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Reviewing First-Line Systemic Therapies for Metastatic Non-Small Cell Lung Cancer

Announcer:
This is ReachMD, and you're listening to *Closing the Gaps in Non-Small Cell Lung Cancer*, sponsored by Lilly.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
The therapeutic landscape for nonsmall cell lung cancer is rapidly evolving as a growing number of local, systemic, and combination treatments are being introduced with hopes of improving survival rates and preserving quality of life. But the challenge is still daunting against a disease representing the most common cause of cancer mortality worldwide, with more than half of patients presenting with stage IV disease at diagnosis. On today's program, we'll take a closer look at various recommended first-line systemic therapies, the rationales behind single agents versus combinations, and strategies to guide patients through their treatment course. Welcome to Closing the Gaps in Nonsmall Cell Lung Cancer on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me is Dr. Stephen Liu, a practicing thoracic medical oncologist and associate professor of medicine at the Lombardi Comprehensive Cancer Center of Georgetown University. Dr. Liu, welcome to the program.

Dr. Liu:
I'm glad to be here.

Dr. Caudle:
Excellent. Well, we're happy that you're here too. So, let's start with a refresher on the main factors you and your colleagues consider toward each patient's diagnosis of metastatic nonsmall cell lung cancer, and how this informs your first-line treatment of choices. So, what are these factors?

Dr. Liu:
Well, I think the first step is to identify what specific type of lung cancer a patient has. You know, we can appreciate the lung cancer is really in a family of related cancers with unique properties and unique vulnerabilities. So it's important to identify those vulnerabilities and use them to really tailor an individual treatment plan. You know, for years we've classified cancers based on their histology. And in the lung world, you know, the squamous, adeno, large cell; now we really need to understand the underlying biology. Are there genomic driver mutations or fusions present? If it's a cancer likely to respond to immunotherapy-based approach, we also need to know how the cancer is affecting the patient. You know, what symptoms is it causing? Is it threatening any specific organs? What is the pace of growth, the acuity of a disease, the specific clinical circumstances that are going to guide our treatment decisions? And we also have to consider the individual traits of each patient. You know, are there relative comorbidities, specific organ dysfunction such as hepatic or renal insufficiency? What's the patient's performance status? The existing social support? Distance to the cancer center? And really the goals of treatment for that patient to take all that and really identify what are the important values that we need to adopt as we move forward together with the patient.

Dr. Caudle:
Well, let's consider the various therapeutic classes that are out there. Which types of treatments have become or are on their way to becoming staples of first-line therapy? And is it a crowded field of options for oncologists?

Dr. Liu:
You know, I think it is becoming more crowded, but obviously that's a good thing for our patients. Now, if we identify a driver alteration

and sequencing, targeted therapy really is the – the therapeutic class we need to focus on. We now have multiple agents approved for the treatment of lung cancer, harbored mutations in EGFR, BRAF, or fusions in ALK. And in those settings, I really think the latest generation of agents provide the highest efficacy, and the most favorable safety profile. An example would be the third generation EGFR kinase inhibitor, osimertinib, which offers a better progression-free survival, better CNS response and a clear survival benefit when compared to the first generation inhibitors like erlotinib 250. And the next generation ALK inhibitors heard the same story in two randomized phase 3 trials, alectinib and brigatinib both had a far greater progression-free survival and much more CNS activity than first generation crizotinib. With those drugs, we can achieve a median progression-free survival approaching three years. In someone with metastatic lung cancer, I think that's quite remarkable. But beyond those standard targets, it's important to know there are many other viable targets where we have agents pretty far in development and a lot of very accessible trials. And I think we're not far from those being standard for both testing and treatment. So we also have some exciting drugs in development that can target KRAS, which not too long ago was thought to be an undruggable target. So to be really sure we're treating patients in the optimal manner, we need full sequencing, preferable RNA-based and that's critical to proper management. And generally when we don't identify a target, early introduction of immunotherapy really is the preferred approach. And there's studies showing benefit with immunotherapy alone the PD1 inhibitor, pembrolizumab and the PDL1 inhibitor, atezolizumab, both improve survival compared to chemotherapy alone in tumors that have been highly expressed PDL1. And with combination, where we're combining immunotherapy with chemotherapy. And those are options that are independent of PDL1 expression: carboplatin, pemetrexed, pembrolizumab. And carboplatin/paclitaxel, bevacizumab/atezolizumab both FDA approved for non squamous lung cancer. Carboplatin and taxol; either paclitaxel or nab-paclitaxel with pembrolizumab for patients with squamous non-small cell lung cancer. So to answer the question, it is quite crowded, and in the coming years, it will become more crowded, not less. But the key is really tailoring those treatment options to each specific individual patient for the best possible outcome.

Dr. Caudle:
Now what about the roles of local therapies via treatment modalities such as radiotherapy, surgical resections, and thermal ablations? You know, do these have a defined place and sequence in the early treatment of advanced non-small cell lung cancer?

Dr. Liu:
You know, so I think this is an important point. You know, we had historically reserved local therapy for patients with early stage lung cancers. Bbut an important development over the recent years, you know, the appreciation that there are some patients with stage IV lung cancer who would benefit from a more aggressive approach. Now we use the term oligo metastatic disease, or oligo metastatic cancer. And it really comes from the realization that cancer is. Someone who has lung cancer with a solitary brain metastasis, um, versus a cancer with many other sites of disease, diffuse involvement of any organ. Those cancers probably represents different biologies and can probably be treated differently. When there's diffuse involvement, I think systemic therapy really is a mainstay of treatment. But if there's one site or two sites of disease outside of the lung, incorporating radiation, ablation, even surgery with systemic therapy, can really lead to long-term control and, possible cure for some patients.

Dr. Caudle:
Excellent. For those of you who are just tuning in, you're listening to Closing the Gaps in Nonsmall Cell Lung Cancer on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Stephen Liu on the various first-line systemic therapies for patients with advanced metastatic disease. So, Dr. Liu, let's focus on the role of combination therapies for a moment since there's a fair amount of debate over whether first-line treatments should incorporate chemoimmunotherapies at the start or stick with monotherapies until the second line. What are your thoughts on this?

Dr. Liu:
With the initial approval of checkpoint inhibitors for advanced nonsmall cell lung cancer was in the second-line setting. After multiple randomized phase 3 trials showed a clear superiority over second-line docetaxel. We had large phase 3 trials with pembrolizumab, nivolumab, and atezolizumab that all provided superior survival and the more favorable toxicities when compared to docetaxel. And although docetaxel was a lower bar, this was then followed by first-line trials that compared pembrolizumab alone for chemotherapy or combination with pembrolizumab or atezolizumab with chemotherapy. And those also showed a benefit to early use.

Dr. Caudle:
So on one side there's the argument that patients not given the most aggressive combination therapies up front may not survive long enough for the second-line treatments. But on the other hand, there are questions on whether survival rates are really all that different, as well as major quality of life impacts. So how do you typically respond to these contrasting views?

Dr. Liu:
You know, personally, I'm a strong advocate for early use of immunotherapy treatment of lung cancer. You know, we have Phase 3 randomized studies that show in the first-line setting, the early introduction of immunotherapy improves survival and it doesn't really

come at a cost of worsening quality of life. The quality of life data the symptom control data, you know, is very reassuring. And I really have very few concerns about tolerability. Adverse events can be seen with checkpoint inhibitors, but are generally well managed and severe events are relatively infrequent. In fact, the safety profile for Chk1 inhibitors alone is consistently better than chemotherapy in the second-line and the front-line setting. And when we combine it with chemotherapy the addition is not clinically that significant. You know, in my experience, combinations are tolerated just as well as chemotherapy alone. And importantly, symptoms often improved because the symptoms are driven by that cancer. And if we get the most effective treatment for that cancer, generally patients feel better. But a lot of the decision is a healthy respect for the disease. You know, lung cancer is an unforgiving and unpredictable disease. And if you wait, you may lose that opportunity. And if I have a patient who is destined to receive long-term benefits from immunotherapy, it's really a shame and a tragedy if I don't give them the opportunity to get that benefit.

Dr. Caudle:
Wow. Well, given all these considerations, what are some methods you use to help counsel patients towards selecting the right treatment plans for them?

Dr. Liu:
In general, I think it's important to lay out options, but you also have to make recommendations and you know, whether a targeted therapy or immunotherapy, our studies have consistently favored using our best drug first and saving treatments for later use. It's just not a viable strategy in non-small cell lung cancer. So I think as an oncologist, it's our job to identify what the best drug is, um, for that individual patient. And while I acknowledge uncertainty, I make a point to provide a clear recommendation to each patient and really explain the reasoning behind it. If we look at those with a driver alteration, I recommend the most effective targeted agents, which often is the most recent latest generation of the drug. And sequencing kinase inhibitors is a strategy that I'm not too fond of. While at first blush it may seem that – that having more drugs in reserve and moving from one drug to the next drug, you know, is an appealing strategy, I think biologically each step that you take increases the biologic complexity, increases the heterogeneity in inducing alternate forms of resistance. And so I think that cancer becomes more and more difficult to treat. Now, I'd rather use a much more comprehensive latest generation kinase inhibitor upfront, um, and so forth. EGFR I prefer mostly front rather than sequencing a first or second followed by a third, fourth. ALK I prefer alectinib or brigatinib up front rather than saving it for – for subsequent lines of therapy. And for those with no alteration, I recommend immunotherapy absolutely, either alone, but usually in combination with chemotherapy. But we have to be willing to adapt our treatment algorithms, um, to each patient and each specific clinical circumstance.

Dr. Caudle:
Now, looking ahead, what treatment approaches are coming into practice or on the horizon that look promising to you for making positive impacts on patient care?

Dr. Liu:
Now we're making tremendous progress in the field of targeted therapy. We're identifying new targets. We're enhancing our upfront approach and overcoming resistance. And I think a major development is how to be more comprehensive in our initial efforts. Um, rather than focusing on salvage, on relapse, on overcoming resistance, I really think the greatest gains will be in preventing resistance. And often this can be by combining therapeutic modalities. By doing that, we can eliminate more of these malignant subclones, try to reduce some of that heterogeneity upfront, um, for a given patient. And hopefully improve the depth of response and the length of response for our first-line treatment strategies. You know, I think a good example is combining chemotherapy with targeted therapy, you know. This is an important step in that direction. And I don't think chemotherapy needs to continue indefinitely. But if we can eliminate some of the clones today that would have given rise to an aggressive relapse two years from now, I think we can significantly improve long-term survival. So I think combinations incorporating alternative modalities such as angiogenesis and chemotherapy with a targeted approach up front are really going to be the better answer long term. And with immunotherapy, we need new biomarkers within each person's cancer that can help tailor an immunotherapy approach. That's really incredibly challenging because the immune system is very dynamic, very individual, but they're important studies underway now that are going to lead us down that right path.

Dr. Caudle:
Wow. Well this has been a really great review, as well as a promising glimpse forward on lung cancer treatments. And I'd really like to thank my guest, Dr. Steven Liu, for joining me today. Dr. Liu, it was wonderful having you on the program.

Dr. Liu:
A pleasure speaking with you. Thanks for having me.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com/NSCLC, where you can Be Part of the Knowledge. Thanks for listening.