Case Based Panel Discussion 2019- Lung cancer Unresectable NSCLC

Case Based Discussion Panel – Stage 3 NSCLC – Tumor Mutational Burden (TMB), and the Value in Testing

Dr. Millie Das specializes in the treatment of thoracic malignancies. She sees and treats patients both at the Stanford Cancer Center and at the Palo Alto VA Hospital. She is Chief of Oncology at the Palo Alto VA and also leads the VA thoracic tumor board on a biweekly basis.

Dr. Matthew Gubens is a thoracic oncologist who treats patients with lung cancer, mesothelioma and other thoracic malignancies, including thymoma and thymic carcinoma, which are rare tumors of the mediastinum. He is an Assistant Clinical Professor of Medicine at UCSF.

Recently the doctors sat down to discuss a series of case-based scenarios. In this video, the doctors discuss Tumor Mutational Burden (TMB) and it's value in testing.

Dr. Jack West: People will often ask what is the value of tumor mutational burden? And whether you use this? We may or may not actually request it, but it often comes with a next generation sequencing panel for a whole array of molecular tests we want. We'll typically get PDL1 and we may have tumor mutational burden, and we hear a bit about it, but we haven't gotten any conclusive signals. So do you think that tumor mutational burden adds a significant incremental benefit to guide your treatment recommendations for patients? Do you rely on PDL1 alone or both? What do you see now and what do you envision for two years from now?

Dr. Millie Das: I am not using TMB to inform my treatment decisions at the current time. It does depend on the NGS panel that you're sending off. And, a lot of times you don't even get the information. And then when you do, I think we don't really know how that fits into this. We know that there, that PDL1 is not the perfect biomarker to predict response. And of course we're seeing responses to immunotherapy and people who don't have PDL1 expression at all. And then folks who have high levels of PDL1 and don't respond to these drugs. So, you know, there's some hope that TMB may help, you know, provide us with more additional information. But I don't think we're there yet. And in terms of understanding, you know, how we can use that data.

Dr. Jack West: And just to clarify, I should have said that tumor mutational burden is basically a measure of the total number, the volume of mutations that are found in a cancer. Of course it depends how hard you look. Some tests look under every rock for extremely, sensitively and some just look at a pretty broad panel and then count them up. It doesn't say which mutations, it just says this cancer has more or this cancer has fewer within a certain number of genes looked at. And I think of that largely like a lottery tickets that you in general have a higher chance of winning something in the lottery if you've bought a stack of tickets. Then if you just have one. And so I think that doesn't say that a lot depends on what that individual lottery test or marker is, but it just enriches the odds. PDL1 is a protein that is on some cancer cells but not all, about 30% or so of lung cancers don't have this protein that is the target of these immunotherapies that have a proven value. And in general, as you say, the studies have largely shown that the ones that have a lot of this protein tend to rely more on this cloaking mechanism to evade the immune system. And so if you remove that with this treatment, they respond. But it's neither necessary nor sufficient. It's not a perfect correlation. It's just more likely if you have high levels, less likely but not a guarantee you won't. So Matt, what's your view on how you use PDL1, how you use tumor mutational burden or TMB and whether you think that's going to change in the next few years?

Dr. Matthew Gubens: The way I think about TMB in a simplistic way is also just how hot, how immune, how angry is the tumor. So the way you know the tumors that tend to have the highest tumor mutation burden happened to be melanomas and why? Because you've been subjected to UV light without sunscreen for years and years and years and years cumulatively. Lung cancer, similarly, some tumors, especially in smokers who've just subjected lungs to more and more tobacco time or maybe radon or air pollution. So I think it's an interesting metric. It's measurable. There's some kind of issues about the replicate ability when you do it on different assays. I think even though TMB hasn't panned out yet in a trial where they looked at it from the beginning to see if it predicted for better or less benefit, it does highlight a group of patients who aren't necessarily PDL1 high or positive, who do have something brewing in their immune system. And so I think that those are patients, even if they're PDL1 low, but have high TMB may be candidates, whether it's for the current generation of drugs, like PD1, PDL1 inhibitors. But this also might be a different population that we handled differently with our next generation of different checkpoints in the immune system process. So I think there's a lot of promise for it. But I do admit that in today's world, with the drugs that I have in front of me, they're not really changing my treatment decisions.