Immuno-Oncology Panel Discussion:
Part 2 - Paying for Outcomes and Only Outcomes

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

Kineticos: The first part of our discussion focused on the evolution of cancer treatment, as well as what we all believed to be the next step change in Immuno-Oncology. Now, let's cast our attention toward patient access. It's one thing to have a lifesaving therapy on the market; it's another for patients to be able to afford it. Alex, hearing your background and thinking about Erytech's approach to addressing pancreatic cancer, what are your thoughts on patient accessibility to some of these new and very costly therapeutics?

AD: It's a huge challenge when we talk about historical cell therapy. The concept of allogeneic source material certainly simplifies one step of the equation to the extent that it's doable. This is the case with Erytech's red blood cell source material for our therapeutic candidates - it is allogeneic, or "off the shelf" homologous erythrocytes matched to the phenotype of the individual patient. In some cases, it really can't be simplified, so we have to make autologous more doable. When I was with Argos Therapeutics, one way we dealt with it was, unlike the CAR-Ts or even PROVENGE (Dendreon) to some extent, we didn't make the patient sit for multiple apheresis draws for each dose. We had one sitting for leukapheresis where we could get enough monocytes for multiple doses that could be cryo-preserved and cryo-shipped. If you can get to a multiple-dose model where the patient only goes through one sitting, it certainly would make their lives easier.

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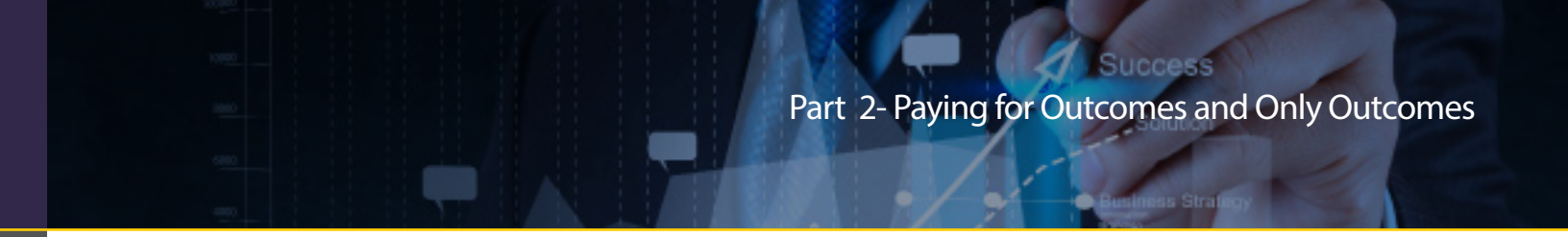
Kineticos: Does that come with a guarantee of effectiveness, you only pay (or get reimbursed) if the patient responds? Are we moving towards those kinds of outcomes-based reimbursement models?

AD: I've always been interested in responder / non-responder analyses and all too often in statistics, and especially medical statistics, we often talk about measures of central tendency and report as average differences with our means and medians. To me, we are finally starting to recognize that there's a distribution of response in and around those medians. Understanding who responds and who doesn't is key. There is a little tension there if you then flip to a completely biomarker driven assessment where you have MSI-high or say, "The responders of this intervention are the 3% of responders that have this characteristic." Then, from a commercial perspective, you are saying that 97% of the market is gone.

I actually think that is a healthy dynamic for individualized therapy because, really, that's how medicine is practiced. If people do this well, it gets approved, and on average, you see this response. That said, there are a lot of people that are paying for non-response. I think [paying for response] is absolutely the right way to go, but you have to reazlize that would come with tension from a commercialization perspective of narrowing the market. You also don't want to be disingenuous and give patients something that they're not going to respond to.



Finally, to reference Argos again, it was really individualized. We pulled the patients' cell(s) in the leukapheresis to get the monocytes to differentiate to dendritic cells. We actually started in kidney cancer. With nephrectomy being the standard of care, we had tumor tissue to start from and we made the personalized vaccine based on the specific tissue of their specific tumor. I also think this concept of neo-antigens that are unique to the patient will be more useful. It's not a guarantee by any means, but it's a more likely hypothesis that they're going to respond better to a therapy that's made specifically for their tumor mutations, rather than off-the-shelf tumor associated antigens or other shared antigens.

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JK: The fundamental issue in making these novel and breakthrough therapies affordable for patients is the way we price. During my career, I've launched 8 drugs into the US and the ex-US markets, and when companies do their pricing analyses, very few of them take into account what Alex referenced – tagging price to response. I suspect anyone else who has worked in big pharma had similar experiences. However, the health authorities are getting wise and Novartis is a perfect example. For their CAR-T, they basically said that if you get the response based upon the literature, you pay full price; if you don't, you pay a deeply discounted price. That is the model that will drive patient access more uniformly.

Kineticos: There are examples of these types of models being considered right now. A short time ago, at JP Morgan, the CEO of Bluebird Bio floated the idea of installment payments for a gene therapy that can potentially carry a 7-figure price tag. While that manages the flow of money or invoicing over time, does it really take the heat out of the system?

JK: The critical thing here is that we're currently, with most drugs in oncology, paying for Progression-Free Survival (PFS). If we would pay for Overall Survival (OS), where you have a more meaningful and tangible benefit, then the price point makes a difference. Right now, we're paying for a PFS improvement of 6 months. In some cancers like pancreatic, that's a lot, but the goal should be to see much more tangible life extension. If you get the cure, yes, you should get the big dollars. If you add 3-5 months of poor quality life, I'm sorry, that's not worth it, no matter what the cancer is. If you set pricing based on OS, then you deserve it because then you've done the right due diligence with your therapies and you've proven it beyond what Alex said - it's not just medians. When you use OS, you will have actually made a difference because you're using the reference points of chemotherapy that didn't do all that good PFS. That's what the healthcare system has gotten used to paying for. I personally think we have to change our governor.

Kineticos: You're right, Jeff. Historically, OS endpoints are typically secondary endpoints in clinical trials, not primary. Chris, I've been trying to get you in here, so I'll give you a moment to add your perspective.

CH: My take on this particular subject might be a bit more nihilistic, but I think we work in an industry where the incentives are upside down if we ever want to see costs go down. There is really no market factor that drives costs down and there's no historical precedent which I'm aware of, demonstrating that undercutting the cost of a (competitive) therapy is good business model. In my opinion, if we want, as a society and particularly as a country, to see drug prices get under control, there's going to have to be some form of intervention that comes from outside of our industry. That's either going to have to be a payer system that has more control over negotiating prices based on metrics such as overall

survival, clinical relevance, and quality of life; or, there is going to have to be regulation of some sort put in place. I don't believe that such regulations will ever pass any legislative approval, so I think it's going to have to be a payer system that makes more sense. Frankly, I don't know when and how that happens.

With all that said, if we are just talking about things that we could do as an industry to see cost get under better control, we realistically need to think about interventions that don't just achieve regulatory approval but solve a lot of the complexity of the problems that we create when we get new drugs approved. For example, if we have a drug that only works in combination with 4 other drugs, maybe we need to think about a better drug, or maybe we need to think about an intervention that can stand on its own. I haven't been in this business nearly as long as the others on this panel, but I treated patients directly for a while and saw the financial toxicity that they dealt with. I personally don't see the motivation anywhere in this industry to result in a paradigm shift.

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AD: Chris, do you think that some of the European regions have a better system than we do in the US? Is that the type of direction you're arguing for?

CH: I wouldn't say exactly how they do it but having a central body that can put the relative value of an agent compared to others into context is a very powerful tool. I believe it would make us all hold ourselves to higher standards when designing clinical trials and deciding to move a drug from pre-clinical to clinical settings. As it is today, we always know there is a fallback, and because the US is the biggest market and there is a relatively the low threshold for reimbursement, the dynamic of the incentives is upside down. Using NICE as an example, if the UK were the only market out there, I guarantee there would be far less drugs getting into phase 3 trials than there are today. Furthermore, the design of those phase 3 programs would be under much more scrutiny than what we have in the US.

Kineticos: In wrapping up this installment, it is clear that patient access is a challenge when thinking about some of these newer and more costly therapies. We still have a long way to go, but at least there are a number of different programs and schemes designed to combat this issue that are currently being tested in the marketplace. While all are aimed at fostering near-term access for patients, and making those therapies more palatable to insurers, it remains to be seen which will gain the most traction. I speculate those schemes emphasizing patient response and some indemnity against treatment resistance will be most attractive to formulary and reimbursement committees.

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