Aiming TILs at Melanoma, Cervical Cancer

For patients with advanced melanoma or cervical cancer whose disease is refractory to standard treatment, tumor-infiltrating lymphocyte (TIL) therapy may merit a closer look, according to two ongoing multisite phase II trials. Findings were presented during the 2019 American Society of Clinical Oncology Annual Meeting in Chicago, IL, in June.

The studies, innovaTIL-01 and innovaTIL-04, are evaluating two autologous cell therapies—lifileucel/LN-144 and LN-145 (Iovance Biotherapeutics), respectively. Enrolled patients have a tumor lesion resected for TIL harvesting; the cells are then massively expanded in number at a central facility, aided by high amounts of IL2, as well as allostimulation with donor-derived irradiated feeder cells. After this 22-day process, the TILs are cryopreserved and can be infused at patients’ convenience, explained principal investigator Amod Sarnaik, MD, of Moffitt Cancer Center in Tampa, FL.

Unlike chimeric antigen receptor (CAR) T cells, “these TILs aren’t really manipulated in any way,” Sarnaik added. “The idea is that because they’ve previously trafficked into the tumor, hopefully they can do so again after in vitro expansion.”

Sarnaik reported results from 66 patients with advanced melanoma who had all relapsed on immune checkpoint blockade and, where appropriate, BRAF/MEK inhibitors (J Clin Oncol 37, 2019 [suppl; abstr 2518]). Nearly half (44%) also had brain or liver metastases. The objective response rate (ORR) to lifileucel was 38%, including two complete responses. Another 42% experienced stable disease, and the median duration of response (DOR) has not been reached.

“This is pretty much unmatched when compared with any other treatment we’ve seen for melanoma following progression on anti–PD-1 therapy,” Sarnaik observed.

Among 27 patients with metastatic cervical carcinoma refractory to the standard of care—chemotherapy, VEGF-targeted agents, and radiation—the ORR with LN-145 was 44.4%, including three complete responses (J Clin Oncol 37, 2019 [suppl; abstr 2538]). Stable disease was seen in another 40.7%, and the median DOR has not been reached.

“These are striking results so far,” said principal investigator Amir Jazaeri, MD, of The University of Texas MD Anderson Cancer Center in Houston. “We need longer follow-up to see how the DOR translates to progression-free survival, but I think this is pretty exciting for a difficult-to-treat population.”

In both studies, most toxicity issues were due to patients receiving preparatory regimens of lymphodepleting chemotherapy as well as six doses of IL2 to spur TIL growth in vivo. “There were some cases of febrile neutropenia and chills right after TIL infusion,” Sarnaik said; otherwise, lifileucel and LN-145 were well tolerated.

Ignacio Melero, MD, PhD, of Clínica Universidad de Navarra in Pamplona, Spain, suggested that in cases of melanoma progression after lifileucel, the investigators might want to consider re-treating these patients with checkpoint inhibitors. “It makes sense, because once TILs have been engrafted, the rules of the game could be different” in the tumor microenvironment, he said.

“A tumor’s immune responsiveness is certainly dynamic, and any therapeutic intervention could change it in some way,” agreed Tara Mitchell, MD, of the University of Pennsylvania in Philadelphia. Overall, lifileucel and LN-145 appear “really impressive,” she said, showing significant promise in solid tumors, where CAR T cells have been more disappointing than not.

“I think many clinicians are convinced that the efficacy is there” with TIL therapy, Mitchell added, but because its potential has so far been reported anecdotally, studies such as Iovance’s are “a big step forward in demonstrating that this technology is feasible and more broadly accessible.”

The innovaTIL-01 trial is enrolling 75 more patients to support lifileucel’s FDA registration. Meanwhile, LN-145 has received the agency’s fast track and breakthrough therapy designations, Jazaeri said, and “considering that pembrolizumab [Keytruda; Merck] was approved for PD-L1–positive cervical cancer based on an ORR of just 14%, I think our data, although early, could be registration-enabling.” —Alissa Poh

Mechanism of Cediranib–Olaparib Combo Revealed

The combination of olaparib (Lynparza; AstraZeneca) and cediranib (Recurrent; AstraZeneca) has shown promise in recurrent non–BRCA-mutant ovarian cancer, and a recent study offers a possible mechanistic explanation: Cediranib may confer sensitivity to olaparib by increasing tumor hypoxia and inhibiting platelet-derived growth factor receptor (PDGFR), which reduces BRCA1/2 and RAD51 expression, thus decreasing homology-directed DNA repair (Sci Transl Med 2019;11:eaa4508).

A PARP inhibitor, olaparib was developed for patients with cancers such as ovarian and breast that harbor BRCA mutations, which interfere with DNA repair, thus making cancer cells more dependent on PARP to fix DNA. However, in a 2014 phase II trial, combining olaparib with the antiangiogenic VEGFR inhibitor cediranib significantly increased progression-free
survival in patients with recurrent, platinum-sensitive non–BRCA-mutant ovarian cancer compared with olaparib alone (16.5 months vs. 5.7 months; Lancet Oncol 2014;15:1207–14).

“That was something that was a little bit unexpected but was initially explained by the idea that the inhibition of angiogenesis would lead to decreased oxygen delivery—and therefore, a state of hypoxia in the tumors,” says Peter Glazer, MD, PhD, of Yale University in New Haven, CT, senior author of the new study. “We were interested to see if hypoxia-induced DNA-repair deficiency would explain the results.”

Glazer and his team set out to test this hypothesis and characterize other potential mechanisms underlying the apparent synergistic interaction between olaparib and cediranib. In a series of experiments using patient-derived mouse xenografts of ovarian and breast cancers, the researchers found that cediranib did induce hypoxia, which decreased BRCA1/2 and RAD51 expression, causing a DNA-repair deficit that made cancer cells sensitive to olaparib. However, they noticed that even nonhypoxic cells had decreased DNA repair, a result they confirmed using ovarian cancer cells in culture.

The researchers then conducted follow-up experiments on patient-derived cancer cell lines in culture, establishing that cediranib decreases DNA repair by acting on the PDGFR pathway: The drug inhibits PDGFR signaling, which activates protein phosphatase 2A and, subsequently, the E2F4/p130 transcriptional corepressor, downregulating expression of BRCA1/2 and RAD51.

“We think it’s a dual effect, and in fact there may be other effects of cediranib, because one of the things we learned is cediranib is quite potent for the VEGF receptor for which it was developed, but it also inhibits other receptor tyrosine kinases, including the PDGF receptor,” Glazer says. “I think it highlights that this is a potentially viable approach to developing DNA-repair inhibitors that is distinct from directly drugging the repair enzymes.”

Currently, studies are investigating olaparib plus cediranib in an array of solid tumors that lack BRCA mutations, such as prostate and pancreatic cancers. Glazer is also interested in whether PDGFR expression could be used to predict patient responses.

“It’s gratifying to see continued understanding of why we’re seeing a synergistic effect of putting a PARP inhibitor together with a drug that has antiangiogenic properties—it provides preclinical rationale for why you would test the combination,” says Ursula Matulonis, MD, of Dana-Farber/ Harvard Cancer Center in Boston, MA, who led the phase II trial, but was not involved in the new study.

Matulonis wants to know how these preclinical results will translate into the ongoing phase III GY004 and GY005 trials testing the combination in patients with recurrent ovarian cancer. “The question is going to be in the case of this drug combination, ‘Is what happens in the mouse model really what happens in a human patient?’”

—Catherine Caruso

For more news on cancer research, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.
Mechanism of Cediranib–Olaparib Combo Revealed


Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2019-064

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/9/8/990.2. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.