BIOBUSINESS BRIEFS

DEAL WATCH

Genentech dives deeper into the next wave of cancer immunotherapies

Genentech is partnering with NewLink Genetics on the development of NLG919 — a Phase I indoleamine 2,3-dioxygenase (IDO) pathway inhibitor that could complement other cancer immunotherapies — by paying US$150 million upfront and potentially more than $1 billion in milestones. The companies have also established a research collaboration for the discovery of further IDO inhibitors and tryptophan 2,3-dioxygenase (TDO) inhibitors.

Immunotherapies are among the hottest drugs in oncology, with agents that target immune checkpoints demonstrating impressive efficacy in a growing range of cancers and garnering blockbuster sales predictions (*Nature Rev. Drug Discov.* **13**, 883–884; 2014). However, "we still have to learn how to activate antitumour T cells in a better and more specific manner," says Benoît Van den Eynde, Director of The Ludwig Institute for Cancer Research, Brussels, Belgium, and co-founder of iTeos Therapeutics. "The main challenge now is to combine current immunotherapy approaches with strategies to overcome the barriers put in place by many tumours to resist immune attack."

IDO inhibitors or TDO inhibitors may help to do just that. IDO and TDO — key enzymes in the tryptophan catabolism pathway — are overexpressed in a variety of cancers, leading to depletion of tryptophan and an accumulation of immunosuppressive tryptophan catabolites. "This pathway is an important mediator of cancer immune evasion, and so inhibiting IDO or TDO could enhance current immunotherapy strategies," says Hatem Soliman, at the Moffitt Cancer Center, Tampa, Florida, USA.

Indeed, preclinical studies suggest that small-molecule IDO inhibitors may synergize with, and help overcome resistance to, existing clinical cancer immunotherapies, such as antibodies that target the immune checkpoint programmed cell-death protein 1 (PD1) or its ligand PDL1 (*Clin. Cancer Res.* **20**, 5290–5301; 2014). "Given their unique mechanism of action, IDO inhibitors and TDO inhibitors have the potential to synergize with any approach that stimulates antitumour T lymphocyte responses, including checkpoint inhibitors, cancer vaccines or adoptive transfer of T cells; as well as other, more classical approaches, including chemotherapy and radiotherapy, whose clinical efficacy also depends to some extent on the immune system," says Van den Eynde.

Soliman is excited about the ease with which these drugs can be combined with other therapies. "As a class, these drugs exhibit mild toxicity profiles that make them ideal combination partners and since they are oral agents, they can be conveniently dosed," he says.

Among the agents that Genentech could combine with NLG919 is its PDL1-specific antibody MPDL3280A, which is in late-stage development and under investigation in combination with an IDO inhibitor from Incyte, INCB24360, as agreed in a deal signed last year.

iTeos Therapeutics, IOmet Pharma and Curadev Pharma are also developing IDO and TDO inhibitors, and NewLink has another IDO inhibitor, indoximod, in Phase II trials in combination with docetaxel in metastatic breast cancer. "The data with chemotherapy are showing some intriguing early signals, and we eagerly await completion of these trials to see if IDO inhibitors can build upon the therapeutic activity of these agents," says Soliman.

Sarah Crunkhorn