

Prof. Jean-Yves BLAY

Professor of Medical Oncology,
Lyon

jean-yves.blay@lyon.unicancer.fr



Dr. Axel LE CESNE

Doctor of Medical Oncology,
Villejuif

axel.lecesne@gustaveroussy.fr



Prof. Jean-Michel COINDRE

Professor of Pathology, Bordeaux

j.coindre@bordeaux.unicancer.fr

OVERVIEW

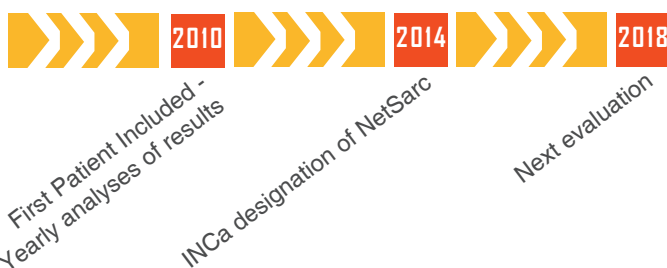
AT A GLANCE

- > Oncology
- > Sarcomas, Gastrointestinal Stromal Tumor (GIST), desmoid tumor, connective tumors
- > Coordinated by a three-head reference center
- > Centre Léon Bérard Lyon sponsorship
- > Funded by INCa & DGOS
- > Key words: sarcoma, management indicators, expert center, relapse, survival, clinical trial, real life, translational research

KEY FACTS & FIGURES

- > Registrations started in January 2010
- > 5,000 enrolled patients per year
- > Currently 31,206 enrolled patients since January 2010 in the RREPS/NetSarc database
- > Follow-up period: >3 years (unlimited)
- > National coverage: 29 regional centers of expertise
- > Biobank through the Conticabase

Through a real-time integration of patients into a database, Netsarc aims to follow all patients suffering from sarcomas, GIST, desmoid tumor, or connective tumors in a 65 millions inhabitant country in order to generate a real-time national and regional descriptive data providing national indicators of patient care and equal access, providing innovative treatments to patients, improving knowledge of rare tumors, and investigating the link between sarcomas and genetics.



Positioning

- > The only cohort on sarcoma in the world
- > Will be involved in the European Reference Network program
- > In support for other national epidemiologic studies:
 - >> International case control study (ISKS) and biobank about genetic factors and sarcoma National study with InVS about professional liver angiosarcoma (Angi-He)
 - >> Geographical study of national healthcare access
- > Partnerships with private companies on-going

LEADERSHIP

NetSarc organization is centered on a tripartite national reference center of expertise located in Lyon, Paris and Bordeaux, linked to a national network of expert centers. This 3 renown clinicians have been committed in the field for 25 years.

Prof. Jean-Yves BLAY, Professor of medical oncology

- General Director of the comprehensive cancer center of Lyon, the Centre Léon Bérard
- President of the French Sarcoma Group (GSF-GETO)
- Head of the LYRIC (French NCI Integrated site of Innovative Research on Cancer)
- Director of the European network EUROSARC
- Past President of EORTC (2009-2012)
- Past Director of the European CONTICANET Network of excellence
- Member of several scientific societies including 5 Cancer centers in France, the Protocol Review Committee of EORTC and the European Union Committee of Experts on Rare Diseases (EUCERD)
- Over 500 peer-reviewed articles, in addition to over 200 abstracts and book chapters

Dr. Axel LE CESNE, Doctor of medical Oncology

- Head of Sarcoma committee, Gustave Roussy Institute, Villejuif
- Co-President of the French Sarcoma Group (GSF-GETO)
- Vice-President of the patient association "Info Sarcomes" and co-founder of the patient association "Ensemble contre le GIST"

- Chairman of Systemic Treatment of the EORTC Soft Tissue and Bone Sarcoma Group
- Founding member of World Sarcoma Network
- Member of several societies including the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and the Connective Tissue Oncology Society (CTOS)
- Over 230 research articles in the field of sarcoma, lung and breast cancer, immunotherapy and gene Ttherapy

Prof. Jean-Michel COINDRE, Professor of Pathology

- University of Bordeaux, Inserm U916, Bergonié Institute
- Head of RRePS (French reference network for histological review of sarcomas, GIST and desmoid) and BCB sarcomas (multidisciplinary clinical and research platform)
- European coordinator of sarcomas and GIST databases
- Coordinator of the national post-graduate teaching on soft tissue tumors
- Member of International Academy of Pathology, International Society of Bone and Soft Tissue Pathology and Connective Tissue Oncology Society
- Over 360 peer-reviewed articles in addition to book chapters

SCIENTIFIC NETWORK & MANAGEMENT

■ **CONTICANET** is a Network of Excellence funded by the FP6. CONTICANET is working to harmonize research projects, by developing joint research activities, establishing standard operating procedures and distributing databases and tissue banks

■ **EUROSARC** (European Clinical trials in Rare Sarcomas within an integrated translational trial network), funded by FP7, overall objectives is to design, structure and implement 9 innovative investigators driven clinical trials of different scales, on a multinational level, evaluating novel treatment strategies

■ **Both projects were completed from 2010 by the national database call NetSarc, and RRePS**, which gather clinical information for all patients with sarcomas in France, and review all sarcoma samples into a network of pathologist experts, respectively

■ NetSarc closely collaborates with the integrated **ImmunoSarc** Research Program aiming at interpreting sarcoma biology to better understand the immune response in cancer. ImmunoSarc investigators include:

- > **Torsten O. Nielsen:** Professor of pathology and laboratory medicine at the University of British Columbia and a clinician-scientist and musculoskeletal consultant pathologist based at the Vancouver Coastal Health Research Institute and the British Columbia Cancer Agency
- > **Elizabeth Demicco:** Assistant professor of pathology at the Mount Sinai Hospital in New York City
- > **Robert Maki:** Professor of medicine, pediatrics, and orthopaedics at Mount Sinai Hospital in New York City
- > **David Thomas:** Director of the Kinghorn Cancer Centre and head of the cancer division at the Garvan Institute of Medical Research in Sydney, Australia
- > **Jean-Yves Blay**

A group of pathologists (RRePS) and clinicians (NetSarc) has preferentially worked on the study of connective tissue and soft tissue sarcomas in adults. Thanks to their perseverance, major advances have been achieved, both technically and organizationally. Two networks have been set-up in order to enable systematic double-reading of all rare malignant tumors and lymphomas that is essential for diagnostic confirmation

Clinical network: NetSarc

Prof. Jean-Yves BLAY
Dr. Axel LE CESNE
Dr. Antoine ITALIANO
Prof. François GOUIN
Dr. Nicolas PENEL
Prof. Philippe ANRACT
Prof. Florence DUFFAUD

Dr. Maria RIOS
Dr. Emmanuelle BOMPAS
Dr. Sophie PIPERNO-NEUMANN
Prof. François BERTUCCI
Prof. Céleste LEBBE
And 17 other expert centers (see more at: www.netsarc.org)

Pathology network: RRePS

Prof. Jean-Michel COINDRE
Dr. Dominique RANCHERE-VINCE
Dr. Philippe TERRIER
Prof. Gonzague DE PINIEUX
Dr. Anne MOREAU
Prof. Philippe ROCHAIX
And 15 other expert centers (see more at: www.rreps.org)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Clinical Reference Network for Sarcoma-GIST-Desmoid Tumors NetSarc pursues five objectives: the definition of recommendations for clinical management, organization of referral resources for patient management, coordination of research, participation in epidemiological surveillance and organization of a structured care pathway for patients and for physicians training and continuing education
- To meet these network objectives, NetSarc has built a clinical database aiming at making available an exhaustive epidemiological, clinical and disease-specific data collection of sarcoma patients in France since 2010
- Secondary objectives of these database are:
 - > Assessment of outcomes in relation to practice
 - > Descriptive approaches of rare subsets
 - > Molecular characterization
 - > Translational research programs
 - > Medico economic studies

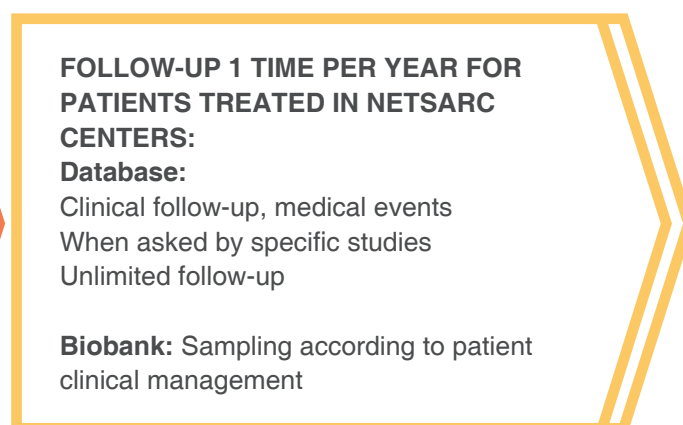
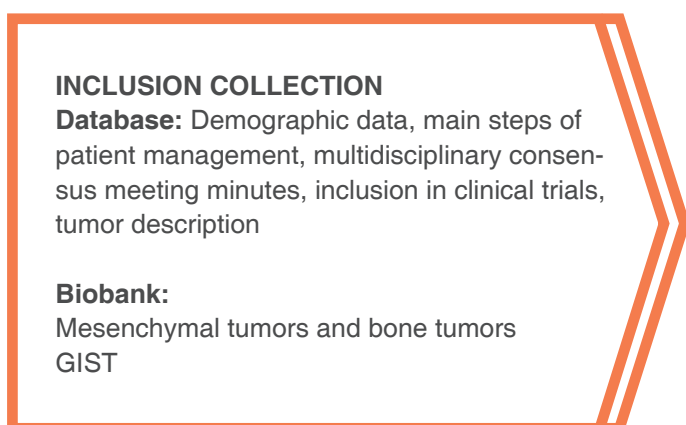
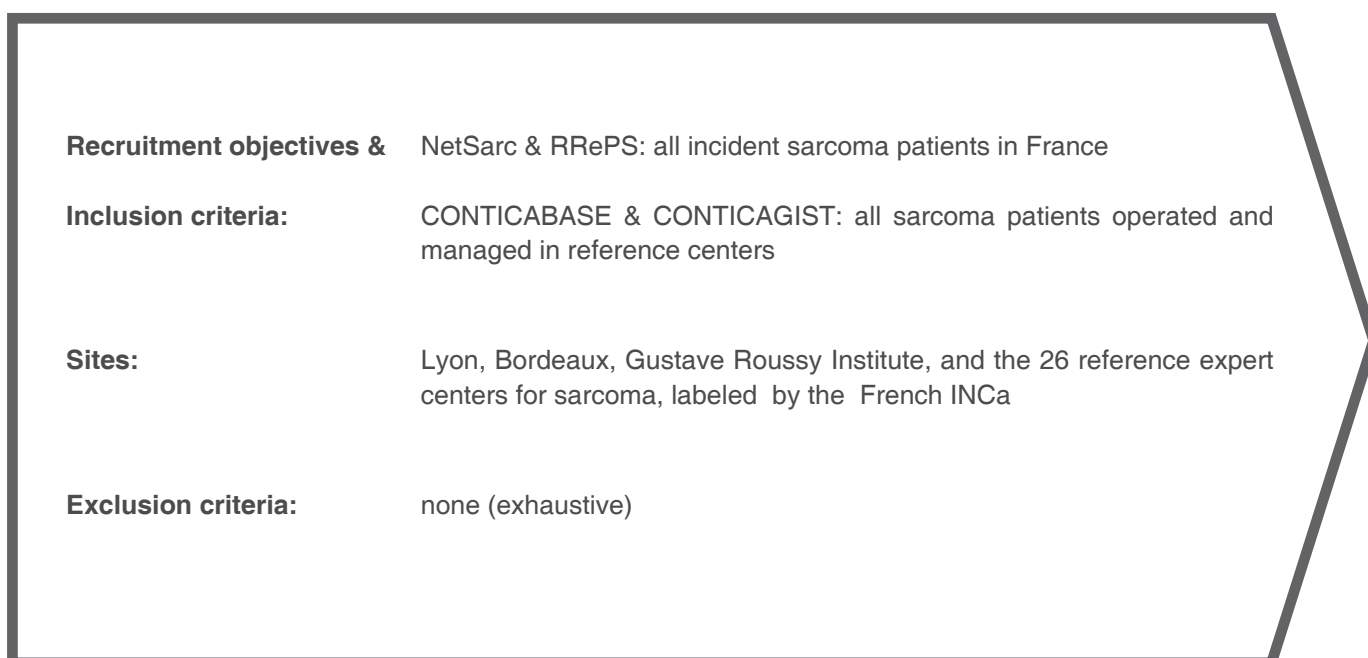
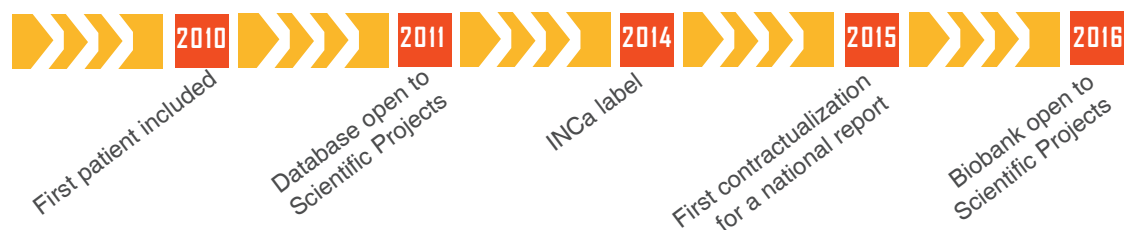
INNOVATIVE SCIENTIFIC FEATURES

- The certified NetSarc network offers a structured approach to make a formal diagnosis of soft tissue sarcoma as well as facilitate access to the necessary pathology, imaging and clinical tools to characterize the tumor, assess its scope, and arrange for appropriate medical and surgical treatment in a specialized center
- NetSarc database collects all cases discussed in the 29 expert centers
- The prospective collection of clinical data, expert decision and patient follow-up is implemented in the national database (40 items)

METHODOLOGY QUALITY

- OVH, an independent company that is specialised in web hosting, hosting the database and providing protection against direct attack or massive data theft (under ISO 27001 and SOC certifications)
- All personal data are anonymized
- Data management quality program is organized through a personal training, a duplicate search tool before patient inclusion, a standardized clinical and anatomic pathology report form and standard operating procedures

DESIGN, METHODOLOGY & TIMELINE



DATABASE & BIOBANK CONTENTS

DATABASE

Database was set up by the Clinical Reference Network for Sarcomas-GIST-Desmoids (NetSarc) which is a **group of practitioners** certified for their expertise by the INCa. NetSarc operates in coordination with RRePS, the Reference Network for Pathology of Soft Tissue-GIST-Desmoid-Visceral Sarcomas which is a **grouping of expert pathologists** certified by INCa aiming at offering a second reading of any new cases of soft tissue sarcoma or visceral sarcoma

NetSarc & RRePS databases:

- > **Demographic (shared):** date of birth, initial, gender, current geographic residence, antecedents
- > **Tumor (shared):** location, size, depth of invasion
- > **Tumor sample description (from RRePS):** case origin, sample type, sample date, diagnosis established by anatomic pathology structure, by the national reference center, by the coordination site, tumor immunohistochemistry, tumor molecular biology, tumor FISH exam
- > **Main steps of patient management (from NetSarc):** tumor type, diagnosis, date of the first diagnosis, stages of cancer, imaging data before resection, biopsy, place and quality of surgery
- > **Multidisciplinary consensus meeting (from NetSarc):** date, expert center, timing, decisions
- > **Inclusion in clinical trials (from NetSarc):** date, name of clinical trial
- > **Relapse, date of death, date of last follow-up (from NetSarc)**

NetSarc database is closely connected to the research platform “BCB Sarcomes”. This platform regroups the following databases:

- > **The CONTICABASE database and tumor bank:** This database contains information describing the tumor molecular typing, treatment and follow-up as well as tumor sample availability and molecular biology analyses for mesenchymal tumors except GIST and bone tumors
- > **The CONTICAGIST database and tumor bank** contain information describing the tumor molecular typing, treatment and follow-up as well as tumor sample availability and molecular biology analyses for GIST patients

Patients in CONTICABASE and CONTICAGIST come from NetSarc & RRePS since 2010: the inclusion criteria to be included in those databases are treated in a reference center

BIOBANK

Originality

- > **Size of the cohort (nationwide):** a large scale biobank with 6,000 frozen tumors described by around 170 parameters
- > **Central path review and follow-up**
- > The biobank belongs to the French Sarcoma Group (GSF-GETO), a well placed and visible network on an international level
- > Member of an **international network** as a part of the EU Conticanet Network of Excellence, project aiming to establish a virtual annotated tumor bank on mesenchymal tumors

Scientific objective

- > Biobank aims to provide a clinical description and prognosis of **homogeneous group of tumors** and to build virtual tumor bank
- > Biobank is associated with research projects: Radio-induced sarcoma (SARI study ; DNA, RNA, RNAseq), International Cancer Genome Consortium program (ICGC leiomyosarcoma ; comprehensive description of genomic, transcriptomic and epigenomic changes), etc.

Samples

- > The collections currently registered in databases cover:
 - >> frozen: 6,000 tumors
 - >> paraffin-embedded: 9,000 tumors
 - >> tissue micro-array blocks: 1,430 tumors
 - >> **products derived from frozen tumors (DNA and RNA), frozen normal tissues, preserved peripheral blood and cell lines generated from tumors**

Associated resources

- > Specific technological platforms: virtual slide server from University of Bordeaux 2 & Genomic platform from Curie Institute

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

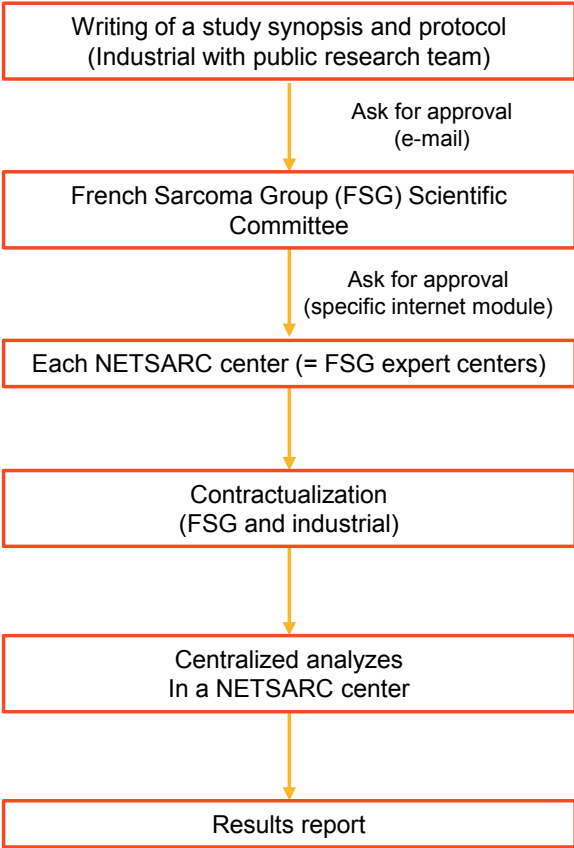
- The tumors (frozen and paraffin tissues) are locally stored in the participating centers
- In daily clinical practice, each participating centre collects sarcoma, GIST and desmoid tissue samples to be examined macroscopically by the pathologist for histological diagnosis and prognosis. If enough material is left over, the pathologist selects samples for the tumor banking
- Samples are rapidly frozen and stored at -80°C
- Conticabase and ConticaGist serve as virtual tumor banks
- Samples belong to the center. Standardized methods of sample treatments (Standard Operating Procedure) are available in each center

SPECIFICATIONS

- First sampling at initial diagnosis
- Sampling occurrence according to surgical excision at diagnosis and/or relapse
- Responsible for the biobank: Prof. JM Coindre and Dr. A Neuville (associated to a manager of each biobank site)
- Protocol for the biological sample collection is available from each site, and consistent across sites
- **Tumor biobanking is associated to two databases** containing information describing the tumor, treatment and follow-up as well as tumor sample availability and molecular biology analyses:
 - > The CONTICABASE database for mesenchymal tumors except GIST and bone tumors
 - > The CONTICAGIST database for GIST patients
- **Label of quality:**
 - > Standardized procedures related to the collection, preparation, storage and delivery of biological samples
 - > Certification in progress (NFS 96-900 AFNOR) for a network of accredited biological resources centers (CRB)
- Biological samples available in 2016

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	No. of subjects who have been sampled
CONTICANET: mesenchymal tumors except GIST and bone tumors	
Primary tumors	15,471
Metastasis	4,310
Local recurrences	4,249
Paraffin	20,861
Frozen tissues	8,589
Chemotherapy lines	4,661
Cell lines	25
Immuno-Histochemistry	13,666
Molecular cytogenetics	4,494
Blood	760
CONTIGAGIST: GIST	
Paraffin-embedded tumors	2,482
Frozen tumors	413



BIOBANK SAMPLE ACCESS MODALITIES

- A **document** specifying rules for access and use of data and material in CONTICAGIST and CONTICABASE exists
- Biological samples **are accessible** to public research teams. Private research teams need to collaborate with a public research team to conduct a project based on tumor bank
- Each access to biospecimen is granted on the **acceptation of the research project proposal submitted to the scientific committee**
- To access biological samples, the industrial research team need to fill out a **detailed protocol**
- Biological sample **transfer is not allowed**
- Biological samples **are not shareable with a foreign company**

BIOLOGICAL SAMPLE ANALYSES

- Analysis are performed by a molecular biology platform of the NetSarc/French Sarcoma Group center
- All diagnosis are systematically reviewed and validated by RRePS expert pathologists
- Biological sample analysis-derived data are accessible to the local centers, the researchers, and the patient, and through contract with private/industrial teams

COST

- A financial estimation of the biological samples is in progress
- A price list of the cost of each biological sample is not yet available (depending on each center)

RESEARCH COLLABORATION OPPORTUNITIES

Phase I Pre-clinical Proof of concept
Phase II
Phase III
Phase IV Product approval

Translational research

- > Identify sarcomas specific biomarker (such as specific site methylation) predictive for both metastasis-free and overall survival which may be relevant for identifying patients likely to derive greater benefit from treatment
- > Investigate the prognostic value of expressing factors in a cohort of patients with localized GIST, sarcomas, GIST, desmoid tumor, or connective tumors
- > Assess the genetic profiling to identify prognostic factors of soft-tissue leiomyosarcomas and their correlation with molecular profile

Clinical development

- > Develop technologic innovation (surgery technicity, nanoparticles, sequencing, robotic, per operating imaging...)
- > Assess the added value of a clinical practice in a real-life cohort of adult soft tissue sarcoma patients treated (or not)
- > Perform feasibility studies for randomized clinical trial design
- > Analyze management and outcome in a large cohort of patients with advanced sarcomas, considering main histological subtypes separately

Outcomes research

- > Identify factors associated with a perspective of prolonged survival or a better outcome in non-resected patients
- > Assess the adherence to adult sarcoma management guidelines across France
- > Investigate the added value of tumoural genomic profiles to conventional clinico-biological factors to predict progression-free survival and overall survival in patients with sarcoma
- > Describe the epidemiology of soft tissue sarcoma:
 - >> Socio-demographic characteristics
 - >> Percentage of metastatic STS at diagnosis
 - >> Percentage benefiting from a double anapath reading

BIBLIOGRAPHY

Translational research

- > AL Peille *et al.* **Prognostic value of PLAGL1-specific CpG site methylation in soft-tissue sarcomas.** *PLoS One.* 2013 Nov 15; 8(11):e80741 (100)
- > S Rusakiewicz *et al.* **Immune infiltrates are prognostic factors in localized gastrointestinal stromal tumors.** *Cancer Res.* 2013 Jun 15; 73(12):3499-510
- > A Italiano *et al.* **Genetic profiling identifies two classes of soft-tissue leiomyosarcomas with distinct clinical characteristics.** *Clin Cancer Res.* 2013 Mar 1; 19(5):1190-6 (73)

Clinical development

- > PG Casali *et al.* **Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial.** *J Clin Oncol.* 2015 Nov 16. pii: JCO.2015.62.4304
- > P Pautier *et al.* **Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial.** *Lancet Oncol.* 2015 Apr; 16(4):457-64.
- > S Taieb *et al.* **Comparison of response evaluation criteria in solid tumours and Choi criteria for response evaluation in patients with advanced soft tissue sarcoma treated with trabectedin: a retrospective analysis.** *Eur J Cancer.* 2015 Jan; 51(2):202-9

Medical evaluation

- > M Toulmonde *et al.* **Retroperitoneal sarcomas: patterns of care in advanced stages, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group.** *Ann Oncol.* 2014 Mar; 25(3):730-4 (586)
- > N Isambert *et al.* **Primary cardiac sarcomas: a retrospective study of the French Sarcoma Group.** *Eur J Cancer.* 2014 Jan; 50(1):128-36 (124)
- > S Mathoulin-Pélissier *et al.* **Adherence to consensus-based diagnosis and treatment guidelines in adult soft-tissue sarcoma patients: a French prospective population-based study.** *Ann Oncol.* 2014 Jan; 25(1):225-31. doi: 10.1093/annonc/M.D.t407. Epub 2013 Nov 26

Pharmacoepidemiologic study

- > JM Coindre *et al.* **Management of soft tissue sarcoma in France – A retrospective analysis of the French clinical biological sarcoma database (GSF-GETO).** ISPOR 18th Annual European Congress - 7-11 November 2015 - Milan, Italy - PRM64
- > A Patrikidou *et al.* **Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group.** *Eur J Cancer.* 2016 Jan; 52:173-80