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Soft Tissue Sarcomas - Update 2019 / Ongoing & Upcoming Clinical Trials in STS

2nd of February 2020, 10th SPAEN Annual Conference 2020, Marriot Hotel Milan, Milan, Italy

DKG
KREBSGESELLSCHAFT
Zertifiziertes Sarkomzentrum für
Weichteilsarkome
Knochensarkome

Prof. Dr. med. Bernd Kasper

University of Heidelberg

Sarcoma Unit @ Mannheim University Medical Center (UMM)

German Interdisciplinary Sarcoma Group (GISG)

Chair-Elect EORTC / Soft Tissue and Bone Sarcoma Group (STBSG)

European Reference Network
for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)
Member Universitätsklinikum Mannheim — Deutschland

Soft tissue sarcomas - Basic characteristics

- **Rare disease:**
  - Germany: ~5-6 / 100.000 inhabitants per year*
- **Heterogeneous disease:**
  - > 50 different histological subtypes according to WHO
- **Unfavorable prognosis:**
  - Median overall survival ~12-15 months (M1)

RARE CANCERS EUROPE
Joining forces for action

EURACAN

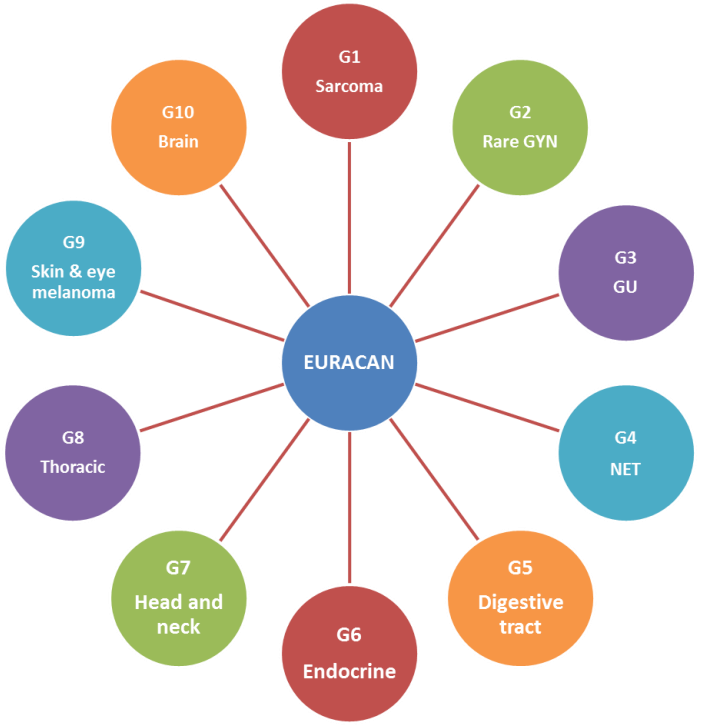
JARC
JOINT ACTION ON RARE CANCERS

** Ressing M et al. BMC Public Health 2018; 18: 235*

European Reference Network
for rare or low prevalence complex diseases

Network
Adult Cancers
(ERN EURACAN)

EURACAN



Melanoma Patient Network Europe

RARE SOLID ADULT CANCERS

Practice-changing (?) News in 2019: ANNOUNCE & Co

- **1st line Therapy with Olaratumab for Advanced STS:**
  - Phase III Doxorubicin + Olaratumab *vs* Doxorubicin + Placebo (ANNOUNCE)
- **Neoadjuvant Chemotherapy for High-Risk STS:**
  - Phase III Epirubicin + Ifosfamide *vs* Histology-specific regimens (ISG-STS 1001)
- **Preoperative Radiotherapy for Retroperitoneal Sarcomas:**
  - Phase III Preoperative Radiotherapy + Surgery *vs* Surgery alone (EORTC STRASS)
- **Ongoing & Upcoming Clinical Trials in STS**

CANCER *January* 1974

ADRIAMYCIN CHEMOTHERAPY—EFFICACY, SAFETY, AND PHARMACOLOGIC BASIS OF AN INTERMITTENT SINGLE HIGH-DOSAGE SCHEDULE

ROBERT S. BENJAMIN, MD, PETER H. WIERNIK, MD, AND NICHOLAS R. BACHUR, MD, PHD

A study designed to correlate clinical and pharmacologic observations was undertaken in 96 patients treated with adriamycin. The basic dosage schedule was 60 mg/m² I.V. q 3 weeks. Pharmacokinetic studies showed a prolonged plasma half-life, low urinary excretion, and undetectable levels in CSF. Patients with significantly impaired liver function had marked elevation and prolongation of plasma drug levels associated with severe toxicity unless dosage was reduced by 50–75%. Of the 82 evaluable patients, 10/25 with sarcomas, 9/31 with carcinomas, and 15/26 with hematologic malignancies have achieved complete or partial remission. An additional 22/48 have improved. Six patients with solid tumors had progressive CNS disease while responding systemically. Adriamycin can be used with relative safety and high efficacy in a dosage schedule that resulted from pharmacologic studies. Dosage reduction in patients with liver disease is essential to avoid life-threatening toxicity.

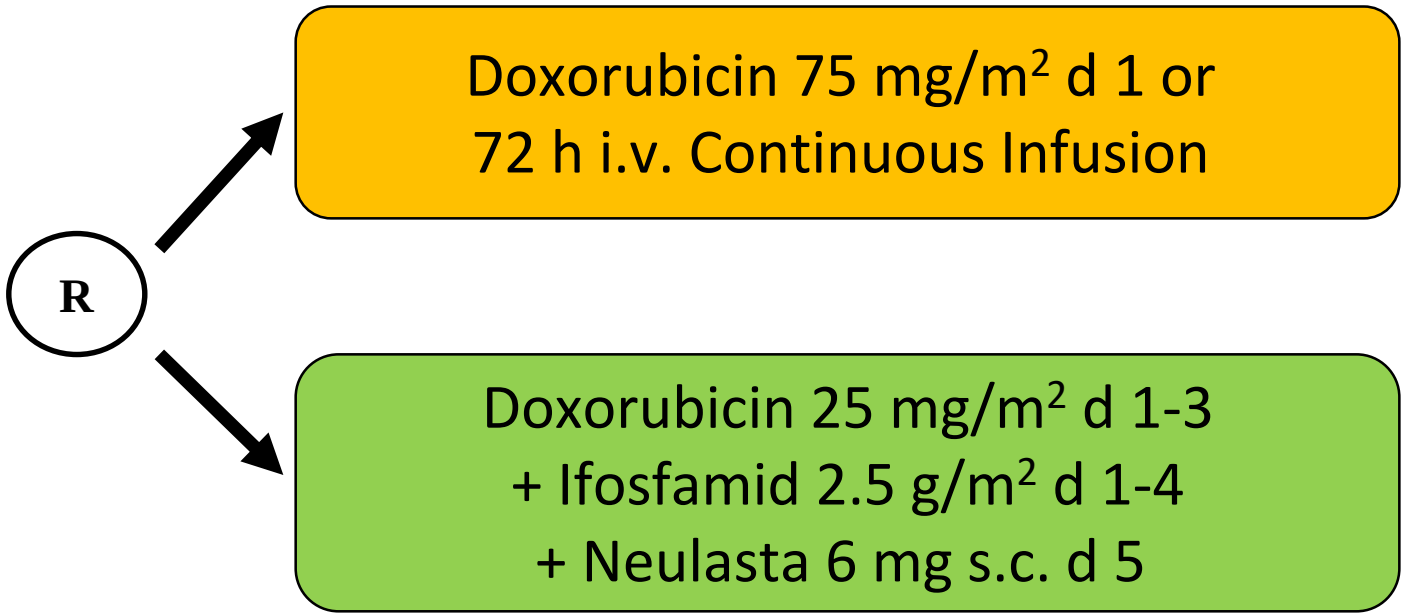
Advanced STS - Role of Poly-Chemotherapy

Authors	Chemotherapy	N	Response Rate		Survival
Muss et al. 1985	A/AC	104	NS		**NS**
Omura et al. 1983	A/AD	146	NS		**NS**
Borden et al. 1987	A/AD	186	**AD = 30 %**	(*p = 0.02*)	**NS**
Lerner et al. 1987	A/AD	66	**AD = 44 %**	(LMS)	**NS**
Santoro et al. 1995	A/AI/CYVADIC	449	NS		**NS**
Borden et al. 1990	A/AVd	295	NS		**NS**
Edmonson et al. 1993	A/AI/APM	262	**AI = 34 %**	(*p = 0.03*)	**NS**
Antman et al. 1993	AD/MAID	340	**MAID = 32 %**	(*p = 0.002*)	**NS**
Judson et al. 2014	A/AI	415	**AI = 26 %**	(A = 14 %)	**NS**
Ryan et al. 2016	A/APal	447	**APal = 28 %**	(A = 19 %)	**NS**

<u>No</u> survival benefit ⇨ Doxorubicin (75 mg/m²) remained 1st line Gold-Standard

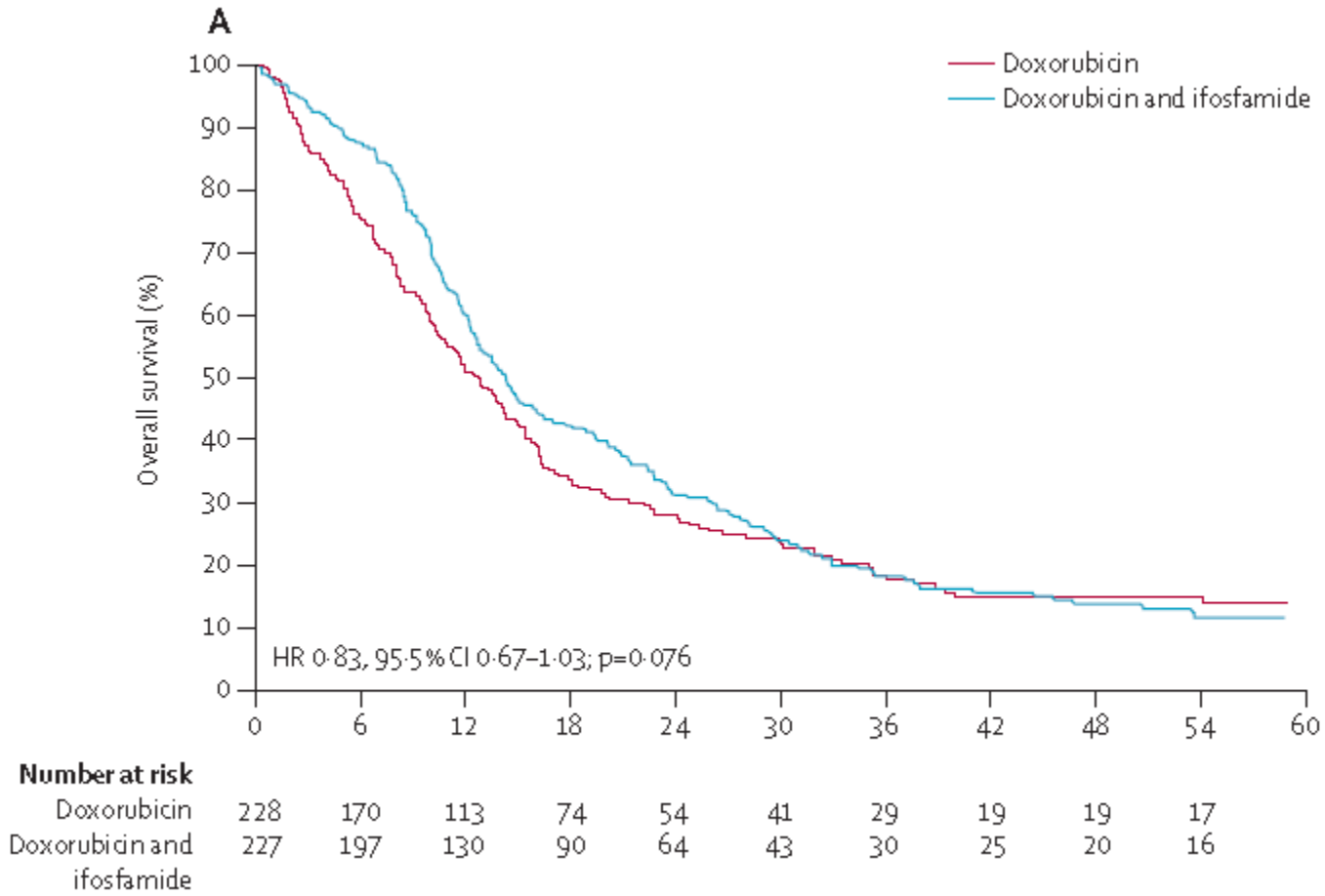
Muss H et al. Cancer 1985; 55: 1648-1653; Omura G et al. Cancer 1983; 52: 626-632; Borden E et al. J Clin Oncol 1987; 5: 840-850; Santoro A et al. J Clin Oncol 1995; 13: 1537-1545; Borden E et al. Cancer 1990; 66: 862-867; Edmonson J et al. J Clin Oncol 1993; 11: 1269-1275; Antman K et al. J Clin Oncol 1993; 11: 1276-1285; Judson I et al. Lancet Oncol 2014; 15: 415-423; Ryan CW et al. J Clin Oncol 2016; 34: 3898-3905

EORTC 62012 - Study Design



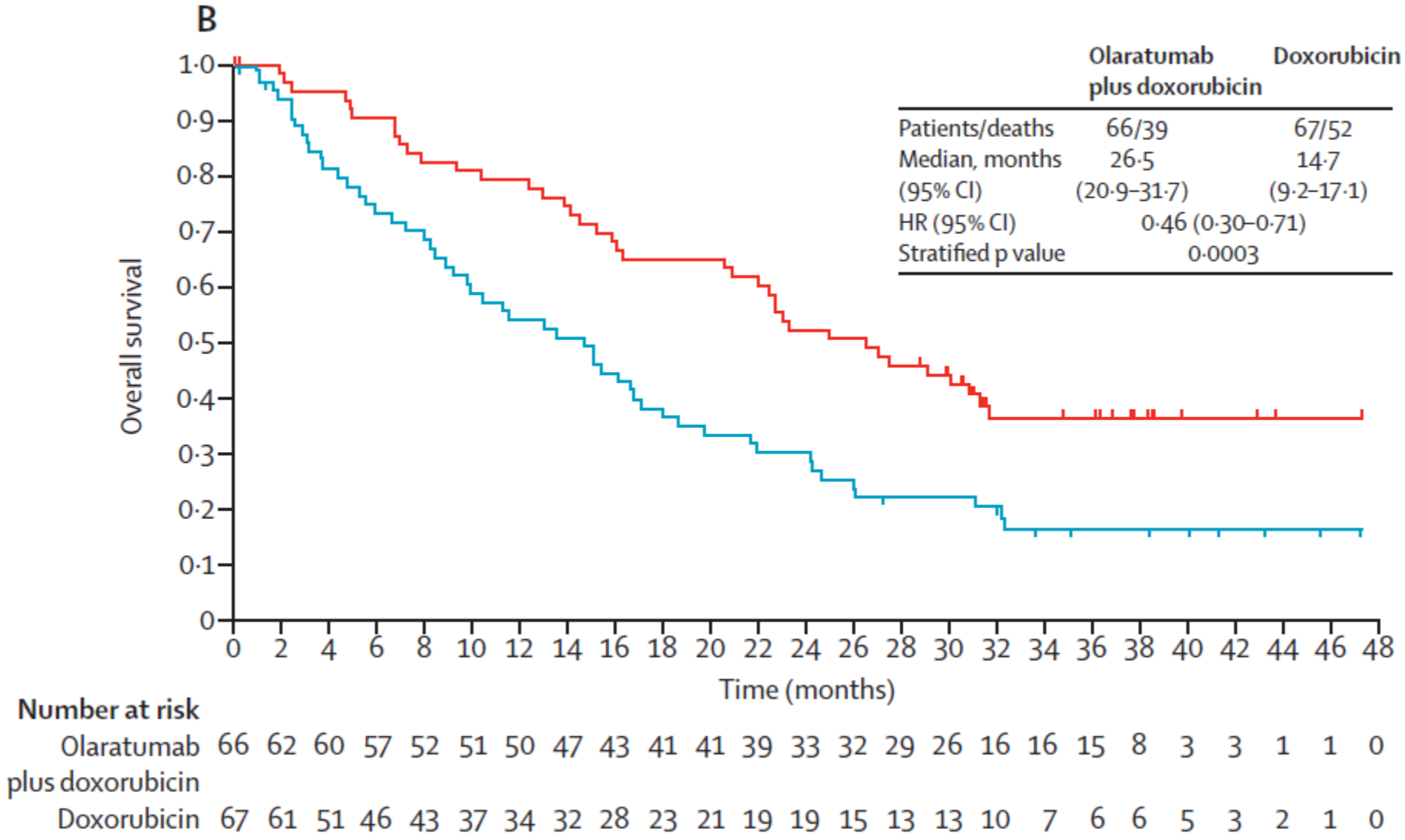
Judson I et al. Lancet Oncol 2014; 15: 415-423

EORTC 62012 - Overall Survival



Judson I et al. Lancet Oncol 2014; 15: 415-423

Olaratumab - Overall Survival (JGDG Phase 1b/2)



Tap WD et al. Lancet 2016; 388: 488-497

ANNOUNCE: A randomized, placebo-controlled, double-blind, phase 3 trial of doxorubicin + olaratumab *vs* doxorubicin + placebo in patients with advanced soft tissue sarcomas

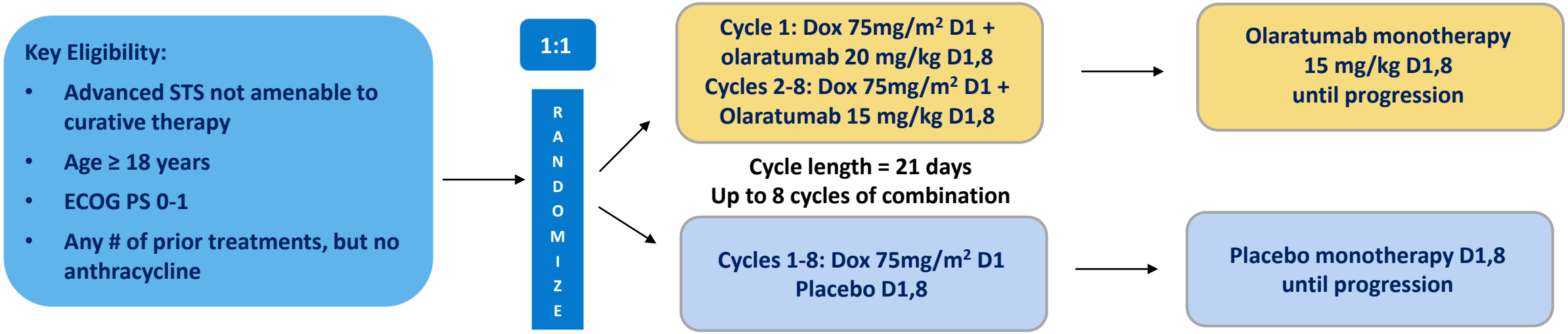
William D. Tap, Andrew J. Wagner, Zsuzsanna Papai, Kristen Ganjoo, Chueh-Chan Yen, Patrick Schöffski, Albiruni Razak, Javier Martin Broto, Alexander Spira, Akira Kawai, Anders Krarup-Hansen, Axel Le Cesne, Brian A. Van Tine, Yoichi Naito, Se Hoon Park, Victoria Soldatenkova, Gary Mo, Ashwin Shahir, Jennifer Wright, Robin L. Jones

On behalf of the ANNOUNCE investigators

ASCO Plenary Session 2 June, 2019

2019 ASCO® ANNUAL MEETING

ANNOUNCE: Randomized, Double-blind, Placebo-controlled Phase 3 Study (n = 509)



Stratification factors: Number of prior therapies (0 *vs* ≥1), histology (LMS *vs* LPS *vs* UPS *vs* Other), ECOG PS (0 *vs* 1)

Primary endpoint: OS in the total STS & LMS populations

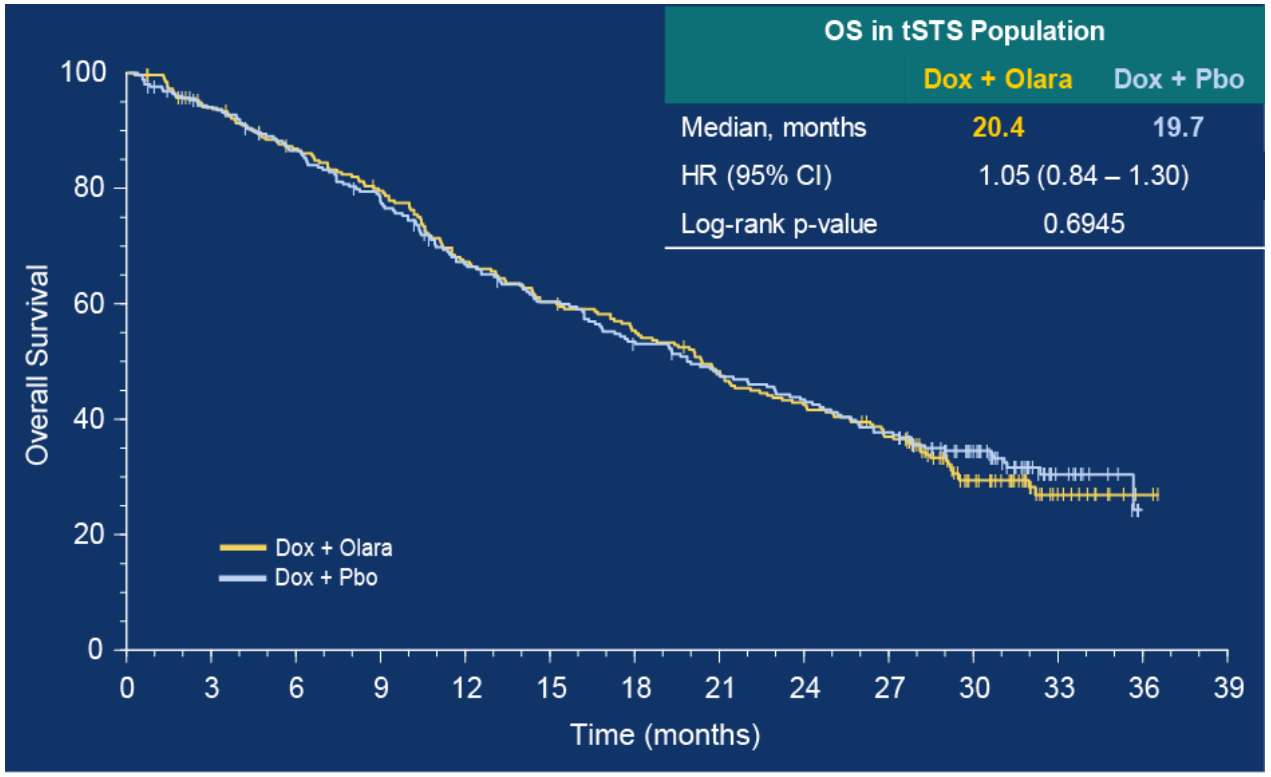
Key secondary endpoints: PFS, ORR, PROs, safety, PK, immunogenicity

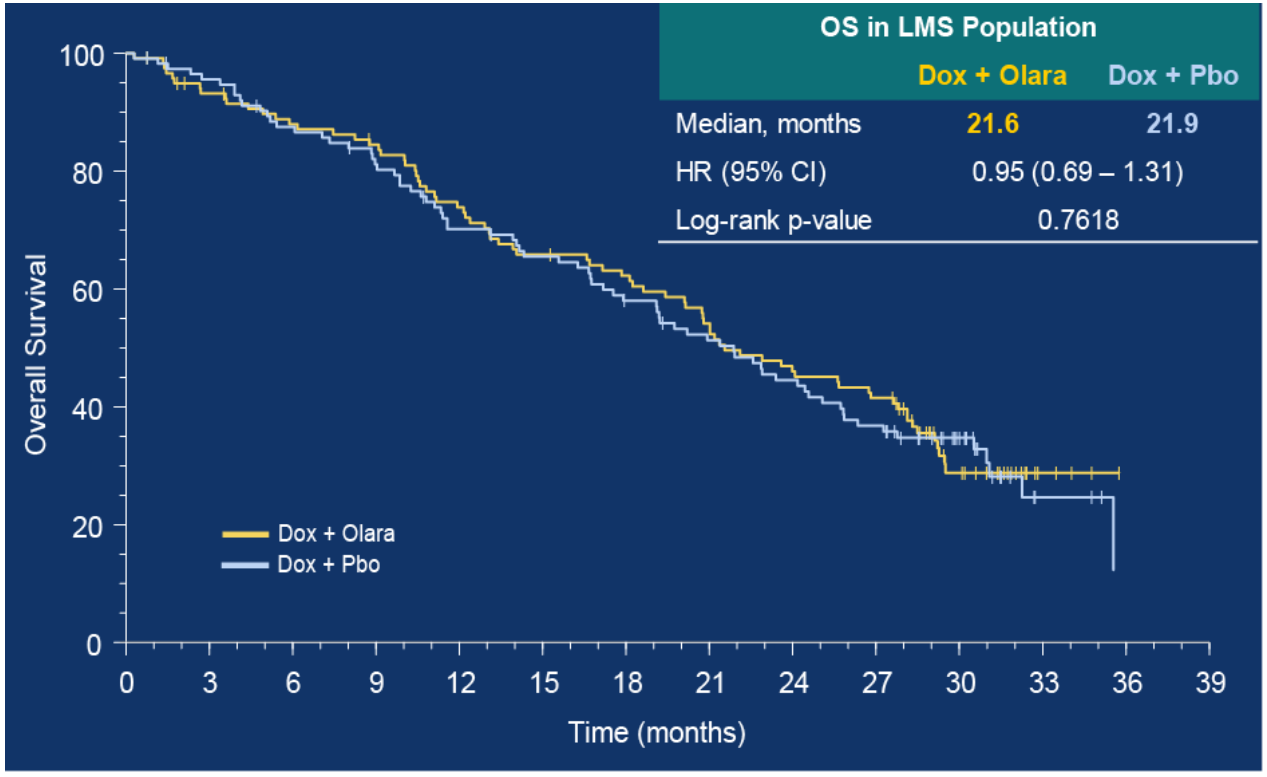
Exploratory: Biomarkers, subgroup analyses

Other features: Dexrazoxane use allowed at any cycle, cardiac monitoring of LVEF prior to cycles 5, 7, & 9 then q3 months

D, day; Dox, doxorubicin; ECOG PS, Eastern Cooperative Oncology Group performance status; LMS, leiomyosarcoma; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcomes; q, every; STS, soft tissue sarcoma; UPS, undifferentiated pleomorphic sarcoma

Overall Survival: tSTS and LMS Populations





Dox, doxorubicin; LMS, leiomyosarcoma; Olara, olaratumab; OS, overall survival; Pbo, placebo; tSTS, total Soft Tissue Sarcoma

Phase 3 Trials in Advanced STS

2012	2014	2015	2016	2017
PALETTE[1] pazopanib vs. placebo mOS: 12.5 vs. 10.7 mo HR: 0.86 (95% CI, 0.67-1.11) PFS: 4.6 vs. 1.6 mo	**EORTC-62012**[2] dox vs. dox + ifosfamide mOS: 12.8 vs. 14.3 mo HR: 0.83 (95% CI, 0.67-1.03) PFS: 4.6 vs. 7.4 mo	**PICASSO-III**[3] dox vs. dox + palifosfamide mOS: 16.9 vs. 15.9 mo HR: 1.05 (95% CI, 0.79-1.39) PFS: 5.2 vs. 6.0 mo	**ET743-SAR-3007**[4] trabectedin vs. dacarbazine mOS: 13.7 vs. 13.1 mo HR: 0.93 (95% CI, 0.75-1.15) PFS: 4.2 vs. 1.5 mo	**SARC 21**[6] dox vs. dox + evofosfamide mOS: 19.0 vs. 18.4 mo HR: 1.06 (95% CI, 0.88-1.29) PFS: 6.0 vs. 6.3 mo
			E7389-G000-309[5] eribulin vs. dacarbazine mOS: 13.5 vs. 11.5 mo HR: 0.77 (95% CI, 0.62-0.95) PFS: 2.6 vs. 2.6 mo	**GeDDiS**[7] dox vs. doce + gemcitabine mOS: 17.6 vs. 15.5 mo HR: 1.14 (95% CI, 0.83-1.57) PFS: 23.3 vs. 23.7 wks

Led to drug approval

First Line | **Second Line +** | **Third Line +**

dox, doxorubicin; doce, docetaxel; 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; mOS, median overall survival; mo, month; PICASSO, palifosfamide-tris with doxorubicin for soft tissue sarcoma; SARC, Sarcoma Alliance for Research Through Collaboration; STS, soft tissue sarcoma; wks, weeks.

1. Van der Graaf et al. *Lancet* 2012; 2. Judson I et al. *Lancet Oncol* 2014; 3. Ryan et al. *J Clin Oncol* 2016; 4. Trabectedin US prescribing information 2019; 5. Schöffski et al. *Lancet* 2016; 6. Tap et al. *Lancet Oncol* 2017; 7. Seddon et al. *Lancet Oncol* 2017

ANNOUNCE

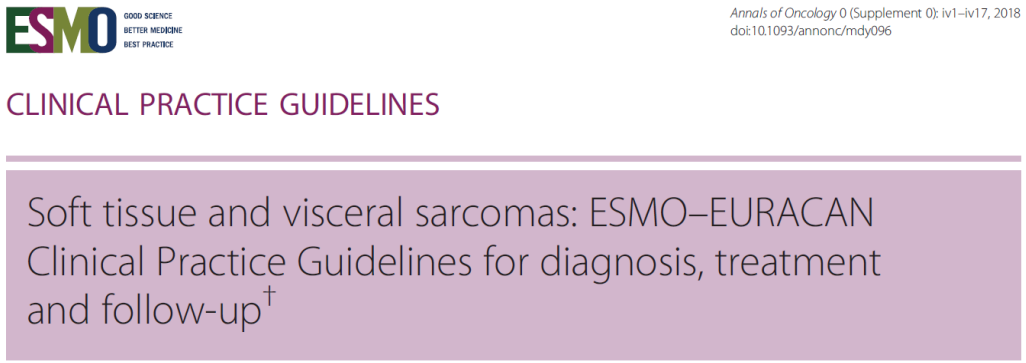
- Was a well controlled and conducted Phase 3 trial which failed to meet its overall survival primary endpoint in all STS histologies and the LMS population
- Did not confirm the benefit seen in the Phase 1b/2 trial
- The control arm had the highest OS for doxorubicin in any randomized STS trial
  - Entry not limited to first line and allowed up to 600 mg/m^2 doxorubicin

- After data read out, the trial sponsor and global regulatory agencies recommended no new patients to be started on olaratumab

- Withdrawal of olaratumab from the market for the treatment of advanced soft-tissue sarcoma patients

Systemic Treatment Options beyond 1st line

• **All STS (Europe)** ***since 2007***	**Trabectedin**
• **LMS + LPS (USA)** ***since 2015***	**Trabectedin**
• **All STS <u>without</u> LPS** ***since 2012***	**Pazopanib**
• **<u>Only</u> Liposarcomas** ***since 2016***	**Eribulin**
Doxorubicin pretreated STS	Gem/DTIC or Gem/Docetaxel (*ESMO-EURACAN 2018*)
Pretreated, non-adipocytic STS	Regorafenib (*ESMO-EURACAN 2018*)
All STS	Inclusion in clinical trials (*ESMO-EURACAN 2018*)



2019 ASCO ANNUAL MEETING

NEOADJUVANT CHEMOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMAS: FINAL RESULTS OF A RANDOMIZED CLINICAL TRIAL FROM THE ITALIAN SARCOMA GROUP (ISG), THE SPANISH SARCOMA GROUP (GEIS), THE FRENCH SARCOMA GROUP (FSG) AND THE POLISH SARCOMA GROUP (PSG).

Gronchi A; Palmerini E; Quagliuolo V; Martin Broto J; Lopez Pousa A; Grignani G; Brunello A; Blay JY; Tendero O; Beveridge RD; Ferraresi V; Lugowska I; Merlo FD; Fontana V; Marchesi E; Donati DM; Palassini E; Bianchi G; Marrari A; Morosi C; Stacchiotti S; Bagué S; Coindre JM; Dei Tos AP; Picci P; Bruzzi P and Casali PG

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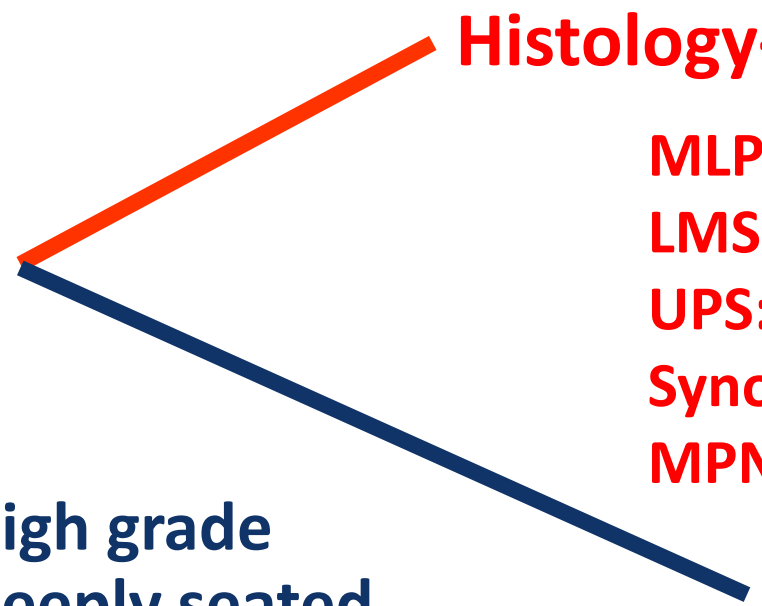
ISG - STS 1001



R

- High grade
- Deeply seated
- ≥ 5 cm

Histology-tailored Chemo x 3 → Surgery ± RT

MLPS: Trabectedin
LMS: GEM + DTIC
UPS: GEM + TAX
Synovial Sa: HD-IFX
MPNST: IFX + ETO

epiADM + IFX x 3 → Surgery ± RT

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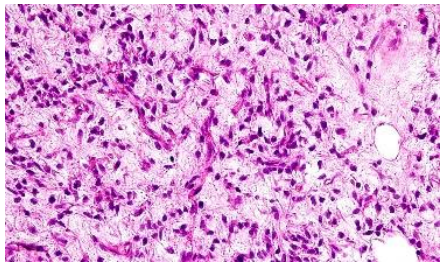
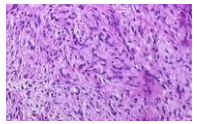
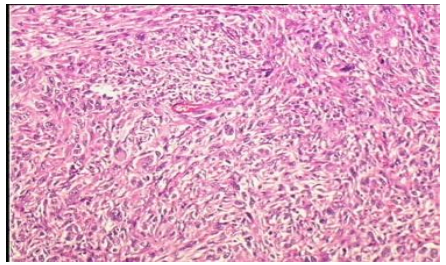
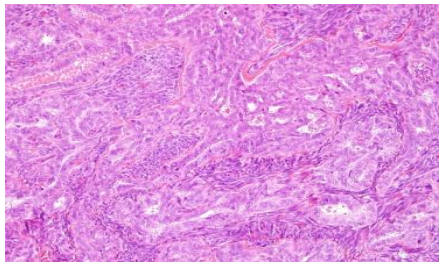
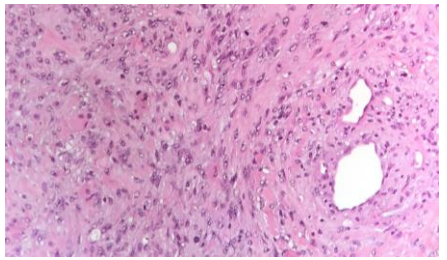
287 patients: Histology

MLPS	LMS	UPS	Synov Sa	MPNST
				
65 (23 %)	28 (10 %)	97 (34 %)	70 (24 %)	27 (9 %)
HT = 28 (10 %)	HT = 16 (6 %)	HT = 52 (18 %)	HT = 34 (12 %)	HT = 12 (4 %)
S = 37 (13 %)	S = 12 (4 %)	S = 45 (16 %)	S = 36 (12 %)	S = 15 (5 %)

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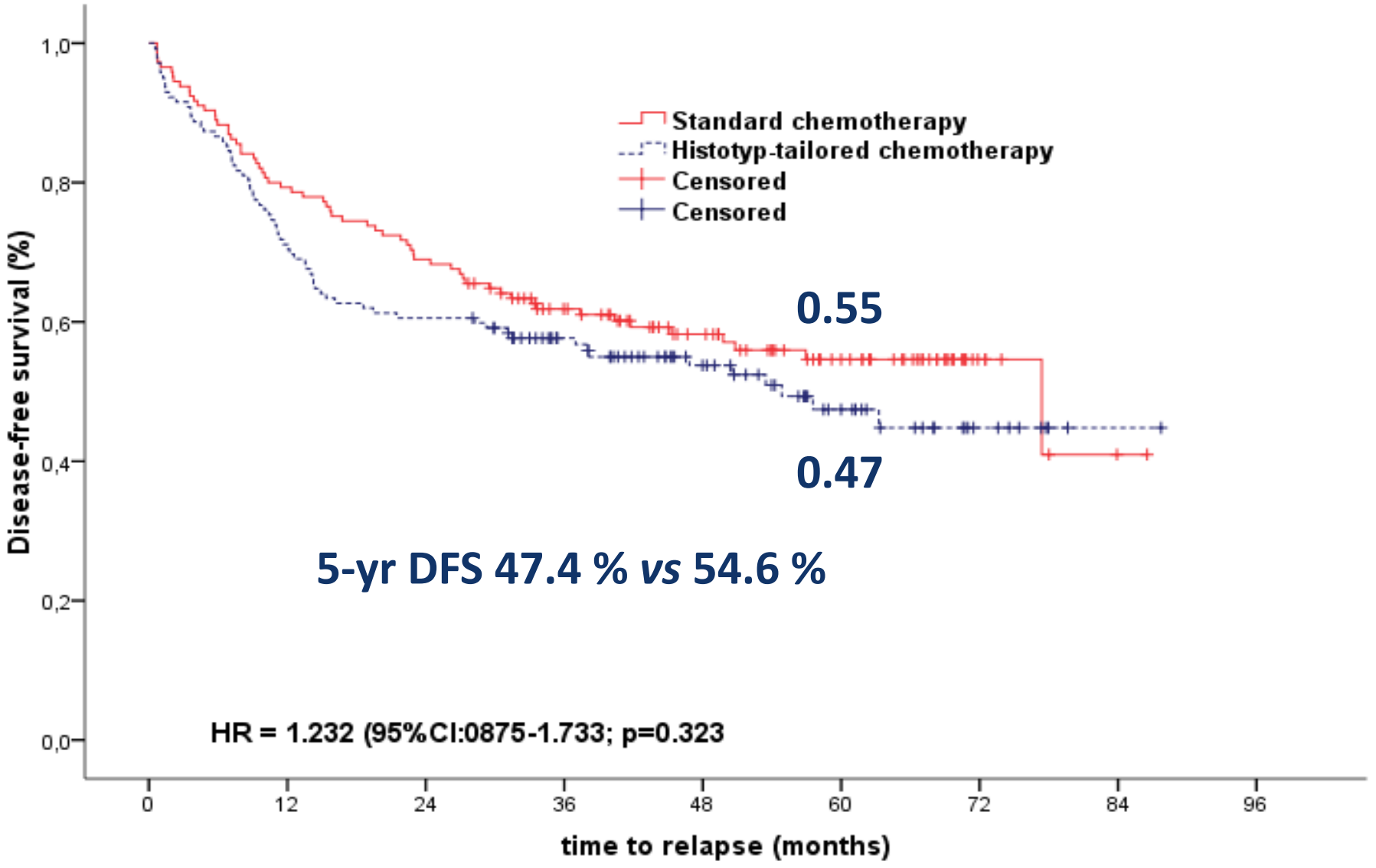
Disease Free Survival



5-yr DFS 47.4 % *vs* 54.6 %

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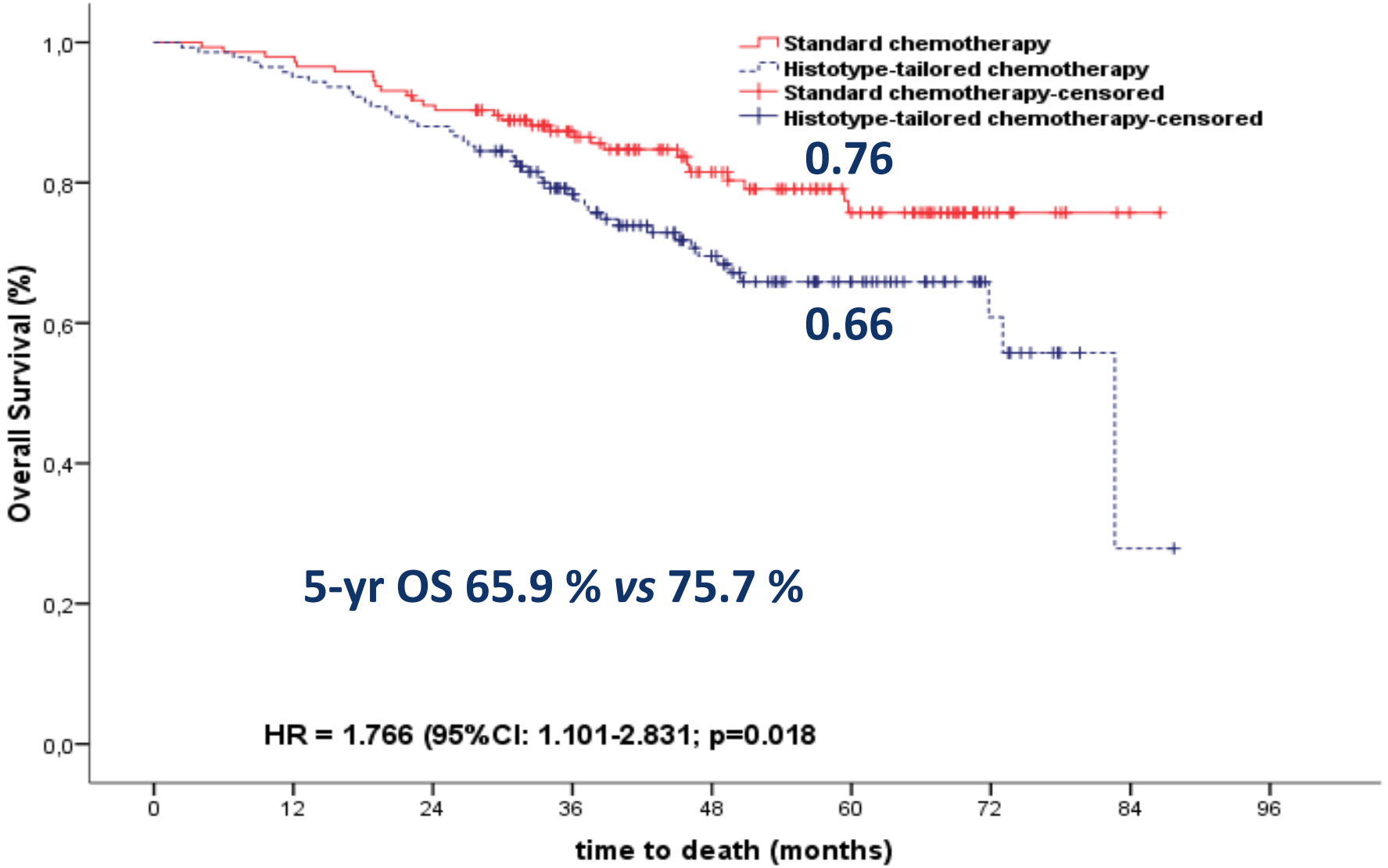
Overall Survival



5-yr OS 65.9 % *vs* 75.7 %

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Conclusions

- **Was a Histology-tailored CT superior to a DOX-based CT?** **NO**
- **Was this DOX-based CT superior to the other arm?** **Possibly**
  - OS difference
  - non statistically significant trend in DFS
- **Did the DOX-based neoadjuvant CT perform?** **YES**
  - overlapping to the two previous ISG trials

➢ **The final study analysis confirms that DOX + IFO is essential - as of today - to (neo)adjuvant CT in STS.**

➢ **These results add to, but cannot contribute to settle the long-lasting debate about its efficacy.**

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STRASS

A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma
EORTC protocol [62092-22092]

Bonvalot S (Institut Curie Paris, **STBSG**)
Gronchi A, Le Péchoux C
Swallow C, Strauss D, Meeus P, van Coevorden F
Stoldt S, Stoeckle E, Rutkowski P
Rastrelli M, Raut C, Sangalli C, Honoré C, Chung P, Fiore M
Litière S, Marreaud S, Gelderblom H
Haas R (NKI Amsterdam, **ROG**)

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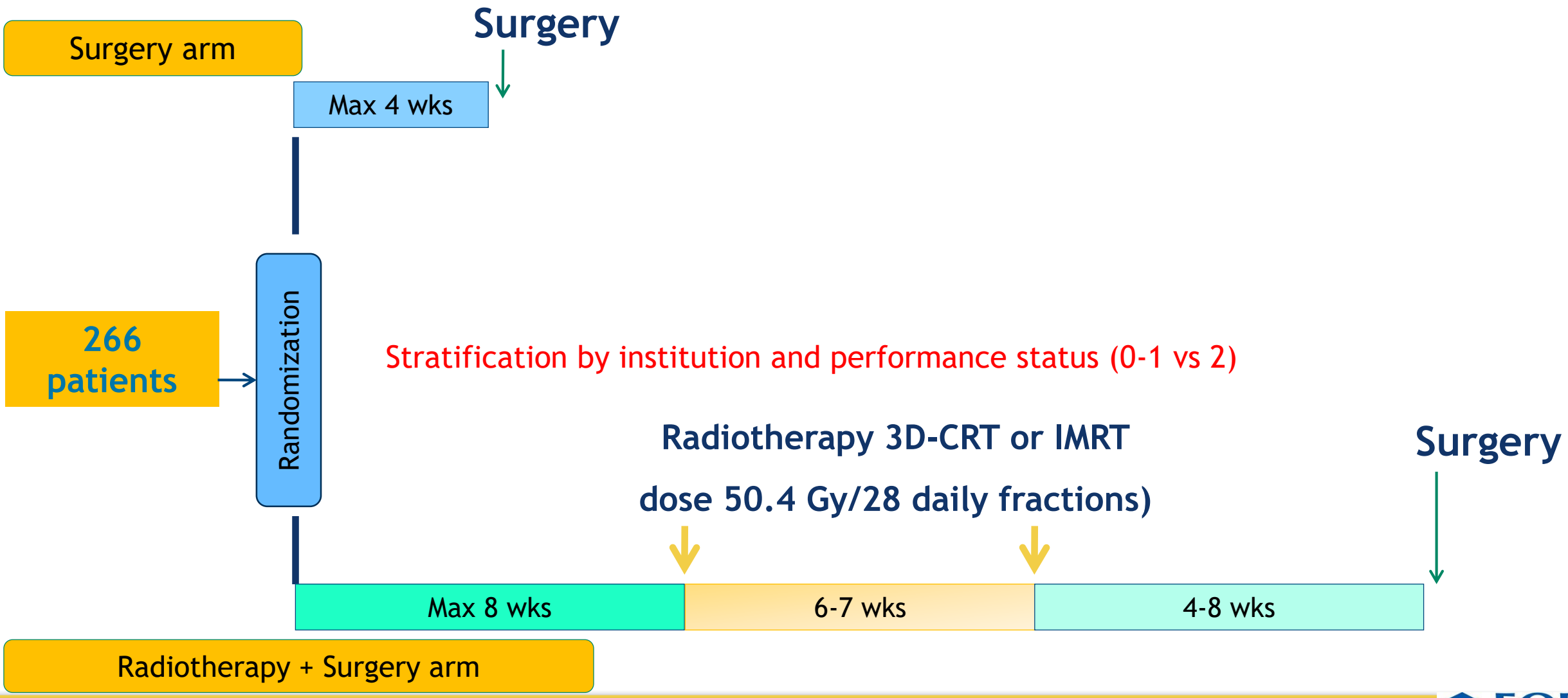
STRASS: Study Design



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Patient Characteristics (January 2012 - April 2017)

	Surgery alone (N = 133)	Preoperative RT (N = 133)	Total (N = 266)
	N (%)	N (%)	N (%)
Age: Median /Range	61 (26 - 81)	61 (24 - 83)	61 (24 - 83)
WHO performance status			
0/1	100 (75.2)/33 (24.8)	110 (82.7)/ 22 (16.5)	210 (78.9)/ 55 (20.7)
2	0 (0.0)	1 (0.8)	1 (0.4)
Tumor size (mm) Median	167	160	160
Histological subtype			
Well-differentiated liposarcoma	42 (31.6)	46 (34.6)	88 (33.1)
Dedifferentiated liposarcoma	54 (40.6)	51 (38.3)	105 (39.5)
Other liposarcoma	4 (3.0)	1 (0.8)	5 (1.9)
Leiomyosarcoma	22 (16.5)	16 (12.0)	38 (14.3)
Other	11 (8.3)	18 (13.5)	29 (10.9)
Missing	0 (0.0)	1 (0.8)	1 (0.4)
Grade			
Low	43 (32.3)	44 (33.1)	87 (32.7)
Intermediate	38 (28.6)	47 (35.3)	85 (32.0)
High	19 (14.3)	12 (9.0)	31 (11.7)
Not evaluable	21 (15.8)	17 (12.8)	38 (14.3)
Missing	12 (9.0)	13 (9.8)	25 (9.4)

75 %

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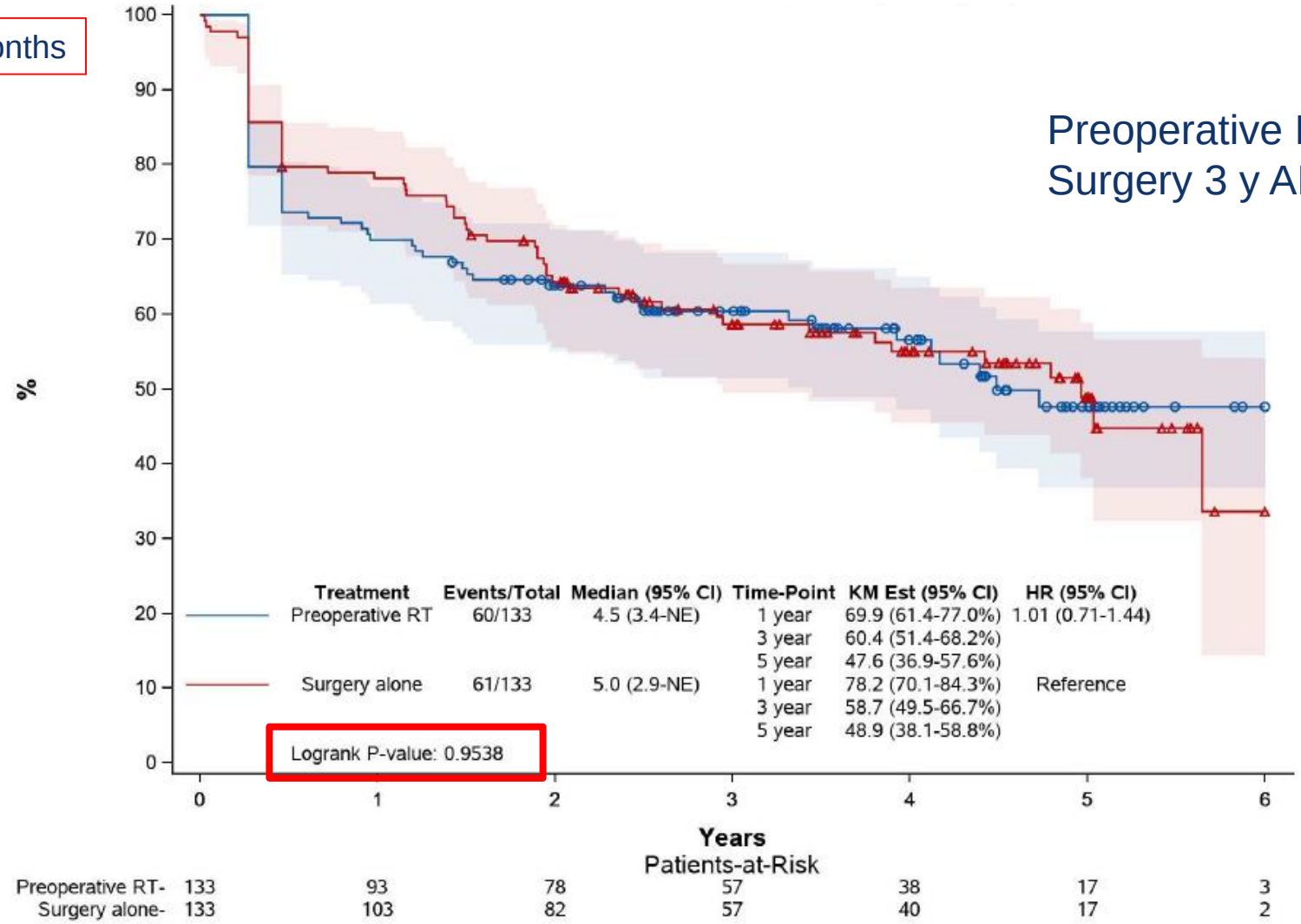
Results: Primary Endpoint (ARFS)

Median Follow-up 43 months



Preoperative RT 3 y ARFS: 60.4 %
Surgery 3 y ARFS: 58.7 %

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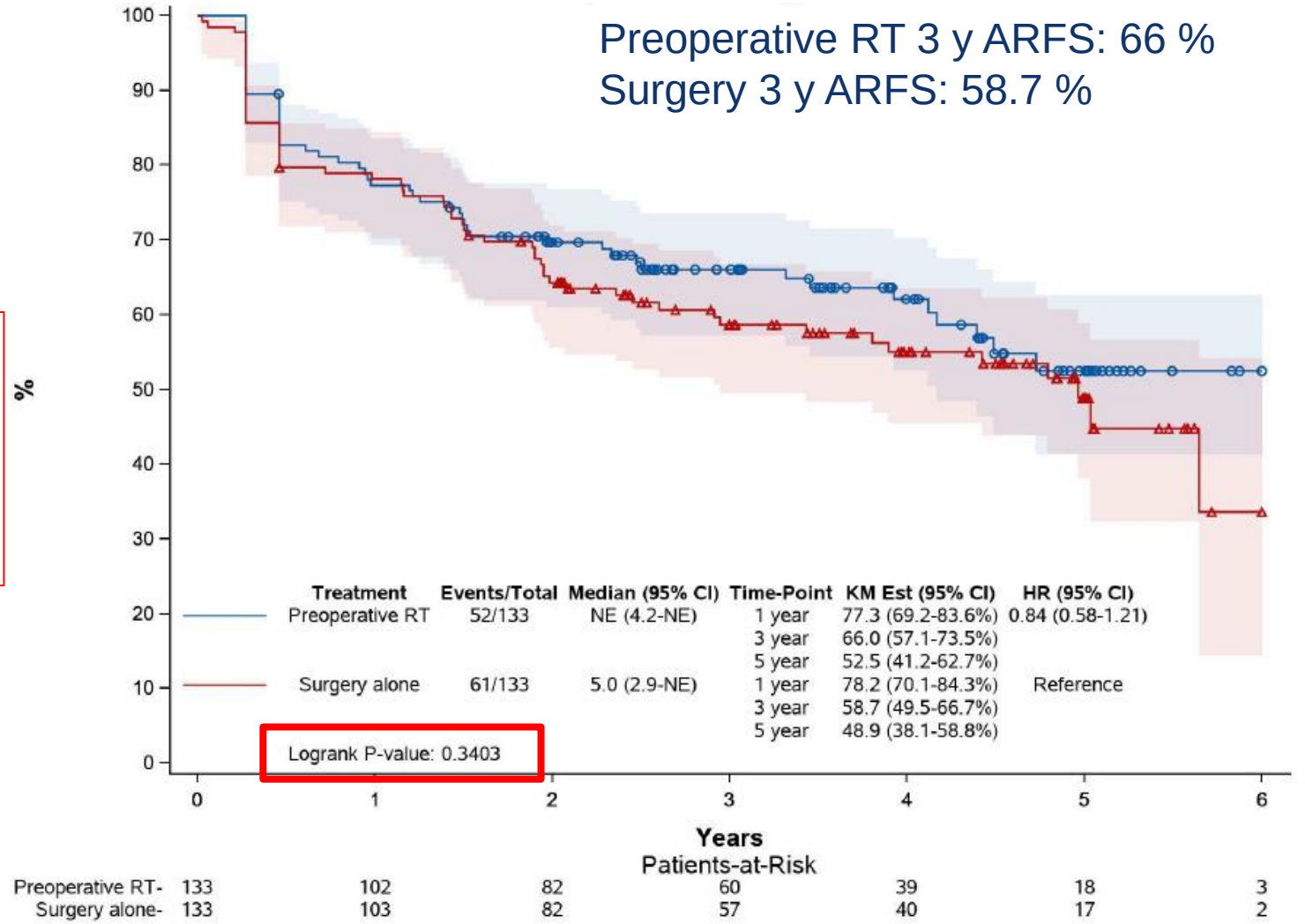
Results: IDMC sensitivity analysis (ARFS all population)

Median Follow-up 43 months

Local progression on RT is not regarded as a primary endpoint event for the patients who subsequently achieve a complete surgical resection

Preoperative RT 3 y ARFS: 66 %
Surgery 3 y ARFS: 58.7 %



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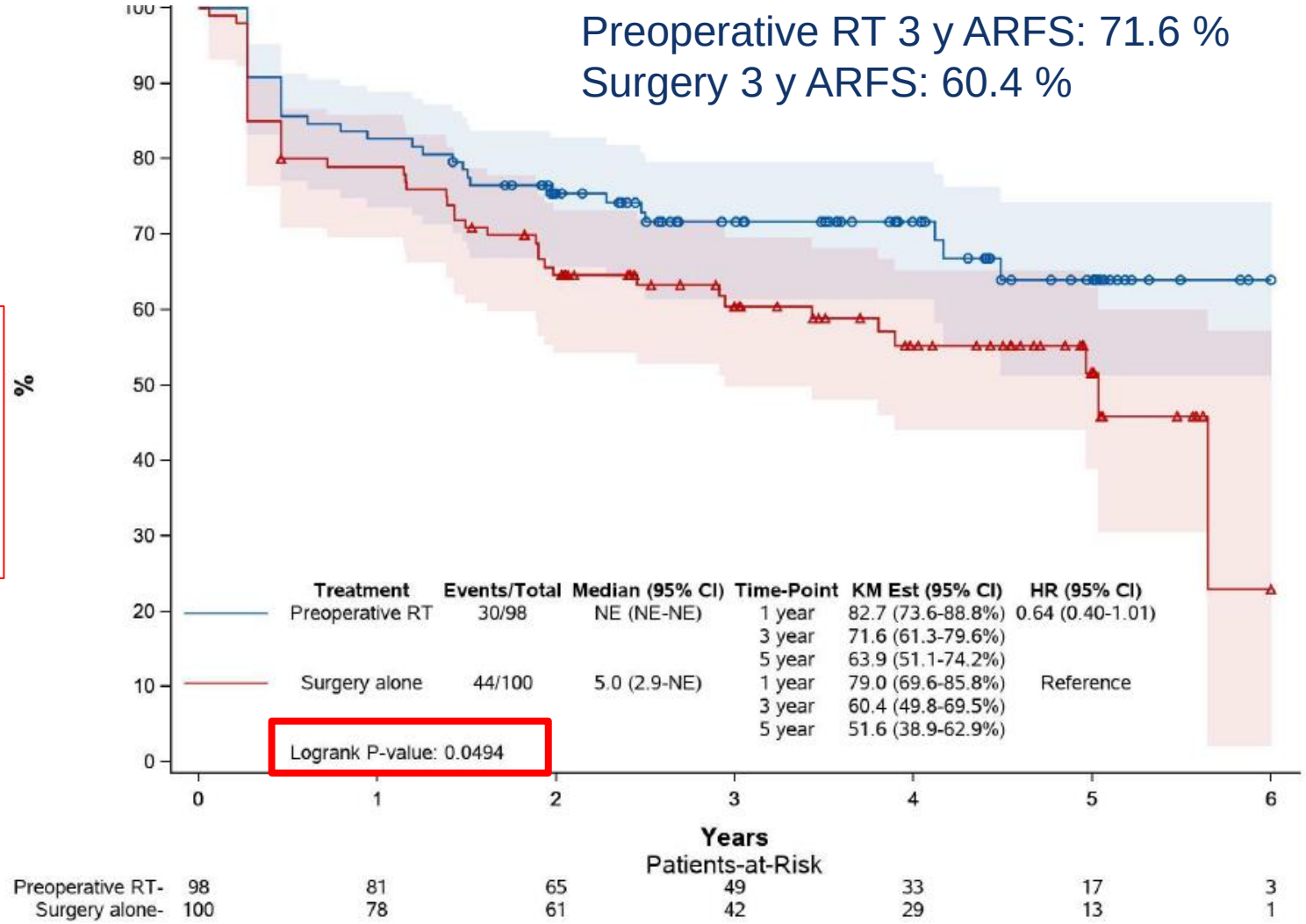
Results: IDMC sensitivity analysis (ARFS LPS subgroup)

Median Follow-up 43 months

Local progression on RT is not regarded as a primary endpoint event for the patients who subsequently achieve a complete surgical resection

Preoperative RT 3 y ARFS: 71.6 %
Surgery 3 y ARFS: 60.4 %



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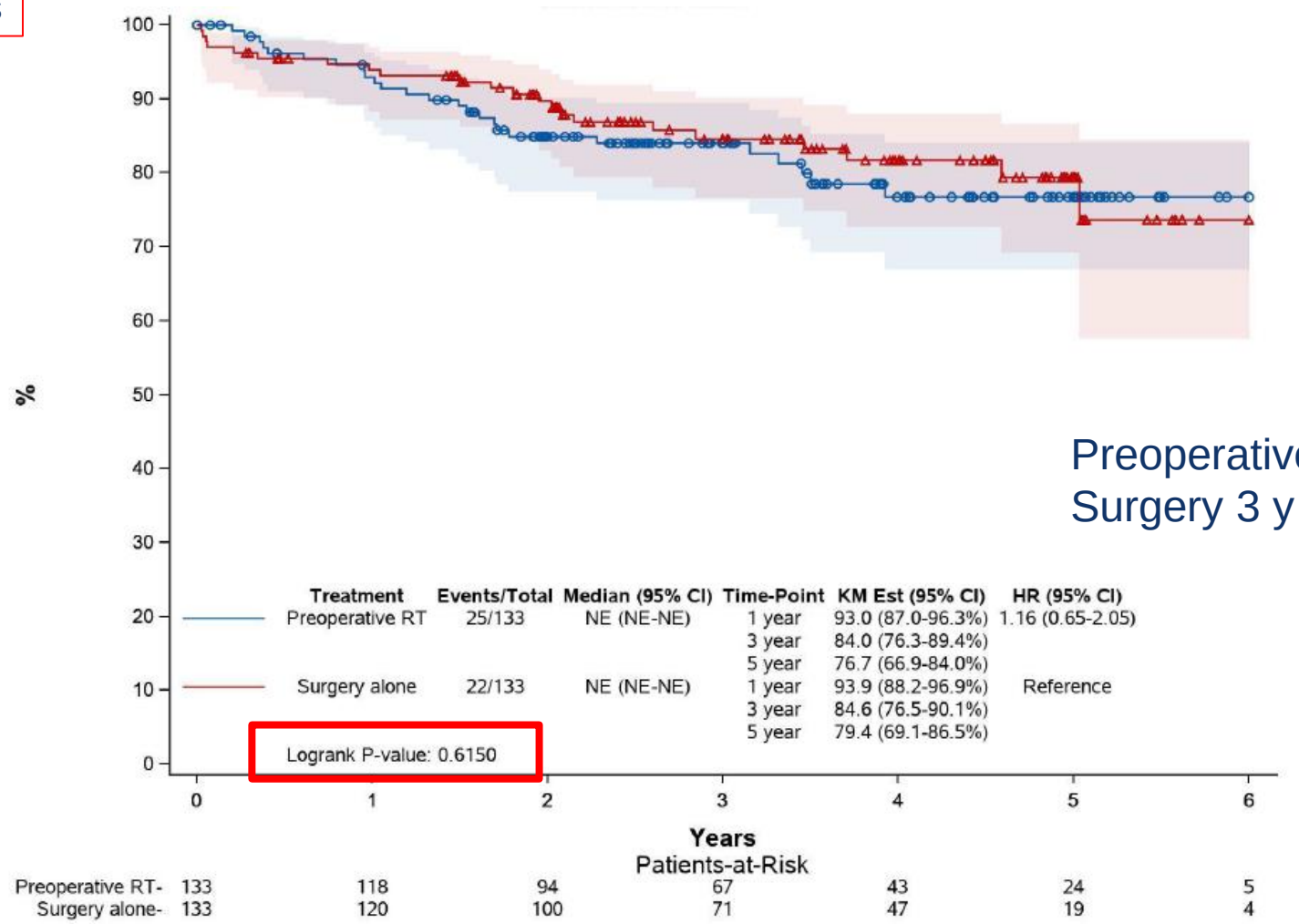
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Results: Secondary Endpoint (OS)

Median Follow-up 43 months



Preoperative RT 3 y OS: 84 %
Surgery 3 y OS: 84.6 %

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STRASS - Conclusions

- Academic randomized trial on a rare disease is feasible thanks to transatlantic collaboration
- The additional morbidity associated with preoperative RT (mostly IMRT) was acceptable
- No impact of RT on OS

Primary Endpoint: whole patient population

- With a median FU of 43 months, ARFS was similar in both groups

IDMC Sensitivity Analyses of ARFS

- ARFS was significantly better after RT in the LPS subgroup
- High grade sarcomas and LMS do not seem to benefit from preoperative RT

→ Further follow up needed

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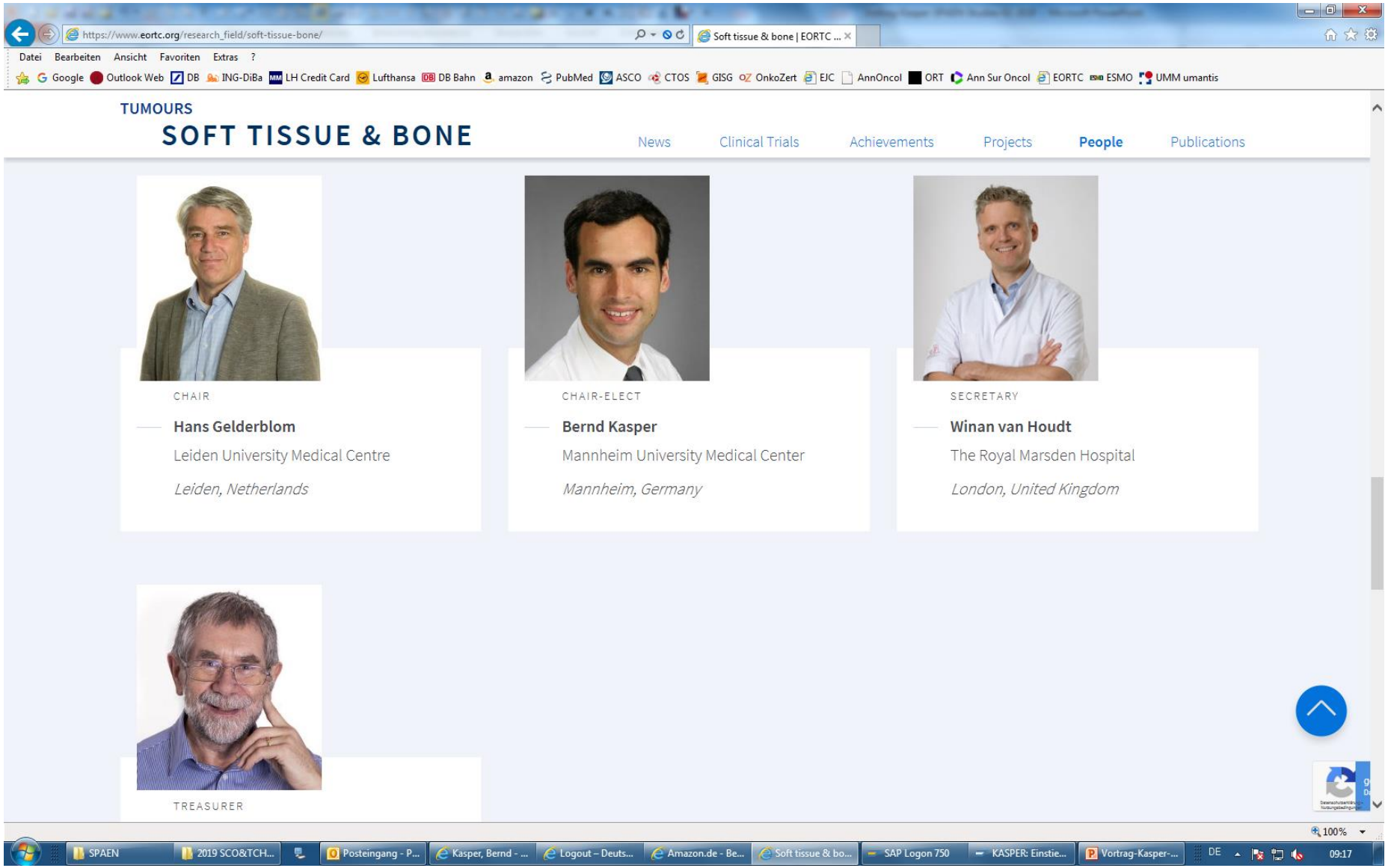
EORTC Soft Tissue & Bone Sarcoma Group (STBSG)

EORTC
European Organization for Research and Treatment of Cancer

SOFT TISSUE & BONE



EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

EORTC-STBSG
Study **1809 (STRASS 2)**

A randomized phase lll study of neoadjuvant chemotherapy followed by surgery *versus* surgery alone for patients with High Risk RetroPeritoneal Sarcoma

Study coordinator: **Alessandro Gronchi**

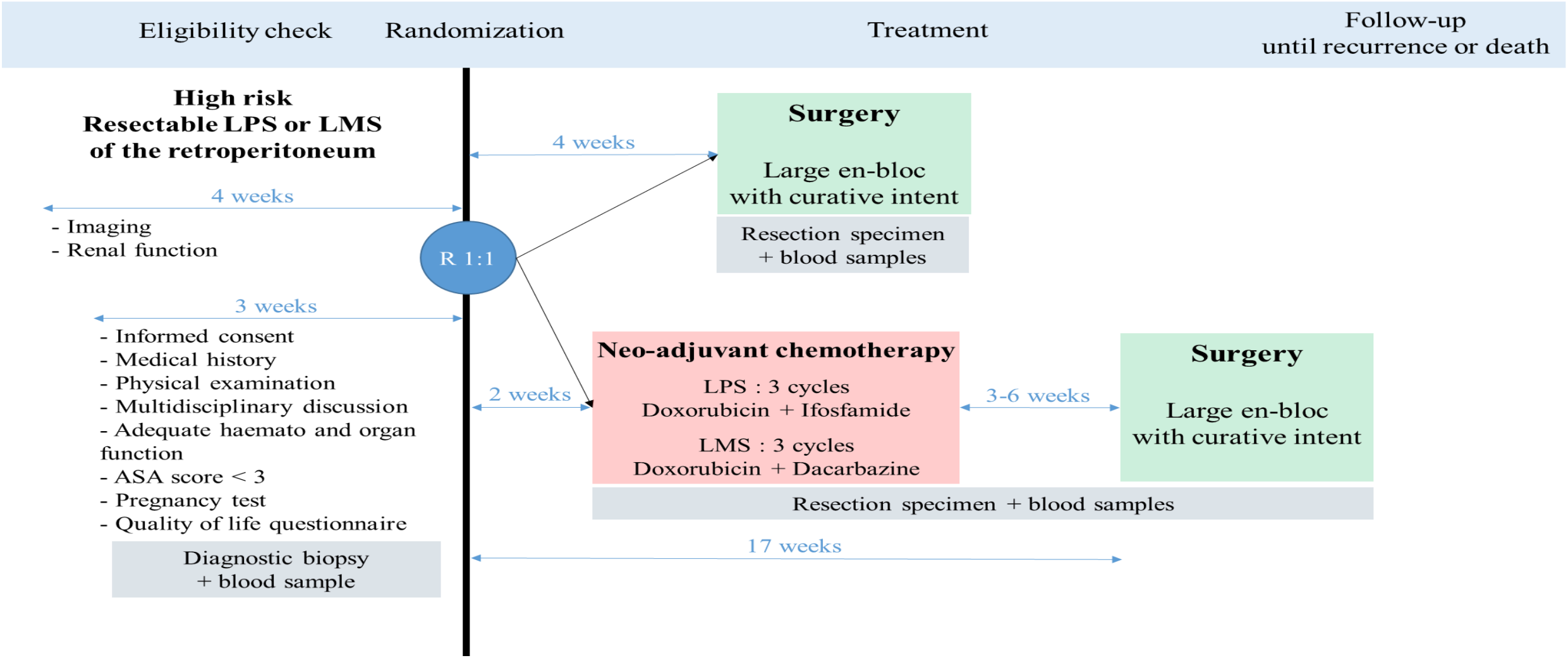
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Study co-coordinator: **Winan van Houdt**

The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Study design



EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

EORTC-STBSG
Study **1983 - DODECANESO**

An open label, randomized, phase II study on **DO**xorubicin, Doxorubicin plus **D**acarbazin**E**, or Gem**C**it**A**bine plus Dacarbazi**NE** for the first-line treatment of advanced leiomyo**S**arc**O**ma

Study coordinators:

Lorenzo D'Ambrosio

Nadia Hindi

Bernd Kasper

EORTC
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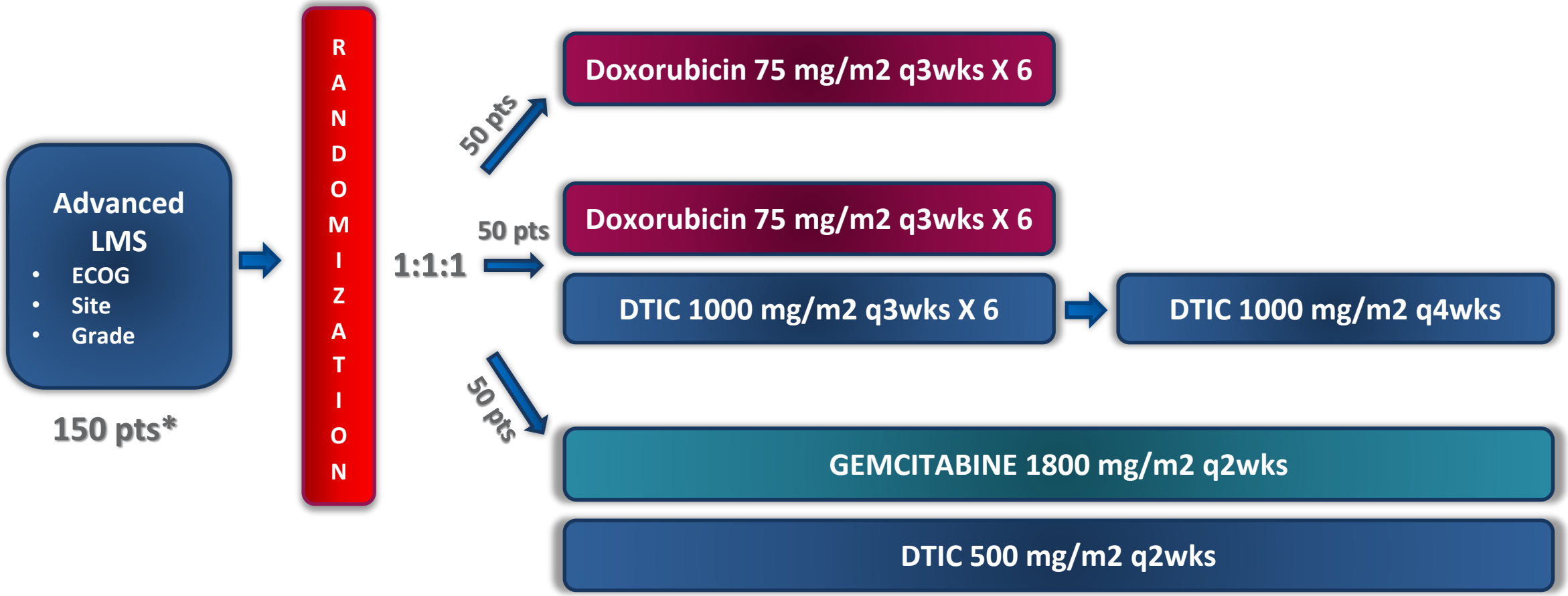
The future of cancer therapy

Study design



*at least 30 % (15 pts) in each arm should be uLMS
The probability of selecting the better arm will be 0.772

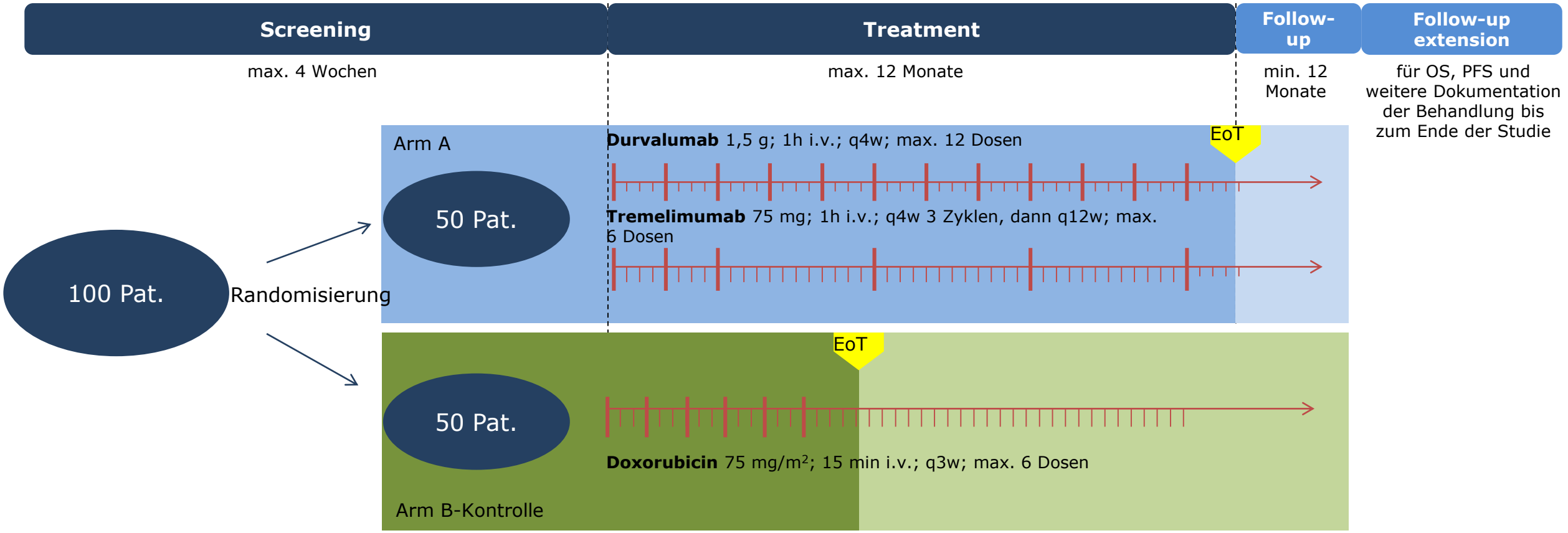
ASCO 2019 - Sarcoma - Trials in Progress (*TPS*)

- Phase I/II clinical trial of NY-ESO-1-specific TCR-engineered T-cell transfer combined with a novel T-cell stimulator CHP:NE1 for patients with refractory soft tissue sarcoma (*TPS11074*)
- **A randomized phase II study of durvalumab and tremelimumab compared to doxorubicin in patients with advanced or metastatic soft tissue sarcoma (MEDISARC, AIO-STS 0415) (*TPS11075*)**
- MDM2 inhibitor AMG-232 and radiation therapy in treating patients with soft tissue sarcoma with wild-type TP53: A phase IB study (NRG-DT001) (*TPS11076*)
- CBT-1 in combination with doxorubicin in patients with metastatic, unresectable sarcomas who previously progressed on doxorubicin (*TPS11077*)
- Benefit of intensified perioperative chemotherapy within high-risk CINSARC patients with resectable soft tissue sarcomas (CIRSARC) (*TPS11078*)
- A phase II study of ADI-PEG 20 in combination with gemcitabine and docetaxel for the treatment of soft tissue sarcoma (*TPS11079*)

AIO-Studien-gGmbH

DR. NOTGHI CONTRACT RESEARCH N

MEDISARC - Studiendesign



EoT= "End of Treatment"

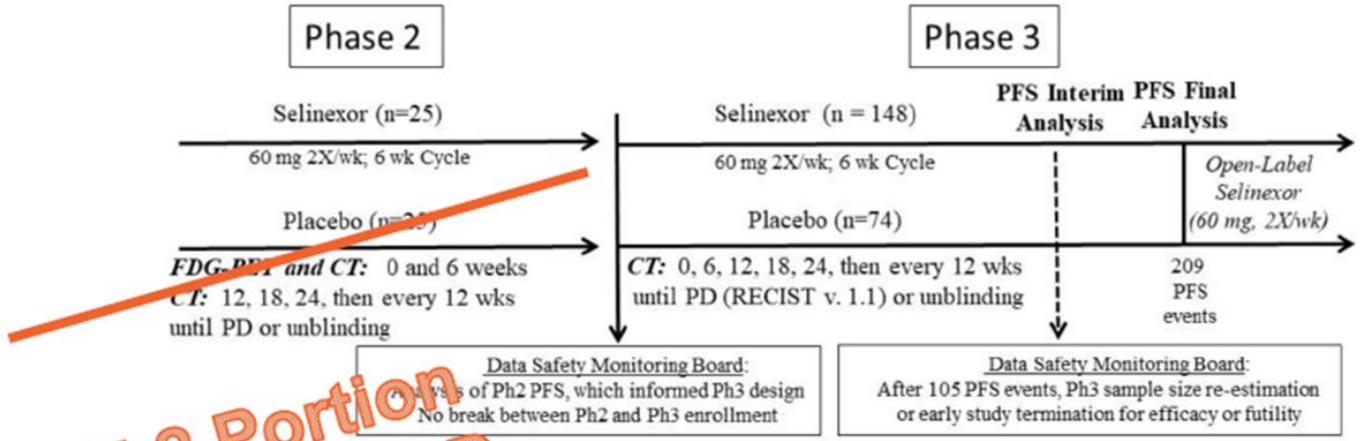
GISG Study Portfolio (2)

- **GISG-10:** Trabectedin combined with regional hyperthermia as 2nd line treatment for advanced STS (**Hyper-TET**, Issels / Lindner)
- **GISG-11:** QoL in patients with STS undergoing palliative chemotherapy or treatment with Pazopanib (**PazoQoL**, Schuler)
- GISG-12: Patient directed intervention towards a multidimensional recommendation guideline to improve the QoL for STS patients under palliative treatment with Trabectedin (**YonLife**, Schuler)
- **GISG-13:** 1st line Trabectedin in elderly “unsuited” patients incl. geriatric assessment (**E-TRAB,** Kasper)
- GISG-14: Data collection of STS patients treated with Trabectedin (**ReTraSarc**, Pink / Reichardt)
- ➢ **GISG-15:** Immunotherapy with **Nivolumab plus Trabectedin** in advanced STS (**NiTraSarc**, Pink)
- **GISG-16:** Trabectedin plus Olaparib in solid tumors harboring DNA repair deficiencies (**Top-Art**, Fröhling)

Evidence for Immunotherapy in Soft Tissue Sarcomas

REGIMEN	n	mPFS [months]	3m-PFS	6m-PFS	ORR (RECIST)	INCLUDED SUBTYPES	RESPONDING SUBTYPES	REF
Pembrolizumab (SARC028)	42 (STS)	4.2	55 %	NA	18 %	4 (UPS, LPS, LMS, SS)	UPS, LPS, SS	Tawbi
Nivolumab	43	1.7	~35 %	15 %	5 %	> 10 (ASPS-1pt, UPS, LMS, LPS, ES, SS, MPNST, …)	ASPS, LMS	D'Angelo
Nivolumab + Ipilimumab	42	4.1	~60 %	28 %	16 %	> 10 (ASPS-1pt, UPS, LMS, LPS, ES, SS, MPNST, …)	LMS, UPS, Myxofibro, Angio	D'Angelo
Axitinib + Pembrolizumab	33	4.7	70 %	50 % (**38 %**)	25 % (**55 %**)	Several (**ASPS 36 %**)	ASPS, LMS, ES	Wilky
Sunitinib	50	1.8	39 %	22 %	2 %	Several (LMS 23 %, SS 8 %, …)	DSRCT	George
Sunitinib + Nivolumab (Phase II)	50	5.9	69 %	50 %	11 %	Several (SS 18 %, **ASPS 6 %**)	ASPS, Angio, EMC, SS	Martin-Broto

SEAL Study: *Selinexor* for Liposarcomas



PH 2 Portion COMPLETED

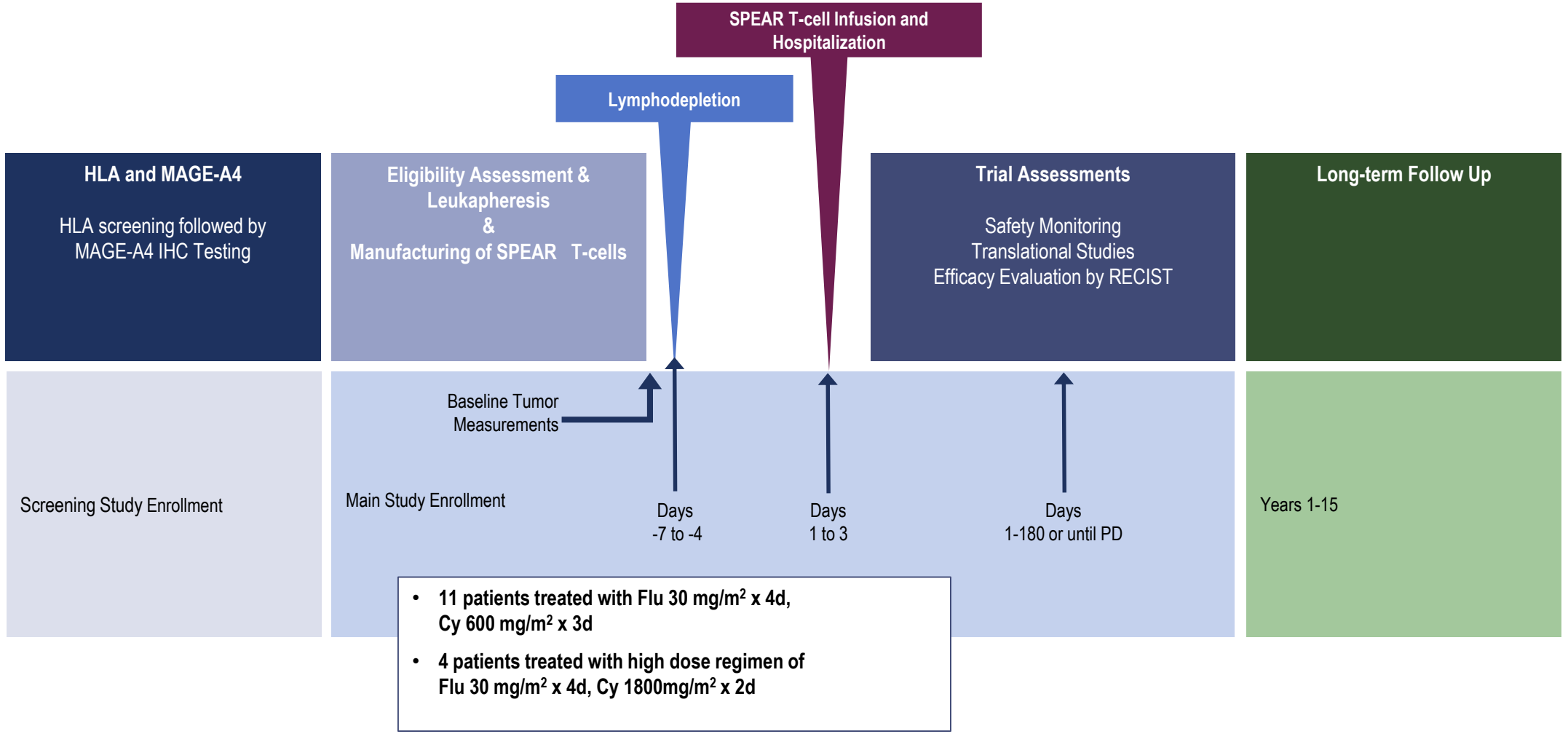
Phase 2

- 1:1 randomized/blinded enrolled (planned: n=50: 25 pbo, 25 selinexor; actual: n=57). As of 11 August 2017: 26 pbo, 24 selinexor, 7 still blinded.
  - Stratified by prior eribulin vs no prior eribulin and number of prior systemic therapies (1 vs ≥ 2)
- Primary efficacy endpoint: PFS by RECIST v. 1.1
- Key secondary efficacy endpoints
  - TTP
  - ORR/DOR
  - Tumor glucose metabolism, density and size
- Patients who have PD (per Who Response Criteria under protocol versions ≤ 3 or per RECIST v. 1.1 under protocol versions ≥ 4) determined by the central reader will be unblinded: 1) if in the placebo arm may cross over to open-label selinexor; 2) if in the selinexor arm and the patient may derive benefit from continued treatment, the patient may elect to continue selinexor but as open-label treatment

Phase 3

- 2:1 randomized/blinded (n=222: 74 pbo, 148 selinexor)
  - Stratified by prior eribulin vs no prior eribulin, prior trabectedin vs no prior trabectedin, and number of prior systemic therapies (2 vs ≥ 3)
- Interim analysis after 105 PFS events for possible sample size re-estimation
- Primary efficacy endpoint: PFS by RECIST v. 1.1
- Key secondary endpoints
  - OS for non-inferiority
  - OS for superiority
  - TTP
- Patients who have PD per RECIST v. 1.1 determined by the central reader will be unblinded; if in the placebo arm may cross over to open-label selinexor; 2) if in the selinexor arm and the patient may derive benefit from continued treatment, the patient may elect to continue selinexor but as open-label treatment
- Patients receiving blinded study treatment when all patients are unblinded at the primary PFS analysis at the end of Phase 3 may receive open-label selinexor until PD

CTOS 2019: ADP-A2M4 SPEAR T-cell therapy



CTOS 2019: ADP-A2M4 SPEAR T-cell therapy

- Clinical activity and safety of **ADP-A2M4 SPEAR** (Specific Peptide Enhanced Affinitor Receptor) **T-cells** directed towards MAGE-A4^{+} peptide in a Phase I, first-in-human T-cell dose escalation study in the subset of patients with **synovial sarcoma**
- **15** pts with synovial sarcoma were treated (6 female; median age 49 years, range 31-76)
- **Procedure**: Following apheresis T-cells are isolated, transduced, expanded and re-infused
- **AEs**: leukopenia, lymphopenia, neutropenia, thrombocytopenia, anemia, cytokine release syndrome, fatigue, pyrexia, nausea, and diarrhea
  - ➢ 1 fatal **aplastic anemia** (elderly patient + high dose conditioning regimen!)
- RECIST v1.1 **responses**:
  - 7 PR
  - 6 SD
  - 1 PD

  } **ORR = 7/14 = 50 %**

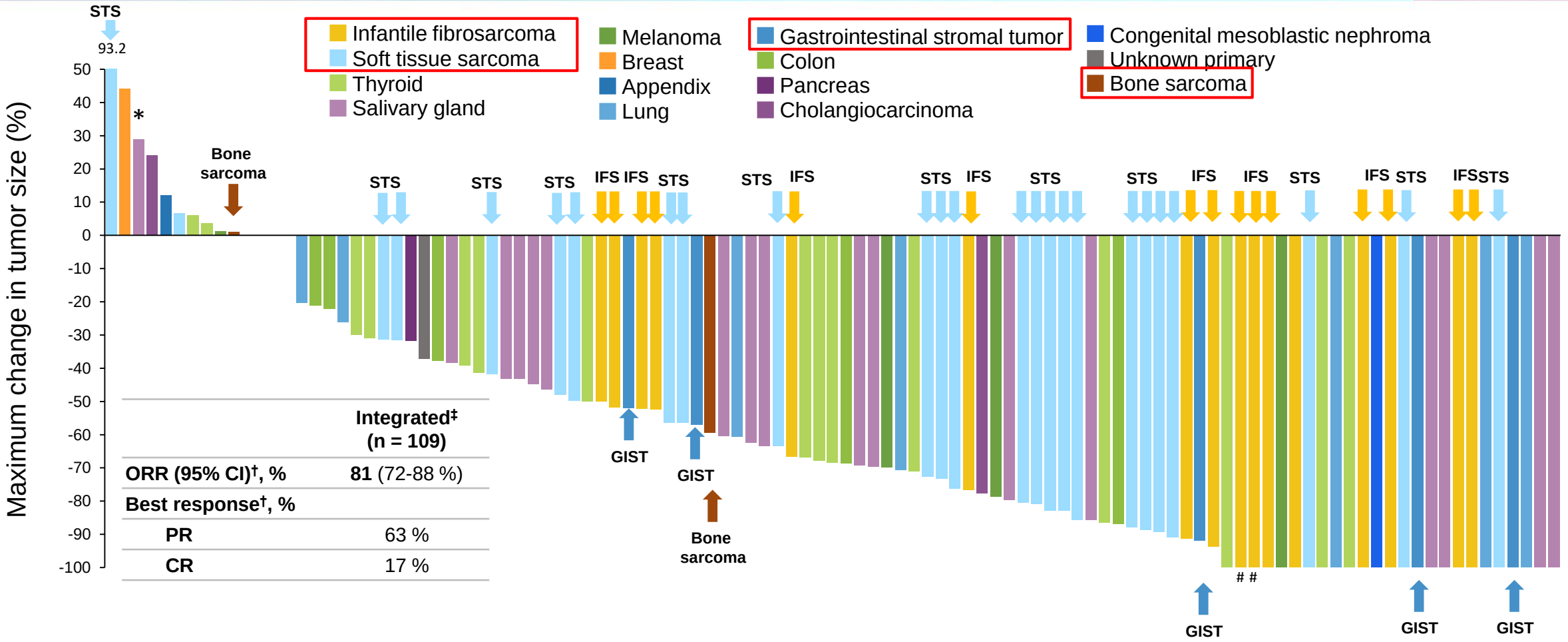
SPEARHEAD-1: ADP-A2M4 SPEAR T-cell therapy

- **ADP-A2M4 SPEAR T-cell therapy** induced RECIST responses in 50 % of pts and disease control in almost all (13/14) pts with **synovial sarcoma**.
- This complex therapeutic model works: transduced T-cells expand and are functional.

- Duration of responses? Feasibility in daily practice? Costs? Hospitalization!
- A focus should be set on severe and possible long-term side effects of this rather complex treatment strategy.

➢ **SPEARHEAD-1 (Phase II) in synovial sarcoma and MRCLS is currently enrolling.**

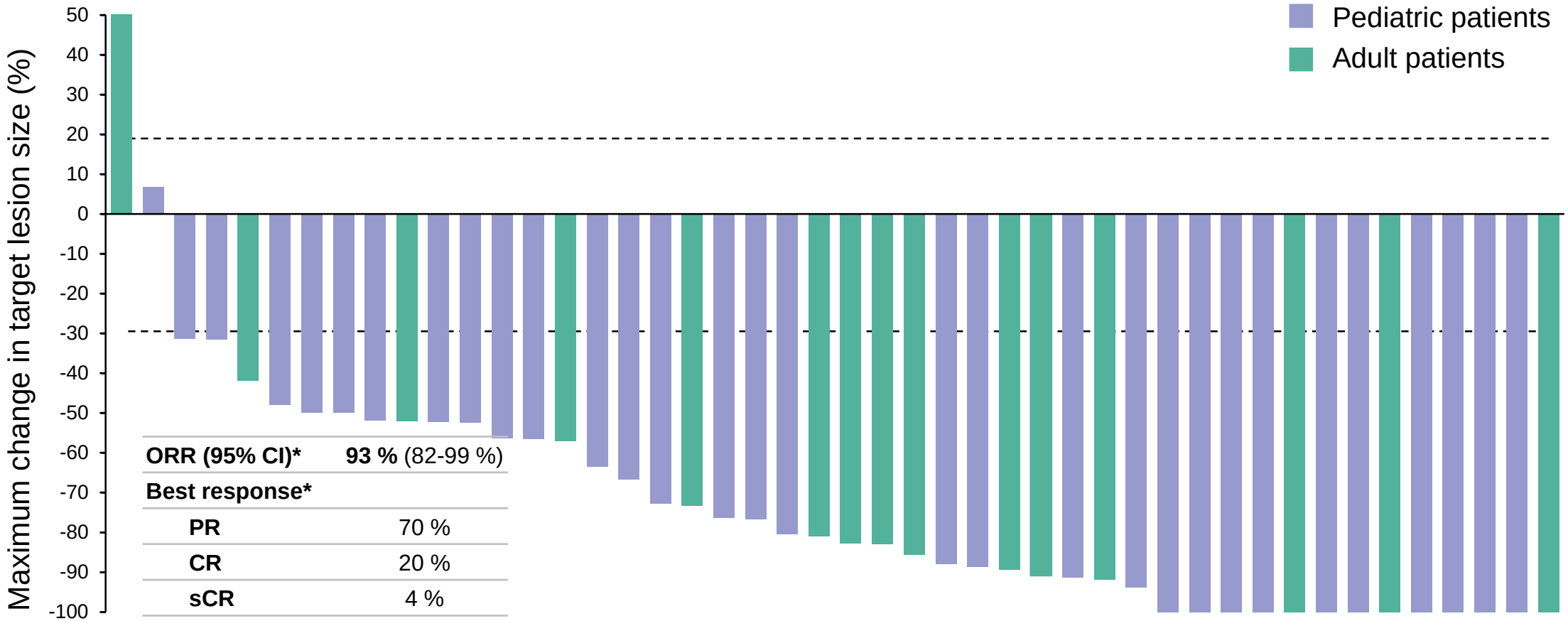
Larotrectinib has shown efficacy across tumor types, including sarcomas and GIST



Investigator response assessments, as of July 30, 2018. Note: Two patients are not shown here; these patients discontinued treatment prior to any post-baseline tumor measurements. *Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; †RECIST v1.1; ‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment; #Surgical CR. CI, confidence interval; CR, complete response; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; STS, soft-tissue sarcoma.

Lassen UN, et al. ESMO 2018. Abstract 4090.

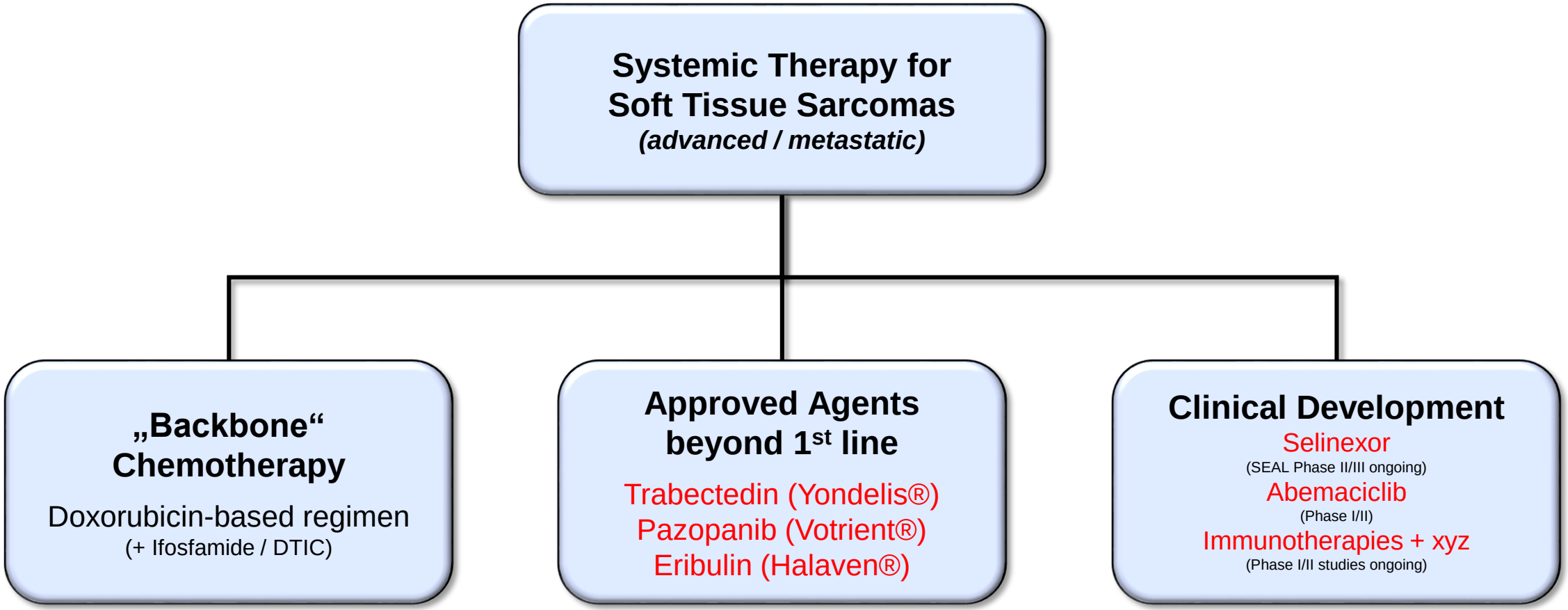
Efficacy of larotrectinib in patients with *TRK* fusion sarcoma



Investigator response as of July 30, 2018.
*n = 46 patients; includes 3 unconfirmed PRs pending confirmation; does not include 5 patients continuing on study and awaiting initial response assessment. Age <21 years.
CI, confidence interval; CR, complete response; ORR, objective response; PR, partial response; sCR, surgical complete response.
Federman N, et al. CTOS 2018.

Sarcoma of The Year 2020: **„NTRK fusion positive adult sarcomas“**

Take-Home-Messages I



Take-Home-Messages II

- **A Doxorubicin-based chemotherapy remains the “backbone” in 1st line treatment for advanced / metastatic STS patients.**
- **ANNOUNCE did not confirm the benefit for Olaratumab seen in the phase 2 study.**
- **Approved drugs for 2nd line+ are Trabectedin, Pazopanib and Eribulin.**
- **An Anthracycline plus Ifosfamide remains the standard of care regimen if (neo)adjuvant chemotherapy is applied for localized high-risk STS patients (ISG 1001).**
- **The addition of a preoperative chemotherapy to surgery in retroperitoneal STS did not result in a significant survival benefit, only for liposarcomas (EORTC STRASS).**
- **There are numerous new compounds and treatment strategies such as Immunotherapy, NTRK, T-cell therapy, …**

Discussion & Questions

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Chair-Elect EORTC / Soft Tissue and Bone Sarcoma Group

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