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Review

Targeted Therapy and Checkpoint Immunotherapy Combinations for the Treatment of Cancer

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Many advances in the treatment of cancer have been driven by the development of targeted therapies that inhibit oncogenic signaling pathways and tumor-associated angiogenesis, as well as by the recent development of therapies that activate a patient's immune system to unleash antitumor immunity. Some targeted therapies can have effects on host immune responses, in addition to their effects on tumor biology. These immune-modulating effects, such as increasing tumor antigenicity or promoting intratumoral T cell infiltration, provide a rationale for combining these targeted therapies with immunotherapies. Here, we discuss the immune-modulating effects of targeted therapies against the MAPK and VEGF signaling pathways, and how they may synergize with immunomodulatory antibodies that target PD1/PDL1 and CTLA4. We critically examine the rationale in support of these combinations in light of the current understanding of the underlying mechanisms of action of these therapies. We also discuss the available preclinical and clinical data for these combination approaches and their implications regarding mechanisms of action. Insights from these studies provide a framework for considering additional combinations of targeted therapies and immunotherapies for the treatment of cancer.

Trends

Targeted therapies inhibit tumor-intrinsic drivers of growth and can elicit significant but transient clinical responses.

Immunotherapies enhance host antitumor immunity and can elicit durable responses in subsets of patients across multiple tumor types. Checkpoint inhibitors are immunotherapies that relieve suppressive signals acting on host T cells to unleash antitumor T cell activity.

In some cases, targeted therapies can enhance aspects of cancer immunity, such as tumor antigenicity, T cell trafficking, or T cell infiltration into tumors, which provides a rationale for combining them with checkpoint inhibitors or other cancer immunotherapies that may lead to synergistic efficacy.

Considerations for the clinical development of combinations of targeted therapies and immunotherapies include optimizing dosing regimens, minimizing treatment related toxicities, and selecting appropriate biomarkers and endpoints to assess efficacy.

Introduction

The treatment of cancer has advanced significantly over the past 15 years, driven by many scientific insights including those that have led to the approval of targeted therapies that inhibit tumor angiogenesis and intrinsic drivers of cancer cell growth, as well as immunomodulatory therapies that enhance host antitumor immunity (Table 1). Targeted therapies can elicit dramatic clinical responses in several tumor types, but these responses are transient, with tumor escape and clinical relapse usually occurring within months after an initial response. By contrast, cancer immunotherapies can elicit durable responses in subsets of treated patients across multiple tumor types, and this striking clinical activity has led to a surge of research and clinical development in the field of cancer immunotherapy.

The key steps involved in a productive antitumor immune response have been outlined by Chen and Mellman and termed the 'cancer-immunity cycle' (Figure 1) [1]. Briefly, cancer-specific antigens created during the process of oncogenesis are captured and processed by dendritic cells in the tumor microenvironment. Upon additional proinflammatory signals, these dendritic cells are activated and travel to tumor-draining lymph nodes, where they prime the activation and differentiation of naïve T cells to become effector T cells that are capable of killing cancer cells. Activated effector T cells traffic from the lymph nodes through blood vessels to the

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Table 1. Approved Targeted Therapies and Immunotherapy Checkpoint Inhibitors for the Treatment of Solid Tumors.

Drug	Target	Targeted Therapy/ Immunotherapy	Modality	Indication(s)
Vemurafenib	BRAF	Targeted therapy	Small molecule	Melanoma
Dabrafenib	BRAF	Targeted therapy	Small molecule	Melanoma
Trametinib	MEK	Targeted therapy	Small molecule	Melanoma
Cobimetinib	MEK	Targeted therapy	Small molecule	Melanoma
Ipilimumab	CTLA-4	Immunotherapy	Antibody	Melanoma
Nivolumab	PD-1	Immunotherapy	Antibody	Melanoma, renal cell carcinoma, lung cancer
Pembrolizumab	PD-1	Immunotherapy	Antibody	Melanoma, lung cancer
Bevacizumab	VEGF-A	Targeted therapy	Antibody	Renal cell carcinoma, brain cancer, cervical cancer, colorectal cancer, lung cancer, ovarian epithelial, fallopian tube, peritoneal cancers
Axitinib	Multikinase inhibitor (VEGFR, PDGFR, KIT, ABL)	Targeted therapy	Small molecule	Renal cell carcinoma
Pazopanib	Multikinase inhibitor (VEGFR, PDGFR, FGFR, KIT, LTK, LCK)	Targeted therapy	Small molecule	Renal cell carcinoma, soft tissue sarcoma
Sorafenib	Multikinase inhibitor (VEGFR, PDGFR, KIT, RET, RAF)	Targeted therapy	Small molecule	Renal cell carcinoma, thyroid cancer, liver cancer
Sunitinib	Multikinase inhibitor (VEGFR, PDGFR, KIT, RET)	Targeted therapy	Small molecule	Renal cell carcinoma, gastrointestinal stromal tumor, pancreatic cancer
Temsirolimus	mTOR	Targeted therapy	Small molecule	Renal cell carcinoma
Everolimus	mTOR	Targeted therapy	Small molecule	Renal cell carcinoma, breast cancer, brain cancer, pancreatic cancer, gastrointestinal cancer, lung cancer
Ceritinib	ALK	Targeted therapy	Small molecule	Lung cancer
Alectinib	ALK	Targeted therapy	Small molecule	Lung cancer
Gefitinib	EGFR	Targeted therapy	Small molecule	Lung cancer
Afatinib	EGFR	Targeted therapy	Small molecule	Lung cancer
Osimertinib	EGFR	Targeted therapy	Small molecule	Lung cancer
Nectumumab	EGFR	Targeted therapy	Antibody	Lung cancer
Crizotinib	Multikinase inhibitor (MET, ALK, ROS)	Targeted therapy	Small molecule	Lung cancer
Erlotinib	EGFR	Targeted therapy	Small molecule	Lung cancer, pancreatic cancer
Ramucirumab	VEGFR2	Targeted therapy	Antibody	Lung cancer, adenocarcinoma of stomach or gastroesophageal junction, colorectal cancer