Clinical Trial

Major Finding: Neoadjuvant nivolumab plus ipilimumab improved major pathologic responses in early-stage NSCLC.

Concept: The efficacy analysis included 44 patients with resectable non–small cell lung cancer (NSCLC).

Impact: This immunotherapy combination is worth investigating further in patients with nonmetastatic NSCLC.

COMBINATION IMMUNE CHECKPOINT BLOCKADE PROMISING IN OPERABLE NSCLC

The addition of ipilimumab (anti-CTLA4) to nivolumab (anti–PD-1) has been shown to improve outcomes in some patients with metastatic non–small cell lung cancer (NSCLC), but the efficacy of this combination in resectable NSCLC—in which the rate of recurrence after surgery with curative intent is more than 50%—is not known. To test this, Cascone and colleagues initiated a randomized, phase II clinical trial of neoadjuvant nivolumab or nivolumab plus ipilimumab in 44 patients with resectable NSCLC, with 23 patients being randomized to receive nivolumab alone and 21 patients being randomized to receive the combination treatment followed by surgery, and using major pathologic response (MPR) as primary endpoint, defined as having ≤ 10% of tumor cells from resected tumors being viable as determined histopathologically. (Due to its previously reported positive association with survival outcomes, MPR is being investigated as a surrogate endpoint in operable NSCLC.). Thirty-seven patients (21 in the monotherapy group and 16 in the combination therapy group) ultimately received on-trial surgery (two additional patients underwent surgery off trial after other therapies); the seven patients who did not undergo surgery on trial were considered to have no MPR in the intention-to-treat (ITT) analysis. Patients could also receive additional treatments postoperatively: Of those who underwent surgery on trial, postoperative chemotherapy or radiotherapy was given to 17 patients (46%) or 4 patients (11%), respectively. Among the 44 patients included in the ITT analysis, 22% (5/23 patients) of those who received nivolumab alone and 38% (8/21 patients) of those who received the combination treatment had an MPR. Additionally, an analysis of only the 37 patients whose tumors were resected on trial showed that the MPR rate was 24% (5/21 patients) in the nivolumab arm and 50% (8/16 patients) in the nivolumab plus ipilimumab arm. Interestingly, an exploratory investigation of possible interactions between gut microbiota and response revealed that response to the combination treatment was associated with higher levels of gut *Ruminococcus* and *Akkermansia* species. The investigators also found higher levels of immune cell infiltration in tumors treated with combination therapy. In summary, these results suggest that the combination of nivolumab plus ipilimumab may be promising in the neoadjuvant setting in NSCLC. ■

Cascone T, William Jr WN, Weissferdt A, Leung CH, Lin HY, Pataer A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nat Med 2021;27:504–14.

Metabolism

Major Finding: CTLA4 blockade improved T-cell infiltration and function in glycolysis-low tumors.

Concept: *In vivo*, anti-CTLA4 had increased efficacy against tumors that had decreased tumor cell glycolysis.

Impact: Whether CTLA4 blockade is more effective in glycolysis-low tumors in humans warrants investigation.

ANTI-CTLA4 PERTURBS T_{REG}-BASED IMMUNOSUPPRESSION IN GLYCOLYSIS-LOW TUMORS

Metabolic perturbation is characteristic of cancer, with increased glucose catabolism via glycolysis being a common feature. Because effector T cells also depend on glycolysis, their functions may be dysregulated in glycolysis-high tumors, potentially affecting the efficacy of immunotherapies. Zappasodi and colleagues investigated this using a mouse breast cancer model in which the tumors have high rates of glycolysis, finding that knocking down the gene encoding lactate dehydrogenase A (LDHA) to reduce tumor cell glycolysis led to increased tumor infiltration by immune cells, especially following CTLA4 blockade. Correspondingly, neoadjuvant anti-CTLA4 treatment increased survival in mice bearing *Ldha*-knockdown (glycolysis-low) but not wild-type (glycolysis-high) mammary tumors. Additionally, tumor-infiltrating $CD4^+$ T cells in *Ldha*-knockdown tumors exhibited upregulation of IFNγ and TNFα, an effect that was particularly pronounced in regulatory T (T_{reg}) cells. Further, increased IFNγ production by T_{reg} cells was positively correlated with increased IFNγ production by cytotoxic $CD8^+$ T cells in tumors. Finally, *in vitro* experiments showed that the abnormal T_{reg}-cell function caused by CTLA4 blockade was dependent on glycolysis by the T_{reg} cells along with CD28 signaling. Collectively, these results suggest that the efficacy of CTLA4 blockade is limited in tumors depleted of glucose via elevated tumor cell glycolysis because of poor immune infiltration due to this metabolic competition and the presence of highly stable and immunosuppressive T_{reg} cells. In contrast, in glycolysis-low tumors, in which glucose is more abundant in the tumor microenvironment, intratumoral immune infiltration is increased and T_{reg} cells forced to engage in glycolysis after anti-CTLA4 treatment lose their immunosuppressive function, effects that contribute to the development of long-lasting antitumor immune responses. These results suggest that an investigation of whether CTLA4 blockade is more effective in glycolysis-low tumors in humans or whether CTLA4 blockade synergizes with inhibitors of tumor glycolysis may be warranted. ■

Zappasodi R, Serganova I, Cohen IJ, Maeda M, Shindo M, Senbabaoglu Y, et al. CTLA-4 blockade drives loss of T_{reg} stability in glycolysis-low tumours. Nature 2021;591:652–8.