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TRANSCRIPT

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Comparing Combination Therapies for Lung Cancer: Rationales & Risks

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

Dr. Nacinovich:
The therapeutic landscape for lung cancer has changed rapidly with ever more sophisticated characterizations of driver mutations, immune properties and tumor microenvironments. On today's program we'll explore how these refined understandings have changed the way we think about combination therapies, their benefits versus limitations, and what's on the horizon for improving patient survival.

Welcome to Closing the Gaps in Non-small Cell Lung Cancer on ReachMD. I'm Mario Nacinovich, and I'm joined today by Dr. Jonathan Riess, Associate Professor of Oncology and Hematology at the UC Davis Medical Center.

Dr. Riess, welcome to the program.

Dr. Riess:
Thanks so much for having me.

Dr. Nacinovich:
To start, let's get a better sense of the current playing field for combination therapies. First, can you just walk us through the tumor categories that help steer appropriate combination choices early on, such as levels of oncogene addiction and PD-L1 expression?

Dr. Riess:
So, when we look at metastatic non-small cell lung cancer, several of the things that we look at is the histology, so is it squamous or nonsquamous, which is typically predominantly adenocarcinoma, and are there any special oncogene driver mutations that drive the cancer. So, whenever we get that pathologists look under the microscope and say is it squamous non-small cell lung cancer, is it adeno non-small cell lung cancer, and that has implications for treatment selection. And then for nonsquamous non-small cell lung cancer, we also typically do next-generation sequencing and broad genomic profiling to look for those specific oncogene drivers where we have excellent targeted therapies, such as osimertinib for EGFR-mutant non-small cell lung cancer, alectinib for ALK fusion non-small cell lung cancer and crizotinib for ROS1 fusion non-small cell lung cancer and then dabrafenib and trametinib for BRAF-mutant non-small cell lung cancer. We're finding more and more of these mutations that we can act upon.

If we don't find one of these special oncogene drivers, we also look at PD-L1 expression, and so that's the marker of how high that expression is that predicts response to immunotherapy, and if it's high, 50% or more we often look to pembrolizumab, which is approved based on KEYNOTE-024 trial that showed an overall survival benefit compared to chemotherapy alone.

Now, if it's low or zero and there's none of these oncogene drivers and it's nonsquamous non-small cell lung cancer, we typically combine chemotherapy with carboplatin and pemetrexed with pembrolizumab, and that's based on the KEYNOTE-189 trial that showed an overall survival benefit compared to chemotherapy alone. For the 50% and above, it also showed that benefit.

Now, if it's squamous non-small cell lung cancer, there was the KEYNOTE-407 trial, and that looked at carboplatin and a taxane, either paclitaxel or albumin-bound paclitaxel, with pembrolizumab versus the chemotherapy alone, and that also showed with the 3-drug regimen an overall survival benefit, so that's what we look at for squamous cell lung cancer.

Our treatment algorithms for initial treatment of metastatic lung cancer is really dependent on what kind of histology it is, are there any of these special oncogene drivers and what's the level of PD-L1 expression.

Dr. Nacinovich:
Just to stay on this level-setting track for a moment, can you speak to the emergence of targeted therapies and immunotherapy respectively and their impacts on the field's thinking toward combination therapies for lung cancer?

Dr. Riess:
So when you're looking at targeted therapies, we are discovering more and more of these special mutations we can match to targeted therapies. Right now there are drugs approved for EGFR-mutant lung cancer with osimertinib and others, ALK fusion lung cancer with alectinib and others, ROS1 non-small cell lung cancer with crizotinib, entrectinib—and there's others in development—BRAF (V600E) mutations with dabrafenib and trametinib, and we're discovering more and more, such as MET exon 14 insertions, MET amplification, HER2 mutations where there are some really exciting data with new targeted-therapy combinations, so that's a really exciting part of the field of lung cancer.

Immunotherapy, we have the PD-1 and PD-L1 antibodies that are approved— pembrolizumab, nivolumab, atezolizumab and others in development—and then there are other combination strategies that are being looked at, so it's a really exciting time in the field.

And thinking about combination therapies, we're always looking for targeted therapies to find combinations to not just hit the oncogene driver but potential ways that the tumor can signal around the oncogene driver to develop resistance—we call them bypass tracks—as well as to come with new drugs on target mutations that can prevent these targeted therapies from working effectively in the setting of acquired resistance. Now, we do not combine immunotherapy and targeted therapy because we found a high incidence and potentiation of immune-related adverse events, such as pneumonitis, when you combine them, so we do not combine immunotherapy and targeted therapy because prior studies have shown that in many cases it's not safe.

Dr. Nacinovich:
So, with these distinctions in mind, what are the current combination therapies that come top of mind for you in first-line setting? How do they compare?

Dr. Riess:
Well, with immunotherapy, I think the clear advances have been combining chemotherapy with pembrolizumab in the first-line setting—as we talked about, the KEYNOTE-189 trial in nonsquamous non-small cell lung cancer as well as the KEYNOTE-407 trial in squamous non-small cell lung cancer with platinum-based chemotherapy in combination with pembrolizumab. There's also the IMpower-150 trial that looked at carboplatin+paclitaxel+ bevacizumab and adding the PD-L1 antibody atezolizumab, and that's also a regimen that is sometimes used that showed a survival benefit compared to chemotherapy alone. And in particular, the 4-drug regimen, at least in a subset analysis, there's a signal of potential activity in EGFR-mutant lung cancer where typically immunotherapy alone does not suffice and is not very active in those types of nonsmoking oncogene-driven tumors, but this requires further study. It was in a subset analysis and currently is not FDA-approved for that indication. There's also the first-line—the regimen

of nivolumab PD-1 antibody with the CTLA-4 inhibitor ipilimumab which also has shown potential activity and may be appropriate in certain circumstances, for example, depending on the PD-L1 expression.

Dr. Nacinovich:
For those just tuning in, you're listening to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD. I'm Mario Nacinovich, and joining me today is Dr. Jonathan Riess to talk about our evolving understanding of combination therapies for non-small cell lung cancer.

So, Dr. Riess, if we turn to second-line combination therapies, are there any key considerations or precautions to keep in mind?

Dr. Riess:
Well, in terms of second-line therapies, if they're not one of these oncogene drivers where there's approved drugs, after platinum-based chemotherapy and immunotherapy, one of the standard treatments is additional chemotherapy, and then there's the REVEL study with the taxane docetaxel that looked at patients who were randomized to receive the VEGF receptor antibody ramucirumab. The consideration of ramucirumab, adding it to docetaxel, is a potential option in these patients. And so, ramucirumab is a VEGF receptor antibody, and there are potential toxicities to that, such as hypertension, a bleeding tendency and wound healing tendency, so these are the things we talk to our patients about when considering whether to add ramucirumab to docetaxel in subsequent lines of therapy. For example, if they're having any hemoptysis, coughing up blood, that would be a no-go in terms of considering ramucirumab. If we anticipate they would need some type of procedure in the next several weeks where wound healing would be an issue, is their blood pressure controlled, those are the things that we think about when considering that drug, and that is often in these non-oncogene-driven metastatic lung cancers a standard treatment after progression on platinum-based chemotherapy and immunotherapy.

Dr. Nacinovich:
Looking ahead, where do you see combination therapies trending or evolving into within the treatment landscape for lung cancer?

Dr. Riess:
So, in terms of the future of combination therapies in metastatic non-small cell lung cancer, I think we've spent a lot of time and had a tremendous number of advances in targeted therapies of broad genomic profiling, overcoming resistance to targeted therapies, and then immunotherapy typically with chemotherapy in the majority of situations for those non-oncogene-driven tumors. And I think the future of the targeted therapy is to widen the playing field by finding more of these oncogene drivers but also finding ways to forestall resistance up front and not just wait for resistance to develop, and I think looking at things to do that and potentially plasma monitoring and other things and then intervening early with targeted therapy combination strategies is where I see the field evolving.

For immunotherapy, I think there's a number of combination trials. We're learning about the mechanisms of resistance to immunotherapy, and ultimately, I think allocating treatment based on the mechanism of resistance similar to how we do with targeted therapy. I think that's an area—a major endeavor for future study to keep the momentum going in advancing patient care in metastatic non-small cell lung cancer.

Dr. Nacinovich:
Those are all great things for us to keep in mind. And as that brings us to the end of today's program. I want to thank my guest, Dr. Jonathan Riess, for sharing insights with us on combination therapies for patients with non-small cell lung cancer.

Dr. Riess, it was great having you on the program.

Dr. Riess:
Great. Thank you 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

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