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Pexidartinib Provides Modest Pain Relief in Patients With Tenosynovial Giant Cell Tumor: Results From ENLIVEN

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Abstract

Background The double-blind, randomized, placebo-controlled phase 3 study of orally administered PLX3397 in patients with pigmented villonodular synovitis or giant cell tumor of the tendon sheath (ENLIVEN) showed that pexidartinib provides a robust objective tumor response in adults with tenosynovial giant cell tumors (TGCT) not amenable to improvement with surgery. Based on these results, in 2019, pexidartinib received accelerated approval

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in the United States in this population as a breakthrough therapy under an orphan drug designation. However, the ability of pexidartinib to relieve pain in ENLIVEN was not fully detailed, and the relationship between pain relief and objective tumor response was not described.

Questions/purposes (1) What level of pain relief was achieved by pexidartinib treatment in ENLIVEN? (2) How was pain relief related to objective tumor responses? (3) How durable was pain relief?

Methods The current study included planned primary and exploratory assessments of patient-assessed worst pain at the site of the tumor in the ENLIVEN trial. ENLIVEN was a phase 3 randomized, placebo-controlled clinical trial in which adults with TGCT not amenable to improvement with surgery received pexidartinib or placebo for 24 weeks, after which eligible patients could receive open-label pexidartinib. Of 174 patients assessed for eligibility, 121 were randomized (50% [60] to placebo, 50% [61] to pexidartinib), and 120 were given either placebo or pexidartinib (59 received placebo and 61 received pexidartinib) and were included in an intent-to-treat analysis. Fifty-nine percent (71 of 120) of the overall treated population was female, and 88% (106 of 120) were White. Mean age was 45 ± 13 years. Tumors were mostly in the lower extremities (92% [110 of 120]), most commonly in the knee (61% [73 of 120]) and ankle (18% [21 of 120]). As a secondary outcome, patients scored worst pain at the site of the tumor in the past 24 hours on an 11-point numeric rating scale (NRS). The primary definition of a pain response was a decrease of at least 30% in the weekly mean worst-pain NRS score and increase of less than 30% in narcotic analgesic use between baseline and week 25. Planned exploratory assessments of pain included the frequency of a pain response using alternative thresholds, including a decrease in worst-pain NRS score of 50% or more and a decrease of at least 2 points (minimum clinically important difference [MCID]), the magnitude of pain reduction between baseline and week 25, correlation between worst-pain NRS score and tumor shrinkage by RECIST 1.1 criteria, and the durability of the pain response during the open-label extension. Pain responses during the randomized portion of the trial were compared according to intention-to-treat analysis, with a one-sided threshold of $p < 0.025$ to reduce the risk of false-positive results. Pain assessment was complete for 59% (35 of 59) of patients in the placebo group and 54% (33 of 61) of patients in the pexidartinib group. Demographic and disease characteristics did not differ between the two treatment groups.

Results A difference in the primary assessment of a pain response was not detected between pexidartinib and placebo (response percentage 31% [19 of 61] [95% CI 21% to 44%] versus 15% [9 of 59] [95% CI 8% to 27%]; one-sided $p = 0.03$). In the exploratory analyses, pexidartinib provided a modest improvement in pain (response percentage 26% [16 of 61] [95% CI 17% to 38%] versus 10% [6 of 59] [95% CI 5% to 20%]; one-sided $p = 0.02$ using the 50% threshold and 31% [19 of 61] [95% CI 21% to 44%] versus 14% [8 of 59] [95% CI 7% to 25%]; one-sided $p = 0.02$ using the MCID threshold). The least-squares mean change in the weekly mean worst-pain NRS score between baseline and week 25 was larger in patients treated with pexidartinib than placebo (-2.5 [95% CI -3.0 to -1.9] versus

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-0.3 [95% CI -0.9 to 0.3]; p < 0.001), although the mean difference between the two groups (-2.2 [95% CI -3.0 to -1.4]) was just over the MCID. Improvement in the weekly mean worst-pain NRS score correlated with the reduction in tumor size (r = 0.44; p < 0.001) and tumor volume score (r = 0.61; p < 0.001). For patients in the open-label extension, the change in the worst-pain NRS score from baseline was similar to the change at the end of the randomized portion and just above the MCID (mean -2.7 ± 2.2 after 25 weeks and -3.3 ± 1.7 after 50 weeks of receiving pexidartinib).

Conclusion Based on the current study, a modest reduction in pain, just larger than the MCID, may be an added benefit of pexidartinib in these patients, although the findings are insufficient to justify the routine use of pexidartinib for pain relief.

Level of Evidence Level II, therapeutic study.

Introduction

Tenosynovial giant cell tumor (TGCT) is a rare, neoplastic disease diagnosed most commonly in young and middle-aged adults [7, 16]. TGCT affects joints, bursae, and tendon sheaths, and seldomly metastasizes [7]. TGCT disrupts patient function and quality of life in multiple ways, but pain has been cited by patients as the most important symptom [11, 13, 14, 18]. Surgery is commonly used to treat TGCT but does not always eliminate the tumor or reduce pain and can result in postoperative complications [14, 15]. A retrospective study of patients who underwent surgery to remove diffuse-type TGCT found that, at a median follow-up of 54 months, pain had decreased by 59%, but that 44% of patients had developed recurrent disease [14].

Pexidartinib is an orally active inhibitor of the colony-stimulating factor-1 receptor that received accelerated approval in the United States in 2019 as a breakthrough therapy under an orphan drug designation for adults with symptomatic TGCT who have severe morbidity or functional limitations and who are not amenable to improvement with surgery [21]. Approval for this indication was primarily based on the results of a double-blind, randomized, placebo-controlled phase 3 study of orally administered PLX3397 in patients with pigmented villonodular synovitis or giant cell tumor of the tendon sheath (ENLIVEN) [19]. In the study, patients with a symptomatic, advanced TGCT were randomized to receive pexidartinib (n = 61) or placebo (n = 59) for 24 weeks. At week 25, more patients receiving pexidartinib than placebo had a tumor response according to RECIST, version 1.1, criteria (39% versus 0%) and tumor volume score (56% versus 0%). Improvements in patient-reported stiffness and physical function were also greater in patients treated with pexidartinib than in those who received placebo [22]. Pain is one of the most prominent symptoms of TGCT. This fact coupled with evidence suggesting a relationship between pain and tumor responses [14] caused us to wonder whether pexidartinib could help reduce pain in patients with TGCT. Pain was assessed in ENLIVEN as a secondary endpoint using a worst pain numeric rating scale (NRS), but the ability of pexidartinib to relieve pain was not fully detailed in the initial report [19], and the relationship between pain relief and objective tumor responses has not been described.

We therefore provide the results of a planned analysis of data from the ENLIVEN trial to answer three questions: (1) What level of pain relief was achieved by pexidartinib treatment? (2) How was pain relief related to objective tumor responses? (3) How durable was the pain response?

Patients and Methods

Study Design, Setting, Participants, Randomization, and Treatment

This was a protocol-specified analysis of data on worst-pain NRS score from the ENLIVEN trial (NCT02371369) [19]. Briefly, ENLIVEN was a two-part, double-blind, randomized, placebo-controlled, multicenter phase 3 study (part 1) with an open-label extension (part 2) to compare the safety and efficacy of pexidartinib and placebo in adults with symptomatic TGCT not amenable to surgery. In part 1, patients were randomized via an integrated web response system in a 1:1 ratio to receive either pexidartinib (1000 mg per day for 2 weeks, followed by 800 mg per day for 22 weeks) or an identical placebo (24 weeks). Treating clinicians and individuals performing assessments were blinded to treatment assignment. Patients who completed part 1 were eligible to enter part 2, in which they received open-label pexidartinib. More details about the protocol for ENLIVEN can be found at https://clinicaltrials.gov/ct2/show/results/NCT02371369.

The trial was conducted at 39 hospitals and cancer centers in Australia, North America (Canada and United States), and Europe (Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, and United Kingdom). The study enrolled adults (≥ 18 years) with a histologically confirmed diagnosis of TGCT and advanced disease for which surgical resection would be associated with potentially worsening functional limitation or severe morbidity. Patients also had to have a worst pain or worst stiffness NRS score of 4 or more (scored on an 11-point scale from 0 [none] to 11 [worst stiffness possible]) and a tumor size of at least 2 cm. Patients were excluded if they had previous treatment with pexidartinib or any biologic targeting colony-stimulating factor-1 or colony-stimulating

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factor-1 receptor, metastatic TGCT, or active cancer requiring therapy.

The primary endpoint of ENLIVEN was the tumor response proportion at week 25 according to the RECIST version 1.1 criteria, based on a blinded, independent central review of MRIs, wherein the tumor size is measured as the sum of tumor diameters [9]. We assessed tumor volume score as a secondary endpoint which corresponded to the percentage of the volume of the maximally distended synovial cavity or tendon sheath involved [20].

We assessed pain as a secondary endpoint using the worst-pain NRS, which was adapted from the Brief Pain Inventory-short form [5]. Patients scored the worst pain "at the site of the tumor" in the past 24 hours on an 11-point NRS from "0 – no pain" to "10 – pain as bad as you can imagine" [11, 19]. Worst-pain NRS data were collected daily on an electronic handheld device. A daily pain score was determined by the 11-point rating of pain intensity by the patient. Each patient's weekly mean pain score was calculated as a predefined assessment based on completed records. Data needed to be provided for at least 4 of 7 days to compute a weekly mean. A decrease in worst-pain NRS of at least 2 points was defined as the minimum clinically important difference (MCID) in ENLIVEN because it corresponded to a clinically meaningful change in the Brief Pain Inventory worst-pain NRS item [8, 10].

We measured narcotic analgesic use because it was included in the definitions of a pain response to consider the potential confounding effect by the use of these pain relief drugs. Narcotic analgesic use was quantified by multiplying the daily dose unit by the number of units taken, averaged by the number of days with available data [1]. For patients who had a change in narcotic type or dosage because of concomitant use of different narcotic types, narcotic analgesic use was calculated following equianalgesic conversion to morphine-equivalent doses [24]. A minimum of 4 of 7 days of valid recorded data was necessary to compute the arithmetic mean, which included recording of no narcotic analgesic use for 1 day.

Accounting for all Patients

Between May 11, 2015 and September 30, 2016, 174 patients were assessed for eligibility, of whom 121 were randomized (50% [60] to placebo, 50% [61] to pexidartinib) (Fig. 1). One patient randomized to placebo was not dosed. Part 1 of the study (randomized portion) was completed by 81% (48 of 59) of patients in the placebo group and 85% (52 of 61) in the pexidartinib group. Data cutoff for part 1 was March 27, 2017, which was when all patients had completed the final assessment for part 1. Due to discontinuations, nonadherence, and data collection issues, both baseline and week 25 worst-pain NRS data were available for 59% (35 of 59) of patients in the placebo group and 54% (33 of 61) of patients in the pexidartinib group. The detailed reasons for discontinuation were reported elsewhere [19]. Part 2 (open-label portion) included 78 patients who were enrolled between September 29, 2016 and March 27, 2017. Of these, 30 patients who received placebo in part 1 switched to pexidartinib in part 2; the remaining 48 received pexidartinib in part 1 and continued to receive it in part 2. Data reported here were collected up to January 31, 2018.

Demographics

The overall treated population was 59% (71 of 120) female and 88% (106 of 120) White (Supplementary Table 1; http://links.lww.com/CORR/A902). The mean age was 45 ± 13 years. Tumors were mostly in the lower extremities (92% [110 of 120]), most commonly in the knee (61% [73 of 120]) and ankle (18% [21 of 120]). As described previously [19], patient baseline characteristics (age, race, geographical region, disease location, number of previous surgeries for TGCT, previous systemic therapy, tumor size, ROM, and analgesic use) were similar in the two treatment groups.

Sample Size Estimation

As described previously [19], the study was powered to detect a clinically meaningful difference between baseline and week 25 in objective tumor response (that is, not based on the pain response). Briefly, a sample size of 126 patients was planned to provide 90% power to detect a 25% difference in the proportion of patients who had a response (based on an objective tumor response of 10% of patients in the placebo group and 35% in the pexidartinib group) and a two-sided, two-sample comparison at $\alpha = 0.05$. Post hoc power calculations based on the primary definition of a pain response and a one-sided $\alpha = 0.025$ indicate that ENLIVEN (52% power) was underpowered for the primary assessment of pain (Supplementary Table 2; http://links.lww.com/CORR/A903).

Ethical Approval

The ENLIVEN trial was approved by the institutional review board at each participating center and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council on Harmonisation, and the United States Health Insurance Portability and Accountability Act. All patients provided written informed consent to participate. This trial was

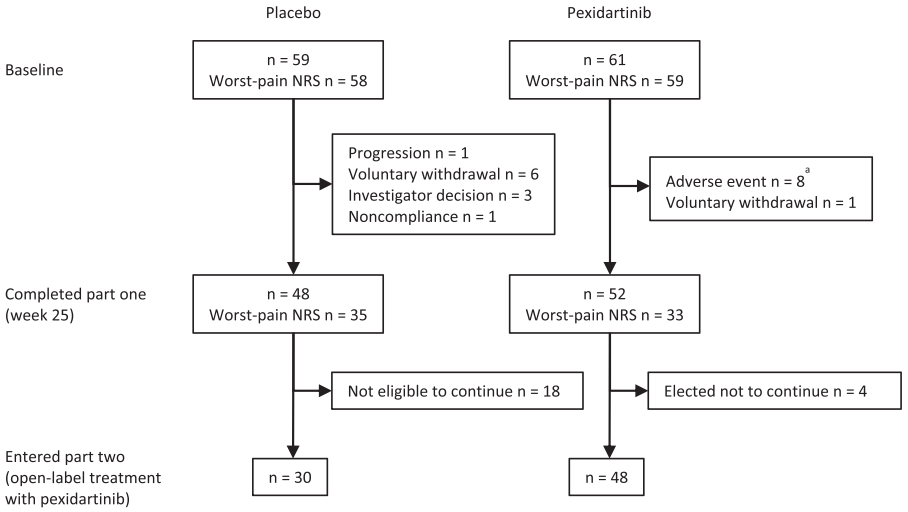

Fig. 1. This flowchart shows the patients who were included in this study. In part 1 of the ENLIVEN trial, patients were randomized to receive a placebo or pexidartinib for 24 weeks. At the completion of part 1 (week 25), patients could enter part 2, in which all patients received open-label treatment with pexidartinib. [a]Seven of the eight adverse events leading to study discontinuation were liver related.

registered in ClinicalTrials.gov (number NCT02371369), and the results of the primary endpoint and other secondary endpoints were reported elsewhere [19]. This manuscript reports the complete analysis of the pain responses reported by the patients in the randomized and open label portions of the trial.

Study Outcomes and Statistical Analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute). For part 1, analyses were conducted in the intent-to-treat population according to randomization. For part 2, analyses were conducted in all patients receiving open-label pexidartinib. No replacements or imputations for missing data were made.

The primary goal of the current study was to determine the level of pain relief achieved by pexidartinib treatment in part 1 (randomized portion) of the ENLIVEN trial. As specified in the protocol for ENLIVEN, the primary definition of a pain response was at least a 30% decrease in the weekly mean worst-pain NRS score and a less than 30% increase in narcotic analgesic use between baseline and week 25. Protocol-specified exploratory assessments of the pain response used the same threshold for narcotic analgesic use but alternative thresholds for weekly mean worst-pain NRS score of a decrease of at least 50% and of at least the MCID (2 points) in the weekly mean worst-pain NRS score between baseline and week 25. Patients with no narcotic analgesic use at both baseline and week 25 were considered as having a less than 30% increase in narcotic use. To reduce the possibility of false-positive results, we compared response percentages between treatment groups using a one-sided Fisher exact test, with a threshold for statistical significance of $p \leq 0.025$. Patients were assigned a nonresponder status if assessments were missing or if sufficient data were not available. In a planned supportive analysis, we compared the mean change in the weekly mean worst-pain NRS score from baseline to week 25 between treatment groups using a mixed model for repeated measures, wherein change in scores from baseline was the dependent variable and treatment group, visit, treatment group-by-visit interaction, site (US versus non-US), baseline worst-pain NRS score, and baseline-by-visit interaction were independent variables. Because of non-negligible missing post-baseline data, post hoc sensitivity analyses were conducted, including a comparison of changes from baseline to week 25 between treatment groups using unconditional jump-to-reference [3] and delta adjustment tipping-point analysis [17] without the missing-at-random assumption (Supplementary Digital Content 1; http://links.lww.com/CORR/A904).

A second goal of the current study was to examine how pain relief was related to objective tumor responses in part 1 of the ENLIVEN trial. For this assessment, we used a Pearson correlation to analyze the relationship between changes from baseline to week 25 of treatment in the weekly mean worst-pain NRS score and the changes in tumor size as measured by RECIST version 1.1 criteria and tumor volume score.

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The final goal of the current study was to explore the durability of the pain response. This was assessed by examining the pain response in patients who received pexidartinib during the open-label extension of ENLIVEN (part 2). In this case, descriptive statistics are provided for changes from baseline in the weekly mean worst-pain NRS score after 25 weeks and 50 weeks of treatment with pexidartinib during part 2.

Results

What Level of Pain Relief Was Achieved by Pexidartinib Treatment in ENLIVEN?

A difference in the primary assessment of a pain response was not detected between pexidartinib and placebo, wherein a pain response was defined by a 30% or more decrease in weekly mean pain NRS score with a less than 30% increase in narcotic use between baseline and week 25 (31% [19 of 61] [95% CI 21% to 44%] for pexidartinib versus 15% [9 of 59] [95% CI 8% to 27%] for placebo; one-sided p = 0.03; threshold for significance = 0.025) (Table 1). In prespecified exploratory analyses, response percentages were higher in patients receiving pexidartinib than in those receiving placebo using alternative thresholds of a decrease in the worst-pain NRS score of at least 50% (26% [16 of 61] [95% CI 17% to 38%] for pexidartinib versus 10% [6 of 59] [95% CI 5% to 20%] for placebo; one-sided p = 0.02) or the MCID (≥ 2 points) (31% [19 of 61] [95% CI 21% to 44%] for pexidartinib versus 14% [8 of 59] [95% CI 7% to 25%] for placebo; one-sided p = 0.02). The least-squares mean change in weekly mean worst-pain NRS score between baseline and week 25 was larger in patients treated with pexidartinib than in patients treated with a placebo (-2.5 [95% CI -3.0 to -1.9] versus -0.3 [95% CI -0.9 to 0.3]; p < 0.001), although the mean difference between the two groups (-2.2 [95% CI -3.0 to -1.4]) was just larger than the MCID of a 2-point decrease (Table 1). This was supported by post hoc sensitivity analysis using an unconditional jump-to-reference method to account for missing data (least-squares mean -2.3 [95% CI -2.9 to -1.6] versus -0.5 [95% CI -1.2 to 0.2]; p < 0.0001) and by tipping point analysis, which showed that the required delta for loss of statistical significance (1.9) was greater than the estimated treatment effect based on the observed data.

How Was Pain Relief Related to Objective Tumor Responses?

Changes in the weekly mean worst-pain NRS score moderately correlated with a reduction in tumor size measured by the RECIST version 1.1 (r = 0.44; p < 0.001) and tumor

Table 1. Change in pain assessments from baseline at the end of part 1 (week 25) of the ENLIVEN trial: primary and exploratory analyses

Analysis	Placebo (n = 59) (95% CI)	Pexidartinib (n = 61) (95% CI)	Mean difference (95% CI)	p value
Patients with baseline and week 25 worst-pain NRS data available	35	33		
Primary analysis of pain response				
≥ 30% decrease in weekly mean worst-pain NRS score and < 30% increase in narcotic analgesic use	15% (9) (8% to 27%)	31% (19) (21% to 44%)	16% (1% to 30%)	0.03 NS[a]
Planned exploratory analyses of pain response				
≥ 50% decrease in weekly mean worst-pain NRS score and < 30% in narcotic analgesic use	10% (6) (5% to 20%)	26% (16) (17% to 38%)	16% (2% to 29%)	0.02[a]
≥ 2-point decrease in weekly mean worst-pain NRS score and < 30% in narcotic analgesic use	14% (8) (7% to 25%)	31% (19) (21% to 44%)	18%[b] (3% to 32%)	0.02[a]
Change in weekly mean worst-pain NRS score (LS mean)	-0.3 (-0.9 to 0.3)	-2.5 (-3.0 to -1.9)[c]	-2.2[b](-3.0 to -1.4)	< 0.001[d]

Data presented as % (n).
[a]Calculated with a one-sided Fisher exact test with a 0.025 level of significance.
[b]The apparent discrepancy in the mean difference is because of rounding effects.
[c]The CI spans the MCID (2-point improvement) in worst-pain NRS.
[d]Calculated by mixed model for repeated measures; LS = least-squares; NS = not statistically significant.

volume score (r = 0.61; p < 0.001) (Fig. 2). The correlation plots and the spider plot of the individual worst-pain NRS scores over time revealed that pain increased in fewer patients receiving pexidartinib than in those receiving a placebo (Supplementary Fig. 1; http://links.lww.com/CORR/A905).

How Durable Was Pain Relief?

During part 2 of the trial, patients who received a placebo during part 1 could switch to open-label pexidartinib, whereas those who received pexidartinib during part 1 could continue to receive it open label. Overall, for all patients included in part

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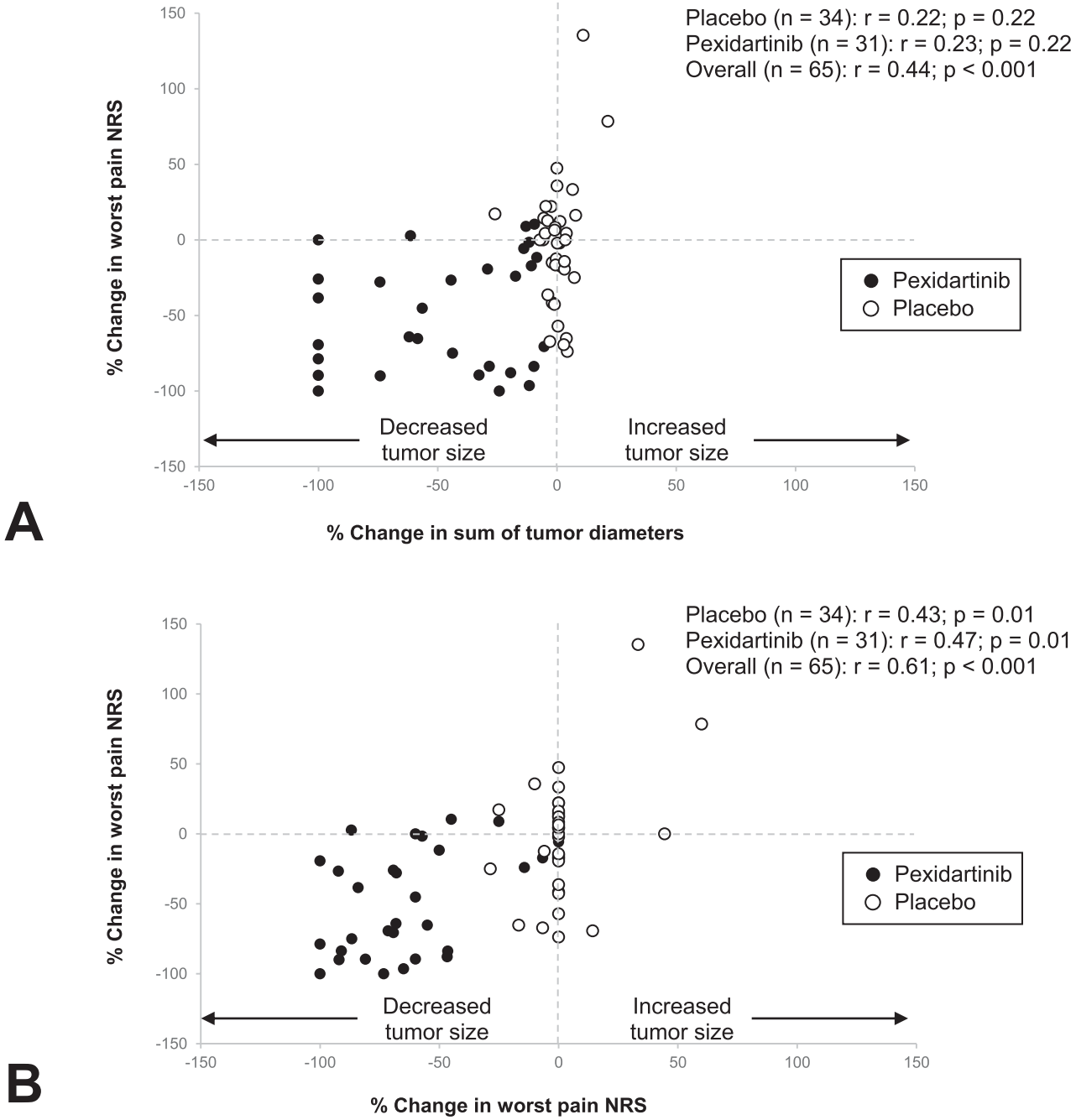

Fig. 2 **A**-**B** These graphs show the correlation between changes in the worst-pain NRS score and tumor response. Tumor response was measured by RECIST, version 1.1 **(A)** sum of tumor diameters and **(B)** tumor volume score at the end of part 1 of the trial; r = Pearson correlation coefficient.

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2, the change in the weekly mean worst-pain NRS score from baseline was -2.7 ± 2.5 after 25 weeks of receiving pexidartinib (51 of 91) and -3.2 ± 2.3 after 50 weeks (32 of 91) (Table 2). When limited to patients who started on pexidartinib during part 1 of the trial and continued to receive it, the weekly mean worst-pain NRS score changed by -2.7 ± 2.2 after 25 weeks (33 of 61) and by -3.3 ± 1.7 after 50 weeks (22 of 61). Similarly, when limited to patients who started on placebo during part 1 and switched to pexidartinib, the change was -2.6 ± 3.1 after 25 weeks of receiving pexidartinib (18 of 30) and -2.8 ± 3.4 after 50 weeks (10 of 30).

Discussion

Pain is one of TGCT patients' major complaints [2, 12], and its mitigation is one of the pressing needs in the management of this neoplastic and inflammatory disease [12]. Given the ability of pexidartinib to provide objective tumor responses and improve physical function and stiffness in patients with TGCT [20, 22], we theorized that pexidartinib could help relieve pain in these patients. This secondary analysis of data from the ENLIVEN phase 3 trial showed that, in patients unlikely to benefit from surgery, pexidartinib resulted in a reduction in pain that was small overall but occasionally dramatic. This suggests that a modest pain reduction may be an added benefit of pexidartinib in these patients; however, because this was based on an exploratory assessment from a randomized trial, it is not sufficient to justify the regular use of pexidartinib for pain relief. The results also indicate that future studies on pain relief in TGCT should examine what patients consider meaningful instead of, or in addition to, extrinsically validated measures.

Limitations

Two main limitations of this study are that it did not demonstrate a difference in the primary pain assessment and that the worst-pain NRS score was a secondary outcome measure in ENLIVEN. This means that the results of this study can be considered suggestive but not conclusive. Another limitation was that complete pain data were unavailable for nearly half the patients, mostly owing to early discontinuations, technical issues with electronic data capture, institutional and patient adherence, and enrollment being halted just short of the target because of hepatotoxicity [19]. Combined with the small sample size, the study was therefore underpowered for assessing differences in worst-pain NRS score. A further limitation of this study is that blinding may have been compromised by hair lightening, a reversible effect experienced by up to 80% of patients treated with pexidartinib [20]. Likewise, the open-label design of the study extension could have influenced results supporting durability of the pain response. Finally, the impact of NSAID use is not clear because it was not included in response definitions. Thus, confirmation of the current results would require a study specifically designed to assess pain while limiting the impact of potential biases. Finally, the population included in this study appeared to be generally representative of patients with TGCT, including a higher frequency of females, a mean age of older than 40 years, and the knee as the most common joint affected [16]. However, TGCT is a rare disease and consequently, the study population was small, so it was not practical to examine differences in response between subpopulations, for example by sex or age.

What Level of Pain Relief Was Achieved by Pexidartinib Treatment in ENLIVEN?

Overall, the current results indicate that pexidartinib may provide modest pain relief, just larger than the MCID, to patients with TGCT who choose not to have or who are not candidates for surgery. Emactuzumab, a monoclonal antibody targeting colony-stimulating factor-1 receptor [4],

Table 2. Exploratory analysis of the durability of the pain response after study extension (part 2)

Outcome	All patients treated with pexidartinib (n = 91)	Received pexidartinib during part 1 and part 2 (n = 61)	Received a placebo during part 1, switched to pexidartinib during part 2 (n = 30)
Change in the weekly mean worst-pain NRS score after 25 weeks on pexidartinib	51 (-2.7 ± 2.5)	33 (-2.7 ± 2.2)	18 (-2.6 ± 3.1)
Change in the weekly mean worst-pain NRS score after 50 weeks on pexidartinib	32 (-3.2 ± 2.3)	22 (-3.3 ± 1.7)	10 (-2.8 ± 3.4)

Data presented as n (mean ± SD). At the completion of part 1 of the trial (week 25), patients could enter part 2, in which all patients received open-label treatment with pexidartinib; therefore, some patients received pexidartinib for up to 50 weeks; NRS = numeric rating scale.

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and imatinib mesylate, an inhibitor of the colony-stimulating factor-1 receptor tyrosine kinase [23], have also been shown to improve TGCT symptoms based on retrospective studies, but the magnitude of pain relief has not been reported. Indeed, to our knowledge, ENLIVEN is the only randomized clinical trial to have included a patient-reported outcome measure specific to pain [11].

The different findings of the primary and exploratory analyses imply that the threshold for a pain response needs to be carefully chosen. Specifically, although pexidartinib did not provide a benefit over placebo according to the primary threshold of 30% or more improvement in pain NRS score, it did according to the exploratory thresholds of at least 50% and a 2-point or greater MCID improvement. Repeated-measures analysis and related sensitivity analyses also supported a difference between pexidartinib and placebo. This difference between the primary and exploratory thresholds was likely due to a substantial placebo effect, which is common in clinical pain studies [6], coupled with the relatively small sample size. Accordingly, a higher threshold for a pain response may be warranted for clinical trials in this population. These results also highlight the deficiencies of unidimensional measures and aggregate reporting of pain, as with the worst-pain NRS score and other measures. A more nuanced, multidimensional method for assessing pain may be needed to better capture patients' experiences.

How Was Pain Relief Related to Objective Tumor Responses?

Pain relief in patients treated with pexidartinib moderately correlated with objective tumor responses. Similarly, we recently showed that improvements in stiffness and physical function correlated with objective tumor responses in ENLIVEN [22]. In a few patients (3 of 33) treated with pexidartinib, pain remained unchanged or worsened slightly, which may be due to a residual tumor affecting surrounding tissues, secondary osteoarthritis, continuing synovitis, underlying degenerative joint disease, or sequalae from earlier surgeries. However, worsening of pain associated with disease progression was not found.

How Durable Was Pain Relief?

Based on results of the open-label extension, pain relief appeared to be sustained for at least 50 weeks. Among patients who crossed over to receive an active drug, pain relief during the initial 25 weeks of treatment was similar to that seen in patients randomized to receive pexidartinib originally. Thus, the half year on placebo did not appear to preclude pain relief once the drug was started. However, the results are suggestive only because of the limitations of the open-label design of the study extension.

Conclusion

Pain is the most important symptom in patients with TGCT, and it is often exacerbated by secondary degenerative arthritis [2, 12]. Particularly when a patient with TGCT chooses not to have or is not a good candidate for surgery, there is a compelling need to shrink the tumor and to mitigate pain [12]. Clinicians must consider the alternatives to systemic drug therapy, including surgery (which has real risks), watchful waiting for disease progression and joint destruction, and radiotherapy (which can produce local morbidity or even secondary sarcoma) [12]. The limitations of these options make systemic treatment attractive, despite a lack of data on its ability to preserve joints over the long term and its potential for adverse effects. When TGCT is not amenable to surgery without unacceptable morbidity, pexidartinib should be considered for its ability to cause tumor shrinkage and improve physical function and stiffness [19, 22], although this must be balanced against the risk for liver toxicity [20]. Based on the current study, a modest pain reduction, just larger than the MCID, may be an added benefit of pexidartinib in these patients, although the findings are insufficient to justify the routine use of pexidartinib for pain relief.

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