Sarcomas Ginecológicos: leiomiosarcoma uterino

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XIV CURSO AVANZADO DE SARCOMAS GEIS 2022

Universidad Europea MADRID

GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos

Introducción

Leiomiosarcoma <1% tumores malignos

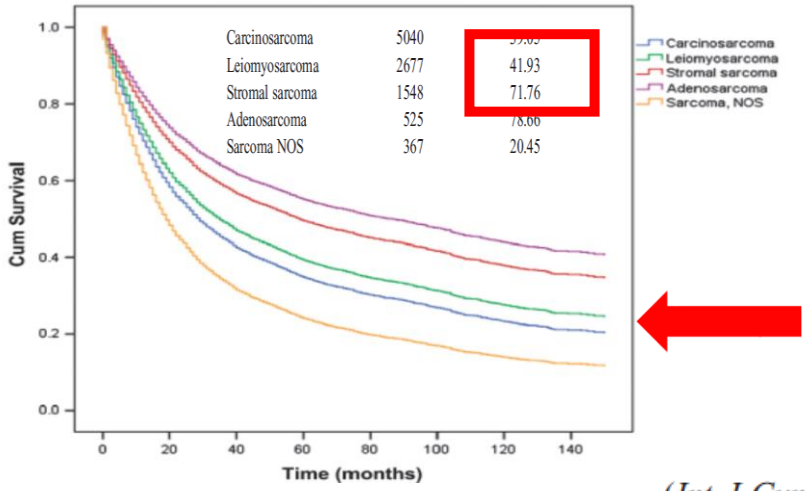
- 3-10% de tumores uterinos
- 0,8casos/100000mujeres/a
- Factores de riesgo : nuliparidad, obesidad. Tamoxifeno y radioterapia pélvica previa. Postmenopaúsicas. Raza afroamericanas
- Suelen ser esporádicos, a veces asociados a LiFraumeni, Retinoblastoma hereditario, leiomiomatosis hereditaria, Mutación de la vía germinal de la fumarato hidratasa

- Clasificación WHO 2014
- Estadiaje: FIGO, AJCC

- Leiomiosarcoma 65-70%

- Sarcoma estroma endometrial 20%
- Sarcoma del estroma endometrial de alto grado
- Sarcoma indiferenciado

6%



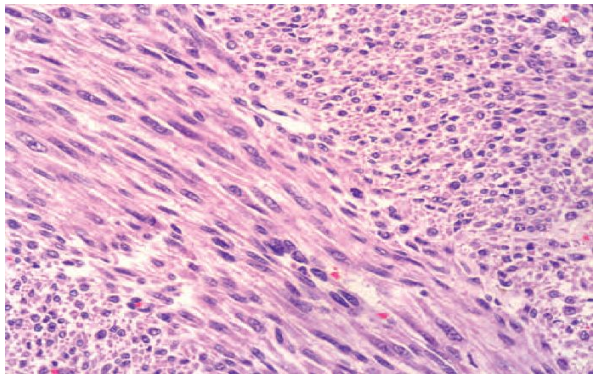
Supervivencia

(*Int J Gynecol Cancer* 2016;00: 00–00)

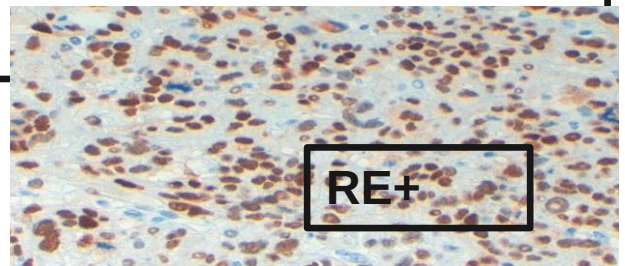
Leiomiosarcoma : clínica, dx y AP

- **Clínica**: metrorragia 56%
  Dolor abdominal 22%
  Masa uterina 54%
- 69% localizados al diagnóstico
- 45-75% de localizados desarrollan metástasis sobre todo en los dos primeros años
- Ocasionalmente metástasis tardías

Síntomas vagos difíciles de diferenciar de mioma



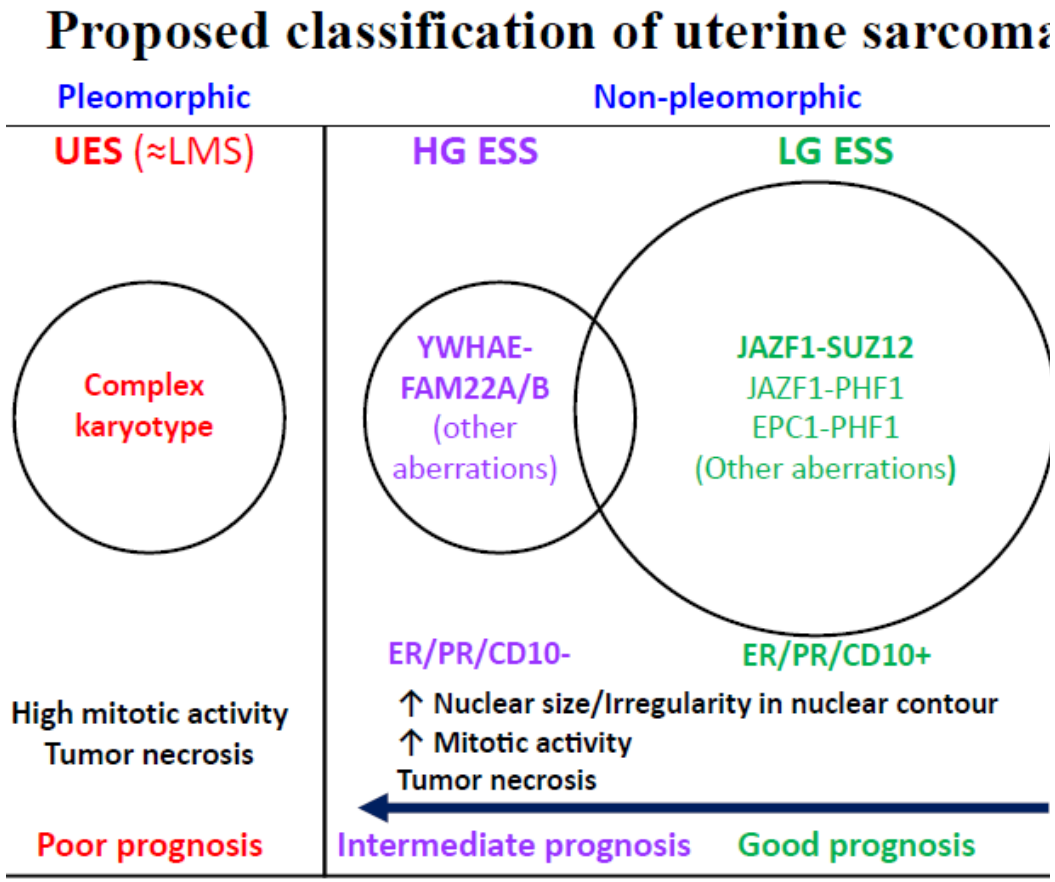
- **RX** Masa uterina con necrosis, hemorragia y puede tener calcificaciones
- A veces difícil de diferenciar de mioma. La bp preoperatoria con frecuencia negativa
- Datos de malignidad: necrosis, captación temprana de contraste, >10cm, infiltración local, crecimiento rápido, restricción a la difusión. RNM
- Metástasis: ganglios, hígado, pulmón (40%), peritoneo. Otras localizaciones más raras (cerebro, hueso…). Estudio de extensión TAC toracoabdominopelvis.



- **AP** Tumores solitarios de >5 cm con invasión a través del miometrio
- Células fusiformes con citoplasma eosinófilo
- Hipercelularidad, atipia, necrosis, mitosis>o=10M/10CGA, hemorragia
- Desmina, caldesmon, actina y CD10 positivos
- No se gradan
- Variantes raras: leiomiosarcoma mixoide(25% fusiones PLAG1), epitelioide (algunos con reordenamiento del gen del receptor de progesterona)(puede ser queratina +)
- RE y RP positivos 30-40% casos
- Se describen casos ckit positivos (no mutaciones)

Diagnostic and Interventional Imaging (2019) **100**, 619–634

Biología molecular

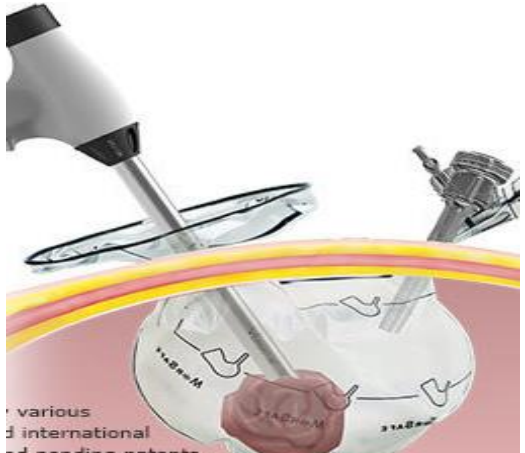


Problemas de los estudios en sarcomas uterinos

- Estudios pequeños
- Con frecuencia análisis de casos o estudios retrospectivos
- Fase II
- Mezcla de estadios
- Mezcla de localizaciones
- Mezcla de histologías
- Con frecuencia se cierran por falta de reclutamiento
- Difícil sacar conclusiones

Tratamiento. Tumor localizado leiomiosarcoma

- Cirugía: histerectomía total
- Doble anexectomía si afectación macroscópica (5%). Qué ocurre en casos con RH +?
- Afectación ganglionar rara (6-9%)
- Linfadenectomía si afectación macroscópica o afectación extrauterina
- Cirugía no planeada (histerectomía subtotal o morcellation) se aconseja nueva cirugía (upstaging 15%)
- Morcellation Aumento de riesgo de diseminación y peor pronóstico (JCO Sept 2019)
- FDA en 2014 y 2018 aconseja no realizar esta técnica
- No se aconseja cirugía para preservar fertilidad



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)

EUROPEAN JOURNAL OF CANCER 44 (2008) 808–818

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]

Table 6 – Sites of recurrence

	Sites of recurrence			
	CS, n = 91		LMS, n = 99	
	Radiotherapy (n = 46)	Observation (n = 45)	Radiotherapy (n = 50)	Observation (n = 49)
No local recurrence	28 (61%)	21 (47%)	22 (44%)	26 (53%)
Local recurrence only	2 (4%)	11 (24%)	1 (2%)	7 (14%)
Distant metastases	7 (15%)	3 (7%)	18 (36%)	7 (14%)
Local followed by distant	1 (2%)	3 (7%)	0 (0%)	2 (4%)
Distant followed by local	2 (4%)	0 (0%)	2 (4%)	3 (6%)
Simultaneous local and distant	6 (13%)	7 (16%)	7 (14%)	4 (8%)
Any local recurrence	11 (24%)	21 (47%)	10 (20%)	12 (24%)
Any distant metastases	16 (35%)	13 (29%)	27 (54%)	16 (33%)

50,4 Gy hasta 8 semanas tras cirugía. NO disminución de recidiva local, ni a distancia, ni aumento de supervivencia

RT adyuvante Se valora en casos seleccionados: margen afecto, cirugía no reglada, afectación de parametrios, afectación cervical

Máster en Tumores Musculoesqueléticos

Quimioterapia adyuvante:SARCGYN análisis global mezcla histologías

	Arm A CT + RT 39	Arm B RT 42
Median follow-up	4.3 years (0.5–8.7)	4.3 years (0.3–7.9)
Relapse (patients)	15 (38.5%)	26 (62%)
3-year DFS (95% CI)	55% (40% to 70%)	41% (27% to 57%)
3-year OS (95% CI)	81% (66% to 91%)	69% (52% to 82%)
5-year OS (95% CI)	72% (53% to 85%)	55% (37% to 72%)

- Adriamicina 50mg/m2,Ifos 6gr/m2,Cisplatino 75mg/m2 x 4-----RT Vs RT
- Se cerró por falta de reclutamiento
- 24/29 leiomiosarcomas
- Estadios I-III

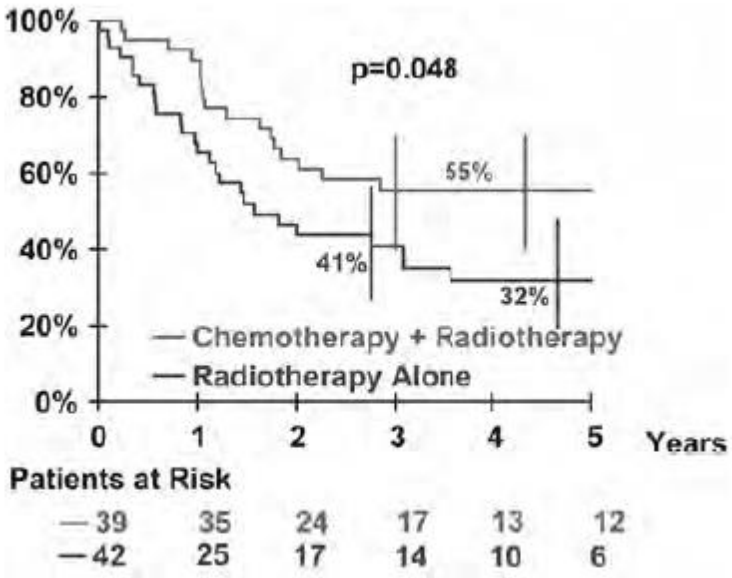
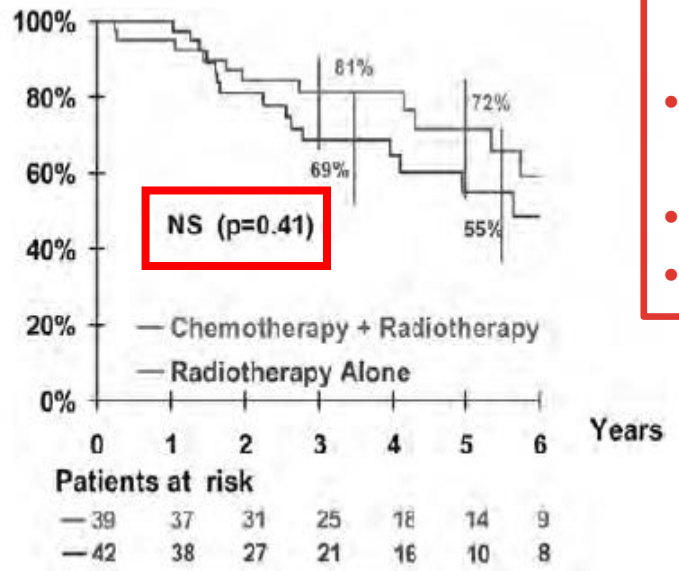


Figure 1. Disease-free survival according to adjuvant therapy group.



re 2. Overall survival according to adjuvant therapy group. Vertical

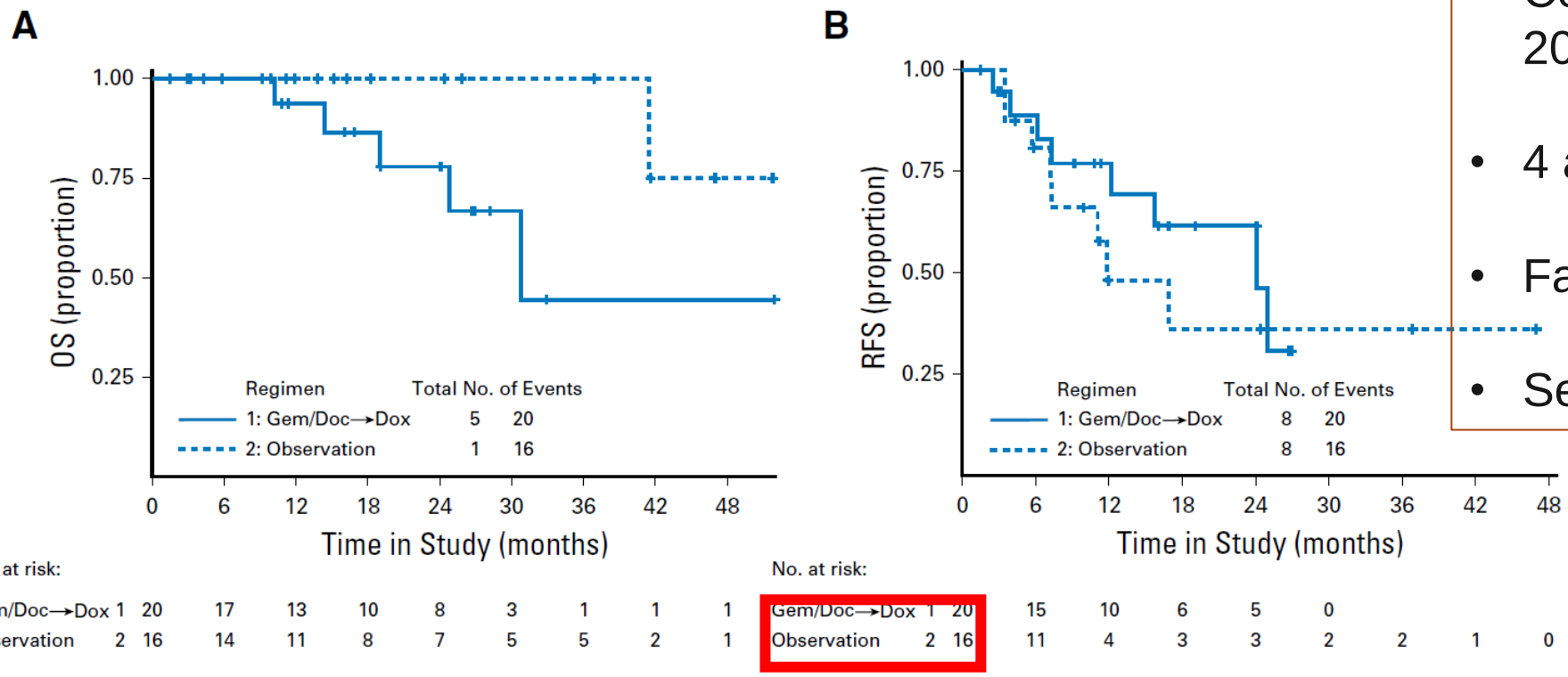
- Estudio pequeño Mezcla histologías
- No aumento de supervivencia 3% mortalidad

Ann Oncol 2013

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

J Clin Oncol 36:3324-3330. © 2018

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



. at risk:

m/Doc→Dox	1	20	17	13	10	8	3	1	1	1
servation	2	16	14	11	8	7	5	5	2	1

No. at risk:

Gem/Doc→Dox	1	20	15	10	6	5	0			
Observation	2	16	11	4	3	3	2	2	1	0

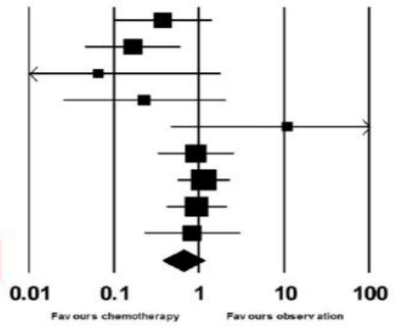
- Cerrado en Septiembre 2016
- 4 años abierto
- Falta de reclutamiento
- Se incluyeron 36 pacientes

A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

Effect of adjuvant therapy on the risk of recurrence in early-stage leiomyosarcoma: A meta-analysis

Gynecologic Oncology 154 (2019) 638–650

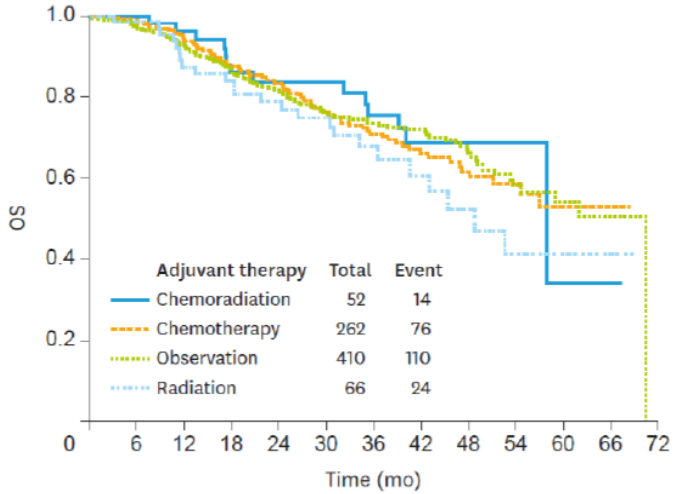
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Omura , 1985	0.377	0.099	1.430	-1.435	0.151
Hornback, 1986	0.167	0.045	0.612	-2.700	0.007
Piver, 1988	0.065	0.002	1.794	-1.615	0.106
Wu , 2006	0.227	0.025	2.062	-1.317	0.188
Kim, 2009	10.818	0.463	252.789	1.481	0.139
Ricci, 2013	0.916	0.326	2.574	-0.166	0.868
Mancari, 2014	1.127	0.553	2.296	0.328	0.743
Littell, 2017	0.933	0.412	2.111	-0.167	0.868
Hensley, 2018	0.833	0.229	3.028	-0.277	0.782
	0.652	0.368	1.154	-1.470	0.142



- 747 pts/12 estudios
- Analiza QT y RT
- Cualquier recurrencia
- Se incluyen los datos de Gemcitabina TXT
- NO BENEFICIO

Characterizing the efficacy and trends of adjuvant therapy versus observation in women with early stage (uterine confined) leiomyosarcoma: a National Cancer Database study

J Gynecol Oncol. 2020 May;31(3):e21



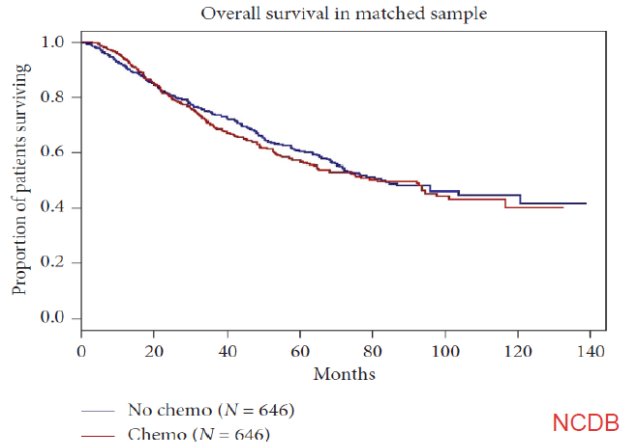
Supervivencia NO BENEFICIO

1030 mujeres
Leiomiosarcoma uterino localizado
2008-2014

Research Article

Adjuvant Chemotherapy in Uterine Leiomyosarcoma: Trends and Factors Impacting Usage

Sarcoma 2019



NO BENEFICIO

NCDB 2004-14

A randomized phase II study of letrozole vs. observation in patients with newly diagnosed uterine leiomyosarcoma (uLMS)

Brian M. Slomovitz[a,*], Michael C. Taub[a], Marilyn Huang[a], Charles Levenback[b],

Gynecologic Oncology Reports 27 (2019) 1–4

Enfermedad limitada al útero
>10%RE
Cerrado por falta de reclutamiento

9 pacientes

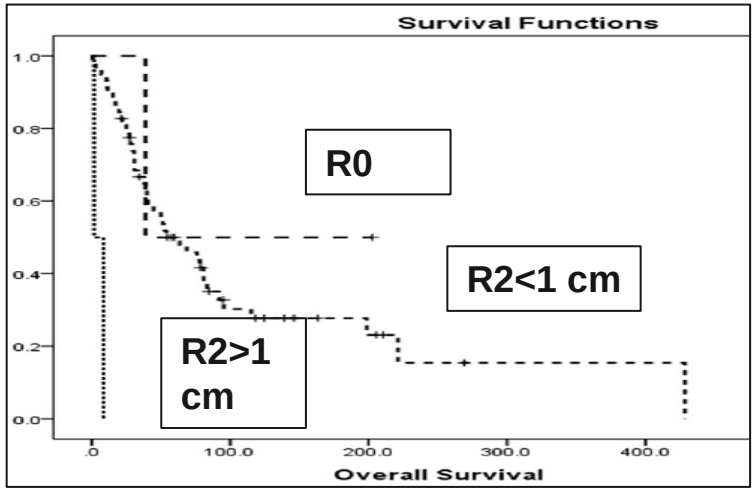
- Tratamiento estándar cirugía
- No quimioterapia ni radioterapia adyuvante salvo casos seleccionados

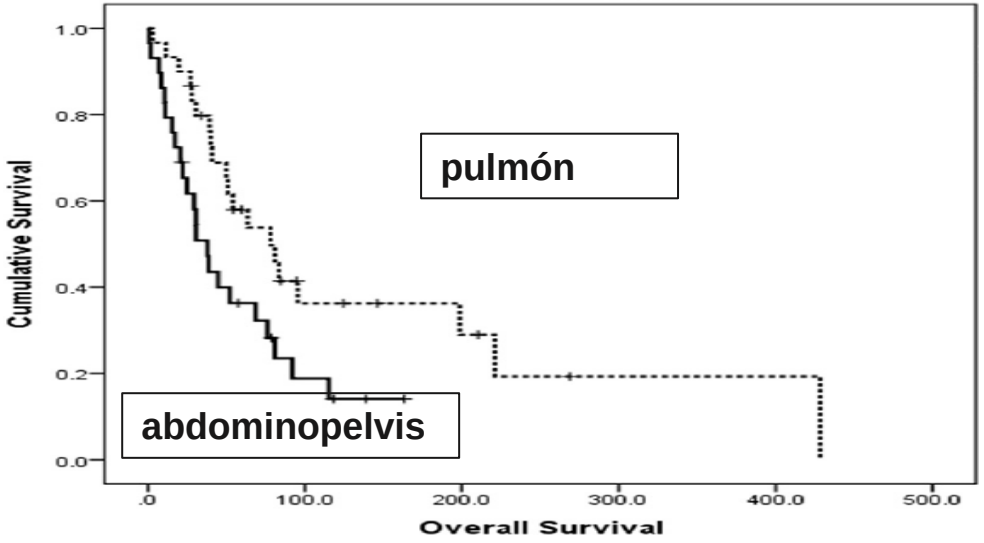
Secondary surgical resection for patients with recurrent uterine leiomyosarcoma

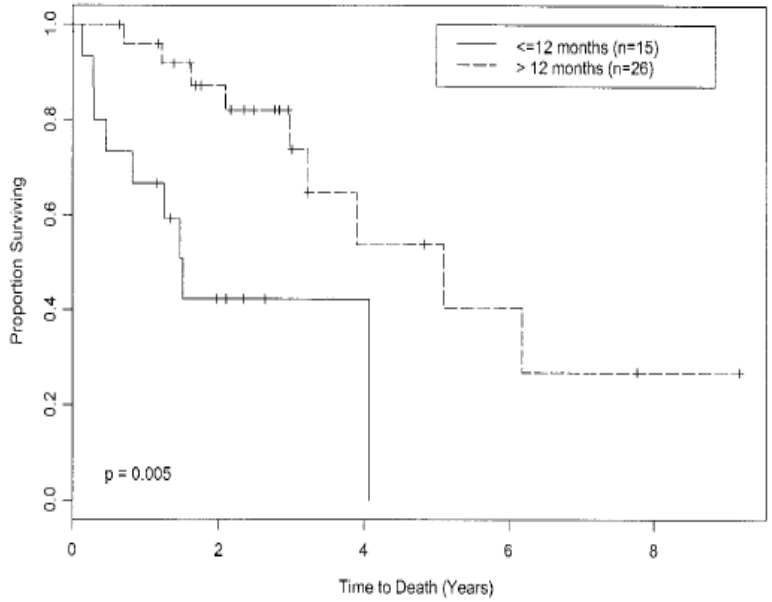
Gynecologic Oncology 154 (2019) 333–337

Mario M. Leitao Jr

- 62 pacientes
- 29 recidiva abdominopélvica
- 30 recidiva pulmonar
- 3 pulmonar y abdominopélvica
- Cirugía R0 58 p (93%)
- Supervivencia R0 54,1 m
- NO beneficio de tratamiento adyuvante







Leiomiosarcoma uterino metastásico: primera línea

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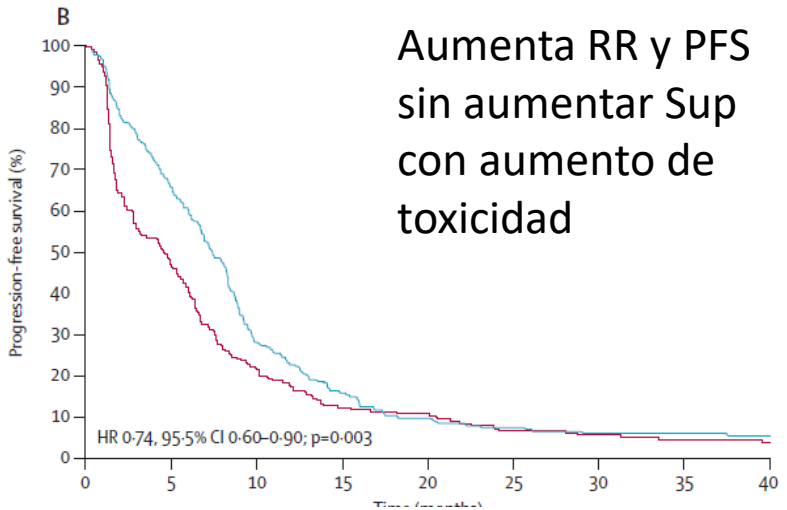
Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan,

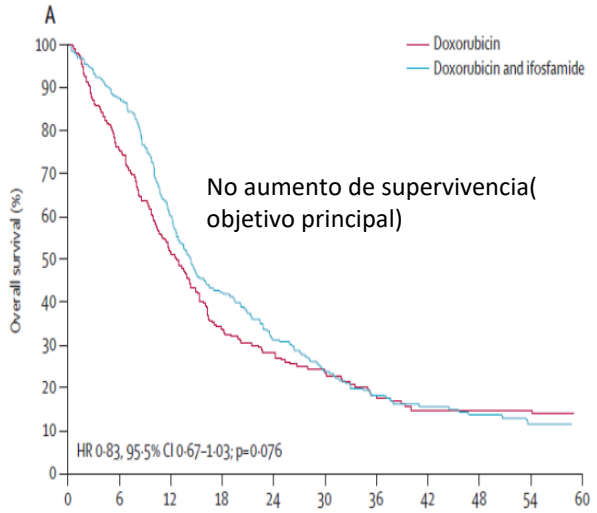
	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

Data are n (%).

Table 3: **Responses to treatment**



Aumenta RR y PFS sin aumentar Sup con aumento de toxicidad

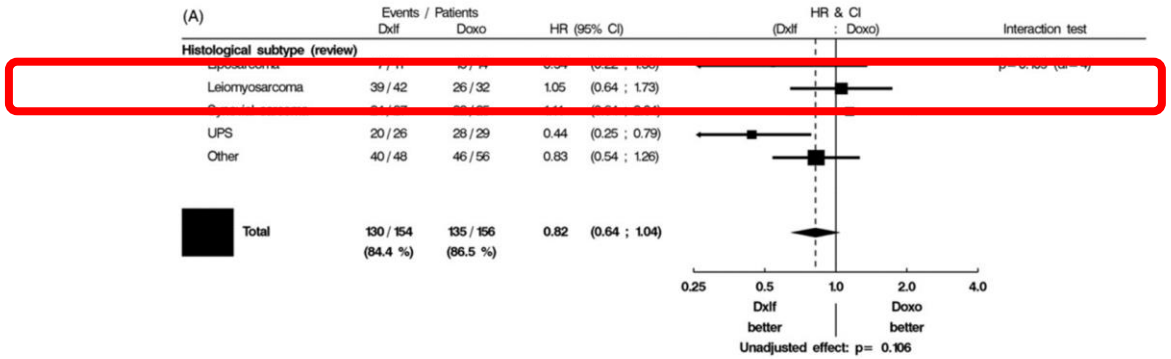


No aumento de supervivencia(objetivo principal)

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
~~Progression of disease or death caused by progressive disease~~	~~95 (42%)~~	~~47 (21%)~~
Toxic effect (including toxic death)	6 (3%)	40 (18%)
Toxic death	5 (2%)	2 (1%)
Patient's refusal (not related to toxic effects)	4 (2%)	10 (4%)
Intercurrent death (not related to malignant disease or toxic effects)	4 (2%)	1 (<1%)
Other	12 (5%)	11 (5%)

Data are n (%).

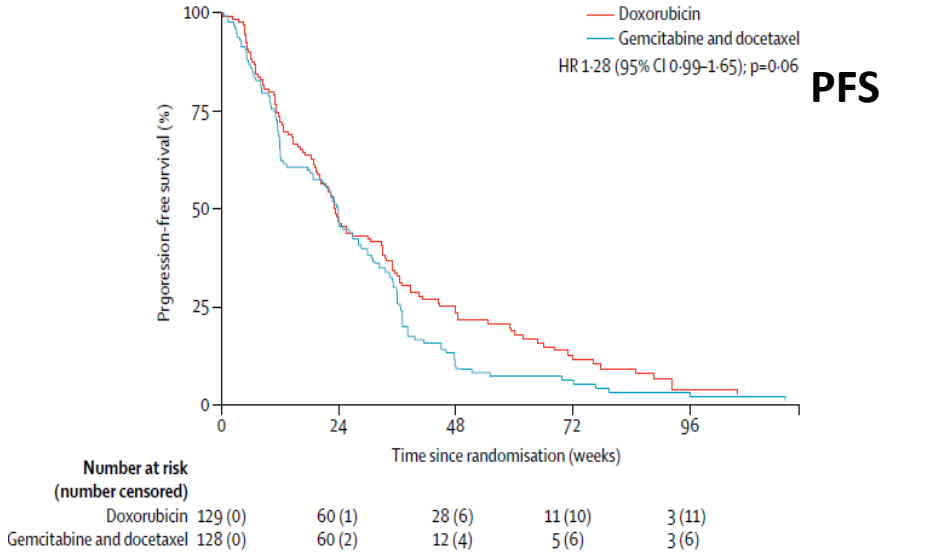
Table 4: **Reasons for discontinuation of treatment**



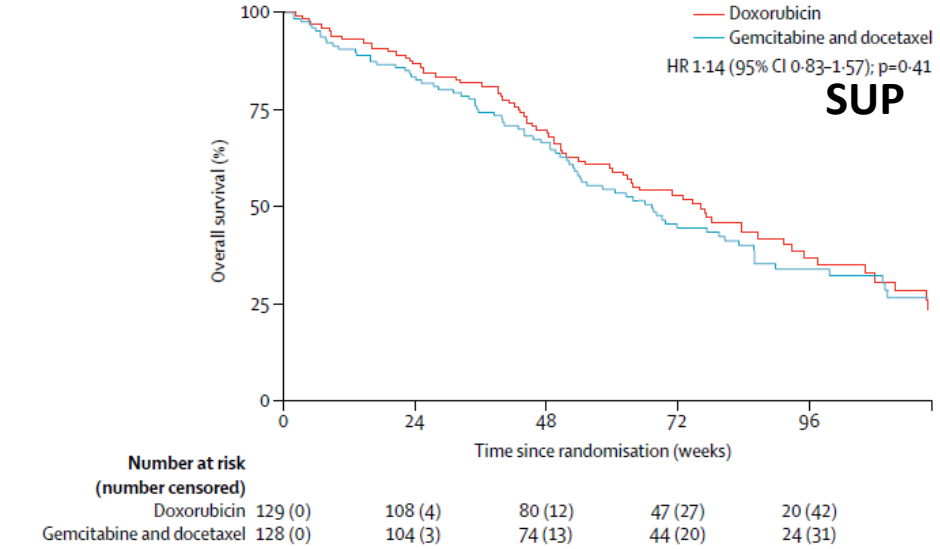
Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial

Lancet Oncol. 2017

Beatrice Seddon, Sandra J Strauss, Jeremy Whelan, Michael Leahy, Penella J Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood,



PFS



SUP

	Doxorubicin (n=129)	Gemcitabine and docetaxel (n=128)
Complete response	2 (2%)	0
Partial response	23 (18%)	25 (20%)
Stable disease	60 (47%)	50 (39%)
Progressive disease	25 (19%)	27 (21%)
Not evaluable	19 (15%)	26 (20%)

Data are n (%).

La Gemcitabina-Taxotere no aumenta la tasa de respuestas ni la supervivencia libre de progresión, ni la supervivencia con aumento de toxicidad

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

. *Cancer* 2020;0:1-11.

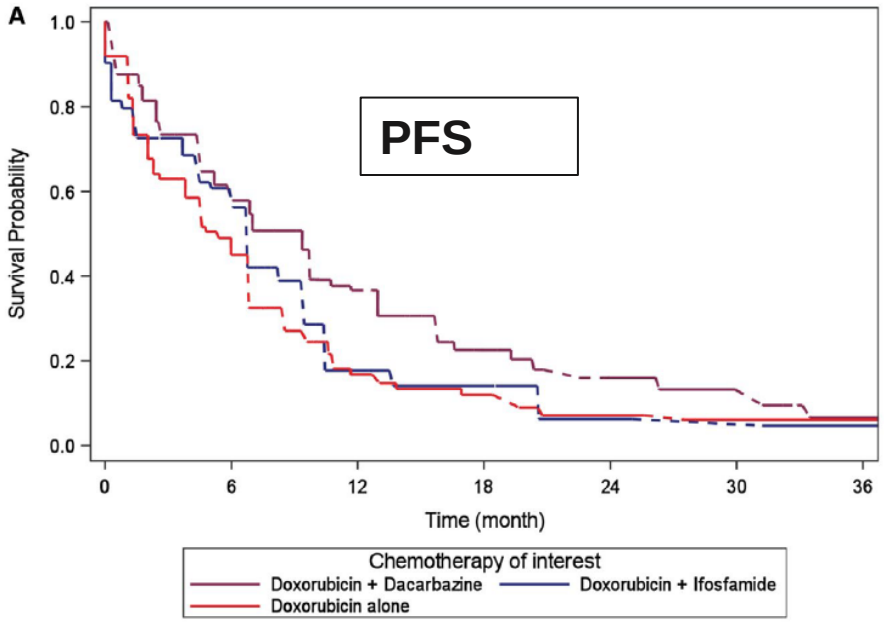
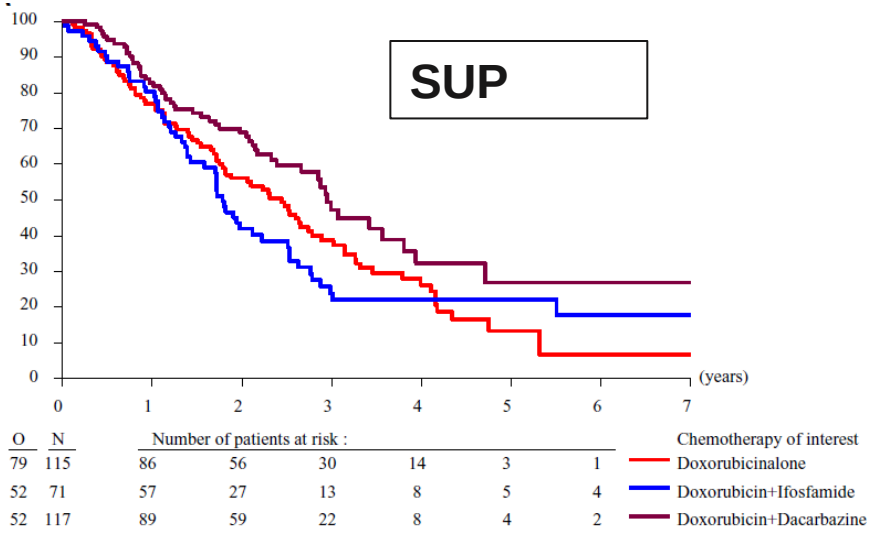


Table 4
Response to chemotherapy regimen.

	Treatment				
	Anthracyclins (N = 119)	DOX + IFO (N = 87)	CYVADIC N = 23)	IFO alone (N = 40)	Total (N = 269)
	N (%)	N (%)	N (%)	N (%)	N (%)
Best overall response					
Complete response	3 (2.5)	2 (2.3)	3 (13.0)	0 (0.0)	8 (3.0)
Partial response	26 (21.8)	19 (21.8)	5 (21.7)	2 (5.0)	52 (19.3)
No change	51 (42.9)	29 (33.3)	7 (30.4)	15 (37.5)	102 (37.9)
Progression	33 (27.7)	28 (32.2)	5 (21.7)	17 (42.5)	83 (30.9)
Non evaluable	6 (5.0)	9 (10.3)	3 (13.0)	6 (15.0)	24 (8.9)

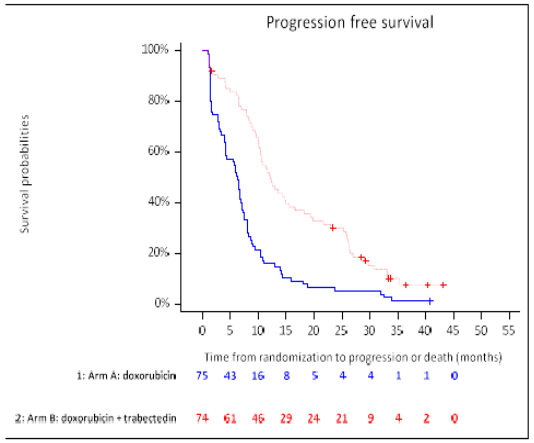


RR 30,9%AD, 19,5% AI,25,6% A

Estudio retrospectivo

LMS-04 study: a randomised, multicenter phase-III study comparing doxorubicin alone *versus* doxorubicin with trabectedin followed by trabectedin in non-progressive patients as first-line therapy, in patients with metastatic or unresectable leiomyosarcoma.

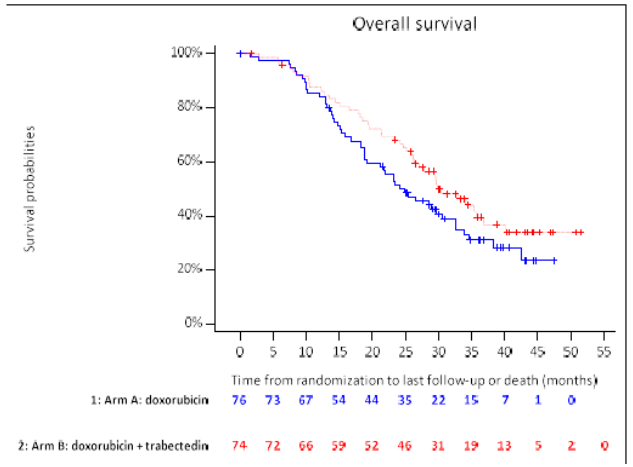
PFS by BICR, ITT population



	Doxo (N = 76)	Doxo + Trab (N = 74)
Events, n (%)	74 (97%)	65 (88%)
Median PFS, months	6.2	12.2
	HR 0.41	
	95% CI 0.29-0.58; *P*<0.0001	

BICR, blinded independent central review; ITT: intent to treat; CI, confidence interval; HR, hazard ratio; PFS: progression-free survival; **Median follow-up was 37 months.**

Overall survival



	Doxo (N = 76)	Doxo + Trab (N = 74)
Deaths, n (%)	50 (66%)	42 (57%)
Median OS, months	24.1	30.5
	HR 0.73	
	95% CI: 0.49-1.12	

Median follow-up : 37 months

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; Doxo: Doxorubicin; Trab: Trabectedin.

ESMO 2021

LMS 04: Ph-III first-line therapy for locally advanced/metastatic LMS

Primary endpoint
PFS (RECIST v1.1) RX review

Secondary endpoints
PFS inv
Response rate
CBR
PFS2
OS
Safety and tolerability

FIRST LINE
- Ut-LMS; ST-LMS
- Locally advanced /meta
- No previous CT

N = 150

Randomization

1:1

Doxorubicin 75 mg/m² q3weeks*
Max 6 cycles
n = 76

Surgery if indicated

Doxorubicin 60 mg/m² + **trabectedin** 1,1 mg/m² q3 weeks**
Max 6 cycles
n = 74

Surgery if indicated

PR or SD

Trabectedin 1,1 mg/m² 3h q3 weeks; until PD
max 17 cycles

Stratification
- Uterus *vs* soft tissue
- Locally advanced *vs* metastatic

* + Lenograstim 150 µg/m²/day s.c. d3-9; **+ Pegfilgrastim 6 mg s.c. day 2.

Efficacy

	Doxo N = 76	Doxo + Trab N = 74
Response		
➢ CR	0	4 (5%)
➢ PR	10 (13%)	24 (32%)
➢ SD	50 (66%)	40 (54%)
Response Rate before surgery n (%)	**10 (13%)**	**28 (38%)**
Ut-LMS (n = 67)	5 (15%)	12 (36%)
ST-LMS (n = 83)	5 (12%)	16 (39%)
CBR (CR + PR + SD)	60 (79%)	68 (92%)
Duration of response (months) Median [IQR]	5.6 [4.1-6.9]	12.5 [7,8-20.3]

Most common Gr 3-4 AEs

Gr 3-4 AEs n (%)	Doxo N = 76	Doxo + Trab N = 74
Number pts with at least 1 Gr3-4 AEs	20 (26%)	35 (47%)
Fatigue	7 (9%)	8 (11%)
Anemia	1 (1%)	10 (14%)
Neutropenia	5 (7%)	32 (43%)
Febrile neutropenia	8 (11%)	18 (24%)
Thrombocytopenia	0	15 (20%)
Transaminase elevation	0	13 (19%)
Nausea/Vomiting	1 (1%)	9 (12%)*
Cardiac failure	2 (3%)	1 (1%)
Toxic death	1 (1%)	0

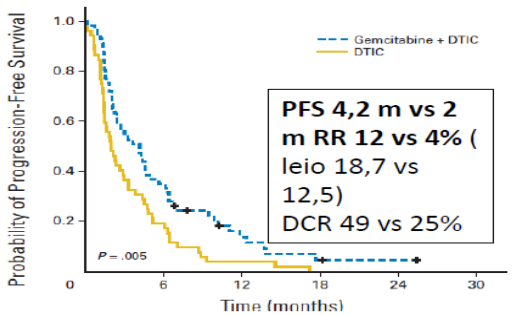
Leiomiosarcoma uterino metastásico pretratado

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

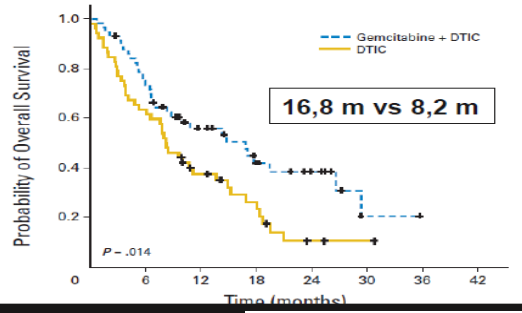
Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

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

Characteristic	DTIC (n = 52) No.	%	Gemcitabine + DTIC (n = 57) No.	%
Histologic diagnosis				
Leiomyosarcoma	16	31	16	28
Liposarcoma	9	17	10	18
Undifferentiated pleomorphic	8	15	11	19
Synovial sarcoma	5	10	6	11
Miscellaneous sarcoma	14	27	14	25
Histologic grade				
Low	5	10	4	7
High	41	79	48	84
Unknown	6	12	5	9
Site of primary				
Extremity and trunk wall	27	52	23	40
Retroperitoneum	6	12	11	19
Gynecologic	10	19	5	9
Other	9	17	18	32



PFS 4,2 m vs 2 m RR 12 vs 4% (leio 18,7 vs 12,5)
DCR 49 vs 25%



16,8 m vs 8,2 m

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

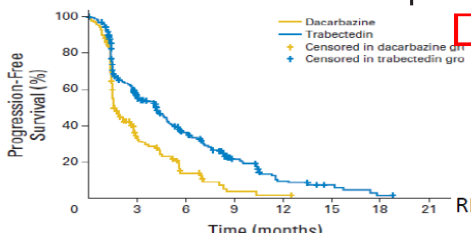
JCO 2015

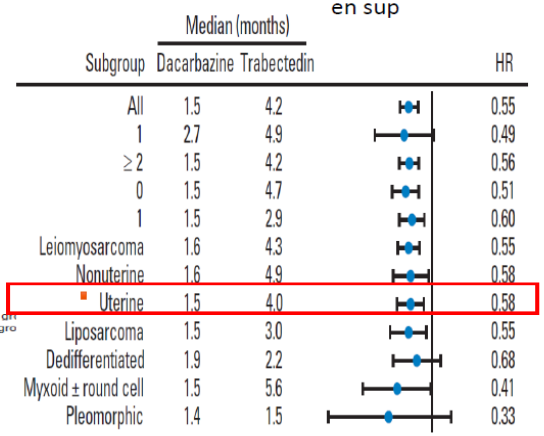
George D. Demetri, Margaret von Mehren, Robin L. Jones, Martee L. Hensley, Scott M. Schuetze,

Aumento de PFS 1,5 m vs 4,2 m sin aumento en sup

Table 1. Baseline Demographic and Disease Characteristics

Variable	No. (%) of Patients: Trabectedin (n = 345)	Dacarbazine (n = 173)
Age, years		
Median (range)	57 (18.0-81.0)	56 (17.0-79.0)
Sex		
Male	107 (31)	47 (27)
Female	238 (69)	126 (73)
Baseline BMI, kg/m²		
Median (range)	28.21 (14.5-78.1)	27.05 (13.3-66.7)
Histology		
Leiomyosarcoma	252 (73)	126 (73)
Uterine	134 (39)	78 (45)
Nonuterine	118 (34)	48 (28)
Liposarcoma	93 (27)	47 (27)
Myxoid ± round cell	38 (11)	19 (11)
Pleomorphic	10 (3)	3 (2)
Dedifferentiated	45 (13)	25 (15)





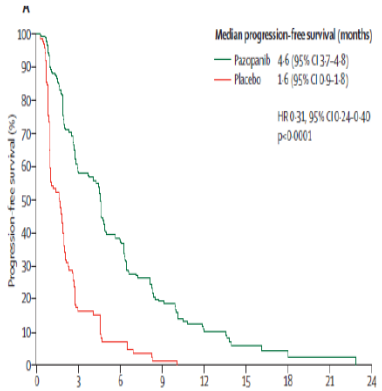
RR 9,9% vs 6,9% (beneficio clínico 34 vs 18%)

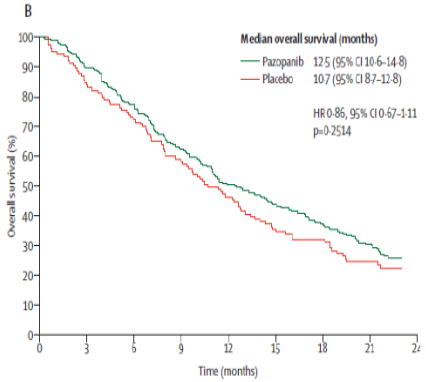
Máster en Tumores Musculoesqueléticos

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,

Lancet 2012; 379: 1879-86





123pts placebo/246 pts pazopanib
Objetivo principal

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]

The Oncologist 2012;17:1213–1220

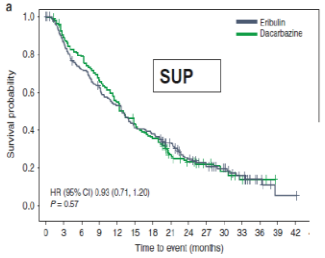
2ªlinea tras antraciclina

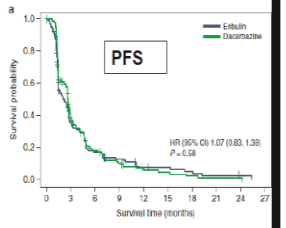
Table 4. Responses to treatment

	Uterine group (%) Gemcitabine	Gemcitabine + docetaxel
n	21	21
Assessable patients	21	21
Complete response, *n* (%)	1 (5)	0
Partial response, *n* (%)	3 (14)	5 (24)
Stable disease	9 (43)	10 (48)
Progression	8 (38)	6 (28)
Objective response, % (95% CI)	19 (5–42)	24 (8–47)
Nonprogression rate, % (95% CI)	62 (38–82)	71 (48–89)
Progression-free survival, % (95% CI)		
3 mos	57 (37–76)	71 (50–86)
6 mos	48 (28–68)	48 (28–68)
Median progression-free survival (mos)	5.5	4.7
Median overall survival (mos)	20	23

Eribulin versus dacarbazine in patients with leiomyosarcoma: subgroup analysis from a phase 3, open-label, randomised study

British Journal of Cancer (2019) 120:1026–1032; h





usculoesqueléticos

A Phase II Trial of Temozolomide as a 6-Week, Continuous, Oral Schedule in Patients with Advanced Soft Tissue Sarcoma

Cancer 2005;104:1706–12.

A Study by the Spanish Group for Research on Sarcomas

- **Temodal 75-100 mg/m2/d x 6 semanas/9 semanas**
- **45 pts**
- **7RP (15,5%)**
- **PFS 2,2 m**
- **Sup 8,1 m**
- **5/11 leiomiosarcomas ginecológicos responden**
- **2 pts SLP > 3 años**

Treatment of advanced uterine leiomyosarcoma with aromatase inhibit

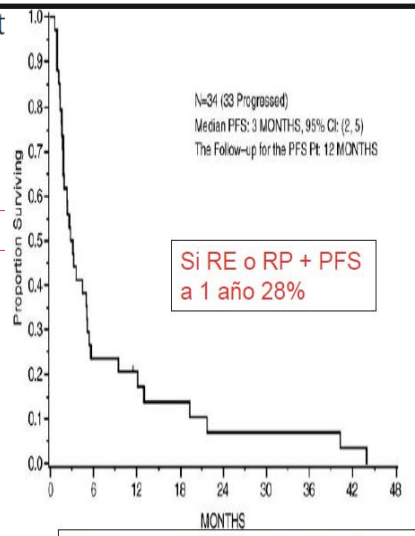
Roisin O'Cearbhaill [a], Qin Zhou [b], Alexia Iasonos [b], Robert A. Soslow [c], Mario. M. Leitao [d], Carol Aghajanian [a], Martee L. Hensley [a,*]

Gynecologic Oncology 116 (2010) 424–429

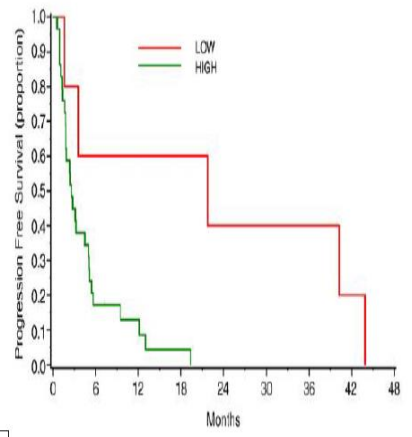
Variable	n (%), median (range)
Initial management at diagnosis of uLMS	
Surgical resection alone	22 (65%)
Surgical resection and chemotherapy	11 (33%)
Chemotherapy alone	1 (3%)
Number of prior chemotherapy regimens	
0	11 (32%)
1	10 (29%)
2–3	11 (32%)
≥4	2 (6%)
Prior hormonal treatment (medroxyprogesterone, tamoxifen)	7 (21%)
Prior pelvic radiotherapy	12 (35%)
Median interval between diagnosis and AI initiation	1.2 years (0.02–22)
AI used	
Letrozole [with leuprolide]	25 (74%) [3 (9%)]
Anastrozole	7 (21%)
Exemestane	2 (6%)

34 pts

Response	n (%)
Complete response	0 (0%)
Partial response	3 (9%)
Stable disease	11 (32%)
Progressive disease	20 (59%)



Si RE o RP + PFS a 1 año 28%



Valorar en escaso volumen de enfermedad, lento crecimiento,R+

Máster en Tumores Musculoesqueléticos

Thanopoulou *et al. Clinical Sarcoma Research* 2014, **4**:5
http://www.clinicalsarcomaresearch.com/content/4/1/5

CLINICAL SARCOMA R

RESEARCH Open

Treatment of hormone positive uterine leiomyosarcoma with aromatase inhibitors

Eirini Thanopoulou*, Khin Thway, Komel Khabra and Ian Judson

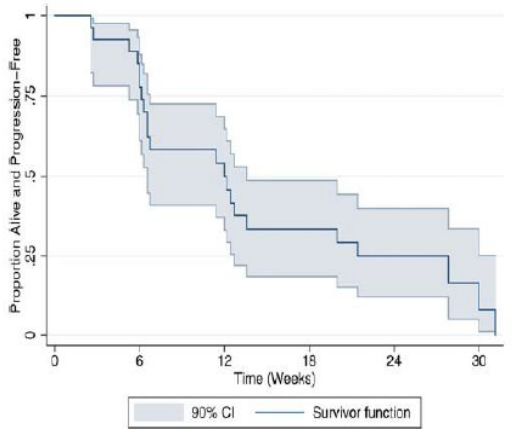
16 pacientes RE/RP +
Letrozol
PFS14 m Bajo grado 20m vs 11m.RE +++ 20m vs 12m
RR 12,5% CBR 62%

volumen de enfermedad y lento crecimiento

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

Cancer 2014;120:738–43

- **27 pacientes**
- **Mediana 2 líneas previas (0-9**
- **EE 54%**
- **PFS 12 s**
- **3 pts>24 s**



Máster en Tumores Musculoesqueléticos

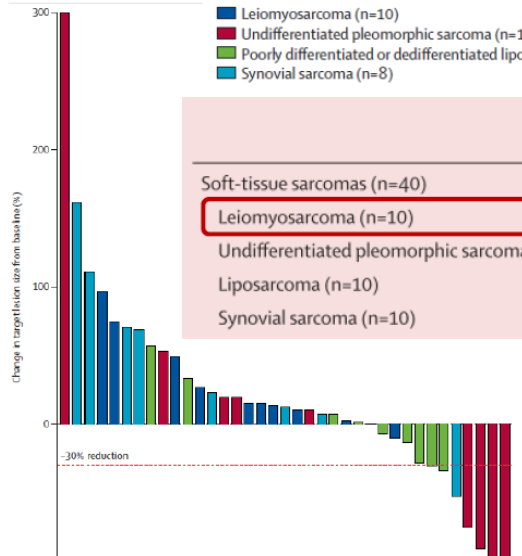
Inmunoterapia

	population	n (%(u)LMS)		RR (%)	3mo PFR (%)	6mo PFR (%)	PFS (months)	OS (months)
nivolumab (Ben-Ami et al., 2017)	uLMS	12	PDL1 + 20%	0	-	-	1.8	-
pazopanib (Benson et al., 2016)	US	44		11	-	-	3	17.5
regorafenib vs. placebo (Mir et al., 2016)	STS, 1 cohort LMS	56 LMS of who 22 uLMS		0	57 vs. 25	21 vs. 7	3.7 vs. 1.8	21 vs. 9.1
sunitinib (Hensley et al., 2009b)	uLMS	23		8.7	-	17.4	1.5	15.1
thalidomide (McMeekin et al., 2007)	uLMS	30		0	-	-	1.9	8.3
aflibercept (Mackay et al., 2012)	uLMS	41		0	-	17	1.8	18.1
alisertib (Hyman et al., 2017)	uLMS	21		0		0	1.7	14.5

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

Hussein A Tawbi, Melissa Burgess, Vanessa Bolejack, Brian A Van Tine, Scott M Schuetze, James Hu, Sandra D'Angelo, Steven Attia, Richard F Riedel, Dennis A Priebat, Sujana Movva, Lara E Davis, Scott H Okuno, Damon R Reed, John Crowley, Lisa H Butterfield, Ruth Salazar, Jaime Rodriguez-Canales, Alexander J Lazar, Ignacio I Wistuba, Laurence H Baker, Robert G Maki, Denise Reinke, Shreyaskumar Patel

Lancet Oncol 2017; 18: 1493–150



	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)

uLMS	HER-2	HER-2 inhibitors (e.g., trastuzumab, CP-724714, CUDC-101)
	EGFR	EGFR inhibitors (e.g., gefitinib, erlotinib, cetuximab, vandetanib)
	PDGFR	PDGFR inhibitors (e.g., pazopanib, imatinib, sunitinib, sorafenib)
	VEGF-VEGFR	VEGF-VEGFR inhibitors (e.g., bevacizumab, aflibercept, vandetanib, cediranib)
	IGF1R	Figitumumab, cixutumumab, AVE1642
	BDNF-NTRK2	BDNF-NTRK2 inhibitors (e.g., K252a)
	PIK3/AKT/mTOR Loss of PTEN	PIK3/AKT/mTOR pathway inhibitors (e.g., curcumin, rapamycin, ridaforolimus)
	AURKA	AURKA inhibitors (e.g., MLN8237, MK-5108, VE465)
	Wnt/β-catenin	β-catenin inhibitors (e.g., LGK-974, PKF118-310, PNU-74654)
	ROR2	ROR2 inhibitors (not yet developed)
	Endoglin/CD105	Anti-CD105 antibodies (in development)
	MDM2	MDM2 inhibitors (e.g., AMG232, RG7112)
	HDAC	HDAC inhibitors (e.g., vorinostat, valproate)
	CD47	Anti-CD47 antibodies (in development)
	ER, PR	Aromatase inhibitors (e.g., letrozole, exemestane) Progestins (e.g., medroxyprogesterone acetate, megestrol acetate)
	Loss of TSG	Synthetic lethality principle (e.g., PARP inhibitors)

Ensayos clínicos

- Fase III de Adriamicina- trabectidina vs adriamicina seguida de trabectidina NCT02997358
- Fase II de nivolumab en leiomiosarcoma uterino, SEE y sarcoma indiferenciado NCT03241745
- Fase II Pembrolizumab en sarcomas de partes blandas y hueso NCT02301039
- Fase I-II pembrolizumab+ Adriamicina en sarcomas de partes blandas NCT02888665
- Fase II pembrolizumab- TVEC NCT 03069378
- Neoadyuvancia con Durvalumab+ Tremelimumab + RT en sarcomas de alto riesgo NCT03116529
- Pembroliziumab+ axitinib en leiomisarcoma NCT02636725
- Fase I-II para sarcomas avanzados primera línea Trabectidina+ Nivolumab+ Ipilimumab NCT03138161
- Fase II randomizado Pazopanib+ Gemcitabina vs Gemcitabina taxotere en sarcomas de partes blandas NCT01593748
- Gemcitabina Taxotere+ Olaratumab Fase Ib-II en sarcomas de partes blandas NCT02659020
- Inhibidores PARP en BRCA2

Conclusiones

LOCALIZADO:

- Histerectomía, no tratamiento adyuvante

PRIMERA LINEA:

- MTS La sustitución de adriamicina por otros fármacos no mejora los resultados
- La combinación de adriamicina con trabectedina aumenta la tasa de respuestas y la PFS respecto a adriamicina sola en un estudio fase III
- La combinación de adriamicina con DTIC mejora los resultados de adriamicina sola en un estudio retrospectivo

- **2as lineas** Gem, Gem TXT,Gem DTIC, Trabectedina, Pazopanib.
- Mejor secuencia desconocida
- Ocasionalmente hormonoterapia
- Inclusión en ensayos clínicos

Universidad Europea MADRID

GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos