Uterine Leiomyosarcoma: profile, diagnosis and challanges

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Roberta Sanfilippo
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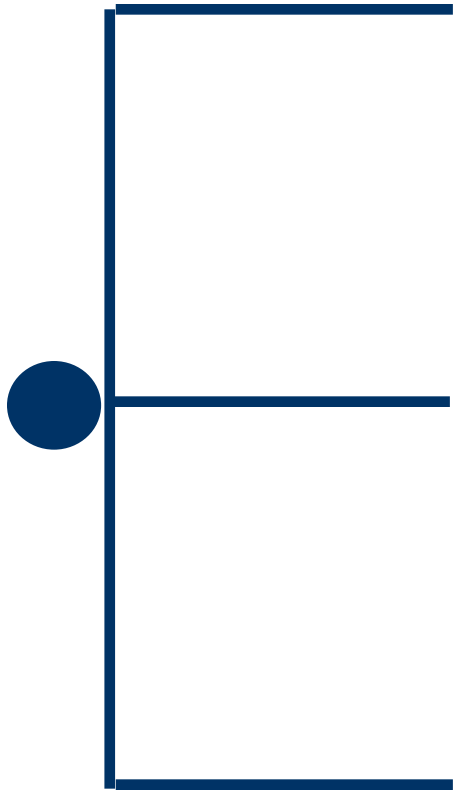
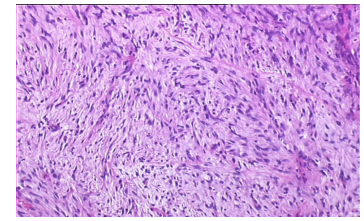
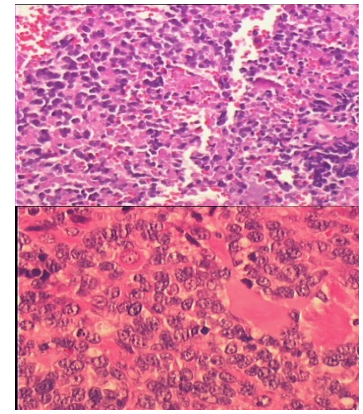
Sarcomas



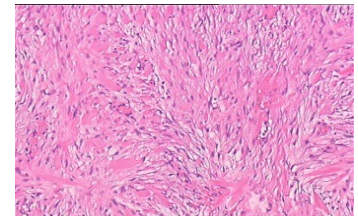
- adult-type soft tissue sarcoma



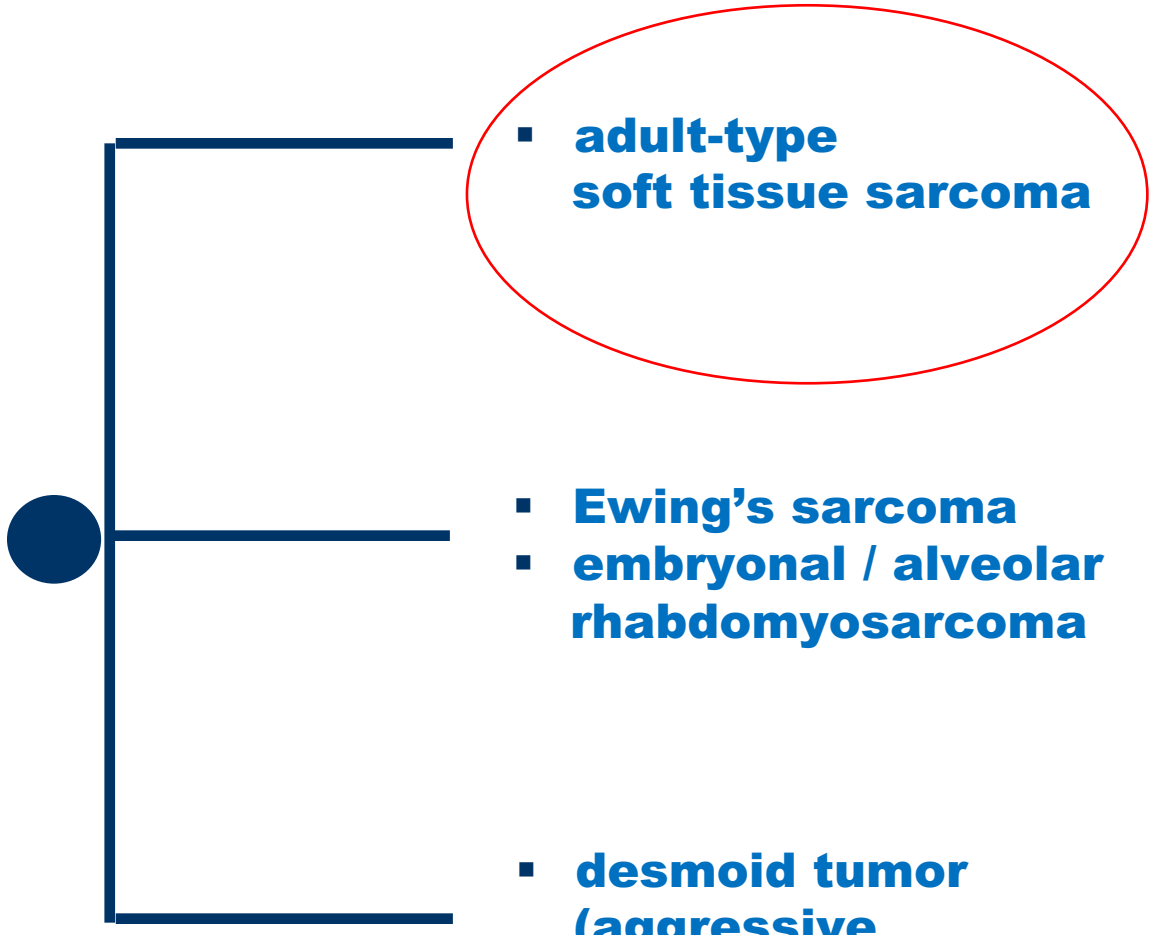
- Ewing's sarcoma
- embryonal / alveolar rhabdomyosarcoma



- desmoid tumor (aggressive fibromatosis)



Sarcomas



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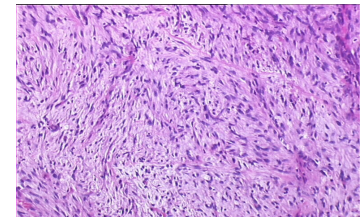
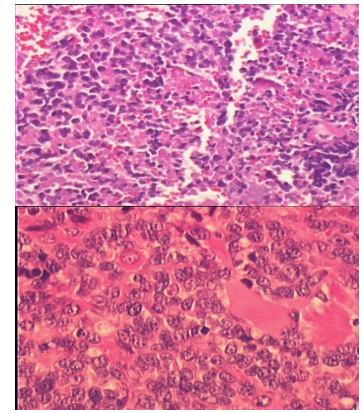
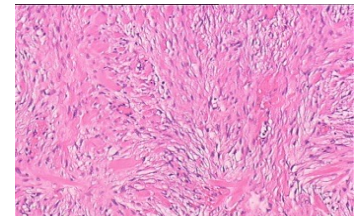
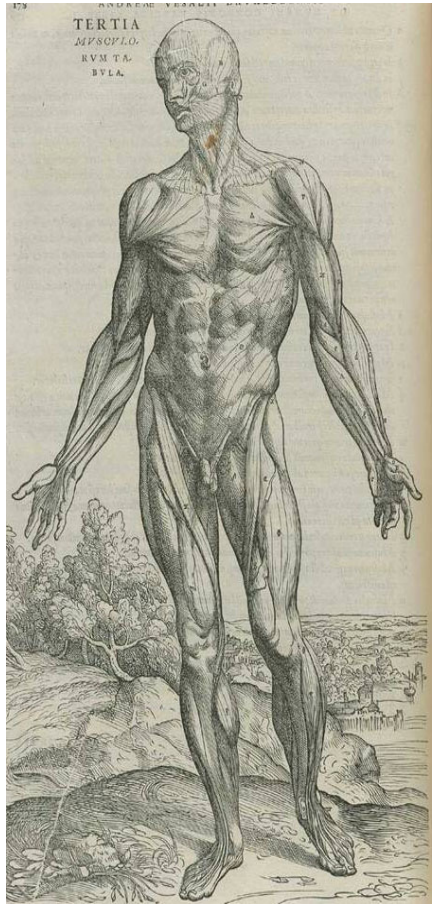






Adult soft tissue sarcoma

Anatomical sites

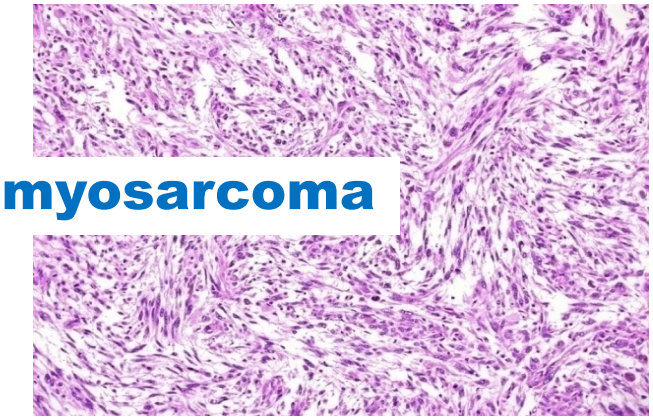


•Extremities	36%
•Trunk wall	16%
•Retroperitoneum	8%
•Gastrointestinal (GIST included)	8%
•H&N	6%
•Uterus	5%
•Others	21%

Blay et al. Ann Oncol 2019

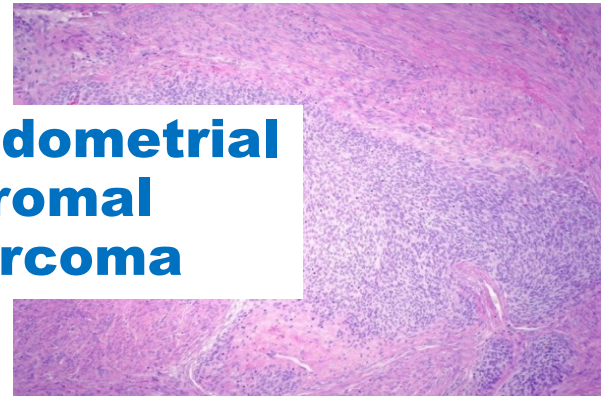
Uterine sarcomas

leiomyosarcoma

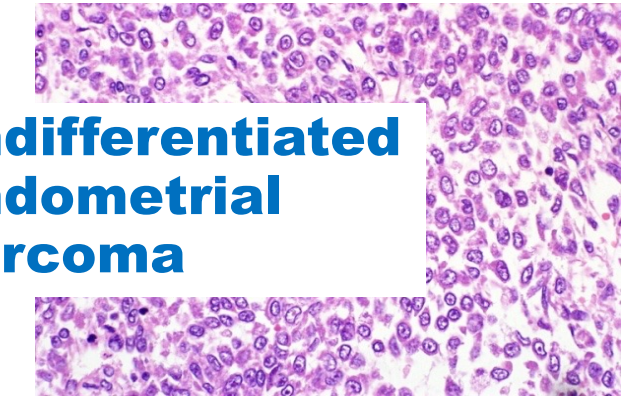


adenosarcoma

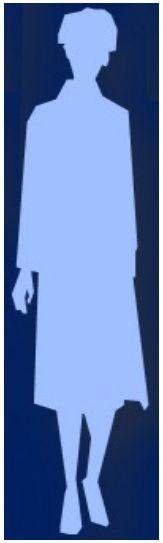
endometrial stromal sarcoma



undifferentiated endometrial sarcoma



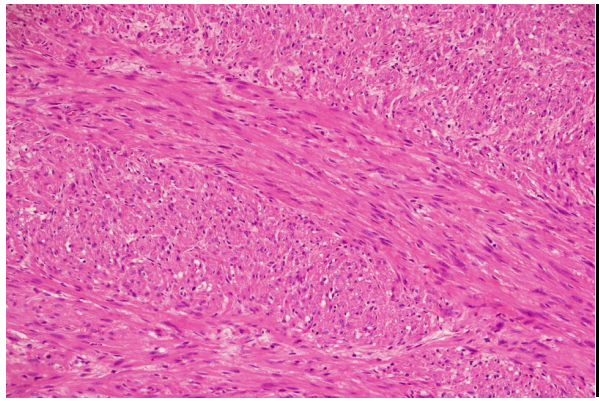
Incidence

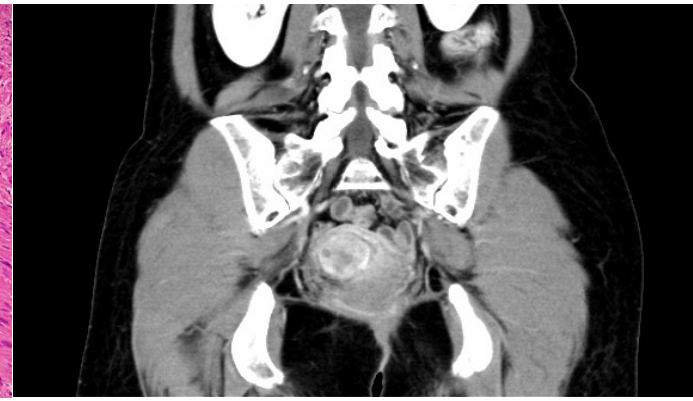


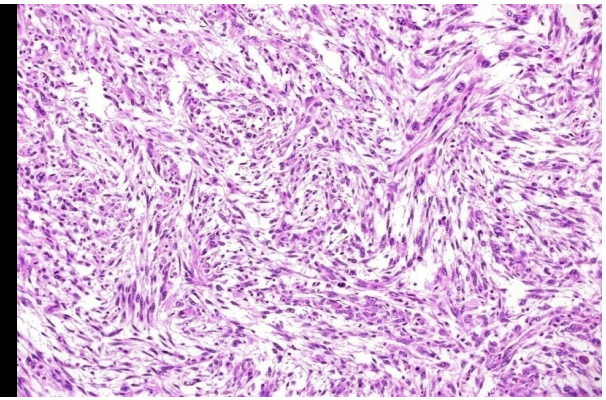
~ 0.5 /100.000/years

1% malignant uterine tumor

Leiomyoma versus Leiomyosarcoma





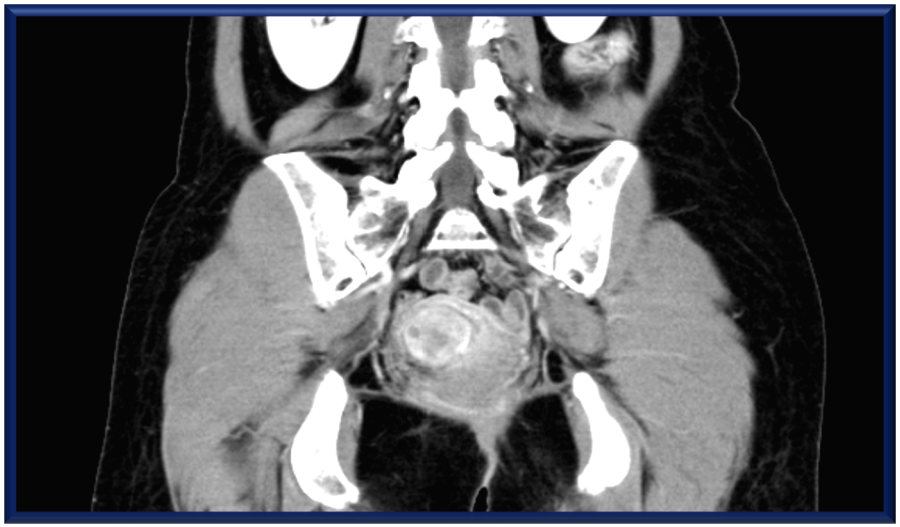


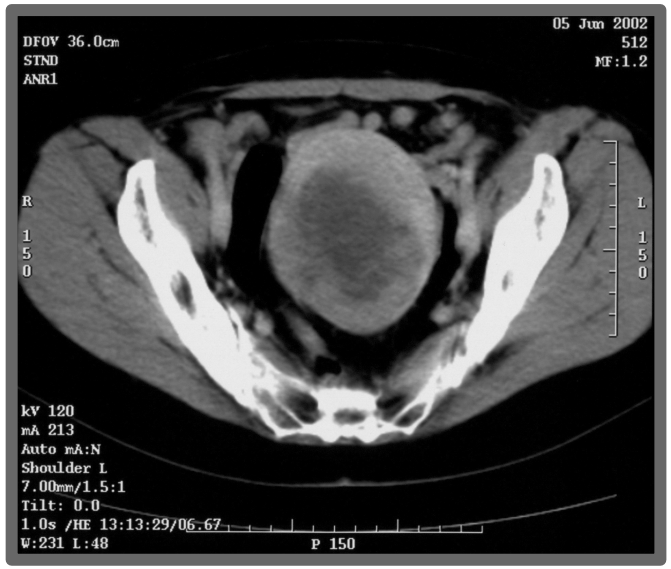
leiomyoma

leiomyosarcoma

- **1/3 of women have fibroids**
- **1/100.000 has a uterine sarcoma**
- **no reable preoperative tecniche to differenziate**
- **1/500 fibroid operated turns out to be LMS**

Post-operative diagnosis





Original Article

Retrospective Cohort Study Evaluating the Impact of Intraperitoneal Morcellation on Outcomes of Localized Uterine Leiomyosarcoma

Suzanne George, MD[1]; Constance Barysauskas, MS[2]; César Serrano, MD[1]; Titilope Oduyebo, MD[3]; Jose A. Rauh-Hain, MD[4]; Marcela G. Del Carmen, MD[4]; George D. Demetri, MD[1]; and Michael G. Muto, MD[3]

BACKGROUND: Uterine leiomyosarcoma (ULMS) is identified in 0.1% to 0.2% of hysterectomy specimens of presumed leiomyoma. To date, there is no preoperative technique that reliably differentiates ULMS from uterine leiomyoma. Increasing use of minimally invasive approaches for the management of leiomyomas may result in inadvertently morcellated ULMS with resultant intraperitoneal dissemination of tumor. The objective of this study was to assess the impact of intraperitoneal morcellation on the outcomes of patients with ULMS. **METHODS:** In this retrospective cohort study, all patients with ULMS who attended the authors' institutions from 2007 to 2012 were reviewed. Demographics and outcomes were compared between those who underwent morcellation or total abdominal hysterectomy (TAH) as their first surgery for uterus-limited ULMS. **RESULTS:** In total, 58 patients were identified, including 39 who underwent TAH and 19 who underwent intraperitoneal morcellation. Intraperitoneal morcellation was associated with a significantly increased risk of abdominal/pelvic recurrences ($P = .001$) and with significantly shorter median recurrence-free survival (10.8 months vs 39.6 months; $P = .002$). A multivariate adjusted model demonstrated a >3 times increased risk of recurrence associated with morcellation (hazard ratio, 3.18; 95% confidence interval, 1.5-6.8; $P = .003$). **CONCLUSIONS:** Intraperitoneal morcellation of presumed leiomyoma worsens the outcomes of women with ULMS. Because there are no reliable preoperative techniques to distinguish ULMS from benign leiomyoma, all efforts to minimize intraperitoneal uterine morcellation should be considered. [See editorial on pages 000-000, this issue.] ***Cancer* 2014;120:3154-8.**

KEYWORDS: uterine leiomyosarcoma, uterine sarcoma, morcellation, hysterectomy, outcomes.

Study Quantifies Cancer Risk of Morcellation

CME & CE

Published: Jul 23, 2014 | Updated: Jul 24, 2014

By Charles Bankhead, Staff Writer, MedPage Today
Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner

save | A A

One of every 368 women treated with a power morcellator had unsuspected uterine cancer identified during or after their procedures, a review of more than 200,000 patients showed.

Medical records showed that morcellation, or the fragmentation of the uterus into smaller pieces, was performed in 36,470 cases and 99 of the women subsequently had uterine cancer diagnoses. In addition, 26 other gynecologic malignancies were identified, along with 39 uterine lesions of uncertain malignant potential and 368 cases of endometrial hyperplasia.

A review of potentially predictive factors showed that older age was the only factor associated with underlying uterine malignancy or endometrial hyperplasia, as reported in a research letter published

For best viewing, click the bottom right corner for full screen.

Action Points

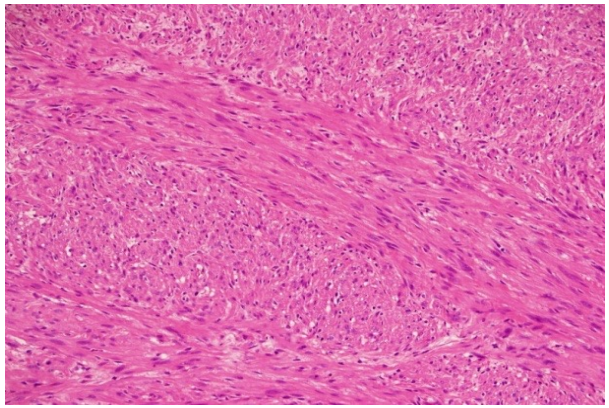
- One of every 368 women treated with a power morcellator -- a device that fragments the uterus into smaller pieces -- had unsuspected uterine cancer identified during or after their procedures.

FDA NEWS RELEASE

For Immediate Release: April 17, 2014
Media Inquiries: Jennifer Rodriguez, 301-796-8232, jennifer.rodriguez@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA, dice@fda.hhs.gov

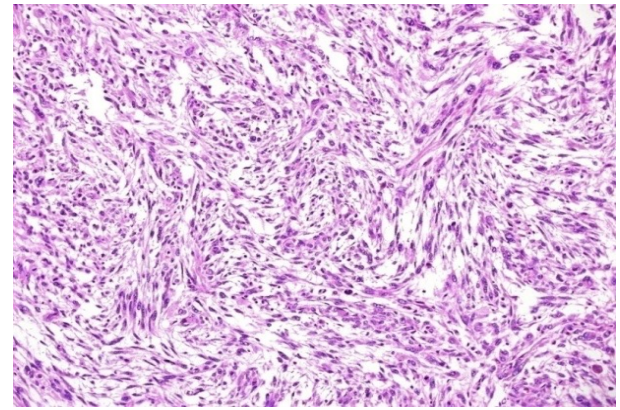
FDA discourages use of laparoscopic power morcellation for removal of uterus or uterine fibroids
Procedure poses risk of spreading undetected cancerous tissue in women with unsuspected cancer

In a safety communication notice issued today, the U.S. Food and Drug Administration discouraged the use of laparoscopic power morcellation for the removal of the uterus (hysterectomy) or uterine fibroids (myomectomy) in women because, based on an analysis of currently available data, it poses a risk of spreading unsuspected cancerous tissue, notably uterine sarcomas, beyond the uterus.



leiomyoma

STUMP



leiomyosarcoma

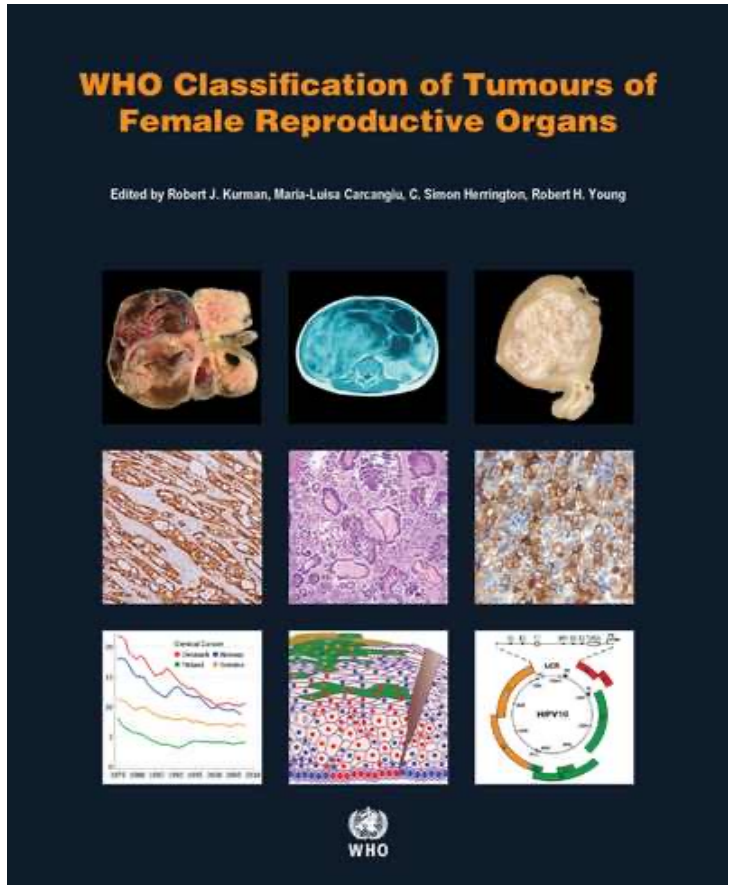
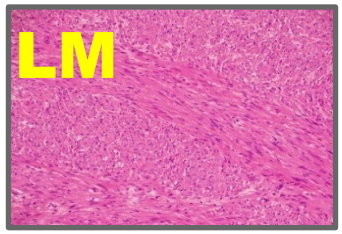
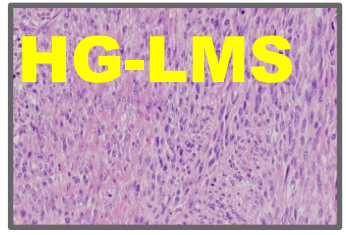


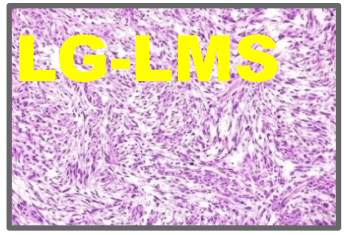
Table 5.1 Uterine smooth-muscle tumours with spindle-cell differentiation of uncertain malignant potential.

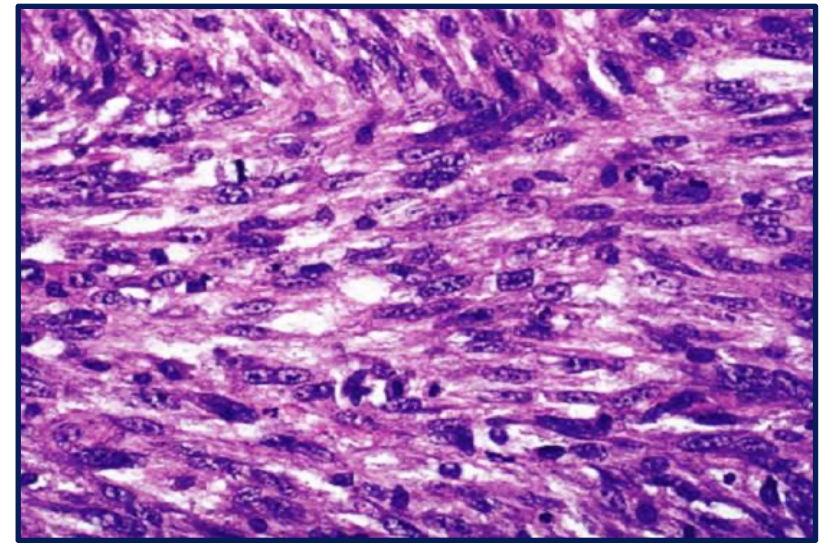
Tumour cell necrosis	Moderate-to-severe atypia	Mitotic count (per 10 HPF)	Mean mitotic count in tumours with recurrence (per 10 HPF)	Cases with recurrence
Absent	Focal/multifocal	< 10	4 (range 3–5)	13.6% (3 of 22 cases) {68 ,811}
	Diffuse	< 10	4.3 (range 2–9)	10.4% (7 of 67 cases) {129,145,1865,1981}*
Present	None	< 10	2.8 (range 1–4)	26.7% (4 of 15 cases) {41,68,129}
Absent	None	≥ 15	Not applicable	0% (0 of 39† cases) {129,811}

*One of the four tumours also had epithelioid cells
†Three had ≥ 20 mitotic figures per 10 HPF; an unknown proportion also had counts between 10 and 14 {129}.









STUMP

"Low-Grade Leiomyosarcoma" and Late-Recurring Smooth Muscle Tumors of the Uterus: A Heterogenous Collection of Frequently Misdiagnosed Tumors Associated With an Overall Favorable Prognosis Relative to Conventional Uterine Leiomyosarcomas

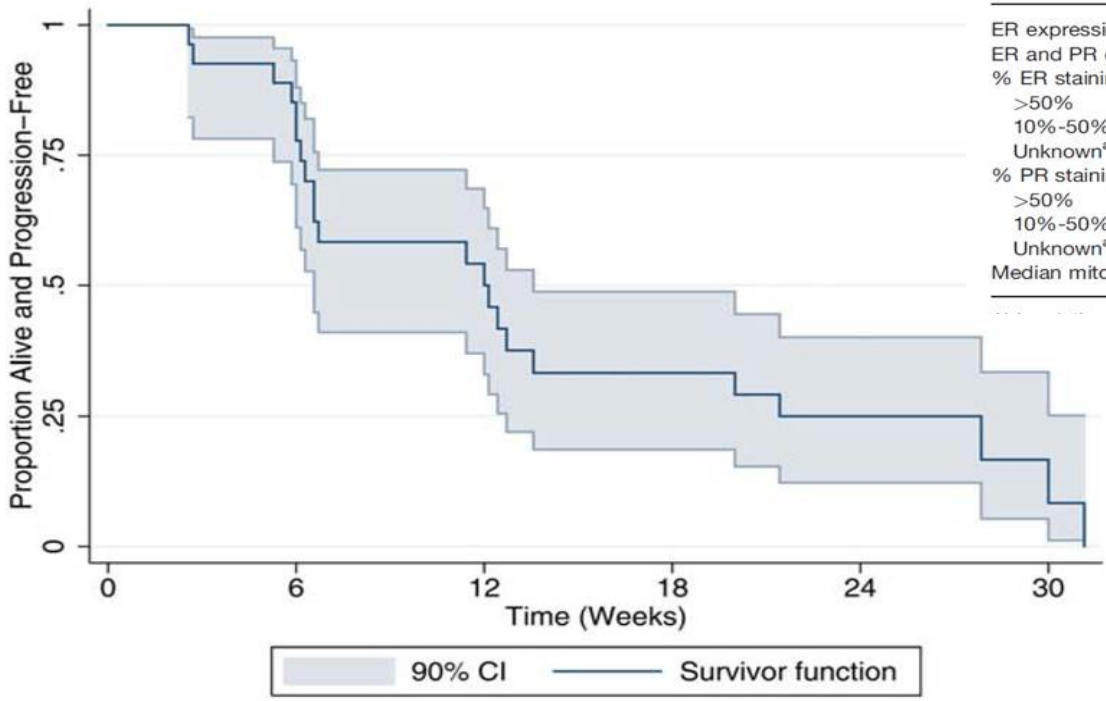
Emanuela Veras, Oliver Zivanovic,† Lindsay Jacks,‡ Daniel Chiappetta,* Martee Hensley,§ and Robert Soslow, MD**

Whether "low-grade" uterine LMSs indeed exist is a matter still open for debate; however, when Stanford criteria are strictly applied, all tumors classified as LMSs should be regarded as intrinsically "high grade."

(*Am J Surg Pathol* 2011;35:1450–1461)

Phase 2 Trial of Aromatase Inhibition With Letrozole in Patients With Uterine Leiomyosarcomas Expressing Estrogen and/or Progesterone Receptors

Suzanne George, MD[1]; Yang Feng, MS[2]; Judith Manola, MS[2]; Marisa R. Nucci, MD[3]; James E. Butrynski, MD[1]; Jeffrey A. Morgan, MD[1]; Nikhil Ramaiya, MD[4]; Richard Quek, MD[1]; Richard T. Penson, MD[5]; Andrew J. Wagner, MD, PhD[1]; David Harmon, MD[5]; George D. Demetri, MD[1]; and Carolyn Krasner, MD[5]

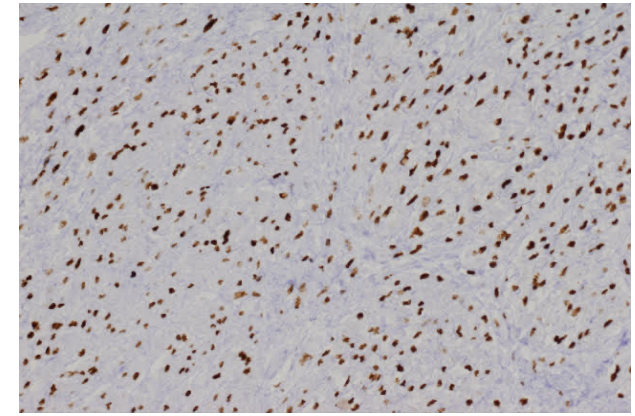


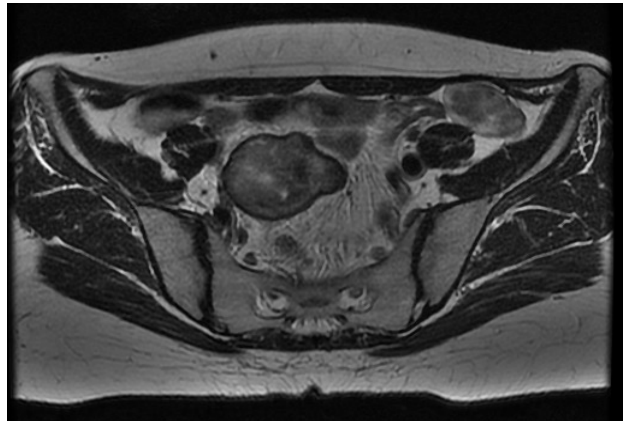
Characteristic	No. (%)
ER expression only	4 (15)
ER and PR coexpression	22 (85)
% ER staining	
>50%	8 (31)
10%-50%	8 (31)
Unknown[a]	10 (38)
% PR staining	
>50%	7 (27)
10%-50%	7 (27)
Unknown[a]	12 (46)
Median mitotic count per 10 HPF (range)	23 (3-100)

Cancer 2013, Epub

Leiomyosarcoma with an indolent clinical course

- F, 40 yrs
- Diagnosis of U-LMS with ERr+ PRGr+
- Only locally relapsing disease
- Response to aromatase inhibitors after progression to chemotherapy





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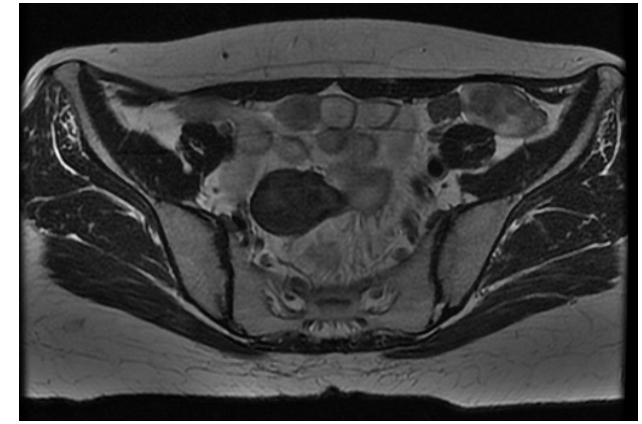


2 mos of aromatase inhibitors

Established in 1997, the National Leiomyosarcoma Foundation meets the needs of patients, caregivers, and families through education, resources, and research funding.

NLMSF - SPAEN

INTERNATIONAL LMS RESEARCH ROUNDTABLE

Achieving More Together in the Quest for the Cure

THE HEROES OF HOPE AMONG US!

A global initiative bringing together the Sarcoma Research Community for a collaborative focus on the future of Leiomyosarcoma investigational research/clinical trials with a mission of:

- **Bringing together the sarcoma experts to have a focused meeting only on Leiomyosarcoma**
- **Discussing/Understanding the present state of LMS and the continued challenges of diagnosis/treatment**
- **Developing work plans to close the gaps/Improve LMS patient-care protocol**
- **Advising and directing the NLMSF on LMS precision research projects for solicitation and funding for 2020 and beyond**


LMS established cell lines
Mercer University
LMS1
University of Sheffield
NCC report
Toulouse-France
SYLVESTER

Working Group

▪Gyn Onc Working Group	Roberta Sanfilippo, MD Istituto Tumori, Milan
▪Clinical Trials Working Group	Bernd Kasper, MD, PhD Mannheim University
▪PDX/Cell line Working Group	Matthew Hemming, MD, Dana-Farber Cancer
▪Multiomics Working group	Paul Huang, Ph Institute of Cancer Research, London

Gynecological Leiomyosarcoma working group

Scientific coordinator: **Roberta Sanfilippo**

Objectives

1) To work out a clinical-radiological tool improving the differential diagnosis of leiomyosarcomas (LMS) from leiomyomas (LM).

2) To give rise to an international consensus process about the existence of low-grade uterine leiomyosarcoma.

Rationale

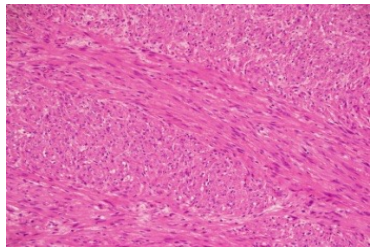
Uterine leiomyosarcomas (ULMS) represent 1-2% of all uterine neoplasms. They are the most common type of uterine sarcoma, with an incidence around 0.5/100,000 women per year. While 10-20% of cases present as metastatic, the long-term survival of localized-disease patients averages 50%. Thus, they are challenging diseases. Two challenges are highly peculiar.

The first challenge is that we lack clinical criteria to differentiate radiologically leiomyosarcomas from leiomyomas (fibroids), these being one of the most common benign conditions (1 woman in 3 has a uterine leiomyoma). Thus, leiomyosarcomas are usually diagnosed as an unexpected finding of the pathology report after a surgical intervention made with the clinical diagnosis of leiomyoma. Therefore, establishing clear-cut and reliable differential diagnostic criteria between leiomyomas and leiomyosarcomas would be crucial.

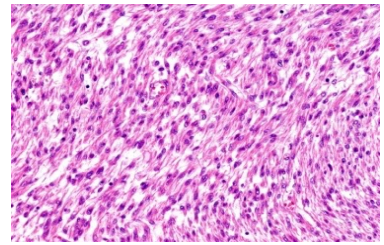
The second challenge is pathological. First, the differential pathologic diagnosis of a leiomyosarcoma may be challenging. However, a special challenge is posed by the so-called "smooth muscle tumors of undefined malignant potential" (STUMP). This label essentially reflects a difficulty in the differential diagnosis between a leiomyoma and a leiomyosarcoma. In essence, this might be viewed as a mere challenging diagnostic issue. Alternatively, one might speculate that a subgroup of uterine leiomyosarcomas have features of essentially "low-grade" tumors, such that their differential diagnosis from leiomyomas may be less easy and their behaviour may be less aggressive. Possibly, both alternatives might take place in different patients. Indeed, pathologists are sometimes confronted with uterine leiomyosarcomas that they would label as "low-grade" if arising from other anatomical sites. Actually, the relapse rate of STUMP is low (in the 10-20% range) and the time to relapse may be rather long. Current classifications do not recognize an entity such as a low-grade leiomyosarcoma, leiomyosarcomas being assumed to be high-grade malignancies by default. On the contrary, if a subset of low-grade leiomyosarcomas do exist, they might be sensitive to hormonal therapies. This means that a better understanding of their nature could have therapeutic implications.

Objectives…

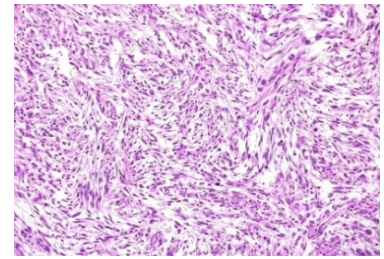
1) To work out a clinical-radiological tool improving the differential diagnosis of leiomyosarcoma from leiomyoma



leiomyoma



STUMP



leiomyosarcoma

2) To give rise to an international consensus process about the existence of “low grade uterine leiomyosarcoma”

EXPERTS...


NORTH
AMERICA
EUROPE
AFRICA
SOUTH
AMERICA
AUSTRALIA
SOUTHWEST
PACIFIC
BASIN
ANTARCTICA

EXPERTS...

Pathologists

- ***A. Paolo Dei Tos, Padova, IT***
- ***Marta Sbaraglia, Padova, IT***
- ***Marisa Nucci, BWH, Boston, US***
- ***Christopher Fletcher, DFC Boston, US***

EXPERTS...

Clinicians

- Roberta Sanfilippo, INT , Milan, IT
- PaoloG. Casali, INT, Milan, IT
- Jonathan Trent, SCC, Miami, US
- Susanne George, DFCC, Boston, US
- Robin Jones, RM, London, England
- Oliver Mir, CRC, Lyon , FR
- Martee Hensley, MSKCC, NY
- Evan Rosenbaum , MSKCC, NY
- Isabel Raycoquard, Lyon , FR
-Rebecca Gladdy , Toronto
Peter Hohenberger, Mannheim, Germany

EXPERTS...

Radiologists:

-Fiona Fennessey, Brigham and Women's Hospital/Dana-Farber Cancer Institute, US
-Antonella Messina, INT Milan

Molecular biologists:
-Roberta Maestro, Aviano, IT

Epidemiologists:
-Annalisa Trama, INT, Milano, IT

Statisticians:
-Paolo Bruzzi, Genoa, IT

NATIONAL LEIOMYOSARCOMA FOUNDATION
NLMSF.ORG
Support • Education • Advocacy • Research
Moving forward in the quest for the cure!

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

SMOOTH MUSCLE TUMORS OF UNCERTAIN MALIGNANT POTENTIAL (STUMP): AN OBSERVATIONAL STUDY

CLINICAL STUDY PROTOCOL

Sponsor
Fondazione IRCCS Istituto Nazionale Tumori
Via G. Venezian, 1
20133 Milano

Principal Investigator
Roberta Sanfilippo, MD
Fondazione IRCCS Istituto Nazionale Tumori
Via G. Venezian, 1
20133 Milano

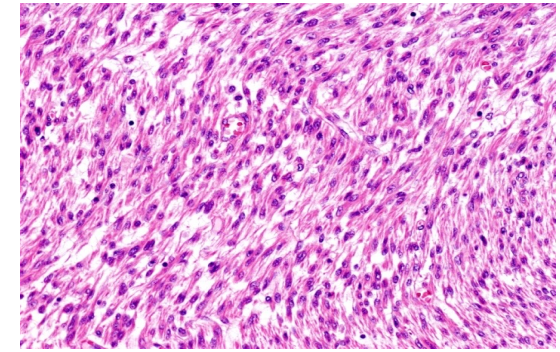
Version June 2020

Study population:

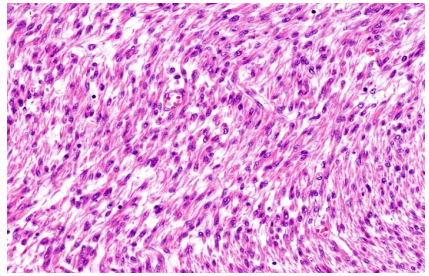
- All patients with a diagnosis of localized, advanced, or relapsed STUMP (according to WHO 2020) will be included in this study

Objectives:

- ✓to provide new data on the natural history of STUMP;
- ✓to highlight some main issues in pathologic diagnosis of these tumors and their classification;
- ✓to establish the activity of hormonal treatment in the advanced and metastatic setting;

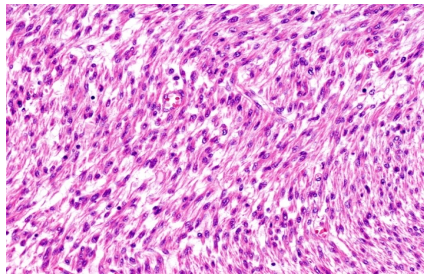


- **INT, Milan, Italy (R. Sanfilippo)**
- **→ Italian Sarcoma Group**
- **Centre Leon Berard, Lyon, France (I. Ray Coquard)**
- **Royal Marsden H, London (R. Jones)**
- **……**



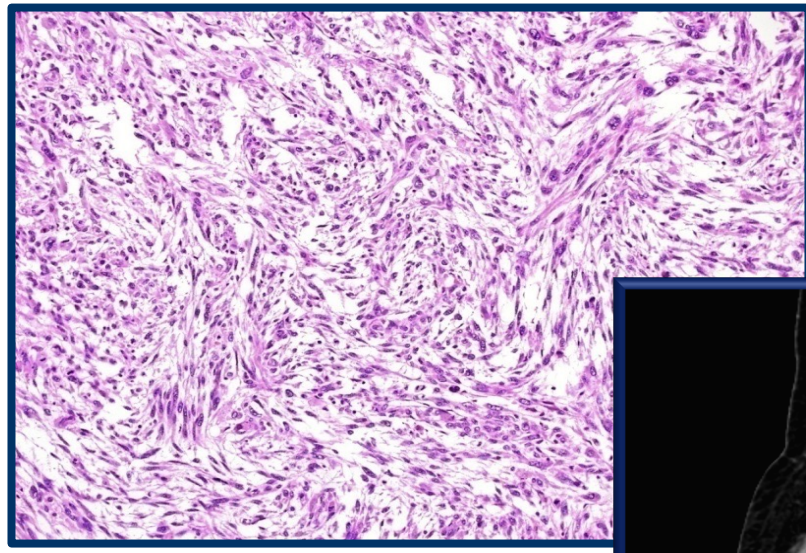
Professor Dei Tos , Padua

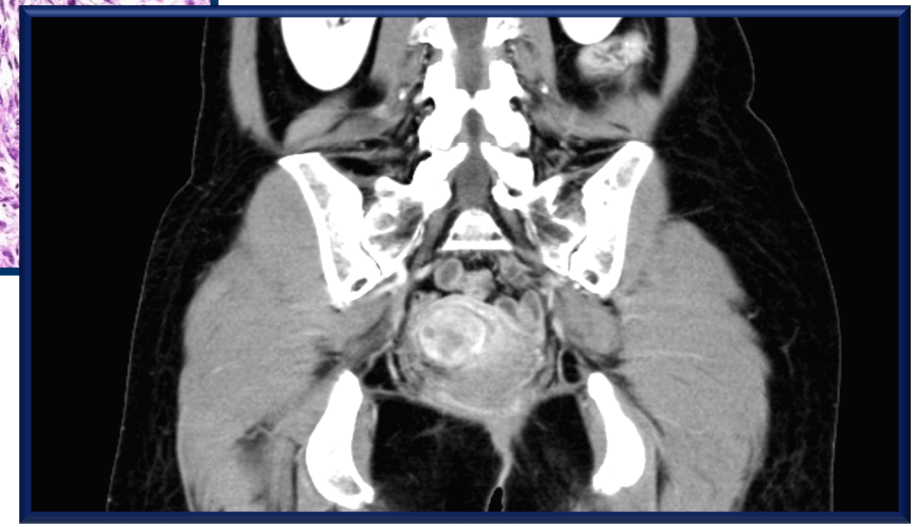
- Dana Faber, Boston (S. George)
- MSKCC, NY (M Hensly)
- SCC, Miami (J. Trent)
- Mayo Clinic, Rochester (S. Okuno)
- Mount Sinai Hospital, Toronto (R. Gladdy)



M. Nucci , Boston

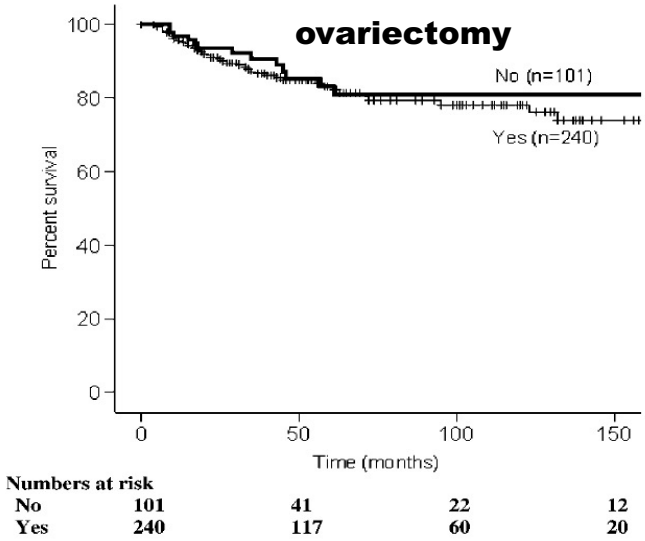
Leiomyosarcoma

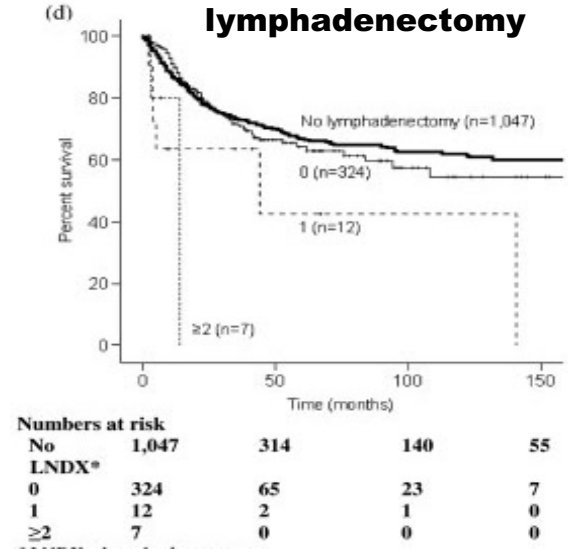




Standard Treatment

- Histerectomy + ovariectomy
- Ovaries preserved in pre menopausal
  <3% M ovaries
- No lymphadenectomy
  N+ 2-5%



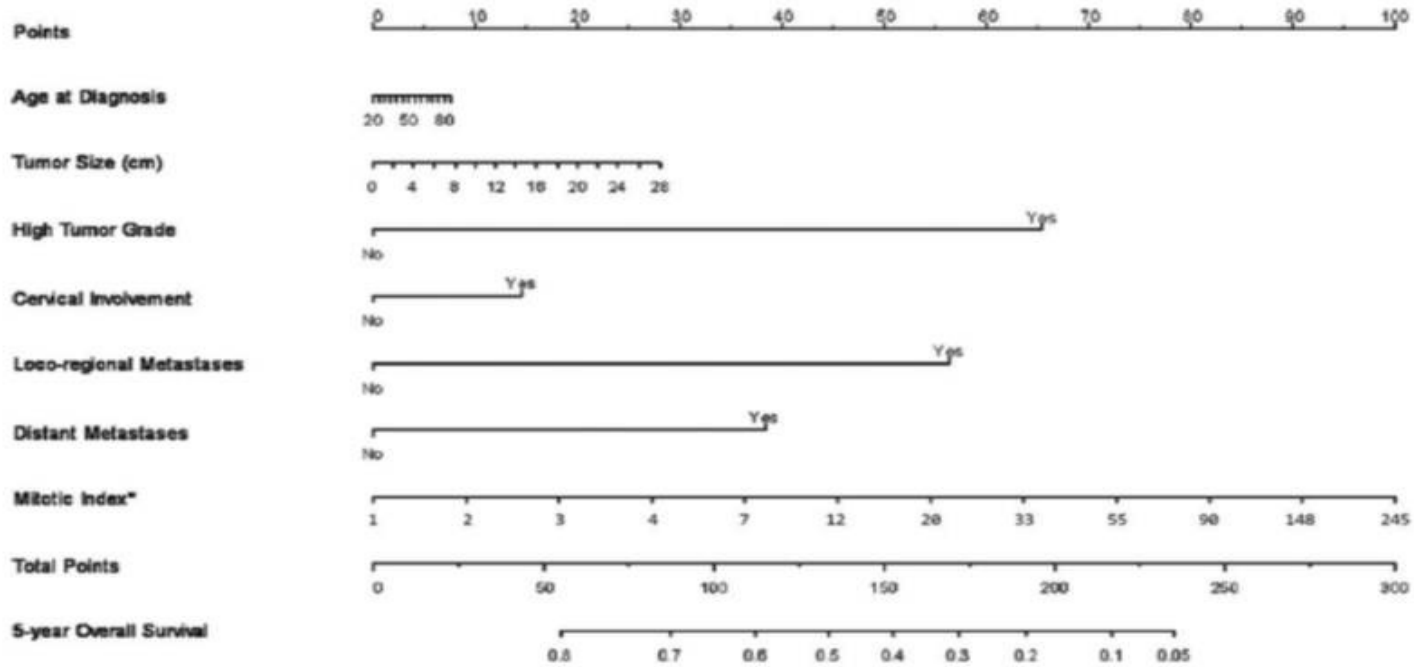


Kapp DS, et al. Cancer 2008;15: 820-830.

Original Article

A Nomogram to Predict Postresection 5-Year Overall Survival for Patients With Uterine Leiomyosarcoma

Oliver Zivanovic, MD[1]; Lindsay M. Jacks, MS[2]; Alexia Iasonos, PhD[2]; Mario M. Leitao, Jr., MD[1]; Robert A. Soslow, MD[3]; Emanuela Veras, MD[3]; Dennis S. Chi, MD[1]; Nadeem R. Abu-Rustum, MD[1]; Richard R. Barakat, MD[1]; Murray F. Brennan, MD[4]; and Martee L. Hensley, MD[5]



Cancer 2011

Radiotherapy ?

EUROPEAN JOURNAL OF CANCER 44 (2008) 808–818

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ScienceDirect

journal homepage: www.ejconline.com

Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874)

N.S. Reed[a,*], *C. Mangioni*[b], *H. Malmström*[c], *G. Scarfone*[d], *A. Poveda*[e], *S. Pecorelli*[f], *S. Tateo*[g], *M. Franchi*[h], *J.J. Jobsen*[i], *C. Coens*[j], *I. Teodorovic*[j], *I. Vergote*[k], *J.B. Vermorken*[l]

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Gynaecological

ABSTRACT

The management of uterine sarcomas continues to present many difficulties. Primary surgery is the optimal treatment but the role of post-operative radiation remains uncertain. In the mid-1980s, the European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study proposed a trial to evaluate adjuvant radiotherapy, as previous non-randomised studies had suggested a survival advantage and improved local control when post-operative radiation was administered. The study opened in 1987 taking 13 years to accrue 224 patients. All uterine sarcoma subtypes were permitted. Patients were required to have undergone as a minimum, TAH and BSO and wahsings (166 patients) but nodal sampling was optional. There were 103 leiomyosarcomas (LMS), 91 carcinosarcomas (CS) and 28 endometrial stromal sarcomas (ESS). Patients were randomised to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks. Hundred and twelve were recruited to each arm. The initial analysis has shown a reduction in local relapse (14 versus 24, $p = 0.006$) but no effect on either OS or PFS. No unexpected toxicity was seen in the radiation arm. No difference in either overall or disease-free survival was demonstrated but there is an increased local control for the CS patients receiving radiation but without any benefit for LMS. Prognostic factor analysis shows that stage, age and histological subtype were important predictors of behaviour which may explain differences

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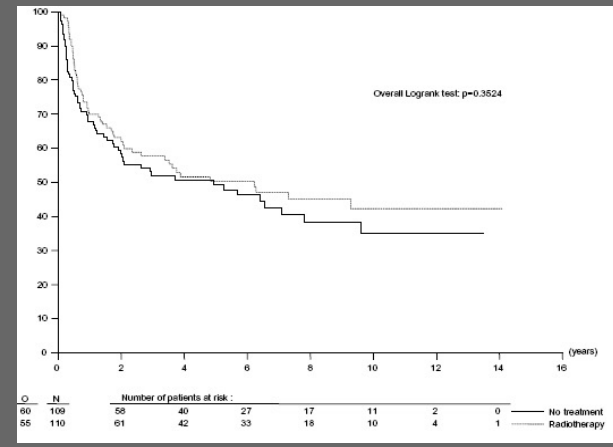
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.01.019

DFS



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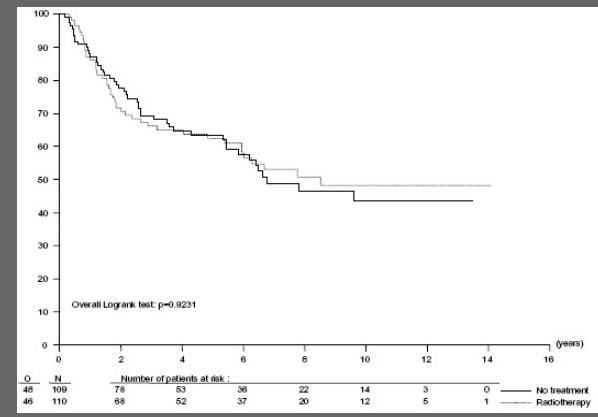


Adjuvant chemotherapy ?

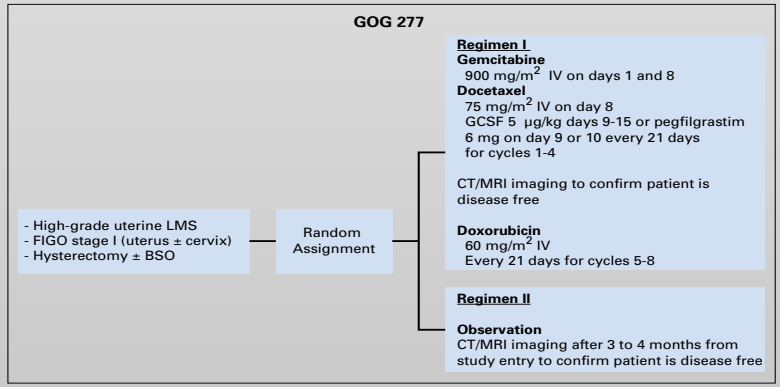
VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study

Martee L. Hensley, Danielle Enserro, Helen Hatcher, Petronella B. Ottevanger, Anders Krarup-Hansen, Jean-Yves Blay, Cyril Fisher, Katherine M. Moxley, Shashikant B. Lele, Jayanthi S. Lea, Krishnansu S. Tewari, Premal H. Thaker, Oliver Zivanovic, David M. O'Malley, Katina Robison, and David S. Miller



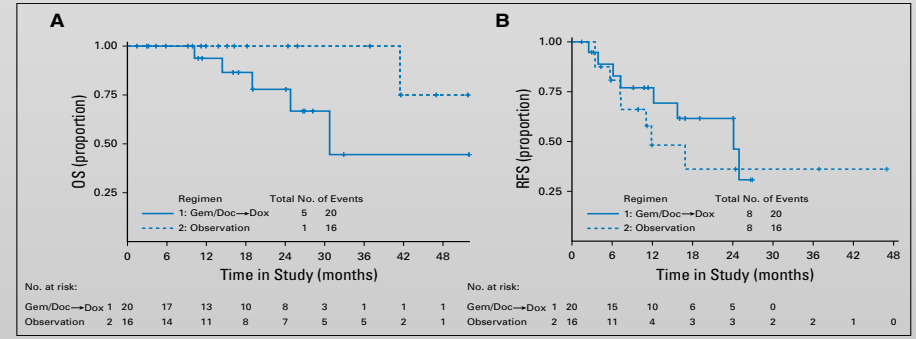


Fig 3. (A) Overall survival (OS) for adjuvant gemcitabine plus docetaxel followed by doxorubicin versus observation in GOG 0277. (B) Recurrence-free survival (RFS) for gemcitabine-docetaxel followed by doxorubicin versus observation in GOG 0277. Doc, docetaxel; Dox, doxorubicin; Gem, gemcitabine.

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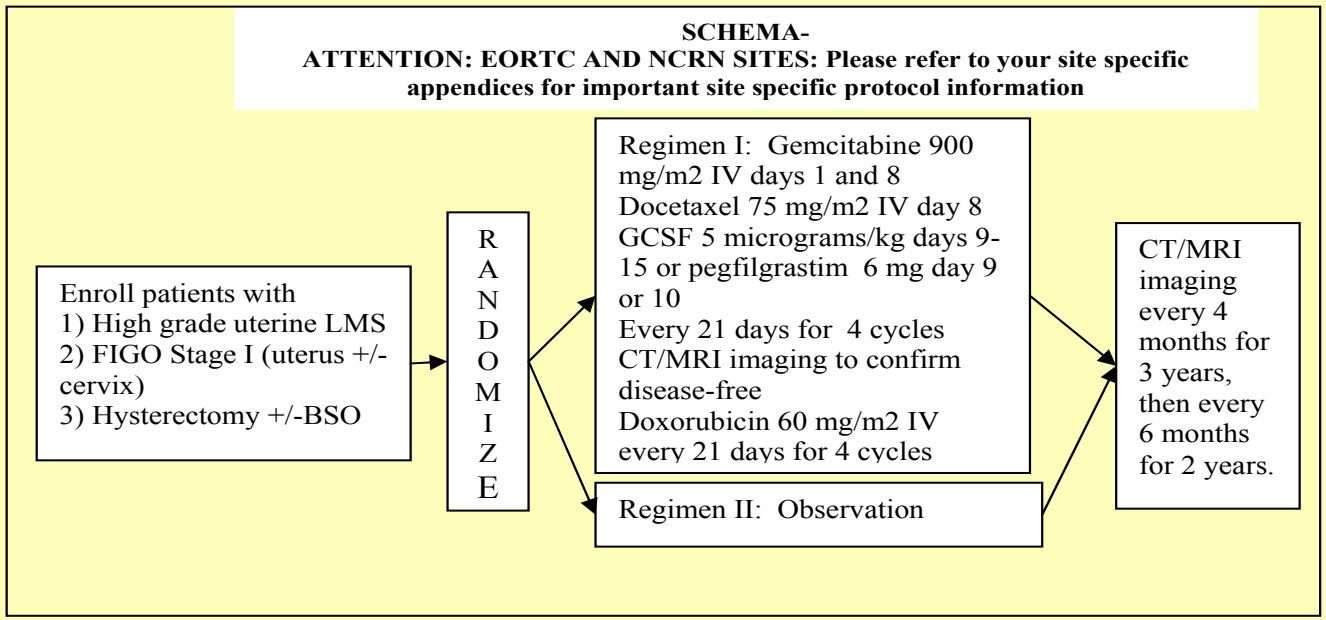
SCHEMA-
ATTENTION: EORTC AND NCRN SITES: Please refer to your site specific appendices for important site specific protocol information



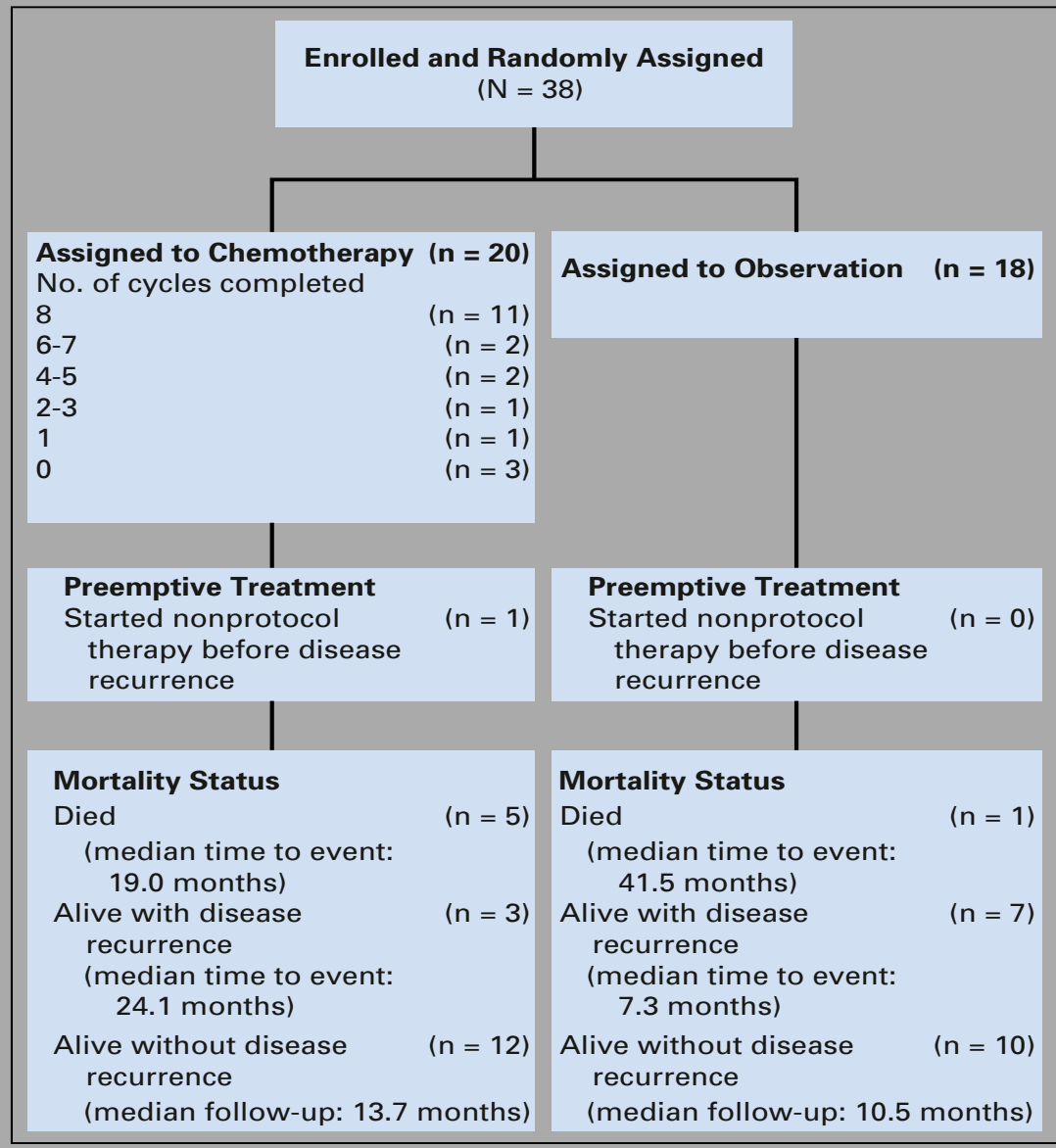


Fig 2. CONSORT diagram for GOG 0277, a randomized phase III trial.

Original Article

Adjuvant Therapy for High-Grade, Uterus-Limited Leiomyosarcoma

Results of a Phase 2 Trial (SARC 005)

Martee L. Hensley, MD[1,2]; J. Kyle Wathen, PhD[3]; Robert G. Maki, MD, PhD[4]; Dejka M. Araujo, MD[5]; Gregory Sutton, MD[6]; Dennis A. Priebat, MD[7]; Suzanne George, MD[8]; Robert A. Soslow, MD[9]; and Laurence H. Baker, DO[10]

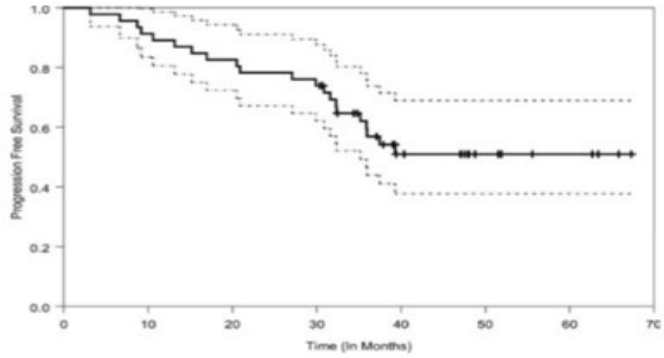


Figure 1. Progression-free survival is illustrated (n = 47). At 2 years, 75% of patients remained progression-free (95% confidence interval, 67%-91%); and, at 3 years, 57% of patients remained progression-free (95% confidence interval, 44%-74%). The median progression-free survival has not been reached.

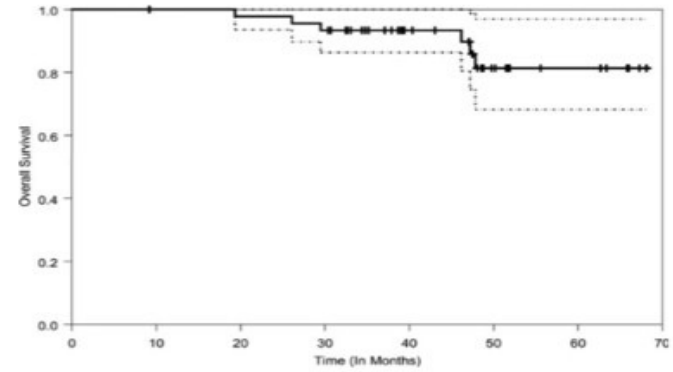
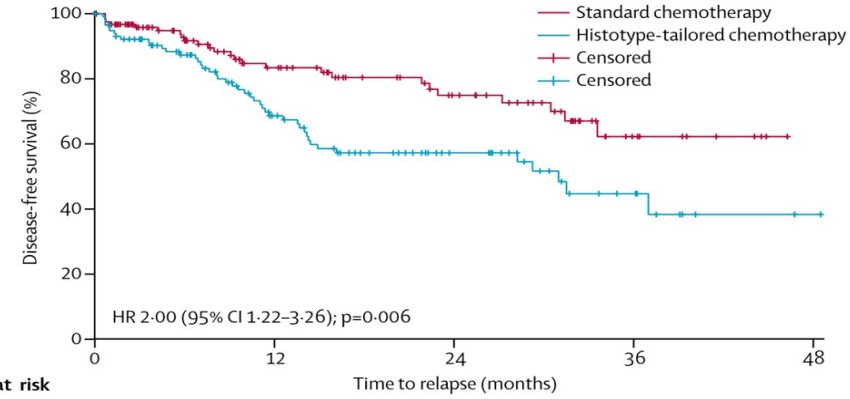


Figure 2. Overall survival is illustrated (n = 47). The median overall survival has not been reached.

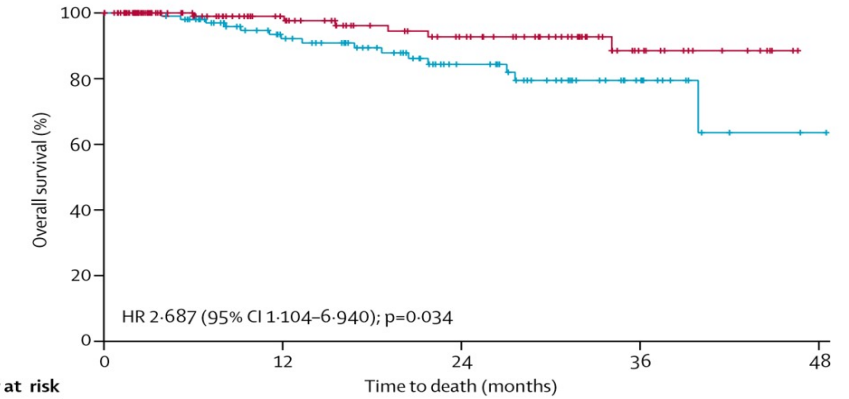
Cancer 2013;119:1555

Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali



Number at risk (number censored)					
Standard chemotherapy	144 (0)	63 (65)	37 (72)	9 (103)	0 (119)
Histotype-tailored chemotherapy	142 (0)	57 (54)	28 (70)	9 (87)	1 (95)

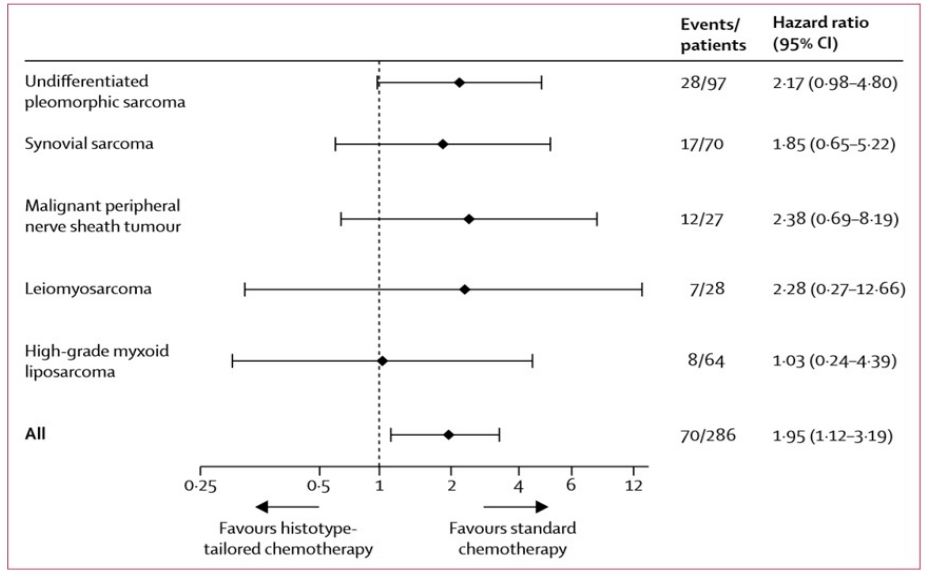


Number at risk (number censored)					
Standard chemotherapy	144 (0)	75 (68)	48 (83)	15 (89)	0 (138)
Histotype-tailored	142 (0)	72 (63)	40 (74)	13 (91)	1 (125)

Lancet Oncol 2017 [Epub]

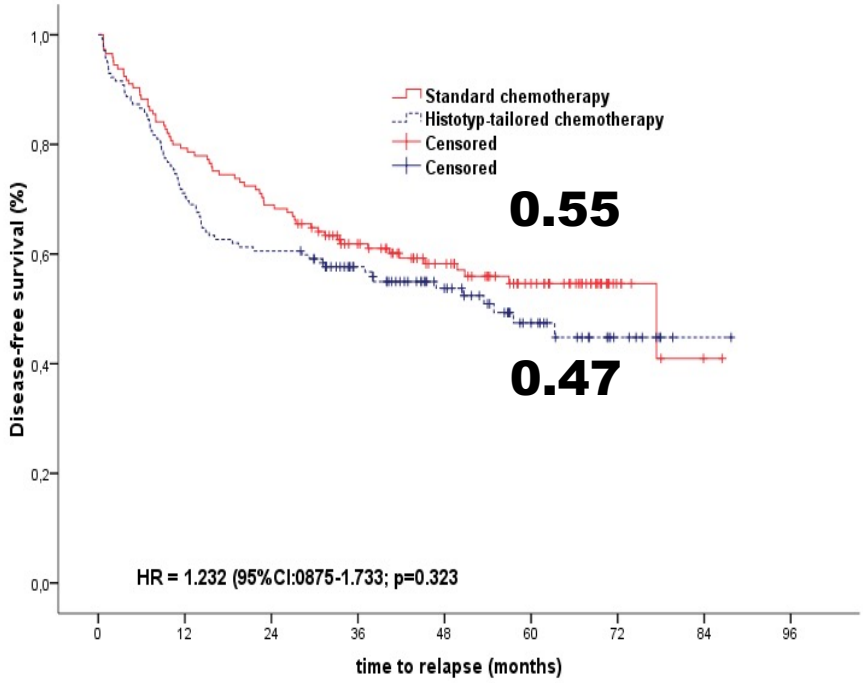
Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

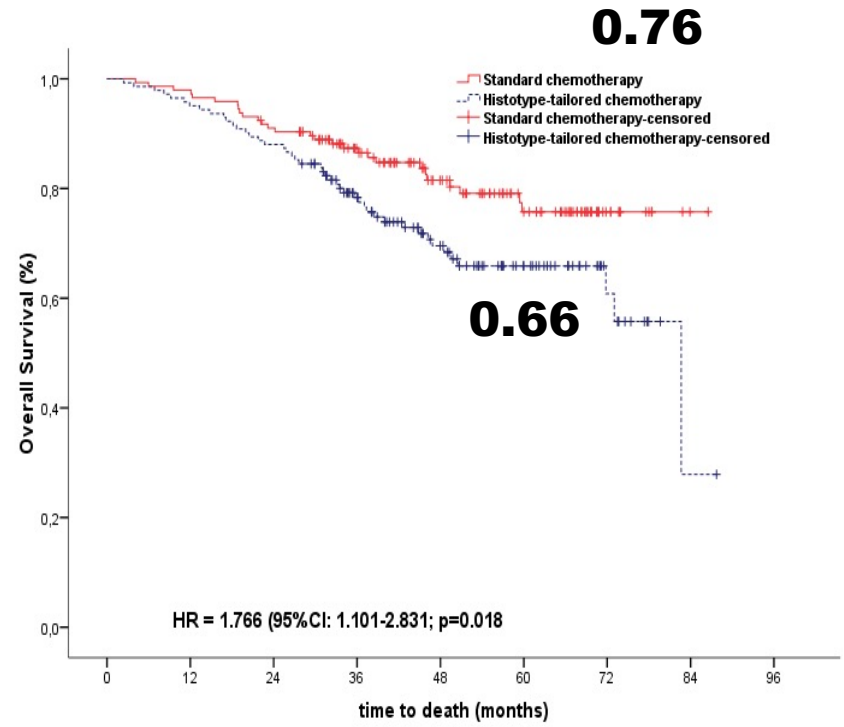
Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali



Lancet Oncol 2017 [Epub]

Median FU: 51.75 months (IQ 28.03)





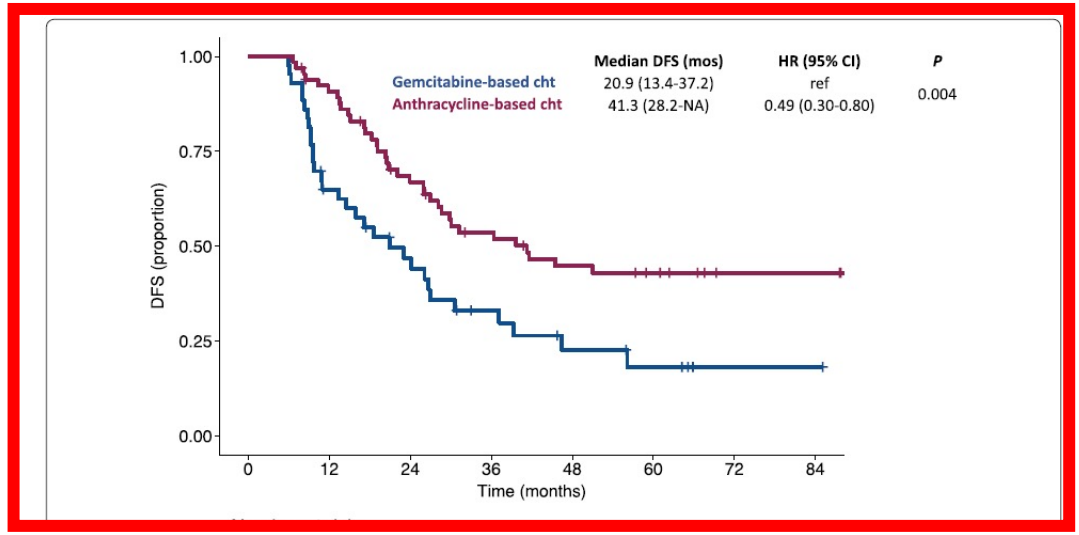
Fucà *et al. Clin Sarcoma Res* (2020) 10:17
https://doi.org/10.1186/s13569-020-00139-3

Clinical Sarcoma Research

RESEARCH Open Access

Anthracycline-based and gemcitabine-based chemotherapy in the adjuvant setting for stage I uterine leiomyosarcoma: a retrospective analysis at two reference centers

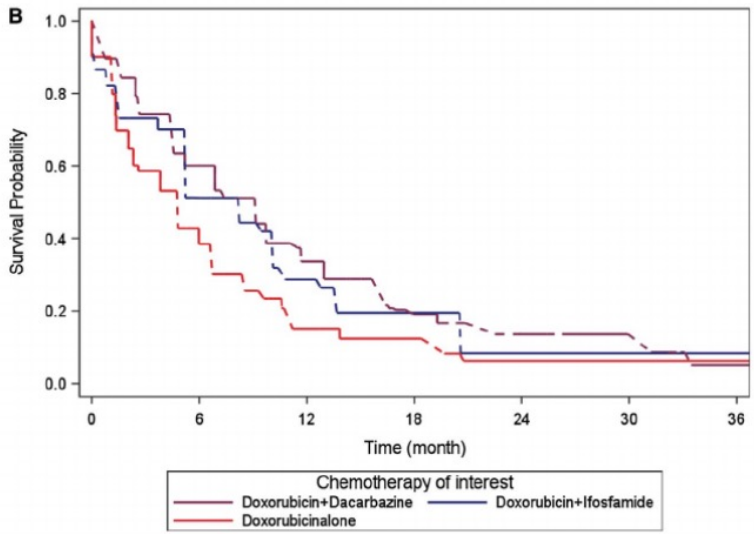
Giovanni Fucà[1], Chiara Fabbroni[1], Rosanna Mancari[2], Sara Manglaviti[1], Giorgio Bogani[3], Elena Fumagalli[1], Rossella Bertulli[1], Carlo Morosi[4], Paola Collini[5], Francesco Raspagliesi[3], Nicoletta Colombo[2,6], Paolo G. Casali[1,7] and Roberta Sanfilippo[1*]

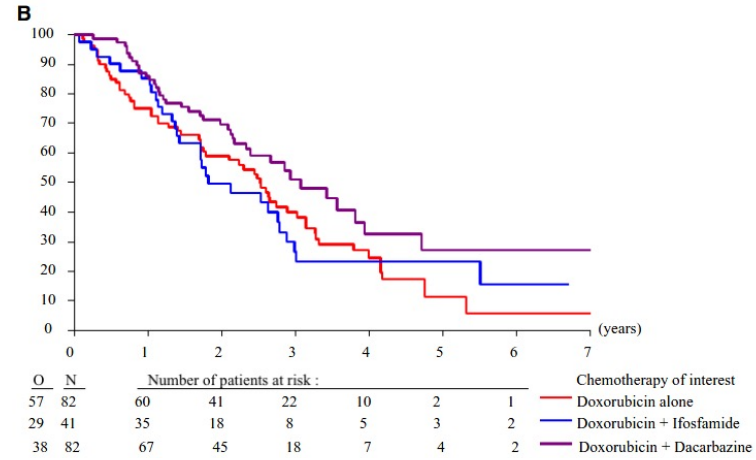


Original Article

Doxorubicin Plus Dacarbazine, Doxorubicin Plus Ifosfamide, or Doxorubicin Alone as a First-Line Treatment for Advanced Leiomyosarcoma: A Propensity Score Matching Analysis From the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

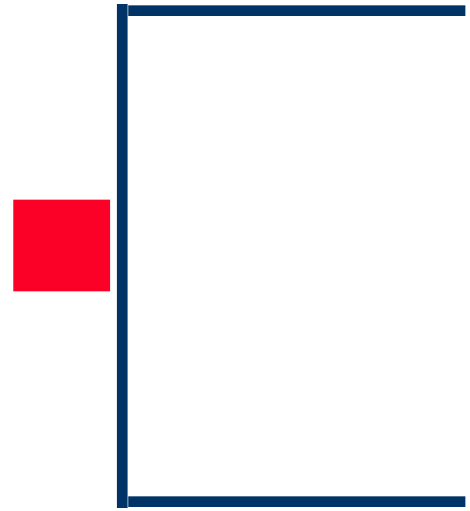
Lorenzo D'Ambrosio, MD, PhD [1,2]; Nathan Touati, PhD[3]; Jean-Yves Blay, MD [4]; Giovanni Grignani, MD [2]; Ronan Flippot, MD[5]; Anna M. Czarnecka, MD[6,7]; Sophie Piperno-Neumann, MD[8]; Javier Martin-Broto, MD[9]; Roberta Sanfilippo, MD[10]; Daniela Katz, MD[11]; Florence Duffaud, MD[12]; Bruno Vincenzi, MD[13]; Daniel P. Stark, MD[14]; Filomena Mazzeo, MD[15]; Armin Tuchscherer, MD[16]; Christine Chevreau, MD [17]; Jenny Sherriff, MD[18]; Anna Estival, MD[19]; Saskia Litière, PhD[3]; Ward Sents, PhD[3]; Isabelle Ray-Coquard, MD, PhD[4]; Francesco Tolomeo, MD[2]; Axel Le Cesne, MD[5]; Piotr Rutkowski, MD [6,7]; Silvia Stacchiotti, MD [10]; Bernd Kasper, MD [20]; Hans Gelderblom, MD[21]; and Alessandro Gronchi, MD [22]; on behalf of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group





U-LMS : treatments

- Local disease

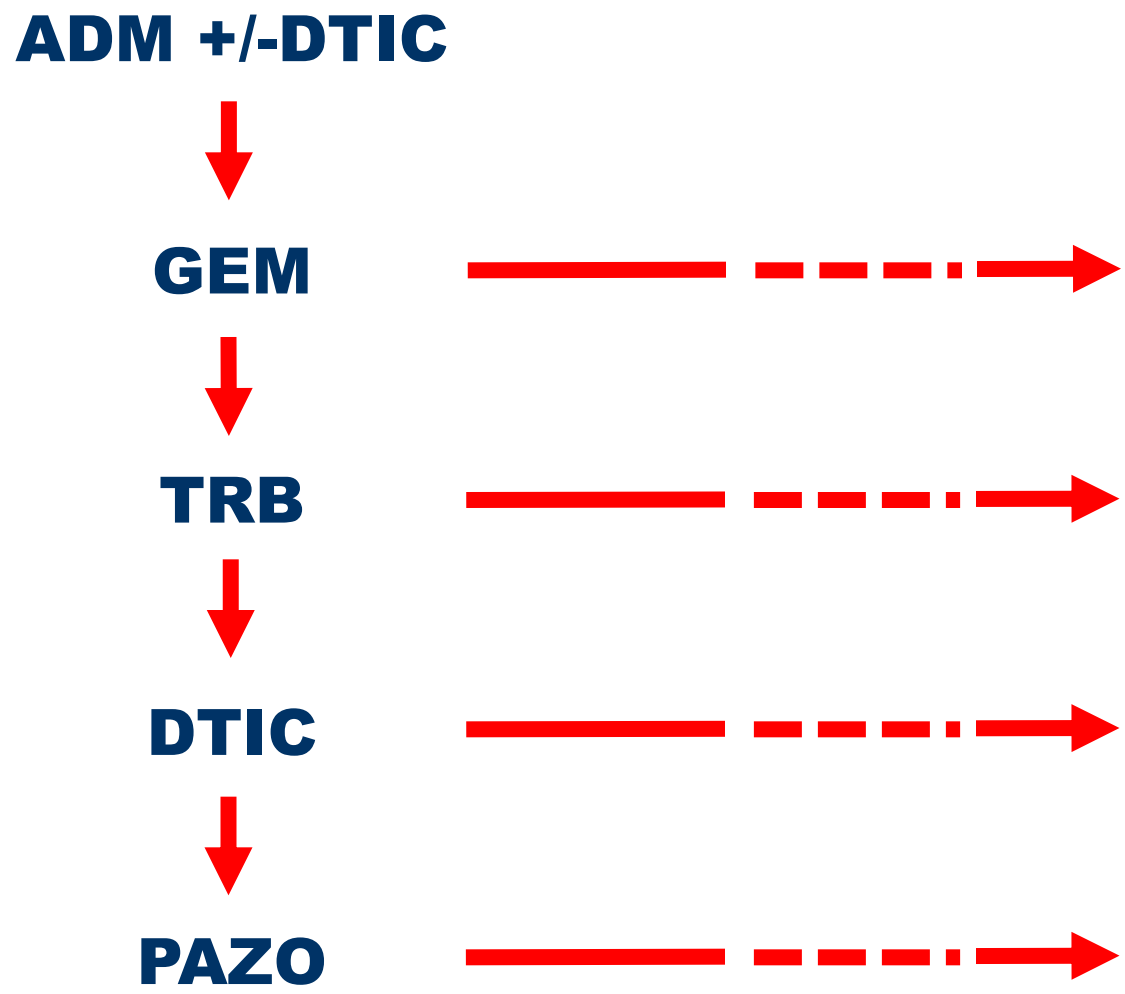


- Surgery +/- AD CT

- Advance disease

- ADM+/-DTC
- GEM
- TRABE
- DTC
- PAZOPANIB

Leiomyosarcoma



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]

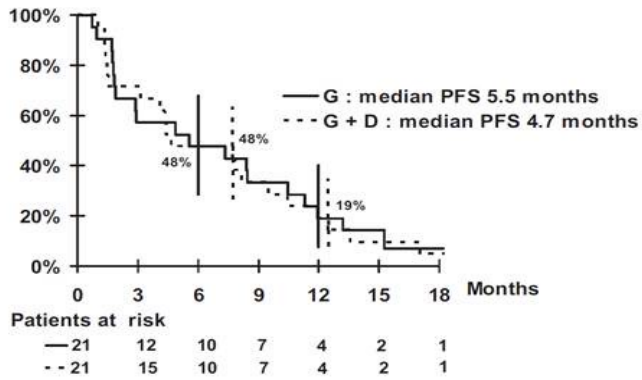


Figure 1. Kaplan–Meier curve of progression-free survival for the uterine leiomyosarcoma group.

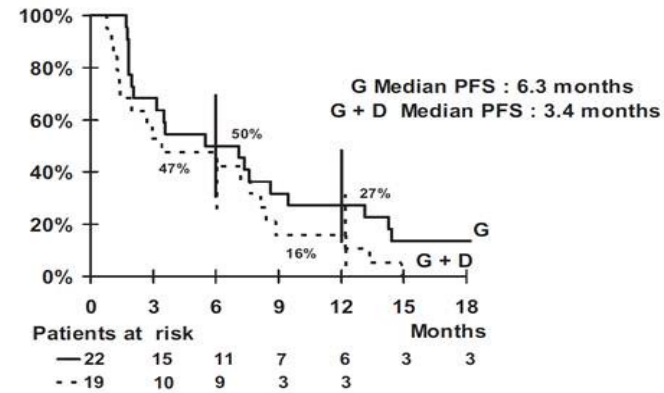
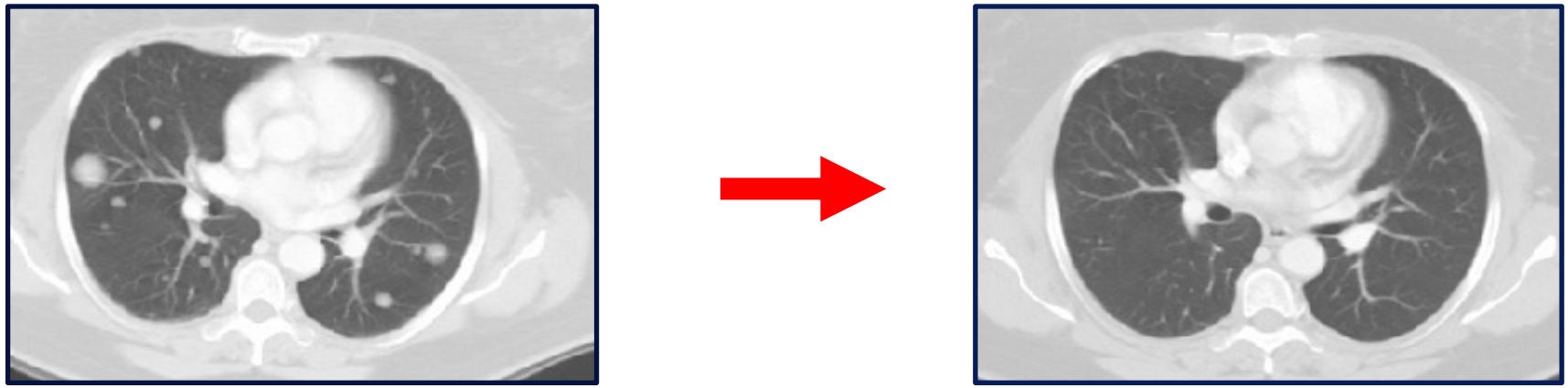


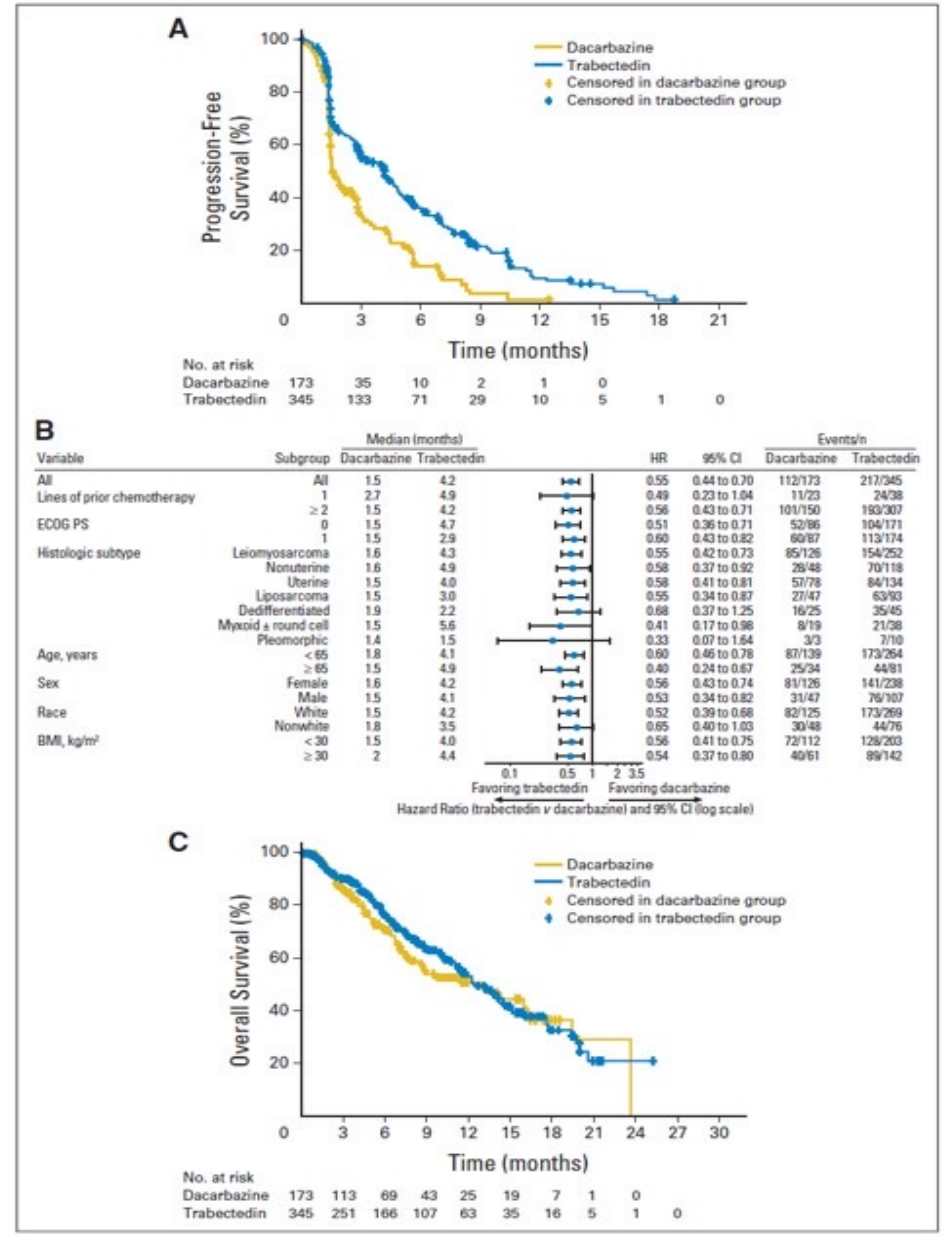
Figure 2. Kaplan–Meier curve of progression-free survival for the nonuterine leiomyosarcoma group.

Gemcitabine in LMS



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

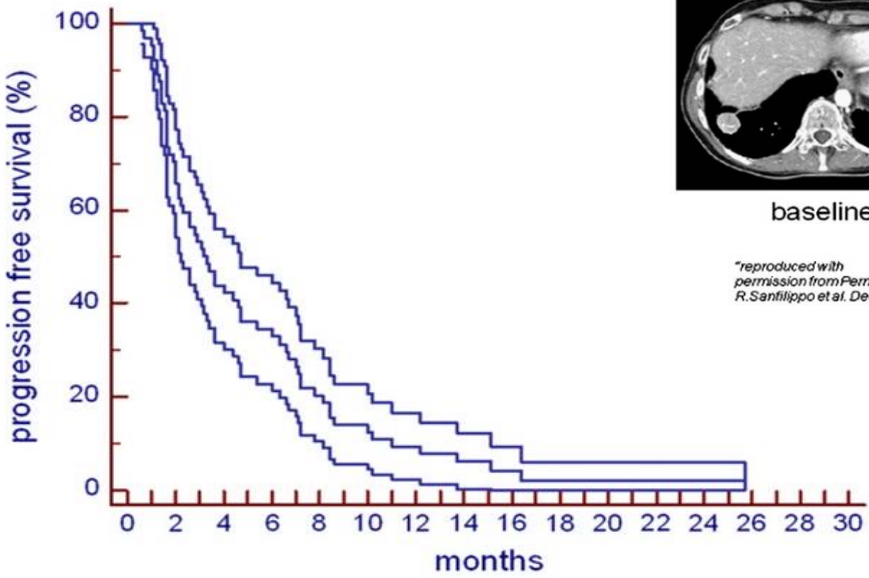
Contents lists available at SciVerse ScienceDirect

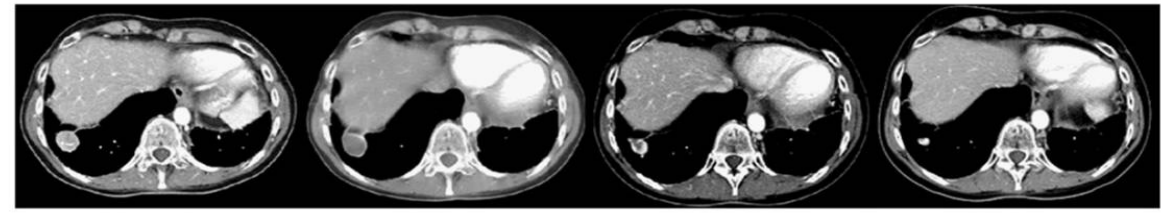
Gynecologic Oncology

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]





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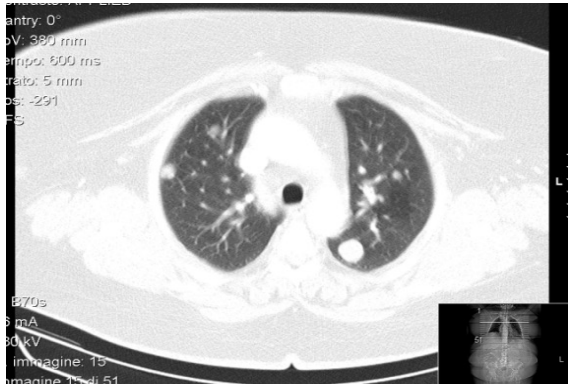
R.Sanfilippo et al. Decrease in tumor density with Yondelis® as a prelude to tumor response

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

Trabectedin



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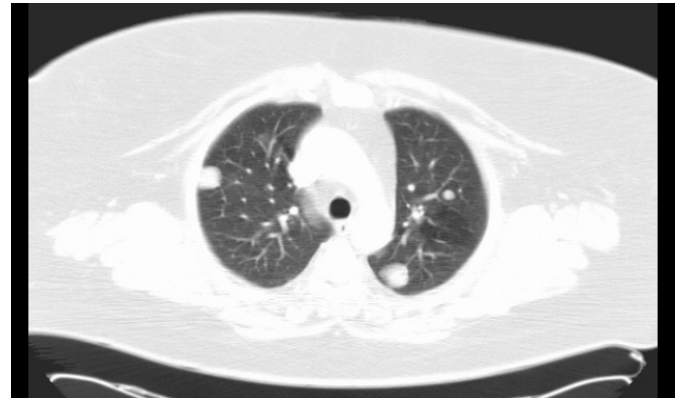

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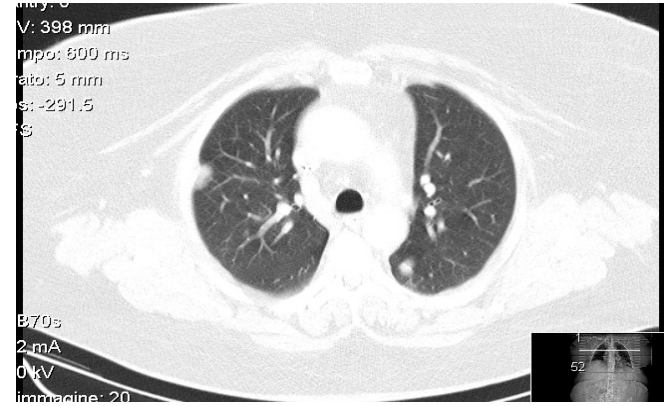


+10 c

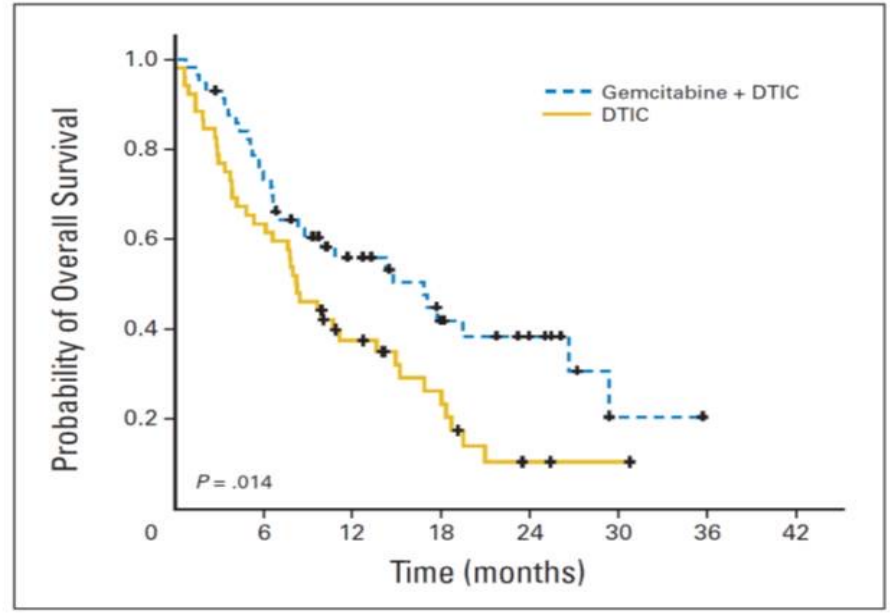
VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

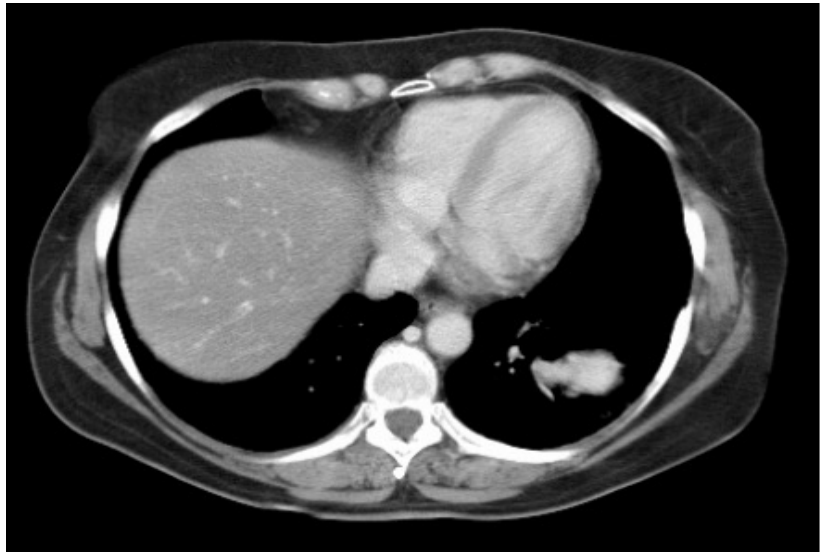
ORIGINAL REPORT

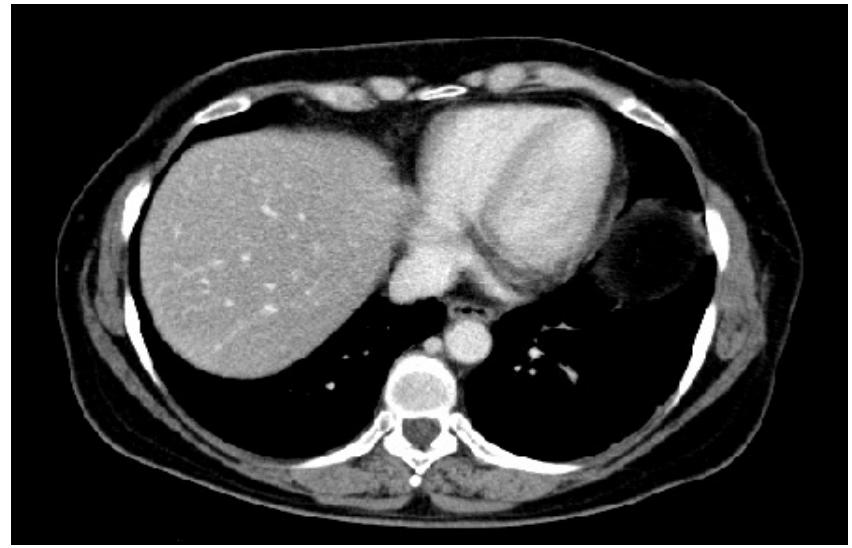
Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

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†



Leiomyosarcoma: Dacarbazine



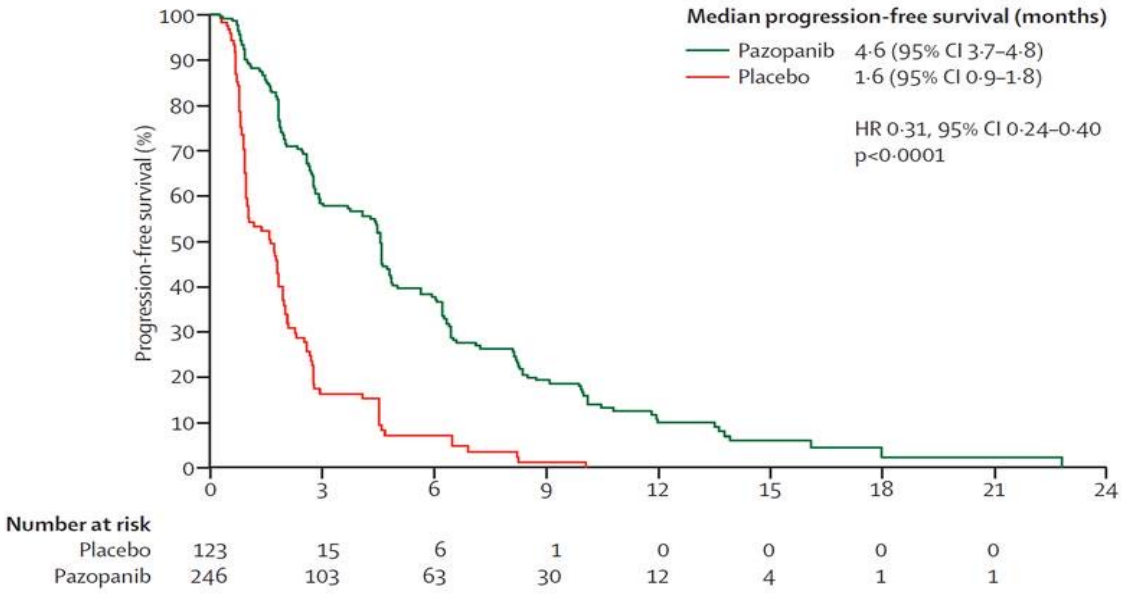


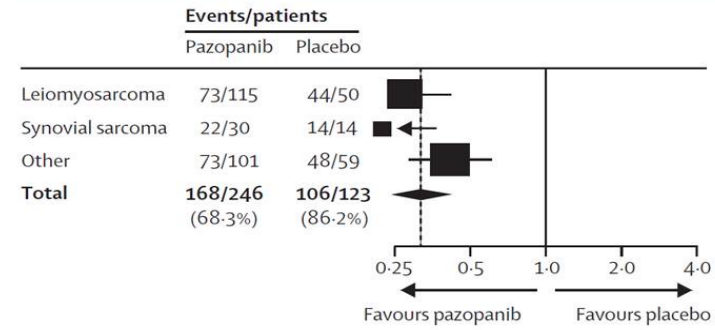
0

DTIC x 2….52 tot !

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

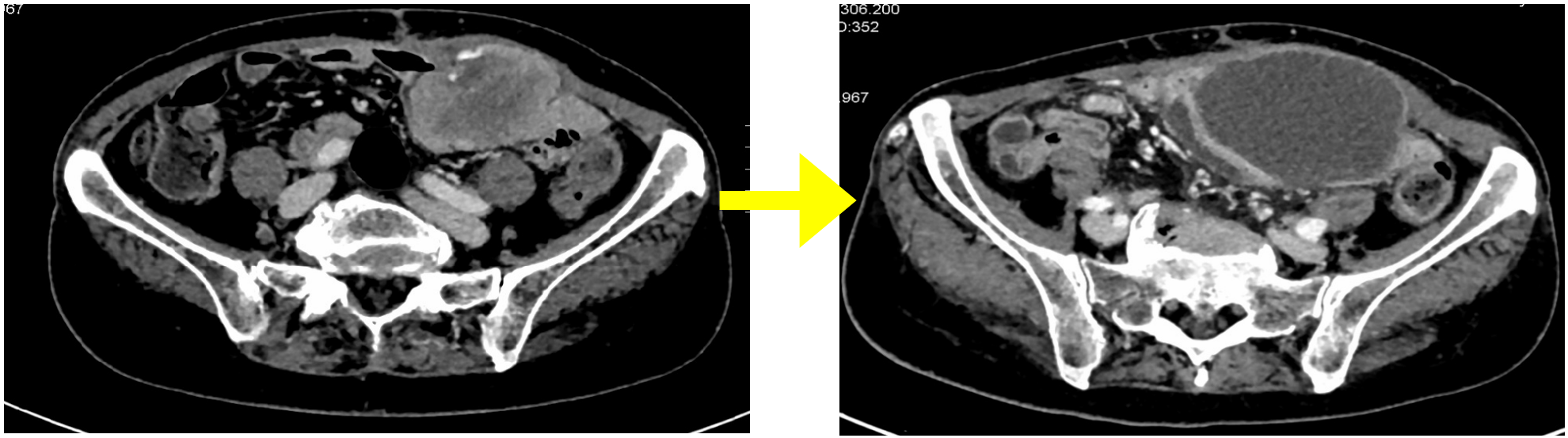
Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel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





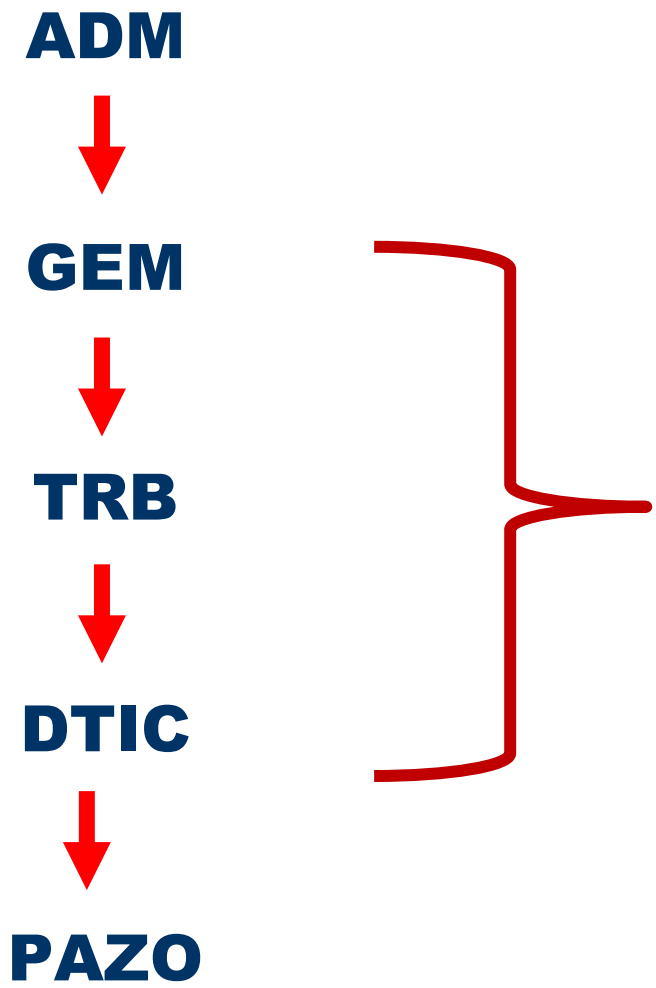
Lancet 2012;379:1879

Pazopanib



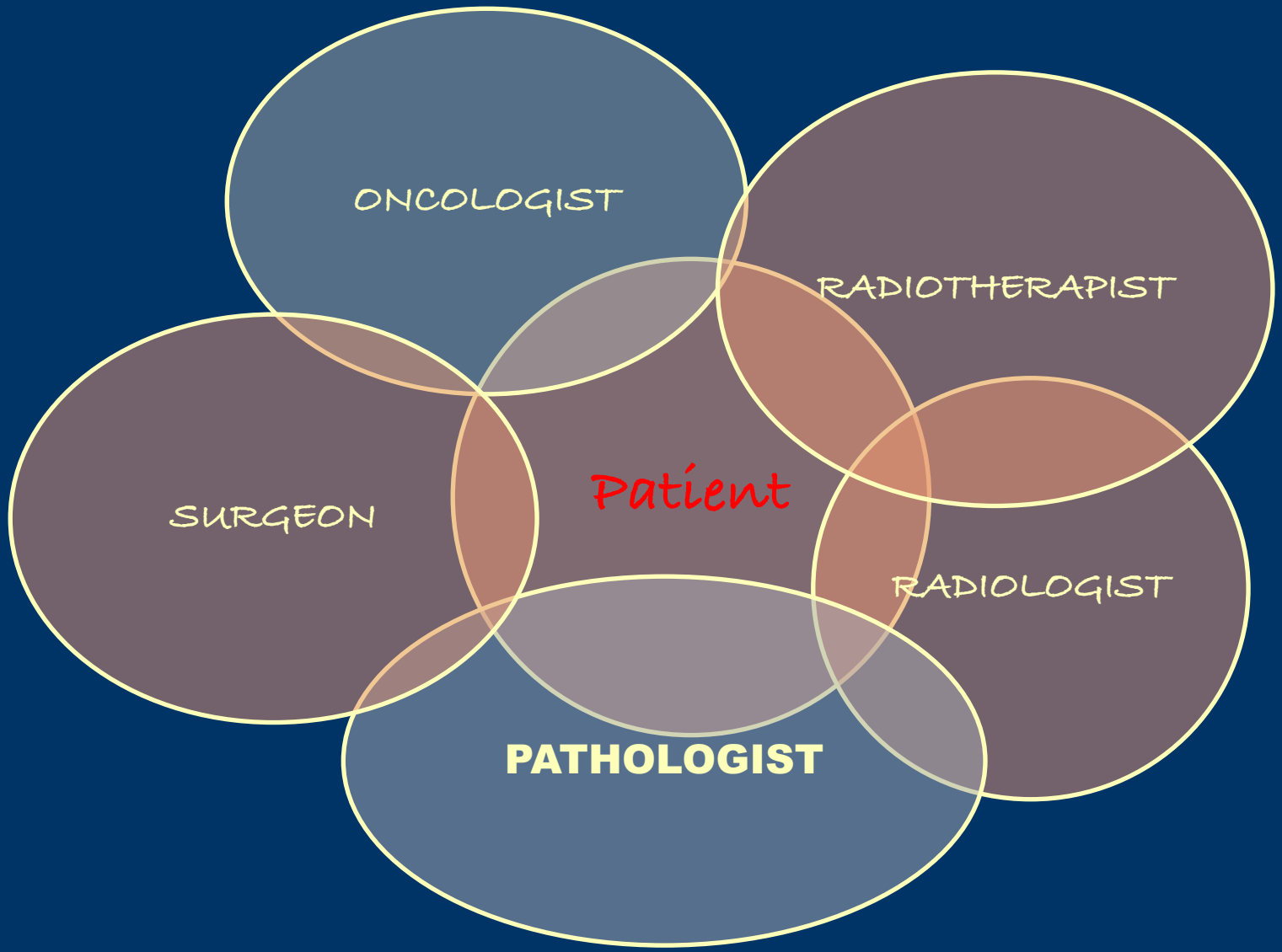
+ 2 months

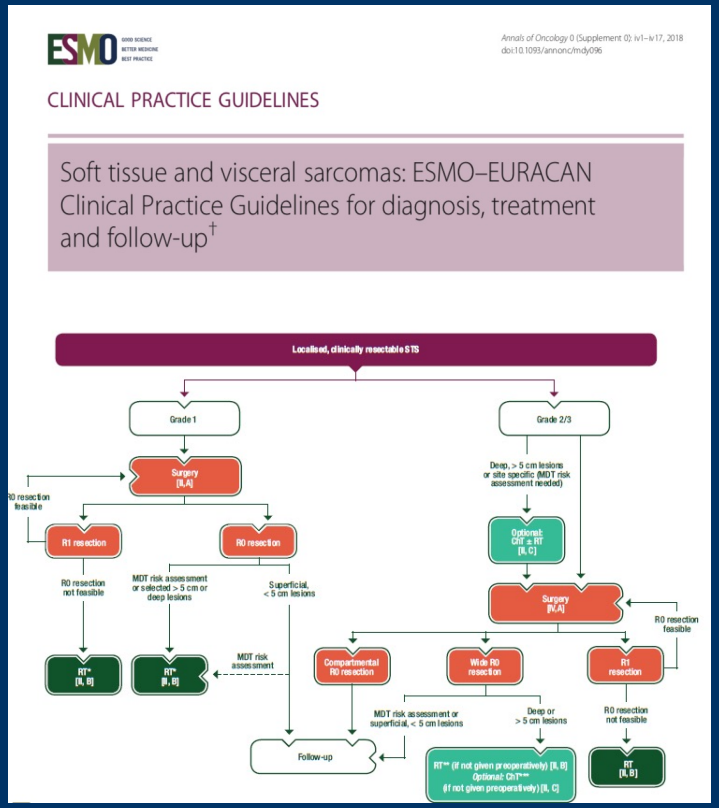
Leiomyosarcoma



- ✓ Good QoL
- ✓No TOP dose
- ✓ Limited side effects
- ✓No alopecia

Integrated Treatments





ESMO

Annals of Oncology 0 (Supplement 0): iv1–iv17, 2018
doi:10.1093/annonc/mdy096

CLINICAL PRACTICE GUIDELINES

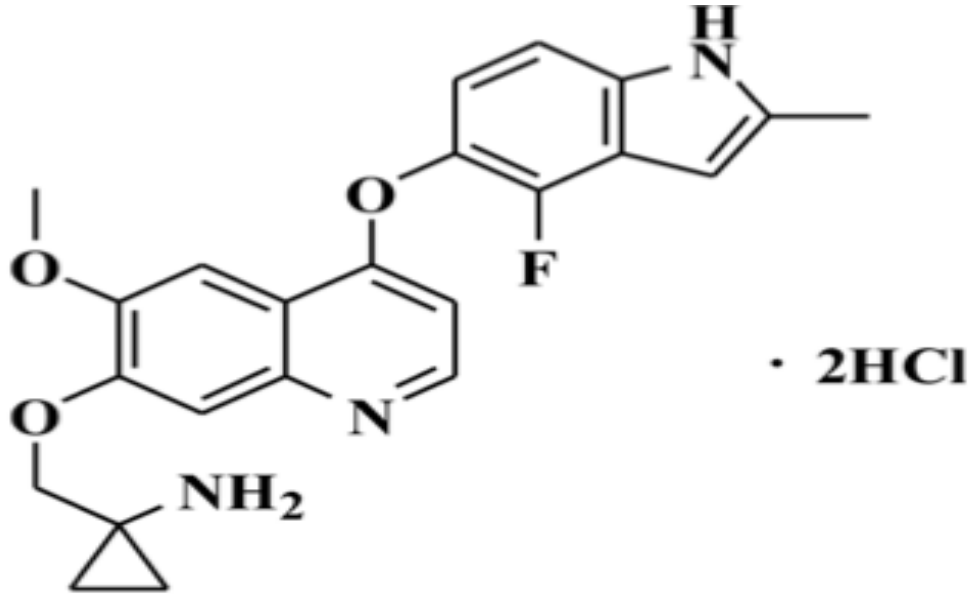
Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

.....What next?

1. Adriamycin+/-dacarbazine
2. Gemcitabine
3. Trabectedin
4. Pazopanib
5. Dacarbazine
6. ?.....

7. Clinical study ?
8. Immunotherapy ?
9. NGS?
10. .....

A phase 3 study of Anlotinib in metastatic or adavanced Alveolar Soft Part sarcoma, Synovial Sarcoma and Leiomyosarcoma



Published in final edited form as:
Cancer. 2017 September 01; 123(17): 3285–3290. doi:10.1002/cncr.30738.

Immunotherapy with Single Agent Nivolumab for Advanced Leiomyosarcoma of the Uterus: Results of a Phase 2 Study

Eytan Ben-Ami, MD[1], **Constance M. Barysauskas, MS**[2], **Sarah Solomon, BA**[1], **Kadija Tahlil, BS**[1], **Rita Malley, BA**[1], **Melissa Hohos, RN, BSN, OCN**[1], **Kathleen Polson, ANP-BC**[1], **Margaret Loucks, FNP**[1], **Mariano Severgnini, MS**[3], **Tara Patel, BA**[3], **Amy Cunningham, BA**[3], **Scott J. Rodig, MD, PhD**[3,4], **F. Stephen Hodi, MD**[3,5], **Jeffrey A. Morgan, MD**[1], **Priscilla Merriam, MD**[1], **Andrew J. Wagner, MD, PhD**[1], **Geoffrey I. Shapiro, MD, PhD**[6,7], and **Suzanne George, MD**[1]

[1]Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

[2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts

[3]Center for Immuno-oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

[4]Department of Pathology, Brigham an

[5]Department of Medical Oncology, Dan

[6]Department of Medical Oncology, Dan

[7]Department of Medicine, Brigham and
MA, USA

PFS and OS

Survival analysis included all patients. The overall median PFS was 1.8 months (95% confidence interval, 0.8-unknown) (Fig. 1). Because of the small number of patients in the cohort and limited follow-up, the median OS was not met (Fig. 2); however, 4 of the 12 patients died during the 100-day study follow-up period. All deaths were due to disease progression.

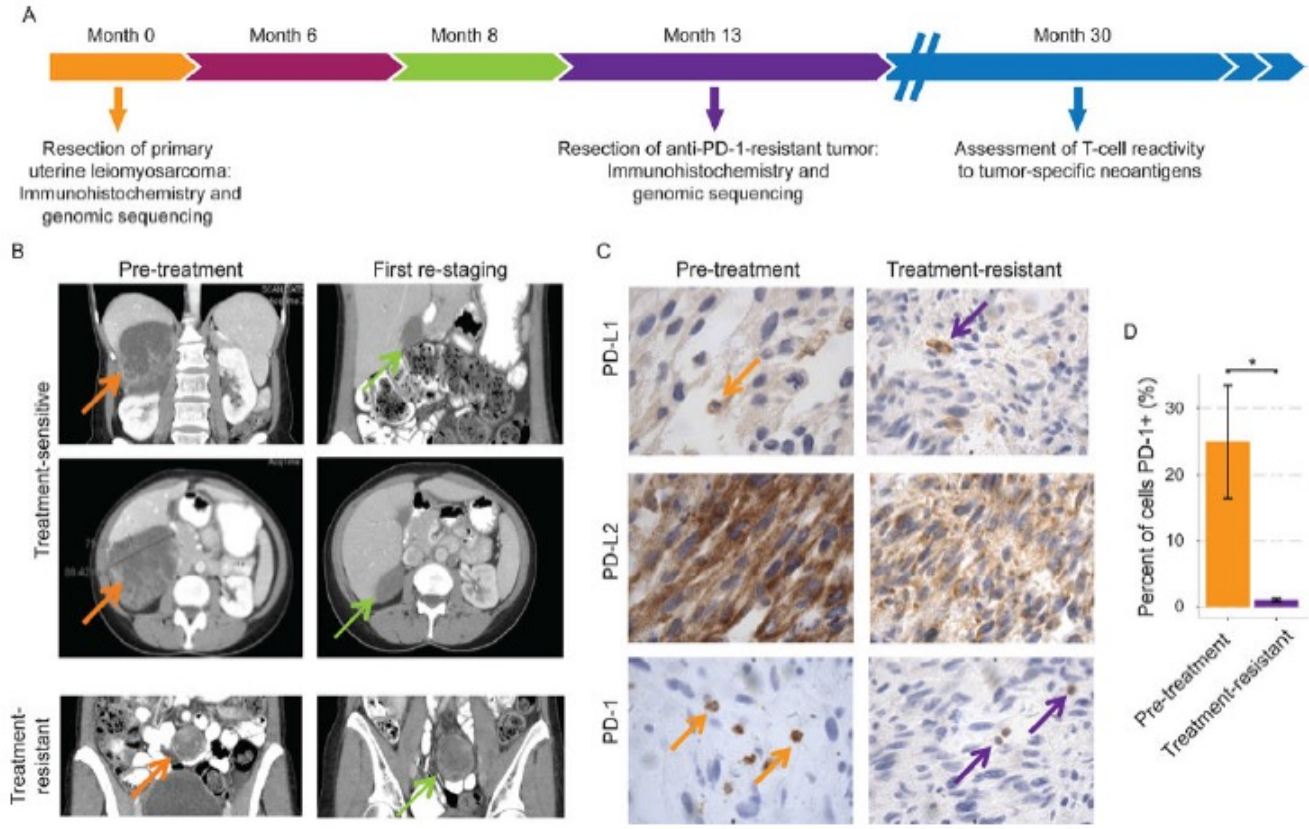


Figure 1. Histologic and radiographic findings in a treatment-naïve patient with metastatic uterine leiomyosarcoma receiving anti-PD-1 monotherapy

(A) Clinical course and tissue collection for immunohistochemical assessment and whole exome and whole transcriptome sequencing. **(B)** Computerized tomography (CT) imaging of treatment-responsive tumors and the sole treatment-resistant lesion. **(C)** Immunohistochemical staining of the primary and treatment-resistant tumors for PD-1, PD-L1, and PD-L2. **(D)** Quantification from representative tumor sections showing decrease in PD-1$^+$ cell infiltration in the treatment-resistant lesion ($p=0.039$; Student's t test). *$p < 0.05$.

Status	Study Title	Conditions	Interventions	Locations
Recruiting	A Study of Rucaparib and Nivolumab in People With **Leiomyosarcoma**	• **Leiomyosarcoma**	• Drug: Rucaparib • Drug: Nivolumab	• Memorial Sloan Kettering Basking Ridge (Limited Protocol Activities) Basking Ridge, New Jersey, United States • Memorial Sloan Kettering Monmouth (Limited Protocol Activitie Middletown, New Jersey, United States • Memorial Sloan Kettering Bergen (Limited Protocol Activities) Montvale, New Jersey, United States • (and 4 more...)
Recruiting	A Study of PTC596 in Combination With Dacarbazine in Participants With Advanced **Leiomyosarcoma** (LMS)	• **Leiomyosarcoma**	• Drug: PTC596 • Drug: Dacarbazine	• Mayo Clinic Florida Jacksonville, Florida, United States • John Hopkins Baltimore, Maryland, United States • Dana-Farber Cancer Institute Boston, Massachusetts, United States • (and 2 more...)
Recruiting	Avelumab in Combination With Gemcitabine in Advanced **Leiomyosarcoma** as a Second-line Treatment	• **Leiomyosarcoma** Metastatic	• Drug: Avelumab and Gemcitabine	• Dong-a University Hospital Busan, Korea, Republic of • Gachon University Gil Medical Center Incheon, Korea, Republic of • Seoul National University Bundang Hospital Seongnam-si, Korea, Republic of • (and 3 more...)

Published OnlineFirst April 16, 2020; DOI: 10.1158/1078-0432.CCR-19-3959

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Genomic Landscape of Uterine Sarcomas Defined Through Prospective Clinical Sequencing

Martee L. Hensley[1,2], Shweta S. Chavan[3], David B. Solit[2,3,4,5], Rajmohan Murali[6], Robert Soslow[6], Sarah Chiang[6], Achim A. Jungbluth[6], Chaitanya Bandlamudi[3], Preethi Srinivasan[6], William D. Tap[2,5], Evan Rosenbaum[5], Barry S. Taylor[2,3,4,7], Mark T.A. Donoghue[3], and David M. Hyman[1,2]

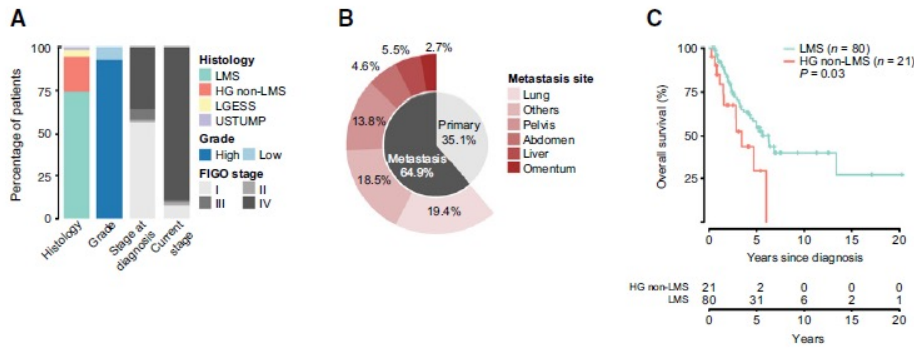


Figure 1.

A, Composition of the MSK uterine sarcoma cohort by histology, grade, and stage. **B,** Distribution of the biopsied primary and metastatic disease sites and sample numbers in the cohort. **C,** Overall survival of high-grade uterine sarcoma cohort split by leiomyosarcoma (LMS) and HG non-leiomyosarcoma.

Figure 1.

A, Composition of the MSK uterine sarcoma cohort by histology, grade, and stage. **B,** Distribution of the biopsied primary and metastatic disease sites and sample numbers in the cohort. **C,** Overall survival of high-grade uterine sarcoma cohort split by leiomyosarcoma (LMS) and HG non-leiomyosarcoma.

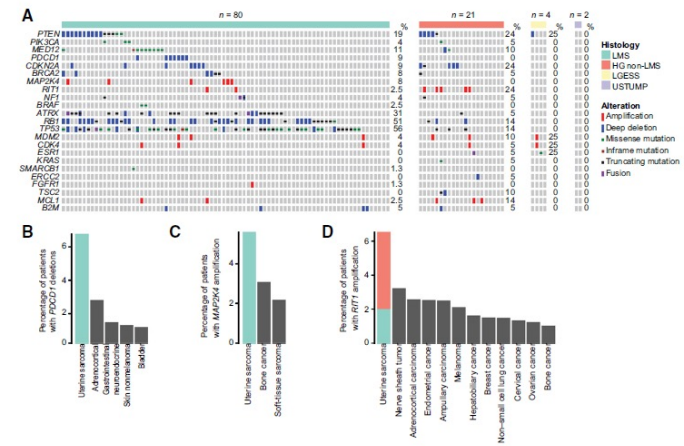


Figure 2.

A, Oncoprint of genomic alterations in the cohort split by histology. Alterations represented were selected by the following criteria: (i) All actionable alterations (OncoKB); (ii) All genes with oncogenic alterations (OncoKB) in at least 5% of cases; (iii) An alteration type in a given gene was found to be most frequent in uterine sarcomas when compared with the contemporary MSK-IMPACT clinical series cohort of prospectively sequenced cancers ($n = 15,816$). **B,** Frequency of *PDCD1* homozygous deletions in the MSK-IMPACT clinical sequencing cohort compared with other cancer types with at least 25 cases and 1% altered cases. **C** and **D,** Frequency of *MAP2K4* and *RIT1* amplifications in the MSK-IMPACT clinical sequencing cohort compared with other cancer types with at least 25 cases and 1% altered cases.

Next Generation Sequencing

- **U-LMS do not have a single defining molecular abnormality**
  (No target therapy !)

- **NGS could identify subset of pts whose tumor harbor targetable mutation**

- **Pts with potentially actionable alteration could recive mached therapy**

Next Generation Sequencing

- U-LMS do not have a single defining molecular abnormality
  (No target therapy !)
- NGS could identify subset of pts whose tumor harbor targetable mutation
- Pts with potentially actionable alteration could receive mached therapy
- Even if actionable mutations can be identified given the complex chromosomal abnormalities characteristic of U-leiomyosarcoma, it's challange to characterize mutation to be either likely drivers or passengers

Next Generation Sequencing

- **Even if actionable mutations can be identified given the complex chromosomal abnormalities characteristic of U-leiomyosarcoma, it's challange to characterize mutation to be either likely drivers or passengers**

In brief....

- **U-LMS is a rare disease often diagnosed post-operatively. We are working to improve the differential diagnosis of leiomyosarcoma from leiomyoma**
- **Standard treatment is hysterectomy**
- **Adjuvant chemotherapy is not standard**
- **Several drugs are available for the advanced disease with limited side effects and good QoL**
- **LMS are a multidisciplinary disease even in the metastatic setting**
- **Up to now check point inhibitors have limted activities**
- **NGS may help in a restricted number of cases, but at the matter of fact it is not the « solution» for a precision medicine in U-LMS**

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

roberta.sanfilippo@istitutotumori.mi.it