BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035546
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2019
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Keywords:	Sarcoma < ONCOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cancer pain < ONCOLOGY

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Original Research

Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: A multicenter, cluster-randomized trial within the Germany 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 yet.

Design: This cluster-randomized multi-center YonLife study explored the effect of a comprehensive supportive intervention on QoL in patients with advanced STS undergoing treatment with trabectedin.

Participants: Patients from seven hospitals were randomized either to the control cluster (CC with electronic assessment of PRO [ePRO] only) or interventional cluster (IC including ePRO and four-step assessment for supportive palliative care).

Primary and secondary outcome measures: The explorative primary endpoint was the change of FACT-G total score after nine weeks. Outcomes included measures of QoL (FACT-G), symptoms (MDASI), anxiety and depression (HADS), pain intensity and interference (BPI), and survival assessment.

Results: After nine weeks of treatment QoL declined less in the IC (Δ FACT-G total score: -2.4) as compared to CC (Δ FACT-G total score: -3.9; *P*=0.765). The effect size of the intervention on the FACT-G score was d=0.269 (small effect). Overall mean survival was longer in IC (648 days) than in CC (389 days, *P*=0.110). Progression-free survival did not differ in both clusters (IC 249 days and CC (232 days, *P*=0.899). QoL was predicted by symptom severity, symptom interference, depression and anxiety; whereas age, gender, performance status, patient-satisfaction and anorexia/cachexia

showed no influence.

Conclusion: This trial adds knowledge and understanding about PRO in advanced STS patients. Unlike previous work, it is the first trial that applies an electronic PRO-assessment in a multi-center approach for a tailored intervention of STS patients. Therefore, our findings can serve as the cornerstone for future research.

Trial registration: ClinicalTrials.gov Identifier: NCT02204111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- YonLife explores the efficacy of a patient-directed intervention in sarcoma based on electronic patient-reported outcomes (ePRO)
- Use of ePRO assessment is feasible in a multi-center study
- ePRO-based intervention shows a favorable trend as improves important outcomes of palliative care
- Main limitation of YonLife was its study design/sample size, set for an explorative purpose only and use of very generic instruments for quality of life (QoL) evaluation
- Research of sarcoma-specific QoL-tools is warranted and a randomized controlled trial needs to confirm trends

KEYWORDS

Sarcoma, quality of life, patient-reported outcomes, trabectedin

INTRODUCTION

Although systemic treatment options in advanced soft tissue sarcoma (STS) have evolved in the past, corresponding toxicity and the varying degrees of long-lasting and cumulative adverse drug reactions cut down the overall clinical benefit and patients' quality of life (QoL). The burden of disease is high, even in patients who experience a long-lasting progression-free survival (PFS). Overall, QoL in sarcoma-patients is more impaired than in the general population[1, 2], but comparable to patients with more frequent cancer diseases.[3] Mental problems such as distress, depression and anxiety are paramount in this disease.[4, 5]

Treatment algorithms for STS beyond first-line treatment do not show superiority between one regimen and another.[6] On the other hand, there are distinct and drug-specific safety profiles. Therefore, the choice of which regimen should be applied becomes a matter of debate within the patient-doctor consultation with considerations comprising preferences, personal beliefs and convenience.[7] Consequently, it is important to assess the treatment effectiveness in two ways. First, in terms of tumor burden as an outcome (e.g., PFS or overall survival), and, secondly, 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 developed. Especially, if there is no superiority in survival, further outcomes should be considered, such as evaluation of the time to deterioration.[8]

Assessment and interventions based on PRO have been proven to yield beneficial outcomes in various settings and entities.[9-14] 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-questionnaire is available.[2, 15] Considering that merely assessing PRO might not be beneficial[16], we believe it should be accompanied by additional interventions like nurse-led patient education, self-care support or a multi-professional expert panel.[17] Despite the increasing knowledge about 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 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 suffering from advanced or metastatic STS that had just started or were currently under treatment with trabectedin (Yondelis®) 1.5 mg/m², given as a 24-hour intravenous infusion every three weeks and who received at least one dose, were included in this study. Physician-assessed life expectancy had to be at least six months and Eastern Cooperative Oncology Group (ECOG)-performance status score had to be ≥2. All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The YonLife trial was approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden on 16 June 2014 (EK241062014), and all participating centres have obtained the approval of the local ethics committee before patient enrolment. All patients will have to provide written informed consent before inclusion in the study.

Patient and public involvement

We appreciated all patients who participated in the study and contributed their personal information to the research. All patients and the public, however, were not involved in the design or planning of the study.

Trial design

Full details of YonLife trial (ClinicalTrials.gov Identifier: NCT02204111) have been reported earlier.[18] Briefly, the YonLife trial was designed as a cluster-randomized,

explorative proof-of-concept study. Seven German centers were cluster-randomized in a 1:1 ratio. The center where supportive care recommendations were gathered served as a reference center. Patients randomized to the control cluster (CC) were assessed using only electronic PRO-assessment without feedback to treatment team. Patients treated in the interventional cluster (IC) received a comprehensive four-step evaluation comprising: 1) PRO 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 (V1); 3) supportive care recommendations were addressed during discussion about patients' vignettes in a multi-professional expert panel; and 4) these treatment-suggestions as well as graphical representation of obtained PRO were provided to the treating physicians in the interventional center. Clinicians in the IC had the opportunity to discuss the graphical presentation with their patients and comply with 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.

Outcome measures

The primary outcome explored the changes of patients QoL in IC and CC after nine weeks (i.e. between visit 1 [V1] and visit 4 [V4]) of treatment as measured with the Functional Assessment for Cancer Therapy (FACT-G) total score. The FACT-G is a PRO measure used to assess health-related QoL in patients undergoing cancer therapy as a total sum score comprising several functional domains of QoL ranging from 0 to 108.[19] 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 in order to represent a minimal clinical important difference (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.*[20]

Secondary outcomes were 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 (i.e. V7)[19]. Additionally, the effect size of the intervention was measured as COHEN's d test by measuring the difference between two means.[21] The M.D. Anderson Symptom Inventory (MDASI)[22] was used to measure the severity of 13 cancer-related symptoms and their impact on six dimensions of daily life. Psychological distress was evaluated by the Hospital Anxiety and Depression scale (HADS).[23] 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 pre-determined cut-off scores.[24] The Functional Assessment of Anorexia/Cachexia Therapy questionnaire (FAACT) measured the impact of cachexia and anorexia on patients' QoL.[25] Finally, the Brief Pain Inventory (BPI) in a scale range from 0-10 measured the intensity of pain and pain-related interference.[26]

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[20] between the groups in FACT-G=15, with an estimated standard deviation (SD) of $\sigma=17$[27] and a

conservatively estimated intra-cluster-correlation coefficient of p=0.1. This calculation resulted in a cluster size of 33 patients (~11 patients per center). Additionally, 11 patients were recruited in the reference center, 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 endpoints 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 visit (V4) and who had no major protocol deviations.

Survival was assessed as means of PFS and overall survival (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 clusters, as median value of OS is not defined for confidence interval (CI) within the observation period of this study.

Mann-Whitney-U, Fisher-exact test, and Chi-squared test were used for the detection of possible differences concerning demographics. 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.

RESULTS

Between September 2014 and March 2018 80 patients in seven sites were screened for study participation. The full analysis set encompasses 79 patients, as one patient had to be excluded from analysis due to lack of required data. Mean age was 58 years (range 22 to 86). Leiomyosarcoma histology was the most frequent (*n*=32), followed by liposarcoma (*n*=23) (Table 1).

Table 1. Patient characteristic at baseline

	Interventional cluster (IC), *N*=38	Control cluster (CC), *N*=29	Reference Center (RF), *N*=12	Full Analysis Set *N*=79
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
Tumor histology				
Leiomyosarcoma	19	5	5	29
Liposarcoma	6	11	3	20
Others*	13	12	4	29
missing	0	1	0	1
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

*All subtypes occurring less than four times were merged into this category.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

Primary Outcome

After nine weeks at V4, FACT-G was higher in IC (Δ FACT-G total score: -2.4) as

compared to the CC (Δ FACT-G total score: -3.9; *P*=0.765) (Table 2). The effect size of the intervention on the FACT-G score was *d*=0.269 (small effect).

Table 2. Change scores after 9 weeks of treatment

	Mean change from baseline (V1) to 9 weeks (V4)			
	Interventional cluster (IC)	**Control cluster (CC)**	***P*-value**	**Interventional trend**
FACT-G total	-2.4	-3.9	0.955	Beneficial
FACT-G physical well-being	-1.2	-2.2	0.722	Beneficial
FACT-G social well-being	-1.6	-0.3	0.193	Adverse
FACT-G emotional well-being	0.9	-0.1	0.561	Beneficial
FACT-G functional well-being	-0.5	-1.3	0.536	Beneficial
HADS depression	0.3	0.2	0.419	Equivalent
HADS anxiety	0.3	-0.8	0.710	Adverse
BPI average pain	0.6	0.2	0.788	Adverse
BPI pain interference	0.4	0.1	0.679	Adverse
MDASI, symptom severity	0.7	0.2	0.442	Adverse
MDASI, symptom interference	1.2	0.8	0.667	Adverse

BPI, Brief Pain Inventory; FACT-G, Functional Assessment for Cancer Therapy; HADS, Hospital Anxiety and Depression scale; MDASI, The M.D. Anderson Symptom Inventory; V, visit.

Figure 1 and Table 3 depicts absolute FACT-scores trajectories over time. The number of patients experiencing a MCID was equal in both groups (IC: 44% and CC: 43%). The median TUD differed slightly between IC (25 days) and IC (22 days, P=0.927).

Table 3. Absolute FACT-scores at each assessment time

Questionnaire	**Visit**	**Interventional cluster (IC)**		**Control cluster (CC)**		***P-value***	**Total**	
		Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**
FACT-G total score								
	V1	74.9	14.8	73.3	11.6	0.788	74.2	13.0
	V2	76.8	15.1	68.2	16.6	0.145	73.1	16.1
	V3	72.0	16.7	70.7	11.8	0.708	72.1	14.3
	V4	73.9	15.2	69.4	18.4	0.512	71.6	16.2
	V5	80.2	10.8	74.9	14.8	0.588	77.3	14.8
	V6	76.6	12.8	80.2	11.8	0.402	77.2	13.2
	V7	79.1	16.4	73.0	8.5	0.582	75.7	14.9
FACT physical well-being (PWB)								
	V1	21.0	5.3	21.2	3.7	0.872	21.2	4.5
	V2	21.4	5.0	18.7	5.4	0.168	20.3	5.2
	V3	19.3	5.6	20.2	3.7	0.890	20.3	4.9
	V4	20.2	6.6	19.0	6.1	0.639	19.6	6.1

	V5	22.6	3.4	20.9	4.5	0.971	21.8	4.0
	V6	22.0	4.4	22.1	3.4	1.000	22.0	4.2
	V7	20.8	7.0	18.0	7.1	0.582	19.4	6.4
FACT social well-being (SWB)								
	V1	20.3	5.4	18.6	5.2	0.304	19.8	5.2
	V2	20.5	4.6	17.7	6.0	0.251	19.6	5.2
	V3	19.5	4.6	17.9	4.6	0.395	19.2	4.5
	V4	19.2	5.0	18.3	6.2	0.896	19.3	5.3
	V5	20.9	3.9	20.4	5.1	0.913	20.5	4.5
	V6	20.7	2.7	22.2	3.2	0.188	21.2	3.2
	V7	21.8	3.1	21.0	1.4	0.727	21.3	3.8
FACT emotional well-being (EWB)								
	V1	16.2	3.8	16.7	2.6	0.986	16.0	3.3
	V2	17.0	3.3	16.6	2.6	0.667	16.5	3.7
	V3	17.0	4.0	17.7	3.1	0.767	16.7	3.8
	V4	17.4	2.7	16.6	3.3	0.377	16.6	3.3
	V5	17.7	2.2	17.1	1.2	0.393	17.1	2.3
	V6	16.8	3.4	16.6	3.2	0.570	16.1	3.6
	V7	17.3	2.4	16.0	1.4	0.327	16.9	3.1
FACT functional well-being (FWB)								
	V1	17.3	5.3	16.8	4.3	0.900	17.2	4.5
	V2	17.9	5.4	15.1	5.9	0.319	16.7	5.4
	V3	16.1	6.4	14.9	4.5	0.679	16.0	5.4
	V4	17.1	5.4	15.5	5.7	0.512	16.2	5.4
	V5	18.8	4.6	16.4	5.3	0.485	17.9	4.5
	V6	17.1	6.1	19.3	3.8	0.441	17.9	5.4
	V7	19.2	7.0	18.0	1.4	0.909	18.0	6.0

FACT-G, Functional Assessment for Cancer Therapy; SD, standard deviation; V, visit.

Secondary Outcomes

Regarding the change of QoL between V1 and V4 (as well as during follow up V7), there was a beneficial impact of the patient-tailored evaluation in IC in all FACT-G subscales except for social well-being (Figure 1). There was less decline in physical well-being subscale in IC (Δ FACT-G PWB: -1.2) than in CC (Δ FACT-G PWB: -2.2; *P*=0.926) (Table 2). Emotional well-being subscale improved slightly in IC (Δ FACT-G EWB: 0.9) and remained almost stable in CC (Δ FACT-G EWB:-0.1; *P*=0.561). Functional well-being subscale declined less in IC (Δ FACT-G FWB: -0.5) than in CC (Δ FACT-G FWB: -1.3; *P*=0.536). Lastly, social well-being subscale remained almost stable (Δ FACT-G SWB:-0.2) in CC while decreasing in IC (Δ FACT-G SWB: -1.6; *P*=0.952). There was no

significant difference among both cohorts in other domains of PRO (MDASI, FAACT, HADS and BPI scales) (Table 2 and Table 4).

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

Table 4. Absolute scores of secondary outcomes

Questionnaire	Visit	Interventional cluster (IC)		Control cluster (CC)		*P-value*	Total	
		Mean	SD	Mean	SD		Mean	SD
FAACT score								
	V1	37,9	4,3	39,1	5,4	0,439	38,3	4,8
	V2	37,9	5,2	39,1	6,0	0,398	38,7	5,3
	V3	37,4	5,5	37,9	5,2	0,828	38,1	5,0
	V4	35,0	6,7	38,6	7,1	0,099	36,9	6,4
	V5	39,3	4,5	37,3	8,9	0,877	37,7	6,2
	V6	38,3	4,7	40,3	4,3	0,365	38,6	4,8
	V7	33,0	11,8	34,0	14,1	1,000	33,2	10,0
MDASI severity								
	V1	1,9	1,5	1,9	1,5	1,000	2,0	1,4
	V2	2,0	1,5	2,5	1,6	0,464	2,2	1,6
	V3	2,5	1,4	2,0	1,0	0,417	2,2	1,3
	V4	2,4	1,6	2,1	1,6	0,561	2,2	1,6
	V5	2,0	0,9	2,7	1,6	0,588	2,1	1,3
	V6	2,1	1,2	2,4	1,7	0,868	2,2	1,5
	V7	2,5	1,6	2,2	1,7	1,000	2,6	1,9
MDASI interference								
	V1	1,9	2,1	2,2	1,6	0,397	2,1	2,0
	V2	2,2	2,0	3,4	1,9	0,065	2,6	2,0
	V3	2,8	2,3	2,9	1,6	0,798	2,8	2,0
	V4	3,0	2,1	2,9	2,2	0,837	2,9	2,2
	V5	2,2	1,8	2,8	2,3	0,588	2,2	1,8
	V6	2,3	1,7	2,9	1,9	0,570	2,4	1,8
	V7	0,6	2,6	3,3	3,1	1,000	2,9	2,6

FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MDASI, The M.D. Anderson Symptom Inventory; SD, standard deviation; V, visit.

QoL-Prediction

Univariate regressions revealed that FACT-G total score was determined by each of the following: symptom severity, symptom interference, depression and anxiety. No

influence on FACT-G total score at the primary endpoint was found for age, gender, ECOG performance status, patient-satisfaction, anorexia and cachexia (Table 5).

Table 5. Univariate regression of parameters at baseline (V1) and after nine weeks (V4) over all groups

	R^2	*P*-value	b1
Gender	0.05	0.154	7.5
Age	0.04	0.228	-0.2
ECOG	0.01	0.509	-3.2
Tumor stadium	0.03	0.284	-1.8
Symptom severity	0.31	0.0	-6.6
Symptom interference	0.16	0.011	-3.4
Depression	0.35	0.0	-2.7
Anxiety	0.12	0.034	-1.4
Patient Satisfaction	0.02	0.451	3.0
Anorexia/Cachexia	0.06	0.143	0.8

R^2 – coefficient of determination; b1 – regression coefficient

DISCUSSION

To the best of our knowledge, this is the first randomized trial using a patient-directed supportive care intervention to improve QoL and other PRO in sarcoma patients. We observed a trend in favor of the intervention considering the primary endpoint (FACT-G sum score) and other secondary outcomes (physical well-being and emotional well-being). Not surprisingly and due to the character of palliative disease, absolute numbers in FACT-G-score decline over time. However, in this study the cumulative score representing several domains of QoL was clearly in favor of the intervention although this trend fails to reach statistical significance. Such an outcome was quite expected as this study was powered for an explorative purpose only as there was no previous experience with a tailored intervention in this setting. Applying outcome measures beyond mere statistical significance might be crucial in order to describe patients' benefits in studies with rare entities. The intervention applied in this trial seems to be beneficial in reducing the decline in overall QoL. On the other side, MCID and TUD assessment, which have been widely adopted in several trials focusing on QoL[8, 28], in our study slightly differed between both groups.

Our study has several limitations. As no preceding studies that incorporate a PRO-based individualized intervention still exist, 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, a sarcoma-specific QoL-measure is still missing, while the FACT-G is a generic instrument 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 now available for calculating sample sizes in larger confirmatory trials.

There are still many unanswered questions regarding comprehensive QoL interventions in general. During the past years, several reports with different designs tried to shed some more light on this issue. Some of them showing very promising results, but conversely with limitations regarding generalizability. This occurred in part due to a monocentric design of studies and a lack to show superiority across different cancer subtypes.[10, 29] Moreover, some of the mechanisms about how a supportive care intervention has to be composed and how it has to be implemented are barely understood[30]. In addition, it is still a matter of investigation on how to overcome obstacles when only remote counseling is applied due to rather disappointing results.[31, 32]

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 wellbeing 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.

FIGURE LEGENDS

Figure 1. Number of evaluated patients for all FACT-G dimensions per visit and cohort: V1: IC N=19, CC N=14; V4: IC N=18, CC N=14; V7: IC N=9, CC N=2. EWB, emotional well-being; FACT-G, Functional Assessment for Cancer Therapy; FWB, functional well-being; PWB, physical well-being; SD, standard deviation; SWB, social well-being; V, visit.

CONTRIBUTORS

LH and MKS proposed the conception and design of the study, performed data analysis, interpretation and quality control of data and algorithms, and drafted the manuscript. MB, LH and MKS are responsible for the manuscript editing. MKS, SR, HGK, BK, AK, VG, TK and JMC performed the data acquisition. All authors participated in the manuscript review with equal contribution.

FUNDING

This work was supported by an unrestricted grant from PharmaMar, Spain

DATA AVAILABILITY STATEMENT

No additional data available

COMPETING INTERESTS

None declared

ACKNOWLEDGEMENTS

The trial was coordinated by GWT-TUD, Dresden, Germany. We acknowledge the German Interdisciplinary Sarcoma Group (GISG) for providing support for this trial. The YonLife trial was associated with the German Interdisciplinary Sarcoma Group as GISG-12 project and as AIO-STS-0215 within the 'Arbeitsgemeinschaft Internistische Onkologie' of the 'Deutsche Krebsgesellschaft' (DKG). We would also like to thank Kristian Zinke and Rocco Haase for their support on statistical aspects of the study and Felicitas Lenz and Adnan Tanović for proof-reading.

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Table 1. Patient characteristic at baseline

	Interventional cluster (IC), *N*=38	Control cluster (CC), *N*=29	Reference Center (RF), *N*=12	Full Analysis Set *N*=79
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
Tumor histology				
Leiomyosarcoma	19	5	5	29
Liposarcoma	6	11	3	20
Others*	13	12	4	29
missing	0	1	0	1
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

*All subtypes occurring less than four times were merged into this category.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

Table 2. Change scores after 9 weeks of treatment

	Mean change from baseline (V1) to 9 weeks (V4)			
	Interventional cluster (IC)	Control cluster (CC)	*P*-value	Interventional trend
FACT-G total	-2.4	-3.9	0.955	Beneficial
FACT-G physical well-being	-1.2	-2.2	0.722	Beneficial
FACT-G social well-being	-1.6	-0.3	0.193	Adverse
FACT-G emotional well-being	0.9	-0.1	0.561	Beneficial
FACT-G functional well-being	-0.5	-1.3	0.536	Beneficial
HADS depression	0.3	0.2	0.419	Equivalent
HADS anxiety	0.3	-0.8	0.710	Adverse
BPI average pain	0.6	0.2	0.788	Adverse
BPI pain interference	0.4	0.1	0.679	Adverse
MDASI, symptom severity	0.7	0.2	0.442	Adverse
MDASI, symptom interference	1.2	0.8	0.667	Adverse

BPI, Brief Pain Inventory; FACT-G, Functional Assessment for Cancer Therapy; HADS, Hospital Anxiety and Depression scale; MDASI, The M.D. Anderson Symptom Inventory; V, visit.

Table 3. Absolute FACT-scores at each assessment time

Questionnaire	Visit	Interventional cluster (IC)		Control cluster (CC)		*P-value*	Total	
		Mean	SD	Mean	SD		Mean	SD
FACT-G total score								
	V1	74.9	14.8	73.3	11.6	0.788	74.2	13.0
	V2	76.8	15.1	68.2	16.6	0.145	73.1	16.1
	V3	72.0	16.7	70.7	11.8	0.708	72.1	14.3
	V4	73.9	15.2	69.4	18.4	0.512	71.6	16.2
	V5	80.2	10.8	74.9	14.8	0.588	77.3	14.8
	V6	76.6	12.8	80.2	11.8	0.402	77.2	13.2
	V7	79.1	16.4	73.0	8.5	0.582	75.7	14.9
FACT physical well-being								
	V1	21.0	5.3	21.2	3.7	0.872	21.2	4.5
	V2	21.4	5.0	18.7	5.4	0.168	20.3	5.2
	V3	19.3	5.6	20.2	3.7	0.890	20.3	4.9
	V4	20.2	6.6	19.0	6.1	0.639	19.6	6.1
	V5	22.6	3.4	20.9	4.5	0.971	21.8	4.0
	V6	22.0	4.4	22.1	3.4	1.000	22.0	4.2
	V7	20.8	7.0	18.0	7.1	0.582	19.4	6.4
FACT social well-being								
	V1	20.3	5.4	18.6	5.2	0.304	19.8	5.2
	V2	20.5	4.6	17.7	6.0	0.251	19.6	5.2
	V3	19.5	4.6	17.9	4.6	0.395	19.2	4.5
	V4	19.2	5.0	18.3	6.2	0.896	19.3	5.3
	V5	20.9	3.9	20.4	5.1	0.913	20.5	4.5
	V6	20.7	2.7	22.2	3.2	0.188	21.2	3.2
	V7	21.8	3.1	21.0	1.4	0.727	21.3	3.8
FACT emotional well-being								
	V1	16.2	3.8	16.7	2.6	0.986	16.0	3.3
	V2	17.0	3.3	16.6	2.6	0.667	16.5	3.7
	V3	17.0	4.0	17.7	3.1	0.767	16.7	3.8
	V4	17.4	2.7	16.6	3.3	0.377	16.6	3.3
	V5	17.7	2.2	17.1	1.2	0.393	17.1	2.3
	V6	16.8	3.4	16.6	3.2	0.570	16.1	3.6
	V7	17.3	2.4	16.0	1.4	0.327	16.9	3.1
FACT functional well-being								
	V1	17.3	5.3	16.8	4.3	0.900	17.2	4.5
	V2	17.9	5.4	15.1	5.9	0.319	16.7	5.4
	V3	16.1	6.4	14.9	4.5	0.679	16.0	5.4
	V4	17.1	5.4	15.5	5.7	0.512	16.2	5.4
	V5	18.8	4.6	16.4	5.3	0.485	17.9	4.5
	V6	17.1	6.1	19.3	3.8	0.441	17.9	5.4
	V7	19.2	7.0	18.0	1.4	0.909	18.0	6.0

FACT-G, Functional Assessment for Cancer Therapy; SD, standard deviation; V, visit.

Table 4. Absolute scores of secondary outcomes

Questionnaire	Visit	Interventional cluster (IC)		Control cluster (CC)		*P-value*	Total	
		Mean	SD	Mean	SD		Mean	SD
FAACT score								
	V1	37,9	4,3	39,1	5,4	0,439	38,3	4,8
	V2	37,9	5,2	39,1	6,0	0,398	38,7	5,3
	V3	37,4	5,5	37,9	5,2	0,828	38,1	5,0
	V4	35,0	6,7	38,6	7,1	0,099	36,9	6,4
	V5	39,3	4,5	37,3	8,9	0,877	37,7	6,2
	V6	38,3	4,7	40,3	4,3	0,365	38,6	4,8
	V7	33,0	11,8	34,0	14,1	1,000	33,2	10,0
MDASI severity								
	V1	1,9	1,5	1,9	1,5	1,000	2,0	1,4
	V2	2,0	1,5	2,5	1,6	0,464	2,2	1,6
	V3	2,5	1,4	2,0	1,0	0,417	2,2	1,3
	V4	2,4	1,6	2,1	1,6	0,561	2,2	1,6
	V5	2,0	0,9	2,7	1,6	0,588	2,1	1,3
	V6	2,1	1,2	2,4	1,7	0,868	2,2	1,5
	V7	2,5	1,6	2,2	1,7	1,000	2,6	1,9
MDASI interference								
	V1	1,9	2,1	2,2	1,6	0,397	2,1	2,0
	V2	2,2	2,0	3,4	1,9	0,065	2,6	2,0
	V3	2,8	2,3	2,9	1,6	0,798	2,8	2,0
	V4	3,0	2,1	2,9	2,2	0,837	2,9	2,2
	V5	2,2	1,8	2,8	2,3	0,588	2,2	1,8
	V6	2,3	1,7	2,9	1,9	0,570	2,4	1,8
	V7	0,6	2,6	3,3	3,1	1,000	2,9	2,6

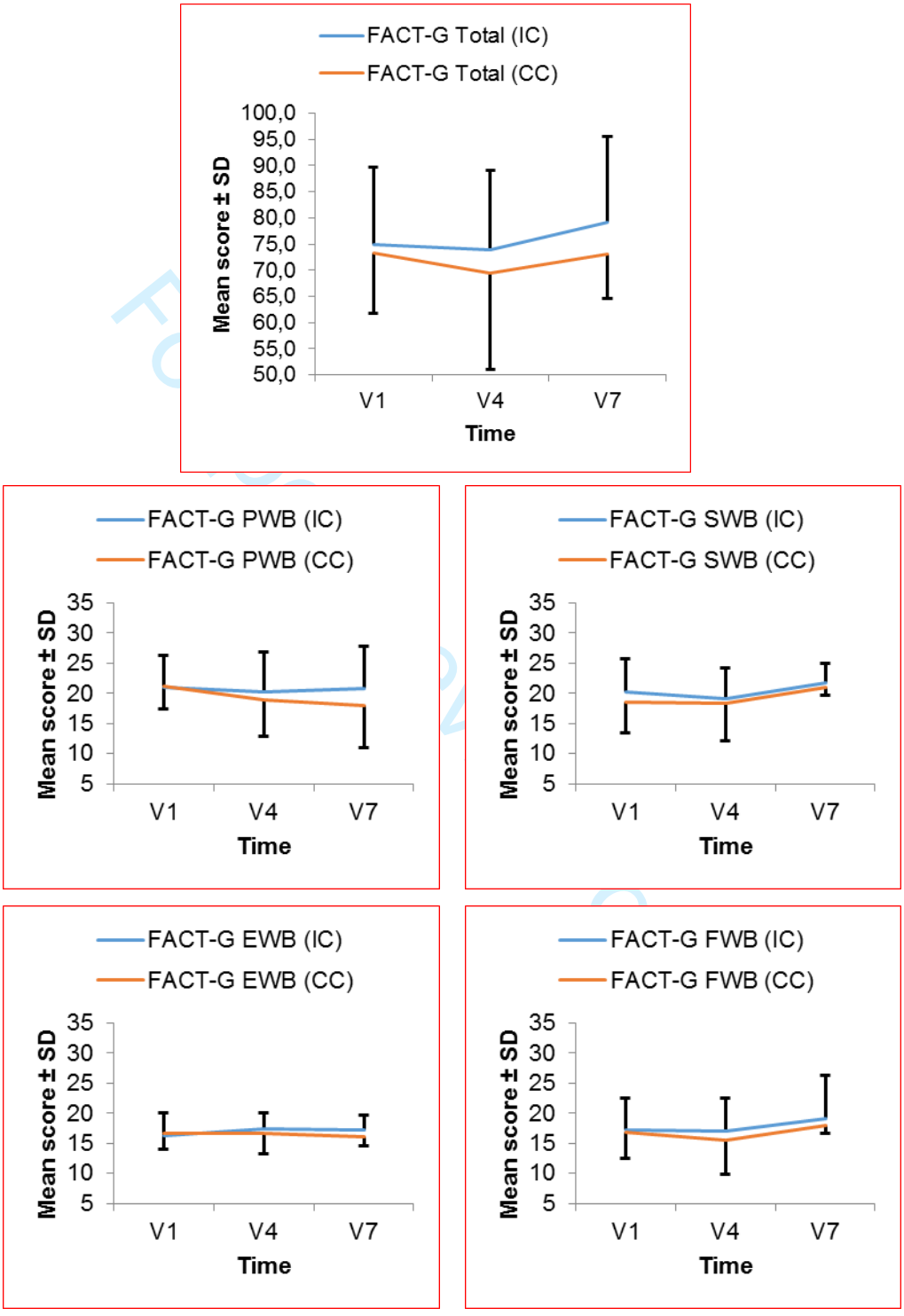
FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MDASI, The M.D. Anderson Symptom Inventory; SD, standard deviation; V, visit.

Table 5. Univariate regression of parameters at baseline (V1) and after nine weeks (V4) over all groups

	R^2	*P*-value	b1
Gender	0.05	0.154	7.5
Age	0.04	0.228	-0.2
ECOG	0.01	0.509	-3.2
Tumor stadium	0.03	0.284	-1.8
Symptom severity	0.31	0.0	-6.6
Symptom interference	0.16	0.011	-3.4
Depression	0.35	0.0	-2.7
Anxiety	0.12	0.034	-1.4
Patient Satisfaction	0.02	0.451	3.0
Anorexia/Cachexia	0.06	0.143	0.8

R^2 – coefficient of determination; b1 – regression coefficient

Figure 1. Absolute FACT-scores at baseline (V1), after nine weeks of treatment (V4; primary endpoint) and during follow up visit (V7)



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of ***cohort studies***

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	8-10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035546.R1
Article Type:	Original research
Date Submitted by the Author:	27-Mar-2020
Complete List of Authors:	Hentschel, Leopold; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Richter, Stephan; University Hospital Carl Gustav Carus, Department of Internal Medicine I Kopp, Hans-Georg; Robert-Bosch-Center of Tumor Diseases, Interdisciplinary Center for Soft-Tissue-Sarcoma, GIST and Bone-Tumor Kasper, Bernd; University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Sarcoma Unit, Interdisciplinary Tumor Center Kunitz, Annegret; Vivantes Clinic Spandau, Internal Medicine Grünwald, Viktor ; University Hospital Essen, Interdisciplinary Genitourinary Oncology/West-German Cancer Center Kessler, Torsten; University Hospital of Münster, Hematology Oncology Chemnitz, Jens Marcus; ev. Stift St. Martin, Internal Medicine Pelzer, Uwe; Charité Medical University, Division of Hematology, Oncology and Tumor Immunology Schuler, Ulrich; University Hospital Carl Gustav Carus, University Palliative Center Freitag, Janet; University Hospital Carl Gustav Carus, Department of Internal Medicine I Schilling, Andrea; University Hospital Carl Gustav Carus, Department of Social Work Hornemann, Beate; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Arndt, Karin; Das Lebenshaus e.V, Patient Advocacy Bornhaeuser, Martin; University Hospital Carl Gustav Carus, Department of Internal Medicine I; Deutsches Krebsforschungszentrum, National Center for Tumor Diseases (NCT) Schuler, Markus Kajo; University Hospital Carl Gustav Carus, Department of Internal Medicine I; HELIOS Hospital Emil von Behring, Department of Internal Medicine II
Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Oncology, Patient-centred medicine

Keywords:	Sarcoma < ONCOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cancer pain < ONCOLOGY

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Original Research

Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: A multicenter, cluster-randomized trial within the Germany 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 multi-step 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-randomized, open-label, proof-of-concept study. The intervention incorporates electronic PRO-assessment, a case-vignette and expert-consented treatment recommendations.

Participants: Six hospitals were randomized to the control arm (CA) or interventional arm (IA). Seventy-nine patients were included.

Primary and secondary outcome measures: The primary endpoint was the change of FACT-G total score after nine weeks. Secondary outcomes included measures of QoL (FACT-G subscales), anorexia and cachexia (FAACT), symptoms (MDASI), anxiety and depression (HADS), pain intensity and interference (BPI), and survival assessment.

Results: After nine weeks of treatment QoL declined less in the IA (Δ FACT-G total score: -2.4, 95% CI: -9.2 to 4.5) as compared to CA (Δ FACT-G total score: -3.9; 95% CI:-11.3 to 3.5; *P*=0.765). A beneficial trend of the patient-tailored evaluation in IA was observed in almost all FACT-G subscales. Smaller adverse trends between arms were observed for MDASI, FAACT, HADS and BPI scales. 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 that a tailored intervention based on ePRO may improve global QoL and subscales, while it did not have a beneficial impact on single symptoms.

Trial registration: ClinicalTrials.gov Identifier: NCT02204111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- YonLife explores the value and efficacy of a patient-directed intervention on quality of life (QoL) in sarcoma patients
- YonLife captures patient-reported outcomes (PRO) electronically and provides a tailored expert-derived intervention in a multi-center setting
- The intervention yields beneficial impact on global QoL but not on single symptoms

KEYWORDS

Sarcoma, quality of life, patient-reported outcomes, trabectedin

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 to 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 tumor burden as an outcome (e.g., progression-free survival or overall survival), and, secondly, 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 or the time to deterioration of QoL.[10]

Trabectedin (Yondelis®) is a semi-synthetic 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 United States 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 PROs 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 STAR (Symptom Tracking and Reporting) intervention in prolonging time on chemotherapy, less unexpected admission and longer quality-adjusted survival.[17] In brief, they randomized 766 patients from a single institution under chemotherapy for solid tumors 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 randomized multi-center trial evaluated the effect of a web-based, self-report assessment and educational intervention on symptom distress during

cancer therapy in 752 ambulatory patients from different entities and with various diagnoses.[18] In this multicenter 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 it should be accompanied by additional interventions such as nurse-led patient education, self-care support or a multi-professional expert panel that discusses PRO-results and derive 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-randomized 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 three weeks, were included in this study. Physician-assessed life expectancy of patients had to be at least six months and Eastern Cooperative Oncology Group (ECOG)-performance status score had to be ≤2. All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The YonLife trial was approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden on June 2014 (EK241062014), and all participating centers obtained the approval of the local ethics committee before patient enrolment. All patients provided written informed consent before inclusion in the study.

Patient and public involvement

We are grateful to all patients that 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-randomized, 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 (i.e. visit [V] 1) and after 3 weeks (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 nine weeks (V4) between interventional arm and control arm. Secondary objectives included explorative comparison between other PRO such as anxiety, depression, pain as well as survival. Furthermore, factors that predict QoL after nine 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) PRO 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 multi-professional 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 center. 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.

Randomization

Six German centers were cluster-randomized in a 1:1 ratio in an IA (3 centers) and a CA (3 centers). This trial was designed as a cluster-randomized trials to avoid contamination that might result in a type 2 error. If randomized 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. Randomization was conducted by a colleague not actively involved in this trial using random numbers generated in excel.

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

Outcome measures

The primary outcome explored the changes of patients QoL in IA and CA after nine 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, 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 in order to represent a minimal clinical important difference (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 endpoints measured throughout the study are depicted in Table 1.

Table 1: Visit schedule and outcomes

Study period	**SCR**	**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
Tumor-specific & socio-demographic parameters	x			x	x	x	x
Feasibility Scoring based on patients' and doctors' opinion*				x			

* Data is currently being analyzed and is available upon request.

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 (i.e. V7). [24] Moreover, the effect size of the intervention was measured as COHEN's *d* test by measuring the difference between

two means.[28] The M.D. Anderson Symptom Inventory (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 pre-determined cut-off scores.[31] The Functional Assessment of Anorexia/Cachexia Therapy questionnaire (FAACT) measured the impact of cachexia and anorexia on patients' QoL.[32] Finally, the Brief Pain Inventory (BPI) in a scale range from 0-10 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), tumor stage (UICC-classification), symptom severity (MDASI), symptom interference (MDASI), depression (HADS), anxiety (HADS), patients satisfaction (IN-PATSAT32)[34], 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 standard deviation (SD) of $\sigma=17$ and a conservatively estimated intra-cluster-correlation coefficient of $P=0.1$.[35] This calculation resulted in a cluster size of 11 patients. Additionally, 11 patients were recruited in the reference center, 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 endpoints 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 visit (V4) and who had no major protocol deviations.

Survival was assessed as means of PFS and overall survival (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 confidence interval (CI) within the observation period of this study. Mann-Whitney-U, Fisher-exact test, and Chi-squared test were used for the detection of possible differences concerning demographics. 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.

RESULTS

Patients and treatment arms

Between September 2014 and March 2018, 80 patients from seven sites were screened for study participation (figure 1). The FAS encompasses 79 patients, as one 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 consists 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 tumor stage (*P*=0.083) and less patients suffer from leiomyosarcoma (Table 2).

Table 2. Patient characteristic at baseline

	Interventional arm (IA; 3 centers) *N*=38	Control arm (CA; 3 centers) *N*=29	Reference Center (RF; 1 center) *N*=12	Full Analysis Set *N*=79
Full Analysis Set (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
Tumor 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

Per-protocol analysis set (PPS)

	Interventional arm (IA; 3 centers), *N*=19	**Control arm (CA; 3 centers), *N*=14**	**Reference Center (RF; 1 center), *N*=8**	**Per Protocol Set *N*=41**
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
Tumor 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
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.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; M0, no distant metastasis; M1, distant metastasis.

Primary Outcome

After nine weeks at V4, FACT-G was higher in IA (Δ FACT-G total score: -2.4, 95% CI: -9.2-4.5) as compared to the CA (Δ FACT-G total score: -3.9, 95% CI: -11.3-3.5; *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 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: 6.2-43.8) and CA (22 days, 95% CI: 16.5-27.5; *P*=0.927).

Table 3. Change scores after 9 weeks of treatment

	Mean change from baseline (V1) to 9 weeks (V4)							
	Interventional arm			Control arm			*P*-value	Interventional trend
	mean	95% CI	N	mean	95% CI	N		
FACT-G total	-2.4	-9.22-4.50	18	-3.9	-11.29-3.45	14	0.955	Beneficial
FACT-G physical well-being	-1.2	-4.43-2.09	18	-2.2	-5.40-0.98	14	0.722	Beneficial
FACT-G social well-being	-1.6	-3.06--.09	18	-0.3	-2.20-1.71	14	0.193	Adverse
FACT-G emotional well-being	0.9	-0.62-2.40	18	-0.1	-2.34-2.06	14	0.561	Beneficial
FACT-G functional well-being	-0.5	-2.67-1.67	18	-1.3	-4.03-1.40	14	0.536	Beneficial
HADS depression	0.3	-0.64-1.20	18	0.2	-2.05-2.47	14	0.419	Equivalent
HADS anxiety	0.3	-1.65-2.23	18	-0.8	-2.99-1.41	14	0.710	Adverse
BPI average pain	0.6	-0.34-1.50	19	0.2	-0.54-0.96	14	0.788	Adverse
BPI pain interference	0.4	-0.31-1.05	18	0.1	-0.51-0.71	13	0.679	Adverse
MDASI symptom severity	0.7	-0.08-1.39	18	0.2	-0.38-0.82	14	0.442	Adverse
MDASI symptom interference	1.2	0.89-1.59	18	0.8	-0.37-1.90	13	0.667	Adverse

BPI. Brief Pain Inventory; CI, confidence interval; FACT-G. Functional Assessment for Cancer Therapy; HADS. Hospital Anxiety and Depression scale; MDASI. The M.D. Anderson Symptom Inventory; V. visit; N. number of evaluable patients in respective cluster.

Secondary Outcomes

Regarding the change of QoL between V1 and V4 (as well as during follow up V7), there was a beneficial impact 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 (Δ FACT-G PWB: -1.2, 95% CI: -4,43-2,09) than in CA (Δ FACT-G PWB: -2.2, 95% CI: -5,40-0,98; *P*=0.926). Emotional well-being subscale improved slightly in IA (Δ FACT-G EWB: 0.9, 95% CI: -0,62-2,40) and remained almost stable in CA (Δ FACT-G EWB: -0.1, 95% CI: -2,34-2,06; *P*=0.561). Functional well-being subscale declined less in IA (Δ FACT-G FWB: -0.5, 95% CI: -2,67-1,67) than in CA (Δ FACT-G FWB: -1.3, 95% CI: -4,03-1,40; *P*=0.536). Lastly, social well-being subscale remained almost stable (Δ FACT-G SWB:-0.2, 95% CI: -3,06- -0,09) in CA while decreasing in IA (Δ FACT-G SWB: -1.6, 95% CI: -2,20-1,71; *P*=0.952). Overall, there were non-significant, adverse trends in other domains of PRO (MDASI, FAACT, HADS and BPI scales) (Table 3 and 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, anorexia and cachexia (Table 4). In a multivariable

regression, depression was determined variable for the FACT-G total score (Table 4).

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

	Univariate regression		
	P-value	estimate	95% confidence interval
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
Tumor 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		
	P-value	estimate	95% confidence interval
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
Tumor 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.

DISCUSSION

Principal findings

To the best of our knowledge, this is the first randomized trial using a patient-directed supportive care intervention to improve QoL and other PRO in sarcoma patients. We observed a trend in favor of the intervention considering the primary endpoint (total FACT-G score) and other secondary outcomes (i.e. 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 multi-center randomized trial, which reported a comparable decline in FACT-G score of ~2 in 281 patients suffering from advanced solid cancers who received early palliative care or standard oncologic care.[36] In addition, the total FACT-G score they observed after twelve weeks (70.1 and 69.6) was comparable to the score found in IA (73.9) and CA (69.4) after nine week of treatment. The total FACT-G score (76.4) was also comparable to the YonLife baseline score (74.2) in a sample of 42 patients suffering from different sarcoma histotypes in a single center, cross-sectional study.[37]

As the intervention yields beneficial effects on QoL, 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 take several days. Complex syndromes such as anxiety and depression need ongoing treatment, either psycho-oncological or pharmaceutical, which usually take 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 programs like providing treating physician with pre-collected PROs[17, 24] and, creating a QoL-profile and using expert's recommendations.[19] In contrast, unlike recently evolving programs[38], YonLife did not provide possibility to answer questions using web based questionnaires accessible from home or mobile device. Furthermore, the PRO-results were automatically calculated, but were not automatically compared to pre-defined 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 specialized sarcoma centers.

Weaknesses and strengths

Our study has several limitations. As no preceding studies that incorporate a PRO-

based individualized 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 now 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 wellbeing 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.

CONTRIBUTORS

LH and MKS proposed the conception and design of the study, performed data analysis, interpretation and quality control of data and algorithms. MB, LH and MKS are responsible for the manuscript editing. MKS, SR, HGK, BK, AK, VG, TK, UP and JMC performed the data acquisition. All aforementioned authors as well as US, JF, AS, BH and KA participated in the manuscript drafting and review with equal contribution.

FUNDING

This work was supported by an unrestricted grant from PharmaMar, Spain.

DATA AVAILABILITY STATEMENT

Complete data sets are available upon reasonable request

COMPETING INTERESTS

None declared.

ACKNOWLEDGEMENTS

The trial was coordinated by GWT-TUD, Dresden, Germany. We acknowledge the German Interdisciplinary Sarcoma Group (GISG) for providing support for this trial. The YonLife trial was associated with the German Interdisciplinary Sarcoma Group as GISG-12 project and as AIO-STS-0215 within the 'Arbeitsgemeinschaft Internistische Onkologie' of the 'Deutsche Krebsgesellschaft' (DKG). We would also like to thank Michael Kramer, Kristian Zinke and Rocco Haase for their support on statistical aspects

of the study and Felicitas Lenz and Adnan Tanović for proof-reading.

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Table 1: Visit schedule and outcomes							
Study period	**SCR**	**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
Tumor-specific & socio-demographic parameters	x			x	x	x	x
Feasibility Scoring based on patients' and doctors' opinion*				x			

* Data is currently being analyzed and is available upon request.

Table 2. Patient characteristic at baseline

	Interventional arm (IA; 3 centers) *N*=38	Control arm (CA; 3 centers) *N*=29	Reference Center (RF; 1 center) *N*=12	Full Analysis Set *N*=79
Full Analysis Set (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
Tumor 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
Per-protocol analysis set (PPS)				
	Interventional arm (IA; 3 centers), *N*=19	**Control arm (CA; 3 centers), *N*=14**	**Reference Center (RF; 1 center), *N*=8**	**Per Protocol Set *N*=41**
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
Tumor 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
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.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; M0, no distant metastasis; M1, distant metastasis.

Table 3. Change scores after 9 weeks of treatment

	Mean change from baseline (V1) to 9 weeks (V4)							
	Interventional arm			Control arm			*P*-value	Interventional trend
	mean	95% CI	N	mean	95% CI	N		
FACT-G total	-2.4	-9.22-4.50	18	-3.9	-11.29-3.45	14	0.955	Beneficial
FACT-G physical well-being	-1.2	-4.43-2.09	18	-2.2	-5.40-0.98	14	0.722	Beneficial
FACT-G social well-being	-1.6	-3.06--.09	18	-0.3	-2.20-1.71	14	0.193	Adverse
FACT-G emotional well-being	0.9	-0.62-2.40	18	-0.1	-2.34-2.06	14	0.561	Beneficial
FACT-G functional well-being	-0.5	-2.67-1.67	18	-1.3	-4.03-1.40	14	0.536	Beneficial
HADS depression	0.3	-0.64-1.20	18	0.2	-2.05-2.47	14	0.419	Equivalent
HADS anxiety	0.3	-1.65-2.23	18	-0.8	-2.99-1.41	14	0.710	Adverse
BPI average pain	0.6	-0.34-1.50	19	0.2	-0.54-0.96	14	0.788	Adverse
BPI pain interference	0.4	-0.31-1.05	18	0.1	-0.51-0.71	13	0.679	Adverse
MDASI symptom severity	0.7	-0.08-1.39	18	0.2	-0.38-0.82	14	0.442	Adverse
MDASI symptom interference	1.2	0.89-1.59	18	0.8	-0.37-1.90	13	0.667	Adverse

BPI, Brief Pain Inventory; CI, confidence interval; FACT-G, Functional Assessment for Cancer Therapy; HADS, Hospital Anxiety and Depression scale; MDASI, The M.D. Anderson Symptom Inventory; V, visit; N, number of evaluable patients in respective cluster.

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

Univariate regression			
	P-value	estimate	95% CI
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
Tumor 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			
	P-value	estimate	95% confidence interval
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
Tumor 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

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

Figure 1. CONSORT Flowchart

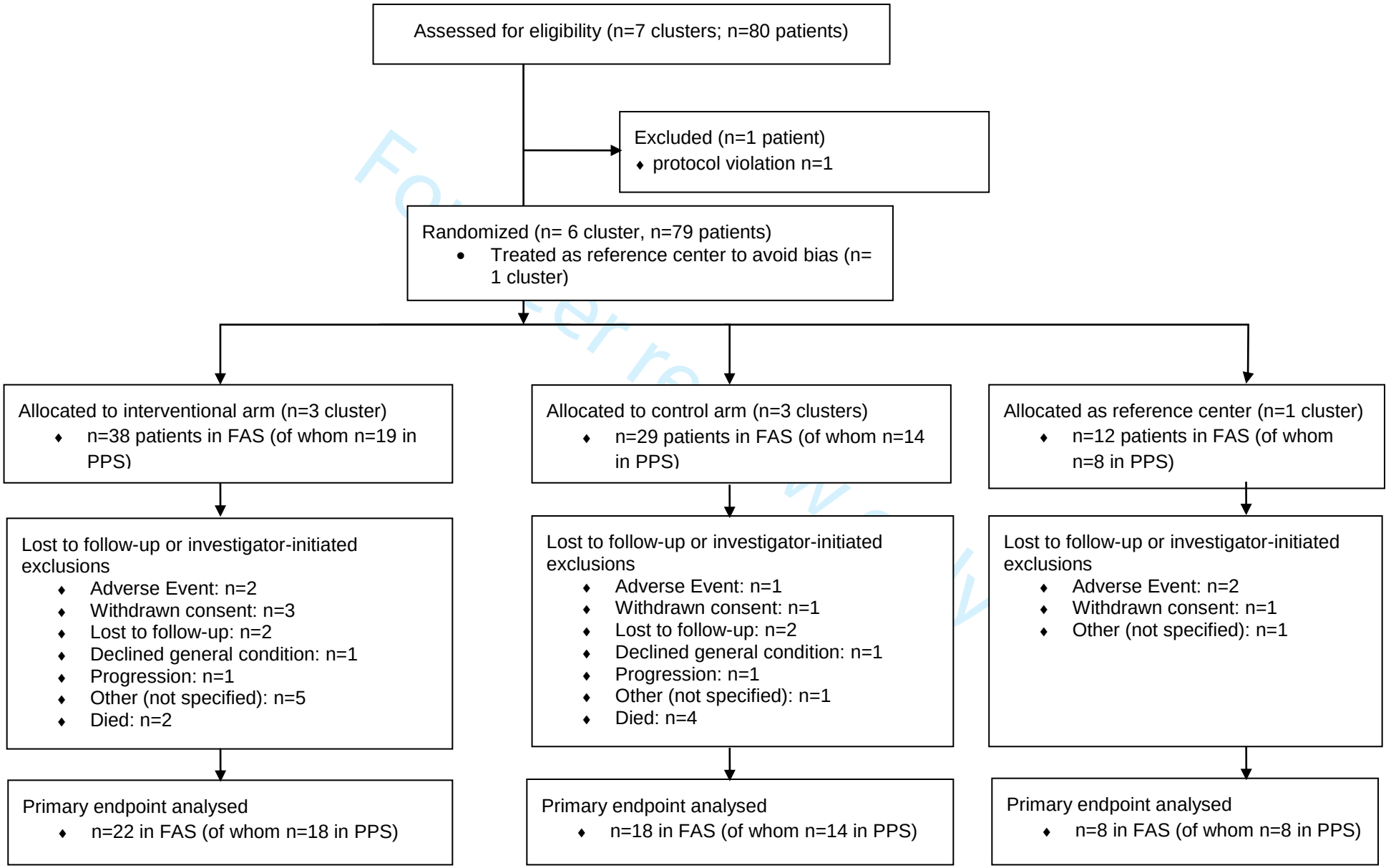
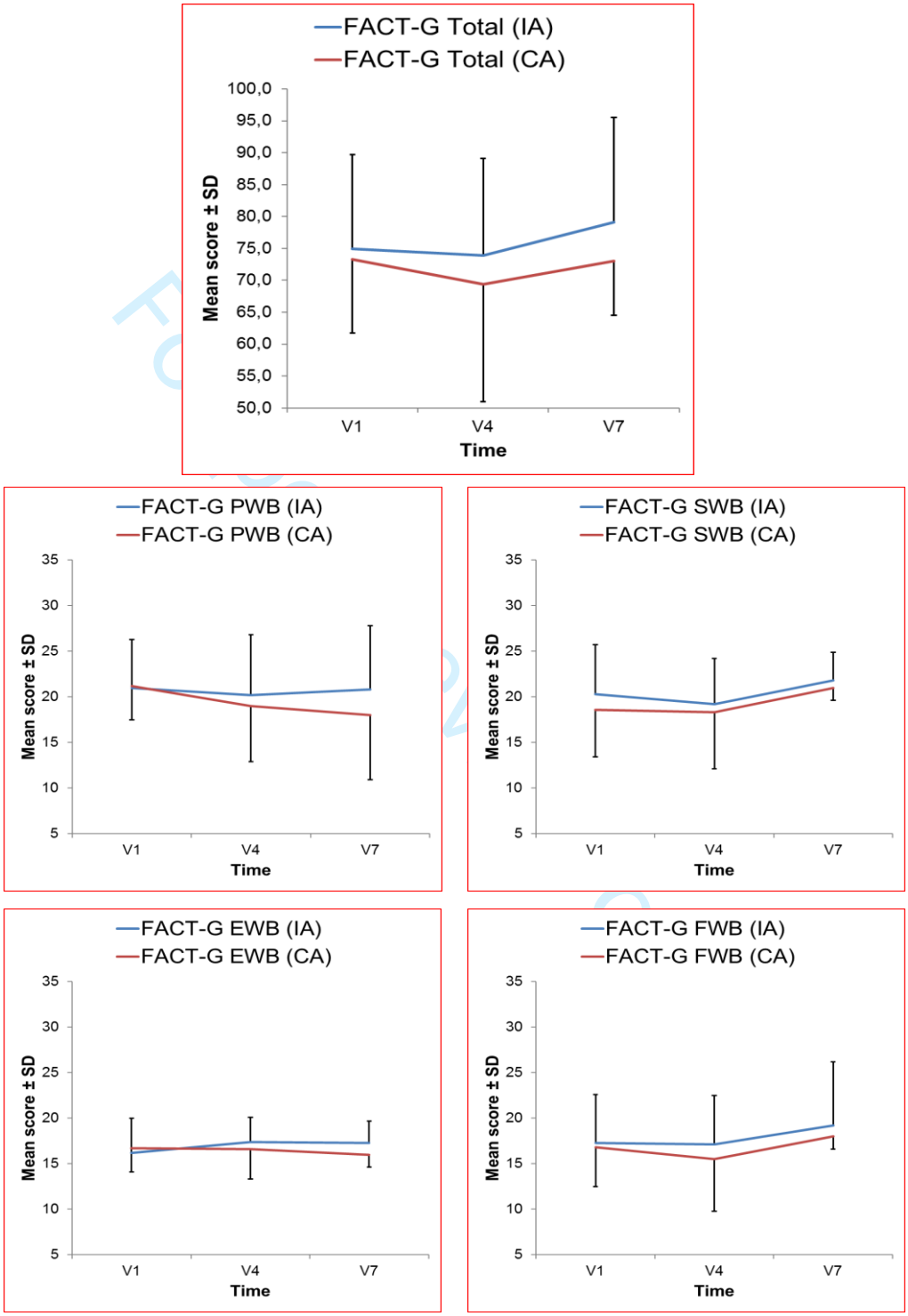


Figure 2. Absolute FACT-scores at baseline (V1), after nine weeks of treatment (V4; primary endpoint) and during follow up visit (V7)



FACT-G, Functional Assessment for Cancer Therapy; EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SD, standard deviation; SWB, social well-being; V, visit.
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.

Supplementary Table 1. Absolute FACT-scores at each assessment time

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FACT-G total score	V1	19	74.9	14.8	14	73.3	11.6	0.788	74.2	13.0	
	V2	18	76.8	15.1	14	68.2	16.6	0.145	73.1	16.1	
	V3	18	72.0	16.7	13	70.7	11.8	0.708	72.1	14.3	
	V4	18	73.9	15.2	14	69.4	18.4	0.512	71.6	16.2	0,267
	V5	13	80.2	10.8	7	74.9	14.8	0.588	77.3	14.8	
	V6	14	76.6	12.8	8	80.2	11.8	0.402	77.2	13.2	
	V7	9	79.1	16.4	2	73.0	8.5	0.582	75.7	14.9	
FACT physical well-being	V1	19	21.0	5.3	14	21.2	3.7	0.872	21.2	4.5	
	V2	18	21.4	5.0	14	18.7	5.4	0.168	20.3	5.2	
	V3	18	19.3	5.6	13	20.2	3.7	0.890	20.3	4.9	
	V4	18	20.2	6.6	14	19.0	6.1	0.639	19.6	6.1	0,189
	V5	14	22.6	3.4	7	20.9	4.5	0.971	21.8	4.0	
	V6	14	22.0	4.4	8	22.1	3.4	1.000	22.0	4.2	
	V7	9	20.8	7.0	2	18.0	7.1	0.582	19.4	6.4	
FACT social well-being	V1	19	20.3	5.4	14	18.6	5.2	0.304	19.8	5.2	
	V2	18	20.5	4.6	14	17.7	6.0	0.251	19.6	5.2	
	V3	18	19.5	4.6	13	17.9	4.6	0.395	19.2	4.5	
	V4	18	19.2	5.0	14	18.3	6.2	0.896	19.3	5.3	0,161
	V5	14	20.9	3.9	7	20.4	5.1	0.913	20.5	4.5	
	V6	14	20.7	2.7	8	22.2	3.2	0.188	21.2	3.2	
	V7	9	21.8	3.1	2	21.0	1.4	0.727	21.3	3.8	
FACT emotional well-being	V1	19	16.2	3.8	14	16.7	2.6	0.986	16.0	3.3	
	V2	18	17.0	3.3	14	16.6	2.6	0.667	16.5	3.7	
	V3	18	17.0	4.0	13	17.7	3.1	0.767	16.7	3.8	
	V4	18	17.4	2.7	14	16.6	3.3	0.377	16.6	3.3	0,267
	V5	13	17.7	2.2	7	17.1	1.2	0.393	17.1	2.3	
	V6	14	16.8	3.4	8	16.6	3.2	0.570	16.1	3.6	
	V7	9	17.3	2.4	2	16.0	1.4	0.327	16.9	3.1	
FACT functional well-being	V1	19	17.3	5.3	14	16.8	4.3	0.900	17.2	4.5	
	V2	18	17.9	5.4	14	15.1	5.9	0.319	16.7	5.4	
	V3	18	16.1	6.4	13	14.9	4.5	0.679	16.0	5.4	
	V4	18	17.1	5.4	14	15.5	5.7	0.512	16.2	5.4	0,288
	V5	13	18.8	4.6	7	16.4	5.3	0.485	17.9	4.5	
	V6	14	17.1	6.1	8	19.3	3.8	0.441	17.9	5.4	
	V7	9	19.2	7.0	2	18.0	1.4	0.909	18.0	6.0	

FACT-G, Functional Assessment for Cancer Therapy; SD, standard deviation; V, visit; N, number of patients

Supplementary Table 2. Absolute scores of secondary outcomes

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FAACT score											
	V1	19	37,9	4,3	14	39,1	5,4	0,439	38,3	4,8	
	V2	18	37,9	5,2	14	39,1	6,0	0,398	38,7	5,3	
	V3	18	37,4	5,5	13	37,9	5,2	0,828	38,1	5,0	
	V4	18	35,0	6,7	14	38,6	7,1	0,099	36,9	6,4	-0,522
	V5	13	39,3	4,5	7	37,3	8,9	0,877	37,7	6,2	
	V6	14	38,3	4,7	8	40,3	4,3	0,365	38,6	4,8	
	V7	9	33,0	11,8	2	34,0	14,1	1,000	33,2	10,0	
MDASI severity											
	V1	19	1,9	1,5	14	1,9	1,5	1,000	2,0	1,4	
	V2	18	2,0	1,5	14	2,5	1,6	0,464	2,2	1,6	
	V3	18	2,5	1,4	13	2,0	1,0	0,417	2,2	1,3	
	V4	18	2,4	1,6	14	2,1	1,6	0,561	2,2	1,6	0,188
	V5	13	2,0	0,9	7	2,7	1,6	0,588	2,1	1,3	
	V6	14	2,1	1,2	8	2,4	1,7	0,868	2,2	1,5	
	V7	9	2,5	1,6	2	2,2	1,7	1,000	2,6	1,9	
MDASI interference											
	V1	19	1,9	2,1	14	2,2	1,6	0,397	2,1	2,0	
	V2	18	2,2	2,0	14	3,4	1,9	0,065	2,6	2,0	
	V3	18	2,8	2,3	13	2,9	1,6	0,798	2,8	2,0	
	V4	18	3,0	2,1	14	2,9	2,2	0,837	2,9	2,2	0,047
	V5	13	2,2	1,8	7	2,8	2,3	0,588	2,2	1,8	
	V6	14	2,3	1,7	8	2,9	1,9	0,570	2,4	1,8	
	V7	9	0,6	2,6	2	3,3	3,1	1,000	2,9	2,6	

FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MDASI, The M.D. Anderson Symptom Inventory; SD, standard deviation; V, visit; N, number of patients.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Yes, p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	Yes, p. 2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Yes, 5-7 and p10
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	Yes, p.8-9
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	Yes, p.8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		Not applicable
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	Yes, p.8
	4b	Settings and locations where the data were collected		Yes, p.8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	Yes, p.9

Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	Yes, 10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons		Not applicable
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Yes, 12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines		Not applicable
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		Yes, p.10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	Yes, p.10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	Yes, p. 10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	Yes
	10a		Who generated the random allocation sequence, who	Yes

			enrolled clusters, and who assigned clusters to interventions	
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Yes
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	Yes
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		Not done
	11b	If relevant, description of the similarity of interventions		Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Yes, p.12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		Yes, p.12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Yes, figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Yes, figure 1

Recruitment	14a	Dates defining the periods of recruitment and follow-up		Yes, p.9
	14b	Why the trial ended or was stopped		Yes
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Yes, table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		Yes
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Yes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		Not applicable
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Yes, p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	Yes

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes, p.16-17
Other information			
Registration	23	Registration number and name of trial registry	Yes, p.3
Protocol	24	Where the full trial protocol can be accessed, if available	Yes, p.8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Yes, p.19

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035546.R2
Article Type:	Original research
Date Submitted by the Author:	27-May-2020
Complete List of Authors:	Hentschel, Leopold; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Richter, Stephan; University Hospital Carl Gustav Carus, Department of Internal Medicine I Kopp, Hans-Georg; Robert-Bosch-Center of Tumor Diseases, Interdisciplinary Center for Soft-Tissue-Sarcoma, GIST and Bone-Tumor Kasper, Bernd; University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Sarcoma Unit, Interdisciplinary Tumor Center Kunitz, Annegret; Vivantes Clinic Spandau, Internal Medicine Grünwald, Viktor ; University Hospital Essen, Interdisciplinary Genitourinary Oncology/West-German Cancer Center Kessler, Torsten; University Hospital of Münster, Hematology Oncology Chemnitz, Jens Marcus; ev. Stift St. Martin, Internal Medicine Pelzer, Uwe; Charité Medical University, Division of Hematology, Oncology and Tumor Immunology Schuler, Ulrich; University Hospital Carl Gustav Carus, University Palliative Center Freitag, Janet; University Hospital Carl Gustav Carus, Department of Internal Medicine I Schilling, Andrea; University Hospital Carl Gustav Carus, Department of Social Work Hornemann, Beate; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Arndt, Karin; Das Lebenshaus e.V, Patient Advocacy Bornhaeuser, Martin; University Hospital Carl Gustav Carus, Department of Internal Medicine I; Deutsches Krebsforschungszentrum, National Center for Tumor Diseases (NCT) Schuler, Markus Kajo; University Hospital Carl Gustav Carus, Department of Internal Medicine I; HELIOS Hospital Emil von Behring, Department of Internal Medicine II
Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Patient-centred medicine

Keywords:	Sarcoma < ONCOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cancer pain < ONCOLOGY

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Original Research

Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: A multicenter, cluster-randomized trial within the Germany 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 multi-step 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-randomized, open-label, proof-of-concept study. The intervention incorporates electronic PRO-assessment, a case-vignette and expert-consented treatment recommendations.

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

Primary and secondary outcome measures: The primary endpoint was the change of FACT-G total score after nine weeks. Secondary outcomes included QoL (FACT-G subscales), anorexia and cachexia (FAACT), symptoms (MDASI), anxiety and depression (HADS), pain intensity and interference (BPI), and survival assessment.

Results: After nine weeks of treatment QoL declined less in the IA (Δ FACT-G total score: -2.4, 95% CI: -9.2 to 4.5) as compared to CA (Δ FACT-G total score: -3.9; 95% CI:-11.3 to 3.5; *P*=0.765). A beneficial trend of the patient-tailored evaluation in IA was observed in almost all FACT-G subscales. Smaller adverse trends between arms were

observed for MDASI, FAACT, HADS and BPI scales. These trends failed to reach statistical significance. 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 indicate a potentially beneficial effect of an ePRO-based intervention on QoL that needs to be reappraised in confirmatory studies.

Trial registration: ClinicalTrials.gov Identifier: NCT02204111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

KEYWORDS

Sarcoma, quality of life, patient-reported outcomes, trabectedin

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 to 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 tumor burden as an outcome (e.g., progression-free survival or overall survival), and, secondly, 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 or the time to deterioration of QoL.[10]

Trabectedin (Yondelis®) is a semi-synthetic 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 United States 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 PROs 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 STAR (Symptom Tracking and Reporting) intervention in prolonging time on chemotherapy, less unexpected admission and longer quality-adjusted survival.[17] In brief, they randomized 766 patients from a single institution under chemotherapy for solid tumors 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 randomized multi-center trial evaluated the effect of a web-based, self-report assessment and educational intervention on symptom distress during

cancer therapy in 752 ambulatory patients from different entities and with various diagnoses.[18] In this multicenter 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 it should be accompanied by additional interventions such as nurse-led patient education, self-care support or a multi-professional expert panel that discusses PRO-results and derive 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-randomized 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 three weeks, were included in this study. Physician-assessed life expectancy of patients had to be at least six months and Eastern Cooperative Oncology Group (ECOG)-performance status score had to be ≤2. All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The YonLife trial was approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden on June 2014 (EK241062014), and all participating centers obtained the approval of the local ethics committee before patient enrolment. All patients provided written informed consent before inclusion in the study.

Patient and public involvement

We are grateful to all patients that 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-randomized, 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 (i.e. visit [V] 1) and after 3 weeks (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 nine weeks (V4) between interventional arm and control arm. Secondary objectives included explorative comparison between other PRO such as anxiety, depression, pain as well as survival. Furthermore, factors that predict QoL after nine 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) PRO 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 multi-professional 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 center. 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.

Randomization

Six German centers were cluster-randomized in a 1:1 ratio in an IA (3 centers) and a CA (3 centers). This trial was designed as a cluster-randomized trials to avoid contamination that might result in a type 2 error. If randomized 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. Randomization was conducted by a colleague not actively involved in this trial using random numbers generated in excel.

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

Outcome measures

The primary outcome explored the changes of patients QoL in IA and CA after nine 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, 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 in order to represent a minimal clinical important difference (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 endpoints measured throughout the study are depicted in Table 1.

Table 1: Visit schedule and outcomes

Study period	**SCR**	**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
Tumor-specific & socio-demographic parameters	x			x	x	x	x
Feasibility Scoring based on patients' and doctors' opinion*				x			

* Data is currently being analyzed and is available upon request.

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 (i.e. V7). [24] Moreover, the effect size of the intervention was measured as COHEN's *d* test by measuring the difference between

two means.[28] The M.D. Anderson Symptom Inventory (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 pre-determined cut-off scores.[31] The Functional Assessment of Anorexia/Cachexia Therapy questionnaire (FAACT) measured the impact of cachexia and anorexia on patients' QoL.[32] Finally, the Brief Pain Inventory (BPI) in a scale range from 0-10 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), tumor stage (UICC-classification), symptom severity (MDASI), symptom interference (MDASI), depression (HADS), anxiety (HADS), patients satisfaction (IN-PATSAT32)[34], 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 standard deviation (SD) of $\sigma=17$ and a conservatively estimated intra-cluster-correlation coefficient of $P=0.1$.[35] This calculation resulted in a cluster size of 11 patients. Additionally, 11 patients were recruited in the reference center, 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 endpoints 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 visit (V4) and who had no major protocol deviations.

Survival was assessed as means of PFS and overall survival (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 confidence interval (CI) within the observation period of this study. Mann-Whitney-U, Fisher-exact test, and Chi-squared test were used for the detection of possible differences concerning demographics. 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.

RESULTS

Patients and treatment arms

Between September 2014 and March 2018, 80 patients from seven sites were screened for study participation (figure 1). The FAS encompasses 79 patients, as one 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 consists 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 tumor stage (*P*=0.083) and less patients suffer from leiomyosarcoma (Table 2).

Table 2. Patient characteristic at baseline

	Interventional arm (IA; 3 centers) *N*=38	Control arm (CA; 3 centers) *N*=29	Reference Center (RF; 1 center) *N*=12	Full Analysis Set *N*=79
		Full Analysis Set (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
Tumor 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

Per-protocol analysis set (PPS)

	Interventional arm (IA; 3 centers), *N*=19	**Control arm (CA; 3 centers), *N*=14**	**Reference Center (RF; 1 center), *N*=8**	**Per Protocol Set *N*=41**
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
Tumor 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
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.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; M0, no distant metastasis; M1, distant metastasis.

Primary Outcome

After nine weeks at V4, FACT-G was higher in IA (Δ FACT-G total score: -2.4, 95% CI: -9.2-4.5) as compared to the CA (Δ FACT-G total score: -3.9, 95% CI: -11.3-3.5; *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 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: 6.2-43.8) and CA (22 days, 95% CI: 16.5-27.5; *P*=0.927).

Table 3. Change scores after 9 weeks of treatment

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

BPI. Brief Pain Inventory; CI, confidence interval; FACT-G. Functional Assessment for Cancer Therapy; HADS. Hospital Anxiety and Depression scale; MDASI. The M.D. Anderson Symptom Inventory; V. visit; N. number of evaluable patients in respective cluster.

Secondary Outcomes

Regarding the change of QoL between V1 and V4 (as well as during follow up V7), there was a beneficial impact 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 (Δ FACT-G PWB: -1.2, 95% CI: -4.4-2.1) than in CA (Δ FACT-G PWB: -2.2, 95% CI: -5.4-1.0; *P*=0.926). Emotional well-being subscale improved slightly in IA (Δ FACT-G EWB: 0.9, 95% CI: -0.6-2.4) and remained almost stable in CA (Δ FACT-G EWB: -0.1, 95% CI: -2.3-2.1; *P*=0.561). Functional well-being subscale declined less in IA (Δ FACT-G FWB: -0.5, 95% CI: -2.7-1.7) than in CA (Δ FACT-G FWB: -1.3, 95% CI: -4.0-1.4; *P*=0.536). Lastly, social well-being subscale remained almost stable (Δ FACT-G SWB:-0.2, 95% CI: -3.1 -0.1) in CA while decreasing in IA (Δ FACT-G SWB: -1.6, 95% CI: -2.2-1.7; *P*=0.952). Overall, there were non-significant, adverse trends in other domains of PRO (MDASI, FAACT, HADS and BPI scales) (Table 3 and 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, anorexia and cachexia (Table 4). In a multivariable

regression, depression determines the FACT-G total score (Table 4).

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

	Univariate regression		
	P-value	estimate	95% confidence interval
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
Tumor 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		
	P-value	estimate	95% confidence interval
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
Tumor 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.

DISCUSSION

Principal findings

To the best of our knowledge, this is the first randomized trial using a patient-directed supportive care intervention to improve QoL and other PRO in sarcoma patients. We observed a trend in favor of the intervention considering the primary endpoint (total FACT-G score) and other secondary outcomes (i.e. 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 multi-center randomized trial, which reported a comparable decline in FACT-G score of ~2 in 281 patients suffering from advanced solid cancers who received early palliative care or standard oncologic care.[36] In addition, the total FACT-G score they observed after twelve weeks (70.1 and 69.6) was comparable to the score found in IA (73.9) and CA (69.4) after nine week of treatment. The total FACT-G score (76.4) was also comparable to the YonLife baseline score (74.2) in a sample of 42 patients suffering from different sarcoma histotypes in a single center, cross-sectional study.[37]

As the intervention yields beneficial effects on QoL, 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 take several days. Complex syndromes such as anxiety and depression need ongoing treatment, either psycho-oncological or pharmaceutical, which usually take 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 programs like providing treating physician with pre-collected PROs[17, 24] and, creating a QoL-profile and using expert's recommendations.[19] In contrast, unlike recently evolving programs[38], YonLife did not provide possibility to answer questions using web based questionnaires accessible from home or mobile device. Furthermore, the PRO-results were automatically calculated, but were not automatically compared to pre-defined 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 specialized sarcoma centers.

Weaknesses and strengths

Our study has several limitations. As no preceding studies that incorporate a PRO-

based individualized 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 now 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 wellbeing 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.

CONTRIBUTORS

LH and MKS proposed the conception and design of the study, performed data analysis, interpretation and quality control of data and algorithms. MB, LH and MKS are responsible for the manuscript editing. MKS, SR, HGK, BK, AK, VG, TK, UP and JMC performed the data acquisition. All aforementioned authors as well as US, JF, AS, BH and KA participated in the manuscript drafting and review with equal contribution.

FUNDING

This work was supported by an unrestricted grant from PharmaMar, Spain.

DATA AVAILABILITY STATEMENT

Complete data sets are available upon reasonable request

COMPETING INTERESTS

None declared.

ACKNOWLEDGEMENTS

The trial was coordinated by GWT-TUD, Dresden, Germany. We acknowledge the German Interdisciplinary Sarcoma Group (GISG) for providing support for this trial. The YonLife trial was associated with the German Interdisciplinary Sarcoma Group as GISG-12 project and as AIO-STS-0215 within the 'Arbeitsgemeinschaft Internistische Onkologie' of the 'Deutsche Krebsgesellschaft' (DKG). We would also like to thank Michael Kramer, Kristian Zinke and Rocco Haase for their support on statistical aspects

of the study and Felicitas Lenz and Adnan Tanović for proof-reading.

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Figure 1. CONSORT Flowchart

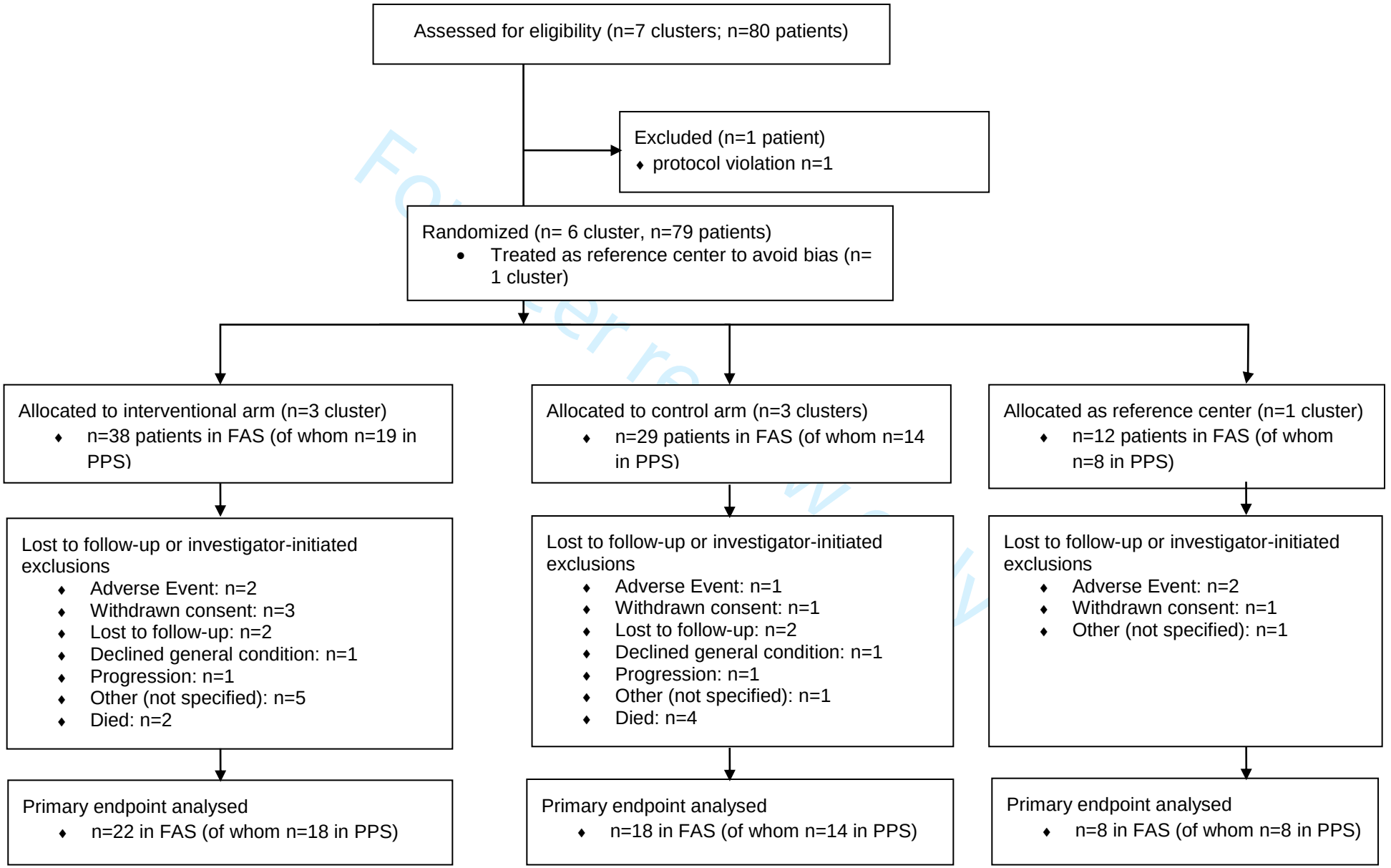
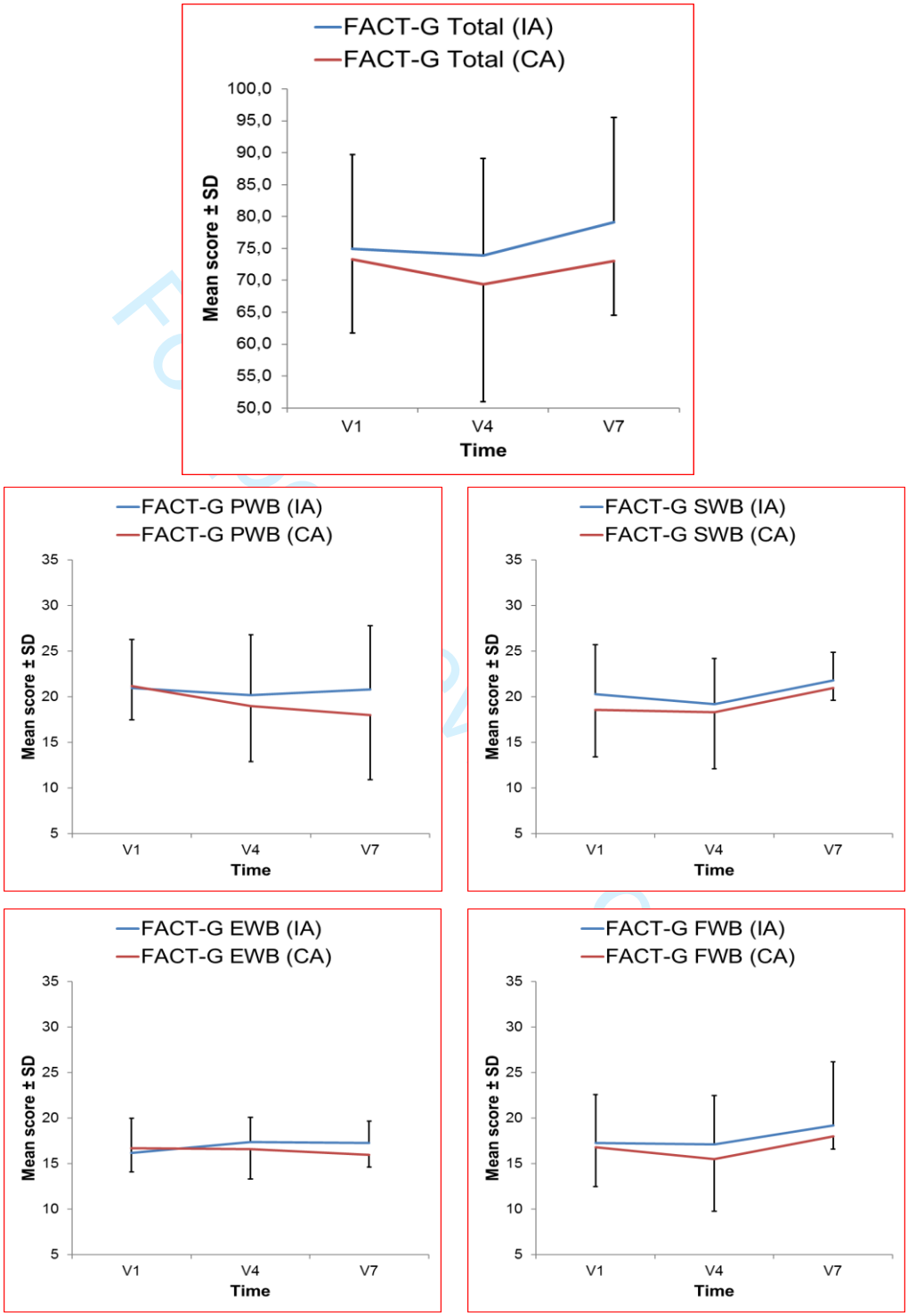


Figure 2. Absolute FACT-scores at baseline (V1), after nine weeks of treatment (V4; primary endpoint) and during follow up visit (V7)



FACT-G, Functional Assessment for Cancer Therapy; EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SD, standard deviation; SWB, social well-being; V, visit.
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.

Supplementary Table 1. Absolute FACT-scores at each assessment time

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FACT-G total score	V1	19	74.9	14.8	14	73.3	11.6	0.788	74.2	13.0	
	V2	18	76.8	15.1	14	68.2	16.6	0.145	73.1	16.1	
	V3	18	72.0	16.7	13	70.7	11.8	0.708	72.1	14.3	
	V4	18	73.9	15.2	14	69.4	18.4	0.512	71.6	16.2	0,267
	V5	13	80.2	10.8	7	74.9	14.8	0.588	77.3	14.8	
	V6	14	76.6	12.8	8	80.2	11.8	0.402	77.2	13.2	
	V7	9	79.1	16.4	2	73.0	8.5	0.582	75.7	14.9	
FACT physical well-being	V1	19	21.0	5.3	14	21.2	3.7	0.872	21.2	4.5	
	V2	18	21.4	5.0	14	18.7	5.4	0.168	20.3	5.2	
	V3	18	19.3	5.6	13	20.2	3.7	0.890	20.3	4.9	
	V4	18	20.2	6.6	14	19.0	6.1	0.639	19.6	6.1	0,189
	V5	14	22.6	3.4	7	20.9	4.5	0.971	21.8	4.0	
	V6	14	22.0	4.4	8	22.1	3.4	1.000	22.0	4.2	
	V7	9	20.8	7.0	2	18.0	7.1	0.582	19.4	6.4	
FACT social well-being	V1	19	20.3	5.4	14	18.6	5.2	0.304	19.8	5.2	
	V2	18	20.5	4.6	14	17.7	6.0	0.251	19.6	5.2	
	V3	18	19.5	4.6	13	17.9	4.6	0.395	19.2	4.5	
	V4	18	19.2	5.0	14	18.3	6.2	0.896	19.3	5.3	0,161
	V5	14	20.9	3.9	7	20.4	5.1	0.913	20.5	4.5	
	V6	14	20.7	2.7	8	22.2	3.2	0.188	21.2	3.2	
	V7	9	21.8	3.1	2	21.0	1.4	0.727	21.3	3.8	
FACT emotional well-being	V1	19	16.2	3.8	14	16.7	2.6	0.986	16.0	3.3	
	V2	18	17.0	3.3	14	16.6	2.6	0.667	16.5	3.7	
	V3	18	17.0	4.0	13	17.7	3.1	0.767	16.7	3.8	
	V4	18	17.4	2.7	14	16.6	3.3	0.377	16.6	3.3	0,267
	V5	13	17.7	2.2	7	17.1	1.2	0.393	17.1	2.3	
	V6	14	16.8	3.4	8	16.6	3.2	0.570	16.1	3.6	
	V7	9	17.3	2.4	2	16.0	1.4	0.327	16.9	3.1	
FACT functional well-being	V1	19	17.3	5.3	14	16.8	4.3	0.900	17.2	4.5	
	V2	18	17.9	5.4	14	15.1	5.9	0.319	16.7	5.4	
	V3	18	16.1	6.4	13	14.9	4.5	0.679	16.0	5.4	
	V4	18	17.1	5.4	14	15.5	5.7	0.512	16.2	5.4	0,288
	V5	13	18.8	4.6	7	16.4	5.3	0.485	17.9	4.5	
	V6	14	17.1	6.1	8	19.3	3.8	0.441	17.9	5.4	
	V7	9	19.2	7.0	2	18.0	1.4	0.909	18.0	6.0	

FACT-G, Functional Assessment for Cancer Therapy; SD, standard deviation; V, visit; N, number of patients

Supplementary Table 2. Absolute scores of secondary outcomes

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FAACT score											
	V1	19	37,9	4,3	14	39,1	5,4	0,439	38,3	4,8	
	V2	18	37,9	5,2	14	39,1	6,0	0,398	38,7	5,3	
	V3	18	37,4	5,5	13	37,9	5,2	0,828	38,1	5,0	
	V4	18	35,0	6,7	14	38,6	7,1	0,099	36,9	6,4	-0,522
	V5	13	39,3	4,5	7	37,3	8,9	0,877	37,7	6,2	
	V6	14	38,3	4,7	8	40,3	4,3	0,365	38,6	4,8	
	V7	9	33,0	11,8	2	34,0	14,1	1,000	33,2	10,0	
MDASI severity											
	V1	19	1,9	1,5	14	1,9	1,5	1,000	2,0	1,4	
	V2	18	2,0	1,5	14	2,5	1,6	0,464	2,2	1,6	
	V3	18	2,5	1,4	13	2,0	1,0	0,417	2,2	1,3	
	V4	18	2,4	1,6	14	2,1	1,6	0,561	2,2	1,6	0,188
	V5	13	2,0	0,9	7	2,7	1,6	0,588	2,1	1,3	
	V6	14	2,1	1,2	8	2,4	1,7	0,868	2,2	1,5	
	V7	9	2,5	1,6	2	2,2	1,7	1,000	2,6	1,9	
MDASI interference											
	V1	19	1,9	2,1	14	2,2	1,6	0,397	2,1	2,0	
	V2	18	2,2	2,0	14	3,4	1,9	0,065	2,6	2,0	
	V3	18	2,8	2,3	13	2,9	1,6	0,798	2,8	2,0	
	V4	18	3,0	2,1	14	2,9	2,2	0,837	2,9	2,2	0,047
	V5	13	2,2	1,8	7	2,8	2,3	0,588	2,2	1,8	
	V6	14	2,3	1,7	8	2,9	1,9	0,570	2,4	1,8	
	V7	9	0,6	2,6	2	3,3	3,1	1,000	2,9	2,6	

FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MDASI, The M.D. Anderson Symptom Inventory; SD, standard deviation; V, visit; N, number of patients.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Yes, p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	Yes, p. 2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Yes, 5-7 and p10
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	Yes, p.8-9
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	Yes, p.8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		Not applicable
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	Yes, p.8
	4b	Settings and locations where the data were collected		Yes, p.8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	Yes, p.9

Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	Yes, 10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons		Not applicable
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Yes, 12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines		Not applicable
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		Yes, p.10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	Yes, p.10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	Yes, p. 10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	Yes
	10a		Who generated the random allocation sequence, who	Yes

			enrolled clusters, and who assigned clusters to interventions	
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Yes
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	Yes
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		Not done
	11b	If relevant, description of the similarity of interventions		Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Yes, p.12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		Yes, p.12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Yes, figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Yes, figure 1

Recruitment	14a	Dates defining the periods of recruitment and follow-up		Yes, p.9
	14b	Why the trial ended or was stopped		Yes
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Yes, table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		Yes
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Yes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		Not applicable
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Yes, p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	Yes

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes, p.16-17
Other information			
Registration	23	Registration number and name of trial registry	Yes, p.3
Protocol	24	Where the full trial protocol can be accessed, if available	Yes, p.8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Yes, p.19

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

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1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035546.R3
Article Type:	Original research
Date Submitted by the Author:	05-Jun-2020
Complete List of Authors:	Hentschel, Leopold; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Richter, Stephan; University Hospital Carl Gustav Carus, Department of Internal Medicine I Kopp, Hans-Georg; Robert-Bosch-Center of Tumor Diseases, Interdisciplinary Center for Soft-Tissue-Sarcoma, GIST and Bone-Tumor Kasper, Bernd; University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Sarcoma Unit, Interdisciplinary Tumor Center Kunitz, Annegret; Vivantes Clinic Spandau, Internal Medicine Grünwald, Viktor ; University Hospital Essen, Interdisciplinary Genitourinary Oncology/West-German Cancer Center Kessler, Torsten; University Hospital of Münster, Hematology Oncology Chemnitz, Jens Marcus; ev. Stift St. Martin, Internal Medicine Pelzer, Uwe; Charité Medical University, Division of Hematology, Oncology and Tumor Immunology Schuler, Ulrich; University Hospital Carl Gustav Carus, University Palliative Center Freitag, Janet; University Hospital Carl Gustav Carus, Department of Internal Medicine I Schilling, Andrea; University Hospital Carl Gustav Carus, Department of Social Work Hornemann, Beate; University Hospital Carl Gustav Carus, Department of Psychooncology of the University Cancer Center Arndt, Karin; Das Lebenshaus e.V, Patient Advocacy Bornhaeuser, Martin; University Hospital Carl Gustav Carus, Department of Internal Medicine I; Deutsches Krebsforschungszentrum, National Center for Tumor Diseases (NCT) Schuler, Markus Kajo; University Hospital Carl Gustav Carus, Department of Internal Medicine I; HELIOS Hospital Emil von Behring, Department of Internal Medicine II
Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Patient-centred medicine

Keywords:	Sarcoma < ONCOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cancer pain < ONCOLOGY

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Original Research

Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: A multicenter, cluster-randomized trial within the Germany 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 multi-step 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-randomized, open-label, proof-of-concept study. The intervention incorporates electronic PRO-assessment, a case-vignette and expert-consented treatment recommendations.

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

Primary and secondary outcome measures: The primary endpoint was the change of FACT-G total score after nine weeks. Secondary outcomes included QoL (FACT-G subscales), anorexia and cachexia (FAACT), symptoms (MDASI), anxiety and depression (HADS), pain intensity and interference (BPI), and survival assessment.

Results: After nine weeks of treatment QoL declined less in the IA (Δ FACT-G total score: -2.4, 95% CI: -9.2 to 4.5) as compared to CA (Δ FACT-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. 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 favorable effect of an ePRO-based intervention on QoL that needs to be reappraised in confirmatory studies.

Trial registration: ClinicalTrials.gov Identifier: NCT02204111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

KEYWORDS

Sarcoma, quality of life, patient-reported outcomes, trabectedin

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 to 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 tumor burden as an outcome (e.g., progression-free survival or overall survival), and, secondly, 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 or the time to deterioration of QoL.[10]

Trabectedin (Yondelis®) is a semi-synthetic 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 United States 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 PROs 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 STAR (Symptom Tracking and Reporting) intervention in prolonging time on chemotherapy, less unexpected admission and longer quality-adjusted survival.[17] In brief, they randomized 766 patients from a single institution under chemotherapy for solid tumors 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 randomized multi-center trial evaluated the effect of a web-based, self-report assessment and educational intervention on symptom distress during

cancer therapy in 752 ambulatory patients from different entities and with various diagnoses.[18] In this multicenter 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 it should be accompanied by additional interventions such as nurse-led patient education, self-care support or a multi-professional expert panel that discusses PRO-results and derive 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-randomized 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 three weeks, were included in this study. Physician-assessed life expectancy of patients had to be at least six months and Eastern Cooperative Oncology Group (ECOG)-performance status score had to be ≤2. All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The YonLife trial was approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden on June 2014 (EK241062014), and all participating centers obtained the approval of the local ethics committee before patient enrolment. All patients provided written informed consent before inclusion in the study.

Patient and public involvement

We are grateful to all patients that 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-randomized, 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 (i.e. visit [V] 1) and after 3 weeks (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 nine weeks (V4) between interventional arm and control arm. Secondary objectives included explorative comparison between other PRO such as anxiety, depression, pain as well as survival. Furthermore, factors that predict QoL after nine 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) PRO 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 multi-professional 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 center. 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.

Randomization

Six German centers were cluster-randomized in a 1:1 ratio in an IA (3 centers) and a CA (3 centers). This trial was designed as a cluster-randomized trials to avoid contamination that might result in a type 2 error. If randomized 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. Randomization was conducted by a colleague not actively involved in this trial using random numbers generated in excel.

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

Outcome measures

The primary outcome explored the changes of patients QoL in IA and CA after nine 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, 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 in order to represent a minimal clinical important difference (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 endpoints measured throughout the study are depicted in Table 1.

Table 1: Visit schedule and outcomes

Study period	**SCR**	**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
Tumor-specific & socio-demographic parameters	x			x	x	x	x
Feasibility Scoring based on patients' and doctors' opinion*				x			

* Data is currently being analyzed and is available upon request.

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 (i.e. V7). [24] Moreover, the effect size of the intervention was measured as COHEN's *d* test by measuring the difference between

two means.[28] The M.D. Anderson Symptom Inventory (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 pre-determined cut-off scores.[31] The Functional Assessment of Anorexia/Cachexia Therapy questionnaire (FAACT) measured the impact of cachexia and anorexia on patients' QoL.[32] Finally, the Brief Pain Inventory (BPI) in a scale range from 0-10 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), tumor stage (UICC-classification), symptom severity (MDASI), symptom interference (MDASI), depression (HADS), anxiety (HADS), patients satisfaction (IN-PATSAT32)[34], 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 standard deviation (SD) of $\sigma=17$ and a conservatively estimated intra-cluster-correlation coefficient of $P=0.1$.[35] This calculation resulted in a cluster size of 11 patients. Additionally, 11 patients were recruited in the reference center, 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 endpoints 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 visit (V4) and who had no major protocol deviations.

Survival was assessed as means of PFS and overall survival (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 confidence interval (CI) within the observation period of this study. Mann-Whitney-U, Fisher-exact test, and Chi-squared test were used for the detection of possible differences concerning demographics. 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.

RESULTS

Patients and treatment arms

Between September 2014 and March 2018, 80 patients from seven sites were screened for study participation (figure 1). The FAS encompasses 79 patients, as one 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 consists 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 tumor stage (*P*=0.083) and less patients suffer from leiomyosarcoma (Table 2).

Table 2. Patient characteristic at baseline

	Interventional arm (IA; 3 centers) *N*=38	Control arm (CA; 3 centers) *N*=29	Reference Center (RF; 1 center) *N*=12	Full Analysis Set *N*=79
Full Analysis Set (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
Tumor 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

Per-protocol analysis set (PPS)

	Interventional arm (IA; 3 centers), *N*=19	**Control arm (CA; 3 centers), *N*=14**	**Reference Center (RF; 1 center), *N*=8**	**Per Protocol Set *N*=41**
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
Tumor 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
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.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; M0, no distant metastasis; M1, distant metastasis.

Primary Outcome

After nine weeks at V4, FACT-G declined less in IA (Δ FACT-G total score: -2.4, 95% CI: -9.2-4.5) as compared to the CA (Δ FACT-G total score: -3.9, 95% CI: -11.3-3.5; *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 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: 6.2-43.8) and CA (22 days, 95% CI: 16.5-27.5; *P*=0.927).

Table 3. Change scores after 9 weeks of treatment

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

BPI. Brief Pain Inventory; CI, confidence interval; FACT-G. Functional Assessment for Cancer Therapy; HADS. Hospital Anxiety and Depression scale; MDASI. The M.D. Anderson Symptom Inventory; V. visit; N. number of evaluable patients in respective cluster.

Secondary Outcomes

Regarding the change of QoL between V1 and V4 (as well as during follow up V7), there was a beneficial impact 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 (Δ FACT-G PWB: -1.2, 95% CI: -4.4-2.1) than in CA (Δ FACT-G PWB: -2.2, 95% CI: -5.4-1.0; *P*=0.926). Emotional well-being subscale improved slightly in IA (Δ FACT-G EWB: 0.9, 95% CI: -0.6-2.4) and remained almost stable in CA (Δ FACT-G EWB: -0.1, 95% CI: -2.3-2.1; *P*=0.561). Functional well-being subscale declined less in IA (Δ FACT-G FWB: -0.5, 95% CI: -2.7-1.7) than in CA (Δ FACT-G FWB: -1.3, 95% CI: -4.0-1.4; *P*=0.536). Lastly, social well-being subscale remained almost stable (Δ FACT-G SWB:-0.2, 95% CI: -3.1 -0.1) in CA while decreasing in IA (Δ FACT-G SWB: -1.6, 95% CI: -2.2-1.7; *P*=0.952). Overall, there were non-significant, adverse trends in other domains of PRO (MDASI, FAACT, HADS and BPI scales) (Table 3 and 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, anorexia and cachexia (Table 4). In a multivariable

regression, depression determines the FACT-G total score (Table 4).

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

	Univariate regression		
	P-value	estimate	95% confidence interval
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
Tumor 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		
	P-value	estimate	95% confidence interval
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
Tumor 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.

DISCUSSION

Principal findings

To the best of our knowledge, this is the first randomized trial using a patient-directed supportive care intervention to improve QoL and other PRO in sarcoma patients. We observed a trend in favor of the intervention considering the primary endpoint (total FACT-G score) and other secondary outcomes (i.e. 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 multi-center randomized trial, which reported a comparable decline in FACT-G score of ~2 in 281 patients suffering from advanced solid cancers who received early palliative care or standard oncologic care.[36] In addition, the total FACT-G score they observed after twelve weeks (70.1 and 69.6) was comparable to the score found in IA (73.9) and CA (69.4) after nine week of treatment. The total FACT-G score (76.4) was also comparable to the YonLife baseline score (74.2) in a sample of 42 patients suffering from different sarcoma histotypes in a single center, cross-sectional study.[37]

As the intervention appears to be favorable 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 take several days. Complex syndromes such as anxiety and depression need ongoing treatment, either psycho-oncological or pharmaceutical, which

usually take 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 programs like providing treating physician with pre-collected PROs[17, 24] and, creating a QoL-profile and using expert's recommendations.[19] In contrast, unlike recently evolving programs[38], YonLife did not provide possibility to answer questions using web based questionnaires accessible from home or mobile device. Furthermore, the PRO-results were automatically calculated, but were not automatically compared to pre-defined 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 specialized sarcoma centers.

Weaknesses and strengths

Our study has several limitations. As no preceding studies that incorporate a PRO-

based individualized 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 now 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 wellbeing 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.

CONTRIBUTORS

LH and MKS proposed the conception and design of the study, performed data analysis, interpretation and quality control of data and algorithms. MB, LH and MKS are responsible for the manuscript editing. MKS, SR, HGK, BK, AK, VG, TK, UP and JMC performed the data acquisition. All aforementioned authors as well as US, JF, AS, BH and KA participated in the manuscript drafting and review with equal contribution.

FUNDING

This work was supported by an unrestricted grant from PharmaMar, Spain.

DATA AVAILABILITY STATEMENT

Complete data sets are available upon reasonable request

COMPETING INTERESTS

None declared.

ACKNOWLEDGEMENTS

The trial was coordinated by GWT-TUD, Dresden, Germany. We acknowledge the German Interdisciplinary Sarcoma Group (GISG) for providing support for this trial. The YonLife trial was associated with the German Interdisciplinary Sarcoma Group as GISG-12 project and as AIO-STS-0215 within the 'Arbeitsgemeinschaft Internistische Onkologie' of the 'Deutsche Krebsgesellschaft' (DKG). We would also like to thank Michael Kramer, Kristian Zinke and Rocco Haase for their support on statistical aspects

of the study and Felicitas Lenz and Adnan Tanović for proof-reading.

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Figure captions

Figure 1. CONSORT Flowchart

Figure 2. Absolute FACT-scores at baseline (V1), after nine weeks of treatment (V4; primary endpoint) and during follow up visit (V7)

Figure 1. CONSORT Flowchart

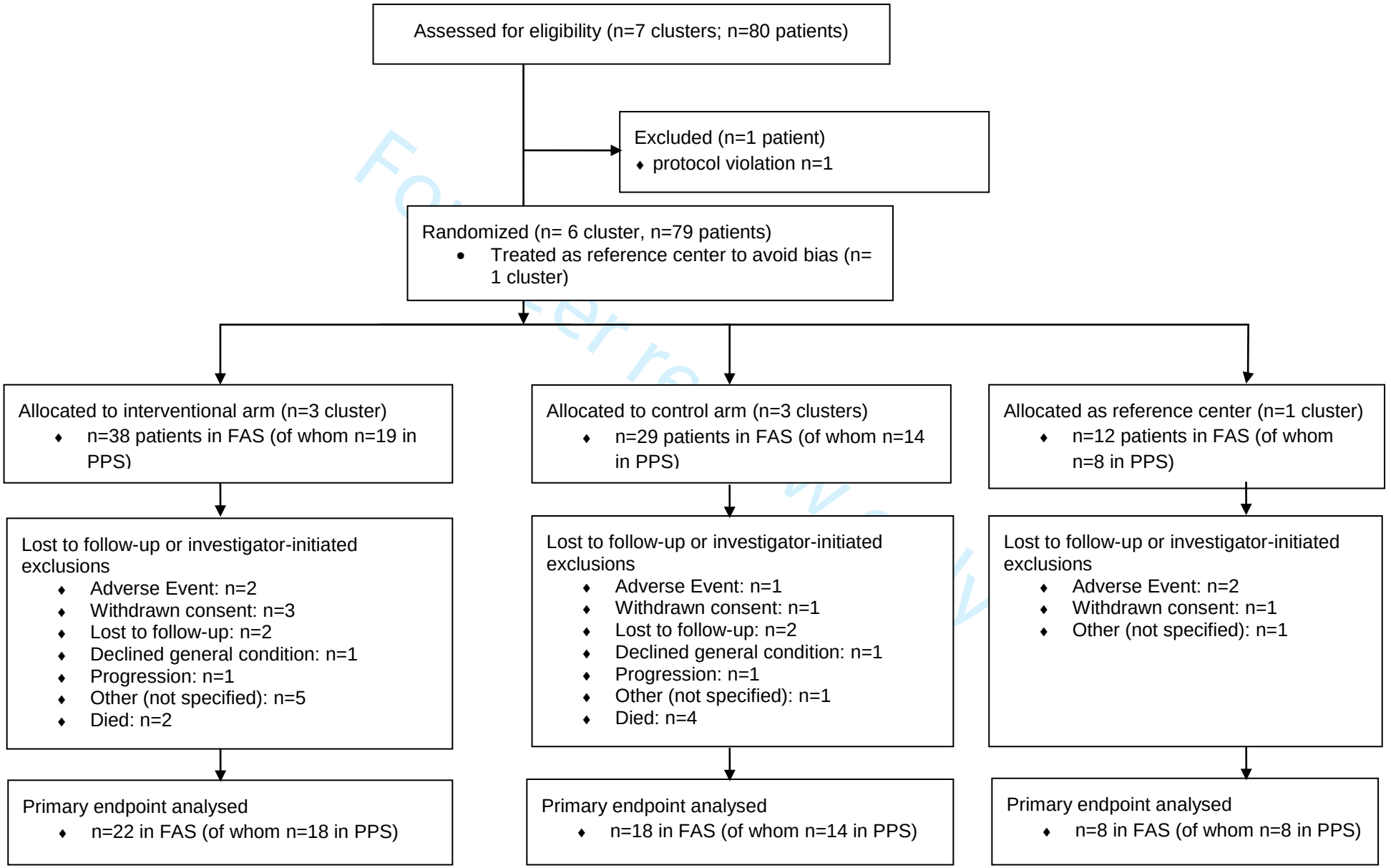
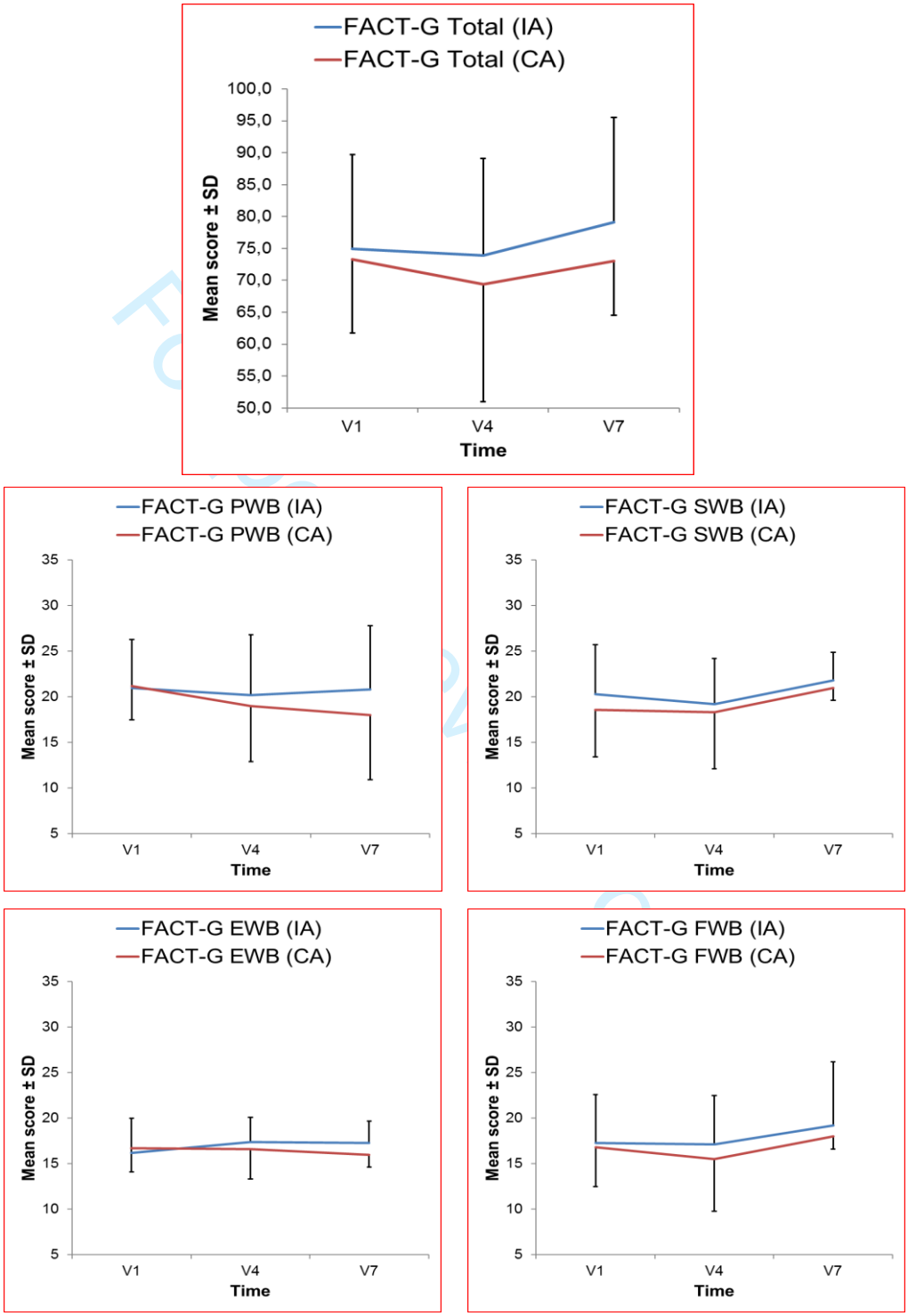


Figure 2. Absolute FACT-scores at baseline (V1), after nine weeks of treatment (V4; primary endpoint) and during follow up visit (V7)



FACT-G, Functional Assessment for Cancer Therapy; EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SD, standard deviation; SWB, social well-being; V, visit.
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.

Supplementary Table 1. Absolute FACT-scores at each assessment time

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FACT-G total score	V1	19	74.9	14.8	14	73.3	11.6	0.788	74.2	13.0	
	V2	18	76.8	15.1	14	68.2	16.6	0.145	73.1	16.1	
	V3	18	72.0	16.7	13	70.7	11.8	0.708	72.1	14.3	
	V4	18	73.9	15.2	14	69.4	18.4	0.512	71.6	16.2	0,267
	V5	13	80.2	10.8	7	74.9	14.8	0.588	77.3	14.8	
	V6	14	76.6	12.8	8	80.2	11.8	0.402	77.2	13.2	
	V7	9	79.1	16.4	2	73.0	8.5	0.582	75.7	14.9	
FACT physical well-being	V1	19	21.0	5.3	14	21.2	3.7	0.872	21.2	4.5	
	V2	18	21.4	5.0	14	18.7	5.4	0.168	20.3	5.2	
	V3	18	19.3	5.6	13	20.2	3.7	0.890	20.3	4.9	
	V4	18	20.2	6.6	14	19.0	6.1	0.639	19.6	6.1	0,189
	V5	14	22.6	3.4	7	20.9	4.5	0.971	21.8	4.0	
	V6	14	22.0	4.4	8	22.1	3.4	1.000	22.0	4.2	
	V7	9	20.8	7.0	2	18.0	7.1	0.582	19.4	6.4	
FACT social well-being	V1	19	20.3	5.4	14	18.6	5.2	0.304	19.8	5.2	
	V2	18	20.5	4.6	14	17.7	6.0	0.251	19.6	5.2	
	V3	18	19.5	4.6	13	17.9	4.6	0.395	19.2	4.5	
	V4	18	19.2	5.0	14	18.3	6.2	0.896	19.3	5.3	0,161
	V5	14	20.9	3.9	7	20.4	5.1	0.913	20.5	4.5	
	V6	14	20.7	2.7	8	22.2	3.2	0.188	21.2	3.2	
	V7	9	21.8	3.1	2	21.0	1.4	0.727	21.3	3.8	
FACT emotional well-being	V1	19	16.2	3.8	14	16.7	2.6	0.986	16.0	3.3	
	V2	18	17.0	3.3	14	16.6	2.6	0.667	16.5	3.7	
	V3	18	17.0	4.0	13	17.7	3.1	0.767	16.7	3.8	
	V4	18	17.4	2.7	14	16.6	3.3	0.377	16.6	3.3	0,267
	V5	13	17.7	2.2	7	17.1	1.2	0.393	17.1	2.3	
	V6	14	16.8	3.4	8	16.6	3.2	0.570	16.1	3.6	
	V7	9	17.3	2.4	2	16.0	1.4	0.327	16.9	3.1	
FACT functional well-being	V1	19	17.3	5.3	14	16.8	4.3	0.900	17.2	4.5	
	V2	18	17.9	5.4	14	15.1	5.9	0.319	16.7	5.4	
	V3	18	16.1	6.4	13	14.9	4.5	0.679	16.0	5.4	
	V4	18	17.1	5.4	14	15.5	5.7	0.512	16.2	5.4	0,288
	V5	13	18.8	4.6	7	16.4	5.3	0.485	17.9	4.5	
	V6	14	17.1	6.1	8	19.3	3.8	0.441	17.9	5.4	
	V7	9	19.2	7.0	2	18.0	1.4	0.909	18.0	6.0	

FACT-G, Functional Assessment for Cancer Therapy; SD, standard deviation; V, visit; N, number of patients

Supplementary Table 2. Absolute scores of secondary outcomes

Questionnaire	Visit	Interventional arm (IA)			Control arm (CA)			*P-value*	Total		Effect size at V4
		N	Mean	SD	N	Mean	SD		Mean	SD	Cohen's d
FAACT score											
	V1	19	37,9	4,3	14	39,1	5,4	0,439	38,3	4,8	
	V2	18	37,9	5,2	14	39,1	6,0	0,398	38,7	5,3	
	V3	18	37,4	5,5	13	37,9	5,2	0,828	38,1	5,0	
	V4	18	35,0	6,7	14	38,6	7,1	0,099	36,9	6,4	-0,522
	V5	13	39,3	4,5	7	37,3	8,9	0,877	37,7	6,2	
	V6	14	38,3	4,7	8	40,3	4,3	0,365	38,6	4,8	
	V7	9	33,0	11,8	2	34,0	14,1	1,000	33,2	10,0	
MDASI severity											
	V1	19	1,9	1,5	14	1,9	1,5	1,000	2,0	1,4	
	V2	18	2,0	1,5	14	2,5	1,6	0,464	2,2	1,6	
	V3	18	2,5	1,4	13	2,0	1,0	0,417	2,2	1,3	
	V4	18	2,4	1,6	14	2,1	1,6	0,561	2,2	1,6	0,188
	V5	13	2,0	0,9	7	2,7	1,6	0,588	2,1	1,3	
	V6	14	2,1	1,2	8	2,4	1,7	0,868	2,2	1,5	
	V7	9	2,5	1,6	2	2,2	1,7	1,000	2,6	1,9	
MDASI interference											
	V1	19	1,9	2,1	14	2,2	1,6	0,397	2,1	2,0	
	V2	18	2,2	2,0	14	3,4	1,9	0,065	2,6	2,0	
	V3	18	2,8	2,3	13	2,9	1,6	0,798	2,8	2,0	
	V4	18	3,0	2,1	14	2,9	2,2	0,837	2,9	2,2	0,047
	V5	13	2,2	1,8	7	2,8	2,3	0,588	2,2	1,8	
	V6	14	2,3	1,7	8	2,9	1,9	0,570	2,4	1,8	
	V7	9	0,6	2,6	2	3,3	3,1	1,000	2,9	2,6	

FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MDASI, The M.D. Anderson Symptom Inventory; SD, standard deviation; V, visit; N, number of patients.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Yes, p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	Yes, p. 2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Yes, 5-7 and p10
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	Yes, p.8-9
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	Yes, p.8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		Not applicable
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	Yes, p.8
	4b	Settings and locations where the data were collected		Yes, p.8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	Yes, p.9

Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	Yes, 10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons		Not applicable
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Yes, 12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines		Not applicable
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		Yes, p.10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	Yes, p.10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	Yes, p. 10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	Yes
	10a		Who generated the random allocation sequence, who	Yes

			enrolled clusters, and who assigned clusters to interventions	
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Yes
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	Yes
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		Not done
	11b	If relevant, description of the similarity of interventions		Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Yes, p.12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		Yes, p.12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Yes, figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Yes, figure 1

Recruitment	14a	Dates defining the periods of recruitment and follow-up		Yes, p.9
	14b	Why the trial ended or was stopped		Yes
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Yes, table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		Yes
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Yes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		Not applicable
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Yes, p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	Yes

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes, p.16-17
Other information			
Registration	23	Registration number and name of trial registry	Yes, p.3
Protocol	24	Where the full trial protocol can be accessed, if available	Yes, p.8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Yes, p.19

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.