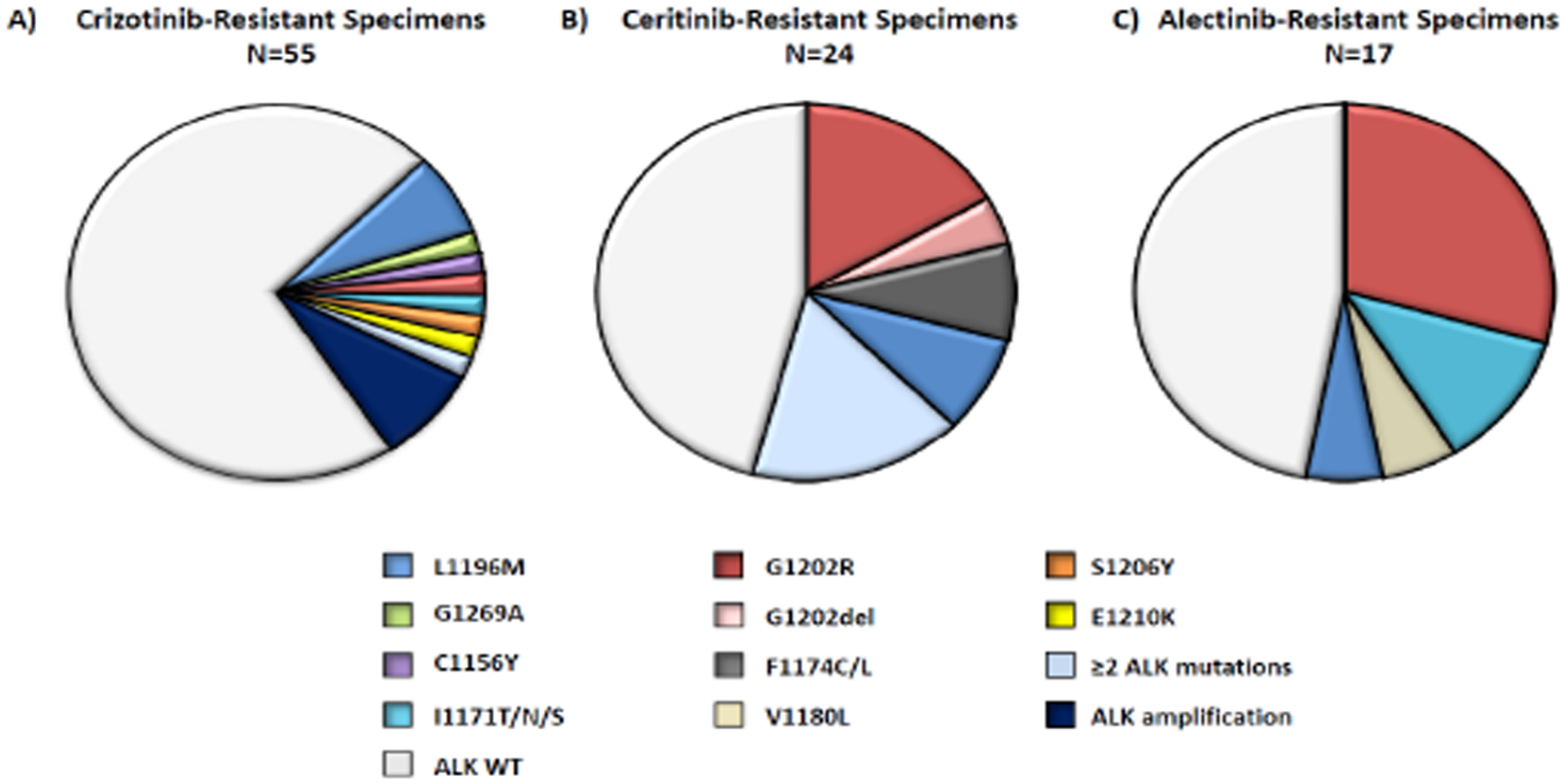
Second-generation ALK TKI

- **Alectinib has generally been better tolerated than ceritinib**
  - **Ceritinib phase II trial reported 46% incidence of grade 3-4 drug-related AE (LFT, N/V, diarrhea), with dose reduction in 54% of patients**
  - **Alectinib phase II trials reported low incidence of grade 3-4 drug-related AE, with dose reduction in 16%-20% of patients**
- **Alternate ceritinib dosing (with light snack) is being studied and is better tolerated**

Crino et al. JCO 2016;
Shaw et al. Lancet Oncol 2016; Ou et al. JCO 2016.

ALK resistance

- **Emerging data suggests that newer ALK inhibitors alter the spectrum of resistance mutations, inducing more ALK resistance mutations**



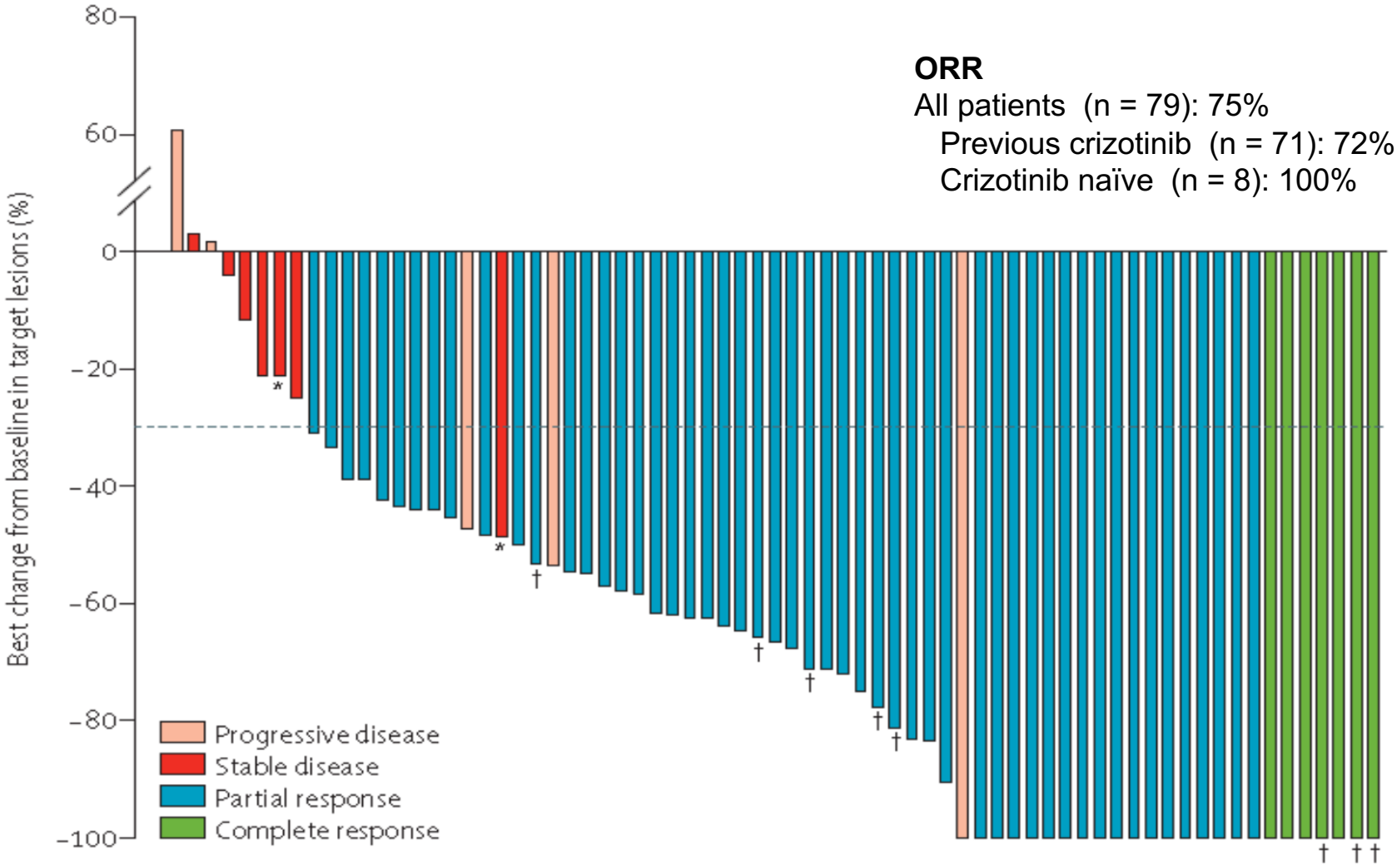
Gainor et al. Cancer Disc 2016.

Activity and safety of brigatinib in *ALK*-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial

Scott N Gettinger, Lyudmila A Bazhenova, Corey J Langer, Ravi Salgia, Kathryn A Gold, Rafael Rosell, Alice T Shaw, Glen J Weiss, Meera Tugnait, Narayana I Narasimhan, David J Dorer, David Kerstein, Victor M Rivera, Timothy Clackson, Frank G Haluska, David Ross Camidge

Lancet Oncol **2016; 17: 1683–96**

Response to Brigatinib in ALK+ NSCLC

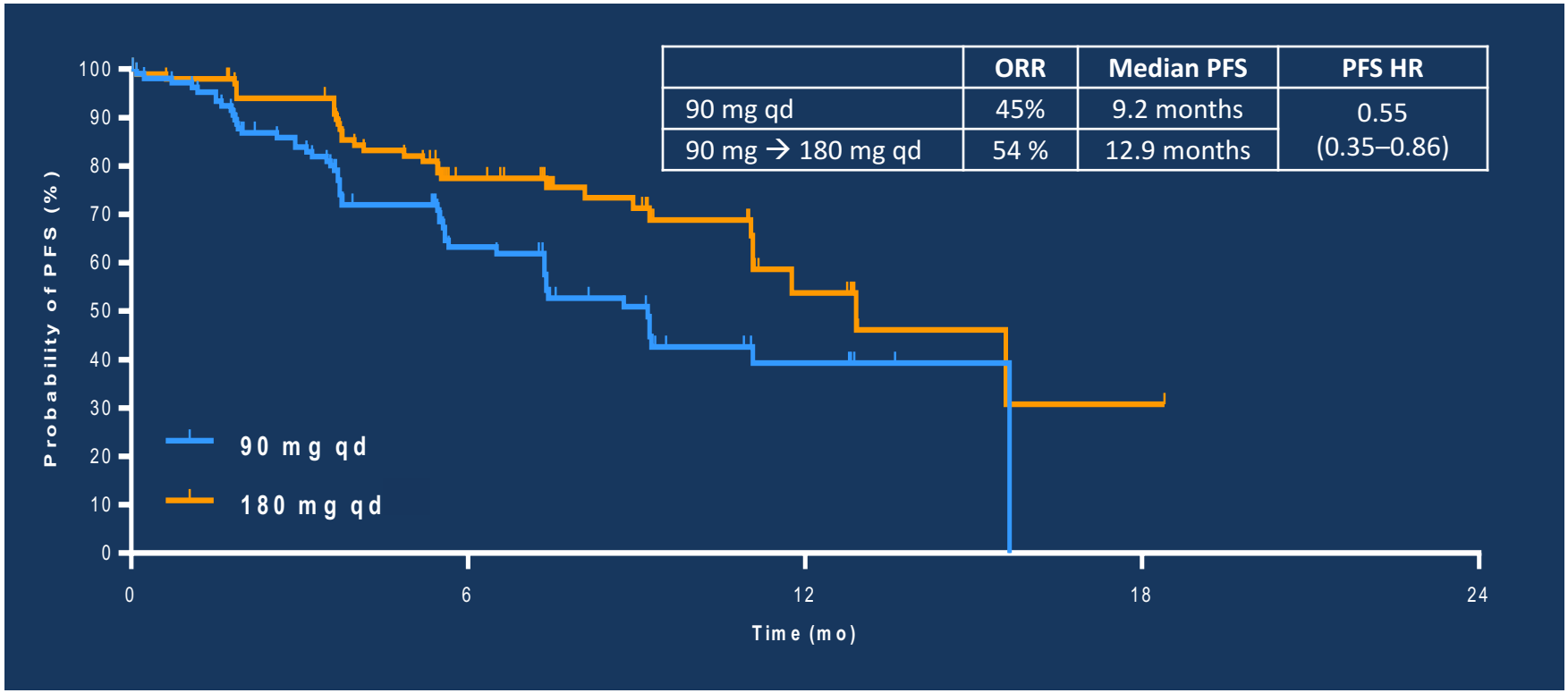


ORR
All patients (n = 79): 75%
Previous crizotinib (n = 71): 72%
Crizotinib naïve (n = 8): 100%

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

Brigatinib

- **Broad activity against a range of resistance mutations**
- **ALTA trial randomized 222 patients with NSCLC with crizotinib resistance to two different doses:**



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

Gettinger et al. Lancet Oncol 2016; Kim et al. ASCO 2016; Zhang et al. CCR 2016.

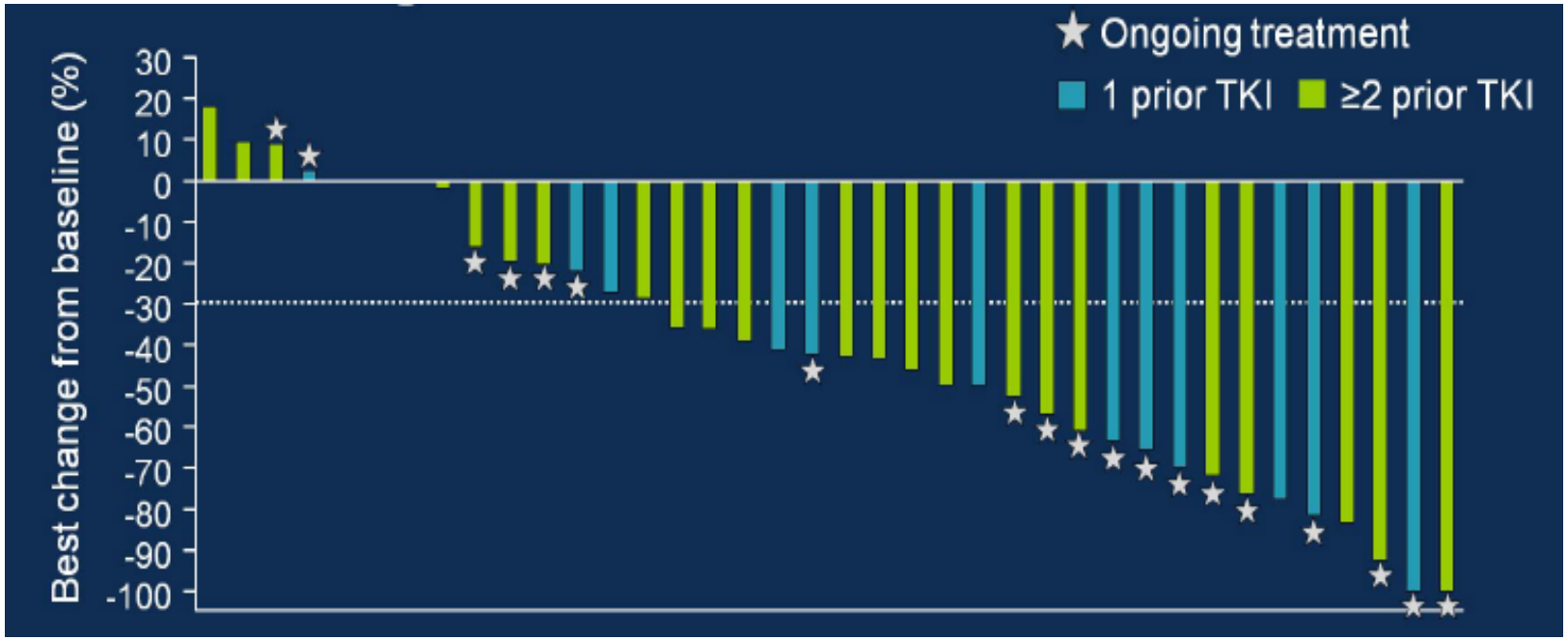
ALTA: Select Adverse Events

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 et al. ASCO 2016;17:Abstract 9007.

Phase I study of Lorlatinib in ALK+ NSCLC



Lorlatinib demonstrated robust clinical activity in patients with ALK+ and patients with ROS1+ NSCLC, most of whom had brain metastases and had received ≥ 1 prior ALK TKI

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

Phase I/II Trial of Ensartinib (X-396) in ALK+ NSCLC

Response	All patients (n=27)	Crizotinib treated (n=12)
Partial response	19 (70%)	10 (83%)
Stable disease	2 (7%)	1 (8%)

Most adverse events were grade 1/2 and included rash, nausea, vomiting and fatigue

Lovly CM et al. Proc AACR 2016;Abstract CT088.

Lots of ALK inhibitors

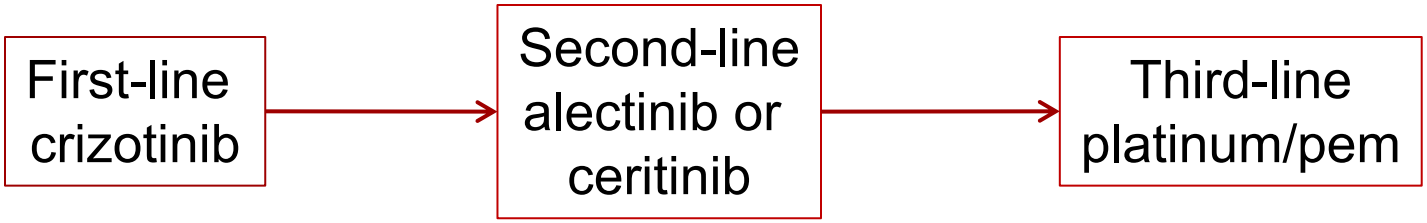
	Crizotinib	Ceritinib	Alectinib	Brigatinib
Indication	ALK+ NSCLC	ALK resistance	ALK resistance	(Not yet approved)
Highly active	Yes	Yes	Yes	Yes
Tolerability	Good	Moderate	Good	Good
CNS activity	Some	Good	Good	Good
Potency against resistance	Poor	Moderate	Moderate	Good

- **Potent CNS activity of newer ALK inhibitors, combined with favorable toxicity profile, means that patients can stay on therapy for a durable period**
- **Moving potent ALK inhibitors into first line to prevent resistance is intuitive**

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

Summary

- **Current standard approach for ALK+ NSCLC:**



- **Future approach envisioned for ALK+ NSCLC?**