Olaratumab in Soft Tissue Sarcomas

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Disclosures

- Consultant for:
  - Adaptimmune
  - Blueprint
  - Clinigen
  - Eisai
  - Epizyme
  - Daichii
  - Deciphera
  - Immunedesign
  - Lilly
  - Merck
  - Pharmamar
  - Tracon

Sarcomas – biological groups

- COMPLEX
- Multiple complex genetic alterations

- SIMPLE
- Specific translocations generating fusion oncogenes

- Specific kinase mutations (GIST)

- Gene inactivation (NF1 in MPNST, INI1 in rhabdoid tumours, APC in desmoid)

- Simple genetic alterations (amplifications – *mdm2*+/ *cdk4* in well- / dedifferentiated liposarcoma)

Different drugs for different diseases

- Localized
  - Osteosarcoma — MAP
  - Ewing — VDC/ IE
  - Rhabdomyosarcoma — VAC
  - GIST — Imatinib

- Metastatic
  - Dermato fibrosarcoma protuberans — Imatinib
  - Giant cell tumor of bone — Denosumab
  - Alveolar soft part sarcoma — Cediranib/ sunitinib
  - Inflammatory myofibroblastic tumor — ALK inhibitors
  - PEComas — mTOR inhibitors
  - Endometrial stromal sarcoma — Aromatase inhibitors
  - Chordoma — Imatinib/ mTOR Inhibitors
  - Ewing/ Rhabdomyosarcoma — Cyclo/ topotecan
  - Ewing/ Rhabdomyosarcoma — Irinotecan/ temozolamide
  - Solitary fibrous tumor — Anti angiogenic agents

Imatinib in metastatic GIST

- Phase I: EORTC trial (n=36)[1]
  - 400mg→1000mg (DLT=1000mg)
  - Responses 25/ 36 (19 confirmed PRs)

- Phase II trials
  - US group 150 patients (B2222)[2] — 400 versus 600mg
    - No difference seen between two doses
    - Objective response rate 68%
    - Estimated median overall survival 57 months
  - EORTC 27 patients (+24 STS)[3] — 400mg bid
    - 4% CR, 67% PR, 19% SD — 73% 1 year PFS
    - Not effective in unselected patients with STS

- Phase III trials: S0033 (n=740)[4] vs EORTC 62005 (n=940)[5]
  - Randomised to 400mg vs 800mg daily
  - Cross over allowed if PD on 400mg
  - PFS as primary endpoint
- Similar Conclusions
  - No significant difference in response rate/ overall survival
  - Increased toxicity with 800mg

[1]Van Oosterom A et al, Lancet 358(9291); 1421-3: 2001
[2]Blanke C et al, JCO 26(4); 620-625: 2008
[3]Verweij J et al, EJC 39(14); 2006-11: 2003
[4]Blanke C et al, JCO 26(4); 626-32: 2008
[5]Verweij J et al, Lancet 364(9440); 1127-34: 2004

GIST: 2nd- and 3rd-line therapy

- Sunitinib[1]
  - Randomized placebo controlled Phase III trial
- Regorafenib[2]
  - Randomized placebo controlled Phase III trial
- Other agents under evaluation

[1]Demetri G et al. Lancet 368; 1329-1338: 2006
[2]Demetri G et al. Lancet 381; 295-302: 2013

Phase II trial of Olaratumab in GIST

- N=30 patients
- Cohort 1: with *PDGFRa* mutations (n=6)
  - Stable disease, n=3 (50%)
  - Median PFS: 32.1 weeks (5 – 35.9)
  - Median OS: not reached

- Cohort 2: without *PDGFRa* mutations (n=14)
  - Stable disease, n=2 (14%)
  - Median PFS 6.1 weeks (5.7 – 6.3)
  - Median OS: 24.9 weeks (14.4 – 49.1)

Wagner A et al. Ann Oncol 28; 541-546: 2017

NCCN Guidelines for Metastatic Soft Tissue Sarcoma

Disseminated metastases or unresectable

Options:
Observation, if asymptomatic.
Chemotherapy
Radiation
Palliative surgery
Best supportive care
Ablation procedures
- **RFA**
- **Cryotherapy**

Embolization procedures

NCCN Practice Guidelines 2013

First-line metastatic disease

- Retrospective data: Improvement OS

- European (EORTC) trial
  - Doxorubicin vs
  - Doxorubicin + ifosfamide

- PICASSO trial
  - Doxorubicin + placebo vs
  - Doxorubicin +palifosfamide

- SARC 21 trial
  - Doxorubicin vs
  - Doxorubicin + evofosfamide

- British (GEDDIS) trial
  - Doxorubicin vs
  - Gemcitabine + docetaxel

Judson I et al Lancet Oncol 15(14); 415-23: 2014
Ryan CW et al. JCO 2016
Tap WD et al. Lancet Oncol 18(8); 1089-1103: 2017
Seddon B et al. Lancet Oncol 2017.

Results of EORTC 62012

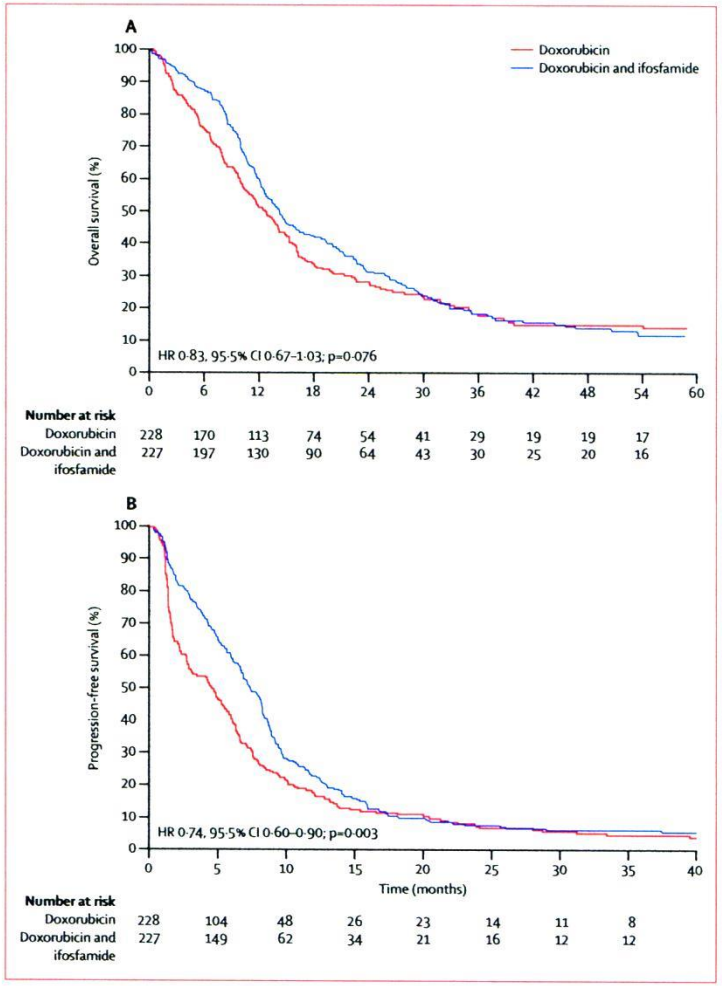


Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

<u>Median overall survival:</u>
Doxorubicin: 12.8 months
Doxorubicin + ifosfamide: 14.3 months

<u>Survival at 1 year:</u>
Doxorubicin: 51%
Doxorubicin + ifosfamide: 60%

<u>Median PFS</u>
Doxorubicin: 4.6 months Doxorubicin + ifosfamide: 7.4 months

<u>Overall response rate:</u>
Doxorubicin: 13.6%
Doxorubicin + ifosfamide: 26.5%

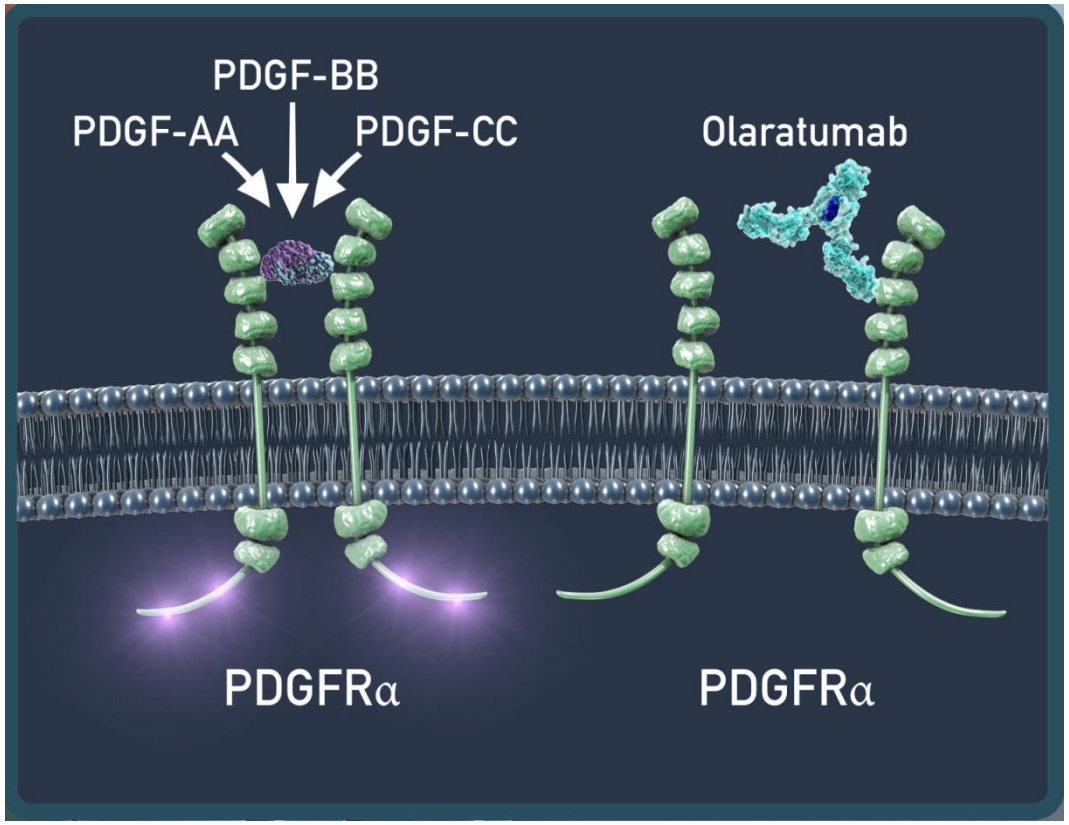
Judson et al Lancet Oncol 2014;15(14):415-23

Options: 2nd/ 3rd / 4th Line

- Ifosfamide
- Gemcitabine/ docetaxel
- Gemcitabine/ DTIC
- Pazopanib
- Trabectedin
- Eribulin
- DTIC

Olaratumab: An Anti-PDGFRα Human Monoclonal Antibody

- A human IgG1 monoclonal antibody
- Selectively binds PDGFRα with high affinity[1]
- Blocks PDGF binding and PDGF-induced activation of PDGFRα[1]
- Demonstrated activity in both in vitro and in vivo cancer models driven by a PDGF-PDGFRα autocrine loop[2]
- Demonstrated antitumor activity alone[1] or in combination with doxorubicin in human sarcoma xenograft models[3]



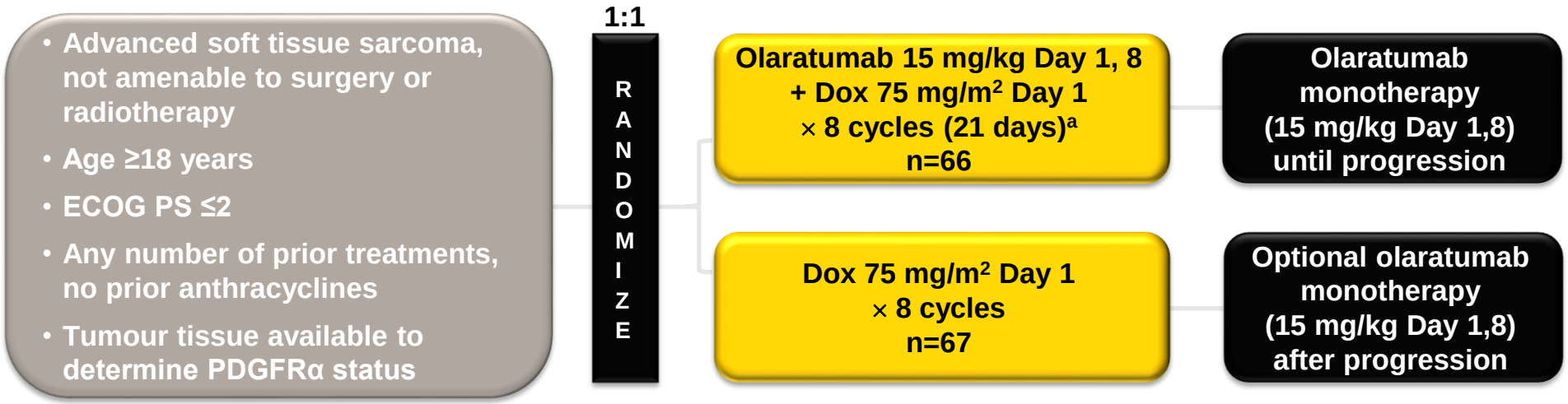
1. Loizos N et al. *Mol Cancer Ther* 4; 369-79: 2005
2. Gerber DE et al. *Mol Cancer Ther* 11; 2473-82: 2012
3. Tonra J et al. Poster presented at AACR-NCI-EORTC Abstract A67; 2005
4. Heldin CH et al. *Biochim Biophys Acta* 1378; F79-113: 1998

Olaratumab Overview

- Olaratumab clinical development
  - Phase 1
    - Two dose-escalation studies in patients with advanced solid tumours
  - Phase 1b/2
    - Randomized, multicentre, open-label study in patients with advanced soft tissue sarcomas
- Olaratumab in combination with doxorubicin improved overall survival

1. Chiorean EG et al. *Cancer Chemother Pharmacol* 73; 595-604: 2014
2. Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Design and Objectives



Stratification factors
- PDGFRα
- Lines of prior treatment
- ECOG PS
- Histology

Primary objective
- Progression-free survival

Secondary objectives
- Overall survival
- Objective response rate
- Progression-free survival at 3 months
- Change in tumour size
- Pharmacokinetics
- Immunogenicity
- Association between PDGFRα expression and clinical outcomes

[a]During Cycles 5-8, patients receiving doxorubicin could receive dexrazoxane at the investigator's discretion

Tap WD et al. *Lancet* 388; 488-97: 2016

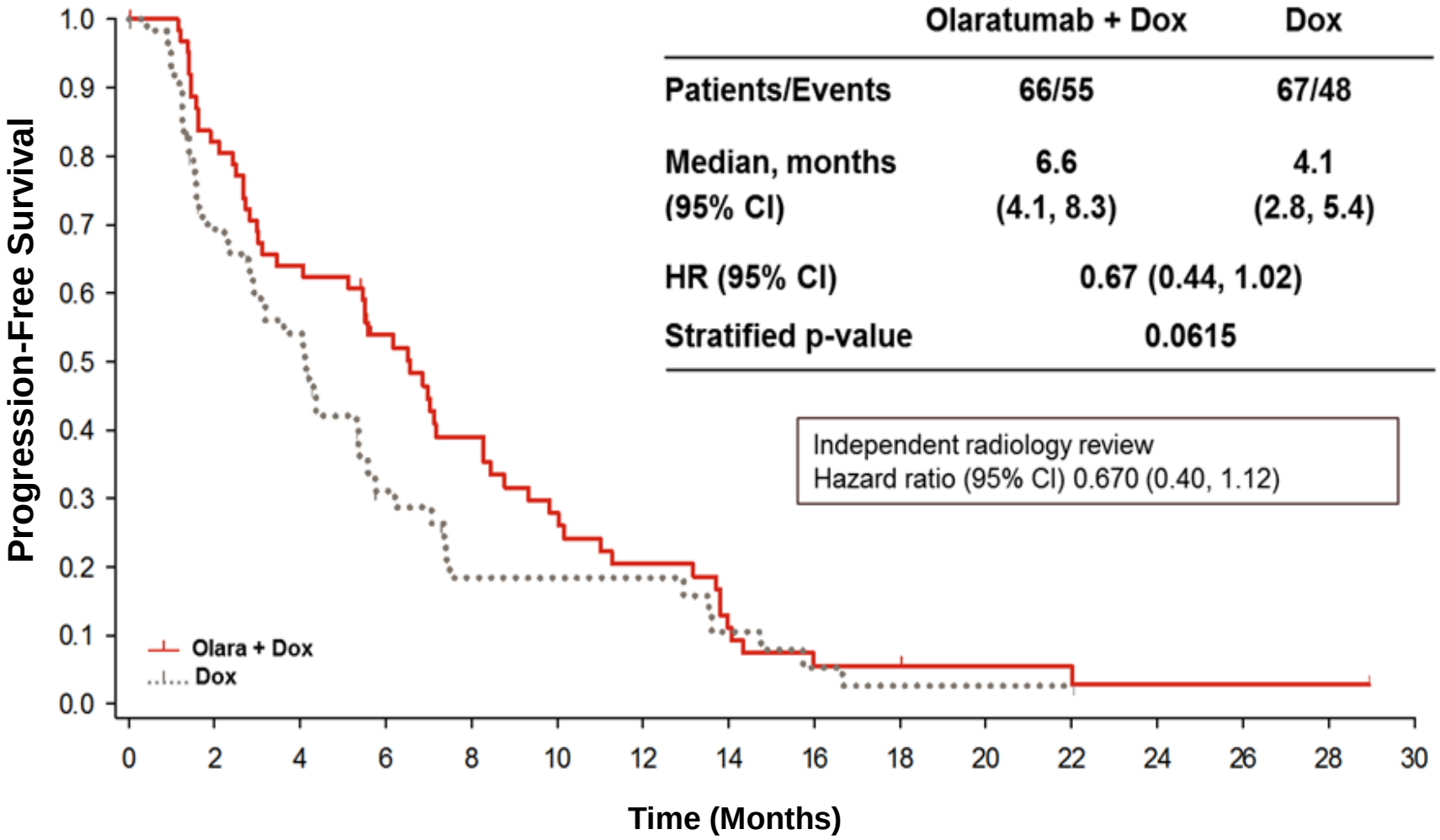
Phase II Trial: Tumour Histological Subtype

Histological type,[a] n (%)	Olaratumab + Dox (n=66)	Dox (n=67)
Leiomyosarcoma	24 (36.4)	27 (40.3)
Undifferentiated pleomorphic sarcoma	10 (15.2)	14 (20.9)
Liposarcoma	8 (12.1)	15 (22.4)
Angiosarcoma	4 (6.1)	3 (4.5)
Synovial sarcoma	1 (1.5)	2 (3.0)
Fibrosarcoma	1 (1.5)	0
Neurofibrosarcoma	1 (1.5)	0
Other	17 (25.8)	6 (9.0)

[a]The following 8 subtypes were pre-specified in the original study case report form: angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, neurofibrosarcoma, pleomorphic sarcoma, synovial sarcoma, and other. Other subtypes were entered into the case report form as free text fields

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Progression-Free Survival



	Olaratumab + Dox	Dox
Patients/Events	66/55	67/48
Median, months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
HR (95% CI)	0.67 (0.44, 1.02)	
Stratified p-value	0.0615	

Independent radiology review
Hazard ratio (95% CI) 0.670 (0.40, 1.12)

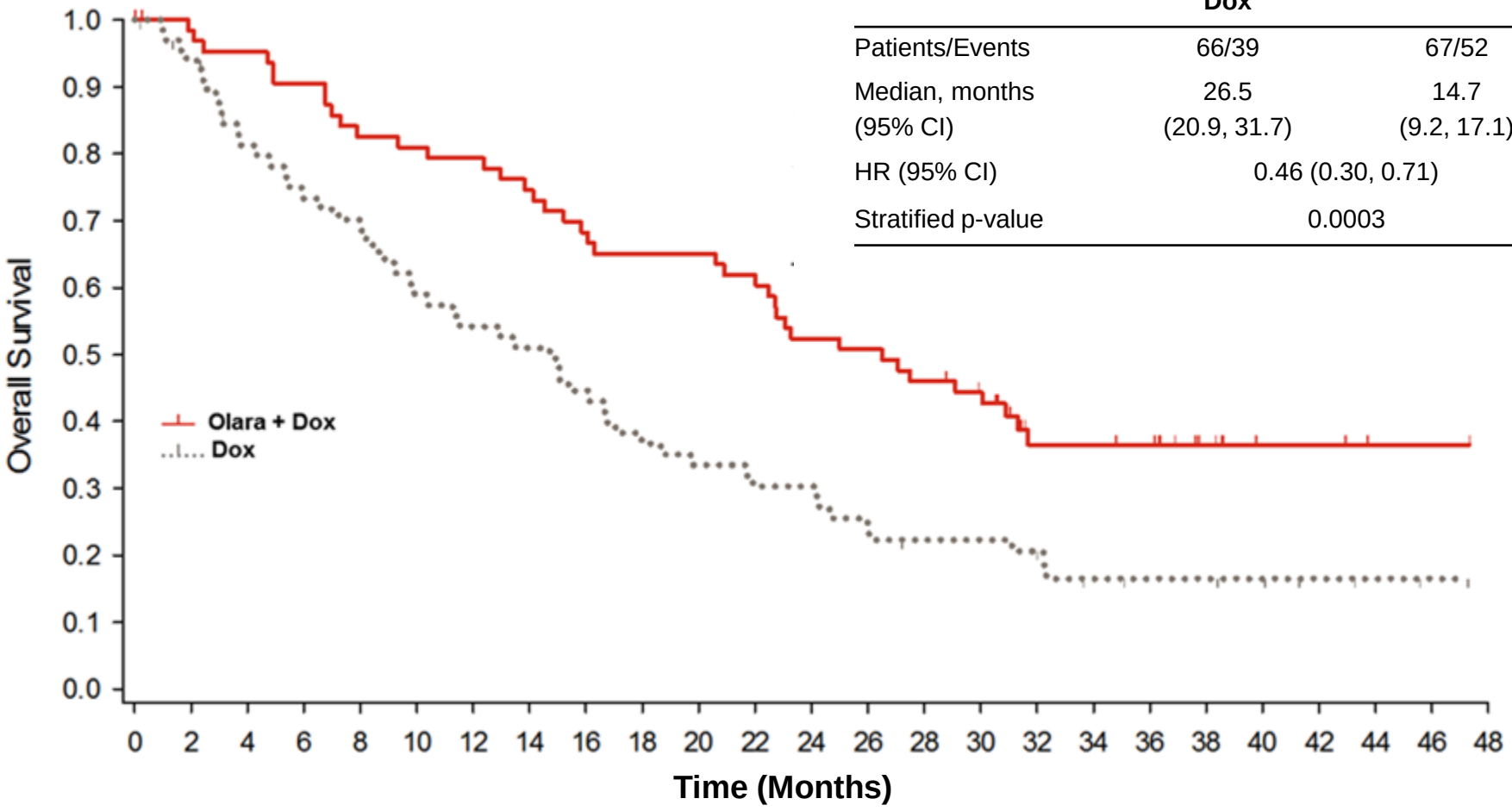
Investigator Assessment	Olaratumab + Dox	Dox
Patients/Events	66/55	67/48
Median, months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
HR (95% CI)	0.67 (0.44, 1.02)	
Stratified p-value	0.0615[a]	

[a]Met predefined criterion of α=0.20

Independent Review Assessment	Olaratumab + Dox	Dox
Patients/Events	66/37	67/34
Median, months (95% CI)	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
HR (95% CI)	0.67 (0.40, 1.12)	
Stratified p-value	0.1208	

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Overall Survival

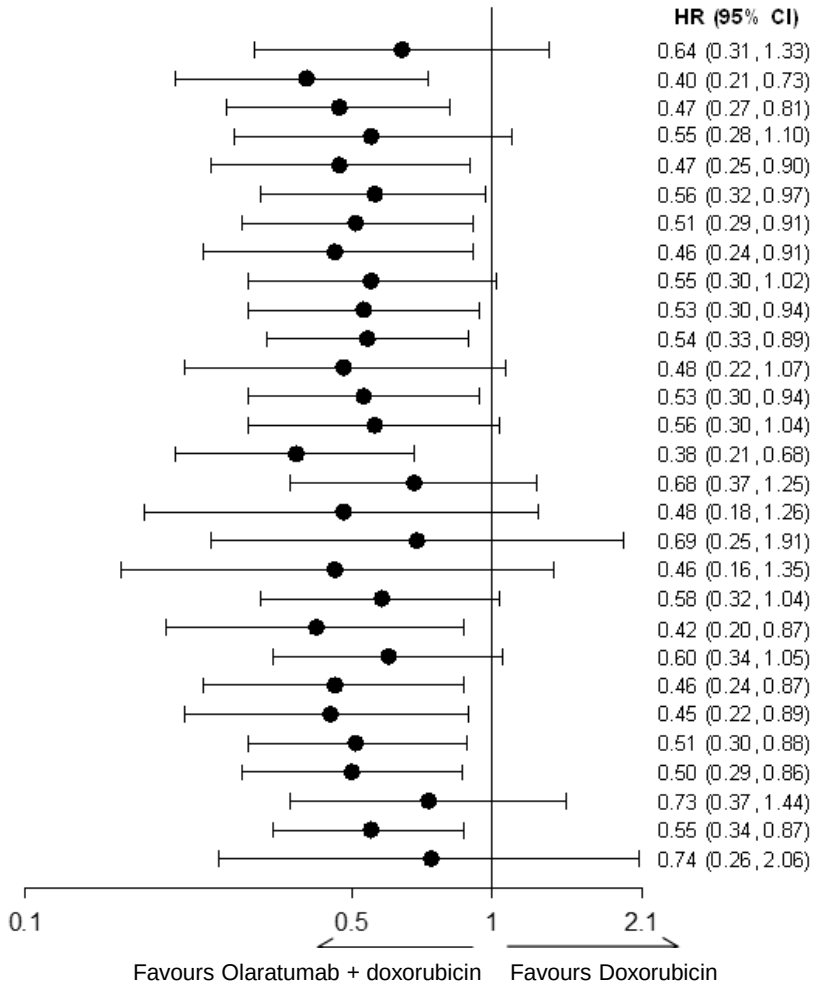


	Olaratumab + Dox	Dox
Patients/Events	66/39	67/52
Median, months (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
HR (95% CI)	0.46 (0.30, 0.71)	
Stratified p-value	0.0003	

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Overall Survival by Stratification Factor

Category	Subgroup	Olaratumab + doxorubicin # Events	N	Doxorubicin # Events	N	HR (95% CI)
PDGFRα (Exploratory assay)	Positive	14	18	17	19	0.64 (0.31, 1.33)
	Negative	19	37	26	37	0.40 (0.21, 0.73)
Number of lines of previous treatment	0	21	40	36	47	0.47 (0.27, 0.81)
	1 or more	18	26	16	20	0.55 (0.28, 1.10)
Histological tumor type	Leiomyosarcoma	16	24	24	27	0.47 (0.25, 0.90)
	Other	23	42	28	40	0.56 (0.32, 0.97)
ECOG PS	0	20	36	30	38	0.51 (0.29, 0.91)
	1	16	26	19	26	0.46 (0.24, 0.91)
Sex	Male	16	26	28	33	0.55 (0.30, 1.02)
	Female	23	40	24	34	0.53 (0.30, 0.94)
Age (y)	18-<65	30	48	33	43	0.54 (0.33, 0.89)
	≥65	9	18	19	24	0.48 (0.22, 1.07)
Weight (kg)	<81.4	19	29	31	37	0.53 (0.30, 0.94)
	≥81.4	20	37	21	30	0.56 (0.30, 1.04)
Duration of disease (mo)	<14.95	20	33	29	34	0.38 (0.21, 0.68)
	≥14.95	19	33	23	33	0.68 (0.37, 1.25)
Duration of most recent prior systemic treatment (mo)	<4.12	8	11	10	12	0.48 (0.18, 1.26)
	≥4.12	10	15	6	8	0.69 (0.25, 1.91)
Grade	Grade 1-2	5	12	10	15	0.46 (0.16, 1.35)
	Grade 3	21	29	25	29	0.58 (0.32, 1.04)
	Unknown/Not assessed	13	25	17	23	0.42 (0.20, 0.87)
Albumin at baseline (g/L)	<38.0	22	29	30	37	0.60 (0.34, 1.05)
	≥38.0	17	37	22	30	0.46 (0.24, 0.87)
Liver metastases	Yes	17	26	19	22	0.45 (0.22, 0.89)
	No	22	40	33	45	0.51 (0.30, 0.88)
Platelets at baseline (10E9/L)	≤300	26	49	29	41	0.50 (0.29, 0.86)
	>300	13	17	23	26	0.73 (0.37, 1.44)
WBC at baseline (10E9/L)	≤10	34	59	38	52	0.55 (0.34, 0.87)
	>10	5	7	14	15	0.74 (0.26, 2.06)



Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Tumour Response

Response	Olaratumab + Dox (n=66)	Dox (n=67)	p-value
Best overall response, n (%)			
Complete response	2 (3.0)	1 (1.5)	
Partial response	10 (15.2)	7 (10.4)	
Stable disease	39 (59.1)	34 (50.7)	
Progressive disease	11 (16.7)	15 (22.4)	
Not evaluable	4 (6.1)	10 (14.9)	
Objective response,[a] n (%) [95% CI]	12 (18.2) [9.8, 29.6]	8 (11.9) [5.3, 22.2]	0.3421[b]
Disease control,[c] n (%) [95% CI]	51 (77.3) [65.3, 86.7]	42 (62.7) [50.0, 74.2]	
Duration of response, median months [95% CI]	8.3 [2.7, 12.7]	8.2 [2.8, 14.5]	

[a]Includes patients with a complete response and patients with a partial response; [b]Fisher's exact test; [c]Includes patients with a complete response, patients with a partial response, and patients with stable disease

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Summary of Efficacy

- This study of olaratumab in combination with doxorubicin:
  - Met its predefined, statistical, primary endpoint for progression-free survival
  - Achieved a highly statistically significant improvement of 11.8 months in median overall survival compared with doxorubicin alone
- The improvement in median overall survival was achieved without an increase in serious toxicity
  - Despite a higher cumulative exposure to doxorubicin

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Exposure to Doxorubicin and Olaratumab

Exposure Variable, median (range)	Olaratumab + Dox	Dox
Doxorubicin	n=64	n=65
Duration of treatment (weeks)	21.3 (3.0-29.0)	12.3 (3.0-25.4)
Number of infusions	7.0 (1.0-8.0)	4.0 (1.0-8.0)
Cumulative dose level (mg/m^2)	487.6 (73.9-617.0)	299.6 (74.9-751.3)
Dose intensity (mg/m^2/week)	24.8 (16.7-37.2)	24.7 (18.4-31.3)
Relative dose intensity (%)	99.1 (66.8-148.6)	99.0 (73.5-125.2)
Olaratumab[a]	n=64	n=30
Duration of treatment (weeks)	26.1 (3.0-128.0)	-
Number of infusions		-
Olaratumab	16.5 (1.0-83.0)	-
Olaratumab monotherapy postcombination (n=34)	9.0 (2.0-68.0)	-
Olaratumab monotherapy postprogression (n=30)	-	4.0 (1.0-81.0)

[a]Administered twice per cycle

Tap WD et al. *Lancet* 388; 488-97: 2016

Phase II Trial: Adverse Events

	Olaratumab + Dox (n=64)			Dox (n=65)		
Adverse Event, % patients	**Any Grade**	**Grade 3**	**Grade ≥4**	**Any Grade**	**Grade 3**	**Grade ≥4**
Any event	98.4	37.5	42.2	98.5	38.5	30.8
Nausea	73.4	1.6	0	52.3	3.1	0
Fatigue[a]	68.8	9.4	0	69.2	3.1	0
Neutropenia[a]	57.8	18.8	34.4	35.4	7.7	24.6
Mucositis[b]	53.1	3.1	0	35.4	4.6	0
Alopecia	51.6	0	0	40.0	0	0
Vomiting	45.3	0	0	18.5	0	0
Anemia[a]	40.6	12.5	0	36.9	9.2	0
Leukopenia	40.6	21.9	14.1	18.5	7.7	9.2
Constipation	34.4	0	0	32.3	1.5	0
Diarrhea	34.4	3.1	0	23.1	0	0
Decreased appetite	31.3	1.6	0	20.0	0	0
Abdominal pain[a]	23.4	3.1	0	13.8	0	0
Pyrexia	23.4	0	0	18.5	0	0
Musculoskeletal pain[b]	64.1	Grade ≥3: 7.8		24.6	Grade ≥3: 1.5	
Febrile neutropenia	12.5	10.9	1.6	13.8	13.8	0
Infections and infestations[c]	42.2	7.8	0	41.5	6.2	4.6
Infusion-related reaction	12.5	0	3.1	0	0	0

[a]Consolidated term; [b]Preferred terms reported were: arthralgia, back pain, spasms, musculoskeletal chest pain, myalgia, pain in extremity; [c]Includes all preferred terms within the MedDRA system organ class of Infections and Infestations

Tap WD et al. *Lancet* 388; 488-97: 2016

Olaratumab Trials

Phase	NCT	Drugs	Geographic Location
III	NCT02451943	Doxorubicin + olaratumab vs doxorubicin + placebo	USA/ Europe/ Asia
I/ II	NCT03283696	Doxorubicin/ ifosfamide + olaratumab	USA, Europe
I/ II	NCT02659020	Gemcitabine/ docetaxel + olaratumab	USA, Europe
Ib	NCT02783599	Pre-operative olaratumab + doxorubicin	USA, Europe
I	NCT03126591	Pembrolizumab + olaratumab	USA, Europe

Olaratumab: Regulatory Approval

- 2016: FDA granted acceleratory approval
- 2016: Conditional approval
  - Pending Phase III trial results

- Audit of ongoing use of doxorubicin and olaratumab in real life setting
  - Co-morbidities

- Results of Phase III due end of 2019

Conclusion

- Increasing number of systemic therapy options to treat metastatic soft tissue sarcoma

- Phase II results of doxorubicin + olaratumab promising
  - Impressive improvement in overall survival
  - Number of ongoing combination trials

- Ongoing audit at Royal Marsden in real life clinic setting

- Results of Phase III trial eagerly awaited