ORIGINAL ARTICLE

Romiplostim versus Placebo for Chemotherapy-Induced Thrombocytopenia

Hanny Al-Samkari, M.D.,[1] César Muñoz, M.D.,[2-4] Çağlayan Geredeli, M.D.,[5,6] Ippokratis Korantzis, M.D., Ph.D.,[7] Beatriz González Astorga, M.D.,[8] Cagatay Arslan, M.D.,[9] Johnny Francisco Cordeiro Camargo, M.D.,[10] Florian Scotté, M.D., Ph.D.,[11] Giuliano Borges, M.D.,[12] Kejia Wang, Ph.D.,[13] Melissa Eisen, M.D.,[14] David J. Kuter, M.D., D.Phil.,[1] and Gerald A. Soff, M.D.[15]

ABSTRACT

BACKGROUND

Chemotherapy-induced thrombocytopenia (CIT) is a common complication of chemotherapy that is associated with bleeding, reduced relative dose intensity, and potentially worse outcomes. No widely available therapies are approved for CIT.

METHODS

We conducted a phase 3, international, double-blind, randomized, placebo-controlled trial involving patients with persistent CIT (platelet count, $\leq 85\times10^9$ per liter on trial day 1) who were receiving oxaliplatin-based multiagent cytotoxic chemotherapy for gastrointestinal cancers. Patients were randomly assigned in a 2:1 ratio to receive romiplostim or placebo for three chemotherapy cycles. The primary end point was the absence of CIT-induced modifications of the chemotherapy dose (reduction, delay, omission, or discontinuation) in both the second and third chemotherapy cycles.

RESULTS

Of the 165 patients who underwent randomization (109 in the romiplostim group and 56 in the placebo group), 75% had colorectal cancer, 13% had gastroesophageal cancer, and 12% had pancreatic cancer; 72% of the patients in the romiplostim group and 61% of those in the placebo group had stage 4 disease. The percentage of patients with no CIT-induced modifications of the chemotherapy dose was 84% (92 of 109 patients) with romiplostim and 36% (20 of 56 patients) with placebo, which corresponded to an odds ratio of 10.16 (95% confidence interval [CI], 4.44 to 23.72; P<0.001) and a risk ratio of 2.77 (95% CI, 1.78 to 4.30; P<0.001). Adverse events of grade 3 or higher occurred in 37% of the patients who received romiplostim and in 22% of those who received placebo, which primarily reflected chemotherapy effects. Adverse events that were considered by the investigator to be related to romiplostim or placebo occurred in 12% of patients who received romiplostim and in 7% who received placebo, with the most frequent being nausea (2% in each group) and headache (2% in the romiplostim group); none were serious or led to death or discontinuation of romiplostim, placebo, or chemotherapy. Thromboembolic events occurred in 2% of patients who received romiplostim and in no patients who received placebo.

CONCLUSIONS

In this phase 3, placebo-controlled trial, romiplostim was efficacious in treating CIT. (Funded by Amgen and the Biomedical Advanced Research and Development Authority; RECITE ClinicalTrials.gov number, NCT03362177.)

Author affiliations are listed at the end of the article. Hanny Al-Samkari can be contacted at hal-samkari@mgh.harvard.edu or at the Division of Classical Hematology, Mass General Brigham Cancer Institute, Bartlett Hall Extension Office 133, 55 Fruit St., Boston, MA 02114.

N Engl J Med 2026;394:1061-73.
DOI: 10.1056/NEJMoa2511882

CME

A Quick Take is available at NEJM.org

Chemotherapy-induced thrombocytopenia (CIT) is a common and challenging complication of myelosuppressive chemotherapy and is associated with an increased risk of bleeding.[1-5] The prevalence of CIT after the initiation of chemotherapy among patients with colorectal cancer is 62% overall and 32% with platinum-based regimens.[4] The incidence of CIT in the 3 months after chemotherapy initiation is 13.5% among patients with colorectal cancer and 12.9% among those with pancreatic cancer.[2] Persistent CIT is typically defined as a platelet count of less than 100×10^9 per liter at chemotherapy cycle completion or day 1 of the following cycle despite sufficient time to recover from the nadir in the previous cycle.[5]

CIT is often managed by reducing chemotherapy doses, delaying treatment cycles, or omitting or discontinuing therapy altogether. This approach lowers chemotherapy relative dose intensity and may hinder the delivery of full-dose, on-time chemotherapy, thereby compromising treatment outcomes in the context of adjuvant therapy or advanced disease.[4-11] No widely available agents are approved for CIT, and platelet transfusions have limited availability and transient benefits and increase the risk of infection.[12]

A clinical benefit for patients with CIT has been observed with the thrombopoietin-receptor agonist romiplostim,[13-15] a subcutaneously administered peptibody that binds and activates c-MPL, the thrombopoietin receptor.[16] In a phase 2 randomized trial involving patients with persistent CIT, romiplostim increased platelet counts to more than 100×10^9 per liter (93% of patients with romiplostim vs. 12% with observation), allowing 85% of patients to resume chemotherapy, with only 7% of patients who received romiplostim having subsequent chemotherapy dose reduction or delay from recurrent CIT.[13] Patients receiving at least 1 year of romiplostim had ongoing benefit.[14] A large observational study also showed that most patients receiving romiplostim who had persistent CIT resumed chemotherapy, with 71% having a platelet response, 79% avoiding chemotherapy dose reductions or delays, 89% avoiding platelet transfusions, and a bleeding rate lower than that in historical controls.[15] The incidence of thromboembolic events was not increased in either study, and no evidence of adverse bone marrow changes or secondary hematologic cancers was seen.[13-15]

To date, no phase 3 trials have assessed romiplostim for CIT, and previous randomized trials of other thrombopoietin-receptor agonists in patients with CIT did not show a benefit with respect to the primary end points.[17,18] We now report results from RECITE, a phase 3, international, randomized, placebo-controlled trial evaluating the efficacy and safety of romiplostim to treat CIT in patients with gastrointestinal cancers treated with oxaliplatin-based multiagent cytotoxic chemotherapy.

METHODS

TRIAL OVERVIEW AND PATIENTS

This phase 3, international, double-blind, randomized, placebo-controlled trial enrolled patients receiving oxaliplatin-based multiagent cytotoxic chemotherapy for colorectal, gastroesophageal, or pancreatic cancer at any stage or line in the context of adjuvant therapy or advanced disease with persistent CIT (platelet count, $\leq85\times10^9$ per liter on trial day 1, despite time to recover from the nadir in the previous cycle [i.e., ≥14 days from the start of the chemotherapy cycle immediately before trial day 1 for 5-fluorouracil, leucovorin, and oxaliplatin {FOLFOX} or 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin {FOLFIRINOX or FOLFOXIRI} or ≥21 days for capecitabine and oxaliplatin {CAPOX}], so as to rule out spontaneously resolving nadir thrombocytopenia) and at least three additional planned chemotherapy cycles. Details of the trial design are provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Among the key exclusion criteria were thrombocytopenia from other causes, a hemoglobin level of less than 8 g per deciliter or an absolute neutrophil count of less than 1×10^9 per liter on trial day 1, past or current hematologic cancer, past arterial thrombosis, and cardiac or cardiovascular abnormalities in the past 4 months. Full inclusion and exclusion criteria are provided in the trial protocol, available at NEJM.org.

Patients received romiplostim or placebo weekly from trial day 1 through reinitiation of chemotherapy and then for up to three additional chemotherapy cycles. When patients received chemotherapy at a trial visit, romiplostim or placebo was administered immediately after chemotherapy or before or during infusions (for 5-fluorouracil).

TRIAL OVERSIGHT

The trial protocol and amendments were approved by the institutional review boards or ethics committees at 55 sites in 14 countries (Table S1). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The main sponsor, Amgen, designed, conducted, and funded this trial and was involved in data collection, analysis, and interpretation and contributed to writing the manuscript and making the decision to submit it for publication. Additional funding was provided by the Biomedical Advanced Research and Development Authority (BARDA). The authors had access to the data and vouch for its accuracy and completeness and for the adherence of the trial to the protocol. Written informed consent was obtained from all the patients before trial-specific screening.

TRIAL PROCEDURES

Eligible patients underwent randomization with the use of an interactive voice-response system in a 2:1 ratio to receive romiplostim or placebo, with stratification according to baseline platelet count ($<50\times10^9$ per liter vs. $\geq50\times10^9$ per liter) and cancer type. The patients and site and sponsor staff were unaware of the trial-group assignments; unblinding occurred if it was essential for clinical management.

Weekly subcutaneous doses of romiplostim or placebo, prepared from identical vials with white powder, were adjusted to maintain platelet counts of 100 to 250×10^9 per liter (Table S2). When patients started receiving romiplostim or placebo, they were not receiving chemotherapy because it was delayed owing to CIT.

When platelet counts were at least 100×10^9 per liter (or $<100\times10^9$ per liter after week 4 of receipt of romiplostim or placebo but the platelet count was considered to be safe to proceed by the investigator), chemotherapy was restarted at the same regimen and doses as received in the cycle administered before trial enrollment. After 12 weeks, patients who did not have a platelet count of at least 100×10^9 per liter or a platelet count considered to be safe to proceed were deemed to have not had a response, stopped romiplostim or placebo, and entered follow-up.

Because oxaliplatin-based chemotherapy cycles are 2 to 3 weeks each and up to 12 weeks was allowed before proceeding with chemotherapy, most patients received per-protocol therapy (chemotherapy and romiplostim or placebo) for 7 to 21 weeks. Chemotherapy regimens contained 5-fluorouracil or capecitabine and oxaliplatin, with or without irinotecan (FOLFOX, CAPOX, FOLFIRINOX, or FOLFOXIRI). Concurrent use of antiangiogenic or epidermal growth factor receptor–targeted agents was permitted. The enrollment period was from September 30, 2019, to October 24, 2023; the primary analysis date was January 25, 2024; and the last trial visit was January 9, 2025.

Follow-up visits occurred 1 week and 30 days after the last dose of romiplostim or placebo and 30 days after chemotherapy ended. Patients remained in long-term follow-up, with follow-up visits every 12 weeks until the last patient completed the follow-up visit 1 year after the last dose of romiplostim or placebo.

PRIMARY AND SECONDARY END POINTS

The primary end point was no dose modifications (reduction, delay, omission, or discontinuation) of any myelosuppressive agent due to CIT in both the second and third planned chemotherapy cycles, with CIT defined as a platelet count of less than 100×10^9 per liter owing to chemotherapy as assessed by blinded independent central review (three medical oncologists). Patients who did not complete chemotherapy, either owing to discontinuation or death, were considered to have a chemotherapy dose modification. All chemotherapy dose modifications underwent adjudication; in cases of discordance between the investigator and the adjudication committee, dose modification due to thrombocytopenia was classified according to the assessment of the adjudication committee.

The key secondary end points, listed in hierarchical testing order, were the platelet nadir from the start of the first chemotherapy cycle during the trial through the end of the treatment period, with the use of all available platelet values for each patient (including those with abbreviated follow-up); the time to platelet response (platelet count of $\geq100\times10^9$ per liter and no platelet transfusions during the previous 7 days) during the treatment period; the duration-adjusted rate of bleeding events of grade 2 or higher according to the Common Terminology Criteria for Adverse Events, version 5.0, measured

from trial day 1 to 30 days after the last dose of romiplostim or placebo or the end of the trial, whichever occurred first; overall survival from trial day 1 to death, with data from patients being censored at the last contact date; platelet transfusion during the treatment period; and platelet response from day 1 to week 4. Secondary safety end points included adverse events through the follow-up visits at 30 days after the last dose of romiplostim or placebo and 30 days after chemotherapy ended, laboratory changes, antiromiplostim or antithrombopoietin antibodies, and myelodysplastic syndromes or secondary cancers through long-term follow-up.

STATISTICAL ANALYSIS

The overall two-sided type I error rate was set at 5%. A hierarchical testing strategy was implemented to control for type I error across multiple tests of the primary and key secondary end points. Specifically, the primary and key secondary end points were tested in a prespecified order. Formal statistical testing of a subsequent end point was performed only if statistical significance was achieved for the preceding end point.

With 162 patients randomly assigned in a 2:1 ratio to receive romiplostim or placebo, we calculated that the trial would have 93% power for the primary end point, under the assumption of an incidence of no thrombocytopenia-induced dose modification of 52.8% for the romiplostim group and 23.7% for the placebo group in cycles 2 and 3.[13,19,20] Treatment effect was analyzed with a two-sided Cochran–Mantel–Haenszel test with adjustment for baseline stratification factors. Patients with missing platelet counts were imputed as having thrombocytopenia-induced dose modification. Testing methods for secondary end points included linear regression models (platelet nadir), stratified Cox regression models (time to response), and Andersen–Gill models (grade ≥2 bleeding). Statistical analyses were performed with SAS software, version 9.4 (SAS Institute). An independent data monitoring committee conducted safety reviews and futility analyses. In post hoc analyses over all three cycles, relative dose intensity was defined as actual dose intensity (actual dose received ÷ actual dose duration) divided by planned dose intensity (planned dose ÷ planned dose duration).

RESULTS

PATIENT CHARACTERISTICS

The 165 enrolled patients (109 in the romiplostim group and 56 in the placebo group) were from 14 countries. The median age was 63 years; 90% were White, 4% Black, and 24% Hispanic (Table 1). The representativeness of the trial population is shown in Table S3. The median platelet count at baseline was 69×10^9 per liter; 11% had a baseline platelet count of less than 50×10^9 per liter. Most patients had colorectal cancer (75%) (Table 1 and Table S4), less than two previous chemotherapy lines (73%), and more than two previous chemotherapy cycles (84%). More patients receiving romiplostim than those

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Romiplostim (N=109)	Placebo (N=56)
Male sex — no. (%)	63 (58)	36 (64)
Median age (range) — yr	64 (34–84)	62 (35–81)
Race — no. (%)†		
White	95 (87)	54 (96)
Black	4 (4)	2 (4)
Other‡	10 (9)	0
Hispanic ethnic group — no. (%)†	28 (26)	11 (20)
Platelet count		
Median (range) — $\times10^{-9}$/liter	70 (16–85)	67 (8–84)
Distribution — no. (%)		
<50×10^9/liter	12 (11)	6 (11)
≥50×10^9/liter	97 (89)	50 (89)

Table 1. (Continued.)

Characteristic	Romiplostim (N = 109)	Placebo (N = 56)
Previous bleeding — no. (%)	6 (6)	3 (5)
Tumor type — no. (%)		
Colorectal	82 (75)	42 (75)
Gastroesophageal	14 (13)	7 (12)
Pancreatic	13 (12)	7 (12)
Disease stage — no. (%)		
1	1 (1)	0
2	4 (4)	4 (7)
3	23 (21)	14 (25)
4	78 (72)	34 (61)
Recurrent	2 (2)	4 (7)
Missing data	1 (1)	0
Chemotherapy regimen — no. (%)§		
FOLFOX	70 (64)	34 (61)
CAPOX	21 (19)	9 (16)
FOLFIRINOX	10 (9)	3 (5)
FOLFOXIRI	5 (5)	2 (4)
ECOG performance-status score — no. (%)¶		
0	51 (47)	33 (59)
1	58 (53)	23 (41)
Previous lines of chemotherapy — no. (%)		
<2	78 (72)	43 (77)
≥2	30 (28)	12 (21)
Missing data	1 (1)	1 (2)
Cycles of any chemotherapy — no. (%)		
≤2	15 (14)	7 (12)
>2	91 (83)	48 (86)
Missing data	3 (3)	1 (2)
Median no. of chemotherapy cycles (range)	6 (1–29)	5 (1–22)
Use of bevacizumab — no. (%)		
Previous	38 (35)	11 (20)
Concurrent	27 (25)	8 (14)
Use of PD-1 or PD-L1 agents — no. (%)		
Previous	5 (5)	1 (2)
Concurrent	1 (1)	0

* Percentages may not total 100 because of rounding. PD-1 denotes programmed cell death protein 1, and PD-L1 programmed death ligand 1.
† Race was reported by the patients.
‡ "Other" was reported as mestizo or mixed race (7 patients), Hispanic (2), and Latino (1).
§ The regimens received were 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX); 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX or FOLFOXIRI); or capecitabine and oxaliplatin (CAPOX). Data are for the 154 patients who restarted chemotherapy during the trial. For the 11 patients who did not restart chemotherapy during the trial, the planned regimens were as follows: in the romiplostim group, FOLFOX in 1 patient and CAPOX in 2 patients; in the placebo group, FOLFOX in 6 patients, CAPOX in 1 patient, and FOLFOXIRI in 1 patient.
¶ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. An inclusion criterion was a score of 0 to 2, but no patients had a score of 2.

receiving placebo had stage 4 disease (72% vs. 61%), an Eastern Cooperative Oncology Group (ECOG) performance-status score (on a scale 0 to 5, with higher scores indicating greater disability) of more than 0 (53% vs. 41%), at least two previous treatment lines (28% vs. 21%), previous bevacizumab use (35% vs. 20%), or concurrent bevacizumab use (25% vs. 14%). Although 75% of the patients completed the randomly assigned regimen, the likelihood of completion was higher with romiplostim than with placebo (82% vs. 61%); the most common reasons for discontinuation were patient request (1% with romiplostim and 12% with placebo) and nonresponse (0% and 11%, respectively) (Fig. 1).

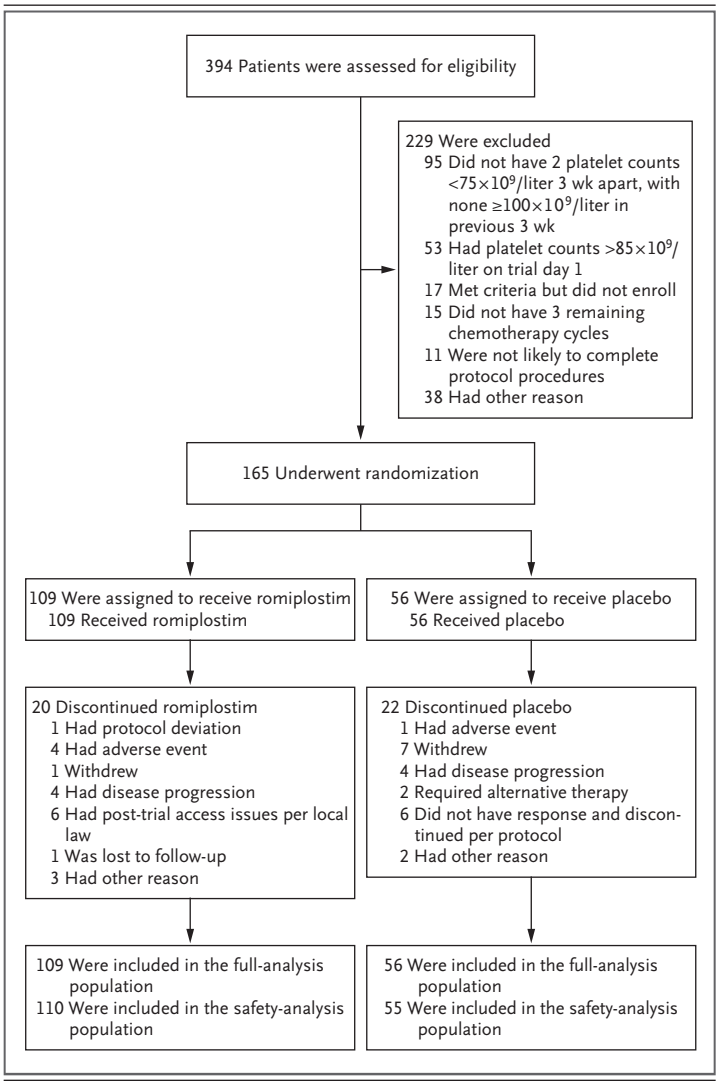


Figure 1. Screening, Randomization, and Follow-up.

Eligibility criteria with respect to platelet count were modified over the course of the trial (see the trial protocol, available at NEJM.org). Other reasons for exclusion included active chronic hepatitis B or C virus infection according to positivity for hepatitis B surface antigen or core antibody (in 7 patients); no receipt of an oxaliplatin-based regimen containing 5-fluorouracil or capecitabine, with or without irinotecan (FOLFOX, CAPOX, FOLFIRINOX, or FOLFOXIRI), or no chemotherapy-induced thrombocytopenia (CIT) from another regimen, with plans to start one of the above delayed at least 1 week owing to CIT (in 9); a duration of less than 14 days from the start of the chemotherapy cycle for FOLFOX, FOLFIRINOX, or FOLFOXIRI or less than 21 days for CAPOX (in 4); inadequately treated secondary cancer in the past 5 years (in 4); evidence of active infection in the previous 2 weeks (in 4); an impaired ability to provide consent (in 3); no diagnosis of gastrointestinal or colorectal cancer (in 2); a hemoglobin level of less than 8 g per deciliter (in 1); an absolute neutrophil count of less than 1×10^9 per liter (in 1); a creatinine clearance of less than 30 ml per minute (in 1); an Eastern Cooperative Oncology Group performance-status score (on a scale from 0 to 5, with higher scores indicating greater disability) of more than 2 (in 1); and a condition posing a safety risk or interfering with trial conduct (in 1). In some cases, country-specific laws or regulations required post-trial access (PTA) to the trial drug for patients enrolled in clinical trials. The investigator requested PTA for 6 patients in the romiplostim group, 5 of whom received treatment with commercial romiplostim after completing the trial treatment phase. The PTA standard operating procedure of the primary sponsor required that patients be removed from ongoing trial participation when they switched to the PTA program. Other reasons for discontinuation of romiplostim or placebo were as follows: in the romiplostim group, 1 patient was withdrawn by the investigator, 1 was receiving commercial romiplostim, and 1 was hospitalized; in the placebo group, 1 patient withdrew, and 1 was subject to coronavirus disease 2019 control measures. Two patients assigned to the romiplostim group also received placebo, and 1 patient assigned to the placebo group also received romiplostim; all 3 patients are included in the romiplostim safety-analysis population of 110 patients.

PRIMARY END POINT

No chemotherapy dose modifications due to thrombocytopenia in cycles 2 and 3 (primary end point) occurred in 92 of 109 patients (84%) receiving romiplostim and in 20 of 56 patients (36%) receiving placebo, which corresponded to an odds ratio of 10.16 (95% confidence interval [CI], 4.44 to 23.72; P<0.001) and a risk ratio of 2.77 (95% CI, 1.78 to 4.30; P<0.001) (Fig. 2A).

Platelet counts were higher over time with romiplostim than with placebo (Fig. 2B), and the percentage of patients with no thrombocytopenia-related chemotherapy dose modification in prespecified patient subgroups was generally similar to that in the overall analysis (Fig. 2C and Fig. S2). Figure S3 shows platelet counts relative to the timing of the restart of chemotherapy.

KEY SECONDARY EFFICACY END POINTS

The median platelet nadirs during the treatment period (within three chemotherapy cycles) were higher with romiplostim than with placebo (87×10^9 per liter [interquartile range, 62 to 112] vs. 58×10^9 per liter [interquartile range, 48 to 64]; estimated mean difference, 26×10^9 per liter [95% CI, 8 to 44]; P=0.005) (Table 2). The median time to first platelet response was faster with romiplostim than with placebo (1.1 weeks [95% CI, not estimable] vs. 2.1 weeks [95% CI, 1.1 to 3.0]; P<0.001), with a hazard ratio of 2.67 (95% CI, 1.81 to 3.95; P<0.001) across all patients. Platelet responses (platelet count of $\geq100\times10^9$ per liter and no platelet transfusions during the previous 7 days) were seen in 97% of patients with romiplostim and 77% of patients with placebo. Duration-adjusted rates of bleeding events of grade 2 or higher per 100 patient-years were 4.0 in the romiplostim group and 7.6 in the placebo group (hazard ratio, 0.53; 95% CI, 0.04 to 6.77; P=0.63). Because the between-group difference was not significant, no further testing was performed for subsequent secondary end points, and results are presented descriptively (Table 2).

Through long-term follow-up, death occurred in 58 patients (53%) in the romiplostim group and 25 patients (45%) in the placebo group, with the most common reason being progressive disease (41 of 58 patients [71%] with romiplostim and 18 of 25 [72%] with placebo) (Table S5 and Fig. S4). No other single cause accounted for 5% or more of the deaths in either group; no deaths were attributed to adverse events considered by the investigator to be related to romiplostim or placebo (Table 3).

POST HOC ANALYSES

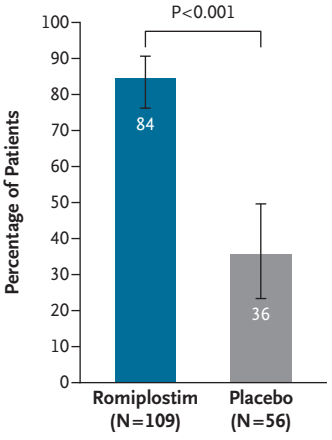
In a post hoc analysis, the percentage of patients with a chemotherapy relative dose intensity of more than 85% was 75% in the romiplostim group and 38% in the placebo group (Fig. S5). The median relative dose intensity was 98% (interquartile range, 87 to 100) with romiplostim and 77% (interquartile range, 56 to 98) with placebo across the three planned cycles, and the percentage of patients who received all three planned chemotherapy cycles during the trial was 95% for romiplostim and 73% for placebo (Table S6).

EXPOSURE AND SAFETY

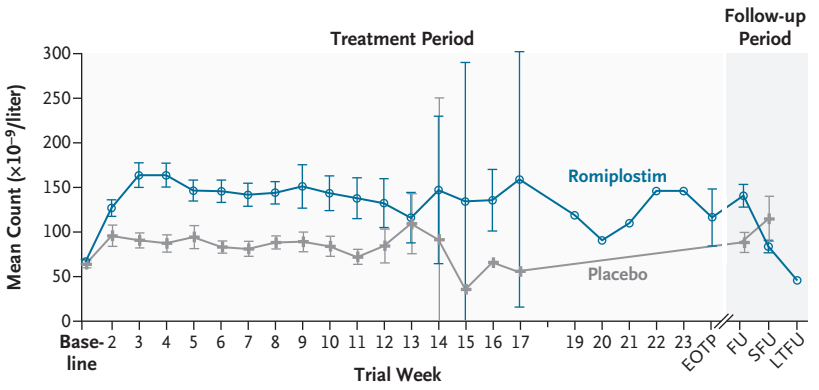
Patients were treated with romiplostim, with dose adjustment to maintain platelet counts of 100 to 250×10^9 per liter, for a median of 7.1 weeks (range, 0.1 to 22.0), with a median average weekly dose of 2.4 μg per kilogram of body weight and a maximum dose of no more than 5 μg per kilogram for 88% of patients (Table S7); patients received placebo for a median of 8.9 weeks (range, 0.1 to 16.0) (Fig. S6). The median duration of trial participation including long-term follow-up was 17.4 months (range, 0.3 to 61.4) for all the patients, 16.0 months (range, 1.9 to 61.4) for the romiplostim group, and 19.0 months (range, 0.3 to 59.2) for the placebo group.

Overall, most patients (87% in the romiplostim group and 62% in the placebo group) reported adverse events (Table 3), which included adverse events of grade 3 or higher (37% and 22%, respectively), adverse events that were considered by the investigator to be related to romiplostim or placebo (12% and 7%), and serious adverse events (21% and 5%). No serious adverse events were considered to be related to romiplostim or placebo, and no adverse events considered to be related to romiplostim or placebo led to death or discontinuation of romiplostim, placebo, or chemotherapy. No adverse events of thrombocytosis were reported. The most frequent adverse events considered to be related to romiplostim or placebo were nausea (2% with romiplostim and 2% with placebo) and headache (2% and 0%, respectively). The most common serious adverse events were anemia (3% with romiplostim and 0% with placebo) and coronavirus disease 2019 (Covid-19) pneumonia (3% and 0%, respectively). Neutropenia of grade 3 or higher was observed in 9 patients (8%) who received romiplostim and in 4 patients (7%) who received placebo; febrile neutropenia of grade 3

A Primary End Point: No CIT-Induced Dose Modifications



B Platelet Count



No. at Risk

Romiplostim	109	106	106	103	105	99	93	74	48	32	22	13	11	5	3	3	3	1	1	1	1	1	2	91	85	1
Placebo	56	55	51	50	48	47	46	44	37	28	17	13	6	2	1	1	1	0	0	0	0	0	0	45	43	0

C Subgroup Analysis of Primary End Point

Subgroup	Romiplostim	Placebo	Risk Ratio (95% CI)
	no. of events/no. of patients (%)		
All patients	92/109 (84)	20/56 (36)	2.77 (1.78–4.30)
Tumor type at randomization			
Colorectal	72/82 (88)	14/42 (33)	2.63 (1.70–4.07)
Gastroesophageal	10/14 (71)	3/7 (43)	1.67 (0.67–4.17)
Pancreatic	10/13 (77)	3/7 (43)	1.79 (0.73–4.44)
Platelet count at randomization			
<50×10⁹/liter	7/11 (64)	2/6 (33)	1.91 (0.57–6.44)
≥50×10⁹/liter	85/98 (87)	18/50 (36)	2.41 (1.65–3.51)
Age			
≤65 yr	55/65 (85)	12/34 (35)	2.40 (1.50–3.82)
>65 yr	37/44 (84)	8/22 (36)	2.31 (1.31–4.08)
Sex			
Male	57/63 (90)	11/36 (31)	2.96 (1.80–4.88)
Female	35/46 (76)	9/20 (45)	1.69 (1.01–2.82)
Ethnic group			
Hispanic or Latino	26/28 (93)	7/11 (64)	1.46 (0.92–2.31)
Not Hispanic or Latino	66/81 (81)	13/45 (29)	2.82 (1.76–4.51)
Stage of disease			
1–3	26/28 (93)	7/18 (39)	2.39 (1.33–4.30)
4 or recurrent disease	65/80 (81)	13/38 (34)	2.38 (1.51–3.74)
No. of lines of chemotherapy treatment			
<2	68/78 (87)	16/43 (37)	2.34 (1.57–3.49)
≥2	23/30 (77)	4/12 (33)	2.30 (1.01–5.24)
Chemotherapy regimen			
FOLFOX	64/70 (91)	12/34 (35)	2.59 (1.63–4.11)
CAPOX	17/21 (81)	5/9 (56)	1.46 (0.78–2.71)
FOLFIRINOX	8/10 (80)	2/3 (67)	1.20 (0.51–2.83)
FOLFOXIRI	3/5 (60)	1/2 (50)	1.20 (0.25–5.71)
No. of previous chemotherapy cycles			
≤2	13/15 (87)	3/7 (43)	2.02 (0.84–4.87)
>2	76/91 (84)	17/48 (35)	2.36 (1.59–3.49)
Previous bevacizumab use			
Yes	31/38 (82)	4/11 (36)	2.24 (1.01–4.97)
No	61/71 (86)	16/45 (36)	2.42 (1.61–3.62)
Concurrent bevacizumab use			
Yes	22/27 (81)	4/8 (50)	1.63 (0.80–3.33)
No	70/82 (85)	16/48 (33)	2.56 (1.70–3.86)

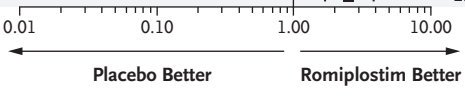


Figure 2 (facing page). Primary End Point and Platelet Count over Time.

Panel A shows the primary end point: no dose modifications (reduction, delay, omission, or discontinuation) of any myelosuppressive agent in both the second and third planned chemotherapy cycles due to CIT (platelet count, $<100\times10^9$ per liter), as assessed by an independent adjudication committee of three board-certified oncologists who were unaware of the trial-group assignments. Panel B shows the platelet count over time. The first follow-up (FU) visit occurred 1 week after the last dose of romiplostim or placebo, and the safety follow-up (SFU) visit occurred 30 days after the last dose. Patients received romiplostim for a median of 7.1 weeks (range, 0.1 to 22.0) or placebo for a median of 8.9 weeks (range, 0.1 to 16.0) before moving to follow-up. EOTP denotes end of treatment period, and LTFU long-term follow-up. The I bars in Panels A and B indicate 95% confidence intervals. Panel C shows the subgroup analysis of the primary end point.

or higher occurred in 1 patient (1%) who received romiplostim. Granulocyte colony-stimulating factor (G-CSF) or pegylated G-CSF was received by 20% of patients in the romiplostim group and 13% of those in the placebo group. These adverse events primarily reflected known chemotherapy effects.

Thromboembolic events occurred in two patients who received romiplostim (2% total): one portal vein thrombosis (platelet count, 143×10^9 per liter) in a patient with pancreatic cancer and one splenic infarct (platelet count, 184×10^9 per liter) in a patient with colorectal cancer. No patients who received placebo had thromboembolic events. Newly diagnosed myelodysplastic syndrome and secondary cancers, respectively, were observed in 1% and 2% of patients receiving romiplostim and in 0% and 5% of patients receiving placebo. The myelodysplastic syndrome occurred 19 weeks after the first romiplostim dose and was considered to be unrelated to romiplostim. Two fatal adverse events occurred in the romiplostim group (i.e., occurring within 30 days after the last dose): Covid-19 pneumonia and multiple organ dysfunction syndrome; neither event was considered to be related to romiplostim. Discontinuation of romiplostim or placebo due to adverse events was reported in three patients who received romiplostim (one patient had chronic obstructive pulmonary disease, one had thrombocytopenia, and one had both mucosal inflammation and renal failure) and in one patient who received placebo (anaphylaxis).

DISCUSSION

CIT presents substantial management challenges for patients with cancer worldwide. Unlike chemotherapy-induced anemia and neutropenia, CIT has no widely available approved treatment; platelet transfusions are often unavailable, and their effects on platelet counts are short-lived. These factors result in recurring chemotherapy dose reductions or delays, drug omissions or discontinuations, and even discontinuation of chemotherapy treatment, which limits the ability to deliver planned antineoplastic therapy. A phase 2 randomized trial and observational studies previously showed that romiplostim may mitigate CIT and related chemotherapy modifications,[13-15] which suggests the potential for improved clinical outcomes. On the basis of these studies, oncology guidelines recommend considering romiplostim for CIT; however, data have been lacking from randomized, controlled trials of romiplostim for CIT.[3,21]

In this phase 3, randomized, placebo-controlled trial, weekly romiplostim was effective in treating persistent CIT and preventing its recurrence in patients with gastrointestinal cancers, despite primarily enrolling patients with advanced cancer who were receiving chemotherapy regimens containing two or three myelosuppressive cytotoxic agents. With objective, drug label–based thresholds for chemotherapy dose reductions or delays (standard treatment approaches for CIT), one sixth of patients receiving romiplostim had chemotherapy dose modifications due to CIT, as compared with nearly two thirds of those receiving placebo. Accordingly, a post hoc analysis showed that the relative dose intensity of delivered chemotherapy appeared to be higher with romiplostim than with placebo. Although studies have shown deleterious effects of reduced chemotherapy relative dose intensity on survival,[6-11] the evidence is largely retrospective. Whether the improved relative dose intensity that can be achieved with romiplostim is sufficient to have an effect on response and survival end points is not yet proven, and this critical point requires further investigation.

Table 2. Key Secondary End Points.*

End Point	Romiplostim (N=109)	Placebo (N=56)	P Value
Median platelet-count nadir (range) — $\times 10^{-9}$/liter	87 (14–167)	58 (22–95)	
Estimated mean difference (95% CI)	26.1 (7.9–44.4)		0.005
Platelet response — no. (%)†	106 (97)	43 (77)	
Median time to response (95% CI) — wk	1.1 (NE)	2.1 (1.1–3.0)	<0.001
Hazard ratio (95% CI)	2.67 (1.81–3.95)		
Duration-adjusted rate of bleeding events of grade ≥2 per 100 patient-yr	4.0	7.6	
Hazard ratio (95% CI)	0.53 (0.04–6.77)		0.63
Death — no. (%)	58 (53)	25 (45)	NA
Platelet transfusion — % of patients	2	0	NA
Platelet response by week 4 — % of patients	96	66	NA

* NA denotes not applicable owing to hierarchical testing of key secondary end points, and NE could not be estimated.
† Platelet response was defined as platelet count of at least 100×10^9 per liter in the absence of platelet transfusions during the previous 7 days.

The use of romiplostim led to significantly faster platelet recovery (and therefore faster chemotherapy reinitiation) and significantly higher platelet nadirs than placebo; the rate of bleeding events of grade 2 or higher per 100 patient-years was 4.0 with romiplostim and 7.6 with placebo (hazard ratio, 0.53; 95% CI, 0.04 to 6.77; P=0.63). Although the other secondary end points could not be evaluated with formal hypothesis testing because the between-group difference for the bleeding end point was not significant, they were not differentiated between the two groups except for platelet response by week 4: 96% with romiplostim and 66% with placebo. Overall survival (47% with romiplostim and 55% with placebo) reflected the baseline percentage of patients with stage 4 disease in each group and was consistent with published series involving similar patient populations[22-24] and with recent real-world observational studies.[25]

Adverse events of grade 3 or higher occurred in 37% of patients with romiplostim and 22% of patients with placebo. No serious adverse events were considered to be related to romiplostim or placebo, and no adverse events considered to be related to romiplostim or placebo led to death or discontinuation of romiplostim, placebo, or chemotherapy. The most common adverse events were generally as expected for patients with advanced cancer receiving these chemotherapy regimens. Thromboembolic events were observed in 2% of patients who received romiplostim and in no patients who received placebo. These findings are consistent with those of meta-analyses of thrombopoietin-receptor agonist use in patients with CIT or immune thrombocytopenia and studies of recombinant thrombopoietin in patients with CIT.[26-28] In addition, no increased incidence of myelodysplastic syndrome or secondary cancer was noted with romiplostim; however, the duration of follow-up and the number of participants are insufficient to rule out a potential risk.

A low incidence of neutropenia was observed, with neutropenia of grade 3 or higher in 9 patients (8%) who received romiplostim and in 4 patients (7%) who received placebo; febrile neutropenia of grade 3 or higher was observed in 1 patient (1%) who received romiplostim. Consistent with standard care, 20% of patients who received romiplostim and 13% of those who received placebo received G-CSF or pegylated G-CSF for neutropenia. Patients with ongoing severe neutropenia at baseline were excluded from the trial. These findings must be considered in the context of a trial that was powered for the primary end point of chemotherapy dose modifications due to CIT and therefore accrued a patient population (109 patients in the romiplostim group and 56 patients in the placebo group) that was not of an adequate sample size to enable a comprehensive analysis of infrequent adverse events.

Table 3. Adverse Events.*

Event	Romiplostim (N=110)†		Placebo (N=55)	
	All	Related to Romiplostim‡	All	Related to Placebo‡
Any adverse event	96 (87)	13 (12)	34 (62)	4 (7)
Grade ≥3 adverse event	41 (37)	3 (3)	12 (22)	2 (4)
Serious adverse event	23 (21)	0	3 (5)	0
Adverse event leading to discontinuation of romiplostim or placebo	3 (3)	0	1 (2)	0
Adverse event leading to discontinuation of chemotherapy	7 (6)	0	1 (2)	0
Fatal adverse event§	2 (2)	0	0	0
	All	Grade ≥3¶	All	Grade ≥3¶
Most common adverse events				
Thrombocytopenia	22 (20)	9 (8)	11 (20)	4 (7)
Neutropenia	21 (19)	9 (8)	8 (15)	4 (7)
Anemia	16 (15)	6 (5)	5 (9)	1 (2)
Most common serious adverse events				
Anemia	3 (3)		0	
Covid-19 pneumonia	3 (3)		0	
Peritonitis	2 (2)		0	
Pyrexia	2 (2)		0	
Rectal hemorrhage	1 (1)		1 (2)	
Most common adverse events related to romiplostim or placebo‡				
Nausea	2 (2)		1 (2)	
Headache	2 (2)		0	
Thromboembolic event	2 (2)‖		0	
Myelodysplastic syndrome	1 (1)		0	
Secondary cancer	2 (2)		3 (5)	

* Covid-19 denotes coronavirus disease 2019.
† Two patients assigned to the romiplostim group also received placebo, and 1 patient assigned to the placebo group also received romiplostim; all 3 patients are included in the romiplostim safety-analysis population of 110 patients.
‡ Shown are adverse events that were considered by the investigator to be related to romiplostim or placebo. Determinations of relatedness were made before unblinding of the trial-group assignments.
§ These adverse events by definition occurred within 30 days after the last dose of romiplostim or placebo. The fatal adverse events in the romiplostim group were Covid-19 pneumonia and multiple organ dysfunction syndrome; neither event was considered to be related to romiplostim.
¶ Shown are all adverse events of grade 3 or higher, not necessarily those considered to be related to romiplostim or placebo.
‖ There was one portal-vein thrombosis in a patient with pancreatic cancer and one splenic infarct in a patient with colorectal cancer.

Furthermore, safety was assessed at prespecified 1- and 30-day visits with subsequent follow-up every 12 weeks during long-term follow-up (median duration of trial participation, 17.4 months), but the trial was not designed to detect late adverse events during extended follow-up. Ongoing real-world studies, which by their nature can include a much larger and broader patient population that will probably receive a longer duration of therapy, may provide more insights on the safety of romiplostim in patients with CIT.

This trial has a number of strengths. It enrolled an internationally representative cohort of patients with advanced gastrointestinal cancers receiving oxaliplatin-based multiagent chemotherapy. The design of the trial minimized confounding of the primary end point of no chemotherapy dose modifications due to CIT by restricting chemotherapy backbones and used rigorous blinded adjudication for end-point classification. These findings support the usefulness of romiplostim in addressing CIT management and provide a foundation for ongoing investigation in broader populations of persons with cancer, including an ongoing phase 3 trial to evaluate romiplostim as compared with placebo for treatment of CIT in patients with breast, ovarian, or non–small-cell lung cancers (ClinicalTrials.gov number, NCT03937154).

The trial also has limitations. Interpretation of cancer outcomes in this trial was inherently limited by the three-cycle intervention period for CIT and the lack of a standardized follow-up beyond this period, because post-trial therapy was managed at the investigator's discretion. In addition, baseline imbalances between the trial groups (with respect to ECOG performance-status score, disease stage, number of previous treatment lines, and previous or concurrent bevacizumab use) together with the heterogeneity of the patient population across tumor types, stages, chemotherapy regimens, and lines of therapy further confounded interpretation of oncologic end points. Although the trial was adequately powered for its primary end point, it yielded a low number of bleeding events of grade 2 or higher, which limited the ability to statistically assess subsequent secondary efficacy end points. Thus, meaningful interpretation of trial results is limited to end points regarding platelet support and chemotherapy relative dose intensity. Ongoing real-world evidence studies with longer treatment durations and follow-up may better inform the effect of romiplostim-supported CIT treatment on long-term cancer outcomes.

In this trial, romiplostim had few serious side effects and was efficacious to treat and prevent recurrence of persistent CIT in patients with gastrointestinal cancers receiving myelosuppressive chemotherapy. The trial showed that romiplostim, as compared with placebo, resulted in a lower incidence of chemotherapy dose modifications. These findings suggest that romiplostim may be a viable therapeutic option for managing CIT in patients with gastrointestinal cancers undergoing oxaliplatin-based chemotherapy.

Supported by Amgen and the Biomedical Advanced Research and Development Authority (BARDA).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families for their participation in the trial; the investigators and their supporting staff at the participating centers; Ying Zhang of Amgen for biostatistics support; Susanna Mac (on behalf of Amgen) and Qais Al-Hadid of Amgen for medical writing support; and Robert Dawson (Cactus Communications on behalf of Amgen) for graphics support.

AUTHOR INFORMATION

[1] Division of Classical Hematology, Mass General Brigham Cancer Institute, Massachusetts General Hospital, Boston; [2] Medical Oncology, Centro Integral Oncológico Clara Campal, Hospital Universitario HM Sanchinarro, HM Hospitales, Madrid; [3] Facultad HM de Ciencias de la Salud de la Universidad Camilo José Cela, Madrid; [4] Instituto de Investigación Sanitaria HM Hospitales, Madrid; [5] Department of Medical Oncology, Gaziosmanpaşa Medical Park Hospital, Istanbul, Turkey; [6] Department of Internal Medicine, İstinye University Faculty of Medicine, Istanbul, Turkey; [7] Oncology Department, St. Luke's Hospital–Agios Loukas Clinic, Thessaloniki, Greece; [8] Medical Oncology, Hospital Universitario Clínico San Cecilio, Granada, Spain; [9] Medical Oncology Department, Izmir University of Economics, MedicalPoint International Hospital, Izmir, Turkey; [10] Oncology Department, Instituto de Oncologia do Paraná, Oncoville, Curitiba, Brazil; [11] Interdisciplinary Cancer Course Department, Institut Gustave Roussy, Villejuif, France; [12] Oncology Department, Catarina Pesquisa Clínica–Clínica de Neoplasias Litoral, Itajaí, Brazil; [13] Biostatistics, Amgen, Thousand Oaks, CA; [14] Clinical Development, Amgen, Thousand Oaks, CA; [15] Medicine Department, Hematology Division, Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami.

REFERENCES

1. Epstein RS, Aapro MS, Basu Roy UK, et al. Patient burden and real-world management of chemotherapy-induced myelosuppression: results from an online survey of patients with solid tumors. Adv Ther 2020;37:3606-18.
2. Shaw JL, Nielson CM, Park JK, Marongiu A, Soff GA. The incidence of thrombocytopenia in adult patients receiving chemotherapy for solid tumors or hematologic malignancies. Eur J Haematol 2021;106:662-72.
3. National Comprehensive Cancer Network. NCCN guidelines: hematopoietic growth factors. 2024.
4. Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. Clin Ther 2009;31:2416-32.
5. Al-Samkari H, Soff GA. Clinical challenges and promising therapies for chemotherapy-induced thrombocytopenia. Expert Rev Hematol 2021;14:437-48.
6. Crawford J, Denduluri N, Patt D, et al.

Relative dose intensity of first-line chemotherapy and overall survival in patients with advanced non-small-cell lung cancer. Support Care Cancer 2020;28:925-32.
7. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003;21:4524-31.
8. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 2004;22:4302-11.
9. Claessens AKM, Bos MEMM, Lopez-Yurda M, et al. Intermittent versus continuous first-line treatment for HER2-negative metastatic breast cancer: the stop & go study of the Dutch Breast Cancer Research Group (BOOG). Breast Cancer Res Treat 2018;172:413-23.
10. Hanna RK, Poniewierski MS, Laskey RA, et al. Predictors of reduced relative dose intensity and its relationship to mortality in women receiving multi-agent chemotherapy for epithelial ovarian cancer. Gynecol Oncol 2013;129:74-80.
11. Havrilesky LJ, Reiner M, Morrow PK, Watson H, Crawford J. A review of relative dose intensity and survival in patients with metastatic solid tumors. Crit Rev Oncol Hematol 2015;93:203-10.
12. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2018;36:283-99.
13. Soff GA, Miao Y, Bendheim G, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. J Clin Oncol 2019;37:2892-8.
14. Wilkins CR, Ortiz J, Gilbert LJ, et al. Romiplostim for chemotherapy-induced thrombocytopenia: efficacy and safety of extended use. Res Pract Thromb Haemost 2022;6(3):e12701.
15. Al-Samkari H, Parnes AD, Goodarzi K, Weitzman JI, Connors JM, Kuter DJ. A multicenter study of romiplostim for chemotherapy-induced thrombocytopenia in solid tumors and hematologic malignancies. Haematologica 2021;106:1148-57.
16. Bussel JB, Soff G, Balduzzi A, Cooper N, Lawrence T, Semple JW. A review of romiplostim mechanism of action and clinical applicability. Drug Des Devel Ther 2021;15:2243-68.
17. Al-Samkari H, Kolb-Sielecki J, Safina SZ, Xue X, Jamieson BD. Avatrombopag for chemotherapy-induced thrombocytopenia in patients with non-haematological malignancies: an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2022;9(3):e179-e189.
18. Winer ES, Safran H, Karaszewska B, et al. Eltrombopag for thrombocytopenia in patients with advanced solid tumors receiving gemcitabine-based chemotherapy: a randomized, placebo-controlled phase 2 study. Int J Hematol 2017;106:765-76.
19. Al-Samkari H, Marshall AL, Goodarzi K, Kuter DJ. The use of romiplostim in treating chemotherapy-induced thrombocytopenia in patients with solid tumors. Haematologica 2018;103(4):e169-e172.
20. Parameswaran R, Lunning M, Mantha S, et al. Romiplostim for management of chemotherapy-induced thrombocytopenia. Support Care Cancer 2014;22:1217-22.
21. Soff G, Leader A, Al-Samkari H, et al. Management of chemotherapy-induced thrombocytopenia: guidance from the ISTH Subcommittee on Hemostasis and Malignancy. J Thromb Haemost 2024;22:53-60.
22. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
23. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 2014;371:1609-18.
24. Neugut AI, Lin A, Raab GT, et al. FOLFOX and FOLFIRI use in stage IV colon cancer: analysis of SEER-Medicare data. Clin Colorectal Cancer 2019;18:133-40.
25. Soohoo M, Fuglsang C, Kim J-H, et al. Clinical impact of chemotherapy-induced thrombocytopenia (CIT) in patients with solid tumors. Presented at EHA 2025 Congress, Milan, June 12–15, 2025. abstract.
26. Soff GA, Ray-Coquard I, Rivera LJM, et al. Systematic literature review and meta-analysis on use of thrombopoietic agents for chemotherapy-induced thrombocytopenia. PLoS One 2022;17(6):e0257673.
27. Shen N, Qiao J, Jiang Y, et al. Thrombopoietin receptor agonists use and risk of thrombotic events in patients with immune thrombocytopenic purpura: a systematic review and meta-analysis of randomized controlled trials. Biomed Rep 2024;20:44.
28. Fanucchi M, Glaspy J, Crawford J, et al. Effects of polyethylene glycol-conjugated recombinant human megakaryocyte growth and development factor on platelet counts after chemotherapy for lung cancer. N Engl J Med 1997;336:404-9.