Bridges and Barriers to Advancing CAR-T Therapy Part 2

Kineticos: We used the metaphor of an hourglass and viewing our journey as being at a pinch point in terms of patient populations. Let's now discuss the potential for moving through that pinch point in the hourglass by using new tools and understandings to treat broad segments of patient populations. In other words, precision medicine for all patients.

Over the past decade or so, we have been learning about these types of advances that help us identify more specific and appropriate patient populations. What are some of the insights or learnings that would help us get out of the narrow point in the hourglass? If you were starting a clinical program today, what would the requirements be for starting a basket trial that includes hematological, as well as solid tumors?

JS: You must look for common or overlapping biological pathway errors, mutations, or deficiencies. What are those things that, from an individual protein or protein target perspective, we can go after, like BRAF or MEK? Where have we not confined ourselves to a single solid tumor or even solid tumors in general? Another opportunity is to look at targets where the error is systematic. For example, re-regulating the immune thermostat after cancer disrupts it. The role of our therapeutics is to fix the dysregulation caused by cancer; here, a single therapeutic or therapeutic class can be used for multiple tumor types.

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One other opportunity is to take what we often think of as small opportunities and expand them across multiple tumor types, by lumping together common pathway errors. For example, the utility of checkpoint inhibitors, specifically pembrolizumab in microsatellite instability high tumors, has shown us that rather than attack a very small population of patients in one tumor type, we can treat multiple small populations across almost all tumor types. This approach broadens the opportunity because the target applies to multiple tumor types. It might be that PARP inhibitors are similar, when we look at DNA mismatch repair, for example. I would look for those types of events, where you can approach multiple tumor types through the same basic mechanism of action.

Kineticos: That is exactly what I was thinking about – do PARP inhibitors, and what we are starting to understand about the clinical impact, start to move us down the path? We have seen indications of a biological basis for approval from the FDA, but not as a prospectively defined target as of yet. It happens retrospectively. The product comes out for an established tumor type with a specific characteristic, then another, and then perhaps the label will expand. Certainly, it feels like it is headed in the direction where, at some point, it's going to be for something like all MSI disease.

JS: As a pediatric oncologist, I was used to waiting for new drugs to first make it through the adult testing space before being introduced to children with cancer. However, with respect to basket trials, pediatric oncology is in the forefront. For some tumor types, there are so few patients that the approach of molecularlybased basket trials is a great way to bring new agents into the space. The BRAF-MEK pathway is a great example.cytotoxic chemotherapies may affect different types of cancer cells differently, and there are going to be certain cancer types that will be more sensitive to chemotherapeutics or radiation therapy, for example.

Kineticos: All the way up and down MAP kinase in whatever combination? Is that what you're saying here?

JS: Exactly. You could find 5 different diseases and end up with a label for disruption of that particular axis, rather than for the individual disease with this or that individual grade and stage, between ages of X and Y.

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JS (Cont): It is much smarter to say, "Let's be scientifically robust and logical about this, and we are going to pull everybody into one study with a particular mutation." It might be that one or more of those diseases, or sub-types of cancer falls out because the pathway wasn't that important or because there is a back door that the tumor cell manages to find and evade up-front assault. That's OK; you are still asking the question across multiple tumor types with the same type of pathway, which is why I feel like there is no need to always separate drug development into hematological vs. solid tumors.

Kineticos: That's an optimistic view going forward and we've hit on a couple of different ways to take newer assets forward or design new programs. It's rather encouraging, and I didn't think, coming into this, that I would hear such an optimistic view. On the other hand, are there things that you have observed that make you skeptical?

JS: Historically, the evidence has been against co-development. Outside of checkpoint inhibition, it has been hard to co-develop solid with hematological malignancies. This is because efficacy measurements are different, and the toxicity profile may be specific to each type of cancer. The toxicity profile in hematological malignancies vs. solid tumors can be very different. We know that patients with AML are overwhelmed with infections. Is that as true with lung cancer patients? Perhaps not to the same extent.

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A large part of development is defining in whom will this new modality work and what does the risk or toxicity profile look like? The broader the population, the less specific the individual patients may be, the harder it will be to define exactly what those benefit-risk profiles will look like. The CAR T experience has been disheartening for solid tumor drug developers because they expected success based upon what we have seen in the hematological malignancy space, and that has not been the case because the biology is clearly different.

There is also a practical piece on how to run a study that looks at multiple types of tumors or different types of tumors, specifically hematological and solid malignancies? We are used to solid tumor Phase 1 studies, where we look at multiple types of solid tumors in the same study. However, once you try to introduce leukemia or lymphoma into that study, there is no longer agreement. This is because efficacy cannot be assessed the same way across different tumor types, nor can toxicity. However, we can address this by looking at efficacy endpoints individually among specific tumors. For example, with solid tumors we use RECIST assessments. In hematological malignancies, we cannot use RECIST so we have to think about a different way to look at response, and it can become confusing to look at multiple different endpoints in a single study. My sense is that it is doable. It is more effort, but it is doable.

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Kineticos: Thinking about checkpoint inhibitors and other immuno-therapeutics, in the last 5 years or so, we have been at this inflection point in oncology. As great as these advancements have been, even with very well defined and small populations, we're seeing only seeing 20-30% response rates. In your view, what gets you excited and intrigues you regarding our next potential inflection point? What do those therapies look like?

JS: We are not close to done with immunotherapy. We are still learning how to appropriately manipulate the human immune system. Arguably, we are all, every day, developing cancer cells and not all of us are clinically manifesting disease. Most of us get through the average day without generating a living malignant cell. There is a reason why CTLA-4 and PD-L1 have been heralded as huge opportunities in therapeutics. We are just beginning to understand how to manipulate that axis and to combine these particular agents. The new class of immuno-modulatory anticancer agents, whether those be antibody drug conjugates, vaccines as a class, certainly CAR T, or ex-vivo manipulation-based activities; all of that in combination with immuno-modulation is extremely promising.

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JS (Cont): To me, there is nothing more interesting, fascinating, or scary than CRISPR. We are now finally living science fiction. We can manipulate individual cells to express whatever we want them to express, almost. We are at a place where if we can turn on and off the expression of individual proteins, whether that is going to carry through from our I/O space and we are going to activate the immune system in more efficient ways or literally go in and shut down individual cancer promoting proteins or expression-based pathways is unclear. CRISPR is the future and we need to figure out how to do it responsibly and effectively.

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Kineticos: It is at the same time fantastical and scary to think about a tool with the ability to design a genotype to express a specific phenotype. To actually have a tool to edit the genome is incredible, and if you think about the news coming out of China about the designer baby, it should send a shiver up your spine. The scary part is, using this tool on germ-line cells force you to ask what other characteristics would that generationally pass along? It could be a good thing if done responsibly but can have real, transformational, and permanent consequences. At a scientific conference recently, a speaker concluded on gene editing "keep in mind when you change the genotype, you change the species".That is a profound cautionary statement for that avenue of research.

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