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Supplemental online content for:

Real-World Impact of Prophylactic Growth Factor Use on Timing of Febrile Neutropenia and Infection After High-Risk Chemotherapy

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eMethods

Data Sources

Sample patients were selected from a 100% census of data from the US Medicare program on beneficiaries with traditional fee-for-service Medicare insurance coverage for hospital (Part A), physician (Part B), and/or pharmacy (Part D) claims during January 1, 2005, through December 31, 2020. The component research-identifiable data files, made available by the Centers for Medicare & Medicaid Services (CMS), provide a comprehensive and longitudinal picture of healthcare use among Medicare beneficiaries. In addition to claims data for all medical services covered by the program, including information on dates of service, procedures performed, and associated diagnosis codes, the files also include enrollment and select demographic information for all covered beneficiaries, as well as detailed information on prescription drug claims for beneficiaries with coverage under Part D. All data manipulation and analyses were conducted remotely by the licensed authors using SAS software (SAS Institute Inc.) on the CMS Virtual Resource Data Center environment.

Study Patient Samples

The study sample consisted of Medicare beneficiaries initiating select chemotherapy for the treatment of breast cancer during January 1, 2005, through December 31, 2020. Qualifying chemotherapy regimens included 3 with a high risk for febrile neutropenia (FN) per the 2022 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hematopoietic Growth Factors: TAC (docetaxel/doxorubicin/cyclophosphamide), TC (docetaxel/cyclophosphamide), and TCH (docetaxel/carboplatin/trastuzumab).[1] A fourth regimen classified as high risk for FN by NCCN, dose-dense AC-T (dose-dense doxorubicin + cyclophosphamide followed by dose-dense paclitaxel), was omitted from the list of qualifying regimens due to an inability to determine intended cycle duration in administrative claims data. Because intended cycle length is not documented in Medicare claims, and because incident neutropenia may result in dose delays, dose-dense AC-T could not be reliably differentiated from its intermediate-risk counterpart, non–dose-dense AC-T.

Chemotherapy regimens were identified for each patient in the data based on the presence and relative timing of medical claims for component agents (supplemental eAppendix 1). For each patient, the study index date was defined as the earliest date of chemotherapy administration within the first observed 5-day period with evidence of administration of each agent included in a regimen of interest. Patients receiving any other chemotherapy on or up to 4 days after the index date were excluded.

Each sample patient was required to have at least 2 distinct medical claims indicating a diagnosis of breast cancer (supplemental eAppendix 2), including at least one on the index date and at least one during the 6-month baseline period immediately preceding the index date. To ensure complete visibility of medical claims throughout the full observation period, patients were also required to be continuously enrolled in Medicare Parts A and B and geographically located in the 50 US states or Washington DC throughout the baseline period and first chemotherapy cycle. Patients with evidence of chemotherapy administration during the baseline period and/or 5 to 13 days after the index date, evidence of radiation therapy (supplemental eAppendix 3) in the 2 months immediately preceding the index date, evidence of granulocyte colony-stimulating factor (G-CSF) use during the baseline period, and/or evidence of FN or infection (defined below) on the index date were ineligible for this study.

Study Outcomes and Unadjusted Analyses

Proportions of sample patients receiving primary prophylactic (PP) G-CSF therapy in the first chemotherapy cycle were calculated by regimen and for all regimens combined. PP G-CSF use was defined as ≥1 medical claim and/or prescription fill for a long- or short-acting G-CSF (supplemental eAppendix 4) on or up to 3 days after the index date.

Baseline characteristics evaluated during the 6-month baseline period immediately preceding the index date were then summarized separately for and compared between patients receiving and not receiving PP G-CSF therapy during the first chemotherapy cycle. Because all patients in the sample were required to have at least 1 breast cancer diagnosis during the baseline period, a modified Gagne comorbidity index[2] score was calculated for each patient using zero weights for the any tumor and metastatic cancer components.

Finally, a third set of analyses were performed to explore incidence and timing of FN or infection (FN/infection) and 2 related outcomes during the first chemotherapy cycle, defined individually for each patient as the period beginning on the index date and ending the day before the next observed chemotherapy administration occurring 14 to 27 days

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later, if applicable. For patients not receiving additional chemotherapy 14 to 27 days after the index date, a 28-day cycle was assumed in order to avoid falsely excluding patients without further chemotherapy use or missing their FN/infection diagnoses. Proportions of patients experiencing each outcome of interest during the first cycle, overall and by regimen, were estimated separately for and compared between patients receiving and not receiving first-cycle PP G-CSF therapy. Because a diagnosis code specifically for FN does not exist, medical coders may code FN as infection to maximize reimbursement. They may also omit diagnoses unlikely to affect reimbursement. For this reason, FN/infection, our primary outcome measure, was defined algorithmically based on a method designed and validated by Weycker et al[3] as inpatient hospitalization associated with ≥1 diagnosis code indicating neutropenia, infection, or fever (supplemental eAppendix 5). Similar algorithms were used to define 2 secondary endpoints:

1. "Strict" FN (sFN): Inpatient hospitalization with either (1) a primary diagnosis of neutropenia, or (2) a secondary diagnosis of neutropenia with an accompanying infection or fever diagnosis in any position; and
2. Infection-related hospitalization (IRH): Inpatient hospitalization associated with ≥1 infection or fever diagnosis.

Differences in the timing of observed FN/infection, sFN, and IRH events within the first cycle for PP G-CSF users and nonusers were assessed and captured via 2 additional sets of cohort-specific proportions of patients: one focused on events occurring in the first week of the first cycle (week 1), and another focused on events in the remainder of the cycle (beyond week 1). For additional insight into the relative timing of first-cycle FN/infection, sFN, and IRH between PP G-CSF users and nonusers, a subgroup analysis of time from chemotherapy initiation to the given outcome of interest was conducted for each endpoint among those experiencing the outcome during the first chemotherapy cycle.

For all unadjusted analyses, where relevant, cohort-specific shares of patients were compared using chi-squared and Fisher exact tests, whereas numeric variables (eg, age) were compared using Wilcoxon rank sum tests.

Multivariable Analysis

Multivariable regression analyses were conducted to evaluate associations between PP G-CSF use and each of FN/infection, sFN, and IRH in week 1 versus beyond week 1 of chemotherapy cycle 1 while controlling for observed differences in patient characteristics at baseline between those treated with PP G-CSFs and those not treated with PP G-CSFs. Multivariable logistic regression was used to estimate adjusted incidence proportions and odds ratios for PP G-CSF use relative to nonuse for dependent variables FN/infection in week 1 of cycle 1, FN/infection beyond week 1 of cycle 1, sFN in week 1, sFN beyond week 1, IRH in week 1, and IRH beyond week 1. Separate models were fitted to the full (pooled) patient sample and to each unique subgroup of patients defined by chemotherapy regimen. In addition to PP G-CSF status, regimen (models fit to full patient sample, only), and cycle duration (models with dependent variables evaluated beyond week 1 of cycle 1, only), each model controlled for the following patient characteristics for which significant differences ($\alpha < .05$) between patients receiving and not receiving PP G-CSFs were observed at baseline: sex, age, Census region, Medicaid eligibility, year of chemotherapy initiation, modified Gagne comorbidity index score, presence of neutropenia at baseline, total inpatient length of stay prior to chemotherapy initiation, total skilled nursing facility length of stay prior to chemotherapy initiation, number of emergency department visits prior to chemotherapy initiation, and number of outpatient visits prior to chemotherapy initiation.

Adjusted incidence proportions and odds ratios were estimated using multivariable regression in lieu of propensity-score matching for 2 primary reasons. First, adjusted associations generated via multivariable regression are informed by every patient in the sample or designated subgroup, as opposed to only a subset of patients for whom matched counterparts can be found. This may lead to results that are more representative of and generalizable to the full population of interest. Second, in some cases, the total number of sample patients in a designated subgroup and cohort who experienced a given event during a select period of interest is already close to or below the 11-patient minimum required by CMS's privacy policies for reporting patient counts and other summary statistics without suppression. Although post-match patient counts for some measures risk falling below the suppression threshold, regression-adjusted estimates represent all sample patients (not just those with the outcome event) and therefore do not carry the same risk of suppression.

Subgroup Sensitivity Analyses

Lastly, 3 sensitivity analyses were conducted to evaluate the impact of select sample inclusion criteria on estimated proportions of patients experiencing first-cycle FN/infection. In the first, unadjusted proportions of patients experiencing FN/infection

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eMethods (cont.)

were calculated among those patients with continuous enrollment in Medicare Part D throughout the baseline period, on the index date, and throughout the first chemotherapy cycle. The second sensitivity analysis focused on patients aged ≥65 years at the start of the baseline period. In the third sensitivity analysis, proportions of patients with FN/infection were estimated among sample patients who initiated chemotherapy in 2016 or later.

References

1. Griffiths EA, Roy V, Alwan L, et al. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors Version 1.2022. Accessed January 15, 2022. To view the most recent version, visit https://www.nccn.org
2. Gagne JJ, Glynn RJ, Avorn J, et al. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749–759.
3. Weycker D, Sofrygin O, Seefeld K, et al. Technical evaluation of methods for identifying chemotherapy-induced febrile neutropenia in healthcare claims databases. BMC Health Serv Res 2013;13:60.

eAppendix 1. Chemotherapy HCPCS Codes

Agent(s)	HCPCS Code(s)	Agent(s)	HCPCS Code(s)
Ado-trastuzumab emtansine	C9131, J9354	Clofarabine	C9129, J90272
Aldesleukin	J9015	Cyclophosphamide	C9420, C9421, J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097
Alemtuzumab	C9110, J0202, J9010, Q9979, S0087	Cytarabine	C1166, C9422, J9098, J9100, J9110
Arsenic trioxide	C9012, J9017	Dacarbazine	C9423, J9130, J9140
Asparaginase	C9289, J9019, J9020	Dactinomycin	J9120
Atezolizumab	C9483	Daratumumab	C9476, J9415
Avelumab	C9491	Daratumumab hyaluronidase	C9062, J9144
Azacitidine	C9218, J9025, S0168	Daunorubicin	C9424, J9150, J9151
Belantamab mafodotin-blmf	C9069, J9037	Daunorubicin-cytarabine liposome	C9024
Belinostat	J9032	Decitabine	C9231, J0894
Bendamustine	C9243, J9033, J9034	Denileukin diftitox	J9160
Bendamustine hcl	J9036	Denosumab	J0897
Bevacizumab	C9214, C9257, J9035, Q2024, Q5107, Q5118, S0116	Docetaxel	J9170, J9171
Bleomycin	C9417, J9040	Doxorubicin	C9415, J9000, J9001, J9002, Q2048, Q2049, Q2050
Blinatumomab	C9449, J9039	Durvalumab	C9492
Bortezomib	C9207, J9041, S0115	Elotuzumab	C9477, J9176
Brentuximab vedotin	C9287, J9042	Enfortumab vedotin-ejfv	J9177
Busulfan	C1178, J0594, J8510	Epirubicin	C1167, J9178, J9180
Cabazitaxel	C9276, J9043	Eribulin mesylate	C9280, J9179
Calaspargase pegol-mknl	J9118	Etoposide	C9414, C9425, J8560, J9181, J9182
Capecitabine	J8520, J8521	Everolimus	J7527, J8561
Carboplatin	J9045	Fam-trastuzumab deruxtecan-nxki	J9358
Carfilzomib	C9295, J9047	Floxuridine	C9426, J9200
Carmustine	C9437, J9050	Fludarabine	C9262, J8562, J9185, Q2025
Cemiplimab-rwlc	J9113	Fluorouracil	J9190
Cetuximab	C9215, J9055	Gefitinib	J8565
Chlorambucil	S0172	Gemcitabine	J9201
Cisplatin	C9418, J9060, J9062	Gemcitabine HCl	J9198
Cladribine	C9419, J9065	Gemtuzumab ozogamicin	C9004, J9203, J9300
Hydroxyurea	S0176	Obinutuzumab	C9021, J9301
Ibritumomab tiuxetan	A9522, A9523, A9542, A9543, C1082, C1083, C9117, C9118	Ofatumumab	C9260, J9302
Idarubicin	C9429, J9211	Olaratumab	J9285
Ifosfamide	C9427, J9208	Omacetaxine	C9297, J9262
Imatinib mesylate	S0088	Oxaliplatin	C9205, J9263
Interferon alfa-2a	J9213	Paclitaxel	C9127, C9431, J9264, J9265, J9267
Interferon alfa-2b	J9214	Panitumumab	C9235, J9303
Interferon gamma-1b	J9216	Pegaspargase	J9266
Ipilimumab	C9284, J9228	Pembrolizumab	C9027, J9271
Irinotecan	C9474, J9206	Pemetrexed	C9213, J9304, J9305

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eAppendix 1. Chemotherapy HCPCS Codes (cont.)

Agent(s)	HCPCS Code(s)	Agent(s)	HCPCS Code(s)
Isatuximab-irtc	J9227	Pentostatin	J9268
Ixabepilone	C9240, J9207	Pertuzumab	C9292, J9306
Leucovorin	J0640	Pertuzumab, trastuzumab, hyaluronidase-zzxf	J9316
Levamisole	S0177	Plicamycin	J9270
Levoleucovorin	J0641, J0642	Polatuzumab vedotin-piiq	J9309
Lomustine	C9017, S0178	Porfimer sodium	J9600
Lurbinectedin	J9223	Pralatrexate	C9259, J9307
Mechlorethamine	J9230	Procarbazine	S0182
Melphalan	J8600, J9245, J9246	Ramucirumab	C9025, J9308
Mercaptopurine	S0108	Rituximab	J9310, J9312, Q5115, Q5119
Mesna	C9428, J9209	Rituximab and hyaluronidase	J9311
Methotrexate	J8610, J9250, J9260	Romidepsin	C9065, C9265, J9315, J9318, J9319
Mitomycin	C9432, J9280, J9290, J9291	Sacituzumab govitecan-hziy	C9066, J9317
Mitomycin pyelocalyceal instillation	C9064, J9281	Siltuximab	C9455, J2860
Mitoxantrone	J9293	Streptozocin	J9320
Mogamulizumab-kpkc	J9204	Tafasitamab-cxix	C9070, J9349
Moxetumomab-pasudotox-tdfk	J9313	Tagraxofusp-erzs	J9269
Naxitamab-gqgk	J9348	Talimogene laherparepvec	C9472, J9325
Necitumumab	C9475, J9295	Temozolomide	C1086, C9253, J8700, J9328
Nelarabine	J9261	Temsirolimus	C9239, J9330
Nivolumab	C9453, J9299	Teniposide	Q2017
Thiotepa	C9433, J9340	Valrubicin	J9357
Topotecan	J8705, J9350, J9351	Vinblastine	J9360
Tositumomab	A9533, A9534, A9544, A9545, G3001	Vincristine	J9370, J9375, J9380
Trabectedin	C9480	Vincristine liposomal	J9371
Trastuzumab	J9355, Q5112, Q5113, Q5114, Q5116, Q5117	Vinorelbine	C9440, J9390
Trastuzumab and hyaluronidase-oysk	J9356	Ziv-aflibercept	C9296, J9400
Trimetrexate glucuronate	J3305		

eAppendix 2. Breast Cancer Diagnosis Codes

Code Type	Codes
ICD-9-CM	174.0–174.6, 174.8–175.0, 175.9
ICD-10-CM	C50.011–C50.012, C50.019, C50.021–C50.022, C50.029, C50.111–C50.112, C50.119, C50.121–C50.122, C50.129, C50.211–C50.212, C50.219, C50.221–C50.222, C50.229, C50.311–C50.312, C50.319, C50.321–C50.322, C50.329, C50.411–C50.412, C50.419, C50.421–C50.422, C50.429, C50.511–C50.512, C50.519, C50.521–C50.522, C50.529, C50.611–C50.612, C50.619, C50.621–C50.622, C50.629, C50.811–C50.812, C50.819, C50.821–C50.822, C50.829, C50.911–C50.912, C50.919, C50.921–C50.922, C50.929

eAppendix 3. Radiation Procedure Codes

Code Type	Codes
HCPCS	77280, 77285, 77290, 77295, 77299–77301, 77305, 77310, 77315, 77321, 77326–77328, 77331–77334, 77336, 77338, 77371–77373, 77399, 77401–77404, 77406–77409, 77411–77414, 77416–77418, 77421–77425, 77427, 77431–77432, 77435, 77469–77470, 77499, 77520, 77522–77523, 77525, 77750, 77761–77763, 77776–77778, 77785–77787, 77789, 77799, G0173, G0251, G0256, G0261, G0339, G0340
ICD-9-CM	92.20–92.33, 92.39
ICD-10-PCS	D0000ZZ–D027JZZ, D7000ZZ–D728JZZ, D7Y08ZZ–D7Y8FZZ, D8000ZZ–D820JZZ, D8Y07ZZ–D8Y0FZZ, D9000ZZ–D92DJZZ, D9Y07ZZ–D9YF8ZZ, DB000ZZ–DB28JZZ, DBY07ZZ–DBY8KZZ, DD000ZZ–DD27JZZ, DDY07ZZ–DDY8KZZ, DF000ZZ–DF23JZZ, DFY07ZZ–DFY3KZZ, DG000ZZ–DG25JZZ, DGY07ZZ–DGY5KZZ, DH020ZZ–DH0B6ZZ, DHY27ZZ–DHYCFZZ, DM000ZZ–DM21JZZ, DMY07ZZ–DMY1KZZ, DP000ZZ–DP0C6ZZ, DPY07ZZ–DPYCFZZ, DT000ZZ–DT23JZZ, DTY07ZZ–DTY3FZZ, DU000ZZ–DU22JZZ, DUY07ZZ–DUY2FZZ, DV000ZZ–DV21JZZ, DVY07ZZ–DVY1FZZ, DW010ZZ–DW26JZZ, DWY17ZZ–DWY6FZZ

Abbreviation: HCPCS, Healthcare Common Procedure Coding System.

eAppendix 4. G-CSF Procedure and Drug Codes

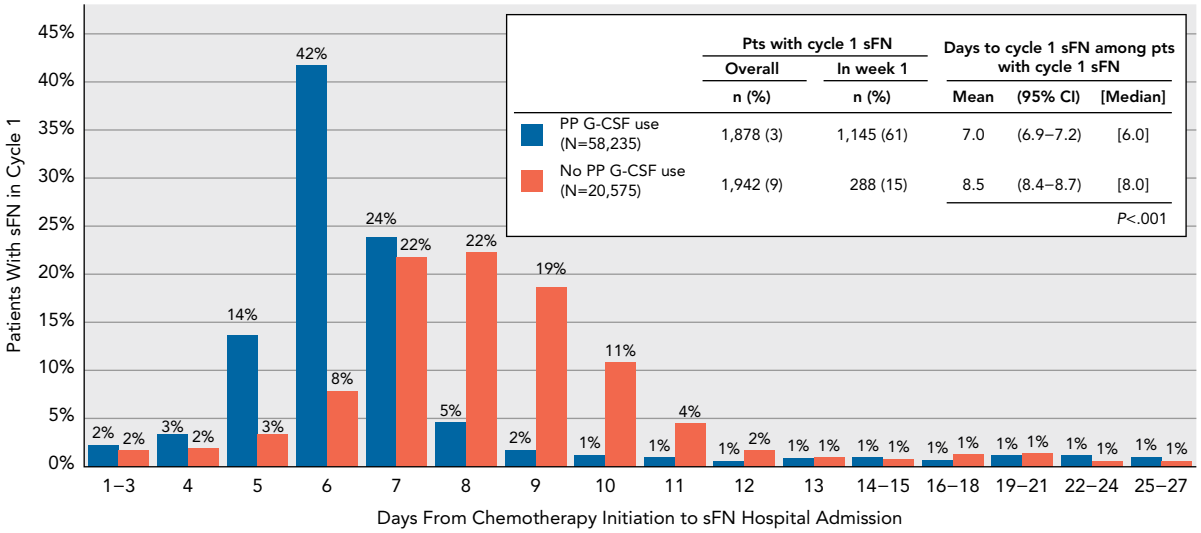
Code Type	Codes
HCPCS	C9058, C9119, J1440–J1442, J1446–J1447, J2505, J3590, Q4053, Q5101, Q5108, Q5110–Q5111, Q5122, S0135
NDC	000690291xx–000690294xx, 000690324xx, 545694824xx, 548682522xx, 548683050xx, 548685020xx, 548685229xx, 555130190xx, 555130192xx, 555130209xx, 555130347xx–555130348xx, 555130530xx, 555130546xx, 555130924xx, 613140304xx, 613140312xx, 613140318xx, 613140326xx, 613140866xx, 634590910xx, 634590912xx, 634590918xx, 634590920xx, 674570833xx, 701140101xx

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Code.

eAppendix 5. Proxy Diagnosis Codes Used to Identify Evidence of FN/Infection[a], sFN[b], and IRH[c]

Condition	ICD-9-CM Diagnosis Codes	ICD-10-CM Diagnosis Codes
Fever	780.6, 780.60–780.66	R50, R50.2, R50.8, R50.81–R50.84, R50.9
Infection	002, 002.0–002.3, 002.9, 003, 003.0–003.2, 003.20–003.24, 003.29, 003.8–003.9, 004, 004.0–004.3, 004.8–004.9, 008.0, 008.00–008.04, 008.09, 008.1–008.4, 008.41–008.47, 008.49, 008.5, 034, 034.0–034.1, 035–036, 036.0–036.4, 036.40–036.43, 036.8, 036.81–036.82, 036.89, 036.9, 038, 038.0–038.1, 038.10–038.12, 038.19, 038.2–038.4, 038.40–038.44, 038.49, 038.8–038.9, 039, 039.0–039.4, 039.8–039.9, 040, 040.0–040.4, 040.41–040.42, 040.8, 040.81–040.82, 040.89, 041, 041.0, 041.00–041.05, 041.09, 041.1, 041.10–041.12, 041.19, 041.2–041.4, 041.41–041.43, 041.49, 041.5–041.8, 041.81–041.86, 041.89, 041.9, 101, 112, 112.0–112.5, 112.8, 112.81–112.85, 112.89, 112.9, 114, 114.0–114.5, 114.9, 115, 115.0, 115.00–115.05, 115.09, 115.1, 115.10–115.15, 115.19, 115.9, 115.90–115.95, 115.99, 116, 116.0–116.2, 117, 117.0–117.9, 118, 320, 320.0–320.3, 320.7–320.8, 320.81–320.82, 320.89, 320.9, 321, 321.0–321.4, 321.8, 324, 324.0–324.1, 324.9, 360, 360.0, 360.00–360.04, 360.1, 360.11–360.14, 360.19, 360.2, 360.20–360.21, 360.23–360.24, 360.29, 360.3, 360.30–360.34, 360.4, 360.40–360.44, 360.5, 360.50–360.55, 360.59, 360.6, 360.60–360.65, 360.69, 360.8, 360.81, 360.89, 360.9, 376, 376.0, 376.00–376.04, 376.1, 376.10–376.13, 376.2, 376.21–376.22, 376.3, 376.30–376.36, 376.4, 376.40–376.47, 376.5, 376.50–376.52, 376.6, 376.8, 376.81–376.82, 376.89, 376.9, 380.14, 383, 383.0, 383.00–383.01, 383.03, 383.1–383.2, 383.20–383.22, 383.3, 383.30–383.33, 383.8, 383.81, 383.89, 383.9, 420.99, 421, 421.0–421.1, 421.9, 461, 461.0–461.3, 461.8–461.9, 462–463, 475, 481–482, 485–486, 491.21, 494, 494.0–494.1, 510, 513, 522.5, 522.7, 526.4, 527.3, 528.3, 540–542, 562.01, 562.03, 562.11, 562.13, 566–567, 569.5, 569.61, 572, 575, 590, 599, 601, 675.1, 680–683, 685–686, 711, 728.86, 730, 785.4, 785.52, 790.7, 958.3, 995.91–995.92, 996.6, 998.5, 999.3	A01–A03, A04.0–A04.9, A38.9, A39–A41, A41.9, A42–A43, A46, A48.0–A48.5, 48.51–A48.52, A48.8, A49.3, A60.1, A69.0–B37.0–B37.1, B37.5–B37.8, B38–B43, B44.9–B45.3, B45.7–B45.9, B46, B47.0–B47.1, B47.9–B48.4, B48.8, B49, B95–B96, E83.2, G00–G02, G04.2, G06, H05.0, H32, H44.0, H60.20, H70.0–I30.8, I32–I33, I39–I39, I96–J01, J02.0, J02.9, J03.00, J03.90, J13–J14, J15.0–J15.6, J15.8–J15.9, J17, J18.0–J18.1, J18.9, J36, J44.1, J47, J85–J86, K04.6–K04.7, K11.3, K12.2–K12.2, K35–K37, K57.12–K57.13, K57.32–K57.33, K61, K63.0, K65, K67, K68.11–K68.12, K68.19, K68.9, K75.0, K81.0, K90.81, K94.02, K94.12, L02, L03.0–L03.3, L03.8–L03.9, L04.9, L05.01–L05.02, L08.0–L08.1, L08.8, L08.81–L08.82, L08.89, L08.9, L88, L98.0, M00, M27.2, M46.2–M46.3, M60.009, M72.6, M86, M89.6, M90.8, N10–N12, N15–N16, N28.84–N28.86, N39.0, N41, N51, O91.1, R65.20–R65.21, R78.81, T79.8, T80.2, T81.4, T82.6–T82.7, T83.6, T84.5–T84.7, T85.7, T88.0
Neutropenia	288.0, 288.00–288.04, 288.09	D70, D70.0–D70.4, D70.8–D70.9

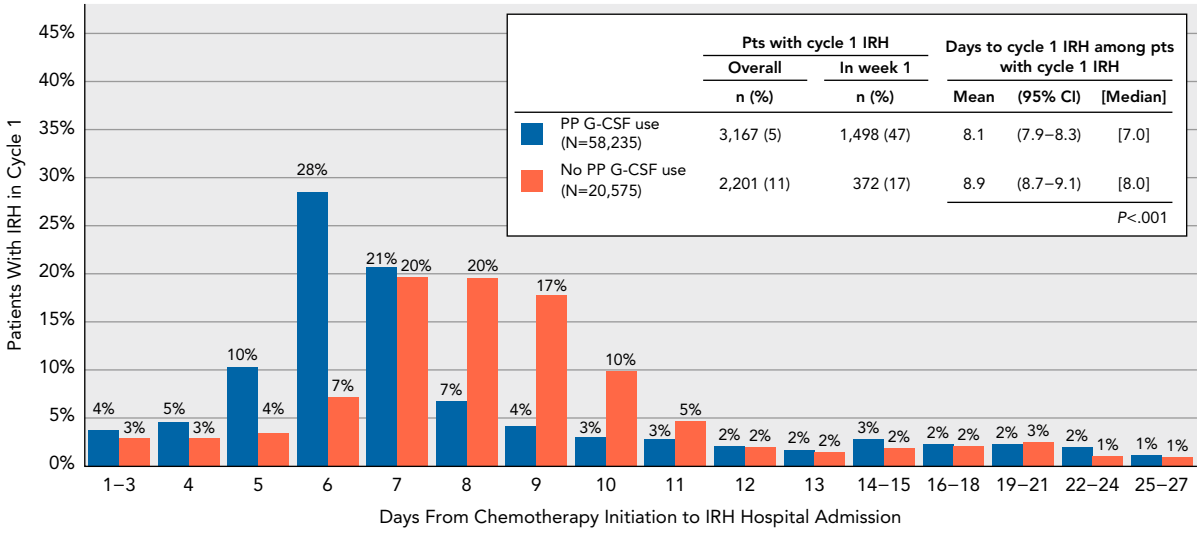
Abbreviations: FN, febrile neutropenia; IRH, infection-related hospitalization; sFN, febrile neutropenia under strict definition.
[a]Defined as inpatient hospitalization with an associated diagnosis code for neutropenia, infection, or fever.
[b]Defined as inpatient hospitalization with either (1) an associated primary diagnosis code for neutropenia, or (2) an associated secondary diagnosis code for neutropenia and an associated primary or secondary diagnosis code for infection or fever.
[c]Defined as inpatient hospitalization with an associated diagnosis code for infection or fever.



Number of patients experiencing sFN

	1–3	4	5	6	7	8	9	10	11	12	13	14–15	16–18	19–21	22–24	25–27
PP G-CSF use:	43	63	256	783	448	87	33	23	18	11	17	19	13	22	23	19
No PP G-CSF use:	32	37	66	153	423	432	362	211	86	32	19	16	24	27	11	11

eFigure 1. Time to first-cycle sFN among patients experiencing first-cycle sFN, by PP G-CSF status.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; PP, primary prophylactic; pts, patients; sFN, febrile neutropenia under strict definition.



Number of patients experiencing IRH

	1–3	4	5	6	7	8	9	10	11	12	13	14–15	16–18	19–21	22–24	25–27
PP G-CSF use:	122	146	328	902	655	217	135	99	93	69	56	93	75	75	63	39
No PP G-CSF use:	65	70	78	159	434	431	365	219	106	46	34	44	47	57	25	21

eFigure 2. Time to first-cycle IRH among patients experiencing first-cycle IRH, by PP G-CSF status.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; IRH, infection-related hospitalization; PP, primary prophylactic; pts, patients.

eTable 1. Sample Selection

Criteria	Patients, n
1) Administration of ≥1 chemotherapy agent (1/1/2005–12/31/2020)	6,181,811
2) ≥1 diagnosis for breast cancer (1/1/2005–12/31/2020)	983,682
3) Evidence of administration of a select high-risk chemotherapy regimen[a] during a 5-day identification period (earliest is index date)	109,365
4) No evidence of chemotherapy administration 5–13 days following the index date	100,751
5) No evidence of chemotherapy administration during the 6-month period immediately preceding the index date (baseline period)	94,354
6) ≥2 breast cancer diagnoses, including ≥1 on the index date and ≥1 during the baseline period	92,026
7) Continuous enrollment in Medicare Parts A and B on the index date	91,320
8) Continuous enrollment in Medicare Parts A and B throughout the baseline and study periods[b]	84,044
9) Geographically located in the 50 US states and Washington DC	83,889
10) No evidence of radiation therapy in the 2 months prior to the index date	79,800
11) No evidence of G-CSF use in the baseline period	78,819
12) No evidence of FN/infection[c] on the index date	78,810
Final sample size	**78,810**

Abbreviations: FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.
[a]High-risk regimens include TAC (docetaxel/doxorubicin/cyclophosphamide), TC (docetaxel/cyclophosphamide), and TCH (docetaxel/carboplatin/trastuzumab).
[b]The study period was defined individually for each patient as the period beginning the day after the index date and ending the earlier of (1) the day before the first observed chemotherapy administration occurring at least 13 days later, if applicable, and (2) day 27 post index date.
[c]FN/infection was defined as inpatient hospitalization with an associated diagnosis code for neutropenia, infection, or fever.

eTable 2. Additional Baseline-Period[a] Characteristics[b]

	All n (%)	PP G-CSF use n (%)	No PP G-CSF use n (%)	*P* Value[c]
Total, N	78,810	58,235	20,575	
Demographics				
Census region				
South	35,281 (45)	25,988 (45)	9,293 (45)	.18
Midwest	18,786 (24)	13,790 (24)	4,996 (24)	.08
West	13,918 (18)	10,126 (17)	3,792 (18)	<.001
Northeast	10,825 (14)	8,331 (14)	2,494 (12)	<.001
Diagnoses				
Modified GCI[d]				
Score, mean [SD], median	0.8 [1.8], 0.0	0.9 [1.8], 0.0	0.8 [1.8], 0.0	<.001
Hypertension	57,510 (73)	42,573 (73)	14,937 (73)	.16
Chronic pulmonary disease	18,268 (23)	13,500 (23)	4,768 (23)	.98
Cardiac arrhythmias	13,778 (17)	10,541 (18)	3,237 (16)	<.001
Deficiency anemia	12,576 (16)	9,345 (16)	3,231 (16)	.25
Congestive heart failure	11,534 (15)	8,524 (15)	3,010 (15)	.98
Psychosis	8,764 (11)	6,703 (12)	2,061 (10)	<.001
Peripheral vascular disease	8,362 (11)	6,257 (11)	2,105 (10)	.04
Complicated diabetes	7,688 (10)	5,932 (10)	1,756 (9)	<.001
Fluid and electrolyte disorders	6,385 (8)	4,652 (8)	1,733 (8)	.05
Renal failure	5,946 (8)	4,572 (8)	1,374 (7)	<.001
Liver disease	4,105 (5)	3,177 (5)	928 (5)	<.001
Coagulopathy	2,877 (4)	2,158 (4)	719 (3)	.17
Pulmonary circulation disorder	1,942 (2)	1,507 (3)	435 (2)	<.001
Weight loss	812 (1)	629 (1)	183 (1)	.02
Alcohol abuse	726 (1)	544 (1)	182 (1)	.52
Dementia	729 (1)	541 (1)	188 (1)	.84
Hemiplegia	351 (0)	257 (0)	94 (0)	.77
HIV/AIDS	104 (0)	81 (0)	23 (0)	.35
Other select comorbidities				
Metastatic cancer	35,627 (45)	26,384 (45)	9,243 (45)	.34
Infection	12,837 (16)	9,449 (16)	3,388 (16)	.42
Neutropenia	1,497 (2)	1,270 (2)	227 (1)	<.001

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GCI, Gagne comorbidity index; PP, primary prophylactic.
[a]The baseline period was defined as the 6-month period immediately preceding the index date.
[b]PP G-CSF use was defined as G-CSF use on or up to 3 days after the index date.
[c]Characteristics were compared between patients receiving and not receiving PP G-CSFs using chi-square/Fisher exact tests for categorical variables and Wilcoxon rank sum tests for numeric variables.
[d]Modified to exclude any tumor and metastatic cancer.

eTable 3. Unadjusted Proportions of Patients Experiencing (A) FN/Infection[a], (B) sFN[b], and (C) IRH[c] in the First Chemotherapy Cycle[d], by PP G-CSF Status[e]

eTable 3A. Proportion Experiencing First-Cycle FN/Infection

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[f]	OR (95% CI)[g]
All, N	58,235	20,575		
Patients with FN/infection in cycle 1	3,558 (6.1)	2,597 (12.6)	<.001	0.45 (0.43–0.48)
Cycle 1, week 1	1,752 (3.0)	470 (2.3)	<.001	1.33 (1.20–1.47)
Cycle 1, beyond week 1	1,806 (3.1)	2,127 (10.3)	<.001	0.28 (0.26–0.30)
TAC, N	4,605	677		
Patients with FN/infection in cycle 1	546 (11.9)	131 (19.4)	<.001	0.56 (0.45–0.69)
Cycle 1, week 1	178 (3.9)	15 (2.2)	.03	1.77 (1.04–3.02)
Cycle 1, beyond week 1	368 (8.0)	116 (17.1)	<.001	0.42 (0.33–0.53)
TC, N	45,906	16,607		
Patients with FN/infection in cycle 1	2,616 (5.7)	1,982 (11.9)	<.001	0.45 (0.42–0.47)
Cycle 1, week 1	1,390 (3.0)	354 (2.1)	<.001	1.43 (1.27–1.61)
Cycle 1, beyond week 1	1,226 (2.7)	1,628 (9.8)	<.001	0.25 (0.23–0.27)
TCH, N	7,724	3,291		
Patients with FN/infection in cycle 1	396 (5.1)	484 (14.7)	<.001	0.31 (0.27–0.36)
Cycle 1, week 1	184 (2.4)	101 (3.1)	.04	0.77 (0.60–0.99)
Cycle 1, beyond week 1	212 (2.7)	383 (11.6)	<.001	0.21 (0.18–0.25)

eTable 3B. Proportion Experiencing First-Cycle sFN

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[f]	OR (95% CI)[g]
All, N	58,235	20,575		
Patients with sFN in cycle 1	1,878 (3.2)	1,942 (9.4)	<.001	0.32 (0.30–0.34)
Cycle 1, week 1	1,145 (2.0)	288 (1.4)	<.001	1.41 (1.24–1.61)
Cycle 1, beyond week 1	733 (1.3)	1,654 (8.0)	<.001	0.15 (0.13–0.16)
TAC, N	4,605	677		
Patients with sFN in cycle 1	390 (8.5)	96 (14.2)	<.001	0.56 (0.44–0.71)
Cycle 1, week 1	133 (2.9)		Suppressed[h]	
Cycle 1, beyond week 1	257 (5.6)			
TC, N	45,906	16,607		
Patients with sFN in cycle 1	1,357 (3.0)	1,489 (9.0)	<.001	0.31 (0.29–0.33)
Cycle 1, week 1	930 (2.0)	219 (1.3)	<.001	1.55 (1.33–1.79)
Cycle 1, beyond week 1	427 (0.9)	1,270 (7.6)	<.001	0.11 (0.10–0.13)
TCH, N	7,724	3,291		
Patients with sFN in cycle 1	131 (1.7)	357 (10.8)	<.001	0.14 (0.12–0.17)
Cycle 1, week 1	82 (1.1)		Suppressed[h]	
Cycle 1, beyond week 1	49 (0.6)			

eTable 3C. Proportion Experiencing First-Cycle IRH

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[f]	OR (95% CI)[g]
All, N	58,235	20,575		
Patients with IRH in cycle 1	3,167 (5.4)	2,201 (10.7)	<.001	0.48 (0.45–0.51)
Cycle 1, week 1	1,498 (2.6)	372 (1.8)	<.001	1.43 (1.28–1.61)
Cycle 1, beyond week 1	1,669 (2.9)	1,829 (8.9)	<.001	0.30 (0.28–0.32)
TAC, N	4,605	677		
Patients with IRH in cycle 1	466 (10.1)	108 (16.0)	<.001	0.59 (0.47–0.74)
Cycle 1, week 1	149 (3.2)	11 (1.6)	.02	2.02 (1.09–3.76)
Cycle 1, beyond week 1	317 (6.9)	97 (14.3)	<.001	0.44 (0.35–0.56)
TC, N	45,906	16,607		
Patients with IRH in cycle 1	2,346 (5.1)	1,683 (10.1)	<.001	0.48 (0.45–0.51)
Cycle 1, week 1	1,190 (2.6)	278 (1.7)	<.001	1.56 (1.37–1.78)
Cycle 1, beyond week 1	1,156 (2.5)	1,405 (8.5)	<.001	0.28 (0.26–0.30)
TCH, N	7,724	3,291		
Patients with IRH in cycle 1	355 (4.6)	410 (12.5)	<.001	0.34 (0.29–0.39)
Cycle 1, week 1	159 (2.1)	83 (2.5)	.13	0.81 (0.62–1.06)
Cycle 1, beyond week 1	196 (2.5)	327 (9.9)	<.001	0.24 (0.20–0.28)

Abbreviations: FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; IRH, infection-related hospitalization; OR, odds ratio; PP, primary prophylactic; sFN, febrile neutropenia under strict definition; TAC, docetaxel/doxorubicin/cyclophosphamide; TC, docetaxel/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab.

[a]FN/infection was defined as inpatient hospitalization with an associated diagnosis code for neutropenia, infection, or fever.

[b]sFN was defined as inpatient hospitalization with either (1) an associated primary diagnosis code for neutropenia, or (2) an associated secondary diagnosis code for neutropenia and an associated primary or secondary diagnosis code for infection or fever.

[c]IRH was defined as inpatient hospitalization with an associated diagnosis code for infection or fever.

[d]The first chemotherapy cycle was defined individually for each patient as the period beginning on the index date and ending the earlier of (1) the day before the first observed chemotherapy administration occurring at least 13 days later, if applicable, and (2) day 27 post index date.

[e]PP G-CSF use was defined as G-CSF use on or up to 3 days after the index date.

[f]Chi-square/Fisher exact tests were used to compare proportions of patients experiencing the given outcome of interest.

[g]Reflects the association between PP G-CSF use and the given outcome of interest.

[h]In compliance with the Medicare 100% Data User Agreement, select results are suppressed to obscure or prevent imputation of cells representing >0 but <11 patients.

eTable 4. Adjusted[a] Proportions of Patients Experiencing (A) FN/Infection[b], (B) sFN[c], and (C) IRH[d] in the First Chemotherapy Cycle[e], by PP G-CSF Status[f]

eTable 4A. Adjusted Proportion Experiencing First-Cycle FN/Infection

	PP G-CSF Use Adjusted %	No PP G-CSF Use Adjusted %	aOR (95% CI)[g]	*P* Value[h]
All, N=78,810	58,235	20,575		
Patients with FN/infection in cycle 1	6.1%	13.1%		
Cycle 1, week 1	3.0%	2.4%	1.24 (1.12–1.38)	<.001
Cycle 1, beyond week 1	3.1%	10.7%	0.25 (0.23–0.26)	<.001
TAC, N=5,282	4,605	677		
Patients with FN/infection in cycle 1	12.1%	17.6%		
Cycle 1, week 1	3.9%	2.3%	1.73 (1.01–2.96)	.05
Cycle 1, beyond week 1	8.2%	15.3%	0.47 (0.37–0.60)	<.001
TC, N=62,513	45,906	16,607		
Patients with FN/infection in cycle 1	5.7%	12.1%		
Cycle 1, week 1	3.0%	2.2%	1.35 (1.19–1.52)	<.001
Cycle 1, beyond week 1	2.7%	9.9%	0.23 (0.22–0.25)	<.001
TCH, N=11,015	7,724	3,291		
Patients with FN/infection in cycle 1	5.1%	14.8%		
Cycle 1, week 1	2.4%	3.1%	0.76 (0.59–0.98)	.04
Cycle 1, beyond week 1	2.7%	11.7%	0.21 (0.17–0.25)	<.001

eTable 4B. Adjusted Proportion Experiencing First-Cycle sFN

	PP G-CSF Use Adjusted %	No PP G-CSF Use Adjusted %	aOR (95% CI)[g]	*P* Value[h]
All, N=78,810	58,235	20,575		
Patients with sFN in cycle 1	3.1%	10.2%		
Cycle 1, week 1	1.9%	1.5%	1.29 (1.13–1.47)	<.001
Cycle 1, beyond week 1	1.2%	8.7%	0.12 (0.11–0.13)	<.001
TAC, N=5,282	4,605	677		
Patients with sFN in cycle 1	8.5%	13.4%		
Cycle 1, week 1	2.9%	1.4%	2.14 (1.08–4.23)	.03
Cycle 1, beyond week 1	5.6%	12.0%	0.43 (0.33–0.56)	<.001
TC, N=62,513	45,906	16,607		
Patients with sFN in cycle 1	2.9%	9.3%		
Cycle 1, week 1	2.0%	1.4%	1.43 (1.23–1.67)	<.001
Cycle 1, beyond week 1	0.9%	7.9%	0.10 (0.09–0.12)	<.001
TCH, N=11,015	7,724	3,291		
Patients with sFN in cycle 1	1.7%	11.2%		
Cycle 1, week 1	1.1%	1.9%	0.56 (0.40–0.79)	<.001
Cycle 1, beyond week 1	0.6%	9.3%	0.06 (0.04–0.08)	<.001

eTable 4C. Adjusted Proportion Experiencing First-Cycle IRH

	PP G-CSF Use Adjusted %	No PP G-CSF Use Adjusted %	aOR (95% CI)[g]	*P* Value[h]
All, N=78,810	58,235	20,575		
Cycle 1, week 1	2.5%	1.9%	1.33 (1.18–1.50)	<.001
Cycle 1, beyond week 1	2.8%	9.2%	0.27 (0.25–0.29)	<.001
TAC, N=5,282	4,605	677		
Patients with IRH in cycle 1	10.2%	14.6%		
Cycle 1, week 1	3.2%	1.7%	1.91 (1.03–3.56)	.04
Cycle 1, beyond week 1	7.0%	12.9%	0.49 (0.38–0.64)	<.001
TC, N=62,513	45,906	16,607		
Patients with IRH in cycle 1	5.0%	9.4%		
Cycle 1, week 1	2.5%	1.8%	1.46 (1.27–1.67)	<.001
Cycle 1, beyond week 1	2.5%	8.6%	0.26 (0.24–0.28)	<.001
TCH, N=11,015	7,724	3,291		
Patients with IRH in cycle 1	5.6%	12.4%		
Cycle 1, week 1	2.1%	2.5%	0.80 (0.61–1.05)	.11
Cycle 1, beyond week 1	2.5%	9.9%	0.23 (0.19–0.28)	<.001

Abbreviations: aOR, adjusted odds ratio; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; IRH, infection-related hospitalization; PP, primary prophylactic; sFN, febrile neutropenia under strict definition; TAC, docetaxel/doxorubicin/cyclophosphamide; TC, docetaxel/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab.

[a]Adjusted proportions and adjusted odds ratios were estimated using multivariable logistic regression controlling for observed differences in patient characteristics at baseline, regimen (all-regimen models, only), cycle duration (models with outcome measure evaluated beyond week 1 of cycle 1, only), and first-cycle PP G-CSF use.

[b]FN/infection was defined as inpatient hospitalization with an associated diagnosis code for neutropenia, infection, or fever.

[c]sFN was defined as inpatient hospitalization with either (1) an associated primary diagnosis code for neutropenia, or (2) an associated secondary diagnosis code for neutropenia and an associated primary or secondary diagnosis code for infection or fever.

[d]IRH was defined as inpatient hospitalization with an associated diagnosis code for infection or fever.

[e]The first chemotherapy cycle was defined individually for each patient as the period beginning on the index date and ending the earlier of (1) the day before the first observed chemotherapy administration occurring at least 13 days later, if applicable, and (2) day 27 post index date.

[f]PP G-CSF use was defined as G-CSF use on or up to 3 days after the index date.

[g]Reflects the regression-estimated association between PP G-CSF use and the given outcome of interest.

[h]*P* values are those associated with the PP G-CSF use covariate in the given models.

eTable 5. Unadjusted Proportions of Select Patients Experiencing FN/Infection[a] in the First Chemotherapy Cycle[b], by PP G-CSF Status[c]

eTable 5A. Patients With Continuous Enrollment in Medicare Part D Throughout the Baseline Period[d] and First Chemotherapy Cycle

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[e]	OR (95% CI)[f]
All, N	36,564	11,942		
Patients with FN/infection in cycle 1	2,315 (6.3)	1,581 (13.2)	<.001	0.44 (0.41–0.47)
Cycle 1, week 1	1,158 (3.2)	305 (2.6)	<.001	1.25 (1.10–1.42)
Cycle 1, beyond week 1	1,157 (3.2)	1,276 (10.7)	<.001	0.27 (0.25–0.30)
TAC, N	2,299	292		
Patients with FN/infection in cycle 1	289 (12.6)	62 (21.2)	<.001	0.53 (0.39–0.72)
Cycle 1, week 1	95 (4.1)		Suppressed[g]	
Cycle 1, beyond week 1	194 (8.4)			
TC, N	29,491	9,709		
Patients with FN/infection in cycle 1	1,765 (6.0)	1,219 (12.6)	<.001	0.44 (0.41–0.48)
Cycle 1, week 1	936 (3.2)	231 (2.4)	<.001	1.34 (1.16–1.55)
Cycle 1, beyond week 1	829 (2.8)	988 (10.2)	<.001	0.26 (0.23–0.28)
TCH, N	4,774	1,941		
Patients with FN/infection in cycle 1	261 (5.5)	300 (15.5)	<.001	0.32 (0.27–0.38)
Cycle 1, week 1	127 (2.7)		Suppressed[g]	
Cycle 1, beyond week 1	134 (2.8)			

eTable 5B. Patients Aged ≥65 Years Throughout the Baseline Period[d] and First Chemotherapy Cycle

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[e]	OR (95% CI)[f]
All, N	50,894	16,939		
Patients with FN/infection in cycle 1	3,035 (6.0)	2,116 (12.5)	<.001	0.44 (0.42–0.47)
Cycle 1, week 1	1,527 (3.0)	357 (2.1)	<.001	1.43 (1.28–1.61)
Cycle 1, beyond week 1	1,508 (3.0)	1,759 (10.4)	<.001	0.26 (0.25–0.28)
TAC, N	3,449	483		
Patients with FN/infection in cycle 1	407 (11.8)	91 (18.8)	<.001	0.58 (0.45–0.74)
Cycle 1, week 1	134 (3.9)		Suppressed[g]	
Cycle 1, beyond week 1	273 (7.9)			
TC, N	40,821	13,834		
Patients with FN/infection in cycle 1	2,297 (5.6)	1,641 (11.9)	<.001	0.44 (0.41–0.47)
Cycle 1, week 1	1,240 (3.0)	271 (2.0)	<.001	1.57 (1.37–1.79)
Cycle 1, beyond week 1	1,057 (2.6)	1,370 (9.9)	<.001	0.24 (0.22–0.26)
TCH, N	6,624	2,622		
Patients with FN/infection in cycle 1	331 (5.0)	384 (14.7)	<.001	0.31 (0.26–0.36)
Cycle 1, week 1	153 (2.3)		Suppressed[g]	
Cycle 1, beyond week 1	178 (2.7)			

eTable 5C. Patients Initiating Chemotherapy in 2016–2020

	PP G-CSF Use n (%)	No PP G-CSF Use n (%)	*P* Value[e]	OR (95% CI)[f]
All, N	20,313	3,793		
Patients with FN/infection in cycle 1	1,209 (6.0)	514 (13.6)	<.001	0.40 (0.36–0.45)
Cycle 1, week 1	622 (3.1)	89 (2.4)	.02	1.31 (1.05–1.64)
Cycle 1, beyond week 1	587 (2.9)	425 (11.2)	<.001	0.24 (0.21–0.27)
TAC, N	412	43		
Patients with FN/infection in cycle 1	51 (12.4)			
Cycle 1, week 1	18 (4.4)		Suppressed[g]	
Cycle 1, beyond week 1	33 (8.0)			
TC, N	18,045	3,284		
Patients with FN/infection in cycle 1	1,070 (5.9)	435 (13.3)	<.001	0.41 (0.37–0.46)
Cycle 1, week 1	563 (3.1)	75 (2.3)	.010	1.38 (1.08–1.76)
Cycle 1, beyond week 1	507 (2.8)	360 (11.0)	<.001	0.23 (0.20–0.27)
TCH, N	1,856	466		
Patients with FN/infection in cycle 1	88 (4.7)			
Cycle 1, week 1	41 (2.2)		Suppressed[g]	
Cycle 1, beyond week 1	47 (2.5)			

Abbreviations: FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; OR, odds ratio; PP, primary prophylactic; TAC, docetaxel/doxorubicin/cyclophosphamide; TC, docetaxel/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab.
[a]FN/Infection was defined as inpatient hospitalization with an associated diagnosis code for neutropenia, infection, or fever.
[b]The first chemotherapy cycle was defined individually for each patient as the period beginning on the index date and ending the earlier of (1) the day before the first observed chemotherapy administration occurring at least 13 days later, if applicable, and (2) day 27 post index date.
[c]PP G-CSF use was defined as G-CSF use on or up to 3 days after the index date.
[d]The baseline period was defined as the 6-month period immediately preceding the index date.
[e]Chi-square/Fisher exact tests were used to compare proportions of patients experiencing the given outcome of interest.
[f]Reflects the association between PP G-CSF use and the given outcome of interest.
[g]In compliance with the Medicare 100% Data User Agreement, select results are suppressed to obscure or prevent imputation of cells representing >0 but <11 patients.