2022 Case Based Panel Discussion

Treatment for KRAS G12C Mutated NSCLC with High Tumor Mutational Burden

Speakers:

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TRANSCRIPT

. Dr. Dagogo-Jack: So a lot of data at once. I apologize for that. But what happened with this patient? So because of the tension on the brain or kind of the worry about whether or not the brain could withstand additional growth of that metastasis or that spot at the bottom of the brain, the base of the brain, or the cerebellum. She ended up having that area of removed, which, as Josh mentioned, allowed us to establish the diagnosis. This established a diagnosis of lung adenocarcinoma. It did not express that immunotherapy marker that we've talked about, Pd-l1.

So when you hear the term Pd-l1 negative, that's what this falls into, that category. It had a KRAS G12C mutation, didn't have a couple of other mutations that we sometimes think about with KRAS, so STK11 or KEAP1. Then it had something called high tumor mutation burden because there were other spots in the brain and she didn't have an EGFR or ALK or those other alterations we talked about where we have pills that get into the brain very well. She did end up receiving whole brain radiation therapy. So, Kathryn, I'm going to ask you a lot of questions at once.

The first being, what is KRAS G12C? How do we think about it and what is high tumor mutational burden? And I'll also let Natalie answer something about maybe we can have you answer KRAS G12C. So, you know, Natalie's done some work in tumor mutational burden, so maybe we can have her talk about that.

Dr. Arbour: Sure. Absolutely. Would love to also have Natalie's thoughts on the tumor mutational burden and its effect on her treatment decisions. But mutation. So mutations in general are found in

about 25% of patients. So a quarter of patients with lung adenocarcinoma. The particular subtype here, the G12C mutation, is the most common subtype of KRAS mutation in lung cancer patients. And overall, it's present at about 12% of patients with lung cancer. It's relevant because we have new targeted therapies that are approved in this setting.

Medications called Sotorasib and Adagrasib that you see here. And those are important therapies for us to keep in mind, though. They're more recently in development and identifying where they are going to fit in a patient's treatment course and how well these drugs work, we can talk about. But identifying this mutation tells us a couple of things. One, it tells us that these other treatments may be available at any point in the patient's treatment course. And two, if you have the patient has a G12C mutation, they these mutations are generally mutually exclusive with other common driver oncogenes, such as EGFR mutations or ALK rearrangements or other things.

And so it helps us to fine the tumor and kind of what makes it tick and identify what might be the best treatments available for it. KRAS mutations can have high Pd-l1 expression. They can have low Pd-l1 expression. They can come along with other mutations like STK11 or KEAP1. And certain combinations of these may or may not lead to kind of more aggressive lung tumors and may somewhat enrich for benefit for some treatments versus others. Though that is an active area of research as opposed to definitively settled territory, I would say.

But I'd be interested to hear, Natalie, your perspective on the high tumor mutational burden and if that impacts what you would recommend for treatment for this patient.

Dr. Vokes: Yeah, I think that these slides are obviously touching on a lot of active areas of research, so none of these are really settled questions. I think up to this point we've talked a lot about Pd-l1 as a marker for how likely a tumor is to respond or not to respond to immunotherapy. And Pd-l1 is a very useful guide, but it's not definitive. So you can have a high Pd-l1 and not respond and you can have a low Pd-l1 and respond. So the likelihood is, you know, it does change the likelihood of that happening.

So there's been a lot of research to try to say how can we build on Pd-l1 and find other markers that will help us predict whether a patient will respond or not to immunotherapy. And so tumor mutation burden is basically just a number that quantifies the rate of mutations in that person's tumor. And the idea is that the more mutations a tumor is acquired, the more foreign it will appear to a person's immune system and the more likely it would be to provoke an immune response.

I think it's also the case that tumor mutation burden often goes along with smoking. And we had already heard Kathryn mentioned earlier how smoking associated with response to immunotherapy. So think those two features often go hand in hand. And there have been a lot of studies that show that tumor mutation burden does associate with response. So the higher the mutation burden is, the higher your likelihood of responding. But like Pd-l1, it's not definitive. So you can have a high TMB and not respond and you can have a low TMB and respond.

There was an FDA approval for tumor mutation burden as a biomarker a couple of years ago, but I think most of us have not adopted it in practice in the same way that we've used Pd-l1. Pd-l1 one is baked into the guidelines for which immunotherapies we can use in which context and TMB is really not that definitive. There's a lot of controversy around what cutoffs to use to define a high versus a low TMB. And I think kind of most relevantly for this case, what does seem clear across the board is that a high TMB with a high Pd-l1 are your highest likelihood of responding patients.

If a patient has a low TMB and a high Pd-l1 or a high TMB and a low Pd-l1, that's kind of an intermediate group. So your rates of response are probably a little lower than in the double highs, but still higher than in the patients who are low Pd-l1, low TMB. So I think, you know, kind of putting it all together for this case, this is a patient who has a low PDL one, a high TMB with a KRAS G12C. In this case, I probably would give chemotherapy with immunotherapy just to give him what I always call his shot at immunotherapy.

If a patient has an excellent response to therapy, that can be a really life changing, life prolonging event. And so I like to give patients a shot when I'm not when there isn't a contraindication. And I particularly like to do it with the KRAS G12Cs just because I also know that I have kind of the backup plan B option with one of those pills if the cancer eventually grows on the immunotherapy. But of course I'm interested in what everybody else says because this is a very active kind of subjective area of practice.

Dr. Dagogo-Jack: Yeah, a big area of controversy. But I agree with you, my leaning was towards the chemo plus immunotherapy as well. And I think that was a very, very excellent discussion on TMB or tumor mutational burden. So sometimes you may get your reports from your doctor or from various companies that your tissue is sent to and be kind of confused by the kind of the alphabet soup of all of these letters and think that that was an excellent kind of summary of what is.