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ORIGINAL ARTICLE

Relationship between severity and duration of chemotherapy-induced neutropenia and risk of infection among patients with nonmyeloid malignancies

Yanli Li[1] · Zandra Klippel[2] · Xiaolong Shih[3] · Maureen Reiner[4] · Hong Wang[5] · John H. Page[6]

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Abstract
Purpose Chemotherapy-induced neutropenia (CIN) may increase infection risk for cancer patients; however, there is limited understanding on the quantitative relationships between severity and duration of CIN and infection risk.
Methods This study combined individual data from adult cancer patients receiving no granulocyte colony-stimulating factor during the first chemotherapy cycle in six trials. We used area over the curve (AOC) of absolute neutrophil count (ANC) time-response curve (below different thresholds) to measure the combined effect of severity and duration of CIN. Time-dependent Cox proportional hazards models quantified the hazard of first infection associated with duration of grade 4 or grade 3/4 CIN and the hazard associated with AOC.
Results We analyzed data from 271 patients who had small cell lung cancer, non-Hodgkin's lymphoma, head and neck cancer, or breast cancer; 63.8 % of the patients had advanced cancer, and 77.5 % received chemotherapy regimens with high risk of febrile neutropenia. In the first cycle, 18.8 % of the patients had infection-related hospitalizations. Each additional day patients had grade 3/4 or grade 4 CIN was associated with 28 % (95 % CI 7, 51 %) and 30 % (95 % CI 10, 54 %) increased risk of infection-related hospitalization, respectively. Each unit increase in AOC (day × 10^9/L ANC), with threshold of ANC < 0.5 × 10^9/L, was associated with a significantly increased risk of infection-related hospitalization (hazard ratio 1.98; 95 % CI 1.35, 2.90).
Conclusions Infection risk increases dramatically with each additional day of grade 3 or 4 CIN. Interventions limiting CIN severity and duration are of critical importance to reduce infection risk in cancer patients receiving chemotherapy.

Keywords Chemotherapy-induced neutropenia · Infection · Infection-related hospitalization · Area over the curve

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✉ Yanli Li
yanli.li@amgen.com

[1] Center for Observational Research, Amgen Inc., 1150 Veterans Blvd, South San Francisco, CA 94080, USA

[2] Hematology/Oncology, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA

[3] SimulStat Incorporated, 4370 La Jolla Village Dr, San Diego, CA 92122, USA

[4] Global Biostatistical Science, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA

[5] TechData Service Company, LLC, 700 American Avenue, King of Prussia, PA 19406, USA

[6] Center for Observational Research, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA

Introduction

Myelosuppressive chemotherapy is regularly used to treat different malignancies; however, it is often complicated by hematopoietic toxicity [1]. Chemotherapy-induced neutropenia (CIN) is the most common hematologic toxicity of myelosuppressive chemotherapy and can result in serious consequences [2]. Neutrophils are the most abundant leukocytes in circulation and play a crucial role in defending against infections [3]. Patients with CIN are thus at high risk for developing infection [2]. For patients with cancer, infection can be a life-threatening complication that is associated with suboptimal

delivery of planned chemotherapy and significant increase in morbidity, mortality, and healthcare resource use [4–6].

Absolute neutrophil count (ANC) is a measure of the concentration of neutrophils in blood and is generally used to grade severity of neutropenia [7]. Myelosuppressive chemotherapy decreases ANC until it reaches its lowest point (the nadir), and ANC subsequently rises after bone marrow recovery. The shape of the ANC trajectory curve during chemotherapy varies based on the type of chemotherapy administered, patient characteristics, and use of granulocyte colony-stimulating factor (G-CSF) [8, 9].

G-CSF regulates production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation and differentiation [10, 11]. Filgrastim (NEUPOGEN®, Amgen Inc., Thousand Oaks, CA, USA) [12] and pegfilgrastim (Neulasta®, Amgen Inc., Thousand Oaks, CA, USA) [13] are recombinant human G-CSFs indicated to decrease the incidence of infection, as manifested by febrile neutropenia (FN; neutropenia with fever), in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. Several randomized controlled trials have shown that chemotherapy-treated cancer patients who received prophylactic G-CSF experienced a substantially earlier and shallower ANC nadir and a more rapid recovery of ANC and lower incidence of infection (characterized by FN) compared with patients who did not receive G-CSF prophylaxis [14–16]. Prior studies provided some evidence that cancer patients with lower ANCs and longer duration of severe CIN during chemotherapy were at higher risk of developing infection [17, 18]. However, there is limited information on the quantitative relationship between ANC trajectory and infection risk.

The current study was conducted to quantify the relationship between severity and duration of CIN and risk of infection. We pooled individual patient data from several randomized controlled trials to estimate the hazard of first infection associated with different severities and durations of CIN among patients with nonmyeloid cancer who did not receive prophylactic G-CSF. An understanding of this relationship will facilitate clinical decision-making with respect to the need for preventing infections in cancer patients receiving chemotherapy.

Methods

Study design

The current study pooled individual patient data from six phase 2 or 3 randomized controlled trials sponsored by Amgen Inc. These trials were originally designed to evaluate the effectiveness of G-CSF (filgrastim or pegfilgrastim) in reducing CIN and infection in cancer patients who were receiving myelosuppressive chemotherapy. In the present study, we focused exclusively on the control/placebo arms in which no prophylactic G-CSF was administered to quantify the relationship between severity and duration of CIN with risk of infection-related hospitalization.

Study population

From the Amgen-sponsored phase 2 or 3 clinical trials in CIN, we included trials that had arms within which patients met the following criteria: adult patients with nonmyeloid malignancies who were treated with myelosuppressive chemotherapy; no prophylactic G-CSF was used; body temperature was measured on a daily basis; ANC was measured at least once at baseline of cycle 1 (days 1–4) and at least three times per week between day 4 and cycle end; and infection or FN was included as a study endpoint.

Patients in the selected trials were considered eligible for inclusion in the current analysis if they had ANC $\geq 1500/\mu L$ and normal body temperature before chemotherapy initiation. Patients were excluded if they had a recent infection before chemotherapy, had prior bone marrow or stem cell transplant, received prophylactic antibiotics, or received pelvic irradiation or radiation therapy extending beyond a single involved field within 4 weeks before chemotherapy initiation or during the first chemotherapy cycle.

Exposure and endpoint

Area over the curve (AOC) of ANC time-response curve, below different thresholds, was used to measure both the severity and duration of CIN. AOC was calculated as the area above the ANC time-response curve in the first chemotherapy cycle and below the threshold of $0.5 \times 10^9/L$ or $1.0 \times 10^9/L$. The threshold is based on the Common Terminology Criteria for Adverse Events: ANC $< 0.5 \times 10^9/L$ is categorized as grade 4 neutropenia, and between $0.5 \times 10^9/L$ and $1.0 \times 10^9/L$ as grade 3 neutropenia [7].

We determined whether patients met our definition of infection-related hospitalization by reviewing reasons for hospitalization in patients' case report forms. Patients were classified as having infection-related hospitalization if at least one reason for hospitalization was an infection-related condition (including FN).

Statistical analysis

Descriptive analyses were conducted to characterize study patients' demographics, disease and treatment characteristics, and medical history. Body surface area (BSA) was calculated using the Mosteller formula [19]. Chemotherapy regimens' risk categories for developing FN were classified based on the National Comprehensive Cancer Network (NCCN) guideline [20]. For regimens that remain unclassified, FN incidence

among patients treated with the regimen but with no G-CSF prophylaxis reported either in the literature or in Amgen-sponsored clinical trials was used to determine FN risk category.

The log interpolation technique was used to derive ANC on days without a measurement, using the two ANC measurements between which it was bounded. ANC nadir was the lowest ANC value that occurred over the chemotherapy cycle. Time to ANC nadir was calculated as the number of days for a patient's ANC to reach the nadir. Study patients were censored from the analyses of ANC trajectory upon occurrence of infection-related hospitalization, since potential treatment changes after infection might affect ANC trajectory. AOC of ANC was calculated using the Riemann sum method assuming ANC values to be constant within each day [21].

Time-dependent Cox proportional hazards models were used to quantify the hazard of first infection associated with each additional day of grade 4 CIN (ANC $< 0.5 \times 10^9$/L) or grade 3/4 CIN (ANC $< 1.0 \times 10^9$/L) as well as the hazard associated with AOC, all in the first chemotherapy cycle. The CIN exposure variable was coded as 0 if the patient had not developed CIN at a specific time *t* and was coded as 1 if the patient had developed CIN prior to or at time *t*. Potential confounders adjusted for in the model included sex, age (per 10 years increase), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2–3; nominal scaled indicator variable with ECOG 0 as the reference category), body mass index (BMI) (per 5 kg/m^2), data source (filgrastim or pegfilgrastim trial), tumor stage (advanced, non-advanced), comorbidities related to impaired neutrophil function (congestive heart failure, diabetes, renal disease, or thyroid disorder), and comorbidities related to disturbance of barrier function (chronic obstructive pulmonary disease) [22]. Standard disease definitions were created to identify patients with history of relevant comorbidities from the clinical trial case report forms. Missing ECOG status for five patients was imputed with the median value. Missing weight and/or height for three patients were imputed with their respective medians by sex to derive BMI and BSA.

Results

Pegfilgrastim and filgrastim CIN clinical trials conducted by Amgen Inc. and for which patient-level data were available in-house were identified. Of the 24 pegfilgrastim and 19 filgrastim phase 2 or 3 trials identified, 22 pegfilgrastim and 15 filgrastim trials were excluded based on the study population or design (Fig. 1). Data from patients who met the eligibility criteria from the remaining six studies (see Online Resource 1) were analyzed.

A total of 271 patients were eligible for inclusion in the current study. Demographic and clinical characteristics of the study population are shown in Table 1. Of the eligible patients, 60.5 % were male, 95.2 % were white, and 94.1 % had ECOG performance status ≤2. Mean (± standard deviation (SD)) age of patients was 59.9 (±8.6) years. Of the patients, 56.1 % had small cell lung cancer, 24.4 % had non-Hodgkin's lymphoma, 11.4 % had head and neck cancer, and 8.1 % had breast cancer. Most (63.8 %) patients had advanced cancer, and most (77.5 %) received chemotherapy regimens associated with greater than 20 % FN risk.

In the first chemotherapy cycle, 238 patients (87.8 %) developed grade 3/4 CIN, and 216 patients (79.7 %) developed grade 4 CIN. Median (Q (quartile) 1, Q3) baseline ANC was 5.24 (3.90, 6.90) $\times 10^9$/L, median (Q1, Q3) ANC at nadir was 0.08 (0.03, 0.32) $\times 10^9$/L, and median time for ANC to reach the nadir was 13 days (Table 2). Figure 2 presents the daily median ANC (Q1, Q3) during cycle 1 on a natural logarithmic scale.

During the first chemotherapy cycle, 51 patients (18.8 %) were hospitalized for infection-related diseases. For each additional day that patients had grade 3/4 or grade 4 CIN, their risk of infection-related hospitalization increased by 28 % (hazard

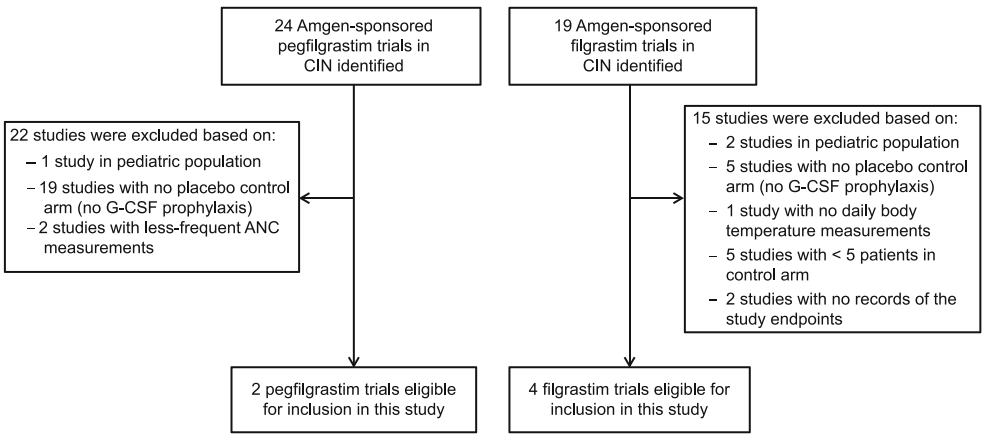

Fig 1 Selection of studies included in the analysis

ANC absolute neutrophil count, *CIN* chemotherapy-induced neutropenia, *G-CSF* granulocyte colony-stimulating factor

Table 1 Demographic and clinical characteristics of study population

	Distribution $N=271$
Sex, *n* (%)	
Male	164 (60.5)
Female	107 (39.5)
Race, *n* (%)	
White or Caucasian	258 (95.2)
Black or African American	9 (3.3)
Asian	3 (1.1)
American Indian or Alaska Native	1 (0.4)
Age, years	
Mean (SD)	59.9 (8.6)
Median (Q1, Q3)	61.0 (55.0, 66.0)
Age group, *n* (%)	
≤40 years	10 (3.7)
>40–50 years	30 (11.1)
>50–60 years	84 (31.0)
>60–70 years	130 (48.0)
>70 years	17 (6.3)
ECOG performance status, *n* (%)	
0	104 (38.4)
1	108 (39.9)
2	43 (15.9)
3	11 (4.1)
Missing	5 (1.8)
BSA, m^2	
Mean (SD)	1.79 (0.22)
Median (Q1, Q3)	1.78 (1.65, 1.93)
BSA group (m^2), *n* (%)	
≤1.7	91 (33.6)
>1.7–1.9	103 (38.0)
>1.9	74 (27.3)
Missing	3 (1.1)
Primary tumor type, *n* (%)	
SCLC	152 (56.1)
NHL	66 (24.4)
Head and neck cancer	31 (11.4)
Breast cancer	22 (8.1)
Tumor stage[a], *n* (%)	
Non-advanced	98 (36.2)
Advanced	173 (63.8)
Chemotherapy regimen, *n* (%)	
Low FN risk	31 (11.4)
Intermediate FN risk	30 (11.1)
High FN risk	210 (77.5)
Medical history, *n* (%)	
COPD	23 (8.5)
Thyroid disorder	10 (3.7)
Diabetes	7 (2.6)
Congestive heart failure	3 (1.1)
Renal disease	3 (1.1)

[a] Tumor stages I, II, and III or "limited" were classified as "non-advanced" and stage IV or "extensive" was classified as "advanced"

BSA body surface area, *COPD* chronic obstructive pulmonary disease, *ECOG* Eastern Cooperative Oncology Group, *FN* febrile neutropenia, *NHL* non-Hodgkin's lymphoma, *Q1* quartile 1, *Q3* quartile 3, *SCLC* small cell lung cancer, *SD* standard deviation

ratio (HR) = 1.28, 95 % confidence interval (CI) 1.07, 1.51) and 30 % (HR = 1.30, 95 % CI 1.10, 1.54), respectively (Table 3).

Table 4 shows elevated risk of infection-related hospitalization associated with each unit (day × 10^9/L ANC) increase in AOC. Each unit increase in the AOC with threshold of ANC < 0.5×10^9/L (grade 4 neutropenia) was associated with an almost two–fold increased risk of infection-related hospitalization (HR = 1.98, 95 % CI 1.35, 2.90). With the threshold of ANC < 1.0×10^9/L (grade 3/4 neutropenia), each unit increase in AOC was also associated with an elevated risk of infection-related hospitalization (HR = 1.42, 95 % CI 1.17, 1.72).

Table 2 Description of ANC trajectory in the first chemotherapy cycle

	Distribution ($N=271$)
Baseline ANC ($\times 10^9$/L)	
Mean	5.87
SD	3.22
Median	5.24
Q1, Q3	3.90, 6.90
ANC at nadir ($\times 10^9$/L)	
Mean	0.44
SD	0.98
Median	0.08
Q1, Q3	0.03, 0.32
Time to ANC nadir (days)	
Mean	13.25
SD	3.25
Median	13.00
Q1, Q3	11.00, 15.00

ANC absolute neutrophil count, *Q1* quartile 1, *Q3* quartile 3, *SD* standard deviation

Discussion

The results of the current study add further evidence to earlier findings that prolonged exposure to severe neutropenia results in an increased risk of infection. Increase in AOC of ANC below given thresholds, a composite measurement for both severity and duration of CIN, is associated with a higher risk of infection in cancer patients receiving chemotherapy. Infection risk increased about 30 % with each additional day of exposure to grade 3 or grade 4 CIN.

Infection has significant clinical consequences and poses a substantial financial cost for cancer patients receiving chemotherapy. The inpatient case fatality rate with FN was reported to be 2.6–10.6 % [4, 23–25]. FN may also result in suboptimal delivery of planned chemotherapy, including reduction or delay of planned doses of chemotherapy or chemotherapy discontinuation [26–29]. Chemotherapy dose delays and dose reductions or discontinuations may lead to poorer disease-free survival, progression-free survival, and overall survival [27, 28, 30–39]. In addition, FN places substantial economic burden on the healthcare system. In the US, the mean (median) hospitalization cost of FN management ranged from

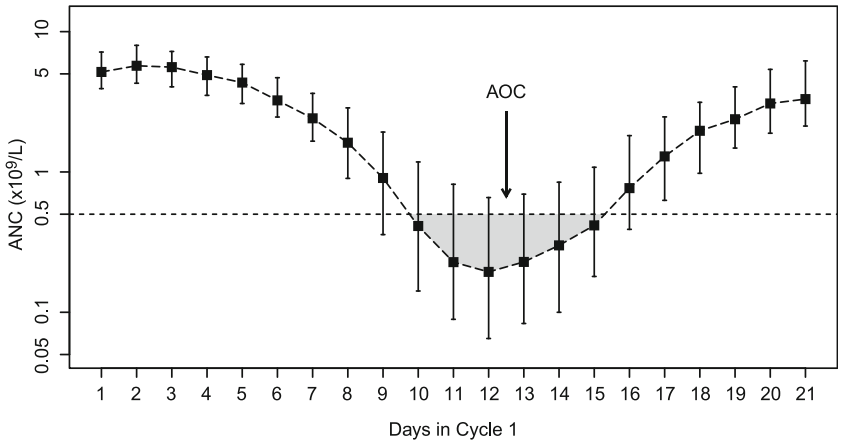

Fig 2 ANC trajectory in the first chemotherapy cycle

Squares represent daily median ANC, *error bars* represent Q1 and Q3 of daily ANC, and AOC is the *grey area* above the ANC time-response curve and below clinical threshold (e.g., ANC < 0.5×10^9/L). ANCs are shown on a natural logarithmic scale. *ANC* absolute neutrophil count, *AOC* area over the curve, *Q1* quartile 1, *Q3* quartile 3

$18,880 to $22,086 ($8376 to $10,396) per episode [4, 23, 40].

Guidelines recommend prophylactic use of G-CSF in patients with a risk of FN greater than 20 % and suggest consideration of G-CSF prophylaxis when the risk is 10–20 % [41–43]. The strong, positive association observed between severity and duration of CIN with risk of infection in the current study provides a more scientific explanation for findings from prior randomized controlled trials, which reported that patients with cancer who received prophylactic G-CSF had significantly lower FN incidence and different ANC trajectories (earlier and shallower ANC nadir and more rapid recovery of ANC) compared with those who did not receive prophylactic G-CSF [14–16].

Our findings are consistent with those of previous studies. Bodey et al. [18] found that risk of infection was higher at lower concentrations of granulocytes (a term that typically includes neutrophils, basophils, and eosinophils) and the risk increased with longer duration (in weeks) of granulocytopenia among 52 leukemia patients receiving chemotherapy. In that study population, any episode of granulocytopenia, regardless of duration, had a 39 % chance of resulting in identified infection. Six weeks of severe granulocytopenia (<100/mm^3) or 12 weeks of persistent granulocytopenia (<1000/mm^3) resulted in 100 % identified infection [18]. However, the extent of myelosuppression experienced by patients with acute leukemia may be different in nature from that experienced by patients with nonmyeloid malignancies who are receiving chemotherapy. Another analysis of two randomized phase 3 trials comparing pegfilgrastim to filgrastim reported that risk of FN increased with duration (1, 2, 3, and ≥4 days) of severe neutropenia (ANC < 0.5×10^9/L), with an odds ratio of 2.28 per day increase in duration of severe neutropenia using logistic regression analysis [17]. In a

Table 3 Risk of infection-related hospitalization associated with each additional day of CIN adjusted for potential confounders

	Infection associated with each additional day of CIN, HR (95 % CI)[a]
Grade 4 CIN (ANC < 0.5×10^9/L)	1.30 (1.10, 1.54)
Grade 3/4 CIN (ANC < 1.0×10^9/L)	1.28 (1.07, 1.51)

[a] Adjusted for sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), data source, tumor stage, comorbidities related to impaired neutrophil function (congestive heart failure, diabetes, renal disease, and thyroid disorder), and comorbidities related to disturbance of barrier function (chronic obstructive pulmonary disease (COPD))

ANC absolute neutrophil count, *CIN* chemotherapy-induced neutropenia, *HR* hazard ratio, *CI* confidence interval

Table 4 Risk of infection-related hospitalization associated with each unit increase in AOC of ANC (day × 10^9/L ANC) adjusted for potential confounders

	Infection associated with each unit increase of AOC, HR (95 % CI)[a]
AOC of ANC (ANC < 0.5×10^9/L)	1.98 (1.35, 2.90)
AOC of ANC (ANC < 1.0×10^9/L)	1.42 (1.17, 1.72)

[a] Adjusted for sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), data source, tumor stage, comorbidities related to impaired neutrophil function (congestive heart failure, diabetes, renal disease, and thyroid disorder), and comorbidities related to disturbance of barrier function (chronic obstructive pulmonary disease (COPD))

ANC absolute neutrophil count, *AOC* area over the curve, *HR* hazard ratio, *CI* confidence interval

previously conducted simulation study, the Cox proportional hazards model with time-updated exposure was shown to provide the least biased estimates compared to logistic regression or Cox proportional hazards model with constant exposure, when studying the relationship between a biomarker and a binary outcome when duration of that biomarker stays beyond a threshold that is the predictor of the event of interest [44]. Further, the use of FN (which includes neutropenia in its definition) as an outcome in a model with neutropenia as an exposure may overestimate the effect estimate.

In the current study, we focused on cancer patients receiving no G-CSF prophylaxis to enable us to get an accurate estimate of the relationship of interest. Moreover, the current study used more quantitative methods to estimate the effects of severity and duration of CIN on risk of infection compared to the previous studies. Specifically, we used a composite variable, AOC of ANC, to measure severity and duration of CIN simultaneously and quantified the risk of infection with each additional day increase of CIN at different severities. Further, we adjusted for potential confounding by controlling for a number of covariates in multivariate regression models to better estimate these relationships (Tables 3 and 4). Where possible, definitions for endpoints and all the covariates were standardized across different trials, and we also used standardized inclusion and exclusion criteria for patient selection into this pooled analysis.

Despite the demonstrated improvements we made to the study methodology, several limitations of the current study should be noted. First, patients enrolled in filgrastim trials conducted in the 1990s as well as those enrolled in more recent pegfilgrastim trials were included in this pooled analysis. Clinical practice patterns and data collection and reporting methods are likely to have changed over this time period. To account for the temporal changes, data source (filgrastim or pegfilgrastim trial) was adjusted for in the analysis. Another limitation is that the analysis relied on existing data collected in the original clinical trials, and there is a possibility of differences in definitions used for evaluated outcomes across studies. Wherever possible, we have standardized to common definitions for this study. Lastly, this study analyzed data from patients originally recruited for clinical trials in which individuals with poor performance status or serious medical illnesses were likely excluded from enrollment.

Conclusions

In this study, we observed that severity and duration of CIN increase the risk of infection in cancer patients receiving chemotherapy. Interventions that limit the extent and duration of CIN are of critical importance in preventing infection and further improving subsequent treatment outcomes in this patient population.

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Compliance with ethical standards

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Conflict of interest Yanli Li, Zandra Klippel, Maureen Reiner, and John H. Page are employees of and own stock in Amgen Inc. Xiaolong Shih and Hong Wang are consultants and are funded by Amgen Inc.

Research involving human participants and/or animals Informed consent was obtained from all individual participants included in the original studies. For this type of study, formal consent is not required.

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