Studies show promise of immunotherapy combinations, including CAR T

April 17 2018

As immunotherapies continue to make up a larger share of new cancer drugs, researchers are looking for the most effective ways to use these cutting edge treatments in combination with each or with other pre-existing options. New studies from the Abramson Cancer Center of the University of Pennsylvania are providing fresh clues on potentially effective combinations with CAR T therapy in brain cancer as well as a novel therapeutic target in head and neck cancer, and also providing greater understanding of the mechanisms of resistance in pancreatic cancer. All three studies will be presented as late breaking abstracts at the American Association for Cancer Research Annual Meeting in Chicago.

Combining CAR T Therapy with Checkpoint Inhibitors in Glibolastoma

The first study combines CAR T cell therapy with immune checkpoint blockade inhibitors in glioblastoma - an aggressive form of brain cancer (Abstract LB-340). Researchers used two different types of CAR T cells. One was specifically engineered to bind to epidermal growth factor receptor variant three (EGFRvIII), a gene that is commonly mutated by glioblastoma. Another targeted a protein known as interleukin-13 receptor subunit alpha-2 (IL-13Rα2). Researchers combined a variety of checkpoint inhibitors and found CARs targeting EGFRvIII were five times more effective when paired with an anti-PD-1 treatment, while CARs targeting IL-13Rα2 were five times more effective when paired

with CTLA4 inhibitors.

"This not only shows that the combination of CAR T cells and checkpoint inhibitors can have an enhanced effect compared to what either can do alone, it also shows some combinations work better than others, and that a more personalized evaluation of each tumor may result in more effective therapy," said the study's lead author Zev A. Binder, MD, PhD, a senior research investigator in Neurosurgery at Penn. Donald M. O'Rourke, MD, the John Templeton, Jr., M.D. Associate Professor in Neurosurgery at Penn, was the senior author.

The authors say this study lays the groundwork for a better understand of CAR T combination therapy in glioblastoma, which is a concept they plan to continue to advance. They also say the IL-13Rα2 CARs may have other implications since that protein is also expressed in dogs. They've partnered with researchers at the University of Pennsylvania School of Veterinary Medicine, and studies in canine patients are already in progress.

The study was partially supported by Tmunity, the Templeton Family Initiative in Neuro-Oncology, and the Maria and Gabriele Troiano Brain Cancer Immunotherapy Fund.

Finding Checkpoints to Target Outside of PD-1/PDL-1 in Head and Neck Cancer

Penn researchers are also at the forefront of another approach to combination immunotherapies that involves exploiting immune checkpoints beyond PD-1/PDL-1 - in this case, in the treatment of advanced head and neck cancer (Abstract CT158). This international, multisite trial evaluated the drug monalizumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

Monalizumab targets an immune checkpoint called CD94/NKG2A that is distinct from the better-known PD-1/PDL-1 system. Inhibition of this checkpoint with monalizumab frees up T cells and Natural Killer (NK) cells to fight off cancer.

This trial combined monalizumab with cetuximab - a drug approved by the U.S. Food and Drug Administration for the treatment of patients with advanced head and neck cancer. Cetuximab is thought to work, in part, by activating NK cells. This study found the combination of these two drugs has more anti-tumor activity together than cetuximab given by itself. Of the 26 patients evaluable on this trial so far, eight had a partial response and 14 had stable disease. Monalizumab was generally well-tolerated, although one patient did stop treatment due to side effects. The trial is ongoing.

"The data so far show that this therapy is active in head and neck cancer, and since monalizumab targets a checkpoint that is different from other inhibitors that are currently available, it's an interesting option as a combination partner for a variety of novel immunotherapeutic approaches," said the trial's principal investigator Roger B. Cohen, MD, a professor of Hematology-Oncology at Penn and Associate Director of Clinical Research in the Abramson Cancer Center.

The trial is supported by Innate Pharma, which manufactures monalizumab.

Translating Early Results Into Future Research in Pancreatic Cancer

Another key to immunotherapies is understanding how cancer is able to fight these therapies off, and a Penn-led trial sheds light on that question in pancreatic cancer (Abstract CT085). The study involved two groups

of patients, both of which received a combination of chemotherapy drugs. One group also got a drug called hydroxychloroquine (HCQ) to block a process called autophagy - a built-in resistance mechanism which allows cells to survive when under attack by breaking down unneeded parts and recycling them to stay alive.

Twenty-one of the 46 patients that got the autophagy blocker showed a partial response (46 percent), compared to just eight out of 48 (17 percent) who didn't get HCQ. However, overall survival at one year was slightly lower in the HCQ group (41 percent) than for the group that only got chemotherapy (51 percent).

"While the trial did not reach its overall goal of prolonged survival, HCQ did improve the response rate, which may mean we can harness this therapy in a different setting, perhaps in patients with locally advanced disease in hopes of getting them to a point where we can surgically remove the tumor after initial chemotherapy," said the study's lead author Thomas B Karasic, MD, an Instructor of Hematology-Oncology at Penn. Peter J. O'Dwyer, MD, a professor of Hematology Oncology and director of the Developmental Therapeutics Program in the Abramson Cancer Center, was the study's senior author.

The authors say they benefitted from Penn's ability to accrue patients for large scale clinical trials like this one, which they believe to be the largest trial ever to evaluate autophagy inhibition. They say that helps provide insights into future therapeutic possibilities.

"If we understand the mechanism of why this didn't extend survival despite the improvement in response, it may be able to help us guide the development of future trials and the use of this therapy in other cancers," Karasic said.