Sequencing of systemic agents in the treatment of uterine sarcoma

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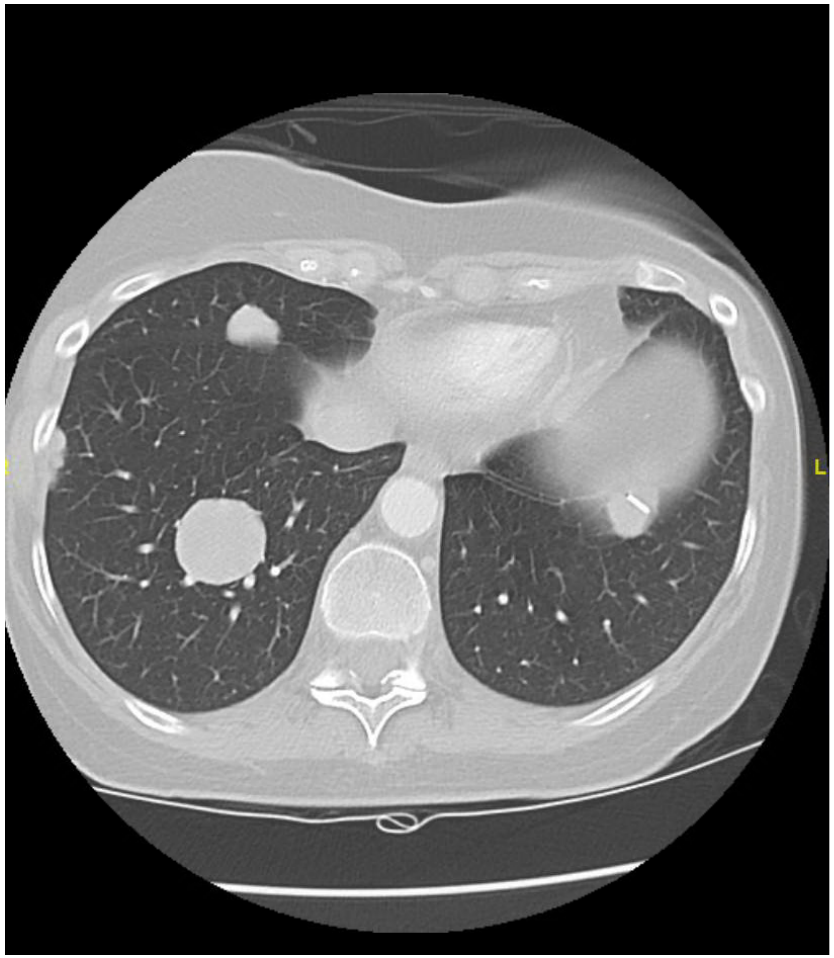
VERBAL DISCLOSURE

- 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

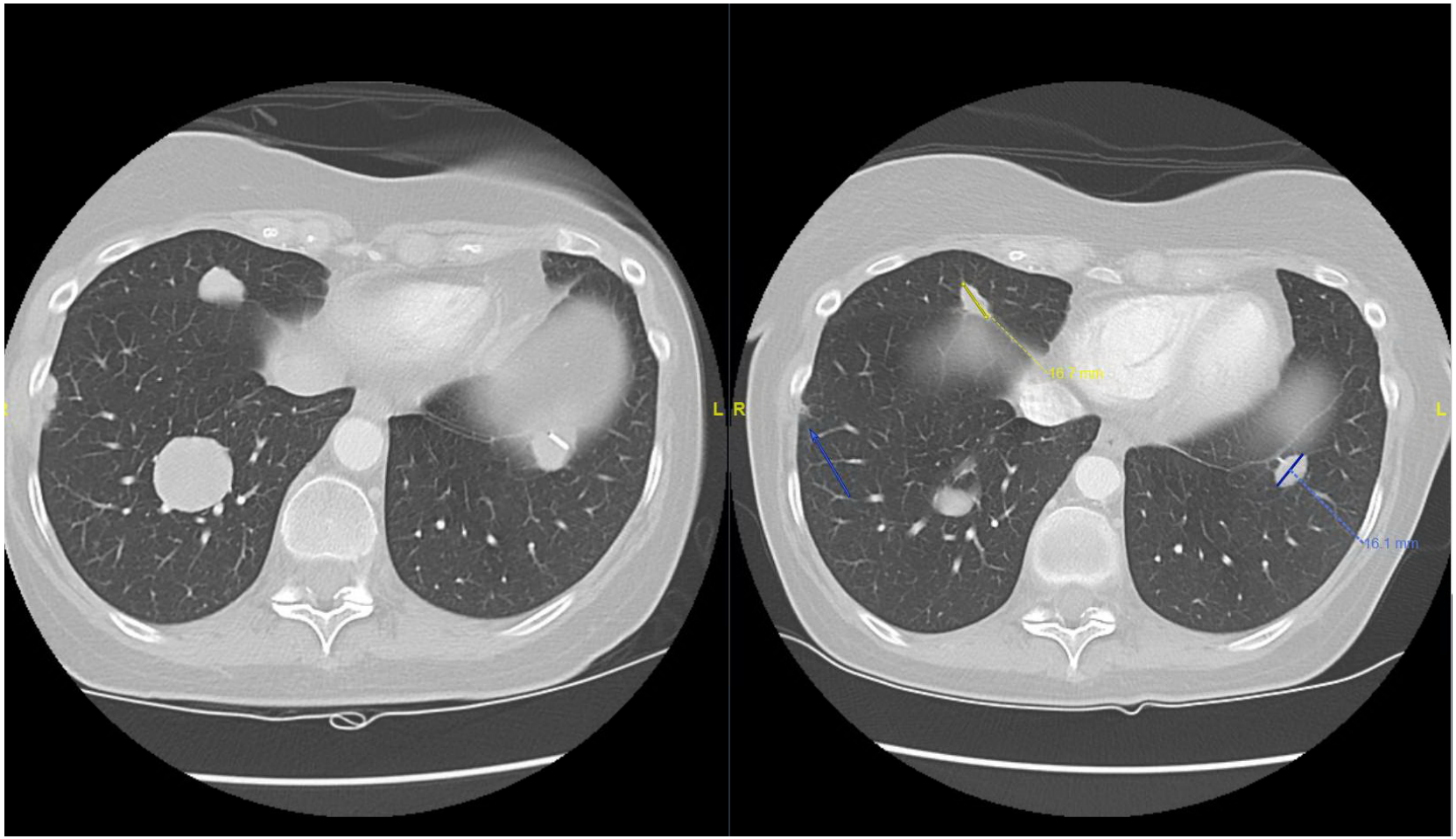


BASELINE

Metastatic ULMS – First line

- Patient was treated with 4 cycles of gemcitabine-docetaxel

Metastatic ULMS – First line

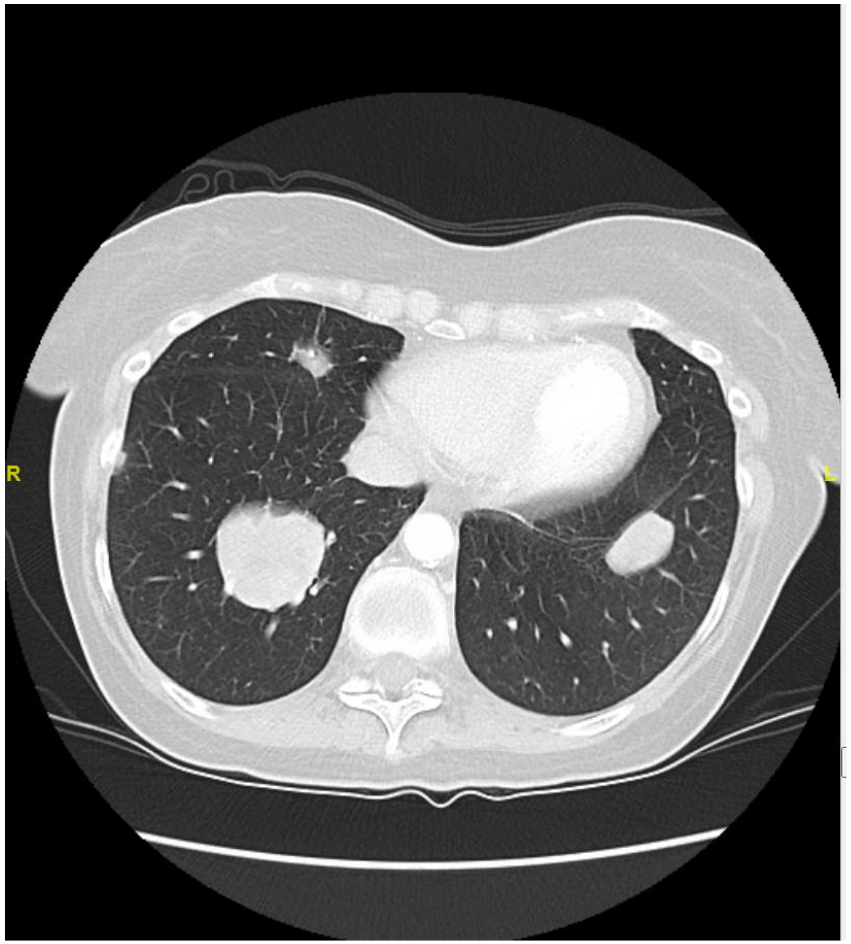


BASELINE **AFTER 4 CYCLES OF GEMCITABINE**

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

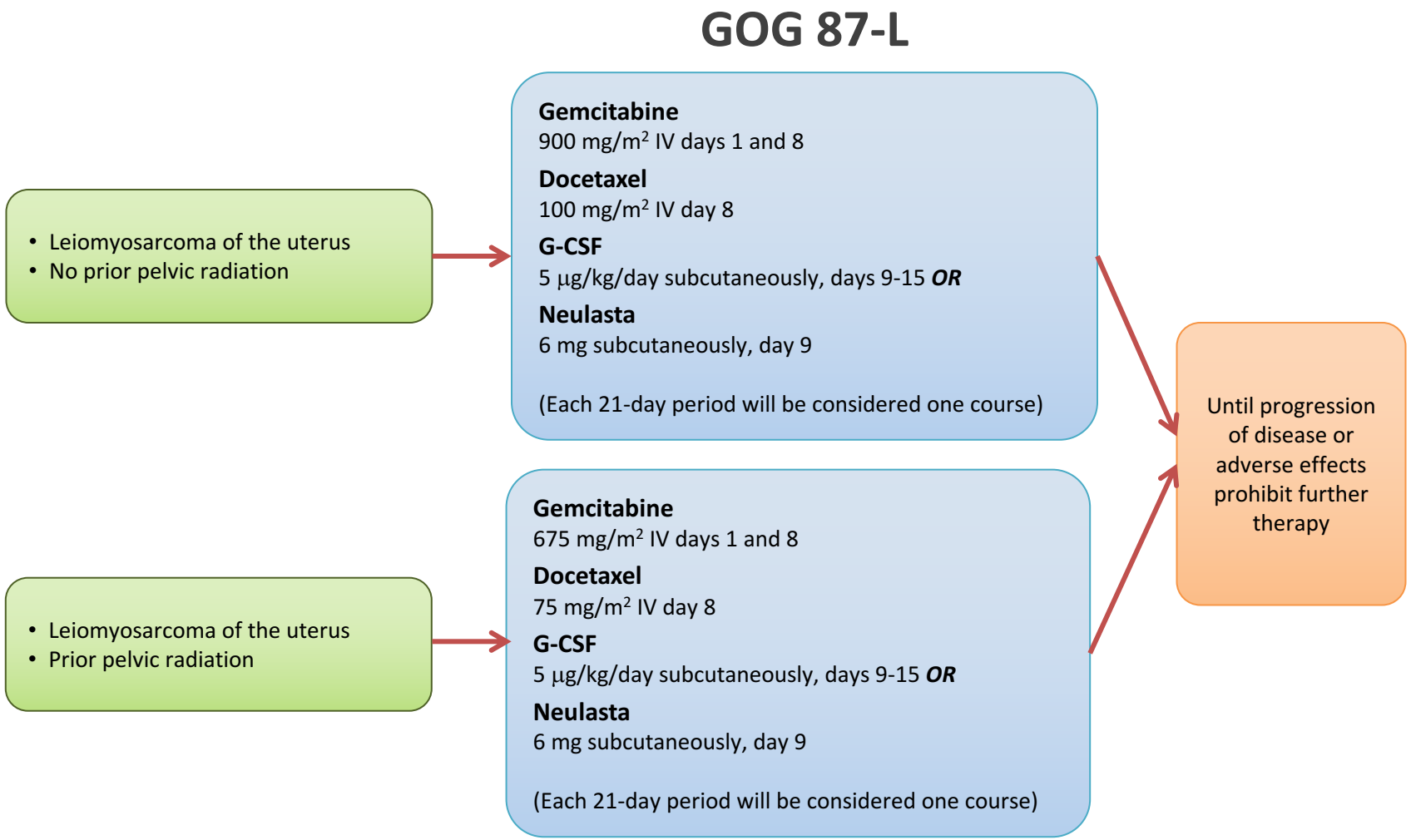
Metastatic ULMS – Second line



BASELINE

Is there an optimal sequence?

GOG 87L: First-line, Measurable Uterine LMS



Hensley et al. *Gynecol Oncol*. 2008;109:329-334.

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%

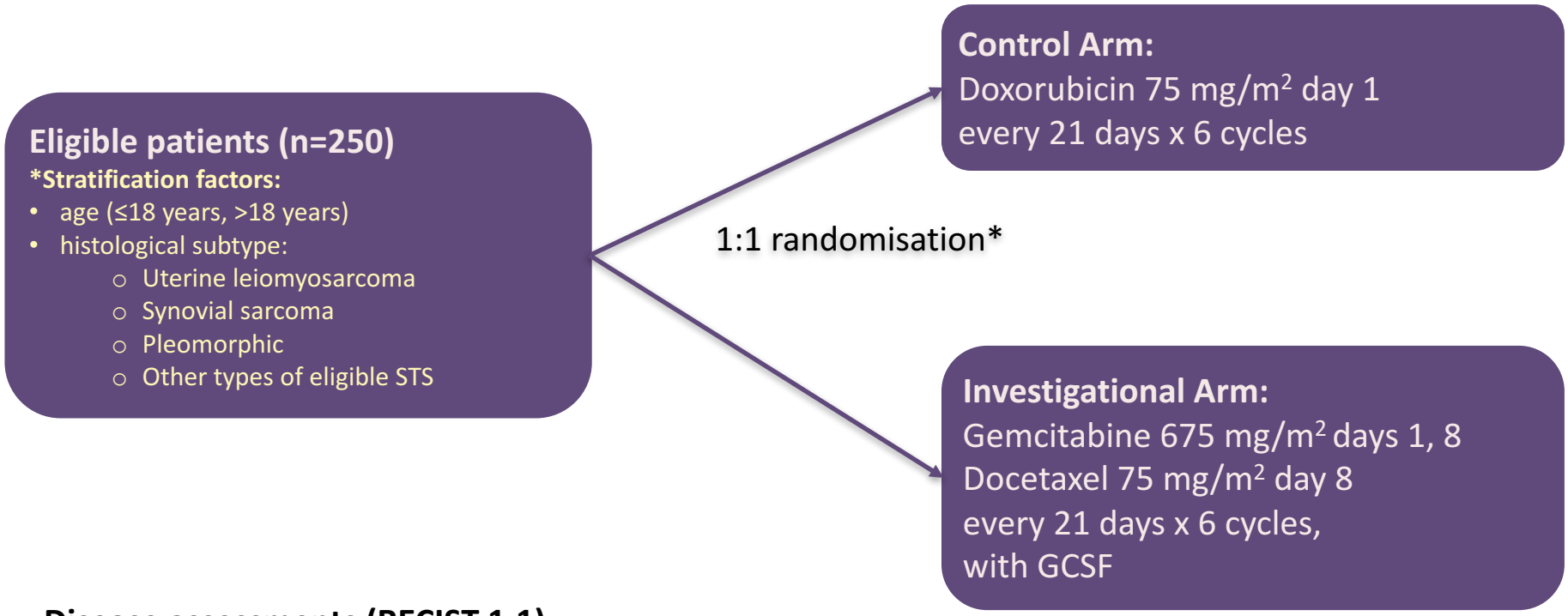
36%

Clinical Benefit Rate: 62%

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

Hensley et al. *Gynecol Oncol*. 2008;109:329-334.

GeDDiS - Trial Design



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

Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

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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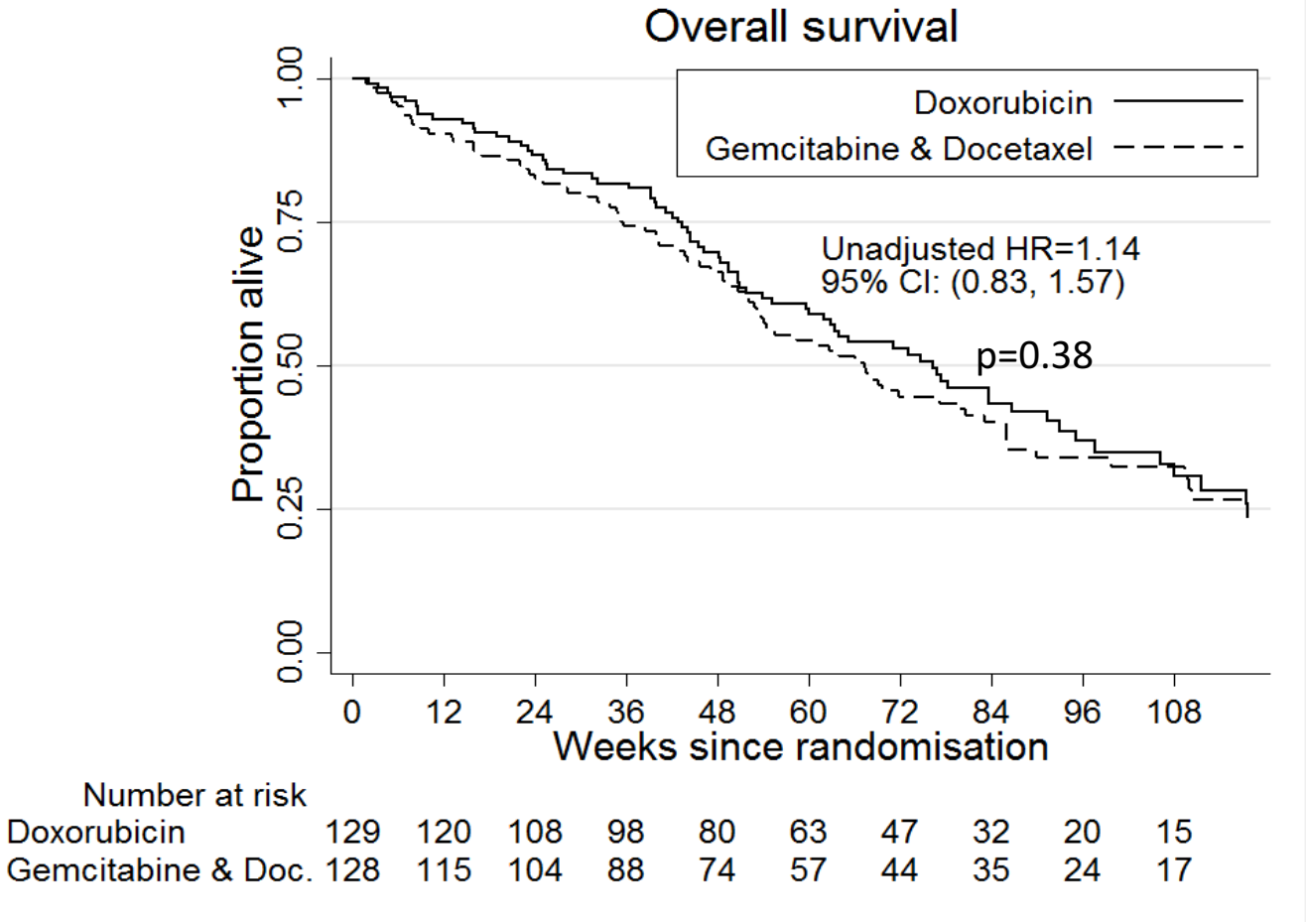
GeDDis - Overall Survival

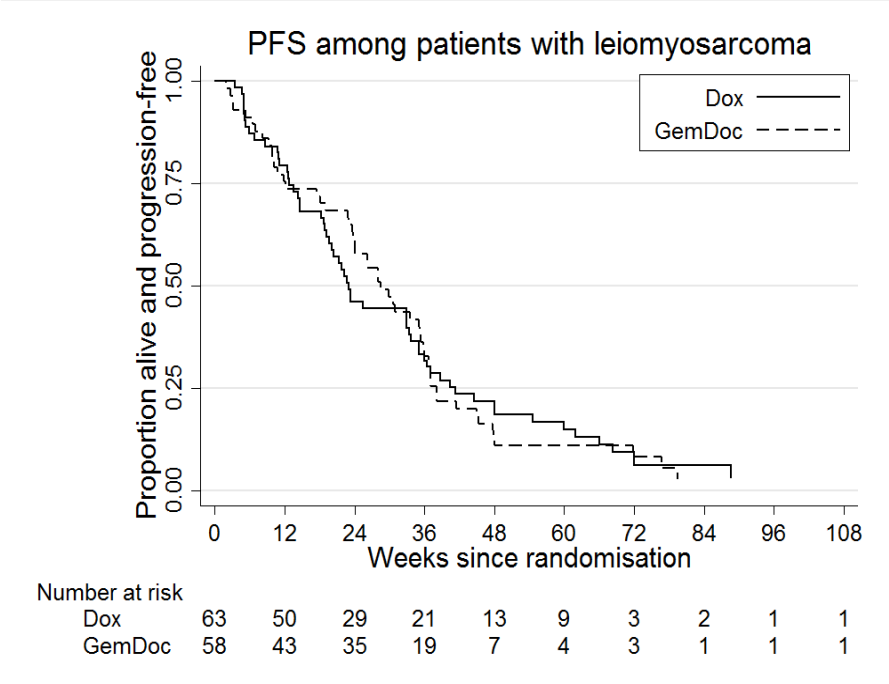


	Median OS (months)	24 week OS
Dox	17.6	86.8%
GemDoc	15.4	82.6%

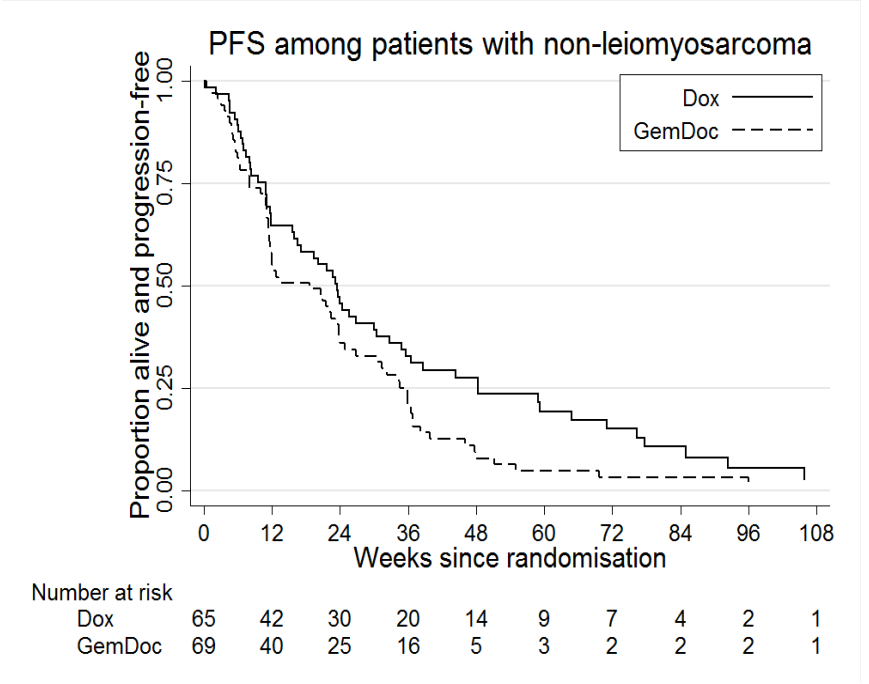
Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

GeDDis - Subgroup Analyses

Leiomyosarcoma



Non-leiomyosarcoma

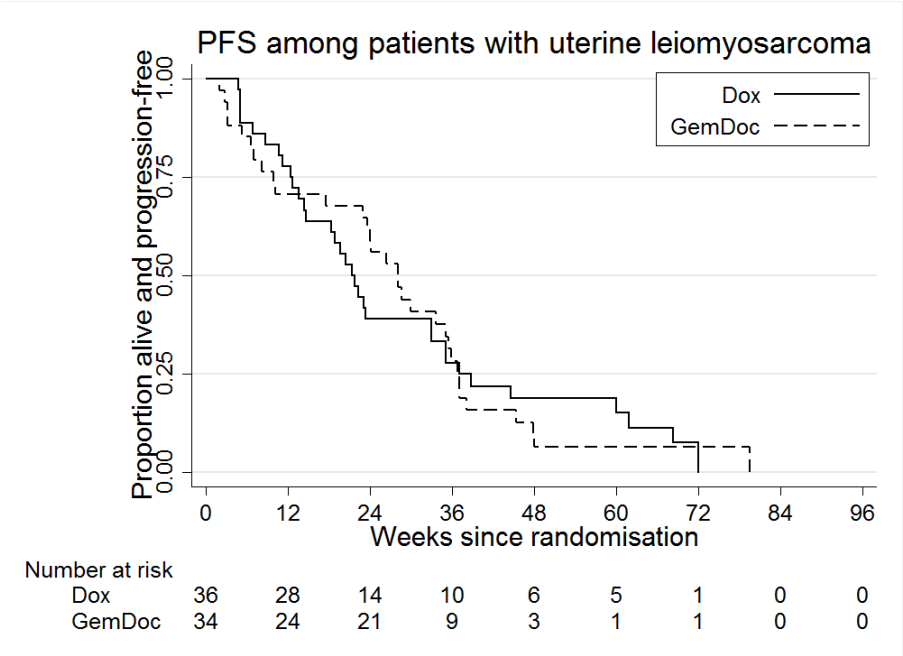


Value	N	Treatment HR	Interaction p value
Leiomyosarcoma	118	1.12 (0.75-1.66)	0.326
Non-leiomyosarcoma	139	1.46 (1.02-2.09)	

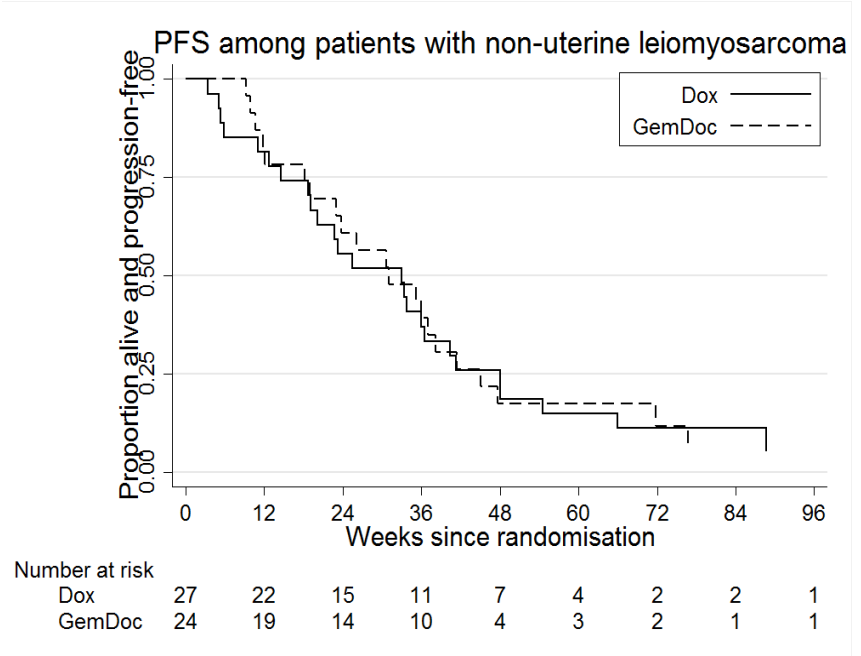
Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

GeDDis - Subgroup Analyses

Uterine leiomyosarcoma



Non uterine leiomyosarcoma

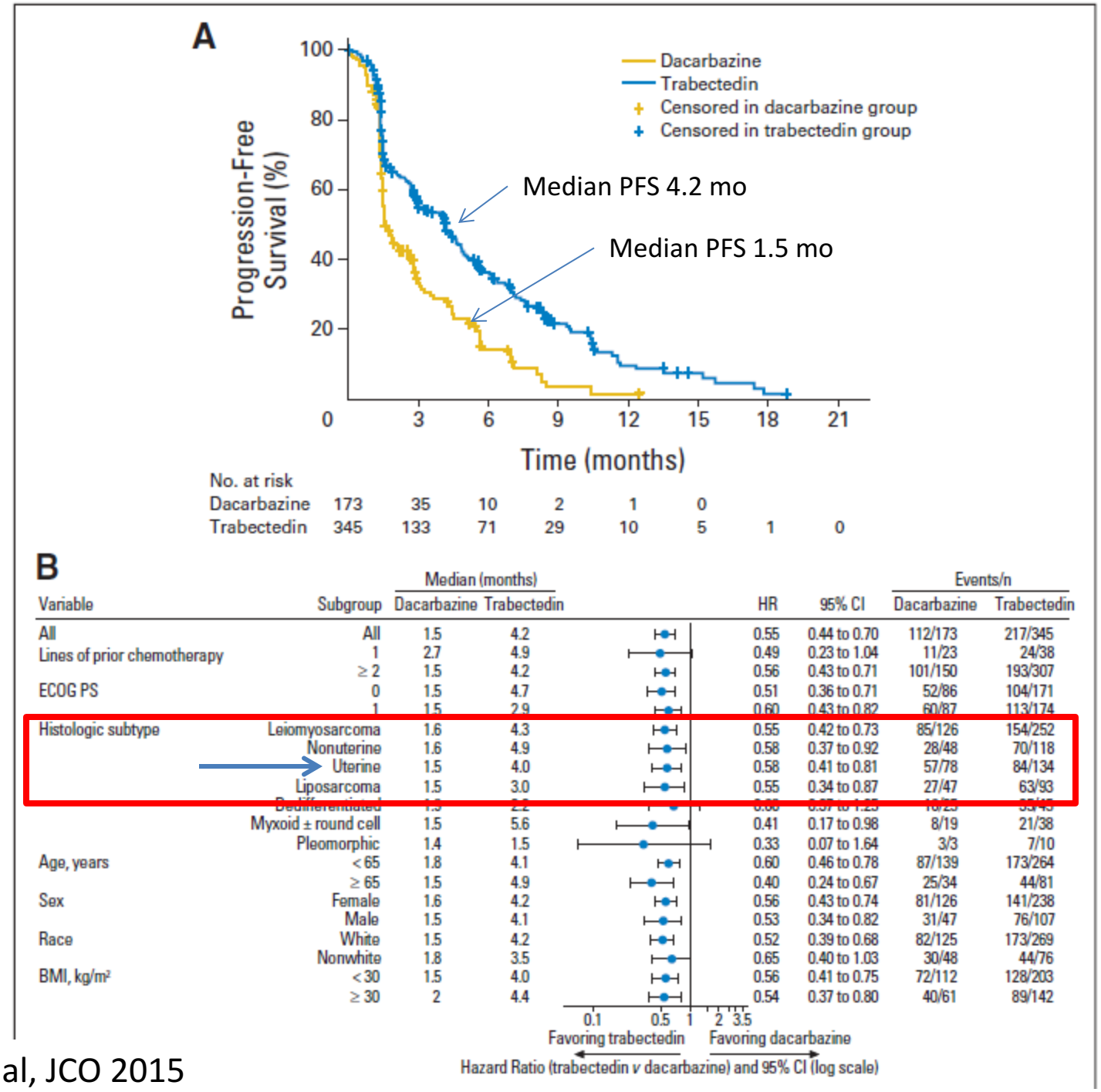


Value	N	Treatment HR	Interaction p value
Uterine leiomyosarcoma	71	1.37 (1.01-1.85)	0.38
Non uterine leiomyosarcoma	186	1.06 (0.65-1.72)	

Seddon et al, ASCO annual meeting, CTOS annual meeting, 2015

Beyond second line: Trabectedin

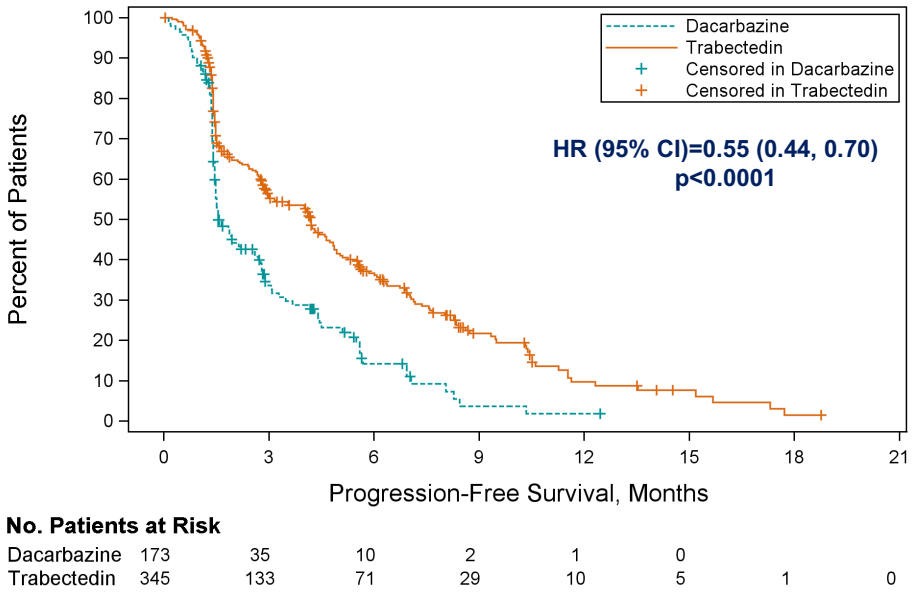
- **Binds to DNA minor groove, bending the helix**
- **Interacts with transcription factors and other DNA binding proteins**
- **FDA Approved in 2015 for the treatment of metastatic LMS and LPS following prior anthracycline**



Demetri et al, JCO 2015

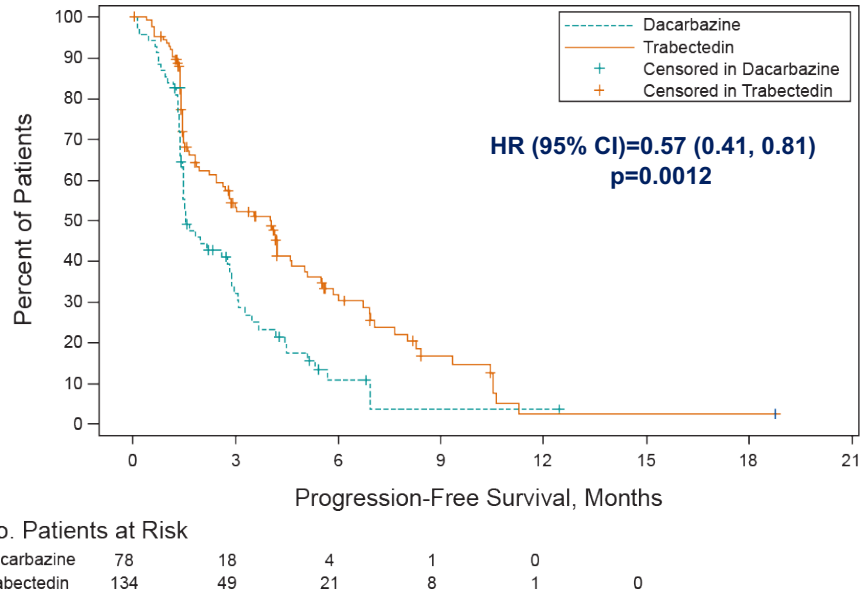
Progression-Free Survival

Total Population[1]



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

Uterine Leiomyosarcoma Population



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

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

Hensley et al. Abstract 3. SGO 2016.

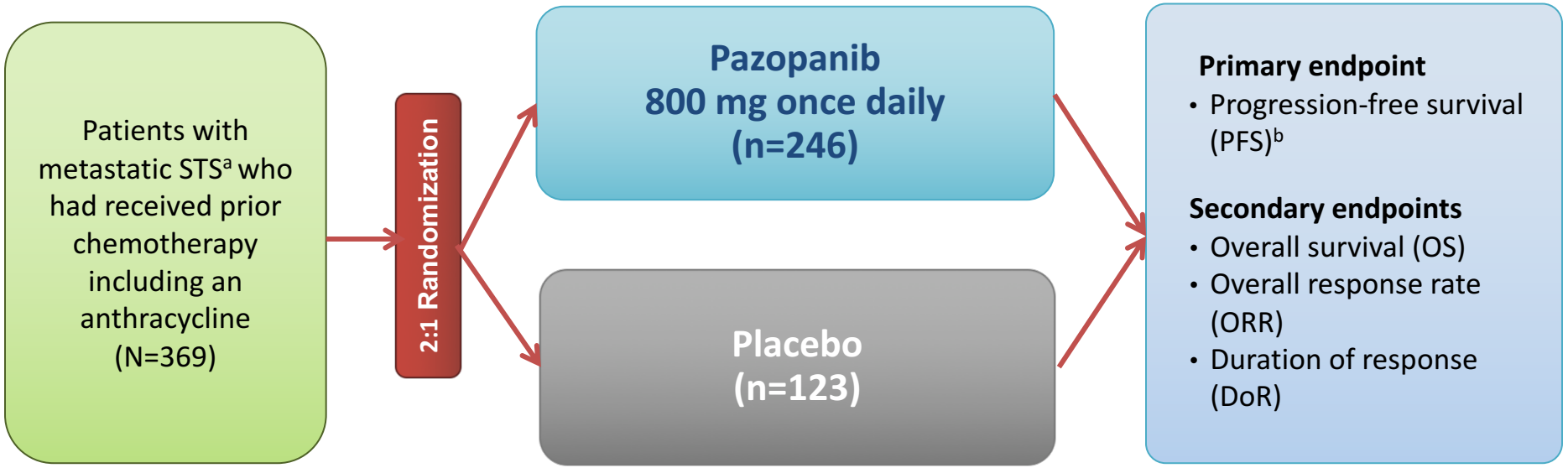
Combination trabectedin + doxorubicin is active in first line LMS

	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

Pautier et al, Lancet Oncology April 2015

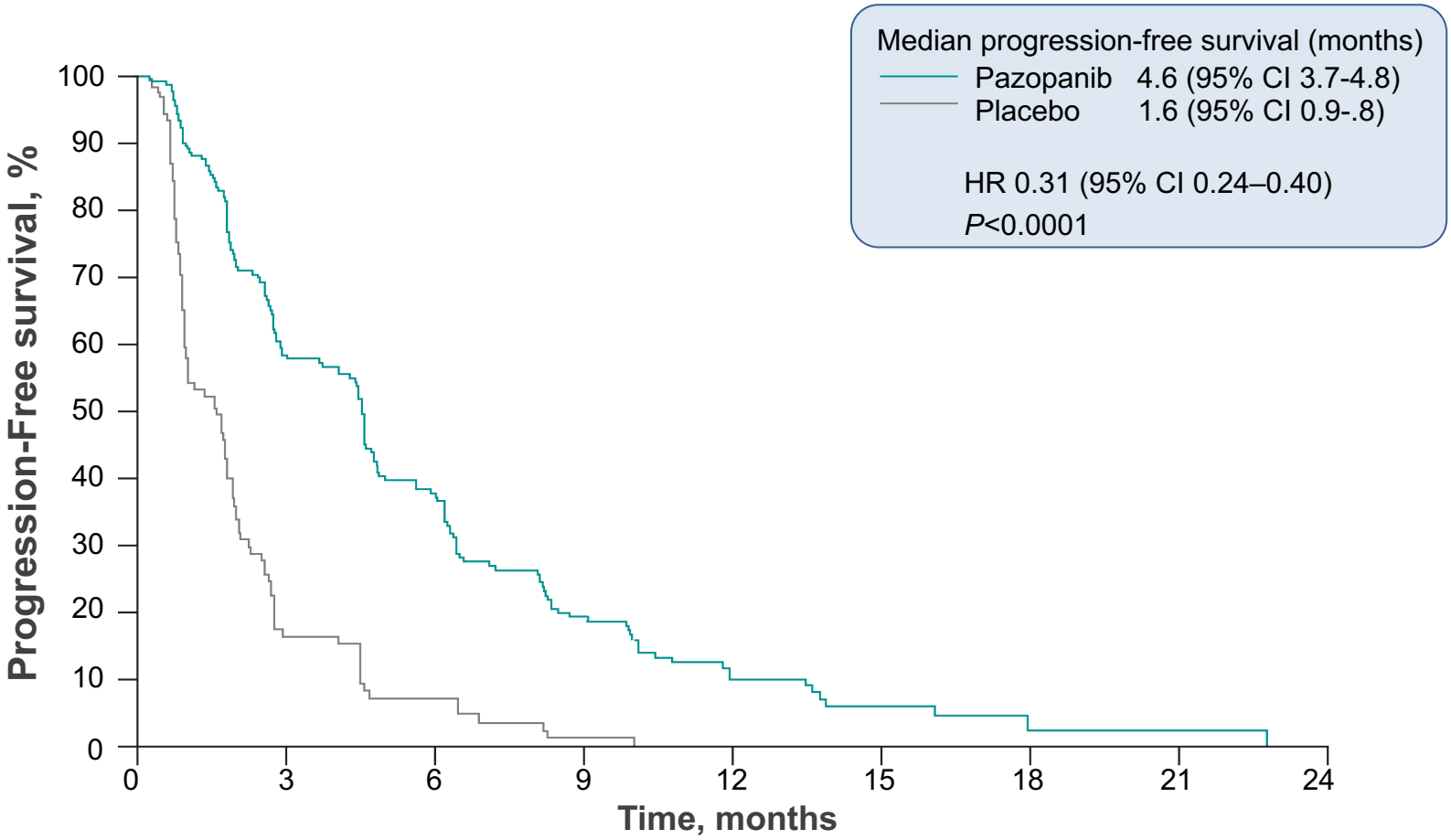
Phase 3 PALETTE Study of Pazopanib for Patients With Metastatic STS: Study Design



PALETTE=**PA**zopanib exp**L**or**E**d in Sof**T**-**T**isue Sarcoma—a phas**E** 3 study.
[a]Excluding GIST and adipocytic sarcomas.
[b]Assessed by independent radiologic review.

van der Graaf et al. *Lancet*. 2012.

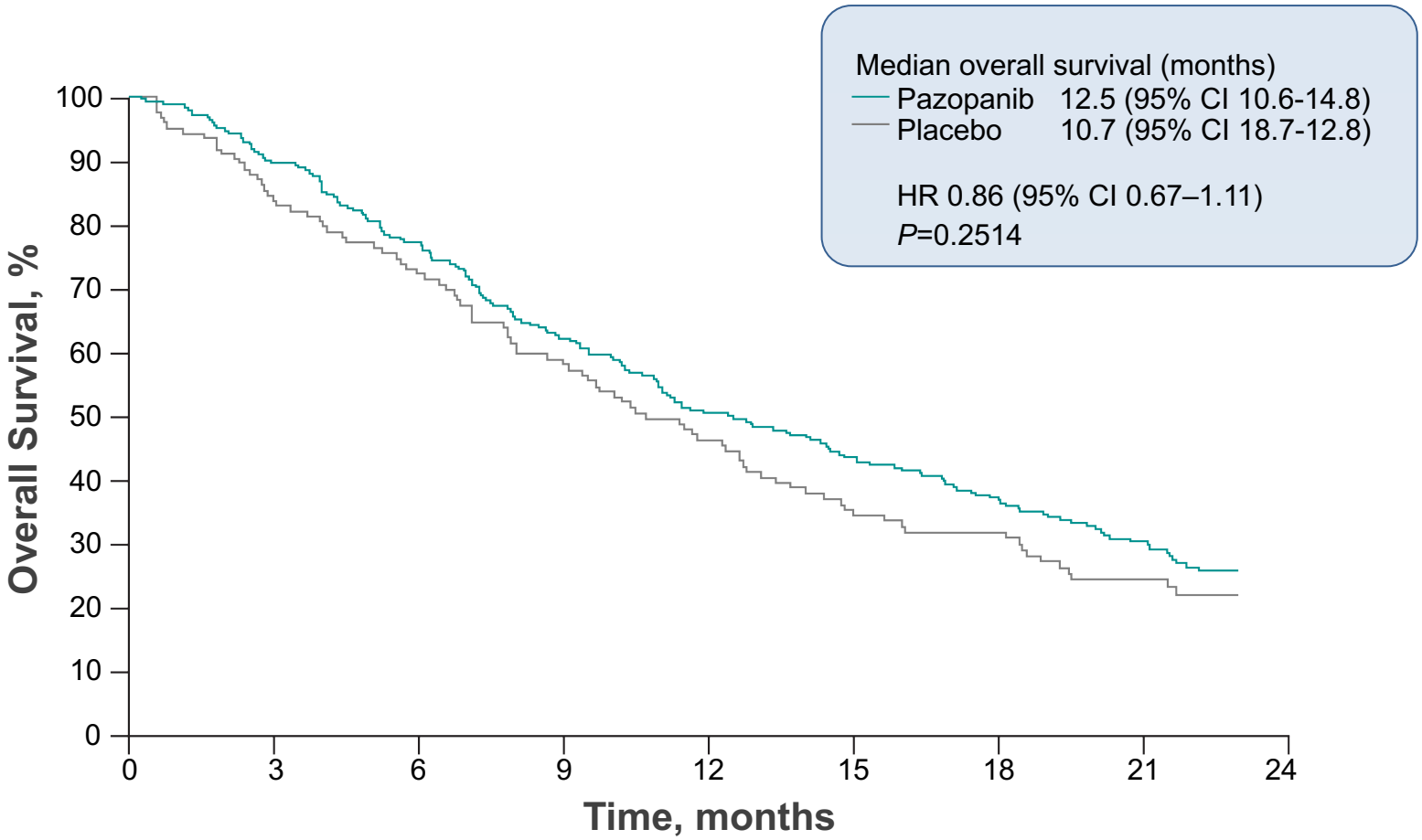
PALETTE: Median PFS



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



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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