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Symptom Management and Supportive Care

Eflapegrastim, a Long-Acting Granulocyte-Colony Stimulating Factor for the Management of Chemotherapy-Induced Neutropenia: Results of a Phase III Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Eflapegrastim • Pegfilgrastim • Chemotherapy-induced neutropenia • Breast cancer

Abstract

Background. Eflapegrastim, a novel, long-acting recombinant human granulocyte-colony stimulating factor (rhG-CSF), consists of a rhG-CSF analog conjugated to a human IgG4 Fc fragment via a short polyethylene glycol linker. Preclinical and phase I and II pharmacodynamic and pharmacokinetic data showed increased potency for neutrophil counts for eflapegrastim versus pegfilgrastim. This open-label phase III trial compared the efficacy and safety of eflapegrastim with pegfilgrastim for reducing the risk of chemotherapy-induced neutropenia.

Materials and Methods. Patients with early-stage breast cancer were randomized 1:1 to fixed-dose eflapegrastim 13.2 mg (3.6 mg G-CSF) or standard pegfilgrastim (6 mg G-CSF) following standard docetaxel plus cyclophosphamide chemotherapy for 4 cycles. The primary objective was to demonstrate the noninferiority of eflapegrastim compared with pegfilgrastim in mean duration of severe neutropenia (DSN; grade 4) in cycle 1.

Results. Eligible patients were randomized 1:1 to study arms (eflapegrastim, n = 196; pegfilgrastim, n = 210). The incidence of cycle 1 severe neutropenia was 16% (n = 31) for eflapegrastim versus 24% (n = 51) for pegfilgrastim, reducing the relative risk by 35% (p = .034). The difference in mean cycle 1 DSN (−0.148 day) met the primary endpoint of noninferiority (p < .0001) and also showed statistical superiority for eflapegrastim (p = .013). Noninferiority was maintained for the duration of treatment (all cycles, p < .0001), and secondary efficacy endpoints and safety results were also comparable for study arms.

Conclusion. These results demonstrate noninferiority and comparable safety for eflapegrastim at a lower G-CSF dose versus pegfilgrastim. The potential for increased potency of eflapegrastim to deliver improved clinical benefit warrants further clinical study in patients at higher risk for CIN. ***The Oncologist*** 2020;25:e1233–e1241

Implications for Practice: Chemotherapy-induced neutropenia (CIN) remains a significant clinical dilemma for oncology patients who are striving to complete their prescribed chemotherapy regimen. In a randomized, phase III trial comparing eflapegrastim to pegfilgrastim in the prevention of CIN, the efficacy of eflapegrastim was noninferior to pegfilgrastim and had comparable safety. Nevertheless, the risk of CIN remains a great concern for patients undergoing chemotherapy, as the condition frequently results in chemotherapy delays, dose reductions, and treatment discontinuations.

Introduction

Myelosuppression, particularly neutropenia, has presented a major challenge in cancer treatment since the introduction of cytotoxic chemotherapy in the 1950s. It was not until 1991 that the approval of filgrastim, the first recombinant (rh) human

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granulocyte-colony stimulating factor (G-CSF), provided a safe and effective means to reduce the considerable burden of infection-related morbidity and mortality associated with chemotherapy-induced neutropenia (CIN) [1]. Addressing this substantial unmet need, filgrastim enabled the investigation and consistent application of the intensive chemotherapy regimens that still provide the foundation of cancer care today.

In 2002, the first long-acting rhG-CSF, pegylated filgrastim (pegfilgrastim), was introduced, simplifying supportive care for CIN with a once-per-chemotherapy-cycle option [2]. Since then, supportive care options for CIN have not changed. Biosimilar alternatives to filgrastim and pegfilgrastim have become available, but these do not improve on the index products beyond possibly offering lower cost [3].

The novel long-acting rhG-CSF, eflapegrastim (Rolontis, SPI-2012, HM10460A), represents the first myeloid growth factor innovation in more than 15 years. The eflapegrastim molecule (72 kDa) consists of an rhG-CSF analog ($17^{th}65^{th}$Ser-G-CSF, no additional *N*-terminal Met) and a recombinant human immunoglobulin (Ig)G Fc fragment conjugated at their *N*-termini via a short (3.4k Da) polyethylene glycol linker. The strategy of adding an Fc fragment to extend drug half-life has been used in marketed biologics safely and effectively administered to hundreds of thousands of patients (e.g., etanercept, aflibercept, dulaglutide) [4]. Eflapegrastim shows the expected decreased clearance due to its size as well as increased uptake to the bone marrow, presumably due to the interaction of its Fc fragment with Fc receptors on the endothelial surface [5]. The resulting increased potency, as demonstrated by pharmacokinetic and pharmacodynamic data from preclinical and phase I and II studies [5–7], gives eflapegrastim the potential to provide improved risk reduction in the clinic.

Here we report the results of the first phase III trial of eflapegrastim (ADVANCE, NCT02643420). This large randomized trial compared the efficacy and safety of eflapegrastim with pegfilgrastim in patients with early-stage breast cancer (ESBC) receiving docetaxel plus cyclophosphamide (TC) chemotherapy. In contrast to earlier eflapegrastim studies using weight-based dosing, this trial tested a fixed dose of 13.2 mg (total weight) containing 3.6 mg G-CSF, or 60% of the 6 mg G-CSF in pegfilgrastim. This fixed dose, approximating 51 μg/kg G-CSF for a 70 kg person (vs. 86 μg/kg for pegfilgrastim), was chosen based on the results of a phase II dose-ranging study, which showed noninferiority for eflapegrastim (37 μg/kg G-CSF) versus pegfilgrastim (86 μg/kg G-CSF) in the primary endpoint, mean cycle 1 duration of severe neutropenia (DSN; 0.44 vs. 0.31 days, p = .002), and statistical superiority at 74 μg/kg G-CSF (0.03 vs. 0.31 days, p = .023) [7].

Materials and Methods

Participants and Study Design

Patients had ESBC and were candidates for adjuvant or neoadjuvant TC chemotherapy [8, 9]. Key inclusion criteria included age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate bone marrow function before the start of chemotherapy (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$ per L, platelets $\geq 100 \times 10^9$ per L, hemoglobin >9 g/dL), and adequate renal function (calculated creatinine clearance >50 mL per minute) and hepatic function (total bilirubin ≤1.5 mg/dL, aspartate aminotransferase and/or alanine aminotransferase ≤2.5 × upper limit of normal (ULN), and alkaline phosphatase ≤2.0 × ULN). Exclusion criteria included known sensitivity to *Escherichia coli*–derived products, L-asparaginase, somatropin growth hormone, or recombinant interferon α-2b; active infection; or ongoing treatment with anti-infectives, prior bone marrow or stem cell transplant, major surgery within 30 days prior to enrollment, or any other malignancy within 5 years prior to enrollment. All patients provided written informed consent, and the study protocol was approved by institutional review boards and/or ethics committees at all sites.

This open-label, multicenter, active-controlled study was designed per a U.S. Food and Drug Administration Special Protocol Assessment to be consistent with the pegfilgrastim registrational trials [10, 11]. The trial aimed to enroll 400 total patients (200 each arm) based on an 87% power to detect noninferiority within a margin of 0.62 days using a two-sided, two-sample *t* test with each side tested at a 2.5% level of significance. Eligible patients were randomized to receive a single, fixed-dose of eflapegrastim 13.2 mg (3.6 mg G-CSF) or standard pegfilgrastim (6 mg G-CSF) by s.c. injection on day 2 of each cycle (~24 hours postchemotherapy). Patients received up to 4 cycles of standard TC chemotherapy (docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2), given by intravenous infusion on day 1 of each cycle. Dose modifications for eflapegrastim or pegfilgrastim were not permitted.

Procedures

Blood samples for complete blood counts (CBCs) with differential were collected pretreatment and on day 1 and daily on days 4–15 of cycle 1 and on days 1, 4, 7, and 15 in subsequent cycles. However, if an ANC $\leq 1.0 \times 10^9$/L was reported at any time in cycles 2–4, daily CBCs were performed until the ANC recovered to $\geq 1.5 \times 10^9$ per L. All blood analyses were performed by an independent central laboratory.

Patients were monitored for adverse events (AEs) for the duration of the study, and serum chemistry was collected in every cycle. AEs and laboratory values were graded according to National Cancer Institute (NCI) CTCAE version 4.03. Safety assessments began with the first dose of TC and lasted until 35 (±5) days after the last dose of study drug. Laboratory work was also performed at the long-term follow-up visits, 6 and 12 months after completion of therapy. To assess immunogenicity, blood samples were collected on day 1 of each cycle, at the end-of-treatment visit, and at the long-term follow-up visits. All immunogenicity tests were performed by independent laboratories.

Endpoints

The primary efficacy endpoint was the DSN in cycle 1, defined as the number of days of severe neutropenia (ANC $< 0.5 \times 10^9$ per L; grade 4 per NCI CTCAE, v. 4.03) from the day of first occurrence of an ANC below that threshold. In addition to DSN in cycles 2–4, other secondary endpoints that were assessed in each cycle included time-to-ANC recovery (time-from-chemotherapy administration to ANC $\geq 1.5 \times 10^9$ per L after the expected nadir), depth of ANC nadir (lowest ANC value), incidence of febrile neutropenia (FN; ANC $< 1.0 \times 10^9$

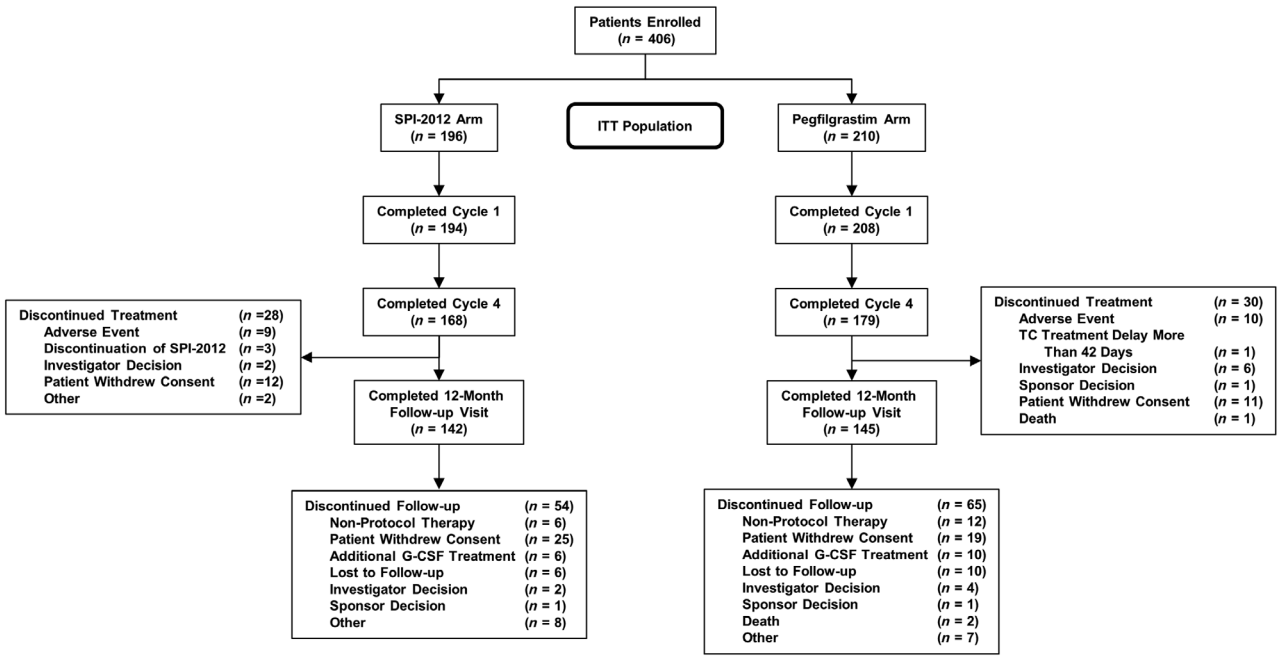

Figure 1. Patient disposition.
Abbreviations: G-CSF, granulocyte-colony stimulating factor; ITT, intent to treat; TC, docetaxel plus cyclophosphamide.

per L and either temperature >38.3°C or two consecutive readings ≥38.0°C over 2 hours), incidence of neutropenic complications (anti-infective use and/or hospitalizations), relative dose intensity (RDI), and safety (overall AE rates; AEs of special interest: musculoskeletal-related, splenic rupture, leukocytosis, and anaphylaxis).

Statistical Analysis

All randomized patients were included in the intent-to-treat efficacy analysis. The safety population included all patients who received at least one dose of any study drug. The primary efficacy analysis compared the mean DSNs in cycle 1 between the study arms based on a prespecified test of noninferiority hypothesis. A two-sided 95% confidence interval (CI) of the difference between the mean DSNs of the two arms was calculated using a bootstrap resampling method, with treatment as the only stratification factor; the same method was used to assess mean DSNs in cycles 2–4 (95% CIs for other secondary endpoints were calculated using standard methods). Eflapegrastim was to be considered noninferior to pegfilgrastim if the upper limit of the two-sided 95% CI for the difference in mean DSN was <0.62 days. This margin, based on the treatment effect observed in the pegfilgrastim pivotal trials [10, 11], eliminates the potential for biocreep when establishing noninferiority of two long-acting G-CSFs. Relative risk of incidence of severe neutropenia between two treatment arms was tested, and the 95% CI was obtained using Cochran–Mantel–Haenszel test at 5% level of significance. Descriptive statistics were used to summarize patient disposition, patient demographics, and safety. Univariate and multivariate analyses were conducted post hoc to explore potential treatment effects for eflapegrastim versus pegfilgrastim for patient subgroups, by age, weight, and other demographic characteristics.

Results

The majority of the 82 active sites (97%) were in the U.S. (n = 77), with additional sites in Canada (n = 3) and South Korea (n = 2). A total of 406 patients were enrolled and randomized between January 19, 2016, and November 29, 2017 (eflapegrastim, n = 196; pegfilgrastim, n = 210; Fig. 1). One patient in the pegfilgrastim arm never received either study drug and was excluded from the safety analysis. Another patient randomized to pegfilgrastim received eflapegrastim on cycle 1, day 2 and was included in the pegfilgrastim arm for the efficacy analysis but included in the eflapegrastim arm for the safety analysis. The safety population therefore included 197 patients in the eflapegrastim arm and 208 in the pegfilgrastim arm.

The two arms were well balanced in terms of demographics and baseline disease characteristics (Table 1). The median age was 61 years, with about 40% of patients in each arm ≥65 years. Most patients were treated in the adjuvant setting (83% both arms) and had an ECOG performance status of 0 (71%). The median weight at baseline was 78.6 kg, and >50% of patients in each treatment arm weighed more than 75 kg.

Severe Neutropenia

The incidence of severe neutropenia (SN) in cycle 1 was 15.8% (n = 31) for the eflapegrastim arm compared with 24.3% (n = 51) for the pegfilgrastim arm, resulting in an 8.5% absolute and a 34.9% relative risk reduction (p = .034) for eflapegrastim versus pegfilgrastim (Fig. 2). Most patients across all cycles did not experience SN. In the eflapegrastim arm, cycle 1 DSN was 1 day in 24 (12%) patients, 2 days in 6 (3%) patients, and 3 days in 1 (1%) patient. In the pegfilgrastim arm, the corresponding results were 1 day in 32 (15%) patients, 2 days in 16 (8%) patients, and 3 days in 3 (1%) patients. Both drugs

Table 1. Patient demographics and baseline characteristics

Characteristic	Eflapegrastim, *n* = 196	Pegfilgrastim, *n* = 210	Total, *n* = 406
Age, yr			
Median (range)	61 (28–83)	60 (24–84)	61 (24–84)
<65, *n* (%)	118 (60)	129 (61)	247 (61)
≥65, *n* (%)	78 (40)	81 (39)	159 (39)
Weight, kg, *n* (%)			
<65	37 (19)	44 (21)	81 (20)
65–75	44 (22)	49 (23)	93 (23)
>75	115 (59)	117 (56)	232 (57)
Gender, *n* (%)			
Female	195 (>99)	209 (>99)	404 (>99)
Race, *n* (%)			
White	156 (80)	159 (76)	315 (78)
Black	26 (13)	32 (15)	58 (14)
Other	14 (7)	19 (9)	33 (8)
ECOG Performance Status, *n* (%)			
0	140 (71)	147 (70)	287 (71)
1	56 (29)	59 (28)	115 (28)
2	0 (0)	4 (2)	4 (1)
Stage at diagnosis, *n* (%)			
Stage I	68 (35)	74 (35)	142 (35)
Stage IIA	83 (42)	77 (37)	160 (39)
Stage IIB	27 (14)	38 (18)	65 (16)
Stage IIIA	18 (9)	21 (10)	39 (10)
Histology type, *n* (%)			
Ductal invasive	174 (89)	182 (87)	356 (88)
Ductal other	6 (3)	6 (3)	12 (3)
Lobular invasive	9 (5)	12 (6)	21 (5)
Mixed	3 (2)	6 (3)	9 (2)
Other	4 (2)	4 (2)	8 (2)
Treatment setting, *n* (%)			
Adjuvant	162 (83)	174 (83)	336 (83)
Neoadjuvant	34 (17)	36 (17)	70 (17)
Number of positive nodes, *n* (%)			
0	116 (59)	114 (54)	230 (57)
1–3	73 (37)	85 (40)	158 (39)
4+	7 (4)	11 (5)	18 (4)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

provided high levels of protection in cycles 2–4, with around 10% of patients experiencing SN in each cycle.

The mean cycle 1 DSN was 0.20 ± 0.503 days for the eflapegrastim arm versus 0.35 ± 0.683 days for the pegfilgrastim arm (Table 2). The −0.148-day difference in mean DSN (95% CI, −0.264 to −0.032) between the two arms met the study's primary endpoint of noninferiority ($p < .0001$). This difference also showed statistical superiority for eflapegrastim ($p = .013$), reflecting a 42% reduction in mean cycle 1 DSN. Noninferiority was maintained throughout treatment ($p < .0001$, all cycles), with the mean DSN similar between treatment arms in cycles 2–4.

Although not prespecified or powered to confirm treatment effects, univariate analyses of cycle 1 DSN for age, race, treatment setting, region, and body weight showed that there were similar treatment effects for eflapegrastim and pegfilgrastim in all subgroups except for a statistical superiority for eflapegrastim in patients aged ≥65 years (~40% of patients; 95% CI, −0.415 to −0.009) and in patients with a body weight >75 kg (>50% of patients; 95% CI, −0.406 to −0.084; Table 3). Multivariate analyses of cycle 1 DSN did not show an effect for any stratification factor and confirmed noninferiority for eflapegrastim versus pegfilgrastim across all subgroups.

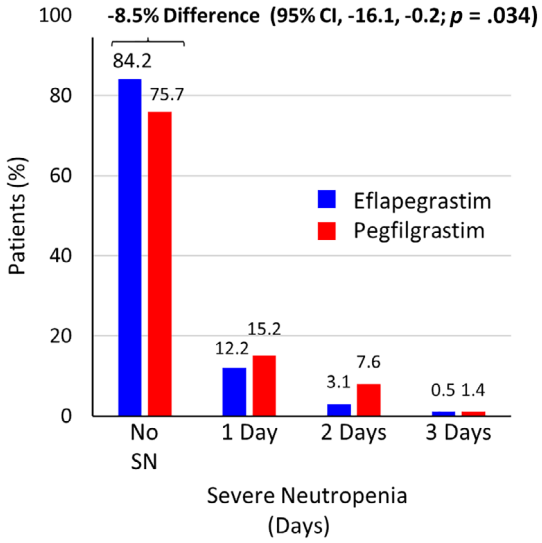

Figure 2. Duration of severe neutropenia (absolute neutrophil count $<0.5 \times 10^9$ per L; grade 4 per National Cancer Institute CTCAE, Version 4.03) in cycle 1 in patients treated with a fixed-dose 13.2 mg eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) or pegfilgrastim (6.0 mg G-CSF).
Abbreviations: CI, confidence interval; SN, severe neutropenia.

ANC Recovery and Nadir

The time-to-ANC recovery was comparable for eflapegrastim and pegfilgrastim, with no statistical differences between treatment arms observed in any cycle. The mean cycle 1 values were 3.24 days for eflapegrastim and 3.49 days for pegfilgrastim (p = .685; Table 4), with equivalent, shorter recoveries in cycles 2–4. An additional analysis of only the patients who experienced SN (31 and 51 patients overall for eflapegrastim and pegfilgrastim, respectively) showed time-to-ANC recovery from nadir to 1.5×10^9 per L was 1.48 days for eflapegrastim and 1.51 days for pegfilgrastim (p = .926). Median cycle 1 ANC nadirs were 1.6×10^9 per L and 1.3×10^9 per L for eflapegrastim and pegfilgrastim, respectively (p = .155). Although overall, the nadir values in cycles 2–4 were numerically higher for both drugs but consistently lower for eflapegrastim versus pegfilgrastim (Fig. 3), the median nadir in cycle 3 was significantly greater (p = .01) in the pegfilgrastim arm (3.7×10^9 per L) compared with the eflapegrastim arm (2.3×10^9 per L; Table 4).

Febrile Neutropenia

The incidence of FN across all cycles was low and not significantly different between the treatment arms, with four (2.0%) patients in the eflapegrastim arm and two (1.0%) patients in the pegfilgrastim arm experiencing FN in cycle 1 (p = .435). Two patients in the eflapegrastim arm who had FN in cycle 1 also had FN in cycle 3. Numerically, eflapegrastim was associated with more patients experiencing FN than pegfilgrastim (9 vs. 4 patients), primarily because of FN in cycle 3 (4 vs. 1). This difference was not associated with a proportional increase in neutropenic complications (anti-infective use and/or hospitalizations), which occurred most frequently in cycle 1 (n = 8 each arm) and at lower rates with both drugs in cycles 2–4. The median RDI of docetaxel and cyclophosphamide administered in both arms of the study was >99%, with four patients on each arm falling outside the range of 80% to 120% of the prescribed RDI.

Safety

Overall, the AEs observed in this trial were consistent with those previously reported for patients receiving TC chemotherapy and other myeloid growth factors. Most patients experienced at least one treatment-emergent AE (eflapegrastim, 97%; pegfilgrastim, 98%), and most of these were attributable to chemotherapy. All-grade study drug–related AEs were reported in 83% of patients receiving eflapegrastim and 70% of those receiving pegfilgrastim. The most common study drug–related AE was bone pain, reported in 32% of patients (all grades) in both treatment arms, although with a higher rate of grade 3 events for eflapegrastim (n = 9, 5%) than pegfilgrastim (n = 1, <1%). No grade 4 study drug–related AEs were reported in cycle 1 for either drug. Other commonly reported AEs in both arms included arthralgia, back pain, and myalgia (Table 5). AEs of special interest related to G-CSF (musculoskeletal AEs, injection site reactions, and hypersensitivity-type events) were similar regardless of grade between the treatment arms. No leukocytosis (white blood cells $>100 \times 10^9$ per L), splenic rupture, or anaphylaxis were reported in either treatment arm.

The incidence of AEs leading to treatment discontinuation was low and comparable (5% both arms); discontinuations due to AEs possibly related to study drug occurred in three patients receiving eflapegrastim (1 each migraine and oral hypoesthesia, rash, arthralgia) and two patients receiving pegfilgrastim (1 each hypersensitivity, generalized rash). The incidence of serious AEs was comparable for eflapegrastim and pegfilgrastim (18% and 14%), with study drug–related serious AEs reported in 2% and 3% of patients in each arm. Two patients in the pegfilgrastim arm died, one during cycle 2 from cardiac arrest unrelated to study treatment and another during the 12-month follow-up period from disease progression. The immunogenicity assays detected a similar overall incidence of antidrug antibodies in both treatment arms. One eflapegrastim-treated patient tested weakly positive (negative control signal to sample signal ratio equal to cut point) for a treatment-induced neutralizing antibody at one time point but not at any of the other seven time points. In all cases, the detected presence of these antibodies was not associated with demonstrable effects on pharmacokinetics, safety, or efficacy.

Discussion

This large, randomized phase III trial met all its primary and secondary endpoints, demonstrating noninferior efficacy and comparable safety for eflapegrastim and pegfilgrastim in reducing neutropenia-related complications, including FN, associated with myelosuppressive TC chemotherapy administered to patients with ESBC. In a systematic review and meta-analysis, the estimated risk of FN for TC without G-CSF prophylaxis was 29% (95% CI,% 24–35%) [12]. In the current study, differences in DSN, an objective measure based on ANC analyzed by an independent central laboratory and widely used in G-CSF pivotal trials as a primary endpoint [1, 2], showed the noninferiority of eflapegrastim to pegfilgrastim in cycle 1, which was maintained for the treatment duration (p < .0001, all 4 cycles). The results of all other secondary efficacy endpoints were

Table 2. Duration of severe neutropenia (ANC < 0.5×10^9/L) for fixed-dose 13.2 mg eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) and pegfilgrastim (6.0 mg G-CSF) in cycles 1–4

Mean DSN (SD), d	Eflapegrastim (*n* = 196)	Pegfilgrastim (*n* = 210)	Difference (95% CI)	*p* value for noninferiority
Cycle 1[a]	0.20 (0.503)	0.35 (0.683)	−0.148 (−0.264 to −0.032)[b]	<.0001
Cycle 2	0.13 (0.383)	0.09 (0.374)	0.042 (−0.036 to 0.116)	<.0001
Cycle 3	0.11 (0.326)	0.08 (0.273)	0.026 (−0.032 to 0.085)	<.0001
Cycle 4	0.11 (0.362)	0.09 (0.281)	0.027 (−0.033 to 0.091)	<.0001

Abbreviations: CI, confidence interval; DSN, duration of severe neutropenia.
[a]Trial primary endpoint.
[b]Eflapegrastim statistically superior to pegfilgrastim, $p = .013$.

Table 3. Cycle 1 duration of severe neutropenia for fixed-dose 13.2 mg eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) and pegfilgrastim (6.0 mg G-CSF) by subgroups

	Eflapegrastim (*n* = 196)		Pegfilgrastim (*n* = 210)		
Subgroup	*n*	Mean DSN (SD)	*n*	Mean DSN (SD)	Difference (95% CI[a])
Age, yr					
<65	118	0.14 (0.458)	129	0.26 (0.641)	−0.112 (−0.253 to 0.029)
≥65	78	0.28 (0.556)	81	0.49 (0.727)	−0.212 (−0.415 to −0.009)
Race					
White	156	0.20 (0.501)	159	0.33 (0.631)	−0.128 (−0.255 to −0.002)
Non-white	40	0.20 (0.516)	51	0.41 (0.829)	−0.212 (−0.509 to 0.086)
Treatment setting					
Adjuvant	162	0.20 (0.496)	174	0.38 (0.717)	−0.182 (−0.315 to −0.048)
Neoadjuvant	34	0.21 (0.538)	36	0.19 (0.467)	0.011 (−0.229 to 0.251)
Region					
U.S.	189	0.20 (0.507)	204	0.33 (0.670)	−0.127 (−0.246 to −0.009)
Non-U.S.	7	0.14 (0.378)	6	1.00 (0.894)	−0.857 (−1.671 to −0.043)
Weight, kg					
<65	37	0.27 (0.560)	44	0.34 (0.645)	−0.071 (−0.340 to 0.199)
65–75	44	0.25 (0.576)	49	0.22 (0.511)	0.026 (−0.198 to 0.249)
>75	115	0.16 (0.451)	117	0.40 (0.755)	−0.245 (−0.406 to −0.084)

Abbreviations: CI, confidence interval; DSN, duration of severe neutropenia.
[a]Two-sided 95% CIs based on normal distribution.

similar between the two treatment arms. Except for depth of nadir in cycle 3 (Table 4), no significant differences were observed between the two treatment arms in all four cycles for time-to-ANC recovery, depth of ANC nadir, incidences of FN and neutropenic complications, and successful delivery of prescribed RDI.

Although study drug–related AEs occurred in this trial at a higher incidence with eflapegrastim (83%) versus pegfilgrastim (70%), the incidence of discontinuations due to AEs was low in both arms (5% each), and no single AE leading to discontinuation was reported in more than one patient. Overall, eflapegrastim was safe in patients receiving TC, and eflapegrastim-related AEs occurred at rates consistent with those previously reported for filgrastim and pegfilgrastim, including for bone pain and musculoskeletal complaints [10, 13–17].

This trial was not designed to demonstrate a clinical benefit associated with the increased potency of eflapegrastim. However, several of its findings support the hypothesis that eflapegrastim could provide an important new option for patients at increased risk for CIN-related complications. Eflapegrastim treatment was associated with a 34.9% relative risk reduction versus pegfilgrastim in the incidence of SN in cycle 1 (15.8% vs. 24.3%, $p = .034$). Eflapegrastim also showed statistical superiority in the primary endpoint of cycle 1 DSN, with a 42% reduction versus pegfilgrastim ($p = .013$). Although not prespecified, univariate subgroup analyses of cycle 1 DSN showed statistical superiority for eflapegrastim versus pegfilgrastim in the elderly (age ≥65 years) and increased bodyweight (>75 kg) subgroups. These subgroups represent a substantial number of "real-world" patients, accounting for about 40% and >50% of the patients enrolled in this trial, respectively.

Despite the wide availability of filgrastim and pegfilgrastim, CIN and its associated complications remain a clinical challenge [18], albeit one of lessened concern relative to the estimated 25%–40% of patients receiving common chemotherapy regimens who would develop FN

Table 4. Secondary endpoints for fixed-dose eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) and standard pegfilgrastim (6.0 mg G-CSF) in cycles 1–4

	Chemotherapy cycle							
	1		2		3		4	
Endpoint	**E**	**P**	**E**	**P**	**E**	**P**	**E**	**P**
Mean time-to-ANC recovery, d	3.2	3.5	2.3	2.1	2.7	1.9	2.8	2.5
p value	.69		.80		.30		.71	
Median depth of ANC nadir ($\times 10^9$/L)	1.6	1.3	2.5	3.3	2.3	3.7	2.0	2.8
p value	.16		.10		.01		.11	
Incidence of FN, *n* (%)	4 (2)	2 (1)	1 (0.5)	1 (0.5)	4[a] (2.0)	1 (0.5)	2 (1.0)	0
p value	.44		NS		.20		.23	
Incidence of neutropenic complications,[b] *n* (%)	8 (4.1)	8 (3.8)	4 (2.0)	4 (1.9)	5 (2.6)	3 (1.4)	3 (1.5)	2 (1.0)
p value	NS		NS		.68		.55	

Abbreviations: ANC, absolute neutrophil count; E, eflapegrastim; FN, febrile neutropenia; NS, not significant; P, pegfilgrastim.
[a]Two patients also had FN in cycle 1.
[b]Anti-infective use and/or hospitalization for neutropenia.

Table 5. Adverse events related to fixed-dose eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) or standard pegfilgrastim (6.0 mg G-CSF) occurring in ≥5% of patients

	Eflapegrastim (*n* = 197), *n* (%)		Pegfilgrastim (*n* = 208), *n* (%)	
Adverse event	**Any grade**	**Grade 3[a]**	**Any grade**	**Grade 3[a]**
Any event	164 (83)	36 (18)	146 (70)	22 (11)
Bone pain	63 (32)	9 (5)	67 (32)	1 (<1)
Arthralgia	38 (19)	4 (2)	26 (13)	1 (<1)
Back pain	32 (16)	4 (2)	24 (12)	0
Myalgia	30 (15)	0	19 (9)	0
Increased WBC count	25 (13)	0[b]	15 (7)	0
Headache	23 (12)	0	18 (9)	1 (<1)
Pain	22 (11)	1 (1)	23 (11)	3 (1)
Fatigue	17 (9)	2 (1)	22 (11)	0
Nausea	16 (8)	0	11 (5)	0
Diarrhea	15 (8)	0	11 (5)	1 (<1)
Pyrexia	13 (7)	1 (1)	17 (8)	0
Hypersensitivity reaction[c]	13 (7)	2 (1)	15 (7)	3 (1)
Lymphopenia	12 (6)	10 (5)	6 (3)	5 (2)
Increased neutrophil count	11 (6)	0	6 (3)	0
Pain in extremity	11 (6)	1 (1)	13 (6)	0
Dizziness	9 (5)	0	5 (2)	0

Abbreviation: WBC, white blood cell.
[a]No grade 4 events reported.
[b]Although one event was reported as grade 3 by the study site, the patient's actual white blood cell count was 35.6×10^9 per L, below the threshold of $>100 \times 10^9$ per L required for a grade 3 event by CTCAE v 4.03.
[c]Includes swollen tongue, hypersensitivity, rash, rash generalized, rash maculopapular, and urticaria.

without any use of rhG-CSF support [19]. However, patients continue to experience CIN and its related complications at concerning rates. In a large (*n* > 3,500) prospective observational study of community oncology practices, 18% of patients receiving chemotherapy for a variety of common tumor types experienced SN, and another 11% developed FN during the first 3 cycles of therapy, with most events (14% SN/6% FN) occurring in the first cycle [20]. Although the rates of FN are relatively small, especially with G-CSF prophylaxis, their impact can be disproportionally great, resulting in use of broad-spectrum antibiotics, costly hospitalizations, and deaths [21, 22]. Furthermore, SN and especially FN frequently trigger chemotherapy delays, dose reductions, and treatment discontinuations, which multiple meta-analyses have indicated worsen long-term outcomes [23–27].

Since the approval of pegfilgrastim in 2002, cancer treatment has evolved considerably, with rapid development and

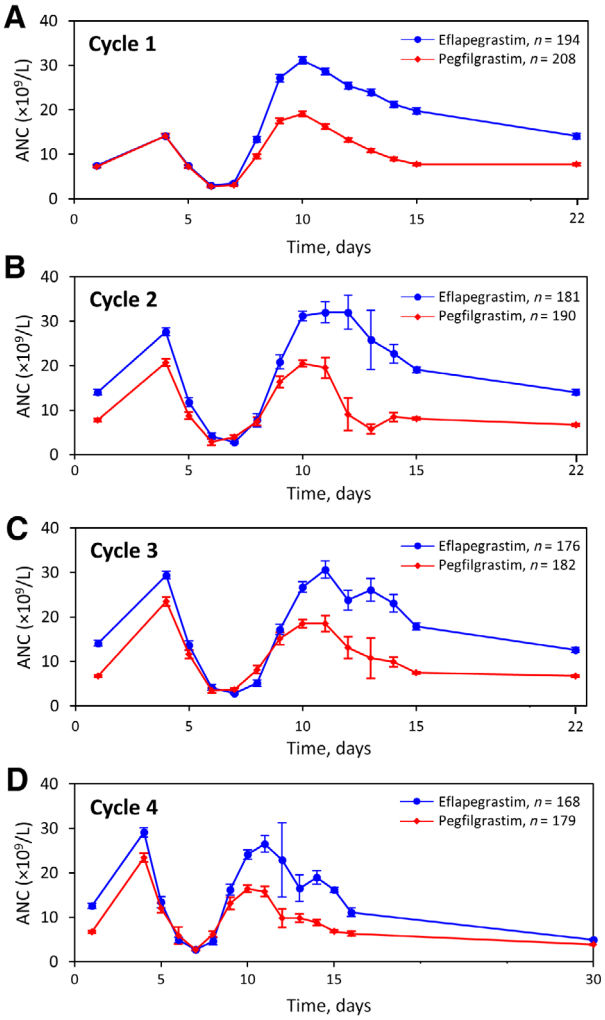

Figure 3. Mean (±SE) ANC profiles for fixed-dose 13.2 mg eflapegrastim (3.6 mg granulocyte-colony stimulating factor [G-CSF]) and standard pegfilgrastim (6 mg G-CSF) in cycles 1–4 in the intent-to-treat population. **(A):** Cycle 1. **(B):** Cycle 2. **(C):** Cycle 3. **(D):** Cycle 4.
Abbreviation: ANC, absolute neutrophil count.

adoption of new, more effective therapies, including an expanding array of targeted and immune-based agents [28, 29]. These new drugs are used as monotherapies but also increasingly in combination regimens with standard cytotoxic chemotherapy and with curative intent in patients with both later- and earlier-stage disease [28, 29]. For this growing number of patients with cancer being treated with curative intent, not receiving full doses of prescribed therapy because of CIN-related complications [20, 25, 26, 28, 30], may be an old problem with newly increasing relevance.

Conclusion

As a novel, long-acting rhG-CSF with increased potency compared with pegfilgrastim, eflapegrastim may represent an attractive option for supporting patients at higher risk for CIN, including for the growing population of patients receiving new, more effective therapies given with curative intent in both later- and earlier-stage disease settings. In addition, ANC profiles for eflapegrastim show a consistently elevated ANC versus pegfilgrastim across all cycles at 14 days post-chemotherapy, which could potentially offer better support for highly myelosuppressive, dose-dense 14-day regimens. Further clinical trials will be needed to explore these possibilities.

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Disclosures

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