Medical Oncology: Latest from ASCO 2015 in Advanced STS

Speaker: Dr Richard Quek
Organization: National Cancer Centre Singapore
Date: Sep 12 2015

General treatment paradigm in Metastatic STS

1st line

- Anthracycline (Ifosfamide)

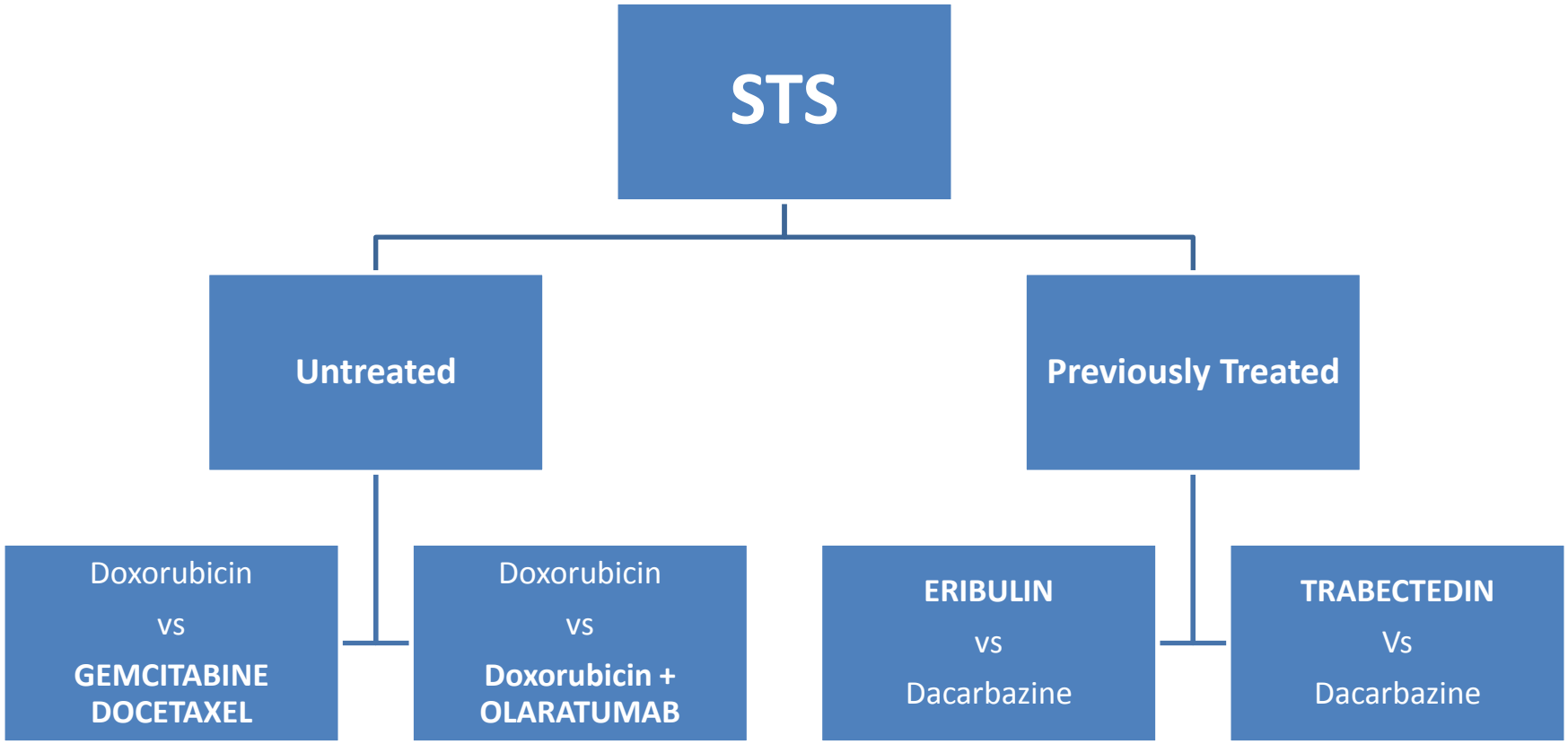
2nd line

- Gemcitabine-Docetaxel
- Pazopanib
- Trabectedin
- Dacarbazine

Post 2nd line

- Off labels
- Clinical Trials

Summary of ASCO 2015



NCRI National Cancer Research Institute

SAKK

GeDDiS

A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcoma

Beatrice Seddon, Jeremy Whelan, Michael Leahy, Penella Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Sharon Forsyth, Paul Patterson, Stephen Nash, Sandy Beare

CANCER RESEARCH UK and UCL Cancer Trials Centre

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Background

- Gemcitabine and docetaxel was shown to be active in an initial phase II study in leiomyosarcoma (Hensley et al, 2002)
- Has been further evaluated since then in retrospective studies and phase II studies in:
  - Leiomyosarcoma
  - Uterine leiomyosarcoma
  - All soft tissue sarcoma types

GeDDiS trial Endpoints

- Primary endpoint:
  - Proportion of patients alive and progression free at 24 weeks after randomization
- Secondary endpoints:
  - Proportion of patients alive and progression free at 12 weeks after randomization
  - Median progression-free survival
  - Overall survival
  - Adverse events (NCI CTCAE v4.03)

Patient inclusion criteria

- Locally advanced or metastatic soft tissue sarcoma
- Histological confirmation of high grade disease (Trojani grade 2 or 3)
- Evidence of disease progression within the previous 6 months
- No prior chemotherapy for sarcoma
- No prior doxorubicin for any previously treated cancer
- WHO performance status 0 – 2
- Age ≥ 13 years
- Measurable disease evaluable by RECIST 1.1
- Life expectancy of at least 3 months
- Adequate organ function

Dose selection

- Phase II study in advanced/metastatic leiomyosarcoma 1st line in 45 patients:
  - Gemcitabine 900 mg/m^2 d1&8, docetaxel 100 mg/m^2 d8
  - Median number of cycles 6 (2 – 8)
    - 13 received 6 cycles, 9 received 8 cycles
  - Commonest adverse events:
    - anemia (95%), fatigue (93%), thrombocytopenia (71%)
  - Grade 3/4 adverse events:
    - fatigue (30%), anemia (24%), dyspnea (16%)
  - 8 (18%) patients stopped early due to toxicity
- **Decision to reduce doses by 25% for phase III study**

Seddon et al Clin Sarcoma Res 2015, 16;5:13

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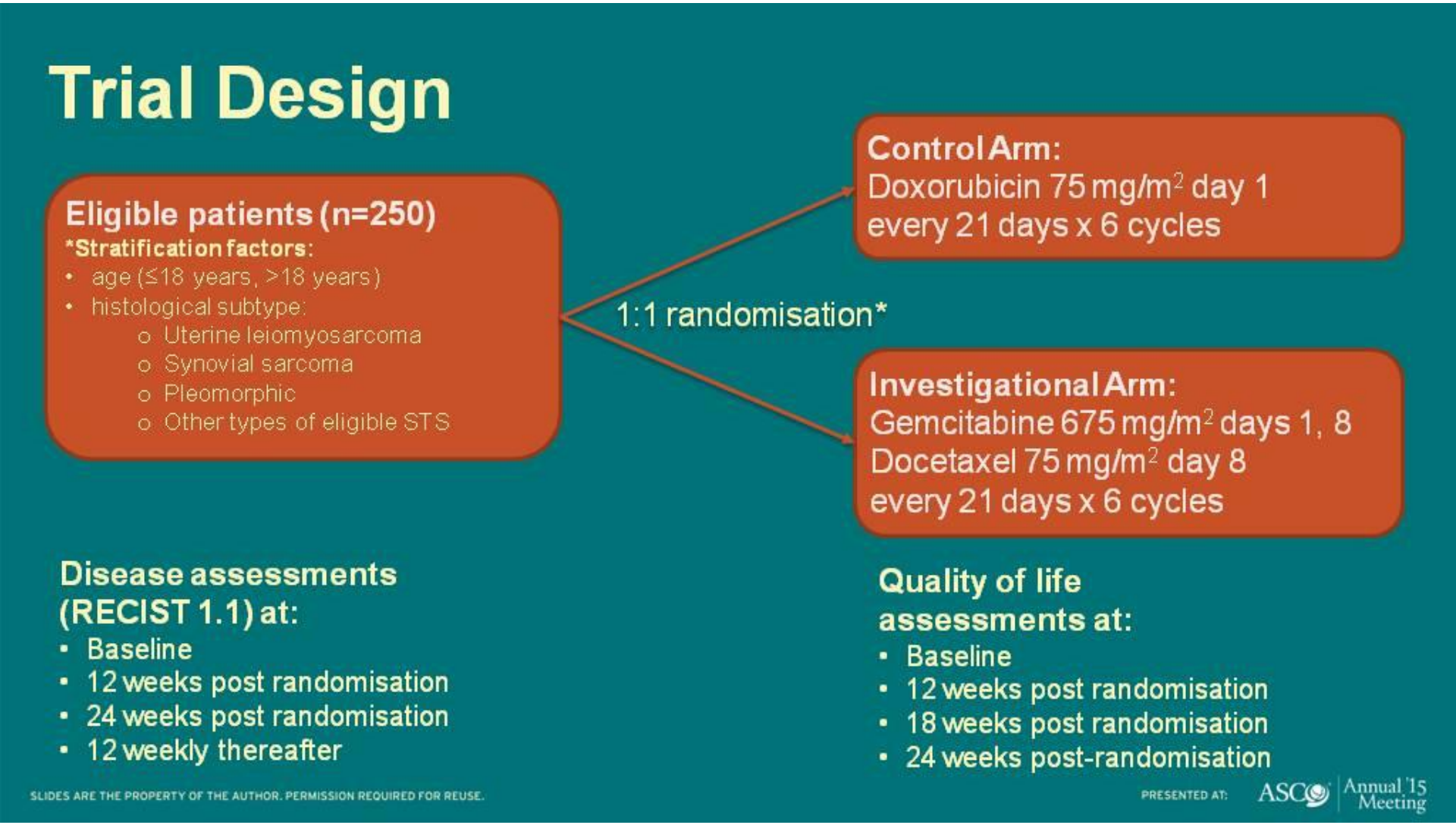

Total 257 randomized

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Patient characteristics

		Dox (N=129) N (%)	GemDoc (N=128) N (%)
Sex	Male	50 (38.8)	51 (39.8)
	Female	79 (61.2)	77 (60.2)
Age (yrs)	median (range)	56 (18.7-82.2)	55 (21.1-75.4)
Weight (Kg)	median (range)	77.0 (42.7-159.0)	77.7 (43.6-130.0)
WHO PS	0	55 (42.6)	52 (40.6)
	1	63 (48.8)	67 (52.3)
	2	11 (8.5)	9 (7.0)
Histology	Uterine leiomyosarcoma	36 (27.9)	35 (27.3)
	Synovial sarcoma	5 (3.9)	6 (4.7)
	Pleomorphic sarcoma	16 (12.4)	16 (12.5)
	Other eligible sarcomas	72 (55.8)	71 (55.5)

Compliance to trial treatment

Reason	Dox (N=129)	GemDoc (N=128)
Total withdrawals during treatment	60 (47%)	80 (63%)
Disease progression	34 (57%)	39 (49%)
Symptomatic deterioration	4 (7%)	3 (4%)
Unacceptable toxicity	1 (2%)	13 (16%)
Serious adverse event	2 (3%)	2 (3%)
Death	5 (8%)	4 (5%)
Other	14 (23%)	19 (11%)

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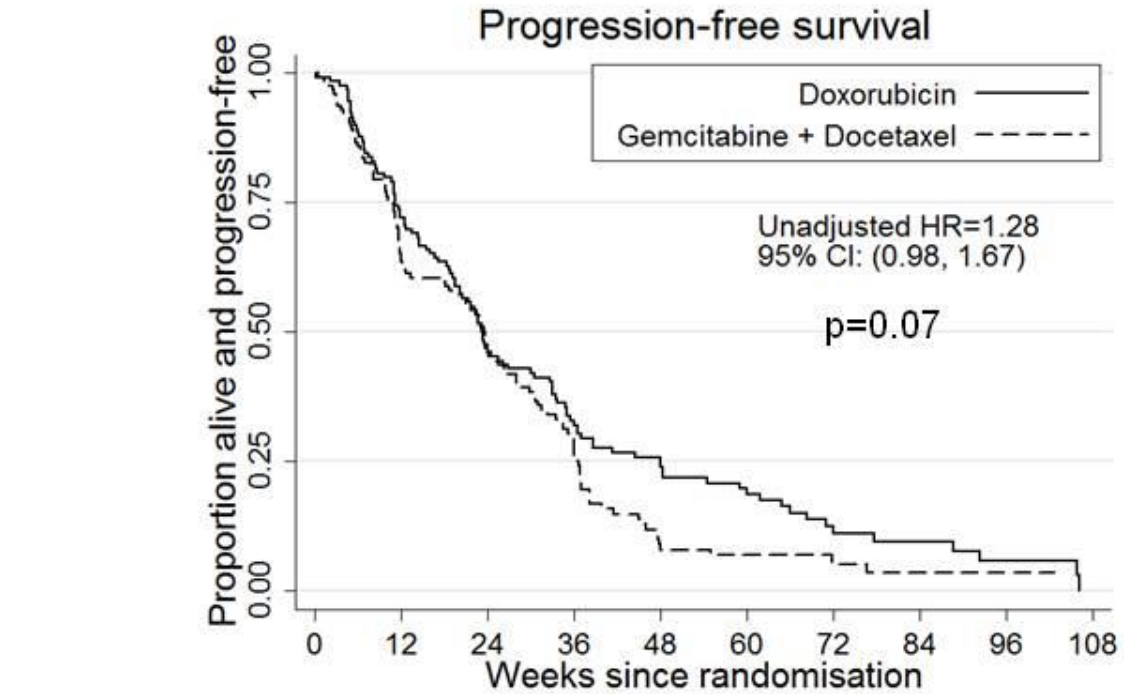
Progression-free survival



	Median PFS (months)	24 week PFS
Dox	5.4	46.1%
GemDoc	5.5	46.0%

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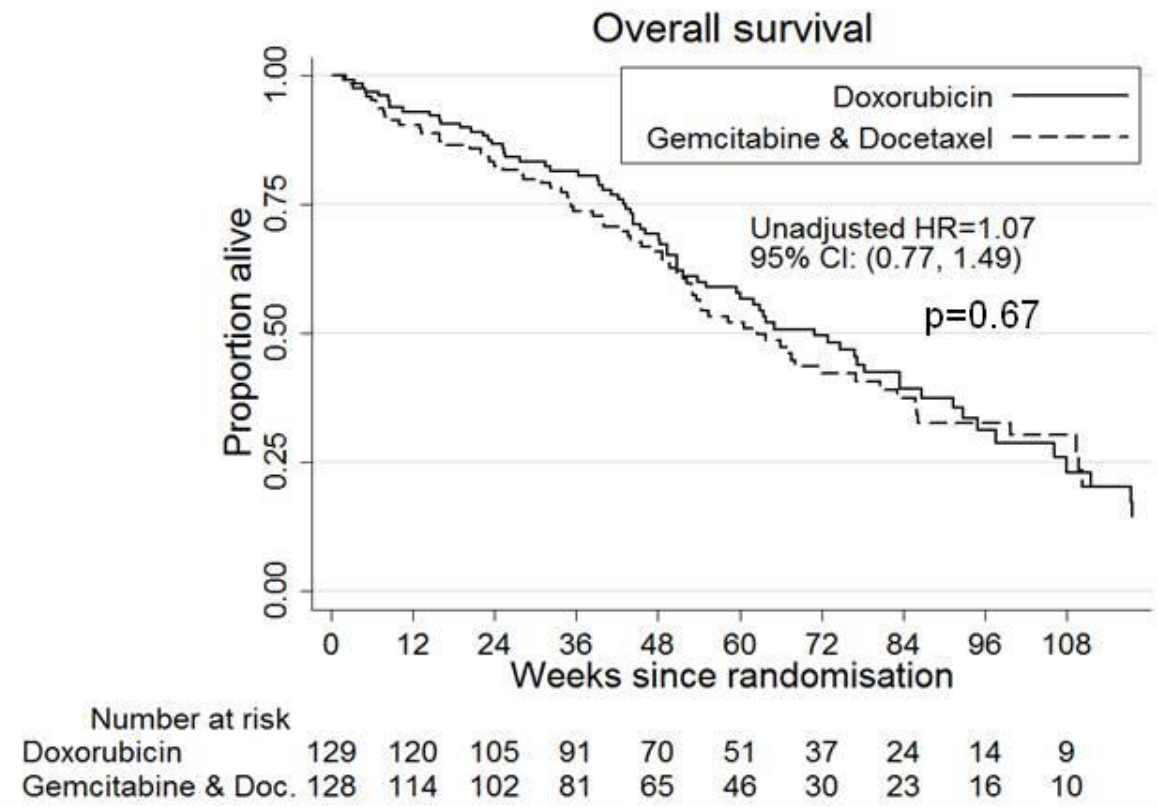
Overall survival



	Median OS (mths)	24 week OS
Dox	16.4	86.7%
GemDoc	14.5	82.5%

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Conclusions

- Doxorubicin should remain standard of care for first line treatment for metastatic/locally advanced soft tissue sarcoma
- It has not been possible to identify any subgroup for which gemcitabine and docetaxel is superior in the first line setting

A Randomized Phase 1b/2 Study Evaluating the Safety and Efficacy of Olaratumab (IMC-3G3), a Human Anti–platelet-derived Growth Factor α (PDGFRα) Monoclonal Antibody, with or without Doxorubicin (Dox), in Advanced Soft Tissue Sarcoma (STS)

William D. Tap*

Robin L. Jones, Bartosz Chmielowski, Anthony D. Elias, Douglas Adkins, Brian A. Van Tine, Mark Agulnik, Matthew Cooney, Michael B. Livingston, Gregory Pennock, Amy Qin, Ashwin Shahir, Robert Ilaria Jr, Ilaria Conti, Jan Cosaert, Gary K. Schwartz

**Presenting Author*

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PDGFRα Implicated Role in Cancer

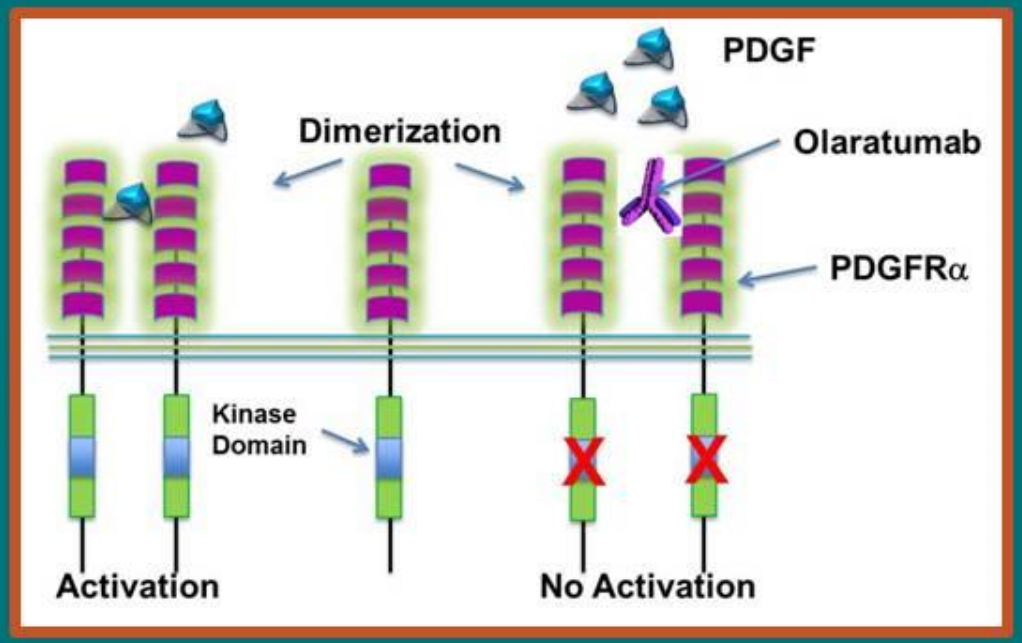
Direct Tumor and Direct Stromal Effect

- PDGFRα is genetically altered and/or overexpressed in multiple tumor types including certain sarcomas.[1-5]
- PDGFRα expression is associated with increased metastatic potential.[5,6]
- PDGFRα signaling on tumor stromal cells can enhance tumor growth and contribute to angiogenesis.[7,8]
- PDGFRα functions via autocrine and paracrine growth of tumor cells.[9,10]

[1]Carvalho et al. *Breast Cancer Res* 2005;7(5):R788-95; [2]Ramos et al. *Cancer Biol Ther* 2009;8(21):2042-50; [3]Corless et al. *J Clin Oncol* 2005;23(23):5357-64; [4]Cancer Genome Atlas Network. *Nature* 2008;455(7216):1061-8; [5]Dolloff et al. *Oncogene* 2005 Oct 13;24(45):6848-54; [6]Fitzer-Attas et al. *Oncogene* 1997;15(13):1545-54; [7]Dong et al. *EMBO J* 2004;23(14):2800-10; [8]Skobe and Fusenig. *Proc Natl Acad Sci USA* 1998;95(3):1050-5; [9]LaRochelle et al. *Cell Growth Differ* 1993;4(7):547-53; [10]Keating and Williams. *Science* 1988;239(4842):914-16;

Olaratumab

- Fully human monoclonal antibody of immunoglobulin G class 1 (IgG1) that selectively binds PDGFRα[1]
- Blocks PDGF binding and PDGF-induced PDGFRα activation[1]
- Demonstrated activity in both in vitro and in vivo cancer models known to be driven by a PDGF-PDGFRα autocrine loop[2,3]
- Demonstrated antitumor activity alone[1] or in combination with Dox in human sarcoma xenograft models[4]



[1]Loizos et al. *Mol Cancer Ther* 2005;4(3):369-79 ; [2] Gerber et al. *Mol Cancer Ther* 2012;11(11):2473-82; [3,4]Data on file, Eli Lilly and Company

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Open-label, Multicenter, Phase 1b/2 Trial

Phase 2

- Same entry criteria as Phase 1b
- Stratification:
  - PDGFRα (IHC)
  - Lines of prior treatment
  - ECOG PS
  - Histology (leiomyosarcoma, synovial sarcoma, other)

RANDOMIZE

Olaratumab 15 mg/kg D1,8 + Dox 75 mg/m^2 D1 × 8 cycles (21 days)* → Olaratumab monotherapy until progression

Dox 75 mg/m^2 D1 × 8 cycles → Optional olaratumab monotherapy after progression

Primary endpoint: Progression-free survival (PFS) (predefined statistical significance: 2-sided alpha = 0.2)

Secondary end points: Overall survival (OS), objective response rate, PFS at 3 months

Biomarker: PDGFRα (IHC) and related ligands

* During Cycles 5-8, patients receiving Dox could receive dexrazoxane, at the investigator's discretion.

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Statistical Assumptions (Phase 2)

- Planned sample size: 130 patients
- Assumed 50% improvement in PFS for olaratumab + Dox group over Dox alone (hazard ratio [HR], 0.67) and 80% statistical power using 2-sided significance level of 0.2
- Analysis populations
  - Intention to treat (ITT) (ie, patients who underwent randomization) (n=133)
  - Safety (ie, patients who received at least 1 dose of study treatment) (n=129)
- Log-rank test was stratified by histology and lines of previous treatment

Safety Overview (Phase 2)

	Olaratumab + Dox (N=64)		Dox (N=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Adverse event, no. pts (%)	63 (98)	49 (77)	64 (99)	43 (66)
Treatment-related adverse event	62 (97)	41 (64)	63 (97)	35 (54)
Serious adverse event, no. pts (%)	27 (42)	27 (42)	25 (39)	22 (34)
Treatment-related serious adverse event	14 (22)	14 (22)	17 (26)	16 (25)
Adverse event leading to discontinuation of any study drug, no. pts (%)	8 (13) [4 SAEs]		14 (22) [8 SAEs]	

- All drugs were reasonably well tolerated

Cardiac Adverse Events and Changes in Function (Phase 2)

- Overall incidence of any cardiac adverse event
  - 14.1% (olaratumab + Dox) vs 9.2% (Dox)
- Ejection fraction decreased
  - 4.7% (olaratumab + Dox) vs 6.2% (Dox)
- Changes in LVEF function
  - LVEF <50% at any time during study*
    - 11.8% (olaratumab + Dox) vs 9.4% (Dox)

Median cumulative Dox dose:
- 525 mg/m^2 (olaratumab + Dox)
- 300 mg/m^2 (Dox)

*Of patients with a baseline assessment and at least 1 post-baseline assessment

AE = adverse event; LVEF = left ventricular ejection fraction

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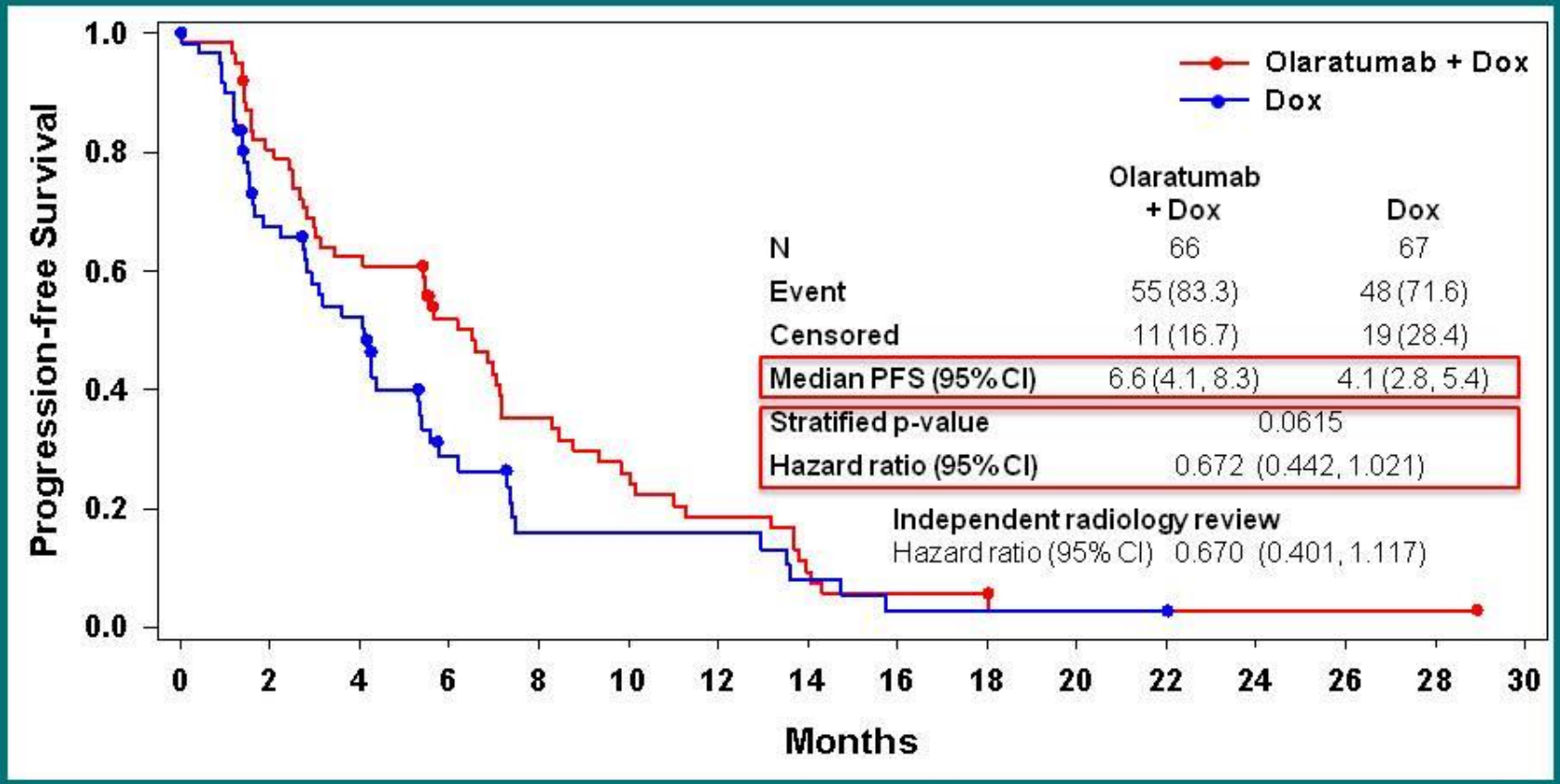
Overall Tumor Response (ITT) (Phase 2)

	Olaratumab + Dox (N=66)	Dox (N=67)
Objective response rate (CR + PR)		
% (95% CI)	18.2 (9.8, 29.6)	11.9 (5.3, 22.2)
p-value	0.34*	

* 2-sided Fisher's exact test

Progression-Free Survival (ITT) (Phase 2)



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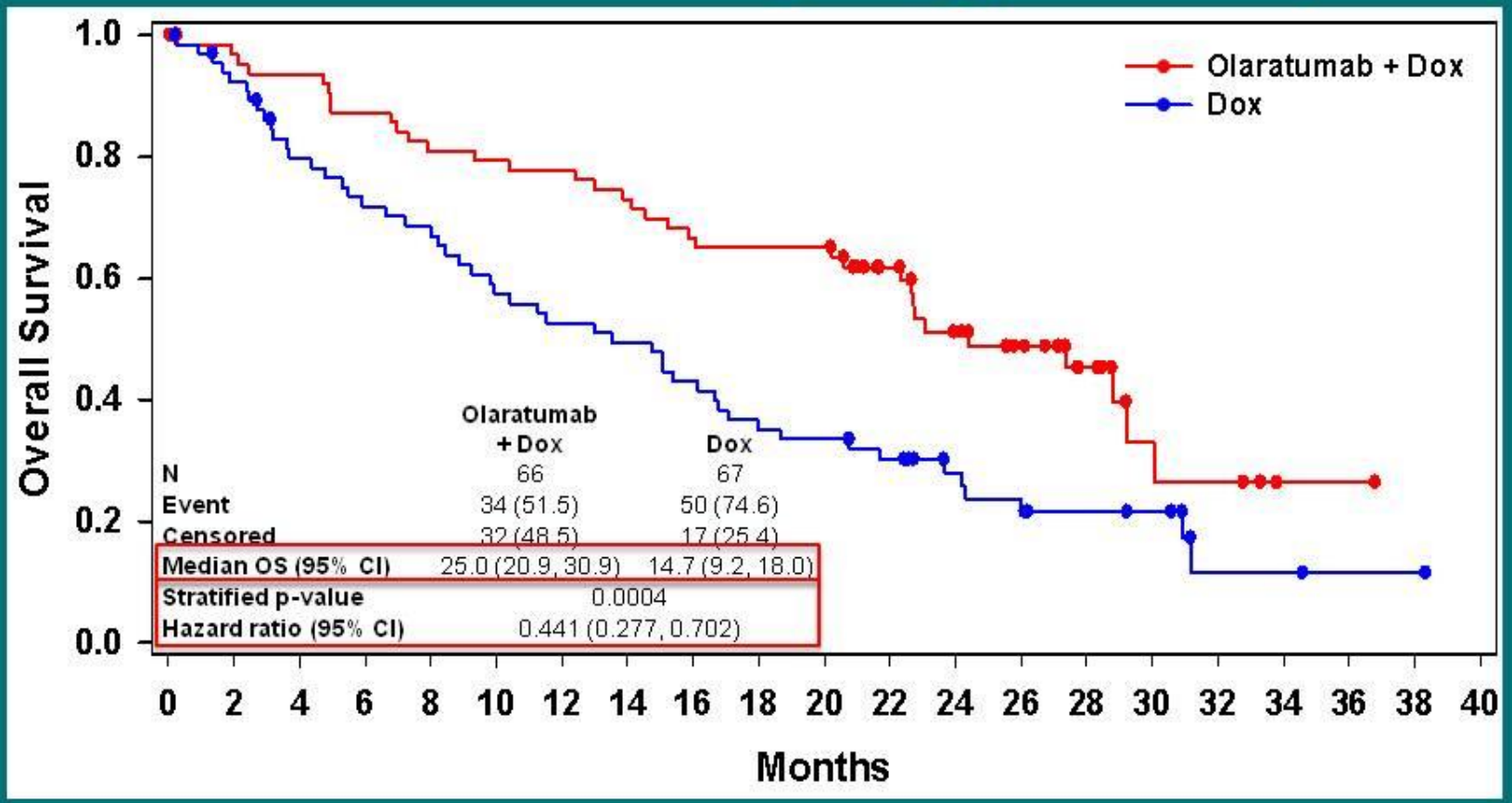
Overall Survival (ITT) (Phase 2)



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Subsequent Treatments

Post-treatment regimens, no. pts (%)	Olaratumab + Dox (N=66)	Dox* (N=67)
1	18 (27.3)	19 (28.4)
2	11 (16.7)	14 (20.9)
3	8 (12.1)	6 (9.0)
4	1 (1.5)	2 (3.0)
>4	4 (6.1)	4 (6.0)

Treatment type, no pts. (%)	Olaratumab + Dox (N=66)	Dox (N=67)
Any treatment	42 (63.6)	45 (67.2)
Gemcitabine/docetaxel	12 (18.2)	8 (11.9)
Ifosfamide	8 (12.1)	8 (11.9)
Pazopanib	14 (21.2)	10 (14.9)

*In the Dox arm, patients who were on olaratumab monotherapy were counted as receiving additional anticancer treatment.

Conclusions

- This study met its predefined, statistical primary endpoint for PFS.
- Olaratumab added to Dox achieved a statistically significant improvement of 10.3 months in median OS over Dox alone (p=0.0004) without an increase in serious toxicity.
- Despite higher cumulative Dox exposure, the olaratumab + Dox combination had an acceptable and monitorable safety profile including cardiac safety.
- Based on these data, olaratumab has received Breakthrough Therapy Designation from the FDA, and a phase 3 study is planned.

Randomized, open-label, multicenter, phase 3 study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI)

Patrick Schöffski, MD, MPH
Department of General Medical Oncology
University Hospitals Leuven, Leuven Cancer Institute
KU Leuven, Leuven, Belgium

Abstract # LBA10502 submitted by **P Schöffski**, R Maki, A Italiano, H Gelderblom, E Choy, G Grignani, V Camargo, S Bauer, SY Rha, S Chawla, JY Blay, P Hohenberger, DR D'Adamo, B Wang, B Chmielowski, A LeCesne, GD Demetri, and S Patel.
Clinicaltrials.gov identifier: NCT01327885.

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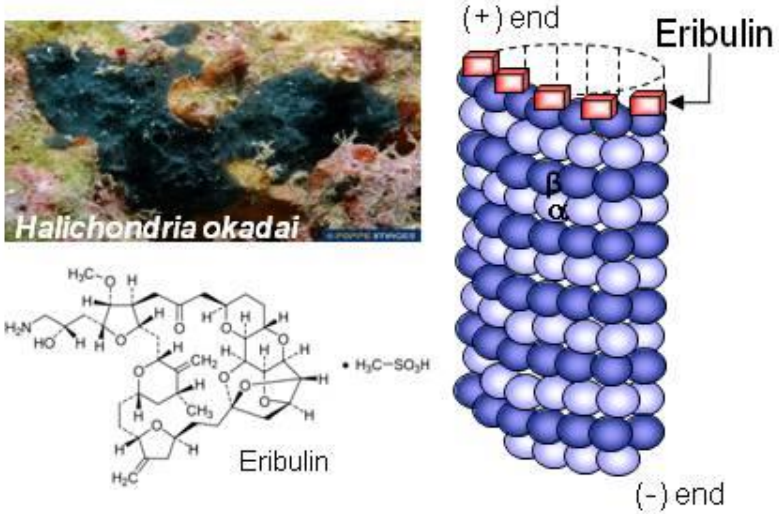
Eribulin: a novel microtubule dynamics inhibitor

- Eribulin is a fully synthetic, optimized analog of the marine sponge natural product halichondrin B[1]
- Approved in 59 countries as third- (USA), second- (EU), or first-line (Japan) monotherapy for patients with advanced/metastatic breast cancer[4,5]
- In preclinical models:
  - Eribulin primarily has antimitotic effects based on a novel mode of inhibiting microtubule dynamics[1,2]
  - Eribulin also exerts other complex effects on tumor biology, including vascular remodeling, reversal of epithelial-mesenchymal transition, and suppression of migration and invasion[6,7]

Eribulin has a distinct mode of action[2,3]

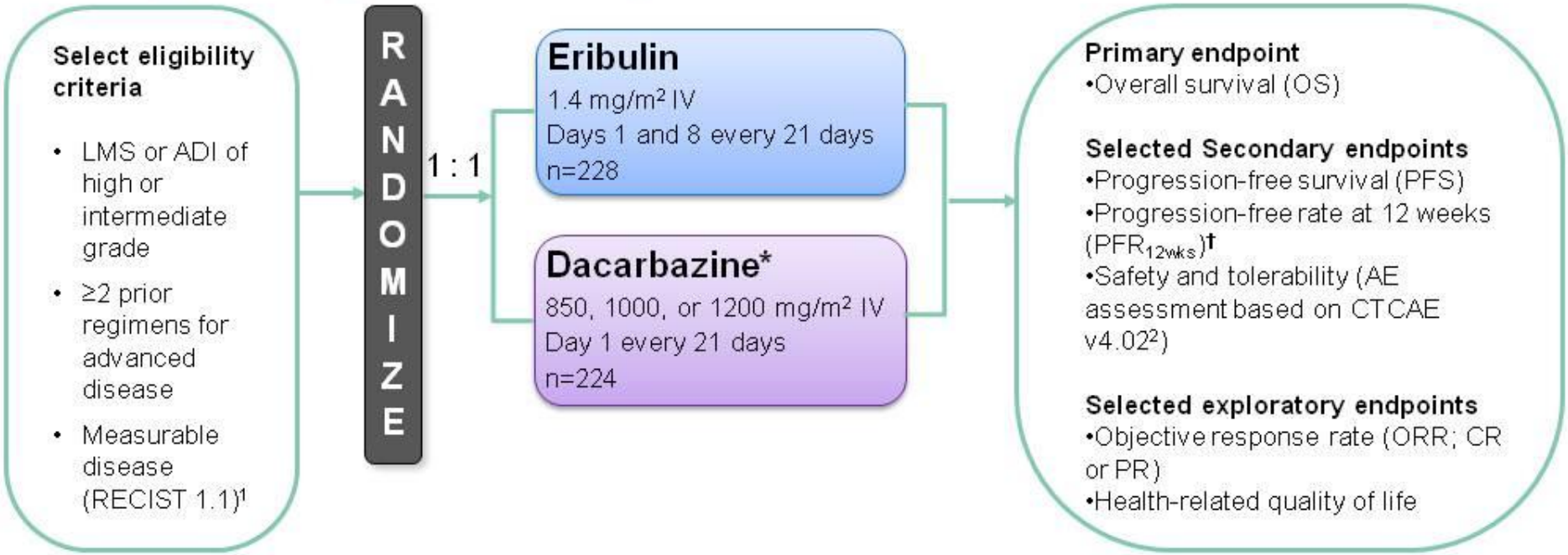


Eribulin binds specifically to (+) ends of microtubules, inhibiting only the growth phase of microtubule dynamics[2,3]

EU, European Union; USA, United States of America.

1. Towle et al. *Cancer Res* 2001; 2. Jordan et al. *Mol Cancer Ther* 2005; 3. Smith et al. *Biochemistry* 2010; 4. Halaven EPAR; 5. Halaven prescribing information; 6. Funahashi et al. *Cancer Sci* 2014; 7. Yoshida et al. *Br J Cancer* 2014. *Halichondria okadai* image (*top left*) © 2015 – Reproduced with the kind permission of G. & P. Poppe; microtubule image (*right*) adapted, with permission, from Macmillan Publishers Ltd: *Nat Rev Cancer* 2004;4:253–65, ©2004.

Study design and objectives

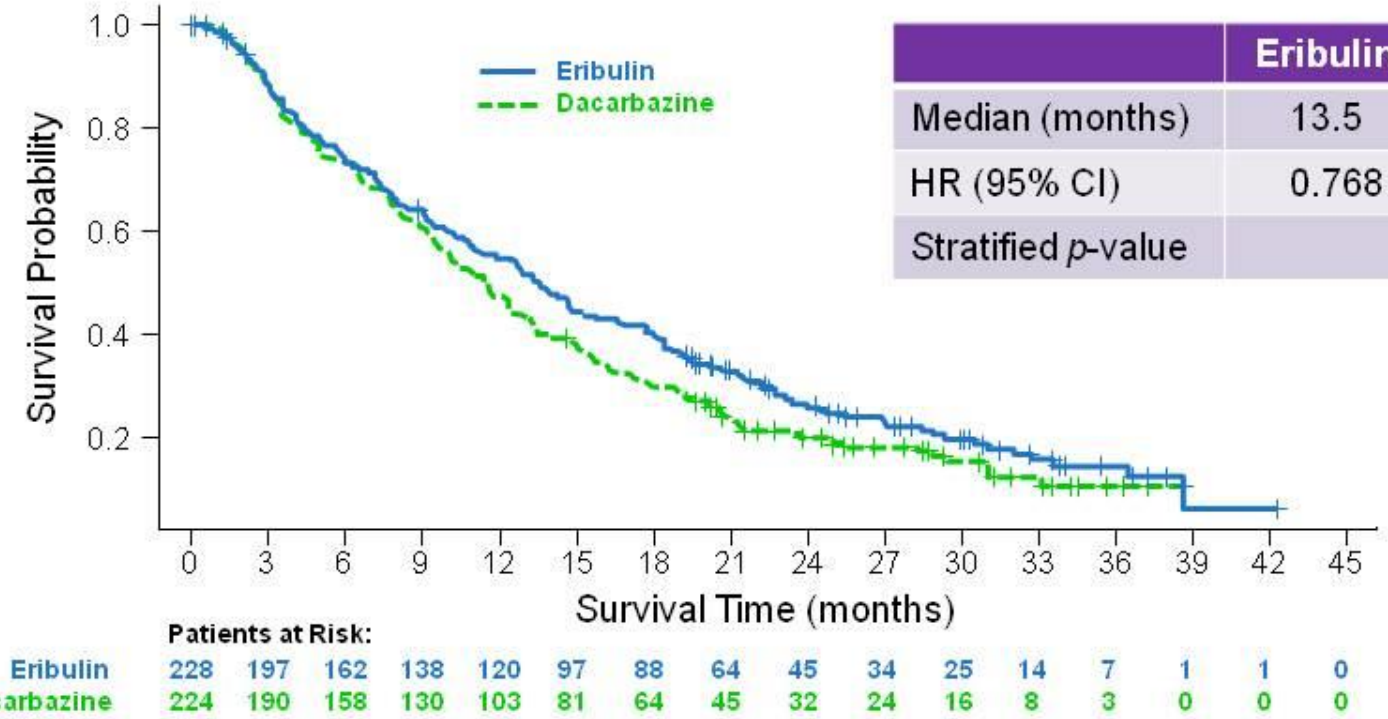


*Starting dose selected by the local investigator at study initiation; †PFR_{12wks}, proportion of patients who were still alive without disease progression at 12 weeks from randomization.

CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Eisenhauer et al. *Eur J Cancer* 2009; 2. CTCAE v4.02 available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf; accessed May 6, 2015.

Primary endpoint: OS



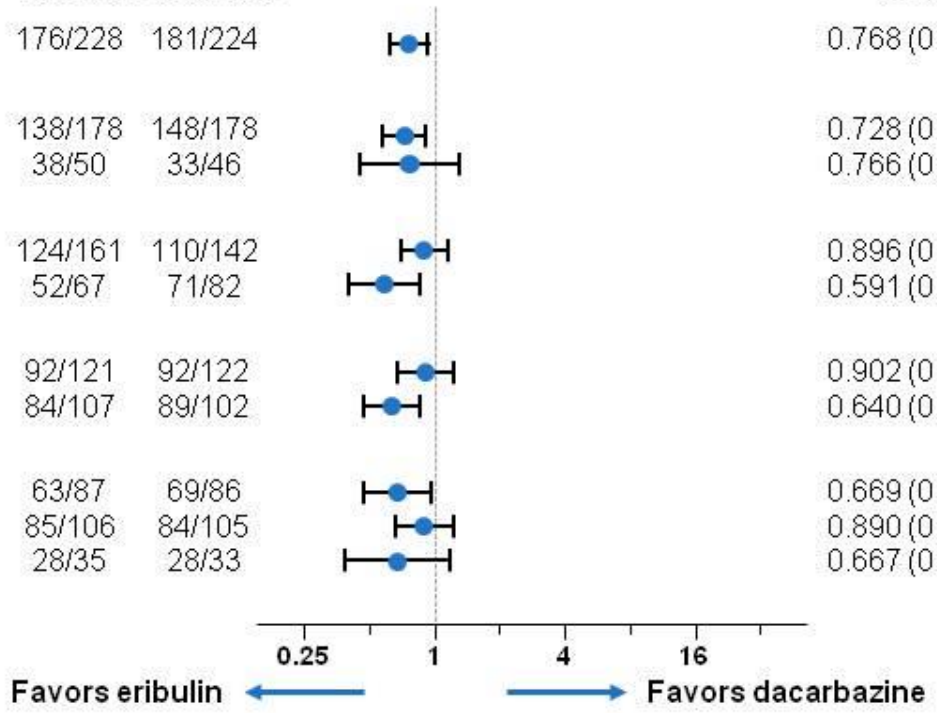
	Eribulin	Dacarbazine
Median (months)	13.5	11.5
HR (95% CI)	0.768 (0.618, 0.954)	
Stratified *p*-value	0.0169	

- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

CI, confidence interval.

Preplanned OS subgroups analysis

Group/Subgroup	Events/n — Eribulin	Events/n — Dacarbazine	HR (95% CI)	Median (months) — Eribulin	Median (months) — Dacarbazine
Overall	176/228	181/224	0.768 (0.618, 0.954)	13.5	11.5
Age group (years)					
<65	138/178	148/178	0.728 (0.569, 0.931)	13.5	11.3
≥65	38/50	33/46	0.766 (0.445, 1.319)	13.5	13.2
Sex					
Female	124/161	110/142	0.896 (0.682, 1.175)	13.2	12.3
Male	52/67	71/82	0.591 (0.402, 0.868)	14.7	9.6
Prior regimens for advanced STS					
2	92/121	92/122	0.902 (0.671, 1.214)	13.9	12.3
>2	84/107	89/102	0.640 (0.466, 0.879)	13.2	10.1
Stratification region*					
Region 1	63/87	69/86	0.669 (0.466, 0.958)	15.3	11.5
Region 2	85/106	84/105	0.890 (0.653, 1.214)	13.3	11.5
Region 3	28/35	28/33	0.667 (0.380, 1.171)	11.4	9.7



*Region 1: USA, Canada; Region 2: Western Europe, Australasia, Israel; Region 3: Eastern Europe, Latin America, Asia.

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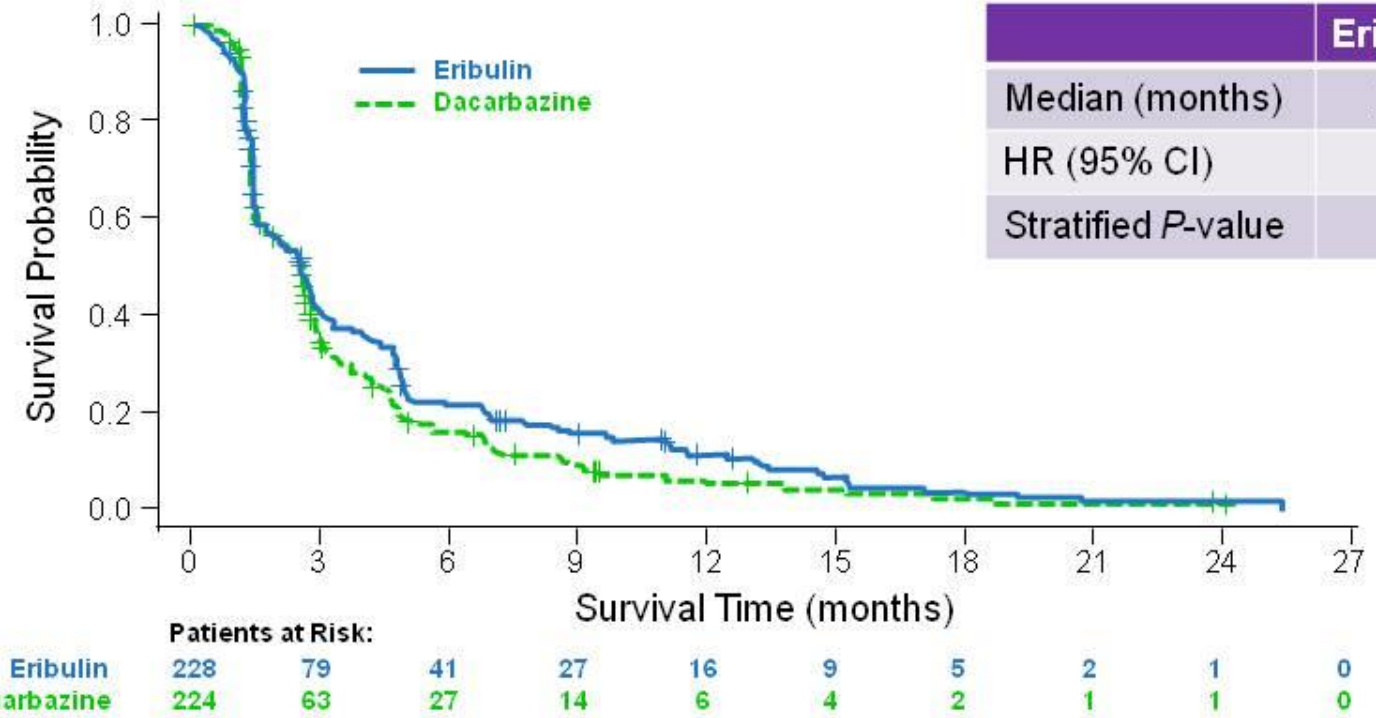
Secondary endpoint: PFS



	Eribulin	Dacarbazine
Median (months)	2.6	2.6
HR (95% CI)	0.877 (0.710, 1.085)	
Stratified *P*-value	0.2287	

Additional efficacy endpoints

	Eribulin (n=228)	Dacarbazine (n=224)
PFR_{12wks}, % (n) [95% CI*]	33.3% (76) [27.2, 39.9]	28.6% (64) [22.8, 35.0]
OR (95% CI); *P*-value†	1.3 (0.8, 1.9); 0.253	
ORR; % (n)	3.9 (9)	4.9 (11)

Best overall response	Eribulin (n=228) % (n)	Dacarbazine (n=224) % (n)
CR	0	0
PR	3.9 (9)	4.9 (11)
SD	52.2 (119)	47.8 (107)
PD	39.0 (89)	39.3 (88)
NE/Unknown	4.8 (11)	8.0 (18)

Tumor assessments are based on RECIST 1.1.[1]
*95% CI was calculated using exact method of binomial distribution; †*P*-value and odds ratio were calculated using the stratified Cochran-Mantel-Haenszel method.
NE, not evaluable; OR, odds ratio; SD, stable disease.
1. Eisenhauer et al. *Eur J Cancer* 2009.

Summary of AEs, based on CTCAE v4.02[1]

	Eribulin (n=226) % (n)	Dacarbazine (n=224) % (n)
Patients with any AEs	99.1 (224)	97.3 (218)
Treatment-related AEs*	92.9 (210)	90.6 (203)
AEs with maximum CTCAE grade ≥3	67.3 (152)	56.3 (126)
3	38.9 (88)	35.7 (80)
4	23.9 (54)	19.2 (43)
5	4.4 (10)	1.3 (3)
AEs leading to study drug		
Withdrawal	7.5 (17)	4.9 (11)
Dose reduction	25.7 (58)	14.3 (32)
Dose interruption	32.7 (74)	32.1 (72)

*Per investigator assessment

1. CTCAE v4.02 available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf; accessed May 6, 2015.

Most common post-study therapies

Post-study systemic therapies	Eribulin (n=228) n (%)	Dacarbazine (n=224) n (%)
Any	158 (69.3)	141 (62.9)
Dacarbazine	78 (34.2)	17 (7.6)
Doxorubicin	26 (11.4)	16 (7.1)
Gemcitabine	48 (21.1)	47 (21.0)
Ifosfamide	27 (11.8)	22 (9.8)
Pazopanib	58 (25.4)	62 (27.7)
Trabectedin	36 (15.8)	27 (12.1)
Eribulin	3 (1.3)	6 (2.7)

- Administration of post-study therapies (including surgery and radiotherapy) was comparable between the 2 arms, except for the higher number of patients in the eribulin arm who received post-study dacarbazine

Summary and conclusions

- This is the first phase 3 trial in STS to demonstrate an OS benefit compared with an active agent in patients with intermediate- and high-grade LMS and ADI:
  - Patients treated with eribulin experienced a statistically significant improvement in median OS compared with dacarbazine (13.5 vs 11.5 months; HR 0.768; 95% CI 0.618–0.954; *P*=0.0169)
- AEs were in line with the known safety profiles of both agents
- This is a clinically meaningful result given the unmet need in this rare, hard-to-treat family of diseases

A Randomized Phase 3 Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma (LPS) or Leiomyosarcoma (LMS)

George D. Demetri, Margaret von Mehren, Robin Lewis Jones, Martee Leigh Hensley, Scott Schuetze, Arthur P. Staddon, Mohammed M. Milhem, Anthony D. Elias, Kristen N. Ganjoo, Hussein Abdul-Hassan Tawbi, Brian Andrew Van Tine, Alexander I. Spira, Andrew Peter Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland E. Knoblauch, Trilok V. Parekh, Robert G. Maki, Shreyaskumar Patel

Dana-Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Seattle Cancer Care Alliance, Seattle, WA; Memorial Sloan Kettering Cancer Center, New York, NY; University of Michigan, Ann Arbor, MI; University of Pennsylvania, Philadelphia, PA; University of Iowa Hospitals and Clinics, Iowa City, IA; University of Colorado Cancer Center, Aurora, CO; Stanford Univ, Stanford, CA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Washington University in St Louis, St Louis, MO; Virginia Cancer Specialists, Fairfax, VA; St. John of God Hospital Subiaco, Subiaco, Australia; Janssen Pharmaceuticals, Raritan, NJ; Janssen Research &Development, LLC, Raritan, NJ; Mount Sinai School of Medicine, New York, NY; MD Anderson Cancer Center, Houston, TX

PRESENTED AT: ASCO Annual '15 Meeting

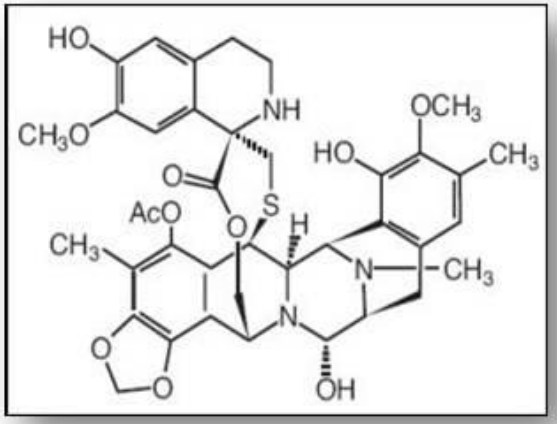
Presented By George Demetri at 2015 ASCO Annual Meeting

Background

Trabectedin has a unique mechanism of action

IMPACTS DNA BINDING and REPAIR:

- ✓ Distorts the DNA structure resulting in the initiation of repair mechanisms
- ✓ Binds and inhibits repair mechanisms thereby activating apoptosis



INHIBITS TRANSCRIPTION:

- ✓ Inhibits activated transcription
- ✓ Induces the specific degradation of RNA Pol II
- ✓ Detachment of fusion chimeras from their target promoters

MODIFIES TUMOR MICROENVIRONMENT:

- ✓ Decreased IL-6 and CCL2 production
- ✓ Decreased macrophage and monocyte recruitment
- ✓ Decreased angiogenesis

D'Incalci and Galmarini *Mol Cancer Therapeutics* 2010 9(8): 2157-63

Historical Overview of Trabectedin Clinical Trial Experience

		N	Progression-Free Rate @ 3 months	Progression-Free Rate @ 6 months	Median PFS	Max # Cycles
EORTC Historical Thresholds[1]	*Active*	*146*	*39%*	*14%*	NA	
	Inactive	*234*	*21%*	*8%*	NA	
Le Cesne A et al[2]	Group A	44	46%	18%	2.6 M	15
	Group B	55	50%	24%	2.9 M	18
Yovine A et al[3]	Group 1	26	38%	23%	1.8 M	10
	Group 2	28	39%	25%	1.9 M	20
Garcia-Carbonero R, et al.[4]		36	31%	14%	1.7 M	21
Demetri G, et al. [5]		136	53%	37%	3.3 M	37

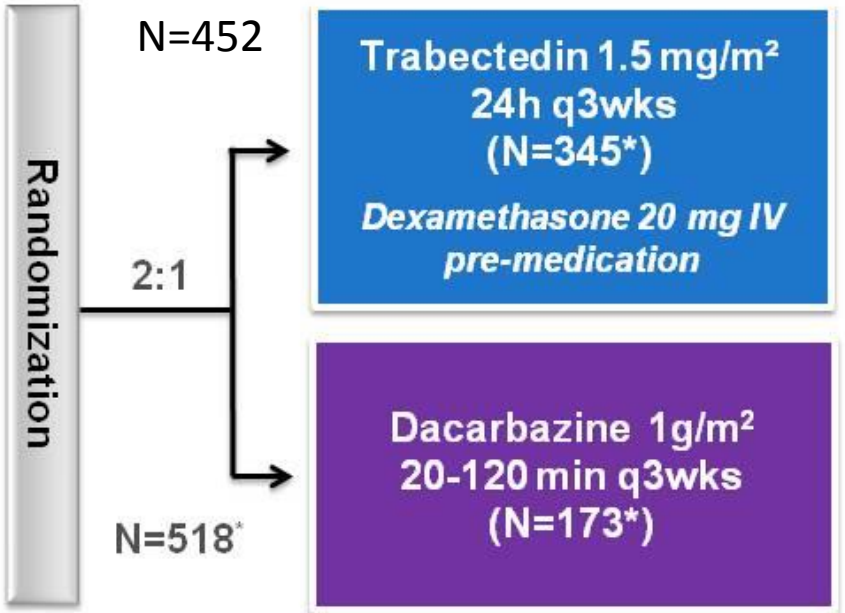
- Samuels et al.[6] : Expanded Access Plan (SAR 3002) (N=1803)
  Clinical Benefit Rate = 54% in Leiomyosarcoma and Liposarcoma patients

[1] Van Glabbeke et al *Eur J Cancer*. 2002;28:543-549.
[2] Le Cesne et al., *J Clinic Oncol*. 2005 23(3):576-584
[3] Yovine A, et al. *J Clinic Oncol*. 2004;22(5):890-899.
[4] Garcia-Carbonero R, et al. *J Clinic Oncol*. 2004;22(8):1480-1490.
[5] Demetri G, et al. *J Clinic Oncol*. 2009;27(25):4188-4196.
[6] Samuels et al . *Annals of Oncol*. 2013; 24(6):1703-1709

Randomized Phase 3 Study of Trabectedin vs Dacarbazine
(ET743-SAR-3007): Study Design and Status at Interim Analysis

Stratification:
- Prior lines chemotherapy (1 vs 2+)
- ECOG PS (0 vs 1)
- Sarcoma subtype (LPS vs LMS)

Key Criteria:
- Histologically proven LPS or LMS
- Previous therapy with an anthracycline containing regimen and ≥ 1 additional cytotoxic chemotherapy regimen
- Adequate bone marrow, renal and liver function



* Numbers reflect randomizations at time of Interim Analysis

•Conducted at 85 sites in 4 different countries (94% of patients were enrolled at US sites)

Primary Endpoint	Overall Survival (OS)
Secondary Endpoints	Progression-free survival (PFS), Overall Response Rate (ORR), Duration of Response (DOR), Safety, Patient-Reported Outcomes (PRO)

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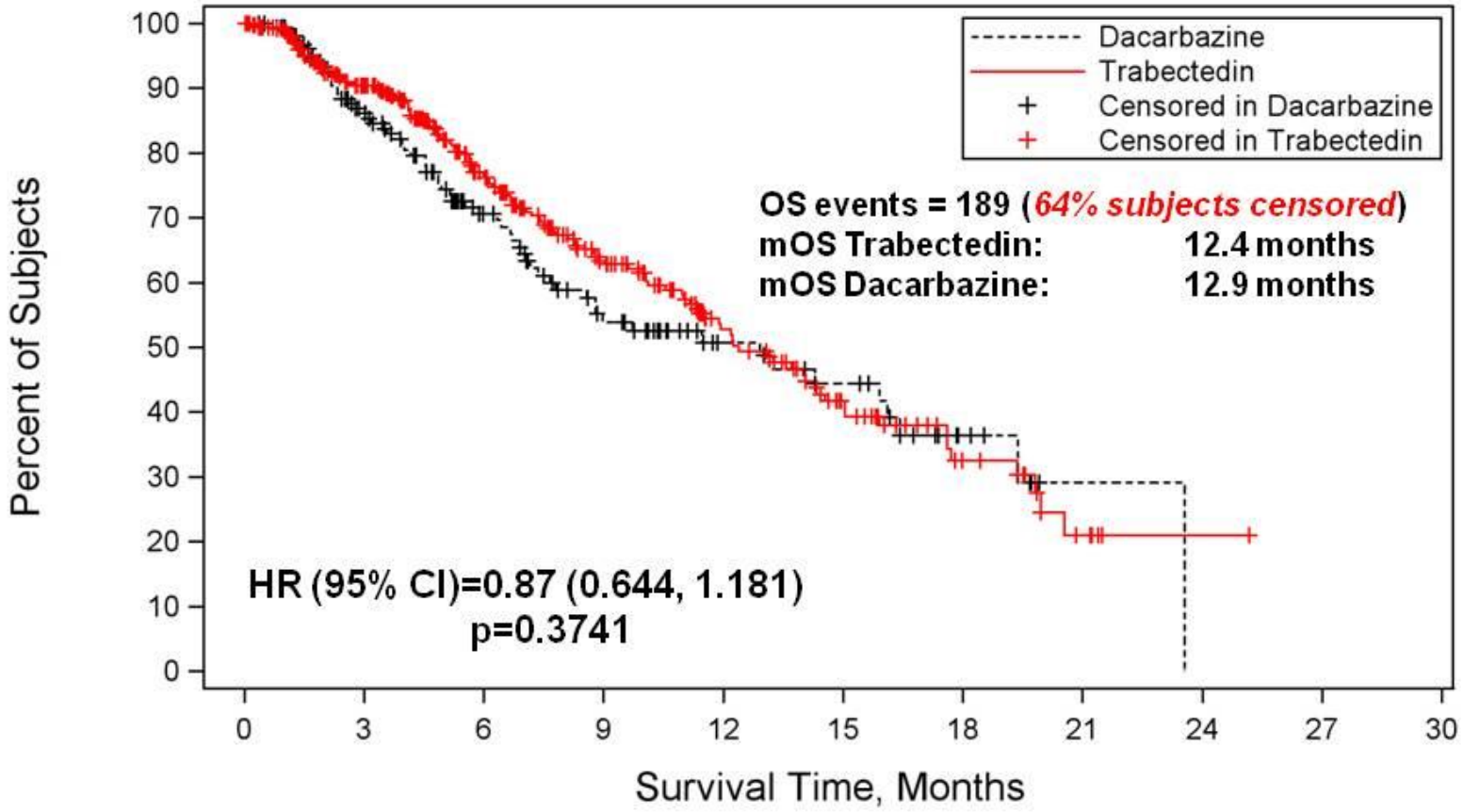
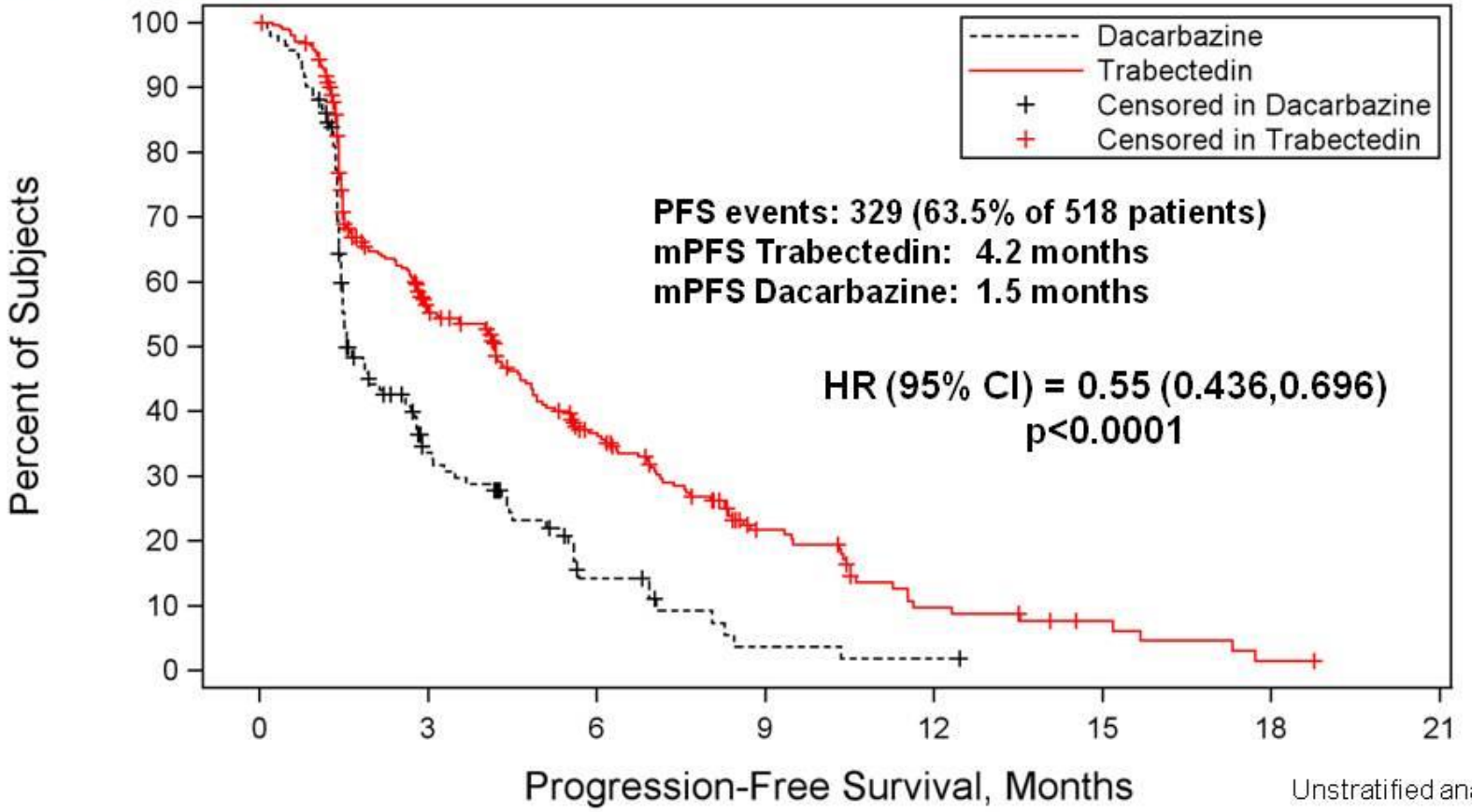
Interim Analysis of Overall Survival



No. Subjects at Risk

Dacarbazine	173	113	69	43	25	19	7	1	0	
Trabectedin	345	251	166	107	63	35	16	5	1	0

Final Analysis of PFS
(Investigator Assessed)



No. Subjects at Risk

Dacarbazine	173	35	10	2	1	0		
Trabectedin	345	133	71	29	10	5	1	0

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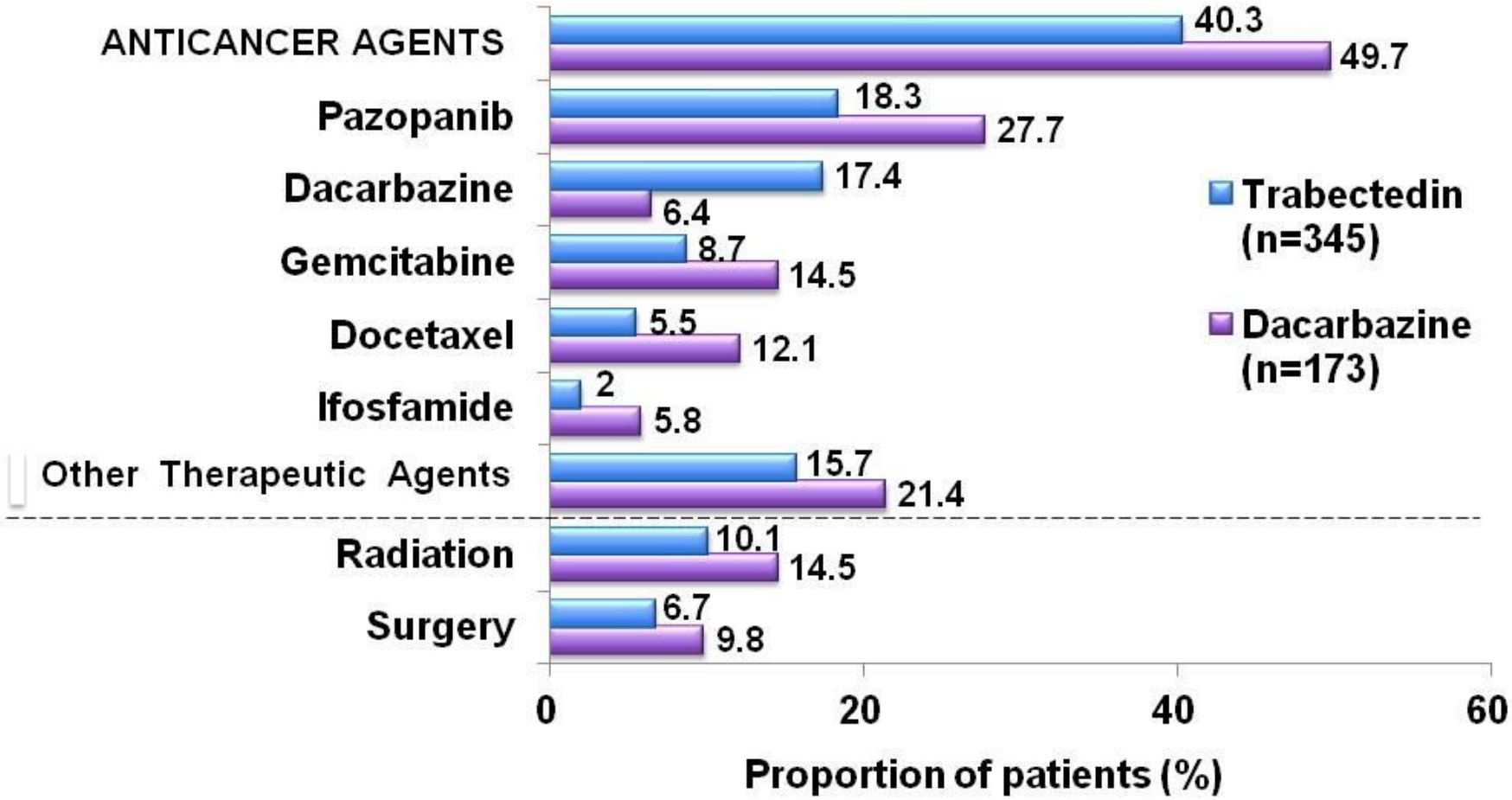
Post-Protocol Anticancer Therapies

- **Post-protocol anti-cancer therapies were reported in 56.1% of patients in the dacarbazine arm and 47.0% in the trabectedin arm**



Presented By George Demetri at 2015 ASCO Annual Meeting

Conclusions

- Primary endpoint of OS was not met at the interim analysis
- Final analysis of PFS demonstrated statistically significant improvement in disease control with trabectedin as compared with dacarbazine
- Despite some increased toxicity in the trabectedin arm, the lack of cumulative toxicities allowed more patients to receive prolonged treatment with 6 or more cycles
- Trabectedin is confirmed as an important treatment option for relapsed/refractory patients with advanced leiomyosarcoma and liposarcoma

My take:

1. Treatment naïve setting

- Doxorubicin remains my 1st line
- Olaratumab interesting but phase III studies needed

2. Pre-treated setting

- Eribulin: survival benefit interesting but questions remain
- Trabetedin: Phase III evidence to show PFS benefit

Thank you

GeDDiS trial objectives

- **Primary** - to compare the efficacy of gemcitabine and docetaxel with doxorubicin
- **Secondary** – to compare:
  - Toxicity
  - Quality of life
  - Cost-effectiveness

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Summary

- No difference between doxorubicin versus gemcitabine and docetaxel for proportion progression-free at 24 weeks
- But, HR in favor of superiority of doxorubicin (HR 1.28, p=0.07)
- No difference in overall survival between the two regimens
- Subgroup analyses :
  - No difference in treatment effects between leio/non-leio, and uterine leio/non uterine leio:
    - No advantage for GemDoc for leiomyosarcoma
    - No advantage for GemDoc for uterine leiomyosarcoma
  - Some evidence for superiority of doxorubicin for males
- Gemcitabine and docetaxel associated with:
  - More withdrawals due to unacceptable toxicity
  - Lower dose intensity and more dose delays

Open-label, Multicenter, Phase 1b/2 Trial

Phase 1b (N=15)

Primary endpoint: Safety

Secondary endpoint: Pharmacokinetics

- **Advanced STS, not amenable to surgery or radiotherapy**
- **Age ≥ 18 years; ECOG PS ≤ 2**
- **Any number of prior treatments; no prior anthracyclines**
- **Available tumor tissue to determine PDGFRα status**

Olaratumab 15 mg/kg D1,8 +
Dox 75 mg/m^2 D1
× 8 cycles (21 days)*

Subsequent cycles: Olaratumab monotherapy if benefit

* During Cycles 5-8, patients receiving Dox could receive dexrazoxane prior to Dox on Day 1, at the investigator's discretion.

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Summary: Improved PFS and Duration of Disease Control Observed With Trabectedin

In patients with relapsed/refractory leiomyosarcoma or liposarcoma, trabectedin has demonstrated:

- Clinically relevant improvement in PFS observed with trabectedin that is superior to dacarbazine
  - Median PFS of 4.2 months vs 1.5 months (HR=0.55; p<0.0001)
- Progression-Free Rates at 3 and 6 months were consistent with published previous experience
  - Trabectedin: 56% and 37%, respectively
  - Dacarbazine: 34% and 14%, respectively
- Prolonged time to initiation of post-protocol anticancer therapies
  - Increased duration of disease control (DOR)
- Increased proportion of patients achieving long-term disease control
  - Improved sum of responses plus prolonged stable disease: 34.2% vs. 18.5%
  - Increased proportion treated for 6+ cycles: 34% vs 17%