Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/what-is-the-role-of-biomarkers-in-predicting-response/14570/

Released: 11/30/2022
Valid until: 11/30/2023
Time needed to complete: 2h 36m

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

What Is the Role of Biomarkers in Predicting Response?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Cottrell:
Hello, my name is Tricia Cottrell and I'm from the Department of Pathology at Queens University in Kingston, Ontario. This presentation is to discuss the role of biomarkers in predicting response to neoadjuvant immune checkpoint blockade. First, I'd like to address the importance of having biomarkers to predict response. We've seen some very exciting data suggesting relatively high response rates to neoadjuvant anti PD1 based therapies, particularly in the Checkmate 816 clinical trial. But we also know that having biomarker driven therapy improves effectiveness, reduces toxicity, improves cost effective care, and will be necessary when many treatment options are available. And I'll dig in a little bit more to some of these ideas as we go through the talk. But I'm mostly going to focus on highlighting the limited available data that we have now to support the role for biomarkers in the neoadjuvant setting.

First, I'd just like to highlight that our existing data really does not support the use of neoadjuvant immune checkpoint blockade in patients who have alterations in EGFR or ALK. Those patients were actually excluded from the Checkmate 816 clinical trials. So that data is not representative of that population. And in the LCMC3 study it was actually found that none of the patients who had these alterations responded to neoadjuvant atezolizumab. And that was 17 patients that were assessed in that study. So while the data is certainly limited, currently it would be best practice to pursue molecular testing and exclude these patients from a neoadjuvant course of therapy.

These plots are representing event pre-survival from the Checkmate 816 study of neoadjuvant nivolumab plus chemotherapy. And on the left we can see the outcomes for those who have pre-treatment PDL1 immunohistochemistry of less than 1% versus greater than 1% on the right. And has been pretty consistent in trials of advanced lung cancer, the higher the expression of PDL1, the more likely patients are to respond. And that includes responses both in terms of event free survival and also in terms of pathologic response. Unfortunately, we also know that PDL1 is an imperfect biomarker. There are PDL1 negative patients who respond and PDL1 positive patients who do not. And there are several factors that contribute to this challenge.

There are two different mechanisms by which PDL1 one can be expressed on tumor cells. One is adaptive expression, which is associated with a lymphocytic infiltration and the expression of interferon gamma in the tumor microenvironment. And that interferon gamma actually drives PDL1 expression in tumor cells as well as other cells in the region. Now this would be contrasted with what you're seeing on the right which is constitutive expression. And that's a situation where there's either a genomic or epigenomic alteration that drives expression in all of the tumor cells completely unrelated to the presence of infiltrating lymphocytes. Importantly, when we're assessing the tumor proportion score or the percentage of tumor cells that are positive for PDL1 expression, we do not make a distinction between the pattern of expression, so we are potentially scoring both adaptive and constitutive expression in not making that distinction.

To add to this complexity, we also know that PDL1 is one of many sets of receptor ligand pairs that represent both positive and negative immune checkpoints. And ultimately it's the balance of signals across all of these checkpoints that determine whether or not an immune response is going to be activated. In addition to the complexity with regard to numerous molecules being involved, we also know that there is a complex spatial arrangement of cell types in the tumor microenvironment. And these cells are physically interacting with each other to regulate this immune response. So, this complexity, I think, explains a lot of the lack of sensitivity and specificity that we see with PDL1 immunohistochemistry. And the fact that many of these alternate immune checkpoint molecules are currently being investigated as potential therapeutic targets, really begs the question of what our next generation of biomarkers are going to look like. And that's where I think we have some very exciting preliminary data.

So many biomarkers have been investigated and this is predominantly in the advanced disease setting where we have much more data. Here you're seeing a meta-analysis of over 8,000 patients across 10 solid tumor types comparing pre-treatment biomarkers for predicting response. And we have PDL1 immunohistochemistry, the current gold standard, gene expression profiling, tumor mutational burden, as well as multiplex immunohistochemistry or immunofluorescence. And what's particularly exciting is the ability of these multiplex IHC or IF approaches to actually capture both the molecular and spatial complexity that characterizes the tumor microenvironment. And early studies have suggested that this approach is actually going to be our most robust way to predict response to anti PD1 therapy and likely to other immune targeting therapies as well. So in the future I would be expecting these biomarkers to become relevant, not only in advanced disease, but also in the neoadjuvant setting.

In conclusion, biomarkers are incredibly valuable for increasing response rates, reducing toxicity, and controlling costs of therapy. So, a really critical aspect to a high-quality delivery of care. In terms of our current data, it does not support the use of neoadjuvant immune checkpoint blockade in patients with EGFR or ALK alterations thus warranting pre-treatment molecular testing prior to starting therapy. We know that PDL1 expression enriches for response and that higher expression levels are more associated with higher rates of response. In the future next generation multiplex IHC and IF based biomarkers are likely to improve our ability to predict response. And I didn't talk about it much, but ctDNA is another exciting biomarker that may play a role in our ability to monitor disease following neoadjuvant therapy and surgical resection. However, highly sensitive assays are going to be needed in this setting and the data is still very early. Thank you for your attention.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.