1 Publishable summary

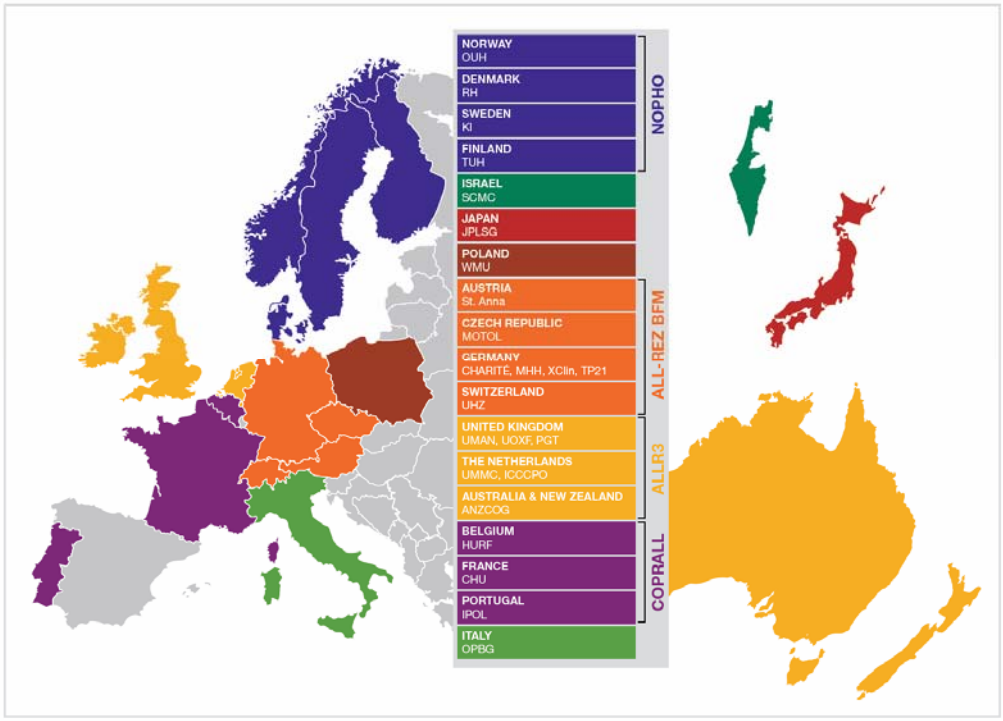
1.1 A summary description of project context and objectives,

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 haematopoietic 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 leukemias and lymphomas 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 1 IntReALL Consortium, participating countries



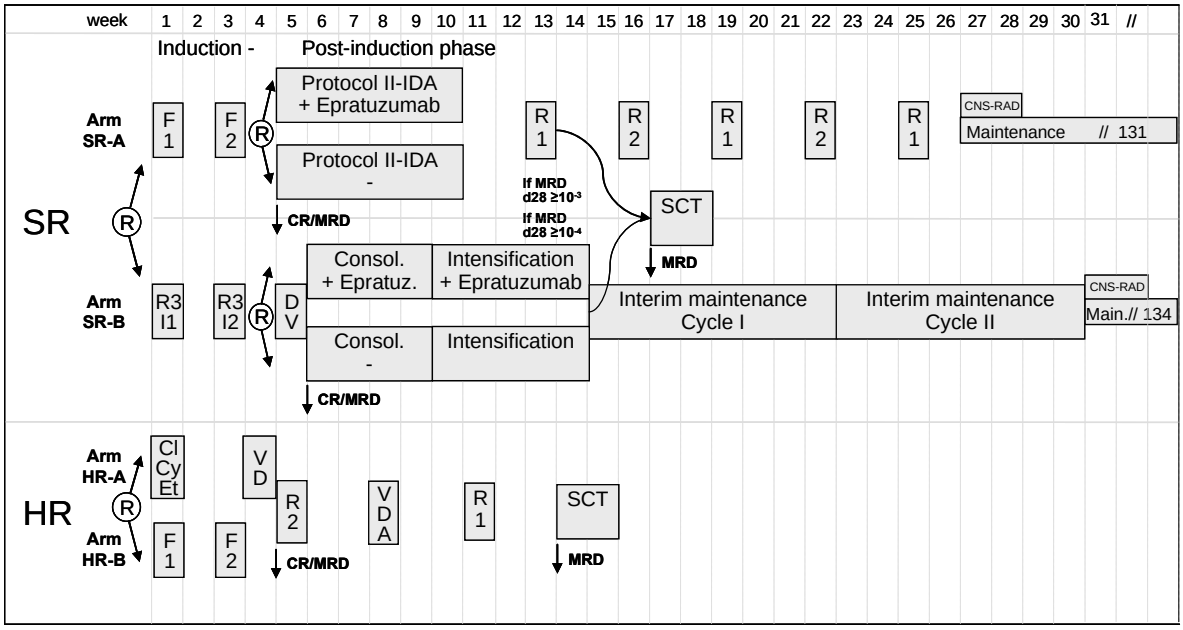
1.2 Description of the work performed since the beginning of the project and the main results achieved so far

In the first 12 month of the 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. The clinicians decided to randomly compare the 2 most successful treatment protocols for Standard Risk (SR) patients, the ALL-REZ BFM 2002 and the ALL-R3 protocol with expected event-free survival rates of around 70%. Furthermore, the unconjugated CD22 directed monoclonal antibody Epratuzumab is randomly added to the respective consolidation therapy. The manufacturer Immunomedics has agreed to label and ship the drug to the participating centres and warrants the availability of the drug throughout the study. For high risk (HR) patients, the course clofarabine / cyclophosphamide / etoposide is randomly compared as induction regime to a standard regimen F1/2, and to historical controls. For both trials, protocols and statistical plans have been written and approved by the participating investigators. Since the responsible Ethical Committee suggested to treat both risk groups in 2 different fully separated trials, the SR trial has been prioritized. After achieving scientific advice from FDA and EMA, the SR protocol has been submitted to the regulatory authorities applying the voluntary harmonized procedure (VHP) and successfully approved. The study is now submitted to national regulatory authorities and Ethical Committees. The protocol for the HR group will now be finalized and likewise submitted.

To establish the GCP compatible infrastructure for the trial, the international sponsor Charité has set up a clinical study and a trial management centre, a central pharmacovigilance, and a monitoring plan. The department for legal affairs has set up a framework of contracts covering all involved parties. All participating investigators have established national trial

centres able to manage the trial on a national level. A study data base for the SR and the HR trials has been set up using the MARVIN system provided by the SME Xclinical. Both data bases are nearly finalized and in a testing phase. Xclinical has improved the system and adapted it to the requirements of the project.
Standardized diagnostic procedures have been established. All countries have reference laboratories for the relevant diagnostic measures. They are included into European quality control strategies. A virtual tissue bank for patient material has been established. 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. For establishing deep sequencing of candidate genes by a pooling technology provided by the biotechnology SME PopGeneTech, a pilot phase has been successfully performed showing the sensitivity and specificity of the method.
A strong network with other relevant academic institutions involved in paediatric oncology and drug development has been implemented. Close interaction with the EMA has been developed to warrant the consideration of the expertise of IntReALL partners on relapsed ALL in drug development strategies. Several meetings have been hold to establish the structure of the Consortium and to discuss the progress of the project. 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. Overall, the main goals of the first 12 month have been achieved for the SR trial whereas the HR trial is in a good progress with some delay.

Figure 2 Overview on treatment schedule of trials IntReALL SR and HR 2010



Arrow down (↓), bone marrow puncture with CR/MRD assessment; Cl, Clofarabine; CNS-RAD, irradiation of the central nervous system, if indicated; Cy, cyclophosphamide; Ep, Epratuzumab; Et, etoposide; HR, high risk group; MRD, minimal residual disease; MTX, methotrexate; Prot II IDA, ALL-REZ BFM consolidation course; ®, randomisation; R1/2, ALL-REZ BFM consolidation courses; R3 I1/2, UK-R3 induction courses; SCT, stem-cell transplantation; SR, standard risk group; VDA, COPRALL chemotherapy course VANDA; VD, vincristine/dexamethasone.

Figure 3 **MARVIN fully integrated clinical data interchange consortium based workflow**

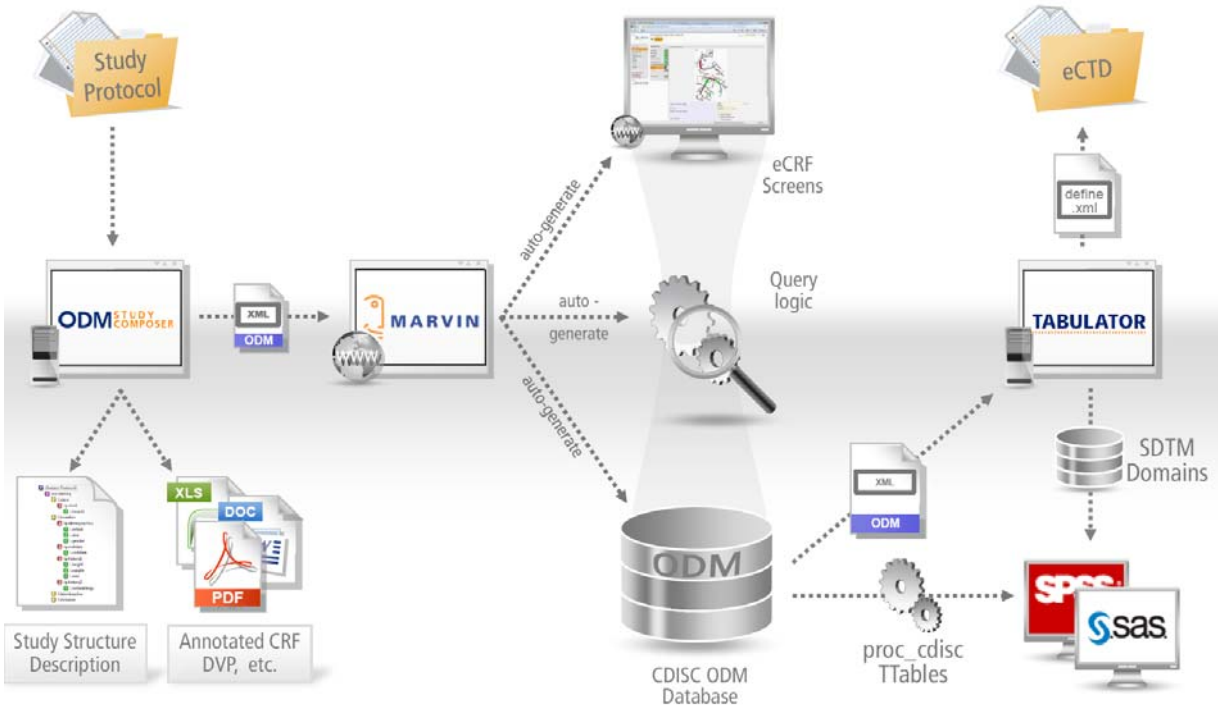


Figure 4 PGT Candidate Gene Sequencing Technology **with pooling of individually tagged patient samples, collective amplification and submission to next generation sequencing platform**

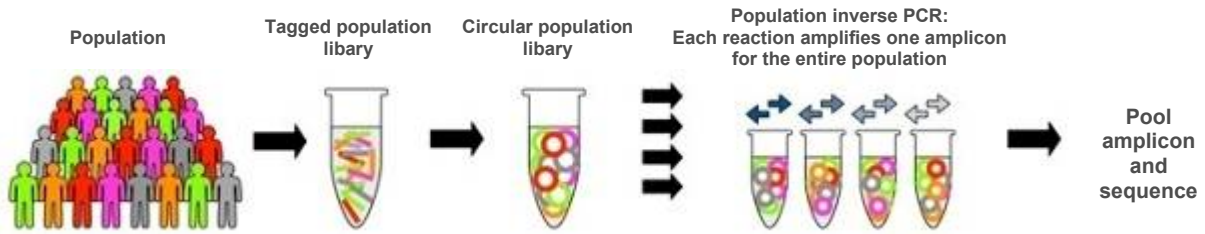
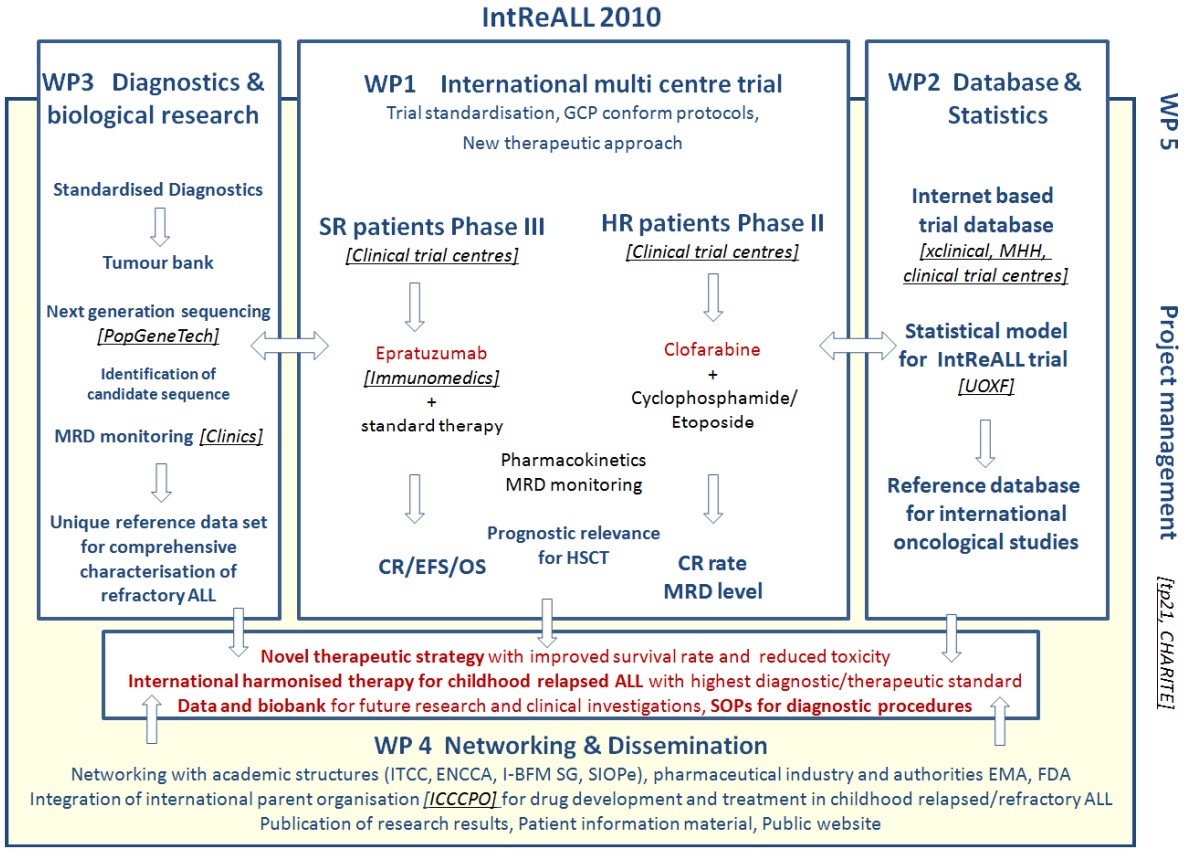


Figure 5 Structure of the IntReALL Consortium



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

The IntReALL project will establish the largest clinical trial for treatment of childhood relapsed ALL in the world allowing for developing the best available standard treatment strategies as backbone for further European trials within randomized 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 provide a unique platform for drug development in childhood ALL with randomized 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. These new agents provide completely different mechanisms of antileukemic action and may break drug resistance of leukemias 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 which will be available for future projects without repeating the labour-intensive implementation phase. With the well established clinical trial platform and the expertise on the disease the IntReALL Consortium will serve as reliable partner on drug development in childhood ALL for industry and authorities warranting realistic paediatric investigational plans. The IntReALL Consortium will warrant drug development strategies in the best interest of the patients by integrating the point of view of the parent groups. The strong academic network will warrant drug development strategies in childhood relapsed ALL fully on a medical and scientific basis free from commercial interests. A tissue bank on childhood relapsed ALL samples of unique size and quality will be 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 will be available 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 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 will improve the awareness of the population on the problems of refractory leukemia 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 world wide will give better health care to children with relapsed leukemia, a disease that was considered to be fatal until recently.

www.intreall-fp7.eu