

lonctura's IOA-244 to revive PI3K delta inhibitors?

By Cormac Sheridan, Staff Writer

Interim phase I data from 16 patients with refractory metastatic uveal melanoma provide a tantalizing hint that lonctura SA's phosphoinositide 3-kinase (PI3K) delta inhibitor IOA-244 PI3 may offer a survival benefit. Thirteen of the 16 patients – 81.25% – remained alive and on therapy after 12 months of treatment. All had received one or more prior therapies.



Catherine Pickering,
CEO, lonctura

The single-arm, dose-escalation study is not controlled, but historically second- or third-line patients who have already received immunotherapy have a median overall survival of 7.2 months, according to the Geneva, Switzerland-based company. “We’re waiting to see what the median overall survival will be, but it’s certainly pointing in the right direction,” CEO Catherine Pickering told *BioWorld*.

Uveal melanoma is a form of melanoma that affects the uvea or middle layer of the eye. As with cutaneous melanoma, the cancers develop from transformed melanocytes. About 7,000 new cases are diagnosed every year, and about half of these progress to metastatic disease. lonctura is positioning IO-244 as a second- or third-line therapy for patients whose cancers have progressed after immunotherapy. “We come in after checkpoint inhibitors or Kimmtrak, as a monotherapy,” Pickering said.

[Kimmtrak \(tebentafusp\)](#) is a new treatment option, having gained FDA approval in early 2022. Developed by Immunocore plc, it is a fusion protein comprising a recombinant T-cell receptor directed at the glycoprotein peptide 100 (gp100) antigen and a CD3-directed T-cell engager. IOA-244 works by shutting down a cell growth signaling pathway down-regulating regulatory T-cells within tumors, thereby derepressing the immune response.



Michael Lahn, chief
medical officer,
lonctura

Ultimately, lonctura aims to target the therapy at patients who have high levels of PI3K delta expression and high levels of regulatory T cells. It is not, at present, prospectively selecting patients with those characteristics, although it is assessing

patients retrospectively, to establish whether those with such a profile respond better to the therapy than those who do not. “It’s one of our secondary endpoints,” chief medical officer Michael Lahn told *BioWorld*.

The study is now enrolling expansion cohorts from additional indications, including non-small cell lung cancer (NSCLC), mesothelioma, lymphoma, myelofibrosis and solid tumors. “The expansion cohorts are predominantly but not exclusively in second- and third-line settings,” Lahn said. It is also testing IOA-244 in first-line NSCLC patients with low programmed death-ligand 1 (PD-L1) expression, as well as high levels of PI3K delta and regulatory T cells. Such patients currently receive checkpoint inhibitors and chemotherapy but do not have long-term responses. “The question is why?” he asked.

The company is exploring a hypothesis that PI3K delta contributes to drug resistance mechanisms, which may be innate – that is, they are an intrinsic feature of the cancer and would necessitate first-line use of PI3K delta inhibitors – or which may be acquired as the cancer evolves.



Lars van der Veen,
chief operating officer,
lonctura

The PI3K delta inhibitor class has had a checkered history, because of the high levels of toxicity and patient deaths. Accelerated approvals in certain indications for four approved products have all been [voluntarily withdrawn](#) because of problems with confirmatory trials: Gilead Sciences, Inc.’s Zydelig (idealisis); Bayer AG’s Aliqopa (copanlisib); Secura Bio Inc.’s Copiktra (duvelisib); and TG Therapeutics Inc.’s Ukoniq (umbralisib).

lonctura is attempting to put clear blue water between IOA-244 and the other members of the class, based on both its structure and its mechanism. “A lot of these drugs are built on the same chemotype,” Lars van der Veen, chief operating officer at lonctura told *BioWorld*. IOA-244, in contrast, “has a very differentiated chemotype and a very differentiated binding mode.” The other drugs inhibit activated PI3K delta, whereas IOA-244 binds the inactive state and locks it into that conformation and prevents activation from occurring. “It stabilizes the inactive form of the kinase,” he said. “It’s a very different mode of action.”

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lonctura's [phase I trial](#) is ongoing. Some patients have been on therapy for a year or more and its safety profile looks different from other PI3K delta inhibitors, said Lahn. No liver enzyme elevations or diarrhea have been seen in patients, for example. "In many ways, it's like a first-in-class molecule, in that sense," he said. "We've seen no grade 3 or 4 toxicities so far." Moreover, none of the patients needed dose alterations or reductions.

The company has so far raised €27 million in seed and series A

financing rounds and a convertible loan. "We're just about to kick off our series B on the back of the ASCO data," Pickering said. It is targeting €70 million to €80 million. That will enable the company to expand the present trial into combination regimens. It aims to test IOA-244 in combination with the PD-L1 inhibitor avelumab, the Janus kinase inhibitor Jakafi (ruxolitinib) and two chemotherapy agents, pemetrexed and cisplatin. "Once we close the series B, we want to get those started as quickly as possible," she said.