Phase Ib study of eltrombopag and azacitidine in patients with high-risk myelodysplastic syndromes and related disorders (the ELASTIC study)

Alexander Sternberg[1] | Rebecca Boucher[2] | Helen Chantal Coulthard[2] | Manoj Raghavan[3] | Dominic Culligan[4] | Aimee Jackson[2] | Catherine Cargo[5] | Mike Dennis[6] | Marlen Metzner[7] | Jennifer O'Sullivan[7] | Rachel Moore[7] | David Bowen[5] | Paresh Vyas[7]

Summary

Treating adverse risk myelodysplastic syndromes with azacitidine exacerbates thrombocytopenia. We report a study of eltrombopag in combination with azacytidine using a 3 + 3 cohort design. Patients with baseline platelets of <150 Å~ 109/l received eltrombopag ranging from 25 to 300 mg. An 8-day pre-phase of eltrombopag was followed by two cycles of combined therapy. Amongst 31 patients, there were no dose-limiting toxicities. The maximum tolerated dose (MTD) was 300 mg. Transient increases in bone marrow blasts at day 8 were common but no patient had protocol-defined progression following eltrombopag monotherapy. Marrow response rates after three and six treatment cycles were 32% and 29% respectively. In all, 70% of patients treated below and 36% treated at the MTD achieved a modified International Working Group 2006 platelet response at the end of cycle two. Of the platelet transfusion independent patients at baseline, 67% treated at the MTD became transfusion dependent during the first two cycles of treatment. Apart from lack of disease progression, our findings concur with a previously reported Phase III study (A StUdy of eltromboPag in myelodysPlastic SyndrOmes Receiving azaciTidine [SUPPORT]). We conclude that eltrombopag/azacitidine is safe in terms of conventional measures defined by adverse-event reporting. However, in light of SUPPORT and our own descriptive findings regarding efficacy, further combination studies in high-risk disease should be considered with caution.

INTRODUCTION

Myelodysplastic syndromes (MDS) are heterogenous disorders defined by clonal haematopoiesis and morphological dysplasia in the bone marrow. The clinical picture is foreshadowed by cytopenias and risk of transformation to acute myeloid leukaemia (AML). Ensuing bone marrow failure can lead to significant complications in what is typically an elderly group of patients who frequently have other comorbidities. Anaemia, infection and bleeding commonly affect patients' quality and length of life. Prognosis in MDS is predicted by the International Prognostic Scoring System (IPSS) and its successor, the Revised IPSS (R-IPSS). The median survival for patients with intermediate-2 or high-risk disease being 0.4–1.2 years.[1,2] Outcomes are further refined by mutational analysis of gene sets related to the biology of myeloid disease; they predict poor outcome independent of the IPSS and effectively convert patients from lower to higher IPSS risk categories.[3]

Azacitidine-based therapy remains a standard of care in transplant-ineligiblepatients. The Aza-001 study (ClinicalTrials.gov Identifier: NCT00071799) demonstrated that azacitidine is superior to conventional care leading to improvement in cytopenias, transfusion independence and reduced risk of AML transformation.[4] However, this is not a curative approach.[5] There is a need to improve on the efficacy of azacitidine to prevent treatment failure, improve cytopenias and prolong survival. Occurring in 40%–65% of patients, thrombocytopenia is an independent adverse prognostic factor for survival in MDS.[6] Grade 3–4 thrombocytopenia affects 85% of patients treated with azacitidine and typically occurs within the first two cycles.[4,7] This can lead to dose delays/reduction of azacytidine and is a burden to patients who may require closer monitoring and regular platelet transfusions. By contrast, a doubling of platelet count after a first cycle of azacytidine has been associated with an overall survival advantage.[8,9] Accordingly, improving the platelet count early in the treatment with azacitidine may reduce haemorrhagic complications and improve overall efficacy.

Eltrombopag is an oral, non-peptide thrombopoietin receptor (TpoR) agonist. Eltrombopag monotherapy in low-and high-risk MDS/AML was safe, improved platelet counts and reduced clinically relevant thrombocytopenic
events compared with placebo.10,11 A Phase I study of eltrombopag and azacitidine in patients with intermediate-
2/ high-risk MDS/AML with platelets <75 Å~ 109/l showed that the combination was safe and well-tolerated.
12 Here, we report a Phase Ib study (ELASTIC; International Standard Randomised Controlled Trial Number
[ISRCTN]05858391) of azacitidine with eltrombopag in patients with MDS/AML with platelets <150 Å~ 109/l. During the course of ELASTIC, a Phase III study of eltrombopag/ azacitidine versus azacitidine/placebo (A
StUdy of eltromboPag in myelodysPlastic SyndrOmes Receiving azaciTidine [SUPPORT]; ClinicalTrials.gov Identifier: NCT02158936) reported.13 Unexpectedly the SUPPORT study was terminated early on the grounds of futility; 16% of patients receiving azacitidine/eltrombopag became platelet-transfusion independent compared with 40% receiving azacitidine/placebo. In the light of these findings ELASTIC was reviewed by an Independent Safety Monitoring Committee (ISMC) who determined that the study should run to completion as the study design and patient population differed from SUPPORT.

PATIENTS AND METHODS

The ELASTIC trial (ISRCTN05858391) is a multicentre, dose-finding study of eltrombopag with azacitidine conducted across eight centres in the UK. The primary aim was to assess the safety and tolerability of the combination and determine the maximum tolerated dose (MTD) of eltrombopag.

Eligibility

Eligible patients were aged ≥16 years with baseline platelet count of <150 Å~ 109/l and IPSS intermediate-2/
high-risk MDS, chronic myelomonocytic leukaemia-2 (CMML-2) or AML with 20%–30% bone marrow blasts. In the 8 weeks before registration, platelet transfusions were recorded and at least two platelet/haemoglobin estimations were required. Baseline bone marrow blast percentage, karyotype and fibrosis were assessed. Key exclusion criteria were Eastern Cooperative Oncology Group performance status >2, previous exposure to azacitidine or TpoR agonist, malignancy within the last 3 years, prior bone marrow transplant and East Asian ancestry (as the pharmacokinetics of eltrombopag are significantly different in this population). All patients provided valid written informed consent. The study was conducted in accordance with the Declaration of Helsinki and received ethical approval (Research Ethics Committee number: 13/SC/0309).

Treatment regimen

All patients received eltrombopag and azacitidine up to a maximum of six cycles in a 3 + 3 trial design.14 Cohorts of three or more patients were treated with eltrombopag at five dose levels (25, 50, 100, 200 or 300 mg/day) with a cohort extension at the MTD (Figure 1). Eltrombopag was administered for 7 days prior to starting the first cycle of azacitidine and continued throughout the first two cycles. No eltrombopag was administered during cycle three to allow a period of 'wash-out' before bone marrow assessment. From cycle four, where platelet response was considered eltrombopag-related by the treating physician, eltrombopag could be continued for three further cycles (Figure 2). When platelets were >250 Å~ 109/l, a 50% reduction in eltrombopag was made. If the following week, the platelet count remained >250 Å~ 109/l, the dose was reduced by a further 50%. Re-escalation was permitted once platelets were <150 Å~ 109/l. No dose escalation above the patient's starting dose was allowed. Azacitidine (75 mg/m2) was administered subcutaneously for 7 days of a 28 day cycle for up to six cycles on a 5–2– 2 schedule. Patients were evaluated after cycle

one (week 5) for dose-limiting toxicities (DLTs). Data on adverse events (AEs) were collected throughout the course of the study.

Study assessments

Baseline assessments included: physical examination, full blood count, film and bone marrow examination, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer/ fibrin degradation products, liver and renal function, next-generation sequencing and assessments for transfusion dependence and bleeding complications according to the World Health Organization (WHO) bleeding scale. Haematological improvement was determined by International Working Group (IWG) 2006 criteria.15 Patients underwent physical examination and bleeding assessment each month. Data on dose modification or discontinuation of eltrombopag and azacytidine were collected after each cycle of azacitidine. For the first two cycles of treatment patients kept diaries and recorded the time that doses of eltrombopag were taken. Full blood count, kidney and liver function were measured weekly over the first 13 weeks and monthly thereafter; bone marrow was taken on day 8 of eltrombopag (immediately prior to the first cycle of azacitidine) and at the end of cycles three and six. Trough eltrombopag levels were determined by liquid chromatography with tandem mass spectrometry (PPD laboratories, Middleton, WI, USA) from plasma samples taken 23 h after the last dose of eltrombopag on days 8, 36 and 65 (pre-cycles one, two and three of azacitidine respectively). An additional sample was
taken at day 92 (pre-cycle four) on completion of the 'wash-out' cycle of azacitidine. Thrombopoietin (Tpo) levels were measured via an enzyme-linked immunosorbent assay (Thermo Fisher Scientific; EHTHPO). Sera for Tpo levels were taken at baseline and days 8, 35, 65, 92 and 175 (end of sixth cycle). The DLTs were formally evaluated at the end of treatment cycle one (week 5). Patients not evaluable for DLT assessment were replaced. AEs were determined to be a DLT when there was eltrombopag relatable: new onset Grade 3–4
non-haematological clinical/laboratory toxicity, Grade 3–4 haematological toxicity, an increase of >3 Å~ upper limit of normal in alanine transferase level or a persistent rise in peripheral blood blast count. Cohort outcomes were reviewed by the ISMC. If no patient had experienced a DLT, the study proceeded to the next dose level. Conversely, if one of three patients experienced a DLT, no dose escalation occurred and a further three patients were recruited. If more than one of the six patients experienced a DLT, the MTD would be determined to be the dose level from the previous cohort (Figure 1).

Outcomes

The primary outcome was safety and tolerability of eltrombopag in combination with azacitidine as determined by Grade 3–4 AEs, serious AEs (SAEs), DLTs and increase in marrow or peripheral blood blasts. From this the MTD of eltrombopag would be established. AEs were assessed from the start of protocol-defined treatment until 30 days after the administration of last trial treatment and reviewed using National Common Terminology Criteria for Adverse Events (CTCAE), version 4. Secondary outcomes included the effect of eltrombopag on: platelet counts, the need for platelet transfusions, bleeding complications, haematological improvement,
azacitidine dose delays/modifications, marrow blast percentage and marrow response as per IWG 2006 criteria.15

Statistical analysis

Data were summarised with standard descriptive statistics, or graphically. Lines of best fit were determined by a least-squares method. Associations between variables were tested via Pearson's correlation coefficient.

RESULTS

Study population (Table 1)

A total of 31 patients with intermediate-2/ High MDS/ CMML-2/ AML ≤30% blasts were recruited between November 2014 and August 2018. One patient, declared ineligible, was withdrawn before starting treatment and
replaced. A total of 30 patients (median age 74, range 62–86 years) were evaluable for analysis in the safety population (intermediate-2 MDS, 12 patients; high-risk MDS, 12; CMML-2, one; AML, five). In all, 47% of patients had complex or other adverse karyotypes. High-risk mutations including Runt-related transcription factor 1 (RUNX1), NRAS proto-oncogene, GTPase (NRAS), tumour protein p53 (TP53) and additional sex combs like-1 (ASXL1) were frequently present. The median (range) platelet count at baseline was 32 (9–118)
Å~ 109/l. Two patients had baseline platelets >75 Å~ 109/l.

Safety and tolerability/toxicities

The first 21 patients (25 mg, five patients; 50 mg, three; 100 mg, four; 200 mg, four; 300 mg, five) were recruited for MTD determination. No DLTs occurred and the MTD was established as 300 mg. A total of 15 patients were recruited at the MTD. All patients experienced AEs. The majority of these were Grade 1–2 events. The commonest AEs were gastrointestinal (GI) disorders, infection, injection site reactions and abnormal investigations (Tables S1 and S2). In the overall safety population (30 patients), there were 51 SAEs including 28 serious adverse reactions (SARs), four suspected unexpected SARs (SUSARs), and 95 episodes of Grade 3, 4 or 5 AEs (Table 2). Local investigators reported three SAEs as being potentially related to eltrombopag alone and six SAEs potentially related to azacitidine and eltrombopag in combination. Infection was the commonest AE and accounted for 33% of all Grade 3–5 AEs and was implicated in 45% of SAEs. There were three Grade 2 SUSARs: a rash due to neutrophilic dermatosis, Sweet syndrome (25 mg) that improved when eltrombopag was discontinued, WHO MF2 bone marrow fibrosis (100 mg) that improved upon discontinuation of eltrombopag and haematuria (300 mg) that resolved spontaneously. One Grade 5 SUSAR occurred; a patient receiving 50 mg of eltrombopag was found deceased following a myocardial infarction. All four SUSARs were regarded as potentially related to eltrombopag by local investigators. Toxicity was cited as a factor for missing doses of eltrombopag on 10 occasions. Five of these were due to transient rises in alanine transferase. Five patients discontinued treatment due to toxicity (25 mg/day, two infection) (300 mg/day, three vascular, GI, respiratory), seven patients due to death (pneumonia, two; disease-related, four; ischaemic heart disease, one),
and one patient withdrew their consent to continue on the study.

Response to treatment

Between baseline and day 8, the median blast percentage increased from 12% (n = 21) to 13% (n = 22). Increases in day 8 blast percentages were seen across all cohorts and typically resolved with ongoing treatment (Figure S2A,B). In all, 21 patients were evaluable for response assessment after cycle three and 16 patients after cycle six. Unevaluable patients were considered as non-responders. After three cycles there were 21 non-responders and 10 responders (complete remission [CR] in three, marrow CR in four and partial remission [PR] in three). After six cycles there were 22 non-responders and nine responders (CR in three, marrow CR in four and PR in two) (Figure S2C,D). Six of 14 patients (43%) treated at the MTD responded and three of 16 (19%) treated at below the MTD responded. During the study, strict IWG 2006 haematological improvement in platelets was seen in nine patients (29%). There was a modest increase in bleeding events in cycle one compared with baseline, but this was not reproduced in subsequent cycles (Table S3). One patient achieved a haematological improvement in haemoglobin and two in neutrophils. In view of the findings of the SUPPORT study, we examined the effect of eltrombopag dose on platelet response using a modified form of the IWG 2006 criteria. Here, the target improvement in platelet count is the same but there is no requirement for a sustained 8-week response. We considered platelet responses immediately before each cycle of azacitidine (Figure S3A,B). After 7 days of single agent eltrombopag, two patients at, and one treated below the MTD had responded. Before the second cycle of azacitidine,

response rates between patients treated at or below the MTD were similar. However, prior to the third cycle, 70% of patients who had a platelet count reported at that time-point, had responded below the MTD whilst only 36% of those treated at the MTD had responded. During cycle three, when patients did not receive eltrombopag; 50% treated below the MTD and 46% treated at the MTD had responded. Thereafter, the responses between the two dose groups were similar with a tendency for the response to be higher in those treated at the MTD. From cycle four, the decision to continue eltrombopag in combination with azacitidine was at the discretion of local investigators. In all, 18 out of 19 patients continued the drug from cycle four onwards. Six of the patients who continued eltrombopag needed at least one dose reduction as the platelet count was >250 Å~ 109/l. The effect of Eltrombopag on platelet transfusion dependence following the first two cycles of the eltrombopag/azacytidine combination was analysed (Figure 3). Considering evaluable patients who were platelet transfusion independent in the 8 weeks before starting treatment: 50% (seven of 14 patients) of those treated below the MTD and 67% (eight of 12) of those treated at the MTD became platelet transfusion dependent by the end of cycle two. Conversely, only two patients (one at and one below the MTD) who were transfusion dependent before treatment became platelet transfusion independent during the first two cycles of treatment.

Thrombopoietin and Eltrombopag

(Figures S4–S8) The Tpo levels varied between patients and were frequently below the limit of detection. During treatment, individual patients' Tpo levels did not change significantly. There was no relationship between Tpo level and platelet response. Day 8 eltrombopag levels were proportionate to dose rising to a maximum pre-cycle two. There was no correlation between eltrombopag level and platelet response or Tpo levels.

DISCUSSION

The ELASTIC trial examined safety and tolerability of eltrombopag/ azacitidine in patients with intermediate-2/
high-risk MDS, CMML-2 and AML with baseline platelets <150 Å~ 109/l. This is an important group as azacitidine monotherapy commonly results in Grade 1–2 thrombocytopenia progressing to Grade 3–4.4,7 However, only two patients had platelets >75 Å~ 109/l at baseline. With median platelets at 32 Å~ 109/l, participants had severe thrombocytopenia, but the study population was not enriched for patients with platelets <20 Å~ 109/l; a group with particularly unmet needs. No DLT was identified; the MTD was eltrombopag 300 mg daily. As expected, most AEs related to anaemia, neutropenia, infection, or GI disorder. Four SUSARs were relatable to eltrombopag: Sweet syndrome, bone marrow fibrosis, haematuria, and myocardial infarction. Sweet syndrome has not been reported as an AE of eltrombopag previously. Reversible bone marrow fibrosis as seen in our patient has also been reported in patients with immune thrombocytopenia.16 Concerns that TPoR agonists promote disease progression have not been borne out for romiplostim or eltrombopag in low-risk MDS.17–19 In high-risk patients, SUPPORT showed a trend to worsening disease progression and AML transformation.13 We did not detect this. A rise in bone marrow blasts was seen in some patients at day 8 compared with baseline but this resolved in subsequent cycles of treatment. Marrow responses rates were comparable to previous reports. 4 By formal IWG criteria, 29% of patients experienced platelet response. However, most patients treated at the MTD did not achieve a platelet response by modified IWG 2006 criteria at the end of cycle two, whilst more patients treated below the MTD did achieve such a response. In keeping with this, 67% of patients treated at the MTD, who were platelet transfusion independent at baseline, became transfusion dependent within two cycles of combined therapy. By comparison, only 29% of patients who were thrombocytopenic in the Aza-001 study received transfusions.4,7 Whilst ELASTIC was not designed to make definitive statements about efficacy, the results mirror the outcome of SUPPORT where only 16% of patients receiving azacitidine/eltrombopag were transfusion independent in the first four cycles. With ELASTIC, during and after the cycle three wash-out, platelet responses in the MTD

cohort improved. Although some of this may have been the result of disease response to azacitidine, six patients had dose reductions/modifications in eltrombopag to maintain a platelet count of <250 Å~ 109/l implying that the level of platelets was, in part, eltrombopag dependent. The SUPPORT study of eltrombopag/azacitidine versus placebo/azacitidine in MDS/AML patients with platelets <75 Å~ 109/l was terminated early on the grounds of futility and safety.13 The SUPPORT study used a stringent and clinically meaningful efficacy measure, namely achieving and maintaining platelet transfusion independence for the first four cycles of treatment. SUPPORT not only demonstrated futility but showed that eltrombopag was actually detrimental to patients using this efficacy measure. It was surprising as both eltrombopag and azacitidine monotherapy had previously shown effects on platelet response in MDS/AML.4,10,11 The reasons for this result remain unknown; it is unclear if this is due to pharmacokinetic or pharmacodynamic changes because of interaction between eltrombopag and azacitidine. The SUPPORT study authors postulated an inhibitory action of eltrombopag on azacitidine. Another possibility might be inhibition between eltrombopag and Tpo leading to reduced megakaryopoietic drive. As we were unable to find correlations between eltrombopag or Tpo levels and platelet count this is an unlikely explanation. We have not explored the hypothesis that treatment with eltrombopag may increase azacitidine levels leading to increased toxicity, including thrombocytopenia. Based on our data, we could have concluded that eltrombopag and azacitidine is a safe combination. Notably, similar conclusions were drawn from two other early phase studies of azacitidine/eltrombopag in MDS/AML.12,20 However, we are mindful that the Phase III SUPPORT study raised concerns about safety and efficacy of the combination and that patients on azacitidine should not receive eltrombopag as part of routine care. Our study serves as a reminder that important adverse safety signals (in this case relating to lack of efficacy) may not be identified in small scale, early phase, studies. ELASTIC was not designed to answer questions around efficacy, yet the pattern of results regarding platelet response chimes with the results from SUPPORT. Azacitidine combined with drugs including venetoclax have become standard of care in elderly AML21 and is under evaluation in high-risk MDS. Disease-and treatment-related thrombocytopenia remain challenging. Understanding why there is a deleterious effect of eltrombopag in combination with azacitidine may refine our approach to MDS/AML patients in future.

AUTHOR CONTRIBUTIONS

Alexander Sternberg, David Bowen, Dominic Culligan, Paresh Vyas and Helen Chantal Coulthard designed the study. Alexander Sternberg, Manoj Raghavan, Dominic Culligan, Catherine Cargo and Mike Dennis recruited patients to the study. Marlen Metzner, Jennifer O'Sullivan, Rachel Moore and Paresh Vyas performed laboratory experiments. Alexander Sternberg, Rebecca Boucher and Aimee Jackson analysed the data. All authors contributed to the writing of the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank all of the patients involved in the study and their families. The trial was supported by the Trials Acceleration Programme (TAP) funded by Blood Cancer UK. Eltrombopag was provided free of charge by Novartis with educational grants from Novartis and Celgene to permit sample collection and analysis. We thank Drs Priyanka Mehta, Timothy Chevassut and Simon Stanworth for their oversight of the study.

DATA AVAILABILITY STATEMENT

Original data and protocol available on request from Alexander Sternberg.

TRIAL REGISTRATION

ClinicalTr ials.gov Identifier: NCT00903422. Trial data can be accessed from https://www.clini caltr ialsr egist er.eu/ctr-search/trial/ 2013-000341-39/results

REFERENCES

1. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood.
1997;89(6):2079–88.
2. Greenberg P, Tuechler H, Schanz J. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–65.
3. Bejar R, Stevenson K, Abdel-Wahab O. Clinical effect of point mutations in myelodysplastic syndrome. N Engl J Med. 2011;364(26):2496–506.
4. Fenaux P, Mufti G, Hellstrom-Lindberg E. Efficacy of azacytidine compared with that of conventional care regimens in the treatment
of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223–32.
5. Prebet T, Gore S. Esterni B outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011;29(24):3322–7.
6. Kantarjian H, Giles F, List A. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. J Cancer. 2007;109(9):
1705–14.
7. Santini V, Fenaux P, Mufti G. Management and supportive care measured for adverse events in patients with myelodysplastic syndromes
treated with azacytidine. Eur J Haematol. 2010;85(2):130–8.
8. van der Helm LH, Alhan C, Wijermans P. Platelet doubling after the first azacitidine cycle is a promising predictor for response in myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML) patients in the Dutch azacitidine compassionate named patient programme. Br J Haematol. 2011;155(5):599–606.
9. Zeiden A, Lee J, Prebet T. Platelet count doubling after the first cycle of azacytidine therapy predicts eventual response and survival in patients with myelodysplastic syndromes and oligoblastic acute myeloid leukaemia but does not add to prognostic utility of the revised IPSS. Br J Hamatol. 2014;167(1):62–8.
10. Oliva EN, Alati C, Santini V. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol. 2017;4(3):e127–36.
11. Mittelman M, Platzbecker U, Afanasyev B. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol. 2018;5(1):e34–43.
12. Svensson T, Chowdhury O, Garelius H. A pilot phase I dose finding safety study of the thrombopoietin-receptor
agonist, eltrombopag, in patients with myelodysplastic syndrome treated with azacytidine. Eur J Haematol. 2014;93(5):439–45.
13. Dickinson M, Cherif H, Fenaux P. Azacitidine with or without eltrombopag for first-line treatment of intermediate-or high-risk
MDS with thrombocytopenia. Blood. 2018;132(25):2629–38.
14. Kurzrock R, Chia-Chi L, Wu T-C, Hobbs B, Carmagnani Pestana R, Hong D. Moving beyond 3+3: the future of clinical trial design. Am Soc Clin Oncol Educ Book. 2021;41:e133–44.
15. Cheson B, Greenberg P, Bennett J. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419–25.
16. Brynes R, Orazi A, Theodore D. Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenia treated with eltrombopag: data from the EXTEND study. Am J Hematol. 2015;90(7):598–601.
17. Giagounidis A, Mufti G, Fenaux P. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/

intermediate-1- risk myelodysplastic syndrome and thrombocytopenia. Cancer. 2014;120(12):1838–46.
18. Kantarjian H, Fenaux P, Sekeres M. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomised double-blind trial. Lancet Haematol. 2018;5(3):e117–26.
19. Comont T, Meunier M, Cherait A. Eltrombopag for myelodysplastic syndromes or chronic myelomonocytic leukaemia with no excess
blasts and thrombocytopenia: a French multicentre retrospective real-life study. Br J Haematol. 2021;194(2):336–43.
20. Dickinson M, Herbert K, Sardjono C. Final analysis of a phase II study of intrapatient dose-escalation of eltrombopag in patients receiving azacytidine for myelodysplasia/AML. Blood. 2014;124:Abstract 4657.
21. DiNardo C, Jones B, Pullarkat V. Azacitidine and venetoclax in previously untreated acute myeloid leukaemia. N Engl J Med.
2020;383(7):617–29.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

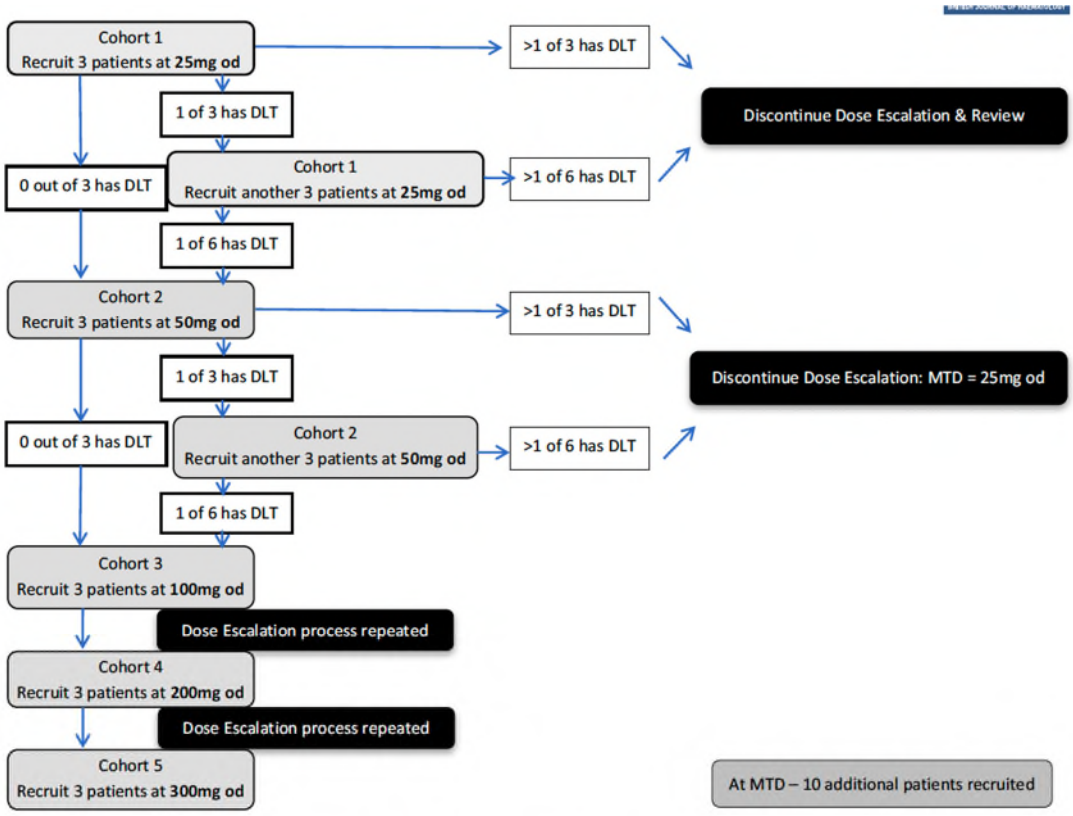

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram – 3 + 3 cohort trial design. If no dose limiting toxicity (DLT) occurred in the first three patients in each cohort, the study proceeded to the next dose level. If one of three patients had a DLT in a cohort, a further three were recruited at that dose level. If no further DLT occurred, the study proceeded to the next dose level. If at any dose level, >one of three or >one of six patients had a DLT, the MTD was determined to be the dose from the previous cohort and a further 10 patients would be studied as an extension to that cohort. If a cohort of five patients was reached, 300 mg would be assigned as the MTD, if there were no more than zero of three or one of six DLTs at that dose level.

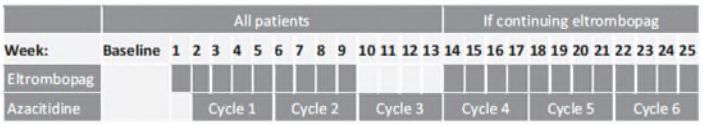

FIGURE 2 Treatment regimen: Patients received a 7 day pre-phase of eltrombopag orally before starting azacitidine. Cycle three (weeks 10–13) was a 'wash-out' cycle where no eltrombopag was given. Eltrombopag could be continued from cycle four if local investigators judged that the patient had previously had a platelet response. Eltrombopag dose 25–300 mg according to trial cohort. Azacitidine dose 75 mg/m^2 subcutaneously given 7 days per cycle.

TABLE 1 Baseline characteristics of patients entered into the ELASTIC study. Prevalence of all mutations identified is shown in Figure S1.

Characteristic	Value
Age, years, median (range)	**74 (62–86)**
Gender, *n* (%)	
Female	9 (29)
Male	22 (71)
Time from diagnosis, months, median (range)	1.2 (0–105.7)
Diagnosis, *n* (%)	
IPSS intermediate-2 MDS	12 (40)
IPSS high-risk MDS	12 (40)
CMML-2	1 (3)
AML	5 (17)
Karyotype, *n* (%)	
Normal	10 (33)
Complex/inv 3q/del7/del5	14 (47)
Other: +8/del20q	4 (13)
Failed	1 (3)
Unknown	1 (3)
Commonest mutations, *n* (%)	
RUNX1	9 (30)
NRAS	8 (27)
TET2	8 (27)
TP53	8 (27)
ASXL1	7 (23)
KMT2D	6 (20)
EZH2	5 (17)
Morphology blasts, %, median (range)	12 (2–30)
Platelets, $\times 10^9$/l, median (range)	32 (9–118)
Haemoglobin, g/l, median (range)	103 (74–122)
Neutrophils, $\times 10^9$/l median (range)	0.8 (0–5.6)

Abbreviations: AML, acute myeloid leukaemia; ASXL1, additional sex combs like-1; CMML, chronic myelomonocytic leukaemia; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; IPSS, International Prognostic Scoring System; KMT2D, histone–lysine N-methyltransferase 2D; MDS, myelodysplastic syndromes; NRAS, NRAS proto-oncogene, GTPase; RUNX1, Runt-related transcription factor 1; TET2, ten–eleven translocation methylcytosine dioxygenase 2; TP53, tumour protein p53.

TABLE 2 (A) Summary of Grade 3–5 adverse events (AEs) seen at a frequency of at least 5%. (B) Summary of serious AEs (SAEs) and relatedness to treatment as determined by local investigators.

	AEs (patients), *n*		
(A) Toxicity	Grade 3	Grade 4	Grade 5
Neutropenia	6 (4)	10 (6)	0 (0)
Anaemia	8 (4)	3 (1)	0 (0)
Febrile neutropenia	7 (6)	1 (1)	0 (0)
Lung infection	4 (4)	0 (0)	2 (2)
Thrombocytopenia	0 (0)	5 (4)	0 (0)
Sepsis	0 (0)	1 (1)	3 (3)
Gastric haemorrhage	3 (1)	1 (1)	0 (0)
Dyspnoea	2 (2)	1 (1)	0 (0)
Hypokalaemia	3 (2)	0 (0)	0 (0)

(B)	Events (patients), *n*
Summary of SAEs	
All SAEs	51 (25)
Unrelated SAE	19 (9)
SAR	28 (17)
Non-fatal SUSAR	3 (3)
Fatal SUSAR	1 (1)
Relatedness of SAE	
Unrelated to both treatments	18 (8)
Related to azacitidine alone	24 (16)
Related to eltrombopag alone	3 (3)
Related to azacitidine and eltrombopag	6 (5)

Abbreviation: (SU)SAR, (serious unsuspected) adverse reaction.

	TI at baseline	TD after two cycles (%)	TD at baseline	TI after two cycles (%)
Overall	26	15 (58)	4	2 (50)
Below MTD	14	7 (50)	2	1 (50)
At MTD	12	8 (67)	2	1 (50)

FIGURE 3 Effect of two cycles of eltrombopag and azacitidine on patients who were either platelet transfusion independent or dependent in the 8 weeks before starting treatment. HI-P, haematological improvement in platelets, TI, transfusion independent, TD, transfusion dependent. MTD, maximum tolerated dose (300 mg of eltrombopag).