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Clinical Trial

Long-term clinical activity, safety and patient-reported quality of life for emactuzumab-treated patients with diffuse-type tenosynovial giant-cell tumour

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KEYWORDS
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Abstract ***Objectives:*** This study investigated the safety, clinical activity and patient-reported outcomes of patients with diffuse-type tenosynovial giant-cell tumour (dTGCT) of the soft tissue who were treated with emactuzumab, a humanised anti-colony stimulating factor 1 receptor (CSF1R) monoclonal antibody and were followed up for up to 2 years after the start of treatment.

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diffuse-type tenosynovial giant-cell tumour (dTGCT); phase I, biomarker; quality of life

Methods: In this open-label phase 1 study (ClinicalTrials.gov NCT01494688), patients received intravenous (IV) emactuzumab from 900 to 2000 mg every two weeks in the dose-escalation phase and at the optimal biological dose of 1000 mg with different schedules in the dose-expansion phase. Adverse event (AE) rates and biomarker assessments from tumour biopsies were analysed. Quality of life was assessed using a standard questionnaire (EuroQol-5D-3L) and the WOMAC® 3.1 Osteoarthritis Index. Tumour responses were determined with magnetic resonance imaging.

Results: Altogether, 63 patients were enrolled into the study. The most frequently reported AEs were pruritus, asthenia and oedema. In 36 patients for whom biopsy tissue was available a substantial decrease of CSF1R-positive and CD68/CD163-positive macrophages was detected. The independently reviewed best overall objective response rate (ORR) (Response Evaluation Criteria in Solid Tumors version 1.1) was 71%. Responses were durable, and an ORR of 70% and 64% was determined after one or two years after enrolment into the study. Clinical activity was accompanied by an improvement in EuroQol-5D-3L and particularly the joint disorder −specific WOMAC score.

Conclusions: Systemic therapy of dTGCT patients with emactuzumab resulted in pronounced and durable responses associated with symptomatic improvement and a manageable safety profile.

1. Introduction

Tenosynovial giant-cell tumour (TGCT) of the soft tissue is a rare tumour or synovial proliferative disorder which arises from the synovium, bursae, and tendon sheaths, usually in young adults between 20 and 40 years of age [1,2]. Pathophysiologically, CSF1 overexpression was consistently found in analysed patients, and the majority of the tumour cell population is composed of CSF1R-expressing mononuclear cells, and also multinucleated giant cells, a phenomenon called tumour landscaping [3].

Lesions can be classified as focal or diffuse. Standard treatment for focal TGCT is surgery. However, dTGCT is more difficult to resect and has a high rate of recurrence (up to 50%), often on multiple occasions, [4] but is very rarely associated with metastasis [5]. The locally destructive process of those tumours results in important functional impairments, significant joint damage, and decline in the Quality of life (QoL) as reflected by the 36-item Short Form Health Survey score [6], which triggers a high healthcare burden and work productivity loss from dTGCT [7,8].

Emactuzumab (RG7155) is a recombinant, humanised monoclonal IgG1 antibody directed against the CSF1R dimerisation domain to block ligand-induced receptor activation that depends on receptor homodimerization. Previously, we characterised the preclinical and pharmacodynamic (PD) activity of emactuzumab on CSF1R-expressing macrophages *in vitro* as well as its clinical activity, pharmacokinetics, PD and safety in patients with dTGCT [9,10]. This study evaluated the long-term clinical benefit and safety of emactuzumab on the largest dTGCT patient set in a clinical study.

2. Materials and methods

2.1. Study design

This was a phase I, open-label, non-randomised, dose-escalation and expansion, multicenter study (ClinicalTrials.gov Identifier: NCT01494688) investigating the safety, PD and clinical activity of emactuzumab in patients with dTGCT. Preliminary results on 29 patients with dTGCT including those from the dose-escalation phase and determination of the optimal biological dose (OBD) were described previously [10].

2.2. Ethics

Local ethics committee approval was obtained, and all patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki in six centres in France and the USA.

2.3. Patients

Patients were enrolled on to the study if they were ≥18 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and had adequate haematology, blood chemistry, and renal and liver function.

Patients continued treatment until disease progression, unacceptable toxicity or consent withdrawal. Some

patients were limited to a pre-specified number of treatment cycles. A follow-up visit with optional tumour assessment was done after one and two years of study drug discontinuation.

2.4. Study drug administration

Patients received emactuzumab IV over 1.5 h at doses of 900–2000 mg. During the dose-escalation phase of the study, emactuzumab was given q2w. Once the OBD was defined, a limited number of cycles (four or five) was introduced and tested for different schedules (including 3 × q2w followed by 1 × q4w; 4 × q3w; and 5 × q2w).

2.5. Tumor response and safety

Assessments of the metabolic response rate was based on (^{18}F)-fluorodeoxyglucose-positron emission tomography (FDG-PET) and were carried out at baseline and on day 7 of cycle 2. Metabolic response assessment was based on the European Organisation for Research and Treatment of Cancer criteria [11]. Radiological assessments with magnetic resonance imaging (MRI) for all patients were done at baseline and after every three cycles of treatment using RECIST version 1.1 [12]. MRI images were centrally reviewed by independent radiologists. Confirmation was not required to define a response as partial or complete.

Safety assessments included physical (ECOG performance status, vital signs) and laboratory examinations, electrocardiogram and echocardiogram. Adverse events (AEs) were defined as per the Common Terminology Criteria for Adverse Events, version 4.0.

2.6. Biomarker assessments

For PD assessments, tumour biopsies were taken at baseline and at four weeks on treatment. Samples were analysed for CD68, CD163 and CSF1R expression with immunohistochemical staining as previously described [10]. Automated staining of sections was done on a BenchMark XT instrument (Ventana Medical Systems).

2.7. Patient-reported outcomes

Two questionnaires were used in this study, a standard QoL questionnaire (EuroQuol-5D-3L [EQ-5D-3L] Health Questionnaire, English Version for the UK, Validated for Ireland) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire which specifically focuses on joint disorders. A detailed description is provided in the supplementary material (online only).

2.8. Statistical considerations

All patients who received at least one dose of study medication were included in the safety, biomarker and efficacy population. Descriptive statistics were used for demographics, safety, biomarker and efficacy. For patient-reported EQ-5D-3L QoL and WOMAC questionnaires, on-treatment changes from baseline were analysed using a mixed-effect model repeated measures (MMRM) model (see supplementary material for details, online only).

3. Results

Altogether, 63 patients were enrolled into the study: 12 patients into the dose-escalation phase and 51 patients into the dose-expansion phase. Emactuzumab was given at doses of 900 mg (n = 3), 1000 mg (n = 51), 1350 mg (n = 5) and 2000 mg (n = 4). As published previously [10], no dose-limiting toxicitis were reported and the maximum tolerated dose was not reached. The OBD was defined as 1000 mg q2w. Given the rapid onset of response and symptomatic improvement observed in the first part of the study, more convenient treatment schedules for the dTGCT patient population were explored: three alternative regimens (q2w, q3w and q2w-q4w) were investigated, and the total number of cycles were limited to four or five depending on the regimen (Supplementary Table 1, online only). No overt

Table 1
Baseline patient demographics and characteristics.

Characteristic	All patients with dTGCT N = 63
Age, median (range), in years	38 (18, 82)
Sex, n (%)	
Male	25 (40)
Female	38 (60)
Anatomical location of disease	
Upper extremity	5 (8)
Wrist	3 (5)
Thumb	1 (2)
Shoulder	1 (2)
Lower extremity	58 (92)
Knee	36 (57)
Hip	5 (8)
Ankle	11 (17)
Foot	6 (10)
Prior surgery for dTGCT, n (%)	38 (60)
Prior systemic therapy for dTGCT, n (%)	12 (19)
Nilotinib	9 (14)[a]
Imatinib	4 (6)[a]
Time between most recent surgery for dTGCT and study start, median (min, max) [months]	22 (2, 165)

n = number of patients; dTGCT = diffuse-type tenosynovial giant-cell tumour.

[a] Please note: One patient received both nilotinib and imatinib as prior therapies.

differences for clinical activity were seen between different doses and schedules.

The median age of patients was 38 years with more women (60%) participating in the study (Table 1). The majority of patients (57%) had the knee as their primary tumour location. More than half of the patients had prior surgery for their disease, and 19% of patients had received prior systemic therapy with nilotinib or imatinib. The median number of treatment cycles administered per patient was 4 cycles (range 1–14) across all patients (Supplementary Table 1, online only).

The most frequent AEs of any grade were pruritus (70%), asthenia (39%) and different kinds of oedema (face oedema [49%], oedema peripheral [44%], periorbital oedema [43%] and eyelid oedema [37%]) (Table 2). No deaths occurred during the study. Nine patients (14%) had an AE that lead to withdrawal from the study.

Altogether, 36 patients (57%) had evaluable paired tumour biopsy samples (taken at baseline and on treatment at four weeks, after two cycles of emactuzumab at doses of 900–2000 mg). A significant reduction of >50% of CD68/CD163-positive macrophages and CSF1R-positive macrophages was seen in 22 patients (61%); however, no correlation with clinical benefit could be demonstrated (Supplementary Fig. 1, online only). Furthermore, absolute CSF1R- and CD68/CD163-positive infiltrates determined before treatment start were not associated with the change in tumour size induced by emactuzumab therapy (data not shown).

Altogether, 45 of 63 patients (71%) had a best overall response of complete response or partial response (PR) and the disease control rate was 98% (62 of 63 patients) (Figure 1a and Table 3). None of the patients were assessed with progressive disease at the time of treatment discontinuation, although the majority of patients (39 patients [62%]) only received a limited number of four or five treatment cycles. After one- and two-year follow-up MRI, 19/27 patients (70%) and 9/14 patients (64%), respectively, were still in response at these time points (Figure 2 and Table 3). Two patients remained in a response beyond the two-year follow-up: one patient with a PR from July 2013 to April 2015 was still in response in October 2019, and one patient with stable disease (SD) from January 2013 to June 2014 was still in response in April 2018 (P. Cassier, personal communication).

For FDG-PET, of 63 patients, a complete metabolic response was observed in two patients (3%), partial metabolic response was observed in 52 patients (83%) and three patients (5%) had stable metabolic disease (Figure 1b).

Retreatment with emactuzumab was allowed per protocol. A 64-year-old woman was diagnosed with dTGCT in 2002 and had multiple surgeries and systemic treatment with nilotinib before entering the study. At baseline, she had lesions in her left wrist and was treated with four cycles of emactuzumab at 900 mg from July to October 2012. The patient had a PR with a lesion reduction by 75% but had to discontinue treatment because of a grade II ischaemic cardiopathy considered unrelated to treatment. After regrowth of the lesion by 150%, the patient received another four cycles of emactuzumab from October to December 2014 and again showed a PR with a lesion reduction by 79%. The patient was discontinued as planned after the fixed number of cycles. The patient benefited with a radiological response until November 2016 (C. Gomez-Roca, personal communication).

EQ-5D-3L QoL assessment was done for 59 patients. There was a decrease of the estimate from baseline for almost all time points (Figure 3a), and statistical significance was reached for cycle 4, 5 and 7 (Figure 3b). For the WOMAC assessed in 18 patients, there was a

Table 2
Summary of adverse events of any grade and of grade ≥III irrespective of the relationship to study drug.

Adverse event	No. of patients having an adverse event (%) N = 63	
	All grades	Grade ≥3
Pruritus	44 (70)	2 (3)
Asthenia	39 (62)	0
Face oedema	31 (49)	0
Oedema peripheral	28 (44)	0
Periorbital oedema	27 (43)	1 (2)
Eyelid oedema	23 (37)	0
Headache	19 (30)	0
Nausea	18 (29)	0
Rash	18(29)	0
Fatigue	15 (24)	2 (3)
Diarrhoea	14 (22)	0
Lacrimation increased	14 (22)	0
Dry skin	10 (16)	0
Erythema	8 (13)	0
Paraesthesia	8 (13)	0
Abdominal pain	7 (11)	0
Conjunctivitis	7 (11)	0
Constipation	7 (11)	0
Pyrexia	7 (11)	0
Vomiting	7 (11)	0
Weight increased	7 (11)	0

Please note: Only adverse events reported by >10% of the patients overall are shown. Adverse events are ordered by decreasing frequency for all grade events in the overall population.
Adverse events that led to discontinuation of study treatment included: asthenia grade II, conjunction of chest discomfort grade II/hypertension grade II/myocardial ischaemia grade I, skin lesions grade II, dermo-hypodermitis grade III, maculo-papular rash grade III, neutropenia grade III, subacute cutaneous lupus erythematosus grade III, mucosal inflammation grade III, conjunction of face oedema grade II/skin discolouration grade II with one patient each. All of these events, with the exception of myocardial ischaemia, were considered related to study drug.

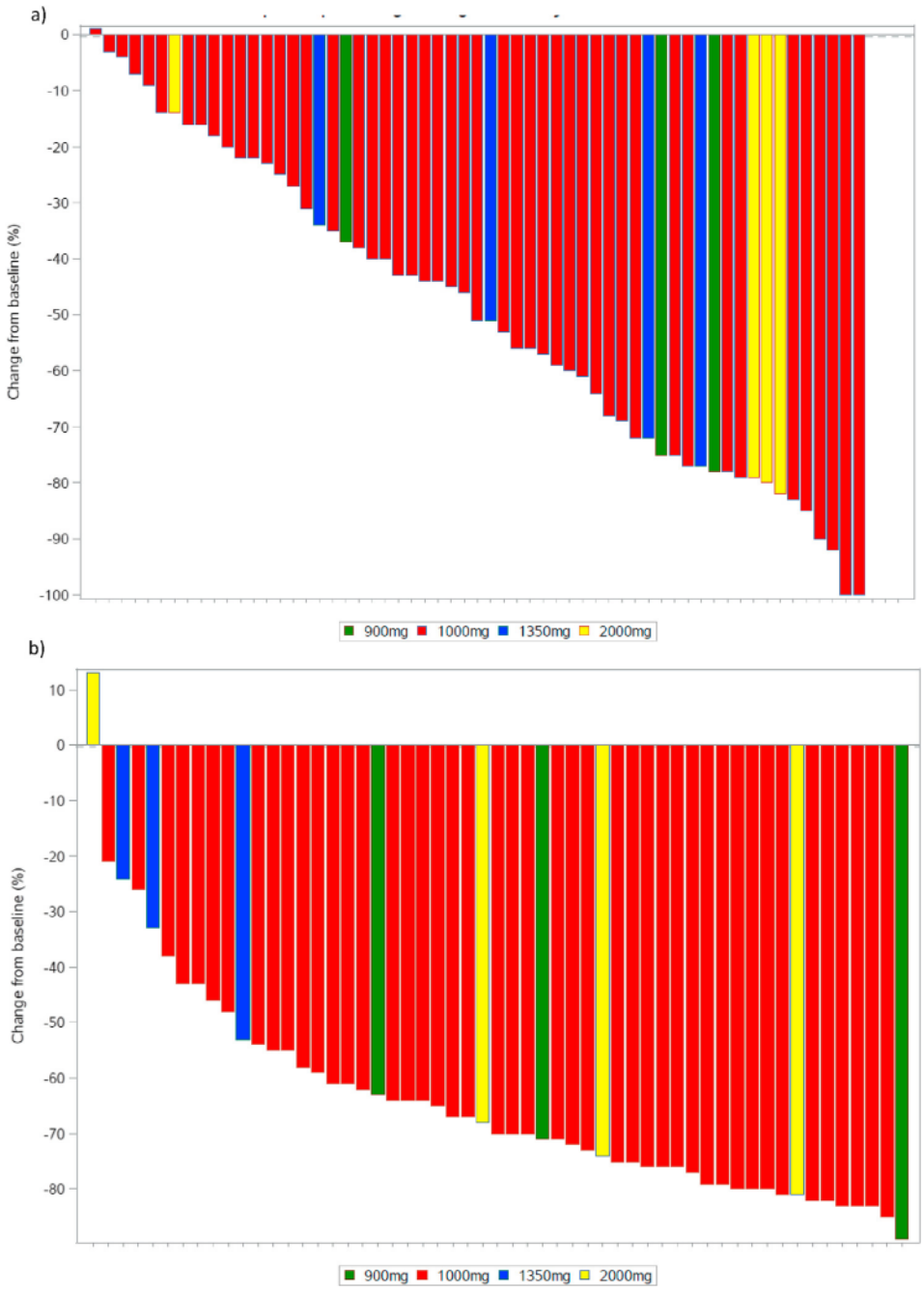

Fig. 1. The waterfall plot of dTGCT patients treated with different doses of emactuzumab. a) based on central read of MRI scans assessed by RECIST criteria b) based on of FDG-PET scans assessed by EORTC criteria at Cycle 2 Day 7. dTGCT, diffuse-type tenosynovial giant-cell tumour; EORTC, European Organisation for Research and Treatment of Cancer; FDG-PET, (18F)-fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors. Please note: For eight patients (13%) no FDG-PET results were available.

pronounced reduction in total score that reached statistical significance at all cycles tested (Figure 3c).

4. Discussion

Here, we present data on the largest cohort of dTGCT patients (n = 63) ever treated with a CSF1R-targeting antibody in a clinical study to date. Strikingly, the ORR (independent review; unconfirmed) was 71%, which is the best clinical activity reported so far for a systemic therapy of dTGCT to our knowledge. Responses were durable, and the ORR was 70% and 64% after one and two years, respectively. Clinical activity appeared early as measured by FDG-PET with a metabolic ORR of 86% within one month of treatment. A considerable number of patients discontinued the

Table 3
Tumour response to treatment based on RECIST by central assessment.

RECIST response	Number of patients (%) with respective assessment N = 63		
	Best overall response while on treatment	Response at optional 1-year follow-up	Response at optional 2-year follow-up
Complete response	2 (3)	1 (2)	0
Partial response	43 (68)	18 (29)	9 (14)
Stable disease	17 (27)	6 (10)	4 (6)
Progressive disease	0	2 (3)	1 (2)
Not applicable [a]	1 (2)	36 (57)	49 (78)
Objective response rate	45 (71)	19 (70)[b]	9 (64)[b]
Disease control rate	62 (98)	25 (93)[b]	13 (93)[b]

Please note: Responses described here are unconfirmed. One patient withdrew consent and never had an on-treatment tumour assessment. Another patient had no measurable target lesion at baseline and could not be evaluated.
[a] These patients were lost to follow-up, underwent surgery or discontinued the study prematurely.
[b] Percentages are excluding patient who were not applicable for tumour assessment.

study during the follow-up phase after emactuzumab treatment was already completed. However, this may be because objective responses had occurred early in this relatively young patient population with a usually non-malignant disease. Remarkably, one patient with a PR had a treatment interruption for two years. After the lesion regrew during this time, the patient regained a PR after retreatment. This case underscores that retreatment with emactuzumab is feasible and results in a further deep clinical response. Patient-reported outcomes were used to capture symptomatic improvement, which is an important indicator of treatment success in this young patient population. A significant improvement of the EQ-5D-3L QoL and the joint disorder-specific WOMAC during treatment indicates for the first time that patients' QoL did improve under therapy with emactuzumab. Furthermore, emactuzumab was well tolerated. Most AEs were of grade I or II in intensity. Pruritus (70%), asthenia (39%) and oedema (up to 49%) were the most frequently reported AEs. Paired tumour biopsy samples showed a profound reduction in tumour-associated CD68/CD163-positive and CSF1R-positive cells in a majority of patients and underscore the PD activity of emactuzumab.

The efficacy shown in this study exceeds that of other systemic therapies investigated so far, both in duration and proportion. For example, non-selective tyrosine kinase inhibitors imatinib and nilotinib have been tested in dTGCT patients with limited success. Imatinib was tested in 27 patients and showed an ORR of 19%, and 74% had stable disease [13]. Nilotinib was tested in 51 patients with dTGCT who were treated for up to one year in a phase II study [14]. No patient had an objective response at week 12 of treatment. The best overall

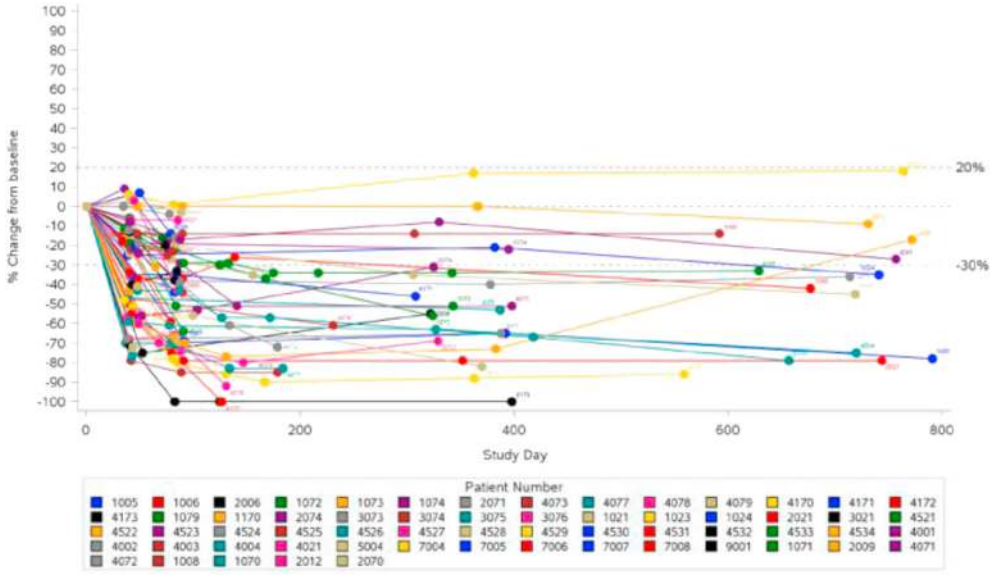

Fig. 2. spider plot of percentage change from baseline over time in the sum of longest diameters (SLDs) according to RECIST 1.1. RECIST, Response Evaluation Criteria in Solid Tumors. Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.

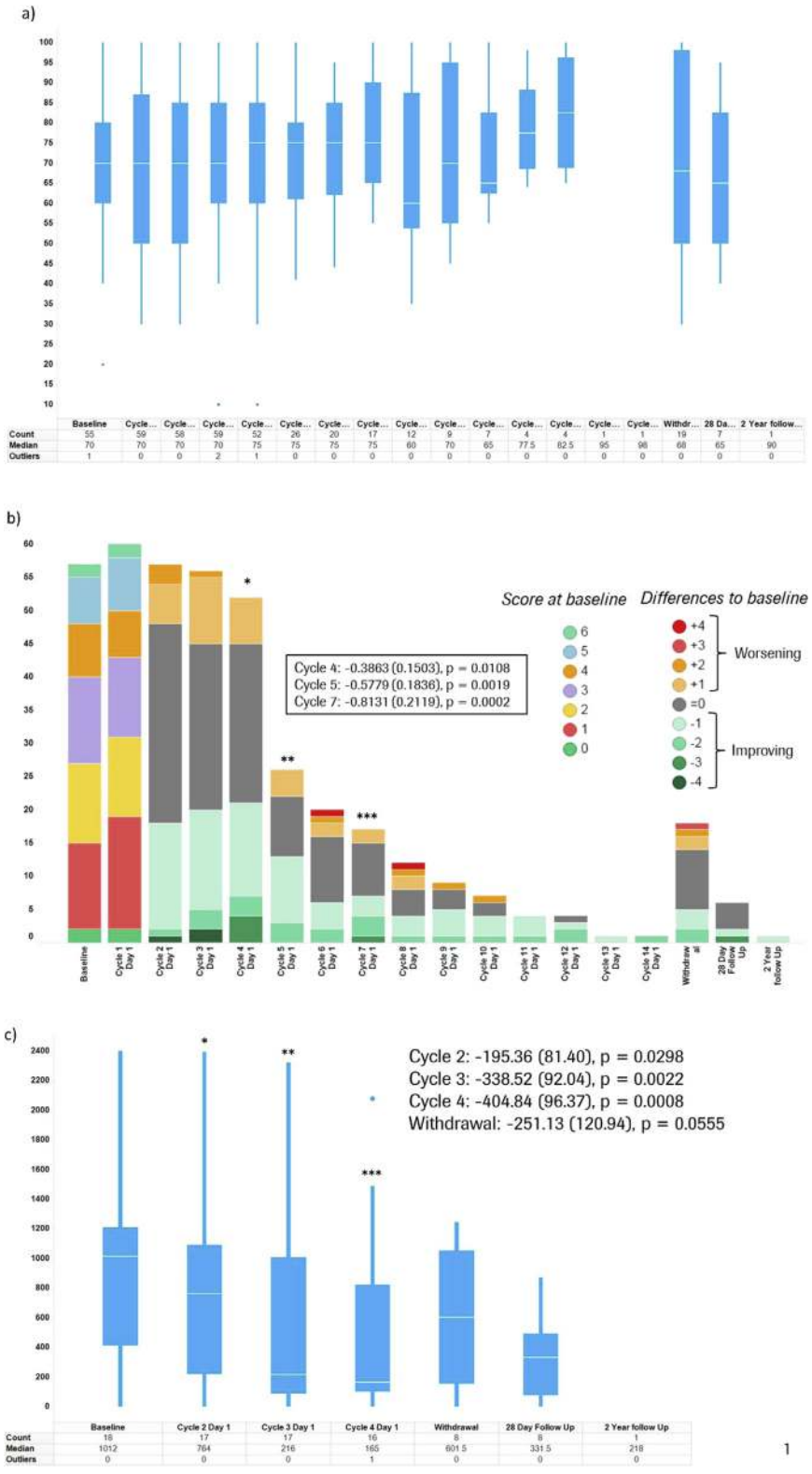

Fig. 3. Quality-of-life analysis. a) The box plot of the overall health status score by visit of EQ-5D-3L. Please note: central line = median; boxes = 25th to 75th percentiles; whiskers = range of observations which are not outliers (within 1.5 times the inter-quartile range from the 25th and 75th percentile); point outside = outliers. b) differences compared with cycle 1 day 1 predose for EQ-5D-3L. Estimates with standard error and respective p-value are shown. Asterisks indicate the level of statistical significance. c) The box plot of the WOMAC score at baseline and for timepoints on treatment. Estimates with standard error and respective p-value are shown. Asterisks indicate the level of statistical significance. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Please note: central line = median; boxes = 25th to 75th percentiles; whiskers = range of observations which are not outliers (within 1.5 times the inter-quartile range from the 25th and 75th percentile); point outside = outliers.

response after one year of treatment was stable disease in 90% of patients and PR in 6% of patients. Phase I data on dTGCT patients have been reported as well for the CSF1R-targeting compounds cabiralizumab and pexidartinib. Five of eleven patients (45%) treated with cabiralizumab had a PR [15]. The best response (unconfirmed and assessed by the investigator) with pexidartinib (PLX3397) was a PR in 12/23 patients (52%) and SD in 7/23 patients (30%) [16]. Most recently, data in a controlled study of 61 advanced TGCT patients treated with pexidartinib versus 59 patients treated with placebo have been reported [17]. At week 25 and based on centrally read RECIST-based, unconfirmed tumour assessment, the ORR was 39% compared with 0% in the placebo group. The best overall response after a median treatment duration of 17 months was 54% [18].

Regarding the safety profile, emactuzumab compares favourably to other CSF1R-targeting agents. Most importantly, no liver toxicity was reported for patients in the present emactuzumab study, although transient, on-target aspartate aminotransferase (AST) increase was observed. In the phase III trial of pexidartinib, seven patients (11%) had to discontinue pexidartinib because of hepatic AEs [17]. In addition, pexidartinib shows some specific AEs which are not seen or are fewer with emactuzumab treatment (e.g. hair colour changes, fatigue, dysgeusia). Long-term treatment with pexidartinib with a median treatment duration of 17 months may even enhance the side-effect profile [18]. These differences might be explained by off-target effects that are common for tyrosine kinase inhibitors such as pexidartinib, which is known to inhibit KIT with comparable potency as CSF1R [16]. Other reported events seem to be similar between pexidartinib and emactuzumab including oedema and skin disorders. However, in the present study, the number of treatment cycles was limited to four or five in the majority of patients (62%) which may underestimate any toxicity as a result of long-term treatment. At the same time, this can be interpreted as an advantage of emactuzumab treatment. Although the oral treatment with pexidartinib may be more convenient compared with the IV infusion of emactuzumab, the deep and durable responses seen with emactuzumab were after 4 or 5 cycles, whereas patients receiving oral treatment were dosed twice a day with pexidartinib for at least 24 weeks and up to 30 months [17]. Superior efficacy of emactuzumab may be caused by the short half-life of pexidartinib with a median of 16.8 h [16], whereas that of emactuzumab is about 2 weeks [10].

Functional and symptomatic improvements are an important aspect for assessing clinical benefit in patients with dTGCT. Validated patient-reported outcomes that have been prospectively implemented in clinical trials to document treatment-induced symptomatic and functional improvement are scarce for patients with dTGCT. Gelhorn et al. [19] recently established the worst pain numeric rating scale, Patient Reported Outcomes Measurement Information System physical functioning items and the WOMAC pigmented villonodular synovitis and the histologically related lesion giant cell tumor of tendon sheath (PVNS-GCTTS) Index, as well as a worst stiffness numeric rating scale in 22 patients with TGCT treated with pexidartinib. In the phase III study of pexidartinib, the range of motion, physical functioning and stiffness improved significantly, and there was a trend in reduction of pain from baseline through to week 25 [17]. This is in line with our findings that the EQ-5D-3L QoL and WOMAC significantly improved over the treatment period.

Future studies may further explore the optimal treatment duration and ascertain the long-term therapeutic effects of CSF1R-targeting therapy with emactuzumab. In addition, the use of emactuzumab as a neoadjuvant or adjuvant treatment, i.e. before or after surgery, should be tested to elucidate long-term outcomes in such patients.

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Conflict of interest statement

Philippe Cassier reports receiving honoraria from Novartis, Roche/Genentech, Blueprint Medicines, Amgen, and AstraZeneca; research funding from Novartis, Roche/Genentech, Eli Lilly, Blueprint Medicines, Bayer, AstraZeneca, Celgene, Plexxikon, Abbvie, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme, Taiho Pharmaceuticals, Toray Industries, Transgene, Loxo, GlaxoSmithKline, Innatre Pharma, and Janssen; and travel grants from Roche, Amgen, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, and Netris Pharma.

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Sandra D'Angelo reports advisory board consultancy roles for Nektar, GlaxoSmithKline, Immunocore, Adaptimmune, Immune Design, Pfizer, EMD Serono, Merck, Incyte, and Amgen; research grants from Nektar, EMD Serono, Deciphera, BMS, Merck, Incyte, and Amgen; and travel grants from Nektar.

Wolfgang Jacob reports being a sponsor employee and having sponsor stock ownership.

Anna-Maria Jegg reports being a former sponsor employee and having a patent issued in the use of emactuzumab.

Francesca Michielin reports being a sponsor employee.

Randolph Christen reports being a sponsor employee and having sponsor stock ownership.

Carl Watson reports being a sponsor consultant.

Michael Cannarile reports being a sponsor employee and having sponsor stock ownership.

Irina Klaman reports being a sponsor employee.

Keelara Abiraj reports being a sponsor employee and having sponsor stock ownership.

Carola Ries reports being a former sponsor employee and having a patent issued in the use of emactuzumab.

Martin Weisser reports being a sponsor employee and having sponsor stock ownership.

Dominik Rüttinger reports being a sponsor employee and having a patent issued in the use of emactuzumab.

Jean-Yves Blay reports receiving research support and honoraria from Roche, Daiichi Sankyo, Plexxikon, and Novartis.

Jean-Pierre Delord reports consulting or advisory roles for Novartis, Roche/Genentech, Bristol-Myers Squibb, and MSD Oncology; and receiving research funding from Genentech, Bristol-Myers Squibb, and MSD Oncology.

All other authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.09.038.

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