JADPRO CE
Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

Managing *ALK*+ and *ROS1*+ Metastatic NSCLC

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Faculty Financial Disclosures

- **Ms. Eaby-Sandy** has served as a consultant and on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda.
- **Dr. Beardslee** has served as a consultant for AstraZeneca and Herron, and on the speakers bureau for AstraZeneca.
- **Dr. Davies** has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Genentech, and Merck.
- **Ms. Gilbert** has no conflicts of interest to disclose.
- **Ms. Persinger** has served on speakers bureaus for Genentech and Guardant Health, and on the advisory board for AstraZeneca.

Planning Committee Financial Disclosures

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Learning Objective

- Evaluate efficacy and safety data supporting the use of targeted and immune checkpoint inhibitor therapy used to treat NSCLC

Audience Response Question

Which ALK inhibitor has the highest rate of pneumonitis?

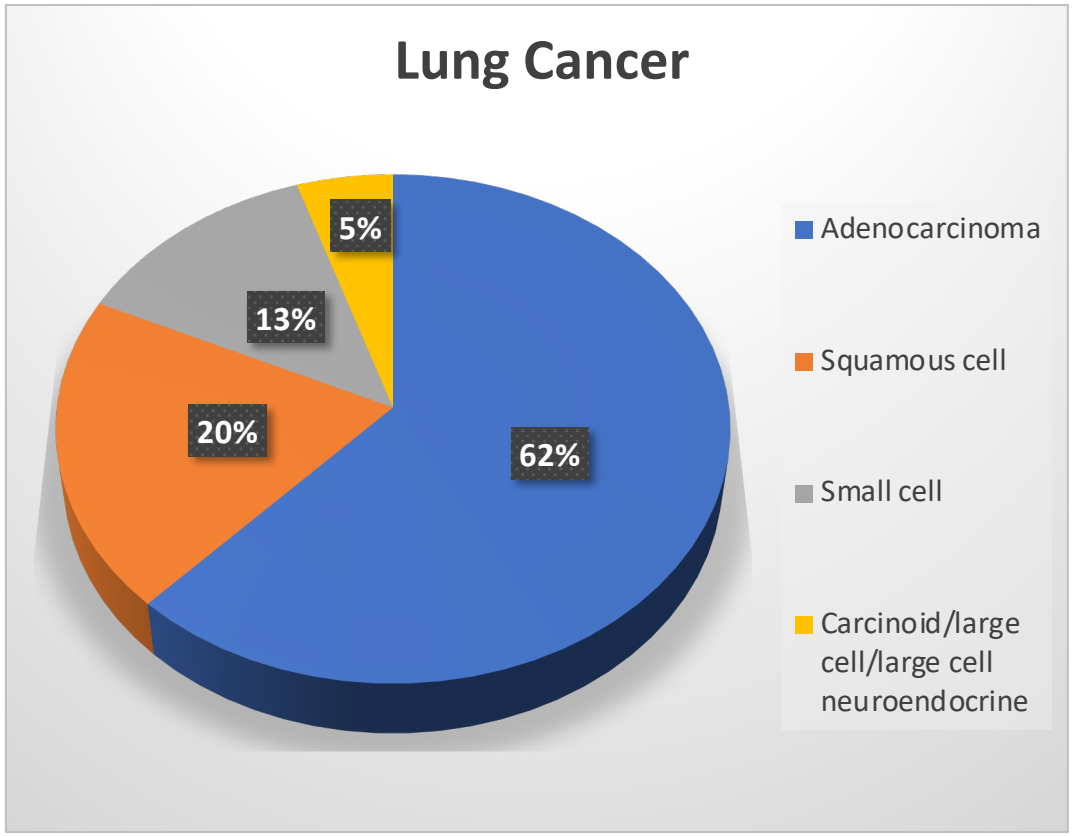
A. Brigatinib
B. Alectinib
C. Lorlatinib
D. Crizotinib
E. Unsure

Audience Response Question

Your 53-year-old female patient with *ROS1*+ NSCLC who is currently on crizotinib now develops new brain metastases. Which of the following agents would you counsel is likely to be best?

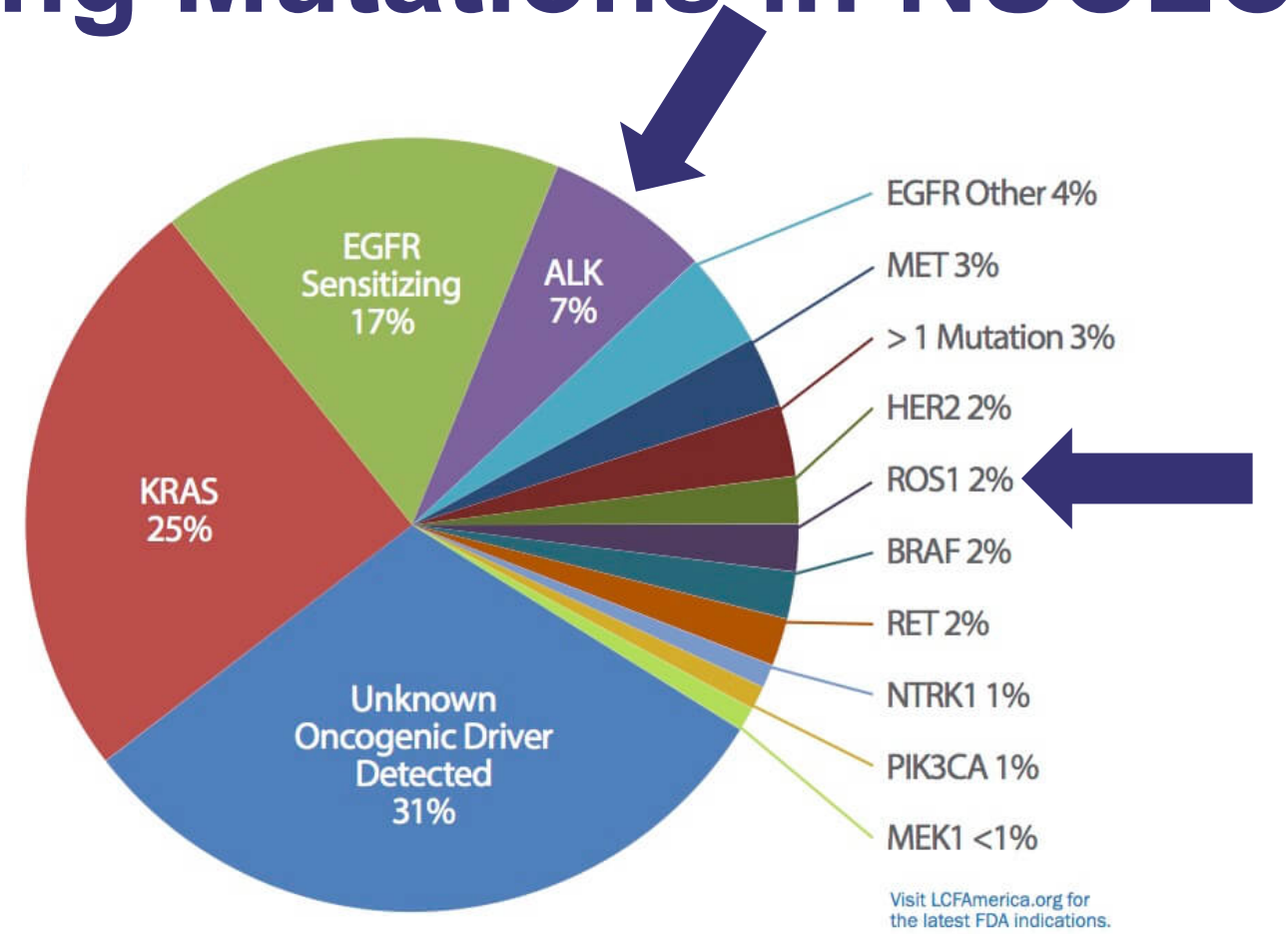
A. Lorlatinib
B. Alectinib
C. Entrectinib
D. Brigatinib
E. Unsure

ALK and ROS1 in NSCLC



- Overwhelming majority of *ALK* and *ROS1* mutations found in adenocarcinoma type of NSCLC
- Rare in squamous
- Also mutually exclusive like other mutations
- *ALK* and *ROS1* are generally found in a younger population than average NSCLC

Sensitizing Mutations in NSCLC



Retrieved from https://lcfamerica.org/research-grants/therapies/available-targeted-therapies

ALK-Positive NSCLC Characteristics

- From ALEX trial, over 300 patients
- Median age mid 50s
- Fairly split between gender
- 45% Asian, but this is usually more in EGFR trials
- Most common in never smokers, but must test everyone, still in some current or former smokers

Table 1. Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N = 151)	Alectinib (N = 152)
Age — yr		
Mean	53.8±13.5	56.3±12.0
Median	54.0	58.0
Range	18–91	25–88
Sex — no. (%)		
Male	64 (42)	68 (45)
Female	87 (58)	84 (55)
Race — no. (%)†‡		
Asian	69 (46)	69 (45)
Non-Asian	82 (54)	83 (55)
ECOG performance status — no. (%)†		
0 or 1	141 (93)	142 (93)
2	10 (7)	10 (7)
Smoking status — no. (%)		
Active smoker	5 (3)	12 (8)
Former smoker	48 (32)	48 (32)
Nonsmoker	98 (65)	92 (61)

Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.

ROS-1 Positive NSCLC Characteristics

- Crizotinib trial in 2014
- Median age 53, again younger
- Male/female split
- Strong association with non-smokers, no current smokers

Table 1. Characteristics of the Patients at Baseline.

Characteristic	ROS1 Cohort (N = 50)
Age — yr	
Median	53
Range	25–77
Sex — no. (%)	
Male	22 (44)
Female	28 (56)
Race — no. (%)*	
White	27 (54)
Asian	21 (42)
Other	2 (4)
Smoking status — no. (%)	
Never smoked	39 (78)
Former smoker	11 (22)

Shaw AT, Ou S-HI, Bang Y-J et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971

ALK Inhibitors

ALK Inhibitors Approved in NSCLC

Drug	Approved dose	Dose formulations	Indication
Crizotinib	250 mg twice a day	250 mg, 200 mg	*ALK*+ NSCLC
Ceritinib	450 mg daily	150 mg	*ALK*+ NSCLC
Alectinib	600 mg twice a day	150 mg	ALK+ NSCLC
Brigatinib	90 mg daily x 7 days, then 180 mg daily	180 mg, 90 mg, 30 mg	*ALK*+ NSCLC after progression or intolerance to crizotinib
Lorlatinib	100 mg once a day	100 mg, 25 mg	*ALK*+ NSCLC after progression on crizotinib + another ALK inhibitor or after progression on ceritinib or alectinib

Crizotinib and Ceritinib

Crizotinib

- First to be approved in *ALK*+ NSCLC, was only drug for years
- For the time had great response rates, but now is significantly inferior to alectinib in first-line setting

Ceritinib

- Second ALK drug to be approved
- Initially was after failure of crizotinib, then in first line; however, never really used much in first line
- Was most toxic drug due to N/V and diarrhea, but newer dosing not as bad

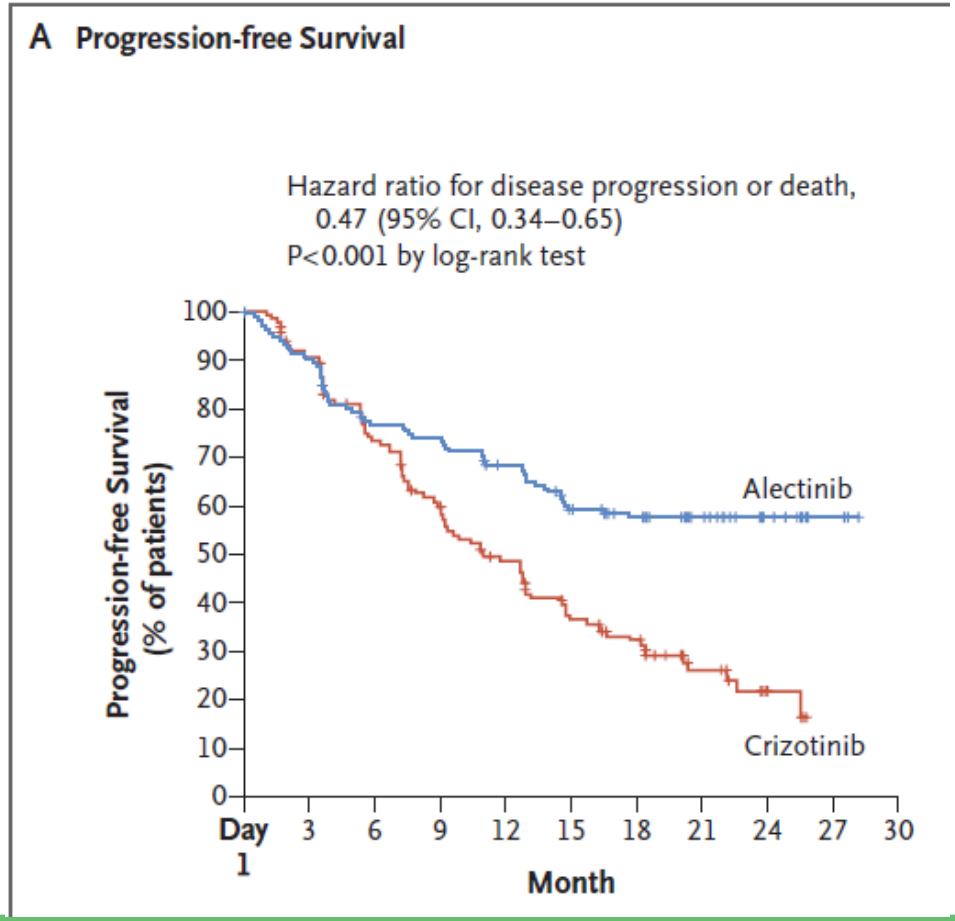
Alectinib

- Third ALK drug to be approved, initially in the second-line setting after failure of crizotinib
- However, the ALEX trial changed everything in 2017. First-line alectinib far superior to crizotinib first-line and better intracranial responses
- Alectinib is now the preferred first-line drug for *ALK*-positive NSCLC per NCCN guidelines

Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.

Alectinib vs. Crizotinib in First-Line ALK-Positive NSCLC

- Original PFS curve in 2017
- Updated ASCO abstract 2018
  - Median PFS 34 vs. 10 months in favor of alectinib
  - CNS mets requiring tx were a little less in the alectinib arm
  - OS data still immature, HR .76 so far in favor of alectinib
  - AEs requiring dose interruption or reduction less in alectinib arm.



Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377:829-838.
Camidge DR et al. 2018. ASCO Abstract. https://meetinglibrary.asco.org/record/160811/abstract

Brigatinib and Lorlatinib

Brigatinib

- 4th ALK drug to be approved
- Currently approved 2nd line post failure crizotinib
- Significant intracranial response rate of 67% with median duration of response 16.6 months
- Ongoing studies evaluating first-line use

Lorlatinib

- 5th ALK drug to be approved
- Approved 2nd line post failure of at least 1 or 2 ALK regimens.
- 45% response rate after failure of 1 or 2 regimens
- Also with significant intracranial responses
- Ongoing studies evaluating first-line use as well

Ou S-H I, Tiseo M, Camidge DR, et al. Intracranial efficacy of brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase (ALK)-non–small cell lung cancer (NSCLC) and baseline CNS metastases. Poster presented at: Annual Congress of the European Society for Medical Oncology; September 8-12, 2017; Madrid, Spain. Poster 1345P.
Solomon BJ, Besse B, Bauer TM. Lorlatinib in patients with ALK-positive non-small cell lung cancer: results from a global phase 2 study. Lancet Oncology. 2018;S1470-245(18)30649-1

ROS1 Inhibitors

Crizotinib for *ROS1*-Positive NSCLC

- 1st drug approved, and only drug for many years
- Studied initially 2010–2013, PROFILE 1001
  - 53 ROS1-positive patients
- Updated results of PROFILE 1001 published 2019
  - Median overall survival 51.4 months!! (over 4 years)
  - Median progression-free survival 19.3 months
  - Response rate 72% plus another 10% stable disease

Shaw A.T. et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001.
Annals of Oncology 0: 1–6; 2019 doi:10.1093/annonc/mdz131

Entrectinib for ROS1-Positive NSCLC

- Just approved in 8/2019. Crizotinib naïve.
- 600 mg daily (comes in 100-mg and 200-mg tablets)
- 51 patients with ROS1+ NSCLC pooled between the 3 entrectinib trials (ALKA, STARK-1, STARK-2)
- 5 out of 7 patients had intracranial responses

	N = 51
Overall Response Rate (95% CI)	78% (65, 89)
Complete Response	6%
Partial Response	73%
Duration of Response (DOR)*	**N = 40**
Range (months)	1.8, 36.8+
% DOR ≥ 9 months	70%
% DOR ≥ 12 months	55%
% DOR ≥ 18 months	30%

Doebele RC, Ahn MJ, Siena S, et al: Efficacy and safety of entrectinib in locally advanced or metastatic *ROS1*-positive non-small cell lung cancer. 2018 World Conference on Lung Cancer.
Abstract 13903. Presented September 24, 2018
Table is from the package insert

Other Agents for ROS1

- Lorlatinib 12 patients in phase 1 study: 50% response rate, 30% progressive disease
- Ceritinib 28 patients in a phase II: 62% response rate, 2% progressive disease
- Brigatinib some limited data: not as promising
- Alectinib does not work well at all in ROS1

Shaw A.T, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial.
Lancet Oncol. 2017 Dec; 18(12): 1590–1599.

Toxicities

Toxicities of ALK/ROS1 Inhibitors

- Some class effects, and some vary significantly by drug

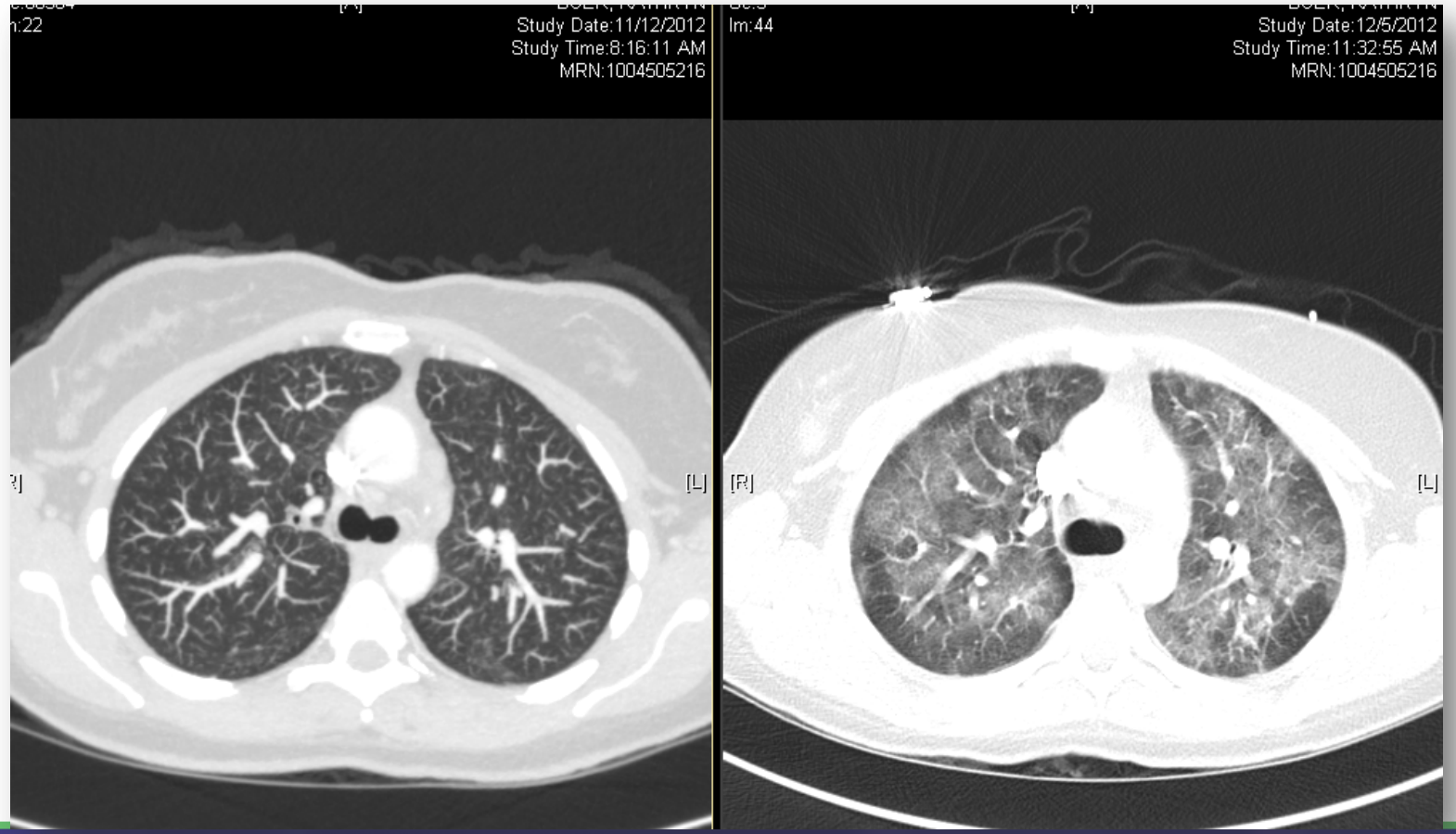
Pneumonitis Can Be Fatal, Although Rarely

- A class effect of TKIs and certainly seen in the *ALK*+ population
- Usually acute onset SOB, must be worked up by CT chest
- It is a permanent discontinuation in ALL ALK inhibitors, EXCEPT
  - Brigatinib: This is the only ALK that causes pneumonitis at higher rate; however, if caught early, can be managed with steroids, dose reduced and rechallenged, often successfully.
  - Other ALK inhibitors: If you rechallenge after pneumonitis, most always fatal.

Pneumonitis: A Class Effect, But Different

Drug	Rate of pneumonitis
Crizotinib	2.9%
Ceritinib	2.4%
Alectinib	0.4%
Brigatinib	9.1%
Lorlatinib	1.5%

Case of Pneumonitis 2 Weeks After Starting Crizotinib for *ALK*+ NSCLC



Images courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Crizotinib 250 mg Twice a Day

Warnings

- Hepatoxicity
- ILD/pneumonitis (2.9%)
- QT prolongation
- Bradycardia
- Severe vision loss (0.2%)
- Embryo-fetal toxicity

Common toxicities

- Visual changes 71%
  - Light and dark accommodation
  - Recommend no driving at night in beginning
- Vomiting 46%
- Diarrhea 61%
- Edema 49%

Ceritinib 750 mg Daily (initially), Now 450 mg Daily (150-mg capsules)

Warnings

- Severe/persistent GI toxicity
- Hepatotoxicity
- ILD (4%)
- QT interval prolongation
- Hyperglycemia
- Bradycardia
- Pancreatitis
- Embryofetal toxicity

Common adverse events

- Diarrhea 86%, 6% grade 3/4
- Nausea 80%
- Vomiting 60%
- Fatigue 52%

Cho BC, et al. *J Thorac Oncol*;2017

Alectinib 600 mg Twice Daily (150-mg capsules)

Warnings

- Hepatotoxicity
- ILD: 0.4%
- Bradycardia
- Severe myalgia/elevated CPK
- Embryo-fetal toxicity

Common adverse events

- Fatigue 41%
- Constipation 34%
- Edema 30%
- Myalgia 29% (1%–4% severe)
  - Check CPKs

Brigatinib: 90 mg daily x 7 days, then 180 mg daily

Warnings

- ILD 9.1%; this is why there is a run-in of 90 mg for 7 days, then 180 mg daily
- HTN
- Bradycardia
- Visual disturbance: not the same as crizotinib
- CPK elevation, pancreatic enzyme elevation, hyperglyemia
- Embryo-fetal toxicity

Common adverse events

- Nausea/diarrhea
  - Grade 3/4 0.9%, 0%
- Fatigue
- Cough
- Headache

Lorlatinib 100 mg daily

Most concerning

- Hypercholesterolemia
  - 59% grade 1/2 and 9% grade 3
- Neurologic changes/confusion
  - 37% of patients experience either “cognitive or mood effects”

Other side effects

- Edema = 39%
- Neuropathy = 39%
- Elevated lipase and amylase

Shaw AT, Felipe E, Bauer TM, Besse B….. Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncology. 2017;18(12):1590-1599.

Entrectinib

- CNS effects (appeared to be a little more in patients with h/o brain radiation)
  - 38% dizziness
  - Cognitive impairment: 27% anything from confusion, amnesia, hallucinations, memory impairment, and many others.
  - Additional 10% developed “mood disorders”: depression, anxiety
- Increased risk for fractures: adults 5% but pediatrics 23% (with no trauma)
- Weight gain: 25%, 7% grade 3 (greater than 20% baseline)
- Lab abnormalities: increase LFTs, some myelosupression
- CHF: 3.4%, almost all were grade 3, baseline was not assessed
  - Should check LVEF prior to starting

Doebele RC, Ahn MJ, Siena S, et al: Efficacy and safety of entrectinib in locally advanced or metastatic *ROS1*-positive non-small cell lung cancer. 2018 World Conference on Lung Cancer.
Abstract 13903. Presented September 24, 2018
Information taken from the PI

Conclusion

- *ALK* and *ROS1* NSCLC are generally uncommon, but should be tested for
- Most commonly never smokers with lung cancer
- Several drugs to manage and long-term survivals, much longer than traditional chemotherapy
- Side effects of each TKI can be different yet important
- Compliance and access always an issue with orals, especially with multiple pills

Audience Response Question

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Questions?