The Landscape of the Advanced NSCLC Treatment Paradigm: Molecular Testing and Actionable Mutations

PRESENTED BY RASHEDA PERSINGER, AGNP-C

Abstract

At JADPRO Live Virtual 2020, Rasheda Persinger, AGNP-C, explained the current lung cancer treatment landscape, including targeted therapies for EGFR and ALK rearrangements, as well as for BRAF, ROS1, NTRK, RET, MET, and KRAS mutations, and described the different testing modalities for molecular markers.

EGFR INHIBITION

As Ms. Persinger reported, EGFR was one of the first mutations indicated for NSCLC, and there are numerous EGFR tyrosine kinase inhibitors (TKIs) approved by the U.S. Food and Drug Administration (including erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], and osimertinib [Tagrisso]).

Osimertinib was approved based on data from the phase III FLAURA trial, which tested osimertinib vs. standard of care EGFR TKI (erlotinib or gefitinib) as first-line treatment for EGFR-mutated, locally advanced metastatic NSCLC (Ramlingsam et al., 2020). Progression-free survival was 18.9 months on osimertinib vs. 10.2 months with standard
of care, and overall survival was 38.6 months vs. 31.8 months, respectively.

Importantly, said Ms. Persinger, there was also a progression-free survival benefit with osimertinib in patients who presented with central nervous system (CNS) involvement (15.2 vs. 9.6 months).

In addition, the safety profile showed clear benefits to patients receiving osimertinib (Soria et al., 2018). Grade 3 and 4 all-cause events were approximately 12% lower vs. standard of care therapies, and adverse events led to discontinuation for 13.3% of patients in the osimertinib arm vs. 18.1% of patients in the comparator arm.

The most common all-grade adverse events with osimertinib were diarrhea (58%) and dry skin (32%).

**ALK INHIBITION**

With a median overall survival of 81 months, patients with ALK-positive NSCLC can live a long time, said Ms. Persinger. Of note, some of the drugs indicated for ALK rearrangements are also indicated for other mutations or other targets (Table 2).

Updated survival and safety data from the randomized phase III ALEX study in untreated advanced ALK-positive NSCLC showed significant improvement in progression-free survival for alectinib (Alecensa) vs. crizotinib (Xalkori; Peters et al., 2020). Alectinib also continues to outperform crizotinib with respect to overall survival, said Ms. Persinger, although the data remain immature. With 37% of events reported, median survival has not been reached with alectinib vs. 57.4 months with crizotinib.

Ms. Persinger also highlighted CNS efficacy results, which have become increasingly important in metastatic NSCLC treatment selection. The ALEX study is the first to include prospective CNS assessments for all patients. In patients who presented with CNS disease at baseline (60%), the overall response rate was 43% with alectinib (Gadgeel et al., 2018). There was also a longer time to CNS disease progression with alectinib vs. crizotinib.

The most common all-grade adverse events with alectinib were constipation (34%), fatigue (32%), edema (22%), and myalgia (23%). The most common grade 3 to 5 adverse events in both groups were laboratory abnormalities.

“When starting patients on alectinib, make sure to bring them back in 2 weeks to check the liver enzymes,” said Ms. Persinger.

A third-generation ALK inhibitor, lorlatinib (Lorbrena), recently demonstrated substantial overall and intracranial activity both in treatment-naive patients with ALK-positive NSCLC, and in those who had progressed on previous ALK TKIs (Solomon et al., 2018).

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**Table 1. Molecular Enrichment Is Paramount**

| Target               | Prevalence     | Drug                  | Outcome |
|----------------------|----------------|-----------------------|---------|
| EGFR                 | 15%-60%        | Osimertinib           | 70%     |
| ALK                  | 5%-10%         | Alectinib, brigatinib | 70%     |
| ROS1                 | 1%-2%          | Crizotinib, entrectinib | 72%   |
| BRAF V600E           | 1%-2%          | Vemurafenib           | 42%     |
|                      |                | Dabrafenib, trametinib | 33%     |
| MET exon 14 alterations | 3%            | Capmatinib, crizotinib | 44%     |
| High MET amplification | 3%-4%        | Crizotinib           | 66%     |
| HER2                 | 1.7%           | Afatinib              | 100%    |
|                      |                | T-DM1                 | 44%     |
|                      |                | TDX                   | 62%     |
| RET                  | 1%-2%          | Selpercatinib (LOXO-292) | 80%   |
|                      |                | Pralsetinib (BLU-667) | 58%     |
| NTRK1/2/3            | 3%             | Entrectinib, larotrectinib | 80% |

**Note.** Information from Camidge et al. (2014); Drilon et al. (2015, 2016); Gainor et al. (2019); Li et al. (2018); Mazières et al. (2013).
The most common all-grade adverse events with lorlatinib are cognitive effects (27%), peripheral neuropathy (47%), and peripheral edema (57%).

“One of the cognitive side effects I’ve observed is really bad dreams,” said Ms. Persinger. The patient was treated with a dose reduction and continues to derive a clinical and radiographic benefit.

Ms. Persinger recommended initiating lipid-lowering agents at the start of lorlatinib and repeating a lipid panel every 2 weeks.

**ROS1 FUSIONS**

Approximately 1% to 2% of patients with NSCLC adenocarcinoma (up to 4,000 patients per year) have ROS1 fusions, which were first detected in 2007.

Entrectinib (Rozlytrek) is an oral, potent and selective ROS1/NTRK/ALK TKI that is CNS active (Rolfo et al., 2015). In preclinical studies, entrectinib was shown to be a more potent ROS1 inhibitor than crizotinib. It’s also demonstrated clinical activity in multiple tumor histologies.

An integrated analysis of three single-arm trials (ALKA, STARTRK-1, and STARTRK-2) showed an overall response rate of 80.0% in patients with no CNS disease at baseline and 73.9% with CNS disease at baseline (Drilon et al., 2017). Of note, said Ms. Persinger, 56% of patients in the study had lung cancer (8% had sarcoma and 5% had colon tumors).

Adverse events led to treatment interruptions in 46% of patients and dose reductions in 29%, while 9% of patients discontinued entrectinib due to treatment-related adverse events, including pneumonia, cardiorespiratory arrest, dyspnea, and fatigue.

“With the newer TKIs, we want to ensure that we are assessing and grading appropriately based on the side-effect profile,” said Ms. Persinger.

**NTRK FUSIONS**

NTRK fusions are not just for NSCLC, said Ms. Persinger, who noted that activity has been demonstrated across 17 unique NTRK fusion-positive tumors (Drilon et al., 2018). The two most NTRK inhibitors that are used are entrectinib and larotrectinib (Vitrakvi).

The most common all-grade adverse events with larotrectinib are fatigue (28%), dizziness (25%), constipation (24%), diarrhea (23%), and nausea (21%). Dose reduction involved grade 2 or 3 increase in aspartate aminotransferase or alanine aminotransferase, dizziness, or decreased absolute neutrophil count. Discontinuation of larotrectinib was not needed due to development of adverse events.

**RET FUSIONS**

RET fusions and NTRK fusion are both treated both with entrectinib, but recent data from the LIBRETTO-001 study of selpercatinib (Retevmo) in RET-altered cancers showed an overall response rate of 64% in previously treated patients and 85% in treatment-naive patients with RET fusion-positive NSCLC (Drilon et al., 2020). Median duration of response was 20.3 months with median follow-up of 8 months.

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**Table 2. Landscape of ALK Inhibitors in Clinical Use**

| ALK tyrosine kinase inhibitor | Additional targets | Status                                      |
|------------------------------|-------------------|---------------------------------------------|
| 1st generation Crizotinib    | MET, ROS1         | FDA approved                               |
| 2nd generation Alectinib     | RET, LTK          | FDA approved, post crizotinib              |
| Brigatinib                  | Mutant EGFR, ROS1 | FDA approved, post crizotinib              |
| Ceritinib                   | IGF-1R, InsR, ROS1| FDA approved, post crizotinib              |
| Ensartinib                  | MET, ABL, AXL     | Investigational                            |
| Entrectinib                 | NTRKs, ROS1       | FDA approved for ROS1 and NTRK, but not ALK|
| 3rd generation Lorlatinib    | ROS1              | FDA accelerated approval in patients who have received one or more ALK inhibitors|

*Note. Information from Awad & Shaw (2014); Roskoski (2017).*
The FDA granted accelerated approval of selpercatinib for the treatment of RET gene alteration based on these data. This is paramount, given no RET inhibitor had previously received regulatory approval for the treatment of RET-dependent cancers.

“RET fusions are bona fide lung cancer drivers and are mutually exclusive with other driver alterations,” said Ms. Persinger. “Up to half of patients with advanced disease have brain metastases.”

The most common all-grade adverse events with selpercatinib are dry mouth, diarrhea, hypertension, fatigue, constipation, and peripheral edema. Serious adverse events included hepatitis, hypertension, bleeding, allergic reaction, and QT prolongation.

**MET EXON 14 SKIPPING**

*MET* exon 14 skipping mutations occur in 3% to 4% of patients with NSCLC, and *MET* amplifications occur in 1% to 6%.

As Ms. Persinger reported, the GEOMETRY mono-1 trial showed a clinically meaningful overall response rate and manageable toxicity profile in patients with *MET* exon 14–mutated NSCLC (Wolf et al., 2019). The overall response rate was 41% in patients who received one to two prior lines of treatment 68% in treatment-naïve patients.

The most common all-grade adverse events reported were peripheral edema, nausea and vomiting, fatigue, dyspnea, and decreased appetite. Clinically relevant adverse events included pruritus, cellulitis, acute kidney injury, urticaria, and acute pancreatitis.

**HER2 MUTATIONS**

HER2 mutations and amplifications are distinct targets, said Ms. Persinger, who noted that there are currently no FDA-approved agents, although there is a drug being studied.

**TESTING**

Finally, obtaining a complete molecular profile is an important part of treating metastatic NSCLC, said Ms. Persinger. Simultaneously adding plasma circulating tumor DNA analysis to tissue testing in treatment-naïve patients can enhance the chances of detecting a relevant actionable mutation.

“Plasma-based testing is indicated for all patients with advanced-stage, treatment-naïve lung cancer for whom tissue sampling may be infeasible or insufficient, but it should be considered for every patient with advanced-stage, treatment-naïve lung cancer who has a tissue biopsy;” Ms. Persinger concluded.

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Ms. Persinger has served on advisory boards for AstraZeneca and Pfizer and has served on the speakers bureau for AstraZeneca and Guardant Health.

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