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CSF1R Inhibition in Patients with Advanced Solid Tumors or Tenosynovial Giant Cell Tumor: A Phase I Study of Vimseltinib

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ABSTRACT

Purpose: Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the *colony-stimulating factor 1* (*CSF1*) gene and overexpression of the CSF1 ligand. Surgery is the standard of care for most patients, but there are limited treatment options for patients with TGCT not amenable to surgery. This study evaluates vimseltinib, an investigational, oral, switch-control tyrosine kinase inhibitor designed to selectively and potently inhibit the CSF1 receptor.

Patients and Methods: This first-in-human, multicenter, open-label phase I/II study of vimseltinib in patients with malignant solid tumors ($N = 37$) or TGCT not amenable to surgery ($N = 32$) followed a pharmacologically guided 3 + 3 study design (NCT03069469). The primary objectives were to assess safety and tolerability, determine the recommended phase II dose, and characterize the pharmacokinetics; exploratory objectives included pharmacodynamics and efficacy.

Results: Vimseltinib was well tolerated; the majority of nonlaboratory treatment-emergent adverse events were of grade 1/2 severity. There was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. The recommended phase II dose was determined to be 30 mg twice weekly (no loading dose), and vimseltinib plasma exposure increased with the dose. In patients with TGCT, the median treatment duration was 25.1 months (range, 0.7–46.9), and the objective response rate as assessed by independent radiological review using RECIST version 1.1 was 72%.

Conclusions: Vimseltinib demonstrated long-term tolerability, manageable safety, dose-dependent exposure, and robust antitumor activity in patients with TGCT not amenable to surgery.

Introduction

The colony-stimulating factor 1 receptor (CSF1R) and its ligand, colony-stimulating factor 1 (CSF1), form a lineage dependency for normal macrophage development (1). Tumor-associated macrophages are dependent on CSF1R kinase activity for their proliferation and immunosuppressive phenotype (1, 2). Tumors with high infiltrating macrophage content include advanced malignant solid tumors (MST), such as gastric cancer, breast cancer, and lung cancer (3–5). Similarly, tenosynovial giant cell tumor (TGCT) is another disease characterized by high infiltrating macrophage content (6, 7). TGCT, previously known as pigmented villonodular synovitis or giant cell tumor of the tendon sheath, is a locally aggressive neoplasm affecting the synovium, bursae, and tendon sheath (8). TGCT is caused by dysregulation of the *CSF1* gene and overexpression of the CSF1 ligand, leading to tumor growth and expansion by recruiting and inducing local proliferation of CSF1R-dependent inflammatory macrophages (2, 6, 8, 9).

TGCT is classified as localized (nodular) or diffuse type, depending on the tumor location and size (7, 8, 10). Surgical resection is the standard of care for most patients, with approximately 90% of localized/nodular TGCT being cured with surgery (10); however, not all patients with TGCT have disease that is amenable to surgery (7, 11). Recurrence rates for diffuse-type TGCT are as high as 50%, and patients who experience a recurrence are significantly more likely to experience additional recurrences (10, 12, 13).

The use of tyrosine kinase inhibitors (TKIs) to target CSF1R started with the broad-spectrum TKIs imatinib and nilotinib, which only showed limited antitumor activity and disease control in studies treating patients with TGCT (14–17). With limited efficacy and specificity for CSF1R, these inhibitors did not gain regulatory approval for TGCT (18,

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Translational Relevance

Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the *colony-stimulating factor 1* (*CSF1*) gene leading to overexpression of the CSF1 ligand. Although surgery is the standard of care for most patients with TGCT, not all patients have disease that is amenable to surgery. Patients with TGCT often experience pain, swelling, and decreased physical function of affected joints. With limited options for treatment, patients with TGCT not amenable to resection could benefit from a safe and effective systemic therapy. Vimseltinib is an investigational, oral, switch-control tyrosine kinase inhibitor (TKI) designed to selectively and potently inhibit the CSF1 receptor. In the phase I part of this ongoing, first-in-human, multicenter, open-label phase I/II study, vimseltinib was well tolerated while demonstrating robust and durable antitumor activity in patients with TGCT not amenable to surgery. Vimseltinib has the potential to provide clinically meaningful benefit for patients with TGCT.

19). The TKI pexidartinib is a more specific CSF1R inhibitor compared with imatinib or nilotinib and was associated with a higher response rate compared with placebo in the phase III ENLIVEN study (20, 21). Pexidartinib subsequently became the only systemic anti-CSF1R agent approved in the United States, Taiwan, and Korea for the treatment of TGCT; however, it did not gain regulatory approval in Europe because of safety concerns related to the risk of severe liver toxicity (20–25). Pexidartinib must be prescribed under a risk evaluation mitigation strategy in the United States because of the risk of off-target serious cholestatic or mixed liver injury; therefore, patients receiving this drug require more frequent clinical and laboratory monitoring (22). Additionally, off-target activity of pexidartinib may indicate low selectivity for CSF1R (26). Patients with TGCT not amenable to surgery require specific and effective therapies with low toxicity due to the need for long-term treatment. Therefore, an unmet need remains for an effective and selective CSF1R-targeted therapy with a favorable safety profile.

Vimseltinib is an investigational, oral, switch-control TKI specifically designed to selectively and potently inhibit CSF1R (9, 27). By binding selectively to the switch pocket region of CSF1R, vimseltinib blocks the activation switch from occupying the pocket and stabilizes the switch in its inactive conformation (9). Vimseltinib inhibits CSF1R activity with nanomolar potency and is >500-fold more selective for CSF1R versus closely related kinases and >1,000-fold more selective versus other kinases (9). Here, we report the safety, pharmacokinetics (PK), pharmacodynamics, and initial efficacy results for vimseltinib in patients with MST or TGCT from the first-in-human, phase I part of an ongoing, phase I/II study (NCT03069469). The phase I part of the study involved dose escalation in patients with MST or TGCT; the phase II dose expansion portion included only patients with TGCT. This article reports results from phase I dose escalation, with a focus on patients with TGCT not amenable to surgery.

Patients and Methods

Study design and treatment

The phase I portion of this open-label, phase I/II study was conducted in eight centers. Dose escalation followed a 3 + 3 design, in which all patients received vimseltinib in 28-day cycles and were grouped by dose and disease type (**Fig. 1A**). A minimum of three patients were enrolled to each dose level, and the cohort was expanded to six patients if one of three experienced a dose-limiting toxicity (DLT) during cycle 1 (see Supplementary Materials for the definition of DLT). If the safety profile of a given dose was manageable, the cohort may have been expanded with additional patients to further investigate PK, tolerability, and efficacy.

Dose escalation began in patients with MST (cohort 1) at a starting dose of 10 mg (no loading dose) once daily (**Fig. 1A**). Vimseltinib was administered on an empty stomach at least 1 hour before and no sooner than 2 hours after ingestion of food and/or beverages other than water. The starting dose was based on results of nonclinical pharmacologic, pharmacodynamic, and toxicology studies per the International Conference on Harmonization S9 guidelines. In subsequent cohorts, a loading dose was included to decrease the time to reach steady-state plasma concentrations due to preliminary PK data indicating that vimseltinib had a relatively long terminal half-life ($t_{½}$). During dose escalation, the loading dose and maintenance dose were both varied and generally escalated in patients with MST (cohorts 2–7). In cohort 5 (30 mg once daily loading dose for 5 days, followed by 30 mg twice weekly maintenance dose), two patients with TGCT were initially enrolled, and after preliminary analysis, patients with TGCT continued to be enrolled both in cohort 5 and in cohorts 8 and 9 with different doses.

Although multiple dosing schedules were explored, a maximum tolerated dose (MTD) was not determined for each dosing schedule. The recommended phase II dose (RP2D) was selected based on overall safety, PK, pharmacodynamics, and efficacy from all dose schedules.

Patients were eligible to receive study drug until tumor progression, occurrence of unacceptable toxicity, withdrawal of consent, or physician decision. The study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonization and Good Clinical Practice guidelines. Applicable local regulatory requirements were followed. The protocol, protocol amendments, and informed consent documents were approved by an institutional review board or ethics committee at each site and by appropriate regulatory authorities. All patients provided written informed consent.

Eligibility criteria

Eligible patients were 18 years or older and had either advanced MST that progressed after treatment with all available therapies known to confer clinical benefit or for which conventional therapy was not considered effective as determined by the investigator, or had a confirmed diagnosis of TGCT for which resection would potentially cause worsening functional limitation or severe morbidity as assessed by the investigator. Patients had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Patients with MST were required to provide a tumor tissue sample and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with TGCT had symptomatic disease with at least moderate pain or stiffness (a score of at least 4 on a numeric scale from 0 to 10, with 10 describing the worst condition).

Patients were excluded if they received anticancer therapy or therapy for TGCT within 2 weeks prior to the administration of study drug or 28 days for therapies with a $t_{½}$ longer than 3 days (prior treatment with specific anti-CSF1/CSF1R therapy was allowed). Additional exclusion criteria included known active

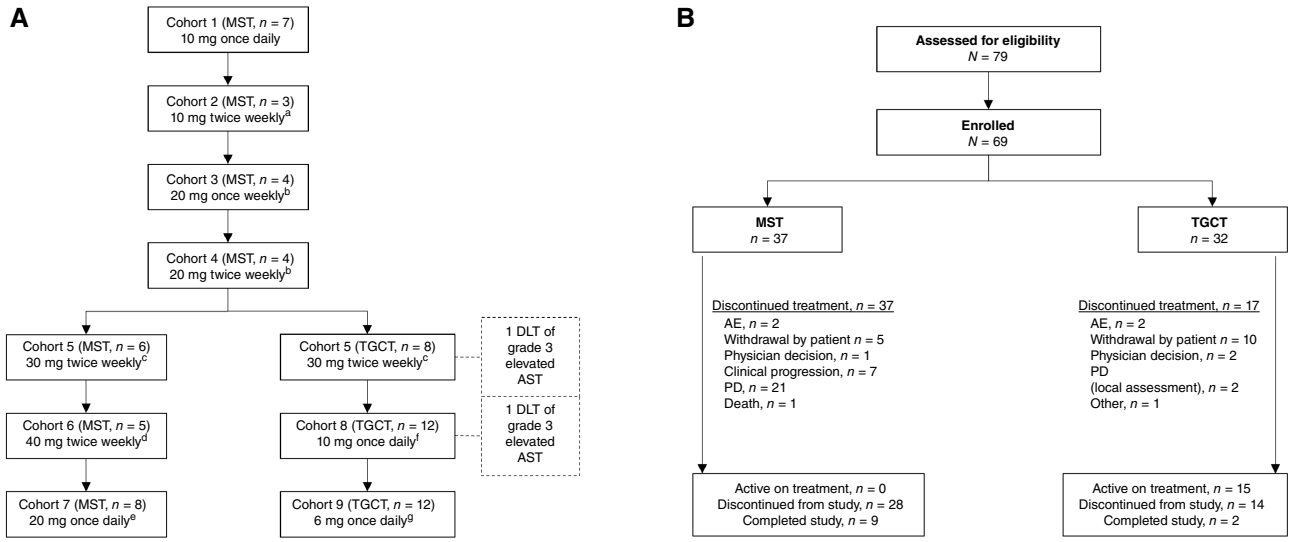

Figure 1.

A, Phase I dose escalation design and enrollment. **B,** Patient enrollment and disposition. One patient with TGCT discontinued treatment but remained on study at the data cutoff. [a]After a 5-day 10 mg once daily loading dose. [b]After a 5-day 20 mg once daily loading dose. [c]After a 5-day 30 mg once daily loading dose. [d]After a 5-day 40 mg once daily loading dose. [e]After a 3-day 50 mg once daily loading dose. [f]After a 3-day 30 mg once daily loading dose. [g]After a 3-day 20 mg once daily loading dose.

central nervous system metastases, history or presence of clinically relevant cardiovascular abnormalities, concurrent treatment with prohibited medications, or major surgery within 2 weeks prior to the administration of study drug. The representativeness of the study population is presented in Supplementary Table S1. For a full list of eligibility criteria, see Supplementary Table S2 and Table S3.

Study assessments and endpoints

Clinical laboratory analyses were performed locally and/or centrally for all patients. Toxicity was graded as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Plasma PK samples were collected for TGCT cohorts during cycle 1 on days 1, 8, and 15; cycle 2 on days 1 and 15; cycle 3 on days 1 and 15; and all subsequent cycles on day 1. For MST cohorts, plasma PK samples were obtained on the same days, with an additional sample taken during cycle 1 on day 22. Plasma and whole-blood pharmacodynamic samples were collected predose on days 1 and 15 of cycle 1 and day 1 of cycles 2, 3, 4, and 7.

Response assessments were performed for patients with MST or TGCT at screening; cycles 3, 5, and 7 and every 3 cycles thereafter; at the end-of-treatment visit; and 12 weeks after the last dose of study drug (patients with TGCT only). For patients with MST, CT or MRI scans of the chest, abdomen, and pelvis were assessed locally by the investigator using RECIST v1.1. For patients with TGCT, MRI of the affected joint was assessed for tumor response by independent radiological review (IRR) using RECIST v1.1 and tumor volume score (TVS; refs. 21, 28). For a detailed description of TVS assessment and the corresponding definition of response, see Supplementary Materials.

The primary endpoints for the dose escalation part of this study were safety and PK. Safety assessments included evaluation of treatment-emergent adverse events (TEAE), serious adverse events (AE), dose reductions or discontinuations due to toxicity, and DLTs. A noncompartmental analysis was performed to determine PK parameters, including the maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration–time curve from time 0 to 4 hours ($AUC_{0-4\ hours}$), area under the concentration–time curve from time 0 to 8 hours ($AUC_{0-8\ hours}$), and $t_{½}$. Exploratory endpoints included pharmacodynamic biomarkers, objective response rate [ORR; complete response (CR) + partial response (PR)] by IRR using RECIST v1.1 and TVS, clinical benefit rate [CBR; CR + PR + stable disease (SD)], duration of response (DOR), and time to response.

Statistical analyses

The safety population included patients who received at least one dose of study drug and was the primary set for all safety data analyses. The PK population included all patients who had at least one valid postdose PK evaluation. The per-protocol population included patients with at least one postbaseline imaging assessment obtained by IRR or local imaging and was the primary population for efficacy analyses. There was no statistical hypothesis testing in this study, and descriptive statistics were calculated to describe continuous and categorical variables.

Data availability

Qualified scientific and medical researchers can make requests for individual participant data that underlie the results reported in this article, after de-identification, at info@deciphera.com. Proposals for data will be evaluated and approved by Deciphera Pharmaceuticals, LLC, at its sole discretion. All approved researchers must sign a data access agreement before accessing the data. Data will be available upon publication of the article and for 6 years after. Deciphera Pharmaceuticals, LLC, will not share data from identified participants or a data dictionary.

Results

Patients

As of June 2023, 32 patients with TGCT and 37 patients with MST were enrolled in phase I and received vimseltinib (**Fig. 1B**).

Table 1. TEAEs in at least 15% of patients with TGCT receiving vimseltinib.

	Cohort 5 30 mg twice weekly[a] *n* = 8		Cohort 8 10 mg once daily[b] *n* = 12		Cohort 9 6 mg once daily[c] *n* = 12		Total *N* = 32	
Preferred term	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Blood CPK increased	7 (88)	4 (50)	8 (67)	4 (33)	6 (50)	2 (17)	21 (66)	10 (31)
Periorbital edema	3 (38)	0	10 (83)	0	6 (50)	0	19 (59)	0
Fatigue	3 (38)	0	6 (50)	0	7 (58)	0	16 (50)	0
AST increased	5 (63)	1 (13)	4 (33)	2 (17)	2 (17)	1 (8)	11 (34)	4 (13)
Arthralgia	3 (38)	0	3 (25)	0	5 (42)	1 (8)	11 (34)	1 (3)
Face edema	1 (13)	0	6 (50)	0	3 (25)	0	10 (31)	0
COVID-19	1 (13)	0	4 (33)	0	5 (42)	0	10 (31)	0
Myalgia	0	0	5 (42)	1 (8)	4 (33)	0	9 (28)	1 (3)
Edema peripheral	1 (13)	0	5 (42)	0	3 (25)	0	9 (28)	0
Pruritus	1 (13)	0	4 (33)	0	4 (33)	0	9 (28)	0
Headache	3 (38)	0	3 (25)	0	2 (17)	0	8 (25)	0
Lipase increased	1 (13)	0	5 (42)	3 (25)	1 (8)	0	7 (22)	3 (9)
Diarrhea	1 (13)	1 (13)	4 (33)	0	2 (17)	0	7 (22)	1 (3)
ALT increased	2 (25)	0	3 (25)	0	2 (17)	1 (8)	7 (22)	1 (3)
Hypertension	0	0	3 (25)	2 (17)	3 (25)	0	6 (19)	2 (6)
Generalized edema	2 (25)	0	2 (17)	0	2 (17)	0	6 (19)	0
Nausea	2 (25)	0	3 (25)	0	1 (8)	0	6 (19)	0
Constipation	1 (13)	0	1 (8)	0	4 (33)	0	6 (19)	0
Rash	1 (13)	0	2 (17)	0	3 (25)	0	6 (19)	0
Amylase increased	1 (13)	1 (13)	4 (33)	1 (8)	0	0	5 (16)	2 (6)
Paresthesia	0	0	5 (42)	0	0	0	5 (16)	0
Dry skin	1 (13)	0	2 (17)	0	2 (17)	0	5 (16)	0
Rash maculopapular	0	0	4 (33)	0	1 (8)	0	5 (16)	0

NOTE: Data shown as *n* (%). The safety population includes patients who received at least one dose of study drug. Severity was assessed by the investigator according to the toxicity grade described in the NCI-CTCAE v4.03 [grade 1 (mild) to grade 5 (death)]. Grade 3/4 represents maximum grade 3/4 TEAEs.
Abbreviations: ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019.
[a]After a 5-day 30 mg once daily loading dose.
[b]After a 3-day 30 mg once daily loading dose.
[c]After a 3-day 20 mg once daily loading dose.

Baseline characteristics were balanced between cohorts with a median age (range) of 51 years (23–73) and 63 years (27–91) for patients with TGCT and MST, respectively (Supplementary Tables S4 and S5). Almost all the patients with TGCT were White (97%), more than half were female (53%), the most common tumor location was the knee (63%), and the majority (59%) did not have prior surgery for TGCT. Among patients with MST, 86% were White and 65% were female; the most common diagnoses included colorectal carcinoma, pancreatic adenocarcinoma, and ovarian carcinoma. Fifteen patients with TGCT remain active on treatment and received vimseltinib for 2 years or longer; the longest time on treatment was approximately 4 years at the time of data cutoff.

Safety

Two DLTs were initially observed in cohort 1 (MST, $n = 7$): asymptomatic grade 3 hypocalcemia and grade 4 lipase elevation. CSF1R targeting results in decreased levels of bone turnover markers, which may be caused by inhibition of osteoclast activity (29, 30). Similarly, CSF1R inhibition leads to increased serum enzyme levels caused by on-target biological activity of inhibiting Kupffer cells in the liver responsible for enzyme clearance (31, 32). Therefore, the definition of DLT was updated in a protocol amendment to exclude asymptomatic grade 3 hypocalcemia and grade ≥3 serum enzyme elevations. In patients with TGCT, there were two DLTs of grade 3 elevated aspartate aminotransferase (AST; related to study drug) that occurred in cohort 5 (30 mg twice weekly; $n = 8$) and cohort 8 (10 mg once daily; $n = 12$). These events were not associated with symptoms, and although grade ≥3 serum enzyme elevations were excluded, these instances met the per-protocol criteria for DLTs because they resulted in dose interruptions during cycle 1 due to treatment-related TEAEs lasting for >7 consecutive days (see Supplementary Materials). The MTD was not reached during the study. The RP2D was selected as 30 mg twice weekly (without a loading dose) based on data from cohort 5 that included PK, pharmacodynamics, safety, and early efficacy.

The majority of non-laboratory TEAEs were of low-grade (grade 1/2) severity for patients with TGCT or MST (**Table 1**; Supplementary Table S6). Grade 3/4 TEAEs in >5% of patients with TGCT included increases in blood creatine phosphokinase (CPK; 31%), AST (13%), lipase (9%), amylase (6%), and hypertension (6%). Increases in blood CPK were not associated with skeletal muscle injury or other organ damage. CPK increase is consistent with the known mechanism of action of CSF1R inhibitors and not clinically relevant (31, 32). No postbaseline bilirubin elevations were observed, and there was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. TEAEs led to dose reduction and treatment discontinuation in 63% (20 of 32) and 6% (2 of 32) of patients with TGCT, respectively (Supplementary

Table 2. Plasma PK parameters of vimseltinib following multiple oral administrations of vimseltinib at cycle 2 day 1 in patients with MST or TGCT.

	Cohort 1, MST 10 mg once daily *n* = 5	Cohort 2, MST 10 mg twice weekly[a] *n* = 3	Cohort 3, MST 20 mg once weekly[b] *n* = 2	Cohort 4, MST 20 mg twice weekly[b] *n* = 3	Cohort 5, MST 30 mg twice weekly[c] *n* = 3	Cohort 5, TGCT 30 mg twice weekly[c] *n* = 6	Cohort 6, MST 40 mg twice weekly[d] *n* = 3	Cohort 7, MST 20 mg once daily[e] *n* = 5	Cohort 8, TGCT 10 mg once daily[f] *n* = 10	Cohort 9, TGCT 6 mg once daily[g] *n* = 12
T_{max},[h] hours	0.6 (0.6, 1.0)[j]	1.0 (0.5, 4.1)	1.0 (1.0, 1.0)	0.6 (0.5, 2.1)	0.6 (0.5, 2.0)	2.0 (1.1. 4.1)	2.0 (1.0, 2.1)	2.0 (1.1, 6.0)	1.6 (1.0, 4.1)	1.2 (1.0, 3.9)
C_{max}, ng/mL	767 (12.3)[i]	149 (68.7)	530 (27.9)	642 (8.2)	953 (85.5)	838 (31.1)	1,140 (31.3)	992 (103.1)	709 (23.0)	371 (51.2)
$AUC_{0-8\ hours}$, hours •ng/mL	4,520 (15.8)[j]	1,030 (63.1)	3,360 (20.1)	4,290 (2.8)	7,580 (17.6)[j]	4,150 (48.5)[j]	7,280 (28.0)	11,700 (40.7)[j]	NC	NC
$AUC_{0-4\ hours}$, hours•ng/mL	2,450 (15.1)[i]	530 (69.5)	1,810 (23.7)	2,270 (5.0)	2,990 (69.9)	2,710 (48.2)[k]	3,820 (31.4)	4,950 (46.2)[l]	2,450 (20.5)[m]	1,210 (52.8)[n]
C_{trough}, ng/mL	447 (65.2)	122 (63.3)	205 (10.0)	441 (19.9)	574 (61.6)	448 (58.5)	570 (97.0)	879 (113.1)	515 (28.4)	291 (55.1)

NOTE: Data shown as geometric mean (geometric CV%) unless noted otherwise.
Abbreviations: C_{trough}, trough plasma concentration; CV%, percent coefficient of variation; NC, not calculated.
[a]After a 5-day 10 mg once daily loading dose.
[b]After a 5-day 20 mg once daily loading dose.
[c]After a 5-day 30 mg once daily loading dose.
[d]After a 5-day 40 mg once daily loading dose.
[e]After a 3-day 50 mg once daily loading dose.
[f]After a 3-day 30 mg once daily loading dose.
[g]After a 3-day 20 mg once daily loading dose.
[h]T_{max} data shown as median (minimum, maximum).
[i]$n = 3$.
[j]$n = 2$.
[k]$n = 5$.
[l]$n = 4$.
[m]$n = 8$.
[n]$n = 9$.

Table S7). Two serious treatment-related TEAEs were reported in patients with TGCT (both in cohort 5 receiving 30 mg twice weekly): metabolic encephalopathy ($n = 1$) and vaginal hemorrhage ($n = 1$). The patient with metabolic encephalopathy had a history of fatty liver disease, increased AST, and excessive alcohol intake during time on study and recovered from this AE; the patient with vaginal hemorrhage was perimenopausal with a history of adenomyosis, and vaginal hemorrhage did not recur following rechallenge with vimseltinib. In TGCT cohorts, 17 patients (53%) discontinued treatment for reasons including AEs ($n = 2$), physician decision ($n = 2$), progressive disease (PD; by investigator radiological assessment, $n = 2$), withdrawal by patient ($n = 10$), and other ($n = 1$). Additional information about the 10 patients that withdrew consent is not available. There were no deaths due to treatment-related TEAEs in patients with TGCT or MST.

Pharmacokinetics and Pharmacodynamics

The steady-state concentration of vimseltinib was generally reached between days 8 and 15 of cycle 1. Most cohorts received loading doses, which decreased the time to reach the steady state. Vimseltinib plasma exposure, as measured by geometric mean plasma $AUC_{0-4\ hours}$, $AUC_{0-8\ hours}$, and C_{max}, increased with the dose in patients with MST or TGCT (**Table 2**; Supplementary Fig. S1). Cohort 5 was the only cohort in which both patient populations were represented and C_{max} and $AUC_{0-4\ hours}$ values were comparable between patients with TGCT and MST. Vimseltinib exposure during cycle 2 on day 1 was comparable in patients with TGCT who received 30 mg twice weekly maintenance doses (cohort 5) and those who received 10 mg once daily maintenance doses (cohort 8), after a 30 mg once daily loading dose for 5 and 3 days, respectively. In TGCT cohort 5, vimseltinib steady-state concentrations seemed to have been reached within approximately 15 days of dosing, and exposure during cycle 2 on day 1 following twice weekly 30 mg doses was approximately 3.6-fold higher than exposure following a single 30 mg dose. Due to the relatively short sampling time, a precise estimation of elimination $t_{½}$ based on a non-compartmental analysis was not available. However, simulations based on a population PK model indicated that the estimated terminal $t_{½}$ of vimseltinib was approximately 1 week (data not shown).

Treatment with vimseltinib resulted in dose-dependent changes in PD parameters. On day 1 of cycle 2, a dose-dependent decrease in the levels of circulating nonclassical monocytes (NCM) was shown by mean percent reduction from baseline of 67% for 30 mg twice weekly (cohort 5; TGCT, $n = 4$; MST, $n = 2$), 80% for 40 mg twice weekly (cohort 6; MST, $n = 2$), 96% for 20 mg once daily (cohort 7; MST, $n = 5$), 88% for 10 mg once daily (cohort 8; TGCT, $n = 3$), and 67% for 6 mg once daily (cohort 9; TGCT, $n = 5$; **Fig. 2A**). In patients with TGCT, the decrease in NCMs over time was similar between cohorts 5, 8, and 9 (**Fig. 2B**). The steady-state mean change from baseline to day 1 of cycle 2 in plasma CSF1 showed a 44-fold increase with vimseltinib 30 mg twice weekly (cohort 5; TGCT, $n = 7$; MST, $n = 2$), a 48-fold increase with 40 mg twice weekly (cohort 6; MST, $n = 2$), a 36-fold increase with 20 mg once daily (cohort 7; MST, $n = 4$), and a 30-fold increase with 10 mg once daily (cohort 8; TGCT, $n = 10$). At a lower dose of 6 mg once daily (cohort 9; TGCT, $n = 12$), only a four-fold increase in the steady-state mean CSF1 level was

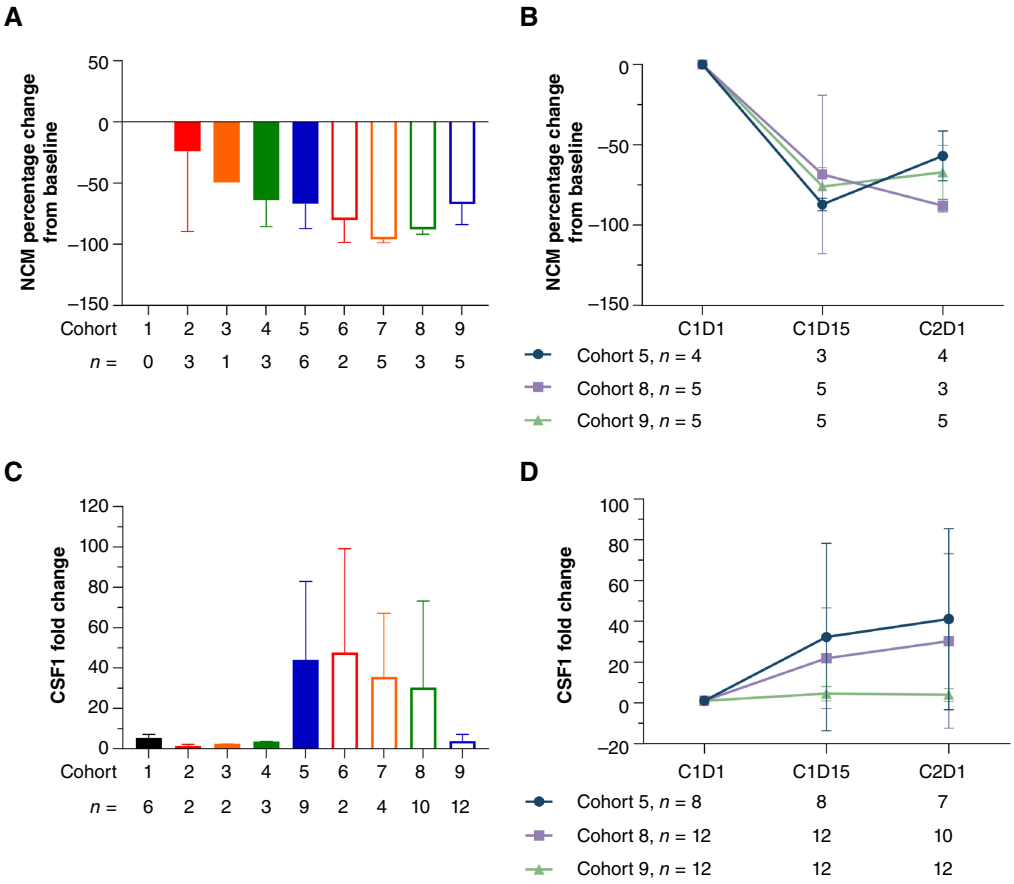

Figure 2.

Pharmacodynamics of vimseltinib in patients with MST or TGCT. **A,** NCM percentage change from baseline at C2D1. **B,** NCM percentage change from baseline over time in TGCT cohorts. **C,** CSF1 fold change in response to vimseltinib at C2D1. **D,** Plasma CSF1 fold change over time in TGCT cohorts. Cohort 5 received vimseltinib twice weekly, whereas cohorts 8 and 9 received vimseltinib daily. All data are shown as mean ± SD. C, cycle; D, day.

Table 3. Response assessed by IRR per RECIST v1.1 in patients with TGCT receiving vimseltinib.

	Cohort 5 ***n*** **= 8**	**Cohort 8** ***n*** **= 12**	**Cohort 9** ***n*** **= 12**	**Total** ***N*** **= 32**
Overall response				
CR	1 (13)	0	0	1 (3)
PR	5 (63)	10 (83)	7 (58)	22 (69)
SD	1 (13)	2 (17)	5 (42)	8 (25)
Not evaluable	1 (13)[a]	0	0	1 (3)[a]
ORR[b], *n* (%)	6 (75)	10 (83)	7 (58)	23 (72)
(95% CI)	(35, 97)	(52, 98)	(28, 85)	(53, 86)
CBR (CR + PR + SD)	7 (88)	12 (100)	12 (100)	31 (97)
DOR, months, median[c] (min, max)	NR (5.7+, 45.2+)	NR (3.8+, 34.2+)	NR (6.6+, 27.9+)	NR (3.8+, 45.2+)
Time to response, months, median (min, max)	2.8 (1.6, 16.6)	6.9 (1.7, 28.4)	3.8 (1.8, 11.1)	3.8 (1.6, 28.4)

NOTE: Data shown as *n* (%) unless otherwise noted.
Abbreviations: CI, confidence interval; max, maximum; min, minimum; NR, not reached.
[a]One patient had a local assessment for efficacy but will never have IRR data.
[b]Includes all available follow-up visits.
[c]Based on the Kaplan–Meier estimate. DOR is defined as the time from the first imaging result showing response to PD or death. + indicates the response is still ongoing at the last assessment.

observed (**Fig. 2C**). In TGCT cohorts specifically, dose-dependent increases in plasma CSF1 were consistent over time during cycle 1 on day 15 and cycle 2 on day 1 (**Fig. 2D**).

Efficacy

The median treatment duration was 25.1 months (range, 0.7–46.9), and the ORR across all cohorts of patients with TGCT receiving

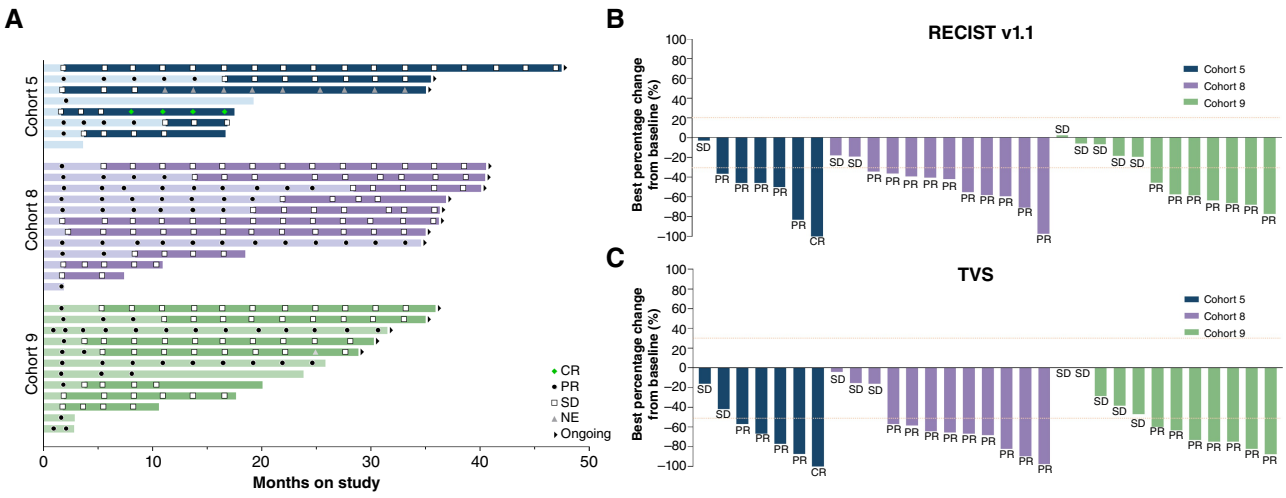

Figure 3.

Best percentage change from baseline in tumor size of the target lesion, assessed by IRR per RECIST v1.1 and TVS, and time on treatment for patients with TGCT receiving vimseltinib. **A,** Swimlane plot of duration of treatment and response based on IRR per RECIST v1.1 and best percentage change assessed by IRR using **B,** RECIST v1.1 and **C,** TVS. In **A,** the shaded regions represent the DOR. The dotted lines at 20% in **B** and 30% in **C** represent the threshold for PD; the dotted lines at −30% in **B** and −50% in **C** represent the threshold for PR. NE, not evaluable.

vimseltinib, as assessed by IRR using RECIST v1.1, was 72% (23 of 32 patients; **Table 3**). Tumor responses were observed in all TGCT dose cohorts with 1 CR (cohort 5) and 22 PRs, with a CBR of 97% (31 of 32 patients). One patient with TGCT did not have a central imaging assessment and was considered a nonresponder for efficacy. No patients with TGCT experienced disease progression on treatment as assessed by IRR, and 25% (8 of 32) of patients had best responses of SD. The median DOR based on Kaplan–Meier estimation for patients with TGCT was not reached at data cutoff, as all responses were still ongoing (range, 3.8+ to 45.2+ months). Among patients who experienced responses, the median time to first response by IRR using RECIST v1.1 was 3.8 months (range, 1.6–28.4 months). The majority of responses [65% (15 of 23)] were achieved within the first 6 months on treatment, 78% (18 of 23) were achieved by 12 months, 96% (22 of 23) by 24 months, and 100% (23 of 23) by 36 months (**Fig. 3A**).

Almost all patients with TGCT experienced a decrease in tumor size as assessed by IRR using RECIST v1.1 (**Fig. 3B**). Similarly, IRR assessment using TVS demonstrated that most patients with TGCT experienced decreases in tumor size (**Fig. 3C**). The ORR by IRR using TVS was 66% (21 of 32 patients), with 1 CR and 20 PRs, and 31% (10 of 32) of patients had best responses of SD. One patient did not have a central imaging assessment and was considered a nonresponder for efficacy. For patients with MST, no objective responses were observed, and the median treatment duration was 1.4 months (range, 0.03–7.7; mean, 1.9 months).

Discussion

In the phase I part of this ongoing, first-in-human, multicenter, open-label phase I/II study (NCT03069469), vimseltinib demonstrated long-term tolerability and a manageable safety profile in patients with TGCT not amenable to surgery, with no evidence of cholestatic hepatotoxicity or drug-induced liver injury. At the data cutoff, the median treatment duration for patients with TGCT was 25.1 months (range, 0.7–46.9; mean, 22.5 months), with nearly half of patients with TGCT (47%) remaining on treatment. The 15 patients remaining on treatment have received vimseltinib for 2 years or longer, and the longest time on treatment was approximately 4 years. The extended follow-up and report on treatment duration in this study are unique compared with other reports of investigational drugs in this setting and provide data on long-term efficacy and safety.

The majority of non-laboratory TEAEs were of low-grade severity for patients with TGCT or MST. Grade 3/4 TEAEs in >5% of patients with TGCT included hypertension and increases in serum enzymes such as CPK, AST, amylase, and lipase. CSF1R inhibition decreases macrophage-derived Kupffer cells in the liver, which normally clear CPK, AST, and other serum enzymes, and increases in these serum enzymes are consistent with prior reports of CSF1R inhibitors (31, 32). Elevations in liver enzymes were observed in both rats and monkeys treated with CSF1R inhibitors with no evidence of liver damage, and the serum enzyme changes were reversible after a recovery period (31, 32). In the current study, there was no evidence of cholestatic hepatotoxicity or drug-induced liver injury in patients with TGCT treated with vimseltinib.

Based on the safety data and early efficacy observed in cohort 5 as well as the MTD not being reached during dose escalation, 30 mg twice weekly (without a loading dose) was selected as the RP2D for vimseltinib. Preliminary PK analysis estimated that the change in time to reach the steady state was approximately 2 weeks with and without a loading dose (30 mg once daily for 5 days) in patients receiving vimseltinib 30 mg twice weekly (data not shown), indicating that a loading dose was unnecessary in patients with TGCT. Pharmacodynamic parameters demonstrated optimal CSF1R engagement, with increases in plasma CSF1 and decreases in NCMs in peripheral blood in patients with TGCT at a 30 mg twice weekly dose (cohort 5). Vimseltinib continues to be evaluated at the RP2D in the expansion (phase II) portion of this study.

Vimseltinib demonstrated robust and durable antitumor activity for patients with TGCT not amenable to surgery across the doses tested in this study. At data cutoff, the ORR by IRR using RECIST v1.1 was 72% (75% at the RP2D), including 1 CR and 22 PRs. The

median DOR was not reached and ranged from 3.8 to 45.2 months, with responses persisting and a median follow-up of 15.0 months. The majority of responses with vimseltinib occurred before 6 months on treatment; however, additional responses were also achieved after 6 months on treatment, indicating that first responses are still possible with prolonged use. Importantly, tumor size continued to decrease in some patients as they remained on treatment, supporting the continued clinical benefit and value of long-term treatment of TGCT with vimseltinib. No patients with TGCT experienced disease progression on treatment as assessed by IRR per RECIST v1.1.

No single-agent activity was observed in evaluated patients with MST during this study, and these results are consistent with those reported in studies evaluating other CSF1R inhibitors (2). Further investigation could focus on tumors with evidence of dependency on CSF1R signaling pathways or on combination approaches.

Limitations of this study include those inherent to the design of most early-phase studies, such as potential bias due to lack of blinding and randomization, the lack of a comparator arm, and small numbers of patients.

Vimseltinib was well tolerated and demonstrated robust and durable antitumor response in patients with TGCT not amenable to surgery. Vimseltinib plasma exposure increased with dose, and pharmacodynamic analyses demonstrated that vimseltinib inhibited CSF1R in a dose-dependent manner. This study was the basis for the evaluation of vimseltinib in symptomatic patients with TGCT not amenable to surgery in the phase III, randomized, placebo-controlled MOTION trial (NCT05059262), which reported statistically significant and clinically meaningful positive top-line results for tumor response, active range of motion, and patient-reported outcome measures (33).

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Note

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