Subjectively, all three patients reported marked improvement in their quality of life with no significant side effects reported. The average daily duration of the patient's epistaxis reduced from baseline of 35 (±19) to 4 (±2) min within 3 months of starting treatment.

Following treatment, the nasal mucosa of all three patients became less vascular and pale on nasendoscopy. The average total number of pulsed laser dye cautery treatments applied to each patient in the 6 months before treatment was 238 (±100) and this was 246 (±30) in the 6 months following initiation of treatment. Therefore, no significant change in the requirement for cautery was found.

Whilst two of the patients had previously received blood transfusions for symptomatic anaemia, none of the patients required any blood products during the study or within 6 months of initiating treatment. The only patient requiring regular parenteral iron was the 67-year-old male on dual anti-platelet therapy. As a result of recurrent symptomatic anaemia due to iron-deficiency, he had required monthly intravenous iron support for over 3 years. Four months after starting treatment, the reduction in his epistaxis allowed him to omit his usual iron infusions for the following 7 months.

In conclusion, bevacizumab can be applied safely as a nasal spray to patients with HHT to produce a sustained reduction in epistaxis severity. The fact that no reduction in the requirement for laser cautery was identified may indicate that bevacizumab acts to reduce the propensity of the telangectasia to bleed rather than reducing their number. The current NHS cost for 100 mg of bevacizumab administered topically is £242·66, significantly lower than the 5–10 mg/kg doses used for intravenous administration in some (Bose *et al*, 2009) but not all reports (Patrizia *et al*, 2011). The sustained response reported here suggests that this treatment may offer a significant financial benefit in patients that are dependent upon regular blood products (a unit of red cells currently costs £123 in the United Kingdom) or intravenous iron support (costs dependent on dose and preparation used, but range between £80 and £170 based upon 1000 mg dose). Further studies are required to optimize the dose intensity and to determine the duration of response.

Charles Alderman[1]
Jonathan Corlett[2]
Jonathan Cullis[1]
[1]*Department of Haematology, Salisbury NHS Foundation Trust, and* [2]*ENT, Salisbury NHS Foundation Trust, Salisbury, Wiltshire, UK*
E-mail: jonathan.cullis@salisbury.nhs.uk

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Ponatinib in patients with refractory acute myeloid leukaemia: findings from a phase 1 study

Activating mutations in the FMS-like tyrosine kinase-3 (FLT3), a tyrosine kinase receptor important in haematopoiesis, are among the most common molecular aberrations in acute myeloid leukaemia (AML), occurring in 30% of adult patients (Levis & Small, 2003). Common FLT3-activating mutations include *FLT3* internal tandem duplications (*FLT3*-ITDs), detected in about 23% of AML patients, and point mutations within the tyrosine kinase domain, found in about 8% (Levis & Small, 2003). These mutations result in a constitutively active FLT3 receptor, leading to growth factor–independent proliferation and survival of leukaemic cells and conferring poor prognosis (Levis & Small, 2003).

Table I. Selected baseline characteristics, treatment duration, response, and reasons for discontinuation by individual patients with AML.

	Selected baseline characteristics										
Patient ID	Age (years)	Time from diagnosis to treatment (months)	History of *FLT3* mutations	*FLT3* ITD at study entry	Prior number of treatment regimens*	Prior transplant	Prior FLT3 inhibitors	Best response to prior therapy†	Duration of ponatinib treatment (d)	Best response to ponatinib	Reason for discontinuation
1	41	14·7	+	ND‡	7	N	Sorafenib, IMC-EB10‡	CR	15	PD	Adverse event (unrelated CNS haemorrhage leading to death)
2	52	11·4	+	+	3	N	Sorafenib, quizartinib§	CR	21	PD	Death (unrelated multiorgan failure)
3	30	48·6	+	+	4	Y	None	CR	10	PD	Death (unrelated multiorgan failure)
4	57	6·8	+	–	3	N	None	SD	61	SD	Death (unrelated disease progression)
5	43	120·5	+	+	4	Y	None	CR	96	SD	Death (unrelated disease progression)
6	48	6·4	+	+	1	N	None	CR	150	PR	Death (probably unrelated pneumonia and unrelated sepsis)
7	49	7·1	+	–	2	Y	None	CR	90	SD	Investigator decision
8	63	17·5	+	+	2	Y	None	CR	90	CRi	Disease progression
9	39	13·4	+	+	5	N	None	CR	43	PD	Disease progression
10	72	9·7	+	+	2	N	None	CR	12	NA	Adverse event (possibly related acute pancreatitis)¶
11	39	11·4	+	ND**	4	Y	Quizartinib††	CR	15	PD	Adverse event (unrelated graft vs host disease)
12	58	15·2	+	ND**	2	Y	None	CR	173	CRi	Investigator decision

FLT3, FMS-like tyrosine kinase-3; ITD, internal tandem duplication; ND, no DNA sample collected; N, no; CR, complete remission; PD, progressive disease; CNS, central nervous system; Y, yes; SD, stable disease; PR, partial remission; CRi, complete remission with incomplete blood count recovery; NA, not assessed.

*Includes transplant regimen, if applicable.

†The best response to any prior cancer therapy was collected as CR, PD, PR, or SD.

‡The best responses to IMC-EB10 and sorafenib were progression and partial remission, respectively.

§The best responses to sorafenib and quizartinib were complete response and partial response, respectively.

¶This patient ultimately died due to unrelated disease progression.

***FLT3*-ITD–positive is defined as positive by history or at study entry, but absent negative assay.

††The best response to quizartinib was partial response.

Clinical studies of single-agent first-generation FLT3 inhibitors have demonstrated clinical activity, with responses that are typically short-lived and mostly partial or complete responses with incomplete haematopoietic recovery. This may be due to suboptimal potency and/or pharmacokinetics, leading to insufficient or transient target inhibition, or concomitant c-kit inhibition (Knapper, 2011). Recently, high potency second-generation FLT3 inhibitors (e.g., quizartinib) have shown substantial efficacy as monotherapy, suggesting a potency threshold for clinical benefit (Knapper, 2011). The validation of *FLT3*-ITD as a therapeutic target has rekindled interest in developing and testing new potent FLT3 inhibitors in AML patients with *FLT3*-ITD mutations (Smith *et al*, 2012).

Ponatinib is a novel, orally administered tyrosine kinase inhibitor (TKI) and a potent pan–BCR-ABL1 inhibitor (O'Hare *et al*, 2009). Based on results in patients with chronic myeloid leukaemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukaemia (Ph^+ ALL) in phase 1 and phase 2 clinical trials (Cortes *et al*, 2012a,b), ponatinib (45 mg once daily) has been approved in the United States for the treatment of patients with CML and Ph^+ ALL that is resistant or intolerant to prior TKI therapy. Preclinical studies revealed that ponatinib also potently inhibits FLT3, leading to apoptosis of leukaemic cell lines carrying the *FLT3*-ITD mutation and tumour regression in xenograft models, suggesting the potential for activity in patients with AML (Gozgit *et al*, 2011). Additionally, ponatinib appears to retain activity against the clinically-relevant quizartinib-resistant mutant FLT3-ITD F691L (Smith *et al*, 2013). Here we report the first clinical experience with ponatinib in 12 AML patients included in the phase 1 study (Methods S1).

The median age of these patients was 49 (30–72) years. The median time from diagnosis to treatment was 1 year. Patients received a median of 3 (1–7) prior therapies; 58% had received three or more prior therapies (Table I and Table S1). Mutational analysis in a central laboratory confirmed the presence of *FLT3*-ITD in seven patients (58%). Three additional patients did not have an adequate DNA sample at study entry; however, they had a history of *FLT3*-ITD mutation – as reported by the investigator – and they are included in the *FLT3*-ITD mutation–positive group for these analyses. Three patients (all *FLT3*-ITD mutation positive) were previously treated with one or more FLT3 inhibitors (sorafenib, quizartinib, and/or IMC-EB10); one patient progressed on IMC-EB10 and had a partial response to sorafenib, one patient had a complete response to sorafenib and a partial response to quizartinib, and one patient had a partial response to quizartinib. Seven patients (70%) with *FLT3*-ITD mutation were FLT3 inhibitor–naïve (Table I). The median treatment duration was 52 (10–173) d. At the time of analysis, all patients had discontinued ponatinib: 5 (42%) due to death (all unrelated to ponatinib), 3 (25%) due to adverse events [AEs: unrelated central nervous system (CNS) haemorrhage, possibly related acute pancreatitis, unrelated graft *versus* host disease], 2 (17%) due to progressive disease (PD), and 2 (17%) due to investigator decision (Table I).

Nine patients experienced at least one treatment-related AE. The most common treatment-related AEs occurring in two or more patients were pancreatitis ($n = 3$) and petechiae ($n = 2$). Three patients experienced a treatment-related serious AE (SAE) of pancreatitis (all grade 2), which was a dose-limiting toxicity in this trial (Cortes *et al*, 2012a). Pancreatitis resolved in two patients after dose interruption, lasting 3 d in one patient and 8 d in the other. These two patients continued therapy at a reduced dose (30 mg) and were subsequently re-escalated to 45 mg without recurrence. The third patient discontinued therapy per investigator decision. Additional details regarding treatment-emergent AEs and SAEs can be found in

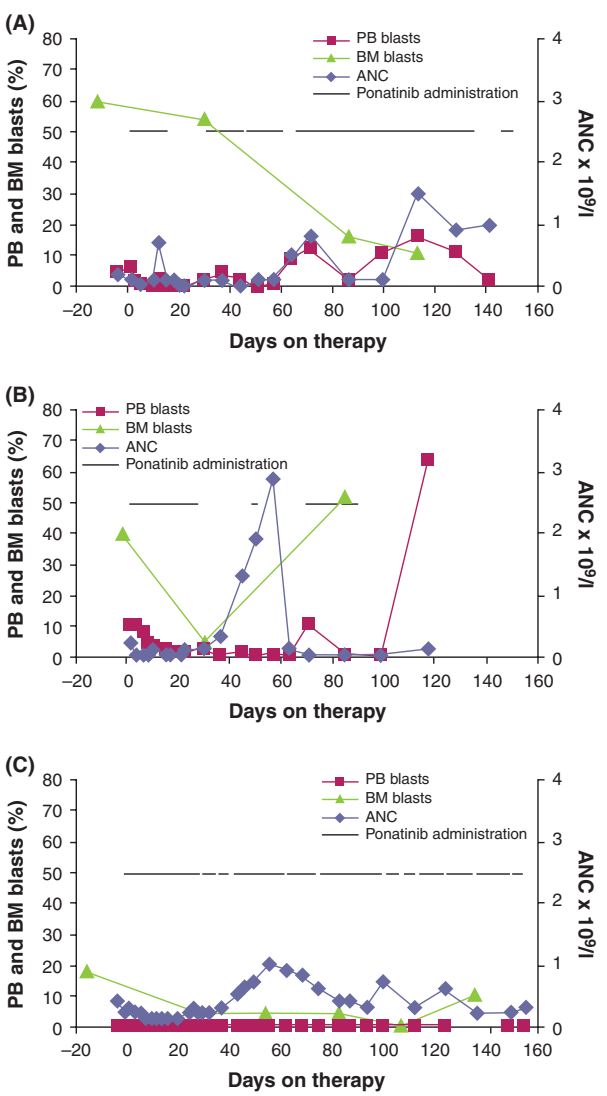

Fig 1. Course of the disease in three responders during ponatinib treatment. (A) Patient 6, who achieved partial remission. (B) Patient 8, who achieved complete remission with incomplete blood count recovery. (C) Patient 12, who achieved complete remission with incomplete blood count recovery. PB, peripheral blood; BM, bone marrow; ANC, absolute neutrophil count.

Table S2. Seven patients died during the study for reasons not related to ponatinib: disease progression ($n = 3$), multiorgan failure ($n = 2$), pneumonia and sepsis ($n = 1$), and CNS haemorrhage ($n = 1$; Table I). Ponatinib had an acceptable safety profile in this small group of patients with refractory AML, similar to that observed in patients with CML and Ph^+ ALL. Few treatment-related AEs were reported; the most common was pancreatitis, which was manageable, and re-challenge with ponatinib was possible in most cases.

The geometric mean maximal concentration and area under the curve of single-dose ponatinib at day 1, cycle 1 in AML patients were 97 and 1441 nmol/l h, respectively, similar to findings across all 31 patients receiving 45 mg ponatinib (98·8 and 1360·1 nmol/l h).

The overall response rate (RR, partial remission or better) was 3/12 (25%): 2 patients achieved complete remission with incomplete blood count recovery and one patient experienced partial remission (Table I, Fig 1). These three responders carried *FLT3*-ITD mutations and were all FLT3 inhibitor–naïve; the duration of ponatinib treatment in these patients was 3–6 months. Among 10 patients with *FLT3*-ITD mutations, RR was 3/10 (30%). Among seven patients with *FLT3*-ITD mutations who were FLT3 inhibitor–naïve, RR was 3/7 (43%). Three patients (2 *FLT3*-ITD negative) had stable disease, as they did not meet criteria for complete/partial remission or PD; however, peripheral blood blasts in two of these patients decreased considerably (~60–90%) during the first treatment cycle. The RR reported with quizartinib in phase 1 testing was 30% (Cortes *et al*, 2009) and 10% with sorafenib (Borthakur *et al*, 2011). Although the sample size reported here is small, these results suggest that ponatinib has clinical activity in AML patients with FLT3-ITD, requiring confirmation in a larger cohort of patients and with additional focus on optimization of response (e.g., combination therapy) and response durability.

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Conflict of interest

Neil P. Shah – Institution received funding for the current clinical trial from ARIAD Pharmaceuticals Inc.; paid member of the Phase II Molecular Steering Committee of ARIAD Pharmaceuticals; institution received funding for clinical trials with FLT3 inhibitors in AML patients from ARIAD Pharmaceuticals Inc., Ambit Biosciences, and Plexxikon. Moshe Talpaz, Ian W. Flinn, Hagop Kantarjian – Institution received funding for the current clinical trial from ARIAD Pharmaceuticals, Inc. Michael W. N. Deininger – Institution received funding for the current clinical trial from ARIAD Pharmaceuticals, Inc., institution received funding from BMS, Celgene, Novartis, and Genzyme; received consulting fee/honorarium from BMS, ARIAD Pharmaceuticals Inc., and Novartis; received payment as member of advisory boards for BMS, ARIAD Pharmaceuticals Inc., and Novartis. For activities outside the submitted work: paid member of boards/advisory committees of BMS, ARIAD Pharmaceuticals Inc., and Novartis; employed by the University of Utah; paid consultant for BMS, ARIAD Pharmaceuticals Inc., and Novartis. Michael J. Mauro – For activities outside the submitted work: paid member of boards/advisory committees for Novartis and BMS; paid consultant for Novartis and BMS; received travel/accommodations/meeting expenses from Novartis and BMS. Dale Bixby – No competing financial interests. Stephanie Lustgarten, Joseph M. Gozgit, Tim Clackson, Christopher D. Turner, and Frank G. Haluska are employees of ARIAD Pharmaceuticals Inc. and own stock/stock options in ARIAD Pharmaceuticals, Inc. Jorge E. Cortes – Institution received funding for the current clinical trial from ARIAD Pharmaceuticals Inc.; received consulting fee/honorarium from ARIAD Pharmaceuticals Inc. For activities outside the submitted work: paid consultant for Pfizer, and Teva; institution received funding from BMS, Novartis, Pfizer, Ambit, Astellas, Arog, and ChemGenex. Professional medical writing assistance for this publication was provided by Francesca Balordi, PhD, Medicus International New York, and funded by ARIAD Pharmaceuticals, Inc. Data from this study have previously been presented at the 2011 American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 3–7, 2011.

Neil P. Shah[1]
Moshe Talpaz[2]
Michael W. N. Deininger[3]*
Michael J. Mauro[3]
Ian W. Flinn[4]
Dale Bixby[5]
Stephanie Lustgarten[6]
Joseph M. Gozgit[6]
Tim Clackson[6]
Christopher D. Turner[6]
Frank G. Haluska[6]
Hagop Kantarjian[7]
Jorge E. Cortes[7]

[1]*Department of Hematology/Oncology, University of California, San Francisco, CA,* [2]*Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI,* [3]*Knight Cancer Institute, Center for Hematologic Malignancies, Oregon Health & Science University, Portland, OR,*

[4]*Hematologic Malignancies Research Program, Sarah Cannon Research Institute, Nashville, TN,* [5]*Division of Hematology and Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI,* [6]*ARIAD Pharmaceuticals, Inc. Cambridge, MA, and* [7]*Division of Cancer Medicine, Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA*
**Presentaddress: Division of Hematology and Hematologic Malignancies, University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA*
E-mail: nshah@medicine.ucsf.edu

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Methods S1. Study methods.
Table S1. Patient characteristics.
Table S2. Adverse events.

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Cyclosporin combined with levamisole for refractory or relapsed severe aplastic anaemia

About one-third of patients with severe aplastic anaemia (SAA) are refractory or relapse after treatment with immunosuppressive therapy (IST) by anti-thymocyte globulin (ATG) plus cyclosporin (CSA; Olnes *et al*, 2012). Allogeneic haematopoietic stem-cell transplantation (HSCT) could be effective as salvage therapy, but it is difficult to find a suitable donor, limited by the family planning policy in China. Intensification of current IST regimen seems to hit the ceiling (Passweg & Tichelli, 2009). However, patients in developing countries cannot afford the repeated courses of ATG due to the high-costs burden.

A novel IST regimen with a practicable and economical solution would be ideal. Levamisole (LMS), which had been originally designed for anthelminthic applications, has a broad range of immunomodulatory effects (Stevenson *et al*,