SIOP Europe

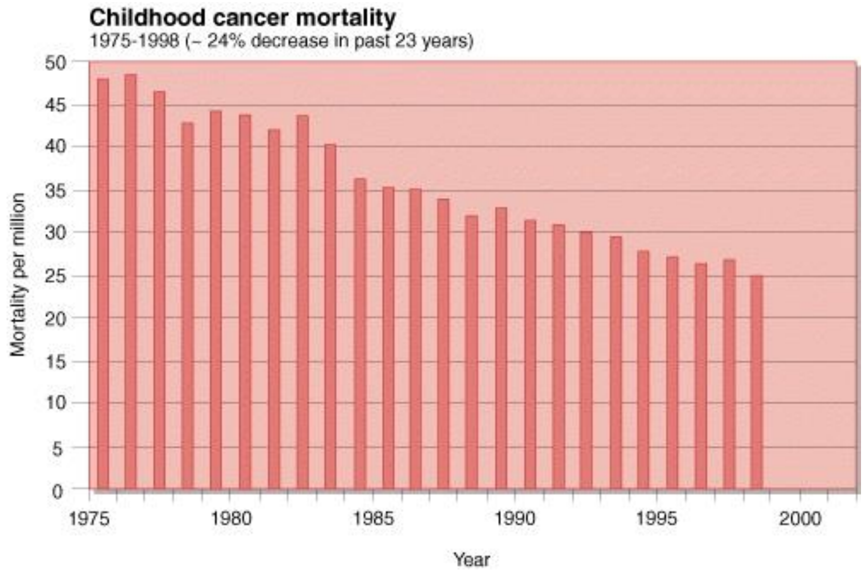
Friday 27 January 2017, 11:35 – 12:00
Amsterdam

SIOPE SOCIETY DAY
Educational Session

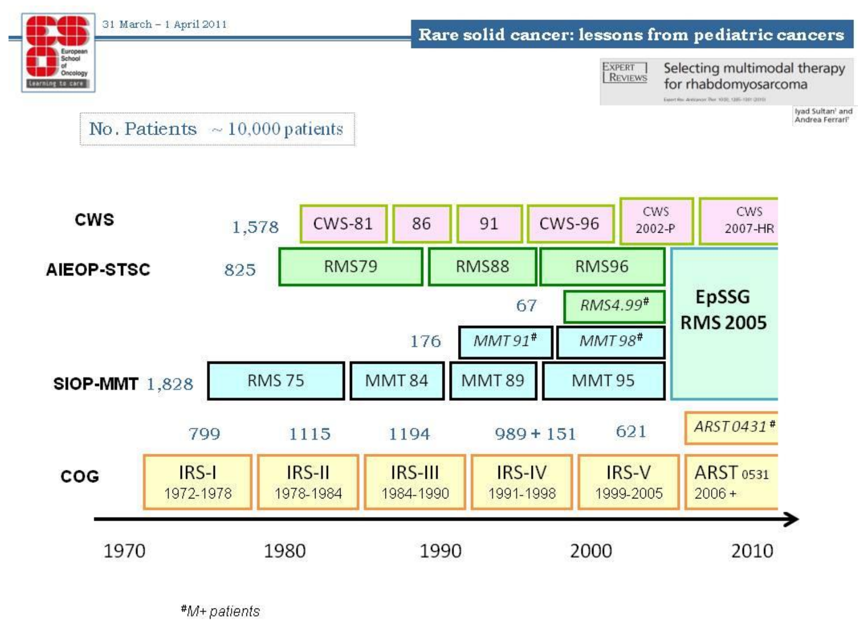
The challenge of very rare cancer in children and adolescents

A. Ferrari (Italy)
on behalf of the EXPeRT board

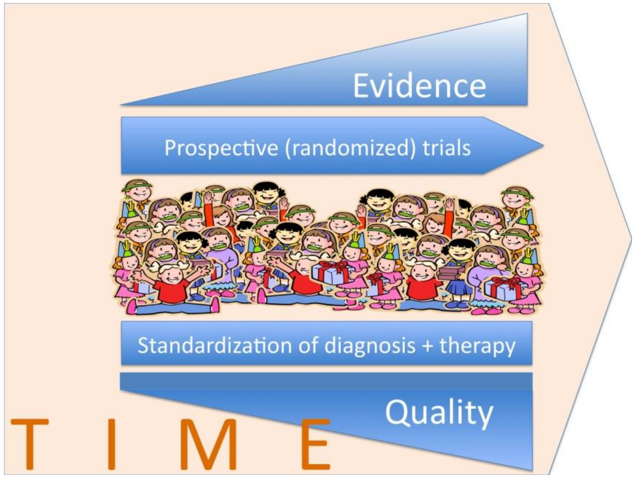
…all cancers are rare in childhood and, having recognized the rarity of the object of their studies, pediatric oncologists have succeeded in improving their treatment and the related research over the years by cooperating increasingly on national and international levels.



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.

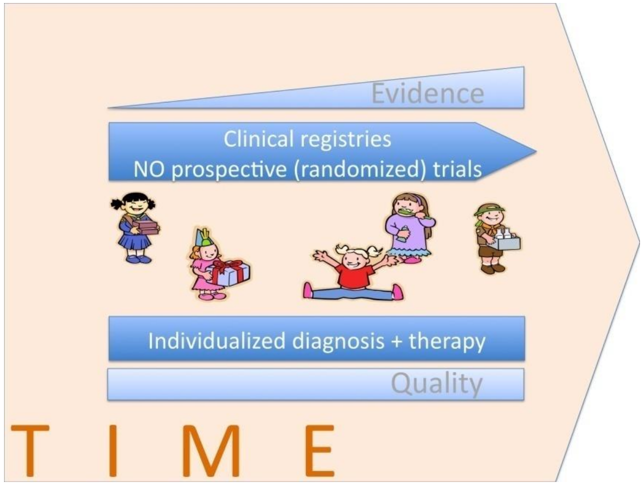


…however, there is a hierarchy in the studies of childhood cancers...



…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:

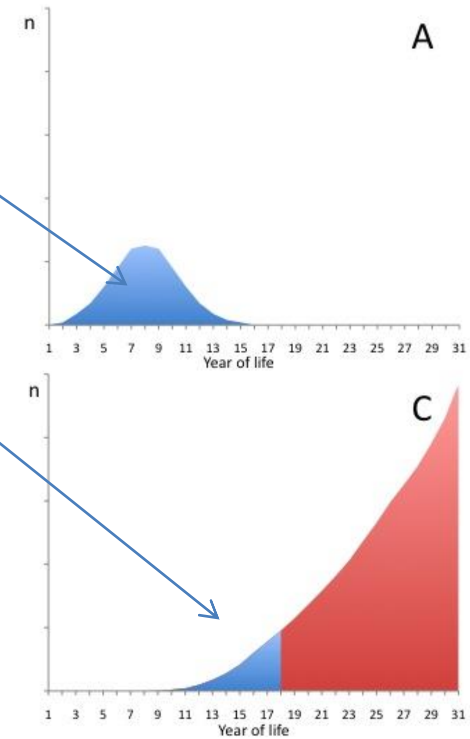
- most pediatricians might encounter them only once in their working lives,
- there are few or no published reports on clinical experiences,
- it is difficult to establish shared treatment guidelines (and there are no evidence-based therapeutic recommendations available), and
- few or no cooperative 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

TREP PROJECT
tumori rari in età pediatrica

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journal homepage: www.ejconline.com
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Position Paper

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

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The pioneering Italian TREP project was launched in 2000

- 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

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

from 39 Centers

Indolfi P, et al. Pediatr Blood Cancer 2007;8(3):318-323	Prognostic factors in **pleuro-pulmonary blastoma**
Dall'Igna P, et al. Pediatr Blood Cancer 2010; 54(5):675-80	**Pancreatic tumors** in children and adolescents: the Italian TREP Project experience
Cecchetto G, et al. J Pediatr Surg. 2010;45(9):1868-73	**Sex cord-stromal tumors of the testis** in children. A clinicopathologic report from the Italian TREP project
Cecchetto G, et al. Ped Blood Cancer 2011;56(7):1062-7	**Sex cord stromal tumors of the ovary** in children. A clinicopathological report from the Italian TREP project
Carretto E, et al. Orphanet J Rare Dis. 2011;6:28	**Epithelial thymic tumours** in paediatric age: a report from the TREP project
Casanova M, et al. Cancer 2012;118(10):2718-25	A prospective protocol for **nasopharyngeal carcinoma** in children and adolescents: the Italian Rare Tumors in Pediatric Age (TREP) project
Bisogno G, et al. BMC Cancer. 2012;5;12:117	**Esthesioneuroblastoma** in pediatric and adolescent age. A report from the TREP project in cooperation with the Italian Neuroblastoma and Soft Tissue Sarcoma Committees
Magro G, et al. Hum Pathol. 2012;43(1):31-9	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
Virgone C, et al. PLoS One. 2012;7(9):e45914	GATA-4 and FOG-2 expression in pediatric ovarian **sex cord-stromal tumors** replicates embryonal gonadal phenotype: results from the TREP Project
Chiaravalli S, et al. Pediatr Blood Cancer. 2014;61(11):1961-8	**Salivary gland carcinomas** in children and adolescents: the Italian TREP project experience
Bisogno G, et al. Pediatr Blood Cancer. 2014;61(4):643-6	**Myoepithelial carcinoma** treatment in children: a report from the TREP project
Ferrari A, et al. J Pediatr. 2014;164(2):376-82.e1-2	**Cutaneous melanoma** in children and adolescents: the Italian Rare Tumors in Pediatric Age project experience
Dall'Igna P, et al. J Pediatr Surg 2014;49(9):1367-71	**Adrenocortical tumors** in Italian children: analysis of clinical characteristics and P53 status. Data from the national registries
Virgone C, et al. J Pediatr Gastroenter Nutr 2014;58(3):333-8	**Appendiceal neuroendorine tumors** (carcinoid of the appendix) in childhood: a clinical report from the Italian TREP project
Virgone C, et al. J Pediatr Adolesc Gynecol. 2015;28(6):441-6	**Epithelial tumors of the ovary** in children and teenagers: a prospective study from the Italian TREP Project
Massi D, et al. J Am Acad Dermatol 2015;72(1):37-46	**Atypical Spitz tumors** in patients younger than 18 years
Virgone C, et al. Epidemiol Infect 2015; 143(7):1552-5	Bowel parasitosis and **neuroendocrine tumours** of the appendix. A report from the Italian TREP project
Di Carlo D, et al. Pediatr Blood Cancer 2015;62(6):1000-3	Management and follow-up of **urothelial neoplasms of the bladder** in children: a report from the TREP project
Spinelli C, et al. J Endocrinol Invest 2016;39(9):1055-9	Surgical management of **papillary thyroid carcinoma** in childhood and adolescence: an Italian multicenter study on 250 patients

Pediatr Blood Cancer 2009;53:152–155

Evaluating Access to Pediatric Cancer Care Centers of Children and Adolescents With Rare Tumors in Italy: The TREP Project

Guido Pastore, MD,[1,2] Gian Luca De Salvo, MD,[3] Gianni Bisogno, MD,[4] Elisa Dama, MD,[1] Alessandro Inserra, MD,[5] Giovanni Cecchetto, MD,[6] and Andrea Ferrari, MD[7]*
on behalf of the TREP Group and the CSD of Epidemiology Biostatistics, AIEOP

AIRTUM

TABLE I. 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)

	0–14			15–17		
Cancer types	O	E	O/E (95% CI)	O	E	O/E (95% CI)
Nasopharyngeal carcinoma	19	14	1.36 (0.65–2.92)	13	13	1.00 (0.43–2.34)
Adrenocortical tumors	23	17	1.35 (0.69–2.70)	2	4.4	0.45 (0.04–2.99)
Pleuro-pulmonary blastoma (and other lung tumors)	13	1.9	6.84 (1.51–67.67)	1	0.0	—
Carcinoids of appendix	49	25	1.96 (1.19–3.31)	7	30	0.23 (0.09–0.54)
Cutaneous melanoma	19	62	0.31 (0.17–0.52)	8	107	0.07 (0.03–0.15)
Renal carcinoma	20	24	0.83 (0.44–1.57)	2	8.7	0.23 (0.02–1.12)
Pancreatoblastoma (and other pancreatic exocrine tumors)	11	1.8	6.11 (1.26–67.16)	1	4.4	0.23 (0.00–2.17)
Gonadal non-germ-cell tumors (ovary/testis)	27	41	0.66 (0.39–1.10)	3	39	0.08 (0.02–0.24)
Pheochromocytoma and paraganglioma	18	3.6	5.00 (1.58–22.21)	0	0.0	—
Thyroid carcinoma	50	91	0.55 (0.38–0.78)	32	159	0.20 (0.13–0.30)
Salivary gland tumors	5	22	0.23 (0.07–0.62)	1	26	0.04 (0.00–0.23)
Breast carcinoma	1	0.0	—	1	0	—
Carcinoma of the gastrointestinal tract	3	1.8	1.67 (0.18–23.40)	3	8.7	0.34 (0.06–1.40)
Carcinoma of the thymus	3	0.0	—	1	0	—

Period 2000-2006	0-14 year	15-17 year
Expexted cases	**305**	**400**
Observed cases	**271**	**75**

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%)

Cooperative rare tumors group	National Society	Year of foundation	National coordinators
TREP project (Tumori Rari in Età Pediatrica)	Associazione Italiana Ematologia Oncologia Pediatrica AIEOP Società Italiana Chirurgia Pediatrica SICP	2000	Gianni Bisogno Giovanni Cecchetto Andrea Ferrari
PPRTSG (Polish Pediatric Rare Tumors Study Group)	Polish Pediatric Solid Tumors Study Group	2002	Ewa Bien Jan Godzinski Teresa Stachowicz-Stenzel
STEP (seltene Tumoren in der Pädiatrie)	German Society of Pediatric Oncology and Hematology	2006	Ines Brecht Dominik T. Schneider
FRACTURE (groupe FRAnCais des TUmeurs Rares de l'Enfant)	French Pediatric Oncological Society SFOP in association with the French National Cancer Registry	2007	Daniel Orbach Yves Reguerre
UK Rare Tumour Working Group	United Kingdom's Children's Cancer & Leukaemia Group UKCCLG	1997 (registry only)	Bernadette Brennan

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.

Editorial

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

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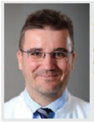
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Hematology-Oncology Division, Department of Pediatrics, Padova University Hospital, Padova, Italy
On behalf of the EXPeRT Board‡

‡The authors belonging to the EXPeRT Board are listed in Appendix 1

"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 cancers – 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 closer-knit, stronger international network, and 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 to 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., pleuropulmonary blastoma or pancreatoblastoma), or that may be rare in childhood but more common in adulthood (e.g., carcinomas and melanoma), although they often seem to be biologically and clinically distinct from their adult counterparts [4]. Taken together, these tumors are not as 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 careers and, when they do, they generally feel unprepared

Keywords: cancer • children • EXPeRT • orphan disease • rare tumors

Expert Reviews

Bisogno 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

G. Bisogno[1, *], A. Ferrari[2, *], E. Bien[3], I. B. Brecht[4], B. Brennan[5], G. Cecchetto[6], J. Godzinski[7], D. Orbach[8], Y. Reguerre[9], T. Stachowicz-Stencel[3], D. T. Schneider[10, *]

EXPeRT

European Cooperative Study 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.

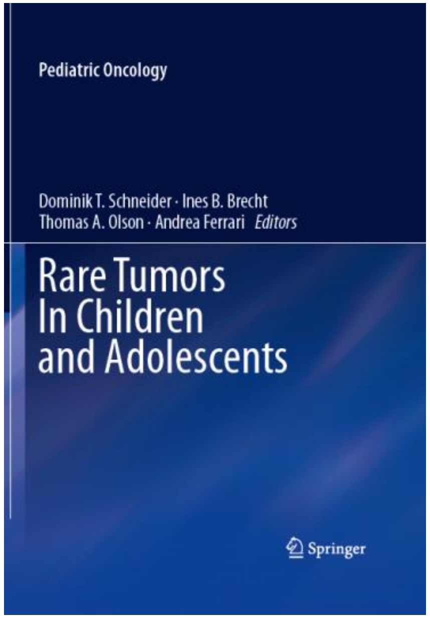
In the absence of financial support, however, the group's first undertakings involved organizing **joint retrospective studies on specific VRTs** in order to collect relatively large series that might enable treatment-related risk stratification and lead to homogeneous therapeutic recommendations.

Published retrospective studies by EXPeRT (European Cooperative Study Group for Pediatric Rare Tumors)

Publication	Series	Main results	Comments
Bien et al., 2011 **Pancreatoblastoma**	20 patients study period 2000 - 2009	5-year EFS 58.8% 5-year OS 79.4% rate of response to chemotherapy 73% outcome correlates with complete surgical excision	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)
Schneider et al., 2010 **Sertoli-Leydig Cell Tumors**	44 patients study period 1993-2008 (depending on country)	5-year EFS 70% 5-year OS 87% stage, histopathological differentiation and intra/preoperative rupture or positive ascitis determine prognosis impact of chemotherapy in incompletely resected and advanced stages still to be assessed	Identification of possible prognostic factors, i.e. intraoperative tumor rupture and histological differentiation. Development of diagnostic and treatment guidelines (including cisplatin-based regimen)
Bisogno et al., 2013 **Pleuropulmonary blastoma**	65 patients study period 2000 - 2009	Type I: 5-year EFS 83.3% OS 91.7% . Type II/III: 5-year EFS 42.9% OS 57.5% favorable prognostic factors: complete tumor resection at diagnosis and absence of invasiveness role of doxorubicin-based chemotherapy in type II/III type (5-year EFS 70% vs 31.3% in patients with or without doxorubicin-based regimens)	Identification of a common therapeutic approach Identification of prognostic factors
Stachowicz-Stencel et al., 2014 **Thymoma and thymic carcinoma**	36 patients 16 thymomas and 20 thymic carcinomas study period 2000 - 2012	16 thymomas: 14 pts are alive with no evidence of disease 20 carcinomas: 5 patients alive, 5-year OS 21% surgical R0 resection: milestone of treatment	Common therapeutic guidelines in pediatric population have yet to be established. Surgical excision remains the milestone of treatment. The role of chemotherapy is unclear. Further studies are needed on larger samples to validate treatment guidelines.
Cecchetto et al., 2017 **Adrenocortical carcinomas**	82 patients study period 2000 - - 2013	3-year EFS 38.8% OS 54.7% survival rates influenced by distant metastases, tumor volume, lymph node involvement, age, vascular involvement and incomplete surgery for localized disease alone: EFS 51.1% OS 73%	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.

“*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!

EXPeRT

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 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

✓***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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European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment

ExPO-r-Net

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)

ExPO-r-Net

Specific objectives of this work package

Specific Objective #	Specific objective title
6	Integrating very rare tumors and soft tissue sarcomas into an European reference network.

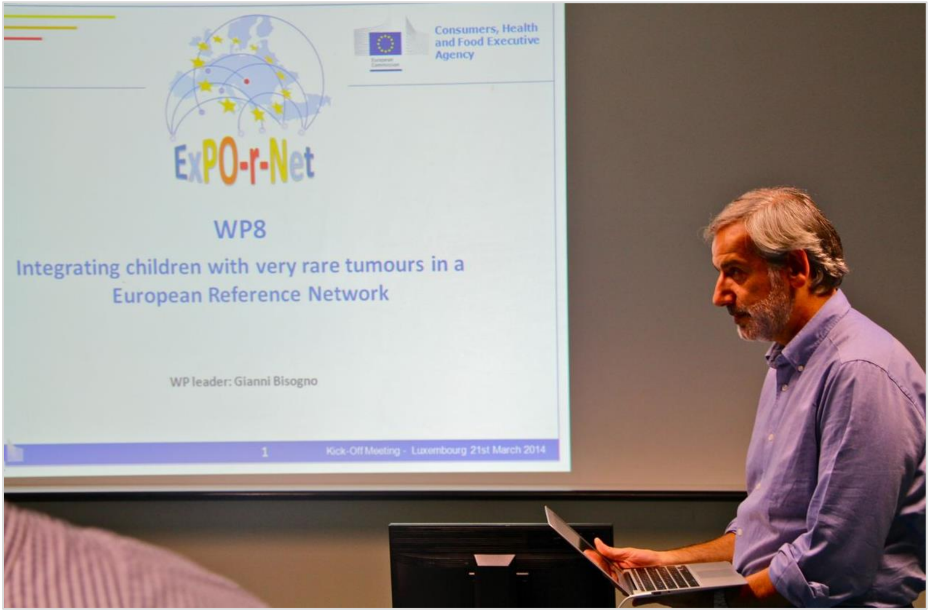
List of deliverable(s) linked to this work package

Deliverable #	Outcomes / Deliverable title
10	Standard of care guidelines for VRT and very rare STS.

Milestones reached by this work package

#	Milestone title	Month of achievement
1	Establishment of VRT Network tumor board and working group on rare STS in collaboration with EpSSG.	8
2	Establishment of a website dedicated to inform families and the public. This website will be linked to the main ExPO-r-NeT webpage.	12
3	European meeting to reach consensus on guidelines for VRTs and rare STS.	24

2



European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment

ExPO-r-Net

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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

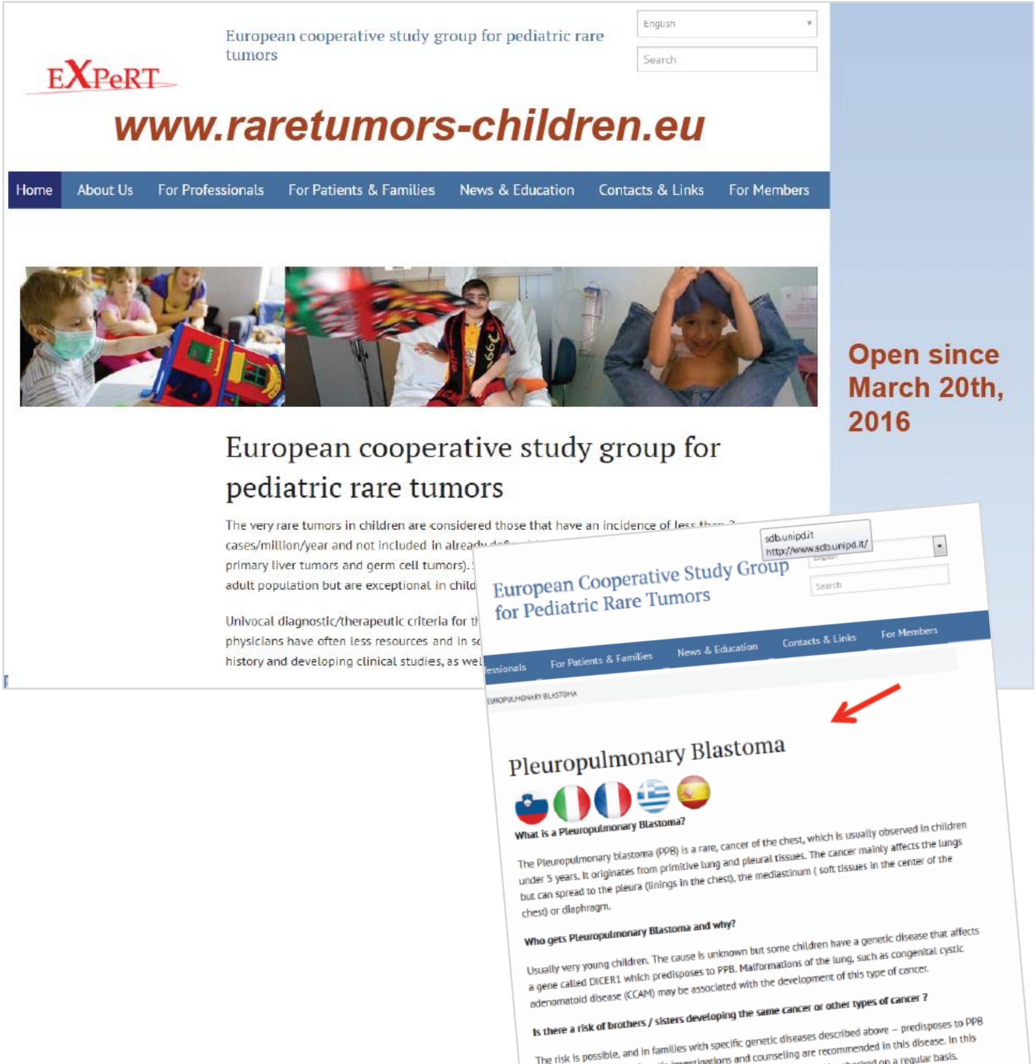
GALOP - *Grupo de América Latina de Oncología Pediátrica*

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

Jordan (twinning programs, multidisciplinary tumor boards with experts in adult oncology)

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



Open since March 20th, 2016

EXPeRT / ExPO-r-Net

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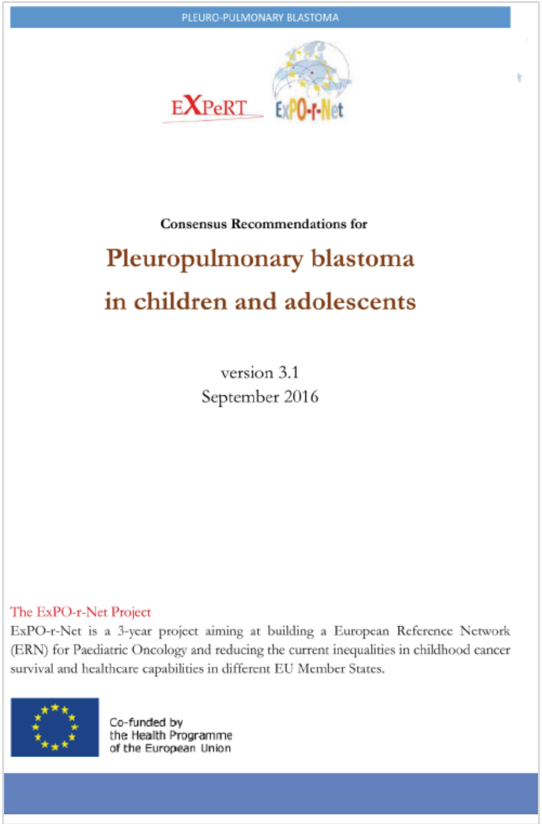


PLEURO-PULMONARY BLASTOMA

EXPeRT ExPO-r-Net

Consensus Recommendations for

Pleuropulmonary blastoma in children and adolescents

version 3.1
September 2016

The ExPO-r-Net Project
ExPO-r-Net is a 3-year project aiming at building a European Reference Network (ERN) for Paediatric Oncology and reducing the current inequalities in childhood cancer survival and healthcare capabilities in different EU Member States.

Co-funded by the Health Programme of the European Union

- ✓ Pleuropulmonary blastoma
- ✓ Pancreatoblastoma
- ✓ Infantile fibrosarcoma
- ✓ Sex cordal stromal tumors
- ✓ Thymoma and thymic carcinoma
- ✓ Alveolar soft part sarcoma

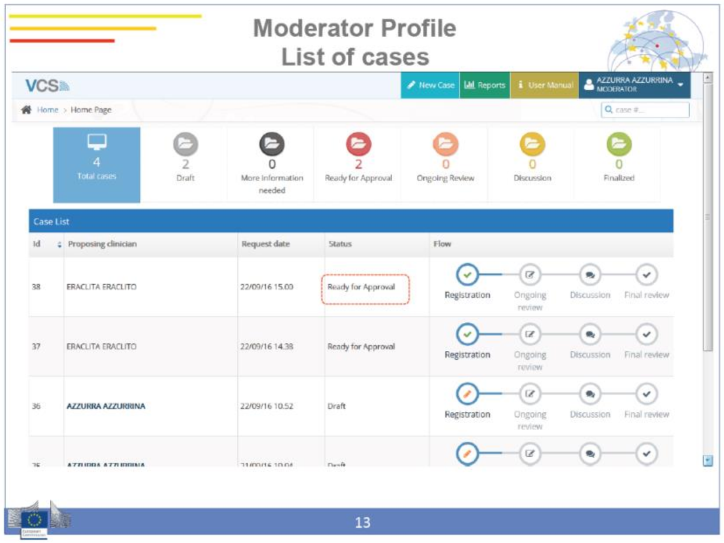
EXPeRT / ExPO-r-Net

1. the website (to inform families and the non-scientific community)
2. harmonized recommendations/guidelines
3. the virtual tumor board and advisory desk

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

EXPeRT / ExPO-r-Net

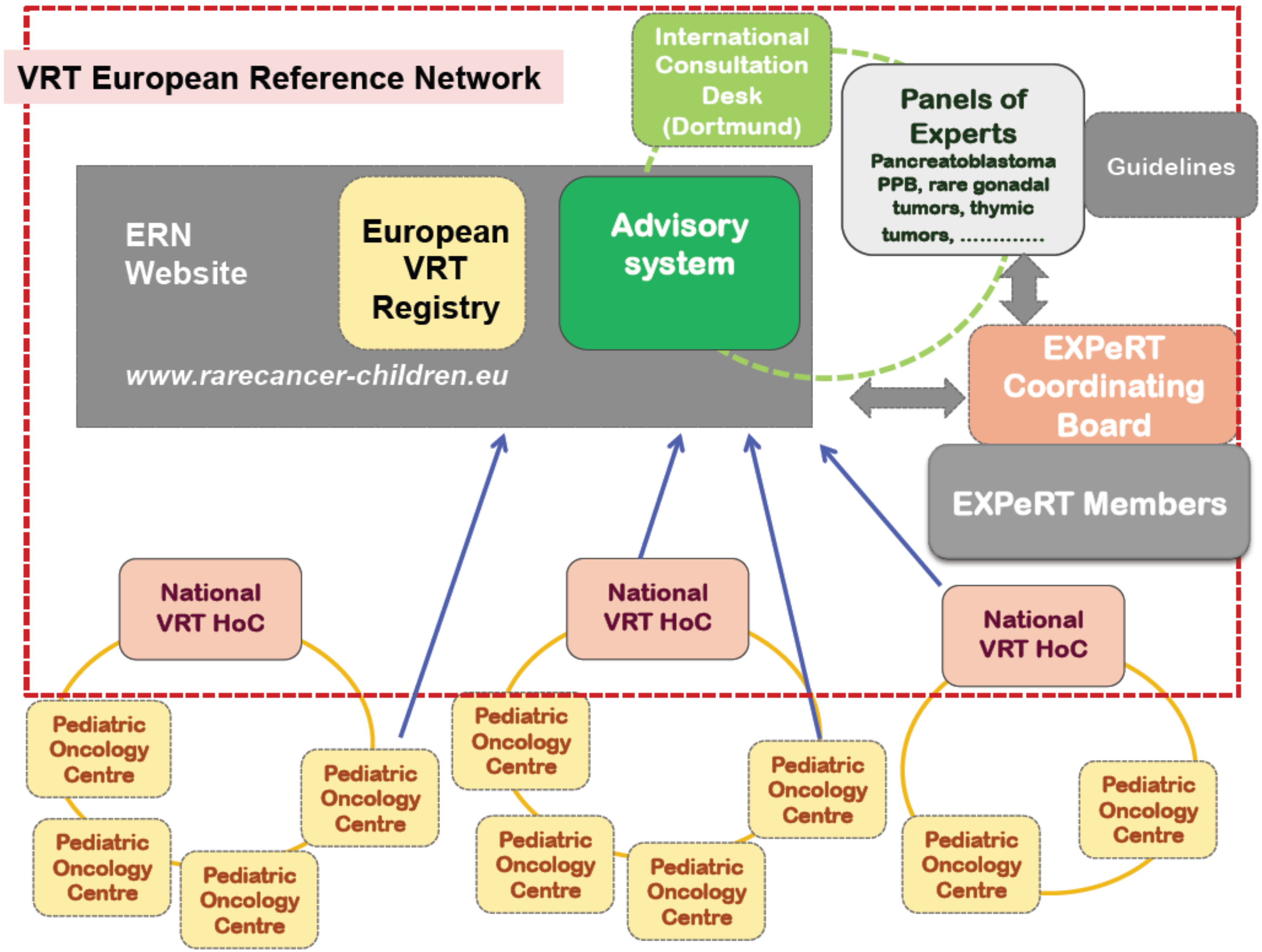


Second phase

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)


VRT European Reference Network
International Consultation Desk (Dortmund)
Panels of Experts
Pancreatoblastoma PPB, rare gonadal tumors, thymic tumors, ...
Guidelines
ERN Website
European VRT Registry
Advisory system
www.rarecancer-children.eu
EXPeRT Coordinating Board
EXPeRT Members
National VRT HoC
National VRT HoC
National VRT HoC
Pediatric Oncology Centre
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EXPeRT / ExPO-r-Net

VERY RARE TUMORS IN PEDIATRIC AGE
INTERNATIONAL WORKSHOP

29-30^h of March 2017
Padova

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.

SIOP Europe

The challenge of very rare cancer in children and adolescents

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

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

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 therapeutc strategies (or ongoing clinical trials) for most of very rare tumors

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

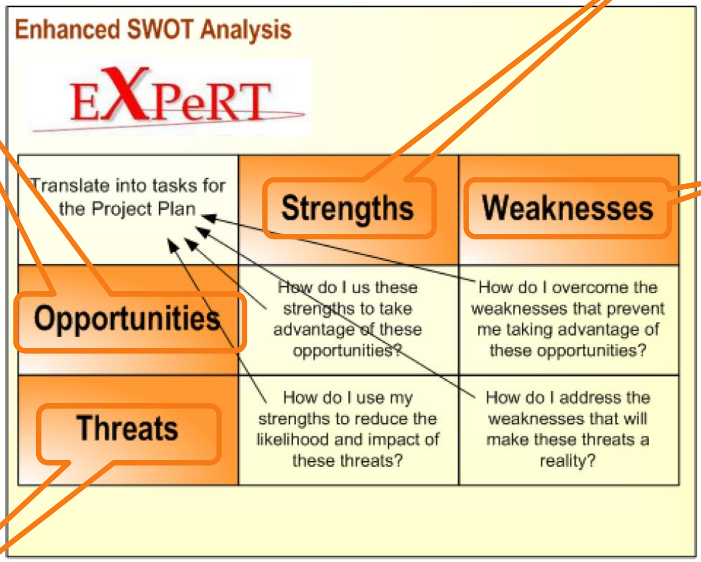
Need to involve “adult” experts

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).

- ✓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)…

…more strenghts than weakness

Thank you