Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/closing-gaps-nsclc/new-approaches-to-treating-non-small-cell-lung-cancer/11349/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New Approaches to Treating Non-Small Cell Lung Cancer

Announcer:
Welcome to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD, sponsored by Lilly.

Dr. Caudle:
The introduction of targeted therapies and immunotherapies has notably improved survival rates for patients with non-small cell lung cancer as proven by some of the latest research in the field, and to learn more about how these new findings are impacting our approach, today we're going to be taking a look at a potentially practice-changing study called KEYNOTE-189.

Coming to you from the ReachMD studios, this is *Closing the Gaps in Non-Small Cell Lung Cancer.* I'm Dr. Jennifer Caudle, and joining me is Dr. Deepa Rangachari, Assistant Professor of Medicine at Harvard Medical School and Director of Inpatient Medical Oncology at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Welcome to the program, Dr. Rangachari.

Dr. Rangachari:
Jennifer, thanks so much for the invitation. I'm delighted to be here with you all.

Dr. Caudle:
So, Dr. Rangachari, I'd like to start by getting a better understanding of KEYNOTE-189. Could you give us a little background on the study?

Dr. Rangachari:
Yes, gladly. So KEYNOTE-189 is really what we could consider a practice-changing phase 3 clinical trial conducted specifically in patients with advanced nonsquamous non-small cell lung cancer. This represented a population of patients, as I said, with advanced-stage disease, specifically whose tumors lack highly actionable genetic alterations in EGFR or ALK. In this clinical trial, basically the question that was being posed is: Is the combination of platinum doublet chemotherapy along with an immune checkpoint inhibitor superior with regards to clinical outcomes and efficacy to the longstanding standard of platinum doublet chemotherapy alone? In the conduct of this trial, patients were randomly assigned to receive either carboplatin, pemetrexed, and pembrolizumab, so combination chemo-immunotherapy every 3 weeks for 4 cycles, followed by maintenance therapy, which in this case was pemetrexed and pembrolizumab every 3 weeks for up to 2 years, versus the historical standard, which would be carboplatin/pemetrexed chemotherapy alone for 4 cycles followed by pemetrexed maintenance therapy without the addition of immune checkpoint inhibitor.

What this trial showed is that patients receiving the combination of chemotherapy with immune therapy had improved overall survival as compared to those patients receiving chemotherapy alone regardless of the tumor PD-L1 status and in the absence of any other actionable genetic alterations. So, on the basis of this clinical trial, the administration of combination chemotherapy with immunotherapy became an FDA-approved, evidence-based standard of care for patients with previously untreated, advanced-stage, non-squamous

non-small cell lung cancer.

Dr. Caudle:
Excellent. Now, with that in mind, how has the KEYNOTE-189 study impacted the way we treat non-small cell lung cancer?

Dr. Rangachari:
I think the simple answer is a lot. Over the course of the past decade or more, the real driving force behind the evolving therapeutic paradigms in all cancers is to create highly personalized therapies that are driven by use of biomarkers. As a result, in the past decade or so in non-small cell lung cancer, we've learned that certain chemotherapy regimens work better than others depending on tumor histology, and then the second major lesson is that certain biomarkers can really help us predict optimal use of very specific types of therapies, whether it is a targeted therapy, an immune therapy or a combination of chemotherapy with immune therapy. KEYNOTE-189 kind of landed squat in the middle of this revolution, so to speak, of using biomarkers to guide best therapy. What we know with existing biomarkers are that about a quarter of all patients will have a tumor that has an actionable genetic alteration amenable to use of targeted therapy.

A second cohort of about roughly one-third of patients will have high tumor PD-L1 expression where there is rigorous evidence to indicate that an immune checkpoint inhibitor used alone will be beneficial, so that, then, accounts for just over 50% of all patients with advanced-stage non-small cell lung cancer. But that means that there's just under 50% of patients for whom there really was no more optimal therapy established or defined beyond just conventional chemotherapy as we have been doing for decades now, and so KEYNOTE-189 really brought hope to that other 45% of patients for whom there was really no other better standard beyond chemotherapy alone.

Dr. Caudle:
Now, Dr. Rangachari, let's dig deeper into the therapeutic space. What are some of the issues or barriers you and your patients encounter in treatment? And how has KEYNOTE-189 thought to address them?

Dr. Rangachari:
I think the barriers are honestly some of the ones already referred to. What is the ultimate goal in the care of all patients with any cancer but specifically advanced-stage non-small cell lung cancer? I think the goal is to define a treatment that is highly effective in terms of its ability to control or reduce the burden of disease that has a durable effect—meaning an effect that will last as long as possible—with least amount of side effects and with the hope of best possible and longest quality of life. Ways to address those barriers are things that we've already begun to talk about, which is creating a rational strategy to define an optimal therapy for a given individual, whether that's using targeted therapies or immune therapies or combination treatment strategies. I think KEYNOTE-189 has helped address one barrier that I already referred to, which is that for a large cohort of patients without any actionable genetic alterations in their tumors and without expression of high levels of proteins like PD-L1 expected to predict benefit from single-agent checkpoint inhibitors, we now have a better standard. I think in terms of delivering this treatment in general, the KEYNOTE-189 regimen is generally fairly well-tolerated and with manageable toxicities, but I think toxicity management and quality of life has also long been a barrier for our patients, meaning we have long had ways to intensify treatment and hopefully improve outcomes a little bit but at what cost to the patient in terms of how they live and feel on a day-to-day basis.

But an important thing to note about KEYNOTE-189 is a recurring theme in lung cancer, which is that the sooner we can introduce the use of a checkpoint inhibitor, specifically in those patients where there is no actionable genetic alteration, the better. Putting your best foot forward first is a very important theme in the care of patients with advanced-stage non-small cell lung cancer because it is not uncommon for patients to become adequately ill after their first or second line of therapy such that they're not well enough to tolerate getting what might be an effective therapy as a third, fourth, or fifth line.

I think the other thing that KEYNOTE-189 reminds us of in terms of the outcome is that there is important synergy between various cancer modalities and immune checkpoint inhibitors. In this case we learned a lot about the synergistic effects between DNA-damaging

agents like platinum doublet chemotherapy and checkpoint inhibitors so that we can use the checkpoint inhibitor more effectively but without necessarily adding too much in terms of toxicity.

Dr. Caudle:
Excellent points. For those of you who are just tuning in, you're listening to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Deepa Rangachari about the impacts of the KEYNOTE-189 study on the treatment of non-small cell lung cancer.

So, Dr. Rangachari, now that we have these findings from the KEYNOTE-189 study, what next steps are needed to help further this line of research?

Dr. Rangachari:
I think KEYNOTE-189 has brought a lot of hope and a lot of possibility, but I think it also leaves some very important questions. I think the number one question that remains in our field is: For the large majority of patients for whom there will not be an actionable genetic target amenable to use of an oral targeted therapy, what is the optimal regimen? One of the things that we don't really know yet is who really needs the combination, because in all of the clinical trials that led to approval of either a checkpoint inhibitor by itself as initial therapy or checkpoint inhibitor with chemotherapy, the comparator arm in all those clinical trials was chemotherapy alone, which is frankly an outdated standard now to compare to. In a given patient who has some degree of tumor PD-L1 expression, >/= 1, where both the checkpoint inhibitor or checkpoint inhibitor plus chemotherapy is an option, how do we know how to pick which of those patients really needs all of the drugs or only one of the drugs is an important question.

I think an additional question that is increasingly emerging is: For how long should we treat our patients? In most of the large-scale phase 3 trials that have been done in lung cancer looking at patients receiving immune checkpoint inhibitors, the treatment interval has generally been defined as 2 years, at which time if patients are not having disease progression or toxicity, there is no protocol-stipulated reason to continue the therapy. But because immune therapies work in a very novel way in terms of creating a mechanistic alteration in the environment, the immune microenvironment in which the tumor lives, it's important to consider that maybe 2 years of therapy is too long in some patients, and there may well be patients for whom a shorter duration of therapy may be just as effective.

How much therapy and for how long are important questions that we are asking ourselves as a result of trials like KEYNOTE-189 in the lung cancer community. And to be honest, this reflects questions and themes that are being raised in other cancers that are highly sensitive to immune therapies too, like melanoma and kidney cancer.

I think ultimately the solution to these questions is coming, and studies are ongoing, specifically using biomarkers—either tissue-based or blood-based biomarkers—to help us define the optimal intensity and duration of treatment. So I think we'll get there, but more information will certainly be needed in guiding us.

Dr. Caudle:
Before we close, Dr. Rangachari, let's look ahead to some of the developments in the pipeline for non-small cell lung cancer. Is there anything up-and-coming that you're excited about?

Dr. Rangachari:
There's a lot to be excited about. This is a really genuinely exciting time to be a thoracic oncologist. For so long we've faced the challenge of people facing a dreadful illness with treatments that either worked but for a short period of time or worked and made them very ill without necessarily making their lives as much better or longer as they deserve. We've talked a lot about immune checkpoint inhibitors, and I think immune checkpoint inhibitors, specifically the PD-1 and PD-L1 agents, have been very exciting in lung cancer, but we're also recognizing that immunotherapy is a broad sphere of potential influence, and so there's been a lot of interest and some exciting developments as they relate to identifying other immune checkpoints or opportunities for immune modulation, other immune targets. The promise of a vaccine and cell-based therapies I think are exciting, and there is preliminary data in lung cancer that's tantalizing.

I think the second other major area of progress and rapidly coming through the pipeline, frankly, is the use of defining actionable targets and having therapies that are effective in controlling disease in patients whose cancers have abnormalities in those targets. Specific examples of new and emerging targets with matched targeted therapies include EGFR exon 20, insertion mutation, so a category of EGFR mutation that is considered sort of non-canonical and historically difficult to target. There have been exciting developments as

they relate to targeted therapies for patients with HER2 mutated lung cancers, very recent FDA approval of new agent for patients with RET-rearranged advanced non-small cell lung cancer, MET, etc., etc.

So I think both in the vast world of immune-based therapies and within the universe of genetically actionable alterations and targeted therapies there's a lot, as we speak, coming through the pipeline in lung cancer.

Dr. Caudle:
Understood. Well, those are some really exciting developments to look forward to, and with that I'd like to thank my guest, Dr. Deepa Rangachari, for joining me to share her thoughts on KEYNOTE-189 and how it will impact our approach to non-small cell lung cancer.

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

Dr. Rangachari:
Thanks so much, Dr. Caudle. It was really a pleasure to be here with you today and share some of these exciting findings that are sure to transform the way in which we deliver care.

Announcer:
The preceding program was sponsored by Lilly. Content for this series is produced and controlled by ReachMD. This series is intended for healthcare professionals only. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com-slash-n-s-c-l-c. Thank you for listening to ReachMD. Be Part of the Knowledge.