SAFETY, EFFICACY, AND PATIENT-REPORTED OUTCOMES WITH VIMSELTINIB IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR WHO RECEIVED PRIOR ANTI–COLONY-STIMULATING FACTOR 1 THERAPY: ONGOING PHASE 2 UPDATE

Abstract: 1545242

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Introduction

- Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplasm caused by aberrant expression of the *colony-stimulating factor 1* (*CSF1*) gene[1]
- There is only 1 systemic agent approved by the US Food and Drug Administration for the treatment of patients with TGCT not amenable to surgery, and none by the European Commission or other regulatory agencies, leaving an unmet need for an effective, CSF1 receptor (CSF1R)–targeted therapy with a favorable safety profile[2]
- Vimseltinib is an investigational, oral switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R[1]
- Here, we report updated safety, efficacy, range of motion (ROM), and patient-reported outcome (PRO) data from the phase 2 part (expansion) of an ongoing phase 1/2 study of vimseltinib for patients with TGCT (Cohort B; NCT03069469)

Methods

- This multicenter, open-label, phase 2 trial is designed to evaluate the safety, tolerability, and efficacy of vimseltinib at the recommended phase 2 dose (30 mg twice weekly) in patients with TGCT not amenable to surgery who received prior specific anti-CSF1/CSF1R agents (cohort B)
- Vimseltinib antitumor activity was evaluated by independent radiological review (IRR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) via magnetic resonance imaging
- Total active ROM (in degrees) of the affected joint was normalized to a reference standard value provided by the American Medical Association to compute active ROM
- Pain was assessed by 2 items from the brief pain inventory (BPI; worst pain and average pain), with BPI response defined as ≥30% reduction in pain without a ≥30% increase in narcotic analgesic use
- PRO questionnaires were completed electronically and included 15 questions from Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) and stiffness from the numeric rating scale (NRS)
  - Clinically meaningful response for these PROs was defined as a ≥3 point increase or ≥1 point decrease from baseline for PROMIS-PF or NRS stiffness, respectively[3]

Results

- As of June 27, 2023, 19 patients were enrolled in cohort B (enrollment ongoing); median age was 46 years (**Table 1**)
- The most common disease location was the knee, and most patients had diffuse TGCT
- Most patients (79%) previously received pexidartinib and discontinued pexidartinib due to disease progression (n = 5), drug-related toxicity (n = 2), and other (n = 8)

Table 1. Baseline demographics and clinical characteristics

	Cohort B (n = 19)
Age, median (min, max), years	46 (26, 65)
Sex	
Female	10 (53)
Male	9 (47)
Race	
White	16 (84)
Black or African American	1 (5)
Pacific Islander	1 (5)
Not reported	1 (5)
Disease location	
Knee	10 (53)
Hip	3 (16)
Ankle	2 (11)
Hand	2 (11)
Jaw	2 (11)
Tumor type	
Diffuse TGCT	15 (79)
Localized TGCT	4 (21)
Patients with ≥1 prior surgery	13 (68)
1 surgery	3 (16)
2–3 surgeries	5 (26)
≥4 surgeries	5 (26)
Patients with ≥1 prior systemic therapy	19 (100)
Pexidartinib	15 (79)
Imatinib[a]	3 (16)
Vimseltinib	2 (11)
Other[b]	3 (16)

Data cutoff: June 27, 2023. Data shown as n (%) unless otherwise noted.
[a]Patients received pexidartinib or surufatinib in addition to imatinib. [b]Includes cabiralizumab and surufatinib.
max, maximum; min, minimum; TGCT, tenosynovial giant cell tumor.

Safety

- The majority of non-laboratory treatment-emergent adverse events (TEAEs) were low grade; observed aminotransferase elevations were also low grade (**Table 2**)
- Grade 3/4 TEAEs (>5% of patients) were elevated creatine phosphokinase (CPK), hypertension, and eczema
- Enzyme elevations were consistent with the known mechanism of action of CSF1R inhibitors
- There was no evidence of cholestatic hepatotoxicity
- Overall, 3 patients reported treatment-related serious TEAEs
  - One patient reported grade 3 eczema (possibly related) and grade 2 edema peripheral (probably related); another patient reported grade 3 myalgia and grade 4 elevated CPK (both probably related)
  - Since previous reporting, 1 new treatment-related serious TEAE of grade 2 squamous cell carcinoma of the skin was reported (assessed as possibly related by investigator and not related by sponsor)

Table 2. TEAEs in ≥15% of patients

	Cohort B (n = 19)			
Preferred term, n (%)	**All grades**	**Grade 1**	**Grade 2**	**Grade 3/4**
Blood CPK increased	11 (58)	1 (6)	3 (16)	7 (37)
Headache[a]	10 (53)	8 (42)	2 (11)	0
Fatigue[a]	10 (53)	8 (42)	1 (5)	1 (5)
Periorbital edema[a]	9 (47)	7 (37)	2 (11)	0
AST increased	8 (42)	6 (32)	2 (11)	0
Nausea[a]	6 (32)	5 (26)	1 (5)	0
Diarrhea	6 (32)	5 (26)	1 (5)	0
Myalgia[a]	5 (26)	4 (21)	0	1 (5)
Hypertension	5 (26)	0	3 (16)	2 (11)
Rash maculopapular[a]	5 (26)	2 (11)	3 (16)	0
Amylase increased	5 (26)	4 (21)	1 (5)	0
Arthralgia[a]	4 (21)	1 (5)	2 (11)	1 (5)
Edema peripheral[a]	4 (21)	3 (16)	1 (5)	0
Rash[a]	4 (21)	3 (16)	1 (5)	0
Pruritus[a]	4 (21)	2 (11)	2 (11)	0
ALT increased	4 (21)	2 (11)	2 (11)	0
Eczema[a]	4 (21)	0	2 (11)	2 (11)
Asthenia[a]	3 (16)	2 (11)	1 (5)	0
Pain in extremity[a]	3 (16)	2 (11)	0	1 (5)
Hypercholesterolemia	3 (16)	2 (11)	1 (5)	0
Dizziness	3 (16)	3 (16)	0	0

Data cutoff: June 27, 2023. Safety population includes patients who received ≥1 dose of study drug. Severity was assessed by the investigator according to the toxicity grade described in the National Cancer Institute CTCAE v4.03 (grade 1 [mild] to grade 5 [death]). Both patients with grade 3/4 hypertension had prior history of hypertension.
[a]Denotes events without a grade 4 severity category in the CTCAE v4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CTCAE v4.03, Common Terminology Criteria for Adverse Events version 4.03; TEAE, treatment-emergent adverse event.

- Median treatment duration was 7.3 months (range, 0.7–27.4; mean, 11.0 months) with 74% (14/19) of patients on treatment at data cutoff
  - Treatment discontinuation reasons included adverse event (n = 2), physician decision (n = 1), withdrawal by patient (n = 1), and other (n = 1)
- TEAEs led to treatment discontinuation in 16% of patients (**Table 3**)

Table 3. Dose modification due to any TEAEs

	Cohort B (n = 19)
Patients with TEAEs leading to dose modification, n (%)	15 (79)
Dose interruption	13 (68)
Dose reduction	7 (37)
Treatment discontinuation	3 (16)[a]

Data cutoff: June 27, 2023.
[a]G2 rash maculopapular; G2 rash; G3 myalgia.
G, grade; TEAE, treatment-emergent adverse event.

Efficacy

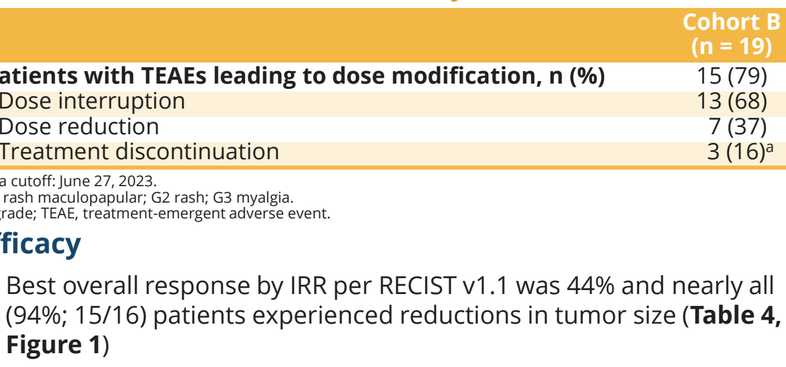
- Best overall response by IRR per RECIST v1.1 was 44% and nearly all (94%; 15/16) patients experienced reductions in tumor size (**Table 4, Figure 1**)
  - Patients who achieved partial response in cohort B included patients who did not achieve objective response or progressed on/after prior CSF1R-directed therapies
  - Most responses (86%) occurred within 6 months of treatment, with median time to first response of 3.7 months (range, 1.6–8.3; **Figure 2**)
- As of data cutoff, no patients progressed as assessed by IRR
- Most patients experienced an increase in active ROM (**Figure 3, Table 5**)

Table 4. Response assessed by IRR using RECIST v1.1

	BOR (n = 16)	Week 25[a] (n = 16)
ORR, n (%)	7 (44)	5 (31)
Complete response	0[b]	0
Partial response	7 (44)	5 (31)
Stable disease	9 (56)	5 (31)
Duration of response, median[c] (min, max), months	NR (4.0+, 21.0+)	

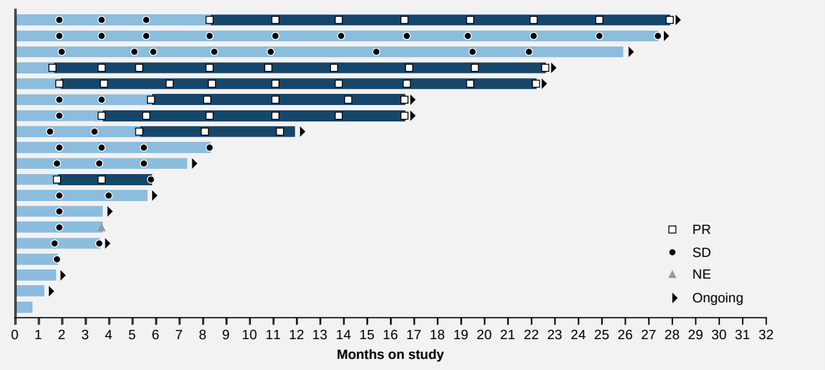
Data cutoff: June 27, 2023; 16/19 patients had at least 1 post-baseline imaging assessment as of the data cutoff (efficacy evaluable population); + indicates that response was ongoing at last assessment.
[a]Patients that either reached week 25 or discontinued treatment or study prior to week 25 were included. [b]Previously presented CR case (ESMO 2022) was changed to PR by IRR based on additional follow-up assessments. [c]Based on Kaplan-Meier estimate. Duration of response is defined as time from first imaging result showing response to progressive disease.
BOR, best overall response; CR, complete response; IRR, independent radiological review; max, maximum; min, minimum; NR, not reached; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 1. Best percent change in target lesions



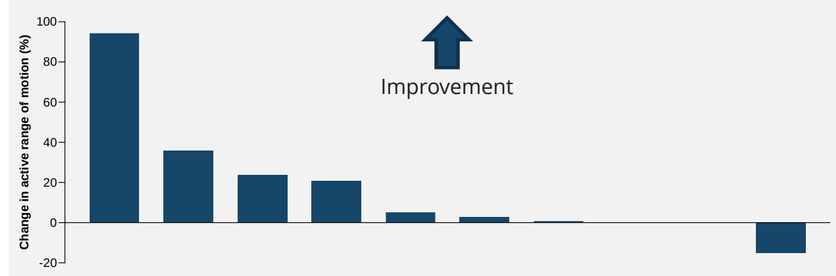
Data cutoff: June 27, 2023. Using RECIST v1.1 by IRR; includes all available follow-up visits. Dotted line at 20% represents threshold for PD; dotted line at −30% represents threshold for PR. Graph shows individual patient values.
IRR, independent radiological review; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 2. Duration of treatment and response



Data cutoff: June 27, 2023. Using RECIST v1.1 by IRR; includes all available follow-up visits. Dark blue shading represents duration of response.
IRR, independent radiological review; NE, not evaluable; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 3. Change in active ROM



Graph shows individual patient values. Increase from baseline: n = 7; no change: n = 2; decrease: n = 1.
ROM, range of motion.

Table 5. Active ROM change from baseline to week 25

	Cohort B (n = 10)
Active ROM of the affected joint, mean (SD), %	
Baseline	50.1 (34.9)
Week 25	67.0 (35.7)
Change from baseline to week 25, mean (SD), % points	16.9 (30.9)

Data cutoff: June 27, 2023. Analysis only includes patients with active ROM assessments at baseline and week 25.
ROM, range of motion; SD, standard deviation.

Patient-reported outcomes

- At week 25, 47% (7/15) of patients experienced BPI response for both worst pain and average pain
- Two patients (40%) with objective responses by RECIST v1.1 at week 25 were also BPI responders (**Table 6**)
  - Most patients (80%) with stable disease at week 25 were also BPI responders
- At week 25, 82% and 73% of patients had clinically meaningful improvements in PROMIS-PF and NRS stiffness, respectively (**Table 7**)

Table 6. Examination of the relationship between RECIST response and BPI worst pain response at week 25

	RECIST v1.1 at week 25 by IRR[a]	
	Partial response (n = 5)	Stable disease (n = 5)
Worst pain responder, n (%)	2 (40)	4 (80)

Data cutoff: June 27, 2023.
[a]Includes patients with both BPI and efficacy data available at week 25 (n = 10); percentages represent proportion of patients with partial response or stable disease with ≥30% pain reduction.
BPI, Brief Pain Inventory; IRR, independent radiological review; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Table 7. PROMIS-PF and NRS stiffness at week 25

	PROMIS-PF (n = 11)		NRS Stiffness (n = 11)	
	Baseline	Week 25	Baseline	Week 25
Mean (SD)	45.6 (8.2)	50.8 (7.3)	4.2 (2.3)	2.3 (1.8)
Change from baseline, mean (SD)	5.2 (7.9)		−2.0 (2.8)	
Response, n (%)	9 (82)		8 (73)	

Data cutoff: June 27, 2023.
NRS, numeric rating scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System Physical Function; SD, standard deviation.

CONCLUSIONS

- Vimseltinib demonstrated promising antitumor activity in this pretreated population, with a best overall response of 44% without disease progression observed in any patient by IRR
- Longer follow-up demonstrated that vimseltinib continued to be well tolerated with a manageable safety profile in patients with TGCT not amenable to surgery who received prior anti-CSF1/CSF1R therapy
  - The safety profile remained consistent with phase 1 and cohort A with a median treatment duration of 7.3 months and 74% of patients remaining on treatment at data cutoff
- Patients experienced clinically meaningful improvements in pain, physical function, and stiffness
  - At week 25, patients had clinically meaningful reductions in pain regardless of objective response; patients with stable disease also experienced clinically meaningful reductions in pain
  - Between baseline and week 25, most patients experienced clinically meaningful improvements in physical function and stiffness

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