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AACR 24: Freezing, of all things, is one way to heat cold tumors

By Anette Breindl, Senior Science Editor

"Hot and cold tumors may need different types of immunotherapy," Jay Berzofsky told the audience as the American Association for Cancer Research's (AACR) 2024 annual meeting kicked off this weekend.

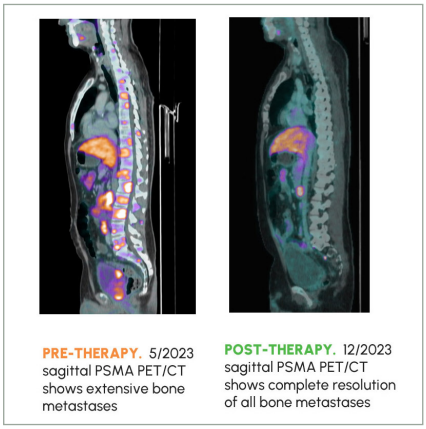
In an educational session on cancer vaccines, Berzofsky, who is head of the National Cancer Institute's Molecular Immunogenetics and Vaccine Research section, explained that when immunotherapy fails in hot tumors, it fails despite the existence of an immune response, due to an immunosuppressive microenvironment. When it fails in cold tumors, it fails because there is no immune response in the first place.

"Vaccines might be able to induce responses in cold tumors," Berzofsky said, which could then be boosted with existing immunotherapies, in particular checkpoint inhibitors.

In an April 7 session on cancer vaccines, two of the more remarkable presentations showed early clinical successes in metastatic castration-resistant prostate cancer (mCRPC) and pancreatic cancer, respectively. Both are tumor types where immune oncology approaches have not made much headway.

Icy hot tumors

Charles Link, executive chairman of Syncromune Inc., presented data from a phase I trial testing SYNC-T, which uses a combination of multiple approaches to induce an immune response, and then boost that response, in men with mCRPC.



Resolution of bone marrow metastases after SYNC-T treatment. Courtesy of Syncromune Inc.

In SYNC-T, ultrasound-guided cryoablation is first used to freeze a ball of tumor that is roughly 1 cm in diameter, killing the tumor cells. As the "ice ball" thaws out, 15 ml of SV-102 is infused into the lesion. SV-102 is a four-part cocktail consisting of checkpoint blockers targeting CTLA-4 and PD-1, a CD40 agonist, and a TLR9 agonist.

After freezing, the frozen and then thawed part of the tumor still sits within an intact system of blood and lymph vessels, which enables the treatment-induced immune reactions to spread beyond the tumor site.

The locoregional approach, Link told *BioWorld*, means that much lower doses of checkpoint blockers are necessary than during systemic infusions – about 10% to 20% of a typical systemic dose. In systemic treatments with only one checkpoint blocker, overall response rates (ORR) in mCRPC are very low – on the order of 3% to 5%. Combining CTLA-4 and PD-1 blockade, on the other hand, causes adverse events to skyrocket, with grade 3 and 4 adverse event rates exceeding 50%, while ORRs are still typically 25% or lower.

At the meeting, Link, who is the primary investigator of the trial, presented data from 13 evaluable patients, who showed an ORR of 85% in the absence of any grade 3 or 4 autoimmune adverse events. Remarkably, seven of the 13 patients experienced complete resolution of their bone metastases. Patients were treated every four weeks, in each case in the most active soft tissue lesion at the time of treatment. "It's our belief that regardless of where you treat, if you treat active cancer you can be successful," Link said.

The trial is ongoing, with results expected in the second half of 2024. At present, Syncromune is expecting to continue clinical development with a phase II trial. Link said that the method is also applicable to other solid tumor types beyond prostate cancer.

"You can use it anywhere you can get a needle," Link said. "And that's basically anywhere these days."

Targeting passenger mutations

Directly preceding Link's presentation was that of Vinod Balachandran, who described phase I results of a pancreatic cancer vaccine being jointly developed by Roche AG subsidiary Genentech Inc. and Biontech SE.

Balachandran, who is a surgical oncologist and physician-scientist at the Memorial Sloan-Kettering Cancer Center's David M. Rubenstein Center for Pancreatic Cancer Research, presented data from a phase I trial of the personalized RNA vaccine autogene cevumeran, (BNT-122) in 16 patients. Autogene cevumeran is now in phase II.

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The therapy is a personalized vaccine consisting of 20 mRNA antigens stemming from patients' resected tumors. In the trials, patients are treated sequentially with checkpoint blocker Tecentriq (atezolizumab, Roche AG), autogene cevumeran, and chemotherapy.

Previously, Balachandran's team had reported that compared to eight nonresponders who failed to mount an immune response after vaccination, eight responders had delayed recurrence of their tumors. Median recurrence-free survival in the nonresponder group was 13.4 months, while in the responder group, median recurrence-free survival has not yet been reached after 3.2 years of follow-up.

Like mCRPC, pancreatic cancer has a very low response rate to checkpoint blockers by themselves. But rare long-term survivors mount an immune response to the tumor, prompting the attempt to induce such an immune response through vaccination.

The idea of using passenger mutations may at first be counterintuitive, as theoretically, tumors can get around approaches that target passenger mutations much more easily than those that target drivers. At his presentation, Balachandran said that "prior work from our work shows endogenous T-cell responses in long-term survivors targeted passenger mutations, not driver." And on a broader level, he added, "we think the selection strategy should be based on immunogenicity rather than prevalence. … The critical factor for vaccine success is having an immunogenic neoantigen."

Neoantigen selection, he added, "is a challenge for the field right now," with no clear rules yet about what makes specific neoantigens more or less immunogenic.

To date, two of the eight responders have relapsed; whether they were still expressing the target neoantigens at the time of their relapse is not yet clear. Balachandran noted, however, that the two had the weakest T-cell responses of the eight responders. The one responder who has died had the shortest lifespan of T cells, while the second recurrent patient had latest onset of a T-cell response.