

Sequencing of systemic agents in the treatment of uterine sarcoma

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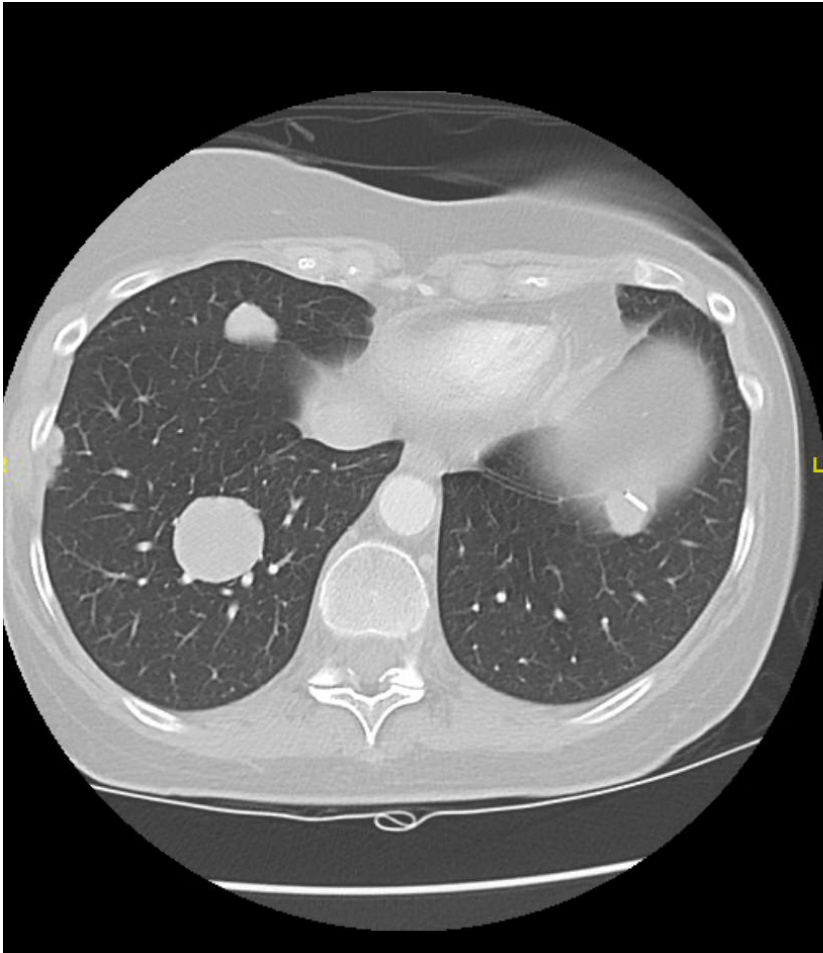
VERBAL DISCLOSURE

- My institution has received grants for me from Amgen, Genentech, Eli Lilly, Array, TESARO Inc., Morphotek, and Janssen/Johnson & Johnson.
- I have received honoraria for speakers' bureaus from Genentech, Roche, AstraZeneca, Myriad, and Janssen/Johnson & Johnson.
- I have received honoraria for my consulting with Merck, TESARO Inc., Gradalis, Advaxis, Amgen, Bayer, Insys, Clovis, Mateon (formally OxiGENE), Roche, Genentech, AstraZeneca, Pfizer, and PPD.
- I agree that the content of this presentation will be well balanced, unbiased, and evidence-based. Opinions that are not supported by evidence or are supported by limited or preliminary evidence will be so identified.

CASE

- 56 yo female with 20 yr h/o uterine fibroids
- Developed pelvic pain and pressure
- TAH BSO – 11 cm high grade LMS
- Baseline staging revealed lesions in lung and liver
- Biopsy of liver – met LMS

Metastatic ULMS – First line

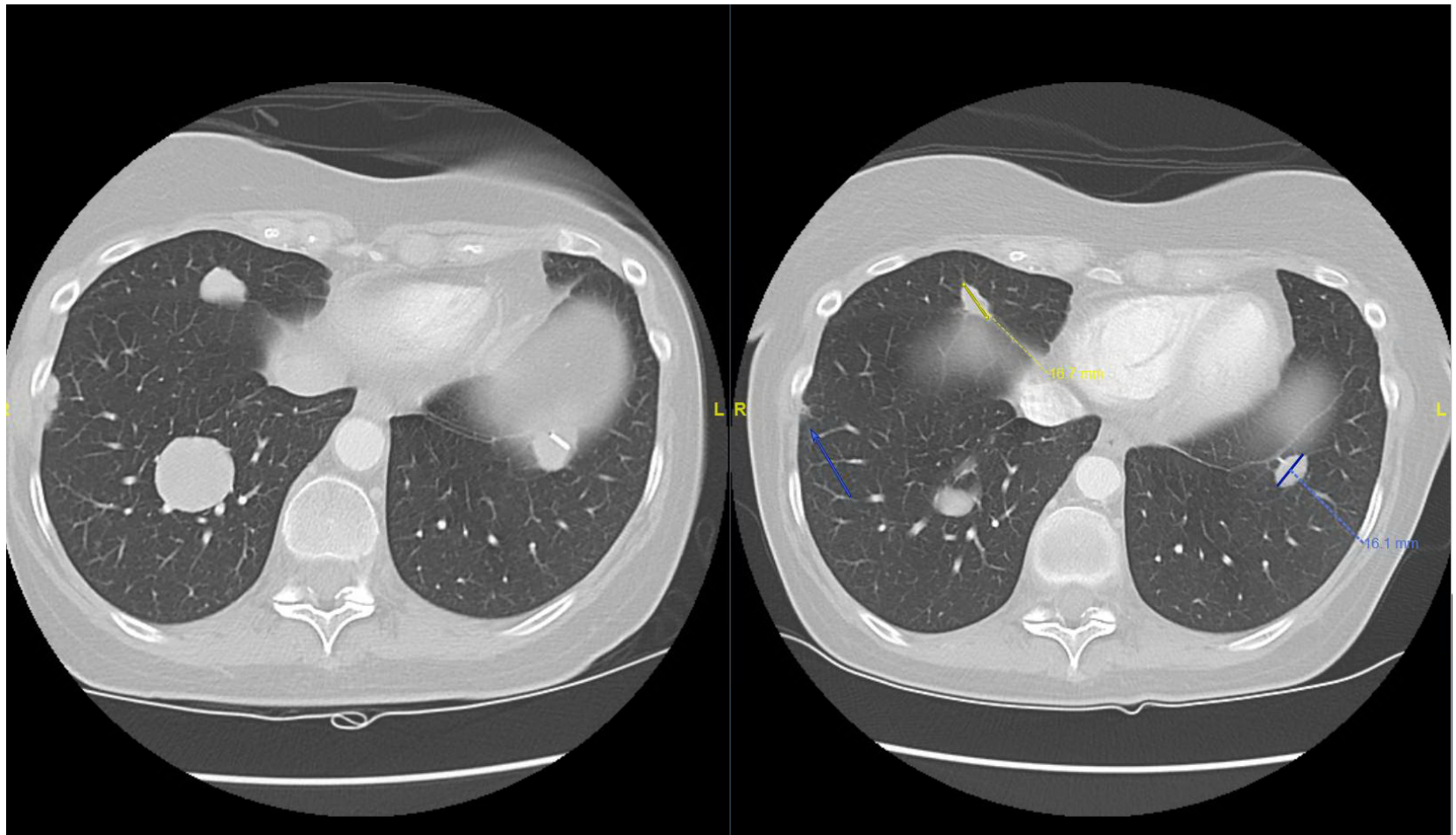


BASELINE

Metastatic ULMS – First line

- Patient was treated with 4 cycles of gemcitabine-docetaxel

Metastatic ULMS – First line



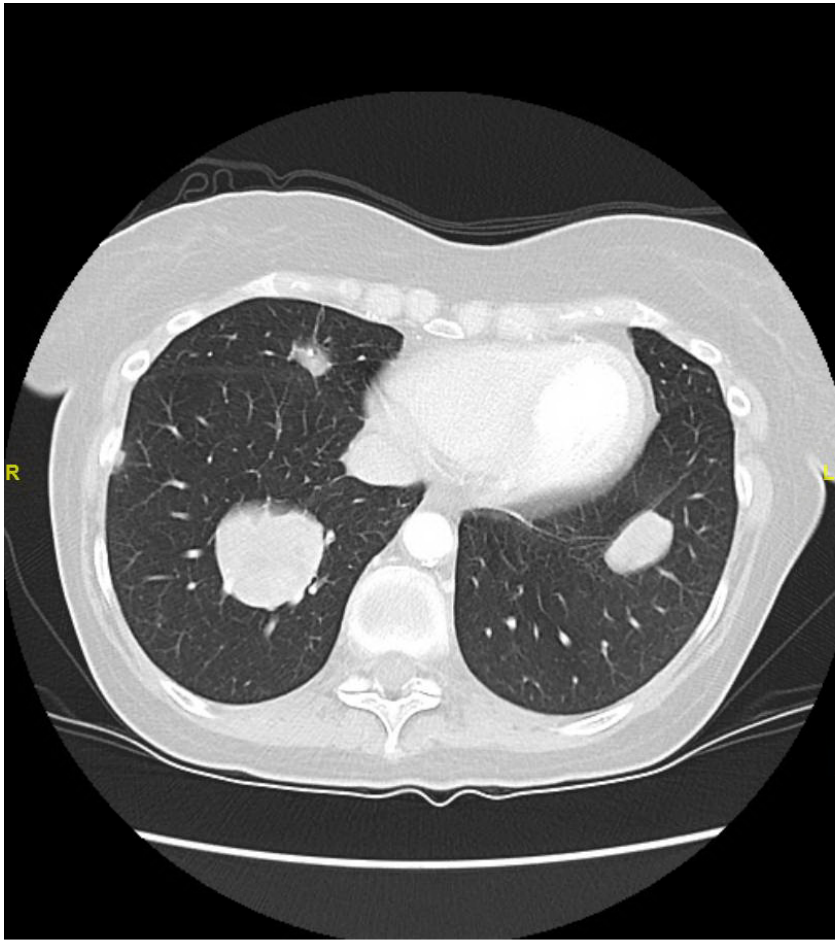
BASELINE

AFTER 4 CYCLES OF GEMCITABINE

Metastatic ULMS – First line

- Continued on through 6 cycles of gem/docetaxel
- Developed notable proximal muscle weakness, neuropathy and edema
- Changed to gemcitabine alone with continued excellent disease control for an additional 4 cycles
- Ultimately, developed disease progression

Metastatic ULMS – Second line

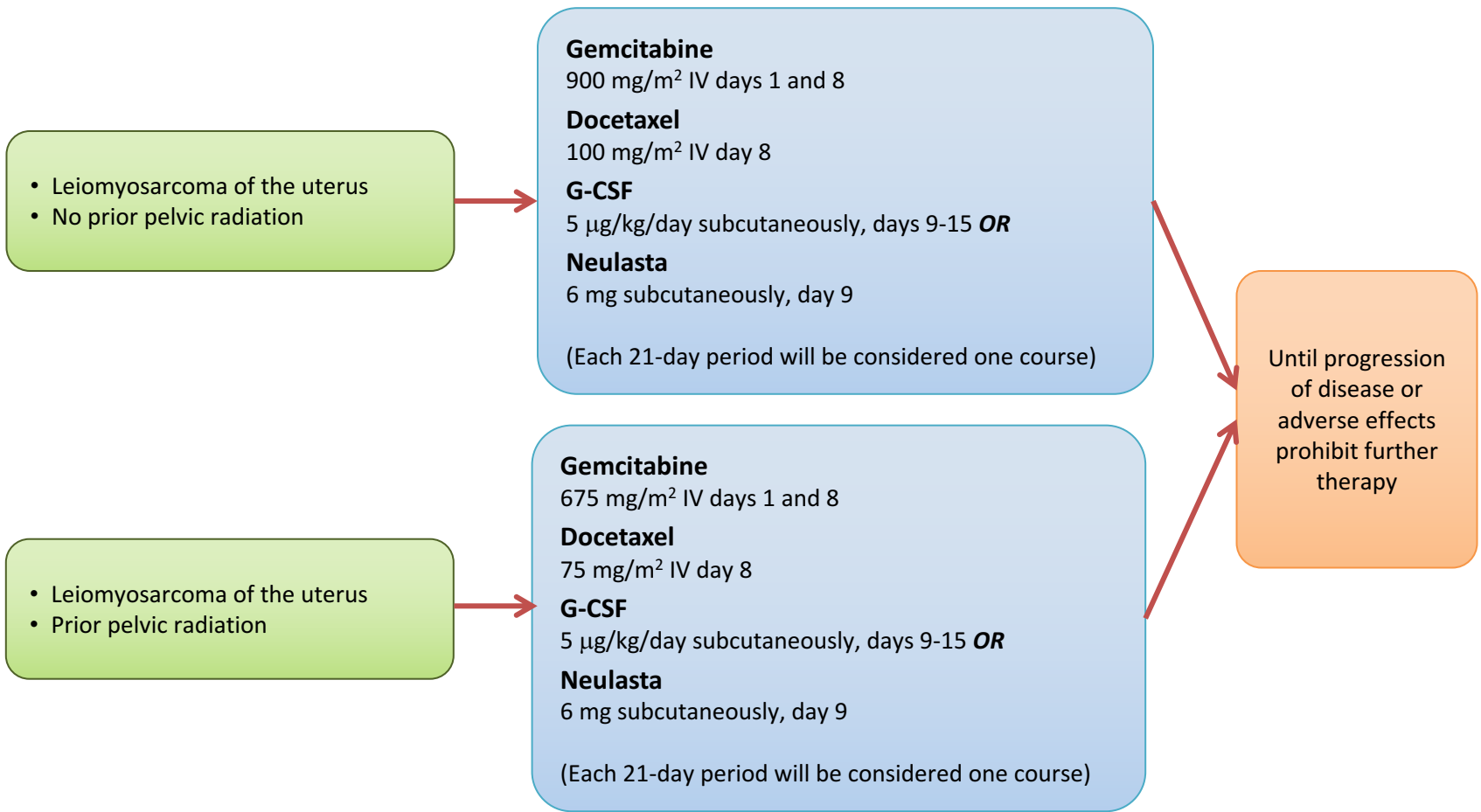


BASELINE

Is there an optimal sequence?


GOG 87L: First-line, Measurable Uterine LMS

GOG 87-L



GOG 87L: RECIST Response

Best Response	39 Patients Evaluable for Response	Response Rate
CR	2/39	4.8%
PR	13/39	31%
SD	11/39	26.2%
POD	12/39	32%



Clinical Benefit Rate: 62%

19/38 (50%) patients received ≥ 6 cycles

GeDDiS - Trial Design

Eligible patients (n=250)

*Stratification factors:

- age (≤ 18 years, >18 years)
- histological subtype:
 - Uterine leiomyosarcoma
 - Synovial sarcoma
 - Pleomorphic
 - Other types of eligible STS

1:1 randomisation*

Control Arm:

Doxorubicin 75 mg/m² day 1
every 21 days x 6 cycles

Investigational Arm:

Gemcitabine 675 mg/m² days 1, 8
Docetaxel 75 mg/m² day 8
every 21 days x 6 cycles,
with GCSF

Disease assessments (RECIST 1.1)

at:

- Baseline
- 12 weeks post randomisation
- 24 weeks post randomisation
- 12 weekly thereafter

Quality of life assessments at:

- Baseline
- 12 weeks post randomisation
- 18 weeks post randomisation
- 24 weeks post-randomisation

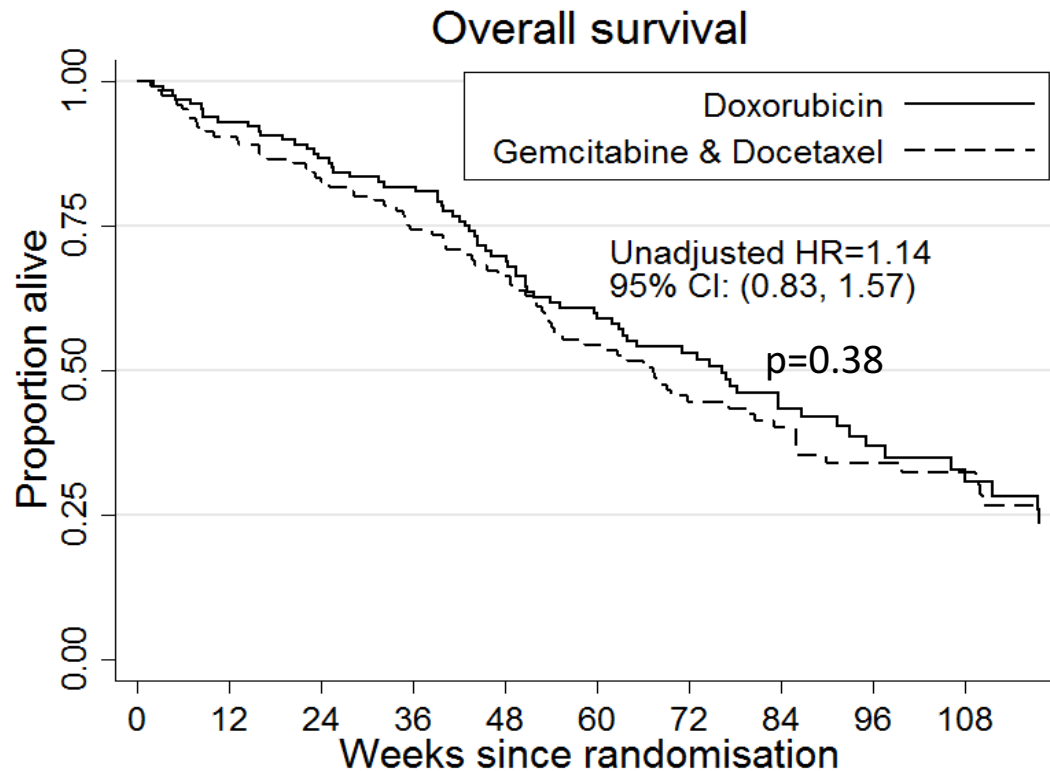
GeDDis - Compliance to Trial Treatment

Reason	Dox (N=129)	GemDoc (N=128)
Total withdrawals during treatment	60 (47%)	80 (63%)
Disease progression	34 (57%)	39 (49%)
Symptomatic deterioration	4 (7%)	3 (4%)
Unacceptable toxicity	1 (2%)	13 (16%)
Serious adverse event	2 (3%)	2 (3%)
Death	5 (8%)	4 (5%)
Other	14 (23%)	19 (11%)

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GeDDis - Overall Survival

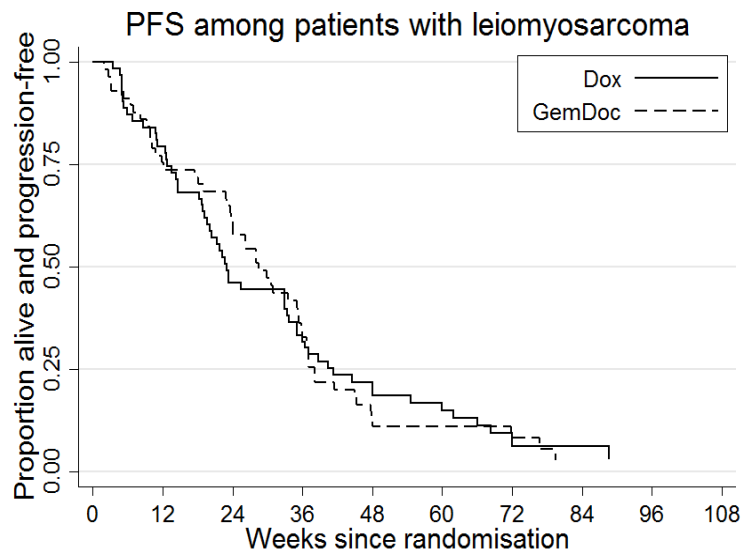


	Number at risk									
Doxorubicin	129	120	108	98	80	63	47	32	20	15
Gemcitabine & Doc.	128	115	104	88	74	57	44	35	24	17

	Median OS (months)	24 week OS
Dox	17.6	86.8%
GemDoc	15.4	82.6%

GeDDis - Subgroup Analyses

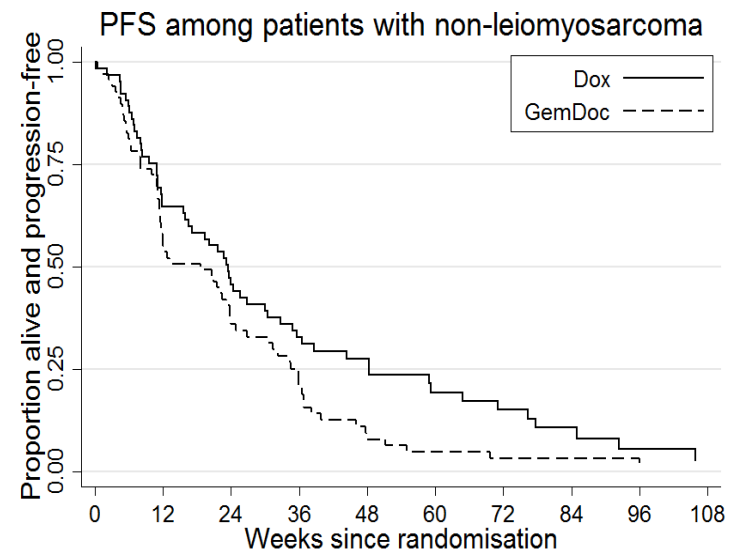
Leiomyosarcoma



Number at risk

Dox	63	50	29	21	13	9	3	2	1	1
GemDoc	58	43	35	19	7	4	3	1	1	1

Non-leiomyosarcoma



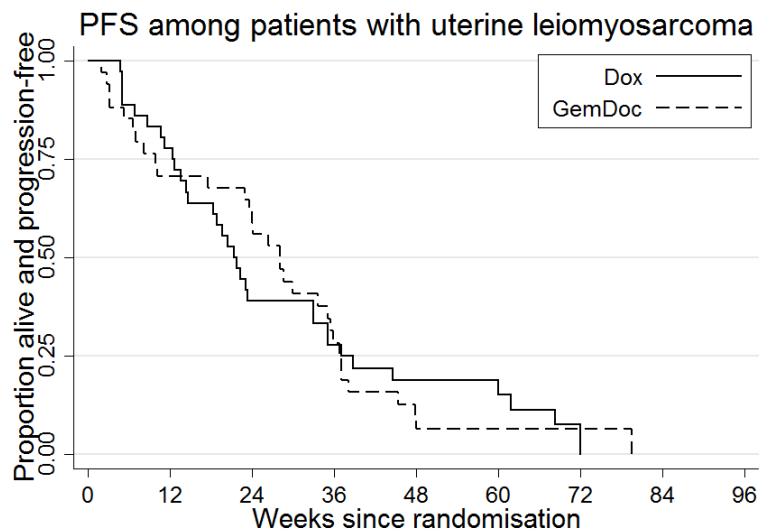
Number at risk

Dox	65	42	30	20	14	9	7	4	2	1
GemDoc	69	40	25	16	5	3	2	2	2	1

Value	N	Treatment HR	Interaction p value
Leiomyosarcoma	118	1.12 (0.75-1.66)	0.326
Non-leiomyosarcoma	139	1.46 (1.02-2.09)	

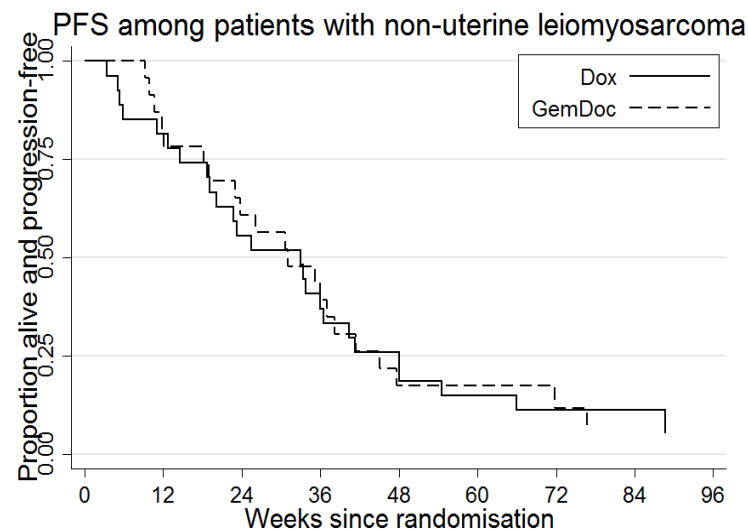
GeDDis - Subgroup Analyses

Uterine leiomyosarcoma



Number at risk	0	12	24	36	48	60	72	84	96
Dox	36	28	14	10	6	5	1	0	0
GemDoc	34	24	21	9	3	1	1	0	0

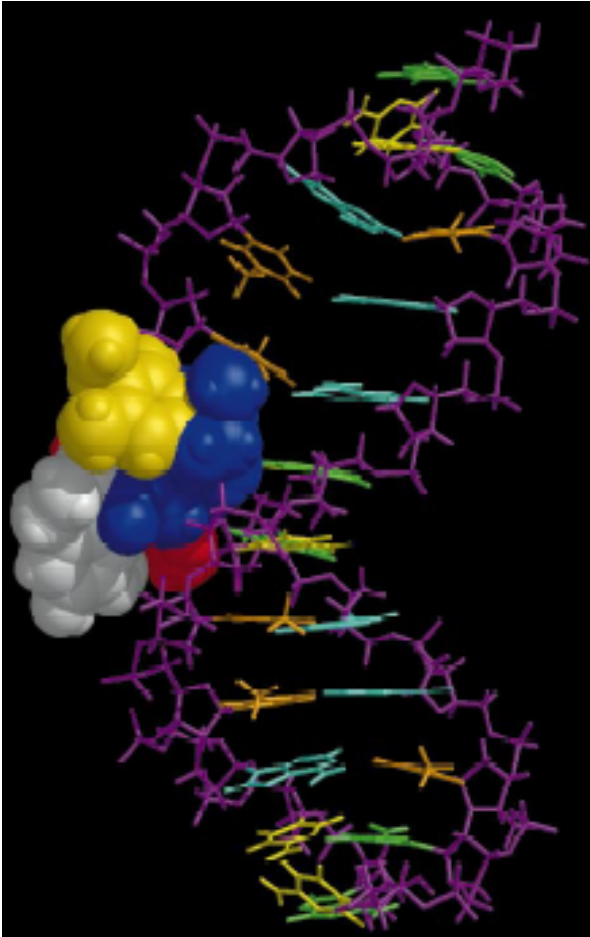
Non uterine leiomyosarcoma



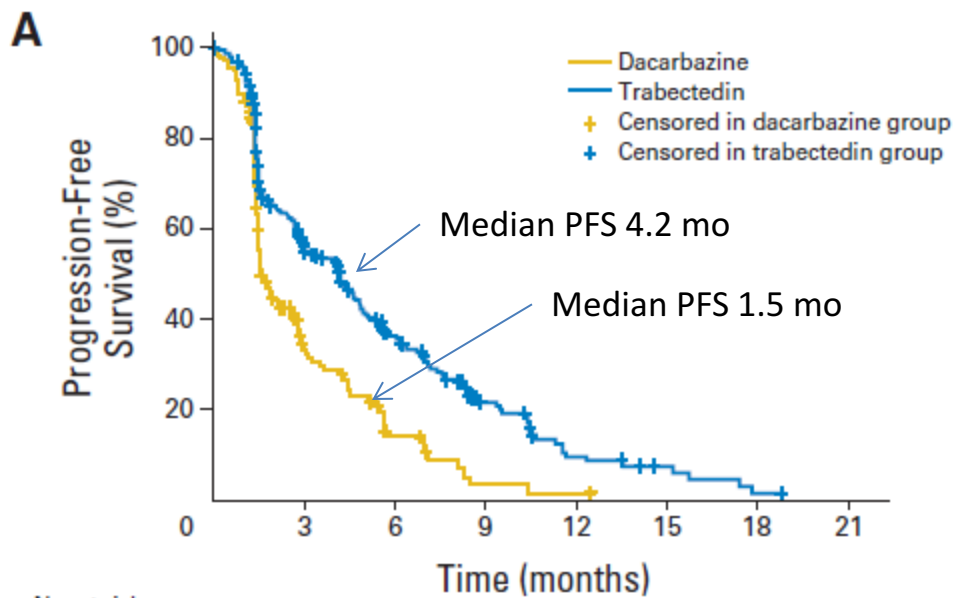
Number at risk	0	12	24	36	48	60	72	84	96
Dox	27	22	15	11	7	4	2	2	1
GemDoc	24	19	14	10	4	3	2	1	1

Value	N	Treatment HR	Interaction p value
Uterine leiomyosarcoma	71	1.37 (1.01-1.85)	0.38
Non uterine leiomyosarcoma	186	1.06 (0.65-1.72)	

Beyond second line: Trabectedin



- **Binds to DNA minor groove, bending the helix**
- **Interacts with transcription factors and other DNA binding proteins**
- **FDA Approved in 2015 for the treatment of metastatic LMS and LPS following prior anthracycline**



No. at risk									
Dacarbazine	173	35	10	2	1	0			
Trabectedin	345	133	71	29	10	5	1	0	

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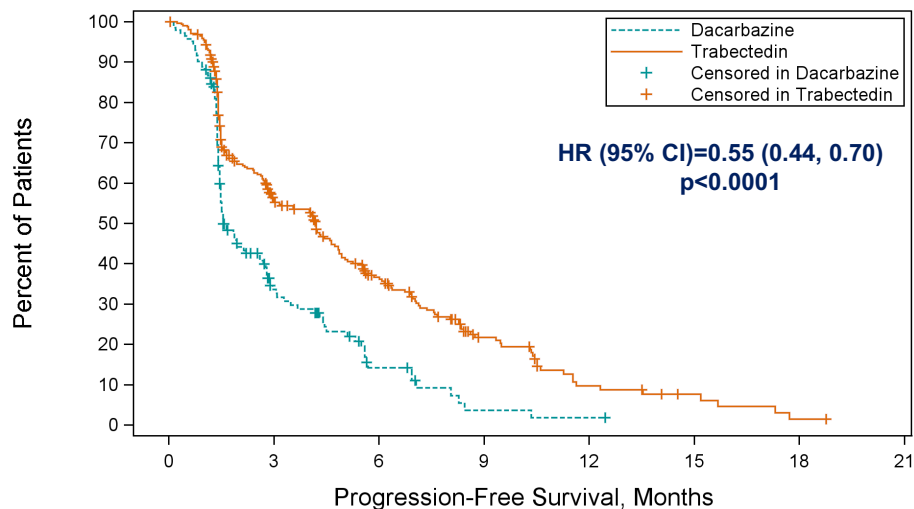
Variable	Subgroup	Median (months)		HR	95% CI	Events/n	
		Dacarbazine	Trabectedin			Dacarbazine	Trabectedin
All	All	1.5	4.2	0.55	0.44 to 0.70	112/173	217/345
Lines of prior chemotherapy	1	2.7	4.9	0.49	0.23 to 1.04	11/23	24/38
	≥ 2	1.5	4.2	0.56	0.43 to 0.71	101/150	193/307
ECOG PS	0	1.5	4.7	0.51	0.36 to 0.71	52/86	104/171
	1	1.5	2.9	0.60	0.43 to 0.82	60/87	113/174
Histologic subtype	Leiomyosarcoma	1.6	4.3	0.55	0.42 to 0.73	85/126	154/252
	Nonuterine	1.6	4.9	0.58	0.37 to 0.92	28/48	70/118
	Uterine	1.5	4.0	0.58	0.41 to 0.81	57/78	84/134
	Liposarcoma	1.5	3.0	0.55	0.34 to 0.87	27/47	63/93
	Undifferentiated	1.5	2.2	0.68	0.37 to 1.23	16/25	35/45
Myxoid ± round cell	Pleomorphic	1.5	5.6	0.41	0.17 to 0.98	8/19	21/38
		1.4	1.5	0.33	0.07 to 1.64	3/3	7/10
Age, years	< 65	1.8	4.1	0.60	0.46 to 0.78	87/139	173/264
	≥ 65	1.5	4.9	0.40	0.24 to 0.67	25/34	44/81
Sex	Female	1.6	4.2	0.56	0.43 to 0.74	81/126	141/238
	Male	1.5	4.1	0.53	0.34 to 0.82	31/47	76/107
Race	White	1.5	4.2	0.52	0.39 to 0.68	82/125	173/269
	Nonwhite	1.8	3.5	0.65	0.40 to 1.03	30/48	44/76
BMI, kg/m ²	< 30	1.5	4.0	0.56	0.41 to 0.75	72/112	128/203
	≥ 30	2	4.4	0.54	0.37 to 0.80	40/61	89/142

Hazard Ratio (trabectedin v dacarbazine) and 95% CI (log scale)

Favoring trabectedin Favoring dacarbazine

Progression-Free Survival

Total Population¹

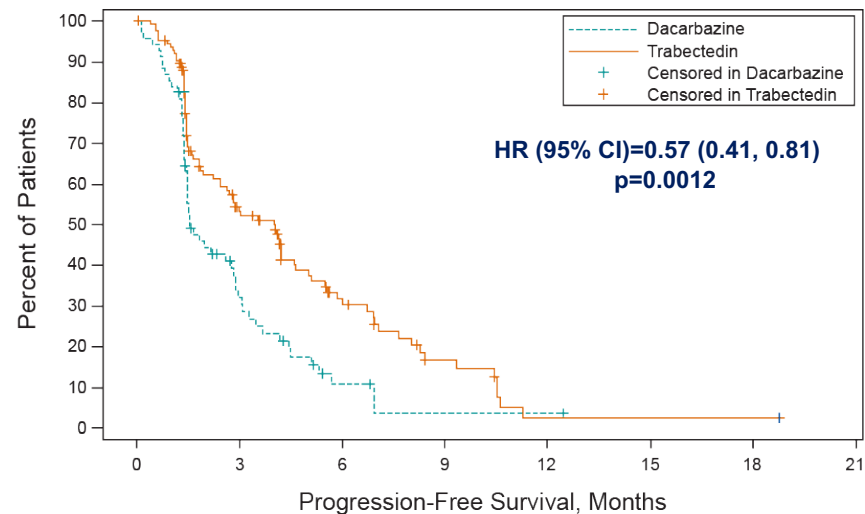


No. Patients at Risk

Dacarbazine	173	35	10	2	1	0		
Trabectedin	345	133	71	29	10	5	1	0

PFS events	329
Median PFS Trabectedin	4.2 months
Median PFS Dacarbazine	1.5 months

Uterine Leiomyosarcoma Population



No. Patients at Risk

Dacarbazine	78	18	4	1	0		
Trabectedin	134	49	21	8	1	0	

PFS events	141
Median PFS Trabectedin	4.0 months
Median PFS Dacarbazine	1.5 months

- ▶ ET743-SAR-3007 PFS results confirmed through independent radiological audit of 60% of study patients¹

¹Demetri et al, JCO, September 2015, doi: 10.1200/JCO.2015.62.4734

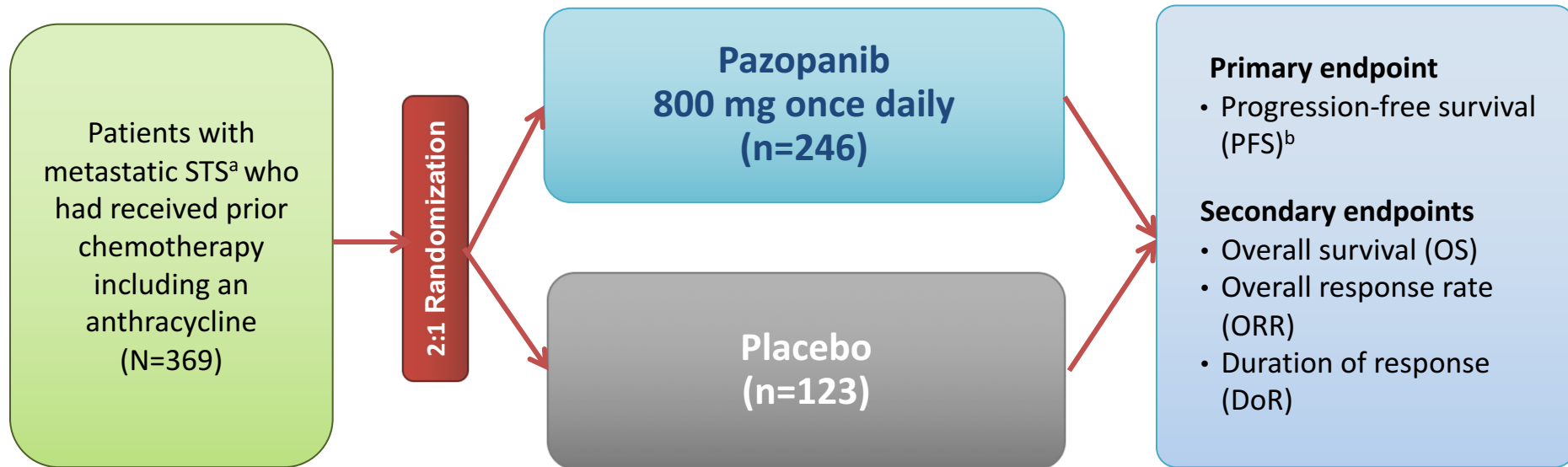
Hensley et al. Abstract 3. SGO 2016.

Combination trabectedin + doxorubicin is active in first line LMS

	Uterine LMS	ST LMS
N	47	61
CR	—	2 (3.3%)
PR	28 (59%)	22 (36%)
SD	13 (27%)	32 (52%)

ONGOING Phase III trial - evaluating doxorubicin vs doxorubicin+ trabectedin

Phase 3 PALETTE Study of Pazopanib for Patients With Metastatic STS: Study Design

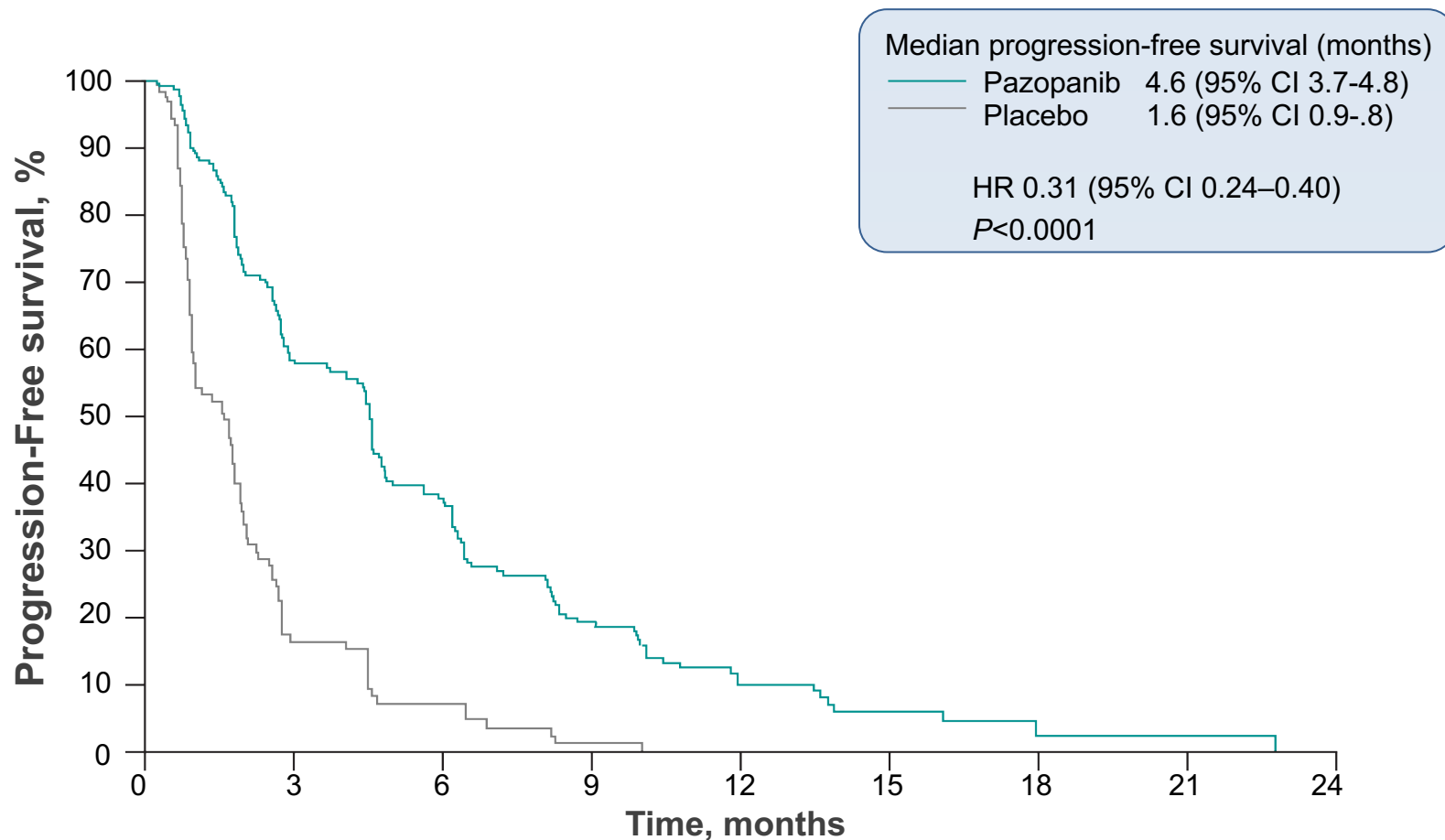


PALETTE=PAzopanib expLorEd in Soft-Tissue Sarcoma—a phase 3 study.

^aExcluding GIST and adipocytic sarcomas.

^bAssessed by independent radiologic review.

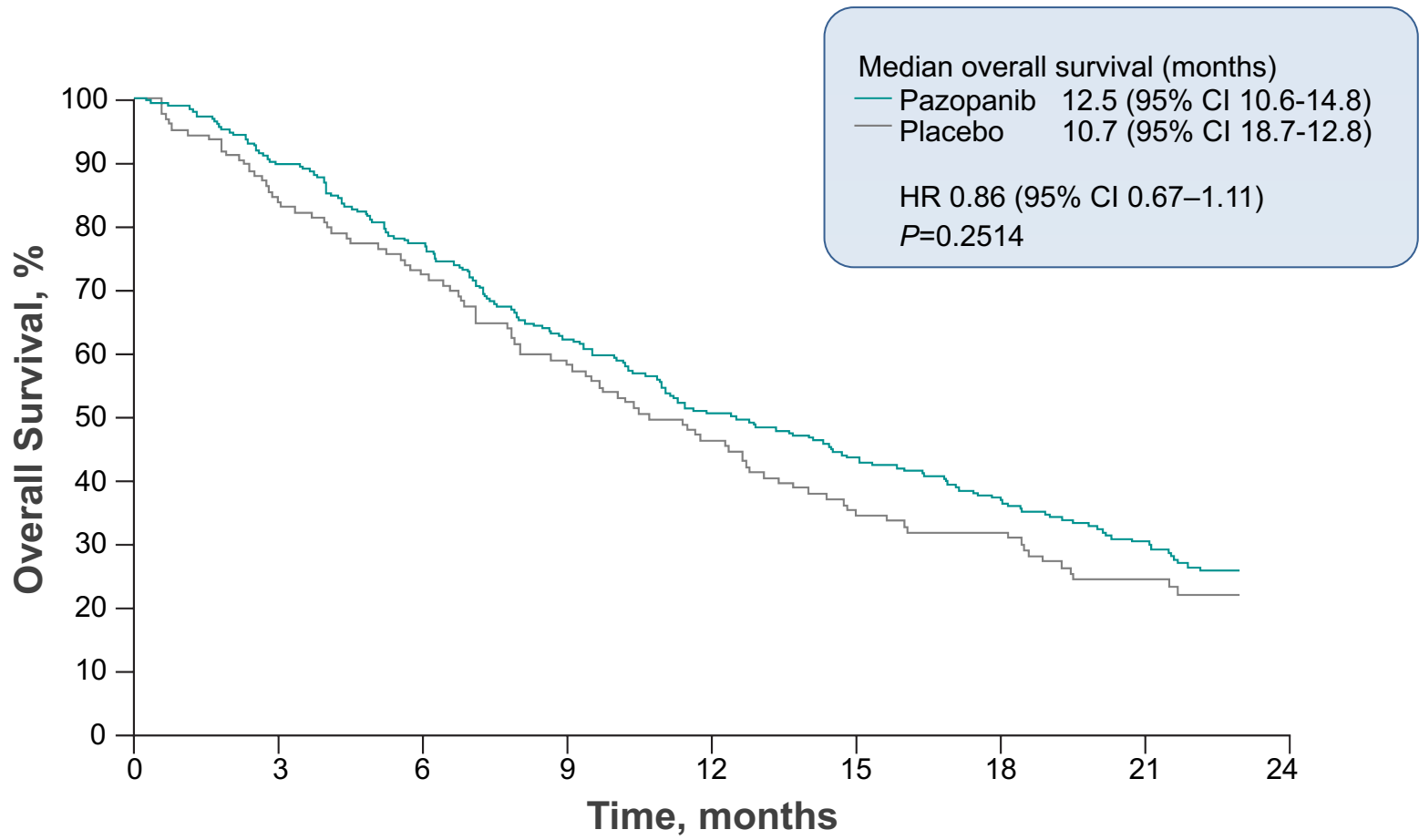
PALETTE: Median PFS



106 patients in the placebo group died or had disease progression, 168 in the pazopanib group (cutoff Nov 22, 2010); 95 patients in the placebo group died, 185 in the pazopanib group (cutoff Oct 24, 2011).

van der Graaf et al. *Lancet*. 2012; 379(9829):1879-1886.

PALETTE: Median OS



106 patients in the placebo group died or had disease progression, 168 in the pazopanib group (cutoff Nov 22, 2010); 95 patients in the placebo group died, 185 in the pazopanib group (cutoff Oct 24, 2011).

van der Graaf et al. *Lancet*. 2012; 379(9829):1879-1886.

Summary

- Uterine sarcomas are a group of mesenchymal malignancies
- Leiomyosarcoma is the most common histologic subtype
- Both anthracycline-based and gemcitabine-based regimens are active in early lines
- Later lines of therapy include trabectedin, pazopanib – others