Can We Create Companion Diagnostics In Oncology With What We Know About Biomarkers?

Moderator

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Kineticos: It's interesting because you mentioned the different checkpoints in our earlier piece, where you see a response in a significant number of patients, but you have to look at these immunological pieces of the puzzle. Does it lead us to combinations? Does it provide a basis for multiplex test kits? By doing so, does it capture more pieces of that puzzle?

CH: This is the really difficult aspect. There are a lot of good assays out there that go through a lot of working and re-working, but in many cases, we have very little clinical activity with which to correlate the results of those assays. One of the misconceptions in the field of biomarker identification is that biomarkers by themselves are useful. Your biomarker isn't going to help you if you don't have clinical activity to compare it to. A good example of this is how complicated PD-L1 is as a biomarker. There was so much activity with PD-1 and PD-L1 blockade, the field was able to evaluate four different assays at the same time and discover that those assays didn't correlate with each other very well despite each one correlating with activity. It tells you that each assay has its own weaknesses, false positives and false negatives. Therefore, for each, sensitivity and specificity are not perfect. So, these assays are useful on a population level, but not ideal for individual patient treatment decisions.

As a result, a decent assay for decisions about patient population selection may not be great as a companion diagnostic for individual treatment decisions.

Kineticos: It's interesting that you mentioned correlation and sensitivity. While it does look like the assays inform or characterize the tumor, do you think it overlooks something about the heterogeneity of tumors?

CH: I do. In many cancers, and almost all solid tumors, there is enormous heterogeneity between tumor sites and within tumor sites. In many cases, it is very difficult for an assay to account for that heterogeneity. Across a population, the heterogeneity may be accounted for, but in a given patient, heterogeneity can undermine the reliability of an assay. In many biomarker analyses, we do not yet know how to account for this problem on a patient to patient basis.

Kineticos: One of the challenges for the scientific team was these tumor biopsies. There were hot spots on these tumors and other areas that didn't line up. While you could engage a target, the question became, "Could you induce shrinkage by targeting these portions of a tumor?" Some evidence is beginning to emerge that is telling us, "Yes, sort of, maybe."

CH: That's really a fascinating approach: using tumor heterogeneity as a target. I believe we will see that become a bigger part of R&D strategies in the future as we're starting to see more of a discussion around the evolutionary biology of tumors. There is the opportunity to use a given therapy to push one subpopulation of tumor cells to express the right targets to be more likely to be targetable by whatever other therapy we have available.

Similar work has been done for many years now for cancer vaccine development where using small molecules can cause up-regulation of MHC complexes to improve T-cell mediated killing. That works really well in preclinical models but it's harder to know that you're optimizing that dose of that small molecule in a human to achieve the same effect unless you're doing a pre- and post-biopsy. You need to feel really confident that you're measuring the right thing with the right assay.

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