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

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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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.

In the past 15 years, the number of targeted therapies for non–small cell lung cancer (NSCLC) has grown from 0 to 17, as the list of oncogenic mutations continues to expand in this heterogeneous group of lung cancers.

At JADPRO Live Virtual 2020, Rasheda Persinger, AGNP-C, of Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center at Sibley Memorial Hospital, explained the current treatment paradigm in advanced NSCLC, including updated treatment options for *EGFR* and *ALK* rearrangements and the latest therapies targeting *BRAF*, *ROS1*, *NTRK*, *RET*, *MET*, and *KRAS* mutations (Table 1). Ms. Persinger also described 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 (Ramalingam et al., 2020). Progression-free survival was 18.9 months on osimertinib vs. 10.2 months with standard

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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 Dabrafenib, trametinib	42% 33%
MET exon 14 alterations	3%	Capmatinib, crizotinib	44%
High MET amplification	3%–4%	Crizotinib	66%
HER2	1.7%	Afatinib T-DM1 TDX	100% 44% 62%
RET	1%–2%	Selpercatinib (LOXO-292) Pralsetinib (BLU-667)	80% 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).

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).

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 • FDA approved, first line
	Brigatinib	Mutant EGFR, ROS1	• FDA approved, post crizotinib • FDA approved, first line
	Ceritinib	IGF-1R, InsR, ROS1	• FDA approved, post crizotinib • FDA approved, first line
	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 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.

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 bonafide 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 hepatotoxicity, 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-naive 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-naive patients can enhance the chances of detecting a relevant actionable mutation.

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

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Disclosure

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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