

## Immunotherapy

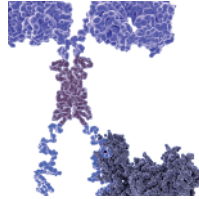
**Major Finding:**  $\gamma$ -Secretase inhibitors with BCMA CAR-T therapy improved survival in a multiple myeloma mouse model.

**Mechanism:**  $\gamma$ -Secretase cleaves BCMA on cell surfaces; thus,  $\gamma$ -secretase inhibitors increase BCMA density.

**Impact:** A clinical trial combining  $\gamma$ -secretase inhibitors with BCMA CAR-T therapy is now under way.

### $\gamma$ -SECRETASE INHIBITORS IMPROVE MULTIPLE MYELOMA BCMA CAR-T THERAPY

Although chimeric antigen receptor T (CAR-T) cell therapies represent a major advance in the treatment of several cancers, limitations include the fact that cancer cells in some patients may not highly express the target molecules on their surfaces and that relapse may occur with antigen-low disease. Pont and colleagues developed a strategy for the treatment of multiple myeloma with a B-cell maturation antigen (BCMA)-based CAR-T therapy combined with drugs intended to increase the density of BCMA on the surfaces of cancer cells. The experimental drugs are inhibitors of  $\gamma$ -secretase, an enzyme that cleaves BCMA on the cell surface, thus reducing BCMA density. Treatment of myeloma cell lines and patient-derived myeloma cells with  $\gamma$ -secretase inhibitors (GSI) dose-dependently increased the amount of BCMA on the surfaces of the cancer cells and decreased the concentration of the soluble portion of BCMA—which may act as a decoy for BCMA-directed CAR-T cells—that is released upon  $\gamma$ -secretase cleavage. GSI treatment also increased the recognition of cancer cells by CAR-T cells *in vitro*. These effects



were replicated in mice engrafted with multiple myeloma cells. In the same mouse model, by the time all mice receiving BCMA-directed CAR-T cells alone had died due to disease progression, 60% of the mice treated with the CAR-T cells plus a GSI remained alive. Preliminary experiments involving three patients with refractory multiple myeloma revealed that GSI treatment also increased BCMA expression on the surface of the cancer cells by a median of 33-fold and raised the percentage of BCMA<sup>+</sup> cancer cells from a median of 27.5% to 99.3%. Based on these results, it may be possible to improve the number of patients who can benefit from this CAR-T therapy and prevent relapse due to low antigen-expressing cells, and the authors have begun a clinical trial combining GSI with BCMA-directed CAR-T cells. ■

*Pont MJ, Hill T, Cole GO, Abbott JJ, Kelliher J, Salter AI, et al.  $\gamma$ -secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma. Blood 2019 Sep 26 [Epub ahead of print].*

## Melanoma

**Major Finding:** In mouse models of melanoma, lower intratumoral heterogeneity (ITH) correlated with lower tumor growth.

**Concept:** In patient data, high levels of ITH predicted reduced survival and poorer response to immunotherapy.

**Impact:** This study shows that ITH is an important factor in melanoma and may be a prognostic biomarker.

### LOW-HETEROGENEITY MELANOMAS ARE MORE IMMUNOGENIC AND LESS AGGRESSIVE

Recent studies have indicated that intratumoral heterogeneity (ITH) may be an important factor in determining the immune response to tumors, but the cause is not known, and the potential interplay between ITH and tumor mutational burden (TMB) is unclear. In a cohort of patients with melanoma, Wolf, Bartok, and colleagues found that those with low levels of ITH had improved survival rates compared with those with higher levels of ITH. When injected into immunocompetent mice, melanoma cells exposed to UVB irradiation (which increases both ITH and TMB) formed tumors that grew at an increased rate compared with non-irradiated melanoma cells. To distinguish between the effects of ITH and TMB, single-cell clones (SCC) from the UVB-irradiated melanoma cells were generated. Injected SCCs formed tumors that grew at reduced rates compared with tumors grown from the heterogeneous parental cells, indicating that low levels of ITH are associated with decreased tumor aggressiveness independently of any effects of TMB. In severely immunocompromised mice, tumors grown from SCCs exhibited as much growth as those grown from the high-ITH, UVB-irradiated parental cells, implying that it was immune rejection that caused the reduced growth

of SCC-derived tumors in the immunocompetent mice used in the prior experiments. Correspondingly, SCC-derived tumors were more immunogenic than tumors derived from the high-ITH parental cells. Experiments in which tumors were derived from defined mixtures of different SCC populations revealed that tumor aggressiveness could be largely explained by both the number of clones injected and their genetic diversity. Highlighting the potential clinical relevance of these findings, a meta-analysis of data from patients with melanoma from four prior studies showed that the number of clones and their genetic diversity mediated response to immunotherapy, with tumors having higher diversity being associated with worse outcomes. Collectively, these data establish ITH as an independent factor that may be associated with prognosis and response to immunotherapy and suggest that this phenomenon can be explained by increased immunogenicity of low-ITH tumors. ■

*Wolf Y, Bartok O, Patkar S, Eli GB, Cohen S, Litchfield K, et al. UVB-induced tumor heterogeneity diminishes immune response in melanoma. Cell 2019;179:219–35.e21.*

Research Watch is written by Cancer Discovery editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit Cancer Discovery online at <http://cancerdiscovery.aacrjournals.org/CDNews>.