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Citation

Tap, W. D., Sharma, M. G., Vallee, M., Smith, B. D., Sherman, M. L., Ruiz-Soto, R., ... Gelderblom, H. (2023). The MOTION study: a randomized, Phase III study of vimseltinib for the treatment of tenosynovial giant cell tumor. *Future Oncology*, 20(10), 593-601. doi:10.2217/fon-2023-0238

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Note: To cite this publication please use the final published version (if applicable).

The MOTION study: a randomized, phase III study of vimseltinib for the treatment of tenosynovial giant cell tumor

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Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplasm that occurs in the synovium of joints, bursae, or tendon sheaths and is caused by upregulation of the *CSF1* gene. Vimseltinib is an oral switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit the CSF1 receptor. Here, we describe the rationale and design for the phase III MOTION trial (NCT05059262), which aims to evaluate the efficacy and safety of vimseltinib in participants with TGCT not amenable to surgical resection. In part 1, participants are randomized to receive vimseltinib 30 mg twice weekly or matching placebo for ≤ 24 weeks. Part 2 is a long-term treatment phase in which participants will receive open-label vimseltinib.

Plain language summary: Tenosynovial giant cell tumor (or TGCT) is a rare, noncancerous tumor that grows in the soft tissue lining the spaces of joints and bursae (fluid-filled sacs that work to reduce friction in the joints). These tumors are linked to increased levels of a protein called CSF1. While this condition is typically treated with surgery, some patients may not be candidates for surgical removal of the tumor due to factors such as location or complexity of the tumor; therefore, drug treatments are needed to help these patients. Vimseltinib is an investigational oral drug specifically designed to inhibit the receptor to which the CSF1 protein binds. In this article, we describe the rationale and design for a phase III clinical trial that will test how well vimseltinib works in participants with TGCT who are not candidates for surgery. In the first part of the study, participants are randomly assigned to receive vimseltinib 30 mg twice weekly or a matching placebo (inactive substance) for up to 24 weeks. This first part is blinded, so participants will not know if they are receiving vimseltinib or the placebo. The second part of the study is a long-term treatment phase in which all participants will receive vimseltinib (unblinded).

Clinical Trial Registration: NCT05059262 (ClinicalTrials.gov)

Tweetable abstract: Vimseltinib is an oral switch-control kinase inhibitor designed to selectively and potently inhibit CSF1R. Here, we describe the rationale and design for the phase III MOTION trial, which aims to evaluate vimseltinib in participants with TGCT not amenable to surgical resection.

First draft submitted: 22 March 2023; Accepted for publication: 13 July 2023; Published online: 18 August 2023

Keywords: CSF1R • MOTION • pigmented villonodular synovitis • tenosynovial giant cell tumor • tyrosine kinase inhibitor • vimseltinib

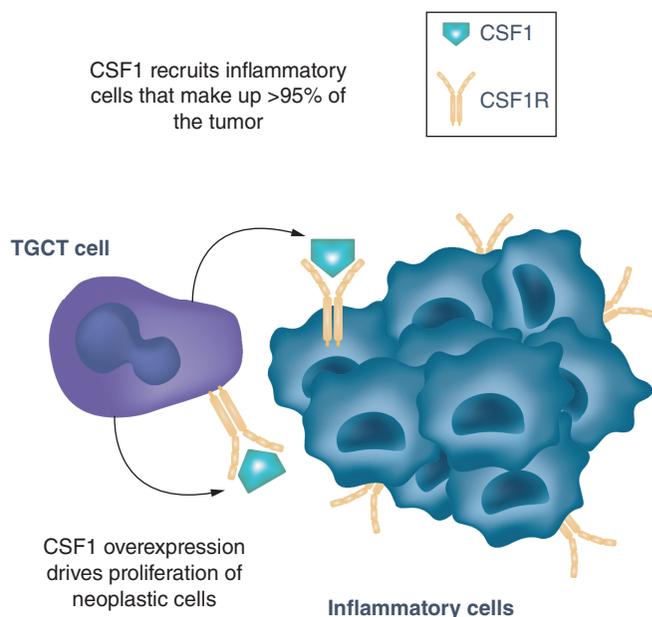


Figure 1. CSF1 involvement in tenosynovial giant cell tumor development.
TGCT: Tenosynovial giant cell tumor.

Tenosynovial giant cell tumor (TGCT), or pigmented villonodular synovitis, is a nonmalignant, locally aggressive soft tissue tumor affecting the synovium of the joint, bursa and tendon sheath [1]. TGCT is caused by upregulation of the *CSF1* gene, resulting in aberrant CSF1 expression and recruitment of CSF1R-dependent inflammatory cells to the affected joint (Figure 1) [2]. Surgical resection is the primary treatment for TGCT and approximately 90% of nodular/localized TGCT is cured with surgery [3]. However, some cases are considered inoperable or difficult to operate on without subsequent morbidity or high recurrence; this is especially true for diffuse-type TGCT [3]. Patients with recurrent TGCT often report pain and swelling, deteriorated physical function and activity limitations; therefore, it is necessary to develop nonsurgical treatment options [4].

Pexidartinib is a tyrosine kinase inhibitor (TKI) with activity against CSF1R approved for systemic treatment of TGCT in the USA [5,6]. Pexidartinib was associated with a higher objective response rate (ORR) compared with placebo and a very rare, but serious cholestatic hepatic toxicity [6]. The US pexidartinib label includes a boxed warning for hepatotoxicity and is only available to patients through a risk evaluation and mitigation strategy program [5,7]. Pexidartinib is not available to patients in Europe [8]. With these considerations, there is a need for alternative CSF1R-targeted therapies.

Trial

The purpose of the phase III MOTION trial (NCT05059262, registered 28 September 2021; EudraCT 2020-04883-25, authorized 22 September 2021) is to evaluate the efficacy and safety of vimseltinib for treatment of TGCT not amenable to surgical resection. Funded by Deciphera Pharmaceuticals (DCC-3014-03-001), the MOTION trial opened in October 2021 and rapidly completed enrollment by March 2023.

Background & rationale

Vimseltinib is an oral, switch-control TKI specifically designed to selectively and potently inhibit CSF1R. Many small molecule TKIs are ATP-competing inhibitors, which interfere with the binding of ATP to the kinase and disrupt phosphorylation [9,10]. Vimseltinib binds to the unique switch pocket region of CSF1R, thus inhibiting signaling by locking the kinase in an inactive conformation [11]. Vimseltinib's unique switch-control design provides greater selectivity for CSF1R, unlike pexidartinib, which also inhibits closely related kinases such as KIT, PDGFRA, PDGFRB and FLT3 [11]. In a preclinical study, vimseltinib was >500-fold more selective for CSF1R vs KIT, PDGFRA, PDGFRB and FLT3 (Figure 2) [11]. For patients with TGCT, off-target effects may limit the dosing needed for optimal CSF1R suppression and contribute to adverse events (AE) [11]. Due to its high specificity for CSF1R, vimseltinib is not associated with AEs linked to KIT inhibition, such as hair color changes [6,12,13].

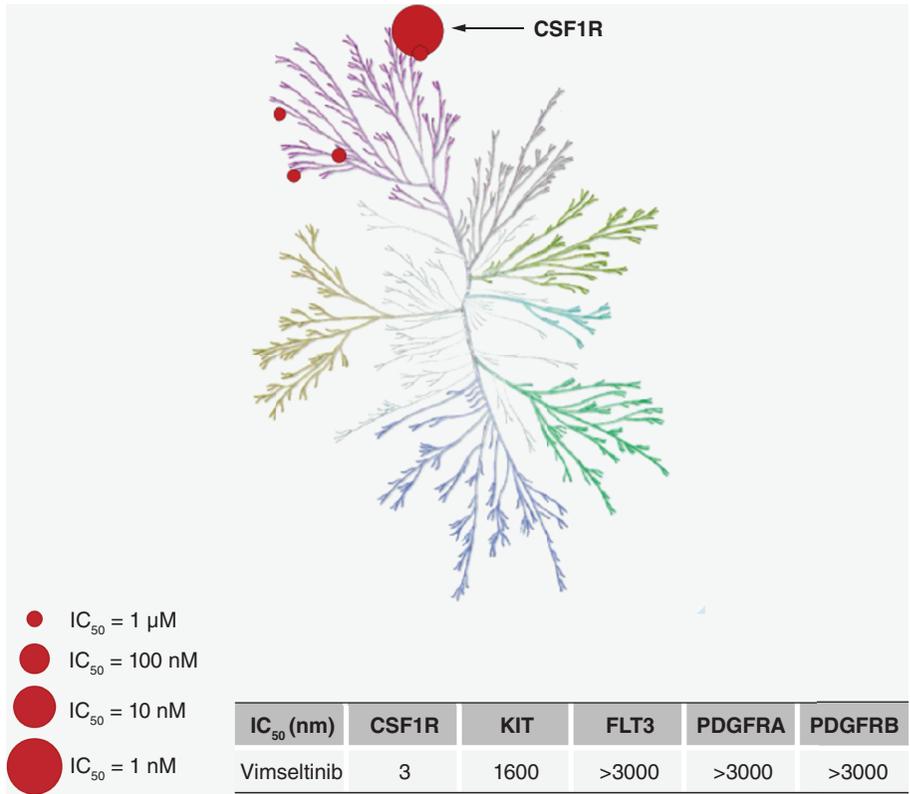


Figure 2. Vimseltinib selectivity for CSF1R.
 IC₅₀ >3000 nM not shown on map.
 IC₅₀: Half maximal inhibitory concentration.

In the expansion portion of a phase I/II study in participants with TGCT not amenable to surgical resection (NCT03069469), vimseltinib (30 mg twice weekly) showed encouraging antitumor activity, with durable responses over time, and was well tolerated [13]. The ORR was 53% in participants who had not received prior anti-CSF1/CSF1R therapy (except imatinib and/or nilotinib) and 46% in participants who had received prior anti-CSF1/CSF1R therapy [13]. Improvement in pain symptoms was observed in approximately 50% or more participants and most treatment-emergent adverse events (TEAE) were Grades 1/2 [13]. These data support further development of vimseltinib in participants with TGCT not amenable to surgery in the phase III MOTION study.

Design

Study design

MOTION is a phase III, randomized, placebo-controlled, double-blind study (Figure 3). This study consists of two parts. In part 1, eligible participants are assigned to receive either vimseltinib 30 mg twice weekly or matching placebo for 24 weeks (28-day cycles) or shorter if disease progression based on independent radiological review (IRR) is observed. Part 2 is a long-term treatment phase in which all participants receive open-label vimseltinib; participants assigned to placebo in part 1 have the option to receive vimseltinib for Part 2. Part 2 will end at week 49 and will be followed by an extension period. MOTION is being conducted globally in the USA, Canada, Europe, Hong Kong and Australia (trial sites can be found on clinicaltrials.gov).

Study subjects & eligibility criteria

Participants must be at least 18 years of age and have histologically confirmed TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity. The participants must have symptomatic disease defined as at least moderate pain or at least moderate stiffness and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) with at least one lesion having a minimum size of 2 cm, as assessed from magnetic resonance imaging scans by a central radiologist. Individuals will be excluded if they received

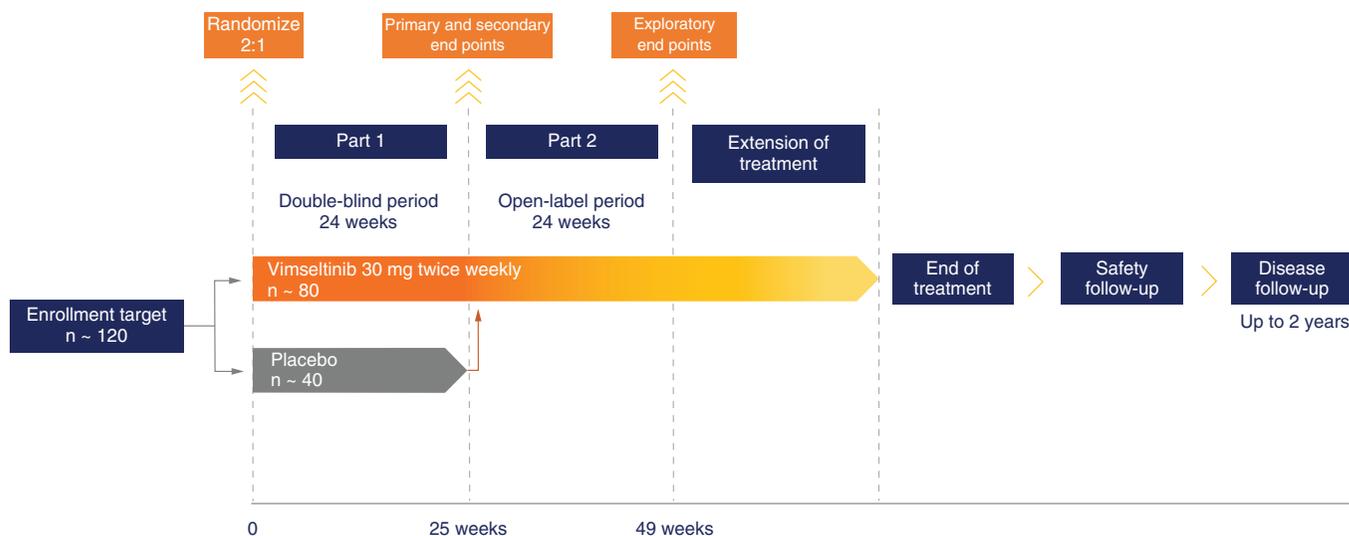


Figure 3. MOTION trial design. Participants are eligible to receive study drug until independent radiologic confirmation of disease progression, lack of clinical benefit, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib. Participants receive vimseltinib or placebo for a full 24 weeks during the double-blind period with the primary and secondary end points collected at the beginning of week 25.

previous systemic therapy targeting CSF1 or CSF1R (previous therapy with imatinib and/or nilotinib is allowed), received any therapy for TGCT (including investigational therapy) during the screening period, had major surgery within 14 days of the first dose of study drug, or participated in a non-TGCT investigational drug study within 30 days of screening. Inclusion and exclusion criteria are listed in [Table 1](#).

Randomization & blinding

Approximately 120 participants will be randomized in a 2:1 ratio to vimseltinib 30 mg twice weekly or matching placebo ([Figure 3](#)). Randomization is stratified for tumor location (lower limb/all other) and region (US/non-US). Participants will receive a unique participant identification number *via* interactive response technology. In part 1, the participants and all site personnel, including the investigator, site monitor and study team, are blinded to study drug treatment. These individuals will become unblinded to a specific participant's treatment assignment if the participant has disease progression based on IRR or has reached week 25 and completed the end of part 1 assessments.

Study interventions

Vimseltinib or matching placebo is administered on day 1 and day 5 each week at approximately the same time of day in a fasted state. Participants randomized to vimseltinib in part 1 and continuing to part 2 are instructed to take the same number of capsules per day on dosing days as they were taking at the end of part 1. Participants randomized to placebo in part 1 and who choose to continue to part 2 will initiate vimseltinib at the 30 mg twice-weekly dose. The study drug may be interrupted and/or modified at the discretion of the investigator at any time due to AEs. The first dose reduction is from 30 mg twice weekly to 20 mg twice weekly; the second dose reduction is from 20 mg twice weekly to 14 mg twice weekly. If more than two dose level reductions are required, the study drug will be discontinued. Compliance will be monitored by conducting reviews of dosing diaries and counting the capsules of study drug taken.

End points

The primary end point of the MOTION study is ORR (complete responses + partial responses) per RECIST v1.1 by blinded IRR at week 25 (end of part 1; [Table 2](#)). MRI of the affected joint is performed at screening; cycle 4, day 1 and the end of part 1 (25 weeks) to evaluate tumor response. MRIs to evaluate tumor response are conducted every third cycle after the end of part 1 starting on cycle 10, day 1 for participants continuing on vimseltinib, or on cycle 4, day 1 on open-label vimseltinib for participants originally randomized to placebo who later cross over. Key secondary end points include ORR by tumor volume score (TVS), change from baseline in range of motion

Table 1. Eligibility criteria.

Inclusion criteria
Male or female participants ≥ 18 years of age
TGCT for which surgical resection is not an option (tumor biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available)
Symptomatic disease with at least moderate pain or at least moderate stiffness (defined as a score of ≥ 4 , with 10 describing the worst condition) within the screening period and documented in the medical record
Participant should complete 14 consecutive days of questionnaires during the screening period
An analgesic regimen, if used, needs to be stable (i.e., no change in dose), as judged by the investigator for ≥ 2 weeks prior to the first dose of study drug
Measurable disease per RECIST v1.1 with at least one lesion having a minimum size of 2 cm
Adequate organ function and bone marrow reserve
Participants of reproductive potential must have a negative serum β -hCG pregnancy test at screening (female participants) and agree to follow the contraception requirements
The participant is capable of understanding and complying with the protocol and has signed the informed consent form; a signed informed consent form must be obtained before any study-specific procedures are performed
Willing and able to complete the PRO assessments on an electronic device
Exclusion criteria
Previous use of systemic therapy (investigational or approved) targeting CSF1 or CSF1R, including vimseltinib; previous therapy with imatinib and nilotinib is allowed
Treatment for TGCT, including investigational therapy, during the screening period Note: Participants may not be part of an ongoing or have prior participation in a non-TGCT investigational drug study within 30 days of screening
Known metastatic TGCT or other active cancer that requires concurrent treatment (exceptions will be considered on a case-by-case basis)
QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
Receive concurrent treatment with any prohibited medications
Major surgery within 14 days of the first dose of study drug
Any clinically significant comorbidities
Active liver or biliary disease, including nonalcoholic steatohepatitis or cirrhosis
Malabsorption syndrome or other illness that could affect oral absorption
Known active human immunodeficiency virus, acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection
If female, the participant is pregnant or breastfeeding
Known allergy or hypersensitivity to any component of the study drug
Contraindication to MRI
PRO: Patient-reported outcome; QTcF: Corrected QT interval by Fredericia; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TGCT: Tenosynovial giant cell tumor.

Table 2. MOTION study end points.

Primary end point
ORR per RECIST v1.1 by blinded IRR at week 25
Key secondary end points
ORR per TVS at week 25
Change from baseline in active ROM of the affected joint, relative to a reference standard, at week 25
Change from baseline in the PROMIS physical function score at week 25
Change from baseline in the Worst Stiffness NRS score at week 25
Change from baseline in EuroQoL Visual Analogue scale at week 25
Response of $\geq 30\%$ improvement in the mean BPI Worst Pain NRS score without a $\geq 30\%$ increase in narcotic analgesic use at week 25
BPI: Brief pain inventory; EuroQoL: European Quality of Life Scale; IRR: Independent radiological review; NRS: Numeric rating scale; ORR: Objective response rate; PROMIS: Patient-Reported Outcomes Measurement Information System; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; ROM: Range of motion; TVS: Tumor volume score.

(ROM) as measured by active and passive goniometry, and changes from baseline in patient-reported outcome (PRO) measures (Table 2). Narcotic analgesic use is recorded in a patient diary and collected at each visit to compare with PROs. ORR by TVS, ROM and PROs are also evaluated at week 25 (end of part 1).

Safety & AEs

An AE is defined as any untoward medical occurrence in a clinical study participant that may or may not have a causal relationship with the investigational treatment. The assessment of study drug relationship to each AE will be reported by the investigator according to his or her best clinical judgment. The investigator must determine and

record the severity of all AEs; the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 will be used for grading the severity of AEs. Per guidance from the US FDA, AEs are considered treatment emergent if they occur at or after administration of the first dose of study drug through 30 days after the last dose of study drug [14].

Data monitoring committee

A data monitoring committee (DMC) will monitor the unblinded safety and efficacy data from this study to help ensure the ongoing safety of the participants. The DMC will consist of an experienced biostatistician and two qualified clinicians who are not employees of the sponsor and who have scientific expertise in TGCT and practical experience conducting clinical studies and monitoring safety and efficacy of clinical studies.

Estimated sample size & power

The sample size selection of approximately 120 participants with TGCT ($n \approx 80$ receiving vimseltinib, $n \approx 40$ receiving placebo) was based on considerations for powering the analyses of the primary end point, key secondary end points, detection of rare safety events, and overall exposure to vimseltinib and assuming a 15% participant dropout rate.

Statistics

The intent-to-treat (ITT) analysis set will consist of all participants who are randomized to a study treatment regimen; the ITT population will be the primary analysis set for all efficacy end point analyses. The safety analysis set will consist of all participants who receive ≥ 1 dose of study treatment; analysis will be performed according to the treatment regimen actually received. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized *via* Kaplan–Meier methodology using the 25th, 50th (median) and 75th percentiles with associated two-sided 95% CIs.

Primary end point

The ORR at week 25 will be compared between the vimseltinib arm and placebo arm using a two-sided Cochran–Mantel–Haenszel test stratified by the randomization stratification factors (tumor location and region). The test will be performed at a 0.05 alpha level on the ITT population; a 95% CI for the proportion in each arm and for the difference in proportion will be presented. Participants who do not have any postbaseline assessment will be considered nonresponders.

Secondary efficacy end points

Most secondary efficacy end points will be analyzed using a mixed model for repeated measurements in which the dependent variable will be the change from baseline. Each of these models will include fixed effects for treatment group, time point, treatment group by time point interaction, stratification factor for region (USA vs non-USA), stratification factor for tumor location, and the baseline value of the corresponding end point. Statistical comparisons between treatment groups will be made at the specified time point.

Missing data

All available data will be included in data listings. Unless specified in the individual end point analysis, missing data will not be imputed except for the purpose of identification of TEAEs and prior or concomitant medications or procedures with a missing start or end time.

Ethics

This study is being performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonisation and Good Clinical Practice guidelines. Applicable local regulatory requirements are being followed, and the investigators ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research. The investigators ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation, and obtain written informed consent from each participant before any study-specific activity is performed.

Conclusion

The methodology of the MOTION study is a strength in that the two-part design will allow for initial blinded efficacy and safety analyses, as well as exploratory analyses during the open-label phase of the trial. Additionally, the placebo crossover aspect of the trial may provide additional support for efficacy and safety of vimseltinib in the open-label period. A crucial aspect of this trial will be the analysis of PRO measures, as it will be important to demonstrate that vimseltinib treatment results in clinically meaningful benefit. Similarly, it will be important to show that vimseltinib is not associated with hepatotoxicity. The results of this study will help define the potential use of vimseltinib in this population of patients who need additional treatment options to preserve physical functioning and improve quality of life.

Executive summary

Background

- Tenosynovial giant cell tumor (TGCT) can be extremely debilitating, especially in diffuse cases where surgical resection is not curative.

Rationale

- There is need for additional nonsurgical treatment options as the only approved systemic therapy for TGCT is only available through a risk evaluation and mitigation strategy program in the USA and is not available in Europe.
- Vimseltinib is an oral, switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R.

Study design

- MOTION is an ongoing, global, phase III, randomized, placebo-controlled, double-blind study evaluating the efficacy and safety of vimseltinib in participants with TGCT not amenable to surgery.
- Eligible participants are adults with histologically confirmed TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity.
- A target of 120 participants will be randomized to receive vimseltinib (30 mg twice weekly) or matching placebo for up to 24 weeks; after 24 weeks, all participants will receive open-label vimseltinib (including those initially randomized to placebo).
- The primary end point (objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent radiological review) will be evaluated at week 25.

Author contributions

MG Sharma, M Vallee, BD Smith, ML Sherman and R Ruiz-Soto conceived the study. All coauthors initiated the study design and contributed to the implementation of the study and to the refinement of the study protocol. All authors contributed to the drafting and critical review of this manuscript. All authors have given their final approval of the submitted version.

Acknowledgments

We thank the participants and their families and caregivers, the investigators, and the investigational site staff of the MOTION study.

Financial disclosure

This study is funded by Deciphera Pharmaceuticals, LLC (Waltham, MA, USA). Protocol number: DCC-3014-03-001 (A phase III, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor [MOTION]). For inquiries about this trial, please contact Deciphera Pharmaceuticals (781-209-6400 or clinicaltrials@deciphera.com). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

WD Tap reports advisory board roles for Lilly, Daiichi Sankyo, Nano Carrier, Blueprint Medicines, Deciphera Pharmaceuticals, C4 Therapeutics, Foghorn Therapeutics, AmMaxBio, MundiBioPharma, Novo Holdings, Servier, Medpacto, Ayala Pharmaceuticals, Kowa Research Institute, Epizyme, Bayer, Cogent Biosciences, Amgen, and Aadi Biosciences; WD Tap reports invited speaker roles for EMD Serono and PER, and owns stock/shares in Certis Oncology Solutions and Atropos; WD Tap reports a patent for Companion Diagnostics for CDK4 inhibitors (14/854,329) and institutional funding from Novartis, Lilly, Plexikon, Daiichi Sankyo, Tracon Pharma, Blueprint Medicines, Immune Design, BioAlta, and Deciphera Pharmaceuticals. MG Sharma is an employee of Deciphera

Pharmaceuticals and owns Deciphera Pharmaceuticals stocks/shares. M Vallee is an employee of Deciphera Pharmaceuticals and owns Deciphera Pharmaceuticals stocks/shares. BD Smith is an employee of Deciphera Pharmaceuticals and owns stocks/shares in Deciphera Pharmaceuticals. BD Smith is an inventor on 10 patents or pending patents with Deciphera Pharmaceuticals. BD Smith has not received and will not receive any royalties. ML Sherman is an employee of Deciphera Pharmaceuticals and an independent board director at Pieris Pharmaceuticals. ML Sherman owns stock/shares in Deciphera Pharmaceuticals and Pieris Pharmaceuticals. R Ruiz-Soto is an employee of Deciphera Pharmaceuticals and owns stock/shares in Deciphera Pharmaceuticals and Immunogen. R Ruiz-Soto is an inventor in three patents with Immunogen and pending patents at Deciphera Pharmaceuticals and has transferred the rights to Immunogen and Deciphera Pharmaceuticals, respectively; R Ruiz-Soto has not received and will not receive any royalties. M van de Sande reports institutional invited speaker fees from Synox Therapeutics LTD and institutional funding from Carbofix, Daiichi Sankyo, and Implantcast. RL Randall reports royalties or licenses from Onkos, Zimmer Biomet, and Daiichi Sankyo; consulting fees from Onkos, Zimmer Biomet/Balmoral, SpringWorks, and Daiichi Sankyo; payment/honoraria from Onkos, SpringWorks, and Zimmer Biomet/Balmoral; and leadership roles for SFA and MSTs. NM Bernthal reports grants from the NIH and DOD, research support from Zimmer Biomet, and advisory board participation for Daiichi Sankyo. H Gelderblom reports institutional funding from Daiichi Sankyo, Deciphera Pharmaceuticals, Novartis, Boehringer Ingelheim, AmMax Bio, Debiopharm, and Cytovation. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Medical writing and editorial support were provided by L Hanlon and S Walker of AlphaBioCom, a Red Nucleus company, and were funded by Deciphera Pharmaceuticals, LLC.

Ethical conduct of research

This study is being performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonisation and Good Clinical Practice guidelines. Applicable local regulatory requirements are being followed, and the investigators ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research. The investigators ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation, and obtain written informed consent from each participant before any study-specific activity is performed.

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