Original Article

Long-Term Outcomes of Pexidartinib in Tenosynovial Giant Cell Tumors

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BACKGROUND: The objective of this study was to report on the long-term effects of pexidartinib on tenosynovial giant cell tumor (TGCT). **METHODS:** This was a pooled analysis encompassing 3 pexidartinib-treated TGCT cohorts: 1) a phase 1 extension study (NCT01004861; 1000 mg/d; n = 39), 2) ENLIVEN patients randomized to pexidartinib (1000 mg/d for 2 weeks and then 800 mg/d; n = 61), and 3) ENLIVEN crossover patients (NCT02371369; 800 mg/d; n = 30). Eligible patients were 18 years old or older and had a histologically confirmed TGCT that was unresectable and symptomatic. Efficacy endpoints included the best overall response (complete or partial response) and the duration of response (DOR) by the Response Evaluation Criteria in Solid Tumors (RECIST) and the tumor volume score (TVS). The safety assessment included the frequency of treatment-emergent adverse events (TEAEs) and hepatic laboratory abnormalities (aminotransferase elevations and mixed/cholestatic hepatotoxicity). The data cutoff was May 31, 2019. **Results:** One hundred thirty patients with TGCT received pexidartinib (median treatment duration, 19 months; range, 1 to 76+ months); 54 (42%) remained on treatment at the end of the analysis (26 months after initial data cut of March 2017). The RECIST overall response rate (ORR) was 60%; the TVS ORR was 65%. The median times to response were 3.4 (RECIST) and 2.8 months (TVS), with 48 of the responding patients (62%) achieving a RECIST partial response by 6 months and with 72 (92%) doing so by 18 months. The median DOR was reached for TVS (46.8 months). Reported TEAEs were mostly low-grade, with hair color changes being most frequent (75%). Most liver abnormalities (92%) were aminotransferase elevations; 4 patients (3%) experienced mixed/cholestatic hepatotoxicity (all within the first 2 months of treatment), which was reversible in all cases (recovery spanned 1-7 months). **Conclusions:** This study demonstrates the prolonged efficacy and tolerability of long-term pexidartinib treatment for TGCT. ***Cancer* 2021;127:884-893**.

KEYWORDS: efficacy, long term, pexidartinib, pooled analysis, safety, tenosynovial giant cell tumor (TGCT), tumor response.

INTRODUCTION

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplasm associated with colony-stimulating factor 1 (CSF1) overexpression,[1-5] and it affects primarily the synovium of joints, bursae, or tendon sheaths.[2,3] Localized-type TGCT is a locally aggressive disease, and this type accounts for 80% to 90% of TGCT cases and most commonly occurs in the digits. Diffuse-type TGCT, formerly called pigmented villonodular synovitis (PVNS), constitutes 10% to 20% of cases, usually occur in large joints (eg, knees, ankles, and hips), and show a higher tendency toward recurrence.[6,7] The diffuse variant often causes debilitating symptoms, including pain, swelling, a limited range of motion, and stiffness.[1,3] Although surgery cures the vast majority of localized TGCT cases, the diffuse type shows a high tendency toward local recurrence, which occurs in approximately 50% of resected cases; therefore, limiting the value of surgery for this subtype.[8,9]

Pexidartinib is an orally administered small-molecule tyrosine kinase inhibitor[10] that acts as a selective, potent inhibitor of colony-stimulating factor 1 receptor (CSF1R), c-kit receptor tyrosine kinase (KIT), and fms-like tyrosine

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TABLE 1. Summary of the PLX108-01 and ENLIVEN Studies

Study ID (NCT No.)	Study Title	Study Design	Dosing Regimen for Patients With TGCT
PLX108-01 (NCT01004861)[10]	A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients With Advanced, Incurable, Solid Tumors in Which the Target Kinases Are Linked to Disease Pathophysiology	Phase 1, first in-human study with a dose escalation (part 1) and an extension (part 2)	TGCT cohort of part 2: pexidartinib (n = 39) at 1000 mg/d (split dose)
ENLIVEN (NCT02371369)[4]	A Double-Blind, Randomized, Placebo-Controlled Phase 3 Study of Orally Administered PLX3397 in Subjects With Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath	Phase 3, multicenter study with 2 parts: a randomized, double-blind, placebo-controlled part and an open-label, long-term part	Randomized cohort (n = 61): pexidartinib at 1000 mg/d (split dose) for 2 wk, then pexidartinib at 800 mg/d (split dose) Crossover cohort (n = 30): pexidartinib at 800 mg/d (split dose)

Abbreviation: TGCT, tenosynovial giant cell tumor.

kinase 3 internal tandem duplication (FLT3-ITD).[11] After positive preliminary results from the phase 1 extension study PLX108-01 (NCT01004861),[10] compelling efficacy in patients with TGCT was demonstrated in the phase 3 ENLIVEN study (NCT02371369), which used the Response Evaluation Criteria in Solid Tumors (RECIST) response according to a blinded, independent central review as the primary endpoint for comparing pexidartinib versus placebo at week 25.[4] The safety profile of pexidartinib was well established in the ENLIVEN study[4] and is supported by data from other studies in the clinical program. Pexidartinib can cause serious and potentially fatal mixed or cholestatic hepatotoxicity. In July 2019, the US Food and Drug Administration multidisciplinary review team determined that the benefit/risk assessment was favorable for a patient population with no treatments (ie, surgical interventions) available or for which treatment with surgery would not be possible because of predicted morbidity. Subsequently, pexidartinib became the first approved systemic therapy for TGCT in the United States, and it was added by the National Comprehensive Cancer Network as a category 1 recommendation for the treatment of adult patients with symptomatic TGCT/PVNS associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[12,13] By contrast, the European Medicines Agency's Committee for Medicinal Products for Human Use considered that the safety and efficacy balance of pexidartinib was not sufficiently demonstrated. This was essentially based on a negative assessment of the balance between the potential risk of life-threatening liver toxicity and the nonmetastatic nature of the disease. On this basis, pexidartinib is currently not available to patients with advanced TGCT in the European Union.

The aim of this pooled analysis is to report on the long-term efficacy and safety of pexidartinib across the phase 3 ENLIVEN study and the TGCT cohort of the PLX108-01 study and extend beyond what has been previously published with insights from prolonged follow-up for a median of 39 months (range, 32-82 months).

MATERIALS AND METHODS

Study Design and Participants

Key eligibility criteria and study designs for the ENLIVEN study (NCT02371369)[4] and the PLX108-01 extension (NCT01004861)[10] have been described elsewhere and are summarized in Table 1. In brief, patients were required to be at least 18 years old and have a histologically confirmed TGCT that was both unresectable and symptomatic; ENLIVEN eligibility specifically required symptoms of pain (a worst pain score of ≥4 on a scale of 0-10, with 10 representing pain as bad as can be imagined) or stiffness (≥4 on a scale of 0-10). Patients provided written informed consent. The institutional review board at each participating centre approved the study; ethics were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation.

The pooled analysis encompassed 3 groups of pexidartinib-treated patients with TGCT: 1) patients from a phase 1 extension study, 2) patients from ENLIVEN who were randomized to pexidartinib at 1000 mg/d for 2 weeks and then 800 mg/d, and 3) crossover patients from ENLIVEN receiving pexidartinib at 800 mg/d. The phase 1 PLX108-01 study was the first in-human study with a dose-escalation phase with an expansion cohort phase (39 patients with TGCT) conducted in patients with solid tumors. Pexidartinib at 1000 mg/d (split in twice daily dosing) was taken until tumor progression or the development of unacceptable toxicities.

ENLIVEN, which included 120 patients with TGCT, was a phase 3, randomized, placebo-controlled, 2-part, multicenter study conducted in patients with symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity.[4] In part 1 (double-blind, randomized, placebo-controlled treatment for 24 weeks), patients received either pexidartinib at 1000 mg/d (n = 61) or matching placebo (n = 59) for the first 2 weeks followed by pexidartinib at 800 mg/d or matching placebo for 22 weeks (with twice daily dosing for both). In part 2, patients were allowed to continue treatment with open-label pexidartinib for a long-term evaluation of safety and efficacy. The crossover population (n = 30) received open-label pexidartinib after receiving a placebo in part 1.

Assessments and Analysis

Efficacy (tumor response) was determined by the best overall response (complete response [CR] or partial response [PR]) and the duration of response (DOR) by RECIST (version 1.1) and the tumor volume score (TVS), with tumor assessments performed by an independent central review. The frequency of imaging was every 8 weeks for the phase 1 extension cohort and every 12 weeks for patients from ENLIVEN.[4,10] DOR was defined as the time from the first recorded response by RECIST to the first documentation of subsequent disease progression. In the ENLIVEN study, the overall response rate (ORR) at week 25 per RECIST (version 1.1) was the primary endpoint, and the overall response measured by TVS was a secondary endpoint. RECIST (version 1.1) and TVS by an independent central review were also used in the PLX108-01 study in measuring tumor response. TVS is a magnetic resonance imaging scoring system describing the tumor volume as a proportion of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A TVS response was defined as a ≥50% reduction in tumor size, and progressive disease was defined as a ≥30% increase in tumor size from the baseline. Notably, the ENLIVEN study required central review confirmation of evaluable disease before enrollment, whereas the PLX108-01 study did not, and 5 of the 39 total patients were not evaluable because of joint replacement hardware (n = 4) or myositis (n = 1). These 5 patients were nonresponders and were included in the denominator for response rate calculations. The tumor response for this analysis followed the definition used in ENLIVEN, which did not require response confirmation.

For safety, the frequency of treatment-emergent adverse events (TEAEs) was tabulated according to the Common Terminology Criteria for Adverse Events by system organ class and preferred term. Hepatic tests were also evaluated, and hepatic abnormalities were classified into 1 of 2 types—aminotransferase elevations or mixed or cholestatic hepatotoxicity—based upon liver test results.

The data cutoff for the efficacy and safety analyses reported here was May 31, 2019; this represented a median follow-up duration of 39 months (range, 32-82 months after patients' first dose) and provided a long-term efficacy and safety evaluation of pexidartinib-treated patients with TGCT.

RESULTS

The 130 patients with TGCT across both studies who received pexidartinib were included in the efficacy analysis, with the patient demographics and baseline disease characteristics summarized in Table 2. The median age in the population was 45 years (range, 20-80 years), and the knee was the most common location of the disease (57%). Seventy-seven patients (59%) had at least 1 prior surgery, and 16 patients (12%) had received prior systemic therapy. Eight of the 130 patients (6%) had received prior radiation therapy.

The pooled population had a median duration of treatment of 19 months, with treatment ongoing in 54 patients (42%) at the May 31, 2019, cutoff. Overall tumor response rates (best response of CR or PR) were high, consistent across the 3 cohorts, and durable (Fig. 1 and Table 3). The best response according to RECIST was CR or PR in 78 patients (ORR, 60%; 95% confidence interval, 51.4%-68.0%), stable disease in 26 patients (20%), and progressive disease in 1 patient (1%; Fig. 1A and Table 3). Eighty-four patients (65%) achieved a complete or partial TVS response (Fig. 1B and Table 3). The median time to an initial response was 3.4 months (range, 1.6-38.3 months) via RECIST and 2.8 months (range, 1.6-33.6 months) via TVS, with most responses (65 of 84 [77%]) occurring within the first 6 months after the start of pexidartinib treatment (first 2 scans) and others (19 of 84 [23%]) developing only after more than 6 months of pexidartinib treatment. Regarding RECIST, of the 78 patients who achieved a response, 32 (41%) had achieved a response by 3 months, 48 (62%) had shown a response by 6 months, and 72 (92%) had shown a response by 18 months (Fig. 1C). Regarding TVS, of the 84 patients who reached a response, 50 (60%) had achieved a response by 3 months, 65 (77%) had shown a response by 6 months, and 82 (98%) had shown a response by 12 months. Two additional patients reached a TVS

TABLE 2. Patient Demographics and Baseline Disease Characteristics

Characteristic	ENLIVEN		PLX108-01 TGCT Cohort: 1000 mg/d[a] (n = 39)	Pooled (N = 130)
	Randomized: 1000 mg/d × 2 wk, Then 800 mg/d (n = 61)	Crossover: 800 mg/d[a] (n = 30)		
Age, median (range), y	44 (22-75)	47 (20-79)	42 (22-80)	45 (20-80)
Sex, n (%)				
Male	26 (43)	14 (47)	17 (44)	57 (44)
Female	35 (57)	16 (53)	22 (56)	73 (56)
Race, n (%)				
White	52 (85)	30 (100)	33 (85)	115 (88)
Asian	3 (5)	0	3 (8)	6 (5)
Black	1 (2)	0	3 (8)	4 (3)
Native American	2 (3)	0	0	2 (2)
Hawaiian/Pacific Islander	2 (3)	0	0	2 (2)
Other (multiracial)	1 (2)	0	0	1 (1)
Disease location, n (%)				
Knee	34 (56)	19 (63)	21 (54)	74 (57)
Ankle	14 (23)	3 (10)	7 (18)[c]	24 (18)
Hip	6 (10)	3 (10)	7 (18)[d]	16 (12)
Other[b]	7 (11)	5 (17)	4 (10)	16 (12)
Prior surgeries for TGCT, n (%)				
0	29 (48)	16 (53)	8 (21)	53 (41)
1	13 (21)	5 (17)	5 (13)	23 (18)
2	7 (11)	6 (20)	10 (26)	23 (18)
≥3	12 (20)	3 (10)	16 (41)	31 (24)
Prior systemic therapy,[e] n (%)				
0	53 (87)	28 (93)	33 (85)	114 (88)
≥1	8 (13)	2 (7)	6 (15)	16 (12)
Prior radiation therapy,[e] n (%)				
0	56 (92)	29 (97)	36 (92)	121 (93)
1	4 (7)	1 (3)	3 (8)	8 (6)
≥2	1 (2)	0	0	1 (1)
Duration of exposure, median (range), mo	16.7 (1.0-46.1)	31.7 (2.0-43.1)	16.8 (0.5-75.5+)	18.7 (0.5-75.5+)

Abbreviation: TGCT, tenosynovial giant cell tumor.
[a]Starting dose.
[b]Included the wrist, foot, shoulder, spine, finger, and elbow.
[c]Included the foot/ankle.
[d]Included the hip/thigh.
[e]Included nilotinib (n = 1) or imatinib (n = 7) in ENLIVEN and imatinib or nilotinib (n = 4) or denosumab or sirolimus (n = 2) in PLX108-01.
[Correction added on 27 January 2021, after first online publication: corrections have been made to some of the data in Table 2]

response between 12 and 34 months after the initiation of pexidartinib (Fig. 1D). Of the 130 patients in the pooled analysis, 34 (26%) achieved a RECIST CR. Fifteen of the 34 patients (44%) who achieved a CR did so by 8 months after the start of pexidartinib treatment. By 20 months, 26 patients (76%) had achieved a CR, whereas the last patient to do so was at approximately 42 months after the initiation of pexidartinib (Fig. 1E). One patient had RECIST progressive disease as the best overall response with no progression per TVS (Table 3). Ultimately, according to RECIST, a total of 16 patients (12%) progressed on treatment or after treatment discontinuation, 14 (11%) progressed on treatment, and 2 (2%) progressed after treatment. One patient (1%) underwent surgery for residual TGCT after a response to pexidartinib therapy.

Pexidartinib was generally well tolerated, with most TEAEs being low grade (1 or 2) even with long-term treatment (Table 4). All 130 patients experienced 1 or more TEAEs; 127 of the patients (98%) experienced at least 1 treatment-related TEAE (Supporting Table 2). The most frequently reported TEAEs by system organ class (all reversible) were hair color change (75%), followed by fatigue (61%), nausea (47%), and arthralgia (39%; Table 4). Sixty-seven patients (52%) had TEAEs of Common Terminology Criteria for Adverse Events grade 3 or higher, of which 57 patients (85%) had events that were treatment-related. There were 23 patients (18%) who experienced a total of 32 serious adverse events. Of these 23 patients, 14 (61%) had treatment-related serious adverse events. One patient (1%) had a grade 5 event in the crossover group

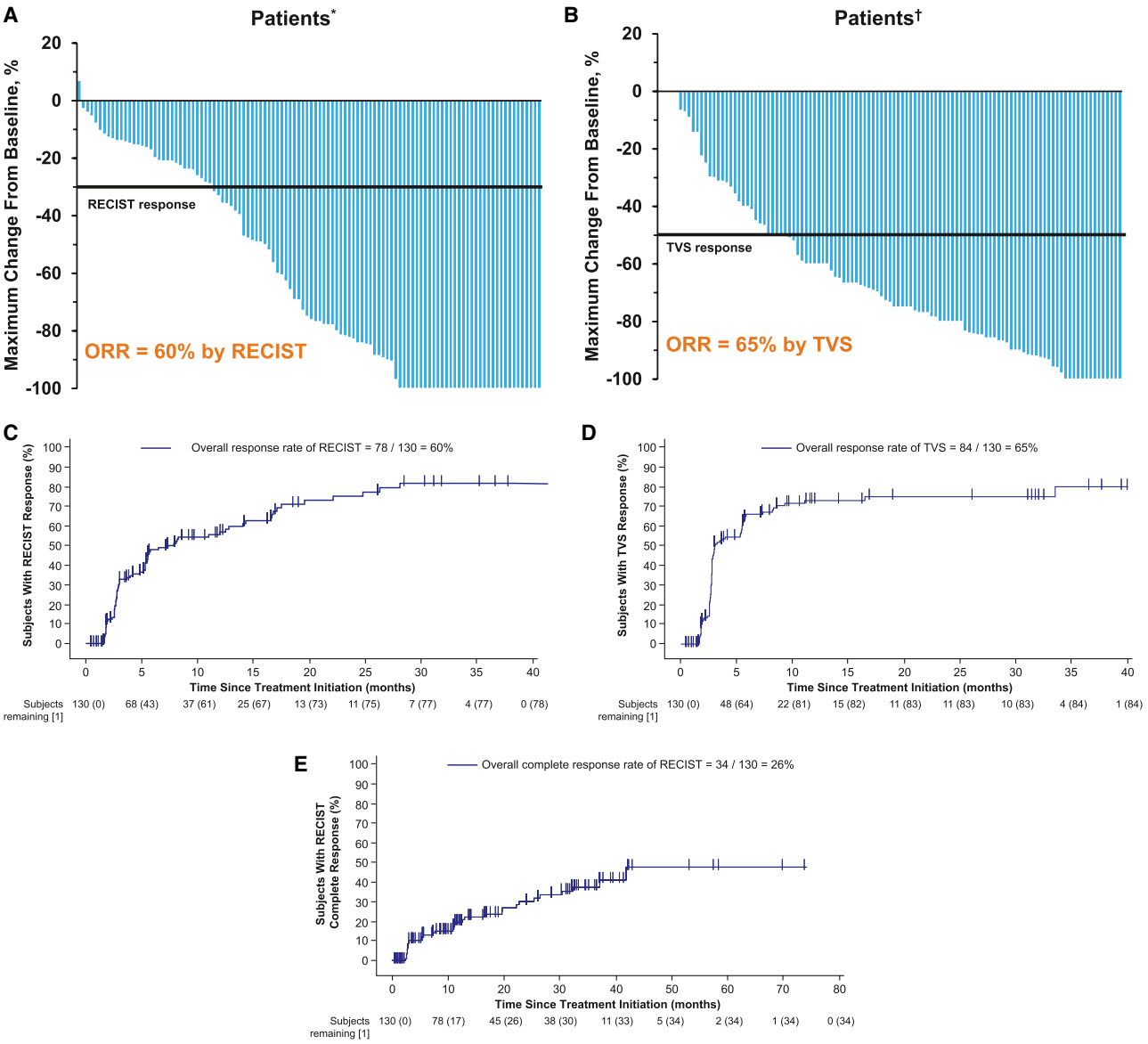

Figure 1. Tumor assessments by independent central review in pexidartinib-treated patients with tenosynovial giant cell tumor: (A) waterfall plot of best tumor size change by RECIST, (B) waterfall plot of best tumor size change by TVS, (C) RECIST time to initial response, (D) TVS time to initial response, and (E) RECIST time to complete response. ORRs were calculated with the pooled population as the denominator. Evaluable patients (RECIST and TVS) were those who had a baseline tumor assessment and at least 1 postbaseline tumor assessment. *For RECIST, there were 110 patients evaluable (78 with a ≥30% reduction). †For TVS, there were 111 patients evaluable (84 with a ≥50% reduction and 5 with no change). Abbreviations: ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1); TVS, tumor volume score.

of ENLIVEN (the cause of death was aortic dissection after a long history of cardiac events, and it was reported as unrelated to pexidartinib; see Table 4 and Supporting Table 2).

There were 89 patients (68%) who experienced TEAEs resulting in a dose reduction or interruption. Treatment discontinuation occurred in 69 of the patients (53%) in the pooled analysis (Supporting Table 1). The most common reason for the discontinuation of pexidartinib was an adverse event, which was the case for 31 patients (24%; Supporting Table 1). These adverse events leading to discontinuation included abnormal laboratory investigations (n = 9 [7%]), nervous system disorders (n = 8 [6%]), and musculoskeletal/connective tissue disorders (n = 6 [5%]). Twenty patients (15%) discontinued because of withdrawal of

TABLE 3. Summary of Efficacy

Endpoint	ENLIVEN		PLX108-01 TGCT Cohort: 1000 mg/d[a] (n = 39)	Pooled (N = 130)
	Randomized: 1000 mg/d × 2 wk, Then 800 mg/d (n = 61)	Crossover: 800 mg/d[a] (n = 30)		
RECIST, n (%) [95% CI]				
Complete response	18 (30) [19.6-41.9]	8 (27) [14.2-44.4]	8 (21) [10.8-35.5]	34 (26) [19.4-34.3]
Partial response	20 (33) [22.3-45.3]	10 (33) [19.2-51.2]	14 (36) [22.7-51.6]	44 (34) [26.3-42.3]
Stable disease	13 (21) [12.9-33.1]	8 (27) [14.2-44.4]	5 (13) [5.6-26.7]	26 (20) [14.0-27.7]
Progressive disease	1 (2) [0.3-8.7]	0 [0.0-11.4]	0 [0.0-9.0]	1 (1) [0.1-4.2]
Not evaluable	9 (15) [8.0-25.7]	4 (13) [5.3-29.7]	12 (31) [18.6-46.4]	25 (19) [13.4-26.8]
Overall response rate (complete or partial)	38 (62) [49.7-73.4]	18 (60) [42.3-75.4]	22 (56) [41.0-70.7]	78 (60) [51.4-68.0]
DOR, median (range), mo	NR (0.0+ to 41.4+)	NR (6.1+ to 39.2+)	NR (1.7 to 70.0+)	NR (0.0+ to 70.0+)
TVS, n (%) [95% CI]				
Complete response	5 (8) [3.6-17.8]	1 (3) [0.6-16.7]	8 (21) [10.8-35.5]	14 (11) [6.5-17.3]
Partial response	35 (57) [44.9-69.0]	19 (63) [45.5-78.1]	16 (41) [27.1-56.6]	70 (54) [45.3-62.2]
Stable disease	13 (21) [12.9-33.1]	6 (20) [9.5-37.3]	3 (8) [2.7-20.3]	22 (17) [11.4-24.3]
Progressive disease	0 [0.0-5.9]	0 [0.0-11.4]	0 [0.0-9.0]	0 [0.0-2.9]
Not evaluable	8 (13) [6.8-23.8]	4 (13) [5.3-29.7]	12 (31) [18.6-46.4]	24 (18) [12.7-26.0]
Overall response (complete or partial)	40 (66) [53.0-76.3]	20 (67) [48.8-80.8]	24 (62) [45.9-75.1]	84 (65) [56.1-72.3]
DOR, median (range), mo	NR (0.0+ to 41.4+)	NR (8.0+ to 39.2+)	41.9 (1.7 to 70.0+)	46.8 (0.0+ to 70.0+)

Abbreviations: CI, confidence interval; DOR, duration of response; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1); TGCT, tenosynovial giant cell tumor; TVS, tumor volume score.
[a]Starting dose of pexidartinib.
[Correction added on 27 January 2021, after first online publication: corrections have been made to some of the data in Table 3]

consent, and 5 (4%) were noncompliant (all from the phase 1 extension study). Five patients (4%) discontinued pexidartinib because of disease progression, and 2 of these (2%) were phase 1 patients with malignant/metastatic disease. Investigator decision resulted in 3 patients (2%) discontinuing pexidartinib treatment (Supporting Table 1).

Pexidartinib was associated with hepatic laboratory abnormalities, which included hepatic adverse reactions (ARs; Table 5). Hepatic ARs were experienced by 95% of the patients (123 of 130) and were of 2 clinically distinct types. The first type was isolated aminotransferase elevations, which were frequent, reversible with dose-interruption, and dose-dependent. The second type of hepatic AR was mixed or cholestatic hepatotoxicity, which in clinically significant cases presented as increases in alkaline phosphatase and total bilirubin with aminotransferase elevations. These events were less frequent, idiosyncratic, and sometimes prolonged. The onset was within the first 8 weeks of treatment, and all resulted in permanent treatment discontinuation.

In the pooled analyses, most patients treated with pexidartinib (n = 119 [92%]) experienced aminotransferase elevations, most commonly alanine aminotransferase and aspartate aminotransferase increases of ≥1 to <3 × the upper limit of normal (ULN; 66%).

Of the 130 patients with TGCT, 4 (3%) experienced mixed or cholestatic hepatotoxicity (Table 5). All cases started within the first 8 weeks of treatment and were reversible, but the duration was prolonged in some cases, with recovery spanning 1 to 7 months. Across all 768 patients who received pexidartinib in clinical trials, there were 2 irreversible cases of cholestatic liver injury (0.3%). One patient died with advanced cancer and ongoing liver toxicity, and 1 patient required a liver transplant.

The time to the first occurrence of laboratory values meeting hepatic laboratory criteria corresponding to a dose reduction, interruption, or withdrawal based on the US Prescribing Information (alanine aminotransferase > 3 × ULN or aspartate aminotransferase > 3 × ULN, alkaline phosphatase > 2 × ULN with γ-glutamyl transferase > 2 × ULN if measured on the same date, total bilirubin > ULN, or direct bilirubin > ULN) was analyzed and evaluated, and the results were previously presented.[14] Most events occurred in the first 2 months, and no additional events occurred later than 24 months after the start of pexidartinib treatment.[14] In the long-term follow-up (median, 39 months from initial dosing [May 2019]), no new cases of mixed or cholestatic hepatotoxicity were observed in patients continuing long-term pexidartinib treatment. A more comprehensive analysis of hepatic safety events will be reported elsewhere.

DISCUSSION

With prolonged follow-up with a median of 39 months (range, 32-82 months), pexidartinib was confirmed to

TABLE 4. Overall Safety: Frequency of Treatment-Emergent Adverse Events by Cohort Reported in ≥10% of Patients

	ENLIVEN							
	Randomized: 1000 mg/d × 2 wk, Then 800 mg/d (n = 61)		Crossover: 800 mg/d[a] (n = 30)		PLX108-01 TGCT Cohort: 1000 mg/d[a] (n = 39)		Total (N = 130)	
Adverse Event	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %
Skin and subcutaneous tissue disorders								
Hair color change	74	NA	83	NA	72	NA	75	NA
Rash	28	2	27	0	31	0	28	1
Pruritus	16	2	20	0	36	0	23	1
Rash maculopapular	16	2	10	0	21	0	16	1
Erythema	3	2	20	0	21	0	12	1
Skin hypopigmentation	8	NA	3	NA	18	NA	10	NA
Gastrointestinal disorders								
Nausea	46	0	23	0	67	0	47	0
Diarrhea	30	0	30	0	38	8	32	2
Vomiting	23	2	7	0	33	3	22	2
Constipation	16	0	10	0	28	0	18	0
Abdominal pain	25	0	10	0	5	0	15	0
Dry mouth	13	0	13	0	10	0	12	0
General disorders and administration site conditions								
Fatigue	57	0	27	0	92	3	61	1
Edema, peripheral	21	0	20	0	28	0	23	0
Face edema	15	2	20	3	15	0	16	2
Asthenia	15	0	23	0	0	0	12	0
Investigations								
AST increased	44	10	20	7	18	8	31	8
ALT increased	31	10	23	10	18	10	25	10
Blood ALP increased	15	7	3	0	10	0	11	3
Nervous disorders								
Dysgeusia	28	NA	23	NA	38	NA	30	NA
Headache	23	2	20	0	33	0	25	1
Dizziness	15	2	13	0	28	0	18	1
Musculoskeletal and connective tissue disorders								
Arthralgia	28	3	33	0	62	3	39	2
Pain in extremity	11	0	13	0	26	0	16	0
Eye disorders								
Periorbital edema	28	2	17	0	38	0	29	1
Metabolic and nutrition disorders								
Decreased appetite	18	0	10	0	23	0	18	0
Hypophosphatemia	5	3	7	3	28	13	12	6
Vascular disorders								
Hypertension	23	7	33	7	21	0	25	5
Blood and lymphatic system disorders								

TABLE 4. *Continued*

	ENLIVEN				PLX108-01 TGCT Cohort: 1000 mg/d[a] (n = 39)		Total (N = 130)	
	Randomized: 1000 mg/d × 2 wk, Then 800 mg/d (n = 61)		Crossover: 800 mg/d[a] (n = 30)					
Adverse Event	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %	All Grades, %	Grade ≥ 3, %
Anemia	10	2	3	0	23	3	12	2
Respiratory, thoracic, and mediastinal disorders								
Cough	7	0	13	0	21	0	12	0
Infections and infestations								
Upper respiratory tract infection	11	0	3	0	15	0	11	0
Psychiatric disorders								
Insomnia	5	0	10	0	18	0	10	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; TGCT, tenosynovial giant cell tumor.
[a]Starting dose of pexidartinib.

be an effective long-term treatment in adult patients with locally advanced TGCT with an overall tumor response rate of 60% and a prolonged DOR. Notably, there was 1 patient who had a RECIST-based best overall response of progressive disease with continued pexidartinib use. A high and comparable best ORR was achieved across all pexidartinib-treated cohorts and evaluation methods. Tumor response rates from the pooled ENLIVEN and PLX108-01 studies increased with long-term pexidartinib treatment. The median treatment duration was 19 months (range, 1 to 76+ months), and this resulted in compelling ORRs of 60% (RECIST, version 1.1) and 65% (TVS). Many patients achieved a tumor response by RECIST and TVS within the first 6 months (first 2 scans) after the start of pexidartinib treatment, but even more patients achieved a response with long-term pexidartinib treatment. Previously, in the published phase 3 study, the RECIST response rate after 24 weeks of pexidartinib treatment was 39% (vs 0% with a placebo; $P < .0001$), and 4 of 5 comparative secondary endpoints, including TVS (56% vs 0%; $P < .0001$), were met.[4]

To date, there has been limited availability of long-term prospective data for TGCT. A retrospective study of patients treated across 12 centers in Europe, the United States, and Australia found that long-term imatinib treatment in patients with TGCT resulted in a 31% RECIST-based response rate among 55 assessable patients with locally advanced or recurrent disease with a median treatment duration of 9 months (range, 1-80 months). At the last follow-up, most patients (66%) had discontinued imatinib treatment.[15] Of the 130 patients with TGCT treated with pexidartinib, 54 (42%) remained on treatment, with only 5 patients (4%) discontinuing because of disease progression (2 of these patients had malignant/metastatic disease). These data further support that pexidartinib provides long-term control of TGCT.

The main reasons for treatment discontinuation were adverse events (24%) and patient withdrawal of consent (15%). Treatment with novel drugs for this disease is discontinued for various reasons. In a prospective study evaluating nilotinib in patients with PVNS (N = 56) with a median duration of treatment of 11.0 months (interquartile range, 7.0-12.0 months), 25 patients (45%) discontinued nilotinib before 12 months because of progressive disease (n = 6), tumor resection (n = 4), toxicity (n = 5), the patient's refusal (n = 8), or the investigator's decision (n = 1) or were lost to follow-up (n = 1).[16]

Long-term treatment with pexidartinib has demonstrated a tolerable safety profile with no late-emerging

TABLE 5. Hepatic Laboratory Abnormalities

Endpoint	ENLIVEN		PLX108-01 TGCT Cohort: 1000 mg/d[a] (n = 39)	Pooled (N = 130)
	Randomized: 1000 mg/d × 2 wk, Then 800 mg/d (n = 61)	Crossover: 800 mg/d[a] (n = 30)		
Aminotransferase elevations (119 [92%]), n (%)				
ALT or AST ≥ 1 to < 3 × ULN	39 (64)	21 (70)	26 (67)	86 (66)
ALT or AST ≥ 3 to < 5 × ULN	7 (12)	4 (13)	4 (10)	15 (12)
ALT or AST ≥ 5 to < 10 × ULN	6 (10)	2 (7)	2 (5)	10 (8)
ALT or AST ≥ 10 to < 20 × ULN	3 (5)	1 (3)	2 (5)	6 (5)
ALT or AST ≥ 20 × ULN	2 (3)	0	0	2 (2)
Mixed or cholestatic hepatotoxicity (4 [3%]), n (%)				
ALT or AST ≥ 3, TBIL ≥ 2, and ALP ≤ 2 × ULN (true Hy's law)	0	0	0	0
ALT/AST ≥ 3, TBIL ≥ 2, and ALP > 2 × ULN	3 (5)	0	1 (3)	4 (3)[b]
TBIL ≥ 2 × ULN (in absence of ALT ≥ 3 or ALP > 2 × ULN)	0	0	1 (3)	1 (1)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal.
[a]Starting dose of pexidartinib.
[b]Included 1 patient with a single–time point elevation of TBIL considered unrelated to treatment.

toxicity. At the original data cutoff (March 2017), the most common toxicities were hair color changes (73%), fatigue (42%), and nausea (32%).[4] In the current pooled analysis, where patients in ENLIVEN were followed for an additional 26 months of pexidartinib treatment, the most common adverse events were similar (Table 4). Of the 130 patients with TGCT exposed to pexidartinib for a median treatment duration of 19 months, 4 had serious hepatic ARs, and all started within the first 8 weeks of treatment. Although all of these events were reversible in the TGCT population, the duration of liver injury was prolonged in some cases, and in the overall clinical program, there were 2 irreversible cases of cholestatic liver injury. One patient died with advanced cancer and ongoing liver toxicity, and 1 patient required a liver transplant. The current analysis showed that no new mixed or cholestatic hepatotoxicity was reported beyond the first 8 weeks of treatment.

Because of the risk of hepatotoxicity, pexidartinib is available only through the Risk Evaluation Management System program in the United States. Frequent monitoring of liver function, early intervention with dose modification, and education on symptoms of emerging hepatotoxicity and the approved indication of pexidartinib are critical for a robust benefit-to-risk assessment on an individual patient basis. The additional long-term safety data did not reveal late-emerging or cumulative toxicities of clinical significance that would require revised risk management procedures beyond those proposed for patients in the first 2 months of pexidartinib treatment. Overall, these findings are encouraging for this rare tumor population with a highly unmet need for effective systemic therapy.

A limitation of the current pooled analysis is the lack of a control group for a comparison of symptomatic and functional improvement and safety with long-term treatment.[17] In addition, it cannot provide data on the time to disease progression in those patients who stopped pexidartinib while they had a response or were stable. Nonetheless, this analysis adds to previous findings showing that systemic therapy targeting the CSF1/CSF1R pathway is an effective therapeutic strategy in patients with TGCT, and it demonstrates the overall long-term benefit of continued treatment with pexidartinib.

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CONFLICT OF INTEREST DISCLOSURES

Hans Gelderblom reports research compensation to his institution from Daiichi Sankyo. Andrew J. Wagner reports personal fees for consulting from Eli Lilly, Novartis, Loxo, Five Prime Therapeutics, and Daiichi Sankyo outside the submitted work. William D. Tap reports a standard budget for site participation in the clinical trial from Daiichi Sankyo during the conduct of the study; personal fees for advisory boards and consulting from Eli Lilly, EMD Serono, Eisai, Janssen, Immune Design, Daiichi Sankyo, Blueprint, Loxo, GlaxoSmithKline, and Agios Pharmaceuticals outside the submitted work; personal fees for advisory boards for NanoCarrier and Deciphera outside the submitted work; a patent pending to the Memorial Sloan Kettering Cancer Center/Sloan Kettering Institute; participation in scientific advisory boards for Certis Oncology Solutions and Atropos Therapeutics; stock ownership in Certis Oncology Solutions and Atropos Therapeutics; and consultancy for Daiichi Sankyo for the Food and Drug Administration Oncologic Drugs Advisory Committee meeting for pexidartinib. Emanuela Palmerini reports personal fees for advisory boards from Amgen, Daiichi Sankyo, Lilly, Eusa Pharma, and Deciphera outside the submitted work; research support from Bristol-Myers Squibb, Pfizer, and PharmaMar outside the submitted work; and travel support from Lilly, PharmaMar, and Takeda outside the submitted work. Zev A. Wainberg reports personal fees for consulting

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AUTHOR CONTRIBUTIONS

Hans Gelderblom: Conceptualization, investigation, resources, supervision, visualization, and writing–review and editing. **Andrew J. Wagner:** Conceptualization, investigation, methodology, resources, and writing–review and editing. **William D. Tap:** Conceptualization, data curation, investigation, methodology, project administration, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Emanuela Palmerini:** Data curation, supervision, writing–original draft, and writing–review and editing. **Zev A. Wainberg:** Investigation, resources, validation, and writing–review and editing. **Jayesh Desai:** Resources, writing–original draft, and writing–review and editing. **John H. Healey:** Investigation, methodology, and writing–review and editing. **Michiel A. J. van de Sande:** Data curation, investigation, supervision, writing–original draft, and writing–review and editing. **Nicholas M. Bernthal:** Conceptualization, data curation, visualization, writing–original draft, and writing–review and editing. **Eric L. Staals:** Conceptualization, investigation, supervision, and writing–review and editing. **Charles G. Peterfy:** Formal analysis and writing–review and editing. **Anna Maria Frezza:** Investigation, writing–original draft, and writing–review and editing. **Henry H. Hsu:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing–original draft, and writing–review and editing. **Qiang Wang:** Conceptualization, data curation, formal analysis, methodology, visualization, writing–original draft, and writing–review and editing. **Dale E. Shuster:** Conceptualization, data curation, methodology, project administration, supervision, visualization, writing–original draft, and writing–review and editing. **Silvia Stacchiotti:** Investigation, resources, writing–original draft, and writing–review and editing.

REFERENCES

1. Mastboom MJL, Palmerini E, Verspoor FGM, et al. Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. *Lancet Oncol*. 2019;20:877-886. doi:10.1016/s1470-2045(19)30100-7
2. de Saint Aubain Somerhausen N, van de Rijn M. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. IARC Press; 2013:100-103.
3. 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. doi:10.1016/j.ejca.2016.04.022
4. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394:478-487. doi:10.1016/s0140-6736(19)30764-0
5. West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci U S A*. 2006;103:690-695. doi:10.1073/pnas.0507321103
6. 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. doi:10.3899/jrheum.160816
7. 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. doi:10.1155/2017/7402570
8. Brahmi M, Vinceneux A, Cassier PA. Current systemic treatment options for tenosynovial giant cell tumor/pigmented villonodular synovitis: targeting the CSF1/CSF1R axis. *Curr Treat Options Oncol*. 2016;17:10. doi:10.1007/s11864-015-0385-x
9. Palmerini E, Staals EL, Maki RG, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. *Eur J Cancer*. 2015;51:210-217. doi:10.1016/j.ejca.2014.11.001
10. 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. doi:10.1056/NEJMoa1411366
11. Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH, Ruttinger D. Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. *J Immunother Cancer*. 2017;5:53. doi:10.1186/s40425-017-0257-y
12. Chassaignac M. Cancer de la gaîne des tendons. *Gaz Hop Civ Mil*. 1852;47:185-186.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma—Version 1.2021. Published 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed November 4, 2020.
14. Bauer S, Lewis JH, Gelderblom H, et al. Pexidartinib (Pex) for locally advanced tenosynovial giant cell tumor (TGCT): characterization of hepatic adverse reactions (ARs) [abstract]. *Ann Oncol*. 2019;30(suppl 5):V695-V696. doi:10.1093/annonc/mdz283.029
15. Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. *Sci Rep*. 2019;9:14551. doi:10.1038/s41598-019-51211-y
16. Gelderblom H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2018;19:639-648. doi:10.1016/s1470-2045(18)30143-8
17. Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. *Lancet Oncol*. 2015;16:949-956. doi:10.1016/s1470-2045(15)00132-1