

Transcript Details

This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting:

<https://reachmd.com/programs/i-o-insights-exploring-bifunctional-fusion-therapies/innovative-molecules-immuno-oncology-revolutionizing-cancer-treatment/10163/>

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Innovative Molecules in Immuno-Oncology: Revolutionizing Cancer Treatment

Announcer:

This is a special episode of I-O Insights: Exploring Bifunctional Fusion Therapies provided in partnership with TOPEC Global and supported by an independent medical educational grant from Merck KGaA, Darmstadt, Germany.

This ReachMD Brief will explain the rationale for using bispecific, bifunctional fusion protein molecules as a treatment modality of patients with a range of cancer types.

Voiceover:

This molecule is an innovative, first-in-class bifunctional fusion protein designed to simultaneously block two signaling pathways used by tumor cells to escape or overcome control by the immune system: The Programmed Death Ligand 1 -- or PD-L1 -- pathway, and the Transforming Growth Factor-Beta -- or TGF- β -- pathway. This investigational cancer immunotherapy is composed of both a fully human IgG1 monoclonal antibody against PD-L1 and the extracellular domain of 2 human TGF- β receptor II molecules on the antibody tail. These bind and trap TGF- β 1, β 2, and β 3, providing a mechanism for dual anti-tumor activity.

PD-L1 is a transmembrane protein normally expressed by antigen presenting cells, which binds to PD-

1 receptors on T cells to inhibit T cell activity. Tumor cells leverage this inhibitory pathway by overexpressing PD-L1 in response to interferon-gamma secretion by activated T cells, which suppresses T cells from infiltrating the tumor and, by extension, avoids immune surveillance.

The monoclonal antibody component of the bifunctional fusion protein blocks PD-L1 on tumor cells to prevent the inactivation of local T cells. The antibody also can mediate antibody-dependent cell cytotoxicity, or ADCC, and by binding with NK cells can lead to triggering of ADCC-mediated tumor cell lysis.

The second half of the bifunctional fusion protein molecule is the TGF- β trap. TGF- β is a key enforcer of immune tolerance and regulates many normal functions such as protein synthesis, inflammation, cell invasion, and microenvironment changes. Cancers exploit these functions by producing high levels of TGF- β , blocking immune responses to support tumor growth, angiogenesis, and metastasis. This cytokine overexpression also recruits other stromal cell types, such as myofibroblasts which induce protective fibrotic thickening at the tumor invasion front, and osteoclasts that produce lytic lesions seeding bone metastasis.

The TGF- β trap within the bifunctional fusion protein is designed to inhibit these critical processes of tumor progression and malignant transformation, blocking the TGF- β signaling mechanisms that lead to fibrosis, angiogenesis, and the epithelial-mesenchymal transition, or EMT. Combined with this agent's PD-L1-blocking attributes through its fused monoclonal antibody, the bifunctional fusion protein provides dual anti-immunosuppressive functions leading to activations of both innate and adaptive immune responses.

Announcer:

This has been a special episode of I-O Insights: Exploring Bifunctional Fusion Therapies on ReachMD. For more information and to find other episodes in this series, go to ReachMD.com/IO.