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Histotype or molecular driven treatment of sarcomas?

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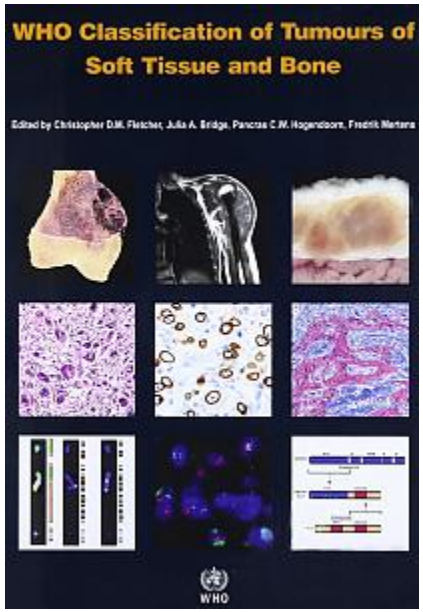
“GistStudyGroup” “Sarcomastudygroup” Bologna

Classification of Sarcoma



soft-tissue sarcomas

bone sarcomas

Osteogenic tumours	Osteosarcoma	9180/3
	Conventional	9180/3
	Chondroblastic	9181/3
	Fibroblastic	9182/3
	Osteoblastic	9180/3
	Telangiectatic	9183/3
	Small cell	9185/3
	Low-grade central	9187/3
	Secondary	9180/3
	Parosteal	9192/3
	Periosteal	9193/3
	High-grade surface	9194/3
Ewing sarcoma/primitive neuroectodermal tumour	Ewing sarcoma	9260/3
Cartilage	Chondrosarcoma	9220/3
	Central, primary, and secondary	9220/3
	Peripheral	9221/3
	Dedifferentiated	9243/3
	Mesenchymal	9240/3
	Clear cell	9242/3
Fibrogenic tumours	Fibrosarcoma	8810/3
Fibrohistiocytic tumours	Malignant fibrous histiocytoma	8830/3
Haematopoietic tumours	Plasma cell myeloma	9732/3
	Malignant lymphoma, NOS	9590/3
Giant cell tumour	Malignancy in giant cell tumour	9250/3
Notochordal tumours	Chordoma	9370/3
Vascular tumours	Angiosarcoma	9120/3
Smooth muscle tumours	Leiomyosarcoma	8890/3
Lipogenic tumours	Liposarcoma	8850/3
Miscellaneous tumours	Adamantinoma	9261/3

Although listed by the WHO as bone tumours, plasma cell myeloma, as well as primary malignant lymphoma of bone are not dealt with by these guidelines.

WHO 2013 Classification

Classification of Soft tissue Sarcoma

The soft-tissue sarcomas are a group of rare but anatomically and histologically diverse neoplasms with diverse outcome and treatment

Approximatevely 50 recognized histologic subtypes of soft-tissue sarcomas

WHO classification of soft tissue tumours (2013)

- ADIPOCYTIC TUMOURS
- FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS
- FIBROHISTIOCYTIC TUMOURS
- SMOOTH MUSCLE TUMOURS
- PERICYTIC (PERIVASCULAR) TUMOURS
- SKELETAL MUSCLE TUMOURS
- VASCULAR TUMOURS
- GASTROINTESTINAL STROMAL TUMOURS
- NERVE SHEATH TUMOURS
- CHONDRO-OSSEOUS TUMOURS
- TUMOURS OF UNCERTAIN DIFFERENTIATION
- UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

- Nodular fasciitis
- Proliferative fasciitis
- Proliferative myositis
- Myositis ossificans
- Ischaemic fasciitis
- Elastofibroma
- Calcifying aponeurotic fibroma
- Angiomyofibroblastoma
- Cellular angiofibroma
- Nuchal-type fibroma
- Gardner fibroma
- Calcifying fibrous tumour
- Giant cell angiofibroma
- fibro-osseous pseudotumour of digits
- Fibrous hamartoma of infancy
- Myofibroma / Myofibromatosis
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis
- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Mammary-type myofibroblastoma

Intermediate (locally aggressive)

- Superficial fibromatoses (palmar / plantar)
- Desmoid-type fibromatoses
- Lipofibromatosis

Intermediate (rarely metastasizing)

- Solitary fibrous tumour
- Inflammatory myofibroblastic tumour
- Low grade myofibroblastic sarcoma
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma
- Giant cell fibroblastoma
- Dermatofibrosarcoma protuberans (DFSP)

Malignant

- Adult fibrosarcoma
- Myxofibrosarcoma
- Low grade fibromyxoid sarcoma
- hyalinizing spindle cell tumour
- Sclerosing epithelioid fibrosarcoma

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

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

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii21–iii26, 2014
doi:10.1093/annonc/mdu255

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii113–iii123, 2014
doi:10.1093/annonc/mdu256

Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

Treatment of Soft tissue Sarcoma

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2000

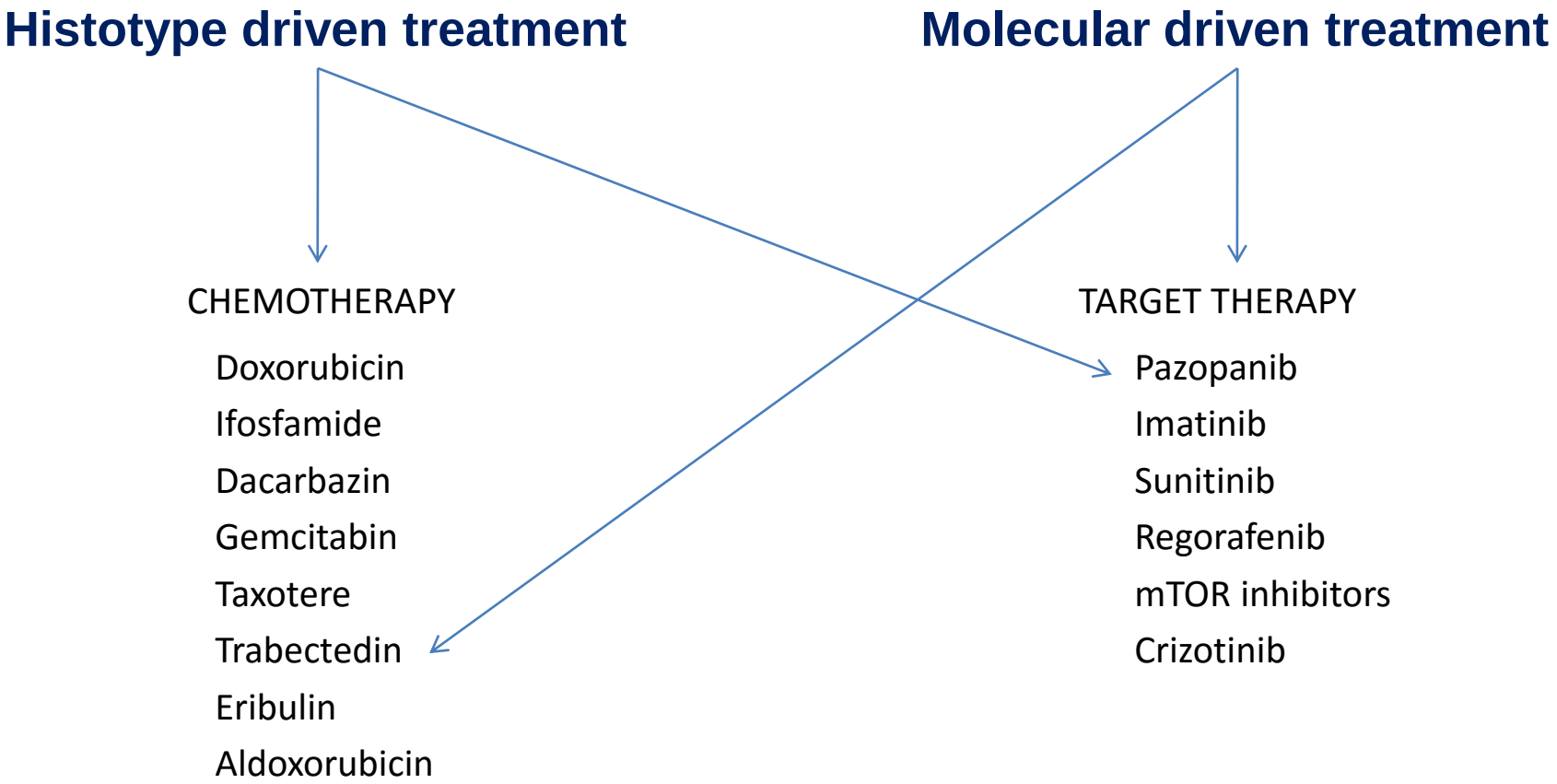
- All sarcomas
  - Doxorubicin
  - Ifosfamide
  - DTIC

2010

- GIST: Imatinib, sunitinib, regorafenib
- LPS: Dox ± Ifo, Trabectedin
- LMS: Dox ± DTC, Trabectedin, Gem, Gem/T
- All but LPS: VEGFR TKI
- Angiosarcoma: Dox ± Ifo, Gem/T, Paclitaxel
- DFSP: imatinib
- PVNS: imatinib
- Desmoid tumors: imatinib, sorafenib
- PECOMAs: m TOR inhibitors
- AlveolarSoft Sarcoma: sunitinib
- Myofibroblastic Inflammatory Sarcoma: crizotinib

Histotype or Molecular driven treatment ?

Histotype or Molecular driven treatment?



BOTH indications!

> Trabectedin in traslocated myxoid liposarcoma

> Pazopanib non in liposarcoma

Molecular driven treatment

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Histopathology

Histopathology 2014, 64, 2–11. DOI: 10.1111/his.12267

REVIEW

The evolving classification of soft tissue tumours – an update based on the new 2013 WHO classification

Christopher D M Fletcher[1,2]
[1]Department of Pathology, Brigham and Women's Hospital, and [2]Department of Pathology, Harvard Medical School, Boston, MA, USA

Common recurrent translocations in soft tissue tumours

Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWS-NR4A3*
	t(9;17)(q22;q11)	*RBP56-NR4A3*
	t(9;15)(q22;q21)	*TCF12-NR4A3*
Fibromyxoid sarcoma, low grade	t(7;16)(q33;p11)	*FUS-CREB3L2*
	t(11;16)(p11;p11)	*FUS-CREB3L1* (rare)
Inflammatory myofibroblastic tumour	t(1;2)(q22;p23)	*TPM3-ALK*
	t(2;19)(p23;p13)	*TPM4- ALK*
	t(2;17)(p23;q23)	*CLTC-ALK*
	t(2;2)(p23;q13)	*RANBP2- ALK*
Myxoid liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3*
	t(12;22)(q13;q12)	*EWS-DDIT3*
Synovial sarcoma	t(X;18)(p11;q11)	*SS18-SSX1*
		SS18-SSX2
		SS18-SSX4 (rare)

Table 1. Recently identified cytogenetic and molecular genetic aberrations in soft tissue tumours

Angiomatoid 'MFH'[41,42]	t(12;22)(q13;q12)	*ATF1–EWSR1*
	t(2;22)(q33;q12)	*CREB1-EWSR1*
Solitary fibrous tumour[37,38]	inv(12)(q13q13)	*NAB2-STAT6*
Low-grade fibromyxoid sarcoma/[5,6,43] sclerosing epithelioid fibrosarcoma (subset)	t(7;16)(q33;p11)	*FUS–CREB3L2*
	t(11;16)(p13;p11)	*FUS-CREB3L1*
Myxoinflammatory fibroblastic sarcoma/ hemosiderotic fibrolipomatous tumour[28,29]	t(1;10)(p22;q24)	*TGFBR3-MGEA5*
Myoepithelial carcinoma[44]	t(6;22)(p22;q12)	*EWSR1-POU5F1*
	t(1;22)(q23;q12)	*EWSR1-PBX1*
	t(19;22)(q13;q12)	*EWSR1-ZNF444*
Epithelioid hemangioendothelioma[45,46]	t(1;3)(p36.3;q25)	*WWTR1-CAMTA1*
Mesenchymal chondrosarcoma[47]	t(8;8)(q21.1;q13.3)	*HEY1-NCOA2*
Undifferentiated (Ewing-like) sarcoma[35,36]	t(4;19)(q35;q13.1)	*CIC-DUX4*
	t(10;19)(q35;q26)	*CIC-DUX4*
Nodular fasciitis[3]	t(17;22)(p13;q12.3)	*USP6-MYH9*
Pseudomyogenic hemangioendothelioma[14]	t(7;19)(q22;q13)	???
Ossifying fibromyxoid tumour[48]	Rearrangement of *PHF1* at 6p21	
PEComa	*TSC2* deletion[49,50]	
	TFE3 rearrangement (small subset)[51,52]	
Angiosarcoma (mammary)	*KDR* mutation[53]	
Angiosarcoma (secondary)	*MYC* amplification*[54,55]	
	FLT4 co-amplification (25%)[55]	

*Also now known to occur in a subset of primary (sporadic) angiosarcomas.[56]

First line recommendations

Histotype driven treatment

Molecular driven treatment

First line treatment:

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Histotype driven treatment

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.

VOLUME 34 · NUMBER 32 · NOVEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

PICASSO III: A Phase III, Placebo-Controlled Study of Doxorubicin With or Without Palifosfamide in Patients With Metastatic Soft Tissue Sarcoma

Christopher W. Ryan, Ofer Merimsky, Mark Agulnik, Jean-Yves Blay, Scott M. Schuetze, Brian A. Van Tine, Robin L. Jones, Anthony D. Elias, Edwin Choy, Thierry Alcindor, Vicki L. Keedy, Damon R. Reed, Robert N. Taub, Antoine Italiano, Xavier Garcia del Muro, Ian R. Judson, Jill Y. Buck, Francois Lebel, Jonathan J. Lewis, Robert G. Maki, and Patrick Schöffski

First line treatment:

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Histotype driven treatment in L – sarcoma

Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial

Patricia Pautier, Anne Floquet, Christine Chevreau, Nicolas Penel, Cécile Guillemet, Corinne Delcambre, Didier Cupissol, Frédéric Selle, Nicolas Isambert, Sophie Piperno-Neumann, Antoine Thyss, François Bertucci, Emmanuelle Bompas, Jerôme Alexandre, Olivier Collard, Sandrine Lavau-Denes, Patrick Soulié, Maud Toulmonde, Axel Le Cesne, Benjamin Lacas, Florence Duffaud, for the French Sarcoma Group

VOLUME 34 · NUMBER 19 · JULY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Study of Trabectedin and Doxorubicin Compared With Doxorubicin Alone as First-Line Treatment in Patients With Advanced Soft Tissue Sarcomas: A Spanish Group for Research on Sarcoma Study

Javier Martin-Broto, Antonio López Pousa, Ramón de las Peñas, Xavier García del Muro, Antonio Gutierrez, Javier Martinez-Trufero, Josefina Cruz, Rosa Alvarez, Ricardo Cubedo, Andrés Redondo, Joan Maurel, Juan A. Carrasco, José A. López-Martin, Ángeles Sala, José Andrés Meana, Rafael Ramos, Jordi Martinez-Serra, José A. Lopez-Guerrero, Isabel Sevilla, Carmen Balaña, Ángeles Vaz, Ana De Juan, Regina Alemany, and Andrés Poveda

			Multivariate Analysis	
Prognostic Factor	HR (95% CI)	*P*	HR (95% CI)	*P*
Experimental *v* control arm	1.16 (0.8 to 1.7)	.45	0.87 (0.5 to 1.4)	.58
Locally advanced *v* metastatic	1.22 (0.8 to 1.9)	.39	1.24 (0.7 to 2.3)	.47
L-sarcoma *v* other	0.63 (0.42 to 0.93)	.021	0.37 (0.22 to 0.62)	< .001
Age > 60 *v* 0-60 years	Not applicable	—	2.3 (1.23 to 4.33)	.009
Grade 3 *v* other	Not applicable	—	2.0 (1.19 to 3.38)	.009

First line treatment:

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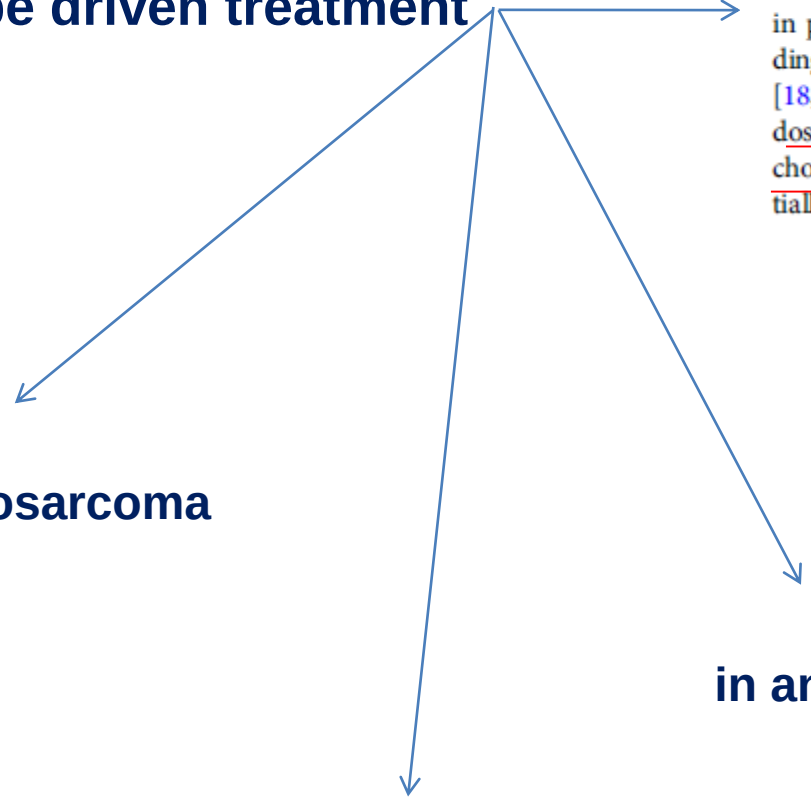
Histotype driven treatment



in leiomyosarcoma

in angiosarcoma

in solitary fibrous tumor

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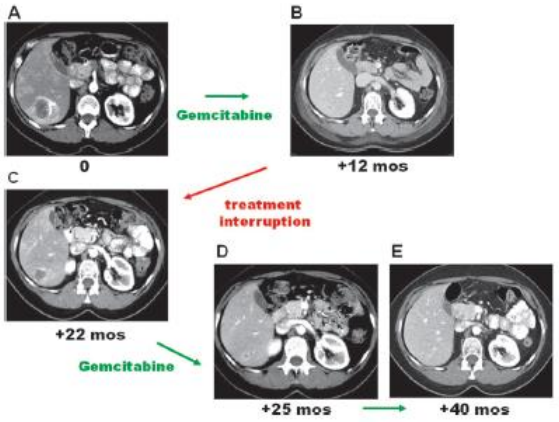
First line treatment:

Histotype driven treatment in angiosarcoma

Annals of Oncology 23: 501–508, 2012
doi:10.1093/annonc/mdr066
Published online 4 April 2011

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]



VOLUME 33 · NUMBER 25 · SEPTEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Paclitaxel Given Once Per Week With or Without Bevacizumab in Patients With Advanced Angiosarcoma: A Randomized Phase II Trial

Isabelle L. Ray-Coquard, Julien Domont, Emmanuelle Tresch-Bruneel, Emmanuelle Bompas, Philippe A. Cassier, Olivier Mir, Sophie Piperno-Neumann, Antoine Italiano, Christine Chevreau, Didier Cupissol, François Bertucci, Jacques-Olivier Bay, Olivier Collard, Ilona Saada-Bouzid, Nicolas Isambert, Corinne Delcambre, Stéphanie Clisant, Axel Le Cesne, Jean-Yves Blay, and Nicolas Penel

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, Maria Jimenez, Nicolas Isambert, Frédéric Peyrade, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay

From the Département de Cancérologie Générale, Unité de Biostatistiques, and

Minichillo *et al. BMC Res Notes (2015) 8:325*
DOI 10.1186/s13104-015-1296-4

BMC Research Notes

CASE REPORT Open Access

Efficacy of weekly docetaxel in locally advanced cardiac angiosarcoma

Santino Minichillo[1], Maria Abbondanza Pantaleo[1,2], Margherita Nannini[1,2], Fabio Coccolo[3], Lidia Gatto[1], Guido Biasco[1,2] and Giovanni Brandi[1*]

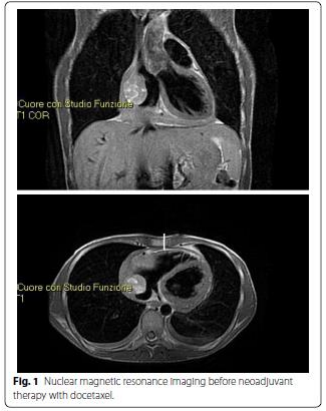


Fig. 1 Nuclear magnetic resonance imaging before neoadjuvant therapy with docetaxel.

First line treatment:

Histotype driven treatment in leiomyosarcoma

↓

Dacarbazine in favor to Ifosfamide

± Doxorubicn

First line treatment:

Histotype driven treatment in solitary fibrous tumor

Abstract #11042

Doxorubicin plus dacarbazine (DTIC) in advanced solitary fibrous tumor (SFT): An Italian retrospective case series analysis

Maristella Saponara[1], Bruno Vincenzi[2], Giuseppe Badalamenti[3], Carlo Morosi[4], Silvana Pilotti[4], Gianpaolo Dagrada[4], Salvatore Provenzano[4], Michela Libertini[4], Rossella Bertulli[4], Vittoria Colia[4], Angelo Paolo Dei Tos[5], Paolo Giovanni Casali[4], Silvia Stacchiotti[4]

[1]Department of specialized, experimental, and diagnostic Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [2]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy; [3]Department of Oncology, Medical Oncology Division, University of Palermo, Palermo, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Azienda ULSS 9 Treviso, Treviso, Italy

Background

The reported response rate to chemotherapy (CT) in SFT is low both with anthracycline-based regimens (≤20%) and with trabectedin (<10%). DTIC can be active. We report on the combination of doxorubicin + DTIC in a retrospective case-series analysis of SFT patients (pts) treated within 3 Italian sarcoma referral centers.

Patients and Methods

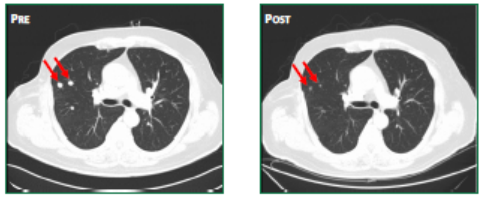
We singled out metastatic SFT pts treated with CT from February 2012 to December 2015 at Fondazione IRCCS Istituto Nazionale Tumori - Milan, University Campus Bio-Medico - Rome and University Hospital "P. Giaccone" - Palermo, reviewing those receiving doxorubicin + DTIC. Pathologic diagnosis on last available tumor sample was centrally reviewed, distinguishing typical, malignant (MSFT) and dedifferentiated (DSFT) subtypes. Pts were treated until unacceptable toxicity or progression. All pts who received at least 1 cycle of chemotherapy were considered. Response was assessed by RECIST.

Patients' Characteristics (n=13)	
Sex (M:F)	9:4
Age (mean, range)	53, 31-71
PS ECOG 0/1	7/6
Front-line/Further-line	11/2
MSFT/DSFT	8/5

Results

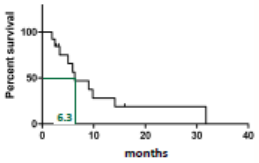
13 cases were retrospectively identified (male/female: 9/4; mean age: 53 years, range 31-71; front-line/further-line: 11/2; MSFT/DSFT: 8/5). All pts were evaluable for response. Treatment was stopped in 11 cases (disease progression: 6 - maximum tolerated dose: 3 - surgery of residual disease: 2), while 2 pts are still on therapy. The mean number of cycles was 5 (3-6). There was no unexpected toxicity. Best response by RECIST was partial response (PR) = 6 (46%) - stable disease (SD) = 2 (15%) - progressive disease (PD) = 5 (39%). At a median follow-up of 19.2 months, median PFS was 6.3 months (range 2-32), with 3 pts being progression-free at 12 months. PR was detected in 3/8 MSFT e 3/5 DSFT, with a median PFS of 6.3 and 9.8 months in MSFT and DSFT, respectively. Median OS was 18.7 months (range 3-33).

Results	
N° of cycles (mean, range)	5, 3-6
Best response by RECIST	6 PR 2 SD 5 PD
Reason for interruption	6 PD 3 max dose reached 2 surgery of residual disease (2 ongoing)

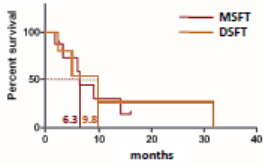


Axial CT scans performed in a man affected by DSFT pre and post chemotherapy. In particular, partial response of two adjacent lung lesions in the middle lobe after 6 cycles of doxorubicin + DTIC: metastases reduced from 12 and 10 mm to 6 and 5 mm, respectively.

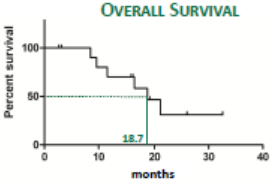
Overall PFS



MSFT *vs* DSFT PFS



Overall Survival



Conclusions

This small retrospective series suggests that doxorubicin + DTIC can be active in SFT. A higher response rate was observed in DSFT in comparison to MSFT (and pts with MSFT may have had an unsampled aggressive evolution). A prospective Phase 2 study on doxorubicin + DITC vs trabectedin in advanced SFT is under evaluation.

First line treatment:

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Moelcular driven treatment

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.

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in dermatofibrosarcoma protuberans (DFSP)

Gstrointestinal stromal tumors (GIST) BRAF or SDH mutant

Gstrointestinal stromal tumors (GIST) KIT mutant

First line treatment:

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Molecular driven treatment in DFPS

Tumor with COL1A1-PDGFB gene fusion

VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; European Organization for Research and Treatment of Cancer Headquarters, Brussels; Catholic University of Leuven, Leuven, Belgium; Leiden University Medical Centre, Leiden, the Netherlands; Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Heidel-

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

Piotr Rutkowski, Martine Van Glabbeke, Cathryn J. Rankin, Włodzimierz 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

A B S T R A C T

Table 2. Response, Progression, and Survival Status of Patients With Dermatofibrosarcoma Protuberans After Imatinib Therapy in the EORTC and SWOG Trials

	Study					
	EORTC (n = 16)		SWOG (n = 8)		Total (N = 24)	
Response, Progression, and Survival Status	No. of Patients	%	No. of Patients	%	No. of Patients	%
Response at 14-16 weeks						
PR	5	31.3	4	50	9	37.5
SD	6	37.5	2	25	8	33.3
PD	3	18.8	1	12.5	4	16.7
Not evaluable	2	12.5	1	12.5	3	12.5
Best overall response						
PR (confirmed)	3	18.8	4	50.0	7	29.2
PR (resected)	4	25.0	0	0.0	4	16.7
SD	4	25.0	2	25.0	6	25.0
PD	3	18.8	1	12.5*	4	16.6
Not evaluable	2	12.5	1	12.5	3	12.5

Cancer Therapy: Clinical

Clinical Cancer Research

Efficacy and Biological Activity of Imatinib in Metastatic Dermatofibrosarcoma Protuberans (DFSP)

Silvia Stacchiotti[1], Maria A. Pantaleo[2], Tiziana Negri[3], Annalisa Astolfi[4], Marcella Tazzari[5], Gian Paolo Dagrada[3], Milena Urbini[4], Valentina Indio[4], Roberta Maestro[6], Alessandro Gronchi[7], Marco Fiore[7], Angelo P. Dei Tos[8], Elena Conca[3], Elena Palassini[1], Bruno Vincenzi[9], Federica Grosso[10], Silvana Pilotti[3], Chiara Castelli[5], and Paolo G. Casali[1]

Table 2. Patient characteristics

ID	Gender	Age at the time of first diagnosis/IM	Location of primary tumor	Disease extent at time of starting IM	Site of metastases at the time of starting IM	Treatment with IM	Best response (RECIST)	Best FDG-PET response	PFS (months)	Reason for IM definitive interruption	Surgery after IM	Response to IM at the time of surgery	Relapse after surgery	Relapse free from IM discontinuation and surgery (months)	Status at last FU
1	Male	35/61	Scalp	L, M	Lung, CNS	Yes	PD	Not assessed	2	Progression	NO	Not applicable	Not applicable	Not applicable	DOD
2	Male	48/70	Trunk	M	Lung, abdomen, soft tissue	Yes	PR	Not assessed	7	Progression	NO	Not applicable	Not applicable	Not applicable	AWD
3	Male	37/50	Groin	M	Lung	Yes	PR	PR	10+	Ongoing	Yes	Yes	Yes	6	AWD
4	F	50/59	Scalp	M	Lung	Yes	PR	PR	25	Progression	Yes	Yes	Yes	12	AWD
5	F	45/55	Trunk	M	Soft tissue, bone	Yes	PR	Not assessed	11	Progression	Yes	Yes	Yes	5	DOD
6	Male	69/73	Trunk	M	Lung	Yes	PR	PR	9	Progression	No	Not applicable	Not applicable	Not applicable	DOD
7	Male	46/49	Trunk	M	Lung	Yes	PR	PR	4	Progression	Yes	No progression	Yes	5	DOD
8	Male	48/53	Scalp	M	Abdomen, soft tissue	Yes	PR	PR	22	Progression	Yes	Yes	Yes	5	AWD
9	Male	41/53	Trunk	M	Abdomen (pancreas)	Yes	PR	Not assessed	5	Toxicity	No	Not applicable	Not applicable	Not applicable	AWD
10	F	43/50	Scalp	L, M	Lung, abdomen (pancreas, stomach), soft tissue	Yes	SD	Not assessed	3+	Ongoing	No	Not applicable	Not applicable	Not applicable	AWD

Abbreviations: AWD, alive with disease; CNS, central nervous system; DOD, dead of disease; F, female; FU, follow up; IM, imatinib; L, local; M, metastatic; PFS, progression free survival.

Gastrointestinal stromal tumors
Imatinib first line therapy

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UNIVERSITÀ DI BOLOGNA

The New England Journal of Medicine

Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.[6]

We used STI571 (Glivec, Novartis, Basel, Switzerland),[7] an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a gastrointestinal stromal tumor.

CASE REPORT

In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitosis per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a c-*kit* mutation consisting of a deletion of 15 bp from exon 11 was de-

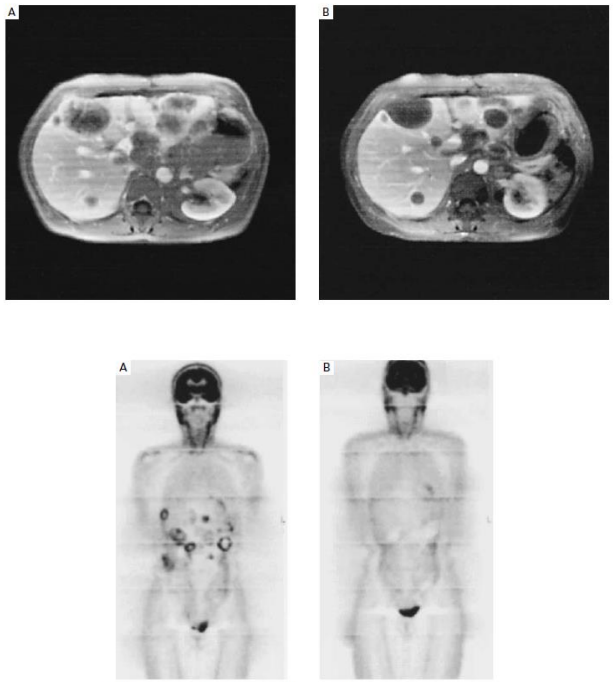


Figure 2. PET Studies with [^{18}F]Fluorodeoxyglucose as the Tracer.
Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of [^{18}F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

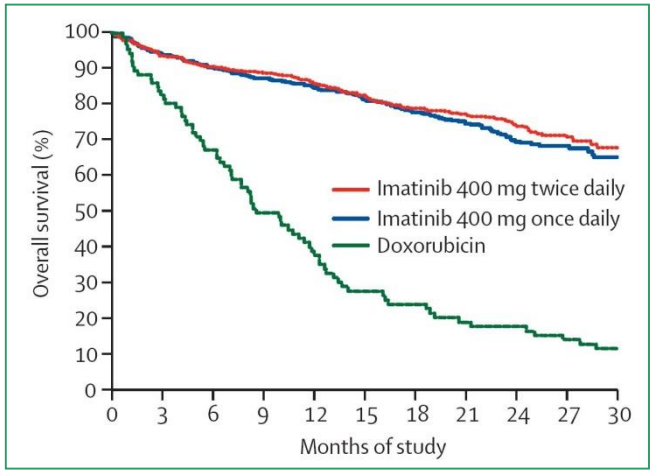
Efficacy and Safety of Imatinib Mesylate in Advanced Gastrointestinal Stromal Tumors

George D. Demetri, M.D., Margaret von Mehren, M.D., Charles D. Blanke, M.D., Annick D. Van den Abbeele, M.D., Burton Eisenberg, M.D., Peter J. Roberts, M.D., Michael C. Heinrich, M.D., David A. Tuveson, M.D., Ph.D., Samuel Singer, M.D., Milos Janicek, M.D., Ph.D., Jonathan A. Fletcher, M.D., Stuart G. Silverman, M.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Beate Kiese, M.Sc., Bin Peng, M.D., Ph.D., Sasa Dimitrijevic, Ph.D., Brian J. Druker, M.D., Christopher Corless, M.D., Christopher D.M. Fletcher, M.D., and Heikki Joensuu, M.D.

Table 2. Responses to Imatinib in Patients with Advanced Gastrointestinal Stromal Tumors.*

Best Response	400 mg (N=73)	600 mg (N=74)	Either Dose (N=147)
	no. (% [95% CI])		
Complete response	0	0	0
Partial response	36 (49.3 [37.4–61.3])	43 (58.1 [46.1–69.5])	79 (53.7 [45.3–62.0])
Stable disease	23 (31.5 [21.1–43.4])	18 (24.3 [15.1–35.7])	41 (27.9 [20.8–35.9])
Progressive disease	12 (16.4)	8 (10.8)	20 (13.6)
Could not be evaluated	2 (2.7)	5 (6.8)	7 (4.8)

*CI denotes confidence interval.



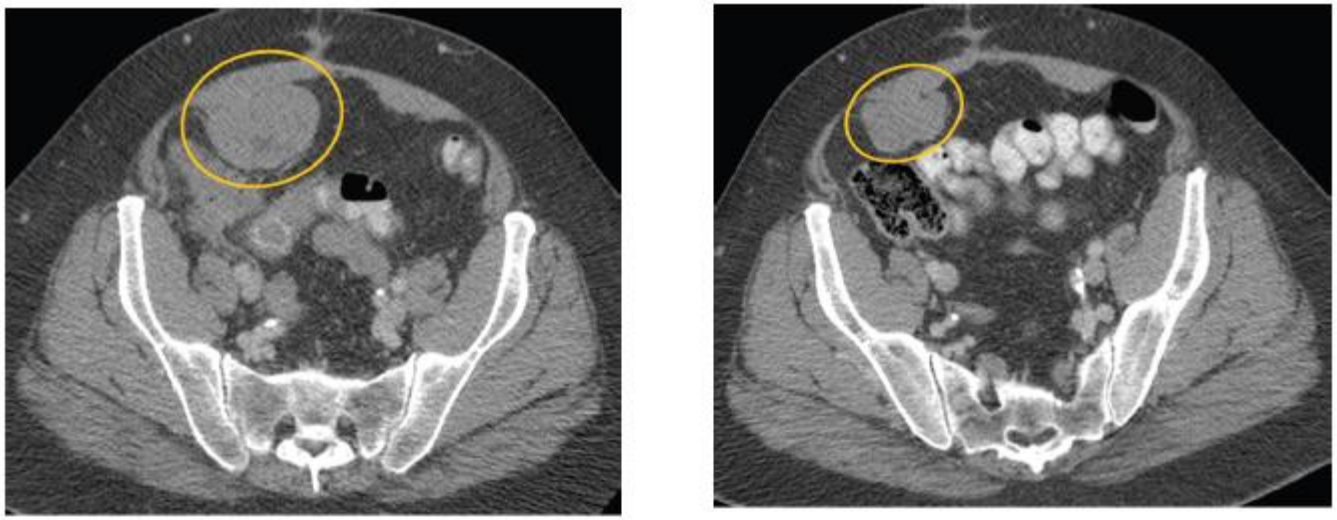
Joensuu H, New Engl J MED 2001
Demetri G, New Engl J Med 2002

First line treatment (prospective) :

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

BRAF inhibitor in BRAF mutant GIST

Falchook GS, Oncotarget 2013



Baseline

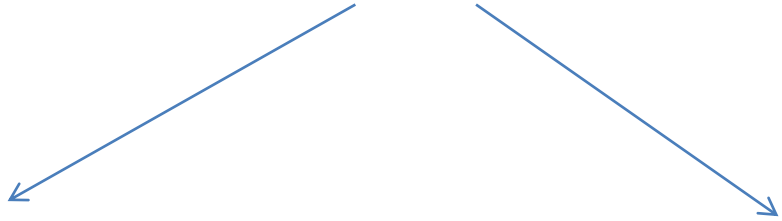
Week 24

Figure 1: Tumor regression of 20% observed in abdominal and pelvic tumors on computerized tomography (CT). CT scan at (a) baseline and after (b) 24 weeks of treatment with BRAF inhibitor dabrafenib (GSK2118436).

Regorafenib in SDH mutant GIST

ClinicalTrials.gov Identifier:NCT02638766:
Single Agent Regorafenib in First-line for Metastatic/Unresectable KIT/PDGFR Wild Type GIST (REGISTRI)

Second line recommendations



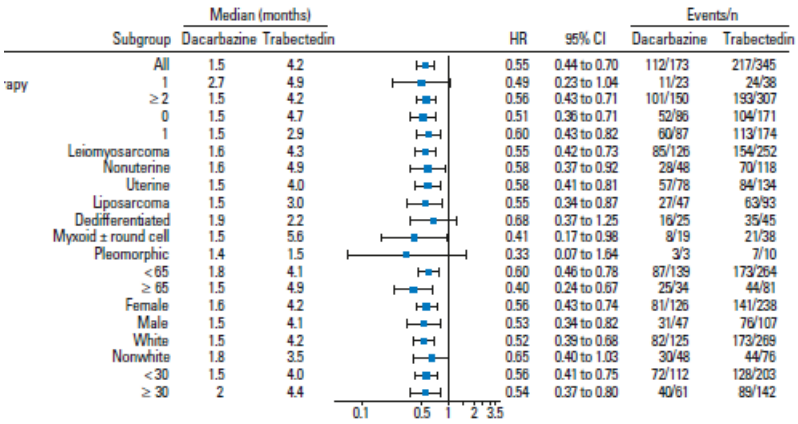
Chemotherapy in all and selceted histotype

Targeted therapy in selected histotype

Second and more line treatment

Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study

Akira Kawai, Nobuhito Araki, Hideshi Sugiura, Takafumi Ueda, Tsukasa Yonemoto, Mitsuru Takahashi, Hideo Morioka, Hiroaki Hiraga, Toru Hiruma, Toshiyuki Kunisada, Akihiko Matsumine, Takanori Tanase, Tadashi Hasegawa, Shunji Takahashi



Subgroup	Median (months) Dacarbazine	Trabectedin	HR	95% CI	Events/n Dacarbazine	Trabectedin
All	1.5	4.2	0.55	0.44 to 0.70	112/173	217/345
1	2.7	4.9	0.49	0.23 to 1.04	11/23	24/38
≥ 2	1.5	4.2	0.56	0.43 to 0.71	101/150	193/307
0	1.5	4.7	0.51	0.36 to 0.71	52/86	104/171
1	1.5	2.9	0.60	0.43 to 0.82	60/87	113/174
Leiomyosarcoma	1.6	4.3	0.55	0.42 to 0.73	85/126	154/252
Nonuterine	1.6	4.9	0.58	0.37 to 0.92	28/48	70/118
Uterine	1.5	4.0	0.58	0.41 to 0.81	57/78	84/134
Liposarcoma	1.5	3.0	0.55	0.34 to 0.87	27/47	63/93
Dedifferentiated	1.9	2.2	0.68	0.37 to 1.25	16/25	35/45
Myxoid ± round cell	1.5	5.6	0.41	0.17 to 0.98	8/19	21/38
Pleomorphic	1.4	1.5	0.33	0.07 to 1.64	3/3	7/10
< 65	1.8	4.1	0.60	0.46 to 0.78	87/139	173/264
≥ 65	1.5	4.9	0.40	0.24 to 0.67	25/34	44/81
Female	1.6	4.2	0.56	0.43 to 0.74	81/126	141/238
Male	1.5	4.1	0.53	0.34 to 0.82	31/47	76/107
White	1.5	4.2	0.52	0.39 to 0.68	82/125	173/269
Nonwhite	1.8	3.5	0.65	0.40 to 1.03	30/48	44/76
< 30	1.5	4.0	0.56	0.41 to 0.75	72/112	128/203
≥ 30	2	4.4	0.54	0.37 to 0.80	40/61	89/142

0.1 0.5 1 2 3.5

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, José Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

VOLUME 27 · NUMBER 25 · SEPTEMBER 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

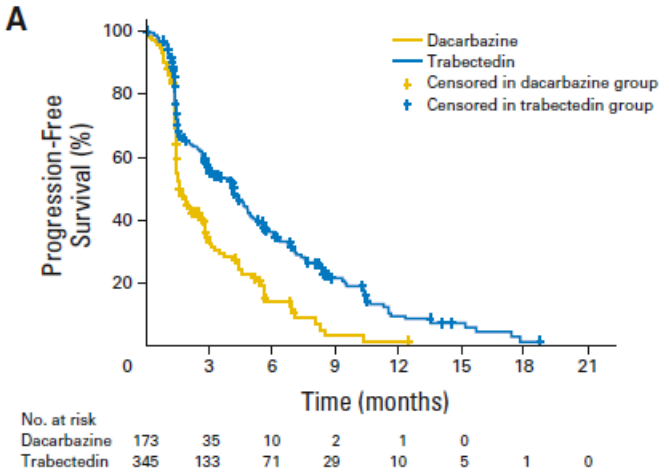
Efficacy and Safety of Trabectedin in Patients With Advanced or Metastatic Liposarcoma or Leiomyosarcoma After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two Different Schedules

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, Yasri A. Elsayed, Miguel A. Izquierdo, Javier Gómez, Youn C. Park, and Axel Le Cesne

VOLUME 34 · NUMBER 8 · MARCH 10, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

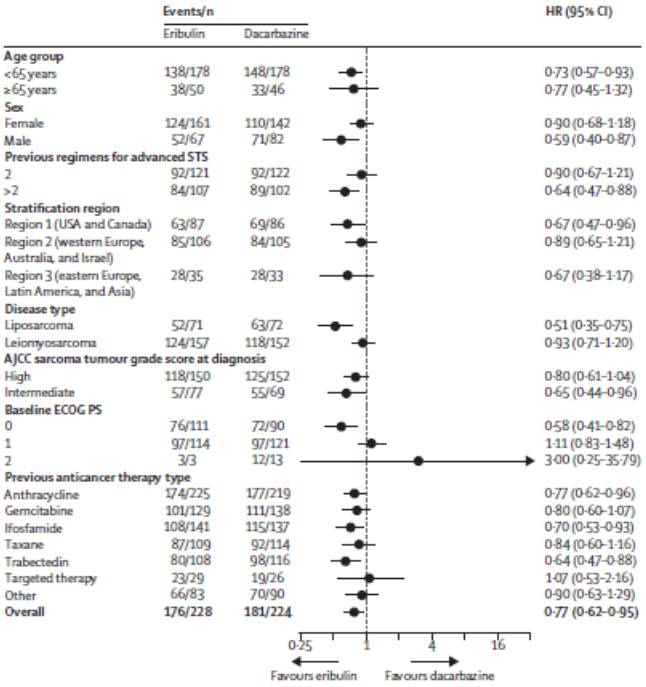
George D. Demetri, Margaret von Mehren, Robin L. Jones, Martee L. Hensley, Scott M. Schuetze, Arthur Staddon, Mohammed Milhem, Anthony Elias, Kristen Ganjoo, Hussein Tawbi, Brian A. Van Tine, Alexander Spira, Andrew Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland E. Knoblauch, Trilok V. Parekh, Robert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

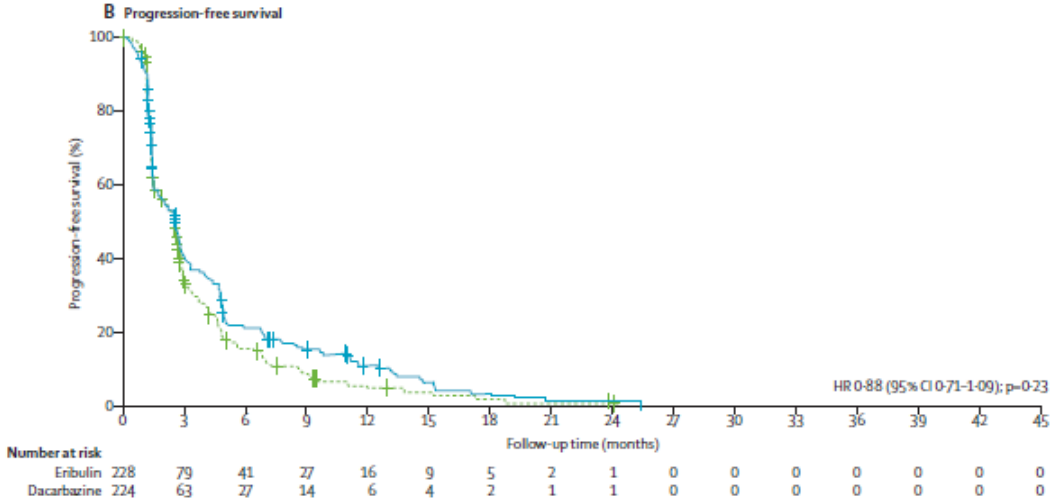


Second and more line treatment

Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial

Patrick Schöffski, Sant Chawla, Robert G Maki, Antoine Italiano, Hans Gelderblom, Edwin Choy, Giovanni Grignani, Veridiana Camargo, Sebastian Bauer, Sun Young Rha, Jean-Yves Blay, Peter Hohenberger, David D'Adamo, Matthew Guo, Bartosz Chmielowski, Axel Le Cesne, George D Demetri, Shreyaskumar R Patel





Second and more line treatment

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

Table 4. Best Response by Treatment Arm and Histology*

	Gemcitabine						Gemcitabine-Docetaxel					
Histology	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable
Leiomyosarcoma		1	2	5	1			5	3	13	8	
MFH/HGUPS		2	2	1	3		1	3	3	2	1	1
Liposarcoma												
Well differentiated/dedifferentiated			2	3	3					4		1
Myxoid-round cell				2	1	1						
Pleomorphic								2		1		
Synovial sarcoma			1	1	2				1	1	2	1
Malignant peripheral nerve sheath tumor				1	1				1		3	
Unclassified sarcoma			1	2	1					1		
Fibrosarcoma			1		2				1	2		
Rhabdomyosarcoma							1				1	
Other sarcoma histology	1			2	4				2	4	4	

Abbreviations: CR, complete response; PR, partial response; MFH/HGUPS, malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma.
*Includes one Response Evaluation Criteria in Solid Tumors Group unconfirmed PR on each arm: gemcitabine (MFH/HGUPS); gemcitabine-docetaxel (uterine leiomyosarcoma).

Second and more line treatment
Gem and DTC

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†

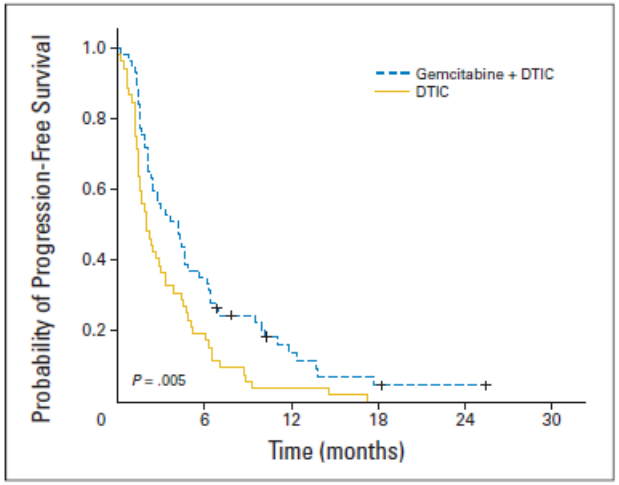


Fig 2. Kaplan-Meier curves for progression-free survival. DTIC, dacarbazine.

Table 2. Univariate and Multivariate Cox Proportional Hazards Analysis

Variable by Survival	Univariate Analyses			Multivariate Analyses		
	HR	95% CI	*P*	HR	95% CI	*P*
Progression-free survival						
PS, 0 *v* 1/2	0.86	0.56 to 1.30	.49			
DFI, < 12 months *v* ≥ 12 months	1.56	0.96 to 2.50	.06			
Histologic grade, low *v* high	1.24	0.60 to 2.49	.53			
Site of metastasis						
Local only	1.05	0.55 to 2.02	.94			
Lung only	0.94	0.62 to 1.40				
Extrapulmonary	1					
Histology, leiomyosarcoma *v* other	0.49	0.32 to 0.76	.001	0.48	0.30 to 0.77	.007
Treatment regimen, G + DTIC *v* DTIC alone	0.58	0.39 to 0.86	.005	0.54	0.36 to 0.83	.01

Second and more line treatment:

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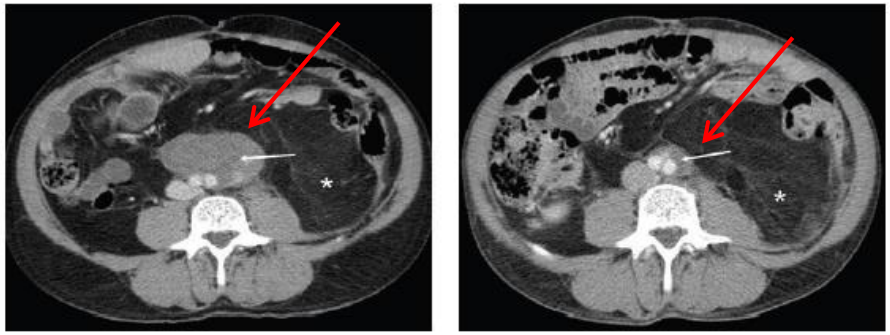
UNIVERSITÀ DI BOLOGNA

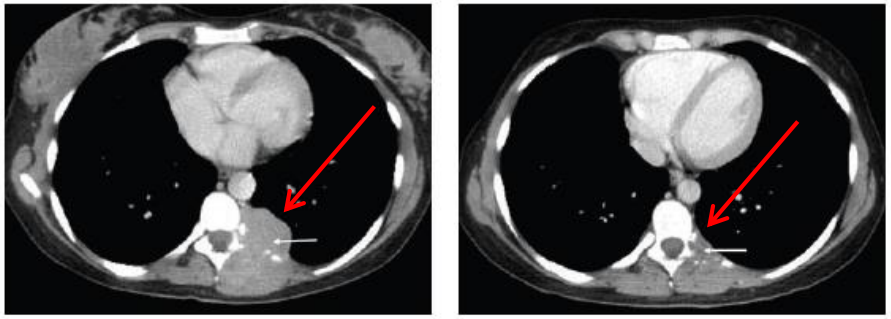
Clinical Study

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]



(a) (b)



(a) (b)

Second and more line treatment

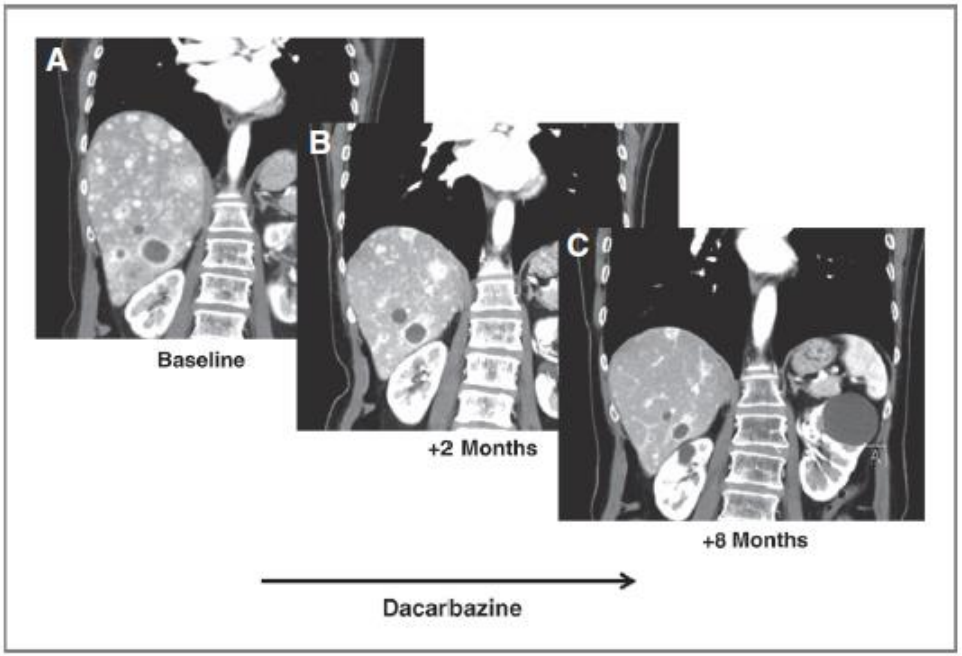
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Clinical Cancer Research

Cancer Therapy: Clinical

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]



Second line

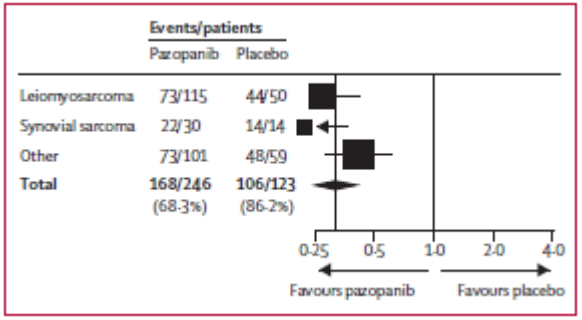
Chemotherapy in all and selceted histotype

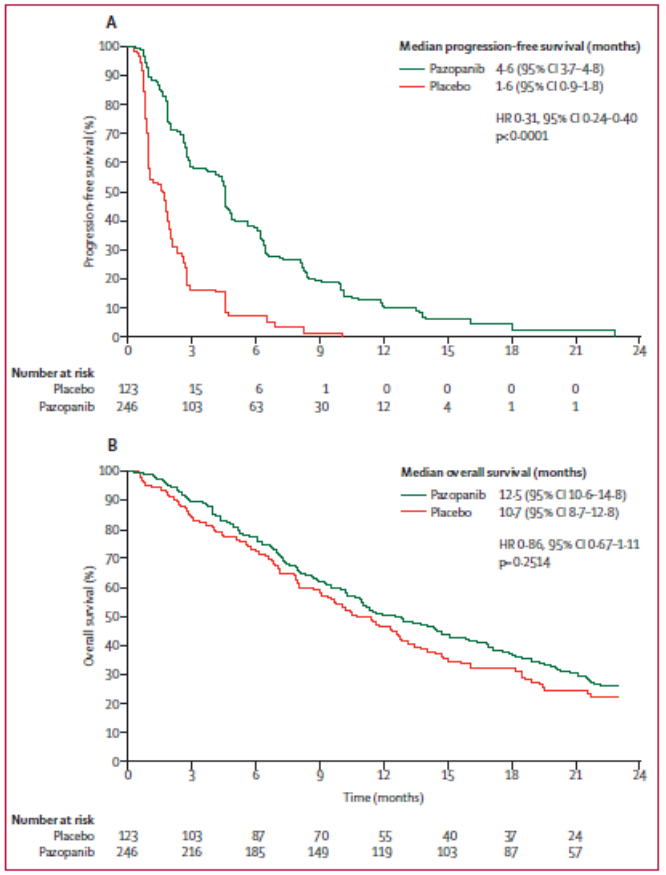
Targeted therapy in selected histotype

Second and more line treatment

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



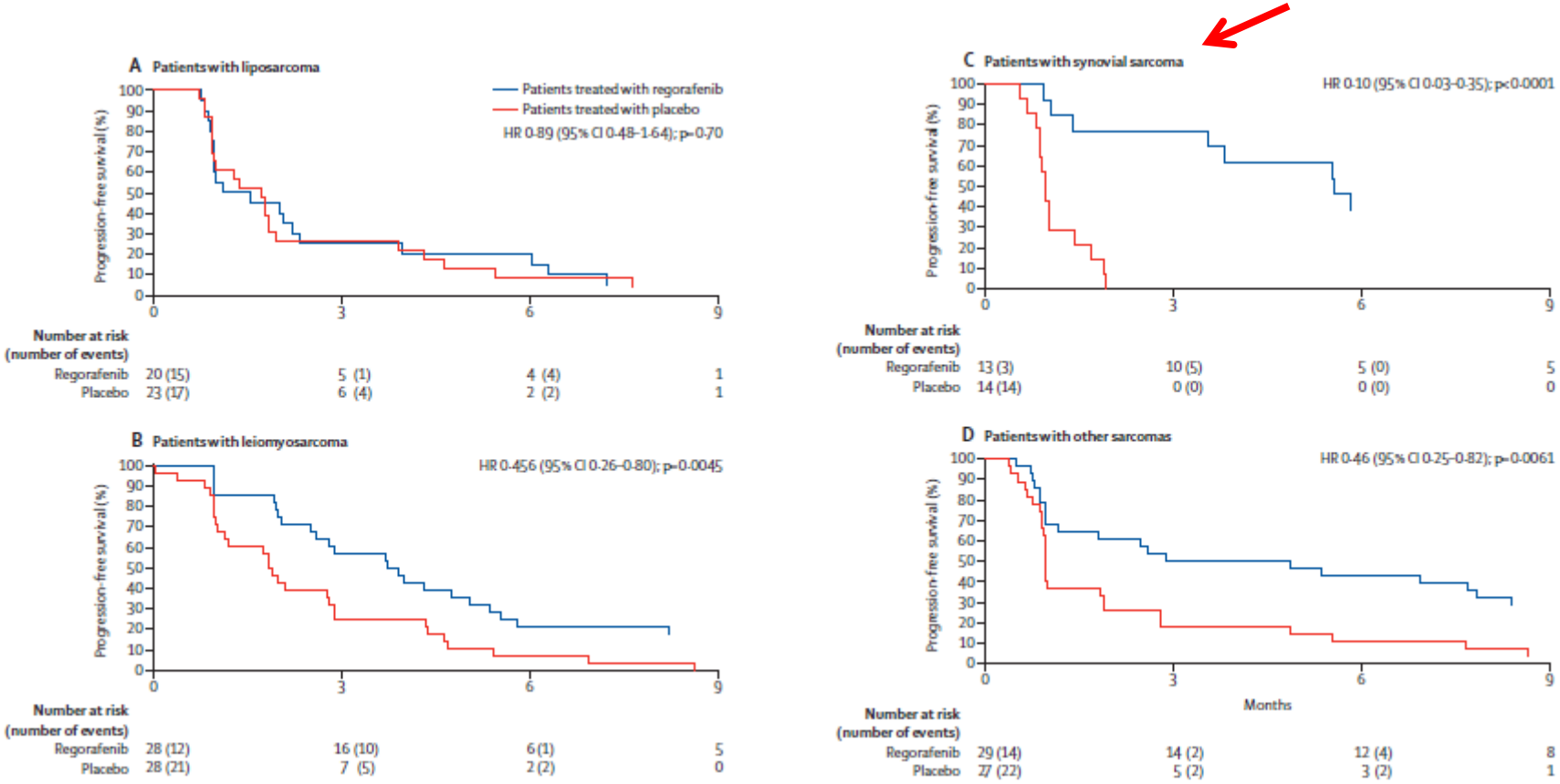


Second and more line treatment

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial

Olivier Mir, Thomas Brodowicz, Antoine Italiano, Jennifer Wallet, Jean-Yves Blay, François Bertucci, Christine Chevreau, Sophie Piperno-Neumann, Emmanuelle Bompas, Sébastien Salas, Christophe Perrin, Corinne Delcambre, Bernadette Liegl-Atzwanger, Maud Toulmonde, Sarah Dumont, Isabelle Ray-Coquard, Stéphanie Clisant, Sophie Taieb, Cécile Guillemet, Maria Rios, Olivier Collard, Laurence Bozec, Didier Cupissol, Esma Saada-Bouzid, Christine Lemaignan, Wolfgang Eisterer, Nicolas Isambert, Loïc Chaigneau, Axel Le Cesne, Nicolas Penel



Second and more line treatment

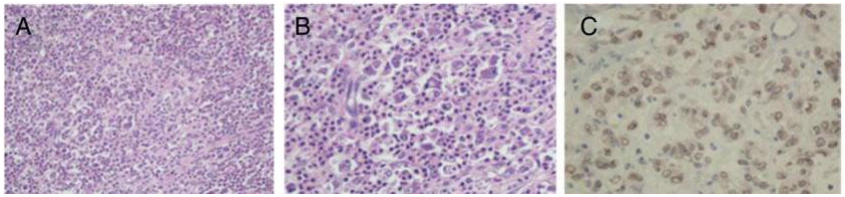
JJCO Japanese Journal of Clinical Oncology

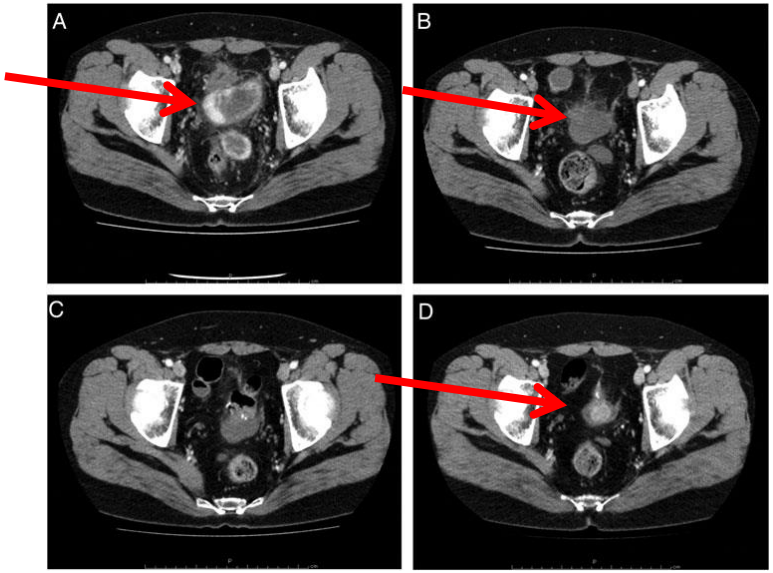
Jpn J Clin Oncol 2014;44(9)868–871
doi:10.1093/jjco/hyu069
Advance Access Publication 15 July 2014

Case Reports

A Case Report of Epithelioid Inflammatory Myofibroblastic Sarcoma with *RANBP2-ALK* Fusion Gene Treated with the ALK Inhibitor, Crizotinib

Shiro Kimbara[1], Koji Takeda[1], Hiroko Fukushima[2], Toru Inoue[3], Hideaki Okada[1], Yumi Shibata[1], Utae Katsushima[1], Asuka Tsuya[1], Shinya Tokunaga[1], Haruko Daga[1], Takahiro Okuno[2] and Takeshi Inoue[2]



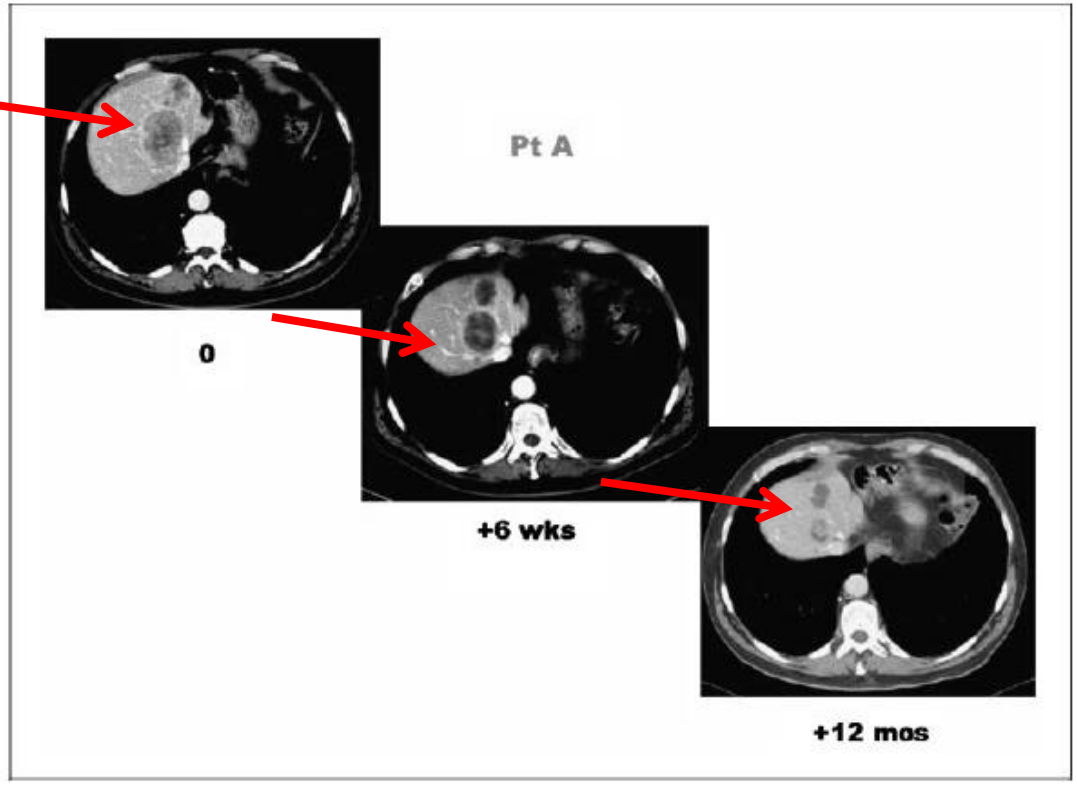


Second and more line treatment

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]



Second and more line treatment

Annals of Oncology

original articles

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doi:10.1093/annonc/mds143
Published online 17 June 2012

Sunitinib malate in solitary fibrous tumor (SFT)

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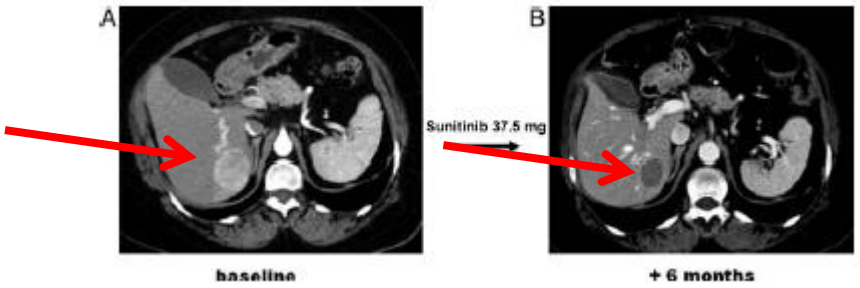
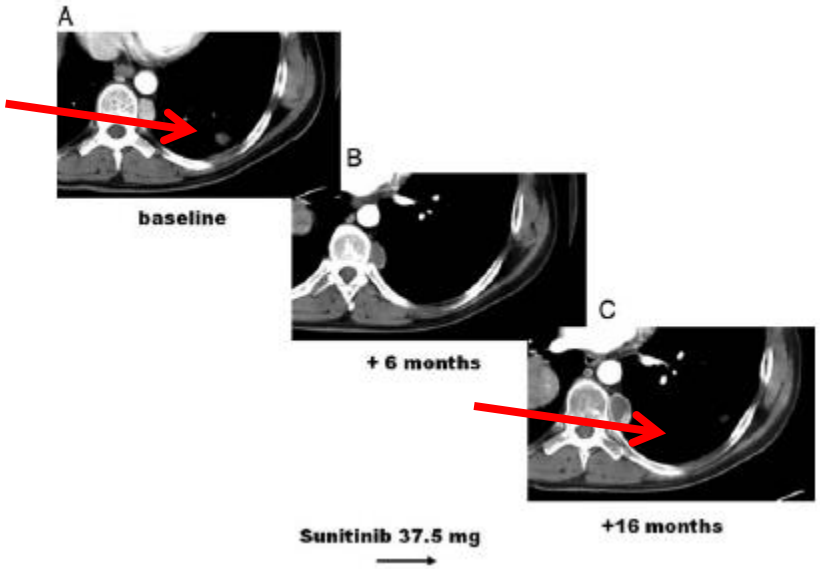




Second and more line treatment

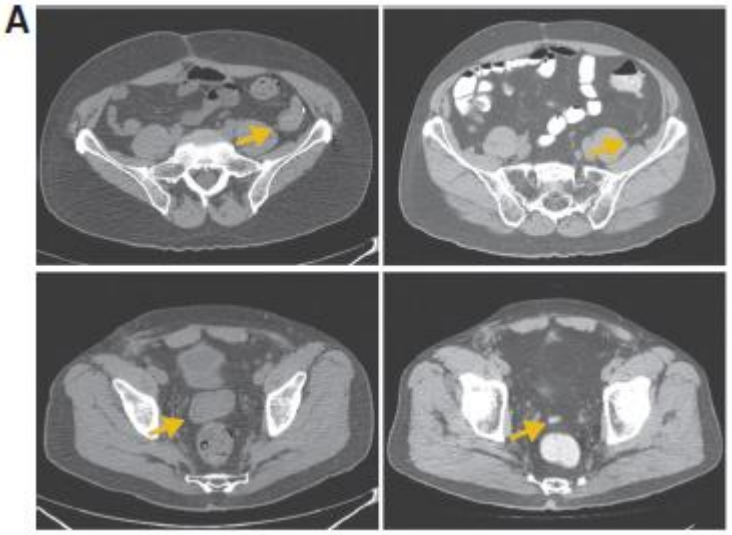
VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

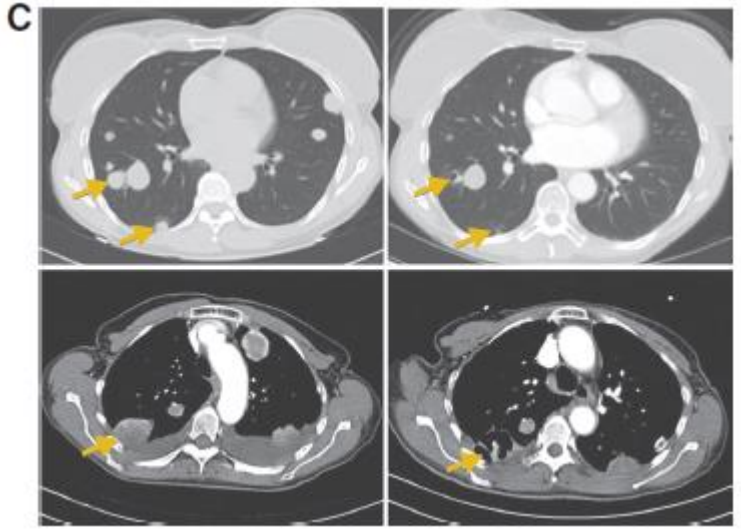
JOURNAL OF CLINICAL ONCOLOGY

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





Other considerations ……..

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> Retroperitoneal surgery as histotype driven treatment

> Neoadjuvant therapy in the sarcoma of the extremities

> Immunotherapy in sarcoma (Pembrosarc study)

> Next generation genome studies as the basis for basket trials

New concepts of clinical research

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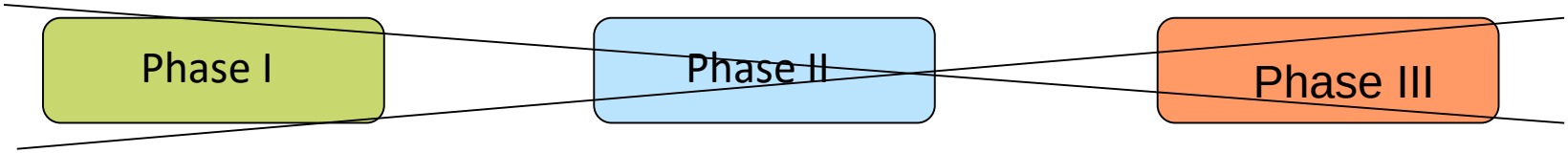
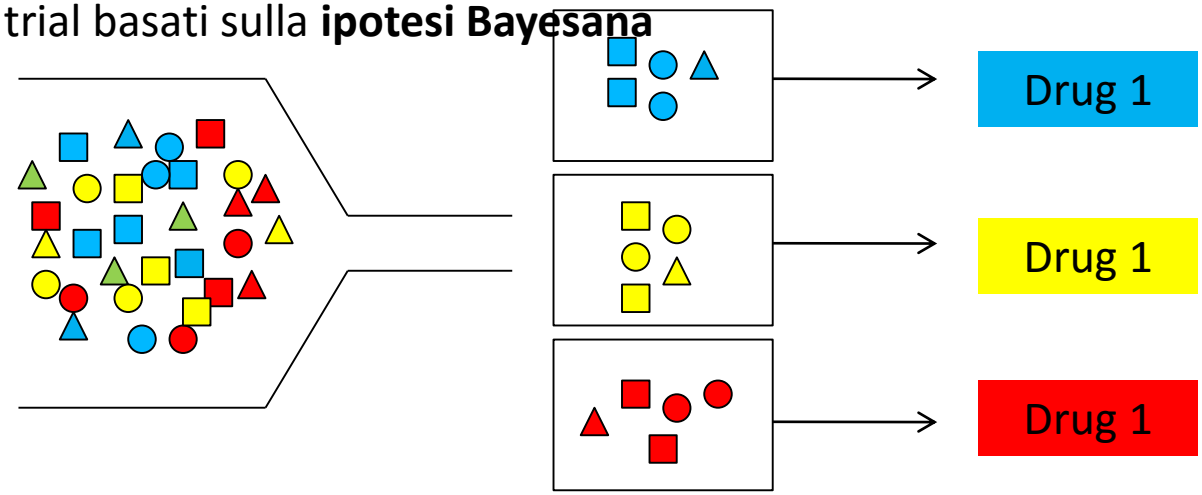
- Study Designs



- Studi osservazionali
- Casistiche retrospettive
- Case report
- Biomarkers
- Nuovi approcci statistici
- Basket trial basati sulla **ipotesi Bayesana**



Project Title:

RF-2016-02361851 Pantaleo Maria Abbondanza

Phase II Basket trial on rare tumors: precision treatments based on genome profiling evaluated with next-generation sequencing approach

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Thank you

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UERACAN member

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