EPSSG ASSOCIATION

THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP

ANNUAL REPORT 2019

THE EPSSG ASSOCIATION

The European Paediatric Soft tissue sarcoma Study Group (EpSSG) is an international organisation for professionals devoted to the care and treatment of children and young people with cancers known as soft tissue sarcoma (STS). This includes the most common STS, rhabdomyosarcoma (RMS), and a wide range of other cancers known collectively, as Non Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS).

The legal entity for EpSSG activities is the EpSSG Association. This exists to promote and manage clinical trials, encourage and facilitate clinical and basic science research, foster optimal standards of care, organise educational meetings for its members and other professionals, and advocate for patients with STS.

It collaborates with other similar groups in Europe, North America and elsewhere.

EpSSG has its administrative and legal home in Padua, Italy. It is managed by an elected board, and its membership is open, by application, to professionals who have an interest in the research or treatment of these diseases when they occur in children, teenagers and young adults.

This report summarises the main EpSSG activities that have been developed in 2019. Importantly, we have had the opportunity to welcome parents of sarcoma patients to collaborate with us and support the development of our activities since 2016.

Further information is available on the EpSSG website: www.epssgassociation.it

EpSSG Board (By dr Julia Daragjati)

Prof. Gianni Bisogno	•Chairman - Padua, Italy
Dr. Hans Merks	•Treasurer, Chair Elect- Utrecht, The Netherlands
Dr. Julia Chisholm	•Sutton, UK
Dr. Soledad Gallego	•Barcelona, Spain
Dr. Heidi Glosli	•Oslo, Norway
Dr. Daniel Orbach	•Paris, France
Dr. Veronique Minard-colin	•Paris, France
Dr. Michela Casanova	•Milan, Italy
Dr. Henry Mandeville	•London, UK
Dr. Julia Daragjati	•Secretary, Italy

Board meetings were held on the following dates in 2019:
May 23rd and 24th in Prague, March 18th in London, October 24th in Lyon and December 5th, 7th in London. TCs were held on: February 6th, August 20th.

Dr. Hans Merks, board member and Association's co-founder became the new chair replacing Prof. Gianni Bisogno who ended his term this December.

Gianni served on the board for six years.

The ceremony was concluded when the president handed back the EpSSG hammer to the New chair. Prof. Gianni Bisogno remains in the board for another year as Past President, but without the right of voting.

Three dedicated and long-standing board members completed their terms and were honored for their dedication by both chairs Gianni and Hans. They are: Julia Chisholm, Soledad Gallego, Daniel Orbach. They will collaborate continuously with the board in the field of Sarcoma.

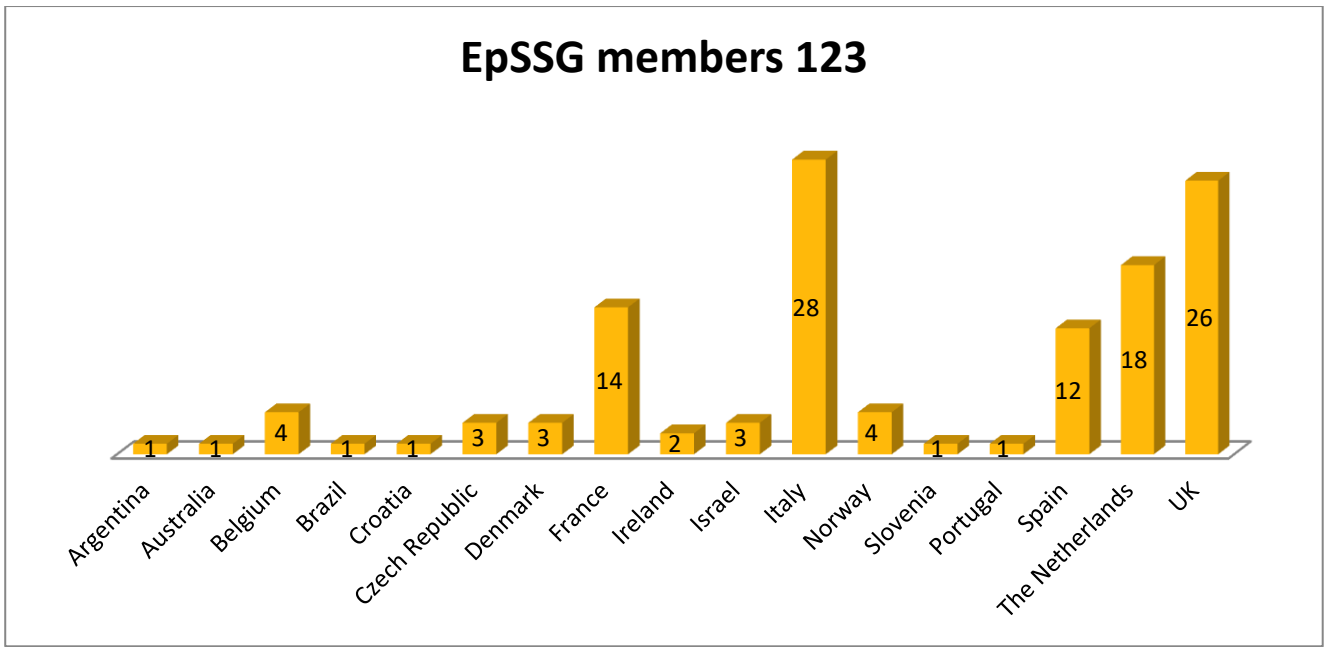
The board also welcomed four new members to join the 5 other sitting members. We are grateful and excited to have again Dr. Andrea Ferrari, and a new diverse group including Dr. Nadege Corradini, Dr. Gabriela Guillen Burrieza and Dr. Timothy Rogers to join the board and bring their unique talents, expertise and perspectives to the work of the association in order to fulfill our mission for best cure, treatment and life improvements for patients with Sarcoma.




EpSSG MEMBERSHIP

EpSSG studies are undertaken in the following countries: Italy, France, UK, The Netherlands, Spain, Belgium, Ireland, Denmark, Norway, Czech Republic, Slovenia, Israel, Argentina, Brazil and Australia. Each country has an EpSSG National Coordinator.

In 2019 there were 123 individual members of the EpSSG from 17 different countries. This year we welcomed a member from Portugal.



EpSSG Subcommittees

	Chair
Biology	Prof Janet Shipley, Sutton, UK
Pathology	Dr Rita Alaggio, Rome, Italy
Radiology	Prof Rick R. van Rijn, Amsterdam, The Netherlands
Surgery	Dr Timothy Rogers, Bristol, UK
Radiotherapy	Dr Henry Mandeville, Sutton, UK
Phase I/II trials	Dr Michela Casanova, Milan, Italy
Biostatistics/Data management	Dr Gian Luca De Salvo, Padua, Italy

EpSSG Meetings 2019

The Spring meeting took place on 23rd and 24th May 2019 in Prague, Czech Republic. The meeting was hosted by the SIOPe, the meeting included discipline panel meetings on surgery, biology-pathology, phase II, radiotherapy. The Welcome dinner was organized by Dr. Peter Mudry.

The Winter meeting took place the 6th and 7th of December at the Allen and Overy Center in London, UK. It was hosted by Dr. Janet Shipley and included discipline panel meetings on biology, radiotherapy, NRSTS TMC, surgery, pathology, phase I/II, radiology, and an International Symposium on the "*Genetics: Germ-line and Somatic Changes and their Significance*".

Our meetings are growing and welcoming more than 100 participants. In Prague and 145 participants in London! Moreover, a half day of the INTERNATIONAL SOFT TISSUE SARCOMA CONSORTIUM (INSTRuCT) meeting was held. This consortium developed to share data from soft tissue sarcoma trials, focused on either RMS rhabdomyosarcoma or on NRSTS non-rhabdomyosarcoma soft tissue sarcomas, has resulted in sharing of data from thousands of children within the EpSSG, RMS and MTS 2008 protocols, CWS and COG group. The first aim is to develop international guidelines for risk stratification in RMS.

The New **F**rontline **a**nd **R**elapse study in **R**habdo**M**yo**S**arcoma

(by Dr. Meriel Jenney and Dr. Julia Chisholm)

The FaR-RMS Trial – Trial Update

An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma

The FaR-RMS trial is an overarching trial for all patients with newly diagnosed and relapsed paediatric-type rhabdomyosarcoma and will be open to patients of all ages. The trial has an innovative multi arm, multi stage design that allows the testing of new combinations of therapy in upfront and relapsed settings in phase Ib, phase II and phase III.

The trial was due to open to recruitment in March 2020, however the outbreak of COVID-19 delayed database development. However we are hopeful this will be completed in June 2020 and the trial will then be ready to open. The trial will open as soon as the database has been released.

We are delighted that there is wide international interest and several new countries have formally joined the study in the past year. The participating National Coordinating Centres are forging ahead with country set-up and many have made regulatory submissions. Current participating countries are Australia, New Zealand, Denmark, France, The Netherlands, Ireland, Italy, Belgium, Norway, Slovakia, Czech Republic, Israel, Spain, Slovenia, Portugal, Switzerland United Kingdom and Greece.

The UK and Norway are the first countries to receive full regulatory approvals with a further 9 countries having obtained 1 or more approvals.

The phase 1b dose escalation study to find the dose of irinotrecan in combination with ifosfamide, vincristine and actinomycin-D will be opened at ITCC and early phase approved centres The frontline randomisations will be open at all participating centres and radiotherapy randomisations will be open at all sites where QUARTET approval has been obtained. An important aspect of the study focusses on the Quality of Life of patients when receiving radiotherapy. All sites will open to the maintenance randomisations also. Please note that many younger patients may not be able to swallow cyclophosphamide capsules. Where possible oral liquid cyclophosphamide should be prepared at sites. The UK has amended its clinical trial authorisation to allow powder for solution for injection to be mixed with sodium chloride for oral administration. Where countries need access to oral liquid formulations, country-specific options are being sought.

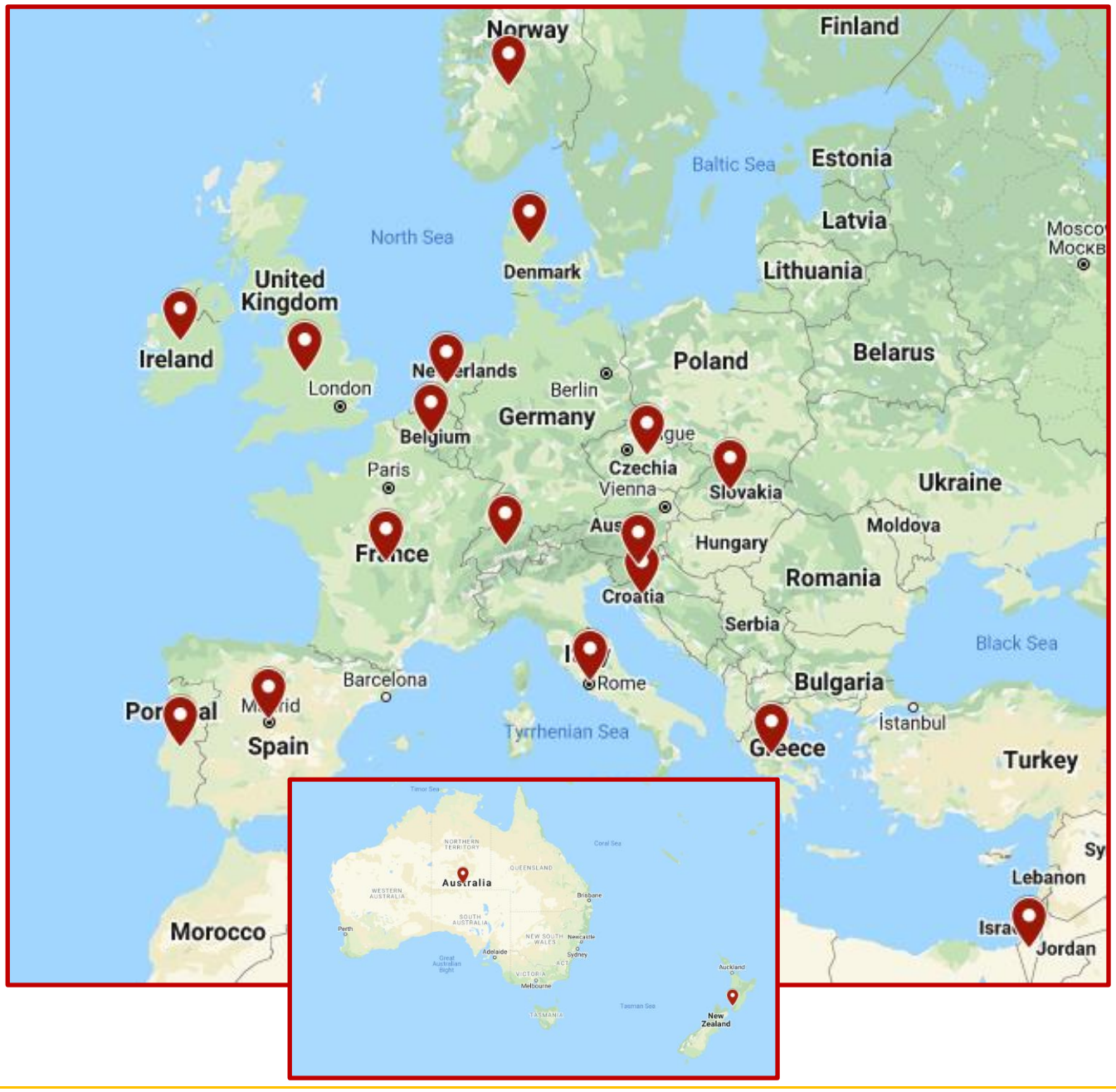
The relapsed randomisation will not open immediately and there will be an update in the next Newsletter. The first new combination to be tested in the relapse setting will be vincristine, irinotecan (VI) + regorafenib, a multityrosine kinase inhibitor, with VI + Temozolomide (VIT) as the control arm. This randomisation is expected to open early in 2021.

Risk group assignment and fusion status are integral part of the trial, molecular diagnostics on all cases of RMS should be carried out at the local centre. All samples will be centrally reviewed by the national pathology coordinator.

We are strongly encouraging NCCs to open the study in as many adult sites as possible – this is a very important opportunity and the first time randomised studies have been possible for adults with RMS.

The Study is coordinated through the Cancer Research Clinical Trials Unit in Birmingham, UK.

Figure 1: FaR-RMS Participating Countries



PARENTS AND EpSSG

PARENTS AND EPSSG 2019 (BY DR. HEIDI GLOSLI AND ANGELIKA SANDAKLY)

We welcomed three parents, to the Spring meeting in Prague, May 2019, and four parents to the Winter meeting in London, December 2019. To date 12 parents in total have attended EpSSG meetings and 7 EpSSG countries are now represented (France, Italy, NL, Norway, Denmark, Belgium and UK). Since the spring meeting is arranged together with the SIOPE-meeting, the schedule was very busy. The parent group therefore had their own separate session at the 2019 Winter meeting. A main topic for the parent group is to define the best way for interaction between the parent group, the EpSSG and the board. At the winter meeting a representative for the kidney tumour group was invited to present their way of working and give information regarding their involvement in research. At the spring meeting the parent group met with Julia Chisholm and Heidi Glosli as representatives from the Board at the end of the meeting. At the winter meeting the parent group met with the entire EpSSG board at the end of the meeting.

The new EpSSG website is now up and running with a "parent corner". A top priority in 2020 will be to launch the FaR-RMS study.

From a parent's point of view:

Both meetings in 2019, first in Prague and then in London, made us feel that we start to be a group with some history, some of us have attended the EpSSG meetings for more than 3 years now. I would like to thank EpSSG, for that opportunity.

The Prague experience was definitely interesting, but it was difficult to keep a clear scope on EpSSG matters because of the huge offer of lectures. Therefore we were really pleased to get together in London in a very focused parents meeting. The fact that we are able to open up to new parents with each meeting is very satisfying. With every new contact we discover new aspects of our mission.

To get an insight in your work and to mirror our - sometimes very personal - experiences with your - sometimes very scientific – approach seems to be helpful for both sides.

On the administrative side we have overcome some funding issues by involving our local associations. We do our best to progress on the gathering of relevant information for the website project.

We continue to be available for all review activity related to the FaR-RMS study. Gaining more understanding for the interest of the participation in clinical studies in general and in the FaR-RMS study in particular is one of the priorities for 2020.

We are looking forward to enlarging our activities to turn our experience into something beneficial for EpSSG and its public. It's good to know that our contribution might be useful for your work, it's a very small give back for the efforts you do for our children..

REPORTS FROM TRIAL COMMITTEES

(By Prof. GIANNI BISOGNO & IDC)

a) RMS 2005

This was the first International EpSSG trial for children and adolescents with localized rhabdomyosarcoma. Patients were included in 4 different risk groups according to 6 prognostic factors (result of initial surgery, histology subtype, tumour site and size, nodal involvement and patient age). Overall, 1760 patients were enrolled from 134 centres in 14 countries.

Low risk Group

73 patients were enrolled and treated with vincristine and actinomycin D for 22 weeks. Results are very satisfying with 5-year Event Free Survival (EFS) of 95.8% (CI95% 87.5-98.6) and 5-year Overall Survival (OS) of 100%.

Standard risk group

650 patients were enrolled and treated with ifosfamide, vincristine and actinomycin D (IVA) but with a higher ifosfamide cumulative dose if patients had not received radiotherapy. 5-year Event Free Survival (EFS) was 77.9% (CI95% 74.3-81.1) and 5-year Overall Survival (OS) was 91.1% (CI95% 88.3-93.2).

High Risk Group

875 enrolled patients are in the high risk group. 5-year Event Free Survival (EFS) of the entire cohort was 66.5% (CI95% 63.2-69.6) and 5-year Overall Survival (OS) was 75.5% (CI95% 72.3-78.3).

In the first randomized question there were 645 eligible patients were and in the second there were 670 eligible patients. In the 1st question 484 patients were randomized to receive ifosfamide, actinomycin D and vincristine with or without doxorubicin given in the first 4 courses: no benefit from the addition of doxorubicin was documented.

5-year Event Free Survival (EFS) of the IVA arm was 59.6% (CI95% 52.9-65.7) and 5-year Overall Survival (OS) was 76.0% (CI95% 69.8-81.1). 5-year Event Free Survival (EFS) of the IVADo arm was 65.4% (CI95% 58.9-71.2) and 5-year Overall Survival (OS) was 72.3% (CI95% 65.8-77.7). These results have already been published (Bisogno et al., Lancet Oncology, 2018). In the second randomised trial 371 patients in complete remission after 9xIVA cycles were randomised to stop treatment or to continue with low dose maintenance therapy with a combination of cyclophosphamide and vinorelbine. Initial analysis showed benefit of maintenance chemotherapy and the results were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2018, raising sufficient interest to be included in the plenary session. The full paper has been published (Bisogno et al., Lancet Oncology, 2019) and the intention-to-treat results were: 5-year Disease Free Survival (DFS) of the 'maintenance' arm was 77.6% (CI95% 70.6-83.2) and 5-year Overall Survival (OS) was 86.5% (CI95% 80.2-90.9). 5-year DFS of the 'stop treatment' arm was 69.8% (CI95% 62.2-76.2) and 5-year OS was 73.7% (CI95% 65.8-80.1).

Very High Risk Group

146 patients with alveolar RMS and nodal involvement were included in this group: 5-year EFS and OS were 50.9 (CI95% 42.2-59.0) and 51.8 (CI95% 42.5-60.3), respectively.

Overall, the EpSSG RMS2005 trial showed an improvement in survival for patients with RMS when compared with previous European experiences. This study has been published (Gallego et al., Cancer 2018).

NRSTS 2005 (BY DR. ANDREA FERRARI)

The EpSSG NRSTS Committee is still working on the development of a new protocol dedicated to NRSTS. Meanwhile, the group continues the analysis of selected series of NRSTS histotypes.

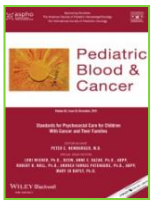
In particular, in 2018 various analyses have been published:

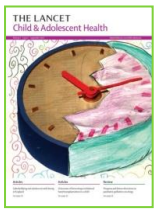
Joint EpSSG/COG analysis on epithelioid sarcoma (Spunt SL, et al. Eur J Cancer. 2019 May;112:98-106): the study included 63 patients; 5-year EFS and OS were 60.7% and 63.6%, respectively. Most low-risk ES patients who have undergone an adequate resection fare well without adjuvant therapy. Large tumour size, high histologic grade, tumour invasiveness, inadequate tumour resection and metastatic disease predict poorer outcomes in higher risk ES patients

EpSSG series on malignant peripheral nerve sheath tumors (MPNST) (van Noesel MM, et al. Pediatr Blood Cancer. Pediatr Blood Cancer. 2019 Oct;66(10):e27833): the study included 51 patients; 5-year EFS and OS were 52.9% and 62.1%, respectively. The outcome was excellent for patients with small resectable tumors (EFS 92%), while in unresectable disease the outcome was at least comparable or better than historic retrospective studies (EFS 42%, OS 57%). Response rate to chemotherapy in patients with measurable disease was 46%. The presence of neurofibromatosis type 1 (NF1; 51% of patients) was an independent poor prognostic factor.

Further analyses are ongoing. The series on inflammatory myofibroblastic tumor, dermatofibrosarcoma protuberans and metastatic NRSTSs included in the Bernie study have been accepted for publication and will be available on 2020.

PAPERS IN 2019





1. INDETERMINATE PULMONARY NODULES AT DIAGNOSIS IN PEDIATRIC RHABDOMYOSARCOMA: ARE WE UNDERTREATING PATIENTS? A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP-RMS-2005 PROTOCOL. J Clin Oncol. 2019 Jan 31:JCO1801535. doi: 10.1200/JCO.18.01535.

Vaarwerk B, Bisogno G, McHugh K, Brisse HJ, Morosi C, Corradini N, Jenney M, Orbach D, Chisholm J, Ferrari A, Zanetti I, De Salvo GL, Van Rijn RR, Merks JHM, EpSSG Radiology Group

January 31, 2019 the EpSSG study was published online in Journal of Clinical Oncology. In this study we assessed the clinical value of small lung nodules, not fulfilling the criteria for pulmonary metastases. This was an EpSSG radiology study, conducted in 15 larger centers in the United Kingdom, France, Italy and the Netherlands. We showed that small lung nodules are a frequently encountered diagnostic problem, occurring in over 20% of the patients with otherwise localized rhabdomyosarcoma. More importantly, this study showed that the presence of small lung nodules did not impact survival in patients with otherwise localized rhabdomyosarcoma, treated according to the RMS2005 protocol for localized disease. This study proves that patients with small lung nodules do not require additional chest radiotherapy and/or intensified chemotherapy. These results will be used in the upcoming EpSSG Frontline and Relapsed-RMS study.

2. **OUTCOME OF LOCALIZED LIVER-BILE DUCT RHABDOMYOSARCOMA ACCORDING TO LOCAL THERAPY. A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP (EPSSG)- RMS 2005 STUDY.** Pediatr Blood Cancer. 2019 Mar 28:e27725. doi: 10.1002/pbc.27725

Guerin F, Rogers T, Minard-Colin V, Gaze M, Terwisscha S, van Noesel M, De Corti F, Guillen Burrieza G, De Salvo GL, Kelsey A, Orbach D, Ferrari A, Bergeron C, Bisogno G, Martelli H

OBJECTIVES:To evaluate the impact of local therapies on the outcome of patients with liver-bile duct rhabdomyosarcoma (LBDRMS).
METHODS:Data of 30 patients included in the EpSSG-RMS 2005 study were analyzed.
RESULTS: The median age at diagnosis was 3 years (11 months-8 years). All patients had non-alveolar histology. Fifteen patients had a tumor > 5 cm and six had enlarged regional lymph nodes on imaging. Eight patients (27%) had primary surgery (1 R0). Six of them received external beam radiotherapy (EBRT). All are in first complete remission (CR1) except one (R1, EBRT+ , local relapse, death). Six patients (20%) received EBRT without surgery: one had local relapse and died. Sixteen patients (53%) underwent delayed surgery, with 12 achieving R0 margins, which were higher than those in the primary surgery group (P = 0.003). Three patients with R0 margins received EBRT; one had a metastatic relapse and died. Nine patients with R0 resection did not receive EBRT, three relapsed locally (two deaths). Four R1 patients received additional EBRT without

relapses. Local relapse occurred in two among 19 patients with EBRT and three among 11 without EBRT (P = 0.326). At a median follow-up of 61 months (48-84 months), five patients died; all had a tumor size > 5 cm (P = 0.01). The five-year overall survival was 85% (95% CI, 65-94), and event-free survival was 76% (95% CI, 54-89).

CONCLUSION: This analysis did not show any significant difference in outcome between irradiated and nonirradiated patients. Local relapse in LBDRMS is related to initial tumor size and is often fatal.

3. **CLINICAL FEATURES AND OUTCOMES OF YOUNG PATIENTS WITH EPITHELIOID SARCOMA: AN ANALYSIS FROM THE CHILDREN'S ONCOLOGY GROUP (COG) AND THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP (EPSSG) PROSPECTIVE CLINICAL TRIALS.** EIC Eur J Cancer. 2019 Apr 4;112:98-106. doi: 10.1016/j.ejca.2019.02.001.

Spunt S, Francotte N, De Salvo GL, Chi YY, Zanetti I, Hayes-Jordan A, Kao S, Orbach D, Brennan B, Weiss A, Van Noesel M, Million L, Alaggio R, Parham D, Kelsey A, Randall RL, McCarville MB, Bisogno G, Hawkins D, Ferrari

The current study represents a joint analysis from European paediatric soft tissue Sarcoma Study Group (EpSSG) and Children's Oncology Group (COG) on clinical features and outcomes of pediatric epithelioid sarcoma.

This is a very rare and aggressive tumor included in the large and heterogeneous group of non-rhabdomyosarcoma soft-tissue sarcomas (NRSTS).

The study included 63 patients (3.24 years, median 13) enrolled between 7/2005 and 11/2015 on the two international prospective clinical trials EpSSG NRSTS 2005 and COG ARST0332.

As major finding, the analysis demonstrated that most low-risk patients who have undergone an adequate resection fare well without adjuvant therapy; large tumour size, high histologic grade, tumour invasiveness, inadequate tumour resection and metastatic disease predict poorer outcomes in higher risk patients, for whom more effective therapies are needed. Estimated 5-year survival was 86.4%, 63.5% and 0%, respectively, for low-, intermediate- and high-risk patients. Partial response to neoadjuvant therapy (chemotherapy for EpSSG cases and chemotherapy plus radiotherapy in COG cases) was observed in 11/22 (50%) patients.

This study demonstrates the value of international collaboration for investigating rare entities.

4. **OUTCOME AND PROGNOSTIC FACTORS IN PEDIATRIC MALIGNANT PERIPHERAL NERVE SHEATH TUMORS: AN ANALYSIS OF THE EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA GROUP (EPSSG) NRSTS-2005 PROSPECTIVE STUDY** Pediatr Blood Cancer. 2019 Jun 26:e27833. doi: 10.1002/pbc.27833.

Van Noesel MM, Orbach D, Brennan B, Kelsey A, Zanetti I, De Salvo GL, Gaze MN, Craigie RJ, McHugh K, Francotte N, Collini P, Bisogno G, Casanova M, Ferrari A.

Malignant peripheral nerve sheath tumors (MPNST) is a rare tumor but it represents one of the most frequent nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) of childhood.
The current study reports the outcome of the prospective cohort of pediatric patients with localised MPNST treated within the the European Pediatric Soft Tissue Sarcoma Group (EpSSG) NRSTS 2005 trial.
Patients were stratified into four treatment groups defined by surgical resection, tumor size, and tumor grade, i.e. surgery-only group, adjuvant radiotherapy group, adjuvant chemotherapy group, and neoadjuvant chemotherapy group.
The study included 51 patients. Event-free survival (EFS) and overall survival (OS) at 5 years were 52.9% and 62.1%, respectively. The outcome was excellent for patients with small resectable tumors (EFS 92%), while in unresectable disease the outcome was at least comparable or better than historic, retrospective studies (EFS 42%, OS 57%). Response rate to chemotherapy in patients with measurable disease was 46%. The presence of neurofibromatosis type 1 (NF1; 51% of patients) was an independent poor prognostic factor.

5. **VINORELBINE AND CONTINUOUS LOW-DOSE CYCLOPHOSPHAMIDE AS MAINTENANCE CHEMOTHERAPY IN PATIENTS WITH HIGH RISK RHABDOMYOSARCOMA (RMS 2005): A MULTICENTRE, OPEN LABEL, RANDOMIZED PHASE 3 TRIAL.** Lancet Oncol. 2019 Sept 24. https://doi.org/S1470-2045(19)30617-5

Bisogno G, De Salvo GL, Bergeron C, Gallego S, Merks JHM, Kelsey A, Martelli H, Minard-Colin V, Orbach D, Glosli H, Chisholm J, Casanova M, Zanetti I, Devalck C, Ben Arush M, Mudry P, Ferman S, Jenney M, Ferrari A

For more than three decades, standard treatment for rhabdomyosarcoma in Europe has included 6 months of chemotherapy. The European paediatric Soft tissue sarcoma Study Group (EpSSG) aimed to investigate whether prolonging treatment with maintenance chemotherapy would improve survival in patients with high-risk rhabdomyosarcoma. Between April 20, 2006, and Dec 21, 2016, 371 patients were enrolled and randomly assigned to the two groups: 186 to stop treatment and 185 to receive maintenance

chemotherapy. Adding maintenance chemotherapy seems to improve survival for patients with high-risk rhabdomyosarcoma. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials.

6. **IS SURVEILLANCE IMAGING IN PEDIATRIC PATIENTS TREATED FOR LOCALIZED RHABDOMYOSARCOMA USEFUL? THE EUROPEAN EXPERIENCE.** Cancer. 2019 Nov 21. doi: 10.1002/cncr.32603.

Vaarwerk B, Mallebranche C, Affinita MC, van der Lee JH, Ferrari A, Chisholm JC, Defachelles AS, De Salvo GL, Corradini N, Minard-Colin V, Morosi C, Brisse HJ, McHugh K, Bisogno G, van Rijn RR, Orbach D, Merks JHM

In November 2019 the EpSSG study entitled 'Is surveillance imaging in paediatric patients treated for localized rhabdomyosarcoma useful? The European experience.' Was published online and March 10, 2020 was published in Cancer journal. In this study we evaluated the clinical value of radiological imaging performed after completion of therapy. This retrospective study was conducted in 21 European hospitals in France, Italy, the United Kingdom and the Netherlands on a group of 199 patients with relapsed rhabdomyosarcoma. We showed that disease relapse was detected because of clinical symptoms in the majority (61%) of these patients, despite the frequent follow-up imaging performed after completion of therapy. Furthermore, we found no survival advantage for patients whose relapse was detected before the emergence of clinical symptoms. The results of this study will be used to develop a new follow-up strategy for the upcoming EpSSG Frontline and Relapsed-RMS study.

EARLY PHASE TRIALS (BY DR. MICHELA CASANOVA)

BERNIE

The BERNIE study was a joint EpSSG/ITCC randomized phase II study of standard chemotherapy +/- bevacizumab in paediatric metastatic soft tissue sarcoma, sponsored by F Hoffman la Roche. The final results of the study were published in Eur J Cancer in 2017; the paper on NRSTS (*Outcomes of metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) treated within the BERNIE study*") was also submitted to Eur J Cancer. The paper on the role of radiotherapy in the rhabdomyosarcoma cohort is in preparation.

VIT 0910

The results of the VIT 0910 study (randomised phase II study of vincristine and irinotecan (VI) +/- temozolomide (T) in refractory/relapsed RMS) were presented at ASCO 2019 and SIOP 2019.

It is a joint ITCC/EpSSG investigator initiated study sponsored by Lille (France) opened in 37 centres from five countries (France, UK, Italy, the Netherlands and Spain). A total of 120 patients (60 patients in the VI arm and 60 patients in the VIT arm) were recruited. The main objective of the study was to evaluate the efficacy of VI and VIT regimens defined as objective response after two courses of treatment in patients with recurrent or refractory rhabdomyosarcoma.

The objective response rate (ORR) after 2 cycles resulted to be 44% (80% CI 34-53%) in VIT arm and 31% (80% CI 23-40%) in the VI arm; If we consider only patients at relapse ORR was 47% in the VIT arm and 33% in the VI arm.

Comparison of ORR at 2 cycles between groups:

- On the whole study population: ORR significantly >20% (P0) in VIT (44%) and in VI (31%)
- In patients at relapse: ORR significantly >35% (P0) in VIT (47%), and not in VI (33%)

VIT was significantly more toxic than VI, but toxicity was manageable.

Compared to the VI arm, the VIT arm resulted to be associated with a large and significant reduction in the risk of death; median overall survival was 15.0 months (95%CI, 10.0-21.2) in the VIT arm and 10.3 months (95%CI, 7.1-12.6) in the VI arm. The Progression-Free Survival benefit was nearly significant (HR=0.68; 95%CI, 0.46-1.01; P=0.059).

On the basis of this study VIT is now considered the standard treatment for relapsed rhabdomyosarcoma.

REGORAFENIB

The phase 1b expansion cohort to evaluate safety and tolerability of regorafenib combined with vincristine/irinotecan (VI) in patients with relapsed/refractory RMS and other solid tumors (Ewing sarcoma, hepatoblastoma, Wilms tumor and neuroblastoma) was introduced as an amendment in the regorafenib pediatric phase 1 study, sponsored by Bayer.

In monotherapy regorafenib in pediatric subjects resulted to be tolerable across dose levels and the safety was consistent with the known safety profile in adults. The RP2D of regorafenib as a single agent in children and adolescents with solid tumors is 82 mg/m2 taken orally qd in a 3 weeks on/1 week off schedule. The only partial response observed was in a patient with an alveolar rhabdomyosarcoma.

The dose expansion phase 1b was opened in 25 centers, from 4 countries (France, UK, Italy, and Spain). The expansion phase study design was agreed by the PDCO in the context of the Stivarga PIP (Paediatric Investigation Plan). Two different dosing schedule were evaluated: concomitant and sequential schedule. A total of 21 patients were included. The results of the study will be presented at ASCO 2020.

Currently efforts are ongoing to incorporate the combination of regorafenib and VI into the Far-RMS relapsed randomized phase II study.

The early phase trials committee continues to work with pharma and the EpSSG Biology Committee to facilitate access to new agents for the FaR-RMS trial and other indications. There are ongoing efforts on the proposal to include volasertib in FaR-RMS.

- **During the recent SIOP congress 2019 held in Lyon, France the following abstracts were presented by EpSSG members:**

1. EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP MTS 2008 STUDY: FIRST RESULTS OF A PROTOCOL FOR METASTATIC RHABDOMYOSARCOMA. (accepted as oral presentation)

J.H.M Merks, & Co

2. ASSESSING THE RISK PROFILE OF RHABDOMYOSARCOMA (RMS) PATIENTS IN A NEW CLASSIFICATION SYSTEM FOR THE NEXT EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP (EPSSG) PROTOCOL (accepted as oral presentation)

G. Bisogno, & Co

3. NON-PARAMENINGEAL HEAD AND NECK RHABDOMYOSARCOMA IN CHILDREN AND YOUNG ADULTS: RESULTS OF THE EpSSG RMS 2005 STUDY

H. Glosli, & Co

4. LOCAL STAGING, AND TREATMENT AND OUTCOME IN EXTREMITY RHABDOMYOSARCOMA.; A REPORT FROM THE EPSSG RMS2005 STUDY

C.E.J. Terwisscha van Scheltinga , & Co

5. LOCO-REGIONAL TREATMENT OF PARATESTICULAR RHABDOMYOSARCOMA (PRMS). A REPORT FROM THE EUROPEAN PEDIATRIC SOFT-TISSUE SARCOMA GROUP (EpSSG).

T. Rogers & Co

6. OUTCOMES OF METASTATIC non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) TREATED WITHIN THE bernie STUDY: a randomised, phase II study evaluating the addition of bevacizumab to chemotherapy

A. Ferrari & Co

During the recent ASCO meeting 2019 the following abstract was presented:

1. RANDOMIZED PHASE 2 TRIAL OF THE COMBINATION OF VINCRISTINE AND IRINOTECAN WITH OR WITHOUT TEMOZOLOMIDE, IN CHILDREN AND ADULTS WITH REFRACTORY OR RELAPSED RHABDOMYOSARCOMA (RMS).

A.S. Defachelles, E. Bogart, M. Casanova, J.H.M. Merks, G. Bisogno, G. Calareso, S. Gallego Melcon, S. Gatz, M.C. Le Deley, K. McHugh, A. Probst, N. Rocourt, R.R. van Rijn, K. Wheatley, V. Minard-Colin, J. Chisholm

Defachelles SIOP award in the clinical trials section for presentation of the VIT study

FINANCIAL STATEMENT 2019 (BY DR. J.H.M. MERKS)

Total income for the association in 2019 was €18.000, mainly from members' fees and meeting registration. Interest on accounts and investments was €1800,00. A donation from a Paduan Parent was €2.000.

Total expenses were almost €17.000; Annual and Board meeting and travel costs were €12.200, accountant's costs (€2200), banking costs (€1000) and website costs (€2000).

For 2020 we expect income from EpSSG membership fees and meeting fees from our Winter meeting; we aim to negotiate with Pharma whenever we substantially invest our expertise and network into Paediatric Investigation Plans or other work. As our association is vital to maintain both expertise and the clinical network this justifies financial support from parties that need substantial input from EpSSG members.

An accountancy and treasurer's Report of the final year's account was presented and approved during the EpSSG Winter meeting held in December 2019, in London.

Funding Sources: The EpSSG is indebted to the Kick Cancer Foundation, founded by one of our parents, Delphine Heenen and King Baudouin Foundation for supporting a new EpSSG data manager and for supporting preclinical pilot research directly supporting the biological studies planned within the EpSSG FaR-RMS study. Moreover, the EpSSG association received a donation of 2000 Euro in 2019 from a Paduan parent for supporting a new EpSSG statistician. Grateful to those who help implementing work resources in research.

WORKPLAN in 2020

1. Launch FaR-RMS study across countries and invite new countries to participate.
2. Launch substudies to FaR-RMS including Imaging and Biology
3. Acquire funding for sponsorship of the Myckids study and subsequently launch Myckids across EpSSG countries.
4. Efficient preparation of reports by International Data Center (IDC) in close collaboration with PI of each project leading to timely delivery of manuscript.
5. Consolidate funding for EpSSG IDC and secretariat activities
6. Optimize collaboration with parents through involvement at meetings and in projects
7. Optimize communication with members through our EpSSG website and mailings on important EpSSG developments

Help support the EpSSG Association

WE HAVE A DONATION BUTTON ON OUR WEBSITE! HELP US SPREAD THE WORD!

photograph taken by dr.Ferrari

DONATE to EpSSG

The EpSSG coordinates European international clinical trials aimed at improving the treatment of soft tissue sarcoma (STS). Through research our goal is to improve the quality of care offered to children, teenagers and young adults with STS and to improve the outcomes of treatment. Your donation will help to support the team of clinicians, scientists, statisticians and data managers in developing and running new clinical trials in paediatric STS in order to help future generations of children with STS.

Association meetings - Calendar 2019-2020

DATE	MEETING	LOCATION	NOTES
2020			
May 4-8 (Mo-Fri)	EpSSG Spring Meeting & Association Assembly	SIOPE Congress, Valencia Spain	NOT HELD! COVID19 emergency
December 3-4 (Th-Fr)	EpSSG Winter Meeting & Association Assembly	Rome jointly with Biology workshop	CONFIRMED
2021			
April 26-30 (Mo-Fri)	EpSSG Spring Meeting & Association Assembly	SIOPE Congress, Valencia Spain	Confirmed
December (Th-Fr)	EpSSG Winter Meeting & Association Assembly	Barcelona	To be confirmed

Prepared by: Nadege Corradini, Julia Daragjati, Marit Borger-Winkelman, Meriel Jenney, Julia Chisholm, Heidi Glosli, Angelika Sandakly, Gianni Bisogno, Andrea Ferrari, Michela Casanova, Hans Merks and with the great collaboration of all EpSSG Members.