Neoadjuvant immune checkpoint blockade: a window of opportunity to advance cancer immunotherapy

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Abstract

Immunotherapies targeting the interaction of the programmed death 1 (PD-1) receptor with its ligands, PD-L1 and PD-L2, have revolutionized modern oncology. The PD-1 pathway is a key mediator of local immunosuppression in the tumor microenvironment. In a proportion of advanced inoperable cancers, drugs blocking this pathway can mediate durable tumor regressions. While anti–PD-(L)1 has demonstrated a broad activity profile across more than 20 cancer types and is therefore regarded as a "common denominator" for cancer therapy, many advanced inoperable tumors manifest de novo or acquired treatment resistance. One potential solution to circumvent resistance is to use anti–PD-(L)1 in the neoadjuvant (pre-surgical) treatment setting, for cancers that are high-risk but potentially "resectable for cure". This approach can prime systemic antitumor immunity to eliminate micrometastatic tumor deposits not evident at the time of surgery, that would otherwise cause postoperative relapse and disease progression. The development of neoadjuvant immunotherapy is based on immunologic mechanisms and clinical considerations, and may provide advantages compared to adjuvant (post-surgical) treatment. For example, neoadjuvant anti-PD-(L)1 administered alone or in combination treatment regimens offers the novel clinical endpoint of immune-mediated pathologic response. Furthermore, it enables in-depth studies of complete surgical resection tissue specimens to discover biomarkers and reveal new mechanistic insights into the PD-1 pathway. In 2021, the US Food and Drug Administration's seminal approval of neoadjuvant chemo-immunotherapy for patients with resectable triple negative breast cancer opened a new era for the clinical application of immune checkpoint blockade. In 2022, this was followed by an approval for neoadjuvant chemo-immunotherapy in resectable non-small cell lung cancer, prolonging relapse-free survival after surgery and improving the outlook for many thousands of patients worldwide. Hundreds of clinical trials are now underway to test neoadjuvant immunotherapy across a wide variety of cancers.

Biography

Dr. Suzanne L. Topalian is the Bloomberg~Kimmel Professor of Cancer Immunotherapy at the Johns Hopkins University School of Medicine, and associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy. She is a physician-scientist whose studies have been foundational in developing cancer immunotherapy as a pillar of oncology. She trained at Tufts University School of Medicine, Thomas Jefferson University Hospital, and the National Cancer Institute, and joined Johns Hopkins in 2006 to lead its Melanoma/Skin Cancer Program. Her research on manipulating "immune checkpoints" such as PD-1 in cancer therapy has led to FDA-approved therapies and associated biomarker tests for patients with over 20 different types of cancer. Dr. Topalian's work has garnered numerous awards, and was recognized with election to the National Academy of Medicine in 2017.