Masked Antibodies & Cytokines As Prodrugs:

a landscape analysis of stakeholders, technologies, pipelines, business and financing from an industry perspective

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La Merie Publishing
Carrer Núria, 10, 3, 2a
E-17500 Ripoll
info@lamerie.com

and the masking moiety is fused to the cytokine moiety or to the carrier moiety through a cleavable peptide linker. In some embodiments, the masking moiety comprises an IL-21 receptor alpha (IL-21Rα) extracellular domain (ECD) or functional analog thereof."

4.1.6 BioAtla

The business of BioAtla was founded in March 2007 and originally operated as a Delaware limited liability company, BioAtla, LLC. BioAtla draws upon the legacy of Diversa, a protein molecular evolution company. In July 2020, the company converted from a limited liability company into a Delaware corporation pursuant to a statutory conversion and changed their name from BioAtla, LLC to BioAtla, Inc.

BioAtla's principal executive offices and lab facility with about 43,000 square foot are located in San Diego, California. The company has operations in Beijing, China through a contractual relationship with BioDuro, a provider of preclinical development services. As of June 2021, the company had 62 employees.

BioAtla's proprietary Conditionally Active Biologic (CAB) technology creates antibodies that conditionally and reversibly bind to tumors, but not normal cells, enabling increased antibody potency and reduced toxicity (BioAtla Presentation June 2021). The company's CEO Jay Short, Ph.D. is a co-founder and an inventor of the company's CAB technology. BioAtla and Carolyn Anderson Short, its co-founder and Chief of Intellectual Property & Strategy, entered into an agreement pursuant to which Ms. Short will devote herself full time as the President & Chief Operating Officer of **Himalaya Therapeutics** SEZC, which she also co-founded. Himalaya is a former subsidiary of the Company, and is engaged primarily in the development, registration and commercialization of several product candidates licensed from BioAtla for the Greater China market, and two product candidates globally.

BioAtla has two CAB programs currently in phase II testing in the USA.

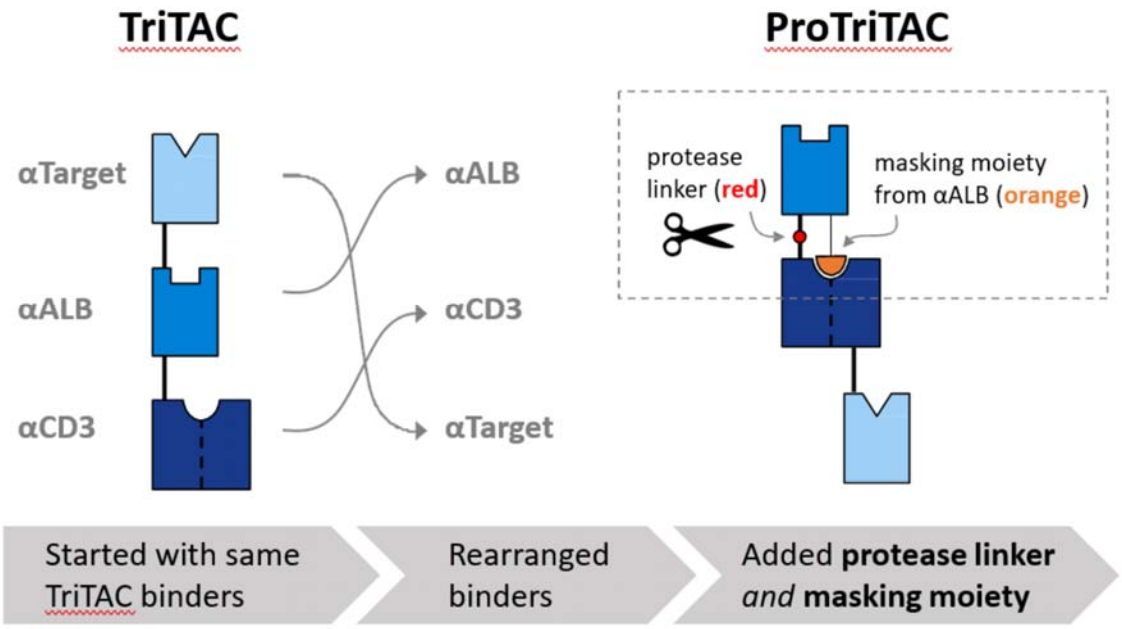
Financial history

Cash and cash equivalents as of June 30, 2021 were $207.6 million. BioAtla expects current cash and cash equivalents will be sufficient to fund planned operations into 2023 (Press Release Aug 13, 2021) In July 2020, BioAtla completed a successful private placement offering with institutional investors, for net proceeds of approximately $68.2 million. In December 2020,

SOURCE: (Harpoon Therapeutics Annual Report 2020 SEC Form 10-K Mar 10, 2021)

The ProTriTAC platform allows to access tumor-associated antigens that have been historically challenging because they are expressed in both tumors and non-tumor tissues. ProTriTAC therapeutics are designed to be serum half-life extended, but do not engage T cells until they are clipped by tumor-associated proteases. Once clipped, a T cell activator is released at the site of the tumor. However, this T cell activator now has a short half-life and is quickly removed from circulation before it can impact non-tumor tissues.

ProTriTACs are engineered with three binding domains on a single polypeptide: anti-albumin for half-life extension, anti-CD3ε for T-cell engagement, and anti-tumor-associated antigen. They have an anti-albumin domain, comprising a masking moiety and a protease-cleavable linker, to keep molecules inert outside the tumor microenvironment. The masking moiety has been engineered into non-CDR loops in the anti-albumin sdAb domain. Activation by tumor-associated proteases removes the anti-albumin domain along with the masking moiety to reveal a short-lived active drug to direct T cell killing within the tumor. The masking moieties were identified using phage display (Lin, 2018).



SOURCE: Lin, Presentation at SITC 2020

cellular cytotoxicity in order to increase the potential for Treg (regulatory T-cells) depletion at the tumor site. This would be expected to increase the activity of the antibody. Both ipilimumab-based Probodies use a dual mask that extends from the light chain of the antibody via a linker sequence that contains cleavage sites for proteases preferentially active at the tumor site relative to healthy tissue.

BMS reported at ASCO 2020 preliminary clinical data indicating that escalating doses of **BMS-986249** ranging from 240 mg to 2400 mg (approximately 3 to 30 mg/kg of ipilimumab) were found to be generally well tolerated, either as a single agent or in combination with nivolumab. TRAEs occurred in 59% of patients (Grade 3/4, 23%) with mono and 74% of patients (Gr 3/4, 30%) with combo. Diarrhea was the most common any-Grade TRAE (mono, 23%; combo, 21%) and Grade 3/4 TRAE (mono, 15%; combo, 7%). The peptide-masked intact probody accounted for most (73%) of the systemic BMS-986249-related species; elimination of the probody indicated involvement of both catabolism and cleavage processes. The clinical investigators concluded that "BMS-986249 ± nivolumab displayed a clinically manageable safety profile, allowing assessment of comparably higher BMS-986249 dose intensity (240-1200 mg; ≈ 3-15 mg/kg) + nivolumab (480 mg Q4W, full dose) than that tested with ipilimumab + nivolumab. The types of TRAEs were consistent with CTLA-4 blockade, and the overall data align with the proposed Probody therapeutic mechanism of action."

In preclinical experiments, BMS-986249 exhibited a 40-fold reduction in CTLA-4 binding affinity vs ipilimumab. When tested in a tumor model, BMS-986249 showed equivalent antitumor activity to ipilimumab and showed equivalent intratumoral pharmacodynamic (PD) activity and reduced peripheral PD activity relative to its parental mAb. Similarly, BMS-986249 resulted in reduced inflammation and peripheral PD responses relative to its parental mAb in cynomolgous macaques.

Clinical data for Bristol Myers Squibb second anti-CTLA4 Probody **BMS-986288** have not yet been published. In preclinical experiments, the non-fucosylated ipilimumab Probody (BMS-986288) showed decreased activity vs ipilimumab and non-fucosylated ipilimumab (BMS-986218), respectively, in non–protease containing in vitro assays. BMS-986218 exhibited a 40-fold reduction in CTLA-4 binding affinity vs ipilimumab. BMS-986288 showed decreased ADCC activity vs BMS-986218 in vitro. When tested in a tumor model, BMS-986218 and BMS-986288 showed equivalent antitumor activity to ipilimumab and BMS-986218, respectively. Both

Construct

A novel, fully-humanized anti-huCTLA-4 mAb was shown to bind human CTLA-4 with improved affinity compared to ipilimumab, as measured by surface plasmon resonance (SPR) technology (Jenkins, 2020). Engineering of the Fc region enhanced FcγR binding and antibody-dependent cellular cytotoxicity (ADCC) function. In addition, CDR-binding peptides identified by phage display were covalently linked to the antibody using a protease-sensitive polypeptide linker. This engineered anti-CTLA-4 antibody (XTX101) showed protease-dependent binding to CTLA-4 both with recombinant and tumor tissue derived proteases.

Preclinical Data

XTX101 demonstrated a 100-fold reduction in binding to human CTLA-4 by ELISA, compared to the non-masked antibody (Jennkins, 2020). Incubation with recombinant protease led to cleavage and release of the masking peptides and restored full binding to CTLA-4. Similarly, in vitro ADCC activity was impaired by masking and restored in a protease-dependent manner. SEB-stimulated human PBMCs were minimally responsive in vitro to XTX101, whereas PBMCs treated with proteolytically-activated XTX101 exhibited robust activation of T cell function. In human CTLA-4 knock-in mice with syngeneic MB49 tumors, XTX101 treatment led to complete tumor regression, enhanced CD8+ T cell proliferation, and depletion of tumor Tregs in the TME. By contrast, XTX101 had minimal pharmacodynamic effects in the periphery. In addition, XTX101 is effectively activated in culture supernatants from human solid tumor explants obtained from a broad range of tumor types.

Jenkins and colleagues (2020) conclude that “XTX101 is a tumor-selective anti-CTLA-4 mAb capable of: 1) effective CTLA-4 blockade, 2) depletion of intratumoral Tregs through enhanced antibody-dependent cellular cytotoxicity (ADCC) function, 3) minimization of systemic immune cell activation, and 4) potent anti-tumor activity.”

Jenkins et al. (2021) presented further data from preclinical studies of XTX101, demonstrating combination potential with anti-PD-1 therapy, as well as enhanced preclinical activity and improved tolerability compared to ipilimumab, an anti-CTLA-4 antibody therapeutic approved by the U.S. FDA.