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Long-term efficacy and safety of pexidartinib in patients with tenosynovial giant cell tumor: Final results from the phase 3 ENLIVEN study

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Background: Tenosynovial giant cell tumor (TGCT) is a rare mesenchymal neoplasm of the joint or tendon sheath that is associated with overexpression of colony-stimulating factor 1 (CSF-1). Pexidartinib, a selective inhibitor of the CSF-1 receptor, KIT, and FLT3-internal tandem duplication, is approved by the United States Food and Drug Administration for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. This approval was based on results from the double-blind, randomized, placebo-controlled phase 3 ENLIVEN study (ClinicalTrials.gov identifier: NCT02371369) which evaluated pexidartinib versus placebo in patients with symptomatic, locally advanced TGCT.

Questions/Purposes: We present here the final long-term efficacy and safety results from the phase 3 ENLIVEN study. The purpose of this analysis is to present patient outcomes after long-term pexidartinib treatment, including overall response rate (ORR), timing of response, and long-term safety.

Patients and Methods: Patients aged ≥18 years with symptomatic TGCT, for whom surgery would be associated with potentially worse function or severe morbidity were enrolled and randomized to pexidartinib (1000 mg/day orally for 2 weeks followed by 800 mg/day orally for 22 weeks) or placebo (Part 1). The blinded phase of the study (Part 1) ended for all patients at 25 weeks, after which all patients were unblinded and allowed to take pexidartinib (800 mg/day without a loading dose) until progression or toxicity (Part 2). This analysis includes patients who received pexidartinib at any time during the study. Centrally reviewed ORR by RECIST v1.1 and tumor volume score (TVS), time to response, duration of response, long-term safety, and patient-reported outcomes (PROs) were assessed.

Results: Overall, 91 patients received pexidartinib; median follow-up was 31.2 (range: 2-66) months. Median treatment duration was 25.8 (range: 1-66) months. Compared to week 25 values obtained in Part 1 of the study, the ORR by RECIST v1.1 (sum of the longest diameters [SLD]) increased from 39% to 60.4% and ORR by TVS increased from 56% to 68.1% (**Table**). The ORR by modified RECIST v1.1 (summed short axis dimensions [SSD]) was 78.0%. Median time to response by RECIST v1.1 from start of treatment was 5.4 (range: 2.4-60.9) months for patients who had a complete response (CR; n=29) and 5.7 (range: 2.6-52.5) months for patients with a partial response (PR; n=26). Median duration of response by RECIST v1.1 was not reached (range: 0.03+ to 63+ months). PROs were consistent with tumor response, demonstrating continued clinical improvement. No new patients discontinued pexidartinib due to progressive disease in Part 2. No new safety signals were observed after long-term pexidartinib treatment. Overall, 88/91 (97%) patients had treatment-emergent adverse events (TEAEs) related to pexidartinib; 40/91 (44%) had treatment-related grade ≥3 TEAEs. Grade 3/4 treatment-related TEAEs occurring in >2 patients were aspartate aminotransferase (n=7; 8%) and alanine aminotransferase (n=9; 10%) increases, blood alkaline phosphatase increase (n=4; 4%), and hypertension (n=5; 5%). As previously reported, 4/91 (4%) patients had mixed or cholestatic hepatotoxicity. Overall, 23/91 (25%) patients had a TEAE leading to study drug dose reduction and 18/91 (20%) patients had a TEAE leading to withdrawal of study drug. 30/35 (86%)

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TEAEs leading to dose reduction resolved after the pexidartinib dose was reduced. 27/36 (75%) TEAEs leading to study discontinuation resolved after the patient stopped taking pexidartinib. At the end of the study, 24/91 (26%) patients continued on pexidartinib in another protocol and 10 (11%) patients received commercial pexidartinib.

Conclusions: Final long-term results from ENLIVEN showed that pexidartinib maintained clinical benefit, with an increase in ORR by RECIST v1.1 with continued pexidartinib treatment compared to week 25 values. Importantly, no new safety signals were observed after long-term pexidartinib treatment.

	All pexidartinib treated (N=91)	
Best ORR on treatment, % (95% CI)	**By RECIST v1.1**	**By TVS**
ORR (CR or PR)	**60.4 (50.2-69.9)**	**68.1 (58.0-76.8)**
CR	31.9 (23.2-42.0)	6.6 (3.1-13.7)
PR	28.6 (20.3-38.6)	61.5 (51.3-70.9)
Stable disease	24.2 (16.5-33.9)	18.7 (12.0-27.9)
Progressive disease	1.1 (0.2-6.0)	0 (0-4.1)
Not evaluable	14.3 (8.5-22.9)	13.2 (7.7-21.7)

CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response; TVS, tumor volume score.