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By Anju Ghangurde

Glenmark's US-based innovation arm Ichnos delivers first licensing deal for IL-1RAP antagonist, while early data for a bispecific antibody demonstates promising activity in multiple in vitro and *in vivo* tumor models relative to daratumumab and magrolimab.

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Things appear to be picking up at Glenmark Pharmaceuticals Limited's innovation spin-out, Ichnos Sciences, Inc., with the US-headquartered firm striking its first licensing deal with Almirall S.A. for an IL-1RAP antagonist (ISB 880) in autoimmune disease.

Further, promising early data for a bispecific antibody in multiple myeloma presented at the 63rd American Society of Hematology (ASH) annual meeting added some luster to the firm's prospects, albeit in an increasingly competitive and crowded field.

The deal for ISB 880, a first-in-class fully human, high affinity monoclonal antibody that targets human IL-1RAP, will see Almirall hold global rights to develop and commercialize the compound for autoimmune diseases. Ichnos will receive an upfront payment of €20.8m as well as additional development and commercial milestone payments and tiered royalties based on future global sales.

"This is an exciting asset in autoimmune diseases and we expect it to work in a broad array of autoimmune

indications. We've retained the rights to oncology because we may end up using the IL-1RAP [pathway] in some of our oncology assets going forward," Glenmark's chairman and managing director Glenn Saldanha told *Scrip*.

Dr Karl Ziegelbauer, Chief Scientific Officer of Almirall, said that given ISB 880's novel mechanism of action, it has "great potential" to treat underserved patients across a range of autoimmune dermatological diseases. Almirall already has a long-running collaboration with Sun Pharmaceutical Industries Ltd. for the Indian company's IL-23p19 inhibitor tildrakizumab for psoriasis in Europe. (Also see "Sun Builds On Tildrakizumab Hopes With Almirall Pact" – *Scrip*, 29 Jul, 2016.)

Saldanha, however, wasn't keen to be drawn into a comparison with others in the space. Biotech Cantargia AB recently reported positive results for its CAN10 antibody in preclinical systemic sclerosis model. The CAN10 antibody binds IL1RAP with high affinity and functions through simultaneous blockade of IL-1, IL-33 and IL-36 signaling.

Ichnos though noted that blockade of IL-1RAP simultaneously abrogates multiple disease drivers among the IL-1 family of proinflammatory cytokine receptors, including IL-1R, IL-33R, and IL-36R, differentiating ISB 880 from single cytokine blockade therapies. These cytokines have been implicated in numerous autoimmune conditions, opening opportunities for ISB 880 to be positioned across broad disease indications, a company statement said.

Global Development Responsibility

Almirall is to assume "full cost and responsibility" for the global development and commercialization of ISB 880 for all autoimmune disease indications. It expects to initiate the first-in-human study in the first half of 2022.

Investors at parent Glenmark have been keeping a sharp eye on the overall spend rate at the innovation arm. At the earnings call for the second quarter of fiscal 2022, Saldanha had indicated that Ichnos's burn rate had tapered and is constantly on the decline because the "big spender" was ISB 830 (telazorlimab, an OX40 antagonist) while running the Phase IIb study. (Also see "Glenmark's Ryaltris 'Ahead Of The Game' In Markets, COVID-19 Nasal Spray Coming" - Scrip, 17 Nov, 2021.)

"Since that's over, we have one asset in clinic and another one entering. So, the overall spend rate has come down for Ichnos and it will stay low," Saldanha said at the time.

For the first six months of the current financial year ending 31 March 2022, Glenmark invested about $47m in Ichnos versus $53.23m in the corresponding period of the previous financial year.

On improving valuation prospects for Ichnos with the Almirall deal and any impact on its fund-raising plans, Saldanha explained that the US firm will "continue doing partnerships".

"The plan at some point is to do a capital raise, and eventually list the company in the US. So that doesn't change. I can't give you a definitive timeline on any of this but that still remains – the roadmap stays the same," he added.

Ichnos has been engaged in out-licensing discussions with potential partners for the Phase 2b OX40 antagonist telazorlimab (ISB 830) as well. Out-licensing deals for these assets will also enable Ichnos to focus on oncology going ahead, though the firm is open to partnering of the oncology portfolio as well.

Bispecific Antibody

Meanwhile, the New York-headquartered Ichnos also presented preclinical data at the ASH meeting in Atlanta, spotlighting the potential for ISB 1442, a first-in-class biparatopic CD38 x CD47 bispecific antibody as a treatment for relapsed/refractory multiple myeloma and other CD38+ hematological malignancies.

Dr Cyril Konto, president and CEO of Ichnos, explained that the data shows the potential for ISB 1442 to overcome "known mechanisms of resistance" to daratumumab [Janssen Pharmaceutical Cos./Genmab A/S's Darzalex], while minimizing unwanted on-target, off-tumor effects associated with targeting CD47, as with magrolimab.

"ISB 1442 engages myeloid cells more prominently with blocking the CD47/SIRPα binding also known as 'don't eat me' signal which allows killing of CD38 expressing tumor cells by macrophages," Konto told *Scrip*.

Last year Gilead Sciences, Inc. acquired Forty Seven Inc. and its potential first-in-class anti-CD47 monoclonal antibody magrolimab. (Also see "Gilead Calls Forty Seven

Buyout Complementary To Kite, Other IO Efforts" – *Scrip*, 2 Mar, 2020.)

Specifically, ISB 1442 enabled a significant increase in phagocytosis in CD38 low tumor cells relative to that of daratumumab, an antibody that targets CD38; it also improved tumor growth inhibition in an *in vivo* preclinical model compared to daratumumab.

On whether trial plans for ISB 1442 envisage head-to-head studies down the line with daratumumab or magrolimab, Konto said the firm was still discussing the details of its clinical trial design. "Our plan is to file an IND for ISB 1442 by the end of March 2022 and start phase 1 clinical trial by mid-2022".

BEAT Platform

Ichnos has been leveraging its proprietary BEAT (Bispecific Engagement by Antibodies based on the T-cell receptor) platform to develop novel immune cell engagers and modulators in oncology.

Konto explained that a key pillar of the BEAT technology comes from nature and hence solves "engineering bottlenecks" that previously prevented making bispecific antibodies in high quality and on a large scale.

"Natural antibodies use light and heavy chains, and so does BEAT," he added.

While Ichnos' clinical-stage potentially first-in-class T-cell engager, ISB 1342 (CD38 x CD3), is from the first generation BEAT platform, ISB 1442 is based on BEAT 2.0.

Konto indicated that the company was holding initial discussions with potential partners on the oncology portfolio and the BEAT technology. "As more data emerge, we will consider the best approach to moving our assets and the platform forward, including which partnership models would be most beneficial to advancing our pipeline," he maintained.

Ichnos also has ISB 2001 and ISB 2005, its TREAT (trispecific) antibodies in the pipeline. Both are in the discovery phase presently and the company believes they hold potential in hematologic malignancies.

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