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touchPANEL DISCUSSION

Advanced soft tissue sarcoma -

how can we address current controversies to
solve a dilemma
in clinical decision making?

An expert panel discussion
recorded January 2019

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Expert panel



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Disclosures

	Advisory role	Research grant
Dr Marie Ahlström	None	None
Prof. Robin Jones	Adaptimmune, Blueprint, Clinigen, Eisai, Eli Lilly, Epizyme, Daichii Sankyo, Deciphera, Immunedesign, Merck, PharmaMar	MSD
Dr. Neeta Somaiah	Bayer, Blueprint, Deciphera and Eli Lilly	None
Prof. Bruno Vincenzi	Abbott, Bayer, Eisai, Eli Lilly, Novartis, Pfizer, PharmaMar	Eli Lilly, Novartis, PharmaMar

Agenda

First-line treatment for STS: what are the key factors influencing effectiveness?

Presentation: Robin Jones

Panel discussion: Marie Ahlström, Neeta Somaiah and Bruno Vincenzi; moderated by Robin Jones

Interpreting data from clinical trials in STS: are we assessing the right endpoints?

Presentation: Marie Ahlström

Panel discussion: Robin Jones, Neeta Somaiah and Bruno Vincenzi; moderated by Marie Ahlström

Learning objectives

Describe first-line treatment options for patients with advanced STS

Understand how patient selection may affect treatment choice and outcome in advanced STS

Discuss how surrogate markers can be used in trial design to assess treatment outcomes in advanced STS

First-line treatment for STS: what are the key factors influencing effectiveness?



Prof. Robin Jones

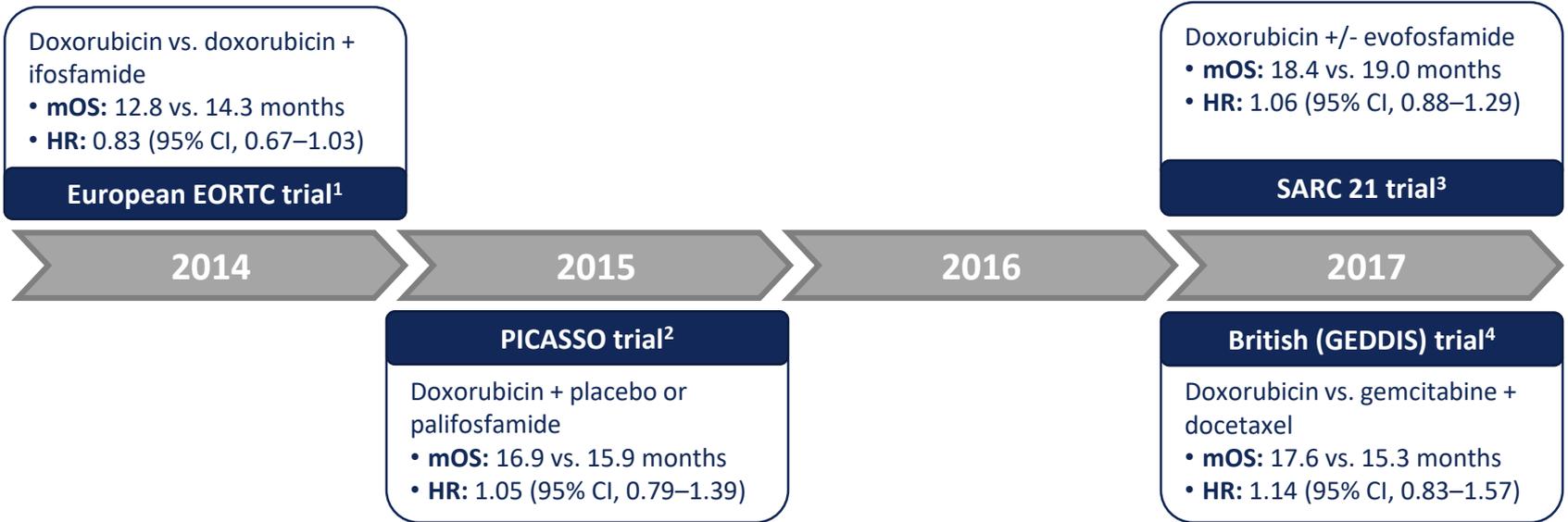
Co-chair

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Anthracyclines are the standard of care in the first-line for advanced STS

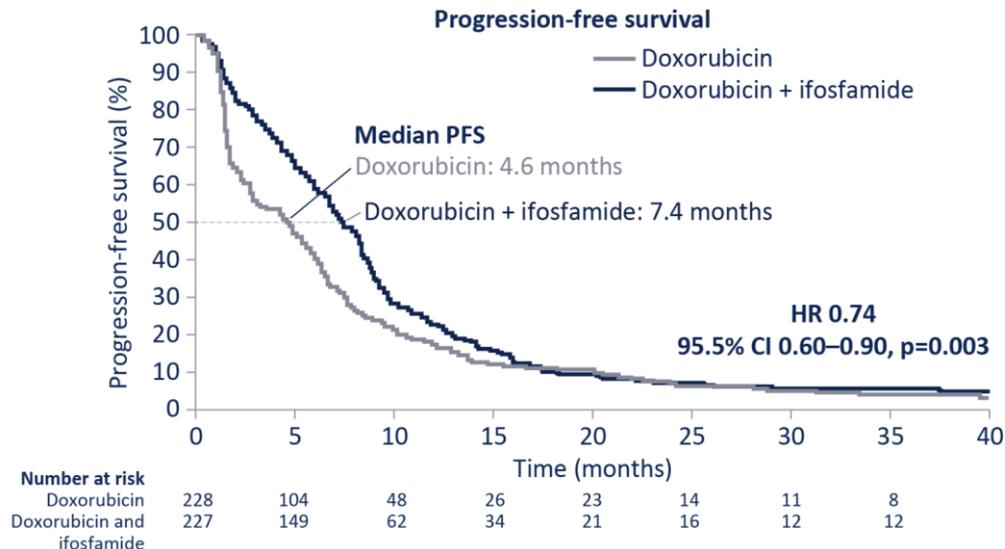
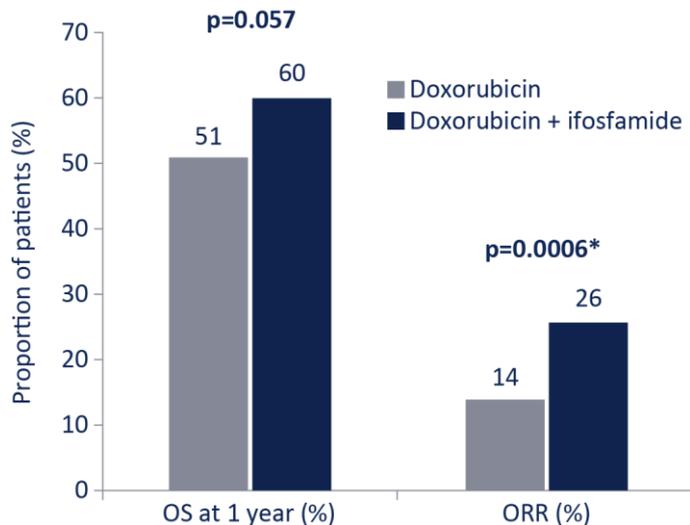


Combination therapies have not significantly improved OS compared with doxorubicin

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GEDDIS, gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas; HR, hazard ratio; mOS, median overall survival; PICASSO, palifosfamide-tris with doxorubicin for soft tissue sarcoma; SARC, Sarcoma Alliance for Research Through Collaboration; STS, soft tissue sarcoma.

1. Judson I, et al. *Lancet Oncol.* 2014;15:415–23; 2. Ryan CW, et al. *J Clin Oncol.* 2016;34:3898–905; 3. Tap WD, et al. *Lancet Oncol.* 2017;18:1089–103; 4. Seddon B, et al. *Lancet Oncol.* 2017;18:1397–410.

EORTC 62012: Assessing combination therapy in advanced STS



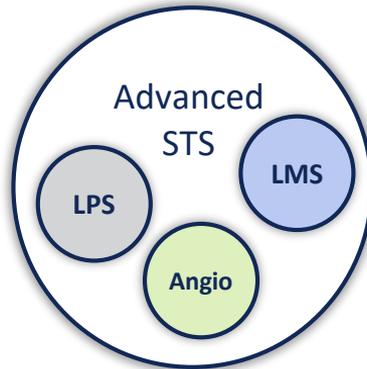
Difference between monotherapy and combination therapy was significant for PFS and ORR, but not for OS

*p value calculated using χ^2 test. EORTC, European Organisation for Research and Treatment of Cancer; ORR, objective response rate; OS, overall survival, PFS, progression-free survival.

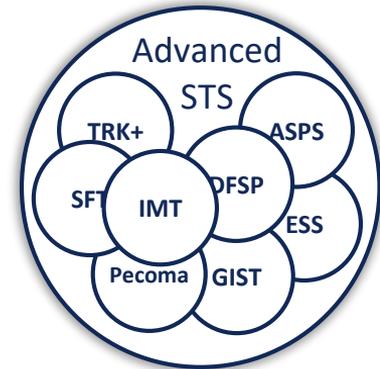
STS is not a single disease



Combination therapy has shown limited survival benefit compared with doxorubicin in the unselected population



Specific histology-driven chemotherapies



Specific histology-driven targeted therapies

STS subtypes may respond differently to different treatments

ASPS, alveolar soft part sarcoma; DFSP, dermatofibrosarcoma protuberans; ESS, endometrial stromal sarcoma; GIST, gastrointestinal stromal tumour; LPS, liposarcoma; LMS, leiomyosarcoma; SFT, solitary fibrous tumour; STS, soft tissue sarcomas; TRK+, tropomyosin receptor kinase fusion protein-positive.

Management of advanced STS remains challenging



STS, soft tissue sarcoma.

Frezza AM, et al. *BMC Med.* 2017;15:109.

A hand holding a white megaphone with a blue wireframe globe overlaid on it. The background is a dark blue gradient.

Panel discussion

Marie Ahlström, Neeta Somaiah and Bruno Vincenzi

Moderated by Robin Jones

What influences individual treatment strategies in patients with advanced disease?

Are the treatments available for STS more effective in some subtypes than others?

Why do we need to look beyond the current standard of care in patients with advanced STS?

Interpreting data from clinical trials in STS: are we assessing the right endpoints?



Marie Ahlström

Co-chair

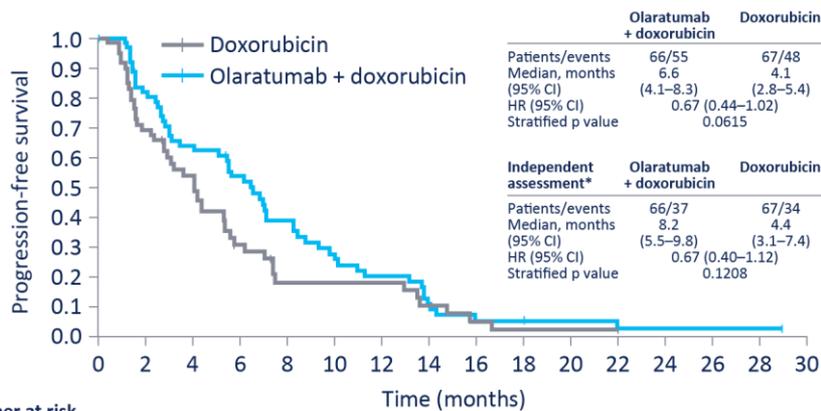
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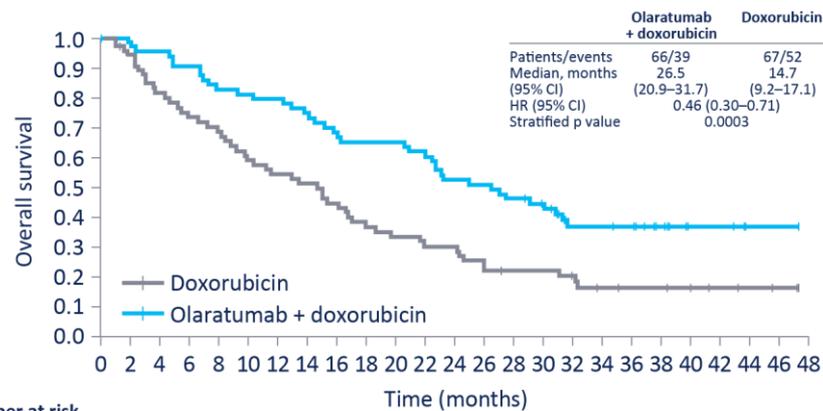
Assessing olaratumab + doxorubicin: results from a Phase II study

Progression-free survival



Number at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Olaratumab + doxorubicin	66	50	39	29	21	15	11	6	3	3	2	2	1	1	1	0
Doxorubicin	67	38	28	13	7	7	7	4	2	1	1	1	0	0	0	0

Overall survival



Number at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Olaratumab + doxorubicin	66	62	60	57	52	51	50	47	43	41	41	39	33	32	29	26	16	16	15	8	3	3	1	1	0
Doxorubicin	67	61	51	46	43	37	34	32	28	23	21	19	19	15	13	13	10	7	6	6	5	3	2	1	0

Study met the primary endpoint* and there was a significant improvement in OS with olaratumab + doxorubicin

*50% improvement in median PFS for the combination treatment group. CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Tap W, et al. *Lancet*. 2016;388;488–97. Figures reproduced from Tap et al. 2016.

Latest news on the Phase III trial of olaratumab + doxorubicin

ANNOUNCE study design¹

- Randomized, double-blind
- Doxorubicin + olaratumab or placebo
- Anthracycline-naïve patients (N=460) with advanced unresectable STS
- Primary endpoint: OS; secondary endpoints included: PFS, response rate and QOL

...there was no difference in survival between the study arms for either population...²

...The study did not meet the primary endpoints of overall survival in the full study population or in the leiomyosarcoma sub-population...²

...There were no new safety signals identified and the safety profile was comparable between treatment arms...²

ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; PFS, progression-free survival; QOL, quality of life; STS, soft tissue sarcoma.

1. www.clinicaltrials.gov NCT02451943 (Accessed January 2019); 2. [Olaratumab press release 2019](#).

Positive Phase II but negative Phase III results in advanced or metastatic STS

Olaratumab: ANNOUNCE Phase II and III studies

Phase II

Doxorubicin + olaratumab recommended as first-line therapy based on Phase II study OS results^{1,2}

Phase III

Doxorubicin + olaratumab did not demonstrate an improvement in OS in the Phase III trial³

Palifosfamide: PICASSO Phase II and III studies

Phase II

Palifosfamide + doxorubicin demonstrated ~doubling in PFS over doxorubicin + placebo in Phase II study⁴

Phase III

Palifosfamide + doxorubicin did not maintain the PFS improvement and the OS was shorter in the Phase III trial⁵

OS, overall survival; PFS, progression-free survival; STS, soft tissue sarcoma.

1. Tap WD, et al. *Lancet*. 2016;38:488–97; 2. Casali PG, et al. *Ann Oncol*. 2018;29(Suppl 4):iv268–9; 3. [Olaratumab press release 2019](#).;
4. Verschraegen CF, et al. *J Clin Oncol*. 2010;28:10004; 5. Ryan CW, et al. *J Clin Oncol*. 2016;34:3898–905.

Assessing new treatments for advanced STS: considering trial endpoints

Recent systemic therapy trials in STS have demonstrated OS benefit without comparable improvement in PFS^{1,2}

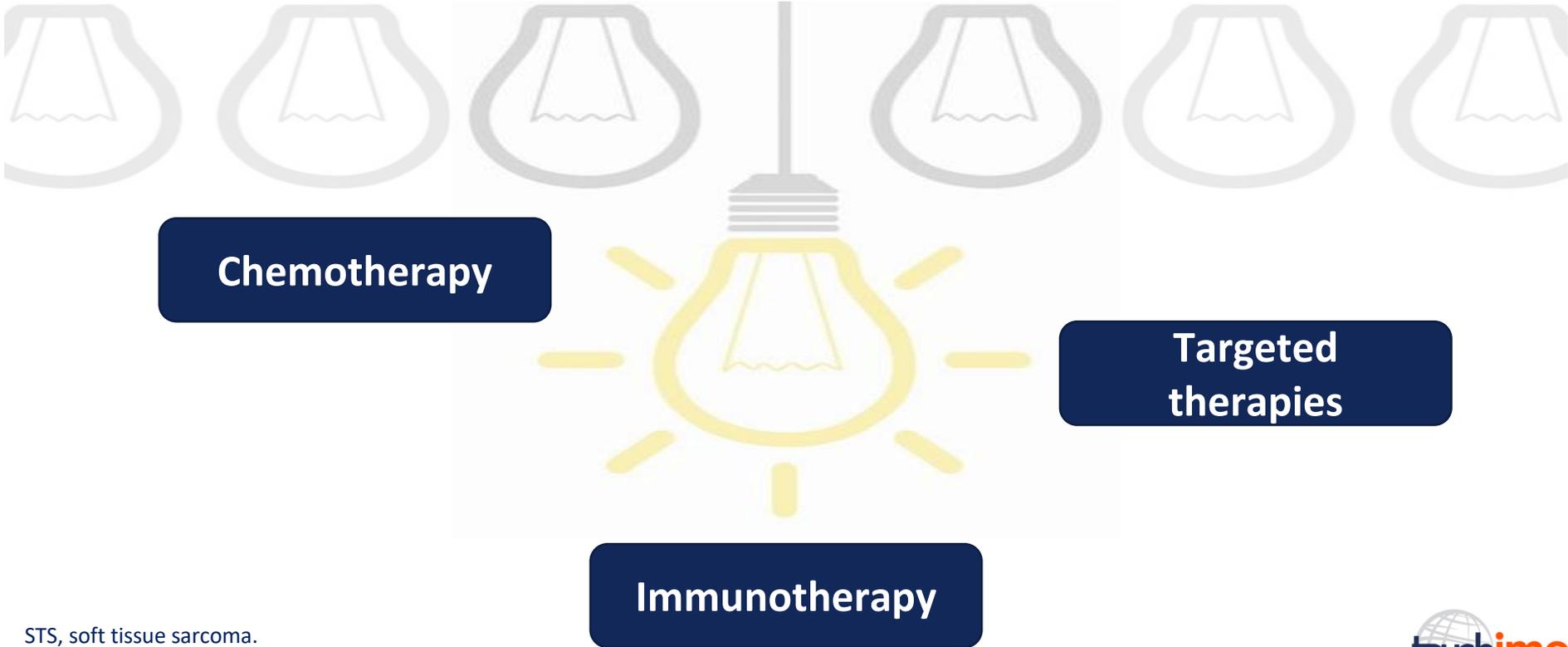
Time-to-event endpoints are used in Phase II studies and are often used instead of OS in Phase III trials³

In a heterogeneous patient population designing with appropriate endpoints is challenging

PFS, progression-free survival; OS, overall survival; RCT, randomised controlled trial; STS, soft tissue sarcoma; TTF, time-to-treatment failure; TTP, time-to-progression.

1. Lee ATJ, et al. *Curr Treat Options Oncol*. 2017;18:19; 2. Schoffski P, et al. *Lancet*. 2016;387:1629–37;
3. Savina M, et al. *Oncotarget*. 2018;9:34617–27.

Clinical development of new agents for advanced STS continues



STS, soft tissue sarcoma.

Martin-Liberal J, et al. *Expert Opin Investig Drugs*. 2019;28:39–50.

Panel discussion

Robin Jones, Neeta Somaiah, and Bruno Vincenzi

Moderated by Marie Ahlström

Why was the Phase II study of olaratumab positive, but the Phase III not? Might the findings be different in other patient subgroups?

What are the most meaningful efficacy endpoints in advanced STS?

How might emerging agents with different mechanisms of action affect outcomes for different patient subgroups?

Conclusions

Robin Jones

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