A Multidisciplinary Approach to Treatment of Tenosynovial Giant Cell Tumor (TGCT)

Introduction

Tenosynovial giant cell tumors (TGCT), also known as GCT of the tendon sheath (GCTTS), are rare, benign tumors that affect the synovium, bursae, and tendon sheath. Subdivisions of TGCT include diffuse-type giant cell tumor, pigmented villonodular synovitis (PVNS), intra-articular GCTTS, and extra-articular GCTTS. Joints of the knee, hip, ankle, elbow, shoulders, hands, or feet are commonly involved.[1] Clinical hallmarks of TGCT include joint swelling, pain, stiffness, and decreased range of motion, all of which lead to a reduced quality of life and a heavy healthcare burden.[2] Surgery has been the mainstay of therapy for patients with TGCT; however, surgery is associated with high rates of recurrence and morbidities for many patients, particularly those with diffuse-type TGCT (**Table 1**).[2-4]

Table 1. Recurrence-Free Surgical Outcomes of Patients with Diffuse-Type TGCT

	No prior therapy (n=758)		**Prior therapy (n=966)**	
	%	**No. at risk**	**%**	**No. at risk**
3 years	70%	372	62%	474
5 years	64%	227	55%	297
10 years	50%	70	40%	89

Data were derived from Mastboom MJL, et al. *Lancet Oncol*. 2019;20(19):877–886.

Until recently, there were no approved systemic therapies for TGCT. On August 2, 2019, the US Food and Drug Administration (FDA) approved the novel, oral, small-molecule tyrosine kinase inhibitor (TKI) pexidartinib for the treatment of adult patients with symptomatic TGCT associated with severe disease or functional limitations and not amenable to improvement with surgery.[5] Pexidartinib is strongly selective against the colony-stimulating factor 1 (CSF1) receptor, KIT, and FLT3 internal tandem duplication. Its approval was based on durable overall response rates (ORR) in patients who received pexidartinib in the phase 3 ENLIVEN clinical trial (NCT02371369).[1] Following this approval, pexidartinib was added as a preferred systemic regimen for TGCT in the National Comprehensive Cancer Network Guidelines for Soft Tissue Sarcoma (category 1 recommendation).[6] Imatinib, although not approved for this indication, is also included by the NCCN as an option for TGCT based on a 19% ORR in a study of 29 patients with TGCT/PVNS.[7] Other investigational CSF1 pathway inhibitors examined in TGCT include nilotinib, emactuzumab, and cabiraluzumab.[4]

Diagnosis and Initial Decision-Making

How to Approach a Patient in Clinical Practice

- Diagnose patient based on MRI results
- Educate the patient on disease management
- Locate and assess affected joints
- Utilize a multidisciplinary approach

Accurate diagnosis is essential for all patients with a soft tissue sarcoma, including those with TGCT. In most cases, a high-quality MRI can detect diagnostic characteristics of TGCT. For example, identification of "blooming artifacts" that are due to hemosiderin deposition obviates the need for biopsy.[8]

Given the morbidities associated with the disease itself as well as the treatment options, thorough patient education and counseling are key elements of clinical management.

Assessment should include an exploration of joint involvement and its impact on the patient's quality of life and activities of daily living.

Decisions about how and when to intervene should involve a multidisciplinary team and shared decision-making with the patient. Important factors that inform treatment planning include patient preference, surgical options and timing, site(s) of disease, symptom burden, goals of therapy, surgeon expertise, and the pros and cons of each intervention versus observation.

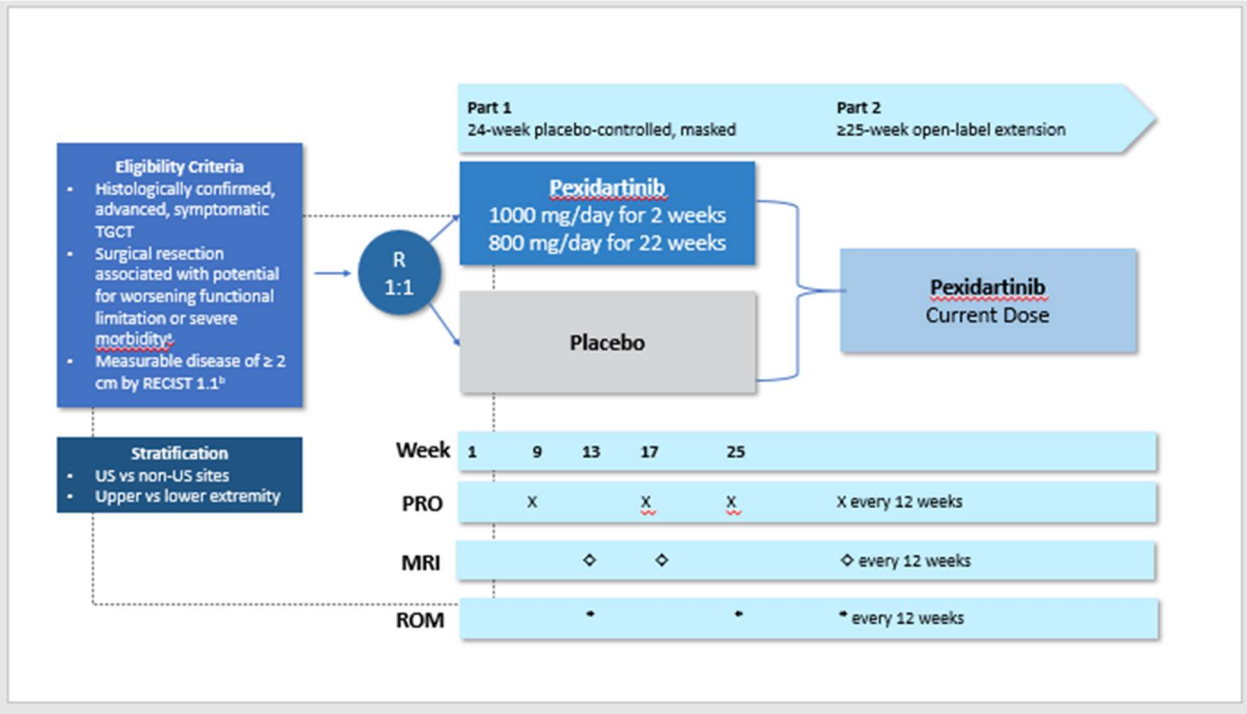
ENLIVEN Clinical Trial

ENLIVEN was a randomized, double-blind, phase 3 clinical study composed of 2 parts (**Figure 1**).[1,9] In part 1, patients were randomized to receive 1000 mg per day of pexidartinib split twice a day (for 2 weeks) and then 800 mg per day split twice a day (for 22 weeks) or matching placebo. The protocol was amended to include part 2, in which patients who completed part 1 were eligible to receive open-label pexidartinib until progression or unacceptable toxicity.[9] Eligibility criteria for the study included histologically confirmed advanced, symptomatic TGCT; surgical resection associated with the potential for worsening of functional limitation or severe morbidity; and measurable disease (≥2cm by the Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria). The primary endpoint was overall response at the end of part 1. Secondary endpoints included range of motion, overall response based on tumor volume score (TVS), patient-reported outcomes, stiffness, pain, and duration of response (DOR). Enrollment of the study was stopped early by the data monitoring committee due to 2 cases of mixed or cholestatic hepatotoxicity.[10] Patients in the pexidartinib arm of part 1 were allowed to continue to part 2, but crossover from placebo to pexidartinib was not permitted.

Tumor Volume Score (TVS)[11,12]

- RECIST is a linear measurement that suboptimally estimates tumor mass for diffuse, irregularly shaped tumors like TGCT
- TVS is a novel scoring method developed specifically for TGCT
- TVS calculates tumor volume as a percentage of the entire synovium, using the synovium cavity for standardization
- Response criteria:
  - Complete response: lesion completely gone
  - Partial response: ≥50% decrease in TVS vs baseline
  - Progressive disease: ≥30% increase in TVS vs nadir
  - Stable disease: dose not meet any of the prior criteria

Figure 1. Phase 3 ENLIVEN Study Design



[a] Morbidity determined consensually by qualified personnel (e.g., 2 surgeons or multidisciplinary tumor board).
[b] Assessed from MRI scans by a central radiologist.
MRI, magnetic resonance imaging; PRO, patient-reported outcomes; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; ROM, range of motion; TGCT, tenosynovial giant cell tumor.

ENLIVEN Clinical Trial: Efficacy Results

In part 1 of ENLIVEN (May 11, 2015, to September 30, 2016), 120 patients were randomized and received ≥1 dose of pexidartinib or placebo. Key baseline characteristics included knee involvement (61%), ≥1 prior surgery for TGCT (53%), and prior imatinib or nilotinib (9%). At week 25, the ORRs were 39% by RECIST (v1.1) and 56% by TVS (**Table 2**). At the January 31, 2018, data cutoff (22-month median follow-up), the best overall response to pexidartinib had increased to 53% by RECIST (v1.1) and 64% by TVS, reflecting additional tumor shrinkage with extended treatment. Importantly, responses were durable, with most complete or partial responses maintained for all measured timepoints and zero instances of disease progression at 6-month follow-up among responders (median DOR not reached by RECIST or TVS). Among 30 patients who crossed over to receive pexidartinib (800 mg/day starting dose) in part 2, ORRs at week 25 were 30% by RECIST (v1.1) and 57% by TVS. In addition to tumor shrinkage, statistically significant improvements in relative range of motion, physical functioning, and stiffness were demonstrated with pexidartinib.

Table 2. Summary of Tumor Responses in the ENLIVEN Clinical Trial

Measurement	Regimen		P Value
	Pexidartinib group (n=61)	**Placebo group (n=59)**	
Response rate based on RECIST (primary endpoint)			
Overall response	39%	0%	<0.0001
Complete response	15%	0%	
Partial response	25%	0%	
Stable disease	39%		
Response rate based on TVS			
Overall response	56%	0%	<0.0001
Complete response	5%	0%	
Partial response	51%	0%	
Stable disease	23%		

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1; TVS, tumor volume score.

ENLIVEN Clinical Trial: Safety

High incidences of any-grade treatment-emergent adverse events (AEs) were reported in both arms of the study (98% pexidartinib vs 93% placebo). The common occurrence of AEs among patients in the placebo group is indicative of the debilitating manifestations of the disease.

The most frequent AEs associated with pexidartinib were changes in hair pigmentation (67%), fatigue (54%), aspartate aminotransferase increase (39%), nausea (38%), alanine aminotransferase increase (28%), and dysgeusia (25%); selected common AEs are summarized in **Table 3**. The incidence of grade 3 or 4 AEs was more common with pexidartinib (44% vs 12%, respectively). Serious AEs occurred in 13% (n=8) of patients in the pexidartinib arm versus 2% (n=1) in the placebo arm.

Aminotransferase elevations ≥3 times the upper limit of normal (ULN) were reported in 3 patients who received pexidartinib (total bilirubin and alkaline phosphatase ≥2 times the ULN), suggestive of mixed or cholestatic hepatotoxicity (1 case was confirmed by biopsy and lasted 7 months). As mentioned previously, incidences of mixed or cholestatic hepatotoxicity caused the data monitoring committee to discontinue enrollment of ENLIVEN. Hepatic AEs in the pexidartinib group were a common cause of dose reductions and treatment interruption/discontinuation. Serious hepatotoxicity was associated with elevated alkaline phosphatase that emerged ≤2 months from treatment initiation.

Table 3. Selected Adverse Events in the ENLIVEN Clinical Trial

	Part 1				Part 2	
	Pexidartinib (n=61)		Placebo (n=59)		Crossover to pexidartinib (n=30)	
Disorder	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Hair color changes	67%	0%	3%	0%	83%	0%
Pruritis	16%	0%	3%	0%	27%	0%
Vomiting	20%	2%	5%	0%	3%	0%
Facial edema	13%	0%	2%	0%	20%	3%
Fatigue	54%	0%	36%	0%	17%	0%
Peripheral edema	13%	0%	3%	0%	17%	0%
Periorbital edema	18%	2%	2%	0%	10%	0%
Eyelid edema	2%	0%	0%	0%	10%	0%
AST elevation	39%	10%	0%	0%	17%	3%
ALT elevation	28%	10%	2%	0%	23%	7%
ALP elevation	15%	7%	0%	0%	3%	3%
Lactate dehydrogenase elevation	12%	2%	0%	0%	10%	0%
Dysgeusia	25%	0%	2%	0%	23%	0%
Hypertension	15%	5%	10%	0%	20%	7%

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Clinical Guidance on Pexidartinib-Associated Hepatotoxicity Mitigation, Monitoring, and Management

Practice Recommendations

- Check for Liver Problems:
  - Before starting treatment with pexidartinib
  - Every week for the first 8 weeks during treatment
  - Every 2 weeks for the next month
  - Every 3 months after that

Two types of hepatic toxicity were reported with pexidartinib: liver enzyme abnormalities (most commonly grade 1-2 aminotransferase elevation) and mixed or cholestatic hepatotoxicity. Serious hepatotoxicity was associated with elevated alkaline phosphatase that emerged within 8 weeks of treatment initiation. Therefore, patients who receive pexidartinib should undergo frequent monitoring for increased aminotransferases, bilirubin, and alkaline phosphatase during the first 2 to 3 months of therapy, with appropriate steps taken for patients with evidence of hepatic toxicity (**Table 4**).[13]

Table 4. Recommended Dose Modifications for Pexidartinib Adverse Reactions[a]

Adverse reaction	Severity	Dosage modification
Elevated AST and/or ALT	>3-5x ULN	• Withhold • Weekly liver test monitoring • If AST/ALT ≤3x ULN within 4 weeks, resume at reduced dose[b] • If AST/ALT >3x ULN in 4 weeks, permanently discontinue
	>5-10x ULN	• Withhold • Twice weekly liver test monitoring • If AST/ALT ≤3x ULN within 4 weeks, resume at reduced dose[b] • If AST/ALT >3x ULN in 4 weeks, permanently discontinue
	>10x ULN	• Permanently discontinue • Twice weekly liver test monitoring until AST/ALT <5x ULN, then weekly until ≤3x ULN
Elevated ALP and GGT	ALP >2x ULN with GGT >2x ULN	• Permanently discontinue • Twice weekly liver test monitoring until ALP ≤ 5x ULN, then weekly until ≤2x ULN.
Elevated bilirubin	TB: >ULN to <2x ULN DB: >ULN to <1.5x ULN	• Withhold • Weekly liver test monitoring • If bilirubin <ULN within 4 weeks and an alternate cause for bilirubin elevation is confirmed, resume at reduced dose • If bilirubin >ULN in 4 weeks, permanently discontinue
	TB: ≥2x ULN DB: ≥1.5x ULN	• Permanently discontinue • Twice weekly liver test monitoring until bilirubin ≤ULN

[a] Turalio. Prescribing Information. Daiichi-Sankyo, Inc; 2020.

[b] Recommended dose reductions for adverse reactions: first, 600 mg total daily dose (200 mg in the morning, 400 mg in the evening); second, 400 mg (200 mg BID); permanently discontinue for patients unable to tolerate 200 mg BID.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DB, direct bilirubin; GGT, gamma-glutamyl transferase; TB, total bilirubin; ULN, upper limit of normal.

Patient Counseling

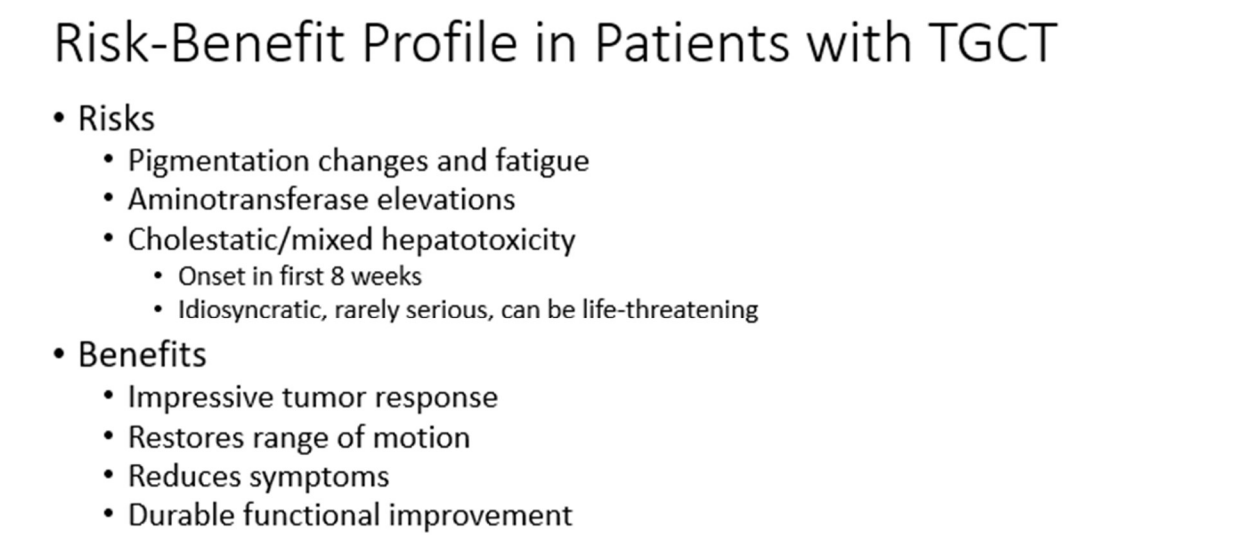
TGCT Multidisciplinary Team

May include:

- Surgical oncologists
- Medical oncologists
- Orthopedic oncologists
- Physical therapists
- Pain and palliative care specialists
- Rheumatologists

The decision of whether to initiate pexidartinib should involve a multidisciplinary team and shared decision-making, and it should consider the relative benefits and risks associated with treatment versus no treatment (**Figure 2**).

Figure 2. Risk-Benefit Profile of Pexidartinib Use for Patients with TGCT



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Conclusions

Unanswered Questions

- Patient selection
- Duration of therapy
- Post-discontinuation management
- Long-term efficacy and safety
- Combination approaches
- Use in earlier stages of disease

Pexidartinib, a novel inhibitor of the CSF1 receptor, is the first systemic therapy approved for the treatment of TGCT. Its approval was based on results of the phase 3 ENLIVEN clinical study demonstrating that it significantly improved ORR, symptoms, and function in patients with symptomatic TGCT for whom surgical intervention was not recommended. Although generally well tolerated, rare but severe mixed or cholestatic hepatotoxicity was reported with pexidartinib. Thus, in the US, it is only accessible via a Risk Evaluation and Mitigation Strategy. Questions about how and when to optimally use pexidartinib or other CFS1 pathway inhibitors in TGCT will hopefully be answered in future clinical trials.[2]

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