A randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for advanced solid tumors


North Mississippi Hematology & Oncology Associates LTD, Tupelo, MO, USA
ZOZ MSWiA z Warminsko-Mazurskim Centrum Onkologii, Olsztyn, Poland
Dnepropetrovsk State Medical Academy, Dnepropetrovsk, Ukraine
GlaxoSmithKline, Stockley Park West, UK

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Original article

A randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for advanced solid tumors

A. Kellum
North Mississippi Hematology & Oncology Associates LTD, Tupelo, MO, USA

A. Jagiello-Gruszfeld
202 MSWiA z Warminska-Mazurskim Centrum Onkologii, Olszyn, Poland

I.N. Bondarenko
Dnepropetrovsk State Medical Academy, Dnepropetrovsk, Ukraine

R. Patwardhan
C. Messam
Y. Mostafa Kamel
GlaxoSmithKline, Stockley Park West, UK

Address for correspondence:
Yasser Mostafa Kamel, MD, MSc, Director, Clinical Development, Oncology MDC, GlaxoSmithKline, Oncology MDC, Building 11, 1–3 Iron Bridge Rd, Uxbridge, Middlesex, Stockley Park West, UB11 1BT, UK.
Tel.: +44 (0)208 990 2740; Fax: +44 (0)208 990 2589; yasser.m.kamel@gsk.com

Key words:
Carboplatin – Chemotherapy – Eltrombopag – Paclitaxel – Solid tumors – Thrombocytopenia

Abstract

Objectives:
Eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist, has been shown to increase platelet counts in adults with chronic immune thrombocytopenia and chronic hepatitis C. This multicenter phase 2 study assessed the efficacy and safety of eltrombopag in patients receiving first-line carboplatin/paclitaxel for the treatment of advanced solid tumors.

Research design and methods:
Patients (N = 183) were randomized to placebo or eltrombopag 50 mg, 75 mg, or 100 mg given orally following chemotherapy on days 2 through 11 of each 21-day cycle, for at least two cycles. The primary endpoint was the difference in platelet count from day 1 in cycle 2 to the platelet nadir in cycle 2.

Clinical trial registry number:
NCT00102726.

Results:
Although the primary endpoint was not met, postnadir platelet counts increased during cycles 1 and 2 in all eltrombopag treatment groups compared with placebo. The most commonly reported adverse events across all study arms (including placebo) were nausea and alopecia and eltrombopag was generally well tolerated.

Conclusions:
This study provides preliminary information that eltrombopag does increase platelets in patients receiving chemotherapy for advanced solid tumors. Further investigation is needed to identify the optimal dose(s) and schedule of eltrombopag in patients receiving myelosuppressive chemotherapy.

Introduction

Chemotherapy-induced myelosuppression affects all three cell lineages in the bone marrow: platelets, leukocytes, and erythrocytes. However, both acute and cumulative thrombocytopenia remain important limiting factors in administering chemotherapy and maintaining dose intensity in some patients. The risk of hemorrhage secondary to decreased platelet counts can potentially increase morbidity or even mortality in patients undergoing cancer treatment.

Treatment for chemotherapy-induced thrombocytopenia (CIT) often results in dose reductions or delays. Platelet transfusions are also used as primary treatment, but subject to significant limitations. Eltrombopag is an oral, nonpeptide thrombopoietin receptor agonist that is approved in over forty countries.
including the United States and the European Union for the treatment of adult patients with chronic immune thrombocytopenia (ITP), who have not responded sufficiently to other ITP therapies or splenectomy. It is currently being developed for the treatment of thrombocytopenia of various etiologies. Eltrombopag interacts with the transmembrane domain of the thrombopoietin receptor and increases platelet counts by inducing proliferation of megakaryocytes from bone marrow progenitor cells. In vitro data show that eltrombopag does not prime platelets for activation or induce platelet aggregation, unlike recombinant thrombopoietin. Eltrombopag produces dose-dependent increases in platelet counts in healthy volunteers, patients with chronic ITP, and patients with chronic hepatitis C infection.

The present study was performed to assess the efficacy and safety of three different doses (50, 75, and 100 mg) of eltrombopag in treating CIT among patients with advanced solid tumors receiving multiple cycles of carboplatin/paclitaxel.

**Patients and methods**

**Study design**

A randomized, double-blind, multicenter phase 2 study of eltrombopag was performed in 87 centers in the United States, European Union, South America, and Asia (NCT00102726). The study was conducted from February 7, 2005, through February 28, 2007. Patients were randomized 1:1:1:1 to placebo or eltrombopag 50 mg, 75 mg, or 100 mg given orally on days 2 through 11 of each 21-day cycle of chemotherapy. To be included in the efficacy analysis, patients had to receive treatment for at least two cycles. Additional cycles (to a maximum of eight) of study medication were permitted if chemotherapy was continued, the patient appeared to benefit from the study drug, and the patient had not encountered greater than grade 2 toxicity associated with the study drug. Treatment was temporarily discontinued if platelet counts increased to ≥400,000/µL. Treatment was restarted at the initially randomized dose when platelet counts returned to <400,000/µL.

Intended chemotherapy consisted of carboplatin (area under the curve [AUC] 5–6 given intravenously over 15–30 minutes) and paclitaxel (175–225 mg/m² given intravenously over 3 hours) given on day 1 and repeated every 21 days. Routine premedications were given with each cycle of chemotherapy.

**Patient population**

Participants were adults age ≥18 years with advanced solid tumor(s) confirmed histologically or cytologically. At baseline, they were chemotherapy-naive but scheduled to receive carboplatin/paclitaxel. Additional inclusion criteria included: no history of platelet disorders or dysfunction, or bleeding disorders; ECOG performance status of ≤1; and adequate hematologic, hepatic, and renal function.

Key exclusion criteria included: known history of central nervous system (CNS) metastases, known clotting disorder associated with hypercoagulability, and history of drug-induced thrombocytopenia; surgery within 2 weeks and radiotherapy within 4 weeks of study entry; the use of aspirin, nonsteroidal anti-inflammatory drugs, or quinidine for more than three consecutive days during the 2 weeks prior to the study; and rosuvastatin or pravastatin within 1 week of the first dose of study medication. All of these medications were also prohibited during the study period.

**Study endpoints**

The primary study endpoint was a change in platelet count from day 1 in cycle 2 to the platelet nadir in cycle 2. During cycles 1 and 2, platelet counts were performed on day 1, the day of chemotherapy, as well as on days 2, 5, 8, 11, and 15, after chemotherapy was completed. During cycles 3 to 8, platelet counts were performed on days 1, 2, 8, and 15.

Other endpoints included change in platelet counts, chemotherapy dose intensity, and safety and tolerability profiles. Chemotherapy dose intensity was assessed by examining the percentage of patients who received the intended dose. Chemotherapy dose reductions and delays were performed at the treating physician's discretion.

Safety analysis included any subjects who received at least one dose of eltrombopag. Safety and tolerability profiles of eltrombopag were evaluated through physical examination, electrocardiogram (ECG), ophthalmologic examination, laboratory tests, and adverse event (AE) reporting. Thrombocytopenia necessitating rescue medication was considered treatment failure rather than an AE, and hospital admission attributable to such failure or related therapy did not qualify as an AE or serious adverse event (SAE). The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was used to assess all toxicities.

**Statistical methods**

The planned sample size was 164 patients, with 41 patients in each group. The study was powered at 90% to detect a difference of 83,000/µL from placebo in the primary endpoint.

An analysis of covariance model, using PROC MIXED procedure in SAS with treatment group and baseline (day 1 of cycle 1) platelet count as terms in the model, was used...
to determine whether there is an overall treatment effect in platelet counts. If established, the same model was used to assess the differences in platelet counts between each dose group and placebo. This difference, together with 95% confidence intervals (CI) and the associated P values are presented.

The intent-to-treat (ITT) population, consisted of all patients who were randomized and administered at least one dose of the study treatment in cycle 1 and for whom baseline and at least one on-therapy platelet count were available.

Results

Study population

One hundred and eighty-three patients were enrolled; and of these, 180 received at least one dose of eltrombopag or placebo (Figure 1). Baseline demographics are summarized in Table 1. One hundred and thirty-four patients (73%) completed two cycles of study medication. Fewer patients completed the second cycle in the 75 mg (67%) and 100 mg (67%) groups compared to 50 mg (82%) and placebo (76%), largely due to elevated platelet counts at the higher doses of eltrombopag (see Platelet counts section for details).

Treatment exposure

The median cumulative study medication (eltrombopag/placebo) doses were consistent with the doses given in each treatment arm. The median duration of exposure to study medication was 40 days in the placebo group, 40 days in the 50 mg group, 36 days in the 75 mg group, and 26 days in the 100 mg group. The median duration of exposure was decreased in the 75 mg and 100 mg groups primarily due to the number of subjects who temporarily interrupted the study medication dosing due to experiencing platelet counts >400,000/µL per protocol.

Eltrombopag did not affect exposure to chemotherapy in different groups. The mean dose of carboplatin (AUC) was 5.0 in the placebo group, 5.0 in the eltrombopag 50 mg group, 5.1 in the eltrombopag 75 mg group, and 4.9 in the eltrombopag 100 mg group. The mean doses of paclitaxel 46 allocated to eltrombopag 100 mg (safety population) 44 received (safety population) 45 in mITT population 45 allocated to placebo 46 received ≥1 dose 46 allocated to eltrombopag 50 mg 44 received ≥1 dose (safety population) 47 allocated to placebo 46 received ≥1 dose (safety population) 45 in mITT population 45 allocated to eltrombopag 50 mg 44 received ≥1 dose (safety population) 45 allocated to eltrombopag 75 mg 44 received ≥1 dose (safety population) 46 allocated to eltrombopag 100 mg 46 received ≥1 dose (safety population) 45 allocated to placebo 46 received at least one dose (safety population) 45 in mITT population 45 allocated to placebo 46 received ≥1 dose (safety population) 45 in mITT population

Figure 1. CONSORT flow diagram.

AE, adverse event; mITT, modified intent-to-treat.

aThe mITT population comprises all subjects who received at least one dose of study treatment in cycle 1 and had both baseline and at least one on-therapy platelet count.
in the four treatment groups were 183.7, 183.0, 182.5, and 183.3 mg/m², respectively.

**Platelet counts**

The study did not meet the primary endpoint of reducing the change in platelet count during cycle 2 (from day 1 to nadir), compared with placebo. Eltrombopag doses given after chemotherapy did not significantly reduce the platelet nadir in the second cycle compared with placebo. However, after platelet nadir was reached between day 8 and day 11 in all groups, patients treated with eltrombopag experienced increases in platelet counts that peaked between day 15 and day 18, whereas platelet counts in the placebo group did not show such an increase (Figure 2A). As a result, patients in all three eltrombopag treatment groups had higher platelet counts on day 1 of cycles 2 and 3 than did patients in the placebo group (Table 2).

Similar to cycle 2, cycle 1 mean platelet counts increased rapidly in the eltrombopag treatment groups but did not rise in the placebo group (Figure 2B). None of the patients in any treatment group required rescue medication, including platelet transfusion, for the treatment of thrombocytopenia.

Platelet counts exceeding 400,000/μL were observed in all treatment groups at an incidence of 7% with placebo, 5% with eltrombopag 50 mg, 9% with eltrombopag 75 mg, and 13% with eltrombopag 100 mg. More patients treated with eltrombopag had platelet counts >600,000/μL on at least one occasion including eight patients in the 50 mg group, 11 in the 75 mg group, and 18 in the 100 mg group, compared with only one in the placebo group.

**Safety and tolerability**

Eighty-seven percent of participants experienced at least one AE (Table 3) and the rates of these AEs were not significantly different across treatment groups (Table 4). Grade 3/4 AEs occurred in 53% of the placebo group, 30% of the eltrombopag 50 mg group, 48% of the eltrombopag 75 mg group, and 48% of the eltrombopag 100 mg group. The overall incidence of AEs decreased with each cycle in all treatment groups.

Thiry patients experienced SAEs; 28 on-therapy, two post-therapy. Of these SAEs, 10 events were reported as related to study medication and were distributed across the placebo and eltrombopag groups. Fatal events were also reported during the study (Table 4): cardiorespiratory arrest, disease progression, and embolism in the placebo group; hemoptysis in the eltrombopag 50 mg group and acute renal failure, cardiorespiratory arrest, and chronic obstructive pulmonary disorder (COPD) in the eltrombopag 75 mg group; and cardiac arrest, ischemic stroke, and CNS metastases in the eltrombopag 100 mg group. Only cardiorespiratory arrest in the placebo group and COPD in the eltrombopag 75 mg group were considered related to study medication (Table 4).

AEs leading to withdrawal occurred in 17% of the placebo group, 7% of the eltrombopag 50 mg group, 18% of the eltrombopag 75 mg group, and 28% of the eltrombopag 100 mg group (Table 4). Two patients in the eltrombopag 100 mg group experienced cardiac arrest, which was the
only nonhematological AE leading to withdrawal. Neither event was deemed related to study medication. A number of AEs of special interest were closely analyzed (Table 3). These included hepatobiliary, renal, cardiac, ocular, thromboembolic, and bleeding events.

Frequencies of elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) \(\geq 3\times\) upper limit of normal (ULN) and total bilirubin \(\geq 1.5 \times\) ULN were 11% and 18% in the 50 mg, 17% and 14% in the 75 mg, and 13% and 23% in the 100 mg groups, compared

**Figure 2.** A. Mean (±standard error) platelet counts during cycle 2 (primary endpoint). B. Mean (±standard error) platelet counts during cycle 1 (secondary endpoint).
Table 3. Incidence of individual adverse events.

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo, n = 46</th>
<th>Eltrombopag 50 mg, n = 44</th>
<th>Eltrombopag 75 mg, n = 44</th>
<th>Eltrombopag 100 mg, n = 46</th>
<th>Total, N = 180</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occurring in ≥5% of Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>39 (85)</td>
<td>39 (86)</td>
<td>38 (86)</td>
<td>42 (91)</td>
<td>157 (87)</td>
</tr>
<tr>
<td>Hematologic AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17 (37)</td>
<td>8 (18)</td>
<td>12 (27)</td>
<td>13 (28)</td>
<td>50 (28)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (24)</td>
<td>6 (14)</td>
<td>10 (23)</td>
<td>8 (17)</td>
<td>35 (19)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (15)</td>
<td>9 (20)</td>
<td>5 (11)</td>
<td>4 (9)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Nonhematologic AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (41)</td>
<td>18 (41)</td>
<td>14 (32)</td>
<td>13 (28)</td>
<td>64 (36)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10 (22)</td>
<td>19 (43)</td>
<td>8 (18)</td>
<td>12 (26)</td>
<td>49 (27)</td>
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<tr>
<td>Vomiting</td>
<td>9 (20)</td>
<td>5 (11)</td>
<td>4 (9)</td>
<td>11 (24)</td>
<td>29 (16)</td>
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<tr>
<td>Fatigue</td>
<td>8 (17)</td>
<td>7 (16)</td>
<td>8 (18)</td>
<td>5 (11)</td>
<td>28 (16)</td>
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<tr>
<td>Arthralgia</td>
<td>3 (7)</td>
<td>10 (23)</td>
<td>4 (9)</td>
<td>5 (11)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (9)</td>
<td>5 (11)</td>
<td>6 (14)</td>
<td>4 (9)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (9)</td>
<td>7 (16)</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td>17 (9)</td>
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<tr>
<td>Pain in extremity</td>
<td>7 (15)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (7)</td>
<td>6 (14)</td>
<td>2 (5)</td>
<td>3 (7)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (7)</td>
<td>6 (14)</td>
<td>1 (2)</td>
<td>4 (9)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (4)</td>
<td>5 (11)</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (11)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>4 (9)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (7)</td>
<td>5 (11)</td>
<td>2 (5)</td>
<td>2 (4)</td>
<td>12 (7)</td>
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<tr>
<td>Peripheral sensory neuropathy</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>5 (11)</td>
<td>11 (6)</td>
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<tr>
<td>Cough</td>
<td>3 (7)</td>
<td>5 (11)</td>
<td>0</td>
<td>2 (4)</td>
<td>10 (6)</td>
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<tr>
<td>Bone pain</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>3 (7)</td>
<td>9 (5)</td>
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<tr>
<td><strong>AEs of Special Interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hepatobiliary abnormalities</td>
<td>8 (17)</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>4 (9)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Renal events</td>
<td>5 (11)</td>
<td>4 (9)</td>
<td>4 (9)</td>
<td>3 (7)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;26.5 μmol/L</td>
<td>1 (2)</td>
<td>6 (5)</td>
<td>7 (4)</td>
<td></td>
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<tr>
<td>Cardiovascular events</td>
<td>7 (15)</td>
<td>7 (16)</td>
<td>4 (9)</td>
<td>9 (20)</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3 (7)</td>
<td>0</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td></td>
</tr>
<tr>
<td>Ocular events</td>
<td>0</td>
<td>4 (9)</td>
<td>2 (5)</td>
<td>2 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>6 (13)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td>4 (9)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event.
with placebo (22% and 17%). Most of these elevations decreased or normalized by the last assessment, despite the fact that almost all patients continued on both chemotherapy and eltrombopag or placebo. One patient (2%) receiving placebo was withdrawn from the study because of ALT elevation.

None of the renal events led to treatment withdrawal, and all but two events (grade 2 cystitis in the placebo group and grade 3 hyponatremia in the 75 mg group) resolved during treatment. Frequencies of renal events were not related to dose of study medication (Table 3); renal events occurred in 11% of the placebo group, 9% in each of the eltrombopag 50 mg and 75 mg groups, and 7% of the eltrombopag 100 mg group.

Cardiovascular events occurred in 15% of patients but none of these events were considered treatment-related by investigators (Table 3). Analysis of the cardiac events revealed that underlying medical conditions were likely to have played a contributory role.

Ocular events were experienced by 9% of patients at 50 mg, 5% at 75 mg, and 4% at 100 mg, in the eltrombopag groups; none were reported in the placebo group. However, a blinded review of ophthalmologic findings by a clinical events committee comprising three external ophthalmologists concluded that there was no evidence of ocular toxicity associated with eltrombopag.

Thromboembolic events were experienced during the study by 7% of patients in the placebo group, 5% in each of the eltrombopag 50 mg and 75 mg groups, and 13% in the eltrombopag 100 mg group. No post-therapy thromboembolic events were recorded at the follow-up assessment 30 days after the last dose of study medication. Most thromboembolic events (69%) occurred when proximal platelet counts were in the normal range. Patients who experienced thromboembolic events had a number of risk factors for such events including current or past history of smoking, diabetes mellitus, hypertension, peripheral vascular disease, coronary artery disease, stroke, and/or myocardial infarction.

Bleeding events occurred in 9% of patients in the placebo group, 9% in the eltrombopag 50 mg group, 2% in the eltrombopag 75 mg group, and 7% in the eltrombopag 100 mg group. Most bleeding events were grade 1. None occurred in patients with thrombocytopenia.

Discussion

Although the present study failed to meet the primary endpoint (a difference in change in platelet count from day 1 of cycle 2 to the nadir of cycle 2 in eltrombopag-treated patients compared with placebo-treated patients), there were several limitations to the study design, including the choice of the carboplatin/paclitaxel regimen, the tested schedule of administration, and possibly the dose of eltrombopag.

Carboplatin/paclitaxel is the most commonly used chemotherapy regimen and was chosen to facilitate comparison of the safety of eltrombopag versus placebo due to ease of administration and low toxicity. Generally, studies have shown that the CIT observed during the carboplatin/paclitaxel regimen is not profound, and in fact, may have a platelet-sparing effect. In this study, platelet counts largely remained above 200,000/μL even in the placebo group.

Pharmacokinetics analysis in this study demonstrated that the eltrombopag coadministered with carboplatin/paclitaxel are similar to that observed in previous studies with healthy subjects, suggesting no clinically important interaction in this setting. In vitro studies have demonstrated that CYP1A2 and CYP2C8 are the major CYP enzymes involved in the oxidative metabolism of eltrombopag. In addition, UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag. Carboplatin and paclitaxel are not significant inhibitors of these enzymes. Although paclitaxel is a substrate and in vitro inhibitor of CYP2C8, the low potency of inhibition compared to other CYP2C8 inhibitors, and lack of clinical pharmacokinetic interactions with paclitaxel, suggest clinically relevant interactions mediated via CYP2C8 are unlikely. Pharmacokinetic interactions mediated by paclitaxel primarily involve inhibition of P-gp (for which eltrombopag is not a substrate), and are likely to be related to the paclitaxel vehicle, Cremophor EL.

In the current study, eltrombopag was given following chemotherapy. However, there is evidence from a preclinical rhesus monkey model with pegylated recombinant human megakaryocyte growth and development factor (PEG-MGDF) that administering a thrombopoietic agent before chemotherapy as well as afterward may enhance its effects on platelet nadir and platelet recovery. This was also observed in patients with sarcoma.

Table 4. Overall incidence of adverse events across eight cycles of treatment.

<table>
<thead>
<tr>
<th>Characteristic, AE category</th>
<th>Placebo n = 46</th>
<th>E Italian</th>
<th>E Italian 50 mg</th>
<th>E Italian 75 mg</th>
<th>E Italian 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>39 (85)</td>
<td>38 (86)</td>
<td>38 (86)</td>
<td>42 (91)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>15 (33)</td>
<td>6 (18)</td>
<td>13 (30)</td>
<td>16 (35)</td>
<td></td>
</tr>
<tr>
<td>AE that led to withdrawal</td>
<td>8 (17)</td>
<td>3 (7)</td>
<td>8 (18)</td>
<td>13 (28)</td>
<td></td>
</tr>
<tr>
<td>Post-treatment AE</td>
<td>4 (9)</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event.

*Four out of 13 patients withdrew due to thrombocytosis.
who received recombinant thrombopoietin before and after doxorubicin-ifosfamide and from a phase 1/2 study in patients treated with romiplostim 10 μg/kg before and after chemotherapy.18

The aforementioned studies demonstrate the importance of dosing thrombopoietic agents before and after chemotherapy. Future studies of eltrombopag in CIT will investigate this dosing schedule.

Although the study failed to meet its primary endpoint, the mean platelet count for eltrombopag-treated patients remained higher and increased more rapidly than in the placebo group. Likewise, post nadir platelet counts increased during both cycles 1 and 2 in all eltrombopag-treatment groups compared with placebo, resulting in higher platelet counts at the start of the next cycles.

Oral eltrombopag was also generally well tolerated at the three doses tested when given after carboplatin/paclitaxel in patients in this study. Clinical laboratory values, vital signs, ECGs, and cataract evaluations were not associated with safety signals, and the infrequent abnormalities as reported were not clinically significant. Most of the observed AEs were associated with underlying malignant disease, medical conditions, or exposure to carboplatin/paclitaxel.

Conclusions
Further investigation is needed to determine the optimal dosing regimen for eltrombopag with chemotherapeutic regimens known to be associated with thrombocytopenia. Ongoing and planned trials will determine the dose and schedule of eltrombopag that is most effective and provide additional data regarding the safety of eltrombopag in the CIT population.

Transparency
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Declaration of financial/other relationships
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