Are Checkpoint Inhibitors Impacting How We Cure Disease?

Moderator

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Kineticos: Perhaps compare and contrast where things have gotten to with the checkpoints like PD-1 and PD-L1 and say a little more about gene editing. It's almost a next step to say, "We are modulating disease? Or is our aim to cure disease?"

CH: It would be good to establish some definitions that allow me to frame this conversation. When I think of cure, I think of an intervention that allows the disease that you have to no longer be the definition of your life in terms of how long you survive or how well you survive with that particular disease. When I say cure, I don't mean that every last possible remnant of that disease has been eliminated – I think that is how it's typically used. It's more along the lines of "is your quality of life what it was prior to the diagnosis, and do you live the length of life that you would have without the diagnosis?" There can be disagreement on that point, but I'll say that's how I define that.

For checkpoint inhibitors, in particular, I feel we've reached a point of a plateau of the effectiveness. That is partially due to our current understanding of biology. We are still seeing successes in clinical trials that are driven largely by the number of shots on goal, not necessarily by the key insight that we had prior to those clinical trials starting. Essentially, many of the major victories of checkpoint inhibitors have already been won. It has become clear that we need to understand biology better to make a better impact. One of the really difficult problems we faced in particular within immuno-oncology was we have an inordinate number of biomarkers that we can evaluate. Because of the relative lack of activity in some groups of patients, you need to know whether you've measured the right thing at the right time in order to answer the mechanistic question.

For instance, when we think about what is different about the patients who respond, specifically within immuno-therapies, we have fairly good insight into what is missing in that equation. We can narrow that down into three key categories – a lack of underlying immune response to the tumor cells themselves in that individual patient, the inability of those cells to infiltrate into the tumor and function properly, and some secondary resistance mechanism where you had some initial small response but it wasn't durable. Within each of those, there are a number of subcategories.

Kineticos: Would you include the framework you just described for other checkpoints, like OX-40, LAG-3? Those that haven't been proven yet but are still part of the checkpoint umbrella that could be mechanistically different?

CH: Those checkpoints can fall into the second or third category I mentioned. They can fall into the group of microenvironment-related factors that prevent cell function. They can also fall into secondary resistance mechanisms because in some cases, after PD-1 or PD-L1 blockade, you expect to see an upregulation of another checkpoint. That is likely highly specific to the tumor in a given patient. This is why these are such difficult problems to solve.

For instance, in a given patient, let's assume we have a strong underlying specific immune response to the tumor so blocking PD-1/L1 should work. However, expression of another "checkpoint" might require you to inhibit both at the same time. One of the really tricky things in the development of those additional checkpoints, or immune mechanisms, has been determining in which patients they need to be targeted. If you take the whole group, you need to treat a large number of patients with a relatively small impact which gets to the core of our discussion, biomarkers and identification of the right patients for the right treatment. We think about this idea of companion diagnostic strategy as you're developing your agent. One of the hardest things to do is, when you have a novel target, is to have patience to optimize your assay to identify the patients in whom the target is most relevant.

For instance, when we saw inhibiting IDO (indoleamine 2,3-dioxygenase) as a strategy, it really reached peak interest a few years back and later, we saw Phase III failures. We're still left wondering mechanistically, could IDO be important?

Kineticos: It's interesting because you mentioned the different checkpoints, where you see a response in a significant number of patients, but you have to look at these immunological pieces of the puzzle.
