Immuno-Oncology Series:
Part 3 - Data is King

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 (Featured in Parts 2 and 4)

Kineticos: In Part 1, we covered some highlights of the history and aspirations related to immuno-oncology from our panelist's perspectives. In Part 2, we talked about general access to the new I/O therapies as well as costing models. While I/O has been established as a new plank in our ability to fight cancer, there are challenges to making them available to as many appropriate patients as possible. Certainly, our clinical experience has exposed a number of limitations that we hope next generation I/O technologies will address.

In this portion of the series, we're going to turn our attention to how biotechs working on I/O programs can gain the attention of partners and investors. Having active programs in one of the hottest scientific areas of investigation does not automatically mean a steady stream of capital is available. Interestingly, of the 50 or so companies we met with a few weeks ago at JP Morgan, at least 1/3 of them were working in I/O. We heard a lot of great stories, some involved data, and quite a number without data, but big aspirations. Furthermore, because of the investment required to deliver clinical proof points, most were doggedly walking the rainy streets of San Francisco in search of funding in one way or another.

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Jeff, you can start on this and ask others to weigh in – besides compelling clinical data, how can emerging I/O therapies differentiate and get the attention of partners, whether it's big pharma or others to help fund these programs?

JK: While the price for these newer therapies have certainly garnered a lot of attention, it doesn't look like the cost to conduct these trials are going to see any relief in a meaningful way. Keeping the goal in mind, it's tough to identify what else is important besides clinical data. Related to having compelling data, designing the trials and selecting appropriate endpoints are really relevant. In the cancer immunity cycle, there are 7 steps where one can intervene. It is critical to ensure you are intervening where it matters. A lot of people are intervening at steps 6 or 7, right around where the PD/L-1s work. It is plausible that you may even be able to get rid of CTLA-4 if you could present antigens to the immune system in a way that is not one dimensional. If you can amplify these neo-antigens, to generate a broad and robust presentation of antigens to both the innate and adaptive immune systems, now that would be novel. To the extent that they can be, trials should be set up with a meaningful endpoint survival, not progression-free survival but overall survival, and with a biomarker that is relevant to response, or even a non-responder. Better yet, have one of each and you have the ability to use evolving technologies, like liquid biopsy to follow not only the responders but their relapses. This would enable doctors to treat patients as early as possible.

There are so many elements in the immune system. If you shut down the tumor microenvironment, that is one element. If you shut down the antigen presentation, that is another. You have to avoid combination immuno-therapies because you are going to end up like combination chemo-therapies, and that will become cost prohibitive. Currently, the investment community is looking for critical mass in patients, not just mice and preclinical models. We need to see tangible, demonstratable responses. If you can show efficacy in a tumor that is hard to treat during your phase 1, you are going to draw a lot of attention and likely investment. That said, a lot of companies and investors wait for a phase 2 to read out before they make their commitments.

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Kineticos: Data is king and data gets everybody's attention because we know these compounds have to start. Is there anything else that can help distinguish these earlier approaches? Is there a way to determine where to place your bets, or is it still wait for the clinical data?

JK: I think it is wait for the data, because at the present, there are no strong and reliable models that work across tumor types.

CH: Speaking specifically about immuno-oncology, it is quite clear where the gaping holes are. We know that if someone has an activated T-cell response, and those T-cells are present in the tumor microenvironment, that if you add a checkpoint inhibitor, they are more likely than not to have an objective response resulting in an overall survival benefit. The challenge is 70-80% of people don't fall into that category. The problem is there are people who don't have specific T-cell response against their tumor, and we need to create a T-cell response, in many cases, in order to get that going. The other big problem is loss of MHC molecules and developing something that can overcome that component.

Tumor microenvironment is probably the biggest of these problems. In any given person, it is unknown what is going on in the tumor microenvironment that is inhibiting T-cells and preventing their infiltration. If any therapy can address more than 1 or 2 of those things at the same time, it will have a significant advantage in its likelihood of being successful in combination with a checkpoint inhibitor. Additionally, it will have a significant long-run cost advantage with its efficiencies because it won't need to combined with 3 other drugs – you can combine it with 1. Most of us are starting to think of checkpoint inhibitors, particularly blocking PD/L-1 and PD-1, as a backbone for any other I/O therapies. Whether that therapy might include checkpoint inhibition in it somehow is a different story, but without blocking PD-1 and PD/L-1, you are really going to have a difficult time.

Address those issues, and particularly many of them would be an advantage to a biotech seeking investment. Telling a compelling story and building up your preclinical data package to demonstrate that you are hitting the biologic mechanisms that you claim to be hitting is key. Then, showing you are going to roll right into clinical trials, whether they win from a clinical perspective or not, is critical. If you can do that, then you can have at least the kind of story that shows enough information to figure out where things went right or where things went wrong. That said, trying to tell that story to an analyst or a group of investors who do not know all of these things in detail is a very difficult process.

Kineticos: My own experience out on the investment trail, whether it's talking to bankers or investors, you feel like you are back to biology / oncology 101, even with some very smart and well-educated people in the room.

The complexity of I/O, and the newness of it as well, presents a challenge. If you describe your approach relative to where some of these obvious gaps are, that is a stronger value proposition, especially for early companies. As with anything related to drug development, it is not any one thing; it is getting several things lined up in the positive column that helps you advance. If there is an absence of data, articulate that you know where the gap is and how your technology addresses that gap. Also, make sure your hypothesis has strong foundational elements. And lastly, be sure to be in Union Square, San Francisco in early January!

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