Issues in sarcoma

The treatment of uterine sarcomas

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Disclosure slide

1. Employment or Leadership Position

no

2. Consultant or Advisory Role

Novartis, Pfizer, Bayer, MSD, PharmaMar, Infinity

3. Stock Ownership

no

4. Honoraria

Novartis, Pfizer, Bayer, MSD, PharmaMar, Amgen, Eisei, GlaxoSmithKline

5. Research Funding

Novartis

6. Expert Testimony

no

7. Other Remuneration

no

Uterine sarcomas

- 3% of all uterine cancers
- 7% of all adult soft tissue sarcomas

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Undifferentiated sarcoma
- Pure heterologous sarcomas
- Carzinosarcoma (mixed Mullerian tumor)
- Adenosarcoma (+/- sarcomatous overgrowth)

Uterine sarcomas – FIGO staging (1)

Stage	Definition
Leiomyosarcomas and endometrial stromal sarcomasa	
I	Tumor limited to uterus
IA	≤5 cm
IB	>5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

adopted from D`Angelo E, Prat J, Gynecol Oncol 2010

Uterine sarcomas – FIGO staging (2)

Adenosarcomas	
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
Carcinosarcomas	
Carcinosarcomas should be staged as carcinomas of the endometrium	

adopted from D`Angelo E, Prat J, Gynecol Oncol 2010

Uterine sarcomas

- Leiomyosarcoma
- most frequent uterine sarcoma (~40%)
- Local therapy:

  total hysterectomy

  bilateral salpingo-oophorectomy and LN dissection not recommended
- LN involvement in <3% of cases
- Hematonenous metastases, mostly in the lungs

EUROPEAN JOURNAL OF CANCER 44 (2008) 808–818

available at www.sciencedirect.com

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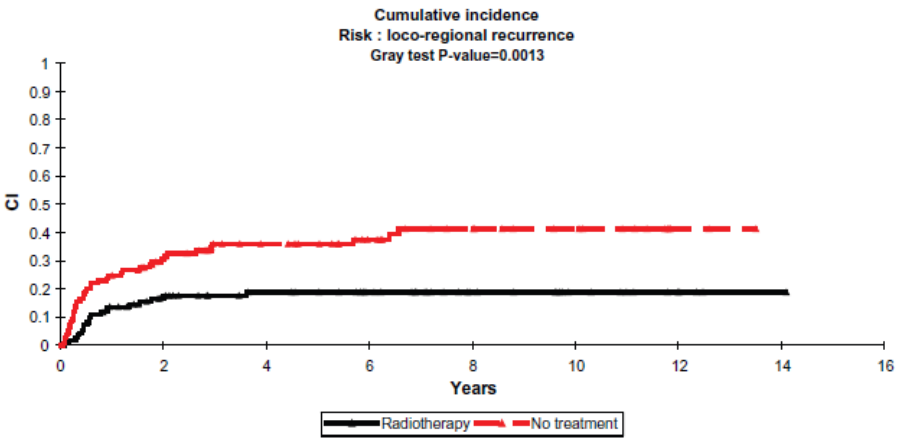
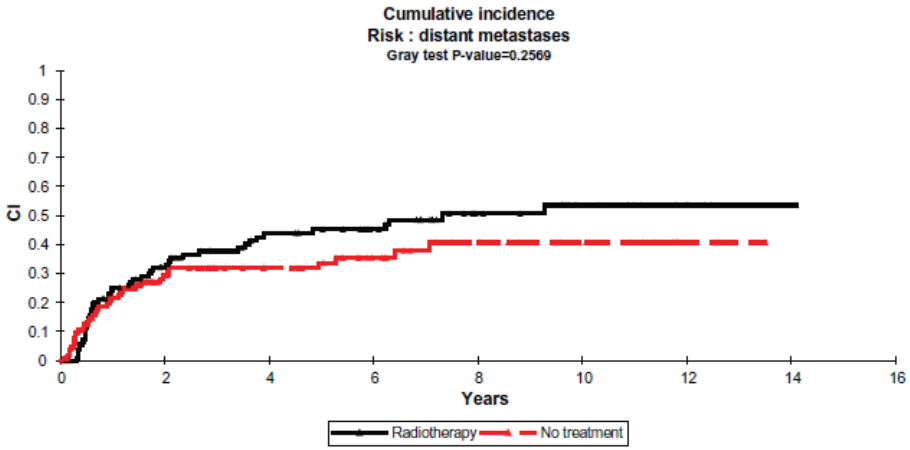
journal homepage: www.ejconline.com

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)

Leiomyosarcoma postoperative radiation





103 leiomyosarcomas, 91 carcinosarcomas and 28 endometrial stromal sarcomas.
Patients were randomised to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks.

Reed NS et al., Eur J Cancer 2008

EUROPEAN JOURNAL OF CANCER 44 (2008) 808–818

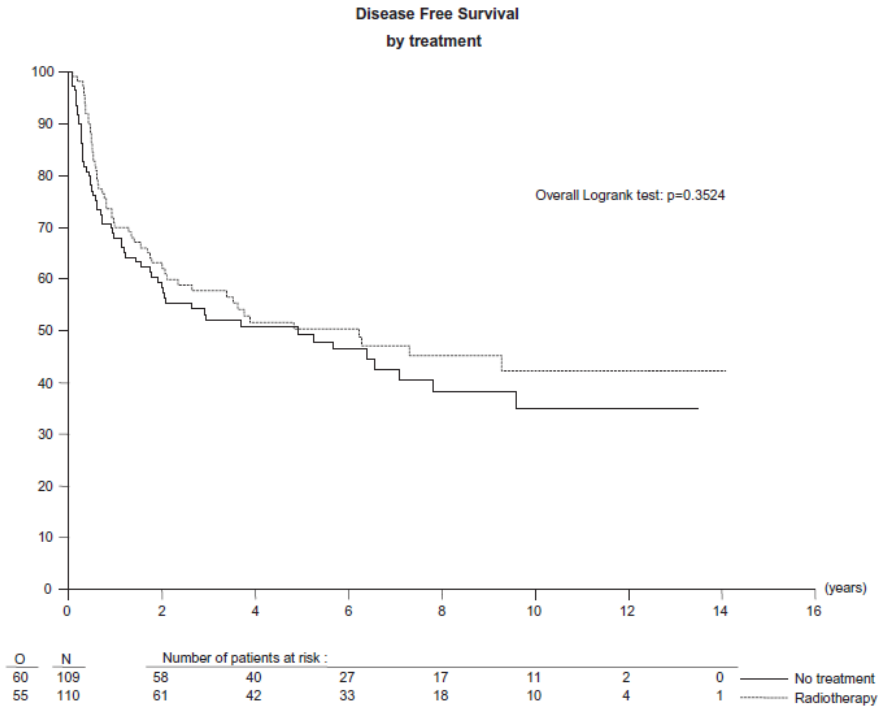
available at www.sciencedirect.com

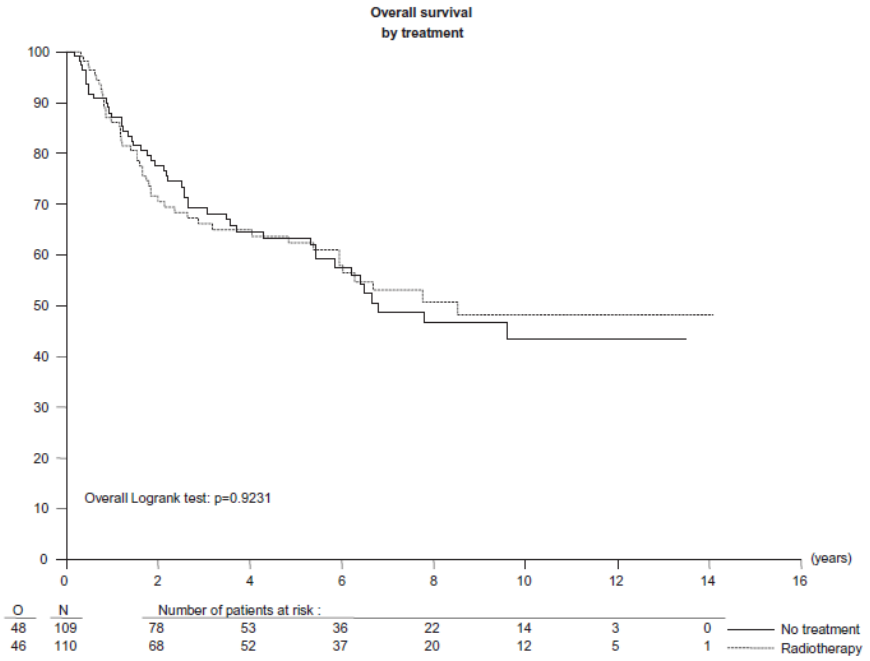
ScienceDirect

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)

Leiomyosarcoma postoperative radiation





Reed NS et al., Eur J Cancer 2008

VIENNA 2012 ESMO congress

www.esmo2012.org

Adjuvant Chemotherapy in Soft Tissue Sarcomas 1973-1997

Meta-analysis

14 Randomized Trials: 1568 Patients

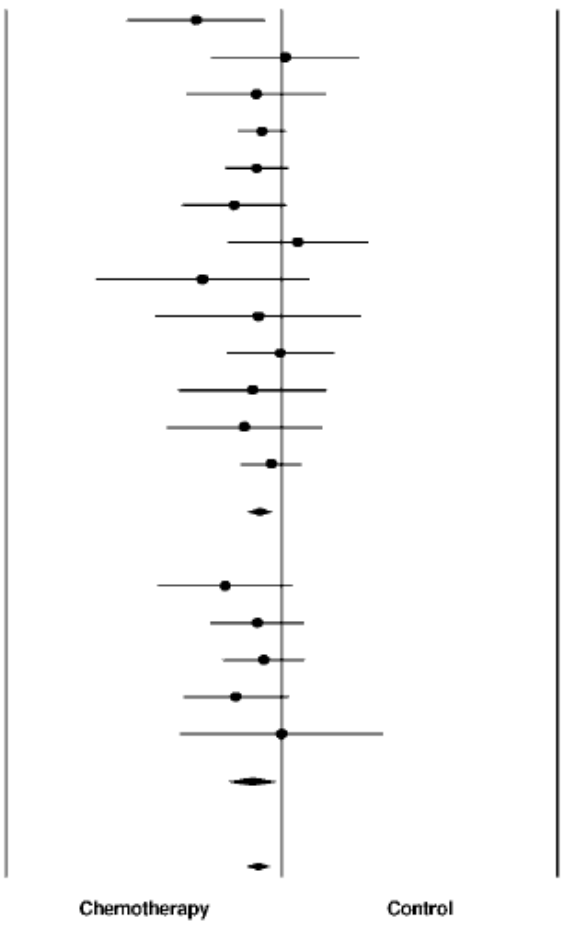
Local RFI	p = 0.016	HR = 0.73 (0.56-0.94)
RFS	p = 0.0001	HR = 0.75 (0.64-0.87)
OS	p = 0.12	HR = 0.89 (0.76-1.03)

ASCO Annual '09 Meeting

Sarcoma Meta-analysis Collaboration, Lancet, 1997

Meta-analysis 2008 - RFS

	Chemotherapy	Citation	Treated	Control	PValue	Effect	Lower	Upper
	Type I	Bergonie et al	11 / 28	19 / 26	.01	.24	.08	.75
	Type I	DFCI/MGH	7 / 21	8 / 25	.92	1.06	.31	3.66
	Type I	ECOG	9 / 24	11 / 23	.47	.65	.20	2.09
	Type I	EORTC	92 / 193	105 / 188	.11	.72	.48	1.08
	Type I	GOG	52 / 112	62 / 109	.12	.66	.39	1.12
	Type I	IGSC	14 / 40	25 / 46	.07	.45	.19	1.08
	Type I	Mayo	12 / 22	11 / 23	.65	1.31	.41	4.23
	Type I	MDA	12 / 18	15 / 17	.13	.27	.05	1.57
	Type I	NCI4	9 / 17	5 / 8	.65	.67	.12	3.77
	Type I	NCI5	22 / 38	24 / 41	.95	.97	.40	2.38
	Type I	NCI6	9 / 21	11 / 20	.44	.61	.18	2.11
	Type I	Rizzoli et al	7 / 16	13 / 22	.35	.54	.15	1.98
	Type I	SSG	65 / 121	69 / 119	.51	.84	.51	1.40
Fixed	**Type I (13)**		**321 / 671**	**378 / 667**	**.00**	**.69**	**.56**	**.86**
	Type II	Brodowicz et al	7 / 31	12 / 28	.10	.39	.13	1.20
	Type II	Frustaci et al	28 / 53	32 / 51	.31	.66	.30	1.46
	Type II	Gortzak et al	30 / 67	35 / 67	.39	.74	.38	1.46
	Type II	Petrioli et al	13 / 45	20 / 43	.09	.47	.19	1.13
	Type II	SAKK	4 / 12	4 / 12	1.00	1.00	.18	5.46
Fixed	**Type II (5)**		**82 / 206**	**103 / 201**	**.02**	**.61**	**.41**	**.92**
Fixed	**Combined (18)**		**403 / 879**	**481 / 868**	**.00**	**.67**	**.56**	**.82**



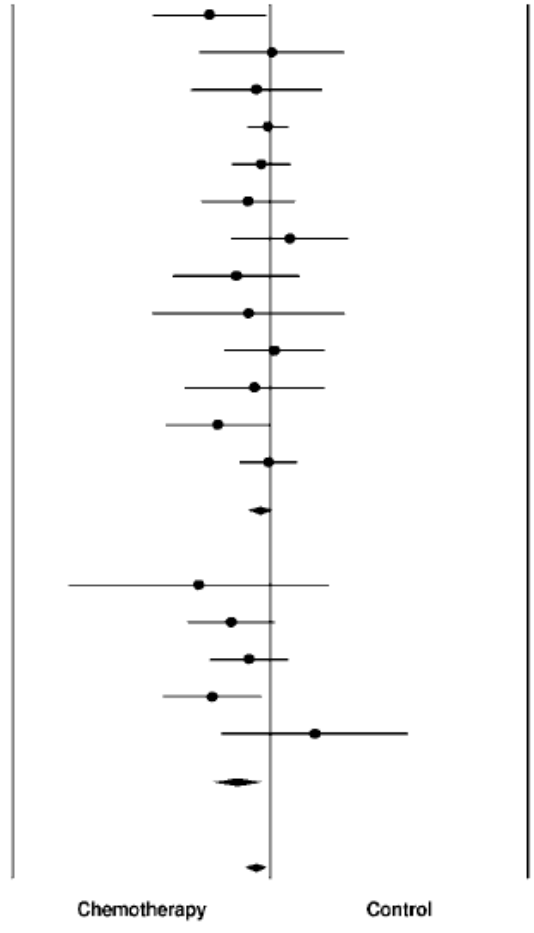
VIENNA 2012 ESMO congress

Pervaiz et al., Cancer 2008

www.esmo2012.org

Meta-analysis 2008 - OS

	Chemotherapy	Citation	Treated	Control	PValue	Effect	Lower	Upper
	Type I	Bergonie et al	10 / 33	18 / 32	.03	.34	.12	.94
	Type I	DFCI/MGH	6 / 21	7 / 25	.97	1.03	.28	3.73
	Type I	ECOG	9 / 24	10 / 23	.68	.78	.24	2.51
	Type I	EORTC	94 / 234	96 / 233	.82	.96	.66	1.39
	Type I	GOG	51 / 113	55 / 112	.55	.85	.50	1.44
	Type I	IGSC	16 / 43	23 / 49	.35	.67	.29	1.54
	Type I	Mayo	14 / 28	12 / 29	.51	1.42	.50	4.03
	Type I	MDA	15 / 26	20 / 28	.29	.55	.18	1.69
	Type I	NCI4	9 / 17	5 / 8	.65	.67	.12	3.77
	Type I	NCI5	22 / 38	23 / 41	.87	1.08	.44	2.62
	Type I	NCI6	8 / 21	9 / 20	.65	.75	.22	2.61
	Type I	Rizzoli et al	12 / 34	25 / 43	.05	.39	.16	.99
	Type I	SSG	57 / 121	57 / 119	.90	.97	.58	1.61
Fixed	**Type I (13)**		**323 / 753**	**360 / 762**	**.09**	**.84**	**.68**	**1.03**
	Type II	Brodowicz et al	1 / 31	3 / 28	.25	.28	.03	2.84
	Type II	Frustaci et al	20 / 53	28 / 51	.08	.50	.23	1.09
	Type II	Gortzak et al	22 / 67	28 / 67	.28	.68	.34	1.38
	Type II	Petrioli et al	13 / 45	23 / 43	.02	.35	.15	.85
	Type II	SAKK	5 / 14	3 / 15	.34	2.22	.42	11.83
Fixed	**Type II (5)**		**61 / 210**	**85 / 204**	**.01**	**.56**	**.36**	**.85**
Fixed	**Combined (18)**		**384 / 963**	**445 / 966**	**.01**	**.77**	**.64**	**.93**



original article

Annals of Oncology 21: 2436–2441, 2010
doi:10.1093/annonc/mdq238
Published online 3 May 2010

Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database

Soft tissue sarcoma adjuvant chemotherapy

- Retrospective analysis of 1.513 patients with localised soft tissue sarcoma
- Central review of histology and grading according FNCLCC system
- median follow-up 9 years
- Impact of adjuvant chemotherapy:
  - multivariat analysis shows a significant improvement in

    5-year MFS: 58 % vs 49 %, HR 0.7, p = 0.01

    5-year OS: 58 % vs 45 %, HR 0.6, p = 0.0002

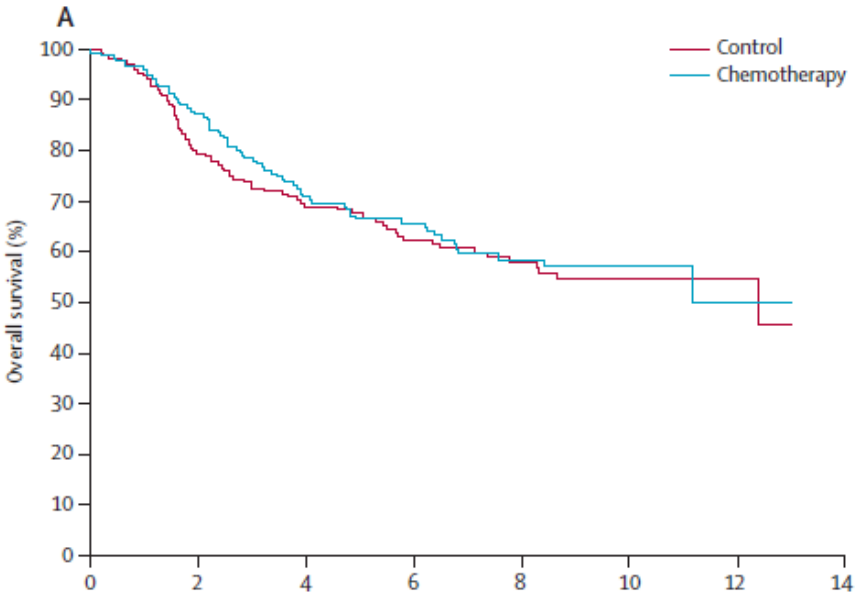
    for patients with grade 3 soft tissue sarcomas only

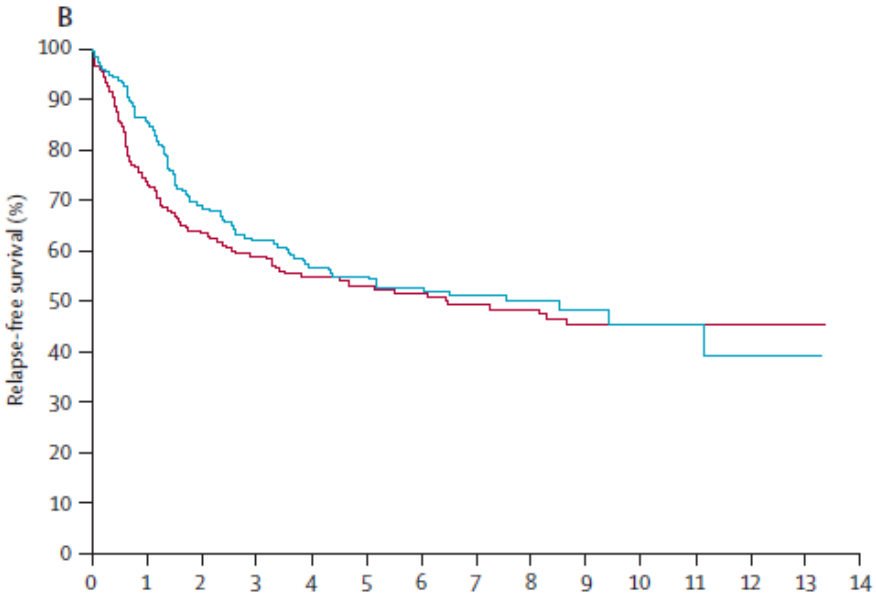
    (no difference in patients with grade 2 soft tissue sarcomas)

Soft tissue sarcoma adjuvant chemotherapy

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

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





Interpretation Adjuvant chemotherapy with doxorubicin and ifosfamide in resected soft-tissue sarcoma showed no benefit in relapse-free survival or overall survival. Future studies should focus on patients with larger, grade III, and extremity sarcomas.

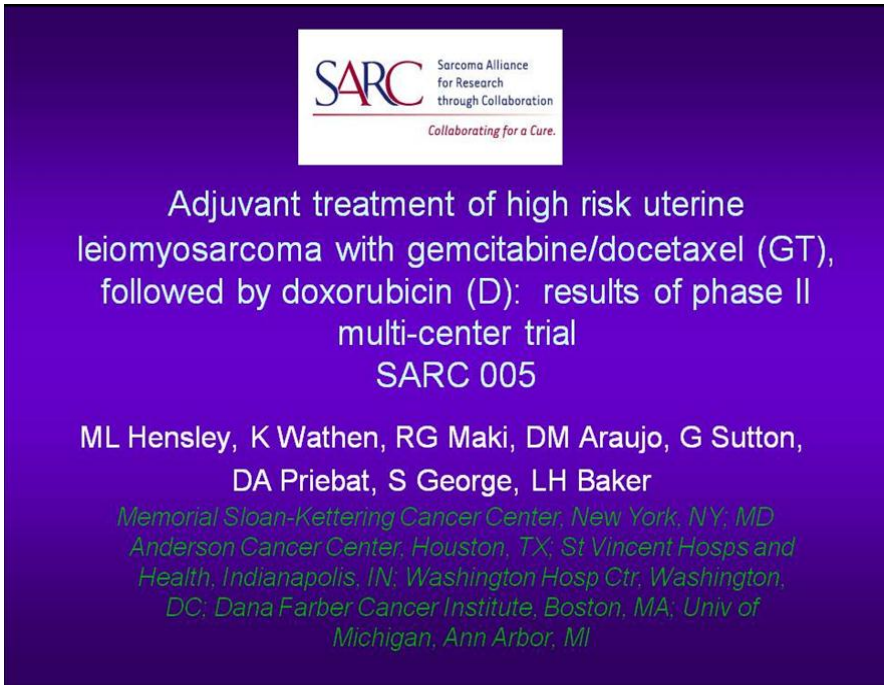
VIENNA 2012 ESMO congress

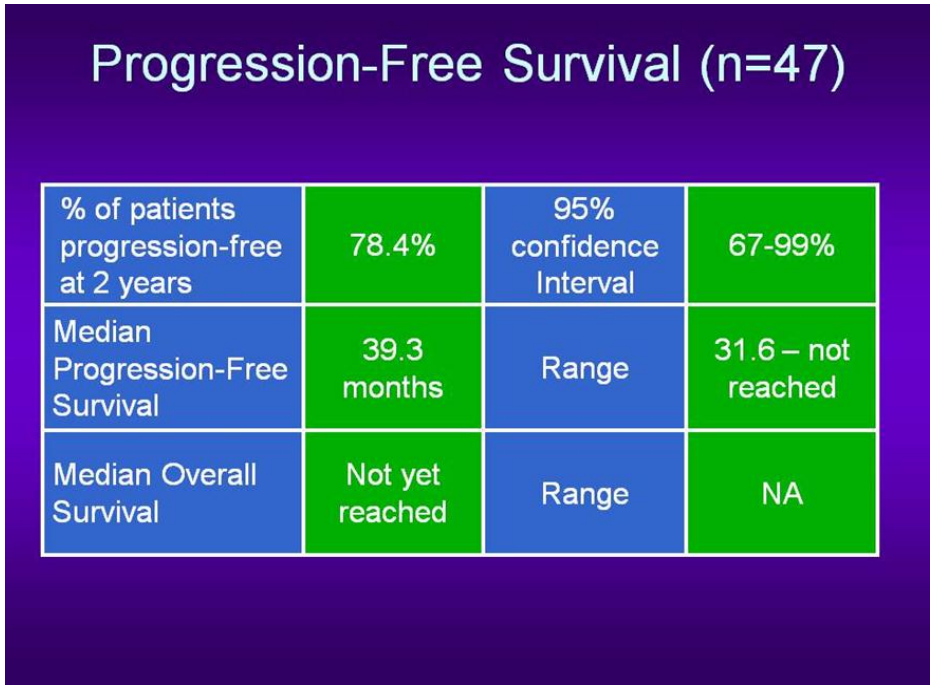
Woll et al., Lancet Oncology 2012

www.esmo2012.org

Uterine leiomyosarcoma – adjuvant chemotherapy

- Interesting phase II data





- No randomised trial available, yet
- No standard, shared decision making

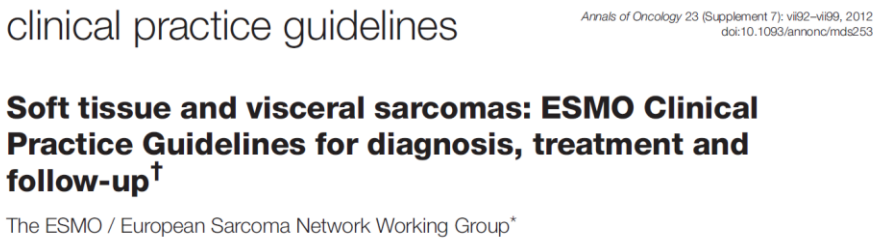
Hensley et al., ASCO 2010, #10021

Uterine sarcomas

- Leiomyosarcoma
- Adjuvant therapy:

  postoperative radiation not recommended

  chemotherapy no standard, tested vs control in ongoing randomised trial


clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii92–vii99, 2012
doi:10.1093/annonc/mds253

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

The ESMO / European Sarcoma Network Working Group*

Uterine sarcomas

- Leiomyosarcoma
- Advanced disease:

  chemotherapy

  targeted therapy

  hormonal treatment

Chemotherapy in STS

Active single agents:

- >20 % response rate:
  ifosfamide, doxorubicin, epirubicin

- <20 %: DTIC, *temozolomide, gemcitabine, docetaxel, trofosfamide*, trabectedin, pazopanib

Gynecologic Oncology 123 (2011) 553–556

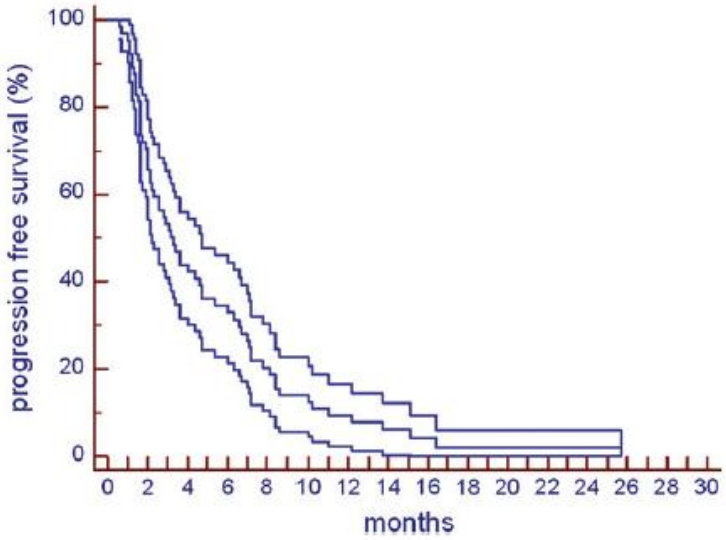
Contents lists available at SciVerse ScienceDirect

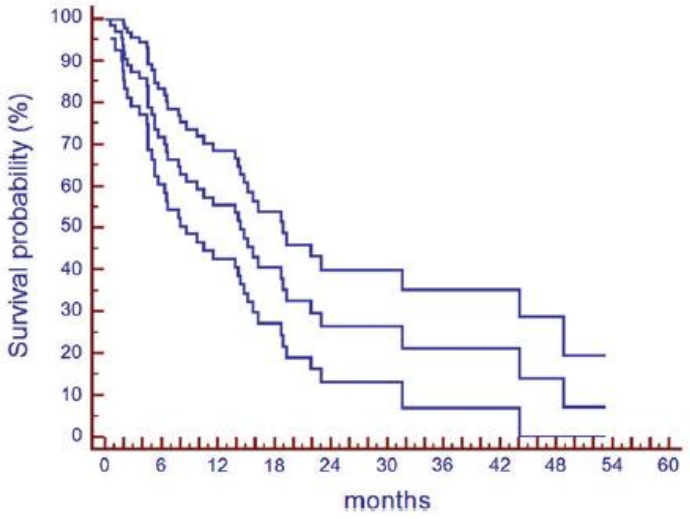
Gynecologic Oncology

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

Uterine leiomyosarcoma trabectedin

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

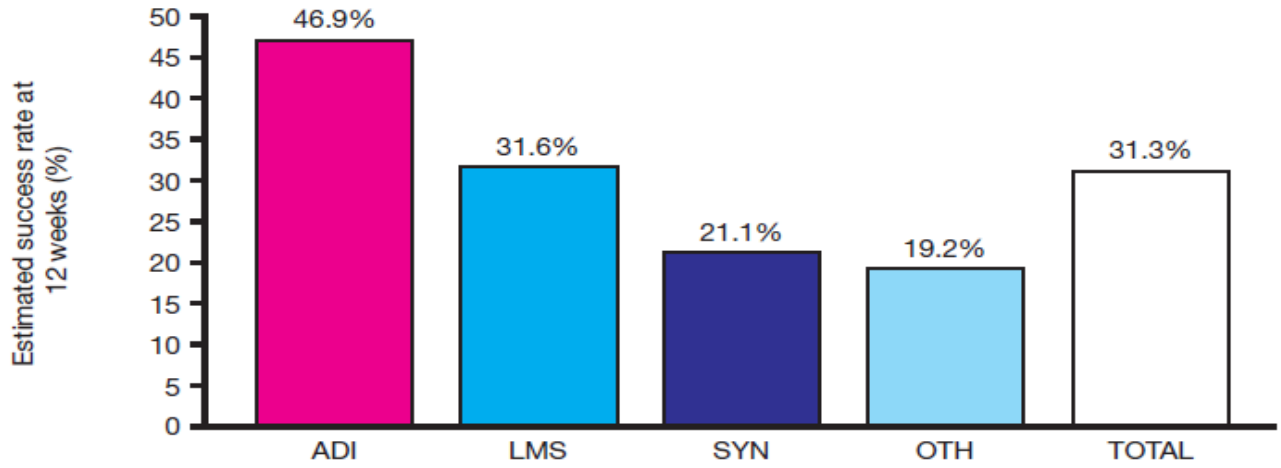




Sanfilippo R et al., Gynecol Oncol 2011

Eribulin: PFR at 12 weeks

Figure 2. Success rate at 12 weeks after the start of therapy (efficacy population, N=115)



Success rate					
Number (n)	15	12	4	5	36
90% 1-sided CI	34.5, 100	21.6, 100	9.5, 100	9.7, 100	25.6, 100
90% 2-sided CI	29.1, 65.3	17.6, 48.7	6.1, 45.6	6.6, 39.4	22.9, 40.6

ADI, adiposytic sarcoma; LMS, leiomyosarcoma; SYN, synovial sarcoma; OTH, other type of sarcoma; CI, confidence interval

Schöffski et al; J Clin Oncol. 2010;28: Abstract 10031.

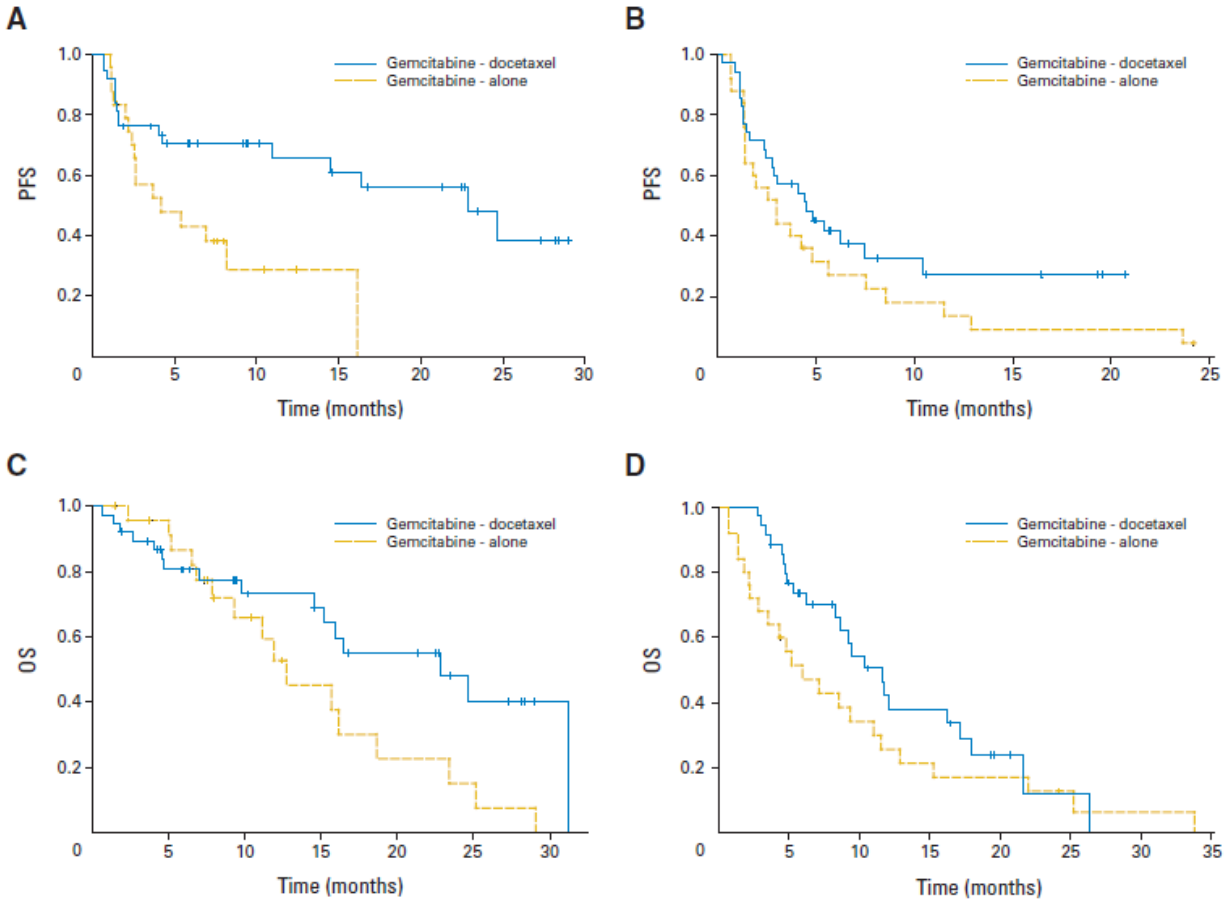
Combination chemotherapy in STS

- combination of doxorubicin or epirubicin with ifosfamide ± DTIC results in response rates of up to 50 % (appr. 10% CR)
- significantly higher response rate and progression-free survival compared to single agent therapy
- significantly higher toxicity
- no significant improvement of overall survival in first-line therapy so far (EORTC 62012: doxo vs. doxo / ifos pending)

VOLUME 25 · NUMBER 19 · JULY 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Combination chemotherapy randomized trial

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



Maki RG et al., J Clin Oncol 2007

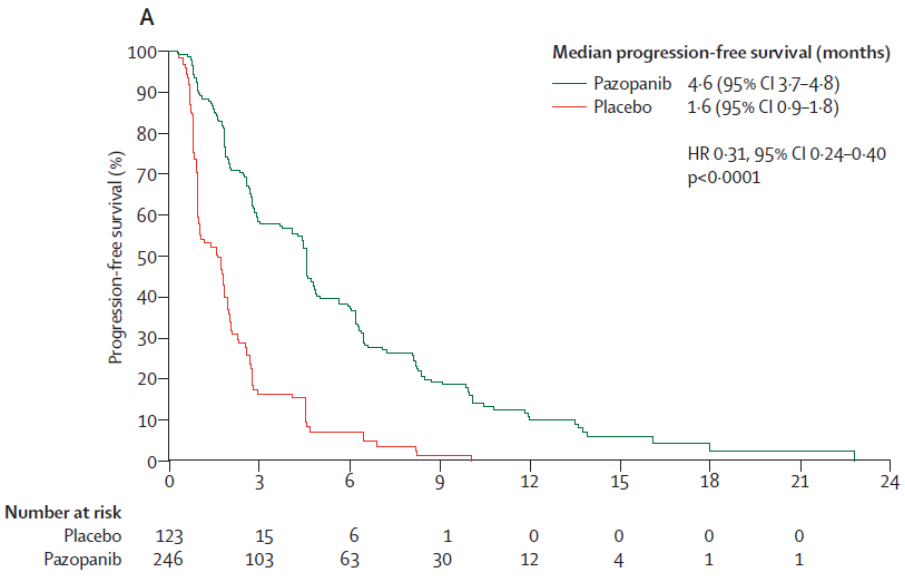
Uterine leiomyosarcoma gemcitabine / docetaxel phase II trials

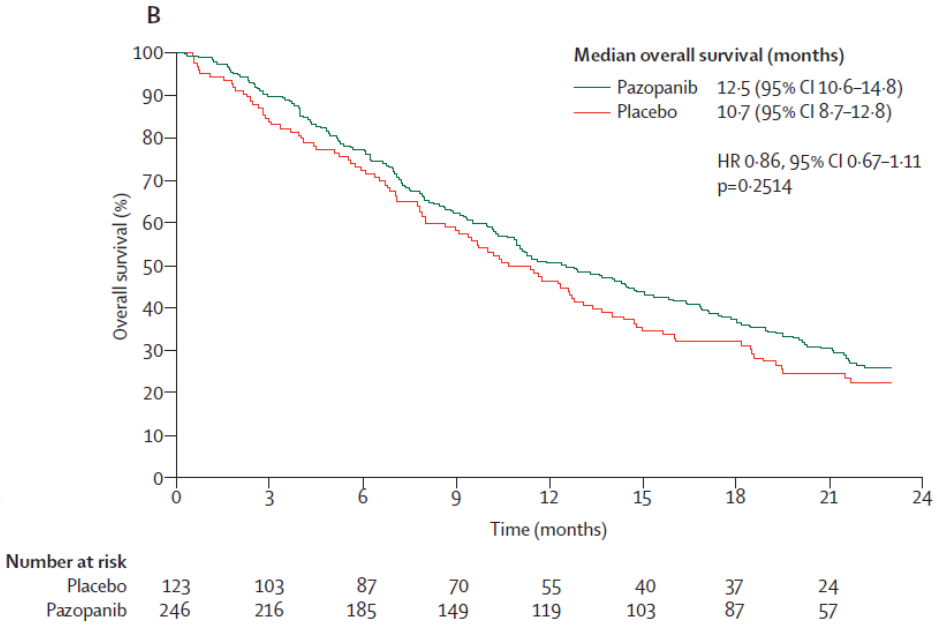
	N (non uterine)	prior therapy	RR
monocentric[1]	34 (5)	0-2	53%
multicentric[2]	42	0	36%
multicentric[3]	48	1	27%

[1]*Hensley ML et al., JCO 2002*
[2]*Hensley ML et al., Gynecol Oncol 2008*
[3]*Hensley ML et al., Gynecol Oncol 2008*

Pazopanib in STS randomized trial

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





van der Graaf et al., Lancet 379: 1879-1886, 2012

Leiomyosarcoma targeted therapies

	RR
Gem / Doce + Bevacizumab	11/25[1]
Cave: toxicity, phase III ongoing	
Sunitinib	2/23[2]
Sorafenib	1/37[3]
Pazopanib	1/41[4]

[1]*Verschraegen et al., JCO 2008 (abstract)*
[2]*Hensley ML et al., Gynecol Oncol 2009*
[3]*Maki RG et al., J Clin Oncol 2009*
[4]*Sleijfer S et al., J Clin Oncol 2009*

Estrogen and progesteron receptor expression in uterine leiomyosarcoma

Author	Patients	ER+	PR+
Wade et al. [36]	16	60%	60%
Mittal et al. [38]	12	–	17%
Kitaoka et al. [39]	22	36%	36%
Leitao et al. [40]	25	40%	38%
Akhan et al. [41]	19	26%	37%
Bodner et al. [42]	21	57%	43%

from Gadducci et al., Critical Reviews in Oncology/Hematology 2008

Gynecologic Oncology 116 (2010) 424–429

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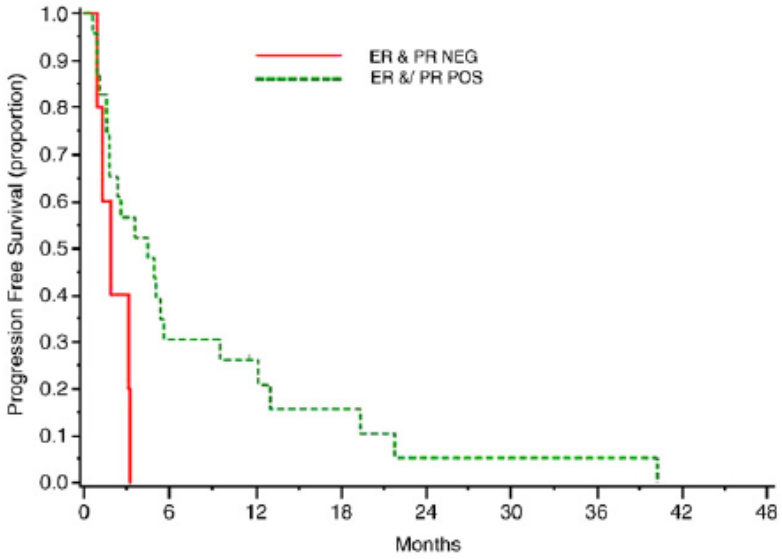
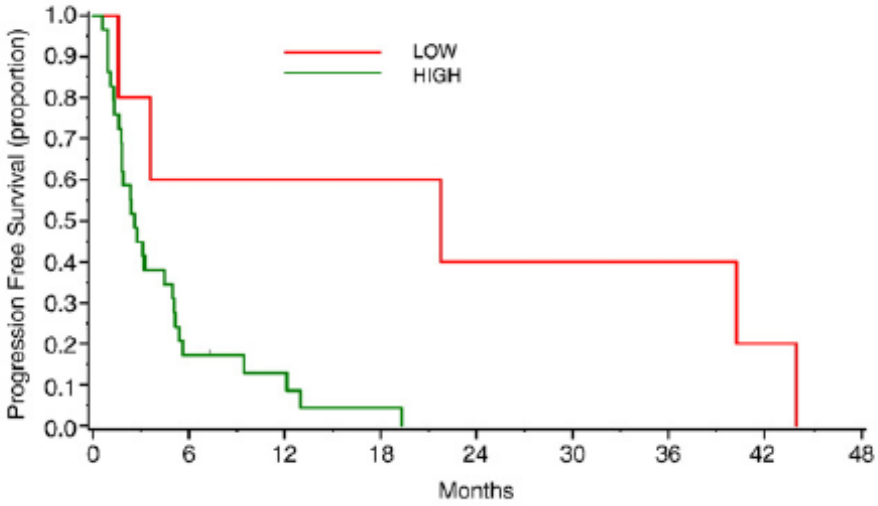
journal homepage: www.elsevier.com/locate/ygyno

Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors

Uterine leiomyosarcoma hormonal therapy





O'Cearbhaill R et al., Gynecol Oncol 2010

Uterine Sarcomas

- Endometrial stromal sarcoma (ESS)
- 10 to 15% of all uterine sarcomas
- Local therapy:

  total hysterectomy

  bilateral salpingo-oophorectomy recommended (no randomized data)

  postoperative radiation results in reduction of local recurrence rate (not recommended due to lack of OS improvement)
- Generally hormonal responsive

Sampath S et al., Int J Radiat Oncol Biol Phys 2010

http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

Available online at www.sciencedirect.com
SCIENCE DIRECT
Gynecologic Oncology xx (2005) xxx – xxx
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: Single center experience with 10 cases and review of the literature

Daniel Pink [a], Tanja Lindner [a], Alicia Mrozek [a], Albrecht Kretzschmar [a], Peter C. Thuss-Patience [b], Bernd Dörken [a,b], Peter Reichardt [a,b,*]

Endometrial stromal sarcoma hormonal therapy

- Patients with a history of ESS must not be treeated with estrogens or tamoxifen
- Withdrawl can result in disease stabilization
- Medroxyprogesterone acetate (2/3) and aromatase inhibitors, in particular (4/5) lead to sustained disease control in most cases
- NCCN guidelines recommend adjuvant hormonal therapy in stages II-IV (no randomized data)

Pink D et al., Gynecol Oncol 2005

http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

Uterine Sarcomas

- Undifferentiated sarcoma
- Pure heterologous sarcomas
- 5 to 10% of all uterine sarcomas
- Local therapy:

  total hysterectomy

  bilateral salpingo-oophorectomy and dissection of pelvic and para-aortal LN not recommended
- Treatment according recommendations for adult soft tissue sarcomas

Uterine Sarcomas

- Carzinosarcoma (mixed Mullerian tumor)
- ~40% of all uterine sarcomas
- Local therapy:

  total hysterectomy

  bilateral salpingo-oophorectomy

  dissection of pelvic and para-aortal LN (diagnostic +, design postoperative treatment +, impact on OS ?)
- Dedifferentiated or metaplastic endometrial carcinoma

Uterine Sarcomas

- Carzinosarcoma (mixed Mullerian tumor)
- Adjuvant therapy

  Chemotherapy:

  lower mortality rate with 3 cycles of cisplatin / ifosfamide compared to radiation[1]

  superior PFS and OS with carboplatin / paclitaxel compared to radiation alone[2]

  Ongoing trial: ifosfamide / paclitaxel vs carboplatin / paclitaxel[3]

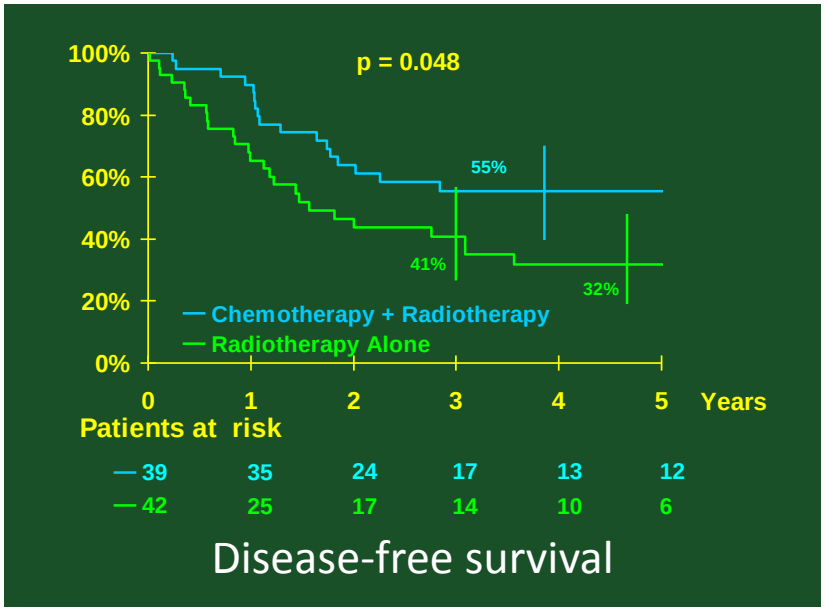
  Pelvic radiation:

  improved local control, no benefit in PFS and OS[4]

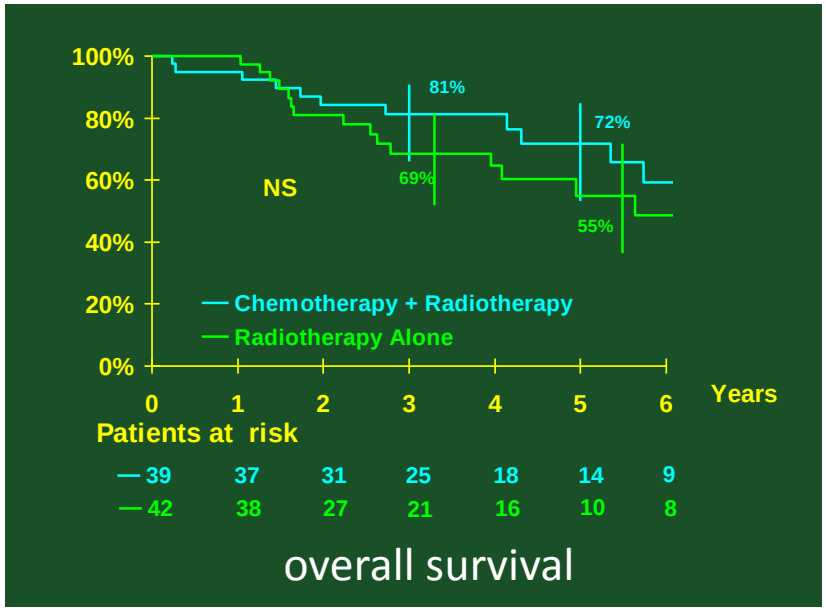
[1]*Wolfson AH et al., Gynecol Oncol 2007*
[2]*Makker V et al., Gynecol Oncol 2008*
[3]*ClinicalTrials.gov Identifier: NCT00954174*
[4]*Reed NS et al., Eur J Cancer 2008*

A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin in localized uterine sarcomas. Results on 81 patients

- Patients with FIGO stage ≤III after complete surgery
- Stratification carcinosarcoma vs. others
- Pelvic radiation with 45 Gy, brachytherapy optional
- Chemotherapy: doxorubicin, ifosfamide, cisplatin
- 2 toxic deaths
- Trial stopped due to low recruitement



Disease-free survival



overall survival

Pautier et al., Eur J Cancer 47 (suppl.2, 30LBA), 2011

Uterine Sarcomas

- Carzinosarcoma (mixed Mullerian tumor)
- Advanced disease

Single agent chemotherapy:

- cisplatin (18-42%), ifosfamide (18-32%), paclitaxel (18%), topotecan (10%)

Combination chemotherapy:

- cisplatin / ifosfamide vs ifosfamide 54 vs. 36%[1]
- paclitaxel / ifosfamide vs ifosfamide 45 vs. 29%[2]
- paclitaxel / carboplatin 54%[3]

[1]*Sutton G et al., Gynecol Oncol 2000*
[2]*Homesley HD et al., J Clin Oncol 2007*
[3]*Powell MA et al., J Clin Oncol 2010*

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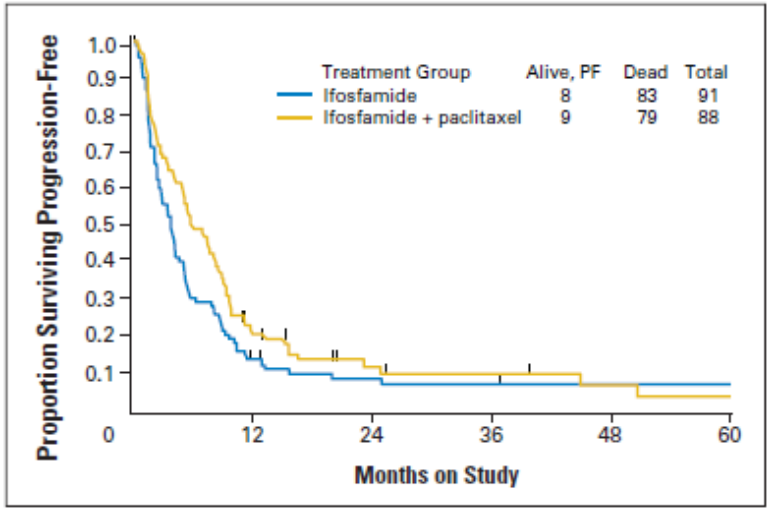
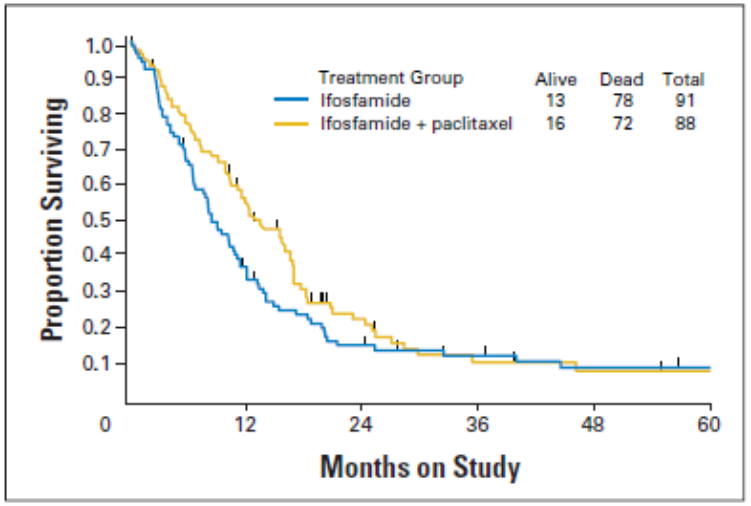
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Carcinosarcoma randomized trial

Phase III Trial of Ifosfamide With or Without Paclitaxel in Advanced Uterine Carcinosarcoma: A Gynecologic Oncology Group Study





Homesley HD et al., J Clin Oncol 2007

Uterine Sarcomas

- Adenosarcoma (+/- sarcomatous overgrowth)
- Local therapy:

  total hysterectomy

  (bilateral salpingo-oophorectomy ?)

  (dissection of pelvic and para-aortal LN ?)
- Sometimes atypical but benign epithelial component + low grade sarcoma (ESS)
- Sarcomatous overgrowth >25% high-grade sarcoma

Uterine Sarcomas

- Adenosarcoma (+/- sarcomatous overgrowth)
- Systemic therapy:
    - adenosarcoma
        - no adjuvant treatment
        - hormonal therapy may be an option in advanced or recurrent disease
    - sarcomatous overgrowth
        - according recommendations for adult high-grade soft tissue sarcomas