Vimseltinib versus placebo for tenosynovial giant cell tumour (MOTION) a multicentre, randomised, doubleblind, placebo-controlled, phase 3 trial

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Summary

Background Tenosynovial giant cell tumour (TGCT) is a locally aggressive neoplasm for which few systemic treatment options exist. This study evaluated the efficacy and safety of vimseltinib, an oral, switch-control, CSF1R inhibitor, in patients with symptomatic TGCT not amenable to surgery.

Methods MOTION is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial done in 35 specialised hospitals in 13 countries. Eligible patients were adults (aged ≥18 years) with a histologically confirmed diagnosis of TGCT for which surgical resection could potentially worsen functional limitation or cause severe morbidity. Patients were randomly assigned (2:1) with interactive response technology to vimseltinib (30 mg orally twice weekly) or placebo, administrated in 28-day cycles for 24 weeks. Patients and site personnel were masked to treatment assignment until week 25, unless progressive disease was confirmed earlier. The primary endpoint was objective response rate by independent radiological review using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) at week 25 in the intention-to-treat population. Safety was assessed in all patients who received the study drug. The trial is registered with ClinicalTrials.gov, NCT05059262, and enrolment is complete.

Findings Between Jan 21, 2022, and Feb 21, 2023, 123 patients were randomly assigned (83 to vimseltinib and 40 to placebo). 73 (59%) patients were female and 50 (41%) were male. Nine (11%) of 83 patients assigned to vimseltinib and five (13%) of 40 patients assigned to placebo discontinued treatment before week 25; one patient in the placebo group did not receive any study drug. Objective response rate per RECIST was 40% (33 of 83 patients) in the vimseltinib group *vs* 0% (none of 40) in the placebo group (difference 40% [95% CI 29–51]; p<0·0001). Most treatment-emergent adverse events (TEAEs) were grade 1 or 2; the only grade 3 or 4 TEAE that occurred in more than 5% of patients receiving vimseltinib was increased blood creatine phosphokinase (eight [10%] of 83). One patient in the vimseltinib group had a treatment-related serious TEAE of subcutaneous abscess. No evidence of cholestatic hepatotoxicity or drug-induced liver injury was noted.

Interpretation Vimseltinib produced a significant objective response rate and clinically meaningful functional and symptomatic improvement in patients with TGCT, providing an effective treatment option for these patients.

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Introduction

Tenosynovial giant cell tumour (TGCT), previously known as pigmented villonodular synovitis or giant cell tumour of the tendon sheath, is a locally aggressive neoplasm affecting the synovium, bursae, and tendon sheath.[1] TGCTs are driven by dysregulation of the colony-stimulating factor 1 gene (*CSF1*), which leads to overproduction of the CSF1 protein.[1–3] *CSF1* overexpression promotes tumour growth and expansion by recruiting and inducing local proliferation of CSF1 receptor (CSF1R)-dependent inflammatory macrophages.[4,5]

Surgical resection is the standard of care for most patients with TGCT, but not all patients have disease that is amenable to surgery.[1,6] Recurrence rates are approximately 50% for diffuse TGCT, and patients who have a recurrence are significantly more likely to have future recurrences than those who do not have recurrence following surgery.[7–9] Although TGCT is not life-threatening, it is associated with a substantial reduction in quality of life for this patient population, for whom the mean age at diagnosis is 35–50 years.[1] Patients can have joint damage requiring total joint replacement and, in extreme cases, amputation might be necessary.[1,10]

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Research in context

Evidence before this study

Treatment options for patients with tenosynovial giant cell tumour (TGCT) whose disease is not amenable to surgery are scarce. Pexidartinib is the only CSF1R inhibitor approved in the USA, but it is associated with the rare and unpredictable risk of serious cholestatic or mixed liver injury. We searched PubMed for original articles and reviews published between Jan 1, 2000, and Oct 1, 2023, on the use of tyrosine kinase inhibitors for the treatment of TGCT using the search terms "TGCT", "tenosynovial giant cell tumor", "PVNS", "tyrosine kinase inhibitor", "CSF1R", "clinical trial", and "vimseltinib". We identified few clinical studies using CSF1R inhibitors for TGCT, especially including both functional and symptomatic outcomes.

Added value of this study

MOTION is the first international, randomised, double-blind, placebo-controlled, phase 3 trial of vimseltinib, an investigational, oral, switch-control, tyrosine kinase inhibitor designed to selectively and potently inhibit CSF1R in patients with TGCT whose disease is not amenable to surgery. Patients treated with vimseltinib had significant and clinically meaningful improvements in the primary endpoint and all six key secondary endpoints versus placebo. These results support CSF1R inhibition as an effective treatment option for patients with TGCT. Specifically, this trial demonstrates that the benefit of CSF1R inhibition with vimseltinib extends beyond antitumor activity by showing a positive impact on the way patients feel and function.

Implications of all the available evidence

Vimseltinib is an additional systemic treatment option to address the unmet therapeutic needs of patients with TGCT and can provide functional health and symptomatic benefit to a population living with substantial morbidity and scarce treatment options. A primary concern with pexidartinib is the rare and unpredictable risk of serious cholestatic or mixed liver injury; however, with vimseltinib in the MOTION trial, no hepatotoxicity or drug-induced liver injury was observed. Vimseltinib has the potential to become the standard-of-care systemic therapy for TGCT.

Treatment options for patients with TGCT not amenable to surgery are scarce. One systemic agent, pexidartinib, is approved in the USA, Taiwan, and South Korea, but in the USA, it can only be prescribed under a risk evaluation mitigation strategy due to its associated rare, but potentially fatal, off-target cholestatic hepatoxicity.[11–13] Pexidartinib did not receive regulatory approval in Europe due to these safety risks and concerns over the extent and durability of symptomatic improvements.[14] Patients with TGCT require long-term treatment and need therapeutic options that can improve the symptoms of TGCT and overall quality of life with manageable toxicity profiles.

Vimseltinib is an investigational, oral, switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R.[2,15] In a phase 1/2 study, vimseltinib was well tolerated and showed promising antitumour activity and clinically meaningful changes in patient-reported outcomes (PROs) in patients with TGCT.[16–19] We herein report the results of the MOTION trial, which compared the efficacy and safety of vimseltinib versus placebo in patients with TGCT not amenable to surgery.

Methods

Study design and patients

MOTION is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial done in 35 specialised hospitals in 13 countries. The full list of active sites and investigators is provided in the appendix (p 2). The protocol, protocol amendments, and informed consent documents were approved by an institutional review board or ethics committee at each site and by the appropriate regulatory authorities. This study was performed in accordance with the Declaration of Helsinki and with International Conference on Harmonisation and Good Clinical Practice guidelines. Applicable local regulatory requirements were followed, and investigators ensured that this study was conducted in full conformity with Regulations for the Protection of Human Subjects of Research. The protocol is available in the appendix (pp 18–123). This study is registered with ClinicalTrials.gov, NCT05059262, and EudraCT, 2020–004883–25.

Eligible patients were aged 18 years or older and had histologically confirmed TGCT for which surgical resection might worsen functional limitation or cause severe morbidity, as assessed by surgical consultation or a multidisciplinary tumour board. Eligible patients had at least one lesion measuring at least 2 cm in size according to Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST), centrally assessed by MRI by a radiologist. Patients were excluded if they had received previous systemic therapy targeting CSF1 or CSF1R, including vimseltinib. Previous therapy was permitted with either or both of the non-selective inhibitors imatinib or nilotinib. Full eligibility criteria are provided in the appendix (pp 5–6). Sex was self-reported and options were male or female. Patients provided written informed consent before participating in any study-specific activity.

Randomisation and masking

Patients were randomly assigned (2:1) to vimseltinib or matching placebo by means of interactive response

technology and stratified by tumour location (lower limb *vs* all other) and region (USA *vs* non-USA). A third party that was not involved in the rest of the trial generated the randomisation schedule. Patients and site personnel were unmasked to treatment assignment before the end of part 1 (double-blind period; beginning of week 25) if progressive disease was confirmed by independent radiological review. Those assessing the outcomes were also masked to group assignment. At the end of 24 weeks, patients could enter an open-label period (part 2, up to week 49); patients who received placebo in part 1 could cross over to receive vimseltinib in part 2. Patients could continue to receive vimseltinib after week 49 in a long-term extension period.

Procedures

Vimseltinib 30 mg twice weekly or matching placebo was administered orally in 28-day cycles for 24 weeks. Vimseltinib was administered each week on day 1 and day 5 (±1 day) at approximately the same time of day on an empty stomach, with at least 24 h between doses. Dosing could be reduced or interrupted at the discretion of the investigator at any time for up to 28 days, or longer if due to an adverse event. If more than two dose reductions were required, vimseltinib was discontinued. Study drug compliance was assessed by review of dosing diaries and ongoing count of study drug capsules taken.

Patients attended two study visits during cycle 1 (on day 1 and day 15) and one study visit on day 1 (±7 days) for all subsequent cycles. Clinical laboratory tests and investigator questionnaires (global impression scales) were administered at each visit. Patient questionnaires were administered electronically at all visits after cycle 1, day 1; patients were also asked to complete electronic questionnaires between visits. Tumour imaging and range of motion assessments were performed on day 1 of cycle 4 and cycle 7 (end of part 1 double-blind period) visits. Narcotic analgesic use during the trial was recorded in a patient diary and reviewed by site staff and the principal investigator at each visit.

Outcomes

The primary endpoint was objective response rate (ie, complete response or partial response) by independent radiological review per RECIST, centrally assessed by MRI at the beginning of week 25. The schedule and definition of response are provided in the appendix (p 3). Key secondary endpoints, all assessed at the beginning of week 25, were: objective response rate by independent radiological review per tumour volume score;[20,21] change from baseline in active range of motion of the affected joint as measured by goniometry assessments; change from baseline in Patient-Reported Outcomes Measurement Information System physical function (PROMIS-PF; TGCT-specific),[22,23] worst stiffness numeric rating scale (NRS), and EuroQoL Visual Analogue Scale (EQ-VAS) health status; and Brief Pain Inventory (BPI) worst pain response rate. BPI worst pain response was defined as at least a 30% improvement, without a 30% or greater increase in narcotic analgesic use.

Supportive analyses for the key secondary endpoints, prespecified in the statistical analysis plan, were response rates for active range of motion, PROMIS-PF, worst stiffness NRS, and EQ-VAS at week 25, which were derived from minimum clinically important difference thresholds (change from baseline ≥10% for active range of motion, ≥3 on PROMIS-PF, ≤–2 on worst stiffness NRS, and ≥7 on EQ-VAS). Change from baseline for BPI worst pain is also reported (prespecified in the statistical analysis plan). The description of independent radiological review, definition of response of tumour volume score, active range of motion calculations, and calculation of minimum clinically important difference thresholds are reported in the appendix (pp 3–4). Other secondary endpoints reported are duration of response per RECIST and tumour volume score. Analysis of data for the additional secondary endpoints (objective response rate per modified RECIST, duration of response per modified RECIST, and change from baseline in laboratory parameters, electrocardiograms, and vital signs) and exploratory endpoints listed in the protocol (appendix pp 56–57) is ongoing and will be reported separately.

Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse event reporting was continuous after receiving informed consent.

Statistical analysis

The target sample size of 120 patients (vimseltinib, n=80; placebo, n=40) was based on the required power for primary endpoint and key secondary endpoints analysis, and overall vimseltinib exposure, assuming a 15% drop-out rate. This sample size was planned to have 98% power to detect significant differences between treatment groups, assuming true objective response rates of 35% in the vimseltinib group and 5% in the placebo group, using a two-sided Fisher's exact test at a 5% type 1 error rate.

All primary and secondary efficacy endpoints were assessed in the intention-to-treat population, which included all randomly assigned patients. The safety population included all patients who received at least one dose of study treatment. Categorical variables were summarised using frequencies and proportions. Time-to-event data were summarised by the Kaplan–Meier method with two-sided 95% CIs. The data cutoff was Aug 22, 2023.

Endpoints were assessed at week 25 and tested hierarchically in the intention-to-treat population in the following prespecified order: objective response rate per RECIST; objective response rate per tumour volume score; change from baseline in active range of motion,

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See **Online** for appendix

PROMIS-PF, worst stiffness NRS, and EQ-VAS; and BPI worst pain response rate. The p values noted as nominal were prespecified but not part of the testing hierarchy. Objective response rate per RECIST, objective response rate per tumour volume score, and BPI worst pain response were compared between treatment groups using a two-sided Cochran–Mantel–Haenszel test stratified by randomisation stratification factors in the intention-to-treat population with an α of 0·05. All other key secondary endpoints were analysed using a mixed model for repeated measurements to estimate the least squares mean, with the dependent variable as change from baseline. The fixed effects for each of these models were treatment group, timepoint, treatment group by timepoint interaction, stratification factors for tumour location (lower limb *vs* all other) and region (USA *vs* non-USA), and baseline value of the corresponding endpoint. For active range of motion only, the stratification factor for tumour location was replaced with affected joint (knee *vs* ankle *vs* other).

Missing data were not imputed except for the purpose of identification of treatment-emergent adverse events (TEAEs) and previous or concomitant medications or procedures with missing start or end times. The mixed model for repeated measurements treats missing data under the missing at random assumption with implicit imputation. Sensitivity analyses of missing data included multiple imputation based on randomised treatment and a pattern mixture model (in which data for patients randomly assigned to vimseltinib who discontinued treatment due to an adverse event were imputed on the basis of the missing not at random assumption and were imputed as if the patient had received placebo). For objective response rate and BPI worst pain, patients who did not have a post-baseline assessment within the week-25 analysis window were considered to have not responded to treatment. Data analysis was performed on SAS software, version 9.4.

An independent data monitoring committee evaluated safety and efficacy approximately every 6 months throughout the study. The committee members were an experienced biostatistician and two qualified clinicians who were not employees of the funder and who had scientific expertise in TGCT and practical experience conducting and monitoring safety and efficacy in clinical studies.

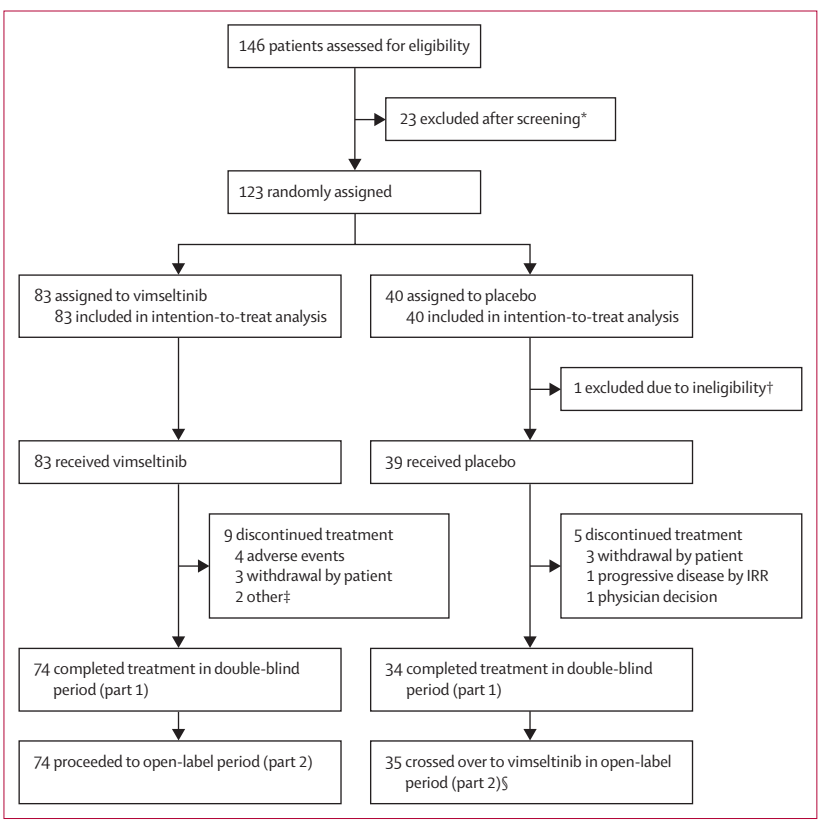

Figure 1: **Trial profile**
IRR=independent radiological review. *Reasons for exclusion at screening were not captured in the database. †One patient was randomly assigned prematurely but was later deemed ineligible to participate and did not receive placebo. ‡Both patients in this category specified lack of clinical benefit as the reason for withdrawal. §One patient discontinued treatment early in part 1 and crossed over to receive vimseltinib in the open-label period (part 2).

Role of the funding source

The funder of the study designed the study with input from the authors and participated in both data collection and interpretation. Data analyses were performed by the funder according to a prespecified statistical analysis plan, and all authors contributed to the interpretation of the results. The first draft was written by a medical writer, contracted by the funder, under direction of the authors; the authors critically revised the manuscript and provided substantive input.

Results

Between Jan 21, 2022, and Feb 21, 2023, 146 adults with TGCT were assessed for eligibility and 123 patients (73 [59%] female and 50 [41%] male) were randomly assigned: 83 to vimseltinib and 40 to placebo (figure 1). Nine (11%) of 83 patients assigned to vimseltinib and five (13%) of 40 patients assigned to placebo discontinued treatment in part 1. Baseline characteristics are shown in table 1. The median age was 44 years (IQR 32–53). The most common disease location was the knee (83 [67%]), and most patients had at least one previous surgery or procedure (91 [74%]).

An objective response by independent radiological review per RECIST at week 25 occurred in 33 (40%) of 83 patients in the vimseltinib group versus none (0%) of 40 patients in the placebo group (difference 40% [95% CI 29–51]; p<0·0001; table 2). In the vimseltinib group, four (5%) of 83 patients had a complete response and 29 (35%) of 83 patients had a partial response. The objective response rate was significantly higher with vimseltinib than placebo in nearly every subgroup (figure 2; appendix p 10). 79 (95%) of 83 patients in the vimseltinib group had a decrease in tumour size per RECIST (figure 3). At data cutoff, the median duration of

response for patients with an objective tumour response at week 25 was not reached (range 0·03 months to 11·7 months).

The objective response rate by independent radiological review per tumour volume score at week 25 was significantly higher in the vimseltinib group than in the placebo group (difference 67% [95% CI 56 to 77]; p<0·0001; table 2), with four (5%) of 83 patients in the vimseltinib group having a complete response and 52 (63%) of 83 patients having a partial response. The least squares mean change from baseline in active range of motion of the affected joint at week 25 was significantly higher with vimseltinib than placebo (difference 14·6 percentage points [4·0 to 25·3]; p=0·0077; table 2). The active range of motion response rate was significantly higher in the vimseltinib group than in the placebo group (difference 28% [12 to 45]; nominal p=0·0025). Improvements in range of motion were not limited to patients with an objective tumour response per RECIST; patients with stable disease also showed improvements in this outcome (appendix p 11). All six key secondary endpoints showed clinically meaningful improvements in the vimseltinib group compared with the placebo group (table 2). Vimseltinib significantly improved physical function as measured by PROMIS-PF (difference 3·3 [1·4 to 5·2]; p=0·0007). The difference in PROMIS-PF response rate was 18% (1 to 36; nominal

	Vimseltinib (n=83)	Placebo (n=40)
Median (IQR) age, years	45 (33–53)	43 (31–53)
Sex		
Female	46 (55%)	27 (68%)
Male	37 (45%)	13 (33%)
Race		
White	59 (71%)	21 (53%)
Asian	1 (1%)	4 (10%)
Black or African American	4 (5%)	0
Other*	19 (23%)	15 (38%)
Region		
Europe	57 (69%)	32 (80%)
USA and Canada	14 (17%)	5 (13%)
Australia	12 (14%)	2 (5%)
Asia	0	1 (3%)
Affected joint		
Knee	56 (67%)	27 (68%)
Ankle	9 (11%)	6 (15%)
Hip	11 (13%)	1 (3%)
Other†	7 (8%)	6 (15%)
Previous TGCT surgery or procedure‡	64 (77%)	27 (68%)
1 surgery	28 (34%)	14 (35%)
2–3 surgeries	26 (31%)	11 (28%)
≥4 surgeries	10 (12%)	2 (5%)
Previous TGCT systemic therapy	19 (23%)	9 (23%)§
Imatinib	16 (19%)	7 (18%)
Nilotinib	2 (2%)	4 (10%)
Other¶	1 (1%)	0
Median (IQR) size of target lesions, mm	63·4 (36·2–88·7)	61·0 (44·0–85·2)
Narcotic analgesic use‖	12 (14%)	5 (13%)

Data are n (%), unless otherwise specified. TGCT=tenosynovial giant cell tumour. *Includes the not reported and unknown categories. †Includes foot (one [1%] participant in the vimseltinib group and three [8%] in the placebo group), wrist (two [2%] and one [3%]), hand (two [2%] and none), shoulder (one [1%] and one [3%]), elbow (one [1%] and none), and temporomandibular joint (none and one [3%]). ‡All patients had histologically confirmed TGCT per diagnostic biopsy or existing pathology report; diagnostic biopsies were not recorded as a previous surgery or procedure. §Two patients in the placebo group received both imatinib and nilotinib. ¶Includes an investigational agent (BP 27 672). ‖Defined as any use during screening.

Table 1: **Baseline clinical characteristics**

	Vimseltinib (n=83)	Placebo (n=40)	Difference between vimseltinib group and placebo group	
			Difference (95% CI)	p value
Overall response by IRR per RECIST				
Complete response	4 (5%)	0	..	..
Partial response	29 (35%)	0	..	..
Stable disease	42 (51%)	33 (83%)	..	..
Not evaluable	8 (10%)	7 (18%)	..	..
ORR by IRR per RECIST	33 (40%)	0	40% (29 to 51)*	<0·0001
Median (range) DOR by IRR per RECIST, months	NR (0·03–11·7)†	NA	..	..
Overall response by IRR per TVS				
Complete response	4 (5%)	0	..	..
Partial response	52 (63%)	0	..	..
Stable disease	19 (23%)	34 (85%)	..	..
Progressive disease	0	1 (3%)	..	..
Not evaluable	8 (10%)	5 (13%)	..	..
ORR by IRR per TVS	56 (67%)	0	67% (56 to 77)	<0·0001
Median (range) DOR by IRR per TVS, months	NR (0·03–13·9)†	NA	..	..
Active ROM				
Mean (SD) at baseline, %	63·0% (29·4)	62·9% (32·2)	..	..
Mean (SD) at week 25, %	83·6% (28·1)	68·3% (35·3)	..	..
LS mean change from baseline, percentage points (SE)	18·4% (6·5)	3·8% (7·2)	14·6% (4·0 to 25·3)	0·0077
Response rate‡	40 (48%)	8 (20%)	28% (12 to 45)	0·0025
PROMIS-PF				
Mean (SD) at baseline	39·0 (6·1)	38·5 (6·0)	..	..
Mean (SD) at week 25	43·7 (6·1)	40·7 (6·7)	..	..
LS mean change from baseline (SE)	4·6 (1·0)	1·3 (0·9)	3·3 (1·4 to 5·2)	0·0007
Response rate§	36 (43%)	10 (25%)	18% (1 to 36)	0·046
Worst stiffness NRS				
Mean (SD) at baseline	5·1 (2·0)	5·2 (1·8)	..	..
Mean (SD) at week 25	2·9 (2·1)	4·3 (1·9)	..	..
LS mean change from baseline (SE)	−2·1 (0·2)	−0·3 (0·3)	−1·8 (−2·5 to −1·1)	p<0·0001
Response rate¶	32 (39%)	6 (15%)	24% (8 to 39)	0·0080

(Table 2 continues on next page)

	Vimseltinib (n=83)	Placebo (n=40)	Difference between vimseltinib group and placebo group	
			Difference (95% CI)	p value
(Continued from previous page)				
EQ-VAS				
Mean (SD) at baseline	61·4 (19·5)	60·2 (20·6)	..	..
Mean (SD) at week 25	74·1 (15·0)	67·5 (15·9)	..	..
LS mean change from baseline (SE)	13·5 (2·4)	6·1 (2·9)	7·4 (1·4 to 13·4)	0·016
Response rate‖	31 (37%)	10 (25%)	12% (−5 to 29)	0·16
BPI worst pain				
Response rate**	40 (48%)	9 (23%)	26% (4 to 42)*	0·0056

Data are n (%), unless otherwise specified. Patients who did not have an assessment at the end of part 1 for any reason or whose week 25 assessment was after the first dose in part 2 (open-label period) or more than 14 days before or after the planned visit schedule were assessed as not evaluable and as not having had a treatment response. BPI=Brief Pain Inventory. DOR=duration of response (defined as time from first imaging result showing response to disease progression or death by any cause). EQ-VAS=EuroQoL Visual Analogue Scale. IRR=independent radiological review. LS=least squares. NA=not applicable. NR=not reached. NRS=numeric rating scale. ORR=objective response rate. PROMIS-PF=Patient-Reported Outcomes Measurement Information System: physical function. RECIST=Response Evaluation Criteria in Solid Tumours, version 1.1. ROM=range of motion. TGCT=tenosynovial giant cell tumour. TVS=tumour volume score. *An unstratified exact 95% CI was used. †Per Kaplan–Meier estimate. ‡A response was defined as at least a 10-percentage point increase in active ROM from baseline at week 25. §A response was defined as at least a 3-point increase in PROMIS-PF from baseline at week 25. ¶A response was defined as having a 2 point or greater decrease from baseline in worst stiffness at week 25. ||A response was defined as an increase from baseline in EQ-VAS at week 25 of at least 7 points. **A response was defined as a 30% decrease or more in mean BPI worst pain without a 30% or greater increase in narcotic analgesic use.

Table 2: **Primary and key secondary endpoints at week 25**

p=0·046). Additionally, the improvement in stiffness was significantly greater with vimseltinib than placebo (difference −1·8 [−2·5 to −1·1]; p<0·0001), and the difference in worst stiffness NRS response rates was 24% (8 to 39; nominal p=0·0080). The least squares mean change from baseline for EQ-VAS was significantly higher with vimseltinib than placebo (difference 7·4 [1·4 to 13·4]; p=0·016). Although the proportion of patients who had an EQ-VAS response did not differ significantly, the result numerically favoured vimseltinib (difference 12% [−5 to 29]; nominal p=0·16). The difference in BPI worst pain response rate for patients receiving vimseltinib placebo was 26% (4 to 42; p=0·0056). Completion rates for all PRO assessments were robust and consistent at week 25, and no substantial differences in the rates of missing data were noted between groups (appendix pp 12–15). In a separate sensitivity analysis, if the missing data for all patients were imputed based on the mean value using multiple imputation for patients that received placebo, the differences in least squares mean change from baseline at week 25 remained significant for all measures (appendix p 7). Vimseltinib provided early and durable improvements versus placebo in mean change from baseline over time for active range of motion and all PROs (appendix p 16). Symptomatic improvements were observed in patients receiving vimseltinib who had either an objective tumour response or stable disease per RECIST, and more patients had improvements in multiple outcomes with vimseltinib than with placebo. Clinically meaningful improvements in three or more measures of functional health or symptoms were observed in 14 (42%) of 33 patients receiving vimseltinib who had a complete response or partial response and 18 (43%) of 42 who had stable disease, compared with two (6%) of 33 patients receiving placebo who had stable disease (appendix p 16).

The safety population consisted of 39 (98%) patients who received placebo (one of the 40 randomised patients was ineligible and did not receive treatment). Grade 3 or 4 TEAEs occurred in 31 (37%) of 83 patients in the vimseltinib group and in four (10%) of 39 patients in the placebo group (appendix p 8). Only one treatment-related serious TEAE occurred in one patient receiving vimseltinib (grade 3 subcutaneous abscess in a patient with a medical history of abscess); no treatment-related serious TEAEs occurred in the placebo group. Treatment-related grade 3 or 4 TEAEs were reported in 25 (30%) of 83 patients in the vimseltinib group and one (3%) of 39 in the placebo group; no deaths due to TEAEs occurred in either treatment group. The majority of TEAEs were grade 1 or 2 for both groups (table 3). The most common TEAEs (occurring in >20% of patients) in the vimseltinib group were periorbital oedema, fatigue, face oedema, pruritus, headache, asthenia, nausea, increased blood creatine phosphokinase, and increased aspartate aminotransferase. The most common TEAEs with placebo were headache, asthenia, diarrhoea, and nausea. The only grade 3 or 4 TEAE occurring in more than 5% of patients receiving vimseltinib was increased blood creatine phosphokinase, and it was not associated with skeletal muscle injury or other organ damage. The observed elevations of serum enzymes were consistent with the known effect of Kupffer cell inhibition of enzyme clearance.[24,25] No evidence of cholestatic hepatotoxicity or drug-induced liver injury was noted (appendix p 9). No grade 3 or 4 TEAE occurred in more than 5% of patients receiving placebo. In the vimseltinib group, TEAEs led to dose reductions in 35 (42%) of 83 patients, dose interruptions in 44 (53%), and treatment discontinuation in five (6%). In the vimseltinib group, the median number of interruptions per patient was one (IQR 0–1) and the number of doses missed per interruption was four (2–6). The median time spent in part 1 on the standard dose (30 mg) of vimseltinib was 23·6 weeks (16·0–23·7). Among patients who had dose reductions of vimseltinib, the median time spent in part 1 on the first reduced dose (20 mg) was 6·9 weeks (4·6–11·7) and on the second reduced dose (14 mg) was 6·6 weeks (5·7–7·3). 58 (70%) of 83 patients in the vimseltinib group were receiving the standard 30 mg twice-weekly dose at the end of the double-blind period.

Discussion

Systemic treatment options with evidence of efficacy for patients with symptomatic TGCT whose disease is not amenable to surgery are scarce, and a substantial unmet

medical need for these patients persists. The randomised, placebo-controlled, MOTION phase 3 trial evaluated the efficacy and safety of vimseltinib in this population. Treatment with vimseltinib provided significant and clinically meaningful improvements *vs* placebo for the primary and all six key secondary endpoints.

The antitumour effect of vimseltinib was robust, and four (5%) of 83 patients had a complete response. For patients receiving vimseltinib, the objective response rate at week 25 was 40% (33 of 83 patients) per RECIST and 67% (56 of 83) per tumour volume score. In the ENLIVEN phase 3 trial of pexidartinib, the objective response rate at week 25 was 39% (24 of 61 patients) per RECIST and 56% (34 of 61) by tumour volume score.[21] In a subsequent analysis, the objective response rate at week 25 for pexidartinib was updated to 38%.[11] Although not directly comparable, patients treated with vimseltinib in MOTION had a substantially higher objective response rate at week 25 than the best overall objective response rate recorded in patients treated with the less CSF1R-selective and unapproved (for this use) tyrosine kinase inhibitor imatinib in a retrospective analysis (17 [31%] of 55 patients) and in those treated with nilotinib in a phase 2 trial (three [6%] of 51 patients).[26,27] The objective response rates by RECIST and tumour volume score at week 25 in the MOTION phase 3 study are consistent with the results of the ongoing phase 2 study of vimseltinib in patients with TGCT who did not receive previous anti-CSF1 or anti-CSF1R therapy.[17]

TGCT can result in severe functional limitations and substantial morbidity, leading to a disabling impact on daily activities.[1,28] With a mean age at diagnosis of 35–50 years,[1] long-term quality of life should be a priority when evaluating treatment options in these young patients. Consistent with the epidemiology of TGCT, the median age for all patients in MOTION was 44 years (IQR 32–53). Vimseltinib provided statistically significant and clinically meaningful improvements in active range of motion, physical function, stiffness, health status, and pain compared with placebo. The PRO results reported here are of high quality due to the robust collection and high completion rates for all PRO measures. In the ENLIVEN trial, high numbers of observations across secondary efficacy measures (range of motion and PROs) were missing, leading the European Medicines Agency to conclude that the evidence was not sufficient to show an association between pexidartinib antitumour activity and functional or symptomatic improvements.[14] Clinically meaningful improvements in endpoints such as active range of motion, stiffness, or pain could translate to impactful differences in quality of life, such as being able to bathe independently, climb stairs without assistance, or perform tasks for employment.[28] Additionally, in MOTION, symptomatic benefit was not limited to patients who had objective responses per RECIST; patients receiving vimseltinib who had stable disease also had a meaningful improvement in active range of motion and PRO measures. These patients probably had reductions in tumour size that did not reach the RECIST threshold for partial response (≥30% reduction), indicating that even small reductions in lesion size can have a large impact on a patient's functional health. Furthermore, many disease symptoms might be caused by the inflammatory nature of TGCT and not necessarily the tumour mass itself.[29] Vimseltinib can drastically reduce these symptoms by blocking CSF1 signalling between neoplastic and inflammatory cells, even in the absence of an objective response. Additionally, measuring the size of TGCT masses using linear methods (such as those used by RECIST) can be difficult due to irregular tumour shapes, complex morphology, and poor imaging contrast in some locations.[20,30–32] Vimseltinib led to a robust response per RECIST, but some patients with stable disease per RECIST were defined as having responded to treatment per tumour

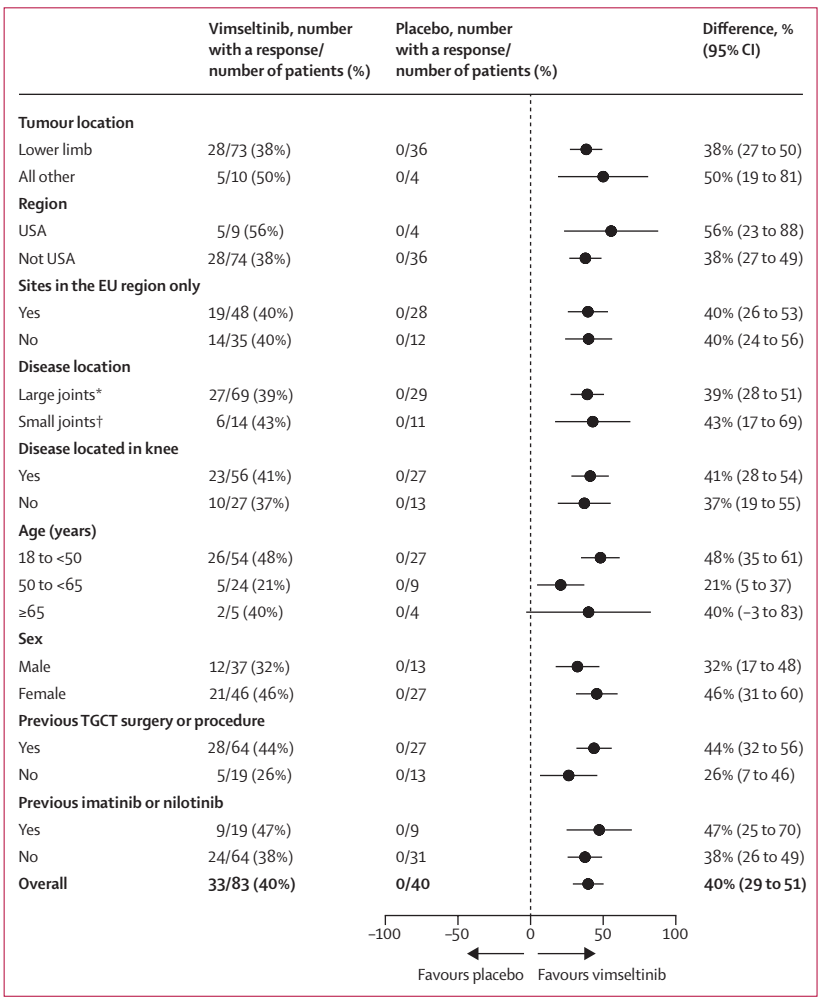

Figure 2: **Forest plot of objective response by patient subgroup**
An unstratified Wald 95% CI is provided. Subgroup analysis by TGCT type (localised *vs* diffuse) was not included because no standard diagnostic criteria to distinguish between the two disease subtypes exist. TGCT=tenosynovial giant cell tumour. *Large joints were shoulder, elbow, hip, or knee. †Small joints were all other joints.

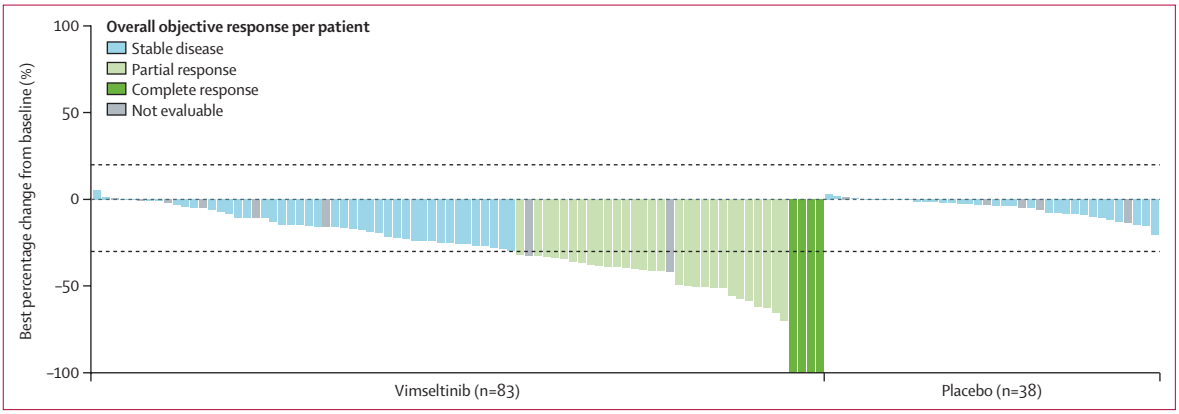

Figure 3: **Best percentage change in target lesions as assessed by independent radiological review per RECIST**
The dotted line at 20% represents threshold for progressive disease. The dotted line at −30% represents the threshold for partial response. Each bar represents an individual patient's best response (for patients who had an assessment at the end of part 1). RECIST=Response Evaluation Criteria in Solid Tumors, version 1.1.

	Vimseltinib (n=83)		Placebo (n=39*)	
	All grades	Grades 3–4	All grades	Grades 3–4
Periorbital oedema	37 (45%)	3 (4%)	5 (13%)	0
Fatigue	27 (33%)	0	6 (15%)	0
Facial oedema	26 (31%)	1 (1%)	3 (8%)	0
Pruritus	24 (29%)	2 (2%)	3 (8%)	0
Headache	23 (28%)	1 (1%)	10 (26%)	0
Asthenia	22 (27%)	1 (1%)	9 (23%)	1 (3%)
Nausea	21 (25%)	0	8 (21%)	1 (3%)
Increased blood CPK	20 (24%)	8 (10%)	0	0
Increased AST	19 (23%)	0	1 (3%)	0
Arthralgia	16 (19%)	0	6 (15%)	1 (3%)
Rash	16 (19%)	0	2 (5%)	0
Maculopapular rash	16 (19%)	1 (1%)	0	0
Peripheral oedema	15 (18%)	0	3 (8%)	0
Hypertension	14 (17%)	4 (5%)	4 (10%)	1 (3%)
Generalised oedema	11 (13%)	1 (1%)	0	0
Eyelid oedema	11 (13%)	0	2 (5%)	0
Increased lacrimation	10 (12%)	0	0	0
Diarrhoea	10 (12%)	0	8 (21%)	1 (3%)
COVID-19	10 (12%)	1 (1%)	1 (3%)	0
Increased ALT	9 (11%)	0	1 (3%)	0

Data are n (%). Adverse event severity was documented using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. No grade 5 events (deaths) occurred during the trial. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CPK=creatine phosphokinase. *One patient randomly assigned to placebo did not receive any treatment.

Table 3: **Treatment-emergent adverse events in at least 10% of patients**

volume score criteria, which might explain the symptomatic benefit reported by patients without a response according to RECIST definitions.[31]

Vimseltinib was well tolerated, with the majority of TEAEs being grade 1 or 2. The only grade 3 or 4 TEAE that occurred in more than 5% of patients treated with vimseltinib was increased blood creatine phosphokinase, which is consistent with the known mechanism of action of CSF1R inhibitors and in general is not considered to be clinically relevant.[24,25] Dose interruptions occurred in approximately half of patients receiving vimseltinib (43 of 83 patients) but were short in duration (median number of doses missed per interruption was four [IQR 2–6]), and the median number of dose interruptions per patient was one (0–1). Although 42% (35 of 83) of patients in vimseltinib group had a dose reduction while in the study, most patients in the vimseltinib group were receiving the 30 mg twice-weekly dose at the end of the double-blind period (70% [58 of 83 patients]), and the rate of discontinuation due to adverse events remained low (6% [five of 83]). A primary concern with pexidartinib is the rare and unpredictable risk of serious cholestatic or mixed liver injury, considered an off-target effect not due to CSF1R inhibition,[14] and which has not been reported for other small molecules or antibodies that inhibit CSF1R.[4] The risk of serious cholestatic or mixed liver injury with pexidartinib means that patients receiving this drug require frequent clinical and laboratory monitoring. However, with vimseltinib, in the MOTION trial, no evidence of cholestatic hepatotoxicity or drug-induced liver injury was observed.[11,12,21,33] The safety profile of vimseltinib and other CSF1R inhibitors suggests that the liver injury associated with pexidartinib is not a class effect of CSF1R inhibitors, but rather specific to the drug itself. Pexidartinib is also a multikinase inhibitor whereas vimseltinib is specific for CSF1R, which could further explain the reduction in off-target effects.[2,31] Pexidartinib's multikinase activity is evidenced by the hair hypopigmentation observed in some patients receiving the drug, which can be attributed to inhibitory effects on the KIT protein[14,21] an adverse event that was not observed in patients receiving vimseltinib.

In the phase 1 portion of the ongoing phase 1/2 trial of vimseltinib, the median treatment duration was 25·1 months (IQR 9·4–33·4), with approximately 4 years being the longest time on treatment.[18] The optimal treatment duration with anti-CSF1R agents for

patients with TGCT remains to be determined. The MOTION study is ongoing and results from the open-label period (part 2) and long-term extension are forthcoming and expected to support the continued efficacy and safety of vimseltinib. The use of a placebo during the double-blind period (part 1) was necessary in MOTION because no globally accepted standard-of-care active comparator is available. Patients receiving placebo in part 1 were able to cross over to receive vimseltinib in the open-label period (part 2; 35 [88%] of 40 patients crossed over). On the basis of the robust activity of vimseltinib observed in part 1, similar response rates are expected in patients who crossed over in the open-label period (part 2). Responses are also expected to improve over time, similarly to the results from the phase 2 portion of the ongoing phase 1/2 study, in which patients who did not receive previous anti-CSF1 or anti-CSF1R therapy had a best overall objective response rate of 64% (29 of 45 patients) with a median treatment duration of 21·0 months (IQR 7·3–23·9).[17]

Limitations of the MOTION study include those inherent to all randomised controlled trials, such as difficulty generalising the findings to the wider population of patients with TGCT. Because TGCT is a rare disease, many study sites are needed to reach target enrolment, which potentially introduces referral bias and differences in treatment patterns. Enrolment was statistically powered for the primary endpoint; however, the low numbers of patients in the subgroup analyses limit the strength of conclusions from those results. The heterogeneity of TGCT is also a limitation because quality of life and PROs can be more affected by tumours in some anatomic locations than others. Patients in the placebo group received best supportive care; therefore, patients receiving placebo in MOTION might have greater improvements than a completely untreated patient population. Additionally, MOTION did not include patients who had previously received anti-CSF1 or anti-CSF1R therapy (excluding imatinib or nilotinib), which probably contributed to the majority of patients being recruited in Europe and Australia, where pexidartinib is not approved. However, preliminary phase 1/2 results indicate that vimseltinib is effective in patients who previously received anti-CSF1 or anti-CSF1R therapy, including pexidartinib.[19]

Overall, vimseltinib showed significant antitumour activity versus placebo, with a favourable safety profile in patients with TGCT not amenable to surgery. Patients had statistically significant and clinically meaningful improvement in active range of motion, which could provide relief from mobility-related limitations in this young population. Finally, patients treated with vimseltinib reported significantly improved stiffness, physical function, health status, and pain. If approved, vimseltinib offers an effective systemic treatment option to patients with TGCT and provides functional health and symptomatic benefit to a population living with substantial morbidity and few treatment options.

Contributors

All authors had access to the data, participated in drafting and revision of the manuscript, and approved the final version for submission. HG, BH, MGS, RR-S, MLS, and WDT participated in the conception and design of the study along with the funder. HG, VB, SS, SB, AJW, MvdS, NMB, ALP, AAR, AI, MA, ALC, GT, KB, JM-B, EP, ST, SP, BCP, PRe, ACH, PRu, J-YB, and WDT, along with the funder, participated in data collection. CT oversaw statistical analyses. CT, HG, and WDT directly accessed and verified the data reported in this manuscript. Authors employed by Deciphera Pharmaceuticals (CT, FZ, BH, MGS, RR-S, and MLS) contributed to the design and conception of the study, analysed and interpreted the data in collaboration with all authors, participated in drafting and revision of the manuscript, and approved the final version for submission. All authors are accountable for all aspects of the work and had final responsibility for the decision to submit for publication.

Declaration of interests

VB reports institutional research funding from Deciphera Pharmaceuticals and participation on a medical advisory board for Deciphera Pharmaceuticals. SS reports institutional research funding from Abbiski, Daiichi Sankyo, and Deciphera Pharmaceuticals, and advisory board roles with Daiichi Sankyo and Deciphera Pharmaceuticals. SB reports honoraria from Blueprint Medicine, Boehringer Ingelheim, Pfizer, PharmaMar, Uptodate, and Deciphera Pharmaceuticals; consulting or advisory roles with Adcendo, Bayer, Boehringer Ingelheim, Cogent Biosciences, Daiichi Sankyo, Lilly, IDRx, and Deciphera Pharmaceuticals; institutional research funding from Adcendo, Blueprint Medicine, Incyte, and IDRx; participation on a board for the University of Aachen; unpaid board of directors positions with The Connective Tissue Oncology Society and Deutsche Sarkomstiftung; and a faculty position with the European Society for Medical Oncology. AJW reports consulting or advisory roles and institutional research funding from Daiichi Sankyo and Deciphera Pharmaceuticals. MvdS reports travel partly supported by Deciphera Pharmaceuticals. NMB reports research support from Deciphera Pharmaceuticals. AAR reports consulting or advisory roles with Boehringer Ingelheim and Medison; institutional research funding from 23andMe, Abbisko, AbbVie, Adaptimmune, Amgen, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, GSK, Inhibrx, Iterion Therapeutics, Karyopharm Therapeutics, MedImmune, Medison, Merck, Neoleukin Therapeutics, Pfizer, Rain Therapeutics, Roche/Genentech, Symphogen, and Deciphera Pharmaceuticals; and participation on an advisory board for Inhibrx. AI reports consulting or advisory roles for Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Merck, Merck Sharp & Dohme, Novartis, Parthenon, PharmaMar, and Roche; and institutional research funding from Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Merck, Merck Sharp & Dohme, Novartis, Parthenon, PharmaMar, and Roche. ALC reports honoraria from Bayer, PharmaMar, and Deciphera Pharmaceuticals. GT reports consulting or advisory roles with Daiichi Sankyo and Servier. KB reports honoraria from Incyte, Lilly, Novartis, and Deciphera Pharmaceuticals; expert testimony for Deciphera Pharmaceuticals; and advisory board participation for Bayer, GSK, and NEC OncoImmunity. JM-B reports consulting or advisory roles for Amgen, Asofarma, Boehringer Ingelheim, Bayer, GSK, Lilly, Novartis, PharmaMar, Roche, and Tecnofarma; speakers bureau involvement for PharmaMar; and institutional research funding from Adaptimmune, Amgen, Ayala Pharmaceuticals, Bayer, Blueprint Medicines, Bristol Myers Squibb, Cebiotex, Celgene, Daiichi Sankyo, Eisai, GSK, IMMIX Biopharma, Inhibrx, Karyopharm Therapeutics, Lilly, Lixte, Novartis, Pfizer, PharmaMar, Philogen, PTC Therapeutics, Rain Therapeutics, and Deciphera Pharmaceuticals; expert testimony for Amgen, Bayer, Boehringer Ingelheim, Eisai, Lilly, PharmaMar, and Roche; travel support from Novartis, Pfizer, and PharMar; advisory board participation for Asofarma and Tecnofarma; and a leadership or fiduciary role for Sarcoma Research solutions. EP reports advisory board roles with Daiichi Sankyo, SynOx, and Deciphera Pharmaceuticals. PRe reports honoraria for participation in advisory

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Data sharing

Qualified scientific and medical researchers can address requests for de-identified individual participant data that underlie the results reported in this Article to info@deciphera.com. Proposals for data will be evaluated and approved by Deciphera Pharmaceuticals at its sole discretion. All approved researchers must sign a data access agreement before accessing the data. Data will be available as soon as possible but no later than within 1 year of the acceptance of the Article for publication and for 3 years after Article publication. Deciphera Pharmaceuticals will not share data from identified participants or a data dictionary.

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