Friday 27 January 2017, 11:35 – 12:00
Amsterdam

SIOPE SOCIETY DAY
Educational Session

The challenge of very rare cancer in children and adolescents

A. Ferrari (Italy)
on behalf of the EXPeRT board
...all cancers are rare in childhood and, having recognized the rarity of the object of their studies, pediatric oncologists have succeeded in improving their treatment and the related research over the years by cooperating increasingly on national and international levels.

The continuous improvement in our knowledge and ultimately in the outcome of almost all pediatric tumors has always been partly thanks to experts sharing their information and networking.
...however, there is a hierarchy in the studies of childhood cancers...

...pediatric oncologists have been able to develop national multicenter and ultimately international cooperative protocols for most tumors, and in particular for the relatively more common histotypes...

...but not for the less common...

...there remains a small group of very uncommon tumors for which international cooperative studies have rarely (or never) been developed, and children with such rare tumors have not benefited to the same extent from the enormous advances made in pediatric oncology
Definition of very rare tumors (VRT) of pediatric age

TREP project: “any malignancies characterized by an annual incidence of <2 per million in the population up to 18 years old and not considered in other trials”

Rather than by their low incidence, rare pediatric tumors are generally identified by the fact that they are “orphan diseases”, in the sense that:
- most pediatricians might encounter them only once in their working lives,
- there are few or no published reports on clinical experiences,
- it is difficult to establish shared treatment guidelines (and there are no evidence-based therapeutic recommendations available), and
- few or no cooperative groups have dedicated and structured projects, and financial support for studies on these tumors

Based on this definition, liver tumors were not included in the TREP VRT list because they were not “orphan diseases”, since they were being studied by the SIOPEL - a successful example of worldwide cooperation on a rare malignancy); the same applied to other infrequent tumors, such as germ cell tumor or retinoblastoma (which had their own protocols), or rare non-rhabdomyosarcoma soft tissue sarcomas
This definition included a heterogeneous assortment of tumors of diverse biology and clinical history...

...some rare at any age
(such as pleuro-pulmonary blastoma or pancreatoblastoma)

...others rare in children but more common in adults
(e.g. carcinomas, melanoma)

Taken together, these tumors are not as rare as their name suggests, since they account for about 5% of all childhood cancers
However, there is no international agreement on this definition

It may be that the incidence of VRT in pediatric age is still underestimated

“orphan diseases” may be inappropriately classified and diagnosed (and consequently inadequately treated)

coding inconsistencies can also lead to an underestimation of the incidence rates
- e.g. pleuropulmonary blastomas are likely to be registered as sarcomas in population-based registries
- the classification of entities as benign, borderline, or malignant neoplasms may be not easy for some rare neoplasms (such as thymic and adrenal gland tumors)

adult-type tumors treated at adult oncology departments may lead to a lack of registration

Taken together, these tumors are not as rare as their name suggests, since they account for about 5% of all childhood cancers
For many years, rare pediatric tumors only seemed to be of interest to a handful of “amateur collectors of rarities”: it seemed pointless to invest in research because it was impossible to generate valuable results within a reasonable amount of time.

But things are changing...
The first decade of the new millennium has apparently inspired the launch of comprehensive projects dedicated specifically to rare pediatric tumors.

When dedicated schemes for rare pediatric tumors began to appear on the scene, two different models emerged:

1. (adopted mainly in Europe) focusing on large cooperative projects that enrolled all rare tumors (or at least a lengthy list of them) within the same framework

2. (adopted for some tumor types in the US) based on the creation of ad hoc tumor registries for specific entities
   - International Pediatric Adrenocortical Tumor Registry (IPACTR)
   - International Pleuropulmonary Blastoma Registry (IPPBR)
   - NUT Midline Carcinoma Registry
The pioneering Italian TREP project was launched in 2000.

**Position Paper**

**The challenge of very rare tumours in childhood: The Italian TREP project**

Andrea Ferrari\(^1\), Gianni Bisogno\(^2\), Gian Luca De Salvo\(^2\), Paolo Indolfi\(^2\), Giorgio Perilongo\(^2\), Giovanni Cecchetto\(^2,1\), for the Italian Study on Rare Tumours in Paediatric Age (TREP), of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)

- **alliance**
- **network**
  - centralization in dedicated centers
  - cooperation with experts on adult cancer
- **framework**
  - method and discipline essential to cooperation
  - coordination by a central committee
  - development of diagnostic and therapeutic guidelines
  - register patients centrally, treat them homogeneously according to the guidelines
  - collected tumor samples and promoted biological studies
- **dual aim**
  a) conduct research
  b) provide practical clinical guidelines / offer an advisory service (telephone or e-mail consulting service)
Patients (under 18 years old) with VRT prospectively registered from September 2000 to September 2016 in the Italian TREP cooperative study

<table>
<thead>
<tr>
<th>Histotypes</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>thyroid carcinoma</td>
<td>166</td>
</tr>
<tr>
<td>carcinoid/neuroendocrine tumors</td>
<td>154</td>
</tr>
<tr>
<td>melanoma and cutaneous tumors</td>
<td>123</td>
</tr>
<tr>
<td>non-germ-cell tumors (ovary/testis)</td>
<td>109</td>
</tr>
<tr>
<td>nasopharyngeal carcinoma</td>
<td>63</td>
</tr>
<tr>
<td>pancreatoblastoma and other pancreatic tumors</td>
<td>57</td>
</tr>
<tr>
<td>adrenocortical carcinoma</td>
<td>53</td>
</tr>
<tr>
<td>renal cell carcinoma</td>
<td>48</td>
</tr>
<tr>
<td>pheochromocytoma/paraganglioma</td>
<td>45</td>
</tr>
<tr>
<td>pleuropulmonary blastoma and other lung tumors</td>
<td>31</td>
</tr>
<tr>
<td>salivary gland tumors</td>
<td>30</td>
</tr>
<tr>
<td>gastrointestinal carcinoma</td>
<td>21</td>
</tr>
<tr>
<td>carcinoma of the thymus</td>
<td>13</td>
</tr>
<tr>
<td>breast tumors</td>
<td>9</td>
</tr>
<tr>
<td>other malignant tumors</td>
<td>33</td>
</tr>
<tr>
<td>other tumors of intermediate malignancy</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>964</td>
</tr>
</tbody>
</table>

from 39 Centers
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carretto E, et al.</td>
<td>Orphanet J Rare Dis. 2011;6:28</td>
<td>Epithelial thymic tumours in paediatric age: a report from the TREP project</td>
<td></td>
</tr>
<tr>
<td>Magro G, et al.</td>
<td>Hum Pathol. 2012;43(1):31-9</td>
<td>Pediatric adrenocortical tumors: morphological diagnostic criteria and immunohistochemical expression of matrix metalloproteinase type 2 and human leucocyte-associated antigen (HLA) class II antigens. Results from the Italian Pediatric Rare Tumor (TREP) Study project</td>
<td></td>
</tr>
<tr>
<td>Virgone C, et al.</td>
<td>Epidemiol Infect 2015; 143(7):1552-5</td>
<td>Bowel parasitosis and neuroendocrine tumours of the appendix. A report from the Italian TREP project</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 1. Number of Children (0–14) and Adolescents (15–17) Enrolled in the TREP Project During 2000–2006 (O) and Expected Number of Cases in Italy on the Basis of the Incidence Rates Recorded by the Italian Network of Cancer Registries-AIRTUM (E)

<table>
<thead>
<tr>
<th>Cancer types</th>
<th>0–14</th>
<th>15–17</th>
</tr>
</thead>
<tbody>
<tr>
<td>O/E (95% CI)</td>
<td>O/E (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>19/14</td>
<td>1.36 (0.65–2.92)</td>
</tr>
<tr>
<td>Adrenocortical tumors</td>
<td>23/17</td>
<td>1.35 (0.69–2.70)</td>
</tr>
<tr>
<td>Pleuro-pulmonary blastoma (and other lung tumors)</td>
<td>13/1.9</td>
<td>6.84 (1.51–67.67)</td>
</tr>
<tr>
<td>Carcinoids of appendix</td>
<td>49/25</td>
<td>1.96 (1.19–3.31)</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>19/62</td>
<td>0.31 (0.17–0.52)</td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td>20/24</td>
<td>0.83 (0.44–1.57)</td>
</tr>
<tr>
<td>Pancreaticoblastoma (and other pancreatic exocrine tumors)</td>
<td>11/1.8</td>
<td>6.11 (1.26–67.16)</td>
</tr>
<tr>
<td>Gonadal non-germ-cell tumors (ovary/testis)</td>
<td>27/41</td>
<td>0.66 (0.39–1.10)</td>
</tr>
<tr>
<td>Pheochromocytoma and paraganglioma</td>
<td>18/3.6</td>
<td>5.00 (1.58–22.21)</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>50/91</td>
<td>0.55 (0.38–0.78)</td>
</tr>
<tr>
<td>Salivary gland tumors</td>
<td>5/22</td>
<td>0.23 (0.07–0.62)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>1/0</td>
<td>—</td>
</tr>
<tr>
<td>Carcinoma of the gastrointestinal tract (VRT)</td>
<td>3/1.8</td>
<td>1.67 (0.18–23.40)</td>
</tr>
<tr>
<td>Carcinoma of the thymus</td>
<td>3/0</td>
<td>—</td>
</tr>
</tbody>
</table>

Comparing the number of cases actually registered under the TREP project with the number of cases to be expected on the grounds of epidemiological data:

A large proportion of the number of under 15-year-olds in Italy expected to develop VRT were registered (85%), but only a small proportion of the adolescents with tumors of adult type (18%).

$$\text{Expected cases: 305} \quad \text{Observed cases: 271}$$
The challenge of very rare cancer in children and adolescents

<table>
<thead>
<tr>
<th>Cooperative rare tumors group</th>
<th>National Society</th>
<th>Year of foundation</th>
<th>National coordinators</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREP project (Tumori Rari in Età Pediatrica)</td>
<td>Associazione Italiana Ematologia Oncologia Pediatrica AIEOP Società Italiana Chirurgia Pediatrica SICP</td>
<td>2000</td>
<td>Gianni Bisogno Giovanni Cecchetto Andrea Ferrari</td>
</tr>
<tr>
<td>PPRTSG (Polish Pediatric Rare Tumors Study Group)</td>
<td>Polish Pediatric Solid Tumors Study Group</td>
<td>2002</td>
<td>Ewa Bien Jan Godzinski Teresa Stachowicz-Stenzel</td>
</tr>
<tr>
<td>STEP (seltene Tumoren in der Pädiatrie)</td>
<td>German Society of Pediatric Oncology and Hematology</td>
<td>2006</td>
<td>Ines Brecht Dominik T. Schneider</td>
</tr>
<tr>
<td>UK Rare Tumour Working Group</td>
<td>United Kingdom’s Children’s Cancer &amp; Leukaemia Group UKCCLG</td>
<td>1997 (registry only)</td>
<td>Bernadette Brennan</td>
</tr>
</tbody>
</table>

very similar goals
some differences
(each organization has its own characteristics, and different registration/classification policies)
These experiences demonstrated that research and prospective studies are feasible even for such rare tumors... 
...but also that the number of patients with a given tumor type recruitable in national-scale protocols within a reasonable period of time will never suffice for the purposes of randomized clinical trials designed to answer certain questions...

In other words, these experiences highlighting the need to go a step further and create larger, international, prospective cooperative projects to improve the quality of the studies.

It is in this setting that the EXPeRT was launched to promote international clinical and biological research on rare pediatric tumors.
The challenge of very rare cancer in children and adolescents

The founding of the European Cooperative Study Group on Pediatric Rare Tumors – EXPeRT


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Gianni Bisignano
Department of Pediatrics, Pediatrics University Hospital Thessaloniki, Greece

If you work on frequent cancers, do randomized trials! If you work on rare cancers – FIND FRIENDS!

The preface to the recently published book on ‘Rare Tumors in Children and Adolescents’, edited by some of the authors of this manuscript, begins with this evocative sentence: “If you work on frequent cancers, do randomized trials! If you work on rare cancer – FIND FRIENDS!” (1). This is exactly the spirit that led to the foundation of the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), the first seeds of which were sown in 2008. National groups working in Italy, France, the UK, Poland and Germany join forces in EXPeRT in the conviction that children with very rare tumors may benefit from a close-knit, stronger international network, and that the project is now officially supported by the International Society of Paediatric Oncology (2).

...the common denominator of rare pediatric tumors lies in their being ‘orphan’ diseases.

In actual fact, all cancers are rare in childhood and, having recognized the rarity of the object of their studies, pediatric oncologists have succeeded in improving their treatment and the related research over the years by increasingly cooperating on national and international levels. The continuous improvement in our knowledge and ultimately in the outcome of almost all pediatric tumors has always been partly thanks to experts sharing their information and networking. There nonetheless remains a small group of very uncommon tumors for which international cooperative studies have rarely or never been developed, and children with such rare tumors have not benefited from the same extent from the enormous advances made in pediatric oncology. This is the case of tumors generally having an annual incidence of <2 in a million (3), a heterogeneous assortment of neoplasms that are rare at any age (e.g., phaeochromocytoma or pancreaticoblastoma), or that may be rare in childhood but more common in adulthood (e.g., carcinomas and melanomas, although they often seem to be biologically and clinically distinct from their adult counterparts (4). Taken together, these tumors are not so rare as their name suggests, since they account for approximately 5% of all childhood cancers. More than their low incidence, however, the common denominator of rare pediatric tumors lies in their being ‘orphan’ diseases, which means that few clinical and biological details are available on them; no specific clinical or scientific organizations have been established to support their clinical management and research, it is very difficult – or even impossible – to conduct clinical trials on them and this makes it hard to arrive at evidence-based (or even shared) treatment guidelines, so their treatment is usually individualized; and dedicated financial resources are limited.

Pediatric oncologists and surgeons only occasionally see patients with these tumors, which they ‘almost never’ diagnose in their clinical cancer and, when they do, they generally feel unprepared.

Bisignano G et al. Rare cancers in children... Klin Padiatr 2012; 224: 416-420

Rare Cancers in Children – The EXPeRT Initiative: A Report from the European Cooperative Study Group on Pediatric Rare Tumors

Seltene Tumoren bei Kindern – die EXPeRT Initiative: Ein Bericht der European Cooperative Study Group on Pediatric Rare Tumors

The EXPeRT started by establishing a board that arrived at a consensus on the definition of VRT, and made plans to develop harmonized and internationally recognized guidelines, a consultation network to assist with difficult clinical decisions, and ultimately to create a joint international prospective case registry.

In the absence of financial support, however, the group’s first undertakings involved organizing joint retrospective studies on specific VRTs in order to collect relatively large series that might enable treatment-related risk stratification and lead to homogeneous therapeutic recommendations.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Series</th>
<th>Main results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bien et al., 2011</td>
<td>Pancreatoblastoma</td>
<td>5-year EFS 58.8% 5-year OS 79.4% rate of response to chemotherapy 73%</td>
<td>Development of a standardized approach to the diagnosis and management of pancreatoblastoma, and a prognostically relevant surgical staging system. Proposal for multimodal treatment approach (conservative surgery followed by cisplatin-doxorubicin chemotherapy and postponed aggressive surgery on primary tumor and metastases)</td>
</tr>
<tr>
<td>Schneider et al., 2010</td>
<td>Sertoli-Leydig Cell Tumors</td>
<td>5-year EFS 70% 5-year OS 87% stage, histopathological differentiation and</td>
<td>Identification of possible prognostic factors, i.e. intraoperative tumor rupture and histological differentiation. Development of diagnostic and treatment guidelines (including cisplatin-based regimen)</td>
</tr>
<tr>
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<td>intra/preoperative rupture or positive ascitis determine prognosis impact</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>of chemotherapy in incompletely resected and advanced stages still to be</td>
<td></td>
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<td></td>
<td></td>
<td>assessed</td>
<td></td>
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<tr>
<td>Bisogno et al., 2013</td>
<td>Pleuropulmonary blastoma</td>
<td>Type I: 5-year EFS 83.3% OS 91.7% . Type II/III: 5-year EFS 42.9% OS 57.5%</td>
<td>Identification of a common therapeutic approach Identification of prognostic factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable prognostic factors: complete tumor resection at diagnosis and</td>
<td>Identification of prognostic factors</td>
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<tr>
<td></td>
<td></td>
<td>absence of invasiveness role of doxorubicin-based chemotherapy in type</td>
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<td></td>
<td></td>
<td>II/III type (5-year EFS 70% vs 31.3% in patients with or without</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>doxorubicin-based regimens)</td>
<td></td>
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<tr>
<td>Stachowicz-Stencel et al., 2014</td>
<td>Thymoma and thymic carcinoma</td>
<td>16 thymomas: 14 pts are alive with no evidence of disease 20 carcinomas:</td>
<td>Common therapeutic guidelines in pediatric population have yet to be established. Surgical excision remains the milestone of treatment. The role of chemotherapy is unclear.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 patients alive, 5-year OS 21% surgical R0 resection: milestone of treatment</td>
<td>Further studies are needed on larger samples to validate treatment guidelines.</td>
</tr>
<tr>
<td>Cecchetto et al., 2017</td>
<td>Adrenocortical carcinomas</td>
<td>3-year EFS 38.8% OS 54.7% survival rates influenced by distant metastases,</td>
<td>Identification of common treatment strategy (exclusive surgery if R0 achievable; if not, neoadjuvant chemotherapy with various regimens and delayed surgery in case of response). Issues: prognostic factors in adult population lack sensitivity and specificity. Different staging systems and pathological malignancy criteria make it difficult to establish comparative studies and identify patients in need of perioperative treatment. Complete surgical resection is fundamental whenever possible. The impact of chemotherapy could not be ascertained.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tumor volume, lymph node involvement, age, vascular involvement and</td>
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<tr>
<td></td>
<td></td>
<td>incomplete surgery for localized disease alone: EFS 51.1% OS 73%</td>
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“find friends” underscores the fundamental need to establish multi-level, wider and wiser international cooperation schemes to improve the quality of care for these patients

“find friends” also somehow expresses the spirit that led to the founding of EXPeRT

*If you work on frequent cancers, do randomized trials! If you work on rare cancers – FIND FRIENDS!*
Structure of the European Cooperative Study Group on Pediatric Rare Tumors

EXPeRT chair:

- The assembly elects the chairperson, who is also the EXPeRT representative to SIOP-E, and the vice chairperson
- The chairpersons are elected for 2 years, they can be re-elected for a second consecutive term
The challenge of very rare cancer in children and adolescents

The harmony between the members of the EXPeRT project, and the fact that it is the outcome of a genuinely spontaneous undertaking by a group of friends is wonderful, but also a potential weakness. For many years, research on pediatric VRT were conducted by a handful of “amateur collectors of rarities”...

What is needed now in order to go forward is a breakthrough in terms of a broad, shared institutional recognition and opportunities to embark on new forms of cooperation, not only with our "friends"

- we need to reinforce the cooperation with adult medical oncology organizations, because many pediatric VRTs are tumors typical of adult age

- we need to increase the resources available for biological studies, especially because there is a growing body of evidence to suggest that a given tumor’s biology (and therefore its clinical history) may not be the same when it occurs in adults or in children

- we need to develop new partnerships that may be more complicated to manage, but are now indispensable, with organizations such as pharmaceutical industries, regulatory authorities, and international funding bodies
**The challenge of very rare cancer in children and adolescents**

- **colorectal cancer** - higher incidence of unfavorable, poorly-differentiated histotypes, advanced clinical stages already at onset, and a significantly worse survival rate for pediatric cases than for adults; faster tumorigenesis

- **renal cell carcinoma** - distinct pediatric subtype characterized by translocations involving chromosome Xp11.2, the TFE3 gene locus

- **papillary thyroid carcinoma** – 100% survival, irrespective of the clinical findings and despite its strong tendency for loco-regional and distant spread; RET/PCR3 translocation (adult tumors: BRAF mutation)

- **GIST** - females, stomach, multifocal and slow-growing; wild-type for KIT and PDGFRA genes.

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The challenge of very rare cancer in children and adolescents

- We need to reinforce the cooperation with adult medical oncology organizations, because many pediatric VRTs are tumors typical of adult age.

- We need to increase the resources available for biological studies, especially because there is a growing body of evidence to suggest that a given tumor’s biology (and therefore its clinical history) may not be the same when it occurs in adults or in children.

- We need to develop new partnerships that may be more complicated to manage, but are now indispensable, with organizations such as pharmaceutical industries, regulatory authorities, and international funding bodies.
ExPO-r-Net is a 3-year project (2014-2017) funded by the European Union (in the framework of its Health Programme 2008-2013) and developed under a EU directive focusing on patients’ rights and healthcare across the Union. This directive concerns the need to develop and support European reference networks for the purpose of improving access to highly specialized health care (and reducing inequalities across European Member States) for patients suffering from low-prevalence diseases requiring particular expertise.

ExPO-r-Net has been designed as a model for a broader subsequent project, the European Reference Network for Paediatric Oncology.
European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment

Among its goals, ExPO-r-Net aims to link existing hubs for coordinating childhood cancer treatment and care. Hence the involvement of EXPeRT, which provides a basis for establishing a pilot European reference network of pediatric oncology centers dealing with VRTs, and with rare soft tissue sarcoma subtypes, in cooperation with the European pediatric Soft tissue sarcoma Study Group (EpSSG)

Specific objectives of this work package

<table>
<thead>
<tr>
<th>Specific Objective #</th>
<th>Specific objective title</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Integrating very rare tumors and soft tissue sarcomas into an European reference network.</td>
</tr>
</tbody>
</table>

List of deliverable(s) linked to this work package

<table>
<thead>
<tr>
<th>Deliverable #</th>
<th>Outcomes / Deliverable title</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Standard of care guidelines for VRT and very rare STS.</td>
</tr>
</tbody>
</table>

Milestones reached by this work package

<table>
<thead>
<tr>
<th>#</th>
<th>Milestone title</th>
<th>Month of achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Establishment of VRT Network tumor board and working group on rare STS in collaboration with EpSSG.</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Establishment of a website dedicated to inform families and the public. This website will be linked to the main ExPO-r-Net webpage.</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>European meeting to reach consensus on guidelines for VRTs and rare STS.</td>
<td>24</td>
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</table>
The financial support obtained through the ExPO-r-Net project has given EXPeRT the chance to conduct its activities, strengthen cooperation with healthcare authorities, and adopt e-Health solutions to facilitate the exchange of information and knowledge rather than transfer patients, whenever possible.
**EXPeRT / ExPO-r-Net**

Aim: seeking to ascertain what action is taken on a national scale for children with VRTs in the various European countries.
This is an important aspect of the ExPO-r-Net project because one of its essential goals is to reduce inequalities in childhood cancer survival and health care capabilities in different Member States.

A simple online survey was conducted by contacting the chairs of each European national pediatric oncology society/association (and/or the coordinators of any national cooperative group dedicated to VRT). Respondents from a total of 36 countries (including Turkey and Israel) took part in the survey.
The results showed that a structured, national cooperative group focusing on VRTs existed in **less than 30% of European countries** (i.e. Italy, Germany and Austria, Poland, France, Spain, and the Netherlands), while a national registry for all pediatric tumors (including VRTs) is in operation in the UK/Ireland and in Hungary.
Two new VRT groups were set up in Croatia and Israel in 2015, after being invited to cooperate with the EXPO-r-Net.
Taken together, these schemes cover **less than 60% of the European population**.

The lack of such groups was justified by the limited clinical and scientific priority of pediatric VRTs and/or the lack of trained staff. Some respondents said that the number of children with VRTs is too small to justify the allocation of dedicated resources.

Conclusions:
1. in many European countries, pediatric VRTs are not managed as effectively as other more common childhood cancers
2. an international network based on the experience gained by EXPeRT, would be important for the purpose of establishing standards of care, enabling consultations, and facilitating access to expert centers
3. the EXPO-r-Net project can help to create the necessary tools (website, tumor board, standard guidelines)
VRT projects outside Europe

COG
Rare Tumors Committee (formed in 2002)
4 subcommittees to address a) infrequent tumors (more or less corresponding to the tumors in the European groups’ VRT lists), b) liver tumors, c) germ cell tumors, d) retinoblastoma

GALOP - Grupo de América Latina de Oncología Pediátrica

Guatemala/AHOPCA - Asociacion de Hemato-Oncologia Pediatrica de Centro America

Jordan (twinning programs, multidisciplinary tumor boards with experts in adult oncology)
The challenge of very rare cancer in children and adolescents

EXPeRT / ExPO-r-Net

1. the website (to inform families and the non-scientific community)
2. harmonized recommendations/guidelines
3. the virtual tumor board and advisory desk
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- Pleuropulmonary blastoma
- Pancreatoblastoma
- Infantile fibrosarcoma
- Sex cordal stromal tumors
- Thymoma and thymic carcinoma
- Alveolar soft part sarcoma
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1. the website (to inform families and the non-scientific community)

2. harmonized recommendations/guidelines

3. the virtual tumor board and advisory desk

First phase
by email (with an ad hoc consultation request form)
to the dedicated EXPeRT address expert-advice@klinikumdo.de

5-months activity report:
• 143 requests sent to the various national coordinators taking part in the EXPeRT project;
• 48 of these requests were also discussed on the EXPeRT international platform
• 24 requests came from within the EU, 24 from elsewhere
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**Second phase**

By mid-2017, a virtual tumor board platform will be online, where clinical data, reports, and images (including DICOM data) can be uploaded.

Different virtual tumor panels (focusing on specific tumor types) with a moderator/panel leader need to ascertain the workload for the members of the various panels, and decide how to quantify this consulting work in terms of the amount of time these professionals spend on this activity instead of their normal jobs (in future, it may be possible, or necessary, to consider some sort of compensation from public and private health care providers for the centers involved in this consulting process).
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The EXPO-r-Net experience goes to show that: adequate economic support is indispensable in order to pursue further improvements in the study and treatment of rare pediatric tumors age; and the quality of a study, especially on rare tumors, is an essential factor when it comes to attracting funds.
Joint Action on Rare Cancers (JARC)
Work Package 9 – Childhood Cancers
Task 3: “Identifying solutions for delivering optimal care and research for young people with extremely rare cancers”

Task 3 Work Plan 2017

Task Leader: GPOH - German Society of Paediatric Oncology and Hematology - University of Tuebingen
An important collaboration that EXPeRT is already seeking to implement is with the European Innovative Therapies for Children with Cancer (ITCC) consortium, based on the idea that EXPeRT could also have a key role in decisions on how to develop early-phase trials with new agents for rare tumors. The expertise and networking capabilities of the pediatric VRT cooperative groups are needed to optimize the planning of such trials, which are extremely difficult to undertake when dealing with rare neoplasms.
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Many different diseases:
- nasopharyngeal carcinoma
- adrenocortical tumor
- pleuro-pulmonary blastoma
- neuroendocrine tumors
- melanoma
- renal cell carcinoma
- pancreatoblastoma
- other pancreatic exocrine tumors
- gonadal non-germ-cell tumors
- pheochromocytoma/paraganglioma
- thyroid carcinoma
- salivary gland tumours
- GIST
- breast carcinoma
- GI carcinoma
- carcinoma of the thymus

Give priorities... according to the prognosis? according to the frequency?

We have been able to create the networks, but we are not real experts of these diseases (most are adult-type tumors)

Similarly, it is difficult (not impossible, but difficult) to find adequate experience on biology within our groups

Need to involve “adult” experts

We have effective networks!
We can offer the framework...
We know “our” centers and “our” samples...

Pharmas are obliged by Pediatric Regulation...
...do they have a real interest for so small numbers...?
Are their needs the same of ours?
Dedicated cohorts in adult protocols (adolescents)?

We do not have standardized therapeutic strategies (or ongoing clinical trials) for most of very rare tumors

How to develop new anticancer drugs in children and prioritize?
through
- Biology driven new drug development strategy by disease
- That is integrated into current therapeutic strategies and ongoing/planned clinical trials
- Towards personalized medicine
- Providing a frame for partnership with Pharma and for PIP evaluation
- To be run through Inter-group coordination and steering of the programme
- Facilitating co-funding at the EU and national levels

Give priorities... according to the prognosis? according to the frequency?
In recent years, there have been several instances of international cooperative clinical trials (e.g. for advanced melanoma or GIST) involving pediatric patients, which have undeniably led to potentially effective, innovative target therapies becoming available for such children too. But they have also brought to light considerable difficulties with recruitment at pediatric oncology centers, and the problem of the excessive amount of time it takes for such trials to be completed.

Stronger cooperation between pediatric reference centers dealing with rare tumors, adult oncology centers, consortia dedicated to the development of new drugs, and pharmaceutical companies could certainly improve this aspect, enabling different courses of action to be taken so that new drugs can be offered to pediatric patients (dedicated cohorts of children could be included in adult protocols, for instance).
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- Our friendship!
- The Network!
- The capability to work together
- ...already demonstrated feasible

- Current general interest... (fashionable)
- Nobody better than us...
- Many spaces for working, publishing, having visibility for everybody want to play
- Do it! Real need of research, data, guidelines
- Cooperation with adult world...
- Many different diseases...
- More doctors than patients!
- We are not real experts!
- (perhaps) not fully dedicated...
- No fund

- Cooperation with adult world...
- ...tremendous effort, unfruitful investment (no valuable results within a reasonable amount of time)...

- Enhanced SWOT Analysis
  - Strengths
    - How do I use these strengths to take advantage of these opportunities?
    - How do I overcome the weaknesses that prevent me taking advantage of these opportunities?
  - Weaknesses
    - How do I use my strengths to reduce the likelihood and impact of these threats?
    - How do I address the weaknesses that will make these threats a reality?
  - Opportunities
    - Translate into tasks for the Project Plan
  - Threats
...more strengths than weakness

Thank you