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Breakthrough Breakdown: Impacts of Keynote-189

Announcer:
This is ReachMD, and you're listening to Closing the Gaps in NSCLC, sponsored by Lilly.

Dr. Johnson:
Non-small cell lung cancer, or NSCLC, accounts for about 85% of lung cancer cases, according to the American Cancer Society, and while treatment options are primarily determined by the stage of the cancer, clinical trials, such as KEYNOTE-189, look to explore alternative avenues to treatment and long-term survival for these patients. I'm Dr. Shira Johnson, and joining me to interpret KEYNOTE-189 is Dr. Jack West, Medical Director of the Thoracic Oncology Program at the Swedish Cancer Institute in Seattle, Washington.

Dr. West, welcome to the program.

Dr. West:
Thank you very much for having me.

Dr. Johnson:
So, to start, could you give us some background on the design and methodology behind this clinical trial, KEYNOTE-189?

Dr. West:
KEYNOTE-189 is a Phase III randomized trial of patients with non-squamous advanced non-small cell lung cancer and who don't have a tumor with an activating EGFR mutation or an ALK rearrangement. This is a large proportion of our patient population. And, importantly, this trial included patients throughout the spectrum of PD-L1 expression from negative to 100%, and it's about a third, a third, a third with negative tumor PD-L1 expression, what we call low-tumor PD-L1 expression in the 1-49% range, or high PD-L1 of 50% or greater. And leading into this trial, a prevailing standard has been chemotherapy alone, a platinum doublet, for many of these patients, but with patients who have high PD-L1—again, about 28 to 30% of our patients—often getting pembrolizumab alone and doing better with that than chemotherapy. So, this trial looked at a very broad range of patients and asked the question of whether adding pembrolizumab to a standard chemotherapy regimen for non-squamous non-small cell improved outcomes. It was a 2:1 randomization in favor of the investigational arm that received cisplatin or carboplatin with pemetrexed and pembrolizumab added to that, all of these agents given every 3 weeks, and the control arm received one of the platinum agents, cisplatin or carboplatin, pemetrexed, as well as placebo every 3 weeks. And then, patients received 4 cycles, or up to 4 cycles, if they had tolerated the therapy well, and if they had not progressed and were doing well, would continue on to pemetrexed maintenance in combination with ongoing pembrolizumab every 3 weeks or pemetrexed with placebo. However, if patients progressed on the placebo with chemotherapy arm, they could cross over to pembrolizumab. And so, this was an important Phase III study, similar in design to a Phase II that looked very encouraging, but many of us in the field did not feel was definitive enough to change our practice until we saw a larger body of evidence.

Dr. Johnson:
Now, what criteria were used to select the patient population for this trial? What were the limitations or exclusions on any subpopulations?

Dr. West:
This was really quite broad. It was for patients with non-squamous histology, which is the most common subgroup of non-small cell lung cancer in the U.S., and most parts of the world these days, so it's a large subgroup of patients. Most of these patients had adenocarcinoma, but about 2% had non-small cell just categorized as not otherwise specified. But patients could have a smoking history—most did, nearly 90%—but about 12% were never-smokers. Some patients, about 17% to 18%, had brain metastases that just

needed to be controlled. And as I mentioned, the PD-L1 tumor proportion score, or PD-L1 expression, was anywhere in that spectrum from undetectable, or less than 1%, to high levels. So, really, this was a treatment option that is now applied to a broad range of patients. It was intended also for patients with good performance status, and nearly all had a performance status of 0 to 1, so really meant for fit patients.

Dr. Johnson:
So, once the patient population was selected, what outcome measures were used to evaluate them?

Dr. West:
The key ones that were looked at were overall survival and progression-free survival as coprimary endpoints, but as with any large study in this space, we're also looking at response rates and tolerability of the therapy. The key points, and I think that the leading issue, was that the overall survival in KEYNOTE-189 was not only positive, but it was extremely positive for an improvement with pembrolizumab combined with a platinum and pemetrexed with a hazard ratio of 0.49. This is well beyond just statistically significant, but clearly a very clinically significant difference where the actual survival curves separate early and stay separated over a very long period of time, so it's really a dramatic benefit. And when we look at the subgroups of patients based on factors like age, sex, performance status, smoking history, whether they had brain metastases at baseline, and importantly, PD-L1 expression, as well as issues like whether they got cisplatin or carboplatin, really across the board the benefits with the pembrolizumab were very comparable, so this was really a treatment approach that was appropriate to consider for just about everybody. Progression-free survival also showed a very impressive benefit with a hazard ratio of 0.52, and this was also seen across that continuum of PD-L1 expression, so it was most dramatic in the patients with high PD-L1, but really still present at a meaningful level in the patients with the lowest or undetectable PD-L1 level of less than 1% where the hazard ratio for PFS was still 0.75. It was just remarkably good in the high PD-L1 group where the hazard ratio for PFS was 0.36. But essentially, the benefits were present in terms of PFS and OS across the board. There was also a higher response rate with the combination that exceeded 50, even 60%. And so, now we're at a point where with these kinds of combinations you can expect the majority of your patients, and approaching now 2/3 of our patients now, to have a significant response with a combination like this. At the same time, the toxicity profile was not anything really unexpected or prohibitive. It's really the superimposition of what we'd come to expect after using both conventional chemo doublets and immunotherapy for years—just a little higher acute renal toxicity but still in the low single digits with that.

Dr. Johnson:
For those just tuning in, this is ReachMD. I'm Dr. Shira Johnson, and I'm speaking with Dr. Jack West from the Swedish Cancer Center Institute in Seattle, Washington, about the design, outcomes and impacts of the KEYNOTE-189 clinical trial. So, Dr. West, let's shift over to what was reported in the results. Can you highlight some more of the key findings for us, and was there an effect on quality of life?

Dr. West:
Quality of life, really no significant impact, no detriment, importantly. These patients who are doing better and living longer certainly are not paying any particularly higher cost in terms of toxicity. Just to highlight again, the key points were that there was a very significant improvement in overall survival, progression-free survival, response rate, all much better in patients who received a combination of platinum, cisplatin or carboplatin—the majority getting carboplatin—with pemetrexed and pembrolizumab in combination, followed by maintenance pemetrexed and pembrolizumab. The toxicity profile was really not unexpected for what we have come to know with these agents we've used for years and years and without any decrease in quality of life, which is, I would say, what we would expect. When patients have shrinking cancer, their cancer-related symptoms improve significantly, even as we have to contend with some treatment-related toxicities, but it comes out as not being a detriment as we get better efficacy.

Dr. Johnson:
You've highlighted the renal toxicity. Were there any other significant adverse event findings you'd like to discuss?

Dr. West:
I would say that there was certainly some nausea, anemia and fatigue in 40 to 50-or-so percent of patients. That was really seen across the board, and really not unexpected. The rates of death were about 6% in both groups, so no clear differences. There were obviously some more immune-mediated side effects in the recipients of pembrolizumab that could range from a little higher rates of rash to more thyroid disease, but these are, again, issues that we routinely manage and were not prohibitive. So, I would say that the toxicity profile was very much what we would expect based on our experience with these agents over the last several years, just with the exception of perhaps a higher rate of renal toxicity that has led some of us who do this to think that we would be more inclined to favor carboplatin than cisplatin, given that cisplatin is known for having nephrotoxic issues.

Dr. Johnson:
So, this kind of leads into my next question. Let's dive a little deeper into the clinical implications from the trial. How do these results

impact approaches to treatment going forward in your view?

Dr. West:
I would say that KEYNOTE-189 was a trial that is among the most important in lung cancer this year or probably over a 5- to 10-year period. It's enormously important. As I alluded to just in the introduction to this and the context, there was a Phase II trial called KEYNOTE-021G that had a very similar design. It was carboplatin, pemetrexed with or without pembrolizumab, and that showed greater efficacy, meaningfully greater with the immunotherapy combination, but that did not have a clear survival difference. And it was 123 patients, which limited our enthusiasm for this being practice-changing just based on the size of the trial. And, importantly, the FDA did give a provisional approval of that combination of carboplatin/pemetrexed with pembrolizumab in May 2017, based on the encouraging, though relatively modest in number, results from KEYNOTE-021G, but that didn't lead to a wholesale change in practice, and I don't think it should have, but many of us were hopeful and waiting on the Phase III data that came in the form of KEYNOTE-189. When those data came with great fanfare at the AACR Meeting, American Association for Cancer Research in mid-April of 2018, accompanied by a synchronous publication in the *New England Journal of Medicine*, it was a watershed event. It was remarkably positive, and it immediately led to a change in, not only my practice, but I think practice for the vast majority of U.S.-based oncologists who had this available, FDA-approved, and were just waiting to see enough data to really corroborate the early report from the Phase II experience. And I would say this has changed practice not just for lung cancer specialists but for general oncologists alike, and it ushered in a new era of chemoimmunotherapy that has been also echoed in some of the work in squamous non-small cell that presented at ASCO 2018 just a few weeks later. So, we've now entered an era where, if not the overwhelming prevailing standard is chemoimmunotherapy for the majority of our patients with advanced non-small cell now in non-squamous as well as the squamous populations, as long as these folks don't have a driver mutation identified prior to first-line therapy.

Dr. Johnson:
So, now that you have this robust Phase III data, what do you see as the ongoing or future investigations that you think will be needed to drive toward better survival outcomes for patients with metastatic non-small cell lung cancer?

Dr. West:
One of the key questions that still remains is, for the approximately 30% of patients who have high PD-L1 expression, we have 2 competing positive trials and standard therapy approaches, specifically pembrolizumab monotherapy or concurrent chemoimmunotherapy as a combination. These patients with high PD-L1 were included in both trials and both got a huge benefit compared to chemotherapy alone, but we don't have a direct comparison of pembrolizumab monotherapy to pembrolizumab with chemo in the high PD-L1 patients. And I think there are arguments to be made for either approach and a good amount of debate among lung cancer experts parsing the data which one we should favor as an initial monotherapy and then sequential chemo or kind of front-loading it, so to speak, by giving everything, chemo and immunotherapy together. At the same time, one of the other issues that is bubbling up is, for the approximately 15% of patients with a driver mutation, which is now maybe nudging up to 20% as we identify more driver mutations and more patients with them as we do more broad genetic testing, genomic testing, should those patients who start with a targeted therapy then go on to a chemoimmunotherapy combination? Should they get a combination with bevacizumab? There's just, at this point, not a lot of data for patients who have progressed on prior targeted therapy. In general, the data for extensively treated patients is that those with driver mutations have not gotten much benefit from immunotherapy as monotherapy, but some of the early combination work suggests that they may benefit from these combinations. So, we have a lot more to learn about whether patients with an EGFR mutation, maybe an ALK rearrangement and other driver mutations, can do very well with subsequent treatment with a chemoimmunotherapy combination, whether that should include bevacizumab, etc. So, as exciting as it is to have these results like KEYNOTE-189, which are incredibly transformative, not just practice-changing, what's also exciting is that we're still babes in the woods with this. These are still early days, and we have a lot more to learn and refine about whether there are differences in outcomes, whether we sequence or give everything concurrently, whether patients who receive immunotherapy early subsequently respond well to even standard chemotherapy better later, whether radiation prior to chemo or immunotherapy improves outcomes, so a lot more to learn.

Dr. Johnson:
Well, I'd like to thank you, Dr. West, for your insightful analysis of KEYNOTE-189 and its clinical implications for better outcomes. It was a pleasure speaking with you.

Dr. West:
Thank you. Take care.

Announcer:
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