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Clinical Protocol CA180372

A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Revised Protocol Number: 05
Incorporates Amendment 04

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	28-Oct-2013	Incorporates Amendment 04
Amendment 04	28-Oct-2013	The key purposes of this amendment are to incorporate the following changes: 1) Add mandatory supportive care measures during the 3 High Risk Blocks 2) Provide updates to the WOCBP language to harmonize this language with the current BMS directives for WOCBP.
Revised Protocol 04	31-Jul-2013	Incorporates Amendment 03
Amendment 03	31-Jul-2013	The key purposes of this amendment are to incorporate the following key changes: 1) Increase the number of treated subjects from 75 to at least 75 and up to 90. 2) Modify language regarding pregnancy prevention. 3) Incorporate recommendations for subject management and supportive care during High Risk (HR) Blocks 1-3. 4) Provides for clarifications, fixes inconsistencies across sections of the protocol and corrects various typographical errors.
Revised Protocol 03	07-Dec-2012	Incorporates Amendment 02
Amendment 02	07-Dec-2012	The key purposes of this amendment are to incorporate the following key changes: 1) Introduce a new pediatric formulation of dasatinib. 2) Address lack of availability of native-asparaginase in the United States and allow use of Peg-Asparaginase upfront in such instances as well as provide more detailed instruction for dose modifications of the various asparaginase formulations. 3) Indicate that the BCR-ABL mutation status will be reported for baseline and at time of progression as a secondary objective instead of as an exploratory objective. 4) Allow Philadelphia chromosome positivity from peripheral blood to be acceptable for study entry. 5) Expand the window for screening activities to 21 days. 6) Modify the definition of high risk group and low/standard risk group in response to Induction 1A treatment. 7) Provides for clarifications, fixes inconsistencies across sections of the protocol and corrects various typographical errors.
Revised Protocol 02	20-Sep-2011	Incorporates Amendment 01

Document	Date of Issue	Summary of Change
Amendment 01	20-Sep-2011	The following amendment was developed to incorporate two key changes including: 1) Changing the statistical design of the trial to allow comparison to historical external controls. Specifically, the 3-year event free survival (EFS) of dasatinib plus chemotherapy will be compared to the 3-year EFS of chemotherapy alone from the Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP BFM 2000) trial and the 3-year EFS of imatinib plus chemotherapy from the European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL). This analysis will improve the ability to interpret the safety and efficacy of dasatinib added to chemotherapy among other treatment options for this pediatric leukemia. 2) Incorporating additional supportive care options for chemotherapy to accommodate the standard of care at sites in the United Kingdom (UK). Additionally, typographical errors were also corrected.
Revised Protocol 01	22-Jun-2011	Incorporates Administrative Letter 01
Administrative Letter 01	22-Jun-2011	Corrects typographical errors. These corrections make the text consistent with other protocol sections in which this text appears.
Original Protocol	01-Jun-2011	Not applicable.

SYNOPSIS

Clinical Protocol CA180372

Title of Study: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Dasatinib 60 mg/m^2 orally, once daily, for 2 years

Study Phase: 2

Research Hypothesis: Dasatinib added to chemotherapy will demonstrate a superior 3-year event free survival (EFS) rate compared to chemotherapy alone in the external historical control trial Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP-BFM 2000) and non-inferior 3-year EFS compared to continuous imatinib added to chemotherapy in the external historical control trial of the amended European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL).

Primary Objective: Compare the 3-year event-free survival (EFS) with the external historical controls of the AIEOP-BFM 2000 and EsPhALL trials.

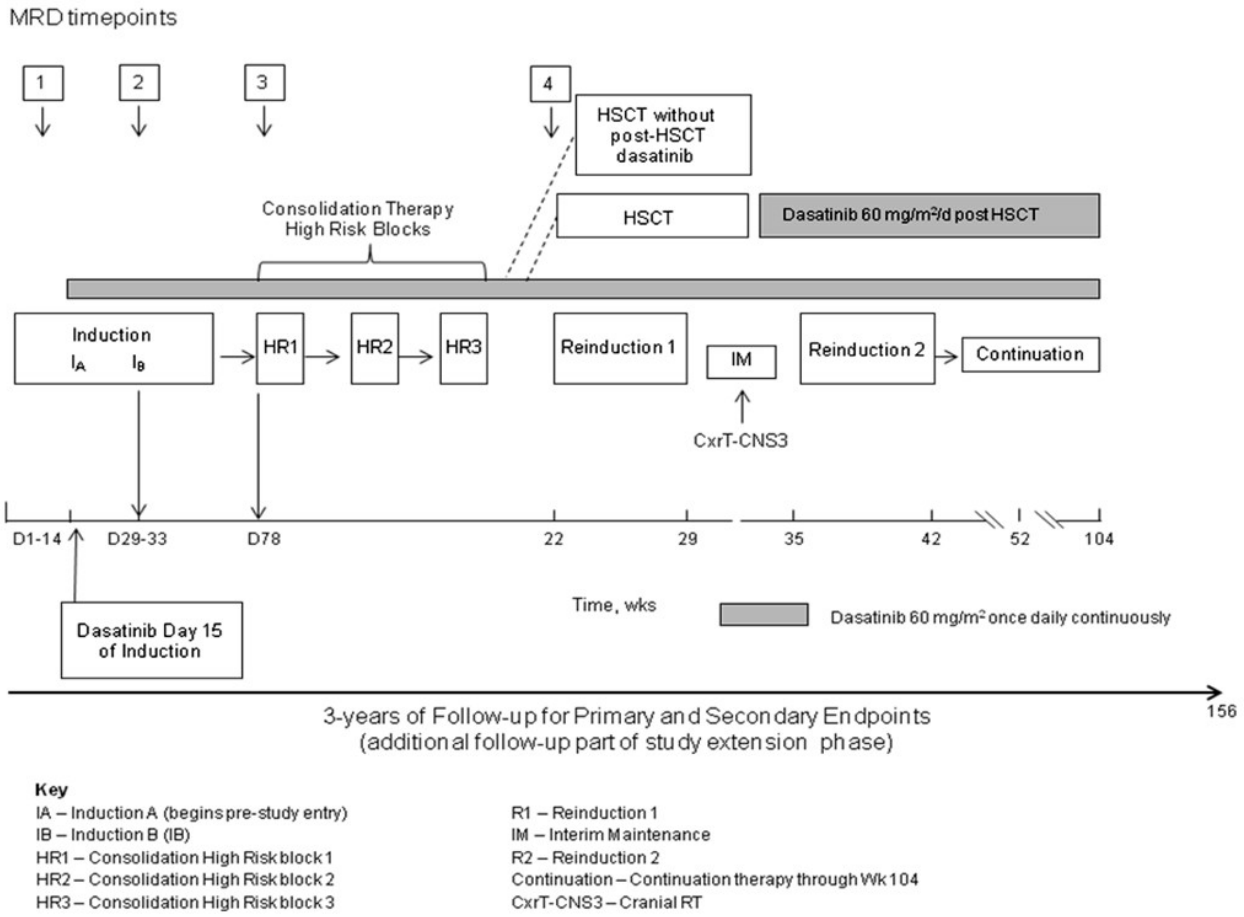
Study Design: Children and adolescents with newly diagnosed Ph+ ALL will be eligible for this open-label, single-arm study and will receive dasatinib added to successive blocks of standard multiagent chemotherapy (AIEOP-BFM ALL 2000 regimen) for a maximum duration of 2 years.

Design: After diagnosis of acute lymphoblastic leukemia (ALL), subjects will begin standard induction chemotherapy (Block IA). Since the diagnosis of ALL typically requires urgent treatment and it takes up to 10-14 days to determine which patients have Philadelphia chromosome positive (Ph+) ALL, frontline induction chemotherapy (Block IA) will start prior to enrollment in this trial (approximately 2 weeks) and will be based upon the investigator's institutional standard of care. Enrollment on this study will occur prior to day 15 of Induction Block IA. At day 15, dasatinib treatment shall begin and continue without planned interruption until the completion of therapy (102 weeks). The components of treatment are divided into blocks as follows: Induction IA (4-5 weeks), induction IB (28 days, 4 weeks), recovery period (2 - 4 weeks), consolidation blocks 1, 2, and 3 (21 days, 3 weeks each), reinduction block 1, including phase IIa and IIb (63 days, 9 weeks), interim maintenance (29 days, 4 weeks, overlaps 2 weeks with end of reinduction block 1), reinduction block 2 (63 days, 9 weeks), and continuation therapy (62 weeks). Chemotherapeutic agents utilized in this regimen include: cyclophosphamide, cytarabine, 6-mercaptopurine, methotrexate, leucovorin, dexamethasone, vincristine, asparaginase, hydrocortisone, daunorubicin, ifosfamide, etoposide, doxorubicin, and thioguanine.

Subjects who meet pre-defined criteria may receive a hematopoietic stem cell transplant (HSCT). The use of dasatinib after transplantation is optional in all HSCT recipients, at the discretion of the treating physician. Subjects may receive 12 additional months of post-HSCT dasatinib. Subjects with CNS3 disease at diagnosis will receive cranial irradiation during the Interim Maintenance period.

The total duration of the trial to determine the primary and secondary endpoints will be approximately 6 years.

Figure 1: **Schematic Study Design**



Key

IA – Induction A (begins pre-study entry)
IB – Induction B (IB)
HR1 – Consolidation High Risk block 1
HR2 – Consolidation High Risk block 2
HR3 – Consolidation High Risk block 3
R1 – Reinduction 1
IM – Interim Maintenance
R2 – Reinduction 2
Continuation – Continuation therapy through Wk 104
CxrT-CNS3 – Cranial RT

Study Population:

Select Inclusion Criteria (See Section 3.3.1 for full criteria):

- Philadelphia chromosome-positive ALL
- Induction chemotherapy approximately ≤ 14 days according to institutional standard of care
- Performance status (Karnofsky or Lansky) ≥ 60%
- Adequate liver, renal, and cardiac function
- Age > 1 year and < 18 years at initial diagnosis of ALL

Select Exclusion Criteria (See Section 3.3.2 for full criteria):

- Prior treatment with a BCR-ABL inhibitor (eg, imatinib)
- Biopsy proven Ph+ ALL extramedullary involvement of the testicles
- Clinically significant cardiovascular disease or disorder of platelet function (eg, von Willebrand's disease)
- Active systemic infection
- Patients who are pregnant or breastfeeding or likely to become pregnant.
- Men whose partner is unwilling or unable to avoid pregnancy.

Study Assessments and Primary Endpoint: Event Free Survival (EFS) is defined as the time from first dasatinib treatment until one of the following events: lack of complete response (induction and consolidation failure), relapse at any site, development of second malignant neoplasm, or death.

External Data Safety Monitoring Board: An independent Data Safety and Monitoring Board will provide oversight of trial to ensure protection of the research participants.

Statistical Methods: The sample size comprises at least 75 treated subjects. A minimum of 20 treated subjects will be distributed in each of the age ranges of 1 - 11 years and 12 < 18 years, respectively.

The primary analysis will compare the 3-year EFS of dasatinib plus chemotherapy with external historical controls in hierarchical order. The trial will be considered positive if at least the first two comparisons are statistically significant. The comparisons will be as follows:

1) Superiority over chemotherapy alone of AIEOP-BFM 2000
2) Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial
3) Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial

For the analysis of the primary endpoints, a hierarchical testing procedure will be used so that the overall experiment-wise one-sided type I error rate is preserved at 0.05.

The differences in 3-year EFS rates will be computed using binomial proportions. The differences in event rates along with exact 2-sided 90% Clopper-Pearson CI's will be provided. Test for difference in event rates will be carried out using a two-sided χ^2 test. Non-inferiority testing against the study treatment in the amended EsPhALL trial will be carried out using the corresponding 2-sided 90% CI for the treatment difference and comparing the lower confidence limit to the non-inferiority margin of -5%. This margin corresponds to 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only control of the original EsPhALL trial. All of the above tests will be performed at the 0.05 (one-sided) significance level.

Secondary endpoints include safety and feasibility of dasatinib added to chemotherapy, an estimate of the EFS of dasatinib added to chemotherapy (including 3 and 5-year rates), complete remission rates at end of induction compared with AIEOP BFM 2000 and the Amended EsPhALL trials, minimal residual disease levels by PCR for immunoglobulin and T-cell receptor gene rearrangement and BCR-ABL mutation status at baseline and time of progression or relapse. Adverse events and laboratory results will be graded utilizing the National Cancer Institute-Common Terminology Criteria (NCI-CTCAE) Version 4.

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[redacted]

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1.2 Research Hypothesis

Dasatinib added to chemotherapy will demonstrate a superior 3-year event free survival (EFS) rate compared to chemotherapy alone in the external historical control trial Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP-BFM 2000) and non-inferior 3-year EFS compared to continuous imatinib added to chemotherapy in the external

historical control trial of the amended European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL).

1.3 Objectives

1.3.1 Primary Objective

The primary analysis will compare the 3-year EFS of dasatinib plus chemotherapy with external historical controls in hierarchical order. The trial will be considered positive if at least the first two comparisons are statistically significant. The comparisons will be as follows:

1) Superiority over chemotherapy alone of AIEOP-BFM 2000
2) Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial
3) Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial

1.3.2 Secondary Objectives

The key secondary objectives are to determine:

1. The safety and feasibility of dasatinib added to standard chemotherapy
2. Estimate the EFS of dasatinib plus chemotherapy (including 3 and 5-year rates)
3. Complete remission rates (< 5% blasts in bone marrow and no peripheral blasts) at end of induction compared with AIEOP BFM 2000 and the Amended EsPhALL trials

Other secondary objectives are to estimate:

1. The difference in 3-year EFS rate with the 3-year EFS rate of available historical controls such as the COG AALL0031 study
2. MRD levels (defined by PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements)
3. BCR-ABL mutation status at baseline and time of disease progression or relapse

1.3.3 Exploratory Objectives

[redacted]

1.4 Product Development Background

Detailed background information on preclinical pharmacology, preclinical pharmacokinetics, preclinical toxicology, and clinical studies of dasatinib may be found in the dasatinib Investigator Brochure 10[26].

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The

investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent/Assent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent and assent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent and assent forms will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent and assent forms and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent and assent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent and assent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent and assent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Children and adolescents with newly diagnosed Ph+ ALL will be eligible for this open-label, single-arm study and will receive dasatinib added to successive blocks of standard multiagent chemotherapy (AIEOP-BFM ALL 2000 regimen)[15] for a maximum duration of 2 years. The study sample size is at least 75 treated patients.

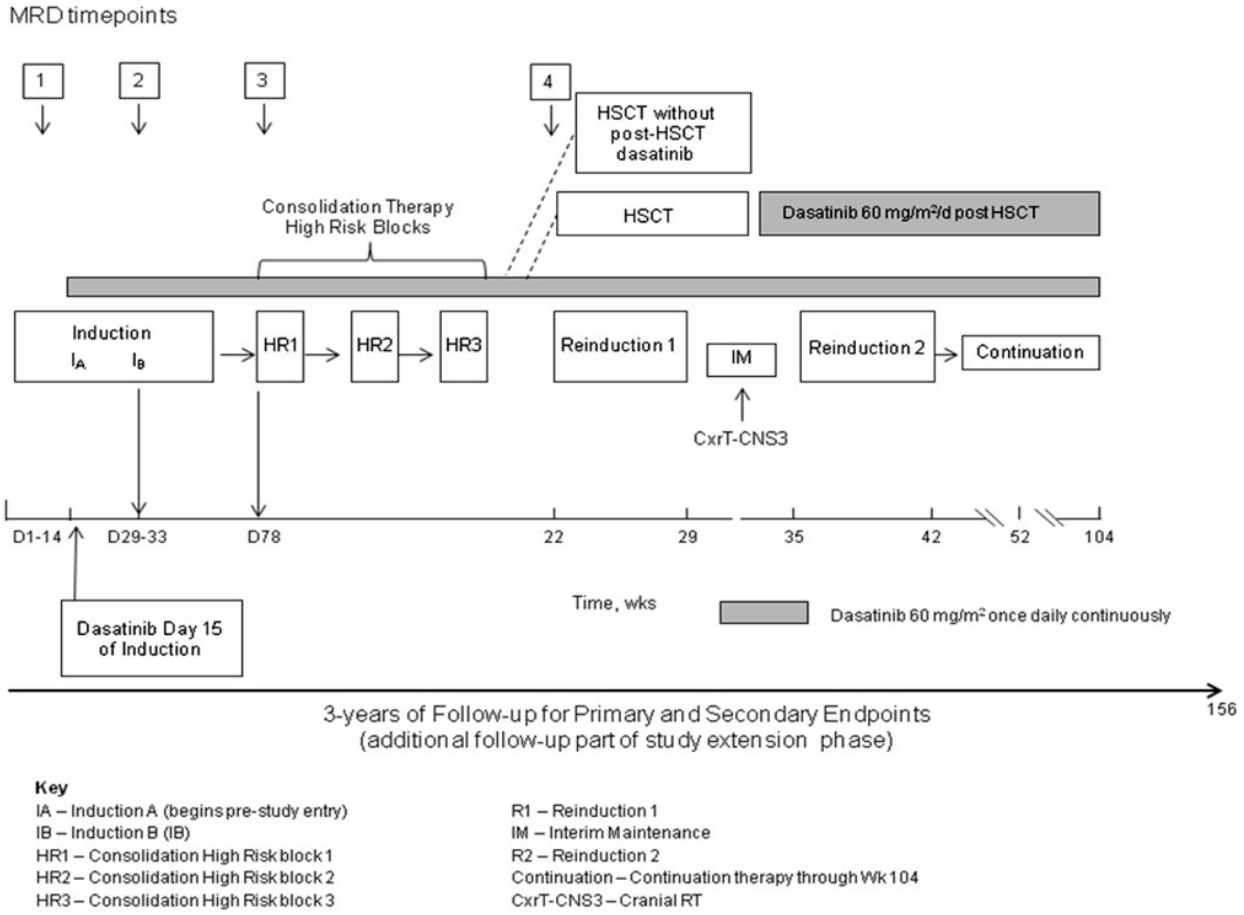
Design

After diagnosis of acute lymphoblastic leukemia (ALL) via cytogenetics, FISH or PCR (via local laboratory), subjects will begin standard induction chemotherapy (Block IA). Since the diagnosis of ALL typically requires urgent treatment and it takes up to 10-14 days to determine which patients have Philadelphia chromosome positive (Ph+) ALL, frontline induction chemotherapy (Block IA) will start prior to enrollment in this trial (approximately 2 weeks) and will be based upon the investigator's institutional standard of care. Enrollment on this study will occur prior to day 15 of Induction Block IA. At day 15, dasatinib treatment shall begin and continue without planned interruption until the completion of therapy (102 weeks).

Subjects who meet pre-defined criteria at specific time points in treatment may receive a hematopoietic stem cell transplant (HSCT). Subjects will have the option to receive 12 additional months of post-HSCT dasatinib (not mandatory). Subjects with CNS3 disease at diagnosis will receive cranial irradiation during the Interim Maintenance period.

A schematic of the study design is shown in Figure 3.1.

Figure 3.1: Schematic Study Design



Key

IA – Induction A (begins pre-study entry)
IB – Induction B (IB)
HR1 – Consolidation High Risk block 1
HR2 – Consolidation High Risk block 2
HR3 – Consolidation High Risk block 3
R1 – Reinduction 1
IM – Interim Maintenance
R2 – Reinduction 2
Continuation – Continuation therapy through Wk 104
CxrT-CNS3 – Cranial RT

The components of treatment are divided into blocks as follows:

- Induction IA (4 - 5 weeks)
- Induction IB (28 days, 4 weeks)
- Recovery period (Dasatinib continues, No chemotherapy given) (2 - 4 weeks)
- Consolidation blocks 1, 2, and 3 (21 days, 3 weeks each)
- Reinduction block 1, including phase IIa and IIb (63 days, 9 weeks)
- Interim maintenance (29 days, 4 weeks)
- Reinduction block 2 (63 days, 9 weeks)
- Continuation therapy (62 weeks)

Subjects who meet pre-defined MRD criteria prior to the start of the first consolidation block (HR1) or after the completion of the third consolidation block (HR3) of chemotherapy and have a genotype-matched donor (9/10 or 10/10) will receive a hematopoietic stem cell transplant (HSCT) instead of continuing the AIEOP-BFM ALL 2000 regimen. The timing of HSCT would

be following the consolidation block 3 (HR3). Subjects should continue on protocol specified chemotherapy until HSCT. If alternative chemotherapy is preferred, the subject must be discontinued from the study treatment but must continue to be followed per protocol for the long term growth assessments. If a subject goes off-treatment to receive a different chemotherapy, dasatinib will no longer be provided via this study. Subjects who do not meet the HSCT criteria are not recommended to receive HSCT. During the HSCT, subjects will not receive dasatinib. Following adequate engraftment of the HSCT, the use of dasatinib is optional at the discretion of the treating investigator. Subjects may receive 12 additional months of post-HSCT dasatinib See section 4.3.1.11 for additional details. Criteria for HSCT eligibility will be based on MRD response at key early timepoints in therapy. MRD will be assessed by quantitative polymerase chain reaction (RQ-PCR) of rearranged immunoglobulin/T-cell receptor genes according to standardized criteria[46]. For subjects with uninformative PCR for Ig/TCR gene rearrangement known at baseline, RQ-PCR for BCR-ABL fusion transcripts or flow cytometry will be substituted (see section 4.3.1.11).

Key criteria for HSCT include:

1) MRD at end of IB/start of consolidation block 1 (HR1) $\geq$ 0.05% (5×10^{-4}) as measured by Ig/TCR PCR
    a. For subjects that do not have informative results of Ig/TCR PCR, see section 4.3.1.11.

    OR

2) MRD at end of IB/start of consolidation block 1 (HR1) 0.005-0.05% (5×10^{-5} to 5×10^{-4})* as measured by Ig/TCR PCR and MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%).

    *This includes if MRD at end of IB is positive but less than the quantifiable range (POS<QR) with QR not at least 0.005% (5×10^{-5})

    a. For subjects that do not have informative results of Ig/TCR PCR, see section 4.3.1.11.

Subjects with CNS3 disease at diagnosis will receive cranial irradiation during the Interim Maintenance period. Subjects with testicular involvement with Ph+ ALL will not be eligible for this trial as testicular radiation will not be part of the therapy (see Section 4.3.1.7).

Duration

The total duration of the trial will be approximately 6 years and includes an estimated recruitment period of 3 years and a minimum follow-up of 3 years for the primary and secondary endpoints. The 3 year recruitment period is based upon the average historical accrual rates in the pediatric Ph+ ALL population[13, 47, 48]. Three years of additional follow-up would ensure that all subjects have sufficient follow-up to assess the primary and secondary endpoints. Subjects recruited near the beginning of the accrual period would have up to 6 years of follow-up while subjects recruited near the end of accrual would have at least 3 years of follow-up. Subjects who

remain in follow-up beyond the study duration of 6 years would enter an extension phase of the protocol and continue receiving long-term follow-up to assess exploratory endpoints.

Individual subjects will have up to 7 years of follow-up in this study, including the time during treatment. The total intended duration of treatment (including chemotherapy and dasatinib) will be approximately 104 weeks (2 years). Subjects will be followed (including time on treatment) for at least 3 years for event-free survival and other secondary endpoints, 5 years for overall survival and 7 years (2 years of treatment + 5 years after completion of treatment) for [redacted] and other exploratory endpoints.

3.2 Post Study Access to Therapy

At the end of the treatment period, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

It is expected that subjects who complete the full 104 weeks of treatment will be considered in a complete continuous remission. The use of dasatinib after transplanation is optional in subjects who complete HSCT at the discretion of the treating investigator. Additional dasatinib may be given for up to 12 months post-HSCT.

3.3 Study Population

The intended population is children and adolescents with newly diagnosed Ph+ ALL who are candidate for standard multiagent chemotherapy (AIEOP-BFM ALL 2000 regimen).

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a. Written informed consent from subject or from parents or legal guardians for minor subjects must be obtained according to local law and regulation. Assent should be obtained according to local law and regulation and if the child is mentally capable.

2) Target Population

a. Philadelphia chromosome-positive ALL
   i. Documented presence of t(9;22) determined by cytogenetics or BCR-ABL fusion via RT-PCR or FISH (local laboratory)

b. Induction chemotherapy approximately ≤ 14 days according to institutional standard of care

c. Performance status ≥ 60% (See Appendix 8)
   i. Karnofsky for patients >16 years of age and Lansky for patients younger 1-16 years of age.

d. Adequate Liver Function defined as (See Table 5.1A for timing of assessments):
   i. Direct bilirubin ≤ 3 times the upper limit of normal (ULN) for age
   ii. ALT and AST ≤ 10 times the upper limit of normal (ULN) for age

e. Adequate Renal Function defined as (See Table 5.1A for timing of assessments):
   i. Serum creatinine ≤ 1.5 times the institutional upper limit of normal for age/gender or creatinine clearance or GFR ≥ 80 ml/min/1.73m^2
f. Adequate Cardiac Function defined as (See Table 5.1A for timing of assessments):
   i. QTc < 450 msec on baseline electrocardiogram as measured by the Frederica or Bazett formula (must be performed within 21 days prior to study enrollment)
   ii. LVEF ≥ 50% by gated radionuclide study/echocardiogram or shortening fraction ≥ 27% by echocardiogram (not required to be repeated if performed prior to induction).
g. For COG sites (excluding DFCI Consortium sites), subjects must be enrolled in the COG Classification Trial (AALL08B1 or successor).

3) Age and Reproductive Status

a. Males and females, Age > 1 year (365 days) and < 18 (17 years and 364 days) years at diagnosis
b. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of the study drug.
c. Women must not be breastfeeding.
d. Sexually active WOCBP must agree to follow instructions for method(s) of contraception starting at the time of enrollment for the duration of treatment with study drug dasatinib plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion.
e. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug dasatinib plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, sexually active WOCBP must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception for all study drugs. Female subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be used in the event that the subject chooses to forego complete abstinence

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Male condom without spermicide
- Female condom*
  - * A male and female condom must not be used together

f. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However the WOCBP must still undergo pregnancy testing as described in these sections.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a. Prior treatment with a BCR-ABL inhibitor (eg. imatinib)
b. Biopsy proven Ph+ ALL extramedullary involvement of the testicles

2) Medical History and Concurrent Diseases

a. Active systemic infection in conjunction with septic shock syndrome that require either vasopressor support or mechanical ventillation. Other infections, resulting in delay of standard chemotherapy until resolution, would not exclude the subject.
b. Known clinically-significant disorder of platelet function (eg von Willebrand's disease)
c. Clinically significant cardiovascular disease including ANY one of the following:
   i. Congenital long QT syndrome
   ii. History of ventricular arrhythmias or heart block
d. Down syndrome (constitutional trisomy 21)
e. Prior stem cell transplant
f. Ph+ ALL occurring as a second malignant neoplasm after treatment of a prior malignancy

3) Allergies and Adverse Drug Reaction

a. Subjects who have experienced hypersensitivity to any of the excipients in dasatinib tablets including: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol.

4) Sex and Reproductive Status

a. Patients who are pregnant or breastfeeding or likely to become pregnant.
b. Men whose partner is unwilling or unable to avoid pregnancy.

5) Other Exclusion Criteria

a. Prisoners or subjects who are involuntarily incarcerated
b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, or bilateral oophorectomy) or is not postmenopausal.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

3.4.1.1 Prohibited Treatments:

Prohibited treatments should not be used concomitantly with trial therapy and will constitute a relevant protocol deviation as one that can have a major impact on the interpretation of the trial.

No other therapy for the treatment of Ph+ ALL other than the AIEOP-BFM ALL 2000 chemotherapy regimen, HSCT (including preparative regimen) and dasatinib are allowed during the treatment phase of the trial. Subjects in follow-up after treatment discontinuation may receive additional treatment for relapsed ALL as medically indicated.

Medications associated with QT interval prolongation are prohibited. Please refer to the Appendix 3 for a website of "Drugs with Risk of Torsades de Points." This list includes:

- quinidine, procainamide, disopyramide
- amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin, azithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

3.4.1.2 Restricted Treatments:

Restricted medications should be limited as concomitant medications during protocol therapy. These medications may create drug-drug interactions. These medications are allowed but must be prescribed with caution and with careful management of potential drug-drug interactions. Use of restricted medications will not be considered a protocol deviation.

Caution should be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Antiplatelet agents or anticoagulants should be avoided in the setting of Grade 3 or 4 thrombocytopenia. If a subject requires anticoagulation for treatment of a thrombus, the platelet count should be adequately maintained to minimize the risk of bleeding.

Ideally, subjects enrolled in this study should not take other medications known to prolong the QT interval. Reference to a list of medications known to prolong the QT interval is found in Appendix 3. While "Drugs with Risk of Torsades de Points" are prohibited, "Drugs with a Possible Risk or Conditional Risk of Torsades de Points" may be given concomitantly should the investigator believe that beginning therapy with a potentially QT prolonging medication (other than the ones explicitly prohibited) is vital to an individual subject's care. Additional ECG(s) will be done at the investigator's discretion to ensure the subject's safety. If such a medication is considered important to a subject's care, the situation should be discussed with the Study Director.

Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. See Appendix 4 for a list of common CYP3A4 substrates with a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving dasatinib[49].

Additionally strong to moderate CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may significantly increase concentrations of dasatinib and should be used with caution when administered concurrently with dasatinib. Strong to moderate CYP3A4 inducers (eg, rifampicin) may decrease the concentration of dasatinib and should be used with caution when administered concurrently with dasatinib. See Appendix 5 and 6 for a list of CYP3A4 inhibitors and inducers respectively.

Dasatinib may have decreased solubility and absorption at pH > 4. Subjects should avoid concomitant use of proton pump inhibitors or H2 antagonists. In a population of 13 subjects, Cmax and AUC were reduced by 42% and 46%, respectively when a single dose of dasatinib 100 mg once daily was administered in the presence of 40 mg omeprazole compared to dasatinib alone, although there was significant intrapatient variability. If proton pump inhibitors or H2 antagonist administration is considered in the best interest of the subject (eg during high dose corticosteroid administration), they may be used. However, based upon the high interpatient variability of dasatinib pharmacokinetics, some subjects may have a reduction and some subjects may have no reduction in the plasma concentration of dasatinib when concomitantly taken with these agents. Short-acting antacid agents (eg aluminum or magnesium hydroxide) may be administered without affecting dasatinib pharmacokinetics, but not within 2 hours of the dasatinib dose.

3.4.2 Other Restrictions and Precautions

Based on pre-clinical data and clinical data, dasatinib might increase the likelihood of bleeding. Hence, subjects undergoing surgical procedures, including dental procedures should be instructed to inform their doctors of this potential increased risk.

3.4.3 Supportive Care Guidelines

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as medically indicated.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unacceptable toxicity despite dose modifications as per Section 4.3.1
- The subject has an event (see Section 8.3.1) including: 1) lack of response by the completion of consolidation block 3 (HR3), 2) relapse at any site, 3) development of second malignancy, and 4) death without relapse.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4 TREATMENTS

All protocol-specified investigational and noninvestigational products are considered study drug.

4.1 Study Treatments

Table 4.1: Product Description: Open Label

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dasatinib Tablet	20 mg	30 tablets per bottle / open label	NA	film coated tablets, biconvex, round, white to off-white in appearance with “20” or “BMS”debossed on one side and “527” on the other side	15°C - 25°C (59°F - 77°F)
Dasatinib Tablet	50 mg	30 tablets per bottle / open label	NA	film coated tablets, biconvex, oval, white to off-white in appearance with “50” or “BMS” debossed on one side and “528” on the other side	15°C - 25°C (59°F - 77°F)
Dasatinib Tablet	5 mg	30 tablets per bottle / open label	NA	film coated tablets, plain, round, white in appearance.	15°C - 25°C (59°F - 77°F)
Dasatinib Powder for Oral Suspension	10 mg/ml in suspension	33 grams Dasatinib blend per bottle (990mg Dasatinib per bottle) 90 mL bottle volume		White to off-white powder that may contain lumps which forms a white to off-white opaque suspension	15°C - 25°C (59°F - 77°F)

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- Dasatinib

This medication will be provided by Bristol-Myers Squibb. See Table 4.1.

Dasatinib will be delivered as a tablet, as an oral dispersed tablet or as an oral suspension from a powder (Powder for oral suspension (PFOS). For children and adolescents capable of swallowing tablets, the existing tablets, in strengths of 5, 20 and 50 mg, are considered a suitable pharmaceutical form and sufficient to cover the anticipated dose range. For children not able to swallow tablets, the dispersed tablet or powder for oral suspension are suitable alternatives. Dasatinib tablets may be dispersed in 100% preservative free juice (ie, orange or apple juice or lemonade). Complete details of the dispersion procedures can be found in Appendix 9. Once constituted with purified water, the PFOS has a mixed berry flavor. The PFOS bottle contains 33 grams of Dasatinib blend (containing 990mg active Dasatinib API). The site constitutes with 77 ml Purified water or Sterile Water for Injection. This generates a total volume of 99ml. The bottle is labeled for 90ml to assume a 10% overage. Once constituted, the Dasatinib suspension is 10mg/ml. Complete details for the preparation of the PFOS can be found in Appendices 13 and 14. These same preparations may be used for administration via a nasogastric or g-tube.

It is not recommended to use a gel-cap to facilitate administration of the tablet as it is unknown if the gel-cap will alter the pharmacokinetics of the investigational product.

If the subject vomits after administration of the dasatinib tablet, the subject should not be redosed unless the tablet was still intact.

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

This study utilizes the standard Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster (AIEOP-BFM) ALL 2000 chemotherapeutic protocol[50].

In this protocol, noninvestigational product(s) are listed in Table 4.1.2 below by block of therapy. Chemotherapy will be obtained by the investigating site's standard prescribing procedures according to country availability and specific regulatory requirements.

Table 4.1.2: Non-investigational Products

Phase	Chemotherapy Regimen	Phase	Chemotherapy Regimen
1. Induction Block IB	Cyclophosphamide Mercaptopurine Cytarabine Methotrexate	5) 1st Reinduction Block (R1)	Dexamethasone Vincristine Doxorubicin L-Asparaginase Cyclophosphamide Cytarabine Thioguanine Methotrexate
2. High Risk Block 1 (HR1)	Dexamethasone Vincristine Methotrexate Leucovorin Cytarabine Hydrocortisone Cyclophosphamide L-Asparaginase	6) Interim Maintenance (IM)	Mercaptopurine Methotrexate
3. High Risk Block #2 (HR2)	Dexamethasone Vincristine Methotrexate Leucovorin Ifosfamide Cytarabine Hydrocortisone Daunorubicin L-Asparaginase	7) 2nd Reinduction Block (R2)	Dexamethasone Vincristine Doxorubicin L-Asparaginase Cyclophosphamide Cytarabine Thioguanine Methotrexate
4. High Risk Block #3 (HR3)	Dexamethasone Cytarabine Etoposide L-Asparaginase Methotrexate Hydrocortisone	8) Continuation Therapy	Mercaptopurine Methotrexate

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

4.2 Method of Assigning Subject Identification

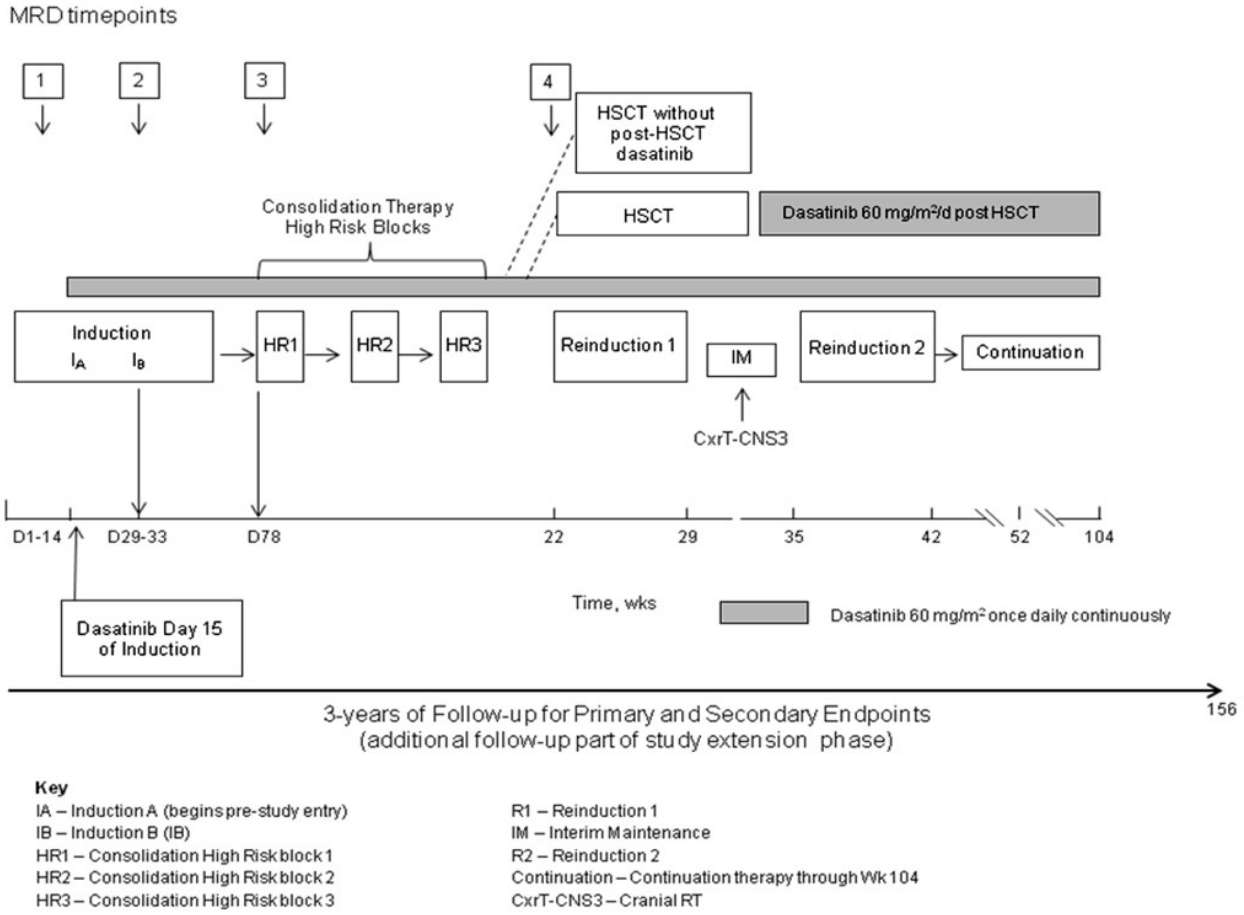
After informed consent and subject assent has been obtained as per local guidelines, the patient must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Instructions on the use of the IVRS will be provided to the study site.

4.3 Selection and Timing of Dose for Each Subject

The summary of the treatment plan is shown below in Figure 4.3 and Table 4.3A. Subjects will receive up to 24 months of treatment during this trial. Since subjects with Ph+ ALL often experience delays in treatment due to toxicities associated with therapy, delays in starting treatment blocks are expected. Therefore, all start dates for the initiation of all treatment blocks are estimates, and should not be considered as strict requirements.

As patients newly diagnosed with Ph+ ALL require urgent treatment, initial therapy for their disease will start outside the protocol with a chemotherapy regimen that is standard at the investigative center (referred to as induction therapy IA). Dasatinib (IMP) at a dose of 60 mg/m^2 once daily will be introduced on day +15 from initiation of treatment or no later than when the day 15 induction chemotherapy is administered in all subjects in addition to ongoing chemotherapy (approximately until day + 29 to 33). From the start of induction therapy IB, all subjects will follow the same treatment plan shown in Table 4.3A. A key for abbreviations is found at the end of the table. If commercial shortages of protocol specified chemotherapy agents occur then sites are to use their best clinical judgment in consultation with the BMS Medical Monitor regarding an appropriate substitution. A summary of hematological counts prior to the start of each block of therapy is presented in Table 4.3B.

Figure 4.3: Treatment Plan Summary



Key

IA – Induction A (begins pre-study entry)
IB – Induction B (IB)
HR1 – Consolidation High Risk block 1
HR2 – Consolidation High Risk block 2
HR3 – Consolidation High Risk block 3
R1 – Reinduction 1
IM – Interim Maintenance
R2 – Reinduction 2
Continuation – Continuation therapy through Wk 104
CxrT-CNS3 – Cranial RT

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
Induction Therapy Phase IA (Until Day 29 - 33)	All patients will receive first induction according to institutional standard of care.		
	Dasatinib/po	60 mg/m^2 once daily	Start day 15 from beginning of IA or no later than when the day 15 induction chemotherapy is administered Continuously
Induction Therapy Phase IB Starts no sooner than day 33	Dasatinib/po	60 mg/m^2 once daily	Continuously
	CPM/iv (1h)	1000 mg/m^2	1, 28
	6-MP/po	60 mg/m^2/d	1-28

Table 4.3A: Treatment Plan Summary			
Phase	**Drug/Administration Route**	**Dose**	**Day**
(Phase lasts 28 days)	ARA-C/iv or sc	75 mg/m^2/d	3-6, 10-13, 17-20, 24-27
	MTX/it	Dose by age (Table 4.3.1.2)	3, 17
Recovery period (Dasatinib continues, No chemotherapy given) (2 - 4 weeks)			
Eligible for hematopoietic Stem Cell Transplant if MRD at end of IB/start of consolidation block 1 ≥ 0.05% (see section 4.3.1.11 for subjects know to have uninformative PCR for Ig/TCR gene rearrangement assessment)			
Consolidation Block 1 (HR-1) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50 x 10^9/L) (Day 78 of therapy). HR-1 lasts 21 days.	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.3)	1
	HD-MTX/iv (24h)	5 g/m^2	1
	CF-Rescue/iv or po	Levo Form: 7.5 mg/m^2 (not available in U.S.) Racemic form: 15 mg/m^2	42, 48, 54 h after start of HD-MTX
	VCR/iv	1.5 mg/m^2/d (max 2 mg)	2, 6
	CPM/iv (1h)	200 mg/m^2 (q12h x 5)	2-4
	HD-ARA-C/iv (3h)	2 g/m^2 (q12h x 2)	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.3)	6
	G-CSF/sc or iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000 mm^3
Consolidation Block 2 (HR-2) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.4)	1
	HD-MTX/iv (24h)	5 g/m^2	1

Table 4.3A: Treatment Plan Summary			
Phase	**Drug/Administration Route**	**Dose**	**Day**
x 10^9/L) HR-2 lasts 21 days.	CF-Rescue/iv or po	Levo Form: 7.5 mg/m^2 (not available in U.S.) Racemic form: 15 mg/m^2	42, 48, 54 h after start of HD-MTX
	VCR/iv	1.5mg/m^2 (max 2 mg)	2, 6
	IFO/iv (1h)	800 mg/m^2 (q12h x 5)	2-4
	DNR/iv (24h)	30 mg/m^2	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.5)	6
	G-CSF/sc or iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000 mm^3
Consolidation Block 3 (HR-3) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50 x 10^9/L) HR-3 last 21 days.	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	HD-ARA-C/iv (3h)	2 g/m^2 x 4 (q12h x 4)	1, 2
	Etop/iv (1h)	100 mg/m^2 (q12h x 5)	3-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.5)	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.5)	6
	G-CSF/sc iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000mm^3
Eligible for hematopoietic Stem Cell Transplant if MRD at end of IB/start of consolidation block 1 (HR1) 0.005-0.05% by Ig/TCR PCR and MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%). (see section 4.3.1.11 for subjects known to have uninformative PCR for Ig/TCR gene rearrangement assessment)			

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
1st Reinduction (Protocol II) Protocol IIa (days 1-35) Protocol IIb (days ~36-63) 1st Reinduction starts after completion of HR-3 and lasts 63 days. Starts when ANC (≥ 500/µl; 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; 50 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po	10 mg/m^2/d	1-7, 15-21
	MTX/it	Dose by age (Table 4.3.1.6)	1, 38, 45
	VCR/iv	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
	DOX/ADR/iv (1h)	25 mg/m^2	8, 15, 22, 29
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.6)	Schedule base on preparation
	CPM/iv (1h)	1000 mg/m^2	36
	ARA-C/sc or iv	75 mg/m^2/d	38-41, 45-48
	6-TG/po	60 mg/m^2/d	36-49
Interim Maintenance This phase starts after completion of the 1st Reinduction and lasts 29 days. Starts when ANC (≥ 750/µl; 0.75 x 10^9/L) and platelet counts (≥ 75,000/µl; 75 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	6-MP/po	50 mg/m^2/d	1-28
	MTX/po	20 mg/m^2	1, 8, 15, 22
	Cranial irradiation	18Gy	CNS3 Only
2nd Reinduction Protocol IIa (days 1-35) Protocol IIb (days ~36-63) This phase starts immediately after Interim Maintenance and lasts 63 days. Starts when ANC (≥ 500/µl; 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; 50 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po	10 mg/m^2/d	1-7, 15-21
	MTX/it (Omit in CNS3 given cranial irradiation)	Dose by age (Table 4.3.1.8)	1, 38, 45
	VCR/iv	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
	DOX/ADR/iv (1h)	25 mg/m^2	8, 15, 22, 29
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.8)	Schedule base on preparation

Table 4.3A: Treatment Plan Summary			
Phase	**Drug/Administration Route**	**Dose**	**Day**
	CPM/iv (1h)	1000 mg/m^2	36
	ARA-C/sc or iv	75 mg/m^2/d	38-41, 45-48
	6-TG/po	60 mg/m^2/d	36-49
Continuation Therapy Starts after completion of the 2nd reinduction and continues for approximately 62 weeks (until a total of 2 years treatment is complete). Starts when ANC (≥ 750/µl; 0.75 x 10^9/L) and platelet counts (≥ 75,000/µl; 75 x 10^9/L)	6-MP/po	50 mg/m^2/d	Daily
	MTX/po	20 mg/m^2 weekly	Weekly
	MTX/it (Omit in CNS3 given cranial irradiation)	Dose by age (Table 4.3.1.8)	Every 6 weeks x 6 doses
	Dasatinib/po	60 mg/m^2 once daily	Continuously

CPM = cyclophosphamide, ARA-C = cytosine arabinoside, 6-MP = 6-mercaptopurine, MTX = methotrexate, DEXA = dexamethasone, VCR = vincristine, HD-ARA-C = high dose cytosine arabinoside, HD-MTX = high dose methotrexate, CF = citrovorum factor (folinic acid, calcium folinate, or leucovorin), ASP = asparaginase, G-CSF = granulocyte-colony stimulating factor, DNR = daunorubicin, IFO = ifosfamide, Etop= etoposide, DOX = doxorubicin, ADR = adriamycin, 6-TG = 6-thioguanine, HC = hydrocortisone, po = oral, iv = intravenous, sc = subcutaneous, it = intrathecal, im = intramuscular

Table 4.3B: Hematological Criteria Prior to Each Treatment Block	
Treatment block	**Count criteria**
Induction IA	None
Induction IB	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
Consolidation blocks; HR1, HR2 and HR3	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
First Reinduction IIa	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
First Reinduction IIb	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
Interim maintenance	ANC > 0.75 x 10^9/L and plt >75 x 10^9/L
Second Reinduction IIA	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
Second Reinduction IIB	ANC > 0.5 x 10^9/L and plt > 50 x 10^9/L
Continuation	ANC > 0.75 x 10^9/L and plt >75 x 10^9/L

4.3.1 Full Treatment Plan

4.3.1.1 Induction Therapy Phase IA

All patients will receive the first induction according to the institutional standard of care. **See Appendix 11 for examples of induction phase IA regimens.**

Dasatinib 60 mg/m^2 daily will be introduced on day 15 from the start of induction IA, or no later than when the day 15 chemotherapy is administered to accommodate any delays for toxicity or scheduling/logistics. Dasatinib will be given continuously until the end of therapy (2 years). Dasatinib should only be interrupted for toxicity. Induction IA will last approximately 29 to 33 days depending on the institutional standard of care. The dasatinib dose may be rounded up to the nearest 5 mg dose. The dasatinib dose will be recalculated based on BSA every 12 weeks, or more often if necessary.

4.3.1.2 Induction Therapy Phase IB

Pneumocystis (jirovecii) pneumonia (PCP) prophylaxis is recommended with trimethoprim/sulfamethoxazole, cotrimoxazole or other appropriate agent against Pneumocystis jirovecii according to the institutional standard of care. Note that pentamidine use is prohibited in this trial due to potential interaction with dasatinib (see Section 3.4.1.1)

Induction IB therapy should begin no sooner than day 33 or when parameters noted below are met.

Requirements for beginning of phase IB:

- Good general condition without serious infections;
- Creatinine level within normal limits according to age;
- ANC > 500/µl (> 0.5 x 10^9/L); platelets > 50,000/µl (> 50 x 10^9/L)

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

CYCLOPHOSPHAMIDE (CPM): 1000 mg/m^2/dose i.v. (1 hour) days 1, 28. (There are no blood count requirements for the initiation of day 28 cyclophosphamide. Please see Appendix 12 for optional hydration guidelines.

Please consider adequate anti-emetic supportive therapy according to standard institutional guidelines

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). Once 6-MP is started in this block it should continue, regardless of hematologic counts. If initiation of ARA-C cycle is delayed due to inadequate blood counts or the cycle is interrupted, then 6-MP should also be delayed/interrupted.

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

The 4-day cycles that begin on days 10, 17, and 24 should be started when WBC > 500/μl (> 0.5 x 10^9/L) and platelets > 30,000/μl (>30 x 10^9/L); each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug). Note: For the cycle starting on day 3, the WBC and platelet counts do not need to be rechecked if adequate to begin this Induction 1B block.

INTRATHECAL METHOTREXATE: days 3, 17 (start with the 4-day cycle of ARA-C in cycles 1 and 3), age-dosed:

Table 4.3.1.2: Intrathecal Methotrexate Therapy Dose by Age

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

4.3.1.3 Consolidation Block 1 (HR1)

If MRD at end of IB/start of consolidation block 1 (HR1) ≥ 0.05% (5 x 10^{-4}) according to RQ-PCR of rearranged immunoglobulin/T-cell receptor genes, then see Section 4.3.1.11 regarding HSCT. See section 4.3.1.11 for subjects known to have uninformative PCR for Ig/TCR gene rearrangement assessment at baseline.

Consolidation therapy will start at least 14 days after the end of Phase IB, provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented (rising counts). Subjects must wait until day 78 even if their blood counts are adequate prior to day 78. Dasatinib 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 no less than 21 days (counting from day 1 of HR-1 to day 1 of HR-2).**

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

DEXAMETHASONE (DXM): 20 mg/m^2/day p.o. or i.v. in 3 doses, days 1-5 (no tapering). See Section 3.4.1.2 regarding the use of proton pump inhibitors and H2 blockers.

VINCRISTINE (VCR): 1.5 mg/m^2/day i.v. (max dose: 2 mg), day 2 and 6. (Dose may be administered via i.v. push over 1 minute, or infusion as per institutional standard of care)

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). Suggested hyperhydration: 3,000 ml/m^2 over 24 hours: Gluc. 5%(D5W)+ NaCl 0,45%+ 90 mEq/m^{2}KCl+NaHCO3 90 mEq/m^2. Urine pH > 7.0 over the time of infusion.

MTX dosing is based upon BSA and the dose should not be capped.

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 1 or 2.

Alternatively, the HD-MTX infusion guidelines in Appendix 2 may be followed in place of the above guidelines.

CITROVORUM FACTOR (CF) (Folinic acid, calcium folinate, or leucovorin): 7.5 mg/m^2 i.v (Levo form; levoleucovorin, not available in the U.S.) or 15 mg/m^2 i.v or po (Racemic form; leucovorin) at hours 42, 48, and if needed 54 hours from start of HD-MTX. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix 1 or 2.

Starting from hour 60, Citrovorum Factor is needed only if serum levels at hour 48 exceed 0.5 µmol/l. In this case, see the nomogram for therapeutic adjustments (Appendix 1 or 2).

CYCLOPHOSPHAMIDE (CPM): 200 mg/m^2 i.v. in 1 hour q 12 hours x 5 doses, days 2-4. Start immediately after the completion of HD-MTX infusion. See Appendix 12 for optional MESNA guidelines.

HIGH-DOSE ARA-C (HD-ARA-C): 2 g/m^2/iv in 3-hour infusion, given every 12 hours for a total of 2 doses on day 5. The use of corticosteroid eye drops is suggested.

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) or PEG-ASPARAGINASE (PEG-ASP):

First-line therapy consists of native E. coli asparaginase. If native E. coli asparaginase is not available or for centers in the United Kingdom (UK), Peg-asparaginase should be used as first-line therapy.

- E. coli (medac or Kidrolase or Elspar): 25,000 IU/m2/dose, over 2 hours i.v. or i.m., 3 hours after completion of the infusion of the second dose of HD-ARA-C.
- Peg-Asp: In non-United Kingdom locations, use 2,500 IU/m2 over 1-2 hours i.v. or i.m.
- Peg-Asp: In the United Kingdom, use 1000 IU/m2 over 1 hour i.v. or i.m.

In subjects developing an allergic reaction to PEG-ASP during Induction IA, neither E.coli ASP or PEG ASP should given. In such subjects, Erwina, if available, should be used.

If an allergic reaction occurs following administration of native asparaginase or Peg-asp during Consolidation therapy, the algorithm specified in section 4.3.2.2 should be used for replacement.

INTRATHECAL THERAPY: Day 1 and should be given 2 hours after start of HD-MTX (window of -6 to + 6 hours in relation to start of HD-MTX is acceptable), dose according to age:

Table 4.3.1.3: Intrathecal Dose by Age			
AGE	**Methotrexate**	**Ara-C**	**Hydrocortisone**
≥ 1 year < 2 years	8 mg	20 mg	8 mg
≥ 2 years < 3 years	10 mg	26 mg	10 mg
≥3 years	12 mg	30 mg	12 mg

SUPPORTIVE CARE: The 3 High Risk Consolidation blocks are profoundly myelosuppressive and also include 5 days of high dose dexamethasone, which can blunt clinical signs of infection: therefore the following precautions are to be taken for all subjects during each High Risk block:

- Mandatory blood counts with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. These blocks are highly myelosuppressive. Recovery is defined as ANC > 0.2 x10^9/L (200/µl) and platelet transfusion independence.
- Mandatory myeloid growth factor support: G-CSF 5µg/kg/day s.c. or i.v. starting anytime from 7 to 11 days the from the start of the block (eg, at least 24 hours after completion of the chemotherapy in each HR block), until the WBC count is > 3.0 x10^9/L (>3000/mm^3). The option of pegfilgrastim 100µg/kg s.c. given once during the 7-11th day from the start of the block may be considered as an alternative. Myeloid growth factor support is routinely included in these blocks in BFM and EsPhALL trials.
- Although not required, STRONGLY consider hospitalizing patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- Because clinical signs of infection can be blunted following high dose dexamethasone therapy, a very low threshold should be used for institution of empiric antimicrobial therapy.

4.3.1.4 Consolidation Block 2 (HR2)

Consolidation therapy will begin 21 days after the start of HR1, provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented (rising counts) and at least 21 days have elapsed since the start of HR1.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

DEXAMETHASONE (DEXA)**:** 20 mg/m^2/day p.o. or i.v. in 3 doses, days 1-5 (no tapering). See Section 3.4.1.2 regarding the use of proton pump inhibitors and H2 blockers.

VINCRISTINE: 1.5 mg/m^2/day i.v. (max dose: 2 mg), day 2 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). Suggested hyperhydration: 3,000 ml/m^2 over 24 hours: Gluc. 5%(D5W)+ NaCl 0,45%+ 90 mEq/m^{2}KCl+NaHCO3 90 mEq/m^2. Urine pH > 7.0 over the time of infusion.

MTX dosing is based upon BSA and the dose should not be capped.

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 1 or 2.

Alternatively, the HD-MTX infusion guidelines in Appendix 2 may be followed in place of the above guidelines.

CITROVORUM FACTOR (CF) (Folinic acid, calcium folinate, or leucovorin): 7.5 mg/m^2 i.v (Levo form; levoleucovorin, not available in the U.S.) or 15 mg/m^2 i.v or po (Racemic form; leucovorin) at hours 42, 48, and if needed 54 hours from start of HD-MTX. For monitoring of MTX serum levels and intensification of LCV rescue, see Appendix 1 or 2.

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 (Appendix 1 or 2).

IFOSFAMIDE (IFO): 800 mg/m^2 i.v. over 1-hour infusion, q 12 hours x 5 total doses, days 2 - 4. Start immediately after completion of HD-MTX infusion. See Appendix 12 for optional MESNA administration.

- Post hydration after HD-MTX(given on Day 1 of this cycle) as detailed in Appendix 1(EsPhALL based) or 2 (COG based) provides adequate hydration on days of ifosfamide administration. However, if MTX level meets criteria for leucovorin to be stopped, total fluids should remain at 125 mL/m2/hour until at least 12 hours after the last dose of ifosfamide.

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) or PEG-ASPARAGINASE (PEG-ASP):

First-line therapy consists of native E. coli asparaginase. If native E. coli asparaginase is not available or for centers in the United Kingdom (UK), Peg-asparaginase should be used as first-line therapy.

- E. coli (medac or Kidrolase or Elspar): 25,000 IU/m2/dose, over 2 hours i.v. or i.m., on day 6.
- Peg-Asp: In non-United Kingdom locations, use 2,500 IU/m2 over 1-2 hours i.v. or i.m.
- Peg-Asp: In the United Kingdom, use 1000 IU/m2 over 1 hour i.v. or i.m.

In subjects developing an allergic reaction to PEG-ASP during Induction IA, E. coli Asp or Peg-Asp should not be given. In such subjects, Erwina, if available, should be used.

If an allergic reaction occurs following administration of native asparaginase or Peg-asp during Consolidation therapy, the algorithm specified in section 4.3.2.2 should be used for replacement.

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

INTRATHECAL THERAPY: day 1, 2 hours after start of HD-MTX (window of -6 to + 6 hours in relation to start of HD-MTX is acceptable), according to age:

Table 4.3.1.4: Intrathecal Dose by Age

AGE	Methotrexate	Ara-C	Hydrocortisone
≥ 1 year < 2 years	8 mg	20 mg	8 mg
≥ 2 years < 3 years	10 mg	26 mg	10 mg
≥ 3 years	12 mg	30 mg	12 mg

SUPPORTIVE CARE: The 3 High Risk Consolidation blocks are profoundly myelosuppressive and also include 5 days of high dose dexamethasone, which can blunt clinical signs of infection: therefore the following precautions are to be taken for all subjects during each High Risk block:

- Mandatory blood counts with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. These blocks are highly myelosuppressive. Recovery is defined as ANC > 0.2 x10^9/L (200/µl) and platelet transfusion independence.
- Mandatory myeloid growth factor support: G-CSF 5µg/kg/day s.c. or i.v. starting anytime from 7 to 11 days the from the start of the block (eg, at least 24 hours after completion of the chemotherapy in each HR block), until the WBC count is > 3.0 x10^9/L (>3000/mm^3). The option of pegfilgrastim 100µg/kg s.c. given once during the 7-11th day from the start of the block may be considered as an alternative. Myeloid growth factor support is routinely included in these blocks in BFM and EsPhALL trials.
- Although not required, STRONGLY consider hospitalizing patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- Because clinical signs of infection can be blunted following high dose dexamethasone therapy, a very low threshold should be used for institution of empiric antimicrobial therapy.

4.3.1.5 Consolidation Block 3 (HR3)

Consolidation therapy will start provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented (rising counts) and at least 21 days have elapsed since the start of HR2.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

DEXAMETHASONE (DEXA)**:** 20 mg/m^2/day p.o. or i.v. in 3 doses, days 1-5 (no tapering). See Section 3.4.1.2 regarding the use of proton pump inhibitors and H2 blockers.

HIGH-DOSE ARA-C (HD-ARA-C): 2 g/m^2 i.v. in 3-hour infusion, q 12 hours x 4 total doses, days 1-2. The use of corticosteroid eye drops is suggested.

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

HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) or PEG-ASPARAGINASE (PEG-ASP):

First-line therapy consists of native E. coli asparaginase. If native E. coli asparaginase is not available or for centers in the United Kingdom (UK), Peg-asparaginase should be used as first-line therapy.

- E. coli (medac or Kidrolase or Elspar): 25,000 IU/m2/dose, over 2 hours i.v. or i.m., on day 6.
- Peg-Asp: In non-United Kingdom locations, use 2,500 IU/m2 over 1-2 hours i.v. or i.m.
- Peg-Asp: In the United Kingdom, use 1000 IU/m2 over 1 hour i.v. or i.m.

In subjects developing an allergic reaction to PEG-ASP during Induction IA, E.coli Asp or Peg-Asp should not be given. In such subjects, Erwina, if available, should be used.

If an allergic reaction occurs following administration of native asparaginase or Peg-asp during Consolidation therapy, the algorithm specified in section 4.3.2.2 should be used for replacement.

INTRATHECAL THERAPY: day 5, dose according to age:

Table 4.3.1.5: Intrathecal Dose by Age

AGE	Methotrexate	Ara-C	Hydrocortisone
≥ 1 year < 2 years	8 mg	20 mg	8 mg
≥ 2 years < 3 years	10 mg	26 mg	10 mg
≥ 3 years	12 mg	30 mg	12 mg

SUPPORTIVE CARE: The 3 High Risk Consolidation blocks are profoundly myelosuppressive and also include 5 days of high dose dexamethasone, which can blunt clinical signs of infection: therefore the following precautions are to be taken for all subjects during each High Risk block:

- Mandatory blood counts with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. These blocks are highly myelosuppressive. Recovery is defined as ANC > 0.2 x10^9/L (200/µl) and platelet transfusion independence.
- Mandatory myeloid growth factor support: G-CSF 5µg/kg/day s.c. or i.v. starting anytime from 7 to 11 days the from the start of the block (eg, at least 24 hours after completion of the

chemotherapy in each HR block), until the WBC count is > 3.0 x10^9/L (>3000/mm^3). The option of pegfilgrastim 100µg/kg s.c. given once during the 7-11th day from the start of the block may be considered as an alternative. Myeloid growth factor support is routinely included in these blocks in BFM and EsPhALL trials.

- Although not required, **STRONGLY** consider hospitalizing patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- Because clinical signs of infection can be blunted following high dose dexamethasone therapy, a very low threshold should be used for institution of empiric antimicrobial therapy

4.3.1.6 First Reinduction (Protocol II)

If MRD at end of IB/start of consolidation block 1 (HR1) 0.005-0.05% (5 x 10^{-5} - 5 x 10^{-4}) or POS<QR with QR not at least 0.005% (5 x 10^{-5}) and MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%) according to RQ-PCR of rearranged immunoglobulin/T-cell receptor genes, then see Section 4.3.1.11 regarding HSCT. See section 4.3.1.11 for subjects known to have uninformative PCR for Ig/TCR gene rearrangement assessment at baseline.

The first re-induction with protocol II starts at least 21 days from the start of HR3 block, provided the patient is in good general condition and adequate ANC (≥ 500/µl; 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; 50 x 10^9/L) are documented. Protocol II comprises two phases, IIa and IIb.

Phase IIa

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

DEXAMETHASONE (DXM): 10 mg/m^2/day p.o. or i.v. in 3 doses, days 1-7 and 15-21. See Section 3.4.1.2 regarding the use of proton pump inhibitors and H2 blockers.

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 in up to 1 hour or according to institutional standards on days 8, 15, 22, and 29.

L-ASPARAGINASE (L-ASP) E. coli (medac or Kidrolase or Elspar) or **PEG-ASPARAGINASE (PEG-ASP):**

First-line therapy consists of native E. coli asparaginase. If native E. coli asparaginase is not available or for centers in the United Kingdom (UK), Peg-asparaginase should be used as first-line therapy.

- L-Asp: 10,000 IU/m2/dose, over 1 hour i.v. or i.m., days 8, 11, 15 and 18,

- Peg-Asp: In non-United Kingdom locations, use a single dose of 2,500 IU/m2 over 1-2 hours i.v. or i.m. on day 8 in place of the 4 doses of native asparaginase
- Peg-Asp: In the United Kingdom, use a single dose of 1,000 IU/m2 over 1 hour i.v. or i.m. on day 8 in place of the 4 doses of native asparaginase

In case of an allergic reaction follow the algorithm specified in section 4.3.2.2 for replacement.

INTRATHECAL METHOTREXATE: day 1, dose according to age. See Table 4.3.1.6

Phase IIb

This portion of treatment starts on day 36 of protocol II provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

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

See Appendix 12 for optional MESNA guidelines.

Please consider adequate anti-emetic supportive therapy.

6-THIOGUANINE (6-TG): 60 mg/m^2/day p.o., taken in the evening on an empty stomach without milk (1 hour before or after dinner), days 36 - 49 (total 14 days). If 6-thioguanine is not available, then an option to substitute 6-mercaptopurine 60 mg/m^2/day p.o. taken in the evening on an empty stomach without milk (1 hour before or after dinner), days 36-49 (total 14 days) is permitted. If initiation of ARA-C cycle is delayed due to inadequate blood counts or the cycle is interrupted, then 6-TG should also be delayed/interrupted.

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

The 4-day cycle that begins on day 45 should be started when WBC > 500/µl (> 0.5 x 10^9/L) and platelets > 30,000/µl (> 30 x 10^9/L); each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug).

Note: For the cycle starting on day 38, the WBC and platelet counts do not need to be rechecked if adequate to begin this protocol IIb block (day 36 of first reinduction).

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

Table 4.3.1.6: Intrathecal Methotrexate Therapy Dose by Age

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

4.3.1.7 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 last chemotherapy of the previous phase (day 49 of protocol II, ie 64 days after the start of First Reinduction) and will last 4 weeks (ie the time comprised between the first and the second administration of protocol II) provided the patient is in good general condition and adequate ANC (≥ 750/µl; 0.75 x 10^9/L) and platelet counts (≥ 75,000/µl; 75 x 10^9/L). Dasatinib administration will not be interrupted between the end of protocol II and the beginning of interim maintenance.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

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 1, 8, 15, and 22.

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

CRANIAL IRRADIATION: During interim maintenance cranial irradiation will be given to patients with CNS3 leukemia at diagnosis (See Appendix 10 for definition). Only subjects ≥ 36 months of age, not receiving a HSCT should receive cranial irradiation during interim maintenance. Cranial irradiation will be administered at the dose of 18 Gy in 10 fractions. It will begin on day 1 of interim maintenance.

CNS3 patients that receive HSCT should receive a total cranial irradiation dose of 18 Gy. This is usually given as a cranial boost during the HSCT preparative regimen. If a non-TBI preparative regimen is used, then a cranial boost of 18 Gy should be considered prior to or following HSCT.

Radiation Therapy Guidelines

Equipment and Calibration

X-ray beams with a nominal energy of 4 or 6 MV. IMRT is not allowed.

Target Volume

The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve superior to the vertex and posterior to the occiput. The caudal border will be below the skull base to at least the C2 vertebral level.

Target Dose

The prescription point in each target volume is at or near the center. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes. The absorbed dose is specified in centigray (cGy)-to-muscle. No corrections for bone attenuation will be made.

The daily dose to the prescription points for the cranial volume will be 1.8 Gy for patients with CNS3 leukemia at diagnosis. The total dose to the prescription point shall be 18 Gy in 10 treatments for patients with CNS3 leukemia at diagnosis.

Fractionation

All radiation fields shall be treated once each day; the treatment shall be given 5 days a week.

Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For any interruptions greater than 7 days, contact the study director.

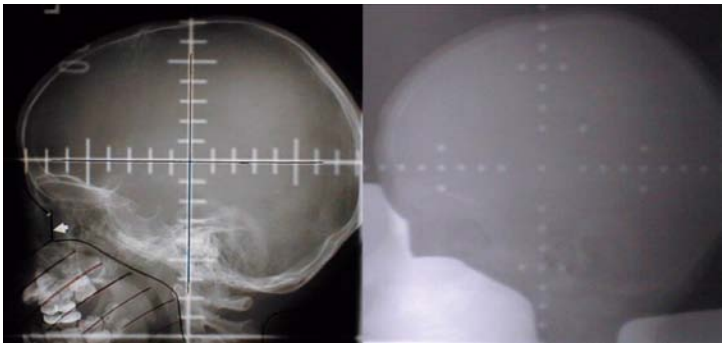
Dose Uniformity

The dose variations in each target volume shall be within +7%, -5% of the prescription-point dose.

Treatment Technique

The patient can be treated prone or supine. The cranial volume is treated with 2 lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp. Field-shaping shall be done with blocks which are at least 5 HVL thick. See Figure 4.3.1.7. Multi-leaf collimators are also acceptable provided coverage is adequate.

Figure 4.3.1.7: Example of radiation simulation radiograph with cerrobend block design (left) and megavoltage portal film (right) for cranial irradiation volume.



Eye protection

A simple method to minimize lens irradiation, while irradiating the posterior halves of the eyes, is to let the central axes of the horizontal cranial beams go through both orbits. The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks cover the anterior halves of the eyes and protect the nose and mouth. Essentially the same geometry can be achieved with the central axes through the center of the head by angling the lateral fields so that the rays through the eyes lie in the same horizontal plane. It is also acceptable to use a parallel-opposed beam-pair, without such angling, with shielding blocks that cover the anterior half of the proximal eye. The dose to the contralateral lens will be higher.

4.3.1.8 Second Reinduction (Protocol II)

It will start immediately after the interim maintenance provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) and platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented.

Phase IIa

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

DEXAMETHASONE (DEXA): 10mg/m^2/day p.o. or i.v. in 3 doses, days 1 - 7 and 15 - 21. See Section 3.4.1.2 regarding the use of proton pump inhibitors and H2 blockers.

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

DOXORUBICIN (DOX)/ADRIAMYCIN (ADR): 25 mg/m^2/dose i.v. to be infused in up to 1 hour or according to institutional standards on days 8, 15, 22, and 29.

L-ASPARAGINASE (L-ASP) E. coli (medac or Kidrolase or Elspar) or **PEG-ASPARAGINASE (PEG-ASP):**

First-line therapy consists of native E. coli asparaginase. If native E. coli asparaginase is not available or for centers in the United Kingdom (UK), Peg-asparaginase should be used as first-line therapy.

- L-Asp: 10,000 IU/m2/dose, over 1 hour i.v. or i.m., days 8, 11, 15 and 18.
- Peg-Asp: In non-United Kingdom locations, use a single dose of 2,500 IU/m2 over 1-2 hours i.v. or i.m. on day 8 in place of the 4 doses of native asparaginase
- Peg-Asp: In the United Kingdom, use a single dose of 1,000 IU/m2 over 1 hour i.v. or i.m. on day 8 in place of the 4 doses of native asparaginase

In case of an allergic reaction follow the algorithm specified in section 4.3.2.2 for replacement.

INTRATHECAL METHOTREXATE: day 1, dose according to age. See Table 4.3.1.8.

Phase IIb

This portion of treatment starts on day 36 of protocol II provided the patient is in good general condition and adequate ANC (≥ 500/µl; ≥ 0.5 x 10^9/L) platelet counts (≥ 50,000/µl; ≥ 50 x 10^9/L) are documented.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

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

See Appendix 12 for optional MESNA guidelines.

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). If 6-thioguanine is not available, then an option to substitute 6-mercaptopurine 60 mg/m^2/day p.o. taken in the evening on an empty stomach without milk (1 hour before or after dinner), days 36-49 (total 14 days) is permitted. If initiation of ARA-C cycle is delayed due to inadequate blood counts or the cycle is interrupted, then 6-TG should also be delayed/interrupted.

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

The 4-day cycle that begins on day 45 should be started when WBC > 500/ml (> 0.5 x 109/L) and platelets > 30,000/ml (> 30 x 109/L); each cycle when started should not be stopped unless for acute infection (please consider that fever might be also induced by the drug.

Note: For the cycle starting on day 38, the WBC and platelet counts do not need to be rechecked if adequate to begin this protocol IIb block (day 36 of second reinduction).

INTRATHECAL METHOTREXATE: days 38 and 45 (together with ARA-C cycles on days 38 and 45).

Omit intrathecal MTX in CNS3 subjects who received cranial irradiation.

Dose according to age:

Table 4.3.1.8: Intrathecal Methotrexate Therapy Dose by Age

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

4.3.1.9 Continuation Therapy

Continuation therapy will start after completion of second reinduction (protocol II) provided the patient is in good general condition with adequate ANC (≥ 750/μl; 0.75 x 10^9/L) and platelet counts (≥ 75,000/μl; 75 x 10^9/L). The duration of treatment in this block is approximately 62 weeks.

DASATINIB: 60 mg/m^2 once daily orally continuously (held only for toxicity). The dasatinib dose may be rounded up to the nearest 5 mg dose.

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).

INTRATHECAL METHOTREXATE: Every 6 weeks x 6 doses. The first dose should be administered on Day 1 of Continuation.

Omit intrathecal MTX in CNS3 subjects who received cranial irradiation.

Dose according to age (Table 4.3.1.9A):

Table 4.3.1.9A: Intrathecal Methotrexate Therapy Dose by Age

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

METHOTREXATE (MTX): 20 mg/m^2/weekly p.o.

The aim is to adjust doses to maintain the ANC between 750 and 1500/μl (0.75 and 1.5 x 10^9/L) and the platelet count between 75,000 and 150,000/μl (75 and 150 x 10^9/L).

Start maintenance at 100% doses and DO NOT give higher doses at the start of continuation therapy even if the subject tolerated higher doses throughout interim maintenance.

During continuation therapy, if the ANC is > 1500/μl (1.5 x 10^9/L) and platelets > 150,000/μl (150 x 10^9/L) for ≥ 8 weeks, the dose of mercaptopurine should be escalated by 25%. Otherwise keep at 100% of dose.

If the subsequent monthly ANC is > 1500/μl (1.5 x 10^9/L):

1) Keep mercaptopurine at the 125% dose and increase oral methotrexate by 25% to a dose of 25 mg/m^2.
2) Continue to increase the mercaptopurine and oral methotrexate dose in 25% steps alternatively every eight weeks as outlined above if ANC > 1500/μl (1.5 x 10^9/L) and platelets > 150,000/μl (150 x 10^9/L) persists. There are no maximum doses for mercaptopurine and methotrexate.

Dose Reduction for Falling Neutrophil Counts

If the neutrophil count falls to between 500/μl (0.5 x 10^9/L) and 750/μl (0.75 x 10^9/L):

- HALVE the dose of mercaptopurine and oral methotrexate

If neutrophil count is < 500/μl (0.5 x 109/L):

- STOP mercaptopurine and methotrexate. ONLY RESTART when the count is over 750/μl (0.75 x 10^9/L). Restart at 100% of last dose when neutrophil > 750/μl (0.75 x 10^9/L).

If counts fluctuate significantly when restarting at 100% of last dose, starting at 50% and titrating upwards is permissible to avoid frequent interruptions of mercaptopurine exposure (this maneuver is often not necessary).

Dose Reduction for Falling Platelet Counts

If the platelet count is < 75,000/μl (75 x 10^9/L):

- HALVE the dose of mercaptopurine and methotrexate.

If the platelet count is <50,000/μl (50 x 10^9/L):

- STOP mercaptopurine and methotrexate. ONLY RESTART when the count is greater than 75,000/μl (75 x 10^9/L). Restart at 100% of last dose when platelet count > 75,000/μl (75 x 10^9/L).

If counts fluctuate significantly when restarting at 100% of last dose, starting at 50% and titrating upwards is permissible to avoid frequent interruptions of mercaptopurine exposure (this maneuver is often not necessary).

4.3.1.10 Completion of Treatment

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

4.3.1.11 Hematopoietic Stem Cell Transplant (HSCT)

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

Criteria for HSCT are:

1) MRD at end of IB/start of consolidation block 1 (HR1) ≥ 0.05% (5 x 10^{-4}) as measured by Ig/TCR PCR
    a. For subjects that do not have informative results of Ig/TCR PCR, the criteria for HSCT will be a less than 3-log reduction in MRD as measured by RQ-PCR for

BCR-ABL. In the rare circumstance that both Ig/TCR and BCR-ABL PCR are uninformative, flow cytometry results may be utilized with the same criteria as the Ig/TCR PCR.

OR

2) MRD at end of IB/start of consolidation block 1 (HR1) 0.005-0.05% (5×10^{-5} to 5×10^{-4})* as measured by Ig/TCR PCR and MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%).

   *This includes if MRD at the end of IB is positive but less than the quantifiable range (POS<QR) with QR not at least 0.005% ($5X10^{-5}$)

   a. For subjects that do not have informative results of Ig/TCR PCR, a positive MRD level as measured by RQ-PCR for BCR-ABL. In the rare circumstance that both Ig/TCR and BCR-ABL PCR are uninformative, flow cytometry results may be utilized with the same criteria as the Ig/TCR PCR.

MRD will be assessed by quantitative polymerase chain reaction (RQ-PCR) of rearranged immunoglobulin/T-cell receptor genes according to standardized criteria[51]. Subjects that fulfill the above criteria and have a genotype-matched donor (9/10 or 10/10) will receive hematopoietic stem cell transplant (HSCT) instead of continuing the AIEOP-BFM ALL 2000 regimen. The timing of HSCT would be following the consolidation block 3 (HR3). Subjects should continue on protocol specified Reinduction chemotherapy until HSCT. If alternative chemotherapy is preferred, the subject must be discontinued from the study treatment but must continue to be followed per protocol for the long term growth assessments. If a subject goes off-treatment to receive a different chemotherapy, dasatinib will no longer be provided via this study. Subjects who do not meet the above criteria should not receive HSCT. Subjects may receive additional dasatinib until the start of the HSCT preparation regimen or until within a 2 week window for HSCT. During the preparative regimen and HSCT, subjects will not receive dasatinib. Subjects with CNS3 disease at diagnosis who are proceeding to HSCT should also receive a cranial boost of radiation to a total of 18 Gy.

The preparative regimen prior to HSCT and the treatment for the HSCT will be according to the institutional standard of care. Subjects who proceed to HSCT will not continue to report AEs or conmeds during the preparation, procedure or recovery period unless considered related to the investigational product. Subjects who proceed to HSCT will continue to be followed on-study for the primary endpoint (ie events), and exploratory endpoints of [redacted]. Follow-up for these endpoints could also continue if subjects proceed to second line therapy.

Use of dasatinib after stem cell transplantation

The use of dasatinib after transplantation is optional in all HSCT recipients at the discretion of the treating physician. There are several reports that the use of dasatinib post-transplant appears safe[52,53].It is recommended that a subject continuing dasatinib treatment post-HSCT may start at

an initial dose of 48 mg/m^2 daily once the subject has a satisfactory engraftment with stable ANC, PTL and WBC count (ANC > 0.5 x 10^9/L for at least 28 days, PTL > 50 x 10^9/L; WBC > 1.5 x 10^9/L. If the initial dose is deemed tolerable by the treating physician, the dose of dasatinib may be escalated to 60 mg/m^2. For those subjects who opt for post-HSCT dasatinib, administration is suggested throughout the first year post-transplantation until day +365 from HSCT. The dasatinib dose may be rounded up to the nearest 5 mg dose. If dasatinib treatment is re-started then all data for adverse events, serious adverse events, concomitant medications and all other medical and diagnostic procedures must be recorded in the eCRF.

4.3.2 Dose Modifications

Dose interruptions or reductions for adverse events are described in the following tables below. Dose modifications should be made for adverse events considered related to the specific drug being modified. Relatedness of an adverse event to a particular drug is determined by the investigator. For an individual subject, dose interruptions, reductions and treatment discontinuation may be more or less conservative than indicated below in Table 4.3.2.1, through 4.3.2.13 based on the clinical judgment of the investigator.

4.3.2.1 Dasatinib

Table 4.3.2.1: Dose Modifications for Dasatinib

Dasatinib Related Event and Severity	**Dasatinib**
Hematologic	
Grade 1-4	No Dose Interruption/Reduction
If neutropenia and/or thrombocytopenia result in delay of next block of treatment > 14 days	Interrupt dasatinib and resume at the same dose level once the next block of treatment is continued. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another ≥ 7 days, a bone marrow assessment will be performed to assess the cellularity and percentage of blasts. If marrow cellularity is < 10%, dasatinib must be held until ANC > 500/µL (0.5 x 10^9/L) at which time treatment may be resumed at full dose. If marrow cellularity if > 10%, consider resumption of dasatinib. If necessary, repeat the bone marrow assessment every 7-10 days until treatment continues.
≥ Gr3 anemia	No dose reductions. Subjects developing anemia may be transfused or prescribed erythropoietin at the investigator's discretion.
Non-Hematologic	
Grade 1-2	No Dose Interruption/Reduction
Grade 2	If does not resolve despite symptomatic treatment, consider interrupting dasatinib Resume at 60 mg/m^2 after recovery to ≤ Grade 1 Consider reduction to 48 mg/m^2 for recurrent events
Grade ≥ 3	Hold therapy until ≤ grade 1 Resume at 48 mg/m^2 after recovery to ≤ Grade 1

Table 4.3.2.1: Dose Modifications for Dasatinib	
Dasatinib Related Event and Severity	**Dasatinib**
Liver Function Tests	
Direct Bilirubin > 5x institutional ULN	Hold until direct bilirubin levels have returned to baseline or < 1.5x institutional ULN. Resume at 60 mg/m^2 Reduce to 48 mg/m^2 if recurrent event
AST/ALT > 15x institutional ULN	Hold until AST/ALT levels have returned to baseline or < 2.5 x institutional ULN Resume at 60 mg/m^2 Reduce to 48 mg/m^2 if recurrent event
Bleeding	
Any bleeding or hemorrhage	Subjects who have evidence of bleeding or hemorrhage of any grade at any site may have dose adjustments or interruption at the discretion of the investigator

4.3.2.2 Asparaginase [PEG, E.coli, or Erwinia]

Table 4.3.2.2: Dose Modifications for Asparaginase	
Event	**Asparaginase**
Allergy	In case of allergy to an asparaginase formulation,: • COG members and sites in Italy should use the algorithm in Table 4.3.2.2a should be used. • United Kingdom sites should use the algorithm in Table 4.3.2.2b
Coagulopathy	If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.
Hyperbilirubinemia	L-asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity.
Hyperglycemia	Do not modify dose. Treat hyperglycemia as medically indicated
Hyperlipidemia	Do not modify dose
Ketoacidosis	Hold asparaginase until blood glucose can be regulated with insulin
Pancreatitis	Hold asparaginase for mild pancreatitis until symptoms and signs subside, and amylase levels return to normal and then resume. Permanently discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and > Grade 3 amylase elevation (> 2 x ULN) or pancreatic pseudocyts).
Thrombosis	Withhold asparaginase until resolved, and treat with appropriate anti-thrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing low molecular weight heparin or anti-thrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate.

Table 4.3.2.2: Dose Modifications for Asparaginase	
Event	**Asparaginase**
CNS Events (bleed, thrombosis, infarct)	Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Resume at full dose when all symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI).

Table 4.3.2.2a: Asparaginase Substitutions for COG and Italy		
Peg-Asparaginase	During HR1-HR3 blocks	Substitute 1 dose of PEG-ASP (Oncaspar) in a single dose of 2500 IU/m^2 over 1-2 hours i.v. or i.m. according to the institutional standard of care.
	During First or Second Reinduction Blocks	For full course substitution: substitute one dose of PEG-ASP (2500 IU/m^2) given on day 8 for the four doses of E. Coli asparaginase. For substitution after E. coli asparaginase given on day 8 or day 11 of reinduction, give a single dose of PEG-ASP (2500 IU/M^2) to replace the remaining scheduled doses of E.coli asparaginase. Substitution after a dose of E.coli asparaginase given at day 15 or day 18 of reinduction, is not recommended
Erwinia	Known allergy to PEG-ASP	In case of an allergy to PEG-ASP during induction therapy before entry on this trial or on this trial, then Erwinia asparaginase should be substituted (if available). If Erwinia asparaginase is not available, then the doses should be omitted.
	During HR1 to HR3 blocks	Substitute 3 doses of Erwinia asparaginase (25,000 IU/m^2) given on a Monday/ Wednesday/ Friday schedule for the single dose of E.coli asparaginase scheduled during HR1 to HR3 blocks.
	During first or second reinduction block (Protocol II)	Substitute 6 doses of Erwinia asparaginase (25,000 IU/m^2) given on a Monday/ Wednesday/ Friday schedule starting at day 8 for the 4 doses of E.coli asparaginase given during the first or second reinduction block (Protocol II). If a reaction occurs to PEG-ASP given on day 8 of the first or second reinduction block, then six doses of Ewinia asparaginase should be administered as above, starting 1-2 days after the dose of PEG-ASP.

Table 4.3.2.2b: Asparaginase Substitutions for United Kingdom

Erwinia	Known allergy to PEG-ASP	In case of an allergy to PEG-ASP during induction therapy before entry on this trial or on this trial, then Erwinia asparaginase should be substituted (if available). If Erwinia asparaginase is not available, then the doses should be omitted.
	During HR1 to HR3 blocks	Substitute 3 doses of Erwinia asparaginase (25,000 IU/m^2) given on a Monday/ Wednesday/ Friday schedule for during each of the HR1 to HR3 blocks.
	During first or second reinduction block (Protocol II)	Substitute 6 doses of Erwinia asparaginase (25,000 IU/m^2) given on a Monday/ Wednesday/ Friday schedule starting at day 8 during the first or second reinduction block (Protocol II). If a reaction occurs to PEG-ASP given on day 8 of the first or second reinduction block, then six doses of Ewinia asparaginase should be administered as above, starting 1-2 days after the dose of PEG-ASP

4.3.2.3 Cyclophosphamide

Table 4.3.2.3: Dose Modification for Cyclophosphamide

Event	Cyclophosphamide
Hematuria	Omit cyclophosphamide in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, consider the use of MESNA as outlined in Section 4.3.1
CrCl < 10 mL/min/1.73 m^2	Reduce cyclophosphamide by 50%.

4.3.2.4 Cytarabine (Ara-C)

Table 4.3.2.4: Dose Modifications for Cytarabine (Cytosine Arabinoside)

Event	Cytarabine
Fever	Do not withhold Ara-C for fever if it is likely to have been caused by the Ara-C.
Grade 3-4 rash	Withhold until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone.
Grade 3-4 conjunctivitis	Withhold until resolved. Make up missed doses and consider concurrent treatment with corticosteroid ophthalmic drops (optional).
Severe infection	Withhold until resolved. Make up missed doses.
CrCl < 60 mL/min/1.73 m^2	Withhold until resolved and omit if recovery requires > 3 weeks

Table 4.3.2.4: Dose Modifications for Cytarabine (Cytosine Arabinoside)	
Event	**Cytarabine**
Grade 2 or higher neurotoxicity (including ataxia, nystagmus, dysarthria, dysmetria, seizures, encephalopathy)	Hold high-dose cytarabine and do not give any further doses of high-dose cytarabine (HR1 and HR3 blocks). Low-dose cytarabine may be given in patients who have experienced neurotoxicity with high-dose cytarabine.

4.3.2.5 Daunorubicin or Doxorubicin

Table 4.3.2.5: Dose Modification for Daunorubicin or Doxorubicin	
Event	**Daunorubicin or Doxorubicin**
EF < 50% or SF < 27%	Skip scheduled dose. Future doses may be given if cardiac function documented to be acceptable.
Severe infection or mucositis (grade 3-4) and ANC < 500/μL (0.5×10^9/L)	Delay during phases other than Induction. During induction, continue administration. Subsequent doses should be given at full dose.
Direct Bilirubin 1.2-3 mg/dL	50% dose reduction
Direct Bilirubin 3.1-5 mg/dL	75% dose reduction
Direct Bilirubin > 5 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

4.3.2.6 Etoposide

Table 4.3.2.6: Dose Modifications for Etoposide	
Event	**Etoposide**
Allergic Reaction	Premedicate with diphenhydramine or similar antihistamine (1-2 mg/kg slow IV push). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension.
Hypotension	If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.
Creatinine clearance 10-50 mL/min/1.73 m^2	Dose reduce by 25%

Table 4.3.2.6: Dose Modifications for Etoposide	
Event	**Etoposide**
Creatinine clearance < 10 mL/min/1.73 m^2,	Dose reduce by 50%
Direct bilirubin is > 2 mg/dL	Dose reduce by 50%
Direct bilirubin is > 5 mg/dL	Hold dose.

4.3.2.7 Ifosfamide

Table 4.3.2.7: Dose Modification for Ifosfamide	
Event	**Ifosfamide**
Gross hematuria	For persistent gross hematuria occurring during the ifosfamide cycle, withhold further ifosfamide.
Grade 4 neurotoxicity	Consider administration of methylene blue at 2 mg/kg [Maximum dose: 50 mg] on the day this occurs. The methylene blue dose may be repeated at 4 hours and 8 hours after ifosfamide administration, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Hypersensitivity, renal impairment and glucose-6-phosphate dehydrogenase (G-6PD) deficiency are contraindications to administer methylene blue.

4.3.2.8 High-Dose Methotrexate (HD MTX) and Leucovorin Rescue

Review of methotrexate dosing on AIEOP-BFM-based protocols indicated that excessive methotrexate toxicity has not been encountered in patients > 2 m^2 who receive more than 10 grams of methotrexate. The investigator should base the methotrexate on the patient's meter-squared dosing and not cap at 10 grams of methotrexate.

Blood samples for the determination of creatinine and ALT values must be drawn immediately within 72 hours prior to a course of intravenous MTX. Blood samples for ALT should not be drawn immediately following the MTX infusions as 100% of patients are expected to have significant elevations at that time.

Table 4.3.2.8: Dose Modification of High-Dose Methotrexate	
Event	**High-Dose Methotrexate**
Creatinine is > 1.5 x baseline or creatinine clearance < 65 mL/minute/1.73m^2	Postpone course. If renal function does not recover, omit MTX. Do not give HD MTX to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase.
ALT 10 – 20 X ULN	Give HDMTX without modification. If problem recurs with next course of HDMTX consider discontinuing TMP/SMX and delay HDMTX until ALT <10 X ULN.
ALT 10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
ALT > 20 X ULN	Discontinue TMP/SMX. Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
ALT > 20 X ULN for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given.
Direct hyperbilirubinemia of > 2.0 mg/dL	Hold IV MTX
Grade 3-4 mucositis	Hold IV MTX. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m2/hr and continue increased leucovorin as above.

4.3.2.9 Intrathecal Methotrexate / Triple Intrathecal Therapy

Table 4.3.2.9: Dose Modification for Intrathecal Methotrexate / Triple Intrathecal Therapy	
Event	**Methotrexate / Triple Intrathecal Therapy**
Systemic Toxicity (myelosuppression, mucositis)	No dose reduction. Leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered.
Acute neurotoxicity	Consider holding the next dose of IT therapy, or substituting IT Ara-C for one dose of IT MTX or triple IT therapy.

Table 4.3.2.9:	Dose Modification for Intrathecal Methotrexate / Triple Intrathecal Therapy
Event	**Methotrexate / Triple Intrathecal Therapy**
Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via LP	Ommaya catheter may be used in place of IT therapy. Intraventricular chemotherapy should be given according to the same schedule but at 50% of the corresponding age-based doses that would be given by LP.
Viral, bacterial or fungal meningitis	Omit until resolved.

4.3.2.10 PO Methotrexate (MTX) and 6-Mercaptopurine (MP)

Doses may be interrupted during Induction Ib and the 2 applications of protocol IIb but doses should not be modified unless there is evidence of TPMT polymorphisms.

- If homozygous deficient for TPMT, administer 10% of the original dose.
- If heterozygous for TPMT, administer 30-50% of the original dose and escalate to 100% dose as tolerated.
- If wild type, continue at original dose.

During Interim Maintenance and Continuation blocks the aim is to adjust doses to maintain the ANC between 750 and 1500/μl (0.75 and 1.5 x 10^9/L) and the platelet count between 75,000 and 150,000/μl (75 and 150 x 10^9/L).

Start maintenance at 100% doses and DO NOT give higher doses at the start of continuation therapy even if the subject tolerated higher doses throughout interim maintenance.

During continuation therapy, if the ANC is > 1500/μl (1.5 x 10^9/L) and platelets > 150,000/μl (150 x 10^9/L) for ≥ 8 weeks, the dose of mercaptopurine should be escalated by 25%. Otherwise keep at 100% of dose.

If the subsequent monthly ANC is > 1500/μl (1.5 x 10^9/L):

1) Keep mercaptopurine at the 125% dose and increase oral methotrexate by 25% to a dose of 25 mg/m^2.
2) Continue to increase the mercaptopurine and oral methotrexate dose in 25% steps alternatively every eight weeks as outlined above if ANC > 1500/μl (1.5 x 10^9/L) and platelets > 150,000/μl (150 x 10^9/L) persists. There are no maximum doses for mercaptopurine and methotrexate.

Dose Reduction for Falling Neutrophil Counts

If the neutrophil count falls to between 500/μl (0.5 x 10^9/L) and 750/μl (0.75 x 10^9/L):

- HALVE the dose of mercaptopurine and oral methotrexate

If neutrophil count is < 500/μl (0.5 x 109/L):

- STOP mercaptopurine and methotrexate. ONLY RESTART when the count is over 750/μl (0.75 x 10^9/L). Restart at 100% of last dose when neutrophil > 750 μl (0.75 x 10^9/L).

If counts fluctuate significantly when restarting at 100% of last dose, starting at 50% and titrating upwards is permissible to avoid frequent interruptions of mercaptopurine exposure (this maneuver is often not necessary).

Dose Reduction for Falling Platelet Counts

If the platelet count is < 75,000/μl (75 x 10^9/L):

- HALVE the dose of mercaptopurine and methotrexate.

If the platelet count is <50,000/μl (50 x 10^9/L):

- STOP mercaptopurine and methotrexate. ONLY RESTART when the count is greater than 75,000/μl (75 x 10^9/L). Restart at 100% of last dose when platelet count > 75,000/μl (75 x 10^9/L).

If counts fluctuate significantly when restarting at 100% of last dose, starting at 50% and titrating upwards is permissible to avoid frequent interruptions of mercaptopurine exposure (this maneuver is often not necessary).

4.3.2.11 Steroids (Dexamethasone and Prednisone)

Table 4.3.2.11: Dose Modifications for Dexamethasone

Event	Dexamethasone
Hypertension	Dose should not be reduced.
Hyperglycemia	Dose should not be reduced.
Pancreatitis	Do not modify dose for asymptomatic elevations of amylase and/or lipase. Hold steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain >72 hours and > Grade 3 amylase elevation (> 2x ULN). Consider resuming once improved. Do not make up missed doses.
Severe psychosis	Dexamethasone dose may be decreased by 50% for severe psychosis or switch to prednisone.
Osteonecrosis	Do not modify corticosteroid therapy for osteonecrosis Grade 1 (clinically

Table 4.3.2.11: Dose Modifications for Dexamethasone	
Event	**Dexamethasone**
	asymptomatic, radiographic finding only). For ≥ Grade 2 avoid prolonged treatment with dexamethasone for 6 months and until joint symptoms have resolved and any MRI findings have improved (if applicable).

4.3.2.12 Thioguanine

Doses may be interrupted during the 2 applications of protocol IIb but doses should not be modified unless there is evidence of TPMT polymorphisms.

- If homozygous deficient for TPMT, administer 10% of the original dose.
- If heterozygous for TPMT, administer 30-50% of the original dose and escalate to 100% dose as tolerated.
- If wild type, continue at original dose.

4.3.2.13 Vincristine

Table 4.3.2.13: Dose Modification for Vincristine	
Event	**Vincristine**
Grade ≥ 3 neuropathic pain	Hold dose(s). When symptoms subside, resume at 50% previous dose (maximum dose: 1 mg), then escalate to full dose as tolerated.
Vocal cord paralysis	Hold dose(s). When symptoms subside, resume at 50% previous dose (maximum dose: 1 mg), then escalate to full dose as tolerated.
Grade ≥ 3 motor neuropathy	Consider holding dose(s). When symptoms subside, consider resuming at 50% previous dose (maximum dose: 1 mg), then escalate to full dose as tolerated.
Jaw pain	Do not modify dose.
Direct bilirubin 3.1 - 5 mg/dL	50% dosage decrease (maximum dose: 1 mg)
Direct bilirubin 5.1 - 6 mg/dL	75% dosage decrease (maximum dose: 0.5 mg)
Direct bilirubin > 6 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.
Grade ≥ 3 constipation or ileus	Consider holding dose(s). When symptoms subside, resume at 50% previous dose (maximum dose: 1 mg), then escalate to full dose as tolerated.

4.4 Blinding/Unblinding

Not applicable for this open-label study.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the patient's medication diary, medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Key to Abbreviations: IA - Induction A; IB - Induction B; HR1-HR3 - High Risk Blocks; R1 - Reinduction #1; IM - Interim Maintenance; R2 - Reinduction #2; C - Continuation; EOT - End of Treatment; F/U - Follow-up

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table

Procedure	Screening[a]	IA	IB	HR1	HR2	HR3	End I/HR Blocks	R1	IM	R2	C	HSCT Subjects[b] WITH post-HSCT Dasatinib	EOT[c]	F/U[d]	Notes
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Medical History	X														
Physical Examination	X	X	X	X	X	X		X	X	X	X	X	X	X	Physical exam includes vital signs (heart rate, respiratory rate, blood pressure), height and weight, performance status, and extramedullary assessment prior to the start of each block. End of I/HR blocks perform extramedullary exam only for disease assessment.
Assessment of adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	
HSCT Summary												X			For subjects who receive a HSCT, summary data will be collected.
Chest X-Ray	X														
12-Lead ECG	X	X						X							Prior to the start of each indicated block and as clinically indicated.

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table															
Procedure	**Screening[a]**	**IA**	**IB**	**HR1**	**HR2**	**HR3**	**End I/HR Blocks**	**R1**	**IM**	**R2**	**C**	**HSCT Subjects[b] WITH post-HSCT Dasatinib**	**EOT[c]**	**F/U[d]**	**Notes**
Echocardiogram or MUGA as per local practice	X							X		X					Prior to the start of each indicated block and as clinically indicated.
CBC & Differential	X	X	X	X	X	X		X	X	X	X	X	X		Prior to the start of each block and as indicated **NOTE: In HR1, HR2 and HR3 every 2 days after completion of chemotherapy until recovery as defined in sections 4.3.1.3-4.3.1.5.**
Serum Chemistry	X	X	X	X	X	X		X	X	X	X	X			Chemistry panel includes: BUN (or UREA), creatinine, HCO3, ALT, AST, total bilirubin, direct bilirubin (at screening and if clinically indicated), LDH, Na, K, Cl, Mg, PO4, total serum or ionized Ca and uric acid. Prior to the start of each block and as clinically indicated
Pregnancy Test	X	X	X	X	X	X		X	X	X	X	X	X		For women of childbearing potential pregnancy tests must be performed monthly. The pregnancy test at screening must be performed within 24 hours prior to the start of dasatinib.
CSF sample and analysis	X		X	X	X	X		X		X			X		Cell count including RBC and WBC and cytopathology including blast cells performed at each intrathecal dose
Mutation analysis	X													X	Mutation testing performed at baseline and if evidence of relapse during follow-up. Mutation testing at baseline will be performed off of previously banked diagnostic samples. Bone marrow is preferred specimen, peripheral blood is also acceptable.
Bone Marrow Blast %	X		X	X			X						X	X	And as clinically indicated to confirm relapse

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table															
Procedure	**Screening**[a]	**IA**	**IB**	**HR1**	**HR2**	**HR3**	**End I/HR Blocks**	**R1**	**IM**	**R2**	**C**	**HSCT Subjects**[b] **WITH post-HSCT Dasatinib**	**EOT**[c]	**F/U**[d]	**Notes**
Cytogenetic or Molecular analysis for Philadelphia Chromosome status	X														To be performed via local practice
Bone Marrow MRD Assessment	X		X	X			X					X	X	X	Bone marrow MRD assessments will be assessed via: 1) PCR for Ig/TCR gene rearrangement, 2) PCR for BCR-ABL ratio, and 3) multiparameter flow cytometry. Bone marrow samples prior to each indicated treatment block should be obtained once peripheral blood counts have recovered. Subjects with HSCT and post-HSCT dasatinib should have a bone marrow MRD assessment at 3 and 12 months after transplant. Additional assessments as clinically indicated. If a bone marrow cannot be obtained, assessment could be done from peripheral blood provided the peripheral blood percentage of blasts is ≥ 40%. See Lab Manual for details.
Assessment of survival and second malignancies														X	All subjects should be contacted by phone every 3 months if not seen at the site. Assessment must be performed at the 3 and 5 year milestones following 1st dose of dasatinib. A visit window of one month after each of these milestones is acceptable. In subjects remaining event free at 3 and 5 years, assessments at 3 and 5 years should include at a minimum: CBC with diff, PE for extramedullary relapse and second malignancy. Any death or second malignancy should be reported within

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table

Procedure	Screening[a]	IA	IB	HR1	HR2	HR3	End I/HR Blocks	R1	IM	R2	C	HSCT Subjects[b] WITH post-HSCT Dasatinib	EOT[c]	F/U[d]	Notes
															1 and 4 weeks, respectively, of the investigator or study personnel being informed while the subject is on study. See Section 3.1 for details.
Cranial Irradiation									X						Cranial irradiation during interim maintenance for patients with CNS3 disease only
Dispense Dasatinib		X	X	X	X	X		X	X	X	X	X			

[a] Screening activities should be conducted within 21 days prior to treatment with dasatinib, except the screening CBC, and serum chemistries which should be performed within 72 hours prior to the start of dasatinib therapy. The pregnancy test at screening must be performed within 24 hours prior to the start of dasatinib. If test results for these assessments are available within the above time periods, repeat testing is not necessary. Screening bone marrow MRD and mutation detection assessments will be performed on samples that have been previously banked prior to this study. No additional bone marrow sample needs to be collected at screening.

[b] Subjects who receive post-HSCT dasatinib should be assessed monthly while receiving dasatinib. Subjects who undergo HSCT and opt not to receive post-HSCT dasatinib may proceed to the EOT assessment.

[c] All subjects will be followed for a minimum of 30 days after the last dose of dasatinib to assess dastinib related adverse events. Additional follow-up visits will be required every 4 weeks until all dasatinib related toxicities resolve to baseline values (or CTC Grade ≤ 1), stabilize, or are deemed irreversible. Refer to Section 5.3 for timing for the end of treatment procedures.

[d] Assessments yearly for up to 5 years after the completion of therapy with dasatinib for all subjects, with or without HSCT. Mutation analysis in the blood and bone marrow assessment for % blasts and MRD should only be performed to document relapse if clinically indicated. Adverse event assessment during follow-up is only for ongoing dasatinib related toxicities until resolved to baseline values (or CTC Grade ≤ 1), stabilize, or are deemed irreversible.

Table 5.1B: Long-Term Growth & Development and Bone Mineral Content				
Assessments	**Baseline[a]**	**Annually During Treatment**	**Annually for 5 years after completing dasatinib**	**Notes**
Height / Weight	X	X	X	
X-ray of Left Hand & Wrist for assessment of bone-age	X	X	X	
Pubertal status (Tanner Stage)	X	X	X	Visual exam only (See Appendix 7). Done at baseline and then yearly until 5 years after completion of therapy with dasatinib. Assessments performed 1 year from start of treatment for HSCT patients and annually for 5 years following dasatinib completion.
Free T4, TSH	X	X	X	
FSH, LH in children ≥ 8 years of age	X	X	X	
IGF-1, IGFbeta-3	X	X	X	
Electrolytes	X	X	X	
Urinary N-Telopeptide	X	X	X	
Bone Alkaline Phosphatase	X	X	X	
Bone densitometry (DXA scans)	X	X	X	For children < 5 years of age, DXA scanning may be omitted. Once a child is ≥ 5 years of age, DXA scanning required yearly until 5 years after completion of therapy with dasatinib. See section 5.3.3.

[a] Baseline assessments should be performed within 3 weeks before starting dasatinib except DXA scans and bone age x-rays which can be done within a window of 3 weeks prior or 4 weeks after starting dasatinib.

5.2 Study Materials

Study sites will receive the following additional study material:

- NCI CTCAE v 4.0 booklets for grading criteria
- Dasatinib Investigator Brochure
- Instruction Manual for IVRS
- Instructional manual and/or kits for collection, processing and shipment of blood and tissue samples
- Instructional manual and requisition forms for submission of local safety laboratory data
- Medication diary

5.3 Safety Assessments

Informed consent must be obtained prior to any study screening procedures that would not have been performed as part of normal subject care. Screening activities should be conducted within 3 weeks prior to treatment with dasatinib, except the screening CBC, and serum chemistries and which should be performed within 72 hours prior to the start of dasatinib therapy. The pregnancy test at screening must be performed within 24 prior to the start of dasatinib. Collection of samples for long term growth and bone mineral content should be performed within 3 weeks before starting dasatinib. DXA scans and bone age x-rays can be done within a window of 3 weeks prior or 4 weeks after starting dasatinib. If test results for these assessments are available within the above time periods, repeat testing is not necessary.

End of treatment procedures must be completed within 30 days after the last dose of dasatinib. The end of treatment visit will depend on a subject's course of treatment and will be performed after:

- Completion of 104 weeks of chemotherapy in subjects who do not receive a HSCT
- Completion of 12 months of post-HSCT dasatinib in subjects who receive a HSCT and post-HSCT dasatinib
- Completion of at least consolidation block 1 or 3 (HR1 or HR3) in subjects who received a HSCT but opt for no post-HSCT dasatinib
- Subject withdrawal from the study as per any of the reasons listed in Section 3.5

All subjects will be followed for a minimum of 30 days after the last dose of dasatinib to assess dasatinib-related adverse events. Additional follow-up visit(s) will be required every 4 weeks until all dasatinib related toxicities resolve to baseline values (or CTC Grade ≤ 1), stabilize, or are deemed irreversible.

Any additional medical testing and procedures, whether more frequent or in addition to those described, should be performed as medically indicated.

5.3.1 Physical Examination

Physical exam includes vital signs (heart rate, respiratory rate, blood pressure), height and weight, performance status, and extrameduallary assessment. Extramedullary assessment of disease outside of the bone marrow and CNS, including hepatosplenomegaly by palpation or other extramedullary involvement proven by biopsy. After completion of treatment, extramedullary assessment must be performed 3 and 5 years following the first dose of dasatinib in subjects remaining free of any evidence of progression. A visit window of 1 month after but not before each of these milestones is acceptable.

5.3.2 Laboratory Test Assessments

All laboratory assessments should follow the schedule as detailed in Table 5.1A and Table 5.1B.

5.3.2.1 Serum Hematology Tests

Serum hematology tests include CBC and full differential counts. Hematology tests should be conducted according to Table 5.1A and as clinically indicated when relapse/progression is suspected.

5.3.2.2 Serum Chemistry Tests

Chemistry panel includes: BUN (or urea), creatinine, HCO_3, ALT, AST, total bilirubin, direct bilirubin (at screening and if clinically indicated), LDH, Na, K, Cl, Mg, PO_4, total serum or ionized Ca and uric acid.

During the long-term follow up period (5 years after completion of dasatinib therapy) serum chemistries need only include the electrolyte parameters (Na, K, CL, Mg, PO4, serum or ionized Ca).

5.3.2.3 CSF examination

CSF sampling should occur at the same time that subjects receive intrathecal therapy (IT) and CSF cell counts should be assessed according to the schedule in Table 5.1A.

5.3.2.4 Pregnancy Test

For women of child-bearing potential, a serum or urine pregnancy test should have a minimum sensitivity of 25 IU/L or equivalent units of βHCG. All on-study pregnancy testing should follow the schedule detailed in Table 5.1A.

5.3.3 Long-term Growth and Development and Bone Mineral Content

Assessments for bone growth, development and bone mineral content should follow the schedule detailed in Table 5.1B. The physical exam, laboratory and radiological assessments are further summarized in Table 5.1B.

See Appendix 7 for details regarding the Tanner staging. Bone age will be assessed by an anteroposterior radiograph of the left hand and wrist.

DXA Scanning

Bone mineral content and density will be evaluated with dual-energy-x-ray absorptiometry (DXA). Bone mineral content, density and bone area will be evaluated with dual energy x-ray absorptiometry (DXA) utilizing pediatric normal reference ranges and pediatric-specific scanner software. If possible, subjects should be scanned on the same make and model of DXA scanner throughout the study. For subjects below the age of 20 years, scans of the posterior-anterior (PA) lumbar spine (L1-L4) and if feasible total body less head (TBLH) should be performed. Subjects in long-term follow-up who reach the age of 20 years should have scans of posterior-anterior (PA) lumbar spine (L1-L4), total hip and femoral neck performed[54]. The decision to administer sedation medication to reduce ancillary movement and alleviate distress to the subject should be carefully considered.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

5.4.1.1 Bone Marrow Assessment

A bone marrow aspirate (biopsy optional) will be utilized in determining the primary endpoint of the trial and is one of the most critical elements of data for collection. A bone marrow assessment will be performed for cytology, conventional cytogenetics and MRD assessment as outlined in Table 5.1A. Since these assessments are critical in determining EFS, a bone marrow aspirate should be performed as clinically indicated if relapse is suspected in order to document an event for the primary endpoint of this trial.

Detailed instructions for the processing and shipment of samples for MRD assessment will be provided to all study sites in a separate manual.

5.4.2 Secondary Efficacy Assessments

5.4.2.1 Overall Survival and Secondary Malignancy

Overall survival and secondary malignancies should be assessed according to the schedule in Table 5.1A. As these data contribute to the analysis of the primary endpoint and the key secondary endpoint of safety, timely reporting of these events is important. Deaths and second malignancies should be reported in the case report form within 1 and 4 weeks, respectively of the investigator or study personnel being informed.

To fulfill the objective of reporting the 3 year and 5 year EFS rates, all subjects should have a follow-up visit performed at the 3 year and 5 year timepoint (or within 1 month thereafter) following first dose of dasatinib. For subjects remaining free of any evidence of progression, this visit should include an assessment for secondary malignancies.

5.4.3 Mutation Analysis

Detailed instructions for the processing and shipment of samples for mutation analysis will be provided to all study sites in a separate manual.

5.5 Pharmacokinetic Assessments

Not Applicable.

5.6 Pharmacodynamics Assessments

Not Applicable.

5.7 Pharmacogenomic/Pharmacogenetic Assessments

Not Applicable.

5.8 Outcomes Research Assessments

Not Applicable.

5.9 Other Assessments

Not Applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 5 half lives of dasatinib (ie 24 hours) of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. As noted in section 4.3.1.11, AEs do not need to be reported for subjects going on to HSCT unless considered related to the investigational product.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All adverse events, including those that are serious, will be graded according to the NCI CTCAE version 4.0.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for all BMS clinical study AEs:

- Related - There is a reasonable causal relationship to study drug administration and the AE.
- Not Related - There is not a reasonable causal relationship to study drug administration and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures described in Section 6.1.1

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing or any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An independent Data Safety Monitoring Board (DSMB) is in place for this trial. The DSMB was initiated prior to the start of the study and will review data for all patients starting from the date each subject signs informed consent. The DSMB will review safety data to determine if unacceptable toxicity rates warrant a recommendation to discontinue the study due to excessive and unacceptable toxicities. Specifics of DSMB activities will be detailed in the DSMB charter. An interim analysis will be performed for the DSMB members to review data. Guidelines for stopping the study based on excess mortality are pre-specified.

The independent DSMB will communicate their recommendation regarding the continuation of the trial to the Sponsor, COG and EsPhALL. The accrual will continue during the review of the data.

Schedules of analyses and meeting of the DSMB will be specified in the DSMB charter.

Guidelines for stopping the trial will be used to ensure that the study be terminated as early as possible if its application is associated with a treatment related mortality higher than acceptable with standard treatments. In the standard treatment, the rates of deaths that will be considered acceptable are rates lower than 3% in the induction period or 7% during any further study time point, excluding deaths after HSCT.

The DSMB may recommend to stop the trial if there is a high observed to expected rate of death over this acceptable limit.

The tables below show the minimum number of treatment related deaths in induction (after day 15) and in continuous complete remission (CCR), excluding deaths after HSCT, at which the DSMB and the study steering committee should evaluate stopping the study. The method applied for developing these guidelines follows a Bayesian approach, extending that of Metha and Caine[55, 56]. In these guidelines, the maximum acceptable level of probability of treatment related

deaths in induction (IND) and in CCR were pIND = 3% and pCCR = 7% respectively. 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 Table 7A and Table 7B below are the experimental results that give a posterior probability of 90% or more, of observing pIND ≥ 3% and pCCR ≥ 7%, respectively.

Table 7A: Guidelines for Early Stopping Due to Treatment Related Mortality in Induction

No. of subjects on treatment	No. of Death Events
11-36	2
37-58	3
59-82	4
83-106	5

Table 7B: Guidelines for Early Stopping Due to Treatment Related Mortality in CCR

No. of Subjects on Treatment	No. of Death Events
11 - 15	2
16 - 25	3
26 - 35	4
36 - 45	5
46 - 56	6
57 - 67	7
68 - 78	8
79 - 90	9
91 - 101	10

Interim Monitoring for Inferior Event-Free survival

Assumptions specific to efficacy are presented in Section 8.1 Interim analysis will be conducted to protect against poor EFS. Under the exponential assumption, three-year EFS of 78% (lower limit the 95% confidence interval for an observed ≥ 88% EFS rate) translates to a hazard rate of 0.083. Interim analysis will be based on the estimated hazard rate, testing the alternate hypothesis that the hazard rate is > 0.083 (at an alternative of 0.119 which corresponds to a 3-year EFS of 70%).

Testing H0: $S(3) \geq 0.78$ vs. H1: $S(3) < 0.78$ where S(3) is the 3-year EFS rate.

Test statistics:

Z_i = (lambda_hat – lambda_0) / sqrt (lambda_0 / T_i)
Where
Z_i = value of the test statistic at the time of the ith interim analysis
Lambda_hat = estimate of hazard rate at the time of ith interim analysis
Lambda_0 = estimate of hazard rate under the null hypothesis
T_i = Total time at risk for patients at the time of ith interim analysis

The αt^2 spending function will be used to maintain an overall one-sided Type I error rate of 10%. The total number of expected events is 26. Interim analyses will be performed as close as possible to when 33%, 66%, 100% of the expected information (events), respectively have been observed. The corresponding critical values (boundaries) are Z_c: 2.29, 1.76, and 1.37.

At the time of interim monitoring, if Z_i > Z_c, then the monitoring boundary would be crossed and the study will be stopped for inferior EFS.

8 STATISTICAL CONSIDERATIONS

[redacted]

8.2 Populations for Analyses

The following data sets will be used in this study:

- All treated/evaluable subjects: Subjects who received at least one dose of dasatinib. Demographic, baseline characteristics, safety, efficacy and bone growth and maturation assessments will be performed on all treated/evaluable subjects.
- Mutation Data Set: All treated subjects who have mutation data available will be included in the mutation data set.

8.3 Endpoint Definitions

8.3.1 Primary Endpoint

The 3-year event-free survival (EFS) rate is the primary endpoint where EFS is defined as the time from the starting date of dasatinib until an event and will be computed using binomial proportions.

Events for EFS are defined as ANY first one of the following:

- Lack of complete response in bone marrow (see below definition)
- Relapse at any site
- Development of second malignant neoplasm
- Death from any cause

The primary analysis will compare the 3-year EFS rate of dasatinib plus chemotherapy with the following historical controls:

1. 3-year EFS rate of chemotherapy alone from the AIEOP-BFM 2000 trial
2. 3-year EFS rate of continuous imatinib added to chemotherapy from the amended EsPhALL trial.

Response Criteria for EFS

Criteria for Response in Bone marrow (BM) are:

- M1: < 5% lymphoblasts (Complete Response in BM)
- M2: 5 - 25% lymphoblasts
- M3: > 25% lymphoblasts

For the primary analysis, complete response (CR) in the bone marrow will be assessed between the start of dasatinib and completion of consolidation block 3 (HR3)/start of first reinduction (Protocol II). Those subjects who reach CR within this window will be considered at risk for relapse or death without relapse.

Those who do not reach CR (ie, M1 bone marrow) between the start of dasatinib and the last day of consolidation block HR3/start of first reinduction (Protocol II) will be considered as an event (resistant). For subjects who undergo HSCT, the date of the HSCT will not be considered as an event. These subjects will continue to be followed for an event during and after HSCT.

The primary analysis will be performed once the last subject treated has passed the 3-year follow-up period to ensure all subjects have the opportunity for 3-year EFS assessments. Subjects without an event and lost to follow-up before their 3-year assessments will not be considered as an event in the primary analysis, however, will be considered an event in the sensitivity analysis. The term "lost to follow-up" should be interpreted as discontinuation from the study resulting in a stop of any further data collection.

Relapse Criteria for EFS

Relapse is defined as any recurrence of disease, whether in the marrow or extramedullary site:

- CNS relapse: Positive cytomorphology and 5 or more WBC/μL in CSF, or any signs of CNS leukemia such a facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.
- Testicular relapse: Must be documented by testicular biopsy, in the absence of concomitant bone marrow or CNS relapse.
- Bone marrow relapse: Patients with an M3 marrow (>25% blasts) after first CR has been achieved

Relapse should be histopathologically determined.

All BM samplings, CSF evaluations, physical examinations and death information subsequent to achievement of a CR will be utilized to determine relapse, second malignancy and death for EFS analysis.

Sensitivity analysis of the primary endpoint of EFS will include stratification of subjects by high risk and low/standard risk[57,58]. These risk groups are defined as follows:

Definition of high risk group: MRD at end of Induction 1A ≥ 0.01%

Definition of low/standard risk: MRD at end of Induction 1A of < 0.01%

8.3.2 Secondary Endpoints

8.3.2.1 Safety and Feasibility

Treatment related mortality shall define the endpoint of safety and feasibility. A minimum number of treatment related deaths in induction (after day 15) and in continuous complete remission (CCR) will be pre-specified in the stopping rules. Subjects in CCR are patients who reach CR and do not have an event (relapse, death or second malignant neoplasm).

Adverse events and laboratory results will be graded according to the Common Terminology Criteria (CTCAE) Version 4.0. Additional laboratory results that are not graded by CTCAE Version 4.0 will be presented according to the following categories: below normal limits, within normal limits, and above normal limits.

8.3.2.2 Event Free Survival (EFS)

The EFS endpoint is also considered for secondary/sensitivity analyses, including:

1. HSCT considered as an event if the subject discontinues
2. Lost to follow-up considered as an event (at the date of last contact)
3. Induction failures considered as an event at time 0
4. Stratified subgroup analysis of 3-year EFS rates for HSCT status looking at 3 groups: subjects who had HSCT, subjects who were eligible to have HSCT but did not, and subjects who were ineligible for HSCT.
5. Using Kaplan-Meier estimates of EFS probabilities (for overall EFS estimation including the 3-year and 5-year Kaplan-Meier estimates)
6. Stratified by high versus low/standard risk (as defined in Section 8.3.1)
7. Comparing 3-year EFS with results in COG AALL0031 (with alignment of EFS definition)

8.3.2.3 Minimal Residual Disease (MRD)

The MRD levels are the proportion of leukemic cells in a sample at a specific time point. The method of reference is the quantitative PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR). The limit of detection of this assay will be approximately 10^{-4} - 10^{-5} or 0.01% - 0.001%.

PCR for BCR-ABL will be expressed as a ratio of BCR-ABL transcripts compared to a control gene (eg ABL) with log reduction compared to baseline.

8.3.2.4 Complete Remission Rate

Complete remission will be defined as < 5% lymphoblasts in the bone marrow (ie, M1 bone marrow) and CSF with no evidence of other extra medullary disease.

8.3.2.5 BCR-ABL Mutation

A BCR-ABL mutation is defined as the presence of a detectable amino acid substitution in the ABL kinase domain.

8.3.3 Exploratory Endpoints

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics.

8.4.2 Efficacy Analyses

8.4.2.1 Event Free Survival (EFS)

Comparison of 3-Year EFS Rates with Historical, External Controls

The primary analysis will compare the 3-year EFS of dasatinib plus chemotherapy with external historical controls in hierarchical order. The trial will be considered positive if at least the first two comparisons are statistically significant. The comparisons will be as follows:

1. Superiority over chemotherapy alone of AIEOP-BFM 2000
2. Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial
3. Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial

For the analysis of the primary endpoints, a hierarchical testing procedure will be used so that the overall experiment-wise one-sided type I error rate is preserved at 0.05. The difference with the 3-year EFS rate from the chemotherapy alone control arm will be tested first. If that test is significant in favor of dasatinib, then non-inferiority against imatinib plus chemotherapy in the amended EsPhALL trial will be tested second. If that test is significant and non-inferiority of dasatinib is declared, then superiority testing of the difference with the 3-year EFS rate in the continuous imatinib added to chemotherapy arm from the amended EsPhALL trial will be tested last.

The differences in 3-year EFS rates will be computed using binomial proportions of subjects who are free of event at 3 years over all treated subjects. Subjects lost to follow-up without an event will be considered event free in the primary analysis. All subjects will have the opportunity to be followed for 3 years prior to the analysis and the denominator will include all treated/evaluable subjects.

The differences in event rates along with exact 2-sided 90% Clopper-Pearson CI's will be provided. Test for difference in event rates will be carried out using a two-sided χ^2 test. Non-inferiority testing against the study treatment in the amended EsPhALL trial will be carried out using the corresponding 2-sided 90% CI for the treatment difference and comparing the lower confidence limit to the non-inferiority margin of -5%. This margin corresponds to 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only control of the original EsPhALL trial.

All of the above tests will be performed at the 0.05 (one-sided) significance level. Analyses will be conducted in the treated population (ie, subjects enrolled but never treated with study drug will not be part of the co-primary endpoints).

The difference in 3-year EFS rate with the 3-year EFS rate of available historical controls such as COG AALL0031 will be computed using binomial proportions as a secondary objective. When comparing with these controls, the definition of event in EFS may be modified in order to align the endpoints for a relevant comparison.

Overall EFS

Overall estimation of EFS is one of the key secondary endpionts. Overall estimation of the EFS of dasatinib plus chemotherapy will be performed utilizing the Kaplan-Meier (KM) Product Limit method. The medians will be provided with their 2-sided 95% CI computed using the method of Brookmeyer and Crowley. The 3-year and 5-year EFS rates will be computed with the corresponding 95% CI's using Greenwood's formula for computing the standard error will be provided. Analyses of EFS will include KM plots with number of patients at risk.

In the secondary endpoint of overall EFS estimation via the KM method, subjects who neither relapse nor die or who are lost to follow-up will be censored on the date of their last bone marrow, CSF assessment or physical exam, whichever occurs last.

Additionally, sensitivity analyses will be performed on the primary endpoint, EFS as described in section 8.3.2.2.

[redacted]

8.4.2.3 Complete Remission Rate

Complete remission will be assessed between the start of dasatinib and the last day of induction IA in all treated subjects.

[redacted]

Rates

The rates of MRD negative subjects will be computed for each of the time points, and defined as the number of MRD negative among all treated subjects. In order to include all treated subjects in the MRD rate analysis, those without any valid Ig/TCR assessment (eg. missing data) will be considered as MRD positive (ie non-responders) for response rates computations. The exact 2-sided 95% Clopper-Pearson Confidence Interval will be used.

MRD Levels as a Prognostic Factor for EFS Methods

For the 3 methods of MRD evaluation, Kaplan-Meier plots will be used to estimate the time from the MRD assessment until the event given the category of MRD levels (landmark analyses for MRD-negative, very low positive, low positive and high positive). The medians will be provided with their 2-sided 95% CI computed using the method of Brookmeyer and Crowley.

Comparison Between MRD Methods

Concordance tables between the reference test (Ig/TCR) and each of the 2 other methodologies will be done for each of the MRD time points and for 3 different thresholds (0.1 %, 0.01 %, no leukemia cells detected).

McNemar tests will be done on 2 x 2 tables (subjects with $< 0.1\%$ vs. subjects with $\geq 0.1\%$; subjects with $< 0.01\%$ vs. subjects with $\geq 0.01\%$; subjects with no cells detected vs. subjects with cells detected).

Kappa coefficients will be computed on 4 x 4 tables (0.1 %; 0.01 - 0.1 %; detected with a level $< 0.01\%$; undetectable).

To describe the correlation between the methods, Pearson correlation coefficient and graphical methods (Ig/TCR vs. BCR-ABL and Ig/TCR vs. flow cytometry) will be used.

8.4.2.5 Mutation Analysis

BCR-ABL mutation status will be analyzed at baseline and at disease progression or relapse. The specific type and frequency of mutations in BCR-ABL kinase domain will be summarized using descriptive statistics.

[redacted]

8.4.3 Safety Analyses

Death rates during induction as well as in subjects in CCR will be monitored as per the stopping rules described in protocol Section 7.

Overall safety analysis will include the frequency of all adverse events and laboratory abnormalities as well as frequency of dose interruptions, dose reductions and treatment discontinuations for study drug related toxicity. Toxicities will be coded using the most current version at the time of analysis of Medical Dictionary for Regulatory Activities (MedDRA) system organ classes.

In subjects opting to continue dasatinib post HSCT, the safety of dasatinib will be described separately.

[redacted]

8.4.4 Pharmacokinetic Analyses

Not Applicable.

8.4.5 Pharmacodynamic Analyses

Not Applicable.

8.4.6 Pharmacogenomic Analyses

Not Applicable.

8.4.7 Outcomes Research Analyses

Not Applicable.

8.4.8 Other Analyses

Not Applicable.

8.5 Interim Analyses

Interim analyses of efficacy and safety will occur for the Data Safety and Monitoring Board (DSMB) review as described in section 7.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

In the event of any conflict between the publication provisions detailed above and those stated in the clinical trial agreement, the publication terms in the clinical trial agreement shall prevail.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

Term	Definition
ACI	As Clinically Indicated
ADR	Adriamycin
AE	Adverse Event
AIEOP	Associazione Italiana di Ematologia Pediatrica
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotranferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ARA-C	Cytarabine Arabinoside
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCR-ABL	Oncogene fusion protein
BFM	Berlin-Frankfurt-Müenster Leukemia Backbone Therapy
βHCG	Beta Human Chorionic Gonadotropin
Bili	Bilirubin
BM	Bone Marrow
BMS	Bristol-Myers Squibb
BP	Blood Pressure
BP - CMP	Blast Phase Chronic Myeloid Leukemia
BUN	Blood Urea Nitrogen
C2	2nd Cervical Vertebrae
C	Continuation
Ca	Calcium
CBC	Complete Blood Count
cc	cubic centimeter
c-FMS	Macrophage Colony-Stimulating Factor
CF-Rescue	Citrovorum Factor (Leucovorin)
CCR	Complete Cytogenetic Response
CFR	Code of Federal Regulations
CHR	Complete Hematologic Remission
CI	Confidence Interval
Cl	Chloride
Cmax	Peak Serum Concentration
CML	Chronic Myeloid Leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COG	Children's Oncology Group
CPM	Cyclophosphamide

Term	Definition
CrCl	Creatinine Clearance
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
CTA	Clinical Trial Agreement
CYP3A4	Cytochrome P450 3A4
CxRT	Cranial Radiotherapy
DEXA/DXM	Dexamethasone
DFS	Disease Free Survival
DFCI Consortium	Dana Farber Cancer Institute Consortium
DLT	Dose Limiting Toxicity
dL	Deciliter
DNR	Daunorubicin
DOX	Doxorubicin
DSMB	Data Safety Monitoring Board
DXA	Dual-Energy-x-ray absorptiometry
EBV	Epstein - Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event Free Survival
EMA	European Medicines Agency
EOT	End of Treatment
EsPhALL	European InterGroup Study on Post Induction Treatment of Philadelphia Positive Acute Lymphoblastic Leukemia
Etop	Etoposide
FFP	Fresh Frozen Plasma
FISH	Fluorescent in situ Hybridization
FSH	Follicle Stimulating Hormone
F/U	Follow-up
G	Glucose
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
GFR	Glomerular Filtrate Rate
GI	Gastrointestinal
G-6PD	Glucose-6-phosphate dehydrogenase
Gy	Gray (amount of radiation in photon radiation therapy)
H2	Histamine
HC	Hydrocortisone

Term	Definition
HCO3	Bicarbonate
HD	High Dose
HD-ARA-C	High Dose Cytarabine
HD-MTX	High Dose Methotrexate
h or hr	Hour
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HMG COA	3-hydroxy-methyl-glutaryl COA
HR	Hour
HR 1	Consolidation High Risk Block 1
HR 2	Consolidation High Risk Block 2
HR 3	Consolidation High Risk Block 3
HRT	Hormone Replacement Therapy
HSCT	Hematopoietic Stem Cell Transplant
HVL	Half Value Layer
Hyper-CVAD	Hyperfractionated doses of Cyclophosphamide, Vincristine, Adriamycin (Doxorubicin), and Dexamethasone (Methotrexate and Cytarabine also used)
IA	Induction Phase A
IB	Induction Phase B
ICH	International Conference of Harmonization
ID	Identification
IEC	Independent Ethics Committee
IFO	Ifosfamide
IGF-1	Insulin Like Growth Factor - 1
IGFB-3	Insulin like Growth Factor Binding Protein - 3
Ig/TCR	Immunoglobulin and T-cell Receptor
IM	Interim Maintenance or Intramuscular
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiation
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IT	Intrathecal
IU	International Unit
IVRS	Interactive Voice Response System
IV	Intravenous
K	Potassium
KCl	Potassium Chloride
Kg	Kilogram

Term	Definition
KM	Kaplan Meier
L	Liter
LAAM	Levo-alpha-acetyl-methadol
L-ASP	L-Asparaginase
LCV	Leucovorin
LDH	Lactate dehydrogense
LH	Luteinizing Hormone
LP	Lumbar Puncture
LVEF	Left Ventricular Ejection Fraction
MaHR	Major Hematologic Response
Max	Maximum
Min	Minute
Msec	Millisecond
MCyR	Major Cytogenetic Response
MEdDRA	Medical Dictionary for Regulatory Activities
MESNA	2-Mercaptoethane Sulfonate Sodium
mEq	Milliequivalents
meTIMP	Methythionosine-5-Monophosphate
Mg	Magnesium
Mg	Milligram
mm HG	Millimeters of Mercury
mL	Milliliter
6-MP	Mercatopurine
MRD	Minimum Residual Disease
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
MV	Megavolt
N	Number or Sample Size
NA	Not Applicable
Na	Sodium
NaCL	Sodium Chloride
NaHCO3	Sodium Bicarbonate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria
non-TBI	non-total body irradiation
nM	Nanometer
NS	Normal Saline
OS	Overall Survival
OZ	Ounce
PA	Posterior-anterior
PEG-ASP	Polyethylene Glycol Asparaginase

Term	Definition
Ph-	Philadelphia Chromosome Negative
Ph+	Philadelphia Chromosome Positive
pCCR	Probability in Continuous Complete Remission
PCR	Polymerase Chain Reaction
PDGFR	Platelet Derived Growth Factor Receptor
pH	Concentration of Hydronium Ions
pIND	Probability in Induction
PO	Orally
PT	Prothrombin Time
PTL	Platelet
PO4	Phosphate
Q	Every
qPCR	Quantitative Polymerase Chain Reaction
QT; QTc	QT interval; Corrected QT Interval
R1	Reinduction 1
R2	Reinduction 2
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RQ-PCR	Real Time Quantitative Polymerase Chain Reaction
RT-PCR	Real Time Polymerase Chain Reaction
SAE	Serious Adverse Event
SC	Subcutaneous
SFK	Src Family Kinases
Src	Src Tyrosine Kinase
TBI	Total Body Irradiation
TBLH	Total Body Less Head
T-cell	Thymus Cell
6-TG	Thioguanine
TKI	Tyrosine Kinase Inhibitor
TMP/SMX	Trimethoprim/sulfamethoxazole
TSH	Thyroid Stimulating Hormone
T4	Thyroxine
μg	Microgram
μL	Microliter
μM	Micromolar
ULN	Upper Limit of Normal
VCR	Vincristine
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

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APPENDIX 1 MONITORING OF MTX SERUM LEVELS AND INTENSIFICATION OF LCV RESCUE BASED ON ESPHALL PRACTICES

Guidelines for intravenous administration of high dose Methotrexate

Cotrimoxazole should be stopped 7 days before the start of the intravenous infusion and can be recommenced 7 days after.

Prehydration

Time: Start hydration at least 6 hours prior to the commencement of the intravenous methotrexate.

Fluid: 4% glucose with 0.18% normal saline. To each 500 mL add 25 mmol of sodium bicarbonate and 10 mmol of potassium chloride.

Infusion rate: 125 mL/m^2/h (3 L/m^2/day)

NB: Adjust the sodium bicarbonate concentration to maintain the urinary pH between 7 and 8. Do not start the infusion until a urinary pH of at least 7 has been achieved.

Dose of Methotrexate:

Dilute the methotrexate in an appropriate volume of saline (0.9%). Infuse 500 mg/m^2 of methotrexate over 30 minutes and then 4,500 mg/m^2 of methotrexate to be infused over 23.5 hours. Note, even if the infusion is not complete at this time point, it must be stopped.

Hydration during Methotrexate infusion:

Fluid: 4% glucose with 0.18% normal saline. To each 500 mL add 25 mmol of sodium bicarbonate and 10 mmol of potassium chloride.

Infusion rate: Hydration needs to continue during the 24 hours of methotrexate infusion to maintain a combined infusion rate of 125 mL/h. This may be achieved either by using a Y extension set or using both lumens of the central venous line.

Post Methotrexate Hydration:

Continue hydration until Calcium folinate rescue is completed

Fluid: 4% glucose with 0.18% normal saline. To each 500 mL add 25 mmol of sodium bicarbonate and 10 mmol of potassium chloride. Infusion rate: 125 mL/m^2/h (3 L/m^2/day)

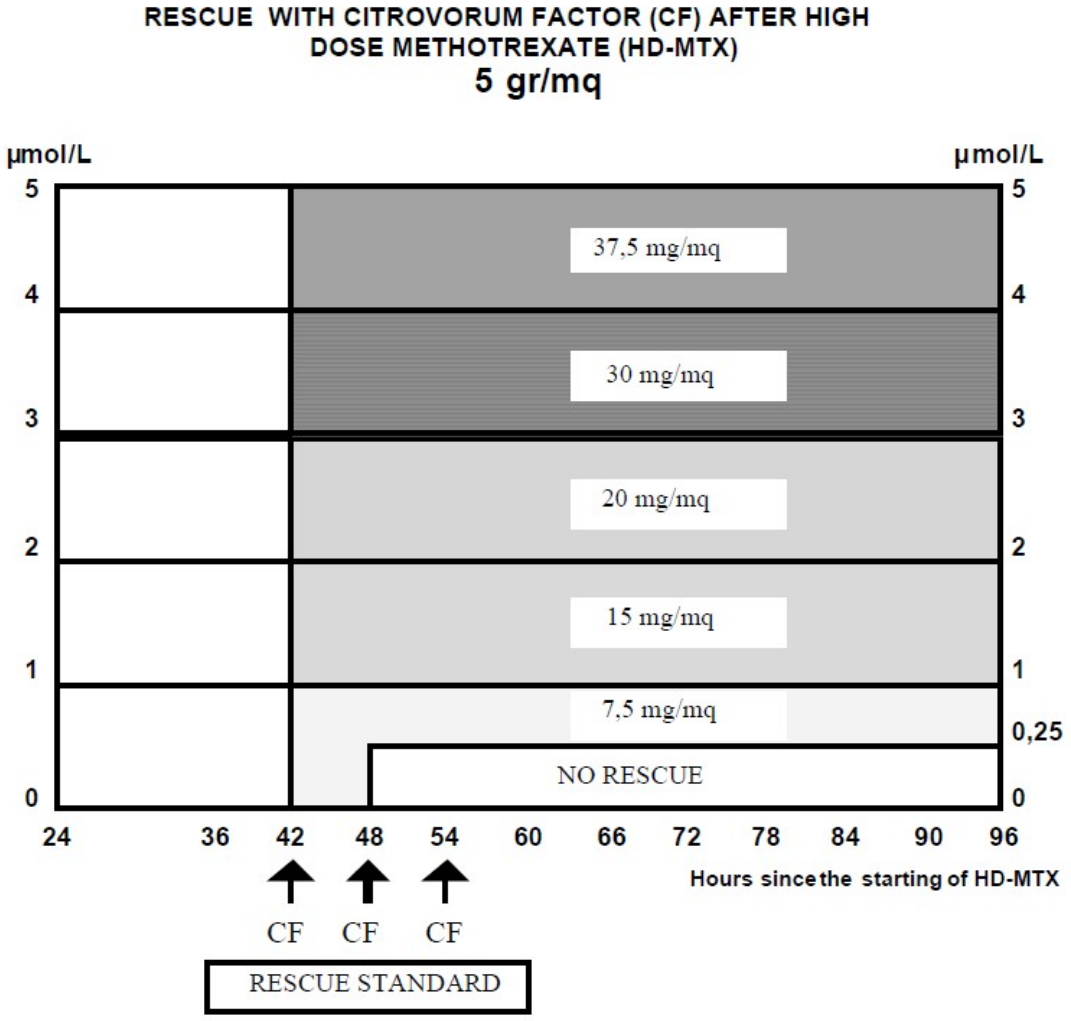
Methotrexate levels: Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤ 0.5 micromol/L (< 1 x 10^{-6} M or 0.227 mg/mL), then do not give more than three doses of Calcium folinate (42, 48 and 54 hours). If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Calcium folinate rescue every 6 hours until MTX levels are < 0.25 micromol/L as per nomogram.

Calcium folinate Rescue: 15 mg/m^2 intravenously at 42, 48 and 54 hours and subsequently only if the plasma methotrexate level is high (see above). Subsequent doses maybe given orally if necessary. Intravenous hydration is stopped when the last dose of Calcium folinate is given.

Intrathecal Methotrexate: This is ideally as close to 2 hours after the start of the methotrexate infusion as possible. The infusion must not be discontinued to carry out the intrathecal administration. Intrathecal methotrexate should not be given once the intravenous methotrexate infusion has been stopped at 24 hours.

Note: Maintain output at 400 mL/m2 at any 4 hour period.

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



APPENDIX 2 HD-MTX INFUSION AND RESCUE GUIDELINES AND FLOW CHART BASED ON COG PRACTICES

When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold TMP-SMX on the days of HDMTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 μM. In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 μM.

For patient's allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (1-2 mg/kg/day, maximum dose 100 mg/day), or atovaquone (30 mg/kg/day if 1-3 mo. or > 2 years, 45 mg/kg/day if between 3 mo. & 2 years) may be considered.

Hold any nonsteroidal anti-inflammatory medications, penicillin, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 μM. In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 μM.

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour for at least 6 hours and until urine specific gravity is ≤ 1.010 and pH is ≥ 7 and ≤ 8. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. Give a bicarbonate bolus (25 mEq/m^2 over 15 min) to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD MTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 μM.

Hour 0: MTX 500 mg/m^2 IV mixed in a final volume of 65 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L and infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 mixed in a final volume of 2935 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L given by continuous IV infusion over 23.5 hours at 125 mL/m^2/hr. Be certain that the HD MTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see below)

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the

fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (See below). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.

If the 24 hour level is < 150 μM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 150 μM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc. described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.4 μM, respectively, give leucovorin (racemic form) at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

Table Appendix 2: Leucovorin Dose Modifications Based Upon MTX Levels			
(36 hr MTX level)	**42 hr MTX level**	**48 hr MTX level**	**Leucovorin Rescue[a]**
Only required if 24 hr level ≥ 150 µM. See guidelines below[b]	1.01 to 9.9 µM	0.41 to 5.9 µM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 µM (draw q12-24 h).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.

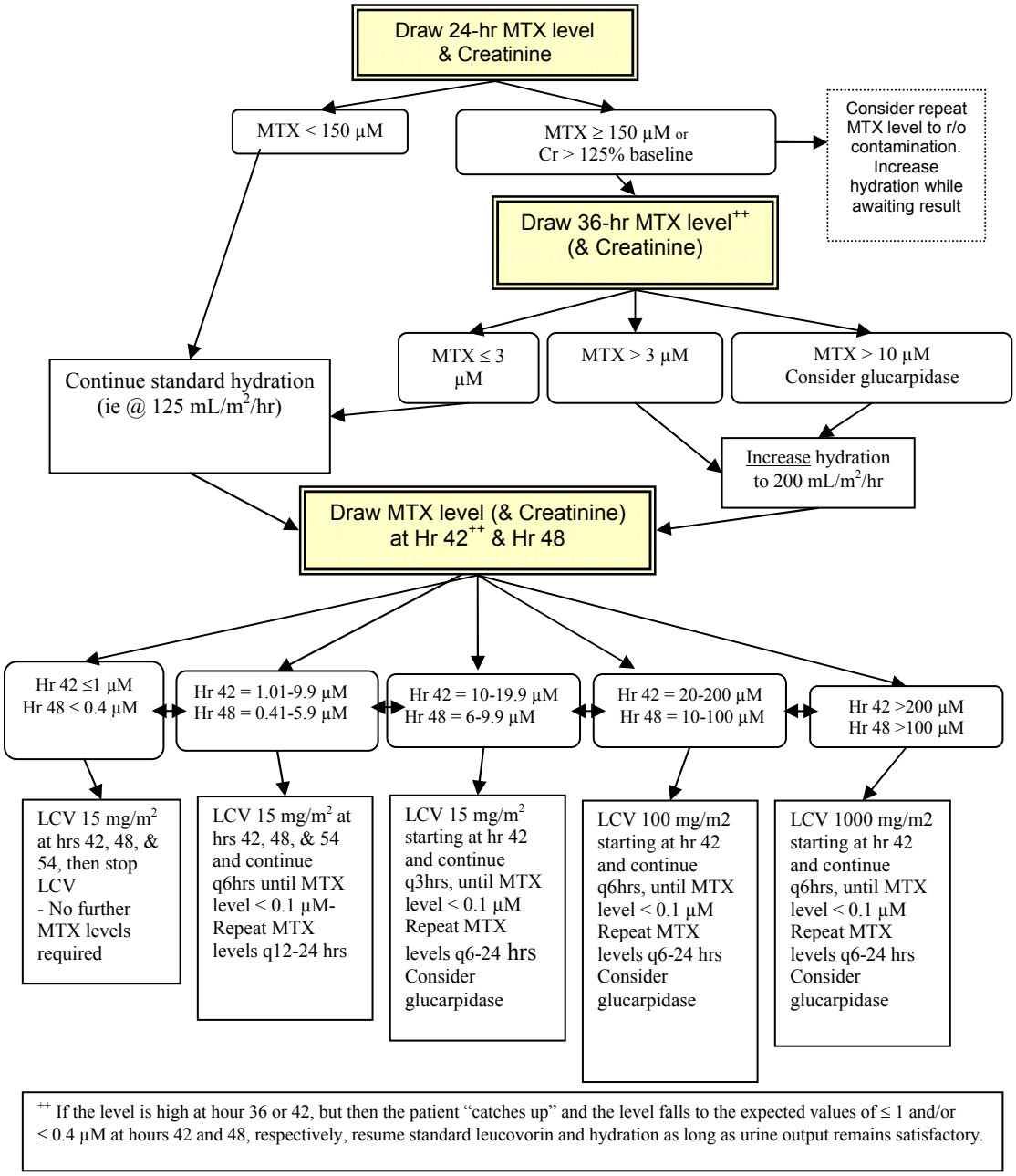
[a] If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

[b] **If the 36 hour level exceeds 3 micromolar**, increase hydration to 200 mL/m2/hr, monitor urine pH to assure a value ≥ 7 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider glucarpidase if 36 hour MTX level exceeds 10 micromolar** (see below).

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2). To obtain supplies of glucarpidase (carboxypeptidase G_2, Voraxaze™) in the US contact the Voraxane 24-hour Access Call Center. Additional information can be found at http://www.btgplc.com/products/speciality-pharmaceuticals/voraxaze. Canadian sites can contact McKesson at (877)384-7425 for further information. Sites in Australia and New Zealand should contact medialinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Figure Appendix 2: High Dose Methotrexate Flow Chart

All levels are timed from the start of the HDMTX infusion.



APPENDIX 3 MEDICATIONS WHICH MAY CAUSE QTC PROLONGATION AND TORSADE DE POINTES (NOT ALL INCLUSIVE)

Refer to http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm

Patients are prohibited from taking medications listed in Category 1: Drugs with Risk of Torsade de Pointes. Caution is warranted when administering dasatinib to subjects taking drugs associated with prolongation of QTc listed in Category 2: Drugs with Possible Risk of Torsade de Pointes.

APPENDIX 4 COMMON CYP3A4 SUBSTRATES (NOT ALL INCLUSIVE)

The following lists describe medications which are common CYP3A4 substrates. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity for metabolism by CYP3A4.

Macrolide Antibiotics:
clarithromycin
erythromycin
NOT azithromycin

Anti-arrhythmics:
quinidine

Benzodiazepines:
alprazolam
diazepam
midazolam
triazolam

Immune Modulators:
cyclosporine
tacrolimus (FK506)

HIV Antivirals:
indinavir
nelfinavir
ritonavir
saquinavir

Antihistamines:
astemizole
chlorpheniramine
terfenidine

Calcium Channel Blockers:
amlodipine
diltiazem
felodipine
lercanidipine
nifedipine
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors:
atorvastatin
cerivastatin
lovastatin
NOT pravastatin
simvastatin

Steroid 6beta-OH:
estradiol
hydrocortisone
progesterone
testosterone

Others:
alfentanyl
buspirone
cafergot
caffeine
cocaine
dapsone
codeine-N-demethylation
dextromethorphan
eplerenone
fentanyl
finasteride
gleevec
haloperidol
irinotecan
LAAM
lidocaine
methadone
odanestron
pimozide
propranolol
quinine
salmetrerol
sildenafil
sirolimus
tamoxifen
taxol
terfenadine
trazodone
vincristine
zaleplon
zolpidem

APPENDIX 5 COMMON CYP3A4 INHIBITORS (NOT ALL INCLUSIVE)

The following lists describe medications and foods which are strong to moderate inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

Table Appendix 5: CYP3A4 Inhibitors

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	Weak CYP3A4 Inhibitors
≥ 5-fold increase in AUC	≥ 2 but < 5-fold increase in AUC	≥ 1.25 but < 2-fold increase in AUC
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycins	amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice(a), verapamil	cimetidine

APPENDIX 6 COMMON CYP3A4 INDUCERS (NOT ALL INCLUSIVE)

The following lists describe medications which are common inducers of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

HIV Antivirals:
efavirenz
nevirapine

Others:
barbiturates
carbamazepine
glucocorticoids
modafinil
phenobarbital
phenytoin
rifampin
St. John's wort
troglitazone
pioglitazone
rifabutin

APPENDIX 8 FOR PERFORMANCE STATUS SCALES

Table Appendix 8: For Performance Status Scales

STATUS		SCALES		STATUS
KARNOFSKY	**LANSKY**	**KARNOFSKY or LANSKY**	**ZUBROD (ECOG)**	**ZUBROD (ECOG)**
Normal, no complaints	Fully active, normal	100	0	Normal activity
Able to carry on normal activities; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity	90	1	Symptoms, but fully ambulatory
Normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly	80		
Cares for self. Unable to carry on normal activity or to do active work	Substantial restriction of, and less time spent, in play activity	70	2	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	Out of bed, but minimal active play; keeps busy with quiet activities	60		
Requires considerable assistance and frequent medical care	Gets dressed, but inactive much of day; no active play, able to participate in quiet play	50	3	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	Mostly in bed; participates in some quiet activities	40		
Severely disabled. Hospitalization indicated though death non imminent	In bed; needs assistance even for quiet play	30	4	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	Often sleeping; play limited to passive activities	20		
Moribund	No play; does not get out of bed	10	5	Moribund

APPENDIX 10 DEFINITION OF CNS LEUKEMIA AT DIAGNOSIS

- CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).
- CNS 2: In CSF, presence < 5/μL WBCs and cytospin positive for blasts, or > 5/uL WBCs but negative by Steinherz/Bleyer algorithm:
- CNS 2a: < 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts;
- CNS 2b: ≥ 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts; and
- CNS 2c: ≥ 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).
- CNS 3: In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:
- CNS 3a: < 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts;
- CNS 3b: ≥ 10/μL RBCs, ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (see below);
- CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of Evaluating Traumatic Lumbar Punctures (Steinherz/Bleyer algorithm)

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥5 WBC/μL and blasts, the following algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/μL, CSF RBC ≥ 10/μL, and cytospin positive for blasts, whose CSF WBC/RBC ratio is at least 2 X greater than the blood WBC/RBC ratio, has CNS3b disease at diagnosis. Otherwise, the patient has CNS2c disease.

Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3.0 X 10^6/μL:

$$\frac{60}{1500} = 0.04 > 2X \quad \frac{46000}{3.0 \times 10^6} = 0.015$$ (patient has CNS3b disease)

APPENDIX 11 EXAMPLE INDUCTION THERAPIES PHASE IA

Example Children's Oncology Group Therapies for Induction 1A

Induction: Weeks 1 - 2 base upon patient subgroup:

Standard Risk B-cell precursor ALL (Age 1-9.99 years, WBC<50,000/µl; 50 x 10^9/L)

Day 1	Intrathecal cytarabine (dose per age)
Day 1-14	Dexamethasone 6 mg/m^2/day
Day 1,8	Vincristine 1.5 mg/m^2
Day 4	Peg-asparaginase 2500 IU/m^2
Day 8	Intrathecal methotrexate (dose per age)

High Risk B-cell precursor ALL (does not meet standard risk criteria above)

Day 1	Intrathecal cytarabine (dose per age)
Day 1-14	Dexamethasone 10 mg/m^2/day (ages 1 - 9.99 years)
OR	Prednisone 60 mg/m^2/day (ages 10+ years)
Day 1,8	Vincristine 1.5 mg/m^2
Day 1,8	Daunorubicin 25 mg/m^2
Day 4	Peg-asparaginase 2500 IU/m^2
Day 8	Intrathecal methotrexate (dose per age)

T-Cell ALL

Day 1	Intrathecal cytarabine (dose per age)
Day 1-14	Prednisone 60 mg/m^2/day
Day 1,8	Vincristine 1.5 mg/m^2
Day 1,8	Daunorubicin 25 mg/m^2
Day 4	Peg-asparaginase 2500 IU/m^2
Day 8	Intrathecal methotrexate (dose per age)

Induction: Weeks 3 - 4

Begin Week 3 Induction therapy regardless of peripheral blood counts.
Do not interrupt Induction therapy for myelosuppression.

Day 15-28	Prednisone 60 mg/m^2/day (all subjects will receive prednisone regardless of steroid use for first 14 days)
Day 15, 22	Vincristine 1.5 mg/m^2
Day 15, 22	Daunorubicin 25 mg/m^2
Day 29	Intrathecal methotrexate (dose per age; also on day 15 and 22 if CNS3)
Day 15-28	Dasatinib 60 mg/m^2/day (continue after day 28)

Age-based dosing:

Table Appendix 11A: Cytarabine Intrathecal Chemotherapy Dosages	
Age	**ARA-C**
1 to < 2	16 mg
2 to < 3	20 mg
3 to < 9	24 mg
≥ 9	30 mg

Table Appendix 11B: Methotrexate Intrathecal Chemotherapy Dosages	
Age	**Methotrexate**
1 to < 2	8 mg
2 to < 3	10 mg
3 to < 9	12 mg
≥ 9	15 mg

Alternative Example Dana-Farber Cancer Institute ALL Consortium Induction IA

Day 1	Intrathecal cytarabine (dose per age as below)*
Day 1-3	Methylprednisolone 32 mg/m^2/day
Day 4-17	Methylprednisolone 32 mg/m^2/day or Prednisone 40 mg/m^2/day
Day 4,5	Doxorubicin 30 mg/m^2 (with Dexrazoxane 300 mg/m^2 in high risk subjects)
Day 4,11	Vincristine 1.5 mg/m^2 (maximum dose 2 mg)
Day 5	Methotrexate 40 mg/m^2
Day 7	PEG-asparaginase 2500 IU/m^2

*IT cytarabine continued twice-weekly for CNS2 and CNS3 subjects until 3 consecutive clear CSF specimens

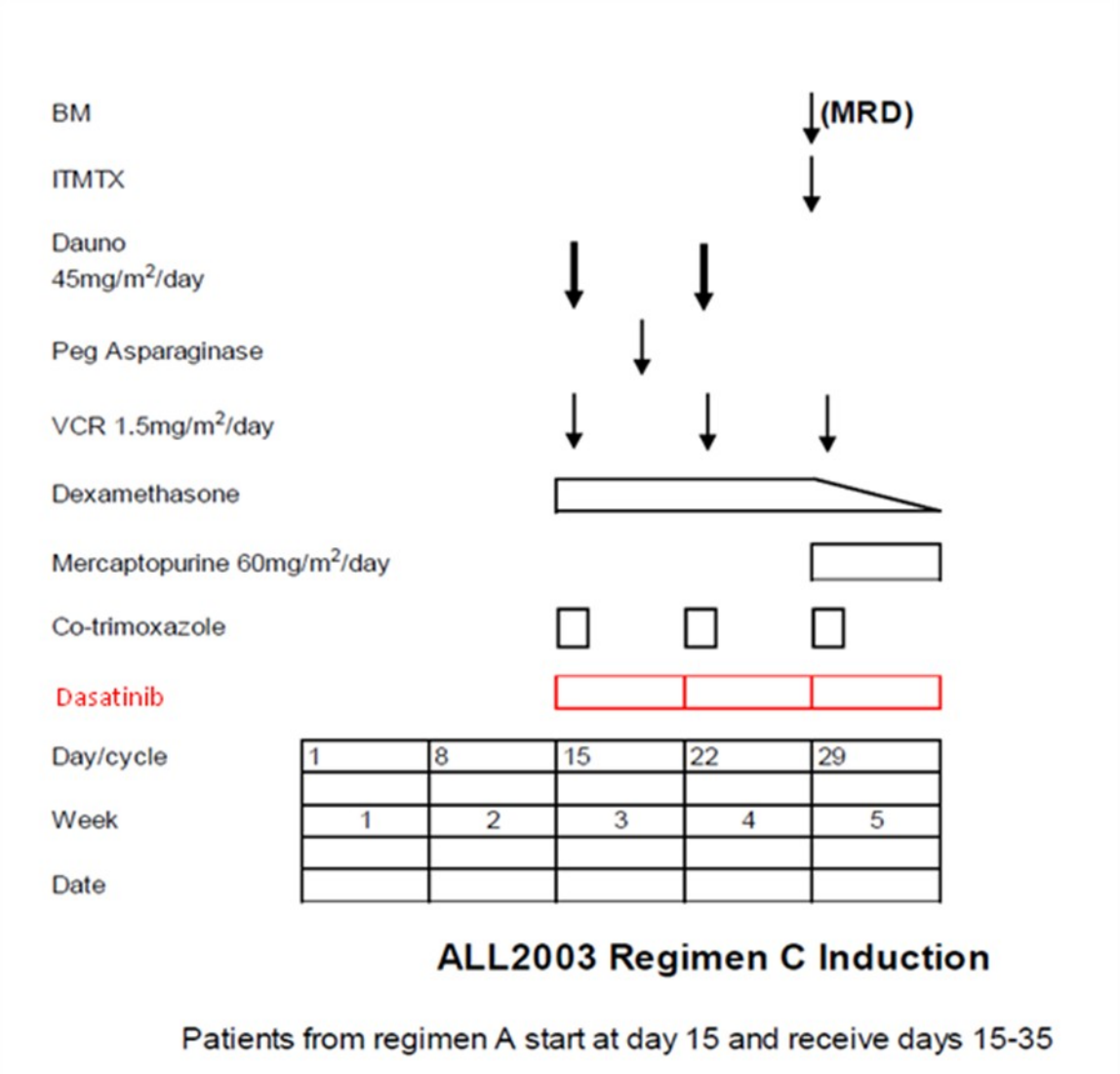
Day 18-32	Methylprednisolone 32 mg/m^2/day or Prednisone 40 mg/m^2/day
Day 18,25	Vincristine 1.5 mg/m^2 (maximum dose 2 mg)
Day 18	IT Methotrexate/Cytarabine/Hydrocortisone (dose per age)
Day 32	IT Methotrexate (dose per age)
Day 15-32	Dasatinib 60 mg/m^2/day (continue after day 32)

Table Appendix 11C: Intrathecal Dose by Age

AGE	Methotrexate	Ara-C	Hydrocortisone
≥ 1 year < 2 years	8 mg	20 mg	8 mg
≥ 2 years < 3 years	10 mg	26 mg	10 mg
≥ 3 years	12 mg	30 mg	12 mg

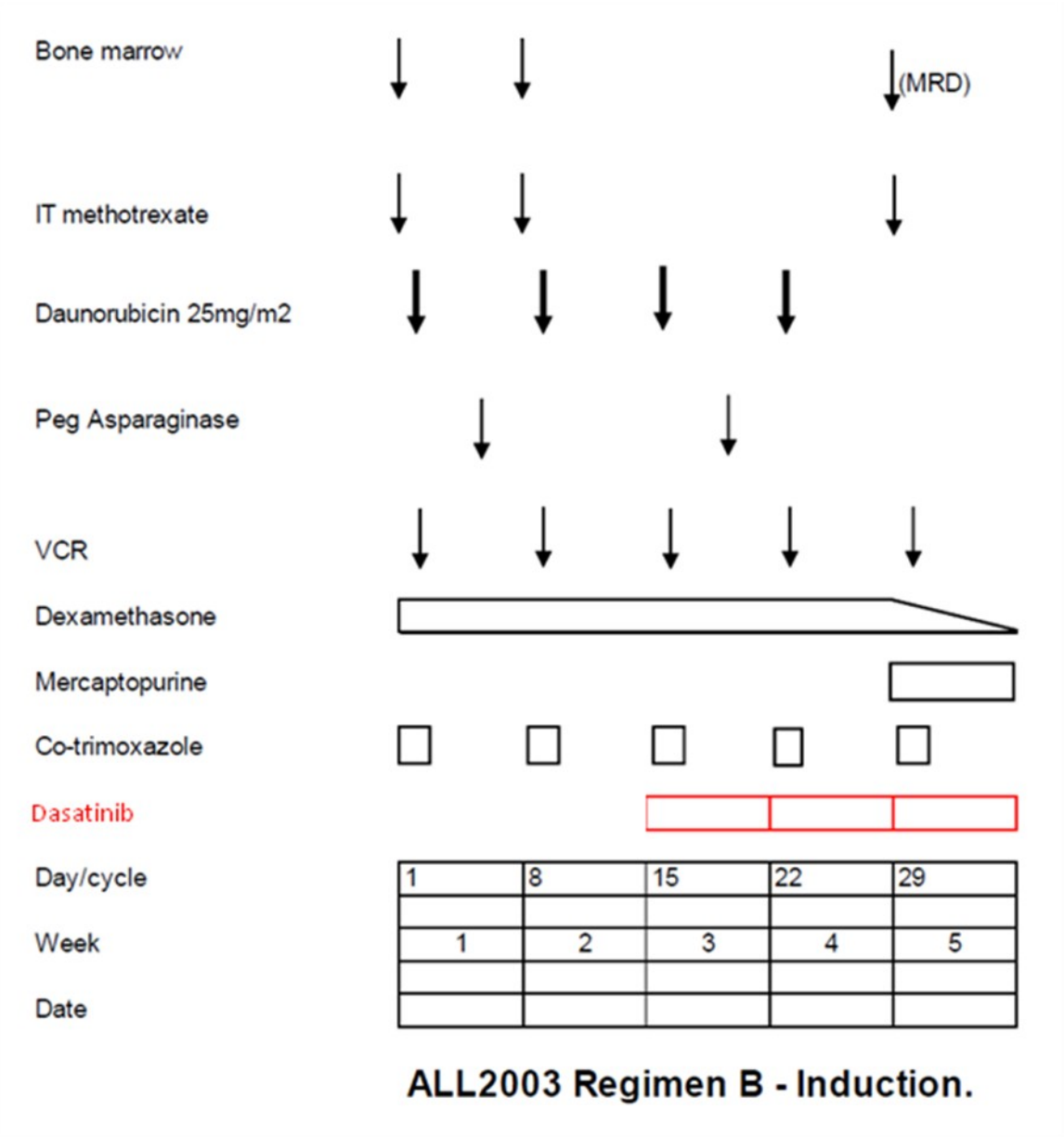
Example therapies for Induction IA in the United Kingdom (UK)

In the UK, at the time of being identified as having Ph+ALL, patients will be undergoing induction on either Regimen A or B of UKALL 2003. Those on Regimen B will continue induction as per the protocol. Those on Regimen A should move to the Regimen A to C induction switch. This is to ensure that all patients receive anthracyclines during induction.



ALL2003 Regimen C Induction

Patients from regimen A start at day 15 and receive days 15-35



ALL2003 Regimen B - Induction.

APPENDIX 12 OPTIONAL SUPPORTIVE TREATMENT GUIDELINES

Induction Therapy Phase IB:

Optional hydration guidelines during cyclophosphamide administration:

- hyperhydration 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.

Consolidation Block 1 (HR1):

Optional MESNA guidelines during cyclophosphamide administration:

- MESNA 70 mg/m^2 hours 0, 4 and 8 from start of CPM may be used.

Suggested corticosteroid eye drops with high-dose Ara-C:

- Prednisolone eye drops every 2-3 hours to both eyes from the start of the cytarabine infusion for a total of 5 days.

Consolidation Block 2 (HR2):

Optional MESNA guidelines during ifosfamide administration:

- MESNA 300 mg/m^2 i.v hour 0, 4 and 8 from start of infusion.

  Hydration following ifosfamide administration: If a patient stops methotrexate hydration for whatever reason, need to continue until 12 hours post ifosfamide infusion.

Consolidation Block 3 (HR3):

Suggested corticosteroid eye drops with high-dose Ara-C:

- Prednisolone eye drops every 2-3 hours to both eyes from the start of the cytarabine infusion for a total of 5 days.

First Reinduction (Protocol II), Phase IIb:

Optional hydration guidelines during cyclophosphamide administration:

- hyperhydration 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.

Second Reinduction (Protocol II), Phase IIb:

Optional hydration guidelines during cyclophosphamide administration:

- hyperhydration 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.

Protocol Number: CA180372
IND Number: 66,971
EUDRACT Number 2011-001123-20
Date: 20-Sep-2011

Protocol CA180372: A Phase 2 Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Amendment Number 01
Site Number: All

Study Director	**Medical Monitor**
[redacted]	M. Brigid Bradley-Garelik, MD [redacted]
Co-Principal Investigator	**Co-Principal Investigator**
[redacted]	[redacted]

24-hr Emergency Telephone Number:
[redacted]

Bristol-Myers Squibb Research and Development
[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The following amendment was developed to incorporate two key changes including:

1) Changing the statistical design of the trial to allow comparison to historical external controls. Specifically, the 3-year event free survival (EFS) of dasatinib plus chemotherapy will be compared to the 3-year EFS of chemotherapy alone from the Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP BFM 2000) trial and the 3-year EFS of imatinib plus chemotherapy from the European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL). This analysis will improve the ability to interpret the safety and efficacy of dasatinib added to chemotherapy among other treatment options for this pediatric leukemia.
2) Incorporating additional supportive care options for chemotherapy to accommodate the standard of care at sites in the United Kingdom (UK).

Additionally, typographical errors were also corrected. This amendment impacts the study conduct (supportive care options with chemotherapy) and data analysis (primary endpoint). The amendment applies to all subjects and should be implemented after IRB/IEC/HA review.

Details regarding changes are outlined in sequential order of the protocol.

1) Study title, research hypothesis and primary endpoint were modified to incorporate comparison to historical controls
2) Complete remission rates added as a key secondary objective
3) Changed vincristine dose from day 1 to day 2 in HR1 and HR2 blocks of treatment
4) Included recommendation for pneumocystis pneumonia (PCP) prophylaxis
5) Moved optional hydration guidelines with cyclophosphamide and ifosfamide to Appendix 12 (supportive care guidelines)
6) Added additional option for alternative hydration and methotrexate infusion guidelines commonly used in the UK to Appendix 1
7) Included “calcium folinate” and “leucovorin” as additional nomenclature for citrovorum factor (folinic acid)
8) Clarified that corticosteroid eye drops are suggested with high dose Ara-C administration
9) Clarified that G-CSF incorporated in HR1, HR2, and HR3 blocks are optional and incorporated into Appendix 12 (supportive care guidelines)
10) Clarified that asparaginase formulation, PEG-ASP (ONCOSPAR), may be administered either i.v. or i.m.

11) Corrected timing of asparginase dose in HR2 and HR3 block as day 6
12) Revised section 8.1, sample size determination to reflect revised primary endpoint of comparison with historical, external controls
13) Included the definition of "high risk" and "low/standard risk" Ph+ ALL
14) Incorporated the method of analysis for the added secondary endpoint of complete remission rate
15) Incorporated standard induction IA regimens common in the UK as subjects will receive this therapy prior to consenting to this trial. This was added in Appendix 11.
16) Added Appendix 12 (supportive care guidelines)
17) Included hematology lab parameters in SI units (Système International d'Unités)

Changes to the Protocol: Cover Page, Title:

Title modified to reflect the comparison to historical controls. The Children's Hospital name has been modified to reflect the institutional name change.

2) Synopsis, Title of Study

   Title modified to reflect the comparison to historical controls

3) Synopsis, Research Hypothesis

   Modified to reflect the comparison to historical controls. Specifically, dasatinib added to chemotherapy will demonstrate a superior 3-year EFS rate compared to chemotherapy alone in the external historical control trial AIEOP BFM 2000 and superior 3-year EFS rate compared to imatinib added to chemotherapy in the external historical control trial EsPhALL Synopsis, Primary Objective

   Revised to compare the 3-year event-free survival (EFS) with the external historical controls of the AIEOP BFM 2000 and EsPhALL trials.

5) Synopsis, Study Population

   Clarified inclusion criteria

6) Synopsis, Statistical Methods

   Revised to reflect the new primary endpoint.

7) Section 1.1, Study Rationale

   Added 3-year EFS data from the AIEOP BFM 2000 trial and expected 3-year EFS data from the amended EsPhALL trial.

8) Section 1.2, Research Hypothesis

   Revised to reflect the new primary endpoint.

9) Section 1.3.1, Primary Objective

   Revised to reflect the new primary endpoint.

10) Section 1.3.2, Secondary Objectives

   Added the key secondary objective of complete remission rates (< 5% blasts in bone marrow and no peripheral blasts) at end of induction

11) Section 1.3.3, Exploratory Objectives

   Removed overall EFS as this is included in the revised secondary endpiont.

12) Section 3.3.1, Inclusion Criteria

   Clarified inclusion criteria.

13) Section 4.3, Selection and Timing of Dose for Each Subject, Table 4.3

   Changed to Table 4.3.1. Changed vincristine dosing in HR1 and HR2 block from day 1 to day 2 and added SI units to hematology parameters. Corrected the day of administration of L-asparaginase in HR2 and HR3 to day 6. Added Table 4.3.2 to summarize hematological counts prior to the start of each block of therapy. Ordered chemotherapy according to days of administration. Added Table 4.3B to clarify hematological parameters prior to each treatment block.

14) Section 4.3.1.2, Induction Therapy IB.

   Added that pneumocystis pneumonia (PCP) prophylaxis is recommended with trimethoprim/sulfamethoxazole, cotrimoxazole or other appropriate agent against Pneumocystis jirovecii according to the institutional standard of care. SI units were added to hematology parameters. Hydration guidelines for cyclophosphamide were clarified as optional and added to a new appendix 12. Clarified that anti-emetic support should be according to standard institutional guidelines.

15) Section 4.3.1.3, Consolidation Block 1 (HR1)

   SI units were added to hematology parameters. Vincristine dose was moved from day 1 to day 2. Methotrexate hydration guidelines were modified to incorporate the standard of care in UK institutions. Clarified nomenclature for citrovorum factor to include calcium folinate and leucovorin. Clarified that MESNA guidelines were optional and moved to appendix 12. Clarified that corticosteroid eye drops are suggested during high-dose Ara-c administration. Included i.m. administration of the asparaginase preparation, PEG-ASP and removed reference to brand name ONCASPAR. Clarified that G-CSF use was optional and moved to appendix 12.

16) Section 4.3.1.4, Consolidation Block 2 (HR2)

SI units were added to hematology parameters. Vincristine dose was moved from day 1 to day 2. Methotrexate hydration guidelines were modified to incorporate the standard of care in UK institutions. Clarified nomenclature for citrovorum factor to include calcium folinate and leucovorin. Clarified that MESNA guidelines were optional and moved to appendix 12. Included i.m. administration of the asparaginase preparation, PEG-ASP (ONCOSPAR) and corrected day of administration to day 6. Removed reference to brand name of PEG-ASP, ONCASPAR. Clarified that G-CSF use was optional and moved to appendix 12.

17) Section 4.3.1.5, Consolidation Block 3 (HR3)

SI units were added to hematology parameters. Clarified that corticosteroid eye drops are suggested during high-dose Ara-c administration. Included i.m. administration of the asparaginase preparation, PEG-ASP and corrected day of administration to day 6. Removed reference to brand name of PEG-ASP, ONCASPAR. Clarified that G-CSF use was optional and moved to appendix 12.

18) Section 4.3.1.6, First Reinduction (Protocol II), Phase IIa

SI units were added to hematology parameters. Included i.m. administration of the asparaginase preparation, PEG-ASP (ONCOSPAR).

19) Section 4.3.1.6, First Reinduction (Protocol II), Phase IIb

SI units were added to hematology parameters. Clarified that MESNA guidelines were optional and moved to appendix 12. Removed reference to brand name of PEG-ASP, ONCASPAR.

20) Section 4.3.1.7, Interim Maintenance

Added the following hematological parameters to proceed with interim maintenance therapy: adequate ANC ($\geq$ 750/µl; 0.75 x 10^9/L) and platelet counts ($\geq$ 75,000/µl; 75 x 10^9/L). Clarified dose and age range for cranial irradiation.

21) Section 4.3.1.8, Second Reinduction (Protocol II), Phase IIa

SI units were added to hematology parameters. Included i.m. administration of the asparaginase preparation, PEG-ASP and removed reference to brand name, ONCOSPAR.

22) Section 4.3.1.8, Second Reinduction (Protocol II), Phase IIb

SI units were added to hematology parameters. Clarified that MESNA guidelines were optional and moved to appendix 12.

23) Section 4.3.1.9, Continuation Therapy

SI units were added to hematology parameters. Added the following hematological parameters to proceed with continuation therapy: adequate ANC ($\geq$ 750/µl; 0.75 x 10^9/L) and platelet counts ($\geq$ 75,000/µl; 75 x 10^9/L). Clarified the dose modification guidelines for chemotherapy.

24) Section 4.3.1.11 Hematopoietic Stem Cell Transplant (HSCT)

Added the use of flow cytometry results for HSCT determination in the event other MRD assessments are uninformative.

25) Section 4.3.2.1, Dasatinib

SI units were added to hematology parameters.

26) Section 4.3.2.4, Cytarabine (Ara-C)

SI units were added to hematology parameters.

27) Section 4.3.2.5, Daunorubicin or Doxorubicin

SI units were added to hematology parameters.

28) Section 4.3.2.8, High-Dose Methotrexate (HD MTX) and Leucovorin Rescue

SI units were added to hematology parameters. Criteria for ANC and platelets removed as these were greater than criteria to start blocks with HD MTX.

29) Section 4.3.2.10, PO Methotrexate (MTX) and 6-Mercaptopurine (MP)

SI units were added to hematology parameters. Modified dose interruption, reduction and escalation guidelines to be consistent with standard supportive care guidelines.

30) Section 4.3.1.11, Hematopoietic Stem Cell Transplant (HSCT)

In the rare circumstance that both Ig/TCR and BCR-ABL PCR are uninformative, flow cytometry results may be utilized for the HSCT decision.

31) Section 5.1, Flow Chart/Time and Events Schedule

Added a new column to Table 5.1A of "End of I/HD blocks" to clarify that extramedullary assessment of leukemia, bone marrow blasts and bone marrow MRD assessment may be done at the end of induction/HR blocks or beginning of the first reinduction block. Removed reference to growth curve in Table 5.1B as these will be automatically derived from height/weight data. Added clarification about bone marrow MRD assessments.

32) Section 5.3.1, Physical Exam

Removed reference to growth curve as these will be automatically derived from height/weight data.

33) Section 8.1, Sample Size Determination

Revised to reflect the new primary endpoint.

Additional language was added to ensure that at least 20 evaluable subjects for the primary endpoint were accrued including for each of the following age ranges: 1 to < 12 years and 12 to < 18 years.

34) Section 8.3.1, Primary Endpoint

Added the definition of high risk and low/standard risk Ph+ ALL for stratification in the sensitivity analysis of EFS.

35) Added Section 8.3.2.2, Event Free Survival (EFS)

Definitions for secondary and sensitivity analyses of EFS are described.

36) Section 8.3.2.2, Minimal Residual Disease (MRD)

Clarified that PCR for BCR-ABL will be compared to baseline values.

37) Add Section 8.3.2.4, Complete Remission Rate

Added the definition for the complete remission rate at end of induction therapy.

38) Section 8.4.2.1, Estimation of 3-yr EFS rate

Revised to reflect the modified primary and secondary endpoints.

39) Section 8.4.2.2, Differences in 3-Year EFS Rate With Other Studies

Removed as this is now part of the primary endpoint. This section now reflects time to event analysis for DFS and OS.

40) Section 8.4.2.3, Complete Remission Rate

Added the method of analysis of complete remission rate to include assessments between the start of dasatinib and the last day of induction IB. Subsequent headers renumbered.

41) Appendix 1, Monitoring of MTX Serum Levels and Intensification of LCV Rescue

Added guidelines for intravenous administration of high dose Methotrexate commonly used at UK institutions.

42) Appendix 2, HD-MTX Infusion and Rescue Guidelines and Flow Chart

Removed reference to aerosolized pentamidine as this is a prohibited mediction as stated in section 3.4.1.1 due to the potential risk of QTc prolongation when combined with dasatinib.

43) Appendix 11, Example Induction Therapies Phase IA

SI units were added to hematology parameters. Example Induction IA therapy common among UK institutions was added. This chemotherapy would be administered as part of the standard of care to patients prior to participation in this trial.

44) Appendix 12, Optional Supportive Treatment Guidelines

Optional supportive treatment for use during chemotherapy administration were moved from the body of the protocol to this new appendix.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

[redacted]

Protocol Number: CA180372
Site Number:
Amendment Number: 01

Protocol Number: CA180372
IND Number: 66,971
EUDRACT Number 2011-001123-20
Date: 07-Dec-2012

Protocol CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Amendment Number 02
Site Number: All

Study Director	**Medical Monitor**
[redacted]	M. Brigid Bradley-Garelik, MD [redacted]
Co-Principal Investigator	**Co-Principal Investigator**
[redacted]	[redacted]

24-hr Emergency Telephone Number:

[redacted]

Bristol-Myers Squibb Research and Development

[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The key purposes of this amendment are to incorporate the following key changes:

1. Introduce a new pediatric formulation of dasatinib, a berry flavored oral suspension constituted from a powder (also known as the powder for oral suspension (PFOS)) as an alternative for administering dasatinib to children unable to swallow tablets. This revision should have no impact on study conduct or data analysis. This revision applies to all subjects not able to swallow tablets.
2. Address lack of availability of native-asparaginase in the United States and allow use of Peg-Asparaginase upfront in such instances as well as provide more detailed instruction for dose modifications of the various asparaginase formulations. This revision should have no impact on study conduct or data analysis. This revision applies to all subjects as indicated in the protocol.
3. Indicate that the BCR-ABL mutation status will be reported for baseline and at time of progression as a secondary objective instead of as an exploratory objective in order to bring into alignment with the binding elements of the Pediatric Investigational Plan with the EMA. These baseline samples were being collected prior to this amendment as per the Time and Events table. This revision should have no impact on study conduct and is applicable to all subjects.
4. Since Philadelphia chromosome status determined by RT-PCR with peripheral blood is unlikely to result in a false positive result, Philadelphia chromosome positivity from peripheral blood will be acceptable for study entry as well as the conventional approach in this setting using a bone marrow aspirate. This revision should have no impact on study conduct or data analysis. This revision applies to all subjects.
5. The acceptable window for screening activities was expanded from 15 days prior to treatment with dasatinib to 21 days, except when noted otherwise, for two reasons; 1) so that tests that may have been performed as part of the initial diagnostic work up such as chest X-ray, ECG, echocardiogram or MUGA and CSF sampling would not need to be repeated and 2) in the event there is a delay in initiating day 15 backbone chemotherapy treatment with dasatinib for recovery of adverse events or logistical scheduling. This expanded window is not expected to increase any potential risk for subjects. This revision should have no impact on study conduct or data analysis. This revision applies to all subjects.
6. Prior stem cell transplant and Ph+ ALL occurring as a second malignant neoplasm after treatment of a prior malignancy were added as exclusion criteria. Although these circumstances are rare the prognosis may be different, therefore, in this small study such prior conditions will be excluded. This revision should have no impact on study conduct or data analysis. This revision applies to all subjects.
7. The definition of high risk group and low/standard risk group in response to Induction 1A treatment has been modified. In Europe, for induction treatment not adopting a steroid

prephase, a day 15 bone marrow is still obtained. However the AIEOP BFM 2000 study has been reported using the day 29 BM for risk group assignment. Bone marrow aspirates are no longer performed in COG centers before day 29. So as not to require the study subjects to undergo a BM aspiration at a time point in the therapy that is no longer a consistent standard of practice and is not needed for clinical management decisions, the protocol will use the end of Induction 1A BM result for defining risk groups. The high risk group would be defined by a MRD ≥ 0.01%; low/standard risk would be defined as day 29 MRD < 0.01%. This approach is consistent with the criteria used in other COG trials, and/or NCI risk group and being adopted by EsPhALL trials. This revision will impact study conduct by improving compliance with obtaining this data point with no added risk for subjects. The data analysis will be used to conduct a sensitivity analysis around the EFS endpoint. This revision applies to all subjects.

This amendment also provides for clarifications, fixes inconsistencies across sections of the protocol and repairs typographical errors as described below. These revisions should improve consistency in study conduct but is not expected to have an impact on data analysis. These revisions apply to all subjects as they proceed through the treatment blocks.

Changes to the Protocol:

1. Synopsis: Study Design Section, Design paragraph
   a) 1st Paragraph, 2nd to last sentence "recovery period (14 days, 2 weeks)," deleted as this period is already included as the last 2 weeks of HR3 when only dasatinib is administered.
   b) 1st Paragraph, last sentence "L" deleted from asparaginase as various forms are allowed.
   c) 2nd Paragraph, added a new second sentence and revised subsequent sentence to more clearly indicate that the use of dasatinib is optional in HSCT subjects. This change was made to be consistent with the in-body text of the existing protocol.
2. Synopsis: Statistical Methods
   a) 1st sentence added less than symbol for clarity.
   b) Last Paragraph, objective regarding BCR-ABL mutation status moved from exploratory objectives to secondary objectives and added "at baseline" to text to bring into alignment with the binding elements of the Pediatric Investigational Plan with the EMA. These baseline samples were being collected prior to this amendment as per the Time and Events table.
3. Section 1.3.2 Secondary Objectives and Section 1.3.3 Exploratory Objectives
   a) Objective regarding BCR-ABL mutation status moved from exploratory objectives to secondary objectives and added "at baseline" to bring into alignment with the binding elements of the Pediatric Investigational Plan with the EMA. These baseline samples were being collected prior to this amendment as per the Time and Events table.

4. Section 1.4.4.1 Formulation
   a) Section has been updated to include information on the age appropriate dasatinib Powder for Oral Suspension formulation provided for use in this study.
5. Section 3.1 Study Design and Duration - Design Paragraph
   a) 2nd Paragraph, first sentence reworded for clarity.
   b) 2nd Paragraph, 5th bullet deleted as this period is actually already included as the last 2 weeks of HR3 when only dasatinib is administered.
   c) 2nd Paragraph, 7th bullet deleted "overlaps 2 weeks with end of reinduction block 1)" to make consistent with Table 4.3A and section 4.3.1.7 which indicate Interim maintenance will start 2 weeks after completion of the last backbone chemotherapy administered in the previous phase (which is day 49 of a 63 day block). Dasatinib should continue through day 63 of the Reinduction block, until Interim Maintenance begins.
   d) 3rd Paragraph, third sentence added to clarify that patients receiving chemotherapy other than that prescribed in the protocol should be discontinued from the study and to specifically state that dasatinib will not be provided if the patient receives non-protocol chemotherapy and 4th, 5th and 6th sentences reworded.
   e) 4th Paragraph, added OR between the 1rst and 2nd bullet for clarity and added an additional bullet to clarify the quantifiable range.
6. Section 3.2 Post Study Access to Therapy
   a) 2nd Paragraph, 2nd and 3rd sentences reworded to emphasize that treatment with dasatinib for an additional 12 months post-HSCT is optional.
   b) 2nd Paragraph, deleted last sentence which stated there was "no evidence that subjects who relapse after multi-agent chemotherapy or HSCT with the addition of dasatinib would benefit from further dasatinib treatment" since there is also no evidence that that these subjects would not benefit from continued dasatinib treatment. Since this is not a question addressed in this study, this sentence was deleted.
7. Section 3.3.1 Inclusion Criteria, Target Population
   a) Item 2 a i, "deleted conventional bone marrow" to allow use of PH positivity determined from peripheral blood as well.
   b) Item 2 c iv, reorganized acceptable tests for assessment of renal function and added gender as an additional qualifier for the upper limit of normal for serum creatinine as normal serum creatinine levels in children can differ by gender as well as by age.
   c) Item 2 d i, expanded screening window to 21 days prior to starting dasatinib to avoid unnecessary repeat of assessments preformed during diagnostic work-up and to accommodate delays in initiating day 15 of the backbone chemotherapy.
   d) Added new criteria letter e to remind COG sites (excluding DFCI Consortium sites) that subjects must be enrolled in the COG Classification Trial (AALL08B1 or successor).
8. Section 3.3.1 Inclusion Criteria, Age and Reproductive Status
   a) Item b changed acceptable method to highly effective method of contraception and 72 to 24 hours prior as per updates to BMS SOP.

9. Section 3.3.2 Exclusion Criteria, Medical History and Concurrent Diseases
   a) Item a, reworded for clarity. The intent of the exclusion criteria regarding active systemic bacterial, fungal or viral infections was to prevent the enrollment of patients with ongoing serious infections. Infection alone is not a concern for enrolling in the trial. Serious infections, with the noted complications of septic shock syndrome that require either vasopressor support or mechanical ventilation would be severe enough so that study enrollment may not be in the best interest of the patient.
   b) Added new criteria letters e and f.
10. Section 3.4.1.1 Prohibited Treatments
   a) 3rd bullet, added azithromycin to complete the list of macrolide antibiotics in this category of prohibited drugs.
11. Section 4.1 Study Treatments, Table 4.1
   a) Added last row to the table to describe the dasatinib Powder for Oral Suspension.
12. Section 4.1.1 Investigational Product
   a) Last Paragraph added to provide information about the dasatinib Powder for Oral Suspension.
13. Section 4.1.2 Noninvestigational Product, Table 4.1.2
   a) Methotrexate added under 2nd Reinduction Block as it was accidentally omitted in the original table.
14. Section 4.3 Selection and Timing of Dose for Each Subject
   a) 2nd Paragraph, ”or no later than when the day 15 induction chemotherapy is administered” added in the 2nd sentence to allow for a window for treatment.
15. Section 4.3 Selection and Timing of Dose for Each Subject and Table 4.3A
   a) 2nd Paragraph, or no later than when the day 15 induction chemotherapy is administered” added in the 2nd sentence. This will allow for minor delays due to scheduling adjustments or toxicity of Induction 1A backbone chemotherapy.
   b) L-ASP/iv (2h) or im clarified to ASP/iv (1-2h) or im for all Phases to accomodate different asparaginase forms and their associated infusion times.
   c) L-ASP clarified to asparaginase in the abbreviations at the end of the table.
   d) “ Starts no sooner than day 33” added to the Induction Therapy Phase 1B column to provide clarity.
   e) Sentence regarding recovery period under Consolidation Block 3 was deleted to eliminate confusion. This recovery period refers to the 2 weeks in Consolidation Block 3 when no backbone chemotherapy is given however dasatinib continues, therefore the 2 weeks are already included in the 21 days of Block 3 and this additional recovery period is not necessary.
16. Section 4.3.1.1 Induction Therapy Phase 1A
   a) 2nd Paragraph, 1st and 2nd sentences modified for clarity and to allow for a window for treatment. This will allow for minor delays due to scheduling adjustments or toxicity of Induction 1A backbone chemotherapy.

17. Section 4.3.1.2 Induction Therapy Phase 1B
    a) New sentence added after 1st paragraph for clarity and consistency with other sections of the protocol.
    b) New sentence added at the end of the 6-MERCAPTOPURINE paragraph for clearer guidance.
    c) CYTOSINE ARABINOSIDE paragraph, 2nd sentence modified and a new sentence added at the end of the paragraph for clarity.
18. Section 4.3.1.3 Consolidation Block 1 (HR1)
    a) 2nd Paragraph, 1st sentence modified for clarity.
    b) DEXAMETHASONE (DXM) paragraph, fixed typographical error so that 2nd sentence refers to appropriate section.
    c) HIGH-DOSE METHOTREXATE (HD-MTX) paragraph, Gluc. 5%+ modified to Gluc. 5%(D5W)+ for clarity and reference to relevant appendices added.
    d) CITROVORUM FACTOR paragraph, added reference to relevant appendices.
    e) HIGH-DOSE ARA-C (HD-ARA-C) paragraph modified for clarity.
    f) HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) paragraph modified for clarity and new wording added to provide additional guidance regarding choice of asparaginase to be used.
19. Section 4.3.1.4 Consolidation Block 2 (HR2)
    a) DEXAMETHASONE (DEXA) paragraph, fixed typographical error so that 2nd sentence refers to the appropriate section.
    b) HIGH-DOSE METHOTREXATE (HD-MTX) paragraph, Gluc. 5%+ modified to Gluc. 5%(D5W)+ for clarity.
    c) IFOSFAMIDE paragraph, new wording added at end of paragraph to eliminate any potential confusion about hydration administrated with and following ifosfamide.
    d) HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) paragraph modified for clarity and new wording added to provide additional guidance regarding choice of asparaginase to be used.
20. Section 4.3.1.5 Consolidation Block 3 (HR3)
    a) DEXAMETHASONE (DEXA) paragraph, 2nd sentence modified to refer to Section 3.4.1.2.
    b) HIGH-DOSE L-ASPARAGINASE (HD-L-ASP) paragraph modified for clarity and new wording added to provide additional guidance regarding choice of asparaginase to be used.
21. Section 4.3.1.6 First Reinduction (Protocol II)
    a) 1st Paragraph, 1st sentence modified to provide additional interpretation of the MRD rule existing.
    b) 2nd Paragraph, 1st sentence modified for clarity.
    c) DEXAMETHASONE (DXM) paragraph, fixed typographical error so that the 2nd sentence refers to the appropriate section.

d) DOXORUBICIN (DOX)/ADRIAMYCIN (ADR) paragraph modified to accomodate institutional standards.

e) L-ASPARAGINASE (L-ASP) paragraph modified for clarity and new wording added to provide additional guidance regarding choice of asparaginase to be used.

f) New INTRATHECAL METHOTREXATE paragraph added. This Day 1 administration originally appeared with the Phase IIb doses. This change makes the text consistent with Table 4.3A

g) CYTOSINE ARABINOSIDE paragraph, 2nd sentence modified to be consistent with Section 4.3.1.8 and a new sentence added at the end of the paragraph for clarity.

h) INTRATHECAL METHOTREXATE paragraph in Phase IIb modified for clarity.

22. Section 4.3.1.7 Interim Maintenance

a) 1st Paragraph, 2nd sentence modified for clarity.

b) Days adjusted in the METHOTREXATE paragraph to be consistent with AIEOP-BFM 2009. Dosing logistics are improved but total dose remains the same.

23. Section 4.3.1.8 Second Reinduction (Protocol II)

a) DEXAMETHASONE (DEXA) paragraph, fixed typographical error so that the 2nd sentence refers to the appropriate section.

b) L-ASPARAGINASE (L-ASP) paragraph modified for clarity and new wording added to provide additional guidance regarding choice of asparaginase to be used.

c) New INTRATHECAL METHOTREXATE paragraph added. This Day 1 administration originally appeared with the Phase IIb doses. This change makes the text consistent with Table 4.3A.

d) CYTOSINE ARABINOSIDE paragraph, 2nd sentence modified to be consistent with Section 4.3.1.8 and a new sentence added at the end of the paragraph for clarity.

e) Last sentence in the INTRATHECAL METHOTREXATE paragraph modified and moved up to the CYTOSINE ARABINOSIDE paragraph where it should be.

f) INTRATHECAL METHOTREXATE paragraph in Phase IIb modified for clarity.

24. Section 4.3.1.9 Continuation Therapy

a) Corrected typographical errors in the METHOTREXATE paragraph under Dose Reduction for Falling Neutrophil Counts and Dose Reduction for Falling Platelet Counts.

25. Section 4.3.1.11 Hematopoietic Stem Cell Transplant (HSCT)

a) Added OR between the 1st and 2nd criteria bullet for clarity and added an additional bullet to provide an additional interpretation of the MRD rule.

b) 2nd, 3rd and 4th Paragraphs modified to clarify that patients receiving chemotherapy other than that prescribed in the protocol should be discontinued from the study, to state that dasatinib will not be provided if the patient receives non-protocol chemotherapy, to clarify reporting of concomitant medications and adverse events during the HSCT period and to clarify use of dasatinib after HSCT.

26. Section 4.3.2.1 Dasatinib, Table 4.3.2.1 Dose Modifications for Dasatinib

a) First row of Table modified to include Grade 4 events. Grade 4 events are expected to occur frequently, especially early in the treatment plan as a result of the backbone chemotherapy. Dasatinib can continue despite a grade 4 hematologic event unless the

event results in a delay in the next treatment block of > 14 days, in which case dasatinib should be interrupted as per instructions in the subsequent row of this table. A typographical error was also corrected in the fifth row.

27. Section 4.3.2.2 Asparaginase [PEG, E. coli, or Erwinia]
    a) Modified Table 4.3.2.2 and added new Tables 4.3.2.2a and 4.3.2.2b to provide more specific guidance regarding substitution of asparaginases during different blocks of treatment.
28. Section 4.3.2.4 Cytarabine (Ara-C)
    a) Table 4.3.2.4 modified to include additional dose modification for neurotoxicity.
29. Section 4.3.2.5 Daunorubicin or Doxorubicin
    a) Table 4.3.2.5, 1st row modified to allow subsequent doses with improvement of cardiac function.
30. Section 4.3.2.8 High-Dose Methotrexate (HD MTX) and Leucovorin Rescue
    a) 2nd Paragraph, 1st sentence modified to allow for window to obtain results.
    b) Table 4.3.2.8, 2nd row modified for clarity and 4th row modified to be consistent with other recommendations regarding increased ALT related to HDMTX.
31. Section 4.3.2.10 PO Methotrexate (MTX) and 6-Mercaptopurine (MP)
    a) 1st Paragraph and 2nd paragraph, 1st sentence modified for additional guidance.
    b) Corrected typographical errors in the paragraph under Dose Reduction for Falling Neutrophil Counts and Dose Reduction for Falling Platelet Counts.
32. Section 4.3.2.11 Steroids (Dexamethasone and Prednisone)
    a) Table 4.3.2.11 last row of table modified for additional guidance.
33. Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1A and 5.1B
    a) ECG, Echocardiogram, Mutation analysis, and Cytogenetic analysis rows modified for clarity to provide additional guidance or to be consistent with changes made in the protocol text. A note was added to the pregnancy test row that the pregnancy test needs to be performed within 24 hours prior to the start of dasatinib.
    b) Bone marrow MRD assessment note after transplant changed from 6 months to 3 months in order to allow for an earlier assessment of maintained disease control. This change is in line with current practice. Also added to the note was guidance to have bone marrow sample obtained once peripheral blood counts have recovered.
    c) Table Note a modified to expand screening window to 21 days prior to first dose of dasatinib. Also added was that the pregnancy test needs to be performed within 24 hours prior to start of dasatinib and a clarification that screening bone marrow MRD and mutation detection assessments will be performed on samples that have been previously banked prior to this study. No additional bone marrow sample needs to be collected at screening.
    d) Requirement for DXA scan changed from ≤ 5 years of age to simply < 5 years of age to be consistent with the International Society for Clinical Densitometry Pediatric Official Positions of 2007.

34. Section 5.3 Safety Assessments
    a) 3rd bullet modified to include “at least” since subjects undergoing HSCT may continue on protocol treatment beyond HR3 until logistic around the transplant procedures are set.
35. Section 5.3.3 Long-term Growth and Development and Bone Mineral Content
    a) DXA Scanning paragraph modified to include “if feasible” and to increase age limit to 20 years. The age limit was increased to be consistent with the International Society for Clinical Densitometry Pediatric Official Positions of 2007.
36. Section 6.2.1 Nonserious Adverse Event Collection and Reporting
    a) Added information about reporting requirements while a subject is preparing for, undergoing or recovering from HSCT and it is expected there will be a long interruption in protocol treatment during this period. This is consistent with Section 4.3.1.11.
37. Section 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES
    a) 1st Paragraph, 1st and 2nd sentences updated to reflect that the DMC has been established.
    b) 1st sentence in Interim Monitoring for Inferior Event-Free survival paragraph added to provide reference to assumptions.
38. Section 8.1 Sample Size Determination
    a) 2nd Paragraph, last sentence modified to correct typographical error.
39. Section 8.3.1 Primary Endpoint
    a) 1st bullet added “complete” to be consistent with section 8.3.2.4.

    b) 2nd Paragraph, 1st sentence in the Response Criteria for EFS modified to correct typographical error.

    c) In the Relapse Criteria for EFS, definitions of high risk group and low/standard risk group revised so as not to require the study subjects to undergo a BM aspiration at a time point in the therapy that is no longer a consistent standard of practice and is not needed for clinical management decisions. The end of Induction 1A BM result will be used for defining risk groups to be used in the sensitivity analysis around the EFS endpoint.
40. Section 8.3.2.2 Event Free Survival (EFS)
    a) Typographical error corrected in item 4 and 5.
41. Section 8.3.2.4 Complete Remission Rate
    a) Further defined to require no evidence of extramedullary disease.
42. BCR-ABL Mutation definition moved from Exploratory Endpoint Section 8.3.3.4 to Secondary Endpoint Section 8.3.2.5.
43. Section 11 LIST OF ABBREVIATIONS
    a) DFCI added to list.
44. Section 12 References
    a) New reference numbers 52, 55 and 56 added.
45. Appendix 1 Title modified for clarity.
46. Appendix 2 Title modified for clarity and revisions made to be consistent with COG guidelines updated in May 2012.

47. Appendix 3 modified to indicate listed website to be used as source for category 1 and 2 medications.
48. Appendix 9 Title modified for clarity and effective added preceding date of appendix for clarity.
49. Appendix 12 modified to eliminate any potential confusion about hydration administration with and following ifosfamide.
50. New Appendix 13 inserted to describe PFOS reconstitution procedure.
51. New Appendix 14 inserted to describe oral suspension dosing administration.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

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[redacted]

Protocol Number: CA180372
Site Number:
Amendment Number: 02

Protocol Number: CA180372
IND Number: 66,971
EUDRACT Number 2011-001123-20
Date: 31-Jul-2013

Protocol CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Amendment Number 03
Site Number: All

Study Director	**Medical Monitor**
[redacted]	M. Brigid Bradley-Garelik, MD [redacted]
Co-Principal Investigator	**Co-Principal Investigator**
[redacted]	[redacted]

24-hr Emergency Telephone Number:

[redacted]

Bristol-Myers Squibb Research and Development

[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The key purposes of this amendment are to incorporate the following key changes:

1. Increase the number of treated subjects from 75 to at least 75 and up to 90. The rate of subjects discontinuing study participation prior to reaching 3 years of follow-up from the start of dasatinib without having an event may potentially reach 20%. In order to assure robustness of the long-term efficacy and safety analysis results, up to 15 additional subjects may be treated in the trial.
2. Modify language regarding pregnancy prevention. Dasatinib has not been formally studied in pregnant women. However, the dasatinib team has recently completed a comprehensive review of the BMS Dasatinib safety database (CARES) for all pregnancies in female patients or female partners of male patients in order to reassess the risk of use of dasatinib during pregnancy. Pregnancies in female patients on dasatinib sometimes resulted in spontaneous abortions or infant and fetal anomalies. Based on this analysis and a revision to an internal BMS directive related to "Women of Childbearing Potential (WOCBP) in clinical trials", BMS protocols in the dasatinib program are being amended to:
   - update language related to WOCBP to harmonize with the new BMS directive including the requirement of 2 forms of birth control one of which is regarded as a highly effective form.
   - define highly effective forms of birth control
   - adjust language related to sexually active fertile male study participants with WOCBP partners and define the duration of birth control use after the last dose of investigational product as 90 days (duration of spermatogenesis).
3. Incorporate recommendations for subject management and supportive care during High Risk (HR) Blocks 1-3. The three HR blocks are profoundly myelosuppressive and also include 5 days of high dose dexamethasone. Because clinical signs of infection can be blunted following high dose dexamethasone therapy, a very low threshold should be considered for admission to the hospital and/or institution of empiric antimicrobial therapy, growth factor support should be considered starting anytime 24 hours or more after completion of chemotherapy (as noted in protocol appendix) and blood counts should be monitored 2-3x week until recovery. This guidance has been further highlighted within each of the HR blocks.

This amendment also provides for clarifications, fixes inconsistencies across sections of the protocol and repairs typographical errors as described below.

These revisions should improve consistency in study conduct but are not expected to have an impact on data analysis. These revisions apply to all subjects as they proceed through the treatment blocks.

Changes to the Protocol:

1. Synopsis: Select Exclusion Criteria
   a) Last bullet updated WOCBP wording.

2. Synopsis: Statistical Methods
   a) 1st sentence updated to reflect change in sample size.
   b) 1st sentence of last paragraph updated for clarity.
3. Section 1.3.2 Secondary Objectives Synopsis:
   a) Item number 3 updated to be consistent with the Pediatric Investigational Plan.
4. Section 1.4.4.1 Formulation
   a) 4th paragraph added clarity to define the single agent study as CA180226.
5. Section 3.1 Study Design and Duration
   a) Last sentence of first paragraph updated to reflect change in sample size.
6. Section 3.1 Study Design and Duration, Design
   a) Last sentence of fourth paragraph updated for clarity.
7. Section 3.3.1 Inclusion Criteria, Age and Reproductive Status
   a) Items 3b, 3c and 3d provide updated WOCBP wording.
8. Section 3.3.2 Exclusion Criteria, Sex and Reproductive Status
   a) Items a and b provide updated WOCBP wording.
9. Section 3.3 3 Women of Childbearing Potential
   a) 1st and 2nd paragraphs provide updated WOCBP wording.
10. Section 4.1 Study Treatments, Table 4.1
    a) 2nd column of the fourth row corrected typographical error and provide additional clarification regarding primary packaging of dasatinib powder for oral suspension.
11. Section 4.1.1 Investigational Product
    a) 5th paragraph added sentence to provide clarity regarding the constitution of the dasatinib PFOS.
12. Section 4.3 Selection and Timing of Dose for Each Subject
    a) 2nd paragraph added 2nd to last sentence to provide guidance in situations of drug shortages pertaining to the standard chemotherapy agents.
13. Section 4.3 Selection and Timing of Dose for Each Subject, Table 4.3A
    a) 3rd column under Interim Maintenance revised methotrexate p.o. dosing days to be consistent with Section 4.3.1.7.
14. Section 4.3.1.2 Induction Therapy 1B, 6-Mercaptopurine (6-MP)
    a) Last sentence updated to provide clarity.
15. Sections 4.3.1.3, 4.3.1.4 and 4.3.1.5 Consolidation Blocks 1, 2 and 3 (HR1, HR2 and HR3)
    a) Wording added to enhance subject managment and supportive care guidelines during the High Risk Blocks.
16. Section 4.3.1.6 First Reinduction (Protocol II), Phase IIa
    a) Dexamathasone (DXM) paragraph updated to allow i.v. administration.
17. Section 4.3.1.6 First Reinduction (Protocol II), Phase IIb, 6-Thioguanine (6-TG)
    a) Last sentence updated to provide clarity.

18. Section 4.3.1.8 Second Reinduction (Protocol II), Phase IIa
    a) Dexamathasone (DEXA) paragraph updated to allow i.v. administration.
    b) Doxorubicin (DOX)/Adriamycin (ADR) paragraph updated to be consistent with Section 4.3.1.6.
19. Section 4.3.1.8 Second Reinduction (Protocol II), Phase IIb
    a) 6-Thioguanine paragraph updated to provide clarity.
    b) Cytosine Arabinoside (ARA-C) last paragraph corrected typographical error.
20. Section 4.3.1.9 Continuation Therapy
    a) 1st paragraph updated for clarity.
    b) Intrathecal Methotrexate paragraph updated for clarity.
    c) Methotrexate paragraph updated second bullet under Dose Reduction for Falling Neutrophil Count and subsequent paragraph to indicate that the dosage upon restart should be the last dose administered rather than the original prescribed dose and to correct a typographical error.
21. Section 4.3.1.11 Hematopoetic Stem Cell Transplant (HSCT) Use of dasatinib after stem cell transplant
    a) Updated paragraph to provide clarity around re-starting dasatinib treatment.
22. Section 4.3.2.4 Cytarabine (Ara-C), Table 4.3.2.4
    a) 4th row refined event term for clarity.
23. Section 4.3.2.10 PO Methotrexate (MTX) and 6-Mercaptopurine (MP)
    a) Revised 1st sentence and added bulleted text for clarity.
    b) Updated second bullet under Dose Reduction for Falling Neutrophil Count and subsequent paragraph to indicate that the dosage upon restart should be the last dose administered rather than the original prescribed dose and to correct a typographical error.
24. Section 4.3.2.12 Thioguanine, Table 4.3.2.12
    a) Replaced Table 4.3.2.12 with indicated text for clarity.
25. Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1A
    a) X in Physical Exam line removed from EndI/HR blocks since this would be redundant with the Physical Exam required at R!.
    b) Echocardiogram / MUGA row now indicates MUGA in all capital letters.
    c) Serum Chemistry row added text to indicate direct bilirubin is required at screening which is consistent with the inclusion criteria.
    d) Mutation analysis row updated note column for clarity.
    e) Bone Marrow MRD Asssessment row updated note column for clarity.
    f) Assessment of survival and secondary malignancies row updated note column to assure assessment specifically at the 3 year and 5 year timepoint following first dose of dasatinib.
26. Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1B
    a) Table note item a is updated to provide consistency with 3 week screening period.

27. Section 5.3 Safety Assessments
    a) 1st paragraph updated to reflect pregnancy testing to be performed 24 hours prior to start of dasatinib therapy and to provide consistency of screening assessment timepoints noted in Tables 5.1A and 5.1B.
28. Section 5.3.1 Physical Examination
    a) Added last sentence to assure assessment specifically at the 3 year and 5 year timepoint following first dose of dasatinib.
29. Section 5.3.2.2 Serum Chemistry Tests
    a) Added text to indicate that direct bilirubin is required at screening which is consistent with the inclusion criteria.
30. Section 5.4.2.1 Overall Survival and Secondary Malignancy
    a) Added 2nd paragraph to assure assessment at the 3 year and 5 year timepoint following first dose of dasatinib.
31. Section 6.5 Overdose
    a) Corrected the section referenced in the last sentence.
32. Section 7 Data Monitoring Committee and Other External Committees
    a) Updated Tables 7A and 7B to accomodate the increase in sample size.
    b) Updated 2nd to last paragraph to reflect increase in sample size and correct errors.
33. Section 8.1 Sample Size Determination
    a) Added the last paragraph to address the change in sample size.
34. Section 8.3.1 Primary Endpoint, Response Criteria for EFS
    a) Added last sentence to the third paragraph to provide clarity.

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[redacted]

Protocol Number: CA180372
Site Number:
Amendment Number: 03

Protocol Number: CA180372
IND Number: 66,971
EUDRACT Number 2011-001123-20
Date: 28-Oct-2013

Protocol CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Amendment Number 04
Site Number: All

Study Director	**Medical Monitor**
[redacted]	M. Brigid Bradley-Garelik, MD [redacted]
Co-Principal Investigator	**Co-Principal Investigator**
[redacted]	[redacted]

24-hr Emergency Telephone Number:
[redacted]

Bristol-Myers Squibb Research and Development
Oncology Clinical Research and Development
[redacted]

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Amendment Rationale:

The key purposes of this amendment are to incorporate the following changes:

1. Add mandatory supportive care measures during the 3 High Risk Blocks

As of October 16, 2013, 73 subjects have initiated treatment in the CA180372 trial. Three subjects died due of complications after the HR3 block among the 54 patients who had initiated this block of treatment. The first two deaths were both associated with overwhelming infection. The cause of death for the 3rd event is unknown. The subject died at home while sleeping after having missed a scheduled visit for interim lab work. None of the deaths were attributed to dasatinib, the investigational medicinal product. The Data Monitoring Committee (DMC) has been informed and has confirmed that the number of deaths does not meet the protocol defined stopping rules.

From the published experience in EsPhALL as well as the unpublished experience in the amended EsPhALL setting, up to 10% of high-risk patients treated with the AIEOP-BFM-2000 chemotherapy backbone plus imatinib suffer from fatal complications which are typically septic/ infectious in etiology after the intensive High Risk chemotherapy blocks[1,2].

Based on the events observed in this study a number of changes are being instituted to the supportive care measures during the High Risk treatment blocks.

- **Mandatory blood counts with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery.** These blocks are highly myelosuppressive. Recovery is defined as ANC > 0.2 $x10^9$/L (200/µl) and platelet transfusion independence.
- **Mandatory myeloid growth factor support:** G-CSF 5µg/kg/day s.c. or i.v. starting anytime from 7 to 11 days from the start of the block, until the WBC count is > 3.0 $x10^9$/L (> 3000/mm^3). The option of pegfilgrastim 100µg/kg s.c. given once during the 7-11th day from the start of the block may be considered as an alternative.
- Although not required, the investigators should STRONGLY consider hospitalizing patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until blood count recovery because this is the intervention most likely to reduce the death rate.
- A low threshold should be used for institution of empiric antimicrobial therapy as clinical signs for infection can be blunted following high dose dexamethasone therapy. This particular guidance remains consistent with the revised protocol of July 31, 2013.

These supportive measures should be implemented immediately in all patients during the High Risk treatment blocks. The impact of these supportive measures on the conduct of the study will be more frequent subject monitoring with the potential for prompt intervention, thereby improving patient safety. No impact on data analysis is expected.

2. Provide updates to the women of childbearing potential (WOCBP) language to harmonize this language with the current BMS directives for WOCBP.

Changes to the Protocol:

1. Section 1 Introduction and Study Rationale, Imatinib & Chemotherapy in Newly Diagnosed Pediatric Ph+ ALL (EsPhALL Trial)
   a) Updated information and references in the first and second paragraphs
2. Section 1.1 Study Rationale
   a) Updated information in the second paragraph and updated the reference
   b) Updated reference in the third paragraph.
   c) Added last paragraph to provide rationale for changes being made in the protocol.
3. Section 3.3.1 Inclusion Criteria, Age and Reproductive Status
   a) Updated WOCBP wording to harmonize with the current BMS directives on WOCBP.
4. Section 3.3 3 Women of Childbearing Potential
   a) Updated WOCBP wording to harmonize with the current BMS directives on WOCBP.
5. Section 4.3. Selection Timing of Dose for Each Subject, Table 4.3A Treatment Plan Summary
   a) Updated wording for mandatory myeloid growth factor support.
6. Sections 4.3.1.3, 4.3.1.4 and 4.3.1.5 Consolidation Blocks 1, 2 and 3 (HR1, HR2 and HR3)
   a) Updated wording and Add mandatory supportive care measures during the 3 High Risk Blocks
7. Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1A
   a) Added note for mandatory CBC & Differential counts every 2 days after completion of chemotherapy in HR1, HR2 and HR3 until recovery.
8. Section 6.4 Pregnancy
   a) Updated WOCBP wording to harmonize with the current BMS directives on WOCBP.
9. Appendix 12, Optional Supportive Treatment Guidelines
   a) Updated wording for mandatory myeloid growth factor support.

References

1. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for the treatment of children and adolescents with Philadelphia-chromosome positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet-Oncology 2012 http://dx.doi.org/10.1016/S1470-2045(12)70377-7.
2. Andrea Biondi, MD, unpublished data 2013.

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Site Number:
Amendment Number: 04