Sidney Kimmel Cancer Center at Jefferson
NCI – designated

Until every cancer is cured

ALK NSCLC What's next?

Rita Axelrod MD

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- No disclosures

ALK rearranged NSCLC

- Distinct molecular and clinical entity
- Usually in younger, light or never smoking patients
- Pathology: often solid growth pattern, signet ring cells >10%, sometimes acinar, s times focal squamous differentiation
- Higher frequency of brain metastases
- Presentation at advanced stage
- Respond to molecularly targeted agents, chemotherapy +/- immunotherapy
- 3-5% of all NSCLC
- Mandated search as part of molecular screening for lung cancer
- ALK testing is category 1 NCCN

ALK mutations: characteristics

- ALK rearrangement is a driver oncogene for NSCLC (3-5%)
- Can occur with different point mutations within the ALK tyrosine kinase domain (L1196M, G1269A, F1174L, L1152R, 1151Tins, S1206Y, C1156Y, and G1202R)
    - https://doi.org/10.1016/j.canlet.2014.05.020 Kodama
  - Chimeric proteins that retain ALK kinase domain
  - *EML4* encodes Echinoderm microtubule associated protein-like 4- a protein that may function in microtubule assembly
      - Rodig et al. Clin Ca Res DOI: 10.1158/1078-0432.CCR-09-0802 Published August 2009
- Ever-expanding assays, such as high-throughput sequencing of tissue samples and cell-free DNA (cfDNA) from peripheral blood sample
- Druggable target
- Crizotinib first approved in 2011
- Resistance happens

Brain Metastases: up to 50% with ALK mutation

- First generation: **crizotinib:** pooled analysis of the PROFILE 1005 and 1007 trials - for 109 BM patients with administration of **crizotinib**, the intracranial (**IC**)-objective response rate (**ORR**; complete response [CR]+partial response [PR]) reached 18%, the disease control rate (DCR; CR+PR+SD) at 12 weeks reached 56%, and the duration of response (DOR) was 26.4 weeks.
- Second generation agents have **better** response/CNS penetrance
- **Ceritinib**, targeting *ALK*, *ROS1*, and IGF1 (insulin-like growth factor 1 receptor kinases), evaluated in the "ASCEND" clinical trial programs **IC-ORR** of 35–73%, IC-DCR of 61–86%, and IC-DOR of 8–11 months in either *ALK*-TKI-naïve and *ALK*-TKI-pretreated patients
- **Alectinib**, targeting *ALK*, *RET*, and *ROS1*, **IC-ORR** of 54–81%, IC-DCR of 78–90%, and IC-DOR of 10.8 to NR (not reached) months in series of randomized trials
- **Brigatinib**, targeting *ALK* and *ROS1*, in the ALTA +activity in the CNS, **IC-ORR** of 42–73% and an IC- DCR of 83–93%
- **Lorlatinib**, selective *ALK*-TKI (activity also against ROS1 kinase) high CNS penetrance in preclinical models and an **IC-ORR of 39%**
- **Sequencing of targeted and radiation therapy for brain mets is not clear**
- WangW et al https://doi.org/10.1159/000502755 Treatment Optimization for Brain Metastasis from Anaplastic Lymphoma Kinase Rearrangement Non-small-Cell Lung Cancer

Brain mets, cont..

- alectinib and crizotinib effect on brain met lesions from ALK-inhibitor naive NSCLC patients. ORR (81 vs. 50%), CR (38 vs. 5%), and DOR (17.3 vs. 5.5 months) of alectinib were all higher than those of crizotinib.
- for patients without Brain mets at start of targeted therapy, cumulative brain met rate at 12 months of treatment was lower (4.6 vs. 31.5%) in patients receiving alectinib than in those receiving crizotinib
- For lorlatinib, CR for brain mets was 25%
  - WangW et al https://doi.org/10.1159/000502755 Treatment Optimization for Brain Metastasis from Anaplastic Lymphoma Kinase Rearrangement Non-Small-Cell Lung Cancer

Diagnosis of ALK rearrangement

- tissue-based ALK rearrangement detection
  - **FISH** fusion events (fluorescence in situ hybridization) or fusion protein expression (immunohistochemistry, **IHC**) as recommended by International Association for the Study of Lung Cancer (IASLC)/College of American Pathology (CAP) guideline
- addition of hybrid capture-based next-generation sequencing (NGS) to these techniques can overcome the limits of multiple single-gene tests, has similar performance to IHC and can identify ALK-acquired resistance mutations outside of gene fusions
- Plasma-based cfDNA techniques or 'liquid biopsy'
  - cfDNA detects all guideline 7 (G7) biomarkers (epidermal growth factor receptor (EGFR), ALK, C-ros oncogene 1 (ROS1), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), REarranged during Transfection (RET), hepatocyte growth factor receptor (MET) and, human epidermal growth factor receptor 2 (ERBB2)) included in IASLC/CAP guidelines at a rate similar to a tissue-based assay.
  - **IASLC liquid biopsy statement :** positive diagnosis of ALK rearrangement by a liquid biopsy is sufficient to initiate ALK-targeted therapy.

Testing ACP 2018

- Can use tissue or cell block, other cytologic preparations
- using fluorescence in situ hybridization (FISH) for rearrangements involving *ALK*
  - *ALKFISH break-apart assay,*
  - *interpreted as positive if at least 15% of tumor cells show signals separated by at least 2 probe*
- Should be able to use with samples containing as little as 20% cancer cells
- immunohistochemistry as an alternative to fluorescence in situ hybridization for ALK 2013 (Ventana D5F3 is FDA approved)
- Immunohistochemistry is an equivalent alternative to FISH for ALK testing.: Ventana D5F3, 5A4
  - IHC-positive ALK protein expression correlates with tumor response to ALK inhibitors even in *ALK* FISH–negative cases. US: assay using the D5F3 antibody (Ventana) approved by the FDA for selection of lung cancer patients to receive treatment with crizotinib.
- Until recently, RT-PCR and NGS were not approved by FDA in the United States as first-line methods for determining ALK status but are comparable to performance with IHC
  - highly specific for most fusions; patients with positive results should be treated with an ALK inhibitor, although patients with negative results may benefit from a more sensitive method to exclude the possibility of a variant fusion
  - https://doi.org/10.1016/j.jtho.2017.12.001 Guideline From the College of American Pathologists,the International Association for the Study of Lung Cancer, andthe Association for Molecular Pathology

Selection of agents

- Crizotinib: first licensed drug based on superiority to chemotherapy in the phase III PROFILE trial
- Ceritinib: second drug USA approved
  - Ceritinib showed superiority to standard of care platinum-pemetrexed chemotherapy in the phase III ASCEND-4 trial (ORR, 72.5% vs 26.7%; PFS, 16.6 vs 8.1 months)
- Alectinib: most commonly used now in first line
  - ALEX trial, alectinib was shown to be superior to crizotinib in terms of ORR (82.9% vs 75.5%, p=0.09), PFS (34.8 vs 10.9 months; HR, 0.43) and toxicity profile (adverse events (AE) grade 3–5; 44.7% vs 51.0%) .
  - Better PFS, decreased brain metastases
  - Peters et al N Engl J Med 2017;377:829–38.

Selection of agents, cont

- **Brigatinib**
- brigatinib showed superiority to crizotinib in the phase III ALTA-1L trial (estimated 12 month PFS, 67% vs 43%; HR, 0.49; p<0.001)
- Lorlatinib: 3rd generation
- All these drugs, including the third-generation ALK inhibitor lorlatinib, have demonstrated activity in the CNS
- Ensartinib: second generation, better than crizotinib, not FDA approved, better toxicity profile (eXalt 3)

Resistance to ALK inhibitors

- Via ALK pathway
  - gatekeeper mutation' L1196M is analogous to the T790M EGFR mutation
  - G1202R substitution that confers resistance to all second-generation ALK TKIs[17] is found in only approximately 2% of crizotinib-resistant patients; most frequently after treatment with a second-generation ALK TKI (21%–43%)
- Non ALK pathways

- Mc Cusker et al BMJ http://dx.doi.org/10.1136/esmoopen-2019-000524

ALK Resistance/ treatment

- After progression on a second-generation, ALK TKI,
- third-generation ALK inhibitor lorlatinib is active
- Lorlatinib -- high potency regardless of the
- resistance mechanism including against several ALK-dependent resistance mechanisms including L1196M andG1202R substitutions
- most crizotinib-resistant tumors are still driven by ALK and are sensitive to subsequent ALK TKI therapy
- ALK inhibited tumor (initially) without detectable ALK mutations in plasma or tissue respond less well to subsequent-generation ALK TKIs ; may indicate development ALK-independent resistance mechanism
- Proposed **ALK-independent** mechanisms of resistance include
  - alteration in EGFR, mast/ stem cell growth factor receptor (KIT) and insulin-like growth factor 1 receptor, and activation of phosphorylation-dependent signalling pathways.
    - Mc Cusker et al BMJ http://dx.doi.org/10.1136/esmoopen-2019-000524

ALK rearranged NSCLC: therapeutic trials

PROFILE

- **Crizotinib 250 bid**
- **Vs platinum/pemetrexed x 6**
- **FISH based assay**
- **171v 172 pts**
- **ORR 75 v 45%**
- **PFS 10.9(8.3-13.9) v 7(6.8-8.2)m**
- **HR 0.76**
  - Solomon BJ, Kim D-W, Wu Y-L, et al. Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-Mutation-P

ALEX

- Alectinib 600 bid
- Vs crizotinib 250 bid
- IHC assay
- 152 v 151 pts
- ORR 82.9 v 75.5%
- PRS 34.8(17.7-NR)v10.9(9.1-12.9)
- HR 0.76
  - . Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-posi

ALK rearranged NSCLC: therapeutic trials

ALTA 1L

- **Brigatinib** 180 daiy
- Vs **crizotinib** 250 bid
- Local testing platform
- 137v 138 pts
- ORR 71 v 60%
- PFS NR v 9.8 (9-12.9) m
- HR 0.49
  - Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018;379:2027–39

ASCEND 4

- **Ceritinib** 750 mg
- Vs **platinum pemetrexed**
- IHC
- 189 v 187 pts
- PFS 16.8(12.6-27.2)v 8.1(5.8-11.1)m
- HR 0.76
  - . Soria J-C, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged nonsmall-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389:917–29

Treatment of ALK rearranged NSCLC

- First line: crizotinib, ceritinib, brigatinib, alectinib
- Development of resistance
- Retest with NGS to look for resistance mutation
- Second line:
  - If crizotinib was used first, then alectinib, ceritinib, or brigatinib,
  - If second generation therapy was used first, then lorlatinib
- Third and beyond:
  - Chemotherapy +/- immunotherapy
  - Benefit from alk-inhib + chemo in subset analysis
    - Lin, J et al Efficacy of platinum /pemetrexed ….refractory to second generation alk inhibitors.. https://doi.org/10.1016/j.jtho.2019.10.014 JCO Feb 2020
  - Reversal of alectinib resistance: case after chemo bev
    - Nakasuka T eta l primary resistance to A was lost afterbevacizumab combined….
    - https://doi.org/10.1016/j.jtho.2019.03.009 JTO Aug 2019

Adverse effects of ALK targeting drugs

common

- Nausea and vomiting
- Diarrhea
- Constipation
- Fatigue
- Changes in vision

Less common

- Pneumonitis: crizot/cerit >alect
  - Brigatinib early
- Edema
- Hepatotoxicity: check LFTs q 2 wks initially
- nerve damage (peripheral neuropathy)
- heart rhythm problems: QT prolongation: esp. crizotinib/cerit/brigat: also bradycardia

ALECTINIB- ALEX trial

- Active against multiple resistance mutations to crizotinib
- Not a substrate of p glycoprotein (BBB efflux transporter)
- CNS response in ALEX trial 50% (crizot) vs 81% (alect) ALEX trial
  - Longer time to CNS progression vs crizotinib
- AE's alectinib;
  - Nausea, diarrhea, vomiting; elevated AST, ALT, elevated bilirubin
  - Increased weight, incr GGT, peripheral edema
  - Dysgeusia, visual changes, myalgia, musculoskeletal pain
  - Anemia, photosensitivity
  - Gr 3-5 events more frequent with crizotinib
  - Peters, S et al N Engl J Med 2017;377:829-38. DOI: 10.1056/NEJMoa1704795

brigatinib

- Active in crizotinib resistant disease
  - Engineered for potent activity against a broad range of ALK resistance mutations
- **Good CNS activity**
- AE: any-grade GI symptoms (nausea, 33%/40% and diarrhea, 19%/38%)
- headache (28%/27%, arms A/B),
- cough (18%/34%, arms A/B; Table 4).
- most common grade 3 :hypertension (6%/6%, arms A/B), increased blood creatine phosphokinase (3%/9%, arms A/B
- 6% early **pulmonary** toxicity seen early in trial: cough, dyspnea, pneumonitis, and 3% gr 3 or greater
  - Dose interruption, decrease dose and successful re-introduction in 6/14

Kim DW et al Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial J Clin Oncol 35:2490-2498

Lorlatinib: ALK/ROS1tyrosine kinase inhibitor

- Third generation drug ALK inhibitor: brain-penetrant, third-generation kinase (ALK)/ROS1
- Designer drug: ALK Gly1202Arg active (can impair drug binding through steric hindrance)
- ALK mutations -observed after the failure of crizotinib- more commonly detected after failure of second-generation ALK TKIs (here ALK mutations are approx. 50% of acquired resistance cases
- AE: predominantly grade 1 or 2 in severity, with hypercholesterolemia and hypertriglyceridemia among the most frequently reported
- AE: cognitive impairment, edema, peripheral neuropathy, mood, fatigue, diarrhea, arthralgia, AST, ALT, lipase, amylase, decrease in EF, hypertension, abdominal pain.
- Among patients who were treated with prior crizotinib, objective response rate (ORR) with lorlatinib was 69% and median progression-free survival (PFS) was not reached (NR). Among patients who had failed two or more ALK TKIs, ORR was 39% and median PFS was 6.9 months.
    - Shaw AT et al ..ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer J Clin Oncol. 2019 Jun 1; 37(16): 1370–1379
    - Solomon B Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study Lancet Oncol 2018 Dec;19(12):1654-1667. doi: 10.1016/S1470-2045(18)30649-1

NCCN GUIDELINES 2020

- ALK testing is category 1 for NSCLC with adenocarcinoma or histology NOS
- First line therapy: alectinib (preferred), brigatinib, certinib, crizotinib
- Progression: if a/symptomatic, continue current therapy and use a local therapy such as surgery or radiation therapy to control locally
- Progression: brain: local therapy (SRS or surgery for single lesion), continue/modify targeted therapy
- Progression: beyond targeted therapy: chemotherapy +/- immunotherapy

summary

- ALK rearranged lung cancer account for approx. 3-5% of NSCLC
- Clinical: younger, less tobacco, late stage presentation
- High incidence of CNS metastases
- Lab detection: IHC (D5F3) and FISH; NGS liquid biopsy approved
- Respond to targeted TKIs and to chemotherapy +/- immunotherapy
- Longer survival with new agents, but no cure available

Until every cancer is cured

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