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/project-oncology/checkpoint-inhibitor-combination-therapy-for-first-line-advanced-nsclc/12852/

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

Checkpoint Inhibitor Combination Therapy for First-Line Advanced NSCLC

Dr. Sands:
Immunotherapy using checkpoint inhibitors has become a standard of practice in advanced non-small cell lung cancer. But can combination therapy further improve patient outcomes? Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and here to share his insights on checkpoint inhibitor combination therapy for first-line advanced non-small cell lung cancer is Dr. Shirish Gadgeel, Chief of the Division of Hematology and Oncology at Henry Ford Cancer Institute. Dr. Gadgeel recently spoke about this topic at the American Society of Clinical Oncology's annual meeting. Dr. Gadgeel, welcome to the program.

Dr. Gadgeel:
Thank you very much, Dr. Sands. It's truly a pleasure to be here to discuss this important topic in the management of advanced non-small cell lung cancer patients.

Dr. Sands:
Let's start off with some background. So first of all, maybe you can highlight the importance of doing genomic analysis prior to any of the immunotherapy discussion, and then also give us some background on immunotherapy, with checkpoint inhibitors in particular, and the treatment landscape for advanced non-small cell lung cancer.

Dr. Gadgeel:
You're absolutely right it is quite critical in deciding therapy where we do a complete profile of the patient's tumor before making the therapeutic decision. Though there is a tremendous amount of excitement about use of immunotherapy, it is quite clear that it is beneficial only in a population of patients. And one population that does not appear to benefit as much from checkpoint inhibitors is our patients who have a targetable alteration, and in those patients we do prefer using appropriate targeted therapy. I also would like to emphasize that the relevance of PD-L1 expression in patients with, say, EGFR mutations or translocations may not be the same as in patients without these alterations in their tumor, in that the PD-L1 expression in these patients may reflect effect from downstream signaling of the altered pathway, such as EGFR-signaling pathway or the ALK-signaling pathway, and may not represent effect of the presence of immune cells in the tumor microenvironment. And so when we use checkpoint inhibitors in patients with tumors with high PD-L1 that is because we expect it to be a result of presence of immune cells within the tumor microenvironment which are being limited in their ability to attack the tumor by expression of tumor PD-L1. Whereas in EGFR in our patients, it could be a result of down-signaling pathway, and therefore it may not have the same relevance.

So, because targeted therapy has greater clinical activity in patients with targetable alterations, and because PD-L1 expression may not have the same relevance, it is quite critical that we not only decide therapy based on tumor PD-L1 expression, but also based on genomic analysis of the tumor. And the final point in this regard is that there are now at least clinical reports of patients who received, up front checkpoint inhibitor therapy, either single agent or in combination, and then subsequently these patients were found to have targetable alterations in their tumors, and they were started on appropriate targeted therapy, but if it occurred relatively soon after stopping the checkpoint inhibitors, there have been toxicities that have been observed. Specific examples are instances of pneumonitis in patients who received osimertinib, or hepatitis in patients who received crizotinib.

So one needs to be mindful that there may be toxicities that may occur in patients who go immediately to targeted therapy after checkpoint inhibitors. And so for those reasons, it is very important to assess genomic analysis and tumor PD-L1 expression, and only after that do initial therapy. One last point I would like to make in this instance is there are occasions where the patient is very ill and we have to make treatment decisions even before receiving all the necessary information. And in those patients, it is perfectly appropriate to start platinum-based chemotherapy while we are awaiting the results, and not initiate immune checkpoint inhibitors. And then with the second cycle or third cycle, once all the information is available patients could be started on appropriate treatment.

Dr. Sands:
With that important background established, can you share some highlights from the panel at the American Society of Clinical Oncology's annual meeting?

Dr. Gadgeel:
So this was a very interesting panel. Starting off with the first case that was discussed this was a never smoker who had squamous cell histology. And, despite the fact that this patient had a high PD-L1, Dr. Juergens decided to initiate chemotherapy plus pembrolizumab because in general, in the checkpoint inhibitor trials, never smokers have not performed as well, and even though the patient's PD-L1 was about 50 percent in this squamous cell patient the patient received chemotherapy plus pembrolizumab because he was a never smoker. In addition, we highlighted the fact that even though this patient was a squamous cell patient because he was a never smoker it was critical to get the molecular analysis before initiating checkpoint inhibitors. As the audience members know, the NCCN guidelines not only recommend genomic testing in non-squamous patients, but also recommend, genomic testing in squamous cell patients who are never smokers or light smokers. And the final issue in this patient was that the patient got admitted for neutropenic fever and the patient's scans showed evidence of changes on the scans that were suggestive of pneumonitis though the patient himself was not symptomatic. And if one observes these changes on the scans, how best to proceed with treatment, in that particular patient Juergens decided to hold the checkpoint inhibitor and continue with the chemotherapy. But her plan was that if a patient remained asymptomatic, to reintroduce the checkpoint inhibitor. Those were the sort of practical points that were highlighted in that case.

Dr. Sands:
Dr. Gadgeel, thank you for sharing those highlights. Let's dive a little bit deeper into checkpoint inhibitor combination therapy. How do we know if this treatment is right for our patients, and what kind of qualities or clinical aspects are you looking at when you're making this decision with your patients?

Dr. Gadgeel:
So, we have now multiple combinations that have been approved for our front-line therapy. We have the chemotherapy plus pembrolizumab combination, both in non-squamous and squamous, based on KEYNOTE-189 and KEYNOTE-407 trials. We also have the nivolumab/ipilimumab non-chemo immunotherapy combination, based on CheckMate 227. The FDA approval is in patients whose tumor PD-L1 expression is 1% or greater. And we have combination of chemotherapy plus nivolumab and ipilimumab, where the platinum-based chemotherapy is administered during the first two cycles, and this approval is based on, CheckMate 9LA trial. This approval is in all histologies as well as in all subsets of PD-L1 expression.

And so we have these multiple options and how do we decide what combination to choose for an individual patient? Based on sort of my analysis of the three trials, in non-squamous patients, I tend to use chemotherapy and pembrolizumab in most patients. In PD-L1-high patients, I still prefer to use pembrolizumab with the exception of patients who, in my opinion, have high tumor burden, and generally in patients who have a lot of liver meds, bone meds, those patients also I would consider chemotherapy and pembrolizumab. It is important to note that in KEYNOTE-189, patients were maintained on both pemetrexed and pembrolizumab after the first four cycles. There has been a practice pattern identified, particularly in the United States where many times patients are just maintained on pembrolizumab. And though we don't know the actual contribution of maintenance pemetrexed in this patient population, I do believe, based on prior data, that maintenance pemetrexed does have clinical relevance.

In PD-L1-negative, non-squamous patients, I also prefer to use chemotherapy plus pembrolizumab, because I believe the hazard ratios in KEYNOTE-189 were consistent across all PD-L1 subsets, ranging from approximately 0.52 to 0.64. And so there was a level of consistency in KEYNOTE-189.

As far as the immunotherapy combinations explored in both 227 and CheckMate 9LA, I tend to use them in patients who have comorbidities that may limit the ability to administer chemotherapy, or at least chemotherapy beyond two cycles. And so based on certain comorbid illnesses there may be some reluctance to use chemotherapy, and now we have options of either using immune therapy combination alone, or the combination of two cycles of chemotherapy with nivolumab/ipilimumab.

The final point I would make is that I've been intrigued by the retrospective subset analysis of squamous cell patients in both CheckMate 227 and CheckMate 9LA. Particularly in PD-L1-negative squamous cell patients, the hazard ratio with nivolumab/ipilimumab combination in CheckMate 227, as well as, two cycles of chemotherapy with nivo/ipi inCheckMate 9LA, seems very promising, in the range of about 0.55.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Shirish Gadgeel about checkpoint inhibitor combination therapy for first-line advanced non-small cell lung cancer.

Well, thankfully, the immunotherapy has generally been pretty well tolerated, but there are certainly some described immune-related adverse events. Can you take us through some of the explanation as to how frequently you're seeing those, and some important management input on that?

Dr. Gadgeel:
In most instances, the immune-related AE's tend to occur within the first six months, but delayed onset of immune-related AE's definitely occurs. It is important to know that adverse events may occur not only late, but may occur after the the checkpoint inhibitor treatment has been discontinued. The most common adverse events, would be particularly with the PD1/PD-L1, based treatments, would be, endocrine, specifically thyroid abnormalities, skin rashes, and colitis. But there is, of course, a major concern in lung cancer patients of, pneumonitis that occurs in a grade 3-4, in anywhere from three to five percent of the patients. It does not appear to be greater when checkpoint inhibitors are combined with chemotherapy, as compared to what would be observed with checkpoint inhibitors alone.

One important aspect of managing immune-related AE's is that if a particular symptom profile, or a laboratory profile emerges that suggests, that it could be related to immune-related AE, it is prudent to initiate immunosuppressive therapy, such as steroids, right away while diagnostic workup is being initiated.

Another important aspect of managing these patients, at least in my opinion, is to get appropriate consultants engaged as early as possible. So if you have a patient with a renal dysfunction, and that seems to be immune-related AE's, get your nephrologist involved, or if there is a liver toxicity get your hepatologist involved as early as possible, because their insights into managing these toxicities can be very valuable in taking care of the patients.

Dr. Sands:
And before we close, are there any final points you'd like to make to highlight the use of the combination chemotherapy and checkpoint inhibitor and management?

Dr. Gadgeel:
The most exciting part about using checkpoint inhibitors in advanced non-small cell lung cancer is that there's a minority of patients that have sustained benefit, and I would like the audience to be aware that there are a lot of clinical trials going on that are using other checkpoint inhibitors and identifying biomarkers, so that we can improve the proportion of patients that have that sustained benefit. And so either in patients who have been treated with checkpoint inhibitors and have progression of disease, or are newly diagnosed, it would be critical to consider such clinical trials for our patients, so that they may benefit and derive that sustained benefit. There's more and more data emerging in use of these checkpoint inhibitors in earlier stages of non-small cell lung cancer and it is quite possible that in patients with earlier stages, the benefit would be even greater. And so, one needs to be well aware of the emerging data in earlier stages of non-small cell lung cancer.

Dr. Sands:
Well, there is certainly a lot to consider when thinking about first line treatment for advanced non-small cell lung cancer, and utilization

of chemotherapy plus immunotherapy. I want to thank my guest today, Dr. Gadgeel, for joining me and sharing his insights.

Dr. Gadgeel:
Thank you very much. It was truly a pleasure.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening.