THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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Personalizing "good old chemotherapy" for soft-tissue sarcomas

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Houston, Texas

SOFT-TISSUE SARCOMAS
Personalizing therapy
a.k.a. good clinical judgment?

- **Predictive Factors to consider:**
  - **PS**
  - **Organ function**
  - **Co-morbidities**
  - **Tumor grade / growth kinetics**
- **Limited number of approved agents**
  - **Most patients end up getting all available agents**
  - **Personalizing vs. Prioritizing the lines of treatment**
  - **Insurance coverage - variable**

Soft-Tissue Sarcomas

2014 Incidence

12,020 new cases

>50 different subtypes

Paradigm Shift

Lumpers -> Splitters

Histology (subset)-specific Rx

Target specific therapy

SOFT-TISSUE SARCOMAS
CHEMOTHERAPEUTIC AGENTS
Anthracycline +/- Ifosfamide

- Ewing sarcoma family of tumors
- Rhabdomyosarcoma
- Synovial sarcoma
- Angiosarcoma
- UPS
- Unclassified Sarcoma
- Liposarcomas (myxoid, pleo, dediff)
- Leiomyosarcoma
- MPNST
- Extraskeletal myxoid chondrosarcoma

First-line chemotherapy for met. STS

- EORTC 62012, randomized phase 3 study, n=455
- 18-60 yrs, locally advanced or metastatic STS
- Median follow-up = 56 months
- Dox (75) vs. Dox/Ifex (75/10) + Pegfilgrastim

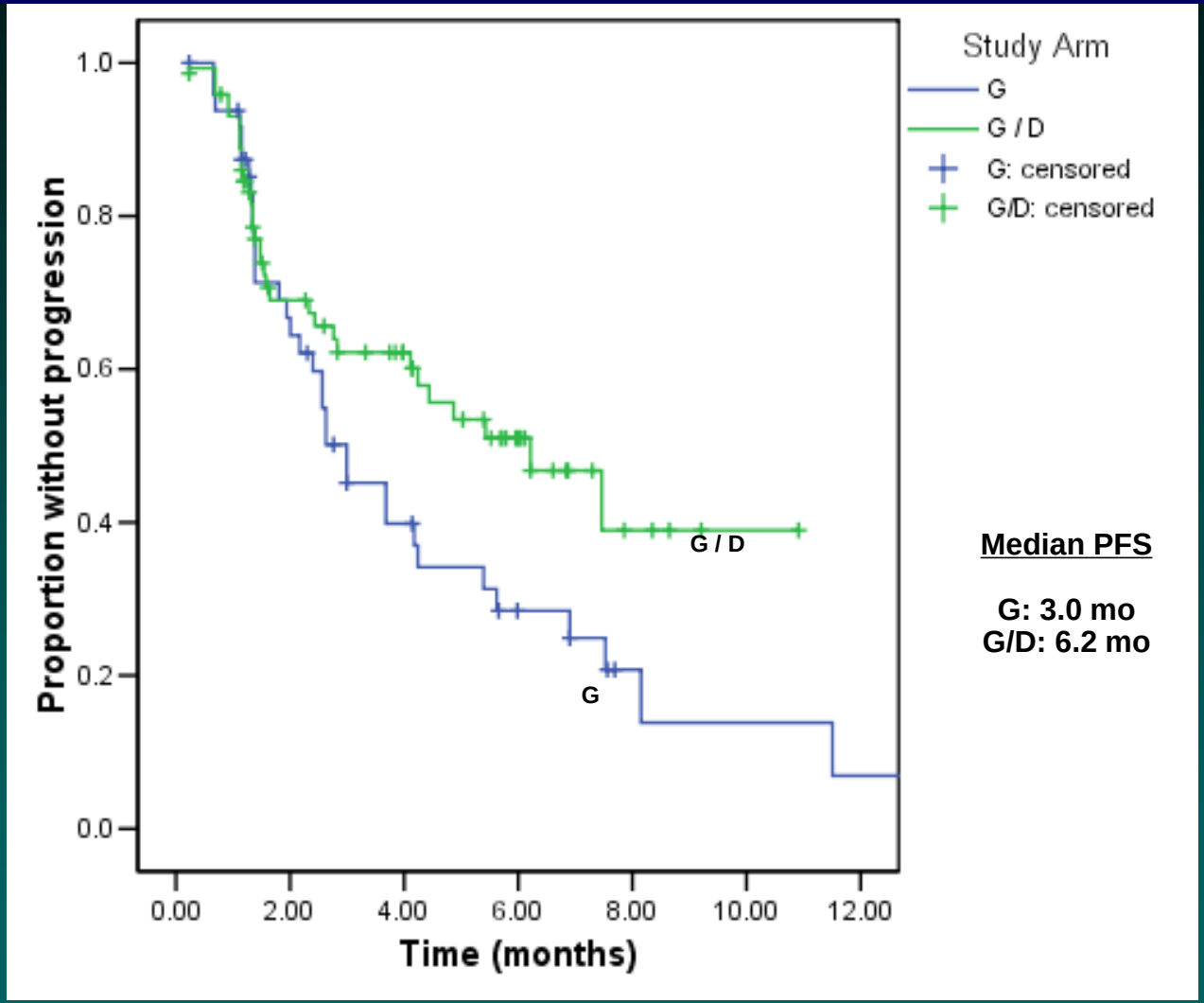
Endpoint	HR	D vs. DI	p Value
RR (RECIST)		14 vs. 27%	
Median PFS	0.74	4.6 vs. 7.4 mo	0.003
Median OS	0.83	12.8 vs. 14.3 mo	0.076
1 yr Overall Surv		51% vs. 60 %	

ESMO Oct 2012, Ann Oncol 23(9): abstr LBA 7

SOFT-TISSUE SARCOMAS
CHEMOTHERAPEUTIC AGENTS
Gemcitabine +/- Docetaxel

- Leiomyosarcoma (Gyn and others)
- Angiosarcoma
- Liposarcomas (myxoid, pleo, dediff)
- UPS
- Unclassified sarcoma
- Epithelioid sarcoma
- ? Synovial sarcoma

PFS: Intention to treat analysis

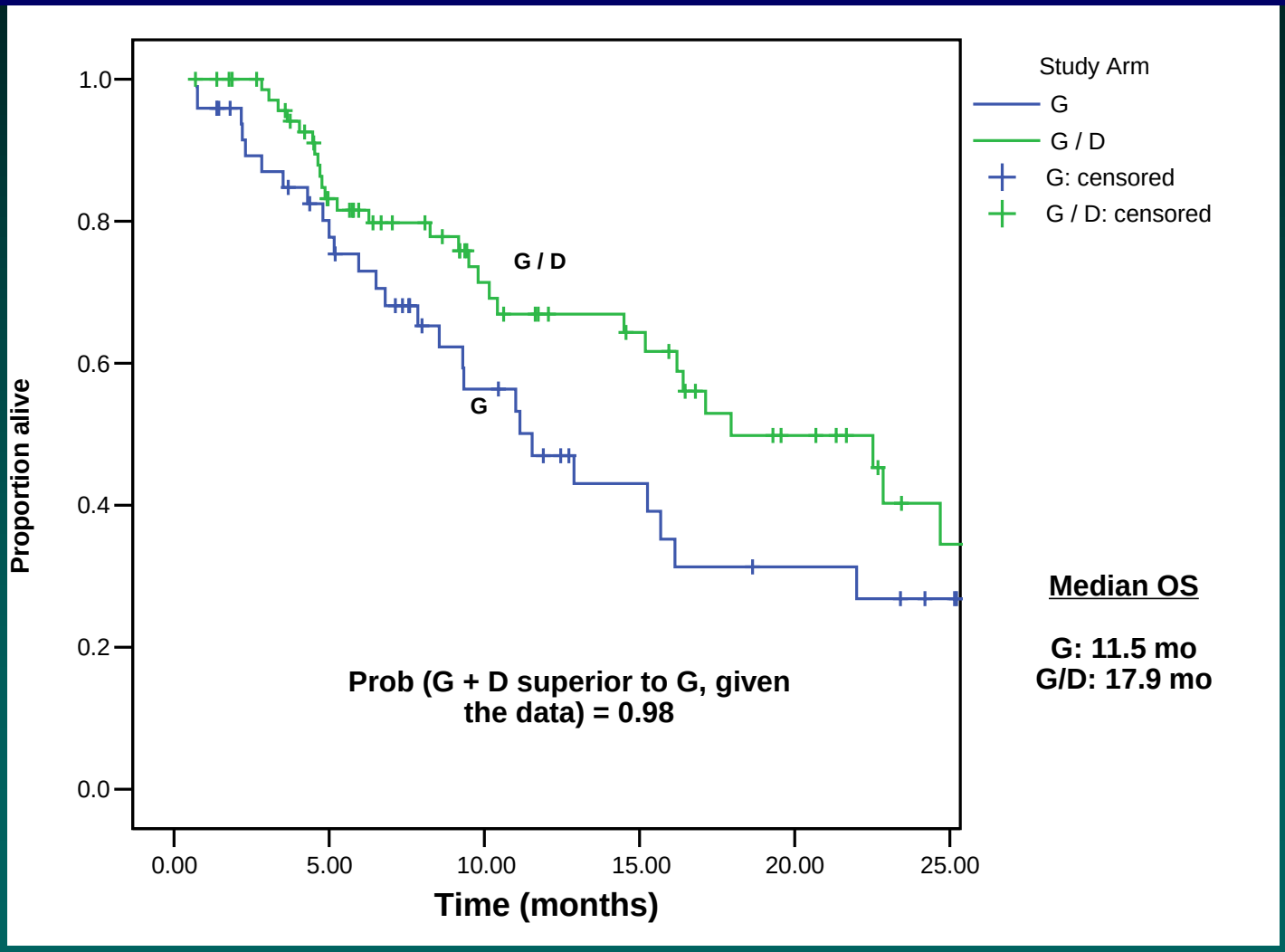


Median PFS

G: 3.0 mo
G/D: 6.2 mo

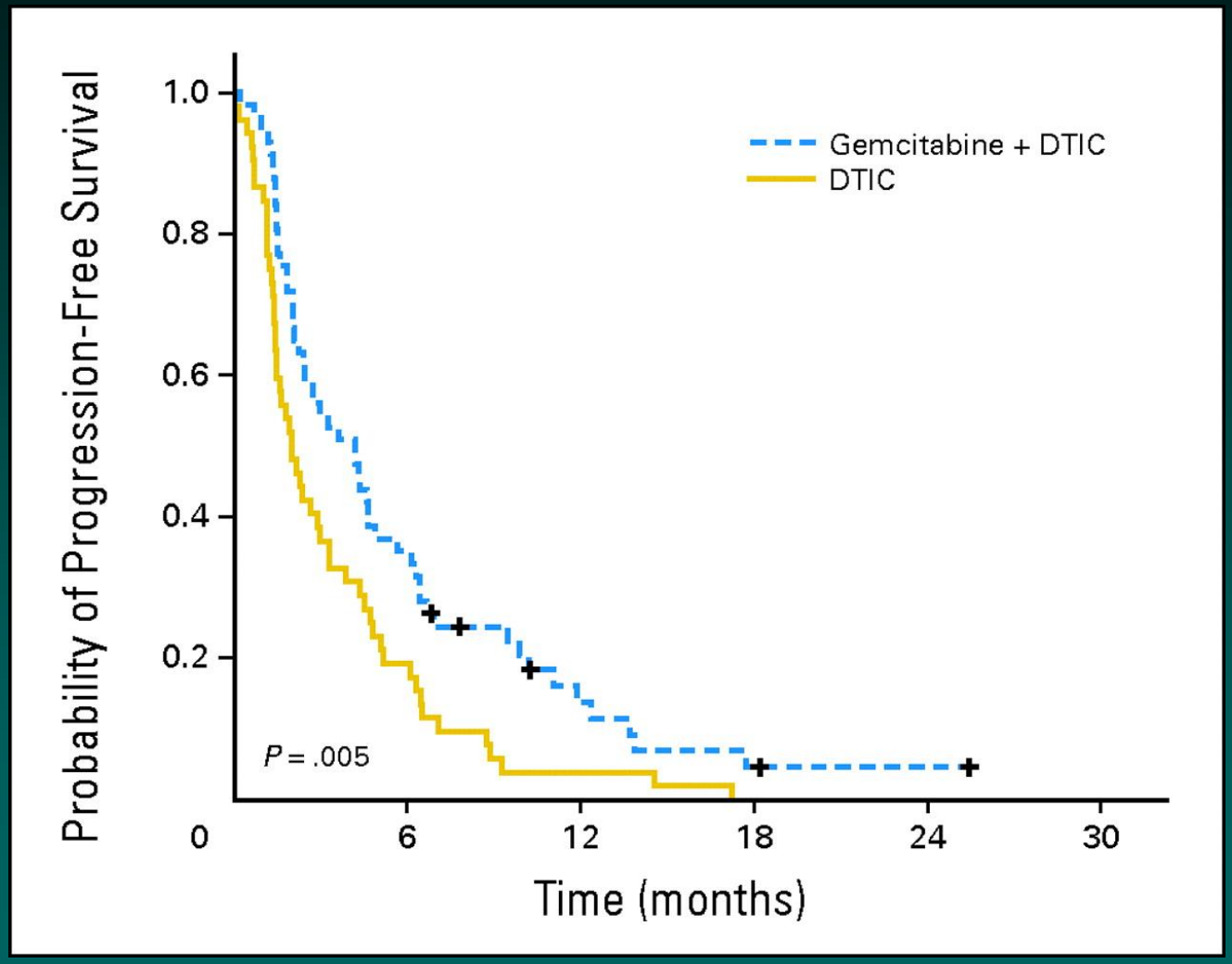
Prob (G+D is superior to G, given the data) is 0.98

Overall survival superior with Gem/Doc



García-del-Muro X et al. JCO 2011;29:2528-2533

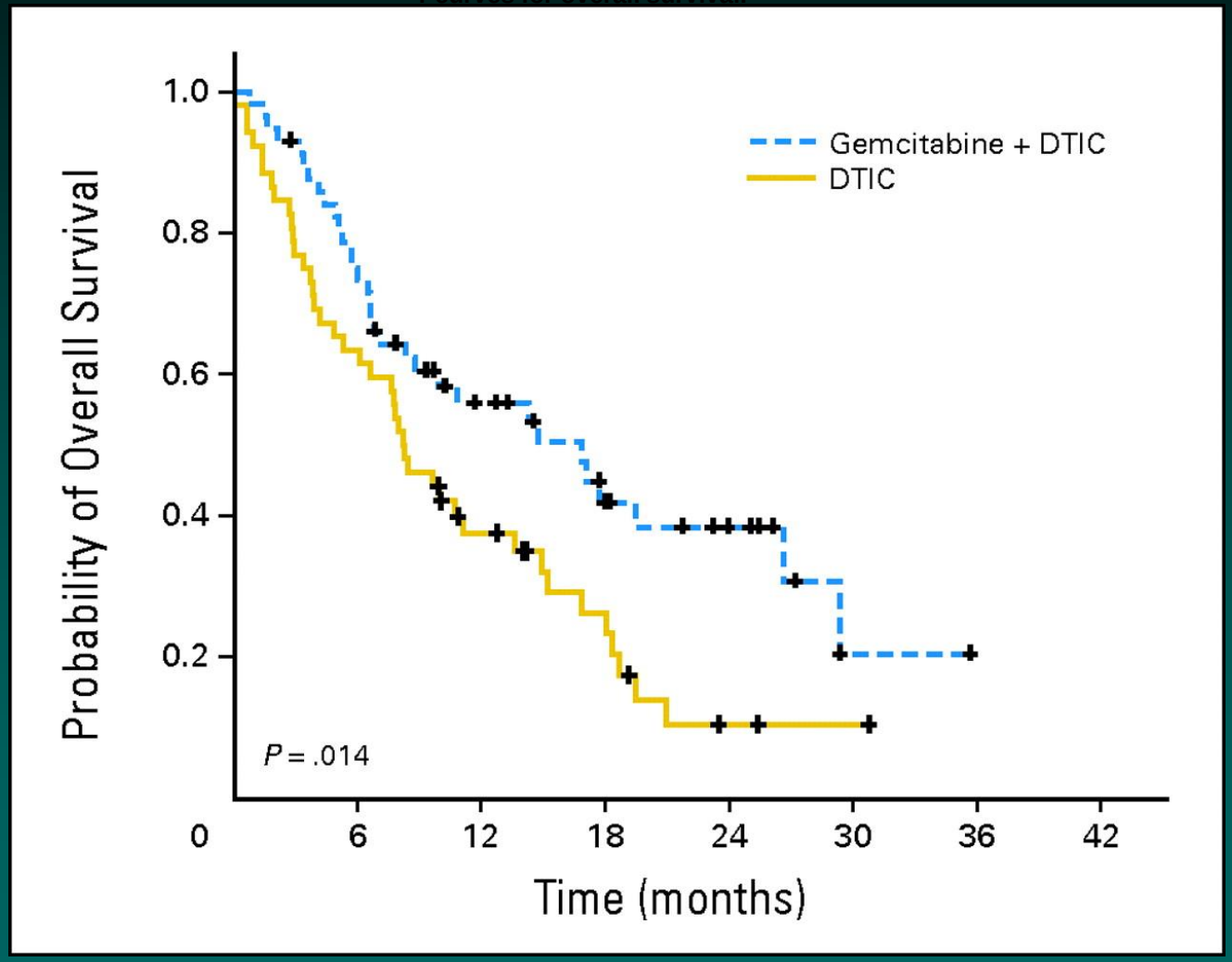
Progression-Free Survival



Kaplan-Meie García-del-Muro X et al. JCO 2011;29:2528-2533

Overall Survival

r curves for overall survival.



SOFT-TISSUE SARCOMAS
CHEMOTHERAPEUTIC AGENTS
Trabectedin

- Liposarcoma (myxoid)
- Leiomyosarcoma
- UPS
- Endometrial stromal sarcoma
- Synovial sarcoma
- Others (? TRS)

Trabectedin – initial signal of activity in myxoid liposarcomas

VOLUME 22 · NUMBER 8 · APRIL 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II and Pharmacokinetic Study of Ecteinascidin 743 in Patients With Progressive Sarcomas of Soft Tissues Refractory to Chemotherapy

R. Garcia-Carbonero, J.G. Supko, J. Manola, M.V. Seiden, D. Harmon, D.P. Ryan, M.T. Quigley, P. Merriam, J. Cunniff, G. Goss, U. Mandavia, R.G. Maki, T. Lopez, T.A. Puchalski, M.A. Sandoo, J. Gomez, C. Guzman, J. Jimeno, and G.D. Demetri

From the Dana-Farber Cancer Institute and Massachusetts General Hospital, Harvard Medical School, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; and Clinical Research and Development, PharmaMar, Madrid, Spain.

Submitted February 21, 2003; accepted February 2, 2004.

Supported in part by a grant of the Ministerio de Educacion y Cultura, Spain.

A B S T R A C T

Purpose
To assess the efficacy of the marine-derived alkaloid ecteinascidin 743 (ET-743) in patients with soft tissue sarcomas that progressed despite prior conventional chemotherapy and to characterize the pharmacokinetic profiles of ET-743 in this patient population.

Patients and Methods
Thirty-six previously treated soft tissue sarcoma patients from three institutions received ET-743 as a 24-hour continuous intravenous (IV) infusion at a dose of 1,500 $\mu g/m^2$ every 3 weeks. Pharmacokinetic studies were also performed. Patients were restaged every two cycles for response by objective criteria.

types. However, potentially important differences in response to therapy clearly exist between histologic subsets of soft tissue sarcomas. It should be noted that two of the major responses observed in our study and one minor response (48% tumor reduction) occurred in patients with liposarcomas, two of which comprised the myxoid/round-cell subtype. This represents a response rate of 30% for the subset of 10 patients included in the study with the histo-

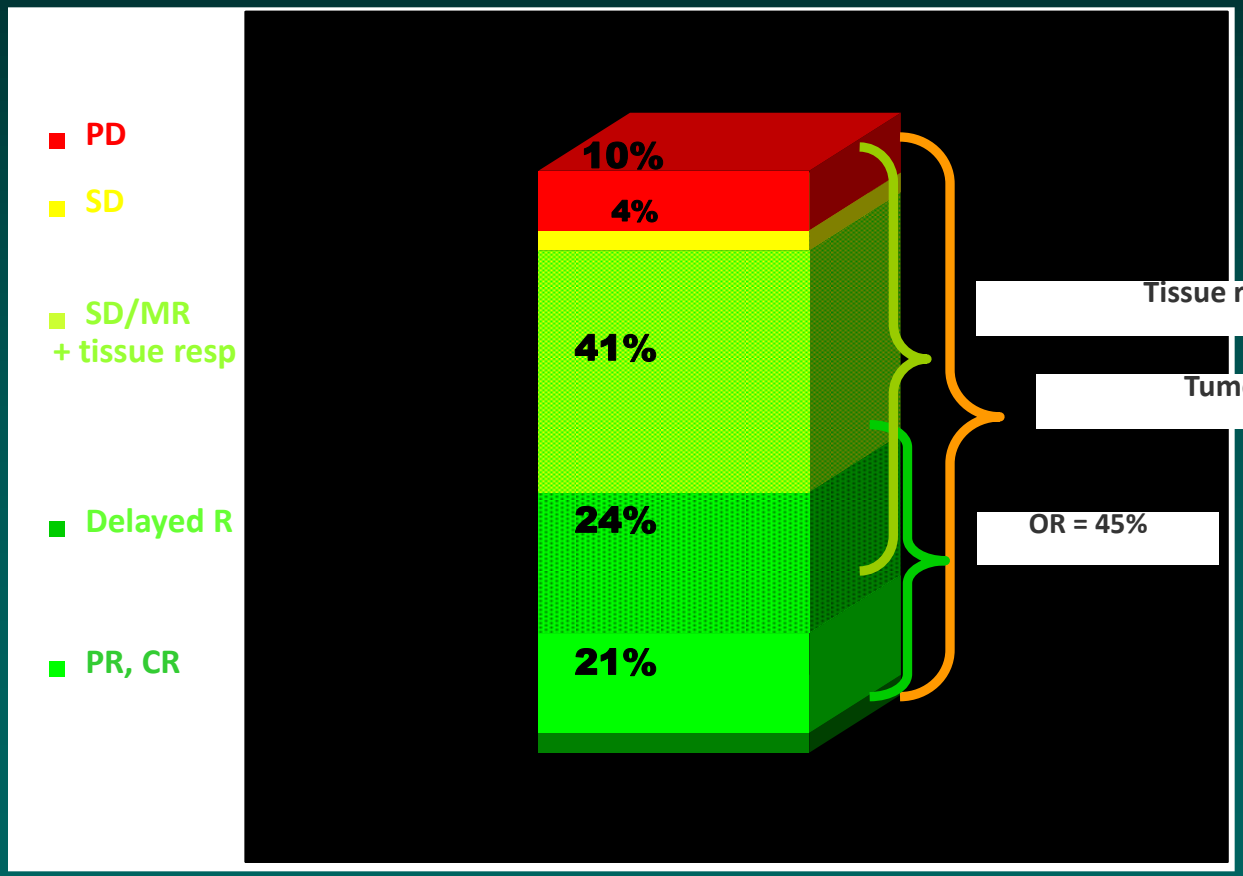
majority of patients present with a clinically localized tumor, 30% to 60% will eventually develop local recurrence or metastatic disease.[2,3] Once the tumor has progressed beyond surgical resectability, the disease is nearly always incurable.[2,3] The median sur-

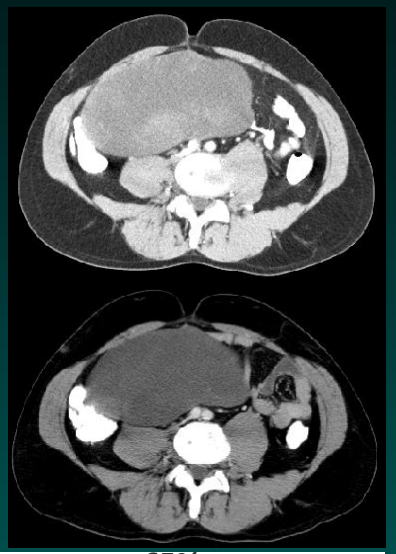
the treatment of advanced soft tissue sarcomas. Prospective studies of these drugs administered as single agents to sarcoma patients with no prior chemotherapy have demonstrated response rates ranging from 11% to 30%.[4-6] Other less active drugs in-

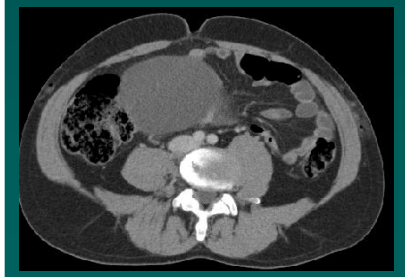
MLPS /trabectedin responses

F. Grosso, Lancet Oncology, 2007

n=44

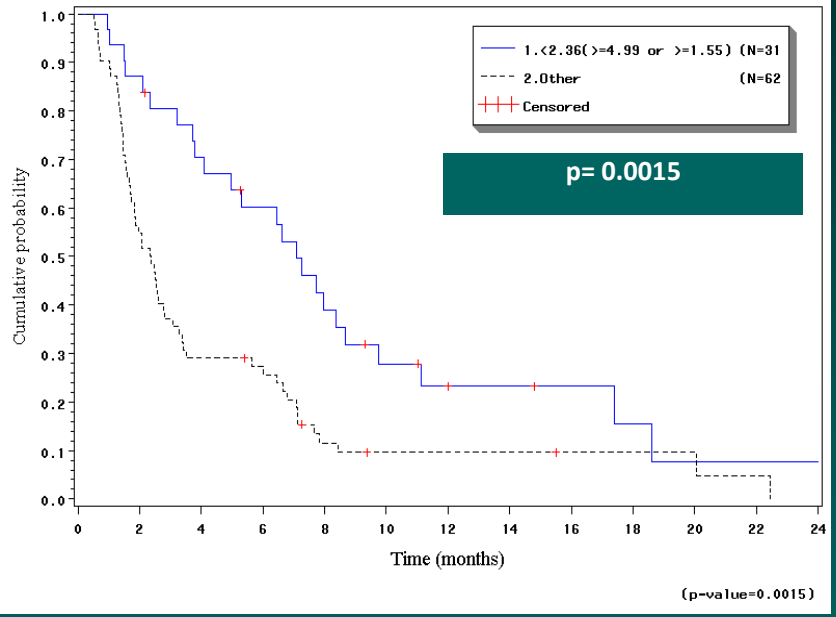




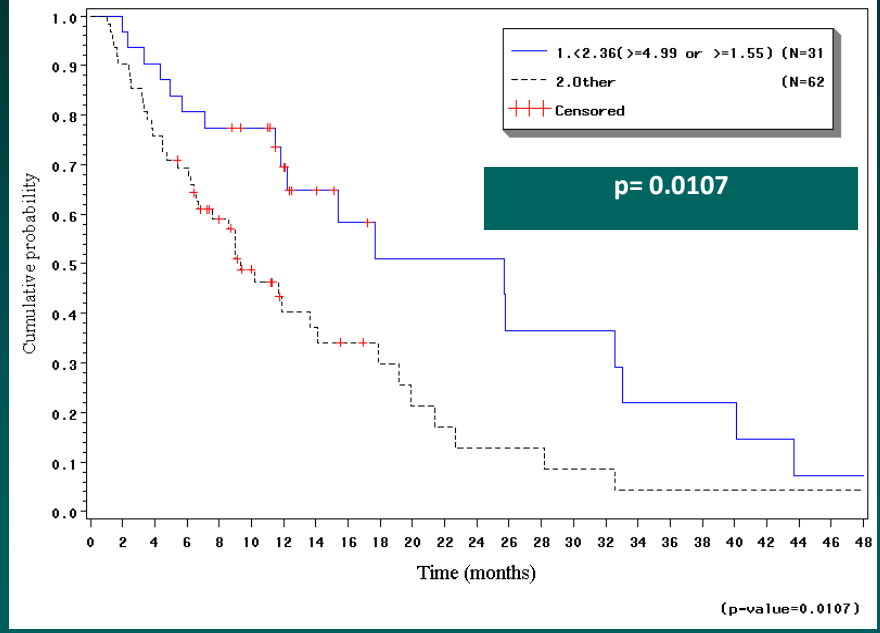


Impact of combined Low BRCA1 + High (ERCC1 or XPG) mRNA expression in the outcome of sarcoma patients treated with Trabectedin

PFS



Survival

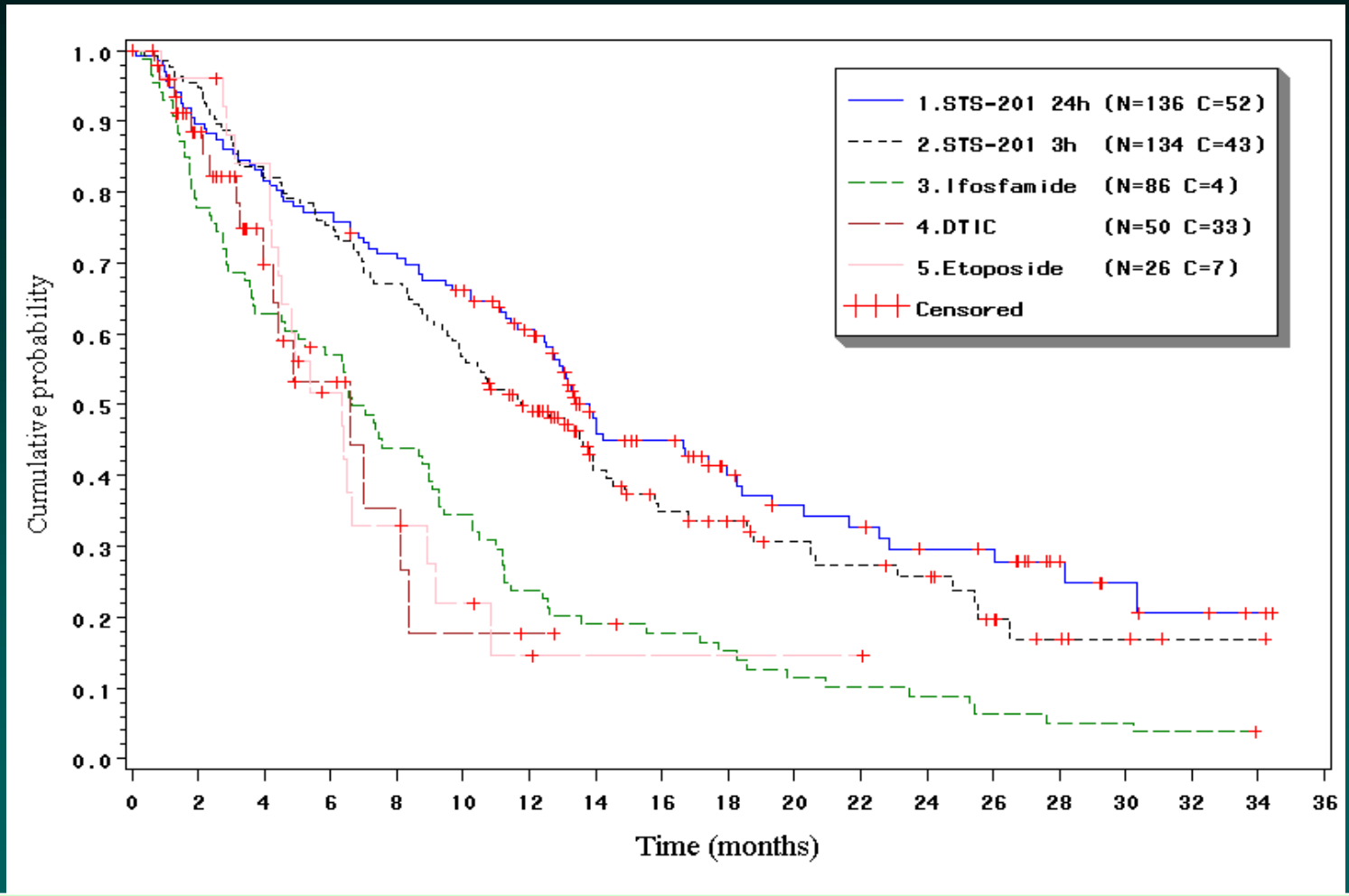


Favorable subpopulation: low BRCA1 + high (XPG or ERCC1)

Remaining STS patients

JC Tercero, PharmaMar, data on file

STS-201 and Historical Comparators - OS
Active vs Inactive Agents - STS pretreated pts



Acknowledging the limitations of historical comparisons, both trabectedin schedules show substantially longer OS than "active" drugs in similar setting

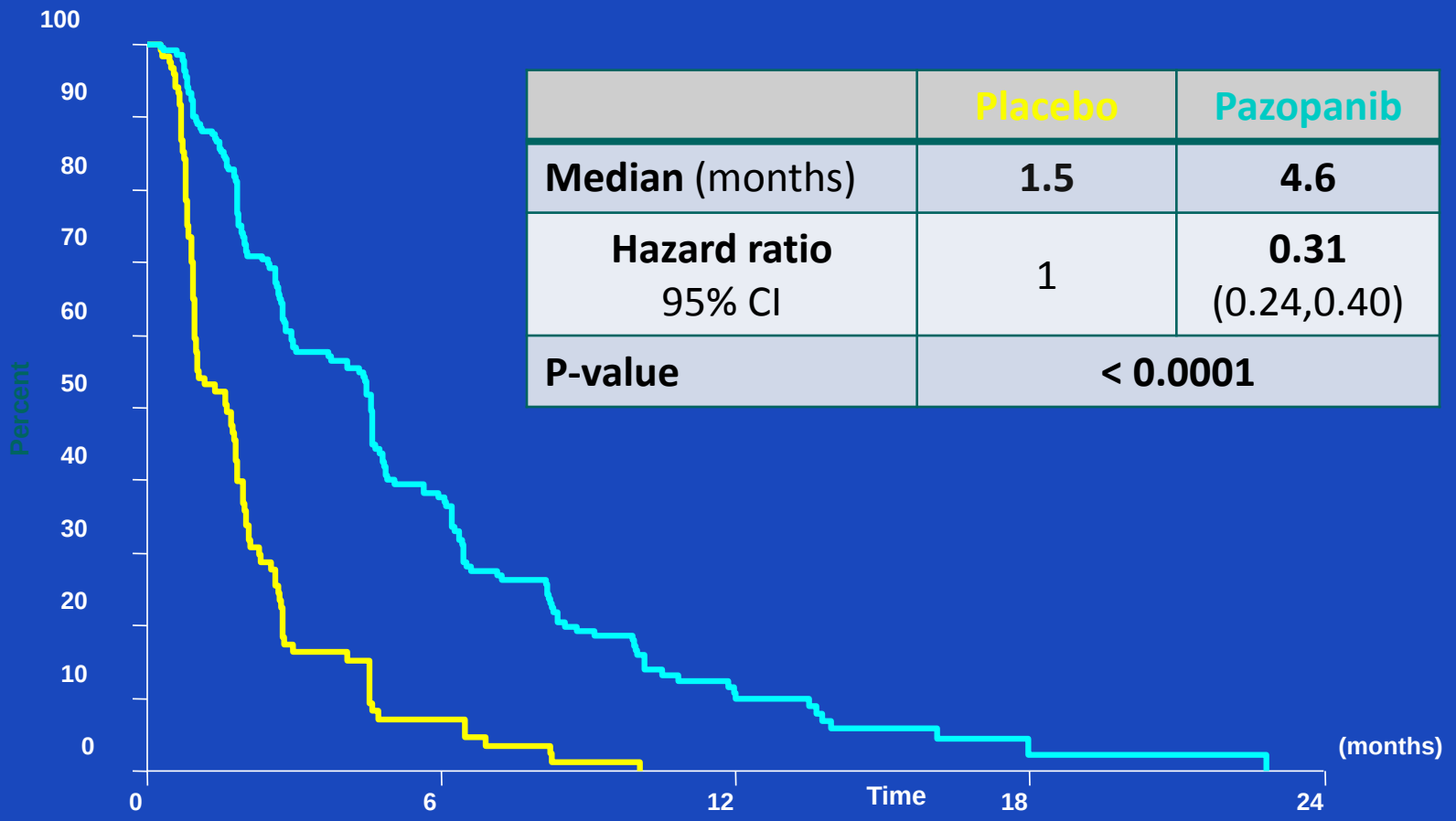
SOFT-TISSUE SARCOMAS

Pazopanib

- All STS histologies except
- Liposarcomas?

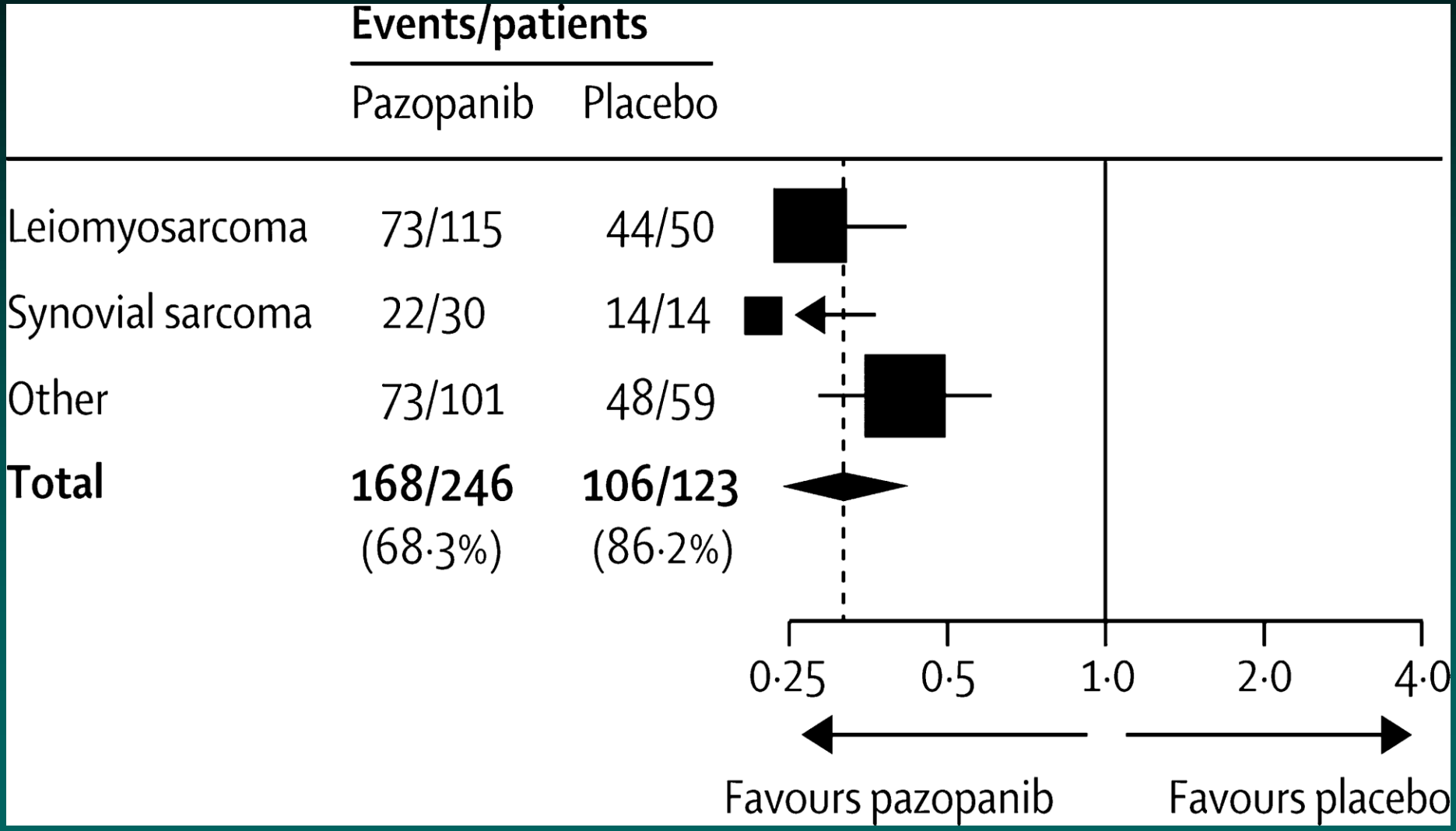
PALETTE

Progression Free Survival



	Placebo	Pazopanib
Median (months)	**1.5**	**4.6**
Hazard ratio 95% CI	1	**0.31** (0.24,0.40)
P-value	**< 0.0001**	

PALETTE
Cox model Predictive analysis - NS



PFS by Histology

Consistent benefit in PFS across all 3 strata

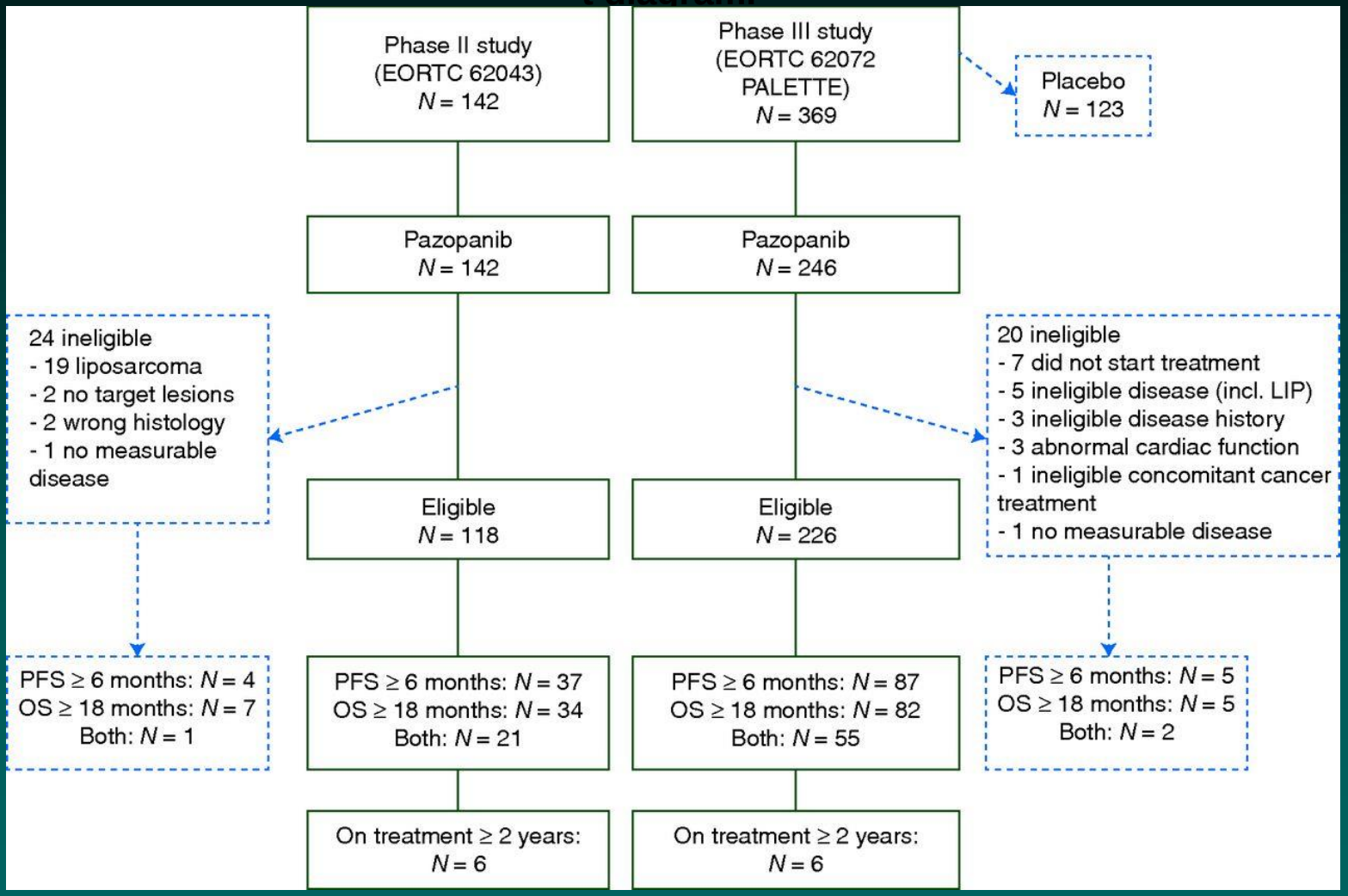
	n (%)	HR	CI	P-value
Overall	**369 (100%)**	**0.31**	**0.24-0.40**	**<0.0001**
Leiomyosarcoma	158 (43%)	**0.31**	**0.20-0.47**	**<0.0001**
Synovial	38 (10%)	**0.19**	**0.23-0.60**	**0.0002**
other STS*	173 (47%)	**0.36**	**0.25-0.52**	**<0.0001**

Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas

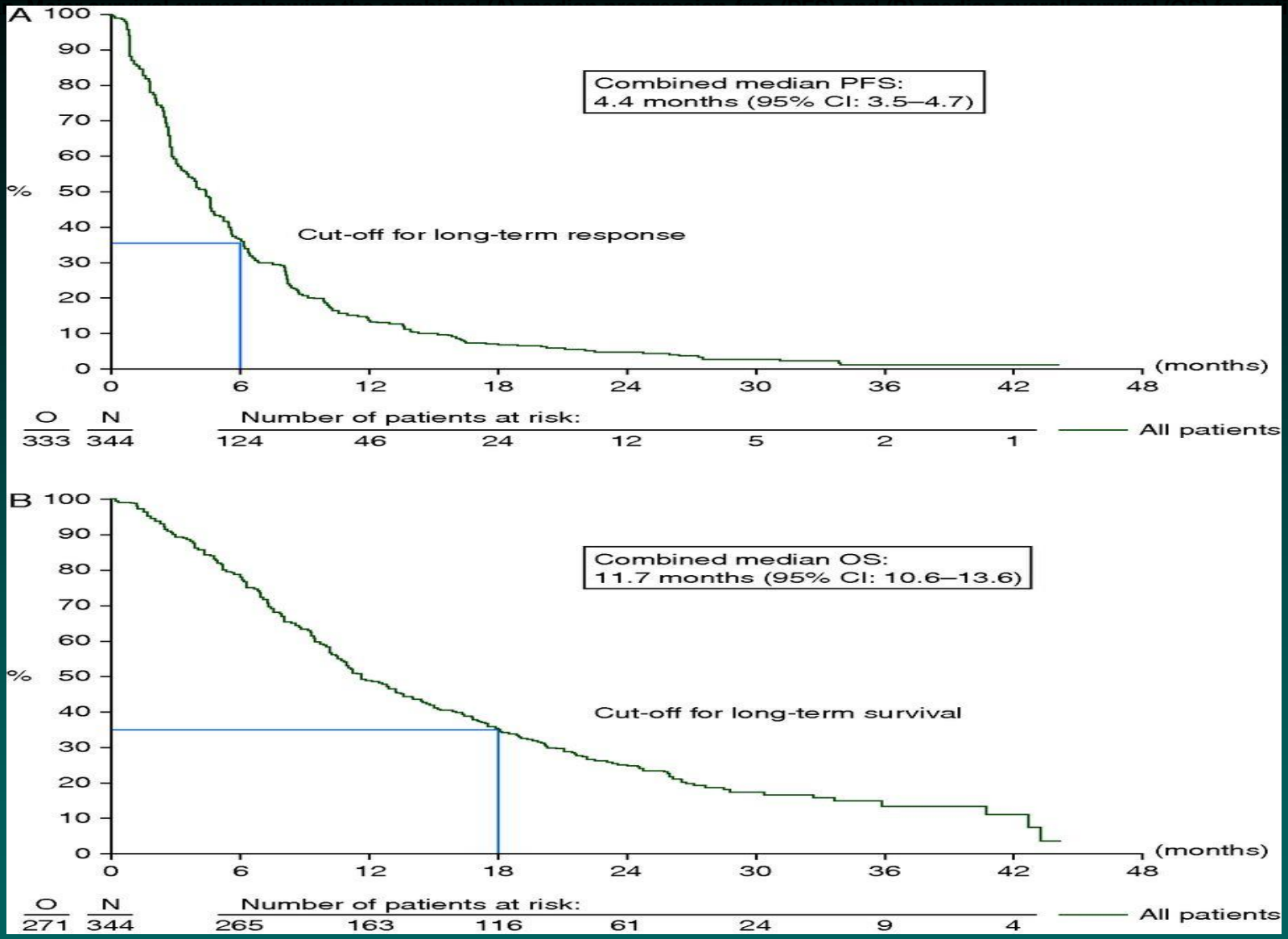
Kasper B Sleijfer S Litière S Marreaud S Verweij J Hodge RA Bauer S Kerst JM van der Graaf WT

Ann Oncol. 2014 Feb 6. [Epub ahead of print]

t diagram.



Annals of Oncology



Kasper B et al. Ann Oncol 2014;annonc.mdt586

Annals of Oncology

Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two EORTC clinical trials 62043 and 62072.

Kasper B, Sleijfer S, Litière S, Marreaud S, Verweij J, Hodge RA, Bauer S, Kerst JM, van der Graaf WT

Ann Oncol. 2014 Feb 6. [Epub ahead of print]

- Patients 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.
- 36%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.
- Median follow-up was 2.3 years.
- Seventy-six patients (22.1%) were both long-term responders and long-term survivors.
- 12 patients (3.5%) remained 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.
- Good performance status, low/intermediate grade of the primary tumor and a normal hemoglobin level at baseline were advantageous for long-term outcome.

SOFT-TISSUE SARCOMAS
CHEMOTHERAPEUTIC AGENTS
Miscellaneous

- DTIC (dacarbazine) for leiomyosarcomas
- Taxanes for angiosarcomas
- Vinca alkaloids/Topotecan / Irinotecan for rhabdomyosarcomas / Ewing sarcoma
- Temozolamide + Bevacizumab for Hemangiopericytoma / Solitary Fibrous Tumor
- Methotrexate + Vinblastine/Vinorelbine for Desmoid tumors

SOFT-TISSUE SARCOMAS
Poor sensitivity to standard therapy

- GIST
- Clear cell sarcoma
- Alveolar soft-part sarcoma
- Hemangiopericytoma/Solitary Fibrous Tumor
- (Sclerosing epithelioid) Fibrosarcomas
- Sarcomatoid mesothelioma -pleural/peritoneal

TARGETED THERAPY FOR SARCOMAS

Few successes

Several failed attempts

Some promises

Need more work

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