Botensilimab, an FC-enhanced CTLA-4 antibody, enhances innate and adaptive immune activation to promote superior anti-tumor immunity in cold and I-O refractory tumors

Chloe Delepine, Daniel Levey*, Shanmugarajan Krishnan, Kwang-Soo Kim, Adam Sonabend, Margaret Wilkens, Antoine Tanne, Pilar Garcia-Brocano, Claire Galand, Hyo Jong Han, Christopher MacDermaid, Jacky Chow, Sylvia Vincent, Shalu Karkwal, Yan Sun, Rachele Smith, Xavier Michelet, Kah Teong, Katherine Rosenthal, David Savitsky, Cailin Joyce, Steven O’Day, Joseph Grossman, Kah Teong, Katherine Rosenthal, Joseph Grossman, Jaymin Patel, Dhan Chand, Daniel Levey*. Agenus Inc., Lexington, MA, United States; Northwestern University, Chicago, IL, United States; The Translational Genomics Research Institute, Phoenix, AZ, United States; Mink Therapeutics, Lexington, MA, United States

Background Botensilimab is a novel fragment crystallizable (Fc)-enhanced anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody designed to promote superior immune activation and tumor killing relative to first-generation IgG1 CTLA-4 antibodies. In patients with advanced solid tumors, botensilimab ± balstilimab (anti-PD-1), demonstrated durable clinical responses across nine different immunotherapy-resistant or poorly immunogenic tumor types. The deep and broad activity observed with botensilimab is attributed to its enhanced binding to Fc gamma receptor IIIA (FcyRIIIA). This binding strengthens the immune synapse between CTLA-4-expressing T cells and FcyRIIIA-expressing antigen-presenting cells (APC) or natural killer (NK) cells, resulting in superior T cell priming, memory formation, intratumoral regulatory T cell (Treg) depletion, and APC functionality. We show that this diversity of immune functions, distinct from that of first-generation anti-CTLA-4, correlates with more effective control of ‘cold’ tumors alone or in combination with other therapies.

Methods Human ex vivo peripheral blood mononuclear cells (PBMCs) assays were used to assess effects of botensilimab on T cell responses, APC activation and Treg depletion. Pre- and post-treatment tumor biopsies and PBMCs from botensilimab-treated patients from a Phase 1 dose-escalation trial were analyzed by next-generation sequencing (NGS), flow cytometry or immunohistochemistry to assess neoantigen burden, immune gene signatures, T cell clonality and CD8:Treg ratios in the tumor. The efficacy of a mouse surrogate (ms) of botensilimab, alone or combined with other agents, was assessed in poorly immunogenic and anti-PD-1 refractory mouse tumor models.

Results In human ex vivo cell-based assays, botensilimab enhanced T cell responses as measured by IL-2 secretion, increased the frequency of activated FcyRIIIA+ CD11c+ myeloid cells, as determined by CD40, HLA-DR and CD86 expression, and promoted Treg depletion superior to a first-generation IgG1 anti-CTLA-4 antibody. Tumor-bearing mice (CT26 colon carcinoma, MC38 colon carcinoma, and CT2A orthotopic glioblastoma) treated with botensilimabms showed superior tumor shrinkage and survival compared to mice treated with first-generation anti-CTLA-4. When combined with chemotherapy, radiotherapy, vaccines, adoptive cell therapy, tumor-targeted ultrasound or iNKT-activation, botensilimabms was therapeutically effective across several tumor models including GL261 glioblastoma, KPC pancreatic cancer and B16 melanoma. In both preclinical and clinical studies, botensilimab enhanced peripheral T cell clonality and expansion of T cell clonotypes and increased intratumoral CD8:Treg ratio. Concordant with preclinical observations, response to botensilimab in patients with advanced solid cancers was independent of FcγR polymorphism or neoantigen burden.

Conclusions Botensilimab demonstrates unprecedented activity in ‘cold’ and immunotherapy-resistant tumors consistent with its novel mechanism of action.


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J ImmunoTher Cancer 2022;10(Suppl 2):A1–A1595