I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Eribulin **zur Behandlung des nicht-resektablen Liposarkoms** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Eine nicht-medikamentöse Behandlung kommt nicht in Betracht.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	– Hyperthermie: Richtlinien zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Stand: 19. Februar 2015), Anlage II: Methoden, die nicht als vertragsärztliche Leistungen zu Lasten der Krankenkassen erbracht werden dürfen: Hyperthermie (u. a. Ganzkörperhyperthermie, Regionale Tiefenhyperthermie, Oberflächenhyperthermie, Hyperthermie in Kombination mit Radiatio und/oder Chemotherapie) – Etoposid: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) - (Stand: 5. Mai 2015); Wirkstoffe, die im Off-Label-Use nicht verordnungsfähig sind: Etoposid bei (Weichteil-)Sarkomen des Erwachsenen in Kombination mit Carboplatin
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Eribulin L01XX41 Halaven®	Eribulin wird angewendet zur Behandlung von erwachsenen Patienten mit nicht resezierbarem Liposarkom, die wegen einer fortgeschrittenen oder metastasierten Tumorerkrankung eine Vorbehandlung mit einer Anthrazyklin enthaltenden Therapie (sofern sie geeignet war) erhalten haben.
Chemotherapien	
Dacarbazin L01AX04 Dacarbazin Lipomed	Weitere Anwendungsgebiete von Dacarbazin als Bestandteil einer Kombinationschemotherapie sind: • fortgeschrittene Weichteilsarkome im Erwachsenenalter (ausgenommen Mesotheliome und Kaposi-Sarkome) […]
Doxorubicin L01D B01 Doxorubicin Bendalis	• fortgeschrittenes Weichteilsarkom des Erwachsenenalters
Epirubicin L01DB03 Epirubicin onkovis	Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt: – fortgeschrittenes Weichteilsarkom […]
Ifosfamid L01AA06 Holoxan	Weichteilsarkome (inkl. Osteosarkom und Rhabdomyosarkom): Zur Einzel- oder Kombinationschemotherapie des Rhabdomyosarkoms oder des Osteosarkoms nach Versagen der Standardtherapien. Zur Einzel- oder Kombinationschemotherapie anderer Weichteilsarkome nach Versagen der Chirurgie und Strahlentherapie.
Trabectedin L01CX01 Yondelis®	Yondelis ist indiziert für die Behandlung von erwachsenen Patienten mit fortgeschrittenem Weichteilsarkom nach Versagen von Anthrazyklinen und Ifosfamid, bzw. von Patienten, bei denen sich die Anwendung dieser Mittel nicht eignet. Die Wirksamkeitsdaten basieren vorwiegend auf Patienten mit Liposarkom und Leiomyosarkom.
Immunstimulanzien	
Tasonermin (Tumor-Nekrose-Faktor α-1a) L03AX11 Beromun®	Beromun wird bei nichtresezierbaren Weichteilsarkomen der Extremitäten in Kombination mit Melphalan über eine isolierte Extremitäten- Perfusion (ILP – isolated limb perfusion) bei Erwachsenen unter milder Hyperthermie verabreicht – zur Vorbereitung auf eine operative Entfernung des Tumors, um eine Amputation zu vermeiden bzw. zu verzögern, – oder zur palliativen Behandlung.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2015-B-116 Eribulin

Datum: 07.10.2015

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche:

Zur Behandlung von Patienten mit inoperablem Weichteilsarkom, die im Rahmen ihrer fortgeschrittenen oder metastasierten Erkrankung bereits chemotherapeutisch vorbehandelt wurden.

Berücksichtigte Wirkstoffe/Therapien:

Siehe Übersicht „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Weichteilsarkom, Leiomyosarkom und Liposarkom “ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 10.09.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of

Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, CADTH, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.
Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, NCCN, ESMO, NCI.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.
Die Recherche ergab 504 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 100 Quellen eingeschlossen. Insgesamt ergab dies 6 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRC	Independent review committee
LMS	Leiomyosarcoma
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PEBC	Program in Evidence-Based Care
TRIP	Turn Research into Practice Database
WHO	World Health Organization

Mulder RL et al., 2012 [3]. **Cyclophosphamide versus ifosfamide for paediatric and young adult bone and soft tissue sarcoma patients**	**Fragestellung** To compare the possible effectiveness of cyclophosphamide with that of ifosfamide for paediatric and young adult patients with sarcoma.
	Methodik Population: Paediatric and young adult patients (< 30 years of age at diagnosis) with soft tissue sarcoma, osteosarcoma or Ewing's sarcoma of all stages who received either ifosfamide or cyclophosphamide. Intervention: Patients should have received either cyclophosphamide or ifosfamide as part of their treatment. However, differences in the dosage and duration of administration of cyclophosphamide and ifosfamide were allowed. Chemotherapy, other than either cyclophosphamide or ifosfamide, should have been the same in both treatment groups. Endpunkt Primary outcomes: 1. Response rate (defined as the number of patients with a complete or partial remission). 2. Event-free survival (defined as the time to recurrence or progression of disease). 3. Overall patient survival (defined as the time to death from any cause) secondary outcomes: 1. Toxicities including late effects of treatment, in particular gonadotoxicity, nephrotoxicity, urotoxicity, neurotoxicity and cardiotoxicity. 2. Quality of life. Suchzeitraum (Aktualität der Recherche): the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed (from1966 to March 2012) and EMBASE/Ovid (from 1980 to March 2012). Anzahl eingeschlossene Studien/Patienten (Gesamt): 0 (n=0)
	Ergebnisdarstellung *Keine Studien auffindbar*
	Anmerkungen/Fazit der Autoren No RCTs or CCTs comparing the effectiveness of cyclophosphamide and ifosfamide in the treatment of bone and soft tissue sarcoma in children and young adults were identified. Based on the currently available evidence we are not able to give recommendations for clinical practice. More high quality research is needed.

Systematische Reviews

Sharma S et al., 2013 [6]. **Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review**	**Fragestellung** Current guidelines recommend anthracycline-based chemotherapy primarily with doxorubicin either as monotherapy or in combination with ifosfamide as the first-line treatment for most advanced STS subtypes. Therapeutic options after failure of doxorubicin and/or ifosfamide are limited. This study aimed to comprehensively review available data on the activity and safety of interventions in second- or later-line treatment of advanced STS.
	Methodik Population: patients had received prior anthracycline and/or ifosfamide therapy since these are generally considered to be the standard of care for the first-line treatment of advanced STS Intervention: carboplatin, cyclophosphamide, dacarbazine, docetaxel, doxorubicin, epirubicin, etoposide, gemcitabine, ifosfamide, liposomal doxorubicin, paclitaxel, pazopanib, trabectedin, vincristine, cisplatin, vinblastine, methotrexate, tamoxifen, sunitinib, sorafenib, deforolimus, temsirolimus, everolimus, gefitinib, erlotinib, cetuximab, or brostallicin alone or in combination. Komparator: placebo, best supportive care, or any of the included interventions Endpunkte: • overall survival (OS), • progression-free survival (PFS), • overall response rate (ORR), • complete response (CR), • partial response (PR), • stable disease (SD), • progressive disease (PD), • time to progression (TTP), • duration of response (DOR), • time to response (TTR), • EORTC Quality of Life-Questionnaire C30 score, • EQ-5D score, • adverse events, and • withdrawals Suchzeitraum (Aktualität der Recherche): Embase®, MEDLINE®, MEDLINE® In-Process, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) were searched from 1980 to 01 March 2012, additional search for conference abstracts and ongoing trials

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 RCTs, 94 non-randomized studies Qualitätsbewertung der Studien: Quality assessment of RCTs was performed using a comprehensive critical appraisal tool based on the National Institute for Health and Clinical Excellence's and Cochrane's critical appraisal tool Ergebnissynthese: There was considerable heterogeneity across studies in terms of interventions, comparisons, patient population, and study designs. Therefore meta analysis, indirect, and mixed treatment comparison of the included interventions were not appropriate. Qualitative summary of the results.
	Ergebnisdarstellung • All included RCTs were Phase II trials, except for the PALETTE study, which was the only Phase III RCT (siehe Anhang I) • leiomyoscaroma was the most commonly enrolled subtype of STS followed by liposarcoma and undifferentiated pleomorphic sarcoma. • None of the RCTs included in the review were identified as being at a high risk of bias. *Phase III Trial: PALETTE trial: pazopanib vs. placebo* • significantly prolonged primary endpoint of PFS (per independent review) for pazopanib compared with placebo (Hazard Ratio (HR): 0.35 [95% CI: 0.26 - 0.48]; p<0.001) • effect consistent across all three histological sub-types: (leiomyosarcoma [p<0.001], synovial sarcoma [p=0.005], and other STS sub-types [p<0.001]). • No difference in OS, but data on potentially biased due to differing subsequent therapy • QoL data: EORTC QLQ-C30: no clinically meaningful or statistically significant differences between groups • Safety: grade 3/4 AEs >5% in pazopanib group: fatigue (14%), lymphopenia (10%) tumour pain (8%), increased alanine transaminase (ALT) (10%), increased aspartate aminotransferase (AST) (8%), hypertension (7%), dyspnoea (6%), anaemia (6%), decreased appetite (6%), and diarrhoea (5%) *Phase II trials:* *Trabectedin q3w 24-h dosing schedule vs. qw 3-hour:* • Median TTP favoured the trabectedin q3w 24-hour dosing schedule (N=136) over the qw 3-hour dosing schedule when assessment was made by investigator (4.2 months vs. 2.5 months; HR: 0.668 [95% CI: 0.506 – 0.883]; p=0.0042) and IRC (3.7 months vs. 2.3 months; HR: 0.734 [95% CI: 0.554 - 0.974];

	p=0.03) • median PFS was significantly longer with the q3w 24-hour schedule than the qw 3-hour schedule (p=0.0418), • no significant differences between the two dosing schedules were observed in median OS • The PFS rate, 1-year OS rate, and ORR also favoured the q3w 24-hour dosing schedule over the qw 3-hour dosing schedule • Safety: Grade 3/4 nausea, vomiting, and AST increase were also experienced by ≥5% of patients treated with trabectedin 24-hour schedule Ergebnisdarstellung in tabellarischer Form siehe nächste Seite:

Table 2 Summary of various efficacy/activity outcomes observed across randomised controlled trials

Intervention	Study	N	Progression free survival			Overall survival		Response rate				Progressive disease
			PFS rate, n (%)		PFS in months	1 year OS	OS in months	ORR	CR	PR	SD	PD
			3-month	6-month	median (95% CI)	n (%)	median (95% CI)	n (%)	n (%)	n (%)	n (%)	n (%)
Pazopanib	PALETTE study 2011/2	246	-	-	4.6†	-	12.6	11 (4.5) †	0 (0.0) †	11 (4.5) †	134 (54.5)†	66 (26.8) †
Placebo	PALETTE study 2011	123	-	-	1.6†	-	10.7	0 (0.0) †	0 (0.0) †	0 (0.0) †	33 (26.8) †	76 (61.8) †
Trabectedin 1.5 mg/m2 q3w	Demetri 2009	136	70 (51.5)	48 (35.5)	3.3† (2.1 - 4.6)	82 (60.0)	13.9 (12.5 - 18.6)	8 (5.6)†	-	-	-	-
Trabectedin 0.58 mg/m2 qw	Demetri 2009	134	60 (44.7)	37 (27.5)	2.3† (2.0 - 3.4)	67 (50.0)	11.8 (9.9 - 14.9)	2 (1.6)†	-	-	-	-
Dacarbazine	GEIS study	54	19 (35.2); p=0.001	-	2.0#	-	8.2§	2 (3.7)‡, p=0.16	-	2 (4.0)*#	10 (19.0)*#	-
Gemcitabine + Dacarbazine	GEIS study	59	32 (54.2); p=0.001	-	4.2#	-	16.8§	7 (11.9)‡, p=0.16	-	5 (9.0)* #	22 (38.0)*#	-
Sorafenib	Pacey 2011	2	-	-	-	-	-	-	-	-	-	0 (0.0) #
Placebo	Pacey 2011	2	-	-	-	-	-	-	-	0 (0.0) #	2 (100) #	0 (0.0) #
Gemcitabine	Pautier 2009	-	-	-	-	-	-	-	-	-	-	-
Gemcitabine + Docetaxel	Pautier 2009	-	-	-	-	-	-	-	-	-	-	-
Ifosfamide 5 g/m^2/day	van Oosterom 2002	27	-	-	-	-	-	-	-	-	-	-
Ifosfamide 3 g/m^2/day	van Oosterom 2002	31	-	-	-	-	-	-	-	-	-	-

CI: Confidence Interval; CR: Complete Response; INV: Investigator; IRC: Independent Review Committee; N: Number of evaluable Patients; n: Number with Outcome; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; PR: Partial Response; q3w: Every Three Weeks; qw: Every Week; SD: Stable Disease; *p=0.01; †Assessments were made by the independent review committee; ‡Assessments were made by the investigator; #Unclear if assessed by investigator or the Independent Review Committee; §Kaplan-Meier estimates reported; -Represents data not reported.

	Anmerkungen/Fazit der Autoren Across the RCTs, pazopanib over placebo, […] and trabectedin 3-weekly over weekly regimen clearly demonstrated a PFS advantage in the second- and later-line treatment of advanced STS. **Hinweise durch FB Med)** • Population nicht genau deckungsgleich mit der Patientenpopulation laut Beratungsanforderung: Einschränkung auf inoperables STS fehlt • Review betrachtet auch Vergleich zu Gemcitabine, welches im AWG in Deutschland nicht zugelassen ist → Vergleich wurde nicht dargestellt • Es wurden nur Ergebnisse aus den RCTs dargestellt.

Leitlinien

Gupta A. et al., 2013 [2]. **Cancer Care Ontario** Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma : a clinical practice guideline	**Fragestellung** the current guideline focuses on the role of systemic chemotherapy in uterine lms (leiomyosarcoma) exclusively: **Methodik** Grundlage der Leitlinie: This guideline was developed by cco's pebc, the Sarcoma disease site group (DSG) and the Gynecologic Cancer dsg • Literature Search: Suchzeitraum: medline and embase (from January 2004 to June 2011), the Cochrane Library, main guideline Web sites, and the American Society of Clinical Oncology and Connective Tissue Oncology Society annual meeting abstracts from 2005 to 2010 • 4.2 DSG Consensus Process: The draft guideline, based on the systematic review, was circulated for review and discussion and was approved by the Sarcoma dsg and the Gynecologic Cancer dsg in February 2012. • Internal review: Before the draft report was sent for external review, it was reviewed and approved by the pebc Report Approval Panel, which consists of 3 members: 2 oncologists with expertise in clinical and methodology issues, and a methodologist. • External review: The pebc external review process is two-pronged and includes: a targeted peer review (3 reviewers) that is intended to obtain direct feedback on the draft report from a small number of specified content experts (via email and telephone conference), and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners (65 experts contacted, 19 responded) via a brief online survey LoE: k.A. (wird über die Formulierung ausgedrückt) GoR: k. A. (wird über die Formulierung ausgedrückt) Sonstige methodische Hinweise *„Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt."* *Keine näheren Angaben zum LoE und GoR.*

	Freitext/Empfehlungen • Based on current available evidence from the medical literature [four single-arm phase ii studies, one arm of a randomized controlled trial (rct), and one abstract], **doxorubicin alone, gemcitabine alone, or gemcitabine plus docetaxel <u>may be</u> treatment options for first- and second line therapy** in women with inoperable, locally advanced, recurrent, or metastatic uterine lms. • Hematologic toxicity is common and should be monitored, and granulocyte colony–stimulating factor should be considered when gemcitabine plus docetaxel is used. • Other toxicities, such as neurotoxicity, pulmonary toxicity, and cardiovascular toxicity should be monitored. Ausschnitt aus Evidenztabelle: TABLE III Clinical outcomes for each chemotherapy regimen in advanced uterine leiomyosarcoma *Regimen* | *1st- or 2nd-line therapy* | *Median OS (months)* | *Median PFS (months)* | *Response rate, CR+PR [% (95% CI)]* | *Grades 3–4 toxicity (%)* Doxorubicin[5,a] | 1st and 2nd | 12.1 | NR | 25 (9–41) | Leukopenia: 16 Thrombocytopenia: 4 Questionable cardiac toxicity: 3 (no detail) [a] Adverse effects were assessed using study-defined criteria. [b] Standard Gynecologic Oncology Group response criteria were used for toxicity grading. [c] The U.S. National Cancer Institute Common Toxicity Criteria were used for toxicity grading. [d] Duffaud F, Pautier P, Nguyen BB, *et al.* A pooled analysis of the final results of the 2 randomized phase II studies comparing gemcitabine vs. gemcitabine+docetaxel in patients with metastatic/relapsed leiomyosarcoma [abstract 898573]. Presented at the Connective Tissue Oncology Society 16th Annual Meeting; Paris, France; November 11–13, 2010. OS = overall survival; PFS = progression-free survival; CR = complete response; PR = partial response; CI = confidence interval; NR = not reported. Dosis: Doxorubicin: 60–80 mg/m2 intravenously (IV) every 3 weeks Qualität der Evidenz: No trials of high methodologic quality have documented the outcomes of patients with advanced or metastatic uterine lms when no prior systemic therapy was administered. Doxorubicin has been considered the standard of care for more than 30 years. Evidenzbasis: 5. Omura GA, Major FJ, Blessing JA, *et al.* A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer* 1983;52:626–32. Funding: The pebc is supported by the Ontario Ministry of Health and Long-Term Care through cco. All work produced by the pebc is editorially independent from its funding source.
ESMO 2014 [1]. The	**Methodik** Grundlage der Leitlinie: Konsensfindung:

ESMO/European Sarcoma Network Working Group Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-upl	These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organised by ESMO in Milan, Italy, in December 2013 and refined by July 2014. This involved experts from the community of the European sarcoma research groups and ESMO faculty.[Name are listed in the guideline] The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The panel worked on the text of ESMO Guidelines of previous years, whose authorship should also be credited. LoE und GoR: **Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)[a]** Levels of evidence I — Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity II — Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity III — Prospective cohort studies IV — Retrospective cohort studies or case–control studies V — Studies without control group, case reports and experts opinions Grades of recommendation A — Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B — Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C — Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional D — Moderate evidence against efficacy or for adverse outcome, generally not recommended E — Strong evidence against efficacy or for adverse outcome, never recommended [a]By permission of the Infectious Diseases Society of America [64]. Sonstige methodische Hinweise *„Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.“* • *Fehlende Darstellung der Evidenzrecherche, - auswahl, -*

	bewertung • *Empfehlungen sind nicht mit Literaturquellen belegt*
	Empfehlungen: After failure of anthracycline-based chemotherapy, or the impossibility to use it, the following criteria may apply, although high-level evidence is lacking: • Patients who have already received chemotherapy may be treated with **ifosfamide**, if they did not progress on it previously. High-dose ifosfamide (around 14 g/m2) may be an option also for patients who have already received standard dose ifosfamide [25, 26] [IV, C]. • **Trabectedin** is a second-line option [II, B] and is approved for advanced previously treated STS in the EU. It has proved effective in leiomyosarcoma and liposarcoma [27]. In myxoid liposarcoma, a high antitumour activity was described. A peculiar pattern of tumour response has been reported, with an early phase of tissue changes preceding tumour shrinkage [28]. Clinical benefit with trabectedin was also obtained in other histological types. • **Dacarbazine** has some activity as a second-line therapy (mostly in leiomyosarcoma and solitary fibrous tumour). The combination of dacarbazine and gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomised trial [30] [II, B]. • A randomised trial showed a benefit in PFS averaging 3months for **pazopanib** given up to progression to advanced, previously treated, STS patients (excluding liposarcomas) [31]. Thus, it is an option in non-adipogenic STS [I, B]. Evidenzbasis:

25. Le Cesne A, Antoine E, Spielmann M et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol 1995; 13: 1600–1608.
26. Martin-Liberal J, Alam S, Constantinidou A et al. Clinical activity and tolerability of a 14-day infusional Ifosfamide schedule in soft-tissue sarcoma. Sarcoma 2013; 2013: 868973.
27. Demetri GD, Chawla SP, von Mehren M et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009; 27: 4188–4196.
28. Grosso F, Jones RL, Demetri GD et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. Lancet Oncol 2007; 8: 595–602.
29. Maki RG, Wathen JK, Patel SR et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. J Clin Oncol 2007; 25: 2755–2763.
30. García-Del-Muro X, López-Pousa A, Maurel J et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol 2011; 29: 2528–2533.
31. van der Graaf WT, Blay JY, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379: 1879–1886.

Best supportive care alone is an alternative for pre-treated patients with advanced STS, especially if further-line therapies have already been used in the patient

NCCN 2015 [4].

National Comprehensive Cancer Network

Soft Tissue Sarcoma

Methodik: keine Angaben zur Methodik

LoE

GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Sonstige methodische Hinweise

„Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund fehlender höherwertiger Evidenz ergänzend dargestellt.“

	• *Fehlende Darstellung der Evidenzrecherche, - auswahl, -bewertung* • *Konsentierung nicht erwähnt/beschrieben* • *Empfehlungen unzureichend mit Literaturquellen belegt*
	Soft tissue sarcoma **Advanced, Unresectable, or Metastatic Disease** Chemotherapy with single agents (dacarbazine, doxorubicin, epirubicin, or ifosfamide) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) have been widely used for patients with advanced, unresectable, or metastatic disease.[81-92] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials. **Gastrointestinal stroma tumor:** For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if the majority of disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesion(s) is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable.[324,329,333] However, incomplete resections are frequent with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection, RFA, chemoembolization, or palliative RT (for rare patients with bone metastases) as an option.[247] Evidenzbasis: 81. Mouridsen HT, Bastholt L, Somers R, et al. Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol 1987;23:1477-1483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3479329. 82. Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 1989;7:1208-1216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2504890. 83. Antman KH, Elias A. Dana-Farber Cancer Institute studies in advanced sarcoma. Semin Oncol. 1990;1:7-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2106162 84. Buesa JM, Mouridsen HT, van Oosterom AT, et al. High-dose DTIC in advanced soft-tissue sarcomas in the adult. A phase II study of the E.O.R.T.C. Soft Tissue and Bone Sarcoma Group. Ann Oncol 1991;2:307-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1868027.

85. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993;11:1276-1285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8315425.

86. Bramwell VHC, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane Database Syst Rev 2003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12917960.

87. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993;11:1269-1275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8315424.

88. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. J Natl Cancer Inst 1991;83:926-932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2067035.

89. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995;13:1537-1545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7602342.

90. Reichardt P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. J Clin Oncol 1998;16:1438-1443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9552049.

91. Palumbo R, Neumaier C, Cosso M, et al. Dose-intensive first-line chemotherapy with epirubicin and continuous infusion ifosfamide in adult patients with advanced soft tissue sarcomas: a phase II study. Eur J Cancer 1999;35:66-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10211090.

92. Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 2007;25:3144-3150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17634494.

324. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325-2331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16710031.

333. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19898902.

329. Sym SJ, Ryu M-H, Lee J-L, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452195.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

pan-Canadian Oncology Drug Review 2012 (pCODR) [5]. Pazopanib (Votrient) for Soft Tissue Sarcoma I	Objective: Evaluation of the efficacy and safety of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior systemic therapies or who are unsuited for such therapies. Patients diagnosed with gastrointestinal stromal tumour (GIST) or adipocytic sarcoma were excluded. Methods: Systematic literature search Results and Conclusion: an international, multicentre, double-blind, randomized control trial (RCT) (the PALETTE study, n=123) was found. The pCODR Sarcoma Clinical guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic non-adipocytic STS, based on data from one high quality randomized trial (PALETTE) that demonstrated a clinically and statistically significant 3-month improvement in median PFS for patients receiving pazopanib compared with those receiving placebo. Pazopanib was well tolerated. Fatigue, diarrhea, nausea and vomiting were the most common toxicities, but were rarely severe. Over the initial 12-week treatment period, global QoL did not differ between the arms. The Clinical Guidance Panel also considered that from a clinical perspective: • Although there was only a small 1.8 month non-significant improvement in OS, this is consistent with data from several randomized trials evaluating standard palliative chemotherapy for advanced STS. • Patients with adipocytic sarcomas and GIST were excluded from the PALETTE trial. There are insufficient data to recommend its use in these subtypes of sarcoma. • In PALETTE, pazopanib was evaluated as a second line (or greater) systemic therapy, and 99% of patients had received previous chemotherapy. • In studies of palliative chemotherapy for advanced STS, patients with high PS usually have improved outcomes. PS 0 or 1 was an eligibility requirement of the PALETTE study, and multivariate analysis across both groups showed that PS 0 (vs 1) was associated with improved PFS (HR 0.73, p=0.045). • Important patient concerns with currently available chemotherapy options are addressed by the convenience of oral administration, and the relatively mild toxicities associated with pazopanib therapy.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 08.09.2015**

#	Suchfrage
1	MeSH descriptor: [Leiomyosarcoma] explode all trees
2	MeSH descriptor: [Liposarcoma] explode all trees
3	leiomyosarcoma* or liposarcoma*:ti,ab,kw
4	(Soft tissue sarcoma) or softtissue sacroma:ti,ab,kw
5	#1 or #2 or #3 or #4
6	#5 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 09.09.2015

#	Suchfrage
1	(Leiomyosarcoma[MeSH Terms]) OR Liposarcoma[MeSH Terms]
2	(leiomyosarcoma*[Title/Abstract]) OR liposarcoma*[Title/Abstract]
3	(soft tissue sarcoma*[Title/Abstract]) OR Softtissue sarcoma*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
6	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	#5 OR #6
8	(#7) AND ("2010/09/01"[PDAT] : "2015/09/09"[PDAT])

Leitlinien in Medline (PubMed) am 09.09.2015

#	Suchfrage
1	(Leiomyosarcoma[MeSH Terms]) OR Liposarcoma[MeSH Terms]
2	(leiomyosarcoma*[Title/Abstract]) OR liposarcoma*[Title/Abstract]
3	(soft tissue sarcoma*[Title/Abstract]) OR Softtissue sarcoma*[Title/Abstract]
5	sarcomas/ DT
6	#1 OR #2 OR #3 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
8	(#7) AND ("2010/09/01"[PDAT] : "2015/09/09"[PDAT])

Literatur:

1. **European Sarcoma Network Working Group (ESMO)**. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 ((Suppl 3)): iii102-12.

2. **Gupta AA, Yao X, Verma S, Mackay H, Hopkins L**. Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a clinical practice guideline. Curr Oncol 2013; 20 (5): e448-e454.

3. **Mulder RL, Paulides M, Langer T, Kremer Leontien CM, van Dalen EC**. Cyclophosphamide versus ifosfamide for paediatric and young adult bone and soft tissue sarcoma patients. Cochrane Database of Systematic Reviews 2012; (12): CD006300.

4. **NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**. Soft tissue sarcoma, Vers. 1.2015. National Comprehensive Cancer Network 2015; http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf, Zugriff am 11.09.2015.

5. **pan-Canadian Oncology Drug Review (pCODR)**. Pazopanib (Votrient) for Soft Tissue Sarcoma. Final Clinical Guidance Report. Toronto (CAN): Canadian Agency for Drugs and Technologies in Health 2012; https://www.cadth.ca/sites/default/files/pcodr/pcodr-votrientsts-fn-cgr.pdf, Zugriff am 11.09.2015.

6. **Sharma S, Takyar S, Manson SC, Powell S, Penel N**. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review. BMC Cancer 2013; 13 385.

Anhang:

Anhang I: Zusammenfassung der relevanten RCTs in Sharma S et al. 2013 [6]

Table 1 Summary of relevant randomised controlled trials included in the review

Interventions	Study	Study design	N*	Age median (range)	Males (%)	Median duration of follow-up (weeks)	Prior therapy for advanced disease	Performance status, n (%)	STS subtypes, (%)
Pazopanib 800 mg per day orally	PALETTE study 2011 [18,19,30]	R, DB, PC, MC-I, Phase III	246	56.0 (20.0-83.0)	40.0%	49.5 weeks	Anthracycline: 98.8%; ifosfamide: 66.7%	PS 0: 118 (48.0); PS 1: 128 (52.0)	Leiomyosarcoma: 44.3%; Synovial sarcoma: 10.2%; Others: 45.5%
Placebo	PALETTE study 2011 [18,19,30]		123	51.0 (18.0-78.0)	44.0%	45.3 weeks	Anthracycline: 98.4%; ifosfamide: 75.6%	PS 0: 60 (48.8); PS 1: 67 (51.2)	Leiomyosarcoma: 39.8%; Synovial sarcoma: 10.6%; Others: 49.6%
Trabectedin 1.5 mg/m2 24-hour infusion q3w	Demetri 2009 [22-26]~	R, OL, DR, MC-I, Phase II	136	53 (20–80)	32.4%	177.67 weeks	Anthracycline: 100%; anthracycline and ifosfamide: 99.3%	PS 0: 70 (51.5); PS 1: 66 (48.5)	Leiomyosarcoma: 61.5%; Liposarcoma: 25.6%; Others: 12.8%
Trabectedin 0.58 mg/m2 3-hour infusion qw	Demetri 2009 [22-26]~		134	54 (23–77)	41.8%			PS 0: 67 (50.0); PS 1: 67 (50.0)	Leiomyosarcoma: 55.5%; Liposarcoma: 37.8%; Others: 6.7%
Gemcitabine 1800 mg/m2 as a fixed dose infusion rate (10 mg/m2/minutes) + dacarbazine 500 mg/m2 q2w	GEIS study [20,21]~	R, BU, AC, MC, Phase II	59	49 (18–78)	53.0%	62.83 weeks	Out of total eligible population of 109 patients 107 patients had received anthracycline and two patients had received ifosfamide	PS 0:22 (38.6); PS 1:30 (52.6); PS 2:5 (8.8)	Leiomyosarcoma: 28.1%; Liposarcoma/adipocytic sarcoma: 17.5%; Undifferentiated pleomorphic: 19.3%; Miscellaneous sarcoma: 24.6%; Synovial sarcoma: 10.5%
Dacarbazine 1200 mg/m2 q3w	GEIS study [20,21]~		54	51 (25–73)	54.0%	60.67 weeks		PS 0: 17 (32.7); PS 1: 31 (51.6); PS 2: 4 (7.7)	Leiomyosarcoma: 30.8%; Liposarcoma/adipocytic sarcoma: 17.3%; Undifferentiated pleomorphic: 15.4%; Miscellaneous sarcoma: 26.9%; Synovial sarcoma: 9.6%
Gemcitabine 900 mg/m2 over 90 minutes, D1+D8 + docetaxel 100 mg/m2 over 60 min, D8 q21 days	Pautier 2009 [27,31]~	R, BU, AC, MC, Phase II	84**	-	-	Unclear	Anthracycline: 100%	-	Leiomyosarcoma: 100%
Gemcitabine 1000 mg/m2 over 100 minutes, d1+d8+d15 q28 days	Pautier 2009 [27,31]~			-	-		Anthracycline: 100%	-	Leiomyosarcoma: 100%
Sorafenib 400 mg twice daily orally	Pacey 2011 [28]	R, DB, PC, MC-I, Phase II	2	-	-	Unclear	Anthracycline and/or ifosfamide: 100%	-	Fibrosarcoma: 0.0%
Placebo	Pacey 2011 [28]		2	67 (62–72)	0			PS 0: 2 (100) PS 1: 0 (0.0)	Leiomyosarcoma: 50.0%; Fibrosarcoma: 50.0%
Ifosfamide 5 g/m2/1 day given as 24-hour infusion; all cycles were repeated q3w	van Oosterom 2002 [29]	R, BU, DR, MC-I, Phase II	27	-	-	Unclear	Anthracycline: 100%	-	-
Ifosfamide 3 g/m2/day given over 4 hour on 3 consecutive days; all cycles were repeated q3w	van Oosterom 2002 [29]		31	-	-		Anthracycline: 100%	-	-

AC: Active-controlled; BU: Blinding Unclear; DB: Double-blind; DR: Dose Ranging; ECOG: Eastern Cooperative Oncology Group; q3w: Every Three Weeks; q2w: Every Two weeks; qw: Every week; MFH: Malignant Fibrous Histiocytoma; min: Minutes; MC: Multicentre; MC-I: Multicentre International; OL: Open Label; PS: Performance Status; STS: Soft Tissue Sarcoma; *N represents number of patients randomised except for Pacey 2011 study and van Oosterom 2002 where N represents the patient population of interest with respect to prior treatment for advanced disease; **Represents total number of patients randomised in the study (number of patients randomised to each arm not reported); -Represents data not reported; ¶Represents data for the complete study population; ~Represents secondary reference.