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RESEARCH ARTICLE

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A prospective real-world study of the diffuse-type tenosynovial giant cell tumor patient journey: A 2-year observational analysis

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Abstract

Background and Objectives: Diffuse-tenosynovial giant cell tumor (D-TGCT) is a rare, locally aggressive, typically benign neoplasm affecting mainly large joints, representing a wide clinical spectrum. We provide a picture of the treatment journey of D-TGCT patients as a 2-year observational follow-up.

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Methods: The TGCT Observational Platform Project registry was a multinational, multicenter, prospective observational study at tertiary sarcoma centers spanning seven European countries and two US sites. Histologically confirmed D-TGCT patients were categorized as either those who remained on initial treatment strategy (determined at baseline visit) or those who changed treatment strategy with specific changes documented (e.g., systemic treatment to surgery) at the 1-year and/or 2-year follow-up visits.

Results: A total of 176 patients were assessed, mean diagnosis age was 38.4 (*SD* ± 14.6) years; most patients had a knee tumor (120/176, 68.2%). For the 2-year observation period, most patients (75.5%) remained on the baseline treatment strategy throughout, 54/79 patients (68.4%) remained no treatment, 30/45 patients (66.7%) remained systemic treatment, 39/39 patients (100%) remained surgery. Those who changed treatment strategy utilized multimodal treatment options.

Conclusions: This is the first prospectively collected analysis to describe D-TGCT patient treatments over an extended follow-up and demonstrates the need for multidisciplinary teams to determine an optimal treatment strategy.

KEYWORDS

diffuse-tenosynovial giant cell tumor (D-TGCT), pexidartinib, prospective, real-world, TGCT observational platform project (TOPP)

1 | INTRODUCTION

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive, typically benign neoplasm of joints, bursae, and tendon sheaths that affects both small and large joints.[1,2] Symptoms of TGCT include pain, stiffness, swelling, and limited range of motion.[3,4] Localized- and diffuse-type (L-TGCT and D-TGCT) are the two subtypes of TGCT.[5,6] These subtypes have a common pathogenesis driven by a fusion protein involving the colony stimulating factor (CSF) gene, which drives tumor growth,[7–9] and are defined based on clinical and radiological characteristics.[5,6] TGCT is a rare disease with an overall annual incidence in the United States of 11 cases per million, including 1.8 cases per million for D-TGCT, and 9.2 cases per million for L-TGCT.[10] However, the true incidence is likely higher as TGCTs are likely underreported and underdiagnosed since their clinical presentation is wide and mimics other pathologies. D-TGCT tends to be more aggressive, often recurring locally up to 56% after surgery.[11] D-TGCT mainly affects the knee and can have a major impact on quality of life. In very rare instances, D-TGCT can undergo malignant transformation.[11–15]

The current standard of care for D-TGCT is surgical resection of the tumor to reduce symptoms, preserve joint structures, and improve function.[16] Systemic treatment with tyrosine kinase inhibitors (TKIs) or monoclonal antibodies that target the colony-stimulating factor-1 receptor, i.e., imatinib (off-label), nilotinib, emactuzumab, cabiralizumab, and pexidartinib, have been used for treatment in cases where surgery is not an option.[17–26] Most findings to date are from small, retrospective studies that focus on radiological and pathological characteristics, as well as surgical outcomes of the disease.[1,27,28] The experience of patients who live with this disease, often chronically, is not well described. Hence, there is a need for improved understanding of the natural history of this tumor. Additionally, there is a need to understand both the burden of D-TGCT from a patient perspective and the treatment landscape beyond a single institution using prospective data collection.

This prospective registry was conducted to describe the experience in D-TGCT care, specifically the details of patient demographics, patient experience, disease management strategies, clinical and patient-reported outcomes (PRO), and resource usage in Europe and in the United States. This is the first comprehensive global disease registry to improve the understanding of D-TGCT patients' pathways, treatment patterns, health outcomes, and health economics.

Previously, the prospective international TGCT Observational Platform Project (TOPP) registry described the journey of patients with D-TGCT and the impact of TGCT on PRO from a baseline snapshot.[29] This analysis provides a picture of the treatment journey of D-TGCT patients and evaluates the evolution of treatment strategies of these patients starting from the moment they enter the orthopedic sarcoma referral center through the 2-year observational follow-up period.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This global multicenter prospective sponsored study included all consecutive patients from 12 tertiary sarcoma centers spanning 7 EU countries and 2 US sites. Key eligibility criteria and study designs for

the TOPP registry have been described elsewhere.[29] In brief, patients had primary or recurrent D-TGCT, and the diagnosis of TGCT had to be histologically confirmed and assessed as diffuse based on magnetic resonance imaging (MRI) or clinical presentation if this was missing. The patient breakdown for the full analysis set (FAS, [$N = 176$]) during the 2-year observation period based on prior treatment at baseline was as follows: surgery only ($n = 81/176$, 46.0%), surgery and other treatment (radiotherapy, ^{90}Yttrium, or systemic treatment, $n = 53/176$, 30.1%), systemic treatment only ($n = 14/176$, 8.0%), and no prior treatment/treatment-naïve ($n = 28/176$, 15.9%). The severity of D-TGCT was classified as moderate diffuse (with intra- and/or extra-articular disease without involvement of muscular/tendinous tissue/ligaments)[30] within the first year ($n = 66$) and within the second year ($n = 63$); or severe diffuse (including intra- and extra-articular involvement and involvement of at least one of the three structures [muscular/tendinous tissue/ligaments])[30] within the first year ($n = 90$) and within the second year ($n = 90$). For patients without a closest MRI to baseline or with missing details of the closest MRI, the severity was set to not assessable ($n = 20$). Tumor status during the 2-year observational period was defined as stable (unchanged), improved, recurrent, degraded (worsened), or resolved (completely removed), determined by clinical evaluation via MRI and/or patient complaints. The observation period per patient was 24 ± 2 months. Patients were followed prospectively, and data was collected at baseline about the type of treatment strategy or, alternatively, was classified as no current/planned treatment [denoted as wait-and see ($n = 79$)]. Wait-and-see was considered a treatment strategy where the patients were actively surveilled during the 2-year observation period but were not actually being treated nor did they have a planned treatment. Current/planned treatment (e.g., surgery/future surgery or systemic therapy) was the treatment status for 97 patients. Of these 97 patients, 84 (45 systemic treatment; 39 surgery) were assessed and reported on for the 2-year follow-up. The other 13 patients (5 radiotherapy, 4 future surgery, 2 surgery + systemic, 1 surgery + radiotherapy, 1 systemic + future surgery) were not assessed as the populations were too small to draw any significant conclusions from. Thus, a total of 163 patients (79 wait-and-see, 84 current/planned treatment) were followed based on treatment strategies from baseline through the 2-year follow-up visit. Patients who remained on surgery as their treatment strategy were considered surgical follow-ups and does not imply a procedure at each time point (baseline, 1-year, 2-year). The treatment strategy (wait-and-see, systemic, surgery) was collected at baseline (at the time of enrollment in the observational study/start of treatment plan), and at the 1- and 2-year follow-up collection points (Figure 1).

Patients were categorized as either those who remained on the initial treatment strategy (treatment plan determined at baseline visit), or those who changed treatment strategy with specific changes to treatment noted (i.e., systemic treatment to surgery) during the 2-year observation period. Patients who received treatment intervention at baseline (systemic treatment or surgery), followed by no specific treatment at 1 year and/or 2 years, were documented as remaining on the same treatment strategy/no treatment intervention. This analysis focuses the treatment plan from the time the patients entered the sarcoma referral center through the 2-year follow-up visit.

2.2 | Statistical analysis

Binary, categorical, and ordinal parameters have been summarized by means of absolute and percentage numbers within the various categories. Missing data are not included in percentage calculations. Numerical data were summarized by means of standard statistics (i.e., number of available data, number of missing data, mean, standard deviation, and minimum, median, maximum, lower, and upper quartile).

3 | RESULTS

3.1 | Subjects

All 183 patients from the all-document patient set (APS) fulfilled the inclusion criteria and were available for baseline analysis, resulting in identical APS and baseline analysis set (BAS). Of the 183 patients from BAS, 4 patients withdrew their informed consent, and 3 patients had no postbaseline documented information, leaving 176 patients in the FAS (Figure 2). Most of the patients (120/176 patients [68.2%]) had D-TGCT in the knee, and 108/176 (61.4%) were female. The mean age at enrollment was 43.5 years (SD ± 14.3), whereas the mean age at diagnosis of D-TGCT was 38.4 years (SD ± 14.6). Baseline demographics are summarized in Table 1.

At baseline, 97/176 patients (55%) had a current or planned treatment, whereas 79/176 patients (44.9%) were not currently being treated nor did they have a planned treatment (wait-and-see).

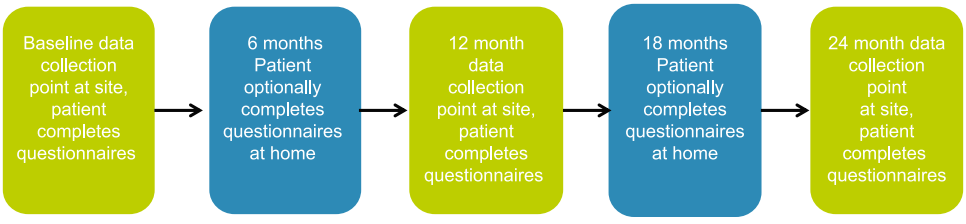

FIGURE 1 Study design. *Additional data collection points may occur at any time the patient visits the site, even if it is outside this schedule

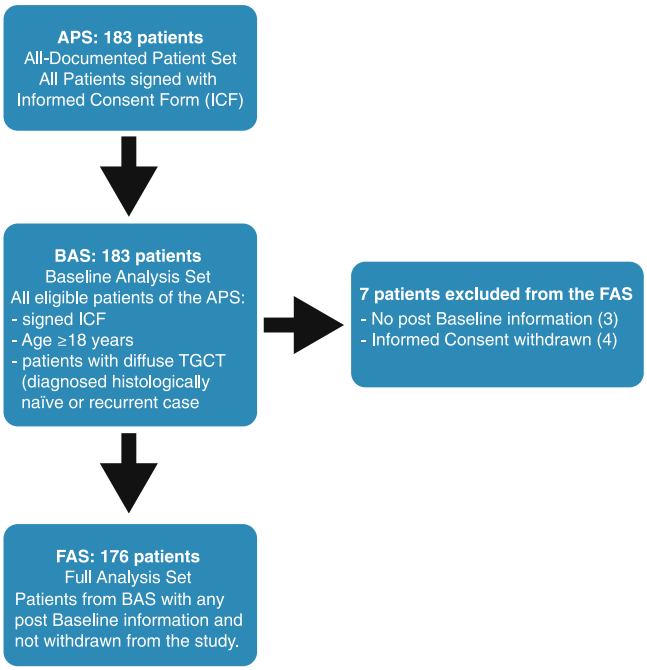

FIGURE 2 Patient eligibility. APS, all-documented patient set; BAS, baseline analysis set; FAS, full analysis set; ICF, informed consent form

TABLE 1 Demographics and treatments at baseline of TOPP (full analysis set)

Features	*N* = 176
Age at enrollment, mean, years ± *SD*	43.5 ± 14.3
Age at diagnosis, mean, years ± *SD*	38.4 ± 14.6
Gender, *n* (%)	
Female	108 (61.4)
Male	68 (38.6)
Tumor site, *n* (%)	
Knee	120 (68.2)
Ankle	18 (10.2)
Hip	12 (6.8)
Shoulder	8 (4.5)
Foot	7 (4.0)
Elbow	4 (2.3)
Wrist	3 (1.7)
Hand	3 (1.7)
Temporomandibular	1 (0.6)
Treatment plan at baseline, *n* (%)	
No current/planned treatment	79 (44.9)
Treatment/planned treatment	97 (55.1)

Abbreviations: *SD*, standard deviation; TOPP, TGCT Observational Platform Project.

Of these 79 patients, 28 were classified as naïve (no documented prior treatment) at baseline enrollment. Of the 97 patients with a current or planned treatment at baseline, 45 had systemic treatment only and 39 had surgery only as their treatment strategy. All specific treatment plans/strategies at baseline including the 13 patients with other treatments (i.e., radiotherapy) are summarized in Figure 3. Of the 176 patients in the FAS, 165 patients (93.8%) had a follow-up visit at 1 year and 168 (95.5%) had a follow-up visit at 2 years.

3.2 | Tumor status during the 2-year observational period

This section summarizes the change of the tumor status within the observation period by prior TGCT treatment at baseline. Of the 176 patients in the FAS, prior TGCT treatments at baseline included only surgery (*n* = 81/176, 46.0%); surgery and other treatment (*n* = 53/176, 30.1%); only systemic treatment (*n* = 14/176, 8.0%); no prior treatment (*n* = 28/176, 15.9%) (Table 2). Furthermore, of the patients who received only systemic treatment before baseline and for the 2-year observation period, most (8/14, 57.1%) were classified as stable disease, while improvement of TGCT was observed in systemic-only treated patients (4/14, 28.6%) (Table 2). Patients showing the highest percentage of improved tumor status during the 2-year observation were those with no prior TGCT treatment at baseline (11/27, 40.7%), while 9/27 patients (33.3%) in the same group remained as stable disease (Table 2). Moreover, stable disease was observed in patients who were either previously treated with surgery in combination with another treatment (27/53, 50.9%) or surgery only (30/75, 40.0%), over the entire observation period while improvement of tumor status was seen in 12/75 surgery-only patients (16%) and in 8/53 patients (15.1%) treated with surgery combined with another treatment. Recurrence was not observed in patients treated only with systemic treatment; however, tumor progression was seen in 10/75 surgery-only patients (13.3%), in 7/53 surgery + other treatment patients (13.2%), and in 2/27 patients (7.4%) that did not receive prior treatment.

The tumor status worsened in 6/75 surgery-only patients (8%) and in 7/53 surgery + other treatment patients (13.2%), as compared to 1/14 systemic-only patients (7.1%) and 1/27 patients (3.7%) who did not receive prior treatment. The tumor status was resolved in 10/75 surgery-only patients (13.3%) and in 4/53 surgery + other treatment patients (7.5%) as compared to systemic-only patients (1/14, 7.1%) (Table 2).

3.3 | Treatment plan during the 2-year observational period based on tumor status at baseline

This section summarizes the TGCT-related treatment during the entire observation period by tumor status at baseline. Within the first year (*N* = 176), 78 patients (44.3%) were categorized as having

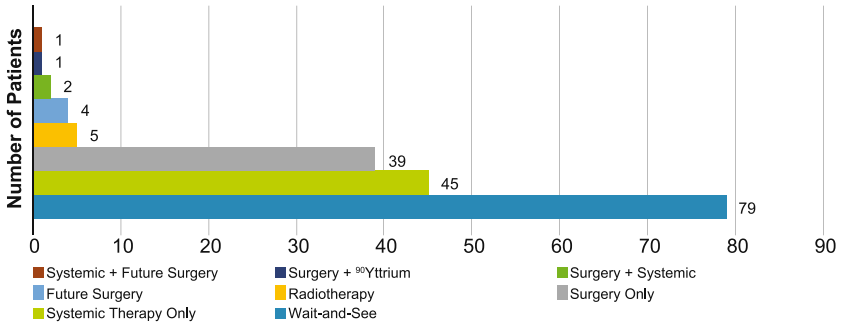

FIGURE 3 Breakdown of patient treatment plans at baseline (full analysis set)

TABLE 2 Tumor status during the observation period by prior TGCT treatment at baseline (full analysis set)

	Only surgery	Only systemic treatment	Surgery and other treatment[a]	No prior treatment
Within whole observation period, *n* (%)				
Total	81	14	53	28
Total (without missing)	75 (100)	14 (100)	53 (100)	27 (100)
Stable	30 (40.0)	8 (57.1)	27 (50.9)	9 (33.3)
Degraded	6 (8.0)	1 (7.1)	7 (13.2)	1 (3.7)
Improved	12 (16.0)	4 (28.6)	8 (15.1)	11 (40.7)
Recurrent	10 (13.3)	0	7 (13.2)	2 (7.4)
Resolved	10 (13.3)	1 (7.1)	4 (7.5)	3 (11.1)
No conclusion possible	7 (9.3)	0	0	1 (3.7)
Missing	6 (8.0)	0	0	1 (3.7)

Abbreviation: TGCT, tenosynovial giant cell tumor.

[a]Other treatment in combination with surgery includes radiotherapy, ^{90}Yttrium, systemic treatment.

recurrent disease and ≥1 prior treatment; 70 patients (39.8%) were categorized as having a primary diagnosis and ≥1 prior treatment; 28 patients (15.9%) were naïve (no prior treatment) (Table 3). Within the second year ($N = 173$), 76 patients (46.6%) were categorized as having recurrent and ≥1 prior treatment; 69 patients (39.9%) were categorized as having a primary diagnosis and ≥1 prior treatment; 28 patients (16.2%) were naïve (no prior treatment) (Table 3). Further breakdown of each tumor status showed that, within the first year (including baseline) of the observation period, 17/28 patients (60.7%) with no prior treatment were treated with surgery, while the other 11 patients (39.3%) were not treated and were classified as wait-and-see (Table 3). Most of the patients in this group (26/28, 92.9%) remained as wait-and-see during the second year, and the remaining 2 patients (7.1%) were treated with surgery. Of the patients with primary diagnosis and treatment before baseline ($n = 70$), 37 (52.9%) were not treated for TGCT within the first year, and 59/69 patients (85.5%) remained without treatment during the second year of the observation period (Table 3). The most common treatment strategy during the first year was systemic therapy (22/70, 31.4%), followed by surgery (with or without other treatment) received in 9/70 patients (12.9%). Within the second year of the observation period, and of the 69 patients with primary disease, 6 patients received surgery (8.7%) and 4 patients received systemic therapy (5.8%).

A total of 78 patients had recurrent disease and prior treatment, 43/78 (55.1%) received TGCT treatment within the first year of the observation period, with 21/78 (26.9%) receiving systemic-only therapy, 21/78 (26.9%) receiving surgery (with or without other treatment) and 1/78 (1.3%) patients receiving other treatment (Table 3). During the second year, 62/76 patients (81.6%) with recurrent disease remained without a treatment strategy, whereas 7/76 patients (9.2%) each were treated with surgery-only or systemic-only therapy, respectively (Table 3).

3.4 | Treatment plans by TGCT severity classification

This section outlines the specific treatment plans during the 2-year observation period based on severity of TGCT. Within the first year ($N = 176$), 90 patients (51.1%) were categorized as severe diffuse; 66 patients (37.5%) were moderate diffuse; 20 patients (11.4%) were not assessable (Table 4). Within the second year ($N = 173$), 90

TABLE 3 TGCT treatment during the observation period by tumor status at baseline (full analysis set)

Tumor status at baseline, *n* (%)	Within 1st year (including baseline) *N* = 176	Within 2nd year *N* = 173
Naïve (no prior treatment)	**28 (15.9)**	**28 (16.2)**
Only surgery	17 (60.7)	2 (7.1)
Only systemic treatment	0	0
Surgery and other treatment[a]	0	0
Other treatment[b]	0	0
Wait and see	11 (39.3)	26 (92.9)
Primary diagnosis and at least one prior treatment	**70 (39.8)**	**69 (39.9)**
Only surgery	6 (8.6)	6 (8.7)
Only systemic treatment	22 (31.4)	4 (5.8)
Surgery and other treatment[a]	3 (4.3)	0
Other treatment[b]	2 (2.9)	0
Wait and see	37 (52.9)	59 (85.5)
Recurrent disease and at least one prior treatment	**78 (44.3)**	**76 (46.6)**
Only surgery	14 (17.9)	7 (9.2)
Only systemic treatment	21 (26.9)	7 (9.2)
Surgery and other treatment[a]	7 (9.0)	0
Other treatment[b]	1 (1.3)	0
Wait and see	35 (44.9)	62 (81.6)

Note: [a]Other treatment in combination with surgery includes radiotherapy, ^{90}Yttrium, systemic treatment. [b]Other treatment includes radiotherapy,^{90}Yttrium.

Abbreviation: TGCT, tenosynovial giant cell tumor.

TABLE 4 TGCT treatment during the observation period by TGCT severity classification (full analysis set)

TGCT severity classification, *n* (%)	Within 1st year (including baseline) *N* = 176	Within 2nd year *N* = 173
Moderate diffuse	**66 (37.5)**	**63 (36.4)**
Only surgery	11 (16.7)	4 (6.3)
Only systemic treatment	16 (24.2)	4 (6.3)
Surgery and other treatment[a]	1 (1.5)	0
Other treatment[b]	3 (4.5)	0
Wait and see	35 (53.0)	55 (87.3)
Severe diffuse	**90 (51.1)**	**90 (52.0)**
Only surgery	21 (23.3)	10 (11.1)
Only systemic treatment	25 (27.8)	7 (7.8)
Surgery and other treatment[a]	7 (7.8)	0
Other treatment[b]	0	0
Wait and see	37 (41.1)	73 (81.1)
Not assessable	**20 (11.4)**	**20 (11.6)**
Only surgery	5 (25.0)	1 (5.0)
Only systemic treatment	2 (10.0)	0
Surgery and other treatment[a]	2 (10.0)	0
Other treatment[b]	0	0
Wait and see	11 (55.0)	19 (95.0)

Note: [a]Other treatment in combination with surgery includes radiotherapy, ^{90}Yttrium, systemic treatment. [b]Other treatment includes radiotherapy, ^{90}Yttrium.

Abbreviation: TGCT, tenosynovial giant cell tumor.

patients (52.0%) were categorized as severe diffuse; 63 patients (36.4%) were categorized as moderate diffuse; 20 patients (11.6%) were not assessable (Table 4). The severity of TGCT was categorized as severe diffuse, moderate diffuse, or not assessable (Table 4). Including baseline and during the first year of observation, 37/90 patients with severe-diffuse TGCT (41.1%), 35/66 patients with moderate-diffuse TGCT (53.0%), and 11/20 patients with nonassessable TGCT (55.0%) were not treated but were actively surveilled and labeled as wait-and-see. Of the 53 severe-diffuse patients who received treatment during the first year, 28 (52.8%) received surgery (with or without other treatment) and 25 patients (47.2%) received systemic treatment only. Regarding patients categorized as moderate diffuse, 16/66 (24.2%) received systemic treatment only and 12/66 (18.2%) had surgery. Of the 20 patients with non-assessable TGCT, 7 (35.0%) had surgery, and 2 (10.0%) received systemic treatment only (Table 4). During the second year of observation, wait-and-see was the most common treatment strategy for all severity classes (moderate-diffuse, 55/63 patients [87.3%]; severe-diffuse, 73/90 patients [81.1%]; not assessable TGCT, 19/20 patients [95.0%]) (Table 4). Surgery only or systemic treatment only was applied 4/63 patients (6.3%) each in moderate-diffuse TGCT compared to 10/90 patients (11.1%, surgery only) or 7/90 patients (7.8%, systemic therapy), respectively, in severe-diffuse patients (Table 4).

3.5 | Antitumor strategies during the 2-year observational period

This section encompasses the concomitant therapies (antitumor surgeries [including related to TGCT]; adjuvant therapy, radiation therapy, systemic therapy) within the 1st year [including

baseline], 2nd year as well as the entire 2-year observation period. Within the whole 2-year observation period and regarding the entire FAS population ($N = 176$), 59 patients (33.5%) received concomitant tumor-related surgery (e.g., arthroscopic resection/synovectomy, open resection/one-stage synovectomy) (Table 5). Furthermore, 47/176 patients (26.7%) received concomitant tumor-related surgery within the first year of observation and 15/173 (8.7%) were treated during the second year. During the entire observation period, 64 concomitant tumor-related surgeries were performed, of which 49 were performed in the first year. The most common surgery was open resection/one-stage or two-stage synovectomy, performed in 44/61 patients (72.1%). Most of these patients ($n = 37$) were treated in the first year (Table 5). In two cases (3.3%), arthroscopic resection was carried out as concomitant tumor-related surgery. Aside from concomitant tumor-related surgery, 11/63 patients (17.5%) received adjuvant therapy. During the first year, 10 patients were treated for managing surgery related symptoms, of which 2 were additionally treated with radiation therapy (Table 5).

TABLE 5 Concomitant antitumor surgeries during the observation period (full analysis set)

	Within 1st year (including baseline) $N = 176$	Within 2nd year $N = 173$	Within whole 2-year period $N = 176$
Any concomitant antitumor surgery related to treatment of TGCT, *n* (%)	47 (26.7)	15 (8.7)	59 (33.5)
Type of surgery			
Arthroscopic resection/ synovectomy	2 (4.3)	0	2 (3.3)
Open resection/one-stage synovectomy	28 (59.6)	6 (42.9)	34 (55.7)
Open resection/two-stage synovectomy	9 (19.1)	1 (7.1)	10 (16.4)
Tumor (prosthesis)	1 (2.1)	2 (14.3)	3 (4.9)
Arthrodesis	1 (2.1)	1 (7.1)	2 (3.3)
Amputation	0	0	0
Other	7 (14.9)	4 (28.6)	11 (18.0)
Missing	0	1 (7.1)	1 (1.6)
Number of concomitant antitumor surgeries, *n* (%)	49 (100)	15 (100)	64 (100)
Adjuvant therapy, *n* (%)			
Yes	10 (20.4)	1 (7.1)	11 (17.2)
No	39 (79.6)	13 (86.7)	52 (81.3)
Missing	0	1 (6.7)	1 (1.6)
Radiation therapy, *n* (%)			
Yes	2 (20.0)	0	2 (18.2)
No	8 (80.0)	1 (100)	9 (81.8)
Systemic therapy, *n* (%)			
Yes	0	1 (100)	1 (9.1)
No	10 (100)	0	10 (90.9)
Concomitant therapies for managing surgery-related symptoms, *n* (%)			
Yes	10 (100)	0	10 (90.9)
No	0	1 (100)	1 (9.1)

Note: Percentage calculation can sum to >100% because patients can fall into more than one category.
Abbreviation: TGCT, tenosynovial giant cell tumor.

3.6 | Treatment-related imaging (MRIs) over the 2 years

This section summarizes patients who had MRIs related to treatment of TGCT during the observation period. Over 2-year observation period, 130/176 patients (73.9%) underwent a total of 270 MRIs, with most MRIs ($n = 170$) performed within the first year (Table 6). Furthermore, and over the 2 years, regular postoperative follow-up was the most common reason for MRIs being conducted (144/224, 64.3%), followed by MRIs conducted due to assess patient symptoms (72/224, 32.1%) (Table 6). MRIs were performed on average 9.3 ± 23.5 months before baseline (median: 2.5 months), within 6.4 ± 4.5 months from the baseline visit during the first year of observation, and within 19.9 ± 5.0 months from the baseline visit during the second year of observation (Table 6). During the 2 years, MRIs were performed on average within 11.4 ± 8.0 months after the baseline visit.

3.7 | Treatment strategy from baseline (start of treatment plan) through 2-year follow-up

3.7.1 | No current/planned treatment at start of treatment plan (off-treatment)

Of the 79 patients at baseline who did not have a current or planned treatment, 60 (75.9%) remained without any treatment at 1 year, whereas 11 patients (13.9%) switched treatment course (6 to systemic, 5 to surgery) (Figure 4). At 2 years, the majority who did not have any treatment at 1 year remained without treatment (54/60, 90.0%), whereas 3 patients switched to surgery and 2 switched to systemic therapy as their treatment (Figure 4). Only 1/11 patients (9.1%) switched treatment course (systemic to surgery) between years 1 and 2 (Figure 4). Of the 79 total patients at baseline who had no current or planned treatment 54 (68.4%) remained without current or planned treatment from baseline through the 2-year follow-up (Figure 4).

3.7.2 | Systemic treatment at start of treatment plan through entire observation period

Of the 45 patients at baseline with systemic treatment, 38 (84.4%) remained with systemic therapy as their treatment strategy at 1 year, while 6 patients (13.3%) switched treatment course to surgery (Figure 5). At 2 years, most patients who had systemic therapy as their treatment strategy at 1 year remained that way (30/38, 78.9%), 4 patients switched to surgery, and 2 switched to systemic therapy + surgery as their treatment strategy (Figure 5). All 6 patients who switched from systemic therapy to surgery at 1 year remained with surgery as their treatment strategy at the 2-year follow-up visit (Figure 5). Taken together, 30/45 patients (66.7%) who had systemic therapy as their treatment strategy at baseline remained on systemic treatment through the 2-year follow-up visit. Furthermore, before

TABLE 6 MRIs related to treatment of TGCT (full analysis set)

	Prior baseline	Within 1st year (including baseline)	Within 2nd year	Within whole 2-year period
Number of MRIs	159	170	100	270
Indication for MRI, *n* (%)				
n	159	108	84	130
Primary diagnosis	40 (27.4)	1 (0.7)	2 (2.5)	3 (1.3)
Presurgery	15 (10.3)	4 (2.8)	1 (1.3)	5 (2.2)
Regular postoperative follow-up	53 (36.3)	88 (60.7)	56 (70.9)	144 (64.3)
Follow-up due to complaints	38 (26.0)	52 (35.9)	20 (25.3)	72 (32.1)
Missing	13 (8.2)	25 (23.1)	21 (25.0)	46 (35.4)
Time since baseline (months)				
Mean (*SD*)	9.28 (23.48)	6.44 (4.49)	19.91 (5.01)	11.43 (8.02)
Median	2.5	5.88	20.85	10.98
Q1, Q3	0.85, 7.98	2.53, 10.51	17.25, 23.35	4.50, 18.20
Min, Max	0.1, 247.0	0.0, 17.2	0.1, 29.7	0.0, 29.7

Abbreviations: MRI, magnetic resonance imaging; *SD*, standard deviation; TGCT, tenosynovial giant cell tumor.

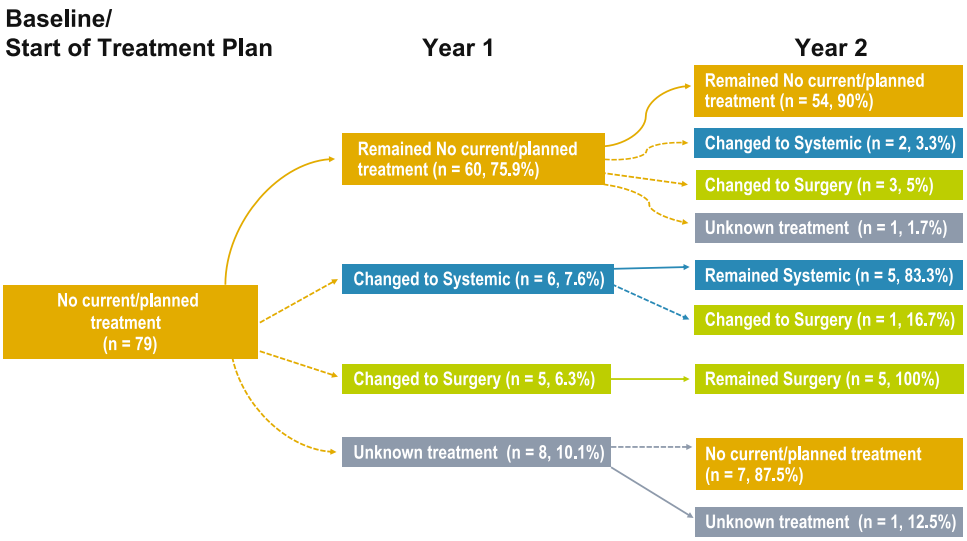

FIGURE 4 Treatment strategy during 2-year observation period with no current/planned treatment at baseline
Solid lines indicate patients who remained on the same treatment strategy. Dotted lines indicate patients who changed treatment strategy

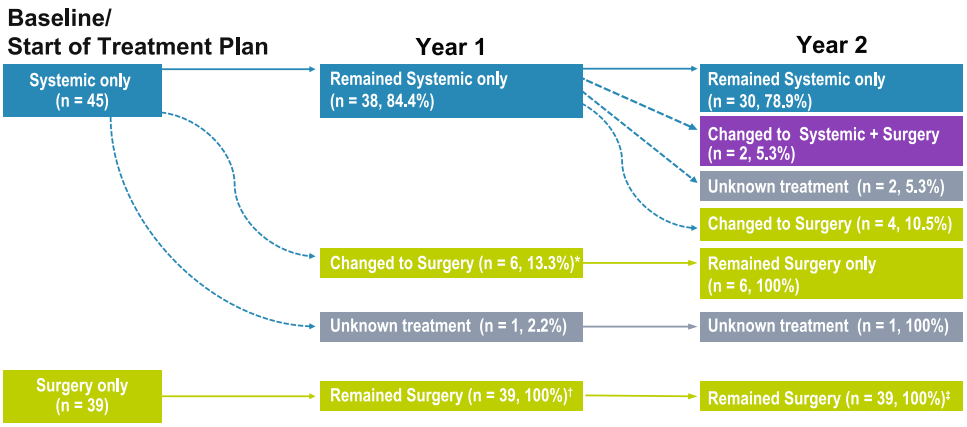

FIGURE 5 Treatment strategy during 2-year observation period with no current/planned treatment at baseline
Solid lines indicate patients who remained on the same treatment strategy. Dotted lines indicate patients who changed treatment strategy. *Surgery ($n = 5$) and future surgery ($n = 1$). †Seven were classified as unknown treatment. ‡Two were classified as unknown treatment

and ongoing at baseline, 37/176 patients (21.0%) had concomitant systemic therapy related to TGCT, and all were either pexidartinib ($n = 22$) or imatinib ($n = 15$). Between baseline and 2-year observational follow-up, 55/176 patients (31.3%) received systemic therapy, of which 52 received either pexidartinib ($n = 27$) or imatinib ($n = 25$).

3.7.3 | Surgery at start of treatment plan through 2-year observation period

A total of 39 patients had surgery as their treatment strategy at baseline. Contrary to the other treatment strategies (i.e., no current/planned treatment, systemic therapy), none of the patients who started with surgery at baseline switched to a different treatment strategy. All 39 patients (100%) were classified as surgery throughout the 2-year observational period as they were managed as postoperative follow-up, referred to as watchful waiting/wait-and-see (Figure 5).

4 | DISCUSSION

TOPP is the first large, prospective, multinational, multicenter observational disease registry conducted for D-TGCT. This registry allowed for gaining insight into the characteristics of D-TGCT and its treatment options by assessing the journey of these patients from disease onset to diagnosis, management and treatment of the disease, disease severity, rate of recurrence and impact of the disease on PRO. This analysis included 176 patients over approximately 2 years from 12 sites (6 oncologic sites, 6 orthopedic sites) and demonstrated that conduction of collaborative observational studies for a rare tumor is achievable.

Previously, the TOPP registry described the impact of TGCT on PRO from a baseline snapshot.[29] This analysis is the first to provide a picture of the treatment journey of D-TGCT patients as a 2-year observational follow-up. In accordance with previous reports, this study confirms that D-TGCT has its onset in a relatively young working population and is more common in females.[11,12] With TCGT being a chronic disease, both the disease itself but also the treatments may have a high impact on the ability to work. Diagnosis of D-TGCT can take many years, likely due to the unspecific disease symptoms and treating physicians' lack of familiarity with the disease.[29,31] This results in several general practitioner and specialist visits until patients receive the proper diagnosis and are adequately treated. As treatment options are limited and treatment guidelines are lacking, the treatment of D-TGCT is complex and often based on the disease status at diagnosis (primary vs. recurrent disease and D-TGCT severity), the clinical expertize of the treating physician, and clinical symptoms.

In this analysis, the most common treatment method for D-TGCT patients was surgery, with the most common procedure during the 2 years being open resection/one-stage synovectomy. This is consistent with previous reports in which the main types of surgery being performed were open resection or arthroscopy, or a combined approach.[2,8,29,32] However, due to the often invasive extra- and intra-articular tumor growth, complete resection of the tumor is difficult to achieve, which results in residual disease, recurrence, and repetitive surgeries.[33,34] As previously reported, some physicians had better outcomes with open surgery and others had more favorable outcomes with arthroscopy, while some studies were inconclusive,[29] leaving the optimal surgical approach up for debate and the overall treatment strategy for patients with D-TGCT still ill-defined. The outcome of surgery may depend on a surgeon's experience but could also reflect the lack of a "staging" and standards for timing and type of surgery.

Besides surgery, several systemic treatments (mostly TKIs) have been studied as potential therapies for TGCTs. Discovery of the underlying molecular mechanism of the disease involving the CSF1 pathway has led to the development of medications that block the activity of the CSF1-receptor.[9,35] Of these systemic therapies, pexidartinib, an oral small-molecule TKI and CSF1 inhibitor, is currently the only FDA-approved agent for the treatment of adult patients with symptomatic TGCT associated with severe disease or functional limitations and not amenable to improvement with surgery. More specifically, it is approved only in the United States at a dosage of 400 mg twice daily and has been added by the National Comprehensive Cancer Network as a category 1 recommendation.[36,37]

Targeted systemic therapy was most performed in patients with severe D-TGCT to stabilize progressive or recurrent disease. Systemic therapies were administered mostly in combination with other treatment (75.9%, $n = 44/58$). The most common systemic treatment before baseline was pexidartinib (30/58, 51.7%) followed by off-label imatinib (20/58, 34.5%), which is the result of the studies performed in the participating centers. Of note, some of the centers located within the EU did not have pexidartinib as a treatment option.

Wait-and-see was the common treatment approach utilized for patients who received prior treatment and/or presented with less severe D-TGCT-related symptoms at the baseline visit. During the 2-year observation period, most patients (123/163, 75.5%) remained on the same treatment strategy. A total of 54/79 patients (68.4%) with no planned treatment at baseline continued that way, 30/45 (66.7%) of patients on baseline systemic therapy continued with this treatment course, and 100% (39/39) of patients treated with surgery at the time of enrollment were followed postoperatively without transitioning to alternative therapy pathways during study follow up. Those who changed treatment strategy utilized multimodal treatment options.

Within the context of these findings, developing multidisciplinary guidelines for the treatment of primary and refractory cases is of the utmost importance. If patients with D-TGCT are evaluated by multidisciplinary teams, they are given treatment plans that often do not require change, as evidenced by the low rate of changing treatment strategy over the 2-year observational period. To date, the literature lacks treatment guidelines and does not present relevant clinical findings that support clinical decision making. Creating a framework for risk-benefit treatment discussions of primary and relapsed-TGCT are of paramount importance, including how to effectively incorporate simple clinical observation (wait-and-see).[34,38–40] This study design has successfully shown that disease registries in rare diseases can be used as a critical tool to expand the knowledge about rare diseases, optimize treatment strategies, and identify unmet needs.

4.1 | Limitations

Baseline data were checked during on-site visits by local clinical research associates for all patients enrolled in Europe. Due to the COVID-19 pandemic, the planned on-site monitoring visits in the United States could not be performed. Instead of on-site monitoring visits, more frequent and detailed remote monitoring visits were performed for these sites. The study oversight was adequately maintained despite the challenges imposed by COVID restrictions. Follow-up data for all enrolled patients were regularly monitored remotely. Therefore, a certain amount of incorrect or incomplete data is assumed for all study sites. The study spanned only 2 years which arguably is a short window for a slowly growing disease. Nonetheless, this study reports the longest prospective follow up to date of the TGCT patient experience and is thus still of value both to TGCT patients and treating physicians. The study sites are tertiary sarcoma centers, and as such may not fully represent the entire spectrum of TGCT disease, which may be managed at non-referral centers in earlier disease stages. There remains a lack of systemic treatment options with only one agent approved and only in the United States. Patients in clinical studies and expanded access programs were allowed to enter the study.

5 | CONCLUSION

This prospectively collected longitudinal assessment of D-TGCT treatment demonstrates the durability of multidisciplinary teams decision making in the treatment of this rare, potentially chronic disease. As a result, patients can be presented with all treatment options at diagnosis and followed closely which could explain the lower rates of change from initial treatment strategies.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at https://vivli.org/ourmember/daiichi-sankyo//. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-DS.aspx.

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CONFLICTS OF INTEREST

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ETHICS STATEMENT

All patients provided written consent.

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