Bridges and Barriers to Advancing CAR T Therapy

Moderator

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Fireside Participant

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Kineticos: Thanks for being with us today and sharing your perspective on our topic. Given your experience, and what you have seen in some development programs, what do you see as the evidence that supports co-development programs in both solid and hematological tumors?

JS: The strongest rationale to think about co-development programs in hematological malignancies and solid tumors would be the revolution we have seen over the last decade or two really focusing on targeted therapies. Where we once were generic in our approach to treating particular cancers and sub-types of cancers with a nonspecific cytotoxic chemotherapeutic agents, we are no longer that specific with the way we approach our therapies. We know that different 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.

In the past we have ironically focused our "nontargeted" chemotherapeutic/radiation therapies on specific, sensitive cancers. We tended to develop those individual agents in one specific disease, defined by a histological, rather than molecular, pathology. From a regulatory perspective, it had been easier to think about where we can approve drugs, not based on mechanism of action but based upon a disease subtype. However, most recently, we are seeing that it is mechanism of action-based therapeutics that are making a difference. Whether that is from targeted tyrosine kinase inhibitors, where we can look at a particular pathway that is disrupted across multiple tumor types, or most recently with the immuno-therapy revolution, where we can target different tumor types if they have the same pathway abnormality or if they would benefit from either adding to or disrupting basic immune mechanisms of the body. This allows us to look at several, very different, tumor types that we would not necessarily look at in the same clinical study, such as a hematological malignancy and a solid tumor, as long as the molecular pathology overlaps.

Kineticos: Historically, hematological malignancies and solid tumors have been viewed as completely different classifications and there was a higher standard to take a new approach or molecular entity into one or the other tumor type. This is an hourglass type of journey. We started at the wide end of this hour glass, a wide range and number of patients were available for treatment. As we start to understand the biological basis and defining characteristics of disease and pathways irrespective of the location of the tumor in the body, that has tended to narrow the patient population down. As it narrows down, you come

into the narrow part of the hourglass with the expectation that there is higher efficacy or greater benefits to the patient. While we see some benefits to smaller groups of patients, does that feel like it is adding to or taking away from our ability to effectively treat patients?

JS: It is interesting that you use "hourglass" as opposed to "funnel," because a funnel is unidirectional; things moving through to the narrow end, never getting wider, whereas with an hourglass, the glass can be turned, allowing a broadening rather than just a narrowing. I wonder, as we continue to understand more on the molecular pathogenesis of cancer across multiple tumor types, if we will ever end up "flipping the hourglass" to broaden our disease sub-populations, instead of continuing to narrow them.

By using sub-populations in which we are currently investigating new drugs, we believe the efficacy of new drugs will simply be better. We drill down into very specific molecular subtyping, mutational analyses, or mechanisms of action because it is assumed that the benefit is specific to that specific molecular sub-type, mutation, or gene signature. The justification for exposing a patient with the subsequent risks of that toxicity, or even better, avoiding the exposure of that therapy to someone who will not benefit from it, is helped by this sub-classification of different molecule sub-types. Even though we get into smaller and smaller sized populations, we can now successfully develop novel agents in those populations because the efficacy is better.

The question of 'In whom will this drug be the most helpful for the longest period of time,' is what oncologists should ask when they see patients in the clinic. When you look at the standard checkpoint inhibitors, whether they are PD1, PD-L1, or CTLA-4 inhibitors, we know that, overall, only 20% of patients will receive clinical benefit in the form of an objective response. This means that for the majority of patients, we are doing nothing for them. We should not tolerate the chance of "no benefit" if you are getting a conventional chemotherapy or being forced to receive radiation every day for 6 weeks. Yet for the checkpoint inhibitors, we allow it because there is a real, durable, long-term benefit for many of those 20% of patients. We want to get to a place where we can identify the 20% of patients that will respond to a checkpoint inhibitor, or the 80% that will not and offer them something in addition, something novel that will increase their chances of responding. If we cannot do that, then we must be able to identify the small population of patients that will benefit from the therapy, and limit the exposure of that drug to only that population. This is one way we can improve upon our ability to manage the benefit-risk balancing act for our patients.

Kineticos: Your example of the checkpoint inhibitors really illustrates the point of the question. When you have a group of patients who molecular qualify for a checkpoint inhibitor, but only a few respond, that becomes the frustrating part. You are in the narrow part of the hourglass and the aspiration is how do we get to the other side of this bottleneck so that we can open up, find that ubiquitous key, pathway, or target receptor that enables us to prescribe with confidence so that the entire cohort will respond in a clinically meaningful way.

We talked about the benefits of being able to better target patients and go beyond the broad chemo/radiation/surgical approach. What about toxicology tradeoffs? Where do you think we are on this journey? While we see greater gains in efficacy for identifiable sub-populations, does that come with a commensurate risk?

JS: Yes, it can, specifically when your agent is targeting something that turns out to be important for vital life functions, organs, or tissue, but is coincidentally being expressed in your tumor, like HER2. We know HER2 is expressed in cardiac tissue, and we are looking at HER2positive disease with a targeted treatment modality that also runs the risk of a specific, target-directed toxicity. If we look back at our core question, can you develop new molecules and therapies for both solid tumors and hematological malignancies simultaneously. We know it's possible with checkpoint inhibitors. You can treat Hodgkin's Lymphoma patients with PD-1 inhibitors, and see a remarkable response rate and, arguably, an improvement in progression free and overall survival. You can also treat a solid tumor like non-small cell lung cancer with the same drug. The downside is that the toxicity seen with checkpoint inhibitors may be additive with the toxicities already seen secondary to, for example, a B cell malignancy like Hodgkin's disease. To date, toxicities in Hodgkin's disease to checkpoint inhibition have been similar to that seen in solid tumors, but over time we may see newer toxicities or dysregulation in the immune system specific to these patients.

We always have to pay attention to what the novel agent or drug is doing. How does the cancer arise in the first place? Are those two things synergistic? Is there a reason to think the modality, the target itself, is going to be important in manifesting a toxicity? In the general cancer population, receiving a checkpoint inhibitor is thought to be easier than receiving a conventional cytotoxic. Toxicities like nausea, alopecia, mucositis are less likely, but the incidence of autoimmune disease like encephalitis, pneumonitis, kidney injury, and hepatitis are higher. Is there a specific patient population at risk for these events? Is there a specific tumor type at risk? We do not know yet.

Kineticos: I am reminded of the CAR T therapies, and while we see remarkable outcomes with B cell lymphomas. Certainly, some patients respond exceedingly well but what happens to otherwise healthy individuals with permanent B cell dysplasia?

JS: CAR T therapy is a fascinating new therapeutic modality that is changing and saving the lives of patients. When you are seeing patients, who have had evidence of residual disease after initial therapy, historically these patients do not live long. Patients have not been able to be "rescued" when progressing after first- or second-line therapy, for example in the adult leukemia population. To see 60% or 70% of patients who have been unresponsive to chemotherapy, and who respond with no evidence of disease following CAR T therapy, that is indeed miraculous.

As we have gotten more comfortable and have started to see more programs for hematological malignancies with CAR T, there are studies out there researching CAR T therapy in solid malignancies. In general, these studies have been less positive clinically than the hematological malignancy CAR T therapy programs, and this gets to the mechanism of action.

It is easier to target cells that are floating through your blood stream or sitting in lymph nodes, waiting to head out to the periphery, with an antibody-based therapy or a engineered T cell-based therapy, whether it's a CAR T, a bi-specific T cell engager (BiTE), or an antibody drug conjugate (ADC), versus a solid bulk of tumor sitting in a compartment that is just not as accessible. It is also notable that CAR T cells are designed to attack specific cell-surface targets that, for example in leukemia, define their mechanism of action and specifically hone in on the offending cancer cell. Whereas, you can target a CD19-positive B tumor cell for hematological malignancies, it has proven harder to do that for a solid tumor. While some

cancer antigens are similarly co-expressed on normal tissue, as we discussed earlier with HER2, generally speaking, if you are expressing a cancer antigen, you can go after it.

It also turns out that you cannot obliterate whole organs the way you can the B cell compartment; we can return your B cell compartment to you, but it is harder to return normal epithelial tissue to you and is thus harder to do if you are looking at epithelial proteins that are expressed on a majority of normal tissue. Thus, co-development in the CAR T space in hematological malignancies and solid tumors at the same pace has been particularly challenging.

Kineticos: While there has been great progress in translating newfound understanding of the basis of disease into clinically meaningful medicines, it seems we have entered the narrow part of the hour glass. Certainly, there are reasons to celebrate in terms of achieving better outcomes. Yet, much more work remains as we focus on developing ways for broader patient populations to benefit from these discoveries.

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.

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 molecularly based basket trials is a great way to bring new agents into the space. The BRAF-MEK pathway is a great 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. 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.

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.

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.

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.

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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