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CLINICAL TRIAL PROTOCOL

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TANGENT study design: a phase III, randomized study of emactuzumab for the treatment of tenosynovial giant cell tumors

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ABSTRACT

Tenosynovial giant cell tumors (TGCT) are rare, locally aggressive neoplasms causing pain, stiffness, swelling, limited range of motion, and joint degeneration, which can be debilitating. Therapeutic options include surgery or systemic therapy with colony-stimulating factor 1 receptor (CSF-1R) pathway inhibitors. However, many are not amenable to surgery or have high postsurgical recurrence rates. Available systemic therapies require long-term administration and can have burdensome side effects. Emactuzumab is a novel, potent, CSF-1R inhibiting monoclonal antibody with a unique mechanism of action targeting the receptor dimerization interface of the CSF-1R to reduce tumor-associated macrophages and inflammation within the TGCT microenvironment. It is the only short-course, intravenous therapy in development for TGCT. In a phase I study, emactuzumab resulted in robust and durable responses, and a manageable safety profile in patients with TGCT, supporting further research as a treatment option to address unmet need and improve quality of life in patients with TGCT. TANGENT is a randomized, double-blind, global, phase III study (NCT05417789) to investigate the safety and efficacy of intravenous emactuzumab versus placebo in patients with TGCT not amenable to surgery.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT05417789 initially registered on 1 June 2022.

PLAIN LANGUAGE SUMMARY

What is this article about?

The TANGENT trial examines a new treatment for tenosynovial giant cell tumors (TGCTs). TGCTs are rare tumors in the joints or tendon. TGCTs have two types, nodular (N-TGCT), which is typically a single tumor, and diffuse (D-TGCT), which spreads out more. TGCTs grow quickly and can cause joint damage, pain, stiffness, and decrease joint movement. Surgery is usually done to remove the tumor. However, surgery is not an option for all tumors and some tumors may return after surgery. Oral medications that target a pathway involved in TGCT development (CSF-1 inhibitors) are another treatment option. These are taken long term and can have side effects.

Emactuzumab is a new treatment for TGCT given intravenously for 8-weeks. In an earlier study, patients treated with emactuzumab responded to treatment and side effects were manageable.

What will the study look at?

This article describes a trial looking at the safety and effectiveness of emactuzumab in patients with TGCT that cannot have surgery. The trial evaluates a short 8-week Intravenous treatment. If emactuzumab reduces tumor burden and improves function, it could become a new treatment for TGCT.

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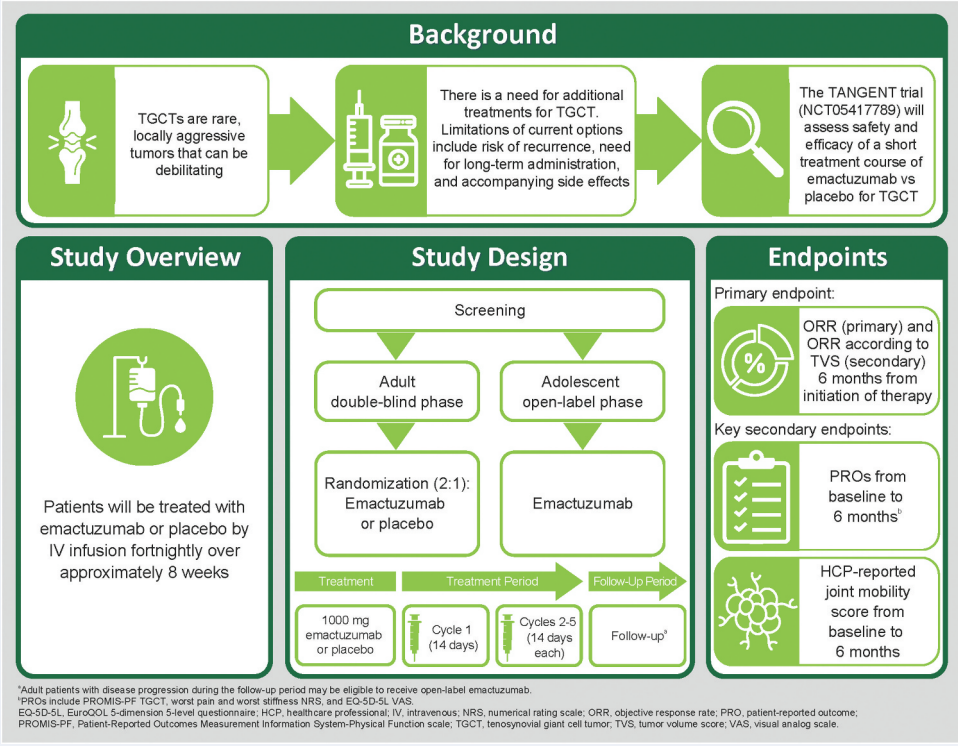
KEYWORDS

Emactuzumab; tenosynovial giant cell tumor; TANGENT; CSF-1; CSF-1R; monoclonal antibody

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1. Introduction

1.1. Background and rationale

Tenosynovial giant cell tumors (TGCT), formerly known as pigmented villonodular tenosynovitis, are rare mesenchymal neoplasms that most often arise in the synovium of joints, bursae, or tendon sheaths [1–4]. They are locally aggressive and destructive and can cause joint erosion, joint space loss and effusion, and bony mineralization, ultimately resulting in pain, limited range of motion, stiffness, joint degeneration, and swelling [2,3,5–7]. The prevalence of TGCTs was estimated to be between 12–44 per 100,000 persons at the end of 2012, and they typically present in younger people between 35–50 years old, but can occur at any age [1,8,9]. In the United States, TGCT is associated with high healthcare use, disability, and work loss, reflecting substantial, underrecognized burden [10].

TGCTs have two radiologically distinct subtypes, localized (L-TGCT, also referred to as nodular N-TGCT) and diffuse (D-TGCT), based on tumor location and growth pattern [1,7,11,12]. L-TGCT commonly presents as a unique or single limited lesion, whereas D-TGCT has more extensive and infiltrative involvement [1]. L-TGCT and D-TGCT share common mechanisms of pathogenesis, most of which involve translocations of the colony-stimulating factor 1 (*CSF-1*) gene, ultimately resulting in the overexpression of *CSF-1* [13,14]. CSF-1 regulates the survival, proliferation, and differentiation of mononuclear phagocytes, and its overexpression results in tumor expansion through the recruitment of inflammatory cells to the tumor microenvironment [15–17].

Treatment for TGCT may involve surgical resection of the tumor [1]. However, not all tumors are amenable to surgery, and for those that are, postsurgical recurrence can occur (up to 36% recurrence reported for L-TGCT and 72% for D-TGCT), with rate of recurrence varying by affected joint [1,7,12,18]. Surgery may also lead to complications and morbidity, including, but not limited to, infection and wound healing problems, hemorrhage (including hemarthrosis, requiring drainage), nerve damage, joint stiffness and dysfunction, and the potential need for joint replacement [1,19–22]. Patients may require additional surgeries throughout their lifetime, and the risk of morbidity increases with subsequent procedures [1,7,19].

In cases where tumors are not amenable to surgery, systemic therapies such as oral CSF-1 receptor (CSF-1R) pathway inhibitors are available [1], but these therapies have limitations, such as chronic administration burden (including impact on family planning), drug-drug interactions, chronic side effects, food effect, and adherence challenges [23,24]. Currently, three oral CSF-1R inhibitors are approved for the treatment of TGCT, pexidartinib (approved in the US, Taiwan, and South Korea), vimseltinib (approved in the US and European Union), and recently, pimicotinib (approved in China) [23–27]. Pexidartinib resulted in a 39% overall response in a phase III trial of patients with TGCT, but has a black box warning and is only available to patients through a risk evaluation and mitigation strategy (REMS) program due to its association with hepatotoxicity [23,28]. In phase III trials of patients with TGCT, vimseltinib and pimicotinib demonstrated objective response rates of 40% and 54% at 25 weeks, respectively [29,30]. However, oral CSF-1R inhibitors require long-term administration and can result in side effects such as periorbital edema, fatigue, pruritus, itching, headache, asthenia, and nausea, among others [23,24,28,29], which may affect treatment adherence.

Article highlights

- Tenosynovial giant cell tumors (TGCT) are rare, mesenchymal, benign neoplasms with the potential of malignant transformation, often arising in the synovium of joints, bursae, or tendon sheaths. They are locally aggressive and destructive and can cause joint erosion, joint space loss and effusion, and bony mineralization, resulting in pain, limited range of motion, stiffness, joint degeneration, and swelling.
- Treatment for TGCT may involve surgical resection of the tumor or systemic therapies such as oral CSF-1 pathway inhibitors. However, many tumors are not amenable to surgery, and for those that are, postsurgical recurrence and complications associated with surgery are concerns. Another treatment option is oral CSF-1R inhibitors, which also have limitations as they are associated with chronic administration burden (including impact on family planning), drug-drug interactions, chronic side effects, food effects, and adherence challenges.
- Emactuzumab is a novel, potent, highly selective, monoclonal immunoglobulin G1 (IgG1) antibody directed against CSF-1R. Emactuzumab has a distinct mechanism of action targeting the CSF-1R dimerization interface with high affinity to block ligand-induced and ligand-independent receptor activation at the surface of cells expressing this receptor in the TGCT microenvironment.
- Emactuzumab also offers a new, differentiated treatment option, as it is has a short treatment course (delivered by intravenous infusion) of approximately 8 weeks.
- In a phase I study, emactuzumab resulted in robust and durable responses with a manageable safety profile, supporting further research as a treatment option to address the unmet need and improve quality of life in patients with TGCT.
- The phase III TANGENT study was designed to assess the safety and efficacy of a short treatment course of emactuzumab, consisting of 5 doses of emactuzumab administered as intravenous infusion once every 2 weeks, with the possibility for retreatment in the case of progression in patients with TGCT.

Therefore, there remains an unmet medical need for alternative therapies for TGCT.

Emactuzumab (formerly RG7155 and RO5509554) is a novel, potent, highly selective, monoclonal immunoglobulin G1 (IgG1) antibody directed against CSF-1R [31,32]. Emactuzumab has a distinct mechanism of action targeting the CSF-1R dimerization interface with high affinity to block ligand-induced- and ligand-independent receptor activation at the surface of cells expressing this receptor, such as macrophages and monocytes in the TGCT microenvironment [31]. By inhibiting CSF-1R and downstream signaling pathways, emactuzumab induces apoptosis of tumor-associated macrophages and reduces recruitment of inflammatory cells to the tumor microenvironment [31]. Emactuzumab selectively binds to human CSF-1R but not to similar tyrosine kinase receptors such as c-Kit and PDGFR, thus enabling highly specific targeting of CSF-1R [31].

Emactuzumab offers a new differentiated treatment option delivered as a short-course intravenous (IV) infusion, with a treatment course of approximately 8 weeks (5 visits). While IV administration requires repeat visits to an infusion center for treatment it has the advantage of ensuring compliance with treatment, enables patient healthcare provider interactions during infusions, and avoids issues of adherence that have been observed with oral anti-cancer medications, including tyrosine kinase inhibitors [33,34]. In addition, because CSF-1R inhibitors are contraindicated in pregnancy for both male and female patients, from a family planning standpoint, short course therapy allows patients to complete a course of treatment and move forward with their lives. The overall treatment duration is also shorter than that of oral TKIs.

In early phase clinical trials, emactuzumab has been explored as a single agent and a combination treatment in patients with advanced solid tumors, and safety data are available in over 450 patients [31,32,35–38]. From the early phase clinical data of emactuzumab in patients with D-TGCT or advanced solid tumors, the optimal biological dose was determined to be 1000 mg once every 2 weeks (Q2W), leading to target saturation and optimal reduction in tumor-associated macrophages in tissue biopsies [39]. In a phase Ia/b, open-label dose-escalation and extension study of 63 adult patients with D-TGCT, the best overall objective response rate over all dose levels was 71% (45/63) in patients treated with emactuzumab, with 3% (2/63) of patients having a complete response and 68% (43/63) a partial response [35]. The disease control rate was 98%, and clinical responses were durable, with objective response rates of 70% and 64% observed at 1- and 2-year follow-up, respectively [35]. Across all patients, the median (min, max) number of treatment cycles administered was 4 (1, 14) [35]. Adverse events reported with emactuzumab were comparable to other CSF-1R agents, with common events including pruritus, asthenia, and various types of edema [35]. Therefore, based on these data and the unmet medical need for therapeutic options for TGCT, the phase III TANGENT study was designed.

1.2. Objectives

The phase III TANGENT study will assess the safety and efficacy of 5 cycles of emactuzumab once every 2 weeks, with the possibility of retreatment in the case of progression, in patients with TGCT.

1.3. Trial design

TANGENT is a randomized, double-blind, global, phase III study (NCT05417789) to investigate the efficacy and safety of emactuzumab versus placebo in patients with TGCT. During the 8-week treatment period, patients enrolled in this study will receive five doses of either emactuzumab or placebo.

The TANGENT study is being conducted at multiple centers in North America, Europe, and Asia. This study includes an option for open-label treatment in adolescent patients (Figure 1). Additionally, adults may receive open-label emactuzumab, if indicated, after the initial six months of the study. The approximate total duration of study participation is 2 years.

2. Methods

2.1. Participants, interventions, and outcomes

This study allows for the enrollment of both adult and adolescent patients (≥12 years of age), per local legislation requirements. Eligible patients must have measurable disease, biopsy-confirmed local or diffuse TGCT, and be determined

as not amenable for surgery by the investigator and one other qualified physician (an orthopedic surgeon or medical oncologist) not involved in this study. The key eligibility criteria for study entry are summarized in Table 1, while the full eligibility criteria are available in Supplemental Table S1.

Adult patients will be randomized (2:1) to receive either 1000 mg of emactuzumab or placebo administered by IV infusion over 90 minutes on day 1 of each 2 week cycle (Q2W) for 5 cycles, or treatment for approximately 8 weeks over a 10-week treatment phase (Figure 2). By comparing to a placebo control, the current study intends to demonstrate that emactuzumab offers a safe and effective treatment in patients with TGCT not amenable to improvement with surgery, including those who have been unsuccessfully treated with other systemic agents. The total duration of the adult double-blind phase of the study is 2 years, which consists of screening, treatment, and follow-up periods. Patients who complete the first 6 months of the double-blind trial and have disease progression (either objective progressive disease as measured locally by noncontrast magnetic resonance imaging [MRI] or symptomatic progression) will be eligible for open-label emactuzumab between visit 10 (day 181) and visit 13 (day 541). Adult patients eligible for open-label emactuzumab will receive the treatment regimen described above, and will be followed for up to 2 years from initial randomization.

Adolescent patients who qualify for the trial and are enrolled will receive open-label emactuzumab. Each patient will receive 1000 mg of emactuzumab administered by IV infusion Q2W over 90 minutes for 5 cycles, or approximately 8 treatment weeks. Follow-up will occur for 21 months after the end of treatment or up to 18 years of age, whichever is longer. If under the age of 18, biannual follow-up will occur after visit 13 (day 541) until 18 years of age.

The primary objective is to assess the efficacy of emactuzumab compared to placebo 6 months from the initiation of treatment by objective response rate (ORR) according to RECIST v1.1 (primary endpoint) and tumor volume score (TVS, key secondary endpoint) based on an independent, blinded central review. Tumor volume score is an estimation of tumor volume relative to the total size of the affected joint or tendon that can provide a more comprehensive measure of disease burden and treatment effects in diffuse TGCT [40]. Additional key secondary endpoints are change in healthcare professional (HCP)-reported joint mobility score by goniometry from baseline to 6 months, and change in patient-reported outcomes (PROs) from baseline to 6 months. Additional secondary endpoints are shown in Table 2 and will assess safety, tolerability, and efficacy, further characterize the pharmacokinetic profile of emactuzumab, and estimate the effect of emactuzumab on surgical intervention rate and clinical benefit and outcome assessments.

2.2. Assignment of interventions

After screening for eligibility, adult patients will be centrally randomized using an Interactive Web Response System in a 2:1 ratio to receive an IV infusion of emactuzumab or placebo Q2W for 5 cycles. Randomization will be stratified by prior tyrosine kinase inhibitor use. Study participants and all persons involved in the conduct of the study will be blinded to treatment (which are indistinguishable from each other) during the primary analysis period. Unblinding prior to the primary analysis data lock can only occur in emergencies on a case-by-case basis if specific emergency treatment would be dictated by knowing the study medication status of the participant.

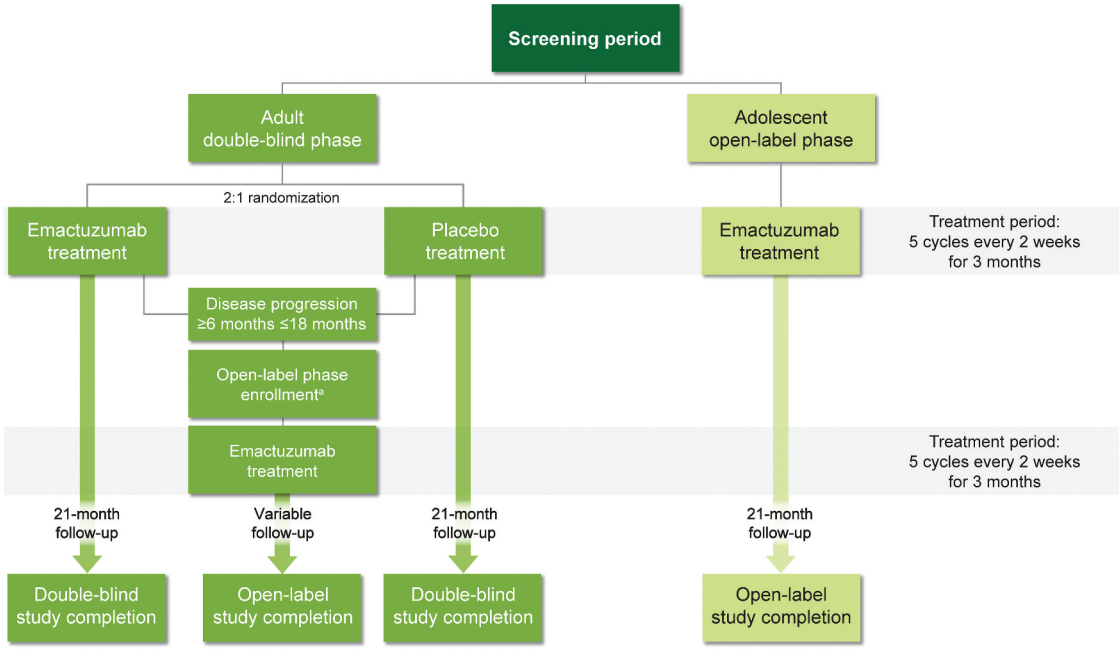


Figure 1. TANGENT Study Design. After screening for eligibility, adults will be randomized 2:1 to emactuzumab or placebo. The treatment period is 8 weeks followed by a 21-month follow-up period. Adults who complete the first 6 months of the double-blind trial and have disease progression (either objective progressive disease as measured locally by magnetic resonance imaging [MRI] or symptomatic progression) will be eligible for open-label emactuzumab between visit 10 (day 181) and visit 13 (day 541). This study includes an option for open-label treatment in adolescent patients.

[a]There must be at least 3 months between the adult double-blind phase and enrollment in the open-label phase.

Table 1. Key eligibility criteria.

Inclusion criteria	Exclusion criteria
Biopsy-confirmed local or diffuse TGCT in which a multidisciplinary tumor board or equivalent[a] determines: • Surgical resection is predicted to not improve or worsen clinical outcomes • There is a high risk of early postoperative recurrence • Patient presents with a significant morbidity or has other reasons for why surgery is not recommended	Metastatic TGCT or TGCT currently affecting multiple joints Prior use of systemic therapy targeting CSF-1 or CSF-1R, any multi-TKI, or any investigational systemic therapy[b] Clinically significant toxicity from prior therapy not resolved to grade ≤1
Measurable disease: ≥20 mm on central read at longest diameter	Active cancer requiring concurrent or planned treatment or a history of malignancy other than TGCT[c]
Adequate organ and bone marrow function: hemoglobin: >10.0 g/dL; neutrophils: >1.5×10^9/L; platelets: >100×10^9/L	Any chemotherapy, radiotherapy,[b] or surgery except for dental treatment
Mean scores of ≥4 on NRS for worst pain and worst stiffness within 7 days prior to randomization based on a ≥4 days of completed diary data[d]	Current or chronic history of liver disease
Negative urine and serum pregnancy test	Patients with autoimmune disease[e]
Contraception use (men and women) during and for a period after treatment ends[f]	Previous exposure to emactuzumab in adult patients enrolled in the double-blind phase

Key inclusion and exclusion criteria for the study. Full eligibility criteria can be found in Supplemental Table S1.
CSF-1, colony-stimulating factor 1; CSF-1R, colony-stimulating factor 1 receptor; NRS, numerical rating scale; TGCT, tenosynovial giant cell tumor; TKI, tyrosine kinase inhibitor.
[a]The multidisciplinary tumor board or equivalent must consist of at least the investigator and one other qualified physician (an orthopedic surgeon or medical oncologist) that is not involved in the study.
[b]Within 3 months of screening or 5 half-lives, whichever is longer.
[c]Except for when there is an expectation that the malignancy has been cured and tumor-specific treatment for the malignancy has not been administered in the last 5 years.
[d]If applicable, patients should be on a stable analgesic regimen for pain for 2 weeks prior to randomization.
[e]Including but not limited to autoimmune thyroid disease, systemic lupus erythematosus, Sjögren syndrome, glomerulonephritis, multiple sclerosis, rheumatoid arthritis, vasculitis, idiopathic pulmonary fibrosis (including bronchiolitis obliterans organizing pneumonia), and inflammatory bowel disease.
[f]Women of childbearing potential must use a highly effective method of contraception throughout the treatment and for 7 months after discontinuation of treatment. Men with partners of childbearing potential or whose partners are pregnant must use barrier contraception for the duration of dosing and for 5 months postdosing, unless surgically sterile.

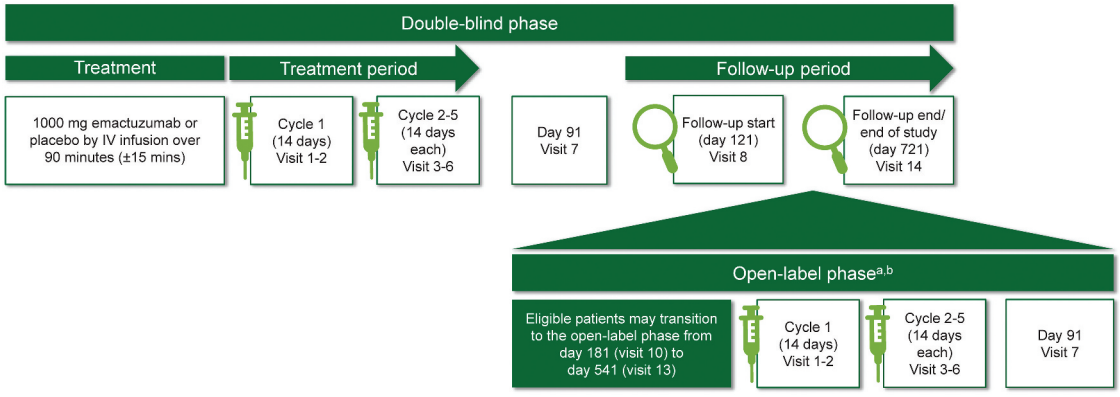


Figure 2. Double-Blind and Open-Label Study Interventions and Schedule of Activities in Adults. During the double-blind phase, patients will receive either 1000 mg of emactuzumab or placebo administered by IV infusion over 90 minutes on day 1 of each 2-week cycle (Q2W) for 5 cycles. Adult patients eligible for open-label emactuzumab will receive the same treatment regimen as in the double-blind phase, and will be followed for up to 2 years from initial randomization.

[a]Patients must wait at least 3 months between the double-blind and open-label treatments. Additional eligibility criteria for patients entering the open-label phase are shown in Supplemental Table S1.

[b]In adults, the follow-up period is up to 2 years after randomization into the double-blind phase. Therefore, depending on the time of entry into the open-label phase, there may be a longer or shorter follow-up period.

Abbreviations: IV, intravenous.

Table 2. Study objectives and endpoints.

Primary objective and endpoint
Effect of emactuzumab on ORR 6 months from initiation of therapy in the blinded phase vs placebo
• ORR by RECIST v1.1 6 months from initiation of therapy based on independent, blinded central review
Key secondary objectives and endpoints
Effect of emactuzumab on clinical outcome assessments:
• ORR by TVS 6 months from initiation of therapy based on independent, blinded central review
• Change in PROMIS-PF TGCT from baseline to 6 months
• Change in physician/healthcare professional-reported joint mobility score by goniometry from baseline to 6 months
• Change in worst pain and worst stiffness NRS from baseline to 6 months
• Change in EQ-5D-5L VAS from baseline to 6 months
Other secondary objectives and endpoints
Effect of emactuzumab on clinical outcome assessments:
• Change in PROMIS-PF TGCT from baseline over time
• Change in the physician/healthcare professional-reported joint mobility score by goniometry from baseline over time
• Change in worst pain and worst stiffness NRS from baseline over time
• Change in EQ-5D-5L VAS from baseline over time
• Change in EQ-5D-5L 5-dimension scores from baseline over time
• Change in SF-12v2 from baseline over time
• Change in PGI-severity from baseline over time
• PGI-change over time
Effect of emactuzumab on durability of response
• DOR by RECIST v1.1 based on independent, blinded central review
Effect of emactuzumab on clinical benefit derived from antitumor activity vs placebo
• DCR per RECIST v1.1 at 6 months based on independent, blinded central review
• TTR by RECIST v1.1 based on independent, blinded central review
• TTP by RECIST v1.1 based on independent, blinded central review
• Change in TVS from baseline over time
Effect of emactuzumab on surgical intervention rate
• Surgical intervention rate[a]
Safety and tolerability of emactuzumab vs placebo
• AEs/deaths
Assess the health economic impact of treatment with emactuzumab
• Healthcare utilization
• Ability to work
Further characterize the pharmacokinetic profile of emactuzumab
• Serum concentrations of emactuzumab

A description of the primary and secondary objectives and endpoints for the study.

Abbreviations: AE, adverse event; DCR, disease control rate; DOR, duration of response; EQ-5D-5L, EuroQOL 5-dimension 5-level questionnaire; NRS, numerical rating scale; ORR, overall response rate; PROMIS-PF, Patient-Reported Outcomes Measurement Information System Physical Function scale; PGI, Patient Global Impressions; RECIST, response evaluation criteria in solid tumors; SF-12v2, Short Form 12-Item Survey version 2; TGCT, tenosynovial giant cell tumor; TTR, time to response; TTP, time to progression; TVS, tumor volume score; VAS, visual analog scale.

[a]Defined as the number of patients who undergo surgery during the study for TGCT.

Discontinuation or modification of study interventions can occur based on investigator discretion, disease progression, or clinically relevant adverse events or lab toxicities that indicate continuation in the study is not in the best interest of the patient.

2.3. Data collection, management, and analysis

Study assessments will be performed prior to study drug administration, unless otherwise specified. The primary endpoint of ORR at 6 months by RECIST 1.1 will be measured by noncontrast MRI scans with contiguous slices (<5 mm) performed at approximately 6 weeks (visit 5) and 13 weeks (visit 7) or at early treatment discontinuation. Subsequently, during the follow-up period, MRI scans will be performed every 6 weeks for up to 6 months, then every 8 weeks for up to 1 year, and then every 12 weeks until study completion.

Disease will be measured by following a target lesion, with its longest diameter ≥20 mm at the diseased joint or tendon, from baseline. Assessments will be made on the longest diameter for the target lesion, and if the lesion becomes too small to measure or disappears completely, it will be recorded as either 5 mm or 0 mm, respectively. Response to treatment will be determined using serial radiologic longest diameter measurements for the target lesion, and RECIST v1.1 will be used for classification of the primary efficacy endpoint. Observed disease response (eg, partial response [PR], complete response [CR]) will be determined by the centrally adjudicated tumor assessment. As a secondary, clinically meaningful measure of response to treatment, the relative volume of the lesion at the diseased joint or tendon will be followed from baseline using TVS by blinded central independent radiology review, which will estimate the tumor volume relative to that of the synovial cavity of the diseased joint or

tendon in 10% increments. Antitumor activity will be further assessed by RECIST v1.1 for duration of response, disease control rate, time to response, and time to progression.

Functional outcomes will be measured by the PROMIS-PF scale, which has been validated in patients with TGCT [41]. Additional secondary endpoints will be measured by additional clinical outcome assessments, and based on the HCP-reported joint mobility score, worst pain and worst stiffness numerical rating score (NRS), Short Form 12-Item Survey version 2 (SF-12v2), Patient Global Impressions (PGI) of Severity and Change for Physical Functioning, Euro-Quality of Life 5-Dimension 5-Level Questionnaire (EQ-5D-5L), and patient interviews.

Safety assessments will include general physical examination, vital signs, electrocardiogram measurements, clinical safety laboratory tests, pregnancy tests, and antidrug antibody testing. Adverse and serious adverse events, as well as adverse events of special interest (AE, SAE, and AESI, respectively) will be monitored throughout the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the investigator will assess severity using the 1–5 scale of the Cancer Therapy Evaluation Program (CTCAE) version 5.0.

Participant retention will be achieved by several strategies. The sponsor has actively focused on a patient-centered approach applied to all trial activities and interactions with trial participants. The study staff at each site will be accessible to participants to answer their questions and respond to any concerns. To minimize the burden on a participant's time, where possible assessments conducted by different departments will be scheduled for the same visit day. Travel expenses will be reimbursed for visits that are study-specific. Practical guidance and suggestions for participant retention will be discussed at the site initiation visits. For participants who withdraw from the trial, no further information will be collected from the date of withdrawal.

2.4. Analysis populations and missing data

Efficacy analyses will be performed in the full analysis set, which will include all randomized patients who receive at least one dose of study drug or placebo. The safety analyses set will include all adults who sign informed consent and receive at least one dose of study drug or placebo. The primary analysis will occur when patients have completed their month 6 visit or withdrawn from the study. For secondary analyses that include data from the whole of the double-blind phase (ie, to month 24), patients that enter the open-label phase will have subsequent data set to missing and assumed to be and a penalized imputation will be used. Data collected after the first dose of study drug in the open-label phase will be summarized under the open-label phase only. Patients who received at least 1 dose of open-label study drug will be included in the open-label full analysis set and open-label safety analysis set.

For ORR, if a participant has a missing or nonevaluable scan at month 6, but has been classified as CR or PR in adjacent scans prior to and after month 6, they will be classified as a responder. Otherwise, they will be classified as a nonresponder. Participants who withdraw from the study or die before the 6-month visit will be classified as nonresponders. For other endpoints, a penalized imputation will be used for participants who discontinue treatment and withdraw from the study for reasons related to TGCT, with the assumption that subsequent data would be associated with a moderately worse change from baseline. For participants who withdraw from the study due to a treatment-related AE, it will be assumed that subsequent data will follow a similar pattern to placebo and therefore a placebo trajectory imputation will be used. For all other missing data, a missing at random (MAR) approach will be used.

2.5. Statistical analyses

Statistical comparisons for ORR, the primary endpoint, and key secondary endpoints will occur in a hierarchical order. If the ORR is met at the ≤0.025 1-sided level, then PROMIS-PF T-scores will be tested sequentially at the ≤0.025 1-sided level. The order of hierarchical testing for the additional key secondary endpoints will be: TVS ORR, HCP-reported joint mobility score, worst stiffness NRS, worst pain NRS, and EuroQol visual analogue scale (EQ-VAS). The ORR is expected to be 10% in the placebo arm and 42% in the emactuzumab arm; therefore, a total of 96 patients (64 emactuzumab and 32 placebo) randomized on a 2:1 basis will provide 90% power based on Fischer's exact test at the 1-sided 2.5% alpha level.

A 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by prior tyrosine kinase inhibitor use (yes/no), at the 2.5% level of significance, will be used to compare month 6 ORR between the two treatment arms for the full analysis. A Fisher's exact test with corresponding exact 95% confidence interval (CI) for the difference in proportions will be provided as a sensitivity analysis. A logistic regression analysis for the FAS will be performed as a sensitivity analysis. The model will include treatment and prior tyrosine kinase inhibitor use as categorical factors. The estimated odds ratio and difference in proportions, along with their associated 2-sided 95% CIs, and the *P* value will be presented.

Subgroup and sensitivity analyses may also be conducted for ORR, the primary endpoint, and key secondary endpoints and will be analyzed in the same way as the primary analysis. Pharmacokinetic analyses will include geometric mean, geometric coefficient of variation, and number of patients with serum concentration of emactuzumab above the limit of quantification. The other secondary endpoints in this study will be analyzed as change from baseline to six months, and change from baseline over time. Safety data will also be summarized and descriptive statistics will be calculated for quantitative safety data.

2.6. Monitoring

The data safety monitoring board (DSMB) consists of three experts at minimum, including a medically qualified chair (with expertise in the field of TGCT, where possible), an expert medical statistician, and a second physician with pertinent clinical and/or DSMB experience. The DMSB will meet approximately every 6 months after the first patient is dosed, and will review the study safety listings and determine if any safety measures or protocol modifications are required.

2.7. Ethics and dissemination

The study was approved by the institutional review board (First (central) IRB approval, WCG IRB; IRB tracking number, 20221064) and independent ethics committee and was conducted according to the recommendations of Good Clinical Practice, Declaration of Helsinki, the Council for International Organizations of Medical Sciences, and any applicable laws and regulations. All patients or their legally authorized representatives provided written informed consent to participate in the study.

Clinical information relating to study participants is strictly held in trust by the site principal investigator, participating investigators, research staff, and the sponsor and their agents. To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken: (1) The number of private/confidential variables collected for each individual has been minimized. The data collected will be limited to that required to address the primary and secondary objectives. (2) Participant data and samples will be identified through use of a unique participant study number assigned to the study participant ("reidentifiable"). The site principal investigator is responsible for the storage of a master file of names and other identifiable data with the participant ID; access to this document will be restricted to members of the research team and authorized persons as listed previously. The master file will be stored securely, and separately, from study data in locked/password-protected databases with passwords kept separately. (3) Separation of the roles responsible for management of identifiers and those responsible for analyzing content. The data will be analyzed by members of the research team, who will be provided with anonymized data identified only by the unique participant study ID. To ensure confidentiality, any data dispersed to investigators will be blinded of any identifying participant information.

Participants will receive ancillary care beyond the scope of the trial as required. Any adverse events or complications arising from trial participation will be promptly addressed, and necessary medical interventions will be provided at no cost to the participants. Ancillary care will extend to managing conditions unrelated to the trial that may arise during the study period, ensuring the overall well-being of the participants. Posttrial care will be provided to participants for any ongoing effects or complications related to the trial interventions. Participants will have access to their routine medical care and follow-up visits, ensuring continuity of care beyond the trial's conclusion. Provisions for compensation will be in place for participants who may suffer harm from trial participation. In the event of an adverse event directly attributable to the study interventions, compensation will cover medical expenses, additional treatments, and any other related costs. The compensation process will be transparent, fair, and in compliance with local regulations and ethical guidelines.

The results from the TANGENT trial will be submitted for presentation at relevant congresses and published in peer-reviewed journals. Patients are still being followed, and long-term follow-up results will be presented in subsequent publications.

3. Conclusion

TGCTs are rare mesenchymal neoplasms affecting joints, bursae, or tendon sheaths that can result in pain, functional impairment, and a reduced quality of life [1–3]. Surgical resection is the primary treatment for TGCT and local resection can be curative; however, additional treatment options are needed for patients with TGCT who are not amenable to surgery [1]. Research on the mechanisms underlying TGCT has led to the development of therapeutic agents targeting CSF-1R signaling as a treatment option for patients with TGCT that cannot be managed with surgery [1,20,21]. Pexidartinib, an oral tyrosine kinase inhibitor (TKI) inhibitor that blocks CSF-1R signaling, was the first systemic targeted therapy approved for TGCT; however, it is only available through a risk mitigation strategy (REMS program) in the US due to potential for hepatotoxicity, which precluded approval in the EU [23,27,28]. Subsequently, additional oral TKI inhibitors have been approved for the treatment of TGCT in some countries, offering additional treatment options for TGCT [24,26,29,30]. Future TGCT treatments, including novel targeted CSF-1R therapies, have the potential to further shift the treatment landscape from dependence on surgery or chronic treatments to systemic approaches that offer clinically meaningful tumor reduction, pain relief, and functional gains, with manageable toxicity, shortened treatment duration, and reduced tumor recurrence in patients with TGCT.

Emactuzumab is a novel, IV-administered, monoclonal immunoglobulin G1 antibody against the CSF-1R, with a unique mechanism of action (blocking the receptor dimerization interface) and a short treatment duration, with the potential to offer durable benefit without the challenges associated with chronic oral therapies [31,32,35].

The TANGENT trial will evaluate the safety and efficacy of emactuzumab in adult and adolescent patients with TGCT. The trial design is consistent with prior trials for targeted CSF-1R therapies in patients with TGCT (ie, ENLIVEN, MOTION, and MANEUVER), including similar design, study population, and primary and secondary endpoints. TANGENT is a double-blind placebo-controlled phase III study with a study population comprised of patients with TGCT not amenable to surgery. The primary objective of TANGENT was ORR at six months, as measured by RECIST v1.1 (primary endpoint) and tumor volume score (TVS) (key secondary). Additional key secondary endpoints included clinically functional endpoints to evaluate the effect of emactuzumab on range of motion, pain, stiffness, and functional outcomes (PROMIS PF) [28–30,42]. Differences between TANGENT and prior trials for targeted CSF-1R therapies in patients with TGCT include earlier MRI assessment in TANGENT (first postbaseline assessment at 6 weeks vs 13 weeks) and exclusion of patients with prior TKI treatment in TANGENT.

The TANGENT study introduces a distinctive treatment paradigm for TGCT, and is the only study evaluating a short-course, intravenous CSF-1R antibody, rather than continuous oral inhibition. PROs will also be prospectively assessed after treatment, which are relevant for treatment decisions [43]. If sustained tumor control, functional improvement, and meaningful patient-reported benefit can be demonstrated after

completing a treatment course, emactuzumab could represent a shift toward a time-limited, disease-modifying therapeutic option to help reduce hospital visits, lower economic costs, and potentially improve patients' quality of life.

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Author contributions

CRediT: **Hans Gelderblom:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Emanuela Palmerini:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Michiel van de Sande:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Javier Martin-Broto:** Investigation, Resources, Writing – review & editing; **Gabriel Tinoco:** Investigation, Resources, Writing – review & editing; **Elyse Seltzer:** Methodology, Supervision, Writing – original draft; **Madhu Davies:** Methodology, Supervision, Writing – original draft; **Ruth Coll:** Methodology, Supervision, Writing – original draft; **Sander Veltkamp:** Conceptualization, Methodology, Writing – original draft; **Jean-Yves Blay:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Javier Martin-Broto: Received honoraria for consulting or advisory board participation and expert testimony from PharmaMar, Bayer, GSK, Deciphera, Boehringer Ingelheim, Cogent Biosciences, Roche, Tecnofarma, and Asofarma and research funding for clinical studies (institutional) from Deciphera, PharmaMar, Eli Lilly and Company, BMS, Pfizer, Boehringer Ingelheim, SynOx, Abbisko, Biosplice, Lixte, Karyopharm, Rain Therapeutics, INHIBRX, Immunome, Philogen, Cebiotex, PTC Therapeutics Inc., and SpringWorks therapeutics. Javier Martin-Broto is CEO of Sarcoma Research Solutions.

Gabriel Tinoco: Served on advisory boards for SynOx, Servier, Deciphera, and Merck Serono.

Elyse Seltzer, **Madhu Davies**, and **Ruth Coll** are employees and **Sander Veltkamp** is a former employee of SynOx Therapeutics.

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A reviewer on this manuscript has disclosed that they have once presented a talk on the multidisciplinary care of TGCT that was sponsored by Daichi Sankyo, more than 1 year ago. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Ethical declaration

The study was approved by the institutional review board (First (central) IRB approval, WCG IRB; IRB tracking number, 20221064) and independent ethics committee and was conducted according to the recommendations of Good Clinical Practice, Declaration of Helsinki, the Council for International Organizations of Medical Sciences, and any applicable laws and regulations. All patients or their legally authorized representatives provided written informed consent to participate in the study.

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Data availability statement

All relevant information for the study design is included in this manuscript. The datasets generated and/or analyzed during the present study are not publicly available because the trial is ongoing and the primary results have not yet been published. Deidentified participant data and related documents, the full protocol (SNX-301–020, IND number 153633, July 16, 2025) and the statistical analysis plan may be made available from the corresponding author upon reasonable request, subject to appropriate approvals and execution of a data-sharing agreement. Plans for data entry, coding, security, and storage, including any related processes to promote data quality are fully described in the Data Management Plan which may be made available from the corresponding author upon reasonable request, subject to appropriate approvals and execution of a data-sharing agreement.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Stacchiotti S, Dürr HR, Schaefer I-M, et al. Best clinical management of tenosynovial giant cell tumour (TGCT): a consensus paper from the community of experts. Cancer Treat Rev. 2023;112:102491. doi: 10.1016/j.ctrv.2022.102491
   •• **A recent publication on evidence-based practice recommendations for the optimal approach to TGCT based on global expert consensus.**
2. Chan AS, Katiyar V, Dy P, et al. Updates on the treatment of tenosynovial giant cell tumor. Hematol Oncol STEM Cell Ther. 2023;16(4):307–315. doi: 10.56875/2589-0646.1032

3. Burton TM, Ye X, Parker ED, et al. Burden of illness associated with tenosynovial giant cell tumors. Clin Ther. 2018;40(4):593–602.e1. doi: 10.1016/j.clinthera.2018.03.001
4. Kager M, Kager R, Fałek R, et al. Tenosynovial giant cell tumor. Folia Med Cracov. 2022;62(2):93–107. doi: 10.24425/fmc.2022.141702
5. Gelhorn HL, Tong S, McQuarrie K, et al. Patient-reported symptoms of tenosynovial giant cell tumors. Clin Ther. 2016;38(4):778–793. doi: 10.1016/j.clinthera.2016.03.008
6. Al-Nakshabandi NA, Ryan AG, Choudur H, et al. Pigmented villonodular synovitis. Clin Radiol. 2004;59(5):414–420. doi: 10.1016/j.crad.2003.11.013
7. Stern S, McKenzie PF, Bernthal N, et al. Localized and diffuse tenosynovial giant cell tumor: real-world results from a patient observational registry. Future Oncol. 2025;21(12):1501–1510. doi: 10.1080/14796694.2025.2488635
8. Bernthal NM, Spierenburg G, Healey JH, et al. The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective multicenter study. Orphanet J Rare Dis. 2021;16(1):191. doi: 10.1186/s13023-021-01820-6
9. Ehrenstein V, Andersen SL, Qazi I, et al. Tenosynovial giant cell tumor: incidence, prevalence, patient characteristics, and recurrence. A Registry-based cohort study in Denmark. J Rheumatol. 2017;44(10):1476–1483. doi: 10.3899/jrheum.160816
10. Lin F, Ionescu-Ittu R, Pivneva I, et al. The economic burden of tenosynovial giant cell tumors among employed workforce in the United States. J Occup Environ Med. 2021;63(4):e197–e202. doi: 10.1097/JOM.0000000000002159
11. Spierenburg G, Ballesteros CS, Stoel BC, et al. MRI of diffuse-type tenosynovial giant cell tumour in the knee: a guide for diagnosis and treatment response assessment. Insights Imag. 2023;14(1):22. doi: 10.1186/s13244-023-01367-z
12. Siegel M, Bode L, Südkamp N, et al. Treatment, recurrence rates and follow-up of tenosynovial giant cell tumor (TGCT) of the foot and ankle-A systematic review and meta-analysis. PLOS ONE. 2021;16(12):e0260795. doi: 10.1371/journal.pone.0260795
13. Humbert P, Vialle C, Chevalerias M, et al. Targeting the colony-stimulating factor 1 axis for the treatment of tenosynovial giant cell tumors. Cytokine Growth Factor Rev. 2025;86:137–148. doi: 10.1016/j.cytogfr.2025.10.007
14. West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci USA. 2006;103(3):690–695. doi: 10.1073/pnas.0507321103

•• **Identified overexpression of CSF1 and CSF-R1 in TGCT and the target alteration which led to all CSF1R inhibitoers in this disease.**

15. Stanley ER, Berg KL, Einstein DB, et al. Biology and action of colony–stimulating factor-1. Mol Reprod Dev. 1997;46(1):4–10. doi: 10.1002/(SICI)1098-2795(199701)46:1<4:AID-MRD2>3.0.CO;2-V
16. Mastboom MJL, Hoek DM, Bovée JVMG, et al. Does CSF1 overexpression or rearrangement influence biological behaviour in tenosynovial giant cell tumours of the knee? Histopathology. 2019;74(2):332–340. doi: 10.1111/his.13744
17. Tap WD, Healey JH. Role of colony-stimulating factor 1 in the neoplastic process of tenosynovial giant cell tumor. Tumour Biol. 2022;44(1):239–248. doi: 10.3233/TUB-220005
18. Mastboom MJ, Planje R, van de Sande MA. The patient perspective on the impact of tenosynovial giant cell tumors on daily living: crowdsourcing study on physical function and quality of life. Interact J Med Res. 2018;7(1):e4. doi: 10.2196/ijmr.9325
19. Spierenburg G, van der Heijden L, Mastboom MJL, et al. Surgical management of 144 diffuse-type TGCT patients in a single institution: a 20-year cohort study. J Surg Oncol. 2022;126(6):1087–1095. doi: 10.1002/jso.26991
20. Wytiaz V, Siegel G, Chugh R. Emerging therapeutics in the management of tenosynovial giant cell tumor (TGCT). Expert Rev Anticancer Ther. 2024;24(12):1229–1236. doi: 10.1080/14737140.2024.2445754
21. Assi T, Moussa T, Ngo C, et al. Therapeutic advances in tenosynovial giant cell tumor: targeting the CSF1/CSF1R axis. Cancer Treat Rev. 2025;134:102904. doi: 10.1016/j.ctrv.2025.102904
22. Colman MW, Ye J, Weiss KR, et al. Does combined open and arthroscopic synovectomy for diffuse PVNS of the knee improve recurrence rates? Clin Orthop Relat Res. 2013;471(3):883–890. doi: 10.1007/s11999-012-2589-8
23. Turalio. Prescribing information. Daiichi Sankyo. 2019 [cited 2026 Feb 5]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211810s009lbl.pdf
24. Romvimza. Prescribing information. Deciphera Pharmaceuticals LLC; 2025 [cited 2026 Feb 5]. Available from: https://www.romvimza.com/content/files/prescribing-information.pdf
25. Caldwell TM, Ahn YM, Bulfer SL, et al. Discovery of vimseltinib (DCC-3014), a highly selective CSF1R switch-control kinase inhibitor, in clinical development for the treatment of tenosynovial giant cell tumor (TGCT). Bioorg Med Chem Lett. 2022;74:128928. doi: 10.1016/j.bmcl.2022.128928
26. Pimicotinib. NMPA approval information. National Medical products administration. 2025 [cited 2026 Feb 5]. Available from: https://www.nmpa.gov.cn/
27. Wagner AJ, Tap WD, Bauer S, et al. Long-term efficacy and safety of pexidartinib in patients with tenosynovial giant cell tumor: final results of the ENLIVEN study. Oncologist. 2025;30(7):oyae345. doi: 10.1093/oncolo/oyae345
28. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet. 2019;394(10197):478–487. doi: 10.1016/S0140-6736(19)30764-0

•• **The pivotal ENLIVEN trial, which evaluated targeting CSF-1R with pexidartinib in patients with TGCT, leading to the approval of the first targeted CSF-1R therapy.**

29. Gelderblom H, Bhadri V, Stacchiotti S, et al. Vimseltinib versus placebo for tenosynovial giant cell tumour (MOTION): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403(10445):2709–2719. doi: 10.1016/S0140-6736(24)00885-7

• **The pivotal trial of the second TKI in this disease, first approved in EU.**

30. Xu H, Niu X, Ravi V, et al. Pimicotinib versus placebo for tenosynovial giant cell tumour (MANEUVER): an international, randomised, placebo-controlled, phase 3 trial. Lancet. 2026;407(10533):1072–1083. doi: 10.1016/S0140-6736(25)02602-9

• **The pivotal trial of pimicotinib.**

31. Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell. 2014;25(6):846–859. doi: 10.1016/j.ccr.2014.05.016

•• **Preclinical and clinical study showing the anti CSF1R activity of emactuzumab.**

32. Gomez-Roca CA, Italiano A, Le Tourneau C, et al. Phase I study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. Ann Oncol. 2019;30(8):1381–1392. doi: 10.1093/annonc/mdz163
33. Seal BS, Anderson S, Shermock KM. Factors associated with adherence rates for oral and intravenous anticancer therapy in commercially insured patients with metastatic colon Cancer. J Manag Care Spec Pharm. 2016;22(3):227–235. doi: 10.18553/jmcp.2016.22.3.227
34. Shen C, Zhao B, Liu L, et al. Adherence to tyrosine kinase inhibitors among Medicare part D beneficiaries with chronic myeloid leukemia. Cancer. 2018;124(2):364–373. doi: 10.1002/cncr.31050
35. Cassier PA, Italiano A, Gomez-Roca C, et al. Long-term clinical activity, safety and patient-reported quality of life for emactuzumab-treated patients with diffuse-type tenosynovial giant-cell tumour. Eur J Cancer. 2020;141:162–170. doi: 10.1016/j.ejca.2020.09.038

•• **Phase 1 study that demonstrated the long-term clinical benefit and safety of emactuzumab in patients with diffuse TGCT.**

36. Gomez-Roca C, Cassier P, Zamarin D, et al. Anti-CSF-1R emactuzumab in combination with anti-PD-L1 atezolizumab in advanced solid tumor patients naive or experienced for immune checkpoint blockade. J Immunother Cancer. 2022;10(5):e004076. doi: 10.1136/jitc-2021-004076
37. Machiels J-P, Gomez-Roca C, Michot J-M, et al. Phase ib study of anti-CSF-1R antibody emactuzumab in combination with CD40 agonist selicrelumab in advanced solid tumor patients. J Immunother Cancer. 2020;8(2):e001153. doi: 10.1136/jitc-2020-001153
38. Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. Lancet Oncol. 2015;16(8):949–956. doi: 10.1016/S1470-2045(15)00132-1
39. Smart K, Bröske A-M, Rüttinger D, et al. PK/PD mediated dose optimization of emactuzumab, a CSF1R inhibitor, in patients with advanced solid tumors and diffuse-type tenosynovial giant cell tumor. Clin Pharmacol Ther. 2020;108(3):616–624. doi: 10.1002/cpt.1964
40. Peterfy C, Chen Y, Countryman P, et al. CSF1 receptor inhibition of tenosynovial giant cell tumor using novel disease-specific MRI measures of tumor burden. Future Oncol. 2022;18(12):1449–1459. doi: 10.2217/fon-2021-1437
•• **Identified TVS (estimated tumor volume relative to the size of the involved joint cavity or tendon sheath) and m-RECIST (linear short-axis measurements rather than the longest diameters) to be better than RECIST in assessing the effectiveness of treatment in TGCT.**
41. Gelhorn HL, Ye X, Speck RM, et al. The measurement of physical functioning among patients with tenosynovial giant cell tumor (TGCT) using the patient-reported outcomes measurement information System (PROMIS). J Patient Rep Outcomes. 2019;3(1):6. doi: 10.1186/s41687-019-0099-0
42. Niu X, Ravi V, Shan B, et al. MANEUVER: a phase III study of pimicotinib to assess efficacy and safety in tenosynovial giant cell tumor patients. Future Oncol. 2026;22(5):507–514. doi: 10.1080/14796694.2024.2396227
43. Palmerini E, Healey JH, Bernthal NM, et al. Tenosynovial giant cell tumor observational platform project (TOPP) Registry: a 2-year analysis of patient-reported outcomes and treatment strategies. Oncologist. 2023;28(6):e425–e435. doi: 10.1093/oncolo/oyad011
• **The first analysis to assess the impact of D-TGCT on PRO as a prospective 2-year follow-up that could represent a benchmark for future clinical trials.**