Should PD-L1 be Used as a Biomarker for Immunotherapy in Lung Cancer?

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TRANSCRIPT & FIGURES
So, the role of PD-L1 as a biomarker may be among the most controversial areas in the checkpoint inhibitor story. So, in melanoma, they have seen tremendous results with the checkpoint inhibitors, and early on in the development, the melanoma physicians were very dismissive of the role of a biomarker, in general, because they were seeing such good responses. Nonetheless, many of the studies in non-small cell lung cancer have specifically sought out the biomarker and there have been many different biomarkers that have been assessed, but the one that has been assessed most strongly in a clinical setting is the expression of PD-L1.

Again, PD-1 inhibitors are blocking the interaction between PD-1 and PD-L1, so it seems reasonable, perhaps, that the degree of expression of PD-L1 would correlate with the response to drug. And, in a very large study, in which we required all patients to have a biopsy around the time of therapy, looking at Keytruda, we saw that there were tremendous differences with respect to response rate, progression-free survival, as well as overall survival, with patients who had a high degree of staining for PD-L1, doing significantly better than patients who had a low degree of staining. When that data was published, there was some concern because there certainly were patients who had low level of PD-L1 staining, or even absent PD-L1 staining, who did have responses to the drug, and the thought was, how could you leave people behind? How could you not give patients the PD-1 or PD-L1 inhibitors, for instance, if you are in a situation where there are some patients who have no staining, who still respond – and that’s a very fair criticism. However, when you look at the data from the CheckMate 057 study, what you see is that there, again, now, in this case, they actually weren’t treating everyone with Opdivo, they were randomizing patients to receive either Opdivo or Taxotere,
and they did identify one cutoff where, if you look, there was tremendous benefit in patients who had high level staining, but in patients who had lower level staining, those patients did equally well, whether they were on Taxotere or Opdivo; and the data from the POPLAR study with atezolizumab, where they look at it slightly different – they look at not only tumor cells, but they also look at the PD-L1 expression on infiltrating immune cells. In that study, again, they identified patients who had higher degrees of staining who did particularly better, and at least numerically, when you look, there was a group that they were able to identify where it looked like they did a little bit better if they got Taxotere.

So, this is still an area that is under active investigation, it is quite controversial, and the additional thing that’s important for patients to know is that it’s going to be a very hard situation, because, the way drug development currently is, one essentially gets credit, additional credit, for developing a biomarker along with the drug. And, so, for instance, in Keytruda, even though they had just a phase 1 study, that phase 1 study which showed clear correlation with a biomarker, may hasten that drug being available for patients. But, the challenge in that is that each company has their own diagnostic test, and it can be confusing because the tests are not identical. As I mentioned, atezolizumab evaluates both tumor cells and immune infiltrating cells, while the other tests really evaluate tumor cells alone, and similarly, the sensitivity and specificity of the antibody can differ – now that, I know, gets very technical, but I think what a patient could take from it is that 30% staining for PD-L1, for instance, with one antibody, doesn’t mean that you would have 30% staining for PD-L1 with another antibody. And, so, to some extent, each company has looked at their own
antibody with their own drug, and I think this is going to be something that is confusing to patients as these things roll out. And, there are many efforts underway of sort of harmonize this, and hopefully we will be able to get to a point where it is easier for patients and clinicians to interpret the data.
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