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ELASTIC

Clinical Trial Summary Report

A Phase Ib Study of **El**trombopag and **A**zacitidine in Patients with High Risk Myelodysplas**tic** Syndromes and Related Disorders

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Sponsor:	University of Birmingham
Sponsor reference number:	RG_12-268
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CANCER RESEARCH UK | BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT

UNIVERSITY OF BIRMINGHAM

CLINICAL TRIAL SUMMARY REPORT

Acronym:	ELASTIC
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EudraCT Number:	2013-000341-39
REC Reference Number:	13/SC/0309
Details of Investigational Medicinal Products:	Azacitidine – hypomethylating agent administered subcutaneously. Eltrombopag – oral thrombopoietin receptor agonist. Supplied by GSK initially, then by Novartis.
Details of Trial Arms:	See table below
Start Date: *Date trial opened to recruitment*	15th October 2014
End of Trial: *Date of declaration of the end of the trial*	7th September 2020

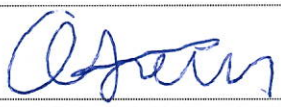
Cohort	Eltrombopag Dose
1	25mg OD
2	50mg OD
3	100mg OD
4	200mg OD
5	300mg OD

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

Contact Details

Cancer Research UK Clinical Trials Unit (CRCTU)
Institute of Cancer and Genomic Sciences
University of Birmingham
Edgbaston
Birmingham
B15 2TT
☎0121 371 4366
✉ ELASTIC@trials.bham.ac.uk

SIGNATORY:

Name:	Dr Alex Sternberg	Function:	Chief Investigator
Signature:		Date:	07/04/2021

GENERAL INFORMATION

Trial Design

This is a single arm, multicentre, phase Ib dose finding study of eltrombopag combined with azacitidine in IPSS INT-2/high-risk myelodysplastic syndromes, CMML-2 and AML with less than 30% blasts.

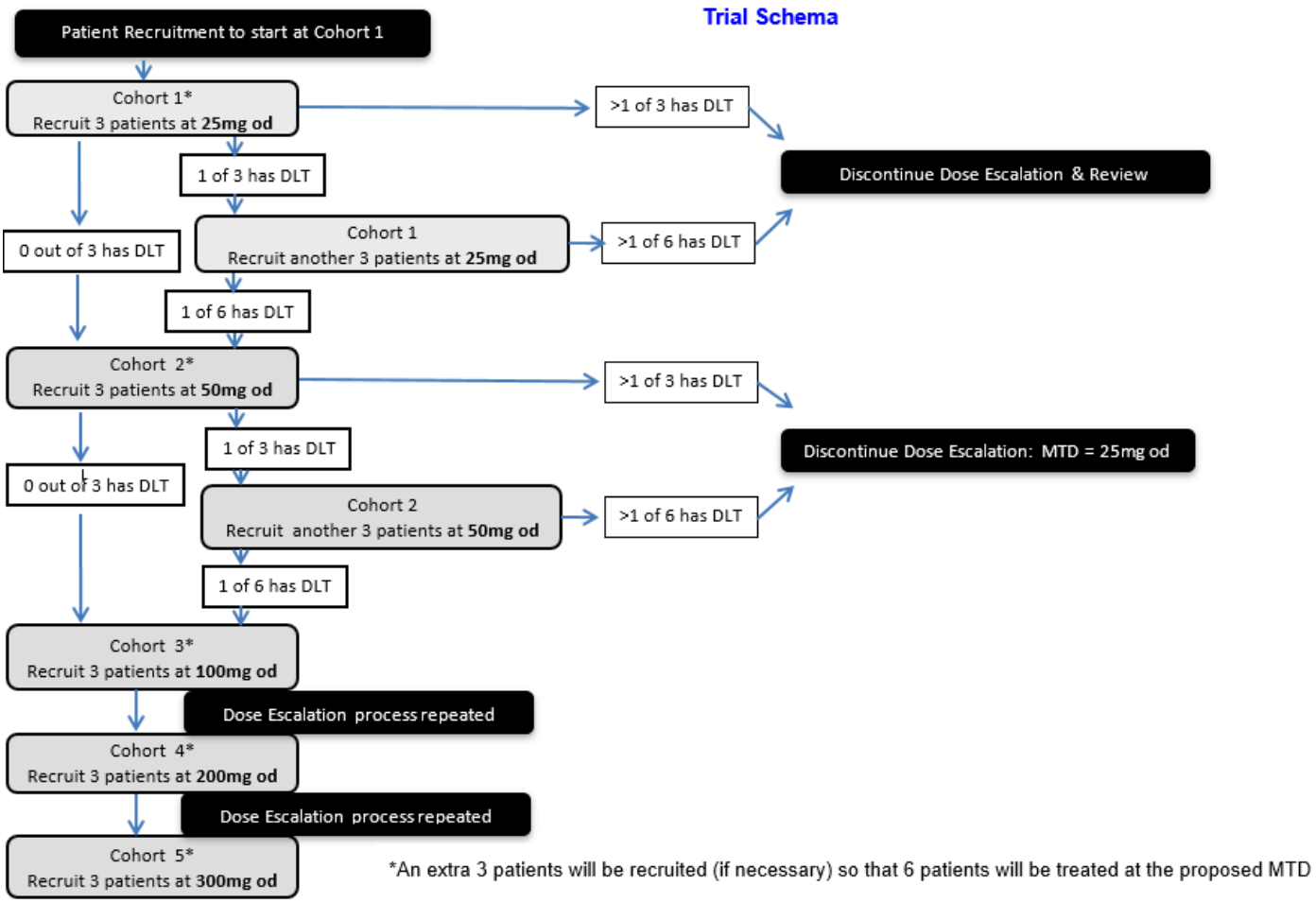
The aim of this study is to define an MTD and OBD for eltrombopag, in combination with azacitidine, whilst allowing adaptive dosing based on platelet counts.

The dose levels of eltrombopag are 25mg, 50mg, 100mg, 200mg and 300mg once daily.

3 patients will initially be enrolled at a starting dose of 25mg once daily (Cohort 1). After receiving a minimum of five weeks treatment with eltrombopag (one azacitidine cycle), the first three patients will be evaluated by a safety committee. The safety committee will review all reported DLTs, possible interactions, Adverse Events (AEs) (regardless of grade) and laboratory parameters. If no significant interactions or AEs are reported, and the safety committee decide to continue the study, Cohort 2 will be opened.

- If 1/3 patients experience a DLT, an additional 3 patients will be enrolled at this dose level and an escalation decision will be made once a total of 6 patients complete 5 weeks of treatment.
- If 1/6 patients experience a DLT, 3 new patients will be enrolled at the next dose level.
- If >1/6 patients experience a DLT at any dose level, the previous dose level will be determined as the MTD.

At the MTD, a further 10 patients will be recruited.



Patients who are not evaluable for DLT assessment (i.e., have not completed the 5 week assessment period) will be replaced.

Patients in Cohort 1 will continue with eltrombopag 25mg for a second cycle of azacitidine followed by a third course of azacitidine alone. A second cycle of combination treatment is required to understand the impact on the OBD and the potential for toxicity in a patient previously exposed to azacitidine.

Patients may receive a further 3 cycles of combination treatment if they have a documented platelet response judged by the treating physician to be due to eltrombopag and the patient is considered to be in need of eltrombopag in order to receive an adequate dose of azacitidine.

Subsequent cohorts will be opened until the MTD is reached and will follow the same process.

Definition of a Dose Limiting Toxicity (DLT)

DLTs will be formally evaluated after 5 weeks (i.e. at the end of treatment cycle 1).

A DLT is defined by the following safety and tolerability parameters assessed using the NCI CTC Criteria v4:

- Non-haematological toxicities

New onset non-haematological clinical and laboratory Grade 3//4 toxicities considered to be related to eltrombopag by the Investigator with the exception of the following grade 3 or 4 events:

- Febrile neutropenia - a disorder characterised by a neutrophil count of <1.0 x 10^9/L and a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour
- Fever - a disorder characterised by elevation of the body's temperature above the upper limit of normal
- Sepsis – a disorder characterised by the presence of pathogenic microorganisms in the blood stream and that can cause a rapidly progressing systemic reaction that may lead to shock

- Other infections – any grade 3 or 4 adverse events listed in the infections and infestations section of the NCI CTCAE criteria
- Grade 3 or 4 laboratory abnormalities that are part of a sepsis syndrome
- Grade 3 or 4 laboratory abnormalities that are part of a tumour lysis syndrome
- Grade 3 or 4 hyper or hypophosphataemia

- Liver toxicities

ALT levels increase to > 3x the upper limit of normal (ULN) considered related to eltrombopag by the Investigator **and** meeting **at least one** of the following criteria:

- Progressive (any further increases beyond the initial increase),
- or persistent for more than 3 weeks within 5 weeks of treatment,
- or accompanied by increased direct bilirubin (>49µmol/L),
- or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

- Treatment (Eltrombopag) related death is also considered a DLT.

Progression of disease is not considered a DLT. However, a number of studies in this patient population have described disease progression in patients receiving TpoR agonists. In some cases there were transient blast percentage rises whilst in others there was true disease progression. The precise role of TpoR agonists in this is unclear. All cases of disease progression whilst receiving Eltrombopag were discussed with the Chief Investigator.

An AE deemed to be unrelated to Eltrombopag will not be considered a DLT.

Scientific Background

Myelodysplastic Syndromes (MDS) are a heterogeneous group of myeloid neoplasms, characterised by dysplastic changes in myeloid, erythroid, and megakaryocytic precursors that occur predominantly in the elderly (median age at diagnosis is 74 years). Approximately 2000 new cases of MDS are diagnosed per year in the United Kingdom [1].

MDS may progress to life-threatening bone marrow failure or Acute Myeloid Leukaemia (AML). Patients often present with complications related to anaemia (fatigue), neutropenia (infections) and/or thrombocytopenia (bleeding). "High-risk (advanced)" MDS may be distinguished from "low-risk" MDS by increased marrow myeloblasts, cytogenetic abnormalities and degree of cytopenia. These factors have allowed the establishment of an International Prognostic Scoring System (IPSS) to predict survival and progression to AML [2]. The IPSS has more recently been refined into the Revised IPSS (R-IPSS). This takes into account the prognostic effect of certain cytogenetic abnormalities as well as a wider range of bone marrow blast percentages[3]. A best estimate would indicate that at least 700 of such new UK cases will be patients with IPSS INT-2/High (advanced MDS) and the prevalence will roughly equate to the incidence.

The therapeutic options for MDS remain limited. A small percentage of patients are candidates for a curative approach with allogeneic stem cell transplant. For the vast majority, however, the lack of acceptable donors, advanced age, and/or serious co-morbid medical conditions preclude this option [4].

Azacitidine is the first DNA hypomethylating agent approved by the USA Food and Drug Administration agency (FDA) and the European Medicines Agency (EMEA) for the treatment of MDS and has demonstrated superior efficacy and improvements in patients' quality of life and bone marrow function over supportive care. Subcutaneous azacitidine remains the only drug shown to significantly prolong overall survival in MDS patients with IPSS INT 2/high-risk MDS, AML with 20-30% blasts and Chronic Myelomonocytic Leukaemia -2 (CMML-2) compared with conventional care (i.e. best supportive care, low-dose cytarabine or intensive chemotherapy) [5], [6].In addition, azacitidine is associated with a lower risk of AML progression and higher rates of complete remission, partial remission, haematological improvement and red blood cell (RBC) transfusion independence [7]. Azacitidine is well tolerated and leads to less episodes of hospitalisation compared with other management strategies. Azacitidine was approved by NICE in March 2011. Whilst azacitidine is certainly an advance in the management of patients with high risk MDS, the prognosis for many remains disappointing. Only 51% of patients responded to azacitidine in the AZA-001 study. The outlook for patients who fail azacitidine is poor with median overall survival of 5.6 months [8].

Thrombocytopenia (platelets <100 x 10^9/l), is an independent adverse prognostic factor for survival in MDS, and increased severity of thrombocytopenia correlates with shorter time to AML progression [9].Thrombocytopenia and platelet dysfunction contribute to hemorrhagic complications in MDS and there is little consensus regarding its optimal treatment [10]. Platelet transfusions are the only current treatment option but are however associated with adverse effects that include febrile or allergic reactions, transmission of bacterial and viral infections, transfusion-related acute lung injury, and most commonly in patients with MDS, alloimmunisation (which render platelet transfusions ineffective) [10].

Thrombocytopenia, attributable to ineffective platelet production by dysfunctional megakaryocytes, has been estimated to occur in 40-65% of patients with MDS [9]. In IPSS INT-2 and high-risk patients the incidence of thrombocytopenia in this series was 72% and 82% respectively. Furthermore, thrombocytopenia can be aggravated initially during treatment with azacitidine. In AZA 001, cytopenia was the most common grade 3-4 adverse event. Baseline grade 1-2 thrombocytopenias progressed to grade 3-4 in 74% of patients. Dose reductions due to thrombocytopenia were needed in 14% of patients. Dose delays were needed in 46% of cycles and in 21% of cycles the intervals were prolonged beyond 35 days (recommended cycle length is 28 days) [5]. Pre-treatment platelet count and degree of haematological improvement following azacitidine predicts improved survival in azacitidine treated patients compared with patients with low baseline platelets or poor improvement in the platelet and other elements of the blood count [11]. Indeed a doubling of platelet count after a first cycle of azacitidine is an independent positive predictor for overall survival [12].

Recently, second generation thrombopoietin receptor (TpoR) agonists such as eltrombopag have become available. Combination treatment with a TpoR agonist could prevent delays in treatment or the need for dose reduction and improve on the baseline efficacy of azacitidine.

In addition, eltrombopag may improve tri-lineage response per se as patients treated with severe aplastic anaemia showed responses in erythroid and granulocytic lineages as well as platelets [13]. This might be explained by the fact that TpoR is not only expressed in megakaryocyte/erythroid progenitors but is also in ontologically earlier stem cell compartments [14]. Finally, pre-clinical data suggests there may be an anti-leukaemic effect of eltrombopag specifically [15]. The scientific element of the study will allow pilot experiments aimed at examining the effect of eltrombopag on leukaemia/MDS stem/progenitor fate.

Whilst, many other drug classes are being developed for use in combination with azacitidine, it is not clear, which drugs will emerge as the best candidate for combination. In addition, most of the drugs in development in this area are significantly myelotoxic and in combination with azacitidine are likely to enhance the myelotoxic potential of azacitidine itself. In this context, thrombocytopenia presents a significant problem leading to dose delays or reductions as well as causing significant morbidity and mortality as outlined above. Combining azacitidine with other agents directed against the MDS clone are only likely to potentiate this problem.

Trial Rationale

- Justification for patient population

Globally, azacitidine has become the standard of care for patients with IPSS INT-2 and high risk MDS, CMML-2 and AML with <30% blasts for whom a curative strategy involving allogeneic stem cell transplant is not appropriate.

Although azacitidine improves survival in high-risk MDS by 9 months compared with conventional care regimens, median survival remains only 24 months [5]. For patients who fail azacitidine, the outlook is particularly bleak with the majority of patients surviving less than six months [8]. Therefore, there is a need to improve on the efficacy of azacitidine in this group of patients.

- Justification for design

This study has been designed to assess the safety and tolerability of eltrombopag in combination with azacitidine. A 3+3 cohort trial design will be used to evaluate the Maximum Tolerated Dose (MTD) and Optimal Biological Dose (OBD) of eltrombopag in combination with azacitidine. Dose Limiting Toxicities (DLT) will be used as the go/ no-go criteria for subsequent cohorts.

Once the MTD has been established, the trial will recruit a further 10 patients to allow an assessment of activity to be made.

This study will provide dose and safety information about the combination of these drugs which will be used in planning future randomised trials.

- Choice of treatment

Azacitidine is the standard of care for this group of patients and is known to be effective in MDS. Eltrombopag offers the potential to improve upon the efficacy of azacitidine. Another TpoR agonist, romiplostim has been used in lower risk forms of MDS, both as a single agent and in combination with azacitidine or decitabine where improvement in platelets and bleeding complications have been demonstrated [16,17]

Eltrombopag is a small, oral, non-peptide molecule and is structurally different to romiplostim, which is a large fusion molecule, that needs to be administered subcutaneously. Eltrombopag offers a more convenient choice of treatment as well as providing a potential for multi-lineage responses and an anti-leukaemic effect.

This study is an important step towards understanding the nature of the therapeutic effect of eltrombopag in terms of both haematopoietic lineage responses as well as its anti-leukaemic effect in patients with advanced MDS and related disorders.

Objectives

- To evaluate the safety and tolerability of the oral thrombopoietin receptor agonist eltrombopag in combination with azacitidine in patients with advanced MDS and establish the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD).
- To investigate the effect of eltrombopag with azacitidine on the fate of MDS/AML stem cell progenitors from patients so treated. The feasibility of Leukaemic Stem Cell (LSC) tracking as a marker of response and predictor of treatment failure in future Phase II/III studies will be explored

Outcome Measures

Primary Outcome

Safety and tolerability (including establishing the Maximum Tolerated Dose) of eltrombopag in combination with azacitidine when administered to patients with MDS who are suitable for azacitidine treatment.

Secondary Outcomes

- To establish the Optimal Biological dose (OBD) of eltrombopag in combination with azacitidine where this is not limited by MTD.
- To evaluate the effect of eltrombopag on platelet counts
- To evaluate the effect of eltrombopag on the need for platelet transfusions
- To evaluate the effect of eltrombopag on azacitidine treatment delays and dose reductions
- To evaluate the effect of eltrombopag on bleeding complications
- To evaluate evidence for a dose response effect of eltrombopag on bone marrow blast percentage
- To evaluate the activity of eltrombopag plus azacitidine per modified IWG 2006 haematological improvement criteria for MDS ([1])
- To evaluate the activity of eltrombopag plus azacitidine per modified IWG 2006 response criteria for MDS ([1])
- To evaluate the dosage effect of eltrombopag on stem/progenitor subset numbers and fate

Statistical Considerations

Power Calculations

As this is a 3+3 design, no formal power calculation has been carried out and analysis will be descriptive only.

A maximum of 27 patients will be recruited to the 3+3 dose finding component of the study and a minimum of 3. The number of patients recruited is determined by the maximum dose of 300mg.

An additional 10 patients will then be recruited at the MTD to allow a preliminary estimate of activity.

A maximum of 37 patients in total will be recruited to this study.

Analyses

This is a phase I dose finding study and the MTD will be assessed by means of a standard 3+3 design.

Basic descriptive analyses will be produced for the trial outcome measures. In addition, an attempt will be made to carry out statistical modelling of the relationship between dose and each of the following outcomes:

- Platelet counts
- Bone marrow blast percentages
- stem/progenitor subset numbers and fate

All modelling will be post hoc in nature, and will include a range of covariates. A key aim of the modelling will attempt to recommend an Optimum Biological Dose (OBD) of the drug, based on platelet counts.

Patient Safety

Whilst the defined `safety population' is defined as patients who received at least one dose of both treatments, the data presented here includes all patients registered to the trial for completeness.

Trial Populations

31 patients with IPSS INT-2/high-risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukaemia (CMML-2) and Acute Myeloid Leukaemia (AML) with less than 30% blasts were recruited from the UK.

DLT evaluable population: patients who continued in the trial up to or after Week 5 of Cycle 1 and who received at least 28 / 35 (80%) doses of eltrombopag, and at least one dose of azacitidine will be evaluable for DLTs. Patients who experience a DLT, having received at least one dose of combination.

Safety population: Any patient who received at least one dose of eltrombopag and one dose of azacitadine.

Efficacy population: An intention-to-treat approach will be used, meaning that any patient registered to the study will be included in the efficacy population.

SUBJECT DISPOSITION

Eligibility Criteria

Inclusion Criteria

- Age ≥16 years of age
- Platelet count at baseline <150 x 10^9/L
- Myelodysplastic Syndromes (MDS) classified as Intermediate 2-risk or high risk according to the International Prognostic Scoring System (IPSS) at registration [2] OR
- Chronic Myelomonocytic Leukaemia (CMML) with 10-29% bone marrow blasts without proliferation (peripheral white blood cell count <13 x 10^9/L) OR
- Acute Myeloid Leukaemia (AML) with 20-30% bone marrow blasts

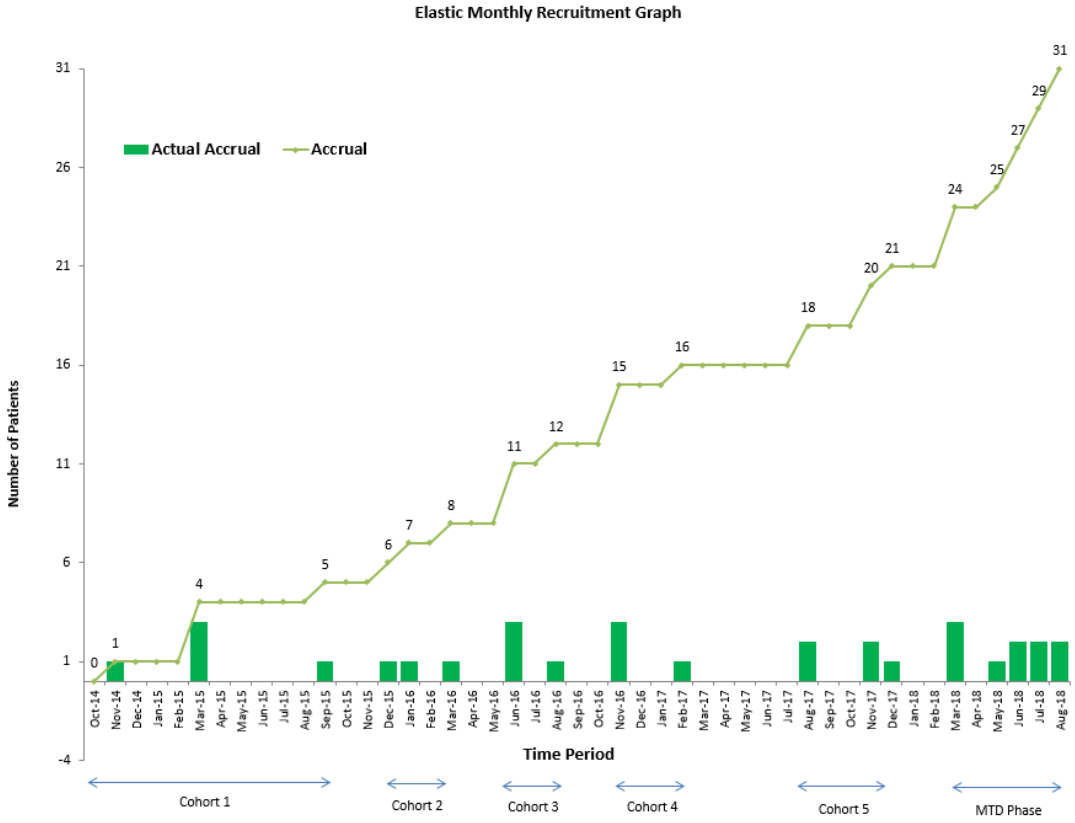
- Subjects must have a minimum of two platelet and haemoglobin counts available from a period of up to 8 weeks prior to registration, as well as a record of any platelet transfusions conducted during that period.A baseline bone marrow examination to evaluate blast percentage, karyotype and assessment of fibrosis within 8 weeks prior to registration
- ALT/AST < 3 x upper limit of normal
- ECOG ≤ 2
- Valid informed consent

Exclusion Criteria

- AML with >30% blasts
- Patients who have received allogeneic bone marrow transplantKnown HIV positive
- Known liver cirrhosis
- Uncontrolled infection (grade 4 CTCAE v4)
- Previous exposure to azacitidine
- Previous exposure to thrombomimetic agents
- Use of prior investigational agents within 4 weeks
- Other severe, concurrent diseases or mental disorders that in the opinion of the investigator make the patients unsuitable for the trial
- Concurrent active or previous malignancy within the last 3 years – except controlled, localised prostate cancer on hormone therapy or non-melanoma skin malignancy or cervical carcinoma *in situ* or completely resected colonic polyps carcinoma *in situ*
- Grade 4 bone marrow fibrosis according to the European consensus [3]
- Clinical evidence of splenomegaly
- Known hypersensitivity to study drugs or any of their excipients
- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry)
- Females of childbearing potential (i.e. not post-menopausal or surgically sterilised) who are not willing to use adequate methods of contraception to prevent pregnancy or abstain from heterosexual activity for the duration of the trial and for at least 3 months following treatment discontinuation.
- Male patients who are not willing to use an adequate method of contraception for the duration of the trial treatment if engaged in sexual activity with a female of childbearing potential and for at least 3 months following treatment discontinuation
- Patients of east Asian ancestry*

* Patients will be excluded if either parent is East Asian (such as Chinese, Japanese, Taiwanese or Korean). In previous studies, the pharmacokinetics of eltrombopag in patients of East Asian ancestry differs significantly from the non-East Asian patients. The SPC for eltrombopag recommends patients receive 50% of the recommended dose. As this is a dose finding study, inclusion of these patients may impair an accurate finding of MTD and OBD that could be applied to the UK population.

Recruitment



31 patients were recruited from 8 sites between November 2014 and August 2018. 5 patients were recruited to cohort 1, 3 to cohort 2, 4 to cohort 3, 4 to cohort 4 and 15 to cohort 5.

Withdrawals

1 patient withdrew consent from the trial but were willing for further data to be collected at routine visits. No reason was provided.

Treatment Discontinuations

Table 5: Treatment discontinuations

Dose	25 mg (5)	50 mg (3)	100 mg (4)	200 mg (4)	300 mg (15)	Overall (31)
Status						
Completed cycles	1 (20.0)	2 (66.7)	3 (75.0)	2 (50.0)	9 (60.0)	17 (54.8)
Discontinued treatment early	4 (80.0)	1 (33.3)	1 (25.0)	2 (50.0)	6 (40.0)	14 (45.2)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)

Table 6: Reasons for treatment discontinuation

Dose	25 mg (4)	50 mg (1)	100 mg (1)	200 mg (2)	300 mg (6)	Overall (14)
Reason for discontinuation						
Death	2 (50.0)	1 (100.0)	0 (0.0)	2 (100.0)	1 (16.7)	6 (42.9)
Disease progression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.1)
Other	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (16.7)	2 (14.3)
Other toxicity	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)
Other toxicity, Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.1)
Other toxicity, Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (14.3)
Total	4 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)	6 (100.0)	14 (100.0)

BASELINE CHARACTERISTICS

Median Age, yrs (range)		74 (53-85)
Gender, n (%)	Female	9 (29)
	Male	22 (71)
Time from diagnosis, median months (range)		1.3 (0-112)
Diagnosis, n (%)	IPSS Int-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)
Median bone marrow blasts, % (range)*		11 (1-47)
Platelets, median (range)		32 (9-118)
Haemoglobin, median (range)		102 (74-122)
Neutrophils, median (range)		0.8 (0-5.6)

Baseline characteristics of patients entered into the ELASTIC study. * One patient recruited on the basis of trephine histology blast percentage of 20% was found to have 47% blasts on the bone marrow aspirate. The median blast percentage and range without this patient was 11 (1-26).

ENDPOINTS

Definitions and statistical analyses

Dose limiting toxicity (DLT) is defined by safety and tolerability parameters within 5 weeks (1 cycle of treatment).

Patients eligible for Dose Limiting Toxicity Assessment

Dose	25 mg (5)	50 mg (3)	100 mg (4)	200 mg (4)	300 mg (5)	Overall (21)
Evaluable?						
No	2 (40.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (40.0)	6 (28.6)
Yes	3 (60.0)	3 (100.0)	3 (75.0)	3 (75.0)	3 (60.0)	15 (71.4)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	5 (100.0)	21 (100.0)

Summary of Dose Limiting Toxicities

Dose	25 mg (3)	50 mg (3)	100 mg (3)	200 mg (3)	300 mg (3)	Overall (15)
Did patient experience a DLT?						
No	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	15 (100.0)
Total	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	15 (100.0)

The OBD is defined as that dose of eltrombopag, which maintains a platelet count within the range 100-250 x 10^9/L immediately prior to a cycle of azacitidine. This has been summarised in two ways, by time point and per patient.

- By time point:

The analysis summarises the number of patients whose met the OBD definition at each time point. In this analysis, immediately prior is taken to be: Cycle 1 Week 1 for prior to azacitidine in Cycle 1, Cycle 1 Week 5 for prior to Cycle 2, Cycle 2 Week 4 for Cycle 3, Cycle 3 Week 4 for Cycle 4, Cycle 4 for Cycle 5, and Cycle 5 for Cycle 6. Note, patients are only included when they have a platelet count at the relevant time point.

Time point	Dose (r/n, %)	25 mg	50 mg	100 mg	200 mg	300 mg
Cycle 1: Week 1		0/1 (0.0)	0/3 (0.0)	0/4 (0.0)	0/3 (0.0)	0/14 (0.0)
Cycle 1: Week 5		0/3 (0.0)	0/3 (0.0)	1/4 (25.0)	1/3 (33.3)	2/14 (14.3)
Cycle 2: Week 4		0/1 (0.0)	0/3 (0.0)	2/4 (50.0)	1/2 (50.0)	0/11 (0.0)
Cycle 3: Week 4		0/1 (0.0)	1/3 (33.3)	1/4 (25.0)	1/2 (50.0)	3/11 (27.3)
Cycle 4		0/1 (0.0)	1/3 (33.3)	0/3 (0.0)	0/2 (0.0)	5/12 (41.7)
Cycle 5		0/1 (0.0)	0/3 (0.0)	1/3 (33.3)	1/2 (50.0)	3/11 (27.3)

In line with the Statistical Analysis Plan any patient who is on treatment is included in the denominator for the proportions in this table. Patients are determined to be off treatment if the time point (e.g. Cycle number) is after the last cycle started.

r/n, % (95% CI)	25 mg	50 mg	100 mg	200 mg	300 mg
Cycle 1: Week 1	0/5, 0% (0%, 52%)	0/3, 0% (0%, 71%)	0/4, 0% (0%, 60%)	0/4, 0% (0%, 60%)	0/14, 0% (0%, 23%)
Cycle 1: Week 5	0/5, 0% (0%, 52%)	0/3, 0% (0%, 71%)	1/4, 25% (1%, 81%)	1/4, 25% (1%, 81%)	2/14, 14% (2%, 43%)
Cycle 2: Week 4	0/3, 0% (0%, 71%)	0/3, 0% (0%, 71%)	2/4, 50% (7%, 93%)	1/3, 33% (1%, 91%)	0/12, 0% (0%, 26%)
Cycle 3: Week 4	0/1, 0% (0%, 98%)	1/3, 33% (1%, 91%)	1/4, 25% (1%, 81%)	1/2, 50% (1%, 99%)	3/11, 27% (6%, 61%)
Cycle 4	0/1, 0% (0%, 98%)	1/3, 33% (1%, 91%)	0/3, 0% (0%, 71%)	0/2, 0% (0%, 84%)	5/10, 50% (19%, 81%)
Cycle 5	0/1, 0% (0%, 98%)	0/3, 0% (0%, 71%)	1/3, 33% (1%, 91%)	1/2, 50% (1%, 99%)	3/9, 33% (7%, 70%)

- Per patient level:

Dose	25 mg (5)	50 mg (3)	100 mg (4)	200 mg (4)	300 mg (15)	Overall (31)
Met the OBD definition for at least one time point						
No	5 (100.0)	2 (66.7)	1 (25.0)	3 (75.0)	10 (66.7)	21 (67.7)
Yes	0 (0.0)	1 (33.3)	3 (75.0)	1 (25.0)	5 (33.3)	10 (32.3)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)

Platelet response will be assessed pre- and post cycles of azacitidine as responsiveness to eltrombopag may be affected by azacitidine. The following two methods of assessing response will be used:

- The IWG 2006 criteria. These define platelet response as an absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L platelets or increase from baseline < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.
- Azacitidine SPC criteria. After cycles 1 and 2 of Azacitidine, response will be defined by the recovery of platelet count to nadir platelet count + (0.5 x [baseline count – nadir count]). Non- response will be defined as the failure to achieve this.

The anticipated schedule for use of the methods is as follows, although this may be adjusted if a patient's treatment gets delayed:

Timepoint	Assessment (s)
Day 1	Baseline platelet count
Day 8	Haematological Improvement (HI) according to modified IWG 2006 criteria and bone marrow assessment
Day 15	HI according to modified IWG 2006 criteria
Day 22	HI according to modified IWG 2006 and azacitidine SPC criteria
Day 29	HI according to modified IWG 2006 and azacitidine SPC criteria
Day 36	HI according to modified IWG 2006 and azacitidine SPC criteria
Day 43	HI according to modified IWG 2006 criteria
Day 50	HI according to modified IWG 2006 and azacitidine SPC criteria
Day 57	HI according to IWG 2006 and azacitidine SPC criteria
Day 64	HI according to IWG 2006 and azacitidine SPC criteria
Day 71	HI according to IWG 2006
Day 78	HI according to IWG 2006
Day 85	HI according to IWG 2006
Day 92	Bone marrow assessment

From weeks 14-25, platelets will be measured monthly in patients continuing azacitidine IWG 2006 criteria only should be applied.

- Platelet Response IWG Criteria

Dose	25 mg	50 mg	100 mg	200 mg	300 mg	Overall
Time point: Cycle 1, Week 1						
IWG Response						
No	1 (100.0)	3 (100.0)	4 (100.0)	2 (66.7)	12 (85.7)	22 (88.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (14.3)	3 (12.0)
Total	1 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	25 (100.0)
Time point: Cycle 1, Week 2						
IWG Response						
No	4 (100.0)	2 (66.7)	4 (100.0)	2 (66.7)	13 (92.9)	25 (89.3)
Yes	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (7.1)	3 (10.7)
Total	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	28 (100.0)

Time point: Cycle 1, Week 3						
IWG Response						
No	4 (100.0)	1 (33.3)	4 (100.0)	1 (33.3)	13 (92.9)	23 (82.1)
Yes	0 (0.0)	2 (66.7)	0 (0.0)	2 (66.7)	1 (7.1)	5 (17.9)
Total	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	28 (100.0)
Time point: Cycle 1, Week 4						
IWG Response						
No	3 (75.0)	2 (66.7)	4 (100.0)	2 (66.7)	12 (85.7)	23 (82.1)
Yes	1 (25.0)	1 (33.3)	0 (0.0)	1 (33.3)	2 (14.3)	5 (17.9)
Total	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	28 (100.0)
Time point: Cycle 1, Week 5						
IWG Response						
No	2 (66.7)	2 (66.7)	2 (50.0)	1 (33.3)	8 (57.1)	15 (55.6)
Yes	1 (33.3)	1 (33.3)	2 (50.0)	2 (66.7)	6 (42.9)	12 (44.4)
Total	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	27 (100.0)
Time point: Cycle 2, Week 1						
IWG Response						
No	2 (100.0)	1 (33.3)	2 (50.0)	2 (66.7)	6 (50.0)	13 (54.2)
Yes	0 (0.0)	2 (66.7)	2 (50.0)	1 (33.3)	6 (50.0)	11 (45.8)
Total	2 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	12 (100.0)	24 (100.0)
Time point: Cycle 2, Week 2						
IWG Response						
No	2 (100.0)	0 (0.0)	2 (50.0)	1 (50.0)	8 (66.7)	13 (56.5)
Yes	0 (0.0)	3 (100.0)	2 (50.0)	1 (50.0)	4 (33.3)	10 (43.5)
Total	2 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	12 (100.0)	23 (100.0)
Time point: Cycle 2, Week 3						
IWG Response						
No	1 (100.0)	1 (33.3)	2 (50.0)	1 (50.0)	7 (63.6)	12 (57.1)
Yes	0 (0.0)	2 (66.7)	2 (50.0)	1 (50.0)	4 (36.4)	9 (42.9)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Time point: Cycle 2, Week 4						
IWG Response						
No	1 (100.0)	0 (0.0)	1 (25.0)	1 (50.0)	7 (63.6)	10 (47.6)
Yes	0 (0.0)	3 (100.0)	3 (75.0)	1 (50.0)	4 (36.4)	11 (52.4)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Time point: Cycle 3, Week 1						
IWG Response						
No	1 (100.0)	0 (0.0)	1 (25.0)	1 (50.0)	5 (45.5)	8 (38.1)
Yes	0 (0.0)	3 (100.0)	3 (75.0)	1 (50.0)	6 (54.5)	13 (61.9)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Time point: Cycle 3, Week 2						
IWG Response						
No	1 (100.0)	0 (0.0)	1 (25.0)	1 (50.0)	6 (54.5)	9 (42.9)
Yes	0 (0.0)	3 (100.0)	3 (75.0)	1 (50.0)	5 (45.5)	12 (57.1)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Time point: Cycle 3, Week 3						
IWG Response						
No	1 (100.0)	1 (33.3)	1 (25.0)	1 (50.0)	7 (63.6)	11 (52.4)
Yes	0 (0.0)	2 (66.7)	3 (75.0)	1 (50.0)	4 (36.4)	10 (47.6)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)

Time point: Cycle 3, Week 4						
IWG Response						
No	1 (100.0)	1 (33.3)	2 (50.0)	1 (50.0)	6 (54.5)	11 (52.4)
Yes	0 (0.0)	2 (66.7)	2 (50.0)	1 (50.0)	5 (45.5)	10 (47.6)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Time point: Cycle 4						
IWG Response						
No	1 (100.0)	0 (0.0)	1 (33.3)	1 (50.0)	3 (25.0)	6 (28.6)
Yes	0 (0.0)	3 (100.0)	2 (66.7)	1 (50.0)	9 (75.0)	15 (71.4)
Total	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	12 (100.0)	21 (100.0)
Time point: Cycle 5						
IWG Response						
No	1 (100.0)	1 (33.3)	1 (33.3)	1 (50.0)	3 (27.3)	7 (35.0)
Yes	0 (0.0)	2 (66.7)	2 (66.7)	1 (50.0)	8 (72.7)	13 (65.0)
Total	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	11 (100.0)	20 (100.0)
Time point: Cycle 6						
IWG Response						
No	1 (100.0)	0 (0.0)	2 (66.7)	1 (50.0)	4 (44.4)	8 (44.4)
Yes	0 (0.0)	3 (100.0)	1 (33.3)	1 (50.0)	5 (55.6)	10 (55.6)
Total	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	9 (100.0)	18 (100.0)

- Platelet Response SPC Criteria

Dose	25 mg (5)	50 mg (3)	100 mg (4)	200 mg (4)	300 mg (15)	Overall (31)
Cycle 1						
No	3 (60.0)	0 (0.0)	1 (25.0)	1 (25.0)	4 (26.7)	9 (29.0)
Yes	2 (40.0)	3 (100.0)	3 (75.0)	3 (75.0)	11 (73.3)	22 (71.0)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Cycle 2						
No	5 (100.0)	0 (0.0)	1 (25.0)	2 (50.0)	8 (53.3)	16 (51.6)
Yes	0 (0.0)	3 (100.0)	3 (75.0)	2 (50.0)	7 (46.7)	15 (48.4)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)

Frequency and number of units of platelet transfusions during treatment (trigger for platelet transfusion is recommended as a platelet count below $10x10^9$/L and/or severe bleeding symptoms).

Summary of platelet transfusions given

Dose	**25 mg (62)**	**50 mg (9)**	**100 mg (80)**	**200 mg (8)**	**300 mg (177)**	**Overall (336)**
Product given (N (%))						
Red Cells	24 (38.7)	7 (77.8)	39 (48.8)	3 (37.5)	93 (52.5)	166 (49.4)
Platelets	38 (61.3)	2 (22.2)	41 (51.2)	5 (62.5)	84 (47.5)	170 (50.6)
Total	62 (100.0)	9 (100.0)	80 (100.0)	8 (100.0)	177 (100.0)	336 (100.0)
Number of platelets units given (N (%))						
1	36 (94.7)	1 (50.0)	41 (100.0)	5 (100.0)	78 (92.9)	161 (94.7)
2	2 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	6 (7.1)	9 (5.3)
Total	38 (100.0)	2 (100.0)	41 (100.0)	5 (100.0)	84 (100.0)	170 (100.0)
Number of platelets units given						
N	38	2	41	5	84	170
Mean (sd)	1.1 (0.2)	1.5 (0.7)	1.0 (0.0)	1.0 (0.0)	1.1 (0.3)	1.1 (0.2)
Range	1.0, 2.0	1.0, 2.0	1.0, 1.0	1.0, 1.0	1.0, 2.0	1.0, 2.0

Number of azacitidine treatment delays.

Dose	25	50	100	200	300	Overall
Cycle: Treatment Cycle 1						
Was the cycle delayed?						
No	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	12 (85.7)	26 (92.9)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (7.1)
Total	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	28 (100.0)
Cycle: Treatment Cycle 2						
Was the cycle delayed?						
No	2 (100.0)	2 (66.7)	3 (75.0)	3 (100.0)	11 (91.7)	21 (87.5)
Yes	0 (0.0)	1 (33.3)	1 (25.0)	0 (0.0)	1 (8.3)	3 (12.5)
Total	2 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	12 (100.0)	24 (100.0)
Cycle: Treatment Cycle 3						
Was the cycle delayed?						
No	1 (100.0)	2 (66.7)	4 (100.0)	2 (100.0)	10 (90.9)	19 (90.5)
Yes	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)	2 (9.5)
Total	1 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	21 (100.0)
Cycle: Treatment Cycle 4						
Was the cycle delayed?						
No	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	9 (90.0)	18 (94.7)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (5.3)
Total	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	10 (100.0)	19 (100.0)
Cycle: Treatment Cycle 5						
Was the cycle delayed?						
No	1 (100.0)	3 (100.0)	2 (66.7)	2 (100.0)	7 (77.8)	15 (83.3)
Yes	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	3 (16.7)
Total	1 (100.0)	3 (100.0)	3 (100.0)	2 (100.0)	9 (100.0)	18 (100.0)
Cycle: Treatment Cycle 6						
Was the cycle delayed?						
No	1 (100.0)	2 (100.0)	3 (100.0)	2 (100.0)	6 (75.0)	14 (87.5)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	2 (12.5)
Total	1 (100.0)	2 (100.0)	3 (100.0)	2 (100.0)	8 (100.0)	16 (100.0)

Azacitidne delays: Summary per patient

Dose	25 (4)	50 (3)	100 (4)	200 (3)	300 (14)	Overall (28)
Number of cycles delayed (per patient)						
0	4 (100.0)	1 (33.3)	3 (75.0)	3 (100.0)	8 (57.1)	19 (67.9)
1	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	3 (21.4)	5 (17.9)
2	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	3 (21.4)	4 (14.3)
Total	4 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	14 (100.0)	28 (100.0)
Number of cycles delayed (per patient)						
N	4	3	4	3	14	28
Median	0.0	1.0	0.0	0.0	0.0	0.0
IQR	0.0, 0.0	0.0, 1.0	0.0, 1.0	0.0, 0.0	0.0, 1.0	0.0, 1.0
Range	0.0, 0.0	0.0, 1.0	0.0, 2.0	0.0, 0.0	0.0, 2.0	0.0, 2.0

Length of azacitidine treatment delays:

Dose	25 mg (12)	50 mg (17)	100 mg (21)	200 mg (15)	300 mg (64)	Overall (129)
Average days until Cycle start						
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0, 0.0	0.0, 7.0	0.0, 0.0	0.0, 0.0	0.0, 22.0	0.0, 22.0
Breakdown of days until Cycle start						
0	12 (100.0)	15 (88.2)	21 (100.0)	15 (100.0)	56 (87.5)	119 (92.2)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.7)	3 (2.3)
7	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	1 (1.6)	3 (2.3)
9	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.8)
13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.8)
21	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.8)
22	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.8)
Total	12 (100.0)	17 (100.0)	21 (100.0)	15 (100.0)	64 (100.0)	129 (100.0)

Total is total number of AZA cycles given across the cohort

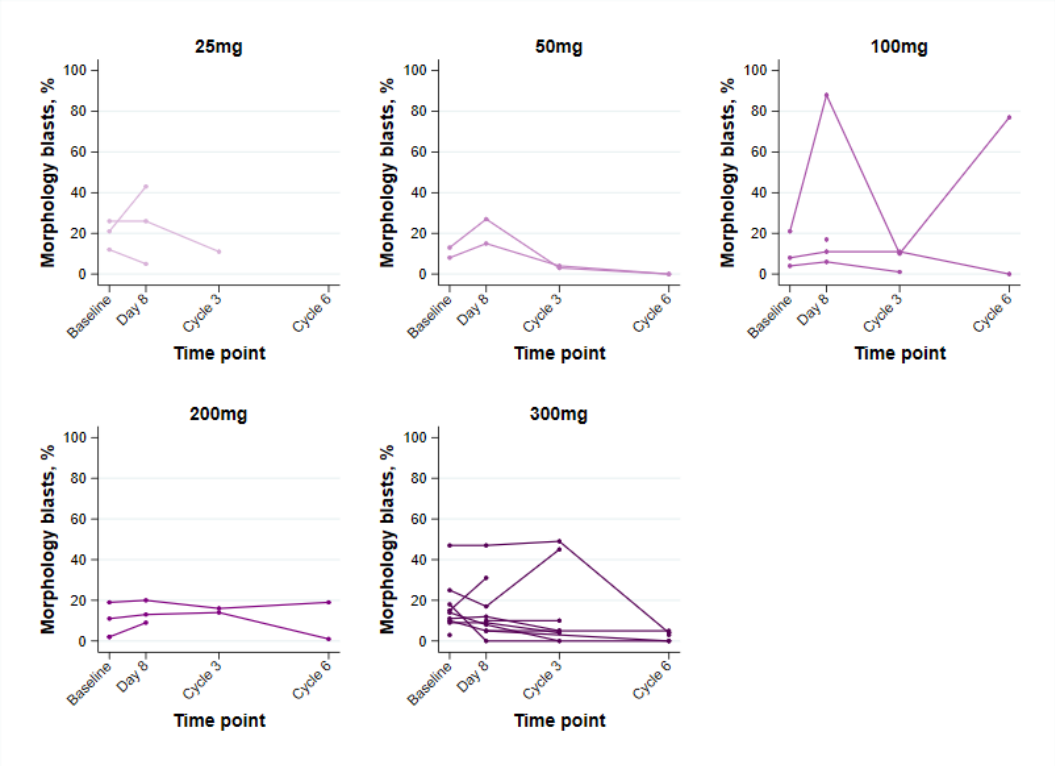
No patients had their azacitidine dose reduced from the 75mg prescribed, unless the dose was missed and missed doses have not been counted as dose reductions.

Incidence and severity of bleeding events during treatment, measured using the WHO Bleeding Scale.

Grade, events (patients, %)	25 mg	50 mg	100 mg	200 mg	300 mg	Overall
All cycles						
Any grade	4 (1; 20.0)	12 (2; 66.7)	14 (2; 50.0)	6 (2; 50.0)	12 (5; 33.3)	48 (12; 38.7)
Grade 0	2 (1; 20.0)	10 (2; 66.7)	9 (2; 50.0)	4 (1; 25.0)	8 (3; 20.0)	33 (9; 29.0)
Grade 1	2 (1; 20.0)	1 (1; 33.3)	3 (1; 25.0)	2 (1; 25.0)	1 (1; 6.7)	9 (5; 16.1)
Grade 2	0 (0; 0.0)	1 (1; 33.3)	1 (1; 25.0)	0 (0; 0.0)	2 (1; 6.7)	4 (3; 9.7)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	1 (1; 25.0)	0 (0; 0.0)	1 (1; 6.7)	2 (2; 6.5)
Cycle 1						
Any grade	1 (1; 20.0)	2 (2; 66.7)	3 (2; 50.0)	1 (1; 25.0)	6 (4; 26.7)	13 (10; 32.3)
Grade 0	0 (0; 0.0)	1 (1; 33.3)	1 (1; 25.0)	0 (0; 0.0)	3 (3; 20.0)	5 (5; 16.1)
Grade 1	1 (1; 20.0)	1 (1; 33.3)	1 (1; 25.0)	1 (1; 25.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 2	0 (0; 0.0)	0 (0; 0.0)	1 (1; 25.0)	0 (0; 0.0)	2 (1; 6.7)	3 (2; 6.5)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Cycle 2						
Any grade	1 (1; 20.0)	3 (2; 66.7)	2 (1; 25.0)	0 (0; 0.0)	1 (1; 6.7)	7 (5; 16.1)
Grade 0	1 (1; 20.0)	2 (2; 66.7)	1 (1; 25.0)	0 (0; 0.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 1	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 2	0 (0; 0.0)	1 (1; 33.3)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	1 (1; 3.2)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	1 (1; 25.0)	0 (0; 0.0)	0 (0; 0.0)	1 (1; 3.2)
Cycle 3						
Any grade	1 (1; 20.0)	2 (2; 66.7)	2 (2; 50.0)	5 (2; 50.0)	2 (2; 13.3)	12 (9; 29.0)
Grade 0	1 (1; 20.0)	2 (2; 66.7)	1 (1; 25.0)	4 (1; 25.0)	1 (1; 6.7)	9 (6; 19.4)
Grade 1	0 (0; 0.0)	0 (0; 0.0)	1 (1; 25.0)	1 (1; 25.0)	0 (0; 0.0)	2 (2; 6.5)
Grade 2	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	1 (1; 6.7)	1 (1; 3.2)
Cycle 4						
Any grade	1 (1; 20.0)	1 (1; 33.3)	2 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 0	0 (0; 0.0)	1 (1; 33.3)	2 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	4 (4; 12.9)
Grade 1	1 (1; 20.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	1 (1; 3.2)
Grade 2	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Cycle 5						
Any grade	0 (0; 0.0)	2 (2; 66.7)	3 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	6 (5; 16.1)
Grade 0	0 (0; 0.0)	2 (2; 66.7)	2 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 1	0 (0; 0.0)	0 (0; 0.0)	1 (1; 25.0)	0 (0; 0.0)	0 (0; 0.0)	1 (1; 3.2)
Grade 2	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Cycle 6						
Any grade	0 (0; 0.0)	2 (2; 66.7)	2 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 0	0 (0; 0.0)	2 (2; 66.7)	2 (2; 50.0)	0 (0; 0.0)	1 (1; 6.7)	5 (5; 16.1)
Grade 1	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 2	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)
Grade 3	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)	0 (0; 0.0)

Bone marrow blast percentage. Possible signs of antineoplastic effects after treatment will be measured via improvement in blood values and bone marrow blasts.

- Changes in blast percentage for each dose cohort of Eltrombopag



- Changes in bone marrow (BM) blast % from baseline, at day 8 (after 7 days single agent Eltrombopag), following cycles 3 and cycles 6 of Azacitidine

	Baseline (n=30)	day 8 (n=22)	Cycle 3 (n=16)	Cycle 6 (n=11)
BM blast %, median (range)	11 (2-47)	13 (0-88)	8 (0-49)	1 (0-77)

Activity of MDS treatment per IWG response criteria

Dose	25 mg (5)	50 mg (3)	100 mg (4)	200 mg (4)	300 mg (15)	Overall (31)
Disease response at Cycle 3						
Complete Remission (CR)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (13.3)	3 (9.7)
Marrow CR	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	2 (13.3)	4 (12.9)
Partial Remission (PR)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (13.3)	3 (9.7)
Stable disease	0 (0.0)	2 (66.7)	1 (25.0)	2 (50.0)	4 (26.7)	9 (29.0)
Disease progression	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (6.5)
Missing, no response assumed	4 (80.0)	0 (0.0)	0 (0.0)	2 (50.0)	4 (26.7)	10 (32.3)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Overall response at Cycle 3						
Non-responder	5 (100.0)	2 (66.7)	1 (25.0)	4 (100.0)	9 (60.0)	21 (67.7)
Responder (PR + marrow CR+ CR)	0 (0.0)	1 (33.3)	3 (75.0)	0 (0.0)	6 (40.0)	10 (32.3)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Disease response at Cycle 6						
Complete Remission (CR)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (13.3)	3 (9.7)
Marrow CR	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	3 (20.0)	4 (12.9)
Partial Remission (PR)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (6.7)	2 (6.5)
Stable disease	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	2 (13.3)	5 (16.1)
Disease progression	1 (20.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (6.5)
Missing, no response assumed	4 (80.0)	1 (33.3)	1 (25.0)	2 (50.0)	7 (46.7)	15 (48.4)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Overall response at Cycle 6						
Non-responder	5 (100.0)	1 (33.3)	3 (75.0)	4 (100.0)	9 (60.0)	22 (71.0)
Responder (PR + marrow CR+ CR)	0 (0.0)	2 (66.7)	1 (25.0)	0 (0.0)	6 (40.0)	9 (29.0)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Best disease response						
Complete Remission (CR)	0 (0.0)	1 (33.3)	1 (25.0)	0 (0.0)	3 (20.0)	5 (16.1)
Marrow CR	0 (0.0)	1 (33.3)	2 (50.0)	0 (0.0)	4 (26.7)	7 (22.6)
Stable disease	0 (0.0)	1 (33.3)	1 (25.0)	2 (50.0)	3 (20.0)	7 (22.6)
Disease progression	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (6.5)
Missing, no response assumed	4 (80.0)	0 (0.0)	0 (0.0)	2 (50.0)	4 (26.7)	10 (32.3)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)
Best overall response						
Non-responder	5 (100.0)	1 (33.3)	1 (25.0)	4 (100.0)	8 (53.3)	19 (61.3)
Responder (PR + marrow CR+ CR)	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	7 (46.7)	12 (38.7)
Total	5 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	15 (100.0)	31 (100.0)

ADVERSE EVENTS

Adverse Events

In total 421 adverse events were reported; 30 out of the 30 patients treated reported at least one adverse event. The following table lists all adverse events experienced by at least 2 patients, this equates to reporting all events which affected more than 5% of the patients treated.

Category	Toxicity	Affected	Exposed	Occurences	Percentage Affected
Blood and lymphatic system disorders	Anemia	8	30	23	26.7
	Febrile neutropenia	7	30	8	23.3
	Blood and lymphatic system disorders - Other, specify	6	30	7	20.0
Cardiac disorders	Chest pain - cardiac	3	30	3	10.0
	Cardiac disorders - Other, specify	2	30	3	6.7
Ear and labyrinth disorders	Vertigo	2	30	2	6.7
Gastrointestinal disorders	Constipation	16	30	19	53.3
	Diarrhea	15	30	26	50.0
	Nausea	15	30	18	50.0
	Vomiting	9	30	10	30.0
	Abdominal pain	6	30	7	20.0
	Gastrointestinal disorders - Other, specify	5	30	5	16.7
	Oral hemorrhage	2	30	2	6.7
General disorders and administration site conditions	Fatigue	14	30	16	46.7
	Injection site reaction	11	30	12	36.7
	Fever	9	30	10	30.0
	Edema limbs	5	30	5	16.7
	General disorders and administration site conditions - Other, specify	4	30	5	13.3
	Flu like symptoms	2	30	3	6.7
	Non-cardiac chest pain	2	30	2	6.7
	Pain	2	30	2	6.7
Immune system disorders	Allergic reaction	2	30	2	6.7
Infections and infestations	Lung infection	8	30	9	26.7
	Infections and infestations - Other, specify	5	30	7	16.7
	Sepsis	4	30	4	13.3
	Skin infection	3	30	3	10.0
	Lip infection	2	30	2	6.7
	Upper respiratory infection	2	30	2	6.7
	Wound infection	2	30	2	6.7
Injury, poisoning and procedural complications	Fall	5	30	5	16.7
	Bruising	3	30	3	10.0
Investigations	Neutrophil count decreased	7	30	38	23.3
	Platelet count decreased	5	30	13	16.7
	Alanine aminotransferase increased	2	30	4	6.7
	Blood bilirubin increased	2	30	6	6.7
Metabolism and nutrition disorders	Hypokalemia	3	30	4	10.0
	Anorexia	2	30	2	6.7
	Hypophosphatemia	2	30	5	6.7
Musculoskeletal and connective tissue disorders	Back pain	3	30	4	10.0
	Musculoskeletal and connective tissue disorder - Other, specify	3	30	4	10.0
	Arthralgia	2	30	2	6.7
Nervous system disorders	Dizziness	6	30	6	20.0
	Headache	4	30	6	13.3
	Lethargy	4	30	7	13.3
Psychiatric disorders	Confusion	4	30	4	13.3
	Insomnia	3	30	3	10.0
Renal and urinary disorders	Acute kidney injury	2	30	2	6.7
	Hematuria	2	30	2	6.7
Respiratory, thoracic and mediastinal disorders	Epistaxis	9	30	12	30.0
	Dyspnea	7	30	11	23.3
	Respiratory, thoracic and mediastinal disorders - Other, specify	4	30	4	13.3
	Cough	2	30	2	6.7
	Pleural effusion	2	30	2	6.7
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders - Other, specify	6	30	8	20.0
	Pruritus	5	30	6	16.7
	Rash maculo-papular	5	30	7	16.7
	Dry skin	2	30	2	6.7
	Purpura	2	30	2	6.7
	Skin hyperpigmentation	2	30	3	6.7
Vascular disorders	Hypotension	3	30	4	10.0

Serious Adverse Events

In total 25 patients reported at least one SAE, from these 25 patients a total of 51 SAE's were reported. Of the 31 patients that were registered, 15 patients died; 9 of these deaths were reported as resulting from adverse or serious adverse events. The toxicity listed in the following table is the toxicity which sites identified as the adverse event which prompted the SAE report.

Category	Toxicity	Occurences	Patients	Fatalities	Related occurences	Related fatalities
Blood and lymphatic system disorders	Febrile neutropenia	8	7	3	8	3
	Anemia	1	1	0	0	0
Cardiac disorders	Left ventricular systolic dysfunction	1	1	0	1	0
	Heart failure	1	1	1	0	0
	Myocardial infarction	1	1	1	1	1
Ear and labyrinth disorders	Middle ear inflammation	1	1	0	0	0
Gastrointestinal disorders	Gastric hemorrhage	2	1	0	0	0
	Diarrhea	1	1	0	1	0
General disorders and administration site conditions	Fever	7	5	0	5	0
	Non-cardiac chest pain	2	2	0	1	0
Immune system disorders	Immune system disorders - Other, specify	1	1	0	1	0
Infections and infestations	Sepsis	2	2	1	0	0
	Upper respiratory infection	2	2	0	2	0
	Infections and infestations - Other, specify	1	1	0	0	0
	Lung infection	1	1	1	0	0
	Skin infection	1	1	0	1	0
	Tooth infection	1	1	1	1	1
Investigations	Neutrophil count decreased	1	1	0	1	0
	Blood bilirubin increased	1	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	1	1	0	1	0
Nervous system disorders	Dizziness	1	1	0	0	0
	Movements involuntary	1	1	1	0	0
	Intracranial hemorrhage	1	1	1	1	1
Renal and urinary disorders	Hematuria	1	1	0	1	0
	Renal and urinary disorders - Other, specify	1	1	0	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	2	1	0	2	0
	Pleural effusion	1	1	0	1	0
Skin and subcutaneous tissue disorders	Rash maculo-papular	2	2	0	2	0
	Skin and subcutaneous tissue disorders - Other, specify	1	1	0	0	0
Vascular disorders	Hematoma	1	1	0	1	0
	Thromboembolic event	1	1	0	1	0
	Hypotension	1	1	0	0	0

MORE INFORMATION

Substantial Amendments

The following amendments and/or administrative changes were made to the ELASTIC protocol since the implementation of the first approved version:

Date of amendment	Protocol version number	Summary of amendment
09-Jun-2015	2.0	Update to eligibility criteria Update to definition of Dose Limiting Toxicity Update to schedule of events Update to trial personnel Update to registration phone number Clarification of allowed dose modifications Update to Adverse Event reporting Update to CRF list Update to response assessment reporting Update to archiving period Addition of Appendices 7 and 8 Minor corrections and clarifications
25-Apr-2016	3.0	Update to trial personnel Update to registration phone number Update to Trial Treatment details (Eltrombopag only) Update to definition of Dose Limiting Toxicity Update to Adverse Event reporting Clarification of Sample Collection Update to Data Collection Minor corrections and clarification
15- Aug- 2018	3.0a	Change in Data Protection Regulations (Notification)

CONCLUSIONS

ELASTIC examined the safety and tolerability of Eltrombopag in combination with Azacitidine in patients with Intermediate-2/high risk MDS, CMML-2 and AML with baseline platelets less than $150x10^9$/L. This was an important group to consider as Azacitidine monotherapy commonly results in grade 1-2 thrombocytopenia progressing to grade 3-4 [5,18] However, only two patients had platelets greater than 75 at baseline. The study was designed to show potential dose related toxicity and establish the MTD. No dose limiting toxicity was identified and the MTD was defined as 300mg daily of Eltrombopag. The majority of AEs were a consequence of infection and gastrointestinal disorder and would be expected in this patient population. There were four SUSARs potentially relatable to Eltrombopag: Sweet's syndrome, bone marrow fibrosis, haematuria and myocardial infaction. Sweet's syndrome has not been reported as an AE of Eltrombopag previously. Bone marrow fibrosis has been reported in ITP patients receiving Eltrombopag and has been shown to improve following discontinuation of the drug as was the case with our patient

[19]. The SUPPORT study showed a trend to worsening disease progression and AML transformation [20]. This was not something that we detected in the course of the study. A rise in bone marrow blasts was seen at day 8 compared with baseline but this resolved in subsequent cycles of treatment.

In terms of efficacy, the marrow responses rates were comparable to previously reported outcomes [5]. By formal IWG 2006 criteria, 29% of patients experienced a sustained 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 2 whilst more patients treated below the MTD did achieve such a response. In keeping with this, 70% of patients treated at the MTD, who were platelet transfusion independent at baseline, became transfusion dependent within 2 cycles of combination therapy. By comparison, only 29% of patients who were thrombocytopenic in the Aza-001 study received transfusions [5,18] Whilst ELASTIC was not designed or powered to make definitive statements about efficacy, this result mirrors the outcome of SUPPORT where only 16% of patients receiving combination treatment were transfusion independent in the first 4 cycles of treatment. During and after the cycle 3 wash-out, platelet responses in the MTD cohort improved. Although some of this may have been due to improvement in overall disease status as a result of treatment with Azacitidine, 7 patients had dose reductions/modifications in Eltrombopag to maintain a platelet count less than 250 $x10^9$/l in the latter part of the study indicating that the level of platelets was at least, in part, dependent on Eltrombopag.

Trough Eltrombopag levels at day 8 showed a clear dose response relationship with no plateau at the maximum dose of 300mg. There was no correlation between platelet count and Eltrombopag level. At the MTD, Eltrombopag levels peaked at cycle 2 but fell below baseline at cycle 3. This can be explained by the fact that, in some patients, doses were reduced or omitted during cycle 2. Eltrombopag levels were taken 19 days after the previous Azacitidine dose. Since the half-life of subcutaneous Azacitidine is only 1.6 hours [21], it's doubtful that this was due to an inhibitory interaction of Azacitidine on Eltrombopag. The finding of low thrombopoietin levels in intermediate-2/high risk MDS has been described before [22]. For individual patients, levels remained consistent during the course of the study and were not influenced by treatment with Eltrombopag or changes in platelet count.

The SUPPORT study of Eltrombopag/Azacitidine v Placebo/Azacitidine in MDS/AML patients with platelets <75 was terminated early on the grounds of futility and safety [20]. SUPPORT 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 [5,23,24]. The reasons for this unexpected result remain unknown; it is unclear if this is due to pharmacokinetic or pharmacodynamic changes as a consequence of interaction between Eltrombopag and Azacitidine. The authors of the SUPPORT study postulated an inhibitory action of Eltrombopag on Azacitidine. Another possibility might be inhibition between Eltrombopag and Tpo leading to reduced megakaryopoietic drive. However, we were unable to demonstrate any form of correlation between Eltrombopag and thrombopoietin levels and cannot advocate this as an explanation for poorer responses experienced by patients receiving Eltrombopag. We have not explored an alternative hypothesis that treatment with Eltrombopag may increase Azacitidine levels and lead to increased toxicity, including thrombocytopenia.

On the basis of our data we could have concluded that Eltrombopag and Azacitidine is a safe and tolerable combination. Notably, a similar conclusion was drawn from two other early phase studies of Azacitidine/Eltrombopag in MDS/AML [25,26]. However, we

are mindful that the Phase 3 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 with regard to platelet response chimes with the results from SUPPORT. Azacitidine based treatment in combination with other drugs such as Venetoclax is becoming a standard of care in older patients with AML [27] and is currently 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 these patients in future.

DISSEMINATION

Sternberg, A; Boucher, R; Coulthard, H.C; Raghavan, M; Culligan, D; Jackson, A; Cargo, C; Dennis, M; Metzner, M; Moore, R; Bowen, D; Vyas, P; (2020) "A Phase Ib Study of Eltrombopag and Azacitidine in Patients with High Risk Myelodysplastic Syndromes and Related Disorders: results from the Phase Ib UK Trials Acceleration Programme ELASTIC trial"; **ASH 2020 – 62th American Society of Hematology Annual Meeting and Exposition, 5-8 December 2020, poster**

A manuscript for Haematologica has been written and this will be submitted in Autumn 2021.

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