SOFT TISSUE SARCOMA

"Exceptions" to "standard" medical treatment

Paolo G. Casali
paolo.casali@istitutotumori.mi.it

Potential conflicts of interest

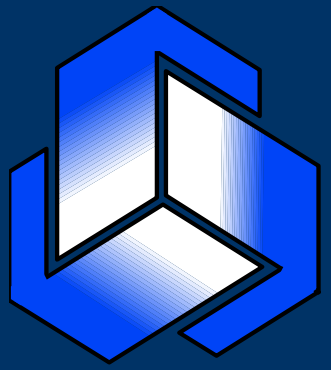
	Empl	Cons	Stocks	Honor	Res (inst.)	Test	Travels
Amgen Dompé		●			●		
ARIAD		●					
Bayer		●			●		
Blueprint Medicines		●					
Eisai		●			●		
Glaxo SK		●			●		
Lilly		●			●		
Merck SD		●					
Merck Serono		●					
Novartis		●		●	●		●
Pfizer		●		●	●		
PharmaMar		●		●	●		●

STS: advanced disease

R <

ADM 75 mg/sqm

ADM 75 mg/sqm + IFX 7.5 g/sqm



EORTC
Soft Tissue & Bone Sarcoma Group

Doxorubicin Versus CYVADIC Versus Doxorubicin Plus Ifosfamide in First-Line Treatment of Advanced Soft Tissue Sarcomas: A Randomized Study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

By Armando Santoro, Thomas Tursz, Henning Mouridsen, Jaap Verweij, Will Steward, Reiner Somers, Jose Buesa, Paolo Casali, David Spooner, Elaine Rankin, Anne Kirkpatrick, Martine Van Glabbeke, and Allan van Oosterom

Purpose: **The aim of this trial was to compare the activity and toxicity of single-agent doxorubicin with that of two multidrug regimens in the treatment of patients with adult advanced soft tissue sarcomas.**

Patients and Methods: **This was a prospective randomized phase III trial performed by 35 cancer centers within the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC). Six hundred sixty-three eligible patients were randomly allocated to receive either doxorubicin 75 mg/m^2 (arm A), cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CYVADIC) (arm B), or ifosfamide 5 g/m^2 plus doxorubicin 50 mg/m^2 (arm C).**

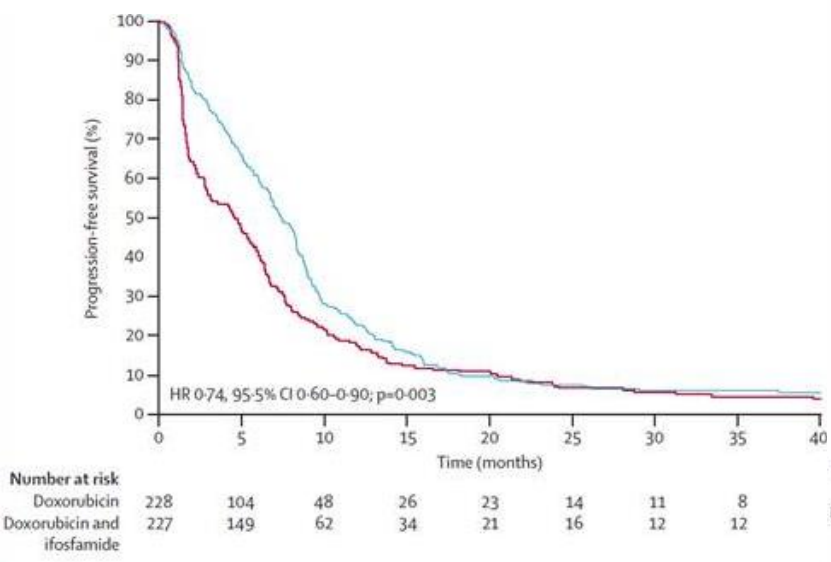
Results: **The overall response rate was 24% (95% confidence interval, 20.7% to 27.3%) among eligible patients and 26% among assessable patients. No statistically significant difference was detected among the three study arms in terms of response rate (arm A, 23.3%; arm B, 28.4%; and arm C, 28.1%), remission duration (median, 46 weeks on arm A, 48 weeks on arm B, and 44 weeks on arm C), or overall survival (median, 52 weeks on arm A, 51 weeks on arm B, and 55 weeks on arm C). The degree of myelosuppression was significantly greater for the combination of ifosfamide and doxorubicin than for the other two regimens. Cardiotoxicity was also more frequent in this arm, but other toxicities were similar.**

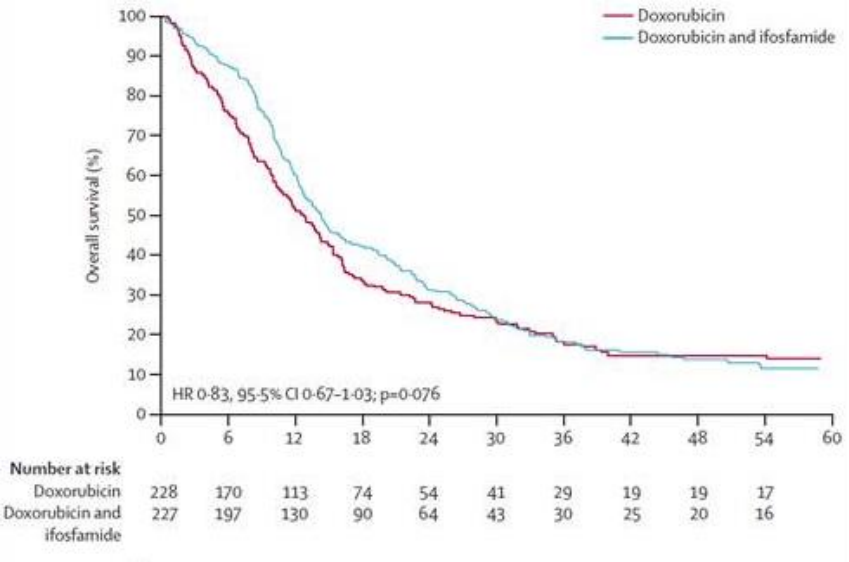
Conclusion: **In advanced soft tissue sarcomas of adults, single-agent doxorubicin is still the standard chemotherapy against which more intensive or new drug treatments should be compared. Combination chemotherapy cannot be recommended outside a controlled clinical trial with the exclusion of some subsets of sarcoma patients for whom significant tumor volume reduction may be an important end point of a chemotherapy regimen.**

J Clin Oncol 13:1537-1545.

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

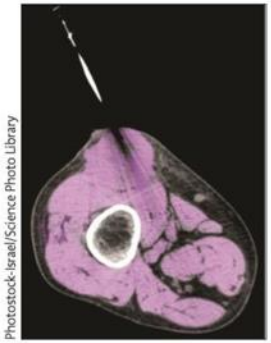
*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo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





Lancet Oncol 2014;15:415

One step forward, two steps back



Photostock-Israel/Science Photo Library

See Articles page 415

Doxorubicin was shown to have activity against soft-tissue sarcomas in 1969.[1] Combination treatment with dacarbazine[2] and ifosfamide[3] improves responses but not progression-free survival or overall survival.[4] Single-agent doxorubicin is still standard treatment in much of Europe. Dose-intensive doxorubicin and ifosfamide, taking advantage of the steep dose–response curves for both drugs, results in high responses and improved progression-free survival and possibly overall survival.[5,6]

In *The Lancet Oncology*, Ian Judson and colleagues[7] report results of a randomised phase 3 study of 455 patients with metastatic soft-tissue sarcoma. Patients entering the study had to have disease progression within 6 weeks of study entry. Doxorubicin alone failed to prevent further progression in 32% of patients, while the combination failed in only 13%. The combination group had a higher overall response than the doxrubicin only group (26% *vs* 14%) and longer median progression-free survival (7·4 months *vs* 4·6 months). Judson and colleagues interpreted their data negatively, concluding that that the difference for the primary endpoint—overall survival—was not statistically significant. We believe that their findings provide convincing evidence that dose-intensive doxorubicin and ifosfamide is superior to doxorubicin alone. Readers should draw their own conclusions.

The ESMO/European Sarcoma Network Working Group*

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
- Sylvie Bonvalot, France
- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
- Palma Dileo, UK
- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
- Stefano Ferrari, Italy
- Hans Gelderblom, Belgium
- Robert Grimer, UK
- Alessandro Gronchi, Italy
- Rick Haas, Netherlands
- Kirsten Sundby Hall, Norway
- Peter Hohenberger, Germany
- Rolf Issels, Germany
- Heikki Joensuu, Finland
- Ian Judson, UK
- Axel Le Cesne, France
- Saskia Litière, Belgium
- Javier Martin-Broto, Spain
- Ofer Merimsky, Israel
- Michael Montemurro, UK
- Carlo Morosi, Italy
- Piero Picci, Italy
- Isabelle Ray-Coquard, France
- Peter Reichardt, Germany
- Piotr Rutkowski, Poland
- Marcus Schlemmer, Germany
- Silvia Stacchiotti, Italy
- Valter Torri, Italy
- Annalisa Trama, Italy
- Frits Van Coevorden, Netherlands
- Winette Van der Graaf, Netherlands
- Daniel Vanel, Italy
- Eva Wardelmann, Germany

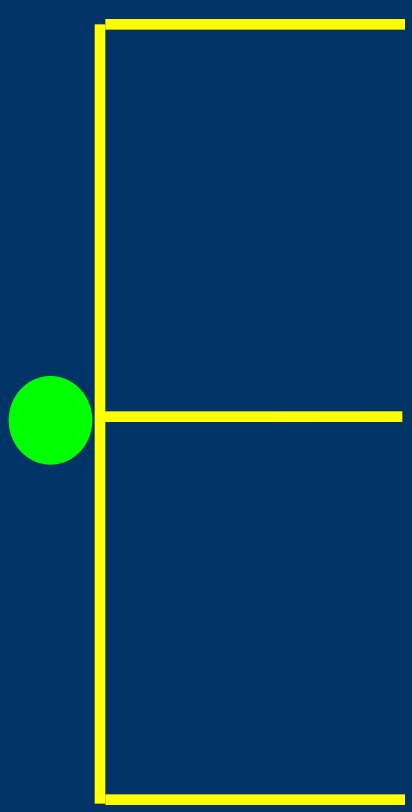
Standard chemotherapy is based on anthracyclines as the first-line treatment [I, A]. As of today, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival (OS). However, a higher response rate can be expected, in particular in a number of sensitive histological types, according to several, although not all, randomised clinical trials [18, 19]. Therefore, multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and patient performance status is good.

In angiosarcoma, taxanes are an alternative option, given their high antitumour activity in this specific histological type [20] [III, B]. An alternative option is gemcitabine ± docetaxel [21] [V, B].

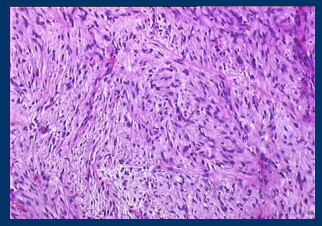
Doxorubicin plus dacarbazine is an option for multiagent first-line chemotherapy of leiomyosarcoma, where the activity of ifosfamide is far less convincing in available retrospective evidence, or solitary fibrous tumour [22] [V, B].

Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating surgery or with metastases deserving medical therapy [23, 24] [III, A].

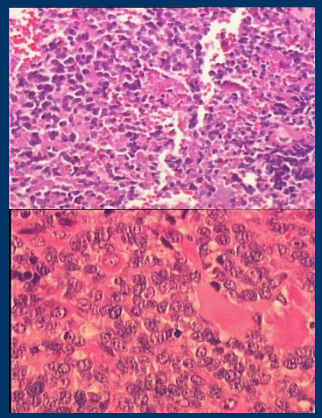
The good old way...



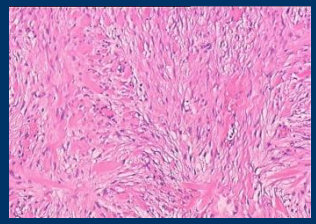
- adult-type soft tissue sarcoma

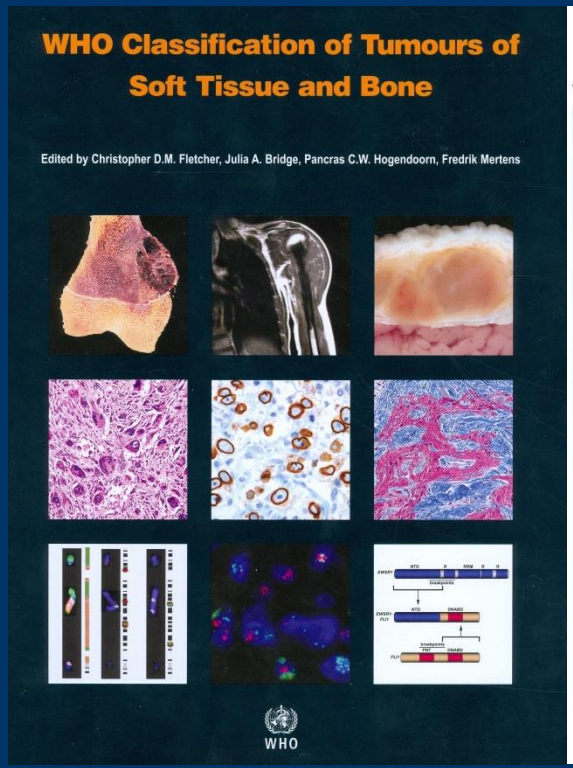


- Ewing's sarcoma
- embryonal / alveolar rhabdomyosarcoma



- desmoid tumor (aggressive fibromatosis)





WHO classification of tumours of soft tissue[a,b]

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
Extra-renal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/pleomorphic lipoma	8857/0
Hibernoma	8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/ well differentiated liposarcoma	8850/1 8850/3

Malignant

Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Pleomorphic liposarcoma	8854/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

Nodular fasciitis	8828/0*
Proliferative fasciitis	8828/0*
Proliferative myositis	8828/0*
Myositis ossificans	
Fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8813/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8816/0*
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Nuchal-type fibroma	8810/0
Gardner fibroma	8810/0
Calcifying fibrous tumour	8817/0*

Intermediate (locally aggressive)

Palmar/plantar fibromatosis	8813/1*
Desmoid-type fibromatosis	8821/1
Lipofibromatosis	8851/1*
Giant cell fibroblastoma	8834/1

Intermediate (rarely metastasizing)

Dermatofibrosarcoma protuberans	8832/1*
Fibrosarcomatous dermatofibrosarcoma protuberans	8832/3*
Pigmented dermatofibrosarcoma protuberans	8833/1*
Solitary fibrous tumour	8815/1*
Solitary fibrous tumour, malignant	8815/3
Inflammatory myofibroblastic tumour	8825/1
Low-grade myofibroblastic sarcoma	8825/3*
Myxoinflammatory fibroblastic sarcoma/ Atypical myxoinflammatory fibroblastic tumour	8811/1*
Infantile fibrosarcoma	8814/3

Malignant

Adult fibrosarcoma	8810/3
Myxofibrosarcoma	8811/3
Low-grade fibromyxoid sarcoma	8840/3*
Sclerosing epithelioid fibrosarcoma	8840/3*

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Tenosynovial giant cell tumour localized type	9252/0
diffuse type	9252/1*
malignant	9252/3
Deep benign fibrous histiocytoma	8831/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissues	9251/1

SMOOTH MUSCLE TUMOURS

Benign

Deep leiomyoma	8890/0

Malignant

Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
Glomangiomatosis	8711/1*
Malignant glomus tumour	8711/3
Myopericytoma	8824/0
Myofibroma	8824/0
Myofibromatosis	8824/1
Angioleiomyoma	8894/0

SKELETAL MUSCLE TUMOURS

Benign

Rhabdomyoma	8900/0
Adult type	8904/0
Fetal type	8903/0
Genital type	8905/0

Malignant

Embryonal rhabdomyosarcoma (including botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma (including solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3
Spindle cell/sclerosing rhabdomyosarcoma	8912/3

VASCULAR TUMOURS OF SOFT TISSUE

Benign

Haemangioma	9120/0
Synovial	
Venous	9122/0
Arteriovenous haemangioma/malformation	9123/0
Intramuscular	9133/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma	9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma	9136/1*
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3

Malignant

Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

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

GASTROINTESTINAL STROMAL TUMOURS

Benign gastrointestinal stromal tumour	8936/0
Gastrointestinal stromal tumour, uncertain malignant potential	8936/1
Gastrointestinal stromal tumour, malignant	8936/3

NERVE SHEATH TUMOURS

Benign

Schwannoma (including variants)	9560/0
Melanotic schwannoma	9560/1*
Neurofibroma (incl. variants)	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9671/0
Malignant perineurioma	9671/3
Granular cell tumour	9580/0
Dermal nerve sheath myxoma	9562/0
Solitary circumscribed neuroma	9570/0
Ectopic meningioma	9530/0
Nasal glial heterotopia	
Benign Triton tumour	
Hybrid nerve sheath tumours	9563/0*

Malignant

Malignant peripheral nerve sheath tumour	9540/3
Epithelioid malignant peripheral nerve sheath tumour	9542/3*
Malignant Triton tumour	9561/3
Malignant granular cell tumour	9580/3
Ectomesenchymoma	8921/3

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma	8811/0
Intramuscular myxoma (including cellular variant)	8840/0
Juxta-articular myxoma	8840/0
Deep ("aggressive") angiomyxoma	8841/0*
Pleomorphic hyalinizing angiectatic tumour	8822/1*
Ectopic hamartomatous thymoma	8587/0

Intermediate (locally aggressive)

Haemosiderotic fibrolipomatous tumour	8811/1*

Intermediate (rarely metastasizing)

Atypical fibroxanthoma	8830/1
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
Ossifying fibromyxoid tumour, malignant	8842/3*
Mixed tumour NOS	8940/0
Mixed tumour NOS, malignant	8940/3
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Phosphaturic mesenchymal tumour, benign	8990/0
Phosphaturic mesenchymal tumour, malignant	8990/3

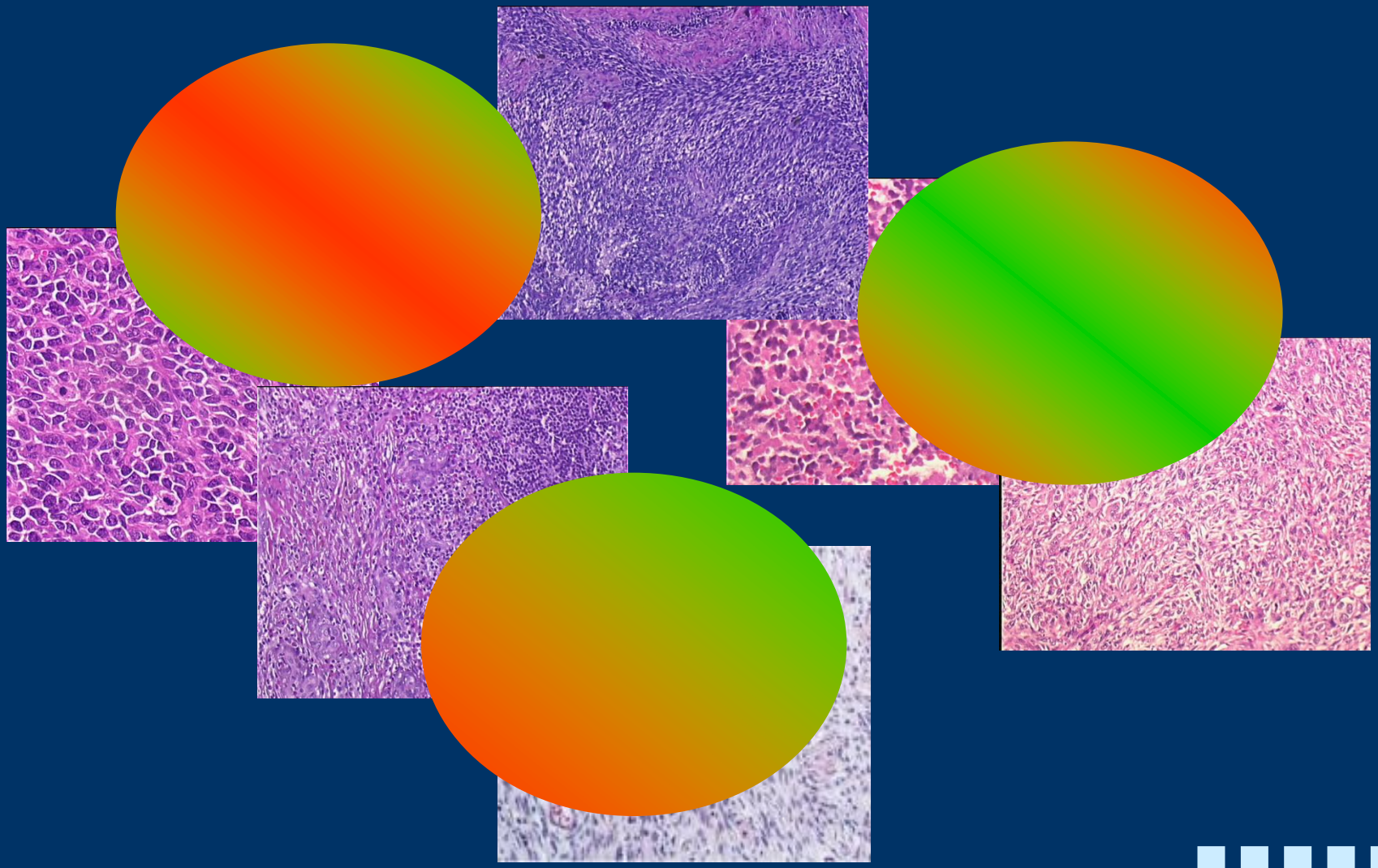
Malignant

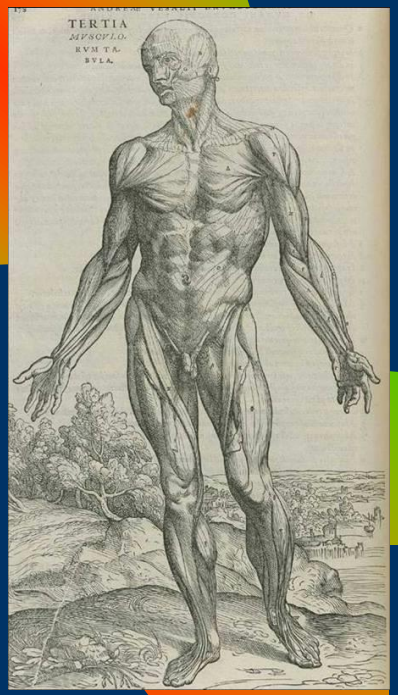
Synovial sarcoma NOS	9040/3
Synovial sarcoma, spindle cell	9041/3
Synovial sarcoma, biphasic	9043/3
Epithelioid sarcoma	8804/3
Alveolar soft-part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
Extraskeletal Ewing sarcoma	9364/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	
PEComa NOS, benign	8714/0*
PEComa NOS, malignant	8714/3*
Intimal sarcoma	9137/3*

UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

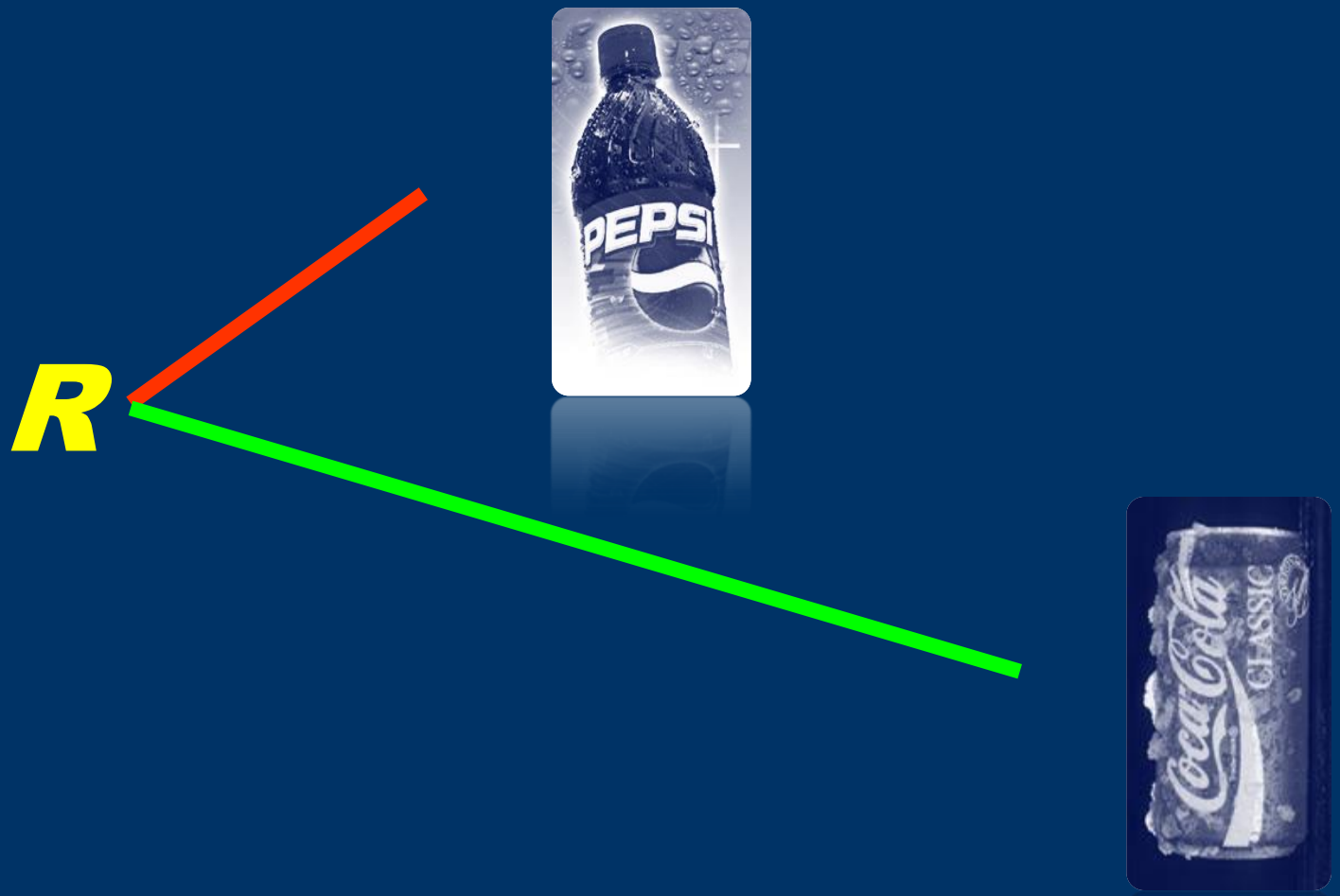
Undifferentiated spindle cell sarcoma	8801/3
Undifferentiated pleomorphic sarcoma	8802/3
Undifferentiated round cell sarcoma	8803/3
Undifferentiated epithelioid sarcoma	8804/3
Undifferentiated sarcoma NOS	8805/3

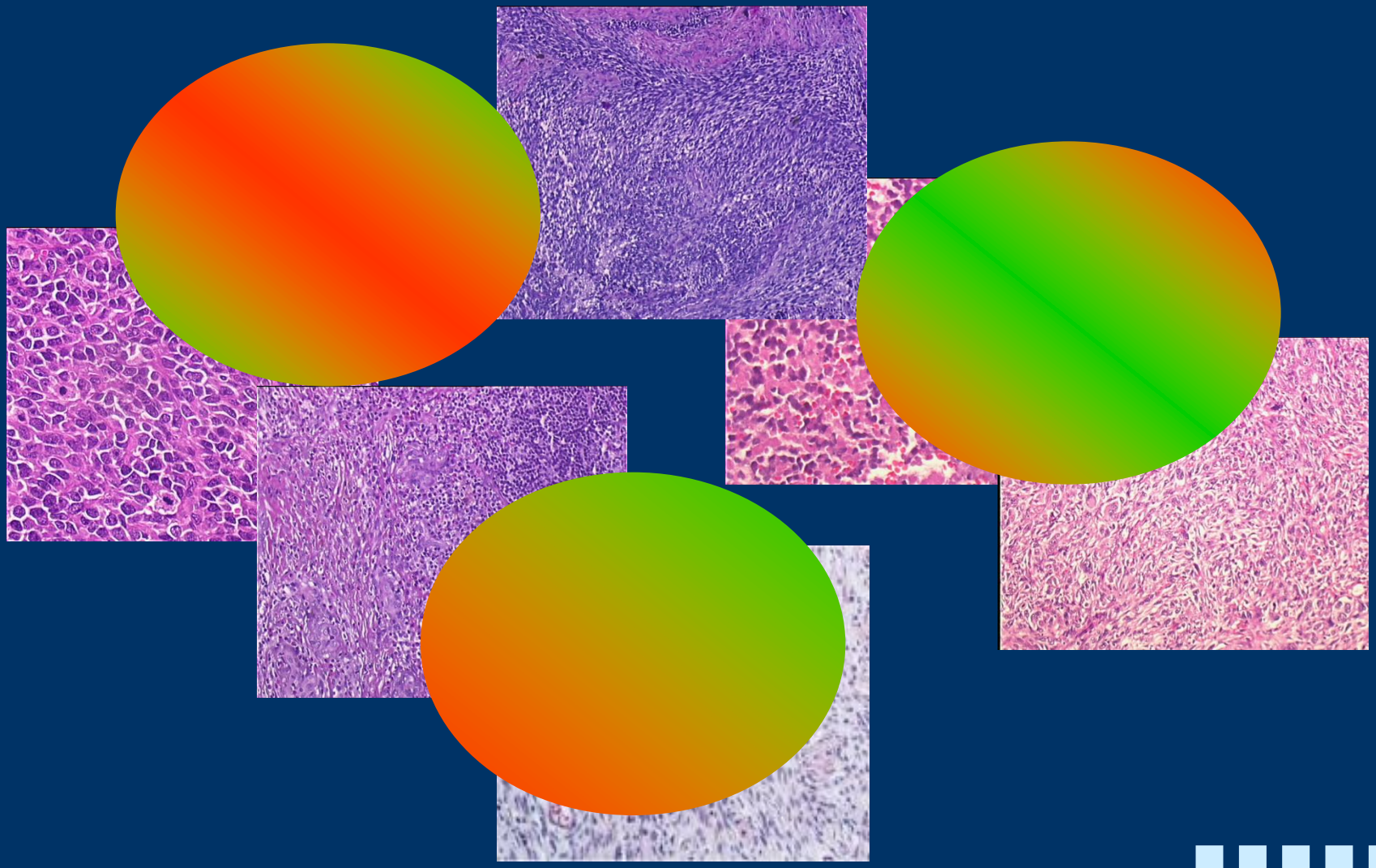
[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (916A). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumours. [b] The classification is modified from the previous WHO histological classification of tumours (870A) taking into account changes in understanding of these lesions. * These new codes were approved by the IARC/WHO Committee for ICD-O in 2012.





Head & neck	5%
Superficial trunk	10%
Retroperitoneum	15%
Viscera	10%
Limbs	60%


R
PEPSI
Coca-Cola
CLASSIC



PHASE II EVALUATION OF ADRIAMYCIN IN HUMAN NEOPLASIA

ROBERT M. O'BRYAN, MD,* JAMES K. LUCE, MD,† ROBERT W. TALLEY, MD,‡
JEFFREY A. GOTTLIEB, MD,§ LAURENCE H. BAKER, DO,‖
AND GIANNI BONADONNA, MD**

Four hundred and seventy-two patients with treated with two or more doses of adriamycin risk" patients was 75 mg/m² every 3 weeks, was 60 mg/m² every 3 weeks. Objective rem patients, with best results noted in lymphom and carcinoma of the breast (16/50). Eight occurred within three courses. Hematopoietic t of patients; nausea, vomiting, and/or stoma Changes in electrocardiograms were seen in 42 doses of adriamycin ranging from 45 mg/m congestive heart failure occurred in two patie 555 mg/m² and 825 mg/m², respectively. It is an active agent, most remissions occur pro toxic reactions appear to be cumulative.

Sarcoma		
Osteogenic sarcoma	5/9	
Leiomyosarcoma	3/8	
Fibrosarcoma	2/14	
Rhabdomyosarcoma	3/11	
Ewing's sarcoma	2/7	
Chondrosarcoma	1/3	
Liposarcoma	1/3	
Hemangiosarcoma	2/3	
Hemangiopericytoma	1/2	
Neuroepithelioma	1/1	
"Others"	0/3	
	21/64	33%

Cancer 1973;32:1

A Phase II Trial of Temozolomide in Patients with Unresectable or Metastatic Soft Tissue Sarcoma

Susan M. Talbot, M.D.[1]
Mary Louise Keohan, M.D.[1]
Mary Hesdorffer, B.S.N.[1]
Russell Orrico, B.S.[1]
Emilia Bagiella, Ph.D.[2]
Andrea B. Troxel, Sc.D.[2]
Robert N. Taub, M.D., Ph.D.[1]

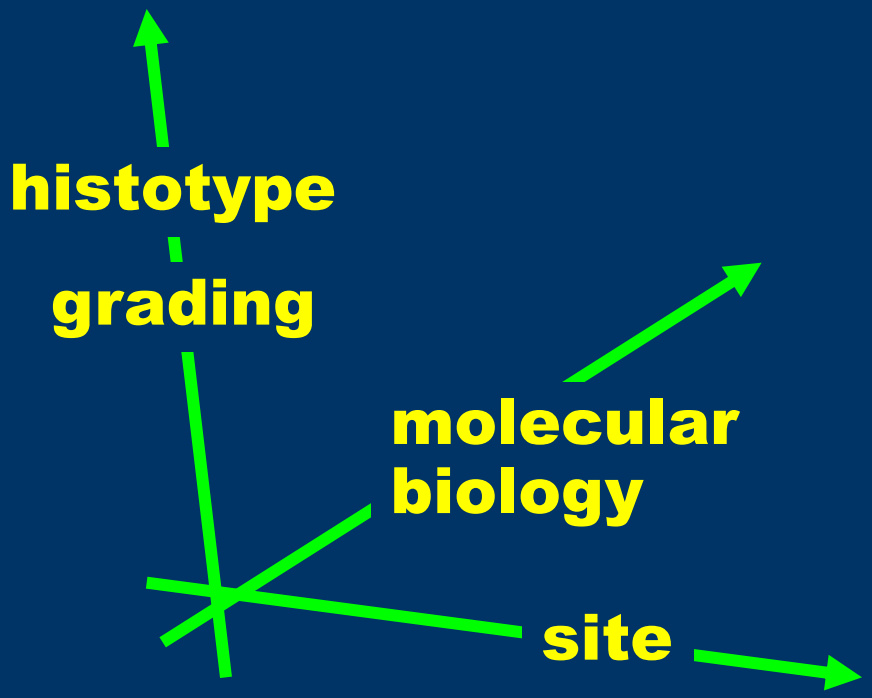
[1] Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, New York.

[2] Department of Biostatistics, Columbia University, College of Physicians and Surgeons, New York, New York.

Response

Among the 25 evaluable patients, there were 2 objective responses (partial responses), 2 mixed responses, and 3 patients with stable disease that lasted > 6 months, for an overall objective response rate of 8%. All of these patients had leiomyosarcoma (of uterine and nonuterine origin).

CONCLUSIONS. Temozolomide at the dose schedule employed in the current study was tolerated well and had modest activity against previously treated unresectable or metastatic leiomyosarcoma of both uterine and nonuterine origin. ***Cancer*** **2003; 98:1942–6.**


histotype
grading
molecular
biology
site

Ann Surg Oncol
DOI 10.1245/s10434-014-3965-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach From the Trans-Atlantic RPS Working Group

Trans-Atlantic RPS Working Group

ABSTRACT

Background. Retroperitoneal soft tissue sarcomas (RPS) are rare tumors that include several well-defined histologic subtypes. Although surgery is the mainstay of curative therapy, no universally accepted recommendations concerning the best management have been developed to date. Optimization of the initial approach is critical for maximizing patient outcomes.

Methods. An RPS Trans-Atlantic Working Group was established in 2013. The primary aim was to evaluate the current evidence critically and to develop a consensus document on the approach to this difficult disease. The outcome applies to primary RPS that is nonvisceral in origin. The evaluation included sarcomas of major veins (inferior vena cava, renal vein, ovarian/testicular vein), undifferentiated pleomorphic sarcoma of the psoas, and ureteric leiomyosarcoma (LMS). It excluded desmoid, lipoma and angiomyolipoma, gastrointestinal stromal tumors, visceral sarcomas such as those arising from the gut or its mesentery, uterine LMS, prostatic sarcoma, paratesticular/spermatic cord sarcoma, Ewing's sarcoma, alveolar/embryonal rhabdomyosarcoma, primitive peripheral neuro-ectodermal tumor, sarcoma arising from teratoma, carcinosarcoma, sarcomatoid carcinoma, clear cell sarcoma, radiation-induced sarcoma, paraganglioma, and malignant pheochromocytoma.

Results. Management of RPS was evaluated from diagnosis to follow-up, and a level of evidence was attributed to each statement. This rare and complex malignancy is best managed by an experienced multidisciplinary team in a specialized referral center. The best chance of cure is at the time of primary presentation, and an individualized management plan should be made based on the statements included in this article.

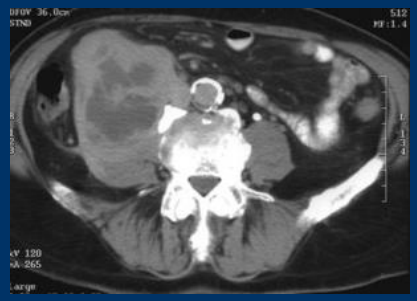
Conclusions. International collaboration is critical for adding to the current knowledge. A prospective registry will be set up.

Correspondence to: Alessandro Gronchi
Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, e-mail: alessandro.gronchi@istitutotumori.mi.it

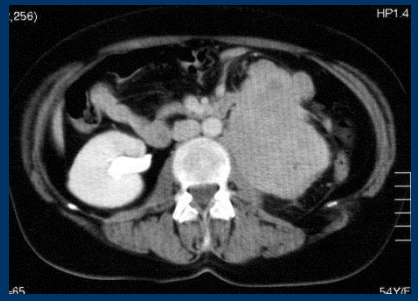
First Received: 16 June 2014

Trans-Atlantic RPS Working Group

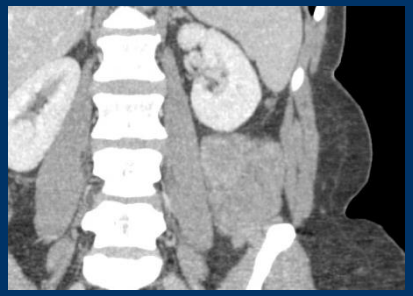
Sylvie Bonvalot, Department of Surgery, Institute Gustave Roussy, Villejuif, France
Alessandro Gronchi, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Peter Hohenberger, Department of Surgical Oncology and Thoracic Surgery, University Hospital of Mannheim, Mannheim, Germany
Saskia Litiere, Department of Biostatistics, European Organization for Research and Treatment of Cancer (EORTC) Head Quarters, Bruxelles, Belgium
Raphael E. Pollock, Department of Surgery, Division of Surgical Oncology, Ohio State University Medical Center, Columbia, USA
Chandrajit P. Raut, Department of Surgery, Division of Surgical Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Piotr Rutkowski, Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
Dirk Strauss, Department of Surgery, Royal Marsden Hospital, NHS Foundation Trust, London, UK
Carol J. Swallow, Department of Surgery, University of Toronto, Toronto, Canada
Frits Van Coevorden, Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands



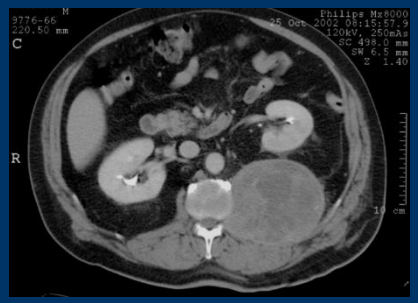
liposarcoma



leiomyosarcoma



solitary f. tumor



MPNST

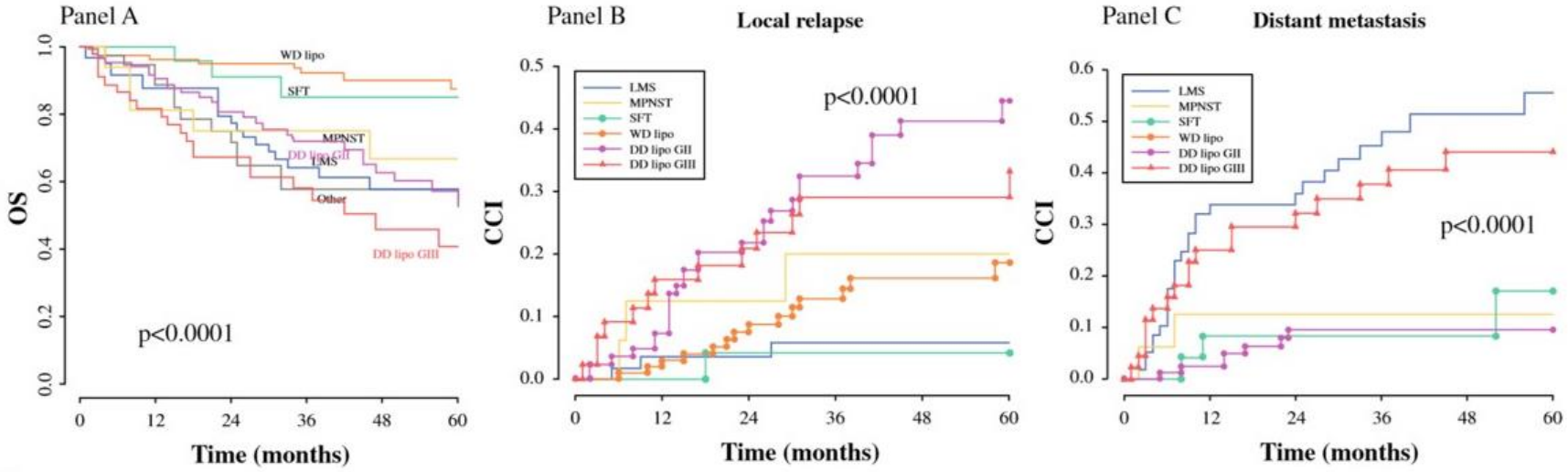
Ann Surg Oncol
DOI 10.1245/s10434-014-4130-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

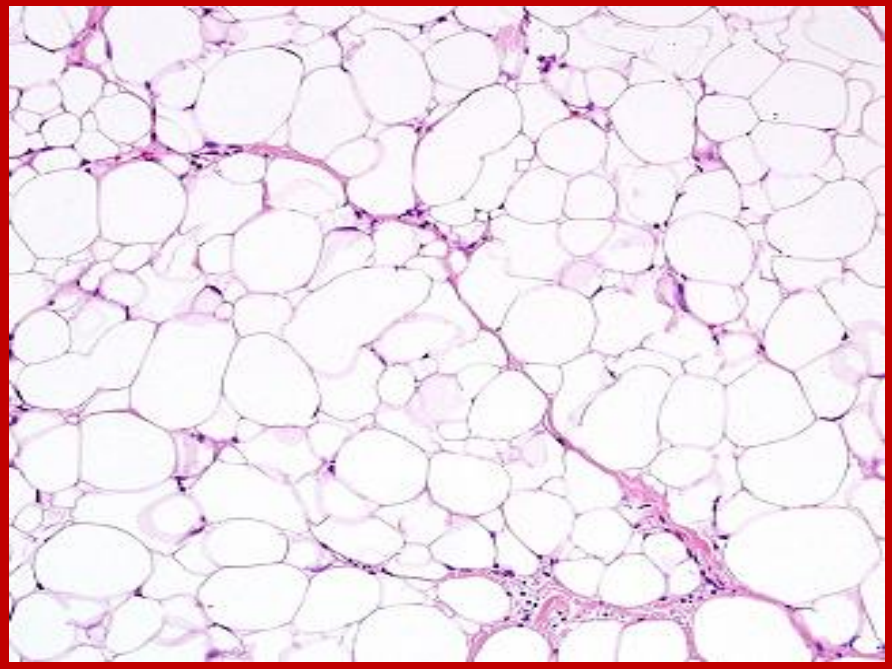
Personalizing the Approach to Retroperitoneal Soft Tissue Sarcoma: Histology-specific Patterns of Failure and Postrelapse Outcome after Primary Extended Resection

Alessandro Gronchi, MD[1], Rosalba Miceli, PhD[2], Marc Antoine Allard, MD[3], Dario Callegaro, MD[1], Cecile Le Péchoux, MD[4], Marco Fiore, MD[1], Charles Honoré, MD[3], Roberta Sanfilippo, MD[5], Sara Coppola, MD[3], Silvia Stacchiotti, MD[5], Philippe Terrier, MD[6], Paolo G. Casali, MD[5], Axel Le Cesne, MD[7], Luigi Mariani, MD[2], Chiara Colombo, MD[1], and Sylvie Bonvalot, MD, PhD[3]

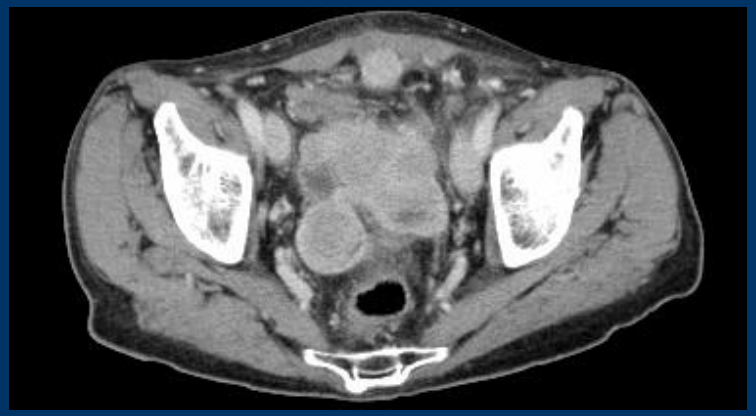


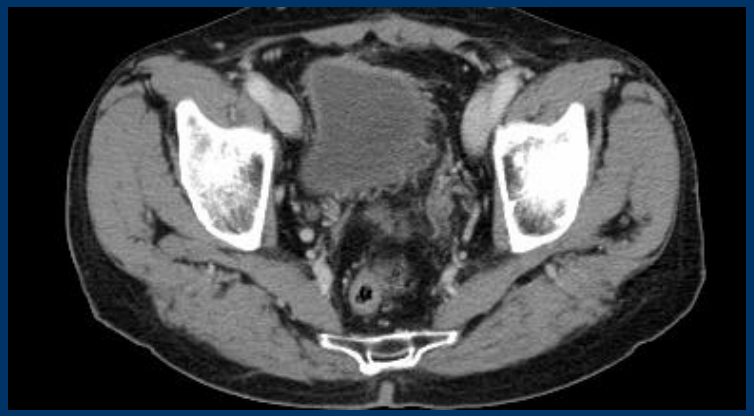
At risk:

Liposarcoma, dedifferentiated



Dedifferentiated liposarcoma: continuous-infusion high-dose Ifosfamide





0

cihdIFX x 3

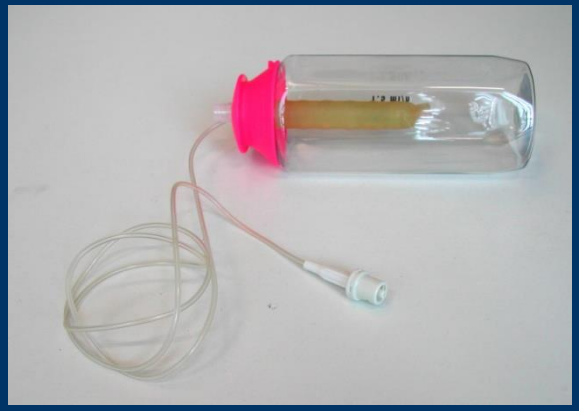
cihdIFX

IFOSFAMIDE
7 g/sqm

Mesna
7 g/sqm

in Saline up to 250 mL (1,5 mL/h)

x 2 (14 g/sqm in 14 d) / 28 d



Hindawi Publishing Corporation
Sarcoma
Volume 2013, Article ID 868973, 6 pages
http://dx.doi.org/10.1155/2013/868973

Hindawi

Clinical Study

Clinical Activity and Tolerability of a 14-Day Infusional Ifosfamide Schedule in Soft-Tissue Sarcoma

Juan Martin-Liberal,[1] Salma Alam,[1] Anastasia Constantinidou,[1] Cyril Fisher,[2] Komel Khabra,[3] Christina Messiou,[4] David Olmos,[5] Scott Mitchell,[6] Omar Al-Muderis,[1] Aisha Miah,[1] Mark Linch,[1] Robin L. Jones,[1] Michelle Scurr,[1] Ian Judson,[1] and Charlotte Benson[1]

Sanfilippo *et al. Clinical Sarcoma Research* 2014, **4**:16
http://www.clinicalsarcomaresearch.com/content/4/1/16

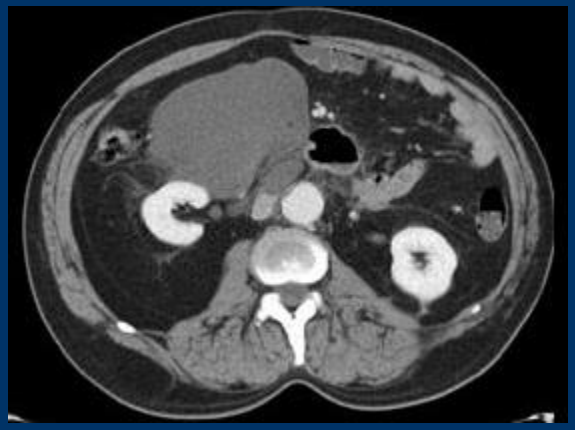
CLINICAL SARCOMA RESEARCH

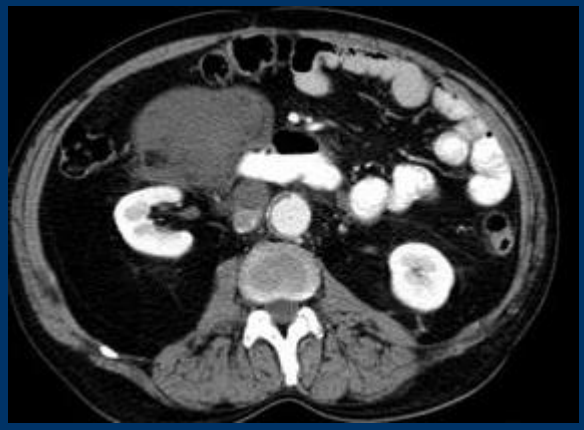
RESEARCH Open Access

High-dose continuous-infusion ifosfamide in advanced well-differentiated/dedifferentiated liposarcoma

Roberta Sanfilippo[1*], Rossella Bertulli[1], Andrea Marrari[1], Elena Fumagalli[1], Silvana Pilotti[2], Carlo Morosi[3], Antonella Messina[3], Angelo Paolo Dei Tos[4], Alessandro Gronchi[5] and Paolo Giovanni Casali[1]

Dedifferentiated liposarcoma: Trabectedin

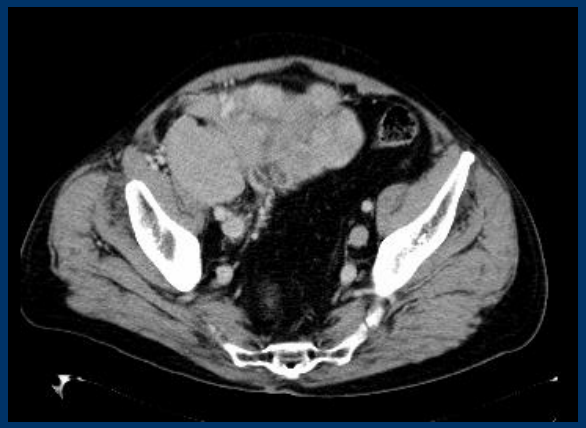




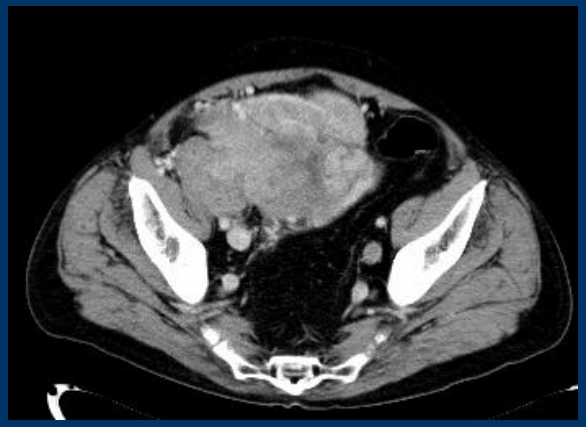
0

TRAB x 16 mos

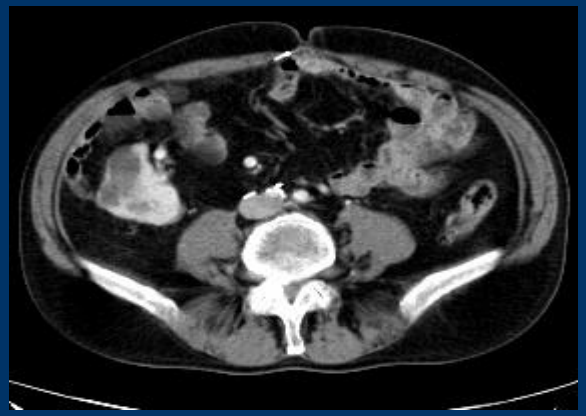
Dedifferentiated liposarcoma



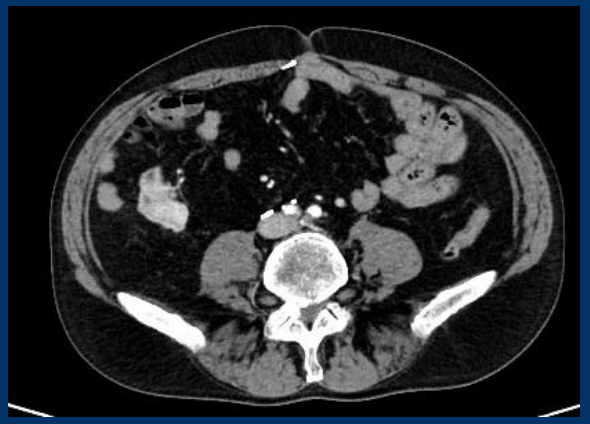
0



EPI+IFX x 2

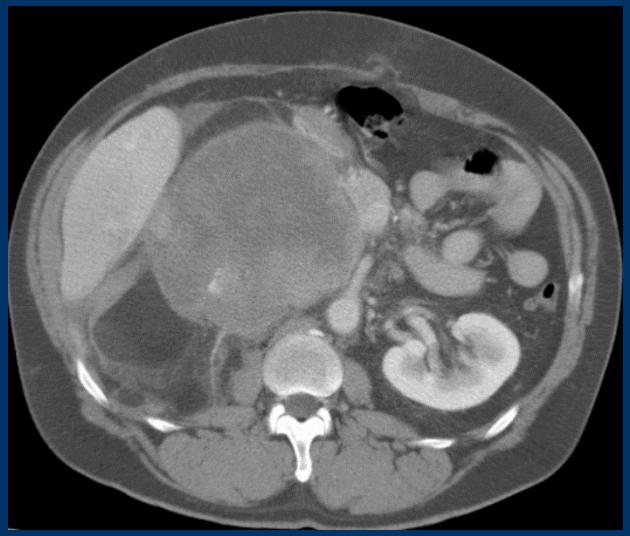


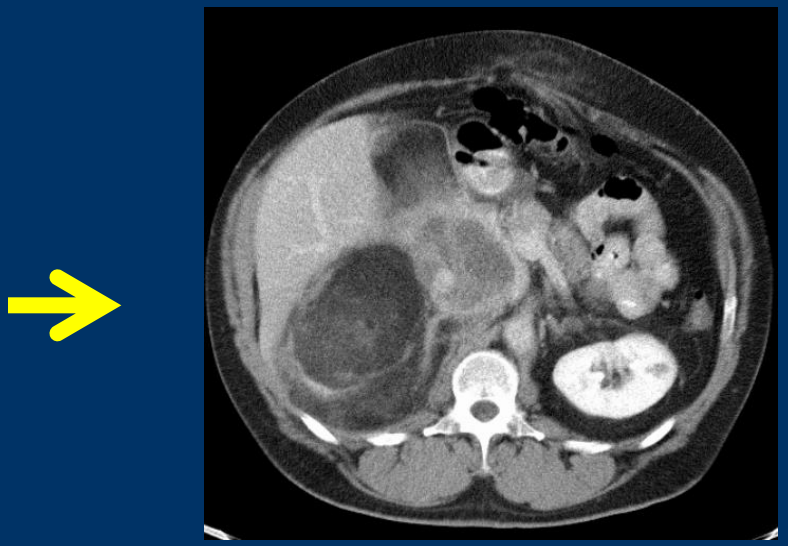
0



cihdIFX x 4

Dedifferentiated liposarcoma



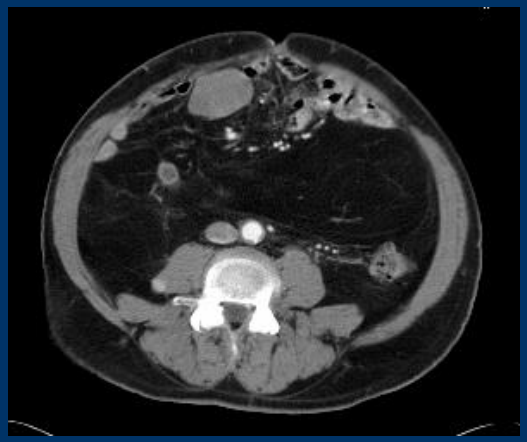


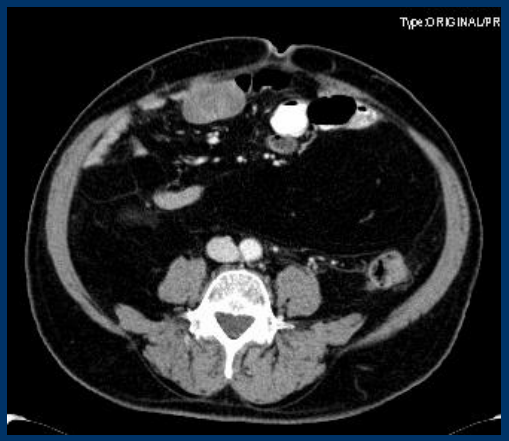
0

cihdIFX x 5

Well differentiated liposarcoma

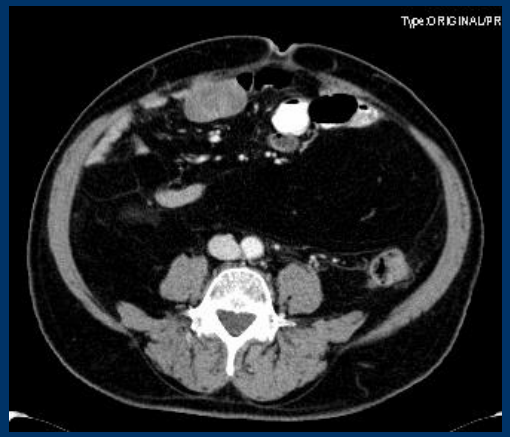
0



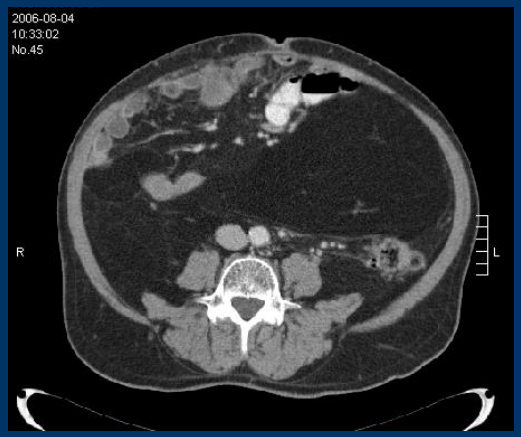


EPI+IFX
x 2

cihdIFX
x 3



TRAB
x 6



Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

Isabelle Ray-Coquard, Jean-Yves Blay, Antoine Italiano, Axel Le Cesne, Nicolas Penel, Jianguo Zhi, Florian Heil, Ruediger Rueger, Bradford Graves, Meichun Ding, David Geho, Steven A Middleton, Lyubomir T Vassilev, Gwen L Nichols, Binh Nguyen Bui

Summary

Background We report a proof-of-mechanism study of RG7112, a small-molecule MDM2 antagonist, in patients with chemotherapy-naive primary or relapsed well-differentiated or dedifferentiated *MDM2*-amplified liposarcoma who were eligible for resection.

Methods Patients with well-differentiated or dedifferentiated liposarcoma were enrolled at four centres in France. Patients received up to three 28-day neoadjuvant treatment cycles of RG7112 1440 mg/m² per day for 10 days. If a patient progressed at any point after the first cycle, the lesion was resected or, if unresectable, an end-of-study biopsy was done. The primary endpoint was to assess markers of RG7112-dependent MDM2 inhibition and P53 pathway activation (P53, P21, MDM2, Ki-67, macrophage inhibitory cytokine-1 [MIC-1], and apoptosis). All analyses were per protocol. This trial is registered with EudraCT, number 2009-015522-10.

Results Between June 3, and Dec 14, 2010, 20 patients were enrolled and completed pretreatment and day 8 biopsies. 18 of 20 patients had *TP53* wild-type tumours and two carried missense *TP53* mutations. 14 of 17 assessed patients had *MDM2* gene amplification. Compared with baseline, P53 and P21 concentrations, assessed by immunohistochemistry, had increased by a median of 4·86 times (IQR 4·38–7·97; p=0·0001) and 3·48 times (2·05–4·09; p=0·0001), respectively, at day 8 (give or take 2 days). At the same timepoint, relative *MDM2* mRNA expression had increased by a median of 3·03 times (1·23–4·93; p=0·003) that at baseline. The median change from baseline for Ki-67-positive tumour cells was −5·05% (IQR −12·55 to 0·05; p=0·01). Drug exposure correlated with blood concentrations of MIC-1 (p<0·0001) and haematological toxicity. One patient had a confirmed partial response and 14 had stable disease. All patients experienced at least one adverse event, mostly nausea (14 patients), vomiting (11 patients), asthenia (nine patients), diarrhoea (nine patients), and thrombocytopenia (eight patients). There were 12 serious adverse events in eight patients, the most common of which were neutropenia (six patients) and thrombocytopenia (three patients).

Discussion MDM2 inhibition activates the P53 pathway and decreases cell proliferation in *MDM2*-amplified liposarcoma. This study suggests that it is feasible to undertake neoadjuvant biopsy-driven biomarker studies in liposarcoma.

Funding F Hoffmann-La Roche.

Lancet Oncol 2012; 13: 1133–40

Published Online
October 17, 2012
http://dx.doi.org/10.1016/S1470-2045(12)70474-6

See Comment page 1070

Centre Leon Bérard, Lyon, France (I Ray-Coquard MD, Prof J-Y Blay MD); **EAM 4128 Santé-Individu-Société, Université Claude Bernard Lyon I, Lyon, France** (I Ray-Coquard); **CRCL Unité INSERM 1052, Equipe 11, Lyon, France** (J-Y Blay); **Institut Bergonie, Bordeaux, France** (A Italiano MD, B N Bui MD); **Institut Gustave-Roussy, Villejuif, France** (A Le Cesne MD); **Centre Oscar Lambret, Lille, France** (N Penel MD); **Department of Preclinical Drug Development and Translational Research, F Hoffmann-La Roche, Nutley, NJ, USA** (J Zhi PhD, B Graves PhD, M Ding PhD, D Geho MD, S A Middleton PhD, L T Vassilev PhD, G L Nichols MD); **and Roche Diagnostics, Penzberg, Germany** (F Heil PhD, R Rueger MD)

Correspondence to:
Dr Isabelle Ray-Coquard, Département de Cancérologie médicale, Centre Léon Bérard, 28 rue Laennec, Lyon 69008, France
isabelle.ray-coquard@lyon.unicancer.fr

Small Molecule Therapeutics

Molecular Cancer Therapeutics

Antiproliferative Effects of CDK4/6 Inhibition in *CDK4*-Amplified Human Liposarcoma *In Vitro* and *In Vivo*

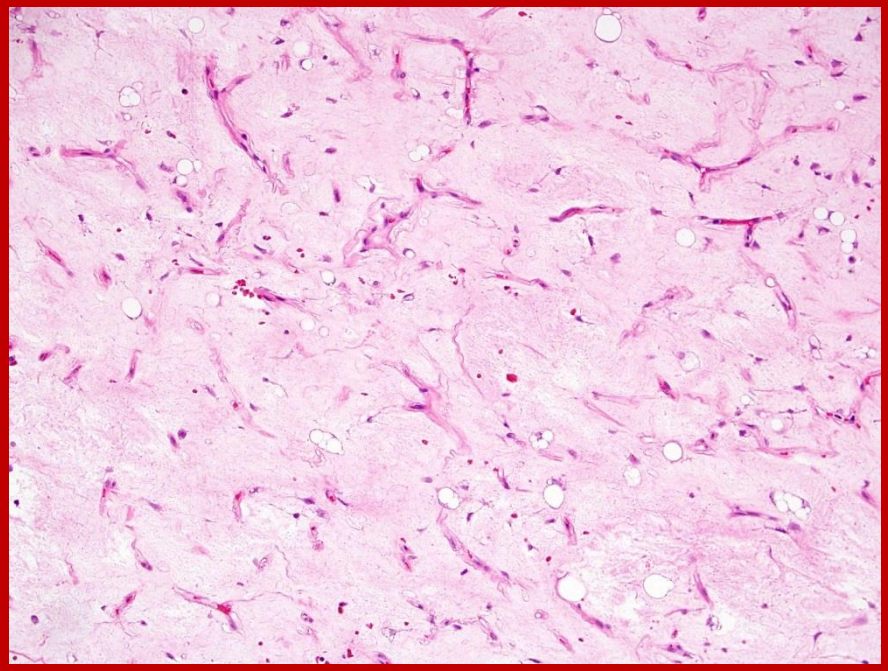
Yi-Xiang Zhang[1,2], Ewa Sicinska[1,3], Jeffrey T. Czaplinski[1,3], Stephen P. Remillard[1,2], Samuel Moss[1,3], Yuchuan Wang[4], Christopher Brain[5], Alice Loo[5], Eric L. Snyder[6,7], George D. Demetri[1,2], Sunkyu Kim[5], Andrew L. Kung[8], and Andrew J. Wagner[1,2]

Abstract

Well-differentiated/dedifferentiated liposarcomas (WD/DDLPS) are among the most common subtypes of soft tissue sarcomas. Conventional systemic chemotherapy has limited efficacy and novel therapeutic strategies are needed to achieve better outcomes for patients. The cyclin-dependent kinase 4 (*CDK4*) gene is highly amplified in more than 95% of WD/DDLPS. In this study, we explored the role of CDK4 and the effects of NVP-LEE011 (LEE011), a novel selective inhibitor of CDK4/CDK6, on a panel of human liposarcoma cell lines and primary tumor xenografts. We found that both CDK4 knockdown by siRNA and inhibition by LEE011 diminished retinoblastoma (RB) phosphorylation and dramatically decreased liposarcoma cell growth. Cell-cycle analysis demonstrated arrest at G_0–G_1. siRNA-mediated knockdown of RB rescued the inhibitory effects of LEE011, demonstrating that LEE011 decreased proliferation through RB. Oral administration of LEE011 to mice bearing human liposarcoma xenografts resulted in approximately 50% reduction in tumor ^{18}F-fluorodeoxyglucose uptake with decreased tumor biomarkers, including RB phosphorylation and bromodeoxyuridine incorporation *in vivo*. Continued treatment inhibited tumor growth or induced regression without detrimental effects on mouse weight. After prolonged continuous dosing, reestablishment of RB phosphorylation and cell-cycle progression was noted. These findings validate the critical role of CDK4 in maintaining liposarcoma proliferation through its ability to inactivate RB function, and suggest its potential function in the regulation of survival and metabolism of liposarcoma, supporting the rationale for clinical development of LEE011 for the treatment of WD/DDLPS. *Mol Cancer Ther; 13(9); 2184–93.* ©2014 AACR.

Clin Cancer Res 2012;18:2638

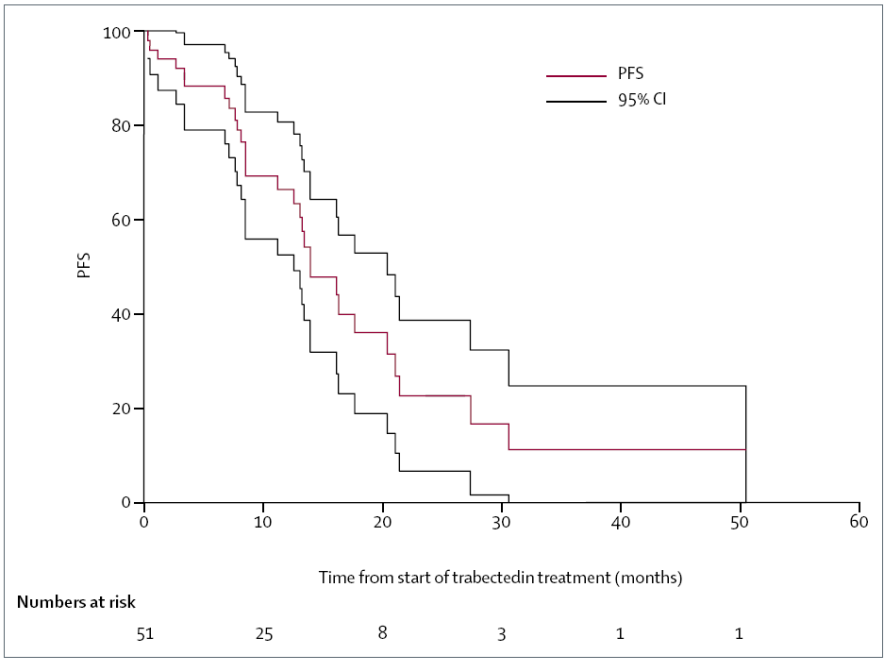
Liposarcoma, myxoid

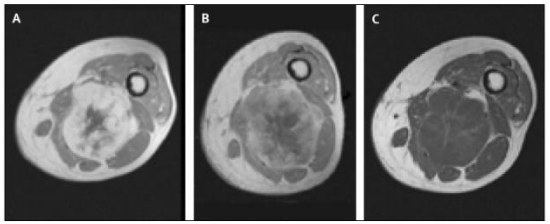


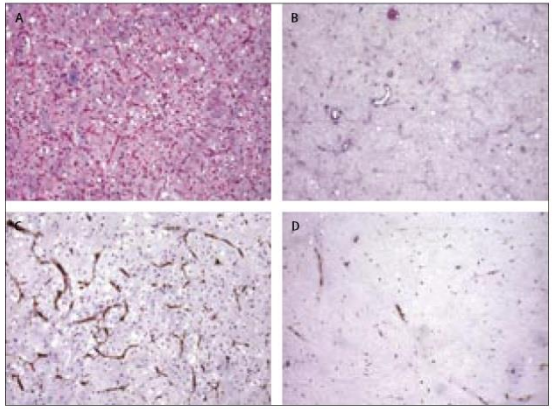
Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Federica Grosso, Robin L Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sanfilippo, Paola Casieri, Paola Collini, Palma Dileo, Carlo Spreafico, Silvia Stacchiotti, Elena Tamborini, Juan Carlos Tercero, Josè Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

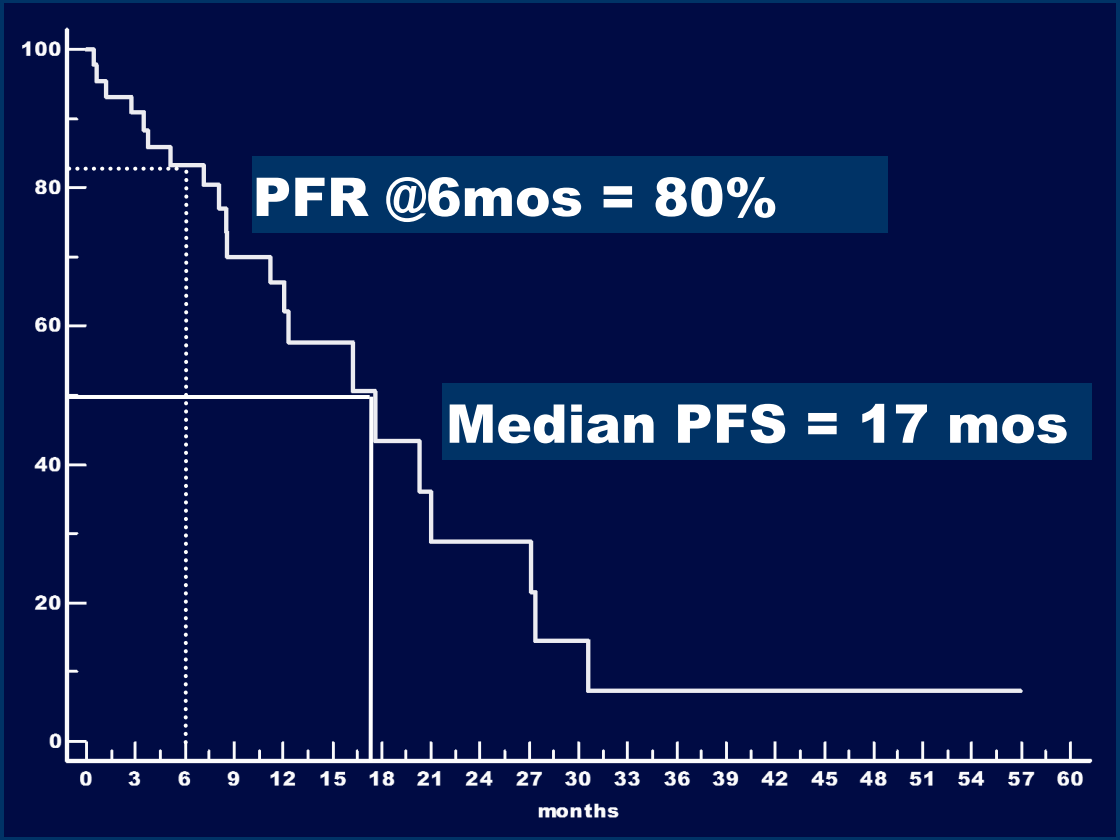
Lancet Oncol 2007; 8: 595–602





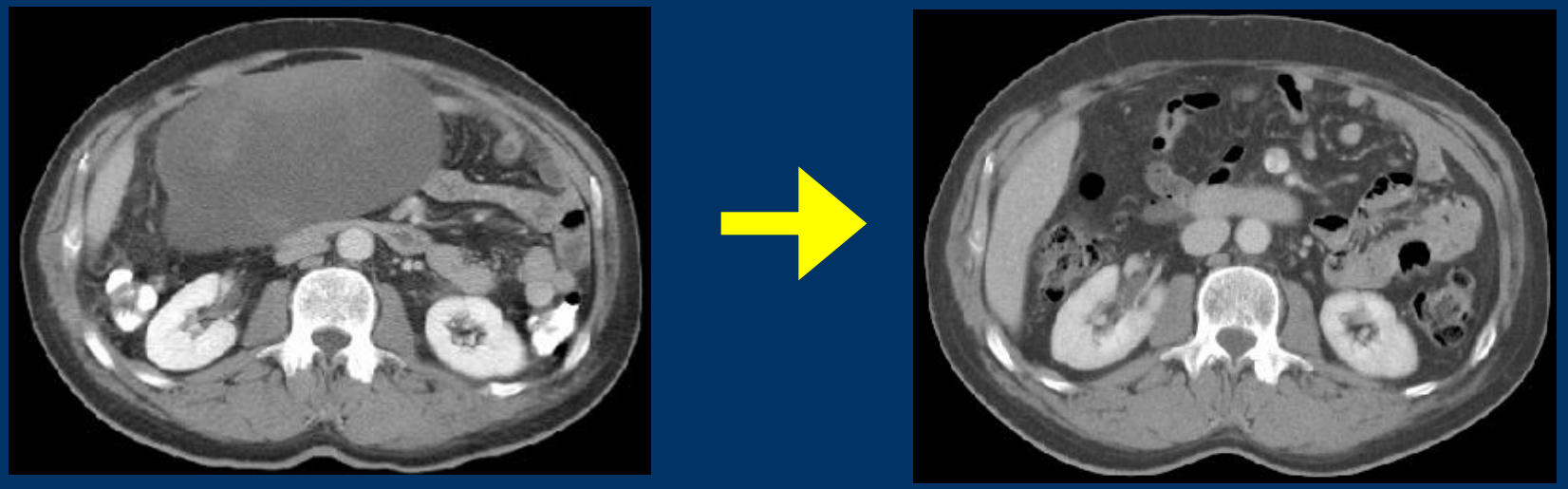


PFS



median follow-up: 14 mos

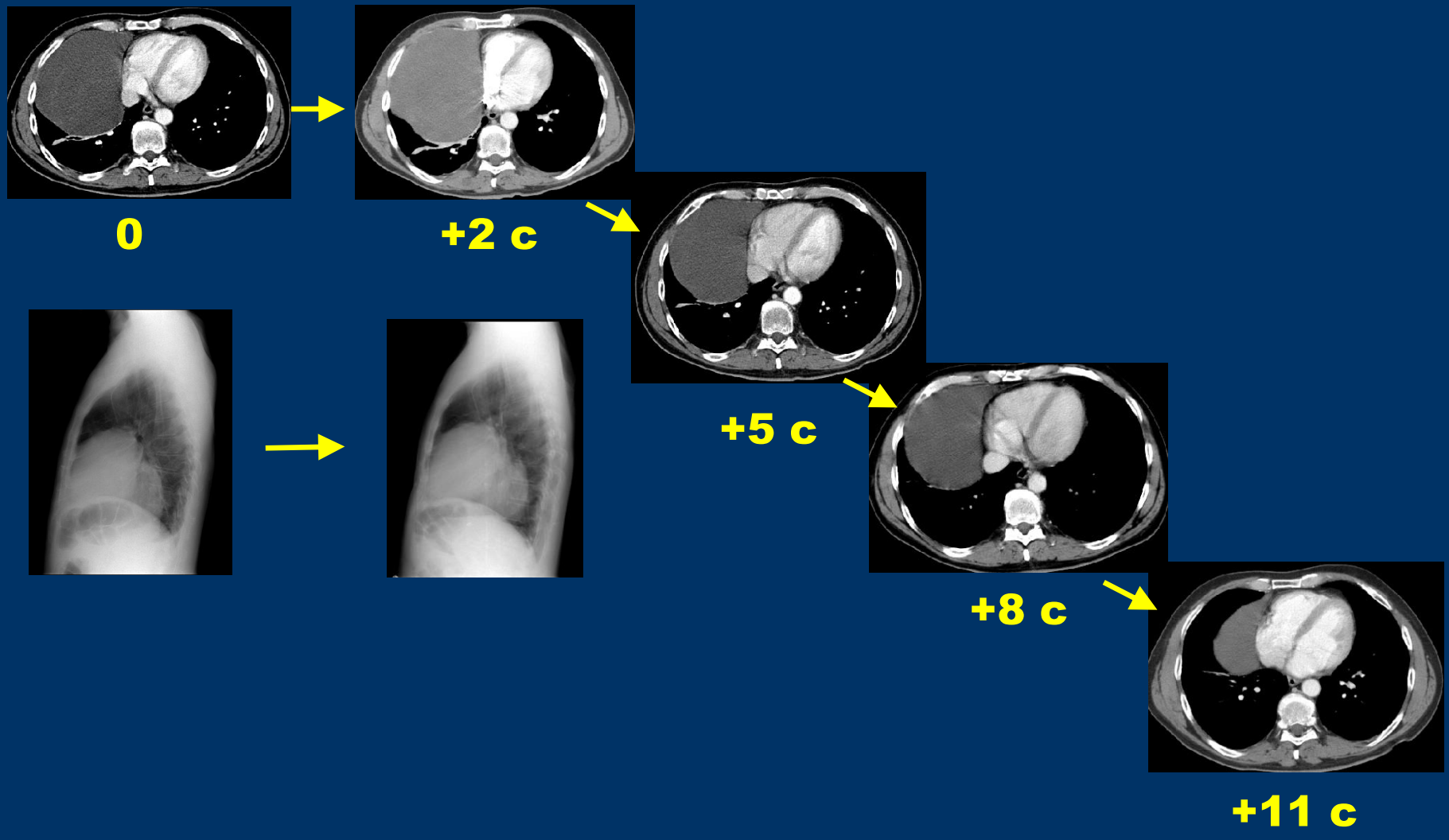
Tumor response patterns

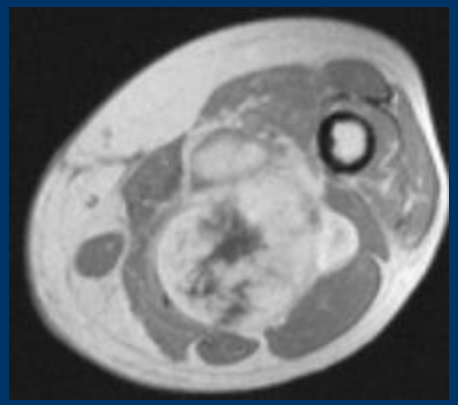


0

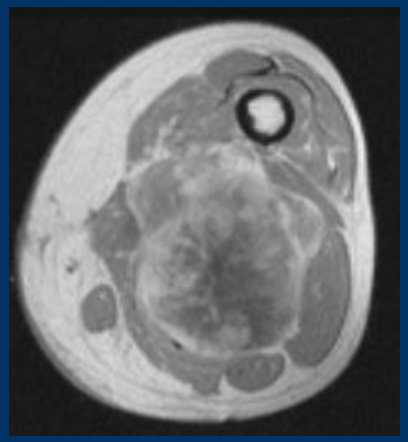
Trabectedin x 3

Tumor response patterns

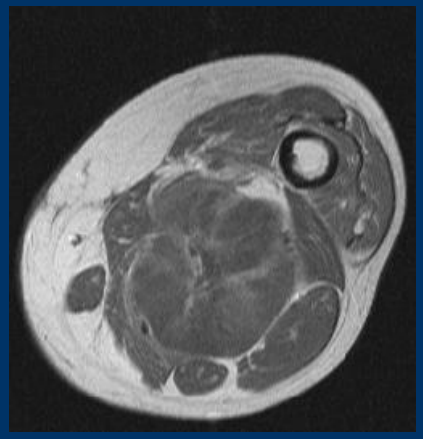




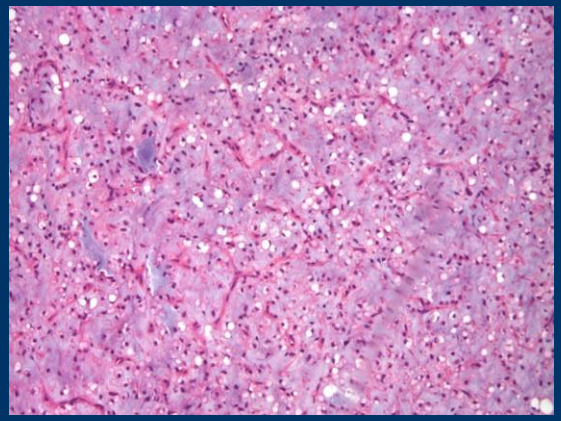
0

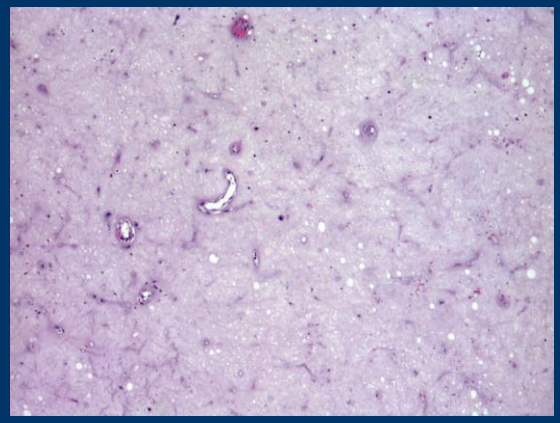


+ 1 c



+4 c

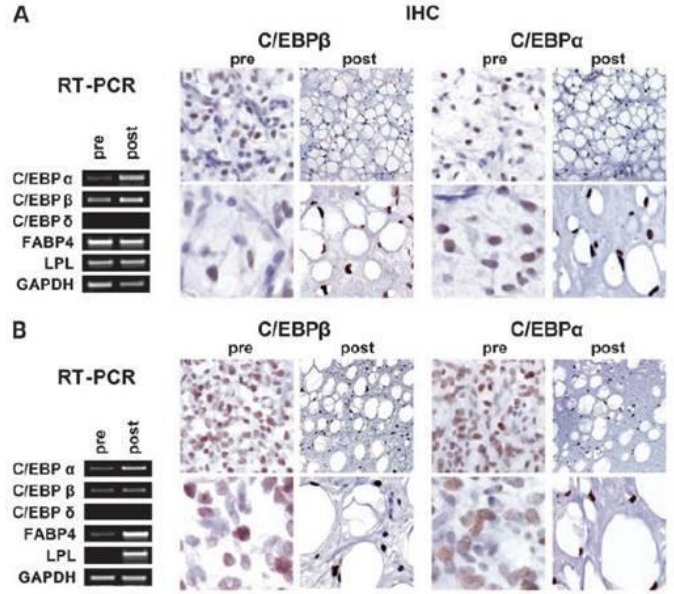


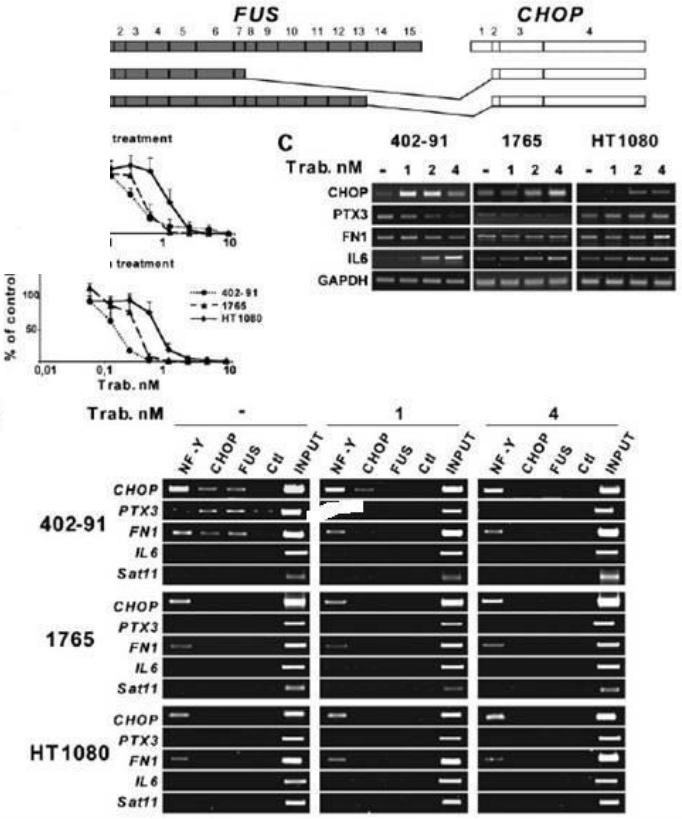


Trabectedin (ET-743) promotes differentiation in myxoid liposarcoma tumors

Claudia Forni,[1] Mario Minuzzo,[1] Emanuela Virdis,[2] Elena Tamborini,[2] Matteo Simone,[3] Michele Tavecchio,[3] Eugenio Erba,[3] Federica Grosso,[2] Alessandro Gronchi,[2] Pierre Aman,[4] Paolo Casali,[2] Maurizio D'Incalci,[3] Silvana Pilotti,[2] and Roberto Mantovani[1]

[1]Dipartimento di Scienze Biomolecolari e Biotecnologie, Università degli Studi di Milano; [2]Fondazione IRCCS, Istituto Nazionale Tumori; [3]Dipartimento di Oncologia, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; and [4]Lundberg Laboratory for Cancer Research, Department of Pathology, Göteborg University, Gothenburg, Sweden



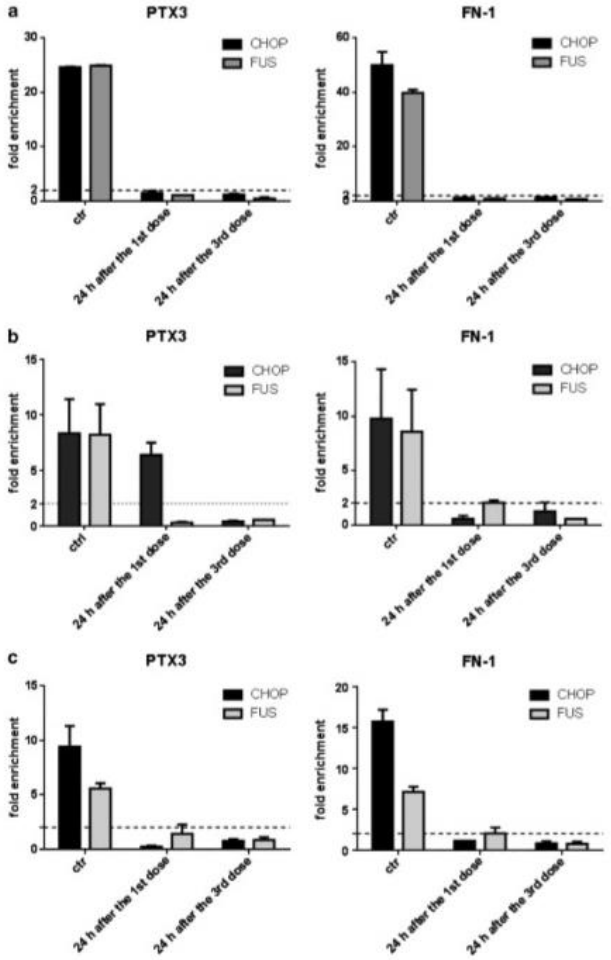


Mol Cancer Therap 2009;8:449

ORIGINAL ARTICLE

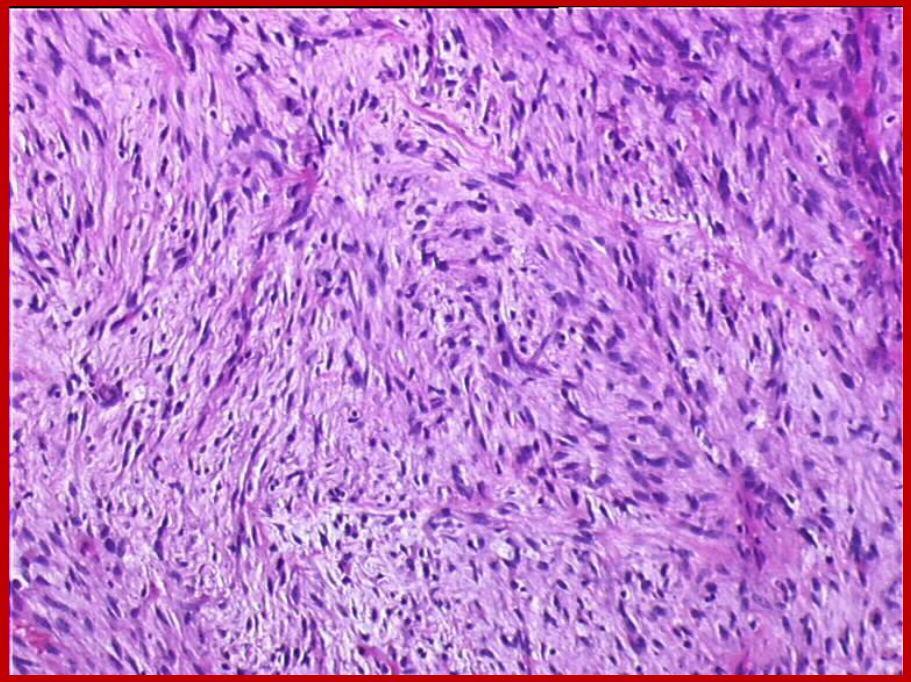
Mode of action of trabectedin in myxoid liposarcomas

S Di Giandomenico[1,8], R Frapolli[1,8], E Bello[1], S Uboldi[1], SA Licandro[1], S Marchini[1], L Beltrame[1], S Brich[2], V Mauro[2], E Tamborini[2], S Pilotti[2], P Casali[3], F Grosso[4], R Sanfilippo[3], A Gronchi[5], R Mantovani[6], R Gatta[6], CM Galmarini[7], JMF Sousa-Faro[7] and M D'Incalci[1]

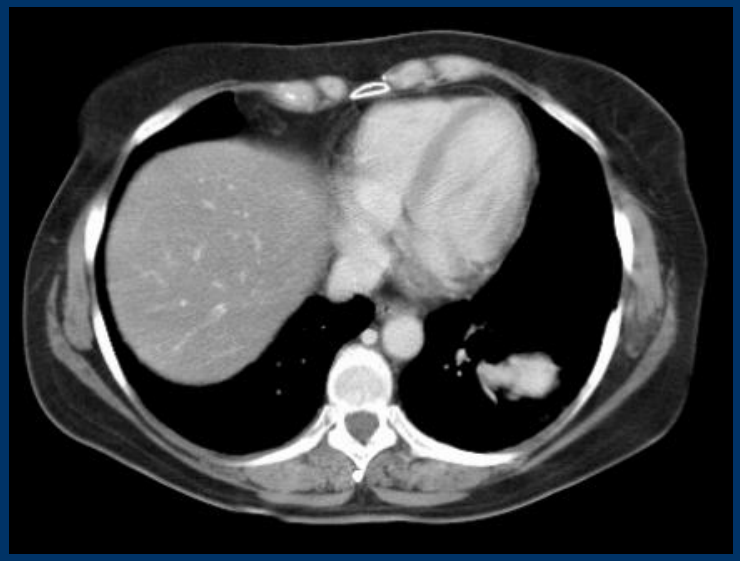


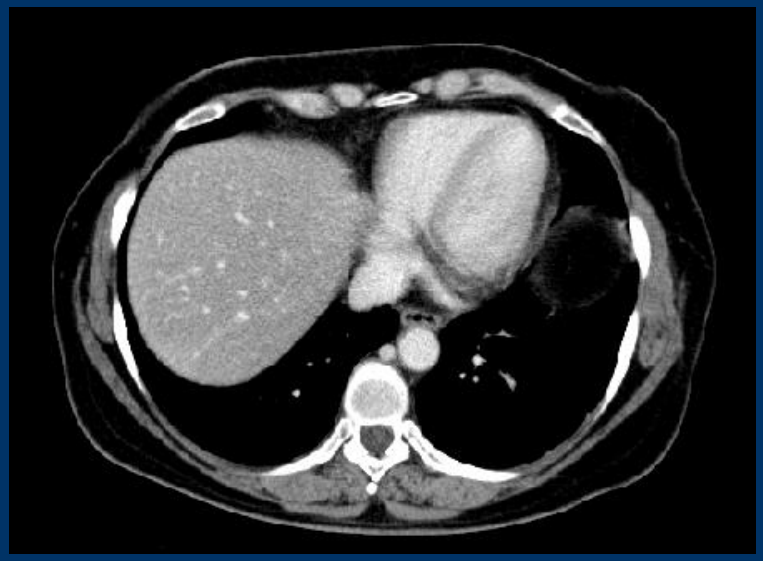
Oncogene 2014;33:5201

Leiomyosarcoma



Dacarbazine





0

DTIC x 2

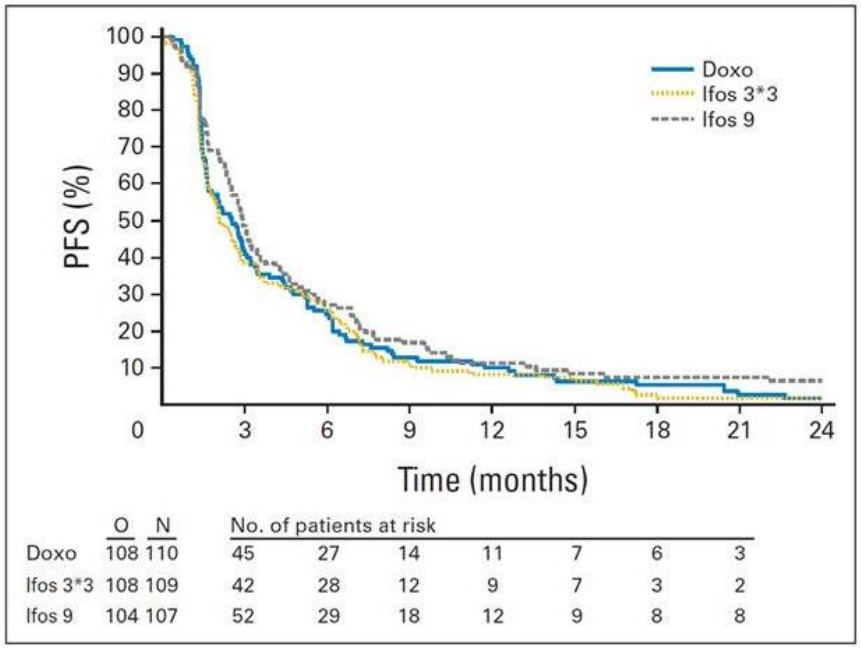
VOLUME 25 · NUMBER 21 · JULY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Two Investigational Schedules of Ifosfamide Compared With Standard-Dose Doxorubicin in Advanced or Metastatic Soft Tissue Sarcoma: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study

Paul Lorigan, Jaap Verweij, Zsuzsa Papai, Sjoerd Rodenhuis, Axel Le Cesne, Michael G. Leahy, John A. Radford, Martine M. Van Glabbeke, Anne Kirkpatrick, Pancras C.W. Hogendoorn, and Jean-Yves Blay



	Dox		Ifos 3*3		Ifos 9		Total		3-Year Survivors	
Condition	No.	%	No.	%	No.	%	No.	%	No.	%
Leiomyosarcoma									8/58	13.8
PR	2	13.3	1	4.8	1	4.5	4	6.9		
NC	10	66.7	10	47.6	10	45.5	30	51.7		
PD	3	20	8	38.1	7	31.8	18	31		
Synovial									2/23	8.7
PR	2	25	3	37.5	3	42.9	8	34.8		
NC	2	25	3	37.5	3	42.9	8	34.8		
PD	4	50	1	12.5	1	14.3	6	26.1		
Liposarcoma									5/32	15.5
PR	2	15.4			1	8.3	3	9.4		
NC	4	30.8	1	14.3	7	58.3	12	37.5		
PD	7	53.8	5	71.4	3	25	15	46.9		
GIST									3/28	10.7
PR			1	7.7			1	3.6		
NC	2	20	4	30.8	3	60	9	32.1		
PD	8	80	7	53.8	2	40	17	60.7		
Neurogenic									3/19	15.8
CR	1	12.5					1	5.3		
NC	3	37.5	3	50			6	31.6		
PD	4	50	3	50	3	60	10	52.6		

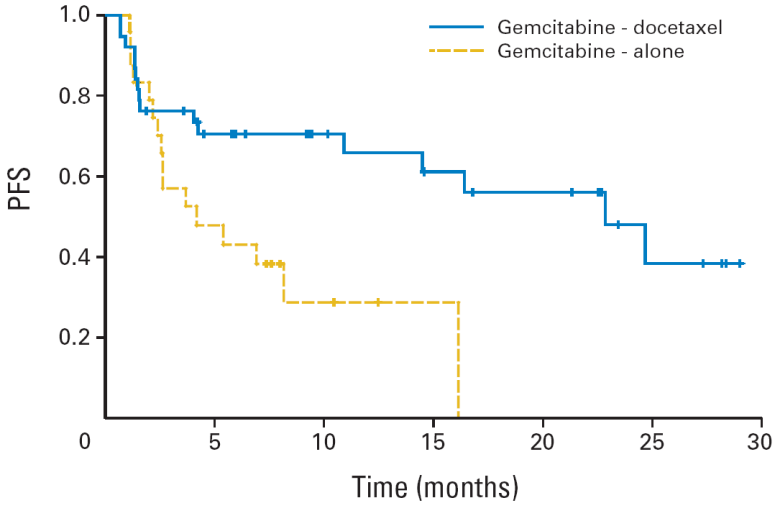
VOLUME 25 · NUMBER 19 · JULY 1 2007

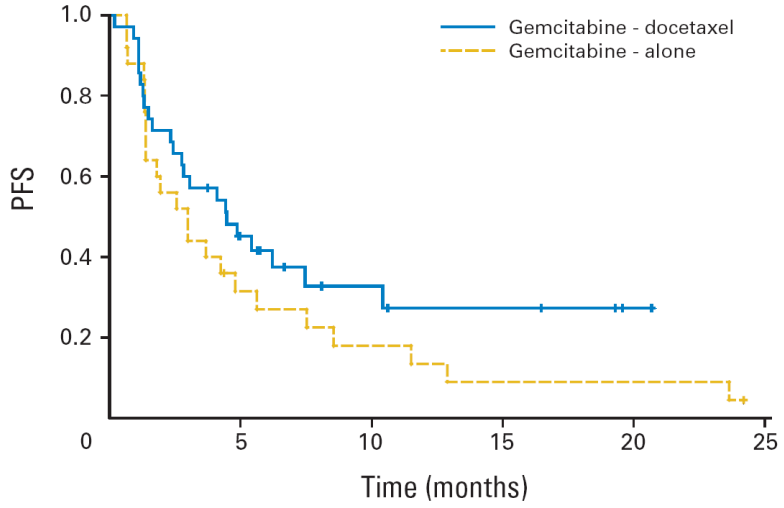
JOURNAL OF CLINICAL ONCOLOGY

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





Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 109 (2008) 313–315
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Editorial

Gemcitabine/docetaxel—Welcome to a new standard

The Oncologist®

Sarcomas

Randomized Multicenter and Stratified Phase II Study of Gemcitabine Alone Versus Gemcitabine and Docetaxel in Patients with Metastatic or Relapsed Leiomyosarcomas: A Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study)

PATRICIA PAUTIER,[a] ANNE FLOQUET,[c] NICOLAS PENEL,[d] SOPHIE PIPERNO-NEUMANN,[e] NICOLAS ISAMBERT,[g] ANNIE REY,[b] EMMANUELLE BOMPAS,[h] ANGELA CIOFFI,[a] CORINNE DELCAMBRE,[i] DIDIER CUPISSOL,[j] FRANCOISE COLLIN,[f] JEAN-YVES BLAY,[k] MARTA JIMENEZ,[l] FLORENCE DUFFAUD[m]

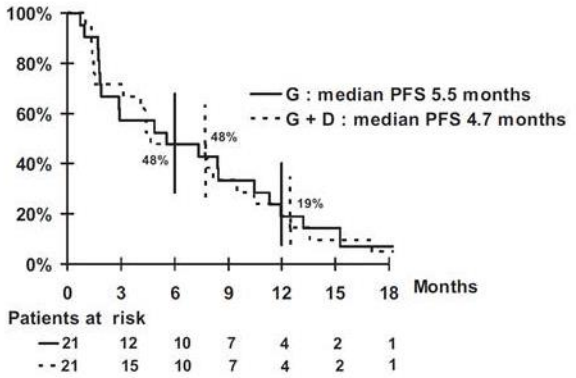


Figure 1. Kaplan–Meier curve of progression-free survival for the uterine leiomyosarcoma group.

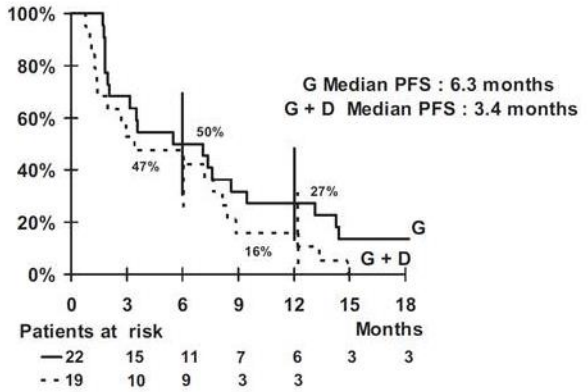
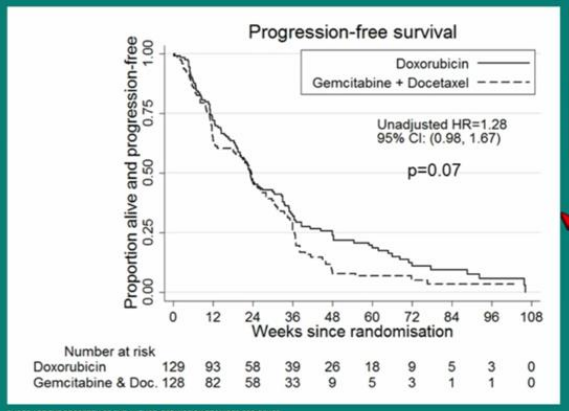


Figure 2. Kaplan–Meier curve of progression-free survival for the nonuterine leiomyosarcoma group.

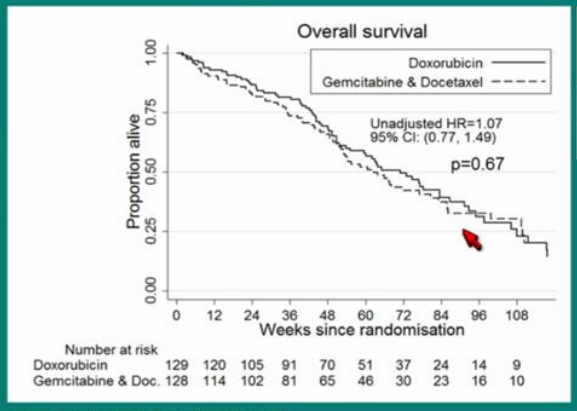
The Oncologist 2012;17:1213

Progression-free survival



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

Overall survival



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

from: ASCO 2015 Virtual Meeting

Seddon B et al, ASCO 2015; #10500

Grade 3 or 4 adverse events

Adverse Event	Dox (N=128)	GemDoc (N=126)	P value
Any grade 3 or 4 AE	83 (64.8%)	90 (71.4%)	0.26
Haematological			
Anemia	10 (7.8%)	8 (6.3%)	0.65
Neutropenia	31 (24.2%)	24 (19.0%)	0.32
Thrombocytopenia	1 (0.8%)	0 (0.0%)	0.32
Leucopenia	10 (7.8%)	9 (7.1%)	0.84
Febrile neutropenia	26 (20.3%)	15 (11.9%)	0.07
Non-haematological			
Fatigue	8 (6.3%)	17 (13.5%)	0.05
Pain	10 (7.8%)	13 (10.3%)	0.49
Mucositis oral	16 (12.5%)	2 (1.6%)	0.001
Diarrhea	2 (1.6%)	10 (7.9%)	0.02
Thromboembolic event	7 (5.5%)	4 (3.2%)	0.37
Anorexia	5 (3.9%)	3 (2.4%)	0.49
Dyspnoea	3 (2.3%)	5 (4.0%)	0.46
Lung infection	5 (3.9%)	3 (2.4%)	0.49
Nausea	5 (3.9%)	3 (2.4%)	0.49

PRESENTED AT: ASCO Annual '15 Meeting

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%)

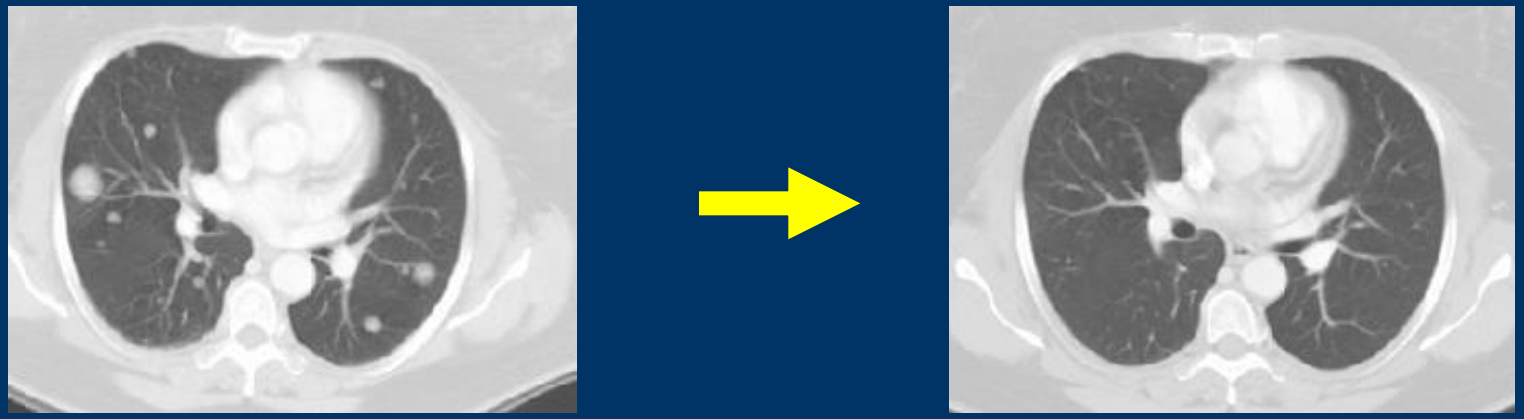
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual '15 Meeting

from: ASCO 2015 Virtual Meeting

Seddon B et al, ASCO 2015; #10500

Gemcitabine



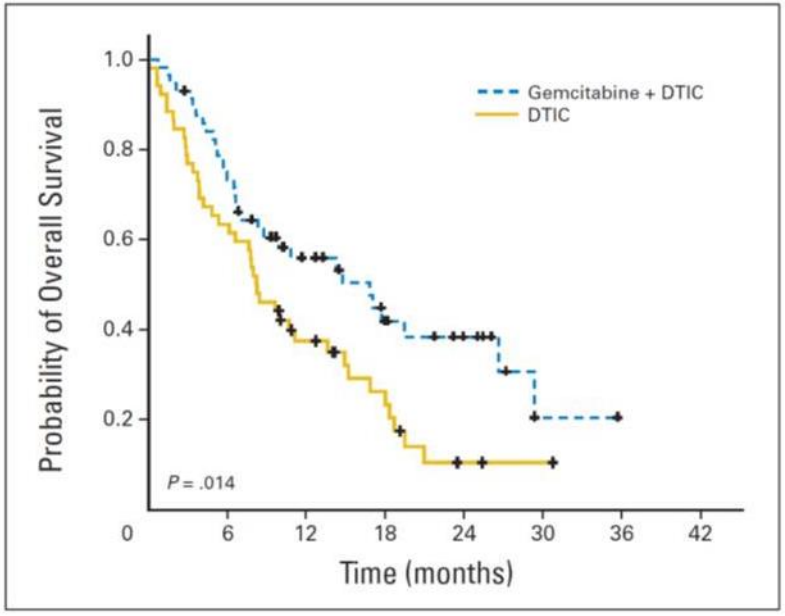
VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

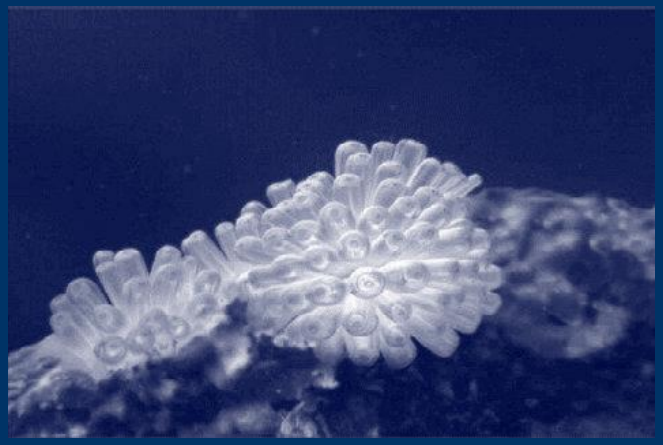
ORIGINAL REPORT

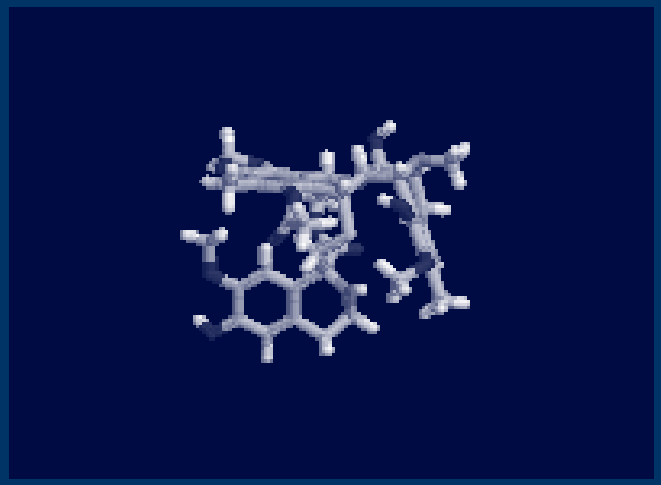
Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

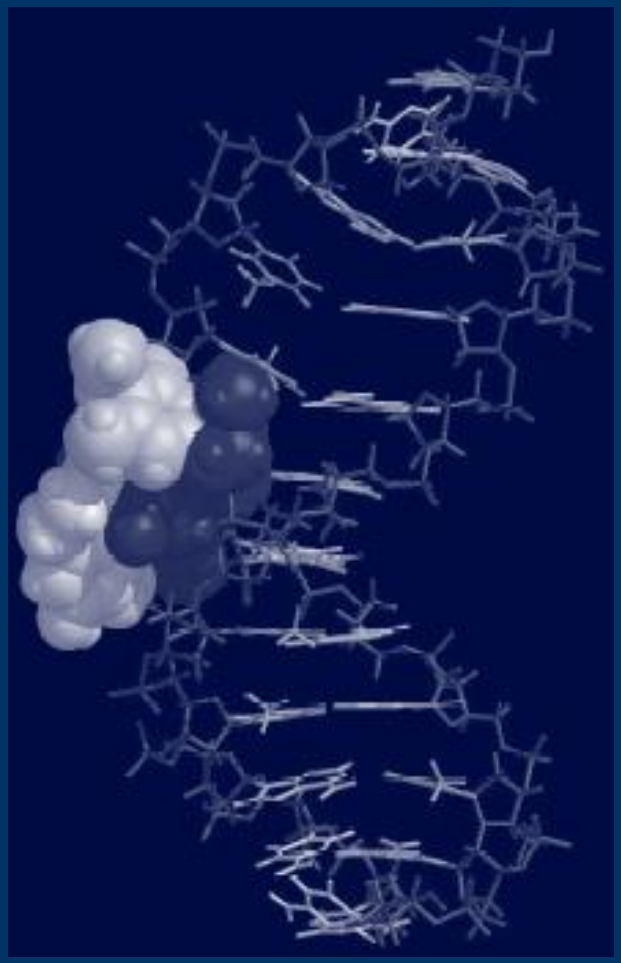
Xavier García-del-Muro, Antonio López-Pousa, Joan Maurel, Javier Martín, Javier Martínez-Trufero, Antonio Casado, Auxiliadora Gómez-España, Joaquín Fra, Josefina Cruz, Andrés Poveda, Andrés Meana, Carlos Pericay, Ricardo Cubedo, Jordi Rubió, Ana De Juan, Nuria Laínez, Juan Antonio Carrasco, Raquel de Andrés, and José M. Buesa†



Trabectedin







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

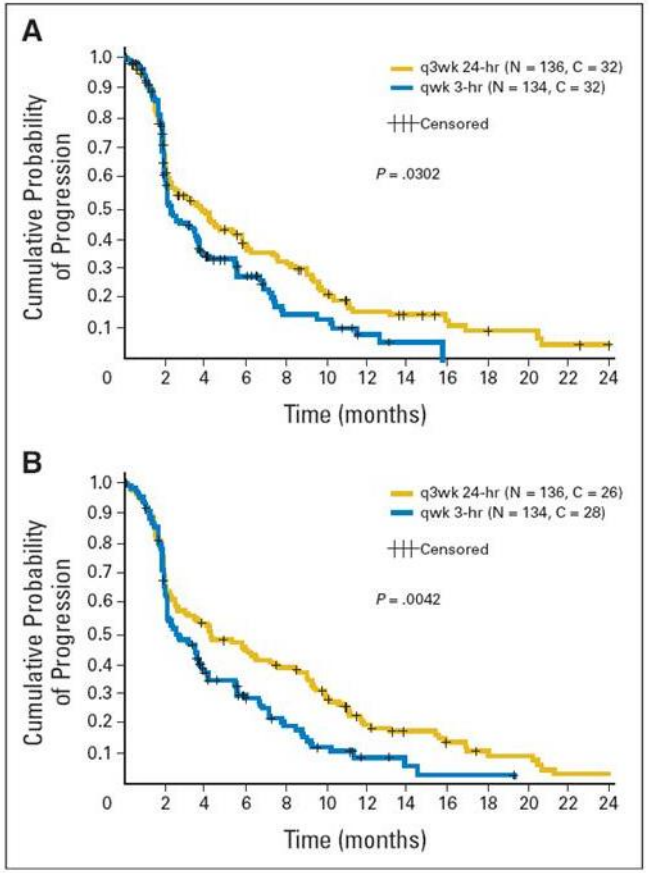
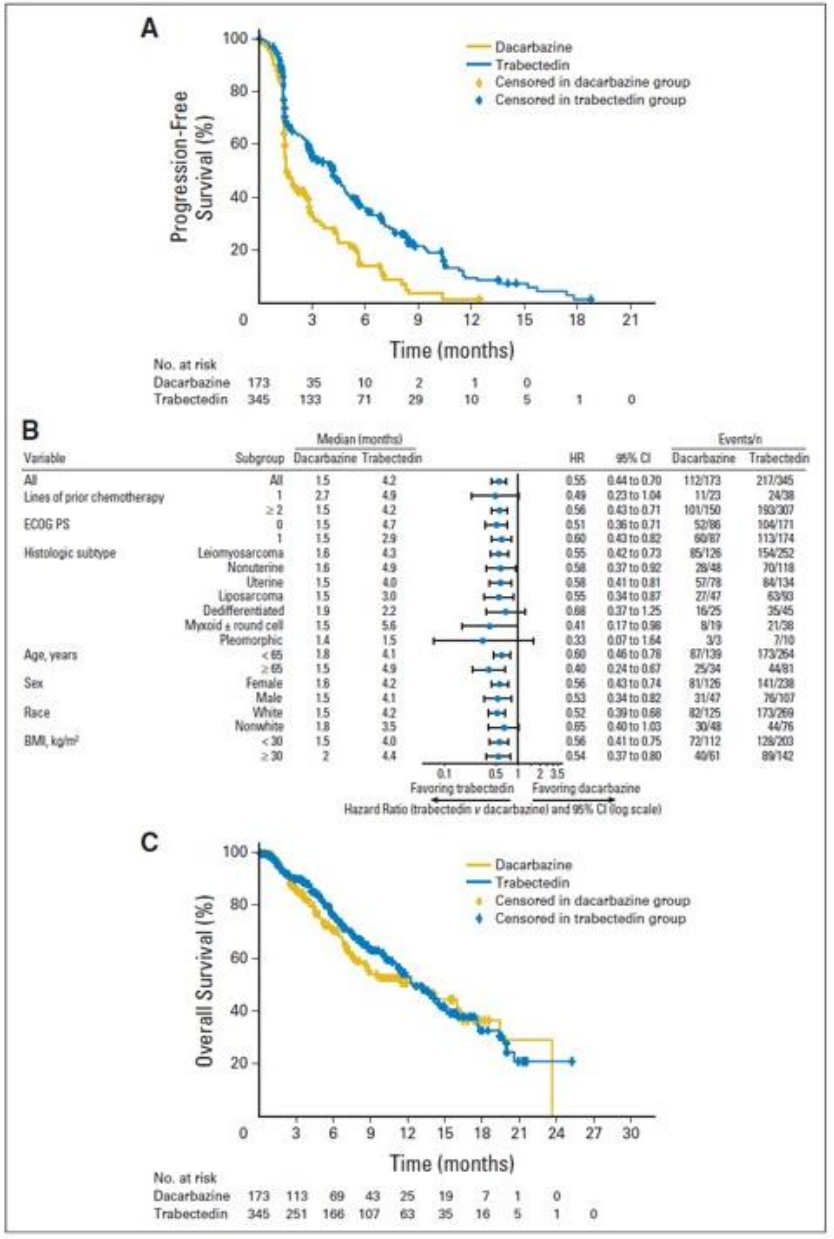


Fig 2. Kaplan-Meier plot of time to progression. (A) Independent review. (B) Investigator's assessment. qwk 3-hour, 3-hour IV infusion every week for 3 consecutive weeks of a 4-week cycle; q3wk 24-hour, 24-hour IV infusion once every 3 weeks; N, number of patients; C, censored patients.

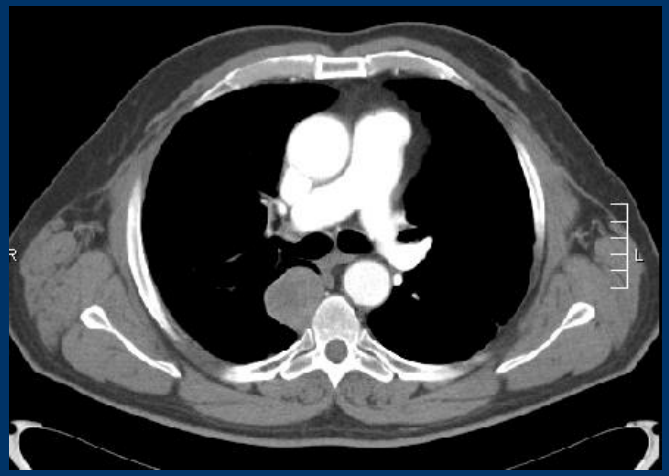
Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

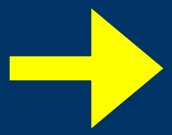
George D. Demetri, Margaret von Mehren, Robin L. Jones, Martee L. Hensley, Scott M. Schuetze, Arthur Staddon, Mohammed Milhem, Anthony Elias, Kristen Ganjoo, Hussein Tawbi, Brian A. Van Tine, Alexander Spira, Andrew Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland E. Knoblauch, Trilok V. Parekh, Robert G. Maki, and Shreyaskumar R. Patel

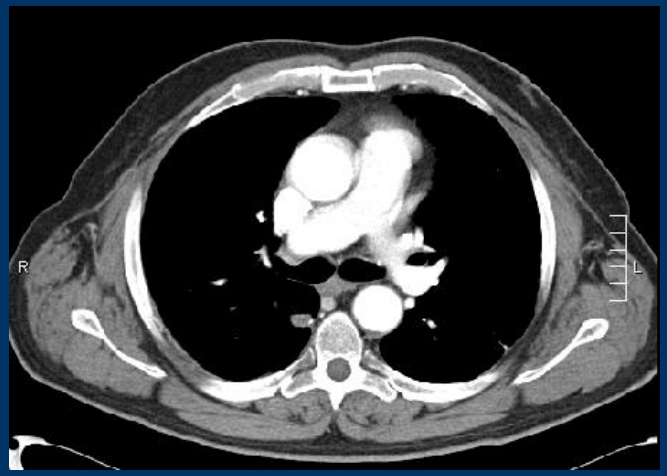


J Clin Oncol 2015;Epub

Leiomyosarcoma (4th line)







0

TRAB x 6

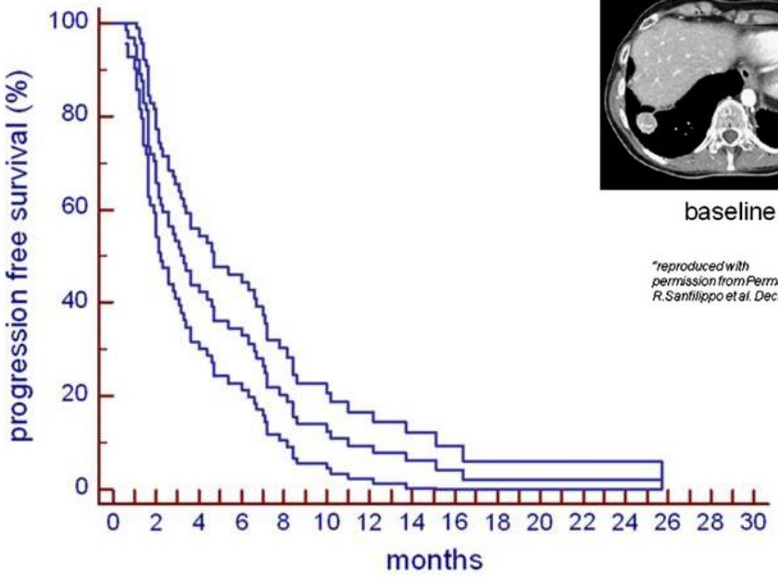
Contents lists available at SciVerse ScienceDirect

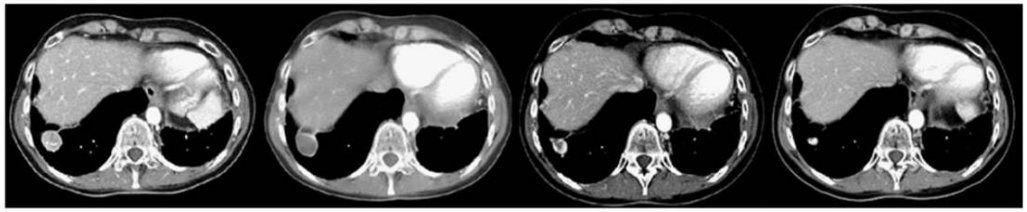
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Trabectedin in advanced uterine leiomyosarcomas: A retrospective case series analysis from two reference centers ☆

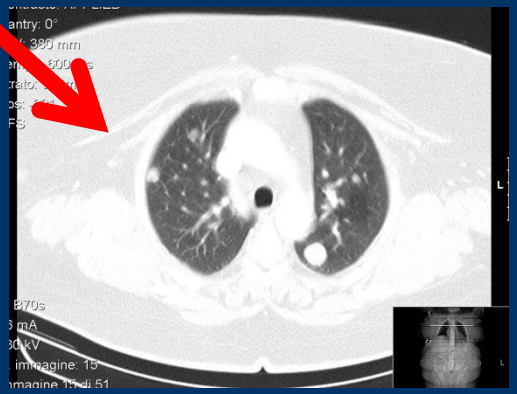
Roberta Sanfilippo [a,*,1], Federica Grosso [a,1,2], Robin L. Jones [b,3], Susana Banerjee [b], Silvana Pilotti [c], Maurizio D'Incalci [d], Angelo Paolo Dei Tos [e], Francesco Raspagliesi [f], Ian Judson [b], Paolo Giovanni Casali [a]



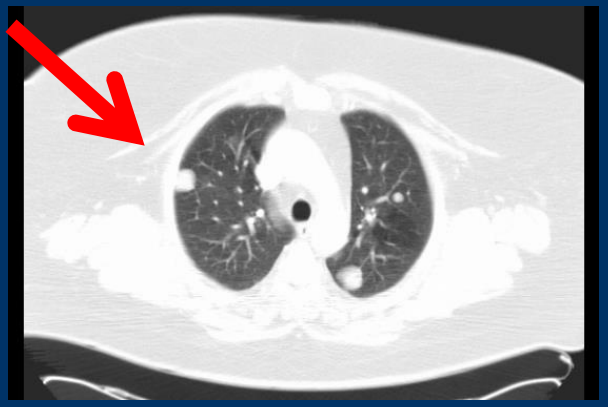


"reproduced with permission from Permanyer Publications".
R.Sanfilippo et al. Decrease in tumor density with Yondelis® as a prelude to tumor response

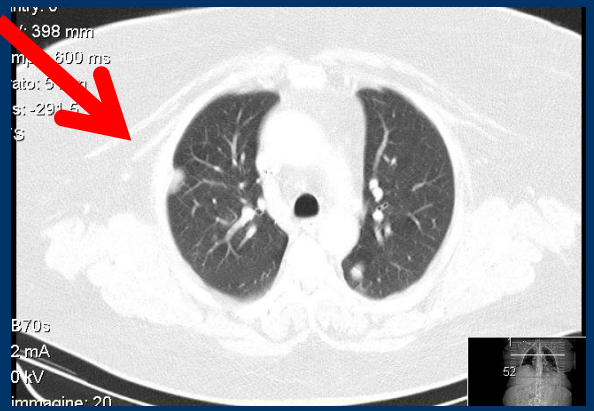
Fig. 3. Tumor shrinkage preceded by a decrease in tumor density.



0



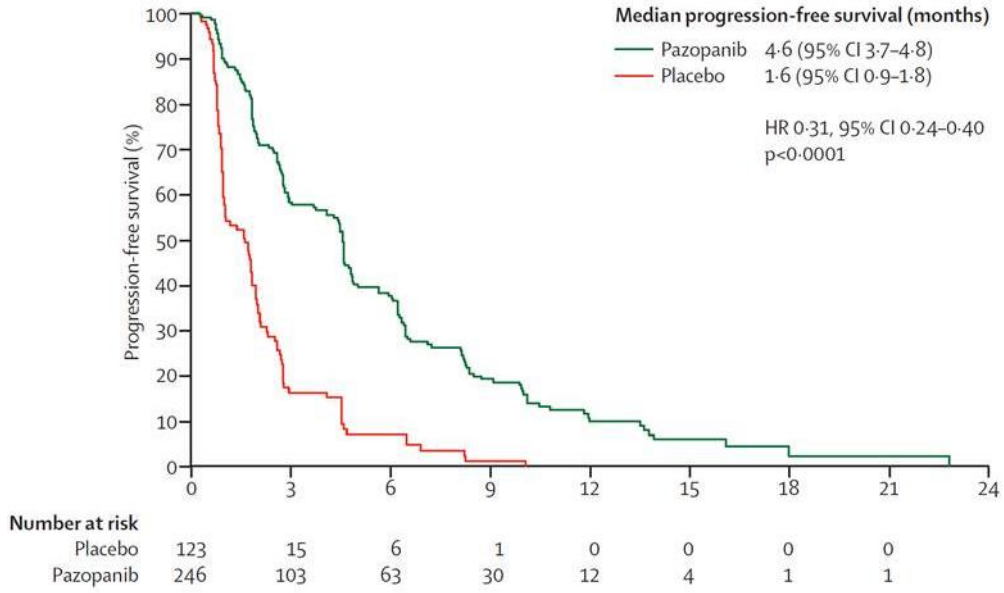
Trabectedin x 2

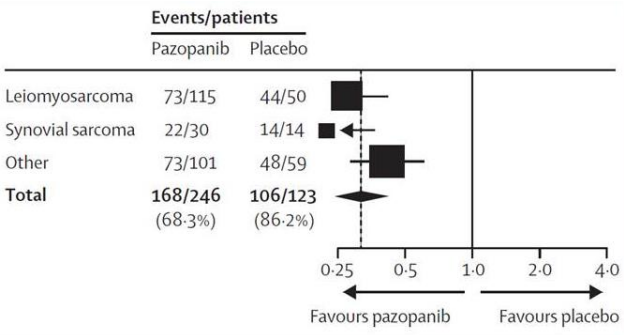


Trabectedin x 10

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

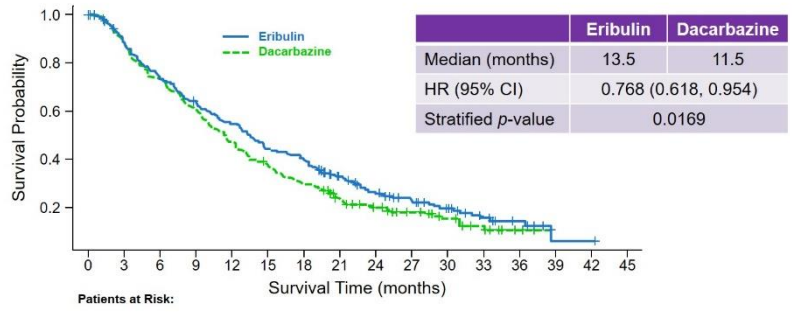




Lancet 2012;379:1879

Eribulin

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 (continued)

Group/Subgroup	Events/n Eribulin	Events/n Dacarbazine	HR (95% CI)	Median (months) Eribulin	Median (months) 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

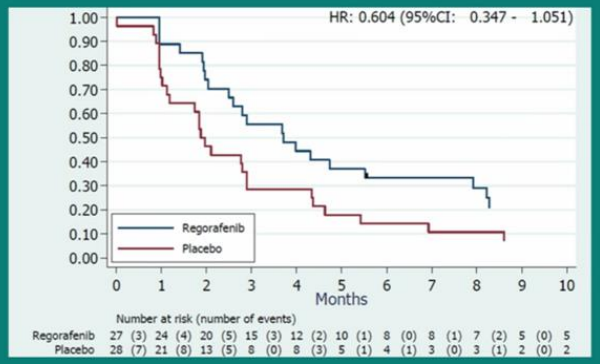
AJCC, American Joint Committee on Cancer.

from: ASCO 2015 Virtual Meeting

Schoffski P et al, ASCO 2015; #10502

Regorafenib

PFS - Leiomyosarcoma

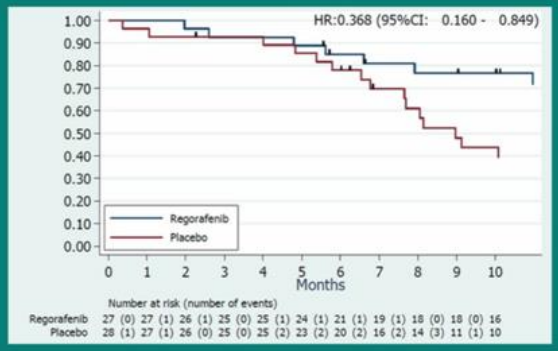


Median PFS
3.7 months vs
1.9 months

P=0.07

PRESENTED AT: ASCO Annual '15 Meeting

OS - Leiomyosarcoma



P=0.01

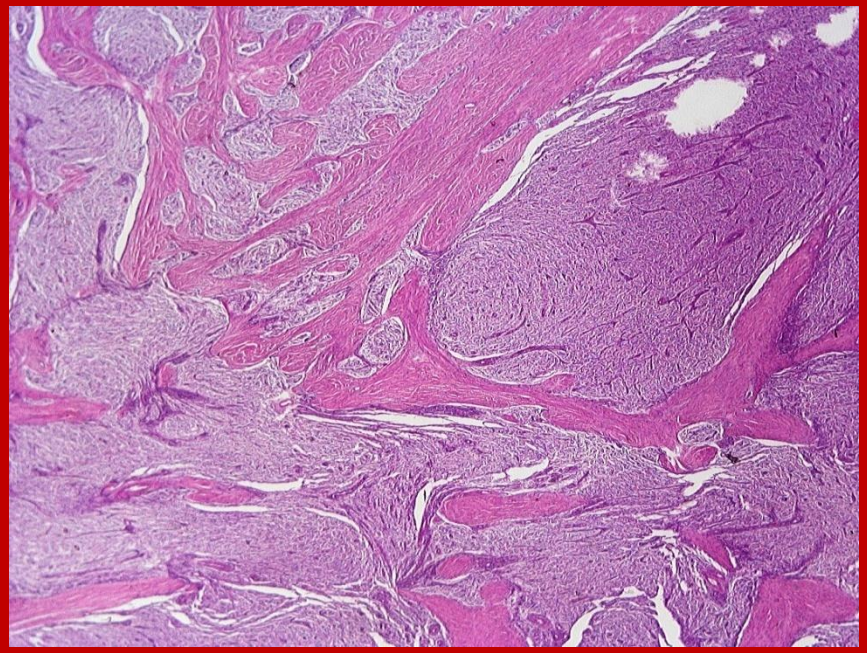
Cross-over in Placebo arm: 20/28

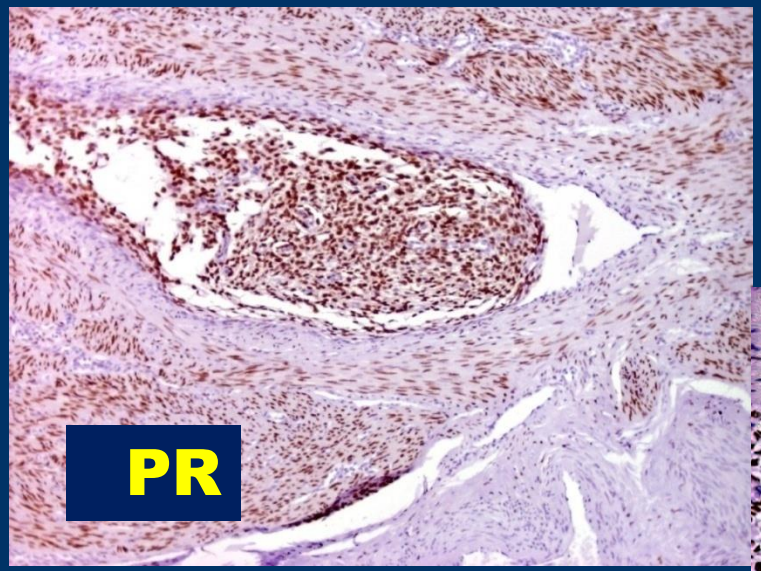
PRESENTED AT: ASCO Annual '15 Meeting

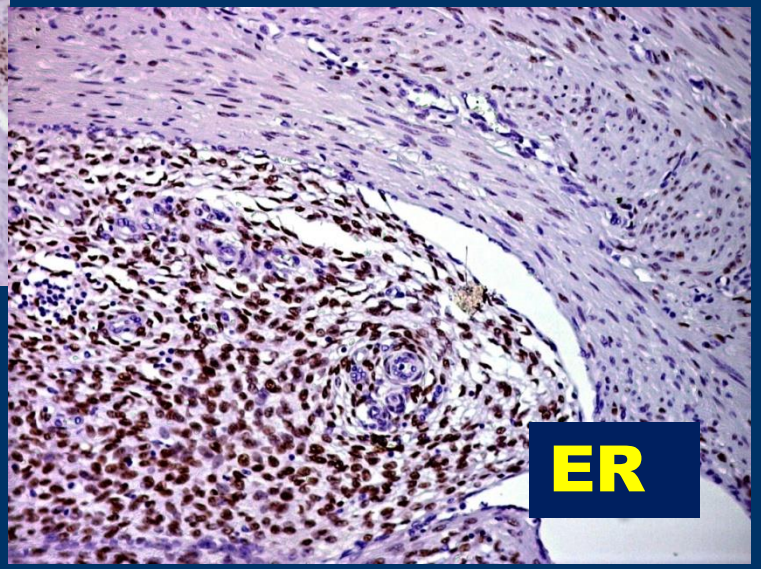
from: ASCO 2015 Virtual Meeting

Mir O et al, ASCO 2015; #10504

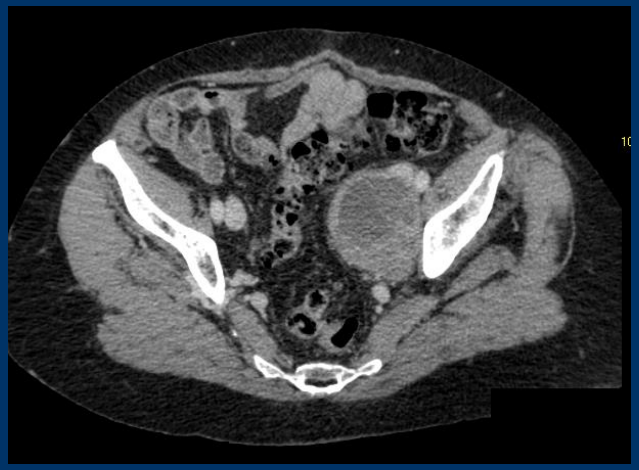
Endometrial stromal sarcoma

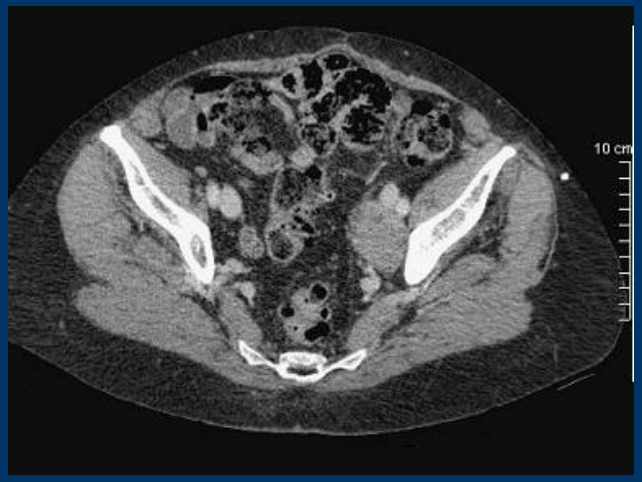



PR


ER

Progestins / Aromatase inhibitors





0

+5 mos

Table 1. Overview of data on progestins for the treatment of uterine sarcomas, in both recurrent/metastatic setting and adjuvant settings.

Study (year)	n	Treatment	Clinical response	Response duration (months)	Ref.
ESS					
Metastatic setting: first line					
Chu *et al.* (2003)	8/10	Meg/progestins NOS	4 CR/3 SD/1 PD	18–180	[18]
Pink *et al.* (2006)	3/10	MPA	1 CR/1 SD/1 PD	0/50/9	[31]
Dahhan *et al.* (2009)	8/11	Meg	4 CR/3 PR/1 SD	36–252/ 18–144/26	[41]
Ioffe *et al.* (2009)	5/7	Meg 4/Depot MPA (1)	1 PR/3 SD/1 PD	124/6–35/ NA	[40]
Cheng *et al.* (2011)	30/47	Meg (28/30) mifeprostine (3/30)	5 CR/3 PR/ 16 SD/6 PD	24	[20]
Adjuvant setting					
Katz *et al.* (1987)	2/9	Meg	2 NED	24–72	[72]
Chu *et al.* (2003)	13/24	Meg	9 NED/4 recurred	18–56	[18]
Malouf *et al.* (2010)	4/54	Meg	4 NED	NA	[22]
Cheng *et al.* (2011)	25/35	NOS	NED	132	[20]
ULMS					
Metastatic setting: first line					
Uchida *et al.* (1996)	1	MPA	PR	>45	[56]
Lo *et al.* (2005)	1	MPA	PR	19	[55]
Koivisto-Korander *et al.* (2007)	1/3	Mifepristone	1 PR/2 PD	>36	[57]

CR: Complete response; ESS: Endometrial stromal sarcoma; Meg: Megestrol; MPA: Medroxyprogesterone acetate; NA: Not applicable; NED: No evidence of disease; NOS: Not otherwise specified; PD: Progression of disease; PR: Partial response; SD: Stable disease; ULMS: Uterine leiomyosarcoma.

Thanopoulou E, Judson I. Expert Rev Anticancer Ther 2012;12:885

Table 2. Overview of data on aromatase inhibitors for the treatment of endometrial stromal sarcomas in both recurrent/metastatic setting and adjuvant settings.

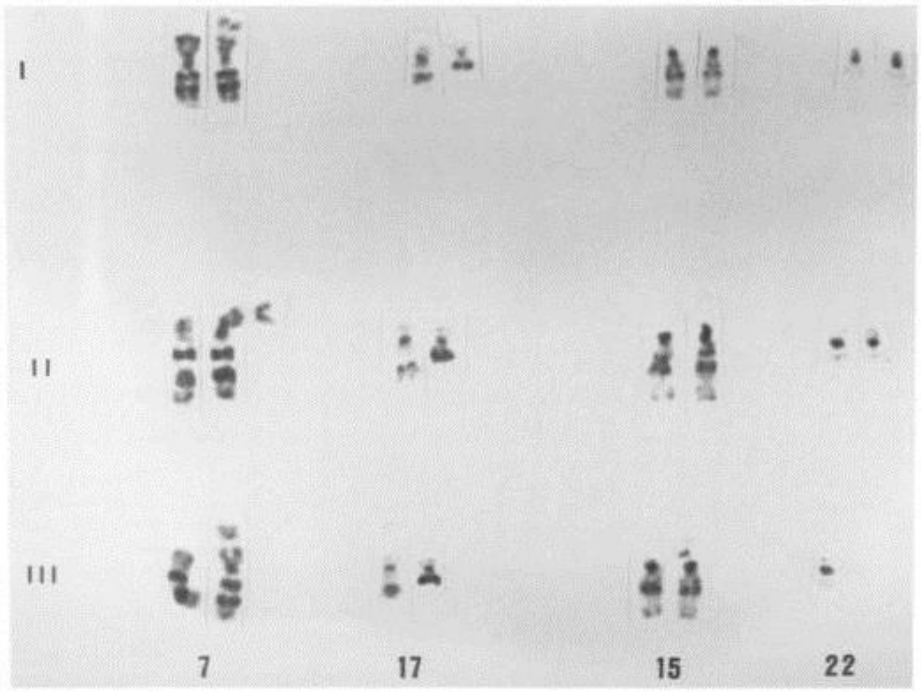
Study (year)	n	Treatment	Clinical response	Response duration (months)	Ref.
Metastatic setting: first line					
Spano *et al.* (2003)	2	Aminoglutethimide	2 CR	84–168	[6]
Leunen *et al.* (2004)	1	Letrozole	PR	36	[42]
Pink *et al.* (2006)	5	Letrozole	4 PR/1 PD	3–37/NA	[31]
Ioffe *et al.* (2009)	3	Letrozole	1 CR/2 PR	88–124/53	[40]
Dahhan *et al.* (2009)	3	Letrozole	2 PR/1 PD		[41]
Sylvestre *et al.* (2010)	1	Letrozole	1 CR	>24	[73]
Metastatic setting: second line					
Maluf *et al.* (2001)	1	Letrozole	PR	9	[59]
Spano *et al.* (2003)	1	Letrozole	1 CR	84	[6]
Shoji *et al.* (2010)	1	Anastrozole	1 PR	16	[43]
Adjuvant setting					
Malouf *et al.* (2010)	6/54	AIs	NED	NA	[22]

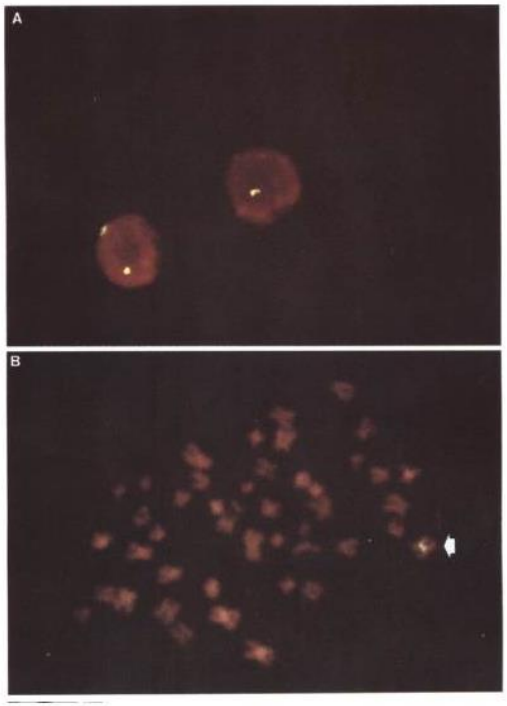
AI: Aromatase inhibitor; CR: Complete response; NA: Not applicable; NED: No evidence of disease; PD: Progression of disease; PR: Partial response.

Thanopoulou E, Judson I. Expert Rev Anticancer Ther 2012;12:885

Endometrial Stromal Sarcoma t(7;17)(p15–21;q12–21) is a Nonrandom Chromosome Change

Paola Dal Cin, Magdy Sayed Aly, Ivo De Wever, Philippe Moerman, and Herman Van Den Berghe

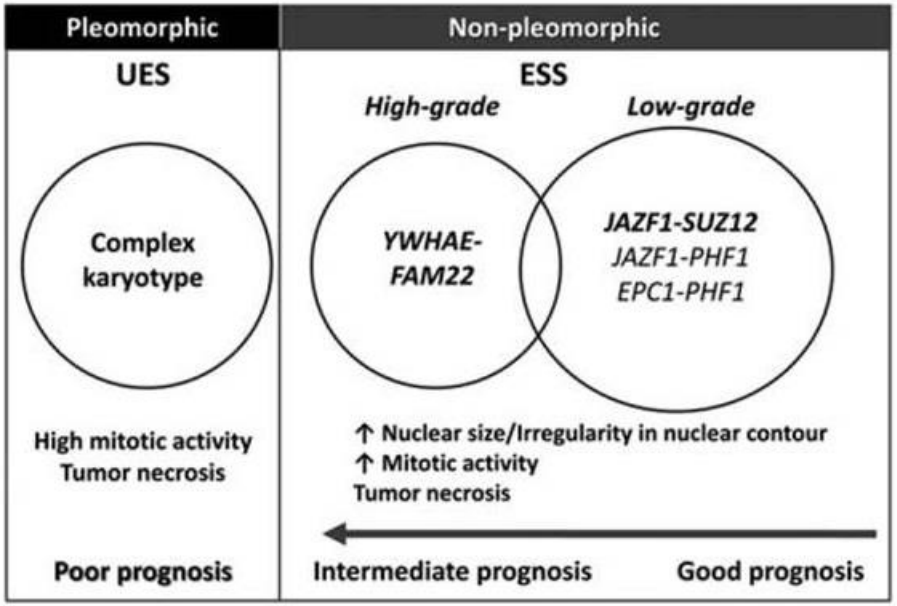




Cancer Genet Cytogenet 1992;63:43

The Clinicopathologic Features of *YWHAE-FAM22* Endometrial Stromal Sarcomas: A Histologically High-grade and Clinically Aggressive Tumor

Cheng-Han Lee, MD, PhD,† Adrian Mariño-Enriquez, MD,* Wenbin Ou, PhD,* Meijun Zhu, PhD,* Rola H. Ali, MD,† Sarah Chiang, MD,‡ Frédéric Amant, MD,§ C. Blake Gilks, MD,† Matt van de Rijn, MD, PhD,‖ Esther Oliva, MD,‡ Maria Debiec-Rychter, MD,¶ Paola Dal Cin, PhD,* Jonathan A. Fletcher, MD* and Marisa R. Nucci, MD**



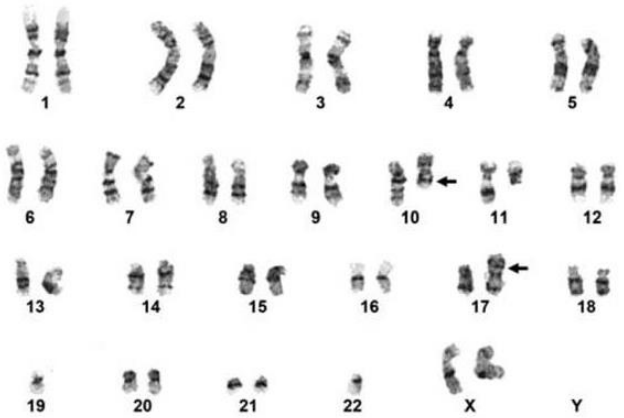


FIGURE 6. Karyotype of *YWHAE-FAM22* ESS (case 3, Table 1) showing t(10;17)(q22;p13) (arrows).

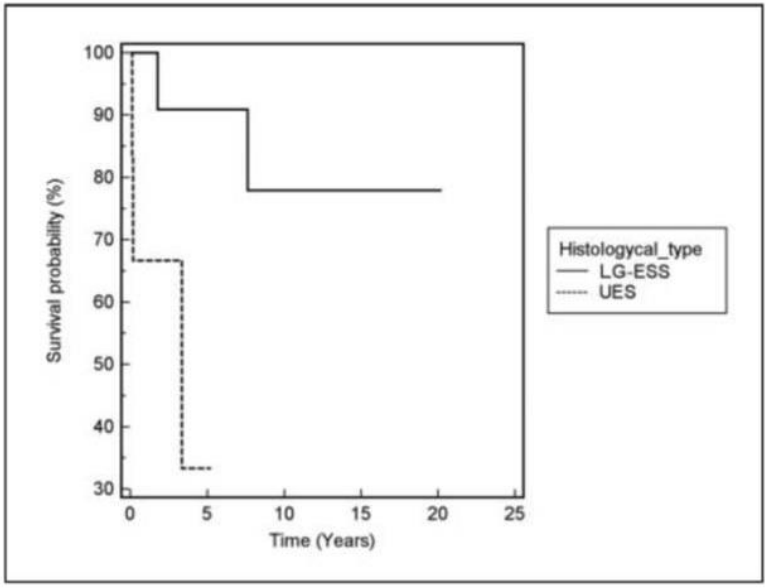
Am J Surg Pathol 2012;36:1641

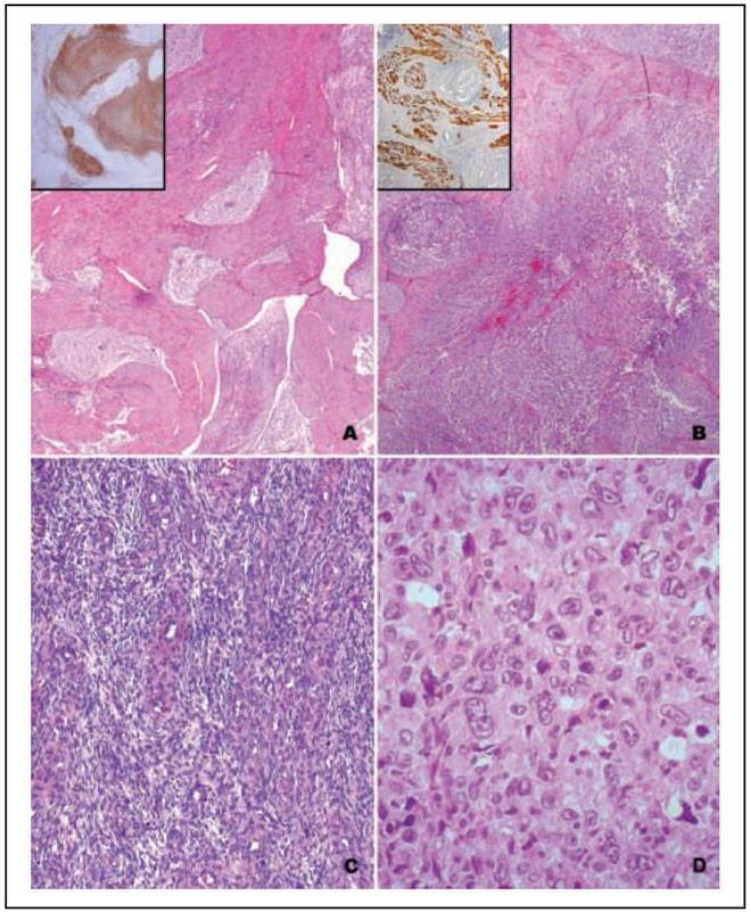
Low-Grade Endometrial Stromal Sarcoma and Undifferentiated Endometrial Sarcoma: A Comparative Analysis Emphasizing the Importance of Distinguishing Between These Two Groups

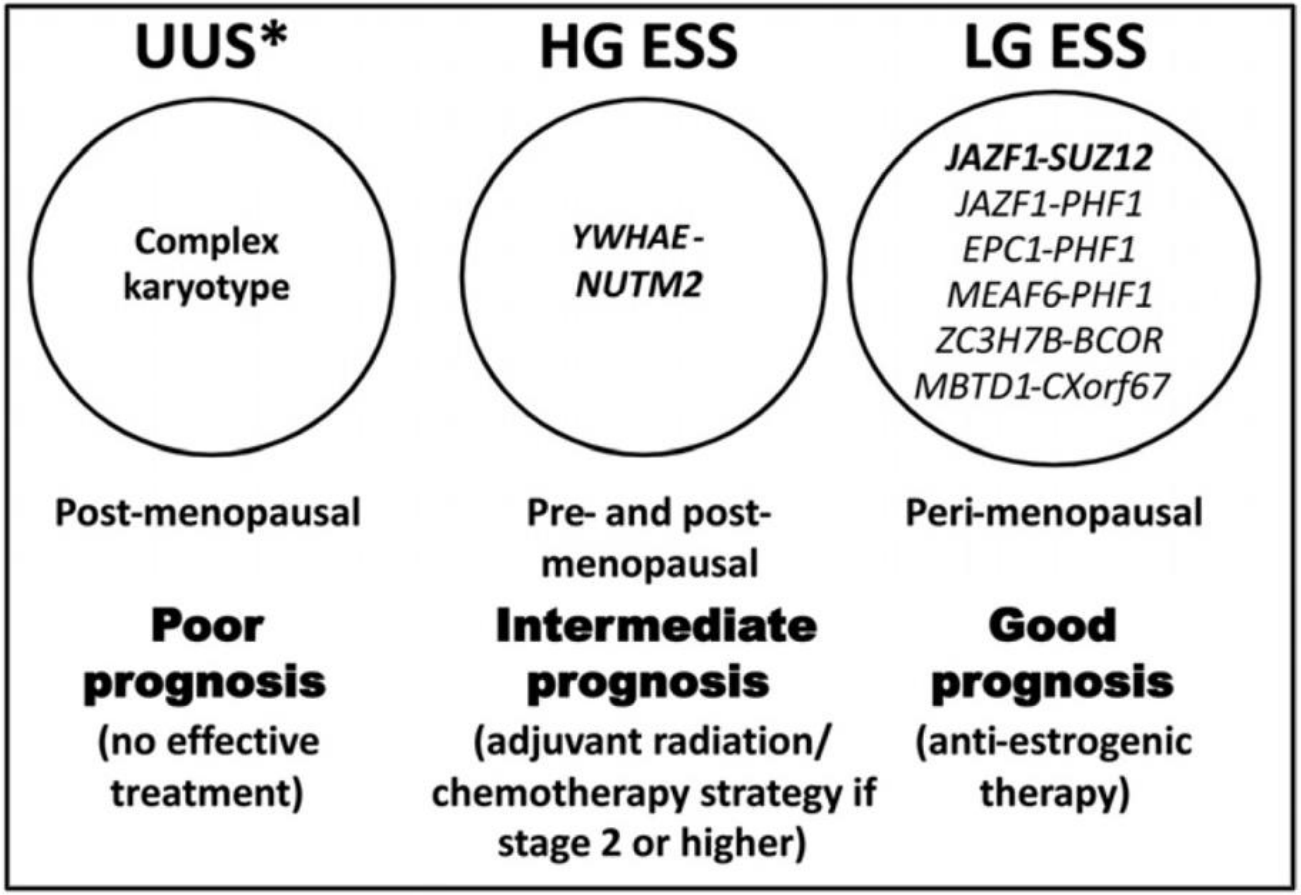
Carla Bartosch, MD,[1] Maria Isabel Exposito, MD,[1,2] and José Manuel Lopes, MD, PhD[1,2,3]

International Journal of Surgical Pathology
18(4) 286–291

DOI: 10.1177/1066896909337600
http://ijsp.sagepub.com
SAGE

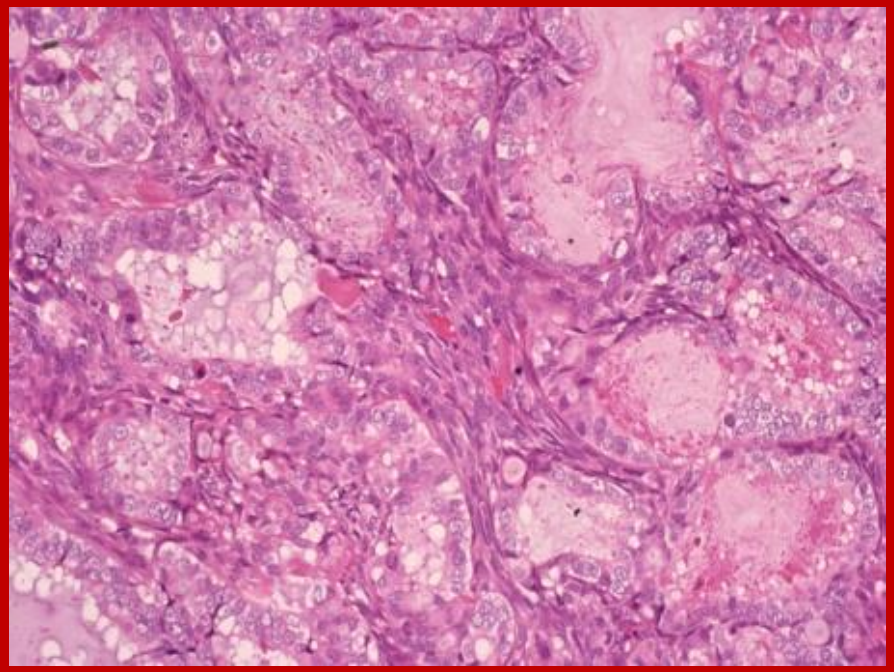




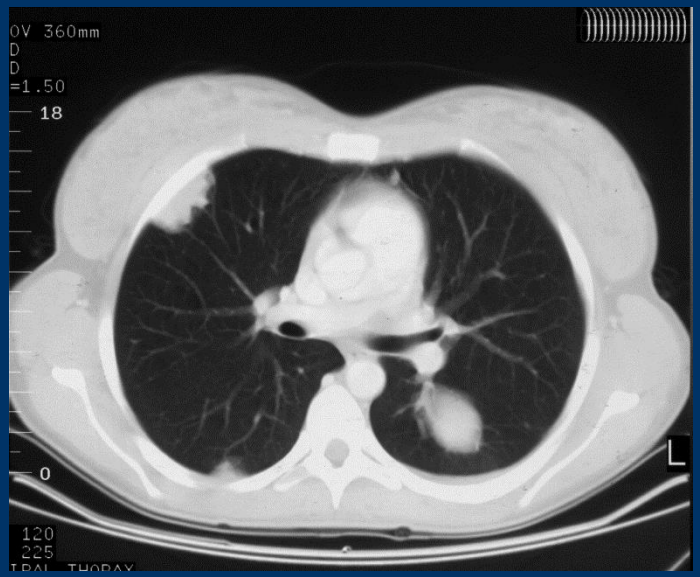


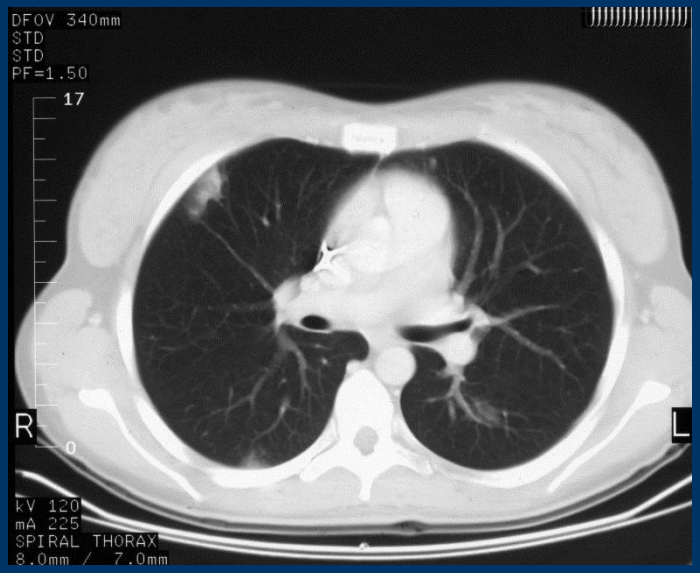
Lee C-H, Nucci M. Histopathology 2014 [Epub]

Synovial sarcoma



Synovial sarcoma: Ifosfamide



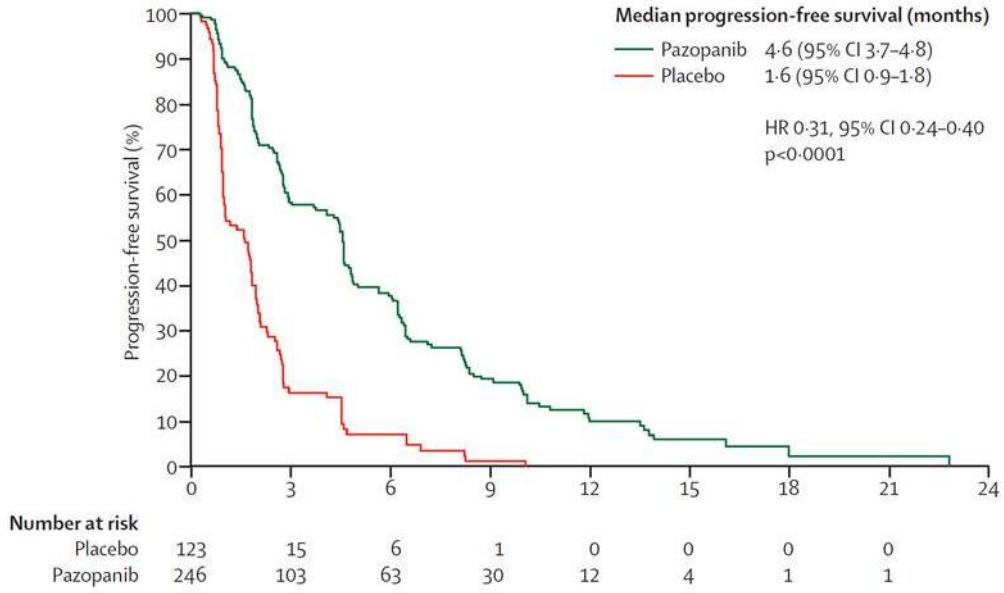


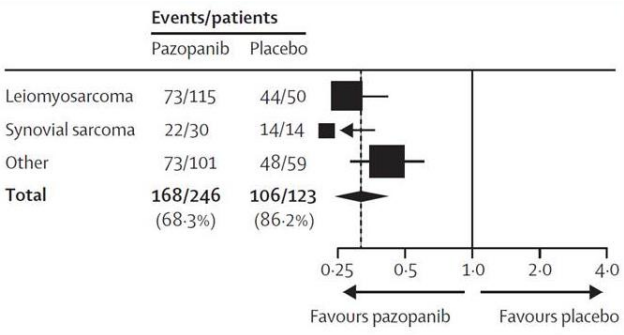
0

cihdFX x 3 mos

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

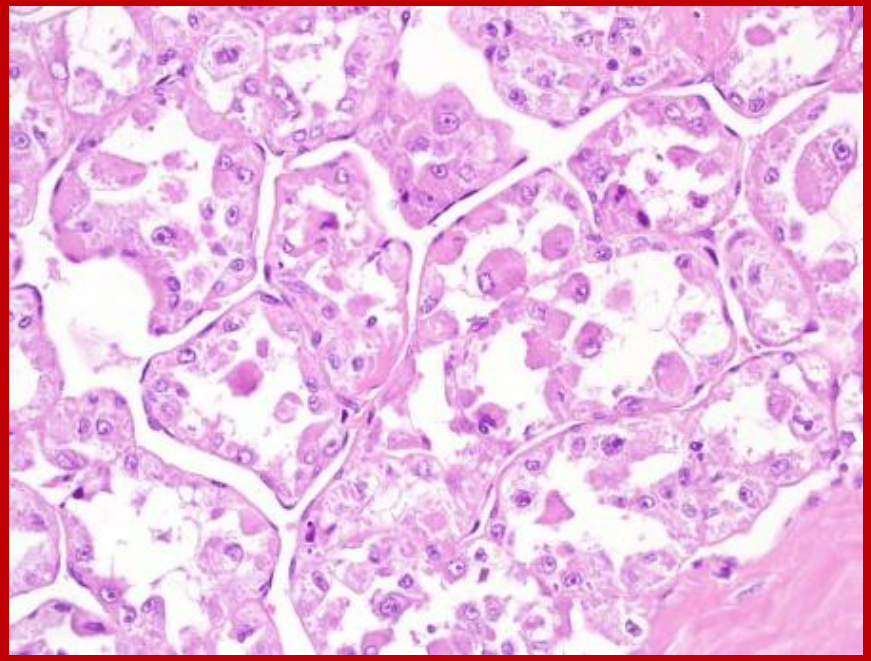
Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel 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





Lancet 2012;379:1879

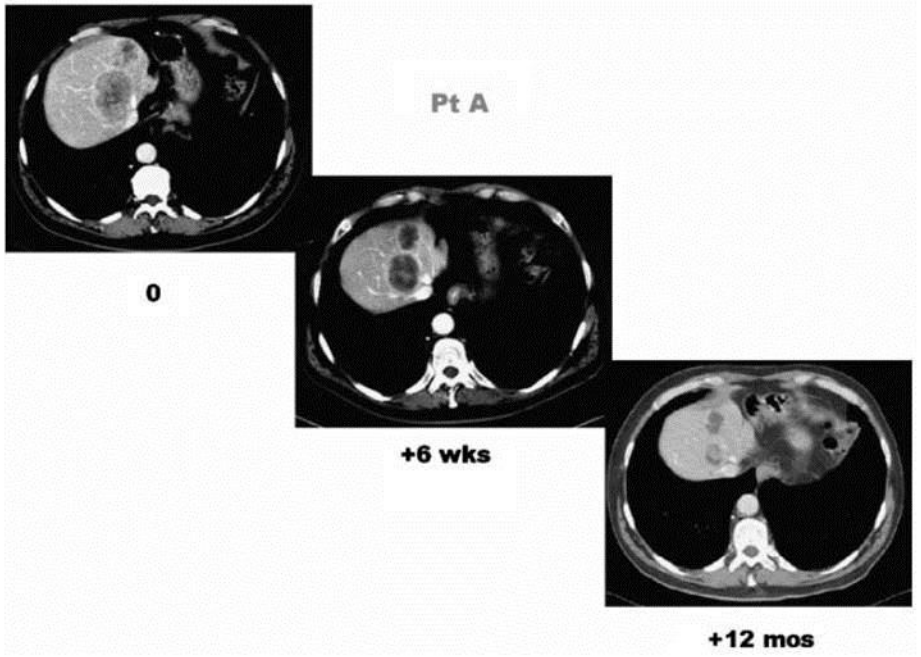
Alveolar soft part sarcoma

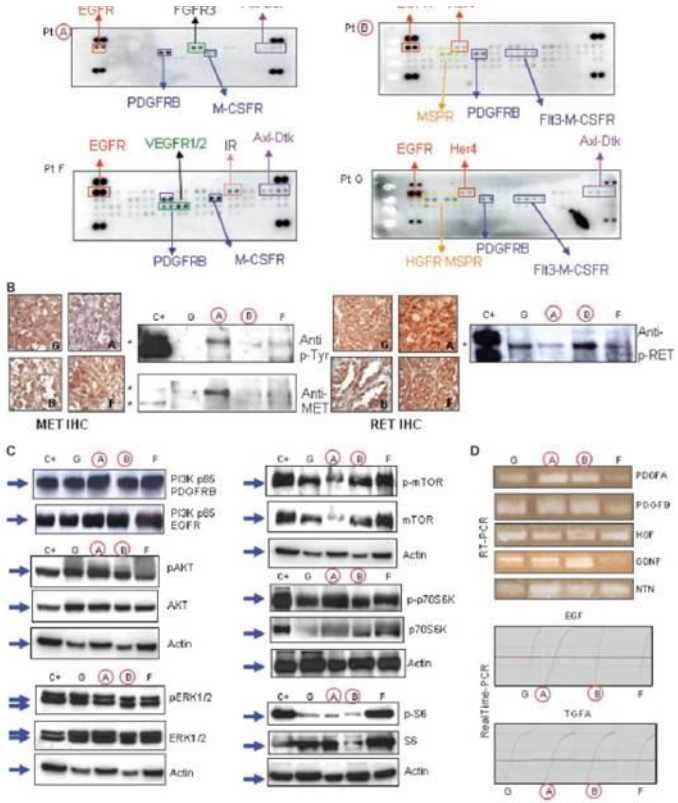


Cancer Therapy: Clinical

Response to Sunitinib Malate in Advanced Alveolar Soft Part Sarcoma

Silvia Stacchiotti,[1] Elena Tamborini,[2] Andrea Marrari,[1] Silvia Brich,[2] Sara Arisi Rota,[2] Marta Orsenigo,[2] Flavio Crippa,[3] Carlo Morosi,[4] Alessandro Gronchi,[5] Marco A. Pierotti,[2] Paolo G. Casali,[1] and Silvana Pilotti[2]





original article

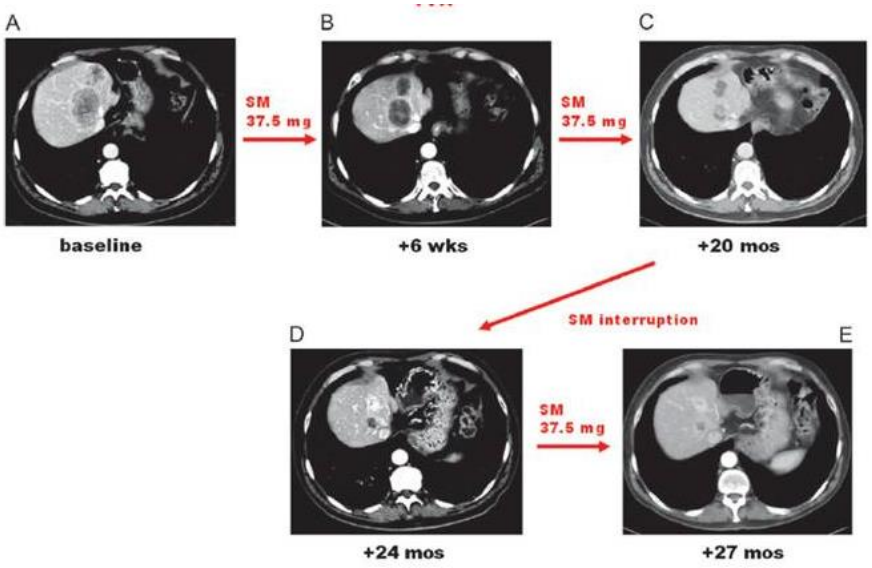
Annals of Oncology
doi:10.1093/annonc/mdq644

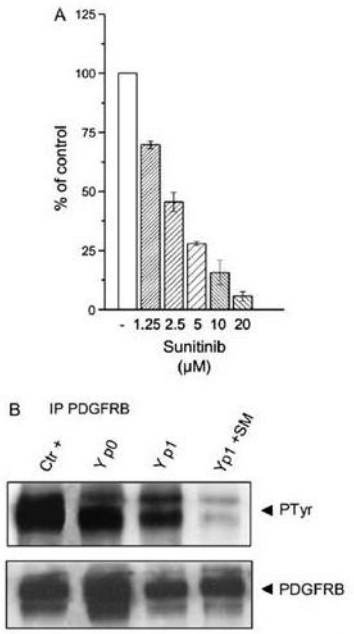
Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect

S. Stacchiotti[1]*, T. Negri[2], N. Zaffaroni[3], E. Palassini[1], C. Morosi[4], S. Brich[2], E. Conca[2], F. Bozzi[2], G. Cassinelli[3], A. Gronchi[5], P. G. Casali[1] & S. Pilotti[2]

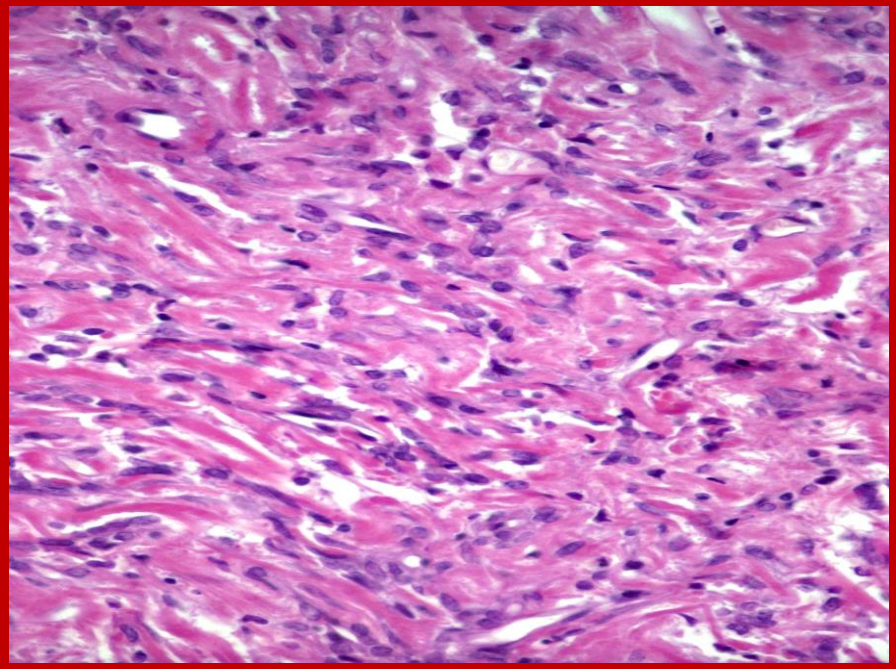
Departments of [1]Cancer Medicine; [2]Pathology, Laboratory of Experimental Molecular Pathology; [3]Experimental Oncology and Molecular Medicine; [4]Radiology; [5]Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

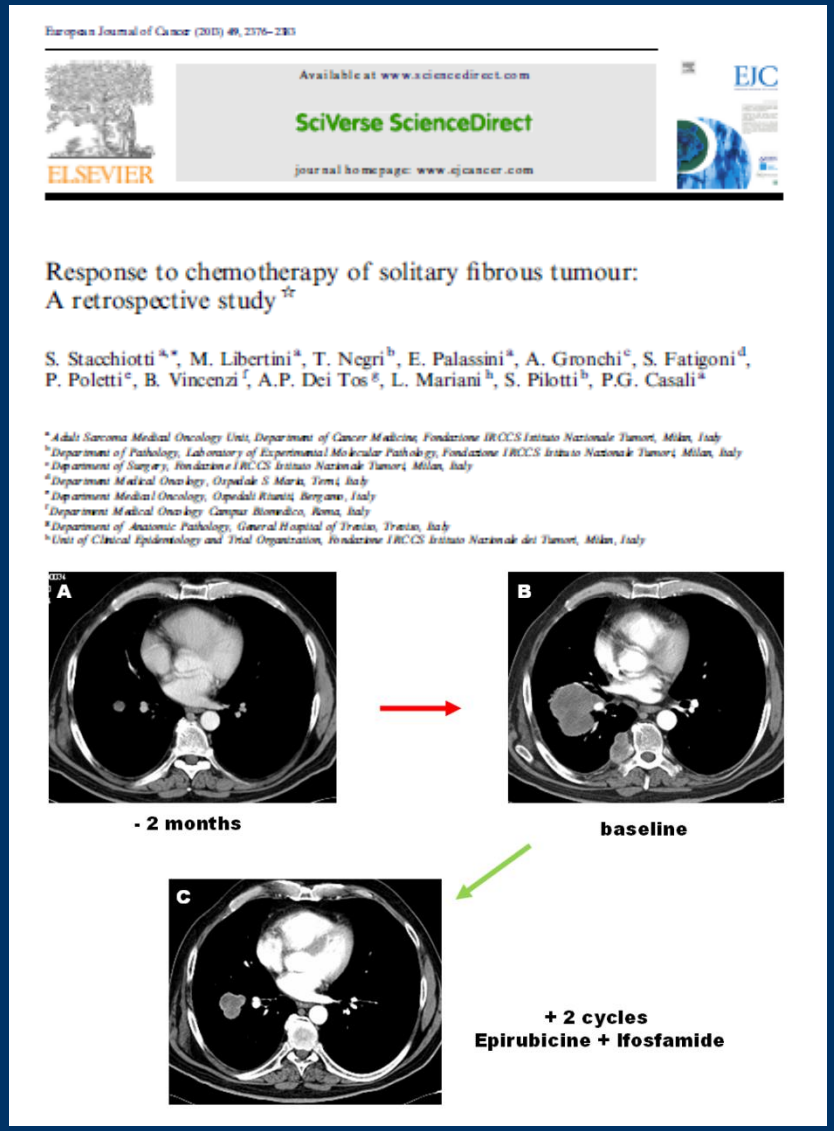
Received 17 August 2010; revised 5 October 2010; accepted 6 October 2010





Solitary fibrous tumor





European Journal of Cancer (2013) 49, 2376–2383

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Response to chemotherapy of solitary fibrous tumour: A retrospective study ☆

S. Stacchiotti [a,*], M. Libertini [a], T. Negri [b], E. Palassini [a], A. Gronchi [c], S. Fatigoni [d], P. Poletti [e], B. Vincenzi [f], A.P. Dei Tos [g], L. Mariani [h], S. Pilotti [b], P.G. Casali [a]

[a] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Department of Pathology, Laboratory of Experimental Molecular Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[d] Department Medical Oncology, Ospedale S. Maria, Terni, Italy
[e] Department Medical Oncology, Ospedali Riuniti, Bergamo, Italy
[f] Department Medical Oncology Campus Biomedico, Roma, Italy
[g] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[h] Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

31 pts, 18 mal / 12 dediff

anthracyclin-based CT

RECIST: **20% PR**
27% SD
53 PD

median PFS: **4 mos**

European Journal of Cancer (2013) 49, 2376–2383

Available at www.sciencedirect.com

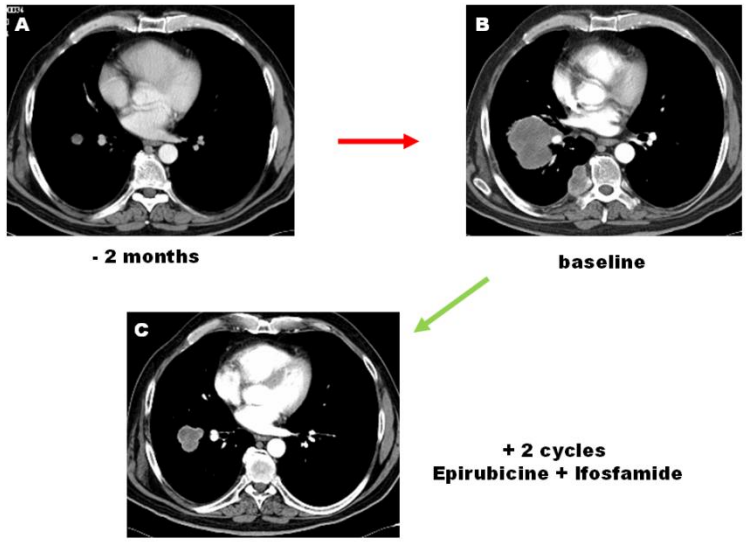
SciVerse ScienceDirect

journal homepage: www.ejcancer.com

Response to chemotherapy of solitary fibrous tumour: A retrospective study ☆

S. Stacchiotti [a,*], M. Libertini [a], T. Negri [b], E. Palassini [a], A. Gronchi [c], S. Fatigoni [d], P. Poletti [e], B. Vincenzi [f], A.P. Dei Tos [g], L. Mariani [h], S. Pilotti [b], P.G. Casali [a]

[a] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Department of Pathology, Laboratory of Experimental Molecular Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[d] Department Medical Oncology, Ospedale S. Maria, Terni, Italy
[e] Department Medical Oncology, Ospedali Riuniti, Bergamo, Italy
[f] Department Medical Oncology Campus Biomedico, Roma, Italy
[g] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[h] Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy



mal

RECIST: 11% PR
median PFS: 3.5 mos

dediff

RECIST: 30% PR
median PFS: 5 mos

Cancer Therapy: Clinical

Clinical Cancer Research

Dacarbazine in Solitary Fibrous Tumor: A Case Series Analysis and Preclinical Evidence vis-à-vis Temozolomide and Antiangiogenics

S. Stacchiotti[1], M. Tortoreto[2], F. Bozzi[3], E. Tamborini[3], C. Morosi[4], A. Messina[4], M. Libertini[1], E. Palassini[1], D. Cominetti[2], T. Negri[3], A. Gronchi[5], S. Pilotti[3], N. Zaffaroni[2], and P.G. Casali[1]

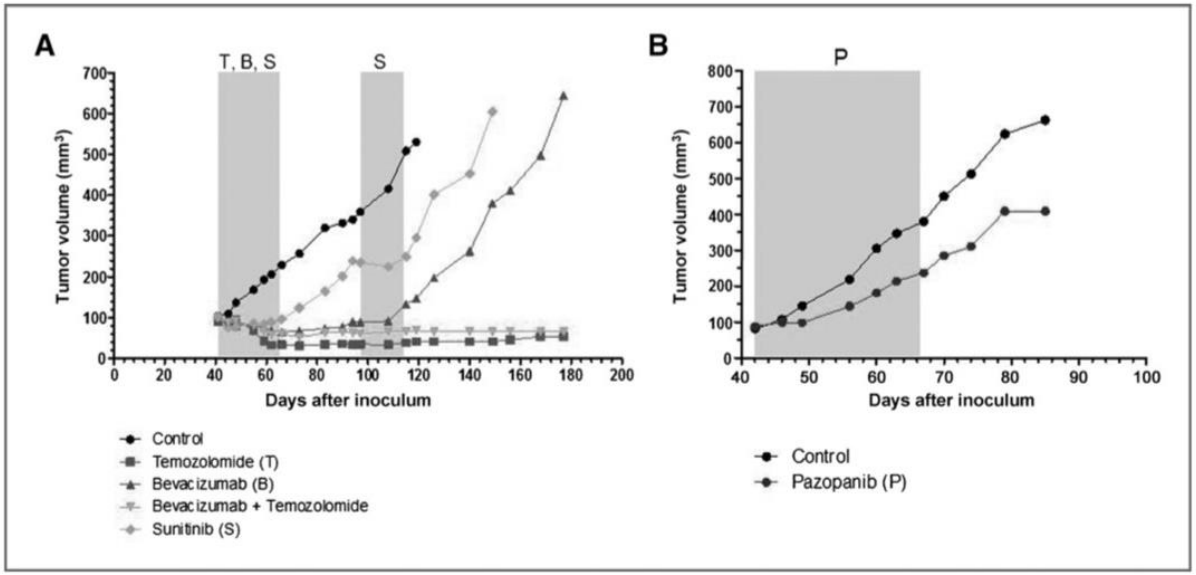


Figure 2. A, efficacy of oral temozolomide (50 mg/kg, q2-3d/w × 4w), intraperitoneal bevacizumab (4 mg/kg, q3-4d/w × 4w) alone and in combination, and oral sunitinib (40 mg/kg, qdx5d/w × 4w) against SFT xenotransplanted in SCID mice. The treatment duration is indicated by the gray bar. B, efficacy of oral pazopanib (100 mg/kg, qdx5d/w × 4w) against SFT xenotransplanted in SCID mice. The treatment duration is indicated by the gray bar.

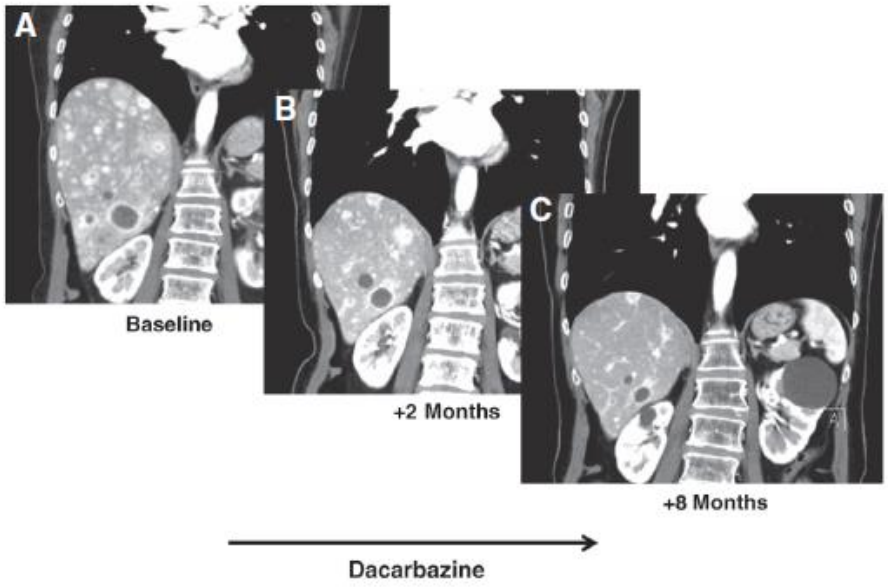
Clin Cancer Res 2013;19:5192

Cancer Therapy: Clinical

Clinical Cancer Research

Dacarbazine in Solitary Fibrous Tumor: A Case Series Analysis and Preclinical Evidence vis-à-vis Temozolomide and Antiangiogenics

S. Stacchiotti[1], M. Tortoreto[2], F. Bozzi[3], E. Tamborini[3], C. Morosi[4], A. Messina[4], M. Libertini[1], E. Palassini[1], D. Cominetti[2], T. Negri[3], A. Gronchi[5], S. Pilotti[3], N. Zaffaroni[2], and P.G. Casali[1]

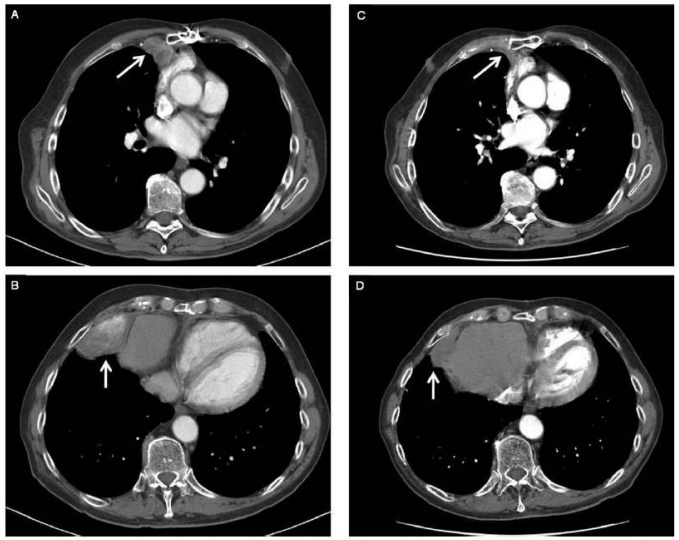


Clin Cancer Res 2013;19:5192

Original Article

Activity of Temozolomide and Bevacizumab in the Treatment of Locally Advanced, Recurrent, and Metastatic Hemangiopericytoma and Malignant Solitary Fibrous Tumor

Min S. Park, MD[1]; Shreyaskumar R. Patel, MD[1]; Joseph A. Ludwig, MD[1]; Jonathan C. Trent, MD, PhD[1]; Charles A. Conrad, MD[2]; Alexander J. Lazar, MD, PhD[3]; Wei-Lien Wang, MD[3]; Piyaporn Boonsirikamchai, MD[4]; Haesun Choi, MD[4]; Xuemei Wang, MS[5]; Robert S. Benjamin, MD[1]; and Dejka M. Araujo, MD[1]



Patient No.	Tumor	Maximum Change in Tumor Size (%)	Maximum Change in Density (%)	Best Response (Choi Criteria)			Best Response (RECIST)
1	HPC	−56.2	−41.3	PR	↓Size	↓HU	PR
2	SFT	−42.1	−67.6	PR	↓Size	↓HU	PR
3	SFT	−26.7	−16.2	PR	↓Size	↓HU	SD
4	HPC	−19.5	−19.1	PR	↓Size	↓HU	SD
5	HPC	−18.5	−39.4	PR	↓Size	↓HU	SD
6	SFT	−13.7	−83.1	PR	↓Size	↓HU	SD
7	SFT	−6.5	−23.7	PR	↓Size	↓HU	SD
8	HPC	−26.9	ND[a]	PR	↓Size		SD
9	HPC	−6.1	−28.7	PR		↓HU	SD
10	HPC	−3.4	−60.5	PR		↓HU	SD
11	HPC	4.9	−15.5	PR		↓HU	SD
12	HPC	0	ND[a]	SD			SD
13	HPC	4.6	4.4	SD			SD
14	HPC	15.5	5.4	PD			SD
Median		−10.1	−26.2				

Cancer 2011;117:4939

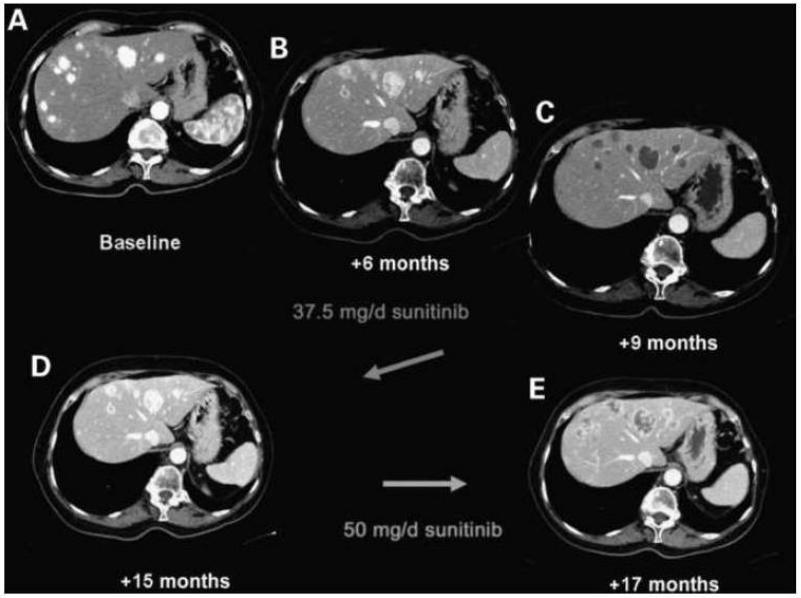
Mol Cancer Ther; 9(5) May 2010

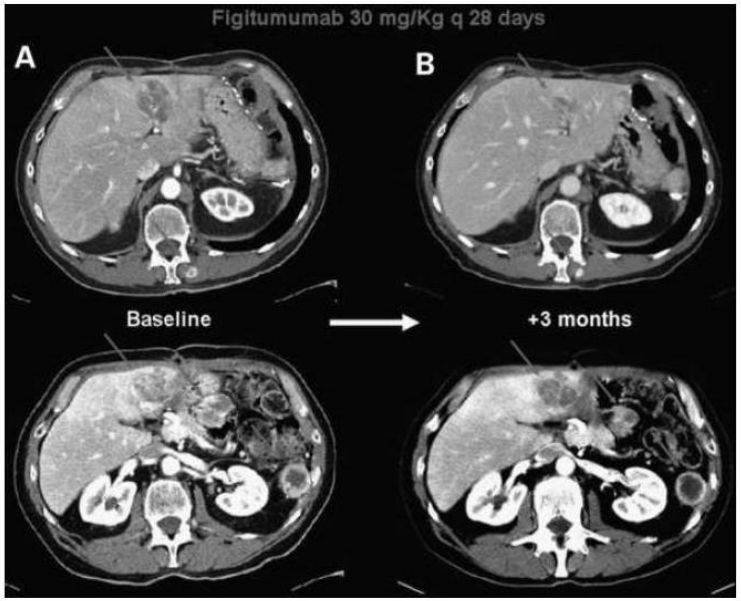
Research Article

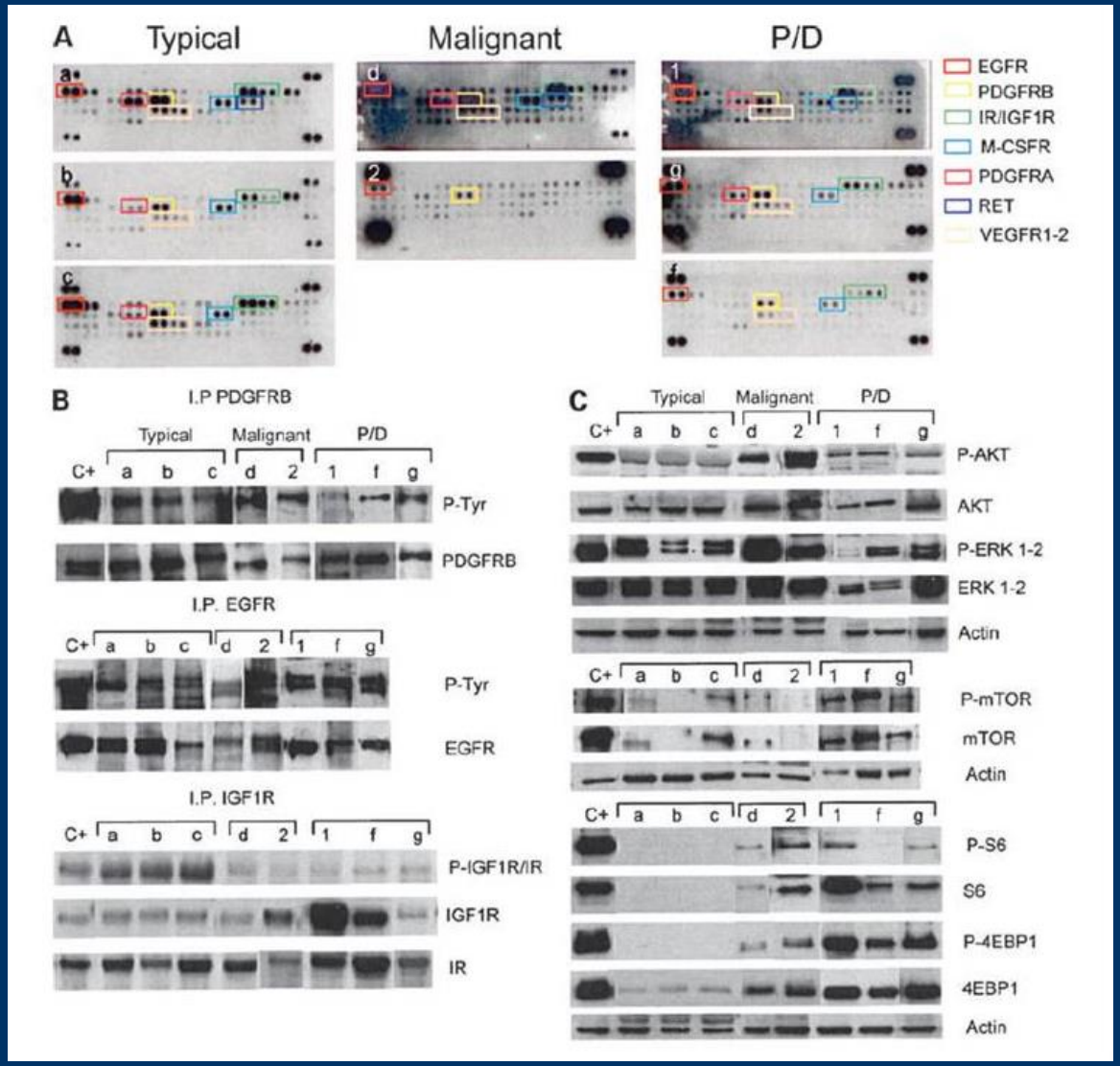
Molecular Cancer Therapeutics

Sunitinib Malate and Figitumumab in Solitary Fibrous Tumor: Patterns and Molecular Bases of Tumor Response

Silvia Stacchiotti[1], Tiziana Negri[2], Elena Palassini[1], Elena Conca[2], Alessandro Gronchi[3], Carlo Morosi[4], Antonella Messina[4], Ugo Pastorino[3], Marco A. Pierotti[5], Paolo G. Casali[1], and Silvana Pilotti[2]







Stacchiotti S et al, Mol Cancer Ther 2010;9:1286

European Journal of Cancer (2014) 50, 3021–3028

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

S. Stacchiotti [a,*,1], M. Tortoreto [b], G.G. Baldi [c], G. Grignani [d], A. Toss [e], G. Badalamenti [f], D. Cominetti [b], C. Morosi [g], A.P. Dei Tos [h], F. Festinese [i], E. Fumagalli [a], S. Provenzano [a], A. Gronchi [j], E. Pennacchioli [k], T. Negri [l], G.P. Dagrada [l], R.D. Spagnuolo [l], S. Pilotti [l,1], P.G. Casali [a,1], N. Zaffaroni [b]

[a] Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Medical Oncology Unit "Sandro Pitigliani", S. Stefano Civil Hospital, Prato, Italy
[d] Medical Oncology, IRCCS – Istituto di Candiolo, Candiolo, Italy
[e] Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy
[f] Department of Oncology, University Hospital of Palermo, Palermo, Italy
[g] Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[h] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[i] Pharmacy Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[j] Melanoma and Sarcoma Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[k] Melanoma and Sarcoma, Surgery Department, Istituto Europeo di Oncologia, Milan, Italy
[l] Laboratory of Experimental Molecular Pathology, Department of Diagnostic Pathology and Laboratory, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Received 5 June 2014; received in revised form 10 August 2014; accepted 8 September 2014
Available online 27 September 2014

KEYWORDS
Sarcoma
Solitary fibrous tumour
Pazopanib
Sunitinib
Tyrosine kinase
Chemotherapy

Abstract ***Background:*** To explore the activity of pazopanib in solitary fibrous tumour (SFT). ***Patients and methods:*** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplantat into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm³. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

* Corresponding author at: Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, Milano, Italy. Tel.: +39 0223902803; fax: +39 0223902404.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).
[1] These authors equally contributed to the paper.

http://dx.doi.org/10.1016/j.ejca.2014.09.004

Manuzzo et al. Clinical Sarcoma Research (2015) 5:5
DOI 10.1186/s13569-015-0022-2

CLINICAL SARCOMA RESEARCH

RESEARCH Open Access

Pazopanib as first line treatment for solitary fibrous tumours: the Royal Marsden Hospital experience

Marco Manuzzo[1], Juan Martin-Liberal[1], Christina Messiou[2], Aisha Miah[1], Khin Thway[3], Rolyn Alvarado[1], Ian Judson[1] and Charlotte Benson[1*]

Abstract

Background: Solitary Fibrous Tumour (SFT) is a rare soft tissue neoplasm, described in several locations in the body. It is classified as intermediate malignant potential with low risk of metastasis and has a low tendency to recur after primary surgery.

Methods: We performed a prospective data collection of the patients with SFT presented to the Royal Marsden Hospital from January to December 2013, and treated with pazopanib in first line. Demographics, anatomic primary sites, treatment and survival outcomes were collected from patients' electronic records.

Results: 13 patients (54% females) were identified with a median age of 51 years (range 37–77). Most of the patients (77%) were diagnosed with extra-thoracic SFT. All the patients received first line treatment with pazopanib for metastatic disease. Median overall survival (OS) was 13.3 months. Median progression free survival (PFS) was 4.7 months. No statistically significant difference was found in OS and PFS between primary thoracic SFT and primary extra-thoracic SFT. According to RECIST, one partial response (9%) and eight disease stabilizations (73%) were found as best responses. Using Choi criteria, there were 5 partial responses (46%) and 4 stabilizations (36%).

Conclusion: Our prospective data confirm that anti-angiogenic drugs are active in SFT. PFS and overall response do not appear significantly lower than other reported series on the same disease. Furthermore, pazopanib is a drug already licensed in soft tissue sarcomas and these data suggest its activity also in this particular subtype of sarcomas.

Keywords: Pazopanib, Solitary fibrous tumour, SFT, Sarcoma

Introduction

Solitary Fibrous Tumour (SFT) is a rare soft tissue neoplasm, initially thought to occur exclusively within the thorax [1] and now known to arise from all anatomical sites [2]. In the past, SFT has also been called hemangiopericytoma, a term used over the years to describe a wide variety of tumours with some common morphological characteristics. Different biological entities have progressively been identified for this category, and most of them are now recognized as SFTs [3].

Recently, STFs have been described in several locations also outside the thoracic cavity, including head and neck, abdomen, retroperitoneum, and other soft tissue sites [4–6].

SFTs are classified as having intermediate malignant potential with low risk of metastasis under the WHO classification [7] and they have a low tendency to recur after primary surgery [8]. However, the clinical behaviour is hard to predict and several prognostic factors have been considered in order to assess the behaviour of the disease. In a recent analysis of a large cohort of SFTs, the size and the mitotic index have been proposed as factors to consider after primary surgery which may help to stratify the follow-up of the patients that might have an increased risk of recurrence [5]. Generally, treatment for metastatic SFTs is not curative and is of palliative intent.

* Correspondence: charlotte.benson@rmh.nhs.uk
[1]Sarcoma Unit, The Royal Marsden NHS Foundation Trust, Fulham Road, SW3 6JJ London, UK
Full list of author information is available at the end of the article

European Journal of Cancer (2014) 50, 3021–3028

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

S. Stacchiotti [a,*,1], M. Tortoreto [b], G.G. Baldi [c], G. Grignani [d], A. Toss [e], G. Badalamenti [f], D. Cominetti [b], C. Morosi [g], A.P. Dei Tos [h], F. Festinese [i], E. Fumagalli [a], S. Provenzano [a], A. Gronchi [j], E. Pennacchioli [k], T. Negri [l], G.P. Dagrada [l], R.D. Spagnuolo [l], S. Pilotti [l,1], P.G. Casali [a,1], N. Zaffaroni [b]

[a] Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Medical Oncology Unit 'Sandro Pitigliani', S. Stefano Civil Hospital, Prato, Italy
[d] Medical Oncology, IRCCS – Istituto di Candiolo, Candiolo, Italy
[e] Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy
[f] Department of Oncology, University Hospital of Palermo, Palermo, Italy
[g] Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[h] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[i] Pharmacy Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[j] Melanoma and Sarcoma Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[k] Melanoma and Sarcoma, Surgery Department, Istituto Europeo di Oncologia, Milan, Italy
[l] Laboratory of Experimental Molecular Pathology, Department of Diagnostic Pathology and Laboratory, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

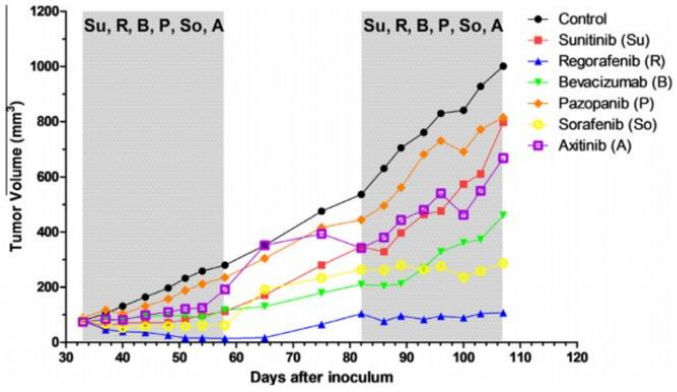
Received 5 June 2014; received in revised form 10 August 2014; accepted 8 September 2014
Available online 27 September 2014

KEYWORDS
Sarcoma
Solitary fibrous tumour
Pazopanib
Sunitinib
Tyrosine kinase
Chemotherapy

Abstract ***Background:*** To explore the activity of pazopanib in solitary fibrous tumour (SFT). ***Patients and methods:*** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplantat into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm³. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

* Corresponding author at: Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, Milano, Italy. Tel.: +39 0223902803; fax: +39 0223902404.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).
[1] These authors equally contributed to the paper.

http://dx.doi.org/10.1016/j.ejca.2014.09.004



European Journal of Cancer (2014) 50, 3021–3028

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

S. Stacchiotti [a,*], M. Tortoreto [b], G.G. Baldi [c], G. Grignani [d], A. Toss [e], G. Badalamenti [f], D. Cominetti [b], C. Morosi [g], A.P. Dei Tos [h], F. Festinese [i], E. Fumagalli [a], S. Provenzano [a], A. Gronchi [j], E. Pennacchioli [k], T. Negri [l], G.P. Dagrada [l], R.D. Spagnuolo [l], S. Pilotti [l,1], P.G. Casali [a,1], N. Zaffaroni [b]

[a] Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Medical Oncology Unit 'Sandro Pitigliani', S. Stefano Civil Hospital, Prato, Italy
[d] Medical Oncology, IRCCS – Istituto di Candiolo, Candiolo, Italy
[e] Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy
[f] Department of Oncology, University Hospital of Palermo, Palermo, Italy
[g] Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[h] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[i] Pharmacy Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[j] Melanoma and Sarcoma Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[k] Melanoma and Sarcoma, Surgery Department, Istituto Europeo di Oncologia, Milan, Italy
[l] Laboratory of Experimental Molecular Pathology, Department of Diagnostic Pathology and Laboratory, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

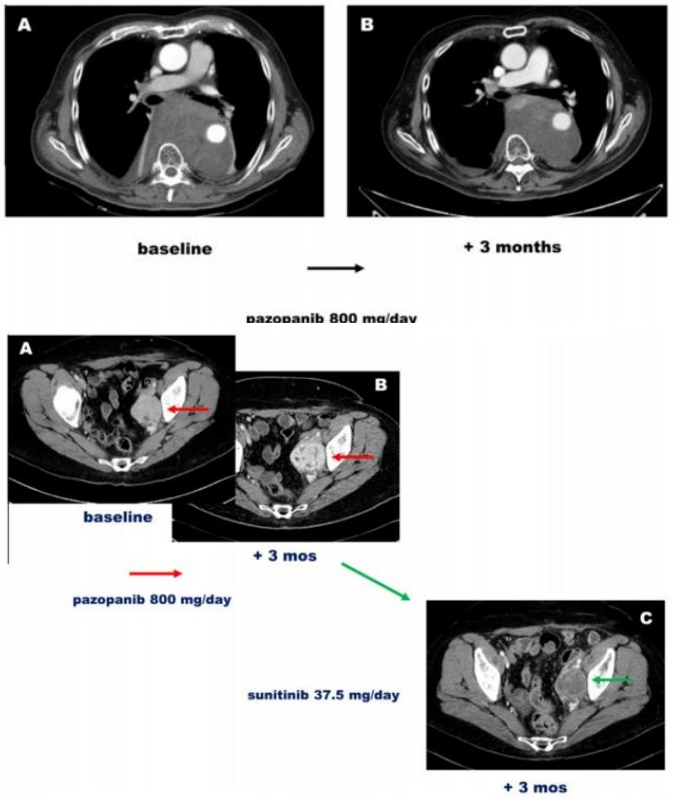
Received 5 June 2014; received in revised form 10 August 2014; accepted 8 September 2014
Available online 27 September 2014

KEYWORDS
Sarcoma
Solitary fibrous tumour
Pazopanib
Sunitinib
Tyrosine kinase
Chemotherapy

Abstract ***Background:*** To explore the activity of pazopanib in solitary fibrous tumour (SFT). ***Patients and methods:*** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplantat into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm³. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

* Corresponding author at: Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, Milano, Italy. Tel.: +39 0223902803; fax: +39 0223902404.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).
[1] These authors equally contributed to the paper.

http://dx.doi.org/10.1016/j.ejca.2014.09.004



FULL PAPER

BJC

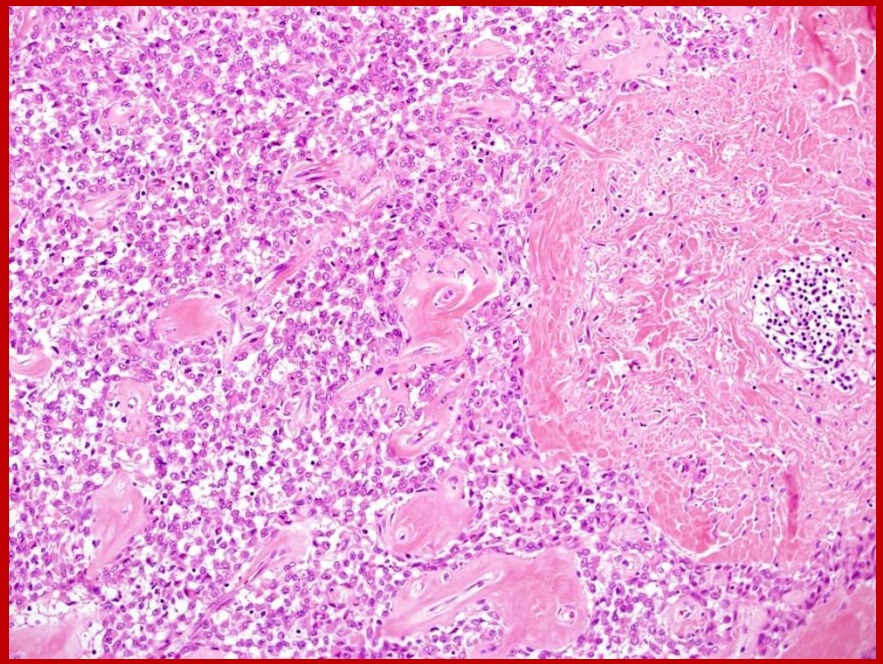
British Journal of Cancer (2014), 1–13 | doi: 10.1038/bjc.2014.437

Keywords: soft tissue sarcoma; solitary fibrous tumour; anti-angiogenic therapy; anti-tumour response; myeloid-derived suppressor cells; tumour-infiltrating lymphocytes; tumour microenvironment; immunohistochemistry

Adaptive immune contexture at the tumour site and downmodulation of circulating myeloid-derived suppressor cells in the response of solitary fibrous tumour patients to anti-angiogenic therapy

M Tazzari[1,2], T Negri[2,3], F Rini[1,2], B Vergani[4], V Huber[1,2], A Villa[4], P Dagrada[2,3], C Colombo[2,5], M Fiore[2,5], A Gronchi[2,5], S Stacchiotti[2,6], P G Casali[2,6], S Pilotti[2,3], L Rivoltini[1,2] and C Castelli*[,1,2]

PEComas



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

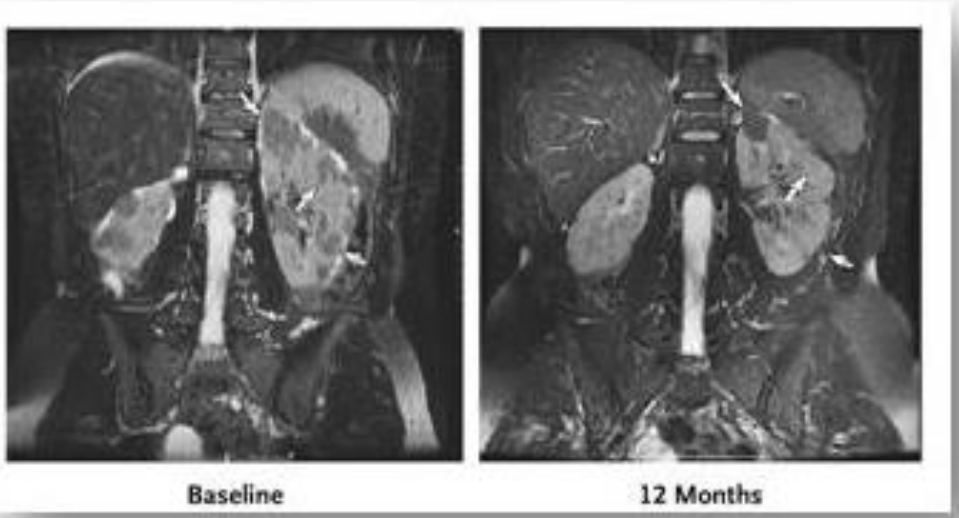
Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmithorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

From the Divisions of Nephrology and Hypertension (J.J.B.), Pulmonary Medicine (L.R.Y.), Neurology (G.C., J.M.L., D.N.F.), Radiology (V.J.S., T.L., A.S.B.), and Biostatistics (J.B., S.S.), Cincinnati Children's Hospital Medical Center; and the Division of Pulmonary and Critical Care, University of Cincinnati College of Medicine (F.X.M., L.R.Y., J.M.E.) — both in Cincinnati. Address reprint requests to Dr. Bissler at Cincinnati Children's Hospital Medical Center, MLC 7022, 3333 Burnet Ave., Cincinnati, OH 45229-3039, or at john.bissler@cchmc.org.

Drs. McCormack, Young, and Franz contributed equally to the article.

N Engl J Med 2008;358:140-51.



Baseline 12 Months

mount height and radius estimates.
20. The marine portions of the ETOPO5 data set derive from SYNPARS [R. J. Van Wyckhouse, Tech. Rep. TR-233 (U.S. Naval Oceanographic Office, NOO-Washington, DC, 1973)] and contain numerous artifacts caused by the combination of poor data coverage, gridding of contours instead of depth soundings, and inappropriate gridding methodology [W. H. F. Smith, *J. Geophys. Res.* **99**, 9591 (1994)].
21. R. A. Duncan and D. A. Clague, in *The Ocean Basins and Margins*, A. E. M. Nairn, F. G. Stehli, S. Uyeda, Eds. (Plenum, New York, 1985), pp. 89–121; R. D. Jarrard and D. A. Clague, *Rev. Geophys.* **15**, 57 (1977); C. Y. Yan and L. W. Kroenke, *Proc. ODP Sci. Results* **130**, 697 (1993).
22. J. P. Morgan, W. J. Morgan, E. Price, *J. Geophys. Res.* **100**, 8045 (1995).
23. U. S. ten Brink, *Geology* **19**, 397 (1991).
24. P. Wessel and L. W. Kroenke, *Nature* **387**, 365 (1997).
25. R. D. Müller, W. R. Roest, J. Y. Royer, L. M. Gahagan, J. G. Sclater, *J. Geophys. Res.* **102**, 3211 (1997).
26. Robust regression of the envelope in Fig. 3 gives $VGG/\Delta t = 61.8 + 10.5\sqrt{Z}$. This is inverted to yield the empirical relation

$$\text{pseudo age} = \text{seafloor age} - \left[\frac{VGG/\Delta t - 61.8}{10.5}\right]^2 \quad (2)$$

27. The flexural modeling also allowed numerical estimation of most volumes.
28. R. Sleziak, *Earth Planet. Sci. Lett.* **60**, 195 (1982).
29. W. H. F. Smith, thesis, Columbia University (1988).
30. The Ontong Java plateau was emplaced during two distinct episodes at ~121 Ma and ~89 Ma [D. Gevorkovici and J. Mahoney, *Science* **266**, 1357 (1994)]; the Manihiki plateau also formed at ~123 Ma, whereas the Hess rise (90 to 100 Ma) and the Mid-Pacific Mountains (75 to 130 Ma) have longer ranges of ages. The oldest plateau is Shatsky rise (135 to 145 Ma) [R. Larson and P. Olson, *Earth Planet. Sci. Lett.* **107**, 437 (1991)].
31. I thank W. Smith for providing the WGG grid. Supported by NSF grant EAR-9303402, School of Ocean and Earth Science and Technology, University of Hawaii, contribution no. 4517.

17 April 1997; accepted 13 June 1997

Identification of the Tuberous Sclerosis Gene *TSC1* on Chromosome 9q34

Marjon van Slegtenhorst, Ronald de Hoogt, Caroline Hermans, Mark Nellist, Bart Janssen, Senno Verhoef, Dick Lindhout, Ans van den Ouweland, Dicky Halley • Janet Young, Mariwyn Burley, Steve Jeremiah, Karen Woodward, Joseph Nahmias, Margaret Fox, Rosemary Ekong, John Osborne, Jonathan Wolfe, Sue Povey • Russell G. Snell, Jeremy P. Cheadle, Alistair C. Jones, Maria Tachataki, David Ravine, Julian R. Sampson • Mary Pat Reeve, Paul Richardson, Friederike Wilmer, Cheryl Munro, Trevor L. Hawkins • Tiina Sepp, Johari B. M. Ali, Susannah Ward, Andrew J. Green, John R. W. Yates • Jolanta Kwiatkowska, Elizabeth P. Henske, M. Priscilla Short, Jonathan H. Haines, Sergiusz Jozwiak, David J. Kwiatkowski*

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the widespread development of distinctive tumors termed hamartomas. TSC-determining loci have been mapped to chromosomes 9q34 (*TSC1*) and 16p13 (*TSC2*). The *TSC1* gene was identified from a 900-kilobase region containing at least 30 genes. The 8.6-kilobase *TSC1* transcript is widely expressed and encodes a protein of 130 kilodaltons (hamartin) that has homology to a putative yeast protein of unknown function. Thirty-two distinct mutations were identified in *TSC1*, 30 of which were truncating, and a single mutation (2105delAAAG) was seen in six apparently unrelated patients. In one of these six, a somatic mutation in the wild-type allele was found in a TSC-associated renal carcinoma, which suggests that hamartin acts as a tumor suppressor.

TSC is a systemic disorder in which hamartomas occur in multiple organ systems, particularly the brain, skin, heart, lungs, and kidneys (*1*, *2*). In addition to its distinct clinical presentation, two features serve to distinguish TSC from other familial tumor syndromes. First, the tumors that occur in TSC are very rare in the general population, such that several TSC lesions are, by themselves, diagnostic of TSC. Second, TSC hamartomas rarely progress to malignancy. Only renal cell carcinoma occurs at increased frequency in TSC (~2.5%) and with earlier age of onset; it appears to arise in TSC renal hamartomas, termed angiomyolipomas (*3*). Nonetheless, TSC can be a devastating condition, as the cortical tubers (brain hamartomas) frequently cause epilepsy, mental retardation, autism, or attention deficit–hyperactive disorder, or a combination of these conditions (*1*, *4*).

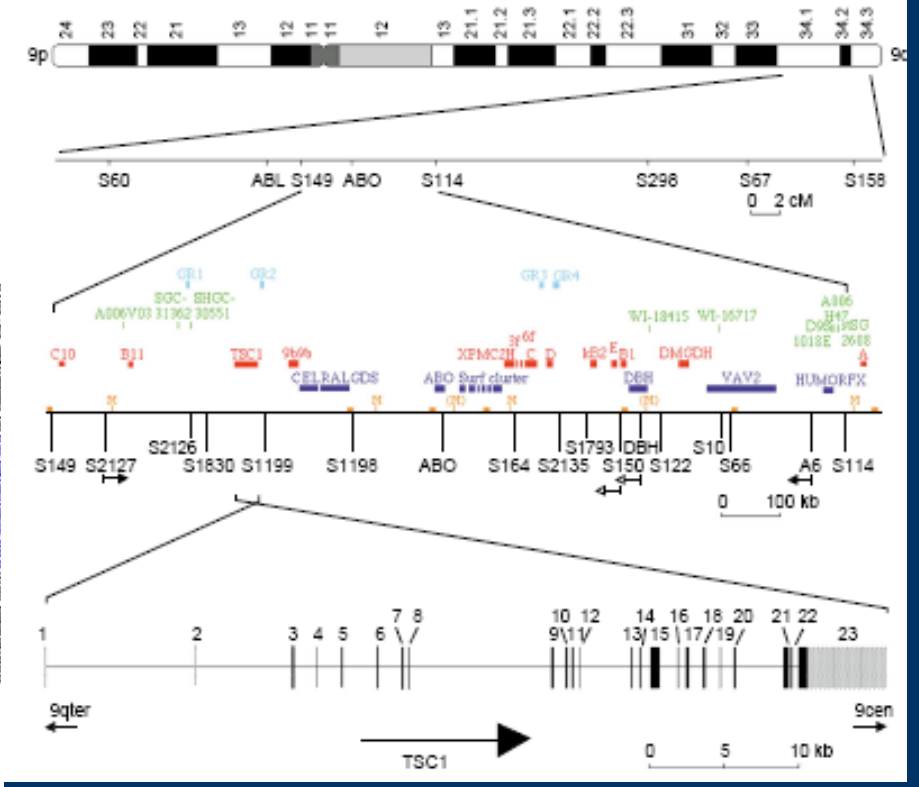
TSC affects about 1 in 6000 individuals, and ~65% of cases are sporadic (*5*). Linkage of TSC to chromosome 9q34 was first reported in 1987, and this locus was denoted *TSC1* (*6*). Later studies provided strong evidence for locus heterogeneity (*7*) and led to the identification of chromosome 16p13 as the site of a second TSC locus (denoted *TSC2*) (*8*). The *TSC2* gene was identified by positional cloning, and the encoded protein, denoted tuberin, contains a domain near the COOH-terminus with homology to a guanosine triphosphatase (GTPase) activating protein (GAP) for rap1, a Ras-related GTPase (*9*).

The focal nature of TSC-associated hamartomas has suggested that *TSC1* and *TSC2* may function as tumor suppressor genes. The occurrence of inactivating germline mutations of TSC2 in patients with tuberous sclerosis (*9–11*) and of loss of heterozygosity (LOH) at the *TSC2* locus in about 50% of TSC-associated hamartomas (*12–14*) supports a tumor suppressor function for *TSC2*. In contrast, LOH at the *TSC1* locus has been detected in <10% of TSC-associated hamartomas (*13*, *14*), suggesting the possibility of an alternative pathogenic mechanism for lesion development in patients with *TSC1* disease.

As part of a comprehensive strategy to identify *TSC1*, we identified 11 microsatellite markers from the 1.4-Mb *TSC1* region and developed an overlapping contig (with only a single gap of 20 kb) of cosmid, PI

The *TSC1* Consortium:
M. van Slegtenhorst, R. de Hoogt, C. Hermans, M. Nellist, B. Janssen, S. Verhoef, D. Lindhout, A. van den Ouweland, D. Halley, Department of Clinical Genetics, Erasmus University and University Hospital, Rotterdam, Netherlands.
J. Young, M. Burley, S. Jeremiah, K. Woodward, J. Nahmias, M. Fox, R. Ekong, J. Wolfe, S. Povey, MRC Human Biochemical Genetics Unit and Galton Laboratory, University College of London, London NW1 2HE, UK.
J. Osborne, University of Bath, Bath BA2 7AY, UK.
R. G. Snell, J. P. Cheadle, A. C. Jones, M. Tachataki, D. Ravine, J. R. Sampson, Institute of Medical Genetics, University of Wales College of Medicine, Cardiff CF4 4XN, Wales, UK.
M. P. Reeve, P. Richardson, F. Wilmer, C. Munro, T. L. Hawkins, Whitehead Institute, MIT Center for Genome Research, Cambridge, MA 02139, USA.
T. Sepp, J. B. M. Ali, S. Ward, A. J. Green, J. R. W. Yates, Department of Pathology and Medical Genetics, University of Cambridge, Addenbrooke's NHS Trust, Cambridge CB2 2QQ, UK.
M. P. Short, Department of Child Neurology, University of Chicago School of Medicine, Chicago, IL 60637, USA.
J. H. Haines, Molecular Neurogenetics Unit, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA.
S. Jozwiak, Division of Child Neurology, Children's Health Center, 04-736 Warsaw, Poland.
J. Kwiatkowska, E. P. Henske, D. J. Kwiatkowski, Division of Experimental Medicine and Medical Oncology, Brigham and Women's Hospital, Boston, MA 02115, USA.

*To whom correspondence should be addressed. E-mail: kwiatkowski@calvin.bwh.harvard.edu



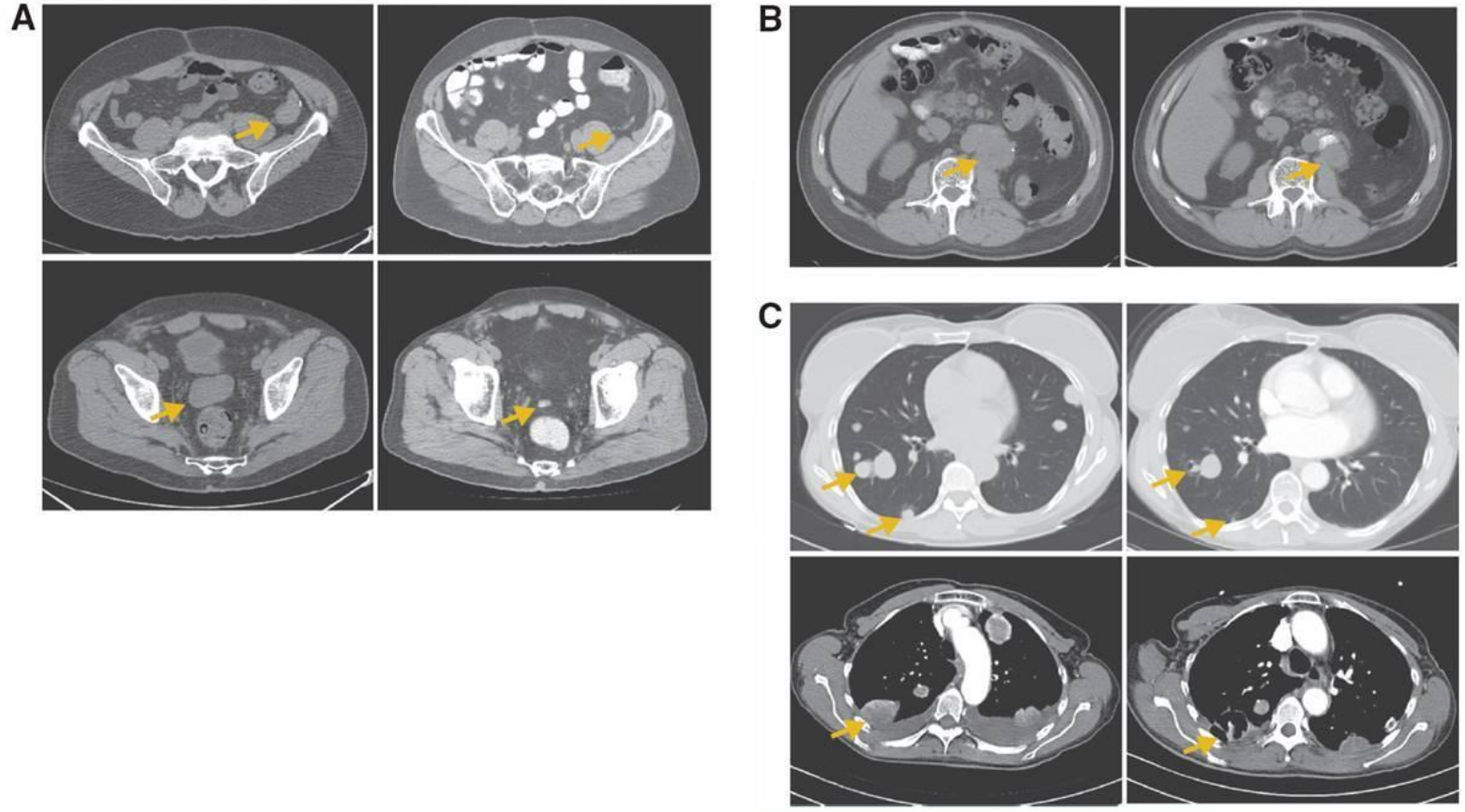
VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

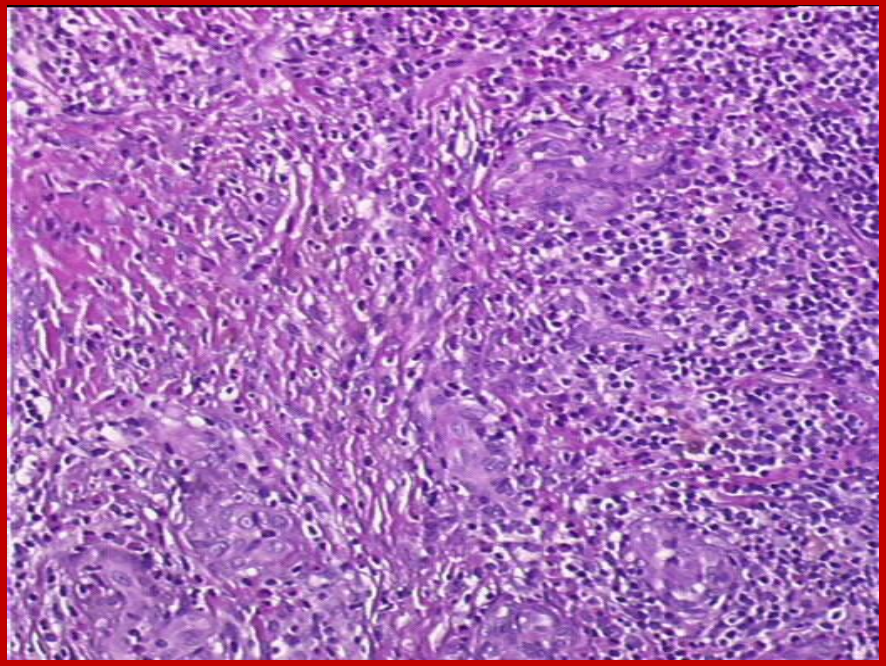
ORIGINAL REPORT

Clinical Activity of mTOR Inhibition With Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors

Andrew J. Wagner, Izabela Malinowska-Kolodziej, Jeffrey A. Morgan, Wei Qin, Christopher D.M. Fletcher, Natalie Vena, Azra H. Ligon, Cristina R. Antonescu, Nikhil H. Ramaiya, George D. Demetri, David J. Kwiatkowski, and Robert G. Maki



Angiosarcoma



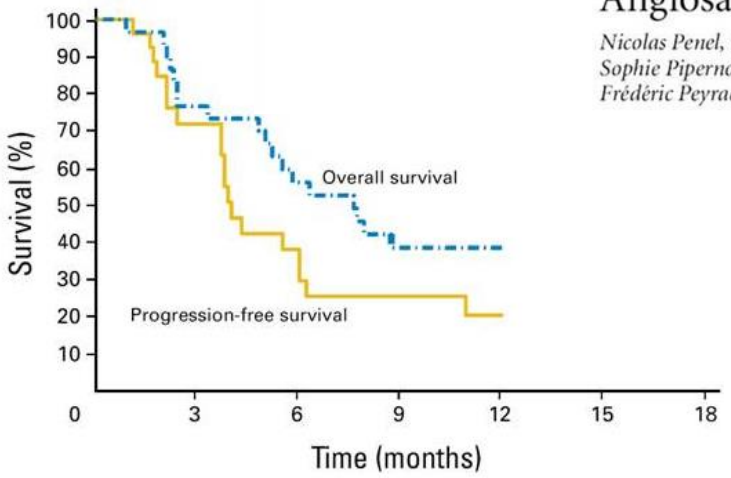
VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study

Nicolas Penel, Binh Nguyen Bui, Jacques-Olivier Bay, Didier Cupissol, Isabelle Ray-Coquard, Sophie Piperno-Neumann, Pierre Kerbrat, Charles Fournier, Sophie Taieb, Marta Jimenez, Nicolas Isambert, Frédéric Peyrade, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay



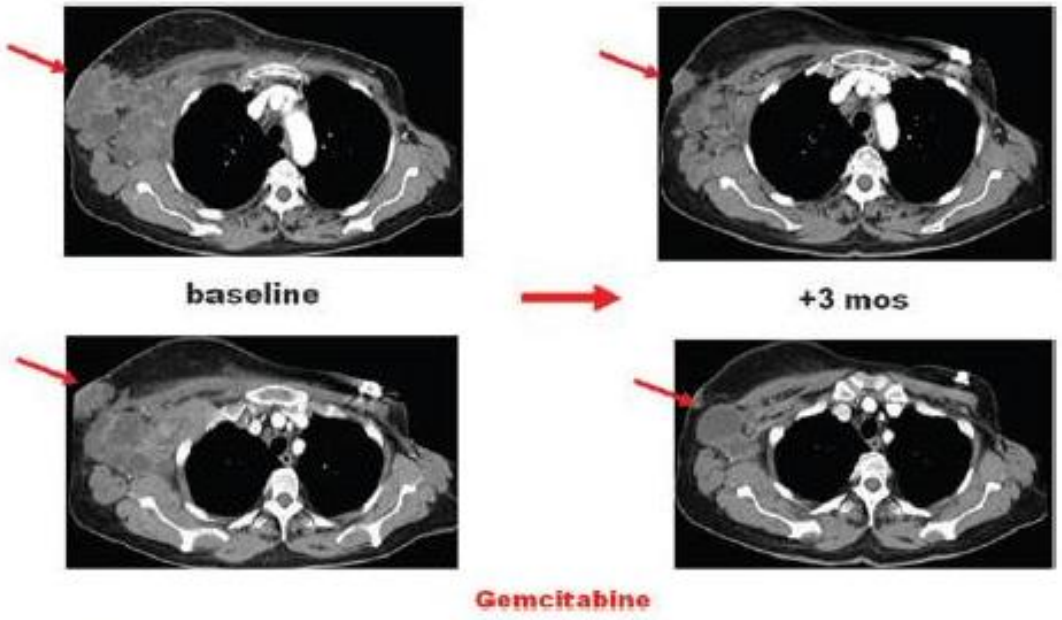
Patient	Baseline Disease Characteristics	Clinical and Histologic Response	Outcome
11	Relapsed multinodular radiation-induced angiosarcoma	Partial response after 6 cycles Mastectomy Complete histologic response	Disease-free survival, 19 months after inclusion
13	Primary multinodular angiosarcoma with rapid evolution	Partial response after 4 cycles Mastectomy Complete histologic response	Disease-free survival, 17 months after inclusion
17	Multinodular radiation-induced angiosarcoma with skin ulceration and rapid progression	Stable disease after 5 cycles Mastectomy Complete histologic response in 2 nodules but persistent disease in third nodule (10 mm, grade 3)	Diagnosis of glioblastoma at 8 months, death at 9 months

original article

Annals of Oncology
doi:10.1093/annonc/mdr066

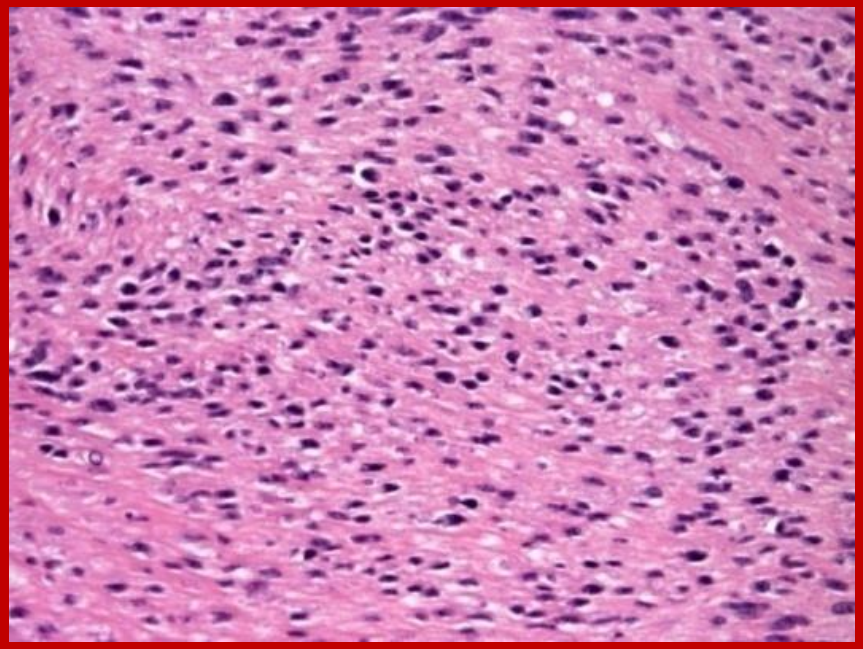
Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network

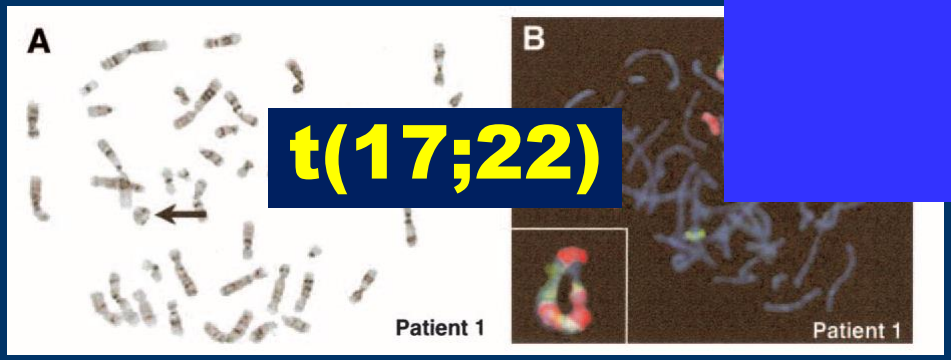
S. Stacchiotti[1], E. Palassini[1], R. Sanfilippo[1], B. Vincenzi[2], M. G. Arena[3], A. M. Bochicchio[4], P. De Rosa[5], A. Nuzzo[6], S. Turano[7], C. Morosi[8], A. P. Dei Tos[9], S. Pilotti[9] & P. G. Casali[10]



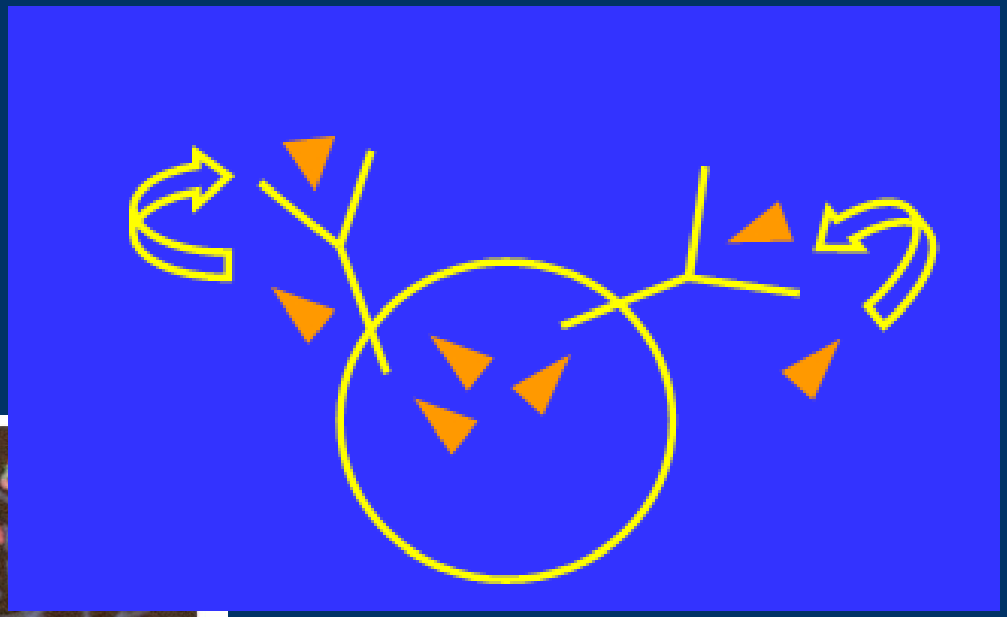
Ann Oncol 2012;23:501

Dermatofibrosarcoma





t(17;22)



COL1A1-PDGFB → PDGFB

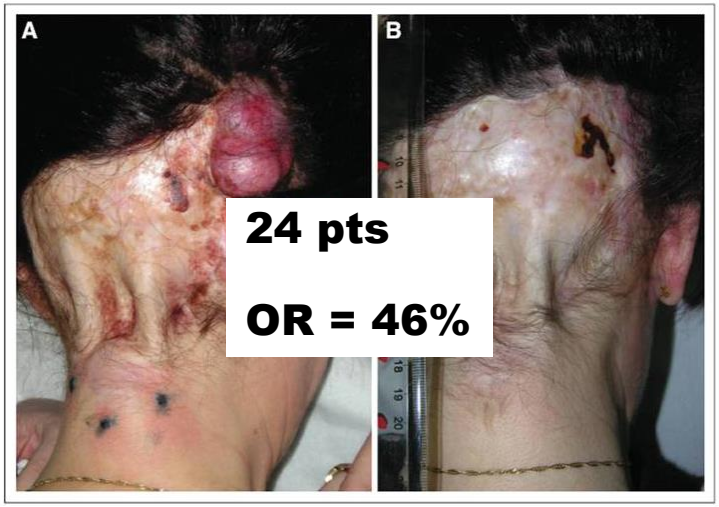
VOLUME 28 · NUMBER 10 · APRIL 1 2010

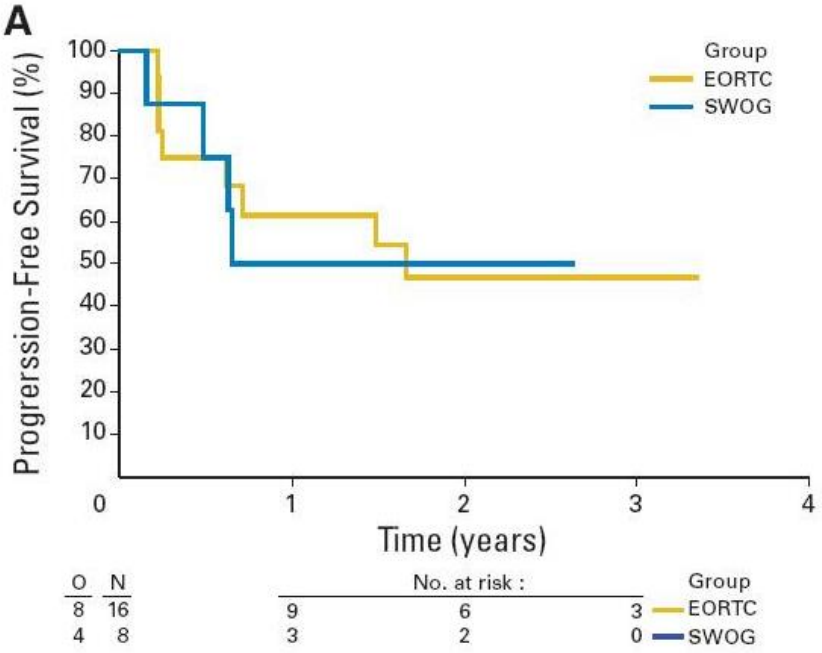
JOURNAL OF CLINICAL ONCOLOGY

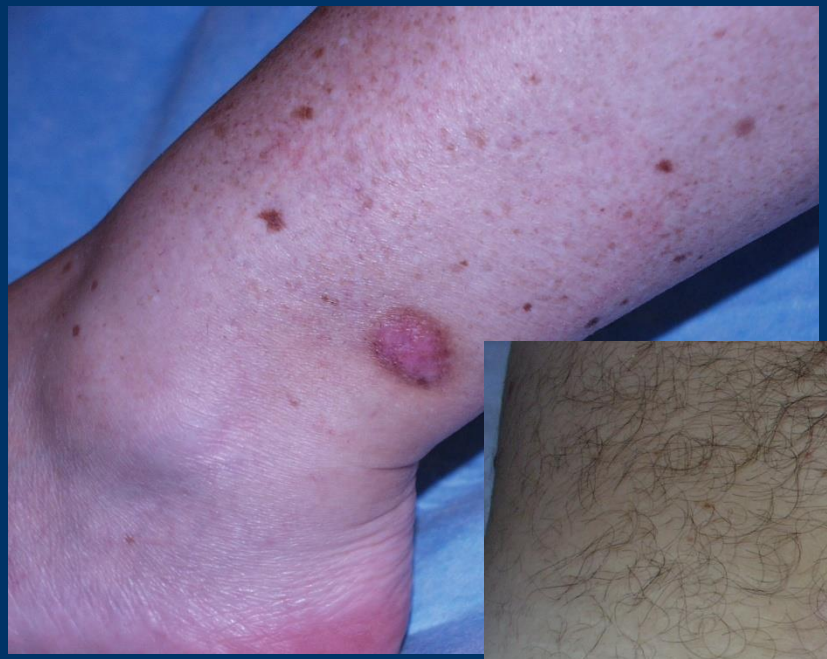
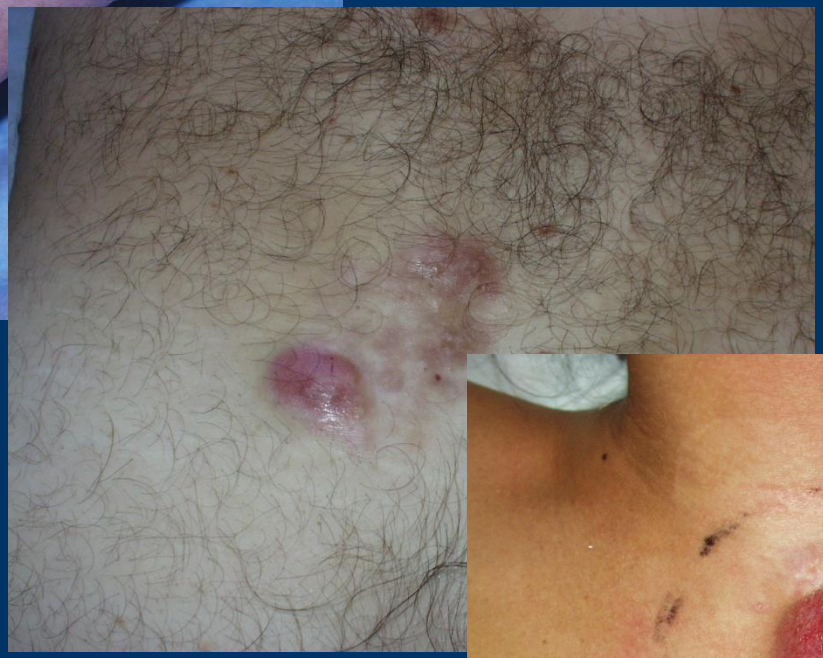
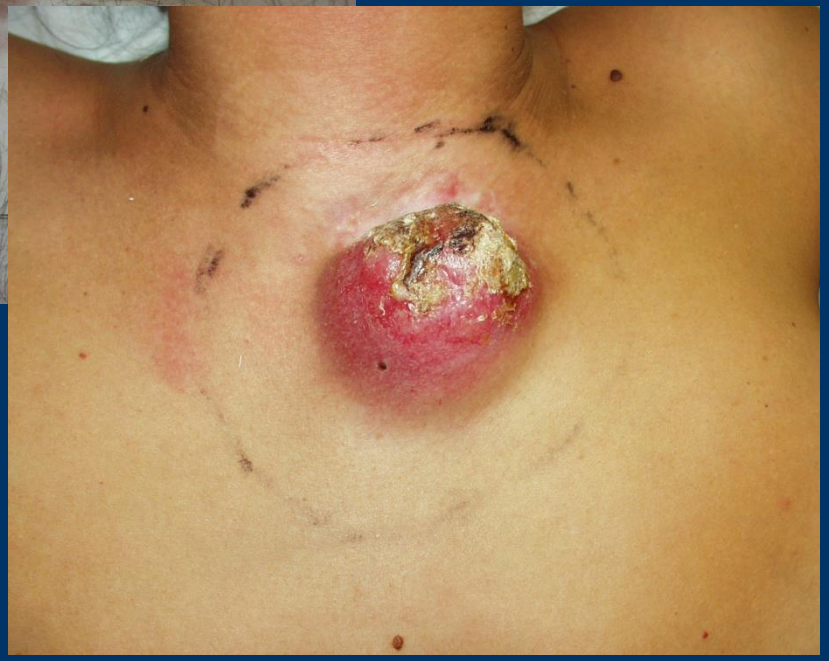
ORIGINAL REPORT

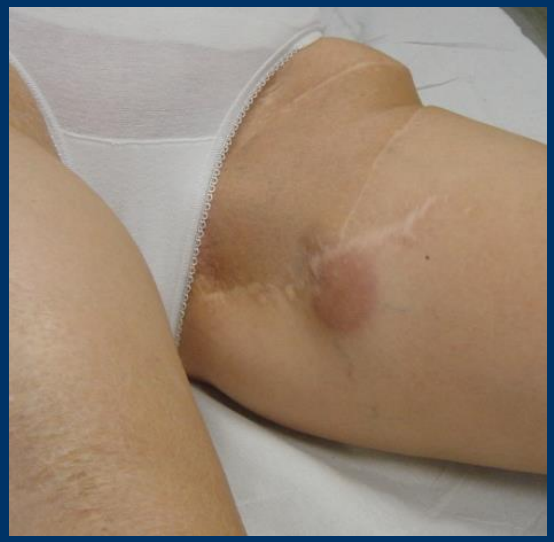
Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

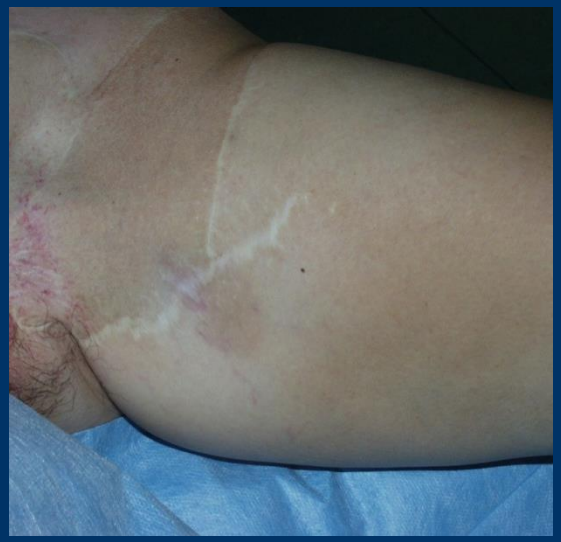
Piotr Rutkowski, Martine Van Glabbeke, Cathryn J. Rankin, Wlodzimierz Ruka, Brian P. Rubin, Maria Debiec-Rychter, Alexander Lazar, Hans Gelderblom, Raf Sciot, Dolores Lopez-Terrada, Peter Hohenberger, Allan T. van Oosterom, and Scott M. Schuetze



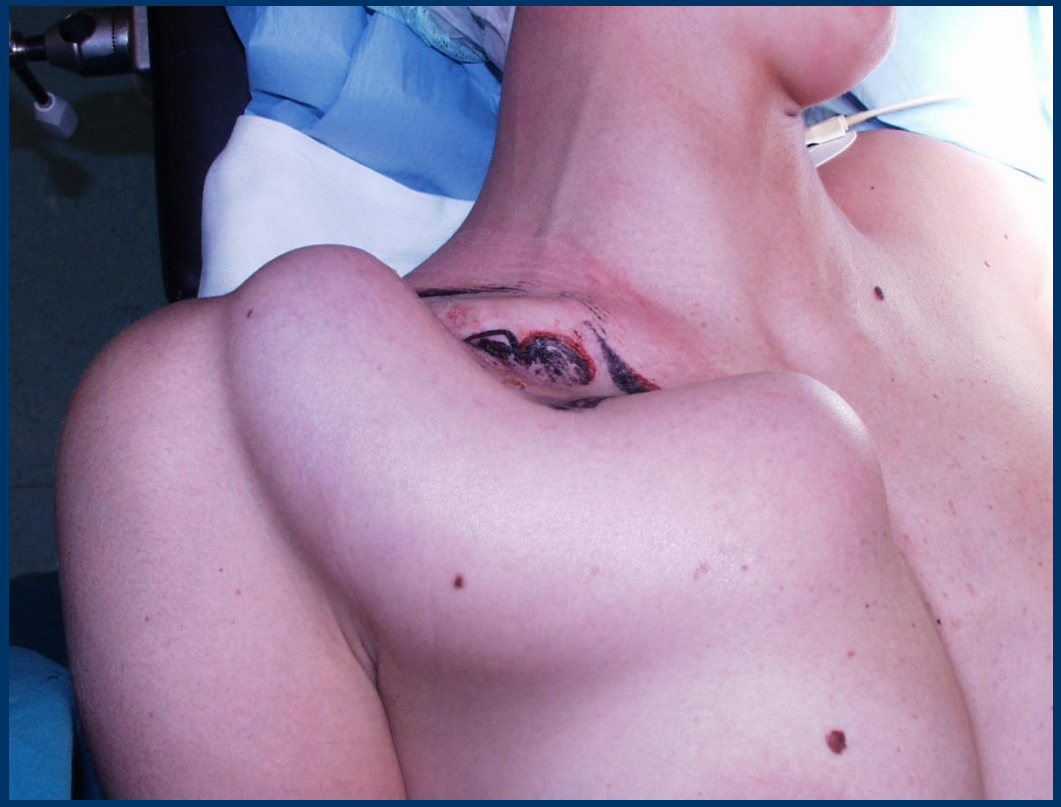


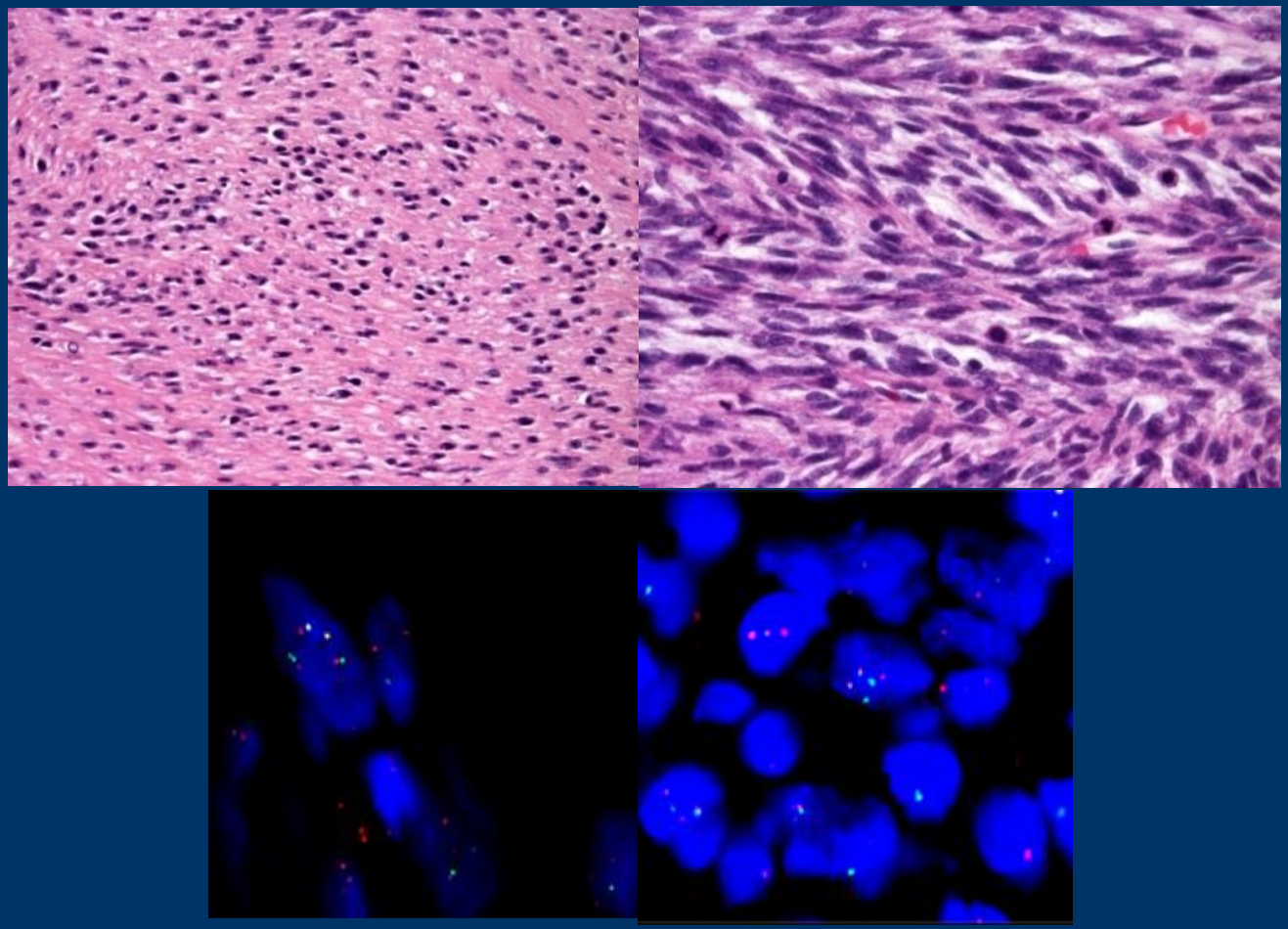




IM 400 mg/d x 8 mos



FS-DFSP



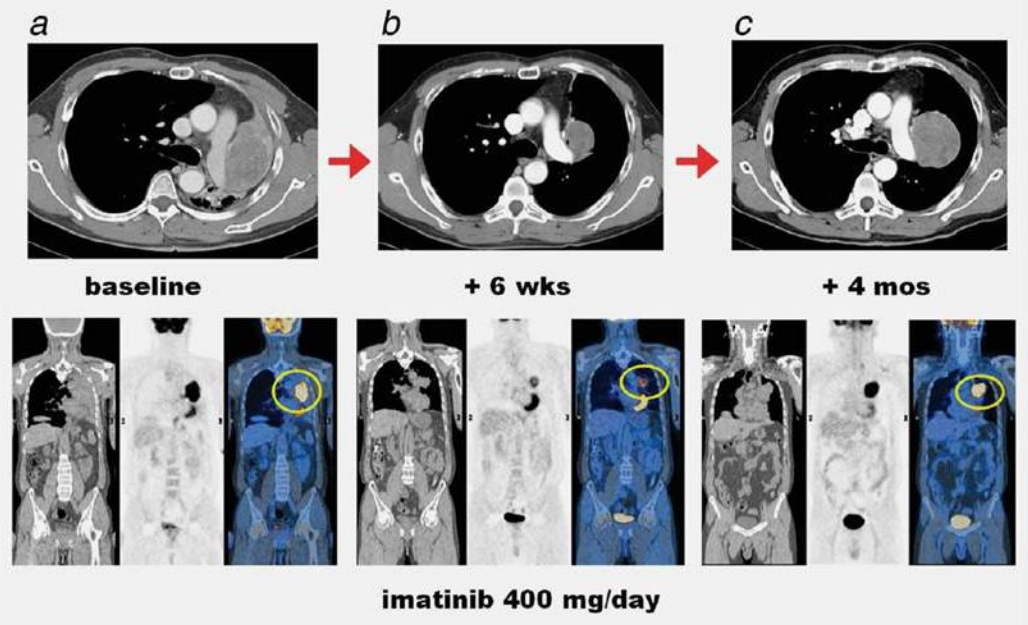
uicc
global cancer control

IJC
International Journal of Cancer

Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib

Silvia Stacchiotti[1], Florence Pedeutour[2], Tiziana Negri[3], Elena Conca[3], Andrea Marrari[1], Elena Palassini[1], Paola Collini[3], Frederique Keslair[2], Carlo Morosi[4], Alessandro Gronchi[5], Silvana Pilotti[2] and Paolo G. Casali[1]

[1] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[2] Laboratory of Solid Tumors Genetics, University of Nice-Sophia-Antipolis, CNRS UMR 6543, Nice University Hospital, Faculty of Medicine, Nice, France
[3] Anatomic Pathology Unit 2, Department of Diagnostic Pathology and Laboratory, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[4] Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[5] Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy



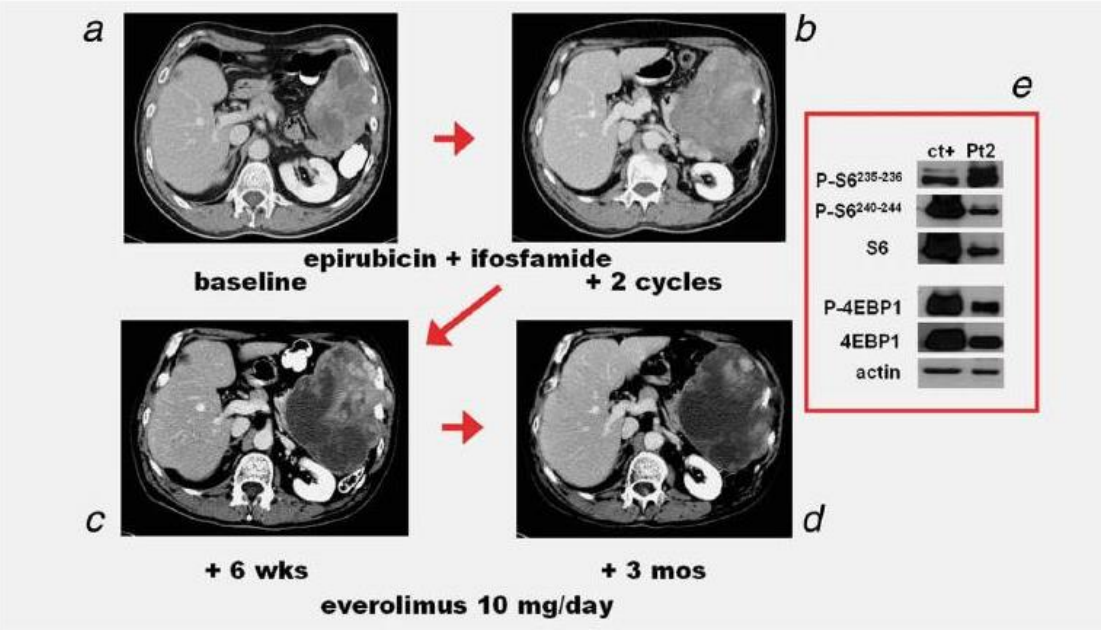
uicc
global cancer control

IJC
International Journal of Cancer

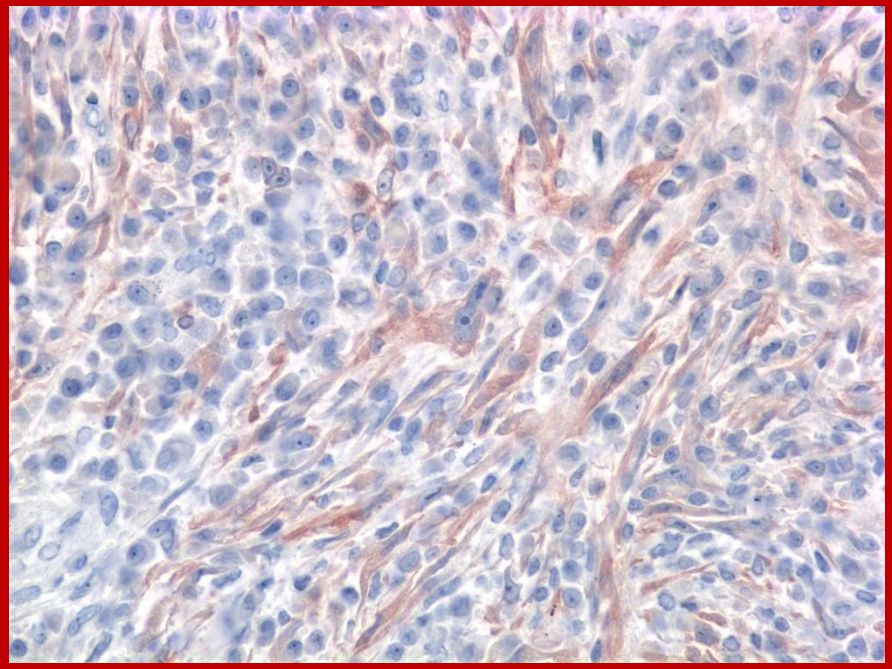
Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib

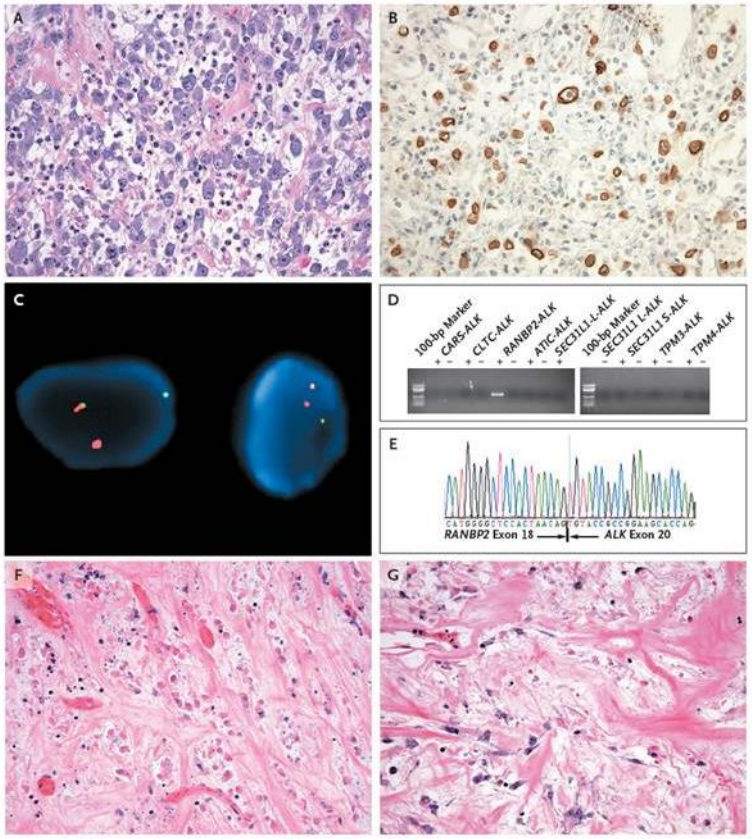
Silvia Stacchiotti[1], Florence Pedeutour[2], Tiziana Negri[3], Elena Conca[3], Andrea Marrari[1], Elena Palassini[1], Paola Collini[3], Frederique Keslair[2], Carlo Morosi[4], Alessandro Gronchi[5], Silvana Pilotti[2] and Paolo G. Casali[1]

[1] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[2] Laboratory of Solid Tumors Genetics, University of Nice-Sophia-Antipolis, CNRS UMR 6543, Nice University Hospital, Faculty of Medicine, Nice, France
[3] Anatomic Pathology Unit 2, Department of Diagnostic Pathology and Laboratory, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[4] Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[5] Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy



Myofibroblastic inflammatory t.



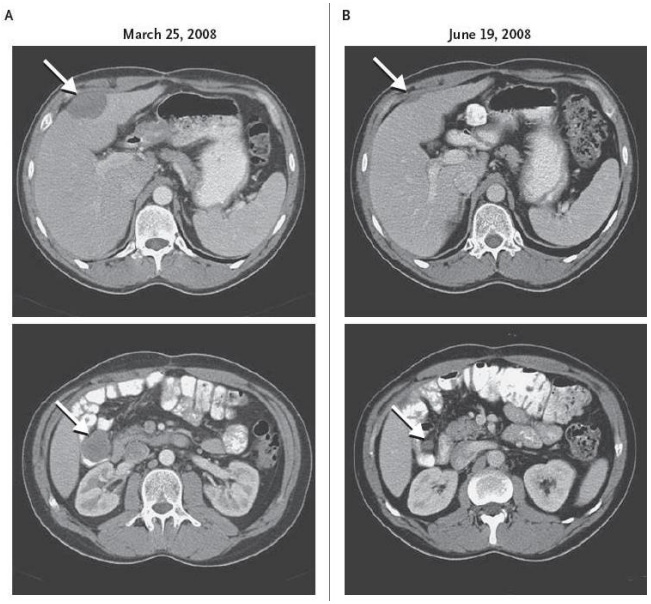


N Engl J Med 2010;363:1727-33.

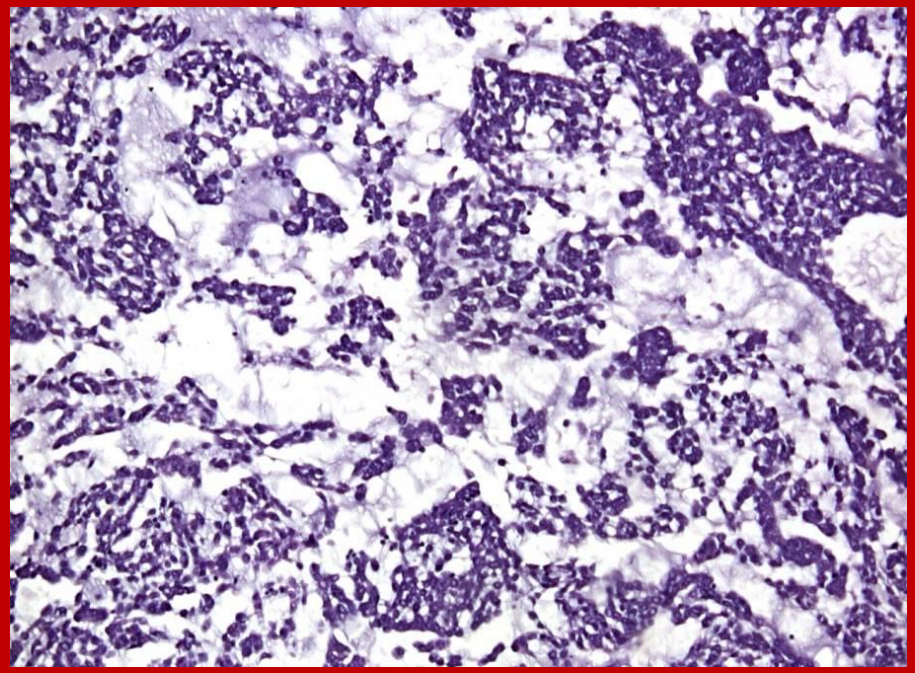
BRIEF REPORT

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

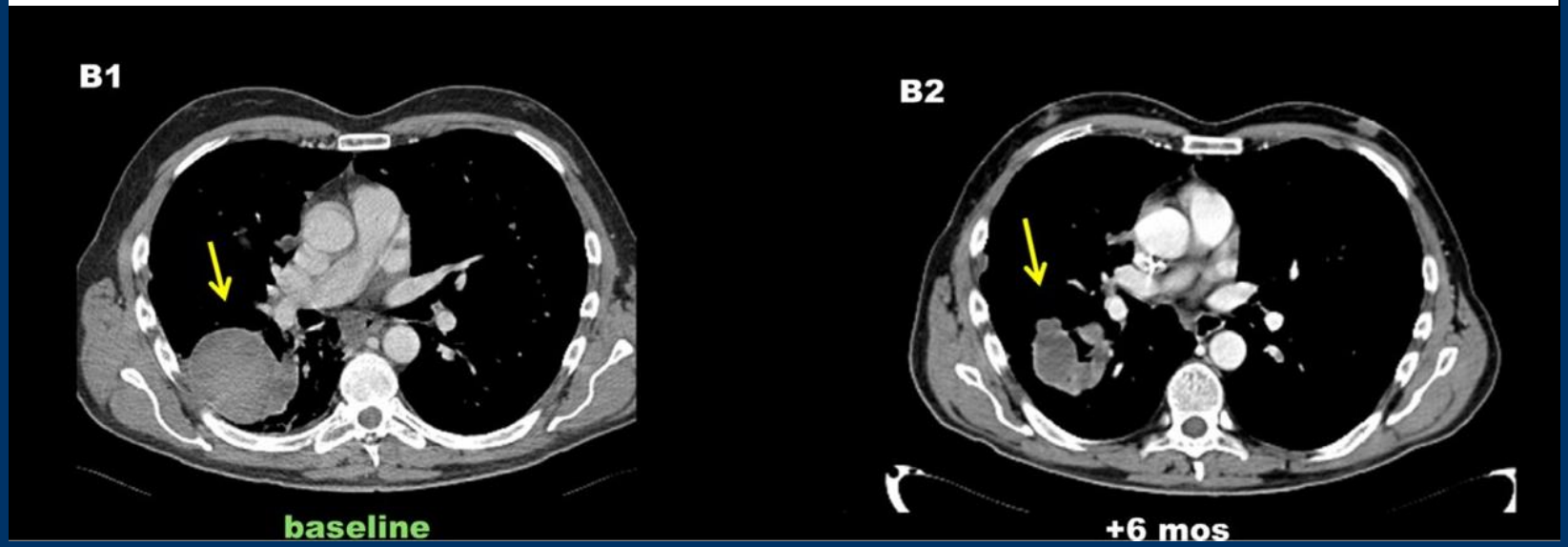


Extraskeletal myxoid chondrosa



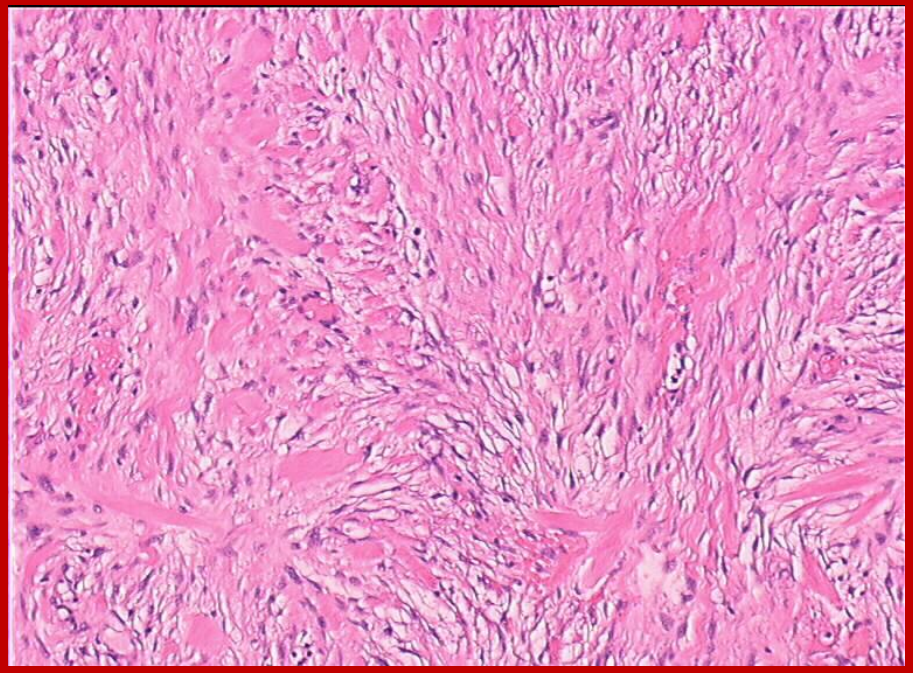
Activity of sunitinib in extraskeletal myxoid chondrosarcoma ☆

S. Stacchiotti [a,*], M.A. Pantaleo [b,1], A. Astolfi [c], G.P. Dagrada [d], T. Negri [d], A.P. Dei Tos [e], V. Indio [c], C. Morosi [f], A. Gronchi [g], C. Colombo [g], E. Conca [d], L. Toffolatti [e], M. Tazzari [h], F. Crippa [i], R. Maestro [j,1], S. Pilotti [d,1], P.G. Casali [a,1]



Eur J Cancer 2014

Desmoid tumors (AF)



Orthopaedics & Traumatology: Surgery & Research (2010) 96, 884–889

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

Primary or recurring extra-abdominal desmoid fibromatosis: Assessment of treatment by observation only

O. Barbier[a,*], P. Anract[a], E. Pluot[b], F. Larouserie[c], F. Sailhan[a], A. Babinet[a], B. Tomeno[a]

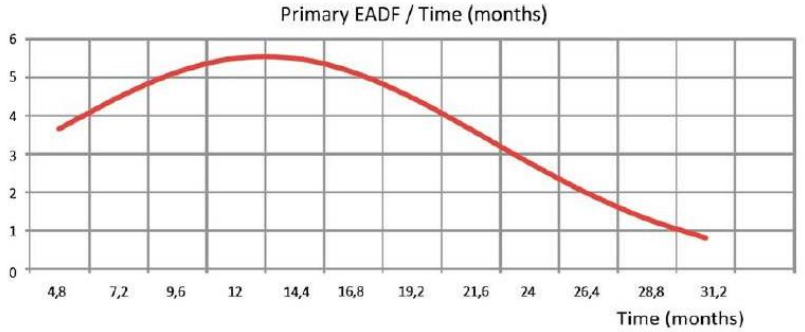


Figure 4 Normal curve of the length of evolution of primary extra-abdominal desmoid fibromatosis managed by surveillance.

Figure 5 Normal curve of the length of evolution of recurrent extra-abdominal desmoid fibromatosis managed by surveillance.

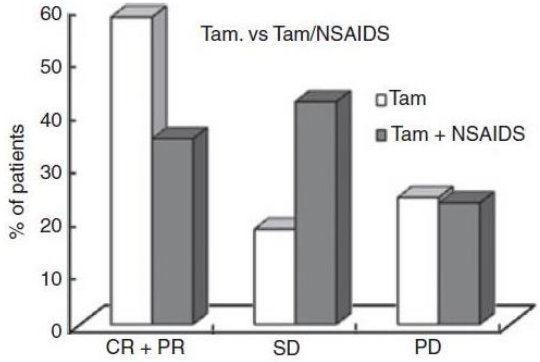
Systematic review

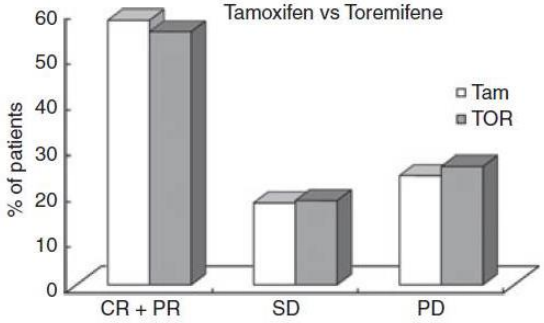
doi:10.1111/j.1463-1318.2011.02758.x

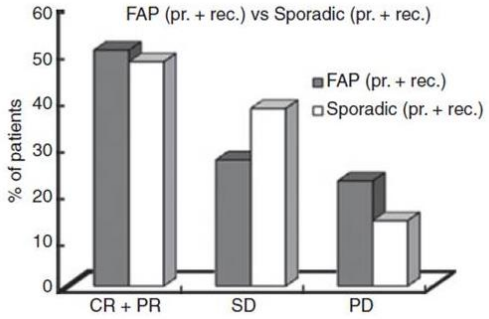
Anti-oestrogen therapy in the treatment of desmoid tumours: a systematic review

D. Bocale*, M. T. Rotelli*, A. Cavallini† and D. F. Altomare*

*Department of Emergency and Organ Transplantation, General Surgery and Liver Transplantation Units, University 'Aldo Moro' of Bari, Bari, Italy and †Laboratory of Biochemistry, Scientific Institute for Digestive Diseases, IRCCS 'Saverio de Bellis', Castellana G., Bari, Italy



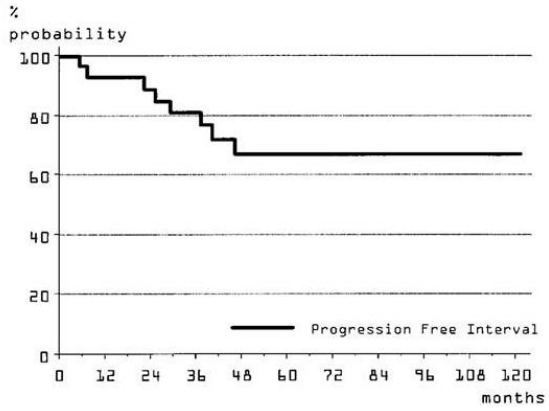


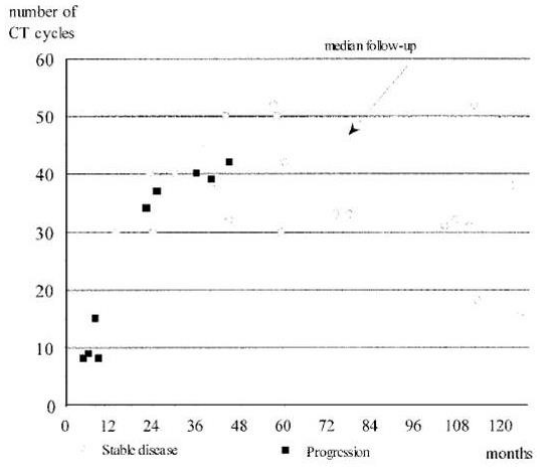


Colorect Dis 2011;13:e388

Low-Dose Chemotherapy with Methotrexate and Vinblastine for Patients with Advanced Aggressive Fibromatosis

Alberto Azzarelli, M.D.[1]
Alessandro Gronchi, M.D.[1]
Rossella Bertulli, M.D.[2]
John D. Tesoro Tess, M.D.[3]
Dario Baratti, M.D.[1]
Elisabetta Pennacchioli, M.D.[1]
Paltia Dileo, M.D.[2]
Alessandro Rasponi, M.D.[1]
Andrea Ferrari, M.D.[5]
Silvana Pilotti, M.D.[4]
Paolo G. Casali, M.D.[2]





Cancer 2001;92:1259

Annals of Oncology 23: 182–186, 2012
doi:10.1093/annonc/mdr051
Published online 28 March 2011

Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG)

D. Garbay[1], A. Le Cesne[2], N. Penel[3], C. Chevreau[4], P. Marec-Berard[5], J.-Y. Blay[6], M. Debled[1], N. Isambert[7], A. Thyss[8], E. Bompas[9], O. Collard[10], S. Salas[11], J.-M. Coindre[12], B. Bui[1] & A. Italiano[1*]

Protocol	Drugs
Mesna, adriamycin, ifosfamide, dacarbazine	Doxorubicin 20 mg/m^2 (day 1–day 3) Ifosfamide 2.5 g/m^2 (day 1–day 3) Dacarbazine 300 mg/m^2 (day 1–day 3) 21 days cycle
Adriamycin, dacarbazine	Doxorubicin 20 mg/m^2 (day 1–day 3) Dacarbazine 300 mg/m^2 (day 1–day 3) 21 days cycle
Metronomic etoposide	Oral etoposide 75 mg/day for 21 days of 28 days cycle
Metronomic cyclophospamide	Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle
Doxorubicin	Doxorubicin 60–75 mg/m^2 21 days cycle
Methotrexate–vinblastine	Vinblastine 6 mg/m^2 Methotrexate 30 mg/m^2 (J1, J8, 15, 21) 28 days cycle
Methotrexate	Methotrexate 30 mg/m2 (J1, J8, 15, 21) 28 days cycle
Vinorelbine	Vinorelbine 20 mg/m^2 (J1, J8) 21 days cycle

Targeted therapies

	Study design	Treatment schedule	Patients (n)	Response
Imatinib				
Heinrich et al.	Retrospective	800mg daily	19	3 (16%)
Penel et al.	Phase II	400mg daily	40	4/35 (12%)
Chugh et al.	Phase II	600mg daily (BSA $\geq 1.5m^2$), 400mg daily (BSA 1.0 - $1.5m^2$), or 200mg daily (BSA $<1.0m^2$)	51	3 (6%)
Sorafenib				
Gounder et al.	Retrospective	400mg daily	26	6/24 (25%)
Sunitinib				
Cheol Jo et al.	Phase II	37.5mg daily	19	5 (26%)

Martin-Liberal *et al. Clinical Sarcoma Research* 2013, **3**:13
http://www.clinicalsarcomaresearch.com/content/3/1/13

CLINICAL SARCOMA RESEARCH

CASE REPORT Open Access

Pazopanib is an active treatment in desmoid tumour/aggressive fibromatosis

Juan Martin-Liberal[1*], Charlotte Benson[1], Heather McCarty[2], Khin Thway[1], Christina Messiou[1] and Ian Judson[1]

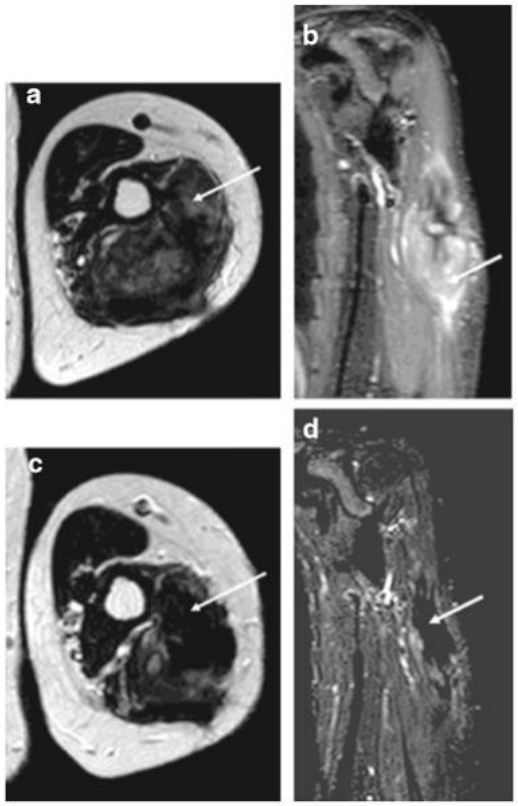


Figure 2 Axial T2 weighted and coronal STIR MRI images of the proximal left arm at baseline (a and b) and following 11 months of pazopanib (c and d). A large focus of fibromatosis expands the triceps muscle and following 11 months of treatment reduced in size from 10.2 cm in maximum craniocaudal dimension to 8.0 cm. Predominantly intermediate/high signal tissue (**a** and **b**, arrows) showed a marked reduction in signal (**c** and **d**, arrows) indicating diminished cellularity.

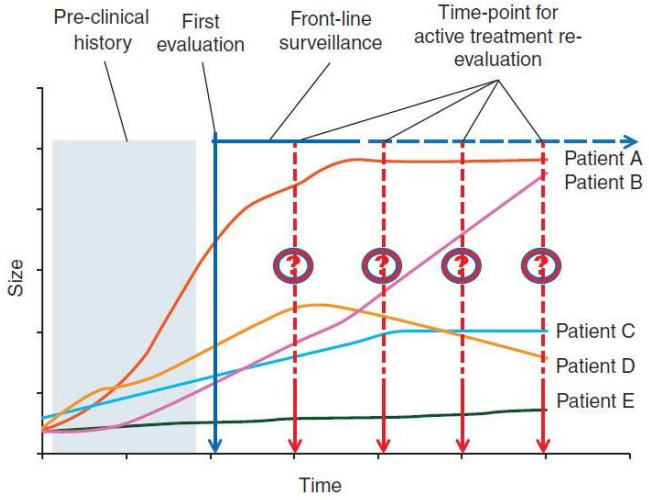
Annals of Oncology Advance Access published December 9, 2013

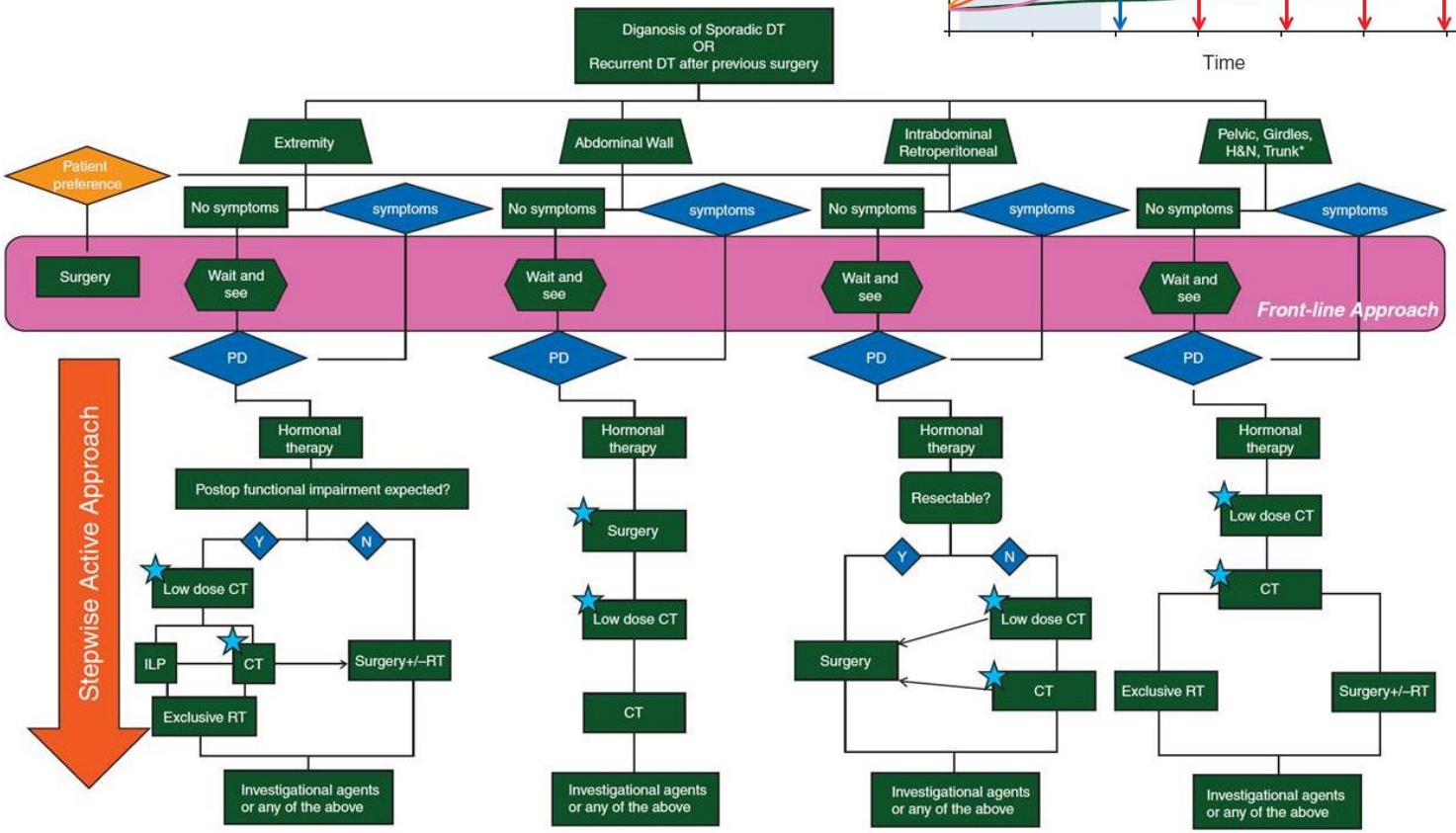
review

Annals of Oncology 00: 1–6, 2013
doi:10.1093/annonc/mdt485

Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm—a position paper from the Italian and the French Sarcoma Group

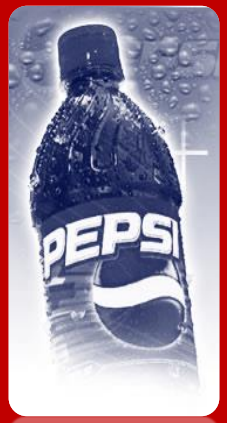
A. Gronchi[1*], C. Colombo[1], C. Le Péchoux[2], A. P. Dei Tos[3], A. Le Cesne[4], A. Marrari[5], N. Penel[6], G. Grignani[7], J. Y. Blay[8], P. G. Casali[5], E. Stoeckle[9], F. Gherlinzoni[10], P. Meeus[11], C. Mussi[12], F. Gouin[13], F. Duffaud[14], M. Fiore[1], S. Bonvalot[15] & on behalf of ISG and FSG





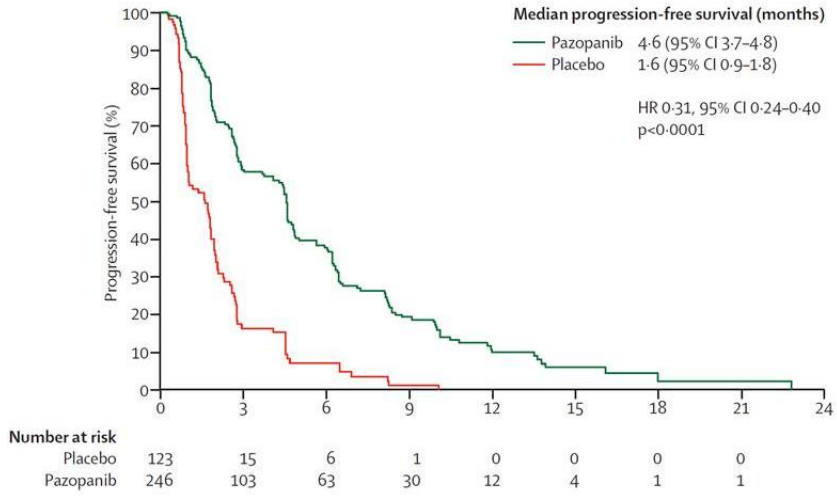
H&N=head and neck *abdominal wall excluded ★ first choice in case of rapid PD

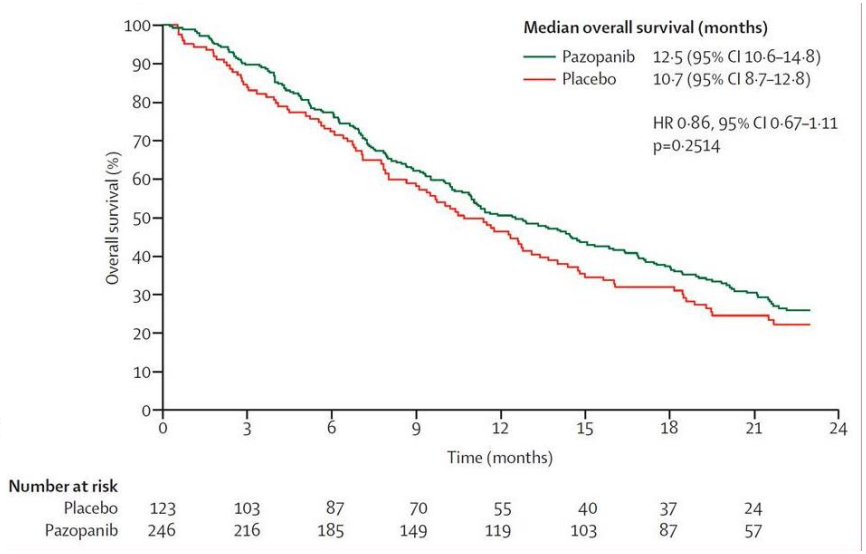
R



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

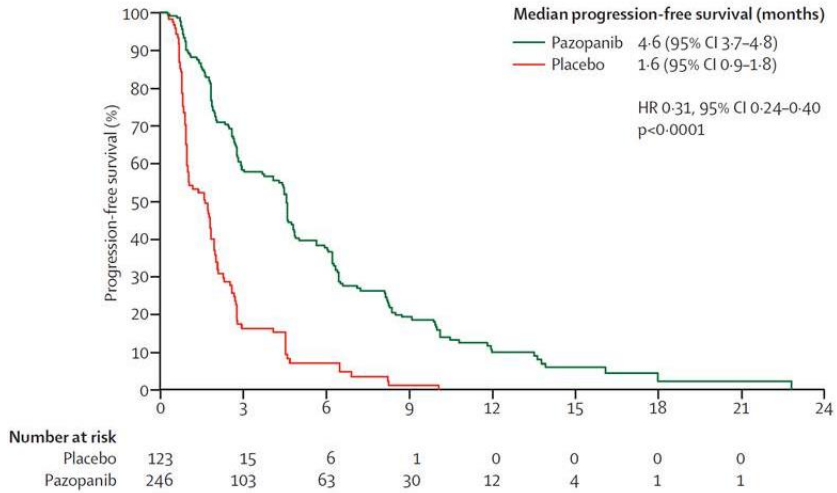


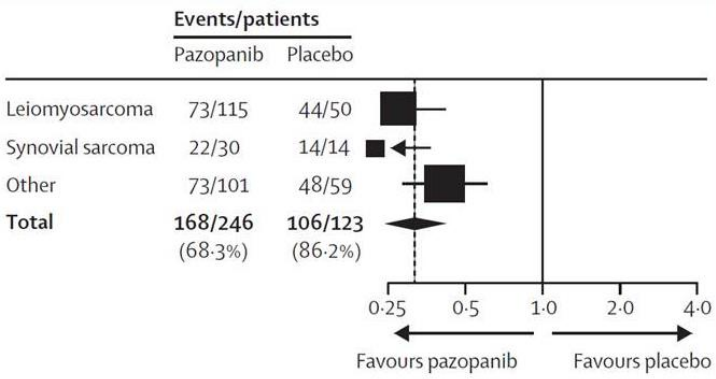


Lancet 2012;379:1879

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

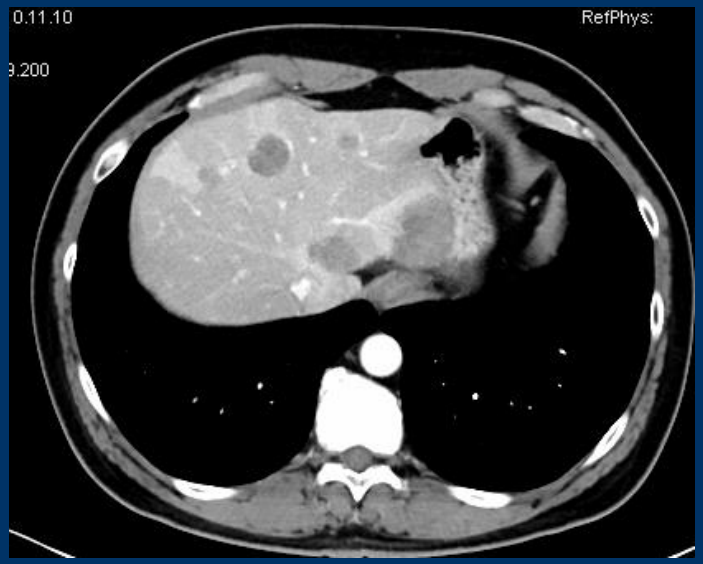
Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel 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

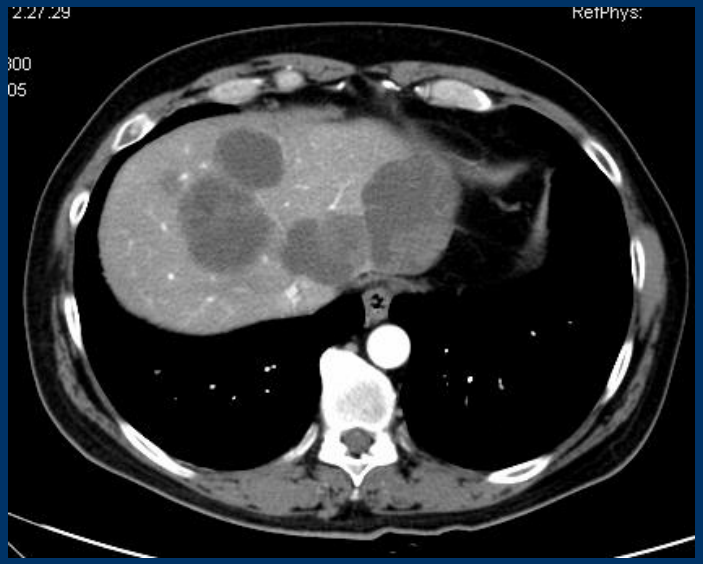




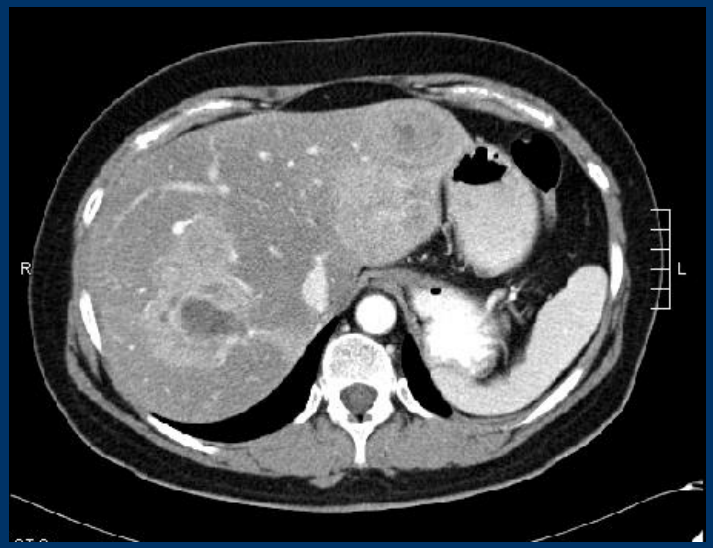
Lancet 2012;379:1879

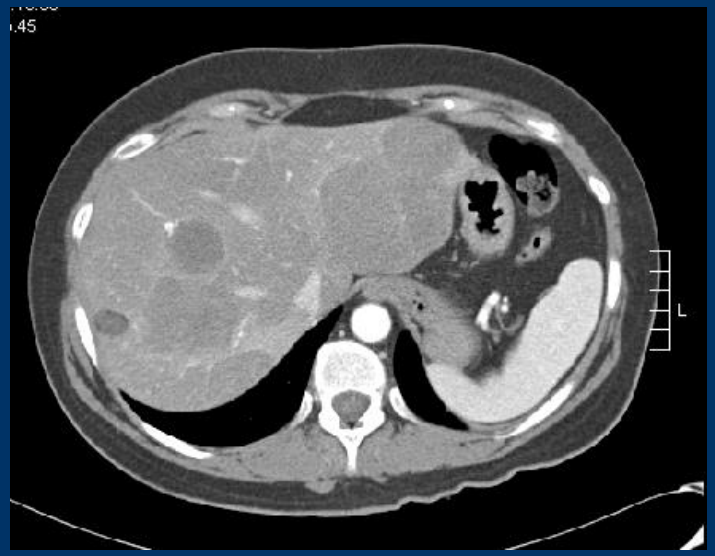
Leiomyosarcoma



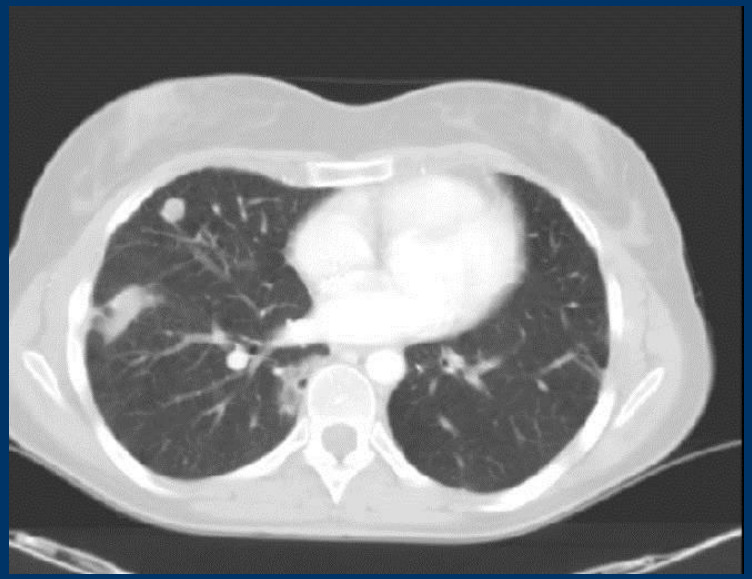


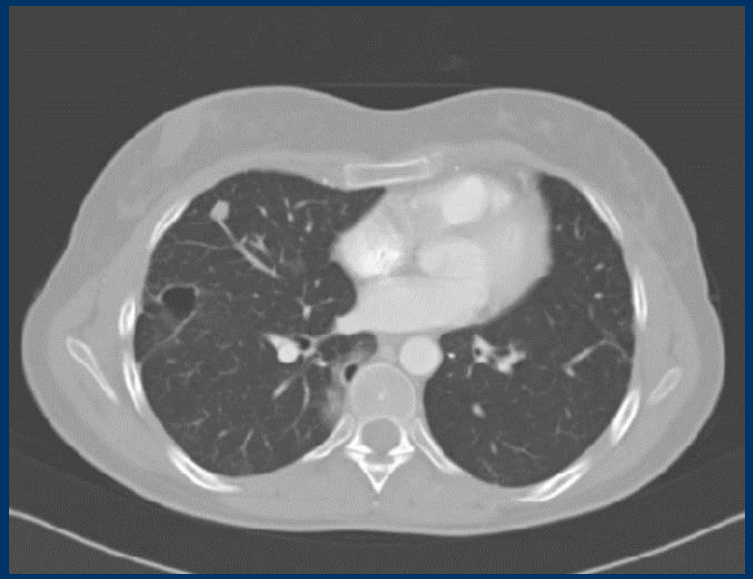
Uterine leiomyosarcoma, 4th line





Synovial sarcoma, 4th line



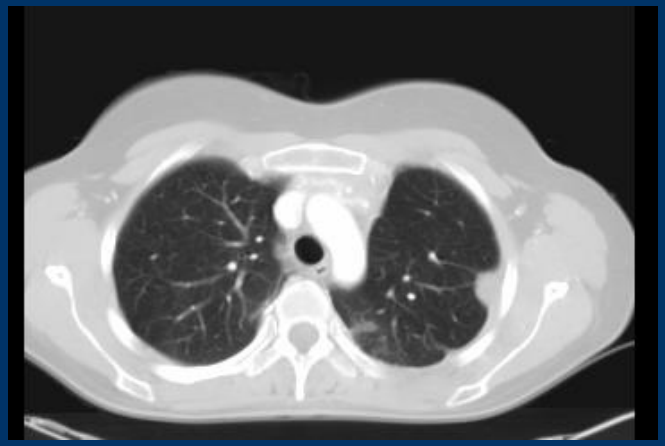


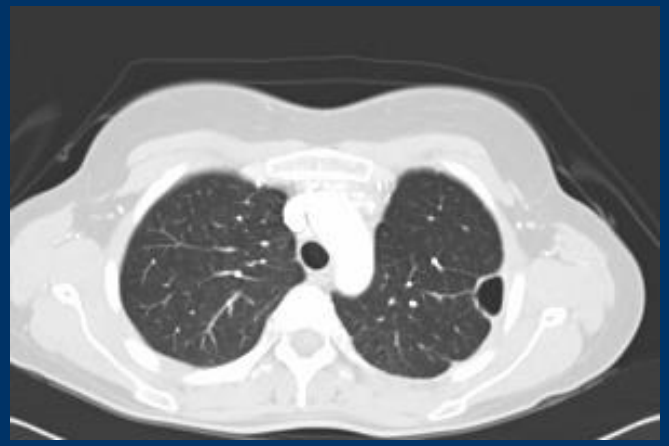
0

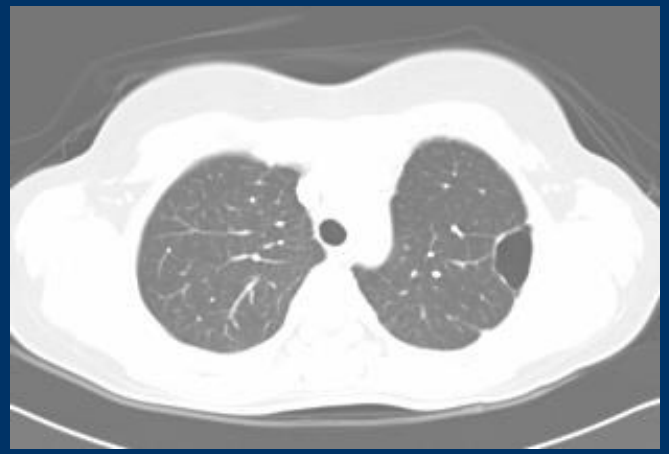
4 wks

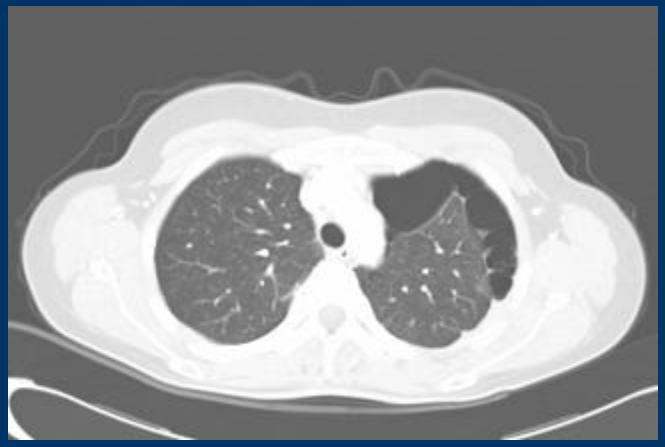
Synovial sarcoma, 4th line

0



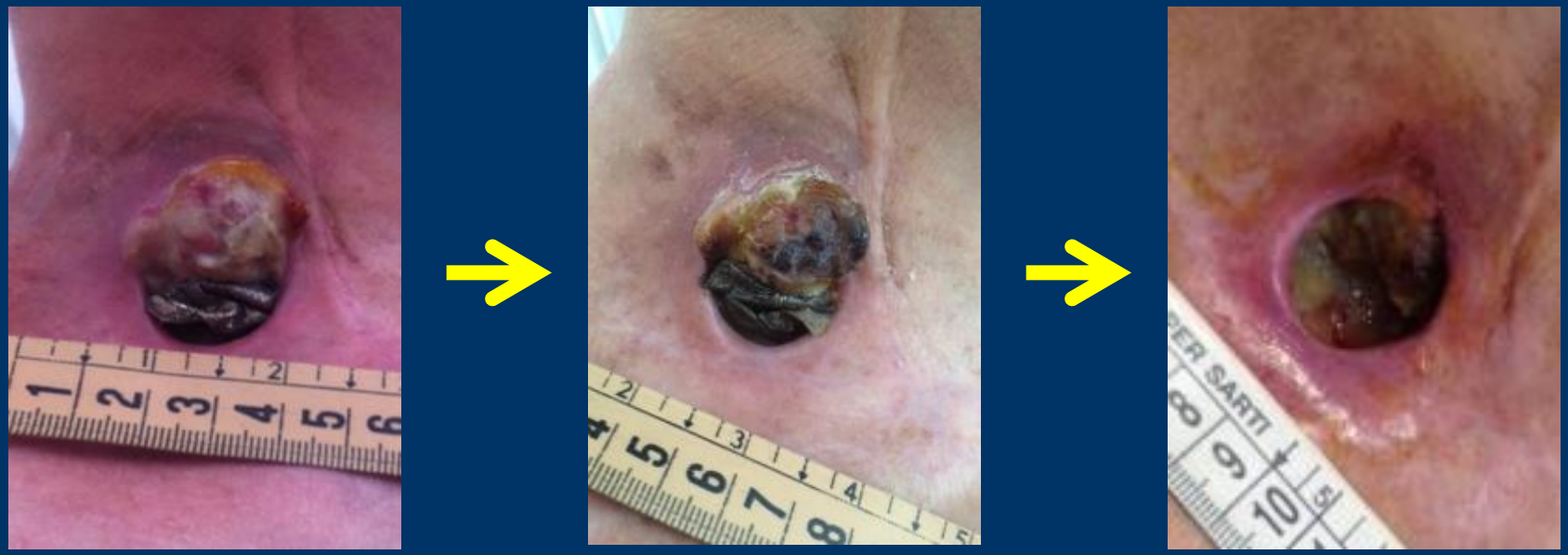






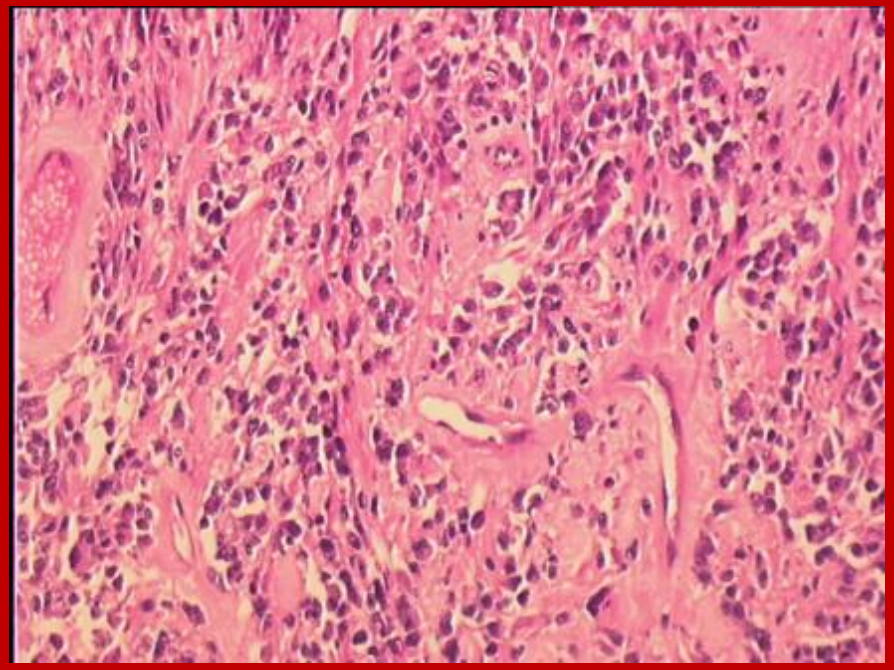
8 mos

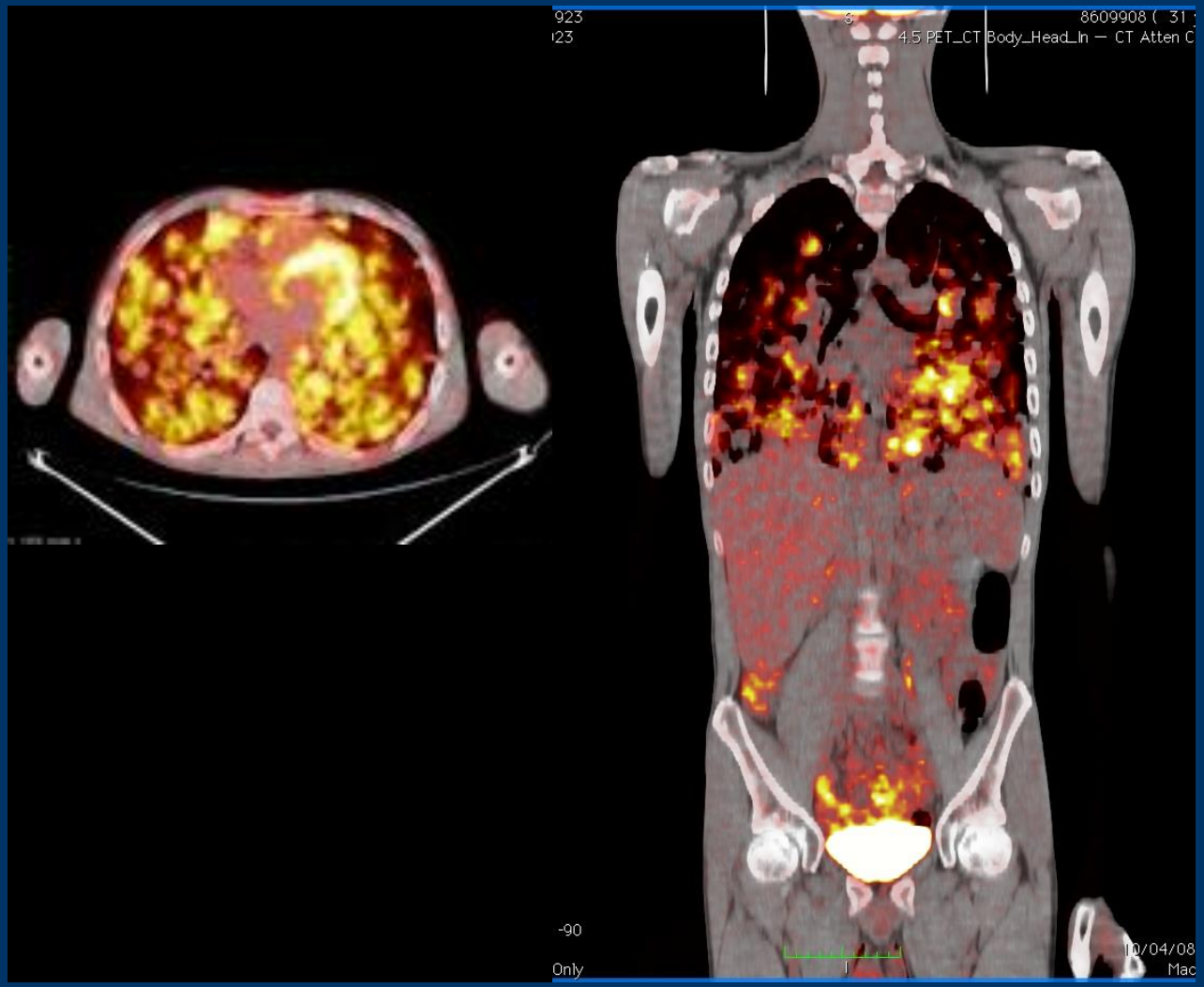
MPNST, RT-induced, 4th line



0 7 d 2 mos

MPNST



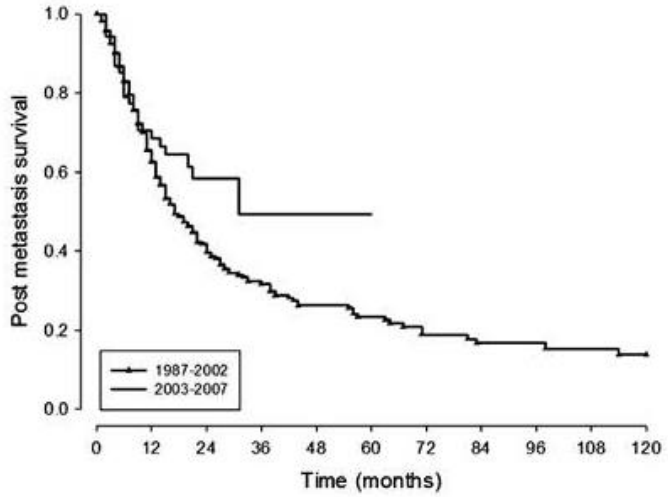

923
123
3
8609908 (31
4.5 PET_CT Body_Head_In — CT Atten C
-90
Only
10/04/08
Mac

original article

Annals of Oncology 22: 1675–1681, 2011
doi:10.1093/annonc/mdq643
Published online 17 January 2011

Primary extremity soft tissue sarcomas: outcome improvement over time at a single institution

A. Gronchi[1*], R. Miceli[2], C. Colombo[1], P. Collini[3], S. Stacchiotti[4], P. Olmi[5], L. Mariani[2], R. Bertulli[4], M. Fiore[1] & P. G. Casali[4]



Gronchi a et al, Ann Oncol 2011;22:1675

The ESMO/European Sarcoma Network Working Group*

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
- Sylvie Bonvalot, France
- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
- Palma Dileo, UK
- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
- Stefano Ferrari, Italy
- Hans Gelderblom, Belgium
- Robert Grimer, UK
- Alessandro Gronchi, Italy
- Rick Haas, Netherlands
- Kirsten Sundby Hall, Norway
- Peter Hohenberger, Germany
- Rolf Issels, Germany
- Heikki Joensuu, Finland
- Ian Judson, UK
- Axel Le Cesne, France
- Saskia Litière, Belgium
- Javier Martin-Broto, Spain
- Ofer Merimsky, Israel
- Michael Montemurro, UK
- Carlo Morosi, Italy
- Piero Picci, Italy
- Isabelle Ray-Coquard, France
- Peter Reichardt, Germany
- Piotr Rutkowski, Poland
- Marcus Schlemmer, Germany
- Silvia Stacchiotti, Italy
- Valter Torri, Italy
- Annalisa Trama, Italy
- Frits Van Coevorden, Netherlands
- Winette Van der Graaf, Netherlands
- Daniel Vanel, Italy
- Eva Wardelmann, Germany

After failure of anthracycline-based chemotherapy, or the impossibility to use it, the following criteria may apply, although high-level evidence is lacking:

- Patients who have already received chemotherapy may be treated with ifosfamide, if they did not progress on it previously. High-dose ifosfamide (around 14 g/m^2) may be an option also for patients who have already received standard-dose ifosfamide [25, 26] [IV, C].
- Trabectedin is a second-line option [II, B] and is approved for advanced previously treated STS in the EU. It has proved effective in leiomyosarcoma and liposarcoma [27]. In myxoid liposarcoma, a high antitumour activity was described. A peculiar pattern of tumour response has been reported, with an early phase of tissue changes preceding tumour shrinkage [28]. Clinical benefit with trabectedin was also obtained in other histological types.
- One trial showed that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy, with special reference to leiomyosarcoma and undifferentiated pleomorphic sarcoma, but data are conflicting and toxicity is different [29] [II, C]. Gemcitabine was shown to have anti-tumour activity in leiomyosarcoma and angiosarcoma also as a single agent.
- Dacarbazine has some activity as a second-line therapy (mostly in leiomyosarcoma and solitary fibrous tumour). The combination of dacarbazine and gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomised trial [30] [II, B].
- A randomised trial showed a benefit in PFS averaging 3 months for pazopanib given up to progression to advanced, previously treated, STS patients (excluding liposarcomas) [31]. Thus, it is an option in non-adipogenic STS [I, B].

Best supportive care alone is an alternative for pre-treated patients with advanced STS, especially if further-line therapies have already been used in the patient.

The ESMO/European Sarcoma Network Working Group*

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
- Sylvie Bonvalot, France
- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
- Palma Dileo, UK
- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
- Stefano Ferrari, Italy
- Hans Gelderblom, Belgium
- Robert Grimer, UK
- Alessandro Gronchi, Italy
- Rick Haas, Netherlands
- Kirsten Sundby Hall, Norway
- Peter Hohenberger, Germany
- Rolf Issels, Germany
- Heikki Joensuu, Finland
- Ian Judson, UK
- Axel Le Cesne, France
- Saskia Litière, Belgium
- Javier Martin-Broto, Spain
- Ofer Merimsky, Israel
- Michael Montemurro, UK
- Carlo Morosi, Italy
- Piero Picci, Italy
- Isabelle Ray-Coquard, France
- Peter Reichardt, Germany
- Piotr Rutkowski, Poland
- Marcus Schlemmer, Germany
- Silvia Stacchiotti, Italy
- Valter Torri, Italy
- Annalisa Trama, Italy
- Frits Van Coevorden, Netherlands
- Winette Van der Graaf, Netherlands
- Daniel Vanel, Italy
- Eva Wardelmann, Germany

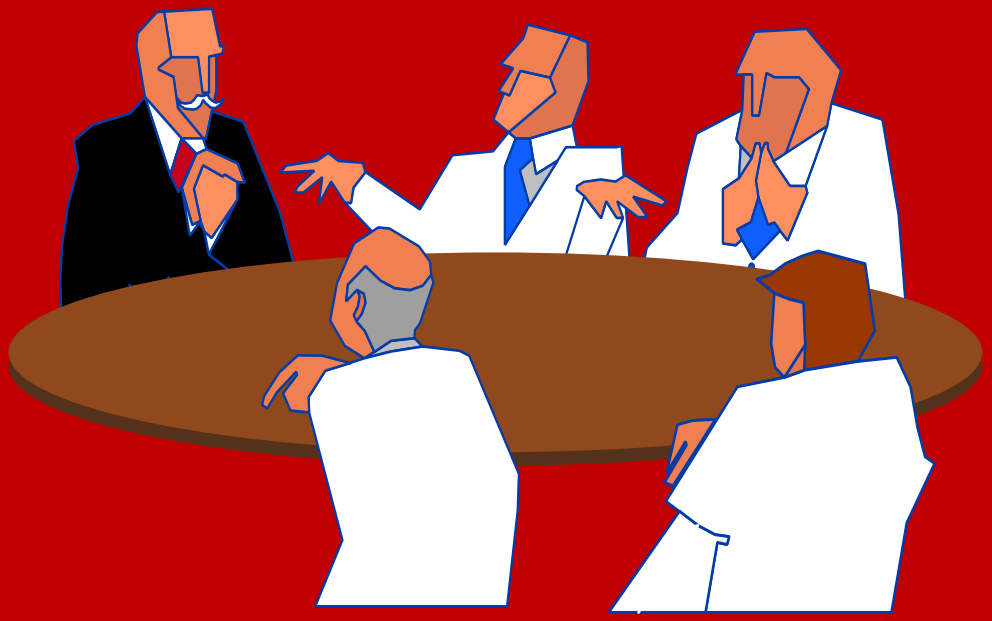
With reference to selected histological types, there is anecdotal evidence of activity of several molecular targeted agents, building on consistent preclinical data. Examples are:

- mammalian target of rapamycin inhibitors in malignant perivascular epithelioid cell tumours (PEComas), which are often associated with the loss of tuberous sclerosis complex 1 (TSC1)/TSC2 [32];
- crizotinib in inflammatory myofibroblastic tumour associated with anaplastic lymphoma kinase translocations [33];
- sunitinib and cediranib in alveolar soft part sarcoma, where the molecular target is as yet unclear [34, 35]
- sunitinib in solitary fibrous tumours, where the molecular target is as yet unclear [36].

These patients can be sent to reference centres, to be treated accordingly, preferably within clinical studies or prospective clinical recordings [III, C].

Surgery
of isolated lung metastases

Multidisciplinary “tumor boards”



review

Annals of Oncology 00: 1–7, 2014
doi:10.1093/annonc/mdu459

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali[1]*, P. Bruzzi[2], J. Bogaerts[3] & J.-Y. Blay[4] on behalf of the Rare Cancers Europe (RCE) Consensus Panel

[1]*Adult Mesenchymal Tumour Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan;* [2]*Clinical Epidemiology Unit, National Institute for Cancer Research, Genova, Italy;* [3]*European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium;* [4]*Department of Medical Oncology, Centre Léon Bérard, Centre de Recherche en Cancérologie, Université de Lyon, Lyon, France*

Received 29 July 2014; revised 18 September 2014; accepted 19 September 2014

While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are unpractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate end points is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, clinical trials, research methodology

- **Clinical decision-making**
- **Methods to combine evidence**
- **New study designs**
- **Surrogate end points**
- **Organization of studies**

REPORTS FROM PAST EVENTS / Rare Cancers Conference 2012

Rare Cancers Conference 2012

Exploring ways to improve clinical research on rare cancers

Date : 01 Mar 2012

Organised by the European Society for Medical Oncology (ESMO) and Rare Cancers Europe, the Rare Cancers Conference, held on 10 February 2012 in Brussels, provided a multi-stakeholder platform for rare cancer and rare disease experts from across Europe to exchange views and share insights into what can be done to improve the methodology of clinical research on rare cancers.

The first two conference sessions offered an overview of rare cancers and associated challenges for clinical research and drug development and also presented a variety of (potential) solutions as well as best practice examples. Where traditional frequent clinical research approaches are not possible, due to the small numbers of patients, it is particularly challenging to make sure that rare cancer patients are not being left without appropriate clinical research and therapeutic progress.

The third session of the conference therefore also highlighted the need for reaching a broad multi-stakeholder consensus on a set of recommendations on improving the methodology of clinical research on rare cancers. These recommendations will be the product of an ongoing multidisciplinary and multi-stakeholder online consensus discussion, promoted by Rare Cancers Europe. They will focus on best methods, including innovative ones, for clinical research on rare cancers, and rare subgroups of frequent cancers, with the goal of encouraging:

- clinical researchers to exploit innovative solutions for the design and analysis of clinical studies;
- clinicians to exploit innovative solutions for the combination of all available knowledge;
- regulators to accept evidence built through these solutions;
- clinicians' and patients' communities to exploit all forms of collaboration to put together as large series as possible for prospective and retrospective clinical and translational research;
- methodologists to advance research into new methodological solutions better fitting the needs of studies on small series

All interested stakeholder groups are encouraged to actively participate in this open discussion, the result of which will be a consensus paper to be publicly presented in autumn 2012. This paper could then be used for related advocacy efforts. All parties interested in joining this discussion are invited to contact Rare Cancers Europe.

RARE CANCERS EUROPE

Joining forces for action

paolo.casali@istitutotumori.mi.it

@casali_pg