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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Moderne Chemotherapie bei Weichgewebesarkomen

25. April 2015, Swiss Sarcoma Patiententag, Zürich (CH)

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Sarkom Zentrum
German Interdisciplinary Sarcoma Group (GISG)

Weichgewebesarkom - Definition

Das **Sarkom** (v. griech. *σάρκωμα*, *sárkoma*, zu σάρξ, *sárx* „Fleisch“, „Weichteile“ und *-om* „Geschwulst“) ist ein bösartiger Tumor, der vom Stützgewebe (präziser: dem Mesoderm) ausgeht und frühzeitig in die Blutgefäße (hämatogen) metastasiert.

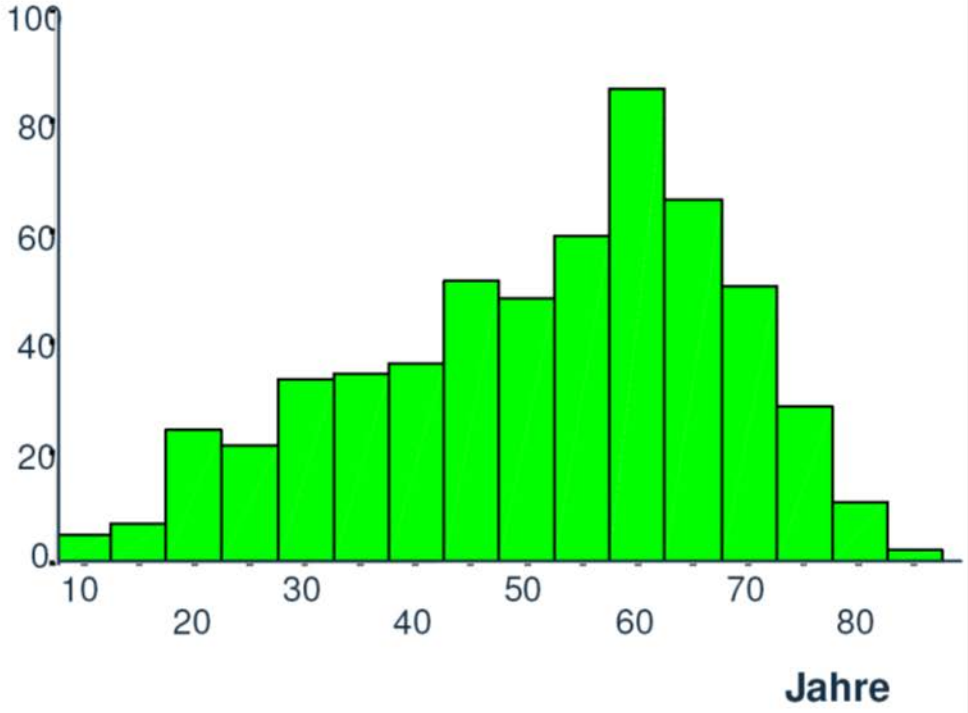
Weichgewebesarkome - Grundlagen

- Ca. 1 % aller malignen Tumore
- 3-4/100.000 pro Jahr
- Keine Geschlechtsunterschiede
- Lokalisation:
    - 12 % Retroperitoneum
    - 15 % obere Extremität
    - 15 % Kopf-Hals-Bereich
    - 18 % Stamm
    - 40 % untere Extremität

Weichgewebesarkome - Altersverteilung

30 % der Patienten
> 60 Jahre

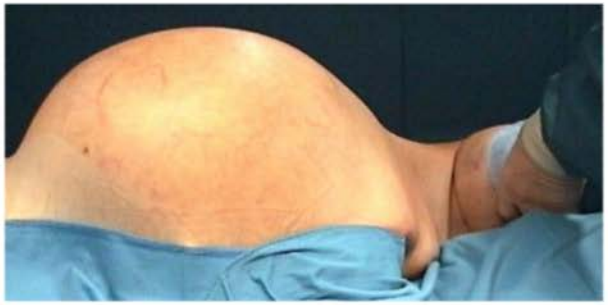
am häufigsten
zwischen dem
40.-70. Lebensjahr



Weichgewebesarkome - Klinik

Schwellung im Bereich der Extremitäten

Funktionseinschränkung, Schmerz



Ausnahme: Becken

Retroperitoneum

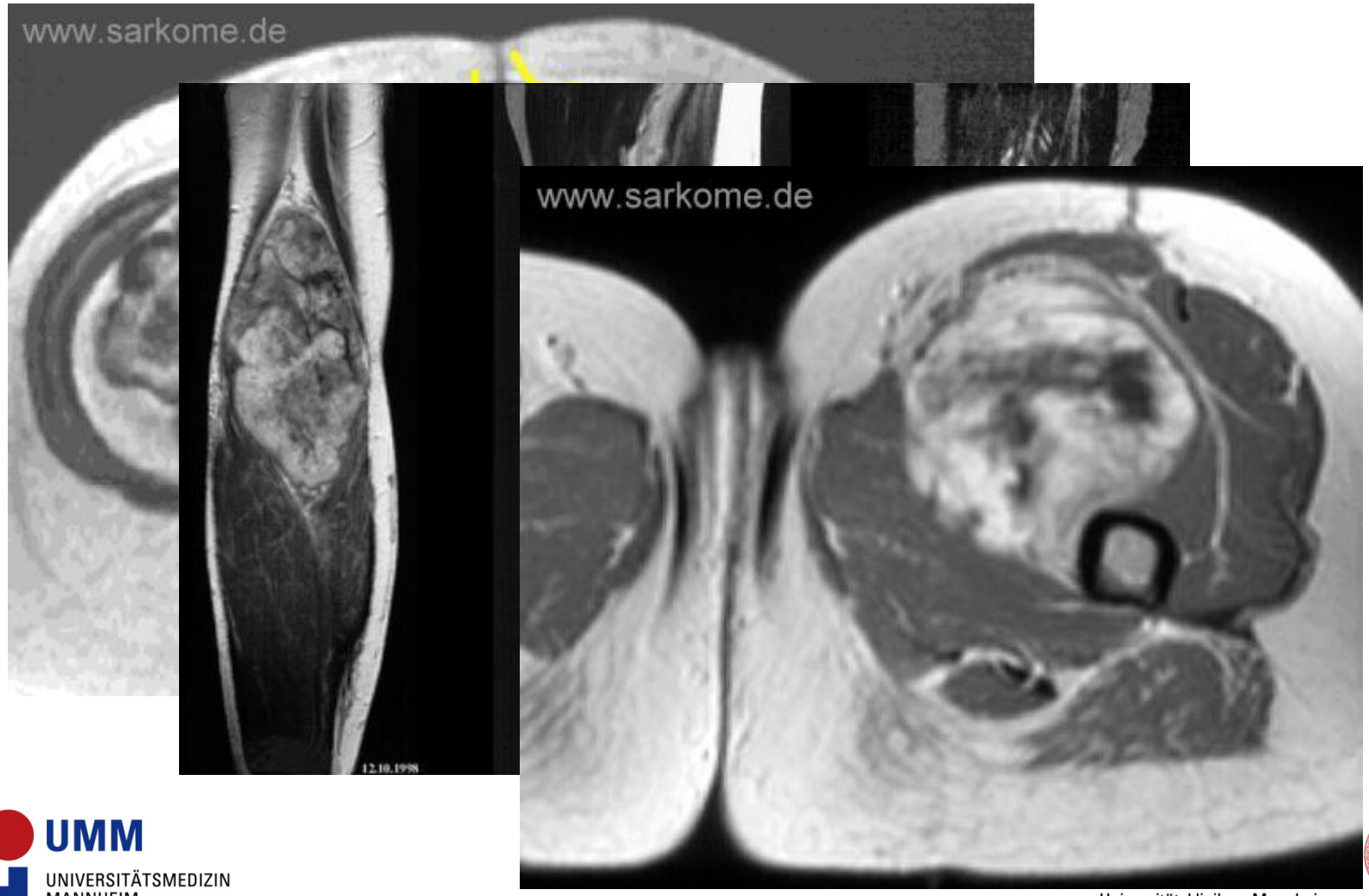
Abdomen

Weichgewebesarkome - Diagnostik

Malignitätsverdacht:

- Alter > 50 Jahre
- Tumorgröße > 8 cm
- Schmerzen
- Schnelle Größenzunahme
- Tiefe Lokalisation

„Sarkom ist nicht gleich Sarkom!“



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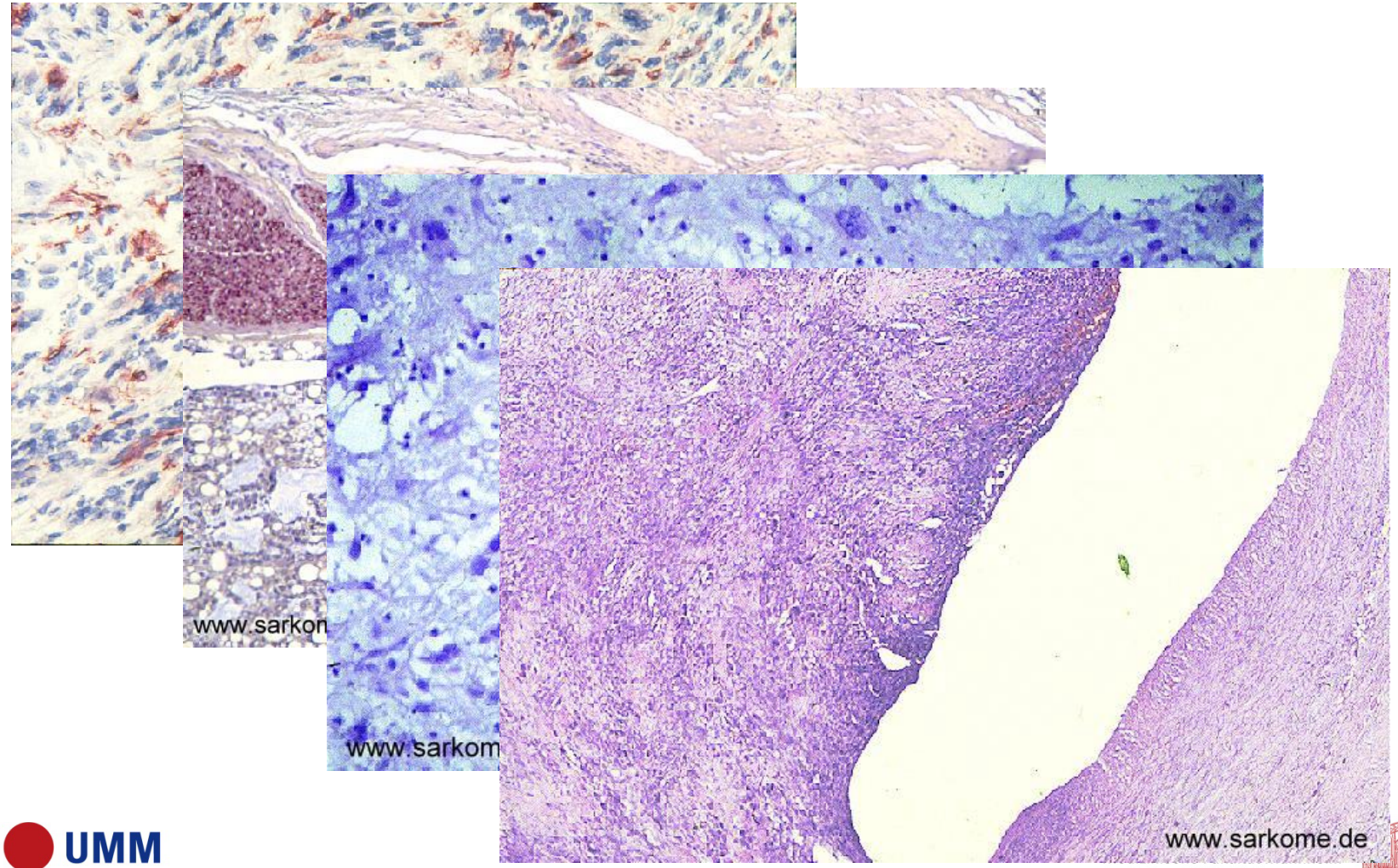
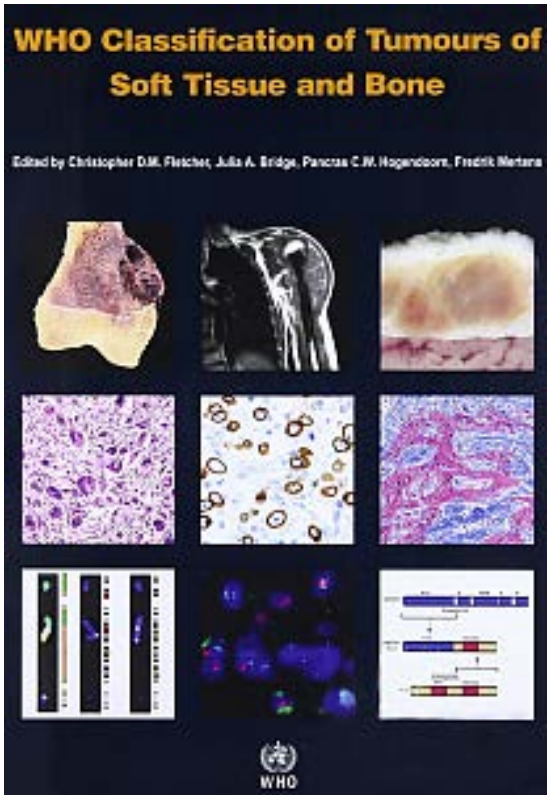


„Sarkom ist nicht gleich Sarkom!“



Fletcher CDM et al. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed; 2013

Weichgewebesarkome - Diagnostik

- Bei klinischem Verdacht zunächst lokale Bildgebung:
  - Methode der 1. Wahl = Gadolinium **MRT**
- Histologische Sicherung mittels Stanz- oder Inzisionsbiopsie unter strenger Berücksichtigung der definitiven Operation
- Staging: CT-Thorax, weitere Untersuchungen nach Klinik / Symptomen
- **Die möglichst korrekte histologische Diagnose ist entscheidend für die weitere Behandlung (Referenzpathologie!)**

Weichgewebesarkome - Metastasierung

- Meist hämatogen: v.a. Lunge, Knochen, Leber
- Selten lymphogen (< 5 %)
  - ➢ Ausnahmen: Rhabdomyosarkom, Synovialsarkom (15 - 20 %)

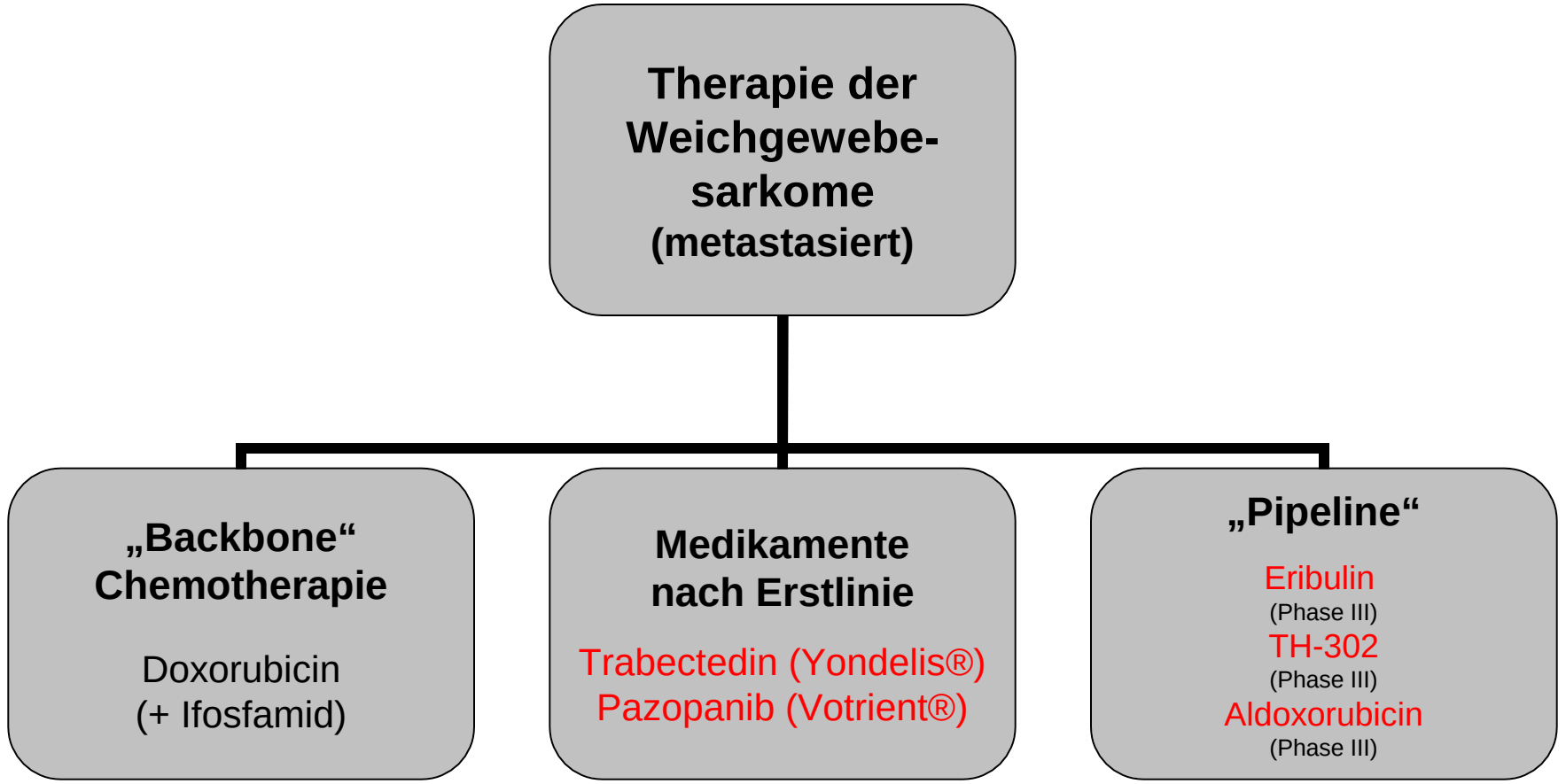
Weichgewebesarkome - Therapieprinzipien

Lokalisierte Erkrankung:

- Radikale Operation (Kompartmentresektion)
- Additive Strahlentherapie (prä / post OP)
- (neo-) adjuvante Chemotherapie

Fortgeschrittene Erkrankung:

- ➢ **Chemotherapie**
- Operation


Therapie der Weichgewebe-sarkome (metastasiert)
„Backbone“ Chemotherapie
Doxorubicin
(+ Ifosfamid)
Medikamente nach Erstlinie
Trabectedin (Yondelis®)
Pazopanib (Votrient®)
„Pipeline“
Eribulin
(Phase III)
TH-302
(Phase III)
Aldoxorubicin
(Phase III)

CANCER *January* 1974

ADRIAMYCIN CHEMOTHERAPY—EFFICACY, SAFETY, AND PHARMACOLOGIC BASIS OF AN INTERMITTENT SINGLE HIGH-DOSAGE SCHEDULE

ROBERT S. BENJAMIN, MD, PETER H. WIERNIK, MD, AND NICHOLAS R. BACHUR, MD, PHD

A study designed to correlate clinical and pharmacologic observations was undertaken in 96 patients treated with adriamycin. The basic dosage schedule was 60 mg/m² I.V. q 3 weeks. Pharmacokinetic studies showed a prolonged plasma half-life, low urinary excretion, and undetectable levels in CSF. Patients with significantly impaired liver function had marked elevation and prolongation of plasma drug levels associated with severe toxicity unless dosage was reduced by 50–75%. Of the 82 evaluable patients, 10/25 with sarcomas, 9/31 with carcinomas, and 15/26 with hematologic malignancies have achieved complete or partial remission. An additional 22/48 have improved. Six patients with solid tumors had progressive CNS disease while responding systemically. Adriamycin can be used with relative safety and high efficacy in a dosage schedule that resulted from pharmacologic studies. Dosage reduction in patients with liver disease is essential to avoid life-threatening toxicity.

Fortgeschrittene STS - Mono vs. Poly CT

Autoren	Chemoprotokoll	N	Ansprechrate		Überleben
Muss et al. 1985	A/AC	104	NS		**NS**
Omura et al. 1983	A/AD	146	NS		**NS**
Borden et al. 1987	A/AD	186	**AD = 30 %**	(p = 0.02)	**NS**
Lerner et al. 1987	A/AD	66	**AD = 44 %**	(LMS)	**NS**
Santoro et al. 1995	A/AI/CYVADIC	449	NS		**NS**
Borden et al. 1990	A/AVd	295	NS		**NS**
Edmonson et al. 1993	A/AI/APM	262	**AI = 34 %**	(p = 0.03)	**NS**
Antman et al. 1993	AD/MAID	340	**MAID = 32 %**	(p = 0.002)	**NS**
Judson et al. 2014	A/AI	415	**AI = 26 %**	(A = 14 %)	**NS**
Ryan et al. 2013	A/APal	447	**APal = 28 %**	(A = 19 %)	**NS**

<u>Kein</u> Überlebensvorteil: Doxorubicin (75 mg/m²) bleibt der Gold-Standard!

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Muss H et al. Cancer 1985; 55: 1648-53; Omura G et al. Cancer 1983; 52: 626-32; Borden E et al. J Clin Oncol 1987; 5: 840-50; Santoro A et al. J Clin Oncol 1995; 13: 1537-45; Borden E et al. Cancer 1990; 66: 862-7; Edmonson J et al. J Clin Oncol 1993; 11: 1269-75; Antman K et al. J Clin Oncol 1993; 11: 1276-85; Judson I et al. Lancet Oncol 2014; 15: 415-423; Ryan C, ESMO 2013

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Systemtherapien bei vorbehandelten STS

Alle STS (Europa)	**Trabectedin**
Alle STS ohne Liposarkome	**Pazopanib**
Alle STS (USA)	Gemcitabine + Docetaxel
Alle STS	Ifosfamid hoch dosiert (ESMO 2014)
	DTIC (ESMO 2014, v.a. LMS)
Leiomyosarkome (Europa)	Gemcitabine (Option, ESMO 2014)
	Gem + DTIC (Option, ESMO 2014)
Alle STS	Einschluss in klinische Studien

Einsatz von Trabectedin bei STS

Trabectedin (ET-743, Yondelis™):

= „Minor groove binder“ marinen Ursprungs

- Vorbehandelte Patienten:

  8 % RR, 26 % SD > 6 Monate

  (Le Cesne et al. JCO 2005)

- Unbehandelte Patienten:

  17 % RR, 21 % Progressions-frei nach 1 Jahr

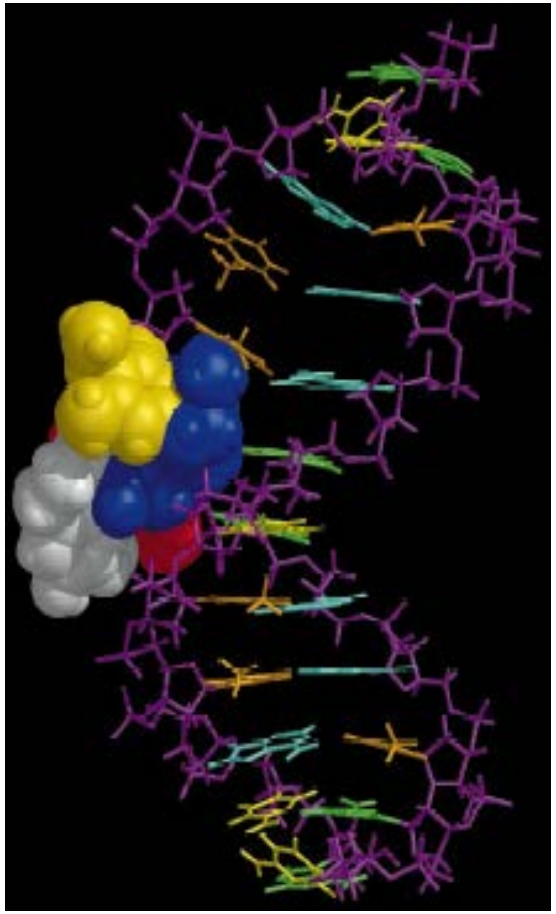
  (Garcia-Carbonero et al. JCO 2005)

- Dosierung: 1,5 mg/m^2 als 24h Infusion, Intervall 3 Wochen

- Prämedikation: 20 mg Dexamethason 30 Min. vor Infusion

Einsatz von Trabectedin bei STS

European Medicines Agency:
“Trabectedin (Yondelis®, q3wk 24-h) ist indiziert für die Behandlung von Patienten mit fortgeschrittenem Weichgewebesarkom nach dem Versagen von Anthrazyklinen und Ifosfamid, oder bei Patienten, bei denen sich die Anwendung dieser Mittel nicht eignet.
Die Daten zur Wirksamkeit basieren hauptsächlich auf Patienten mit Liposarkom und Leiomyosarkom.”



Sicherheitsprofil von Trabectedin

Nebenwirkung	Doxorubicin (75 mg/m²)	Ifosfamide (≥ 10 g/m²)	Trabectedin (1.5 mg/m²)
Neutropenie Grad 3-4	85 %	100 %	52 %
Neutropenes Fieber	29 %	40 %	5 %
AST/ALT Grad 3-4	NR	NR	51 %
Kardiotoxizität	5-10 %	–	–
Neurotoxizität	10 %	30 %	2 %
Tod	0-4 %	0-4 %	1 %
Alopezie	100 %	100 %	3 %

Keine spezifische Organtoxizität und keine kumulative Toxizität unter Trabectedin!

Verweij J et al. J Clin Oncol 2000; 18: 2081-6; Nielsen O et al. Eur J Cancer 2000; 36: 61-7; Judson I et al. Eur J Cancer 2001; 37: 870-7; Le Cesne A et al. J Clin Oncol.1995; 13: 1600-8; Demetri G et al. J Clin Oncol 2009; 27: 4188-96; Le Cesne A et al. Invest New Drugs 2012; 30: 1193-202

Optimaler Einsatz von Trabectedin

- Effektivität in frühen Linien
- Behandlung über 6 Zyklen hinaus
- Trabectedin bei älteren Patienten

Effektivität in frühen Linien

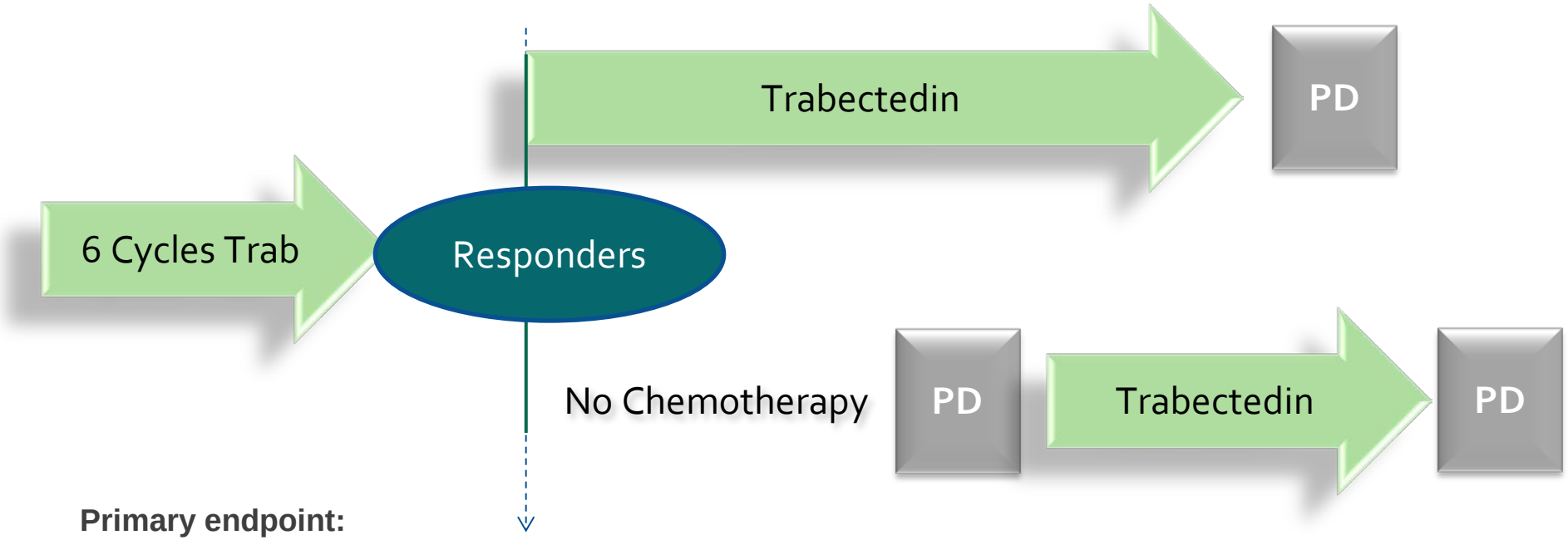
- **Französische Datenbank „RetrospectYon“ (2008 - 2011)**
- **N = 885 (486 Frauen, medianes Alter 54 Jahre)**
- **Histologien: LMS (36 %), LPS (18 %), Synoviale Sarkome (11 %)**
- **Ansprechrate bei 16.1 % (135/835 Patienten)**

	Median PFS	Median OS
All population	4	12.2
Number of trabectedin line		
2nd	4.3	12.9
3rd	4.2	12.3
4 or more	3.4	9.5

➢ **Median PFS und OS sind in frühen Behandlungslinien günstiger**

Le Cesne A et al. J Clin Oncol 2013; 31 (suppl; abstract 10563)

T-DIS Studie mit Trabectedin (ASCO 2014 #10523)



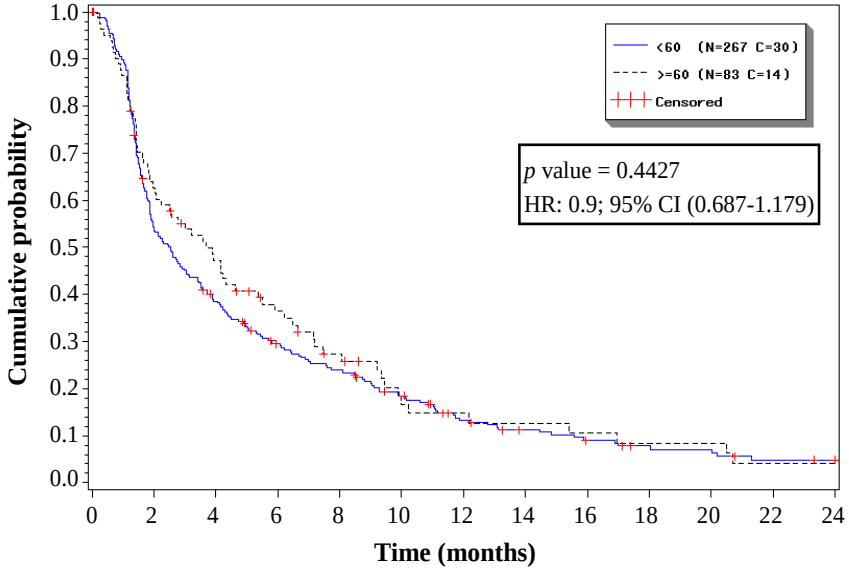
Primary endpoint:
- PFR 24 weeks post randomization

Secondary endpoints:
- ORR
- PFR at 12 & 54 weeks
- Survival at 12 & 24 months

Le Cesne A et al. J Clin Oncol 2014; 32: 5s (abstract 10523)

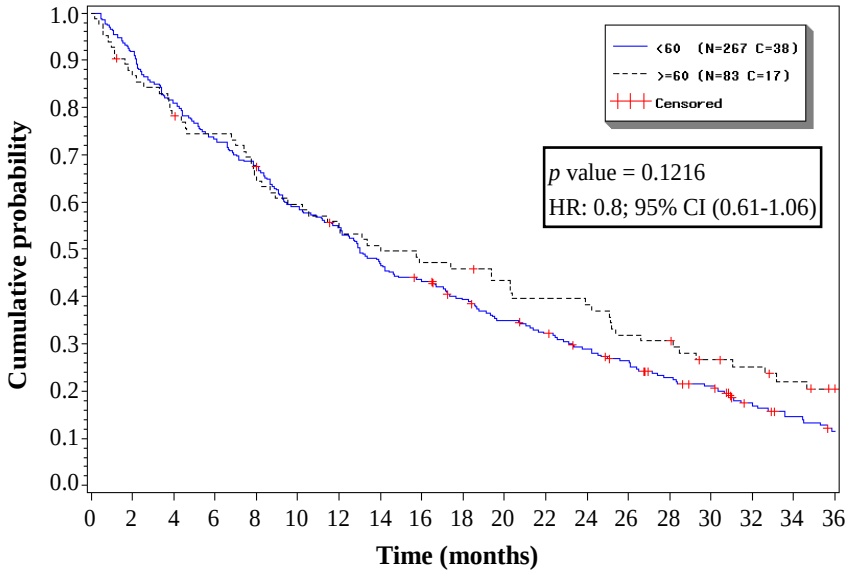
Trabectedin bei älteren Patienten

Progression-free survival



Median PFS (95% CI): <60: 2.5 (1.9-3.1) *vs*. ≥60: 3.7 (2.1-5.5)
PFS at 3 mo (95% CI): <60: 45.1% (39.1-51.1) *vs*. ≥60: 55.1% (44.2-66.0)
PFS at 6 mo (95% CI): <60: 29.5% (23.9-35.0) *vs*. ≥60: 36.4% (25.6-47.1)

Overall survival



Median OS (95% CI): <60: 13.0 (11.3-14.9) *vs*. ≥60: 14.0 (9.5-23.9)
OS at 12 mo (95% CI): <60: 54.6% (48.6-60.6) *vs*. ≥60: 55.8% (45.0-66.6)
OS at 24 mo (95% CI): <60: 28.9% (23.4-34.4) *vs*. ≥60: 38.2% (27.6-48.9)

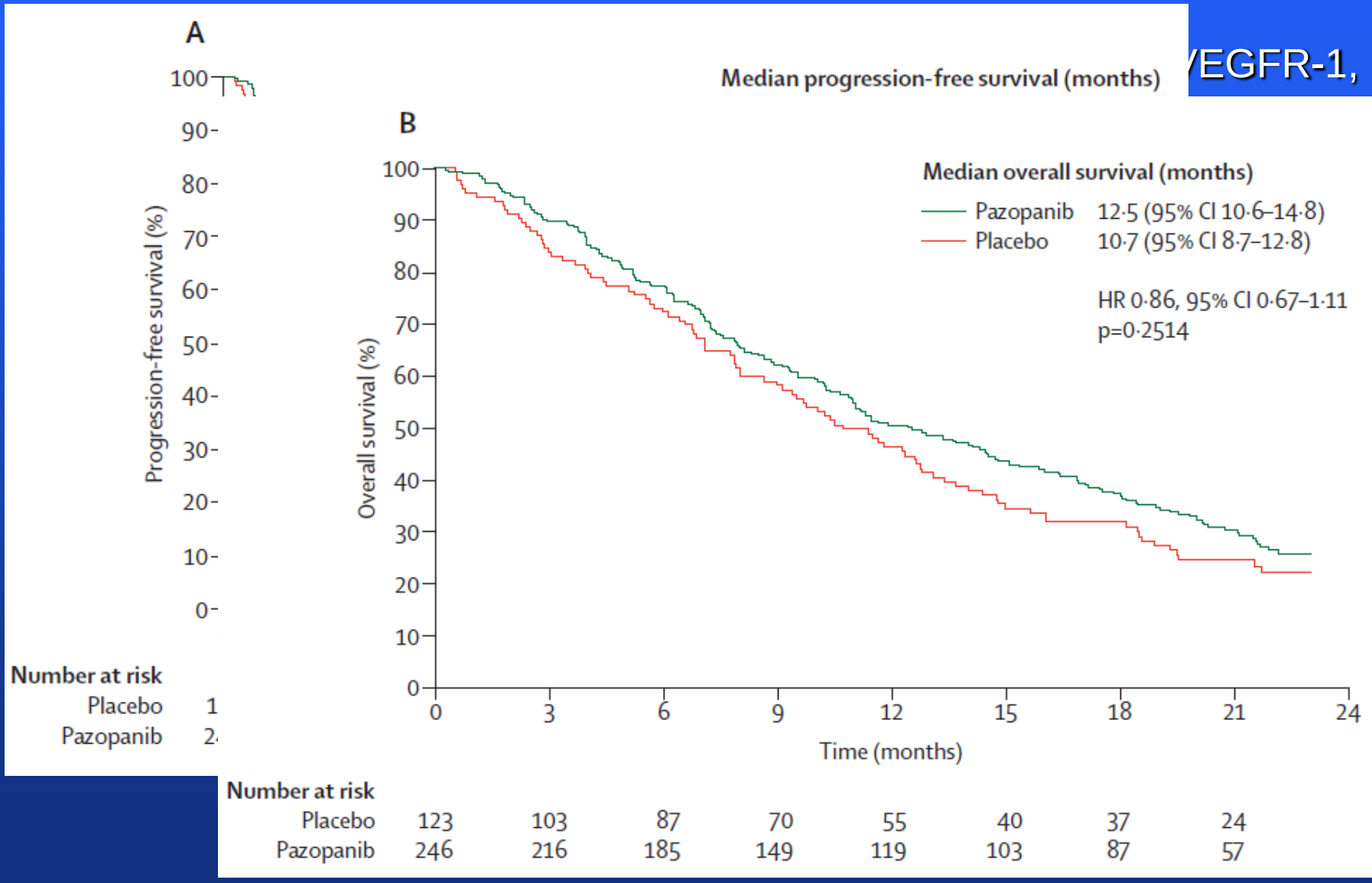
CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival; PFS, progression-free survival.

Keine wesentlichen Unterschiede hinsichtlich Effektivität und Toxizität bei Patienten ≥ 60 Jahre

Le Cesne et al. Eur J Cancer 2012; 48: 3036-3044

Van der Graaf WTA et al. Lancet 2012; 379: 1879-1886

VEGFR-1,



PALETTE - Sicherheitsprofil von Pazopanib

Unerwünschte Ereignisse	Placebo (n = 123)		Pazopanib (n=240)	
	Alle Grade	Grad 3/4	Alle Grade	Grad 3/4
Fatigue	48%	5%	65%	14%
Durchfall	15%	< 1%	59%	5%
Übelkeit	22%	2%	56%	3%
Gewichtsverlust	15%	0%	48%	4%
Hypertonie	6%	0%	42%	7%
Appetitverlust	19%	0%	40%	6%
Veränderung der Haarfarbe	2%	0%	39%	0%
Erbrechen	11%	< 1%	33%	3%
Tumorschmerzen	21%	9%	29%	8%
Dysgeusie	3%	0%	28%	0%
Kopfschmerzen	8%	0%	23%	< 1%
Schmerzen der Skelettmuskulatur	20%	2%	23%	2%

Abstract # 10553

EORTC European Organisation for Research and Treatment of Cancer

The future of cancer therapy

www.eortc.org

LONG TERM RESPONDERS AND SURVIVORS ON PAZOPANIB FOR SOFT TISSUE SARCOMAS (STS). SUBANALYSIS OF TWO EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) CLINICAL TRIALS 62043 AND 62072

Bernd Kasper[1], Saskia Litière[2], Sandrine Marreaud[2], Stefan Sleijfer[3], Jaap Verweij[3], Sebastian Bauer[4], Jan-Martijn Kerst[5], Winette van der Graaf[6]

[1]University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany - [2]EORTC Headquarters, Brussels, Belgium - [3]Erasmus University Medical Center - Daniel den Hoed Cancer Center, Rotterdam, The Netherlands - [4]West German Cancer Center, Essen, Germany - [5]The Netherlands Cancer Institute, Amsterdam, The Netherlands - [6]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

BACKGROUND

Pazopanib has recently received approval in US, EU & Japan for use in certain STS subtypes. We conducted a retrospective analysis on pooled data from two EORTC clinical trials on pazopanib in STS in order to characterize long term responders and survivors.

METHODS

Patients selected for this analysis were treated with pazopanib in the EORTC 62043 phase II study (n = 142) and EORTC 62072 phase III study (n = 246) (see Figure 1 & Table 1).

TABLE 1: KEY CHARACTERISTICS AND DIFFERENCES OF THE TWO TRIALS

	EORTC 62043	EORTC 62072 - PALETTE
Type of trial	Phase II	Phase III
Design	One treatment arm: pazopanib 800 mg daily	Randomization (2:1) between pazopanib (800 mg daily) and placebo
Eligibility	• Metastatic STS • No more than one combination or two single agent chemotherapy for advanced disease	• Metastatic STS, except adipocytic tumors • Maximum 4 prior lines of systemic therapy (incl. up to 2 combination regimens) for advanced disease
Primary endpoint	Progression free survival at 12 weeks	Progression free survival (independent central review)
Secondary endpoints	Overall progression free survival Response to treatment Overall survival Safety profile	Response to treatment Overall survival Safety profile
Other	Disease burden assessed every 3 months until disease progression	Disease burden assessed every 4 weeks till week 12, then every 8 weeks till progression
Reference	Sleijfer et al. JCO 2009	Van der Graaf et al. Lancet 2012

Long-term responders and survivors were identified as the 30-35 % of patients with longest duration of response and survival, respectively. Time to event endpoints were estimated using KM techniques:

- **Progression-free survival (PFS):** from the date of registration/randomization to the first documentation of progression or death, whichever occurred first.
  - the radiological assessment of the principal investigator is used for the definition of progression; clinical progression in the absence of radiologically documented progression is also taken into account
- **Overall survival (OS):** from the date of registration/randomization to the date of death.

Patients are censored at the date of last patient visit (before the clinical cut-off date). Clinical cut-off dates for this analysis resulted in a pooled database with a median follow-up of 2.3 years.

Combined median progression-free survival (PFS) and median overall survival (OS) are depicted in Figure 2. 34 % of all patients had a PFS ≥ 6 months (n = 133) and were defined as long term responders; 33 % of all patients survived ≥ 18 months (n = 128), defined as long term survivors. The following patient characteristics were studied: gender, age, performance status, tumor localization, histology, grading, treatment exposure and dose modifications, severity of adverse events and post protocol therapy.

FIGURE 1: CONSORT-LIKE DIAGRAM

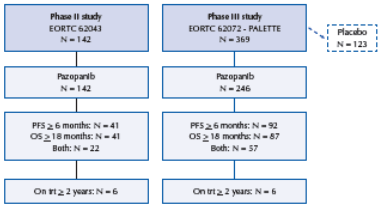
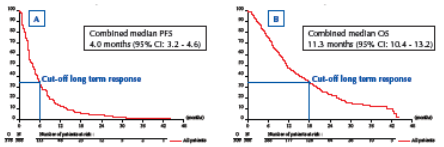


FIGURE 2: COMBINED PROGRESSION-FREE SURVIVAL (A) AND OVERVALL SURVIVAL (B)



RESULTS

Patient characteristics were compared between four subgroups based on short / long term PFS and OS, respectively. 79 patients were both long term responders and long term survivors (Table 2). The descriptive analysts confirmed the importance of known prognostic factors such as age, performance status and tumor grading, but did not add additional characteristics translating into long term response or survival.

TABLE 2: PATIENT CHARACTERISTICS

		RESPONSE CATEGORIES					
		PFS<6 months & OS<18 months (N = 206)	PFS<6 months & OS≥18 months (N = 49)	PFS≥6 months & OS<18 months (N = 54)	PFS≥6 months & OS≥18 months (N = 79)	Total (N = 388)	Patients on pazopanib for ≥ 2 years (N = 12)
Age (years)	Median	55	56	56	51	54	42
	Q1-Q3	43 - 65	45 - 62	46 - 66	34 - 62	41 - 64	30 - 55
Gender N (%)	Male	98 (47.6)	19 (38.8)	28 (51.9)	25 (31.6)	170 (43.8)	3
	Female	108 (52.4)	30 (61.2)	26 (48.1)	54 (68.4)	218 (56.2)	9
Performance status	0	82 (39.8)	35 (71.4)	18 (33.3)	50 (63.3)	185 (47.7)	7
	1	124 (60.2)	14 (28.6)	36 (66.7)	29 (36.7)	203 (52.3)	5
Site of primary	Extremities	69 (33.5)	15 (30.6)	21 (39.6)	27 (38.9)	133 (34.3)	7
	Retro-intra abdominal	43 (20.9)	9 (18.4)	8 (14.8)	16 (20.3)	76 (19.6)	2
	Visceral	45 (21.8)	15 (30.6)	9 (16.7)	18 (22.8)	86 (22.2)	2
	Other	49 (23.8)	10 (20.4)	16 (29.6)	18 (22.8)	93 (24.0)	1
Histology (central review)	Leiomyosarcoma	65 (31.6)	26 (53.1)	19 (35.2)	33 (41.8)	143 (36.9)	4
	Synovial sarcoma	38 (18.4)	4 (8.2)	11 (20.4)	10 (12.7)	63 (16.2)	2
	Other	103 (50.0)	19 (38.8)	24 (44.4)	36 (45.6)	182 (46.9)	6
Tumor grade at time of initial diagnosis (central review)	Low	11 (5.3)	3 (6.1)	3 (5.6)	14 (17.7)	31 (8.0)	2
	Intermediate	66 (32.0)	17 (34.7)	18 (33.3)	29 (36.7)	130 (33.5)	7
	High	128 (62.1)	28 (57.1)	32 (59.3)	36 (45.6)	224 (57.7)	3
	Unknown	1 (0.5)	1 (2.0)	1 (1.9)	0 (0.0)	3 (0.8)	
Best overall response	Partial Response	7 (3.4)	3 (6.1)	9 (16.7)	18 (22.8)	37 (9.5)	2
	Stable Disease	86 (41.7)	26 (53.1)	40 (74.1)	61 (77.2)	213 (54.9)	10
	Progressive Disease*	113 (54.9)	20 (40.8)	5 (9.2)	0 (0.0)	138 (35.6)	

*Including patients dying before first response assessment (early death) and non-evaluable best response

We identified 12 patients remaining on pazopanib for more than two years:

- 9 aged younger than 55 years,
- 9 females,
- 4 with smooth muscle tumors and
- 9 with low or intermediate grade tumors at initial diagnosis.

Only two of those patients achieved a partial response; the remaining 10 experienced stable disease as best overall response.

Median time on pazopanib in these patients was 2.4 years with the longest duration of 3.7 years.

Four patients were still on pazopanib at the clinical cut-off dates of the studies with a median PFS of 2.3 years and a median OS of 2.8 years.

LIMITATIONS OF THIS ANALYSIS

- Differences in patient populations and disease characteristics (i.e., prior treatment and histological subtype), the different study designs and endpoints of the phase II and the phase III studies have to be taken into account when interpreting these results.
- The different follow-up schedules can be a potential source of bias when combining the PFS data from the two studies.

CONCLUSIONS

- 34% of soft tissue sarcoma patients achieved a long term response (i.e. PFS > 6 months)
- 33% of soft tissue sarcoma patients survived beyond 18 months
- 20% of soft tissue sarcoma patients achieved both (i.e. PFS > 6 months and OS > 18 months)
- 3 % (12) of the patients demonstrated a clinical benefit even beyond 2 years

ACKNOWLEDGMENTS

The Phase II and III studies were collaborations between GSK and the EORTC. We thank all investigators, patients, and their families, for their contributions to this study.

Poster design: Stéphanie Vandergoten, EORTC Communications Office.

EORTC The future of cancer therapy

Patienten und Methoden

- Ausschluss der Liposarkome und nicht auswertbaren Patienten führte zu einem Kollektiv von **344 Patienten**.

- Die folgenden Charakteristika wurden untersucht:
  - Geschlecht
  - Alter
  - Performance Status
  - Tumorlokalisation
  - Histologie und Tumor Grading
  - Behandlung
  - Nebenwirkungen

- 36 %
- 34 %
-
-

original article

Annals of Oncology 00: 1–6, 2014
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Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072

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Background: Pazopanib recently received approval for the treatment of certain soft tissue sarcoma (STS) subtypes. We conducted a retrospective analysis on pooled data from two EORTC trials on pazopanib in STS in order to characterize long-term responders and survivors.

Patients and methods: Selected patients were treated with pazopanib in phase II ($n = 118$) and phase III study (PALETTE) ($n = 226$). Combined median progression-free survival (PFS) was 4.4 months; the median overall survival (OS) was 11.7 months. Thirty-six percent of patients had a PFS ≥ 6 months and were defined as long-term responders; 34% of patients survived ≥18 months, defined as long-term survivors. Patient characteristics were studied for their association with long-term outcomes.

Results: The median follow-up was 2.3 years. Patient characteristics were compared among four subgroups based on short-/long-term PFS and OS, respectively. Seventy-six patients (22.1%) were both long-term responders and long-term survivors. The analysis confirmed the importance of known prognostic factors in metastatic STS patients treated with systemic treatment, such as performance status and tumor grading, and additionally hemoglobin at baseline as new prognostic factor. We identified 12 patients (3.5%) remaining on pazopanib for more than 2 years: nine aged younger than 50 years, nine females, four with smooth muscle tumors and nine with low or intermediate grade tumors at initial diagnosis. The median time on pazopanib in these patients was 2.4 years with the longest duration of 3.7 years.

Conclusions: Thirty-six percent and 34% of all STS patients who received pazopanib in these studies had a long PFS and/or OS, respectively. For more than 2 years, 3.5% of patients remained progression free under pazopanib. Good performance status, low/intermediate grade of the primary tumor and a normal hemoglobin level at baseline were advantageous for long-term outcome.

NCT00297258 (phase II) and NCT00753688 (phase III, PALETTE).

Key words: EORTC, long-term responders, long-term survivors, pazopanib, soft tissue sarcoma, STBSG

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EORTC *The future of cancer therapy*

German Interdisciplinary Sarcoma Group

- Gegründet auf der Grundlage des Kompetenznetzes Sarkome (Ko.Sar)
- Ko.Sar = Wissenschaftsnetzwerk zur Förderung der interdisziplinären Erforschung und Therapie von Sarkomen
- Ko.Sar wird von der Deutschen Krebshilfe gefördert (2008-2011, 2012-2014)
- GISG wurde 2008 als Verein eingetragen
- GISG = Plattform zur Förderung klinischer, akademischer Studien (v.a. IIT)
- Vorstand: Prof. Dr. med. P. Hohenberger (MA) + PD Dr. med. P. Reichardt (B)
- Studienzentrale: Universitätsmedizin Mannheim
- Leiter der Studienzentrale: Prof. Dr. med. Bernd Kasper (Mannheim)
- Studienmanagement (Mannheim)

German Interdisciplinary Sarcoma Group

GISG
German Interdisciplinary Sarcoma Group

Membership Status (04/2015):

- Full members: 86 (doctors, study coordinators, study nurses, pharmas, …)
- Promoting members: PharmaMar GmbH Germany

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Study Portfolio (1)

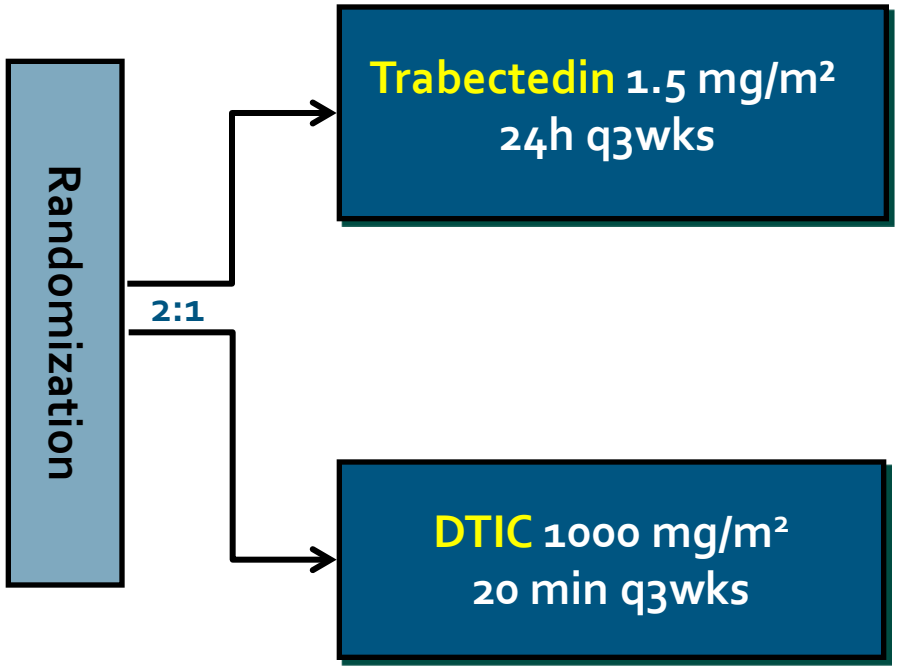
- GISG-01: Imatinib in desmoid tumors (Phase II, **DESMOID**, Kasper)
- GISG-02: Combination therapy of Gemcitabine and Trabectedin in L-sarcomas (Phase I, **GEMYON**, Kasper)
- GISG-03: Neoadjuvant radiotherapy + Sunitinib in resectable soft tissue sarcomas (Phase I, **SUNRASE**, Jakob)
- **GISG-04:** Window of opportunity study of neoadjuvant Pazopanib in high-risk soft tissue sarcomas (Phase II, **NOPASS**, Ronellenfitsch)
- **GISG-05:** Randomized phase II trial comparing Pazopanib with Doxorubicin as first line treatment in elderly patients with metastatic or advanced soft tissue sarcoma (Phase II, **EPAZ**, Grünwald)
- **GISG-06:** Pazopanib + Paclitaxel in angiosarcoma patients (Phase II, **EVA**, Pink)
- **GISG-07:** Pazopanib in liposarcomas (Phase II, GEIS + GISG, Kasper)
- GISG-08: Outcome evaluation of Trabectedin treatment by RECIST/CHOI (Non-interventional study, **Y-IMAGE**, Kasper)

Study Portfolio (2)

- **GISG-09:** Pazopanib maintenance in retroperitoneal STS following first line treatment with Doxorubicin / Ifosfamide + regional Hyperthermia (Phase II, **NEOPAMAIN**, Lindner)
- **GISG-10:** Trabectedin combined with regional Hyperthermia as second line treatment for advanced STS (Phase II, **Hyper-TET**, Lindner)
- GISG-11: Quality of life in patients with soft tissue sarcoma undergoing palliative chemotherapy or treatment with Pazopanib - a randomized controlled study (Phase II, **PazoQoL**, Schuler)
- **GISG-12:** Patient directed intervention towards a multidimensional recommendation guideline to improve the quality of life for patients with soft tissue sarcoma under palliative treatment with Trabectedin (Non-interventional study, **YonLife**, Schuler)

SAR-3007 Study Design

Population: Locally advanced, metastatic L-sarcomas after previous treatment with anthracyclines and ifosfamide



- **Primary endpoint: OS**
- **Statistical Assumptions**
  - **DTIC, OS = 10.0 mo**
  - **Trabectedin, OS = 13.5 mo**
  - **35% improvement in median OS (HR=0.74), 80% power**
  - **Two-sided significance level of 0.05**
- **Need ~570 patients to observe 376 deaths**
- **Interim analysis for futility or superiority for potential early stopping**
  - **~188 death events**

Stratification:

- ECOG PS
- Lines of prior therapy
- L-subtypes

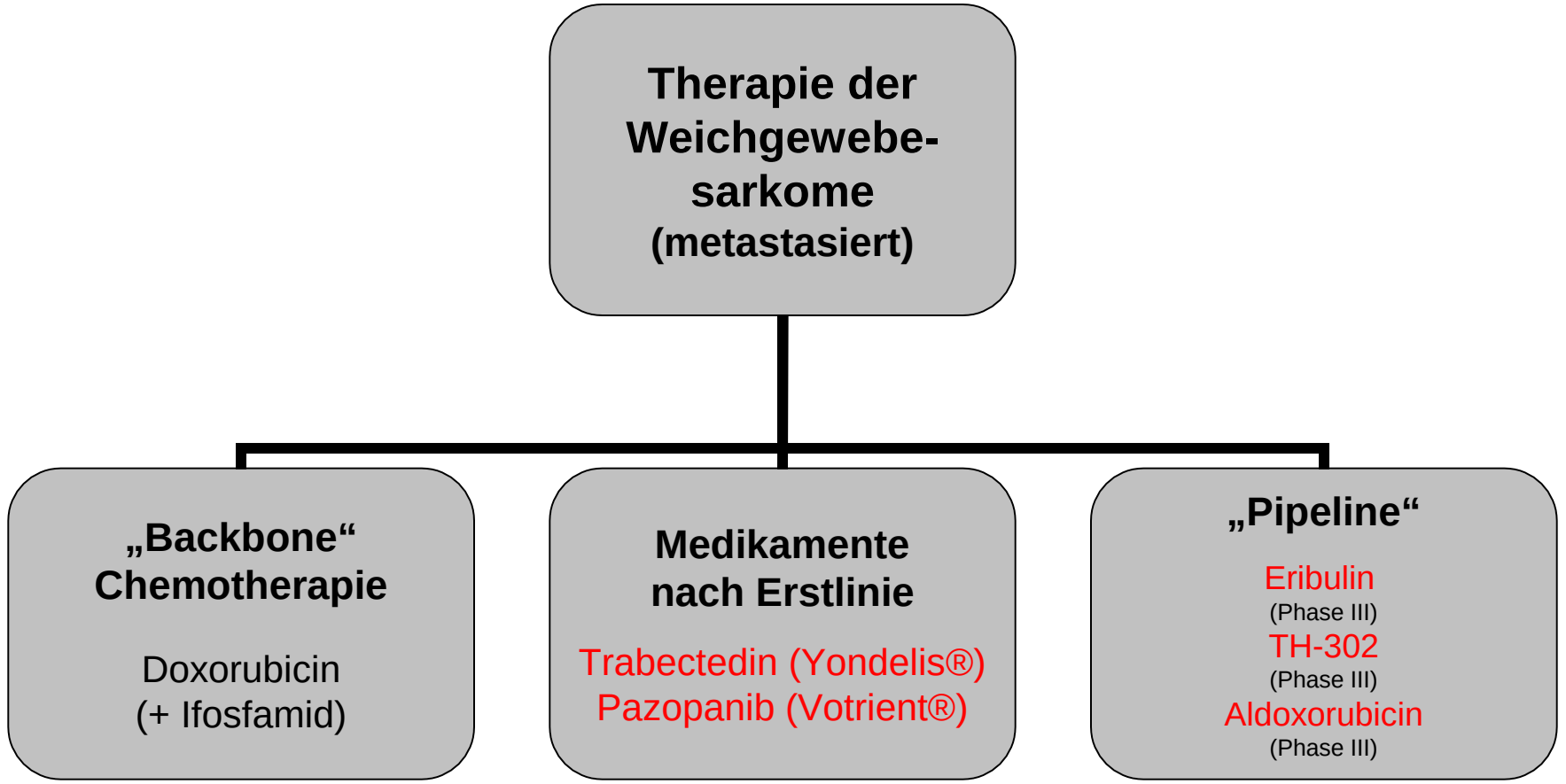
ASCO 2015

A randomized, open-label, multicenter, phase III study to evaluate the efficacy and safety of Eribulin (E7389) *vs* Dacarbazine in adult patients with STS

- **Primary endpoint:** OS
- **Patient number:** n = 450
- **Randomization:** 1:1 ratio to one of the two arms
- **Treatment (every 21 days):**

  Arm A: Eribulin 1.4 mg/m² i.v. over 2-5 minutes on days 1 + 8

  Arm B: DTIC 850 mg/m² i.v. over 15 to 30 minutes on day 1


Therapie der Weichgewebe-sarkome (metastasiert)
„Backbone“ Chemotherapie
Doxorubicin
(+ Ifosfamid)
Medikamente nach Erstlinie
Trabectedin (Yondelis®)
Pazopanib (Votrient®)
„Pipeline“
Eribulin
(Phase III)
TH-302
(Phase III)
Aldoxorubicin
(Phase III)

Zusammenfassung

GISG
German Interdisciplinary Sarcoma Group

ITM Interdisziplinäres Tumorzentrum Mannheim

DKG Krebsgesellschaft
Zertifiziertes Onkologisches Zentrum

Sarkom Zentrum

Prof. Dr. P. Hohenberger
Prof. Dr. B. Kasper
Prof. Dr. A. Marx
Prof. Dr. H.P. Scharf
Prof. Dr. F. Wenz

- Eine seltene Erkrankung erfordert Expertise
- Frühzeitige Vorstellung und Behandlung der Patienten im Zentrum
- Aktuelle Therapieleitlinien und -empfehlungen (ESMO Guidelines)
- Zugang zu laufenden klinischen Studien
- Wichtigkeit der interdisziplinären Zusammenarbeit (MDTs)

Fragen?