Inhaltsverzeichnis

1. Systemtherapie - Neoadjuvante Chemotherapie

1.1. Evidenztabelle Systemtherapie - Neoadjuvante Chemotherapie

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (all or the five most frequent ae)	Study type, level of evidence and risk of bias
Gortzak E, Azzarelli A, Buesa J, Bramwell VH, van Coevorden F, van Geel AN, et al. A randomized phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. European journal of cancer. 2001;37(9):1096-103.	**Region/Setting** NR **Inclusion criteria** - age 15–75 years - potentially radically resectable histologically proven soft-tissue sarcoma located in the limbs, head and neck, trunk or pelvis - good World Health Organization (WHO) performance score (0–2) - appropriate bone marrow White Blood Cell (WBC)>4.0x10^9/l - platelet count >120x10^9/l), - cardiac, renal and hepatic function - no evidence of regional or distant metastases as shown by computed tomography (CT) scans - meet the criteria for a 'high risk' tumor; defined as tumors 58 cm of any grade (independent of mitotic count), or grade II/III (three or more mitoses per 10 high power field; HPF), tumors <8 cm, or grade II/III locally recurrent tumors or grade II/III tumors with inadequate surgery performed in the previous 6 weeks and therefore requiring further surgery. **Exclusion criteria** The following histological types were excluded: (extra-osseous) Ewing's sarcoma, osteo and chondrosarcomas, Kaposi's sarcoma, embryonal rhabdomyosarcoma, malignant mesothelioma and radiation-associated sarcomas. **Patient characteristics** Gender: male/female ratio 1.23/2.35 Age [y] Median (range) 56(15–69)/49(19–74)	**Intervention** The neo-adjuvant regimen consisted of three cycles of doxorubicin at a dose of 50 mg/m2 by intravenous (i.v.) bolus on day 1, immediately followed by ifosfamide given as a 24 h infusion at a dose of 5 g/m2 /24 h. Ifosfamide was combined with mesna 600 mg/m2 i.v. bolus, given at the start of the infusion, followed by 5 g/m2/24 h infusion for a total of 36 h. Chemotherapy cycles were to be repeated every 21 days. In cases of progression during the neo-adjuvant chemotherapy, before the completion of three cycles, chemotherapy was terminated and surgery was performed. **Control** No preoperative chemotherapy **Randomized patients** 75/75	Grade3; Grade4; toxicity; severe toxicity Nausea/vomiting: n=18; n=1; 95%; 29% Leucopenia n=5; n= 0; 32%; 8% Other n=1; n=0; 21%; 2% Cardiotoxicity n=1; n=1; 2%; 0% Infection n=0; n=1; 6%; 2%	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Performance status n(%) status 0: 51(76)/52(78) status 1: 13(19)/13(19) status 2: 3(4)/2(3) Distribution according to histopathology n(%) malignant fibrous histocytoma 20(30)/19(28) Fibrosarcoma 1(1)/2(3) Liposarcoma 11(16)/9(13) Leiomyosarcoma 12(18)/10(15) Rhabdomyosarcoma 2(3)/3(4) Angiosarcoma 0/1(1) Synovial sarcoma 11(16)/9(13) Neurogenic sarcoma 3(4)/8(12)			
Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Pousa AL, Grignani G, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomized, controlled, phase 3, multicentre trial. Lancet Oncol 2017; 18(6):812-822.	**Region/Setting** Patients were enrolled in 32 hospitals in Italy, Spain, France, and Poland. **Inclusion criteria** - age ≥18 years - histologically proven and centrally reviewed (before randomization) diagnosis of localized soft-tissue sarcoma (belonging to one of the following subtypes: high-grade myxoid liposarcoma [cellular component >5%], leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, or undifferentiated pleomorphic sarcoma), originating in an extremity or trunk wall, with a high malignancy grade (grade 3 according to Federation Nationale des Centers de Lutte Contre le Cancer grading system16 or grade 2 if >50% necrosis was present at baseline radiological assessment), deeply located according to the investing fascia, and 5 cm or longer in largest diameter at baseline radiological assessment; had an Eastern Cooperative Oncology Group performance status of less than 1; - baseline bone marrow (white blood cell count >3500 cells per µL, neutrophil >1500 cells per µL, platelets >150 000 platelets per µL, and hemoglobin >110 g/L) - renal function: creatinine <1·3 mg/dL - hepatic function: total bilirubin <1·5 mg/dL and transaminase less than twice normal value - cardiac function: left ventricular ejection fraction >50% **Exclusion criteria** - distant metastases - other malignancies within the past 5 years, with the exception of carcinoma in situ of cervix and basocellular skin cancers treated with eradicating intent - previous chemotherapy or radiotherapy - serious psychiatric disease - medical disease limiting survival to less than 2 years - cardiovascular diseases resulting in a New York Heart Association Func-	**Intervention** histotype-tailored chemotherapy *high-grade myxoid liposarcoma* trabectedin 1·3 mg/m² via 24-h continuous infusion, repeated every 21 days *leiomyosarcoma* gemcitabine 1800 mg/m² on day 1 intravenously over 180 min plus dacarbazine 500 mg/m² on day 1 intravenously over 20 min, repeated every 14 days *synovial sarcoma* high dose ifosfamide 14 g/m², given over 14 days via an external infusion pump, every 28 days *malignant peripheral nerve sheath tumor* intravenous etoposide 150 mg/m² per day (days 1, 2, and 3) plus intravenous ifosfamide 3 g/m² per day (days 1, 2, and 3), repeated every 21 days; *undifferentiated pleomorphic sarcoma*	**Grade 3:4** **IG [%]** Anemia 1; 0 Leucopenia 6; 8 Neutropenia 7; 15 Thrombocytopenia 2; 1 Febrile neutropenia 4; 1 **CG [%]** Anemia 17;2 Leucopenia 10; 42 Neutropenia 9; 51 Thrombocytopenia 10; 7 Febrile neutropenia 14; 11	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	tional Status of 2 or higher - uncontrolled bacterial, viral, or fungal infection **Patient characteristics** <u>Gender n(%)</u> NR <u>Age [y] Median(range)</u> 49.47(13.45)/48.33(12.70) <u>Tumor size [mm] mean(SD)</u> 111.30 (71-36)/112.99 (52-68) <u>Histology n(%)</u> High-grade myxoid liposarcoma 28(20)/36(25) Synovial sarcoma 34(24)/36(25) Malignant peripheral nerve sheath tumor 12(8)/15(10) Leiomyosarcoma 16(11)/12(8) Undifferentiated pleomorphic sarcoma 52(37)/45(31) <u>Tumor site n(%)</u> Thoracic wall 3(3)/4(3) Abdominal wall 2(2)/ 2 (2) Paravertebral 0/4(3) Shoulder girdle 7(6)/13(10) Upper limb 8(7)/ 8(6) Pelvic girdle 18(15)/10(8) Lower limb 81(68)/83(67)	gemcitabine 900 mg/m² on days 1 and 8 intravenously over 90 min plus docetaxel 75 mg/m² on day 8 intravenously over 1 h, repeated every 21 days **Control** epirubicin 60 mg/m² per day (short infusion, days 1 and 2) plus ifosfamide 3 g/m² per day (days 1, 2, and 3), repeated every 21 days **Randomized patients** 142/144		

+ low risk of bias; - high risk of bias; ? unclear risk of bias; IG: intervention group; CG: control group; NR: not reported; WHO: World Health Organization; WBC: White Blood Cell; CT: computed tomography; HPF: high power field; ae: adverse event; RCT: randomized controlled trial

1.2. SoF Tables Systemtherapie - Neoadjuvante Chemotherapie

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Summary of findings:

Neoadjuvant doxorubicin and ifosfamide compared to surgery alone for STS

Patient or population: STS
Intervention: neoadjuvant doxorubicin and ifosfamide
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with neoadjuvant doxorubicin and ifosfamide**				
Overall survial (median follow-up: 7.3 years)	418 per 1.000	**330 per 1.000** (209 to 510)	**RR 0.79** (0.50 to 1.22)	134 (1 RCT)	⨁⨁◯◯ LOW	
Disease free survival (median follow-up: 7.3 years)	522 per 1.000	**449 per 1.000** (313 to 637)	**RR 0.86** (0.60 to 1.22)	134 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Gortzak 2001

Summary of findings:

Histotype-tailored chemotherapy compared to Epirubicin + Ifosfamide for STS

Patient or population: STS
Intervention: Histotype-tailored chemotherapy
Comparison: Epirubicin + Ifosfamide

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Epirubicin+Ifosfmide	**Risk with Histotype-tailored chemotherapy**				
Overall survival (median follow-up: 12.3 months)	42 per 1.000	**108 per 1.000** (46 to 256)	**HR 2.687** (1.104 to 6.940)	286 (1 RCT)	⊕⊕⊕◯ MODERATE	
Disease free survival (median follow-up: 12.3 months)	174 per 1.000	**317 per 1.000** (208 to 463)	**HR 2.00** (1.22 to 3.26)	286 (1 RCT)	⊕⊕⊕◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Gronchi 2017

2. Systemtherapie - Adjuvante Chemotherapie

2.1. Evidenztabelle Systemtherapie - Adjuvante Chemotherapie

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (all or five most frequent, chemotherapy group only)	Study type, level of evidence and risk of bias
Alvegard TA, Sigurdsson H, Mouridsen H, Solheim O, Unsgaard B, Ringborg U, et al. Adjuvant chemotherapy with doxorubicin in high-grade soft tissue sarcoma: a randomized trial of the Scandinavian Sarcoma Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1989;7(10):1504-13.	**Region/Setting** This study was conducted by the Scandinavian Sarcoma Group (SSG) between January 1981 and February 1986. **Inclusion criteria** - age 15 - 70 years - resectable, localized, histologically verified high-grade soft tissue sarcoma - no evidence of metastatic disease at the time of presentation - careful physical examination, chest x-ray, and laboratory tests, including blood counts and liver function tests, were performed in all randomized patients - no history of any other type of malignancy except basal cell carcinoma of the skin or history of previous chemotherapy or radiotherapy **Exclusion criteria** NR **Patient characteristics** <u>Gender n(%)</u> Male 43(42)/60(58)/10(56)/9(56) Female 60(58)/43(42)/8(44)/7(44) <u>Age [y] Median(range)</u> 56(16-71)/55(15-73)/48(15-78)/58(25-78) <u>Tumor diagnosis (external pathology review) n(%)</u> Malignant fibrous histiocytoma 40(39)/38(37)/3(17)/5(31) Myofibrosarcoma 2(2)/1(1)/0/0 Synovial sarcoma 12(12)/18(17)/2(11)/2(13) Liposarcoma 12(12)/10(10)/2(11)/1(6) Leiomyosarcoma 10(10)/9(9)/3(17)/2(13) Neurofibrosarcoma 7(7)/4(4)/1(6)/0 Fibrosarcoma 2(2)/5(5)/2(11)/2(13)	**Intervention** Group I Radical: Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH) 60 mg/m^2 administered as an intravenous (IV) bolus every 4 weeks; nine cycles; starting 6 weeks after operation except for patients who received postoperative radiotherapy, who received chemotherapy within 10 weeks after the operation. Group III Marginal+XRT Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH) 60 mg/m^2 administered as an intravenous (IV) bolus every 4 weeks; nine cycles; starting 6 weeks after operation except for patients who received postoperative radiotherapy, who received chemotherapy within 10 weeks after the operation **Control** Group II Radical: No chemotherapy Group IV Marginal+XRT No chemotherapy	Cardiomyopathy n=4 Other AEs not systematically reported	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: +

	Extraskeletal osteosarcoma 1(1)/1(1)/0/0 Extraskeletal chondrosarcoma 3(3)/1(1)/0/0 Malignant mesenchymoma 3(3)/2(2)/0/0 Malignant hemangiopericytoma 1(1)/2(2)/1(6)/1(6) Hemangiosarcoma 1(1)/2(2)/0/0 Clear-cell sarcoma 1(1)/0/1(6)/0 Rhabdomyosarcoma 1(1)/4(4)/2(11)/0 Extraskeletal Ewing's sarcoma 1(1)/0/1(6)/0 Unclassified sarcoma 6(6)/6(6)/1(6)/3(19) <u>Tumor site n(%)</u> Extremity 85(83)/93(90)/13(72)/10(63) Nonextremity 18(17)/10(10)/5(28)/6(37) <u>Grade of tumor n(%)</u> III 59(57)/55(53)/12(67)/12(75) IV 44(43)/48(47)/6(33)/4(25)	**Randomized patients** 103/103/18/16		
Antman K, Suit H, Amato D, Corson J, Wood W, Proppe K, et al. Preliminary results of a randomized trial of adjuvant doxorubicin for sarcomas: lack of apparent difference between treatment groups. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1984;2(6):601-8.	**Region/Setting** This study was conducted between 1978 and 1982 at the Dana-Farber Cancer Institute/Brigham and Women's Hospital (DFCI/BWH) and the Massachusetts General Hospital (MGH). **Inclusion criteria** - stages IIB-IVA sarcoma - grossly resected tumor, pathologically documented, microscopically involved margins remained eligible if no further resection other than an amputation or removal of a vital organ was possible - no prior chemotherapy or radiotherapy - no contraindication to intensive doxorubicin chemotherapy **Exclusion criteria** - Osteogenic, Ewing's and Kaposi's sarcomas, embryonal rhabdomyosarcoma and mesotheliomas **Patient characteristics** <u>Gender n(%)</u> Male 14(70)/11(50) Female 6(30)/11(50) <u>Age [y] Median</u> 48/47 <u>Tumor diagnosis (external pathology review) n(%)</u> Liposarcoma 8(40)/7(32) Leiomyosarcoma 4(20)/3(14) Malignant fibrous histiocytoma 4(20)/0 Undifferentiated sarcoma 1(5)/3(14)	**Intervention** Adjuvant chemotherapy: five cycles of adjuvant doxorubicin 90 mg/m^2 every three weeks. For patients undergoing primary surgery (DFCI/BWH), two courses of chemotherapy were delivered between surgery and the start of radiotherapy, three additional courses followed the completion of radiotherapy. **Control** Observatory group **Randomized patients** 20/22	mucositis n=2 Cardiomyopathy n=2 Other AEs not systematically reported died of intractable failure and arrhythmias n=1.	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: +

	Synovial sarcoma 0/3(14) Malignant schwannoma 1(5)/2(9) Fibrosarcoma 1(5)/1(5) Spindle-cell sarcoma 1(5)/1(5) Angiosarcoma 0/1(5) Endometrial stromal sarcoma 0/1(5) <u>Tumor site n(%)</u> Extremity lesions 10(50)15(68) Trunk/head or neck 9(45)/5(23 Retroperitoneum 1(5)/2(9) <u>Stage n(%)</u> IIB 5(25)/6(27) IIA 2(10)/7(32) IIIB 12(60)/8(36) IIIC 0/0 IVA 1(5)/1(5)			

Bramwell V, Rouesse J, Steward W, Santoro A, Schraffordt-Koops H, Buesa J, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma--reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1994;12(6):1137-49.	**Region/Setting** This study was conducted between January 1977 and June 1988. **Inclusion criteria** - age 15 - 70 years - histologically proven soft tissue sarcoma - adequate hematologic function (WBC count > 4.0 x 10^9/L and platelet count > 120 x 10^9/L) - no evidence of metastases, either hematogenous or in regional nodes - patients with locally recurrent tumors previously treated by surgery alone - all histologic subtypes, with the exception of borderline (fibromatoses) or very low-grade sarcomas, such as well-differentiated liposarcomas **Exclusion criteria** - prior chemotherapy - prior radiotherapy for other malignancies - poor physical or psychologic condition - severe hepatic dysfunction, bleeding disorders, significant symptomatic cardiac disease, serious infections, and a history of other malignant disease, excluding basal cell skin cancer **Patient characteristics** <u>Gender (male:female ratio)</u> 1.42/1.26 <u>Age [y] Median(range)</u> 44(15-70)/42(15-70) <u>Tumor site n(%)</u> Head, neck trunk 33(14)/36(15) Limbs 100(43)/116(50) Intraabdominal/thoracic 4(2)/9(4) Uterine 8(3)/11(5)	**Intervention** Adjuvant CYVADIC Chemotherapy: Cyclophosphamide 500 mg/m^2 intravenously (IV) bolus on day 1, vincristine 1.4 mg/m^2 IV bolus on day 1, doxorubicin (Adriamycin; Adria Laboratories, Columbus, OH) 50 mg/m^2 IV bolus on day 1, and dacarbazine (DTIC) 400 mg/m^2 by 1-hour infusion on days 1 to 3 (CYVADIC) cycles repeated every 8 days for eight courses **Control** no chemotherapy **Randomized patients** 234/234	**n (moderate/severe)** Alopecia n=63 (17/46) Nausea/vomiting n=28 (18/10) Neurologic n=10 (6/4) Anorexia n=8 (6/2) Infection n=4 (3/1)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: - Selective reporting: ? Other source of bias: +

Brodowicz T, Schwameis E, Widder J, Amann G, Wiltschke C, Dominkus M, et al. Intensified Adjuvant IFADIC Chemotherapy for Adult Soft Tissue Sarcoma: A Prospective Randomized Feasibility Trial. Sarcoma. 2000;4(4):151-60.	**Region/Setting** This study was conducted according to the declaration of Helsinki starting in January 1992. **Inclusion criteria** - histopathologically verified grade 2 (tumor size >5 cm) or grade 3 (any tumor size) STS - performance status World Health Organization (WHO) 0± 1 (=Karnofsky ≥ 60) - age 18 - 80 years - serum total bilirubin and/or transaminase levels ≤ 1.25 times the upper limits of normal, serum creatinine ≤ 2 mg/100 ml - adequate hematologic function (as defined by white blood cells ≥ 3.03 10^9/l, platelets ≥100 X10^9/l). Histologic entities included fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, malignant schwannoma, epithelioid sarcoma, clear cell sarcoma and mixed tumors of soft tissue origin **Exclusion criteria** - previous chemo- or radiotherapeutic treatment of the current disease - intralesional resection of the primary tumor (see `Treatment protocol' section) - local relapse of previous STS - presence of distant metastases at time of diagnosis - surgical resection being carried out >4 weeks before randomization - second malignancy with the exception of in situ cervical cancer or adequately excised basal cell or squamous cell carcinoma of the skin, left ventricular ejection fraction ≤ 50% - history of atrial or ventricular arrhythmias - histologic entities including neuroblastoma, primitive neuroectodermal tumor (PNET), Ewing sarcoma, extraskeletal osteosarcoma and embryonal rhabdomyosarcoma - active infection - any other serious underlying medical condition that would impair the ability of the patient to receive treatment according to the protocol - altered mental status - pregnancy and breastfeeding **Patient characteristics** Gender n(%) Male 18(58)/14(50) Female 13(42)/14(50) Age [y] Median(range) 49(20-71)/54(21-77) Tumor diagnosis n(%) Liposarcoma 6(19)/9(32) MFH 6(19)/5(18)	**Intervention** Intensified adjuvant IFADIC chemotherapy: Radiotherapy and six courses of ifosfamide (1500 mg/m2, days 1± 4), dacarbazine (DTIC) (200 mg/m2, days 1± 4) and doxorubicin (25 mg/m2, days 1± 2) administered in 14-day-intervals supported by granulocyte-colony stimulating factor (303 106 IU/day, s.c.) on days 5± 13 **Control** Radiotherapy alone **Randomized patients** 31/28	n(ae) WHO grad (I/II/III/IV) Leukopenia 27 (11/8/4/4) Thrombocytopenia 9 (5/2/1/1) Alopecia 31 (0/0/31/0)	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Synovial sarcoma 4(13)/3(11) Leiomyosarcoma 6(19)/0 Malignant schwannoma 1(3)/0 Fibrosarcoma 2(6)/2(7) Rhabdomyosarcoma 0/2(7) Other types of STS 6(19)/7(25) <u>Tumor site n(%)</u> Upper extremity 9(21)/2(7) Lower extremity 16(52)/20(71) Trunk 5(16)/6(21) Retroperitoneum 1(3)/0 <u>Tumor grading n(%)</u> G2 6(19)/12(43) G3 25(81)/16(57)			

Edmonson JH, Fleming TR, Ivins JC, Burgert EO, Jr., Soule EH, O'Connell MJ, et al. Randomized study of systemic chemotherapy following complete excision of nonosseous sarcomas. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1984;2(12):1390-6	**Region/Setting** This study was conducted between June 1975 and April 1981. **Inclusion criteria** - patients whose nonosseous sarcomas of extremity or trunk origin had been completely excised primarily or after local recurrences - good nutritional status - satisfactory bone marrow, hepatic, and renal function as indicated by blood leukocyte count and platelet count of at least 4,000 cells/pL and 130,000 cells/.L, respectively, and no increase in direct serum bilirubin or increase in serum creatinine above 1.5 mg/dL. - freedom from active infection or active heart disease **Exclusion criteria** - dermatofibrosarcoma, lymphomas, myeloma, Kaposi's sarcoma, embryonal rhabdomyosarcoma - significant second primary cancers - prior preoperative or postoperative radiation therapy **Patient characteristics** <u>Gender n(%)</u> Male 16(53)/11(35) Female 14(47)/20(65) <u>Age [y] Median(range)</u> 54(7-73)/51(8-70) <u>Tumor diagnosis n(%)</u> Malignant fibrous histiocytoma 9(30)/9(29) Leiomyosarcoma 6(20)/7(23) Synovial sarcoma 8(27)/5(16) Liposarcoma 5(17)/3(10) Other 2(7))/7(23) <u>Histologic grade n(%)</u> Broder’s grades 3 and 4 22(73)/24(77) Broder’s grades 1 and 2 8(27)/7(23) <u>Site of origin n(%)</u> Somatic 26(87)/25(81) Visceral 4(13)/6(19) <u>Status of disease n(%)</u> Primary tumor 24(80)/24(77) Locally recurrent tumor 6(2)/7(23)	**Intervention** Adjuvant chemotherapy: Vincristine/ cyclophosphamide/ dactinomycin, and vincristine/doxorubicin/dacarbazine at six-week intervals for one year **Control** Six-week intervals without adjuvant chemotherapy **Randomized patients** 30/31	Alopecia 90% Vomiting 50% (despite the use of prochlorperazine) Diarrhea 8% Stomatitis 4%	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Eilber FR, Giuliano AE, Huth JF, Morton DL. A randomized prospective trial using postoperative adjuvant chemotherapy (adriamycin) in high-grade extremity soft-tissue sarcoma. American journal of clinical oncology. 1988;11(1):39-45.	**Region/Setting** This study was conducted between March 1981 and December 1984. **Inclusion criteria** - primary grade III extremity soft-tissue sarcoma confirmed by the UCLA Department of Pathology - primary tumor control obtained by surgery - no evidence of distant metastases by whole lung tomography or chest computerized tomography (CT) scan **Exclusion criteria** NR **Patient characteristics** <u>Gender n(%)</u> Male 65 (55) Female 54 (45) <u>Age [y] Median(range)</u> 59 (12-83) <u>Histology types</u> 75% of the patients had malignant fibrous histiocytoma, synovial cell sarcoma or liposarcoma	**Intervention** Adjuvant chemotherapy: Single agent Adriamycin 90mg/m^2 over 2 days once a month for 5 months **Control** No adjuvant chemotherapy **Randomized patients** 57/62	NR	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: +
Frustaci S, Gherlinzoni F, De Paoli A, Bonetti M, Azzarelli A, Comandone A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2001;19(5):1238-47.	**Region/Setting** This study was conducted under the auspices of the Italian National Council for Research (CNR) between June 1992 and November 1996. **Inclusion criteria** - age 18 to 65 years - Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2 - primary tumors subfascially localized with diameter greater than or equal to 5 cm; high-grade spindle-cell or polymorphous sarcomas (fibrosarcoma, malignant fibrous histiocytoma, polymorphous liposarcoma, leiomyosarcoma, synovial sarcoma, malignant schwannoma, angiosarcoma, and polymorphous rhabdomyosarcoma) - local relapse of any size - no previous radio/chemotherapy - adequate bone marrow (WBC count of $ 4,000/mL, platelets ≥ 120.000/mL, and hemoglobin ≥ 10 g/dL), renal (creatinine ≤ 1.3 mg/dL), hepatic (SGOT ≤ 2.5 X normal value and bilirubin ≤ 1.2 mg/dL), and pulmonary functions **Exclusion criteria** **-** distant or regional lymph-node metastases - previous malignancy, medical or psychiatric illness - pregnancy	**Intervention** Adjuvant chemotherapy: (five cycles of 4' epidoxorubicin 60 mg/m^2 days 1 and 2 and ifosfamide 1.8 g/m^2 days 1 through 5, with hydration, mesna, and granulocyte colony-stimulating factor) **Control** no chemotherapy **Randomized patients** **53/51**	<u>Hematologic toxicity (first Cycle)</u> grade 4 leukopenia 35% grade 4 thrombocytopenia 4% <u>nonhematologic toxicities</u> reversible alopecia 100% grade 3 mucositis 10% grade 3 nausea and vomiting 3%	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

	- uncontrolled infections - risk of being lost to follow-up. **Patient characteristics** <u>Gender n(%)</u> Male 33(62)/28(55) Female 20(38)/23(45) <u>Age n</u> 18-39 years: 16/16 40-54 years: 19/19 55-65 years: 18/16 <u>Tumor diagnosis n(%)</u> Malignant fibrous histiocytoma 14(26)/14(27) Synovialsarcoma 15(28)/12(24) Liposarcoma 12(23)/9(18) Fibrosarcoma 1(2)/1(2) Leiomyosarcoma 3(6)/5(10) Schwannoma 6(11)/3(6) Rhabdomyosarcoma polymorphous 0/1(2) Other 2(2)/6(12) <u>Grading n(%)</u> G3 24(45)/22(43) G4 29(55)/29(57) <u>Tumor site n(%)</u> Upper extremity 14(26)/10(20) Proximal 9(17)/5(10) Distal 5(9)/5(10) Lower extremity 39(74)/41(80) Proximal 25(47)/30(59) Distal 14(27)/11(22)			
Gherlinzoni F, Bacci G, Picci P, Capanna R, Calderoni P, Lorenzi EG, et al. A randomized trial for the treatment of high-grade soft-tissue sarcomas of the extremities: preliminary observations. Journal of clinical oncology: official journal of the American Society of Clinical	**Region/Setting** This study was conducted at the Istituto Ortopedico Rizzoli between August 1981and December 1984. **Inclusion criteria** - lesions localized in or distal to the shoulder or pelvic girdle - typical histologic features of high-grade STS, Broder's malignancy grade 3 or 4 (Enneking's stage IIA or IIB)15"16 - age 16 to 70 years - radical or wide surgical excision - no previous radiotherapy and/or chemotherapy - absence of any contraindication to treatment with ADM	**Intervention** Adjuvant chemotherapy: Adriamycin [Farmitalia-Carlo Erba, Milan, Italy], 450 mg/m^2) **Control** No adjuvant chemotherapy **Randomized patients** 24/35	NR	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Oncology. 1986;4(4):552-8.	- absence of regional or distant metastases on clinical and radiographic examination **Exclusion criteria** NR **Patient characteristics** Gender n(%) Male 16(66.5)/19(55) Female 8(33.5)/16/45) Age n/%) 16-30 9(37.5)/14(40) 31-40 6(25)/3(8.5) 41-50 2(8.5)/6(17) 51-60 4(16.5)/7(20) 61-70 3(12.5)/5(14.5) Tumor diagnosis n(%) Malignant fibrous histiocytoma 7(29)/10(28.5) Synovial sarcoma 7(29)/12(34) Adult fibrosarcoma 4(16.5)/2(5.5) Liposarcoma 2(8.5)/2(5.5) Malignant schwannoma 0/3(8.5) Rhabdomyosarcoma 0/2(6) Malignant hemangiopericytoma 1(4.2)/1(3) Epithelioid sarcoma 1(4.2)/1(3) Soft-tissue osteogenic sarcoma 1(4.2)/0 Soft-tissue alveolar sarcoma 0/1(3) Soft-tissue mesenchymal chondrosarcoma 0/1(3) Soft-tissue undifferentiated sarcoma 1(4.2)/0 Tumor site n(%) Shoulder girdle 1(4)/2(5.5) Arm 2(8.5)/5(14.5) Elbow 0/2(5.5) Forearm 3(12.5)/1(3) Wrist 0/1(3) Pelvic girdle 0/1(3) Thigh 9(37.5)/19(54) Leg 7(29)/4(11.5) Foot 2(8.5)/0			

Glenn J, Kinsella T, Glatstein E, Tepper J, Baker A, Sugarbaker P, et al. A randomized, prospective trial of adjuvant chemotherapy in adults with soft tissue sarcomas of the head and neck, breast, and trunk. Cancer. 1985;55(6):1206-14.	**Region/Setting** This study was conducted since 1977. **Inclusion criteria** - grade 2 or 3 sarcoma of the head, neck, breast, or trunk exclusive of the retroperitoneum - gross tumor completely resectable at the time of Presentation - no evidence of metastatic disease - no prior history of cancer except basal cell carcinoma of the skin - no prior history of receiving chemotherapy or radiation therapy **Exclusion criteria** - visceral sarcoma - age <21 years with the diagnosis of rhabdomyosarcoma **Patient characteristics** <u>Gender n(%)</u> Male 18(60)/18(67) Female 12(40)/9(33) <u>Age n(%)</u> <20 5(17)/1(4) 21-40 13(43)/12(44) 41-68 12(40)/14(52) <u>Tumor diagnosis n(%)</u> Malignant fibrous histiocytoma 6(20)/6(22) Unclassified sarcoma 5(17)/5(19) Liposarcoma 3(10)/4(15) Synoviosarcoma 2(7)/6(22) Neurofibrosarcoma 4(13)/2(7) Angiosarcoma 2(7)/3(11) Leiomyosarcoma 3(10)/1(4) Rhabdomyosarcoma 3(10)/0 Fibrosarcoma 2(7)/0 <u>Tumor site n(%)</u> Head and Neck 6(20)/6(22) Breast 2(7)/4(15) Trunk 22(73)/17(63) <u>Grade of tumor n(%)</u> 2 8(27)/5(19) 3 22(73)/22(81)	**Intervention** Adjuvant chemotherapy: Doxorubicin (≤550 mg/m^2), cyclophosphamide (≤5500m g/m^2), and methotrexate (≤1000m g/kg) **Control** No chemotherapy **Randomized patients** 30/27	Cardiomyopathy requiring digitalis n=4 Bone marrow toxicity requiring hospitalization n=2 Cardiomyopathy causing death n=1 Clinically evident cystitis n=1 Decreased creatinine clearance n=1	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: +

Gronchi A, Stacchiotti S, Verderio P, Ferrari S, Martin Broto J, Lopez-Pousa A, et al. Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): Long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. Annals of Oncology. 2016;27(12):2283-8.	**Region/Setting** This study was conducted between January 2002 and April 2007 Italy and Spain. **Inclusion criteria** - high-risk (grade 3, deep site, size >5 cm) localized adult-type STS arising from extremities or trunk wall - age ≥18 years - histologically proven localized adult-type STS located to the extremities or trunk wall that was deeply seated (according to the investing fascia), with largest diameter of ≥5 cm if primary or any size if locally recurrent and with histologic grade of aggressiveness equal to 3 according to the Federation Nationale des Centres de Lutte Contre le Cancer - Eastern Cooperative Oncology Group performance status ≤1 - adequate bone marrow (WBC >3,500/μL, neutrophils >1,500/μL - platelets>150,000/μL, and hemoglobin>11 g/dL), - renal (serum creatinine<1.3 mg/dL) - hepatic (total bilirubin≤1.5 mg/dL and ALT and AST <2x normal value) - cardiac (left cardiac ejection fraction ≥ 50%) function. **Exclusion criteria** NR **Patient characteristics** Age [y] median(range) 47(16-74)/51(15-79) Histologic subtype n(%) Undifferentiated pleomorphic sarcoma 57(17.38)/69(21.04) Leiomyosarcoma 23(7.01)/20(6.10) Synovial sarcoma 39(11.89)/32(9.76) Other 45(13.72)/43(13.11) Tumor size [cm] Median(range) 10(3-30)/10(2-45)	**Intervention** three preoperative cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 plus two postoperative cycles **Control** three preoperative cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 **Randomized patients** 161/160	Hematologic toxicity (Grade 3/Grade 4) bone marrow (WBC) 23/%62% Absolute neutrophil count 13%/70% Platelets 20%/2% Nonhematologic toxicity Febrile neutropenia 6.1% GI 4.6% Renal failure 1.5%	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +
Lerner HJ, Amato DA, Savlov ED, DeWys WD, Mittleman A, Urtasun RC, et al. Eastern Cooperative Oncology Group: a comparison of adjuvant doxorubicin and observation for patients with localized soft tissue sarcoma.	**Region/Setting** This study was conducted by the Eastern Cooperative Oncology Group (ECOG). **Inclusion criteria** - age 16 – 75 years - no medical contraindications to chemotherapy - no postoperative complications or acute side effects of radiotherapy - no previous therapy with doxorubicin or radiation to the involved area - no previous tumors other than basal-cell or squamous-cell tumors of	**Intervention** Adjuvant chemotherapy: Adriamycin was administered at 70 mg/m^2 IV (slow push, every 3 weeks for seven courses for a maximum of 550 mg/m^2) **Control** No chemotherapy /observation	Lethal or life-threatening toxicities reported n=0 Moderate or worse cardiac toxicities n=0 At least one severe reaction 24% At least one moderate or severe toxicity 70%	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: Selective reporting: ?

Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1987;5(4):613-7.	the skin - stage IIB to IVA disease, unless they had either synovial sarcoma, adult rhabdomyosarcoma, alveolar soft parts sarcoma, or a sarcoma type not designated, in which case they could have stage I to IVA disease - recent curative treatment for localized soft tissue sarcoma - conservative or radical primary treatment for local cure - free of clinically detectable disease following local treatment - time elapsed between the completion of local therapy and study entry had to be < 6 weeks for patients receiving surgery alone, and < 12 weeks for those receiving radiotherapy - WBC>5,000, platelets> 100,000, hematocrit> 32%, BUN <25, creatinine <1.2, bilirubin<l.5, and SGOT<50 **Exclusion criteria** - mesothelioma, lesions of hollow viscera or parenchymatous organs, and lesions within the dura **Patient characteristics** <u>Gender n(%)</u> Male 12(71)/4(31) Female 5(29)/9(69) <u>Age [y] Median(range)</u> 46(19-71)/43(16-75) <u>Tumor diagnosis n (%)</u> Malignant fibrous histiocytoma NR(53)/NR(33) Synovial sarcoma NR(13)/NR(25) Liposarcoma NR(13)/NR(8) Leiomyosarcoma NR(13)/NR(8) Malignant schwannoma NR(7)/NR(8) Angiosarcoma 0/NR(8) Other 0/NR(8) <u>Stage of tumor n (%)</u> IIB NR(25)/NR(33) IIA NR(6)/NR(8) IIIB NR(44)/NR(42) IIIX NR(6)/NR(8) IVA NR(19)/NR(8)	**Randomized patients** 17/13		Other source of bias: +

Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gyneco-logic Oncology Group Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1985;3(9):1240-5.	**Region/Setting** This study was conducted by the Gynecologic Oncology Group (GOG) in 1973. **Inclusion criteria** - stage I or II histologically proven leiomyosarcomas, heterologous or homologous mixed mesodermal sarcomas, and other uterine sarcomas **Exclusion criteria** - abnormal cardiac status - wrong stage - poor performance status **Patient characteristics** Gender n(%) Male 0/0 Female 75(100)/81(100) Age [y] Median(range) 58(25-77)/58.5(18-80) Tumor diagnosis (external pathology review) n(%) Leiomyosarcoma 25(33)/23(28) Heterologous mixed mesodermal sarcomas 25(33)/23(28) Homologous mixed mesodermal sarcomas 19(25)/26(32) Other uterine sarcomas 6(8)/9(11)	**Intervention** Adjuvant chemotherapy: Adriamycin 60 mg/m^2 (Adria Laboratories, Columbus, Ohio) every three weeks for eight doses, to be started one to four weeks postoperatively or after irradiation for six months **Control** no further treatment **Randomized patients** 75/81	Leukopenia n=51 Cardiac toxicity n=6	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: ? Other source of bias: +

Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Annals of oncology: official journal of the European Society for Medical Oncology. 2013;24(4):1099-104.	**Region/Setting** This study was conducted at 19 institutions between October 2001 and July 2009. **Inclusion criteria** **-** histologically confirmed by a sarcoma pathologists experts panel - age >18 – 65 years - FIGO 1989 modified classification for endometrial carcinoma stage lower than or equal to III, with complete surgery (at least hysterectomy and bilateral oophorectomy) - ECOG performance status of 0 or 1 - adequate hematologic (granulocyte blood count and platelet count exceeded, respectively, 1500/µl and 100.000/µl); hepatic (total bilirubin < 1.5 times the upper limit of normal, transaminases < 2.5 N), renal (creatinine < 1.25 N) and cardiac (LVEF measurement (per ultrasound or scintigraphy) >50%) functions - normal thoracic, abdominal, and pelvic CT scans **Exclusion criteria** **Patient characteristics** Gender n(%) NR Age [y] Median(range) 55(40-69)/54.5(39-66) Tumor diagnosis n(%) Leiomyosarcoma 24(NR)/29(NR) Carcinosarcoma 9(NR)/10(NR) High-grade stromal sarcoma 6(NR)/3(NR)	**Intervention** Chemotherapy: four cycles of doxorubicin 50 mg/m² d1, ifosfamide 3 g/m²/day d1–2, cisplatin 75 mg/m² d3, (API) + G-CSF q 3 weeks followed by radiotherapy **Control** Radiotherapy alone **Randomized patients** 39/42	**Grade 3–4** Thrombocytopenia 76% Anemia 58% Neutropenia 58% Febrile neutropenia 24% Nausea/vomiting 21%	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: +
Rosenberg SA, Tepper J, Glatstein E, Costa J, Young R, Baker A, et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcomas of the extremities. Cancer. 1983;52(3):424-34. Chang 1988 Chang AE, Kinsella T, Glatstein E, Baker AR, Sindelar WF, Lotze MT, et al. Adjuvant chemotherapy for patients with	**Region/Setting** This study was conducted in the USA between June 1977 and July 1981. **Inclusion criteria** - diagnoses of round-cell or pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, synovial cell sarcoma, fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma - standard work-up including history, physical examination, blood chemistries, chest x-ray, lung tomograms, liver scan, bone scan, and computerized axial tomography through the area of the primary lesion - free of clinical evidence of metastatic disease, either in regional lymph nodes or more distant sites **Exclusion criteria** **-** any prior chemotherapy or radiation therapy prior to referral to the National Cancer Institute - history of any other malignant disease except basal cell carcinoma	**Intervention** Adjuvant chemotherapy: Doxorubicin and cyclophosphamide intravenously on day 1 of a 28-day cycle. Doxorubicin was 50 mg/m^2 and was escalated by 10 mg/m^2 to a maximum of 70 mg/m^2 depending on bone marrow toxicity, never exceeding a cumulative dose of doxorubicin of 550 mg/m^2. Cyclophosphamide was started at a dosage of 500 mg/m^2 and was escalated by 100 mg/m^2 in conjunction with doxorubicin to a maximum	NR	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: ? Other source of bias: ?

high-grade soft-tissue sarcomas of the extremity. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1988;6(9):1491-500.	- serious infections, active bleeding disorders, or concomitant severe diseases such as cirrhosis, ischemic heart disease, or evidence of severe impairment of renal function - patients younger than age 30 years with a diagnosis of embryonal or alveolar rhabdomyosarcoma **Patient characteristics** <u>Gender n(%)</u> NR <u>Age n(%)</u> 0-20 4(11)/5(18) 21-40 17(46)/10(36) 41-60 15(41)/9(32) >60 1(2)/4(14) <u>Tumor site n(%)</u> Arm 5(13)/5(18) Forearm and hand 7(19)/3(11) Thigh 17(46)/16(57) Leg and foot 8(22)/4(14) <u>Tumor diagnosis n(%)</u> Fibrosarcoma 0/4(15) Malignant fibrous histiocytoma 9(24)/9(33) Liposarcoma 5(14)/6(21) Leiomyosarcoma 2(5)/2(7) Rhabdomyosarcoma 2(5)/0 Synovial sarcoma 12(33)/4(14) Neurofibrosarcoma 3(8)/2(7) Unclassified 4(11)/1(3) <u>Grade n(%)</u> 1 0/0 2 6(16)/8(29) 3 31(84)/20(71)	of 700 mg/m^2 depending on toxic side effects. **Control** No chemotherapy **Randomized patients** 37/28		

Woll PJ, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomized controlled trial. The Lancet Oncology. 2012;13(10):1045-54.	**Region/Setting** This study was conducted at 36 sarcoma treatment centers in 12 European countries and Canada between February 1995 and December 2003. **Inclusion criteria** **-** histologically proven, intermediate or high-grade (Trojani grade II or III),5 soft-tissue sarcoma at any site (excluding Ewing sarcoma and embryonal rhabdomyosarcoma), - definitively resected within 8 weeks of biopsy or preliminary surgery - no regional lymph node involvement and no evidence of metastases on CT scan of thorax - age >16 - 70 years - WHO performance status of 0 or 1 - white blood cell count greater than 4×10^9 cells per L, platelet count greater than 120×10^9 platelets per L, serum creatinine concentration lower than 140 µmol/L or creatinine clearance greater than 60 mL/min, total bilirubin lower than 1·25 times the upper limit of normal - no previous malignancy or systemic chemotherapy - no bleeding or cardiac disorders. **Exclusion criteria** **Patient characteristics** <u>Gender n(%)</u> Male 96(55)/98(56) Female 79(45)/78(44) <u>Age [y] Median(range)</u> 49.2(17.3-68.5)/49.1(17.5-71.4) <u>Tumor site n(%)</u> Extremity 116(66)/118(67) Limb girdle 20(11)/24(14) Central 39(22)/34(19) <u>Histological type local diagnosis n(%)</u> MFH 33(19)/51(29) Liposarcoma 24(14)/35(20) Leiomyosarcoma 36(21)/22(12) Synovial sarcoma 28(16)/22(12) Other 54(31)/46(26) <u>Histological type review diagnosis n(%)</u> MFH 15(10)/25(18) Liposarcoma 20(14)/25(18) Leiomyosarcoma 32(22)/23(17)	**Intervention** Adjuvant chemotherapy: Doxorubicin (75 mg/m²) intravenously for 20 min and ifosfamide (5 g/m²) with mesa intravenously for 24 h at day 1, and lenograstim (3 µg/kg) subcutaneously daily for 14 days, starting 24 h after completing ifosfamide. Five cycles were given at 3-week intervals. **Control** no chemotherapy **Randomized patients** 175/176 **Analysed patients** 131/166	**<u>Grade3/Grade4</u>** White blood cells 19%/28% Neutrophils 9%/30% Platelets 13%/8% Hemoglobin 8%/1% Alopecia 17%/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: ? Other source of bias: +

	Synovial sarcoma 22(15)/18(13) Other 56(39)/45(33) <u>Trojani grade local diagnosis n(%)</u> Grade I 0/0 Grade II 72(41)/69(39) Grade III 103(59)/107(61) <u>Trojani grade review diagnosis n(%)</u> Grade I 10(7)/7(5) Grade II 70(49)/64(47) Grade III 64(44)/66(48)			

+ low risk of bias; - high risk of bias; ? unclear risk of bias; AEs: adverse events; ADM: adriamycin; ALT: alanine transaminase; AST: aspartate transaminase; CG: control group; CNR: Italian National Council for Research; CSF: granulocyte colony-stimulating factor; CYVADIC: cyclophosphamide / vincristine / adriamycin / dimethyltriazenylimidazolecarboxamide;DFCI/BWH: Dana-Farber Cancer Institute/Brigham and Women's Hospital; DTIC: dacarbazine; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; GOG: Gynecologic Oncology Group; HFM: malignant fibrous histiocytoma; IFADIC: ifosfamide-doxorubicin-DTIC; IG: intervention group; IV: intravenous; NR: not reported; MFH: malignant fibrous histiocytoma; MGH: Massachusetts General Hospital; OH: Ohio; PNET: primitive neuroectodermal tumor; RCT: randomized controlled trial; s.c.: subcutan; SGOT: serum glutamic-oxaloacetic transaminase; SSG: Scandinavian Sarcoma Group; STS: soft tissue sarcoma ; UCLA: University of California, Los Angeles; WBC: White Blood Cell; WHO: World Health Organization; XRT: external radiation therapy

2.2. SoF Tables Systemtherapie - Adjuvante Chemotherapie

AG Systemtherapie, Kasper

Summary of findings:

Doxorubicin compared to surgery alone for STS

Patient or population: STS
Intervention: Doxorubicin
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with Doxorubicin**				
Overall survival (range follow-up: 16 - 40 months)	333 per 1.000	**270 per 1.000** (210 to 350)	**RR 0.81** (0.63 to 1.05)	528 (5 RCTs)	⨁⨁◯◯ LOW	
Disease free survival (range follow-up: 11 - 30 months)	450 per 1.000	**360 per 1.000** (293 to 437)	**RR 0.80** (0.65 to 0.97)	587 (6 RCTs)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Alvegard 1989; Antman 1984; Eilber 1988; Gherlinzoni 1986; Lerner 1987; Omura 1985

Summary of findings:

DTIC-Regime compared to surgery alone for STS

Patient or population: STS
Intervention: DTIC-Regime
Comparison: surgery alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with DTIC-Regime**				
Overall survival (median follow-up 80 months)	384 per 1.000	**357 per 1.000** (269 to 480)	**RR 0.93** (0.70 to 1.25)	317 (1 RCT)	⨁⨁◯◯ LOW	
Disease free survival (median follow-up 80 months)	570 per 1.000	**439 per 1.000** (353 to 553)	**RR 0.77** (0.62 to 0.97)	317 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Bramwell 1994

Summary of findings:

IFADIC-Regime compared to surgery alone for STS

Patient or population: STS
Intervention: IFADIC-Regime
Comparison: surgery alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with IFADIC-Regime**				
Overall survival (mean follwow-up: 41 +/- 19.7 months; range 8.1-84 months)	107 per 1.000	**32 per 1.000** (3 to 293)	**RR 0.30** (0.03 to 2.73)	59 (1 RCT)	⨁⨁◯◯ LOW	
Recurrent free survival (mean follow-up: 41 +/- 19.7 months; range: 8.1-84 months)	429 per 1.000	**227 per 1.000** (103 to 493)	**RR 0.53** (0.24 to 1.15)	59 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Brodowicz 2000

Summary of findings:

VCR-Cyclo-DACT/VCR-Doxo-DTIC compared to surgery alone for STS

Patient or population: STS
Intervention: VCR-Cyclo-DACT/VCR-Doxo-DTIC
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with VCR-Cyclo-DACT/VCR-Doxo-DTIC**				
Overall survival (median: 64.3 months)		Not reported	p= 0.55	61 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; VCR: Vincristine; Cyclo: Cyclophosphamide; DACT: Dactinomycin; Doxo: Doxorubicin; DTIC: Dacarbazine

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Edmonson 1984

Summary of findings:

Epidoxorubicin + Ifosfamide compared to surgery alone for STS

Patient or population: STS
Intervention: Epidoxorubicin + Ifosfamide
Comparison: surgery alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with Epi-doxorubicin + Ifos-famide**				
Overall survival (median follow-up: 59 months)	549 per 1.000	**604 per 1.000** (434 to 840)	**RR 1.10** (0.79 to 1.53)	104 (1 RCT)	⊕⊕◯◯ LOW	
Disease free survival(median follow up: 48 months Epi/ 16 months control)	627 per 1.000	**527 per 1.000** (376 to 734)	**RR 0.84** (0.60 to 1.17)	104 (1 RCT)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Frustaci 2001

Summary of findings:

Neoadjuvant + surgery + adjuvant compared to neoadjuvant + surgery for STS

Patient or population: STS
Intervention: Neoadjuvant + surgery + adjuvant
Comparison: neoadjuvant + surgery

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with neoad-juvant+surgery	**Risk with Neoadju-vant+surgery+adjuvant**				
Overall survival (median Follow-up: 117 months)	359 per 1.000	**398 per 1.000** (302 to 531)	**RR 1.11** (0.84 to 1.48)	314 (1 RCT)	⨁⨁◯◯ LOW	
disease free survival (median follow-up: NR)	417 per 1.000	**400 per 1.000** (304 to 521)	**RR 0.96** (0.73 to 1.25)	314 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Gronchi 2016

Summary of findings:

Doxorubicin + Cyclophosphamide compared to surgery alone for STS

Patient or population: STS
Intervention: Doxorubicin + Cyclophosphamide
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	Risk with Doxorubicin+Cyclophosphamide				
Overall survival (follow-up, range: 21,5 - 35 months)	286 per 1.000	**134 per 1.000** (26 to 737)	**RR 0.47** (0.09 to 2.58)	96 (2 RCTs)	⊕⊕◯◯ LOW	
Disease free survival (follow-up, range: N.R. - 21,5 months)	429 per 1.000	**141 per 1.000** (64 to 321)	**RR 0.33** (0.15 to 0.75)	96 (2 RCTs)	⊕⊕⊕◯ MODERATE	
Overall survival (follow-up: 5 years)	393 per 1.000	**181 per 1.000** (79 to 405)	**RR 0.46** (0.20 to 1.03)	67 (1 RCT)	⊕⊕◯◯ LOW	
Disease free survival (follow-up: 5 years)	464 per 1.000	**232 per 1.000** (116 to 464)	**RR 0.50** (0.25 to 1.00)	67 (1 RCT)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Glenn 1985; Chang 1988; Rosenberg 1983

Summary of findings:

Doxorubicin + Ifosfamide + Cisplatin compared to surgery alone for STS

Patient or population: STS
Intervention: Doxorubicin + Ifosfamide + Cisplatin
Comparison: surgery alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with Doxorubicin+Ifosfamide+Cisplatin**				
Overall survival (median follow-up: 4.3 years)	310 per 1.000	**180 per 1.000** (80 to 402)	**RR 0.58** (0.26 to 1.30)	81 (1 RCT)	⨁⨁◯◯ LOW	
Disease free survival (median follow-up: 4.3 years)	619 per 1.000	**384 per 1.000** (241 to 613)	**RR 0.62** (0.39 to 0.99)	81 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Pautier 2013

Summary of findings:

Doxorubicin + Ifosfamide + Lenograstim compared to surgery alone for STS

Patient or population: STS
Intervention: Doxorubicin + Ifosfamide + Lenograstim
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with Doxorubicin+Ifosfamide+Lenograstim**				
Overall survival (median follow-up: 7.99 years)	585 per 1.000	**563 per 1.000** (450 to 684)	**HR 0.94** (0.68 to 1.31)	351 (1 RCT)	⊕⊕◯◯ LOW	
Disease free survival (median follow-up: 7.99 years)	497 per 1.000	**465 per 1.000** (369 to 568)	**HR 0.91** (0.67 to 1.22)	351 (1 RCT)	⊕⊕◯◯ LOW	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Woll 2012

Summary of findings:

Adjuvant doxorubicin based chemotherapy compared to surgery alone for STS

Patient or population: STS
Intervention: Adjuvant chemotherapy
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	Risk with Adjuvant chemotherapy				
Overall survival (range follow-up: 8.1-96 months)	351 per 1.000	**292 per 1.000** (246 to 344)	**RR 0.83** (0.70 to 0.98)	1117 (10 RCTs)	⊕⊕⊕◯ MODERATE	
disease free survival (range follow-up: 8.1-84 months)	464 per 1.000	**334 per 1.000** (283 to 399)	**RR 0.72** (0.61 to 0.86)	825 (10 RCTs)	⊕⊕⊕◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Alvegard 1989; Antman 1984; Brodowicz 2000; Chang 1988; Eilber 1988; Gherlinzoni 1986; Glenn 1985; Lerner 1987; Omura 1985; Pautier 2013; Woll 2012

3. Systemtherapie - Adjuvante Imatinibtherapie

3.1. Evidenztabelle Systemtherapie - Adjuvante Imatinibtherapie

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (all or five most frequent, chemotherapy group only)	Study type, level of evidence and risk of bias
Joensuu H., et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor, JAMA, March 28,2012 307 (12): 1265-1272. Joensuu, H., et al., Adjuvant imatinib for high-risk GI stromal tumor: Analysis of a randomized trial. Journal of Clinical Oncology, 2016. 34(3): p. 244-250.	**Region/Setting** Open-label phase 3 study conducted in 24 hospitals in Finland, Germany, Norway, and Sweden **Inclusion criteria** - ≥18 years - Histologically diagnosed, KIT - (CD117) positive GIST removed at open surgery - more than 1 week but less than 12 weeks between the date of surgery and the date of randomization - high estimated risk of recurrence according to the modified National Institutes of Health (NIH) Consensus Criteria - Eastern Cooperative Oncology Group performance status ≤ 2 - adequate renal, hepatic, and bone marrow function **Exclusion criteria** - inoperable, metastatic, or recurrent GIST - congestive heart failure or myocardial infarction within 6 months of study entry - other severe or uncontrolled medical disease - patients with other invasive cancer diagnosed within 5 years prior to study entry - pregnant or breastfeeding patients - patients with human immunodeficiency virus infection - patients who had received either chemotherapy or neoadjuvant imatinib for GIST prior to randomization - patients who had operable intra-abdominal GIST metastases and could be rendered free from all macroscopic tumors at surgery after October 2006 - **Patient characteristics** Gender n (%) Female 101 (51)/ 95 (48)	**Intervention** Oral imatinib 400 mg once daily 36 months **Control** Oral imatinib 400 mg once daily 12 months **Randomized patients** 198/199	Any event n (%) 198 (100)/ 192 (99) **Hematological n (%)** anemia 159 (80.3)/ 140 (72.2) Leukopenia 93 (47.0)/ 67 (34.5) **Nonhematological n (%)** Periorbital edema 147 (74.2)/ 115 (59.3) Fatigue 96 (48.5)/ 94 (48.5) Nausea 101 (51.0)/ 87 (44.8) Diarrhea 107 (54.0)/ 85 (43.8) Muscle cramps 97 (49.0)/ 60 (30.9) Leg edema 81 (40.9)/ 64 (33.0) **Biochemical** Elevated blood lactate dehydrogenase 119 (60.1)/ 84 (43.3) Elevated serum creatine 88 (44.4)/ 59 (30.4)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data:+ Selective reporting: + Other source of bias: +

	Age [y] Median(range) 60 (22-81)/ 62 (23-84) Resected intra-abdominal metastasis 11(6)/ 13(7) Complete resection (R0) 160 (81)/169(85%) Tumor site n (%) Stomach 105 (53)/ 97 (49) Small intestine 62 (31)/ 74 (37) Colon or rectum 19 (10)/ 16 (8) Other 11 (6)/ 11 (6) Not available 1 (1)/ 1 (1) Primary tumor diameter, median (range) [cm]:10 (2-40)/ 9 (2-35) <5.1 n(%): 18 (9)/ 29 (15) 5.1 – 10.0 n(%): 81 (41)/ 91 (46) >10.0 n(%): 98 (50)/ 78 (39) Not available: 1 (1)/ 1 (1) Primary tumor mitotic count: local, median (range): 8 (0-165)/ 10 (0-250) <6/HPF n(%): 56 (28)/ 52 (26) 6-10/HPF n(%): 53 (27)/ 48 (24) >10/HPF n(%): 69 (35)/ 85 (43) Not available: 20 (10)/ 14 (7) Primary tumor mitotic count: central, median (range): 4 (0-135)/ 6 (0-129) <6/HPF n(%): 98 (49)/ 86 (43) 6-10/HPF n(%):25 (13)/ 29 (15) >10/HPF n(%):59 (30)/ 74 (37) Not available: 16 (8)/ 10 (5) Tumor rupture prior to or at surgery n (%) No: 154 (78)/ 164 (82) Yes: 44 (22)/ 35 (18) Tumor mutation type n (%) KIT exon 9: 14 (7)/ 12 (6) Kit exon 11: 127 (64)/ 129 (65) PDGFRA exon 12: 2 (1)/ 3 (2) PDGFRA exon 18: 19 (10)/ 22 (11) PDGFRA exon 18 mutation D842V: 14 (7)/ 18 (9)			

	Other mutation: 2 (1)/ 3 (2) Wild type for KIT and PDGFRA: 14 (7)/ 19 (10) Not available: 20 (10)/ 11 (6) <u>Modified consensus classification risk group n (%)</u> High risk 181 (91)/ 178 (89) Intermediate risk: 8 (4)/ 15 (8) Low risk: 3 (2)/ 2 (1) Very low risk: 0/ 0 Not available: 6 (3)/ 4 (2)			

3.2. SoF Tables Systemtherapie - Adjuvante Imatinibtherapie

AG Systemtherapie, Kasper

Summary of findings:

Imatinib 36 months compared to Imatinib 12 months for GIST

Patient or population: GIST
Intervention: Imatinib 36 months
Comparison: Imatinib 12 months

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Imatinib 12 months	Risk with Imatinib 36 months				
Survival follow up: median 54 months	817 per 1.000	**913 per 1.000** (835 to 957)	**HR 0.45** (0.22 to 0.89)	397 (1 RCT)	⊕⊕⊕⊕ HIGH	
Reccurence free survival follow up: median 54 months	479 per 1.000	**713 per 1.000** (620 to 790)	**HR 0.46** (0.32 to 0.65)	397 (1 RCT)	⊕⊕⊕⊕ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Joensuu 2012, Joensuu 2016

4. Systemtherapie - Therapie der metastasierten Erkrankung

4.1. Evidenztabelle Systemtherapie - Therapie der metastasierten Erkrankung

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (IG/CG or IG only) (all or the five most frequent ae)	Study type, level of evidence and risk of bias
Baker LH, Frank J, Fine G, Balcerzak SP, Stephens RL, Stuckey WJ, et al. Combination chemotherapy using adriamycin, DTIC, cyclophosphamide, and actinomycin D for advanced soft tissue sarcomas: a randomized comparative trial. A phase III, Southwest Oncology Group Study (7613). Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1987;5(6):851-61.	**Region/Setting** NR **Inclusion criteria** - biopsy-confirmed diagnosis of a soft tissue sarcoma and convincing clinical or biopsy-documented evidence of metastatic disease - life expectancy of at least 10 weeks - Karnofsky performance status of 50 to 100 - a clearly measurable lesion that could be monitored for tumor response - WBC count >3,000 cell/mL, a platelet count > 100,000/mL, and adequate renal function defined as a BUN concentration < 50 mg/dL, and a serum creatinine level <2.5 mg/dL - adequate hepatic function with a serum bilirubin content of <2 mg/dL and no evidence of biliary obstruction **Exclusion criteria** - prior chemotherapy - chondrosarcoma, osteogenic sarcoma, Ewing's sarcoma, mesothelioma and Kaposi's sarcoma - significantly clinically relevant abnormal electrocardiogram findings - uncontrolled hypertension or a history of significant - debilitating heart disease - radiotherapy within 1 month of trial start **Patient characteristics IG1/IG2/CG** Gender n Male 54/45/38 Female 58/74/66	**Intervention(s)** IG1 (CIA) A-DIC and cyclophosphamide Cyclophosphamide, 500 mg/m 2, on day I if they had an adequate bone marrow reserve (BMR). If they had an inadequate BMR, they received 40 mg/m2 on day 1, 200 mg/m 2 days I to 5, and 400 mg/m2 on day 1 of Doxorubicin, DTIC, and cyclophosphamide, respectively. IG2 (A-DIC-DACT) A-DIC and actinomycin D Actinomycin D, 1.2 mg/m 2 intravenously, on day 3. Patients assigned to the A-DIC-DACT arm with an inadequate BMR received Doxorubicin, 40 mg/m 2, DTIC, 200 mg/m 2, and actinomycin D, 1.0 mg/m2. A complete cycle of chemotherapy was repeated every 22 days, counting the first day of therapy as day 1. If on day 22 the WBC count was < 2,000 cells/mL, the platelet count was < 75,000 platelets/mL, or stomatitis had not been resolved, the next cycle of therapy was delayed. **Control**	**IG1/IG2/CG** Thrombocytopenia n moderate 6/7/7 severe 4/7/6 Leukopenia n moderate 18/20/16 severe 29/20/16 Nausea/vomiting/anorexia n moderate 37/37/30 severe 17/28/14 Alopecia n moderate 9/12/13 severe 21/23/11 Mucositis/ulcer/stomatitis n moderate 5/5/4 severe 2/9/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Age [y] Median(range) 56(22-87)/53(11-77)/56(16-88) Pathology review diagnosis Rhabdomyosarcoma 6/6/2 Hemangiosarcoma 2/2/8 Neurosarcoma 3/4/7 Leiomyosarcoma 24/29/21 Liposarcoma 6/7/3 Fibrosarcoma 2/5/1 Malignant fibrous histiocytoma 13/14/16 Synovial sarcoma 5/3/2	Doxorubicin and DTIC (A-DIC) **Dosing and treatment A-DIC** Doxorubicin, 60 mg/m2 on day 1 intravenously. DTIC was administered at a dose of 250 mg/m2 days I to 5 intravenously. Inadequate BMR patients on this arm received 45 mg/m2 on day 1 and 200 mg/m2 days I to 5 of Doxorubicin and DTIC, respectively. **Randomized patients** 112/119/104		
Blay et al. Randomized phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. European journal of cancer. 2014;50(6):1137-47.	**Region/Setting** This study was conducted at 22 investigational sites from United States of America (USA) (n = 8), France (n = 5), United Kingdom (UK) (n = 4), Germany (n = 2), Italy (n = 2) and Spain (n = 1). **Inclusion criteria** - age ≥18 year - initial pathological diagnosis of TRS of following subtypes: alveolar soft part sarcoma, angiomatoid fibrous histiocytoma, clear cell sarcoma, esmoplastic small round cell tumor, low grade endometrial stromal sarcoma, low grade fibromyxoid sarcoma, myxoid chondrosarcoma, MRCL and synovial sarcoma - confirmed translocation, unresectable locally advanced or metastatic progressive disease - measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.0); Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 0–2; adequate cardiac function [left ventricular ejection function (LVEF) within normal limits] - adequate hematological (hemoglobin P9 g/dl; absolute neutrophil count P1.5 10^9/l; platelets P100 10^9/l) - renal (serum creatinine 61.5 mg/dl) - hepatic function [bilirubin 6 upper limit of normal (ULN); aspartate aminotransferase (AST)/alanine aminotransferase (ALT) 6 2.5 ULN; alkaline phosphatase (AP)62.5 ULN (if total AP >2.5 ULN, AP liver fraction and/or gamma glutamyltransferase and/or 50-nucleotidase had to be 6ULN) and albumin >25 g/l] **Exclusion criteria** - Ewing's sarcoma and dermatofibrosarcoma protuberans	**Intervention(s)** Trabectedin 1.5 mg/m2 24-h intravenous (i.v.) infusion every 3 weeks (q3wk), with antiemetic and liver-protecting prophylaxis (dexamethasone 20 mg i.v.) 30 min before **Control** Doxorubicin 75 mg/m^2 i.v. q3wk, single agent, or at 60 mg/m^2 i.v. plus ifosfamide (range, 6–9 g/m^2) i.v. q3wk, with proper hydration and mesna administration **Randomized patients** 61/60	**National Cancer Institute-Common Toxicity Criteria for Adverse Events Grade3-4** ALT increase [%] 53.3/1.9 Anemia [%] 16.4/16.1 AST increase [%] 33.3/1.9 Leukopenia [%] 29.5/58.9 Neutropenia [%] 55/75 Thrombocytopenia [%] 16.4/14.3	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	- prior chemotherapy - prior lesion irradiation (if administered to a single target lesion) - malignancy within the previous 5 years (except for basal cell carcinoma or treated cervical carcinoma in situ) - relevant clinical conditions: active infection, active viral hepatitis or chronic liver disease, brain and/or leptomeningeal metastasis, congestive heart failure or angina pectoris, myocardial infarction within the previous year, uncontrolled arterial hypertension, arrhythmias or abnormal LVEF - Pregnant or breast-feeding women or patients not using appropriate contraceptive measures **Patient characteristics** Gender n(%) Male 36(59.0)/38(63.3) Female 25(41.0)/22(36.7) Age [y] Median(range) 47(19-47)/49(19-78) Tumor diagnosis (external pathology review) n(%) MRCL 23(37.3)/17(28.3) Other TRS 28(45.9)/20(33.3) Not confirmed 10(16.4)/23(38.3) Primary tumor site n(%) Lower extremity 39(63.9)/37(61.7) Trunk/abdominal wall 2(3.3)/10(16.7) Upper extremity 8(13.1)/1(1.7) Face and neck 2(3.3)/1(1.7) Other 10(16.4)/11(18.3) Extent of disease n(%) Metastatic 43(70.5)/47(78.3) Locally advanced 18(29.5)/13(21.7) No. of sites Median(range) 2(1–8)/2(1–5) Most common sites of disease n(%) Soft tissue 33(54.1)/33(55.0) Lung 29(47.5)/29(48.3) Lymph node 17(27.9)/11(18.3)			

Borden EC, Amato DA, Edmonson JH, Ritch PS, Shiraki M. Randomized comparison of doxorubicin and vindesine to doxorubicin for patients with metastatic soft-tissue sarcomas. Cancer. 1990;66(5):862-7.	**Region/Setting** cooperative group **Inclusion criteria** - age ≥14 years - histologically confirmed sarcoma reviewed by a member-institution pathologist - cell types: fibrosarcoma, spindle-cell sarcoma, synovial-cell sarcoma, malignant schwannoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, hemangiopericytoma, liposarcoma, other sarcomas, and sarcoma not otherwise specified (NOS).measurable residual, recurrent, or metastatic disease; - Lesions documented only by isotropic scans or ultrasound were not considered measurable. - ECOG performance status 0 to 2 - leukocytes > 4000/mm³ - platelets > 125,000/mm³ - hematocrit >*28* - creatinine <1.8, or blood-urea nitrogen <25 mg% - bilirubin <2 mg%. - Patients must have recovered from any major surgical procedures (elapsed time of at least 3 weeks) and have no serious concomitant illness that might be aggravated by therapy **Exclusion criteria** - prior chemotherapy or radiotherapy to the pelvis of more than 4000 cGy, or any radiotherapy within the previous 3 weeks unless given only to the long bones - Cardiac impairment, but patients with cardiac disease could be entered if the investigator considered the risk warranted. - Concomitant malignancy other than previously treated basal cell carcinoma of the skin or stage O-IIa squamous cell carcinoma of the cervix **Patient characteristics** NR	**Intervention(s)** Doxorubicin 70g/m² intravenously day 1 every 3 weeks plus vindesine 3 mg/m² intravenously day 1 every 3 weeks. The suggested maximum total doxorubicin dose on both arms was 550 mg/m². Once this total doxorubicin dose was exceeded on any of these regimens, the patient could be either given vindesine 3 mg/m² on alternate weeks, considered for surgery at the discretion of the investigator, or after discussion of the risks with the patient, continued on doxorubicin at a weekly schedule of 15 mg/m². Dose modification allowed weekly delays in scheduled therapy, if leukocytes were <3500 and/or platelets < 100,000, and dose reduction of 25%, if nadir leukocyte count was <1.5 X 10^9/1 or platelets <*75* x10^9/l. All patients were to receive chemotherapy for at least 21 days unless unacceptable toxicity necessitating termination of therapy developed. **Control** Doxorubicin 70 mg/m² intravenously day,1 every 3 weeks **Randomized patients** 171/ 176	Nausea/vomiting [%] Moderate 31/25 Severe 3/6 Hematologic [%] Moderate 24/28 Severe 32/29 Skin/mucosa membrane [%] ≥ moderate 23/16 Cardiac [%] Severe 3/3 life-threatening 1/2 Neurologic [%] ≥ moderate 10/7	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +
Bramwell VH, Mouridsen HT, Mulder JH, Somers R, Van Oosterom AT, Santoro A, et al. Carminomycin vs adriamycin in advanced soft tissue sarcomas: an EORTC randomized phase II study. European journal of cancer &	**Region/Setting** 13 European centers. **Inclusion criteria** - age15-80 years - histologically proven advanced and/or metastatic soft tissue sarcoma - measurable progressive disease - Karnofsky performance status of at least 50%.	**Intervention(s)** Carminomycin (CMM) 20 mg/m² was given as an i.v. bolus once every 3 weeks. The potential for cardiotoxicity was unknown and no specific recommendations were made about cumulative dose.	*Hematologic* Anemia [%] Grade3 0/10 Grade4 0/0 Leucopenia [%] Grade3 33/33 Grade4 5/10	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ?

clinical oncology. 1983;19(8):1097-104.	- adequate hepatic excretory function (serum bilirubin <50 µmol/l) and bone marrow reserve (leucocytes <4.0 X 10^9/l, platelets >100 X 10^9/l). **Exclusion criteria** - Recurrent tumor in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. - prior treatment with cytotoxic agents, - a previous or concomitant different malignant tumor, - congestive cardiac failure, - other serious concurrent disease, - central nervous system metastases. **Patient characteristics** Gender n(%) Male 20(61)/15(39) Female 13 (39)/ 23 (61) Age [y] Median(range) 54(28-74)/ 56.5 (22-73) Sites of disease locoregional only: 10/7 metastases only: 10/19 both 13/12 Metastases (n) Lung 14/25 Lever 6/3 Subcutaneous 5/1 lymph nodes 2/1 intra-abdominal 3/1	**Control** Doxorubicin 75 mg/m^2 was given as an i.v. bolus once every 3 weeks. Continuation of therapy beyond a cumulative dose of 550 mg/m^2 was not recommended but was left at the discretion of the individual investigator. The dose was reduced by 50% if the serum bilirubin was between 35 and 50 µmol/l, and the drug was discontinued if the bilirubin was above50 µ mol/l. If the WBC count was below 3.0 X 10^9/1 or the platelets below 100 X $10^{9/}$ 3 weeks after the last course, treatment was postponed for 1 week. At this time, if the WBC were between 2.0 and 2.9 X lo10^9/1 or platelets 75-99 X 10^9/l, therapy was continued at 50% dose. Counts below these levels precluded treatment. Adjustments for the nadir count in previous courses were WBC 2.0-2.9 X 10^9/1 or platelets 50-74 X 10^9/l, doxorubicin 75% dose, carminomycin 90% dose; WBC <2.0 X 10^9/1 or platelets <50 X 10^9/1, Doxorubicin 50% dose, carminomycin 75% dose. Dose escalation was not permitted. Patients went off-study if hematological toxicity delayed retreatment for more than3 weeks. **Randomized patients** 35/38	Granulocytopenia [%] Grade3 18/17 Grade4 18/17 Thrombocytopenia [%] Grade3 0/5 Grade4 0/5 *Non-hematologic Grade3* Nausea/vomiting [%] 13/9 Anorexia [%] 0/3 Bleeding [%] 3/3 Alopecia [%] 45/0	Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Bramwell VH, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verwey J, et al. Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. European journal of cancer & clinical oncology. 1987;23(3):311-21.	**Region/Setting** 18 European centers **Inclusion criteria** - renal (serum creatinine < 150 µmol/l) - hepatic excretory function (serum bilirubin < 20 µmol/l) - bone marrow reserve (leucocytes > 3.5 x 10^9/l and platelets > 100 x 10^9/l) - age 15-70 years, - histologically proven advanced and/or metastatic soft tissue - measurable progressive disease - WHO performance status of 0, 1 or 2. **Exclusion criteria** - Recurrent tumor in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. - Prior treatment with classical alkylating agents (excluding DTIC) - a previous or concomitant different malignant tumor - any serious concurrent disease - central nervous system metastases **Patient characteristics** Age [y] Median 47/49 Gender (female[%] Male 55/41 Female 45/59 Previous radiotherapy(%) 31/31 Previous chemotherapy(%) 43/41 Metastases(%) 91/91 Performance status 0-1(%) 76/79	**Intervention(s)** 24-h intravenous infusion Ifosfamide 5 g/m^2, repeated every 3 weeks. **Control** 24-h intravenous infusions Cyclophosphamide 1.5 g/m^2 repeated every 3 weeks. The total dose of each drug was diluted in 3 l of dextrose saline and infused over 24 hr. This was followed by 2 1l of dextrose saline over 12 hr. Mesna was administered as an i.v. bolus 400 mg/m² every 4 hr for 9 doses, commencing at the start of the oxazophosphorine infusion. *Dose modifications during treatment* *Reduction.* The initial dose was reduced by 25% for WBC nadir < 1.5 x10^9/l or platelet nadir< 50 x10^9/l during the previous cycle. Treatment was delayed by 1 week if the WBC was < 3 x10^9/l and/or platelets < 100 x10^9/l at the time scheduled for the next cycle. If treatment was delayed 3 weeks without hematological recovery, the patients went off study. Subsequent doses were reduced by 25% if treatment was delayed for 2 consecutive courses. Chemotherapy was not given if the serum creatinine was above 150 µmol/l at the time of retreatment. Escalation. If the WBC nadir > 2.0 x x10^9/l, platelet nadir > 100 x10^9/l, serum creatinine< 120 µmol/l, there was no microscopic or macroscopic hematuria and no cerebral symptoms, there was provision for dose	Nausea/vomiting [%] Grade3 14/24 Grade4 0/1 Diarrhea [%] Grade3 1.5/0 Grade4 0/0 Infection [%] Grade3 1.5/1.5 Grade4 0/0 Hemorrhage [%] Grade3 0/1.5 Grade4 0/0 Leucopenia [%] no previous chemo Grade3 33/31 Grade4 23/7 previous chemo Grade3 56/17 Grade4 13/4	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

		escalation of Cyclophosphamide to 2.5 g/m², and Ifosfamide to 8 g/ m² (maximum 12 g) in subsequent courses together with concomitant increases in Mesna to 600 mg/m²/dose. **Randomized patients** 67/68		
Bui-Nguyen B, Butrynski JE, Penel N, Blay JY, Isambert N, Milhem M, et al. A phase IIb multicenter study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. European journal of cancer. 2015;51(10):1312-20.	**Region/Setting** This study was conducted in 28 institutions **Inclusion criteria** - age ≥18 year - one of the following histologically confirmed advanced and/or metastatic STS of grades II/III and with progressive disease as assessed by the local investigator. All types eligible (excluding well-differentiated liposarcoma, embryonal rhabdomyosarcoma, Ewing tumors, gastro-intestinal stromal tumors and dermatofibrosarcoma protuberans - no previous chemotherapy - presence of measurable disease according to response evaluation criteria in solid tumors (RECIST 1.1); WHO performance status (PS) 0 or 1; adequate bone marrow (absolute neutrophils count (ANC)P 1.5 _ 109/L, hemoglobin (HB) P 9 g/dL or HB P 5.6 mmol/L, platelets (PLT) P 100 _ 109/L), hepatic (bilirubin 6 ULN, alanine aminotransferase (SGPT/ALT) and aspartate aminotransferase (SGOT/AST) 6 2.5 _ ULN) and renal (serum creatinine 6 1.5 _ ULN) functions, normal left ventricular ejection fraction (LVEF) assessed by echocardiography or multiple gated acquisition scan (MUGA), alkaline phosphatase 6 2.5 _ ULN and albumin P 25 g/L - no previous anti-cancer therapy including other systemic therapy, radiotherapy and surgery, within 28 days prior to treatment start. - mandatory use of an effective contraception for women of childbearing potential and men **Exclusion criteria** - central nervous system metastases - or leptomeningeal tumor spread - history of malignancies other than STS (except basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, resected incidental prostate cancer staged pT2 with Gleason score 66 and postoperative prostate-specific antigen (PSA) < 0.5 ng/ml) within the past 5 years	**Intervention(s)** IG1 Trabectedin 1.3 mg/m^2 3-h intravenous (i.v.) infusion on day 1 every 3 weeks every IG2 Trabectedin 1.5 mg/m^2 24-h intravenous (i.v.) infusion on day 1 every 3 weeks + IV bolus of 20mg dexamethasone 30min before trabectedin i.v. **Control** Doxorubicin 75 mg/m^2 infusion on day 1 every 3 weeks **Randomized patients IG1/IG2/CG** 47/43/43	**IG1/IG2/CG** SGPT Grade3-4 [%] 67.4/48.8/2.5 SGOT Grade3-4 [%] 34.8/21.9/0 GGT Grade3-4 [%] 39.1/48.8/7.5 Lymphopenia Grade3-4[%] 45.7/48.8/57.5 Leucopenia Grade3-4[%] 26.1/24.4/40	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Patient characteristics Gender n(%) Male 18(38.3)/20(46.5)18(41.9) Female 29(61.7)/23(53.5)/25(58.1) Age [y] Median(range) 60(34-84)/60(23-78)/60(24-77) Primary tumor site n(%) Neck 1(2.1)/0/0 Trunk 1(2.1)/5(11.6)/0 Thoracic 7(14.9)/3(7.0)/4(9.3) Abdominal 6(12.8)/9(20.9)/12(27.9) Lower extremity 8(17.0)/13(30.2)/8(18.6) Upper extremity 5(10.6)/3(7.0)/1(2.3) Visceral GU 1(2.1)/2(4.7)/3(7.0) Visceral GI 7(14.9)/3(7.0)/7(16.3) Visceral GYN 2(4.3)/0/0 Visceral other 1(2.1)/1(2.3)/3(7.0) Type of disease at the time of sampling n(%) Primary 25(53.2)/31(72.1)/30(69.8) Recurrent 3(6.4)/1(2.3)/3(7.0) Metastatic 9(19.1)/8(18.6)/6(14.0) Recurrent and metastatic 3(6.4)/0/1(2.3) Unknown 7(14.9)/3(7.0)/3(7.0) Tumor type (local pathology) n(%) Adipocytic 6(12.8)/10(23.3)/13(30.2) Fibroblastic 5(10.6)/3(7.0)/1(2.3) fibrohistiocytic tumors 3(6.4)/3(7.0)/1(2.3)1(2.1)/0/0 Smooth muscle tumors 18(38.3)/8(18.6)/14(32.6) Pericytic (perivascular) tumors 0/1(2.3)/0 Vascular tumors 1(2.1)/2(4.7)/0 Chondro-osseous tumors 0/1(2.3)/1(2.3) Tumors of uncertain differentiation 7(14.9)/7(16.3)/8(18.6) Undifferentiated sarcoma 4(8.5)/7(16.3)/5(11.6) Other 3(6.4)/1(2.3)/0			
Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, et al. First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized	**Region/Setting** This study was conducted in 31 sites in Australis, Hungary, India, Romania, Russia, Ukraine and the United States. **Inclusion criteria** - patients age 15-80 years (US sites) or 18-80 years (non-US sites) - locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade	**Intervention(s)** Aldoxorubicin 350 mg/m2 as a 30min i.v. on day 1 of each 21-day cycle for up to 6 cycles administration **Control** Doxorubicin 75 mg/m^2 as a 30min	*Hematologic* Anemia Grade3 or 4 [%] 16.9/20.0 Neutropenia Grade3 or 4 [%] 28.9/12.5 Leukopenia Grade3 or 4 [%]	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: -

Clinical Trial. JAMA oncology. 2015;1(9):1272-80.	- ECOG performance status 0 to 2 - life expectancy greater than 12 weeks - disease measurable by Response Evaluation Criteria in Solid Tumors, version 1.1 **Exclusion criteria** - prior adjuvant or neoadjuvant chemotherapy if a tumor recurred within 12 months since the last measurement - prior chemotherapy for advanced disease - prior treatment with doxorubicin or pegylated liposomal doxorubicin of more than 3 cycles or greater than 225 mg/m2 cumulative dose, palliative surgery or radiation treatment less than 4 weeks before randomization, or exposure to any investigational agent within 30 days of randomization - evidence or diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma, Ewing sarcoma, Kaposi sarcoma, mixed mesodermal tumor, clear-cell sarcomas, or unresectable low-grade liposarcomas, - ongoing infection, or either current or past history of clinically significant cardiac events. **Patient characteristics** Gender n(%) Male 38(46)/18(45) Female 45(54)/22(55) Age [y] Median(range) 54(21-77)/54(23-77) Tumor histopathologic subtype n(%) Leiomyosarcoma 28(34)/14(35) Liposarcoma 13(16)/6(15) Fibrosarcoma 12(14)/4(10) Synovial sarcoma 5(6)/4(10) Other 25(30)/12(30) Prior adjuvant or neoadjuvant chemotherapy n(%) Yes 8(10)/5(12) No 75(90)/35(88)	i.v. on day 1 of each 21-day cycle for up to 6 cycles **Randomized patients** 86/40	9.6/5.0 Febrile neutropenia Grade3 or 4 [%] 14.5/17.5 Thrombocytopenia Grade3 or 4 [%] 8.4/5.0 *Non-hematologic* Stomatitis Grade3 or 4 [%] 6/2.5 Fatigue Grade3 or 4 [%] 3.6/0 Asthenia Grade3 or 4 [%] 2.4/2.5 Mucosal inflammation Grade3 or 4 [%] 4.8/0 Abdominal pain Grade3 or 4 [%] 2.4/5.2	Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Demetri GD, Le Cesne A, Chawla SP, Brodowicz T, Maki RG, Bach BA, et al. First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: a phase I/II open-label and double-blind study. European journal of cancer. 2012;48(4):547-63.	**Region/Setting** This study was conducted at 19 centers in the United States, Belgium, France, Austria and Netherlands. **Inclusion criteria** - age ≥18 years - ECOG performance status 0 or 1 - pathologically confirmed metastatic - locally advanced/unresectable or recurrent FNCLCC Grade 2 or 3 soft tissue sarcoma with at least one measurable lesion per RECIST **Exclusion criteria** - any prior chemotherapy, radiotherapy or target lesion, uncontrolled CNS disease, concurrent other malignancy, infection requiring systemic anti-infective treatment within the prior 14 days - uncontrolled cardiovascular disease within the prior 12 months - left ventricular ejection fraction below the lower limit of normal - hepatitis or HIV - major surgery within the prior 28 days - minor surgery within the prior 7 days - pregnancy and breast feeding - Patients with alveolar soft part sarcoma, clear cell sarcoma, chondrosarcoma, desmoid tumor, desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, Ewing sarcoma/primitive neuroectodermal tumor, gastrointestinal stroma tumor, Kaposi sarcoma, mesothelioma, mixed mesodermal tumor, neuroblastoma or osteosarcoma **Patient characteristics** Gender n(%) Male 42(49)/17(40) Female 44(51)/25(60) Age [y] Median(range) 57.5(23-88)/56.5(32-82) Target lesion sites n(%) Lung parenchyma 46(53)/16(38) Other 23(27)/15(36) Pelvis 23(27)/9(21) Liver 21(24)/8(19) Retroperitoneum 15(17)/5(12) Peritoneum 8(9)/6(14) Primary histologic type n(%)	**Intervention(s)** Conatumumab 15mg/kg plus Doxorubicin 75mg/m2 every 3 weeks for up to 6 cycles **Control** Placebo plus doxorubicin 75mg/m2 every 3 weeks for up to 6 cycles **Randomized patients** 86/42	Alopecia [%] Grade3 2/3 Grade4 0/0 Fatigue[%] Grade3 8/3 Grade4 0/0 Neutropenia[%] Grade3 13/8 Grade4 15/35 Anemia**[%]** Grade3 15/10 Grade4 2/5 Stomatitis**[%]** Grade3 5/0 Grade4 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Leiomyosarcoma 30(35)/15(36) Liposarcoma 15(17)/7(17) Well-differentiated liposarcoma 3(3)/2(5) Dedifferentiated liposarcoma 7(8)/2(5) Myxoid liposarcoma 4(5)/2(5) Pleomorphic liposarcoma 1(1)/1(2) Malignant peripheral nerve sheath tumor 4(5)/7(17) Fibrohistiocytic 6(7)/4(10) Fibroblastic/myofibroblastic 7(8)/1(2) Tumors of uncertain differentiation 5(6)/3(7) Vascular 2(2)/2(5) Skeletal muscle 2(2)/0(0) Other 15(17)/3(7) <u>FNCLCC grade n(%)</u> Grade 2 29(34)/19(45) Grade 3 55(64)/21(50) Unknown 2(2)/2(5) <u>No. of sites target lesions n(%)</u> 1 30(35)/22(52) 2 35(41)/9(21) 3 11(13)/7(17) >5 4(5)/1(2) <u>No. of sites of non-target lesions</u> 0 31(36)/14(33) 1 32(37)/16(38) 2 14(16)/10(24) 3 5(6)/1(2) 4 2(2)/1(2) >5 2(2)/0(0)			
Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. Journal of clinical oncology : official journal of the American Society of Clinical On-	**Region/Setting** This study was conducted at 85 sites in four countries. **Inclusion criteria** - age ≥15 years - unresectable, locally advanced or metastatic liposarcoma or leiomyosarcomas - previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus one or more additional cytotoxic chemotherapy regimen(s) - adequate bone marrow, renal and liver functions - ECOG performance status 1 or lower **Exclusion criteria** - known CNS metastasis, myocardial infarct within 6 months	**Intervention(s)** Trabectedin dose of 1.5 mg/m2 as a 24-hour i.v. infusion on day one of each 21-day treatment cycle after premedication with dexamethasone. **Control** Dacarbazine dose of 1 g/m2 as a 20- to 120-minute IV infusion on day 1 of each 21-day treatment cycle **Randomized patients**	<u>Neutropenia n(%)</u> Grade3 70(21)/17(11) Grade4 56(16)/15(10) <u>Alanine aminotransferase increase n(%)</u> Grade3 85(25)/1(1) Grade4 4(1)/0 <u>Anemia n(%)</u> Grade3 49(14)/17(11) Grade4 0/1(1) <u>Aspartate aminotransferase increase n(%)</u>	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

cology. 2016;34(8):786-93.	before enrollment - New York Heart Association class II or greater heart failure **Patient characteristics** Gender n(%) Male 107(31)/47(27) Female 238(69)/126(73) Age [y] Median(range) 57(18-81)/56(17-79) Primary histologic type n(%) Leiomyosarcoma 252(73)/126(73) Uterine 134(39)/78(45) Nonuterine 118(34)/48(28) Liposarcoma 93(27)/47(27) Myxoid +/- round cell 38(11)/19(11) Pleomorphic 10(3)/3(2) Dedifferentiated 45(13)/25(15)	345/173	Grade3 40(12)/0 Grade4 4(1)/0 Thrombocytopenia n(%) Grade3 27(8)/15(10) Grade4 31(9)/13(8)	
Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1993;11(7):1269-75.	**Region/Setting** NR **Inclusion criteria** - histologically confirmed nonosseous sarcomas, which were residual, recurrent, or metastatic and measurable by physical examination, x-rays, or computed tomographic scanning. - leukocyte, platelet, and hematocrit levels of ≥4,000/μ*L,* ≥125,000/μL, and ≥28%, respectively. - a serum creatinine level ≤1.5 mg/dL, serum bilirubin ≤2 mg/dL, - ECOG performance status 0, 1, or 2 - Patients had recovered from any recent surgery and were free of significant infection or other illness that might be aggravated by chemotherapy. **Exclusion criteria** - patients with New York Heart Association class III or IV cardiac disease - patients who had received prior chemotherapy, as were patients with previous pelvic irradiation (> 40 Gy). - patients with a history of other malignancy, excepting previously treated basal cell skin carcinoma or stage 0 to IIA squamous cell cervical carcinoma. **Patient characteristics** Among 262 assessable patients, 145 (55%) were male and 117 (45%) were female, with a median age of 57 years (range, 20 to	**Intervention(s)** IG1: ifosfamide 750 mg/m² daily for 2 days plus doxorubicin 30 mg/m² daily for 2 days IG2: mitomycin 8 mg/m², doxorubicin 40 mg/m ²; and cisplatin 60 mg/m². **Control** doxorubicin 80 mg/m² Each regimen was administered at 3-week intervals and the use of ifosfamide (regimen B) was accompanied by intravenous (IV) mesna 750 mg/m² immediately preceding and then 4 and 8 hours after ifosfamide administration. All of the chemotherapy could be administered in the clinic by rapid IV infusion, excepting regimen B, which required infusion of ifosfamide in the hospital over 4 hours each day accompanied by deliberate IV hydration (300 mL/h) beginning 3 hours before each treatment cycle and for 3 days (at	*Hematologic* Leukopenia Grade 4 [%] 9/5/44 *Non-hematologic* Myelosuppression Grade ≥3 [%] 80/55/53 Gastrointestinal toxicity severe or worse [%] 18.2/16.7/6.7	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: - Other source of bias: +

	83). White patients represented 82%, blacks 14%, and other races 3%, and in 1% of our participants, racial background was unknown. Study population was distributed according to ECOG performance status scores as follows: 0, 43%, 1, 42%, and 2, 15%. Leiomyosarcoma, with 44% of the cases, was by far the most common histologic type. Malignant fibrous histiocytoma (14%), synovial sarcoma (8%), neurofibrosarcomas (5%), and liposarcoma (6%) were also relatively common tumor types in this study.	100 mL/h) after each day-1 ifosfamide infusion. **Randomized patients** 94/90/95		
Gelderblom H, Blay JY, Seddon BM, Leahy M, Ray-Coquard I, Sleijfer S, et al. Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: an European Organi-sation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomized phase II and pharmacogenetic study. European journal of cancer. 2014;50(2):388-96.	**Region/Setting** This study was conducted at 20 institutions in Europe and USA from October 2006 to August 2008. **Inclusion criteria** - locally advanced or metastatic intermediate to high-grade STS not amenable to curative treatment - proven Response Evaluation Criteria in Solid Tumors (RECIST) progression in the 6 months before study entry - no previous chemotherapy for metastatic disease - at least 60 years of age, or at least 18 years of age if nonamenable to intensive combination chemotherapy - World Health Organization (WHO) performance status <2 - clinically normal cardiovascular function - adequate bone marrow, hepatic and renal function - pathology material available for mandatory central review. **Exclusion criteria** NR **Patient characteristics** Histology of soft tissue sarcoma n(%) Adipocytic 10(12.7)/9(23.1) Fibroblastic 9(11.4)/3(7.7) Fibrohistiocytic 7(8.9)/4(10.3) Smooth muscle 29(36.7)/15(38.5) Skeletal muscle 2(2.5)/1(2.6) Vascular 3(3.8)/0 Uncertain different 4(5.1)/1(2.6) Malignant Fibrous Histiocytoma 4(5.1)/1(2.6) Malignant solitary fibrous 2(2.5)/0 Undifferentiated NOS 6(7.6)/3(7.7) Other 2(2.5)/2(5.1) Unknown 1(1.3)/0	**Intervention(s)** Brostallicin 10 mg/m2 by 10-min IV infusion on day 1 of a 3 weekly cycle. **Control** Doxorubicin 75 mg/m2 by IV bolus over 5–20 min on day 1, of a 3 weekly cycle **Randomized patients** 79/39	Neutropenia Grade3-4[%] 67/95 Systolic dysfunction Grade 2-3 [%] 0/11 Alopecia Grade2-3 [%] 17/61 Mucositis Grade2-3 [%] 0/18 Tumor pain Grade3-4 [%] 14/3	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: - Selective reporting: + Other source of bias: +
Hensley ML, Miller A, O'Malley DM, Mannel RS, Behbakht K, Bakkum-Gamez JN, et al.	**Region/Setting** NR	**Intervention(s)** Day 1 Gemcitabine 900mg/m2 i.v. over 90	Neutropenia [%] Grade3 15/14 Grade4 7/9	**Study type** RCT

Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(10):1180-5.	**Inclusion criteria** - advanced or recurrent uLMS with documented disease progression - measurable disease as defined by RECIST 1.1 - Gynecologic Oncology Group (GOG performance status of 0, 1, or 2 - free of active infection and recovered from effects of recent surgery or radiotherapy - adequate bone marrow function (platelet count ≥ 100,000/uL; absolute neutrophil count ≥ 1,500/uL), renal function (creatinine ≤ 1.5X institutional upper limit of normal [ULN] - hepatic function (bilirubin within normal range; AST and alkaline phosphatase ≤ 2.5X ULN) - neurologic function (grade ≤ 1, no history of transient ischemic attack or stroke, or CNS hemorrhage within the past 6 months) - baseline urine protein:creatinine ratio less than 1 - international normalized ratio ≤1.5X the institutional ULN (or an in-therapeutic-range international normalized ratio, usually between 2 and 3, if a patient was being given a stable dose of therapeutic warfarin - Histologic confirmation of the original primary tumor **Exclusion criteria** - prior cytotoxic chemotherapy for management of uterine sarcoma - prior VEGF-pathway-targeted agent - prior treatment with a multikinase inhibitor such as pazopanib, sorafenib, or sunitinib - prior therapy with docetaxel or gemcitabine - major surgery or significant traumatic injury within 28 days before study entry or a history of abdominal fistula or perforation within the past 12 months - current serious nonhealing wound, ulcer, or bone fracture - blood pressure ≥ 140/90 mmHg - history of myocardial infarction or unstable angina within 6 months of the first date of bevacizumab or placebo therapy - history of New York Heart Association grade 2 or worse congestive heart failure - significant peripheral vascular disease, - history of cerebrovascular accident, transient ischemic attack, or subarachnoid hemorrhage within 6 months of the first date of bevacizumab or placebo therapy - history of pulmonary embolism or deep vein thrombosis within the 6 months before enrollment. **Patient characteristics** Age [y] Median(range)	min + Bevacizumab i.v.15mg/kg over 90 min Day 8 Gemcitabine 900mg/m2 i.v. over 90 min and Docetaxel 75 mg/m2 IV over 60 min **Control** Day 1 Gemcitabine 900mg/m2 i.v. over 90 min + Placebo i.v. Day 8 Gemcitabine 900mg/m2 i.v. over 90 min and Docetaxel 75 mg/m2 IV over 60 min **Randomized patients** 53/54	Thrombocytopenia [%] Grade3 25/21 Grade4 11/7 Anemia [%] Grade3 13/33 Grade4 0/0 Thromboembolic [%] Grade3 6/6 Grade4 4/2	**Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	54.8(28.9-69.1)/56.2(44.2-75.6) Performance status n(%) 0 (asymptomatic) 41(77.4)/38(70.4) 1 (fully ambulatory) 11(20.8)/15(27.8) 2 (in bed < 50% of the time) 1(1.9)/1(1.9)			
Judson I, Radford JA, Harris M, Blay JY, van Hoesel Q, le Cesne A, et al. Randomized phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. European journal of cancer. 2001;37(7):870-7.	**Region/Setting** Multicenter study **Inclusion criteria** - histologically confirmed diagnosis of one of the following sarcoma types- malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, including hemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, miscellaneous sarcoma including mixed mesodermal tumors of the uterus - no prior chemotherapy; - at least one dimensionally measurable lesion of ≥ 2.5 cm in diameter or ≥ 2 cm in the case of lung metastases and progressive disease in the previous 4 weeks - World Health Organization (WHO) performance status ≤ 2 - cardiac ejection fraction within normal limits - adequate bone marrow function, i.e. hemoglobin ≥10 g/l - neutrophils ≥ 2.0 x 10^9/l platelets ≥ 100 x 10^9/l - adequate organ function as defined by creatinine ≤ 140 µmol/l and bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 1.25 x upper limit of normal unless related to cancer - metastatic a disease or locally advanced disease not amenable to curative surgery - age ≥18 years; - use of adequate contraception **Exclusion criteria** - the following histologies: malignant mesothelioma, chondrosarcoma, neuroblastoma, Ewing's sarcoma, embryonal rhabdomyosarcoma; - patient pregnant or breast feeding; - cardiac disease NYHA class II or greater; - uncontrolled infection; - radiotherapy in the last 6 weeks or to >35% of haemopoietic sites; - symptomatic brain metastases; - any other active malignant tumor apart from basal or squamous, cell carcinoma of skin or cervical carcinoma in situ **Patient characteristics** Gender n(%)	It was intended that patients would receive a total of six cycles in view of the possible cardiotoxicity of doxorubicin. **Intervention(s)** CAELYX® was administered as a 1 h i.v. infusion at 50 mg/m² every 4 weeks. Dose modifications for toxicity were allowed: for CAELYX® from 50 mg/m² down to 37.5 or 25 mg/m² **Control** Doxorubicin was given at a dose of 75 mg/m² as a 5 min i.v. bolus injection every 3 weeks. Dose modifications for toxicity were allowed: doxorubicin from 75 mg/m² down to 60 or 45 mg/m², i.e. by one dose level or two dose levels in each case. **Randomized patients** 50/44	*Hematologic[%]* Leukopenia Grade3 2/47 Grade4 0/12 Neutropenia Grade3 4/30 Grade4 2/47 Thrombocytopenia Grade3 0/2 Grade4 0/0 Hemoglobin Grade3 4/5 Grade4 6/0 *Non-hematologic[%]* Anorexia Grade3 2/5 Grade4 0/0 Any infection Grade3 4/7 Grade4 0/0 Alopecia Grade3 2/21 Grade4 0/0 Palmar-plantar erythrodysesthesia Grade3 18/0 Grade4 2/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Male 26(52)/20(44) Female 24(48)/25(56) Age [y] Median(range) 52(19-80)/52(27-77) WHO performance n(%) Status 0 20(40)/12(27) Status 1 23(46)/28(62) Previous surgery n(%) No 8(16)/4(9) Biopsy only 3(6)/3(7) Previous radiotherapy No 36(72)/31(69) Previous chemotherapy n(%) No 48(96)/44(98) Yes – (neo)adjuvant 2(4)/1(2)			
Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomized controlled phase 3 trial. The Lancet Oncology. 2014;15(4):415-23.	**Region/Setting** This study was conducted at 38 hospitals in ten countries (Belgium, Canada, Denmark, France, Germany, Netherlands, Slovakia, Spain, Switzerland, UK) **Inclusion criteria** - locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma - age 18–60 years - WHO performance status of 0 or - histological evidence of high-grade soft-tissue sarcoma (grades 2–3) according to the Federation Nationale des Centres de Lutte Contre le Cancer grading system 15 when applicable and radiological evidence of measurable unresectable or metastatic disease progression within 6 weeks before treatment according to RECIST 1.0 - absolute neutrophil count more than 2 × 10^9 cells per L, more than 100 × 10^9 platelets per L - serum creatinine of 120 µmol/L or less or calculated creatinine clearance (Cockroft and Gault method) more than 65 mL/min - two functioning kidneys, bilirubin 30 µmol/L or less, and albumin more than 25 g/L. - normal left ventricular ejection fraction by multiple gated acquisition scan or echocardiogram **Exclusion criteria**	**Intervention(s)** Doxorubicin 25 mg/m² per day on days 1–3 and Ifosfamide (2·5 g/m² per day, days 1–4) plus mesna (0·5 g/m² by intravenous bolus before ifosfamide, 1·5 g/m² concurrent with ifosfamide, and 1 g/m² orally 2 h and 6 h after completion of ifosfamide infusion), followed by pegfi lgrastim (6 mg subcutaneously, day 5 Every 3 weeks, max. 6 cycles **Control** Doxorubicin 75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion Every 3 weeks, max. 6 cycles **Randomized patients** 227/228	Grade3-4 [%] Neutropenia 42/37 Leucopenia 43/18 Febrile neutropenia 46/13 Anemia 35/4 Thrombocytopenia 33/<1	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

	- gastrointestinal stromal tumor, mixed mesodermal tumor, chondrosarcoma, malignant mesothelioma, neuroblastoma, osteosarcoma, Ewing's sarcoma, desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, and alveolar soft part sarcoma - severe illness (e.g., psychosis or previous history of cardiovascular disease) - symptomatic or known CNS metastases - previous or concurrent second primary malignant tumors (except adequately treated in situ carcinoma of cervix or basal cell carcinoma) - prior radiotherapy to the sole available index lesion - prior chemotherapy for advanced disease - previous adjuvant chemotherapy (preoperative or postoperative) if disease progression occurred within 6 months of completion **Patient characteristics** Gender n(%) Male 114(50)/103(45) Female 113(50)/125(55) Age [y] Median(range) 47(39-54)/48(41-55) Histological type (local diagnosis) n(%) Liposarcoma 31(14)/26(11) Leiomyosarcoma 59(26)/54(24) Synovial sarcoma 26(11)/38(17) Other 111(49)/110(48) Histological grade (local diagnosis) n(%) Low (but clinically high) 7(3)/5(2) Intermediate 103(45)/103(45) High 109(48)/118(52) Unknown 8(4)/2(1)			
PALETTE study Coens C, van der Graaf WT, Blay JY, Chawla SP, Judson I, Sanfilippo R, et al. Health-related quality-of-life results from PALETTE: A randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has	**Region/Setting** This study was conducted in 72 institutions, across 13 countries **Inclusion criteria** - age ≥ 18 years - metastatic soft-tissue sarcoma - progressive disease according to RECIST 1.0 during the 6 months before start of study drug or 12 months for previous adjuvant treatment - at least one regimen containing anthracycline and a maximum of four previous lines of systemic therapy for metastatic disease (no more than two lines of combination regimens) - WHO performance status of 0 or 1	**Intervention(s)** Pazopanib 800 mg once daily Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death **Control** Placebo using a central, stratified, permuted block procedure Treatment continued until disease progression, unacceptable toxicity,	*Non-hematologic* Fatigue [%] Grade3 13/5 Grade4 1/1 Hypertension [%] Grade3 7/3 Grade4 0/0 Nausea [%] Grade3 3/2 Grade4 0/0 Diarrhea [%] Grade3 5/1	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: +

progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer. 2015;121(17):2933-41. Van Der Graaf WTA, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomized, double-blind, placebo-controlled phase 3 trial. The Lancet. 2012;379(9829):1879-86.	- absence of CNS metastases and leptomeningeal metastases - adequate bone marrow function (absolute neutrophil count ≥1·5×10⁹ cells/L, platelets ≥100×10⁹ per L, hemoglobin ≥9 g/dL) - renal function (serum creatinine ≤1·5 mg/dL, or, if >1·5 mg/dL, calculated creatinine clearance >50 mL/min) - hepatic function (bilirubin ≤1·5×upper limit of normal, aspartate aminotransferase and alanine aminotransferase ≤2·5×upper limit of normal) - cardiac function (based on the institution's lower limit of normal [left ventricular ejection fraction assessed by multigated acquisition scan or echocardiogram] - normal 12 lead electrocardiogram [no prolongation of corrected QT interval >480 ms] - no history of any of the following in the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease class III or IV congestive heart failure, as defined by the New York Heart Association - Blood pressure <150/90 mm Hg, spontaneously or controlled with antihypertensive medication **Exclusion criteria** - all types of adipocytic sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumors, primitive neuro ectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, and mixed mesodermal tumors of the uterus - cerebrovascular accident, pulmonary embolism, or untreated deep venous thrombosis in the past 6 months **Patient characteristics (Japanese Population)** Gender n(%) Male 18(58)/7(44) Female 13(42)/9(56) Age [y] Mean(SD) 53.5(17.14)/50.1(16.26) Histological type (local diagnosis) n(%) Leiomyosarcoma 8(26)/5(31) Undifferentiated Sarcoma 4(13/0 Undifferentiated pleomorphic sarcoma 4(13)/0 Alveolar soft part sarcoma 3(10)/2(13) Solitary fibrous tumor 3(10)/0 Synovial sarcoma 2(6)/3(19) Epithelioid sarcoma 2(6)/1(6) Desmoplastic small cell tumor 1(3)/0	withdrawal of consent, or death **Randomized patients** 246/123 Japanese Population 31/16	Grade41 0/0 Anorexia [%] Grade3 6/0 Grade4 0/0	Other source of bias: +

	Extra-renal cell rhabdoid tumor 1(3)/0 Clear cell sarcoma 0/2(13) Myxofibrosarcoma 0/2(13) Malignant peripheral nerve sheath tumor 0/1(6) Other soft tissue sarcoma histologies 3(10)/0			
Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomized, open-label, phase 2 study. The Lancet Oncology. 2015;16(4):406-16.	**Region/Setting** This study was conducted in Japan. **Inclusion criteria** - translocation-related sarcoma: myxoid round-cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, extraskeletal Ewing sarcoma/ primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, low-grade fibro myxoid sarcoma, alveolar soft part sarcoma, clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small-round cell tumor, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, giant cell fibroblastoma, or endometrial stromal sarcoma - renal and liver functions (neutrophil count of ≥1500 cells per μL, hemoglobin of ≥9·0 g/dL, platelet count of ≥10 × 104 cells per μL, albumin of ≥2·5 g/dL, total bilirubin of ≤1·5 mg/dL, aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, and alkaline phosphatase of ≤2·5 times of upper limit of normal, and creatinine clearance [measured or calculated] of ≥30 mL/min) **Exclusion criteria** - surgery within 28 days before enrolment - chemotherapy or radiotherapy within 21 days before enrolment - severe concurrent diseases - clinically significant cardiovascular conditions - pregnancy, breastfeeding women or fertile patients not using appropriate contraceptive measures **Patient characteristics** <u>Gender n(%)</u> Male 21(57)/22(61) Female 16(43)/14(39) <u>Age [y] Median(range)</u> 39(32-56)/39(31-50) <u>Histological type (central pathology review) n(%)</u> Myxoid liposarcoma/round-cell liposarcoma 14(38)/10(28) Synovial sarcoma 7(19)/11(31) Mesenchymal chondrosarcoma 2(8)/3(8) Extraskeletal Ewing sarcoma/primitive neuroectodermal 3(8)/2(6) Alveolar soft part sarcoma 3(8)/2(6) Alveolar rhabdomyosarcoma 2(5)/3(8)	**Intervention(s)** Trabectedin (lyophilised powder for injection, standard starting dose of 1·2 mg/m²; Taiho Pharmaceutical Co., Ltd, Tokyo, Japan), diluted in at least 500 mL of normal saline, via a central venous line over 24 h from on day 1 of a 21-day cycle prophylaxis (dexamethasone 20 mg i.v.) 30 min before **Control** Best supportive care, no anti-tumor therapy but treatment to relieve symptoms. **Randomized patients** 39/37	<u>Nausea [%]</u> Grade3 8/0 Grade4 0/0 <u>Decreased appetite [%]</u> Grade3 8/0 Grade4 0/0 <u>Anemia [%]</u> Grade3 19/3 Grade4 0/0 <u>Febrile neutropenia [%]</u> Grade3 11/0 Grade4 3/0 <u>Hyperglycemia [%]</u> Grade3 8/0 Grade4 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Clear cell sarcoma 1(3)/4(11) Extraskeletal myoxoid chondrosarcoma 2(5)/0 Dermatofibrosarcoma protuberans 1(3)/0 Angiomatoid fibrous histiocytoma 1(3)/0 Desmoplastic small-round-cell tumor 0/1(3) Histological grade n(%) Low 2(5)/0 Median 8(22)/9(25) High 23(62)/24(67) Not assessed or unknown 4(11)/3(8) Site by independent radiological image assessment n(%) Lung 25(68)/20(56) Peritonea 12(32)/13(36) Lymph node 11(30)/9(25) Pleura 11(30)/7(19) Muscle 9(24)/9(25) Bone 11(30)/4(11) Others 10(27)/7(19)			
Lorigan P, Verweij J, Papai Z, Rodenhuis S, Le Cesne A, Leahy MG, et al. Phase III trial of two investigational schedules of ifosfamide compared with stand-ard-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. Journal of clinical on-cology : official journal of the American Society of Clinical Oncology. 2007;25(21):3144-50.	**Region/Setting** This study was conducted 40 institutions **Inclusion criteria** - 16-65 years - histologically confirmed advanced or metastatic soft tissue sar-coma - measurable disease - WHO performance status <2 - no prior chemotherapy - adequate renal, hepatic and bone marrow function (measured creatinine clearance >70 mL/min, albumin >25 g/L, biliru-bin<30umol/L, neutrophils>2 x 10^9/L, platelets>100 X 10^9/L) **Exclusion criteria** **-** Ewing sarcoma, chondrosarcoma, osteosarcoma and embryonal rhabdomyosarcoma - a history of other malignancy - prior radiotherapy to a solitary measurable lesion - active cardiac disease **Patient characteristics IG1/IG2/CG** Gender n(%) Male 60(55)/66(61.7)/57(51.8) Female 49(45)/41(38.3)/53(48.2) Age [y] Median(range)	**Intervention(s)** IG1 Ifosfamide short infusion (Ifos 3*3): a bolus ofmesna0.6g/m2 followed by ifosfamide 3g/m2 and mesna1.5g/m2 in 1,000 mL of saline 0.9% over 4 hours, followed by mesna 1.2 g/m2 either orally at 2 and 6 hours, or intravenously at 4 and 8 hours, repeated daily for 3 days IG2 Ifosfamide 9 g/m2 infusion (Ifos 9): a bolus of mesna 0.6 g/m2 followed by ifosfamide 3 g/m2 in 3 L normal saline with mesna 3 g/m2 infused intravenously over 24 hours, re-peated for 3 days in total followed by either a further 1.8 g/m2 of mesna in1Lof dextrose saline over 12 hours, or 1.2 g/m2 mesna orally at 0, 2, and 6 hours Patients receiving ifosfamide also received sodium bicarbonate 150 mmol intravenously daily during the 3-day infusion.	IG1/IG2/CG Leukopenia [%] Grade 3 29.5/29.4/27.3 Grade 4 28.6/27.5/6.4 Granulocytopenia [%] Grade 3 8.6/13.7/20 Grade 4 51.4/49/33.6 Anemia [%] Grade 3 8.6/14.7/8.2 Grade 4 2.9/2.9/1.8 Febrile neutropenia [%] Grade 3 18.1/2019.6/9.1 Grade 4 NR Alopenia [%] Grade 3 22.9/16.7/20.9 Grade 4 NR	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	53/23-65)/51(21-68)/50(20-65) Liver involvement n(%) 27(24.8)/25(23.4)/25(22.7) Histological type (central pathology review) n(%) Leiomyosarcoma 35(32.1)/33(30.8)/34(30.9) Synovial 8(7.3)/10(9.3)/10(9.1) Other 66(60.6)/64(59.9)/66(60) Histological grade n(%) I 20(18.3)/15(14)/13(11.8) II 38(34.9)/43(40.2)/45(40.9) III 51(46.8)/49(45.8)/52(47.3) Site n(%) Head and neck 6(5.5)/6(5.6)/1(0.9) Trunk 6(5.5)/5(4.7)/5(4.5) Thorax 7(6.4)/9(8.4)/8(7.3) Retroperitoneal 17(15.6)/19(17.8)/27(24.5) GI 15(13.8)/9(8.4)/12(10.9) Lower limp 33(30.3)/30(28)/33(30) Upper limp 9(8.3)/11(10.3)/8(7.3) Gynecologic 11(10.1)/12(11.2)/12(10.9) Other 5(4.5)/6(5.6)/4(3.7)	**Control** Doxorubicin 75 mg/m2 by intravenous bolus every 3 weeks **Randomized patients** 109/107/110		
Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, 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 [corrected]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2755-63.	**Region/Setting** This study was conducted at eight Sarcoma Alliance for Research through Collaboration sites in the United States. **Inclusion criteria** - diagnosis of soft tissue sarcoma - age >10 years - recurrent or progressive disease by examination or imaging studies - lack of evidence that a second cancer, was the disease requiring therapeutic intervention - zero to three prior chemotherapy regimens - disease measurable per RECIST - ECOG performance status ≤ 2 - peripheral neuropathy grade ≤ 1 by NCI CTCAE version 3.0 - at least 3 weeks since prior radiation or cytotoxic chemotherapy - neutrophil count ≥1,000/uL, hemoglobin ≥8.0 g/dL; platelet count ≥100,000/uL; total bilirubin ≤ institutional upper limit of normal; ALT and AST ≥5 x the institutional upper limit of normal; alkaline phosphatase ≤ 2.5X the institutional upper limit of normal; serum creatinine ≤ 2.0 mg/dL - negative serum pregnancy test in women of child-bearing poten-	**Intervention(s)** Gemcitabine-docetaxel arm, the gemcitabine dose was a fixed dose rate 900 mg/m2 intravenous infusion during 90 minutes days 1 and 8, with docetaxel 100 mg/m2 intravenously during 60 minutes day 8, every 21 days + Filgrastim 5 ug/kg subcutaneously daily for 7 to 10 days, or pegfilgrastim 6 mg subcutaneously once, was administered to all patients starting on day 9 to 10 of each cycle **Control** Gemcitabine fixed dose rate of 10 mg/m2/min10 during a 120-minute intravenous infusion, at 1,200 mg/m2 days 1 and 8, every 21 days + Filgrastim 5 ug/kg subcutaneously daily for 7 to 10 days, or pegfilgrastim 6 mg subcutaneously once,	Neutrophils grade3-4 [%] 16/28 Hemoglobin grade 3 [%] 7/13 Blood transfusion [%] 16/20 Platelets grade3-4[%] 40/35 Platelet transfusion [%] 15/11	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	tial - use of effective contraception while on study **Exclusion criteria** - GI stromal tumor and Kaposi sarcoma - active or uncontrolled infection - prior therapy with gemcitabine or docetaxel - known hypersensitivity to polysorbate 80 - pregnancy or lactating - presence of uncontrolled CNS metastases **Patient characteristics** Gender n(%) Male 40(55)/23(47) Female 33(45)/26(53) Age [y] Median(range) 55(23-80)/55(21-79) Primary site (number of patients) n(%) Extremity/trunk 28(38)/24(49) Retroperitoneal/abdominal 41(56)/23(47) Other 4(5)/2(4) Histology n(%) Leiomyosarcoma 29(40)/9(18) Nonleiomyosarcoma 44(60)/40(82)	was administered to all patients starting on day 9 to 10 of each cycle **Randomized patients** 73/49		
Martin-Broto J, Pousa AL, de Las Penas R, Garcia Del Muro X, Gutierrez A, Martinez-Trufero J, et al. Ran-dom-ized Phase II Study of Trabectedin and Doxorubicin Com-pared With Doxorubicin Alone as First-Line Treat-ment in Patients With Advanced Soft Tissue Sarcomas: A Spanish Group for Research on Sarcoma Study. Journal of clini-cal oncology : official journal of the American Society of Clinical Oncology.	**Region/Setting** This study was conducted at Spanish centers and one Portuguese center. **Inclusion criteria** - age ≥ 18 years - locally advanced nonresectable or metastatic STS - measurable disease according to RECIST 1.0 criteria - histologic subtypes including undifferentiated pleomorphic sar-coma, liposarcoma, leiomyosarcoma, synovial sarcoma, myxofi-brosarcoma, malignant peripheral nerve sheath tumor, fibrosar-coma, angiosarcoma, epithelioid hemangioendothelioma, solitary fibrous tumors, epithelioid sarcoma, and unclassified sarcoma - ECOG performance status 0-2 - adequate bone marrow, renal and liver function - normal cardiac function with left ventricular ejection fraction ≥ 50% by echocardiogram or multigated acquisition scan **Exclusion criteria** - previous chemotherapy administration	**Intervention(s)** Trabectedin 1.1 mg/m2 in a 3-hour infusion plus doxorubicin 60 mg/m2 + intravenous dexamethasone 30 minutes before the trabectedin + 4 mg of dexamethasone orally 24 and 12 hours before the trabectedin **Control** Doxorubicin 75 mg/m2 for up to six cycles **Randomized patients** 55/60	*Hematologic [n](Grade3 or 4)* Neutropenia 55/36 Anemia 6/2 Thrombopenia 18/2 Febrile neutropenia 32/24 *Non-hematologic [n](Grade3 or 4)* Nausea 8/2 Vomiting 10/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

2016;34(19):2294-302.	- previous radiation therapy involving target lesions - central nervous system metastases - women with positive pregnancy test **Patient characteristics** Gender n(%) Male 32(59)/30(51) Female 22(41)/29(49) Age [y] Median(range) 53(18-73)/52(20-68) Primary location n(%) Extremity 20(37)/17(29) Head and neck 2(4)/3(5) Trunk wall 5(9)/4(7) Retroperitoneum 14(26)/12(21) Other 13(24)/22(38) Histologic grade n(%) 1 10(19)/9(16) 2 10(19)/16(29) 3 33(62)/31(55) Size cm n(%) 0-5 11(22)/12(23) 5-10 16(32)/15(28) >10 23(46)/26(49) Disease type n(%) Locally advanced 12(22)/19(33) Metastatic 42(78)/39(67) Histology n(%) Undifferentiated pleomorphic sarcoma 12(22)/7(12) Somatic leiomyosarcoma 12(22)/8(14) Visceral leiomyosarcoma 3(5)/12(20) Liposarcoma 7(13)/10(17) WD/DD 4(7)/7(12) Myxoid/round cell 3(6)/3(5) Synovial sarcoma 2(4)/5(8) MPNST 3(6)/3(5) Other 15(28)/14(24)		Asthenia 25/4 Bilirubin 29/12 ALT 19/0	

Maurel J, Lopez-Pousa A, de Las Penas R, Fra J, Martin J, Cruz J, et al. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish group for research on sarcomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(11):1893-8.	**Region/Setting** This study was conducted at 23 sites in Spain and Portugal **Inclusion criteria** - age 18-65 years - histologically proven metastatic or locoregional unresectable soft tissue sarcoma - measurable disease by RECIST - ECOG performance status 0 or 1 - no functionally relevant cardiovascular disease - no prior history of malignant disease (except for adequately treated cervical carcinoma in situ or basal cell carcinoma) - no CNS metastases - no major surgery fewer than 3 weeks before study entry - adequate bone marrow, renal and hepatic function **Exclusion criteria** - prior chemotherapy in an adjuvant setting or for metastatic disease - malignant mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, embryonal and alveolar rhabdomyosarcoma, or gastrointestinal stromal sarcoma **Patient characteristics** <u>Gender n(%)</u> Male 36(55)/41(61) Female 29(45)/26(39) <u>Age [y] Median(range)</u> 49.5(18-65)/49(18-68) <u>Metastatic sites n(%)</u> Lung 33(51)/40(60) Liver 13(20)/13(19)/ Lymph nodes 18(27)/16(24) Other 24(37)/26(39) <u>Histologic diagnosis n(%)</u> Leiomyosarcoma 20(31)/15(22) Liposarcoma 19(15)/14(20) Undifferentiated pleomorphic 7(11)/8(12) Synovial sarcoma 4(6)/7(11) Miscellaneous sarcoma 24(37)/23(35)	**Intervention(s)** Doxorubicin at 30 mg/m2 per day for 3 consecutive days once every 2 weeks for 3 cycles followed by ifosfamide at 12.5 g/m2 delivered by continuous infusion over 5 days once every 3 weeks for 3 cycles + filgastrim 5ug/kg subcutaneously daily for 7 days, or pegfilgastrim 6 mg subcutaneously once after each cycle **Control** Doxorubicin 75mg/m2 bolus injection every 3 weeks for 6 cycles **Randomized patients** 65/67	*Hematologic* <u>Leucopenia [%]</u> Grade3 4.5/6 Grade4 9.3/6.2 <u>Neutropenia [%]</u> Grade3 4.6/13.4 Grade4 21.8/8.9 <u>Thrombocytopenia [%]</u> Grade3 4.6/3 Grade4 4.6/1.4 <u>Anemia n(%)</u> Grade3 18.7/10.4 Grade4 4.6/0 <u>Febrile neutropenia [%]</u> Grade3 23.4/7.4 Grade4 NR *Non-hematologic* <u>Nausea [%]</u> Grade3 6.2/1.5 Grade4 0/0 <u>Vomiting [%]</u> Grade3 4.6/1.5 Grade4 0/1.5 <u>Diarrhea [%]</u> Grade3 1.5/1.5 Grade4 0/1.5 <u>Stomatitis [%]</u> Grade3 23.4/4.5 Grade4 0/0 <u>Asthenia [%]</u> Grade3 14.1/4.5 Grade4 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Mouridsen HT, Bastholt L, Somers R, Santoro A, Bramwell V, Mulder JH, 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. European journal of cancer & clinical oncology. 1987;23(10):1477-83.	**Region/Setting** 18 institutions **Inclusion criteria** Prior to entry patients were required to have adequate hepatic excretory function (serum bilirubin ≤ 50 µmol/l) and bone marrow reserve (WBC count ≥4 x 10^3/l, platelet count ≥ 100 x 10^3/l). - patients between the ages of 15 and 80 years - histologically proven, locally advanced and/or metastatic soft tissue sarcoma - measurable progressive disease - Karnofsky score of at least 50 **Exclusion criteria** - recurrent tumor in irradiated areas was not permitted as the sole evaluable lesion and pleural effusion or bone metastases were not considered to be evaluable - prior chemotherapy - history of another malignant tumor (except for adequately treated carcinoma *in situ* of the cervix and/or carcinoma of the skin) - congestive heart failure - central nervous system metastases. **Patient characteristics** Gender n(%) Male 42(50)/45(54) Female 42(50)/38(46) Age [y] Median(range) 51(18-78)/ 56(16-80) Karnofsky score Median (range) 90(50-100)/90(60-100) Prior radiotherapy n(%) 29(35)/23(28) Extent and site of disease n(%) local only 22(26)/23(28) distant only 43(51)/41(49) local and distant 19(23)/19(23)	**Intervention(s)** 4-EpiDoxorubicin (EPI) was given at 75 mg/m² as an i.v. bolus injection. Treatment was repeated every 3 weeks. **Control** Doxorubicin was given at 75 mg/m² as an i.v. bolus injection. Treatment was repeated every 3 weeks. **Randomized patients** 83/84	*Hematologic* Leucocyte nadir after 1st course [%] Grade3 4/24 Grade4 0/5 *Non-hematologic Grade3-4* Nausea/vomiting [%] 6/4 Diarrhea [%] 0/1 Anorexia [%] 0/1 Mucositis [%] 1/0 Alopecia [%] 43/62	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +
Nielsen OS, Dombernowsky P, Mouridsen H, Daugaard S, Van Glabbeke M, Kirkpatrick A, et al. Epirubicin is	**Region/Setting** EORTC STBSG initiated this study. A total of 334 patients from 34 centers were included.	**Intervention(s)** **IG** epirubicin at a dose of 160 mg m² as a single i.v. bolus injection repeated every 3 weeks or epirubi-	*Hematologic* Leucopenia [%] Grade3-4 63/38 Neutropenia [%]	**Study type** RCT **Risk of bias**

not Superior to Doxorubicin in the Treatment of Advanced Soft Tissue Sarcomas. The Experience of the EORTC Soft Tissue and Bone Sarcoma Group. Sarcoma. 2000;4(1-2):31-5.	**Inclusion criteria** - histologically proven soft tissue sarcomas, who either had relapsed locally or developed metastases after primary surgery and/or radiotherapy or who initially presented with advanced inoperable disease. - age between 18 and 70 years, - performance status 0-2 on the WHO scale, - normal creatinine (≤ 150 µmol l^{-1}), bilirubin (≤ 25 µmol l^{-1}), leucocytes (> 3.5 x 10^9 l^{-1}) and thrombocyte counts (> 100 x 10^9 l^{-1}) at entry. -presence of measurable lesions not previously irradiated. **Exclusion criteria** - patients who had received prior chemotherapy, whether as adjuvant treatment or for advanced disease - history of significant cardiovascular disease. - no prior malignant tumor (except for adequately treated carcinoma in situ of the cervix and/or carcinoma of the skin), - CNS metastases - Patients with mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma and dermatofibrosarcoma protuberans **Patient characteristics** Age [y] Median(range) IG1/IG2/CG 55(23-73)/47(19-70)/52(20-62) Gender n(%) Male 53(49)/50(47)/51(49) Female 51(51)/56(53)/53(51) Performance status n(%) 0 37(36)/33(31)/32(31) 1 50(48)/58(55)/57(55) 2 17(16)/15(14)/15(14) Histological grade n(%) 1 18(17)/25(24)/22(21) 2 50(48)/36(34)/38(37) 3 36(35)/45(42)/44(42) Lung metastases n(%) 49(47)/54(51)/49(47) Liver metastases n(%) 20(19)/19(18)/22(21) Bone metastases n(%) 4(4)/10(9)/7(7)	cin three epirubicin i.v. bolus injections of 60 mg m² on days 1. 2 and 3 repeated every 3 weeks Because of severe and lethal neutropenia in the first patients the epirubicin doses were reduced to 150 mg m² and 3 x 50 mg m² day. respectively and administered as a 30-min i.v. infusion. Only 20 patients (28 cycles) received the higher doses. **Control** an i.v. bolus injection of doxorubicin 75 mg m² every 3 weeks **Randomized patients** 104/106/104	Grade3-4 73/51 Thrombocytopenia[%] Grade3-4 14/2 *Non-hematologic* Nausea [%] Grade 3-4 22/13 Infection [%] Grade3-4 8/3 Mucositis [%] Grade3-4 15/6 Local reaction [%] Grade3-4 10/1 Cardiotoxicity [%] Grade3-4 0/1	Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). The oncologist. 2012;17(9):1213-20.	**Region/Setting** This study was conducted in 17 institutions across France **Inclusion criteria** - metastatic or unresectable LMS, histologically confirmed by an expert sarcoma pathologist at the local center, originated in either the uterus or another site (nonuterine LMS) - measurable disease according to RECIST 1.0 - previously only one doxorubicin-containing chemotherapy regimen - at least one progressive target lesion outside the radiation field based on computed tomography or magnetic resonance imaging - adequate organ function, defined as an absolute neutrophil count (ANC) ≥1,000/uL, platelet count ≥100,000/uL, total bilirubin ≤1.5-fold the institutional upper limit of normal (ULN), alanine transaminase, aspartate aminotransferase, and alkaline phosphatase ≤2.5-fold the institutional ULN - serum creatinine ≤1.5-fold the institutional ULN - ECOG performance status ≤2 - any completed previous chemotherapy, radiotherapy, or hormonotherapy at least 4 weeks before enrollment **Exclusion criteria** - pregnancy, lactating women - history of malignancy - history of grade 3 or 4 neuropathy - known CNS metastases **Patient characteristics** ***Uterine group*** Age [y] Median(range) 54(41-80)/58(43-76) Metastases (lung/liver) n(%) (20/10)22(100)/(20/11)23(96) ***Nonuterine group*** Gender n(%) Male 12(55)/9(41) Female 10(45)/13(59) Age [y] Median(range) 64(35-74)/62(29-78) Primary tumor site n(%) Extremity 9(41)/9(41) Retroperitoneal/abdominal/GI 8(36)/7(32)	**Intervention(s)** Gemcitabine-only arm: 1,000 mg/m2 of Gemcitabin fixed-dose rate of 10 mg/m2 per minute via a 100-minute i.v. infusion on days 1, 8, and 15 every 28 days **Control** Gemcitabine plus docetaxel arm: Gemcitabine fixed-dose rate of 900 mg/m2 in a 90-minute infusion on days 1 and 8, with Docetaxel at 100 mg/m2 in a 60- minute infusion on day 8 after gemcitabine, every 21 days with lenograstim, a recombinant human G-CSF, in a daily injection of 150 g/m2 from day 9 to day 15 **Randomized patients** ***Uterine group*** 22/24 ***Nonuterine group*** 22/22	***Uterine**: Hematologic* Leucopenia [%] Grade3-4 11/37 Neutropenia [%] Grade3-4 14/32 Thrombocytopenia[%] Grade3-4 26/11 Anemia [%] Grade3-4 8/1 ***Uterine:** Non-hematologic* Nausea [%] Grade 3-4 0/0 Fever/infection [%] Grade3-4 3/1 Asthenia [%] Grade3-4 4/0 Pulmonary [%] Grade3-4 1/1 Hepatic [%] Grade3-4 0/1 ***Non-uterine**: Hematologic* Leucopenia [%] Grade3-4 7/13 Neutropenia [%] Grade3-4 6/11 Thrombocytopenia [%] Grade3-4 9/7 Anemia [%] Grade3-4 12/2 ***Non-uterine:** Non-hematologic* Nausea [%] Grade 3-4 0/0 Fever/infection [%]	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Trunk 1(4.5)/3(13.5) Other 4(18)/3(13.5) FNCLCC primary tumor grade 2/3 n(%) 20(91)/16(73) Metastases (lung/liver) n(%) (18/6)20(91)/(17/21)21(95)		Grade3-4 1/0 Asthenia [%] Grade3-4 4/7 Pulmonary [%] Grade3-4 1/0 Hepatic [%] Grade3-4 1/2	
Presant CA, Bartolucci AA, Lowenbraun S. Effects of amphotericin B on combination chemotherapy of metastatic sarcomas. Cancer. 1984;53(2):214-8.	**Region/Setting** NR **Inclusion criteria** - histologically proven, advanced, metastatic sarcoma, - the patients were not considered to be candidates for curative surgery or radiation therapy. - measurable disease of recently documented progression; - older than 15 years of age; - untreated previously with chemotherapy drugs used in this study - histopathologic types of sarcomas: angiosarcoma, chondrosarcoma, Ewings, fibrosarcoma, leiomyosarcoma, liposarcoma, mesothelioma, osteogenic sarcoma, rhabdomyosarcoma, schwannoma, synovial sarcoma, uterine sarcoma, other **Exclusion criteria** - patients with solitary pulmonary nodules - hyperbilirubinemia (> 1.2 mg/dl), azotemia (creatinine > 1.4 mg/dl), congestive heart failure, abnormal cardiac rhythm, a granulocyte counts less than 2000/mm³ or a platelet count less than 100,000/mm³. **Patient characteristics** Age [y] Median(Mean) 56.1(52.9)/57.6(54.1) Gender n(%) Male 22(45)/27(60) Female 27(55)/18(40) Performance status mean(median) 78.4(80)/75.8(80) Diagnosis n(%) Angiosarcoma 2(4)/2(4) Chondrosarcoma 1(2)/0(0) Ewing's 0(0)/1(2) Fibrosarcoma 9(18)/14(31) Leiomyosarcoma 9(18)/9(20)	**Intervention(s)** AMB + ACM Amphotericin B was administered in 500 ml of 5% dextrose in water with 100 mg of hydrocortisone over 6 hours; the doses were 7.5 mg/m² day 1, 15 mg/m² day 2, and 30 mg/m² days 3 and 4, with ACM on the fourth day following the conclusion of the AMB infusion. Prior to administration of AMB, diphenhydramine and acetaminophen were administered. If the patient got a chill during the course of AMB administration, meperidine 25 mg was administered intravenously. Following the conclusion of AMB during each course, ACM was administered in the doses listed below. Courses of ACM plus AMB were repeated 21 days following the administration of ACM. Three weeks following the second course of therapy, response was evaluated. Patients who did not show evidence of progression of disease continued to receive two further courses of ACM plus AMB. For courses 3 and 4, AMB doses were decreased to 7.5 mg/m² day 1, and 30 mg/m² day 2, with ACM being administered on day 2, following completion of AMB. ACM + AMB Courses 1,2; mg/m²intraveneously	*Hematologic (Moderate-severe)* Hemoglobin fall >3g/dl [%] 8/2 Granulocytopenia [%] 51/51 Thrombocytopenia [%] 4/4 *Non-hematologic (Moderate-severe)* Nausea [%] 47/35 Stomatitis [%] 6/7 Congestive heart failure [%] 2/4 Increased blood-urea nitrogen [%] 2/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Liposarcoma 7(14)/7(16) Mesothelioma 1(2)/2(4) Osteogenic sarcoma 1(2)/1(2) Rhabdomyosarcoma 1(2)/1(2) Schwannoma 2(4)/0(0) Synovial sarcoma 1(2)/0(0) Uterine sarcoma 1(2)/0(0) Other 14(29)/8(18) Prior therapy n(%) Surgery 36(73)/38(84) Radiotherapy 12(24)/14(31) Metastatic disease site n(%) Lung 30(61)/23(51) Pleura 5(10)/2(4) Liver 8(16)/8(18) Bone marrow Bone 9(18)/7(15) Skin 1(2)/3(7) Subcutaneous 6(12)/4(9) G.I. 4(8)4/(9) Nodes 5(10)/4(9) Spleen 0(0)/2(4) Brain 1(2)/0(0) Other 2(4)/5(11)	AMB: 7.5 day 1, 15 day 2, 30 day 3 and day 4 Doxorubicin 40 day 4 Cyclophosphamide 400 day 4 Methotrexate 20 day 4 Courses 3,4; mg/m²intraveneously: AMB: 7.5 day 1, 30 day 2, Doxorubicin 40 day 2 Cyclophosphamide 400 day 2 Methotrexate 20 day 2 **Control** ACM Chemotherapy was given every 3 weeks for 2 consecutive courses, following which response was evaluated. Patients who did not have progressive disease were then continued on courses 3 and 4. Courses 1,2; mg/m² intravenously: Adriamycin 60 Cyclophosphamide 600 Methotrexate 25 Courses 3,4; mg/m² intravenously: Adriamycin 60 Cyclophosphamide 600 Methotrexate 25 **Randomized patients** 61/61		
Presant CA, Lowenbraun S, Bartolucci AA, Smalley RV. Metastatic sarcomas: chemotherapy with adriamycin, cyclophosphamide, and methotrexate alternating with actinomycin D, DTIC, and vincristine. Cancer. 1981;47(3):457-65.	**Region/Setting** NR **Inclusion criteria** - histologically proven, advanced, metastatic sarcoma, - the patients were not considered to be candidates for curative surgery or radiation therapy. - measurable disease of recent documented progression; - older than 15 years of age; - untreated previously with chemotherapy agents used in this study - the following histopathologic types of sarcomas were eligible: liposarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, angiosarcoma, osteogenic sarcoma, Ewing's	Induction chemotherapy: All patients received two courses of induction chemotherapy, which was administered 21 days apart. Each course consisted of Doxorubicin, 60 rng/m², intravenously (maximum dose 120 mg), CTX, 600 mg/m², i.v. (maximum dose 1200 mg), plus MTX, 25 mg/m², i.v. (maximum dose 50 mg). If the nadir granulocyte counts and platelet counts did not demonstrate moderate toxicity, then the doses of CTX and MTX were increased by 25%	*Hematologic (Moderate-severe)* Hemoglobin >3g/dl [%] 6/18/6 Granulocytopenia [%] 15/38/32 Thrombocytopenia [%] 0/15/16 *Non-Hematologic (Moderate-severe)* Gastrointestinal [%]	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: +

	sarcoma, chondrosarcoma, malignant schwannoma, alveolar soft part sarcoma, malignant mesothelioma, and uterine sarcoma. **Exclusion criteria** - patients with solitary pulmonary nodules - hyperbilirubinemia (>1.2 mg/dl), azotemia (> 1.4 mg/dl creatinine), congestive heart failure, abnormal cardiac rhythms, granulocyte count less than 2000 cells/mm³ or platelet count less than 100,000/mm³ **Patient characteristics** NR	for the second course. If the nadir of the granulocyte count was less than 750/mm³ or nadir of the platelet count less than 50,000/mm³, the doses of ADR, CTX, and MTX were reduced by 50%. Retreatment was delayed until the granulocyte count had recovered to greater than 2000/mm³, and platelet count had recovered to greater than 100,000/mm³ **Intervention(s)** Maintenance therapy**:** **IG1:** ADV consisted of ACT, 1.0 mg/m², i.v. (maximum 2 mg), DTIC, 250 mg/m² i.v. (maximum 500 mg) plus VCR, 1.4 mg/m², i.v. (maximum 2 mg). Therapy was repeated weekly for 21 weeks. **IG2**:ADV-ACM three weeks of ADV followed by ACM on the fourth week. There was no further therapy during the ensuing two weeks. This six-week course was repeated until the patient had received a total of 12 weekly courses of ADV and three courses of ACM. **Control** ACM Doxorubicin plus CTX plus MTX every three weeks for an additional seven courses. **Randomized patients** 279 patients were entered into this treatment program.	68/66/28 Oral [%] 9/22/9 Cardiovascular [%] 0/0/2 Peripheral neutropenia [%] 15/6/0	Other source of bias: +
Ray-Coquard IL, Domont J, Tresch-Bruneel E, Bompas E, Cassier PA, Mir O, et	**Region/Setting** This study was conducted at 14 centers in	**Intervention(s)** Paclitaxel 90 mg/m2 intravenously on days 1, 8, and 15 of a 28-day cycle for six cycles + Bevacizumab	*Hematologic* Neutropenia [%] Grade3 12/8.7	**Study type** RCT

al. Paclitaxel Given Once Per Week With or Without Bevacizumab in Patients With Advanced Angiosarcoma: A Randomized Phase II Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(25):2797-802.	**Inclusion criteria** - age ≥18 years - histologically proven metastatic or advanced AS, reviewed by the Pathology Committee of French Sarcoma Group - not amenable to curative-intent surgery - measurable tumor according to RECIST 1.1 - WHO performance status ≤1 - adequate contraception during treatment - adequate hematologic function (granulocytes ≥ 1,500/uL and platelet count > 100,000/uL) - adequate liver function (total bilirubin <1.5 X the upper limit of normal; ALT and AST each < 2.5X the upper limit of normal) - adequate renal function (calculated creatinine clearance, ≥50 mL/min) - normal cardiac function (left ventricular ejection fraction, ≥ 50%) - no hematuria or proteinuria - absence of risk of bleeding - normal coagulation tests **Exclusion criteria** - weight loss of 20% or more before illness - brain or leptomeningeal metastasis - surgical procedure or radiotherapy within 4 weeks of enrolment - active gastroduodenal ulcer - previous condition associated with the risk of bleeding or requiring anticoagulation - severe or active underlying cardiovascular disease - uncontrolled arterial hypertension - proteinuria or hematuria - denutrition with albuminemia less than 35 g/L - pregnant or breastfeeding status - Kaposi's sarcoma - positive HIV serology - hepatic failure - known allergy to paclitaxel or to polyoxyethylated castor oil (Cremophor EL; BASF, Ludwigshafen, Germany) - severe underlying comorbid disease that may alter compliance **Patient characteristics** Gender n(%) Male 6(25)/5(20) Female 18(75)/20(80) Stratification n(%) Superficial angiosarcoma 16(66)/16(64) Visceral angiosarcoma 8(34)/9(36) Radiation induced 12(50)/12(48)	10 mg/kg during the chemotherapy cycles every 2 weeks until intolerance or progression occurred **Control** Paclitaxel 90 mg/m2 intravenously on days 1, 8, and 15 of a 28-day cycle for six cycles + intravenous premedications, including dexamethasone 8 mg, cimetidine 200 mg, and dexchlorpheniramine 5 mg **Included/randomized patients** 26/24	Grade4 0/0 Hypokalemia [%] Grade3 4/0 Grade4 0/0 Hyperglycemia [%] Grade3 0/1 Grade4 0/0 Anemia [%] Grade3 0/0 Grade4 0/4.8 Arterial Hypertension [%] Grade3 8/0 Grade4 0/0 *Non-hematologic* Fatigue [%] Grade3 4/4.3 Grade4 0/0 Delirium [%] Grade3 4/0 Grade4 0/0 Neuropathy [%] Grade3 8.0/4.3 Grade4 0/0 Diarrhea [%] Grade3 8/0 Grade4 0/0 Dyspnea [%] Grade3 8/4.3 Grade4 0/0	**Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	De novo 12(50)/13(52) Primary site of angiosarcoma n(%) Breast 12(50)/12(48) Skin 3(12.5)/3(12) Liver 3(12.5)/0 Bone 2(8.3)/1(4) Heart 0/2(8) Spleen 0/2(8) Pleura 2(8.3)/0 Mesentery 1(4.2)/1(4.0) Parotid 0/1(4) Perineal wall 1(4.2)/0 Retroperitoneum 0/1(4.0) Unknown 0/1(4) Grade† n(%) 1 2(8.3)/3(12) 2 5(20.8)/7(28) 3 11(45.8)/8(32) Unknown 6(25)/7(28) Metastatic disease n(%) 13(54.2)/16(64) Only one metastatic site n(%) 9(37.5)/10(40) Most common metastatic site n(%) Lung 4(16.7)/7(28) Liver 4(16.7)/6(24) Bone 2(8.3)/2(8.3) Soft tissue 2(8.3)/0 Skin 5(20.8)/3(12) Lymph nodes 1(4.2)/1(4)			

Ryan CW, Merimsky O, Agulnik M, Blay JY, Schuetze SM, Van Tine BA, et al. PICASSO III: A phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. Journal of Clinical Oncology. 2016;34(32):3898-905.	**Region/Setting** This study was conducted at 113 investigational sites across 19 countries **Inclusion criteria** - age ≥ 18 years - Eastern Cooperative Oncology Group performance status of 0 to 2 - no prior systemic treatment for metastatic sarcoma (although neoadjuvant or adjuvant gemcitabine and docetaxel were allowed) - no prior anthracycline use - adequate bone marrow, liver, renal, and cardiac function **Exclusion criteria** - other typical phase III trial exclusion criteria for safety were applied **Patient characteristics** Gender n(%) Male 123(54.4)/118(53.4) Female 103(45.6)/103(46.6) Age [y] Median(range) n(%) 58(19-85)/56(18-83) <65 166(73.5)/163(73.8) ≥65 60(26.5)/58(26.2) Primary tumor site n(%) Extremity 60(26.5)/74(33.5) Retroperitoneal 43(19)/39(17.6) Other 118(52.2)/103(46.6) Unknown 5(2.2)/5(2.3) Histologic subtype n(%) Local report Leiomyosarcoma 77(34.1)/76(34.4) Synovial sarcoma 15(6.6)/13(5.9) Other 134(59.3)/132(59.7) Central review Pleomorphic/undifferentiated/sarcoma, NOS 85(37.6)/63(28.5) Leiomyosarcoma 69(30.5)/69(31.2) Liposarcoma 27(11.9)/40(18.1) Synovial sarcoma 12(5.3)/10(4.5) Angiosarcoma 8(3.5)/6(2.7) Myxofibrosarcoma 6(2.7)/5(2.3) Malignant peripheral nerve sheath tumor 4(1.8)/6(2.7) Other 15(6.6)/22(10)	**Intervention(s)** Doxorubicin plus Palifosfamide: Doxorubicin 75 mg/m2 intravenously (IV) on day 1 and a palifosfamide 150 mg/m2 infusion IV over 30 minutes once per day on days 1 to 3; one cycle was 21 days long, repeated up to six times **Control** Doxorubicin plus Placebo: Doxorubicin 75 mg/m2 IV on day 1 and matching saline placebo IV once per day on days 1 to 3; one cycle was 21 days long, repeated up to six times **Randomized patients** 226/221	*Hematologic* Neutropenia [%] Grade3-4 29.5/21 Febrile Neutropenia [%] Grade3-4 20/11.7 Thrombocytopenia [%] Grade3-4 4.1/3 Anemia [%] Grade3-4 16.8/8.9 *Non-hematologic* Nausea [%] Grade 3-4 4.5/1.9 Diarrhea [%] Grade3-4 2.7/0 Fatigue [%] Grade3-4 4.5/4.7 Dehydration [%] Grade3-4 2.7/.2.3 Hypokalemia [%] Grade3-4 8.6/2	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1995;13(7):1537-45.	**Region/Setting** 35 cancer centers within the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC). **Inclusion criteria** - histologically confirmed diagnosis of soft tissue sarcoma - metastatic disease with measurable lesions (without CNS involvement) and/or locoregional advanced disease that was not amenable to potentially curative surgery - acceptable age range was 15 to 70 years - entry performance status had to be ≤ 2 according to the World Health Organization (WHO) scale - radiotherapy was accepted only if given to lesions other than the index ones, i.e., those chosen to evaluate tumor response - adequate renal (serum creatinine level ≤ 150 mmol/L), hepatic (bilirubin level ≤ 20 mmol/L), and bone marrow (leukocyte count ≤ 3.5 x 10^9/L and platelet count > 100 x 10^9/L) function. **Exclusion criteria** - Ewing's sarcoma, embryonal rhabdomyosarcoma, mesothelioma, paraganglioma, chondrosarcoma, neuroblastoma, and osteosarcoma - prior chemotherapy - other severe medical illness could be present, including psychosis or cardiovascular disease - other primary malignant tumors (except adequately treated in situ carcinoma of the cervix or basal cell carcinoma). **Patient characteristics IG1/IG2/CG** Gender n(%) Male 129(59)/71(50)/125(47.5) Female 129(50)71(50)/138(52.5) Age [y] Median 50/51/52 Performance status n(%) 0: 88(34.1)/46(32.4)/94(35.7) 1: 124(48.1)/68(47.9)/124(47.1) 2: 45(17.4)/28(19.2)/45(17.1) Metastatic disease n(%) 191(74)/115(81)/200(76)	**Intervention(s)** **IG1** doxorubicin plus ifosfamide doxorubicin was administered at 50 mg/m² as an intravenous push injection, immediately followed by ifosfamide administered as a 24-hour infusion at a dose of 5 g/m². Mesna (2-mercaptoethane sodium sulfonate [600 mg/m²]) was administered as an intravenous bolus immediately preceding the continuous infusion of ifosfamide. The total dose of ifosfamide was diluted in 3 L of dextrose/saline with 2.5 g/m² of mesna. At the end of the infusion of ifosfamide, an additional 2 L of dextrose/saline containing 1.25 g/m² of mesna was given over 12 hours. **IG2** CYVADIC cyclophosphamide 500 mg/m², vincristine 1.5 mg/m² (maximum dose, 2 mg), and doxorubicin 50 mg/m², all as intravenous push injections. Dacarbazine was administered at a dose of 750 mg/m², diluted in 250 mL of saline over 30 minutes. **Control** Single-agent doxorubicin was administered as an intravenous push injection at a dose of 75 mg/m². For all regimens, cycles were repeated, in the presence of adequate blood counts, every 3 weeks. **Randomized patients** NR **Analyzed patients**	*Hematologic* Leucopenia [%] Grade 4 15/32/13 Thrombocytopenia[%] Grade3-4 10/5/4 *Non-hematologic* Nausea [%] Grade 3-4 40/-/17 Stomatitis [%] Grade3-4 1/2/4 Neurologic toxicity [%] Grade3-4 14/2/-	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: - Other source of bias: +

		258/142/263		
Schoffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomized, open-label, multicentre, phase 3 trial. Lancet (London, England). 2016;387(10028):1629-37. Hudgens S, Forsythe A, Kontoudis I, D'Adamo D, Bird A, Gelderblom H. Evaluation of Quality of Life at Progression in Patients with Soft Tissue Sarcoma. Sarcoma. 2017;2017.	**Region/Setting** This study was conducted at 110 study sites in 22 countries across North America, Latin America, Europe, Asia, and Australia. **Inclusion criteria** - age ≥ 18 years - histologically confirmed locally recurrent, locally advanced, or metastatic liposarcoma (de-differentiated, myxoid or round-cell, or pleomorphic liposarcoma) or leiomyosarcoma - a disease that was not amenable to curative surgery or radiotherapy - disease measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 - disease progression occurred within 6 months before randomization after at least two standard systemic regimens for advanced soft-tissue sarcoma, including an anthracycline (unless contraindicated) - Eastern Cooperative Oncology Group performance status of 0–2 - adequate organ function **Exclusion criteria** - pregnancy - any anticancer therapy or major surgery within 21 days before randomization - prior treatment with eribulin or dacarbazine **Patient characteristics** Gender n(%) Male 67(29)/82(37) Female 161(71(/142(63) Age [y] Median(range) n(%) 56(28-83)/56(24-83) <65 178(78)/178/79) ≥65 50(22)/46(21) Disease type n(%) Liposarcoma 75(33)/78(35) Leiomyosarcoma 152(67)/145(65) Other 1(<1)/1(<1) Liposarcoma histological subtype n(%) De-differentiated 32(14)/37(17) Myxoid or round-cell 30(13)/26(12) Pleomorphic 13(6)/15(7)	**Intervention(s)** Eribulin mesylate was given at a dose of 1·4 mg/m² (equivalent to eribulin 1·23 mg/m² [expressed as free base]) intravenously over 2–5 min on day 1 and day 8 of every 21 day cycle **Control** Dacarbazine at a dose of 850 mg/m², 1000 mg/m², or 1200 mg/m² as an intravenous infusion over 15–60 min on day 1 of every 21 day cycle. **Randomized patients** 228/224	*Hematologic* Leucopenia [%] Grade3 8/3 Grade4 2/2 Neutropenia [%] Grade3 20/9 Grade4 15/7 Thrombocytopenia [%] Grade3 1/15 Grade4 0/8 Anemia [%] Grade3 6/10 Grade4 1/2 *Non-hematologic* Nausea [%] Grade3 1/1 Grade4 0/0 Fatigue [%] Grade3 3/1 Grade4 0/0 Dyspnea [%] Grade3 2/1 Grade4 1/1 Hypokalemia [%] Grade3 3/1 Grade4 0/1 Abdominal pain [%] Grade3 1/4 Grade41 1/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Leiomyosarcoma primary site n(%) Uterine 68(30)/63(28) Non-uterine 83(36)/82(37) Unknown 1(<1)/0 Tumor grade High 150(66)/10(4) Intermediate 77(34)/69(31) Not known 1(<1)/3(1)			
Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomized phase 2 trial. Lancet (London, England). 2016;388(10043):488-97.	**Region/Setting** This study was conducted at 16 clinical sites in 16 cities and 15 states in the USA. **Inclusion criteria** - age ≥ 18 years - histologically confirmed diagnosis of locally advanced or metastatic soft-tissue sarcoma not previously treated with anthracycline - ECOG performance status of 0-2 - available tumor tissue to determine PDGFRα expression by immunohistochemistry **Exclusion criteria** - histologically or cytologically confirmed Kaposi's sarcoma - untreated metastases to the CNS - previous treatment with doxorubicin, daunorubicin, idarubicin, or other anthracyclines and anthracenediones (mitoxantrone), or therapy with any drug that targets the PDGF or PDGFR - previous radiation therapy to the mediastinal or pericardial area; received concurrent treatment with other anticancer therapy including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, chemoembolization, targeted therapy, an investigational agent or the non-approved use of a drug or device within 4 weeks before study entry - a known allergy to any of the treatment components - unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry - infection by HIV - pregnancy or lactating **Patient characteristics** Gender n(%) Male 26(39)/33(49) Female 40(61)/34(51) Age [y] Median(range) n(%) 58.5(22-85)/58(29-86)	**Intervention(s)** Olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles **Control** Doxorubicin alone (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles **Randomized patients** 66/67	*Hematologic* Leucopenia [%] Grade3 22/8 Grade4 14/9 Neutropenia [%] Grade3 19/8 Grade4 34/25 Febrile neutropenia [%] Grade3 11/14 Grade4 2/0 Anemia [%] Grade3 13/9 Grade4 0/0 *Non-hematologic* Nausea [%] Grade3 2/3 Grade4 0/0 Fatigue [%] Grade3 9/3 Grade4 0/0 Mucositis [%] Grade3 3/5 Grade4 0/0 Infections/Infestations [%] Grade3 8/6 Grade4 0/5 Diarrhea [%] Grade3 3/0 Grade41 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Histological type n(%) Leiomyosarcoma 24(36)/27(40) Non-leiomyosarcoma‡ 42(64)/40(60) Undifferentiated pleomorphic sarcoma 10(15)/14(21) Liposarcoma 8(12)/15(22) Angiosarcoma 4(6)/3(5) Synovial sarcoma 1(2)/2(3) Neurofibrosarcoma 1(2)/0 Fibrosarcoma 1(2)/0 Other 17(26)/6(9)			
Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomized phase 3 trial. The Lancet Oncology. 2017.	**Region/Setting** This study was conducted at 81 academic or community investigational sites in the USA, Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Poland, Russia, and Spain. **Inclusion criteria** - age ≥ 15 years - diagnosis of an advanced unrespectable or metastatic soft-tissue sarcoma, intermediate or high grade, no curative therapy available - ECOG performance status of 0-1 - life expectancy at least 3 months - measurable disease according to RECIST 1.1 - adequate end-organ and haemopoietic function **Exclusion criteria** - previous systemic therapy for advanced or metastatic disease (neoadjuvant therapy followed by surgical resection and adjuvant therapy was permitted) - previous therapy with ifosfamide, cyclophosphamide, another nitrogen mustard, or another hypoxic cytotoxin - previous systemic therapy with an anthracycline or anthracenedione, or previous mediastinal or cardiac radiotherapy - low-grade tumor according to standard grading systems (e.g., American Joint Committee on Cancer grade 1 and 2 or Fédération Nationale des Centres de Lutte Contre le Cancer grade 1) - significant cardiac dysfunction - severe chronic obstructive pulmonary disease - a known infection with HIV or active infection with hepatitis B or hepatitis C - known brain metastases unless previously treated and well controlled for a period of 3 months or longer - pregnancy or breastfeeding **Patient characteristics** Gender n(%)	**Intervention(s)** Evofosfamide was administered intravenously at 300 mg/m² for 30–60 min on day 1 and day 8 of every 21-day cycle; after 2–4 h completion of evofosfamide administration: Doxorubicin at 75 mg/m² on day 1 of every 21-day cycle by either a bolus injection (no less than5 min, but generally less than 20 min) or continuous intravenous infusion for 6–96 h for up to six cycles **Control** Doxorubicin at 75 mg/m² on day 1 of every 21-day cycle by either a bolus injection (no less than5 min, but generally less than 20 min) or continuous intravenous infusion for 6–96 h for up to six cycles **Randomized patients** 317/323	*Hematologic* Leucopenia [%] Grade3 3/4 Grade4 4/1 Neutropenia [%] Grade3 4/7 Grade4 11/22 Febrile neutropenia [%] Grade3 13/7 Grade4 5/4 Anemia [%] Grade3 47/20 Grade4 1/1 Thrombocytopenia [%] Grade3 6/1 Grade4 8/1 *Other* Fatigue [%] Grade3 5/4 Grade4 0/0 Pulmonary embolism [%] Grade3 66 Grade4 1/0 Hypokalemia [%] Grade3 3/3 Grade4 1/0 Hyponatremia [%] Grade3 3/1 Grade41 0/0 Stomatitis [%] Grade3 8/2	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Male 144(45)/151(47) Female 173(55)/172(53) Age [y] Median(range) n(%) 60(49-67)/58(49-66) <65 211(67)/220(68) ≥65 106(33)/103(32) Extent of disease n(%) Locally advanced 32(10)/41(13) Metastatic disease 285(90)/282(87) Highest histological grade n(%) Low grade 1 0/(<1) Intermediate grade 99(31)/105(33) Intermediate/high grade 5(2)/11(3) High grade 213(67)/205(63) Unknown grade 10/(<1) Cellular classification site review n(%) Leiomyosarcoma 117(37)/113(35) Liposarcoma 62(20)/49(15) Undifferentiated pleomorphic sarcoma 36(11)/43(13) Other† 102(32)/118(37)		Grade4 0/0	
Zong XY, Yu Y, Yang HJ. Oxaliplatin-dacarbazine combination chemotherapy for the treatment of advanced soft tissue sarcoma of the limbs. Journal of experimental & clinical cancer research : CR. 2009;28:119.	**Region/Setting** This study was conducted at the Department of Surgical Oncology of Zhejiang Provincial Hospital in China **Inclusion criteria** - age 14-70 years - no history of chronic primary organ disease, heart failure or other major organ malfunction - sarcoma originated in limb soft tissue - Belong to G1-3T3N0M0 or G1-3T1- 3N0-1M1, that is, stage IV according to the Russell GTNM staging system - no prior chemotherapy or radiation therapy **Exclusion criteria** - pregnancy and lactating **Patient characteristics** Age [y] Median(range) n(%) 41(18-66)/50(18-66) Metastasis n Lymph node 2/3 Lung 2/1	**Intervention(s)** 120 mg/m2 d1 Oxaliplatin (L-OHP) with 175 mg/m2 d13 Dacarbazine (DTIC); surgery four weeks after the second cycle, followed by another 24 cycles of chemotherapy using the same pre-surgical treatment **Control** Standard VAC chemotherapy 1 mg/m2/d1 vincristine (VCR), 60 mg/m2 d1 epirubicin (Epi- ADM), and 600 mg/m2 d1 cyclophosphamide (CTX); surgery four weeks after the second cycle; followed by another 24 cycles of chemotherapy using the same pre-surgical treatment **Randomized patients** 15/16	Nausea [%] moderate 26.6/31.25 Vomiting [%] moderate 6.7/6.25 Granulocytopenia [%] moderate 13.3/0 Peripheral Neuropathy [%] moderate 20/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Tumor location n Upper arm 3/3 Thigh 7/11 Lower leg 5/2 Pathological phenotypes n Malignant fibrous histiocytoma 8/6 Rhabdomyosarcoma 3/3 Synovial sarcoma 0/4 Malignant nerve sheath tumor 1/1 Clear cell sarcoma 2/0 Unclassifiable 1/2 Cytological grading n G2 0/1 G3 15/15			

+ low risk of bias; - high risk of bias, ? unclear risk of bias; ACM: Adriamycin Cyclophosphamide Methotrexate; ACT: actinomycin D; ADR: Adriamycin; ADV: Actinomycin-D DTIC Vincristine; ALT: Aminotransferase; ANC: absolute neutrophil count; AP: alkaline phosphatase; AST: aminotransferase; BMR: bone marrow reserve; CG: control group; CI: confidence interval; CMM: Carminomycin; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; CTX: cyclophosphamide; DTIC: Dacarbazine; DXCT: doxorubicin-based chemotherapy; ECOG: Eastern Cooperative Oncology Group; ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC: European Organisation for Research and Treatment of Cancer; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; G-CSF: Granulocyte colony-stimulating factor; GI: Gastrointestinal; GIST: gastrointestinal stromal tumor; GOG: Gynecologic Oncology Group; IG: intervention group; LMS: leiomyosarcoma; LVEF: left ventricular ejection function; MPNST: malignant peripheral nerve sheath tumor; MRCL: Myxoid/round-cell liposarcoma; MTX: methotrexate; MUGA: multiple gated acquisition scan; NCI: National Cancer Institute; NOS: not otherwise specified; NR: not reported; NYHA: New York Heart Association; PDGF: Platelet-derived growth factor; PDGFR: platelet-derived growth factor receptor; PDGFRα: platelet-derived growth factor receptor A; PS: Performance Status; RECIST: Response Evaluation Criteria In Solid Tumors; SD: Standard Deviation; STBSG: Soft Tissue and Bone Sarcoma Group; TRS: translocation-related sarcomas; uLMS: uterine leiomyosarcoma; ULN: upper limit of normal; VCN: vincristine; VEGF: vascular endothelial growth factor; WBC: White blood cells; WD/DD: Well-Differentiated/Dedifferentiated Liposarcoma; WHO: World Health Organization

4.2. SoF Tables Systemtherapie - Therapie der metastasierten Erkrankung

AG Systemtherapie, Kasper

Summary of findings:

Doxorubicin plus DTIC plus cyclophasphamide (CIA) compared to Doxorubicin plus DTIC (A-DIC) for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus DTIC plus cyclophasphamide (CIA)
Comparison: Doxorubicin plus DTIC (A-DIC)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (median)	CIA 10.5 months; A-DIC 9.25 months; *p*=0.52	276 (1 RCT)	⨁⨁◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
DTIC: Dacarbazine

Baker 1987 (Comparison 1)

Summary of findings:

Doxorubicin plus DTIC plus actinomycin D (A-DIC-DACT) compared to Doxorubicin plus DTIC (A-DIC) for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus DTIC plus actinomycin D (A-DIC-DACT)
Comparison: Doxorubicin plus DTIC (A-DIC)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (median)	A-DIC-DACT 12.5 months; A-DIC 9.25 months; *p=0.32*	276 (1 RCT)	⨁⨁◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Baker 1987 (Comparison 2)

Summary of findings:

Trabectedin compared to Doxorubicin for metastatic STS

Patient or population: STS
Intervention: Trabectedin
Comparison: Doxorubicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Trabectedin**				
Overall survival (median follow-up: 17.6 months)	583 per 1.000	**490 per 1.000** (295 to 706)	**HR 0.77** (0.40 to 1.40)	121 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: N.R.)	567 per 1.000	**513 per 1.000** (342 to 715)	**HR 0.86** (0.50 to 1.50)	121 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
N.R.: not reported

Blay 2014

Summary of findings:

Doxorubicin plus Vindesine compared to Doxorubicin alone for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus Vindesine
Comparison: Doxorubicin alone

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (median follow-up: NR)	Doxorubicin plus Vindesine > Doxorubicin; *p=0.24*	298 (1 RCT)	⨁⨁◯◯ LOW
Progression free survival (median)	Doxorubicin plus Vindesine 4 months; Doxorubicin 3 months; *p=0.29*	298 (1 RCT)	⨁⨁◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; NR: not reported

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
N.R.: not reported

Borden 1990

Summary of findings:

Carminomycin compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Carminomycin
Comparison: Doxorubicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Carminomycin**				
Overall survival (median follow-up: NR)	718 per 1.000	**862 per 1.000** (682 to 1.000)	**RR 1.20** (0.95 to 1.52)	75 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: NR)	921 per 1.000	**939 per 1.000** (829 to 1.000)	**RR 1.02** (0.90 to 1.16)	71 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR**:** Risk ratio; NR: not reported

GRADE Working Group grades of evidence
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Bramwell 1983

Summary of findings:

Cyclophosphamide compared to Ifosfamide for metastatic STS

Patient or population: metastatic STS
Intervention: Cyclophosphamide
Comparison: Ifosfamide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Ifosfamide	Risk with Cyclo-phosphamide				
Overall survival (median follow-up: NR)	761 per 1.000	**792 per 1.000** (662 to 951)	**RR 1.04** (0.87 to 1.25)	135 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: NR)	925 per 1.000	**944 per 1.000** (861 to 1.000)	**RR 1.02** (0.93 to 1.11)	135 (1 RCT)	⨁⨁◯◯ LOW	

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Bramwell 1987

Summary of findings:

Trabectedin compared to doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Trabectedin
Comparison: doxorubicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with doxorubicin	**Risk with Trabectedin**				
Overall survival (median follow-up: 7.9 months Trabectedin24h, 7.8 months Doxorubicin)	767 per 1.000	**746 per 1.000** (434 to 962)	**HR 0.94** (0.39 to 2.25)	86 (1 RCT)	⊕⊕◯◯ LOW	
Progression free survival (median follow-up: 7.9 months Trabectedin24h, 7.8 months Doxorubicin)	395 per 1.000	**434 per 1.000** (286 to 616)	**HR 1.13** (0.67 to 1.90)	86 (1 RCT)	⊕⊕◯◯ LOW	

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Bui-Nguyen 2015

Summary of findings:

Aldoxorubicin compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Aldoxorubicin
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Aldoxorubicin**				
Overall survival (median follow-up: 13 months)	350 per 1.000	**270 per 1.000** (173 to 404)	**HR 0.73** (0.44 to 1.20)	123 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 13 months)	The median progression free was 4.6	The median progression free survival group was 8.3 (6,4 to 9,7)	*p<0.001*	126 (1 RCT)	⨁⨁◯◯ LOW	

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Chawla 2015

Summary of findings:

Conatumumab with Doxorubicin compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Conatumumab with Doxorubicin
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Conatumumab with Doxorubicin**				
Overall survival (median follow-up: 8.6 months)	214 per 1.000	**197 per 1.000** (96 to 405)	**RR 0.92** (0.45 to 1.89)	128 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression free survival (Re-analysis, median follow-up: 6.2 months)	286 per 1.000	**286 per 1.000** (194 to 410)	**HR 1.00** (0.64 to 1.57)	128 (1 RCT)	⨁⨁⨁◯ MODERATE	

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Demetri 2012

Summary of findings:

Trabectedin compared to Dacarbazine for metastatic STS

Patient or population: metastatic STS
Intervention: Trabectedin
Comparison: Dacarbazine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Dacarbazine	**Risk with Trabectedin**				
Overall survival (median follow-up: 8.6 months)	NR	NR	**HR 0.*87*** *p=0.37*	(1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (8.6 months)	647 per 1.000	**436 per 1.000** (368 to 518)	**HR 0.55** (0.44 to 0.70)	518 (1 RCT)	⨁⨁⨁◯ MODERATE	

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CI: Confidence interval; HR: Hazard Ratio; NR: not reported

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Demetri 2016

Summary of findings:

Ifosfamide plus Doxorubicin compared to Mitomycin plus Doxorubixin plus Cisplatin vs. Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention 1: Ifosfamide plus Doxorubicin
Intervention 2: Mitomycin plus Doxorubixin plus Cisplatin
Comparison: Doxorubicin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Progression (median follow-up: Ifosfamide plus Doxorubicin 2.2 months; Mitomycin plus Doxorubicin plus Cisplatin 1.7 months; Doxorubicin 1.4 months)	Ifosfamide plus Doxorubicin: 34%; Mitomycin plus Doxorubicin plus Cisplatin 32% Doxorubicin: 20% ; Ifosfamide plus Doxorubicin vs. Doxorubicin *p=0.03*	262 (1 RCT)	⨁◯◯◯ VERY LOW
Overall survival (median follow-up: Ifosfamide plus Doxorubicin 2.2 months; Mitomycin plus Doxorubicin plus Cisplatin 1.7 months; Doxorubicin 1.4 months)	No statistical significant difference (according authors)	262 (1 RCT)	⨁◯◯◯ VERY LOW

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CI: Confidence interval

GRADE Working Group grades of evidence
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Edmonson 1993

Summary of findings:

Brostallicin compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Brostallicin
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Brostallicin**				
Overall survival (median follow up: 20.75 months)	615 per 1.000	**683 per 1.000** (511 to 911)	**RR 1.11** (0.83 to 1.48)	118 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow up: 20.75 months)	846 per 1.000	**939 per 1.000** (702 to 1.000)	**RR 1.11** (0.83 to 1.28)	118 (1 RCT)	⨁⨁◯◯ LOW	

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CI: Confidence interval; RR: Risk ratio

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Gelderblom 2014

Summary of findings:

Gemcitabine plus Docetaxel plus Bevacizumab compared to Gemcitabine plus Docetaxel plus Placebo for metastatic STS

Patient or population: metastatic STS
Intervention: Gemcitabine plus Docetaxel plus Bevacizumab
Comparison: Gemcitabine plus Docetaxel plus Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Gemcitabine plus Docetaxel plus Placebo	**Risk with Gemcitabine plus Docetaxel plus Bevacizumab**				
Overall survival (median follow-up: 25 months)	500 per 1.000	**524 per 1.000** (354 to 715)	**HR 1.07** (0.63 to 1.81)	107 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 25 months)	833 per 1.000	**866 per 1.000** (734 to 952)	**HR 1.12** (0.74 to 1.70)	107 (1 RCT)	⨁⨁◯◯ LOW	

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Hensley 2015

Summary of findings:

CAELYX compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: CAELYX
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with CAELYX**				
Overall survival (median follow-up: NR)	22 per 1.000	**80 per 1.000** (9 to 690)	**RR 3.60** (0.42 to 31.03)	95 (1 RCT)	⨁◯◯◯ VERY LOW	
Progression free survival (median follow-up: NR)	444 per 1.000	**480 per 1.000** (311 to 742)	**RR 1.08** (0.70 to 1.67)	95 (1 RCT)	⨁⨁◯◯ LOW	

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Judson 2001

Summary of findings:

Doxorubicin plus Ifosfamide compared to Doxorubicin alone for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus Ifosfamide
Comparison: Doxorubicin alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin alone	**Risk with Doxorubicin plus Ifosfamide**				
Overall survival (median follow-up: Doxorubicin plus Ifosfamide 59 months; Doxorubicin 56 months)	825 per 1.000	**764 per 1.000** (688 to 833)	**HR 0.83** (0.67 to 1.03)	455 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: Doxorubicin plus Ifosfamide 59 months; Doxorubicin 56 months)	912 per 1.000	**835 per 1.000** (768 to 888)	**HR 0.74** (0.60 to 0.90)	455 (1 RCT)	⨁⨁◯◯ LOW	

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Judson 2014

Summary of findings:

Trabectedin compared to best supportive care for metastatic STS

Patient or population: metastatic STS
Intervention: Trabectedin
Comparison: best supportive care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best supportive care	**Risk with Trabectedin**				
Overall survival (median follow-up: 8.9 months)	459 per 1.000	**228 per 1.000** (105 to 453)	**HR 0.42** (0.18 to 0.98)	76 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression free survival (median follow-up: 8.9 months)	Median 5.6 months	Median 0.9 months	**HR 0.07** (0.03 to 0.16)	76 (1 RCT)	⨁⨁◯◯ LOW	

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Kawai 2015

Summary of findings:

Ifosfamide compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Ifosfamide
Comparison: Doxorubicin

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Doxorubicin	**Ifosfamide**				
Overall survival (median follow-up: 45 months) Ifosfamide 3x3	Median 12.0 months	Median 10.92 months	**HR 1.291** (0.973 to 1.712)	310 (1 RCT)	⨁⨁◯◯ LOW	
Overall survival (median follow-up: 45 months) Ifosfamide 9	Median 12.0 months	Median 10.92 months	**HR 1.120** (0.842 to 1.495)	310 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 45 months) Ifosfamide 3x3	Median 2.52 months	Median 2.16 months	**HR 1.083** (0.829 to 1.415)	310 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 45 months) Ifosfamide 9	Median 2.52 months	Median 3.0 months	**HR 0.856** (0.653 to 1.122)	310 (1 RCT)	⨁⨁◯◯ LOW	

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Lorigan 2007

Summary of findings:

Gemcitabine plus Docetaxel compared to Gemcitabine alone for metastatic STS

Patient or population: metastatic STS
Intervention: Gemcitabine plus Docetaxel
Comparison: Gemcitabine alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Gemcitabine alone	**Risk with Gemcitabine plus Docetaxel**				
Overall survival	Median: Gemcitabine plus Docetaxel 17.9 months; Gemcitabine 11.5 months; p=0.97		NR	122 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: NR)	367 per 1.000	**246 per 1.000** (143 to 426)	**RR 0.67** (0.39 to 1.16)	122 (1 RCT)	⨁⨁◯◯ LOW	

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Maki 2007

Summary of findings:

Trabectedin plus Doxorubicin compared to Doxorubicin alone for metastatic STS

Patient or population: metastatic STS
Intervention: Trabectedin plus Doxorubicin
Comparison: Doxorubicin alone

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Doxorubicin alone	**Trabectedin plus Doxorubicin**				
Overall survival (median follow-up: 13 months)	13.7 months	13.3 months)	**HR 1.21** (0.77 to 1.92)	113 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 13 months)	5.7 months	5.5 months	**HR 1.16** (0.79 to 1.71)	113 (1 RCT)	⨁⨁◯◯ LOW	

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Martin-Broto 2016

Summary of findings:

High dose Doxorubicin plus Ifosfamide compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: High dose Doxorubicin plus Ifosfamide
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with High dose Doxorubicin plus Ifosfamide**				
Overall survival (median follow-up:12.3 months)	NR	NR	**HR 0.71** (0.45 to 1.13)	132 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 12.3 months)	836 per 1.000	**844 per 1.000** (723 to 931)	**HR 1.03** (0.71 to 1.48)	132 (1 RCT)	⨁⨁◯◯ LOW	

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CI: Confidence interval; HR: Hazard Ratio; NR: not reported

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Maurel 2009

Summary of findings:

Pazopanib plus best supportive care (BSC) compared to BSC alone for metastatic STS

Patient or population: metastatic STS
Intervention: Pazopanib plus best supportive care (BSC)
Comparison: BSC alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with BSC alone	**Risk with Pazopanib plus best supportive care (BSC)**				
Overall survival (median follow-up: Pazopanib 26.4 months, BSC 28.9 months)	756 per 1.000	**735 per 1.000** (546 to 889)	**HR 0.94** (0.56 to 1.56)	81 (1 RCT)	⨁⨁◯◯ LOW	
progression free survival (median follow-up: Pazo-panib 26.4 months, BSC 28.9 months)	951 per 1.000	**832 per 1.000** (673 to 945)	**HR 0.59** (0.37 to 0.96)	81 (1 RCT)	⨁⨁◯◯ LOW	

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CI: Confidence interval; HR: Hazard Ratio

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Mir 2016

Summary of findings:

Epirubicin compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Epirubicin
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Epirubicin**				
Overall survival (median follow-up: NR)	620 per 1.000	**658 per 1.000** (583 to 732)	**RR 1.06** (0.94 to 1.18)	375 (2 RCTs)	⨁⨁◯◯ LOW	
Time to Progression (median follow-up: NR)	964 per 1.000	**877 per 1.000** (810 to 964)	**RR 0.91** (0.84 to 1.00)	167 (1 RCT)	⨁⨁◯◯ LOW	
Progression Free Survival (Follow-up: 1 year)	135 per 1.000	**116 per 1.000** (57 to 237)	**RR 0.86** (0.42 to 1.76)	208 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; NR: not reported

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Mouridsen1987, Nielsen 1998

Summary of findings:

Pazopanib compared to Placebo for metastatic STS

Patient or population: metastatic STS
Intervention: Pazopanib
Comparison: Placebo

Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Pazopanib**				
Overall Survival (Median months: IG: 12.5, CG: 10.7)	772 per 1.000	**720 per 1.000** (629 to 807)	**HR 0.86** (0.67 to 1.11)	362 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression Free Survival (Median months: IG: 4.6, CG: 1.6)	862 per 1.000	**459 per 1.000** (378 to 547)	**HR 0.31** (0.24 to 0.40)	362 (1 RCT)	⨁⨁⨁⨁ HIGH	
Health-related quality of life	The mean change from baseline until last score was **-5.13**	The mean change from baseline until last score was -6.82	MD -1.69 [-5.58, 2.20]	369 (1 RCT)	⨁⨁⨁◯ MODERATE	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; MD: Mean difference; IG: Intervention group; CG: control group

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

PALETTE STUDY Coens 2015; van der Graf 2012

Summary of findings:

Gemcitabine plus Docetaxel compared to Gemcitabine for uterine group of STS

Patient or population: uterine group of STS
Intervention: Gemcitabine plus Docetaxel
Comparison: Gemcitabine

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Gemcitabine	**Risk with Gemcitabine plus Docetaxel**				
Overall Survival (median)	Gemcitabine plus Docetaxel: 23 months; Gemcitabine: 20 months			42 (1 RCT)	⨁◯◯◯ VERY LOW	
Progression Free Survival (follow-up NR)	619 per 1.000	**712 per 1.000** (464 to 1.000)	**RR 1.15** (0.75 to 1.78)	42 (1 RCT)	⨁◯◯◯ VERY LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Pautier 2012

Summary of findings:

Gemcitabine plus Docetaxel compared to Gemcitabine for nonuterine group of STS

Patient or population: nonuterine group of STS
Intervention: Gemcitabine plus Docetaxel
Comparison: Gemcitabine

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Gemcitabine	**Risk with Gemcitabine plus Docetaxel**				
Overall Survival (median)	Gemcitabine plus Docetaxel: 13 months; Gemcitabine: 15 months			41 (1 RCT)	⨁◯◯◯ VERY LOW	
Progression Free Survival (median follow-up NR)	682 per 1.000	**634 per 1.000** (402 to 989)	**RR 0.93** (0.59 to 1.45)	41 (1 RCT)	⨁◯◯◯ VERY LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; NR: not reported

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Pautier 2012

Summary of findings:

Adriamycin, Cyclophosphamide, Methotrexate plus Amphotericin B compared to Adriamycin, Cyclophosphamide, Methotrexate for metastatic STS

Patient or population: metastatic STS
Intervention: Adriamycin, Cyclophosphamide, Methotrexate plus Amphotericin B
Comparison: Adriamycin, Cyclophosphamide, Methotrexate

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall Survival (Median in months)	ACM+AMB: 6 months; ACM: 7 months; *p=0.4*	94 (1 RCT)	⨁◯◯◯ VERY LOW
Progression free survival	ACM+AMB: 5 months; ACM: 5 months; *p=0.4*	94 (1 RCT)	⨁⨁◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Presant 1984

Summary of findings:

ACT, DTIC plus VCR vs. ACT, DTIC plus VCR plus ADR, CTX plus MTX compared to ADR, CTX plus MTX for metastatic STS

Patient or population: metastatic STS
Intervention: ACT, DTIC plus VCR vs. ACT, DTIC plus VCR plus ADR, CTX plus MTX
Comparison: ADR, CTX plus MTX

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall Survival (Median months)	ACT, DTIC plus VCR: 13 months; ACT, DTIC plus VCR plus ADR, CTX plus MTX: 10 months; ADR, CTX plus MTX:12 months	(1 RCT)	⨁⨁◯◯ LOW
Progression free survival	All patients relapsed after 70 weeks; p>0.5 all comparisions	(1 RCT)	⨁⨁◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; ACT: actinomycin D; DTIC: dimethyl triazeno imidazole carboxamide; VCR: vincristine; ADR: adriamycin; MTX: methotrexate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Presant 1981

Summary of findings:

Paclitaxel plus Bevacizumab compared to Paclitaxel for metastatic STS

Patient or population: metastatic STS
Intervention: Paclitaxel plus Bevacizumab
Comparison: Paclitaxel

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Paclitaxel	**Risk with Paclitaxel plus Bevacizumab**				
Overall survival (median follow-up: 21.0 months)	500 per 1.000	**560 per 1.000** (330 to 950)	**RR 1.12** (0.66 to 1.90)	49 (1 RCT)	⨁⨁◯◯ LOW	
Progression Free Survival (median follow-up: 21.0 months)	583 per 1.000	**607 per 1.000** (373 to 986)	**RR 1.04** (0.64 to 1.69)	49 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Ray-Coquard 2015

Summary of findings:

Doxorubicin plus Palifosfamide compared to Doxorubicin plus Placebo for STS

Patient or population: STS
Intervention: Doxorubicin plus Palifosfamide
Comparison: Doxorubicin plus Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin plus Placebo	**Risk with Doxorubicin plus Palifosfamide**				
Overall Survival (median follow-up: 11 months Doxorubicin plus Palifosfamide; 11.5 months Doxorubicin plus Placebo)	Median 15.9 months	Median 16.9 months	**HR 1.05** (0.79 to 1.39)	(1 RCT)	⨁⨁◯◯ LOW	
Progression Free Survival (median follow-up: 11 months Doxorubicin plus Palifosfamide; 11.5 months Doxorubicin plus Placebo)	Median 5.2 months	Median 6.0 months	**HR 0.86** (0.68 to 1.08)	(1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; HR: Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Ryan 2016

Summary of findings:

CYVADIC vs. Doxorubicin plus Ifosfamide compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: CYVADIC vs. Doxorubicin plus Ifosfamide
Comparison: Doxorubicin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall Survival (Median weeks)	CYVADIC: 51 months; Doxorubicin plus Ifosfamide: 55 months; Doxorubicin: 52 months	663 (1 RCT)	⨁◯◯◯ VERY LOW
Progression free survival (Median weeks)	CYVADIC: 48 months; Doxorubicin plus Ifosfamide: 44 months; Doxorubicin: 46 months	663 (1 RCT)	⨁◯◯◯ VERY LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
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Santoro 1995

Summary of findings:

Eribulin compared to Dacarbazine for STS

Patient or population: STS
Intervention: Eribulin
Comparison: Dacarbazine

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Dacarbazine	**Risk with Eribulin**				
Overall Survival (Median Follow-up: 31 months)	Median 11.5 months	Median 13.5 months	**HR 0.77** (0.62 to 0.95)	452 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression Free Survival (Median Follow-up: 2.6 months)	Median 2.6 months	Median 2.6 months	**HR 0.88** (0.71 to 1.09)	452 (1 RCT)	⨁⨁◯◯ LOW	
Global health (QLQ-C30, at progression)	The mean global health status at progression was **0**	The mean global health status at progression in the intervention group was 6 higher (1.57 higher to 10.43 higher)	-	399 (1 RCT)	⨁⨁⨁◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; HR: Hazard Ratio; MD: Mean difference; QLQ-C30: European Organization for Research and Treatment of Cancer 30-item core QoL questionnaire

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Schoffski 2016, Hudgens 2017

Summary of findings:

Doxorubicin plus Olaratumab compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus Olaratumab
Comparison: Doxorubicin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Doxorubicin plus Olaratumab**				
Overall Survival (follow-up duration: NR)	776 per 1.000	**498 per 1.000** (362 to 654)	**HR 0.46** (0.30 to 0.71)	133 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression Free Surivival (follow-up duration: NR)	716 per 1.000	**570 per 1.000** (426 to 723)	**HR 0.67** (0.44 to 1.02)	132 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio; NR: not reported

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Tap 2016

Summary of findings:

Doxorubicin plus Evofosfamide compared to Doxorubicin for metastatic STS

Patient or population: metastatic STS
Intervention: Doxorubicin plus Evofosfamide
Comparison: Doxorubicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Doxorubicin	**Risk with Doxorubicin plus Evofosfamide**				
Overall Survival (Median months: IG: 19, CG: 18.4	644 per 1.000	**665 per 1.000** (597 to 713)	**HR 1.06** (0.88 to 1.21)	640 (1 RCT)	⨁⨁◯◯ LOW	
Progression Free Survival (Median months: IG: 6.3, CG: 6.0)	598 per 1.000	**539 per 1.000** (471 to 608)	**HR 0.85** (0.70 to 1.03)	640 (1 RCT)	⨁⨁◯◯ LOW	
QoL (Follow-up: 6 and 12 months) (EQ-5D-5L health utilities index)	The median QoL (Follow-up: 6 and 12 months) was **0.87**	The median QoL (Follow-up: 6 and 12 months) in the intervention group was 0,02 lower (0.87 to 0.85)	-	(1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; HR**:** Hazard Ratio; IG: Intervention group; CG: control group; EQ-5D-5L: EuroQol five dimensions questionnaire with five-level scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Tap 2017

Summary of findings:

Oxaliplatin plus Dacarbazine compared to Vincristine, Epirubicin, Cyclophosphamide for metastatic STS

Patient or population: metastatic STS
Intervention: Oxaliplatin plus Dacarbazine
Comparison: Vincristine, Epirubicin, Cyclophosphamide

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Vincristine, Epirubicin, Cyclo-phosphamide	**Risk with Oxaliplatin plus Dacarbazine**				
Overall survival (Median Follow-up: 24 months)	125 per 1.000	**66 per 1.000** (6 to 661)	**RR 0.53** (0.05 to 5.29)	31 (1 RCT)	⨁◯◯◯ VERY LOW	
Progression Free Survival (Median Follow-up: 24 months)	750 per 1.000	**330 per 1.000** (158 to 720)	**RR 0.44** (0.21 to 0.96)	31 (1 RCT)	⨁◯◯◯ VERY LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Zong 2009

5. Systemtherapie (GIST) - Adjuvante Chemotherapie

5.1. Evidenztabelle Systemtherapie (GIST) - Adjuvante Chemotherapie

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (IG/CG or IG only) (all or the five most frequent ae)	Study type, level of evidence and risk of bias
Casali, P.G., et al., Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol, 2015. 33(36): p. 4276-83.	**Region/Setting** This study was conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group in collaboration with the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas in 2004. **Inclusion criteria** -histologically proven diagnosis of primary resected GIST -positive immunostaining for KIT (CD117) -risk of relapse documented on the surgical specimen according to the 2002 National Institutes of Health (NIH) Consensus Diagnosis of GIST9 as high risk (tumor size >10 cm, mitotic rate >10/50 HPF, or tumor size >5 cm and mitotic rate >5/50 HPF) or intermediate risk (tumor size ≤5 cm and mitotic rate 6/50 to 10/50HPFor tumor size >5 to10 cm and mitotic rate ≤5/50 HPF) -surgery had to be performed from 2 weeks to 3 months before random assignment -surgical margins either R0 or R1/ Intraoperative tumor rupture was coded as R1 and properly recorded by a panel of expert surgeons who had access to the original surgical reports -no prior radiation therapy or systematic treatment for GIST -age ≥18 years -WHO performance status 0 to 2 **Exclusion criteria** -Distant metastases, including any peritoneal lesions not contiguous to the primary tumor -Severe and/or uncontrolled concurrent medical disease, nor any prior or ongoing other malignancy, except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cancer adequately treated with eradicative intent from which the patient	**Intervention(s)** Imatinib 400 mg per day for 2 years Guidelines were circulated after amending the protocol, recommending restarting imatinib at a dose of 400 mg daily or possibly 800 mg for patients with an exon 9 KIT-mutated GIST, with the only logical exception being those patients who experienced relapse during imatinib therapy **Control** No further antitumoral therapy **Randomised patients** 454/454	Neutropenia Grade 3 and/or 4 [%] 6.2 Weight loss or gain Grade 3 and/or 4 [%] 3.3 Infection Grade 3 and/or 4 [%] 3.1 ALT increase Grade 3 and/or 4 [%] 2.8	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

	had been continuously free for ≥5 years **Patient characteristics** Gender n(%) Male 232(51.1)/ 234(51.5) Female 222(48.9)/ 220(48.5) Age median(range) 59(18-86)/58(20-89) Tumor site Gastric 250(55.1)/253(55.7) Other 204(44.9)/201(44.3) Tumor size[cm] n(%) <2 1(0.2)/2(0.4) 2-5 53(11.7)/43/9.5 5-10283(62.3)/290(63.9) ≥10 117(25.8)/119(26.2)			
Cohen, M.H., et al., Approval summary: imatinib mesylate in the adjuvant treatment of malignant gastrointestinal stromal tumors. Oncologist, 2010. 15(3): p. 300-7.	**Region/Setting** This study was conducted by the American College of Surgeons Oncology Group at 234 study sites in the U.S. and Canada in 2002. **Inclusion criteria** -age ≥18 years -informed consent -Eastern Cooperative Oncology Group performance status score ≤2 -histologic diagnosis of primary GIST (without peritoneal or distant metastasis) expressing Kit protein by immunochemistry and with a tumor size ≥3 cm in the maximum dimension -complete gross resection (i.e., including R0 [negative microscopic margins] and R1 [positive microscopic margins] resections) of the primary GIST within 70 days prior to registration -appropriate laboratory values -negative postoperative radiologic studies -negative pregnancy test -no postoperative cancer therapy -no active infection -no New York Heart Association class 3 or 4 cardiac disease **Exclusion criteria** NR **Patient characteristics** Gender n(%) Male 170(47.4)/191(54.0) Female 189(52.6)/163(46.0)	**Intervention(s)** 400 mg imatinib orally once daily for 1 year **Control** Matched placebo **Randomised patients** 359/354	Diarrhea grade ≥3 [%] 3.0/1.4 Rash (exfoliative) grade ≥3 [%] 2.7/0 Abdominal pain grade ≥3 [%] 3.0/1.4 ALT increase grade ≥3 [%] 2.7/0 Neutropenia grade ≥3 [%] 3.3/0.9	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Age[y] Median 59.0/58.0 Location of tumor n(%) Stomach 209(58.2)/234(66.1) Small intestine 2(0.6)/4(1.1) Rectum 5(1.4)/5(1.4) Other 141(39.3)/111(31.4) Unknown 2(0.6)/0 Tumor size[cm] n(%) 3-6 143(39.8)/149(42.1) 6- <10 123(34.3)/119(33.6) ≥10 93(25.9)/86(24.3)			
ACOSOG Z9001 Trial Corless, C.L., et al., Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol, 2014. 32(15): p. 1563-70. Dematteo, R.P., et al., Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet, 2009. 373(9669): p. 1097-104.	**Region/Setting** 230 insitutions **Inclusion criteria** -histologic diagnosis of localized, primary GIST measuring at least 3 cm that expressed KIT protein (CD117) by immunohistochemistry using the Dako antibody (Denmark) -Patients were to be registered within 70 days following complete gross tumor resection (regardless of microscopic margins) and start therapy by 84 days -age≥18 years -Eastern Cooperative Oncology Group (ECOG)/Zubrod performance status of ≤ 2 -Within 28 days prior to registration, patients must have been deemed free of tumor -adequate renal, hematologic, and hepatic function -negative serum pregnancy test **Exclusion criteria** -Prior imatinib use or chemotherapy, radiation therapy, or investigational treatment following surgery -active infection requiring antibiotics within 14 days prior to registration -female patients who were breast feeding -patients with New York Heart Association Class 3 or 4 cardiac disease -patients taking full dose warfarin **Patient characteristics** Gender n(%) Male 154(48.5)/180(54.9) Female 163(51.5)/148(45.1) Age[y] Median(range) 59(18-88)/58(18-91)	**Intervention(s)** 400 mg imatinib daily for 1 year. Four capsules of 100 mg imatinib daily with food. **Control** Placebo **Randomised patients** 359/354	**median follow up74 months** Adverse events in imatinib group n=57 Adverse events in placebo group n=11 **median follow-up19.7 months** Dermatitis [%] Grade3 3/0 Grade4 0/0 Abdominal pain [%] Grade3 3/1 Grade4 0/0 Nausea [%] Grade3 2/0 Grade4 0/0 Neutropenia [%] Grade3 2/<1 Grade4 1/<1 Diarrhea [%] Grade3 2/1 Grade4 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Tumor location n(%) Stomach 184(58.2)/218(66.5) Small intestine 111(35.1)/93(28.4) Rectum 4(1.3)/5(1.5) Other 17(5.4)/12(3.7) Tumor size[cm] Median(range) 6.5(3-37)/6.5(3-43)			

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; EORTC : European Organisation for Research and Treatment of Cancer; GIST: gastrointestinal stromal tumor; KIT: tyrosine-protein kinase Kit/CD117; NIH: National Institutes of Health; HPF: high power field; WHO: World Health Organization; ALT: alanine transaminase; RCT: randomized controlled trial; ECOG: Eastern Cooperative Oncology Group

5.2. SoF Tables Systemtherapie (GIST) - Adjuvante Chemotherapie

AG Systemtherapie, Kasper

Summary of findings:

Imatinib compared to observation for GIST

Patient or population: GIST
Intervention: Imatinib
Comparison: control

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with Imatinib**				
Overall survival (median follow-up: Imatinib 56.4 months; control 55.2 months)	64 per 1.000	**73 per 1.000** (45 to 118)	**RR 1.14** (0.70 to 1.84)	908 (1 RCT)	⊕⊕◯◯ LOW	
Relapse free survival (median follow-up: Imatinib 56.4 months; control 55.2 months)	355 per 1.000	**266 per 1.000** (220 to 323)	**RR 0.75** (0.62 to 0.91)	908 (1 RCT)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Casali 2015

Summary of findings:

Imatinib compared to placebo for GIST

Patient or population: GIST
Intervention: Imatinib
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Imatinib**				
Overall survival (median follow-up: NR)	23 per 1.000	**14 per 1.000** (5 to 42)	**RR 0.62** (0.20 to 1.87)	713 (1 RCT)	⊕◯◯◯ VERY LOW	
Overall survival (median follow-up: 19.7 months)[1]	NR	**NR**	**HR 0.66** (0.22 to 2.03)	713 (1 RCT)	⊕⊕◯◯ LOW	
Overall survival (median follow-up: 74 months)[1]	*p*=0.19			713 (1 RCT)	⊕⊕◯◯ LOW	
Recurrence free survival (median follow-up: 19.7 months)[1]	NR	**NR**	**HR 0.35** (0.22 to 0.53)	713 (1 RCT)	⊕⊕◯◯ LOW	
Recurrence free survival (median follow-up: 74 months)[1]	NR	**NR**	**HR 0.60** (0.43 to 0.75)	713 (1 RCT)	⊕⊕◯◯ LOW	
Recurrence free survival (median follow-up: 14 months)	198 per 1.000	**84 per 1.000** (55 to 126)	**HR 0.398** (0.259 to 0.610)	713 (1 RCT)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
[1] ACOSOG Z9001 Trial

Cohen 2010; ACOSOG Z9001 Trial (Corless 2014; Dematteo 2009)

6. Systemtherapie (GIST) - Therapie der metastasierten Erkrankung

6.1. Evidenztabelle Systemtherapie (GIST) - Therapie der metastasierten Erkrankung

AG Systemtherapie, Kasper

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (IG/CG or IG only) (all or the five most frequent ae)	Study type, level of evidence and risk of bias
Adenis, A., et al., Masitinib in advanced gastrointestinal stromal tumor (GIST) after failure of imatinib: a randomized controlled open-label trial. Ann Oncol, 2014. 25(9): p. 1762-9.	**Region/Setting** nine study centers across France **Inclusion criteria** - Patients showing disease progression while treated under imatinib ≥400 mg/day - aged 18 years or older; - histological confirmation of metastatic or locally advanced nonoperable GIST; - immunohistochemical detection of KIT (CD117) expression; - Eastern Cooperative Oncology Group (ECOG) performance status ≤2; - no prior TKI therapy other than imatinib, with the last imatinib administration being at least 4 days before randomization; - normal renal, cardiac and hepatic functions. **Exclusion criteria** NR **Patient characteristics** Age[y] mean (range) 62(31-82)/67(41-85) Gender n(%) Female 12(52)/10(48) Primary tumor localization n(%) Small bowel 11(48)/11(52) Gastroesophageal 8(35)/6(27) Other 4(17)/4(19) Tumor classification confirmed n(%) Locally advanced 2(9)/3(14) Metastatic 21(91)/18(86) Metastases tumor localization n(%)	**Intervention(s)** Masitinib (12 mg/kg/day administered orally in two daily intakes) **Control** Sunitinib (50 mg/day administered orally in a 4-weeks-on/2-weeks-off regimen) **Randomised patients** 23/21	All ae [%] 96/100 Severe ae [%] 52/91 Nausea/vomiting[%] 16/7 Diarrhea[%] 12/12 Edema[%] 11/9 Rash/pruritus[%] 13/12 Anemia [%] 12/6	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Liver 18(78)/13(62) Peritoneum 6(26)/8(38) Lung 2(9)/1(5) Pelvis (nonbone) 0(0)/2(10) Other 11(48)/9(43) KIT exon mutation n(%) Not done: 4(17)/4(17) Exon 11: 15(79)/14(82) Exon 9: 3(16)/2(12) Exon 13: 0(0)/1(6) None (wild-type): 1(5)/0(0) Ratio exon 11:9: 5:1/7:1			
Blay, J.Y., et al., Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol, 2015. 16(5): p. 550-60.	**Region/Setting** Multicentre trial **Inclusion criteria** - aged ≥18 years, - histologically confirmed unresectable or metastatic GIST, - no prior systemic therapy for GIST or recurrence of GIST ≥6 months after stopping adjuvant treatment with imatinib; - at least one measurable site of disease on computed tomography/magnetic resonance imaging, as defined by Response Evaluation Criteria In Solid Tumors based on investigator assessment, - a World Health Organization performance score of 0 to 2 (capable of self-care, but not any work), - normal organ, electrolyte and marrow function. **Exclusion criteria** -active non-GIST malignancy within 10 years (except basal cell skin cancer and cervical carcinoma in situ) - impaired cardiac function (eg, QTcF >450 msec, left ventricular ejection fraction <45%, complete left bundle branch block, clinically significant bradycardia [<50 beats per minute], history of myocardial function or unstable angina within 12 months). - Bleeding disorders unrelated to cancer - known symptomatic brain metastases **Patient characteristics** Age[y] mean(range) 59.0(18-84)/59.0(18-88) Gender n(%) Male 179(55.2)/187(58.4) WHO performance status n(%) 0 204(63.0)/194(60.6)	**Intervention(s)** oral nilotinib hydrochloride monohydrate (AMN107; Novartis Pharmaceuticals; East Hanover, NJ, USA) 400 mg twice daily **Control** oral imatinib mesylate (STI571; Novartis Pharmaceuticals; East Hanover, NJ, USA) 400 mg once daily. In the imatinib arm, 400 mg twice daily was recommended for patients with a KIT exon 9 mutation. **Randomised patients** 324/320	Abdominal pain [%] Grade3 3.1/3.8 Grade4 0.3/0.3 ALT increase [%] Grade3 3.4/1.6 Grade4 0.3/0 Anemia [%] Grade3 3.4/3.2 Grade4 2.2/2.2 Hypophosphatemia [%] Grade3 1.9/6.0 Grade4 0/0 Lipase increase [%] Grade3 4.0/3.5 Grade4 0.6/0.3	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	1 106(32.7)/112(35.0) 2 11(3.4)/9(2.8) Primary GIST site n(%) Stomach 103(31.8)/123(38.4) Small intestine 117(36.1)/98(30.6) Large intestine 17(5.2)/21(6.6) Other 81(25)/69(21.6) Unknown 6(1.9)/9(2.8)			
GRID Study Demetri, G.D., et al., Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 2013. 381(9863): p. 295-302. Poole, C.D., et al., Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer, 2015. 18(3): p. 627-34.	**Region/Setting** 57 hospital sites in 17 countries (Austria, Belgium, Canada, China, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Singapore, South Korea, Spain, UK, and USA). **Inclusion criteria** - histologically confirmed, metastatic and/or unresectable GIST, with failure of at least: (1) prior imatinib (due to either disease progression or intolerance) and (2) prior sunitinib (due solely to progression to decrease heterogeneity, since the definition of intolerance is more variable with this agent). Patients could have received other systemic therapies, including investigational agents, except any VEGFR inhibitors other than sunitinib. - at least one measurable lesion on computed tomography or magnetic resonance imaging; - resolution of all toxic effects of prior therapy to grade 1 or less; - adequate haematological, hepatic, cardiac, and renal function; - an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. **Exclusion criteria** Subjects who meet any of the following criteria at the time of screening will be excluded from the study. 1. Prior treatment with regorafenib. Subjects permanently withdrawn from study participation will not be allowed to re-enter the study. 2. Prior treatment with any vascular endothelial growth factor receptor (VEGFR) inhibitor except sunitinib. 3. Subjects who have received: – Any other approved tyrosine kinase inhibitor within 1 week or a minimum of 5 drug half-lives, whichever is longer (i.e. within 7 days for imatinib, or within 10 days for sunitinib); – Any other investigational new drugs within 4 weeks or 5 drug half-lives (if drug half-life in subjects is known), whichever is shorter. 4. Cancer other than GIST within 5 years before randomisation EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumours (Ta [non-invasive tumour], and Tis [carcinoma in situ]). 5. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication. 6. Pregnancy or breast feeding. Women of childbearing potential not employing	**Intervention(s)** regorafenib 160 mg orally once daily **Control** Matching placebo for the first 3 weeks of each 4-week cycle **Randomised patients** 133/66	Any ae [%] Grade3 58.3/7.6 Grade4 1.5/1.5 Hand–foot skin reaction [%] Grade3 19.7/0 Grade4 1.5/0 Hypertension [%] Grade3 22.7/3.0 Grade4 0.8/0 Diarrhea [%] Grade3 5.3/0 Grade4 0/0 Fatigue [%] Grade3 2.3/0 Grade4 0/0 Rash, maculopapular [%] Grade3 2.3/0 Grade4 0/0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	adequate contraception. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of study medication and a negative result must be documented before start of study medication. Women of childbearing potential and men must agree to use adequate contraception (barrier method of birth control) since signing of the informed consent form until at least 3 months after the last study drug administration. The definition of adequate contraception will be based on the judgment of the treating investigator or a designated associate. 7. Congestive heart failure New York Heart Association class ≥ 2. 8. Unstable angina (angina symptoms at rest, new-onset angina, i.e. within the past 3 months) or myocardial infarction within the past 6 months before start of study medication. 9. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted). 10. Uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management. 11. Phaeochromocytoma. 12. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) or pulmonary embolism within the 6 months before start of study drug. 13. Venous thrombotic events such as deep vein thrombosis within the 3 months before start of study drug. 14. Ongoing infection NCI-CTCAE version 4·0 grade > 2. 15. Known history of human immunodeficiency virus infection. 16. Seizure disorder requiring medication. 17. Symptomatic metastatic brain or meningeal tumours. 18. History of organ allograft. 19. Evidence or history of bleeding diathesis. Any haemorrhage or bleeding event NCI-CTCAE version 4·0 grade ≥3 within 4 weeks before the start of study drug. 20. Non-healing wound, ulcer, or bone fracture. 21. Renal failure requiring haemodialysis or peritoneal dialysis. 22. Dehydration NCI-CTCAE version 4·0 grade ≥ 1. 23. Substance abuse or medical, psychological, or social conditions that may interfere with the subject's participation in the study or evaluation of the study results. 24. Known hypersensitivity to the study drug, study drug class, or excipients in the formulation. 25. Any illness or medical conditions that are unstable or could jeopardise the safety of the subject and his or her compliance in the study. 26. Interstitial lung disease with ongoing signs and symptoms at the time of screening. 27. Inability to swallow oral medications. 28. Persistent proteinuria of NCI-CTCAE version 4·0 grade ≥ 3 (> 3·5 g/24 hours, measured by urine protein:creatinine ratio on a random urine sample). 29. Any malabsorption condition. 30. Close affiliation with the investigational site, e.g. a close relative of the investigator or dependent person (e.g. employee of or student at the investigational site who would have access to study records and case report form data).			

	31. Unresolved toxicity higher than NCI-CTCAE version 4·0 grade 1 (excluding alopecia, anaemia, and hypothyroidism) attributed to any prior therapy/procedure. 32. Concomitant participation in another clinical study. 33. Left ventricular ejection fraction < 50% or below the lower limit of normal for the institution (whichever is higher). 34. Pleural effusion or ascites that causes respiratory compromise (NCI-CTCAE version 4·0 grade ≥2 dyspnoea). **Patient characteristics** Age[y] median(range) 60(18–82)/61(25–87) Gender n(%) Male 85(63.9)/42(63.6) Female 48(36.1)/24(36.4) Race n(%) White 90(67.7)/45(68.2) Black or African American 0/1(1.5) Asian 34(25.6)/16(24.2) Not reported or missing 9(6.8)/4(6.1) ECOG performance status n(%) 0: 73(54.9)/37(56.1) 1: 60(45.1)/29(43.9) Previous systemic anticancer therapy n(%) 2 lines: 74(55.6)/39(59.1) >2 lines 59(44.4)/27(40.9) Duration of previous imatinib therapy n(%) ≤6 months: 18(13.5)/4(6.1) 6-18 months: 26(19.5)/7(10.6) >18 months: 89(66.9)/55(83.3)			
Demetri, G.D., et al., Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet, 2006. 368(9544): p. 1329-38.	**Region/Setting** 56 centres in 11 countries **Inclusion criteria** - histologically proven malignant gastrointestinal stromal tumour that was not amenable to surgery, radiation, or a combination of different approaches with curative intent, and confirmed objective failure of previous imatinib therapy. - evidence of disease that was unidimensionally measurable with CT or MRI; - failure of treatment with imatinib - based either on progression of disease (according to Response Evaluation Criteria in Solid Tumours [RECIST] or WHO criteria) or on unacceptably severe toxic effects during imatinib therapy that precluded further treatment; - imatinib last administered at least 2 weeks before randomisation;	**Intervention(s)** Initial sunitinib daily for 4 consecutive weeks followed by a 2-week period without treatment, comprising a 6-week cycle. Sunitinib was given at a starting daily dose of 50 mg. Study drugs were given orally in the morning with water and without regard to meals beginning on day 1 of the study	Fatigue [%] Grade 3 5/2 Grade 4 0/0 Hand-foot-Syndrome [%] Grade 3 4/0 Grade 4 0/0 Neutropenia [%] Grade 3 8/0 Grade 4 2/0 Lymphopenia [%] Grade 3 9/2	**Study type** Cross-over RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: +

Demetri, G.D., et al., Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res, 2012. 18(11): p. 3170-9.	- resolution of all toxic effects of imatinib or other therapy to grade 1 or less; - adequate hepatic, renal, and cardiac function; - absolute neutrophil count of at least 1500 per µL; - platelet count of at least 100 000 per µL; - haemoglobin concentration of 90 g/L or greater; - an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. **Exclusion criteria** NR **Patient characteristics** Age[y] median(range) 58.0(23-84)/55.0(23-81) Gender n(%) Male 132(63.8)/64(61.0) Female 75(36.2)/41(39.0) ECOG status 0: 92(44.4)/48(45.7) 1: 113(54.6)/55(52.4) 2: 2(1.0)/2(1.9) GIST histology n(%) Spindle cell 125(60.4)/74(70.5) Mixed spindle+epithelioid 33(15.9)/13(12.4) Epithelioid 17(8.2)/7(6.7) Other 31(15.0)/10(9.5) Missing 1(0.5)/1(1.0) Tumour burden at baseline [mm] Median(Range) 233(26-722)/239(29-749)	**Control** Initial: Placebo daily for 4 consecutive weeks followed by a 2-week period without treatment comprising a 6-week cycle. **Randomised patients** 207/105	Grade 4 1/1 Thrombocytopenia [%] Grade 3 4/0 Grade 4 1/0	Selective reporting: + Other source of bias: +
RIGHT Kang, Y.K., et al., Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib	Region/Setting investigator-initiated study consisted of a randomised, placebo-controlled, double-blind, phase 3 trial accrued at a single institution (Asan Medical Center, Seoul, Korea) **Inclusion criteria** - Patients with histologically proven metastatic and/or unresectable GISTs if their tumors had progressed during active treatment with at least prior imatinib and sunitinib sequentially, in accordance with the Response Evaluation Criteria In Solid Tumor (RECIST) version 1.0 - Documented clinical benefit (i.e. lack of primary resistance) with prior first-line	**Intervention(s)** once daily dose of 400 mg of imatinib was given **Control** patients each received four capsules of placebo **Randomised patients** 41/40	Any toxicity [%] Grade3 or 4 49/18 Neutropenia Grade 3 or 4 [%] 2/0 Anemia Grade 3 or 4 [%] 29/8 Fatigue Grade 3 or 4	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: +

(RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol, 2013. 14(12): p. 1175-82. QoL Yoo, C., et al., Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: Sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT). Eur J Cancer, 2016. 52: p. 201-8.	imatinib therapy, defined as complete response (CR), partial response (PR), and stable disease for at least 6 months - age ≥18 years, - Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, - at least one measurable lesion, - adequate hematologic, hepatic, and renal function. **Exclusion criteria** NR **Patient characteristics** Age [y] (IQR) 57(52–65)/61(54–67) Gender n(%) Male 29(71)/26(65) ECOG performance status n(%) 0-1: 28(68)/28(70) 2-3: 13(32)/12(30) Primary Site n(%) Stomach 16(39)/13(33) Small bowel 20(49)/25(62) Other 5(12)/2(5) Previous third or more lines of therapy n(%) 16(39)/16(40) Prior nilotinib 7(17)/9(22) Prior regorafenib or sorafenib 5(12)/10(25) Prior dovitinib 7(17)/3(8) Duration of previous first-line imatinib therapy (400 mg/day) n(%) ≥6 and <12 months: 3(7)/5(13) ≥12 and <24 months: 14(34)/10(25) ≥24 months: 24(59)/25(62) Duration of previous second-line sunitinib n(%) ≥6 months: 26(63)/18(45) Primary genotype n(%) 38/39 KIT exon 11 mutation: 31(82)/30(77) KIT exon 9 mutation: 4(10)/5(13)		[%] 10/0 Anorexia Grade 3 or 4 [%] 2/3 Hyperbilirubinemia Grade 3 or 4 [%] 7/3	Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Others: 3(8)/4(10)			
Mir O, Cropet C, Toulmonde M, Cesne AL, Molimard M, Bompas E, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. The Lancet Oncology. 2016;17(5):632-41.	**Region/Setting** This study was conducted at 12 authorised comprehensive cancer centers or university hospitals in France. **Inclusion criteria** - age ≥ 18 years - unresectable, metastatic or locally advanced histologically documented GIST - measurable disease according to RECIST 1, previously progressed on or discontinued due to toxic effects treatments including both imatinib (400 mg per day then subsequently 600 mg or 800 mg per day for GIST without KIT exon 9 mutation, or 800 mg per day for GIST with KIT exon 9 mutation) and sunitinib (50 mg per day for 4 to 6 weeks or 37·5 mg in a continuous dosing schedule) - ECOG performance status 0, 1 or 2 - adequate haematological function absolute neutrophil count ≥1·5 × 10^9 cells per L, platelets ≥100 × 10^9 cells per L, haemoglobin concentration ≥90 g/L, prothrombin rate or international normalised ratio ≤1·2 × upper limit of normal [ULN], activated partial thromboplastin time ≤1·2 × ULN) adequate hepatic function (bilirubin ≤1·5 × ULN, aspartate amino transferase and alanine amino transferase ≤2·5 × ULN) - adequate renal function adequate renal function (serum creatinine ≤15 mg/L, proteinuria-to-creatininuria ratio <1 [if ≥1, 24 h proteinuria should be <1 g]) - adequate biochemical function (serum potassium concentration ≥1 × lower limit of normal) - a left ventricular ejection fraction value within the local normal ranges (>45%) **Exclusion criteria** - history of another cancer within the previous 3 years - history or suspicion of metastases in the CNS or carcinomatous meningitis - any anticancer treatment within the 14 days before enrolment - any contraindication to pazopanib - any haemorrhagic risk or predispositions, uncontrolled hypertension or recent history of cardiovascular events - expected poor patient compliance to treatment **Patient characteristics** Age[y] median(range) 65(33-85)/59(27-81) Gender n(%) Male 25(63)/32(78) Female 15(37)/9(22) Disease status at inclusion n(%) Locally advanced non-metastatic 1(3)/3(7) Exclusively metastatic 29(72)/26(63)	**Intervention(s)** Pazopanib plus best supportive care group received 800 mg oral pazopanib once daily, administered continuously in 4-week cycles **Control** Best supportive care group received care according to the investigators' practices (eg, pain control, psychological support, dietetic assistance as needed) **Randomised patients** 40/41	Hypertension [%] Grade3 37 Grade4 0 Fatigue [%] Grade3 11 Grade4 0 Diarrhoea [%] Grade3 8 Grade4 0 Anaemia [%] Grade3 7 Grade4 0 Lymphopenia [%] Grade3 7 Grade4 0	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Locally advanced and metastatic 10(25)/12(29) Primary site at diagnosis n(%) Small intestine 19(48)/20(49) Stomach 11(28)/13(32) Colon/rectum 4(10)/3(7) Mesentery 4(10)/2(5) Oesophagus 0/1(2) Pelvis 2(5)/2(5) Metastatic disease sites at diagnosis n(%) 19(48)/19(46) Liver 17(43)17(41) Ganglion 0/2(5) Lung 1(3)/0 Peritoneum 5(13)/4(10) Mesentery 2(5)/0 Pelvis 1(3)/0 Spleen or pancreas 2(5)/0			
Reichardt, P., et al., Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol, 2012. 23(7): p. 1680-7.	**Region/Setting** This phase III, randomized, open-label multicenter study was conducted at 50 clinical sites in 13 countries **Inclusion criteria** - aged ≥18 years, - a World Health Organization (WHO) performance status (PS) of ≤2, - histologically confirmed unresectable and/or metastatic GIST with either (i) prior progression (radiologically confirmed by RECIST) on imatinib (≥400 mg/day) and sunitinib therapy (initiated at 50 mg/day even if progression on a reduced dose) or (ii) were intolerant to imatinib and/or sunitinib. **Exclusion criteria** - Treatment with approved and/or investigational cytotoxic agents within 4 weeks (6 weeks for nitrosourea or mitomycin C) before the first visit. - Prior treatment with TKIs other than imatinib and sunitinib **Patient characteristics** Age[y] mean(range) 57.4(18-83)/58.6(37.0-82.0) Gender n(%) Male 101(61.2)/47(56.6) Female 64(38.8)/36(43.4) WHO performance status n(%) Grade 0: 90(54.5)/33(39.8) Grade1: 62(37.6)/41(49.4) Grade2: 13(7.9)/8(9.6) Missing: 0(0)/1(1.2)	**Intervention(s)** nilotinib 400 mg b.i.d **Control** BSC alone, BSC plus imatinib (BSC + I), or BSC plus sunitinib (BSC + S). If a TKI was used in BSC, the dose was also left to the investigator's discretion; however, higher doses than used previously were not allowed. Patients in the BSC + S group received sunitinib per the approved regimen of 50 mg/day (4 weeks on/2 week off) or continuous dosing at 37.5 mg/day. **Randomised patients** 165/83	Any ae [%] 17.6/12 **Events >2% in one group** Anemia Grade 3 or 4 [%] 1.2/4.8 Asthenia Grade 3 or 4 [%] 3/0 Increase lipase Grade 3 or 4 [%] 1.8/0 Neutropenia Grade 3 or 4 [%] 0/2.4	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

	Primary site of cancer n(%) Liver 2(1.2)/1(1.2) Esophagus 1(0.6)/0(0) Stomach 56(33.9)/27(32.5) Small intestine 67(40.6)/31(37.3) Large intestine 9(5.5)/5(6.0) Abdomen 11(6.7)/11(13.3) Unknown 6(3.6)/2(2.4) Other 13(7.9)/6(7.2) Site of metastasis n(%) Lung 1(0.6)/1(1.2) Liver 93(56.4)/54(65.1) Abdomen 30(18.2)/12(14.5) Bone 1(0.6)/0(0) Other 40(24.2)/16(19.3)			

+ low risk of bias; - high risk of bias; ? unclear risk of bias; IG: intervention group; CG: control group; NR: not reported; GIST: gastrointestinal stromal tumor; KIT: tyrosine-protein kinase Kit/CD117; ECOG: Eastern Cooperative Oncology Group; TKI: tyrosine kinase inhibitor; ae: adverse event; RCT: randomized controlled trial; WHO: World Health Organization; AMN107: nilotinib; NJ: New Jersey; STI571: imatinib mesylate; ALT: alanine transaminase; VEGFR: vascular endothelial growth factor receptor; Ta: non-invasive tumour; Tis: carcinoma in situ; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; CT: computed tomography; MRI: magnetic resonance imaging ; RECIST: Response Evaluation Criteria in Solid Tumours; CR; complete response; PR: partial response; IQR: interquartile range; ULN: upper limit of normal; CNS: central nervous system; PS: performance status; BSC: best supportive care; S: sunitinib

6.2. SoF Tables Systemtherapie (GIST) - Therapie der metastasierten Erkrankung

AG Systemtherapie, Kasper

Summary of findings:

Masitinib compared to sunitinib for metastatic GIST

Patient or population: GIST
Intervention: masitinib
Comparison: sunitinib

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sunitinib	Risk with masitinib				
Overall survival (median follow-up: 14 months)	667 per 1.000	**356 per 1.000** (161 to 652)	**HR 0.40** (0.16 to 0.96)	44 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 14 months)	857 per 1.000	**882 per 1.000** (689 to 986)	**HR 1.1** (0.6 to 2.2)	44 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Adenis 2014

Summary of findings:

Nilotinib compared to imatinib for metastatic GIST

Patient or population: GIST
Intervention: nilotinib
Comparison: imatinib

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with imatinib	Risk with nilotinib				
Overall survival (follow-up: 24) months	100 per 1.000	**177 per 1.000** (119 to 260)	**HR 1.850** (1.198 to 2.857)	644 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (follow-up: 24)	275 per 1.000	**376 per 1.000** (299 to 465)	**HR 1.466** (1.104 to 1.945)	644 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Blay 2015

Summary of findings:

Sunitinib compared to placebo for GIST

Patient or population: GIST
Intervention: sunitinib
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sunitinib				
Overall survival (median follow-up: 41.7 months)	Median 9.75 months	**Median18.175 months**	**HR 0.505** (0.262 to 1.134)	361 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: 41.7 months)	Median 1.5 months	**Median 5.725 months**	**HR 0.347** (0.253 to 0.475)	361 (1 RCT)	⨁⨁◯◯ LOW	
Overall survival (median follow-up: NR)	NR	**NR**	**HR 0.49** (0.29 to 0.83)	312 (1 RCT)	⨁⨁⨁◯ MODERATE	
Progression free survival (median follow-up: NR)	Median 1.6 months	**Median 6.825 months**	**HR 0.33** (0.23 to 0.47)	312 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Demetri 2012 Sunitinib; Demetri 2006

Summary of findings:

Regorafenib compared to placebo for GIST

Patient or population: GIST
Intervention: regorafenib
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with regorafenib**				
Overall survival (median follow-up: NR)	NR	**NR**	**HR 0.27** (0.19 to 0.39)	199 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: NR)	Median 0.9 months	Median 4.8 months	**HR 0.77** (0.42 to 1.41)	199 (1 RCT)	⨁⨁⨁◯ MODERATE	
Quality of life (EQ-5D, during treatment)	*p*=0.233			185 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Demetri 2013 Regorafenib; Poole 2015

Summary of findings:

Imatinib compared to placebo for metastatic GIST

Patient or population: metastatic GIST
Intervention: imatinib
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with imatinib				
Overall survival (median follow-up: 5.2 months)	7.5 months	**8.2 months**	**HR 1.00** (0.58 to 1.83)	81 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow up: 5.2 months)	0.9 months	**1.8 months**	**HR 0.46** (0.27 to 0.78)	81 (1 RCT)	⨁⨁⨁⨁ HIGH	
Quality of life (EORTC QLQ-C30, Global health status, 8 weeks after treatment)	Least squares mean Imatinib: 57.4/ Placebo: 57.7 ; *p*=0.97			72 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Kang 2013; Yoo 2016

Summary of findings:

Pazopanib plus best supportive care (BSC) compared to BSC alone for metastatic STS

Patient or population: metastatic STS
Intervention: Pazopanib plus best supportive care (BSC)
Comparison: BSC alone

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with BSC alone	**Risk with Pazopanib plus best supportive care (BSC)**				
Overall survival (median follow-up: Pazopanib 26.4 months, BSC 28.9 months)	756 per 1.000	**735 per 1.000** (546 to 889)	**HR 0.94** (0.56 to 1.56)	81 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: Pazopanib 26.4 months, BSC 28.9 months)	951 per 1.000	**832 per 1.000** (673 to 945)	**HR 0.59** (0.37 to 0.96)	81 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; HR: Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Mir 2016

Summary of findings:

Nilotinib compared to best supportive care for metastatic GIST

Patient or population: metastatic GIST
Intervention: nilotinib
Comparison: best supportive care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best supportive care	Risk with nilotinib				
Overall survival (all followed up to 60 months)	300 days	**361 days**	**HR 0.84** (0.62 to 1.15)	248 (1 RCT)	⨁⨁◯◯ LOW	
Progression free survival (median follow-up: NR)	111 days	**109 days**	**HR 0.90** (0.65 to 1.26)	248 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
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Reichhardt 2012

7. Chirurgie - Hyperthermie

7.1. Evidenztabelle Chirurgie - Hyperthermie

AG Therapie des lokalisierten Weichgewebetumors, Hohenberger

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (all or the five most frequent ae)	Study type, level of evidence and risk of bias
Angele MK, Albertsmeier M, Prix NJ, Hohenberger P, Abdel-Rahman S, Dieterle N, et al. Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection: a subgroup analysis of a randomized phase-III multicenter study. Annals of surgery. 2014;260(5):749-54; discussion 54-6. Subgroups Analysis of Issels 2010	**Region/Setting** 1997 - 2006 at 9 centers; Germany (n=6), Norway (n=1), Austria (n=1), and USA (n=1). **Inclusion criteria** - age 18-70 years - abdominal and extremity soft-tissue sarcomas -macroscopically complete resection (R0,R1) - risk factors FNCLCC Grade 2 and 3 - tumor diameter > 5 cm **Exclusion criteria** - evidence of distant disease **Patient characteristics** Gender n(%) Male 39(51.3)/43(58.9) Female 37(48.7)/30(41.1) Age [y] Median(range) 53.0(19.0-69.0)/49.0(18.0-69.0) Presentation n(%) Primary 69(90.8)/64(87.7) Recurrent 7(9.2)/9(12.3) Size of tumor [cm] Median(range) 12.0(5.0-36.0)/11.0(5.0-40.0) Pathology n(%) Liposarcoma 16(21.1)/13(17.8) Leiomyosarcoma 18(23.7)/16(21.9) Fibrosarcoma 7(9.2)/10(13.7)	**Intervention** Surgery + CT(EIA) + RHT EIA: Perioperative chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA: etoposide 250 mg/m^2 on day 1 and 4, ifosfamide 6g/m^2 on days 1-4, doxorubicin 50 mg/m^2 on day 1 every 3 weeks). RHT: tumor temperatures of 42°C for 60 minutes were given on day 1 and day 4 of each EIA cycle. RHT and thermal mapping were done according to the ESHO guidelines for quality and safety assurance. The BSD-2000 hyperthermia system (BSD Medical Corporation, Salt Lake City, UT) was used. **Control** Surgery + CT(EIA) alone Perioperative chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA: etoposide 250 mg/m^2 on day 1 and 4, ifosfamide 6g/m^2 on days 1-4, doxoru-	Superficial wound infection 4(5,3)/2(2,7) Deep infection 3(4,0)/4(5,5) Bleeding 6(7,9)/1(1,4) Neurological 4(5,3)/2(2,7) Skin necrosis 4(5,3)/3(4,1) Other 11(14,5)/8(11,0)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Malignant fibrous histiocytoma 2(2.6)/1(1.4) Other sarcomas 33(43.4)/33(45.2) Type of surgery n(%) Compartmental resection 17(22.4)/17(23.4) Wide excision 55(72.4)/51(69.9) Marginal excision 4(5.3)/5(6.8) Days after surgery until discharge, Median(range) 14(6-49)/12(4-76)	bicin 50 mg/m^2 on day 1 every 3 weeks). **Both** For radiotherapy, if indicated, a total dose of 50 to 60 Gy was delivered, with daily fractions of 1.8 to 2.0 Gy, administered 4 to 6 weeks after surgery. The recommended doses were adjusted depending on the individual situation and potential radiosensitive tissue within the radiation field. Radiation therapy was applied in 95 of 149 patients. The distribution was similar in both study groups [50 patients (65.8%) EIA + RHT vs 45 patients (61.6%) EIA, P = 0.54]. **Randomized patients** 76/73		
Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem BC, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomized phase 3 multicentre study. The Lancet Oncology. 2010;11(6):561-70. AND Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, et al. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma: The EORTC 62961-ESHO 95	**Region/Setting** July 1997 - November 2006 at 9 centers. **Inclusion criteria** - age 18-70 years - abdominal and extremity soft-tissue sarcomas - risk factors FNCLCC Grade 2 and 3 - tumor diameter > 5 cm **Exclusion criteria** - evidence of distant disease **Patient characteristics** Age [y] Median(range) 51.0(18.0-70.0)/52.0 (19.0-70.0) Gender n(%) Male 91(56.2)/91(54.5) Female 71(43.8)/76(45.5) WHO performance status n(%) 0 106 (65.4) 112 (67.1)	**Intervention** CT(EIA) + RHT EIA: etoposide 125 mg/m^2 on day 1 and 4, ifosfamide 1500 mg/m^2 on days 1-4, and doxorubicin 50 mg/m^2 on day 1) were given every 3 weeks. RHT: Regional hyperthermia aiming for tumor temperatures of 42°C for 60 minutes were given on day 1 and 4 of each EIA cycle during both induction and post-induction therapy. Regional hyperthermia and thermal mapping were done according to the ESHO guidelines for quality and safety assurance.16 The BSD-2000 hyperthermia	Grade 3/4 Leucopenia 128 (77.6)/106 (63.5) Thrombocytopenia 28 (17.0)/23(13.8) Nausea 23(13.9)/26(15.6) Vomiting 15(9.1)/9(5.4) Neurotoxicity 15(9.1)/ 8(4.8)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

Randomized Clinical Trial. JAMA oncology. 2018;4(4):483-92.	1 48 (29.6) 48 (28.7) 2 8 (4.9) 7 (4.2) Site of tumor n(%) Nonextremity 93(57.4)/93(55.7) Extremity 69(42.6)/74(44.3) Presentation n(%) Primary 75(46.3)/82(49.1) Recurrent 19(11.7)/18(10.8) Prior surgery 68(42.0)/67(40.1) Size of tumor [cm] n(%) 5.0-12 93(57.4)/106(63.5) >12 69(42.6)/61(36.5) Grading n(%) G2 79(48.8)/74(44.3) G3 83(51.2)/93(55.7) Pathology n(%) Liposarcoma 30(18.5)/30(18.0) Leiomyosarcoma 25(15.4)/27(16.2) Synovial sarcoma 24(14.8)/19(11.4) Sarcoma NOS 33(20.4)/35(21.0) Other sarcomas 37(22.8)/39(23.4) Not soft tissue sarcomas 2(1.2)/4(2.4) Unreviewed sarcomas 11(6.8)/13(7.8)	system was used. Treatment was stopped or omitted if severe adverse events occurred. **Control** CT(EIA) alone Cycles of the EIA regimen (etoposide 125 mg/m^2 on day 1 and 4, ifosfamide 1500 mg/m^2 on days 1-4, and doxorubicin 50 mg/m^2 on day 1) were given every 3 weeks. **Randomized patients** 169/172		

+ low risk of bias; - high risk of bias, ? unclear risk of bias; BSD-2000: BSD Medical Corporation, Salt Lake City, USA; CT: chemotherapy; EIA: etoposide, ifosfamide, and doxorubicin; ESHO: European Society for Hyperthermic Oncology; FNCLCC: Fédération Nationale des Centres de Lutte contre le Cancer; NOS: not otherwise specified; RHT: regional hyperthermia

7.2. SoF Table Chirurgie - Hyperthermie

AG Therapie des lokalisierten Weichgewebetumors, Hohenberger

Summary of findings:

RHT + EIA compared to EIA alone for STS

Patient or population: STS
Intervention: RHT + EIA
Comparison: EIA alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EIA alone	Risk with RHT + EIA				
Overall survival (follow-up: 98,4 months) for complete tumor resection	603 per 1.000	531 per 1.000 (387 to 688)	**HR 0.82** (0.53 to 1.26)	149 (1 RCT)	⊕⊕⊕◯ MODERATE	
Disease free survival (median follow-up: 99 months) for complete tumor resection	NR	NR	**HR 0.72** (0.49 to 1.05)	149 (1 RCT)	⊕⊕◯◯ LOW	
Local progression-free survival (median follow-up:99 months) for complete tumor resection	NR	NR	**HR 0.63** (0.40 to 0.99)	149 (1 RCT)	⊕⊕◯◯ LOW	
Survival (follow-up: 135,6 months) ITT	NR	NR	**HR 0.73** (0.54 to 0.98)	341 (1 RCT)	⊕⊕⊕◯ MODERATE	
Local progression free survival (follow-up: 135,6 months)	NR	NR	**HR 0,65** (0.49 to 0.86)	341 (1 RCT)	⊕⊕⊕◯ MODERATE	
Disease free survival (follow-up: 135,6 months)	NR	NR	**HR 0.71** (0.55-0.93)	341 (1 RCT)	⊕⊕⊕◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **EIA**: Etoposide, ifosfamide and doxorubicin; **HR:** Hazard Ratio; **NR**: not reported; **RHT**: regional hyperthermia; **STS**: soft tissue sarcoma

Summary of findings:

RHT + EIA compared to EIA alone for STS

Patient or population: STS
Intervention: RHT + EIA
Comparison: EIA alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EIA alone	**Risk with RHT + EIA**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Angele 2014, Issels 2018

8. Chirurgie - OP

8.1. Evidenztabelle Chirurgie - OP

AG Therapie lokalisierter Weichgewebetumor, Hohenberger

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Study type, level of evidence and risk of bias
Chang HR, Gaynor J, Tan C, Hajdu SI, Brennan MF. Multifactorial analysis of survival in primary extremity liposarcoma. World journal of surgery. 1990;14(5):610-8.	**Region/Setting** Memorial Sloan-Kettering Cancer Center, 1968 - 1978 **Inclusion criteria** -the tumor had to be a primary localized extremity liposarcoma -diagnosis of various histologic subtypes had to be confirmed by slide review - definitive surgery was performed at Memorial Hospital **Exclusion criteria** NR **Patient characteristics** Age [years] n(%) <50 34(41.0) ≥50 49(59.0) Gender n(%) Male 39(47.0) Female 44(53.0) Tumor size n(%)[cm] <5cm 30(37.0) ≥5cm, <10cm 19(23.5) ≥10cm 32(39.5) Grade n(%) Low 45(54.2) High 38(45.8) Subtype n(%) Well-differentiated 10(12.0) Myxoid 33(39.8) Fibroblastic 10(12.0)	**Intervention** Adequate/marginal margin **Control** Inadequate margin/amputation **Included patients** 52/31	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) - *Outcome* 1) + 2) + 3) -

	Pleomorphic 25(30.1) Lipoblastic 5(6.0) Type of surgery/margin n(%) LSS/adequate 41(49.4) LSS/marginal 11(13.3) LSS/inadequate 17(20.5) AMP/adequate 14(16.9) Location n(%) Upper extremity Proximal 9(75.0) Distal 3(25.0) Lower extremity Proximal 51(71.8) Distal 20(28.2) Depth n(%) Superficial 38(49.4) Deep 39(50.6) Invasion of vital structures n(%) No 62(75.6) Yes 20(24.4) Painful symptoms at presentation n(%) No 63(75.9) Yes 20(24.1)		
Ghert MA, Abudu A, Driver N, Davis AM, Griffin AM, Pearce D, et al. The indications for and the prognostic significance of amputation as the primary surgical procedure for localized soft tissue sarcoma of the extremity. Annals of surgical oncology. 2005;12(1):10-7.	**Region/Setting** January 1986 - March 2000 **Inclusion criteria** patients who presented with a deep, intermediate-, or high-grade STS of the extremity and underwent surgical treatment **Exclusion criteria** - patients presented with metastatic disease - patients presented to with recurrent disease after resection elsewhere **Patient characteristics IG/CG** Age [years] mean(range) 54(15-89)/61(37-89) Gender n(%) Male 195(49.9)/15(60) Female 196(50.1)/10(40) Tumor size [cm] median(range) 9.3(1-40)/13(1.5-29)	**Intervention** Limb-sparing surgery **Control** Amputation **Included patients** 391/25	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) + *Outcome* 1) +

	Tumor size n(%) <8cm 204(52)/6(24) ≥8cm 187(48)/19(76) Tumor grade n(%) 2 149(38)/6(24) 3 242(62)/19(76) AJCC/UICC stage n(%) II (T1b, N0, M0) 117(30)/5(20) III (T2b, N0, M0) 274(70)/20(80) Histological subtype n(%) MFH 134(34)/9(36) Synovial sarcoma 34(9)/5(20) MPNST 30(8)/3(12) Leiomyosarcoma 32(8)/2(8) Liposarcoma 47(12)/2(8) Other 114/4 Prior unplanned excision n(%) Yes 133(34)/8(32) No 258(66)/17(68) Anatomical location n(%) Upper extremity 96(25)/3(12) Lower extremity 295(75)/22(88)		2) - 3) -
Okamoto M, Yoshimura Y, Aoki K, Kito M, Tanaka A, Suzuki S, et al. Clinical outcomes of patients 80 years of age and older with soft tissue sarcoma. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. 2017;22(5):951-7.	**Region/Setting** January 2006 - May 2014 **Inclusion criteria** - patients of ≥80 years with STS visiting the orthopedic unit **Exclusion criteria** - metastasis at presentation **Patient characteristics IG/CG** Age [years] median(range) 85.0(80-94)/90.0(80-91) Gender n Male 18/1 Female 15/3 Tumor size median [cm] 7.4/7.8 ECOG PS n	**Intervention** Surgery (Wide, marginal or amputation) **Control** Conservative therapy **Included patients** 33/4	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) + *Outcome* 1) + 2) -

	0 11/0 1 17/2 2 4/0 3 1/2 4 0/0 <u>Comorbidities n</u> Cardiovascular disease 23/1 Other cancer 9/1 Prostatic hyperplasia 8/0 Diabetes mellitus 6/0 Dementia 1/1 <u>Histological type n</u> UPS 13/2 Myxofibrosarcoma 6/2 Liposarcoma 6/0 Leiomyosarcoma 4/0 Others 4/0 <u>Histological grade n</u> High 29/4 Low 4/0 <u>Tumor site n</u> Lower extremity 19/3 Upper extremity 8/0 Trunk 6/1 <u>Tumor depth n</u> Superficial 8/1 Deep 25/3		3) +
Shiu MH, Castro EB, Hajdu SI, Fortner JG. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. Annals of surgery. 1975;182(5):597-602.	**Region/Setting** Memorial Sloan-Kettering Cancer Center, 1949 - 1968 **Inclusion criteria** Soft tissue sarcomas of the lower extremity with definitive surgical treatment **Exclusion criteria** - distant metastases on initial presentation - consultations only - palliative surgical therapy - patients who underwent radiation therapy or chemotherapy **Characteristics of all patients (n=297)** <u>Age [y] median(range)</u> 48(2-80)	**Intervention** Soft part resections (previously untreated cases) **Control** Amputation (previously untreated cases) **Included patients** 74/49	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) -

	Gender n Male/Female 159/138 Size n(%)[cm] >5cm 135 (45.5) <5cm 62 (54.5) Site n Thigh 221 Leg 60 Foot 16 Histologic type n(%) Liposarcoma 82(28) Fibrosarcoma 60(20) Rhabdomyosarcoma 52(18) Synovial sarcoma 42(14) Malignant schwannoma 16(NR) Leiomyosarcoma 7(NR) Angiosarcoma 6(NR) Undifferentiated sarcoma 21 Miscellaneous sarcomas 11		*Outcome* 1) + 2) + 3) -
Shiu MH, McCormack PM, Hajdu SI, Fortner JG. Surgical treatment of tendosynovial sarcoma. Cancer. 1979;43(3):889-97. AND Hajdu, S. I., Shiu, M. H., and Fortner, J. G.: Tendosynovial sarcoma: A clinicopathological study of 136 cases. *Cancer* 39:1201-1217, 1977.	**Region/Setting** Memorial Sloan-Kettering Cancer Center, USA, 1949 - 1973 **Inclusion criteria** - primary tendosynovial sarcoma for which surgical resection was carried out with curative intent **Exclusion criteria** - patients who received consultations only - palliative treatment because of unresectability of the tumor or concomitant serious medical illness **Patient characteristics of all patients (n=136)** Age [y] median(range) 33(4-78) Gender n(%) Male/Female 78(57)/58(43) Size n(%) >5cm 39(29) <5cm 97(71) Site n(%)	**Intervention** Wide monobloc soft part resection (previously untreated cases) **Control** Amputation (previously untreated cases) **Included patients** 28/46	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) - *Comparability* 1) - *Outcome* 1) + 2) + 3) +

	Lower extremity 91(67) Upper extremity 36(26) Other anatomic regions 9(7) Neck and shoulder 16(12) Arm and elbow 5(4) Forearm and wrist 15(11) Hand and finger 5(4) Back and pelvis 4(3) Buttock and groin 11(8) Thigh 26(19) Knee 16(12) Leg and ankle 13(10) Foot 25(18) <u>Histologic type n(%)</u> Biphasic 20(15) Monophasic (spindle cell type) 59(43) Monophasic (epithelioid type) 35(26) Epithelioid sarcoma 12(9) Clear cell sarcoma 8(6) Chordoid sarcoma 2(1)		

+: high quality assessment; -: low quality assessment; AJCC: American Joint Committee on Cancer; AMP: amputation; CG: control group; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; IG: intervention group; incl.: including; LS: liposarcoma; LSS: limb-sparing surgery; MFH: malignant fibrous histiocytoma; MPNST: malignant peripheral nerve sheath tumor; N.A.: not applicable; NR: not reported; RR: relative risk; RT: radiotherapy; SD: standard deviation; STS: soft tissue sarcoma; UICC: International Union Against Cancer; UPS: undifferentiated pleomorphic sarcoma; y: years

8.2. SoF Tables Chirurgie - OP

AG Therapie lokalisierter Weichgewebetumor, Hohenberger

Summary of findings:

Soft part resection compared to amputation for STS

Patient or population: STS
Intervention: soft part resection
Comparison: amputation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with amputation	Risk with soft part resection				
10 year survival free of disease, minimum follow-up: 60 months	735 per 1.000	463 per 1.000 (338 to 617)	RR 0.63 (0.46 to 0.84)	123 (1 observational study)	⊕⊕◯◯ LOW	
Local recurrence, minimum follo-up: 60 months	41 per 1.000	176 per 1.000 (42 to 744)	RR 4.30 (1.02 to 18.24)	123 (1 observational study)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Shiu 1975

Summary of findings:

Monobloc resection compared to amputation for tendosynovial sarcoma

Patient or population: tendosynovial sarcoma
Intervention: monobloc resection
Comparison: amputation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with amputation	**Risk with monobloc resection**				
10 year survival, follow-up (range): 60-300 months	696 per 1.000	431 per 1.000 (271 to 682)	RR 0.62 (0.39 to 0.98)	74 (1 observational study)	⨁⨁◯◯ LOW	
Local recurrence, follow-up (range): 60-300 months	43 per 1.000	179 per 1.000 (37 to 859)	RR 4.11 (0.85 to 19.76)	74 (1 observational study)	⨁◯◯◯ VERY LOW	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Shiu 1979

Summary of findings:

Surgery compared to conservative therapy in eldery for STS

Patient or population: STS
Intervention: surgery
Comparison: conservative therapy in eldery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conservative therapy in eldery	**Risk with surgery**				
Overall survival, median follow-up: 25.3 months	1.000 per 1.000	510 per 1.000 (320 to 810)	RR 0.51 (0.32 to 0.81)	37 (1 observational study)	⨁⨁⨁◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Okamoto 2017

Summary of findings:

Adequate/marginal margin compared to inadequate margin/amputation for liposarcoma

Patient or population: liposarcoma
Intervention: adequate/marginal margin
Comparison: inadequate margin/amputation

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
tumor mortality, median follow-up for survivors: 93.6 months	p=0.00014	(1 observational study)	⊕⊕◯◯ LOW

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Chang 1990

Summary of findings:

Limb-sparing surgery compared to amputation for STS

Patient or population: STS
Intervention: limp salvage
Comparison: amputation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with amputation	**Risk with limb salvage**				
5 year metastasis free survival, follow-up: N.R.	p=0.008		N.R.	(1 observational study)	⊕◯◯◯ VERY LOW	
risk factor for metastasis, follow-up: N.R.	N.R.	N.R.	**RR 0.66** (0.38 to 1.14)	(1 observational study)	⊕◯◯◯ VERY LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **N.R.**: not reported; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Ghert 2005

9. Chirurgie - Resektionsränder

9.1. Evidenztabelle Chirurgie - Resektionsränder

AG Therapie des lokalisierten Weichgewebetumors, Hohenberger

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG/CG; relative effect measure or mean difference; 95% CI or *p*)	Adjustment	Study type, level of evidence and risk of bias
Catena F, Di Battista M, Ansaloni L, Pantaleo M, Fusaroli P, Di Scioscio V, et al. Microscopic margins of resection influence primary gastrointestinal stromal tumor survival. Onkologie. 2012;35(11):645-8. **GIST**	**Region/Setting** 1999 - 2009 GISTologist Database of the University of Bologna (St. Orsola-Malpighi University Hospital in Bologna, Italy, Catholic University Hospital in Rome, Italy and Modena University and National Cancer Institute in Naples, Italy). **Inclusion criteria** NR **Exclusion criteria** NR **Patient characteristics** Age n(%) ≥50 years 110(72.8) < 50 years 41(27.2) Gender n(%) Male 90(59.7) Female 61(40.3) Size n(%)[cm] < 5 70(46.3) 5-10 52(34.4) > 10 29(29.3) Histological typing n(%)	**Intervention** Complete surgical resection (R0) The excision of all gross disease with negative microscopic margins. **Control** Presence of microscopic residual tumor (R1) **Included patients** 151	**Multivariate** Survival RR 2.4[1.1.-4.3], p=0.02 **Median follow-up** 101 months	Age (≥ 50/< 50 years) Gender (female/male) Tumor size (< 5/5–10/ >10cm) Histological typing (Spindle cell/Epithelioid) Localization in the stomach (Fundus/Body/Antrum) Kit mutations PDGFRA mutations Lymph node involvement Mitotic index (< 5/> 5 per 50 HPFs)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) + 3) -

	Spindle cell 139(92.0) Epithelioid 12(8) <u>Localization in the stomach n(%)</u> Fundus 19(12.5) Body 86(56.9) Antrum 46(30.6) <u>Kit mutations n(%)</u> 129(85.4) <u>PDGFRA mutations n(%)</u> 22(14.6) <u>Lymph node involvement n(%)</u> 10(6.6) <u>Surgical margins n(%)</u> - Gross – Micro 132(87.4) - Gross + Micro 19(12.6) <u>Mitotic index n(%)</u> < 5 per 50 HPFs 70(46.3) > 5 per 50 HPFs 81(53.7) <u>Recurrence n(%)</u> Local 26(37.1) Metastasis 25(35.7) Local + metastasis 19(27.6) <u>Survival status n(%)</u> Alive 80(52.9) Dead of disease 50(33.1) Dead of other causes 21(14)				
Engstrom K, Bergh P, Gustafson P, Hultborn R, Johansson H, Lofvenberg R, et al. Liposarcoma: outcome based on the Scandinavian Sarcoma Group register. Cancer. 2008;113(7):1649-56.	**Region/Setting** Scandinavian Sarcoma Group Register, March 1986 - December 1998 Specialized sarcoma centers in Norway (3 centers) and Sweden (5 centers) **Inclusion criteria** Diagnosed liposarcoma of the superficial trunk **Exclusion criteria** - other type of sarcomas	**Intervention** Wide surgical margin There is a cuff of healthy tissue all around the tumor. Myectomy and compartmental margin are included in the category “wide”. **Control** Intralesional and marginal surgical margins “Intralesional”: macroscopic or microscopic tumor is	**Multivariate** <u>Local recurrence</u> RR 0.36 [0.23-0.56], p<.001 **Median follow-up** Still alive 96 months Dead 48 months	Radiotherapy (no/yes) Grade (I-IV)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) -

	- other malignancies - benign lesions - metastases - gross tumor where complete local excision was not feasible - refused amputation - other reasons **Patient characteristics** <u>Norway/Sweden n(%)</u> 106(45)/131(55) <u>Gender n(%)</u> Male 128(54) Female 109(46) <u>Age [y] median(range)</u> 54(13-90) <u>Median tumor size [cm] (range)</u> 11(2-33) <u>Primary tumor site n(%)</u> Lower extremity 200(84) Upper extremity 18(8) Trunk 19(8) <u>Tumor depth n(%)</u> Subcutaneous 49(21) Deep 188(79) <u>Tumor grade n(%)</u> I-II/ 159(67) III-IV 78(33) <u>Histological type n</u> Well-differentiated LS 85 Myxoid LS 64 Myxoid/round cell LS 26 Round cell LS 9 Pleomorphic LS 25 Dedifferentiated LS 7 Mixed LS 21 <u>Referral to sarcoma center n(%)</u> Before open biopsy or surgery 177(75) After incisional biopsy 8(3)	left at the surgical margin. "Marginal": the surgical margin is close to the tumor in 1 or more places. **Included patients** 237			*Comparability* 1) + *Outcome* 1) + 2) + 3) -

	After intralesional or marginal surgery 45(19) After local recurrence 7(3) <u>Preoperative diagnostic procedure n(%)</u> FNA/core-needle biopsy 161(68) Incisional biopsy 38(16) No biopsy 38(16) CT/MRI 205(86)				
Gingrich AA, Bateni SB, Monjazeb AM, Darrow MA, Thorpe SW, Kirane AR, et al. Neoadjuvant Radiotherapy is Associated with R0 Resection and Improved Survival for Patients with Extremity Soft Tissue Sarcoma Undergoing Surgery: A National Cancer Database Analysis. Annals of surgical oncology. 2017;24(11):3252-63.	**Region/Setting** National Cancer Data Base, January 2003 - December 2012. **Inclusion criteria** - diagnosis of STS of the extremity according to the International Classification of Diseases for Oncology, 3rd revision **Exclusion criteria** - patients less than 18 years of age - no surgery - unknown surgical margin status, tumor grade, tumor size, or vital status, with stage IV disease at diagnosis - received a combination of pre- and post-operative RT, intraoperative RT, or had unknown delivery of RT **Patient characteristics** <u>Age</u> N.R. <u>Gender n(%)</u> Male 15135(54.1) Female 12834(45.9) <u>Race n(%)</u> White 23749(84,9) Black 2768(9.9) American Indian, Aleutian or Eskimo 97(0.4) Asian 556(2.0) Pacific Islander 183(0.7)	**Intervention** R0 **Control** R1 **Included patients** 27969	**Multivariate** <u>Overall Survival</u> HR 1.1438 [1.1024-1.1869] p<0.001 **Median follow-up** N.R.	Age Gender (male/female) Race (White/Black/(American Indian, Aleutian, Eskimo)/Asian/Pacific Islander/Other/unknown) Facility type (Community Cancer Program/Comprehensive Community Cancer Program/Academic/Research Program/Integrated Network Cancer Program/Unknown) Histology (Sarcoma, NOS/Ewing's sarcoma/ Epithelioid sarcoma) High grade undifferentiated (pleomorphic sarcoma/Fibrosarcoma/ Solitary fibrous tumor/ Dermatofibrosarcoma protuberans/ Liposarcoma, NOS/ Liposarcoma, well differentiated/Myxoid liposarcoma/Round cell liposarcoma/Pleomorphic liposarcoma/Dedifferentiated liposarcoma/Leiomyosarcoma/Vascular sarcoma/Rhabdomyosarcoma/Synovial sarcoma/Clear cell sarcoma/Chondrosarcoma/Malignant giant cell tumor/Malignant peripheral nerve sheath tumor/Alveolar soft part sarcoma) Grade (1/2/3/4) Charlson-Deyo Score (no comorbid conditions/1 comorbid condition/>1 comorbid condition) Radiation-Surgery Sequence (No radiation therapy/Radiation therapy before	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) - 3) -

	Other 209(0.8) Unknown 407(1.5) <u>Histology n(%)</u> Sarcoma, NOS 5681(20.31) Ewing's sarcoma 237(0.85) Epithelioid sarcoma 262(0.94) High grade undifferentiated pleo-morphic sarcoma 3775(13.5) Fibrosarcoma 2747(9.82) Solitary fibrous tumor 196(0.7) Dermatofibrosarcoma protuberans 339(1.21) Liposarcoma, NOS 1251(4.47) Liposarcoma, well differentiated 2237(8.0) Myxoid liposarcoma 1567(5.6) Round cell liposarcoma 167(0.6) Pleomorphic liposarcoma 637(2.28) Dedifferentiated liposarcoma 865(3.9) Leiomyosarcoma 4091(14.63) Vascular sarcoma 839(3.0) Rhabdomyosarcoma 329(1.18) Synovial sarcoma 1061(3.79) Clear cell sarcoma 74(0.26) Chondrosarcoma 504(1.8) Malignant giant cell tumor 33(0.12) Malignant peripheral nerve sheath tumor 1050(3.75) Alveolar soft part sarcoma 27(0.1) <u>Grade n(%)</u> Grade 1 6530(23.35) Grade 2 4851(17.34) Grade 3 9842(35.19) Grade 4 6746(24.12) <u>Tumor size n</u> <5 cm 9412 5-10 cm 9660 >10-15 cm 4567 >15 cm 3970			surgery/Radiation therapy after surgery) Chemotherapy (No/yes/Unknown)	

	Margins n(%) R0 22171(79.27) R1 3426(12.25) R2 2372(8.48) Chemotherapy n(%) Yes 4272(15.27) No 22942(82.03) Unknown 755(2.7)				
Jebsen NL, Engellau J, Engstrom K, Bauer HC, Monge OR, Muren LP, et al. Patterns of local recurrence and dose fractionation of adjuvant radiation therapy in 462 patients with soft tissue sarcoma of extremity and trunk wall. International journal of radiation oncology, biology, physics. 2013;86(5):949-55.	**Region/Setting** Scandinavian Sarcoma Group Register, 1998-2009 **Inclusion criteria** - age ≤ 16 years - diagnosed extremity or trunk wall STS -patients who underwent both primary surgery and RT at a sarcoma center, - complete recordings of parameters of prognostic importance and follow-up data **Exclusion criteria** - dermatofibrosarcoma protuberans, Kaposi sarcoma, extraosseous osteo- and chondrosarcoma, and Ewing family tumors - synchronous metastases **Patient characteristics** Age at diagnosis [y] median(range) 61(16-94) Tumor size [cm] median(range) 9.0(1-40) EQD2 (Gy) median(range) 50(20-70) Gender n(%) Male 257(55.6) Female 205(44.4)	**Intervention** Wide surgical margin **Control** Marginal surgical margin **Included patients** 462	**multiple Cox regression analysis (fully adjusted model)** Local recurrence Wide vs. marginal HR 1.62 [0.62-4.20], p<.001 **Median follow-up** 49.2	Age at diagnosis per 10 y Gender (male/female) Tumor size per 10 cm Tumor depth (deep/subcutaneous) Location (trunk/extremity) Malignancy grade (high/low) Subgroups histotype (UPS/liposarcoma/leiomyosarcoma /synovial sarcoma/MPNST/other types) Number of operations (2/1) Chemotherapy (yes/no) Timing of RT (preoperative/ postoperative) RT groups (50 Gy /< 50 Gy/36 Gy/45 Gy/45 Gy/> 50-60 Gy/> 60 Gy) EQD2	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) - *Comparability* 1) ++ *Outcome* 1) + 2) - 3) -

	Tumor site n(%) Lower extremity (incl. gluteal) 297(64.4) Upper extremity (incl. shoulder) 88(18.9) Trunk wall (incl. axillae and groin) 77(16.7) Location n(%) Subcutaneous 78(16.9) Deep 384(83.1) Malignancy grade n(%) Low grade (grade 1 and 2) 55(11.9) High grade (grade 3 and 4) 407(88.1) Histopathologic subtype n(%) UPS 181(39.2) Liposarcoma 90(19.5) Synovial sarcoma 49(10.6) Leiomyosarcoma 45(9.7) MPNST 26(5.6) Other types 71(15.4) Number of operations n(%) 1 439(95.0) ≥2 23(5.0) Surgical margin n(%) Intralesional 72(15.6) Marginal 270(58.4) Wide 120(26.0) Chemotherapy n(%) Adjuvant 142(30.7) No chemotherapy 320(69.3)				
Jebsen NL, Trovik CS, Bauer HC, Rydholm A, Monge OR, Hall KS, et al. Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a Scandinavian sarcoma group	**Region/Setting** Scandinavian Sarcoma Group Register , 1986-2005 **Inclusion criteria** - STS of the extremity or trunk wall	**Intervention(s)** Wide surgical margin A wide margin was recorded when the excised tumor all around was surrounded by a cuff of healthy tissue or unin-	**Multivariate** Local recurrence Marginal vs. wide HR 2.6 [1.7-4.0] **Median follow-up** Whole group 36 months	Age at diagnosis (per 10 y) Gender (male /female) Location (deep/subcutaneous) Site (trunk/extremity) Size (per 10 cm)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection*

study. International journal of radiation oncology, biology, physics. 2008;71(4):1196-203.	- >16 years **Exclusion criteria** - dermatofibrosarcoma protuberans, Kaposi's sarcoma, mesothelioma, myxoid chondrosarcoma, Ewing's sarcoma/peripheral primitive neuroectodermal tumor, or Grade 1 liposarcoma/atypical lipomatous tumor (not considered for adjuvant RT in Scandinavia) - overt metastases at diagnosis of the primary tumor -first referred after local recurrence - referred after surgery - referred after open biopsy **Patient characteristics** Gender n(%) Male 553(51) Female 540(49) Age at diagnosis [y] median(range) 65(16-95) Tumor site n(%) Lower extremity Gluteal 73(7) Thigh 469(43) Knee 39(4) Lower leg 127(12) Foot 28(2) Upper extremity Shoulder 57(5) Upper arm 78(7) Elbow 17(1) Lower arm 47(4) Hand 7(1) Trunk Upper trunk 76(7) Lower trunk 35(3) Groin 40(4)	volved fascia. **Control** Marginal surgical margin A marginal margin was recorded when the plane of excision passed outside the tumor, but in any part too close to the tumor to merit a wide margin. **Included patients** 1093	Still alive 60 months	Malignancy grade (high/low) Radiotherapy (no/yes) Chemotherapy (no/yes)	1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) - 3) -

	Location n(%) Subcutaneous 274(25) Deep seated 817(75) Tumor size [cm] median(range) 8(1-47) Malignancy grade n(%) 1 26(2) 2 145(14) 3 332(31) 4 585(53) Histopathologic type n(%) MFH 473(43) Liposarcoma 171(16) Leiomyosarcoma 91(8) Synovial sarcoma 86(8) MPNST 66(6) Fibrosarcoma 47(4) Myxofibrosarcoma 36(3) Other 37(3) Unclassified 86(8)				
Li B, Luo CH, Zheng W. Risk factors for recurrence and survival in patients with primary retroperitoneal tumors. Journal of BUON : official journal of the Balkan Union of Oncology. 2013;18(3):782-7.	**Region/Setting** 1980 – 2005 Department of General Surgery of the General Hospital of the People's Liberation Army (PLA), and the Department of Colorectal & Anal Surgery of the Beijing Shijitan Hospital of Capital Medical University **Inclusion criteria** Pathologically proven primary retroperitoneal tumors **Exclusion criteria** - patients who didn't receive any treatment from primary surgery to subsequent recurrence in the 2 hospitals; -patients who received neoadjuvant	**Intervention** Microscopic negative margin RO **Control** Microscopic positive margin R1 **Included patients** 231	**Multivariate** recurrence-free survival HR 1.769 [1.162-2.694] p=0.008 **Median follow-up** 35 months	Age (N.R.) Gender (N.R.) Tumor size (N.R.) Histological subtypes (Liposarcoma/Neurinoma/MFH/Others) Tumor grade (Low/intermediate/high) Type of surgery (incomplete tumor resection/simple complete resection/compartmental complete resection/involved organ tumor resection)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) - *Comparability* 1) ++ *Outcome* 1) +

	chemoradiotherapy **Patient characteristics** Gender n(%) Male 117(50.6 Female 114(49.4) Age [years] Median(range) 45 (2-76) Age n(%) <50 years 141(61.0) ≥ 50 years 90(39.0) Tumor size [cm] Median(range) 16(3-65) Tumor size n(%) < 10 cm 106(49.3) ≥ 10 cm 109(50.7) Histological subtype n(%) Liposarcoma 93(40.3) Neurinoma 41(17.7) MFH 46(19.9) Others 53(22.1) Tumor grade, FNCLCC n(%) Low 90(39.0) Intermediate 82(35.5) High 59(25.5) Type of surgery n(%) Incomplete tumor resection 53(22.9) Simple complete resection 36(15.6) Compartmental complete resection 70(30.3) Contiguously involved organ resection 72(31.2) Histologic margins, UICC n(%) Microscopic negative margins, R0 109(47.2) Microscopic positive margins, R1 69(29.9) Gross residual disease, R2 53(22.9)				2) - 3) +
Seagle BL, Shilpi A, Buchanan S, Goodman C, Shahabi S.	**Region/Setting**	**Intervention(s)**	**Multivariate**	**Multivariate**	**Study type**

Low-grade and high-grade endometrial stromal sarcoma: A National Cancer Database study. Gynecologic oncology. 2017;146(2):254-62.	(American) National Cancer Database, 1998-2013 **Inclusion criteria** - ICD-O-3 histology code 8931 for low-grade ESS and 8930/8935 for ESS - consistency of histology, grade and survival phenotype, or consistency of the grade and survival phenotype if these together were inconsistent with the reported histology code or if the histology code was ambiguous as to ESS type **Exclusion criteria** - women who received palliative care, died within thirty-days of diagnosis, or who had follow-up of less than one month **Patient characteristics** Age NR Comorbidity score n(%) 0 2024(53.31) 1 306(8.06) 2 82(2.16) NR 1385(36.48) Race n(%) White 3045(80.19) Black 529(13.93) Asian/Pacific/other 174(4.58) NR 49(1.29) Hispanic ethnicity n(%) No 3278(86.33) Yes 198(5.21) NR 321(8.45) History of cancer n(%) No 3341(87.99) Yes 456(12.01) Metastasis at diagnosis n(%)	Negative surgical margin **Control** Positive surgical margin **Included patients** 3797	Survival Low-grade p=0.31 Survival High-grade p<0.001 **Median follow-up** low-grade ESS 74.8months high-grade ESS 66.6 months	Age Comorbidity score (0/1/2) History of cancer (no/yes) Race (White/Black/(Asian/Pacific/other) Hispanic ethnicity (no/yes) Community median income quartile (<30,000/30,000-35,999/36,000-45,999/>$46,000) Insurance (private/Medicaid/medicare/uninsured) Community dropout rate (<14/14-19.9/20-28.9/≥29%) Population type (metro/urban/rural) Cancer center type (academic/community/integrated) Metastasis at diagnosis (no/yes) Tumor size (<5/5-10/≥10) Lymph node status (negative/positive/no nodes examined) Surgical procedure type (hysterectomy/exenteration/non-hysterectomy/procedure not specified/none) Chemotherapy (no/yes) Hormonal therapy (no/yes) Radiotherapy(no/yes)	cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) + 3) -

	No 1729(45.54) Yes 356(9.38) NR 1712(45.09) <u>Tumor size</u> NR <u>Lymph node status n(%)</u> Negative 1330(35.03) Positive 228(6.00) No nodes examined 2093(55.12) NR 146(3.85) <u>Surgical procedure type n(%)</u> Hysterectomy 3368(88.7) Exenteration 148(3.9) Non-hysterectomy 99(2.61) Not specified 62(1.63) None 119(3.13) NR 0 <u>Surgical margin status n(%)</u> Negative 2568(67.63) Positive 314(8.27) NR 915(24.10) <u>Chemotherapy n(%)</u> No 3104(81.75) Yes 559(14.72) NR 134(3.53) <u>Radiotherapy n(%)</u> No 2861(75.35) Yes 868(22.86) NR 68(1.79) <u>Hormonal therapy n(%)</u> No 3323(87.52) Yes 376(9.90) NR 98(2.58)				
Sinnamon AJ, Neuwirth MG, McMillan MT, Ecker BL, Bartlett EK, Zhang PJ, et al. A prognostic model for resectable soft tissue and cutaneous angiosarcoma. Journal of surgical oncology. 2016;114(5):557-63.	**Region/Setting** National Cancer Data Base, 2004-2012 **Inclusion criteria** - tumors of primary site in connective and soft tissue	**Intervention(s)** Negative surgical margin **Control** Positive surgical margin **Included patients**	**Multivariate** <u>Overall survival</u> HR1.60 [1.15–2.23], p=0.005 **Median follow-up** 54 months	Age (≤70/>70years) Gender (female/male) Race (White/Black/other) Site (trunk/head and neck/upper extremity/lower extremity/unknown)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection*

	Exclusion criteria - evidence of metastatic disease beyond regional lymph nodes - underwent palliative care - missing follow-up data - died within 90 days of operation - missing data for tumor size, grade, chemotherapy, or radiation therapy **Patient characteristics** <u>Age [y] median(IQR)</u> 71(58–80) <u>Gender n(%)</u> Male 282(34.3) Female 539(65.7) <u>Race n(%)</u> White 745(90.7) Black 55(6.7) Other 21(2.6) <u>Site n(%)</u> Trunk 353(43) Head and neck 211(25.7) Upper extremity 38(4.6) Lower extremity 139(16.9) Unknown 80(9.7) <u>Tumor size [cm] median(IQR)</u> 4.5(2.0–7.5) Tumor size n(%) <3 cm 254(30.9) 3–7 cm 315(38.4) >7 cm 252(30.7) <u>Depth n(%)</u> Superficial 323(39.3) Deep 298(36.3) Unknown 200(24.4) <u>Grade n(%)</u> 1 110(13.4)	821		Tumor size (<3/3–7/>7cm) Depth (superficial/deep/unknown) Grade (1/2/3) Lymph Node Status (negative/positive /not examined) Chemotherapy (none/neoadjuvant/adjuvant) Radiation Therapy (none/neoadjuvant/adjuvant)	1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) + 3) +

	2 114(13.9) 3 597(72.7) <u>Lymph Node Status n(%)</u> Negative 107(13) Positive 16(2) Not examined 698(85) <u>Resection margin n(%)</u> Negative 628(76.5) Microscopic 91(11.1) Macroscopic 13(1.6) Positive, NOS 58(7.1) Unknown 31(3.8) <u>Chemotherapy n(%)</u> None 655(79.8) Neoadjuvant 38(4.6) Adjuvant 128(15.6) <u>Radiation Therapy n(%)</u> None 517(63.3) Neoadjuvant 21(2.6) Adjuvant 279(34.2)				
Stahl JM, Corso CD, Park HS, An Y, Rutter CE, Han D, et al. The effect of microscopic margin status on survival in adult retroperitoneal soft tissue sarcomas. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(1):168-74.	**Region/Setting** (American) National Cancer Data Base, 1998-2011 **Inclusion criteria** - non-metastatic, adult retroperitoneal soft tissue sarcoma - no prior cancer - R0 or R1 resection **Exclusion criteria** - ≤ 17 years - diagnosis in 2012, insufficient follow-up - missing values for variables of interest **Patient characteristics** <u>Age n(%)</u> <60 years 1288 (49.7) 632 (44.4)	**Intervention** Microscopically negative margins (R0) **Control** Microscopically positive margins (R1) **Included patients** 4015	**Multivariate** <u>Overall survival</u> HR 1.43 [1.23-1.67], p<0,001 **Median Follow-up** 67 months	Age (<60/>60 years) Gender (female/male) Race (Other/ white) Charleson/Deyo score(0/1-2) Tumor size (≤15.5/ >15.5 cm) Grade (Low/intermediate/high) Histology (Liposarcoma/ other) Date of Diagnosis (2005/2011) Radiotherapy (yes/no) Chemotherapy (yes/no)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) +

	≥60 years 1305 (50.3) 790 (55.6) Gender n(%) Male 1131(43.6)/683(48.0) Female 1462(56.4)/739(52.0) Race White 2150 (82.9) 1198 (84.2) Other 394 (15.2) 205 (14.4) Unknown 49 (1.9) 19 (1.3) Charleson/Deyo score n(%) 0 1479 (57.0) 814 (57.2) 1e2 372 (14.3) 238 (16.7) Unknown 742 (28.6) 370 (26.0) Tumor size [cm] n(%) ≤15.5 1273(49.1)/584(41.1) >15.5 1149(44.3)/734(51.6) Unknown 171(6.6)/104(7.3) Liposarcoma histology n(%) Yes 1388(53.5)/983(69.1) No 1205(46.5)/439(30.9) Tumor grade n(%) Low 861(33.2)/489(34.4) Intermediate or high 1363(52.6)/734 (51.6) Unknown 369(14.2)/199(14.0) Received radiotherapy n(%) Yes 674(26.0)/458(32.2) No 1855(71.5)/917(64.5) Unknown 64(2.5)/47(3.3) Received pre-op radiotherapy Yes 179/674 (26.6) 75/458 (16.4) No 455/674 (67.5) 366/458 (79.9) Intra-operative RT 40/674 (5.9)/17/458 (3.7) Received chemotherapy n(%) Yes 258(10.3)/187(13.6) No 2256(89.7)/1191(86.4) Unknown 79(3.0)/44(3.1)				2) + 3) -
Trovik CS, Bauer HC, Alvegard TA, Anderson H, Blomqvist C, Berlin O, et al. Surgical margins,	**Region/Setting** Scandinavian Sarcoma Group Reg-	**Intervention** Adequate margin	**Univariate** Cox regression stratified by	N.A.	**Study type** cohort study

local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register. European journal of cancer (Oxford, England : 1990). 2000;36(6):710-6.	ister, 1986-1991 **Inclusion criteria** N.R. **Exclusion criteria** - referred after local recurrence or metastasis - metastasis at diagnosis - non-operative treatment **Patient characteristics** Age n(%) ≤50 years 147(80)/36(20) >50 years 273(73)/103(27) Gender n(%) Male 237(77)/71(23) Female 183(73)/68(27) Malignancy grade n(%) Low (I±II) 95(68)/44(32) High (III±IV) 325(77)/95(23) Tumor size [cm] n(%) ≤7 237(80)/61(20) >7 cm 183(70)/77(30) Site n(%) Superficial 166(82)/37(18) Deep 254(71)/102(29) Location n(%) Extremity 322(79)/87(21) Central 98 (65) 52 (35)	**Control** Inadequate margin **Included patients** 559	histotype Local recurrence Inadequate surgical margin RR 2.9 [1.8-4.6] p<0.001(Kaplan-Meier) Metastasis free survival inadequate surgical margin RR 1.1 [0.8-1.7], p=0.6 **Median follow-up** Still alive 88.8 months		**Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) - *Outcome* 1) + 2) + 3) -
Trovik LH, Ovrebo K, Almquist M, Haugland HK, Rissler P, Eide J, et al. Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients. Acta oncologica (Stockholm, Sweden). 2014;53(9):1165-72.	**Region/Setting** Haukeland University Hospital Bergen, Norway, and Skåne University Hospital Lund, Sweden,1988-2009 **Inclusion criteria** - morphologically confirmed RPS of the resected specimen **Exclusion criteria** - local recurrence while the primary tumor had been treated prior to the	**Intervention** Negative surgical margin R0 **Control** Positive surgical margin R1/R2 **Included patients** 97	**Multivariate** Local recurrence HR 2.44 [1.25-4.77], p=0.009 Metastasis-free survival HR 0.79 [0.37-1.71], p=0.556 Overall survival HR 1.23 [0.64-2.34], p=0.538 **Median follow-up**	Gender (male/ female) Age/10 year Size/10 cm Malignancy grade (high/low) Histopathology (Leiomyosarcoma/ liposarcoma)/(Other/liposarcoma) RT (yes/no) Chemotherapy (yes/ no)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) +

	inclusion period - synchronous metastasis - lack of consent - revised histology showed a diagnosis other than STS **Patient characteristics** Gender n(%) Male 50 (51.5) Female 47(48.5) Age [y] median(range) 62(15-83) Tumor size [cm] median(range) 20(4-60) High malignancy grade n(%) 71(73.2) Histopathological subtype n(%) Liposarcoma 60(61.9) Leiomyosarcoma 28(28.9) Other 9(9.3) First operation at center n(%) 80(82.5) Surgical margin n(%) Negative 54(55.7) Positive 37(38.1) Unknown 6(6.2) Radiotherapy n(%) 42(43.3) Chemotherapy n(%) 15(15.5)		Whole group 56,4 months Still alive 82.8 months		4) + *Comparability* 1) ++ *Outcome* 1) + 2) + 3) -
Willeumier JJ, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, et al. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas	**Region/Setting** Four tertiary referral centers for orthopedic oncology, 2000-2010 **Inclusion criteria** - primary, non-disseminated, high-grade (as defined by FNCLCC larger	**Intervention** Surgical margin 0mm **Control** Surgical margin ≤2mm Surgical margin >2mm	**Multivariate** Overall survival 0mm vs. ≤2mm HR 0.89 [0.66-1.20], p=0.433 0mm vs. >2mm HR 0.83 [0.58-1.20],	Age (<25/25-50/>50) Tumor presentation (whoops/ primary) Tumor location (lower/upper) Tumor size [cm] Depth (Deep/Superficial/Deep and superficial)	**Study type** cohort study **Newcastle Ottawa Scale – cohort studies** *Selection*

of the extremities: a multistate model. BMJ open. 2017;7(2):e012930.	than grade 2) sarcoma - sarcomas: angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma and (pleomorphic) STS not-otherwise-specified **Exclusion criteria** - metastatic disease at the time of diagnosis - presentation with recurrent disease - treatment without curative intent (i.e., no primary intent of (limb-sparing) surgery with intended sufficient margins) - adjuvant treatment other than radiotherapy or chemotherapy - unknown margin status **Patient characteristics** Age [y] mean(SD) 57.9(19.8) Age n(%) <25 49(7.1) 25–50 170(24.7) >50 468(68.1) Gender n(%) Male 389(56.6) Female 298(43.4) Tumor presentation n(%) Primary 555(80.8) 'Whoops' 132(19.2) Tumor location n(%) Upper extremity 162(23.6) Lower extremity 525(76.4) Tumor size [cm] mean(SD) 10.0(6.2) Depth, n(%) Deep 531(77.3) Superficial 115(16.7) Deep and superficial 41(6)	**Included patients** 687	p=0.319 **Median follow up** 71 months	Histopathology(Angiosarcoma/MPNST/ Myxofibrosarcoma/Synovial sarcoma/Spindle cell sarcoma/Sarcoma NOS/(MFH/UPS)) Type of surgery (limb-sparing/amputation) Local recurrence (yes/no)¶	1) + 2) + 3) + 4) + *Comparability* 1) ++ *Outcome* 1) + 2) + 3) -

	Histopathology n(%) Angiosarcoma 19(2.8) MPNST 81(11.8) Myxofibrosarcoma 217(31.6) Synovial sarcoma 134(19.5) Spindle cell sarcoma 165(24.0) Sarcoma NOS 17(2.5) MFH/UPS 54(7.9) Surgical margin n(%) 0 mm 114(16.6) ≤2 mm 325(47.3) >2 mm 248(36.1) Type of surgery n(%) Limb-sparing 611(88.9) Amputation 76(11.1) Radiotherapy n(%) Neoadjuvant 154(22.4) Adjuvant 359(52.3) No radiotherapy 174(25.3) (Neo)Adjuvant chemotherapy n(%) Yes 82(11.9) No 605(88.1)				

+: high quality assessment; -: low quality assessment; CT/MRI: computed tomography/magnetic resonance imaging; EQD2: biologically effective radiation therapy dose equivalent to 2 Gy fractions; FNA: fine-needle aspiration; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; HPF: high-power field; HR: hazard ratio; incl.: including; LS: liposarcoma; N.A.: not applicable; MFH: malignant fibrous histiocytoma; MPNST: malignant peripheral nerve sheath tumor; NOS: not otherwise specified; PDGFRA: Platelet-derived growth factor receptor A; RR: relative risk; RT: radiotherapy; SD: standard deviation; UPS: malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; y:years

9.2. SoF Table Chirurgie - Resektionsränder

AG Therapie des lokalisierten Weichgewebetumors, Hohenberger

Summary of findings:

R0 surgical margin compared to R1 surgical margin for STS

Patient or population: STS
Intervention: R0 surgical margin
Comparison: R1 surgical margin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Local recurrence	RO reduces local recurrences	(6 observational studies)	⊕⊕⊕◯ MODERATE
Overall survival	RO improves overall survival	(7 observational studies)	⊕⊕⊕⊕ HIGH
Metastasis free survival	Surgical margin has no impact on metastasis free survival.	(2 observational studies)	⊕⊕⊕◯ MODERATE

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Catena 2012, Engstrom 2008, Gingrich 2017, Jebsen 2008, Jebsen 2013, Li 2013, Seagle 2017, Sinnamon 2016, Stahl 2017, Trovik 2000, Trovik 2014, Willeumier 2017

10. Chirurgie - Strahlentherapie

10.1. Evidenztabelle Chirurgie - Strahlentherapie

Kapitel Therapie des lokalisierten Weichgewebetumors, Budach

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Adverse events (all or the five most frequent ae) (IG/CG)[n(%)]	Study type, level of evidence and risk of bias
Alektiar KM, Zelefsky MJ, Brennan MF. Morbidity of adjuvant brachytherapy in soft tissue sarcoma of the extremity and superficial trunk. International journal of radiation oncology, biology, physics. 2000;47(5):1273-9. AND Arbeit JM, Hilaris BS, Brennan MF. Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1987;5(3):480-8. AND Brennan MF, Hilaris B, Shiu MH, Lane J, Magill G, Friedrich C, et al. Local recurrence in adult soft-tissue sarcoma. A randomized trial of brachytherapy. Archives of surgery (Chicago, Ill : 1960). 1987;122(11):1289-93. AND Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. International	**Region/Setting** July 1982 and June 1992, NY, USA **Inclusion criteria** - adult patients - primary or recurrent soft tissue sarcomas - completely resected, localized, superficial trunk sarcomas - localized extremity lesions that could be completely resected by a limb-sparing procedure **Exclusion criteria** - required amputation for local control of an extremity sarcoma - metastases at the time of presentation - previous treatment with chemotherapy or radiation therapy - incomplete resection (positive or indeterminate gross surgical margin) **Baseline patient characteristics (1987)** Gender n(%) Male 41(53)/53(62) Female 37(47)/33(38) Age [y] Median(range) 54(17-89) Age n(%) < 60 years: 54(69)/50(58) ≥ 60 years: 24(31)/36(42) Presentation n(%) Primary 71(90)/76(88) Recurrent 7(10)/10(12) Tumor site n(%) Proximal extremity 59(76)/61(71) Distal extremity 8(10)/13(15)	**Intervention** Adjuvant brachytherapy A loading plan was designed to deliver 42 to 45 Gy over 4-6 days with 192 Ir. The dose rate ranged from 0.25 to 0.66 Gy/hr (mean, 0.43 Gy/hr). The interval between surgery and loading of the catheters ranged from 1-9 days (median, 5 days), with 30% (22/78) of patients being loaded before the fifth postoperative day. The skin dose ranged from 7 to 44 Gy with a mean of 24 Gy. **Control** Surgery alone **Randomized patients (1996)** 78/86	Median follow-up:100 months Wound complications 19(24,4)/12(14,0) Wound complications that require reoperations 8(10,3)/0(0) Bone fracture 3(4,5)/0(0) Peripheral nerve damage 5(7,5)/5(6,8)	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

journal of radiation oncology, biology, physics. 1993;27(2):259-65. AND Pisters PW, Harrison LB, Woodruff JM, Gaynor JJ, Brennan MF. A prospective randomized trial of adjuvant brachytherapy in the management of low-grade soft tissue sarcomas of the extremity and superficial trunk. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1994;12(6):1150-5. AND Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1996;14(3):859-68.	Trunk 11(14)/12(14) <u>Tumor grade n(%)</u> Low 22(28)/23(27) High 56(72)/63(73) <u>Tumor size n(%)</u> < 5cm: 41(53)/40(47) ≥ 5cm: 37(47)/46(53) <u>Tumor depth n(%)</u> Superficial 25(32)/24(30) Deep 53(78)/62(70) <u>Microscopic margin n(%)</u> Positive 15(19)/14(16) Negative 63(81)/72(84) <u>Histopathology n(%)</u> Liposarcoma 32(41)/35(41) MFH 19(24)/20(23) Synovial sarcoma 8(10)/4(7) MPNT 6(7)/3(3) Fibrosarcoma 6(7)/4(7) Leiomyosarcoma 4(5)/8(9) Rhabdomyosarcoma 1(1)/4(5) Other 2(3)/8(9) <u>Postoperative chemotherapy n(%)</u> Yes 34(44)/34(40) No 44(56)/52(60)			
Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Annals of surgical oncology. 2014;21(8):2484-9. AND Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of	**Region/Setting** 1983 – 1991, N.R. **Inclusion criteria** - patients with extremity STS who had undergone LSS **Exclusion criteria** - gross residual tumor - evidence of metastatic disease - history of a second malignancy - contraindications to receiving doxorubicin, cyclophosphamide, or EBRT. **Patient characteristics**	**Intervention** Surgery plus EBRT 4,500 cGy of radiation were delivered to a wide field followed by a 1,800 cGy boost to the tumor bed; 180 cGy fractions were administered 5 days a week for 6-7 weeks. **Control** Surgery alone **Randomized patients**	Wound complications grade 2/3 5(16,7)/3(12,5) Presence of Edema grade 2/3 7(25,0)/3(12,5)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ?

soft tissue sarcomas of the extremity. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(1):197-203.	Gender n(%) Male 35(50)/43(61) Female 35(50)/28(39) Age NR Tumor site n(%) Proximal upper extremity 13(19)/12(17) Distal upper extremity 3(4)/6(8) Proximal lower extremity 33(47)/40(56) Distal lower extremity 21(30)/13(18) Tumor n(%) Benign 4(6)/5(7) Grade 1 22(31)/19(27) Grade 2 24(34)/26(37) Grade 3 20(29)/21(30) Tumor size (maximum diameter) n(%) 0-1.9cm 5(7)/6(8) 2-4.9cm 24(34)/19(27) 5-9.9cm 27(39)/25(35) ≥10.0cm 13(19)/21(30) Not available 1(1)/0(0) Surgical resection margin n(%) Positive (<1mm) 7(10)/11(15) Negative; close (1-10mm) 12(17)/20(28) Negative; wide (>10mm) 13(19)/5(7) Negative; not specified 11(16)/7(10) No tumor in re-resection 27(39)/27(38) Not available 0(0)/1(1)	70/71 patients completed telephone interview 30/24		Incomplete outcome data: - Selective reporting: + Other source of bias: +
Davis AM, O'Sullivan B, Bell RS, Turcotte R, Catton CN, Wunder JS, et al. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(22):4472-7. AND O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative	**Region/Setting** October 1994 - December 1997, Canada **Inclusion criteria** - age ≥ 16 years - potentially curable extremity STS - require of combined radiotherapy and limb-preserving surgery (based on an inability to excise tumor or surgically contaminated tissues with a minimum of 2 cm of normal tissue) - diagnosis of a primary or recurrent STS by an approved reference pathologist - staged by chest computed tomography and local computed tomography or magnetic resonance imaging	**Intervention** Preoperative RT Preoperative radiotherapy consisted of 50 Gy in 25 fractions with a boost dose of 16 Gy after operation if the resection margins were microscopically positive or 20 Gy if the margins were grossly positive for tumor on pathologic review of the surgical specimen. **Control**	Wound complications 31(35,2)/16(17,0) Grade ≥2 acute toxic skin effects 32(36,4)/64(68,1) Grade ≥2 fibrosis 23(31,5)/27(48,2) Grade ≥2 edema 11(15,1)/13(23,1) Grade ≥2 joint stiffness 13(17,8)/13(23,2)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ?

radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. Lancet (London, England). 2002;359(9325):2235-41. AND Davis AM, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2005;75(1):48-53.	**Exclusion criteria** - prior chemotherapy - prior radiotherapy to the local site - previous or concurrent malignancy - presence of regional or distant metastasis - benign histologic diagnoses, including aggressive fibromatosis - histologic subtypes generally treated with chemotherapy - specific histologic diagnosis of embryonal or alveolar rhabdomyosarcoma, soft tissue osteosarcoma or Ewing's sarcoma, or primitive neuroectodermal tumor or dermatofibrosarcoma protuberans **Patient characteristics** Gender n(%) Male 48(55)/51(54) Female 40(45)/43(46) Age n(%) <50years: 30(34)/44(47) ≥50 to <70years: 38(43)/33(35) ≥70years: 20(23)/17(18) Tumor size n(%) ≤10cm: 57(65)/63(67) >10cm: 31(35)/31(33) Lesion presentation n(%) Primary 79(90)/87(93) Recurrent 9(10)/7(7) Tumor grade n(%) Low 15(17)/16(17) Intermediate/high 73(83)/78(83) Histological subtype n(%) Malignant fibrous histiocytoma 28(32)/23(24) Liposarcoma 23(26)/26(28) Leiomyosarcoma 9(10)/9(10) Other histology 28(32)/36(38) Anatomical site (limbs) n(%) Upper arm 10(11)/11(12) Lower arm (include elbow) 8(9)/8(9) Upper leg (include knee) 44(50)/54(57) Lower leg 26(30)/21(22)	Postoperative RT All patients in the postoperative radiotherapy group received 66 Gy in 33 fractions. **Randomized patients** 91/94		Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Tumor depth n(%) Superficial and deep to fascia 22(25)/28(30) Deep to fascia 52(59)/46(49) Superficial to fascia 14(16)/20(21) Final resection margins n(%) Negative on gross examination 14(16)/13(14) Negative on gross and microscopic examination 73(83)/80(85) Missing 1(1)/0			
Kinsella TJ, Sindelar WF, Lack E, Glatstein E, Rosenberg SA. Preliminary results of a randomized study of adjuvant radiation therapy in resectable adult retroperitoneal soft tissue sarcomas. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1988;6(1):18-25. AND Sindelar WF, Kinsella TJ, Chen PW, DeLaney TF, Tepper JE, Rosenberg SA, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Archives of surgery (Chicago, Ill : 1960). 1993;128(4):402-10.	**Region/Setting** January 1980 - September 1985, N.R. **Inclusion criteria** - age ≥ 18 years - histologically confirmed or clinically suspected sarcomas arising in the soft tissues of the retroperitoneum - histologic types: liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, fibrosarcoma, synovialsarcoma, angiosarcoma, rhabdomyosarcoma (nonjuvenile type), malignant mesenchymoma, and unclassified sarcoma - patients who had undergone biopsy or excision of a retroperitoneal sarcoma at another hospital were eligible if the original surgery was performed within 3 months of referral **Exclusion criteria** - visceral sarcomas - aggressive fibromatosis and desmoids - prior adjuvant chemotherapy or radiation therapy - previous history of malignancy (except basal cell carcinoma) - severe concomitant medical problems - detectable metastatic disease - unresectability - prior radiation therapy - prior chemotherapy - medical contraindications to surgery, radiation therapy, or chemotherapy - desmoid tumors **Patient characteristics** Gender NR Age	**Intervention** Surgery plus IORT and low-dose EBRT IORT was delivered to the tumor bed using electron beams (11 to 15 MeV) in a dose of 20 Gy, using the 90% isodose line at a dose rate of 4 to 5 Gy/min. Multiple (two to six) IORT fields were routinely used to encompass the tumor bed delineated during surgery. misonidazole, an electron-affinic hypoxic cell sensitizer, was given at 3.5 mg/m^2 by rapid intravenous (IV) infusion approximately 15 to 30 minutes before IORT. EBRT was delivered with a linear accelerator generating 6 to 10 MV photons and was initiated after surgical recovery, within 3-4 weeks of operation and was delivered for 4-5 weeks in a dose of 35 to 40 Gy in daily fractions of 1.5 to 1.8 Gy, given 5 times per week. **Control** Surgery plus high dose EBRT	Acute enteritis 1(6,7)/12(60,0) Chronic enteritis 2(13,3)/10(50,0) Radiation nephritis 1(6,7)/5(25,0) Moderate to severe neuropathy 7(46,7)/0(0) Intra-abdominal abscess 1(6,7)/6(30,0)	**Study type** RCT **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

	NR <u>Tumor stage n</u> Stage I 0(0)/0(0) Stage II 1(6,7)/5(25,0) Stage III 4(26,7)/7(35,0) Stage IV 10(66,7)/8(40,0) <u>Chemotherapy n(%)</u> None 13(57)/16(64) Chemotherapy given 2(9)/4(16)	Postoperative EBRT (50 to 55 Gy) was initiated within 3-4 weeks of surgery and was delivered with a linear accelerator generating a 6 to 10 MV photon beam in a dose of 35 to 40 Gy for 4-5 weeks in 1.5 to 1.8 Gy daily fractions (5 times per week). Patients then received a coned-down boost to the tumor bed of an additional 15 Gy in 1.5 to 1.8 Gy fractions. Care was taken to limit the radiation dose to less than 30 Gy to the liver; to less than 45 Gy to the spinal cord. **Randomized patients** 15/20		
Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24(4):1099-104.	**Region/Setting** October 2001 - July 2009, N.R. **Inclusion criteria** - age between 18 and physiological 65 years - US (LMS, CS, high-grade ESS, according to histological classification at that time) histologically confirmed by a sarcoma pathologist experts panel - FIGO 1989 modified classification for endometrial carcinoma stage ≤ III - complete surgery (at least hysterectomy and bilateral oophorectomy) - ECOG performance status of 0 or 1 - adequate hematologic (granulocyte blood count and platelet count exceeded, respectively, 1500/µl and 100.000/µl); hepatic (total bilirubin < 1.5 times the upper limit of normal, transaminases < 2.5 N), renal (creatinine < 1.25 N) and cardiac (LVEF measurement (per ultrasound or scintigraphy) >50%) functions - normal thoracic, abdominal, and pelvic CT scans. **Exclusion criteria** NR **Patient characteristics** <u>Gender n(%)</u> Male 0/0	**Intervention** Surgery plus RT External pelvic RT was delivered for a total dose of 45 grays in 5 weeks (1.8 grays per fraction). Patients had to begin the treatment within 8 weeks following surgery. After the RT completion, vaginal brachytherapy was optional (choice of each center at the beginning of the study). **Control** Surgery plus chemotherapy followed by RT Chemotherapy consisted in four cycles of API regimen: doxorubicin 50 mg/m² day 1, ifosfamide 3 g/m² per day, days 1 and 2, with mesna 3 g/m² per	Breast cancer 2(4,8)/2(7,1) Renal cell carcinoma 1(2,4)/0(0) **IG** Grade 3 gastrointestinal toxicity 1(2,4) **CG** <u>Grade3-4</u> Neutropenia 22(57,9) febrile neutropenia 9(23,7) Thrombocytopenia 29(76,3) Anemia 22(57,9) Nausea/vomiting 8(21,1)	**Study type** RCT **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

	Female 42(100)/39(100) Age [y] Median (range) 54.5(39-66)/55(40-69) Histology n(%) Leiomyosarcoma 29(69)/ 24(62) Carcinosarcoma 10(24)/ 9(23) High-grade stromal sarcoma 3(7)/ 6(15) Vaginal brachytherapy n 24(57,2)/26(66,7)	day, days 1 and 2, cisplatin 75 mg/m² day 3, and lenograstim 150 µg/m² per day, days 7–14; API regimen was administered every 3 weeks. External pelvic RT was delivered for a total dose of 45 grays in 5 weeks (1.8 grays per fraction), starting 4 weeks after the last administration of chemotherapy. **Randomized patients** 42/39		

+ low risk of bias; - high risk of bias, ? unclear risk of bias; API: doxorubicin, ifosfamide, and cisplatin; BRT: brachytherapy; CS: carcinosarcoma; CT: computer tomography; EBRT: external beam radiation therapy; ECOG: Eastern Cooperative Oncology Group; ESS: endometrial stromal sarcoma; FIGO: International Federation of Gynecology and Obstetrics; IORT: intraoperative radiation therapy; LMS: leiomyosarcoma; LSS: limb sparing surgery; LVEF: left ventricular ejection fraction; MFH: malignant fibrous histiocytoma; MPDR: median peripheral dose rate; MPNT: malignant peripheral nerve tumor; n: number of cases; NR: not reported; RT: radiotherapy; SD: standard deviation; STS: soft tissue sarcoma; US: uterine sarcoma; y: years;

10.2. SoF Tables Chirurgie - Strahlentherapie

Kapitel Therapie des lokalisierten Weichgewebetumors, Budach

Summary of findings:

Surgery plus BRT compared to surgery alone for STS

Patient or population: STS
Intervention: surgery plus BRT
Comparison: surgery alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with surgery plus BRT**				
Overall survival (range follow-up: 16 months)	92 per 1.000	115 per 1.000 (40 to 337)	RR 1.25 (0.43 to 3.65)	117 (1 RCT)	⊕⊕⊕◯ MODERATE	Different number of participants caused by multiple publishing of just one study (e.g. different points in time)
Disease specific survival (follow-up:76 months)		*p*=0.65		164 (1 RCT)	⊕⊕⊕◯ MODERATE	
Overall survival low grade STS (follow-up: 67 months)	43 per 1.000	91 per 1.000 (9 to 933)	RR 2.09 (0.20 to 21.45)	45 (1 RCT)	⊕⊕⊕◯ MODERATE	
Local recurrence (follow-up: 76 months)		*p*=0.04		164 (1 RCT)	⊕⊕⊕◯ MODERATE	Effect IG>CG
Free from distant metastasis (follow-up:76 months)		*p*=0.50		164 (1 RCT)	⊕⊕⊕◯ MODERATE	Effect IG>CG

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BRT: brachytherapy; **CI:** Confidence interval; **RR:** Risk ratio; **STS**: soft tissue sarcoma

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Brennan 1987, Pisters 1994, Pisters 1996

Summary of findings:

EBRT + surgery compared to surgery alone for STS

Patient or population: STS
Intervention: EBRT + surg
Comparison: surg alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery alone	**Risk with EBRT+surgery**				
Overall survival (follow-up: 240 months)	357 per 1000	296 per 1000 (182 to 475)	RR 0.83 (0.51 to 1.33)	141 (1 RCT)	⨁⨁◯◯ LOW	
Local recurrence (follow-up:232,7 months)	254 per 1.000	15 per 1.000 (3 to 104)	RR 0.06 (0.01 to 0.41)	141 (1 RCT)	⨁⨁⨁◯ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; EBRT: external beam radiotherapy; **RR:** Risk ratio; **STS**: soft tissue sarcoma

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Beane 2014

Summary of findings:

Intra- + post RT compared to post RT for STS

Patient or population: STS
Intervention: intra- + post RT
Comparison: post RT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with post RT	**Risk with intra- + post RT**				
Overall survival (follow-up: 96 months)	750 per 1.000	803 per 1.000 (563 to 1.000)	RR 1.07 (0.75 to 1.53)	35 (1 RCT)	⨁⨁⨁◯ MODERATE	
Local recurrence (follow-up: 96 months)	800 per 1.000	400 per 1.000 (208 to 768)	RR 0.50 (0.26 to 0.96)	35 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **RT**: radiotherapy; **STS**: soft tissue sarcoma

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Sindelar 1993

Summary of findings:

Surgery + RT compared to Surgery + CT + RT for localized uterine sarcomas

Patient or population: STS
Intervention: Surgery + RT
Comparison: Surgery + CT + RT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Surgery+CT+RT	**Risk with Surgery+RT**				
Overall survival (follow-up: 60 months)	282 per 1.000	451 per 1.000 (248 to 826)	RR 1.60 (0.88 to 2.93)	81 (1 RCT)	⨁⨁◯◯ LOW	
Relapse (follow-up: 51,6 months)	385 per 1.000	619 per 1.000 (388 to 985)	RR 1.61 (1.01 to 2.56)	81 (1 RCT)	⨁⨁◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CT**: chemotherapy; **RR:** Risk ratio; **RT**: radiotherapy; **STS**: soft tissue sarcoma

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Pautier 2013

Summary of findings:

Preoperative RT compared to postoperative RT for STS

Patient or population: STS
Intervention: Preoperative RT
Comparison: postoperative RT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with postoperative RT	**Risk with Preoperative RT**				
Overall survival (follow-up: 39,6 months)	146 per 1.000	80 per 1.000 (45 to 144)	RR 0.55 (0.31 to 0.99	190 (1 RCT)	⊕⊕⊕◯ MODERATE	
Local recurrence (follow-up: 39,6 months)	*p*=0.7119			190 (1 RCT)	⊕⊕◯◯ LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **RT**: radiotherapy; **STS**: soft tissue sarcoma

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

O´Sullivan 2002

11. Rehabilitation

11.1. Evidenztabelle Rehabilitation

AG Rehabilitation und Nachsorge, Schubert

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Study type, level of evidence and risk of bias
Michot, A., et al., The introduction of early patient rehabilitation in surgery of soft tissue sarcoma and its impact on post-operative outcome. Eur J Surg Oncol, 2015. 41(12): p. 1678-84. Stoeckle, E., et al., The risk of postoperative complications and functional impairment after multimodality treatment for limb and trunk wall soft-tissue sarcoma: Long term results from a monocentric series. Eur J Surg Oncol, 2017. 43(6): p. 1117-1125.	**Region/Setting** Bordeaux, France Single institute **Inclusion criteria** Adult patients ≥16 years with primary non-metastatic STS located in the trunk wall or the limbs that were operated at Institut Bergonié between 1989 and 2012 were included in the study. **Exclusion criteria** NR **Patient characteristics** <u>Age [years] mean (SD)</u> 58 (18)/55 (17) <u>Sex n(%)</u> Female 126 (46)/223 (49) Male 149 (54)/236 (51) <u>Localization n(%)</u> Shoulder girdle 30 (6) 18 (6) Upper limb 51 (11) 31 (11) Trunk wall 76 (17) 46 (17) Pelvic girdle 40 (9) 32 (12) Lower limb 262 (57) 148 (54) <u>Size [mm]median(range)</u> 70 (10-480)/80 (8-600) <u>Tumor depth n(%)</u> Superficial 83 (30)/77 (17)	**Intervention(s)** Enhanced recovery after surgery (ERAS) program The role of the physiotherapist was crucial in helping the patients to reacquire their autonomy in the postoperative period. By his reassurance and technical support, he helped them to retrieve confidence, allowing them to move their body without pain and walk around as early as day 0. After treatment, patients were regularly followed-up at the clinic with a physical examination of the tumor bed and a chest X-ray. The rhythm of follow-up was every four months for three years, then every six months for two years and then annually. Follow-up was alternately performed by the surgeon, the radiotherapist and the oncologist. **Control** Prior standard recovery after surgery (SRAS) period (1989-2007) **Included patients** 275/459	**Study type** Non concurrent cohort study **Newcastle Ottawa Scale – cohort studies** *Selection* 1) + 2) + 3) + 4) + *Comparability* 1) - *Outcome* 1) + 2) + 3) -

	Deep 192 (70)/382 (83) <u>Histological subtypes n(%)</u> Undifferentiated sarcoma 84 (31)/121 (26) Muscular sarcoma (LMS + RMS) 45 (16)/84 (18) Other LPS 55 (20)/70 (15) Myxoid LPS 23 (8)/48 (10) Synovial Sarcoma 11 (4)/39 (9) Others 57 (20)/97 (21) <u>Grade n(%)</u> 1 75 (27)/108 (24) 2 92 (34)/125 (27) 3 95 (34)/216 (47) N/A 13 (5)/10 (2)		

+: high quality assessment; -: low quality assessment; CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; ECOG PS: Eastern Cooperative Oncology Group performance status; DT: desmoid tumor; FAP: familiar adenomatous polyposis ; NR: not reported

11.2. SoF Table Rehabilitation

AG Rehabilitation und Nachsorge, Schubert

Summary of findings:

Enhanced recovery after surgery programm compared to standart recovery after surgery for STS

Patient or population: STS
Intervention: Enhanced recovery after surgery programm
Comparison: standart recovery after surgery

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standart recovery after surgery	**Risk with Enhanced recovery after surgery programm**				
Overall survival (median follow-up: 140 months SRAS; 40 months ERAS)	791 per 1.000	**815 per 1.000** (751 to 870)	**RR 1.03** (0.95 to 1.10)	734 (1 observational study)	⨁◯◯◯ VERY LOW	
Risk of local recurrence (median follow-up: 140 months SRAS; 40 months ERAS)	120 per 1.000	**120 per 1.000** (80 to 180)	**RR 1.00** (0.67 to 1.50)	734 (1 observational study)	⨁◯◯◯ VERY LOW	
Overall morbidity (median follow-up: 140 months SRAS; 40 months ERAS)	420 per 1.000	**362 per 1.000** (299 to 437)	**RR 0.86** (0.71 to 1.04)	734 (1 observational study)	⨁◯◯◯ VERY LOW	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **ERAS**: Enhanced recovery after surgery; **SRAS**: Prior standard recovery after surgery

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Michot 2015, Stoeckle 2017

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