Ponatinib with FLAG-IDA chemotherapy for patients with blast-phase chronic myeloid leukaemia (MATCHPOINT): a single-arm, phase 1-2 trial

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Research in context

Evidence before this study

A formal systematic review was not performed before undertaking this study. Relevant evidence was sought from PubMed, and the published abstracts of key conferences (including ASH, ASCO and EHA annual meetings). No prospective trials of a ponatinib-chemotherapy combinations were identified before MATCHPOINT. Existing evidence was from retrospective analyses, or prospective trials using imatinib. This limited evidence suggested that long-term, disease-free survival may be more likely with tyrosine kinase inhibitor (TKI)-chemotherapy combinations, consolidated with allogeneic stem cell transplant.

Added value of this study

To our knowledge, MATCHPOINT is the first trial to prospectively test the activity and feasibility of delivering ponatinib with FLAG-IDA chemotherapy for the treatment of blast-phase CML. When used to achieve a second chronic phase pre-allogeneic stem cell transplantation, this regimen can result in durable overall and disease-free survival. The trial demonstrates that valuable dose-finding, activity and tolerability data can be generated from small patient numbers, through use of an efficient Bayesian trial design.

Implications of all the available evidence

For patients presenting with blast-phase CML, combination treatment with ponatinib and FLAG-IDA chemotherapy may be considered an option to induce a second chronic phase in advance of allogeneic stem cell transplantation, as now recommended within the European LeukemiaNet guidelines (2020). Additional research is required to investigate whether treatment should be adapted according to disease response, and to establish the predictive significance of additional genetic mutations in blast-phase CML.

Abstract

Background

Outcomes of patients with blast-phase chronic myeloid leukaemia (BP-CML) are poor. Long-term survival depends on achieving a second chronic-phase (CP2), followed by allogeneic stem cell transplantation (alloSCT). The prospective, phase I/II MATCHPOINT trial investigated the novel combination of the tyrosine kinase inhibitor ponatinib with fludarabine, cytarabine, G-CSF and idarubicin (ponatinib-FLAG-IDA) to improve response and optimise transplant outcomes in BP-CML. The aim was to identify a dose of ponatinib, which combined with FLAG-IDA, demonstrated clinically meaninful activity and tolerability.

Methods

Adults with BP-CML, suitable for intensive chemotherapy, received up to two cycles of ponatinib with FLAG-IDA. Experimental dose levels of ponatinib were between 15mg alternate days and 45mg once daily, the starting dose was 30mg once daily. Fludarabine (30mg/m^2 IV for 5 days), cytarabine (2g/m^2 IV for 5 days), G-CSF (if used) and idarubicin (8mg/m^2 IV for 3 days) were delivered according to local protocols. MATCHPOINT (ISRCTN 98986889) used an innovative EffTox design to investigate the activity and tolerability of ponatinib-FLAG-IDA; the primary endpoint was the optimal ponatinib dose meeting pre-specified thresholds of activity and toxicity. Analyses were planned on an intention-to-treat basis. MATCHPOINT has competed recruitment and the final results are presented.

Findings

Seventeen patients (12 men, 5 women) were recruited between 19th March 2015 and 26th April 2018, median follow-up is 41 months (interquartile range 36 to 48 months). The EffTox model simultaneously considered clinical responses and dose-limiting toxicities (DLT), and determined the optimal ponatinib dose as 30mg daily, combined with FLAG-IDA. Eleven patients achieved CP2 (defined as either haematological or minor cytogenetic response) after one cycle of treatment, four experienced a DLT, fulfilling the criteria for clinically relevant activity and toxicity. Twelve patients proceeded to alloSCT. Most common grade 3-4 non-haematological adverse events were lung infection (n=4), fever (n=3) and hypocalcaemia (n=3). There were 12 serious adverse events; three patients experienced treatment-related mortality (due to cardiomyopathy, pulmonary haemorrhage, and bone marrow aplasia).

Interpretation

Ponatinib-FLAG-IDA can induce CP2 in BP-CML patients, representing an effective salvage therapy to bridge to alloSCT. The number of treatment-related deaths is not in excess of what would be expected, in this very high risk group of patients receiving intensive chemotherapy. The efficient EffTox method is a model for investigating novel therapies in ultra-orphan cancers.

Funding

Blood Cancer UK, and Incyte.

Introduction

The prognosis of chronic myeloid leukaemia (CML) presenting in first chronic-phase (CP) has improved remarkably since the introduction of BCR-ABL1 tyrosine kinase inhibitors (TKIs). Started in CP, TKIs induce remission, prolong survival, and reduce progression to blast-phase (BP)-CML.[1-3] However, for the 5-7% of patients treated with imatinib, and 2-5% with second-generation TKIs progressing to BP,[1,2,4] and the 5-10% who present in BP at diagnosis, prognosis remains dismal.[5] Allogeneic stem cell transplantation (alloSCT), the only curative therapy, critically depends on patients achieving remission with salvage therapy.[6] There is no consensus approach to achieving a second CP (CP2) in patients with BP-CML, and induction chemotherapy with or without adjunctive TKI therapy has been trialled with modest effect.[7] Novel drug combinations that can reliably induce remission, allowing alloSCT consolidation and post-transplant TKI maintenance, are therefore urgently needed to improve outcomes in BP-CML. Progress has been limited by the rarity of BP-CML, and like many ultra-orphan diseases, the unrealistic sample sizes required by traditional trial designs have impeded the evaluation of promising therapeutic approaches. The statistically advanced EffTox method simultaneously evaluates activity and toxicity, combining dose-finding and activity assessment trial phases, using Bayesian methods to maximise the power of small patient populations.[8] By evaluating posterior probabilities of both activity and toxicity, the 'desirability' of each dose is measured. Informed by pre-specified, clinically important thresholds of minimal activity and maximal toxicity, EffTox uses 'utility contours' to recommend future doses.[8,9]

Ponatinib is an oral TKI with activity against treatment-resistant BCR-ABL1 kinase domain mutations.[10,11] In the PACE trial, single agent ponatinib showed activity in patients with BP-CML with 18% of patients achieving complete cytogenetic response (CCyR), although duration of response was short, with overall survival (OS) of 9% at 3 years.[12] An historical case series combining dasatinib with the intensive chemotherapy regimen fludarabine, cytarabine, idarubicin and granulocyte-colony stimulating factor (FLAG-IDA) in BP-CML has shown promise.[13] We therefore devised the MAnagement of Transformed CHronic myeloid leukaemia with POnatinib and INTensive chemotherapy (MATCHPOINT) trial, using the innovative EffTox method[8,9] to investigate ponatinib in combination with FLAG-IDA in both myeloid and lymphoid BP-CML. The primary objective was to determine the optimal dose of ponatinib in combination with FLAG-IDA that is both tolerable and efficacious.

Methods

Study design

MATCHPOINT is a prospective, seamless phase I/II multicentre study of ponatinib-FLAG-IDA, for the treatment of BP-CML incorporating both dose-finding and estimations of activity and tolerability. An adaptive Bayesian EffTox model was used to determine the optimal ponatinib dose, simultaneously considering activity and toxicity.[9] EffTox was chosen as it efficiently answers both phase 1 (dose-finding) and phase 2 (estimating activity and toxicity) questions, with overall clinical utility guiding dose recommendations, using relatively small numbers of patients. MATCHPOINT received UK Research Ethics Committee approval (13/SC/0583), all participants provided written informed consent, and the trial was carried out in compliance with the Declaration of Helsinki.

Participants

Eligible patients had Philadelphia chromosome (Ph)-positive or *BCR-ABL1*-positive CML, with BP defined according to established criteria.[14] Other inclusion criteria were: age ≥16; suitable for FLAG-IDA chemotherapy; adequate renal (creatinine ≤1.5x upper limit of normal (ULN)), liver (transaminase <2.5x ULN, or <5x ULN if CML liver involvement; bilirubin <1.5x ULN), pancreatic (amylase <1.5x ULN) and cardiac (normal QT interval) function. Patients were ineligible if they had received high-dose chemotherapy within 4 weeks of registration; changed TKI more than once since confirmation of BP; had prior treatment with ponatinib; had prior allogeneic or autologous SCT; had a history of significant cardiovascular disease (including ischemic heart disease, arrhythmia, heart failure, uncontrolled hypertension, stroke, unprovoked venous thromboembolism or uncontrolled hypertriglyceridaemia) or pancreatitis; were galactose intolerant; had undergone surgery within two weeks of registration; suffered from any condition that would compromise their safety if they entered the trial. Patients who were pregnant or breastfeeding were not eligible, due to the toxicity of FLAG-IDA and the unknown effect of ponatinib on a fetus or breast-fed infant.

Procedures

During induction, ponatinib was commenced from day 1 of FLAG-IDA, at a dose recommended by the EffTox model, initially set at 30mg/day by mouth, and given up to day 28. Ponatinib could be given continuously beyond 28 days, if there was haematological recovery following each FLAG-IDA cycle. The 30mg starting dose was recommended by the independent Trial Steering Committee (TSC). There was potential to increase ponatinib dose to 45mg for lack of response (if tolerated), or reduce dose to 15mg for toxicity. The four experimental dose levels are shown in appendix p 2. During treatment, dose reductions were permitted for non-haematological toxicities, full details are provided in the protocol (see appendix). FLAG-IDA consisted of fludarabine 30mg/m^2 days 1-5 intravenously (IV), cytarabine 2g/m^2 days 1-5 IV, and idarubicin 8mg/m^2 days 3-5 IV, with G-CSF given subcutaneously as a priming agent according to local protocols if leukocyte count was below locally-permitted thresholds (appendix p 11). FLAG-IDA dose modifications were permitted for liver or renal impairment, according to local practice. Supportive medications were given according to local protocols, including for *Pneumocystis jirovecii* prophylaxis. Patients received one or two cycles of ponatinib-FLAG-IDA. For consolidation, alloSCT was not mandated, but was recommended for patients starting this intensive treatment regimen. For maintenance, patients received ponatinib after recovery from FLAG-IDA until the beginning of alloSCT conditioning (if applicable); transplanted patients restarted ponatinib from 45 days post-alloSCT if no clinically significant ongoing toxicity. Ponatinib maintenance continued indefinitely for as long as clinical benefit was maintained or until disease relapse occurred. Maintenance ponatinib was started at the dose recommended by the EffTox model, and reduced to 15mg/day once major molecular remission (MMR) had been attained.

Outcomes

The primary endpoint was to establish the dose of ponatinib, which, when combined with FLAG-IDA chemotherapy, demonstrated clinically relevant activity and tolerability. The co-primary outcomes were treatment activity and tolerability. Activity was assessed locally without central review, and was defined as achievement of CP2, comprising either a complete haematological response (CHR: platelet count >50 x10^9/L, neutrophil count >1·0 x10^9/L, and peripheral blood or bone marrow blasts <5%), or at least a minor cytogenetic response (CyR) (Ph-positive cells ≤65%). Tolerability was defined in terms of dose-limiting toxicity (DLT) as: clinically significant grade 3 or 4 non-haematological toxicity related to ponatinib, that in the judgement of the investigator, cannot be adequately managed; pancreatitis grade

2 or above; raised serum pancreatic amylase grade 3 or 4; QT interval prolongation grade 3 or 4; or any arterial or venous thromboembolic event. Toxicities were measured according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. Both activity and tolerability co-primary outcomes were assessed prior to the second cycle of chemotherapy, after haematological recovery (if applicable), between 4 and 8 weeks after commencing treatment. Lack of activity was imputed if a patient died before outcome assessment.

Secondary outcomes were: toxicity profile of ponatinib-FLAG-IDA, collected continually, within 6 months of starting treatment or up to alloSCT; CCyR (0% Ph-positive cells), MMR (*BCR-ABL1* $\leq$0.1% on international scale), and CHR within 2 cycles of treatment, up to 8 weeks after starting each cycle; disease-free survival (DFS; from CCyR to date of relapse or death from CML); OS (from registration to date of death from any cause); relapse rate post-alloSCT or on maintenance; treatment-related mortality (TRM) due to ponatinib-FLAG-IDA; incidence of cytomegalovirus (CMV) reactivation and graft-versus host disease (GvHD) post-transplant. All response outcomes are reported in accordance with 2013 European LeukemiaNet recommendations. [15]

EffTox statistical model

Activity and toxicity rates were used to update an EffTox model to establish the optimal dose of ponatinib with FLAG-IDA – the trial's primary endpoint. The adaptive Bayesian EffTox method, and its application to MATCHPOINT and operating characteristics, have been described previously (including a discussion of alternative methods).[8,9] In summary, bivariate binary outcomes were incorporated into the model seeking probability of activity of 45% or more, and probability of toxicity (DLT) of 40% or less. Activity was modelled using a quadratic form, allowing for a non-monotonic dose-response, such as a plateau of activity at higher doses. Toxicity was incorporated into the model using a linear form. The prior probabilities of activity and toxicity were agreed by consensus of the trial management group (appendix p 2). Dose transition pathways (DTP) were incorporated alongside the EffTox method to visualise all potential dose pathways, be it escalation/de-escalation, remaining at the same dose, or stopping early.[9,16] They provided a simple means of assessing the impact of different data permutations of outcomes for future patients on the EffTox recommendations during the progress of trial. Additionally they would prove a useful design calibration tool to ensure the EffTox design would behave as anticipated given its chosen design parameters.[9]

Outcomes of the first three patients were incorporated into the EffTox model, which provided an optimal ponatinib dose level at which the TSC could recommend treating a second cohort of three patients. Thereafter, the TSC met after each new cohort of one to three patients was assessed, and the model continually updated to determine the dose for each subsequent patient. Recruitment continued until the maximum sample size was reached, or none of the dose levels showed acceptable levels of activity (<3% probability of ≥45% activity) or toxicity (>95% probability of ≥40% toxicity).[9] A minimum target sample size of 15, revised from a preliminary target of 30, pragmatically reflects recruitment of patients with this rare clinical scenario (protocol amendment version 6, approved 7th November 2017). An additional three patients (total sample size 18) would be required if a dose escalation/de-escalation was recommended, to confirm the reliability of the recommendation and increase the precision of the estimates of activity and toxicity rates. This approach has a number of advantages over traditional designs: it considers a non-monotonic dose-response relationship, requires fewer pauses in patient recruitment for outcome assessments of separate cohorts, and patients are more likely to be treated at the optimal dose, reducing exposure to potentially toxic or inefficacious doses.

The EffTox software is available from the MD Anderson Cancer Centre (https://biostatistics.mdanderson.org/softwaredownload), version 4.0.12 was used. All other statistical analysis were performed in R (R Foundation, Vienna, Austria) version 4.0.3. Descriptive statistics were used to report all secondary outcomes, time-to-event outcomes using the Kaplan-Meier method. All statistical analyses were planned on an intention-to-treat basis.

This trial is registered as an International Standard Randomised Controlled Trial number ISRCTN 98986889.

Genetic and molecular assessments

Peripheral blood samples were collected at diagnosis and following achievement of CP2 after one or two cycles of ponatinib-FLAG-IDA. DNA was extracted using an EASY-DNA kit (Invitrogen, ThermoFisher Scientific, UK). Targeted next generation sequencing (NGS) was performed with Illumina MiSeq, aligning data to GRCh38, and utilising the Illumina TruSight myeloid panel (performed as per manufacturer's instructions) (Illumina, California, USA). Data were analysed with MiSeq reporter and visualised in VarSeq (Golden Helix, Montana, USA) with variant nomenclature described according to current Human Genome Variation Society (HGVS) guidelines (http://www.hgvs.org).[17] Variant detection level (% variant detectable in a background of wild type DNA) was 5% for single nucleotide variants that are clonally represented in the sample. A minimum read depth of 200x coverage was achieved in all samples at >97%.

Whole exome sequencing was performed on one patient (TNO-01) following relapse post-transplant with lineage switch from myeloid to T-lymphoid BP. Buccal mucosa at trial entry was used as a 'non-malignant' control to eliminate germline background mutations. DNA was extracted from the buccal, CP diagnostic (before trial entry), myeloid BP, and relapsed T-lymphoid BP (post-transplant) samples using QIAamp DNA mini kit (Qiagen, USA). Exome sequencing was performed as per manufacturer's protocol using the NextSeq500 platform with a read length of 75bp and paired ends. Paired read counts captured were as follows: buccal 80,452,595; CP 119,135,733; myeloid BP 110,805,066; T-lymphoid BP 110,021,429. Data were processed by Glasgow Polyomics.

Role of the funding source

The trial funders reviewed the trial protocol, but had no role in the study design, nor the collection, analysis or interpretation of the data, nor in writing the report or decision to submit for publication. DS and RF had access to the data.

Results

Seventeen patients were recruited from eight UK Trials Acceleration Programme-funded centres between 19th March 2015 and 26th April 2018 (appendix p 3). Sixteen were evaluable for the co-primary outcomes. One patient was judged not evaluable by the independent TSC, as complications attributable to the underlying BP-CML caused significant interruptions and delays in administering the first cycle of treatment, of which only 4 days were completed. However, this patient completed the second cycle of ponatinib-FLAG-IDA, and all 17 patients are included in analyses of the secondary outcomes. A CONSORT flow diagram is shown in Figure 1, and baseline patient characteristics are summarised in Table 1 and listed in Table 2. Of the five patients tested, one demonstrated the T315I *BCR-ABL1* kinase domain mutation. Nine patients completed a single cycle of ponatinib-FLAG-IDA only. Of the eight patients completing both planned cycles, this was to consolidate responses in six, and to reattempt induction in

two. Twelve patients successfully proceeded to alloSCT. Median follow-up is 41 months (Kaplan Meier method, interquartile range 36 to 48 months).

Eleven of 16 (69%) evaluable patients, including myeloid, lymphoid and mixed phenotype BP-CML, achieved CP2 after one cycle of ponatinib-FLAG-IDA. Individual patient outcomes are shown in Table 2, and are summarised in appendix p 4. Failure to achieve CHR was due to incomplete count recovery in all fully evaluated patients, none showing persistent blasts >5%. Notably, the five (31%) patients achieving MMR did so after one cycle of ponatinib-FLAG-IDA.

Four (25%) patients experienced DLTs in cycle 1 of ponatinib-FLAG-IDA, all of whom received 30mg ponatinib with combination chemotherapy. The patients experiencing DLTs were: one with fulminant cardiomyopathy and grade 4 raised ALT, one with cerebral venous sinus thrombosis, one with grade 3 raised amylase, and one with grade 4 raised ALT.

The most common grade 3-4 adverse events (AEs) within the reporting period were haematological, including neutropenia (n=12 patients, 71%), thrombocytopenia (n=11, 65%), anaemia (n=7, 41%), and febrile neutropenia (n=5, 29%). The most common non-haematological grade 3-4 AEs were lung infection (n=4, 24%), fever (n=3, 18%), and hypocalcaemia (n=3, 18%). Table 3 lists common (occurring in >10% of patients) and all grade 3-4 AEs. Appendix p 5 shows the same data, disaggregated according to sex; appendix p 6 lists less frequent grade 1-2 AEs according to sex. Twelve serious AEs among 11 (65%) patients were reported; six were treatment-related, experienced by six patients (appendix p 7). TRM occurred in three patients during ponatinib-FLAG-IDA therapy, 29, 71 and 94 days after trial registration. TRM was due to cardiomyopathy, pulmonary haemorrhage, and bone marrow aplasia.

Of the 16 patients evaluable after one cycle of ponatinib-FLAG-IDA, 9 (56%) demonstrated a response without DLT, 2 (13%) responded but also experienced a DLT, and 2 (13%) experienced a DLT with no response; the remaining 3 (19%) patients showed neither activity nor toxicity. After assessment of the first and second cohorts of three patients, and after each subsequently assessed patient, the updated EffTox model recommended continuing treatment at dose level 1 (30mg ponatinib). Every dose recommendation was based on the primary outcomes of all accrued patients at each point of analysis. Appendix p 8 shows how the model was updated. The final model provided a posterior probability of activity of 68% (95% credible interval 47-84%) and toxicity of 25% (95% credible interval 8-41%). There is a 97% probability that ponatinib-FLAG-IDA meets the pre-specified activity threshold of ≥45%, and a 91% probability that it falls below the 40% toxicity threshold. Appendix p 2 shows the posterior probabilities of activity and toxicity for all dose levels. Overall, 30mg/day ponatinib with FLAG-IDA chemotherapy is recommended as the dose that best balances activity and toxicity.

Twelve (71%) patients underwent alloSCT after ponatinib-FLAG-IDA. Six stem cell donors were siblings, five were matched unrelated, and one was haploidentical family member. Appendix p 9 describes further details and transplant outcomes. Five patients proceeded to alloSCT after one cycle of induction, of whom three had attained CCyR, and one partial CyR (Ph positive cells ≤35%). Seven patients were transplanted after two cycles of ponatinib-FLAG-IDA, of whom five had maintained CCyR since cycle 1. Three patients underwent alloSCT without achieving any cytogenetic response. Of the five patients demonstrating MMR after the first cycle of ponatinib-FLAG-IDA, one underwent alloSCT directly, and four completed a second cycle as consolidation before transplant.

Ponatinib was re-started in five patients (42%) post-transplant, including one patient at a reduced dose of 15mg alternate days due to valganciclovir-induced cytopenias. The remaining patients did not restart ponatinib due to inadequate blood count recovery (n=3), hepatic dysfunction (n=2), previous DLT (raised serum amylase, n=1), and sepsis with multi-organ failure (n=1).

Two patients relapsed five and seven months after alloSCT, both subsequently dying of CML. One patient experienced disease relapse at seven months after alloSCT (localised, treated with donor lymphocyte infusion (DLI), orchidectomy and radiotherapy) and again at 27 months (molecular relapse, treated with DLI), and is alive 40 months post-transplant. Three further patients died within six months of alloSCT, due to transplant-related complications.

Five (29%) patients did not undergo alloSCT; one attained a partial CyR and one a minor CyR to ponatinib-FLAG-IDA. Three of the four DLTs included in the primary outcome occurred in this group. Median survival was two months in this adverse risk cohort; all died within seven months of trial entry.

There were 10 deaths in total, median OS was 12 months (95% CI 6 months to non-calculable) (Figure 2, see also appendix p 12 for OS censoring for alloSCT). The Kaplan-Meier-estimated rates of 1- and 3-year OS were 47% (95%; CI 28-78%) and 41% (95%; CI 23-73%), respectively. Median DFS has not been reached, with only two events among the ten patients achieving CCyR (appendix p 13). The median OS in those receiving alloSCT has not been reached, with 7 of 12 patients alive with a median follow-up of 36 months post-transplant.

An exploratory investigation of the genetic determinants of BP-CML and response to treatment was carried out. Targeted NGS was performed on 15 baseline and nine post-ponatinib-FLAG-IDA peripheral blood samples (appendix p 10). Eight patients had paired data available for comparison. Variants with known clinical significance (tier I and II) were detectable in seven baseline samples (47%), variants of unknown clinical significance (tier III and IV) detectable in five samples (33%). For paired data, there were significant reductions in the detected variant allele frequencies (VAF), 4/6 (67%) patients demonstrating complete eradication following ponatinib-FLAG-IDA. No new mutations were detected following treatment. Somatic mutations do not appear correlated with clinical outcomes, however patient numbers are small. Appendix p 10 also describes additional cytogenetic abnormalities (ACAs) at trial entry.

Whole exome sequencing was performed on the diagnostic CP, myeloid BP and post-transplant relapsed T-lymphoid BP samples for patient TNO-001. Summary data are presented in appendix p 14. Two hundred and forty-three somatic mutations were common to all samples, with 40 somatic mutations identified that differed between CP and myeloid BP. Over 30,000 somatic mutations were identified on relapse to T-lymphoid BP compared to the myeloid BP and CP samples, suggesting genomic instability post-transplant.

Discussion

The innovative MATCHPOINT trial design allowed simultaneous, prospective evaluation of both safety and activity, combined into a seamless phase I/II dose-finding study. Combined with FLAG-IDA, ponatinib 30mg/day resulted in an acceptable toxicity profile and a promising response rate. The 68% estimated probability of activity and 25% probability of toxicity are considerably superior to the pre-specified thresholds; a substantial proportion of patients remain disease-free post-alloSCT. Altogether, MATCHPOINT demonstrated that ponatinib-FLAG-IDA is tolerable, efficacious, and may be considered as a new standard-of-care for BP-CML, as reflected in the 2020 European LeukemiaNet guidelines.[18] It is notable that responses were seen in myeloid, lymphoid and mixed phenotype BP-CML. Further evaluation through a prospective international trial could provide greater precision on the estimated rates of clinical response and toxicity with ponatinib-FLAG-IDA, and investigate whether one or two cycles of ponatinib-FLAG-IDA is optimal, considering treatment toxicities and the importance of

achieving MMR. Incorporating translational science into future trials is essential to build on the genetic data obtained through MATCHPOINT.

There are some limitations to this study.The relatively young age of the MATCHPOINT cohort and the comparatively few patients with BP-CML progressing through TKI therapy could limit its generalisability, however this also reflects the intensity of FLAG-IDA chemotherapy. One limitation of the molecular data is the absence of *BCR-ABL1* kinase domain mutation status in many patients, also not included on the NGS panel, preventing further interpretation of its prognostic significance in this setting. Additional toxicity data, including time to neutrophil and platelet recovery, and using serum lipase to more accurately test for pancreatitis, could have provided further detail about the tolerability and deliverability of the ponatinib-FLAG-IDA regimen.

During the time that patients were enrolling onto MATCHPOINT, a higher ponatinib dose of 45mg was successfully combined with chemotherapy, although for a shorter duration.[19] The starting dose in MATCHPOINT was determined by the independent TSC, guided by the prior assumptions of activity and toxicity. The influence of the prior probabilities was tested in simulation before the trial opened, to ensure satisfactory performance of the model if data departed from the prior.[9] However, it could be considered a limitation that only one dose level was tested: the potentially increased activity of the 45mg dose was not tested, due to the significantly increased toxicity predicted by the EffTox model. As in all dose-finding studies, the definition of DLTs has a strong influence over dose-escalation recommendations. The DLTs in MATCHPOINT were pre-defined according to known risks of ponatinib, although these can be seen commonly with treatments aimed at inducing CP2. Whilst it is possible that the stringency of DLT definition precluded escalation to a theoretically more effective dose, DLTs were only experienced by four patients, half of whom also demonstrated clinical response. An alternative method could have been to assess toxicities at a later timepoint than activity, for which the modified Late-Onset EffTox model would be more suitable.[20]

Previous trials combining imatinib with cytotoxic chemotherapy have achieved median OS of 5-17 months, with longer survival following alloSCT,[21-24] and retrospective analyses suggest a survival advantage for combination therapy.[7,13,25,26] An approach trialled more recently in phase 1, combining dasatinib with decitabine, has shown response rates of up to 50% in patients with myeloid BP-CML, again with better outcomes achieved following alloSCT.[27] Novel TKI combinations with targeted agents, including venetoclax and blinatumomab, have also been associated with promising outcomes in retrospective studies, inviting confirmation through prospective trials.[28,29] *BCR-ABL1* mutations are associated with advanced stage CML,[30,31] with patients in BP likely to have already received first- or second-generation TKIs (71% of MATCHPOINT cohort). As the most potent BCR-ABL1 inhibitor, with the greatest coverage against kinase domain mutations,[10] ponatinib is especially well-suited to treatment of BP-CML, although its limited single-agent activity underscores the importance of combination therapy.[12,32] Ultimately, alloSCT is the only curative therapy for BP-CML patients, with success relying on attainment of CP2 pre-transplant.[6,33,34] Outcomes for the MATCHPOINT cohort reflect this: 7 of 12 transplanted patients are still alive, whereas none survived without transplant, and ponatinib-FLAG-IDA could be considered an appealing bridge to alloSCT. Although small numbers prevent further interpretation, patients progressing to BP on TKI and inadequate response to induction therapy are poor prognostic features, and additional treatment options are urgently needed.

The rarity of BP-CML in the TKI era precludes many of the traditional approaches to early-phase trials, which risk inadequate recruitment and inefficient use of information. The use of the innovative and statistically advanced EffTox method, which has only rarely been applied in haemato-oncology trials, was instrumental to the successful completion of this prospective BP-CML trial. This approach has

several advantages, particularly in ultra-orphan diseases. The seamless phase I/II design allowed simultaneous evaluation of both activity and toxicity, reflecting that real-world utility of a treatment depends on both attributes. The MATCHPOINT model explicitly allowed for divergent dose-responses, wherein dose escalation leads to increased toxicity while activity might plateau.[9] The Bayesian method incorporated the outcomes of all patients, to provide final probability distributions of activity and toxicity of the recommended dose. Through continual reassessment and updating of posterior probabilities, the accuracy and precision of activity and toxicity estimates were improved during the trial. By integrating DTP methodology to model every possible EffTox outcome and dose recommendation, interim analysis demonstrated that the 30mg ponatinib dose was unlikely to change even if the trial continued to recruit more patients. Similarly, clinically relevant activity and toxicity could be shown, with associated posterior probabilities exceeding the pre-specified thresholds, with the lower sample size. This revised sample size pragmatically reflects the rarity of BP-CML, was agreed by the independent TSC, and highlights the flexibility and efficiency of this innovative trial design. This approach also allowed for the inclusion and contribution of the final two patients, who were recruited simultaneously at different sites, taking the sample size above the minimum 15 required. Overall, this highly efficient use of patient data brings a level of confidence in the trial outcome that would not be achievable with a traditional design and is highly suited to very rare patient cohorts such as BP-CML.

Molecular mechanisms responsible for the progression to BP-CML remain poorly understood, with genomic instability believed to be important.[35] Ten of 15 (67%) MATCHPOINT patients had mutations (tiers I-IV) identified, with 8/15 (53%) having ACAs. Interestingly, seven patients had no identified cytogenetic abnormalities. Of these, five had previously described NGS abnormalities, namely *ASXL1, RUNX1* and *STAG2* mutations;[35] one patient also demonstrated a *CEBPA* mutation; one patient had no cytogenetic or NGS abnormality. Importantly, targeted NGS demonstrated a significant reduction of VAF following treatment with ponatinib-FLAG-IDA; some samples showed complete eradication of the mutation detected at diagnosis. Ongoing evaluation of gene mutations will help deepen understanding of the pathophysiology of BP-CML.

In summary, MATCHPOINT demonstrated that ponatinib-FLAG-IDA is a feasible and effective treatment strategy, tolerable to the majority of high-risk patients with myeloid, lymphoid or mixed phenotype BP-CML. While durable remissions can be induced and consolidated with alloSCT, long-term OS remains <50% in BP-CML, even with this intensive treatment approach. Improving our understanding of the biology of BP and widening access to novel therapies in this rare and poor prognosis patient group will be essential for providing a personalised precision medicine approach to combatting the disease in the future. MATCHPOINT underscores the feasibility and appeal of the innovative EffTox design; its broader application will allow more patients with the rarest cancers to benefit from novel therapies.

Data sharing statement

The full trial protocol is included in the appendix. De-identified participant data collected during the trial can be provided by (and after approval from) the Trial Management Group on behalf of the Sponsor; requests should be sent to the corresponding author. Data are available immediately following publication.

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This use of ponatinib was outside of the approved label.

Authorship contributions

M.C., R.E.C, D.S., G.H., J.B., K.B., R.B., D.M. and C.Y. designed the research; M.C., D.S., G.M., G.H., K.B., C.Y. and R.F. performed the research; M.C., J.B., K.R., H.D.L., C.C.,R.E.C., M.L.S. and D.M. collected data; D.S. and R.F. verified the data; M.C., D.S., G.M., G.H., J.B., R.F., D.M. and C.Y. analysed and interpreted the data; M.C., D.S., G.M. and G.H. wrote the manuscript; All authors critically revised the manuscript; All authors approve the final version of the manuscript. All authors had access to primary clinical data.

Declaration of interests

Mhairi Copland: research funding from Novartis, Bristol-Myers Squibb, Cyclacel and Takeda/Incyte; advisory board member for Bristol-Myers Squibb, Novartis, Incyte, Daiichi Sankyo, and Pfizer; honoraria from Astellas, Bristol-Myers Squibb, Novartis, Incyte, Pfizer and Gilead.

Daniel Slade – none

Graham McIlroy – none

Gillian Horne – none

Jenny L. Byrne: advisory board and honoraria from Incyte

Kate Rothwell: advisory board for Novartis; honoraria from Novartis, Incyte, Pfizer, Daiichi Sankyo

Kristian Brock: employed by UCB; personal fees from Eli Lily, Invex Therapeutics; reimbursement from Merck, Roche; holds shares in Astra Zeneca and GlaxoSmithKline.

Hugues De Lavallade: research funding from Incyte and Bristol-Myers Squibb; speaker fees from Incyte, Bristol-Myers Squibb and Pfizer

Charles Craddock – none

Richard E. Clark: research support and honoraria from Novartis and Bristol Myers Squibb; honoraria from Pfizer in the past 3 years.

Matthew L. Smith: advisory board for Daiichi Sankyo and Pfizer; honoraria from ARIAD

Rachel Fletcher – none

Rebecca Bishop – none

Dragana Milojkovic: honoraria and speakers bureau for Novartis, Incyte, BMS and Pfizer

Christina Yap: personal fees from Celgene and Faron Pharmaceuticals, outside the submitted work

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Figure legends

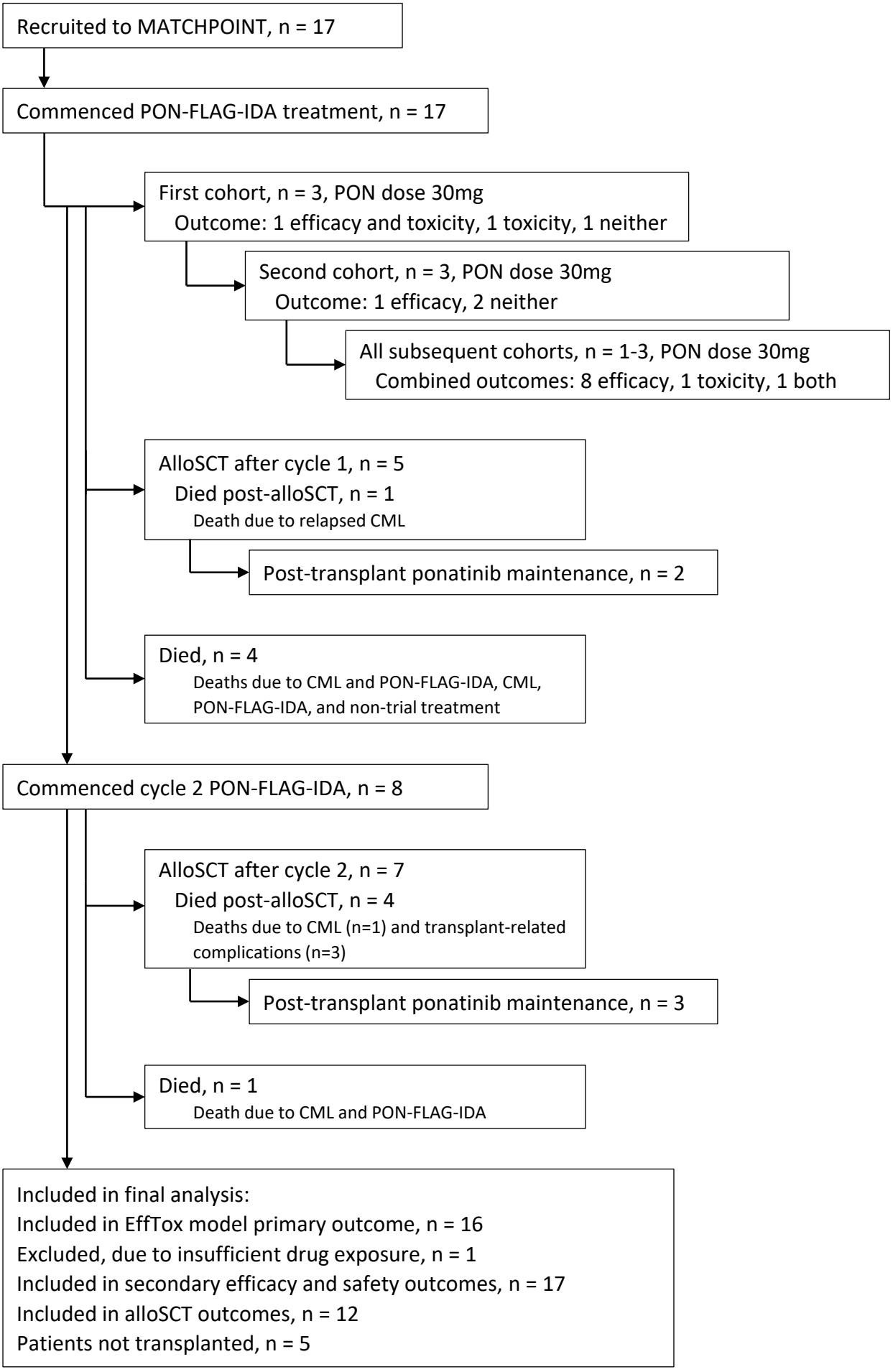
Figure 1. CONSORT flow diagram

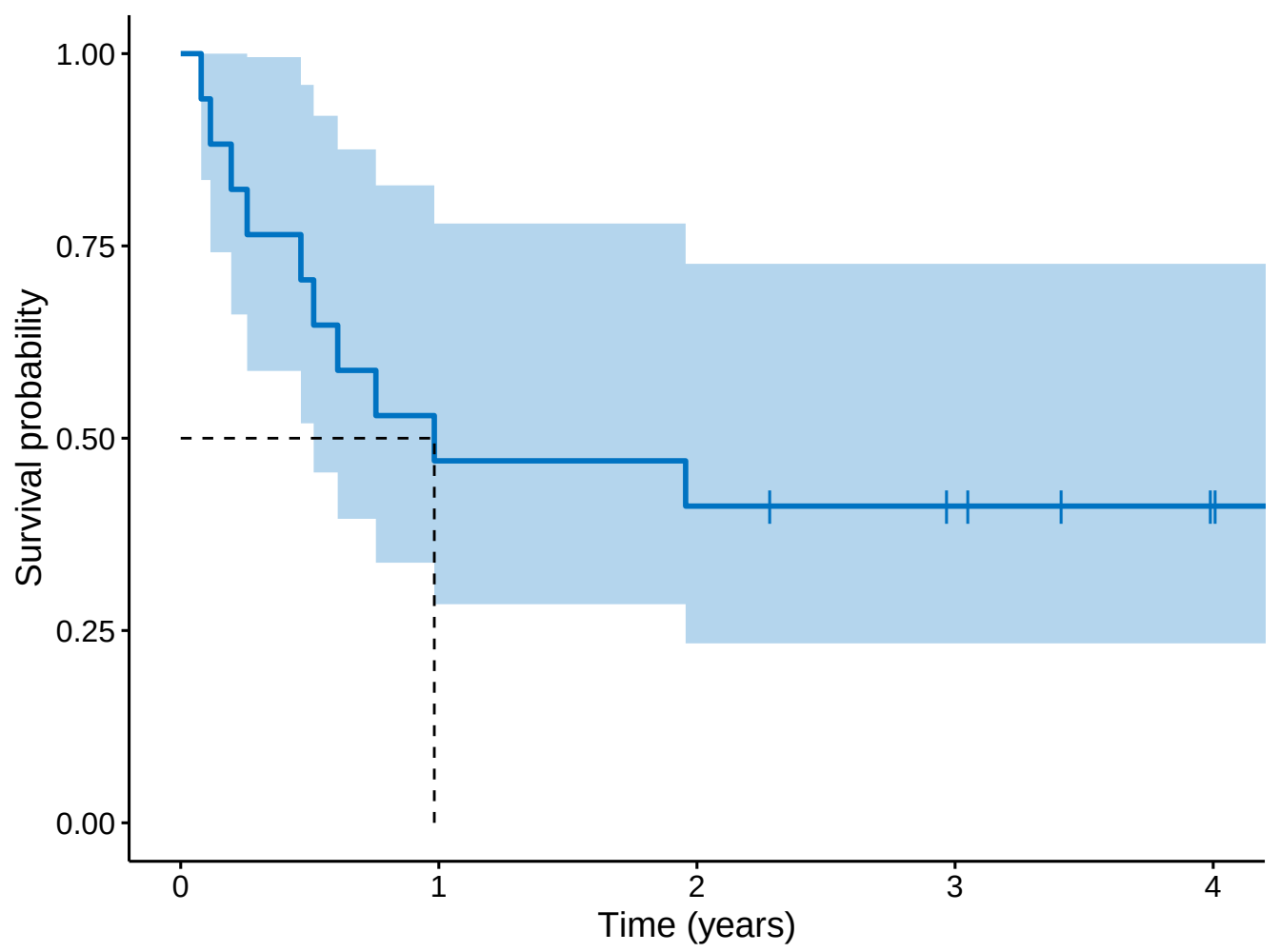
CONSORT flow diagram showing patient treatment and numbers included in final analyses.

Figure 2. Overall survival

Kaplan-Meier estimate of overall survival from trial entry. 95% confidence intervals and median overall survival are indicated.

Figure 1.


Recruited to MATCHPOINT, n = 17
Commenced PON-FLAG-IDA treatment, n = 17
First cohort, n = 3, PON dose 30mg
Outcome: 1 efficacy and toxicity, 1 toxicity, 1 neither
Second cohort, n = 3, PON dose 30mg
Outcome: 1 efficacy, 2 neither
All subsequent cohorts, n = 1-3, PON dose 30mg
Combined outcomes: 8 efficacy, 1 toxicity, 1 both
AlloSCT after cycle 1, n = 5
Died post-alloSCT, n = 1
Death due to relapsed CML
Post-transplant ponatinib maintenance, n = 2
Died, n = 4
Deaths due to CML and PON-FLAG-IDA, CML, PON-FLAG-IDA, and non-trial treatment
Commenced cycle 2 PON-FLAG-IDA, n = 8
AlloSCT after cycle 2, n = 7
Died post-alloSCT, n = 4
Deaths due to CML (n=1) and transplant-related complications (n=3)
Post-transplant ponatinib maintenance, n = 3
Died, n = 1
Death due to CML and PON-FLAG-IDA
Included in final analysis:
Included in EffTox model primary outcome, n = 16
Excluded, due to insufficient drug exposure, n = 1
Included in secondary efficacy and safety outcomes, n = 17
Included in alloSCT outcomes, n = 12
Patients not transplanted, n = 5



Number at risk (number censored)

17 (0)	8 (0)	7 (0)	5 (2)	2 (5)

Table 1. Baseline characteristics

Baseline characteristics of patients recruited to MATCHPOINT (n=17)		
Age	Mean (SD)	36 years (13.4)
	Range	16 to 64
Gender	Female	5 (29%)
	Male	12 (71%)
ECOG performance status	0	8 (47%)
	1	5 (29%)
	2	3 (18%)
	3	1 (6%)
BCR-ABL1 transcript type	e13a2	3 (18%)
	e14a2	6 (35%)
	e13a2/e14a2	5 (29%)
	e13a3	1 (6%)
	e1a2	1 (6%)
	b3a2, b2a2, e1a2	1 (6%)
Additional chromosomal abnormality	Present	8 (47%)
	Absent	6 (35%)
	Unknown	3 (18%)
Detectable *BCR-ABL1* mutation	T315I	1 (6%)
	E255K	2 (12%)
	None	3 (18%)
	Unknown	11 (65%)
Blast phase phenotype	Myeloid	9 (53%)
	Lymphoid	4 (24%)
	Mixed phenotype	4 (24%)
Disease status	De-novo	10 (59%)
	Progression	7 (41%)
Extramedullary disease	Yes	2 (12%)
	No	15 (88%)
Previous tyrosine kinase inhibitor	Imatinib	7 (41%)
	Dasatinib	1 (6%)
	Nilotinib	1 (6%)
	Bosutinib	1 (6%)
	Imatinib (first line), dasatinib (second line)	1 (6%)
	Nilotinib (first line), dasatinib (second line)	1 (6%)
	None	5 (29%)

Number (%), except where indicated

Table 2. Patient-level outcomes

Patient-level baseline and trial outcome data

Patient number	Patient sex	De novo or progressive BP	BP-CML lineage	Previous TKI treatment (months)	Number of PON-FLAG-IDA cycles	Cycle 1 HR	Cycle 1 CyR	Cycle 1 MR	Cycle 1 DLT	Cycle 2 HR	Cycle 2 CyR	Cycle 2 MR	AlloSCT	Survival at last follow-up
001	Female	Progressive	Myeloid	Nilotinib (1)	1	No	-	-	No				Yes	Died
002	Male	Progressive	Myeloid	Imatinib (78)	1	-	-	-	Yes					Died
003	Female	Progressive	Myeloid	Bosutinib (2)	2	Complete	Partial	No	Yes	Complete	Partial	-		Died
004	Male	De novo	Myeloid	Imatinib (<1)	1	No	Complete	MR2	No				Yes	Alive
005	Male	De novo	Lymphoid	No	2	-	No	No	No	No	No	MR1	Yes	Alive
006	Female	Progressive	Myeloid	Imatinib (3)	1	No	-	-	No					Died
007	Male	De novo	Myeloid	No	2	No	Complete	MR2	No	No	Complete	MR2	Yes	Alive
008	Male	De novo	Lymphoid	Imatinib (<1)	2	No	Complete	MMR	No	Complete	Complete	MMR	Yes	Died
009	Female	De novo	Myeloid	No	1	No	Complete	MMR	No				Yes	Alive
010	Female	Progressive	Mixed	Nilotinib (70) Dasatinib (3)	1	No	Minor	No	No					Died
011	Male	Progressive	Myeloid	Imatinib (16) Dasatinib (<1)	1	No	Complete	MR2	Yes				Yes	Alive
012	Male	De novo	Myeloid	Imatinib (2)	2	-	-	-	-	-	-	-	Yes	Died
013	Male	De novo	Mixed	Dasatinib (<1)	1	-	-	-	Yes					Died
014	Male	De novo	Mixed	No	2	Complete	Complete	MMR	No	Complete	Complete	-	Yes	Died
015	Male	De novo	Lymphoid	Imatinib (<1)	1	No	Partial	No	No				Yes	Alive
016	Male	Progressive	Lymphoid	Imatinib (5)	2	No	Complete	MMR	No	Complete	Complete	MMR	Yes	Died
017	Male	De novo	Mixed	No	2	Complete	Complete	MMR	No	Complete	Complete	MMR	Yes	Alive

BP, blast phase; TKI, tyrosine kinase inhibitor; PON, ponatinib; HR, haematological response; CyR cytogenetic response; MR, molecular response; MMR, major molecular remission; DLT, dose-limiting toxicity; AlloSCT, allogeneic stem cell transplantation

Table 3. Adverse events

Grade 1-2 adverse events occurring in at least 10% of patients, and all patients with grade 3 and 4 adverse events.

Adverse event	Number of events (number [percent] of patients)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Haematological, haemorrhagic					
Bone marrow hypocellular					1 (1 [6%])
Bronchopulmonary haemorrhage					1 (1 [6%])
Neutrophil count decreased	3 (2 [12%])	4 (2 [12%])	9 (5 [29%])	14 (11 [65%])	
Platelet count decreased	5 (3 [18%])	1 (1 [6%])	9 (7 [41%])	11 (8 [47%])	
White blood cell decreased		2 (2 [12%])	6 (3 [18%])	9 (6 [35%])	
Lymphocyte count decreased	2 (1 [6%])	1 (1 [6%])	1 (1 [6%])	4 (2 [12%])	
Febrile neutropenia			9 (5 [29%])	1 (1 [6%])	
Leukocytosis				1 (1 [6%])	
Blood and lymphatic system disorders - Other	1 (1 [6%])	1 (1 [6%])	4 (2 [12%])	1 (1 [6%])	
Anaemia	4 (3 [18%])	8 (4 [24%])	26 (7 [41%])		
Epistaxis	7 (5 [29%])		1 (1 [6%])		
Infective					
Fever	8 (6 [35%])	4 (2 [12%])	7 (3 [18%])		
Lung infection			4 (4 [24%])		
Appendicitis			2 (2 [12%])		
Infections and infestations - Other	2 (2 [12%])		2 (1 [6%])		
Cardiovascular					
Cardiac disorders - Other	1 (1 [6%])	1 (1 [6%])	1 (1 [6%])		1 (1 [6%])
Pulmonary oedema				2 (2 [12%])	
Ejection fraction decreased				1 (1 [6%])	
Pericardial effusion	1 (1 [6%])	2 (2 [12%])	1 (1 [6%])		
Vascular disorders - Other			1 (1 [6%])		
Pancreatic					
Serum amylase increased	1 (1 [6%])		2 (2 [12%])		
Others					
Alanine aminotransferase increased	5 (4 [24%])	4 (3 [18%])	3 (2 [12%])	2 (2 [12%])	
Acute kidney injury			2 (1 [6%])	2 (1 [6%])	
Hypocalcaemia	3 (2 [12%])	3 (3 [18%])	2 (2 [12%])	1 (1 [6%])	
Hypophosphatemia		2 (1 [6%])	2 (1 [6%])	1 (1 [6%])	
Blood bilirubin increased	2 (2 [12%])	1 (1 [6%])	1 (1 [6%])	1 (1 [6%])	
Dyspnoea	3 (3 [18%])			1 (1 [6%])	
GGT increased	3 (1 [6%])	1 (1 [6%])	3 (1 [6%])		
Investigations - Other	8 (5 [29%])		2 (2 [12%])		
Hypoxia			2 (2 [12%])		
Skin and subcutaneous tissue disorders - Other	8 (4 [24%])	1 (1 [6%])	1 (1 [6%])		
Headache	4 (2 [12%])	1 (1 [6%])	1 (1 [6%])		
Rash maculo-papular	3 (3 [18%])	1 (1 [6%])	1 (1 [6%])		
Gastrointestinal disorders - Other	7 (5 [29%])		1 (1 [6%])		
Non-cardiac chest pain	2 (2 [12%])		1 (1 [6%])		
Hypokalaemia	1 (1 [6%])		1 (1 [6%])		
Confusion			1 (1 [6%])		
Dental caries			1 (1 [6%])		
Urticaria			1 (1 [6%])		
Constipation	1 (1 [6%])	4 (2 [12%])			
Diarrhoea	9 (9 [53%])	2 (2 [12%])			
Nausea	4 (4 [24%])	2 (2 [12%])			
Abdominal pain	4 (2 [12%])	2 (2 [12%])			
Vomiting	2 (2 [12%])	2 (1 [6%])			
Eye disorders - Other	5 (3 [18%])	1 (1 [6%])			
Hyperkalaemia	3 (1 [6%])	1 (1 [6%])			
Back pain	2 (2 [12%])	1 (1 [6%])			
Respiratory, thoracic and mediastinal disorders - Other	2 (2 [12%])	1 (1 [6%])			
Musculoskeletal and connective tissue disorder - Other	7 (3 [18%])				
Hypoalbuminemia	4 (3 [18%])				
Metabolism and nutrition disorders - Other	4 (2 [12%])				
Hypomagnesemia	3 (3 [18%])				
Lethargy	3 (3 [18%])				