DeFi trial: Smart design and impressive results for the benefit of patients with rare cancers

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Significant improvement in progression free survival and response rate combined with reduced symptoms and better quality of life are reported

as outcomes of a new treatment approach for patients with desmoid tumors, which are benign, but locally aggressive and invasive soft tissue tumors. By targeting the Notch pathway with the novel gamma secretase inhibitor nirogacestat, researchers from the DeFi trial have obtained positive results for the first time with this approach. The results are reported at the ESMO Congress 2022.

Desmoid tumors are rare, with an incidence of 3–5 cases per million people worldwide each year. Patients have an unpredictable disease course and, although not generally fatal, the soft tissue tumors can cause symptoms that greatly impair quality of life. "Due to local and aggressive growth, desmoid tumors can cause pain, disfigurement and functional problems that can be a real burden for patients," said lead author Bernd Kasper, Mannheim Cancer Center, Germany.

The DeFi study included 142 patients with progressive desmoid tumors who were recruited from 37 centers across the world. "This is the largest and most rigorous randomized controlled study ever carried out in this tumor type," reported Kasper. "Results showed a statistically significant improvement in progression-free survival in patients randomized to nirogacestat compared to the placebo group, with a 71% lower risk of disease progression on average." The response rate was also much higher—41% in the nirogacestat arm and only 8% in the placebo arm; nearly one in ten patients (7%) showed a complete response with the agent.

The study measured patient reported outcomes because of the major impact of desmoid tumors on quality of life. "We saw a statistically significant benefit in reduction of pain and symptom burden and improvement in physical and role functioning and in health-related quality of life, which was really impressive," noted Kasper. "In providing treatment we try to optimize local tumor control and reduce the symptom burden. But we have previously had no approved therapy for

desmoid tumors. This study has the potential to lead to the first registration of a drug to treat patients with this disease."

"This is a unique study, very important in many aspects," said Jean-Yves Blay, Cancer Center of Lyon, France, who was not involved in the study. "The results show benefit for the first time with a novel treatment with a new mode of action in patients where treatment options are currently limited." The Notch signaling pathway is implicated in the development and progression of many tumor types.

"The findings are practice changing," added Blay. He predicted: "We are going to use nirogacestat as part of the treatment armamentarium for patients with desmoid tumors. But we will have to figure out how best to use it." Remaining questions include which patients should be offered this treatment, where it fits in relation to current approaches, how to identify responders and the optimal duration of treatment. DeFi included patients with progressing tumors but both Blay and Kasper said that nirogacestat could also be considered in patients with pain and impaired functioning.

"This was a very smart study: it demonstrated the feasibility of carrying out a large, placebo-controlled trial—which is the highest quality clinical study to investigate the activity of an agent—in a rare cancer by recruiting patients from a multinational group of reference centers and it demonstrated the importance of targeting the right patients with the right drug when designing clinical trials," Blay said.

"The trial included patients with volumetrically progressive disease, which provided a measurable way to select patients in need of treatment." He added, "The success of this study puts even more emphasis to the concept of having patients with rare cancers referred into reference centers, where clinical studies can be accomplished in record times with the potential to deliver new treatments to patients with

orphan diseases." The number of cancer patients being referred to reference centers is increasing but could still be better in some regions, improving the outlook for patients with rare cancers.

More information: BA2 'DeFi: a phase 3, randomized controlled trial of nirogacestat versus placebo for progressing desmoid tumours (DT)' will be presented by Bernd Kasper during Presidential Symposium 1 on Saturday, 10 September, 16:30 to 18:00 CEST in Paris Auditorium. Annals of Oncology, Volume 33 Supplement 7, September 2022

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