Translating the
Academic Medicine Vision

Current landscape of systemic chemotherapy in soft tissue sarcoma

Speaker: Dr Richard Quek
Organization: National Cancer Centre Singapore
Date: 26 Apr 2014

Partners in Academic Medicine

SingHealth

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

National Cancer Centre Singapore
SingHealth

Sarcoma is a Rare Cancer

- <1% of all cancers
- Heterogeneous disease > 40 subtypes
- Incidence USA / year
  - 11,280 new cases of soft tissue sarcomas[1]
  - Incidence : ≈ 3 per 100,000 population
- In National Cancer Centre Singapore
  - 160 to 180 new cases per year

[1] Jemal A et al. CA Cancer J Clin. 2010;60(5):277-300

Adjuvant Chemotherapy in Soft Tissue Sarcoma

Remains Controversial

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Adjuvant CYVADIC Chemotherapy for Adult Soft Tissue Sarcoma—Reduced Local Recurrence but No Improvement in Survival: A Study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

By Vivien Bramwell, Jacques Rouesse, Will Steward, Armando Santoro, H. Schraffordt-Koops, Jose Buesa, Wlodzimierz Ruka, Julio Priario, Theo Wagener, Marion Burgers, Jan Van Unnik, Genevieve Contesso, Denis Thomas, Martine van Glabbeke, David Markham, and Herbert Pinedo

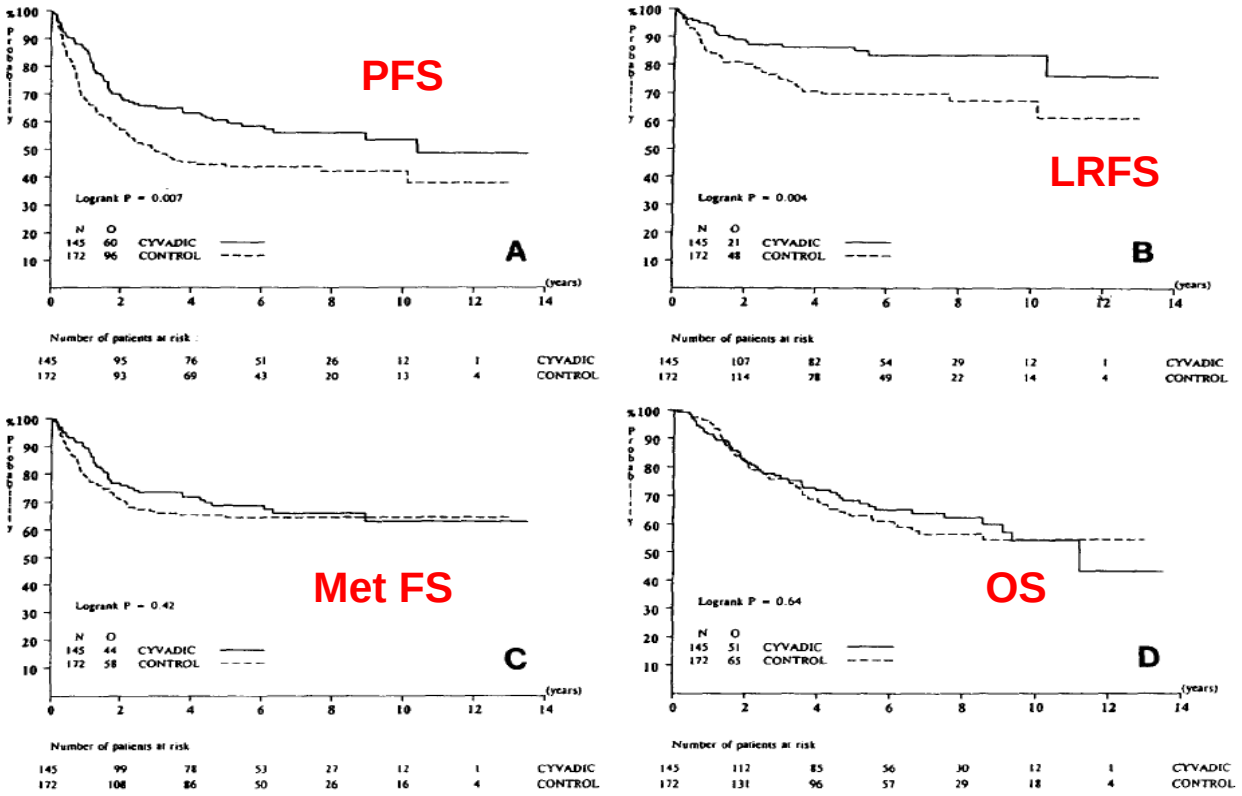


Fig 2. (A) Progression-free survival, (B) local relapse-free survival, (C) metastasis-free survival, and (D) overall survival for CYVADIC v control, all eligible patients.

- 1977 – 1988
- 468 pts
- CYVADIC
  - Cyclophosphamide
  - Vincristine
  - Doxorubicin
  - Dacabazine

Bramwell. J Clin Oncol. 1994;12:1137-49

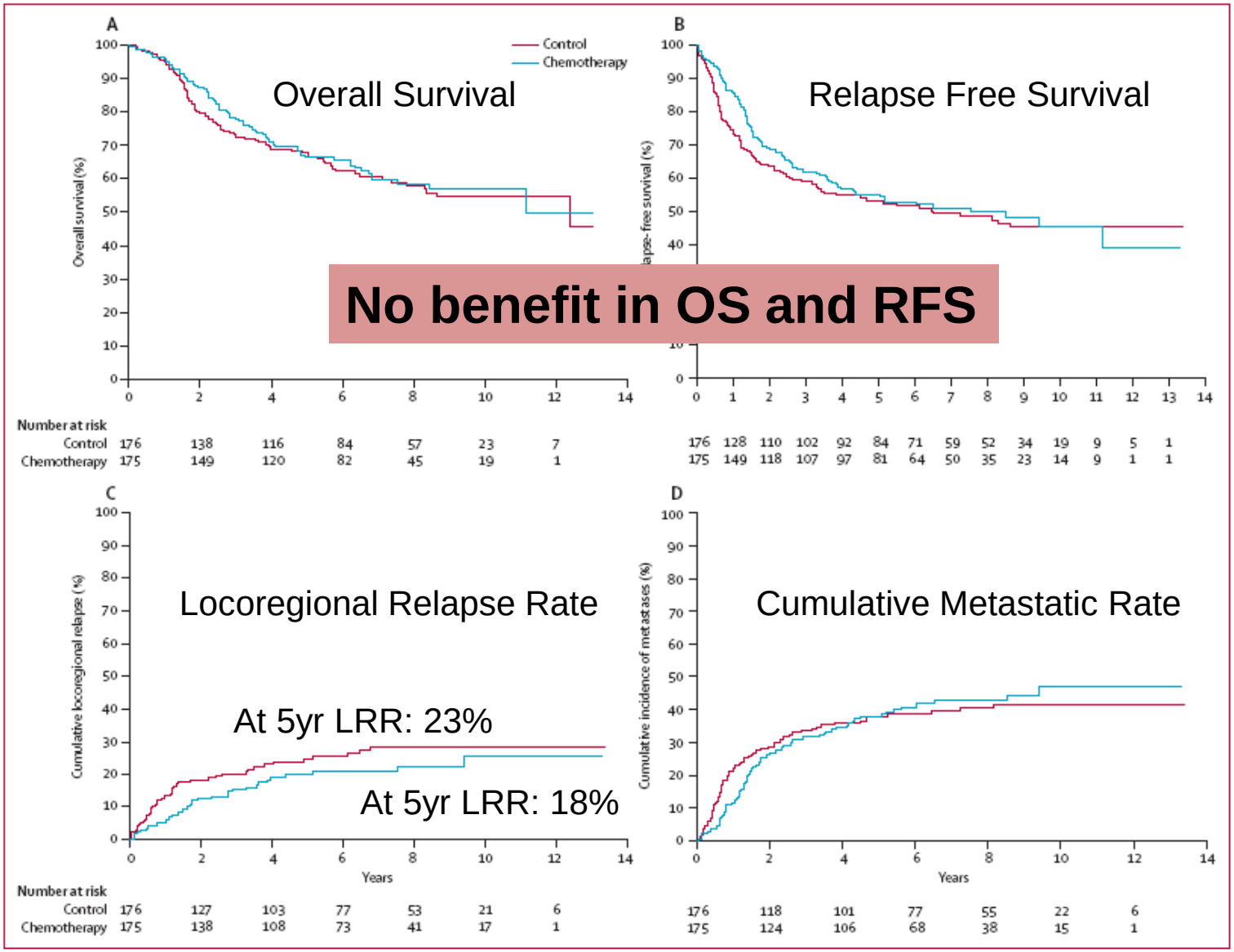
Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli†, Harald J Hoekstra, Michael Leahy, Frits Van Coevorden, Jaap Verweij, Pancras C W Hogendoorn, Monia Ouali, Sandrine Marreaud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee

- Intermediate/ High Grade STS with complete/ marginal excision
- Randomized to adjuvant chemotherapy vs no chemotherapy
- 5 cycles Doxorubicin-ifosfamide q3weeks
  - Doxorubicin (75 mg/m2)
  - Ifosfamide (5 g/m2) with mesna intravenously for 24 h at day 1
  - Lenograstim (3 µg/kg) x 14 days
- Adjuvant radiotherapy to be delayed until the end of chemotherapy

Lancet Oncol 2012; 13: 1045–54

Results EORTC 62931



Meta-Analysis on Adjuvant Chemo

- 1568 pts; 14 trials
- Individual patient data
- Doxorubicin-based chemo (50-90mg/m^2)
- 46% single agent
- 2% doxo-ifos

	Local Recurrence Free Interval	Distant Recurrence Free Interval	Overall Recurrence Free Interval	Overall Survival
Absolute benefit of Adjuvant chemo	**6% (p=0·016)**	10% (p=0·0003)	10% (p=0·0001)	4% (p=0·12)

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

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Systemic Chemotherapy in Advanced Soft Tissue Sarcoma

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General treatment paradigm in Metastatic STS

1st line

- Anthracycline with or without Ifosfamide

2nd line

- Gemcitabine-Docetaxel
- Pazopanib
- Trabectedin
- Dacarbazine

Post 2nd line

- Off labels
- Clinical Trials

Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group**

Doxorubicin 75mg/m2

46% went on to ifosfamide at time of progression

Doxorubicin 75mg/m2 +
Ifosfamide 10grams/m2

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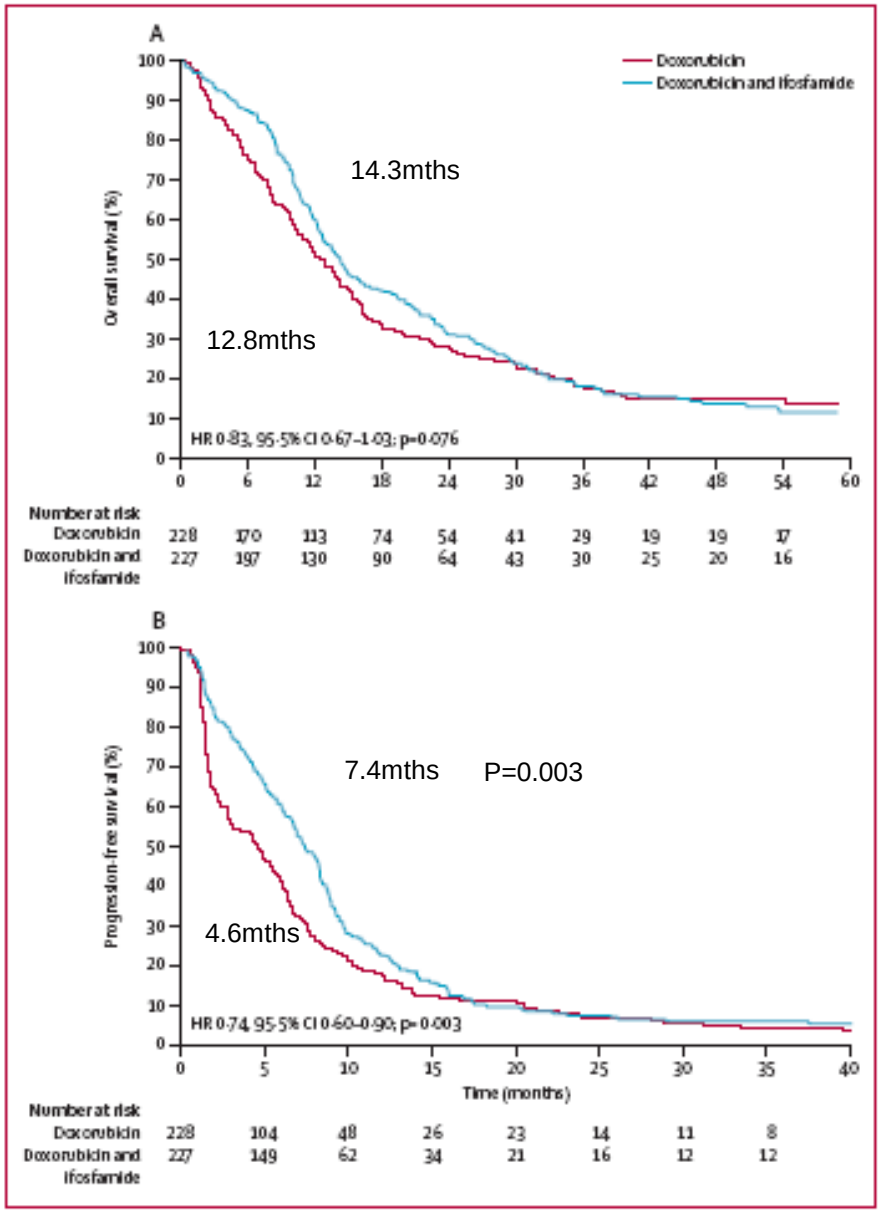
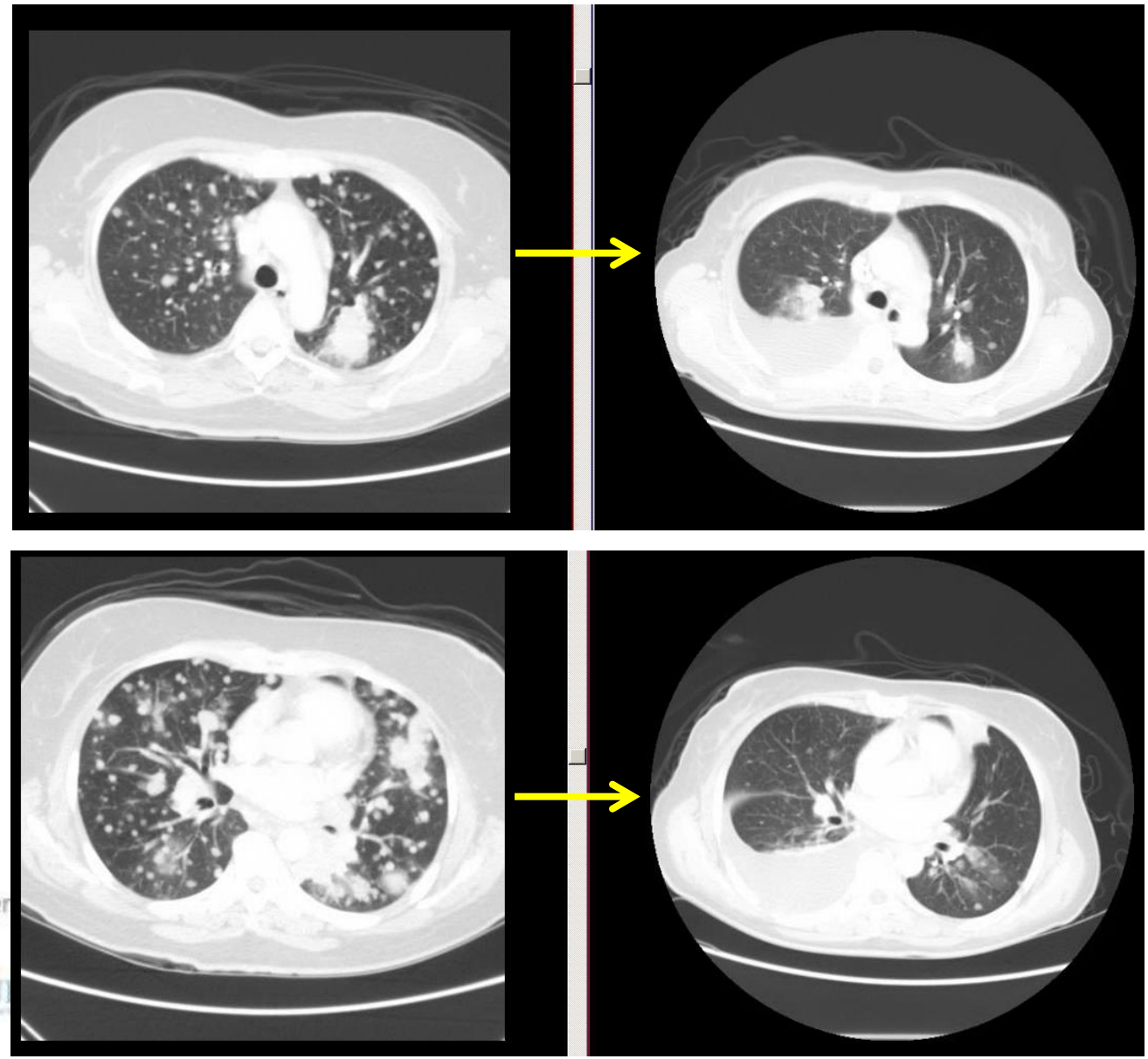
Lancet Oncol. 2014 Apr;15(4):415-23

EORTC 62012

	Response Rate
Doxorubicin	14%
Doxo-Ifosfamide	26% (p<0.0006)



Met LMS s/p 1st Line #5 AI



Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL®/CAELYX®) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group

I. Judson [a,*], J.A. Radford [b], M. Harris [b], J.-Y. Blay [c], Q. van Hoesel [d], A. le Cesne [e], A.T. van Oosterom [f], M.J. Clemons [b], C. Kamby [g], C. Hermans [h], J. Whittaker [i], E. Donato di Paola [h], J. Verweij [j], S. Nielsen [k]

- DOXORUBICIN 75mg/m2 q3wk
- LIPOSOMAL DOXORUBICIN 50mg/m2 q4wks
- N=94

• ORR	10% vs 9%
• Median Time to Progression	2.3mths vs 2.9mths
• Median Overall Survival	11.4mths vs 8.8mths

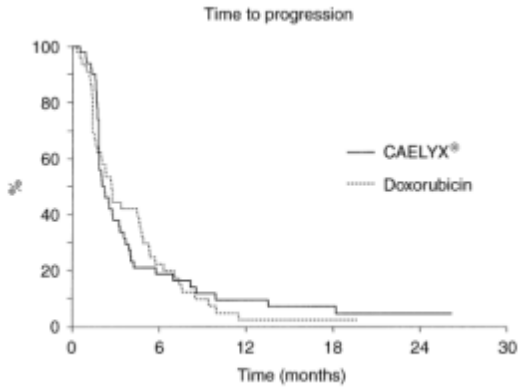
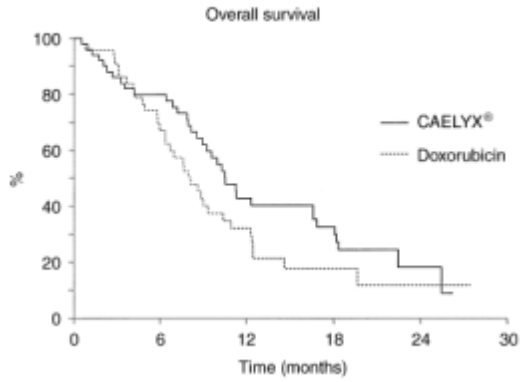
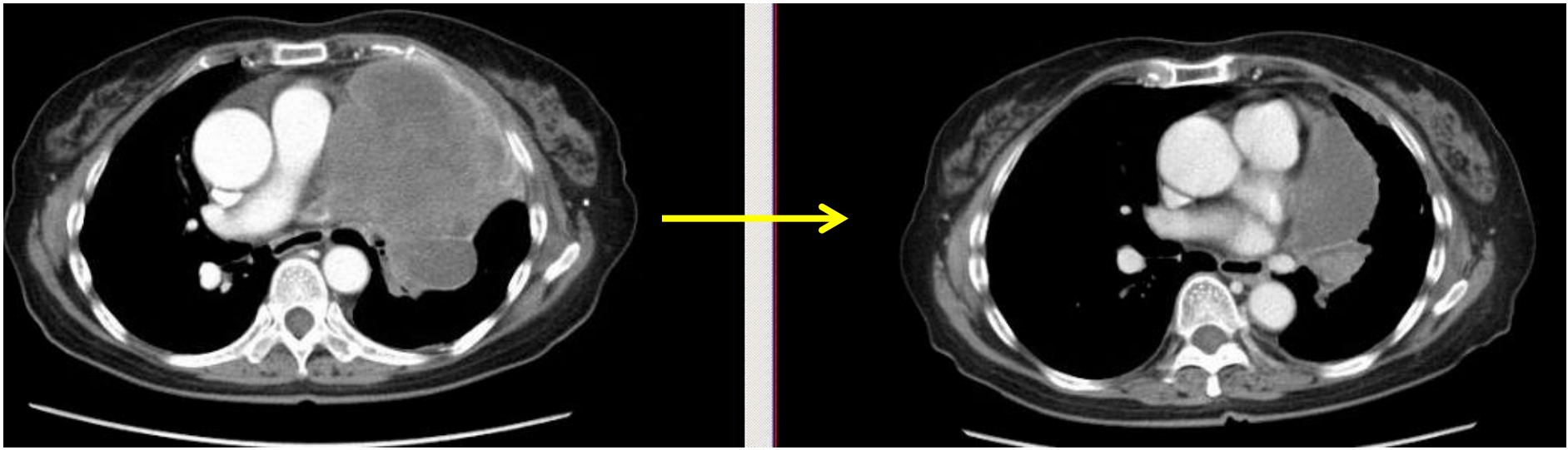


Fig. 2. Percentage probability of progression-free survival versus time.



European Journal of Cancer. 2001;37:870-877

Met Undiff Pleomorphic Sarcoma s/p 1st line #6 Liposomal Doxorubicin



High-Dose Ifosfamide: Circumvention of Resistance to Standard-Dose Ifosfamide in Advanced Soft Tissue Sarcomas

By A. Le Cesne, E. Antoine, M. Spielmann, T. Le Chevalier, E. Brain, C. Toussaint, N. Janin, L. Kayitalire, F. Fontaine, J. Genin, D. Vanel, G. Contesso, and T. Tursz

- High dose ifosfamide 12grams/m2 q4wks
- N=40pts
- 28 pretreated with standard dose ifosfamide

- Significant toxicities
- Response rate 33%
- All but one responding pt had prior standard dose ifosfamide
- High dose ifosfamide may circumvent ifosfamide resistance

J Clin Oncol. 1995;13:1600-1608

2nd line therapy Gemcitabine-based chemotherapy

VOLUME 25 · NUMBER 19 · JULY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

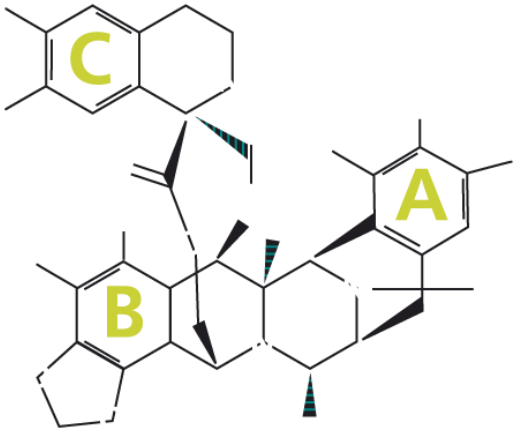
Robert G. Maki, J. Kyle Wathen, Shreyaskumar R. Patel, Dennis A. Priebat, Scott H. Okuno, Brian Samuels, Michael Fanucchi, David C. Harmon, Scott M. Schuetze, Denise Reinke, Peter F. Thall, Robert S. Benjamin, Laurence H. Baker, and Martee L. Hensley

- Gemcitabine-Docetaxel [1]
  - Single center MSKCC study ORR 53%
- SARC 002 Gemcitabine +/- Docetaxel [2]
  - Met STS; n=122
  - Randomized phase II
  - 0-3 prior regimens
  - Improved PFS (6 vs 3mth)
  - Improved OS (18 vs 11 mth)
  - RR 16% vs 8%

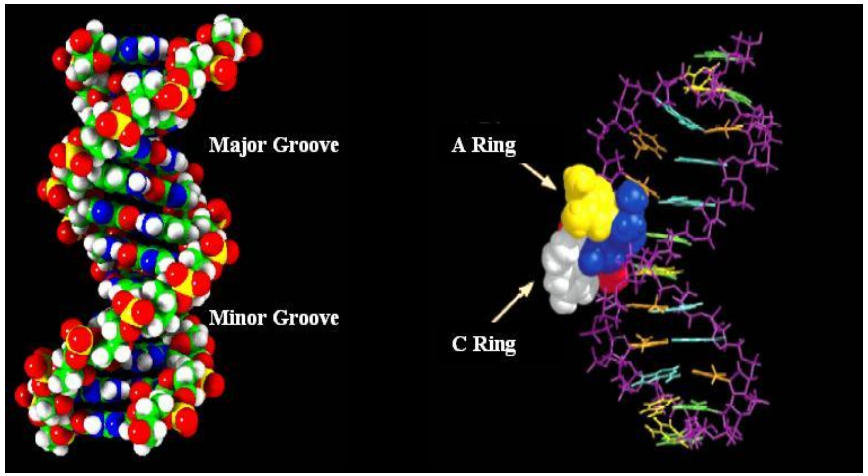
1 Hensley. J Clin Oncol. 2002;20:2824-31
2 Maki. Clin Oncol. 2007;25:2755-63

Trabectedin

- **Originally derived from the Carribean marine tunicate *Ecteinascidia turbinata***



- Trabectedin binds to guanine-rich regions on minor groove of DNA
- Affects binding of transcriptional factors
- Cycle cell arrest in G2/M phase



VOLUME 27 · NUMBER 25 · SEPTEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

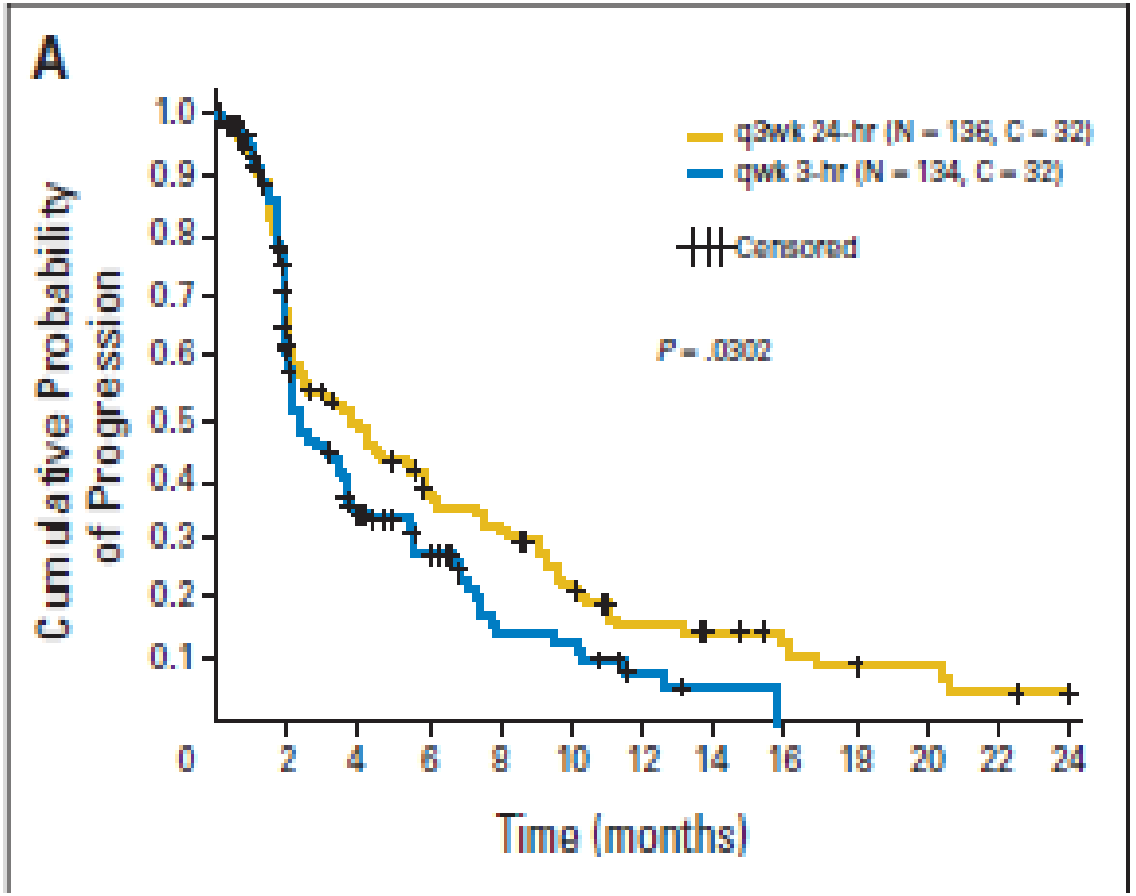
ORIGINAL REPORT

Efficacy and Safety of Trabectedin in Patients With Advanced or Metastatic Liposarcoma or Leiomyosarcoma After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two Different Schedules

George D. Demetri, Sant P. Chawla, Margaret von Mehren, Paul Ritch, Laurence H. Baker, Jean Y. Blay, Kenneth R. Hande, Mary L. Keohan, Brian L. Samuels, Scott Schuetze, Claudia Lebedinsky, Yusri A. Elsayed, Miguel A. Izquierdo, Javier Gómez, Youn C. Park, and Axel Le Cesne

- Inclusion
  - Leiomyosarcoma and liposarcoma
  - Previous treatment with doxorubicin and ifosfamide
- Study arms
  - Arm A: Trabectedin infusion over 24hr q3wks
  - Arm B: Trabectedin infusion over 3hr qwkly 3 out of 4 wks
- Primary end point: Time to progression

Final Results: Time to Progression



Median TTP (mths)
Arm A: 3.7
Arm B: 2.3 (p=0.0302)

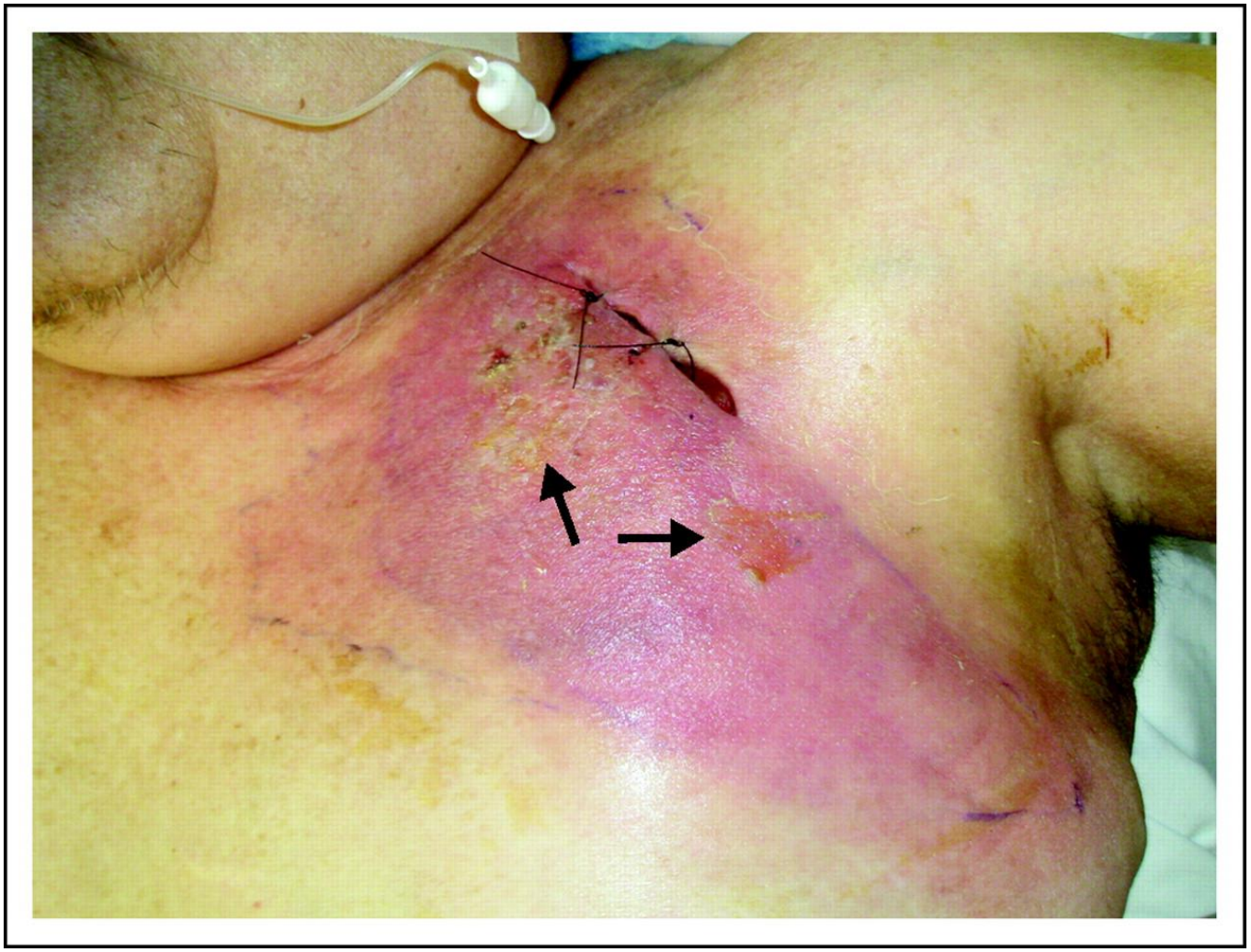
Response Rate
Arm A: 5.6%
Arm B: 1.6%

Progression free 3mths
Arm A: 52%
Arm B: 45%

Median OS (mths)
Arm A: 13.9
Arm B: 11.8 (p=not sig)

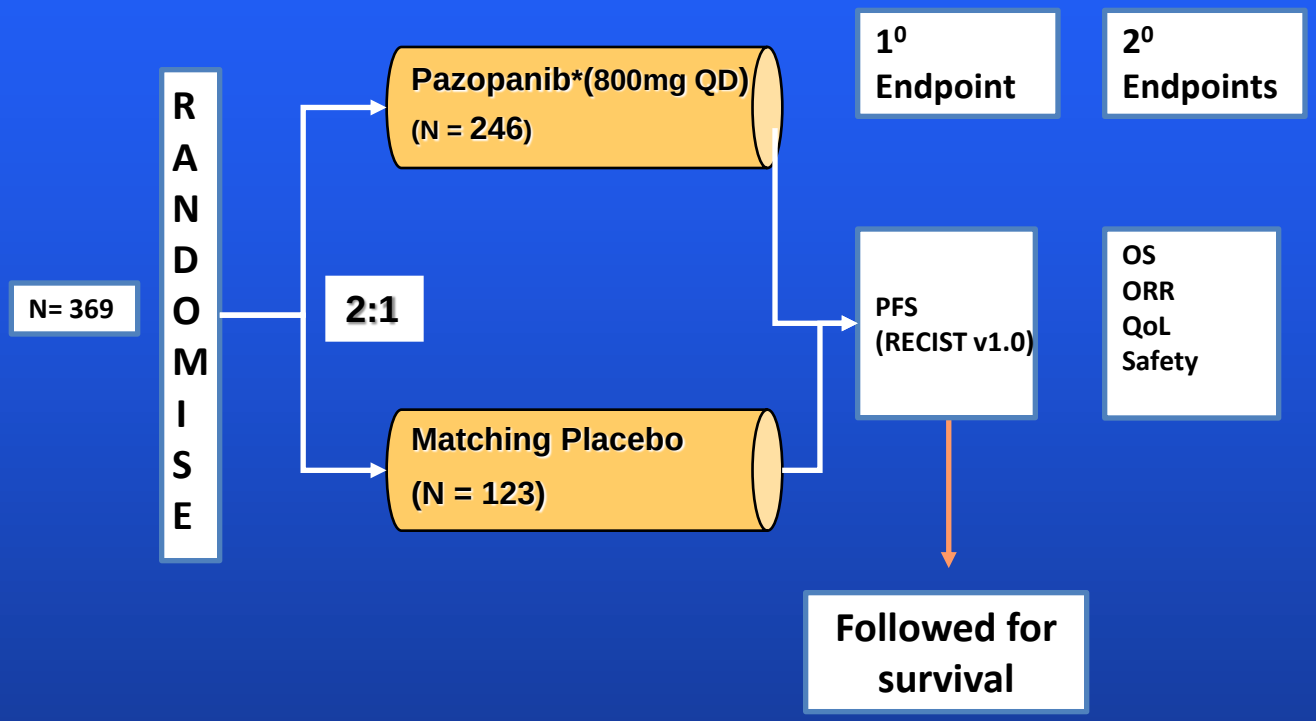
Demetri et al. J Clin Oncol. 2009;27(25):4188-96.

Toxicities: Vesicant



Theman, T. A. et al. J Clin Oncol; 27:e198-200e 2009

PALETTE: Pazopanib Phase III Study Design



Stratification factors

- Performance status (0 vs 1)
- Number of prior lines of systemic therapy for advanced disease (0/1 vs 2+)

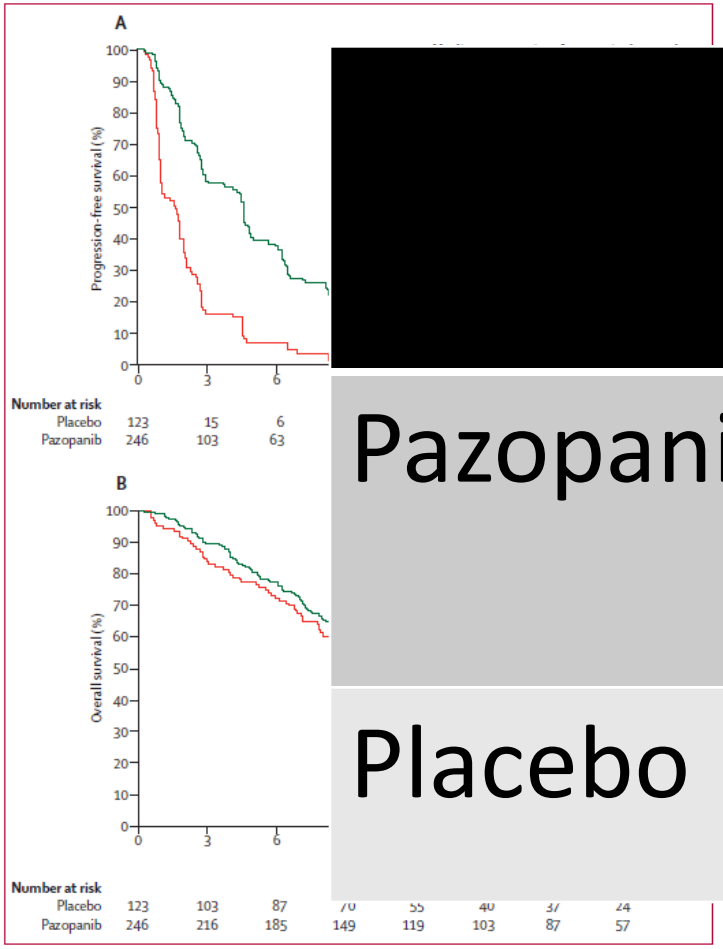
Disease assessment

at week 4-8-12-20 and at 8 week intervals thereafter

* Until disease progression, unacceptable toxicity, withdrawal of consent for any reason, or death

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

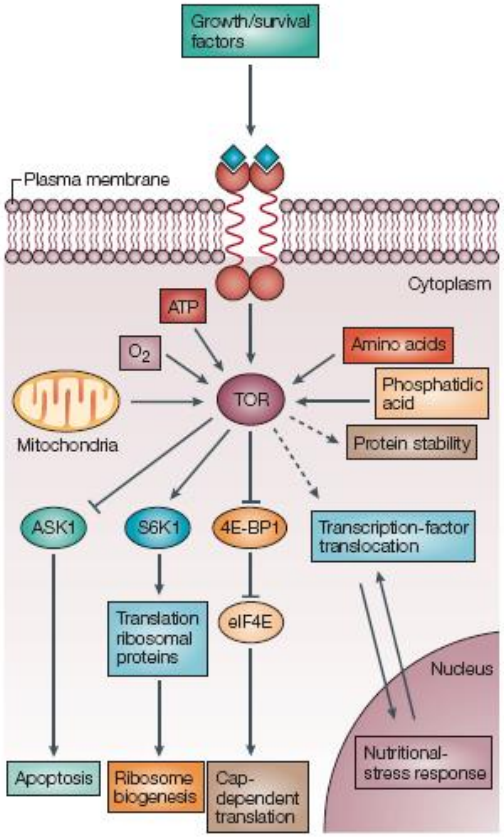


	Response Rate
Pazopanib	**6%**
Placebo	**0%**

Lancet. 2012 May 19;379(9829):1879-86

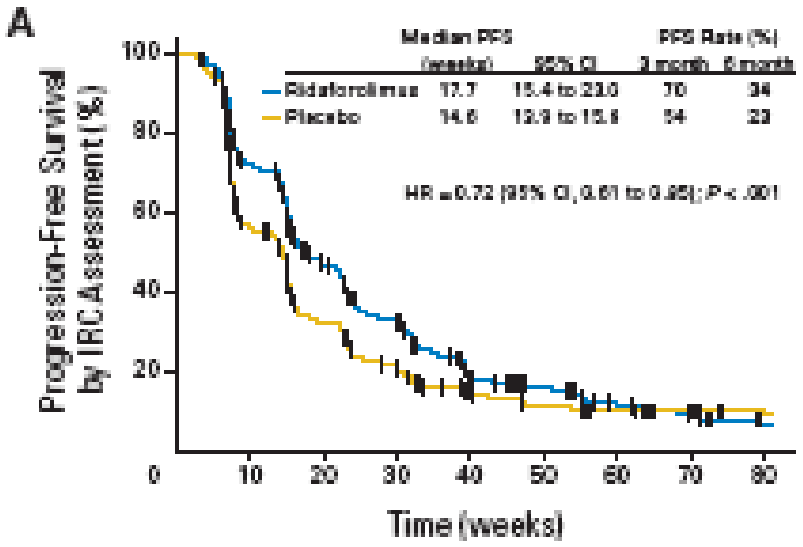
Results of an International Randomized Phase III Trial of the Mammalian Target of Rapamycin Inhibitor Ridaforolimus Versus Placebo to Control Metastatic Sarcomas in Patients After Benefit From Prior Chemotherapy

George D. Demetri, Sant P. Chawla, Isabelle Ray-Coquard, Axel Le Cesne, Arthur P. Staddon, Mohammed M. Milhem, Nicolas Penel, Richard F. Riedel, Binh Bui-Nguyen, Lee D. Cranmer, Peter Reichardt, Emmanuelle Bompas, Thierry Alcindor, Daniel Rushing, Yang Song, Ruey-min Lee, Scot Ebbinghaus, Joseph E. Eid, John W. Loewy, Frank G. Haluska, Pierre F. Dodion, and Jean-Yves Blay



Nat Rev Cancer. 2004 May;4(5):335-48

- **Largest STS trial conducted**
- **N=711 pts**
- **Tested role of mTOR maintenance in STS after chemo**



J Clin Oncol. 2013 Jul 1;31(19):2485-92

P<0.001

Benefit 3 week delay in progression of disease

Soft Tissue Sarcoma

Guidelines Index
Sarcoma Table of Contents
Staging, Discussion, References

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA[a,b]

Extremity, Retroperitoneal, Intra-abdominal

Combination regimens
- AD (doxorubicin, dacarbazine)[1,2]
- AIM (doxorubicin, ifosfamide, mesna)[3,4]
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[5]
- Ifosfamide, epirubicin, mesna[6]
- Gemcitabine and docetaxel[7,8]
- Gemcitabine and vinorelbine[9]

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- Gemcitabine
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- Temozolomide[13]

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- Sunitinib[18]
- Bevacizumab[19]
- All other systemic therapy options as per extremity sarcoma

Desmoid Tumors (Fibromatosis)
- Sulindac[20] or other non-steroidal anti-inflammatory drugs (NSAIDS) including celecoxib[c]
- Tamoxifen[21]
- Toremifene[22]
- Methotrexate and vinblastine[23]
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- Doxorubicin-based regimens[25,26]
- Imatinib mesylate[27]

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- Sunitinib[39,40] (category 2B)

PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
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- Imatinib and cisplatin[46]
- Imatinib and sirolimus[47]

Single agents
- Erlotinib[48]
- Imatinib[49,50]
- Sunitinib[37]

[a] Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.

[b] References for regimens, see SARC-E 2 of 3.

[c] The risk of cardiovascular events may be increased in patients receiving celecoxib. Physicians prescribing celecoxib should consider this emerging information when weighing the benefits against risks for individual patients. (FDA Talk Paper T04-61, Dec 23, 2004)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Summary of Developments in last 12 months

1. Role of adjuvant chemotherapy in resected soft tissue sarcoma (STS) remains controversial

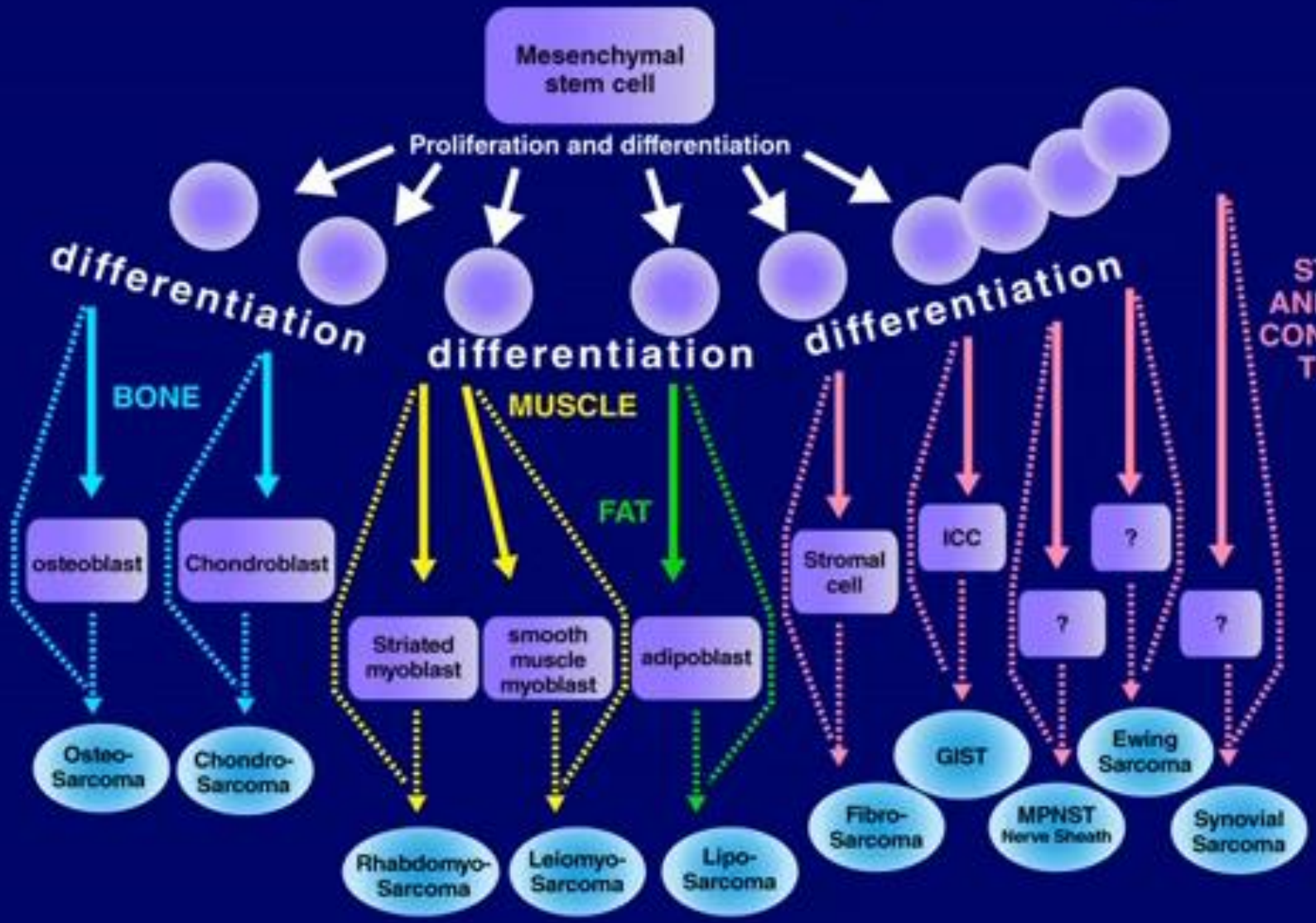
2. HSA approval of Pazopanib for use in advanced STS

3. Limited benefit of maintenance mTOR in STS

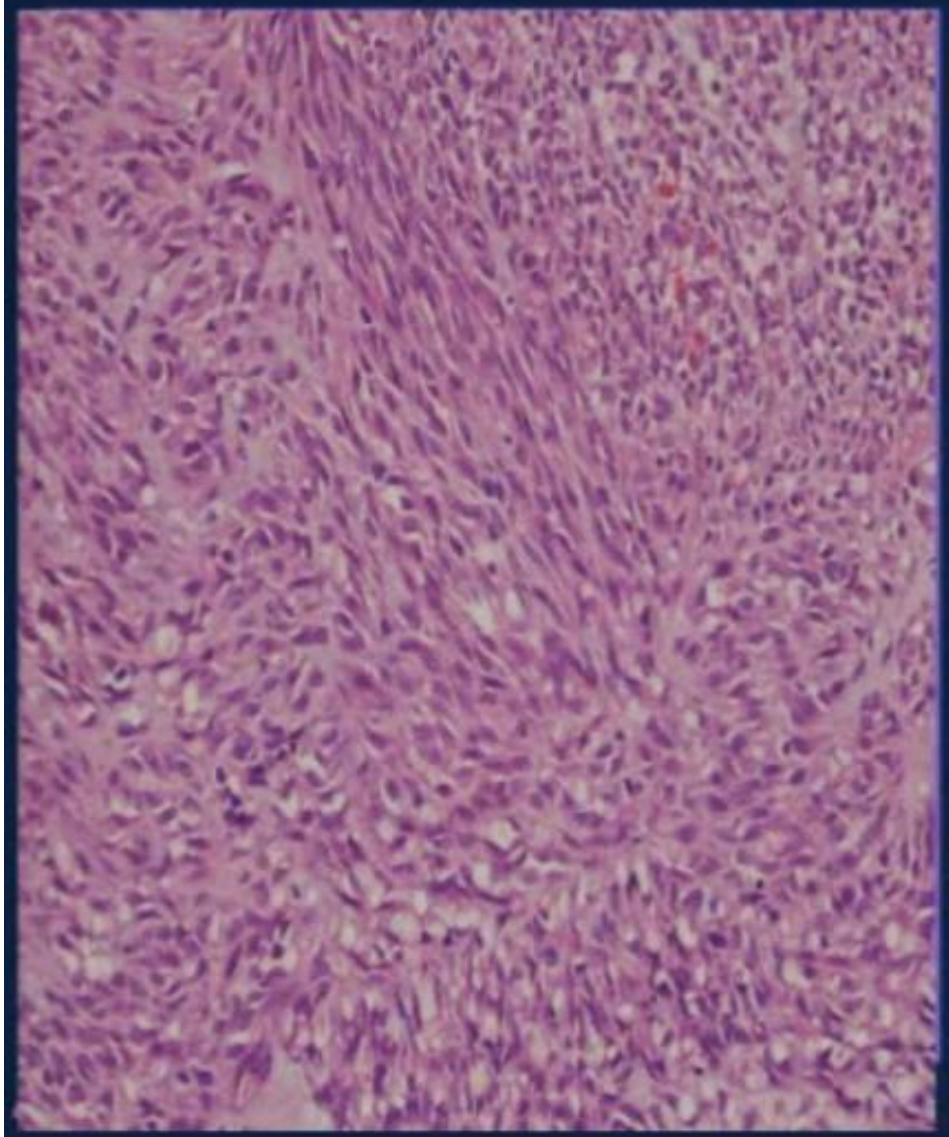
4. Failure of palifosfamide trials in STS

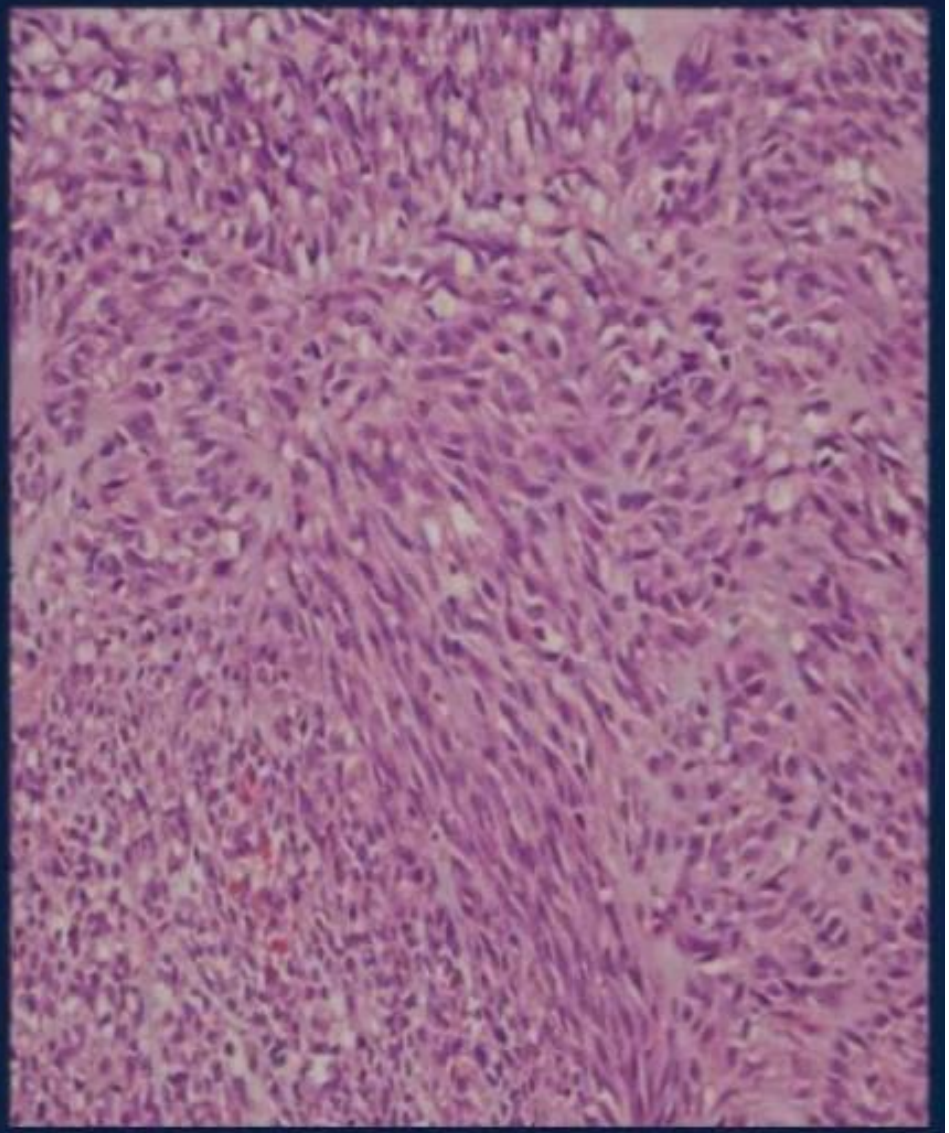
LOOKING AHEAD INTO THE NEXT 12 MONTHS

Sarcomas Are Uncommon Cancers Linked by Mesenchymal Origin

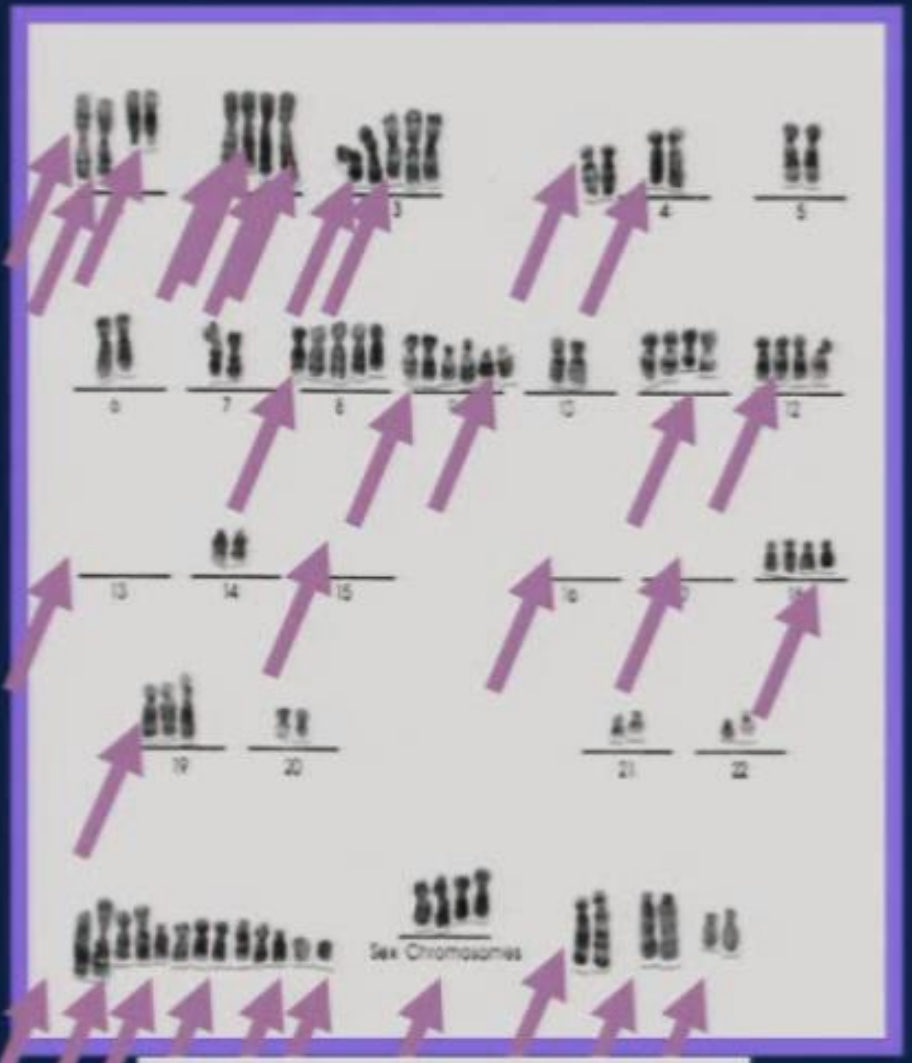


Same Disease? Or Completely Different?

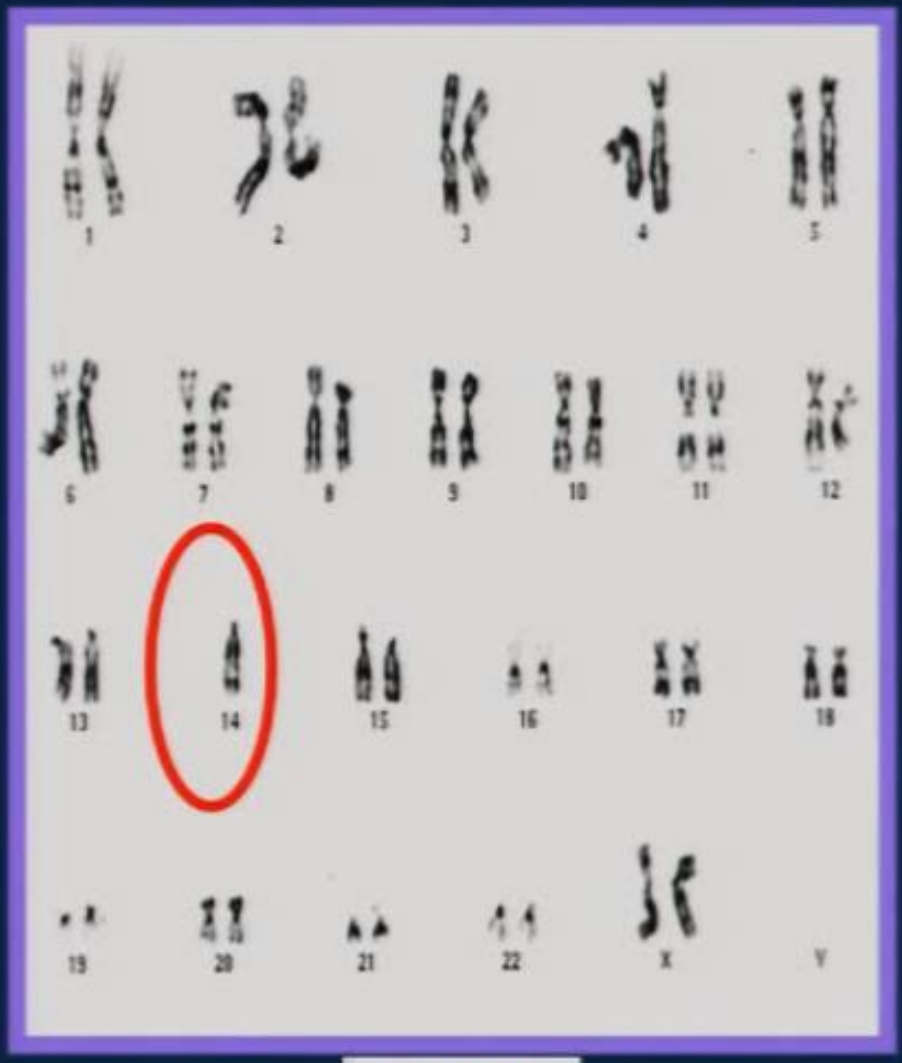




Same Disease? Or Completely Different?



Leiomyosarcoma



GIST

Molecular Classification of STS

	Molecular biology	Genes/chromosomes	STS sub-type
1	Kinase mutation	KIT, PDGFRA	GIST
2	Recurrent translocation	t(11,22) t(X,18) t(2,13); t(1,13)	Ewing's sarcoma Synovial sarcoma Alveolar rhabdomyosarcoma
3	Gene inactivation	Loss of INI1	Epitheloid sarcoma
4	Simple genetic alterations	MDM2 amplification	Liposarcoma
5	Complex cytogenetics		Leiomyosarcoma Angiosarcoma

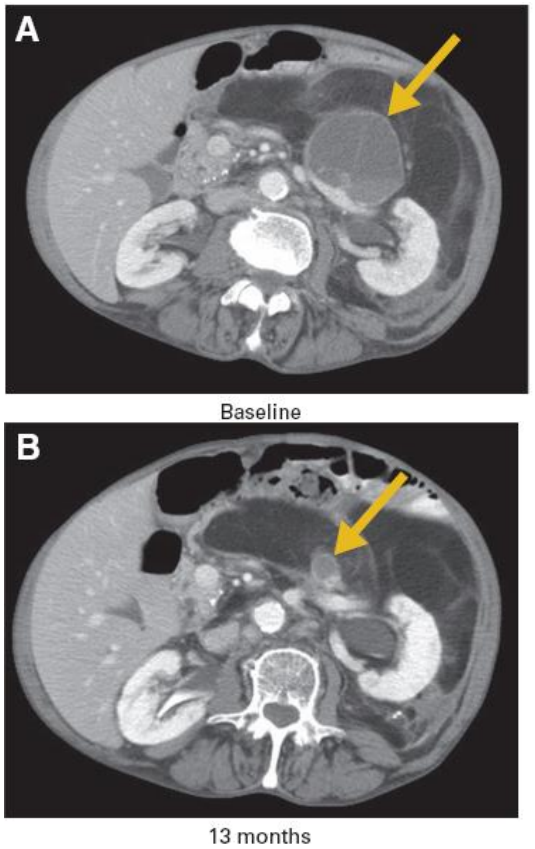
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of the CDK4 Inhibitor PD0332991 in Patients With Advanced *CDK4*-Amplified Well-Differentiated or Dedifferentiated Liposarcoma

Mark A. Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Mercedes M. Condy, Yelena Ustoyev, Aimee M. Crago, Samuel Singer, and Gary K. Schwartz

- CDK4 amplified in well/de-differentiated liposarcoma
- Phase II study of PD0332991 in WD/DD LPS
- Failure of 1st line therapy and prior progression
- N=48
- 66% were progression free at 12 weeks
- 1 objective response



J Clin Oncol. 2013 Jun 1;31(16):2024-8.

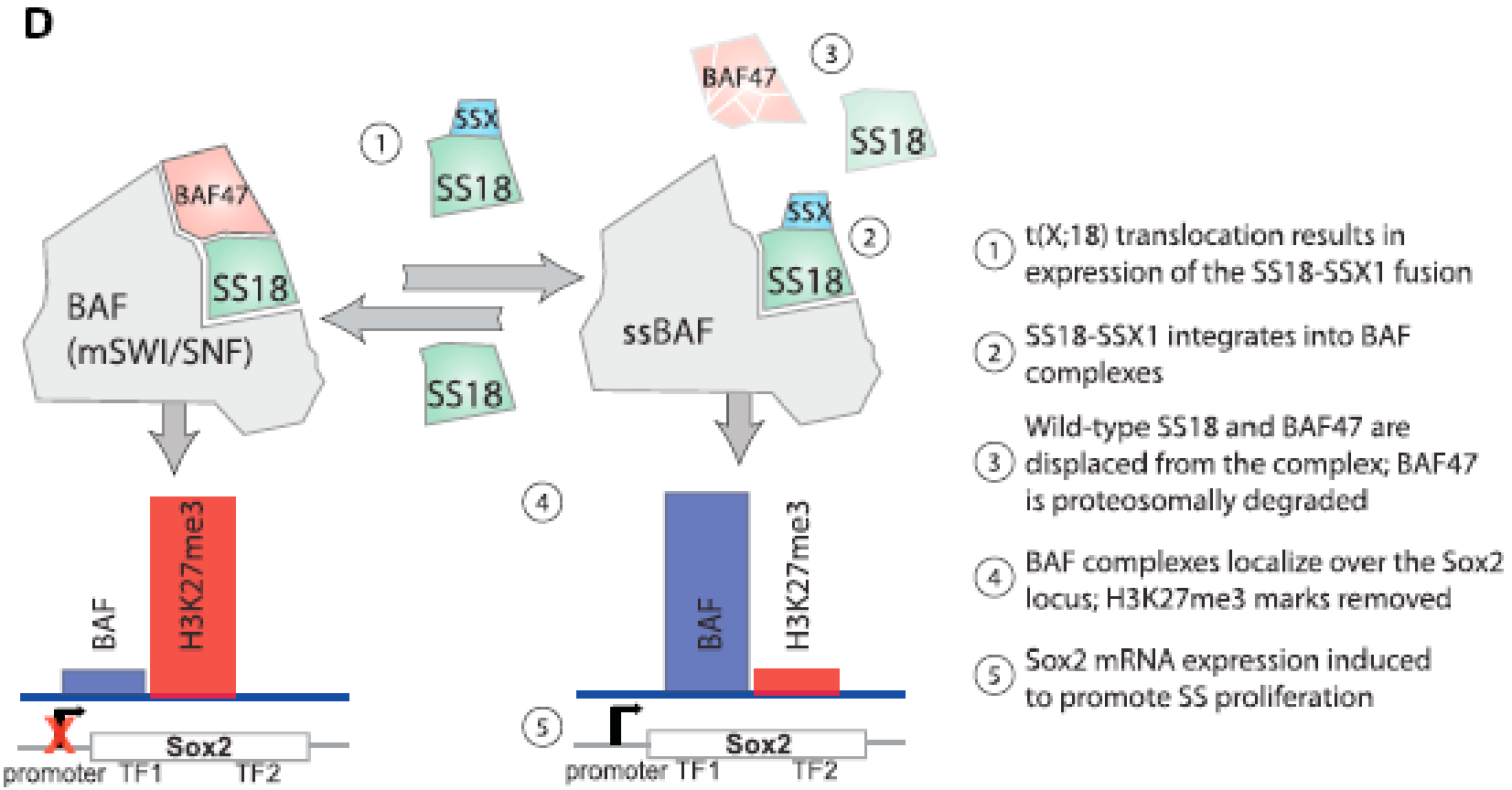
Sarcomas Chromosomal Rearrangements

Tumour	Translocation	Gene fusion	Incidence (%)
ES/PNET	t(11;22)(q24;q12)	*EWS-Fli1*	85
ES/PNET	t(21;22)(q22;q12)	*EWS-ERG*	10
ES/PNET	t(7;22)(p22;q12)	*EWS-ETV1*	rare
ES/PNET	t(17;22)(q12;q12)	*EWS-E1AF*	rare
ES/PNET	t(2;22)(q33;q12)	*EWS-FEV*	rare
DSRCT	t(11;22)(q13;q12)	*EWS-WT1*	95
Myxoliposarcoma	t(12;16)(q13;p11)	*TLS-CHOP*	95
Myxoliposarcoma	t(12;22)(q13;q12)	*EWS-CHOP*	5
Extraskel. Myxoliposarcoma	t(9;22)(q22;q12)	*EWS-CHN*	75
Clear Cell Sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*	n.k.
Synovial sarcoma	t(X;18)(p11.23;q11)	*SYT-SSX1*	65
Synovial sarcoma	t(X;18)(p11.21;q11)	*SYT-SSX2*	35
Alveolar RMS	t(2;13)(q35;q14)	*PAX3-FKHR*	*75*
Alveolar RMS	t(1;13)(p36;q14)	*PAX7-FKHR*	*10*
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*	n.k.
Congenit. FS + mesoblast nephroma	t(12;15)(p13;q25)	*ETV6-NTKR3*	n.k.

aus: De Alava et al.: Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. J Clin Oncol 18:204-213, 2000

Reversible Disruption of mSWI/SNF (BAF) Complexes by the SS18-SSX Oncogenic Fusion in Synovial Sarcoma

Cigall Kadoch[1,2,3,4] and Gerald R. Crabtree[2,3,4,*]



Cell. 2013 Mar 28;153(1):71-85.

And stay tuned for sarcoma symposium 2015…

Thank you !