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Case 4: In Patients Ineligible for Platinum-Based Chemotherapy, What Is the Ideal IO-Based Approach?

Announcer:
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Dr. Reuss:
My name is Dr. Joshua Reuss. I'm a Thoracic Medical Oncologist at Georgetown Lombardi Cancer Center and Assistant Professor of Medicine at Georgetown University School of Medicine. And in this session, we're going to discuss patients ineligible for platinum-based chemotherapy, what is the ideal immunotherapy-based approach?

So to begin with the case, this is an 85-year-old female with a history of coronary artery disease, peripheral vascular disease, chronic kidney disease, type 2 diabetes and chronic left toe wounds who presents following a diagnosis of stage IV non-small cell lung cancer. She initially presented to her PCP with fatigue and shortness of breath, where CT imaging identified bilateral lung nodules with bulky mediastinal and right hilar lymphadenopathy. An MRI of the brain was negative for CNS metastases and a PET/CT identified no concerning sites of extrathoracic disease. Bronchoscopic biopsy confirmed poorly differentiated TTF-1 positive carcinoma of the right upper lobe as well as R11, R4, subcarinal, and L4 lymph nodes. Additional molecular testing reveals alterations in STK11, KEAP1, and TP53, PDL-1 is 5%, and the mutational burden is 11 mut/Mb. At home, Ms. R is independent in her ADLs and ambulates with the assistance of a walker but does spend the majority of time in a chair. She enjoys attending adult daycare 3 days a week. So what is your recommended treatment approach for this patient?

And I think this is an important discussion of what are the barriers and limitations to platinum-based chemotherapy. I think chief among them is functional status. A lot of our patients are older with the diagnosis of advanced lung cancer. So frailty and how a patient really performs at home is very important. It's difficult to gauge this in clinic. That's why a detailed history is of paramount importance. In addition,

I was just saying, you know, for patients who are just maintaining acceptable functional status, right, they're getting by, they're able to do the day-to-day, but you worry that if you add in chemotherapy, you're quickly going to knock them over a cliff from a functional standpoint, and that's something to keep in mind.

Then there are more specific comorbidities, I would say, you know, significant neuropathy, you think about platinums, taxanes of potentially having limited ability to get significant doses in, kidney disease when you talk about cisplatin and pemetrexed, wounds and infection risk, hearing problems cisplatin, and other chronic medical problems can play a role as well. In today's day and age, we'd have to talk about national drug shortages. And then of course, patient preference is important as well.

Unfortunately, I think there still is a significant stigma associated with chemotherapy. You know, usually we can talk patients kind of out of that educate that not all cancers are the same, but that is important as well.

So when looking at PD-1/PD-L1 monotherapy options, we're fortunate to have three approvals in this space. For the PD-L1 high, that's

greater than or equal to 50% PD-L1 expression, that's data from the EMPOWER-Lung 1 study, KEYNOTE-024, and IMpower110 for cemiplimab, pembrolizumab, and atezolizumab, respectively. And as you can see from the slide table on the bottom, response rates, duration of response, and survival all very similar and so I don't have a strong personal preference here. I think it can be provider dependent for what option is pursued.

We also have pembrolizumab as an approved model therapy for PD-L1, TPS of 1% or greater. This is based off of the KEYNOTE-042 study. And while we do believe that the benefit for pembrolizumab is driven primarily by the PD-L1 high population, as shown in the top left corner of this slide, there was benefit seen in the PD-L1 low population of 1 to 49%. And by no means was pembrolizumab clearly a lot worse from a magnitude of survival benefit. So it's definitely something that one can consider in a PD-L1 population - PD-L1 low population when chemotherapy is contraindicated. For those that are fit, where chemotherapy is not indicated, the combination regimen of nivolumab plus ipilimumab is also a reasonable approach. This is data from the CheckMate 227 study and as you can see here, in the PD-L1 who have 1% or greater population, a benefit of nivolumab plus ipilimumab compared to nivolumab alone or chemotherapy alone. I will also note that the combination of nivolumab plus ipilimumab did show benefit in the PD-L1 negative population. There is not an FDA approval in this space, but with the data there it is oftentimes something that I can get approved if I really push.

Then more interesting at ESMO this past year there was data presented from the phase 3 IPSOS trial. This study looked at first-line atezolizumab versus investigator choice single-agent chemotherapy in patients ineligible for platinum-containing therapy. And as you can see here, patients were randomized 2 to 1 to atezolizumab or investigator choice of vinorelbine or gemcitabine, with a primary endpoint of overall survival. And as you can see here from the study, this was a positive result with a median overall survival of 10.3 months with atezolizumab compared to 9.2 months with chemotherapy. And I think an important point here, right, that either way, we are looking at numbers that we have not come to expect for frontline treatment, which I think speaks to the real-world population, frail population that was seen in this study. But it is an important result to show that for those who we are worried can't tolerate a platinum doublet approach that atezolizumab may have benefit in those patients. Though, I would argue that I am not typically grabbing for vinorelbine or gemcitabine as a chemotherapy for my patients.

And here's just a little more data on the subgroups where we saw benefit across subgroups, by and large, with the exception of the older patients of 80 years or greater. But outside of that, there was a trend toward benefit irrespective of histology as well as PD-L1 status and other important demographics.

So in summary, I would say that several factors may prevent administration of platinum-based chemotherapy, including patient functional status, comorbidities, and unfortunately, in today's day and age drug availability. There are multiple approved chemotherapy-free frontline treatment options that exist for our patients with advanced driver mutation negative non-small cell lung cancer, three of which are in the PD-L1 high population. And then we also have pembrolizumab for PD-L1 1% or greater, as well as the CheckMate 227 nivolumab plus ipilimumab in the PD-L1 1% or greater.

And I think the important really key here is to have a patient-centered discussion to determine the most appropriate treatment strategy. This involves a really detailed history and really talking to patients about the toxicity profile, and what their goals are in life with the diagnosis of advanced non-small cell lung cancer.

So to return to our case of Ms. R with significant comorbidities, but still of reasonably good functional status, PD-L1 5%. In this patient, we started the patient on pembrolizumab monotherapy, which she actually tolerated treatment for very well with stable disease ongoing for 8 months. And she actually had continued to have stable disease when she was unfortunately hospitalized with myocardial infarction, which was unrelated to treatment. And at that point, elected to discharge home on hospice care.

So with that, I'd like to transition to our peer discussion and introduce my colleague and friend, Dr. Charu Aggarwal.

Dr. Aggarwal:
Hi, Dr. Reuss. Thank you so much for inviting me. I'm Charu Aggarwal. I'm the Leslye Hassler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania's Abramson Cancer Center. Thrilled to be part of this discussion.

Dr. Reuss:
Thank you, Charu. And so, I guess to recap what we talked about here, when you see a patient that you are worried about chemotherapy, are there any particular factors that you are looking for, in kind of weighing whether or not to add in chemotherapy to your treatment strategy?

Dr. Aggarwal:
Absolutely. So I think if there are patient populations, with PD-L1 less than 1% or 1 to 49% in the absence of driver mutations, my inclination is to offer chemotherapy in combination with immunotherapy, either in a triplet or quadruplet approach. But absolutely we come across situations where either patients are unwilling to get chemotherapy, or you know, they just don't have the performance

status to receive really triplet or quadruplets therapies or they have poor kidney reserve, where giving them platinum-based treatment becomes untenable. And in those situations, I tend to really think about the incremental advantage of using chemotherapy. You know, I tend to think about whether I can use single-agent chemotherapy in combination with immunotherapy. Sometimes I've done that. But I completely agree with you that in the patient example that you presented, I think if somebody has, you know, borderline performance status, elderly, I think we have the approval to use pembro monotherapy or immunotherapy to be able to justify it.

Dr. Reuss:
Absolutely. I absolutely agree with your workflow and your consideration there. Now we have multiple single-agent immunotherapies that are approved, how do you choose between them?

Dr. Aggarwal:
Yeah, so I think that's a really interesting discussion point, because we don't actually have clear data to help us choose between individual immunotherapies. At this point in time, they haven't been compared to each other. I think ultimately it comes down to, we have several different options, especially for, you know, if you look at PD-L1 greater than 50%, I absolutely think that there should be equipoise amongst atezolizumab, pembrolizumab, and cemiplimab. They've all demonstrated superiority over chemotherapy. That's a population I would feel very comfortable omitting chemotherapy and use any of those.

Dr. Reuss:
I couldn't agree more. And I don't think we're ever going to see a trial that that compares these directly, so I think it's left with investigator and physician preference.

Now we also have the approval of chemotherapy-free regimen with combination immunotherapy with nivolumab and ipilimumab. In what patients are you considering this regimen? Is this also something you'd consider for patients who worry about chemotherapy tolerability?

Dr. Aggarwal:
So the nivo/ipi regimen is currently approved for PD-L1 greater than 1%. I think for the 1 to 49% population, if you're not going to use chemotherapy, potentially reasonable to consider it. Does it offer incremental advantage over immunotherapy alone? I don't know. Again, it's an open question, hasn't been answered. So I think it's a fair choice, not one that I choose frequently. For the PD-L1 greater than 50%, I do think we have a prospective large clinical, KEYNOTE-598, showing us that there was actually no incremental benefit of using ipilimumab in combination with pembro over pembro alone. So I tend not to use combination or dual immunotherapy alone for PD-L1 greater than 50%. For the PD-L1 negatives, again, we don't currently have an approval for immunotherapy alone, we should just remember and remind our audience that currently there are no approvals. Of course, we have to use our best judgment in patients that may be completely chemotherapy ineligible.

Dr. Reuss:
Yes, I could not agree more. And Dr. Aggarwal, thank you so much for this really important discussion on how patient-specific factors should guide our treatment approaches, particularly in patients who are ineligible for platinum-based chemotherapy. So just to recap, we do have multiple PD-L1 monotherapy options for the PD-L1 high population of 50% or greater. For the PD-L1 of 1% or greater pembrolizumab is an FDA approved option as is nivolumab plus ipilimumab for those who we think have the functional status to tolerate that approach. Patient-centered discussions are obviously super important in guiding this practice.

So with that, I want to thank everyone for their attention and thank Dr. Aggarwal for this stimulating discussion.

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