Transcript Details

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Case 3: In a PD-L1 Negative Patient, Is There Any Benefit to Using Single Agent IO/Chemotherapy or Dual Agent IO/ Chemotherapy?

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Dr. Aggarwal:
Hello and welcome. I'm Dr. Charu Aggarwal, I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania's Abramson Cancer Center in Philadelphia, Pennsylvania. Today we will discuss management of patients with metastatic non-small cell lung cancer in the setting of PD-L1 negative and in the absence of driver mutations. Is there any benefit of using single-agent immunotherapy, chemoimmunotherapy, or how should we choose between different regimens that may be approved today?

I'd like to start off with a case. I saw a patient, 65 years old, significant smoking history, actually underwent CT screening for lung cancer that revealed a large hilar lung mass, multiple lung nodules in both lungs, and a PET/CT scan confirmed presence of uptake in this mass as well as adrenal uptake. MRI of the brain did not show any evidence of metastatic disease, and the biopsy actually revealed a squamous cell cancer with a PD-L1 level of 0%. And really that led me to think, what should he receive? And you know, I think if we explore the treatment options, if I open up the guidelines, either NCCN or ASCO, IASLC guidelines, you can see that for patients, there are a variety of different options that can be either chemoimmunotherapy or quadruplet chemoimmunotherapy utilizing both CTLA4, as well as PD-1 or PD-L1 blockade. There may also be certain situations where we could use, if you look at the guidelines, if immunotherapy is contraindicated to use, VEGF inhibitors or other drugs that may be indicated.

Specifically looking at squamous cell carcinoma, something that my patient had, we can see that again, we have chemoimmunotherapy or we have quadruplet immunotherapy, and then useful in certain circumstances, depending on whether or not the patient is a candidate for immunotherapy.

We have a lot of clinical trials leading to many approvals. In fact, this has defined the lung cancer space over the last 5 to 10 years. And you can see them summarized here on this slide, specifically for the population that was on these trials that was PD-L1 negative. So starting on the far left, chemoimmunotherapy using a quadruplet or dual immunotherapy setting in CheckMate 9LA using ipilimumab, as well as nivolumab, median overall survival of 17.7 months. You can see KEYNOTE-021, which was the precursor trial to KEYNOTE-189, both of them listed here, median overall survival of about 17.2 months. And KEYNOTE-189 for the PD-L1 negative category. And then same for KEYNOTE-407, which was the squamous cell counterpart, median overall survival of 15 months. And then if we look at IMpower150, that looked at it as atezolizumab, and EMPOWER-Lung 3 that looked at cemiplimab. Again, both in combination with chemotherapy, we are seeing median overall survivals of about 18.6 to 12.8 months. Hazard ratio is for all of these clinical trials you can see vary between 0.5 to 1.9, depending on which clinical trial we're looking at. I'd also like to highlight that the response rates here are in the range of 30 to 40 to 50%, depending on which chemotherapy partner we're using.

So at first glance, when you look at these data, two things jump out at you. Firstly, we have a lot of information on how these patients do with combination chemoimmunotherapy. And second, I think what jumps out at me is that there doesn't seem to be that much of a

difference in terms of chemoimmunotherapy using a triplet approach on the right or a quadruplet approach as demonstrated in the column with CheckMate 9LA.

Giving you some real data here KEYNOTE-189 on the left and IMpower150 on the right, you can see that these curves look very good, starting to come together towards the end. But again, these are looking at PD-L1 negative subsets. Looking at CheckMate 9LA, you can see for PD-L1 less than 1% on the far left, top here median overall survival of about 17.7 months, doing quite well if you compare it to PD-L1 greater than 1%, where the median overall survival was 15.8 months. Again, these are not meant to be compared to each other, but I think it's interesting, especially when we think about our PD-L1 negative population. And then finally, IMpower Lung 3, you can see they did include PD-L1 less than 1%. You can see overall survival curves up on top, but you can also see overall response rate of about 33% with the use of this combination, less than what we expect in the intermediate or the high PD-L1 population, but still better than chemotherapy alone.

And then 5-year update, important for this case, squamous cell, PD-L1 less than 1%, you can see 5-year overall survival displayed here. The curves are starting to come together, maybe slight advantage at 5 years, overall response rate about 67.4% with a median duration of response of 6.5 or 7 months. So in summary, for patients with PD-L1 negative non-small cell lung cancer who don't have a driver mutation form a very distinct subgroup. I think you can see that overall survival for this population as well as response rates are not the same as they are for PD-L1 1 to 49% or greater than 50%. Dual immunotherapy alone without chemotherapy is actually not currently approved in this setting. We do have approvals for chemoimmunotherapy as well as quadruplet chemoimmunotherapy, those may be considered in certain situations, but there is no role for single-agent immunotherapy either.

And to discuss these in more detail, I'd like to invite my colleague. But before I do that, I want to just give you a brief summary of our case again, so that it can set the stage for our discussion; 65 years old, significant smoking history, metastatic squamous cell carcinoma, no brain metastases, PD-L1 level of 0%. And how should we treat him? To transition to my peer discussion, I would like to introduce my colleague, Dr. Joshua Reuss. Welcome.

Dr. Reuss: Thank you, Dr. Aggarwal. Happy to be here. My name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at the Georgetown

University School of Medicine, and I'm happy to be here for this important discussion.

Dr. Aggarwal:
Great. Welcome. So I discussed with you my dilemma. You know, this is a patient who's not very symptomatic, PD-L1 negative squamous. Should I use chemoimmunotherapy as a triplet or a quadruplet? What - help me out here, how do you think about these treatment decisions?

Dr. Reuss:
Yeah, no, and I would say squamous disease is probably the one where, especially when you're getting into PD-L1 low or negative status, where I think there is some debate about what might be the best regimen there. I think the KEYNOTE-407 approach of pembrolizumab with chemotherapy, when you look at that subgroup, may not be performing quite as well. So for patients such as this, who is fit, who has minimal symptoms, I would probably grab for you know, a CheckMate 9LA or 227 off-label approach. I do think that adding in the CTLA4 inhibitor, multiple studies suggest benefit there. And to give our patients the best chance of a durable response, that's probably what I would go for.

Dr. Aggarwal:
Yeah, although I will point out that we don't quite have the long follow-up that we do with triplet regimens for the quadruplet regimens right now. So even though the 5-year overall survival curves for KEYNOTE-407 are starting to come together, we just don't have that length of follow-up for the quadruplet regimens, be it CheckMate 9LA or even POSEIDON for that matter. We definitely would be very interested in looking at long-term outcomes for these patients.

But I completely agree with you that I think we know that this subgroup, about a third of these patients who don't have a driver mutation will fall into this PD-L1 low category or negative category. Of course, this patient has squamous histology. So you know, two strikes, squamous histology and PD-L1 negative. I think they're probably going to do worse overall. So offering them something that may benefit them is completely in line with how I think about these decisions as well. I alluded to this a little bit, Josh, but I am curious, how does histology play into this discussion? Let's keep everything similar and change this patient to have an adenocarcinoma histology. Does that change your decision at all?

Dr. Reuss:
Yeah, I would say a little bit. You know, I think that, you know, it's obviously hard to make cross trial comparisons, but I think the data for chemo plus IO is quite strong, even in adenocarcinoma. I would agree that probably when you look at the incremental magnitude of

benefit, when you get into the PD-L1 negative population, it might not be there to this – to quite as high and extent, perhaps. So that's just more an indication of prognostic of how patients could do kind of alluding to what you said about the squamous population. But for a patient such as this, if they were adenocarcinoma, I would probably still gravitate toward a triplet regimen, especially when you weigh additional toxicity when you add another checkpoint blockade to the mix.

Dr. Aggarwal:
So it's more the histology that's making your decision - making you decide between a quadruplet versus a triplet. And that's based on your observation of the subset analysis of these trials. Of course, we didn't go into detail for this, but there seems to be relative advantage for squamous histology compared to adenocarcinoma.

Dr. Reuss:
Yes, absolutely. And then obviously, we didn't talk about this in as much detail, but then you can throw in additional co-mutations STK11, KEAP1 that may also impact that decision as well.

Dr. Aggarwal:
Exactly. And are there situations where you use chemotherapy alone in today's day and age? Can you share a few examples?

Dr. Reuss:
Few and far between. For me, I think it's more of patients who have very concerning autoimmune disease or significant interstitial lung disease or some primary lung disease where you worry that even a low-grade pneumonitis could be very high-grade and its manifestation for a patient. I think those are the main scenarios where I really think twice about adding in an immunotherapy. But it's a difficult decision, right? Because we really know that really the only chance for patients to have a really durable response is with the addition of the immunotherapy. But there are patients who, unfortunately, we can't prescribe it to.

Dr. Aggarwal:
Absolutely. So in summary, for patients with PD-L1 negative non-small cell lung cancer, it's very important for us to evaluate driver mutations. In the absence of those, I think we still need to look at histology because there may be a preferential advantage to using a quadruplet regimen in those with a squamous cell histology. Chemoimmunotherapy regimens, I think should be the standard of care in the situation, either triplet or quadruplet. And then finally, I think in the future, we'll be looking at molecularly-driven chemotherapy, as well as immunotherapy approaches, depending on the presence or absence of immunotherapy resistance mutations.

With that, we'd like to close this episode. And thank you so much, Josh, for joining in on this excellent conversation. Thank you for your insight.

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