First targeted therapy for cholangiocarcinoma shows clinical benefit in phase III trial

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New data have shown for the first time that targeted therapy can improve the outcome of patients diagnosed with advanced cholangiocarcinoma.

Cholangiocarcinoma is a subtype of bile duct cancer with aggressive behaviour and poor prognosis. Despite the low incidence, most patients die from the disease and therefore new effective therapies are urgently needed.

The data reported at the ESMO Congress 2019 are the first to show clinical benefit with targeted therapy in cholangiocarcinoma. Results of the ClarIDHy phase III trial have shown that ivosidenib, an oral drug targeting the isocitrate dehydrogenase 1 (IDH1) mutation, expected in around 15% of advanced cholagiocarcinoma patients, significantly improved progression-free survival with a trend to improved overall survival compared to placebo.

"The ClarIDHy study demonstrates for the first time the feasibility and clinical benefit of targeting a molecularly defined subgroup in cholangiocarcinoma. It shows that targeting mutated IDH1 with ivosidenib significantly improves progression-free survival and gives a favourable trend in overall survival in patients with advanced IDH1-mutated cholangiocarcinoma," said study author Dr. Ghassan Abou-Alfa, Memorial Sloan-Kettering Cancer Center, New York, USA.

"The findings mean all patients with cholangiocarcinoma should be tested for IDH-1 mutation. Tumour mutation profiling should be a new

standard for the care for patients with this heterogeneous tumour type," he said. He considered that future studies should investigate ivosidenib as first-line treatment for IDH1-mutated cholangiocarcinoma in addition to its use in combination therapy and as adjuvant therapy.

Commenting on the relevance of the new data, Dr. Chris Verslype, University Hospital Leuven, Belgium, said, "What we see in this study is really unprecedented. We previously had no options for patients with cholangiocarcinoma who failed systemic therapy, and they had very limited survival. These are important data. There is a gain in progression free survival with ivosidenib that is clinically relevant for this patient population," he said.

Dr. Angela Lamarca, Christie NHS Foundation Trust, Manchester, UK, representing the ESMO Press & Media Affairs Committee, agreed, "The reported median progression-free survival may seem short and some people may question whether this is clinically meaningful. However, for researchers working in cholangiocarcinoma it is a breakthrough. A treatment that increases the chance of being free from progression by 30% at 6 months after starting treatment and that prolongs survival from 6 months with placebo to 10.8 months with ivosidenib, after adjusting for crossover, is definitely meaningful for our patients with cholangiocarcinoma and their families."

Verslype noted, "It's the first time in cholangiocarcinoma that a phase III study tests a drug targeted to a specific anomaly, and it seems to work. Importantly, you identify suitable patients by selecting them for IDH1 mutation. It's precision medicine brought to the clinic. And it's very likely to change clinical practice. It will, for sure, drive the further development of targeted therapy for this disease."

Verslype considered there were few limitations. Patients selected for the study had to have good performance status after previous chemotherapy,

so may not be representative of patients whose disease progresses rapidly on chemotherapy. "But it is still a strong study because of the randomisation to placebo. It showed a real effect." The study had a high crossover rate from placebo to ivosidenib, making the overall survival endpoint difficult to assess, but he pointed out that allowing patients to crossover was important from an ethical perspective. "Additional analysis suggested a benefit in overall survival if there had been no crossover."

Study results

The global phase 3 ClarIDHy study investigated the first in a new class of targeted drugs, ivosidenib, to target a mutant IDH-1 protein. Around one in six patients with cholangiocarcinoma have IDH1 mutations. These result in the production of a metabolite (D-2-hydroxyglutarate) that promotes oncogenesis.

The study randomised 185 patients with advanced cholangiocarcinoma and IDH1 mutations to ivosidenib or matched placebo. Patients could crossover from placebo to ivosidenib when their disease progressed.

Median progression-free survival was 2.7 months for patients treated with ivosidenib compared to 1.4 months with placebo (hazard ratio [HR] 0.37; 95% confidence interval [CI]: 0.25, 0.54, p