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Why ICIs Have Revolutionized Cancer Care

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Why ICIs Have Revolutionized Cancer Care” is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Forde:
Immune checkpoint inhibitors have improved the prognosis for patients with many different types of cancer. Are you up to date on the guidelines regarding biomarkers so that you can optimize clinical outcomes for your patients?

This is CME on ReachMD. And I'm Dr. Patrick Forde.

Dr. García-Foncillas:
I am Dr. Jesús García-Foncillas.

Dr. Forde:
To start things off Dr. García-Foncillas, why have immune checkpoint inhibitors been successful across multiple tumor types?

Dr. García-Foncillas:
So thank you, Patrick. So breakthroughs have been made in the field of cancer immunotherapy improving survival of cancer patients. And we have different options in immunotherapy, but maybe the most clear approach is simply based in immune checkpoint inhibitors represented by PD-1, PD-L1 inhibitors. That means that we have options in a variety of different solid tumors. So obviously besides antitumor immunotherapeutics at multiple targets and mechanisms we have some new options like LAG3 or CD3 immunomodulators. However, so despite the successful application of all these different immunotherapy in a wide range of human cancers, so their efficacy remains limited and variable. And very few patients with a pan cancer had experienced durable survival. And it means that we have a complex and highly regulated nature of the immune systems.

So we need to pay attention to the tumor immune microenvironment because it's something like complex systems, and we need to identify the potential biomarkers to identify the patients that can respond to chemoimmunotherapy. And in this way, we are currently using this for identifying these patients. First of all, microsatellite instability that can be used to describe a phenotype of mismatch repair genes. It means an impairment in replication of DNA. And you know that tumor can be classified as an MSI high, low, or stable. And the most important, MSI high tumor may indicate a better response to checkpoint inhibitors.

So we are using as well TMB. It’s another predictive biomarker based on the hypothesis that high-level mutations will result in higher level of immunogenic tumor antigens.

So obviously we have 2 potential biomarkers in this way. And as well, PD-L1 expressions, it's true that in the majority of tumors have demonstrated positive correlations between PD-L1 expression and response to immune checkpoint inhibitors and a good correlation with overall survival, even in first-line combination therapy. So you know that we have for instance seen ICI like pembrolizumab currently approved in patients with PD-L1 expressions with level equal or greater to 50% of tumor cells in first-line treatment and equal or greater

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of 1% in second-line treatment in non-small cell lung cancer.

Neoantigen load, it means the number of mutation targeted by T cells and may be related to the response to immune checkpoint inhibitors.

And much more recently, obviously, from translational research, we are using gene expressions. And it means that we can use something like an inflammation signature of the tumor microenvironment for predicting the patients that can respond much better to immuno-oncology.

Dr. Forde:
I think that's an excellent summary, Dr. García-Foncillas, and I think it highlights the complexity of the current situation in the clinic and what we have coming down the line in terms of novel biomarkers, which are not yet in routine practice, but may in the coming years. So I think we have potential predictive markers there, which we can work together to integrate into our clinical practice.

For those just tuning in you're listening to CME on ReachMD. I'm Dr. Patrick Forde, and here with me today is Dr. Jesús García-Foncillas. And we're discussing how immune checkpoint inhibitors have revolutionized cancer care.

Dr. García-Foncillas:
Now that we understand what's behind the success of immune checkpoint inhibitors across multiple tumor types, how do we incorporate proper testing before treatment, Dr. Forde?

Dr. Forde:
Well, we've heard from Dr. García-Foncillas in terms of the efficacy of immune checkpoint inhibitors across multiple tumor types. And I think what has moved us as oncologists in the last 10 years has been the complexity of workup for patients with newly diagnosed cancer has become increasingly an issue.

The baseline test which we need for many tumor types now is PD-L1 immunohistochemistry. This is a relatively straightforward test. It's integral, for example, into the care of lung cancer patients, patients with bladder cancer, and other tumor types. And this can help predict whether a particular tumor will respond to either single-agent immunotherapy or combination therapy.

However, it's more complex than that. In certain tumor types, testing for specific targetable mutations is recommended. For example, in lung cancer, the NCCN guidelines here in the United States recommend that patients have broad-based next-generation sequencing, including all targetable alterations, which at the moment in the US include 7 approved drugs for targeted therapy for lung cancer.

In terms of how do we actually test for these mutations, well, as I said the NCCN recommends broad-based next-generation sequencing as opposed to doing single-gene tests, for example, for EGFR, for ALK, for ROS1. There are pros and cons of this. Broad-based testing uses more tissue. So in general, biopsies need to be more copious and core biopsies are preferred. It's also generally more expensive than doing individual tests. However, it provides a wealth of other information in terms of both tumor mutational burden, which can help predict response to immunotherapy, and also other mutations which are not directly targetable but can predict sensitivity or lack of sensitivity to immunotherapy. And here I'm thinking of things like STK11 mutations or KEAP1 mutations which have been associated with lack of sensitivity to immunotherapy.

There is also the issue more broadly of how we sequence testing in early-stage disease. So as immunotherapy moves into the treatment paradigm for resectable cancers, we may need to do this next-generation sequencing testing. For example, much of the immunotherapy approvals we have seen recently in the US and recommended by the NCCN have excluded patients who have EGFR alterations. So we need to test for that up front now in lung cancer in the US.

I would also ask Dr. García-Foncillas for the international perspective in terms of testing for mutations over in Europe and worldwide.

Dr. García-Foncillas:
So thank you, Patrick. So obviously in Europe, we are looking for the patient that can respond much better to immunotherapy. And most frequently, we are using microsatellite instability because we can classify the tumor as MSI high, low, or stable tumors. As well more frequently, we are using in some tumor types, tumor mutational burden, another predictive biomarker based on the hypothesis that higher-level mutations could identify higher levels of immunogenic tumor antigens. So it means potential biomarkers to predict the patient that can respond as well.

You know that we are using as well PD-L1 expressions. So we have conversations about it because we have good correlations between PD-L1 expression and great response to immune checkpoint inhibitors and a good correlation even with overall survival in some tumor types.

However, we have as well PD-L1-negative patients that can still benefit with treatment with immune checkpoint inhibitors. And even in

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this subset of patients, the objective response rate ranges from roughly 10% to 20%.

And as well we are using in some countries neoantigen load. Obviously, it's much more from translational resources, but it could be a potential biomarker that can identify patients with their response to immune checkpoint inhibitors.

So obviously, we need good biomarkers able to predict the patients with a response to immuno-oncology.

Dr. Forde:
Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. García-Foncillas, can you share your one take-home message with our audience?

Dr. García-Foncillas:
Absolutely. So immuno-oncology therapy has opened a new portal in antitumor therapy with sustained response and significant survival advantages, so across different multiple tumors; however, most patients do not benefit and we need clearly to define the patients that can benefit much more for this approach. These are exciting times for providing a much higher benefit to our cancer patients.

Dr. Forde:
Yeah, an excellent message, and I think I would add to that that as oncologists, it behooves us to work closely with our multidisciplinary colleagues when we're considering the workup of patients with newly diagnosed lung cancer, in particular pathology, pulmonary doctors, and also surgeons as we move into early-stage disease in terms of optimizing immunotherapy for our patients' care.

So unfortunately, that's all the time we have today. So I want to thank our audience for listening in and to thank Dr. García-Foncillas for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. García-Foncillas:
Patrick, thank you and goodbye.

Announcer:
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