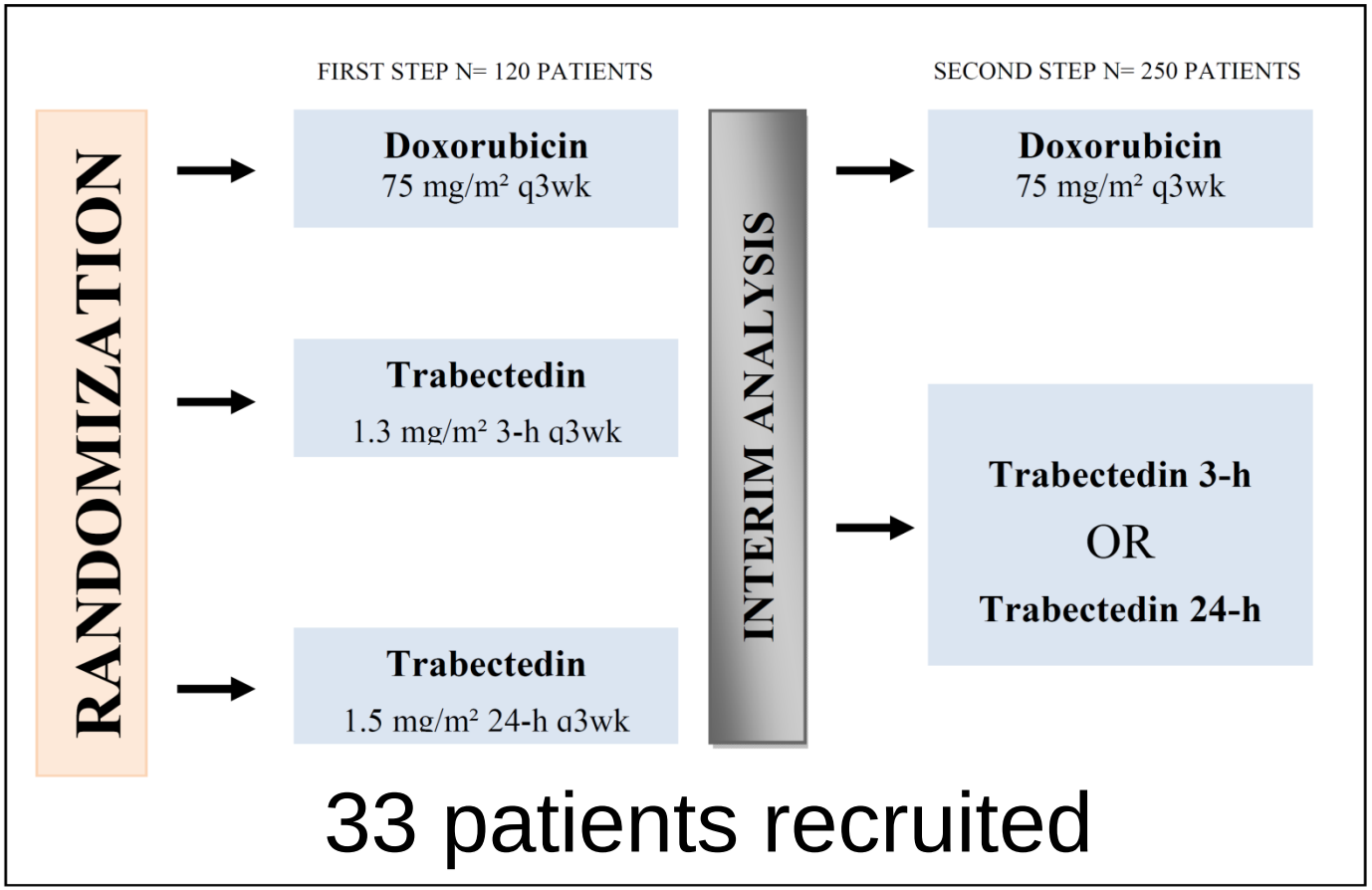
International Collaborations on Sarcomas

Alessandro Gronchi
alessandro.gronchi@istitutotumori.mi.it

- **EORTC STBSG**
- **World Sarcoma Network**
- **Investigators initiated Trials (national groups, centers, etc.)**

EORTC
European Organization for Research and Treatment of Cancer

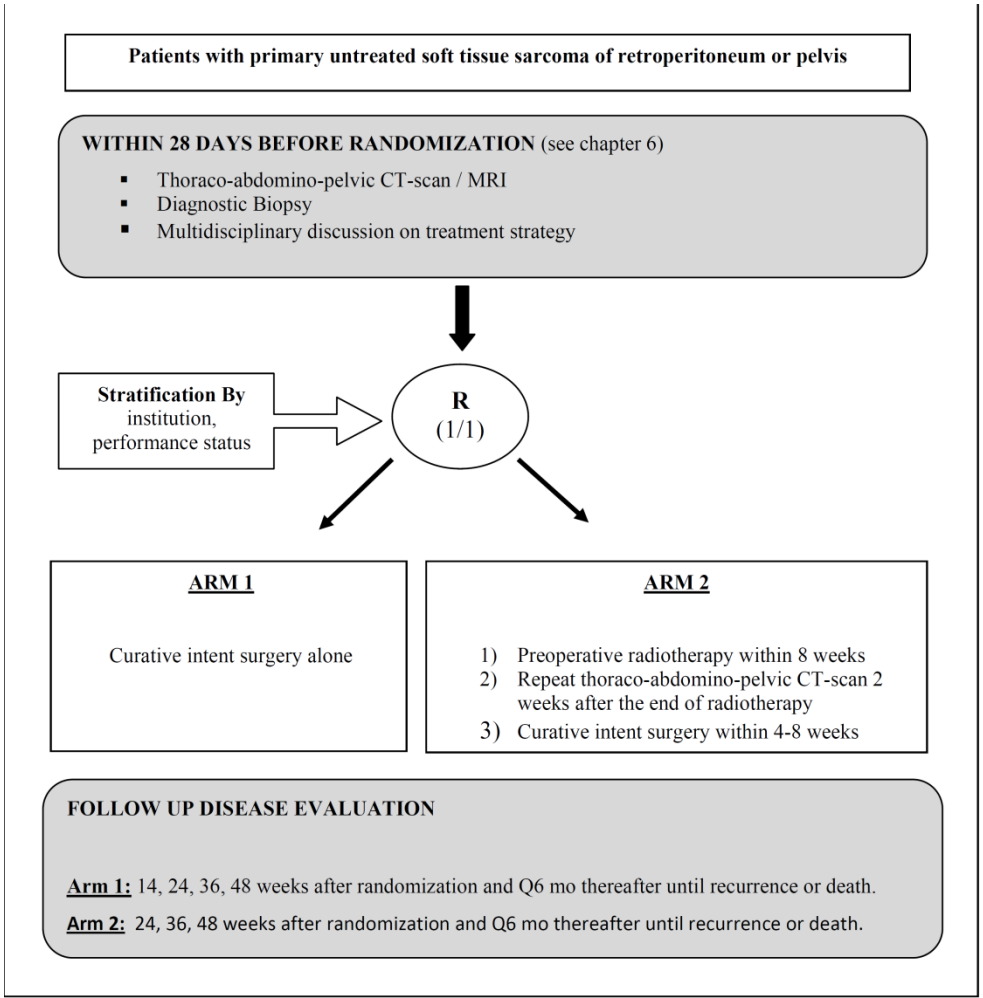
1 Trial # 62091:
TRUSTS: A phase IIb/III multicenter study comparing the efficacy of TRabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic Untreated Soft Tissue Sarcoma



33 patients recruited

EORTC
European Organization for Research and Treatment of Cancer

1 Trial # 62092-22092: A phase III randomised study of pre operative radiation (XRT) plus surgery versus surgery alone for patients with retroperitoneal sarcomas (RPS)



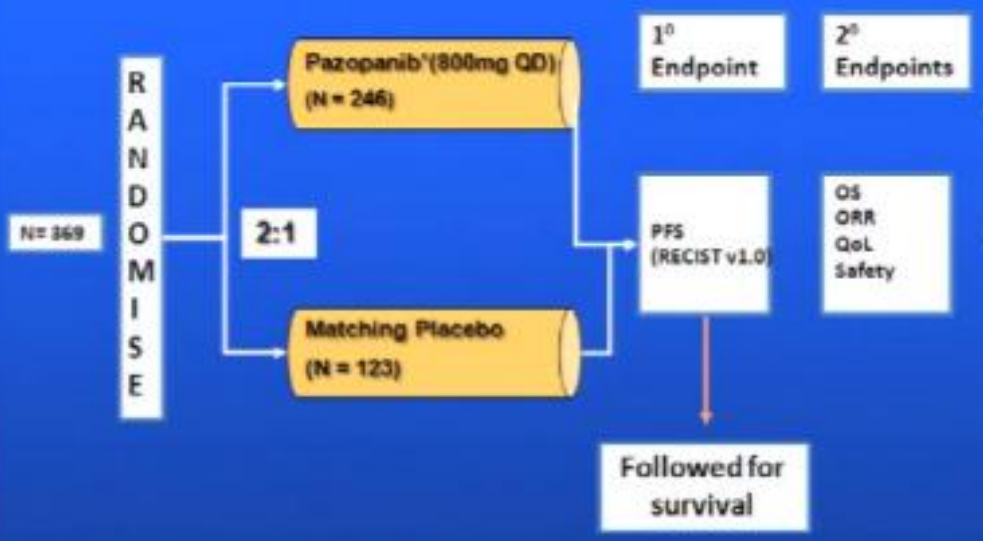
PALETTE

A randomized double blind phase III trial of pazopanib versus placebo in patients with soft tissue sarcoma (STS) whose disease has progressed during or following prior chemotherapy.

An EORTC STBSG and GSK global network study (EORTC 62072)

W. T. A. van der Graaf, J. Y. Blay, S. Chawla, D.W. Kim, B. Bui-Nguyen, P. Casali, P. Schoeffski, M. Aglietta, A. Staddon, Y. Beppu, A. Le Cesne, H. Gelderblom, I.Judson, N. Araki, M. Ouali, S. Marreaud, R A. Hodge, M. Dewji, P. Dei Tos, P. Hohenberger, on behalf of the global PALETTE study team.

Phase III Study Design



Stratification factors

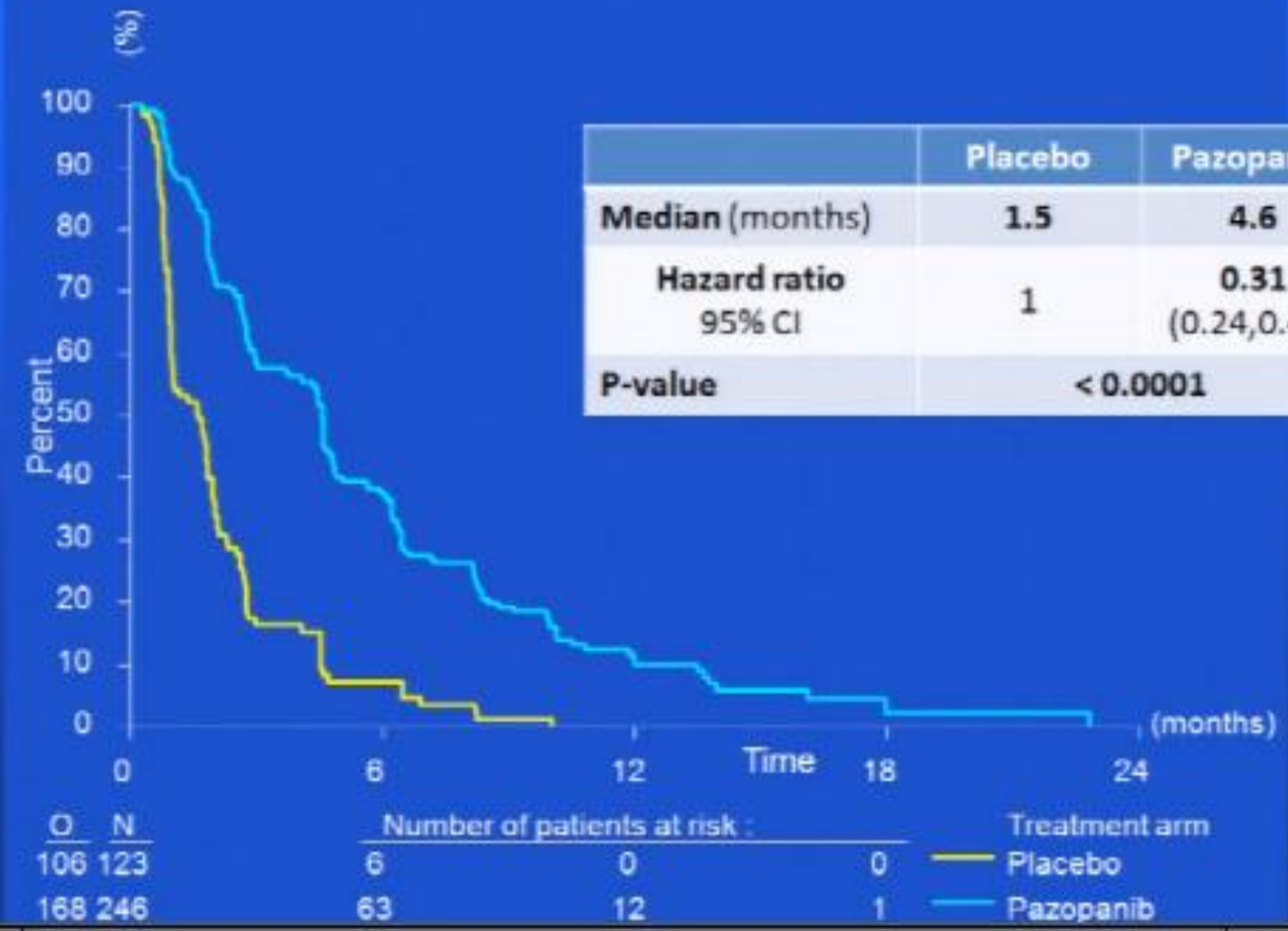
- Performance status (0 vs 1)
- Number of prior lines of systemic therapy for advanced disease (0/1 vs 2+)

Disease assessment

at week 4-8-12-20 and at 8 week intervals thereafter

* Until disease progression, unacceptable toxicity, withdrawal of consent for any reason, or death

RESULTS: Primary end-point
Progression Free Survival



	Placebo	Pazopanib
Median (months)	**1.5**	**4.6**
Hazard ratio 95% CI	1	**0.31** (0.24,0.40)
P-value	**< 0.0001**	

Study Status

- **Accrual**
  - 369 randomized patients over 17 months
  - 4 continents, 13 countries, 72 institutions
  - EORTC: 45% - Other institutions: 55%
- **Clinical cut-off date**
  - November 2010
  - Patients still on protocol therapy: 19
  - Median follow-up:15 months

EORTC
European Organization for Research and Treatment of Cancer

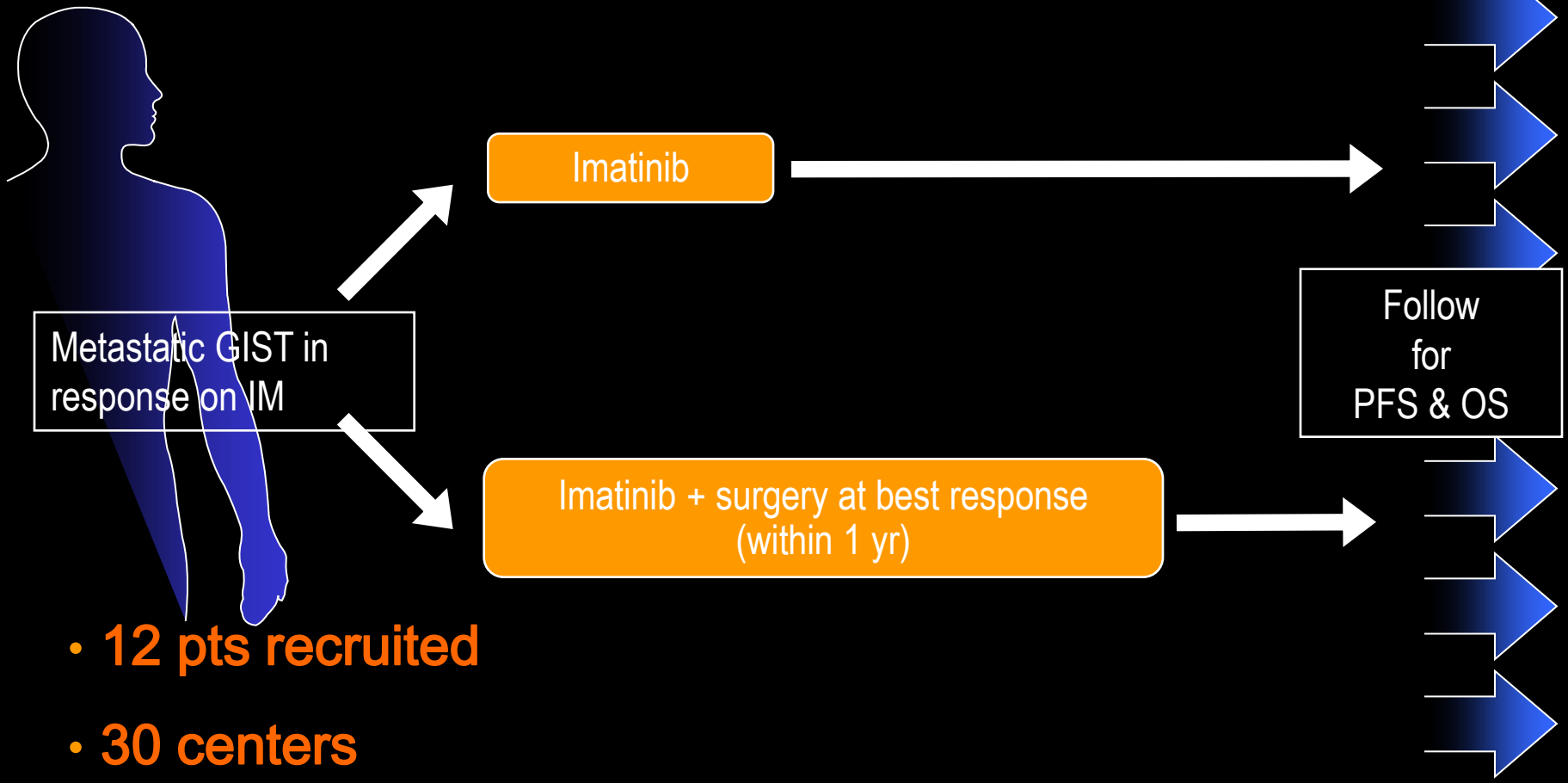
Added value

- Expertise
- Reputation
- Infrastructures
- Biobanking facilities

EORTC
European Organization for Research and Treatment of Cancer

Limitations

- Costs (regulatory burden) → need for a Sponsor
- Lenght of processes
- No formats for non drug trial



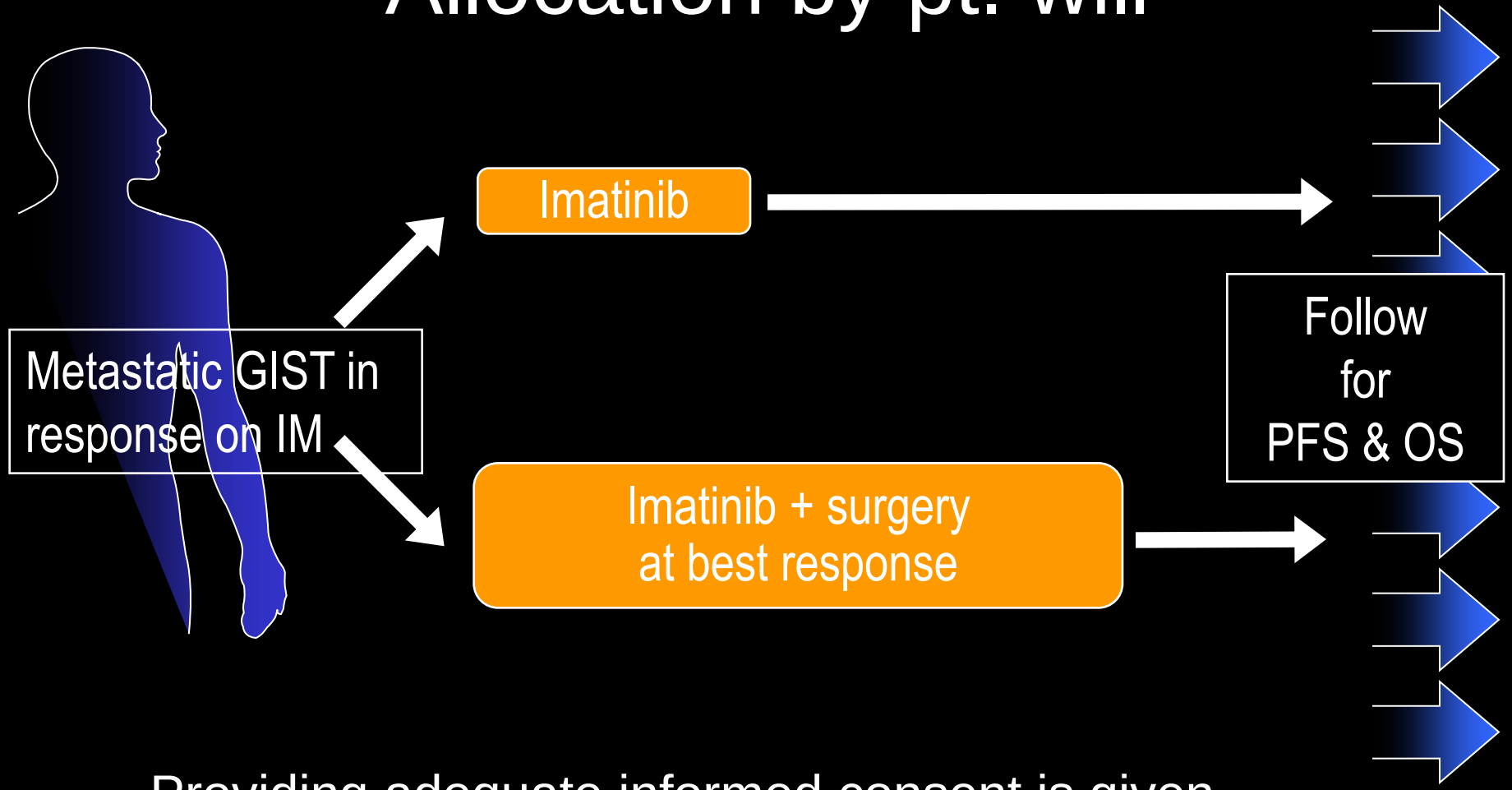
- 12 pts recruited
- 30 centers

Any alternative to randomization ?

Comparative effectiveness

- A prospective, non-randomised study aimed at evaluating the efficacy of surgery designed as a true clinical trial, with all the implications in terms of methodological constraints and quality controls (not an observational study)

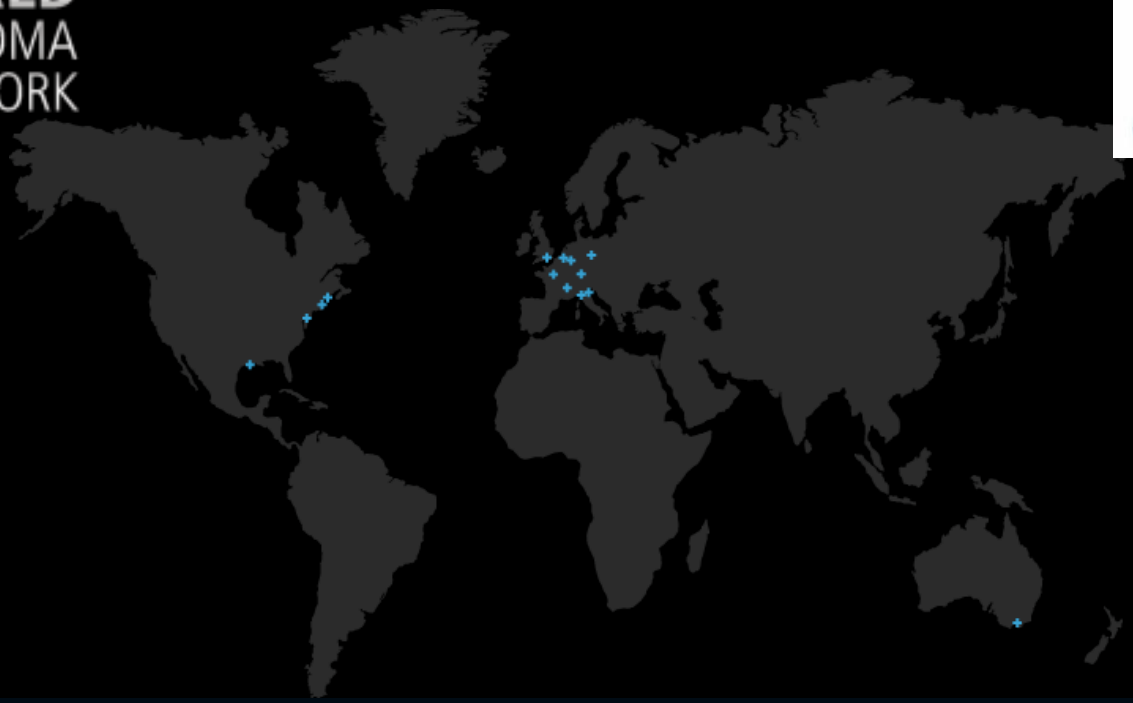
Allocation by pt. will



Providing adequate informed consent is given and eligibility criteria are met

WORLD SARCOMA NETWORK

Conticanet



EUROPE

LYON – Centre Léon Bérard
PARIS – Institut Gustave Roussy
MILAN – Istituto Nazionale dei Tumori
NIJMEGEN – Radboud Medical University and Oncology Centre
ROTTERDAM – Erasmus University Medical Centre
TREVISO – Azienda Unita Locale Socio-Sanitaria N.9
HEIDELBERG – Medical Faculty Mannheim, University of Heidelberg
LONDON – Institute for Cancer Research, Royal Marsden
WARSAW – Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology
LEIDEN – Leiden University Medical Center

USA

NEW-YORK – Memorial Sloan Katering Cancer Centre
BOSTON – Dana Farber Cancer Institute
PHILADELPHIA – Fox Chase Cancer Centre
HOUSTON – MD Anderson Cancer Centre

AUSTRALIA

MELBOURNE – Peter MacCallum Cancer Centre, Ludwig Institute for Cancer Research

Phase II Study of Nilotinib Efficacy in Pigmented Villo-Nodular Synovitis/ Tenosynovial Giant Cell Tumour (PVNS EU)

From adminadmin, 02.02.2012, in Academic

Sponsor:

Centre Leon Berard, FR

Category: Academic

Principal Investigator:

Pr. Jean-Yves BLAY

The purpose of this study is to explore the efficacy of nilotinib as a treatment of patients with progressive or relapsing pigmented villo-nodular synovitis / tenosynovial giant cell tumour (PVNS/TGCT) who cannot be treated by surgery.

An exploratory objective of the study will be to study the relationship between the objective tumour response and the following tumour characteristics (tissues collected in a prior surgery, or by biopsy, upon specific acceptance by the patient; if no tissue is available in the prior surgery, a biopsy will be done at visit 2):

Presence of COL6A3/CSF1 fusion gene Presence of M-CSF, CSF1R, KIT, PDGFRA and B on immunohistochemistry Presence of phosphorylated c-fms on tumour samples Activation of the PI3K/Akt/mTor pathway, presence of activating mutations of ras, and other potential molecular alterations

WORLD SARCOMA NETWORK

Added value

- “easy” process
- reduced costs
- Ideal template for small phase II studies on rare subtypes

WORLD SARCOMA NETWORK

Limitations

- No infrastructures
- No biobanking
- No money

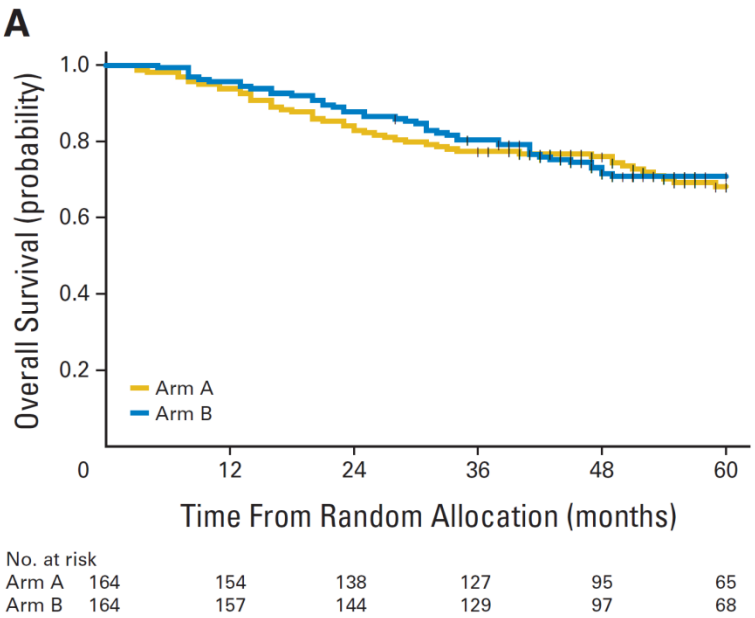
Published Ahead of Print on February 6, 2012 as 10.1200/JCO.2011.37.7218
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.37.7218

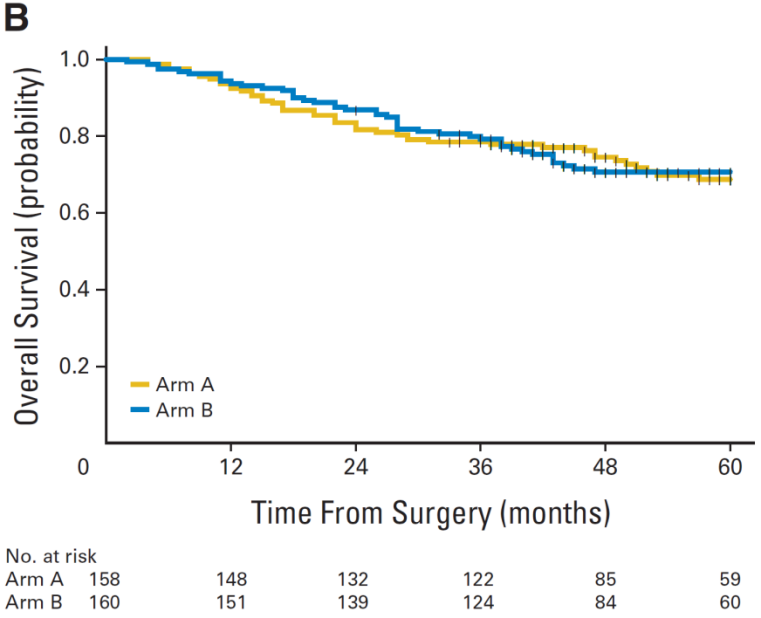
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Short, Full-Dose Adjuvant Chemotherapy in High-Risk Adult Soft Tissue Sarcomas: A Randomized Clinical Trial From the Italian Sarcoma Group and the Spanish Sarcoma Group

Alessandro Gronchi, Sergio Frustaci, Mario Mercuri, Javier Martin, Antonio Lopez-Pousa, Paolo Verderio, Lidia Mariani, Pinuccia Valagussa, Rosalba Miceli, Silvia Stacchiotti, Angelo Paolo Dei Tos, Antonino De Paoli, Alessandra Longhi, Andres Poveda, Vittorio Quagliuolo, Alessandro Comandone, Paolo Giovanni Casali, and Piero Picci





- High grade, adult-type
- Extremity and trunk wall
- ≥5 cm and/or local rec

EI x 3 → Chir ± RT

R

ht-CT x 3 → Chir ± RT

histotypes…

	Frequency in the previous study (222 reiewed cases)
Leiomyosarcoma	16%
Round cell liposarcoma (>5%)	10%
Synovial sarcoma	22%
MFH, pleomorphic sarcoma	30%
Malignant Peripheral Nerve Sheath Tumor	6%
Pleomorphic rhabdomyosarcoma	3%
…?	

Histotype tailored CT

- Leiomyosarcoma → gemcitabine + dacarbazine
- Round cell liposarcoma → trabectedin
- Synovial sarcoma → ifosfamide
- MFH, pleomorphic s → gemcitabine + taxotere
- MPNST → Ifo + VP16

Histotype tailored CT

- Leiomyosarcoma → gemcitabine + dacarbazine
- Round cell liposarcoma → trabectedin
- Synovial sarcoma → ifosfamide
- MFH, pleomorphic s → gemcitabine + taxotere
- MPNST → Ifo + VP16

- Myxofibrosarcoma
- Unclassified Spindle Cell Sarcoma
- Pleomorphic Liposarcoma
- Pleomorphic Rabdomiosarcoma

Primary endpoint

- DFS standard vs ht-CT

Secondary endpoints

- Objective Response standard vs ht-CT in distinct histotypes
- Overall Survival standard vs ht-CT
- Overall Response Rate standard vs ht-CT
- Patterns of tumor response (radiologic/pathologic) standard vs ht-CT

- Efficacy study
- Ortogonal study of surrogacy, aimed at testing whether response correlate with survival

- In practice if those who respond more live longer without disease and eventually survive more; we could then extrapolate that the more active regimens (either stantard or tailored) are also the more effective in each stratum

- The HT approach involves substantial organizational burden and is considered clinically worthwhile if associated, overall, with a 30% reduction in the hazard of relapse, corresponding, for instance, to a reduction in the long term risk of relapse from 50% to 39%. In order to assess such an effect with 80% power at the 5% (1-sided) significance level, 144 events (relapses or deaths) need to be observed. It is expected that the study will be able to recruit approximately 300 patients over a 3-years period, from a pool of 400-450 registered patients. The final analysis will take place after the observation of the 144th event, which should occur 4-5 years after the recruitment of the 1st patient.

- Subgroup analysis: A crucial question in this study relates to the possible different effect of HT CT, as compared to standard CT, in different histotypes. This question will be addressed in 2 ways. First, a standard subgroup analysis according to histotype will be conducted, based on the tests for histotype-by-treatment interaction and on the inspection of the appropriate Forrest plot. It is acknowledged that, due to the limited sample size and to the rarity of some of the subgroups, this subgroup analyses have very low power.

- Second, should the validation study on radiological and pathological response as surrogate endpoints provide positive indications, response rate will be modeled as a binary variable and by means of a logistic regression model the interaction between treatment arm and histological subtype will be assessed. Due to the well known relationship between the effects of a treatment on the true and on a surrogate endpoint, this analysis is expected to have much more power than the one based on RFS.

THEME [HEALTH.2011.2.4.1-1]
[Investigator-driven treatment trials for rare cancers]

Grant agreement for: Collaborative project*

Annex I - "Description of Work"

Project acronym: EUROSARC

Project full title: " European Clinical trials in Rare Sarcomas within an integrated translational trial network "

Grant agreement no: 278742

Version date: 2011-08-25

1.Universite Lyon Claude Bernard
2. Academisch Ziekenhuis Leiden
3. Institut Gustave Roussy
4. The Chancellor, Masters and Scholars of the University of Oxford
5. Fondazione IRCCS Istituto Nazionale Tumori
6. Istituto Ortopedico Rizzoli
7. Institut Bergonie
8. Azienda Unità Locale Socio Sanitaria n.9 Treviso
9. Fundacion de Investigacion del Cancer de la Universidad de Salamanca
10.Maria Sklodowska-Curie Memorial Cancer Center
11.Ruprecht-Karls-Universitaet Heidelberg
12.Servei de Salut de Les Illes Balears
13. European Organitation for Research and Treatment of Cancer
14.Sarcoma Patients Euronet
15.The University of Birmingham
16.Oxford Gene Technology
17.Lyon Ingenierie Projects

EUROsarc

WT1
List of work packages

Project Number [1]	278742	Project Acronym [2]	EUROSARC

LIST OF WORK PACKAGES (WP)

WP Number [63]	WP Title	Type of activity [64]	Lead beneficiary number [65]	Person-months [66]	Start month [67]	End month [68]
WP 1	Project management, coordination and internal communication	MGT	1	14.00	1	60
WP 2	Molecular diagnosis and translational research	RTD	2	142.00	1	60
WP 3	Statistics, Data Handling and Analysis	RTD	15	51.00	1	60
WP 4	Clinical Trial EORTC 62092	RTD	13	119.00	1	60
WP 5	IDCT 5- Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults	RTD	5	87.00	1	60
WP 6	Bone Sarcoma; Phase I/II Histotype and Molecular Driven Programme	RTD	4	99.00	1	60
WP 7	Investigator driven clinical trials in osteosarcoma and giant cell tumour of bone	RTD	13	92.00	1	60
WP 8	Exploitation of the research and clinical findings and dissemination for raising awareness	OTHER	8	49.00	1	60
			Total	653.00		

EUROsarc

WT3:
Work package description

Project Number [1]	278742	Project Acronym [2]	EUROSARC

One form per Work Package

Work package number [53]	WP6	Type of activity [54]	RTD
Work package title	IDCT 6- Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults		
Start month	1		
End month	60		
Lead beneficiary number [55]	6		

Objectives

IDCT 6- Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadjuvant chemotherapy

To carry out a randomized, Phase III, international, collaborative clinical trial comparing the effect on disease-free survival of full-dose standard chemotherapy versus a histotype-tailored chemotherapy within the context of an integrated multimodal strategy (with surgery and radiotherapy) for high-risk localized soft tissue sarcomas of the adult.
Chemotherapy will be administered for 3 cycles pre-operatively. There will be five histological groups (representing 80% of the cases of STS), as follows: 1) leiomyosarcoma, 2) myxoid round cell liposarcoma (MRCLPS), 3) synovial sarcoma, 4) malignant peripheral nerve sheath tumor (MPNST) and 5) undifferentiated pleomorphic sarcoma. The histology-driven chemotherapy for these groups will be, respectively, 1) gemcitabine plus decarbazine, 2) adriamycin, 3) high-dose ifosfamide, 4) ifosfamide plus etoposide, 5) gemcitabine plus docetaxel. Other histotypes, such as myxofibrosarcoma, unclassified spindle cell sarcoma, pleomorphic liposarcoma and pleomorphic rhabdomyosarcoma will also be included and registered, but treated only by standard chemotherapy. Radiotherapy will be preferably delivered in the post-operative setting. Patients who have already undergone definitive surgery will receive all treatment in the post-operative setting and patients requiring a re-excision after inadequate surgery will be treated as patients in the two groups, but of course will not be evaluable for response.
The endpoint will be disease-free survival (DFS) and, secondarily, overall survival (OS) of patients receiving standard chemotherapy versus those receiving histotype-tailored chemotherapy. Additional aims will be to compare the probability of response of standard vs histotype-tailored chemotherapy and to determine the radiological and pathological response with standard chemotherapy vs tailored chemotherapy in each different histological group. Another aim will be to validate the response (both radiological and pathological) to preoperative chemotherapy as a surrogate endpoint for DFS and OS.
Eligibility criteria will include: 1) diagnosis of soft tissue sarcoma of adults, primary or locally recurrent, with spindle-cell or pleomorphic histology, including: MRCLPS, leiomyosarcoma, synovial sarcoma, MPNST, undifferentiated pleomorphic sarcoma for the randomization group; myxofibrosarcoma, unclassified spindle cell sarcoma, pleomorphic liposarcoma, pleomorphic rabdomiosarcoma for the registration group; belonging to either group but not being evaluable for response (re-excision after previous inadequate resection or primary definitive surgery); 2) high malignancy grade: grade 3 of 3, according to Coindre, or grade 2 at biopsy with a radiological evidence of more than 50% of necrosis in the tumor mass; 3) deep seated extremities, girdles and/or superficial trunk (thoracic or abdominal wall) lesion; 4) size of primary tumor (visible or previously inadequately resected) > 5 cm at instrumental staging (CT, MRI), or locally recurrent of any size; 5) age > 18 years; 6) ECOG performance status < 1; 7) adequate bone marrow, renal and hepatic function; 8) adequate cardiac function (FE > 50%)
Exclusion criteria will include: 1) pregnancy or lactation; 2) distant metastasis; 3) other malignancies within past 5 years, with the exception of carcinoma in situ of cervix and basocellular skin cancers treated with eradicating intent; 4) sarcoma histotypes other than those mentioned in the inclusion criteria; 5) prior CT and/or RT.
Three hundred patients will be randomized over a 3-years period, from a pool of 400-450 registered patients.
The study is designed to verify the statistical hypothesis that histotype-tailored approach is associated, overall, with a 30% reduction in the hazard of relapse. However, in each different histological group, the effect of histotype-tailored chemotherapy, as compared to standard chemotherapy, can be different. To address this

EUROsarc

WT6:
Project Effort by Beneficiary and Work Package

Project Number [1]	278742	Project Acronym [2]	EUROSARC

Indicative efforts (man-months) per Beneficiary per Work Package

Beneficiary number and short-name	WP 1	WP 2	WP 3	WP 4	WP 5	WP 6	WP 7	WP 8	Total per Beneficiary
1 - UCBL	2.00	20.00	5.00	10.00	10.00	5.00	10.00	4.00	66.00
2 - LUMC	0.00	25.00	3.00	3.00	0.00	20.00	0.00	1.00	52.00
3 - IGR	0.00	5.00	2.00	23.00	1.00	1.00	1.00	1.00	34.00
4 - UOXF.BV	0.00	0.00	3.00	1.00	1.00	35.00	20.00	1.00	61.00
5 - INT	0.00	1.00	3.00	3.00	10.00	1.00	1.00	1.00	20.00
6 - IGR	0.00	10.00	0.00	0.00	2.00	10.00	5.00	1.00	28.00
7 - Bergonie	0.00	25.00	4.00	6.00	6.00	4.00	4.00	1.00	50.00
8 - ULSS9	0.00	20.00	0.00	0.00	20.00	0.00	0.00	20.00	60.00
9 - CIC	0.00	10.00	0.00	2.00	10.00	15.00	10.00	1.00	48.00
10 - MCMCC	0.00	1.00	1.00	6.00	6.00	2.00	2.00	4.00	22.00
11 - UHEI	0.00	6.00	1.00	5.00	5.00	2.00	2.00	2.00	23.00
12 - SSIB	1.00	1.00	1.00	4.00	10.00	4.00	4.00	0.00	25.00
13 - EORTC	0.00	0.00	10.00	50.00	0.00	0.00	30.00	2.00	92.00
14 - SPAEN	0.00	0.00	0.00	1.00	1.00	0.00	1.00	10.00	13.00
15 - UOB	0.00	0.00	18.00	0.00	0.00	0.00	0.00	0.00	18.00
16 - OGT	0.00	18.00	0.00	0.00	0.00	0.00	0.00	0.00	18.00
17 - LIP	11.00	0.00	0.00	5.00	5.00	0.00	2.00	0.00	23.00
Total	14.00	142.00	51.00	119.00	87.00	99.00	92.00	49.00	653.00

Added value

- “easy” process
- reduced costs
- Investigators’ commitment and enthusiasm…

Limitations

- No infrastructures
- All trial related costs on participating institution
- Light monitoring
- …

alessandro.gronchi@istitutotumori.mi.it