PRECISION ONCOLOGY NEWS

Acepodia's NK Cell Therapy Enters Human Studies in HER2 Expressing Solid Tumors

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NEW YORK – Based on the preliminary safety profile of its experimental natural killer (NK) cell therapy, clinical-stage biotech firm Acepodia recently decided to enroll between a dozen and two dozen more patients with HER2-expressing solid tumors in a Phase I trial.

Forty-five days after the first patient enrolled at MD Anderson Cancer Center received repeat doses of the off-the-shelf NK cell therapy, dubbed ACE1702, there haven't been any adverse events. Notably, there were no signs of serious toxicities that are caused by other cell therapies, such as graft versus host disease and cytokine release syndrome. Encouraged by this data, the San Francisco and Taiwan-based Acepodia is moving ahead with the clinical development of ACE1702, its lead product, hoping that it will prove to be not only safer but more effective and less costly than other cell treatments.

"Acepodia is focusing on next-generation cell therapies," said CEO Sonny Hsiao, who cofounded the company in 2017 with Patrick Yang, a drug manufacturing and engineering expert and former executive at Juno Therapeutics and Genentech.

Hsiao, while he was at the University of California, Berkeley, developed the core Antibody Cell Conjugation (ACC) technology that powers Acepodia's drug development efforts. The ACC platform can attach antibodies to live immune cells through chemical modification of cell surfaces. The company believes that the ACC platform, which avoids the costly genetic engineering necessary with currently approved, autologous CAR T-cell therapies, can enable it to develop off-the-shelf cell therapies that more efficiently and precisely home in on oncogenic targets on cancer cells.

Researchers at the company used the ACC platform to generate a proprietary NK cell line derived from 1 percent of the NK cell population, "with high expression of activation receptors and very low expression of inhibition receptors," explained Hsiao. "Not all NK cells are equal. Some are more potent than others."

In the case of ACE1702, these proprietary NK cells were conjugated to an antibody that Hsiao likened to a "tumor targeting warhead." These attached antibodies "super charge the NK cells … [so] they can recognize and kill the tumor cells," said Hsiao.

Specifically, ACE1702 is designed to home in on HER2 expression on cancer cells. The multi-cohort, Phase I trial will enroll up to 24 patients with immunohistochemistry-based HER2 expression scores of 2+ or 3+ — advanced or metastatic solid tumors with IHC scores of 2+ or above, breast or gastric cancers with IHC scores of 3+, and endometrial cancers with IHC scores of 2 + or above.

Typically, tumors with an IHC score of 0 or 1+ is considered HER2-negative, an IHC score of 2+ is considered to have moderate levels of HER2 expression, and an IHC score of 3+ is considered "HER2 positive" for the purposes of receiving HER2-directed antibody treatments, such as trastuzumab (Genentech's Herceptin), which is approved for breast and gastric cancers.

"Our therapy can apply to all the tumors that can express HER2," Hsiao said, adding that there is an urgent need for better options for endometrial cancer patients. "After first-line chemo, you don't have many options."

Globally, more than 1.4 million patients are diagnosed each year with a solid tumor that expresses HER2 at various levels. In breast cancer, between 20 percent and 30 percent of tumors have HER2 expression, while in endometrial cancer, up to 40 percent of tumors can express this biomarker. There are other tumors types, such as lung cancer, where HER2 expression rates tend to be lower.

In preclinical studies, ACE1702 has shown activity against low, moderate, and high HER2-expressing tumors. In the currently ongoing Phase I trial, since it is the first human study of ACE1702, Acepodia is starting conservatively by enrolling only those patients with IHC HER2 expression scores of 2+ and 3+. If the study shows the treatment to be efficacious in this subset of patients, Acepodia will consider enrolling patients with low HER2 expression (i.e. IHC score of 1+) in future studies of its cell therapy.

Although there are multiple HER2-directed antibody therapy options on the market, only a limited number of cancer patients have "durable" responses to these drugs. Most patients, after responding for a time, eventually relapse. One reason for this may be that HER2-targeted antibodies are eliminating cancer cell populations with high HER2 expression but not those with low expression. "With our treatment there is the potential to target a broader spectrum of these [HER2-expressing] tumors and a better chance to reach longer-term remission," Hsiao said.

Based on the data to date, Acepodia is optimistic that ACE1702 will be able to increase the number of patients with HER2-expressing cancers who won't experience cancer recurrence for a long time. In preclinical animal studies, ACE1702 appeared to kill tumor cells efficiently. "Not only did it kill tumor cells, but it also generated immune responses," Hsiao said. "It activated the immune system, so it could keep fighting these tumors."

The company is now attempting to translate these findings from animal studies into humans in the Phase I trial taking place at MD Anderson in Texas, Northwestern Memorial Hospital in Chicago, and Peninsula Cancer Institute in Newport News, Virginia. The trial is primarily focused on pinning down the safety profile and settling on a Phase Ib/II starting dose for ACE1702. Researchers will also measure the extent to which NK cells persist after the treatment is administered; assess serum cytokine levels to characterize immune function; evaluate tumor responses with radiographic measurements; and gauge tumor markers, such as CA-125, CA 19-9, and CEA levels.

Acepodia colleagues are certainly encouraged by the first HER2-expressing cancer patient's experience so far on ACE1702. Hsiao noted that the data to date suggests ACE1702 is much safer than CAR therapies, not having seen any graft host disease or neurotoxicity. Hsiao couldn't discuss any of the emerging efficacy data but is expecting the first readouts from the trial in the first half of 2021.

Meanwhile, the COVID-19 pandemic has slowed the entire cancer research community's ability to enroll patients in clinical trials, and Hsiao acknowledged that the ACE1702 program was also initially impacted. Now, enrollment is starting up at the three clinical sites in the US, where the necessary precautions are being taken to limit patients and healthcare workers' risk for exposure.

"The challenge during the pandemic is the amount of space that's available in the intensive care unit," because the patients who are severely ill from COVID-19 need to be on a ventilator, said Hsiao. However, unlike currently available autologous CAR T-cell therapies that need to be administered in the inpatient setting, Acepodia's NK cell therapy is being given to patients in the outpatient setting. And because the initial safety signals suggest that ACE1702 causes fewer toxicities than current CAR therapies, Hsiao anticipates there won't be the same concern with patients needing to go to the ICU due to treatment-related toxicities. "From that perspective, I think we'll be less affected by the pandemic," he said.

Acepodia's NK cell therapies also have anti-viral properties, and the company is engaged in early-stage research with hospital collaborators to see if these treatments can charge up the immune system to fight COVID-19. "NK cells are the first-line army in our immune system. Intrinsically, they kill viruses, pathogens, and cancer cells," Hsiao said.

"However, our current focus is in oncology," he stressed. "Even though we're in this pandemic, we still have cancer patients dying every day and they remain our priority."

The clinical trials involving ACE1702 will also allow Acepodia to test a central hypothesis that its treatment is not only more effective, but more cost-effective than CAR therapies. The list prices of current autologous CAR T-cell therapies are above $300,000, and the cost of care can exceed $1 million after factoring in inpatient hospital stays for some patients. Hsiao highlighted several advantages of its allogeneic NK cell therapies, such as faster drug delivery and less variability in cell potency, which can translate into cost savings for Acepodia and help lower the price of treatment.

With autologous CAR therapies, patients can wait several weeks for the immune cells to be engineered and prepared for infusion. After waiting more than a month in some cases, between 10 percent and 30 percent of patients still may end up not receiving treatment because of variability in the product.

"Autologous cell therapies have variation from batch to batch," Hsiao said. "With allogeneic, off-the-shelf therapies, the product quality is consistent because it's all from the same large batch of cells." Further, there is no lag time in treatment delivery with off-the-shelf cell treatments, and cancer patients can be treated soon after diagnosis without needing to be admitted to the hospital.

As ACE1702 advances through clinical trials, Acepodia is working on other off-the-shelf cell therapies in preclinical phases. ACE1708, for example, is an NK cell therapy that the company has designed to target PD-L1-expressing cancers. As with ACE1702, the company is encouraged to see in preclinical studies that ACE1708 can target cancer cells with high and low PD-L1 expression.

"ACE1702 is the frontrunner that will validate our platform and our proprietary NK cells," Hsiao said. "In the future, we have a pipeline of products to extend treatments beyond HER2-expressing cancers to more cancer patients who can benefit."