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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Ongoing and Upcoming Clinical Sarcoma Trials (excerpt)

3rd of February 2018, 8th SPAEN Annual Conference 2018, Marriot Hotel Milan, Milan, Italy

Bernd Kasper
University of Heidelberg
Mannheim University Medical Center
Interdisciplinary Tumor Center
Sarcoma Unit
German Interdisciplinary Sarcoma Group (GISG)

Agenda

- Current and upcoming European EORTC / STBSG trials
- Example: Activities of the German Sarcoma Groups (GISG / AIO)
- Worldwide, international clinical trials of interest

Agenda

- **Current and upcoming European EORTC / STBSG trials**
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- Worldwide, international clinical trials of interest

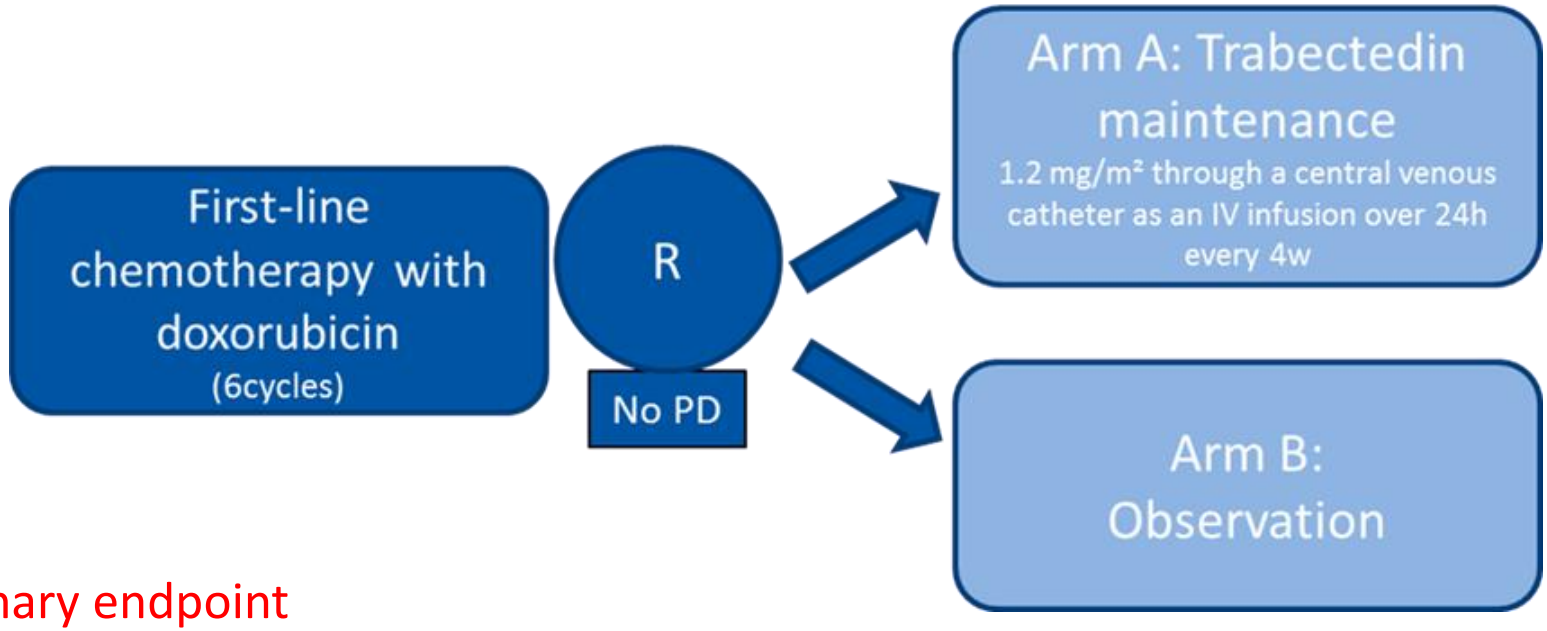
EORTC - STBSG

Study 1447

Maintenance Therapy with Trabectedin *vs* Observation after 1st line Treatment with Doxorubicin of Patients with Advanced or Metastatic Soft Tissue Sarcoma

SC: Prof A.J. Gelderblom, Leiden University Medical Center, The Netherlands

Study Design



Primary endpoint

The primary endpoint is progression-free survival defined from randomization until progression according to RECIST 1.1.

Secondary endpoints

- Safety and tolerability (Common Toxicity Criteria CTCAE 4.0)
- Overall survival
- Time to second progression (PFS2)
- Health related quality of life (QLQ-C30)

Participating Sites

Name	Inst. No.	Institution	Country
Le Cesne Axel	225	Gustave Roussy	France
Blay Jean-Yves	227	Centre Leon Berard	France
Italiano Antoine	228	Institut Bergonie	France
Penel Nicolas	234	Centre Oscar Lambret	France
Kasper Bernd	527	UniversitaetsMedizin Mannheim	Germany
Grünwald Viktor	528	Medizinische Hochschule Hannover	Germany
Livi Lorenzo	762	Azienda Ospedaliero-Universitaria Careggi	Italy
Vincenzi Bruno	3903	Policlinico Universitario Campus Bio-Medico	Italy
Grignani Giovanni	3919	Fondazione del Piemonte per l' Oncologia	Italy
Kerst J.M.	301	The Netherlands Cancer Institute	Netherlands
Gelderblom Hans	310	Leiden University Medical Centre	Netherlands
Reyners Anna	335	University Medical Center Groningen	Netherlands
Rutkowski Piotr	550	Maria Sklodowska-Curie Memorial Cancer Centre	Poland
Estival Anna	381	Institut Catala d'Oncologia - ICO Badalona	Spain
Martin-Broto Javier	177	Virgen del Rocio University Hospital	Spain
Casado Herraez Antonio	366	Hospital Universitario San Carlos	Spain
Garcia Del Muro Xavier	6225	Institut Catala d'Oncologia - ICO L'Hospitalet	Spain
Jones Robin	613	Royal Marsden Hospital - Chelsea, London	United Kingdom
Hennig Ivo	6998	Nottingham University Hospitals NHS Trust	United Kingdom

EORTC - STBSG - GCG

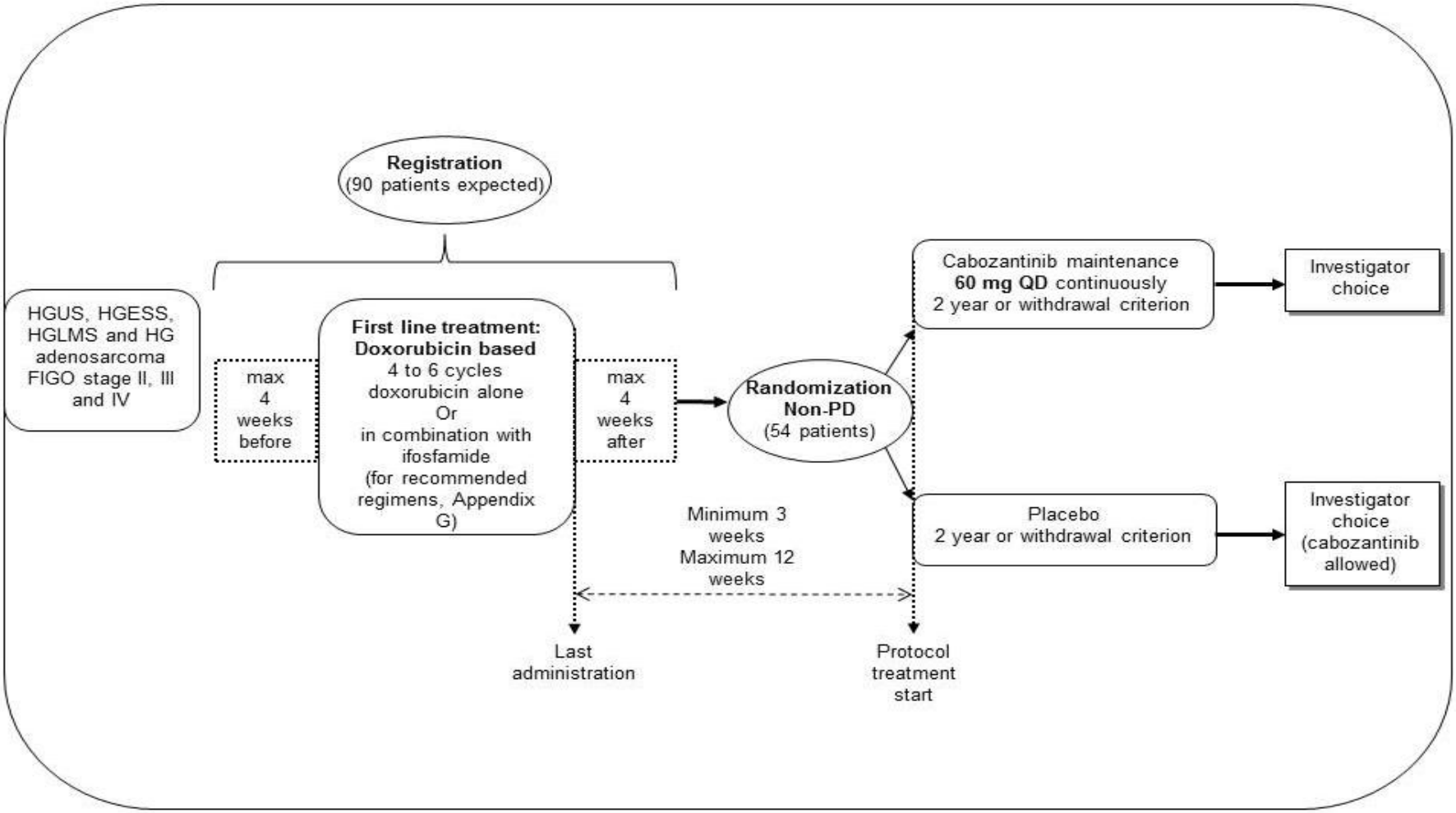
Study 62113-55115:

A randomized double-blind Phase II Study evaluating the role of Maintenance Therapy with Cabozantinib in High Grade Uterine Sarcoma (HGUS) after Stabilization or Response to Doxorubicin +/- Ifosfamide following Surgery or in Metastatic 1st line Treatment

SC: Isabelle Ray-Coquard , Centre Leon Berard, France (STBSG)

SC: Nick Reed , NHS Greater Glasgow & Clyde, UK (GCG)

Study Design



Accrual per Institution (10/2017)

Institution	# Registered	# Randomized
Centre Leon Berard (227)	13	3
Institut de Cancerologie de l'Ouest (ICO) - Centre Rene Gauducheau (235)	3	1
Centre Georges-Francois-Leclerc (229)	3	0
Cambridge University Hospital NHS - Addenbrookes Hospital (632)	2	0
Academisch Medisch Centrum - Universiteit van Amsterdam (342)	1	1
Hospital Universitario San Carlos (366)	1	1
NHS Greater Glasgow and Clyde - Beatson West of Scotland Cancer Centre (6982)	1	1
Universitair Ziekenhuis Antwerpen (117)	1	0
Total	**26**	**7**
Current Status (01/2018)	**33**	**12**

EORTC - STBSG

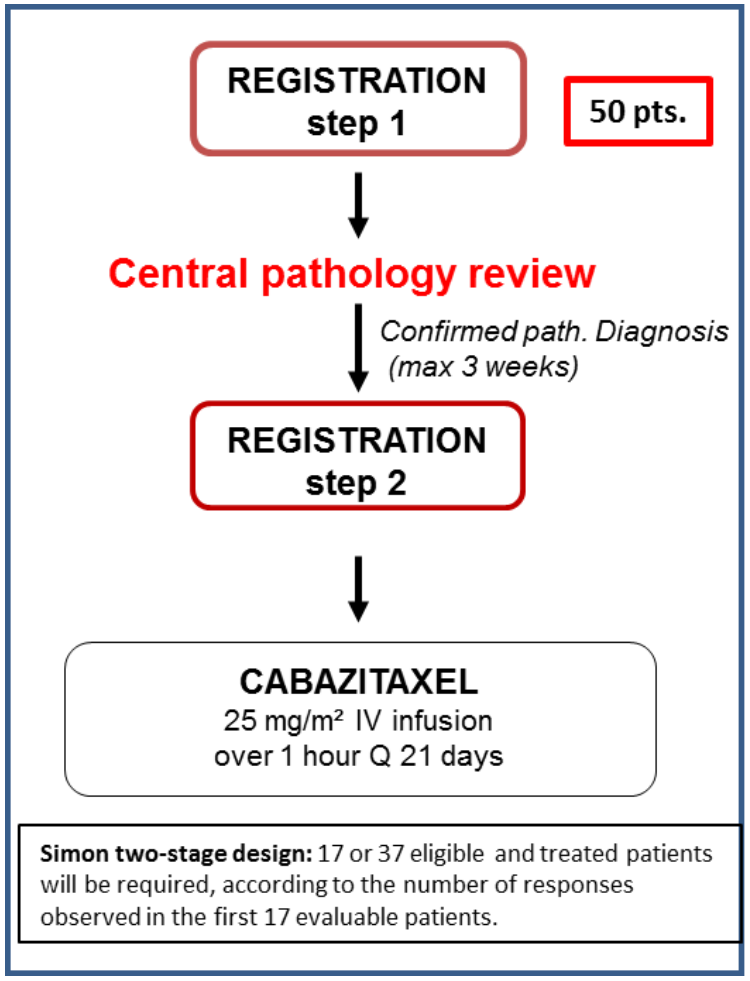
Study **1202**

Phase II trial of Cabazitaxel in metastatic or inoperable locally advanced dedifferentiated Liposarcoma

Study Coordinator: Larry Hayward

NHS Lothian - Western General Hospital, United Kingdom

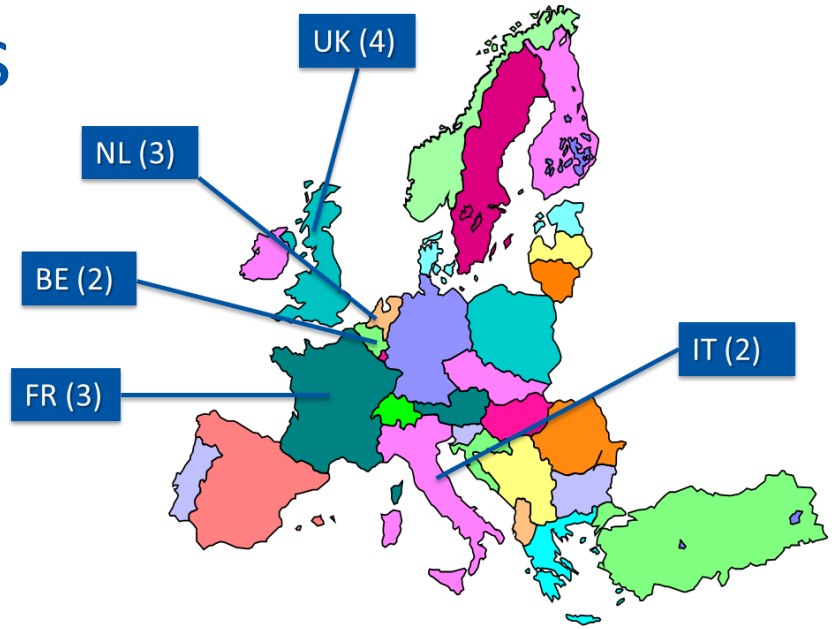
Study Design



Central review of tumor blocks is **mandatory**

Note: Please be sure that the **dedifferentiated** component is included in the shipped tissue

Participating Sites



Name	Inst	Institution	Country
Gil Thierry	101	Hopitaux Universitaires Bordet-Erasme - Institut Jules Bordet	Belgium
Van Den Brande Jan	117	Universitair Ziekenhuis Antwerpen	Belgium
Duffaud Florence	287	Assistance Publique - Hopitaux de Marseille - Hôpital de La Timone	France
Isambert Nicolas	229	Centre Georges-Francois-Leclerc	France
Blay Jean-Yves	227	Centre Leon Berard	France
Casali Paolo Giovanni	704	Fondazione IRCCS Istituto Nazionale dei Tumori	Italy
Basso Umberto	3908	Istituto Oncologico Veneto IRCCS	Italy
Gelderblom Andre Johan (Hans)	310	Leiden University Medical Centre	Netherlands
Desar Ingrid	304	Radboud University Medical Center Nijmegen	Netherlands
Steeghs Neeltje	301	The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis	Netherlands
Ali Nasim	659	Clatterbridge Centre for Oncology NHS Trust - Clatterbridge Cancer Centre NHS Foundation Trust	United Kingdom
Hayward Richard L.	641	NHS Lothian - Western General Hospital	United Kingdom
Benson Charlotte	613	Royal Marsden Hospital - Chelsea, London	United Kingdom
Leahy Michael G.	610	The Christie NHS Foundation Trust	United Kingdom

Accrual (October 2017)

Site	# patients registered	# patients started cabazitaxel
Royal Marsden Hospital - London (C. Benson)	5	2
NHS Lothian-Western General Hospital (L. Hayward)	1	0
Centre Leon Berard (J.Y. Blay)	1	1
Clatterbridge Centre for Oncology NHS Trust (N. Ali)	1	0
Instituto Nazionale dei Tumori (P. Casali)	8	5
Istituto Oncologico Veneto IRCCS (B. Umberto)	5	0
TOTAL	21	8
Current Status (01/2018)	36	**13**

EORTC - STBSG

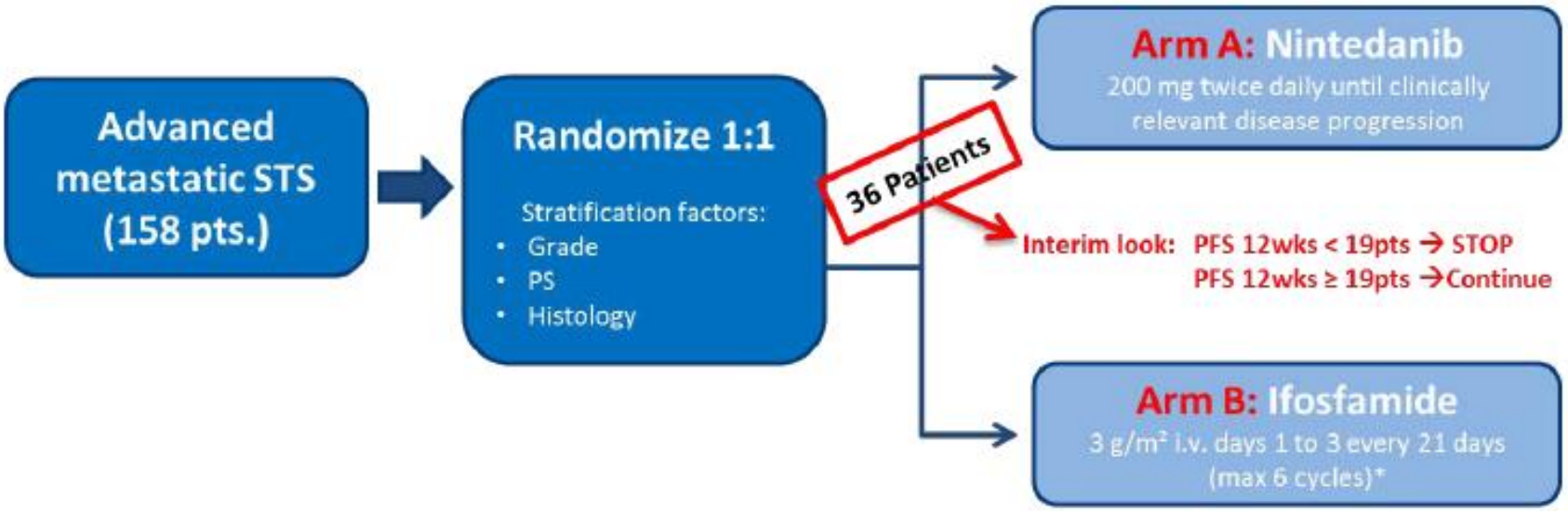
Study **1506** (**ANITA)**

A Phase II multicenter study comparing the efficacy of the oral **A**ngiogenesis inhibitor **N**intedanib with the intravenous cytotoxic compound **I**fosfamide for **T**reatment of patients with **A**dvanced, metastatic soft tissue sarcoma (STS) after failure of systemic non-oxazaphosporine-based first line chemotherapy for inoperable disease

Study Coordinator: Patrick Schöffski

UZ Leuven, Belgium

Study Design



Strictly second line trial; patients do not qualify after having received more than one line of palliative treatment (**one and no more than one line**).

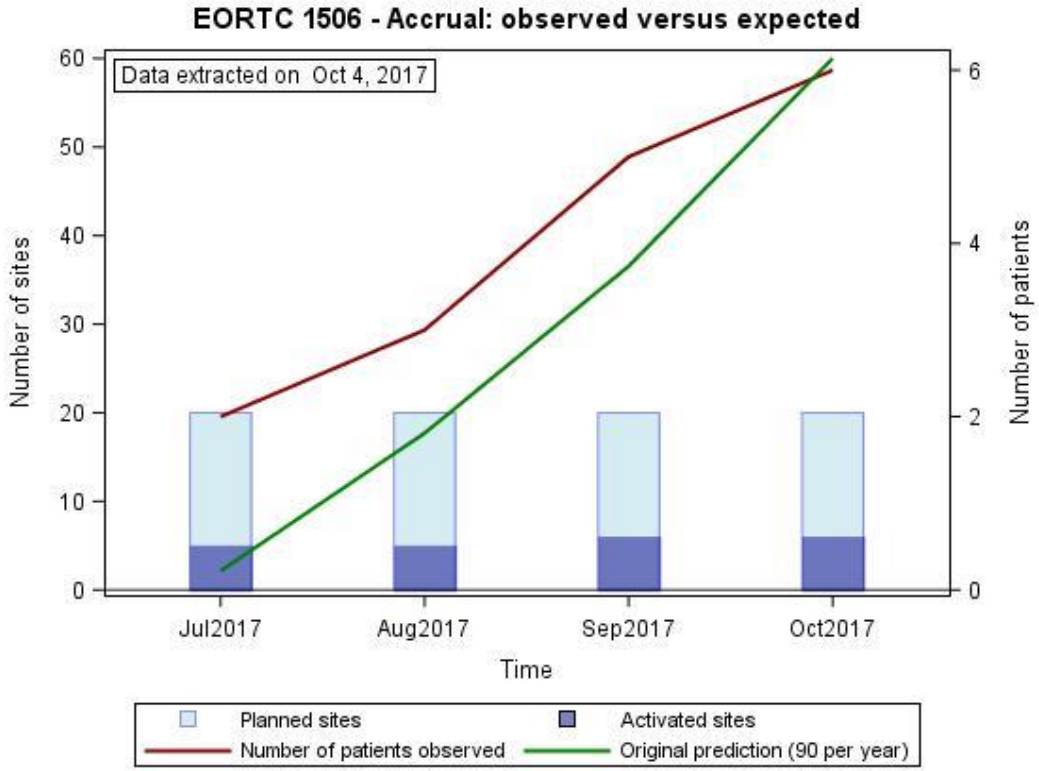
Physicians should start thinking of this trial when starting to prescribe doxorubicin!

Participating Sites

Name	Inst No.	Institution	Country
Mazzeo Filomena	121	Cliniques Universitaires Saint-Luc	Belgium
Schoeffski Patrick	147	U.Z. Leuven - Campus Gasthuisberg	Belgium
Gil Thierry	101	Hopitaux Universitaires Bordet-Erasme - Institut Jules Bordet	Belgium
Mir Olivier	225	Gustave Roussy	France
Blay Jean-Yves	227	Centre Leon Berard	France
Italiano Antoine	228	Institut Bergonie	France
Merimsky Ofer	911	Tel Aviv Sourasky Medical Center	Israel
Katz Daniela	3814	Assaf Harofeh Medical Center	Israel
Rudaitis Vilius	9453	Vilnius University Hospital Santariskiu Clinics	Lithuania
Steeghs Neeltje	301	The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis	Netherlands
Gelderblom Hans	310	Leiden University Medical Centre	Netherlands
Reyners Anna	335	University Medical Center Groningen	Netherlands
Rutkowski Piotr	550	Maria Sklodowska-Curie Memorial Cancer Centre	Poland
Estival Anna	381	Institut Catala d'Oncologia - ICO Badalona	Spain
Casado Herraez Antonio	366	Hospital Universitario San Carlos	Spain
Kollar Attila	454	Inselspital	Switzerland
Stark Daniel	601	Leeds Teaching Hospitals NHS Trust - St. James's University Hospital	United Kingdom
Leahy Michael G.	610	The Christie NHS Foundation Trust	United Kingdom
Karavasilis Vasilios	622	University College London Hospitals NHS Foundation Trust	United Kingdom
van der Graaf Winette	613	Royal Marsden Hospital - Chelsea, London	United Kingdom

Accrual (October 2017)

Site	activation	# patients
U.Z. Leuven - Campus Gasthuisberg (P. Schöffski)	20/07/2017	4
Institut Catala d'Oncologia (A. Estival)	28/07/2017	1
Maria Sklodowska-Curie Memorial Cancer Centre (P. Rutkowski)	28/07/2017	2
TOTAL		7
Current Status (01/2018)		**14**



EORTC - STBSG

Study 1402 (Euro Ewing 2012)

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

International Study coordinator: Bernadette Brennan (UK)

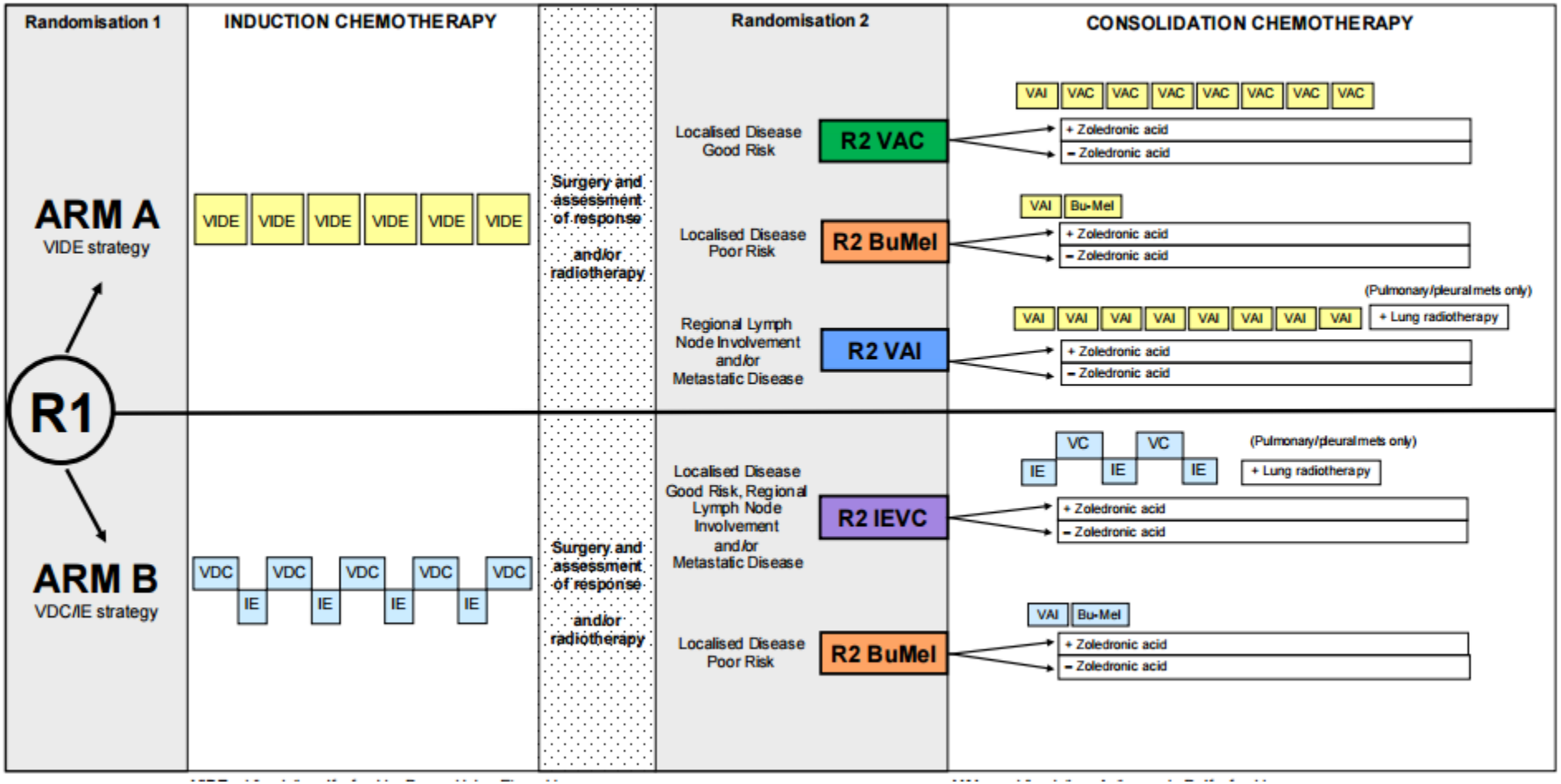
EORTC Study coordinator: Hans Gelderblom

Leiden University Medical Centre

Intergroup trial

- International Sponsor: CRCTU, University of Birmingham
- Participating Countries:
  - United Kingdom (UoB)
  - France (SFCE)
  - Spain (GEIS)
  - BE, CZ, HU, NL, DK, IT (EORTC STBSG)

New design


Randomisation 1
INDUCTION CHEMOTHERAPY
Randomisation 2
CONSOLIDATION CHEMOTHERAPY
ARM A
VIDE strategy
VIDE VIDE VIDE VIDE VIDE VIDE
Surgery and assessment of response and/or radiotherapy
Localised Disease Good Risk
R2 VAC
VAI VAC VAC VAC VAC VAC VAC VAC
+ Zoledronic acid
– Zoledronic acid
Localised Disease Poor Risk
R2 BuMel
VAI Bu-Mel
+ Zoledronic acid
– Zoledronic acid
(Pulmonary/pleural mets only)
Regional Lymph Node Involvement and/or Metastatic Disease
R2 VAI
VAI VAI VAI VAI VAI VAI VAI VAI
+ Lung radiotherapy
+ Zoledronic acid
– Zoledronic acid
R1
ARM B
VDC/IE strategy
VDC IE VDC IE VDC IE VDC IE VDC
Surgery and assessment of response and/or radiotherapy
Localised Disease Good Risk, Regional Lymph Node Involvement and/or Metastatic Disease
R2 IEVC
VC IE VC IE IE
(Pulmonary/pleural mets only)
+ Lung radiotherapy
+ Zoledronic acid
– Zoledronic acid
Localised Disease Poor Risk
R2 BuMel
VAI Bu-Mel
+ Zoledronic acid
– Zoledronic acid

Accrual EORTC **1402** (01/2018)

416/600

(30 EORTC patients)

EORTC - STBSG

1403 (rEECur)

International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma

International Study coordinator: Martin McCabe (UK)

EORTC Study coordinator: Uta Dirksen (DE)

Coordinating group University of Birmingham - CRCTU trial office

EORTC

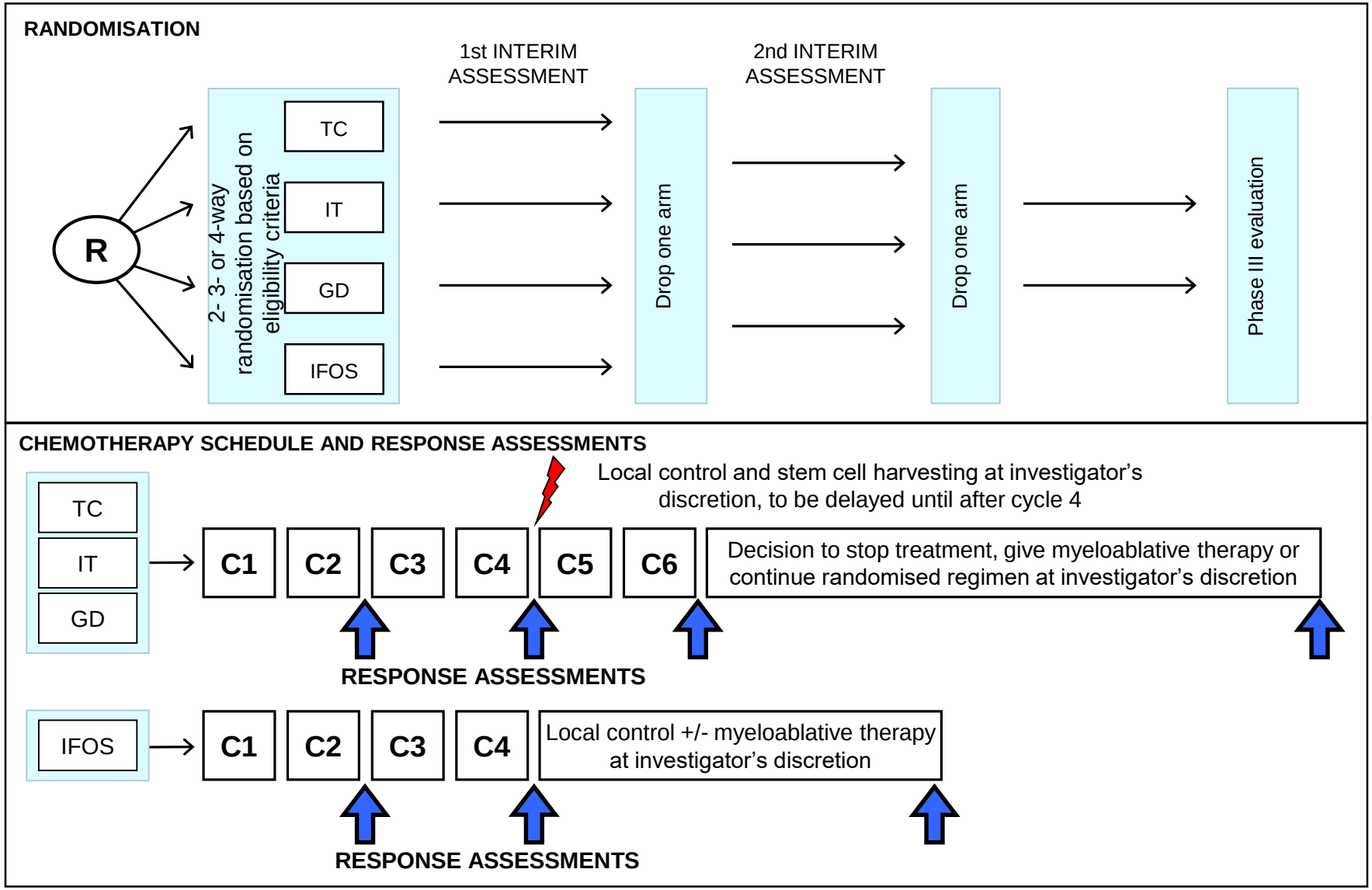
The future of cancer therapy

Intergroup trial

- International Sponsor: CRCTU, University of Birmingham
- Participating Countries:
  - United Kingdom (UoB)
  - Spain (GEIS)
  - Italy (ISG)
  - FI, NO, DK, SW (SSG)
  - DE (GPOH/DKH) *(PHASE II ONLY; V 5.a)*
  - FR, BE, CZ, HU, NL, PL (EORTC STBSG)

Study design

Sample Size
Phase II - 275
Phase III - 400



Accrual EORTC **1403** (01/2018)

216/600

(55 EORTC patients)

Agenda

- Current and upcoming European EORTC / STBSG trials
- **Example: Activities of the German Sarcoma Groups (GISG / AIO)**
- Worldwide, international clinical trials of interest

Study Portfolio (1)

- GISG-01: Imatinib in desmoid tumors (Phase II, **DESMOID**, Kasper) > *published Ann Surg Oncol 2016; 23: 1924-1927 and Eur J Cancer 2017; 76: 60-67*
- GISG-02: Combination therapy of Gemcitabine and Trabectedin in L-sarcomas (Phase I, **GEMYON**, Kasper) > *published Mar Drugs 2015; 13: 379-388*
- GISG-03: Neoadjuvant radiotherapy + Sunitinib in resectable soft tissue sarcomas (Phase I, **SUNRASE**, Jakob) > *published Radiat Oncol 2016; 11: 77*
- GISG-04: Window of opportunity study of neoadjuvant Pazopanib in high-risk soft tissue sarcomas (Phase II, **NOPASS**, Ronellenfitsch) > *manuscript under preparation*
- GISG-05: Randomized phase II trial comparing Pazopanib with Doxorubicin as first line treatment in elderly patients with metastatic or advanced soft tissue sarcoma (Phase II, **EPAZ**, Grünwald) > *Data evaluation*
- GISG-06: Pazopanib + Paclitaxel in angiosarcoma patients (Phase II, **EVA**, Pink)
- GISG-07: Pazopanib in liposarcomas (Phase II, GEIS + GISG, Kasper) > *manuscript under preparation*
- GISG-08: Outcome evaluation of Trabectedin treatment by RECIST/CHOI (NIS, **Y-IMAGE**, Kasper) > *published Anticancer Drugs 2017; Sept 18*

Study Portfolio (2)

- **GISG-10:** Trabectedin combined with regional Hyperthermia as second line treatment for advanced STS (**Hyper-TET**, Lindner)
- **GISG-11:** Quality of life in patients with soft tissue sarcoma undergoing palliative chemotherapy or treatment with Pazopanib (**PazoQoL**, Schuler)
- GISG-12: Patient directed intervention towards a multidimensional recommendation guideline to improve the quality of life for patients with soft tissue sarcoma under palliative treatment with Trabectedin (**YonLife**, Schuler) > *Recruitment finalized*
- **GISG-13:** 1st Line Trabectedin in elderly “unsuited” patients incl. geriatric assessment (**E-TRAB**, Kasper)
- **GISG-14:** Retrospective data collection of STS patients (**ReTraSarc**, Pink / Reichardt)
- **GISG-15:** Nivolumab + Trabectedin (**NiTraSarc**, Pink)
- GISG-16: Trabectedin + Olaparib in solid tumors harboring DNA repair deficiencies (Fröhling/Schlenk) > *FPFV Q1/2018*
- GISG-17: Doxorubicin Rechallenge plus Olaratumab (**OlaReDo**, Pink) > *Setup*

Currently recruiting Studies

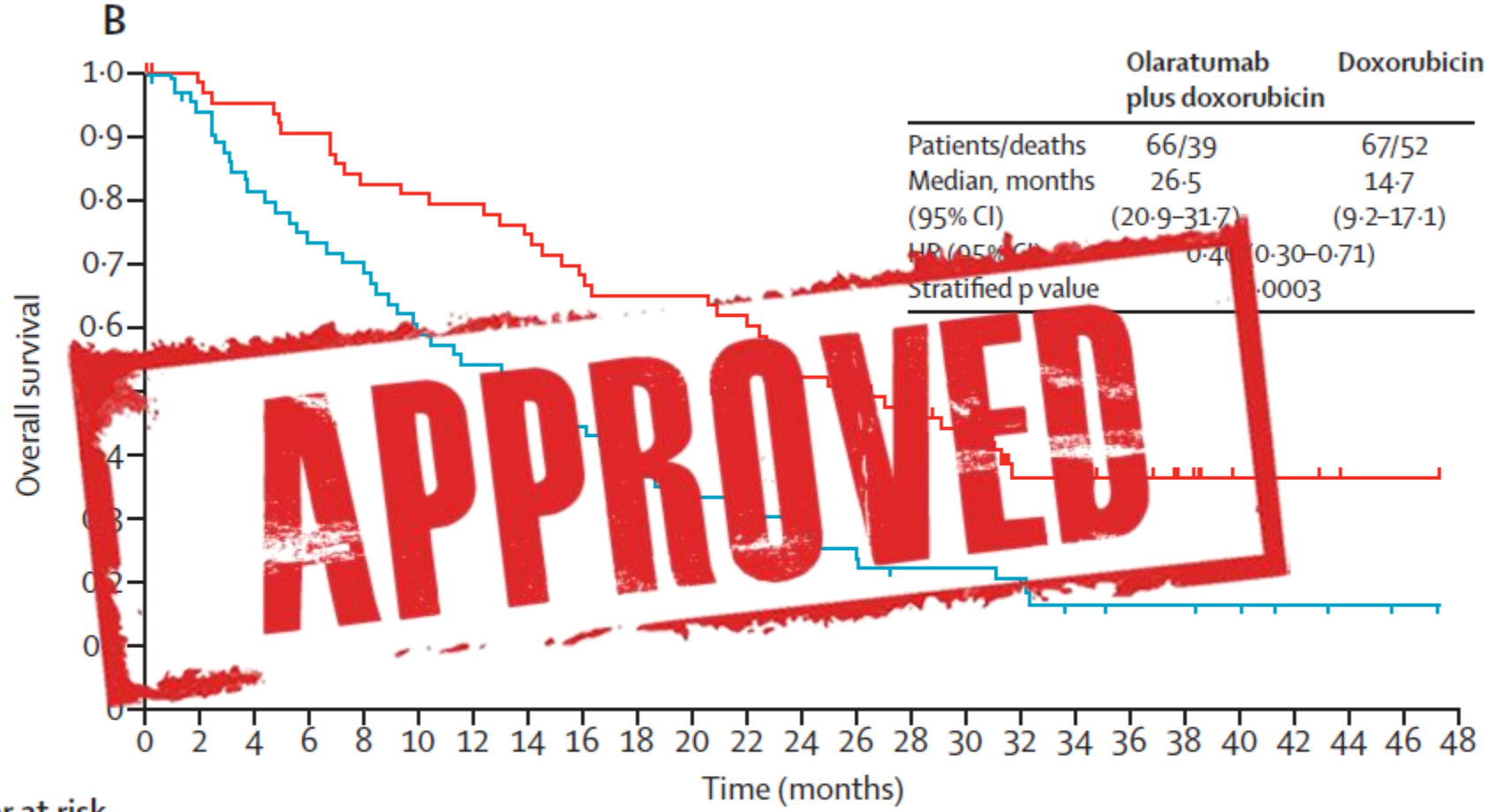
- **MEDISARC (AIO-STS-0415):** Randomized Phase II Study evaluating Durvalumab + Tremelimumab compared to Doxorubicin in Advanced or Metastatic STS Patients (Grünwald)

- **POETIG (AIO-STS-0115):** Phase II Study evaluating Ponatinib after Imatinib Failure in Metastatic/Unresectable GIST Patients (Bauer) > DKTK Cooperation

Agenda

- Current and upcoming European EORTC / STBSG trials
- Example: Activities of the German Sarcoma Groups (GISG / AIO)
- **Worldwide, international clinical trials of interest**

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



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

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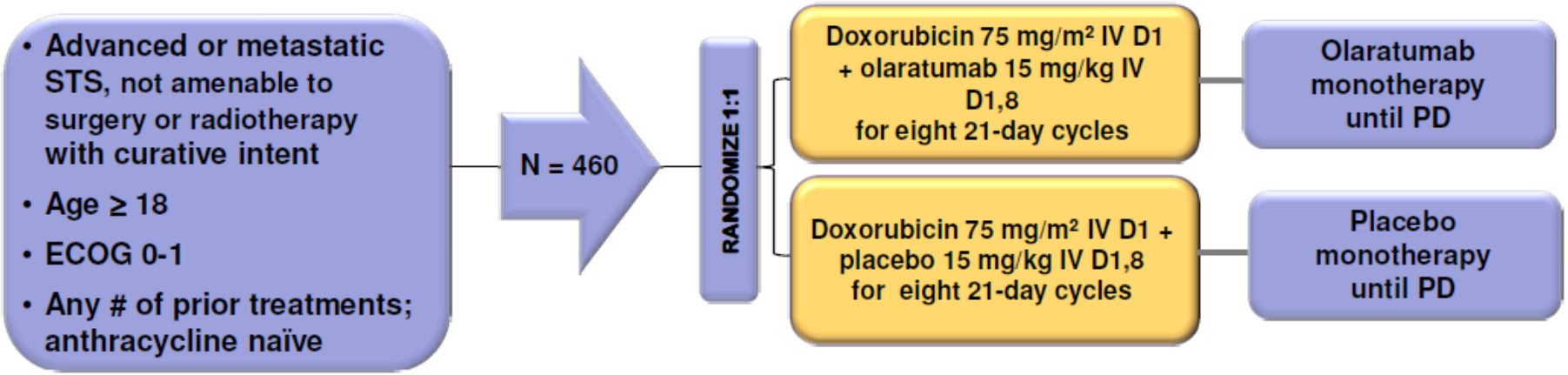
Olaratumab - Clinical Studies

Study	Objectives
JGDJ [*ANNOUNCE 1; NCT02451943*]: Phase 3 Doxorubicin combination in Soft Tissue Sarcoma (STS)	Efficacy and safety in the target population (advanced / metastatic Soft Tissue Sarcoma) Efficacy across histologies Loading dose
JGDL [*ANNOUNCE 2; NCT02659020*]: Phase 1b/2 Gemcitabine / Docetaxel combination in STS	Safety data with Gemcitabine/Docetaxel Efficacy signals with Gemcitabine/Docetaxel
JGDQ [*NCT03126591*]: Phase 1 Pembrolizumab combination in STS	Safe dose in combination with Pembrolizumab
JGDR [*NCT03283696*]: Phase 1 Doxorubicin / Ifosfamide combination in STS	Safe dose in combination with Doxorubicin / Ifosfamide

Olaratumab - JGDJ (*ANNOUNCE 1*)

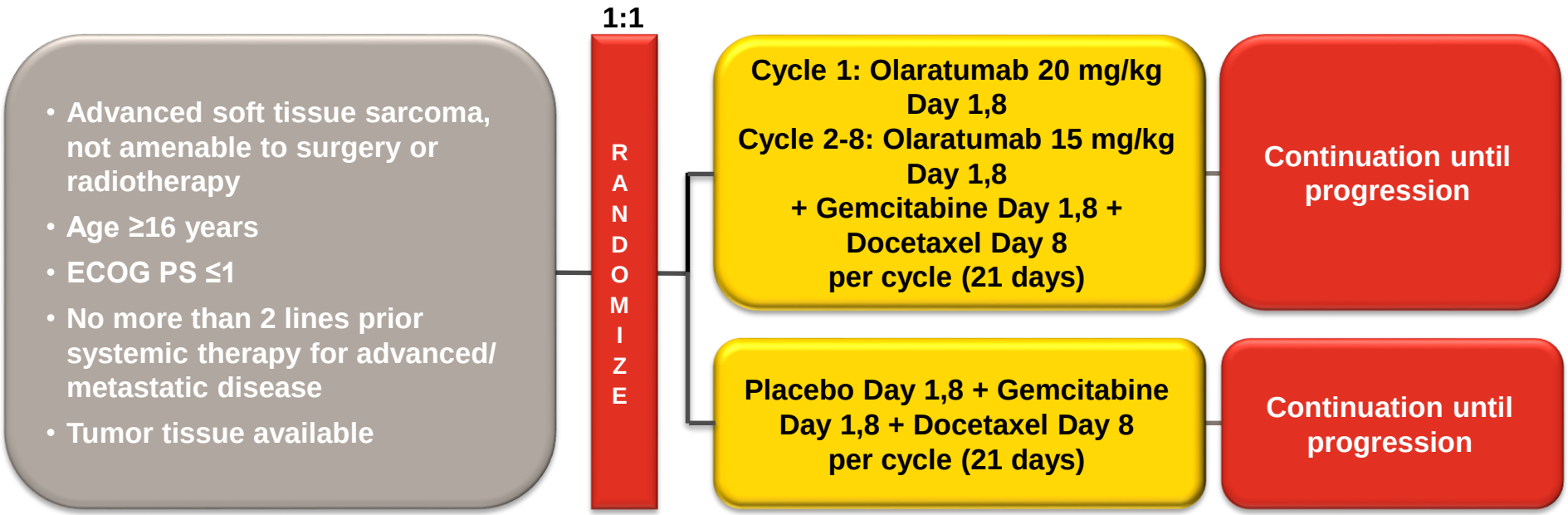


Use of dexrazoxane (in a 10:1 ratio versus doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin is recommended at the investigator's discretion.

Stratification factors:

- Number of prior systemic therapies for advanced/metastatic disease (0 versus ≥1)
  NOTE: any neoadjuvant and adjuvant therapy administered for advanced/metastatic disease will not be considered as a prior line of therapy
- Histological tumor type (leiomyosarcoma versus liposarcoma versus other STS type)
- ECOG performance status (0 versus 1)

Olaratumab - JGDL (*ANNOUNCE 2*)

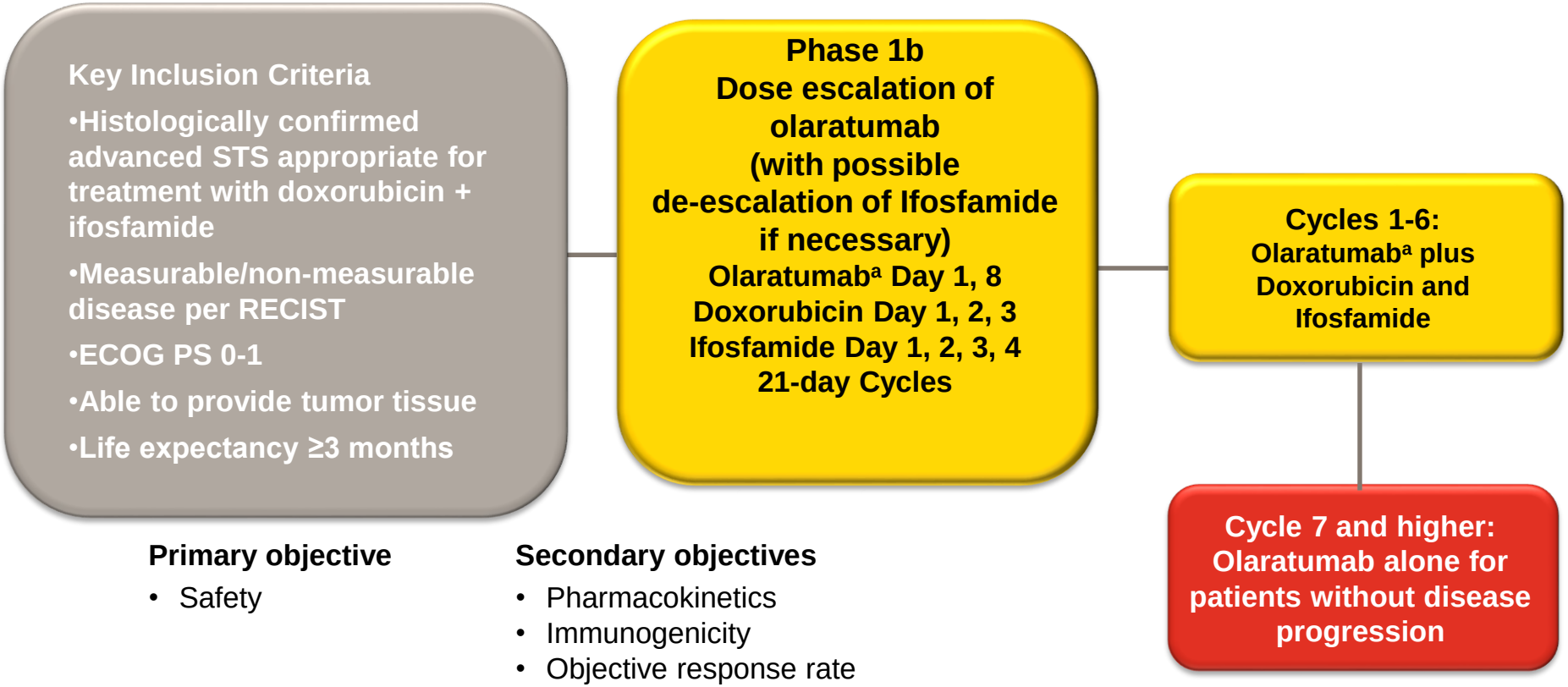


Stratification factors
- PDGFRα
- Lines of prior treatment
- Prior olaratumab
- ECOG PS
- Histology

Primary objective
- Overall survival

Secondary objectives
- Pharmacokinetics
- Progression-free survival
- Tumor response
- Patient pain
- Quality of life

Olaratumab - JGDR (Doxorubicin / Ifosfamide)



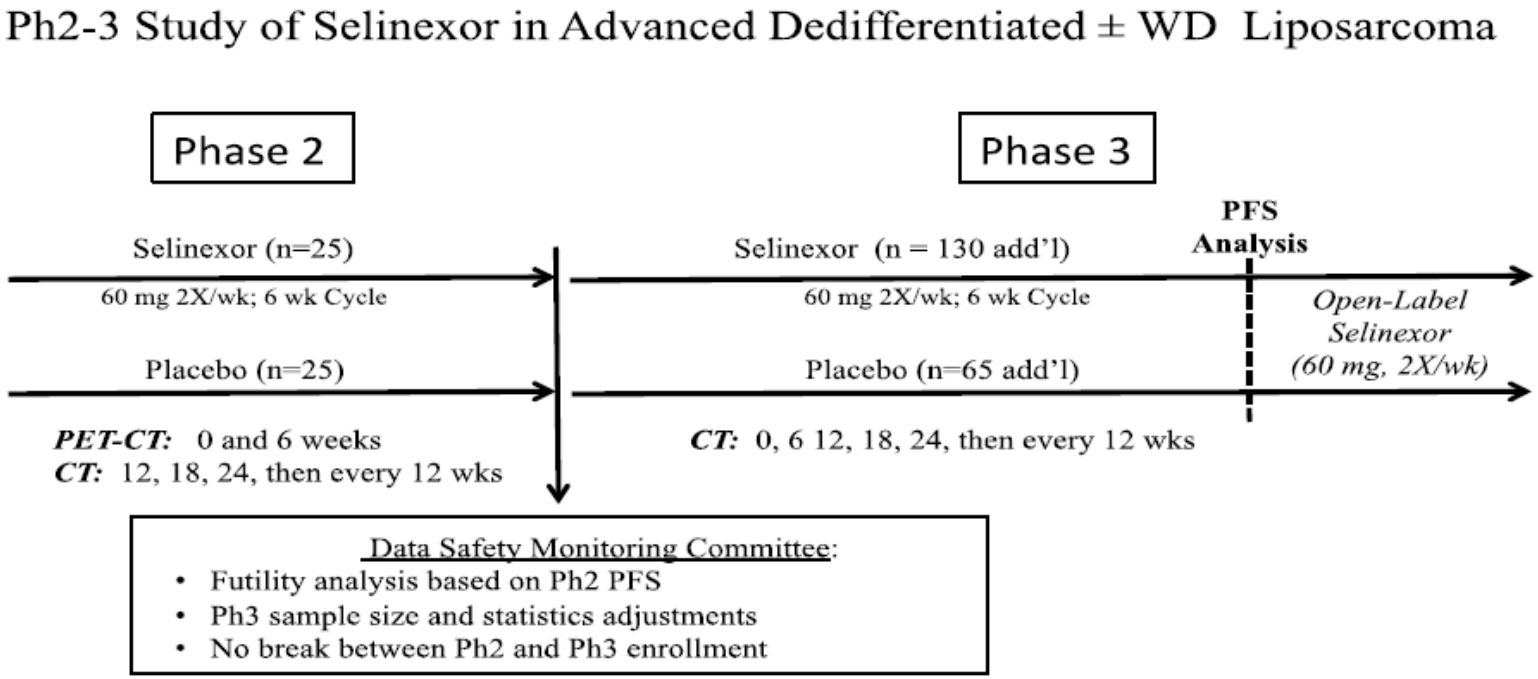
Primary objective

- Safety

Secondary objectives

- Pharmacokinetics
- Immunogenicity
- Objective response rate
- Progression-free survival
- Duration of response
- Disease control rate
- Overall survival

Selinexor - KCP-330-020 ***SEAL*** Study Design



Phase 2

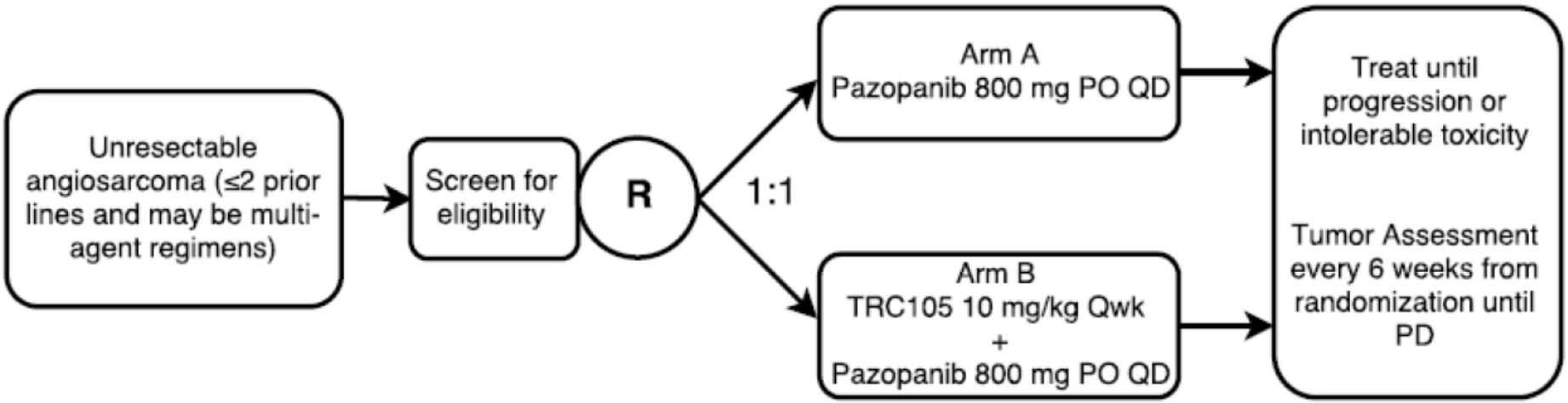
- 1:1 randomization/blinded (n=50: 25 pbo, 25 selinexor)
  - Stratified by number of prior therapies (1 vs ≥2)
- Primary endpoint: PFS by WHO
- Key secondary endpoints
  - ORR
  - DOR
  - PET/CT tumor measurements at 6 wks
- Patients in placebo and selinexor groups included in Ph3 PFS analysis
- Patients who progress will be unblinded: if on placebo may cross-over to open-label selinexor

Phase 3

- 2:1 randomized/blinded (n=195: 65 pbo, 130 selinexor)
  - Stratified by number of prior therapies (1 vs ≥2)
- Primary endpoint: PFS by WHO
- Key secondary endpoints
  - ORR
  - DOR
  - OS
- Patients who progress will be unblinded: if on placebo may cross-over to open-label selinexor
- All patients unblinded at PFS analysis and may continue on open label selinxor until disease progression

TRC105 ± Pazopanib in Angiosarcoma - Study Design

"TAPPAS" Phase 3



Poster #110

TRC105 (Endoglin Antibody) in Combination with Pazopanib in Patients with Advanced Angiosarcoma

K.K. Sankhala[1], S. Attia[2], M.A. Barve[3], J. Wright[4], R.F. Riedel[5], S.I. Robinson[6], R.M. Conry[7], P.M. Boland[8], B.K. Seon[8], D. Alvarez[9], B.J. Adams[9], C.P. Theuer[9], R.G. Maki[10]

[1]Sarcoma Oncology Center, Santa Monica, CA; [2]Mayo Clinic, Jacksonville, FL; [3]Mary Crowley Cancer Research Centers, Dallas , TX; [4]University of Utah, Salt Lake City, UT; [5]Duke University Medical Center, Durham, NC; [6]Mayo Clinic, Rochester, MN; [7]The University of Alabama at Birmingham, Birmingham, AL; [8]Roswell Park Cancer Institute, Buffalo, NY; [9]TRACON Pharmaceuticals, Inc., San Diego, CA; [10]Icahn School of Medicine at Mount Sinai, New York, NY

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Universitätsklinikum Mannheim

Systemic Therapy for Soft Tissue Sarcomas *(advanced / metastatic)*

„Backbone“ Chemotherapy

Doxorubicin
(+ Ifosfamide / DTIC)
+ Olaratumab

Approved Agents beyond 1st line

Trabectedin
Pazopanib
Eribulin

„Pipeline“

Olaratumab
(ANNOUNCE 1, ANNOUNCE 2)
Selinexor
(Phase II/III ongoing)
TRC105
(Phase III ongoing)
Immunotherapies
(Phase I/II studies ongoing)

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der Universität Heidelberg

Universitätsklinikum Mannheim

Discussion and Questions

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