A Look at the Near Future of Lung Cancer Treatment

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This activity is designed to inform physicians about the recent advances, as well as anticipated advances, in the field of lung cancer treatment.

Target Audience
This activity is directed toward medical oncologists, pulmonary care specialists, primary care physicians, nurses, and nurse practioners who treat and/or manage patients with lung cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers interested in the treatment of lung cancer are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Discuss biologically targeted treatment personalization in lung cancer
- Review the emerging role of liquid biopsy in the near future, with respect to lung cancer treatment
- Assess the potential impact of ongoing clinical trials/emerging data on the targeted treatment of lung cancer

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Lung cancer is the second most commonly diagnosed cancer and is the leading cause of cancer-related deaths in the United States. An estimated 224,390 new cases of lung cancer, which is about 14% of all cancer diagnoses, are expected to be diagnosed this year.[1] The most common form of lung cancer is non–small cell lung cancer (NSCLC), and a majority of patients present with a locally advanced or metastatic form of NSCLC at diagnosis. NSCLC is a heterogeneous group of tumors of variable histology, including adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.[2]

Treatment of lung cancer has modulated along with the state of cancer science for 2 decades. Recent advances in the field have led to the recognition that different histological subtypes and driver mutations determine the biology of these malignancies.[2] We now recognize that somatic gene mutations or rearrangements in specific "driver genes" can lead to oncogenic transformation and tumor growth. This recognition stems from the discovery of activating mutations in the epidermal growth factor receptor (EGFR) and rearrangements of the anaplastic large-cell lymphoma kinase (ALK) gene in some advanced NSCLC tumors.[3] Following the recognition that oncogenic driver mutations determine the biology of many NSCLC subtypes, the clinical paradigm has shifted to drug development toward targeted and personalized approaches. For instance, we now recognize that presence of EGFR-activating mutations in patients with NSCLC can serve as a clinical predictor of their sensitivity and efficacy to EGFR-directed therapy.[4] Thus, EGFR mutations and ALK gene rearrangements are successfully being targeted with specific tyrosine kinase inhibitors.[5] Personalized treatment approaches with targeted therapies has led to significant improvements in patient outcomes.

While the estimated median overall survival (OS) for patients with advanced/metastatic NSCLC (stage IV) has been 10 to 12 months, in a recently published study, significant survival improvement with a median OS of >3 years has been reported for patients with an oncogenic driver undergoing targeted therapy.[5] Moreover, data from several clinical trials comparing front-line EGFR tyrosine kinase inhibitor (TKI) treatment with standard platinum chemotherapy in patients with *EGFR*-mutated NSCLC have shown that targeted treatment is more effective than standard chemotherapy in patients with these mutations.[4]

Currently, for *EGFR* mutations identified prior to frontline therapy, gefitinib, erlotinib, or afatinib monotherapy are Category 1 recommended EGFR targeted strategies.[6] The first TKIs that showed treatment benefits in patients with *EGFR* mutations were gefitinib and erlotinib; these TKIs are referred to as first-generation EFGR TKIs. Despite an overall response rate of close to 75%, patients eventually develop resistance to first-generation EGFR TKIs.[7] About 50% of instances of acquired resistance seen in these patients are due to a secondary T790M mutation in exon 20 of the EGFR gene; however, several other mechanisms of resistance also exist.[7] The second- and third-generation EGFR TKIs were designed to provide better inhibition of EGFR and/or to overcome EGFR T790M. With second-generation EGFR TKIs, afatinib binds irreversibly to the tyrosine kinase of EGFR and is approved as a first-line treatment of advanced NSCLC with activating *EGFR* mutations. Third-generation EGFR TKIs such as osimertinib are designed to target tumors harboring acquired EGFR T790M.[8,9] In patients with confirmed T790M mutations, treatment with osimertinib has shown durable responses[10] and is approved for patients with metastatic EGFR T790M mutation–positive tumors.[6] Another third-generation compound that is currently in clinical development is rociletinib. Similarly, in ALK-positive disease, ALK-targeted monotherapy remains a Category 1 recommended frontline approach (ie, crizotinib followed by ceritinib or alectinib in patients progressing on crizotinib).[6] Additionally, multiple new ALK inhibitors are being developed currently, such as brigatinib (AP26113), entrectinib, and PF-06463922.[11,12]

Discovery of EGFR mutations and other clinically significant molecular aberrations in NSCLC has also been key to the development of diagnostic tests to check for these genomic alterations. Advances have also occurred in the diagnostic field to provide less invasive newer techniques such as liquid biopsy as an alternative to tissue-based testing, and for identifying and monitoring patients with these mutations.[13] While liquid biopsy is not yet approved, research is ongoing in testing its utility in NSCLC patients. Some of the emerging approaches that use liquid biopsy for tumor genotyping for NSCLC testing include analyzing techniques that utilize circulating tumor cells, cell-free deoxyribonucleic acid (cfDNA), and exosomes (exoRNA isolation).[14] Recently published data validated the utility of plasma genotyping of cfDNA for detection of *EGFR* and *KRAS* mutations with the high specificity in patients with advanced NSCLC. Additionally, cfDNA may also be useful in detection of EGFR T790M that may be missed by tissue genotyping due to tumor heterogeneity in resistant disease.[15]

Additionally, advances in the diagnostic field have also culminated in the development of sophisticated genomic sequencing technology, such as next-generation sequencing (NGS). Also referred to as "massively parallel sequencing," NGS offers the benefits of high speed and a relatively low cost. Although NGS currently utilizes tumor tissue, it can work with small samples and has the ability to screen the mutational status of different samples such as biopsies, cytological samples, and circulating plasma DNA.[16,17]

While the use of molecular targeted therapies has improved median OS in a select set of patients with NSCLC whose tumors harbor specific genetic alterations, for a majority of patients with NSCLC, molecular alterations are not yet available to utilize targeted therapies. Hence, different approaches have been undertaken to stimulate immune response, including therapeutic vaccines and immune checkpoint blockade therapies.[18] Among these approaches, immune checkpoint blockade with nivolumab (PD-1 inhibitor) or pembrolizumab (PD-L1) is currently approved for the treatment

of advanced lung cancer.[6] Additionally, several other checkpoint inhibitors, such as atezolizumab (MPDL3280A), MEDI4736, and ipilimumab are currently at different stages of clinical development for treatment of NSCLC, as well as small-cell lung cancer.[19]

This is an exciting time in the field of lung cancer treatment with several recent new therapies and several other promising approaches on the horizon, all intended to improve the outcomes of patients.

Benjamin Levy, MD, medical director of Thoracic Medical Oncology for Mount Sinai Health Systems and the associate medical director of the Cancer Clinical Trials Office (CCTO) for Mount Sinai Hospital in New York offered his insights on recent updates and his thoughts on what we might expect to see in the near future in the field of lung cancer treatment.

Moderator: Please summarize how we personalize care for lung cancer now based on tissue and mutational subtype? Also, are there unmet clinical needs in the field?

Dr Levy: We have truly witnessed a seismic paradigm shift in the treatment options for patients with NSCLC. Whereas 10 years ago we were only able to offer patients chemotherapy, we are now able to parse out lung cancer into molecular cohorts that allow for delivery of genotype-driven therapies. Patients whose tumors harbor mutations such as EGFR mutations and ALK rearrangements are now receiving oral targeted therapies. Other less common, yet actionable, mutations have also been identified, including BRAF, ROS, and RET rearrangements, and more recently, non-receptor tyrosine kinase (NRTK) rearrangements.

Targeted therapies are either approved or are being investigated in clinical trials for many of these genetic alterations. The rapid pace of drug discovery and our expanded knowledge of the genomic landscape of lung cancer tumors underscore the importance of next-generation sequencing for patients. Given the availability of existing targeted agents that can be either given as standard of care or are currently being investigated in clinical trials, all patients with NSCLC should have next-generation sequencing performed on their tissue specimens.

Moderator: What is the role of rebiopsy or liquid biopsies for identifying actionable mutations in lung cancer?

Dr Levy: Tissue rebiopsies and liquid biopsies (plasma genotyping) now play an integral role for patients who progress on targeted therapies. The utility of this approach has been most recently highlighted in EGFR-positive patients who have progressed on first- or second-generation TKIs. Up to two-thirds of these patients develop a secondary mutation in EGFR called T790M. Given the impressive responses and recent approval of a T790M–directed therapy/inhibitor, osimertinib, it is paramount that these resistant alterations are identified upon progression in order to identify patients eligible for this therapy. This can be done by tissue procurement (rebiopsy) or, more recently, via a simple, minimally invasive blood assay. I foresee in the near future that liquid biopsies or rebiopsies may not just be restricted to the EGFR-positive patient, as they have already begun to play a role in identifying other genetic cohorts. In addition, liquid biopsies may also be considered for treatment-naïve patients in whom there is insufficient material for molecular analysis. At our center, many of our treatment-naïve patients, as well those who have progressed on EGFR TKI therapy, are being considered for plasma genotyping.

Moderator: What do we need to better personalize immunotherapies?

Dr Levy: The emergence and approval of checkpoint inhibitors (PD-1 and PD-L1 agents) has altered the treatment paradigm for patients with advanced-stage lung cancer. These drugs have provided meaningful improvements in survival when compared to single-agent docetaxel in platinum-refractory patients. Unfortunately, we have yet to define the proper molecular enrichment strategy. While PD-L1 by immunohistochemistry can select patients more likely to respond to these agents, this biomarker has limitations. For one, expression of PD-L1 is heterogeneous within a tumor and varies with the antibody that is utilized. In addition, there are many patients who are PD-L1-negative who still garner meaningful benefits from these drugs. Further refinement of PD-L1 testing is needed, and hopefully, initiatives such as the Blueprint proposal for companion diagnostic comparability will help optimize testing.

In addition, other biomarkers are being evaluated including the mutational load of a tumor as a potential predictor of response to PD-1/PD-L1 blockade. A better understanding of the relationship between certain known driver mutations (EGFR and KRAS) and the efficacy of these drugs is also beginning to unfold. Personalization of immunotherapeutic approaches will also need to include novel combination strategies with other immunotherapies and chemotherapy. We need to keep in mind that only 20% of patients respond to single-agent checkpoint inhibitors, and therefore, further strategies are needed to improve outcomes. One promising strategy currently being evaluated is the combination of hypomethylators and deacetalyters with PD-1 drugs in an effort to exploit epigenetic priming of a tumor to augment checkpoint inhibitor efficacy.

Moderator: What impact will the results from upcoming checkpoint inhibitor trials, such as CheckMate 227, MYSTIC, and NEPTUNE, have in the treatment of NSCLC?

Dr Levy: Now that single-agent checkpoint inhibitors have been cemented as standard-of-care for advanced stage, platinum-refractory patients (second-line), one of the next research initiatives is to understand their efficacy in the treatment-naïve (first-line) setting. CheckMate 227, MYSTIC, and NEPTUNE are each evaluating the optimal strategy of immunotherapies as first-line treatment either as single-agent or in combination with either chemotherapy or CTLA-4 antibodies. It will be interesting to see if these drugs provide meaningful benefit in survival by moving to the first-line

setting and whether any molecular enrichment strategy can be utilized to better predict the efficacy of each strategy. My guess is that there may be a role for these agents in treatment-naïve patients with an optimal enrichment strategy, but I remain skeptical on whether adding these drugs to chemotherapy without selection of the right patients will provide meaningful improvements.

Moderator: What changes in the field of lung cancer can be expected from the PembroPlus that combines pembrolizumab with chemotherapy for treatment of advanced lung cancer?
Dr Levy: PembroPlus is a large phase I/II trial evaluating pembrolizumab in combination with chemotherapy in multiple solid tumors including small cell lung cancer (SCLC). Similar to the first-line studies (NEPTUNE, CheckMate 227), this trial is trying to understand safety, but more importantly, efficacy, by combining pembrolizumab, a PD-1 Ab, with single-agent chemotherapy. Extensive-stage SCLC is a disease with many unmet needs and very little improvement in survival over the past 10 years. There is reasonable scientific rationale to exploit these drugs in SCLC, and the hope is that there will be synergy witnessed by combining pembrolizumab with irinotecan in platinum-refractory SCLC.

Moderator: Do you envision vaccines such as CimaVax becoming a promising option for patients with NSCLC in the future? Why or why not?
Dr Levy: It remains unclear if CimaVax will make an impact in patients with NSCLC. CimaVax works a little differently than checkpoint inhibitors in that it is a vaccine against epidermal growth factor, a protein that plays an integral role in cancer cell signaling and survival. The drug was developed in Cuba and has been administered to over 5000 patients worldwide. Results from a 2008 *Journal of Clinical Oncology* manuscript did demonstrate a competitive survival in stage IIIB/IV patients under the age of 60 who received this agent as a switch maintenance strategy after platinum chemotherapy versus best supportive care. Despite this, there was no difference in survival in the overall intent-to-treat population. It is important to note that further studies are needed before this drug can be viewed as a real therapeutic option in patients, and this will take time. My understanding is that there is currently a partnership between Roswell Park and the Center for Molecular Immunology in Havana that will hopefully expedite its clinical development in the US.

Moderator: What potential do third-generation EGFR TKIs have of being utilized as frontline therapy? What emerging data do we have supporting that concept, and is this strategy being evaluated in a subset of patients with T790M or all patients with lung cancer?
Dr Levy: Now that third-generation EGFR TKIs have been approved for EGFR-positive patients who develop resistance to first- or second-generation TKIs who harbor T790M, the next research initiative has been to exploit their efficacy in treatment-naïve, EGFR-positive patients. The early data on this strategy looks promising, with recent reports demonstrating a response rate of 77% and progression-free survival (PFS) of 19.3 months with osimertinib. This is one of the most competitive outcomes that we have witnessed with any first-line agent in these patients. Given that first-generation TKIs generally yield a PFS of 12 to 13 months, the results of first-line T790M-directed therapies should not be overlooked. If these data hold up in ongoing phase III trials, this may lead to drug approval in the first-line setting and a shift in the standard of care for these patients.

Moderator: Does CAR-T cell therapy have a role in the treatment of lung cancer? Could this be combined with other immunotherapeutic approaches? Why or why not?
Dr Levy: CAR-T cell therapy is an innovative approach for the treatment of multiple malignancies. The strategy, termed "adoptive T-cell transfer," works by isolating T cells from patients, genetically modifying them, and then reintroducing them in an effort to better augment T-cell responses against cancer antigens. This technology is beginning to take shape in many liquid tumors, including lymphoma and leukemia. Recent preclinical data suggest that CAR-T cell therapy could be successful at targeting Erb2, a protein that is expressed in both breast and lung cancer. However, preliminary data utilizing this strategy in solid tumor patients have not been as successful as that witnessed in liquid tumors. With further refinement of this strategy, there may be a day when CAR-T cell therapy could be effective in NSCLC patients. However, there is still a lot of work that needs to be done in the clinical space, and we need to gain a better understanding of how best to exploit this strategy (which proteins to target, combination strategies) before it's ready for prime time.

Moderator: Based on recent developments, how do you envision the treatment of NSCLC evolving in the coming few years?
Dr Levy: I hope to see a day in the near future when we are no longer routinely using chemotherapy to treat our patients with both early- and late-stage disease. This will require further study into potential actionable mutations that could be wedded to targeted therapies, as well as better refinement and optimization of immunotherapy approaches. I also envision a time when liquid biopsies may circumvent the need for tissue biospies in both treatment-naïve and refractory patients. We are certainly not there yet, but as liquid platforms become more accurate, they may be able to serve as a reliable molecular proxy of disease and allow treatment decisions to be made in lieu of tissue procurement.

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