Immuno-Oncology Panel Discussion: Part 1 - Checkpoint Inhibitors and Beyond

Panel Members
Chris Heery – Chief Medical Officer, Bavarian Nordic
Jeff Kmetz – Former Chief Business Officer, Pulse Biosciences
Alex Dusek – Vice President of Commercial Strategy, Erytech Pharma (To be featured in Part 2)

Kineticos: It wasn't long ago that we described cancer by the location in the body, cancer in the breast was breast cancer, cancer in the lung was lung cancer, etc. However, as we learn more about the biological basis of disease, we are starting to describe tumors based on how they grow and how they feed themselves. This insight is leading to new therapeutic discoveries like the PD-1, PD-L1 and CTLA-4 checkpoint inhibitors, as well as engineered cell therapies. This has been good news for a select number of patients. In some areas, like CAR-T, we have been able to use the "C-word" and say cure. However, for most people living with cancer, we still have a long way to go before we can start talking about eliminating disease from the body.

Chris, from your perspective, what are the next step changes in immuno-oncology? What's beyond checkpoint inhibitors for cellular based therapies and how do you see the cancer treatment paradigm evolving?

CH: First, I would look at the underlying assumption to that question…that we are already in the era of being able to identify tumors by some molecular characteristic outside of their tissue of origin. I believe we will get there but it's actually a very small number of interventions that are selected based on some molecular characteristic(s). I suspect we could count those drugs on one hand. Certainly, for MSI High tumors of all types and a very select number of mutation or gene fusion products, there are interventions we could use regardless of the tissue of origin. But, for PD-L1 (IHC staining) for example, the tumor tissue still matters. It's also important to understand whether the PD-L1 expression is high or low.

How do we get there? It's really exciting to see a big company like Merck give us a look behind the curtain in terms of how they made some of their decisions. Last week, they published an article about how they determine which tumors to target with Pembrolizumab. It's not until we all get access to those decision points and the correlating data sets that we can start to try to validate those molecular markers in a way that's true across multiple tumor types. That work will help us identify a pattern consistent across tumor types. So, I think the next step involves aligning academic institutions and companies using the same panels of molecular characterization. This probably means some of the diagnostic companies will have to invest their own money and run their own clinical trials to demonstrate that what they see as a pattern in one trial with a particular intervention is true across multiple different interventions. The more important part is identifying the tumor characteristics, which is not something we've seen much from diagnostic and characterization companies yet. But, there are some out there

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starting to make that move and fund their own trials in efforts to be able to say, "We can help patients and physicians select a treatment based on our test."

Kineticos: It's interesting listening to you talk about those kinds of insights and... maybe… the beginning of a trend. The last couple of meetings I've attended, there has been a buzz around the topic of "Omics" and the related computational and informatics applications.

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It goes beyond the multiplex panels and the testing. How do we utilize this vast amount of information and apply it to a treatment decision? How do we determine if it applies more broadly across populations? Jeff, I know you've thought about this in some of the work you've done. What's your perspective on this?

JK: I agree with much of what Chris said. Keeping PD-L1 in mind, we have to realize that only about 1/3 of patients respond to these treatments. The bigger challenge with checkpoint inhibitors is understanding resistance. We're looking at patients' tissue still, so I agree that tissue of origin is important, but now, it's more specific. Genetics is the next big change; we see some of that with CRISPR and a lot of the work that's been done with epigenetics. We now have figured out how to interface or interfere with genes, whether it be by replacing the defective driver gene or interfering with the mechanics. That is where we'll see another step change.

Also, you talked about CAR-T –- that's another element of the Immune-Oncology space and we're not too far from having off-the-shelf CAR-Ts. I think there is a revolution that's going to happen that is more, in my eyes, genetics based. It will help drive treatments and lead us to the true aspects of personalized medicine. It will mean treating a cancer patient based on their genetics and the mutations of the cancer with the idea that the cancer will mutate. Knowing where that mutation is going is the epigenetics.

Kineticos: In listening to this discussion, I'm reminded of a quote from the famous American astronomer, Edwin Hubble. In the early days, when he looked up into the sky on a clear night, he saw stars. One evening, Hubble having a more powerful telescope in his observatory peered through the telescope and said "… those are not stars, those are galaxies". To me, it seems that's where we are with Immuno-Oncology. We've peered into these cancerous cells and thought singular pathways were the key to arresting cancerous growth, only to discover a vast new biological landscape; genetics, epigenetics, redundancy, and escape mechanisms. We're just now figuring out how to contemplate complex galaxies of information and how to apply those discoveries to therapeutic development.

Stay tuned for Part 2 where we bring Alex Dusek into the debate and share perspectives on how to ensure patients have access to these innovative and costly therapies.

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