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GISG
German Interdisciplinary Sarcoma Group

Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

State-of-the-Art

Soft tissue sarcomas

07th December 2012, Tallinn, Estonia

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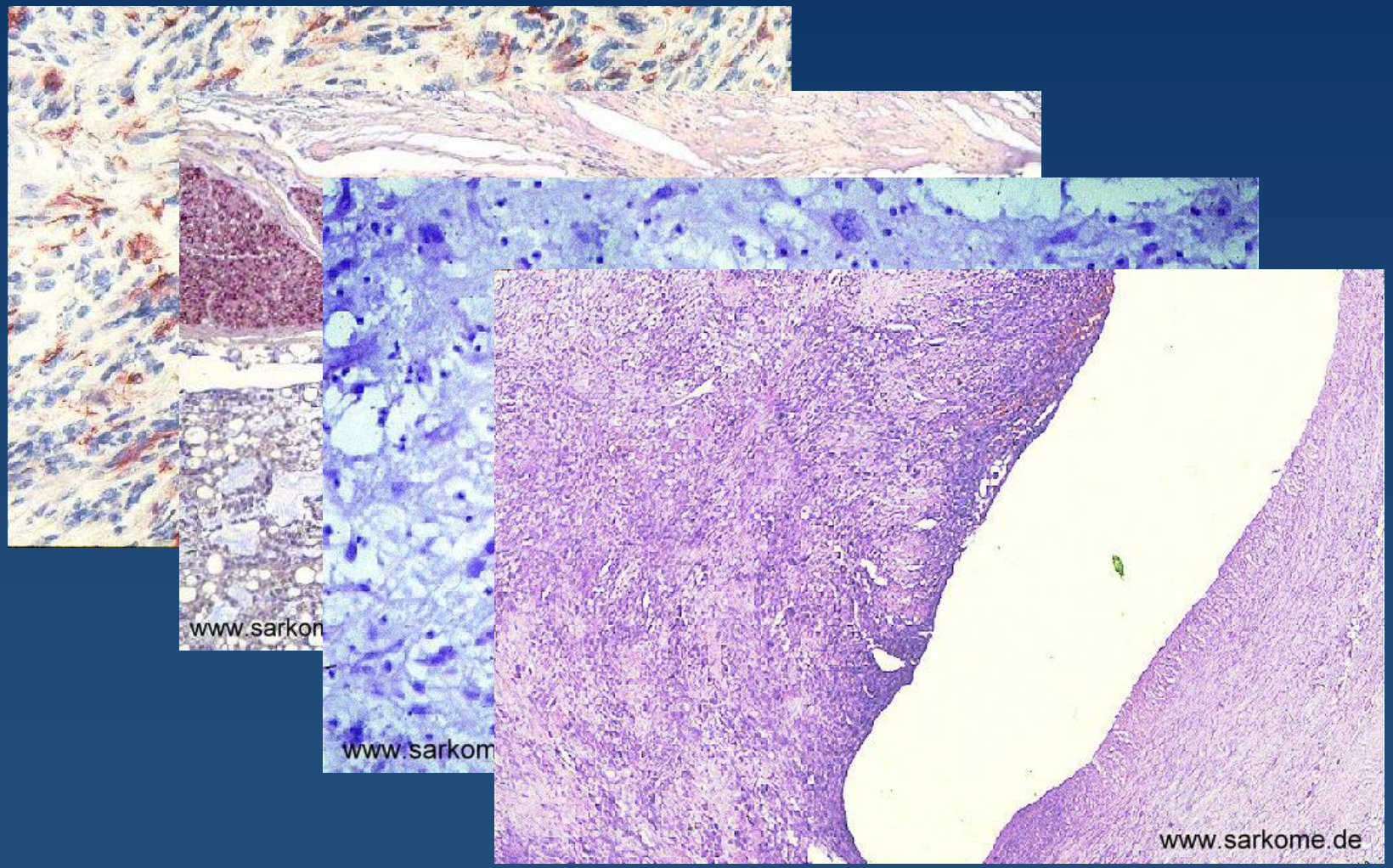
German Interdisciplinary Sarcoma Group (GISG)

Soft tissue sarcoma - **Background**

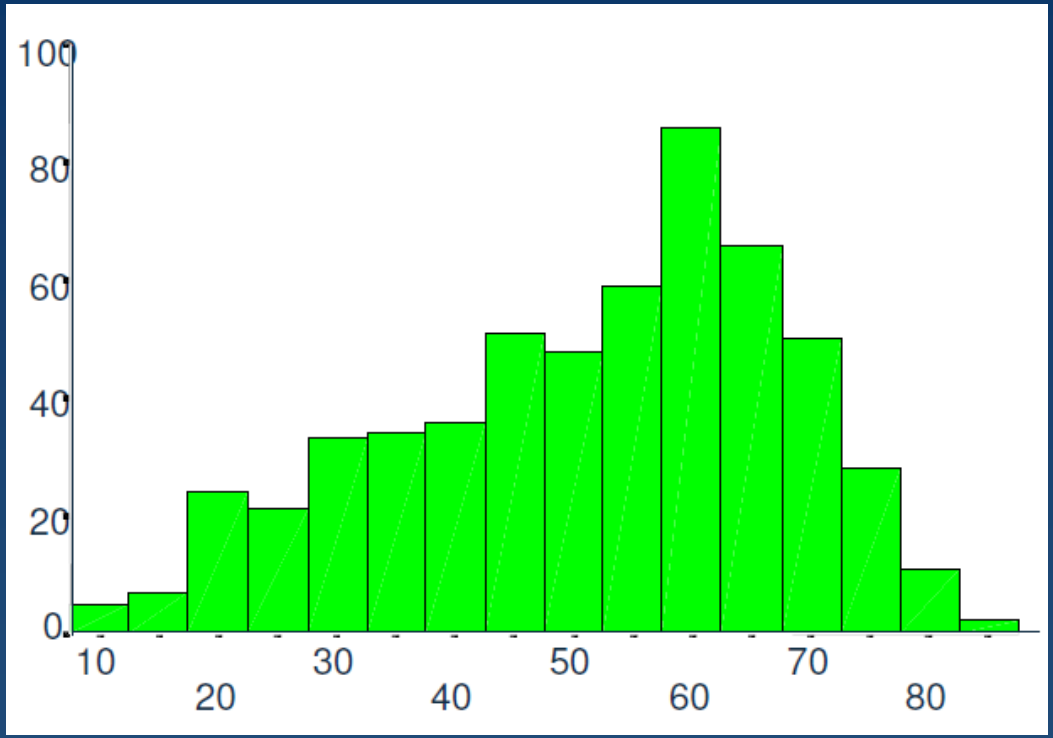
- Rare disease accounting for 0.8 - 1 % of all adult malignancies
- 2-3/100.000 cases per year
- No special gender distribution
- Localization:
  - 12 % Retroperitoneum
  - 15 % Upper extremities
  - 15 % Head & neck
  - 18 % Trunk
  - 40 % Lower extremities

Soft tissue sarcomas are heterogeneous

Soft tissue sarcomas are heterogeneous



Soft tissue sarcoma - **Age distribution**



- 30 % of patients are older than 60 years (design of clinical trials!)
- Peak incidence between the age of 40 and 70 years

Soft tissue sarcoma - **Subtypes (according to WHO 2002)**

WHO classification of soft tissue tumours

ADIPOCYTIC TUMOURS

Benign	
Lipoma	8850/0*
Lipomatosis	8850/0
Lipomatosis of nerve	8850/0
Lipoblastoma / Lipoblastomatosis	8881/0
Angiolipoma	8861/0
Myolipoma	8890/0
Chondroid lipoma	8862/0
Extrarenal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/	8857/0
Pleomorphic lipoma	8854/0
Hibernoma	8880/0
Intermediate (locally aggressive)	
Atypical lipomatous tumour/	
Well differentiated liposarcoma	8851/3
Malignant	
Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Round cell liposarcoma	8853/3
Pleomorphic liposarcoma	8854/3
Mixed-type liposarcoma	8855/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign	
Nodular fasciitis	
Proliferative fasciitis	
Proliferative myositis	
Myositis ossificans	
fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Myofibroma / Myofibromatosis	8824/0
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8810/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	
Angiomyofibroblastoma	
Cellular angiofibroma	
Nuchal-type fibroma	
Gardner fibroma	
Calcifying fibrous tumour	
Giant cell angiofibroma	
Intermediate (locally aggressive)	
Superficial fibromatoses (palmar / p	
Desmoid-type fibromatoses	
Lipofibromatosis	
Intermediate (rarely metastasizin	
Solitary fibrous tumour	
and haemangiopericytoma	
(incl. lipomatous haemangioperi	
Inflammatory myofibroblastic tumour	
Low grade myofibroblastic sarcoma	
Myxoinflammatory	
fibroblastic sarcoma	
Infantile fibrosarcoma	
Malignant	
Adult fibrosarcoma	
Myxofibrosarcoma	
Low grade fibromyxoid sarcoma	
hyalinizing spindle cell tumour	
Sclerosing epithelioid fibrosarcoma	

SO-CALLED FIBROHISTIOCYTIC

Benign	
Giant cell tumour of tendon sheath	
Diffuse-type giant cell tumour	
Deep benign fibrous histiocytoma	
Intermediate (rarely metastasizin	
Plexiform fibrohistiocytic tumour	
Giant cell tumour of soft tissues	
Malignant	
Pleomorphic 'MFH' / Undifferentiate	
pleomorphic sarcoma	
Giant cell 'MFH' / Undifferentiated	
pleomorphic sarcoma	
with giant cells	
Inflammatory 'MFH' / Undifferentiat	
pleomorphic sarcoma with	
prominent inflammation	

SMOOTH MUSCLE TUMOURS

Angioleiomyoma	8894/0
Deep leiomyoma	8890/0
Genital leiomyoma	8890/0
Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
malignant glomus tumour	8711/3
Myopericytoma	8713/1

SKELETAL MUSCLE TUMOURS

Benign	
Rhabdomyoma	8900/0
adult type	8904/0
fetal type	8903/0
genital type	8905/0
Malignant	
Embryonal rhabdomyosarcoma	8910/3
(incl. spindle cell,	8912/3
botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma	
(incl. solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3

VASCULAR TUMOURS

Benign	
Haemangiomas of	
subcut/deep soft tissue:	9120/0
capillary	9131/0
cavernous	9121/0
arteriovenous	9123/0
venous	9122/0
intramuscular	9132/0
synovial	9120/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0
Intermediate (locally aggressive)	
Kaposiform haemangioendothelioma	9130/1
Intermediate (rarely metastasizing)	
Retiform haemangioendothelioma	9135/1
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9130/1
Kaposi sarcoma	9140/3
Malignant	
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma	9220/0
Mesenchymal chondrosarcoma	9240/3
Extraskeletal osteosarcoma	9180/3

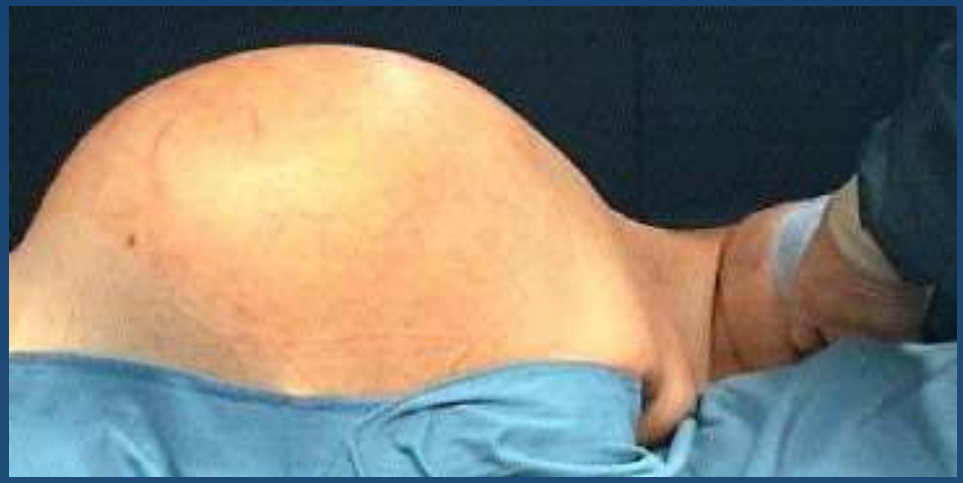
TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign	
Intramuscular myxoma	8840/0
(incl. cellular variant)	
Juxta-articular myxoma	8840/0
Deep ('aggressive') angiomyxoma	8841/0
Pleomorphic hyalinizing	
angiectatic tumour	
Ectopic hamartomatous thymoma	8587/0
Intermediate (rarely metastasizing)	
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
(incl. atypical / malignant)	
Mixed tumour/	8940/1
Myoepithelioma/	8982/1
Parachordoma	9373/1
Malignant	
Synovial sarcoma	9040/3
Epithelioid sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
("chordoid" type)	
PNET / Extraskeletal Ewing tumour	
pPNET	9364/3
extraskeletal Ewing tumour	9260/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Malignant mesenchymoma	8990/3
Neoplasms with perivascular epithelioid	
cell differentiation (PEComa)	
clear cell myomelanocytic tumour	
Intimal sarcoma	8800/3

* Morphology code of the International Classification of Diseases for Oncology (ICD-O) (726) and the Systematize Nomenclature of Medicine (http://snomed.org).

Soft tissue sarcoma - **Clinical presentation**

- Swelling or mass in the extremities ± functional deficit or pain
- Except for localizations in the abdomen, pelvis or retroperitoneum



Soft tissue sarcoma - **Diagnostic dilemma**

Out of 100 resected soft tissue masses only 1 is a malignant tumor !!!

Soft tissue sarcoma - **Diagnostic dilemma**

Criteria for malignant potential:

- Age > 50 years
- Tumor size > 8 cm
- Pain
- Rapid tumor growth
- Deep localization

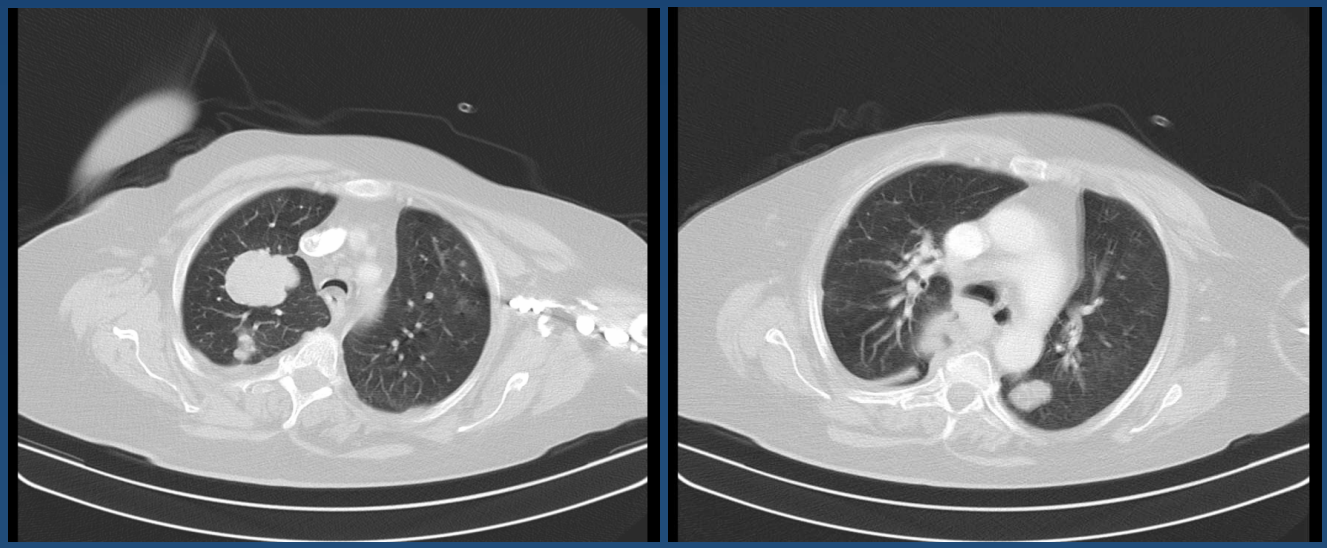
Soft tissue sarcoma - **Diagnosis**

- Gold-standard for local imaging is **Gadolinium MRI.**
- **Biopsy** and histological examination / classification of the soft tissue tumor in the light of a definitive surgical resection.
- **Staging** using CT of the chest (other investigations according to clinical presentation).
- The correct histological diagnosis is essential to plan the further treatment.
- A **reference pathology** might be necessary.

Soft tissue sarcoma - **Metastases**

- Usually hematogeneous: **lungs**, bone, liver
- Rarely lymphogeneous (< 5 %)

  Except: Rhabdomyosarcoma and synovial sarcoma (15 - 20 %)



Soft tissue sarcoma - **Therapeutic principles**

Localized disease:

- Radical resection (compartment resection)
- Radiotherapy (pre / post surgery)
- (neo-) adjuvant chemotherapy

Advanced / metastatic disease:

- Chemotherapy
- Surgery

Soft tissue sarcoma - **Chemotherapy (Monotherapy)**

Where do we stand?

- Only a few active and approved chemotherapeutic agents
- Response rate ca. 20 %: Doxorubicin, Ifosfamide, Epirubicin
- Response rate 15 - 20 %: DTIC
- Response rate < 15 %: Cyclophosphamid, Cisplatin, MTX, Etoposid, Gemcitabine, Paclitaxel, Actinomycin D, Trabectedin

1st line standard therapy: Doxorubicin monotherapy

Soft tissue sarcoma - **Combination therapies**

- Combination therapies including Doxorubicin ± Ifosfamide, Epirubicin or DTIC may increase the response rate up to 50 % (including about 10 % complete responses).
- **But:** Higher toxicity
- **But:** No significant benefit regarding overall survival for combination therapies compared to Doxorubicin monotherapy
- **However:** CR often translates into prolonged survival

Results of a randomised phase III trial (EORTC 62012) of single agent doxorubicin versus doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced, high grade soft tissue sarcoma: a survival study by the EORTC Soft Tissue and Bone Sarcoma Group

Ian Judson, Jaap Verweij , Hans Gelderblom, Joerg-Thomas Hartmann , Patrick Schöffski , Jean-Yves Blay, Angelo Paolo dei Tos, Sandrine Marreaud , Saskia Litiere, Winette van der Graaf

EORTC *The future of cancer therapy*

Previous studies

EORTC study: randomized phase III trial 663 pts *(Santoro et al. 1995)*

A: Doxorubicin 75 mg/m^2

B: Cyclophosphamide, vincristine, doxorubicin and dacarbazine (CYVADIC)

C: Doxorubicin 50 mg/m^2 plus ifosfamide 5 g/m^2

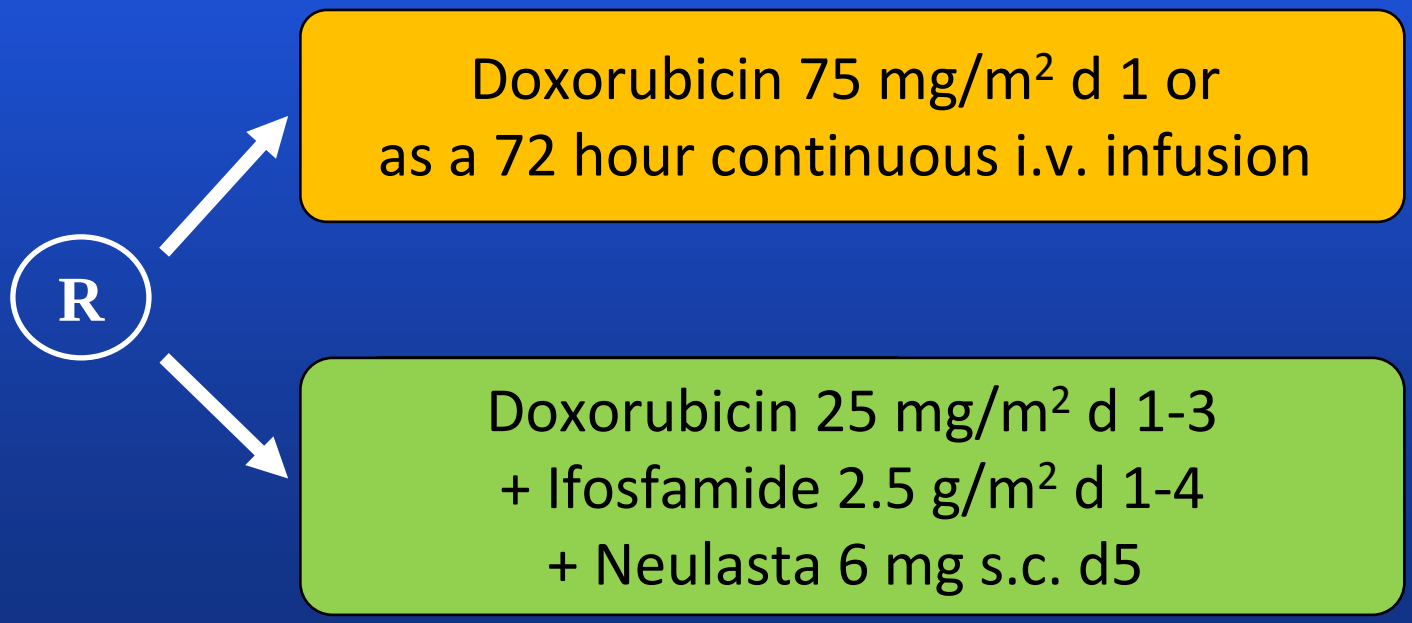
Results:

Overall Response rate:	24 %	Median overall survival:
Arm A: Doxorubicin	23.3 %	52 weeks
Arm B: CYVADIC	28.4 %	51 weeks
Arm C: Dox-IFOS	28.1 %	55 weeks

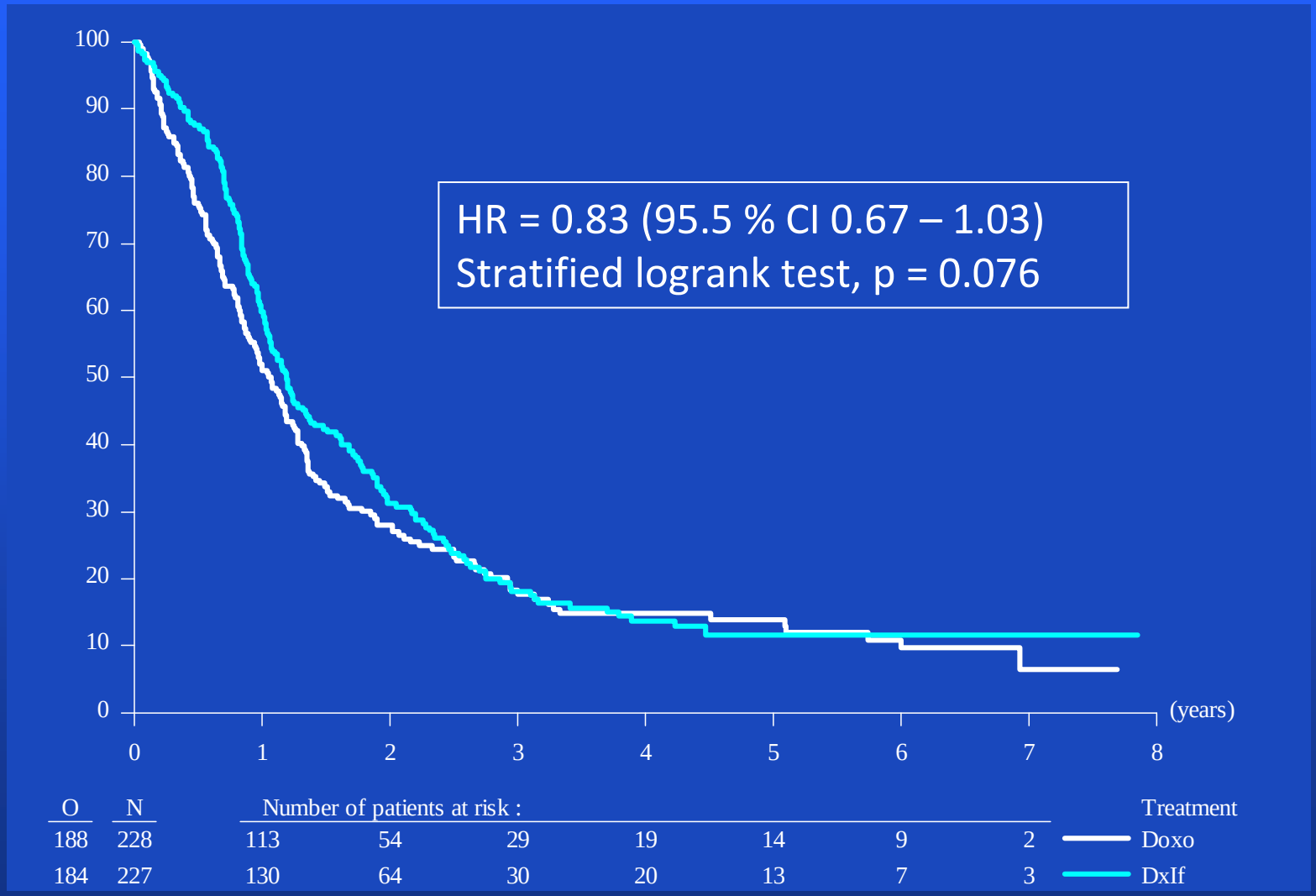
The design

Stratification:

- Age (< 50 vs ≥ 50)
- PS (0 vs 1)
- Liver metastases (0 vs +)
- Histological grade (2 vs 3)



Overall survival



EORTC *The future of cancer therapy*

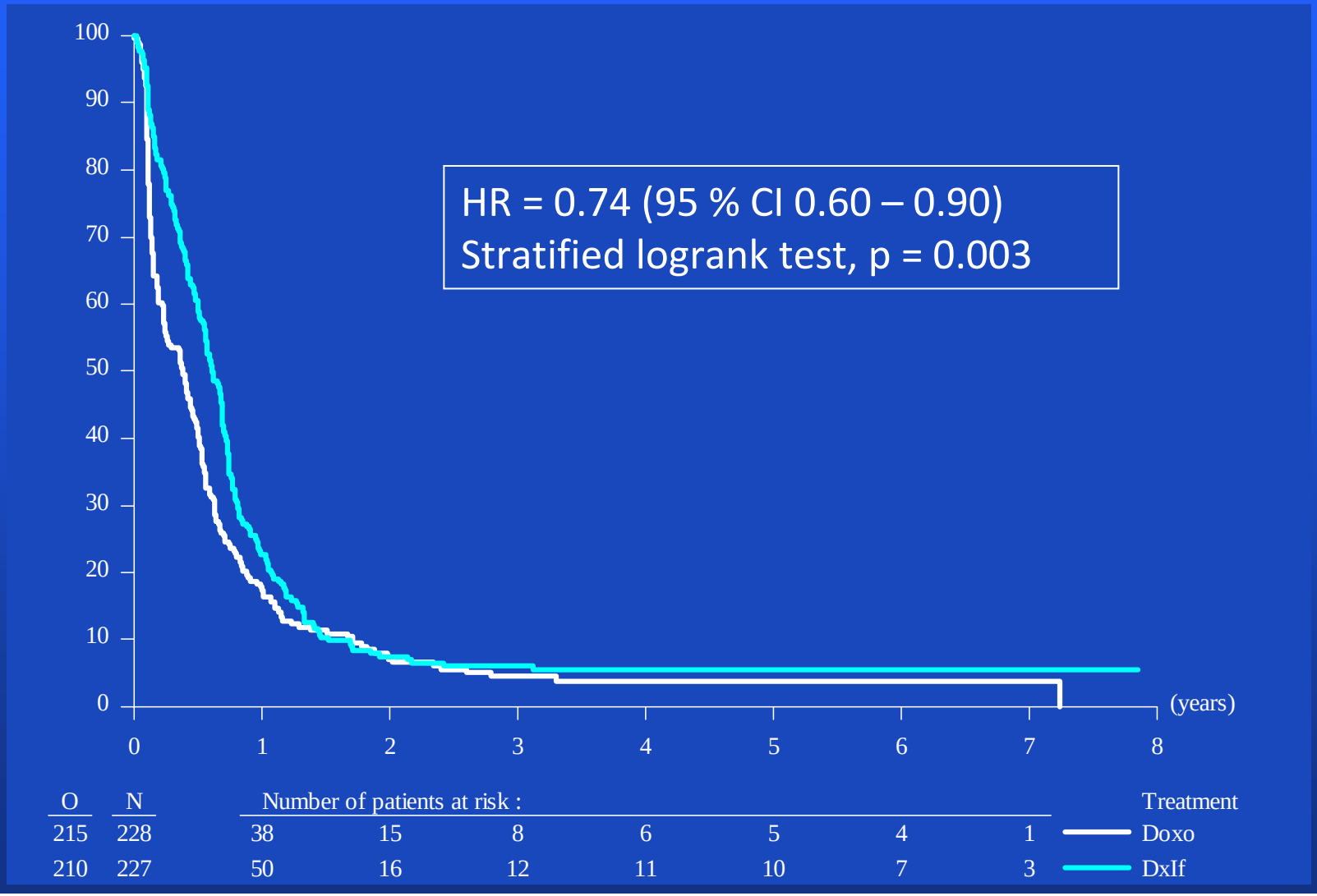
Median overall survival:

- Doxorubicin: 12.8 months (95.5 % CI 10.5-14.3)
- Doxorubicin-Ifo: 14.3 months (95.5 % CI 12.5-16.5)

Survival at 1-year:

- Doxorubicin: 51 % (95.5 % CI 44-58)
- Doxorubicin-Ifo: 60 % (95.5 % CI 53-66)

Progression free survival



EORTC *The future of cancer therapy*

Median PFS

In the doxorubicin arm: 4.6 months (95 % CI 2.9 - 5.6)

In the combination arm: 7.4 months (95 % CI 6.6 - 8.3)

Best overall response

	Treatment		
	Doxo (n = 228)	Doxo-Ifo (n = 227)	Total (n = 455)
	n (%)	n (%)	n (%)
Complete Response	1 (0.4)	4 (1.8)	5 (1.1)
Partial Response	30 (13.2)	56 (24.7)	86 (18.9)
ORR	**13.6**	**26.5**	
No Change	105 (46.1)	114 (50.2)	219 (48.1)
Progressive Disease	**74 (32.5)**	**30 (13.2)**	104 (22.9)
Early Death - Progression	4 (1.8)	5 (2.2)	9 (2.0)
Early Death – Other cause	3 (1.3)	2 (0.9)	5 (1.1)
Not evaluable	11 (4.8)	16 (7.0)	27 (5.9)

Adverse events (grade ≥ 3)

	Doxo (N = 223)	DxIf (N = 224)	Total (N = 447)
Neutropenia	37.2 %	41.5 %	39.4 %
Leucopenia	17.9 %	43.3 %	30.7 %
Febrile neutropenia	**13.5 %**	**45.9 %**	29.8 %
Anemia	**4.6 %**	**34.9 %**	19.7 %
Thrombocytopenia	**0.4 %**	**33.5 %**	17.0 %

Conclusions

The combination of doxorubicin and ifosfamide:

- doubled the response rate
- improved PFS significantly
- did not significantly improve survival
- was considerably more toxic than doxorubicin alone

What now in daily practice?

- The standard treatment remains single agent doxorubicin
- Combination therapy can be considered, if surgery for unresectable tumors or (curative) metastasectomy is foreseen
- In highly symptomatic disease in patients without co-morbidity, combination treatment is optional and pro's and con's should - as always - be discussed with the patient
- … and this is easier now, since we have the results of this study!

Soft tissue sarcoma - **2nd line therapies**

Trabectedin (ET-743, Yondelis™):

- Pretreated patients:

  8 % ORR, 26 % SD > 6 months

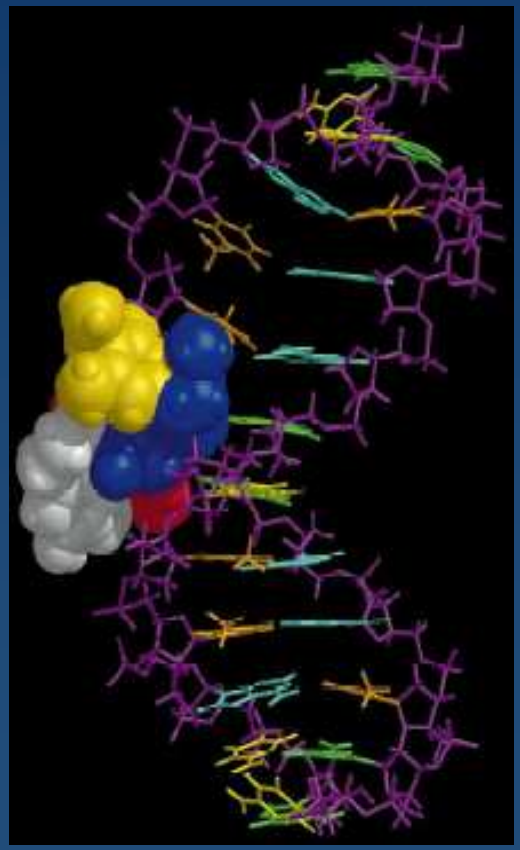
  (Le Cesne et al. JCO 2005)

- Untreated patients:

  17 % ORR, 21 % PFR at 1 year

  (Garcia-Carbonero et al. JCO 2005)

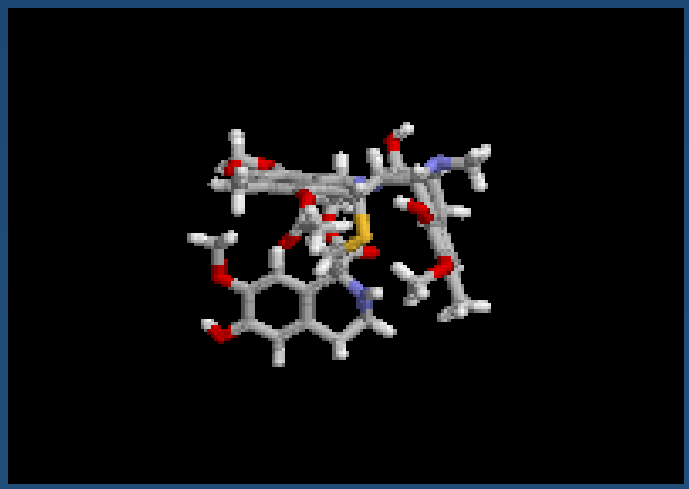
Ecteinascidin turbinata



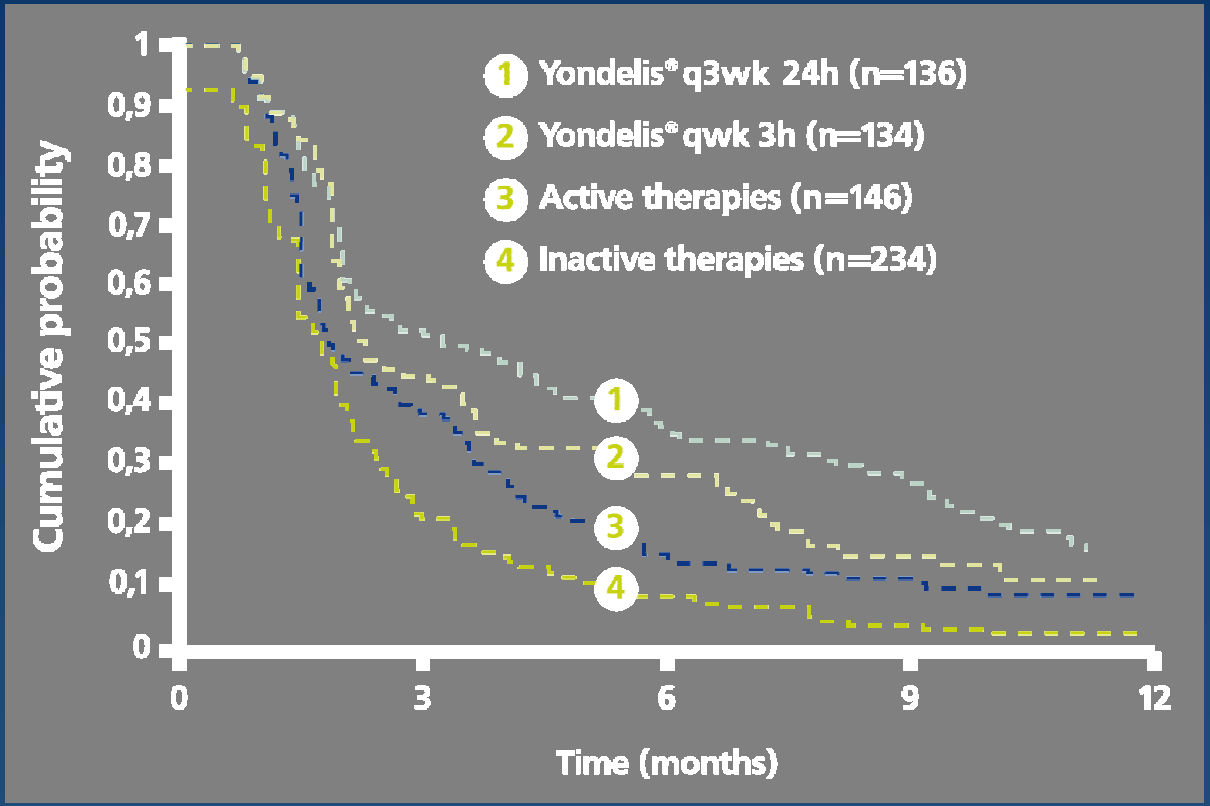
Soft tissue sarcoma - **2nd line therapies**

Trabectedin (ET-743, Yondelis™):

- Since 2007 it is approved as 2nd line therapy for STS after failure with standard chemotherapy of anthracyclines and/or ifosfamide
- **Dose**: 1.5 mg/m^2 as 24h infusion, every 3 weeks
- **Premedication**: 20 mg dexamethason 30 min. before infusion
- **Side effects**: Nausea, vomiting, neutropenia, thrombocytopenia, fatigue, asthenia, transaminase elevations



Soft tissue sarcoma - **2nd line therapies**



The EORTC analysis could demonstrate a substantial prolonged progression-free survival (PFS) in both trabectedin dose schemes compared to „active“ therapies according to EORTC.

* Published data in pretreated STS including 9 trials with “inactive” agents and 3 trials with “active” agents (ifosfamide and DTIC), Van Glabbeke Eur J Cancer 38, 2002; Le Cesne, Dômont, Cioffi. The new era of trabectedin in soft tissue sarcomas. Eur J Hosp Pharm Prac 2008; 14 (2): 72-75

Soft tissue sarcoma - **Subtype specific therapies**

More and more data support a subtype specific treatment strategy:

- Combination therapy if disease is potentially curable
- Trofosfamide might be an option in elderly patients
- Taxanes, Doxorubicin (± Sorafenib) in Angiosarcomas
- Gemcitabine / Docetaxel in (uterine) Leiomyosarcomas
- Trabectedin in patients with L-sarcomas and Synovial Sarcomas
- Imatinib and other TKIs in Gastrointestinal Stromal Tumors (GIST)

Soft tissue sarcoma - **Activity?**

		N	PFR 3 Mo	PFR 6 Mo	Med. OS (months)
1st line therapy	**Active agent (ADM)**	**1154**	**58-77 %**	**38-56 %**	**12-14**
2nd line therapy	***Active* agent (IFS/DTIC)**	**146**	**≥ 40 %**	**14 %**	**6-9**
	***Inactive* agent**	**234**	**≤ 20 %**	**8 %**	**5-7**

Progressions-free rate (PFR) after 3 + 6 months (*EORTC database, van Glabbeke et al. 2002*)

Leiomyosarcoma - **Chemotherapy**

Therapy	N	RR	mPFS (months)	6-Mo-PFS	mOS (months)	Reference
ADM	n.a.	21 %	-	-	12 Mo	EORTC
IFS ± ADM	n.a.	18 %	-	-		
Trabectedin	134*	6 %	3.7	36 %	14 Mo	STS-201
Gemcitabine	9	11 %	-	-	-	SARC-002
	22	5 %	5.5	46 %	-	Taxogem
	7	3/7	4.5	-	-	Essen, 2004
Gemcitabine + Docetaxel	29	17 %	-	-	-	SARC-002
	19	5 %	3.4	46 %	-	Taxogem
	44	27 %	7.2	58 %	19 Mo	RMH**
Sorafenib	37	3 %	3.2	30 %	22 Mo	Maki, 2009
Pazopanib	41	2 %	3	n.a.(~30 %)***	12 Mo	Sleijfer, 2009

Activity of different chemotherapeutic agents in patients with leiomyosarcomas

* ca. 30 % liposarcomas; ** 1st line therapy; ***: 3-Mo-PFS 44 %; estimated 6-Mo-PFS

Soft tissue sarcoma - **Biological therapies**

Which may be the future compounds?

- Pazopanib (EORTC 62072 phase III study - PALETTE)
- Ridaforolimus (phase III study - SUCCEED)
- Eribulin (EORTC 62052 phase II study)

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

PALETTE: A randomized, double-blind phase III trial of pazopanib versus placebo in patients with soft tissue sarcoma (STS) whose disease has progressed during or following prior chemotherapy - An EORTC STBSG Global Network Study (EORTC 62072)

Recruitment 10/08 - 03/10

(n = 369)

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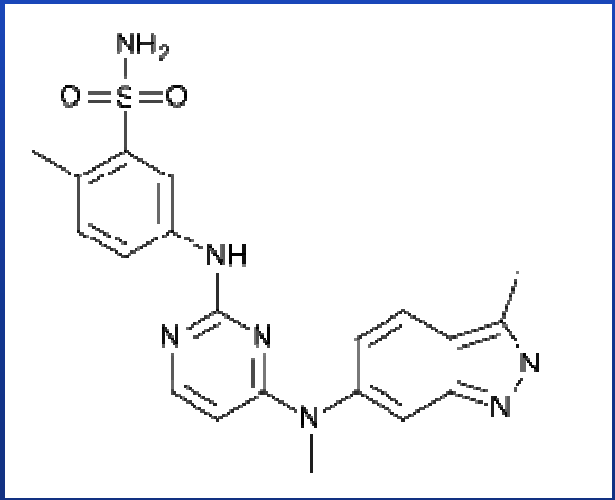
Van der Graaf et al. Lancet 2012; 379: 1879-1886

- **Pazopanib** = selective multi-tyrosine kinase inhibitor including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/-β and c-kit
- Blocks cell growth and inhibits angiogenesis
- Approved in the US and Europe for the treatment of metastatic renal cell carcinoma, also active in ovarian and lung cancer
- Administration: Pazopanib orally 800 mg daily



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Sleijfer et al. JCO 2009; 27: 26-32

VOLUME 27 · NUMBER 19 · JULY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pazopanib, a Multikinase Angiogenesis Inhibitor, in Patients With Relapsed or Refractory Advanced Soft Tissue Sarcoma: A Phase II Study From the European Organisation for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC Study 62043)

Stefan Sleijfer, Isabelle Ray-Coquard, Zsuzsa Papai, Axel Le Cesne, Michelle Scurr, Patrick Schöffski, Françoise Collin, Lini Pandite, Sandrine Marreaud, Annick De Brauwer, Martine van Glabbeke, Jaap Verweij, and Jean-Yves Blay

Results

One hundred forty-two patients were enrolled. The adipocytic STS stratum was closed after the first stage, given insufficient activity ($PFR_{12\ weeks}$, five [26%] of19). $PFR_{12\ weeks}$ was 18 (44%) of 41 patients in the leiomyosarcoma cohort, 18 (49%) of 37 in the synovial sarcomas, and 16 (39%) of 41 in the other STS types. Compared with historical controls who were treated with second-line chemotherapy, progression-free and overall survivals were prolonged in the three cohorts in which the primary end point was reached. The most frequent drug-related toxicities were hypertension, fatigue, hypopigmentation, and nausea. Other toxicities included liver enzyme elevations, myelosuppression, and proteinuria, all of which were mostly grades 1 to 2. The most frequent grades 3 to 4 toxicities were hyperbilirubinemia (6.3%), hypertension (7.7%), and fatigue (7.7%).

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Sleijfer et al. JCO 2009; 27: 26-32

Pazopanib = phase II data (EORTC 62043)

	Leiomyo-sarcoma	Adipocytic sarcoma	Synovial sarcoma	Other types sarcoma
Partial response	1	0	4	1
Stable disease	17	5	14	15
Progressive disease	21	13	14	23
Early death	1	1	3	2
Not evaluable	1		1	
Clinical PD			1	
Total	41	19	37	41
Progression -free rate	**18 / 41 (43.9%)**	**5 / 19 (26.3%)**	**18 / 37 (48.6%)**	**16 / 41 (39.0%)**

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

EORTC 62072 phase III study - PALETTE

- n = 369 at 72 sarcoma centers in 13 countries
- Metastatic soft tissue sarcomas
- Failure after ≥ 1 anthracycline based therapy and up to 4 lines of chemotherapy (≤ 2 lines of combination therapies)
- Age ≥ 18 years, WHO PS 0-1
- 2:1 Randomization for pazopanib versus placebo
- **Treatment:** Pazopanib orally 800 mg daily
- **Primary endpoint:** PFS according to RECIST

EORTC
European Organization for Research and Treatment of Cancer

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

EORTC 62072 phase III study - PALETTE

Results and survival data:

- 369 randomized patients (October 2008 - February 2010)
- 246 pts. in pazopanib arm, 123 pts. in placebo arm
- Median age of 56 years
- Median follow-up of 15 months
- Primary endpoint PFS prolonged: 4.6 versus 1.5 months (*HR = 0.31, p < 0.0001*)
- No statistically significant improvement for OS: 11.9 versus 10.4 months (*HR = 0.83, p = 0.1782*)

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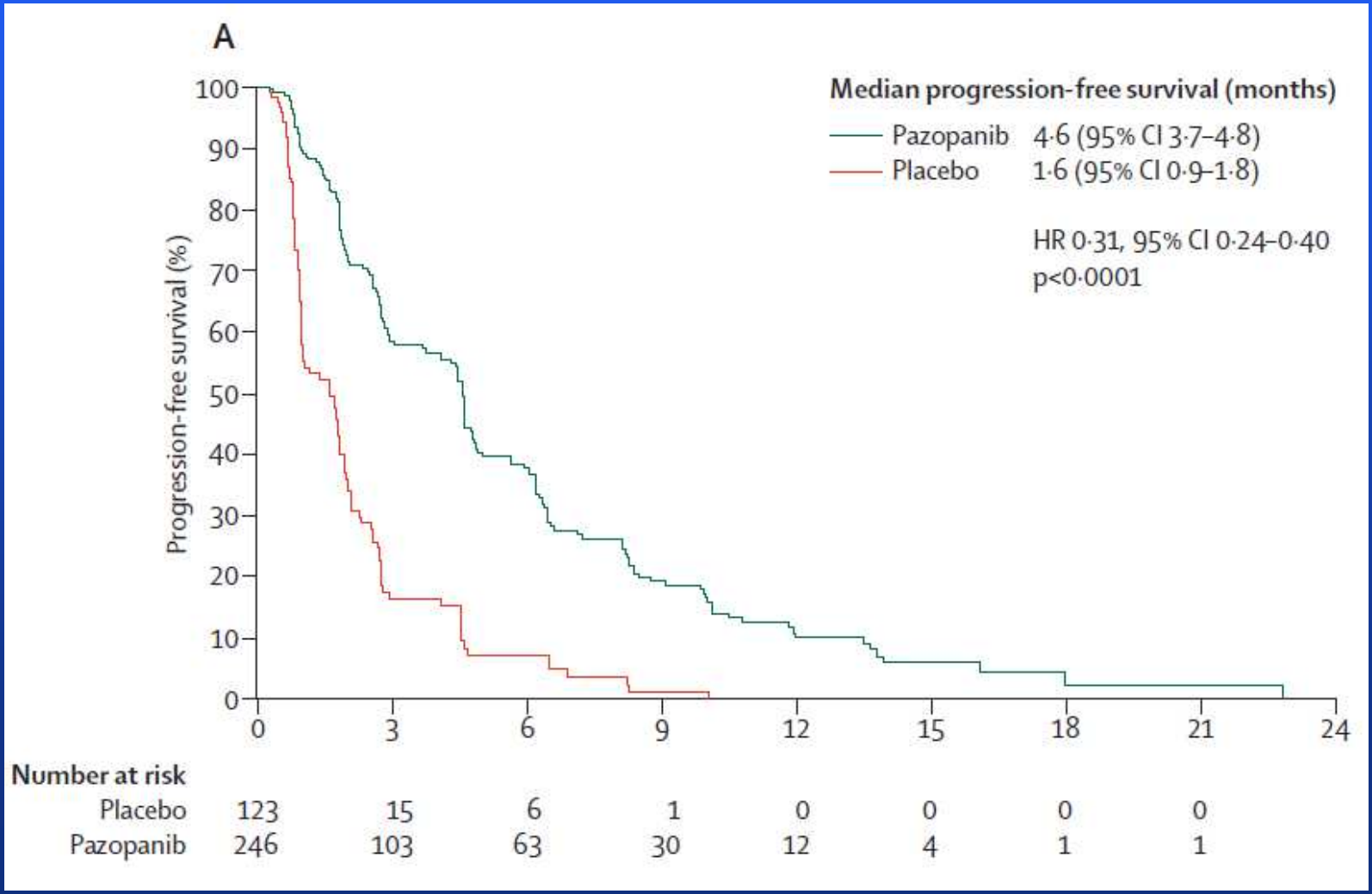
Van der Graaf et al. Lancet 2012; 379: 1879-1886

EORTC Phase III study (62072 - PALETTE)



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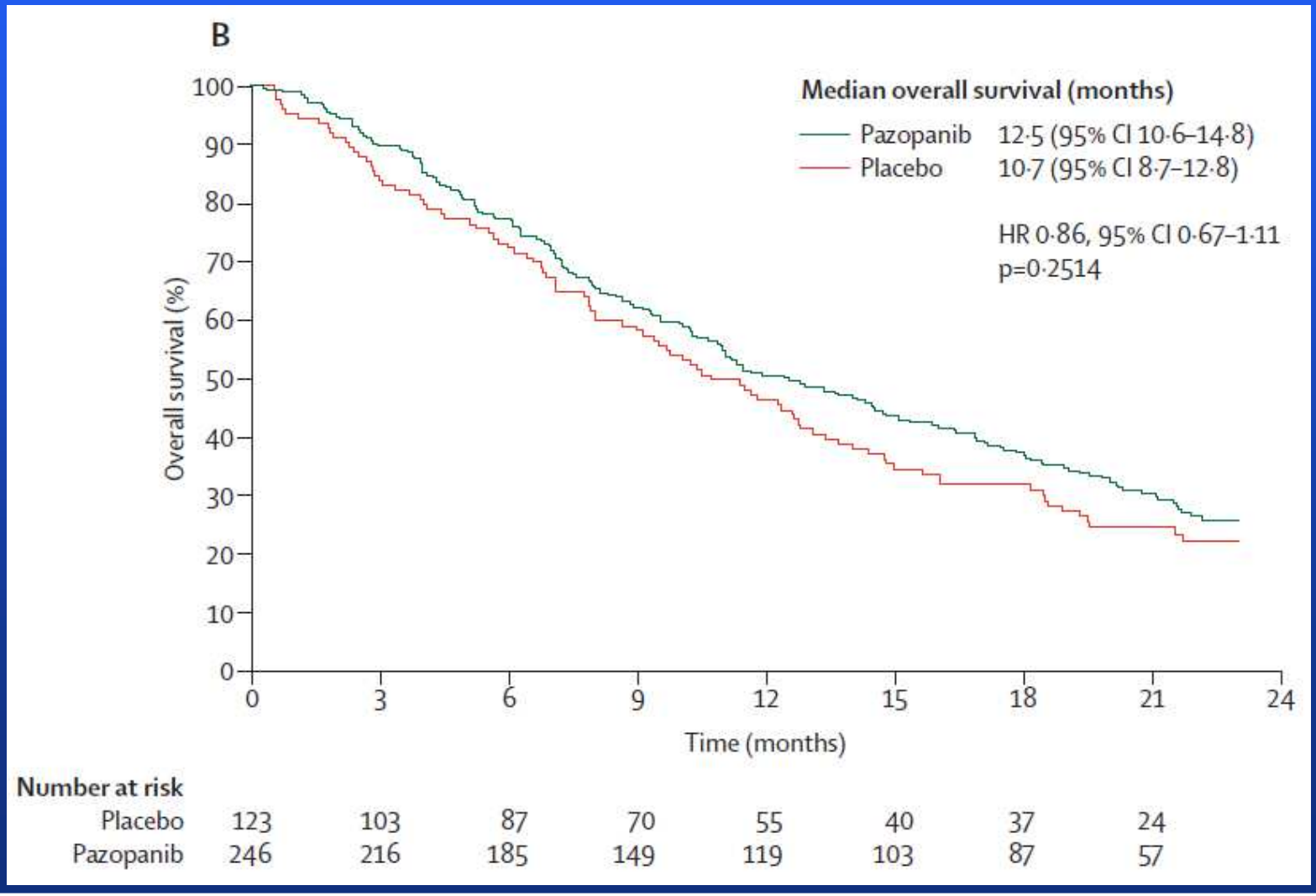
EORTC Phase III study (62072 - PALETTE)



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

EORTC Phase III study (62072 - PALETTE)

Main adverse events:

- Fatigue
- Anorexia
- Hypertension
- Weight loss
- Diarrhea
- LVEF↓ > 15 % in 8 %
- Thrombembolic events (grade 3-5) in 3.3 %

	Placebo group (n=123)			Pazopanib group (n=239)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Fatigue	60 (49%)	6 (5%)	1 (1%)	155 (65%)	30 (13%)	1 (<1%)
Diarrhoea	20 (16%)	1 (1%)	0	138 (58%)	11 (5%)	0
Nausea	34 (28%)	2 (2%)	0	129 (54%)	8 (3%)	0
Weight loss	25 (20%)	0	0	115 (48%)	0	0
Hypertension	8 (7%)	4 (3%)	0	99 (41%)	16 (7%)	0
Anorexia	24 (20%)	0	0	95 (40%)	14 (6%)	0
Hair hypopigmentation	3 (2%)	0	0	92 (38%)	0	0
Vomiting	14 (11%)	1 (1%)	0	80 (33%)	8 (3%)	0
Dysgeusia	5 (4%)	0	0	64 (27%)	0	0
Rash or desquamation	13 (11%)	0	0	43 (18%)	1 (<1%)	0
Mucositis	4 (3%)	0	0	29 (12%)	3 (1%)	0

Data are n (%).

Table 3: Common adverse events

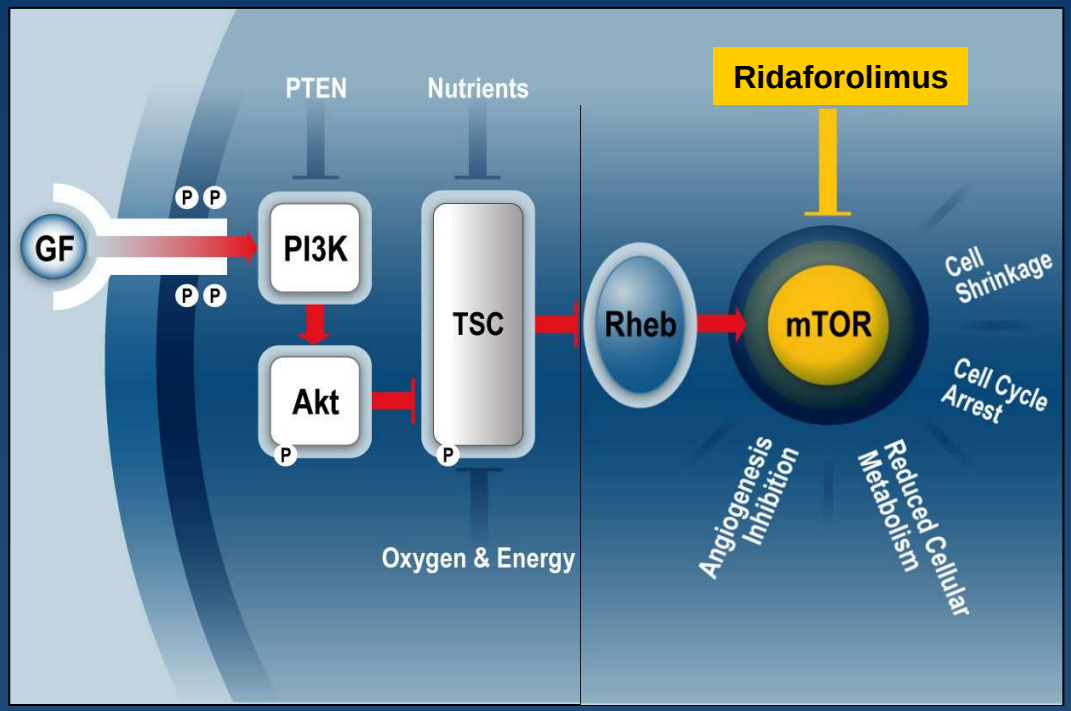
EORTC
European Organization for Research and Treatment of Cancer

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

PALETTE - Summary:

- Positive trial: PFS prolongation of 13 weeks
- Pazopanib is a new active and approved oral agent in the treatment of metastatic soft tissue sarcomas
- First global study performed in soft tissue sarcomas that scientifically demonstrated antitumor efficacy of an antiangiogenic compound
- Stratification: Activity of pazopanib in the adipocytic sarcoma stratum in the phase II did not meet predefined criteria which led to exclusion of this subgroup in the subsequent phase III
- Pipeline of clinical trials incorporating pazopanib

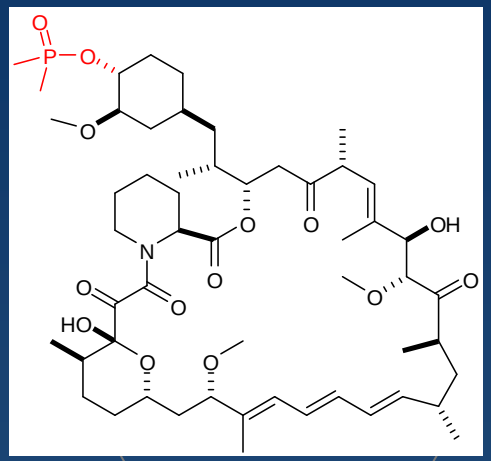
mTOR inhibition in sarcomas

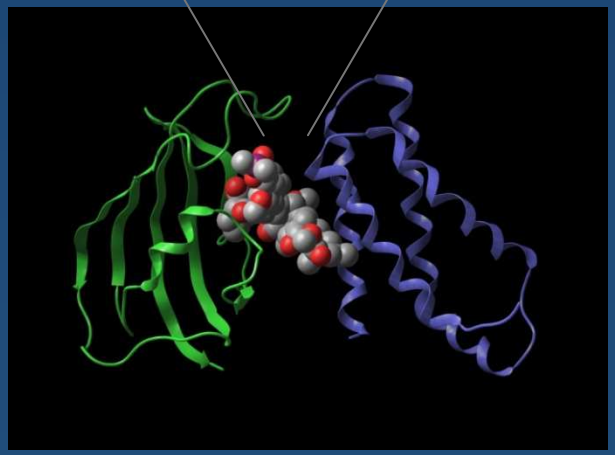


Cell growth, proliferation, metabolism and angiogenesis are influenced.

Faivre S et al. Nature Reviews 2006; 5: 671-688
Shaw RJ, Cantley LC. Nature 2006; 441: 424-430
Vignot S et al. Ann Oncol 2005; 16: 525-537
Wan X, Helman LJ. Oncologist 2007; 12: 1007-1018

Characteristics of ridaforolimus





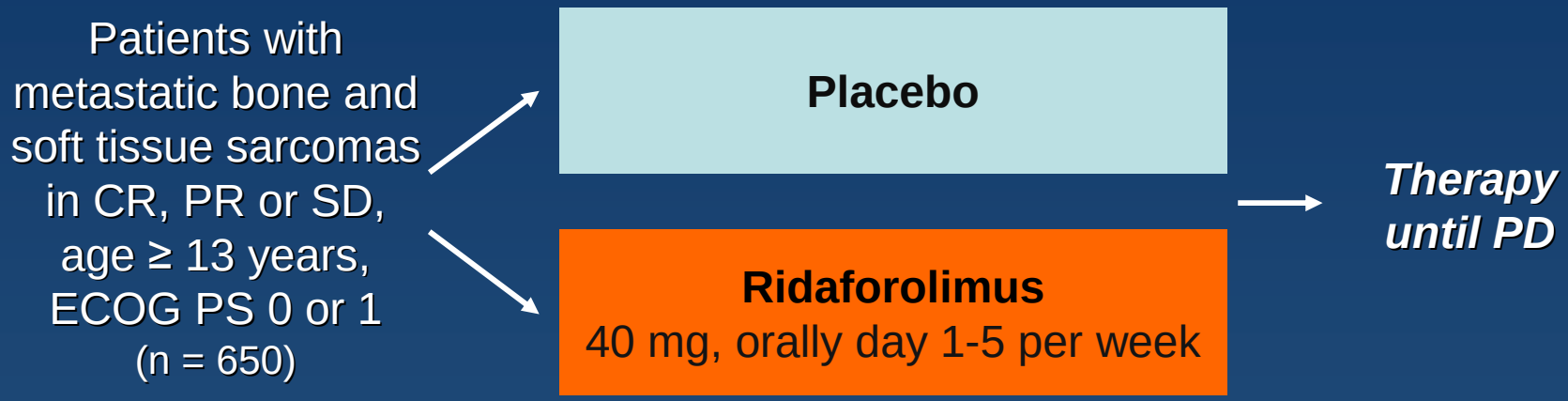
- New mTOR inhibitor
- No prodrug of rapamycin analogue
- Potent and selective mTORI
- IV and orally available
- Tested in sarcomas and other tumor entities

Metcalf CA et al. Proc Am Assoc Cancer Res 2004; 45: 2476

Vignot S et al. Ann Oncol 2005; 16: 525-537

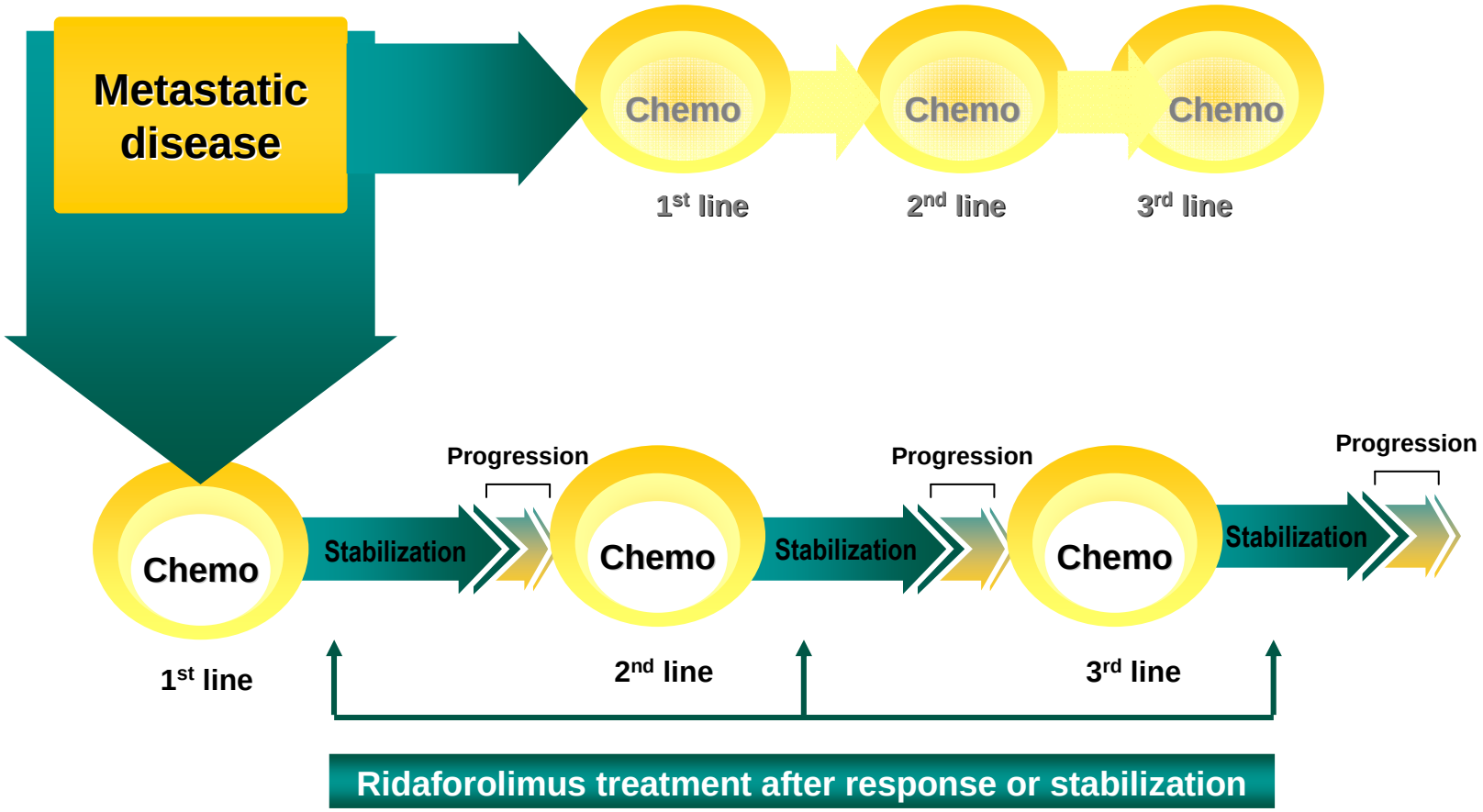
SUCCEED: Phase III ridaforolimus in sarcomas

SUCCEED: Sarcoma M**u**lti-**C**enter **C**linical **E**valuation of the **E**fficacy of Ri**d**aforolimus



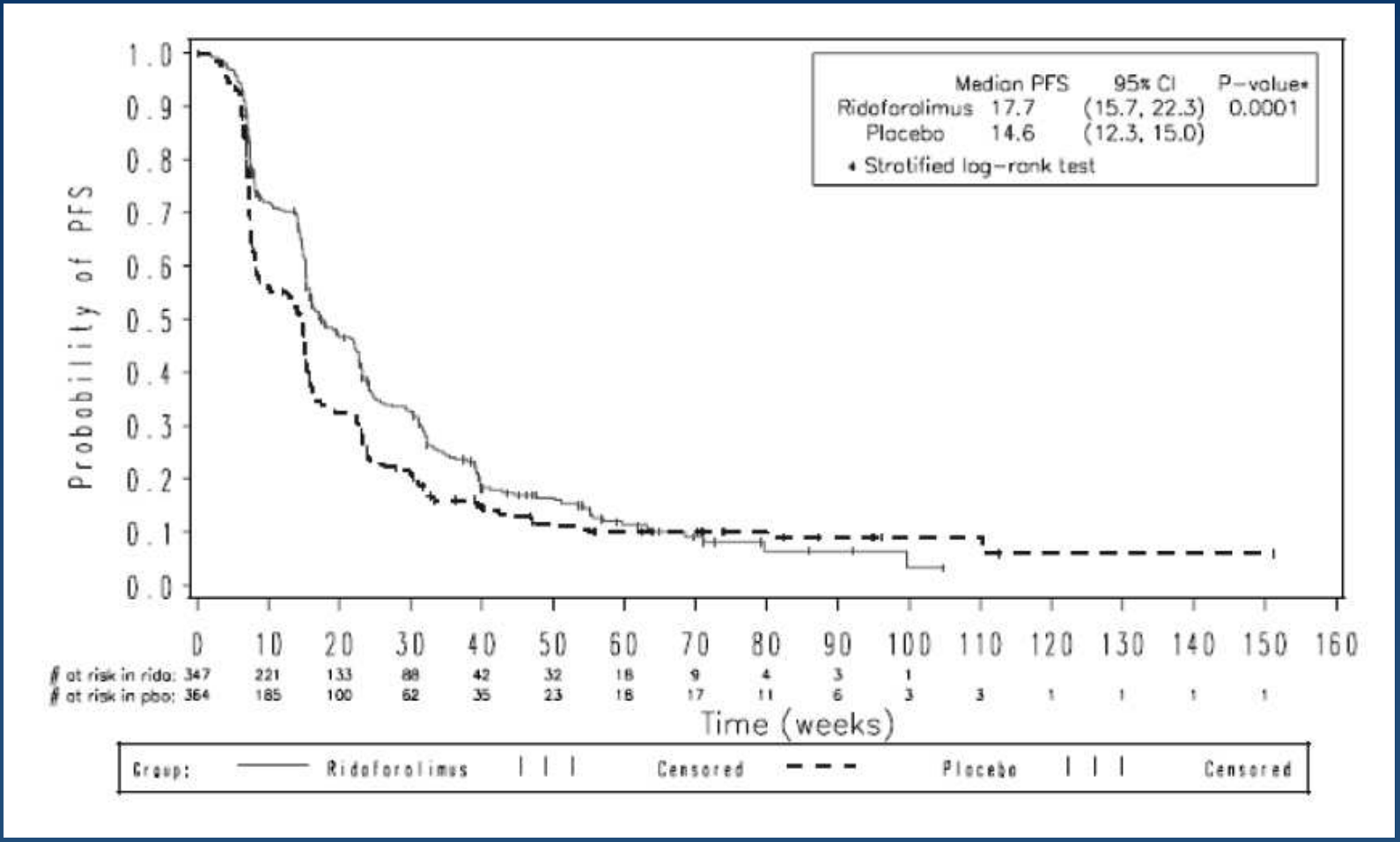
- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, response rate, safety

SUCCEED



SUCCEED: Sarcoma M**u**lti-**C**enter **C**linical **E**valuation of the **E**fficacy of Ri**d**aforolimus

SUCCEED



Chawla SP, et al. J Clin Oncol 2011; 29 (suppl; abstr 10005)

SUCCEED

Safety profile of ridaforolimus:

- **Adverse events (grade ≥ 3):**
  - **Stomatitis (9 %)**
  - **Thrombocytopenia (10 %)**
  - **Fatigue (3 %)**
  - **Diarrhea (3 %)**

- **The most common adverse event under ridaforolimus is the mTOR-Inhibitor-associated stomatitis / oral mucositis**
- **Stomatitis of all grades has been observed in 52 % of patients!!**
- **Comparable toxicity profile to other mTORI**

Chawla SP, et al. J Clin Oncol 2011; 29 (suppl; abstr 10005)

SUCCEED

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio @ (95% CI) Compared to placebo
Ridaforolimus, *with* grade 2+ stomatitis	137	100	37	18.7 (12.1, 21.7)	0.66 (0.53, 0.84)
Ridaforolimus *without* grade 2+ stomatitis	189	154	35	13.1 (11.3, 18.0)	0.78 (0.63, 0.95)
Placebo	364	291	73	10.9 (9.7, 11.1)	

PFS measured starting day 29 in both groups

- **Ridaforolimus demonstrated prolonged PFS compared to placebo in patients with and without stomatitis grade 2+**
- **The effect of ridaforolimus regarding PFS seems higher in patients with rapid onset of stomatitis grade 2+**
- **Stomatitis may be a functional biomarker of the mTOR involvement and thus ridaforolimus activity (phase I data)**

Demetri GD, et al., CTOS Annual Meeting 2011, October 26-29, Chicago, Poster #65

SUCCEED - Summary

+ Positive trial: primary endpoint met (PFS prolonged)
+ New agent - new concept of maintenance therapy
+ Possible change in treatment paradigms from „Watch & Wait" strategy to a more active management
+ Diverse possibilities of sequential therapies
- High rate of adverse events (stomatitis!!) for maintenance therapy versus minor activity
- Only a trend for a better OS

➢ Which subgroup will actually benefit from the drug?

➢ EMA decision regarding approval expected in December 2012

SUCCEED - Summary

Ridaforolimus Fails to Sway FDA Panel in Sarcoma Bid

Elsevier Global Medical News. 2012 Mar 20, E Mechcatie

Find more items about these cancer types:

Bone

Soft-Tissue Sarcoma

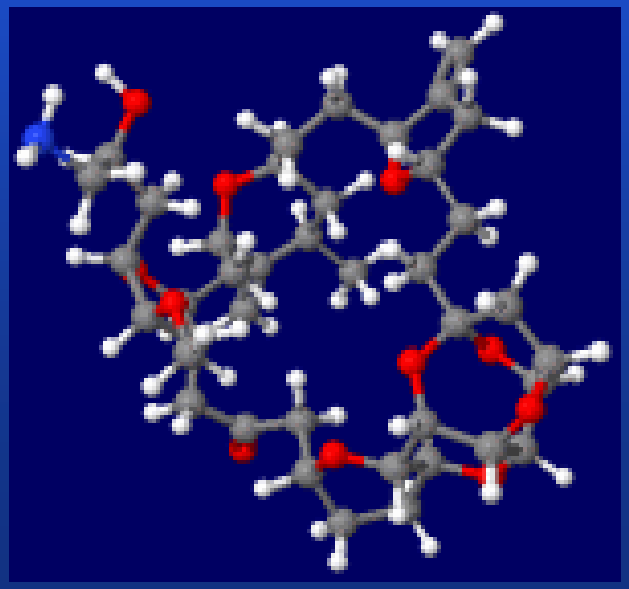
SILVER SPRING , MD. (EGMN) - A Food and Drug Administration advisory panel voted 13-1 that the investigational agent ridaforolimus did not have a favorable risk-benefit profile when used as maintenance therapy in patients with metastatic soft-tissue or bone sarcomas that had stabilized with chemotherapy.

Members of the FDA's Oncologic Drugs Advisory Committee cited the marginal effect on progression-free survival and the toxicity profile associated with the drug in a phase III clinical trial reviewed at a meeting on March 20.

While several panelists noted the need for such a treatment, ODAC's chair, Dr. Wyndham H. Wilson, pointed out that patients are exposed for a longer period of time when a drug is approved as maintenance therapy. Therefore, the data showing benefit have to be more robust than do the data supporting use in a treatment setting, and the drug should be "reasonably well tolerated," said Dr. Wilson, chief of the lymphoma therapeutics section at the National Cancer Institute, Bethesda, Md.

Schöffski et al. Lancet Oncol 2011; 12: 1045-52

- **Eribulin** = E7389 = synthetic analogue of Halichondrin B
- Blocks mitosis due to microtubule inhibition through a distinct mechanism
- Leads to cell cycle arrest and tumor regression in preclinical models
- Administration: Eribulin 1.4 mg/m² i.v. day 1 + 8 every 3 weeks



EORTC
European Organization for Research and Treatment of Cancer

Schöffski et al. Lancet Oncol 2011; 12: 1045-52

EORTC phase II study (62052)

- **n = 128**
- **Locally advanced and/or metastatic soft tissue sarcoma**
- **Stratification:** LMS (40), ADI (37), SYN (19) and others (32)
- **Age ≥ 18 years**
- **Treatment:** Eribulin 1.4 mg/m² i.v. day 1 + 8 every 3 weeks
- **Primary endpoint:** PFR at 12 weeks (PFR_{12wks}) according to RECIST

Schöffski et al. Lancet Oncol 2011; 12: 1045-52

EORTC phase II study (62052)

Results and survival data:

	PFR_{12wks} [%]	Median PFS [months]	OS [months]	1-year-OS [%]
LMS	32 (12/38)	3	20	70
ADI	47 (15/32)	3	10	48
SYN	21 (4/19)	3	11	36
others	19 (5/26)	2	6	30

Toxicity:

- Grade 3/4 AE (> 1 pt.): leucopenia (35 %), anaemia (7 %), fatigue (7 %), febrile neutropenia (6 %), mucositis (3 %) …

Schöffski et al. Lancet Oncol 2011; 12: 1045-52

EORTC phase II study (62052)

Summary:

- Eribulin demonstrated a favorable safety profile in pretreated soft tissue sarcoma patients
- Response and clinical benefit could be observed in different sarcoma subtypes
- Eribulin deserves further study in this setting based on PFS at 12 weeks in leiomyosarcoma and adipocytic sarcoma where predefined EORTC criteria were met
- Phase III study ongoing

A randomized, open-label, multi-center, phase III study to evaluate the efficacy and safety of Eribulin (E7389) versus Dacarbazine in adult patients with soft tissue sarcoma

- **Primary endpoint:** Overall survival
- **Patient number:** n = 450
- **Randomisation:** 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
- **Duration of treatment:** until PD, unacceptable toxicity or withdrawal

Key inclusion criteria:

- Histologically confirmed soft-tissue sarcoma of high or intermediate grade with one of the following subtypes: adipocytic (dedifferentiated, myxoid, round cell, pleomorphic) and leiomyosarcoma
- Documented evidence of advanced adipocytic or leiomyosarcoma, incurable by surgery or radiotherapy
- Patients should have received standard therapies for advanced disease (which must have included an anthracycline and ifosfamide)
- Radiographic evidence of disease progression by RECIST criteria on or after the last anti-cancer regimen within 6 months prior to study enrolment
- Presence of measurable disease
- ECOG performance status 0, 1 or 2
- Adequate renal function, bone marrow / liver function
- Age ≥ 18 years

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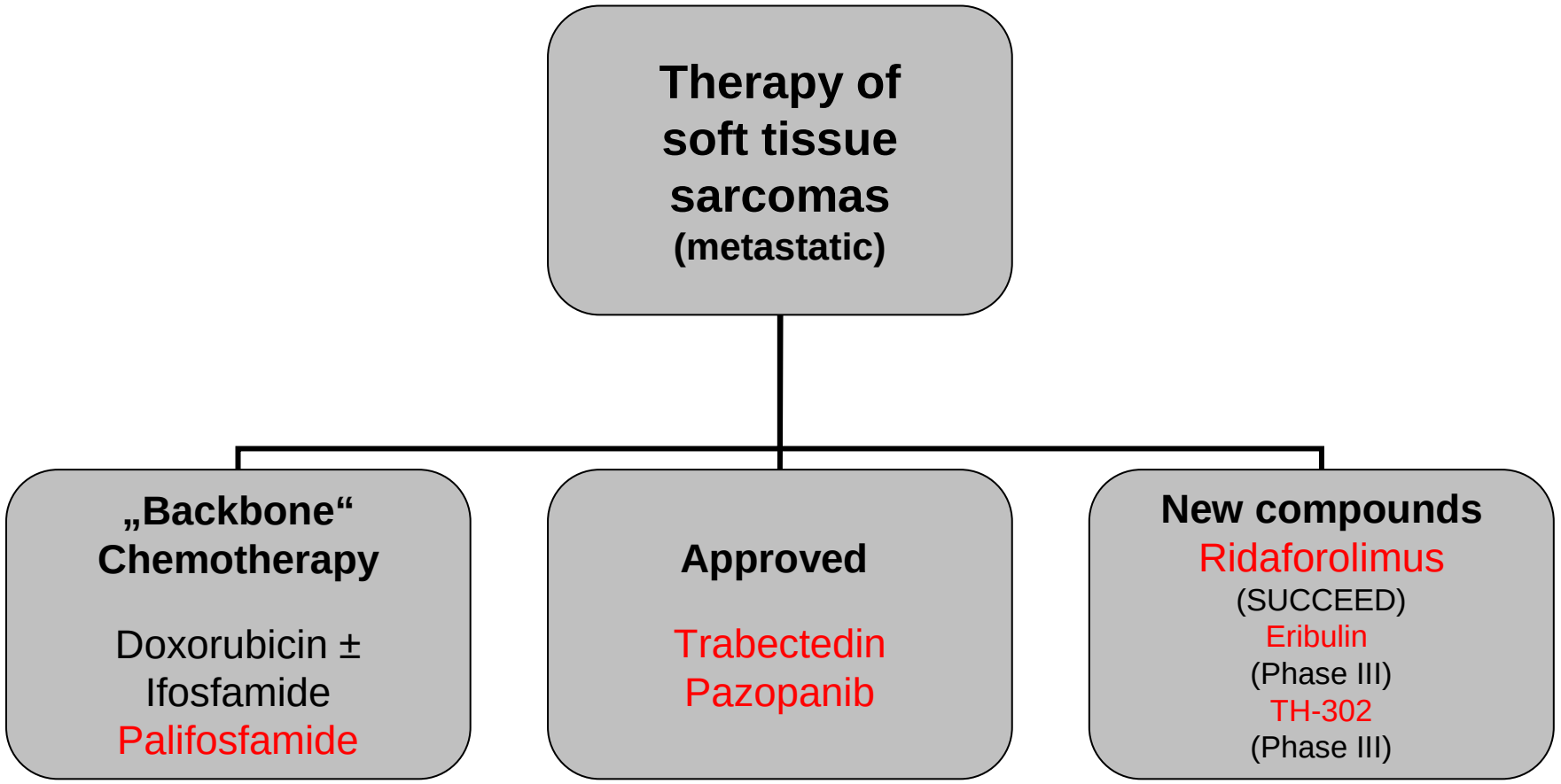
GISG German Interdisciplinary Sarcoma Group

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim



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Selected studies in Germany / Europe

- **Ongoing trials of the GermanInterdisciplinarySarcomaGroup**
- **EORTC 62091 „TRUSTS“ study - Trabectedin 1st line**
- **EISAI Phase III study - Eribulin**
- **SARC021: TH-302 Phase III study**
- **EORTC 90101 „CREATE“ study - Crizotinib**
- **AIO-STS-009 „PAPAGEMO“ study - Pazopanib vs. Pazopanib + Gemcitabine**

German Interdisciplinary Sarcoma Group

- Founded on the basis of the Sarcoma Network of Excellence (Ko.Sar)
- Ko.Sar = Scientific network with the aim to promote and enhance the interdisciplinary research and therapy for soft tissue tumors (sarcoma)
- Ko.Sar = Supported by a grant from the “Deutsche Krebshilfe”
- Organized as an association since 2008
- GISG = Platform to enhance clinical and academic trials
- Chairs = Peter Hohenberger (Mannheim) and Peter Reichardt (Berlin)
- Study Coordinating Physician = Bernd Kasper (Mannheim)
- Project Management = Michaela Sommer + Regine Muczenski-Luz (Mannheim)

German Interdisciplinary Sarcoma Group

Study Portfolio:

- 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, Pink)
- GISG-07: Pazopanib in liposarcomas (Phase II, GEIS + GISG)
- GISG-08: Outcome evaluation of trabectedin treatment by RECIST/CHOI (Non-interventional study, Kasper)

Pazopanib in elderly patients with metastatic STS
(GISG-05, EPAZ)

- **Therapy:** A: Doxorubicin 75 mg/m^2
  B: Pazopanib 800 mg daily per os
- **Design:** Randomized phase II study
  N = 120; 1:2 randomization
- **Primary endpoint:** PFS
- **Secondary endpoint:** ORR, OS, Safety, QoL, $PFR_{12/26wk}$, biomarker
- **Strata:** Center, ECOG

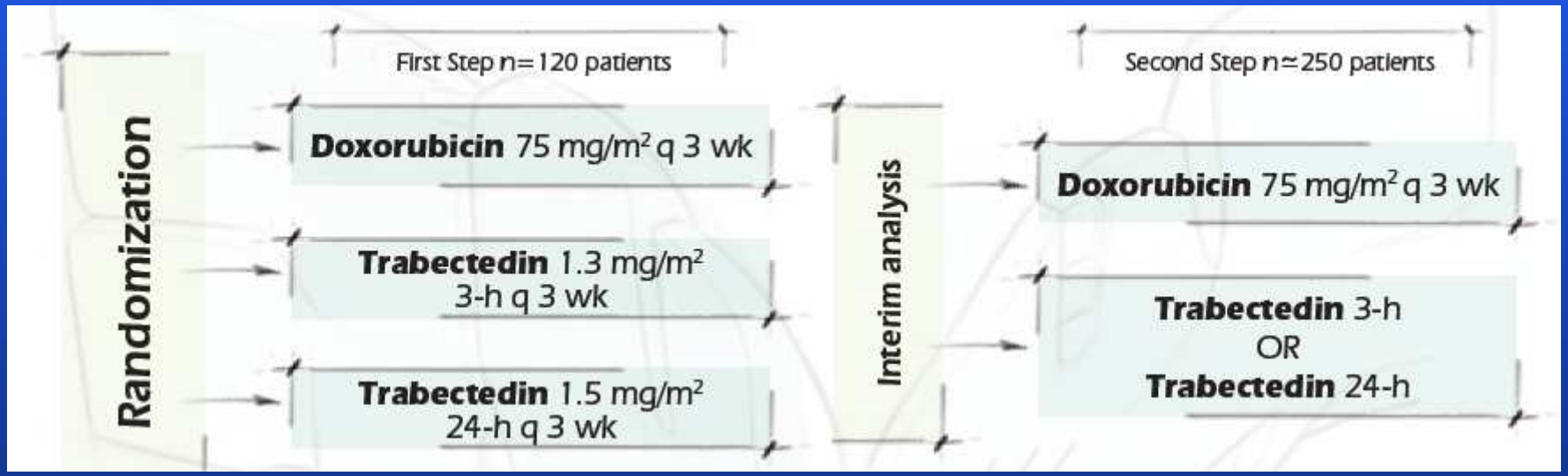
TRUSTS: A phase IIb/III multicenter study comparing the efficacy of trabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma

Recruitment since 05/2011

(n = 370)

EORTC 62091 TRUSTS

- **Primary endpoint:** Progression-free survival (PFS)
- **Secondary endpoints:** Overall Survival (OS), Safety, QoL



Threshold Pharmaceuticals Inc.

TH-CR-406/SARC021

A Randomized Phase 3, Multicenter, Open-Label Study Comparing TH-302 in Combination with Doxorubicin vs. Doxorubicin Alone in Subjects with Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma

Original Release date: 26 Jul 2011

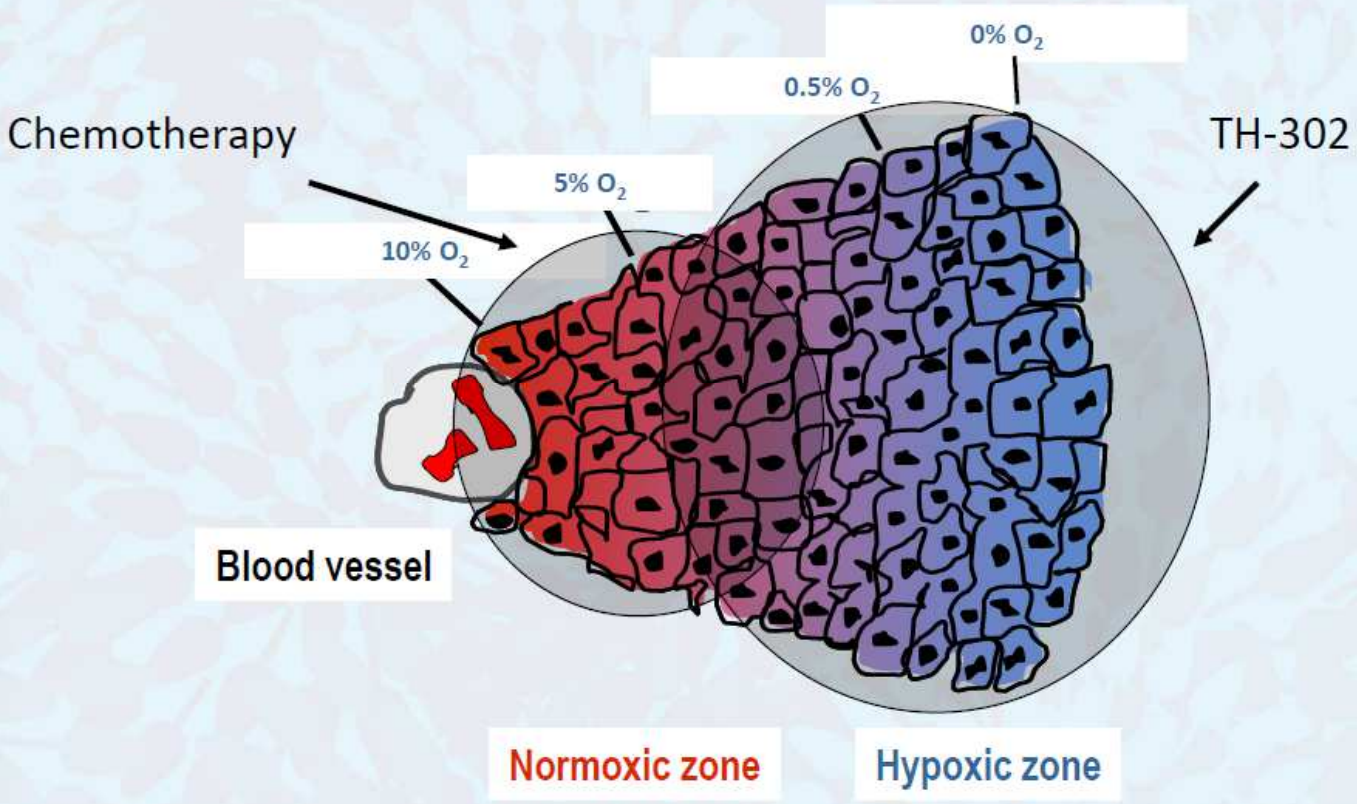
THRESHOLD PHARMACEUTICALS

SARC Sarcoma Alliance for Research through Collaboration
Collaborating for a Cure.

PAREXEL.

CONFIDENTIAL

TH-302+Chemotherapy "Complementary Chemotherapy"



TH-CR-406/SARC021: Study Design

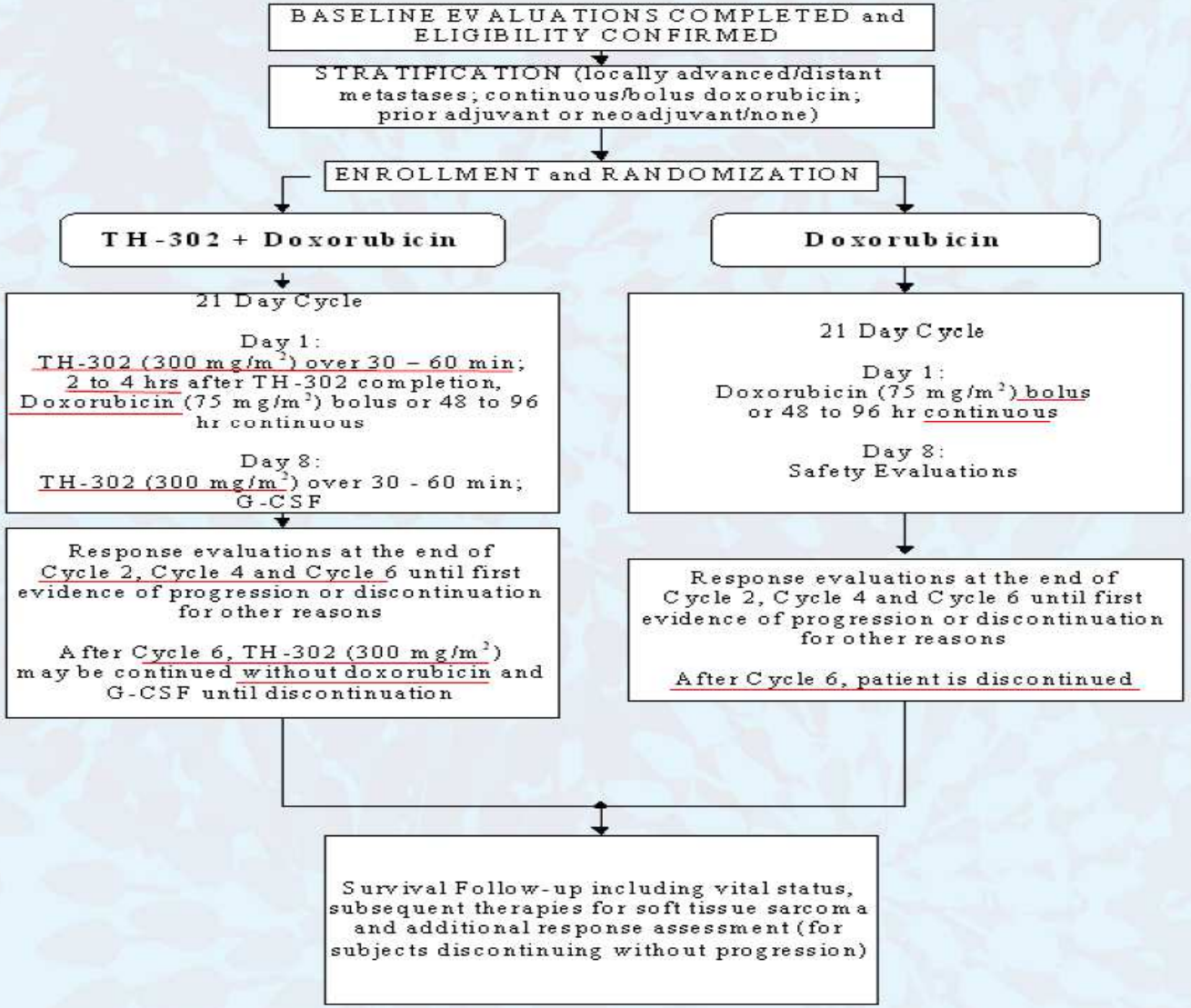


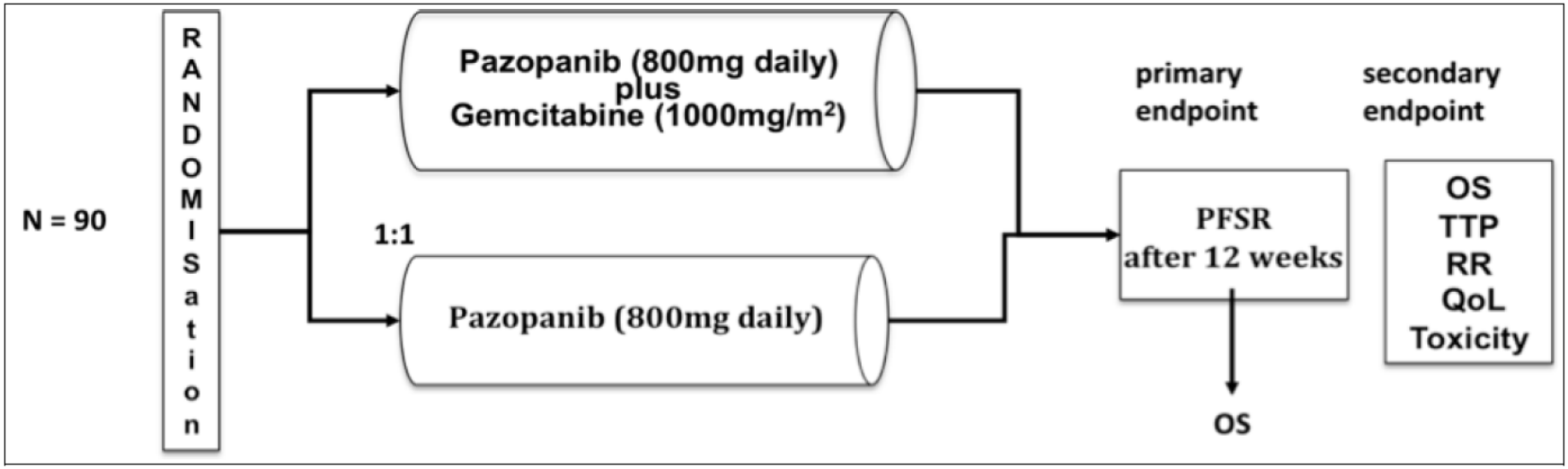
Figure 7: Pivotal Phase 3 Study Schema

Protocol Page: 11

EORTC 90101 CREATE

- EORTC Network of Core Institutions (NOCI) Studie
- **Cross-tumoral phase 2 clinical trial exploring Crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET („CREATE“)**
- Folgende Histologien:
  - Anaplastic large cell lymphoma (ALCL)
  - Inflammatory myofibroblastic tumor (IMT)
  - Papillary renal cell carcinoma type 1 (PRCC)
  - Alveolar soft part sarcoma (ASPS)
  - Clear cell sarcoma (CCS)
  - Alveolar rhabdomyosarcoma (ARMS)
- **Start:** Q2/2012

AIO-STS-009 „PAPAGEMO“ Study



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Take-home-messages (STS)

- **The standard treatment for advanced / metastatic soft tissue sarcomas remains Doxorubicin monotherapy.**
- **With Trabectedin and Pazopanib we have two new active compounds in the treatment armamentarium beyond 1st line chemotherapy.**
- **Lots of national (GISG) + international (EORTC) study activities.**
- **Problem of pharmaceutical interests versus academic questions.**
- **More trials are performed by the industry outside established networks and study groups (e.g. SUCCEED, Eribulin phase III).**

Educational: GIST Track

GISG
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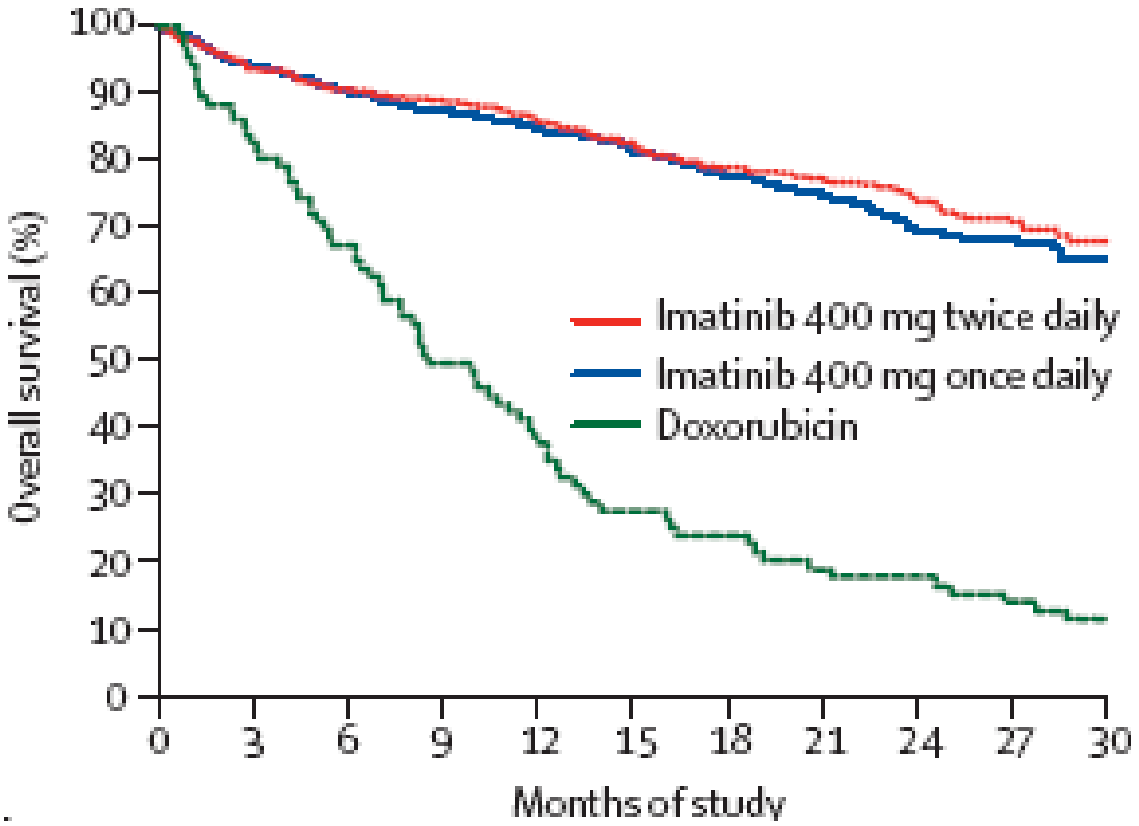
Gastrointestinal Stromal Tumors (GIST) - Background:

- GIST is the most common subtype of sarcomas and the most common mesenchymal malignancy of the gastrointestinal tract.
- Tyrosine kinase inhibitors (TKIs) are the mainstay of therapy for patients in the adjuvant setting as well as for patients with advanced or metastatic GIST.
- Imatinib and sunitinib are currently the only two drugs approved for the treatment of advanced GIST.
- Although imatinib and sunitinib have revolutionized the management of GIST, drug resistance remains a challenge in this disease.

Educational: GIST Track

GIST: Survival of metastatic GIST treated with imatinib

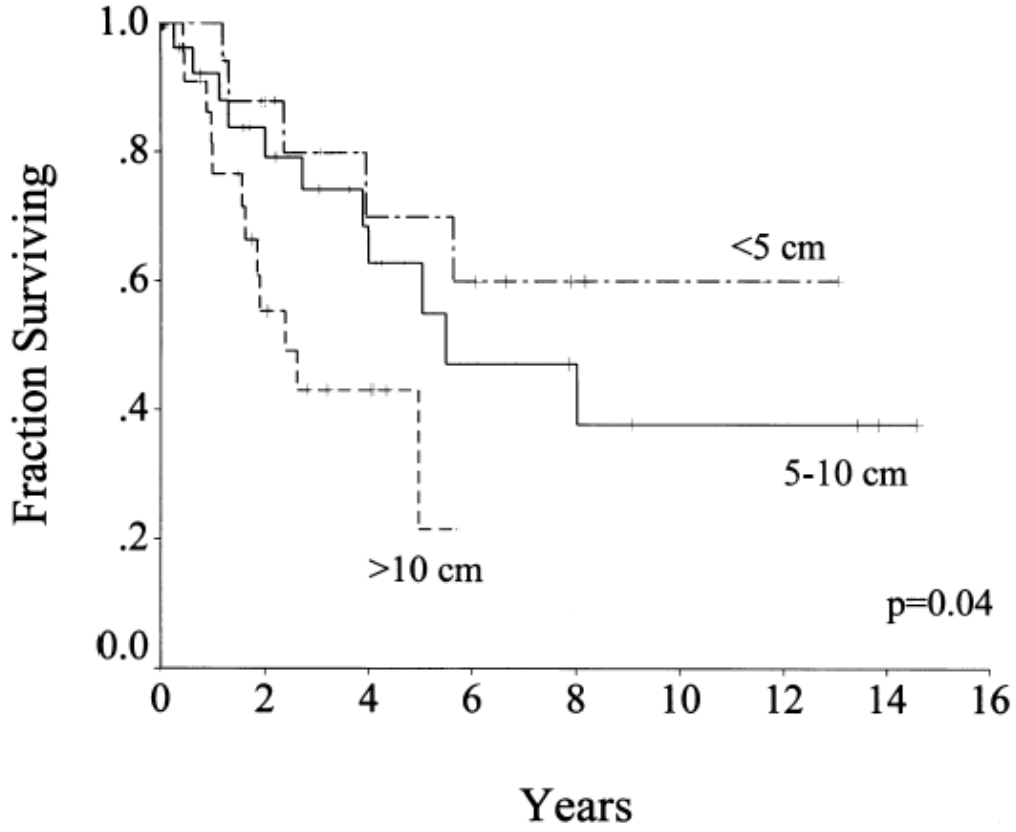


Verweij J, et al. Lancet 2004;364:1127-1134

Educational: GIST Track

German Interdisciplinary Sarcoma Group

GIST: Influence of tumor size on survival

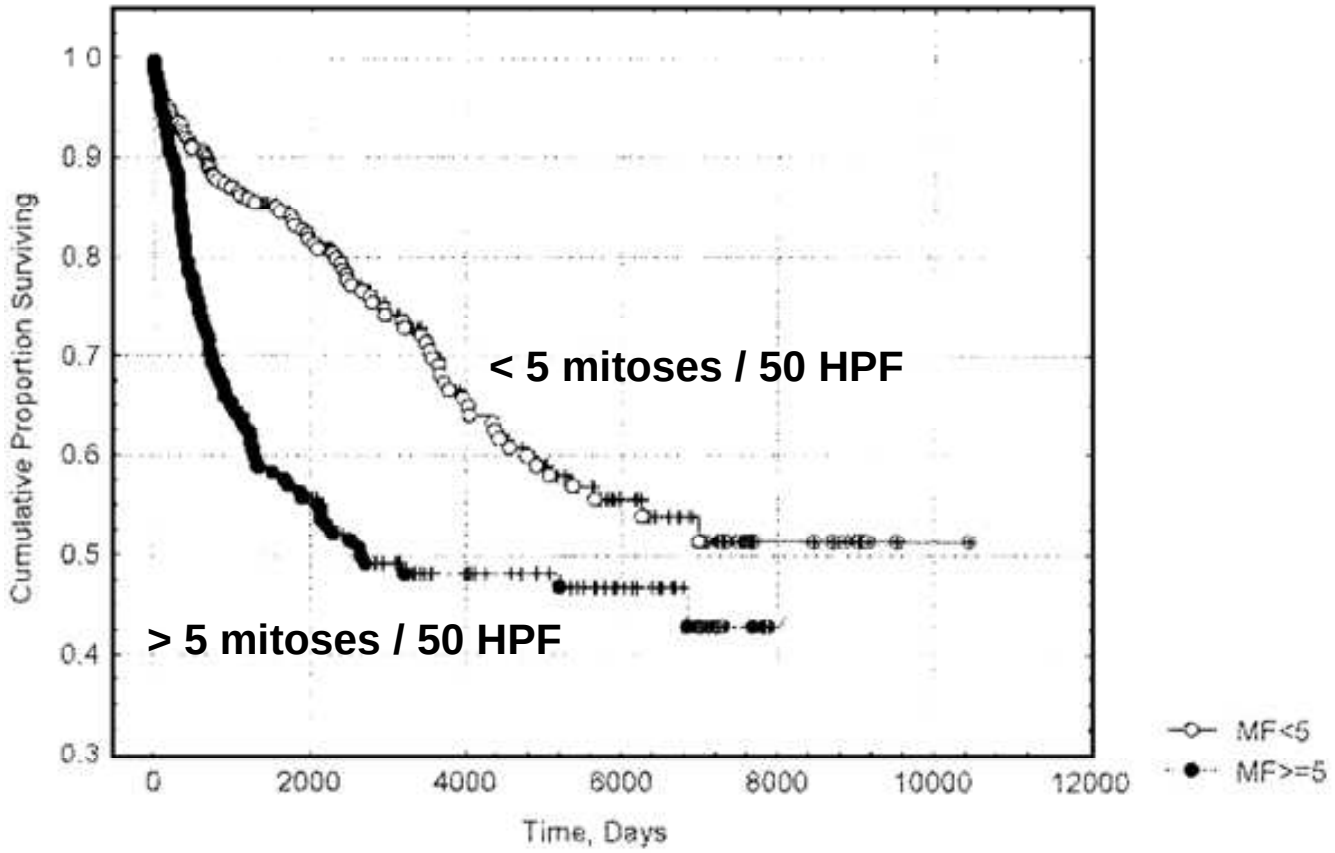


DeMatteo RP, et al. Ann Surg 2000;231:51-58

Educational: GIST Track

German Interdisciplinary Sarcoma Group

GIST: Influence of mitotic rate on survival



Emory TS, et al. Am J Surg Path 1999;23:82-87

Educational: GIST Track

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GIST: Fletcher classification

TABLE 2. Proposed Approach for Defining Risk of Aggressive Behavior in GISTs

	Size*	Mitotic Count†
Very low risk	<2 cm	<5/50 HPF
Low risk	2–5 cm	<5/50 HPF
Intermediate risk	<5 cm	6–10/50 HPF
	5–10 cm	<5/50 HPF
High risk	>5 cm	>5/50 HPF
	>10 cm	Any mitotic rate
	Any size	>10/50 HPF

Fletcher CD, et al. Hum Pathol 2002;33:459-465

Educational: GIST Track

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GIST: Miettinen classification

Table 1. Prognosis of Gastrointestinal Stromal Tumor (GIST) Based on Long-Term Follow-Up of Observation of 1684 Patients in Armed Forces Institute Studies Prior to Imatinib*

	Tumor Parameters		Patients With Progressive Disease During Follow-Up and Characterization of Malignant Potential, %	
Group	Size, cm	Mitotic Rate per 50 HPFs	Gastric GISTs	Small Intestinal GISTs
1	≤2	≤5	0 Very low if any	0 Very low if any
2	>2 ≤5	≤5	1.9 Low	4.3 Low
3a	>5 ≤10	≤5	3.6 Low	24 Intermediate
3b	>10	≤5	12 Intermediate	52 High
4	≤2	>5	0 Low†	50 High†
5	>2 ≤5	>5	16 Intermediate	73 High
6a	>5 ≤10	>5	55 High	85 High
6b	>10	>5	86 High	90 High

Non-gastric localizations have a higher risk of recurrence

Miettinen M, et al. Arch Pathol Lab Med 2006;130:1466-1478

Educational: GIST Track

German Interdisciplinary Sarcoma Group

GIST: Adjuvant imatinib therapy

- Patients with a significant risk of recurrence should receive adjuvant imatinib treatment:

Gastric GIST:	**Tumor size > 10 cm and / or > 5 mitoses per 50 HPF if tumor > 2 cm**
Duodenum, jejunum ileum, rectum GIST:	**Tumor size > 5 cm or > 5 mitoses per 50 HPF (independent from tumor size)**

Educational: GIST Track

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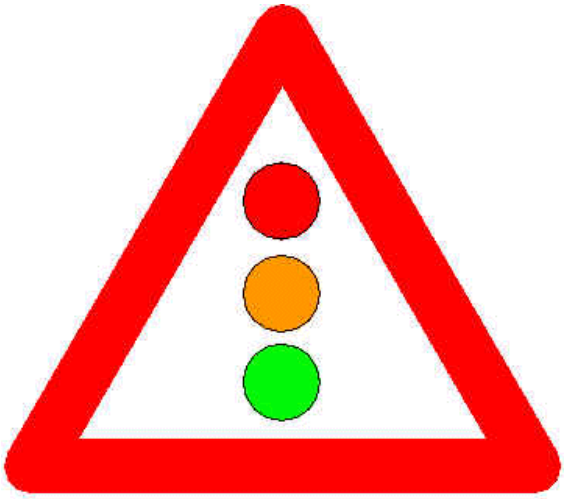
GIST: Adjuvant imatinib therapy



RED	Low risk patients	Should not be treated!
YELLOW	Intermediate risk patients	Could be treated!
GREEN	High risk patients	Should definitely be treated!

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Educational: GIST Track

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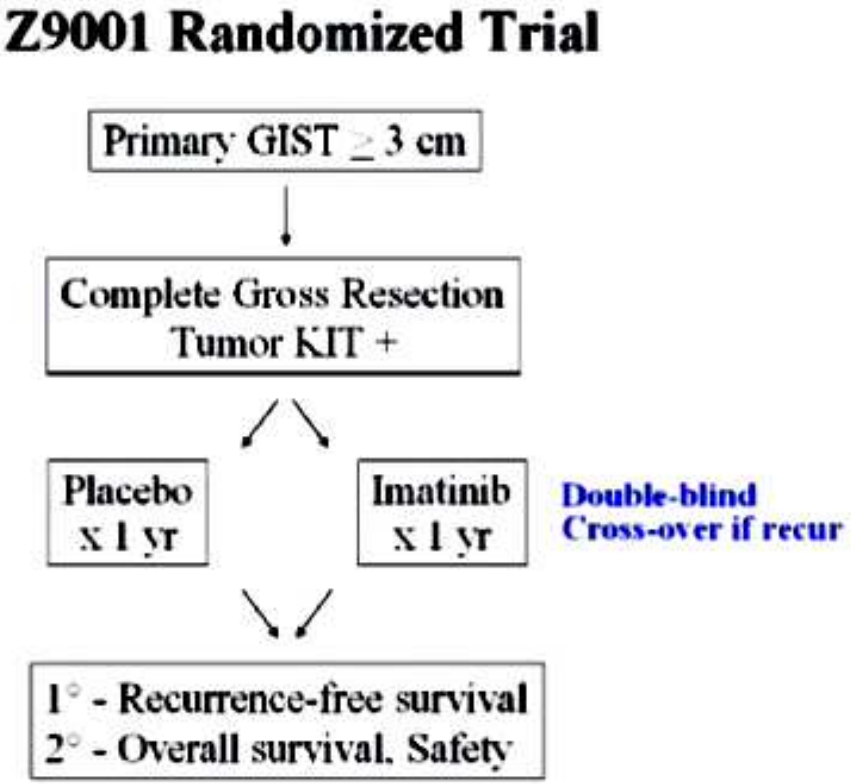
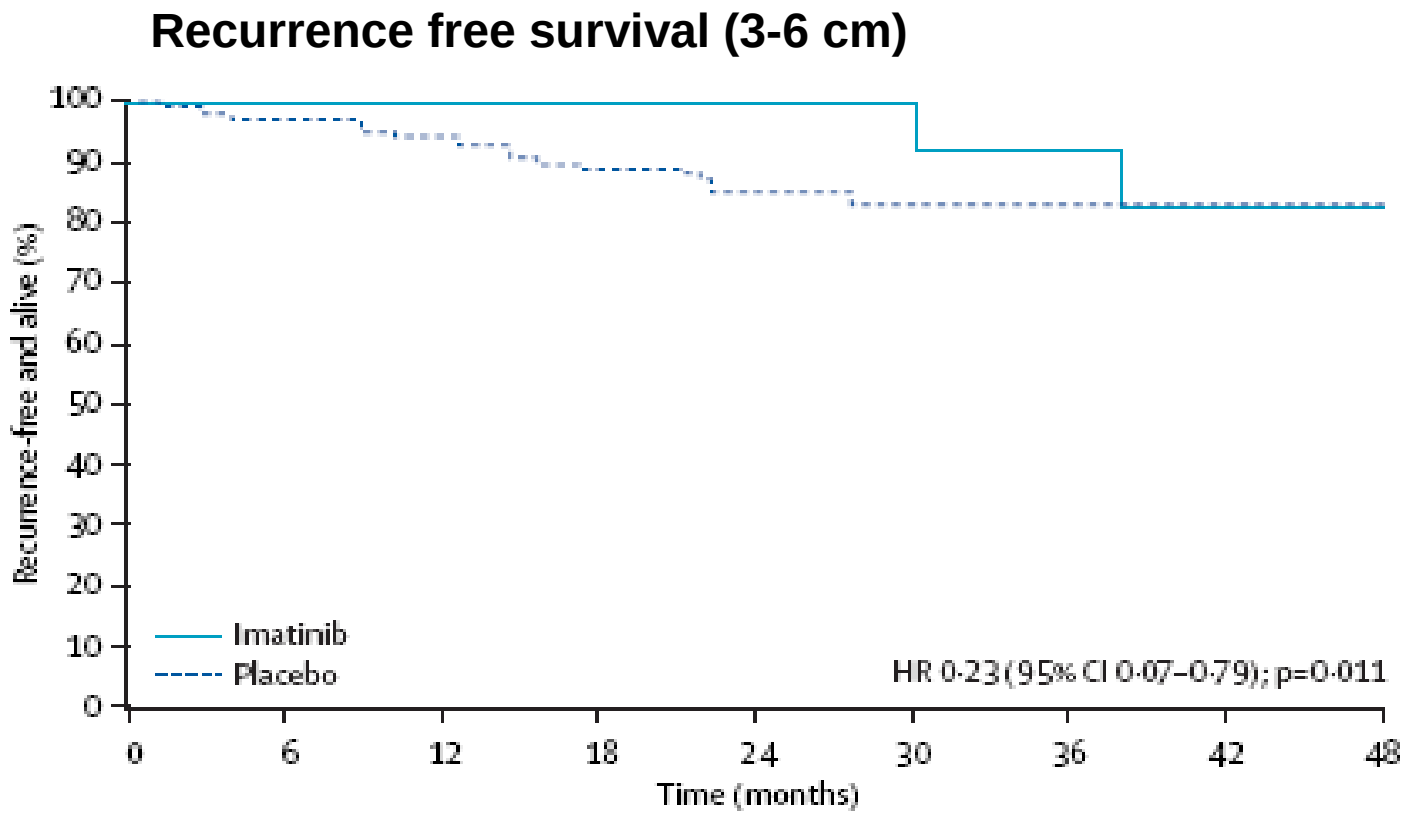
GIST: Adjuvant imatinib - ACOSOG trial



DeMatteo RP, et al. Lancet 2009;373:1097-1104

Educational: GIST Track

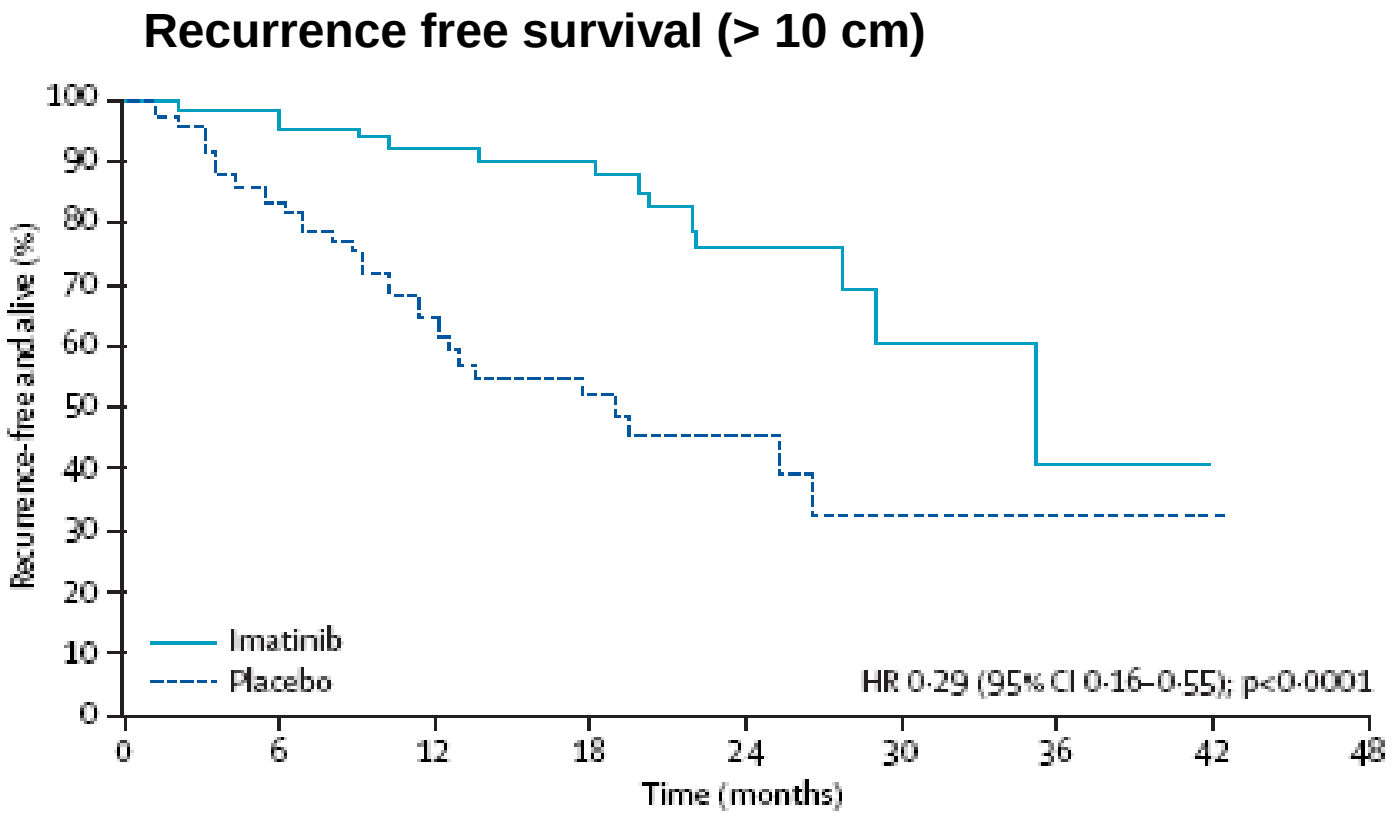
GIST: Adjuvant imatinib - ACOSOG trial



DeMatteo RP, et al. Lancet 2009;373:1097-1104

Educational: GIST Track

GIST: Adjuvant imatinib - ACOSOG trial

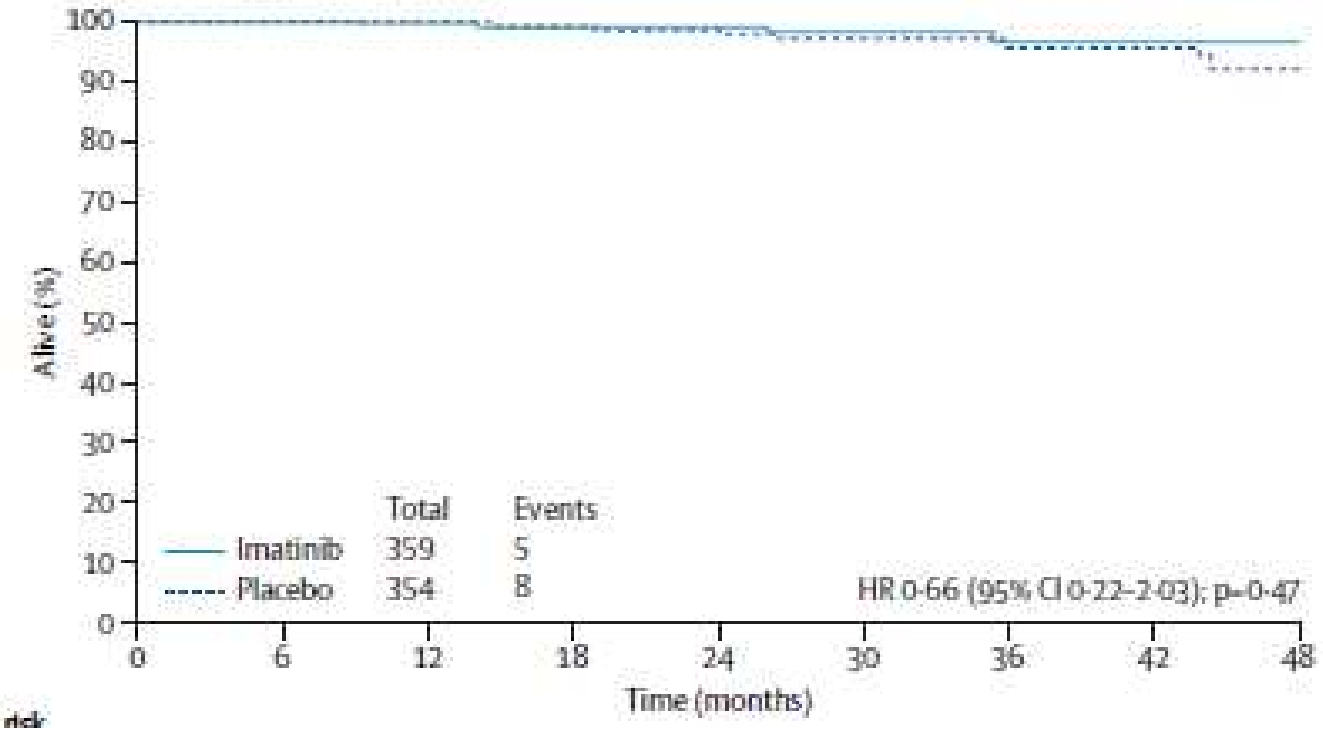


DeMatteo RP, et al. Lancet 2009;373:1097-1104

Educational: GIST Track

GIST: Adjuvant imatinib - ACOSOG trial

Overall survival



DeMatteo RP, et al. Lancet 2009;373:1097-1104

Educational: GIST Track

German Interdisciplinary Sarcoma Group

GIST: Adjuvant imatinib - ACOSOG trial

- Adjuvant imatinib over the period of one year is feasible and well tolerated in GIST patients.
- Adjuvant imatinib over one year does have significant impact on recurrence free survival.
- ACOSOG study without impact on overall survival.
- FDA approval for all GIST tumours ≥ 3 cm.
- EMA excluded GIST patients with “very low risk” and “low risk”, but did not limit the time of administration.

DeMatteo RP, et al. Lancet 2009;373:1097-1104

Educational: GIST Track

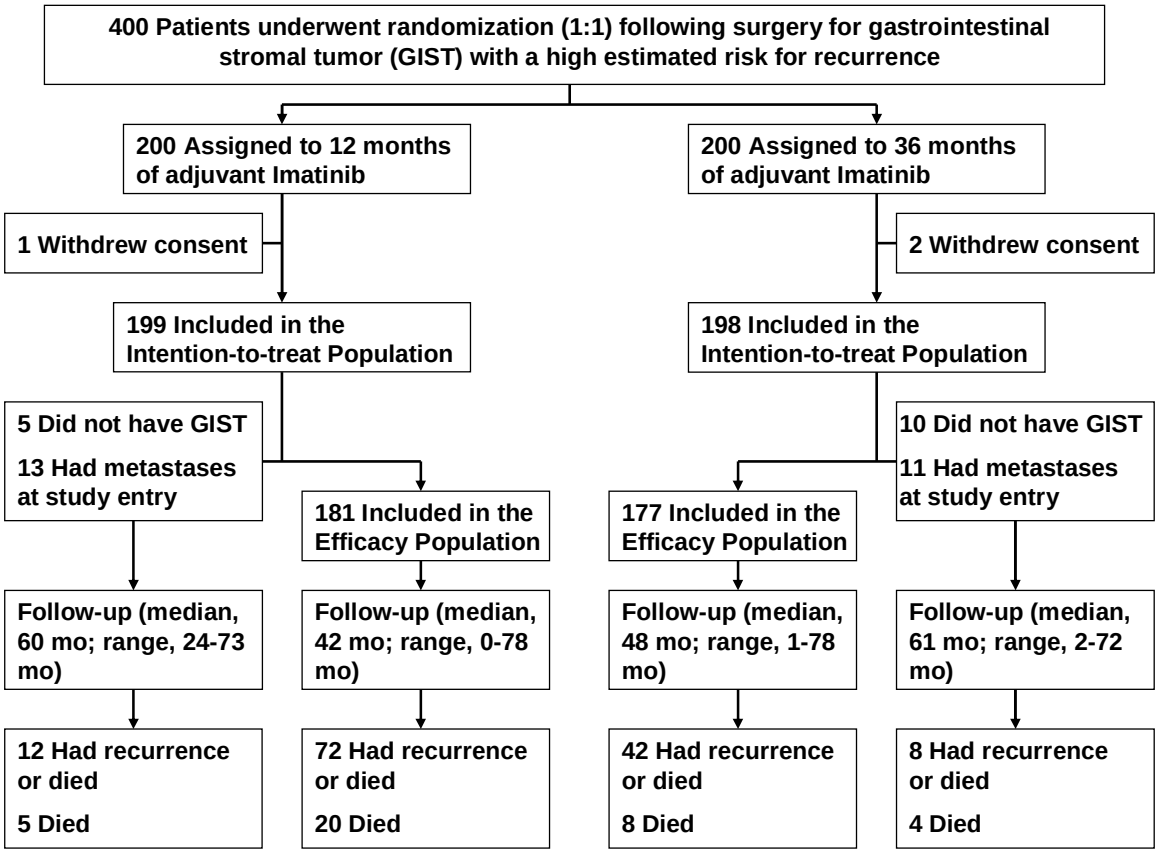
German Interdisciplinary Sarcoma Group

GIST: Adjuvant imatinib - treatment studies

EORTC 62024	400 mg	2 years vs observation (III)
SSG/AIO	**400 mg**	**3 years vs 1 year (III)**
Li et al.	400 mg	3 years vs observation (II)
PERSIST	400 mg	5 years (II, n = 85)

Educational: GIST Track

GIST: Adjuvant imatinib - SSGXVIII/AIO (n = 400)



Joensuu H, et al. JAMA 2012;307:1265-1272

Educational: GIST Track

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GIST: Adjuvant imatinib - SSGXVIII/AIO (n = 400)

Inclusion criteria: high risk of recurrence (modified NIH consensus criteria)

- > 10 cm
- > 10 mitoses / 50 HPF
- > 5 cm and > 5 mitoses / 50 HPF
- Tumor rupture (spontaneous/surgery), R1 resection

Table 1. Prognosis of Gastrointestinal Stromal Tumor (GIST) Based on Long-Term Follow-Up of Observation of 1684 Patients in Armed Forces Institute Studies Prior to Imatinib*

	Tumor Parameters		Patients With Progressive Disease During Follow-Up and Characterization of Malignant Potential, %	
Group	Size, cm	Mitotic Rate per 50 HPFs	Gastric GISTs	Small Intestinal GISTs
1	≤2	≤5	0 Very low if any	0 Very low if any
2	>2 ≤5	≤5	1.9 Low	4.3 Low
3a	>5 ≤10	≤5	3.6 Low	24 Intermediate
3b	>10	≤5	12 Intermediate	52 High
4	≤2	>5	0 Low†	50 High†
5	>2 ≤5	>5	16 Intermediate	73 High
6a	>5 ≤10	>5	55 High	85 High
6b	>10	>5	86 High	90 High

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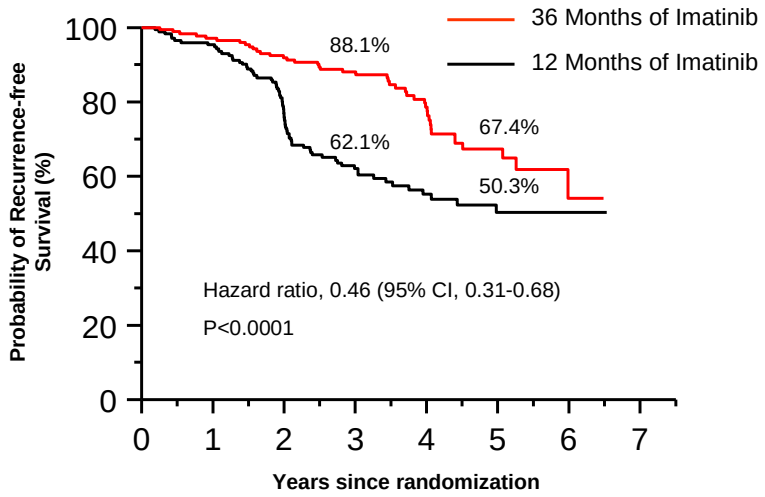
RFS

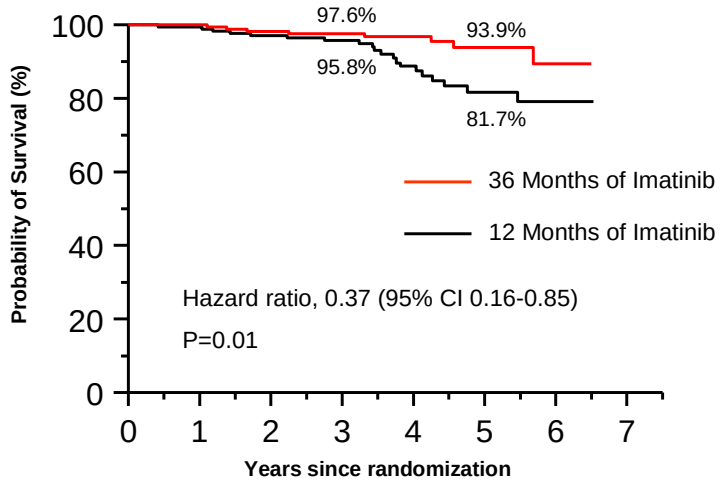


No. at Risk								
36 Months of Imatinib	177	167	157	121	71	35	7	0
12 Months of Imatinib	181	163	126	81	46	25	10	0

ITT: 65.6 vs 47.9 %

+ 17.7%

OS



No. at Risk								
36 Months of Imatinib	177	172	166	138	87	48	12	0
12 Months of Imatinib	181	171	162	128	78	41	19	0

ITT: 92.0 vs 81.7 %

+ 10.3%

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Joensuu H, et al. JAMA 2012;307:1265-1272

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GIST: Adjuvant imatinib - SSGXVIII/AIO (n = 400)

Table 2. Most Frequently Recorded Adverse Events

Events	No. (%)					
	All Grades			Grade 3 or 4		
	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]
Any event	192 (99.0)	198 (100.0)	.24	39 (20.1)	65 (32.8)	.006
Hematological						
Anemia	140 (72.2)	159 (80.3)	.08	1 (0.5)	1 (0.5)	>.99
Leukopenia	67 (34.5)	93 (47.0)	.01	4 (2.1)	6 (3.0)	.75
Nonhematological						
Periorbital edema	115 (59.3)	147 (74.2)	.002	1 (0.5)	2 (1.0)	>.99
Fatigue	94 (48.5)	96 (48.5)	>.99	2 (1.0)	1 (0.5)	.62
Nausea	87 (44.8)	101 (51.0)	.23	3 (1.5)	1 (0.5)	.37
Diarrhea	85 (43.8)	107 (54.0)	.04	1 (0.5)	4 (2.0)	.37
Muscle cramps	60 (30.9)	97 (49.0)	<.001	1 (0.5)	2 (1.0)	>.99
Leg edema	64 (33.0)	81 (40.9)	.12	1 (0.5)	2 (1.0)	>.99
Biochemical						
Elevated blood lactate dehydrogenase	84 (43.3)	119 (60.1)	.001	0	0	
Elevated serum creatinine	59 (30.4)	88 (44.4)	.005	0	0	

[a] Fisher exact test.

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GIST: Adjuvant imatinib - SSGXVIII/AIO (n = 400)

- Adjuvant imatinib over 3 years improves RFS and OS in comparison to one year imatinib.
- New gold-standard for patients with a significant risk of recurrence.
- Mutational analysis has to be taken into account.
- Open questions: Intermediate risk? Which patients? Cure possible? 5 years? Even longer? €€€…?

Joensuu H, et al. JAMA 2012;307:1265-1272

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GIST: ESMO Clinical Practice Guidelines 2012

The risk of relapse can be substantial, as defined by available risk classifications. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival and OS advantage in a randomized trial in comparison with 1 year of therapy in high-risk patients [14]. Previously, a placebo-controlled trial demonstrated that imatinib dosed for a planned duration of one year is able to prolong relapse-free survival in >3 cm localized GISTs with a macroscopically complete resection [15]. Therefore, adjuvant therapy with imatinib for 3 years is standard treatment of patients with a high risk of relapse [I, A]. Adjuvant therapy should not be considered when the risk is low. There is room for shared decision-making when the risk is intermediate [16].

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Current treatment of advanced / metastatic GIST

1st line therapy: 400 mg Imatinib daily (Cave: exon 9 mutation > 800 mg Imatinib)

2nd line therapy: Imatinib 800 mg daily or in the case of further progression Sunitinib (50 mg daily 4 weeks on / 2 weeks off or 37.5 mg daily)

<u>Many treatment options in the pipeline:</u>

Regorafenib

Masitinib

Dasatinib

Sorafenib

Dovitinib

New alternative therapy options

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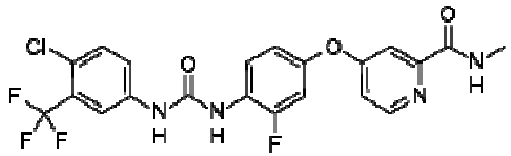
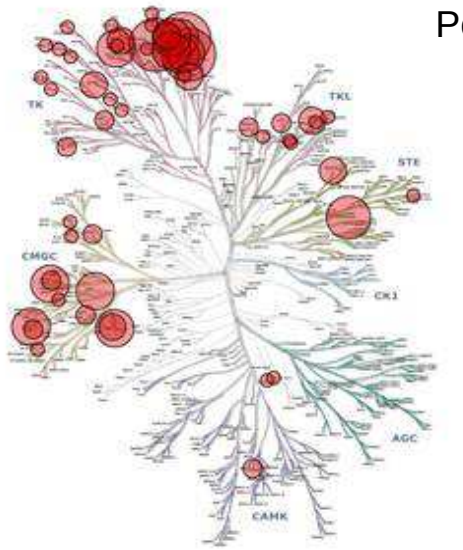
Regorafenib



Regorafenib



Percent control

0%
0.1%
0.1-1%
1-5%
5-10%
10-35%

Biochemical activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

Wilhelm et al. Int J Cancer 2011

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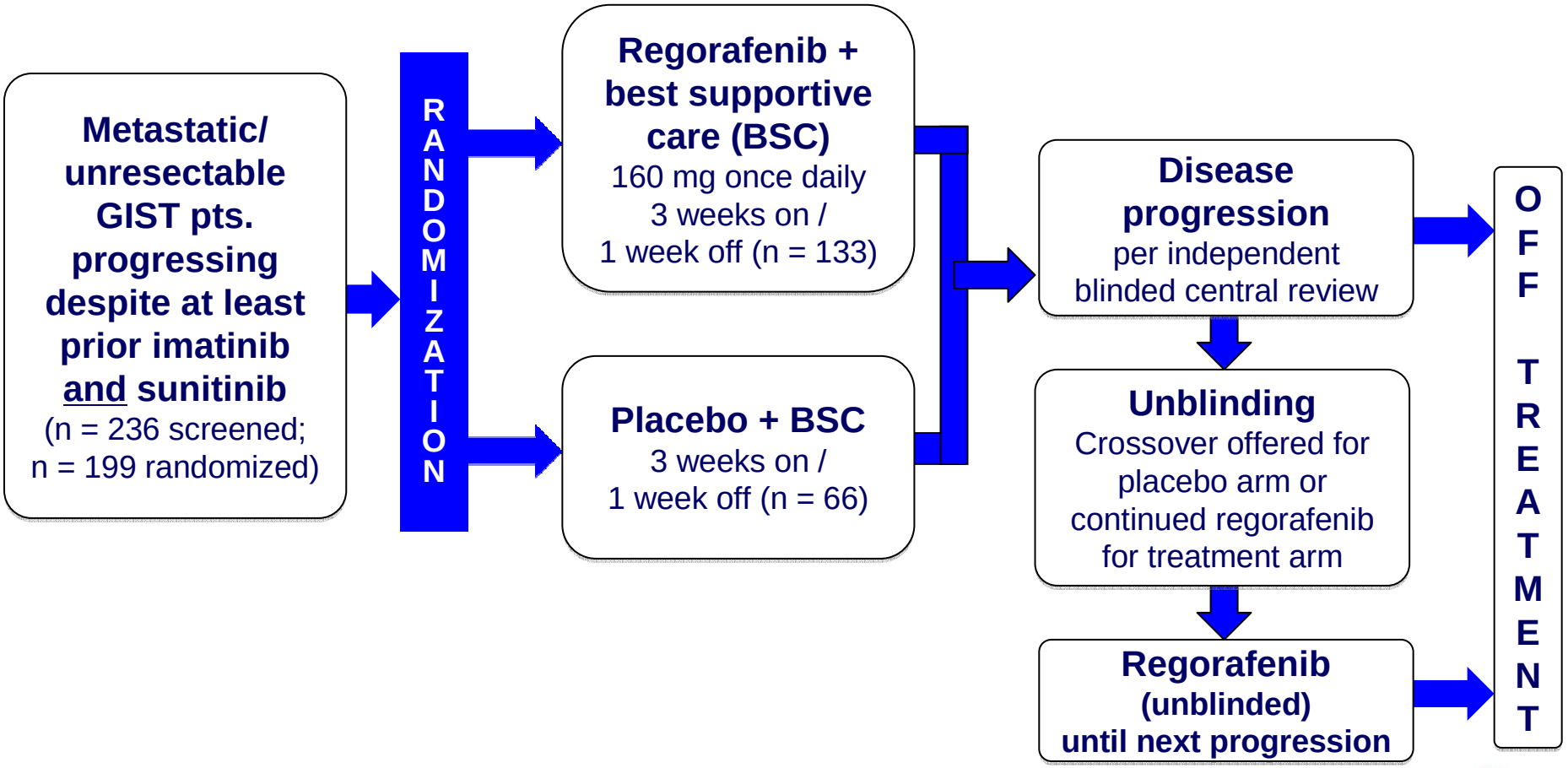
3rd line Placebo-controlled Phase III Regorafenib Study (GRID)



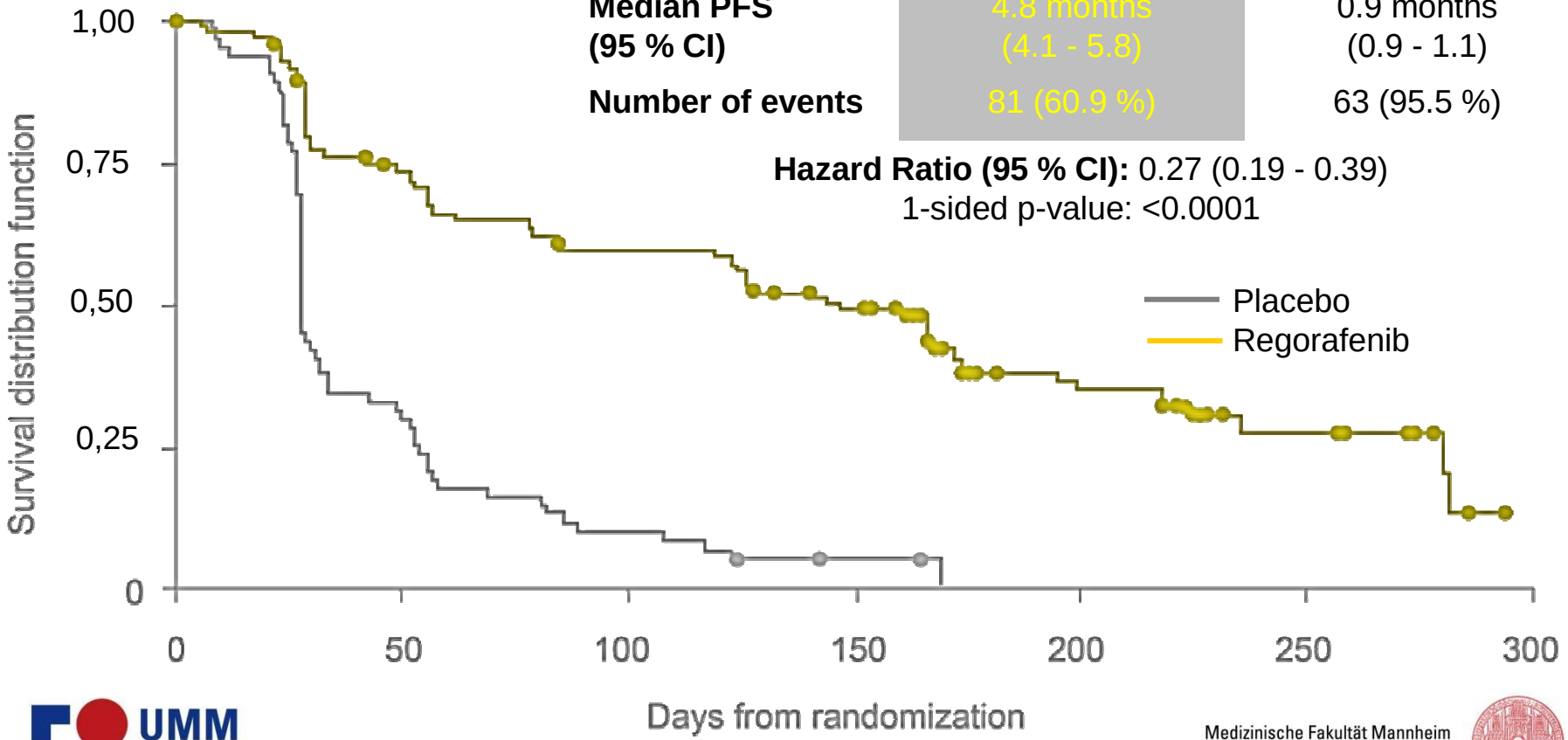
Demetri GD, et al. J Clin Oncol 30, 2012 (suppl; abstr LBA10008).

Educational: GIST Track

GRID: Progression-free Survival

	Regorafenib, N=133	Placebo, N=66
Median PFS (95 % CI)	4.8 months (4.1 - 5.8)	0.9 months (0.9 - 1.1)
Number of events	81 (60.9 %)	63 (95.5 %)

Hazard Ratio (95 % CI): 0.27 (0.19 - 0.39)
1-sided p-value: <0.0001



Demetri GD, et al. J Clin Oncol 30, 2012 (suppl; abstr LBA10008).

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GRID: Adverse events

		Regorafenib (N = 132), % Median exposition 23 weeks				Placebo (N = 66), % Median exposition 7 weeks			
	Grade	All	3	4	5	All	3	4	5
Hand-Foot-Syndrome		56.1	19.7	0	0	15.2	1.5	0	0
Hypertension		48.5	22.7	0.8	0	16.7	3.0	0	0
Diarrhea		40.9	5.3	0	0	7.6	0	0	0
Fatigue		38.6	2.3	0	0	27.3	1.5	0	1.5
Mucositis, oral		37.9	1.5	0	0	9.1	1.5	0	0
Alopecia		23.5	1.5	0	0	3.0	0	0	0
Hoarseness		22.0	0	0	0	4.5	0	0	0
Anorexia		20.5	0	0	0	7.6	0	0	0
Rash		18.2	3.0	0	0	3.0	0	0	0
Nausea		15.9	0.8	0	0	9.1	1.5	0	0
Constipation		15.2	0.8	0	0	7.6	0	0	0
Myalgia		13-6	0.8	0	0	9.1	0	0	0
Voice alteration		11.4	0	0	0	3.0	0	0	0

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Demetri GD, et al. J Clin Oncol 30, 2012 (suppl; abstr LBA10008).

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2nd line Phase II Masitinib Study

- **Masitinib = TKI with higher activity and selectivity than Imatinib**
- **Phase II Study, n = 44**
  - Comparison Masitinib (Cross-over possible) versus Sunitinib (no Cross-over) in progressive GIST patients under Imatinib
  - Median PFS 3.9 months for Masitinib and 3.8 months for Sunitinib
  - Patients in the Masitinib arm demonstrated longer survival
  - Less side effects under treatment with Masitinib compared to Sunitinib regarding SAE (0 % versus 19 %)
- **A randomized phase III study comparing Masitinib versus Sunitinib in 2nd line GIST patients being progressive under therapy with Imatinib will start soon**

Adenis A et al. J Clin Oncol 30, 2012 (suppl; abstr 10007).

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Targets of different tyrosine kinase inhibitors (TKI)

	Zielstruktur
Nilotinib	KIT, PDGFR, ABL
Sorafenib	KIT, PDGFR, VEGFR, RAF
Dasatinib	KIT, PDGFR, ABL
Masitinib	KIT, PDGFR, FGFR3
Motesanib	KIT, PDGFR, VEGFR
Cediranib	KIT, VEGFR1-3
Regorafenib	KIT, VEGFR1-3, RET, B-RAF, PDGFR-b

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Current treatment of advanced / metastatic GIST

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2nd line therapy:	Imatinib 800 mg daily or in the case of further progression Sunitinib (50 mg daily 4 weeks on / 2 weeks off or 37,5 mg daily)

Many treatment options in the pipeline:

Regorafenib	Promising phase III data; Approval is expected for 2013
Masitinib	Currently evaluated in phase III 1st and 2nd line studies
Dasatinib	Moderate activity with significant pulmonary toxicity
Sorafenib	Good therapeutic option (“off-label use”)
Dovitinib	Safety and activity is currently evaluated in phase II studies

New alternative therapy options (mTOR, AKT, PI3K)

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Take-home-messages (GIST)

- **GIST is the most common subtype of soft tissue sarcomas.**
- **Tyrosine kinase inhibitors (TKIs) are the mainstay of GIST therapy.**
- **New gold-standard in adjuvant therapy for patients with a significant risk of recurrence is Imatinib over 3 years.**
- **Imatinib and Sunitinib are currently the only two drugs approved for the treatment of advanced and metastatic GIST.**
- **Promising TKIs which will be incorporated in the treatment armamentarium of advanced GIST are Regorafenib and Masitinib.**

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Questions?