Principles of Systemic Therapy for Sarcomas

Robin L Jones
Royal Marsden Hospital
Institute of Cancer Research

Plan

- Adjuvant/ Neoadjuvant
  - Rhabdomyo, osteo, Ewing, GIST
- ? Role for adjuvant chemotherapy
  - Large, high grade extremity tumours
- Palliative
  - Locally advanced/ metastatic

Sarcoma: Progress

- Limb salvage surgery
- Multi-agent chemotherapy
  - Ewing
  - Osteosarcoma
  - Embryonal rhabdomyosarcoma
- Radiation
  - Extremity and trunk soft tissue sarcomas
- “Targeted therapy”
  - GIST
  - Dermatofibrosarcoma protuberans
  - Inflammatory myofibroblastic tumor

Adult Sarcoma: Issues

- Adjuvant chemotherapy in resected soft tissue sarcoma?
- Soft tissue sarcoma staging
- Limited options for metastatic disease
  - Outcome poor
- Systemic therapy
  - Previously: “One size fits all” approach

Differential Sensitivity

- Sensitive:
  - Synovial sarcoma
  - Myxoid liposarcoma
  - Uterine leiomyosarcoma
- Resistant:
  - Alveolar soft part sarcoma
  - Clear cell sarcoma
  - Low grade fibromyxoid sarcoma
  - Extraskeletal myxoid chondrosarcoma
- NB: Retrospective data

Sarcomas – biological groups

- COMPLEX
- Multiple complex genetic alterations

- SIMPLE
- Specific translocations generating fusion oncogenes

- Specific kinase mutations (GIST)

- Gene inactivation (NF1 in MPNST, INI1 in rhabdoid tumours, APC in desmoid)

- Simple genetic alterations (amplifications – *mdm2*+/ *cdk4* in well- / dedifferentiated liposarcoma)

Different drugs for different diseases

- Localized
  - Osteosarcoma — MAP
  - Ewing — VDC/ IE
  - Rhabdomyosarcoma — VAC
  - GIST — Imatinib

- Metastatic
  - Dermato fibrosarcoma protuberans — Imatinib
  - Giant cell tumor of bone — Denosumab
  - Alveolar soft part sarcoma — Cediranib/ sunitinib
  - Inflammatory myofibroblastic tumor — ALK inhibitors
  - PEComas — mTOR inhibitors
  - Endometrial stromal sarcoma — Aromatase inhibitors
  - Chordoma — Imatinib/ mTOR Inhibitors
  - Ewing/ Rhabdomyosarcoma — Cyclo/ topotecan
  - Ewing/ Rhabdomyosarcoma — Irinotecan/ temozolamide
  - Solitary fibrous tumor — Anti angiogenic agents

Adjuvant / Neoadjuvant

Systemic Therapy: Benefit

- Embryonal rhabdomyosarcoma
  - VAC (vincristine, actinomycin-D, cyclophosphamide)
- Ewing's sarcoma
  - Vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide
- Osteosarcoma
  - MAP (Methotrexate, doxorubicin, cisplatin)
- Gastro intestinal stromal tumor (GIST)
  - Imatinib

Adjuvant Chemotherapy

- 1997 Meta-analysis of 14 randomized trials using an anthracycline-based regimen
  - Surgical resection followed by chemotherapy or observation
  - n=1568
  - 80% extremity/ trunk STS
  - Grade: 67% high; 5% low; 28% unknown
  - Size: 18% <5cm; 45% ≥5cm; 37% unknown
  - 18% subtype not known

Sarcoma Meta-analysis Collaboration. Lancet 1997;350:167-1654

Adjuvant Chemotherapy

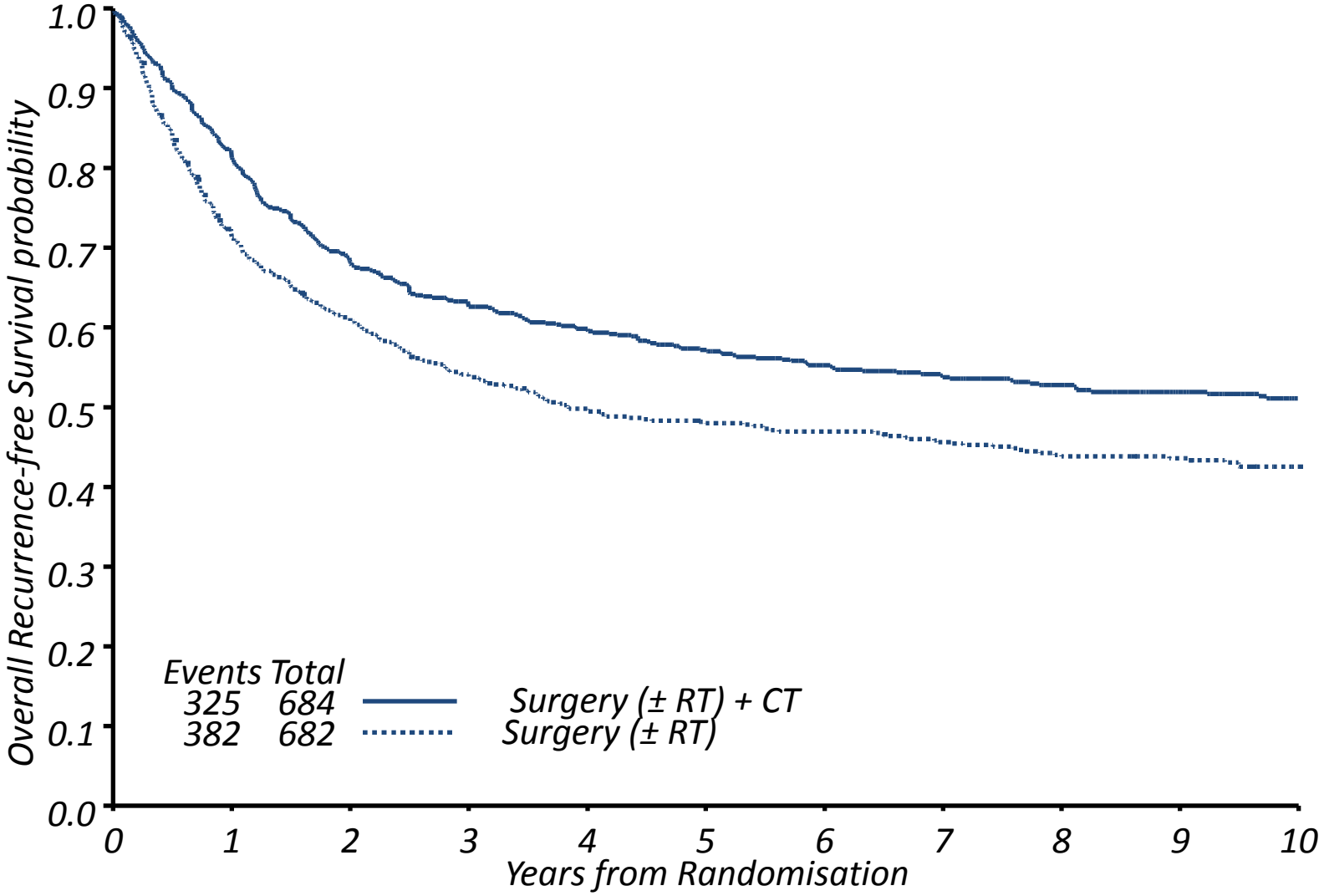
1997 Meta-analysis results:

Arm	Overall DFS 10 yr	p	Local DFS 10 yr	p	Distant DFS 10 yr	p	Overall Survival 10 yr	p
Chemo	55%	.0001	81%	.016	70%	.0003	54%	0.12
Control	45%		75%		60%		50%	

Extremity sarcoma subgroup had a 7% absolute improvement in overall survival (p=0.029)

Sarcoma Meta-analysis Collaboration. Lancet 1997;350:1647-54

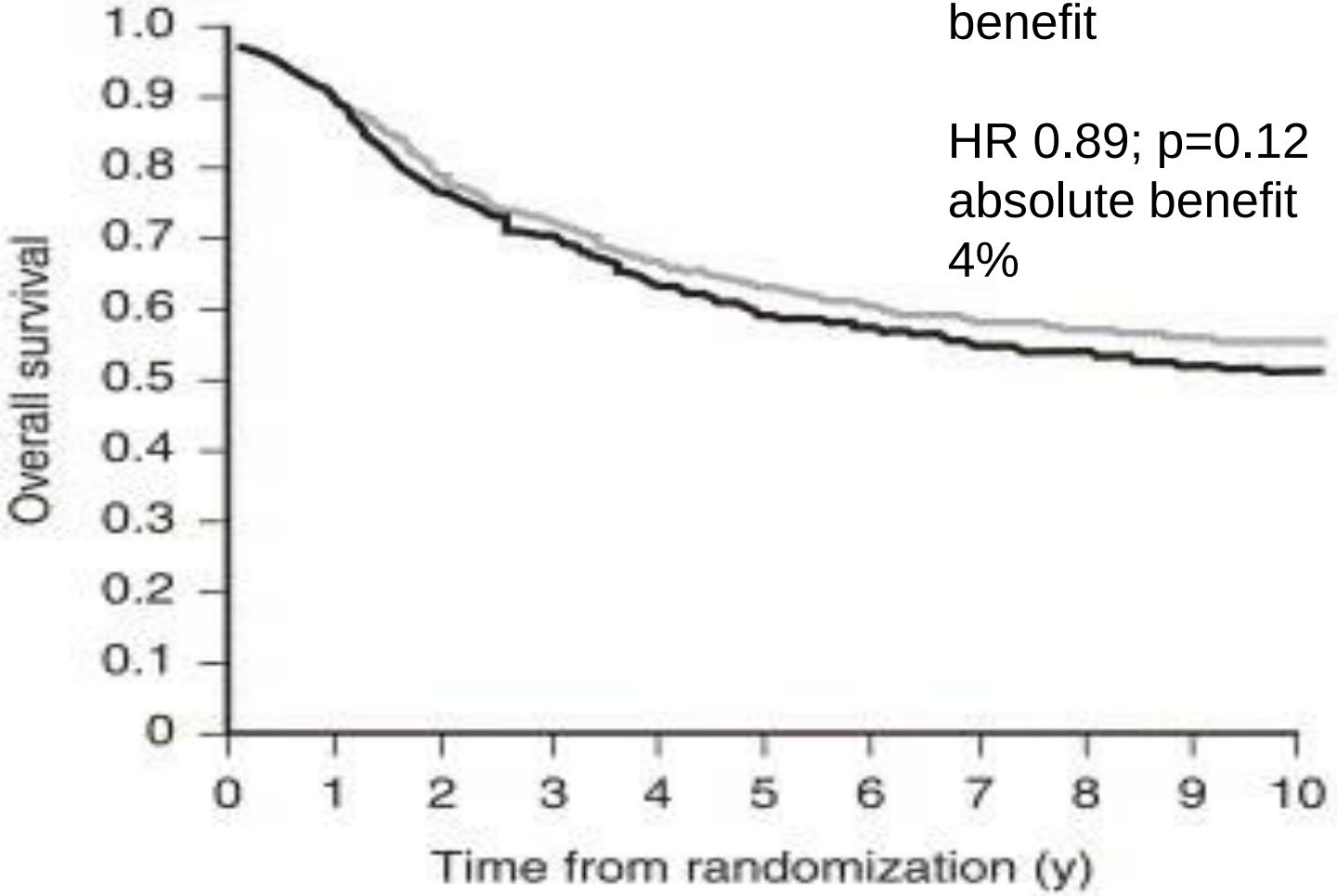
1997 Meta-analysis: RFS



1997 Meta-analysis: Survival

Overall survival benefit

HR 0.89; p=0.12
absolute benefit 4%



Patients at risk

Chemotherapy	572	463	377	311	217
Control	572	444	366	289	202

Author	n	Regimen	F/U	OS	p	comment
Frustaci 2001	104	EPI+IFOS x 5 No chemo	59 mos	66% 46%	0.04	Update @90 mos, ITT analysis OS benefit not significant p=0.07; 7% pts did not get planned chemo
Petrioli 2002	88	EPI or EPI+IFOS x 4 No chemo	94 mos	72% 47%	0.06	Also randomized pts to groups with or without post operative RT EPI+IFOS better than EPI
Brodowicz 2000	59	DOXO+DTIC +IFO x 6 No chemo	41 mos	Not reported	0.4	Small trial; low dose ifos; underpowered for survival
Wolf EORTC 2007	351	DOXO+IFOS x 5 No chemo	NR	64% 69%	---	low dose ifos; low grade small tumors included

Adjuvant / Neoadjuvant Chemotherapy Soft Tissue Sarcomas

- Limited evidence base
- NO clear evidence of survival benefit
- Conflicting opinions
- Long-term complications of chemotherapy

Contrast with:

"A landmark in osteosarcoma care"

1600 THE NEW ENGLAND JOURNAL OF MEDICINE June 19, 1986

THE EFFECT OF ADJUVANT CHEMOTHERAPY ON RELAPSE-FREE SURVIVAL IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITY

MICHAEL P. LINK, M.D., ALLEN M. GOORIN, M.D., ANGELA W. MISER, M.D., ALEXANDER A. GREEN, M.D., CHARLES B. PRATT, M.D., JEAN B. BELASCO, M.D., JON PRITCHARD, F.R.C.P., JAMES S. MALPAS, F.R.C.P., ALAN R. BAKER, M.D., JOHN A. KIRKPATRICK, M.D., ALBERTO G. AYALA, M.D., JONATHAN J. SHUSTER, PH.D., HERBERT T. ABELSON, M.D., JOSEPH V. SIMONE, M.D., AND TERESA J. VIETTI, M.D.

Abstract We conducted a randomized controlled trial to determine whether intensive multi-agent adjuvant chemotherapy improves the chances of relapse-free survival in patients with nonmetastatic high-grade osteosarcoma of the extremity, as compared with concurrent controls. After undergoing definitive surgery, 36 patients were randomly assigned to adjuvant chemotherapy or to observation without adjuvant treatment. At two years the actuarial relapse-free survival was 17 percent in the control group, similar to that found in studies before 1970, and 66 percent in the adjuvant-chemotherapy group (P<0.001). Similar results were observed among 77 additional patients who declined to undergo randomization but who elected observation or chemotherapy.

We conclude that the natural history of osteosarcoma of the extremity has remained stable over the past two decades, that adjuvant chemotherapy increases the chances of relapse-free survival of patients with high-grade osteosarcoma, and that it should be given to all such patients. (N Engl J Med 1986; 314:1600-6.)

ALTHOUGH the prognosis for children with osteosarcoma has improved dramatically over the past 15 years, the contribution of adjuvant chemotherapy to this improvement in prognosis has been less certain.[1,2]

Before the 1970s, the prognosis for children with osteosarcoma of the extremity was dismal.[3] Although control of the primary tumor could be achieved in most cases by amputation of the involved extremity, distant metastases developed in the majority of patients, and they died. This discouraging clinical course was documented at a number of centers,[4-6] where metastases developed within six months of amputation in more than half the patients presenting with tumor confined to an extremity who were treated only with surgery of the primary tumor. Overall, the tumor recurred in 80 percent of patients. The inescapable conclusion from these studies was that 80 percent of these patients with osteosarcoma had subclinical metastases at the time of diagnosis that were undetectable by techniques then available.

Because of the reproducible natural history of osteosarcoma and the success of adjuvant chemotherapy in the treatment of other childhood tumors — notably, Wilms' tumor and rhabdomyosarcoma — trials of adjuvant chemotherapy for osteosarcoma were initiated in the 1970s and early 1980s; these trials demonstrated relapse-free survival of 45 to 60 percent at three to five years.[7-17] However, the studies were conducted without concurrent control groups because occult disseminated disease was assumed to exist in virtually all patients.

Subsequently, studies at the Mayo Clinic questioned the assumption that microscopic metastases were present at diagnosis in more than 80 percent of patients with osteosarcoma. In a retrospective review[18-20] it was found that a striking improvement in relapse-free survival had occurred over time independently of the administration of adjuvant therapy. Of the patients at the Mayo Clinic in whom osteosarcoma was diagnosed after 1969 and treated only with surgery without adjuvant therapy, approximately 35 to 40 percent survived without recurrence. On the basis of these findings, investigators at the Mayo Clinic conducted a randomized controlled study of adjuvant high-dose methotrexate between 1976 and 1980,[21] but could demonstrate no benefit from the methotrexate. Moreover, the relapse-free survival in the control group treated only with surgery of the primary tumor and no adjuvant chemotherapy was 44 percent — more than twice what was expected on the basis of historical controls. Thus, the validity of historical experience as a control in modern trials of adjuvant therapy in osteosarcoma was challenged directly by the Mayo Clinic studies.

In an effort to resolve the controversy over the role of adjuvant chemotherapy in the treatment of osteosarcoma of the extremity, the Multi-Institutional Osteosarcoma Study, a randomized controlled trial, was initiated in June 1982. The primary objective of this trial was to determine whether the administration of intensive, multi-agent chemotherapy as adjuvant treatment after definitive surgery of the primary tumor would significantly improve disease-free survival and survival among patients with nonmetastatic osteosarcoma of the extremity, as compared with concurrent controls treated only with surgery without adjuvant therapy. The preliminary results of this study form the basis for this report.

From Stanford University Medical Center, Stanford, Calif.; the Dana-Farber Cancer Institute and Children's Hospital, Boston; the Pediatric Oncology and the Surgery Branch, National Cancer Institute, Bethesda, Md.; St. Jude Children's Research Hospital, Memphis; Children's Hospital of Philadelphia, Philadelphia; Great Ormond Street Hospital and St. Bartholomew's Hospital, London; M.D. Anderson Hospital and Tumor Institute, Houston; the Pediatric Oncology Group Statistical Office, Gainesville, Fla.; and Washington University Medical Center, St. Louis. Address reprint requests to Dr. Link at the Division of Hematology/Oncology, Children's Hospital at Stanford, 520 Sand Hill Rd., Palo Alto, CA 94304.

Supported by grants (CA-33603, CA-31566, CA-03713, CA-19589, CA-29139, CA-05587, and CA-30969) from the National Cancer Institute.

Presented in part at the 21st annual meeting of the American Society of Clinical Oncology, Houston, May 1985, and at the 17th meeting of the International Society of Pediatric Oncology, Venice, September 1985.

- A revolution in treatment with 36 patients randomised!

"……36 patients were randomly allocated to adjuvant chemotherapy or to observation without adjuvant treatment. At two years the actuarial relapse-free survival was **17%** in the control group, similar to that found in studies before 1970, and **66%** in the adjuvant-chemotherapy group (P<0.001)……..and that it should be given to all such patients"

Link et al N Eng J Med 1986; 314: 1600-6

Locally advanced/ metastatic

- First-line chemotherapy

NCCN Guidelines for Metastatic Soft Tissue Sarcoma

Disseminated metastases or unresectable

Options:
Observation, if asymptomatic.
Chemotherapy
Radiation
Palliative surgery
Best supportive care
Ablation procedures
- **RFA**
- **Cryotherapy**

Embolization procedures

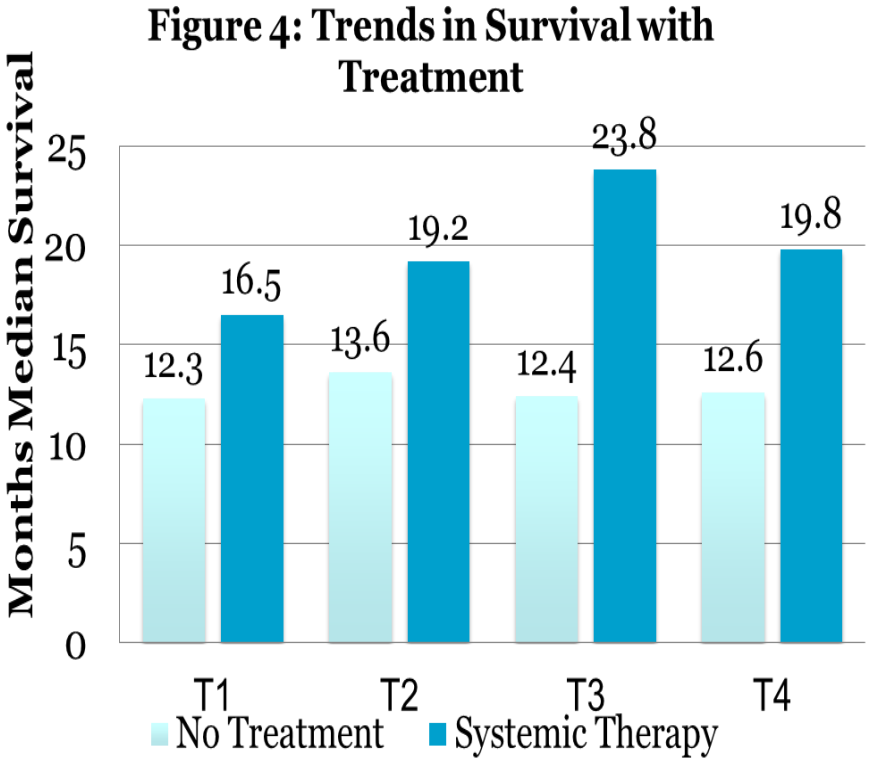
NCCN Practice Guidelines 2013

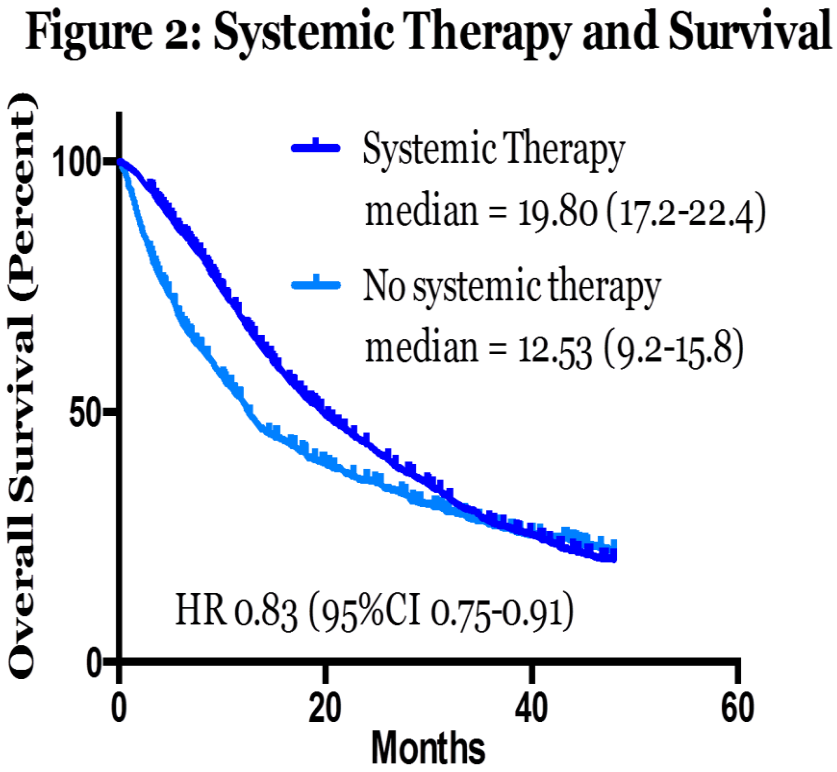
First-line metastatic disease

- Retrospective data: Improvement OS
- PICASSO trial
  - Doxorubicin + placebo vs
  - Doxorubicin +palifosfamide
- European (EORTC) trial
  - Doxorubicin vs doxorubicin + ifosfamide
- British (GEDDIS) trial
  - Doxorubicin vs gemcitabine + docetaxel

Metastatic soft tissue sarcoma: an analysis of systemic therapy and impact on survival

OS has improved over last 20 years to ca. 18 months





Harris S *et al* ASCO 2015 Abs. 10545

Results of EORTC 62012

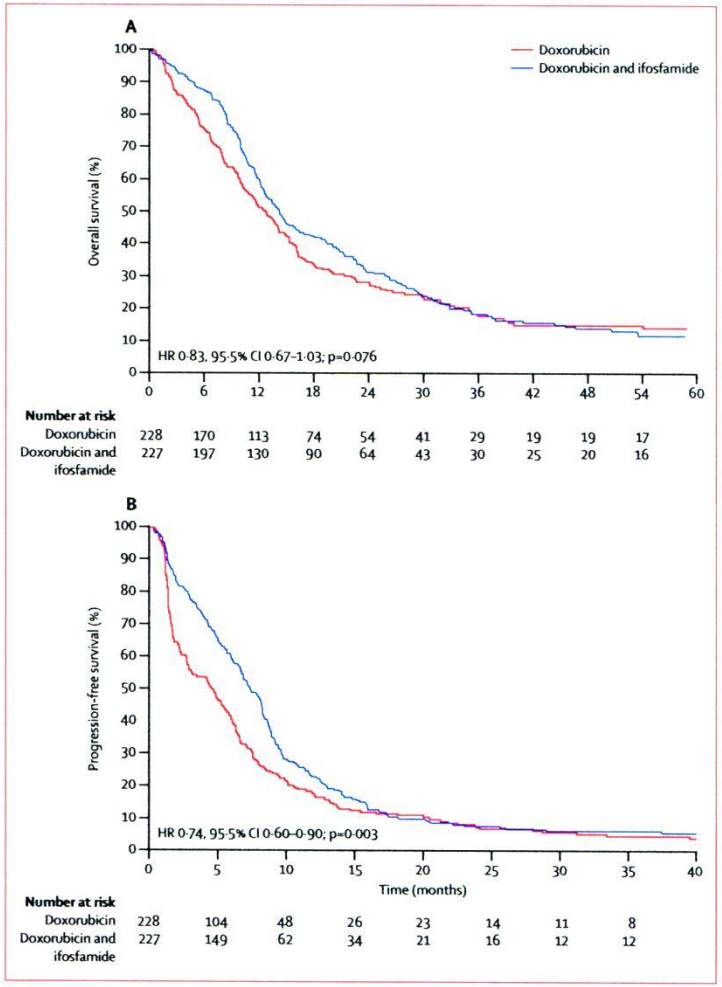


Figure 2: Kaplan-Meier curves for overall survival (A) and progression-free survival (B)
HR=hazard ratio.

Median overall survival:
Doxorubicin: 12.8 months
Doxorubicin + ifosfamide: 14.3 months

Survival at 1 year:
Doxorubicin: 51%
Doxorubicin + ifosfamide: 60%

Median PFS
Doxorubicin: 4.6 months Doxorubicin + ifosfamide: 7.4 months

Overall response rate:
Doxorubicin: 13.6%
Doxorubicin + ifosfamide: 26.5%

Judson et al Lancet Oncol 2014;15(14):415-23

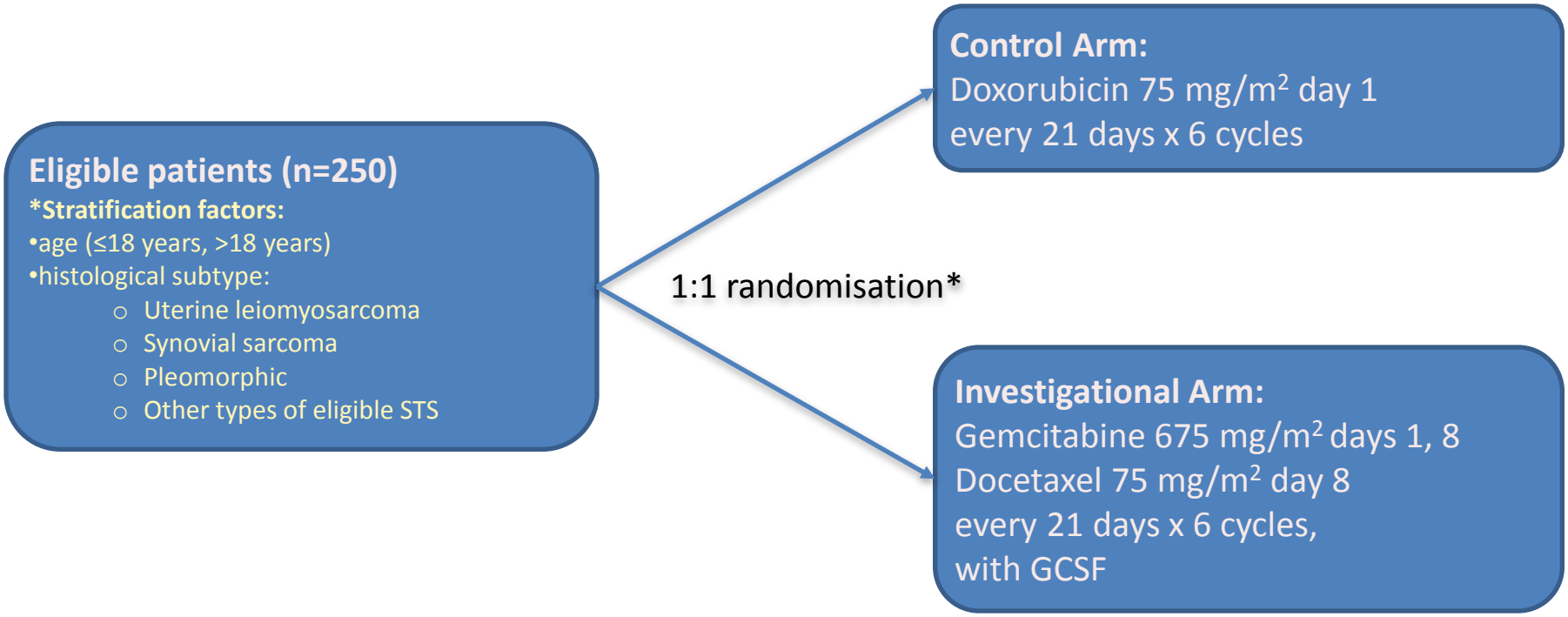
How to use this information?

- No survival benefit from combination therapy
- Single agent doxorubicin is still recommended for palliation and as a reference arm for RCTs

- *But*, combination therapy valuable if:
  - tumour shrinkage is required for symptom control
  - treatment is being given pre-operatively
  - disease is imminently life-threatening
  - treatment is in adjuvant setting

- One could argue that this is a discussion to be had with every patient

GeDDiS Trial Design



Disease assessments (RECIST 1.1) at:

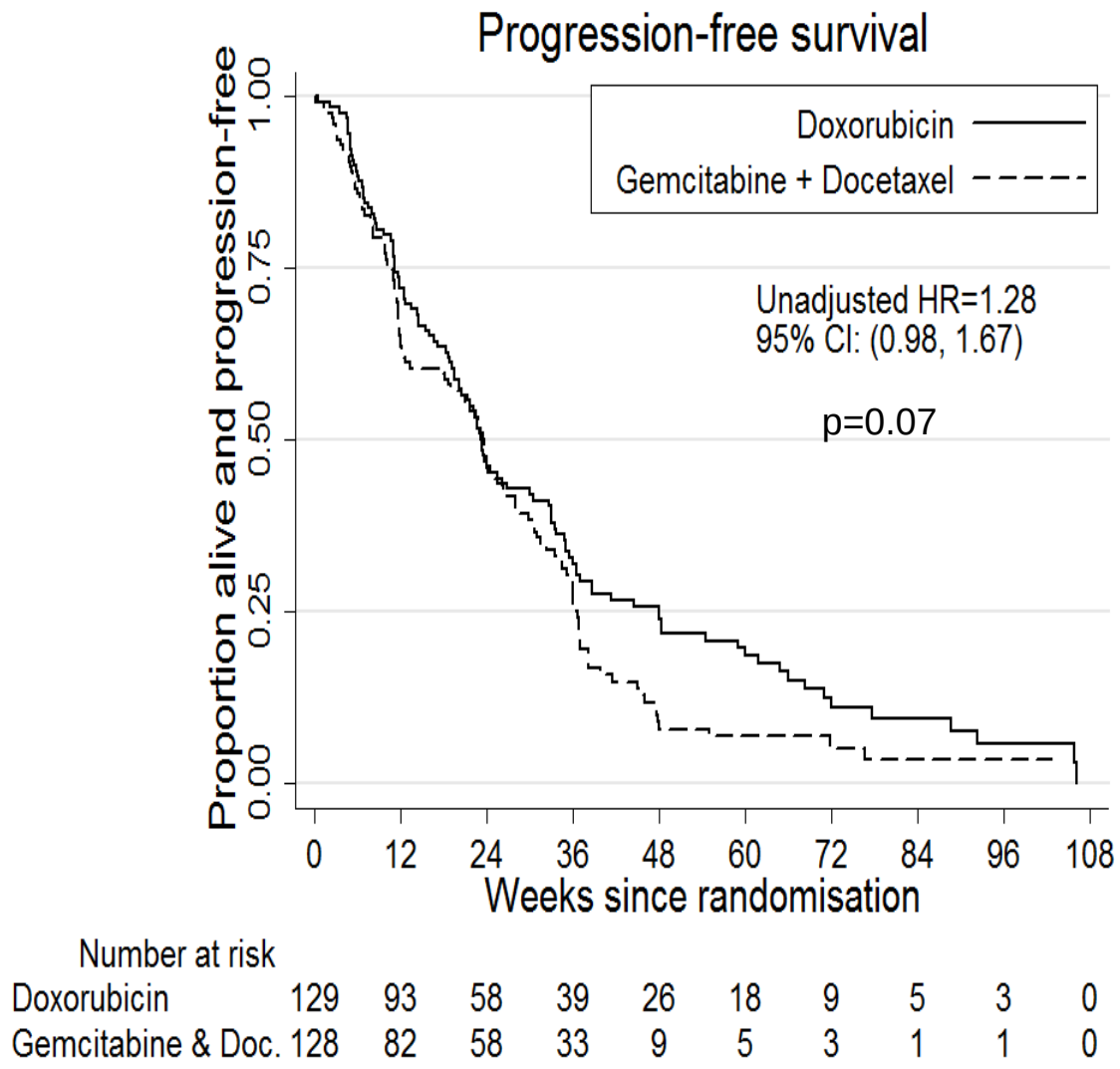
- Baseline
- 12 weeks post randomisation
- 24 weeks post randomisation
- 12 weekly thereafter

Quality of life assessments at:

- Baseline
- 12 weeks post randomisation
- 18 weeks post randomisation
- 24 weeks post-randomisation

Seddon B et al. ASCO 2015

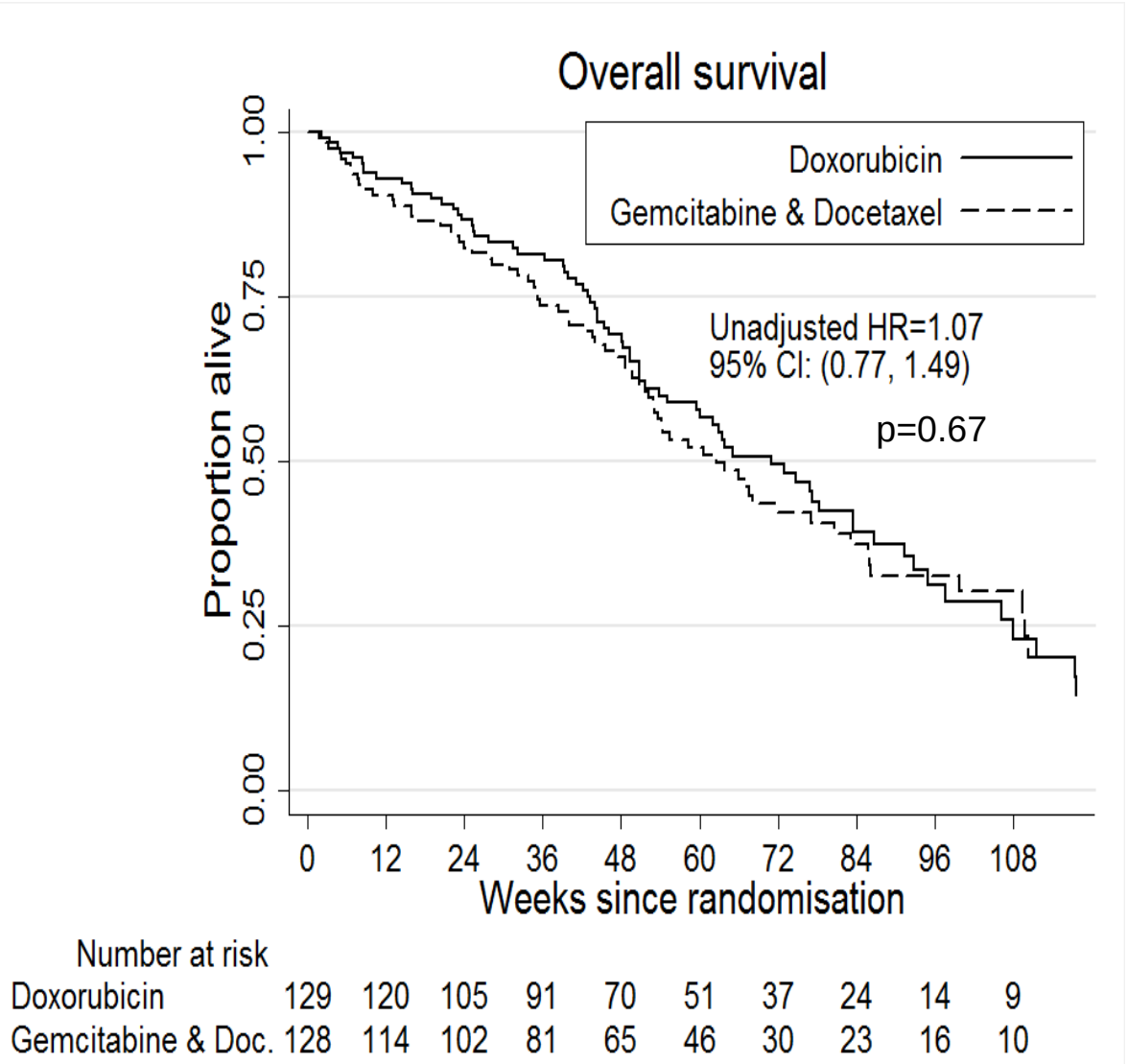
GeDDiS: Progression-free survival



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

Seddon B et al. ASCO 2015

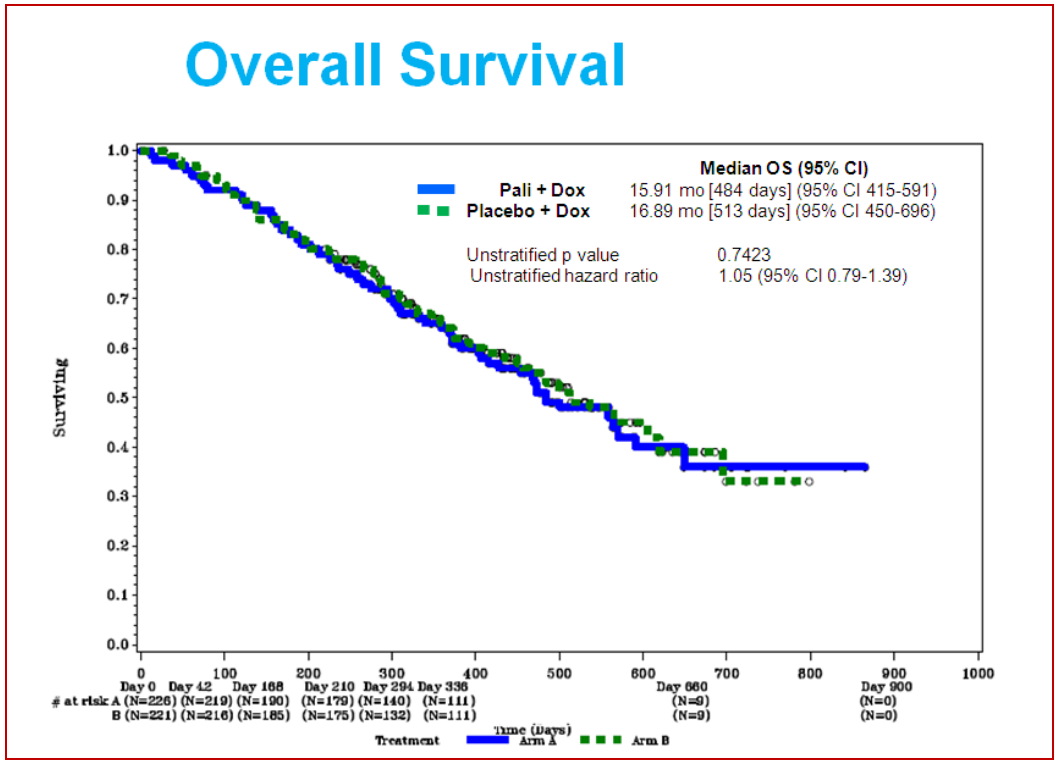
GeDDiS: Overall survival



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

Seddon B et al. ASCO 2015

PICASSO/Palifosfamide – Negative Trial



Why?

- Trial design
- Phase II
- Inactive drug?
- If so, how did we miss signal?
- Victim of heterogeneity?

Ryan C et al. ESMO 2013

Evofosfamide (TH-302)

- Phase II trial
- 91 patients
  - 6 cycles of doxorubicin + TH-302 (300 mg/m^2)
  - Benefit from 6 cycles
  - Maintenance TH-302
- 6-month PFS:58% (95%CI, 46-68%)
- 3-month PFS:83% (95%CI, 74-89%)
- Median PFS: 6.5 months (95%CI, 5.8-7.7 months)

Chawla SP, Cranmer LD, Van Tine BA et al. J Clin Oncol 32(29); 3299-306: 2014

Evofosfamide (TH-302)

- Median OS: 21.5 months (95%CI, 16-26.2 months)

- 1-year OS: 73% (95% CI, 63% to 81%)
- 2-year OS: 44% (95% CI,33% to 54%)

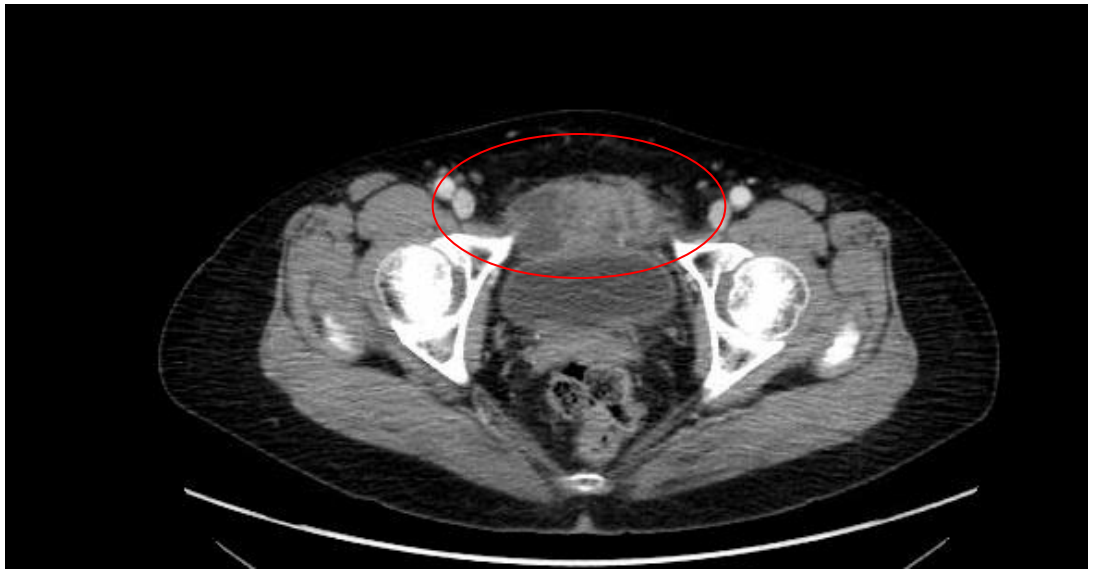
- Multivariable analyses, patients with:
  - Leiomyosarcoma
  - Higher serum albumin
  - Locally advanced disease
  - Fewer sites of disease
- Had significantly longer survival

Chawla SP, Cranmer LD, Van Tine BA et al. J Clin Oncol 32(29); 3299-306: 2014

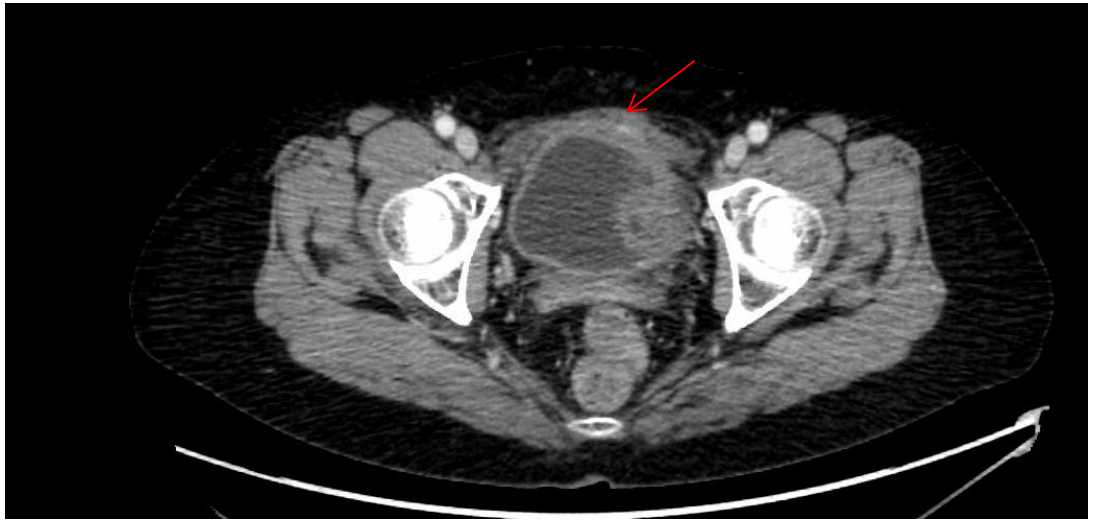
Evofosfamide (TH-302)

- Combination common adverse events:
  - Fatigue n=64 (74.3%)
  - Nausea n=68 (74.7%)
  - Skin/ mucosal n=41 (45.1%)
  - Anemia, thrombocytopenia and neutropenia
- TH-302 alone: Less severe/ frequent
- Randomized trial (NCT01440088)

Chawla SP, Cranmer LD, Van Tine BA et al. J Clin Oncol 32(29); 3299-306: 2014



Baseline



Post 10 cycles

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/m² D1 × 8 cycles (21 days)*

Olaratumab monotherapy until progression

Dox 75 mg/m² D1 × 8 cycles

Optional olaratumab monotherapy after progression

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

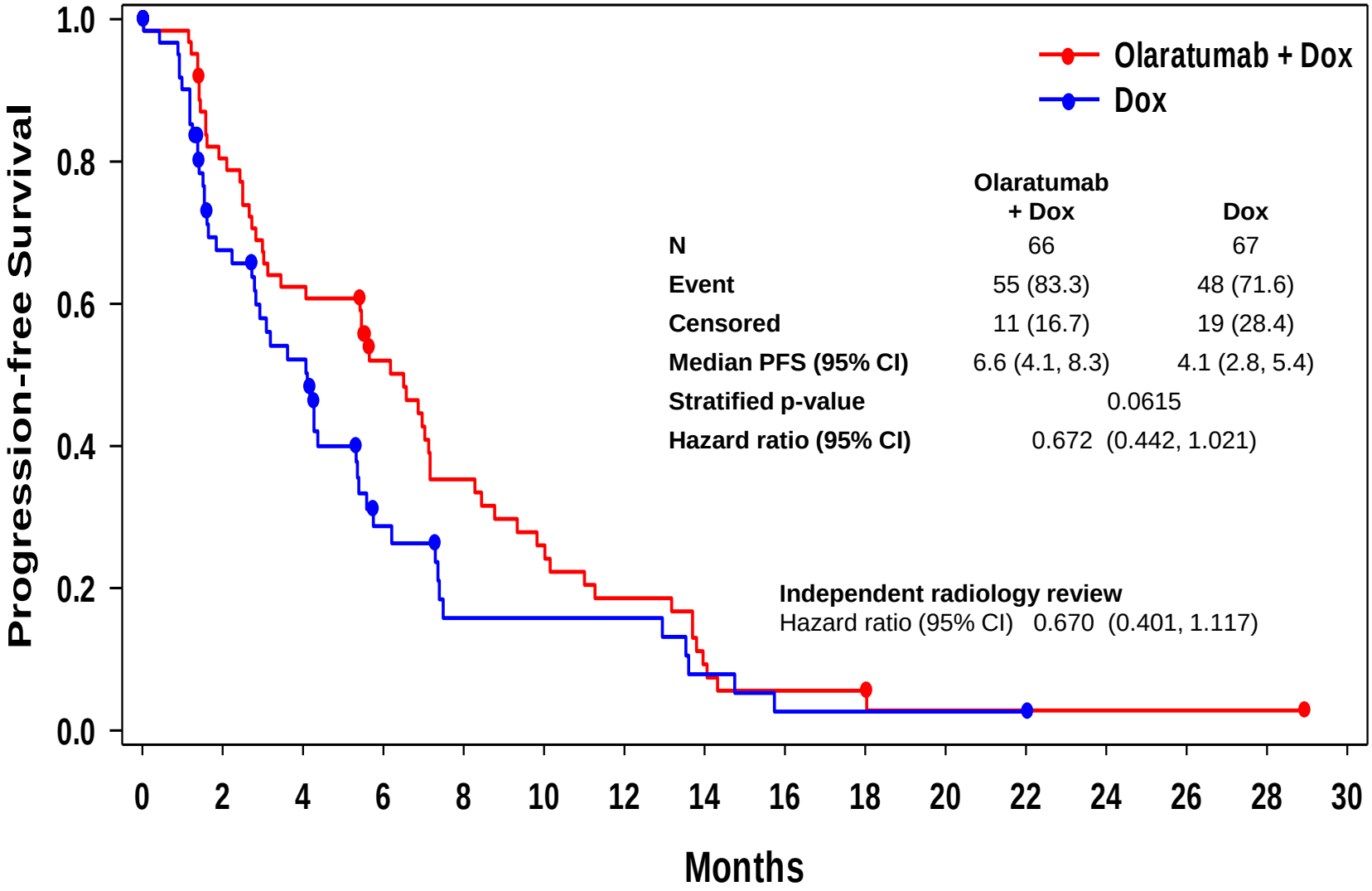
Secondary end points: Overall survival (OS), objective response rate, PFS at 3 months

Biomarker: PDGFRα (IHC) and related ligands

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

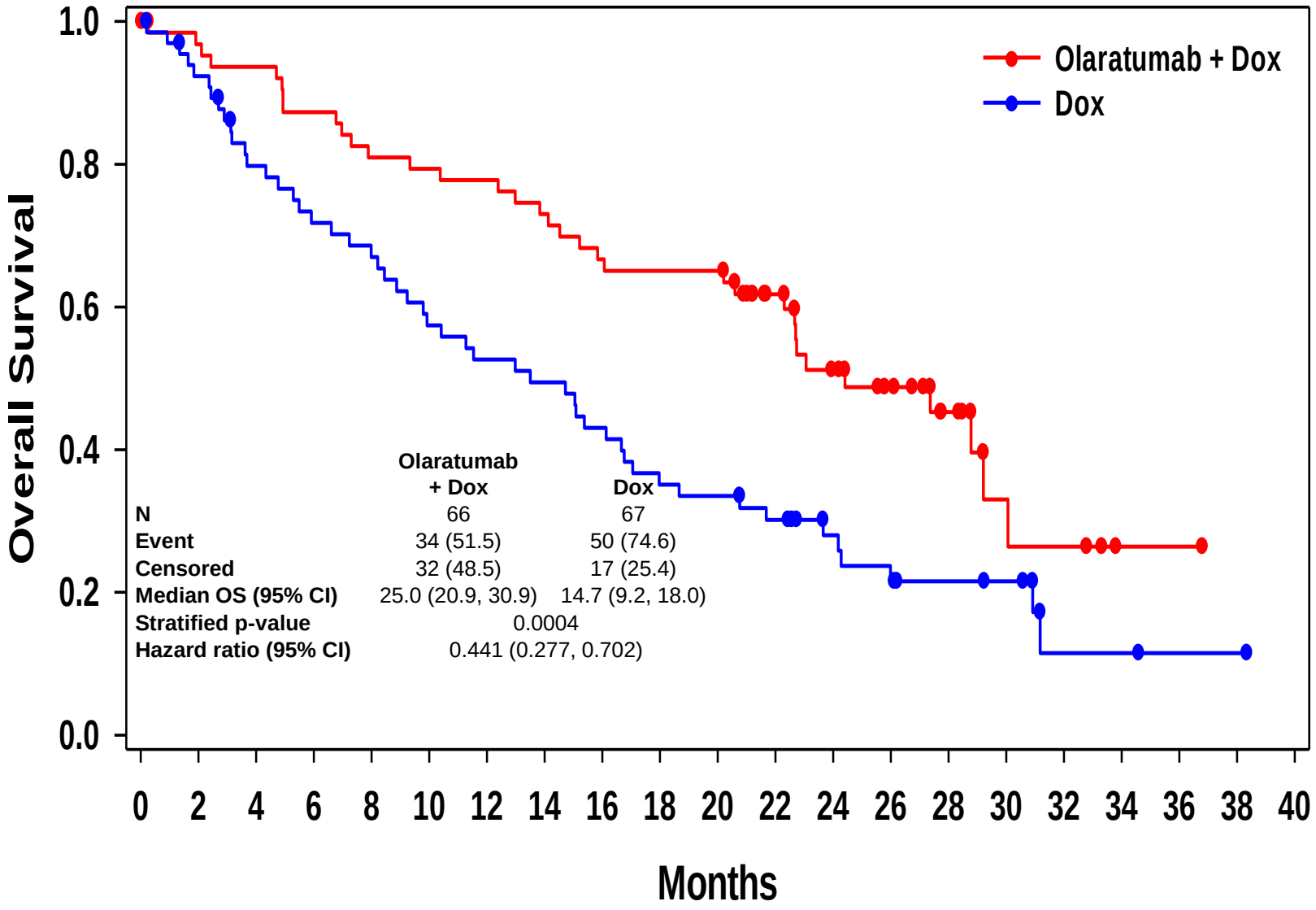
Tap W et al. ASCO 2015

Progression-Free Survival (ITT) (Phase 2)



Tap W et al. ASCO 2015

Overall Survival (ITT) (Phase 2)



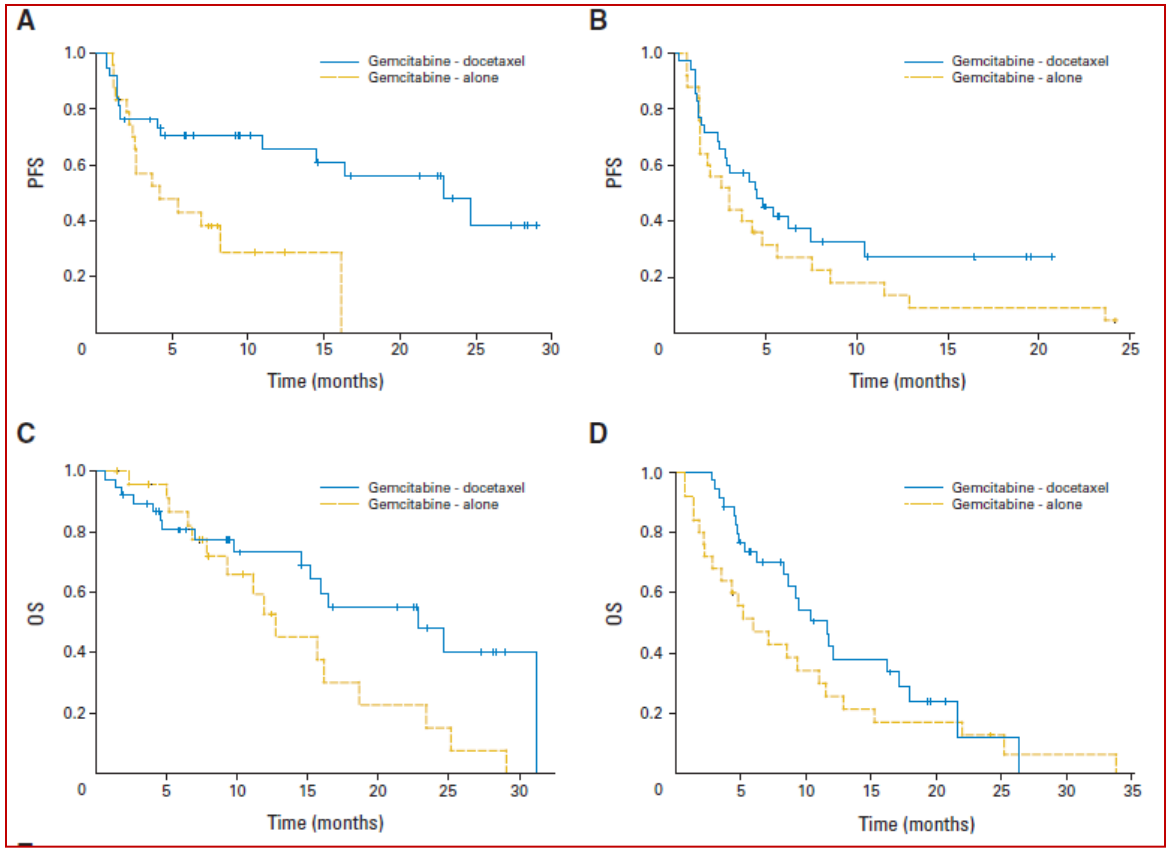
Tap W et al. ASCO 2015

Locally advanced/ metastatic

- 2nd/ 3rd line systemic therapy:
  - Ifosfamide
  - Gemcitabine/ docetaxel
  - Pazopanib
  - Trabectedin
  - Eribulin
  - DTIC

Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002

Robert G. Maki, J. Kyle Wathen, Shreyaskumar R. Patel, Dennis A. Priebat, Scott H. Okuno, Brian Samuels, Michael Fanucchi, David C. Harmon, Scott M. Schuetze, Denise Reinke, Peter F. Thall, Robert S. Benjamin, Laurence H. Baker, and Martee L. Hensley

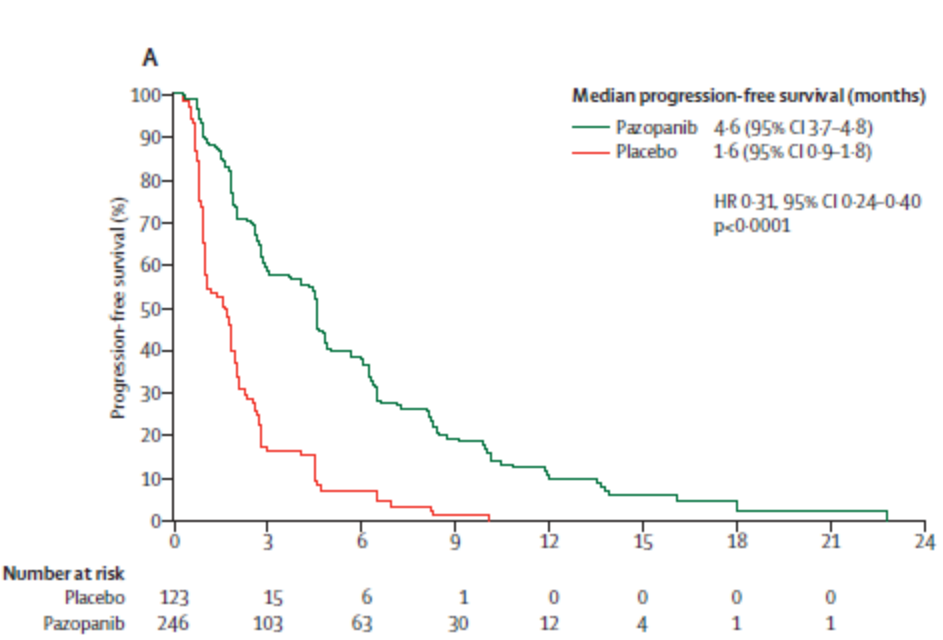


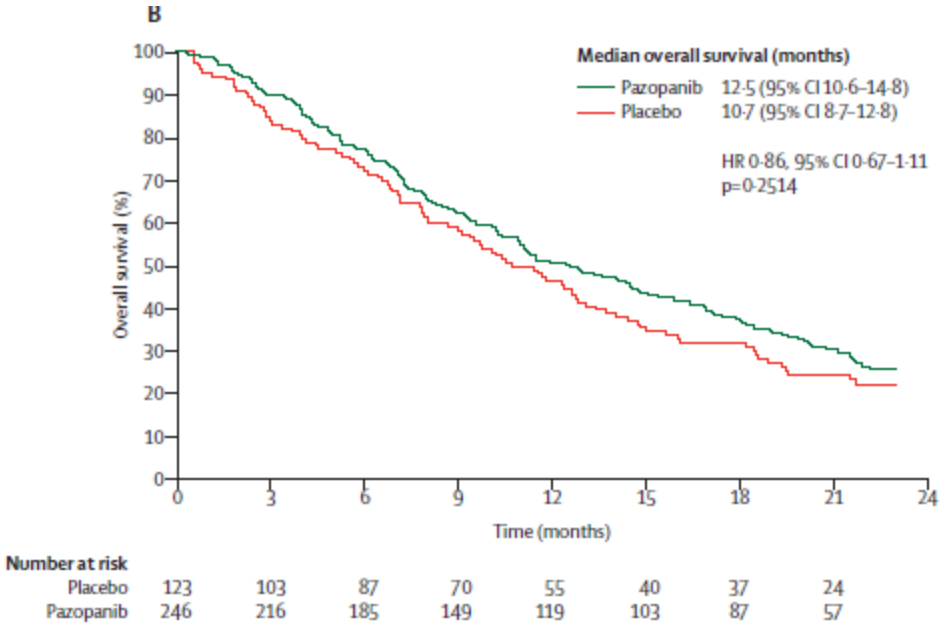
Gem/Doce vs. Gem
ORR: 16% vs 8%
mPFS: 6.2 vs 4 months
mOS: 18 vs. 12 months

JCO 25; 2755-2763: 2007

Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group





Why: Right Mix of Biology and Biological Activity?

Study design: PFS v. Placebo

Powered Correctly

Subtypes and Pt Selection

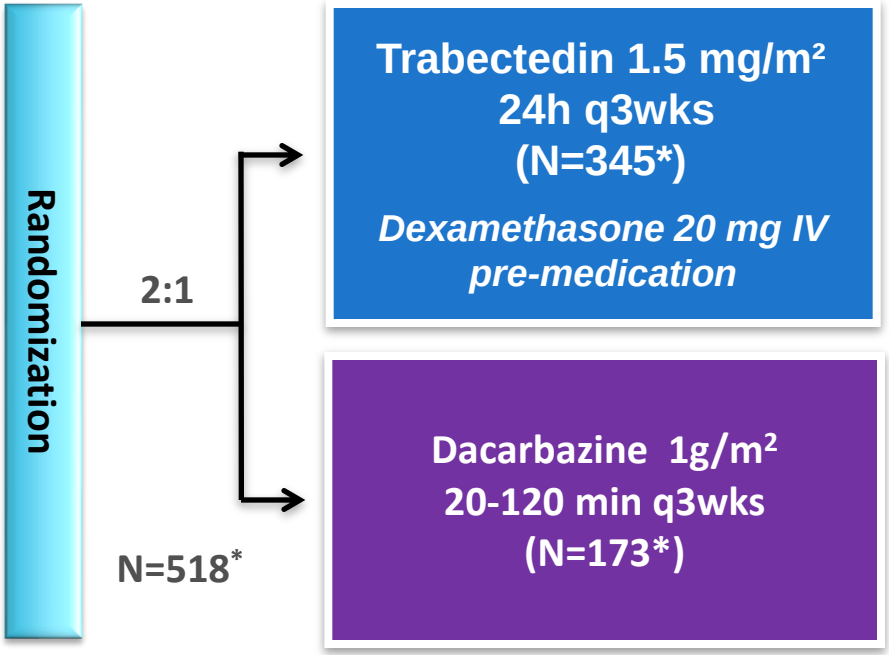
(47% LMS, 10% SS, 47% other)

Lancet 379; 1879-1886: 2012

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



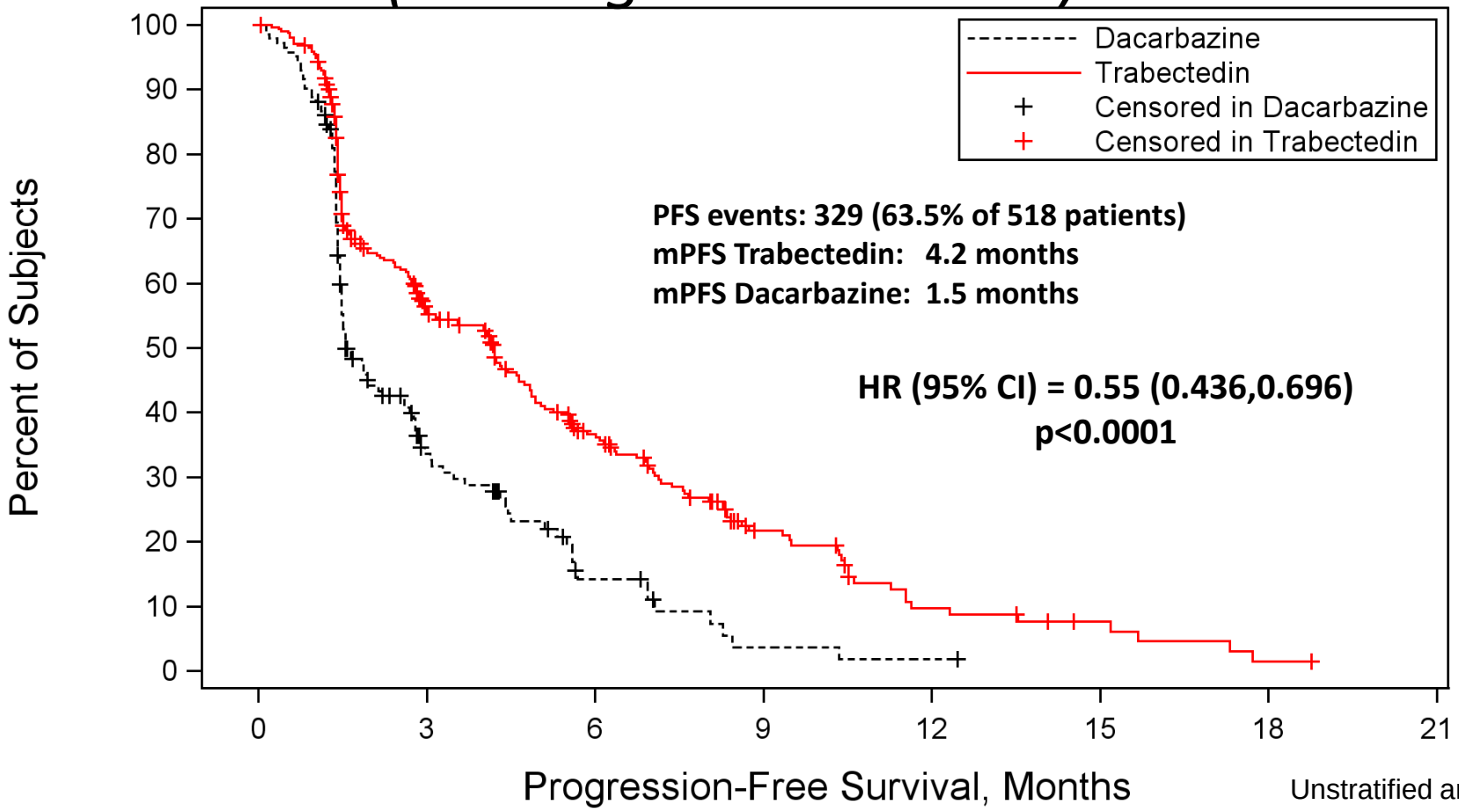
* Numbers reflect randomizations at time of Interim Analysis

•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)**

Demetri G, et al. JCO 2015

Final Analysis of PFS
(Investigator Assessed)

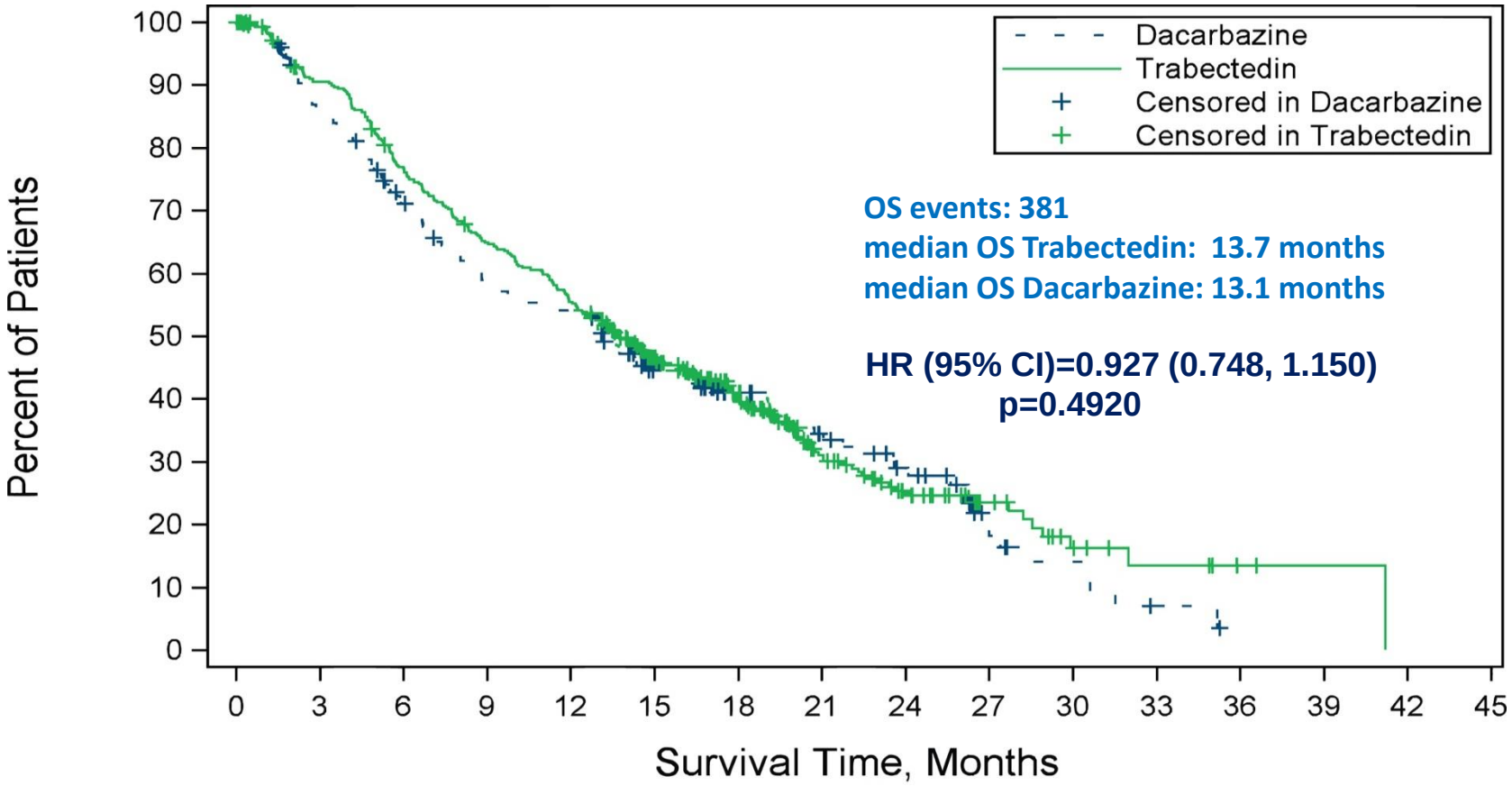


No. Subjects at Risk

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

Demetri G, et al. JCO 2015

Final Analysis of Overall Survival

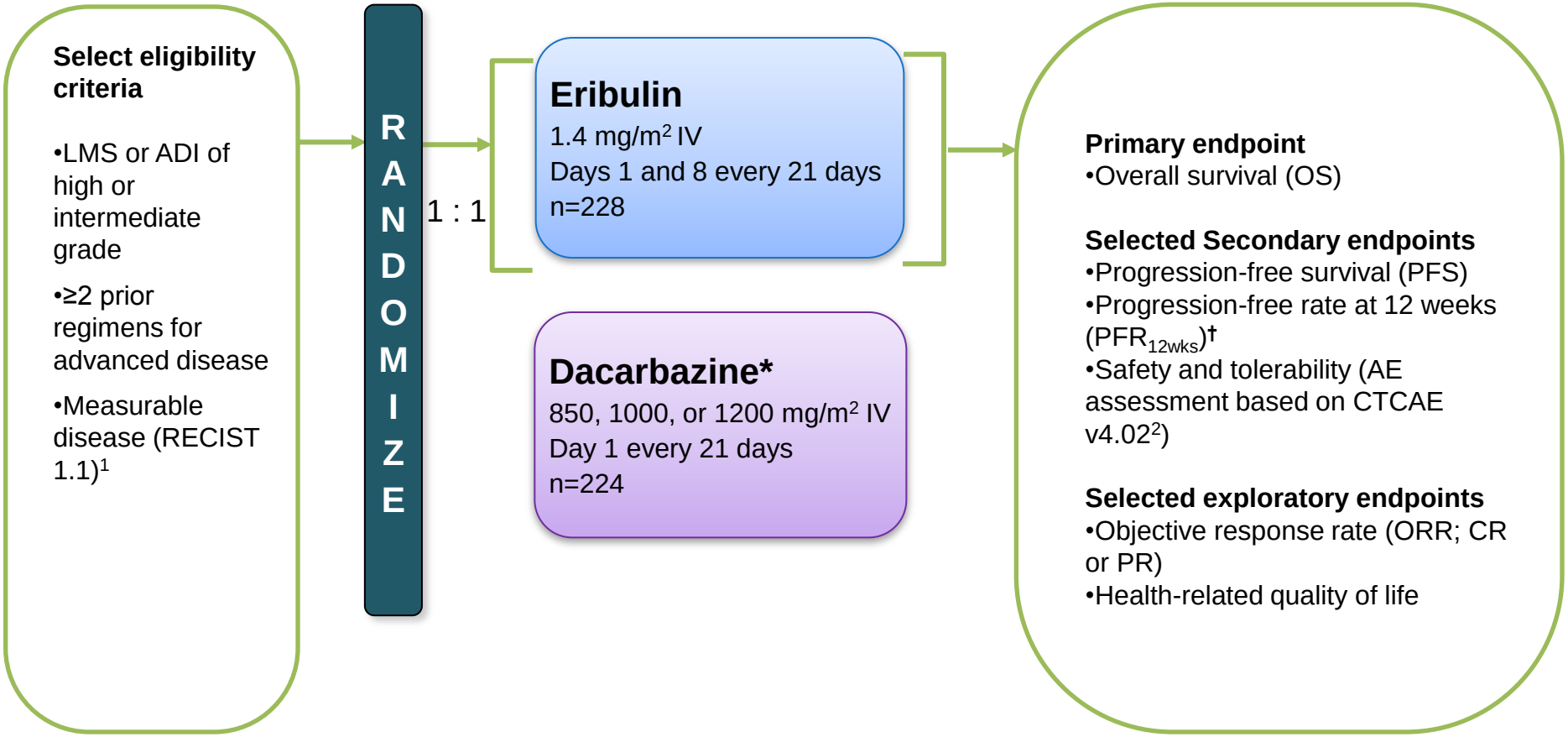


No. Patients at Risk

Dacarbazine	193	149	119	95	89	64	49	33	24	10	6	2	0		
Trabectedin	384	341	287	242	207	153	111	61	35	19	9	5	2	1	0

Patel SR, et al. ECCO 18/ESMO 40; 2015, Sep 25 - 29; Vienna, Austria. Abs. 3403

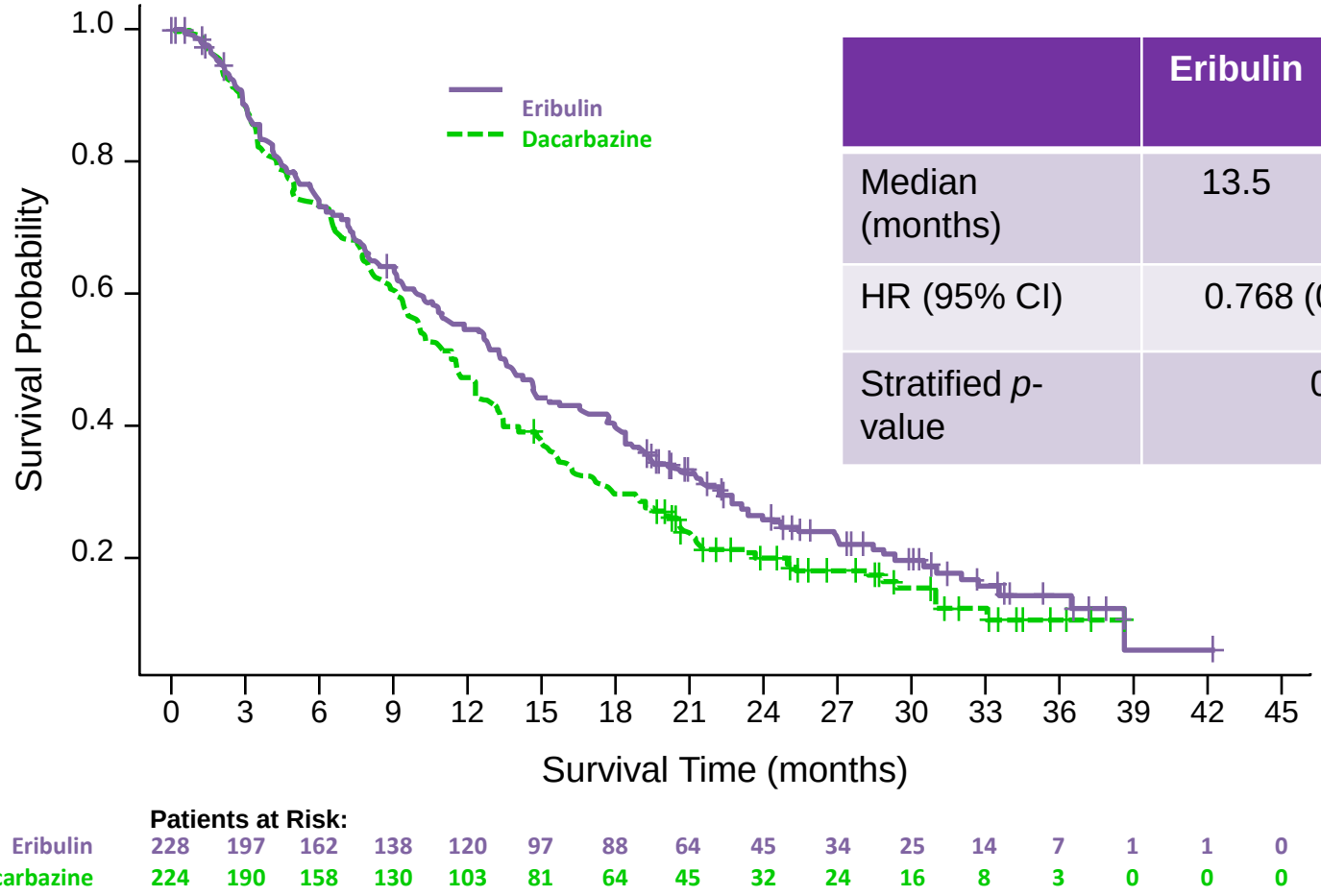
Study design and objectives



*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	

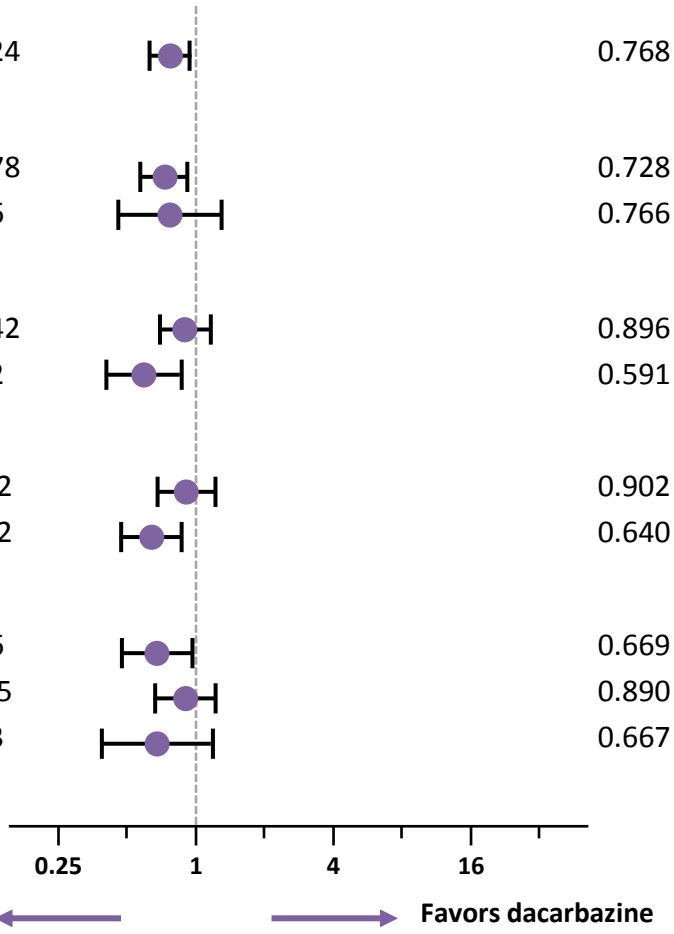
- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

CI, confidence interval.

Schoffski P, et al. ASCO 2015

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

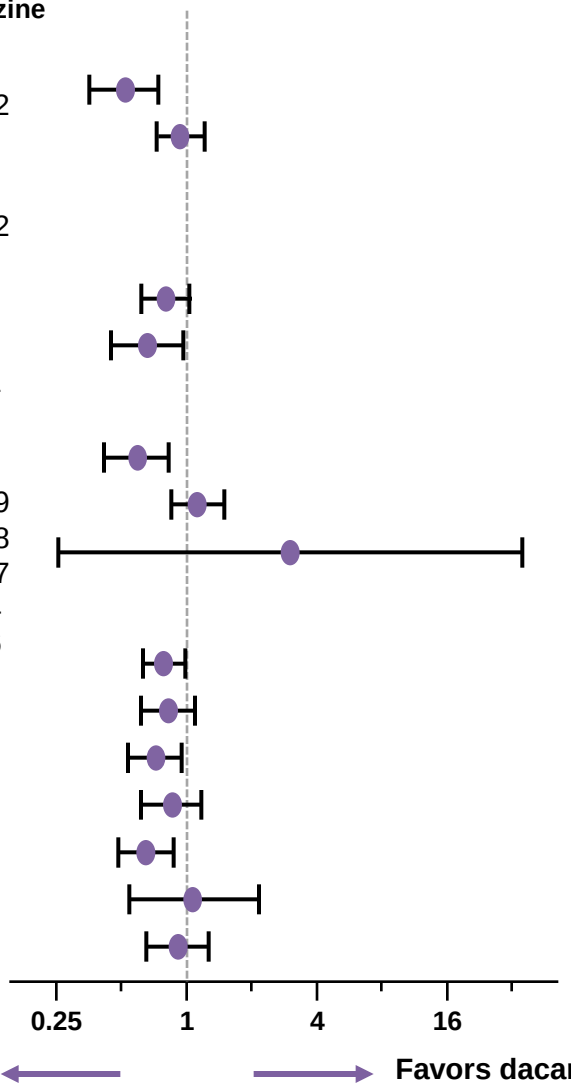


*Region 1: USA, Canada; Region 2: Western Europe, Australia, Israel; Region 3: Eastern Europe, Latin America, Asia.
CI, confidence interval; HR, hazard ratio; STS, soft tissue sarcoma.

Schoffski P, et al. ASCO 2015

Preplanned OS subgroups analysis (continued)

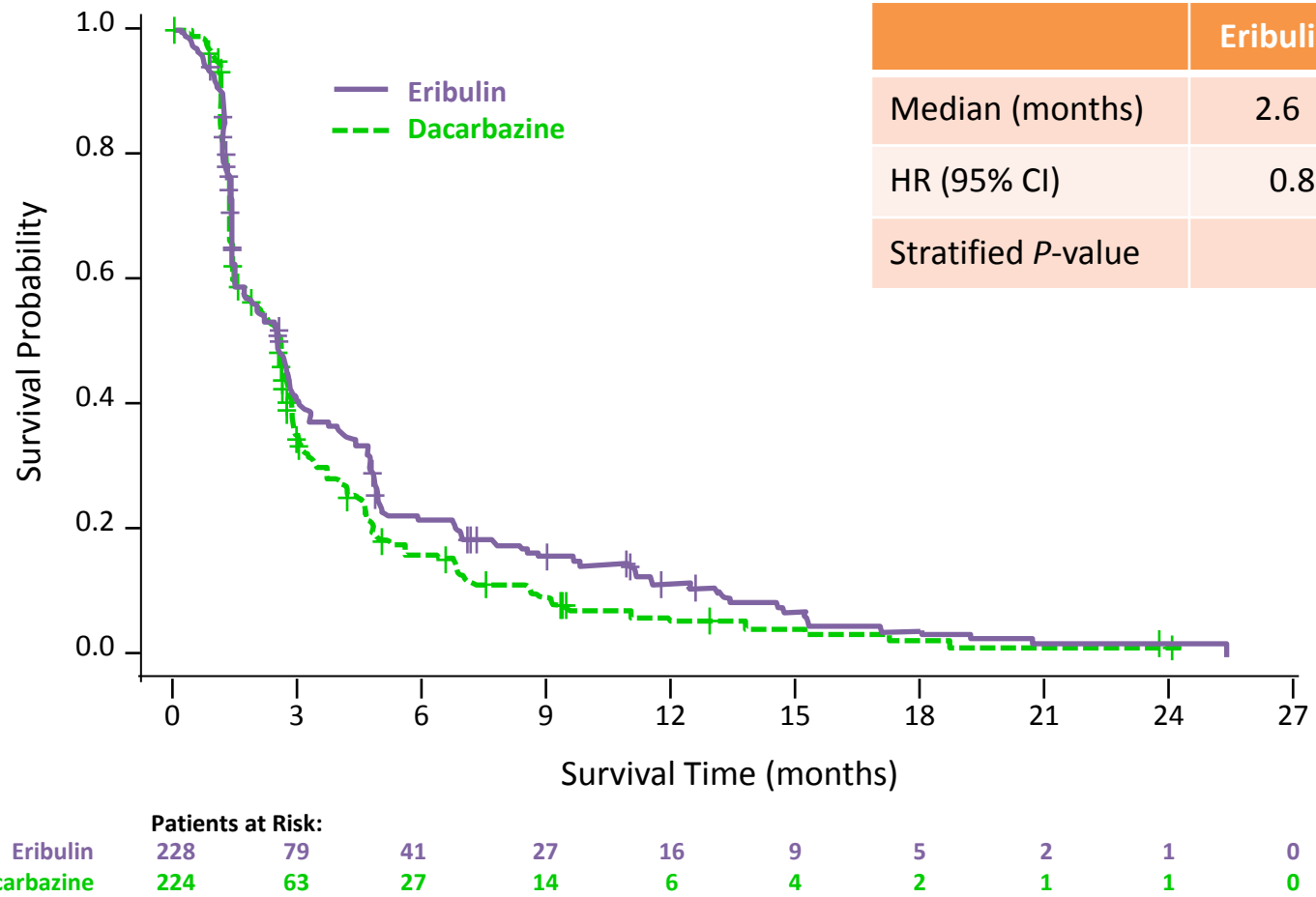
Group/Subgroup	— Events/n — Eribulin	Dacarbazine	HR (95% CI)	Median (months) Eribulin	Dacarbazine
Histology					
ADI	52/71	63/72	0.511 (0.346, 0.753)	15.6	8.4
LMS	124/157	118/152	0.927 (0.714, 1.203)	12.7	13
AJCC sarcoma tumor grade score at the date of diagnosis					
High	118/150	125/152	0.796 (0.607, 1.042)	12.7	11.5
Intermediate	57/77	55/69	0.649 (0.439, 0.961)	14.8	10.1
Baseline ECOG PS					
0	76/111	72/90	0.579 (0.407, 0.823)	19.9	13.1
1	97/114	97/121	1.107 (0.826, 1.484)	9.4	10.1
2	3/3	12/13	3.000 (0.251, 35.794)	1.1	3
Prior anticancer therapy type					
Anthracycline	174/225	177/219	0.770 (0.619, 0.958)	13.5	11.3
Gemcitabine	101/129	111/138	0.803 (0.600, 1.074)	13.2	11.8
Ifosfamide	108/141	115/137	0.701 (0.529, 0.930)	14.7	11
Taxane	87/109	92/114	0.835 (0.604, 1.156)	11.3	11.6
Trabectedine	80/108	98/116	0.643 (0.469, 0.884)	13.3	10.7
Targeted therapy	23/29	19/26	1.067 (0.527, 2.161)	11.3	13.1
Other	66/83	70/90	0.902 (0.631, 1.289)	11.3	12.2



AJCC, American Joint Committee on Cancer.

Schoffski P, et al. ASCO 2015

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	

CI, confidence interval; HR, hazard ratio.

Schoffski P, et al. ASCO 2015

Before treatment you have to answer these questions:

1. What is the aim of giving chemotherapy?
   - Palliation – to prevent progression or to relieve specific symptoms?
   - Down-sizing, i.e. maximum possible tumour shrinkage
   - Prevention of recurrence – systemic, local
2. Does chemotherapy work in this subtype?
3. Are there specific agents that might be best?

Systemic therapy: Conclusion

- Localized Disease:
  - Clear benefit in certain subtypes
  - Unclear in majority soft tissue subtypes

- Advanced / metastatic disease:
  - Mainstay of management
  - Increasing number of agents
  - Clinical trial design
    - Biomarkers
    - Rationale

Thank you – any questions?

Robin.jones@rmh.nhs.uk