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Original Article

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

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Abstract

Background: Pexidartinib is approved in the US, Taiwan, and Korea for adults with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery based on the phase III ENLIVEN study (NCT02371369). We report the final long-term efficacy and safety results from ENLIVEN.

Methods: Adults with symptomatic TGCT not eligible for surgery were enrolled and randomized to pexidartinib or placebo (part 1). The blinded phase (part 1) ended at week 25; patients received pexidartinib (800 mg/day) until progression, toxicity, or study completion (part 2). This analysis includes patients who received pexidartinib at any time during ENLIVEN. Centrally reviewed overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and tumor volume score (TVS), time to response, duration of response (DOR), patient-reported outcomes (PROs), and long-term safety were assessed.

Results: Overall, 91 patients received pexidartinib. With a median follow-up of 31.2 (range: 2-66) months, ORR was 60.4% and 68.1% by RECIST and TVS, respectively. Median DOR by RECIST was not reached (range: 0.03-63.4 months). Most responses were within the first 6 months of treatment; most responders were on 800 mg vs 600/400 mg dose levels, respectively. Throughout parts 1 and 2, 3 (3%) patients had progressive disease per RECIST without dose reduction/interruption. PROs improved or were maintained. The most common grade 3/4 treatment-emergent adverse events were aspartate aminotransferase (AST) increase (9%), alanine aminotransferase (ALT) increase (10%), and hypertension (8%). Twenty-eight (31%) patients had AST or ALT ≥3 times the upper limit of normal (ULN); 17 (19%) patients had AST or ALT ≥5 times the ULN. No new safety signals were observed after long-term pexidartinib treatment.

Conclusions: Final long-term ENLIVEN results demonstrated that pexidartinib sustained clinical benefit, with increased ORR by RECIST and TVS compared to the end of the blinded phase at week 25. No new safety signals were reported.

Keywords: giant cell tumor of tendon sheath; Response Evaluation Criteria in Solid Tumors; patient-reported outcome measures; clinical trial, phase III.

Implications for practice

We report the final ENLIVEN long-term safety and efficacy of pexidartinib in patients with tenosynovial giant cell tumor not amenable to surgery. Although most tumor responses per Response Evaluation Criteria in Solid Tumors (RECIST) or tumor volume score occur within the first 6 months of treatment, responses generally deepen over time. Three patients had progressive disease (per RECIST) after response at 800 mg/day. The risk of hepatotoxicity was highest during the first few months of treatment; no new safety signals occurred. This study demonstrated that long-term treatment with pexidartinib is safe and effective and informs physicians and patients on what to expect during prolonged treatment with pexidartinib.

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Introduction

Tenosynovial giant cell tumor (TGCT) is a rare mesenchymal neoplasm that most frequently occurs in the synovium of joints, bursae, or tendon sheaths.[1,2] Patients with TGCT often experience increased pain and impaired daily functioning compared with the general population.[3] Diffuse-type TGCT occurs in approximately 10%-20% of patients with TGCT.[4,5] Patients with diffuse TGCT report worse quality of life compared with those with localized TGCT.[3,6] Surgical resection is standard treatment for TGCT; however, in some cases, surgery may not be possible due to the potential for morbidity and recurrence after surgery, particularly in patients with diffuse-type TGCT.[7]

Pexidartinib is an orally administered small-molecule tyrosine kinase inhibitor with strong selective activity against the colony-stimulating factor 1 (CSF-1) receptor; it also inhibits KIT receptor tyrosine kinase and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication.[8,9] Pexidartinib has been approved in the US, Taiwan, and Korea for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery (or other treatment; Taiwan only).

Approval of pexidartinib was based on the results of the phase III ENLIVEN study (NCT02371369), a double-blind, randomized study in which patients with TGCT received pexidartinib or placebo. The proportion of patients who achieved overall response (ORR) at week 25 by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST) was higher for pexidartinib (39%) than placebo (0%).[9] Response by tumor volume score (TVS) was 56% in the pexidartinib group vs 0% in the placebo group.[9] Pexidartinib also significantly increased patients' relative range of motion and improved their stiffness and overall physical functioning.[9] The most common adverse events (AEs) included hair color changes, fatigue, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increase, nausea, and dysgeusia.[9] According to clinical laboratory values, 3 patients had AST/ALT elevations ≥3 times the upper limit of normal (ULN), with bilirubin and alkaline phosphatase (ALP) ≥2 times the ULN, which indicated mixed or cholestatic hepatotoxicity.[9] Because TGCT can be a chronic condition, particularly for those with diffuse TGCT not amenable to surgery, it is important to understand the long-term efficacy and safety of pexidartinib in these patients. Indeed, additional studies have already demonstrated that pexidartinib continued to show benefit: in a pooled analysis of patients with TGCT enrolled in the ENLIVEN study and in a phase I study, response rates per RECIST and TVS were 60% and 65%, respectively, at 3 years, with no new safety concerns.[10]

Here we report the final long-term efficacy and safety results from the ENLIVEN study.

Methods

The ENLIVEN study was a randomized, placebo-controlled, phase III study in patients with TGCT.[9] The methods for this study have been described; the primary analysis examined efficacy and safety at the end of the double-blind portion of the study at 25 weeks (part 1; data cutoff: March 27, 2017).[9] Part 2 involved open-label continuation of pexidartinib or crossover to pexidartinib for participants previously on placebo (Supplementary Figure S1). This analysis reports data from the final cutoff of April 2021 and includes patients who received pexidartinib at any time during the ENLIVEN study.

Eligible patients had histologically confirmed, advanced, symptomatic TGCT with measurable tumors ≥2 cm per RECIST v1.1 for which surgical resection was associated with a potential for worsening of functional limitation or severe morbidity.[9] Symptomatic disease was defined as a worst pain or worst stiffness numeric rating scale (NRS) of ≥4. All patients provided written informed consent. An independent data monitoring committee was responsible for assessing study drug safety during the study, monitoring overall study conduct, and making recommendations about continuing, modifying, or stopping the study. The institutional review board at each participating center approved the study, and study ethics were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. This study is registered with ClinicalTrials.gov, number NCT02371369.

In part 1, patients received pexidartinib 1000 mg (or matching placebo) delivered as 400 mg in the morning and 600 mg in the evening for 2 weeks, followed by 800 mg delivered as 400 mg twice a day for 22 weeks. In part 2, patients either crossed over from placebo to receive pexidartinib 800 mg split twice a day (without loading dose) or continued the dose of pexidartinib that they received at the end of part 1 until tumor progression, toxicity, or study completion. Tumors were measured by magnetic resonance imaging (MRI) at baseline, week 13, and week 25 in part 1 and every 12 weeks in part 2. Safety was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0.

The primary endpoint was RECIST v1.1 ORR (ie, the proportion of patients who achieved a response at the end of part 1 based on centrally read MRI and RECIST). Secondary endpoints were mean change from baseline in range of motion of the affected joint (relative to a reference standard for the same joint), centrally evaluated proportion of patients with response based on TVS, mean change from baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS)–Physical Function scale,[11,12] mean change from baseline in worst stiffness NRS (stiffness), mean change from baseline in Brief Pain Inventory worst pain NRS, and duration of response based on RECIST and TVS. The PROMIS–Physical Function scale addresses symptoms of immobility, with a score of 50 representing average level of physical functioning in the US general population. A 3-point change is considered to represent a clinically meaningful difference. One-item questionnaires were used to assess stiffness and pain: stiffness rating was based on an NRS ranging from 0 (no stiffness) to 10 (stiffness as bad as you can imagine). The NRS for pain assessed the worst pain experienced in the past 24 hours, ranging from 0 (no pain) to 10 (pain as bad as you can imagine).

Statistical analysis

This analysis includes patients who received pexidartinib in part 1 and/or part 2 of the ENLIVEN study. The modified intent-to-treat (ITT) analysis set includes patients who were randomized in part 1 and received ≥1 dose of pexidartinib. The part 2 analysis set includes patients who crossed over from placebo in part 1 to pexidartinib in part 2. The all pexidartinib-treated analysis set includes all randomized

patients who received pexidartinib in part 1 and those who received open-label pexidartinib in part 2.

Baseline values are dependent on the patient's randomized group: for patients randomized to pexidartinib, this is the same baseline as in part 1. For patients randomized to placebo, the part 2 baseline value is the last assessment before the first dose of open-label pexidartinib. Descriptive analysis was used to summarize the data. For continuous variables, analysis included the number of patients with nonmissing data, mean, median, 95% CIs, minimum, and maximum. Frequency and percentage of observed levels are reported for categorical measures. ORR and other efficacy endpoints were calculated in the modified ITT group, which included patients randomized to pexidartinib in part 1 and those who received open-label pexidartinib in part 2. Two-sided 95% CIs for the ORR proportions were calculated using the Wilson method. The best overall response (OR) was based on RECIST or TVS and determined among all responses recorded from the start of treatment until the last radiographic assessment. Time to response was measured as the time from baseline to any response per RECIST or TVS in those patients who had an objective response.

Duration of response was defined from the date of the first recorded response to the date of the first documented disease progression. For patients with no radiological progression, duration was censored from the date of the last MRI scan. The Kaplan-Meier method was used to compute the median duration of response. SAS 9.4 was used for statistical analyses.

Results

Patients

From May 11, 2015 (the start of part 1) to April 30, 2021 (data cutoff for part 2), 91 patients received pexidartinib. Enrollment to ENLIVEN part 1 was terminated early due to the emergence of mixed or cholestatic hepatotoxicity and subsequent review of the study design. This led to total enrollment at 95% of the original target and increased patient withdrawal following the safety signal. Seventy-eight patients continued pexidartinib in part 2 and received ≥1 dose of pexidartinib; this included 48 patients who continued pexidartinib from part 1 and 30 patients who crossed over from the placebo arm in part 1 (Figure 1). Baseline characteristics for all pexidartinib-treated patients are shown in Table 1. The median age was 46 years, 56% of patients were

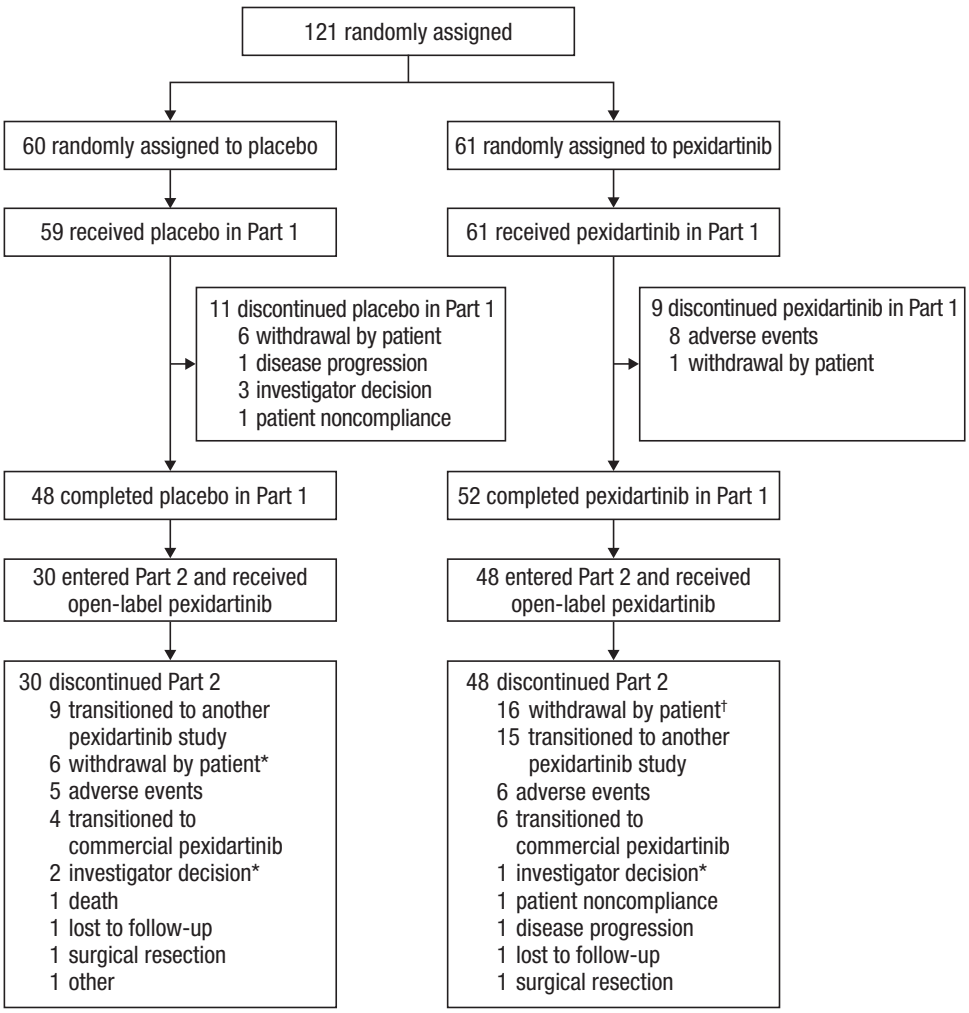

Figure 1. Patient flow through parts 1 and 2 of ENLIVEN. *After urgent safety measure. †15 patients discontinued after the urgent safety measure; 1 discontinued prior to the urgent safety measure.

Table 1. Baseline demographic and disease characteristics.

Characteristic, *n* (%)	All pexidartinib-treated (*N* = 91)
Age, median (range), years	46.0 (20-79)
Sex, female	51 (56)
Race	
White	82 (90)
Black or African American	3 (3)
American Indian or Alaska Native	2 (2)
Native Hawaiian or Other Pacific Islander	2 (2)
Asian	1 (1)
Multiracial	1 (1)
Time from diagnosis to randomization, median (range), days	1251 (15-14,912)
TGCT subtype	
Diffuse	79 (87)
Localized	12 (13)
Tumor location	
Upper body	9 (10)
Shoulder	2 (2)
Elbow	1 (1)
Wrist	3 (3)
Hand	0
Finger	1 (1)
Spine	2 (2)
Lower body	82 (90)
Hip	9 (10)
Knee	53 (58)
Ankle	17 (19)
Foot	3 (3)
Toe	0

Abbreviation: TGCT, tenosynovial giant cell tumor.

female, and the most common tumor site was the knee (58%). The median treatment duration was 112 weeks (range: 4-288 weeks [1 month-5.5 years]). All patients enrolled in part 2 discontinued from the study as of the final data cutoff. A complete list of reasons for discontinuation is shown in Supplementary Table S1 and Figure 1. The most common reasons reported for discontinuation were transition to another sponsored protocol with pexidartinib (NCT04526704: 24 patients; 31%) and withdrawal of consent (22 patients; 28% [21/22 discontinued after an urgent safety measure]). Eleven (14%) patients discontinued due to an AE and 10 (13%) transitioned to a commercial supply of pexidartinib. One (1%) patient discontinued due to disease progression in part 2.

Specifically among the 55 patients who responded to treatment with pexidartinib per RECIST during ENLIVEN, the primary reasons for discontinuation were transition to another protocol with pexidartinib (20 patients; 36%), withdrawal of consent (14 patients; 25%), transition to a commercial supply (10 patients; 18%), and AEs (6 patients; 11%). The full list of reasons for discontinuation in responders is shown in Supplementary Table S2.

Dosing

The average (standard deviation) daily dose for parts 1 and 2 was 651.4 (167.6) mg. Thirty-six (40%) patients had a dose reduction (<800 mg/day) to either 600 or 400 mg/day. By the end of the study, 57 (63%) patients were receiving 800 mg/day, 16 (18%) 600 mg/day, and 18 (20%) 400 mg/day. The median time to first dose reduction (from 800 mg) was 5.7 (Q1, 1.9; Q3, 15.6) months.

OR

With a median follow-up of 31.2 (range: 2-66) months, the ORR by RECIST was 60% (Table 2). There was no discernible difference in ORR between patients randomized to pexidartinib in part 1 and those who received pexidartinib in part 2 only (61% vs 60%). The ORR by TVS was 68%, with no discernible difference between the patients randomized to pexidartinib in part 1 and the crossover group (67% vs 70%). In part 1, 1 patient each in the placebo and pexidartinib groups had progressive disease (PD) as their best OR. No patient in part 2 had PD as their best OR. Forty-six (51%) patients achieved response on 800 mg. Two patients randomized to placebo had PD per TVS as their best OR in part 1. No patient receiving pexidartinib had PD per TVS as their best response.

Figure 2 shows the waterfall plots for tumor responses (percent change from baseline of the sum of the longest diameter) after the database locks in 2017 and 2018 and the last database lock in 2021. The median decrease in the sum of diameters of the target lesion per RECIST was 28% in 2017 (at the first analysis) and increased to 68% in 2021, demonstrating that responses deepen over time.

Time to response

The median time to response by RECIST was 5.1 (range: 2-53) months; 36 (66%) patients responded within the first 6 months of treatment (Figure 3). Spider plots showing the percent change in the sum of diameters from baseline in target lesions for individual patients for parts 1 and 2 are shown in Supplementary Figure S2. The median duration of response for all responders with a median follow-up of 50 months for RECIST was not reached; the range was 0.03-63.4 months. The median duration of response by TVS was also not reached; the range was 0.03-63.5 months. Tumor response over the course of treatment for individual patients is shown in Supplementary Figure S3.

Per RECIST, 14/91 (15%) patients treated with pexidartinib had PD; 13 of these patients had PD after an objective response (ie, secondary progression); the remaining patient had a primary progression. Eleven of the 14 patients had PD after either a dose reduction or a treatment-emergent AE (TEAE) requiring dose interruption. Three of the 14 patients had PD without (or prior to) a dose reduction/interruption. Per TVS, 12/91 (13%) patients had PD; 11 of these 12 PD occurred after an objective response, and 7/12 PD occurred after either a dose reduction or a TEAE requiring a dose interruption. One patient in the placebo group had PD and discontinued the study.

Surgery

At baseline for part 1, 32/61 (52%) and 31/59 (53%) patients randomized to the pexidartinib and placebo arms, respectively, had prior surgery for TGCT; the median number of

Table 2. Best ORR and duration of response by RECIST v1.1 and TVS.

	Randomized to placebo (Part 1 only; *n* = 59)	Randomized to pexidartinib (parts 1 and 2; *n* = 61)	Crossover pexidartinib (part 2 only; *n* = 30)	All pexidartinib- treated (N = 91)
Response per RECIST v1.1*				
ORR	0 (0; 0–6)	37 (61; 48–72)	18 (60; 42–75)	55 (60; 50–70)
SD	36 (61; 48–72)	14 (23; 14–35)	8 (27; 14–44)	22 (24; 17–34)
PD	1 (2; 0.3–9)	1 (2; 0.3–9)	0 (0; 0–11)	1 (1; 0.2–6)
Not evaluable	22 (37; 26–50)	9 (15; 8–26)	4 (13; 5–30)	13 (14; 9–23)
Duration of response per RECIST v1.1,† median (range), months	–	NR (4.6+ to 63.4+)	NR (0.03+ to 56.0+)	NR (0.03+ to 63.4+)
Response per TVS*				
ORR	0 (0; 0–6)	41 (67; 55–78)	21 (70; 52–83)	62 (68; 58–77)
SD	35 (59; 47–71)	12 (20; 12–31)	5 (17; 7–34)	17 (19; 12–28)
PD	2 (3; 1–12)	0 (0; 0–6)	0 (0; 0–11)	0 (0; 0–4)
Not evaluable	22 (37; 26–50)	8 (13; 7–24)	4 (13; 5–30)	12 (13; 8–22)
Duration of response per TVS,† median (range), months	–	NR (0.03+ to 63.5+)	NR (8.0+ to 56.0+)	NR (0.03+ to 63.5+)

*Data are n (%; 95% CI), unless otherwise specified.
†All patients with best overall response of CR or PR whilst on treatment are summarized.
Abbreviations: CR, complete response; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TVS, tumor volume score.

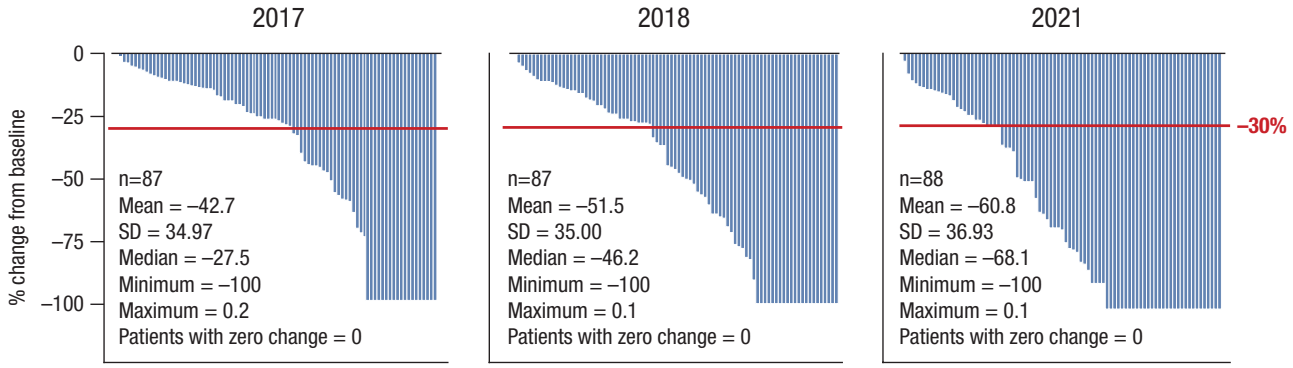

Figure 2. Tumor responses for the March 2017, January 2018, and April 2021 data cutoffs. Abbreviations: SD, standard deviation.

prior surgeries was 2. The most common type of surgery was synovectomy: 14/32 (44%) patients in the pexidartinib group and 11/31 (35%) in the placebo group. RECIST response rates at week 25 for pexidartinib-treated patients were 34% and 41% for patients with and without prior surgery, respectively; the rates increased to 56% and 66% in part 2.

Three of the 61 patients randomized to pexidartinib had post-treatment surgery (1 had prior surgery, 2 did not). While receiving pexidartinib, 1 patient had an objective response and the other 2 patients had stable disease per RECIST (2 patients had OR per TVS). Two patients had complete macroscopic tumor resections. Per surgeon reports, post-treatment surgery was possible due to "reduced morbidity" and "improved probability of complete resection."

Patient-reported outcomes

Patient-reported outcome results are shown in Supplementary Figure S4. Results for time points with data from ≥10 patients are shown; toward the later visits in part 2 when sample sizes are smaller, the results can be biased and therefore should be considered descriptive in nature. The improvements in range of motion (Supplementary Figure S4A), PROMIS–Physical Function (Supplementary Figure S4B), worst stiffness NRS (Supplementary Figure S4C), and Brief Pain Inventory worst pain NRS (Supplementary Figure S4D) with pexidartinib at week 25 were maintained, on average, through part 2 of the study.

Safety

Table 3 lists a summary of TEAEs for part 1, part 2, and all patients who received pexidartinib at any time during the study. Overall, the incidence of TEAEs was similar between parts 1 and 2. In part 2, most patients (88/91; 97%) had TEAEs related to pexidartinib; 40/91 (44%) had treatment-related grade ≥3 TEAEs. In parts 1 and 2, 30/35 (86%) TEAEs leading to dose reduction resolved after the pexidartinib dose was reduced. The 5 TEAEs that were not resolved after dose reduction were increased AST (2 events), memory impairment (2 events), and peripheral swelling. Of the 36 TEAEs leading to study discontinuation, 27 (75%) resolved after the patient stopped taking pexidartinib. TEAEs not resolved after discontinuation by the end of the study were elevated transaminases (3 events) and 1 event each of photophobia, arthralgia, hypesthesia, skin hypopigmentation, and

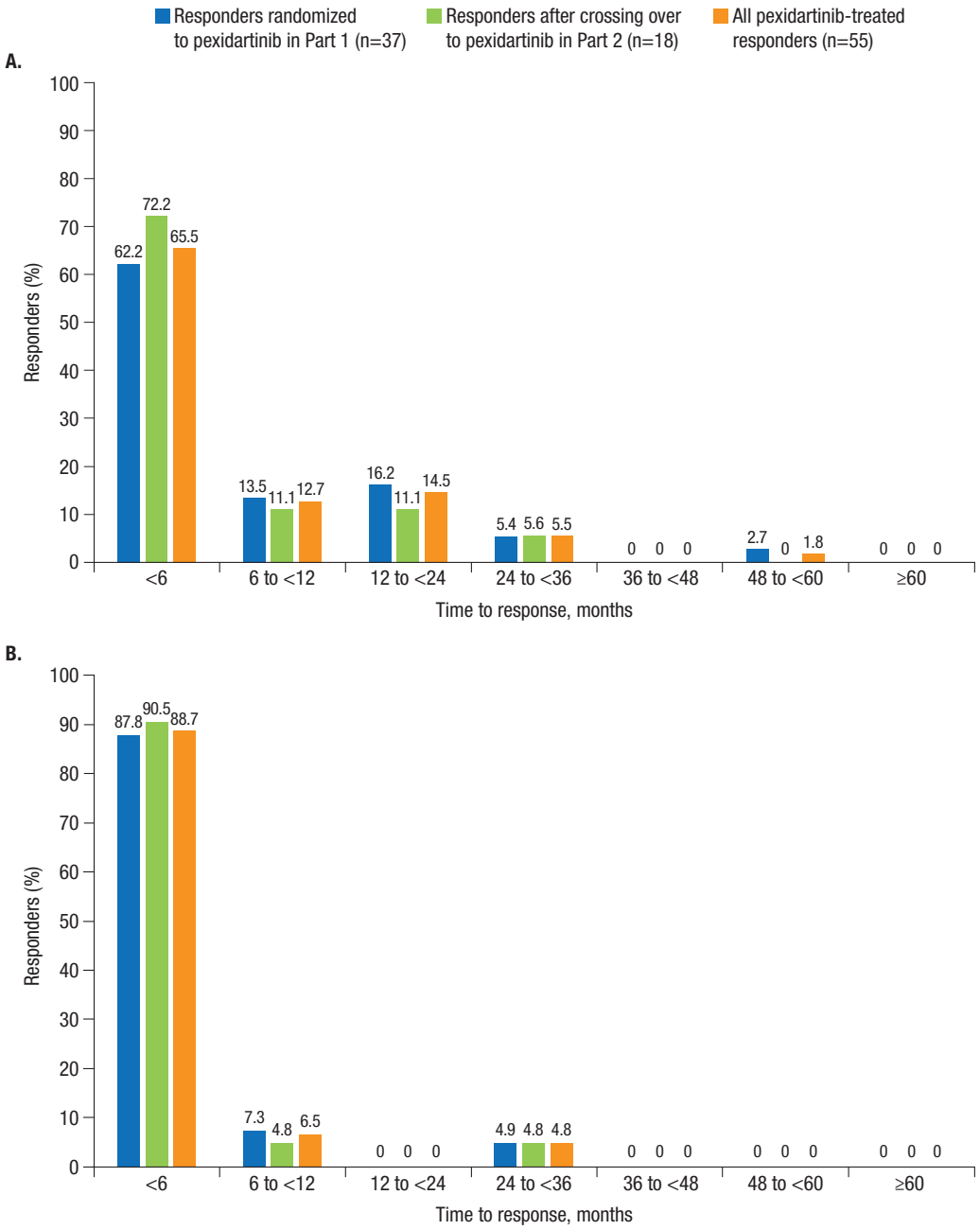

Figure 3. Time to response for part 1, part 2, and all pexidartinib-treated patients per (A) RECIST v1.1 and (B) TVS. Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; TVS, tumor volume score.

increased blood bilirubin. Treatment-related grade 3/4 TEAEs occurring in >2 patients were AST (n = 7; 8%) and ALT (n = 9; 10%) increases, blood ALP increase (n = 4; 4%), and hypertension (n = 5; 6%).

Liver function tests over time are shown in Supplementary Table S3. Twenty-eight (31%) patients had AST or ALT ≥3 times the ULN; 17 (19%) patients had AST or ALT ≥5 times the ULN. During part 1, 3 (3%) patients had concurrent total bilirubin and ALP ≥2 times the ULN with AST or ALT ≥3 times the ULN, consistent with mixed or cholestatic hepatotoxicity; no additional cases were observed in patients who crossed over to pexidartinib from placebo, and no cases of Hy's law were observed. All cases were adjudicated by the Hepatic Event Adjudication Committee. TEAEs occurring in >20% of patients treated with pexidartinib are listed in Table 4. The most common of any grade were hair color changes (76%), fatigue (47%), nausea (39%), arthralgia (37%), and AST increase (37%). The most common grade 3/4 TEAEs were AST increase (9%), ALT increase (10%), and hypertension (8%).

Discussion

This study reports the final results from the phase III ENLIVEN study of pexidartinib in patients with symptomatic, advanced TGCT. The findings are consistent with the primary analysis[10] and also show that tumor responses deepen over time. In the primary analysis, ORs per RECIST

Table 3. AEs.

AE, *n* (%)	Mar 2017 All pexidartinib-treated (*N* = 91)	Jan 2018 All pexidartinib-treated (*N* = 91)	Apr 2021 All pexidartinib-treated (*N* = 91)
TEAE	90 (98.9)	91 (100)	91 (100)
Worst CTCAE grade ≥3	39 (42.9)	43 (47.3)	50 (54.9)
TEAE related to pexidartinib	88 (96.7)	88 (96.7)	88 (96.7)
Worst CTCAE grade ≥3	33 (36.3)	35 (38.5)	40 (44.0)
Serious TEAE	12 (13.2)	14 (15.4)	21 (23.1)
Worst CTCAE grade ≥3	10 (11.0)	12 (13.2)	16 (17.6)
Serious TEAE related to pexidartinib	8 (8.8)	9 (9.9)	10 (11.0)
Worst CTCAE grade ≥3	8 (8.8)	8 (8.8)	9 (9.9)
Discontinued pexidartinib due to TEAE	14 (15.4)	17 (18.7)	18 (19.8)
Discontinued pexidartinib due to TEAE related to pexidartinib	13 (14.3)	16 (17.6)	17 (18.7)
Discontinued pexidartinib due to serious TEAE	3 (3.3)	3 (3.3)	3 (3.3)
Discontinued pexidartinib due to serious TEAE related to pexidartinib	3 (3.3)	3 (3.3)	3 (3.3)
TEAE leading to pexidartinib interruption or dose reduction	39 (42.9)	54 (59.3)	59 (64.8)
TEAE leading to pexidartinib interruption	35 (38.5)	49 (53.8)	53 (58.2)
TEAE leading to pexidartinib dose reduction	10 (11.0)	15 (16.5)	23 (25.3)
TEAE leading to pexidartinib interruption or dose reduction related to pexidartinib	35 (38.5)	47 (51.6)	55 (60.4)
TEAE leading to pexidartinib interruption related to pexidartinib	31 (34.1)	42 (46.2)	48 (52.7)
TEAE leading to pexidartinib dose reduction related to pexidartinib	10 (11.0)	15 (16.5)	22 (24.2)
TEAE leading to death	1 (1.1)	1 (1.1)	1 (1.1)
TEAE leading to death related to pexidartinib	0	0	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

and TVS were 39% and 56% for TVS at week 25. In the present analysis, with a median follow-up of 31 months, ORs were 60% and 68%, respectively, demonstrating that patients who remained on pexidartinib continued to experience clinical benefit while on treatment. The median time to response per RECIST was 5.1 months, suggesting a rapid response for most patients. The median duration of response was not reached, demonstrating that responses to pexidartinib are durable up to over 2 years. In addition to durable tumor responses, improvements in patient-reported outcomes that were observed at week 25 with pexidartinib compared with placebo were maintained through part 2. Importantly, no new safety signals were identified and there were no new significant cases of hepatotoxicity. These results build upon those presented in the primary analysis of 120 patients (61 pexidartinib; 59 placebo)[9] and those reported in a pooled analysis of 130 patients with TGCT at 40 months.[10]

Several aspects of this study are clinically relevant to patients: patients with symptomatic disease have a chance for further improvement as tumors may continue to shrink beyond 1 year of treatment. Secondary progression was rare, unlike what is typically seen in other kinase-driven tumors treated with specific inhibitors. This is likely because the pathophysiology of TGCT is different in that most of the cells within the tumor affected by pexidartinib are nonneoplastic cells,[13] which are unlikely to acquire a resistance mutation. This may be reassuring for patients who fear malignization or on-treatment progression following long-term treatment with pexidartinib.

This analysis further explored the risk of progression of patients with TGCT on pexidartinib and the risks and benefits of reducing dosage below 800 mg. Overall, 14 patients had tumor progression while on study; most of these were instances of secondary progression/tumor regrowth (13 patients had previously achieved a response). Of these, 3 progressed while receiving the full dose (800 mg/day) of pexidartinib while 11 progressed after a dose reduction or discontinuation. Patients might require a dose reduction or discontinuation due to AEs, travel, or family planning; indeed, some patients discontinued pexidartinib during ENLIVEN due to family planning. Although most responders (46/55; 84%) in this study achieved response on 800 mg pexidartinib, 9/55 (16%) patients had an objective response on a dose <800 mg. Taken together, these results suggest that remaining on 800 mg provides the best chance of radiologic response while also providing some reassurance that response can still be achieved if dose reduction is needed. It should be noted that in ENLIVEN, patients could decrease dosage

Table 4. Any grade AE occurring in >20% of patients treated with pexidartinib.

AE, *n* (%)	All pexidartinib-treated (*N* = 91)	
	Any grade	Grade 3/4
Skin and subcutaneous tissue disorders		
Hair color changes	69 (75.8)	0
Rash	25 (27.5)	1 (1.1)
Pruritus	19 (20.9)	1 (1.1)
Gastrointestinal disorders		
Nausea	35 (38.5)	0
Diarrhea	29 (31.9)	0
Vomiting	19 (20.9)	1 (1.1)
General disorders and administration-site conditions		
Fatigue	43 (47.3)	0
Edema peripheral	24 (26.4)	0
Investigations		
AST increase	34 (37.4)	8 (8.8)
ALT increase	26 (28.6)	9 (9.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	34 (37.4)	2 (2.2)
Nervous system disorders		
Dysgeusia	25 (27.5)	0
Headache	21 (23.1)	1 (1.1)
Eye disorders		
Periorbital edema	22 (24.2)	1 (1.1)
Vascular disorders		
Hypertension	26 (28.6)	7 (7.7)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

directly from 800 to 400 mg in the event of certain AEs; however, labeling suggested a stepwise approach through 600 mg before decreasing to 400 mg.[14]

Of the 14 patients with PD, 13 had an objective response prior to PD. One patient in the pexidartinib group experienced primary progression at week 13 during part 1 (another patient in the placebo group also had PD during part 1). Two patients had secondary progression (PD while on 800 mg/day) during part 1 or part 2. Although further study is required to determine factors associated with lack or loss of response to pexidartinib, these results show that primary progression is rare and progression after response while on the full dose of pexidartinib occurs in a small minority of patients. Unfortunately, centralized pathologic review of patients with PD was not performed.

The results of the PRO analysis suggest that improvements in range of motion, physical function, stiffness, and pain associated with pexidartinib are sustained throughout >200 weeks of treatment. The interpretation of PRO data is limited, however, due to the low number of patients available for analysis toward the end of the study. It is unknown whether improvement in any of the PROs measured would be observed if greater numbers of patients were available for analysis.

Finally, 3 patients were able to undergo surgery after pexidartinib treatment, demonstrating that pexidartinib may be able to decrease tumor size and/or complexity to an extent that allows surgery for certain patients who were previously ineligible for surgery.

Pexidartinib is only available in the US through a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of hepatotoxicity.[15] According to clinical laboratory values, 3 patients had hepatotoxicity per laboratory assessment (ALT and AST ≥3 times the ULN plus total bilirubin and ALP ≥2 × ULN) during ENLIVEN.[9] Each of these patients started on 1000 mg/day pexidartinib and recovered after discontinuation.[16] Hepatoxicity onset was within the first 8 weeks of treatment. Pexidartinib is associated with 2 types of hepatotoxicity: dose-dependent, reversible, generally low-grade aminotransferase elevations without concurrent elevations in total bilirubin and ALP; and mixed or cholestatic hepatotoxicity, which can be nonreversible. Both types were found to occur in the first 2 months of treatment, highlighting the importance of close monitoring of patients during the first few months of treatment when risk is highest.[16]

Other AEs associated with pexidartinib, such as hair color changes, nausea, fatigue, and AST/ALT increases, occurred at rates similar to those reported in the primary analysis. Of note, hair color changes (76%) are higher than reports of other tyrosine kinase inhibitors, such as pazopanib and sunitinib, which also inhibit KIT and cause hair color changes in 30% and 10% of patients, respectively.[17]

This study had some limitations. Given the crossover design, there was no placebo control group for comparison past week 25. We also did not measure creatine phosphokinase in ENLIVEN, which may be elevated due to decreased clearance due to inhibition of CSFR1.[18] Additionally, nearly all (96.7%) participants treated with pexidartinib in this study utilized ≥1 concomitant medication associated with potential hepatotoxicity; 56.0% used acetaminophen. However, the exact amounts utilized were not systematically captured.

In this study, we used RECIST and TVS to assess tumor size. RECIST has limitations with respect to measuring changes in tumor size for irregularly shaped, nonspherical tumors with poorly defined margins and asymmetrical growth, such as TGCT, and may underestimate or overestimate response rates compared to TVS. These limitations of RECIST have been discussed in detail.[19] Whereas both RECIST and TVS monitor tumor mass, RECIST does so based only on single, linear measurements of the longest dimension. For a diffuse yet solitary tumor, such as TGCT, which usually contains cysts and wraps around normal structures and tissues, such as articular bones and adipose, often only a portion of the tumor can be measured linearly, sometimes leaving a majority of the tumor unassessed. Furthermore, there may be multiple, similarly measurable locations on a tumor for independent readers to choose from, and because TGCT changes asymmetrically, the location of the measurement at baseline can dramatically affect the apparent response at follow-up.

It is important to note that differences in response rates as assessed by RECIST or TVS are research questions and improvement in patient symptoms and reduction in tumor volume are more clinically relevant. Nevertheless, these data have several implications in clinical practice: many patients with TGCT experience recurrence after surgery and many patients with diffuse TGCT have tumors that are not amenable to surgery.[20] Pexidartinib is a treatment option for such patients and provides benefit in terms of reducing tumor size

and volume, as well as improvements in pain and mobility. However, patients need to be monitored carefully in the first months of treatment due to the risk of hepatotoxicity.

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

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Conflicts of interest

Andrew Wagner served as a consultant for Aadi Bioscience, BioAtla, Boehringer Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera, Eli Lilly, InhibRx, Kymera, PharmaEssentia, and Servier; and received institutional research funding from Aadi Bioscience, Boehringer Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera, Eli Lilly, Foghorn, and Rain Therapeutics. William Tap reports a standard budget for site participation in a clinical trial from Plexxikon; personal fees for advisory board, consulting, and travel expenses from Eli Lilly and EMD Serono; personal fees for advisory board and consulting from Mundipharma, C4 Therapeutics, Daiichi Sankyo, Blueprint Medicines, GSK, and Agios Pharmaceuticals; personal fees for advisory board from NanoCarrier and Deciphera; personal fees for consulting from Adcendo, Ayala Pharmaceuticals, Kowa, Servier, and AbMaxBio; he holds a patent Companion Diagnostic for CDK4 inhibitors (14/854,329 pending to MSKCC/SKI); a patent Enigma and CDH18 as Companion Diagnostics for CDK4 inhibition (SKI2016-021-03 pending to MSKCC/SKI); participation on the scientific advisory board for Certis Oncology Solutions and Innova Therapeutics; stock ownership in Certis Oncology Solutions; and stock ownership in and cofounder of Atropos Therapeutics. Sebastian Bauer reports Honoraria: Novartis, Pharmamar, GlaxoSmithKline, Deciphera. Consulting or Advisory Role: Blueprint Medicines, Bayer, Lilly, Deciphera, Nanobiotix, Daiichi Sankyo, Exelixis, Janssen-Cilag, ADC Therapeutics, Mundipharma, GlaxoSmithKline, Adcendo, Boehringer Ingelheim, IDRX. Research Funding: IDRX, Blueprint Medicines, Novartis, Incyte (Institutional). Jean-Yves Blay reports research support from Novartis, Deciphera, and Daiichi Sankyo. Jayesh Desai served in a consulting or advisory role for BeiGene, Pierre Fabre, Bayer, GSK, Merck KGaA, Boehringer Ingelheim, Roche/Genentech, Daiichi Sankyo Europe GmbH, Novartis, Pfizer, Ellipses Pharma, Axelia Oncology, and Amgen; and received institutional research funding from Roche, GSK, Novartis, BeiGene, Lilly, BristolMyersSquibb, AstraZeneca/MedImmune, and Amgen. Hans Gelderblom reports institutional research funding from Abbisko, Deciphera, AmMax Bio, Daiichi Sankyo, Synox Therapeutics. Emanuela Palmerini served on advisory boards for Daiichi Sankyo, Inc., Deciphera Pharmaceuticals, EUSA Pharma, and SynOx Therapeutics. Christopher Ryan received institutional research funding from Ayala Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo, Deciphera, Exelixis, Genentech, Novartis, Karyopharm, Merck, Nektar, Pfizer, Xynomic, Bayer, OSI, PF Argentum IP Holdings, Rain Therapeutics, and Shasqi; received consulting fees from Synox, Daiichi Sankyo, AVEO, Exelixis, AstraZeneca, and Bristol Myers Squibb; and received payment for expert testimony from Pfizer, GSK, and Boehringer Ingelheim. Charles Peterfy is the owner of Spire Sciences, Inc., whose clients include Abbisko, AmMax, Deciphera, Five Prime, Hutchmed and SynOx. John H. Healey reports Stryker, Royalty agreement, Consultant; Daiichi Sankyo, Consultant; Deciphera, Consultant; Musculoskeletal Transplant Foundation, Trustee; Clinical Orthopaedics and Related Research, Editor. Michiel van de Sande received institutional research funding from Daiichi Sankyo, Implantcast and Carbofix; served in a consulting or advisory role for Deciphera, AmMax, Synox. Meng Qian, Dale E. Shuster, Abdul Rajper, Xin Ye, Kristen Tecson, and Margaret Wooddell are employees of Daiichi Sankyo, Inc. Silvia Stacchiotti reports Personal financial interests (honoraria, consultancy or advisory role): Agenus, Bayer, Boheringer, Deciphera, Ikena, Gentili, GlaxoSmithKline,

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Data availability

Anonymized individual participant data on completed studies and applicable supporting clinical study documents may be available upon request at https://vivli.org. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc. will continue to protect the privacy of the company and the clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo.

Supplementary material

Supplementary material is available at *The Oncologist* online.

References

1. de Saint Aubain Somerhausen N, van de Rijn M. *Tenosynovial Giant Cell Tumour, Diffuse Type. World Health Organization Classification of Tumours of Soft Tissue and Bone*. 4th ed. IARC Press, 2013:102-103.
2. Staals EL, Ferrari S, Donati DM, Palmerini E. Diffuse-type tenosynovial giant cell tumour: current treatment concepts and future perspectives. *Eur J Cancer*. 2016;63:34-40. https://doi.org/10.1016/j.ejca.2016.04.022
3. Mastboom MJ, Planje R, van de Sande MA. The patient perspective on the impact of tenosynovial giant cell tumors on daily living: crowdsourcing study on physical function and quality of life. *Interact J Med Res*. 2018;7:e4. https://doi.org/10.2196/ijmr.9325
4. Ehrenstein V, Andersen SL, Qazi I, et al. Tenosynovial giant cell tumor: incidence, prevalence, patient characteristics, and recurrence. A registry-based cohort study in Denmark. *J Rheumatol*. 2017;44:1476-1483. https://doi.org/10.3899/jrheum.160816
5. Mastboom MJL, Verspoor FGM, Verschoor AJ, et al; TGCT Study Group. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop*. 2017;88:688-694. https://doi.org/10.1080/17453674.2017.1361126
6. Bernthal NM, Spierenburg G, Healey JH, et al; TOPP Study Group. The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective multicenter study. *Orphanet J Rare Dis*. 2021;16:191. https://doi.org/10.1186/s13023-021-01820-6
7. Mastboom M, Palmerini E, Stacchiotti S, et al. First prospective observational study in diffuse-type tenosynovial giant cell tumors. *J Clin Oncol*. 2018;36:11560. https://doi.org/10.1200/jco.2018.36.15_suppl.11560
8. Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373:428-437. https://doi.org/10.1056/NEJMoa1411366
9. Tap WD, Gelderblom H, Palmerini E, et al; ENLIVEN Investigators. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394:478-487. https://doi.org/10.1016/S0140-6736(19)30764-0
10. Gelderblom H, Wagner AJ, Tap WD, et al. Long-term outcomes of pexidartinib in tenosynovial giant cell tumors. *Cancer*. 2021;127:884-893. https://doi.org/10.1002/cncr.33312
11. Rose M, Bjorner JB, Gandek B, et al. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol*. 2014;67:516-526. https://doi.org/10.1016/j.jclinepi.2013.10.024
12. HealthMeasures. PROMIS. 2022. Accessed June 23, 2022. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis.
13. van IJzendoorn DGP, Matusiak M, Charville GW, et al. Interactions in CSF1-driven tenosynovial giant cell tumors. *Clin Cancer Res*. 2022;28:4934-4946. https://doi.org/10.1158/1078-0432.CCR-22-1898
14. *TURALIO® (Pexidartinib) Capsules, for Oral Use [package insert]*. Daiichi Sankyo, Inc.; 2020.
15. *TURALIO® (Pexidartinib) Capsules, for Oral Use [package insert]*. Daiichi Sankyo, Inc.; 2023.
16. Lewis JH, Gelderblom H, van de Sande M, et al. Pexidartinib long-term hepatic safety profile in patients with tenosynovial giant cell tumors. *Oncologist*. 2021;26:e863-e873. https://doi.org/10.1002/onco.13629
17. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722-731. https://doi.org/10.1056/NEJMoa1303989
18. Adenis A, Bouché O, Bertucci F, et al. Serum creatine kinase increase in patients treated with tyrosine kinase inhibitors for solid tumors. *Med Oncol*. 2012;29:3003-3008. https://doi.org/10.1007/s12032-012-0204-1
19. Peterfy C, Chen Y, Countryman P, et al. CSF1 receptor inhibition of tenosynovial giant cell tumor using novel disease-specific MRI measures of tumor burden. *Future Oncol*. 2022;18:1449-1459. https://doi.org/10.2217/fon-2021-1437
20. Mastboom MJL, Verspoor FGM, Gelderblom H, van de Sande MAJ. Limb amputation after multiple treatments of tenosynovial giant cell tumour: series of 4 Dutch cases. *Case Rep Orthop*. 2017;2017:7402570. https://doi.org/10.1155/2017/7402570