Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/exploring-the-role-of-biomarkers-in-lung-cancer-treatment/15150/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring the Role of Biomarkers in Lung Cancer Treatment

Dr. Sands:
Treatment for lung cancer can be complex, but biomarkers can help us determine the best therapeutic option for our patients. What do we need to know about the role of biomarkers in the treatment of lung cancer?

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me today to talk about lung cancer biomarkers is Dr. Biagio Ricciuti, a medical oncologist at the Dana-Farber Cancer Institute.

Dr. Ricciuti, thanks for joining me today.

Dr. Ricciuti:
Thank you. It's great to be here.

Dr. Sands:
Dr. Ricciuti, to start us off, what role does the PD-L1 tumor proportion score have in predicting the efficacy of immunotherapy, IO monotherapy, and chemo-immunotherapy in non-small cell lung cancer?

Dr. Ricciuti:
Thank you for the question. So, as we know, PD-L1 is an immune checkpoint molecule that is expressed on the surface of cancers cells, and it's recently emerged as an important biomarker for response to immunotherapies in patients with non-small cell lung cancer. The way it works is that this is a protein that is a ligand that binds to the PD-1 receptor of immune cells, T-cells specifically, and this interaction is a strong inhibitor interaction of both adaptive and innate immune response. And today in clinic, we can commonly assess this biomarker through the tumor proportion score, which is defined as the percentage of tumor cells that express the PD-L1 on their surface, and we can measure these biomarkers on a scale that goes from 0 percent to 100 percent. And as we know, initial studies have found that tumors with a positive PD-L1 expression, usually greater than 1 percent, had improved outcomes with immunotherapies.

And subsequent clinical trials have really tried to validate these biomarkers or response to immunotherapy, and a landmark study has shown that in patients with a PD-L1 of 50 percent or greater on their tumor cells really derived the greatest benefit from immunotherapies. And this study, which was also called KEYNOTE-024 trial, really established a PD-1 monotherapy, specifically pembrolizumab, as a first PD-1 monotherapy for patients with non-small cell lung cancer. We have also tried to lower this threshold and tried to learn, whether patients with a lower PD-1 expression of, for instance, 1, 10 or 20 percent can benefit from immunotherapy, but what we really know is that at low end of PD-1 expression, the benefit from immunotherapy is more limited. And we have really shown that when this biomarker approaches 90–100 percent, we're really seeing the greatest benefit from immunotherapy in patients with such high levels of PD-1 expression, and this suggests that really we can use immunotherapy alone maybe sparing toxicity for chemotherapy when this biomarker is approaching these high thresholds.

Dr. Sands:

Now, we also hear a lot about tumor mutational burden as a biomarker to measure response for immunotherapy or expectations about responses. Is this something we can do in routine clinical practice?

Dr. Ricciuti:
This is a really great question. And the answer is yes, we can use tumor mutational burden as biomarker for selecting patients for immunotherapy, but there are still some challenges. And usually, although we can use it, it's not yet routinely included into clinical practice algorithm. We do know that tumors with a high mutational burden are associated with improved outcomes with immunotherapy, and the reason we think this high level of mutations are associated with outcomes to immunotherapy is because those tumors with elevated mutational load are more likely to develop neoantigens from these mutations, and these neoantigens can be potentially presented to the immune cells and eventually prime T-cell antitumor responses eventually clearing tumor cells. And over the last decade, there have been small studies, usually retrospective in nature, that have shown consistently that elevated levels of mutational burden associated with outcomes to immunotherapies across different tumor types, including non-small cell lung cancer, but we really lack prospective validation on the use of mutational burden as biomarkers for response to immunotherapy in lung cancer.

We do have data from a study called CHECKKMATE-227, which is a study that evaluated immunotherapy with nivolumab plus ipilimumab. These are two immune checkpoint inhibitors that were compared to standard chemotherapy in patients with high mutational burden defined as mutational load greater than 10 mutations per megabase. While this study showed duration of responses were longer among patients treated with immunotherapy and high mutational burden, we didn't really see a benefit in overall survival, and since then, the use of mutational burden has been elusive in small cell lung cancer.

Dr. Sands:
So, to bring these two together in some way, are PD-L1 expression and tumor mutational burden independent biomarkers for patient selection?

Dr. Ricciuti:
We do know that across tumor types but specifically non-small cell lung cancer, some studies have shown some positive correlations between increasing PD-L1 expression levels and increasing TMB levels, but all these sites are converging towards a very weak positive correlation between these two biomarkers. And we do know that, for instance, patients that had a smoking history have high mutational burden, but tobacco use is also strong inducer of PD-L1 expression suggesting that these two measures are at least partially related.

In the study I mentioned before in which we tried to understand, what's the optimal tumor mutational burden threshold to predicting therapy outcomes, and what we found was that TMB, when this measure is high enough, greater than 19 mutations per megabase, really associates with improved response rate and survival outcomes independently from PD-L1 expression levels, suggesting that in terms of prediction of immunotherapy outcomes, these two measures may be complementary and partially independent.

And so we do know from exploratory analysis from prospective clinical trials that patients with tumors with high mutational burden and high PD-L1 expression have consistently the highest response rate and the longest survival. Particularly, this is different compared to those patients that have either high PD-L1 expression or high mutational burden but not both had the high levels, and therefore, this data suggests that although weakly correlated, these are mostly independent predictors of immunotherapy outcomes in lung cancer.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Biagio Ricciuti about lung cancer biomarkers.

Dr. Ricciuti, are there any emerging clinically available biomarkers that would indicate response or testing at resistance to immunotherapies that we can use in routine clinical practice?

Dr. Ricciuti:
That's a great question. Now that we have clinically available next-generation sequencing platform, we are increasingly identifying several genomic

alterations and we are learning that two commonly mutated genes; for instance, in non-small cell lung cancer, called STK11 or KEAP1, which are generally served by most of clinically available NGS platforms, can really give us some helpful information that eventually help us identify patients that may display resistance to immunotherapy, and for these patients we eventually consider different treatment strategies.

So, in non-small cell lung cancer these two genes, STK11 and KEAP1, are commonly mutated in approximately 20 percent of cases, and when such mutations occur in the context of a KRAS mutation, which is another commonly oncogene mutated in lung cancer, well these tumors tend to display high rate of primary resistance to immunotherapies, and for these patients we may consider, for instance, a chemoimmunotherapy approach over a PD-1 monotherapy approach. These are just examples of how we can use information gathered from commonly used NGS platform to redirect patients to their most effective treatment options.

Dr. Sands:
So, to integrate these various topics that you've been discussing, if we focus really on newly diagnosed metastatic non-small cell lung cancer that lacks an actionable driver, how would you choose between PD-L1 monotherapy and chemoimmunotherapy for those patients?

Dr. Ricciuti:
That's a very important question and a scenario that we often see in the clinic where now we have multiple first-line treatment options approved for patients with newly diagnosed non-small cell lung cancer, including PD-1 or PD-L1 monotherapy, but also combination therapy, platinum-based cytotoxic chemotherapy in combination with either PD-1 or PD-L1 or even multiple immune checkpoint inhibitors.

And so, how do we choose between these treatment options? The first information that we need usually is the PDL-1 expression because we know that in patients with a negative PD-L1 expression, PD-1 monotherapy is not approved currently, and the response rate is particularly low, and so, for patients with negative PD-L1 expression, we would favor using a chemoimmunotherapy approach. For patients with intermediate PD-L1 expression levels, for instance, 1–49 percent, we do know that PD-1 monotherapy may not necessarily perform as well as in patients with high PD-L1 expression level, so this is another setting where we may prefer using chemoimmunotherapy unless we feel that chemotherapy may not be tolerated by this specific patient.

By contrast, for patients with PD-L1 expression of 50 percent or greater, PD-1 monotherapy can be a reasonable option, particularly if the PD-L1 levels are trending towards 90-100 percent. But if we do have concurrent mutation in genes, such as STK11 or KEAP1 and KRAS as we previously discussed, even though the PD-1 expression is intermediate or may be high, there are scenarios where we may consider intensifying treatment and consider a chemoimmunotherapy over PD-1 monotherapy.

For patients in which mutational burden is particularly high, maybe around 20 mutations per megabase, or PD-1 expression is trending towards 90-100 percent and these tumors lack STK11 or KEAP1 mutation, then PD-1 monotherapy can represent an option which is reasonable, can spare the toxicity of chemotherapy, and we do expect that the efficacy will be overall similar to combination therapy.

Dr. Sands:
And, finally, many of the patients being treated with chemoimmunotherapy as their first-line treatment, their cancers often eventually progress or develop some resistance to treatment. Can you tell us about the underlying mechanism behind this resistance and share any strategies to help overcome this resistance to immunotherapy in non-small cell lung cancer?

Dr. Ricciuti:
Unfortunately, even among responders we are seeing that a large fraction of them develop acquired resistance after initial benefit. And we do really miss a lot of the information that we need to tailor treatment at the moment of acquired resistance, but the community is really trying to gather information which are mechanisms underlying the development of acquired resistance and what we can do to overcome delay and possibly prevent also the development of acquired resistance. And what we know so far is that at the moment of acquired resistance, there are some changes in the tumor DNA that may occur that leads to the development of acquired resistance.

A study presented by our group at ASCO 2022 last year has shown that at a moment of acquired resistance to immunotherapy, loss of functional

mutation in important genes can occur in a significant proportion of patients, but we also noted that mutation in the beta-2-microglobulin gene, which is a critical component of the HLA class 1 complex, also develop at the moment of acquired resistance. We also noted that the HLA expression in general, which is essential for the efficacy of immunotherapy in patients with non-small cell lung cancer, can decrease significantly at the moment of acquired resistance, so this suggests that at the moment of resistance, there are changes, and we need to be aware of those changes in order to develop strategies to overcome this acquired resistance.

Dr. Sands:
This has been an enlightening discussion around the complex topic of lung cancer biomarkers. I want to thank my guest, Dr. Biagio Ricciuti, for sharing his insights on some of these key biomarkers.

Dr. Ricciuti, thanks for speaking with me today.

Dr. Ricciuti:
Thank you very much for the kind invitation. Thank you.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can be Part of the Knowledge. Thanks for listening.