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ASCO 2023 - Servier's Vorasidenib Puts The Brakes On Brain Cancer In INDIGO

Liver Enzyme Elevations Fly In Ointment?

by Alex Shimmings

Servier's targeted therapy, vorasidenib, can effectively delay the need for more drastic treatment in patients with low-grade glioma, but increases in liver enzymes including two cases of Hy's law have cast some shade over the INDIGO data.

Servier's late 2020 decision to pay $1.8bn for *Agios Pharmaceuticals, Inc.*' cancer portfolio appears to be paying off handsomely with the lead investigational product from that transaction, vorasidenib, looking set to provide the first targeted treatment for low-grade glioma.

Full data from the Phase III INDIGO presented at the American Society of Clinical Oncology meeting in Chicago on 4 June show that it produced a near 2.5-fold increase in progression-free survival, putting off the need for radio and chemotherapy in patients who had already received surgery for their brain tumor but were taking a watchful-waiting approach to further treatment.

Servier announced the positive topline data in March, after the study was unblinded following an interim analysis. (Also see "*Servier's Oncology Strategy Pays Off As Vorasidenib Hits Bullseye In Pivotal Glioma Trial*" - Scrip, 15 Mar, 2023.) The full results, also published in the *New England Journal of Medicine*, show the isocitrate dehydrogenase (IDH) 1/2 inhibitor produced an impressive median PFS of 27.7 months compared with 11.1 months for placebo in patients with grade 2 gliomas with IDH mutation over 30 months, based on centrally reviewed brain MRIs (HR,

0.39; 95% CI, 0.27 to 0.56; 1-sided p=0.000000067).

Median time to next treatment, the key secondary endpoint, was 17.4 months with placebo but has yet to be reached with vorasidenib (HR, 0.26; 95% CI, 0.15 to 0.43; 1-sided p=0.000000019). Delaying the need for more toxic therapies is a consideration for glioma patients who are generally relatively young and otherwise healthy.

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If approved, vorasidenib could provide the first alternative to watchful waiting for these patients, opening up a new market for the private French firm that has some major oncology ambitions. It estimates that there are around 2,400 grade 2 glioma patients in the US in 2019, but said recent changes in how the disease is diagnosed are shifting that number upwards.

However, vorasidenib's therapeutic effects were achieved at the expense of nearly one in ten patients (9.6%) on the drug experiencing grade 3 or higher alanine aminotransferase increases. Moreover, Servier confirmed to *Scrip* that two cases of Hy's law were seen in the study. These were both reversible, it said, and added that liver enzyme increases could be easily managed through routine blood work as part of the clinical management of the patient in the treatment protocol. Servier's oncology head, Susan Pandya, said the firm did "not foresee this as having an impact on the success of vorasidenib."

INDIGO co-author, Patrick Wen of the Dana-Farber Cancer Institute, told *Scrip* the hepatotoxicity was very manageable. "The dose can be reduced if it is severe and relatively few patients stop the drug because of the hepatotoxicity. Chemotherapy is not curative and the side effects are definitely greater (fatigue, nausea, constipation, serious bone marrow suppression, infertility). The same is true for radiotherapy."

Nevertheless, the liver toxicity profile is likely to give regulators, especially the US Food and Drug Administration, some pause. Servier has already begun conversations with regulatory authorities around vorasidenib and the data from the pivotal INDIGO trial, and in the interim, the company is working to ramp up supply of vorasidenib ahead of any approvals –it expects these in the US and EU in the second half of 2024. Vorasidenib has EU and US orphan drug status and US fast-track status for glioma.

Approval would also be boon for Agios as it is eligible to receive $200m milestone payment for vorasidenib upon its US nod, as well as 15% royalties on its US sales under the 2020 deal.

Study Details

INDIGO enrolled 331 patients aged between 16 and 71 years with grade 2 gliomas

(oligodendroglioma or astrocytoma) with IDH mutations who had undergone surgery within the previous one to five years but had received no other treatment and who were considered appropriate candidates for a watch and-wait approach (see box). Median time from the last surgery until randomization was 2.5 years in the vorasidenib arm versus 2.2 years in the placebo arm.

Unlike with grade 3 or high-risk grade 2 glioma, most grade 2 glioma patients are not immediately treated with adjuvant chemoradiotherapy, even though it can bring long-lasting remission, because of its potential for neurocognitive dysfunction and other long-term toxic effects.

“Right now, you have two options,” said lead researcher Ingo Mellinghoff of Memorial Sloan Kettering Cancer Center during an ASCO press briefing. “One says, you watch and wait a little bit and let the tumor grow a little bit because the tumor does grow always in the absence of treatment, or you commit to radiation to the brain and chemotherapy, which does not cure you and has significant toxicity. So that is not a great choice you have to make.”

It does, however, provide a window for targeted therapies like vorasidenib change the disease course. INDIGO shows that treatment with an oral precision medicine therapy can reduce the reduction of the risk of tumor progression by 61%, he added.

Other experts were impressed by the data. “The results are quite striking. And they're statistically highly significant, and more importantly, they're clinically very, very significant,” said ASCO reviewer Glenn Lesser of Wake Forest University School of Medicine.

Future Plans

Servier now plans to expand vorasidenib development to other forms of glioma. It is already under evaluation in combination with *Merck & Co., Inc.*’s anti-PD-1 Keytruda (pembrolizumab) in a Phase I study in grade 2/3 glioma and Servier is also considering rational combination therapy efforts in both low- and high-grade glioma based on findings from tumor biopsies taken before and after vorasidenib therapy.

Mutations in the genes for IDH1 or 2 are present in nearly all grade 2 diffuse gliomas in adults and occur early in the disease course. The mutant enzyme produces the metabolite 2-hydroxyglutarate, which accumulates in glioma tissue and competitively inhibits various α-ketoglutarate-dependent enzymes, resulting in a broad range of changes in DNA hydroxymethylation, gene expression, cellular differentiation, and the tumor microenvironment.

IDH mutations are also recognized as drivers of disease biology in patients with a broad range of cancers including acute myeloid leukemia (AML) and chondrosarcoma. Servier is leading the development of this drug class with most competition still at an early stage (see table, story

continues below).

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Servier's Cancer Ambitions

Servier's decision to buy Agios's cancer pipeline was designed to bolster its oncology ambitions. The deal brought it the IDH1 inhibitor Tibsovo (ivosideniob) as well as several earlier stage candidates that target cancer metabolism including, AG-270, a first-in-class methionine adenosyltransferase 2a inhibitor for methylthioadenosine phosphorylase (MTAP)-deleted non-small cell lung and pancreatic cancers, and AG-636, a dihydroorotate dehydrogenase (DHODH) inhibitor.

Previously in 2020, it had inked deals to acquire the Danish antibody discovery-focused biotech *Symphogen A/S* for an undisclosed amount following a two-year partnership, and also announced a collaboration with *Celsius Therapeutics* worth up to $700m to seek new drug targets for colorectal cancer.

Servier is now allocating 50% of its overall R&D budget to this therapeutic to further its aim of being recognized as a player in the development of treatments targeting hard-to-treat cancers and in the hopes of winning five US Food and Drug Administration approvals between 2021 and 2026. It is concentrating on immuno-oncology and targeted therapies and had 38 oncology R&D projects in its pipeline as of January 2023.

Servier's focus on cancer and particularly the Agios deal have already been paying off financially. Oncology's share in consolidated revenues for full-year 2021/22 rose by more than 35% compared to the previous financial year to reach €848 million, representing 17.4% of revenue, compared with 13.6% in 2020/21. This performance was driven by sales of Tibsovo to €256 million in 2021/22, and that drug is currently in development for the treatment of other hematological malignancies, such as myelodysplastic syndromes, which could lead to important label expansions.