Is Precision Medicine in Oncology Narrowing Patient Population Too Much?

Moderator:

- **Steve Buckanavage, Operating Executive, Kineticos**

Panelist:

- **Christopher Heery, CMO, Precision Biosciences**

Kineticos: Our understanding of biology is saying, "Do we have tractable targets? We're going to exploit the biology to do what it was designed without interference from mutated tissue." Rather than having a toxic type of agent, we want to induce tumor toxicity through protein production or block abhorrent protein to protein interactions.

CH: Absolutely. The better we understand biology, the better we can capitalize on it. Where I see this getting lost is that we have these elegant experiments that occur in the preclinical setting when the retrospective analyses of biopsy samples will tell a nice story but for commercial reasons, the same hypothesis isn't the same one that's tested in the clinical trial that moves toward a registration end point. I do wonder whether hoping to squeeze a little bit more commercial upside out of some very specific biologic findings lead us down a path that undermines the original question. One of the questions that floats around out there is that, "If you aim for something super specific, should you limit your patient population so much that you don't have a commercially viable drug?"

That brings us to a broader question. First, is that really true? If you do not know the patient population where benefit will be most obvious, that often means that you have to increase the number of total patients that are going to be screened for a clinical trial. For the most part, the big costs of clinical trials are in administering the treatment and following up with those patients over an extended period of time.

For instance, if a novel treatment works well for 15% of patients in a given population, then I would have the choice of enrolling 100 unselected patients to have an effect on 15, or I could enroll on the 15 likely to benefit if I knew how to identify them. The difference is spending resources on treatment of 85 patients unlikely to benefit versus screening 100 patients to treat 15. The latter is almost certainly more cost effective.

Kineticos: Exactly. If you want these patients, you're going to have to screen a bunch more people. A 10-1 increase in sample size will help to properly test the approach.

CH: In the scenario where you have the correct, defining characteristics of the population, there's no reason to believe that specific markers shouldn't be applicable to other tumors, as well. Your first trial and population may not be the one that is truly commercially viable on its own but the level of understanding of the biology that you're working with may allow you to think more critically. Can I use this in other populations and expand the footprint of how I can use this therapy more quickly and confidently?

Even more so, it's especially relevant with investigators. When they know that they have a drug that's going to work with a large majority of the people they're going to treat, they're going to bend over backwards to find patients that fit that category because they want to help their patients.

Kineticos: That's a very good point. That package can be extremely motivating to investigators who we're asking to administer experimental medicine to a patient population. I did want to come back to the biology discussion and how we exploit biology. My sense is that particular areas are related to what you mentioned in the beginning of our discussion – there's this upstream with gene editing. I was hoping you could elaborate on that and our understanding and emerging knowledge around checkpoints.

CH: It's been pretty exciting since I've joined Precision and use the opportunities that we've found surrounding those critical cells – the phenotypes and functionalities that you want. In addition to the ability to knock out the TCR (T cell receptor) and knock a CAR (chimeric antigen receptor) in its place, we can also modify those cells through gene knockout or knockdown of receptors that inhibit T cell function.

We can apply this idea to many potential secondary resistance mechanisms. For instance, if we know that a tumor is likely to be resistant to T-cell killing due to expression of TGF-beta, we could knock down the TGF-beta receptor in that T cell. Once we have the right target antigens, we need to understand that microenvironment well enough to know that for this given indication, we're going to have to make these modifications to the cells in order to make them work properly.

There are other ways around this. Those include essentially inhibiting these pathways. The alternative would be an off-the-shelf molecule targeting that pathway when relevant based on a tumor biopsy and reliable assay. When we think about personalizing immunotherapies in the future, those are the solutions we're going to have to understand well. We're not going to be able to treat every patient with every combination. We'll need to know who has what mechanism that needs to be targeted.
