Targeted Therapy

Major finding: An EGFR Probody exhibits antitumor efficacy similar to cetuximab, with decreased skin toxicity.

Concept: Removal of a masking peptide by tumor-specific proteases enables local Probody activation.

Impact: Probodies may facilitate broader use of therapeutic antibodies with improved safety profiles.

ANTIBODY REENGINEERING IMPROVES THERAPEUTIC INDEX IN PRECLINICAL MODELS

The efficacy of therapeutic monoclonal antibodies is often limited by the expression of antigens in both tumor and normal tissue, resulting in dose-limiting, on-target toxicities. For example, the anti-EGF receptor (EGFR) antibody cetuximab induces severe skin reactions that reduce its therapeutic index in patients with solid tumors. As an alternative approach, Desnoyers and colleagues engineered an EGFR-targeting proantibody, or Probody, based on cetuximab and the concept of prodrugs, which remain inert until locally activated at the disease site. The Probody PB1 consists of an N-terminal masking peptide that prevents EGFR binding connected to a linker sequence that is selectively cleavable by proteases known to be upregulated in human tumors, thereby enabling local PB1 activation in the tumor microenvironment. PB1 activation *in vitro* or by proteases within non–small cell lung cancer (NSCLC) xenograft tumors facilitated binding to EGFR, inhibition of tumor cell proliferation, and PB1 accumulation at the tumor site, similar to cetuximab. Moreover, treatment with PB1 inhibited EGFR-mediated signaling and suppressed NSCLC xenograft growth in mice with comparable efficacy to that of cetuximab. However, in contrast with cetuximab, PB1 treatment was associated with decreased cutaneous toxicity in nonhuman primates, even at higher doses, and PB1 remained inactive in the plasma and skin of treated monkeys despite increased exposure and an extended half-life, indicating that the masking effect improves the safety profile of PB1. Furthermore, PB1 activation was detected in EGFR-positive primary human NSCLC and colorectal tumor samples *ex vivo*, suggesting that PB1 may be used to measure proteolytic activity and select patients likely to respond. These results establish Probodies as a strategy to enhance the efficacy and alleviate the on-target toxicity of monoclonal antibodies and suggest that PB1 may allow for broader use of anti-EGFR antibodies in cancer therapy. ■

Desnoyers LR, Vasiljeva O, Richardson JH, Yang A, Menendez EE, Liang TW, et al. Tumor-specific activation of an EGFR-targeting probody enhances therapeutic index. Sci Transl Med 2013;5:207ra144.

Clinical Trials

Major finding: The PD-1 blocking antibody nivolumab has activity in melanomas refractory to CTLA-4 blockade.

Concept: Nivolumab was similarly effective in ipilimumab-naïve and ipilimumab-refractory patients.

Impact: Targeting different immune checkpoint proteins sequentially can lead to clinical responses.

NIVOLUMAB IS ACTIVE IN IPILIMUMAB-REFRACTORY MELANOMA

Cancer cells can evade immune detection by activating T-cell inhibitory immune checkpoint proteins. Blockade of immune checkpoint proteins such as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed death 1 (PD-1) has emerged as a promising approach to increase antitumor immunity and has improved survival in patients with melanoma and other cancers. Ipilimumab, a CTLA-4–blocking monoclonal antibody, has been approved by the FDA to treat melanoma, but it remains unclear if other immune checkpoint antibodies will be effective in ipilimumab-refractory patients. Weber and colleagues report findings from a phase I trial that assessed the safety and tolerability of nivolumab, a monoclonal PD-1–blocking antibody, in patients with ipilimumab-naïve or -refractory melanoma alone or with a peptide vaccine to augment T-cell responses. Assessment of the objective response rate was a secondary endpoint. Fatigue was the most common adverse event, and injection site reactions occurred in patients receiving the vaccine, which had no impact on nivolumab activity. Among 34 ipilimumab-naïve patients, 2 (6%) had a complete response, 6 (18%) had a partial response, and 7 (21%) had stable disease, and of 53 ipilimumab-refractory patients, 14 (26%) had a partial response and 11 (21%) had stable disease. The median duration of response was not reached in either group. Patients with high pre-existing T-cell reactivity to melanoma antigens were less likely to have an objective response than were patients with low or no reactivity. In an unplanned analysis of 12 ipilimumab-naïve patients who received ipilimumab after progression on nivolumab, 2 had a partial response and 2 had a mixed response, suggesting that some nivolumab-refractory tumors also remain sensitive to ipilimumab. Collectively, these results show that sequential use of ipilimumab and nivolumab in melanoma can lead to durable responses with limited toxicity, though future studies are needed to compare sequential with combination treatment. ■

Weber JS, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol 2013 Oct 21 [Epub ahead of print].