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CTLA-4-directed Probody BMS-986249

National Cancer Institute

Source

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A probody composed of ipilimumab, a recombinant human immunoglobulin (Ig) G1 monoclonal antibody directed against the human T-cell receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; CTLA-4), linked to a proprietary masking peptide that covers the active antigen-binding site of the antibody through a protease-cleavable linker, with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration of CTLA-4-directed probody BMS-986249, the masking peptide is cleaved by tumor-associated proteases upon extravasation into the tumor microenvironment (TME). Protease-mediated removal of the linker enables binding of the unmasked monoclonal antibody moiety to CTLA-4, which is expressed on certain T-cells. This inhibits the CTLA4-mediated downregulation of T-cell activation, and leads to both activation of tumor infiltrating T-effector cells and a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells. CTLA4, an inhibitory receptor and member of the immunoglobulin superfamily expressed on activated effector T-cells (Teffs) and regulatory T-cells (Tregs), plays a key role in the inhibition of T-cell activity and downregulation of the immune system. The peptide masking of BMS-986249 minimizes binding to CTLA-4 in normal tissues and may reduce systemic toxicity, when compared to ipilimumab. Tumor-associated proteases are present in high concentrations and aberrantly activated in the TME.