1 Publishable summary

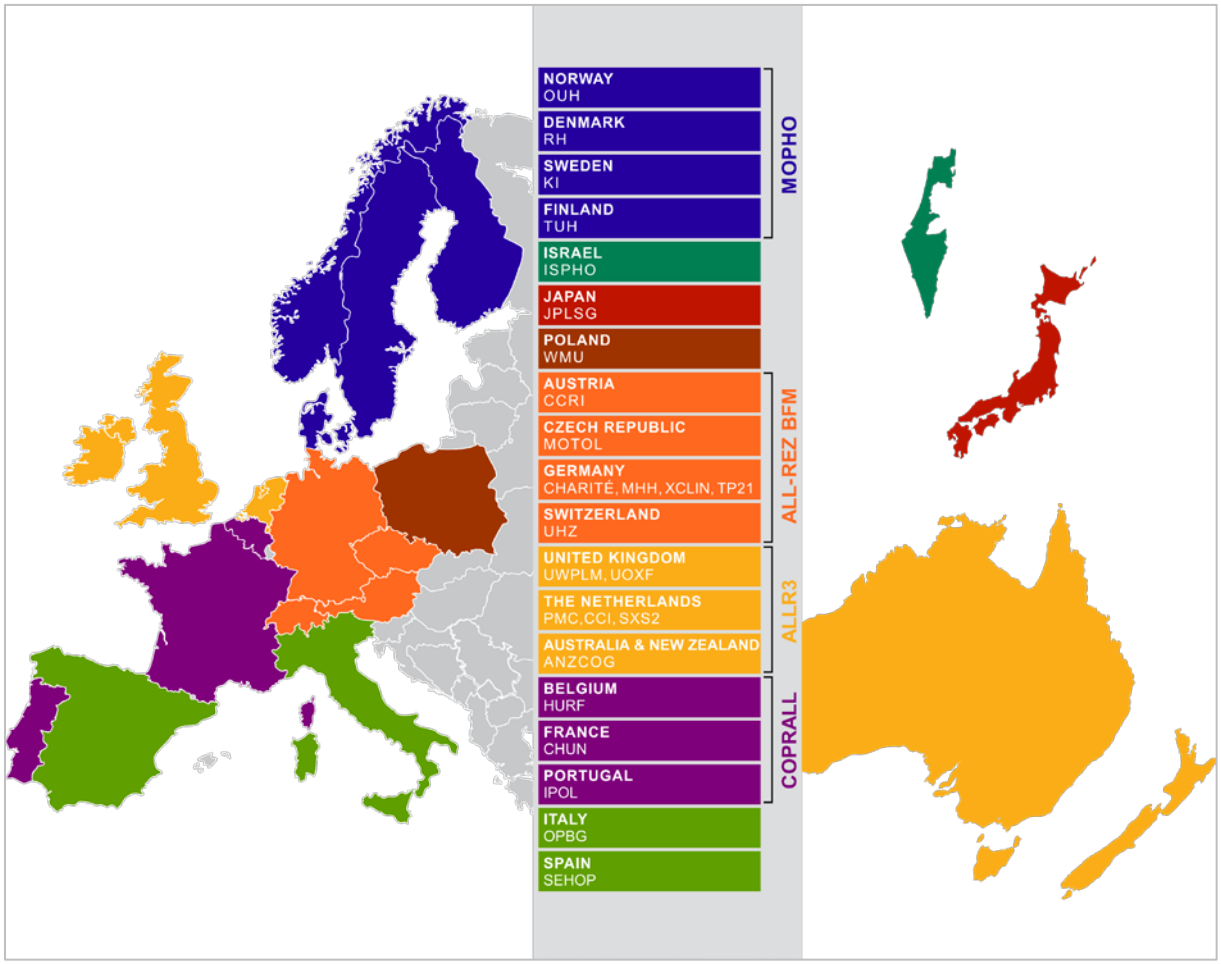
1.1 A summary description of project context and objectives

Acute lymphoblastic leukaemia (ALL) is the most common malignant disease of childhood with an incidence of 4/100.000 children per year in Europe. Over the past 4 decades, survival has improved from less than 20% to over 80%. This is primarily the result of risk stratification and intensification of standard therapy for all categories of patients. As a result, treatment is complex, prolonged and toxic. About 15-20% of patients suffer a relapse of the disease, resulting in an incidence of about 0.7/100.000 children per year in Europe. With the use of intensive combination chemotherapy and hematopoietic stem cell transplantation (HSCT), currently 40-50% of the children with ALL relapse can be cured. Well defined risk factors allow distinguishing between children with acceptable prognosis after chemotherapy alone, and those who can be cured only by additional HSCT. However, a substantial part of patients still relapse after full intensive treatment suggesting that alternative strategies are required. Thus, ALL relapse is one of the most frequent causes of death in childhood malignancies. In the modern era, a number of new drugs are available which could be of benefit for children with ALL. Some of these drugs are targeted to specific pathways or molecules and have little or no side effects and carry the promise of decreasing toxicity and improving outcome. Numbers of paediatric patients with relapsed ALL even in the larger member states are too small to perform prospective controlled clinical trials for improving standard therapy and integrating new agents. Therefore, the IntReALL consortium has been founded as a large international collaborative group with the aim to establish a comprehensive platform for diagnostics and treatment of childhood relapsed ALL in Europe and beyond. The initiative was taken by experts from the International BFM Study Group (I-BFM SG), a collaborative expert group for childhood leukaemia and lymphoma in Europe and other continents.

Main objectives of the IntReALL project are to:

1. implement prospective clinical trials for harmonization and optimization of the best available standard therapy and integration and prospective evaluation of the most interesting new agents,
2. implement the infrastructure for a large international trial including GCP conform clinical trial management and a GCP conform web-based study data base,
3. to establish harmonized diagnostic procedure for relapsed/refractory ALL and a comprehensive harmonized strategy for tissue banking and biologic studies to improve knowledge on the disease, discover new risk factors and potential targets for new drugs,
4. establish a strong and effective network with the other international academic organizations dedicated to paediatric oncology, international regulatory authorities and pharmaceutical industry allowing for optimized development of new agents and with parent organizations to warrant a strategy in the best interests of the children with ALL,
5. involve innovative small and medium sized enterprises (SME's) contributing expertise in diagnostic and therapeutic biotechnology, IT, and management to the Consortium,
6. improve awareness of the public and medical professionals on childhood relapsed ALL thus improving recruitment rates for the trial and informing on the effective use of EU budget with direct impact on improvement of the medical care of the European population.

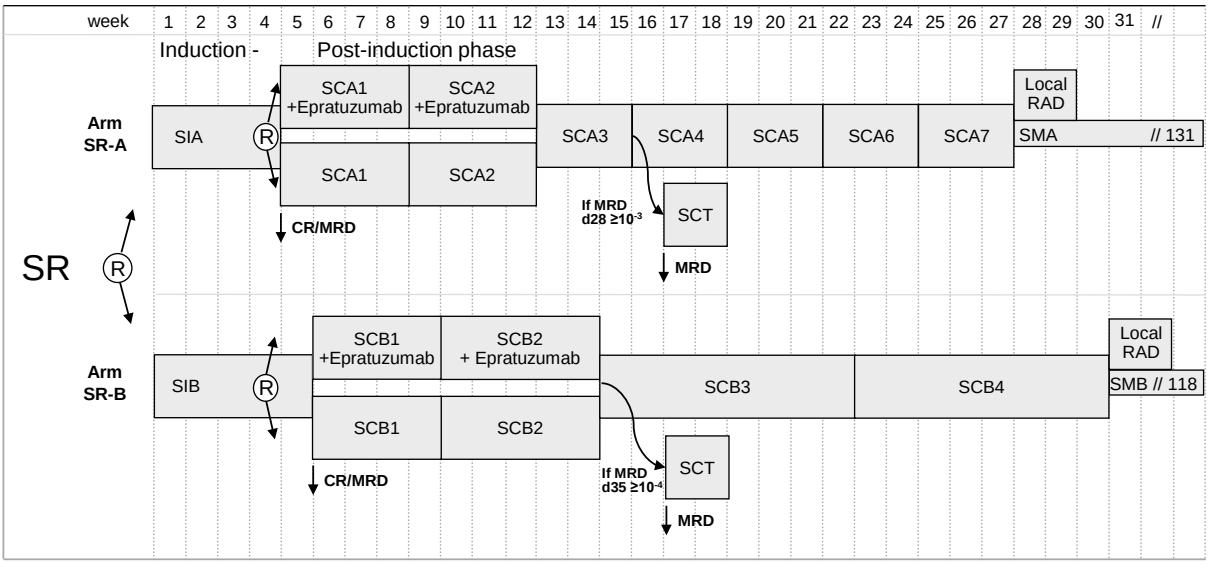
Figure 0.1: IntReALL Consortium, participating countries and study groups (Japan, Australia and Spain are not partners of the FP7 project)



1.2 Description of the work performed since the beginning of the project and the main results achieved

In the first 24 months of the 6 years project, the basis for the project has been established within 5 work packages, clinical trial, data base and statistics, diagnostics and biological research, networking, dissemination and regulatory affairs, and project management. Separate trials for standard- (SR) and high risk (HR) childhood relapsed acute lymphoblastic leukaemia (ALL) have been developed. For SR patients, the ALL-REZ BFM 2002 and the ALL-R3 regimens are randomly compared to establish the best available standard therapy. Furthermore, as first new and targeted drug, the CD22 directed monoclonal antibody Epratuzumab is randomly investigated during consolidation (Fig. 0.2). Production, shipment and labelling are warranted by the manufacturer Immunomedics, SME partner of the project.

Figure 0.2: IntReALL SR 2010 protocol overview



The implementation of the larger SR phase III trial has been prioritized. The trial is fully approved by all required regulatory and ethical instances and has been opened for recruitment in May 2014. A GCP compatible trial infrastructure has been fully established at the international sponsor Charité and the national co-sponsors. The department for legal affairs has set up a framework of contracts covering all involved parties. The finalization of the complex sponsor delegation and site contracts integrating the requirements of the involved pharmaceutical company Immunomedics bound to US law and FDA requirements led to delay of the whole procedure and thus the opening of the SR trial. In the meantime, the majority of participating countries have signed the co-sponsor contracts and have been initiated for start of patient recruitment (Fig. 0.3). One-hundred-seventy-seven (70%) of the planned 252 clinical study sites have signed contracts and been opened. Half (347) of the required patients have been recruited so far showing unexpectedly high randomization compliance. A series of 5 substantial amendments of the IntReALL SR 2010 protocol have been approved by the competent authorities.

The central pharmacovigilance revealed 211 reported serious adverse events so far. The 4th data safety update report (DSUR) has been accepted by the competent authorities.
The Data Safety Monitoring Board (DSMB) has met a 5th time on September 25, 2017 and has approved the further conduct of the trial.

These numbers demonstrate that after solving the demanding organizational, ethical and legal problems there is a high interest in and acceptance of the study among the involved parties and in particular the patients and their families.

Figure 0.3: Sponsor delegation contracts, initiation of countries and sites, and patient recruitment of the IntReALL SR 2010 trial (status 03.08.2017, Japan, Australia and Spain are not partners of the FP7 project)

Country	Co-sponsor contract signed	Initiated	Sites total	Sites Initiated	Patients recruited
Australia / NZ	yes	10.04.2014	10	9 (90%)	25
Austria	yes	17.10.2014	8	5 (63%)	9
Belgium	yes	21.04.2016	8	6 (75%)	2
Czech Republic	yes	12.10.2015	5	2 (40%)	11
Denmark	yes	28.08.2014	4	4 (100%)	11
Finland	yes	10.10.2014	5	5 (100%)	8
France	yes	08.07.2014	29	27 (93%)	57
Germany	yes	01.02.2014	57	43 (75%)	55
Ireland	no		1		0
Israel	yes	14.05.2014	6	6 (100%)	14
Italy	yes	19.05.2014	27	26 (96%)	107
Japan	yes	23.10.2014	28	28 (100%)	26
Netherlands	yes	26.07.2016	6	1 (17%)	2
Norway	yes	16.09.2014	4	4 (100%)	2
Poland	yes		11		0
Portugal	yes	03.06.2014	3	2 (66%)	8
Spain	no		5		0
Sweden	no		6		0
Switzerland	yes	20.01.2015	9	9 (100%)	6
United Kingdom	yes	17.06.2015	20	1 (5%)	4
Total			252	177 (70%)	347

A study database for the SR and the HR trials has been set up using the MARVIN system provided by the SME XClinical. The database for the SR trial is finalized and has been opened for study data entry since March 2015. A 1st amended study-data base version considering the IntReALL SR protocol amendments has been launched. For patients, not being included into the trial due to clinical or organisational reasons, a registry tool is being implemented on the MARVIN system allowing for directing them to open clinical trials and to biologic studies. XClinical has improved the MARVIN system and adapted it to the requirements of the project, including a multi trial feature.

Figure 0.4: Patient visit matrix of the MARVIN data base

IntReALL SR 2010 | Test Doku | Testzentrum

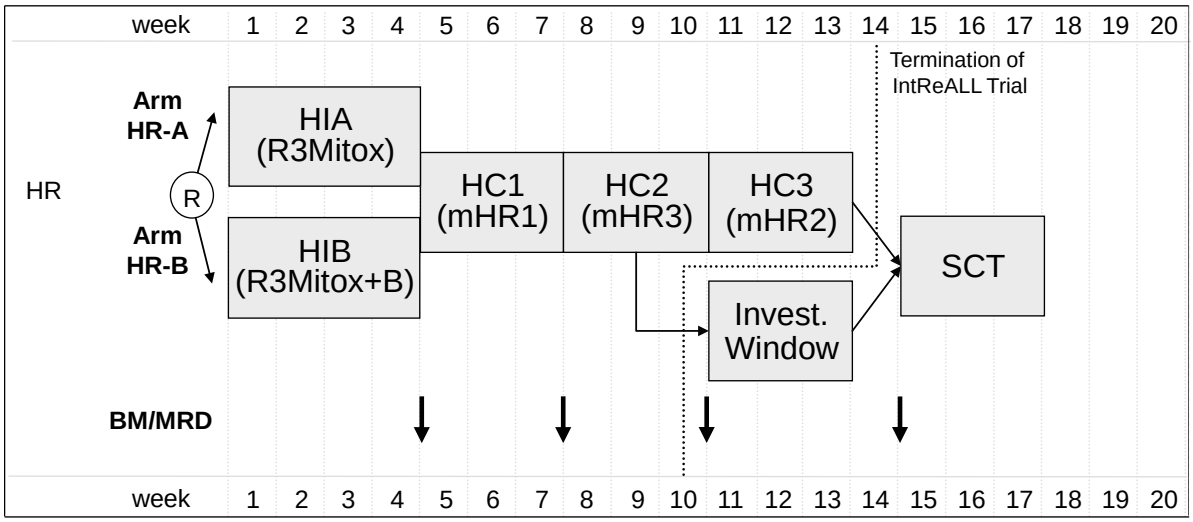
Patient Status

View as role: Investigator

Recruiting center	Subject Id	Registration IntReALL	SR - Trial admittance	SR - 1st Randomisation	SR - Primary ALL	SR - Relapse diagnostics	SR - Phase 1	SR - 2nd Randomisation	SR - MRD	SR - SAE 001	Σ
Testzentrum	123456	✓	✓	✓	!	!	!	!		!	
Testzentrum	GPOH.00328	!									
Testzentrum	GPOH.00417	✓	✓	✓			✓		✓3	Q	
A-Wien, St. Anna Kinderspital, POH	GPOH.00439										
Testzentrum	GPOH.00461	✓	✓								
Testzentrum	GPOH.00462	✓	✓	✓					✎		
Testzentrum	GPOH.00463	✎									
Testzentrum	GPOH.00465	!									
	Incomplete entries	2	0	0	1	1	1	1	0	1	7
	Open queries	0	0	0	0	0	0	0	0	1	1
	Complete entries	1	0	0	0	0	0	0	1	0	2
	Signature level 1:	4	4	3	0	0	1	0	0	0	12
	Signature level 2:	0	0	0	0	0	0	0	0	0	0
	Signature level 3:	0	0	0	0	0	0	0	1	0	1

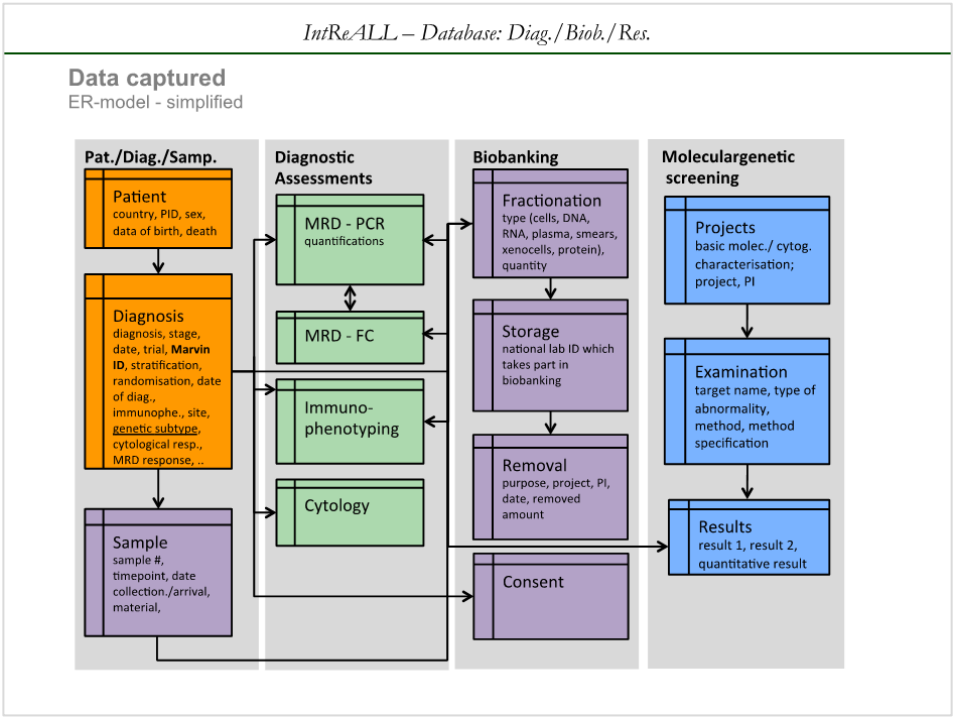
The design of the HR trial investigating the induction regimen Clo/Cyc/Eto had to be modified due to recently reported preliminary adverse data. The Trial Committee (TC) decided to investigate the proteasome inhibitor Bortezomib instead, which had shown an attractive profile in paediatric relapsed ALL. An innovative covariate-adjusted response-adaptive (CARA) randomised design has been developed by the statistics team from Oxford, allowing for early stopping in case of superiority/futility and a flexible randomisation rate based o interim analysis results. The study protocol has been written and agreed by the TC and the involved parties. The study has been submitted to and accepted by the authorities via the voluntary harmonized procedure (VHP). Several changes required by national Ethics committees and a revised Investigational Brochure for Bortezomib required a 1st substantial amendment of the HR protocol before starting the trial. Due to delayed national approval of the HR protocol, the VHP had to be stopped and further submission to be performed on a national level. The protocol has been approved by the competent authorities and ethics committees in Germany and most participating countries. Sponsor delegation and site contracts are circulated and being approved until the end of 2017. An investigational window implemented at the end of consolidation is being used for investigation of the safety and efficacy of the CD3/19 directed bispecific monoclonal antibody Blinatumomab compared to the standard chemotherapy regimen HC3 in a study conducted by the manufacturer Amgen.

Figure 0.5: IntReALL HR 2010 protocol overview, new design randomizing ALL-RE3 backbone (R3Mitox) ± Bortezomib (B), modified BFM HR courses (mHR1-3), optional investigational window, stem-cell transplantation (SCT)



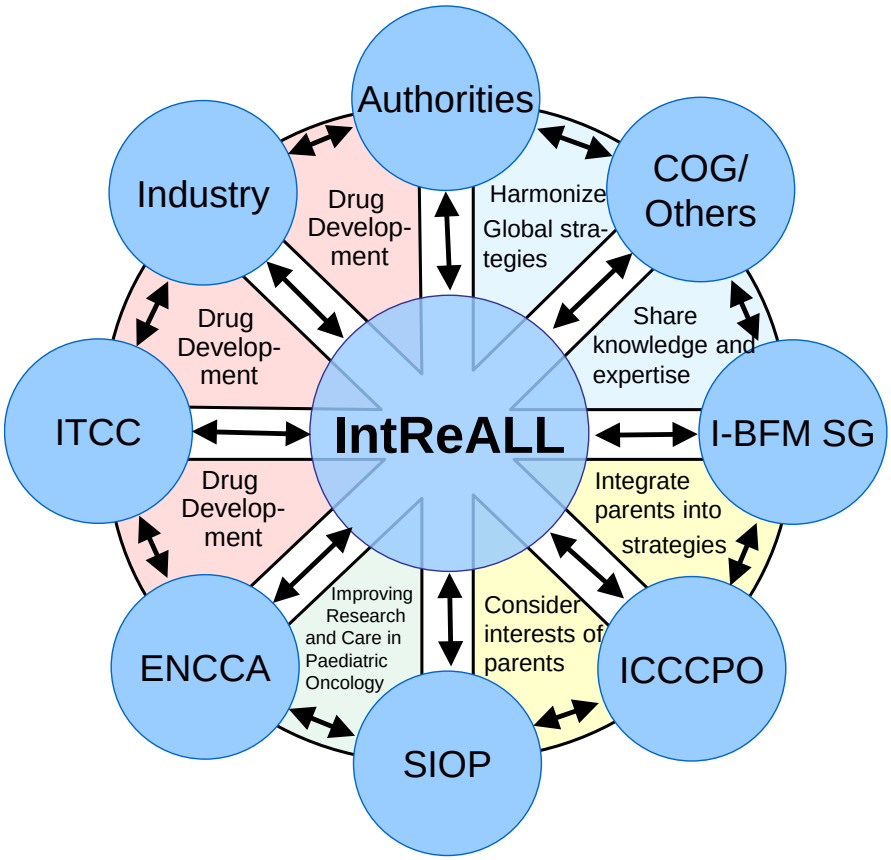
Standardized diagnostic procedures, reference laboratories, and a virtual tissue bank for patient material have been established in all participating countries. The virtual tissue bank is implemented on the SCOPELAND technology data base system, which is already established locally by several participating partners. A comprehensive strategy for biologic research has been agreed with several projects on pathogenesis of the disease, new risk factors and targets for new drugs. The company ServiceXS renamed to GenomeScan has analysed a comprehensive list of relevant candidate genes in leukaemia samples generated from IntReALL patients and from patients treated within preceding trials as controls for genetic screening. An improved genetic classification of childhood relapsed ALL has been established.

Figure 0.6: Structure of biologic research and flow of research data



A strong network with other relevant academic institutions involved in paediatric oncology and drug development has been implemented including regular and close interaction with the EMA and industry. The Consortium is directly involved into several drug development activities and achieved to integrate a decisive phase III trial on Blinatumomab into the treatment strategy for high-risk patients. Several meetings have been held to establish the structure of the Consortium and to discuss the progress of the project. An Ethics Board has developed a strategy to accompany the project and launched a flyer for patient information. A website and the participation of IntReALL partners in numerous congresses support the awareness on the project in the public and among clinical professionals. A straight forward project management for the project has been established to integrate the specific requirements of an international clinical trial into the framework of a FP7 program.

Figure 0.7: IntReALL networking structure



1.3 Expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project)

The IntReALL project is establishing the largest clinical trial platform for treatment of childhood relapsed ALL in the world. It develops the best available standard treatment strategies as backbone for further European trials within randomised phase III trials in a reasonable time span. The IntReALL trials will serve as a reference for this particular disease for the whole world. Furthermore, the IntReALL Consortium provides a unique platform for drug development in childhood ALL with randomised phase III trials investigating the most promising new agents timely and fulfilling all licensing requirements. With the IntReALL SR 2010 trial, the role of Epratuzumab in childhood relapsed ALL will be determined with direct relevance for licensing of the drug. With this particular trial, the Consortium will pave the way for integration of future immune-therapies and other targeted treatment strategies in relapsed and also primary ALL. The investigational window implemented in the IntReALL HR 2010 trial will be used to investigate the efficacy and activity of the bispecific T-cell engaging CD3/19 directed monoclonal antibody Blinatumomab as decisive trial for filing in paediatric indications, sponsored by Amgen. The IntReALL platform allows after registration to allocate patients to suitable early clinical trials or personalised strategies based on the genetic and immunologic characteristics of the individual leukaemias in case of insufficient response of individual dismal prognosis. The new agents investigated by or in cooperation with the IntReALL Consortium provide completely different mechanisms of anti-leukaemic action and may break drug resistance of leukaemias thus contributing to improvement of prognosis of this disease. Furthermore, proven effective targeted agents may replace unspecific and toxic chemotherapy and allow for reducing the burden of acute and long-term side effects for the patients. With IntReALL 2010, a comprehensive infrastructure for the GCP-conform conduction of an international trial is set up which will serve as a platform for consecutive trials, which can fully benefit from the established tools. This includes also the optimized web based data system MARVIN including a registry portal, which will be available for future projects without repeating the labour-intensive implementation phase. The IntReALL Consortium serves as reliable partner on drug development in childhood ALL for industry and authorities warranting realistic paediatric investigational plans. The IntReALL Consortium warrants drug development strategies in the best interest of the patients by integrating the point of view of the parent groups. The strong academic network warrants drug development strategies in childhood relapsed ALL fully on a medical and scientific basis free from commercial interests. An international virtual tissue bank covering the national tissue banks of the involved partners on childhood relapsed ALL samples of unique size and quality is made available for research within the consortium and international collaborations. With gene pooling and next generation sequencing technologies, a unique data set on comprehensive genetic characterization of childhood refractory ALL has been generated for association with clinical and outcome data leading to new insights into pathogenetic mechanisms and development of resistance. Such data will also be made available for the scientific community as reference for further research project. The early integration of the CCI (formerly ICCCPO) as authorized international organization of parents of children with cancer warrants improvement of compliance of the affected families, facilitate the trial processes and will be exemplary for other trials. The broad strategy of public information with a well-established public website, presentation of the project and results at public and scientific events and congresses is improving the awareness of the

population on the problems of refractory leukaemia in children and the way to find solutions within the European Union. Such information will improve the willingness of the public to transfer competence and budget to centralized European institutions, because a direct benefit for all members is evident. Well-trained and informed clinical, documentary and research staff in Europe and worldwide will give better health care to children with relapsed leukaemia, a disease that was considered to be fatal until recently.