Lung Cancer Library

Case Based Panel Discussion

NSCLC KRAS 71 YO Female with Underlying Auto Immune Condition (Scleroderma)

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Dr. Benjamin Levy: Hello, I'm Dr. Benjamin Levy. I'm an associate professor at Johns Hopkins School of Medicine. And it's a pleasure for me to have two fabulous faculty members, one from Georgetown and one from Johns Hopkins as well for this GRACE discussion. And it's a pleasure for us to have a forum where we can discuss cases and work through how we would manage these cases. And so, we'll be doing that over the next 30 to 45 minutes. We'll be looking over separate cases and talking about how we would manage these and maybe even taking a step back and talking about some of the treatment or diagnostic implications of these cases. But before we get started, I just want to turn it over and have each of the panelists introduce themselves before we get to the cases. So, Stephen, I'll start with you.

Dr. Stephen Liu: Thanks, Ben. Happy to be here. My name is Steven Liu. I'm a medical oncologist at Georgetown University in Washington, DC.

Dr. Benjamin Levy: And Julie.

Dr. Julie Brahmer: Hi, thanks for having me. I'm Dr. Julie Brahmer, I'm a medical oncologist at Johns Hopkins.

Dr. Benjamin Levy: That's great. A pleasure to have you both here.

Dr. Julie Brahmer: All right. So, this is the second case. This is a 71-year-old woman who has a local art store owner, she's married and has never had children. She's a previous smoker. And quit over a year ago and has no family history of cancer. Past medical history includes shingles scleroderma though that that is an auto-immune disease, but it's limited high blood pressure and a low thyroid. She's had knee surgery as well as counseling. She has no allergies and is on Synthroid and Metoprolol. And in November, 2018, she presented with worsening cough, chest heaviness and shortness of breath on exertion. And her primary care physician ordered a chest x-ray, which found an abnormality and a CT scan that showed the two lesions in the lower part of your right lung. As you can see here on the left-hand side there is a small mass next to the chest wall.

And then there's a tiny mass in the right picture on the next to the liver but still within the lungs. So, it looks like two lesions within the lot. So, the CT guided biopsy. So, because the mass is close to the chest wall, they chose to do a CT guided biopsy. So that is a needle from the outside in, using CT scans and guide the radiologist to do this. And the biopsy comes back positive for adenocarcinoma. But the PD-L1 staining is 0% and then mutation tests come back with KRAS and SDK 11, a AR1D1A mutation as well as low tumor mutation burden. So, Ben or Stephen your thoughts about this one, the patient is right in front of you, what to do then I'm going to make you talk now.

Dr. Benjamin Levy: This is tough. You know, we're, first of all, there's a little bit of incomplete molecular information. I'd like to know what type of KRAS mutation the patient has. Number one, because we've learned recently that certain KRAS mutations may be wedded to novel therapies that aren't yet approved. And so, assuming that this patient has advanced disease and we will see this on the next slide I think, I think that treatment decisions are very challenging here. But in my mind for the sake of time, I could go through a lot here, but I'll just divide this up into the PD-L1 subset. And then the molecular testing. The PD-L1 subset of zero, we need to remember that these patients still derive meaningful benefit with immunotherapy if combined with chemotherapy. So that's point one that I want to make is that even if their PD-L1 is zero if they don't have a gene that we can wed to a particular targeted therapy, this is a group that still derives a meaningful benefit with immunotherapy, not alone, but in combination with chemo.

And that's something that I have to educate patients about when we talk. When you get to the molecular information outside of the fact that number one should be I, I know that drives Dr. Stephen crazy the you know, getting to the molecular information is very, very confusing here, because I think we're trying to understand outside of PD-L1 what additional molecular information may or may not tell us that a patient's going to respond to immunotherapy. And some of these mutations here suggest including SDK 11, that this patient may not do well with immunotherapy, with chemo. And then some of these mutations like AR1D1A, suggest that patients may well with Immunotherapy. These are very early data. But in my mind, this patient based on the information should be considered for immunotherapy with chemotherapy.

Dr. Julie Brahmer: What about Stephen? What about the did you talk about the TMB Ben?

Dr. Benjamin Levy: I did not. I left that for Stephen to talk about.

Dr. Julie Brahmer: Stephen, what about the TMB? Do you even use that? It always comes back on a lot of reports.

Dr. Stephen Liu: No, it, it you're right. It does come back on a lot of reports. And I look at it, I sort of take note of it. I don't know that it really factors into my decision. And so early on the number of unique sematic or acquired mutations that we saw, seem to correlate with the likelihood of response. And what we suspect is that when you have more mutations, it leads to more different proteins or different antigens that maybe makes it more likely your immune system will recognize those tumors. A high TMB was associated with a higher chance of response to immunotherapy. I think more recent studies have really questioned whether that really impacts the long-term outcomes or their survival. So, I don't really use that to choose therapy. Right now, as Ben said our treatment really is immunotherapy. You know, when you think of lung cancer, if it has a mutation a driver mutation like an EGFR mutation or an ALK fusion, we go down the targeted therapy route.

Everyone else should receive immunotherapy. And our decision is what is the best way to deliver that immunotherapy, whether it's one drug alone or combination of different drugs. And I agree with Ben, if it's a PD-L1 0%, I think the current standard is to combine chemotherapy with immunotherapy. I think that there's an emerging option of combining two different types of immunotherapy, nivolumab and ipilimumab are two immunotherapy drugs that did perform well in a PD-L1 0% group, although that is not currently FDA approved, it would be a reasonable option. However, with the STK 11 and

KRAS mutations, my preference, as Ben's is, is really to combine chemotherapy with immunotherapy.

Dr. Julie Brahmer: Great, well, let's not get ahead of ourselves. We'll go through the rest of her imaging. So, she has a hyper metabolic right lower lobe nodule, which we think that's where the cancer had started with two satellite nodules with some lower uptake within the same lobe of the lung, but there's also lymph nodes on both sides of the lung, as well as both sides of the middle of the chest, media Steinem. And then right behind the clavicle. These are lymph nodes right behind your collar bone that were also felt to be involved. And then also lymph nodes in the abdomen as well, and then spots in the bones. Next slide. So, we talked about some of the therapy options. However, what we didn't talk about was this patient has limited scleroderma. Does that impact your choices of therapies and what you would advise to the patient? Stephen?

Dr. Stephen Liu: I think that it is something worth discussing. And when someone has an underlying autoimmune condition, they are at a greater risk for side effects from immunotherapy, and some of those can be quite serious. They can be dangerous. I also know that a suboptimally treated lung cancer is also a very dangerous condition. We have some data that shows these drugs can be relatively safe. Critically if patients have well controlled or minimally active autoimmune disease. So, for this particular patient, I don't know that I would deprive them the opportunity to really get that benefit from immunotherapy. I would counsel both the patient and their caregivers and my colleagues about what to watch for, for side effects and how to act quickly if they emerge, we're watching very closely, but I don't think that limits [inaudible] dissuades me from using immunotherapy.

Dr. Julie Brahmer: Ben, what were your thoughts?

Dr. Benjamin Levy: I agree. I think this is where you phone a friend. This is where you get in touch with the rheumatologist. You have a conversation with them. You have an understanding of what the preexisting symptoms were. I would agree with Stephen, you know, we have to remember lung cancer is an unforgiving disease, and I don't want to deprive a patient of his or her best chance. And I think that best chance does involve immunotherapy, but I would proceed cautiously and collectively with a team effort and engage those sub-specialists to help me through challenging times or help counsel me on what to look for.

Dr. Julie Brahmer: There are studies that are looking at immunotherapy in patients with active auto immune diseases, but it really depends on the auto immune disease. But I think in this patient, I would definitely agree with the combination of chemotherapy. When you

consider that within monotherapy, I again, would not feel comfortable putting this patient just on immunotherapy. Your guys thought about giving two immunotherapy drugs because now we have Checkmate 9LA that's another study that was done taking nivolumab and ipilimumab, and combining that with chemotherapy for a couple of cycles, and then continuing nivolumab and ipilimumab. How about giving this to this patient? Any thoughts about that? Because why not ask? Stephen?

Dr. Stephen Liu: It would be reasonable. It certainly is an approved option. I think it is a reasonable option. That regimen has shown activity was better than chemotherapy. It's not been compared to one immunotherapy drug with chemo. So, I think both are reasonable options. I might expect a little more risk of immune side effects with that second immunotherapy drug and in someone with limited scleroderma. I think that I probably skew more towards the one immunotherapy drug with chemotherapy, But I wouldn't fault anyone for choosing the other.

Dr. Julie Brahmer: Ben, your thoughts?

Dr. Benjamin Levy: We have to remember now, there are nine immunotherapy approvals in the frontline for advanced stage lung cancer, either a single agent or in combination with chemo or combination with chemo Anti-VEGF and, you know, there are multiple strategies here. I wouldn't use 9LA, I haven't used it yet. It is an aggressive strategy. But it's another strategy to consider. I wouldn't fault anybody for considering it, given that there is an approval based on it.

Dr. Julie Brahmer: Yeah, I think I agree with Stephen and the fact that with a history of limited scleroderma, I don't think we have a lot of data of using combination immunotherapy in these particular patients. So, but it's worth the discussion. All right. So, the decision was made to give chemotherapy, so carboplatinum plus pemetrexed or Olympta plus pembrolizumab, which is also known as Keytruda. And after four cycles of therapy, CT scan shows marked response. Yay. We're all excited when we see this. And so, she continued on after four cycles, typically we drop the carboplatinum. And so, she was continued on Pembotrexit and Keytruda for every three weeks for 26 more cycles for another year. But then she developed worsening cough and shortness of breath. And the CT scan shows disease progression, and the MRI is negative. So, this is what it was shown. And you can see here from the January, 2019 to the 2020 scan again it's that right lung that is a problem again, where it looks concerning for cancer. Being a lung cancer doctor, certainly I'm always concerned for pneumonitis that might look like disease progression. And so, a biopsy was performed and confirmed the fact that this is cancer progression, and again the KRAS mutation was found, and then PD-L1 was 0% again. So, Ben, what do you want to do next for this patient?

Dr. Benjamin Levy: Julie, of course I put them on your study, but I think this is the real therapeutic challenge is that we've got all these great regimens that we just talked about that have moved frontline. Immunotherapy drugs have been frontline, either a single agent in combination with other immunotherapy drugs in combination with chemotherapy. And I think there's just a real vacuum as to what to do next. And this is the call in all honesty for clinical trials. I think we've got to get a better understanding of mechanisms of resistance, why these cancers are growing on immunotherapy and then how to better tailor to those mechanisms of resistance off of a clinical trial. There is a standard regimen that can be used docetaxel with remnisirimab which is a standard second line regimen that has shown survival advantages versus docetaxel alone. This is not an easy regimen to give but it is an option. I think that we always look for clinical trials in this case. And that's what I would really push hard for. And I would just make the argument that for patients, even if their physician doesn't have a clinical trial, that doesn't mean that there aren't clinical trials available in the area and to be their own advocate, to look for those.

Dr. Julie Brahmer: Stephen, do you have any comments about what to do next?

Dr. Stephen Liu: I couldn't agree more. I mean the combination of docetaxel and ramucirumab while it is our standard. And while I think it's a good regimen, the chance of response is only about 20 to 25%. And when we think of clinical trials, they really shouldn't be thought of as last-ditch efforts. A lot of times your best first treatment is going to be a clinical trial. This is where we have exciting drugs where we can do better than what's out there already. So, if there is a trial available, I think we need to seek that out, and even if it means a longer drive, even if it means sort of coming in more frequently many cases, it really can be worth it.

Dr. Julie Brahmer: All right. So, the clinical trial that was tried next was nivolumab plus entinosat plus azacitadine. And you can see here, the therapy from January, 2020 to March, 2020, she had a near if not complete response. So, this was surprising, I think. So entinosat and azacitadine Ben, do you want to tackle that or do you want Stephen to take that?

Dr. Benjamin Levy: I'll try, you know, I think what we've learned these drugs are they modulating the epigenetics of a tumor. What we know with lung cancer is that they're made the way that lung cancer may evade immune system is actually by gene silencing by basically putting a cloak over the genetic product so that the immune system doesn't recognize those products as foreign. And what these drugs do is basically unsilence, those genes, or help unsilence them so that they can upregulate proteins on the cell that can be viewed by the immune system as [inaudible]. That's my best. That's my best guess on it.

Dr. Julie Brahmer: Yeah. Yeah. And certainly, what about Stephen? What if they say, well before you even started this clinical trial, what about that G12C stuff? I hear that that is a great therapy, but they have G12D mutation. Do you think they could, and they want to be on one of the clinical trials with a G12C inhibitor, what do you tell those patients?

Dr. Stephen Liu: I say, it's not a good fit. When we look at the KRAS mutations, there are different KRAS mutations, and that G12C, C stands for cysteine, that new drug binds to the C. And so if C isn't there, that drug will not work. There may be other trials that are worth considering maybe targeting their specific KRAS mutation, but it really is finding the right fit. And if you have a KRAS G12D, G12C drug won't work.