Transcript Details

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Time needed to complete: 1h 34m

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Case 1: How Should I Choose Between Single-Agent IO or IO/Chemotherapy in Patients With PD-L1 = 50% and No Driver Mutations?

Announcer:
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Dr. Aggarwal:
Hello and welcome. I'm Dr. Charu Agarwal. 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'll talk about how we choose between single-agent immunotherapy or chemoimmunotherapy in patients with high PD-L1 expression, those with PD-L1 greater than or equal to 50% without any activating driver mutations.

We'll start with a case study here. This patient that I met in clinic is a 67-year-old male who presented with cough and shortness of breath, primary care physician started antibiotics but, however, when the cough did not improve, imaging was performed that revealed a large left lower lobe mass measuring about 5.2 by 6 cm with mediastinal and hilar lymphadenopathy. A PET/CT scan was confirmed - or was performed that confirmed uptake in this left lower lobe mass, as well as lymphadenopathy. And unfortunately, there was also presence of adrenal and bone metastases. MRI of the brain did not reveal any intracranial metastases.

A CT-guided biopsy of the left lower lobe mass was performed, revealing poorly differentiated carcinoma TTF-1 positive, CK5 and 6 negative, consistent with an adenocarcinoma. This patient's past medical history is significant for diet-controlled diabetes, CAD, hypertension, and hypercholesterolemia no relevant past surgical history or family history. He is a former smoker 10-pack here, quit in 2018. ECOG performance status of 1, PD-L1 level of 60%, and KRAS G12V mutation was present.

So when we think about management options for this patient, it's very important to recognize that first and foremost we need histology for making a treatment decision, we need PD-L1 testing, as well as molecular sequencing. And we have all three. This patient does not have a driver mutation and has a PD-L1 level of 60%. What is the data currently? And how should this patient be managed? Should we use immunotherapy alone? Should we use immunotherapy doublet? Or combination chemo immunotherapy?

If we look at the guidelines, first-line therapy recommendations or first-line recommendations are category 1, for patients with advanced metastatic lung cancer a PD-L1 greater than 50% are various. As you can see, there are immunotherapy-only trial to the left of the slide, as well as combination chemoimmunotherapy trials that may be either doublets with a platinum doublet and immunotherapy, or quadruplets, with the option of using both PD-L1 as well as CTLA4 blockade.

So let's dive deeper into this data a little bit. We know that there are several trials that have formally established the role of immunotherapy and chemoimmunotherapy in metastatic non-small cell lung cancer. Here, I want to show you data on immunotherapy-only trials, on the far left of the slide. And on the right, I want to share some data on the use of combination immunotherapy. Again, these are regimens that did not use chemotherapy. And we're all aware of the KEYNOTE-024 trial, now about 6 years old, which really laid the standard for PD-L1 high patients compared to chemotherapy, showed a significant improvement in not just PFS, but also overall survival. You can see a hazard ratio of 0.62.

Following this, we have two other trials with atezolizumab and cemiplimab that also demonstrated an improvement in PFS and overall survival compared to chemotherapy. KEYNOTE-042 was slightly different in that it included patients with greater than 1%. And the benefit potentially was being driven by PD-L1 high patients with a hazard ratio here, you can see, for overall survival of 0.68. I can share my sentiments and I'm sure many of you share this, that looking at these hazard ratios for overall survival across the board. I think any of these monotherapy options will be very reasonable for a patient who presents without any actionable driver mutations.

We also have data on combination nivo and ipi. Here, you can see for the subset that have PD-L1 greater than 50%, we see a median overall survival of 21.2 months with a hazard ratio of 0.66. But let's dig deeper into is really a benefit of CTLA4 – is there really a benefit of CTLA4 blockade in patients with TPS greater than 50%? This was a randomized trial conducted to test the efficacy of pembrolizumab along with ipilimumab. And as you can see, there were about 284 patients randomized to each arm and no significant benefit in terms of overall survival. For these patients, you can see the hazard ratio was 1.08, really suggesting that we could potentially get as much benefit with pembrolizumab alone and don't have to use combination CTLA4 blockade in this situation.

If we were to explore the data of combination nivo and ipi, you can see this as data from the CheckMate 227 trial. And again, if we focus only on the PD-L1 greater than or equal to 50% cohort here, our median overall survival is about 21.2 months with a hazard ratio of 0.66. Again, this is not compared to nivolumab alone. This has otherwise been compared to chemotherapy. And we can, you know, I think, sure, this may be a potential option, but given the KEYNOTE data that I shared with you on the previous slide, I think we really have to strongly think about the patients that may benefit from PD-L1 and CTLA4 blockade.

We've also looked at CheckMate 9LA, which is quadruplet chemoimmunotherapy. This is the 3-year update, again in the subset of patients with PD-L1 greater than or equal to 50%. Here we see a median overall survival of 18.9 months and a hazard ratio of 0.795 compared to chemotherapy.

So what about chemoimmunotherapy? So we know that immunotherapy trials were better than chemotherapy. We know that chemoimmunotherapy trials were better than chemotherapy. When we look across subsets of these landmark trials in the

TPS greater than 50% population, you can see we have several different trials. So we have IMpowe150, CheckMate 9LA, which was quadruplet. We have EMPOWER-Lung 3, which is cemiplimab as chemotherapy. And then we have KEYNOTE-189, pembrolizumab plus chemotherapy. And then if we look at the squamous cell histology, we have KEYNOTE-407 on the far right.

What I would like to draw your attention to is that if you look at the median overall survival in the bottom row, the overall survival benefit is there across the board. Hazard ratios are very similar for all these trials between 0.5 to 0.7, I think none of these trials tell us that there isn't a survival benefit. In fact, there is. So chemoimmunotherapy as well as quadruplet chemoimmunotherapy could be used for these patients with PD-L1 greater than or equal to 50%. I will point out that none of these trials are comparing chemoimmunotherapy to immunotherapy alone. So that question is still pretty valid in terms of how do you choose, and we'll get into this a little bit later in our peer discussion.

So in summary patients with PD-L1 greater than or equal to 50% benefit from immune checkpoint therapy. I shared with you data from KEYNOTE-024, which was really our first trial that showed benefit in this population. Since then, we've had several trials looking at immunotherapy. There is no clear role of dual ICI therapy. I share data with you on pembrolizumab plus ipilimumab. I also shared with you data from CheckMate 227, as well as CheckMate 9LA. It's not clear if we are getting an incremental or huge benefit by adding CTLA4 blockade. And then finally, chemotherapy plus immunotherapy is a very relevant as well as immediate option available to us. And we'll discuss this a little bit in terms of how we choose patients, but it could be used in patients needing fast disease control, because response rates tend to be slightly higher with chemoimmunotherapy.

So in summary, for this patient 67 years old with metastatic adenocarcinoma that's PD-L1 60% KRAS G12V, so now to discuss this further, we are going to transition to our peer discussion, and I'm going to invite my colleague, Dr. Joshua Reuss. Please introduce yourself.

Dr. Reuss:
Thank you, Dr. Aggarwal. And thank you for that wonderful discussion. My name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown Lombardi Cancer Center in Georgetown University School of Medicine. And I'm happy to be here for the discussion.

Dr. Aggarwal:
Welcome, Josh. So I presented a variety of options, and I think this is a dizzying time in lung cancer because we have just so many options that are all category 1. We have a landmark clinical trials establishing the role of immunotherapy alone as well as chemoimmunotherapy. How do you individualize your choice between these regimens?

Dr. Reuss:
Yeah, no, it's a great question. And I think we're fortunate to have so many options, though it definitely can seem overwhelming, both I think as a provider and a patient. You don't want to just give your patient a big menu of options and say here, choose. You know, I think it's important to have patient-guided discussions on this. And, you know, I think we're going to talk a little bit more detail about other factors that may guide this decision-making, you know, patient preference, first and foremost, patients who have unique comorbidities that may preclude chemotherapy, or perhaps comorbidities that might make you worried for a combination treatment approach. And then obviously, you look at the molecular profile as well. And I think we can sometimes look and see, are there additional mutations that may lead us to believe that addition of chemotherapy or another checkpoint might be needed?

I would say that in my practice, for those that don't have - I would say for your case here, as an example, where we have high PD-L1 KRAS mutated non-small cell lung cancer, I typically let disease burden kind of guide my approach. If the disease burden is not particularly high, I think starting with PD-1/PD-L1 monotherapy is quite reasonable, though I do find that a lot of my patients with metastatic disease present with significant symptoms and high disease burden, whether that's pain, shortness of breath, or some lab abnormality that leads me to believe that adding in chemotherapy has additional benefit.

Dr. Aggarwal:
So that's absolutely right. And that has been my practice as well. Single-agent immunotherapy, we now have three agents that are approved and preferred. So we have pembrolizumab, we have atezolizumab, as well as cemiplimab. And I do tend to use chemoimmunotherapy preferentially if somebody is very symptomatic. One of my patients last week has presented to me with very large symptomatic pleural effusion, requiring thoracentesis frequently, and even though he had a high PD-L1 level, just the fact that he's so symptomatic from his pleural effusion, I tended to use chemoimmunotherapy. So that's one of the - one of my sort of go-to parameters in terms of clinical symptomatology and clinical burden.

What do you think, Josh, about dual immunotherapy and chemotherapy? Both CheckMate 227 and CheckMate 9LA are approved regimens for this population as well. When do you consider these approaches, if at all for these PD-L1 greater than 50%?

Dr. Reuss:
Yeah, so I agree with the presentation that you outlined. You know, I think the KEYNOTE study that looked at the combination of pembrolizumab with ipilimumab was quite illuminating, in the sense that, you know, for I think a large majority of patients that have high PD-L1, the addition of CTLA4 is probably not going to move the needle too much. You know, I think cases where I would at least think about it and consider it intriguing would be looking at some of the co-mutational profiles, where we have seen, perhaps a more resistant tumor type with either IO monotherapy or IO chemo, such as when you add in the KEAP1 and STK11 mutations. Though, the bulk of that data is retrospective, and we still need prospective data to see if a dual IO plus/minus chemo regimen is appropriate for those patients. So when you weigh that with the added toxicity of dual IO, I don't really see a lot of scenarios where I would consider this.

Dr. Aggarwal:
Does histology guide your decision at all in terms of using quadruplet versus triplet?

Dr. Reuss:
Yeah, for PD-L1 high, not typically. If patients are PD-L1 low or negative, I think, and they have squamous disease, that's oftentimes where I might go with, you know, a CheckMate 227 or 9LA, or now POSEIDON. I do think squamous PD-L1 low and negative are a population where that might create added benefit.

I'd say the other scenario where I might be inclined to do something a little different is let's say you have a patient who progressed on maintenance durvalumab following definitive chemoradiation, and you're stuck in a boat of, alright, I just gave chemoradiation, I've had a couple cycles of durvalumab, now I'm seeing progression; is that a patient who's, you know, primarily resistant to a PD-1 based strategy, and will the addition of a CTLA4 create added benefit? Now, we don't have trial data there, but that's another scenario where I will potentially look for an alternative regimen.

Dr. Aggarwal:
That's fantastic. That mirrors my practice. So in summary, for patients with PD-L1 high, or greater than 50%, metastatic non-small cell lung cancer without an actionable driver mutation, we have various options today. We can choose between immunotherapy as monotherapy, a triplet chemoimmunotherapy option. I think both of us agree that potentially little incremental benefit to using dual ICI in the setting. I think in the future we'll be using molecularly defined treatment algorithms, especially taking into account mutations such as STK11, KEAP1, potentially KRAS G12V when we make these treatment decisions.

Thank you for joining us today and hopefully you found this discussion to be stimulating and challenging. Thank you.

Dr. Reuss:

Thank you.

Announcer:
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