PRECISION ONCOLOGY NEWS

Precigen Testing Whether its Vaccine Can Raise T-Cell Army Against HPV-Positive Cancers

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NEW YORK – Biopharmaceutical company Precigen has begun enrolling patients in a Phase I/II clinical trial to explore the activity of its immunotherapy PRGN-2009 alone and in combination with bintrafusp alfa, Merck KGaA and GlaxoSmithKline's investigational bifunctional fusion protein immunotherapy, in human papillomavirus-positive solid tumors.

Precigen's PRGN-2009, an off-the-shelf investigational immunotherapy developed using the company's UltraVector and AdenoVerse platforms, stimulates the immune system to recognize and target HPV-positive tumors.

The US Food and Drug Administration accepted Precigen's investigational new drug application for PRGN-2009 in April allowing for the start of the Phase I/II trial being conducted at the National Institutes of Health's Clinical Center, a hospital dedicated to clinical research at the institutes' Bethesda, Maryland campus. The therapy is being developed through a Cooperative Research and Development Agreement with Jeffrey Schlom of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute's Center for Cancer Research.

"PRGN-2009 is based on our gorilla adenovirus vector that has been modified so it doesn't replicate in the cells like other viruses," Precigen President and CEO Helen Sabzevari said. "There is no or very little seropositivity in humans. That means you can give these drugs multiple times."

The biggest barrier with using viruses as a delivery mechanism, according to Sabzevari, has been that once they're given, they immediately trigger an immune response because the immune system has seen the majority of viruses before. By attacking the virus delivering the vaccine, the immune system limits its ability to direct immune cells to recognize and attack cancer cells instead.

Currently, she noted, adenoviruses that are commonly used — such as the human adenovirus 5, which utilizes the coxsackie-adenovirus receptor as its cellular receptor — can be injected into a patient a limited number of times, and sometimes only once, before inducing an adverse immune response.

By contrast, most humans have not been exposed to the gorilla adenovirus. "When you give it for the first time, the immune system doesn't have a previous memory to it," she explained.

Another advantage to using gorilla-derived adenovirus is its large payload. "We have identified a number of antigens that target both HPV16 and 18, plus some new epitopes," Sabzevari said. "[We have the space to] put not only the typical HPV epitopes that exist, but also in this case the ones that we have identified, and these have been engineered in the gorilla adenovirus platform."

The Phase I portion of the Precigen and NCI clinical trial will use a standard dose escalation model to evaluate the safety of PRGN-2009 administered as a monotherapy and to determine the recommended dose for the Phase II stage of the study. The first cohort of three patients will be treated at a starting dose considered to be safe based on preclinical data, and the subsequent cohort of three patients will be treated with a higher dose.

According to Clint Allen, a principal investigator in the NCI's Section on Translational Tumor Immunology and an investigator on the PRGN-2009 trial, the first cohort will consist of patients who have been diagnosed with recurrent or metastatic P16-positive primary-site agnostic cancers. These patients will all have failed first-line treatment for their metastatic disease.

P16 is a surrogate biomarker for determining whether a tumor is being driven by chronic HPV infection. In order to determine whether a newly diagnosed patient's head and neck cancer has been caused by smoking and drinking versus chronic HPV infection, a doctor would look for P16 expression in the tumor, Allen said.

P16 staining to differentiate HPV-driven from non-HPV-driven malignancies is now considered standard-of-care testing in the US, he added. Any CLIA-certified anatomic pathology laboratory would have a validated P16 immunohistochemistry assay to help a clinician make a diagnosis of whether a tumor is P16-positive or -negative.

PRGN-2009 includes antigens for both HPV16 and HPV18, which together cause more than 90 percent of all HPV-associated cancers, and both the Phase I and Phase II portions of the clinical trial will be enrolling patients with P16-positive tumors, Allen said. The third patient has already been enrolled into the trial for testing at the first dose level. There will likely be a brief pause between testing of dose level one and dose level two to make sure there are no adverse events during that time.

Once the Phase II dose of PRGN-2009 is established, the researchers are planning to evaluate the safety of PRGN-2009 alone and in combination with Merck KGaA and GSK's bintrafusp alfa. The companies began developing the investigational bifunctional fusion protein in early 2019 for the treatment of multiple difficult-to-treat cancers. The drug is designed to simultaneously target two immuno-suppressive pathways cancer cells commonly use to evade the immune system: transforming growth factor-β (TGF-β) and PD-L1.

In the Phase II portion of Precigen's study, PRGN-2009 monotherapy or the combined regimen will be given as a neoadjuvant or induction therapy to patients with newly diagnosed stage II/III HPV16-positive oropharyngeal cancer.

Sabzevari is hoping that PRGN-2009, once injected into a patient with P16-positive cancer, will act as a cancer vaccine that will awaken memory T cells that might already exist and, more importantly, train new T cells to recognize and fight the cancer cells that express various epitopes of the virus on their surfaces.

"It's like taking a very naive bunch of recruits and you specialize them as a force to recognize an enemy from within, which is these tumor cells that express these HPV epitopes," she said. "Once these armies train, as they circulate throughout the body and they hit the areas where you have the cancerous cells, they recognize these cancer cells and then they destroy them. The beauty of this system is that it uses your own immune system to battle the cancer."

According to Allen, the researchers will be able to gauge the success of this attack strategy by studying the peripheral blood of the patients from the Phase I portion of the study, as well as pre- and post-treatment tumor biopsies of the oropharyngeal cancer patients in the Phase II portion of the study.

"With a vaccine like this that's really designed to prime new or expand existing anti-HPV T-cell responses, we can query T cells from the peripheral blood before and after PRGN-2009 [administration] and actually determine if the vaccine is doing its job," Allen said. "In the Phase II portion, where we have biopsies from the tumor before and after vaccine, we can culture tumor-infiltrating lymphocytes from those tumor biopsies and actually determine with high accuracy in the T cells that are actually infiltrating the tumor whether we're inducing new or expanding existing anti-HPV T-cell responses."

He added that it would be a "very powerful validation of the vaccine itself" if the researchers are able to show the presence of antigen-specific T-cell responses in the tumor that correspond to the antigens in the vaccine.

The team is also looking forward to seeing how PRGN-2009 will interact with bintrafusp alfa. The Phase II portion of the trial does have an arm to study the effects of PRGN-2009 as a monotherapy, but Sabzevari and Allen both acknowledged that an ever-growing wealth of scientific evidence shows the power of combination therapies, particularly putting two immunotherapies together to block off different pathways cancer cells are using to proliferate.

The specific combination with bintrafusp alfa yielded promising results in preclinical studies, Sabzevari noted. When the two agents were combined, the researchers saw more efficacious tumor inhibition than from either agent alone. She speculated that the drugs might be complementary because bintrafusp alfa's mechanism of action is to not allow the T cell to become anergized or functionally incapacitated.

"But you still have to develop a good T-cell response in order to go to the next step," she added. "With PRGN-2009, we are creating this army of T cells to combat these HPV cancers. Our hypothesis is that when you add the anti-PD-L1 TGF-β trap, these are complementary because now you have the T cells that are sitting there and you have a molecule that doesn't allow them to become exhausted. And this is a good synergy."

Sabzevari noted, however, that while many cancer trials are exploring combination strategies, often drugs are being paired in a haphazard manner that likely won't benefit patients in the end. For example, she said, it's not enough to just look at the tumor, but the tumor microenvironment must also be analyzed. If the immune system is activated, steps must be taken to keep it from becoming anergized. And even if immune cells are kept active, there are cytokines in a tumor microenvironment, such as TGF-β, that can also inhibit the activity of T cells.

"You have to identify the factors that are prominent in tumor escape and then address those in a combinatorial fashion," she said. "The combination has to be based on the science of the indication and the tumor microenvironment … And this is why we decided that this would be the appropriate combination [with bintrafusp alfa] — we are creating our army, we

are taking the checkpoint inhibition off of it, and removing some of the cytokines that can stop it."

The researchers are hoping to finish enrollment for the dose escalation portion of the study by the end of 2020, and complete both phases in about two years. Allen anticipates being able to enroll two to three patients per month into the Phase II portion of the trial and is aiming to enroll 20 patients into each of the two arms.

Sabzevari also noted that the researchers are planning to analyze a number of biomarkers in each phase, specifically biomarkers for T-cell response that Precigen can then associate with patient outcomes, "and have a predictive biomarker in the future."