EpSSG ASSOCIATION 2016 REPORT

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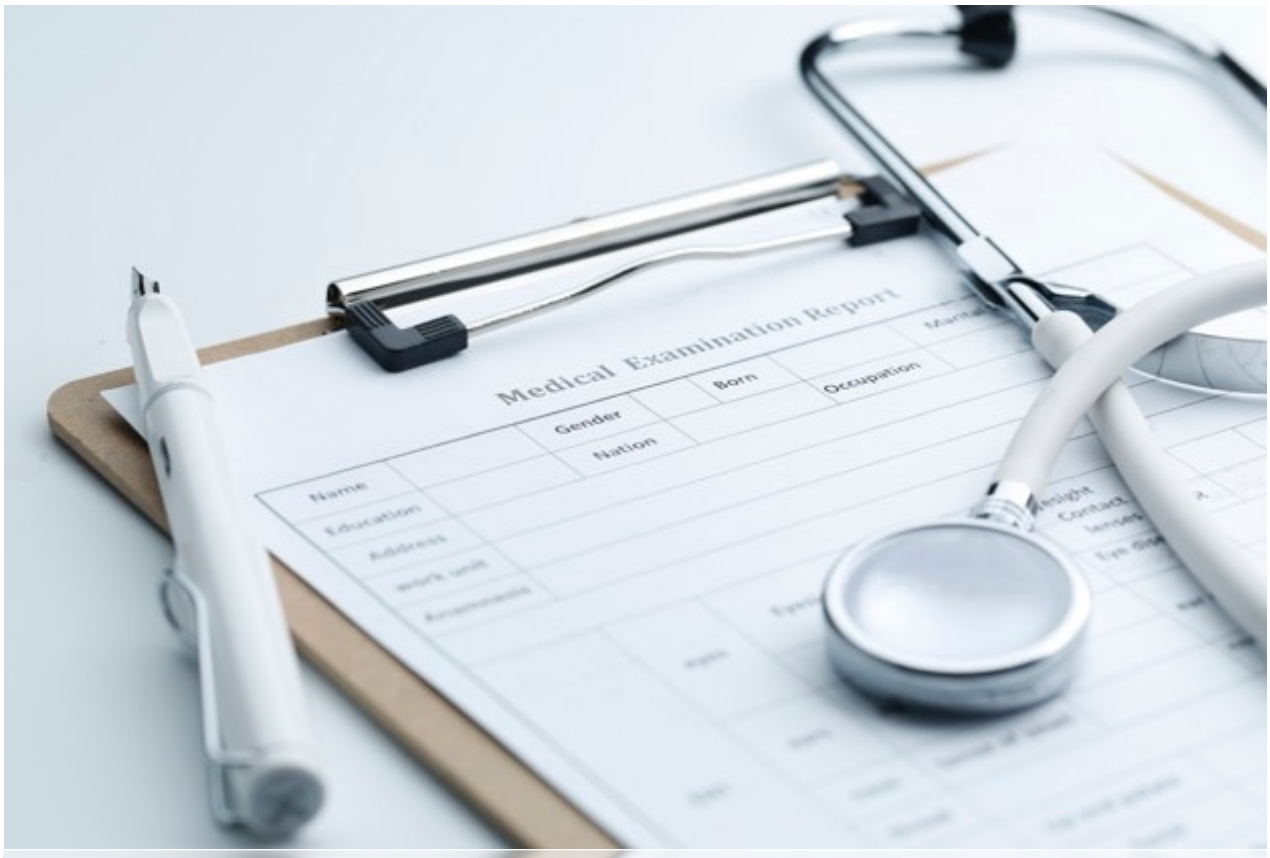


1. The EpSSG Association

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 a cancer called soft tissue sarcoma (STS).

This includes the diagnosis of rhabdomyosarcoma (RMS) and a wide range of other diagnoses known collectively as the 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 teenagers and young adults.

This report summarizes the main EpSSG activities that have been developed in 2016. Importantly we had the opportunity to welcome patients and their families to collaborate with us and support the development of our activities in 2016.
Further information is available on the EpSSG website:
www.epssgassociation.it

2. EpSSG board

Prof. Gianni Bisogno	Padua	Italy (Chair)
Dr Christophe Bergeron	Lyon	France
Dr Julia Chisholm	Sutton	United Kingdom
Dr Andrea Ferrari	Milan	Italy
Dr Soledad Gallego	Barcelona	Spain
Dr Heidi Glosli	Oslo	Norway
Dr Meriel Jenney	Cardiff	United Kingdom
Dr Hans Merks	Amsterdam	The Netherlands
Dr Daniel Orbach	Institut Curie	France

Board meetings were held on the following dates in 2016:
March 14th, May 9th, May 11th, October 22nd, November 30th, December 1st

TCs were held on: January 27th, July 6th, August 31st, September 19th, December 20th.

3. EpSSG Discipline Panels

	Chair of Panels
Biology	Prof Janet Shipley, Sutton, UK
Pathology	Dr Anna Kelsey, Manchester, UK
Radiology	Dr Kieran McHugh, London, UK
Surgery	Prof Hélène Martelli, Paris, FR
Radiotherapy	Dr Henry Mandeville, Sutton, UK
Phase I/II trials	Dr Julia Chisholm, Sutton, UK
Biostatistics/ data management	Dr Gian Luca De Salvo, Padua, IT

4. EpSSG National Coordinators

RMS / NRSTS

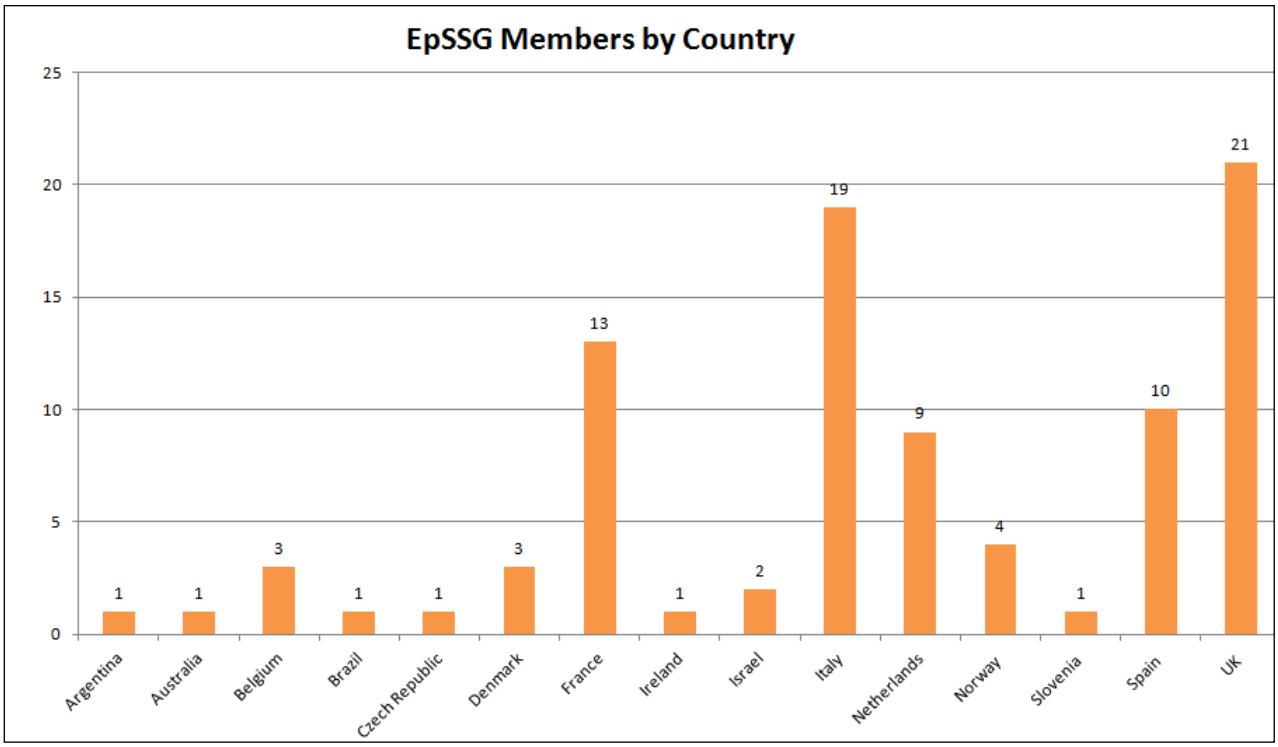
Argentina	Dr. Adrianna Rose / Dr. Marcelo Scopinaro
Belgium	Dr. Christine Devalck
Czech Republic	Dr. Peter Mudry
Denmark	Dr. Niels Clausen
France	Dr. Christophe Bergeron / Dr. Daniel Orbach
Israel	Dr. Myriam Ben Arush
Italy	Prof. Gianni Bisogno / Dr. Andrea Ferrari
Norway	Dr. Heidi Glosli

Slovakia	Dr. Daniela Sejnova
Spain	Dr. Soledad Gallego
Switzerland	Dr. Felix Niggli
The Netherlands	Dr. Hans Merks / Dr. Max van Noesel
United Kingdom and Ireland	Dr. Meriel Jenney / Dr. Bernadette Brennan

5. EpSSG membership

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

In 2016 there were 90 individual members of the EpSSG association.



6. EpSSG meetings 2016

Spring meeting took place on the 10-11 May 2016: was held at the National Art Museum of Catalonia, Parc de Montjuïc, Barcelona.

The meeting was hosted by Dr. Soledad Gallego, it included biology, radiotherapy + surgery workshops and a new protocol discussion.
A retirement celebration took place for Prof. Jose Sánchez de Toledo Codina, Jefe de Servicio Oncología Hematología Pediátricas, Hospital Universitario Vall d'Hebron. Attended by colleagues from the Children's Oncology Group.

Winter meeting took place on the 1-2 Dec. 2016 and was held in Brussels at the Palais des Académies Brussels.
The meeting was hosted by Dr. Christine Devalck and included biology, radiotherapy and surgery workshops and a new protocol discussion.

Other partner meetings:

- EpSSG- CWS meeting, Stuttgart 15-16/12/2016
- COG Fall Group Meeting Atlanta, GA 9/13 – 9/16/2016

- ExPO-r-Net Project (EpSSG is involved in this European project to provide guidelines on very rare STS: 2 have been validated in 2017 (infantile fibrosarcoma, alveolar soft part sarcoma))

- QUARTET project: Quality & Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) kicked-off meeting 20th May 2016 Dr H. Mandeville

- Collaborations with pharmaceutical companies:
    - Roche: Bernie Trial
    - Roche: Atezolizumab development
    - Merck group"advisory work" to develop PIP for TH-302

7. Parents & EpSSG

Parents that attended the meeting:

Angelika Sandakly (France)
Delphine Heenen (Belgium)
Enrico De Tuglie (Italy)

The first Parents meeting was held during the EpSSG winter meeting in Brussels on December 20th. Main points discussed regarded how parents can be active for EpSSG:

1. **Review protocols and study documents** (i.e. Informed consent):

- monitoring and evaluating the implementation of protocols
- making sure we are asking a good question
- important to hear “family perspective” on procedures
- evaluating documents such as informed consent
- New study must have a logical sense when presented to a new family, it is vital that our parents give their comments on it.

2. **Parents help parents**: inform other patients and parents, support the enrollment of patients in clinical trials

3. **Fundraising**

4. **Involve more parents and also patients**

8. Reports from trial committees

(by Bisogno G / De Salvo GL / Zanetti I)

a) RMS 2005 Protocol (by Bisogno G.)

This is the first international EpSSG trial for children and adolescents with localized rhabdomyosarcoma. Patients are included in 4 different risk groups according to 6 prognostic factors (result of initial surgery, histology subtype, tumor site and size, nodal involvement and patient age). Overall 133 centres from 14 countries are enrolling patients. At October 16th 2016, 1697 patients were enrolled.

The different risk groups have different objectives:

Low Risk Group

Objective: to further investigate whether low risk patients can be treated with Vincristine and Actinomycin D (VA) alone.

Standard Risk Group

Objective: to evaluate whether a) the addition of a limited dose of ifosfamide to VA (IVA) may improve the results in SUBGROUP B; b) chemotherapy intensity may be reduced decreasing the cumulative dose of the alkylating agent ifosfamide (SUBGROUP C) or avoiding anthracycline (SUBGROUP D).

High Risk Group

Objective: to improve the EFS of the whole group evaluating through a double randomisation 1) the value of adding doxorubicin in the initial part of the treatment: patients have been randomized to receive the IVA vs. IVADo (IVA + Doxorubicin) over the initial 4 blocks followed by 5 IVA blocks. and 2) the role of low dose maintenance chemotherapy: all patients in complete remission will then be randomised to stop treatment or to continue with low dose maintenance therapy with a combination of cyclophosphamide and vinorelbine.

Very High Risk Group

Objective: to improve the EFS by adding doxorubicin in the initial part of the treatment and low dose maintenance chemotherapy.

In December 2013, the first randomization for the high risk group (IVA vs IVADo) reached its target, patient enrollment was closed and EpSSG reached its first objective. IVA has been taken forward as standard of care. By the end of 2016 the enrollment in the second randomized trial was concluded on December 31, 2016.

b) NRSTS 2005 Protocol (by Ferrari A)

The EpSSG NRSTS 2005 study (EUDRACT 2005-001139-31) has been conducted from August 2005 to December 2016. The study enrolled 1216 cases from 13 different countries. According to NRSTS subtypes, synovial sarcoma was the most common histotypes (213 cases), followed by desmoids-type fibromatosis (179), rhabdoid tumor (92) and infantile fibrosarcoma (84).

COUNTRY	PATIENTS ENROLLED	
	#	%
Italy	404	33.2
France	384	31.6
UK & EIRE	199	16.4
The Netherlands	74	6.1
Spain	41	3.4
Belgium	40	3.3
Israel	33	2.7
Czech Republic	19	1.6
Argentina	8	0.7
Norway	8	0.7
Denmark	2	0.2
Slovakia	2	0.2
Slovenia	2	0.2
Total	**1216**	**100.0**

Histology		
Alveolar soft part sarcoma	19	1.6
Angiosarcoma of soft tissue	10	0.8
Clear Cell Sarcoma of soft tissue	16	1.3
Dermatofibrosarcoma protuberans	54	4.4
Desmoid-type fibromatoses	179	14.7
Desmoplastic small round cell tumour	10	0.8
Ectomesenchymoma	4	0.3
Epithelioid haemangioendothelioma	14	1.2
Epithelioid sarcoma	35	2.9
Ewing tumour pPNET (extraskeletal)	73	6.0
Fibrosarcoma – adult type	14	1.2
Fibrosarcoma – infantile type	84	6.9
Hemangioperycytoma	3	0.2
Inflammatory myofibroblastic tumour	63	5.2
Leiomyosarcoma	21	1.7
Liposarcoma	34	2.8
Malignant Fibrous Histiocytoma	6	0.5
Malignant Peripheral Nerve Sheath Tumour (Malignant Schwannoma)	65	5.3
Malignant mesenchymoma	1	0.1
Mesenchymal Chondrosarcoma	7	0.6
Myxoid Chondrosarcoma ("chordoid" type) (extraskeletal)	3	0.2
Neoplasms with perivascular epithelioid cell differentiation	3	0.2
Other	91	7.5
Rhabdoid tumour	92	7.6
Sarcoma N.O.S.	41	3.4
Synovial Sarcoma	213	17.5
Undifferentiated Soft Tissue Sarcoma	61	5.0

In 2016 two others series were published following the NRSTS 2005 synovial sarcoma series published in 2015.

- **Infantile fibrosarcoma:**
  - 50 patients (median age 1.4 months) between 2005 and 2012
  - 3-year EFS 84.0%, OS 94.0%
  - response rate to VA was 68.0%
  - conservative therapy is possible in IFS as only 3 children required mutilating surgery, and alkylating or anthracycline based chemotherapy was avoided in 71% of patients needing chemotherapy. VA regimen should be first line therapy in order to reduce long term effects

- **Extracranial malignant rhabdoid tumours:**
  - 43 patients (median age 1.4 months) between 2005 and 2014
  - 3-year EFS 32.3%, OS 38.4%
  - localized disease 4-year OS 40%, metastatic disease 2-year OS 13%
  - prognostic factor: patients ≤1 year of age were associated with at higher risk of death
  - intensive therapy can be delivered to extra-cranial MRT patients, with a possible improvement in outcome. The outcome, however, remains poor for patients who progress or with metastatic disease

The **NRSTS Committee** is working to develop the next protocol. It aims to continue to collect data on all histotypes, including the most uncommon and involve all EpSSG centers; we are working on the option to develop a Prospective cohort study with a biological question.

c) Desmoid tumor project (by Orbach D)

The EpSSG is finalizing its "Desmoid tumor Project (DTP)" for children and adolescents suffering from this disease. The project aims at implementing a European standardized treatment approach, thus, a dedicated database has been created in the current EpSSG remote data entry system. The goal of the DTP is to evaluate treatment, patient's history, the biology and to verify the value of current recommendations of this disease. The overall project proposes to verify the possibility of screening a first *wait-and-see strategy* in patients with a non-threatening tumor. First results have been presented in Dublin during the 48th congress of the international society of pediatric oncology (SIOP), Dublin, Ireland, in October 2016. *Submitted to The LancChild andAdolescent Health June 2017*

The study had opportunity to analyze data of 174 pediatric patients diagnosed with desmoid tumours in Europe treated in with a quite conservative strategy. Thanks to the agreement between EpSSG and CINECA and the support of a private fund (*S. Wisnia* donation), this dedicated database has been created and managed with a limited investment.

This large study represents the first

prospective European-wide cooperative series on pediatric desmoid type fibromatosis. As main novelty, it is the first pediatric series that prospectively assess the role of wait and see strategy in such disease. The strategy to offer an initial care as little aggressive as possible was drawn on the experience of adults and is novel in pediatric.

This original experience will allow clinicians to adopt this original strategy for the future for all new cases of desmoid tumors, without jeopardizing outcomes. In addition, our experience is a model of how with collaboration, prospective studies can be performed in very rare tumors at a European level. The overall compliance of pediatric centers was high (e.g. Systematic resection at diagnosis was avoided in more than two third of the patients, minimal morbidity chemotherapy was chosen as first therapy in many cases). This strategy showed that the initial wait and see strategy was feasible and did not jeopardize the results as compared to a more aggressive surgical approach.

d) Early phase trials (by Chisholm J)

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 as part of a Paediatric Investigation Plan. The study opened in 2008 and closed to recruitment on 31st October 2013. Top line results made available in August 2015 showed that the addition of bevacizumab did not improve event free survival in metastatic Soft Tissue Sarcoma but there was a significantly increased objective response rate with bevacizumab. The results were presented in a poster at ASCO 2016 and the full manuscript is accepted with minor modification for publication in Eur J Cancer 2017.

VIT 0910

The VIT 0910 study (randomised phase II study of vincristine and irinotecan (VI) +/- temozolomide (T) in refractory/relapsed RMS) is a joint ITCC/EpSSG investigator initiated study sponsored in Lille, France. The study leader is Dr Anne-Sophie Defachelles. Recruitment was temporarily halted in February 2013 for the interim analysis. As per the protocol there was sufficient activity to continue with the trial, therefore recruitment continued until 80 patients were recruited in June 2014. Data

analysis shows that the VIT arm met its phase II endpoint and the IDMC and Steering Committee recommended continuing the randomization for a further year pending the opening of the next study in relapsed RMS. The study reopened to increased recruitment in relapsed RMS only in 2016 in all countries. International recruitment is ongoing.

The early phase trials committee continues to work with pharma to facilitate access to new agents for the planned FaR-RMS trial (see below) and other indications. In particular it has worked with Bayer to access regorafenib in relapsed RMS. A proposal to include volasertib in FaR-RMS was been made but remains unsuccessful to date as there is no agreed development plan for the drug.

9. Specific projects for specific histotypes

a) The EuroJOSS (European Joint Synovial Sarcoma Study) project: aims to launch a prospective joint European study on synovial sarcoma, including in particular pediatric and adult synovial sarcoma joint together, for the first time in Europe.

b) European project on extra-CNS/CNS Rhabdoid tumors.

c) Genomic Index in Pediatric Synovial Sarcomas (Synobio Study): The European Pediatric Soft Tissue Sarcoma Group (EpSSG) Experience:
A retrospective biologic study is on-going. A genomic index (GI) tool using array comparative genomic hybridization (aCGH) on tumor cells has recently been developed, and shown a high prognostic value in adult soft tissue sarcomas. GI correlates with genomic instability, and has emerged as independent prognostic factor associated with the risk of metastatic relapse in synovial sarcoma (SS). The aim, therefore, was to assess GI in pediatric patients with SS, to assess its value as a prognostic factor and its role in risk stratification. All pediatric/adolescent/young adults' (<25 years) with localized SS prospectively included in the European

EpSSG-NRSTS05 protocol (EUDRACT 2005-001139-31) with a contributive aCGH were selected. Results have been presented in ASCO meeting 2017 and will be completed for the SIOP 2017 meeting. Financial support: SOS Desmoid, Enfant et Cancer.

10. New RMS study (by Jenney M)

a) RMS

The new study Frontline and Relapsed RMS (FaR-RMS) will be the immediate successor to the RMS 2005, VIT 0910 and BERNIE studies. It will be an overarching program of research in RMS in an international multi-centre trial with separate parts for (A) newly diagnosed and (B) relapsed RMS. Both parts will use a multi-arm, multi-stage (MAMS) design, with potential to bring in promising new arms in an efficient rolling program of therapeutic evaluation. Phase I dose-finding components will be included for new agents/regimens.

For newly diagnosed patients fusion status will be used in place of pathology in risk stratification and will be prospectively studied. The trial will use randomised comparisons to examine new treatment combinations in newly diagnosed patients with very high risk (including metastatic) and high risk RMS. Research questions include the duration of maintenance chemotherapy the timing and dose of radiotherapy for patients with in patients with localised RMS and the duration of maintenance chemotherapy and role of radiotherapy in patient with metastatic RMS.

New treatment combinations including targeted agents will be examined in a randomised trial in relapsed RMS with promising agents continuing to phase III evaluation in the relapse setting or moving into upfront combinations. There is a provisional agreement with Bayer to include VI + regorafenib as an arm in the relapse study providing the combination is tolerable in phase Ib (to be undertaken in the context of the current open pharma phase I study).

Tumour samples at diagnosis and relapse and sequential serum samples taken during treatment will be subject to gene sequencing, gene expression profiling, methylome and mutation detection through separately funded studies. It is aimed to establish a well-annotated virtual bio-bank of samples systematically collected across Europe linked to any associated molecular data for use in future studies.

The study will have the CRUK Clinical Trials Unit in Birmingham, UK as international sponsor. Study leads Dr Meriel Jenney, Dr Hans Merks JHM , Dr Julia Chisholm, Prof Gianni Bisogno, Dr Veronique Minard, Dr Henry Mandeville, Prof Janet Shipley and Dr Anna Kelsey. A first-round submission was made to CRUK in Nov 2016 for the costs of international sponsorship and UK trial costs, the outcome of this application is expected in May 2017.

11. EpSSG Publications 2016

Full papers

Orbach D, Brennan B, De Paoli A, Gallego S, Mudry P, Francotte N, Van Noesel M, Kelsey A, Alaggio R, Ranchère D, Casanova M, Bergeron C, Merks JH, Jenney M, Stevens M, Bisogno G, Ferrari A: ***Conservative strategy in infantile fibrosarcoma is possible: the European paediatric Soft tissue sarcoma Study Group (EpSSG) experience.*** *Eur J Cancer. 2016 Apr.*

Ferrari A, Trama A, De Paoli A, Bergeron C, Merks JH, Jenney M, Orbach D, Chisholm JC, Gallego S, Glosli H, De Salvo GL, Botta L, Gatta G, Bisogno G: ***Access to clinical trials for adolescents with Soft tissue sarcomas: enrollment in European paediatric Soft tissue sarcoma Study Group (EpSSG) protocols.*** *Paediatric Blood Cancer. 2016 Nov.*

Brennan B, De Salvo GL, Orbach D, De Paoli A, Kelsey A, Mudry P, Francotte N, Van Noesel M, Bisogno G, Casanova M, Ferrari A. **Outcome of extra-cranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study-EpSSG NRSTS 2005.** *Eur J Cancer. 2016 Jun.*

Abstracts

Ferrari A, Trama A, De Paoli A, Bergeron C, Merks JH, Jenney M, Orbach D, Chisholm J, Gallego S, Glosli H, De Salvo G.L, Botta L, Gatta G, Bisogno G : **Access to clinical trials for adolescents with soft tissue sarcomas: the enrollment into the European paediatric soft tissue sarcoma study group (EpSSG) protocols.** *SIOP abstract book, 2016.*

Chisholm J, Merks JH, Casanova M, Bisogno G, Orbach D, Gentet J, Thomassin Defachelles AS, Chastagner PB, Lowis S, Ronghe M, McHugh K, van Rijn RR, Hilton M, Bachir J, Furst-Recktenwald S, George B, Oberlin O: **Open-label randomised phase II study of bevacizumab plus chemotherapy in paediatric metastatic rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) (the BERNIE study).** *J Clin Oncol 34, 2016.*

Francotte N, D. Orbach, Zanetti I, Brennan B, De Salvo G.L , Mansuy L, Ranchere D, Kelsey A, Gallego S, Alaggio R, Ben Arush M, Casanova M, Van Noesel M, Bisogno G, Ferrari A: **Localized Epithelioid Sarcoma in Children: An European Paediatric Soft Tissue Sarcoma (EpSSG).** *Study Pediatric Blood and Cancer Volume 63, 2016.*

Orbach D, Daragjati J, Van Noesel M, Brennan B, Minard-Colin V, Bisogno G, Corradini N, Jenney M, De Salvo G.L, Defachelles A.S , Kelsey A, Ben Arush M, Francotte N, Ferrari A: **Desmoid Tumors in Children and Adolescents: The Experience of the European Paediatric Soft Tissue Sarcoma Group (EpSSG).** *Pediatric Blood and Cancer Volume 63, 2016.*

12. Financial Statement 2016

(by Merks J.H.M)

Total income for the association in 2016 was €29.548,93, mainly from Merck group (€24.270) to compensate for the "advisory work" done to develop TH-302, membership and meeting fees (€4.160) a private donation (€114), interest on accounts and investments (€1.004).

Total expenses were €57.052,72; Secretary salary (€12.480), Annual and Board meetings costs (€2.787), Data manager (€14.000) accountant's costs (€761.28). Payment made to The Institute of Cancer Research: Royal Cancer Hospital (for the development of TH302 (€12.000).

For 2017 we expect income from EpSSG membership fees and meeting fees from our Spring and Winter meetings; 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 report concerning 2016 has been presented during the EpSSG general assembly held at the Copenhagen spring meeting in 2017.

13. Workplan 2017

Main objectives:

- Increase the communication with members (i.g newsletters, email)
- Increase and support the discipline panel activity
- Develop collaborations with Parents
- Increase the "data delivery" from the International data Centre
- New EpSSG analyses (IDC) and publications
- Develop New RMS protocol: funding for international sponsorship
- Desmoid tumor project

14. EpSSG meetings schedule 2017

- Spring: May 11 - 12 2017 / Copenhagen Denmark
- Winter: December 4 - 5 2017 / Lyon France

Other partner meetings 2017

- COG Meeting Atlanta, 9/13 – 9/15/2017

15. Acknowledgements

Città della speranza

EpSSG thanks the Città della Speranza foundation Padova Italy for its continuous support to the EpSSG research activities.

Support by the *S. Wisnia donation*

The EpSSG thanks the S. Wisnia family for their donation dedicated to develop the Desmoid project.

The EpSSG would like to acknowledge the work of many doctors involved in EpSSG activities and research, a special thank you to our patients and their families for having accepted to be enrolled in EpSSG Studies and for having collaborated with us to further improve treatment and care for STS patients.