IO Biotech, Inc
www.iobiotech.com

Harnessing natural immunity to fight cancer from within

IO Biotech is developing T-win, a therapeutic cancer-vaccine technology designed to recruit naturally occurring T cells to disrupt multiple immunosuppressive processes in the tumor microenvironment. The lead candidate is in advanced clinical development for melanoma with plans to expand to other solid tumor indications.

IO Biotech, a clinical-stage biopharmaceutical company with a global footprint, is developing novel, immune-modulating cancer therapies designed to activate naturally occurring T cells that target immunosuppressive mechanisms in the tumor microenvironment (TME). Developed using the company's T-win technology platform, IO Biotech's product candidates activate immune cells that in turn simultaneously target and disrupt multiple pathways that regulate tumor-induced immunosuppression. Specifically, administration of a T-win vaccine—consisting of one, two or multiple peptides derived from a TME-specific molecular target antigen—activates and expands pre-existing $CD4^+$ and $CD8^+$ T cells in the draining lymph nodes against those antigens. The resulting T cells migrate to the TME where, once they detect their target cells, they either eliminate them directly by cytotoxic lysis or trigger the release of pro-inflammatory cytokines. The elimination of immunosuppressive target cells results in a shift of the state of the TME from an immunosuppressed environment hostile to T cells into an inflamed environment that boosts effector T cell infiltration, enhancing the antitumor response (Fig. 1).

"All previously developed cancer vaccines were aimed at activating the immune system and directing it to target antigens present on some of the cancer cells, but success with such agents has been limited," said Muhammad Al-Hajj, CSO of IO Biotech. "At IO Biotech, we're taking a novel approach by vaccinating against TME antigens. The idea is to mount a focused attack on the tumor microenvironment suppressive elements, removing a key road block for comprehensive larger immune response from within. Based on the clinical success with our lead therapeutic vaccine in melanoma, we believe we will be able to rapidly develop additional candidates to address multiple other TME suppressive elements in solid tumors for which no universal immunotherapies are yet available."

IO Biotech's lead product candidate, IO102-IO103, is a dual-peptide vaccine designed to nullify two different immunosuppressive mechanisms in the TME by targeting indoleamine 2,3-dehydrogenase (IDO) and programmed death ligand 1 (PD-L1). IO102-IO103 has entered a phase 3 clinical trial for melanoma in combination with the programmed death 1 (PD-1) immune checkpoint inhibitor pembrolizumab. The company is also exploring possible applications of IO102-IO103 in additional solid tumors, such as non-small-cell lung cancer (NSCLC) and squamous-cell carcinoma of head and neck (SCCHN). Other programs include IO112, a product candidate containing a single arginase 1 (ARG-1)-derived peptide and designed to engage and activate ARG-1-specific human T cells (Fig. 2).

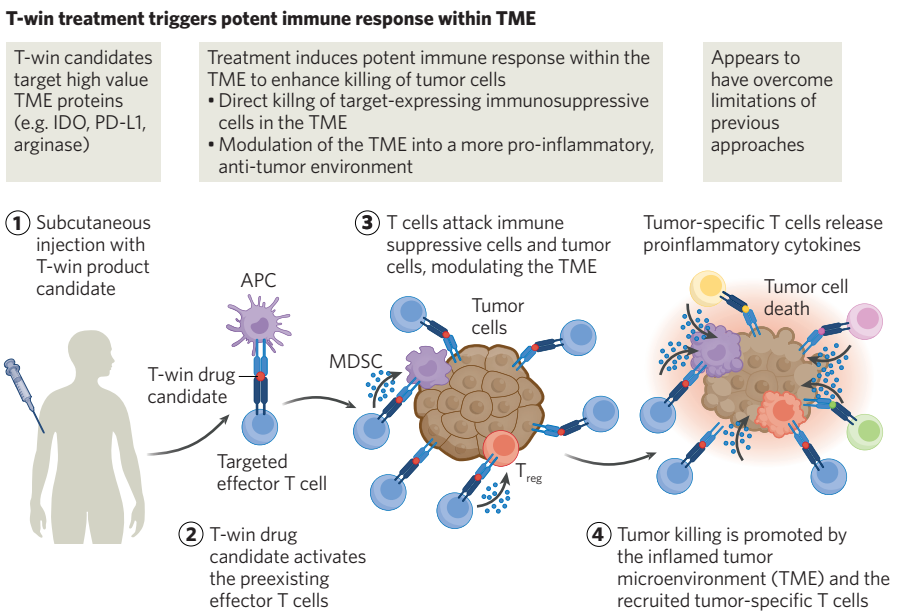

Fig. 1 | Boosting cancer immunotherapy by neutralizing the immunosuppressive response in the tumor microenvironment (TME). IO Biotech's T-win candidates target high-value TME proteins such as IDO, PD-L1 or ARG-1 to kill tumor and non-tumor immunosuppressive cells in the TME. This shifts the TME from an immunosuppressive environment to a more pro-inflammatory, antitumor environment.

IO Biotech has built a deep portfolio of TME-immunomodulating product candidates and is now looking to maximize their impact by combining them with other immune-modulating therapies, such as checkpoint blockade agents (for example, anti-PD-1 or anti-LAG-3), cell therapies—including chimeric antigen receptor T cells (CAR-T), T cell receptor-engineered (TCR) T cells, or natural killer (NK) cells—or other therapeutics that direct immune cells to target tumors, including bispecific monoclonal antibodies (mAbs). The company plans to achieve this goal by exploring this internally and via external preclinical and clinical collaborations.

Winning targets

IO Biotech's T-win platform represents a novel approach to cancer vaccines that uses pre-existing T cells to reduce or eliminate immunosuppressive processes in the TME. T-win product candidates—peptides derived from tumor-specific molecular targets expressed by immunosuppressive cells in the TME—deploy a two-prong attack on a tumor. First, they elicit the T cell-mediated targeting and destruction of immunosuppressive cells, including both tumor cells and genetically stable non-cancerous cells in the TME that express markers such as IDO, PD-L1 and ARG-1. The destruction of immunosuppressive cells is accompanied by the release of pro-inflammatory cytokines, triggering a shift of the TME from an immunosuppressive state to a pro-inflammatory, antitumor environment that reduces the tumor's ability to evade surveillance and destruction by the immune system.

Unlike existing immunotherapy approaches that either block specific immunosuppressive pathways or direct the immune system to target tumor cell-specific antigens, the T-win approach elicits a more universal and sustained TME-centered immune response that is designed to minimize immune escape. The ability to use dual and multi-epitope designs to simultaneously target separate and distinct immune-suppressive pathways in the TME enables IO Biotech's product candidates to potentially be applied to all tumor types, and to treat a potentially larger pool of patients than

is currently possible by being able to safely tackle the complexity of cancer. Typically, individual patients with the same cancer indication exhibit different expression profiles of immunoregulatory antigens, resulting in differential and often unpredictable responses to a single epitope treatment. The ability to repress multiple immunosuppressive pathways, and to do so in both tumor cells and non-cancerous cells in the TME, means T-win is a unique approach that could open new possibilities in immunotherapy.

"With our T-win approach we are able to recalibrate the impact of the immunotherapeutic intervention by relaxing the level of precision typically associated with such approaches in cancer, and allowing for a wider spectrum of effects to take place within the confines of the TME," said Al-Hajj. "The result is a more efficacious response that could benefit more patients without compromising on safety."

All T-win product candidates are designed to be used as off-the-shelf treatments that can be administered subcutaneously and adapted for particular cancer indications and treatment schedules. IO Biotech's pipeline consists of highly versatile product candidates that target a range of immunosuppressive mechanisms present in multiple cancer indications, and mechanisms of action present across different checkpoint-inhibitor systems. Given the extensive body of clinical testing showing that subcutaneously injected peptides are well tolerated, IO Biotech anticipates that its product candidates have the potential to be used as part of combination therapies in many early treatment settings.

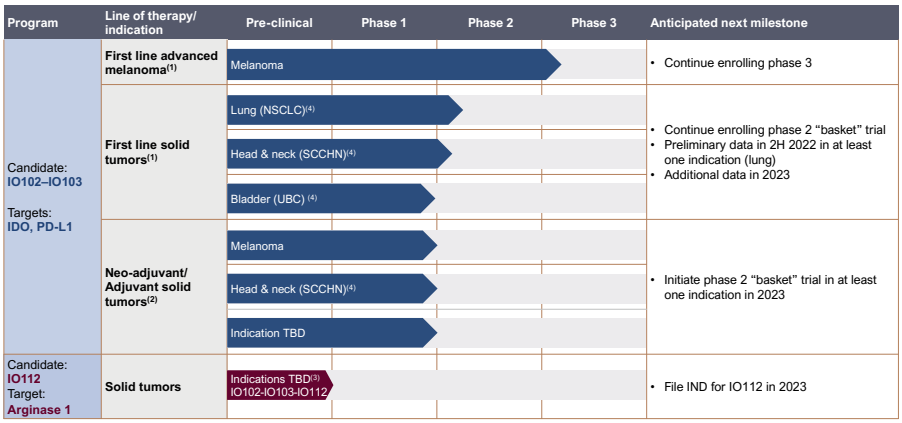

Fig. 2 | IO Biotech's pipeline takes cancer immunotherapy to the next level. Building on its lead candidate product, IO102-IO103, IO Biotech is assembling a pipeline of immunosuppression-targeting cancer immunotherapies. (1) In combination with pembrolizumab. (2) In combination with an anti-PD-1 monoclonal antibody therapy. (3) Expected to be developed in combination with third-party drugs or biologics. (4) NSCLC; non-small cell lung cancer, UBC; urothelial bladder cancer, SCCHN; squamous cell carcinoma of the head and neck.

Leading the way in melanoma

IO Biotech's lead product candidate, IO102-IO103, combines two novel and fully company-owned vaccines, IO102 and IO103, designed to target cells expressing IDO and PD-L1, respectively. In solid tumors, IDO and PD-L1 are often overexpressed by both cancer and non-cancer cells. The overexpression of IDO and PD-L1 results in the inhibition of the body's natural pro-inflammatory and antitumor response within the TME, and has been correlated with poor prognosis, aggressive disease, and reduced survival. In contrast to conventional approaches designed to block just a single immunosuppressive pathway at a time, or to direct the immune system against tumor-specific antigens, IO102-IO103 targets IDO and PD-L1 simultaneously. This dual targeting leads to the suppression of cells expressing IDO and PD-L1 in the TME, and to a shift towards a more pro-inflammatory TME, resulting in a synergistic tumoricidal effect that dramatically enhances anti-PD1 therapeutic efficacy.

In a single-arm phase 1/2 clinical trial of 30 patients with metastatic melanoma, IO102-IO103 in combination with the PD-1 immune checkpoint inhibitor nivolumab demonstrated an ability to induce meaningful tumor regressions and to establish a durable antitumor response. Although the primary objective of the trial was to determine safety and tolerability, the combination therapy demonstrated an ability to induce meaningful tumor regression and establish durable antitumor response while achieving a manageable tolerability profile for patients.

Top-level results of the phase 1/2 trial include a radiologically confirmed overall response rate (ORR) of 73% (22 out of 30 patients) and a complete response rate (CRR) of 47% (14 out of 30 patients)[1]. These high rates of response—for comparison, treatment with nivolumab or pembrolizumab alone results in ORRs of 45–46%, and combination therapy with nivolumab and ipilimumab, a CTLA-4 inhibitor, results in an ORR of 58% and a CRR of 22%[2,3]—were most likely driven by the treatment-induced infiltration of CD3/CD8 T cells into the tumor site observed in responding patients, and the emergence of IO102- and IO103-specific T cells in tumors following treatment.

Based on the favorable outcome of this phase 1/2 trial, the Food and Drug Administration (FDA) granted IO Biotech Breakthrough Designation for IO102-IO103 in combination with pembrolizumab—a PD-1 receptor-targeting IgG4 mAb analogous to nivolumab—for the treatment of patients with unresectable or metastatic melanoma and progression-free survival as the primary clinical endpoint. In late 2021, IO Biotech entered a clinical-trial collaboration and supply agreement with Merck for access to pembrolizumab, and recruiting for a potentially registrational phase 3 clinical trial has already started. Comparative studies have previously shown no difference between the effectiveness of frontline pembrolizumab and nivolumab in patients with advanced melanoma[4].

A basket of possibilities

Building on the early success of IO102-IO103 in melanoma, IO Biotech is now exploring using it in additional solid tumor indications. The company is currently conducting a phase 2 basket trial to investigate multiple first-line solid tumor indications in anti-PD-1/PD-L1 treatment-naive patients with metastatic disease. The trial will investigate the safety and efficacy of IO102-IO103 in combination with pembrolizumab in NSCLC, SCCHN and urinary bladder cancer. IO Biotech started the trial in the first half of 2022.

In addition to first-line cancer indications, the company is planning to investigate the use of IO102-IO103 as a neo-adjuvant or adjuvant therapy before- and after curative surgery. Similarly to the first-line cancer indication basket trial, this trial will look at multiple solid tumor indications in anti-PD-1/PD-L1-naive settings, initially focusing on melanoma and SCCHN. IO Biotech expects to initiate at least one indication of this trial in the second half of 2022.

Additional opportunities

As well as its programs targeting PD-L1 and IDO, IO Biotech is developing other peptides that target immunosuppressive pathways to diversify its pipeline of immunomodulatory therapeutic solutions. After IO102-IO103, the company's most advanced program is IO112, a fully owned product candidate containing a single Arg-1-derived peptide designed to engage and activate Arg-1-specific human T cells. Arg-1 overexpression is a well-documented tumor escape mechanism associated with difficult-to-treat tumors such as colorectal, breast, prostate, pancreatic and ovarian cancers that exhibit high levels of myeloid-derived suppressor cells.

IO Biotech is seeking partners to expand its clinical-programs application with studies exploring its efficacy in combination with established or experimental immune-modulating agents outside checkpoint blockades in relevant indications. The company is further looking to advance its preclinical programs exploring the adjuvant potential of the company's TME vaccines, including ARG-1 and TGF-β1, in combination with immunotherapy agents and with a special focus on CAR-T cells and bispecific mAbs.

"Cancer immunotherapy has come a long way over the past decade, but its impact for patients has been limited due to a scarcity of targets and the complex immunosuppressive nature of the TME," said Al-Hajj. "At IO Biotech we are focused on changing the paradigm through a diverse portfolio of product candidates we are advancing both internally and through strategic partnerships. The aim is to extract the full potential of immune-modulating agents and to increase the number of safe and effective immunotherapeutic options for cancer patients worldwide."

1. Kjeldsen, J. W. et al. *Nature Med.* **27**, 2212–2223 (2021).
2. Larkin, J. et al. *N. Engl. J. Med.* **381**,1535–1546 (2019).
3. Robert, C. et al. *Lancet* **20**, 1239–1251 (2019).
4. Moser, J. C. et al. *Acta Oncol.* **59**, 434–437 (2020).

CONTACT
Mai-Britt Zocca, CEO
IO Biotech, Inc
New York, NY, USA
Email: mz@iobiotech.com