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Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: a multicentre, cluster-randomised trial within the German Interdisciplinary Sarcoma Group (GISG)

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ABSTRACT

Objectives The choice of drug treatment in advanced soft tissue sarcoma (STS) continues to be a challenge regarding efficacy, quality of life (QoL) and toxicity. Unlike other cancer types, where integrating patient-reported outcomes (PRO) has proven to be beneficial for QoL, there is no such evidence in patients with STS as of now. The YonLife trial aimed to explore the effect of a tailored multistep intervention on QoL, symptoms and survival in patients with advanced STS undergoing treatment with trabectedin as well as identifying predictors of QoL.

Design YonLife is a cluster-randomised, open-label, proof-of-concept study. The intervention incorporates electronic PRO assessment, a case vignette and expert-consented treatment recommendations.

Participants Six hospitals were randomised to the control arm (CA) or interventional arm (IA). Seventy-nine patients were included of whom 40 were analysed as per-protocol analysis set.

Primary and secondary outcome measures The primary end point was the change of Functional Assessment for Cancer Therapy (FACT-G) total score after 9 weeks. Secondary outcomes included QoL (FACT-G subscales), anorexia and cachexia (Functional Assessment of Anorexia/Cachexia Therapy (FAACT)), symptoms (MD Anderson Symptom Inventory (MDASI)), anxiety and depression (HADS), pain intensity and interference (Brief Pain Inventory (BPI)) and survival assessment.

Results After 9 weeks of treatment, QoL declined less in the IA (ΔFACT-G total score: -2.4, 95% CI: -9.2 to 4.5) as compared with CA (ΔFACT-G total score: -3.9; 95% CI: -11.3 to 3.5; p=0.765). In almost all FACT-G subscales, average declines were lower in IA, but without reaching statistical significance. Smaller adverse trends between arms were observed for MDASI, FAACT, HADS and BPI scales. These trends failed to reach statistical significance.

Strengths and limitations of this study

► YonLife explores the value and efficacy of a patient-directed intervention on quality of life in sarcoma patients.
► YonLife captures patient-reported outcomes electronically and provides a tailored expert-derived intervention in a multicentre setting.
► Effect sizes are now available for conducting confirmatory trials to examine the YonLife results.

Overall mean survival was longer in IA (648 days) than in CA (389 days, p=0.110). QoL was predicted by symptom severity, symptom interference, depression and anxiety.

Conclusion Our data suggest a potentially favourable effect of an electronic patient-reported outcomes based intervention on QoL that needs to be reappraised in confirmatory studies.

Trial registration number ClinicalTrials.gov Identifier (NCT02204111).

INTRODUCTION

The armamentarium of systemic treatment in advanced soft tissue sarcoma (STS) has evolved over the past decade. Yet, the burden of disease remains high and drug-related adverse events are frequent,[1–3] even in patients who experience long-lasting clinical benefit. Overall, quality of life (QoL) in sarcoma patients is more impaired than in the general population,[2 4] but comparable with patients with more frequent cancer diseases.[5]

Mental health problems such as distress, depression and anxiety are as frequent as in other cancer patients.[6 7]

Treatment algorithms for STS beyond first-line treatment do not show superiority between one regimen and another.[8] On the other hand, there are distinct and drug-specific side effects. Therefore, the choice of which regimen should be applied becomes a matter of debate within the patient–doctor consultation with considerations comprising preferences and personal beliefs.[9] Consequently, it is important to assess the treatment effectiveness in two ways. First, in terms of tumour burden as an outcome (eg, progression-free survival (PFS) or overall survival (OS)), and, second, in terms of symptoms and toxicities as assessed by patient-reported outcomes (PRO). As an individual might experience improvement in symptoms while a treatment is not superior on a group level, appropriate strategies to evaluate the individual patient benefit need to be applied. Especially, if there is no superiority in survival, further outcomes should be considered, such as evaluation of minimal clinical important difference (MCID) or the time to deterioration of QoL.[10]

Trabectedin (Yondelis) is a semisynthetic drug originally isolated from the sea squirt *Ecteinascidia turbinata* with a complex multimodal mechanism of action.[11 12] Trabectedin was the first marine-derived antineoplastic drug approved in 2007 in the European Union and in over 70 countries across the globe for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.[13] In 2015, trabectedin was also approved in the USA based on a pivotal phase III trial, which demonstrated that trabectedin had a significantly longer PFS compared with dacarbazine in patients with advanced liposarcoma or leiomyosarcoma after failure of prior chemotherapy.[14] Noteworthy, an ad hoc analysis of the phase III trial, which compared inpatient with outpatient infusion of trabectedin, showed that safety, efficacy and PRO outcomes were comparable between both treatment settings.[15] In addition, an analysis of the MD Anderson Symptom Inventory (MDASI) PRO scores reported no clinically meaningful differences among patients reporting severe symptoms (MDASI score ≥7) who were treated with trabectedin in either an inpatient or outpatient treatment settings.[15]

Assessment and interventions based on PRO have been proven to yield beneficial outcomes in various settings and entities.[16–21] For instance, Basch *et al* found benefits of their Symptom Tracking and Reporting (STAR) intervention in prolonging time on chemotherapy, less unexpected admissions and longer quality-adjusted survival.[17] In brief, they randomised 766 patients from a single institution under chemotherapy for solid tumours to either usual care or STAR. The intervention consisted of 12 different symptoms collected remotely, providing treating physicians with graphical representations of results and alerting nurses when a preset cut-off of worsening condition was met. Another randomised multicentre trial evaluated the effect of a web-based, self-reported assessment and educational intervention on symptom distress during cancer therapy in 752 ambulatory patients from different entities and with various diagnoses.[18] In this multicentre sample of participants they reported that web-based patients-rated symptoms and communication coaching reduced symptom distress after active cancer treatment, particularly in those aged >50 years. Nevertheless, PRO assessment in patients treated for STS struggle with serious barriers such as a relatively small patient population and the fact that no STS-specific QoL or symptom questionnaires are available.[4 22] Considering that merely assessing PRO might not be beneficial,[23] we believe that it should be accompanied by additional interventions such as nurse-led patient education, self-care support or a multiprofessional expert panel that discusses PRO results and derives treatment recommendations.[24] Despite the increasing knowledge on benefits and assessment of PRO in general and the high symptom-burden of patients suffering from advanced STS, the proof of concept for such interventions remains open. Therefore, the cluster-randomised YonLife study was designed to evaluate the value and efficacy of a tailored, patient-directed palliative intervention based on various domains of QoL and to explore effect sizes using different PRO instruments in patients with advanced STS undergoing treatment with trabectedin.

METHODS

Patients

Adult patients (≥18 years) suffering from advanced or metastatic STS who had received at least one dose of trabectedin 1.5 mg/m², given as a 24-hour intravenous infusion every 3 weeks, were included in this study. Physician-assessed life expectancy of patients had to be at least 6 months and Eastern Cooperative Oncology Group (ECOG) performance status score had to be ≤2.

Patient and public involvement

We are grateful to all patients who participated in the YonLife trial. A member of the national sarcoma patient advocacy group 'Das Lebenhaus' took part in the expert panel discussion.

Trial design and objectives

Full details of YonLife trial (ClinicalTrials.gov Identifier: NCT02204111) have been reported.[25] Briefly, the YonLife trial was designed as a cluster-randomised, explorative, open-label, non-blinded, proof-of-concept study with the aim to compare the overall QoL between patients with STS receiving a multidimensional intervention, on the basis of patients' individual PROs, and those patients receiving usual supportive treatment. Outcomes were assessed at baseline (ie, visit (V) 1) and after 3 (V2), 6 (V3) and 9 (V4) weeks. Follow-up was conducted 21 (V5), 35 (V6) and 61 (V7) weeks after baseline. Primary objective was the explorative comparison of QoL change after

9 weeks (V4) between interventional arm and control arm. Secondary objectives included explorative comparison between other PROs such as anxiety, depression, pain as well as survival. Furthermore, factors that predict QoL after 9 weeks were explored.

Intervention

Patients in the control arm (CA) received only electronic PRO assessment without feedback to the treatment team. Patients treated in the interventional arm (IA) received a comprehensive four-step evaluation comprising: (1) PROs were assessed electronically via handheld tablet PCs at each visit; (2) a case vignette was created based on the obtained PRO and clinical data at baseline; (3) supportive care recommendations were consented during discussion on patients' vignettes in a multiprofessional expert panel and (4) these treatment suggestions as well as graphical representation of obtained PRO were provided to the treating physicians prior to V2 in the interventional centre. Clinicians in the IA had the opportunity to discuss the graphical presentation with their patients and initiate the treatment suggestions. The expert panel consisted of experts in the field of oncology, palliative care, social work, nursing, psycho-oncology as well as a patient advocate.

Randomisation

Six German centres were cluster-randomised in a 1:1 ratio in an IA (three centres) and a CA (three centres). This trial was designed as a cluster-randomised trials to avoid contamination that might result in a type 2 error. If randomised on patient level, contamination might have been occurred as patients talked to each other about the recommendations or the treating physician-transferred recommendations from one patient to another. Randomisation was conducted by a colleague not actively involved in this trial using random numbers generated in excel.

The seventh centre where the supportive care recommendations were created served as a reference centre (RC). Patients treated at the RC received the same intervention as in the IA but they were analysed separately. The RC was invented to avoid bias from a dual role of participating clinicians as being part of treatment staff in the centre and taking part in the expert panel at the same time. Furthermore, we initiated the RC at first centre to get to know and solve any technical or logistical barriers in a monocentre setting before spreading it to a multicentre setting.

Outcome measures

The primary outcome explored the changes of patients QoL in IA and CA after 9 weeks of treatment as measured with the Functional Assessment for Cancer Therapy (FACT-G) total score. Nine weeks was set as time for primary outcome assessment since this period provides enough time to take action concerning interventional proposals. The FACT-G is a PRO measure used to assess health-related QoL in patients undergoing cancer therapy as a total sum score (ranging from 0 to 108) comprising four subscales of QoL (physical, social, emotional and functional well-being).[26] Furthermore, we evaluated the number of patients with a clinical improvement between V1 and V4. This equals a change in the FACT-G total score of at least 3.3 points to represent a MCID. Additionally, the time until QoL deterioration (TUD) was also assessed as a change of at least 3.3 points between V1 and V4 as defined by King *et al*.[27] Analyses of long-term effects included the data collected from V1 until the end of the study at week 67 (V7). Visit schedule and outcomes of all secondary end points measured throughout the study are depicted in table 1.

Secondary outcomes included the subscales of the FACT-G questionnaire: physical (range: 0–28), emotional (range: 0–24), functional (range: 0–28) and social well-being (range: 0–28) explored at V4 and during follow-up (ie, V7).[24] Moreover, the effect size of the intervention was measured as Cohen's d.[28] The MDASI was used to measure the severity of 13 cancer-related symptoms and their impact on six dimensions of daily life.[29] Psychological distress was evaluated by the Hospital Anxiety and Depression Scale (HADS).[30] It provided a total sum score (range: 0–42) and two self-rating subscales for anxiety and depression (range: 0–21). HADS also identified clinically relevant cases of anxiety and depression using predetermined cut-off scores.[31] The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire measured the impact of cachexia and anorexia on patients' QoL.[32] Finally, the Brief Pain Inventory (BPI) in a scale range from 0 to 10 measured the intensity of pain and pain-related interference.[33] We assessed the predictive value of the following variables at V1 for QoL: gender, age, performance status (ECOG), tumour stage (UICC classification), symptom severity (MDASI), symptom interference (MDASI), depression (HADS), anxiety (HADS), patients' satisfaction (IN-PATSAT32)[34] and anorexia/cachexia (FAACT).

Statistical considerations

The patients sample size was calculated for an explorative purpose. We assumed the superiority of our intervention concerning FACT-G total score. Type I error was set to $\alpha=0.05$ (one-sided), with a statistical power of $1-\beta=0.80$ and a medium effect[27] between the groups in FACT-G=15, with an estimated SD of $\sigma=17$ and a conservatively estimated intracluster correlation coefficient of p=0.10.[35] This calculation resulted in a cluster size of 11 patients. Additionally, 11 patients were recruited in the RC, for a total of 77 patients.

The full analysis set (FAS) comprised all patients included in the study and allocated to a treatment group irrespective of their compliance with the planned course of treatment (intention-to-treat principle). Analyses of efficacy end points were performed on the per-protocol analysis set (PPS) defined as the subset of patients of the FAS who have provided complete data at the first (V1) and last (V4) visits and who had no major protocol deviations.

Table 1 Visit schedule and outcomes

Study period	Baseline	Intervention phase			Follow-up phase		
Visit	1	2	3	4	5	6	7
Week (±3 days)	0	3	6	9			
Week (±1 week)					21	35	61
Concomitant medication	x	x	x	x	x	x	x
FACT-G	x	x	x	x	x	x	x
MDASI	x	x	x	x	x	x	x
FAACT	x			x	x	x	x
BPI	x			x	x	x	x
IN-PATSAT32*	x			x	x	x	x
HADS	x			x	x	x	x
Tumour-specific and socio-demographic parameters	x			x	x	x	x
Feasibility scoring based on patients' and doctors' opinion*				x			

*Data are currently being analysed and are available on request.
BPI, Brief Pain Inventory; FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FACT-G, Functional Assessment for Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; IN-PATSAT32, Satisfaction with In-Patient Cancer Care; MDASI, MD Anderson Symptom Inventory.

Survival was assessed as means of PFS and OS. The PFS and OS analyses were defined as the time interval from the first administration of trabectedin to the earliest date of disease progression or death, regardless of cause (whichever occurred first) for PFS, whereas OS was defined as the time between the start of trabectedin and patient death from any cause. Patients were censored after the discontinuation of their study participation. Means of PFS and OS are reported to provide the ability to describe and compare the arms, as median value of OS is not defined for CI within the observation period of this study. Mann-Whitney U test, Fisher exact test and χ^2 test were used for the detection of possible differences concerning demographics. The t-test was applied to detect possible differences between metric outcomes, whereas linear univariate and multivariate regression were calculated to identify determinants of QoL at V4.

Figure 1 CONSORT flow chart. FAS, full analysis set; PPS, per-protocol analysis set.

RESULTS
Patients and treatment arms
Between September 2014 and March 2018, 80 patients from 7 sites were screened for study participation (figure 1). The FAS encompasses 79 patients, as 1 patient had to be excluded from analysis due to protocol violation. In the FAS, mean age was 58 years (range: 22–86). Leiomyosarcoma (n=32) and liposarcoma (n=23) were the most prevalent histological type of sarcomas. At baseline, the IA included 38 patients (19 of whom included in PPS), while CA consisted of 29 patients (14 of whom included in PPS). No difference concerning age, gender and the number of previous cycles of trabectedin was observed between the arms. In the CA, more patients had a higher tumour stage (p=0.083) and less patients suffer from leiomyosarcoma (table 2).

Primary outcome
After 9 weeks at V4, FACT-G declined less in IA (Δ FACT-G total score: −2.4, 95% CI: −9.2 to 4.5) as compared with the CA (Δ FACT-G total score: −3.9, 95% CI: −11.3 to 3.5; p=0.765) (table 3). The effect size of the intervention on the FACT-G score was d=0.269 (small effect). Intra-cluster correlation was 0. Figure 2 and online supplementary table 1 depicts absolute FACT scores trajectories over time. The number of patients experiencing a MCID was equal in both groups (IA: 44% and CA: 43%). The median TUD differed slightly between IA (25 days, 95% CI: 6.2 to 43.8) and CA (22 days, 95% CI: 16.5 to 27.5; p=0.927).

Secondary outcomes
Regarding the change of QoL between V1 and V4 (as well as during follow-up V7), there was a beneficial impact
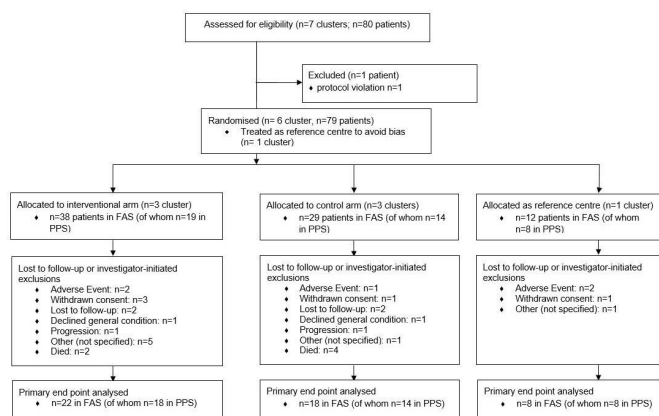
Table 2 Patient characteristic at baseline

	IA (3 centres), N=38	CA (3 centres), N=29	RC (1 centre), N=12	FAS, N=79
FAS				
Gender				
Male	20	15	6	41
Female	18	14	6	38
Age				
Mean (SD)	58 (12)	56 (15)	63 (16)	58 (14)
Range (years)	38–87	22–80	34–82	22–87
Tumour histology				
Leiomyosarcoma	19	5	5	29
Liposarcoma	6	11	3	20
Others*	13	12	4	29
Missing	0	1	0	1
Metastatic disease				
M0	16	11	5	32
M1	12	16	7	35
Missing	10	2	0	12
ECOG PS				
0	20	14	5	39
1	15	13	7	35
2	3	0	0	3
Missing	0	2	0	2
Number of previous cycles of trabectedin				
Median	0	1	1	1
Range	0–15	0–17	0–11	0–17
Number of previous cycles of another chemotherapy				
Median	1.5	1	2	2
Range	0–6	0–5	1–4	0–6
Number of previous lines of another chemotherapy				
Median	2.5	2.5	3	2
Range	0–6	0–6	2–5	0–6
	IA (3 centres), N=19	**CA (3 centres), N=14**	**RC (1 centre), N=8**	**PPS, N=41**
PPS				
Gender				
Male	8	6	3	17
Female	11	8	5	24
Age				
Mean (SD)	61 (12)	55 (15)	59 (17)	58 (14)
Range (years)	44–87	30–80	34–82	30–87
Tumour histology				
Leiomyosarcoma	5	6	4	15
Liposarcoma	11	1	3	15
Others*	3	7	1	11
Missing	0	0	0	0
Metastatic disease				
M0	8	5	2	15
M1	5	9	6	20
Missing	6	0	0	6

Table 2 Continued

	IA (3 centres), N=19	CA (3 centres), N=14	RC (1 centre), N=8	PPS, N=41
ECOG PS				
0	12	8	4	24
1	6	6	4	16
2	1	0	0	1
Missing	0	0	0	0
Number of previous cycles of trabectedin				
Median	0	1	1	1
Range	0–15	0–7	1–11	0–15
Number of previous cycles of another chemotherapy				
Median	1	1	2	2
Range	0–4	0–3	2–4	0–4

*All subtypes occurring less than four times were merged into this category.
CA, control arm; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; IA, interventional arm; M0, no distant metastasis; M1, distant metastasis; PPS, per-protocol analysis set; RC, reference centre.

of the patient-tailored intervention in IA in all FACT-G subscales except for social well-being (figure 2). There was less decline in physical well-being subscale in IA (ΔFACT-G PWB: −1.2, 95% CI: −4.4 to 2.1) than in CA (ΔFACT-G PWB: −2.2, 95% CI: −5.4 to 1.0; p=0.926). Emotional well-being subscale improved slightly in IA (ΔFACT-G EWB: 0.9, 95% CI: −0.6 to 2.4) and remained almost stable in CA (ΔFACT-G EWB: −0.1, 95% CI: −2.3 to 2.1; p=0.561). Functional well-being subscale declined less in IA (ΔFACT-G FWB: −0.5, 95% CI: −2.7 to 1.7) than in CA (ΔFACT-G FWB: −1.3, 95% CI: −4.0 to 1.4; p=0.536). Lastly, social well-being subscale remained almost stable (ΔFACT-G SWB: −0.2, 95% CI: −2.2 to 1.7) in CA while decreasing in IA (ΔFACT-G SWB: −1.6, 95% CI: −3.1 to −0.1; p=0.952). Overall, there were non-significant, adverse trends in other domains of PRO (MDASI, FAACT, HADS and BPI scales) (table 3 and online supplementary table 2).

Overall mean OS was longer in IA than in CA (648 vs 389 days) without reaching statistical significance (p=0.110), while means of PFS were almost identical in IA and CA (249 vs 232 days; p=0.899).

QoL prediction
Univariate regressions revealed that each of the following variables determined the FACT-G total score: symptom severity, symptom interference, depression and anxiety. No influence on the FACT-G total score was found for age, gender, ECOG performance status, patient satisfaction, tumour stage, anorexia and cachexia (table 4). In

Table 3 Change scores after 9 weeks of treatment

	Mean change from baseline (V1) to 9 weeks (V4)							
	Interventional arm			Control arm				Interventional trend
	Mean	95% CI	N	Mean	95% CI	N	P value	
FACT-G total	−2.4	−9.2 to 4.5	18	−3.9	−11.3 to 3.5	14	0.765	Beneficial
FACT-G physical well-being	−1.2	−4.4 to 2.1	18	−2.2	−5.4 to 1.0	14	0.722	Beneficial
FACT-G social well-being	−1.6	−3.1 to −0.1	18	−0.2	−2.2 to 1.7	14	0.193	Adverse
FACT-G emotional well-being	0.9	−0.6 to 2.4	18	−0.1	−2.3 to 2.1	14	0.561	Beneficial
FACT-G functional well-being	−0.5	−2.7 to 1.7	18	−1.3	−4.0 to 1.4	14	0.536	Beneficial
HADS depression	0.3	−0.6 to 1.2	18	0.2	−2.1 to 2.5	14	0.419	Equivalent
HADS anxiety	0.3	−1.7 to 2.2	18	−0.8	−3.0 to 1.4	14	0.710	Adverse
BPI average pain	0.6	−0.3 to 1.5	19	0.2	−0.5 to 1.0	14	0.788	Adverse
BPI pain interference	0.4	−0.3 to 1.1	18	0.1	−0.5 to 0.7	13	0.679	Adverse
MDASI symptom severity	0.7	−0.1 to 1.4	18	0.2	−0.4 to 0.8	14	0.442	Adverse
MDASI symptom interference	1.2	0.9 to 1.6	18	0.8	−0.4 to 1.9	13	0.667	Adverse

BPI, Brief Pain Inventory; FACT-G, Functional Assessment for Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; MDASI, MD Anderson Symptom Inventory; N, number of evaluable patients in respective cluster; V, visit.
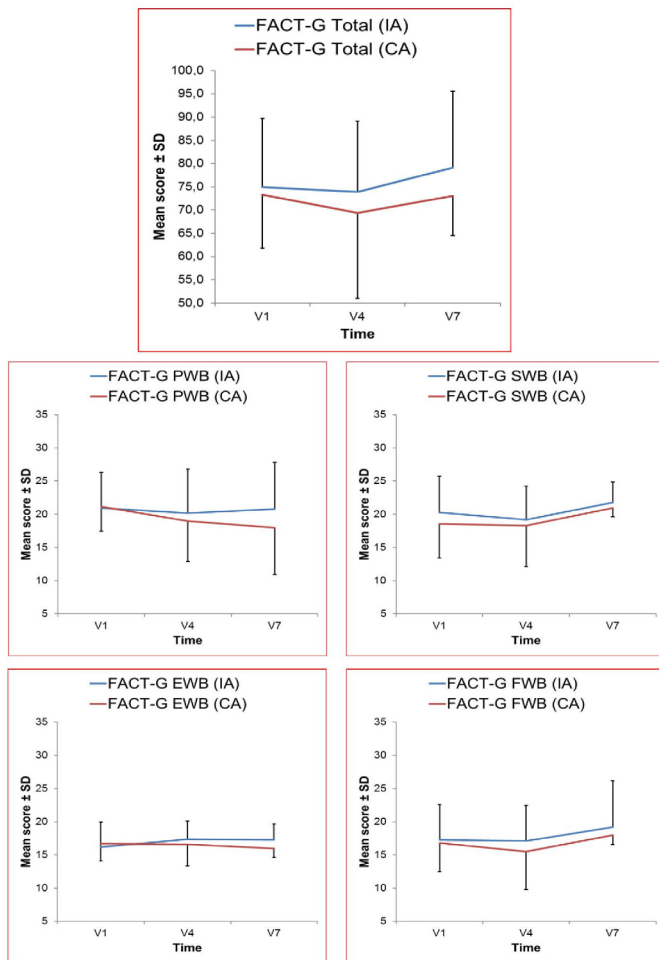
Figure 2 Absolute FACT scores at baseline (V1), after 9 weeks of treatment (V4; primary end point) and during follow-up visit (V7). Number of evaluated patients for all FACT-G dimensions per visit and cohort: V1: IA, N=19, CA, N=14; V4: IA, N=18, CA, N=14; V7: IA, N=9, CA, N=2. CA, control arm; EWB, emotional well-being; FACT-G, Functional Assessment for Cancer Therapy; FWB, functional well-being; IA, interventional arm; PWB, physical well-being; SWB, social well-being; V, visit.

a multivariable regression, depression determines the FACT-G total score (table 4).

DISCUSSION
Principal findings
To the best of our knowledge, this is the first randomised trial using a patient-directed supportive care intervention to improve QoL and other PRO in sarcoma patients. We observed a trend in favour of the intervention, considering the primary end point (total FACT-G score) and other secondary outcomes (ie, physical, functional and emotional well-being QoL subscales). On the other side, MCID and TUD assessments slightly differed between the arms. Not surprisingly and due to the character of palliative disease, absolute numbers in FACT-G score decline over time. This change is well in line with findings from a multicentre randomised trial, which reported a comparable decline in

Table 4 Univariate and multiple regression of FACT-G total score after 9 weeks (V4) on parameters measured at baseline (V1) over all groups

	P value	Estimate	95% CI
Univariate regression			
Gender	0.154	7.5	−2.8 to 17.8
Age	0.228	−0.2	−0.5 to 0.1
ECOG PS	0.509	−3.2	−12.7 to 6.3
Tumour stage	0.284	−1.8	−5.1 to 1.5
Symptom severity	0.0	−6.6	−10.5 to −2.7
Symptom interference	0.011	−3.4	−6.0 to −0.8
Depression	0.0	−2.7	−4.3 to −1.1
Anxiety	0.034	−1.4	−2.7 to −0.1
Patient satisfaction	0.451	3.0	−4.8 to 10.8
Anorexia/cachexia	0.143	0.8	−0.3 to 1.9
Multiple regression			
Gender	0.844	1.0	−7.2 to 9.4
Age	0.103	−0.3	−0.6 to 0.1
ECOG PS	0.746	1.5	−6.1 to 9.1
Tumour stage	0.586	−0.8	−3.4 to 1.7
Symptom severity	0.079	−4.4	−8.3 to −0.2
Symptom interference	0.744	0.5	−1.8 to 2.8
Depression	0.025	−2.2	−3.9 to −0.7
Anxiety	0.869	−0.1	−1.5 to 1.3
Patient satisfaction	0.437	−0.1	−0.4 to 0.1
Anorexia/cachexia	0.161	−0.9	−2.0 to 0.2

ECOG PS, Eastern Cooperative Oncology Group performance status; FACT-G, Functional Assessment for Cancer Therapy.

FACT-G score of ~2 in 281 patients suffering from advanced solid cancers who received early palliative care or standard oncological care.[36] In addition, the total FACT-G score they observed after 12 weeks (70.1 and 69.6) was comparable with the score found in IA (73.9) and CA (69.4) after 9 weeks of treatment. The total FACT-G score (76.4) was also comparable with the YonLife baseline score (74.2) in a sample of 42 patients suffering from different sarcoma histotypes in a single-centre, cross-sectional study.[37]

As the intervention appears to be favourable on QoL (without reaching statistical significance), it seemed adverse on symptom domains such as average pain, as well as anxiety and depression. For the former, the applied intervention might not have been timely enough, as adequate pain management needs immediate action instead of recommendation that takes several days. Complex syndromes such as anxiety and depression need ongoing treatment, either psycho-oncological or pharmaceutical, which usually takes more time to be effective.

YonLife intervention—unanswered questions and future research
There are still many unanswered questions regarding comprehensive QoL interventions. During the past

years, several reports with different interventions tried to shed some more light on this issue. The YonLife intervention incorporates aspects of other programmes such as providing treating physician with precollected PROs[17 24] and creating a QoL profile and using expert's recommendations.[19] In contrast, unlike recently evolving programmes,[38] YonLife did not provide the possibility to answer questions using web-based questionnaires accessible from home or mobile device. Furthermore, the PRO results were automatically calculated, but they were not automatically compared with predefined cut-off or norm data nor were they available in the clinic information system like in other projects.[39 40] Thus, the described YonLife intervention needed human support to create the case vignette that limits the application to busy clinical routine. Advancing technical opportunities could help overcoming these barriers. YonLife also provided recommendations thoroughly based on electronic capturing of PRO. Yet, it demonstrated to be beneficial on QoL in contrast to a palliative intervention based on the personal encounter.[36] This could be even more relevant in a rare disease such as sarcoma care, where patients regularly travel long distances to specialised sarcoma centres.

Weaknesses and strengths

Our study has several limitations. As no preceding studies that incorporate a PRO-based individualised intervention existed, our study design and the sample size were set only for an explorative purpose. Therefore, results were determined to fail statistical significance and should be interpreted with caution. Furthermore, sarcoma-specific QoL or symptom measures are still missing, while the FACT-G and MDASI are generic instruments, which might not cover syndromes and aspects specific for sarcoma patients. On the other hand, to overcome the obstacles of limited statistical power, we applied measures of clinical rather than statistical importance such as the MCID or TUD, which might be even more important to clinicians in daily practice. Effect sizes are currently available for calculating sample sizes in a larger confirmatory trial.

In conclusion, the YonLife trial adds essential knowledge to the scarce data on PRO in patients with advanced STS. Unlike previous work, it is the first trial that applies an electronic PRO assessment and a remote tailored intervention of patients with STS. Our data suggest that incorporation of validated QoL measures in STS clinical treatment may further improve the care and understanding of patient well-being beyond traditional clinical measures. Additionally, beyond proving the statistical significance of clinically important effects, this study is an important prerequisite for future research and holistic care of patients with advanced STS.

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