European Clinical trials in Rare Sarcomas within an integrated translational trial network

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1. Executive Summary

European Clinical trials in Rare Sarcomas within an integrated translational trial network

Sarcoma are rare diseases, heterogenous in nature, whose management is best performed in the context of reference centres. With over 150 different sarcoma histotype, there were not enough involvement for clinical, translational, and basic research aiming to improve our understanding of these disease and their proper management, according to clinical practice guidelines.

Prior to the EuroSARC project, no clinical trial had demonstrated the utility of neoadjuvant chemotherapy, a single attempt of a randomized trial in the USA, failed to explore in a randomized setting the role of radiotherapy in retroperitoneal sarcomas, and the role of IGF1R Ab, mifamurtide, and mTOR inhibitors and TKI for the treatment of subtypes of bone sarcomas was unclear.

The aim of EuroSARC was to launch, execute and complete innovative clinical trials, aiming to change practice in these tumours, with a precise understanding of the mode of action of the agent tested through a robust translational research program, on tumour samples collected in the trial, and on tumour banks established in the previous Conticanet and EuroBoNeT networks of the FP6.

The EuroSARC project enabled the generation of 2 large randomized clinical trials demonstrating practice changing results, and 6 clinical trials on rare sarcomas subentities with proof of concept studies. It has enabled the development of a unique portfolio of clinical trials, in an academic setting on sarcomas. In addition, it enabled to develop associated translational research projects aiming to identify predictive biomarkers and mode of actions of the agent tested. Communication and educational sessions were implemented in major conferences. Novel models for clinical trials of rare entities were generated. This project also fulled collaborations across cooperative groups on other clinical trials, by facilitating exchanges of methods and platforms of research. Seven publications, all in major journal are issued as of Sept 2018, and several more will be issued in the coming years.

Overall the program fulfilled its initial ambitions, and demonstrated the feasibility, and also hurdles to overcome, to generate ambitions academic research programs on rare cancers, with limited access to innovative clinical and translational research projects within FP7.

In this document we summarize the different achievement of the program, describing sequentially the output of its different workpackages.

2. Description of the project context and objectives

2.1. Project context

Clinical trials on specific histological and molecular subtypes of sarcomas are hardly-feasible for most histotype in the absence of a properly organized European and worldwide collaborations between existing networks. Trials in few histotypes of sarcomas (GIST, Ewing, Osteosarcomas) have been possible only through large European or worldwide collaborative clinical trials or research programs, performed through e.g. EORTC (European Organisation for Research and Treatment of cancer). However, altogether, these 3 subsets of sarcomas represent less than 25% of all sarcomas. For other sarcoma subtypes, the standard clinical practices have not been defined through randomized prospective trials.

Two major questions were emerging before the EuroSARC project:

1) **whether local treatment strategies should be or not adapted to histological or molecular subtypes.**
2) **rare subtypes (e.g. chondrosarcomas), or rare clinical presentations (metastatic osteosarcomas) have clearly unmet medical needs, yet could allow for potential proof of concepts for first-in-class targeted treatment and therefore highly necessary and expected. For several reasons, these rare tumours are *not* the main focus of drug developments for the pharmaceutical industry**

Academic clinical trials evaluating either local treatment strategies or systemic treatments using registered agents are particularly difficult to conduct in the absence of industry support.

The goal of EuroSARC was to address major academic questions arising in a selected group of soft tissue and bone sarcomas, in localized and metastatic phase, within a project merging the European networks involved in clinical research in sarcomas, building on the activities of two FP6 networks of excellence EuroBoNeT (www.EuroBoNeT.eu) and Conticanet (www.conticanet.org).

Sarcomas: a heterogeneous group of very rare tumours

Rare cancers are defined by an incidence of less than 6/100.000/year (www.rarecancer.eu). Sarcomas and related cancers are rare malignant tumours, with an overall incidence of 6/100.000/year. Altogether, bone and soft tissue malignant or locally malignant tumours encompass, according to the most recent WHO classification more than 50 different rare histotypes and more than 150 different molecular subtypes. The incidence of most individual sarcomas subtypes is often less than 0.5/100.0000/year, as shown recently within the Conticanet and EuroBoNeT FP6 Networks of Excellence This context has made it difficult, even for large established cooperative networks, to accrue sufficient numbers of patients in specific clinical trials for rare entities. Yet, sarcomas are very favourable models to develop novel agents

targeting specific molecular alterations because molecular alterations are often well characterized. In addition, while the present treatment strategies in local phase are not adapted to histological or molecular subtypes, it is likely that a substantial proportion of histological and molecular subtypes of sarcomas should be treated with specific approaches in localized phases. It had not been possible to explore this question in most subtypes in the past, and this was the objective of EuroSARC.

Histological and molecular diagnoses, central histological review, tumour banks and molecular typing

Central review:

Histological diagnosis of sarcomas remains indeed a significant problem for the routine management of the patients. For this reason, central review of histological diagnosis is mandatory within all recognised clinical research groups in sarcoma, in particular in Europe. The experience in EORTC-STBSG, the FSG, and the ISG studies confirms that central review in reference centres enables to correct for misclassifications or improper diagnosis in >25% of cases. **This issue is particularly critical in a clinical trial where different molecular subsets of sarcomas are considered and should receive different treatments.** Working on sarcoma subtypes in clinical setting therefore requires a highly experienced network of investigators, referral system, possibly virtual slide review to achieve rapid, high quality, and inexpensive cross-validation of the diagnosis.

In parallel to the central histological review, the groups of EuroBoNeT and Conticanet had developed quality assurance manuals for the standardisation of molecular diagnostic procedures for translocation sarcomas, e.g. mutations in GIST, 12q13 amplifications in LPS. These techniques have been cross validated between reference centres in these networks, and showed that it was mandatory to perform these diagnostics in experienced centres with external validation processes, and high volumes of activities (Coindre 2010a &b, Ordonez 2010, Bovée 2010). These centres are partners of the present EuroSARC project, and were able to implement reliable molecular diagnostic criteria for the implementation of clinical trials with molecular inclusion criteria.

Availability of international centrally reviewed tumour banks for the project:

Conticabase (conticabase.org)**, ConticaGIST** (conticagist.org) **and EuroBoNeT** are 3 virtual tumour banks, web accessible, with clinical annotations, including patients with well characterized and centrally reviewed sarcomas and GIST. These tumour banks constitute the ideal setting to investigate user friendly diagnostic tools (Ab, FISH probes) on various sets of tumour samples (FFPE, frozen sections). This drove the inclusion criteria of the protocols to be developed in the consortium, and represented a major sustainability goal of the previous FP6 Conticanet and EuroBoNeT NoE to the service of the present EuroSARC project.

Clinical trials in sarcomas subtypes:

Given the rarity of these tumours, it is important and recommended in most clinical practice guidelines to facilitate their participation of these patients to prospective clinical trials. However, even when an accurate diagnosis can be obtained, the next bottleneck to solve for clinical research in rare sarcoma subtype **is the issue of accrual**, which may be difficult because of the rarity of these tumours. In few specific histological subtypes (GIST, OS, EWS) representing a minority of all sarcomas, trials were developed which took several years to be completed. Importantly, these dedicated trials enable the most significant improvement in outcome for sarcoma patients, with paradigm shifts, and major increases in cure rates. In rarer subsets, no specific prospective clinical trials testing systemic treatments have actually been performed.

Most histological and molecular subsets of soft tissue sarcomas are therefore treated with similar clinical approaches (e.g. with surgery +/- radiotherapy +/- cytotoxic chemotherapy) while it is now becoming clear that the driving mutations of each subsets involve completely different biological processes and should be managed presumably with different therapeutic approaches. As mentioned above, this personalized treatment of sarcoma subtypes represented an important unsolved problem in 2011, constituting the rationale for the development of the EuroSARC proposal, designed to develop specific strategies,

1) **for histotype adapted local treatment strategies**
2) **for the development of a large number and varieties of novel "targeted" therapies directed against oncogenic proteins involved in the neoplastic transformation of tumour cells.**

In 2011, the challenges to address in clinical and translational research on soft tissue, bone and visceral sarcomas were therefore the following:

- Create a reliable, efficient, multinational network of clinical researchers to perform **1) the exploration of therapeutic strategies adapted to the histotype and molecular typing of sarcoma in localized phase, and 2) in advanced phase using targeted therapies guided by the characterisation of the molecular alterations driving the tumour**, in order to allow the implementation of clinical trials which were not previously feasible
- Propose for these clinical trials **standardized molecular and histological inclusion criteria** using a network of European world class experts in sarcoma.
- Utilise the biological and clinical material collected in these clinical trials to perform **translational research on these tumours, and to characterize in depth their molecular alterations and the effects of drug interventions within the tumours**.
- Stimulate and **enable cooperation and collaborations between these networks and with patient advocacy groups on the European and global level, among references centres with established track record**.

In this perspective, the EuroSARC **project represents an important achievement of the 2 FP6 Networks of Excellence Conticanet and EuroBoNeT,** merging the largest contributing centres of the 2 networks, opening to their clinical research networks (EORTC, STBSG, ISG, FSG, GEIS, BSG, GISG, PSG) and implementing in clinical research practices the achievements of the 2 Networks of Excellence. Here under we describe the general and specific objectives of the EuroSARC project.

2.2. Objectives of EuroSARC

The overall objective was to design, structure and implement 9 innovative investigator driven clinical trials (IDCT) of different scales, on a multinational level, evaluating novel treatment strategies : a randomized preoperative radiotherapy trial in retroperitoneal sarcomas (n=1 trial), a randomized neoadjuvant cytotoxic chemotherapy trial in localized tumours (n=2 trials), 6 trials exploring targeted therapies in rare sarcoma subtypes in prospective randomized trials and in phase II proof of concept studies.
The project aimed at developing a specific and rigorous research framework and methodology to pursue these clinical trials testing specific strategies for rare sarcoma subtypes.

We wanted to implement:

1) randomized clinical trials in rare entities and subsets of sarcomas, i.e. retroperitoneal sarcomas, selected histotypes of soft tissue sarcomas in localized phase, as well as GCT of the bone.

2) single arm clinical trials to identify novel active treatment options in subsets (metastatic chondrosarcomas, Ewing, osteosarcomas) where no active systemic treatment is recognized in 2011. These will be proof of Concept clinical trials with inclusion criteria based on the molecular characterization of the tumour. The goals are to investigate innovative targeted treatments including first in class treatments.

A **rigorous methodology to characterize nosological entities**, based on centrally reviewed histological examination, with the development of a network review system. To establish reliable and cross validated techniques for the diagnosis of molecular alterations associated with rare sarcomas.

We aimed to develop a **homogenous translational research programs in all tumours treated within the clinical trials of** EuroSARC **project** to further refine their characterization and prognostication.

In addition, we wanted to analyse the **biological parameters correlated to treatment response in translational research programs** developed in the protocols testing neoadjuvant treatment, or in which rebiopsy is scheduled.

In a broader perspective, with this project, we intended to give to the European Union researchers, **a leading role worldwide for the development of novel treatment strategies in academic setting in sarcomas, and therefore in rare cancers**, with the aim of expanding later, beyond this project for subsequent trials this consortium worldwide, in particular to Asian countries and Russia, and also, importantly to make the tools and strategies available to other consortia addressing similarly rare tumour conditions, or rare subtypes of more frequent neoplastic diseases

Specific objectives: the clinical trials

The specific objectives pursued within EuroSARC were:

1) To develop and perform clinical trials **in homogenous histological and molecular entities.**
2) **To develop and perform prospective, multicentric, intergroup randomized multinational clinical trials** in rare sarcoma subtypes building on the merged networks of Conticanet and EuroBoNeT and their affiliated networks.
3) To design and implement rapidly **proof of Concept clinical trials targeting initial molecular alterations critical for the development of rare connective tissue tumours and sarcomas.**
4) To **develop common processes and methodology for centralized histological and molecular diagnosis of sarcomas** to be used as inclusion criteria for clinical trials developed through EuroSARC, and organized virtual review, central data collection, and virtual tumour banking (supported by the "ConticaBase", and the virtual tumour bank of EuroBoNeT (> 10000 cases)).
5) To **develop "harmonized" translational research programs in academic laboratories and with an SME partner** in each of the clinical research programs.
6) To **integrate pharmacodynamic markers** and translational research in the different protocols.
7) To **foster collaboration with Patients Advocacy Groups (PAG) and Networks**, at the stage of protocol initiation and patient accrual in particular, but also for dissemination and information purposes.
8) To **solve the administrative and legal barriers for international and intergroup cooperation**, to enable a rapid activation of the studies in the different national sites, at EU level, facilitating the required cooperation on an international level.
9) Finally, to **further improve patient outcome by improving the duration of survival and the quality of life of the patients.**

3. Description of the main results

The EuroSARC project and the specific clinical trials run under the auspices of the project are recorded in the following clinical trials registries:
-The **EuroSARC** project itself is registered in the French National Cancer Institute Register of Clinical Trials (Link: http://www.e-cancer.fr/recherche/recherche-clinique/registre-des-essais-cliniques/registre-des-essais-cliniques/details-etude?idFiche=2010).

- STRASS: "A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with Retroperitoneal sarcomas (RPS)" is registered in:
- EORTC registry under: EORTC-62092-22092-STBSG-ROG
- ClinicalTrials.gov under: Identifier: NCT01344018

- ISG-STS 10-01: Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadjuvant chemotherapy is registered in:
- EU Clinical Trials Register under EudraCT Number: 2010-023484-17
- ClinicalTrials.gov under identifier: NCT01710176
- registry of the Associazione Italiana di Oncologia Medica (AIOM) under no. 2010-023484-17

- LINES: Phase II trial of Linsitinib (anti-IGFR/IR) in patients with relapsed and/or refractory Ewing Sarcoma (LINES) is registered in:
- the EU Clinical Trials Register (Eudract no. 2012-000616-28);
- ClinicalTrials.gov with identifier: NCT02546544
- the ISRCTN Register under no. 94236001 (doi 10.1186/ISRCTN94236001).

- MEMOS: "A EuroSARC study of Mifamurtide in advanced osteosarcoma. A mechanistic study of mifamurtide (MTPPE) in patients with metastatic and/or recurrent osteosarcoma" is registered in
- the EU Clinical trials register (Eudract no. 2012-000615-84)
- ClinicalTrials.gov Identifier: NCT02441309

- COSYMO: A phase 2, single arm, multicentre trial evaluating the efficacy of the combination of PKI-587 and cyclophosphamide in the treatment of chondrosarcoma patients is registered in:
- EU Clinical Trials Register under EudraCT Number 2013-005155-32
- ClinicalTrials.gov under identifier: NCT02821507

The PAG and beneficiary SPAEN contributed to the analysis and dissemination of EuroSARC Clinical Trials and methods through its website.

3.1. The scientific management of the project (WP1)

The main objective of this work package was to set up an effective management and coordination framework/operating system for the consortium, to ensure the correct progress of the project towards its planned S&T objectives, based on a smooth and efficient communication and coordination of all partners involved.
The scientific coordination intervened at 3 different levels:
1) Overall scientific co-ordination at project level ensured by the Jean-Yvs Blay (UCBL)-coordinator, on the level of the whole project, assisted by Lyon Ingéniérie Projet (LIP).
2) The monitoring and co-ordination of the technical implementation of the project at the WP level was ensured by the WP leaders and CT leaders.

3) At country level, trials national committees were organised, and when relevant coordinated, the activities of the national group members, and thereby to profit of the geographical proximity and cooperation pre-existing habits among these neighbouring actors, to reinforce the action of the coordinator and WP leaders with respect to the S&T monitoring of the project. These "national groups" representatives also served as a relay of information (top-down and bottom-up) for their national groups, but also for other national groups not represented in the consortium (i.e.Sweden and Belgium).

3.2. The translational research program of EuroSARC (WP2)

Workpackage 2 aimed to support the Translational Research intermingled with the various investigator driven clinical trials that were part of some of the other work packages. This included the study of tumour tissue from patients to investigate whether we can predict which patients might benefit from a certain drug, or the study of cell lines generated from tumour tissue to investigate whether a certain drug, or combination of drugs, might be beneficial for a certain tumour type.

The deliverables were as follows:

1. Methodology for timely diagnostic and molecular assessment.
   Sarcomas are difficult for pathologists to diagnose as they are rare and >50 different histological subtypes exist, that have a different biological behaviour and therefore need different treatment. A subset of sarcomas has specific molecular changes that can be used by pathologists to come to the correct diagnosis. Protocols for molecular diagnostics were shared between partners.

2. Methodology for pharmacodynamics assessment of targets in tumour samples.
   A protocol was made and optimized to evaluate the expression of certain biomarkers in tumour tissue derived from patients included in some of EuroSARC's investigator driven clinical trials. At the end of the trial, the tissue samples were analysed for biomarker expression, and expression correlated to response, aiming to identify predictive biomarkers to predict which patients will benefit from the treatment. This work is still in progress and will continue for a final publication after the conclusion of the project.

3. Telepathology review of bone sarcomas in clinical trial.
   A network of reference pathologists from different centres of expertise reviewed the histology from patients submitted to the clinical trials. For the LINES trial, including patients with Ewing sarcoma, slides were scanned in the LUMC and digital slides were made available to the pathologists involved in EuroSARC. Using web access and teleconference a consensus diagnosis was reached for all cases.

4. Bone and soft tissue integrated biobank.
   At the start of EuroSARC, two different virtual biobanks / databases existed, each emerging from previous EU funded networks of excellence (Conticanet for soft tissue sarcomas and euroBONET for bone sarcomas). For EuroSARC, access to both databases was created through a common portal. The Conticanet database further developed into a warehouse hosting soft tissue, visceral (including GIST) and bone sarcomas with data on the patient, tumour, sample, pathology (including virtual slide access), molecular biology, treatment (including all chemotherapy lines) and follow-up.

5. The CINSARC expression profile of soft tissue sarcomas (Chibon Nat Med 2010) entered in the clinical trials of the EuroSARC portfolio. CINSARC is a gene expression signature which has been proven to a better prognostic factor than the histological grade in adult soft tissue sarcomas. The signature was compared to all molecular prognostic signatures available in the literature. Also, different techniques were used and compared [1]. Moreover, the method was further optimized to also work on archival formalin fixed paraffin embedded core needle biopsies[2] . Currently, now that inclusion in the clinical trials has recently finished and the tissue has been collected, about 200 samples are analysed for two clinical trials.

6. Biomarker investigation of soft tissue sarcomas entered in the clinical trials.
   Tumour tissue from patients with soft tissue sarcomas included in the clinical trials was collected and immunohistochemistry is performed according to the established and standardized protocol (see point 2). Results are correlated to clinical outcome and response to treatment, in order to identify predictive biomarkers for response.

7. Molecular profile of soft tissue sarcomas
   Two preliminary studies made in the context of EuroSARC showed that about 5% of sarcomas with a complex genomics have a recurrent TRIO fusion [3] with an impact on immunity/inflammation programs, and that an integrated approach of OMICS can separate undifferentiated pleomorphic sarcoma in 2 categories of tumours, INFLAMED and NON-INFLAMED tumours. RNA sequencing analysis on samples collected during the EuroSARC WP5 soft tissue sarcoma clinical trial is in progress in order to validate these preliminary results and to evaluate molecular pathways activated during chemotherapy.

In addition to the specific deliverables above, several preclinical studies were performed on cell lines to investigate whether a certain drug, or combination of drugs, might be beneficial for a certain tumour type, which is the basis for rational clinical trial design. To prepare for the MEMOS clinical trial, and to evaluate whether osteosarcomas are good candidates for immunotherapy, immune infiltrates were analysed in osteosarcoma [4]. Moreover, it was shown that specific immune cells, macrophages, inhibit human osteosarcoma cell growth after activation with the bacterial cell wall derivative liposomal muramyl tripeptide in combination with interferon-γ, which supported the rationale of the MEMOS clinical trial [5]. For another bone sarcoma, chondrosarcoma, previous preclinical studies have indicated that it would be beneficial to inhibit Bcl-2 family members, in order to repair the apoptotic machinery, thereby creating sensitivity to conventional chemotherapy. Through collaboration within EuroSARC it was found that among the Bcl-2 family member, Bcl-Xl was the most important for chondrosarcoma cell survival (submitted). Moreover, a cell line was generated from a rare chondrosarcoma subtype (mesenchymal chondrosarcoma) for which we confirmed that also in this rare subtype Bcl-2 inhibition was beneficial [6]. Through collaboration, we found the same for one of the soft tissue sarcomas, leiomyosarcoma [7]. Other targets that were explored in chondrosarcoma were mTOR (submitted) and survivin [8]. For Ewing sarcoma, the efficacy of trabectedin was shown to be increased when combined with either PARP inhibition or IGF inhibition [9,10]. For giant cell tumour of bone, cell lines were generated from patient's tissue that were confirmed to carry the characteristic H3F3A G34W mutation to enable future translational research (manuscript in preparation).

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3.3. Results on statistics, Data Handling and Analysis of the EuroSARC project (WP3)

The main purpose for this work-package within EuroSARC was to develop the statistical methodology in rare cancers, and in particular in the context of bone and soft tissue sarcoma. The rarity of patients eligible and able to enter clinical trials, reduces the statistical options based on frequency of events. A number of solutions were developed and utilized in EuroSARC, including the use of prior data incorporated into what are called Bayesian designed trials.

We provided and used innovative statistical designs for the development of trial protocols with classical or Bayesian-based approaches, and used these to facilitate rapid and efficient clinical trials for rare sarcoma subtypes. Another challenge was to incorporate genomic information from biopsy material. This was more challenging because two independent teams are normally required to develop the expertise. Unique to EuroSARC was our ability to develop trial teams that had integrated expertise, that bridged the integration and bioinformatic evaluation. Importantly, the LINES trial in Ewing sarcoma was pioneering in this regard, and anticipated to have impact in future developments of clinical trials in this context. Importantly, with EORTC and approved trials units, we could integrate PET_CT and imaging data into the data analysis, including independent validation of images with the informatics and clinical trial outcome data.

The sharing of expertise and the initiatives in EuroSARC were highly innovative and the data produced informative, leading to new trials that will contribute to practice changes and clinical opportunities for patients.

3.4. STRASS: a randomized clinical trial, a unique randomized trial in retroperitoneal sarcoma (WP4)

The goal of WP4 was to perform the EORTC clinical study 62092-22092 "A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with Retroperitoneal sarcomas (RPS)" (STRASS). The EORTC is the legal sponsor of this study.
Retroperitoneal (or pelvic) sarcoma is a very rare disease with 2.7 cases per 1 million persons. Surgery is the standard treatment of this cancer. The removal of tumour has to be as larger as possible to avoid the tumour coming back. This resection requires also removal of organ in contact with the sarcoma. For several decades, research has been performed about the possibility that adding radiotherapy to surgery could improve survival for this disease. This benefit has not been formally proven; this may have been due to outdated radiotherapy techniques that were used in the past and the fact that most studies had investigated radiotherapy after surgery that is less tolerable than pre-operative radiotherapy.

The purpose of this study was to investigate the benefit of preoperative radiotherapy using the modern techniques. The question of this study is that preoperative radiotherapy could reduce the risk of the tumour coming back. The results of this study, expect early 2019, will change the clinical practice worldwide.

The current standard of care for retroperitoneal sarcoma is large curative-intent surgery without additional treatment. Half of patients in the trial will receive preoperative radiotherapy before the surgery. This is not a standard treatment. These patients will receive radiotherapy 28 fractions of 1.8 Grays, once a day, five times per week, for about 6-7 weeks, to the areas where the retroperitoneal (pelvic) sarcoma was located.

This study is a phase III study. Only patients affected by retroperitoneal (or pelvic) sarcoma amenable to curative-intent surgery were considered eligible for this study. To find out the best way to treat patients, we need to compare different kinds of treatment. For this reason, patients will be split up into 2 groups and each group will receive a different treatment. The results will then be compared to determine which one is the most efficient. To make sure the groups are equally balanced, it is a computerized selection system that assigns each patient to a group. This process is called "randomization". Neither the patient nor the doctor can make this decision.
Patients were allocated to either group 1 or group 2 and had a '1 out of two' chance (50%) of receiving radiotherapy:

- Group 1: within 4 weeks following the randomization, patient will undergo surgery.

- Group 2: within 8 weeks following the randomization, radiotherapy will start. The disease status will be assessed. If the patient has benefited from radiotherapy then the patient will undergo surgery.

The EORTC activated the clinical study in some 40 clinical sites located in 14 countries. This is a very rare disease so the study has to be international covering Europe, US and Canada in order to recruit the needed patients in a timely manner. 266 patients were randomized by 30 institutions between January 2012 and April 2017. The study primary endpoints analysis has not started yet since we need data covering two years of follow-up after treatment. The analysis is planned for June 2019 when all the events should be recorded and the database validated.

3.5. A randomized clinical trial showing a survival advantage with neoadjuvant chemotherapy: the ISG-10-01 trial (WP5)

The specific aim of Workpackage 5 was to carry out a randomized, international, collaborative clinical trial comparing the effect on disease-free survival of full-dose anthracycline plus ifosfamide standard chemotherapy versus histotype-tailored chemotherapy within the context of an integrated, multimodal strategy (with surgery and radiotherapy) for high-risk localized soft tissue sarcomas (deeply seated, high grade, >5 cm) of the adult.
The work consisted of protocol development, study activation at the sites, preparation of the eCRFs, study implementation, trial coordination, data collection, data monitoring, statistical analysis and, as for all EuroSARC trials, pathology review and translational research. The full trial protocol was developed in compliance with International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), applicable legal requirements, and with the input of the Principal Investigator and all clinical partners.
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, was in charge of trial coordination. Patients were recruited in collaboration with Italian, Spanish, French, and Polish centres, referring to their respective national sarcoma groups. More than 40 centres were opened and 34 centres have been actively recruiting patients to ensure them treatment and follow-up according to ICH GCP.

According to the original study design, 3 cycles of chemotherapy were administered pre-operatively. There were five histological groups (representing 80% of the high-risk cases of STS), as follows:

1) undifferentiated pleomorphic sarcoma,
2) myxoid round cell liposarcoma (MRCLPS),
3) synovial sarcoma,
4) malignant peripheral nerve sheath tumour (MPNST),
5) leiomyosarcoma.

The histology-driven chemotherapy for these groups was, respectively:

1) gemcitabine plus docetaxel,
2) trabectedin,
3) high-dose ifosfamide,
4) ifosfamide plus etoposide,
5) gemcitabine plus dacarbazine.

Other histotypes, such as myxofibrosarcoma, unclassified spindle cell sarcoma, pleomorphic liposarcoma and pleomorphic rhabdomyosarcoma were also included and registered, but treated only by anthracycline plus ifosfamide standard chemotherapy. Radiotherapy was preferably delivered in the post-operative setting.
In May 2016, after the accrual of 287 randomized patients out of a total of 435 registered patients, a third Futility Analysis showed a statistically significant difference in terms of Relapse Free Survival and Overall Survival in favour of the control arm in all the histological subgroups, with the exception of the myxoid liposarcoma subgroup. As a result, the Independent Data Monitoring Committee recommended to stop the recruitment of new patients.

In the myxoid round cell liposarcoma subgroup, the third Futility Analysis supported the hypothesis of equivalent efficacy between the control arm and the experimental arm with trabectebin, while confirming the markedly reduced toxicity of trabectedin as compared to anthracycline plus ifosfamide. Given these results and given the strong rationale suggesting the efficacy of trabectedin in this histotype, an amendment was implemented to re-open the study and to continue randomization in this subgroup, albeit with a different statistical approach. According to the amended study, patients with a histological diagnosis of myxoid liposarcoma were to continue randomization to receive either standard chemotherapy (Arm A) or trabectedin (Arm B_2). Radiation therapy were to be delivered in the post-operative setting as appropriate. All patients with other histotypes were to be registered and treated by standard chemotherapy as in Arm A. Radiation therapy were also to be delivered in the pre- or post-operative setting as appropriate.

This trial, although originally designed to show the superiority of histology tailored chemotherapy over anthracycline plus ifosfamide standard chemotherapy, showed for the first time a statistically significant and clinically relevant difference in RFS and OS at $\geq$3 years in favour of anthracycline plus ifosfamide standard neoadjuvant chemotherapy, strongly supporting its efficacy. The results of the third interim analysis clearly need to be confirmed with a longer follow-up when the planned number of events for the final analysis has been reached. As of February 2017, 106 relapse events were observed (out of 130 estimated for the final analyses) and we believe that a further 24 events will occur in the next few months.

We expect to issue the final report on the clinical trial results in June 2019. The results of the interim analysis have been published by Gronchi A; Ferrari S Quagliuolo V; Martin Broto J; Lopez Pousa A; Grignani G; Basso U; Blay JY; Tendero O; Diaz Beveridge R; Ferraresi V; Lugowska I; Merlo DF; Fontana V; Marchesi E; Donati DM; Palassini E; Palmerini E; De Sanctis R; Morosi C; Stacchiotti S; Bagué S; Coindre JM; Dei Tos AP; Picci P; Bruzzi P and Casali PG. *Neoadjuvant Chemotherapy in High-risk Soft Tissue Sarcomas: 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)*. Lancet Oncol 2017;18:812-822

Specific landmarks of this trial are:

1) Final demonstration of the efficacy of standard chemotherapy in the commonest high-risk soft tissue sarcoma subtypes sited in an extremity or trunk wall.
2) Several translational research projects:
    a. Prospective validation of the prognostic/predictive value of the CINSARC genomic signature
    b. Prospective validation of the prognostic/predictive value of Multidrug Resistant Protein
    c. Prognostic/predictive value of TWIST expression
    d. Evaluation of the tumour immune contexture before and after the study chemotherapy

The results will be correlated with tumour radiological and pathological response to different chemotherapy regimens and patient outcomes.

3) Centralized radiological review of imaging performed before and after chemotherapy.
    a. evaluation of different conventional tumour response assessment (by measuring size and/ tumour density) and correlation of response and outcome.
    b. assessment of functional imaging, such as diffusion and perfusion MRI, as well as PET in a subgroup of patients to understand their role in assessing early response and its correlation with outcome.
4) Assessment of pathological response to chemotherapy and its correlation with radiological response and outcome, with particular reference to the differences among the histotypes included in the study. Pathologists of the Italian Sarcoma Group (ISG) and Spanish Sarcoma Group panel met twice to review the cases of synovial sarcomas and myxoid liposarcomas to highlight their differences.

In essence thanks to the financial support of the European Union to this purely academic study, we were able to advance substantially the knowledge on soft tissue sarcoma, change the state of the art and prepare the ground for testing the new compounds that are becoming available, after having shown activity in the metastatic setting.

Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017 Jun;18(6):812-822. doi: 0.1016/S1470-2045(17)30334-0. Epub 2017 May 9. Erratum in: Lancet Oncol. 2017 Jun;18(6):e301. PubMed PMID: 28499583.

3.6. Developing proof of concept clinical trials in Ewing sarcomas and chondrosarcomas: phase II studies (WP6)

Bone sarcoma: phase I/II histotype and molecular driven programme

The main purpose for this workpackage within EuroSARC was to develop clinical trials for Ewing sarcoma and chondrosarcoma testing novel drugs that are aimed at a specific tumour characteristic, so-called targeted therapies. Patients treated in these trials must have exhausted standard treatment options.

Status of the clinical trials

The **LINES** clinical trial has completed accrual and data analysis has been completed. The trial was a Phase II biomarker directed trial, involving biopsies before and after exposure to the tablet drug Linsitinib. The reason to perform the trial was to identify a rare responder to the target of this drug, the IGF pathway. It was known in previous trials that this target was important for a small subset of Ewing sarcoma patients that had exhausted previous treatments. In fact, some patients did very well with some of the previous therapies, yet it was unknown why such durable and excellent responses occurred. One patient out of sixteen responded well to linistinib, and this was proven with PET-CT scans. The biopsy samples were examined in great depth using RNA sequencing, a method to accurately determine the genes expressed in the tumour. Following analysis of the data, the patient who responded had Ewing sarcoma that had a different gene signature than the other patients. We have subsequently identified the molecules that account for these differences, and validated these data in the laboratory. This information, from a single patient, is now informing the rational design of a LINES2 trial, that combines two agents in order to induce a synergistic treatment for Ewing sarcoma.

The **COSYMO** trial is a phase II trial for patients with advanced or metastatic chondrosarcoma or myoid liposarcoma. Up to date no systemic treatment is available for this group of patients. In this trial patients are treated with oral sirolimus (mTOR inhibitor) in combination with cyclophosphamide (known chemotherapeutic agent). This combination was tested in prior trials in patients with different sarcoma types and in the laboratory in cell lines with promising results, which led to further testing in the COSYMO trial. A total of 105 patients are scheduled to enter the trial in 3 different cohorts: conventional chondrosarcoma, mesenchymal of dedifferentiated chondrosarcoma and myxoid liposarcoma. The trial primarily tests the efficacy of the drug by looking at time to progression of disease on treatment, furthermore analyses will be done on tumour material from patients before and after treatment in order to see the effect of the drug on the tumour and predict which patients might respond better. The trial commenced in the LUMC in Leiden The Netherlands in December 2014, and 6 more centres in Spain opened up in October 2017 (Barcelona, Sevilla, Valencia, Madrid). Since the trial opened, a total of 31 patients have been treated (23 with conventional chondrosarcoma, 7 with mesenchymal and dedifferentiated chondrosarcoma. The project is prospected to run until 2020, after which the results will be published.

3.7. Setting up clinical trials in partnership with pharma companies in osteosarcoma and giant cell tumours: the output (WP7)

Investigator driven clinical trials in osteosarcoma and giant cell tumour of bone

The main purpose for this workpackage within EuroSARC was to test two different novel drugs that have demonstrated activity in specific tumour types:

- Mifamurtide combined with ifosfamide in advanced osteosarcoma
- Denosumab in advanced giant cell tumour of bone (GCTB)

Status of the clinical trials

MEMOS was a Phase II trial investigator-initiated trial that aimed to evaluate if Mifamurtide is effective in patients with advanced osteosarcoma, and whether the patients that gain benefit can be identified from biomarkers in their tumour. The drug has a license for treatment after resection of osteosarcoma in patients with resectable and non-metastatic disease. This is an adjuvant treatment. The question for the MEMOS trial is weather the drug has activity to control advanced disease where it is visible on scans. The trial aimed to collect tumour material from biopsies and surgical material, so that biomarkers could be discovered that might help identify patients that might better respond to the drug, and when the drug is combined with conventional ifosfamide chemotherapy. The trial recruited 8 patients and was halted because of poor recruitment targets based on the funding period. Subsequent extension of funding was obtained from the EU commission but this was too late and the trial was unfortunately terminated.

The OCTO trials office reported delays to contracting and set up, and a number of sites reported delays in regulatory issues and set up time. This delayed the opening of the trial to late in the funding period.

The design was based on real time analysis based on a Bayesian randomised model and independent data monitoring committee. Three patients were recruited to arm A and C, and 2 to arm B between November 2014 to June 2016 from 5 centres in Europe. No data monitoring committee was completed as the recruitment target was not sufficient for first analysis. The data has been communicated, and a trial in France is being designed and will shortly open that addresses similar objectives (Osteo2016 study of the French Sarcoma Group).

Different denosumab related projects have been performed and started up within this workpackage. Initially it was intended to perform a study to test denosumab in patients with advanced GCTB after surgery, so-called adjuvant treatment. However, this study did not take place since the pharmaceutical company Amgen rejected to study protocol.

Instead of a clinical trial a data-collection was performed of patients with advanced GCTB who were treated with denosumab in different European reference centres (Warsaw Poland, Leiden The Netherlands, Bologna / Milan / Prato and Careggi-Firenze Italy, Birmingham United Kingdom), outside of clinical trials. Data was collected on a total of 138 patients and it was concluded that denosumab was effective in advanced and metastastic GCTB and in the neo-adjuvant setting (treatment pre-operatively). Furthermore, denosumab was well tolerated. The optimal duration of treatment is still unknown.

The REDUCE trial (EORTC-STBSG Study 1762), a study investigating maintenance therapy with denosumab in patients with GCTB who have previously been treated with denosumab for 12 months. Rationale for this trial is the fact that the optimal duration of treatment is unknown, and prolonged treatment may result in negative side-effects. A total of 100 patients will be treated with denosumab with longer intervals than the normal treatment protocol (once every 12 weeks instead of once every 4 weeks) as maintenance treatment. Primarily this trial will look at time to progression on treatment and negative side effects like osteonecrosis of the jaw. The study also involves collection of tumour samples in order to look for specific genetic mutations and tumour related proteins that can give us more information on the effects of denosumab on the tumour. The study protocol is currently reviewed and finalized, and the study is predicted to initiate at the end of 2018. The trial will run in the European EORTC centres.

Denosumab in giant cell rich tumours of bone is an LUMC-EuroSARC study which was set up after the successes of denosumab seen in classical GCTB. Giant cell rich tumours of bone are a heterogenous group of tumours including aneurysmal bone cysts (ABC) and giant cell granuloma's of the jaw. These tumours also have the distinct feature of giant cell presence as classical GCTB. Patients will be treated with denosumab 120mg once every 4 weeks until surgery

or progression of tumour. A total of 40 patients with ABCs and 20 with giant cell granuloma's of the jaw will be treated. Primarily this trial will look at avoidance of surgery due to the treatment, response according to radiological examinations and improvement of pain score and negative side effects like osteonecrosis of the jaw. The study also involves collection of tumour samples in order to look for specific genetic mutations and tumour related proteins that can give us more information on the effects of denosumab on the tumour.

Participating countries are LUMC Leiden and AMC Amsterdam in The Netherlands, Centre Léon Bérard in Lyon France, Istituto Rizolli in Bologna Italy and GEIS group in Spain. The study protocol was approved by the ethics committee in the Netherlands and has initiated in Leiden in June 2018. The other European centres will initiate after summer 2018.

4. Impact of the project

The results obtained during the EuroSARC project have had several important scientific, medical and economic impacts. Still the project is still going to produce important scientific information in the coming 2 to 5 years, from the ongoing translational research programs and also from the maturation of clinical trials which are still maturing for longer overall survival (ISG 1001), are still being too early for the primary endpoint analysis (STRASS), are still recruiting (Reduce, Cosymo). The translational research components of these programs are of course expecting the full accrual, complete material collection and analysis of the samples of the patients agreeing to participate to the trial.

We can distinguish here several different types of achievement from EuroSARC, even as if the different projects are still being active

4.1. Medical impact

1-The use of neoadjuvant chemotherapy, 3 courses for large tumours of high grade of the limbs is now strongly supported, for the first time, by a randomized clinical trial (ISG 1001).

In the latest version of the ESMO Guidelines, prepared with the ERN EURACAN, this is now a n option for the treatment of these patients, on the basis of this very trial

2- The utility or lack of utility of radiotherapy administered preoperatively in retroperitoneal sarcoma will be demonstrated and this will guide worldwide recommendations of practice, being the only trial reaching full accrual (a US trial stopped for poor accrual after 2 years and 20 patients included)

3- Optimal duration of denosumab in advanced GCTB will have been established in the first trial performed in an academic testing on this tumour, exploring a less intensive mode of treatment

4- IGF1R TKI linsitinib has limited activity in advanced Ewing sarcoma. The mechanisms of resistance to these agents in these diseases have been characterized and may serve for future development of this class of agents (Lines)

5-mTOR inhibitors activity, in combination with low dose ifosfamide, will be rigorously established in the first phase II study performed in a multinational setting (Cosymo trial)

6-The MEMOS trial showed the difficulty to perform Proof of concept clinical trials in patients with advanced osteosarcomas. While this trial stopped for poor accrual, it enabled the generation of novel statistical models for such trial and lead to identify important bottleneck for the development of these trials in this disease (accrual, heterogeneity of patient's presentation, difficulty of rebiopsies, complexity of centralization of referral in a single country). This will serve the development of future trials

4.2. Scientific impact

The EuroSARC project has enabled the maintenance and development of tumour collections linked with clinical datasets, developed under the Conticanet and EuroBoNeT networks which will be available for future clinical trial programs. Conticabase.org, conticagist.org, and Netsarc.org are the databases serving this purpose, including over 40000 samples and patients with sarcoma.

The EuroSARC project enable the elaboration of academic clinical trials with an innovative methodology, able to address questions in a randomized setting with a minimal number of patients, consistently with the epidemiology of these rare diseases (see publications, in chapter 4.2)

Translational research on biological specimens included 2 components in the program:

1) The investigation of novel targets in preclinical experiments performed of derived cell lines of tumour types investigated in these clinical research programs: an analysis of bcl-2, bcl-X-L family of proteins in chondrosarcomas lead to the conclusion that the bcl-2 pathway had a minimal role in this tumour type, thus preventing the development of a clinical trial anticipated in the 2011 version of the project. Conversely, the analysis of immune cell infiltration in these tumours showed the relevance and complexity of the interactions between tumour cells of bone osteosarcoma and chondrosarcomas and the immune system. This points to original strategies of immunotherapies, after the general failure of the first generations of immune checkpoint therapies in bone sarcomas. The

analysis of leiomyosarcoma tumours collected in the context of the clinical trials of EuroSARC contributed also to the whole genome sequencing programs developed within the ICGC on leiomyosarcoma, providing new potential targets for the treatment of these diseases.

2) The analysis of tumour samples of patients included in the 2 large randomized clinical trials, STRASS and ISG 10-01 is ongoing. It will include a screening of the CINSARC profile of these tumours as predictive factor or efficacy of neoadjuvant treatment. Analysis of the infiltrating cell profile, and of the expression of the mRNA in the whole tumour is also ongoing and will be correlated to this program. This program served a proof of concept for the following clinical trial exploring neoadjuvant chemotherapy for a longer duration in patients with high risk CINSARC profile. This trial initiated in France will be tentatively open to other partners of EuroSARC, this is an important achievement of the present program to enable collaborative research beyond the available funding.

4.3. Economic impact, and lessons for future clinical trials.

EuroSARC had and will have an obvious economic impact on the management of patient with sarcoma, having established further the role of central histological review, the value of neoadjuvant chemotherapy and radiotherapy in selected tumour histotypes and location. Six academic trials, with a strong translational research component, were accomplished with a limited budget and the strong contribution of the participating institution and their national research groups.

This project also brought important lessons on how to develop clinical trial with new drugs, and/or new strategies in rare tumours, taking in account the required collaborations of institutions, clinical research groups and pharma industry. The delay to obtain commitment (and/or finally withdrawal of commitment) from partners required an important agility of the EuroSARC partners, to maintain their visions and ambitions. In the future, such projects will be built with stronger commitments of the pharma partners, or will address pure academic questions using available technologies or drugs. It is interesting to note that other clinical trial involving the industry and associating the same academic partners took more than a decade from conception to final publication (see 4.2.), while the attrition rate of research programs is often superior to 50% in efficient cooperative groups. EuroSARC managed to develop 6 of the 7 trials which were anticipated after the preclinical proof of concept validation, in a period of 5 years (extended 78 months).

4.4. Communication activities of EuroSARC: details on the specific production of WP8

In this sub-chapter of the 4 section, we will describe the contribution of the WP8 of EuroSARC to the whole project, in charge of the dissemination and communication of the project activities and results.

The aim of EuroSARC dissemination and exploitation activities has been to tailor communication, dissemination and networking activities to the various identified target groups in order to convey appropriate information to the right stakeholders in the most appropriate form with a view to achieving the desired impact.

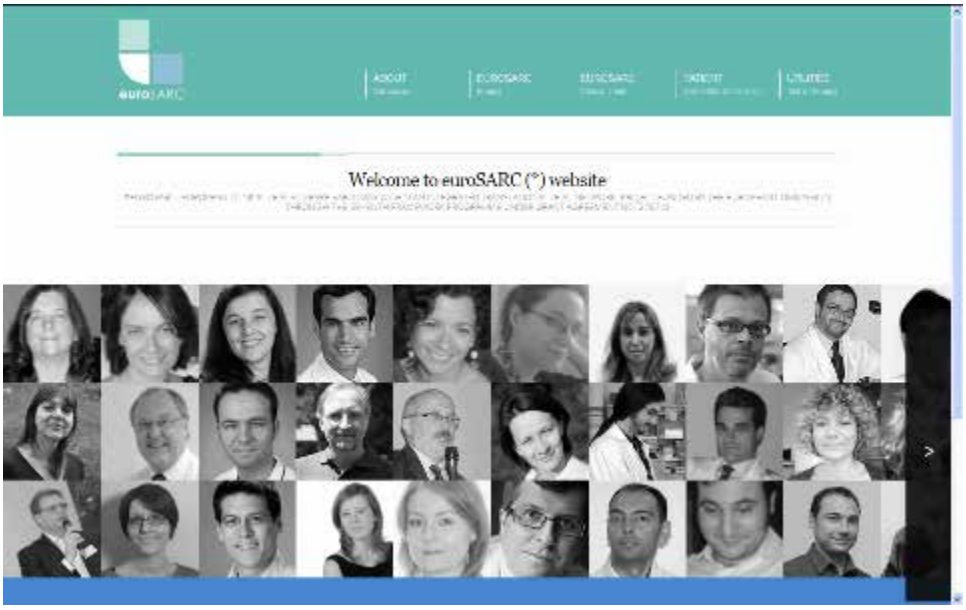
Over the course of the project, activities were undertaken to disseminate:
- overall project activities including scientific results, methodologies and tools;
- finalized studies;
- the status of clinical trials and translational studies;
- the contribution of patient advocacy groups (PAG) to the various project activities (protocol design and implementation, patient information, reported patient outcomes);
- the results achieved in terms of management of soft tissue sarcomas.

Dissemination activities were addressed to the following key stakeholders:
- clinicians, orthopaedists, surgeons, organ specialists and oncologists not participating in the trial studies;
- investigators of the clinical trials;
- patients and patient advocacy groups;
- trainee physicians and biologists, who took part in exchange visits, e.g. between LUMC and UOXF.BV;
- pharmaceutical and diagnostic companies;
- regulatory bodies, in relation to novel indications in EuroSARC clinical studies;
- regional and national health service bodies in relation to policies concerning access to approved and not-yet-approved agents for soft tissue sarcomas;
- other regional and national government bodies, as appropriate.

Below is the EuroSARC logo which appears on all dissemination material, accompanied by a declaration stating that the project is funded by the European Commission and an authorized version of the European flag. *

EuroSarc logo

EuroSARC website



A dedicated project website has been created to give visibility to the project and to facilitate internal communication among the EuroSARC partners. It is managed by ULSS9 and SPAEN and is accessible online at www.eurosarc.eu. It was transferred to a completely new WordPress platform between July and November 2014 to further modernize the website and, more importantly, to enable the partners to directly manage information input.

It has open and closed sections. The open section is designed to raise participation and awareness among target groups specifically candidate patients, patient advocacy groups, the scientific community, policy makers, industry and the public in general. A specific patient corner, developed in collaboration with SPAEN, has been included to ensure that scientific information is also provided in lay terms to facilitate patients' understanding about the different trials and

potential results. Besides basic information about the project objectives and activities, this section provides a description of each partner institute in the consortium and brief profiles of the researchers involved. It has a general news area and houses a section with links, to related patient advocacy groups and relevant association websites, institutions and industries. Website posts also include information on any related training courses and job opportunities.

All authorized partners can access the restricted area of the website by means of a personal log-in. This section houses contractual and internal management, documents, information on project meetings and logistics, the project handbook, project reports and deliverables, protocols, financial guidelines and PDFs of project-related publications. The SOPs produced by the Conticanet and EuroBoNeT Networks of Excellence, which joined forces to form the EuroSARC Consortium, have been uploaded in this section. Following authorization and after publication in peer-reviewed journals, each new SOP drawn up by the Consortium members is placed in the open section of the website. The contact section, providing information on and contact details of each participant involved in the project (phone, email, addresses, short CV, role in the project) is updated as necessary to facilitate direct, rapid and informal communications among collaborators and has helped to create and consolidate the EuroSARC network. The EuroSARC biobank can also be accessed through the website. The website content is regularly updated.

The EuroSARC Newsletter, providing information to the various target groups, is published on the website and automatically sent by e-mail to all interested parties. Anyone can sign up to the newsletter through the website.

Dissemination in scientific journals

Besides presentation of the results of the individual clinical trials, the aim of the scientific publications produced under the EuroSARC project was to address all identified stakeholders, from medical doctors, orthopaedists, surgeons, organ specialists, oncologists not participating in the trials, to epidemiologists and statisticians, patient advocacy groups, pharmaceutical and diagnostic companies, regulatory bodies and health and social policy makers. Publications cover topics ranging from the development of diagnostic, treatment and follow up guidelines, to compliance with guidelines, epidemiology, case reports, reviews, outcomes of treatment protocols, central pathology and cross validation, identification of novel nosological entities, characterisation of novel tumour and pharmacodynamic markers, patient management, statistical aspects and epidemiology.

Key publications referring specifically to the trials and their outcomes include:

1: Gelderblom H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2018 May;19(5):639-648. doi: 10.1016/S1470-2045(18)30143-8. Epub 2018 Mar 20. PubMed PMID: 29571946.

2: Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017 Jun;18(6):812-822. doi: 0.1016/S1470-2045(17)30334-0. Epub 2017 May 9. Erratum in: Lancet Oncol. 2017 Jun;18(6):e301. PubMed PMID: 28499583.

3: Dutton P, Love SB, Billingham L, Hassan AB. Analysis of phase II methodologies for single-arm clinical trials with multiple endpoints in rare cancers: An example in Ewing's sarcoma. Stat Methods Med Res. 2018 May;27(5):1451-1463. doi: 10.1177/0962280216662070. Epub 2016 Sep 1. PubMed PMID: 27587590; PubMed Central PMCID: PMC5863794.

4: Kager L, Whelan J, Dirksen U, et al. The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/Joint Workshop of EU Bone Sarcoma Translational Research Networks;
Vienna, Austria, September 24-25, 2015. Workshop Report. Clin Sarcoma Res. 2016 Mar 16;6:3. doi: 10.1186/s13569-016-0043-5. eCollection 2016. PubMed PMID: 27315524; PubMed Central PMCID: PMC4794847.

5: Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST):
a randomised, multicentre, open-label phase 2 trial. Lancet Oncol. 2016 May;17(5):632-41. doi: 10.1016/S1470-2045(16)00075-9. Epub 2016 Apr 5. PubMed PMID: 27068858.

6: Blay JY, Coindre JM, Ducimetière F, Ray-Coquard I. The value of research collaborations and consortia in rare cancers. Lancet Oncol. 2016 Feb;17(2):e62-e69. doi: 10.1016/S1470-2045(15)00388-5. Review. PubMed PMID: 26868355.

7. 2: van Maldegem AM, Bhosale A, Gelderblom HJ, Hogendoorn PC, Hassan AB. Comprehensive analysis of published phase I/II clinical trials between 1990-2010 in osteosarcoma and Ewing sarcoma confirms limited outcomes and need for translational investment. Clin Sarcoma Res. 2012 Jan 27;2(1):5. doi: 10.1186/2045-3329-2-5. PubMed PMID: 22587841; PubMed Central PMCID: PMC3351714.
- Outcomes from a mechanistic study of Mifamurtide (MTP-PE) in patients with metastatic and/or recurrent osteosarcoma (EuroSarc-MEMOS). Dutton P et al. (In preparation)

- REST determines sensitivity to dual kinase (IR/IGF1R) inhibitor in Ewing Sarcoma; translational outcomes from a Bayesian Phase II biomarker trial of Linsitinib (OSI-906) in relapsed or refractory Ewing sarcoma (EuroSarc-EORTC-1225-OCTO-038). Barnes et al, (submitted).

Among the articles on statistical aspects of the project are: Analysis of phase II methodologies for single-arm clinical trials with multiple endpoints in rare cancers: An example in Ewing's sarcoma. Dutton P et al, Methods Med Res, 27(5):1451-1463, 2018. doi: 10.1177/0962280216662070 and the statistical package, EurosarcBayes: Bayesian single arm sample size calculation software statistical package which is disseminated in free access by the same team at UOXF.BV.

Papers aimed at a policy makers and funding agencies include, The value of research collaborations and consortia in rare cancers. Blay JY, Coindre JM, Ducimetière F, Ray Coquard I. 2016. Lancet Oncol Feb 17(2): e62-9.

The target of Working to improve the management of sarcoma patients across Europe: a policy checklist. Kasper B, et al. 2018. BMC Cancer. doi: 10.1186/s12885-018-4320-y. PMID: 29661168 was patients and patient advocacy groups.

Doctoral these include: Chondrosarcoma models: understanding chemoresistance mechanisms for use in targeted treatment, by Van Oosterwijk JG (2013, LUMC) and the pathogenesis of Ewing sarcoma. Implications of mesenchymal stem cells and new therapeutic strategies, by Monteiro Amaral AT (2014, CIC).

EuroSARC publications also include clinical practice guidelines, specified in the chapter below, targeted at healthcare providers in general and medical oncologists in particular.

Clinical practice guidelines

Expert members of the EuroSARC Consortium contributed to drawing up, “The euroRare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper” Casali PG, Bruzzi P, Bogaerts J, and. Blay JY, on behalf of the Rare Cancers Europe (RCE) Consensus Panel. Ann Oncol. 2015 Feb; 26(2): 300–306. doi: 10.1093/annonc/mdu459

During the life of the project, the following Clinical Practice Guideline revisions were drawn up by the ESMO/European Sarcoma Network Working Group, and published in Annals of Oncology on 1 September, 2014:

- Gastrointestinal stromal tumours (GIST): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (https://doi.org/10.1093/annonc/mdu255).

- Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (https://doi.org/10.1093/annonc/mdu254)

- Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. (https://doi.org/10.1093/annonc/mdu256)

Updated Clinical Practice Guidelines on GIST and soft tissue and visceral sarcomas were subsequently produced by the ESMO Guidelines Committee in partnership with EURACAN, and published in Annals of Oncology on 28 May, 2018. The aim of the guidelines is to provide the standard approach to diagnosis, treatment and survivorship. Recommended interventions are intended to correspond to the 'standard' approaches, according to current consensus among the European multidisciplinary sarcoma community of experts, and in keeping with the patient-centred approach. Revised guidelines have been published as follows:

- Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up" (doi: 10.1093/annonc/mdy095).

These revised guidelines include new treatment algorithms for the management of local/locoregional and advanced/metastatic GIST.

- Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up" (doi:10.1093/annonc/mdy096).

These guidelines provide new recommendations relating to therapy with olaratumab and with eribulin.

The majority of the investigators in the EuroSARC consortium participated as experts in the establishment of these clinical practice guidelines and in their amendment and adaptation to novel scientific information generated by the EuroSARC clinical trials.

Clinical Sarcoma Research

The open-access journal, Clinical Sarcoma Research has been consolidated as the EuroSARC consortium's official journal and will remain as part of the EuroSARC legacy. The journal was originally founded by the EuroBoNeT and Conticanet networks to publish clinical and research material in the field of sarcomas, including negative results and material not published elsewhere due to sample sizes and the preliminary nature of some results. Accordingly, the journal provides an important, otherwise unavailable service to the sarcoma community.

Papers have also been published in the official journal of partner EORTC: European Journal of Cancer.

Presentations at medical and scientific events

EuroSARC Consortium members have presented abundant information on the project at key annual congresses and other speciality meetings in Europe, North America, Asia and Australia. These include ASCO, CTOS, ECCO, ESMO, ESSO, ESTRO, GSF-GETO, NCRI, SIAPEC-IAP, USCAP. Presentations have been given on the EuroSARC project at the annual SPAEN meetings, providing information for patient advocacy groups. Popular press and media releases have been published in various European countries.

5. Conclusion: the future after EuroSARC

The EuroSARC project gathered academic partners who developed innovative and practice changing clinical research programs on sarcomas, models of rare cancers. It was built of the foundations of Conticanet and EuroBoNeT. Its legacy is going to be extended beyond the formal existence of the project in the years to come, in particular with:

- Databases and tumours dedicated to these rare tumours
- Methodologies of work for clinical and translational research on rare tumours applied to forthcoming research programs in national groups and EORTC
- Follow-up clinical trials addressing the next generation of questions in neoadjuvant setting (chemotherapy for high risk tumours, for retroperitoneal sarcoma
- Updated clinical practice guidelines in sarcomas, in the ESMO and EURACAN networks
- Contribution to the development of the EURACAN ERN program.

The EuroSARC project served therefore the community of patients affected with sarcoma and rare cancers beyond the duration of its period of activity. All EuroSARC researchers and members wish to thank patients and patient's advocacy group for their contribution during the project and of course the FP7 program with whom the interactions were of the highest quality, allowing for the flexibility which served best the ambitious objectives of the whole program.