LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Novel Targets in Advanced Non–Small Cell Lung Cancer

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H&O Which targeted agents are approved for use in patients with advanced non–small cell lung cancer (NSCLC)?

SL We are blessed with an embarrassment of riches in NSCLC, with multiple highly active targeted agents for use in this disease.

The first success story for targeted therapy in lung cancer was with epidermal growth factor receptor (EGFR) inhibitors. The EGFR inhibitors that currently have US Food and Drug Administration (FDA) approval for the treatment of NSCLC are gefitinib (Iressa, AstraZeneca), erlotinib, afatinib (Gilotrif, Boehringer Ingelheim), dacomitinib (Vizimpro, Pfizer), and osimertinib (Tagrisso, AstraZeneca). Although all of these are in use, the mutation subtype can determine the specific agent chosen. For example, osimertinib is the preferred agent for patients with an exon 19 deletion or an L858R mutation in exon 21 of the EGFR gene, both of which are common. Afatinib is the approved agent for patients with a G719X mutation, which is the most common of the atypical mutations; another popular choice for these patients is osimertinib, although it is not approved in this setting. Patients with EGFR exon 20 insertions have 2 approved agents: the bispecific antibody amivantamab (Rybrevant, Janssen) and the oral tyrosine kinase inhibitor (TKI) mobocertinib (Exkivity, Takeda). The optimal sequencing of these agents is not yet clear. Identifying patients with exon 20 insertions is especially important because they typically do not respond well to the other available TKIs, whereas patients with typical mutations are likely to get a response with any of the EGFR inhibitors.

The drugs providing some of the best outcomes are the anaplastic lymphoma kinase (ALK)–targeted agents; the median progression-free survival (PFS) of patients treated with these drugs is measured in years. The first agent in this drug class to be approved was crizotinib (Xalkori, Pfizer), and the second was ceritinib (Zykadia, Novartis). The ALK-targeted agents that most recently received approval are alectinib (Alecensa, Novartis), brigatinib (Alunbrig, Takeda), and lorlatinib (Lorbrena, Pfizer); these are the preferred agents in patients with ALK mutations because they are more effective than the older ones.

The 2 agents that are approved for use in ROS1 fusion–positive lung cancer are crizotinib and the newer entrectinib (Rozlytrek, Genentech). Ceritinib and lorlatinib also have activity at ROS1, although they are not approved in that setting. The use of ceritinib has decreased with the introduction of more-potent ROS1 inhibitors, and lorlatinib is generally given only in the resistant setting.

The combination of the BRAF inhibitor dabrafenib (Tafinlar, Novartis) and the MEK inhibitor trametinib (Mekinist, Novartis) is approved for use in patients with a BRAF V600E mutation. The RAF/MEK inhibitors used in melanoma, such as vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and cobimetinib (Cotellic, Genentech), are not approved for use in lung cancer and typically are not given in this setting. Outcomes with RAF/MEK inhibitors are poor in patients with non-V600 BRAF mutations, so alternate strategies are used for them.

Sotorasib (Lumakras, Amgen) is approved for use in KRAS G12C–mutated NSCLC, but it does not work in patients with other KRAS mutations.

The TKIs that are approved for use in patients with
mesenchymal epithelial transition (MET) gene exon 14 skip mutations are capmatinib (Tabrecta, Novartis) and tepotinib (Tepmetko, EMD Serono), which are similar in efficacy and tolerability. These agents are not approved for use in patients with MET amplification or overexpression.

The agents approved for use in RET fusion–positive lung cancer are selpercatinib (Retevmo, Lilly) and pralsetinib (Gavreto, Blueprint/Genentech), both of which are very well tolerated and extremely effective. They have completely taken the place of other multikinase inhibitors with activity in RET fusion–positive lung cancer, such as cabozantinib and vandetanib (Caprelsa, Genzyme), which were used in the past but are much more toxic and not nearly as effective as these newer, more specific agents.

And to round out the list, we have 2 FDA-approved neurotrophic receptor tyrosine kinase (NTRK) inhibitors: larotrectinib (Vitrakvi, Loxo) and entrectinib. Both of these agents are very active in NTRK fusion–positive lung cancer, but not in lung cancer with NTRK mutations. Both agents are fairly well tolerated but do have unique toxicities, including dizziness.

**H&O Which targeted agents are on the horizon for advanced NSCLC?**

**SL** The antibody-drug conjugate (ADC) drug class is the largest class for which we expect to see approvals in the near future. Although not all the ADCs that are being developed in NSCLC are used in a genomically defined subset of lung cancer, they can still be considered targeted agents in the sense that they act against a specific target. The 2 ADCs that target human epidermal growth factor receptor 2 (HER2) are trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), and trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca). Although these agents are not yet approved for use in lung cancer, the National Comprehensive Cancer Network (NCCN) guidelines list them as treatment options for patients who have metastatic NSCLC with a HER2 mutation. Unlike in breast cancer, in which these agents are used for both HER2-amplified and HER2 protein–expressing tumors, their activity in lung cancer is most impressive in NSCLC that is HER2-mutated, with the mutation typically located in exon 20. We hope to see these agents approved for use in NSCLC after larger studies have been conducted. The phase 2 DESTINY-Lung01 trial has shown durable anticancer activity of T-DXd in patients with previously treated HER2-mutant NSCLC.

Telisotuzumab vedotin, which is an experimental ADC that targets MET, has received FDA Breakthrough Therapy designation as a treatment for advanced or metastatic NSCLC with MET overexpression (as opposed to NSCLC with MET exon 14 skip mutations or MET amplification). The experimental ADCs sacituzumab govitcan (Trodovy, Gilead) and datopotamab deruxtecan, both of which target trophoblast cell surface antigen 2 (Trop-2), have also shown activity in NSCLC. Finally, the experimental ADC patritumab deruxtecan, which targets HER3, has received Breakthrough Therapy designation for use in patients with EGFR-mutant lung cancer.

Regarding TKIs, adagrasib is showing very promising activity in KRAS G12C–mutated NSCLC. The phase 1/2 KRYS TAL-1 study, which Dr Alexander Spira presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, showed response rates comparable with those seen with sotorasib, which is already approved for use in patients with KRAS G12C–mutated NSCLC. Because the 2 agents bind to different locations, we expect that the drugs will differ in regard to acquired resistance, so that sequencing them may be of value. Awad and colleagues, in the *New England Journal of Medicine* in 2021, reported on work to identify genomic and histologic mechanisms that impart resistance to KRAS G12C inhibition. In addition, adagrasib and sotorasib may differ in how well they penetrate the blood-brain barrier.

The TKI poziotinib is an irreversible pan-ErbB inhibitor that has FDA Fast Track designation for patients who have locally advanced or metastatic NSCLC with an HER2 exon 20 insertion mutation. Poziotinib has also shown some activity in patients with EGFR exon 20 insertion–positive NSCLC.

CLN-081 is an agent that has FDA Breakthrough Therapy designation for the treatment of patients with NSCLC that has EGFR exon 20 insertions. At the 2022 ASCO Annual Meeting, Dr Helena Yu presented updated results from a phase 1/2 study of CLN-081 in NSCLC, in which encouraging responses to CLN-081 and a favorable toxicity profile, with no grade 3 rash or diarrhea, were seen at the dosage of 100 mg twice daily.

Another agent of note is the bispecific antibody REGN5093, which targets NSCLC with MET alterations (NCT04077099). Multiple other agents and combinations of agents are under investigation, so this is a space that is rapidly evolving.

**H&O What additional targetable pathways have been identified?**

**SL** The neuroregulin 1 (NRG1) pathway is an interesting target. NRG1 fusions are relatively rare, occurring in approximately 0.2% of all cancers, but they are transforming events. Because they are seen in a variety of tumors, including NSCLC, KRAS wild-type pancreatic cancer, breast cancer, colon cancer, cholangiocarcinoma, and sarcoma, NRG1 has the potential to be a tumor-agnostic biomarker. NRG1 fusions are difficult to find with most
next-generation sequencing platforms because the gene is so large, so the best way to detect them is with RNA-based next-generation sequencing. Splicing out the introns makes the gene a little bit more manageable.

NRG1 fusions are different in that they do not create a constitutively active kinase. NRG1 is actually the ligand, and it has an EGF-like domain.

Several agents active against NRG1 fusions are being investigated in ongoing studies. Because NRG1 binds to the HER3 receptor, which usually heterodimerizes to HER2, agents that target HER2 may be effective in patients with NRG1 fusions. The most-reported benefit in patients with NRG1 fusions comes from the EGFR TKI afatinib, which can be explained by the fact that NRG1 contains an EGF-like domain. The phase 2 TAPUR study, which is the first and only clinical trial from ASCO, is a basket study that includes afatinib (NCT02693535). Afatinib is also being examined in a decentralized prospective study of its use in NRG1 fusion–positive cancers; I described this study in a poster at the 2022 ASCO Annual Meeting.

Also being developed for use in NRG1 fusion–positive NSCLC is the bispecific antibody zenocutuzumab, also known as MCLA-128. A phase 2 trial is currently looking at the use of this agent in several types of tumors, including NSCLC (NCT02912949). An additional agent that is being developed for use in these patients is the HER3-targeting monoclonal antibody seribantumab. Dr Daniel Carrizosa presented initial data from the CRESTONE trial at the most recent ASCO annual meeting, which suggested that seribantumab induces durable responses in advanced solid tumors harboring NRG1 fusions and has a favorable safety profile. In patients who had NSCLC with an NRG1 fusion, seribantumab produced an overall response rate of 36% and a disease control rate of 91%. Afatinib, zenocutuzumab, and seribantumab have all demonstrated efficacy in this target across tumor types.

The approval of sotorasib was very important because KRAS mutations are common, and KRAS G12C is the most common KRAS mutation. KRAS G12C mutations account for only a fraction of KRAS mutations, however, so the RAS/MAPK pathway continues to be of tremendous interest in drug development. Because the RAS/MAPK pathway is so central to normal physiology, we do need to be extremely careful when we interrupt it. Newer, selective inhibitors of this pathway that are in development include the dual RAF/MEK inhibitor VS-6766, which targets KRAS G12V—the second most common mutation in KRAS. The RAMP 202 trial is studying the use of VS-6766 with or without the focal adhesion kinase (FAK) inhibitor defactinib in patients with KRAS G12V NSCLC (NCT04620330). VS-6766 also may have activity in cancers with BRAF mutations, either BRAF V600E mutations after the use of dabrafenib plus trametinib or BRAF non-V600 mutations, in which a large unmet need remains.

**H&O What other combination approaches are being studied with targeted agents?**

**SL** We know that targeting angiogenesis seems to be relevant, especially in the EGFR space. We have extensive preclinical data from Dr John Heymach at MD Anderson showing that EGFR-mutant lung cancers depend on vascular endothelial growth factor (VEGF) signaling, and that the use of EGFR kinase inhibitors plus VEGF or VEGFR2 antibodies, such as bevacizumab and ramucirumab (Cyramza, Lilly), shows some promise. Early studies showed an improvement in PFS that did not necessarily translate into an overall survival benefit. Ongoing studies are using newer-generation EGFR TKIs, however—specifically, osimertinib and VEGF inhibitors (NCT03909334). We are eager to see if the addition of these agents translates to a survival benefit.

Combination targeted therapy is also an important way to overcome acquired resistance, which is something we expect to see in all patients receiving targeted therapy. The better we can understand the mechanism of that resistance, the more effectively we can formulate combinations to overcome it. For example, if someone with an EGFR-mutant lung cancer has been responding well to osimertinib but begins to acquire resistance, we can check to see whether MET amplification has developed. If so, the addition of a MET inhibitor can help overcome resistance and restore control. We already have some data supporting the use of capmatinib and tepotinib, which are the FDA-approved MET kinase inhibitors, in this instance. Reports also support the use of crizotinib in these patients. Finally, a study by Sequist and colleagues, published in Lancet Oncology in 2020, supports the use of osimertinib plus the investigational MET inhibitor savolitinib in patients with EGFR mutation–positive, MET-amplified NSCLC after progression on EGFR TKIs.

Just as we can add a MET inhibitor if we see MET amplification, reports suggest that we can add a rearranged during transfection (RET) inhibitor if a RET fusion develops. A case report by Piotrowska in Cancer Discovery supported the use of the investigational agent pralsetinib, also known as BLU-667, when a RET fusion is found at the time of resistance acquisition, and a case series by Rehman in JCO Precision Oncology supported the use of selpercatinib (Retevmo, Lilly) in this situation. This approach has not been studied on a large scale.

If a BRAF V600E mutation develops, should we add dabrafenib/trametinib? The answer to this is unknown, and we need to be cognizant of potential drug-drug interactions.
and overlapping toxicities as we add more drugs to the mix. Understanding the mechanisms of resistance will help us develop novel combinations, however.

**H&O What approaches to targeted therapy would you like to see in the future?**

**SL** In the future, it would be ideal to identify in advance which mutations will eventually occur. Do genomic studies predict the destiny of a particular person’s cancer? Could knowing at diagnosis that MET amplification will eventually develop in an EGFR-mutant lung cancer help us prevent that from happening?

We know that the use of erlotinib or afatinib for EGFR-mutant lung cancer eventually leads to acquired resistance associated with a T790M mutation in exon 20. Because osimertinib retains its activity in the presence of the T790M mutation, researchers have hypothesized that starting with osimertinib could prevent T790M from ever occurring, and therefore the initial benefit could be maintained. Indeed, the FLAURA trial, by Ramalingam and colleagues, showed this to be true in advanced EGFR-mutant NSCLC. The T790M mutation accounts for resistance in 50% to 60% of patients with EGFR-mutant lung cancer.

Would it make sense to add a MET inhibitor for all patients who are at risk for MET amplification? Provided the drug was well tolerated, perhaps it would. Potential drugs to investigate for the prevention of resistance are the TKIs savolitinib and capmatinib and the bispecific antibody amivantamab. However, the overall approach is challenging because we first need to have tests that are extremely sensitive and specific for certain mutations. Liquid biopsy would be ideal if all the relevant clones were in the circulation, but it is unclear whether this is the case. Even when a clone with MET amplification is detected, we do not know whether that always means that MET amplification will develop in the patient at some point.

It is difficult to predict the future, but I think that the long-term goal is to personalize treatment further to account for both the main drivers and the clones that will eventually mediate resistance in an effort to prevent resistance. If it can be done, is the development of strategies to account for every single clone that exists the eventual road to cure with targeted therapy? I hope it will be, but the answer is unclear.

**H&O What advances would it be more realistic to anticipate within the next year?**

**SL** A more realistic advance in the next year would be the development of empiric strategies to improve outcomes for each population as a whole. For that approach to be viable, we need well-tolerated strategies that work in a broad mechanism.

**Disclosure**

Dr Liu has served on the advisory board of or as a consultant for Amgen, AstraZeneca, Bayer, BeiGene, Blueprint Oncology, Boehringer Ingelheim, Bristol Myers Squibb, Catalyst, Daiichi Sankyo, Eisai, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Lilly, Merck/MSD, Novartis, Regeneron, Sanofi, Takeda, and Turning Point Therapeutics. He has also received institutional research support from Alkermes, Bayer, Blueprint Oncology, Bristol Myers Squibb, Elevation Oncology, Genentech, Gilead, Merck, Merus, Nuvalent, Pfizer, Rain Therapeutics, RAPT Therapeutics, and Turning Point Therapeutics.

**Suggested Readings**


Carrirozzi DR, Burkard ME, Elamin YY, et al. CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring NRG1 fusions [ASCO abstract 5006]. J Clin Oncol. 2022;40(16(suppl)).


Yu HA, Daniel Tan S-W, Smit EF, et al. Phase (Ph) 1/2a study of CLN-081 in patients (pts) with NSCLC with EGFR exon 20 insertion mutations (Ins20) [ASCO abstract 9007]. J Clin Oncol. 2022;40(16(suppl)).