Primary Analysis of TANGENT: A Phase 3 Randomised Trial Evaluating the Safety and Efficacy of Emactuzumab in Patients With Tenosynovial Giant Cell Tumours

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Disclosures

- Hans Gelderblom received institutional financial compensation for enrolling patients in TGCT studies or advisory board/speaker compensation for TGCT studies from Abbisko, AmMax Bio, Daiichi Sankyo, Deciphera, Merck, and SynOx Therapeutics

TGCT, tenosynovial giant cell tumour.

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Background and Objectives

- TGCT is a rare, locally aggressive mesenchymal neoplasm of the synovium that causes debilitating reductions in joint function and range of motion in addition to pain, stiffness, and joint destruction[1–3]
  - Tumours emerge due to *CSF-1* gene translocation in a small population of neoplastic synovial cells, leading to persistent overexpression of CSF-1 and perpetual chronic inflammation dominated by CSF-1R-expressing macrophages[4]
- Surgery is standard-of-care treatment; however, postsurgical recurrence is common and many tumours are not amenable to surgery[1,5]
- Treatment with oral TKIs targeting CSF-1R requires chronic administration[6,7]
- Emactuzumab is a novel intravenous monoclonal antibody in development for the treatment of TGCT that inhibits CSF-1R and has demonstrated durable tumour response with only an 8-week course of therapy[8,9]

We present the primary 6-month analysis of the Phase 3 TANGENT trial evaluating the efficacy and safety of emactuzumab, the only short-course treatment in late-stage development for TGCT

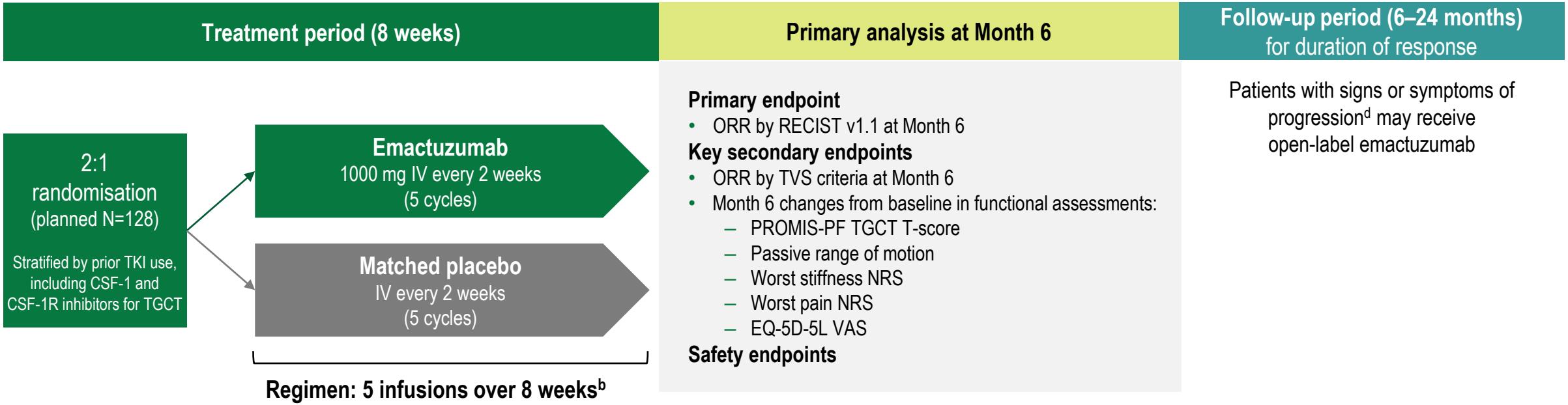
CSF-1(R), colony-stimulating factor-1 (receptor); TGCT, tenosynovial giant cell tumour; TKI, tyrosine kinase inhibitor.

1. Stacchiotti S, *et al*. Cancer Treat Rev 2023;112:102491. 2. Gelhorn HL, *et al*. Clin Ther 2016;38:778–93. 3. Ward TRW, *et al*. J Clin Med 2026;15:2238. 4. Tap WD and Healey JH. Tumour Biol 2022;44:239–48.
5. The TGCT UK Consortium. Bone Jt Open 2026;7:482–90. 6. Romvimza (vimseltinib) USPI. June 2026. 7. Turalio (pexidartinib) USPI. January 2025. 8. Ries CH, *et al*. Cancer Cell 2014;25:846–59. 9. Cassier PA, *et al*. Eur J Cancer 2020;141:162–70.

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TANGENT Trial Design

Global, randomised, double-blind, placebo-controlled Phase 3 trial in 12 countries[a] (NCT05417789)[1]



Key eligibility criteria[c]

Adult patients with biopsy-confirmed localised or diffuse TGCT for whom surgical resection would be associated with:

- Predicted worsening of functional limitations through surgical joint damage, and/or
- Anticipated high risk of early recurrence (as determined by MTB or equivalent) or any other morbidity associated with the surgery, and/or
- No expected improvement in clinical outcomes

[a]Belgium, Canada, France, Italy, the Netherlands, South Korea, Spain, Sweden, Switzerland, Taiwan, UK, and USA. [b]The protocol specified treatment discontinuation for patients who had laboratory enzyme elevations requiring more than two dose delays (this was resolved later in the study by a protocol amendment clarifying the requirement for dose delay due to enzyme elevations). [c]Other key eligibility criteria: measurable disease (longest diameter ≥20 mm on central read), minimum mean score of 4 on NRS for worst pain during 7 days prior to randomisation, and minimum mean score of 4 on NRS for worst stiffness during 7 days prior to randomisation. [d]Patients randomised to emactuzumab or placebo with disease progression (objective progressive disease as measured locally by MRI or symptomatic progression) were eligible for open-label emactuzumab. CSF-1(R), colony-stimulating factor-1 (receptor); EQ-5D-5L, EuroQol 5 Dimension, 5 Level questionnaire; IV, intravenous; MRI, magnetic resonance imaging; MTB, multidisciplinary tumour board; NRS, numerical rating scale; ORR, objective response rate; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function Scale; RECIST, Response Evaluation Criteria in Solid Tumors; TGCT, tenosynovial giant cell tumour; TKI, tyrosine kinase inhibitor; TVS, tumour volume score; VAS, visual analogue scale.

1. Gelderblom H, *et al.* Future Oncol 2026;22:2109–19.

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Baseline Demographics and Clinical Characteristics

		Emactuzumab (n=91)	Placebo (n=45)	Total (N=136)
Mean (SD) age, years		43 (13)	42 (12)	43 (13)
Female, n (%)		51 (56)	26 (58)	77 (57)
Female of childbearing potential, n (%)		31 (61)	18 (69)	49 (64)
Race, n (%)	White	44 (48)	18 (40)	62 (46)
	Asian	7 (8)	6 (13)	13 (10)
	Black/African American	3 (3)	1 (2)	4 (3)
	Not reported/Other/Unknown	37 (41)	20 (44)	57 (42)
Region, n (%)	Europe	69 (76)	31 (69)	100 (74)
	North America	19 (21)	8 (18)	27 (20)
	Asia	3 (3)	6 (13)	9 (7)
Location of TGCT target tumour, n (%)	Knee	60 (66)	29 (64)	89 (65)
	Ankle	10 (11)	7 (16)	17 (13)
	Hip	8 (9)	4 (9)	12 (9)
	Wrist	5 (5)	4 (9)	9 (7)
	Other[a]	8 (9)	1 (2)	9 (7)
TGCT type, n (%)	Localised	33 (36)	12 (27)	45 (33)
	Diffuse	58 (64)	33 (73)	91 (67)
Mean (SD) time from first TGCT diagnosis to first dose, months		64 (63)	64 (75)	64 (67)

[a]Other locations of TGCT target tumours included foot (n=3), elbow (n=2), toe (n=1), spine (n=1), jaw (n=1), and thumb/wrist (n=1).
SD, standard deviation; TGCT, tenosynovial giant cell tumour.

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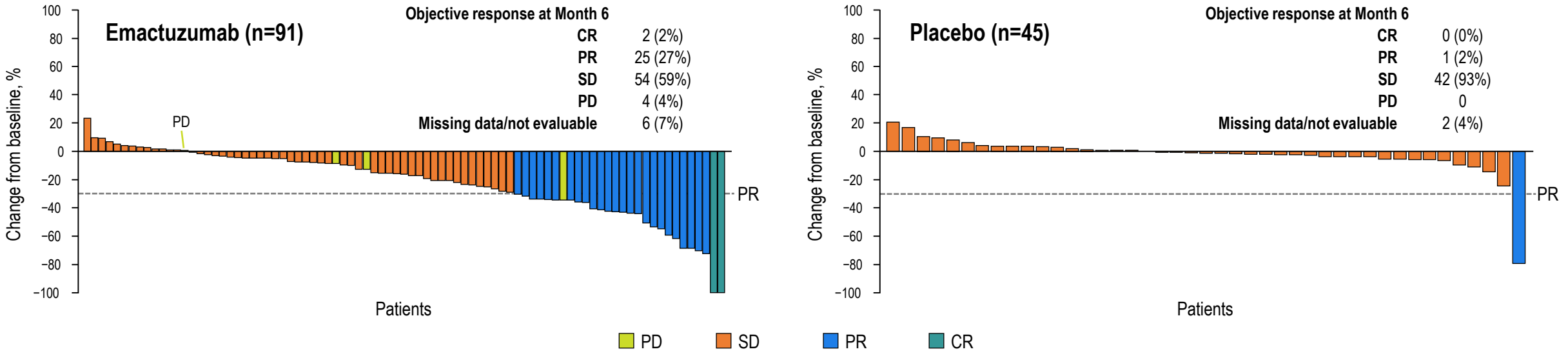
TGCT Treatment History at Baseline

		Emactuzumab (n=91)	Placebo (n=45)	Total (N=136)
Any previous TGCT-related surgeries, n (%)		60 (66)	29 (64)	89 (65)
Number of previous surgeries, n (%)	0	31 (34)	16 (36)	47 (35)
	1	26 (29)	12 (27)	38 (28)
	2	22 (24)	11 (24)	33 (24)
	≥3	12 (13)	6 (13)	18 (13)
Any prior non-surgical TGCT therapy[a,b]		32 (35)	13 (29)	45 (33)
Any prior TKI use		27 (30)	12 (27)	39 (29)
Imatinib		20 (22)	7 (16)	27 (20)
Nilotinib		3 (3)	2 (4)	5 (4)
Pexidartinib		3 (3)	1 (2)	4 (3)
Pazopanib		1 (1)	2 (4)	3 (2)
Yttrium/radiotherapy		6 (7)	1 (2)	7 (5)
Investigational/blinded drug (unknown)		2 (2)	2 (4)	4 (3)

[a]Categories are not mutually exclusive and patients may have received more than one therapy. [b]Four patients had received prior vimseltinib and one had received lacnotuzumab for TGCT (reported without treatment-group attribution due to low frequency and potential for functional unblinding).
TGCT, tenosynovial giant cell tumour; TKI, tyrosine kinase inhibitor.

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Objective Response Rate (RECIST v1.1) at Month 6 (Primary Endpoint)



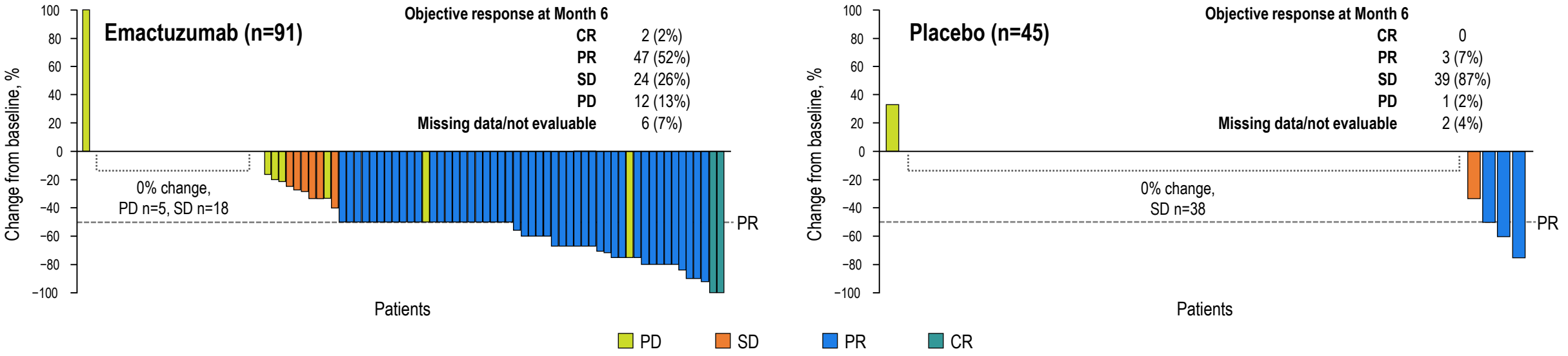
	Emactuzumab (n=91)	Placebo (n=45)
ORR[a] by RECIST v1.1, n (%)	27 (30)	1 (2)
Difference (95% CI)[b]	28% (16, 39); p<0.001	

At Month 6, emactuzumab demonstrated a statistically significant improvement in ORR by RECIST v1.1 compared with placebo (30% vs 2%). Most emactuzumab responders (70%) had responded by Week 6 (first MRI assessment)

[a]CR or PR according to RECIST v1.1 at 6-month assessment. [b]Common risk difference stratified by prior TKI use; CI calculated using the Miettinen and Nurminen method; p value calculated using the Cochran–Mantel–Haenszel test stratified by prior TKI use.
CI, confidence interval; CR, complete response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

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Objective Response Rate (TVS Criteria) at Month 6 (Key Secondary Endpoint)



	Emactuzumab (n=91)	Placebo (n=45)
ORR[a] by TVS criteria, n (%)	49 (54)	3 (7)
Difference (95% CI)[b]	48% (34, 59); p<0.001	

At Month 6, emactuzumab demonstrated a statistically significant improvement in ORR by TVS criteria compared with placebo (54% vs 7%). Most emactuzumab responders (78%) had responded by Week 6 (first MRI assessment)

[a]CR or PR according to TVS criteria at 6-month assessment. [b]Common risk difference stratified by prior TKI use; CI calculated using the Miettinen and Nurminen method; p value calculated using the Cochran–Mantel–Haenszel test stratified by prior TKI use.
CI, confidence interval; CR, complete response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TVS, tumour volume score.

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Best Overall Response During 6 Months

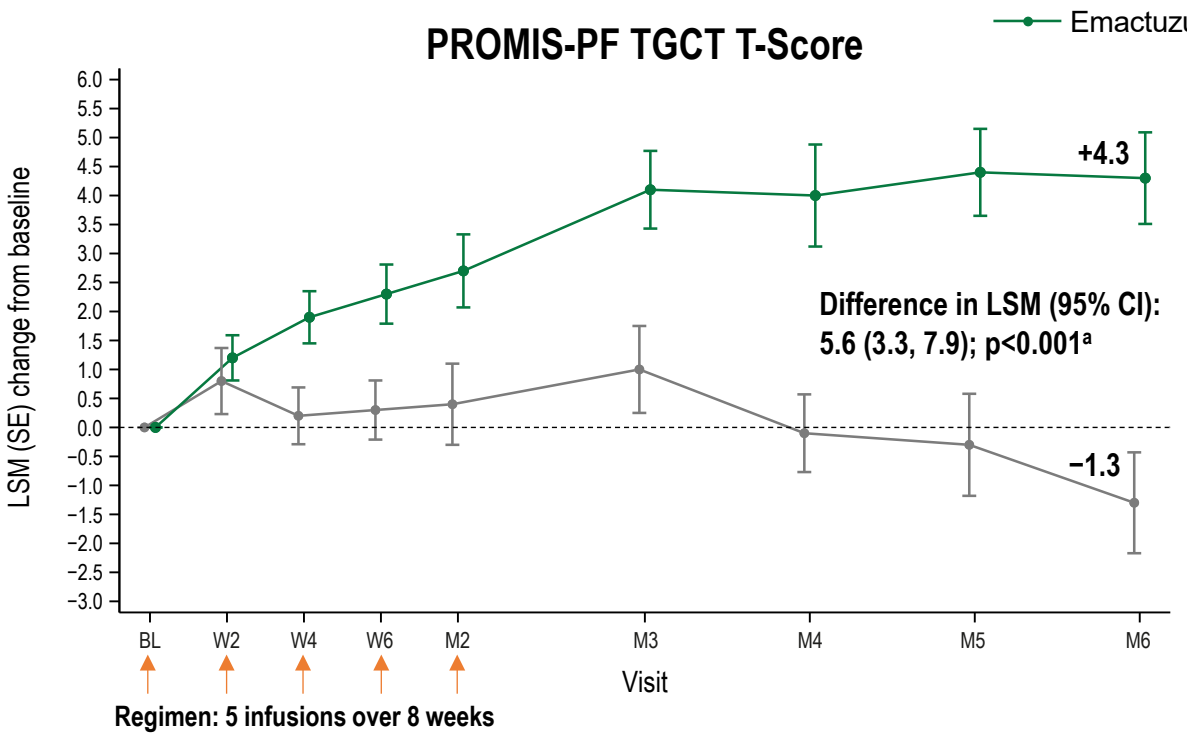
	RECIST v1.1		TVS Criteria	
BOR during 6 months, n (%)	Emactuzumab (n=91)	Placebo (n=45)	Emactuzumab (n=91)	Placebo (n=45)
CR	3 (3)	0	3 (3)	0
PR	37 (41)	1 (2)	62 (68)	3 (7)
SD	50 (55)	43 (96)	25 (27)	41 (91)
Missing data/not evaluable	1 (1)	1 (2)	1 (1)	1 (2)
PD	0	0	0	0
BOR[a]	40 (44)	1 (2)	65 (71)	3 (7)

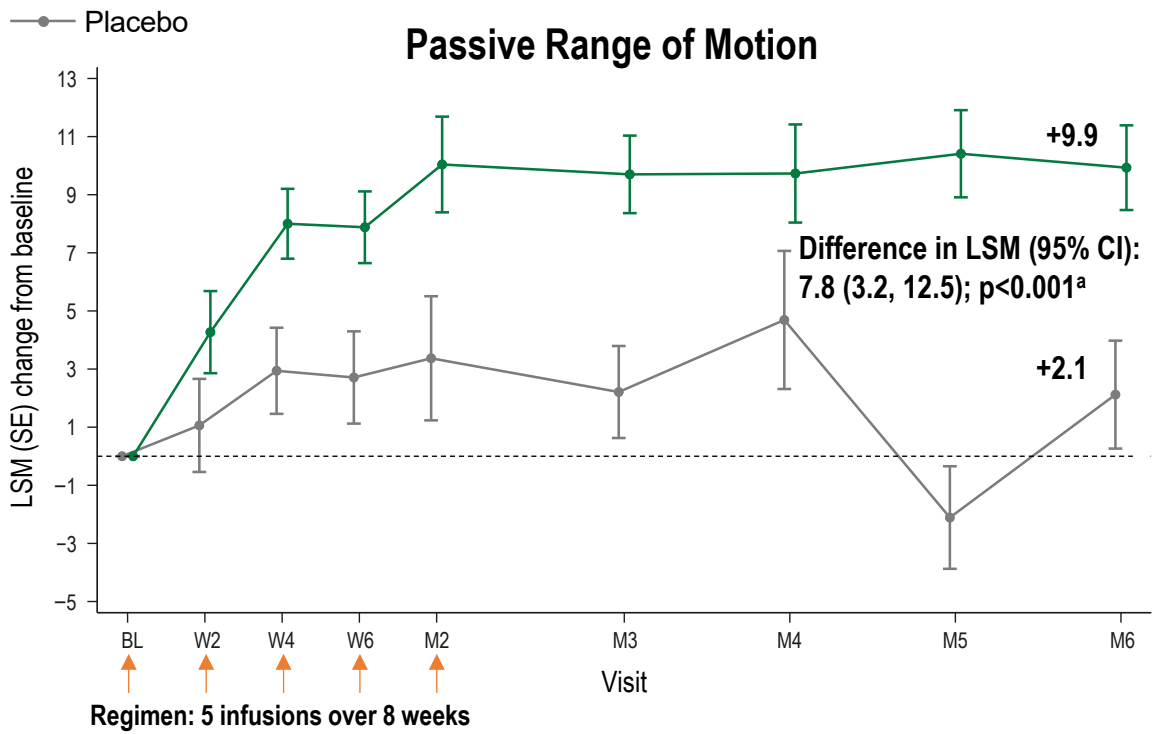
Of patients receiving emactuzumab, 44% and 71% responded according to RECIST v1.1 and TVS criteria, respectively, at some point up to 6 months from baseline

[a]Best response of PR or CR at some point during the first 6 months.
BOR, best overall response, CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TVS, tumour volume score.

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Change at Month 6 in Physical Function and Range of Motion





- In the emactuzumab group, 43/81 (53%) patients had an improvement of ≥3 points[1] in PROMIS-PF TGCT T-score versus 12/44 (27%) in the placebo group at Month 6

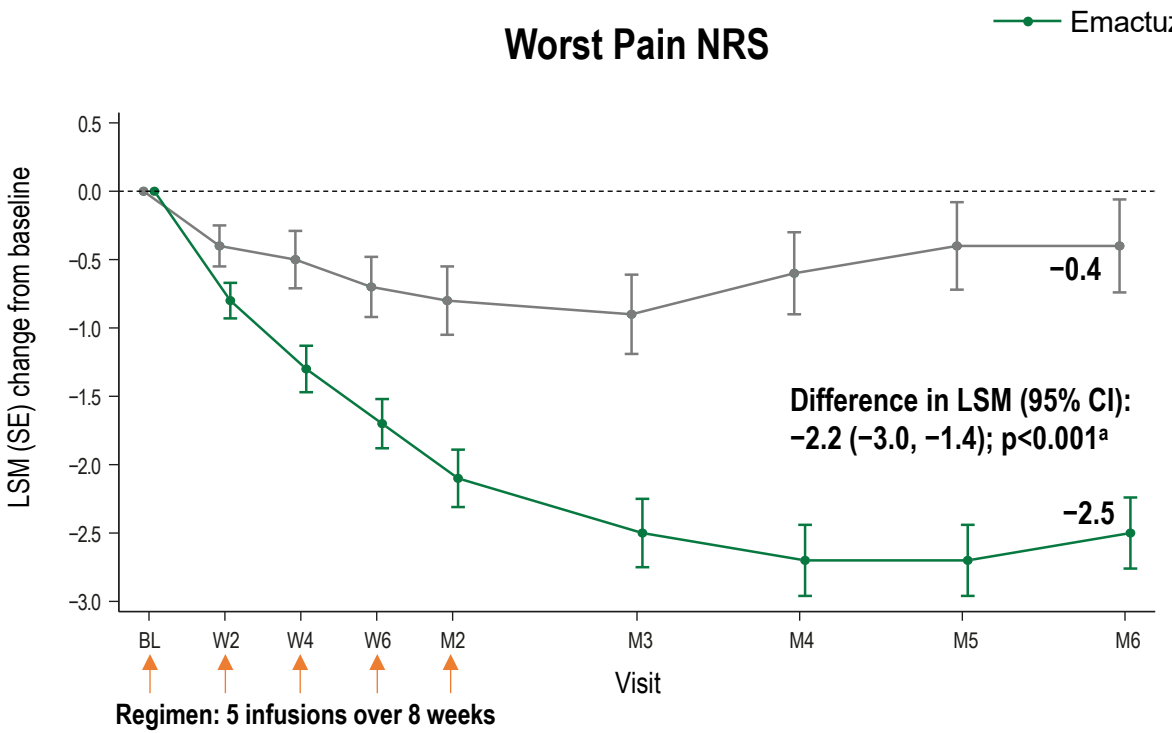
Emactuzumab was associated with rapid and durable clinically meaningful improvements in physical function and range of motion. Differences versus placebo were statistically significant from Week 4 (after two doses) onwards

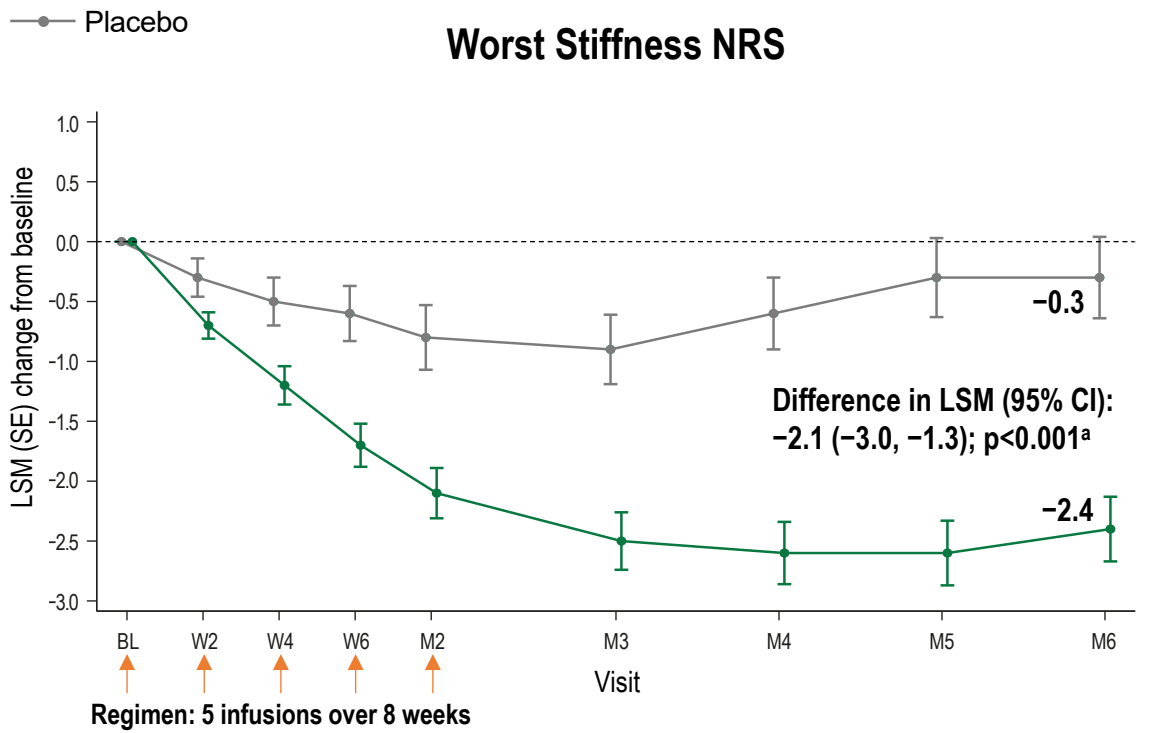
[a]Estimates are from a mixed model for repeated measures with fixed effects for treatment, visit, and the interaction between treatment and visit, and covariates for prior TKI use (yes/no) and baseline score.
BL, baseline; CI, confidence interval; LSM, least-squares mean; M, Month; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function Scale; SE, standard error; TGCT, tenosynovial giant cell tumour; TKI, tyrosine kinase inhibitor; W, Week.

1. Speck RM, *et al.* J Patient Rep Outcomes 2020;4:61.

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Change at Month 6 in Pain, Stiffness, and Quality of Life





- QoL (EQ-5D-5L VAS) showed a numerically greater improvement with emactuzumab (+2.0) compared with placebo (−0.4) at Month 6 (LSM difference [95% CI]: 2.4 [−4.2, 9.1]; p=0.238)[a]

Emactuzumab was associated with rapid and durable clinically meaningful reductions in pain and joint stiffness. Differences versus placebo were statistically significant by Week 2 (after one dose) onwards

[a]Estimates are from a mixed model for repeated measures with fixed effects for treatment, visit, and the interaction between treatment and visit, and covariates for prior TKI use (yes/no) and baseline score.
BL, baseline; CI, confidence interval; EQ-5D-5L, EuroQol 5 Dimension, 5 Level questionnaire; LSM, least-squares mean; M, Month; NRS, numerical rating scale; QoL, quality of life; SE, standard error; TKI, tyrosine kinase inhibitor; VAS, visual analogue scale; W, Week.

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Safety Overview

AEs, n (%)	Emactuzumab (n=91)	Placebo (n=45)
Any AE	91 (100)	38 (84)
Grade ≥3	48[a] (53)	7 (16)
Most common AEs (any grade) occurring in ≥25% of patients in the emactuzumab group		
Pruritus	69 (76)	11 (24)
Periorbital oedema	65 (71)	3 (7)
Oedema peripheral	41 (45)	5 (11)
Fatigue	40 (44)	11 (24)
Face oedema	36 (40)	1 (2)
Blood CPK increased	28 (31)	1 (2)
Hypertension	23 (25)	4 (9)
Any treatment-related AE	91 (100)	31 (69)
Grade ≥3	44 (48)	1 (2)
Any serious AE	14 (15)	2 (4)
Any AE leading to death	0	0
Median (range) overall treatment duration, days	58 (1, 89)	57 (54, 71)

- Pruritus events were predominantly mild/moderate in severity, were observed during dosing, and improved or resolved over time
- A total of 21 serious AEs were observed among 14 patients in the emactuzumab group
- No signal of hepatotoxicity was observed with emactuzumab and no patients with laboratory abnormalities met Hy's law criteria

Emactuzumab demonstrated a manageable safety profile consistent with Phase 1 findings and expectations of CSF-1R inhibition

Post-treatment AEs: any AE with onset or worsening of a pre-existing condition on or after the first administration of study treatment in the double-blind phase and before the first administration of study treatment in the open-label phase.
[a]Nine patients in the emactuzumab group had Grade 4 AEs (n=8 blood CPK increased); no Grade 5 events occurred.
AE, adverse event; CPK, creatine phosphokinase; CSF-1R, colony-stimulating factor-1 receptor.

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Most Common AEs Considered to be Related to Treatment

AE by preferred term in ≥15% of patients in the emactuzumab group, n (%)	Emactuzumab (n=91)		Placebo (n=45)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any treatment-related AE, n (%)	91 (100)	44 (48)	31 (69)	1 (2)
Pruritus	69 (76)	3 (3)	10 (22)	0
Periorbital oedema	63 (69)	1 (1)	3 (7)	0
Fatigue	38 (42)	2 (2)	9 (20)	0
Oedema peripheral	38 (42)	0	0	0
Face oedema	35 (38)	1 (1)	1 (2)	0
Blood CPK increased	28 (31)	22 (24)	1 (2)	0
AST increased	22 (24)	2 (2)	0	0
Eyelid oedema	22 (24)	0	6 (13)	0
Rash	21 (23)	1 (1)	2 (4)	0
Rash maculo-papular	20 (22)	2 (2)	2 (4)	0
Nausea	19 (21)	0	7 (16)	0
Asthenia	17 (19)	1 (1)	4 (9)	0
Dermatitis acneiform	16 (18)	0	0	0
Lacrimation increased	16 (18)	0	0	0
Lichen myxoedematosus	16 (18)	2 (2)	0	0
Blood lactate dehydrogenase increased	14 (15)	0	0	0
Hypertension	14 (15)	8 (9)	1 (2)	1 (2)

- The most common Grade 3 or 4 treatment-related AE was blood CPK increased, observed in 24% of patients in the emactuzumab group

Post-treatment AEs: any AE with onset or worsening of a pre-existing condition on or after the first administration of study treatment in the double-blind phase and before the first administration of study treatment in the open-label phase.
Events were considered by the investigator to be definitely, probably, or possibly related to treatment.
AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

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Emactuzumab Regimen Completion

	Emactuzumab (n=91)	
Completed 5 infusions, n (%)	68 (75)	
Did not complete 5 infusions, n (%)	23 (25)	
Withdrew consent	1 (1)	
Other reason[a]	6 (7)	
Due to an AE	16 (18)	
AE leading to discontinuation by preferred term[b]	**All grades**	**Grade 3/4**
Blood CPK increased	8 (9)	6 (7)
Periorbital oedema	3 (3)	0
AST increased	2 (2)	1 (1)
Face oedema	2 (2)	0
Angioedema	1 (1)	0
Asthenia	1 (1)	0
Constipation	1 (1)	0
Dermatitis acneiform	1 (1)	0
Eczema	1 (1)	0
Generalised oedema	1 (1)	0
Mesenteric lymphadenitis	1 (1)	0
Neutropenia	1 (1)	0
Oedema peripheral	1 (1)	0
Pruritus	1 (1)	0

- Most patients in the emactuzumab group (68/91 [75%]) received all 5 infusions
- The majority of treatment discontinuations were protocol mandated due to asymptomatic elevations of CPK and liver enzymes
  - These elevations are now well understood to be related to the inhibition of Kupfer cells causing delayed clearance of enzymes
  - This was subsequently remediated through a protocol amendment[c]
- In the emactuzumab group, 38 patients experienced dose delays[d]
  - Of these, 33 were associated with the study treatment regimen (predominantly CPK elevation) and 5 were due to scheduling

[a]No further protocol-permitted dose delays were possible (n=3), subject decision (n=2), agreement between the subject and investigator (n=1). [b]Post-treatment AEs: any AE with onset or worsening of a pre-existing condition on or after the first administration of study treatment in the double-blind phase and before the first administration of study treatment in the open-label phase. [c]The protocol specified treatment discontinuation for patients who had laboratory enzyme elevations requiring more than 2 dose delays (this was resolved later in the study by a protocol amendment clarifying the requirement for dose delay due to enzyme elevations). [d]Only dose delays between doses administered are counted.
AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

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Conclusions

- A planned course of 5 infusions of emactuzumab over 8 weeks provided statistically significant reductions in tumour size at Month 6 compared with placebo
- Most responders at Month 6 had responded by Week 6 (first MRI assessment) based on both RECIST v1.1 and TVS criteria
- Clinically meaningful improvements in physical function and range of motion with emactuzumab were observed early and were sustained over time, with statistically significant differences versus placebo emerging from Week 4 onwards
- Improvements in pain and stiffness were statistically significant with emactuzumab compared with placebo by Week 2, after the first infusion
- Emactuzumab had a manageable safety profile consistent with Phase 1 findings and expectations of CSF-1R inhibition

Emactuzumab demonstrated radiographic and functional efficacy and manageable safety in patients with TGCT, and has the potential to be the first short-course, potent treatment option for TGCT

CSF-1R, colony-stimulating factor-1 receptor; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; TGCT, tenosynovial giant cell tumour; TVS, tumour volume score.

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