EsPhALL: Amendment proposal

An open-label study to evaluate the safety and efficacy of IMATINIB with chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia (Ph+ALL)

Version 2010

STUDY COMMITTEE

A. Biondi, M. Schrappe	Study Chair
M.G. Valsecchi	Statistician
M. Aricò	
G. Mann	
G. Janka-Schaub	
Y. Benoit	
V.Gandemer	
A.Castor	
V.Saha	
R.Pieters	
J. Stary	
P. De Lorenzo	Trial Data Center

LIST OF PARTICIPATING GROUPS

AIEOP	Prof. Maurizio Aricò Dipartimento **O**ncoematologia Pediatrica e Cure Domiciliari Azienda Ospedaliero-Universitaria Meyer Viale Pieraccini, 24 50139 Firenze, Italy Tel. +39-055-5662-739 Fax +39-055-5662-746 email:m.arico@meyer.it
ALL-BFM-A	Dr. Georg Mann St. Anna´s Childrens Hospital Kinderspitalgasse 6 1090 Wien, Austria Tel. + 43 140170250 Fax + 43 14017070 Email:georg.mann@stanna.at
ALL-BFM-G/CH	Prof. Dr. M. Schrappe Department of Pediatrics University Medical Center Schleswig-Holstein, Campus Kiel Arnold-Heller-Str. 3, Building 9 D-24105 Kiel Tel: +49 (0) 431-597 1621 Fax: +49 (0) 431-597 3966 Email m.schrappe@pediatrics.uni-kiel.de
COALL	Prof. G. Janka-Schaub Universitätskinderklinik. Martinstraße 52 20246 Hamburg, Germany Tel. + 49 40 4717 3796 Fax + 49 40 4717 4601 Email janka@uke.uni-hamburg.de
EORTC	Prof. Y. Benoit University Hospital Klinik Voor Kinderziekten C. Hooft De Pintelaan 185 9000 Gent, Belgium Tel +32 92403576 Fax + 32 92404986 Email yves.benoit@ugent.be
FRALLE	Dott V. Gandemer Unite d'hemato-oncologie et greffes de moelle CHU Hopital Sud 16d de Bulgarie 35203 Rennes Cedex 2- France Tel. +33 299265835 Fax +33 299267195 Email virginie.gandemer@chu-rennes.fr

NOPHO	Dott. A. Castor Lund University Hospital Getingevägen 4 22185 Lund, Sweden Tel.+ 46 178 264 Fax + 46 130 573 Email:anders.castor@skane.se
MRC	Prof. V. Saha Cancer Research UK Children's Cancer Group Paterson Institute of Cancer University of Manchester Manchester M20 4BX Tel (off): +44 161 446 3094 Fax (off): +44 161 446 3092 Tel (lab): +44 161 446 3234 Email v.saha@cancer.org.uk
DCOG	Prof Rob Pieters Erasmus MC-Sophia Childrens Hospital University Medical Center Rotterdam Dr. Molewaterplein 60 3015 GJ Rotterdam The Netherlands Tel. + 31 10 703 6691 Fax. + 31 10 703 6801 Email rob.pieters@erasmusmc.nl
CPH	Prof. Jan Stary Department of Pediatric Hematology and Oncology University Hospital Motol Vuvalu 84 15018 Praha 5-Motol-Czech Republic Tel.+42 22 443 6401 Fax +42 22 443 6420 Email jan.stary@lfmotol.cuni.cz
PINDA	Prof. Dr. Myriam Campbell, Division of Pediatric Hematology-Oncology Hospital Roberto del Río University of Chile Santiago, Chile Tel.+ 56 2 2392765 Fax +565 2 7350725 Email: myriamcampbellb@gmail.com
HONG KONG	Dr.Chi-Kong Li Department of Paediatrics Prince of Wales Hospital Shatin, Hong Kong, China Tel.+ 852 2 632 1019 Fax +852 2 649 7859 Email ckli@cuhk.edu.hk

COORDINATION UNIT

A.Biondi
G. Lucchini
Centro M.Tettamanti
Clinica Pediatrica Università Milano-Bicocca
Ospedale S.Gerardo
20052 MONZA
Tel. +39-039-2333661
FAX +39-039-2332167
Email: abiondi.unimib@gmail.com
g.lucchini@hsgerardo.org

M.Schrappe
Department of Pediatrics
University Medical Center
Schleswig-Holstein, Campus Kiel
Arnold-Heller-Str. 3, Building 9
D-24105 Kiel
Tel: +49 (0) 431-597 1621
Fax: +49 (0) 431-597 3966
Email m.schrappe@pediatrics.uni-kiel.de

TRIAL DATA CENTER
M.G.Valsecchi
P. D. Lorenzo
CORS (Operating Center for Research and Statistics)
Clinica Pediatrica Università Milano-Bicocca
Ospedale S.Gerardo
Via Donizetti,106
20052 MONZA
Tel. +39-039-2333074
Fax +39-039-2332314/ 2167
Email cors@unimib.it

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List of abbreviations

AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BCR	breakpoint cluster region
BSA	body surface area
BUN	blood urea nitrogen
CML	chronic myeloid leukemia
CRF	case report/record form
ECG	Electrocardiogram
HSCT	hematopoietic stem cell transplantation
IRB/EC	Institutional Review Board/Ethics Committee
LDH	lactic dehydrogenase
Ph chromosome	Philadelphia chromosome
PK	Pharmacokinetic
PLT	platelet count
RT-PCR	reverse-transcriptase polymerase-chain-reaction
SAE	serious adverse event
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
TdT	terminal deoxynucleotidyl transferase
ULN	upper limit of normal range
WBC	white blood cell count

PROTOCOL SYNOPSIS

Title	**An open-label study to evaluate the safety and efficacy of IMATINIB with chemotherapy in pediatric patients with Ph+/BCR-ABL+ Acute Lymphoblastic Leukemia (Ph+ALL).**
Study phase	Phase II
Patients and Stratification	Pediatric patients with Philadelphia-Positive ALL (Ph+ALL) will be stratified as Good-Risk Ph+ALL and Poor-Risk Ph+ALL. a. Poor-Risk group: for protocols which adopt a steroid prephase patients who are Prednisone-poor responder (i.e. blast cell count ≥ 1000/μl in peripheral blood after 7 days of Prednisone given in combination with intrathecal Methotrexate), for protocols which do not adopt steroid prephase patients who have M3 BM at day 15 or M2/M3 BM at day 21; for all protocols patients who do not achieve CR after the induction course. b. Good-Risk group: for protocols which adopt a steroid prephase patients who are Prednisone-good responder (i.e. blast cell count < 1000/μl in peripheral blood after 7 days of Prednisone given in combination with intrathecal Methotrexate) and achieve CR after the induction course; for protocols which do not adopt steroid prephase patients who have M1/M2 BM at day 15 or M1 BM at day 21 and achieve CR after the induction course. The expected stratification of the Ph+ALL population is as follows: 25-30% in the Poor-Risk group and 70-75% in the Good-Risk group.
Primary objective	To evaluate in patients with Ph+ALL the efficacy and safety of IMATINIB continuous exposure on top of intensive, BFM-type chemotherapy. The endpoint for response will be the evaluation on the long-term clinical outcome.
Secondary objectives	A. To compare the outcome with historical controls of patients treated with BFM oriented protocols (including patients treated with Imatinib in the original EsPhALL protocol) and with recent results from the COGAALL0031 (Children Oncology Group-USA) study, which adopts a more intensive chemotherapy approach than BFM. B. To evaluate the overall EFS, DFS and survival in both risk groups. C. To assess the antileukemic potential of IMATINIB given to patients with Ph+ALL. The pattern of the molecular response will be analyzed on the basis of 5 measurements taken at different time points from the beginning of phase IB to the beginning of the reinduction phase or HSCT. The findings will be compared with historical controls. D. To evaluate the impact of HSCT on prognosis (EFS/DFS).

	E. To evaluate the impact of MRD on prognosis (EFS/DFS). F. To evaluate possible delays in chemotherapy administration under Imatinib continuous exposure
Treatment groups	The target population includes patients aged more than 365 days and less than 18 years with documented Ph+ALL enrolled in the national study groups of AIEOP, BFM-G/CH and BFM-A, COALL, DCOG, EORTC, FRALLE, UKALL, NOPHO,CPH, PINDA and HONG KONG.
Study design	International, intergroup, multicenter, open-label, phase II study
Study size	Overall, these groups are expected to contribute 55 Ph+ALL patients per year.
Study duration	Start of patient enrollment in January 2010. Duration of enrollement 2 years.
Eligibility Criteria – Inclusion criteria	Children and adolescents aged 1-17 years at diagnosis, with Ph+ALL documented by either cytogenetics , PCR or FISH for bcr-abl, who are eligible for the current local prospective therapeutic study of childhood ALL and for whom informed consent was given by the parents or by legal guardian.
Eligibility Criteria – Exclusion criteria **On day 15 at the start of The first course of IMATINIB**	1.Abnormal hepatic function (ALAT/ASAT > 10 times the upper limit of the normal range); 2.Abnormal renal function (creatinine > 1.5 times the upper limit of the normal range or a calculated creatinine clearance of 80ml/ min or less, adjusted to a body surface area of 1.73 sqm); 3.Active systemic bacterial, fungal or viral infection as documented by positive cultures, radiological imaging techniques, septic shock symptoms.
Primary endpoint	Long term clinical outcome in Ph+ALL, will be evaluated with Disease free survival (DFS). DFS will be calculated as the time from accrual to either one of the following events: relapse, death in CCR, second malignancies.
Secondary endpoints	1. Feasibility and safety of the addition of IMATINIB to conventional chemotherapy schedule. 2. Long term clinical outcome (EFS, survival) 3. Pattern of molecular response at the 5 scheduled time points for MRD measurement. 4. Conversion rate to CR in patients resistant to the first part of the induction phase of chemotherapy included in the Poor-risk group.

1. Introduction

1.1 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)

Clinical features and results of chemotherapy and stem cell transplantation.

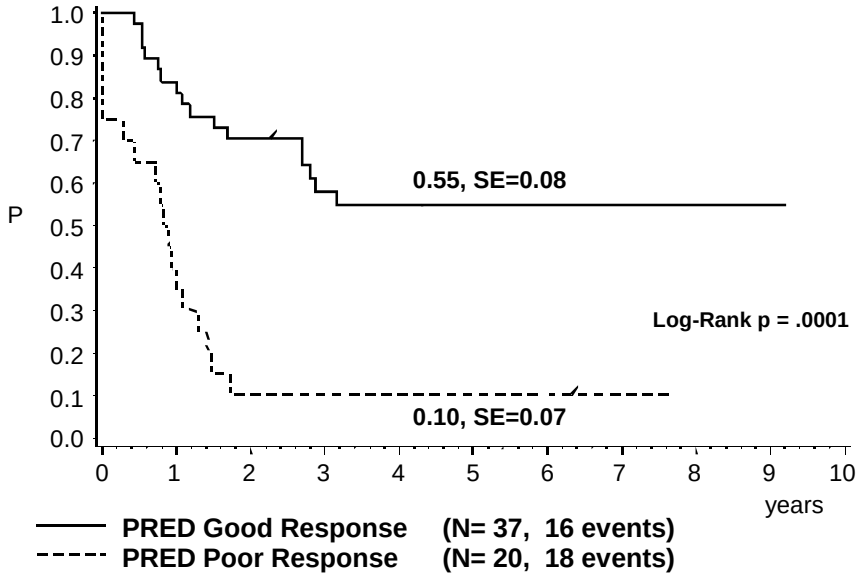
Recent advances in treatment have increased the cure of childhood ALL to 75 percent or better (1,2). However attempts to improve results for resistant subtypes of ALL, such as Ph+ ALL, have been largely unsuccessful. Overall Ph+ALL, which accounts only for 3-5% of children with ALL have a dire prognosis (rates of EFS are 25-30% in children and even less in adults) (3). Some investigators suggest that Ph+ALL in childhood is heterogeneous with regard to sensitivity to treatment. Good initial response to steroids (which are given in combination with intrathecal methotrexate before induction chemotherapy is instituted) as well as age and leukocyte count at diagnosis, have been shown to correlate with a good clinical outcome in children treated only with chemotherapy (3,4). The heterogeneity of Ph+ALL with respect to clinical outcome has been confirmed by the analysis of the largest series of pediatric ALL treated by 10 European and United States study groups or large single institutions from 1986 to 1996 (3). Among patients who presented with WBC higher than 100,000 per cubic millimeter, 85% did not have long-term EFS at five years. The inadequacy of current therapy for such patients, most of whom can be readily identified by their initial response to prednisone, indicates a need for new treatments. Patients who are younger than 10 years old and have a WBC less than than 50,000 per cubic millimeter at the time of diagnosis have about a 50 percent chance of long term DFS whereas the remaining patients (those with WBC of 50,000 to 100,000 per cubic millimeter and those with less than 50.000 leukocytes per cubic millimeter who are older than 10 years of age) have an intermediate prognosis (estimate of five-year DFS, 30 %) (3, 5). Stem cell transplantation from HLA-matched related donor yielded till recent updates a significant better outcome than chemotherapy alone (3,6). The absence of any significant superiority to chemotherapy in patients undergoing SCT from a mismatched donor or matched unrelated donor (MUD), could be explained by the high number of transplantation-related deaths, reported in this study (6). In most recent years better results have been obtained with unrelated donor HSCT, in series which include either children and adults (7). The leukemic cell burden present before HSCT influences the rate of relapse-free survival: patients with detectable BCR-ABL-expression prior to HSCT have a significantly worse prognosis.

Overall these findings underline the need of large prospective cooperative studies worldwide to generate and test relevant hypothesis to gain better clinical results in a dismal subset of ALL in children. For these studies it has been evaluated that initial response to therapy identified patients with different risk (4). This is well documented by the study on the role of response to prednisone in

the “Berlin-Frankfurt-Munster” (BFM) protocols (Fig.1)(4) and it has been confirmed, as far as early morhological bone-marrow evaluation is concerned, by an analysis of the BFM data, as shown in Fig.2 (M.Shrappe, personal communication ,2002)

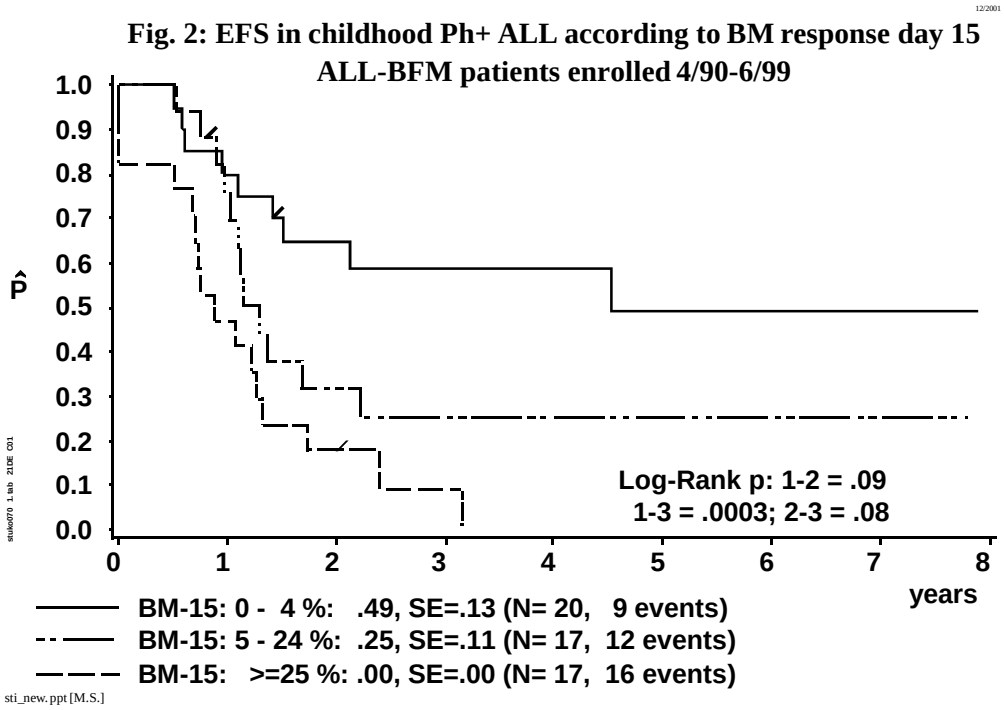
12/2001

Fig. 1: EFS according to Prednisone Response in Childhood Ph+ ALL
Results from BFM and AIEOP (1986-95)



sti_new.ppt [M.S.]

Schrappe M, Arico M, Harbott J, et al. BLOOD 92 (1998): 2730



Pathogenetic role of the BCR-ABL translocation

Ph+ALL is characterised by a reciprocal translocation between chromosomes 9 and 22 (Philadelphia chromosome) that fuses genetic sequences of the bcr gene on chromosome 22 with c-abl sequences translocated from chromosome 9. The chimeric bcr-abl gene generates several types of fusion proteins, of which the $p185^{BCR-ABL}$ form is detectable in 85% of patients with Ph+ALL, whereras the $p210^{BCR-ABL}$ chimeric protein typical of CML is observed in approximately 10% of patients. The BCR-ABL fusion proteins are characterised by a constitutive protein tyrosine kinase (PTK) activity that is absent in the normal ABL protein. This dysregulated PTK activity, which results in changes of multiple signal transduction pathways, is crucial to the transforming activity of the BCR-ABL fusion proteins and their ability to cause leukemias in vivo . Therefore, inhibition of the PTK activity of this oncoprotein is a rational therapeutic approach for BCR-ABL expressing leukemia (15).

The ABL tyrosine kinase inhibitor IMATINIB

IMATINIB is an inhibitor of the protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit, but not of other members of the Type III receptor kinase family, such as Flt-3 and Fms (reviewed in Ref. 16). IMATINIB shows selectivity for the Abl protein-tyrosine kinase at the *in vitro*, cellular and *in vivo* level (17). The compound

specifically inhibits proliferation of Bcr-Abl expressing cells. In colony forming assays using *ex vivo* peripheral blood and bone marrow samples, IMATINIB shows selective inhibition of Bcr-Abl positive colonies from CML patients (18). In animal models, the compound shows potent anti-tumor activity against Bcr-Abl and v-Abl expressing cells at tolerated doses. Studies in bcr-abl CML patients showed a hematological response in 95% of patients in the chronic phase, 60% in accelerated phase and 30% in blast crisis. The cytogenetic response rates in these 3 groups were respectively 60%, 24% and 16% (19-22).

Inhibition of the Bcr-Abl kinase has been shown to have anti-leukemic effects not only in chronic myeloid leukemia but also the subset of B-precursor ALL characterised by the translocation (9;22) which leads to formation of the Philadelphia chromosome. In 2001 IMATINIB has been registered for CML treatment and it is currently being tested in several phase II and III trials covering most Ph+ALL patients (ALL0031, EsPhALL).

Results of IMATINIB in Ph+ ALL

Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) represents a suitable disease target for therapy with IMATINIB given that the Bcr-Abl kinase is believed to play a dominant leukemogenic role in this disease. The activity of single-agent imatinib was initially investigated in patients with relapsed or refractory Ph+ ALL. A phase 1 clinical trial of imatinib at doses of 300 to 1000 mg daily led to a 70% hematologic response rate with a 20% CR rate (19). A phase 2 trial of intermediate-dose imatinib yielded a CR rate of 29% (19,23,24). Disease recurrence was usually observed within a median of 2 months, and responses were durable only in a minority of patients. Relapse in the central nervous system (CNS) was not uncommon, as imatinib concentrations in the cerebrospinal fluid only reach 1% to 2% of detectable serum levels, emphasizing the need for concurrent CNS prophylaxis (25). However, despite its activity in this disease, treatment of patients with advanced, i.e. relapsed or refractory Ph+ALL with IMATINIB, has in most cases had only temporary effects, with frequently rapid occurrence of resistance (23, 24). Resistance to IMATINIB is established via an increase in BCR/ABL mRNA, amplification of the oncogene, altered drug metabolism/transport, point mutations of the ABL catalytic domain (26) or compensatory mutations in genes other than BCR/ABL.

Imatinib was thus incorporated into combination chemotherapy regimens typically used for *de novo* Ph+ ALL, either concurrently (simultaneous imatinib and chemotherapy) or sequentially (alternating imatinib with chemotherapy). The first report of a clinical trial of this nature included 20 patients with *de novo* or minimally treated Ph+ ALL (no age restrictions) (27). Imatinib was given concurrently with the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine,

doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine); CR rate was 96%, with a 2-year DFS rate of 85%. The molecular remission rate or negativity for *BCR-ABL* transcripts by RT-PCR and nested PCR approached 60%. The addition of imatinib to the chemotherapy improved outcome. Lee et al also reported favorable outcomes after incorporating imatinib into a conventional L-asparaginase–based ALL regimen for newly diagnosed Ph+ ALL (28).

Yanada et al observed a CR rate of 96% and molecular remission rate of 71% in *de novo* patients with Ph+ ALL aged less than 65 years after concurrent imatinib and induction chemotherapy followed by alternating blocks of imatinib and consolidation chemotherapy (29). Long-term DFS and overall survival rates were significantly superior to the historical experience in these studies. In a subsequent report of outcome with imatinib-based frontline chemotherapy, two sequential cohorts of patients with *de novo* Ph+ ALL were treated according to German Multi-Centre Acute Lymphoblastic Leukemia (GMALL) protocols. First, a treatment regimen consisting of alternating blocks of chemotherapy and single-agent imatinib was designed because of concerns of potential toxicity. Once the feasibility and tolerance of concurrent imatinib and chemotherapy was demonstrated by other investigators, a concurrent regimen was implemented. The superiority of the latter approach was evidenced by a higher rate of molecular remission (52% vs 19%; *P* >.01), although the greater antileukemia efficacy did not translate into significant improvements in DFS or overall survival compared with the alternating regimen (30).

Tolerability of IMATINIB

In over 3000 patients treated, IMATINIB has been generally well tolerated, enabling chronic once daily oral dosing. There has been one death due to hepatic toxicity in a 58-year-old Indian patient in CML accelerated phase treated at the 600 mg/daily in which the causality assessment to trial drug was suspected. As this patient was taking acetaminophen 0.5 gm 6-8 times/daily, a drug interaction between IMATINIB and acetaminophen has to be considered. This death occurred against a background of Grade 2/3 elevations in liver transaminases in seven patients, without a clear dose-relationship. These elevations were often attributed to progression of the underlying disease. When suspected to be related to study drug, they were managed successfully by temporary discontinuation of drug, whereupon transaminase values promptly decreased. Modest dose reductions upon re-initiation of therapy were performed for Grade 3 toxicity, and no patient has permanently discontinued therapy due to hepatic toxicity.

The most commonly reported adverse event related to imatinib administration was mild nausea, which has been observed in more than 40% of patients. It is now established that nausea may be

prevented or mitigated by the prior ingestion of a small snack. Arthralgias, myalgias and periorbital edema have each been observed in 10% of patients. Interstitial edema and weight gain have been seen in some patients treated with 600 mg and 750 mg/daily; however, these findings were not associated with capillary leak syndrome and no patient has experienced congestive heart failure or other adverse events as a result of fluid retention.

Several patients have experienced episodes of gastrointestinal bleeding associated with erosions at the gastroesophageal junction and presumed due to the irritant effect of the drug.

In a phase II study published by Ottmann in 2002 (24), Imatinib toxicity profile was similar to that observed in the trials of single agent imatinib for Ph+ CML, and included transient myelosuppression, fluid retention syndrome, nausea, muscle cramps, rash, and transient elevations in hepatic transaminases. When incorporated into combination chemotherapy regimens the safety profile of the drug still proved to be tolerable. Not surprisingly, the use of concurrent imatinib and L-asparaginase often resulted in hyperbilirubinemia, requiring dose interruptions or modifications of therapy.

Experience of IMATINIB in pediatric patients

A Phase I study of Imatinib, POG-P9973, was conducted by POG to estimate the maximum tolerated dose (MTD) of Imatinib administered orally once daily, without interruption to children with recurrent Ph+ leukemia.

No MTD was observed up to 570 mg/m^2,equivalent to the adult phase 2 and 3 dose. Grade 3-4 neutropenia was seen in the 23 of 93 courses, thrombocytopenia in 16 of 93 courses. Some of the hematologic toxicity may have been secondary to underlying leukemia as they were present in 25-30% during the first course of treatment. Gr 3-4 diarrhea was observed in 15/ 93, nausea in 16/93 vomiting in 13/93, abdominal cramping 6/ 93. Grade 3 liver enzyme elevation occurred in 1/93. One intracranial hemorrhage occurred in a patient who was thrombocytopenic and was receiving enoxaparin.

The most common toxicity was grade 1 nausea, seen in 7 of 14 patients (50%). Diarrhea, vomiting, abdominal pain and headaches were each reported in 3 patients (21%). Other toxicities reported in 2 patients each included fatigue, stomatitis, bone pain, and various metabolic alterations (increased alkaline phosphatase, increased AST, hyperglycemia). Patients accrued on the first 3 treatment levels cumulate a total of 43 courses of treatment (median 3; range 2-8).

The recently completed COG AALL0031 trial established the safety and tested the efficacy of an intensive chemotherapy backbone plus imatinib in treating children with Ph+ ALL. To date, addition of imatinib has been safe and associated with relatively minor additional toxicity (mild

asymptomatic transaminitis requiring intermittent rather than continuous dosing during Maintenance therapy).

Among pediatric patients with Ph+ ALL, there have been limited reports evaluating the impact of imatinib on either induction CR rates and/or overall outcomes. In a short report by Fuster et al. (31), the authors describe four pediatric patients with Ph+ ALL (ages 2–8 years) treated with imatinib in combination with chemotherapy prior to proceeding to allogeneic HCT. All patients achieved a molecular remission (undetectable bcr/abl transcript by RT-PCR) by 16 weeks (range, 2–16 weeks) from the start of combination therapy and were alive in hematologic remission after a median time of 24 months (range, 11–53 months) from initiating imatinib.

Burke et al reported 37 children diagnosed with Ph+ B-precursor ALL receiving a myeloablative allogeneic HCT (32). Patients received similar pre-HCT chemotherapy with the majority receiving Berlin–Frankfurt–Munster (BFM) based regimens according to Children's Cancer Group (CCG) or COG protocols. Thirteen patients received imatinib therapy either pre- and/or post-HCT comprising the imatinib group. The remaining 24 patients either never received imatinib or received it only at time of relapse post-HCT. IMATINIB doses ranged from 240 to 340 mg/m^2/day. Patients treated with IMATINIB pre-HCT received therapy for a median of 3 months (range, 1–27 months). When IMATINIB therapy was used postallogeneic HCT, it was started, on average, on day 120 (range, 80–180) and continued for a median of 8 (range, 2–10) months. OS and DFS at 3 years was 59% and 62% for the IMATINIB group compared to 58% and 53% for the non-IMATINIB group (P = 0.80 and 0.9 respectively)

Main Study COG AALL0031 (33).

This study was a phase III open, non-controlled, dose-escalation study conducted by the Children's Oncology Group (COG), a NCI supported clinical co-operative group, in the US. Study Participants were male and female patients younger than 21 years old with Very High Risk leukemias including 93 patients with Ph+ leukaemia.

The chemotherapy regimen was based on previous strategies in which patients first received 4 weeks of standard induction chemotherapy and were entered onto AALL0031, which included an intensive consolidation phase followed by a continuation regimen. All patients received a minimum of two consolidation chemotherapy blocks. Patients with an HLA-matched related donor entered the BMT arm following these blocks. Total duration of chemotherapy for those not receiving BMT was approximately 27 months. For patients with Ph+ALL, imatinib 340 mg/m^2/d was introduced into the chemotherapy regimen in a stepwise fashion, with toxicity assessed for each cohort before progression to the next cohort. Each cohort had 12 subjects except for cohort 1 (n=7), which was discontinued early on the basis of published data demonstrating acceptable imatinib toxicity with

high-dose methotrexate. Cohort 5 was expanded to accrue a total of 50 patients to provide a more precise estimate of outcome. The total imatinib exposure (before maintenance) was 42 days in cohort 1, 63 days in cohort 2 (n=17), 84 days in cohort 3, 126 days in cohort 4 (n=22), and 280 days in cohort 5 (n=44). All groups received an additional 336 days of imatinib exposure in maintenance cycles 1 through 12. For all patients receiving BMT on protocol, imatinib was started between week 16 and week 24 after BMT when the absolute neutrophil count was ≥ 750 and the platelet count was ≥75,000 given for a total of 24 weeks. Dosing started at 230mg/m^2/d and increased after 28 days to 340 mg/m^2/d if no grade 3 or 4 toxicity was observed.

This study aimed to determine the the feasibility in terms of patient accrual and toxicity of an intensified chemotherapeutic regimen incorporating novel agents for treatment of children and adolescents with very high risk ALL.

The 3-year EFS of patients in cohort 5 receiving continuous imatinib was 80.5%±11.2% (95% CI, 64.5% to 89.8%), including those assigned to a sibling BMT. This is significantly higher than

historical controls, after excluding induction failures from previous POG studies (N=120; 3-year EFS, 35.0%±4.4%; P< .0001).

Twenty-one patients had matched sibling transplants (8 of 39 in cohorts 1-4 and 13 of 44 in cohort 5). There was no significant difference in 3-year EFS between patients (n = 25) treated with cohort 5 chemotherapy (87.7%±10.9%; 95% CI, 66.4% to 95.8%), patients (n=21) receiving BMT from a sibling donor (56.6% ±21.5%; 95% CI, 30.4% to 76.1%), and patients (n = 11) receiving BMT from an alternative donor (71.6% ± 19.0%; 95% CI, 35.0% to 89.9%; *P* = .14).

Role of Hematopoietic Stem Cell Transplantation (HSCT) in Ph positive ALL

Because of the universally dismal prognosis of *de novo* Ph+ ALL in the pre-imatinib era, all patients who achieved CR were recommended to undergo allogeneic SCT as feasible,inclusive of all stem cell sources such as matched unrelated marrow and umbilical cord blood. The benefits of SCT in first CR were attributed to the intense myeloablative therapy and graft-versus-leukemia effect; the high risk of transplantation-related mortality was accepted given the alternative of poor outcomes with chemotherapy alone. Two large multicenter trials confirmed the benefit of allogeneic SCT in the pre-imatinib era. In the Ph+ subset of patients with ALL (n=167) enrolled in the UKALL XII/ECOG E2993 trial, the 5-year relapse risk was decreased from 81% with either chemotherapy alone or autologous SCT to 32% with allogeneic SCT (8). Five-year event-free survival (EFS) and overall survival rates improved from 17% to 36% and 19% to 42%, respectively. Furthermore, the prospective multicenter French, Belgian, Swiss and Australian LALA-94 trial of

154 patients with Ph+ ALL showed that achievement of negativity for BCR-ABL by RT-PCR and undergoing allogeneic SCT predicted for improved DFS and overall survival (9).

The role of allogeneic SCT for *de novo* Ph+ ALL in the imatinib era continues to be refined, with feasibility of this approach still limited by the availability of an appropriate donor, absence of significant comorbidities, and ability to sustain a complete remission. Advances in SCT such as the application of nonmyeloablative reduced intensity conditioning regimens to patients with comorbidities prohibiting traditional myeloablative regimens, in addition to increased availability of umbilical cord blood as a source of stem cells, have allowed this modality to be applied in a more systematic fashion (10).

Several studies have reported an improvement in the rate of allogeneic SCT in first CR after imatinib-based therapy compared with the prior experience (27,29,30,38). This success is in part related to (1) an increase in the proportion of sustained remissions, offering additional time for identification of a suitable donor, and to (2) an improvement in the quality of the remissions (e.g., lower levels of *BCR-ABL* transcripts after imatinib-based therapy), resulting in a lower pretransplantation tumor burden. Two of the early nonrandomized studies of imatinib-based chemotherapy for *de novo* Ph+ ALL applied allogeneic SCT in first CR as standard of care when feasible. Similar survival outcomes were observed with or without allogeneic SCT, despite the selection biases favoring SCT (27,29,38). Additional experience and longer follow-up is needed to clarify whether allogeneic SCT can be deferred in a select group of patients with Ph+ ALL otherwise eligible for this modality. To this regard, the Gandemer series identified two groups of patients with marked differences in five-year outcome: children with age<10, leukocyte count <100,000/mm3 and day-21 M1 marrow had a more favorable prognosis (14 pts: 100% CR, event free survival [EFS]: 57%, overall survival [OS]: 79%), than the high-risk group (22 patients: 55% CR, EFS: 18%, OS: 27%) ($p < 0.005$) (41). The combination of available tools such as minimal residual disease assessment with determination of these simple factors could be useful for refining indications for BMT in the current era of tyrosine-kinase inhibitor-based treatment.

Postallogeneic SCT maintenance strategies are also being explored, particularly as the detection of minimal residual disease (MRD) following SCT predicts imminent relapse in the absence of intervention (40). Wassmann et al (11) investigated the use of single-agent imatinib in the post transplantation setting after detection of MRD by quantitative RT-PCR for BCR-ABL. Standard-dose (400 mg) imatinib resulted in eradication of molecular disease in 52% of the 27 patients treated. Notably, failure to achieve molecular remission within the first 6 weeks of therapy heralded overt leukemia relapse despite other additional manipulations (e.g., donor lymphocyte infusions). Using imatinib in the post-transplantation setting in a prophylactic manner, immediately after

engraftment and prior to the detection of MRD, may further improve outcome by preventing resurgence of the leukemia clone. Two small series have shown that this approach is feasible, with transient elevations in hepatic transaminases usually responding to dose interruptions or modifications (12, 13). Additional experience will be required to determine whether imatinib monotherapy after transplantation would eventually lead to development of resistance.

2. Study population

2.1 Patient population

The target population includes children and adolescents with newly diagnosed and documented Ph+ALL enrolled in the treatment front-line protocols of the national study groups of AIEOP, BFM-G/CH and BFM-A, COALL, DCOG, EORTC, FRALLE, UKALL, NOPHO,CZECH REPUBLIC, PINDA and HONG KONG.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

The criteria for the patients with newly diagnosed Ph+ALL to enter the study are:

1. Age greater than 1 year (365 days) and less than 18 years (17 years and 365 days) at diagnosis.
2. Documented presence of t(9;22)(q34;q11) determined by institutional cytogenetics or FISH and/or of the presence of BCR-ABL fusion transcript identified by RT-PCR or FISH.
3. Eligibility for the current local prospective therapeutic study of childhood ALL.
4. Informed consent given by the parents or by the legal guardian.

It is important that <u>all</u> children with Ph+ALL, including those who are eligible but are not treated according to the present protocol will be registered so that any selection bias can be monitored.

2.2.2 Exclusion criteria (on day 15 at the time to start IMATINIB)

1. Abnormal hepatic function (ALAT/ASAT > 10 times the upper limit of the normal range);
2. Abnormal renal function (creatinine > 1.5 times the upper limit of the normal range or a calculated creatinine clearance of 80 ml/ min or less, adjusted to a body surface area of 1.73 m^2);
3. Active systemic bacterial, fungal or viral infection as documented by positive cultures, radiological imaging techniques, septic shock symptoms.

2.3 Stratification

All patients will receive the induction phase according to national/group study treatment protocol. Either early response to treatment parameters (PB blast/count after 7 days of prednisone given in combination with intrathecal methotrexate before induction chemotherapy is instituted; or evaluation of BM at day 15 and 21) or no achievement of CR (cytology) at the end of induction,

will allow the definition of Ph+ALL risk- subgroups in the different study groups. More precisely, the following definitions hold:

c. Poor-Risk group: for protocols which adopt a steroid prephase patients who are Prednisone-poor responder (i.e. blast cell count ≥ 1000/μl in peripheral blood after 7 days of Prednisone given in combination with intrathecal Methotrexate), for protocols which do not adopt steroid prephase patients who have M3 BM at day 15 or M2/M3 BM at day 21; for all protocols patients who do not achieve CR after the induction course.

d. Good-Risk group: for protocols which adopt a steroid prephase patients who are Prednisone-good responder (i.e. blast cell count < 1000/μl in peripheral blood after 7 days of Prednisone given in combination with intrathecal Methotrexate) and achieve CR after the induction course; for protocols which do not adopt steroid prephase patients who have M1/M2 BM at day 15 or M1 BM at day 21 and achieve CR after the induction course.

3. Study objectives

3.1 Primary objective

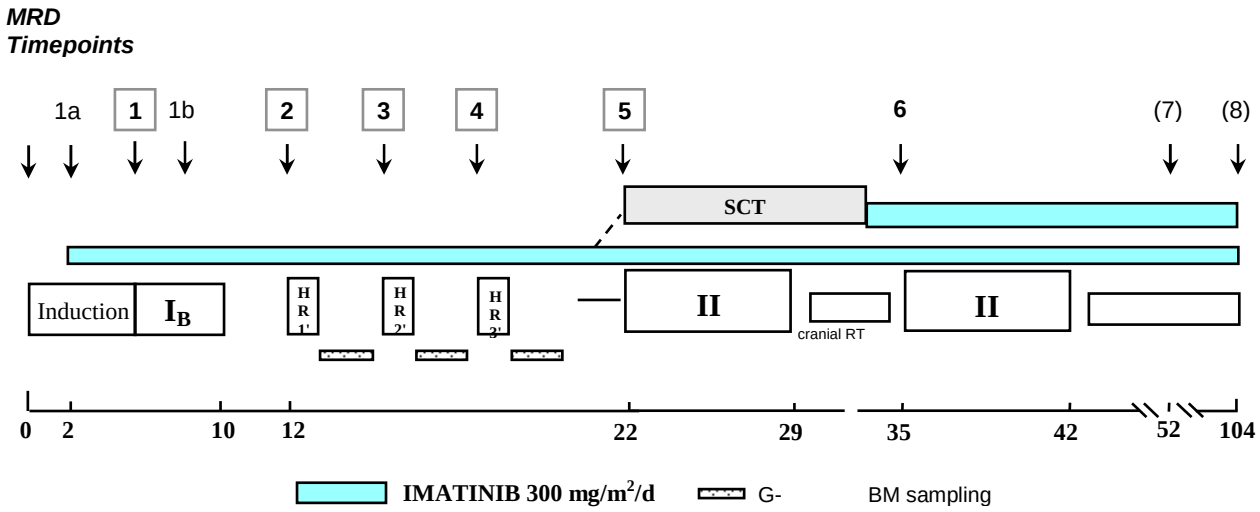
To evaluate in patients with Ph+ALL the efficacy and safety of IMATINIB continuous exposure on top of intensive, BFM-type chemotherapy. The endpoint will be the evaluation on the long-term clinical outcome.

3.2 Secondary objectives

- To compare the outcome with historical controls of patients treated with BFM oriented protocols (including patients treated with Imatinib in the original EsPhALL protocol) and with recent results from the COGAALL0031 (Children Oncology Group-USA) study, which adopts a more intensive chemotherapy approach than BFM.
- To evaluate the overall EFS,DFS and survival.
- To assess the antileukemic potential of IMATINIB by analyzing the pattern of molecular response on the basis of 5 MRD measurements taken at different time points from the beginning of phase IB to the beginning of protocol II or HSCT at week 22.
- To evaluate the impact of MRD on prognosis (EFS/DFS).
- To evaluate the impact of HSCT on prognosis (EFS/DFS).

- To evaluate possible delays in chemotherapy administration under Imatinib continuous exposure

Fig. 3 **European intergroup study on treatment of Ph+ALL with IMATINIB**



4. Overall study design

In the context of Ph+ALL most of the data produced so far have shown only a transient effect in blast cell reduction. These observation prompted several investigators to consider the use of IMATINIB in the context of multi-agent approach. The clinical heterogeneity of Ph+ALL will offer the opportunity to test the impact of IMATINIB in two subgroups of patients as defined by early response to treatment (Poor and Good Risk Ph+ALL).

While we allow for differences in induction therapies applied by different groups, it is very important that all subsequent therapy plan is uniform. For this purpose, the current AIEOP-BFM-ALL 2000 strategy for High-risk patients has been considered appropriate. Treatment starts with approximately 4 weeks of induction therapy according to the national protocol. During this, the Ph+ status of the patient has to be determined. After this first induction therapy, further treatment will be according to the international schedule. This will include a phase IB of induction, followed by three blocks of treatment as shown in detailed in Fig.4 - 7. With respect to the different proposed arms for reinduction therapy, the AIEOP variant which included a modified- BFM protocol II repeated twice, will be used, as shown in Fig.8 , 9.

Good-risk and Poor Risk Ph+ALL patients will receive IMATINIB starting on day 15 during Induction phase and continuously troughout the consolidation and reinduction phase of chemotherapy

All patients will be screened for an HLA-identical family or unrelated donor.

Good-risk patients: patients with a genotype-matched donor (9/10 or 10/10), will receive HSCT, while the others will continue on chemotherapy, thus receiving IMATINIB in combination with the standard chemotherapy.

Poor-risk patients: patients will be eligible for any type of donor (matched or mismatched family donors, unrelated or haploidentical donors). Patients not transplanted will continue on chemotherapy, thus receiving IMATINIB in combination with the standard chemotherapy.

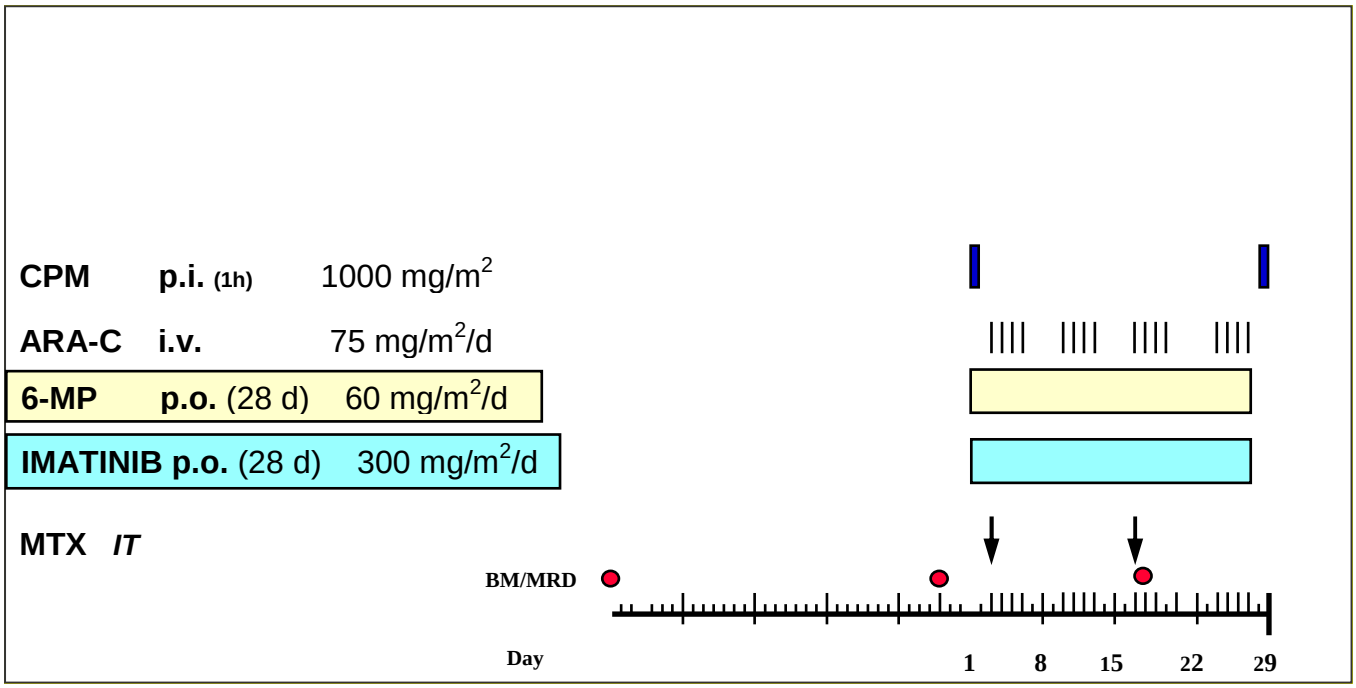
5. Treatment plan

5.1 Frontline induction

All patients will receive the first induction according to national/group study treatment protocol. Imatinib 300 mg/m^2 daily will be introduced on day + 15 from diagnosis in all patients on top of ongoing chemotherapy till day + 33.

5.2 Phase IB

Figure 4.



IMATINIB : 300 mg/m^2/day orally days 1-28 (total 28 days).

All Good and Poor Risk Patients will receive IMATINIB. To allow close patient monitoring, patient will attend outpatient clinics at least weekly because of ARA-C injections.

Requirements for beginning of phase IB:

1.Good general condition without serious infections;

2.Creatinine level within normal limits according to age;

3.WBC> 2000/µl, ANC >500/µl; platelets >50,000/µl

CYCLOPHOSPHAMIDE (CPM): 1000 mg/m^2/dose i.v. (1 hour) days 1,28.

Associate: * hyperhydratation 3.000 ml/m^2 over 24 hours : G 5%+ NaCl 0,45%+ 90 mEq/m^2KCl

* MESNA (1/3 of CPM dose, hours 0, 4, 8 from CPM start).
* FUROSEMIDE 0.5-1 mg/kg i.v if input > output +400ml/ m^2/12 h.

Please consider adequate anti-emetic supportive therapy.

6-MERCAPTOPURINE (6-MP): 60 mg/m^2/day p.o., to be taken in the evening on an empty stomach (1 hour before or after dinner), not together with milk, days 1-28(total 28 days).

CYTOSINE ARABINOSIDE (ARA-C): 75 mg/^{2}/day s.c. o i.v. in one daily dose, days 3-6, 10-13, 17-20,24-27.

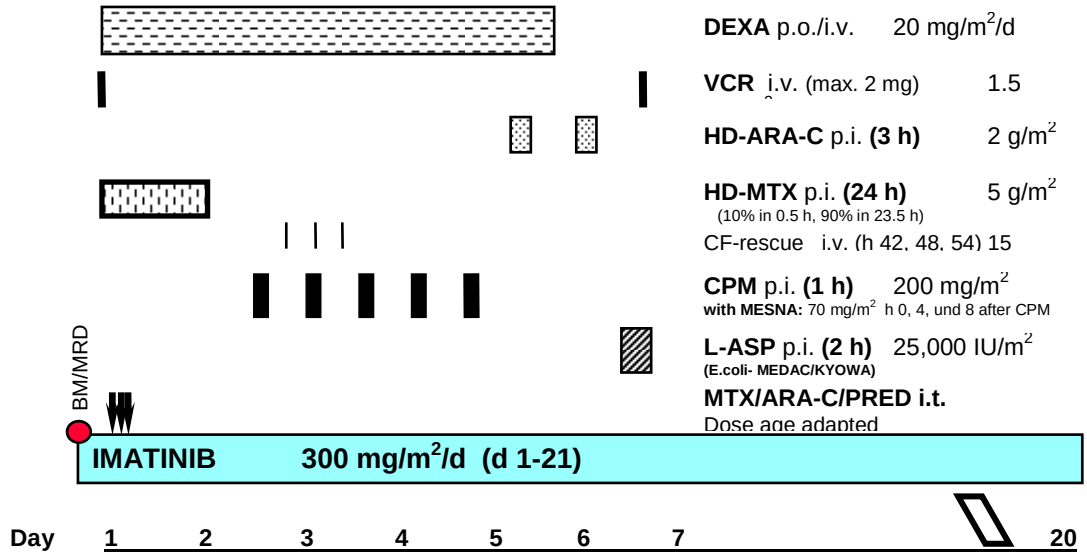
Each 4-day cycle should be started when WBC >500µl and platelets >30.000/µl; each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug).

INTRATECHAL METHOTREXATE : days 3, 17 (together with ARA-C cycles 1 and 3), age-dosed:

AGE	**MTX**
≥1 year <2 years	8 mg
≥2 years <3 years	10 mg
≥3 years	12 mg

5.3 Consolidation Block 1 (HR1')

Figure 5.



Consolidation therapy will start on day 78 of therapy, provided the patient is in good general condition and adequate ANC (≥ 500/µl) and platelet counts (≥ 50.000/µl) are documented (rising counts). Imatinib administration will not be interrupted between the end of phase IB and the beginning of the first HR block. **The interval between each block element should be 21 days (counting from day 1 of HR-1 to day 1 of HR-2).**

DEXAMETHASONE (DXM): 20 mg/m^2/day p.o. or i.v. in 3 doses, days 1-5 (no tapering).

VINCRISTINE (VCR): 1.5 mg/m^2/day i.v.(max dose: 2mg), day 1 and 6.

HIGH-DOSE METHOTREXATE (HD-MTX): 5 g/m^2/dose i.v. over 24 hours on day 1 (1/10 in 30 minutes, the remaining 9/10 in 23.5 hour-infusion). Hyperhydration: 3.000 ml/m^2 over 24 hours : Gluc. 5%+ NaCl 0,45%+ 90 mEq/m^{2}KCl+$NaHCO_3$ 90 mEq/m^2. Urine pH>7.0 over the time of infusion.

Serum levels of MTX must be determined at hours 24, 42, 48 from start of MTX infusion. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix I.

CITROVORUM FACTOR (Folinic acid): 7.5 mg/m^2 i.v (Levo form) or 15 mg/m^2 i.v (Racemic form) at hours 42, 48, 54 from start of infusion. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix I.

Starting from hour 60, Citrovorum Factor is needed only if serum levels at hour 48 exceed 0.5 µmol/l. In this case, see nomogram for therapeutic adjustments.

HIGH-DOSE ARA-C (HD-ARA-C): 2 gr/m^2/iv in 3-hour infusion, repeated after 12 hours, day 5. The use of prednisolone eye drops is suggested.

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP): E. coli (medac or kidrolase): 25.000 IU/m^2/dose, over 2 h i.v., 3 hours after completion of the infusion of the second dose of HD-ARA-C. In case of an allergic reaction , PEG-ASP(ONCASPAR) may be used in a single dose of 1000 I.E./m^2 over 1 h i.v.

CYCLOPHOSPHAMIDE (CPM): 200 mg/m^2 i.v. in 1 hour q 12 hours, 5 doses, days 2-4. Start immediately after the completion of HD-MTX infusion. MESNA 70 mg/m^2 hours 0, 4 and 8 from start of CPM.

INTRATHECAL THERAPY: day 1, 2 hours after start of HD-MTX, dose according to age:

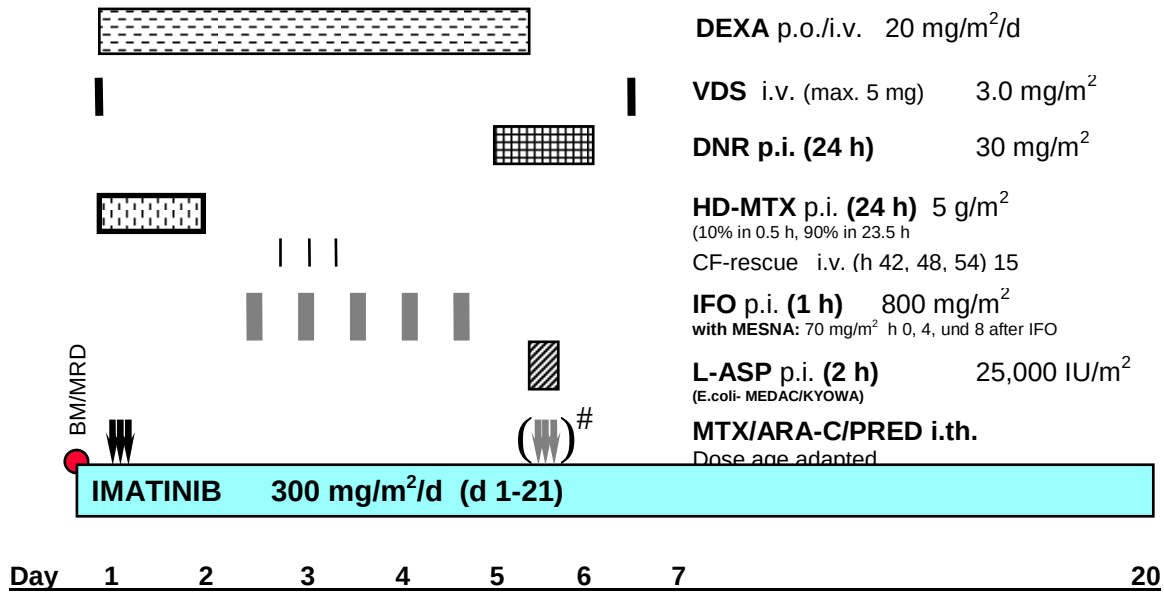
AGE	MTX	ARA-C	PRED
≥1 year <2 years	8 mg	20 mg	6 mg
≥2 years <3 years	10 mg	26 mg	8 mg
≥3 years	12 mg	30 mg	10 mg

G-CSF: 5 µg/kg/day s.c. starting from the 5th day after completion of the block, until the WBC count is >20.000υl

IMATINIB : 300 mg/m^2/day orally starting from the first day of chemotherapy block and given for a total of 21 days. IMATINIB should not be given longer than 21 days if next chemotherapy block has to be postponed.

5.4 Consolidation Block 2 (HR2')

Figure 6.



#only if initially CNS positive

DEXAMETHASONE (DXM)**:** 20 mg/m^2/day p.o. o i.v. in 3 doses, days 1-5 (no tapering).

VINDESINE (VDS)**:** 3 mg/m^2/day i.v.(max 5 mg), days 1 and 6.

HIGH-DOSE METHOTREXATE (HD-MTX): 5 g/m^2/dose i.v. on day 1 over 24 hours (1/10 in 30 minutes, the remaining 9/10 over a 23.5 hour-infusion). Hyperhydration: 3.000 ml/m^2 over 24 hours : Gluc. 5%+ NaCl 0,45%+ 90 mEq/m^{2}KCl+$NaHCO_3$ 90 mEq/m^2. Urine pH>7.0 over the time of infusion.

Serum levels of MTX must be determined at hours 24, 42, 48 from infusion start. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix I.

CITROVORUM FACTOR (Folinic acid): 7.5 mg/m^2 i.v (Levo form) or 15 mg/m^2 i.v (Racemic form) at hours 42, 48, 54 from start of infusion. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix I.

Starting from hour 60, CF is needed only if serum levels at hour 48 exceed 0.5 µmol/l. In this case, see nomogram for therapeutic adjustments.

IFOSPHAMIDE (IFO): 800 mg/m^2 i.v. over 1-hour infusion, q 12 hours, 5 doses, days 2-4. Start immediately after completion of HD-MTX infusion. MESNA 300 mg/m^2 i.v hour 0, 4 and 8 from start of infusion.

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP)**:** E. coli (medac or kidrolase): 25.000 IU/m^2/dose, over 2 h i.v. In case of an allergic reaction , PEG-ASP(ONCASPAR) may be used in a single dose of 1000 I.E./m^2 over 1 h i.v., on day 5

DAUNORUBICIN (DNR): 30 mg/m^{2}m over 24-hour infusion on day 5

INTRATHECAL THERAPY: day 1, 2 hours after start of HD-MTX, according to age:

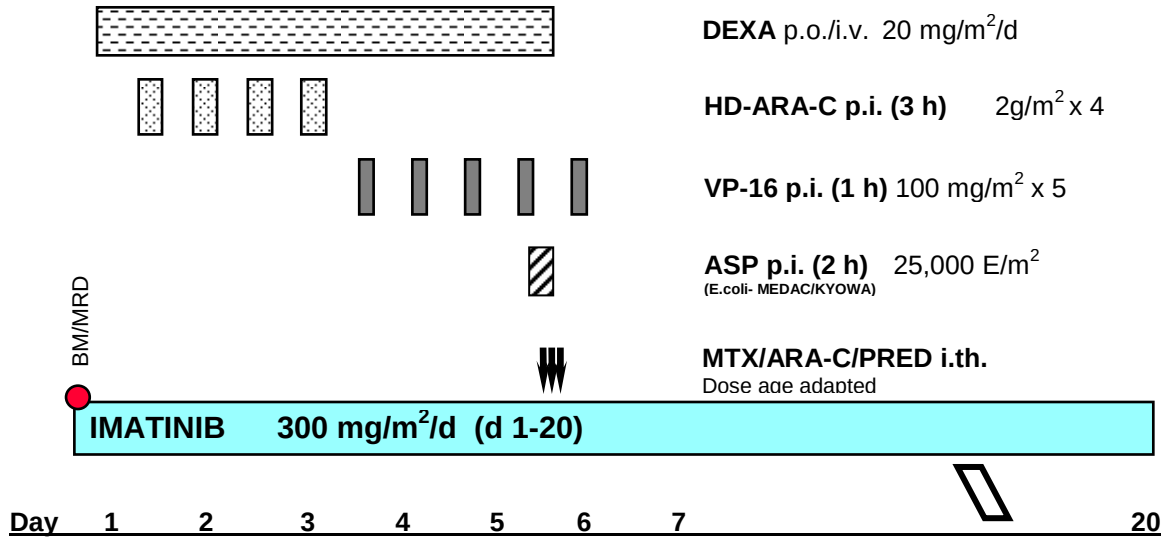
AGE	**MTX**	**ARA-C**	**PRED**
≥1 year <2 years	8 mg	20 mg	6 mg
≥2 years <3 years	10 mg	26 mg	8 mg
≥3 years	12 mg	30 mg	10 mg

G-CSF: 5 µg/kg/day s.c. starting from the 5th day after completion of the block, until the WBC count is >20x10^9/l.

IMATINIB : 300 mg/m^2/day orally starting from the first day of chemotherapy block and given for a total of 21 days. IMATINIB should not be given longer than 21 days if next chemotherapy block has to be postponed.

5.5 Consolidation Block 3 (HR 3')

Figure 7.



DEXAMETHASONE (DXM)**:** 20 mg/m^{2}m/day p.o. o i.v. in 3 doses, days 1-5 (no tapering).

HIGH-DOSE ARA-C (HD-ARA-C): 2 g/m^2 i.v. in 3-hour infusion, q 12 hours, 4 total doses, days 1-2.

VP-16: 100 mg/m^{2}m i.v. in 1 hour , q 12 hours, 5 total doses, days 3-5.

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP)**:** E. coli (medac or kidrolase): 25.000 IU/m^2/dose, over 2 h i.v. In case of an allergic reaction ,PEG-ASP(ONCASPAR) may be used in a single dose of 1000 I.E./m^2 over 1 h i.v. on day 5

INTRATHECAL THERAPY: day 5, dose according to age:

AGE	MTX	ARA-C	PRED
≥1 year <2 years	8 mg	20 mg	6 mg
≥2 years <3 years	10 mg	26 mg	8 mg
≥3 years	12 mg	30 mg	10 mg

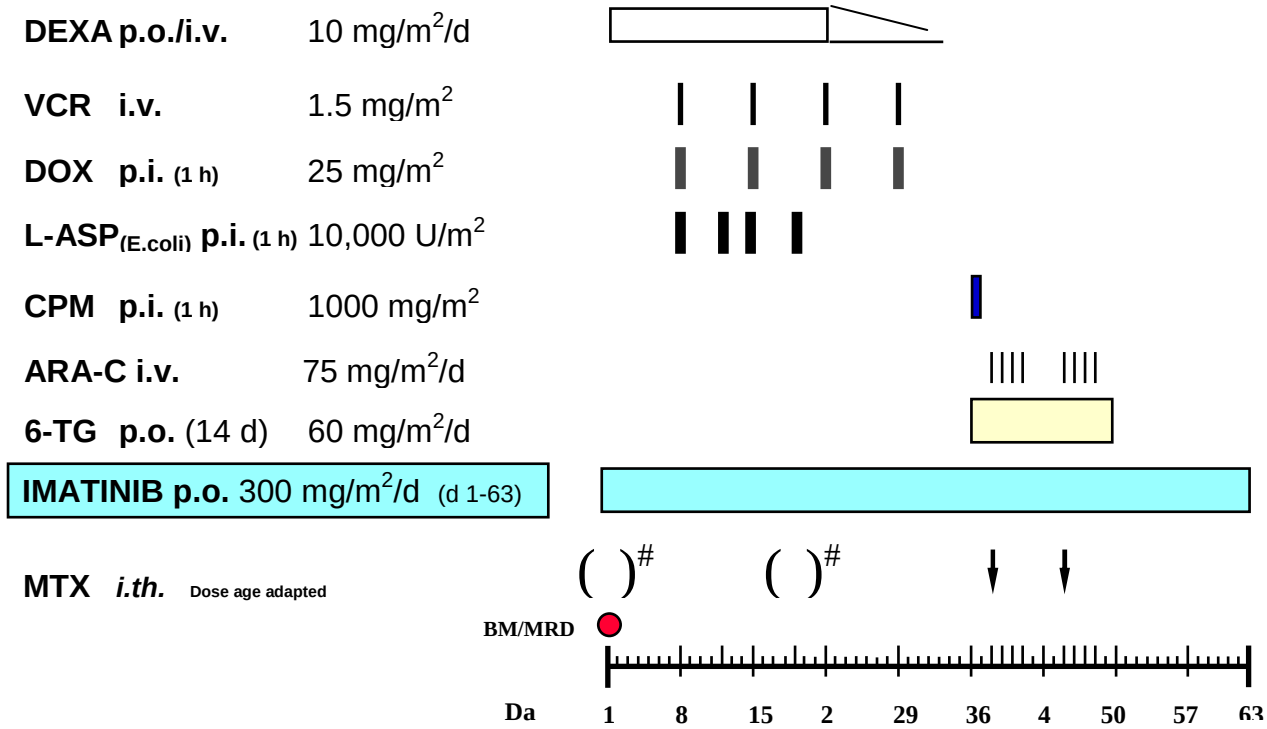
G-CSF: 5 µg/kg/day s.c. starting from the 5th day after completion of the block, until the WBC count is >20x10^9/l.

IMATINIB : 300 mg/m^2/day orally starting from the first day of chemotherapy block and given for a total of 20 days. IMATINIB should not be given longer than 20 days if next chemotherapy block has to be postponed.

5.6 Reinduction (Protocol II)

Reinduction with protocol II starts 14 days after completion of consolidation block-therapy (intended as day 5 of HR block 3) provided the patient is in good general condition and adequate ANC (≥ 500/µl) and platelet counts (≥ 50.000/µl) are documented. Protocol II comprises two phases, IIa and IIb.

Figure 8.



#only if initially CNS positive

5.6.1 Phase IIa

DEXAMETHASONE (DXM) : 10mg/m^2/day p.o. in 3 doses, day 1-21, then tapered over 9 days by reducing the dose by 50% q 3 days.

VINCRISTINE (VCR): 1.5 mg/m^2/dose i.v. (maximum dose 2.0 mg/dose), day 8, 15, 22, 29.

DOXORUBICIN (DOX)/ADRIAMYCIN (**ADR**): 25 mg/m^2/dose i.v. to be infused over 1h on days 8, 15, 22, 29.

L-ASPARAGINASE (L-ASP) E. coli (medac or kidrolase): 10.000 IU/m^2/dose, over 1 h i.v.,days 8,11,15 and 18. In case of an allergic reaction , PEG-ASP(ONCASPAR) may be used in a single dose of 1000 I.E./m^2 over 1 h i.v.

IMATINIB : 300 mg/m^2/day orally, days 1-35 (total 35 days)

5.6.2 Phase IIb

It starts on day 36 of protocol II provided the patient is in good general condition and adequate ANC (≥ 500/μl) and platelet counts (≥ 50.000/μl) are documented.

CYCLOPHOSPHAMIDE (CPM): 1000 mg/m^2/dose i.v. (1 hour) day 36.

Associate:
* hyperhydration 3.000 ml/m^2 over 24 hours : Gluc. 5%+ NaCl 0.45%+ 90 mEq/m^2 KCl .
* MESNA (1/3 of CPM dose, hours 0, 4, 8 from CPM start).
* FUROSEMIDE 0.5-1 mg/kg i.v if input>output +400 ml/m^2/12h.

Please consider adequate anti-emetic supportive therapy.

6-THIOGUANINE (6-TG): 60 mg/m^2/day p.o., taken in the evening on the empty stomach without milk (1 hour before or after dinner), days 36-49 (total 14 days).

CYTOSINE ARABINOSIDE (ARA-C): 75 mg/m^2/day s.c. o i.v. in one daily dose, days 38-41, 45-48.

Each 4-day cycle should be started when ANC >200/μl and platelets >50.000/μl; each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug).

INTRATHECAL METHOTREXATE : days 38, 45 (together with ARA-C cycles),dosage according to age:

AGE	**MTX**
≥1 year <2 years	8 mg
≥2 years <3 years	10 mg
≥3 years	12 mg

IMATINIB : 300 mg/m^2/day orally, days 36-63 (total 28 days) for all patients

5.7 Interim maintenance

This short phase is aimed to allow administration of cranial irradiation during antimetabolite-based non-intensive chemotherapy. It will start 2 weeks after completion of the previous phase (day 49 of protocol II) and will last 4 weeks i.e. the time comprised between the first and the second administration of protocol II. Imatinib administration will not be interrupted between the end of protocol II and the beginning of interim maintenance.

6-MERCAPTOPURINE (6-MP): 50 mg/m^2/day p.o., taken in the evening on the empty stomach without milk (1 hour before or after dinner), days 1-28.

METHOTREXATE (MTX): 20 mg/m^2/dose p.o. once a week days 8,15,22,29.

ⓘ no MTX p.o on day 15 if IT MTX

IMATINIB : 300 mg /m^2/day, days 1-29

In selected cases it could be necessary to start the two drugs with increasing doses according to the patient's compliance and/or haematological reconstitution.

CRANIAL IRRADIATION during interim maintenance:

For CNS prophylaxis :

- Cranial irradiation will **only** be administered to **patients older than 4 years** at the dose of **12 Gy** (single dose: 1.4-1.7 Gy)
- For patients younger than 4 years, 8 additional intrathecal injections will be performed :
    - on days 1 and 15 of interim maintenance
    - on days 1 and 38 of second administration of protocol II
    - and 4 in the continuation therapy

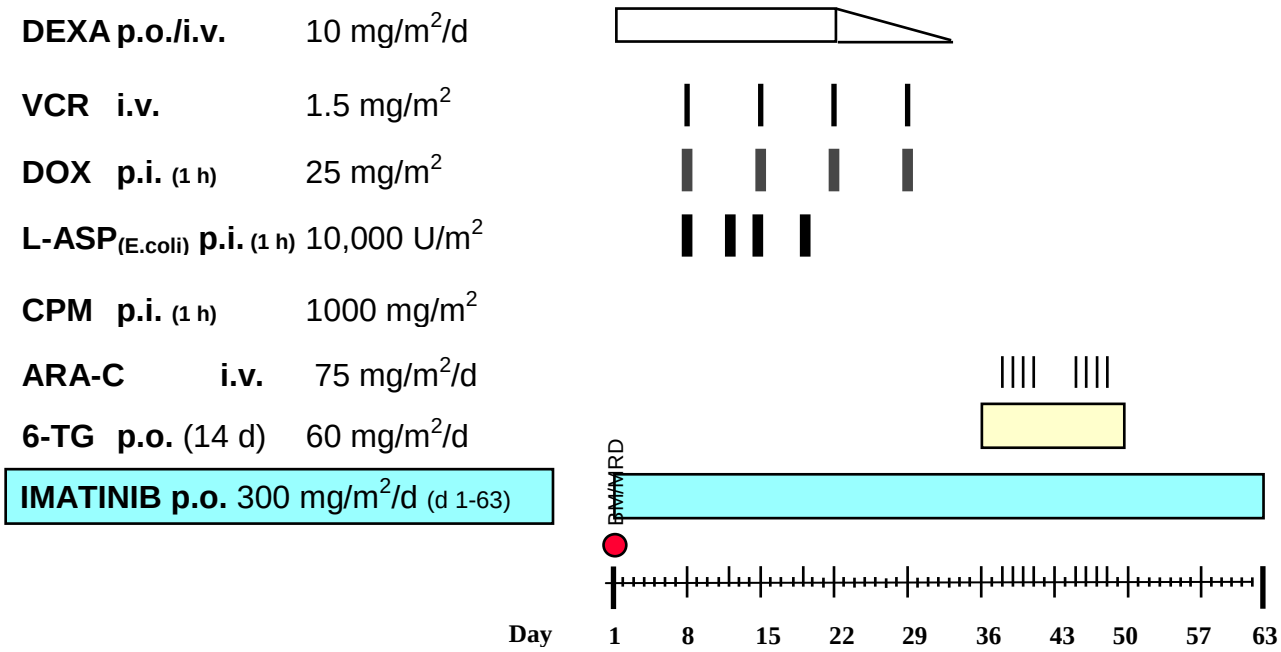
For Patients with CNS-disease:

- Patients **older than 2 years** will receive **18 Gy** (single dose: 1.4-1.7 Gy)**.**
- Patients younger than 2 years will not receive any irradiation but 10 additional intrathecal injections
    - on days 1 and 15 of interim maintenance
    - on days 1, 18, 38 and 45 of second administration of protocol II
    - and 4 in the continuation therapy

5.8 Second administration of Protocol II

It will start immediately after the interim maintenance provided the patient is in good general condition and adequate ANC (≥ 500/µl) and platelet counts (≥ 50.000/µl) are documented.

Figure 9.



5.8.1 Phase IIa

DEXAMETHASONE (DXM) : 10 mg/m^2/day p.o. in 3 doses, day 1-21, then tapered over 10 days by reducing the dose by 50% q 3 days.

VINCRISTINE (VCR): 1.5 mg/m^2/dose i.v. (maximum dose 2.0 mg/dose), day 8, 15, 22, 29.

DOXORUBICIN (DOX)/ADRIAMYCIN (**ADR**): 25 mg/m^2/dose i.v. to be infused over 1 h on days 8, 15, 22, 29.

L-ASPARAGINASE (L-ASP) E. coli (medac or kidrolase): 10.000 IU/m^2/dose, over 1 h i.v. In case of an allergic reaction, PEG-ASP(ONCASPAR) may be used in a single dose of 1000 I.E./m^2 over 1 h i.v.

IMATINIB : 300 mg/m2/day orally, days 1-35 (total 35 days)

INTRATHECAL METHOTREXATE only if NO IRRADIATION in interim maintenance : day 1 (and day 18 if CNS disease), age-dosed:

AGE	MTX
≥1 year <2 years	8 mg
≥2 years <3 years	10 mg
≥3 years <4 years	12 mg

5.8.2 Phase IIb

It starts on day 36 of protocol II provided the patient is in good general condition and adequate ANC (≥ 500/μl) platelet counts (≥ 50.000/μl) are documented.

CYCLOPHOSPHAMIDE (CPM): 1000 mg/m^2/dose i.v. (1 hour) days 36.

Associate:
* hyperhydration 3.000 ml/m^2 over 24 hours : Gluc. 5%+ NaCl 0.45%+ 90 mEq/m^2 KCl.
* MESNA (1/3 of CPM dose, hours 0, 4, 8 from CPM start).
* FUROSEMIDE 0.5-1 mg/kg i.v if input>output +400 ml/m^2/12h.

Please consider adequate anti-emetic supportive therapy.

6-THIOGUANINE (6-TG): 60 mg/m^2/day p.o., taken in the evening on the empty stomach without milk (1 hour before or after dinner), days 36-49 (total 14 days).

CYTOSINE ARABINOSIDE (ARA-C): 75 mg/m^2/day s.c. o i.v. in one daily dose, days 38-41, 45-48.

Each 4-day cycle should be started when WBC>500/μl and platelets >30.000/μl; each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug.

IMATINIB : 300 mg/m^2/day orally, days 36-63 (total 28 days) for all patients.

INTRATHECAL METHOTREXATE only if NO IRRADIATION in interim maintenance: days 38 (and day 45 if CNS disease) (together with ARA-C cycles),dosage according to age:

AGE	MTX

≥1 year <2 years	8 mg
≥2 years <3 years	10 mg
≥3 years <4 years	12 mg

5.9 Continuation therapy

Continuation therapy will start 2 weeks after completion of delayed intensification and is based on antimetabolite drugs. Imatinib administration will not be interrupted between the end of phase IB and the beginning of continuation therapy.

6-MERCAPTOPURINE (6-MP): 50 mg/m^2/day p.o., taken in the evening on the empty stomach without milk (1 hour before or after dinner).

METHOTREXATE (MTX): 20mg/m^2/weekly p.o.
ⓘ no MTX p.o the day of IT MTX/ARAC/PRED

IMATINIB : 300 mg/m^2/day p.o.

INTRATHECAL THERAPY only if NO IRRADIATION in interim maintenance: one intrathecal injection each 3 months with the first one on day 15 for a total of 4 in the continuation therapy

dosage according to age:

AGE	**MTX**	**ARA-C**	**PRED**
≥1 year <2 years	8 mg	20 mg	6 mg
≥2 years <3 years	10 mg	26 mg	8 mg
≥3 years <4 years	12 mg	30 mg	10 mg

Chemotherapy will be modulated to keep WBC count between 1,000 and 3,000/µl. The dosage of the two drugs will be adjusted accordingly:

Leukocyte count /µl	**Dose of 6-MP/MTX**
<1.000	0%
1.000-2000	50%
2000-3000	100%

>3.000	consider to increase the dosage to achieve a WBC count between 2000 and 3000/µl

ANC < 500/µl	0%
Lymphocytes<300/µl	50%

COMPLETION OF TREATMENT

Total duration of chemotherapy will not exceed 24 months. At the time of treatment completion confirm CR by bone marrow aspirate and CSF examination.

6.0 Investigational drug

Glivec® (IMATINIB) will be supplied by Novartis as 100 mg capsules packaged in polyethylene bottles. Medication labels will comply with the legal requirements of each country and will be printed in the local language. They will supply no information about the patient, just the patient identification number. The storage conditions for the study drug will be described on the medication label. Bottles must be stored in a safe, secure location.

Glivec® should be administered once or twice a day. Glivec® is a local irritant and must be taken in a sitting position with a large glass of water (250 ml/8oz; at least 100 ml/4 oz for children $\leq$ 3 years of age).

If the child/patient can not swallow the capsules the drug should be administered according to the following guidelines: pour the contents of a capsule by small portions into 20 ml of water, milk or apple juice. Stir with a spoon and administer the suspension immediately afterwards. Do not use any other beverage like Coca-Cola or orange juice. Note: the excipients used in the capsule will not dissolve. However, they are white whilst the active substance is yellow. Thus if a white solid residue remains in the glass, it does not matter as long as the capsule has been slowly added and well dispersed to allow the active substance to dissolve during stirring. If a yellow residue is observed, it means that the active substance was not completely dissolved and only a fraction of the dose has been swallowed.

Medications, which interfere with P-450 cytochrom metabolism (see Appendix III), should be avoided and recommended doses of acetaminophen, should not be exceeded. **The following**

medications and foods can interfere with P-450 metabolism: grapefruit juice, erythromycin, azithromycin, clarithromycin, rifampin and its analogs, fluconazole, ketoconazole, itraconazole, cimetidine, cannabinoids (marijuana or dronabinol) and the leukotriene inhibitors used in asthma such as zafirleukast and zileuton. **In addition, drug interactions in patients receiving prochlorperazine (Compazine) and coumadin are possible. Patients who require prochlorperazine during therapy should be monitored for extrapyramidal symptons and those on coumadin should have weekly prothrombin times while on therapy. These medications should not be used during IMATINIB administration unless there is unavoidable medical need and no other appropriate alternative agents are available. Also, acetaminophen should not be taken in greater than the recommended dose.**

7.0 Stem cell transplantation: <u>All patients will be screened for an HLA-identical family or unrelated donor.</u>

Good-risk patients: patients with a genotype-matched donor (9/10 or 10/10), will receive HSCT, while the others will continue on chemotherapy, thus receiving IMATINIB in combination with the standard chemotherapy.

Poor-risk patients: patients will be eligible for any type of donors (matched or mismatched family donors, unrelated or haploidentical donors). Patients not transplanted will continue on chemotherapy, thus receiving IMATINIB in combination with the standard chemotherapy.

7.1 <u>Use of Imatinib after stem cell transplantation:</u>

The use of IMATINIB is recommended in all HSCT recipient.

An initial dose of 200 mg/m^2 daily will be administered to all HSCT recipient provided they have a satisfactory PTL and WBC count with stable neutrophils engraftment (PTL > 50 x 10^9/L; WBC > 1.5 x 10^9/L; neutrophils > 0.5 x 10^9/L for at least 15 days).

Imatinib dosage can be increased to a maximum of 300 mg/m^2 daily if well tolerated by the patient.

Imatinib administration is suggested throughout the first year post-transplantation, till day +365 from HSCT.

It is recommended that a bone marrow aspirate with morphologic evaluation and PCR detection of BCR/ABL is done before the beginning of post-transplant Imatinib and every 3 months for the first year post-transplantation.

During Imatinib post-transplant administration weekly assessment of hepatic function and complete blood count is required.

8.0 Therapy modifications for toxicity (all phases)

8.1 Treatment toxicity during chemotherapy of Phase 1B, consolidation and re-induction by using protocol II

Based on the closed treatment protocol AIEOP and BFM-ALL 95, patients enrolled in high-risk schedule, require careful monitoring to prevent fatal or life-threatening complications. On average, these patients spent approximately 100 days in the hospital during the five intensive treatment phases covering the first nine months from diagnosis (27). However, the death rate in first CR was only 2%, justifying wider application of this therapy in patients with high-risk ALL. Although this treatment regimen included a high cumulative dose of anthracyclines (daunomycin and doxorubicin) of 410 mg/m^2, the cardiac function was not reported as a clinical problem after treatment completion in this study. Some relevant parameters related with the treatment burden are summarized in the following table.

	Prot. Ia	**Prot. Ib**	**Consoli-dation blocks****	**Prot. II (1st)**	**Prot. II (2nd)**
Number of patients analysed	182	157	124	109	31
Red blood cells					
Patients receiving ≥1 unit (%)	85	96	90	69	65
No. of units (mean*)	2.9	3.1	3.7	2.4	2.1
Platelets					
Patients receiving ≥1 unit (%)	51	36	70	16	23
No. of units (mean*)	4.3	3.6	5.1	3.6	3.4
IV antibiotic therapy					
Patients (%).	46	37	82	46	74
Duration in days (mean*)	11	7	14	9	14
Central venous line ***					
Patients (%)	67	75	83	80	74
No. days (mean*)	35	50	68	74	78
Hospitalization					
Patients (%)	97	85	99	85	87
No. days (mean*)	22	14	32	11	19
Phase duration (days)					
Scheduled by protocol	42	42	63	64	64
Observed (mean*)	46	59	73	81	89

* Mean values estimated including only patients who actually required the specific support.

** Data presented pertain to the entire phase (3 blocks)

*** Central line data are cumulative

8.2 Therapy modifications for IMATINIB toxicity

Non-Hematologic Toxicity

Grade 3/4

If a patient experiences unexpected non hematological Grade 3-4 toxicity, study drug must be withheld until the toxicity has resolved to < Grade 2 or lower. An assessment of possible drug interactions should be performed, and any drug that is suspected as contributing to the toxicity should be reevaluated regarding its dosage and/or necessity of administration. When toxicity is grade 2 or lower, IMATINIB should be reintroduced at 20% less dose.

Hepatic Toxicity:

Patients with a total serum bilirubin < 1.5 x ULN at baseline who experience Grade 3-4 elevations should be managed using the criteria detailed above for non-hematological toxicity

Hematologic Toxicity

Patients developing anemia are transfused at the discretion of the investigator. No dose reductions are foreseen for any grade of anemia, except for Grade 3 and 4 anemia resulting from an acute cause considered to be related to administration of IMATINIB (e.g. severe gastrointestinal hemorrhage).

In the event of Grade 3 thrombocytopenia (platelets 10.000-<50.000/µl) or neutropenia (500<1000 /µl) not accompanied by clinical manifestations, i.e. significant bleeding or neutropenic fever, potential causes of the cytopenias should be considered (e.g, leukemic progression, infection); if the thrombocytopenia or neutropenia are attributed to the study drug, the dose will be reduced at 20% less dose.

With the occurrence of Grade 4 thrombocytopenia (platelets <10.000/µl) ,not accompanied by clinical manifestations, platelets support and continuation of the drug are suggested.

G-CSF is permitted in the case of neutropenic fever or suspected drug induced neutropenia. If Grade 3 or 4 thrombocytopenia or neutropenia are accompanied by clinically significant bleeding or evidence of an infection, IMATINIB will be interrupted until toxicity has resolved to grade 2 or lower and the clinical situation has stabilized; IMATINIB will then be restarted at 240 mg/m^2 daily.

9.0 Visit schedule and assessments

Visit schedule

Patients must be followed at the study centers according to the visit schedule and assessments according to national study-group policy. Provided there are no safety concerns, patients may be evaluated by the referring physician after the first month of treatment. The referring physician must agree to perform all required evaluations as requested by the protocol for those specific visits, and agree to forward copies to the study center regularly. Patients must be evaluated at the study centers for all bone marrow assessments.

Efficacy assessments

Assessment of efficacy during the first 6 months of treatment is based on bone marrow cytology (histology only in case of a dry aspirate) and molecular evaluation of MRD according to the time points in Fig 3 (at the beginning of Phase IB, of each blocks and before the reinduction). Analysis of residual disease by flow cytometry is optional.

Minimal residual disease

MRD will be assessed by quantitative real-time PCR of mononuclear bone marrow and peripheral blood cells collected at specified time points (see Fig 3). To guarantee comparability of data, it is essential that the analyses are performed in central laboratories (one for each country) that agree on standard procedures. MRD evaluation will be performed by quantitative PCR amplification of the BCR-ABL fusion gene, according to the Guidelines of the European Against Cancer Project on " STANDARDIZATION AND QUALITY CONTROL STUDIES OF REAL TIME RT-PCR FOR MINIMAL RESIDUAL DISEASE DETECTION OF FUSION GENE TRANSCRIPTS IN LEUKEMIA - A EUROPE AGAINST CANCER PROGRAM" (28). Comparative data will be obtained by using Ig and TcR gene amplification as previously reported (29).

Cytogenetic and FISH analysis

It is recommended that a cytogenetic and FISH analysis will be performed on bone marrow samples obtained prior to start of IMATINIB and in the event of relapse or disease progression as determined by substantially increasing MRD levels. A minimum of 20 metaphases should be examined whenever possible.

Hematological remission

For the purpose of this study, a hematological response includes any of the following:

1) complete hematological remission,
2) no evidence of leukemia in peripheral blood and bone marrow, without full peripheral blood recovery,

Each of these response categories is described in detail below. Hematological response must be confirmed after ≥ 4 weeks.

1) Complete hematological remission requires that all of the following are present:

a) Adequate bone marrow cellularity with a blast count < 5%
b) No peripheral blood blasts
c) ANC ≥ 1500/µl
d) Platelet count ≥ 100.000/µl
e) No evidence of extramedullary involvement

2) No evidence of leukemia in peripheral blood and bone marrow, without full peripheral blood recovery requires that the following are present:

a) Blast count < 5% in bone marrow
b) No peripheral blood blasts
c) Platelet count ≥ 20.000/µl platelet transfusion independent and no evidence of bleeding)
d) No evidence of extramedullary involvement

For the purpose of assessing hematological response, peripheral blood samples and bone marrow aspirates will be performed, and extramedullary leukemic involvement will be assessed by physical examination.

Resistance to treatment (only for Poor-risk group)

≥ 5% of blasts in the bone marrow aspirate after the three blocks of consolidation in patients who enter the poor-risk group because of no-CR at the end of induction

Safety assessments

Safety assessments will consist of monitoring and recording all toxicity and serious adverse events. Hematology, liver function tests (SGOT [AST], SGPT [ALT], LDH, alkaline phosphatase and bilirubin) and other biochemistries (BUN [urea], creatinine and uric acid) will be monitored weekly during the time of concomitant IMATINIB administration. Thereafter, hematology and liver function tests will be monitored according to national study protocols.

Toxicity

Information about all toxic events, whether volunteered by the patient, discovered by the responsible investigator, or detected through physical examination, laboratory test, or other means, will be collected and recorded on the Toxicity Form. An adverse event is any undesirable sign, symptom or medical condition occurring after starting treatment , in any arm.

As far as possible, each toxic event will be reported by the NCI/NIH Common Toxicity Criteria severity grades 1 – 4.

Serious adverse events (SAE)

Each Serious Adverse Event (SAE) must be reported by the clinical center to the clinician responsible (contact person) of its own national study group, within 24 hours of learning of its occurrence, even if is not felt to be treatment-related. After ensuring that the forms be accurately and fully completed, the clinician who is the group contact person must send the SAE form immediately to the local Novartis representative and to the Coordination Unit. Follow-up information about a previously reported SAE must also be reported within 24 hours with the same modalities.

Information about all serious adverse events will be collected and recorded on the SAE Form, according to Novartis standard.

A Serious Adverse Event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAE are hospitalizations occurring under the following circumstances:

- planned before entry into the clinical study
- for elective treatment of a pre-existing condition
- occur on an emergency, outpatient basis and do not result in overnight hospitalization (unless fulfilling the criteria above)
- routine treatment or monitoring of the study indication and not associated with any deterioration in condition.

For instructions about returning Serious Adverse Event Report Forms to the study secretariat refer to Novartis standards, see Appendix V.

Laboratory evaluations

Hematology

Peripheral blood will be drawn weekly during the time of concomitant IMATINIB administration. Thereafter, hematology and liver function tests will be monitored according to national study protocols. Hematology includes assessment of hemoglobin, total WBC count, ANC, platelet count, and a differential count including neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, early forms, and blast percentage.

The ANC used by the center to make dose adjustments is to be recorded on the CRF. For analysis purposes however, the ANC will be calculated automatically from WBC x the total segmented neutrophils plus bands x 10^9/L.

Biochemistry

Liver function tests - SGOT (AST), SGPT (ALT), LDH, alkaline phosphatase and bilirubin - will be performed weekly during the time on concomitant IMATINIB administration. During chemotherapy alone, biochemistries will follow the national study treatment policy.

Physical examination

A physical examination, including vital signs, will be performed during screening. The physical examination will be repeated monthly throughout the study, including assessment of vital signs. Information about the physical examination and vital signs must be present in the source documentation at the study site. Clinically significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Clinically significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event Case Report Form

Performance Status

Performance status will be measured at baseline using the Lansky Performance Status Score.

10 Statistical considerations

10.1 Randomization

The randomized part of the study was stopped based on external evidence (COG AALL0031) and on DSMC consensus. Thus this present part of the protocol must be neglected.

Each child who is alive and in CR after induction in the Good-Risk group is eligible for randomization. The request for randomization should be made, after consent from parents or guardians is obtained, when the patient is known to be Ph+ and the parameter of the early response (Prednisone response or BM at day 15, 21) is known. This will allow a timely start of phase Ib. There might be very few cases, randomized in the Good-Risk group thanks to the achievement of an early response, who are not in CR at the end of induction. In these cases there will be a shift to the Poor-Risk group treatment, whatever the assigned arm. Randomization will be performed by the data center of each group, so that treatment arms will be balanced within each group. Patients will be randomized by telephoning to the data center which will perform a check on the eligibility criteria before assignment. Therefore, at the time of randomization, at least the registration, diagnosis and induction/response data should be available at the data center in order to verify eligibility. The random assignment will be produced by an automatic procedure based on random permuted blocks.

If parents do not give consent , the center should not ask for randomization and the treatment arm should be decided case by case.

10.2 Analysis

The **primary analysis** will be the evaluation of the outcome for all Ph+ALL patients in terms of EFS by considering the time from beginning of phase Ib to the following endpoints: resistance, relapse, death in CCR, second malignancy. The evaluation of outcome will also be performed in terms of survival time from beginning of phase Ib (endpoint is death from any cause).

Secondary analyses will include:

1. Evaluation of EFS within each risk group
2. The evaluation of MRD as molecular indicator of disease burden at the end of consolidation (i.e. end of blocks, time point 5, TP5) in all patients: the proportion of patients with negative MRD levels and alive in CCR at TP5 will be the measure of response.

3. The description and analysis of the MRD pattern (slope) based on 5 measurements taken at subsequent time points from the start of phase IB to the beginning of the re-induction phase.
4. The evaluation of the role of the molecular indicator as surrogate for DFS.

An analysis censoring HSCT will also be performed.

10.3 Sample size

This study asks the question whether the continuous exposure to IMATINIB, on top of a BFM oriented protocol affects the prognosis of children with Ph+ALL. As Ph+ALL is estimated to account for 2.5% of the childhood ALL population, the participating groups will have the following expected recruitment per year:

AIEOP (Italy)	8	
BFM (Germany, Switzerland, Austria)	11	
COALL (Germany)	3	
CPH (Czech Republic)	1	
DCOG (the Netherlands)	3	
EORTC-CLCG (France, Belgium)	6	
FRALLE (France)	4	
NOPHO (Scandinavian countries)	4	
UKCCSG (United Kingdom)	9	
HONG KONG	2	
PINDA (Chile)	4	
Total:	55	Ph+ALL cases per year

With a 2 year recruitment and accounting for approximately 15% of patients who do not enter this protocol for lack of consensus, clinical considerations or logistical reasons, a total of 90 patients are expected to be enrolled and evaluable. In keeping with data from COG AALL0031 study, these patients are expected to have better EFS than patients treated with imatinib according to the original EsPhALL protocol. With 90 patients recruited, the study will have 90% power to show an advantage of 20% EFS over the historical EsPhALL figure of 60% 3-year EFS and 80% power to show a 17% advantage (α=0.05, logrank test). A 20% advantage would correspond to the 80.5% 3-year EFS figure reported by COG ALL0031 on cohort 5.

10.4 Interim analysis

The randomized part of the study was stopped based on external evidence (COG) and on DSMC consensus. Thus this present part of the protocol must be neglected.

Interim analysis evaluates, while the trial is still in progress, the randomized question on treatment effect. The aim is to avoid prolongation of the study beyond a time when clear superiority can be demonstrated for one of the randomized treatment schedules. One intermediate analysis is planned to be performed after the first two years of randomization on the primary end-point. The significance level of the interim test, adjusted for the multiplicity of looks according to O'Brien and Fleming (31), is calculated with a total type I error α=0.05 and a power of 80% (two-tailed test) and is shown below:

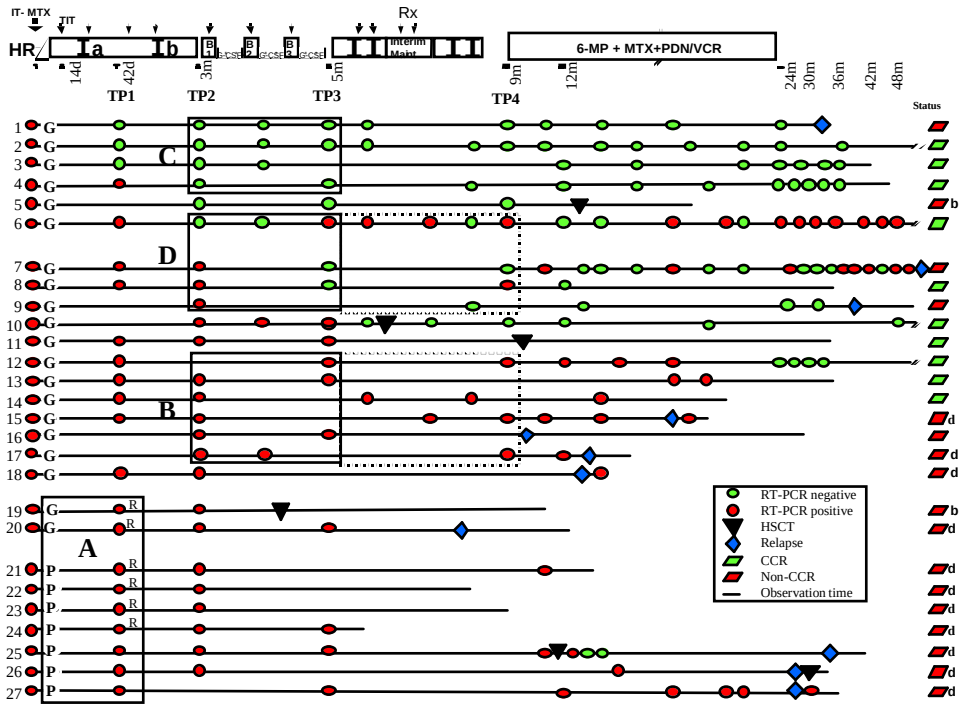
Significance levels for interim analysis

Years	First	Final
p-level	0.003051	0.05
Patients	70	140
Years from 1st randomization	2	4

10.5 Secondary analysis on response

The randomized part of the study was stopped based on external evidence (COG) and on DSMC consensus. Thus this present part of the protocol must be neglected.

Specifically, for the evaluation of response in term of MRD, past experience suggests that a reasonable estimate of the proportion of MRD negative patients, at the end of consolidation, i.e. after blocks (identified in the figure below as TP3), is about 40% as shown by the following data derived from a prospective study on MRD in Ph+ ALL patients (30).



This experience is based on a qualitative, end-stage PCR evaluation of MRD, whereas the protocol will analyze MRD by quantitative-PCR. A negative result for MRD (identified by the green dot) was referred to a "nested-PCR" approach with a sensitivity of at least 10^{-4} (30).

For sample size calculation and analysis based on the secondary end-point, i.e. the negativity of MRD at TP5, either one of the following events would be considered as treatment failure, i.e. non negativity at TP5:

- Positive MRD at TP5
- Death in CR within TP5
- Relapse within TP5.

In the available data used above, none of the 18 patients who were good responders to PDN and in CR at the end of induction Ia, either relapsed or died during consolidation.

We considered a baseline value for response of 35% in order to take into account and additional 5% possibility of occurrence of death in CR or relapse before TP5. Different hypotheses on possible differences in the proportions of MRD negative patients between the two arms were also considered. The table reports the power calculations under each scenario for the final two-sided test on the difference in MRD negative proportions (null hypothesis: no difference) assuming the first type error α=0.05.

Sample size: 140 subjects
35% baseline proportion of MRD negative patients

Proportion of MRD negative patients in experimental group	Absolute difference in proportions as compared to baseline	Power
50%	15%	37
55%	20%	60
60%	25%	80

The power calculations show that, with a 4-year recruitment, in the presence of a marked difference in the proportion of MRD negative patients between the two treatment arms, i.e. 25% absolute difference or more, the study could have sufficient power (80%).
This sample size calculation could be reviewed in the light of the accumulating quantitative data on MRD by considering the comparison of the mean levels of MRD in the two groups at TP5.

10.6 Methods of analysis

The EFS in the overall group of Ph+ patients and in the two risk groups will be calculated using the Kaplan-Meier estimator and the 3 year figure with 95% CI reported (based on Greenwood variance). For historical comparison with the original EsPhALL protocol, a Cox model will be fitted to the data, adjusting for sex, age at diagnosis, WBC count at diagnosis and treatment (HSCT would be censored or, in alternative, included as a time-dependent variable), after check of the model adequacy, in order to compare the two study cohorts.
As for the secondary objectives of the study on response, the proportions of MRD negative patients in CCR at TP5 will be evaluated and compared between poor and good risk patients.
Also, the different longitudinal profiles in MRD response up to TP5 will be evaluated, if possible, in order to study their impact on prognosis, i.e. on the clinical end point (EFS).
The same methods of analysis will be adopted for the set of Poor Risk patients (observational study).

10.7 Early stopping guidelines for treatment related mortality

These guidelines are necessary given the new strategy of the protocol, which introduces IMATINIB into the standard BFM-like chemotherapy for the treatment of childhood leukemia. They are designed to ensure that the treatment would be stopped as early as possible if its application is associated with a treatment related mortality higher than acceptable in standard treatments.

The table below shows the minimum number of treatment related deaths (excluding deaths after HSCT) at which experimenters and DMC should carefully evaluate the possibility of stopping the application of the treatment.

Guidelines for early stopping due to treatment related mortality

No. of events	No. of subjects in study arm
2	11-15
3	16-25
4	26-35
5	36-45
6	46-56
7	57-67
8	68-78

The method applied for developing these guidelines follows a Bayesian approach (32), extending that of Metha and Caine (33). In these guidelines, the maximum acceptable level of p1=7% probability of treatment related deaths was considered. The number of failures is assumed to be taken from a Binomial distribution. The prior distribution for the probability of the endpoint of interest was taken as a Beta (1,1), corresponding to an uninformative Uniform distribution. The stopping bounds reported in the table are the experimental results that give a posterior probability of 90% or more, of observing p1≥7%.

11.0 Organizational aspects and data management

Each participating group will refer to the contact person of the group and to its own usual network of clinical centers, data center and experts (statistician, laboratories, etc) for:

- The implementation of this protocol
- The monitoring of the group's data and of the quality of the data

Pag.2-4 report names and addresses of contact persons of each participating group. The international study coordinators, and the trial data center will act as a co-ordination unit for the exchange of information among groups and for the evaluation of their data.

11.1 Data Collection

The trial data center designed a specific web-based system for data collection which is used by each participating centre.
The participants have agreed upon:

- registration of each new child or adolescent newly diagnosed with Ph+ ALL;
- collection by web of a selected set of data on each patient who enters the protocol;

The set of data to be collected and evaluated by the participants are listed in Appendix IV. Each group will:

- use the same form for data collection that include the data items listed in Appendix IV;
- centralize the forms for input and quality checks in its own data center, according to the approach routinely used in the group;
- input of the data in the same WEB database provided by the trial operation centre;
- provide yearly the data file to the coordination unit.

The major requirements that each group will have to ask to the clinical center are:

1. to register at the group data center each new patient diagnosed with Ph+ ALL, regardless of whether he/she will subsequently enter the present protocol. This is necessary in order to know which percentage of eligible patients is treated according to the protocol. Registration should be done as soon as the presence of t(9;22)(q34;q11) in newly diagnosed childhood ALL has been be documented;
2. to report immediately (within 24 hours recognition) by fax specific events (death,relevant toxicity) to the responsible clinician of each group, to the local Novartis and to the coordination unit, with the appropriate WEB forms. This is strictly necessary for the international standards in phase II studies on IMATINIB;
3. to send to the group data center on a regular basis the forms with information on diagnosis, response, randomization, treatment, and toxicity as soon as they can be completed.
4. to up-date follow-up at the end of each calendar year.

For eligible patients registered but not included in the present protocol, follow-up data only will be routinely requested.

11.2 Data evaluation and analysis (34)

The trial data center, in collaboration with the study chairman and the contact persons and the statisticians of each group, will be responsible to pool and evaluate the data reported in the WEB system according to the protocol aims.

The data evaluation will be done with the following steps:

- Follow up will be updated at December of each year
- The data will be used for the trial aims only;
- A report will be produced each year on the study progress (recruitment, toxicity and so on) and the interim analysis performed when planned;
- Reports will be circulated via WEB by the coordination unit to the contact persons of the groups and to the Data Monitoring Committee (DMC);
- Members of the DMC are experienced researchers (one clinician and one statistician) not involved in the trial who will be responsible of providing the investigators with guidance on the trial conduction and, in case of problems, on whether the trial should be stopped, modified or continued.

The trial database will be used for the trial aims only, under the responsability of the participating groups. Novartis will be informed of the SAE and eventually of trial results.

11.3 Ethics and Good Clinical Practice

The last revision of the Helsinki Declaration as well as the previsions of the Oviedo Declaration, provide the general framework for the ethical conduct of the study.

The study protocol is designed to ensure adherence to Good Clinical Practice (GCP) principles and procedures.

11.4 Informed consent

Informed consent forms have to be written by each group itself, adapted to the local situation.

12. Definitions

Absolute Neutrophil Count (ANC)

The ANC is defined as the WBC/µL times the neutrophil percentage

Absolute Blast Count

The absolute blast count is defined as the WBC/µL times the blast percentage

Central Nervous System (CNS) Disease at Diagnosis

CNS leukemia is defined as an elevated CSF WBC (≥ 5 cells/µL) and a cytocentrifuge preparation demonstrating lymphoblast cells. CNS leukemia may also be diagnosed when the CSF WBC is normal, but clinical signs of CNS leukemia such as facial nerve palsy or hypothalamic syndrome are present. Patients who have less then 5 cell/µL and a positive cytospin will not be considered to be CNS positive.

Overt Testicular Leukemia at Diagnosis

Unilateral or bilateral testiculomegaly with leukemic infiltration confirmed by biopsy. Equivocal findings on testicular exam warrant biopsy

Bone Marrow Status

M1: < 5% blasts of all nucleated cells including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.

M2 : 5-25% blast all nucleated cells including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.

M3: > 25% blasts in a bone marrow aspirate.

Resistance to "Induction"

≥ 5% of blasts in the bone marrow aspirate.

Resistance to protocol IB

≥ 5% of blasts in the bone marrow aspirate at the end of protocol IB (day 78) in patients resistant to "Induction".

Resistance to treatment

≥ 5% of blasts in the bone marrow aspirate after the first three blocks of consolidation in patients not resistant to protocol IB.

Late response

<5% of blasts in the bone marrow after the phase IB or after the three blocks of consolidation.

Complete remission

< 5% blasts in the bone marrow aspirate regardless of the proportion of mature lymphocytes at the end of the"Induction".

Continuos complete remission

Persistence of CR status.

Bone marrow relapse

≥25% blasts in the bone marrow aspirate after that of 1st CR has been achieved.

13. References

Therapy and Diagnosis of ALL

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BCR-ABL and the ABL-Kinase Inhibitor IMATINIB

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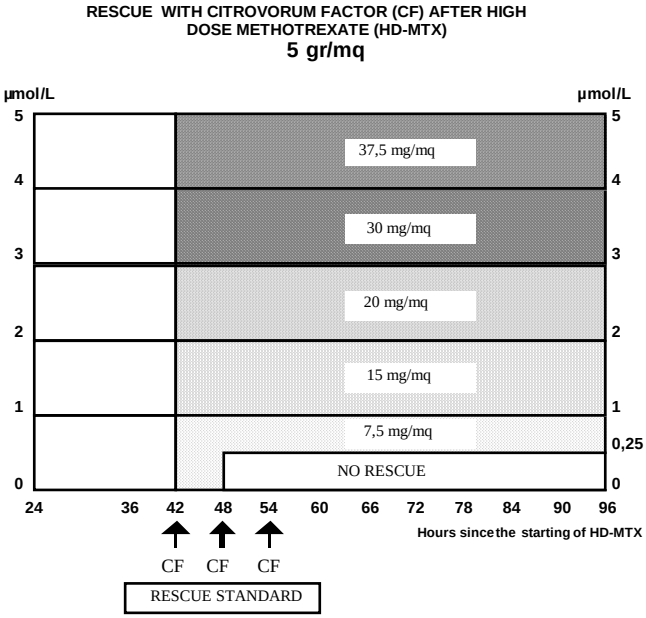
Appendix I

Table for monitoring of MTX serum levels and intensification of LCV rescue



Appendix II

Notable laboratory value criteria, special methods and scales

Special scale

Lansky Performance Status Scale For Children

Score	Performance
100	fully active, normal
90	minor restrictions in physically strenuous activity
80	active, but tires more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play, keeps busy with quieter activities
50	gets dressed, but lies around much of the day, no active play, able to participate in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	in bed; needs assistance even for quiet play
20	often sleeping, play entirely limited to very passive activities
10	no play; does not get out of bed
0	unresponsive

Appendix III: Drugs known to be metabolized by CYP450 isoenzymes

CYP450 isoenzyme	Substrates	Inhibitors	Inducers	Markers
CYP2D6	Several antidepressants Neuroleptics Beta-blockers Antiarrhythmics Codeine Dextromethorphan Ethylmorphine Nicotine	Ajmaline Chinoidine Fluoxetine Paroxetine Quinidine Ritonavir	None known	Debrisoquine Dextromethorphan
CYP3A4	Acetaminophen Carbamazepine Cyclosporin Digitoxin Diazepam Erythromycin Felodipine Fluoxetine Nifedipine Quinidine Saquinavir Steroids (e.g. cortisol) Terfenadine Triazolam Verapamil Warfarin	Clotrimazole Ketoconazole Ritonavir Troleandomycin	Dexamethasone Phenytoin Rifampin Troleandomycin	Dapsone Erythromycin Ketoconazole Lidocaine

Appendix IV Variables in the database

Study conduct is now organized via web, but with the same requirements listed below.

In this WEB database all patients diagnosed with Ph+ ALL will be evaluated, regardless of whether they entered the present protocol or not. For patients who do not enter the protocol (registered only), possibly provide data on follow-up. For patients who enter the protocol, please provide all data. Each group will provide the data according to the variables listed below and the operation unit will produce, based on them, the database. The type of file would be, in order of preference: SAS, Excel and ASCII. Dates are in the DDMMYYYY format.

Diagnosis-treatment-follow-up file

Registration

	Var Name	Code	Format
Identification number	UPN	use your own UPN	C 7
Initials (family, first name)	INIT		C 3
Group	GROUP	1=AIEOP 2=BFM-Austria 3=BFM-Germany/Switzerland 4=ALL-REZ 5=COALL 6=DCLSG 7=EORTC 8=FRALLE 9=NOPHO 10=MRC 11= CPH 12=PINDA 13=HONG KONG	I 2
Date of birth	DOB_		D 8
Sex	SEX	1=Male 2=Female	I 1
Date of diagnosis	DOD_		D 8
Enters the protocol	ENTER	1=No 2=Yes	I 1
Reason for ENTER=No	COENTER	-1=Not applicable Give your own code	I 2

Diagnosis

	Var Name	Code	Format
% blasts (peripheral blood)	BLA	-2=Not evaluable -1=No data	I 3
WBC at diagnosis (/mmc)	WBC	-1=No data	I 7
Platelets (/mmc)	PLT	-1=No data	I 7
Hb (g/dl)	HB	-1=No data	R 4.1
FAB Morphology	FAB	1=L1 2=L2 3=L1/2 4=L3 5=Not classified 9=No data	I 1
Peroxidase	POX	1=Negative 2=Positive 3=Not done 9=No data	I 1
Immunophenotype	IMMPHEN	1=Pro-T 2=Pre-T 3=Intermediate (cortical) T 4=Mature T 5=T-lineage not classified 6= Pro-B 7= Common 8=Pre-B 9=Mature B 10=B-lineage not classified 11=AUL 99=No data	I 2

	Var Name	Code	Format
Chromosomal abnormalities			
Data on t(9;22)(q34;q11)			
Karyotyping	K_CA		C 20
CNS involvement			
CNS involvement	CNS_INV	1=No 2=Yes 9=No data	I 1
Cells in CSF (/µl)	CSF_CELL	**-2=Not evaluable** **-1=No data**	I 3
Blast in CSF (%)	BLA_CSF	**-2=Not evaluable** **-1=No data**	I 3
CSF contaminated with blood	CSF_INV	1=No 2=Yes 3=No puncture 9=No data	I 1
Organ involvement			
Hepatomegaly	HEP_INV	1=No 2=Yes 3=Questionable 4=Not done 9=Not known	I 1
Cm below costal margin of liver	MEA_LIV		I **2.1**
Splenomegaly	SPL_INV	1=No 2=Yes 3=Questionable 4=Not done 9=Not known	I 1
Cm below costal margin of spleen	MEA_SPL		I **2.1**
...			
Other organ involvement	OTH_INV	Please specify	C 20

Response to Prednisone/induction IA

	Var Name	Code	Format
Cumulative dose of Prednisone (mg)	PDN_DOSE	-1=Not known	R 4.1
Blast cell count/µl at day 8	COBLA_8	-2=Not evaluable -1=No data	I 5
WBC/µl at day 8	WBC_B	-1=No data	I 7
BM day 15, % blasts	BLA_15	-2=Not evaluable -1=No data	I 3
BM day 21, % blasts	BLA_21	-2=Not evaluable -1=No data	I 3
BM day 33, % blasts	BLA_33	-2=Not evaluable -1=No data	I 3
Date of first complete remission	DOCR1_		D 8
Risk group	RG	1=Poor 2=Good	I 1

Treatment

	Code	Forma
Induction IA		
Date of start Induction	DOSI_	D 8
Date of end Induction (date of last administration)	DOENDI_	D 8
Induction IB		
...		

Transplantation

	Var Name	Code	Format
Considered eligible for transplantation	ELHSCT	1=No 2=Yes 9=Not known	I 1
Search for unrelated donor	DONOR	1=No 2=Yes 9=Not known	I 1
No. of siblings	SIBL	**-1=No data**	I **2**
Hystocompatibility of siblings	HYSTO	1=No 2=Yes 9=Not known	I 1
Date of HLA typing	DOHLA_		D 8
Date of transplantation	DOHSCT_		D 8
Phase of transplantation	PHSCT	1=In 1st CR 2=Resistant disease	I 1
Type of transplantation	THSCT	1=Autologous 2=Allogeneic (gen. HLA-id, related) 3=Allogeneic (fen. HLA-id, related) 4=Allogeneic (not HLA-id, related) 5=Allogeneic (not specified) 6=Allogeneic (HLA-id, unrelated) 7=Allogeneic (not HLA-id, unrelated) 8=Syngeneic (identical twins) 9=No data	I 1
Source of transplantation	SHSCT	1=BM 2=PBSC 3=Cord blood Give your own code for other types	I 1

Follow-up

	Var Name	Code	Format
Date of first relapse	DOREL_		D 8
Site of first relapse	TOREL	1=BM 2=CNS 3=Testis 4=BM+CNS 5=BM+Testis Give your own code for other sites	I 2
Date of death	DODEAD_		D 8
Cause of death	CODEAD	1=Progressive ALL 2=HSCT related 3=2nd tumor 4=Sepsis 5=Pneumonia 6=Other infection 7=Haemorrhage 8=MOF 9=Other (specify in the note space) 99=Not known	I 2
Phase of death	PH_DEAD	1=Before start therapy 2=In induction, before CR 3=In first CR 4=After relapse 5=After 2nd neoplasm	I 1
Date of last follow-up	DOLFU_	*Equals date of death, if patient died*	D 8
Date of 2° malignant neoplasm	DOSMN_		D 8
Type of 2° malignant neoplasm	T_SMN	Give your own codes	I 2
Note space	NOTE		C 40

Appendix V Serious Adverse Event Report

NOVARTIS

STI571 - GLIVEC® CSTI571AIT07	ID ____ ____ (Center No. / Subject No.) Subject's initials ____ ____ (1. 2. fam.) Randomization number ____	

SERIOUS ADVERSE EVENT REPORT

Page 1 of 3

1. REPORT TYPE: ☐ Initial ☐ Follow-up	2. Country:	3. CASE ID:

I. ADVERSE EVENT INFORMATION

4. DATE OF BIRTH: day month year	5. AGE yrs./mo.	6. RACE ☐ Caucasian ☐ Oriental ☐ Black ☐ Other	7. SEX ☐ Male ☐ Female	8. HEIGHT cm	9. WEIGHT kg	10. ONSET OF FIRST SIGN/SYMPTOM OF SAE day month year

11. SERIOUS ADVERSE EVENT(S) IN MEDICAL TERMS (diagnosis if possible)

Case description of the above SAE (include related sign/symptoms, treatment, course/outcome and suspected cause of the SAE) (continue on p.3 if more space is required):

Is the event due to lack of efficacy? ☐ No ☐ Yes
Is the event due to progression of underlying illness? ☐ No ☐ Yes

EXPEDITED REPORTING CRITERIA
12. CHECK ALL APPROPRIATE TO EVENT

☐ Patient died day month year
☐ Involved or prolonged inpatient hospitalization
☐ Involved persistence of significant disability or incapacity
☐ Life-threatening

Other Seriousness Criteria:
☐ Congenital anomaly/birth defect
☐ Other significant medical events

II. TRIAL DRUG INFORMATION

13. TRIAL DRUG(S) AT OR BEFORE ONSET OF SAE (If blinded, provide drug package no.) TRIAL DRUG PACKAGE NO.: Comments (Continue on P.3 if more space is required): Drug code broken ☐ No ☐ Yes	14. LAST VISIT/WEEK BEFORE ONSET OF SAE VISIT NO.: WEEK NO.:

15. DOSES AT OR BEFORE ONSET OF SAE (total daily dose or specify if other- ADD additional pages)	16. ROUTE OF ADMINISTRATION	17. THERAPY DATES FROM: day month year TO: day month year

18. TRIAL INDICATION	19. THERAPY DURATION UNTIL ONSET OF FIRST SIGNS/SYMPTOM OF SAE hrs/days/months	20. TIME ELAPSED BETWEEN LAST DRUG ADMINISTRATION AND ONSET OF FIRST SIGNS/SYMPTOM OF SAE mins/hrs/days/months

III. HISTORY

21. PATIENT'S PAST MEDICAL HISTORY (e.g. co-existing medical conditions such as disease, allergies, similar experiences)

IV. MANUFACTURER INFORMATION (FOR INTERNAL USE ONLY)

22. DATE MANUFACTURER NOTIFIED OF SAE day month year	23. DATE OF THIS REPORT day month year

24. NAME AND ADDRESS OF REPORTING MANUFACTURER
Novartis Farma S.p.A.
Largo Boccioni 1
21040 - Origgio (VA)

PLEASE FAX FORM TO LOCAL CS&E FAX NO. 02-96703051

sae pg1

NOVARTIS

STI571 - GLIVEC® CSTI571AIT07	ID ____ ____ (Center No. / Subject No.) Subject's initials ____ ____ (1. 2. fam.) Randomization number ____	

SERIOUS ADVERSE EVENT REPORT

1. REPORT TYPE: ☐ Initial ☐ Follow-up | 3. CASE ID:

25. CONCOMITANT DRUGS RELEVANT TO THE SAE (exclude therapy to treat SAE)

DRUG NAME(S)	DOSE / ROUTE	UNIT / SCHEDULE	DATE STARTED day month year	CONT. 0=No 1=Yes	DATE DISCONTINUED day month year	REASON FOR USE

26. COMMENTS (if adverse event is considered to be caused by a comedication, please note it here)

27. ACTION TAKEN (mark all as appropriate)

☐ No Action Taken
☐ Trial drug permanently discontinued due to this adverse event
☐ Concomitant medication taken
☐ Trial drug dosage adjusted/ temporarily interrupted*
☐ Non-drug therapy given**
☐ Hospitalization/prolonged hospitalization

* If ticked, enter new dosage information in field 11
** If ticked, provide therapeutic measures in field 11

28. TEST/LABORATORY FINDINGS (enter only those findings necessary for SAE diagnosis or course description)

TEST/ LAB NAME	UNIT	DATE day month year	VALUE	DATE day month year	VALUE	DATE day month year	VALUE

29. COMMENTS ON TEST/LABORATORY FINDINGS (Provide normal ranges on Pg. 3 if not already provided.)
(If the SAE is a laboratory abnormality, enter comments on clinical findings and/or treatment in field 11.)

30. OUTCOME OF THE PATIENT/SAE

☐ Completely recovered Date of recovery: ____ ____ ____ (day month year)
☐ Recovered with sequelae
☐ Condition improving
☐ Condition still present and unchanged
☐ Condition deteriorated
☐ Death Autopsy: ☐ No ☐ Yes

31. ASSESSMENT OF CAUSALITY
Relationship to study drug: ☐ Not suspected ☐ Suspected

V. **INFORMATION SOURCE**

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature	33. REPORTING DATE BY INVESTIGATOR/ PERSON REPORTING EVENT day month year ____ ____ ____

PLEASE FAX FORM TO LOCAL CS&E FAX NO. 02-96703051

sae pg2

NOVARTIS

STI571 - GLIVEC® CSTI571AIT07	ID Center No. Subject No. Subject's initials 1. 2. fam. Randomization number	

SERIOUS ADVERSE EVENT REPORT

1. REPORT TYPE: ☐ Initial ☐ Follow-up	3. CASE ID:

FOR ADDITIONAL INFORMATION:

V. INFORMATION SOURCE

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature	33. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

PLEASE FAX FORM TO LOCAL CS&E FAX NO. 02-96703051

sae pg3