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Oncology Clinical Development

Glivec®/Imatinib

REDACTED STUDY REPORT

CSTI571I2201
Non-Interventional Study Final Report

A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Philadelphia-positive (Ph+) Acute Lymphoblastic Leukemia (ALL) patients treated with chemotherapy + imatinib, with or without hematopoietic stem cell treatment (+/- HSCT)

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PASS information

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Marketing authorization holder	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	Positive benefit-risk profile of imatinib in combination with chemotherapy in newly diagnosed pediatric Ph+ ALL patients is based on a limited number of patients. The primary objective is to evaluate long-term clinical outcome measured by event-free survival (EFS). Secondary objectives include overall survival (OS) and safety in newly diagnosed Ph+ ALL pediatric patients treated with imatinib in combination of chemotherapy primarily in European countries. This multi-center, observational registry is not designed to test a formal hypothesis, but has been initiated as part of a post-marketing commitment.

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1 Abstract

Title

A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Philadelphia-positive (Ph+) Acute Lymphoblastic Leukemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (HSCT).

Version and date

Final, 19-Jan-2023

NIS Type

Non-interventional study (NIS) with both Primary Data Collection and Secondary Use of Data

Keywords

Observational; Pediatric; Ph+ ALL; Chemotherapy; Imatinib

Rationale and background

The aim of the study is to collect long-term efficacy and safety data of imatinib in combination with chemotherapy with or without HSCT (± HSCT) in newly diagnosed Ph+ ALL pediatric patients.

This is an EMA imposed NI-PASS (post authorization safety study), conducted per Guideline on good pharmacovigilance practices module VIII [EMEA/H/C/000406/II/80]

Research question and objectives

The positive benefit-risk profile of imatinib in combination with chemotherapy in newly diagnosed pediatric Ph+ ALL patients is based on a limited number of patients.

The primary objective of this study is to evaluate long-term clinical outcome measured by event free survival (EFS). Secondary objectives include overall survival (OS) and safety in newly diagnosed Ph+ ALL pediatric patients treated with imatinib in combination with chemotherapy. This multi-center, observational registry was not designed to test a formal hypothesis, but has been initiated as part of a post-marketing commitment primarily in European countries.

Study design

This study is an observational, multi-center disease registry to collect efficacy and safety data in Ph+ ALL pediatric patients treated with chemotherapy + imatinib, with or without HSCT, primarily in European countries. The study concept was endorsed by the EMA as part of the post-marketing commitment [EMEA/H/C/000406/II/80] and the design is aligned with routine medical practice in the treatment of newly diagnosed Ph+ ALL in pediatric patients across Europe. For each patient enrolled in the registry, a minimum of five years observational follow-up data was collected as measured from the date of start of imatinib treatment, unless the patient discontinued the study early.

Setting

The study population includes male or female pediatric patients (ages 1 to <18 years old) with documented, newly diagnosed Ph+ ALL who enrolled into this registry within six months of diagnosis or were enrolled in a clinical trial within six months of diagnosis (although no earlier than January 2012), and who were previously treated or are currently on treatment with chemotherapy + imatinib ± HSCT. Long-term safety and efficacy data are to be collected such that the observational follow-up data for each patient was a minimum of five years from start of imatinib treatment. The registry had a planned enrollment of minimum of 50 patients.

Subjects and study size, including dropouts

A minimum of 50 patients were planned in the study.

[redacted]

Variables and data sources

Event free survival, defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death.

Overall survival, defined as time from diagnosis to death from any cause.

Safety: The incidence of Adverse event (AE), Serious AEs (SAEs) and deaths from start of imatinib treatment. The data for this study are being retrieved from hospital discharge files, clinical records and electronic medical records. Standard measures of growth and development e.g. general physical examination, height, weight, and Tanner staging.

Statistical methods

Primary analysis

The analysis of the primary endpoint EFS was performed in a descriptive manner, without hypothesis testing. EFS was analyzed and presented using the Kaplan-Meier method. Estimated event-free rate by 6, 12, 18, 24 months and then yearly and median EFS was also estimated along with 95% confidence intervals.

For patients who did not experience any of these events, the time will be censored at the date of last contact in the study (i.e. not including the survival follow-up).

Secondary analysis

The key secondary endpoint was OS. The analysis was performed in a descriptive manner without hypothesis testing. OS was analyzed and presented using the Kaplan-Meier method. Estimated survival rate by 6, 12, 18, 24 months and then yearly and median OS was also estimated along with 95% confidence intervals (CI). The time was censored at the date of last contact for patients who are still alive.

Results

A total of 65 patients were screened. Of those 65 patients, 3 patients were screen failures and 62 patients were enrolled in the study. However, the number of enrolled patients was revised to 60 due to a major GCP non-compliance issue. All investigator site files of 2 patients along with source documents for informed consent form (ICF) signature process and ICFs were completely destroyed by the site 4006.

Data from these 2 affected patients was removed from the analysis. However, it did not impact protocol planned sample size as the total number of enrolled patients was revised to 60 patients.

Among the 60 enrolled patients, 20 patients were in the poor risk group and 40 patients in the good risk group. All enrolled patients (100%) discontinued the treatment and the study. The main reason for end of treatment was completion of prescribed regimen in 42 patients (70.0%), the main reason for end of study was follow-up completed as per protocol in 36 patients (60%). The median age of the 60 enrolled patients was 9 years (range: 1 to 17). The majority of patients were Caucasian (93.3%), reflecting the countries that participated in the study.

In all patients, the median time on imatinib prior to transplant was 717 days (range: 16 – 3189 days) and the median exposure to imatinib prior to transplant was 663.5 days (range: 16- 3189 days). The median time on imatinib prior to transplant and the median duration of exposure to imatinib prior to transplant were more than twice as long in the good risk group compared to the poor risk group (726 vs. 326.5 days and 704.5 vs. 312.5 days, respectively).

During the whole duration of the study, overall, 11 patients died (7 in the poor risk group and 4 in the good risk group. Two of those 11 patients died within 30 days after discontinuation of imatinib treatment.

Discussion

Efficacy results

- A total of 28 EFS events were observed during the study. The median EFS time was not reached. The estimated EFS rate at 60 months was 57.1% (43.4, 68.7) in all patients.

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- The median time for OS was not reached. The survival probability estimate at 60 months was 81.1% (95% CI: 68.5, 89.1).
- Overall best CHR status (with 95 % CI) was noted as 65% (95% CI: 51.6, 76.9) in the all patients group. By 12 months the rate of best CHR is 48.3% (95% CI: 35.2, 61.6), i.e. nearly three quarter of patients have reached CHR within the first year after diagnosis.
- Best MRD response (with 95 % CI) was 46.7% (33.7, 60.0) at post induction and 95% (86.1, 99.0) overall in the all patients group.
- Best complete remission status overall (with 95 % CI) was reported by 57 patients (95.0% (95% CI: 86.1, 99.0) in the all patients group. Seven patients out of 57 patients (12.3%) reported loss of CR. The KM estimated rate of CR duration at 60 months is 85.0% (95% CI: 70.7, 92.6).
- Overall, 28 patients received a transplantation. The median time (95% CI) to transplant in all patients was 65.9 months (38.1, NE). The KM estimated rate (95% CI) by 60 months was 48.4% (35.9, 62.6) in all patients.
- For 24 out of 28 (85.7%) transplanted patients engraftment was reported. The median time (95% CI) to engraftment was 1.0 month (0.8, 1.3). The median time to engraftment in those 24 patients is 0.95 months (range: 0.4 - 8.3).
- Of the 28 patients who received a transplantation, 26 (92.9%) patients reported no neutrophil or platelet engraftment failure. For 2 patients no information about engraftment was provided.
- Out of 28 patients in the transplanted set, presence of acute graft versus host disease (GvHD) was noted in 12 (42.9%) patients, no GvHD in 11 (39.3%) patients and GvHD not assessed/missing in 5 (17.9%) patients. Presence of chronic graft versus host disease (GvHD) was noted in 4 (14.3%) patients, no GvHD in 19 (67.9%) patients and GvHD not assessed/missing in 5 (17.9%) patients.
- After adjustment of prognostic factors, the good risk patient group shows a benefit on EFS and OS over the poor risk patient group (HR 0.167; 95% CI: 0.060, 0.468) and (HR 0.197; 95% CI: 0.029, 1.331), respectively.

Safety results

- The most frequently reported AEs regardless of study drug relationship by SOC of all grades were: infections and infestations (88.3%), blood and lymphatic system disorders (86.7%), gastrointestinal disorders (83.3%), general disorders and admistration site conditions (61.7%) and metabolism and nutritiona disorders (58.3%).
- The most frequently reported AEs regardless of study drug relationship by PT of all grades were: stomatitis (66.7%), thrombocytopenia (58.3%), neutropenia (56.7%) and febrile neutropenia (53.3%).
- Of the 60 patients, 11.7% of the patients experienced at least one AE that led to study drug discontinuation regardless of the study drug relationship.
- The most frequently reported AEs suspected to be related to study drug by PT of all grades were: neutropenia (40%), thrombocytopenia (35%), vomiting (31.7%) and febrile neutropenia (30%).
- The most frequently reported AEs of all grades and of grade 3 or 4 observed that required dose adjustment or interruption regardless of the study drug relationship were: neutropenia (30%) and febrile neutropenia (23.3%).
- Two (3.3%) patients died within 30 days after end of treatment with imatinib. The reported cause of death were 'Death' and 'Intracranial hemorrhage'. Review of these two deaths did not reveal any new safety information. During the entire duration of the study 11 patients died (7 in the poor risk group and 4 in the good risk group).
- Among patients in Tanner stage 1 at Baseline, Tanner stage 2 was attained in 4 out of 6 male patients for genital development and pubic hair, and in 7 out of 9 female patients for breast development and pubic hair.

[redacted]

- Of the 23 male patients at risk of delayed puberty at start date of imatinib, puberty was not delayed in 11 patients (47.8%), delayed in 2 patients (8.7%) and was unknown in 10 patients (43.5%).
- Of the 14 female patients at risk for delayed puberty at start date of imatinib, puberty was not delayed in 2 patients (14.3%), delayed in 3 patients (21.4%), and was unknown in 9 patients (64.3%).

Conclusion

- The final analysis demonstrated sustained efficacy of imatinib in combination with chemotherapy with or without HSCT (± HSCT) in newly diagnosed Ph+ ALL pediatric patients
- The safety profile is consistent with previously reported safety of imatinib in combination with chemotherapy with or without HSCT (± HSCT) in newly diagnosed Ph+ ALL pediatric patients
- The overall benefit-risk assessment of imatinib use in pediatric patients with newly diagnosed Ph+ ALL remains favorable.

The reported AEs in I2201 study are known with imatinib exposure. Of note, the reported frequencies of AEs needs to be viewed in relation to the small number of subjects enrolled (N=60). Due to the rarity of the indication, the planned enrollment was reduced to a minimum of 50 patients. The study results didn't reveal any safety finding in long term follow-up of pediatric patients with Ph+ ALL (in this study, long term safety and efficacy data was collected such that the observational follow-up for each patient was a minimum of 5 years from start of imatinib treatment or such available data until early patient discontinuation).

Marketing Authorization Holder

Novartis Europharm Limited

[redacted]

2 List of abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
BMI	Body Mass Index
CI	Confidence Interval
EMA	European Medicines Agency
EU	European Union
EU PAS	European Union Post-Authorization Study
FISH	Fluorescence in situ Hybridization
GCP	Good Clinical Research Practice
HSCT	Hematopoietic Stem Cell Treatment
ICF	Inform Consent Form
NCI	National Cancer Institute
NI-PASS	Non-interventional Post-authorization Safety Study
Ph+	Philadelphia Chromosome Positive
PI	Primary Investigator
PIP	Pediatric Investigation Plan
PRAC	Pharmacovigilance Risk Assessment Committee
RT-PCR	Real Time - Polymerase Chain Reaction
SDS	Standard Deviation Score

3 Investigators

There was no principal or coordinating investigator assigned to this study.

4 Other responsible parties

Not applicable.

5 Milestones

Study milestones are shown in Table 5-1.

Table 5-1 Study milestones

Milestone	Actual date	Comments
Approval of the study protocol by PRAC	9-Jan-2014	
Start of data collection	14-Jul-2014	
Registration in the EU PAS register	30-May-2014	
Annual study progress report	8-Dec-2014	Focused on administrative aspects of the trial such as recruitment details, initiated sites etc. In addition, results related to the patient disposition and deaths were provided.
Annual study progress report 2	18-Nov-2015	
Approval of protocol amendment 1	13-May-2016	PRAC endorsement decision adopted.
Annual study progress report 3	16-Nov-2016	
Annual study progress report 4	29-Nov-2017	
Annual study progress report 5	06-Nov-2018	As requested by EMA, details of adverse events that lead to treatment discontinuation and details of fatal cases with sufficient information to allow causality assessment were added
Annual study progress report 6	09-Dec-2019	
Annual study progress report 7	23-Nov-2020	As requested by EMA, addition of outputs for patients' demographics, disease history, and assessment of growth and development.
Annual study progress report 8	15-Nov-2021	
Final report of study results	19-Jan-2023	

6 Rationale and background

The European Commission approved the use of imatinib (Glivec®) in pediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy on 28-Jun-2013 based on a positive benefit-risk profile. The EMA requested additional long-term efficacy and safety data for 100 patients as a NI-PASS to the type II variation (EMEA/H/C/000406/II/80), to address the

[redacted]

limited size of the efficacy (92 patients) and safety database (220 patients) that was available at the time of registration of the above pediatric indication. In order to provide additional data in this population, a NI-PASS was to be conducted primarily in Europe. This pediatric registry is intended to fulfill this commitment. Due to the rarity of the indication, the Marketing Authorization Holder requested and obtained approval from EMA to expand enrollment activities to Russia (20-Jun-2013) and Ukraine (11-Sep-2013) provided that the majority of patients would be enrolled in Western Europe. In 2016, the planned enrollment was reduced to a minimum of 50 patients as achieving a sample size of 100 patients would have precluded a timely availability of the results.

The first annual report was submitted to the EMA in Dec-2014, with yearly updates until the eighth update to EMA The data cut-off for writing the 8th annual report was 30 Jun 2021. This report included an overview of enrollment activities, demographics, disease history, patient disposition, duration of follow-up since diagnosis, AEs leading to discontinuation, deaths, and growth and development data.

Last patient last visit was on 01-Sep-2022 and the database lock date was 10-Oct-2022. The current report is the final CSR with the final analysis of all available data.

7 Study objectives

Primary objective:

To evaluate long-term clinical outcome measured by event-free survival (events defined as: relapse, death, secondary malignancies).

Main secondary objectives:

- To evaluate overall survival
- To evaluate safety

Other secondary objectives:

- To evaluate hematological remission status
- To evaluate minimal residual disease response
- To evaluate duration of complete remission
- To evaluate time to transplantation, time to engraftment, engraftment failure, graft versus host disease
- To assess growth and development

8 Amendments and updates to the protocol

The study protocol was amended twice. Major changes are listed in Table 8-1 below. The final version of the protocol is provided in Appendix 16.1.1.

Table 8-1 Amendments and updates to the protocol

Number	Date	Amendment or update
1	11-May-2016	The number of patients to be studied was reduced from 100 to a minimum of 50 due to challenges in enrollment.

[redacted]

		The definition of end of study was clarified. The new definition is as follows: “the end of study is defined as the point when a minimum of five years of observational follow-up data are available for each enrolled patient, or such available data until early discontinuation, as measured from the date of start of imatinib treatment”. Administrative updates
2	27-Mar-2017	The use of the Investigator’s Brochure for Glivec® (imatinib) was decided to be discontinued, since Glivec has been in the market for more than 15 years and has a well-established efficacy/safety profile. No further global clinical development is planned for the compound. Therefore, the latest approved national/regional product label (i.e. for this study, the European Union (EU) Summary of Product Characteristics) is to serve as the reference safety information for the compound and reference to the imatinib/Glivec Investigator’s brochure was removed from the protocol.

9 Research methods

9.1 Study design

9.1.1 Description of study design

This study has been designed as an observational, multi-center registry to collect efficacy and safety data in Ph+ ALL pediatric patients (ages 1 to <18 years old) treated with chemotherapy + imatinib, with or without (± HSCT) primarily in European countries. The study concept was endorsed by the EMA as part of the post-marketing commitment EMEA/H/C/000406/II/80 and the design is aligned with ensuing discussions, as well as current medical practice in the treatment of newly diagnosed Ph+ ALL in pediatric patients across Europe.

A minimum of 50 pediatric patients meeting eligibility criteria after informed consent signature were enrolled into the registry primarily from European countries, with some limited recruitment from non-EU countries, e.g. Russia, Ukraine. Due to the descriptive nature of this registry and the lack of a specific hypothesis to be tested, no formal sample size calculation exists. Enrollment was supported through cooperation with approved, clinical trials (e.g. EsPhALL Study). The EsPhALL Study was a Phase II/III, open label, randomized study designed to compare safety and efficacy of imatinib with chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia. The trial was finalized in 2018 and is registered with EudraCT (2004-001647-30) and clinicaltrials.gov - number NCT00287105.

The registry captured an observational follow-up period of minimum 5 years for each enrolled patient, or such information until early patient discontinuation (Appendix 16.1.1-Protocol-Section 7.1.4), as measured from the date of start of imatinib treatment. For the period whilst the database was open, retrospective additions to or revisions of the entered data was possible at any time as additional or corrective data emerges. For patients meeting all inclusion criteria, enrollment was defined as having occurred on the date of patient inclusion into the registry (i.e. signature of informed consent).

No prospective clinical, instrumental or laboratory assessments/ interventions was performed other than those required for disease management according to local best practice or locally

[redacted]

approved summary of product characteristics or as stipulated in a clinical trial protocol, if a patient was taking part in a clinical trial in parallel with this registry (e.g. EsPhALL Study).

The population included patients at different stages of chemotherapy + imatinib treatment upon their enrollment into this registry (Appendix 16.1.1-Protocol-Section 7.2.1). For the purposes of this registry, and in order to achieve its objectives, the notions of "baseline" and "follow-up" are entirely independent of the timing/ date of patient registry enrollment.

- The notion of "baseline" consisted of patient pre-treatment information from the time of diagnosis until just prior to start of treatment with imatinib.
- The notion of "follow-up" information comprised of any data collected by the treating physician and/ or designee from the start of imatinib onwards (i.e. post-"baseline"), regardless of whether this was prior to or after the date of registry enrollment.

Patient follow-up visits (whether prior to or after registry enrollment) was scheduled according to the standard practice of the site and to the treating physician's best judgment or as specified in the visit schedule of any clinical trial in which the patient may be or may have been enrolled. Where disease evaluation was performed frequently, any follow-up information collected that was relevant to the objectives of this registry was recorded in the database. Data was collected such that the observational follow-up for long term safety and efficacy was a minimum 5 years for each enrolled patient or such available data until early patient discontinuation.

Efficacy assessments included standard long-term outcomes such as Overall Survival (OS) and Event Free Survival (EFS) (Appendix 16.1.1-Protocol-Section 7.7.4). Minimal Residual Disease (MRD) was assessed at appropriate time points (Appendix 16.1.1-Protocol-Section 7.4.2.5). In terms of long-term safety, adverse events and serious adverse events in the observation period were collected.

Disease management, disease status and therapeutic interventions were recorded. Follow-up captured patient and disease status, response to treatment and treatment/ regimen changes at a frequency defined by the standard practice of each site.

Designated registry staff entered the data into an electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture. For each patient enrolled in this registry a minimum of a once yearly update of data in the registry database was required to occur (12 ±2 month intervals).

9.1.2 Rationale for registry design

The study objective is to provide additional data to support the positive benefit-risk profile of imatinib in newly diagnosed pediatric Ph+ ALL patients. ALL is a common malignancy in the pediatric population but Ph+ ALL only accounts for up to 5% of pediatric ALL, which makes it a rare disease. Therefore, the conduct of multiple or large clinical trials in this patient population was not feasible. In addition, considering the remarkable benefit shown by the addition of imatinib to chemotherapy in Study COG-AALL0031 (Schultz et al 2009), newly diagnosed Ph+ ALL pediatric patients were treated with imatinib in clinical practice for some time and a prospective randomized trial with a "no imatinib" arm would be unethical in this patient population.

[redacted]

In a NI-PASS registry design the medicinal product, imatinib, was prescribed in a usual manner, according to the terms of the marketing authorization. The therapeutic strategy assigned to the patient was not proscribed by this registry protocol, but was within current medical practice. In order to clearly separate the decision to prescribe medication from the decision to include a given patient in this registry, there was no central provision of medication. In summary, given the rarity of the disease, current clinical practice and unfeasibility of a randomized design, an observational study in imatinib-treated patients was the optimal way to obtain prospective data in a standardized manner and address the study objective. A registry design permits the large scale capture of information across a sizeable international cohort of pediatric patients with newly diagnosed Ph+ ALL, producing a representative dataset without bias towards demographic or social characteristics.

Current standard therapy for pediatric Ph+ALL patients: Studies conducted by children's oncology group (COG) and the european intergroup study of postinduction treatment of Ph-chromosome positive ALL (EsPhALL) consortium over the last decade have demonstrated that the majority of pediatric Ph+ ALL patients are effectively treated with the combination of a tyrosine kinase inhibitor (TKI) and chemotherapy, without (HSCT) in first complete remission (CR1). Ph+ ALL patients will begin daily imatinib at Day 15 of Induction IA. After the Induction IB phase (week 10-12), minimal residual disease (MRD) will be assessed by immunoglubulin-T-cell-receptor (IgH-TCR) PCR, and patients will be classified as standard risk (those with MRD $< 5 \times 10^{-4}$) or High Risk (MRD $> 5 \times 10^{-4}$). Standard risk patients will receive cytotoxic chemotherapy backbone used in EsPhALL and COG protocols. Patients will continue to receive imatinib until the completion of all planned chemotherapy (two years of treatment). For high risk patients (approximately 15-20% of patients), allogeneic HSCT in CR1 is still considered the treatment of choice. High risk patients will receive the EsPhALL chemotherapy backbone and proceed to HSCT after completion of the three consolidation blocks. While there is variability in clinical practice regarding the use of TKI's post-HSCT in Ph+ALL, and controversy regarding their impact on toxicity, graft-versus-host disease (GVHD) and Event Free Survival (EFS) in high risk pediatric Ph+ ALL patients, Imatinib should be administered to high riskpatients from Day +56 until Day +365 post-HSCT (Brown et al 2020).

9.1.3 Timing of study status reporting

A study status update of the registry was provided annually for the duration of the study. This is the final analysis report performed after registry end of study.

9.1.4 Definition of the end of study

The end of study was defined as the point when a minimum of 5 years of observational follow-up data was made available for each enrolled patient, or such available data until early discontinuation (Appendix 16.1.1-Protocol-Section 7.2.5), as measured from the date of start of imatinib treatment.

[redacted]

9.2 Setting

9.2.1 Population

The study population included male or female pediatric patients (ages 1 to < 18 years) with documented, newly diagnosed Ph+ ALL, who enrolled into this registry within 6 months of diagnosis or were enrolled in a clinical trial within 6 months of diagnosis (although no earlier than Jan-2012), and who were previously treated or are currently on treatment with chemotherapy + imatinib ± HSCT.

Data from patients participating in past or present interventional or observational studies was included in this registry. Any concurrent participation of pediatric patients from Ph+ ALL studies was subjected to the aforementioned studies' alignment with the inclusion criteria listed in Appendix 16.1.1-Protocol-Section 7.2.2. Any specific criteria in the concurrent clinical trial protocol explicitly excluding a patient from participating in a registry would render the patient ineligible for this registry.

The enrollment of patients already on treatment when entering the registry population introduced the risk of selection bias, since such patients may have different characteristics to those who progressed and died before registry opening. As a consequence, every effort was made to obtain data for this registry from all patients meeting the inclusion criteria, who enrolled in the EsPhALL Study since Jan-2012. This included patients who died before registry opening, although this was a subject to parent/ legal guardian consent and local regulations. Any chemotherapy regimen in combination with imatinib was permissible.

The investigator or designee ensured that only patients who meet all of the following inclusion criteria were enrolled in the study.

[redacted]

9.2.2 Inclusion Criteria

Patients eligible for inclusion in this registry met the following criteria:

1. Male or female, pediatric patients aged greater than 1 year (≥365 days) and less than 18 years old (<17 years, 365 days) at diagnosis.
2. Documented, newly diagnosed Ph+ ALL.
   - Recorded presence of t(9;22)(q34;q11) is required e.g. determined via institutional cytogenetics or FISH and/ or of the presence of BCR-ABL fusion transcript identified by RT-PCR or FISH.
3. Enrolled into this registry within 6 months of diagnosis or enrolled in a clinical trial within 6 months of diagnosis, although no earlier than Jan-2012.
4. Previously treated or currently on treatment with any chemotherapy regimen + imatinib (of an HA-approved formulation or HA-approved Glivec® generic) ± HSCT.
5. Written informed consent obtained prior to any information being entered into the registry (parent / legal guardian consent, where applicable).
   - Assent from a patient enrolled as a minor by parent / legal guardian consent was required to be obtained wherever possible. Obvious child dissent was required to be respected.
   - A patient enrolled as a minor by parent / legal guardian consent was required to be re-consented as an adult upon reaching the legal age of maturity during the course of the registry (legal age of maturity defined by local regulations).
   - Patients fulfilling the inclusion criteria, but who have died prior to registry opening and without the opportunity to give consent, may still be eligible for inclusion, subject to local requirements regarding the consent process.

9.2.3 Exclusion Criteria

There were no exclusion criteria for this non-interventional study.

Patients voluntarily withdrew from the registry at any time.

9.2.4 Reasons for non-inclusion

The reasons for non-inclusion in the registry was recorded during pre-screening and classified as:

- Did not meet diagnostic criteria
  - Patients for whom the presence of t(9;22)(q34;q11) could not be determined/ confirmed or for whom diagnosis occurred outside of the specified age range or for whom diagnosis was greater than 6 months before first treatment.
- Subject consent not given (e.g. either by parent/ legal guardian or subject themselves)
- Alternative treatment choice (e.g. physician's decision not to treat with imatinib or to treat with a non-HA-approved Glivec® generic).
- Unknown
- Other

[redacted]

9.2.5 Reasons for discontinuation

The reasons for discontinuation from participation in the registry was collected and classified as:

- Death
  - For patients who discontinued due to death, then 'Death' was recorded as reason for discontinuation. Patient's date of death, cause of death and phase of disease during which death occurred was recorded, as permitted by local regulations.
- Lost to follow up
  - Patients lost to follow up was recorded as such on the CRF. For patients who were lost to follow-up, the treating physician and/ or designee showed "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.
- Subject withdrew consent
- Administrative problems
- Follow-up completed as per protocol.
- Protocol deviation

9.3 Variables

A tabular overview of the main variables and their relationship to the defined objectives are outlined in Appendix 16.1.1-Protocol-Table 6-1.

The corresponding data collection schedule at each patient visit was contained within Appendix 16.1.1-Protocol-Table 7-1.

Detailed assessment information and the data to be collected, if available, are outlined in Appendix 16.1.1-Protocol-Section 7.4.2.

EFS, defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death.

OS, defined as time from diagnosis to death from any cause.

Standard hematology panel, including required laboratory parameters to define complete hematological remission. Parameters for complete hematological remission defined in Section 9.4.3.4.

MRD response, defined as any negative level of MRD, i.e. MRD <0.01%.

Time to transplant, time to engraftment, engraftment failure, graft versus host disease

- Time to transplant is defined from the date of diagnosis until the date of the transplant procedure.
- Time to engraftment (neutrophil, platelet and both neutrophil/platelet engraftment) is defined as the time from the date of transplant to the date of engraftment.
- Engraftment failure is defined as either definitive engraftment failure or the absence of engraftment.
- Presence/ absence of graft versus host disease; chronic or acute (Section 9.4.3.8).

[redacted]

Assessment of growth and development

- Physical examination information, including the standard growth & development measures of height and weight, and sexual maturity (Section 9.4.3.9 to Section 9.4.3.12).

More details on variables are described in Appendix 16.1.1-Protocol-Section 7.3.1.

9.4 Data sources and measurement

9.4.1 Data sources

The data for this registry was retrieved from hospital discharge files, clinical records and electronic medical records (e.g. laboratory reports of baseline assessment data etc.).

Initiation of the participating sites were performed by a Novartis representative and/ or designee. Before registry initiation, a Novartis representative and/ or designee would review the protocol and eCRF with the treating physicians and their staff.

Sites enrolling patients in this registry recorded data on eCRFs designed by a Novartis representative and/ or designee. The database captured, performed standard edit checks and stored the data.

Concomitant or prior medications entered into the database was coded using the World Health Organization (WHO) Drug Reference List. Relevant medical history/ current medical conditions and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data was transferred to Novartis on a monthly basis as defined in Appendix 16.1.1-Protocol-Section 9. Clinical data was transferred to Novartis on once yearly (minimum).

9.4.2 Data collection schedule

This is a non-interventional registry and does not impose a therapy protocol, diagnostic/ therapeutic procedure, or a visit schedule. Patients were treated according to the local prescribing information, and routine medical practice in terms of visit frequency and the types of assessments performed for disease evaluation, and only these data was collected as part of the registry. The treating physician and/ or designee are asked to complete the appropriate electronic Case Report Form (eCRF) at every patient visit, where possible. For each patient enrolled in the registry a minimum of a once yearly update (12 ±2 month intervals) of data in the registry database was required to occur to ensure an ongoing data stream, with the exception of safety data which should be entered within a month of new information becoming available. Where disease evaluation is performed frequently, any follow-up information collected that is relevant to the objectives of this registry should be recorded in the database. Long term safety and efficacy data was collected such that the observational follow-up for each patient was a minimum of 5 years from start of imatinib treatment or such available data until early patient discontinuation (Appendix 16.1.1-Protocol-Section 7.2.5).

Table 9-1 is a data collection schedule that outlines all the assessment information required by the registry and indicates with an “X”, the visits when they are recorded. All data obtained from these assessments was required to be supported in the patient’s source documentation. The table indicates which assessments produce data to be entered into the clinical database (D) or remain

[redacted]

in source documents only (S) ("Category" column). The expectation is that laboratory assessments/ interventions shown are those required for the standard disease management of pediatric Ph+ ALL, according to local best practice.

- Where complete laboratory assessments/ interventions were not performed, it was acceptable to indicate not done.

For each patient discontinuation, the reason for discontinuation was determined.

[redacted]

Table 9-1 Data collection schedule

	Category	Protocol Section	Screening & Enrollment	Diagnosis / Baseline	Surveillance Period			Study Evaluation Completion	Survival follow-up
					On Treatment Follow-Up	End of study Treatment (EOT)	Post-Treatment Follow-Up		
					Visit Dates	EOT Date	Visit Dates	EOS Date	SURV Visit
Follow-up Visit			**1**	**2**	**601**	**777**	**602**	**778**	**888**
Obtain Informed Consent	D	8	X						
Patient history									
Inclusion/ exclusion criteria	D	7.2.2	X						
Demography	D	7.4.2.1	X						
Relevant medical history / current medical conditions	D			X					
Prior / Concomitant medications	D			X	X	X			
Concomitant antineoplastic therapy	D			X	X	X			
History and diagnosis of disease	D			X					
Induction Response [Poor / Good]	D	7.4.2.2		X					
Physical examination									
General Physical Examination	S	7.4.2.7		X	X	X	X	X	
Performance status	D	7.4.2.8		X	X	X	X	X	

[redacted]

	Category	Protocol Section	Screening & Enrollment	Diagnosis / Baseline	Surveillance Period			Study Evaluation Completion	Survival follow-up
					On Treatment Follow-Up	End of study Treatment (EOT)	Post-Treatment Follow-Up		
					Visit Dates	EOT Date	Visit Dates	EOS Date	SURV Visit
Follow-up Visit			**1**	**2**	**601**	**777**	**602**	**778**	**888**
Vital Signs [Height / Weight]	D	7.4.2.9		X	X	X	X	X	
Development & Growth [Tanner Staging]	D	7.4.2.10		X	X	X	X	X	
Laboratory assessments									
Response status [Efficacy]	D	7.4.2.3		X	X	X	X	X	
Hematology	D	7.4.2.4		X	X	X	X	X	
BM assessment / cytogenetics	D			X	X	X	X	X	
MRD assessment	D	7.4.2.5		X	X	X	X	X	
Extramedullary involvement [Cerebro-spinal Fluid Exam]	D			X	X	X	X	X	
Safety									
Adverse events / Serious adverse events	D	7.3.1.8		X	X	X	X	X	
Drug administration (imatinib dosing)	D	7.4.2.11		X	X				
Surgery									
Transplantation and engraftment [Hematopoietic Stem	D	7.4.2.6			X	X	X		

[redacted]

	Category	Protocol Section	Screening & Enrollment	Diagnosis / Baseline	Surveillance Period			Study Evaluation Completion	Survival follow-up
					On Treatment Follow-Up	End of study Treatment (EOT)	Post-Treatment Follow-Up		
Follow-up Visit			**1**	**2**	**Visit Dates**	**EOT Date**	**Visit Dates**	**EOS Date**	**SURV Visit**
					601	**777**	**602**	**778**	**888**
Cell Treatment (HSCT)]									
End of study treatment (EOT)	D					X			
Study Evaluation Completion	D							X	
Overall Survival	D	7.3.1.2							X

[redacted]

9.4.3 Asessments

9.4.3.1 Patient demographics and other pre-treatment characteristics

- Demographic information and other background or relevant medical history (i.e. age at diagnosis, sex, race, extent of disease)
- Information relating to patient eligibility and inclusion criteria (i.e. date of diagnosis, date of obtained informed consent).
- Details of all relevant prior concomitant medications, post-diagnosis, updated information and details of new concomitant medications and significant non-drug therapies.
- Concomitant antineoplastic therapy details (i.e. full chemotherapy regimen).

9.4.3.2 Induction response

The patient response to induction treatment provides a measure of the patient-risk category. The commonly used definitions of good-risk / poor-risk suggested below were adopted from Biondi et al 2012. If this was not the definition that was used for a patient, information was obtained with respect to the definition of risk.

- **Good-Risk Group**: Patients with both early response and complete remission at the end of induction e.g. Blast cell count < 1000/µl in peripheral blood after 7 days of Prednisone given in combination with chemotherapy drug(s) before induction is instituted or have M1/M2 BM at day 15 (after start of chemotherapy) or M1 BM at day 21 and achieve CR after induction period.
- **Poor-Risk Group**: Patients with poor early response to induction treatment or absence of complete remission at the end of induction e.g. Blast cell count ≥ 1000/µl in peripheral blood after 7 days of Prednisone given in combination with chemotherapy drug(s) before induction is instituted or have M3 BM at day 15 or M2/M3 BM at day 21 or do not achieve CR after induction period.
    - M1: <5% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.
    - M2: 5-25% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.
    - M3: >25% blasts in a BM aspirate.

9.4.3.3 Efficacy response

The efficacy of treatment with chemotherapy in combination imatinib (Glivec®) was evaluated from diagnosis, and based on the tests performed (e.g. extramedullary, cerebro-spinal fluid exam, hematological, MRD assessment data) by the treating physician and/ or designee for each patient to assess incidence of relapse and secondary malignancy

[redacted]

9.4.3.4 Hematological response

Peripheral blood was used to assess hematological response. Complete hematological remission requires that all of the following are present:

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

The loss of complete remission and thus the end of the duration of complete remission was defined as:

- ≥ 5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes.

Progressive disease (relapse) defined as the new appearance of any of the following:

- ≥ 25% blasts in bone marrow aspirate
- Any increase of at least 25% in the absolute number of circulating leukemic cells.
- ≥ 30% increase of Ph+ metaphase cells as assessed by standard cytogenetic analysis.
- Development (evidence) of extramedullary disease
- Other laboratory or clinical evidence of disease progression.

9.4.3.5 Minimal residual disease (MRD) response

- MRD response assessed via the detection of BCR-ABL transcript, collected at specified time-points. Time-points defined fully in Section 9.4.3.7.

9.4.3.6 Complete remission

- Complete remission is defined as < 5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes.
- The duration of complete remission is defined as the time from the date of first complete remission to the date of loss of complete remission (Appendix 16.1.1-Protocol-Section 7.4.2.4).

9.4.3.7 Molecular response

MRD assessments to detect BCR-ABL transcript were evaluated at specific time-points. Biondi et al 2012 defined the 5 time-points as the following: post-frontline induction; pre-consolidation block 1, pre-consolidation block 2, pre-consolidation block 3, post-consolidation.

MRD assessments might be performed for example via quantitative real-time PCR of mononuclear bone marrow and peripheral blood cells or detection by flow cytometry. Data should be provided if available at the aforementioned time-points.

9.4.3.8 Transplant and engraftment

- Transplant (i.e. date of transplantation, phase of transplantation, type of transplantation, source of transplantation, relationship to donor).

[redacted]

- Time to engraftment, engraftment failure (i.e. date, neutrophil/platelet engraftment success – yes/ no, engraftment failure – yes/no).
- Presence of graft versus host disease (i.e. chronic graft versus host disease presence – yes/ no, acute graft versus host disease presence – yes/no).

9.4.3.9 Physical examination

A general physical examination included the examination of general appearance, and vital signs (e.g. blood pressure [BP] and pulse), although the extent of the examination was at the discretion of the treating physician and/ or designee.

Significant findings that were present prior to first dose of imatinib was included in the Relevant Medical History page on the patient's eCRF. Significant new findings that began or worsened after start of treatment with imatinib (Glivec®) were recorded on the Adverse Event page of the patient's eCRF.

9.4.3.10 Performance status

Performance status was measured using the Lansky/ Karnofsky Performance Status Score. Wherever possible, the same performance scale used at baseline assessment had to be maintained for the duration of follow-up.

9.4.3.11 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) was captured in the database.

9.4.3.12 Tanner stage and development assessments

Tanner staging was evaluated as a measure of pubertal status (Tanner 1-5). Data corresponding to the age of menarche for girls and the age of adrenarche for boys were captured.

9.4.3.13 Dose administration record

Full and complete imatinib (Glivec®) dosing data from medical charts/ prescription records (historic and/ or current) was recorded. Detailed information including total daily dose, regimen and dose changes (e.g. dosing errors) was captured wherever possible.

9.5 Bias

A registry design permits the large scale capture of information across a sizeable international cohort of pediatric patients with newly diagnosed Ph+ ALL, producing a representative dataset without bias towards demographic or social characteristics.

In an effort for the registry population to be as representative as possible of the patient population as a whole, no exclusion criteria was defined. Furthermore, any standard concomitant chemotherapy regimen was permissible. Although this enhances the relevance of the study, it created a source of non-homogeneity with respect to adverse events related to concurrent chemotherapy. Reasons for non-inclusion was also identified to permit a possible analysis of any potential bias.

[redacted]

9.6 Study size

This is a multi-center, observational registry that was not designed to test a formal hypothesis and therefore there was no formal sample size calculation. The registry had a planned enrollment of a minimum of 50 patients.

9.7 Statistical methods

The statistical analysis of this study was performed by Novartis personnel.

SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform all data analyses and to generate tables, figures and listings.

All data from all centers participating in that registry was pooled and analyzed. Due to the expected small size of each center's patient population, no center effect was assessed.

All analyses, summaries, figures, and listings were performed on all patients (represented by the "All patients" column and by risk groups (good risk/poor risk) unless otherwise stated.All data summaries and analyses had descriptive purposes only with no formal inferential testing.

A limitation of the non-interventional, observational study design acknowledged within the protocol was related to the availability/completeness of data. The management of missing information was discussed later in this document in terms of the analyses to be performed.

9.7.1 Main summary measures

Categorical data (e.g., gender, race, etc.) was summarized by means of contingency tables; a "missing" category was included as applicable. Percentages were calculated using the number of patients in the relevant population or subgroup as the denominator. Quantitative data (e.g., age, body weight, etc.) was summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum and maximum).

For the purpose of this document, the word study was synonymous with this Novartis I2201 registry and any other clinical trial or study was appropriately identified (e.g. EsphALL study).

This study included patients at different stages of chemotherapy + imatinib treatment upon their enrollment into this study. However, as defined in the protocol, the notions of "baseline" and "follow-up" was entirely independent of the timing/ date of patient registry enrollment.

- The notion of "baseline" consisted of patient pre-treatment information from the time of diagnosis until just prior to start of treatment with imatinib.
- The notion of "follow-up" information comprised any data collected from the start of imatinib onwards (i.e. post-"baseline"), regardless of whether this was prior to or after the date of registry enrollment.

9.7.2 Main statistical methods

Key points of statistical methods are mentioned in this section, additional details are provided in Appendix 16.1.9-SAP.

9.7.2.1 Analysis sets

The following analysis sets were used for statistical analysis and data reporting.

[redacted]

Enrolled Patients Set: The Enrolled Patient Set inlcuded all patients enrolled into the study.

Full analysis set (FAS): The FAS included all enrolled patients who received at least one dose of imatinib + chemotherapy within the observational period.

Safety set: The Safety set included all enrolled patients who received at least one dose of imatinib and with a valid post-baseline assessment.

Transplanted Patients Set: The Transplanted Patients Set consists of all enrolled patients who were transplanted.

Imatinib Post-transplant Set: The Imatinib Post-transplant Set consists of all transplanted patients who received imatinib post-transplant.

The number of patients in each analysis population (Enrolled Patient Set, FAS, Safety Set, Transplanted Patients Set and Imatinib Post-transplant Set) were summarized.

9.7.2.2 Patient disposition, demographics and other baseline characteristics

9.7.2.2.1 Patient disposition

Data from patients who signed informed consent, but who were found to be screen failures and therefore not enrolled into the study were included in a listing only.

With respect to patient disposition the following information was presented using the Enrolled Patient Set:

- The number of enrolled patients who were treated with imatinib
- The number of patients for whom end of imatinib treatment has occurred (along with their reasons for end of imatinib treatment), and the number still on imatinib treatment at the time of the data cut-off date for the analysis
- The number of patients for whom study evaluation completion has occurred (along with their reasons for study discontinuation) and the number still in post imatinib treatment follow-up at the time of the data cut-off date for the analysis

9.7.2.2.2 Protocol deviations

All protocol deviations were listed.

9.7.2.2.3 Patient demographics

All baseline and demographic summaries and listings were generated using the FAS.

All demographic data, such as age at diagnosis, gender, race, body mass index (BMI), were summarized and listed using the FAS. Relevant medical history and current medical conditions, history and diagnosis of disease, previous or current clinical trial involvement and extramedullary involvement (including CNS involvement) reported at baseline were also listed and summarized (Refer to section Appendix 16.1.9-SAP-Section 2.1.1.7 for definition of baseline assessments).

In addition, the following derived variables were descriptively summarized:

- Age groups according to NCI risk (<10, ≥10 years)

[redacted]

- Age groups according to PIP definition (<2, 2-<12, ≥12-18years)
- Body Mass Index (BMI) calculated as weight [kg] / (height [m]**2) [kg/m^2] was divided into 5 BMI-for-age categories.

BMI-for-age was calculated using the 2000 Centers for Disease Control and Prevention BMI-for-age growth charts to obtain percentile rankings (Ogden and Flegal 2002).

The BMI-for-age categories were defined according to the revised childhood obesity terminology by Ogden and Flegal (Ogden and Flegal 2010):

- underweight: <5th percentile of BMI-for-age;
- at risk for underweight: 5th to <25th percentile;
- normal: 25th to <85th percentile;
- overweight: 85th to <95th percentile;
- obese: ≥95th percentile.

Details on medical history and current medical conditions, history and diagnosis of disease is described in Appendix 16.1.9-SAP-Section 2.3.3.

9.7.2.3 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

9.7.2.3.1 Study treatment / compliance

Imatinib exposure and dose intensity

Number and percentage of patients receiving imatinib in each treatment phase (induction, consolidation, maintenance) were summarized.

Imatinib exposure and dose intensity was summarized overall and by treatment phase (induction, consolidation, maintenance) using the Safety set.

Time on imatinib, duration of exposure to imatinib, percentage of days on treatment, actual dose intensity, and average daily dose was summarized using the definitions as described in Appendix 16.1.9-SAP-Section 2.4.1.1.

All summaries were performed on imatinib administered prior to any transplant.

Prior to transplant was defined as:

- For patients who did not receive any transplantation during the time on imatinib treatment, the whole time on imatinib treatment was considered
- For patients who received transplantation and were still on imatinib treatment at that time, only the time on imatinib treatment prior to transplantation date was considered.

Imatinib exposure was reported separately for imatinib treatment received following transplant for patients in the Imatinib post-transplant set.

Concomitant Antineoplastic therapy (chemotherapy)

Antineoplastic therapy was listed and summarized overall and by treatment phase (induction, consolidation, maintenance), ATC class, and preferred term using the Safety set.

[redacted]

Prior, concomitant and post therapies

Concomitant medications/significant non-drug therapies were listed and summarized using the Safety set. The number and percentage of patients with concomitant medication were presented by Anatomic Therapeutic Chemical (ATC) class and preferred term according to the last available version of the World Health Organization (WHO) Drug Dictionary Enhanced (DDE) at the time of coding. More details on prior, concomitant and post therapies are detailed in Appendix 16.1.9-SAP-Section 2.4.2.

9.7.2.4 Primary objective

The primary objective of the study was to evaluate the long term clinical outcome. The analysis of the primary endpoint was performed in a descriptive manner, without hypothesis testing.

EFS was analyzed and presented using the Kaplan-Meier method. Estimated event-free rate by 6, 12, 18, 24 months and then yearly and median EFS were also estimated along with 95% confidence intervals (using the method given by Brookmeyer & Crowley 1982). For patients who did not experience any of these events, the time was censored at the date of last contact in the study (i.e. not including the survival follow-up).

9.7.2.5 Secondary objective

The key secondary efficacy endpoint was overall survival (OS).

The analysis of OS was performed in a descriptive manner, without hypothesis testing.

OS was analyzed and presented using the Kaplan-Meier method. Estimated survival rate by 6, 12, 18, 24 months and then yearly and median OS were also estimated along with 95% confidence intervals (using the method given by Brookmeyer & Crowley 1982). The time was censored at the date of last contact for patients who were still alive.

Other secondary efficacy endpoints were the following outcomes:

- Rate of Complete Remission (CR)
- Duration of first complete remission
- Rate of Complete Hematological Remission
- Rate of MRD response
- Time to first transplantation
- Time to neutrophil engraftment
- Time to platelet engraftment
- Time to engraftment
- Rate of engraftment failure
- Rate of acute Graft versus Host disease
- Rate of chronic Graft versus Host disease

The efficacy endpoints were summarized descriptively for the FAS.

Details on method of analysis of response rate, analysis of time to event endpoints and analysis of duration of response is presented in Appendix 16.1.9-SAP-Section 2.7.2.

[redacted]

9.7.2.6 Supportive analyses

9.7.2.6.1 Supportive analyses on EFS and OS

Sensitivity analyses was performed on the primary endpoint EFS and on the main secondary endpoint OS taking into account the occurrence of transplantation as detailed in Section 9.7.4.

9.7.2.6.2 Other supportive analyses

- Time to transplant was analyzed and presented according to type of transplant donor (autologous, allogeneic, syngeneic, other, and unknown).
- An analysis was performed with the Cox proportional hazards regression model to evaluate the influence of prognostic factors on EFS and OS. Each potential factor was included in a multivariate Cox regression model for investigating their combined effect on the endpoint. This multivariate analysis included patients for whom data for all variables that was to be available, i.e. if a variable is not available or unknown for a patient, this patient's data was required to be excluded from the multivariate analysis. All hazard ratios were presented with the 95% confidence intervals.

The following potential prognostic variables were included in all multivariate analyses: age (<1, ≥1 to <10, ≥10 years, ≥1 to <10 being the reference category), sex (female vs male, female being the reference category), and extramedullary involvement (yes/no, no being the reference). The multivariate analyses of EFS and OS was additionally included for the early responses (risk categorization: high versus low, low being the reference) as a prognostic variable.

9.7.2.7 Safety analyses

All safety endpoints was summarized overall, and by risk group (good risk/poor risk) unless otherwise stated.

The assessment of safety was based on AEs (including laboratory abnormalities and vital signs constituting AEs), growth status, tanner staging and Lansky/Karnofsky performance status. The analyses are detailed in Appendix 16.1.9-SAP-Section 2.9.

The safety analyses were performed using the Safety set.

9.7.3 Missing values

Patients dropping out early or not providing sufficient data to enable achievement of the response to be evaluated were considered as early discontinuation or not evaluable, respectively, and were counted as non-responders in the analysis of binary response rates.

9.7.4 Sensitivity analyses

Sensitivity analyses was performed on the primary endpoint EFS and on the main secondary endpoint OS taking into account the occurrence of transplantation. The time was censored at the date of last contact for patients who did not undergo transplantation, or at the date of transplantation for patients who underwent transplantation.

In addition, the primary endpoint (EFS) and main secondary endpoint OS was analyzed and presented using the Kaplan-Meier method for the following subgroups:

[redacted]

- Age groups at baseline: <12 years versus≥12 years
- Enrollment into approved clinical studies: yes/no
- Type of transplant donor: autologous, allogenic, syngeneic, other and unknown
- Best MRD rate: negative (<0.01 %)/positive (≥0.01%)

Subgroup analyses was only performed if at least 5 patients were present in each subgroup.

9.7.5 Changes in planned analysis

An analysis was planned to evaluate the impact of prognostic factors on the odds of non-response to induction therapy. This analysis was not performed as the required data were not collected.

All other statistical analyses were provided as foreseen in the latest version of the statistical analysis plan ready before data base lock.

All statistical methods used to perform the analyses presented in this report are described in Section 9.7 and Appendix 16.1.9.

9.8 Quality control

Queries related to the completeness and accuracy of the data entered ensured data quality and integrity. The web-based system had an automatic validation programs to check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the registry site staff.

9.8.1 Site monitoring

Formal site monitoring was performed as described in the Monitoring Plan for this study.

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) reviewed the protocol and eCRFs with the investigators and their staff. During the study, the field monitor visited the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel was required to be available to assist the field monitor during these visits.

The investigator was required to maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs was required to be traceable to source documents in the patient's file. The investigator was required to also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator was required to give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/ exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

[redacted]

10 Results

10.1 Participants

10.1.1 Disposition of patients

A total of 62 patients were enrolled in this study. However, the number of enrolled patients was revised to 60 patients due to the following reason:

The PI at site [redacted]. There were 2 patients ([redacted] and [redacted]) enrolled at this site, both had End of Treatment visits done prior to PI retirement. During the close-out visit conducted on 29-Oct-2019 [redacted], the Clinical Research Associate from the vendor [redacted] on charge of the monitoring discovered that all investigator site files with source documents for ICF signature process and ICFs were completely destroyed by the site. Per protocol, site had to retain trial documents for minimum of 15 years from completion of the registry (unless sponsor provides written permission to dispose of them, which was not the case here). It was considered major GCP non□compliance issue and, therefore, data from these 2 affected patients was removed from the analysis. However, it did not impact protocol planned sample size as the total number of enrolled patients was revised to 60 patients.

Among the 60 enrolled patients, 20 patients were in the poor risk group and 40 patients in the good risk group. All enrolled patients (100%) discontinued the treatment and the study. The main reason for end of treatment was completion of prescribed regimen in 42 patients (70.0%), the main reason for end of study was follow-up completed as per protocol in 36 patients (60%) (Table 10-1).

Table 10-1 Patient disposition by risk group (Enrolled patients set)

Disposition Reason	Poor risk N=20 n (%)	Good risk N=40 n (%)	All patients N=60 n (%)
Patients enrolled			
Treated	20 (100)	40 (100)	60 (100)
Patients treated			
End of treatment	20 (100)	40 (100)	60 (100)
Primary reason for end of treatment			
Adverse events	7 (35.0)	2 (5.0)	9 (15.0)
Subject withdrew consent	1 (5.0)	0	1 (1.7)
Administrative problems	2 (10.0)	0	2 (3.3)
Death	0	1 (2.5)	1 (1.7)
Disease progression	3 (15.0)	2 (5.0)	5 (8.3)
Completed prescribed regimen	7 (35.0)	35 (87.5)	42 (70.0)
Study evaluation after end of treatment			
Patients who did not enter the study evaluation phase@	5 (25.0)	4 (10.0)	9 (15.0)
Patients who completed study evaluation phase	15 (75.0)	36 (90.0)	51 (85.0)

[redacted]

Disposition Reason	Poor risk N=20 n (%)	Good risk N=40 n (%)	All patients N=60 n (%)
Primary reason for study evaluation completion			
Lost to follow-up	2 (10.0)	1 (2.5)	3 (5.0)
Administrative problems	1 (5.0)	1 (2.5)	2 (3.3)
Death	6 (30.0)	3 (7.5)	9 (15.0)
Disease progression	0	1 (2.5)	1 (1.7)
Follow-up completed as per protocol	6 (30.0)	30 (75.0)	36 (60.0)

@ Patients with Death as primary reason for end of treatment OR who refused to be followed for post-treatment evaluation and have no study completion reason entered.
- Percentage is based on N
- Treatment refers to imatinib
Source: Table 14.1-1.1.

10.1.2 Protocol deviations

Protocol deviations are listed in Listing 16.2.2-1. One patient ([redacted]) was enrolled as a [redacted] by the [redacted] consent. [redacted]. Therefore, all data from [redacted] onwards were excluded from the analysis.

10.1.3 Data sets analyzed

The definition of all analysis sets are provided in Section 9.7.2.1

All patients (N=60) enrolled in this study were included in the full analysis set and the safety set. Of the 60 patients who were enrolled, 28 patients (46.7%) received a HSCT. Of those 28 transplanted patients, 9 patients (32.1%) received imatinib post-transplant (Table 10-2).

Table 10-2 Analysis sets (Enrolled Patients Set)

Analysis set	Poor risk N=20 n (%)	Good risk N=40 n (%)	All patients N=60 n (%)
Enrolled patients set	20 (100)	40 (100)	60 (100)
Full analysis set	20 (100)	40 (100)	60 (100)
Safety set	20 (100)	40 (100)	60 (100)
Transplanted patients set	12 (60.0)	16 (40.0)	28 (46.7)
Imatinib post-transplant set	3 (15.0)	6 (15.0)	9 (15.0)

- N is the number of patients in Enrolled patients set.
Source: Table 14.1-2.1

[redacted]

10.2 Demographic and disease history

10.2.1 Demography

The median age of the 60 enrolled patients was 9 years (range: 1 to 17). The majority of patients were Caucasian (93.3%), reflecting the countries that participated in the study. There were more males than females in the study (61.7% vs. 38.3%). Most of the patients had body mass index indicating normal weight (50.0%). Majority of patients (21 patients, 58.3%) with available data had a baseline performance status (Karnofsky or Lansky) of ≥ 90; the status at baseline was missing in 40% of patients (Table 10-3).

The demographics in both risk groups were largely comparable. Age category according to NCI definition indicated slightly higher number of patients of < 10 years of age in the good risk group compared to >= 10 years of age (57.5% vs, 42.5%), while the poor risk group had equal number of patients in ≥ 10 years and < 10 years age categories (50% each). As per PIP age category, both poor risk and good risk groups had most of the patients within 2 to < 12 years of age category (60% vs. 65%, respectively) (Table 10-3).

Table 10-3 Demographics by risk group (Full analysis set)

Demographic Variable	Poor risk N=20	Good risk N=40	All patients N=60
Age at diagnosis (years)			
n	20	40	60
Mean	9.1	8.6	8.8
SD	4.71	4.79	4.73
Median	9.5	9.0	9.0
Minimum	1	1	1
Maximum	17	17	17
Age category according to NCI risk (years) -n (%)			
<10	10 (50.0)	23 (57.5)	33 (55.0)
>= 10	10 (50.0)	17 (42.5)	27 (45.0)
Age category according to PIP definition (years) -n (%)			
<2	1 (5.0)	1 (2.5)	2 (3.3)
2 - <12	12 (60.0)	26 (65.0)	38 (63.3)
>= 12	7 (35.0)	13 (32.5)	20 (33.3)
Sex -n (%)			
Male	12 (60.0)	25 (62.5)	37 (61.7)
Female	8 (40.0)	15 (37.5)	23 (38.3)
Race -n (%)			
Caucasian	20 (100)	36 (90.0)	56 (93.3)

Demographic Variable	Poor risk N=20	Good risk N=40	All patients N=60
Unknown	0	2 (5.0)	2 (3.3)
Other	0	2 (5.0)	2 (3.3)
Body surface area (m^2)			
n	18	38	56
Mean	1.169	1.077	1.107
SD	0.4760	0.4615	0.4639
Median	1.085	0.940	1.010
Minimum	0.55	0.45	0.45
Maximum	2.16	2.08	2.16
Body mass index-for-age categories -n (%)			
Underweight	2 (10.0)	1 (2.5)	3 (5.0)
At risk for underweight	4 (20.0)	9 (22.5)	13 (21.7)
Normal	9 (45.0)	21 (52.5)	30 (50.0)
Overweight	2 (10.0)	5 (12.5)	7 (11.7)
Obese	1 (5.0)	2 (5.0)	3 (5.0)
Missing	2 (10.0)	2 (5.0)	4 (6.7)
Karnofsky/Lansky performance status -n (%)			
100	6 (30.0)	3 (7.5)	9 (15.0)
90	3 (15.0)	9 (22.5)	12 (20.0)
80	2 (10.0)	6 (15.0)	8 (13.3)
70	1 (5.0)	4 (10.0)	5 (8.3)
<70	0	2 (5.0)	2 (3.3)
Missing	8 (40.0)	16 (40.0)	24 (40.0)

Body mass index-for-age categories: underweight: <5th percentile of BMI-for-age; at risk for underweight:5th to <25th percentile; normal: 25th to <85th percentile; overweight: 85th to <95th percentile; obese: >=95th percentile.
Source: Table 14.1-3.1

10.2.2 Disease history

Disease history was comparable in both risk groups except for previous or current clinical trial involvement. Most of the patients were enrolled in previous or current clinical trial in the good risk group (77.5%) compared to the poor risk group (35%). Slightly higher number of patients had Ph+ ALL diagnosis determined by both, RT-PCR and FISH, cytogenetic techniques in the poor risk group (55%) compared to the good risk group (47.5%). The median time from diagnosis to first dose of imatinib was 15 days in both risk groups, and time from first

chemotherapy to first dose of imatinib was 14.5 and 14 days in the poor and good risk group, respectively (Table 10-4).

Table 10-4 Disease history by risk group (Full analysis set)

Disease history	Poor risk N=20	Good risk N=40	All patients N=60
Cytogenetics technique(s) used to determine diagnosis -n (%)			
RT-PCR	7 (35.0)	17 (42.5)	24 (40.0)
FISH	2 (10.0)	4 (10.0)	6 (10.0)
Both	11 (55.0)	19 (47.5)	30 (50.0)
Patients deceased at time of enrollment -n (%)			
No	19 (95.0)	40 (100)	59 (98.3)
Yes	1 (5.0)	0	1 (1.7)
Previous/Current clinical trial involvement -n (%)			
No	13 (65.0)	9 (22.5)	22 (36.7)
Yes	7 (35.0)	31 (77.5)	38 (63.3)
Time from diagnosis to first dose of imatinib (days)			
n	20	40	60
Mean	24.3	16.5	19.1
SD	33.75	4.98	19.92
Median	15.0	15.0	15.0
Minimum	0	10	0
Maximum	149	39	149
Time from diagnosis to first chemotherapy (days)			
n	20	40	60
Mean	-4.5	1.6	-0.5
SD	14.02	2.42	8.69
Median	0.0	1.0	1.0
Minimum	-50	-3	-50
Maximum	5	9	9
Time from first chemotherapy to first dose of imatinib (days)			
n	20	40	60
Mean	28.8	14.9	19.5

[redacted]

Disease history	Poor risk N=20	Good risk N=40	All patients N=60
SD	34.43	4.97	21.02
Median	14.5	14.0	14.0
Minimum	10	7	7
Maximum	148	36	148

Source: Table 14.1-4.1

10.2.3 Relevant medical history and current medical condition

A summary for medical conditions up to first dose of Imatinib is provided in Table 14.1-6.1.

For 20 patients (33.3%) medical conditions active at the start of imatinib were reported. The most commonly reported conditions by SOC at start of imatinib treatment included blood and lymphatic system disorders (13.3%) and gastrointestinal disorders (10%) (Table 14.1-6.2).

Details on current medical conditions is presented in Listing 16.2.4-4. Details on relevant medical history is presented in Listing 16.2.4-3.

10.2.4 Extramedullary involvement at baseline

Of the 60 patients, 28 (46.7%) patients reported no evidence of extramedullary involvement. For 19 patients (31.7%) this data at baseline was missing (Table 10-5).

Table 10-5 Extramedullary involvement at baseline by risk group (FAS)

Characteristics	Poor risk N=20	Good risk N=40	All patients N=60
Extramedullary involvement -n (%)			
No	8 (40.0)	20 (50.0)	28 (46.7)
Yes	4 (20.0)	9 (22.5)	13 (21.7)
Missing	8 (40.0)	11 (27.5)	19 (31.7)
Organ involved -n (%)			
Liver	2 (10.0)	4 (10.0)	6 (10.0)
Spleen	4 (20.0)	5 (12.5)	9 (15.0)
Lymph node	2 (10.0)	5 (12.5)	7 (11.7)
Other	0	1 (2.5)	1 (1.7)
Leukemic CNS involvement -n (%)			
No	11 (55.0)	28 (70.0)	39 (65.0)
Yes	1 (5.0)	1 (2.5)	2 (3.3)
Missing	8 (40.0)	11 (27.5)	19 (31.7)
Blast cells in CSF (%)			
n	1	1	2
Mean	16.6	21.7	19.2
SD			3.61

[redacted]

Characteristics	Poor risk N=20	Good risk N=40	All patients N=60
Median	16.6	21.7	19.2
Minimum	16.6	21.7	16.6
Maximum	16.6	21.7	21.7
CSF contaminated with blood -n (%)			
No	1 (5.0)	1 (2.5)	2 (3.3)
Yes	0	0	0

Source: Table 14.1-5.1

10.2.5 Concomitant treatment

In total, 46 (76.7%) out of 60 patients took concomitant medication and significant non-drug therapies prior to start of imatinib. The most common (>50.0%) concomitant medications by Anatomical Therapeutic Chemical (ATC) drug class was Sulfonamides and trimethoprim (55%). The summary is provided in Table 14.3-2.1.

All 60 patients took at least one concomitant medication and significant non-drug therapy after the start of imatinib prior to transplant. The most common (>80.0%) concomitant medications by ATC class were: antiinfectives (93.3%), antiinfectives and antiseptics, excl. combinations with corticosteroids (91.7%), antimycotics for systemic use (88.3%), intestinal antiinfectives (85%), stomatological preparations (85%), sulfonamides and trimethoprim (83.3%), antifungals for topical use (81.7%) and other beta-lactam antibacterials (81.7%). The summary by ATC class and preferred terms is provided in Table 14.3-2.2.

Eight out of 9 patients (88.9%) in the imatinib post transplant set received concomitant medication and significant non-drug therapies during imatinib treatment post-transplant. The most common (>60.0%) concomitant medications by ATC class were: other beta-lactam antibacterials, intestinal antiinflammatory agents, corticosteroids, plain, corticosteroids for systemic use, plain and antiinflammatory agents; all 66.7%. The summary is provided in the Table 14.3-2.3.

A listing of all prior and concomitant medication and significant non-drug therapies is listed by patient in Listing 16.2.5-3.

Antineoplastic therapy

The most frequently reported antineoplastic therapy by ATC class were anthracyclines and related substances, folic acid analogues, other immunosuppressants, vinca alkaloids and analogues, all in 59 patients (98.3%). A summary of antineoplastic therapy overall and by treatment phases is presented in Table 14.3-3.1. Individual patient data can be found in Listing 16.2.5-2.

10.3 Extend of exposure (Imatinib exposure and dose intensity)

Exposure was analyzed prior to transplant and post-transplant.

Prior to transplant was defined as:

[redacted]

- For patients who did not receive any transplantation during the time on imatinib treatment, the whole time on imatinib treatment was considered
- For patients who received transplantation and were still on imatinib treatment at that time, only the time on imatinib treatment prior to transplantation date was considered.

Post-transplant was defined for patients who received imatinib post-transplant and comprises the time on imatinib from date of transplantation until end of imatinib treatment.

10.3.1 Overall extend of exposure

In all patients, the median time on imatinib prior to transplant was 717 days (range: 16 – 3189 days) and the median exposure to imatinib prior to transplant was 663.5 days (range: 16- 3189 days). The median time on imatinib prior to transplant and the median duration of exposure to imatinib prior to transplant were more than twice as long in the good risk group compared to the poor risk group (726 vs. 326.5 days and 704.5 vs. 312.5 days, respectively) (Table 10-6).

Nine patients received imatinib post-transplant. The median time on imatinib post-transplant and the median duration of exposure to imatinib post- transplant were similar in poor and good risk group, but the ranges are much higher in the poor risk group than in the good risk group. In all 9 patients the time on imatinib post-transplant was 366 days (range: 99 - 1879 days) and duration of exposure to imatinib was 284 (range: 92 - 1806 days) (Table 14.3-1.3).

Table 10-6 Extent of exposure by risk group (safety set): overall

	Poor risk N=20	Good risk N=40	All patients N=60
Time on imatinib (days)			
n	20	40	60
Mean (SD)	479.55 (506.686)	807.15 (548.975)	697.95 (553.301)
Median	326.50	726.00	717.00
25-75th percentiles	90.50 - 703.00	715.50 - 890.00	238.50 - 872.50
Minimum – Maximum	16.0 - 1886.0	164.0 - 3189.0	16.0 - 3189.0
Duration of exposure to Imatinib (days)			
n	20	40	60
Mean (SD)	398.65 (379.947)	738.93 (557.957)	625.50 (527.675)
Median	312.50	704.50	663.50
25-75th percentiles	85.50 - 626.50	554.50 - 793.50	220.00 - 784.50
Minimum – Maximum	16.0 - 1499.0	110.0 - 3189.0	16.0 - 3189.0

- Imatinib is imatinib prior to transplant
- Time on imatinib in days = date of last dose – date of first dose + 1 day
- Exposure to imatinib in days = date of last dose – date of first dose + 1 day – days of zero total daily dose
Source: Table 14.3-1.1

There is no standard chemotherapy regimen in ALL. Treatment of newly diagnosed ALL patients typically consists of several treatment phases, i.e. induction, consolidation,

[redacted]

maintenance and others. Treatment phase are collected from antineoplastic (chemotherapy) eCRF.

Induction phase: The extent of exposure was analyzed during induction phase prior to transplant. In all patients, with data reported (n=57), the median time on imatinib was 80 days (range: 9 – 364 days). the median exposure to imatinib during inductionphase was 68 days (9- 352 days) (Table 14.3-1.1).

Consolidation phase: The extent of exposure was analyzed during consolidation phase prior to transplant. In all patients, with data reported (n=44), the median time on imatinib was 87 days (range: 17 – 3089 days). The median exposure to imatinib was 69.5 days (17- 3089 days) (Table 14.3-1.1).

Maintenace phase: The extent of exposure was analyzed during maintenance phase prior to transplant. In all patients, with data reported (n=34), the median time on imatinib was 372.5 days (range: 1- 1913 days). The median exposure to imatinib was 345.5 days (1- 1913 days) (Table 14.3-1.1).

10.3.2 Dose intensity

10.3.2.1 Overall dose intensity

In all patients, the median average daily dose of imatinib treatment prior to transplant was 300 mg/m^2/day (range: 153.5 - 340 mg/m^2/day). The median actual dose intensity to imatinib prior to transplant was 270.21 mg/m^2/day (106.9 - 340 mg/m^2/day) (Table 10-7).

In the nine patient who were treated with imatinib after transplantation, the median average daily dose and the median actual dose intensity were lower in the good risk group (152.79 mg/m^2/day (range: 75 - 300 mg/m^2/day) and 119.03 mg/m^2/day (range: 24.3 - 158.9 mg/m^2/day), respectively) compared to the poor risk group (249.34 mg/m^2/day (241 - 350 mg/m^2/day) and 231.63 mg/m^2/day (range: 217.5 - 350 mg/m^2/day), respectively) (Table 14.3-1.4).

Table 10-7 Dose intensity by risk group (safety set): overall

Exposure variable	Poor risk N=20	Good risk N=40	All patients N=60
Total number of patients receiving imatinib -n (%)	20 (100)	40 (100)	60 (100)
Average daily dose (mg/m^2/day)			
N	20	40	60
Mean (SD)	298.49 (36.690)	282.86 (38.139)	288.07 (38.082)
Median	300.00	300.00	300.00
25-75th percentiles	298.16 - 316.07	280.88 - 300.00	290.02 - 300.00
Minimum – Maximum	186.6 - 340.0	153.5 - 340.0	153.5 - 340.0
Actual dose intensity (mg/m^2/day)			
N	20	40	60
Mean (SD)	274.37 (56.127)	251.51 (47.335)	259.13 (51.124)
Median	280.45	261.68	270.21

Exposure variable	Poor risk N=20	Good risk N=40	All patients N=60
25-75th percentiles	250.08 - 300.00	215.42 - 293.36	236.08 - 297.26
Minimum – Maximum	106.9 - 340.0	139.8 - 315.7	106.9 - 340.0

- Imatinib is imatinib prior to transplant
- Average daily dose = Total dose / Duration of exposure to imatinib (periods of zero dose are excluded).
- Actual dose intensity = Total dose / Time on imatinib (periods of zero dose are included).
Source: Table 14.3-1.2

The average daily dose prior to transplant and the actual dose intensity prior to transplant were analyzed during induction, consolidation and maintenance phase.

Induction phase: In all patients, with data reported (n=57), the median average dose intensity for the patients receiving imatinib was 300 mg/m^2/day (range: 138.7- 340.0). The median actual dose intensity to imatinib was 300 mg/m^2/day (103.8 - 340.0) (Table 14.3-1.2).

Consolidation phase: In all patients, with data reported (n=44), the median average dose intensity for the patients receiving imatinib was 300 mg/m^2/day (range: 149.8- 340.0). The median actual dose intensity to imatinib was 273.49 mg/m^2/day (128.0-340.0) (Table 14.3-1.2).

Maintenance phase: In all patients, with data reported (n-=34), the median average dose intensity for the patients receiving imatinib was 300 mg/m^2/day (range: 185.8 - 340.0). The median actual dose intensity to imatinib was 283.49 mg/m^2/day (101.6 - 340.0) (Table 14.3-1.2).

10.4 Outcome data and main results

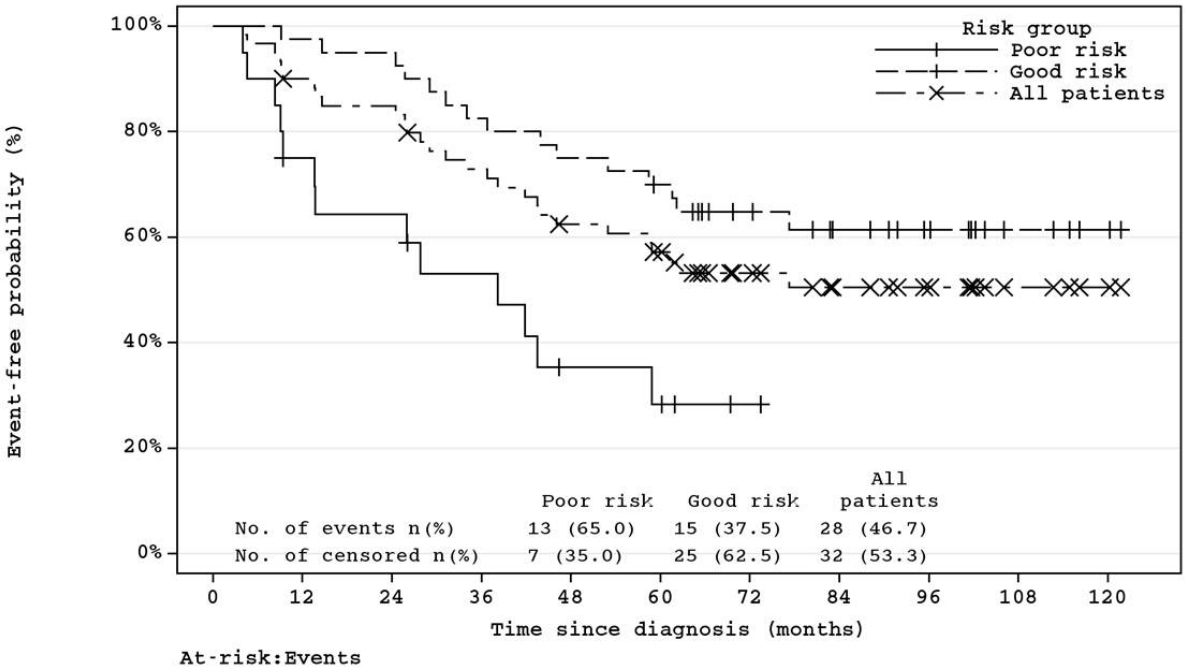
10.4.1 Primary efficacy analysis

The primary efficacy endpoint was EFS, defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death.

The Kaplan-Meier plot for event-free survival by risk group is depicted in Figure 10-1.

[redacted]

Figure 10-1 Kaplan-Meier plot for event-free survival (FAS)



Source: Figure 14.2-1.1

Overall, a total of 28 EFS events were observed during the study. The median EFS time was not reached. The estimated EFS rate at 60 months was 57.1% (95% CI: 43.4, 68.7) in all patients (Table 10-8).

In the poor risk group EFS events were observed in 13 patient (65%) and in the good risk group in 15 patients (37.5%). The Kaplan-Meier estimated EFS rates at 60 months were 28.3% (95% CI: 9.9, 50.2) in the poor risk group and 70.0% (95%: 53.3, 81.7) in the good risk group (Table 10-8) .

In addition, a sensitivity analysis was performed on EFS by risk group. For patients who underwent transplantation and had either an EFS event after transplantation or had no EFS event , the time was censored at the date of transplantation. In this sensitivity analysis, 23 EFS events were observed, 9 in the poor risk and 14 in the good risk group. The median EFS time in all patients was 77.3 (95% CI: 43.9, not estimable). The estimated EFS rate at 60 months was 56.5% (95% CI: 40.8, 69.5) (Table 14.2-1.2).

Details of all EFS and OS times are presented by individual patients in Listing 16.2.6-2.

[redacted]

Table 10-8 Overall summary of EFS by risk group (FAS)

	Poor risk N=20	Good risk N=40	All patients N=60
n/N (%)	13/20 (65.0)	15/40 (37.5)	28/60 (46.7)
Maximum follow-up	73.4	121.8	121.8
Median follow-up	27.0	71.0	60.9
Median time to censoring	60.2	91.8	82.9
Percentiles (95% CI) (1)			
25th	11.5 (4.0, 27.8)	49.5 (29.0, 77.3)	31.2 (13.7, 43.9)
50th	38.2 (9.4, NE)	NE (62.2, NE)	NE (46.1, NE)
75th	NE (38.2, NE)	NE	NE
% Event-free probability estimates (95% CI) (2)			
6 months	90.0 (65.6, 97.4)	100 (100.0,100.0)	96.7 (87.3, 99.2)
12 months	75.0 (50.0, 88.7)	97.5 (83.5, 99.6)	90.0 (79.1, 95.4)
18 months	64.3 (39.3, 81.2)	95.0 (81.5, 98.7)	84.9 (73.0, 91.8)
24 months	64.3 (39.3, 81.2)	95.0 (81.5, 98.7)	84.9 (73.0, 91.8)
36 months	53.0 (28.9, 72.3)	82.5 (66.8, 91.2)	72.9 (59.6, 82.4)
48 months	35.4 (14.9, 56.7)	75.0 (58.5, 85.7)	62.5 (48.8, 73.5)
60 months	28.3 (9.9, 50.2)	70.0 (53.3, 81.7)	57.1 (43.4, 68.7)
72 months	28.3 (9.9, 50.2)	64.8 (47.9, 77.4)	53.2 (39.5, 65.2)
84 months	NE	61.4 (44.1, 74.8)	50.4 (36.5, 62.9)
96 months	NE	61.4 (44.1, 74.8)	50.4 (36.5, 62.9)
108 months	NE	61.4 (44.1, 74.8)	50.4 (36.5, 62.9)
120 months	NE	61.4 (44.1, 74.8)	50.4 (36.5, 62.9)

(1) Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

(2) % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all risk groups; Greenwood formula is used for CIs of KM estimates.

- n : Total number of events included in the analysis.
- N : Total number of patients included in the analysis.

Source: Table 14.2-1.1

10.4.2 Main secondary objective

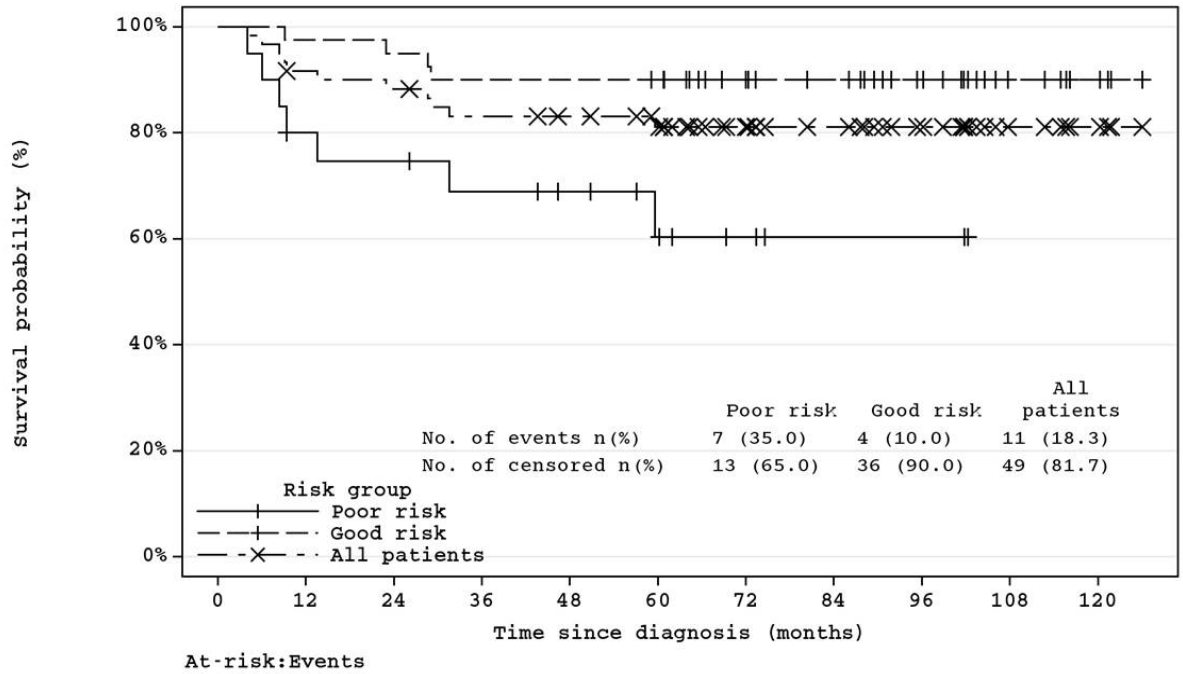
10.4.2.1 Overall summary of overall survival

OS was defined as time from diagnosis to death from any cause.

Eleven deaths were reported during the study. Most of the patients died within the first 24 months after diagnosis. The Kaplan-Meier plot for overall survival by risk group is depicted in Figure 10-2.

[redacted]

Figure 10-2 Kaplan-Meier plot for overall survival (FAS)



At-risk:Events

Poor risk	20:0	15:4	14:5	12:6	10:6	7:7	4:7	2:7	2:7	0:7	0:7
Good risk	40:0	39:1	38:2	36:4	36:4	35:4	27:4	24:4	17:4	8:4	4:4
All patients	60:0	54:5	52:7	48:10	46:10	42:11	31:11	26:11	19:11	8:11	4:11

Source: Figure 14.2-2.1.

The median follow-up from the date of diagnosis was 72.8 months in all patients. The median OS time was not reached. The estimated rate of OS at 60 months was 81.1% (95% CI: 68.5, 89.1) (Table 10-9).

Seven patients (35%) died within the poor risk group, 4 patients (10%) in the good risk group. The estimated OS rate at 60 months is 60.3% (95% CI: 32.8, 79.5) in the poor risk group and 90.0% (95% CI: 75.5, 96.1) in the good risk group (Table 10-9).

Table 10-9 Overall summary of overall survival by risk group (FAS)

	Poor risk N=20	Good risk N=40	All patients N=60
n/N (%)	7/20 (35.0)	4/40 (10.0)	11/60 (18.3)
Maximum follow-up	102.3	126.1	126.1
Median follow-up	48.6	90.1	72.8
Median time to censoring	60.2	93.6	87.6
Percentiles (95% CI) (1)			
25th	13.6 (4.0, NE)	NE	NE (28.6, NE)
50th	NE (13.6, NE)	NE	NE
75th	NE	NE	NE

[redacted]

	Poor risk N=20	Good risk N=40	All patients N=60
% Survival probability estimates (95% CI) (2)			
6 months	95.0 (69.5, 99.3)	100 (100.0,100.0)	98.3 (88.8, 99.8)
12 months	80.0 (55.1, 92.0)	97.5 (83.5, 99.6)	91.7 (81.1, 96.4)
18 months	74.7 (49.4, 88.6)	97.5 (83.5, 99.6)	90.0 (79.0, 95.4)
24 months	74.7 (49.4, 88.6)	95.0 (81.5, 98.7)	88.3 (77.0, 94.2)
36 months	68.9 (43.3, 84.7)	90.0 (75.5, 96.1)	83.1 (70.8, 90.5)
48 months	68.9 (43.3, 84.7)	90.0 (75.5, 96.1)	83.1 (70.8, 90.5)
60 months	60.3 (32.8, 79.5)	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)
72 months	60.3 (32.8, 79.5)	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)
84 months	60.3 (32.8, 79.5)	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)
96 months	60.3 (32.8, 79.5)	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)
108 months	NE	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)
120 months	NE	90.0 (75.5, 96.1)	81.1 (68.5, 89.1)

(1) Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

(2) % Survival probability estimate is the estimated probability that a patient will remain alive up to the specified time point. % Survival probability estimates are obtained from the Kaplan-Meier survival estimates for all risk groups; Greenwood formula is used for CIs of KM estimates.

- n : Total number of events included in the analysis.
- N : Total number of patients included in the analysis.

Source: Table 14.2-2.1

In addition, a sensitivity analysis was performed on OS by risk group. For patients who underwent transplantation, the time was censored at the date of transplantation. With this, 6 OS events were observed, 3 in each risk group. The median OS time in all patients was not reached. The estimated OS rate at 60 months was 87.8% (95% CI: 74.6, 94.4) (Table 14.2-2.2).

10.4.2.2 Other main secondary analyses

The other main secondary objective was to evaluate adverse events and serious adverse events in the observation period which is described in Section 10.5.

10.4.3 Other secondary analyses

10.4.3.1 Hematological remission status

The definition for complete hematological response (CHR) is given in Section 9.4.3.4. The rate of CHR from 6 months after diagnosis up to 66 months is presented in Table 10-10.

The rate of best CHR status overall (with 95 % CI) was noted as 65.0% (95% CI: 51.6, 76.9) in the all patients group. By 12 months the rate of best CHR is 48.3% (95% CI: 35.2, 61.6), i.e. nearly three quarter of patients reached CHR within the first year after diagnosis (Table 10-10).

The overall CHR rate was higher in the good risk group (72.5% (95% CI: 56.1, 85.4)) than in the poor risk group (50% (95% CI: 27.2, 72,8)).

[redacted]

Details of complete hematological remission by individual patients is presented in Listing 16.2.6-5.

Table 10-10 Best complete hematological response by risk group

	Poor risk N=20	Good risk N=40	All patients N=60
Overall best CHR status			
Response - n (%)	10 (50.0)	29 (72.5)	39 (65.0)
95% CI for response (%)	(27.2, 72.8)	(56.1, 85.4)	(51.6, 76.9)
No response - n (%)	10 (50.0)	11 (27.5)	21 (35.0)
Best CHR status up to 6 months			
Response - n (%)	4 (20.0)	16 (40.0)	20 (33.3)
95% CI for response (%)	(5.7, 43.7)	(24.9, 56.7)	(21.7, 46.7)
No response - n (%)	16 (80.0)	24 (60.0)	40 (66.7)
Best CHR status up to 12 months			
Response - n (%)	7 (35.0)	22 (55.0)	29 (48.3)
95% CI for response (%)	(15.4, 59.2)	(38.5, 70.7)	(35.2, 61.6)
No response - n (%)	13 (65.0)	18 (45.0)	31 (51.7)
Best CHR status up to 18 months			
Response - n (%)	8 (40.0)	22 (55.0)	30 (50.0)
95% CI for response (%)	(19.1, 63.9)	(38.5, 70.7)	(36.8, 63.2)
No response - n (%)	12 (60.0)	18 (45.0)	30 (50.0)
Best CHR status up to 24 months			
Response - n (%)	8 (40.0)	23 (57.5)	31 (51.7)
95% CI for response (%)	(19.1, 63.9)	(40.9, 73.0)	(38.4, 64.8)
No response - n (%)	12 (60.0)	17 (42.5)	29 (48.3)
Best CHR status up to 36 months			
Response - n (%)	9 (45.0)	26 (65.0)	35 (58.3)
95% CI for response (%)	(23.1, 68.5)	(48.3, 79.4)	(44.9, 70.9)
No response - n (%)	11 (55.0)	14 (35.0)	25 (41.7)
Best CHR status up to 48 months			
Response - n (%)	10 (50.0)	27 (67.5)	37 (61.7)
95% CI for response (%)	(27.2, 72.8)	(50.9, 81.4)	(48.2, 73.9)
No response - n (%)	10 (50.0)	13 (32.5)	23 (38.3)
Best CHR status up to 60 months			
Response - n (%)	10 (50.0)	29 (72.5)	39 (65.0)
95% CI for response (%)	(27.2, 72.8)	(56.1, 85.4)	(51.6, 76.9)
No response - n (%)	10 (50.0)	11 (27.5)	21 (35.0)
Best CHR status up to 66 months			

[redacted]

	Poor risk N=20	Good risk N=40	All patients N=60
Response - n (%)	10 (50.0)	29 (72.5)	39 (65.0)
95% CI for response (%)	(27.2, 72.8)	(56.1, 85.4)	(51.6, 76.9)
No response - n (%)	10 (50.0)	11 (27.5)	21 (35.0)

- Patients with No complete hematological remission status or missing information at that time point are combined and counted as "No response".
Source: Table 14.2-4.1

10.4.3.2 Minimal residual disease (MRD) response

MRD assessments to detect BCR-ABL transcript was evaluated at specific timepoints to provide a measure of the molecular response Biondi et al 2012 defined the 5 time-points as the following: post induction; pre-consolidation block 1, pre-consolidation block 2, pre-consolidation block 3, post-consolidation.

The best MRD was defined as any negative level of MRD (defined as MRD <0.01%). The rate of MRD response was provided at post induction (i.e. pre-consolidation block 1) and overall.

In all patients the MRD rate (with 95 % CI) was 95.0% (95% CI: 86.1, 99.0) overall and 46.7% (95% CI: 33.7, 60.0) at post-induction. The best MRD rate was reached by 17 patients (85%) in the poor risk group and by all 40 patients (100%) (95% CI: 91.2,100.0)in the good risk group Table 10-11.

Table 10-11 MRD response post-induction and overall by risk group (FAS)

	Poor risk N=20	Good risk N=40	All patients N=60
MRD response post-induction			
Response - n (%)	8 (40.0)	20 (50.0)	28 (46.7)
95% CI for response (%)	(19.1,63.9)	(33.8,66.2)	(33.7,60.0)
No response - n (%)	12 (60.0)	20 (50.0)	32 (53.3)
Best MRD response overall			
Response - n (%)	17 (85.0)	40 (100.0)	57 (95.0)
95% CI for response (%)	(62.1,96.8)	(91.2,100.0)	(86.1,99.0)
No response - n (%)	3 (15.0)	0	3 (5.0)

- Patients with no MRD response or missing information at that time point are combined and counted as "No response".
Source: Table 14.2-5.1

10.4.3.3 Rate and duration of complete remission

The rate of complete remission (CR, defined as <5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes) was analyzed post-induction (i.e. pre-consolidation block 1) and overall. The duration of CR was defined as the time between date of first complete remission to the date of loss of first complete remission.

[redacted]

CR status post-induction was reported by 32 patients (53.3% (95% CI: 40.0, 66.3). CR status overall was reported by 57 patients, 95.0% (95% CI: 86.1, 99.0); by17 patients (95% CI: 62.1, 96.8) in the poor risk group and by all 40 patients (95% CI: 91.2, 100) in the good risk group (Table 10-12).

Seven patients out of these 57 patients (12.3%) reported a loss of CR. The median duration of CR was not reached. The KM estimated rate of CR duration at 60 months is 85.0% (95% CI: 70.7, 92.6) (Table 14.2-3.2).

Details of duration of first complete remission and of overall disease response status are provided in Listing 16.2.6-4 and Listing 16.2.6-3, respectively.

Table 10-12 Complete remission status by risk group (FAS)

	Poor risk N=20	Good risk N=40	All patients N=60
Complete remission status post-induction			
Response - n (%)	11 (55.0)	21 (52.5)	32 (53.3)
95% CI for response (%)	(31.5,76.9)	(36.1,68.5)	(40.0,66.3)
No response - n (%)	9 (45.0)	19 (47.5)	28 (46.7)
Best complete remission status overall			
Response - n (%)	17 (85.0)	40 (100)	57 (95.0)
95% CI for response (%)	(62.1,96.8)	(91.2,100.0)	(86.1,99.0)
No response - n (%)	3 (15.0)	0	3 (5.0)

- Patients with No complete remission status or missing information at that time point are combined and counted as "No response".

Source: Table 14.2-3.1

10.4.3.4 Time to transplant, time to engraftment, engraftment failure, graft versus host disease

10.4.3.4.1 Time to transplant

Time to transplant was measured as time from diagnosis to date of transplantation. Overall, 28 (46.7%) patients received a transplantation during the course of the study, 12 (60%) in the poor risk group and 16 (40%) in the good risk group. The median time (95% CI) to transplant in all patients was 65.9 months (38.1, not estimable), 32.5 months (10.2, 45.6) in the poor risk group and not reached in the good risk group. The KM estimated rate for transplantation (95% CI) by 60 months was 48.4% (35.9, 62.6) in all patients, 78.1% (54.9, 94.5) in the poor risk group and 36.7% (23.6, 54.1)in the good risk group (Table 10-13).

Table 10-13 Overall summary of time to first transplantation by risk group (FAS)

	Poor risk N=20	Good risk N=40	All patients N=60
n/N (%)	12/20 (60.0)	16/40 (40.0)	28/60 (46.7)
Maximum follow-up	73.4	121.8	121.8

[redacted]

	Poor risk N=20	Good risk N=40	All patients N=60
Median follow-up	14.8	64.7	43.5
Median time to censoring	17.8	84.4	71.0
Percentiles (95% CI) (1)			
25th	10.2 (6.2, 26.4)	38.1 (8.4, 65.9)	26.4 (8.2, 38.1)
50th	32.5 (10.2, 45.6)	NE (48.8, NE)	65.9 (38.1, NE)
75th	45.6 (32.5, NE)	NE	NE
% Event probability estimates (95% CI) (2)			
3 months	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
6 months	0.0 (0.0, 0.0)	2.5 (0.4, 16.5)	1.7 (0.2, 11.4)
9 months	22.2 (9.0, 48.9)	15.0 (7.0, 30.4)	17.2 (9.7, 29.6)
12 months	35.2 (17.5, 62.5)	17.6 (8.8, 33.4)	22.7 (13.9, 35.9)
18 months	35.2 (17.5, 62.5)	17.6 (8.8, 33.4)	22.7 (13.9, 35.9)
24 months	41.7 (22.3, 68.4)	17.6 (8.8, 33.4)	24.6 (15.3, 38.0)
36 months	63.5 (40.4, 86.1)	23.0 (12.7, 39.6)	34.4 (23.4, 48.6)
48 months	78.1 (54.9, 94.5)	31.2 (19.0, 48.5)	44.3 (32.2, 58.6)
60 months	78.1 (54.9, 94.5)	36.7 (23.6, 54.1)	48.4 (35.9, 62.6)
72 months	78.1 (54.9, 94.5)	43.6 (29.1, 61.4)	53.7 (40.5, 68.0)
84 months	NE	43.6 (29.1, 61.4)	53.7 (40.5, 68.0)
96 months	NE	43.6 (29.1, 61.4)	53.7 (40.5, 68.0)
108 months	NE	43.6 (29.1, 61.4)	53.7 (40.5, 68.0)
120 months	NE	43.6 (29.1, 61.4)	53.7 (40.5, 68.0)

(1) Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

(2) % Event probability estimate is the estimated probability that a patient will have an event prior to the specified time point. % Event probability estimates are obtained from the Kaplan-Meier survival estimates for all risk groups; Greenwood formula is used for CIs of KM estimates.

- n : Total number of events included in the analysis.

- N : Total number of patients included in the analysis.

Source: Table 14.2-6.1

10.4.3.4.2 Time to engraftment

Engraftment occurred when both neutrophil and platelet engraftments occurred. Time to engraftment was defined as the time from date of transplant to the date of engraftment.

Overall, for 24 out of 28 patients (85.7%) who received a transplant, engraftment for both neutrophils and platelets was reported. The median time to engraftment was 1.0 month (95% CI: 0.8, 1.3). The KM estimated rate of engraftment at 1.0 month was 48.1% (95% CI: 31.5, 68.1) (Table 14.2-7.1).

[redacted]

Time to engraftment for both neutrophils and platelets in transplanted patients who achieved engraftment is summarized in Table 14.2-7.2. The median time to engraftment in these 24 patients is 0.95 months (range: 0.4 - 8.3 months)

Overall, for 25 out of 28 patients (89.3%) who received a transplant, neutrophil engraftment was reported. The median time to neutrophil engraftment was 0.7 months (95% CI: 0.6, 0.8). The KM estimated rate of neutrophil engraftment at 1.0 month was 85.2% (95% CI: 69.6, 95.3) (Table 14.2-7.3).

Time to neutrophil engraftment in transplanted patients who achieved neutrophil engraftment is summarized in Table 14.2-7.4. The median time to neutrophil engraftment in these 25 patients is 0.69 (range: 0.4 – 1.3 months).

Overall, for 25 out of 28 patients (89.3%) who received a transplant, platelet engraftment was reported. The median time to platelet engraftment was 1.0 month (95% CI: 0.8, 1.3). The KM estimated rate at 1.0 month was 51.9% (95% CI: 34.8, 71.3) (Table 14.2-7.5).

Time to platelet engraftment in transplanted patients who achieved platelet engraftment is summarized in Table 14.2-7.6. The median time to platelet engraftment in these 25 patients is 0.95 months (range: 0.4 - 8.3 months).

10.4.3.4.3 Rate of engraftment failure

Engraftment failure was defined as either definitive engraftment failure or the absence of engraftment.

Of the 28 patients from the transplanted set, 26 (92.9%) patients reported no neutrophil or platelet engraftment failure, for 2 patients in the poor risk group any information about engraftment is missing (Table 14.2-8.1).

10.4.3.4.4 Rate of acute graft versus host disease

Overall, out of 28 patients in the transplanted set, presence of acute graft versus host disease (GvHD) was noted in 12 (42.9%) patients. For 5 (17.9%) patients GvHD was not assessed or the data was missing. Acute GvHD by different time points by risk group is presented in Table 14.2-9.1.

10.4.3.4.5 Rate of chronic graft versus host disease

Overall, out of 28 patients in the transplanted set, presence of chronic graft versus host disease (GvHD) was noted in 4 (14.3%) patients. In 5 (17.9%) patients GvHD was not assessed or missing. Chronic GvHD by different time points by risk group is presented in Table 14.2-9.2.

10.4.3.5 Growth and development

10.4.3.5.1 Tanner stage

Age at which Tanner stages 2 to 5 were reached during the study are presented for all patients with Tanner stage less or equal 4 at baseline (Table 14.3-5.1).

Tanner stage at Baseline was available for 26 patients, 22 patients had Tanner stage less or equal to 4, 4 patients had Tanner stage 5 at baseline. For the remaining 34 patients, either no Tanner

[redacted]

stage data were provided or the baseline data was missing. Among the 22 patients with available baseline Tanner stage of less or equal 4, Tanner staging was 1 in 15 patients (6 males and 9 females), Tanner stage 2 in 2 patients (2 males and 0 females), Tanner stage 3 in 0 patients for genitalia and breast development and in 1 patient (1 male and 0 females) for pubic hair, and Tanner stage 4 in 5 patients (2 males and 3 females) for genitalia and breast development and in 4 patients (1 male and 3 females) for pubic hair.

Please note that puberty stage was not collected for all patients with Baseline data at all visits during the course of the study. Therefore, any conclusions drawn regarding the influence of imatinib treatment on attaining puberty are limited.

Overall, among patients in Tanner stage 1 at Baseline, Tanner stage 2 was attained in 4 out of 6 male patients for genital development and pubic hair, and in 7 out of 9 female patients for breast development and pubic hair (Table 14.3-5.1). All patients who had not yet attained Tanner stage 2 at the time of analysis were < 13 years of age at the time of their last Tanner stage assessment (Listing 16.2.9-3).

10.4.3.5.2 Delayed puberty start

Delayed puberty in girls was defined as failure to attain Tanner Stage 2 (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage 2. Delayed puberty in boys was defined as failure to attain Tanner Stage 2 (for both genital development and pubic hair) by age 14.

At risk of delayed puberty includes all patients who have not started puberty and have not delayed puberty prior to start of imatinib.

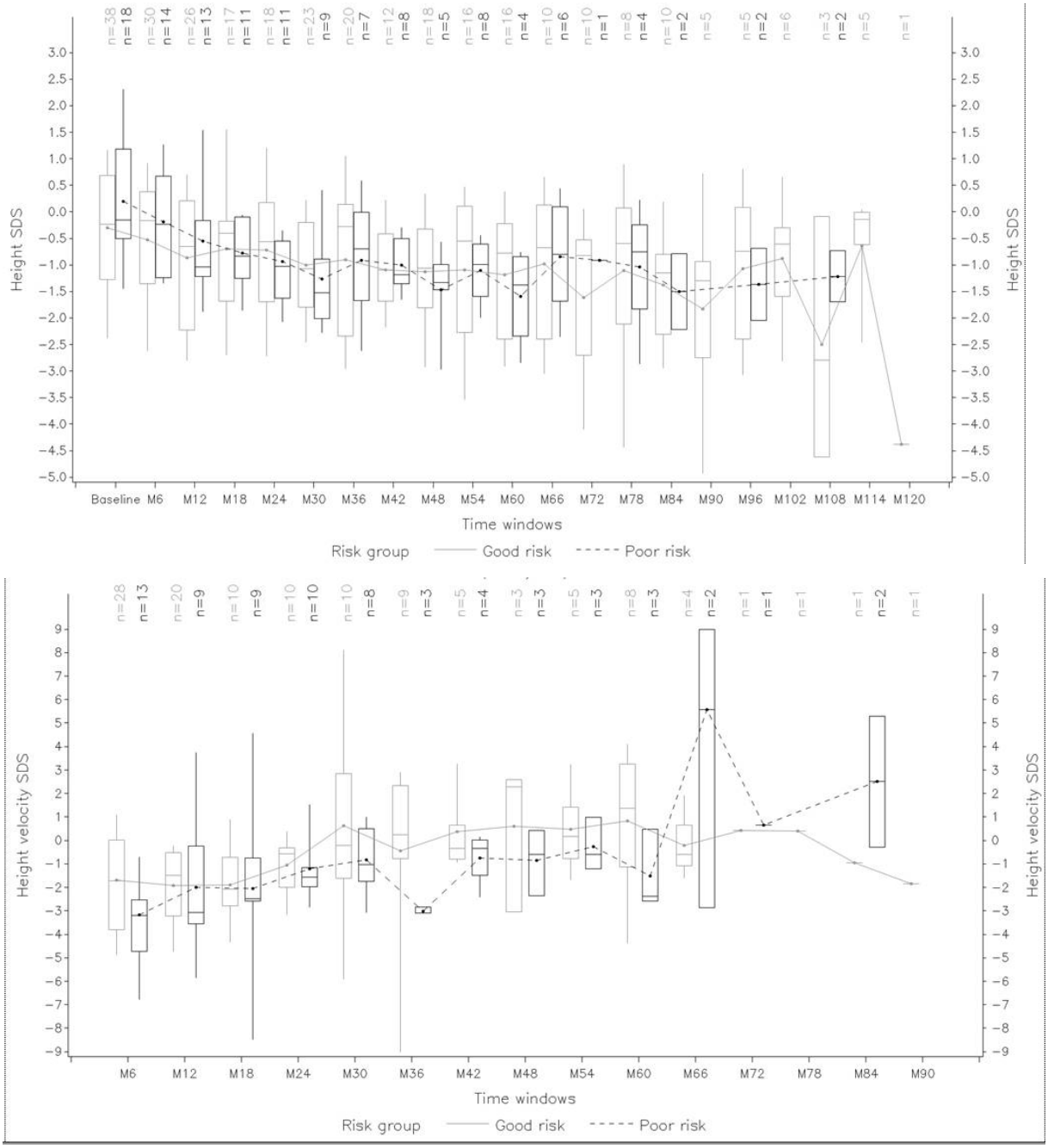
- Of the 23 male patients at risk of delayed puberty at start date of imatinib, puberty was not delayed in 11 patients (47.8%), delayed in 2 patients (8.7%) and was unknown in 10 patients (43.5%) (Table 14.3-5.4).
- Of the 14 female patients at risk for delayed puberty at start date of imatinib, puberty was not delayed in 2 patients (14.3%), delayed in 3 patients (21.4%), and was unknown in 9 patients (64.3%) (Table 14.3-5.4).

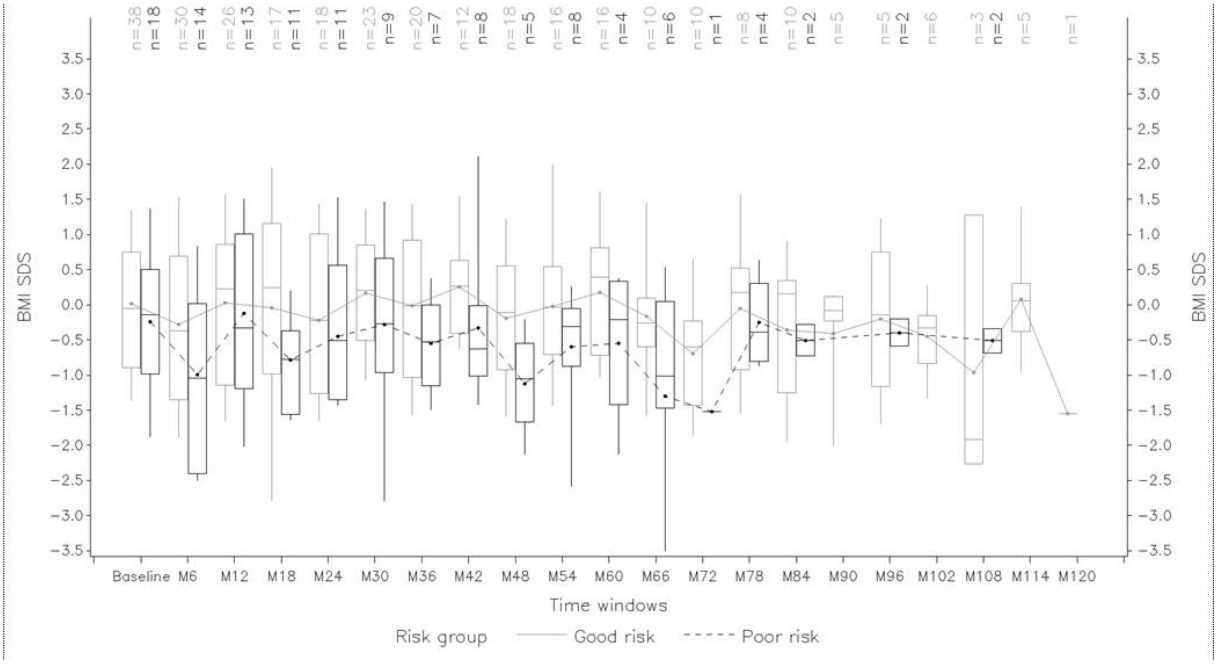
10.4.3.5.3 Growth data

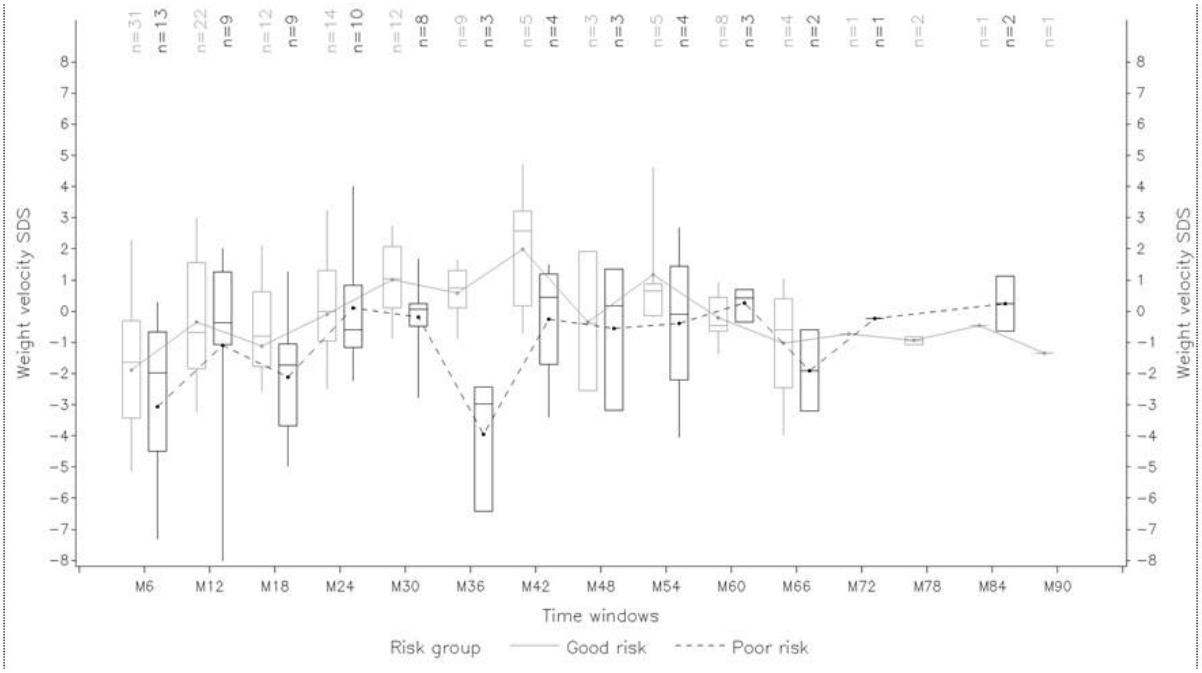
Figure 10-3 displays the box plots of growth data (height SDS, height velocity SDS, BMI SDS, and weight velocity SDS) in 6-month intervals from Baseline to cut-off date by risk group. The proportions of patients with SDS values < 5th percentile (< -1.645) or > 95th percentile (> 1.645) on height, height velocity, BMI, and weight velocity did not change significantly after the start of imatinib (Table 14.3-6.1).

[redacted]

Figure 10-3 Box plot of growth data by time point and risk group (Safety set)







Source: Figure 14.3-1.1

Shift tables for height SDS and BMI SDS are provided in Tables 14.3-6.2 and Table 14.3-6.3, respectively.

Of total 60 patients, height SDS values at Baseline were low, normal, and high in 9 (15%), 43 (71.7%), and 4 (6.7%) patients, respectively; the Baseline value was missing in 4 (6.7%) patients (Table 14.3-6.2).

- Of 9 patients with low height SDS at Baseline, worst post-baseline values remained low in all 9 patients (100%).

[redacted]

- Of 43 patients with normal height SDS at Baseline, worst post-baseline values were low in 12 patients (27.9%) and remained normal in 29 patients (67.4%). For 2 patients (4.7%) the post-baseline value was missing.
- Of 4 patients with high height SDS at Baseline, worst post-baseline values were normal in 1 patient (25%) and remained high in 3 patients (75%).
- Of 4 patients with missing height SDS at Baseline, worst post-baseline values were low in 2 patients (50%) and normal in 2 patients (50%).

Of total 60 patients, BMI SDS values at Baseline were low and high in 3 (5%) patients each, and the value was normal in 50 patients (83.3%); the Baseline value was missing in 4 (6.7%) patients (Table 14.3-6.3).

- Of 3 patients with low BMI SDS at Baseline, worst post-baseline values remained low in 1 patient (33.3%), normal in 1 patient (33.3%), and had both low and high values in 1 patient (33.3%).
- Of 50 patients with normal BMI SDS at Baseline, worst post-baseline values were low in 15 patients (30%), normal in 24 patients (48%), and high in 9 patients (18%). For 2 patients (4%) the post-baseline value was missing.
- Of 3 patients with high BMI SDS at Baseline, worst post-baseline values were normal in 1 patient (33.3.%) and remained high in 2 patients (66.7%).
- Of 4 patients with missing BMI SDS at Baseline, worst post-baseline values were low in 3 patient (75%) and normal in 1 patients (25%)

10.4.3.6 Other supportive analyses

10.4.3.6.1 Multivariate Cox regression model

To evaluate the influence of prognostic factors on EFS and OS, an analysis was performed using the Cox proportional hazards regression model. Each potential factor (age, sex, extramedullary involvement as well as good versus poor risk group) was included in the multivariate Cox regression model for investigating their combined effect on the endpoint. This multivariate analysis included all patients for whom data for all variables were available.

After adjustment of prognostic factors, the results for EFS for patients in the good risk versus poor risk group showed favouring the good risk group with HR: 0.167 (95% CI: 0.060, 0.468). Multivariate Cox regression model of EFS with risk group and other prognostic variables as covariates is presented in Table 14.2-1.7.

Prognostic variable on OS for good risk versus poor risk group among other variables showed favoring the good risk patient group with HR 0.197 (95% CI: 0.029, 1.331). Multivariate Cox regression model of OS with risk group and other prognostic variables as covariates is presented in Table 14.2-2.7.

Please note that the results should be interpreted with caution as the number of patients included is low. Due to missing baseline data for extramedullary involvement only 41 patients (12 patients in poor risk and 29 patients in good risk group) were included in the analysis.

[redacted]

10.4.3.6.2 Subgroup analyses

Subgroup analyses were conducted for EFS and OS. The analyses by age group category show a lower KM estimated rate of EFS at 60 months for patients <12 years (55.7% (95% CI: 38.7, 69.7)) than for patients ≥12 years (60% (95% CI: 35.7, 77.6)) as well as for OS at 60 months (<12 years: 79.2% (95% CI: 62.6, 89.0); ≥12 years: 85% (95% CI: 60.4, 94.9)) (Table 14.2-1.3 and Table 14.2-2.3).

The analyses by enrollment into clinical trials show a lower KM estimated rate of EFS at 60 months for patients not enrolled in clinical trials (41.6% (95% CI: 20.5, 61.6)) than for patients enrolled into clinical trials (65.7% (95% CI: 48.3, 78.4)) as well as for OS at 60 months (not enrolled: 60.9% (95% CI: 36.0, 78.5); enrolled: (92.1% (95% CI: 77.5, 97.4)) (Table 14.2-1.4 and Table 14.2-2.4) .

Subgroup analyses by Type of transplant donor and by best MRD rate could not show any interpretable picture as each had only one subgroup with at least 5 patients. Please note that the results should be interpreted with caution as the number of patients included is low.

10.5 Overview of adverse events

The summary of AEs included all AEs that were reported from start of imatinib treatment up to 30 days after end of imatinib treatment. For patients who received a transplantation the summary was restricted to the imatinib treatment prior to transplantation. Any AEs captured during imatinib received after transplant was summarized separately including only patients who received imatinib after transplant. AEs reported post-transplant are discussed in Section 10.5.1.6.

Full details of all adverse events are presented by individual patient in Listing 16.2.7-1.

A summary of the number of patients who died, experienced AEs, SAEs or other significant AEs is presented in Table 10-14. Further details are given in Sections 10.5.1 and Section 10.5.2.

Table 10-14 Summary of the number of patients who died, had AEs, SAEs, AEs leading to discontinuation or other significant AEs (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
Category	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
All deaths[1]	7 (35.0)		4 (10.0)		11 (18.3)	
On-treatment deaths[2]	1 (5.0)		1 (2.5)		2 (3.3)	
Adverse events	20 (100)	19 (95.0)	39 (97.5)	37 (92.5)	59 (98.3)	56 (93.3)
Suspected to be imatinib-related	12 (60.0)	10 (50.0)	31 (77.5)	27 (67.5)	43 (71.7)	37 (61.7)
Suspected to be study drug-related	12 (60.0)	10 (50.0)	35 (87.5)	32 (80.0)	47 (78.3)	42 (70.0)
Serious adverse events	18 (90.0)	18 (90.0)	34 (85.0)	33 (82.5)	52 (86.7)	51 (85.0)
AEs leading to discontinuation	6 (30.0)	6 (30.0)	1 (2.5)	1 (2.5)	7 (11.7)	7 (11.7)

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
Category	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
AEs requiring dose interruption and/or change	10 (50.0)	10 (50.0)	35 (87.5)	28 (70.0)	45 (75.0)	38 (63.3)
AEs requiring additional therapy	19 (95.0)	17 (85.0)	38 (95.0)	37 (92.5)	57 (95.0)	54 (90.0)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[1]All deaths including those >30 days after end of imatinib.
[2] Deaths occurring >30 days after end of imatinib and after transplant are not included.
CTCAE version 4.03.
Source: Table 14.3.1-3.1, Table 14.3.1-3.2, Table 14.3.1-1.1, Table 14.3.1-4.1, Table 14.3.1-5.1, Table 14.3.1-6.1, Table 14.3.1-7.1, Table 14.3.1-8.1, Table 14.3.1-9.1

10.5.1 Analysis of Adverse events

10.5.1.1 Adverse events regardless of study drug relationship by SOC

Table 10-15 summarized the AEs by SOC observed in at least 50% of patients in the 'all patients' column. The complete table of AEs by SOC and PT is provided in Table 14.3.1-1.1 .

Overall, 59 patients (98.3%) reported at least one AEs and 93.3% of all patients experienced at least one AE of grade 3/4. The most frequent reported SOCs of all grades (>80%) were (Table 10-15):

- Infections and infestations (88.3%)
- Blood and lymphatic system disorders (86.7%)
- Gastrointestinal disorders (83.3%)

Table 10-15 Adverse events (reported in at least 50% of patients) regardless of study drug relationship by primary system organ class, maximum grade and risk group (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
Primary system organ class	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Number of subjects with at least one event	20 (100)	19 (95.0)	39 (97.5)	37 (92.5)	59 (98.3)	56 (93.3)
Infections and infestations	17 (85.0)	12 (60.0)	36 (90.0)	31 (77.5)	53 (88.3)	43 (71.7)
Blood and lymphatic system disorders	17 (85.0)	17 (85.0)	35 (87.5)	34 (85.0)	52 (86.7)	51 (85.0)
Gastrointestinal disorders	15 (75.0)	10 (50.0)	35 (87.5)	24 (60.0)	50 (83.3)	34 (56.7)
General disorders and administration site condistions	11 (55.0)	5 (25.0)	26 (65.0)	7 (17.5)	37 (61.7)	12 (20.0)

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
Primary system organ class	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Metabolism and nutrition disorders	11 (55.0)	7 (35.0)	24 (60.0)	14 (35.0)	35 (58.3)	21 (35.0)

- A subject with multiple severity grades for a system organ class is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-1.1

10.5.1.2 Adverse events regardless of study drug relationship by PT

Overall, the most frequent AEs regardless of the study drug relationship (>50%) of any grade were stomatitis (66.7%), thrombocytopenia (58.3%), neutropenia (56.7%) and febrile neutropenia (53.3%). All 4 PTs were also the most frequent reported AEs of grade 3 or 4. Neutropenia of grade 3 or 4 were reported in 55% of patients, thrombocytopenia, febrile neutropenia and stomatitis were reported in 50% of all patients (Table 10-16).

Table 10-16 Adverse events (reported in at least 20% of patients), regardless of study drug relationship by preferred term, maximum grade and risk group (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Number of subjects with at least one event	20 (100)	19 (95.0)	39 (97.5)	37 (92.5)	59 (98.3)	56 (93.3)
Stomatitis	12 (60.0)	8 (40.0)	28 (70.0)	22 (55.0)	40 (66.7)	30 (50.0)
Thrombocytopenia	13 (65.0)	11 (55.0)	22 (55.0)	19 (47.5)	35 (58.3)	30 (50.0)
Neutropenia	13 (65.0)	13 (65.0)	21 (52.5)	20 (50.0)	34 (56.7)	33 (55.0)
Febrile neutropenia	12 (60.0)	10 (50.0)	20 (50.0)	20 (50.0)	32 (53.3)	30 (50.0)
Pyrexia	9 (45.0)	2 (10.0)	21 (52.5)	5 (12.5)	30 (50.0)	7 (11.7)
Anaemia	13 (65.0)	11 (55.0)	16 (40.0)	15 (37.5)	29 (48.3)	26 (43.3)
Abdominal pain	6 (30.0)	1 (5.0)	18 (45.0)	7 (17.5)	24 (40.0)	8 (13.3)
Vomiting	8 (40.0)	2 (10.0)	16 (40.0)	2 (5.0)	24 (40.0)	4 (6.7)
Hypokalaemia	8 (40.0)	3 (15.0)	15 (37.5)	8 (20.0)	23 (38.3)	11 (18.3)
Diarrhoea	10 (50.0)	1 (5.0)	12 (30.0)	3 (7.5)	22 (36.7)	4 (6.7)
Nausea	5 (25.0)	2 (10.0)	17 (42.5)	4 (10.0)	22 (36.7)	6 (10.0)
Constipation	4 (20.0)	0	13 (32.5)	1 (2.5)	17 (28.3)	1 (1.7)
Pneumonia	3 (15.0)	2 (10.0)	13 (32.5)	10 (25.0)	16 (26.7)	12 (20.0)
Hypoalbuminaemia	2 (10.0)	0	13 (32.5)	3 (7.5)	15 (25.0)	3 (5.0)
Drug hypersensitivity	5 (25.0)	3 (15.0)	8 (20.0)	2 (5.0)	13 (21.7)	5 (8.3)

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Leukopenia	4 (20.0)	3 (15.0)	8 (20.0)	8 (20.0)	12 (20.0)	11 (18.3)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients group.
- A subject with multiple severity grades for an AE is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-1.2

10.5.1.3 Adverse Events leading to study drug (imatinib) discontinuation regardless of study drug relationship

Seven patients (11.7%) experienced at least one AE that led to imatinib discontinuation regardless of the study drug relationship. Reported AEs by PT were reported with singular frequency except thrombocytopenia (all grades, 3 patients (5%); grade 3 or 4, 2 patients (3.3%)) (Table 10-17).

Out of 7 patients with at least one AE leading to study drug discontinuation, one patient ([redacted] had an AE (hemorrhage intracranial) with fatal outcome (Listing 14.3.2-1). Full details of all adverse events leading to study drug discontinuation is presented in Listing 14.3.2-3. Further details related to Death is provided in Section 10.5.2.1.

Table 10-17 Adverse Events leading to study drug discontinuation, regardless of study drug relationship by preferred term, maximum grade and risk group (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	6 (30.0)	6 (30.0)	1 (2.5)	1 (2.5)	7 (11.7)	7 (11.7)
Thrombocytopenia	3 (15.0)	2 (10.0)	0	0	3 (5.0)	2 (3.3)
Alanine aminotransferase increased	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)
Anaemia	1 (5.0)	0	0	0	1 (1.7)	0
Aspartate aminotransferase increased	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)
Aspergillus infection	1 (5.0)	0	0	0	1 (1.7)	0
Face oedema	1 (5.0)	0	0	0	1 (1.7)	0
Febrile neutropenia	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)
Haemorrhage intracranial	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)
Interstitial lung disease	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)
Leukopenia	1 (5.0)	0	0	0	1 (1.7)	0
Muscle contractions involuntary	1 (5.0)	0	0	0	1 (1.7)	0
Nausea	1 (5.0)	0	0	0	1 (1.7)	0

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Pneumonia	0	0	1 (2.5)	1 (2.5)	1 (1.7)	1 (1.7)
Retinal haemorrhage	1 (5.0)	1 (5.0)	0	0	1 (1.7)	1 (1.7)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients group.
- A subject with multiple severity grades for an AE is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-7.2

10.5.1.4 Adverse events suspected to be imatinib-related

Forty-three patients (71.7%) experienced at least one AE of any grade that was suspected to be related to imatinib. In 37 patients (61.7%) at least one AE was of grade 3 or 4 (Table 10-18). The most frequently reported imatinib-related AEs of all grades (>30 %) were:

- Neutropenia (40.0%)
- Thrombocytopenia (35.0%)
- Vomiting (31.7%)

Full list of AEs that were suspected to be related to the study drug is presented in Table 14.3.1-4.2.

Table 10-18 Adverse events (reported in at least 20% of patients) suspected to be imatinib-related by preferred term, maximum grade and risk group (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Number of subjects with at least one event	12 (60.0)	10 (50.0)	31 (77.5)	27 (67.5)	43 (71.7)	37 (61.7)
Neutropenia	6 (30.0)	6 (30.0)	18 (45.0)	17 (42.5)	24 (40.0)	23 (38.3)
Thrombocytopenia	6 (30.0)	5 (25.0)	15 (37.5)	13 (32.5)	21 (35.0)	18 (30.0)
Vomiting	6 (30.0)	1 (5.0)	13 (32.5)	2 (5.0)	19 (31.7)	3 (5.0)
Febrile neutropenia	6 (30.0)	5 (25.0)	12 (30.0)	12 (30.0)	18 (30.0)	17 (28.3)
Anaemia	4 (20.0)	3 (15.0)	12 (30.0)	11 (27.5)	16 (26.7)	14 (23.3)
Nausea	4 (20.0)	1 (5.0)	12 (30.0)	2 (5.0)	16 (26.7)	3 (5.0)
Diarrhoea	5 (25.0)	1 (5.0)	10 (25.0)	3 (7.5)	15 (25.0)	4 (6.7)
Pyrexia	2 (10.0)	0	11 (27.5)	2 (5.0)	13 (21.7)	2 (3.3)
Abdominal pain	1 (5.0)	0	11 (27.5)	2 (5.0)	12 (20.0)	2 (3.3)
Stomatitis	1 (5.0)	1 (5.0)	11 (27.5)	9 (22.5)	12 (20.0)	10 (16.7)

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients group.
- A subject with multiple severity grades for an AE is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-4.2

10.5.1.5 Adverse Events requiring dose adjustment or interruption

AEs requiring dose adjustment or interruptions were reported in 75.0% of patients; in 63.3% of patients the AE was of grade 3 or 4 (Table 10-19). The most frequently reported AEs of all grades (>20 %) were:

- Neutropenia (30.0%)
- Febrile neutropenia (23.3%)

Full list of AEs that required dose adjustment or interruption regardless of the study drug relationship is presented in Table 14.3.1-8.2.

Table 10-19 Adverse Events (reported in at least 10% of patients) requiring dose adjustment or interruption, regardless of study drug relationship by preferred term, maximum grade and risk group (Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	10 (50.0)	10 (50.0)	35 (87.5)	28 (70.0)	45 (75.0)	38 (63.3)
Neutropenia	5 (25.0)	5 (25.0)	13 (32.5)	13 (32.5)	18 (30.0)	18 (30.0)
Febrile neutropenia	2 (10.0)	2 (10.0)	12 (30.0)	12 (30.0)	14 (23.3)	14 (23.3)
Thrombocytopenia	5 (25.0)	3 (15.0)	6 (15.0)	5 (12.5)	11 (18.3)	8 (13.3)
Pyrexia	1 (5.0)	0	9 (22.5)	2 (5.0)	10 (16.7)	2 (3.3)
Stomatitis	2 (10.0)	2 (10.0)	8 (20.0)	7 (17.5)	10 (16.7)	9 (15.0)
Bone marrow failure	1 (5.0)	1 (5.0)	6 (15.0)	5 (12.5)	7 (11.7)	6 (10.0)
Febrile bone marrow aplasia	1 (5.0)	1 (5.0)	6 (15.0)	6 (15.0)	7 (11.7)	7 (11.7)
Pneumonia	2 (10.0)	2 (10.0)	5 (12.5)	4 (10.0)	7 (11.7)	6 (10.0)
Leukopenia	3 (15.0)	2 (10.0)	3 (7.5)	3 (7.5)	6 (10.0)	5 (8.3)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients group.
- A subject with multiple severity grades for an AE is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-8.2

[redacted]

10.5.1.6 Adverse events occurring on post-transplant imatinib

Adverse events occurring on post-transplant imatinib regardless of study drug relationship| by primary system organ class, preferred term, maximum grade and risk group is presented in Table 14.3.1-2.1.

Out of 9 patients in the imatinib post-transplant set, 8 (88.9%) patients experienced at least one AE of all grades regardless of study drug relationship. The most frequent reported (>50%) SOCs of all grades were: infections and infestations (7 patients, 77.8%) and blood and lymphatic system disorders and gastrointestinal disorders (5 pateints, 55.6% each) (Table 14.3.1-2.1).

10.5.2 Deaths and other serious or clinically significant adverse events

10.5.2.1 Deaths

Two (3.3%) patients died within 30 days after discontinuation of imatinib treatment (Table 14.3.1-3.1 and Listing 14.3.2-1). Of these two reported deaths, one concerned a [redacted]-year-old [redacted] patient who dies of unspecified cause 260 days after first dose and 19 days after last dose of imatinib. The investigator causality for death was not provided. The second death concerned a [redacted]-year-old [redacted] patient who died of intracranial hemorrhage 37 days after starting imatinib. Investigator's causality for intracranial hemorrhage was 'Not suspected to be related'. During the whole duration of the study, overall, 11 patients died (7 in the poor risk group and 4 in the good risk group) (Table 10-14, Table 14.3.1-3.2). Case narratives for all the 11 patients who died are provided in Section 14.3.3.

10.5.2.2 Serious adverse events

SAEs, regardless of study drug relationship, were reported in 86.7% of patients, in 85.0% of patients at least one SAE was of grade 3 or 4. The most frequently reported SAEs regardless of study drug relationship by PT of all grades (≥30%) were (Table 10-20):

- Febrile neutropenia (38.3%)
- Stomatitis (30.0%)

Full list of SAEs regardless of study drug relationship by preferred term is presented in Table 14.3.1-6.2.

Case narratives for each patient with an SAE occurring during the study are provided in Section 14.3.3. Full deatils of all SAEs of individual patient is present in Listing 14.3.2-2.

Table 10-20 Serious adverse events (reported in at least 15% of patients) regardless of study drug relationship by preferred term, maximum grade and risk group(Safety set)

	Poor risk N=20		Good risk N=40		All patients N=60	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	18 (90.0)	18 (90.0)	34 (85.0)	33 (82.5)	52 (86.7)	51 (85.0)

[redacted]

	Poor risk N=20		Good risk N=40		All patients N=60	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Febrile neutropenia	8 (40.0)	8 (40.0)	15 (37.5)	15 (37.5)	23 (38.3)	23 (38.3)
Stomatitis	5 (25.0)	4 (20.0)	13 (32.5)	12 (30.0)	18 (30.0)	16 (26.7)
Pyrexia	3 (15.0)	1 (5.0)	11 (27.5)	2 (5.0)	14 (23.3)	3 (5.0)
Neutropenia	7 (35.0)	7 (35.0)	6 (15.0)	6 (15.0)	13 (21.7)	13 (21.7)
Febrile bone marrow aplasia	1 (5.0)	1 (5.0)	10 (25.0)	10 (25.0)	11 (18.3)	11 (18.3)
Pneumonia	2 (10.0)	2 (10.0)	7 (17.5)	7 (17.5)	9 (15.0)	9 (15.0)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients group.
- A subject with multiple severity grades for a serious AE is only counted under the maximum grade.
- MedDRA version: 25.0, CTCAE version 4.03.
Source: Table 14.3.1-6.2

10.6 Other analyses

Details of laboratory measurements by individual patients are presented in Listing 16.2.8-1.

Details of vital signs, physical findings and other observations related to safety listings are presented in Listing 16.2.9-1 to Listing 16.2.9-5.

11 Discussion

11.1 Key results

Efficacy

- A total of 28 EFS events were observed during the study. The median EFS time was not reached. The Kaplan-Meier estimated EFS rate at 60 months was 57.1% (95% CI: 43.4, 68.7) in all patients.
- The median time for OS was not reached. The survival probability estimate at 60 months was 81.1% (95% CI: 68.5, 89.1).
- Overall best CHR status (with 95 % CI) was noted as 65.0% (95% CI: 51.6, 76.9) in the all patients group. By 12 months the rate of best CHR is 48.3% (95% CI: 35.2, 61.6), i.e. nearly three quarter of patients have reached CHR within the first year after diagnosis.
- Best MRD response (with 95 % CI) was 46.7% (33.7, 60.0) at post induction and 95% (86.1, 99.0) overall in the all patients group.
- Best complete remission status overall (with 95 % CI) was reported by 57 patients (95.0% (95% CI: 86.1, 99.0) in the all patients group. Seven patients out of 57 patients (12.3%) reported loss of CR. The KM estimated rate of CR duration at 60.0 months is 85% (95% CI: 70.7, 92.6).
- Overall, 28 patients received a transplantation. The median time (95% CI) to transplant in all patients was 65.9 months (38.1, NE). The KM estimated rate (95% CI) by 60 months was 48.4% (35.9, 62.6).

[redacted]

- For 24 out of 28 (85.7%) transplanted patients engraftment was reported. The median time (95% CI) to engraftment was 1.0 month (0.8, 1.3). The KM estimated rate (95% CI) by 1.0 month was 48.1% (31.5, 68.1). The median time to engraftment in those 24 patients is 0.95 months (range: 0.4, 8.3). Of the 28 patients who received a transplantation, 26 (92.9%) patients reported no engraftment failure. For 2 patients no information about engraftment was provided.
- Out of 28 patients in the transplanted set, presence of acute graft versus host disease (GvHD) was noted in 12 (42.9%) patients with no GvHD in 11 (39.3%) patients and GvHD not assessed/missing in 5 (17.9%) patients. Presence of chronic graft versus host disease (GvHD) was noted in 4 (14.3%) patients with no GvHD in 19 (67.9%) patients and GvHD not assessed/missing in 5 (17.9%) patients.
- After adjustment of prognostic factors, the good risk patient group shows a benefit on EFS and OS over the poor risk patient group (HR 0.167; 95% CI: 0.060, 0.468) and (HR 0.197; 95% CI: 0.029, 1.331), respectively.

Safety

- The most frequently reported AEs regardless of study drug relationship by SOC of all grades were: infections and infestations (88.3%), blood and lymphatic system disorders (86.7%), gastrointestinal disorders (83.3%), general disorders and admistration site conditions (61.7%) and metabolism and nutritiona disorders (58.3%).
- The most frequently reported AEs regardless of study drug relationship by PT of all grades were: stomatitis (66.7%), thrombocytopenia (58.3%), neutropenia (56.7%) and febrile neutropenia (53.3%).
- Of the 60 patients, seven patients (11.7%) experienced at least one AE that led to study drug discontinuation regardless of the study drug relationship.
- The most frequently reported AEs suspected to be related to study drug by PT of all grades were: neutropenia (40%), thrombocytopenia (35%), vomiting (31.7%) and febrile neutropenia (30%).
- The most frequently reported AEs (of all grades and of grade 3 or 4) that required dose adjustment or interruption regardless of the study drug relationship were: neutropenia (30%) and febrile neutropenia (23.3%).
- Two (3.3%) patients died within 30 days after end of treatment with imatinib. The reported cause of death were 'Death' and 'Intracranial hemorrhage'. Review of these two deaths did not reveal any new safety information. During the entire duration of the study, 11 patients died (7 in the poor risk group and 4 in the good risk group).
- SAEs, regardless of study drug relationship, were reported in 86.7% of patients, in 85.0% of patients at least one SAE was of grade 3 or 4. The most frequently reported SAEs regardless of study drug relationship by PT of all grades (≥30%) were: febrile neutropenia (38.3%) and stomatitis (30%).
- Among patients in Tanner stage 1 at Baseline, Tanner stage 2 was attained in 4 out of 6 male patients for genital development and pubic hair, and in 7 out of 9 female patients for breast development and pubic hair

[redacted]

- Of the 23 male patients at risk of delayed puberty at start date of imatinib, puberty was not delayed in 11 patients (47.8%), delayed in 2 patients (8.7%) and was unknown in 10 patients (43.5%)
- Of the 14 female patients at risk for delayed puberty at start date of imatinib, puberty was not delayed in 2 patients (14.3%), delayed in 3 patients (21.4%), and was unknown in 9 patients (64.3%).
- The proportions of patients with SDS values < 5^{th} percentile (< -1.645) or > 95^{th} percentile (> 1.645) on height, height velocity, BMI, and weight velocity did not change significantly after the start of imatinib.
- Available clinical data did not show an impact of imatinib on growth (height, weight, and BMI).

11.2 Limitations

The following limitations were noted:

- The research method outlined in the protocol served as a compromise between a population-based registry assessing the entirely of the pediatric patient population treated with imatinib in this indication, and an interventional, clinical trial, which would not reflect the breadth of the standard clinical setting.
- A non-interventional, observational study design is implicitly associated with known limitations, including difficulty to control external variables and the availability/ completeness of data.
- In an effort for the registry population to be as representative as possible of the patient population as a whole, no exclusion criteria were defined. Furthermore, any standard concomitant chemotherapy regimen was permissible. Although this enhanced the relevance of the study, it did not create a source of non-homogeneity with respect to adverse events related to concurrent chemotherapy.
- This was a single arm design (imatinib + chemotherapy) and lacking an external control. This is because TKIs (including in particular also imatinib) are considered standard of care for the treament of Ph+ ALL in children, making a control arm unfeasible and possibly unethical.
- Start and/or end dates were frequently reported as partially or completely missing.

11.3 Interpretation

The results of this study and their interpretations are presented in Section 9.

11.4 Generalizability

ALL is the most common malignancy in the pediatric population (approximately 80% of childhood leukemias and 25% of all pediatric cancers). Ph+ ALL accounts for up to 5% of pediatric ALL. In addition, the data were collected from regions in which imatinib was adopted and delivered and that were willing to cooperate in this study, wherever region they were in and whoever the founder was. However, the limited number of patients registered in this study (60 patients) inevitably limits generalizability to the safety and efficacy of imatinib used in general pediatric patients with Ph+ ALL.

[redacted]

12 Other information

Not applicable.

13 Conclusion

- The final analysis demonstrated sustained efficacy of imatinib in combination with chemotherapy with or without HSCT (± HSCT) in newly diagnosed Ph+ ALL pediatric patients
- The safety profile is consistent with previously reported safety of imatinib in combination with chemotherapy with or without HSCT (± HSCT) in newly diagnosed Ph+ ALL pediatric patients
- The overall benefit-risk assessment of imatinib use in pediatric patients with newly diagnosed Ph+ ALL remains favorable.

The reported AEs in I2201 study are known with imatinib exposure. Of note, the reported frequencies of AEs needs to be viewed in relation to the small number of subjects enrolled (N=60). Due to the rarity of the indication, the planned enrollment was reduced to a minimum of 50 patients. The study results didn't reveal any safety finding in long term follow-up of pediatric patients with Ph^+ ALL (in this study, long term safety and efficacy data was collected such that the observational follow-up for each patient was a minimum of 5 years from start of imatinib treatment or such available data until early patient discontinuation).

[redacted]