Taking CAR-T Therapy to the Next Level

Moderator
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Panelists
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Kineticos: We touched on this a little when we were talking about pricing but related to our overall topic of autologous vs. allogeneic approaches, what are the advantages and disadvantages of each approach?

AG: At the basic level of autologous, the advantage is that you don't have an issue of injected cells being rejected by the human body because you're using the same antigens. The allogeneic approach has a manufacturing advantage in that you can essentially make one batch of cells that are now injected into any patient. With the allogeneic approach, we still have to see how effective those T-cells can be. Certainly, autologous has demonstrated effectiveness, but allogeneic approaches are really entering the scene right now. Many technologies are being used to make allogeneic cells tolerable to prevent rejection but we have yet to see where the industry is going on the allogeneic side. We do know that there is a tremendous amount of money being invested so one would think if there's an answer, we will find it.

BF: Autologous is a great approach to give us a foothold in understanding the immune system, and it does give us some distinct advantages. Allogeneic approaches have a lot of appeal by not having to HLA-match, manipulate cells, find better ways to expand delta-gamma platforms, or doing cord blood. There could be a dramatic cost-reduction in a variety of platforms that are available, but this approach certainly could pose some issues. Specifically, I don't know if we really understand the degree of risk in regards to immunogenicity when administering multiple doses of allogeneic cells. It's a topic that's been under-addressed as we're going headstrong into this area, and I'm very concerned about patient's immunogenic responses when they receive three or four rounds of therapy.

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MC: I agree with what you both said - allogeneic is sexier. It has great potential to be the future, and it would be great if we can solve it.

AG: One approach that is starting to emerge is autologous CAR-T with allogeneic stem cell transplant. Carl June presented at a CAR-T conference recently and it was related to this whole idea of combining the approaches for the ultimate curative therapy. We're at the beginning of the revolution.

Kineticos: Assuming we will have an autologous approach, an allogeneic approach, and maybe even hybrid approaches, will these three be separate approaches to separate disease states, or is one going to end up dominating? Is it going to be replacement, or will it be different approaches for different patients and different diseases?

AG: The latter based on the extreme complexity of the science of cell therapies. They will coexist and the treatment paradigm will be different for early stage patients vs. late stage patients. Autologous is currently only given after you fail many chemotherapies. We have yet to determine how to get to the earlier stages of treatment.

BF: Eventually, we are going to be able to move beyond transfecting cells and we're going to sample a patient, either blood, marrow, or both. Then, using external strips and stimulatory factors, transform this bolus of materials and then reinfuse this back into the patient, which is similar to what Dr. Rosenberg is doing at the NCI. That is where the ultimate future will come from. We will be able to address some aging in a variety of ways to convert our own bodies' cocktail, either by scavenging bad actors in that soup or re-stimulating other ones to present antigens or antibodies through transfection with external stimuli. That's ultimately what our goal will become.

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AG: One of the topics we have not talked about yet is the timeline for us getting into solid tumors? Those really big diseases haven't been tackled yet, and it's limited by many aspects in the autologous T-cell approach. It's the ability for these CAR-T cells to actually survive in a solid tumor micro-environment, which is more toxic than the blood cancers we are treating. The future is brightest if we can apply an approach like CAR-T in solid tumors with new targets because the blood cancer targets are present on almost all cells. The future lies in finding the right targets to approach in either an autologous or allogeneic approach that will apply to all cancers. Many companies are looking for that and I personally have worked on one target surviving, which is present on almost all tumor cells, on the surface.

BF: We presented data last year at SITC related to an anti-CEA CAR-T and doing regional infusion for treatment of stage 3 and stage 4 colorectal and pancreatic cancer patients. We were able to show significant reduction in metabolic response from applying this CAR-T on a regional basis. When we compared this to systemic dosing where we did not see a response, we saw a profound response by inducing and directly delivering it either into the liver or through the perineum in a four-quadrant approach. We are very encouraged and have approached the agency about doing a pivotal trial next. I'm still a little weary about using a combination and whether it is allogeneic or autologous has yet to be determined. Other than a checkpoint, using something like an onco-virus to heat up these dense tumors in efforts to make them accessible so the CAR-T's can go to work is a very attractive therapy that will be explored over the next 12-18 months.

MC: I view autologous vs. allogeneic as a secondary challenge in CAR-T. The real challenge is with solid tumors. Blood cancers, where we've seen CAR-T successes, are a much smaller proportion of cancers compared to solid tumors. We've taken an approach at Anixa with an ovarian cancer program we're working on now. We've found a specific target that is conserved to the ovary cells of adult women and in our mouse models, it appears to be working exceptionally well. We hope to be in the clinic soon so we can see how it works in humans. The challenge, that everybody knows, is finding a target that isn't present on necessary organ systems. That's really the key. Finding those targets that we can go after without causing any other damage. We're hopeful that we've found something, as many others are.

Kineticos: Michael, the issue of solid tumors is something we're very interested in as well.

Besides the work that you're doing at Anixa, what are some other companies doing in that space?

MC: There's actually quite a few. Bill, Sorrento is working on solid tumors as well aren't you? It seems like everybody is trying to do something with solid tumors.

BF: The CEA treatment that we published data on at SITC was solid liver and we're pretty confident that combining that with a variety of different agents, potentially an onco-virus and others, will give us some insight into what we have on our hands. I'm a little hesitant about checkpoints because all of the challenges that have happened with checkpoints in combination therapies.

Kineticos: Anil, what have you seen in terms of solid tumors that is interesting?

AG: I think there are many approaches. Part of the effort we have at MimiVax is actually getting ready for a pivotal Phase 2. We are starting with an immunogen that can stimulate T-cells and B-cells. We have generated tremendous data in phase 2 already in newly diagnosed glioblastoma patients. In the process of developing this immunogen, we discovered the target is also a cell surface antigen that nobody has discovered before. It is present in almost all cancers and not in normal cells. It's present at very high levels and it's a cell-cycle protein, so no tumor cell escapes from this cycle. We've developed antibodies against this, that we actually discovered in the humans first, that correlated with the response. That antibody has now been constructed into second-generation CAR-Ts and shows activity in both colon and breast cancer cellular models. Our goal is focused on our late stage pivotal program that we are looking to partner. We've had discussions with a few companies for this program and our focus is on who is going to put full effort in developing this across many cancers. We ourselves are not developing the CAR-T program, so are looking to bring in a partner who has the deeper expertise in CAR-T.

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