Ponatinib with fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor chemotherapy for patients with blast-phase chronic myeloid leukaemia (MATCHPOINT): a single-arm, multicentre, phase 1/2 trial

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Summary

Background Outcomes for patients with blast-phase chronic myeloid leukaemia are poor. Long-term survival depends on reaching a second chronic phase, followed by allogeneic haematopoietic stem-cell transplantation (HSCT). We investigated whether the novel combination of the tyrosine-kinase inhibitor ponatinib with fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) could improve response and optimise allogeneic HSCT outcomes in patients with blast-phase chronic myeloid leukaemia. The aim was to identify a dose of ponatinib, which combined with FLAG-IDA, showed clinically meaningful activity and tolerability.

Methods MATCHPOINT was a seamless, phase 1/2, multicentre trial done in eight UK Trials Acceleration Programme-funded centres. Eligible participants were adults (aged ≥16 years) with Philadelphia chromosome-positive or *BCR-ABL1*-positive blast-phase chronic myeloid leukaemia, suitable for intensive chemotherapy. Participants received up to two cycles of ponatinib with FLAG-IDA. Experimental doses of oral ponatinib (given from day 1 to day 28 of FLAG-IDA) were between 15 mg alternate days and 45 mg once daily and the starting dose was 30 mg once daily. Intravenous fludarabine (30 mg/m² for 5 days), cytarabine (2 g/m² for 5 days), and idarubicin (8 mg/m² for 3 days), and subcutaneous granulocyte colony-stimulating factor (if used), were delivered according to local protocols. We used an innovative EffTox design to investigate the activity and tolerability of ponatinib–FLAG-IDA; the primary endpoints were the optimal ponatinib dose meeting prespecified thresholds of activity (inducement of second chronic phase defined as either haematological or minor cytogenetic response) and tolerability (dose-limiting toxicities). Analyses were planned on an intention-to-treat basis. MATCHPOINT was registered as an International Standard Randomised Controlled Trial, ISRCTN98986889, and has completed recruitment; the final results are presented.

Findings Between March 19, 2015, and April 26, 2018, 17 patients (12 men, five women) were recruited, 16 of whom were evaluable for the coprimary outcomes. Median follow-up was 41 months (IQR 36–48). The EffTox model simultaneously considered clinical responses and dose-limiting toxicities, and determined the optimal ponatinib dose as 30 mg daily, combined with FLAG-IDA. 11 (69%) of 16 patients were in the second chronic phase after one cycle of treatment. Four (25%) patients had a dose-limiting toxicity (comprising cardiomyopathy and grade 4 increased alanine aminotransferase, cerebral venous sinus thrombosis, grade 3 increased amylase, and grade 4 increased alanine aminotransferase), fulfilling the criteria for clinically relevant activity and toxicity. 12 (71%) of 17 patients proceeded to allogeneic HSCT. The most common grade 3–4 non-haematological adverse events were lung infection (n=4 [24%]), fever (n=3 [18%]), and hypocalcaemia (n=3 [18%]). There were 12 serious adverse events in 11 (65%) patients. Three (18%) patients died due to treatment-related events (due to cardiomyopathy, pulmonary haemorrhage, and bone marrow aplasia).

Interpretation Ponatinib–FLAG-IDA can induce second chronic phase in patients with blast-phase chronic myeloid leukaemia, representing an active salvage therapy to bridge to allogeneic HSCT. 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.

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Introduction

The prognosis for patients with chronic myeloid leukaemia presenting in the first chronic phase has improved remarkably since the introduction of BCR-ABL1 tyrosine-kinase inhibitors (TKIs). Started in chronic phase, TKIs induce remission, prolong survival, and reduce progression to blast-phase chronic myeloid leukaemia.[1–3] However, for the 5–7% of patients treated

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Research in context

Evidence before this study

A formal systematic review was not carried out before undertaking this study. Relevant evidence was sought from PubMed and the published abstracts of key conferences before the protocol was finalised in 2012 (including American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association annual meetings). No prospective trials of 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 might be more likely with tyrosine-kinase inhibitor–chemotherapy combinations, consolidated with allogeneic haematopoietic stem-cell transplantation (HSCT).

Added value of this study

To our knowledge, MATCHPOINT is the first trial to prospectively test the activity and feasibility of delivering ponatinib with a regimen of fludarabine, cytarabine, idarubicin, and granulocyte-colony stimulating factor (FLAG-IDA) chemotherapy for the treatment of blast-phase chronic myeloid leukaemia. When used to achieve a second chronic phase before allogeneic HSCT, this regimen can result in durable overall and disease-free survival. The trial shows 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 chronic myeloid leukaemia, combination treatment with ponatinib and FLAG-IDA chemotherapy might be considered an option to induce a second chronic phase in advance of allogeneic HSCT, as is 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 chronic myeloid leukaemia.

with imatinib, the 2–5% of patients treated with second-generation TKIs who progress to blast phase,[1,2,4] and the 5–10% who present in blast phase at diagnosis, prognosis remains dismal.[5] Allogeneic haematopoietic stem-cell transplantation (HSCT), the only potentially curative therapy, crucially depends on patients going into remission with salvage therapy.[6] There is no consensus approach to reaching a second chronic phase in patients with blast-phase chronic myeloid leukaemia, 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 allogeneic HSCT consolidation and post-transplantation TKI maintenance, are therefore urgently needed to improve outcomes in blast-phase chronic myeloid leukaemia. Progress has been limited by the rarity of blast-phase chronic myeloid leukaemia, 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 prespecified, clinically important thresholds of minimal activity and maximal toxicity, EffTox uses utility contours to recommend future doses.[8,9]

See Online for appendix

Ponatinib is an oral TKI with activity against treatment-resistant *BCR-ABL1* kinase domain mutations.[10,11] In the PACE trial,[12] single-agent ponatinib showed activity in patients with blast-phase chronic myeloid leukaemia, with 18% of patients having a complete cytogenetic response, although duration of response was short, with overall survival of 9% (95% CI 3–18) at 3 years. A historical case series combining dasatinib with the intensive chemotherapy regimen fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-IDA) in blast-phase chronic myeloid leukaemia has shown promise.[13] We therefore devised the MATCHPOINT trial, with the primary objective to determine the optimal dose of ponatinib in combination with FLAG-IDA that is both tolerable and active.

Methods

Study design and participants

MATCHPOINT was a seamless, phase 1/2, multicentre study of ponatinib–FLAG-IDA for the treatment of blast-phase chronic myeloid leukaemia, incorporating both dose-finding and estimations of activity and tolerability. Patients were recruited from eight UK Trials Acceleration Programme-funded centres (appendix p 3). An adaptive Bayesian EffTox model was used to determine the optimal ponatinib dose, simultaneously considering activity and toxicity.[8,9] EffTox was chosen because 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) and the trial was carried out in compliance with the Declaration of Helsinki.

Eligible patients had Philadelphia chromosome (Ph)-positive or *BCR-ABL1*-positive chronic myeloid leukaemia, with blast phase defined according to European LeukemiaNet criteria.[14] Other inclusion criteria were: age 16 years or older; suitable for FLAG-IDA chemotherapy; adequate renal (creatinine ≤1·5×upper

limit of normal [ULN]), liver (transaminase <2·5×ULN, or <5×ULN if chronic myeloid leukaemia liver involvement; bilirubin <1·5×ULN), pancreatic (amylase <1·5×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 blast phase; had previous treatment with ponatinib; had previous allogeneic or autologous HSCT; had a history of clinically significant cardiovascular disease (including ischaemic heart disease, arrhythmia, heart failure, uncontrolled hypertension, stroke, unprovoked venous thromboembolism, or uncontrolled hypertriglyceridaemia) or pancreatitis; were galactose intolerant; had undergone surgery within 2 weeks of registration; or had 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. All participants provided written informed consent.

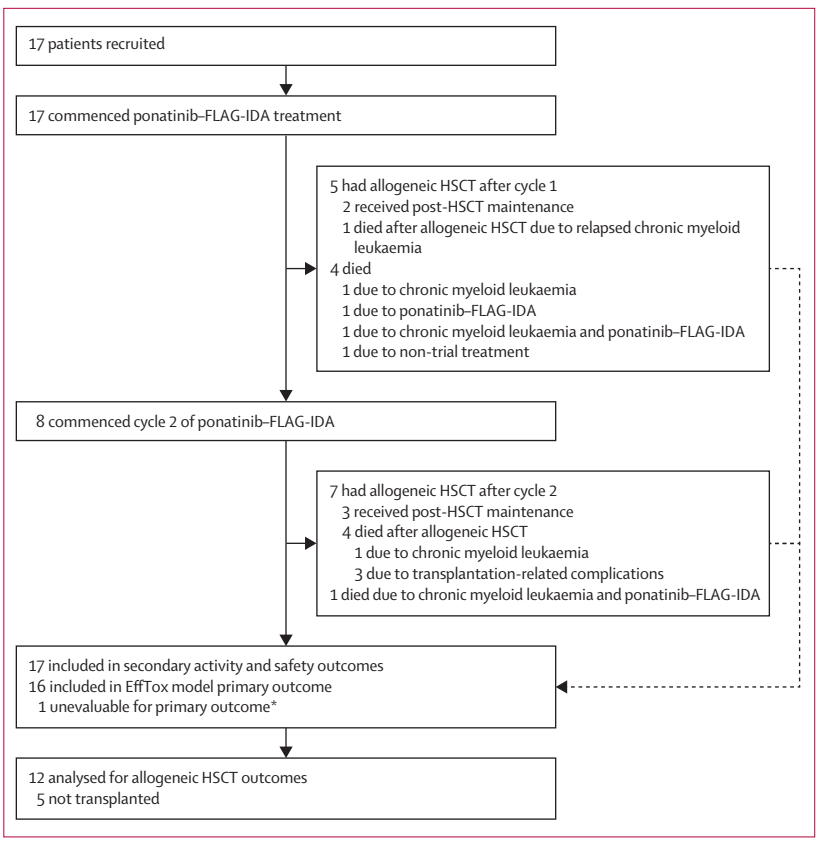

Figure 1: **Trial profile**
FLAG-IDA=fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor. HSCT=haematopoietic stem-cell transplantation. *One patient was judged not evaluable because of substantial treatment interruptions and delays.

Procedures

During induction, ponatinib was commenced from day 1 of FLAG-IDA, at a dose recommended by the EffTox model, initially set at 30 mg/day orally, 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 30 mg starting dose was recommended by the independent trial steering committee. There was potential to increase ponatinib dose to 45 mg for absence of response (if tolerated), or reduce dose to 15 mg for toxicity. The four experimental dose levels are shown in the appendix (p 2). During treatment, dose reductions were permitted for non-haematological toxicities, full details are provided in the protocol (appendix p 15). FLAG-IDA consisted of fludarabine 30 mg/m² on days 1–5 intravenously, cytarabine 2 g/m² on days 1–5 intravenously, and idarubicin 8 mg/m² on days 3–5 intravenously, with granulocyte colony-stimulating factor given subcutaneously as a priming agent according to local protocols if leukocyte count was less than 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 *Pneumocystis jirovecii* prophylaxis. Patients received one or two cycles of ponatinib–FLAG-IDA. For consolidation, allogeneic HSCT 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 allogeneic HSCT conditioning (if applicable); transplanted patients restarted ponatinib from 45 days after allogeneic HSCT if there was 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 15 mg/day once major molecular remission had been attained. There were no specific criteria for removing patients.

Follow-up occurred at baseline, on days 1, 2, 3, 4, 5, 8, 15, 22, and 28 of each cycle, then every week thereafter if a recovery period was required. Full details of assessments done are provided in the protocol in the appendix (pp 48–49). Haematological response was assessed after each cycle of combination therapy (weeks 4–8), every 2 weeks of each cycle during the recovery period, at each visit in the maintenance phase, and as clinically indicated after 12 months. Cytogenetic response was assessed after each cycle of combination therapy, at haematological recovery, or day 56, whichever was soonest, and then annually. Molecular response was assessed after each cycle of combination therapy, at haematological recovery, or day 56, whichever was soonest, then every month for the first 6 months of the maintenance phase and then once every 3 months. Adverse events were measured according to the Common Terminology Criteria for Adverse Events version 4. Adverse events were assessed continually, at

all study visits, and at any time between visits when a patient reported them.

Peripheral blood samples were collected at diagnosis and following inducement of the second chronic phase after one or two cycles of ponatinib–FLAG-IDA. For post-hoc genetic analyses, DNA was extracted using an EASY-DNA kit (Invitrogen, ThermoFisher Scientific, Loughborough, UK). Targeted next-generation sequencing was done with Illumina (San Diego, CA, USA) MiSeq reagents with a read length of 300 bp and paired ends, aligning data to Genome Reference Consortium Human Build 38, and using the Illumina TruSight myeloid panel (carried out as per manufacturer's instructions). Data were analysed with MiSeq reporter and visualised in VarSeq (Golden Helix, Boseman, MT, USA) with variant nomenclature described according to current Human Genome Variation Society guidelines.[15] Variant detection level (proportion of 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 200× coverage was achieved in all samples at more than 97%.

For **Human Genome Variation Society guidelines** see http://www.hgvs.org

	Patients (n=17)
Age, years	
Median (IQR)	33 (28–48)
Range	16–64
Sex	
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 and e14a2	5 (29%)
e13a3	1 (6%)
e1a2	1 (6%)
b3a2, b2a2, and e1a2	1 (6%)
Additional chromosomal abnormality	
Present	8 (47%)
Absent	6 (35%)
Unknown	3 (18%)
Detectable *BCR-ABL1* mutation	
Thr315Ile	1 (6%)
Glu255Lys	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%)

Data are n (%), except where indicated. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

Whole exome sequencing was done in one patient (patient 001) following relapse after HSCT, with lineage switch from myeloid to T-lymphoid blast phase. Buccal mucosa at trial entry was used as a non-malignant control to eliminate germline background mutations. DNA was extracted from the buccal, chronic phase diagnostic (before trial entry), myeloid blast phase, and relapsed T-lymphoid blast phase (post-HSCT) samples using QIAamp DNA mini kit (Qiagen, Germantown, MD, USA). Exome sequencing was dwone as per manufacturer's protocol using the NextSeq500 platform (Illumina) and reagents with a read length of 75 bp, a coverage of 100×, and paired ends. Paired read counts captured were as follows: buccal 80 452 595; chronic phase 119 135 733; myeloid blast phase 110 805 066; T-lymphoid blast phase 110 021 429. Data were processed by Glasgow Polyomics (Glasgow, UK).

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 coprimary outcomes were treatment activity and tolerability. Activity was assessed locally without central review, and was defined as reaching second chronic phase, comprising either a complete haematological response (>50×10^9 platelets per L, >$1{\cdot}0\times10^9$ neutrophils per L, and peripheral blood or bone marrow blasts <5%) or at least a minor cytogenetic response (Ph-positive cells ≤65%). Tolerability was defined in terms of dose-limiting toxicity as: clinically significant grade 3 or 4 non-haematological adverse events related to ponatinib that, in the judgment of the investigator, cannot be adequately managed; pancreatitis grade 2 or worse; increased serum pancreatic amylase grade 3 or 4; QT interval prolongation grade 3 or 4; or any arterial or venous thromboembolic event. Both activity and tolerability coprimary outcomes were assessed before the second cycle of chemotherapy, after haematological

	Sex	De novo or progressive blast phase	Blast-phase chronic myeloid leukaemia lineage	Previous tyrosine-kinase inhibitor treatment	Number of ponatinib–FLAG-IDA cycles	Cycle 1				Cycle 2			Allogeneic HSCT	Survival at last follow-up
						Haematological response	Cytogenetic response	Molecular response	Dose-limiting toxicity	Haematological response	Cytogenetic response	Molecular response		
Patient 001	Female	Progressive	Myeloid	Nilotinib (1 month)	1	No	..	..	No	..	..	..	Yes	Died
Patient 002	Male	Progressive	Myeloid	Imatinib (78 months)	1	..	..	..	Yes	..	..	..	..	Died
Patient 003	Female	Progressive	Myeloid	Bosutinib (2 months)	2	Complete	Partial	No	Yes	Complete	Partial	..	..	Died
Patient 004	Male	De novo	Myeloid	Imatinib (<1 month)	1	No	Complete	MR2	No	..	..	..	Yes	Alive
Patient 005	Male	De novo	Lymphoid	No	2	..	No	No	No	No	No	MR1	Yes	Alive
Patient 006	Female	Progressive	Myeloid	Imatinib (3 months)	1	No	..	..	No	..	..	..	..	Died
Patient 007	Male	De novo	Myeloid	No	2	No	Complete	MR2	No	No	Complete	MR2	Yes	Alive
Patient 008	Male	De novo	Lymphoid	Imatinib (<1 month)	2	No	Complete	Major molecular remission	No	Complete	Complete	Major molecular remission	Yes	Died
Patient 009	Female	De novo	Myeloid	No	1	No	Complete	Major molecular remission	No	..	..	..	Yes	Alive
Patient 010	Female	Progressive	Mixed	Nilotinib (70 months); dasatinib (3 months)	1	No	Minor	No	No	..	..	..	..	Died
Patient 011	Male	Progressive	Myeloid	Imatinib (16 months); dasatinib (<1 months)	1	No	Complete	MR2	Yes	..	..	..	Yes	Alive
Patient 012	Male	De novo	Myeloid	Imatinib (2 months)	2	..	..	..	..	..	..	..	Yes	Died

(Table 2 continues on next page)

	Sex	De novo or progressive blast phase	Blast-phase chronic myeloid leukaemia lineage	Previous tyrosine-kinase inhibitor treatment	Number of ponatinib–FLAG-IDA cycles	Cycle 1			Cycle 2			Allogeneic HSCT	Survival at last follow-up
						Haematological response	Cytogenetic response	Molecular response	Dose-limiting toxicity	Haematological response	Cytogenetic response	Molecular response		
(Continued from previous page)														
Patient 013	Male	De novo	Mixed	Dasatinib (<1 month)	1	..	..	..	Yes	..	..	..	..	Died
Patient 014	Male	De novo	Mixed	No	2	Complete	Complete	Major molecular remission	No	Complete	Complete	..	Yes	Died
Patient 015	Male	De novo	Lymphoid	Imatinib (<1 month)	1	No	Partial	No	No	..	..	..	Yes	Alive
Patient 016	Male	Progressive	Lymphoid	Imatinib (5 months)	2	No	Complete	Major molecular remission	No	Complete	Complete	Major molecular remission	Yes	Died
Patient 017	Male	De novo	Mixed	No	2	Complete	Complete	Major molecular remission	No	Complete	Complete	Major molecular remission	Yes	Alive

FLAG-IDA=fludarabine, cytarabine, idarubicin, and granulocyte-colony stimulating factor. HSCT=haematopoietic stem-cell transplantation. MR1=<10% International Scale *BCR-ABL1* transcript quantification. MR2=<1% International Scale *BCR-ABL1* transcript quantification.

Table 2: **Patient-level outcomes**

recovery (if applicable), between 4 and 8 weeks after commencing treatment. Absence of activity was imputed if a patient died before outcome assessment.

Secondary outcomes were the toxicity profile of ponatinib–FLAG-IDA, collected continually, within 6 months of starting treatment or up to allogeneic HSCT; complete cytogenetic response (0% Ph-positive cells), major molecular remission (*BCR-ABL1* ≤0·1% on international scale), and complete haematological response within two cycles of treatment, up to 8 weeks after starting each cycle; disease-free survival (from complete cytogenetic response to date of relapse or death from chronic myeloid leukaemia); overall survival (from registration to date of death from any cause); relapse rate after allogeneic HSCT or on maintenance; treatment-related mortality due to ponatinib–FLAG-IDA; and incidence of cytomegalovirus reactivation and graft-versus-host disease (GVHD) after HSCT. All response outcomes are reported in accordance with 2013 European LeukemiaNet recommendations.[16]

Exploratory, post-hoc analyses of molecular data and their relation to blast-phase chronic myeloid leukaemia and treatment response were done for early hypothesis generation.

Statistical analysis

Activity and toxicity data 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 dose-limiting toxicity of 40% or less. Activity was modelled using a quadratic form, allowing for a non-monotonic dose–response relationship, 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 were incorporated alongside the EffTox method to visualise all potential dose pathways, be it escalation or de-escalation, remaining at the same dose, or stopping early.[9,17] The dose transition pathways provided a simple means of assessing the effect 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 for the first three patients were incorporated into the EffTox model, which provided an optimal ponatinib dose at which the trial steering committee could recommend treating a second cohort of three patients. Thereafter, the trial steering committee 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 doses 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 Nov 7, 2017). An additional three patients (total sample size 18) would be required if a dose escalation or 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.

Descriptive statistics were used to report all secondary outcomes and time-to-event outcomes were calculated using the Kaplan-Meier method. 95% CIs were calculated using the R survfit function. All statistical analyses were planned on an intention-to-treat basis.

EffTox software (version 4.0.12) was used and is available from the MD Anderson Cancer Center. All other statistical analyses were carried out in R (version 4.0.3).

This trial is registered as an International Standard Randomised Controlled Trial, ISRCTN98986889.

Role of the funding source

The funders of the study reviewed the trial protocol, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 19, 2015, and April 26, 2018, 17 patients were recruited, 16 of whom were evaluable for the coprimary outcomes. One patient was judged not evaluable by the independent trial steering committee because complications attributable to the underlying blast-phase chronic myeloid leukaemia caused substantial interruptions and delays in administering the first cycle of treatment, of which only 4 days were completed. The committee recommended that, for this early-phase trial, insufficient treatment had been delivered to estimate or impute toxicity or activity outcomes. However, this patient completed the second cycle of ponatinib–FLAG-IDA, and all 17 patients were included in analyses of the secondary outcomes (figure 1). Baseline patient characteristics are summarised in table 1. Nine (53%) patients completed a single cycle of ponatinib–FLAG-IDA only. Of the eight (47%) patients completing both planned cycles, this was to consolidate responses in six (75%) patients, and to reattempt induction in two (25%) patients. 12 (71%) patients

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Haematological and haemorrhagic events					
Bone marrow hypocellular	0	0	0	0	1 (1 [6%])
Bronchopulmonary haemorrhage	0	0	0	0	1 (1 [6%])
Neutrophil count decreased	3 (2 [12%])	4 (2 [12%])	9 (5 [29%])	14 (11 [65%])	0
Platelet count decreased	5 (3 [18%])	1 (1 [6%])	9 (7 [41%])	11 (8 [47%])	0
White blood cell count decreased	0	2 (2 [12%])	6 (3 [18%])	9 (6 [35%])	0
Lymphocyte count decreased	2 (1 [6%])	1 (1 [6%])	1 (1 [6%])	4 (2 [12%])	0
Febrile neutropenia	0	0	9 (5 [29%])	1 (1 [6%])	0
Leukocytosis	0	0	0	1 (1 [6%])	0
Other blood and lymphatic system disorders	1 (1 [6%])	1 (1 [6%])	4 (2 [12%])	1 (1 [6%])	0
Anaemia	4 (3 [18%])	8 (4 [24%])	26 (7 [41%])	0	0
Epistaxis	7 (5 [29%])	0	1 (1 [6%])	0	0
Infective events					
Fever	8 (6 [35%])	4 (2 [12%])	7 (3 [18%])	0	0
Lung infection	0	0	4 (4 [24%])	0	0
Appendicitis	0	0	2 (2 [12%])	0	0
Other infections and infestations	2 (2 [12%])	0	2 (1 [6%])	0	0
Cardiovascular events					
Other cardiac disorders	1 (1 [6%])	1 (1 [6%])	1 (1 [6%])	0	1 (1 [6%])
Pulmonary oedema	0	0	0	2 (2 [12%])	0
Ejection fraction decreased	0	0	0	1 (1 [6%])	0
Pericardial effusion	1 (1 [6%])	2 (2 [12%])	1 (1 [6%])	0	0
Other vascular disorders	0	0	1 (1 [6%])	0	0
Pancreatic events					
Serum amylase increased	1 (1 [6%])	0	2 (2 [12%])	0	0
Other events					
Alanine aminotransferase increased	5 (4 [24%])	4 (3 [18%])	3 (2 [12%])	2 (2 [12%])	0
Acute kidney injury	0	0	2 (1 [6%])	2 (1 [6%])	0
Hypocalcaemia	3 (2 [12%])	3 (3 [18%])	2 (2 [12%])	1 (1 [6%])	0
Hypophosphataemia	0	2 (1 [6%])	2 (1 [6%])	1 (1 [6%])	0
Blood bilirubin increased	2 (2 [12%])	1 (1 [6%])	1 (1 [6%])	1 (1 [6%])	0
Dyspnoea	3 (3 [18%])	0	0	1 (1 [6%])	0
Gamma-glutamyltransferase increased	3 (1 [6%])	1 (1 [6%])	3 (1 [6%])	0	0
Other investigations	8 (5 [29%])	0	2 (2 [12%])	0	0
Hypoxia	0	0	2 (2 [12%])	0	0
Other skin and subcutaneous tissue disorders	8 (4 [24%])	1 (1 [6%])	1 (1 [6%])	0	0
Headache	4 (2 [12%])	1 (1 [6%])	1 (1 [6%])	0	0
Rash maculopapular	3 (3 [18%])	1 (1 [6%])	1 (1 [6%])	0	0
Other gastrointestinal disorders	7 (5 [29%])	0	1 (1 [6%])	0	0
Non-cardiac chest pain	2 (2 [12%])	0	1 (1 [6%])	0	0

(Table 3 continues on next page)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
(Continued from pervious page)					
Hypokalaemia	1 (1 [6%])	0	1 (1 [6%])	0	0
Confusion	0	0	1 (1 [6%])	0	0
Dental caries	0	0	1 (1 [6%])	0	0
Urticaria	0	0	1 (1 [6%])	0	0
Constipation	1 (1 [6%])	4 (2 [12%])	0	0	0
Diarrhoea	9 (9 [53%])	2 (2 [12%])	0	0	0
Nausea	4 (4 [24%])	2 (2 [12%])	0	0	0
Abdominal pain	4 (2 [12%])	2 (2 [12%])	0	0	0
Vomiting	2 (2 [12%])	2 (1 [6%])	0	0	0
Other eye disorders	5 (3 [18%])	1 (1 [6%])	0	0	0
Hyperkalaemia	3 (1 [6%])	1 (1 [6%])	0	0	0
Back pain	2 (2 [12%])	1 (1 [6%])	0	0	0
Other respiratory, thoracic, and mediastinal disorders	2 (2 [12%])	1 (1 [6%])	0	0	0
Other musculoskeletal and connective tissue disorders	7 (3 [18%])	0	0	0	0
Hypoalbuminaemia	4 (3 [18%])	0	0	0	0
Other metabolism and nutrition disorders	4 (2 [12%])	0	0	0	0
Hypomagnesaemia	3 (3 [18%])	0	0	0	0
Lethargy	3 (3 [18%])	0	0	0	0

Data are number of events (number of patients [% of patients]). Grade 1–2 adverse events occurring in at least 10% of patients, and all patients with grade 3, 4, or 5 adverse events.

Table 3: **Adverse events**

For the **MD Anderson Cancer Center EffTox software** see https://biostatistics.mdanderson.org/softwaredownload

proceeded to allogeneic HSCT. Median follow-up was 41 months (IQR 36–48).

11 (69%) of 16 evaluable patients were in second chronic phase after one cycle of ponatinib–FLAG-IDA. Individual patient outcomes are shown in table 2, and are summarised in the appendix (p 4). The reason for not having a complete haematological response was incomplete count recovery in all fully evaluated patients, none of whom showed persistent blasts of more than 5%. Notably, the five (31%) patients with major molecular remission were in remission after one cycle of ponatinib–FLAG-IDA.

Four (25%) of 16 patients had dose-limiting toxicities in cycle 1 of ponatinib–FLAG-IDA, all of whom received 30 mg ponatinib with combination chemotherapy. Dose-limiting toxicities were observed in one (6%) patient with fulminant cardiomyopathy and grade 4 increased alanine aminotransferase, one (6%) patient with cerebral venous sinus thrombosis, one (6%) patient with grade 3 increased amylase, and one (6%) patient with grade 4 increased alanine aminotransferase.

The most common grade 3–4 adverse events within the reporting period were haematological, including neutropenia (12 [71%] of 17 patients), thrombocytopenia (11 [65%]), anaemia (seven [41%]), and febrile neutropenia (five [29%]). The most common non-haematological grade 3–4 adverse events were lung infection (four [24%]), fever (three [18%]), and hypocalcaemia (three [18%]). Common adverse events (occurring in >10% of patients) and all grade 3–4 adverse events are shown in table 3. Adverse events disaggregated by sex are shown in the appendix (pp 5–6). 12 serious adverse events in 11 (65%) patients were reported; six were treatment-related (in six [35%] patients; appendix p 7). Treatment-related mortality occurred in three (18%) patients during ponatinib–FLAG-IDA therapy, at 29, 71, and 94 days after trial registration. Treatment-related mortality was due to cardiomyopathy, pulmonary haemorrhage, and bone marrow aplasia.

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

12 (71%) of 17 patients had allogeneic HSCT after ponatinib–FLAG-IDA. Six stem-cell donors were siblings, five were matched unrelated, and one was a haploidentical family member (see appendix p 9 for transplantation outcomes, including cytomegalovirus reactivation and GVHD incidence). Five (42%) transplanted patients proceeded to allogeneic HSCT after one cycle of induction; three (60%) had a complete cytogenetic response and one (20%) had a partial cytogenetic response (Ph-positive cells ≤35%). Seven (58%) transplanted patients were transplanted after two cycles of ponatinib–FLAG-IDA, of whom five (71%) had maintained a complete cytogenetic response since cycle 1. Three (25%) of 12 transplanted patients had allogeneic HSCT without having any cytogenetic response. Of the five (29%) patients with major molecular remission after the first cycle of ponatinib–FLAG-IDA, one (20%) had allogeneic HSCT directly, and four (80%) completed a second cycle as consolidation before transplantation.

Ponatinib was re-started in five (42%) patients after transplantation, including in one (8%) transplanted patient at a reduced dose of 15 mg on alternate days due to

valganciclovir-induced cytopenias. The remaining patients did not restart ponatinib due to inadequate blood count recovery (three [25%] transplanted patients), hepatic dysfunction (two [17%] transplanted patients), previous dose-limiting toxicity (increased serum amylase in one [8%] transplanted patient), and sepsis with multi-organ failure (one [8%] transplanted patient).

Two (17%) of 12 transplanted patients relapsed after allogeneic HSCT (one at 5 months after transplantation, one at 7 months after transplantation), both subsequently dying of chronic myeloid leukaemia. One (8% of transplanted patients) patient had disease relapse at 7 months after allogeneic HSCT (localised, treated with donor lymphocyte infusion, orchidectomy, and radiotherapy) and again at 27 months (molecular relapse, treated with donor lymphocyte infusion), and was alive 40 months post-transplantation. Three (25% of transplanted patients) further patients died within 6 months of allogeneic HSCT, due to transplantation-related complications.

Five (29%) patients did not have an allogeneic HSCT; one (20% of non-transplanted patients) had a partial cytogenetic response and one (20% of non-transplanted patients) had a minor cytogenetic response to ponatinib–FLAG-IDA. Three of the four dose-limiting toxicities included in the primary outcome occurred in this group. Median overall survival was 2 months (IQR 1–3) in this adverse risk cohort; all five of these patients died within 7 months of trial entry.

Ten (59%) patients died. Median overall survival was 12 months (95% CI 6–non-calculable; figure 2; see appendix p 12 for overall survival censoring for allogeneic HSCT). The Kaplan-Meier-estimated 1-year overall survival was 47% (95% CI 28–78) and 3-year overall survival was 41% (23–73). Median disease-free survival has not been reached, with only two events among the ten patients with a complete cytogenetic response (appendix p 13). The median overall survival in patients receiving allogeneic HSCT has not been reached, with seven (58%) of 12 alive with a median follow-up of 36 months (IQR 31–43) after transplantation.

An exploratory investigation of the genetic determinants of blast-phase chronic myeloid leukaemia and response to treatment was carried out. Targeted next-generation sequencing was done on 15 baseline and nine post-ponatinib–FLAG-IDA peripheral blood samples (appendix p 10). Eight (47%) of 17 patients had paired data available for comparison. Variants with known clinical significance (tier I and II) were detectable in seven (47%) baseline samples, variants of unknown clinical significance (tier III and IV) were detectable in five (33%) baseline samples. For paired data, there were substantial reductions in the detected variant allele frequencies, with four (67%) of six patients demonstrating complete eradication following ponatinib–FLAG-IDA. No new mutations were detected following treatment. Somatic mutations do not seem to be correlated with clinical outcomes; however, patient numbers are small. Additional cytogenetic abnormalities at trial entry are described in the appendix (p 10).

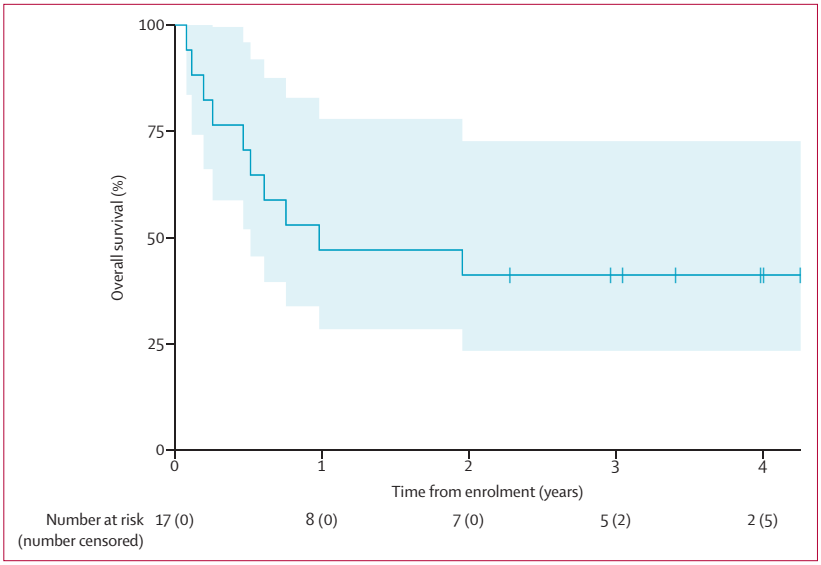

Figure 2: **Overall survival**
Kaplan-Meier estimate of overall survival from trial entry. Shaded areas are 95% CI.

Whole exome sequencing was done on the diagnostic chronic-phase samples, myeloid blast-phase samples, and post-transplantation relapsed T-lymphoid blast-phase samples for patient 001 (appendix p 14). 243 somatic mutations were common to all samples, with 40 somatic mutations identified that differed between chronic phase and myeloid blast phase. More than 30 000 somatic mutations were identified on relapse to T-lymphoid blast phase compared with the myeloid blast-phase and chronic-phase samples, suggesting genomic instability post-transplantation.

Discussion

The MATCHPOINT trial design allowed simultaneous, prospective evaluation of both safety and activity, combined into a seamless phase 1/2 dose-finding study. Combined with FLAG-IDA, ponatinib 30 mg/day resulted in an acceptable toxicity profile and a promising response rate. The 68% (95% CI 47–84) estimated probability of activity and 25% (8–41) probability of toxicity are considerably superior to the prespecified thresholds; a substantial proportion of patients remain disease-free post-allogeneic HSCT. Altogether, the MATCHPOINT findings suggest that ponatinib–FLAG-IDA is tolerable and active and could be considered as a new standard of care for patients with blast-phase chronic myeloid leukaemia, as reflected in the 2020 European LeukemiaNet guidelines.[18] It is notable that responses were seen in myeloid, lymphoid, and mixed phenotype blast-phase chronic myeloid leukaemia. 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 reaching major molecular remission. 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 blast-phase chronic myeloid leukaemia 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 next-generation sequencing 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 45 mg was successfully combined with chemotherapy, although for a shorter duration than the 30 mg starting dose used in the MATCHPOINT regimen.[19] The starting dose in MATCHPOINT was determined by the independent trial steering committee, 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 was tested: the potentially increased activity of the 45 mg dose was not tested, due to the substantially increased toxicity predicted by the EffTox model. As in all dose-finding studies, the definition of dose-limiting toxicity has a strong influence over dose-escalation recommendations. The dose-limiting toxicities in MATCHPOINT were predefined according to known risks of ponatinib, although these can be seen commonly with treatments aimed at inducing second chronic phase. Although it is possible that the stringency of dose-limiting toxicity definition precluded escalation to a theoretically more effective dose, only four patients had dose-limiting toxicities, half of whom also had a 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 shown a median overall survival of 5–17 months, with longer survival following allogeneic HSCT,[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 blast-phase chronic myeloid leukaemia, again with better outcomes following allogeneic HSCT.[27] Novel TKI combinations with targeted drugs, 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 chronic myeloid leukaemia,[30,31] with patients in blast phase likely to have already received first-generation or second-generation TKIs (71% of the 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 blast-phase chronic myeloid leukaemia, although its limited single-agent activity underscores the importance of combination therapy.[12,32] Ultimately, allogeneic HSCT is the only curative therapy for patients with blast-phase chronic myeloid leukaemia, with success relying on attainment of the second chronic phase before HSCT.[6,33,34] Outcomes for the MATCHPOINT cohort reflect this; seven (58%) of 12 transplanted patients were alive at the last follow-up, whereas none survived without transplantation, and ponatinib–FLAG-IDA could be considered an appealing bridge to allogeneic HSCT. Although small patient numbers prevent further interpretation, patients progressing to blast phase on TKI and inadequate response to induction therapy are poor prognostic features, and additional treatment options are urgently needed.

The rarity of blast-phase chronic myeloid leukaemia 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 blast-phase chronic myeloid leukaemia trial. This approach has several advantages, particularly in ultra-orphan diseases. The seamless phase 1/2 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–response relationships, 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 re-assessment and updating of posterior probabilities, the accuracy and precision of activity and toxicity estimates were improved during the trial. By integrating dose transition pathway methodology to model every possible EffTox outcome and dose recommendation, interim analysis showed that the 30 mg 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 prespecified thresholds, with the smaller sample size. This revised sample size

pragmatically reflects the rarity of blast-phase chronic myeloid leukaemia, was agreed by the independent trial steering committee, 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 blast-phase chronic myeloid leukaemia.

Molecular mechanisms responsible for the progression to blast-phase chronic myeloid leukaemia are poorly understood, with genomic instability believed to have an important role.[35] Ten (67%) of 15 MATCHPOINT patients had mutations (tiers I–IV) identified, with eight (53%) of 15 having additional cytogenetic abnormalities. Seven patients had no identified cytogenetic abnormalities. Of these, five had previously described next-generation sequencing abnormalities, namely *ASXL1, RUNX1,* and *STAG2* mutations;[35] one patient also had a *CEBPA* mutation; one patient had no cytogenetic or next-generation sequencing abnormalities. Targeted next-generation sequencing showed a substantial reduction of variant allele frequency 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 blast-phase chronic myeloid leukaemia.

In summary, the MATCHPOINT findings suggest that ponatinib–FLAG-IDA is a feasible and active treatment strategy, tolerable to the majority of high-risk patients with myeloid, lymphoid, or mixed phenotype blast-phase chronic myeloid leukaemia. Although durable remissions can be induced and consolidated with allogeneic HSCT, long-term overall survival remains less than 50% in patients with blast-phase chronic myeloid leukaemia, even with this intensive treatment approach. Improving our understanding of the biology of blast phase, and increasing access to novel therapies in this small patient group with a poor prognosis, will be essential for providing a personalised precision medicine approach to combating 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.

Contributors

MC, REC, DS, GH, JLB, KB, RB, DM, and CY designed the research. MC, DS, GM, GH, KB, CY, and RF did the research. MC, JLB, KR, HDL, CC, REC, MLS, and DM collected data. DS and RF verified the data accessed and verified the data. MC, DS, GM, GH, JLB, RF, DM, and CY analysed and interpreted the data. MC, DS, GM, and GH wrote the manuscript. All authors critically revised the manuscript. All authors approved the final version of the manuscript. All authors had access to primary clinical data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

MC has received research funding from Novartis, Bristol Myers Squibb, Cyclacel, and Takeda/Incyte; is an advisory board member for Bristol Myers Squibb, Novartis, Incyte, Daiichi Sankyo, and Pfizer; has received honoraria from Astellas, Bristol Myers Squibb, Novartis, Incyte, Pfizer, and Gilead. JLB is on the advisory board for and has received honoraria from Incyte. KR is on the advisory board for Novartis; and has received honoraria from Novartis, Incyte, Pfizer, and Daiichi Sankyo. KB is employed by UCB; has received personal fees from Eli Lilly and Invex Therapeutics; has received reimbursement from Merck and Roche; and holds shares in AstraZeneca and GlaxoSmithKline. HDL has received research funding from Incyte and Bristol Myers Squibb; and has received speaker fees from Incyte, Bristol Myers Squibb, and Pfizer. REC has received research support and honoraria from Novartis and Bristol Myers Squibb; and has received honoraria from Pfizer in the past 3 years. MLS is on the advisory board for Daiichi Sankyo and Pfizer; and has received honoraria from ARIAD. DM has received honoraria and been part of the speakers bureau for Novartis, Incyte, Bristol Myers Squibb, and Pfizer. CY has received personal fees from Celgene and Faron Pharmaceuticals, outside the submitted work. All other authors declare no competing interests.

Data sharing

The full trial protocol is included in the appendix (pp 15–88). 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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References

1 Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med* 2017; **376:** 917–27.

2 Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol* 2016; **34:** 2333–40.

3 Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib *vs* imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia* 2016; **30:** 1044–54.

4 Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia* 2021; **35:** 440–53.

5 Hehlmann R, Saußele S, Voskanyan A, Silver RT. Management of CML-blast crisis. *Best Pract Res Clin Haematol* 2016; **29:** 295–307.

6 Radujkovic A, Dietrich S, Blok HJ, et al. Allogeneic stem cell transplantation for blast crisis chronic myeloid leukemia in the era of tyrosine kinase inhibitors: a retrospective study by the EBMT chronic malignancies working party. *Biol Blood Marrow Transplant* 2019; **25:** 2008–16.

7 Jain P, Kantarjian HM, Ghorab A, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. *Cancer* 2017; **123:** 4391–402.

8 Thall PF, Cook JD. Dose-finding based on efficacy-toxicity trade-offs. *Biometrics* 2004; **60:** 684–93.

9 Brock K, Billingham L, Copland M, Siddique S, Sirovica M, Yap C. Implementing the EffTox dose-finding design in the Matchpoint trial. *BMC Med Res Methodol* 2017; **17:** 112.

10 O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell* 2009; **16:** 401–12.

11 Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012; **367:** 2075–88.

12 Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018; **132:** 393–404.

13 Milojkovic D, Ibrahim A, Reid A, Foroni L, Apperley J, Marin D. Efficacy of combining dasatinib and FLAG-IDA for patients with chronic myeloid leukemia in blastic transformation. *Haematologica* 2012; **97:** 473–74.

14 Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006; **108:** 1809–20.

15 Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn* 2017; **19:** 4–23.

16 Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood* 2013; **122:** 872–84.

17 Yap C, Billingham LJ, Cheung YK, Craddock C, O'Quigley J. Dose transition pathways: the missing link between complex dose-finding designs and simple decision-making. *Clin Cancer Res* 2017; **23:** 7440–47.

18 Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* 2020; **34:** 966–84.

19 Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol* 2015; **16:** 1547–55.

20 Jin IH, Liu S, Thall PF, Yuan Y. Using data augmentation to facilitate conduct of phase I–II clinical trials with delayed outcomes. *J Am Stat Assoc* 2014; **109:** 525–36.

21 Rea D, Legros L, Raffoux E, et al. High-dose imatinib mesylate combined with vincristine and dexamethasone (DIV regimen) as induction therapy in patients with resistant Philadelphia-positive acute lymphoblastic leukemia and lymphoid blast crisis of chronic myeloid leukemia. *Leukemia* 2006; **20:** 400–03.

22 Fruehauf S, Topaly J, Buss EC, et al. Imatinib combined with mitoxantrone/etoposide and cytarabine is an effective induction therapy for patients with chronic myeloid leukemia in myeloid blast crisis. *Cancer* 2007; **109:** 1543–49.

23 Quintás-Cardama A, Kantarjian H, Garcia-Manero G, et al. A pilot study of imatinib, low-dose cytarabine and idarubicin for patients with chronic myeloid leukemia in myeloid blast phase. *Leuk Lymphoma* 2007; **48:** 283–89.

24 Strati P, Kantarjian H, Thomas D, et al. HCVAD plus imatinib or dasatinib in lymphoid blastic phase chronic myeloid leukemia. *Cancer* 2014; **120:** 373–80.

25 Saxena K, Jabbour E, Issa G, et al. Impact of frontline treatment approach on outcomes of myeloid blast phase CML. *J Hematol Oncol* 2021; **14:** 94.

26 Ruggiu M, Oberkampf F, Ghez D, et al. Azacytidine in combination with tyrosine kinase inhibitors induced durable responses in patients with advanced phase chronic myelogenous leukemia. *Leuk Lymphoma* 2018; **59:** 1659–65.

27 Abaza Y, Kantarjian H, Alwash Y, et al. Phase I/II study of dasatinib in combination with decitabine in patients with accelerated or blast phase chronic myeloid leukemia. *Am J Hematol* 2020; **95:** 1288–95.

28 Maiti A, Franquiz MJ, Ravandi F, et al. Venetoclax and BCR-ABL tyrosine kinase inhibitor combinations: outcome in patients with Philadelphia chromosome-positive advanced myeloid leukemias. *Acta Haematol* 2020; **143:** 567–73.

29 Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk* 2017; **17:** 897–901.

30 Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. *Clin Cancer Res* 2006; **12:** 7374–79.

31 Nicolini FE, Corm S, Lê QH, et al. Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(phi)-LMC GROUP). *Leukemia* 2006; **20:** 1061–66.

32 Bonifacio M, Stagno F, Scaffidi L, Krampera M, Di Raimondo F. Management of chronic myeloid leukemia in advanced phase. *Front Oncol* 2019; **9:** 1132.

33 Khoury HJ, Kukreja M, Goldman JM, et al. Prognostic factors for outcomes in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. *Bone Marrow Transplant* 2012; **47:** 810–16.

34 Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. *Blood* 2010; **115:** 1880–85.

35 Branford S, Wang P, Yeung DT, et al. Integrative genomic analysis reveals cancer-associated mutations at diagnosis of CML in patients with high-risk disease. *Blood* 2018; **132:** 948–61.