original contributions

# Primary Prophylaxis With Biosimilar Filgrastim for Patients at Intermediate Risk for Febrile Neutropenia: A Cost-Effectiveness Analysis

Edward Li, PharmD, MPH[1]; Dylan J. Mezzio, PharmD, MS[2]; David Campbell, PharmD, MS[2]; Kim Campbell, PharmD[1]; and Gary H. Lyman, MD, MPH[3]

**QUESTION ASKED:** Is it cost-effective to provide primary prophylaxis (PP) with biosimilar filgrastim, compared with secondary prophylaxis (SP), for patients receiving chemotherapy and at intermediate risk of febrile neutropenia?

**SUMMARY ANSWER:** PP with biosimilar filgrastim is cost-effective in patients receiving intermediate-risk, curative chemotherapy regimens for breast cancer, non–small-cell lung cancer (NSCLC), and non-Hodgkin lymphoma. In the era of COVID-19 and value-based care, the use of biosimilar filgrastim has valuable potential to reduce complications associated with unnecessary contact with the health care system among patients undergoing potentially curative chemotherapy.

**WHAT WE DID:** A Markov cycle tree–based model was constructed to evaluate the cost-effectiveness of PP versus SP with a biosimilar filgrastim (specifically filgrastim-sndz) from the US payer perspective. The model evaluated prophylaxis strategies for the most common intermediate-risk chemotherapy regimens in patients with breast cancer (adjuvant docetaxel), NSCLC (adjuvant carboplatin and paclitaxel), and non-Hodgkin lymphoma (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

**WHAT WE FOUND:** Across all three cancer types, biosimilar filgrastim (using filgrastim-sndz) as PP versus SP provided an additional 0.102-0.144 life years and 0.065-0.130 quality-adjusted life years at an incremental cost ranging from $650 to $2,463 in US dollars (USD). The incremental cost-effectiveness ratios ranged from $5,660 to $20,806 USD per febrile neutropenia event avoided, $5,123-$31,077 USD per life year gained, and $7,213-$35,563 USD per quality-adjusted life year gained, with NSCLC reflecting the lowest ICERs.

**BIAS, CONFOUNDING FACTOR(S):** As with any model, the structure of these analyses likely represents a simplification of the complex interplay between disease, treatments, and costs. Furthermore, we only evaluated short-acting growth factors, and long-acting agents are commonly used for prophylaxis.

**REAL-LIFE IMPLICATIONS:** This analysis supports the expanded use of PP with biosimilar filgrastim by practicing oncologists to improve long-term patient outcomes.

**CORRESPONDING AUTHOR**

Edward Li, PharmD, MPH, Sandoz Inc, 100 College Rd W, Princeton, NJ 08540; e-mail: edward-1.li@sandoz.com.

**ASSOCIATED CONTENT**

**Appendix**

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

**Accepted on February 23, 2021 and published at ascopubs.org/journal/op on April 1, 2021: DOI https://doi.org/10.1200/OP.20.01047**

SPECIAL SERIES: QUALITY CARE SYMPOSIUM

original contributions

# Primary Prophylaxis With Biosimilar Filgrastim for Patients at Intermediate Risk for Febrile Neutropenia: A Cost-Effectiveness Analysis

Edward Li, PharmD, MPH[1]; Dylan J. Mezzio, PharmD, MS[2]; David Campbell, PharmD, MS[2]; Kim Campbell, PharmD[1]; and Gary H. Lyman, MD, MPH[3]

abstract

**PURPOSE** Temporary COVID-19 guideline recommendations have recently been issued to expand the use of colony-stimulating factors in patients with cancer with intermediate to high risk for febrile neutropenia (FN). We evaluated the cost-effectiveness of primary prophylaxis (PP) with biosimilar filgrastim-sndz in patients with intermediate risk of FN compared with secondary prophylaxis (SP) over three different cancer types.

**METHODS** A Markov decision analytic model was constructed from the US payer perspective over a lifetime horizon to evaluate PP versus SP in patients with breast cancer, non–small-cell lung cancer (NSCLC), and non-Hodgkin lymphoma (NHL). Cost-effectiveness was evaluated over a range of willingness-to-pay thresholds for incremental cost per FN avoided, life year gained, and quality-adjusted life year (QALY) gained. Sensitivity analyses evaluated uncertainty.

**RESULTS** Compared with SP, PP provided an additional 0.102-0.144 LYs and 0.065-0.130 QALYs. The incremental cost-effectiveness ranged from $5,660 in US dollars (USD) to $20,806 USD per FN event avoided, $5,123 to $31,077 USD per life year gained, and $7,213 to $35,563 USD per QALY gained. Over 1,000 iterations, there were 73.6%, 99.4%, and 91.8% probabilities that PP was cost-effective at a willingness to pay of $50,000 USD per QALY gained for breast cancer, NSCLC, and NHL, respectively.

**CONCLUSION** PP with a biosimilar filgrastim (specifically filgrastim-sndz) is cost-effective in patients with intermediate risk for FN receiving curative chemotherapy regimens for breast cancer, NSCLC, and NHL. Expanding the use of colony-stimulating factors for patients may be valuable in reducing unnecessary health care visits for patients with cancer at risk of complications because of COVID-19 and should be considered for the indefinite future.

**JCO Oncol Pract 17:e1235-e1245. © 2021 by American Society of Clinical Oncology**



## INTRODUCTION

Recent practice guidelines from ASCO and the National Comprehensive Cancer Network recommend hematopoietic colony-stimulating factor (CSF) prophylaxis to patients receiving chemotherapy regimens with a high risk (> 20%) of febrile neutropenia (FN). In patients at intermediate risk of developing FN (10%-20%), the decision to use CSFs as primary prophylaxis (PP) or secondary prophylaxis (SP) is usually made via an individualized risk assessment and patient-physician discussion. In the presence of no additional FN risk factors, practice guidelines recommend the use of SP, whereas PP may be considered if the patient has one or more risk factors.[1,2]

However, the pandemic caused by SARS-CoV-2 has resulted in new considerations for cancer care and supportive care. Patients with cancer are a highly susceptible population at risk of transmission of SARS-CoV-2 and the potential consequences of the associated disease, COVID-19. High susceptibility of patients with cancer is primarily due to their frequent contact with the health care system, cancer- or treatment-related immunosuppression, and advanced age and comorbidities.[3]

Several single- and multicenter studies have described characteristics and outcomes in cancer patients with COVID-19. One cohort study found that of 928 patients with active cancer or history of cancer and COVID-19, 26% developed severe illness, 14% were admitted to

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 23, 2021 and published at ascopubs.org/journal/op on April 1, 2021: DOI https://doi.org/10.1200/OP.20.01047

the intensive care unit, and 12% required mechanical ventilation. The mortality rate within 30 days of COVID-19 diagnosis was 13%. Of 52 intensive care unit patients with 30-day follow-up data, 31% died.[3] Similar findings were published in an earlier Chinese study.[4] These outcomes emphasize the need to strategically coordinate the care of patients with cancer to minimize risk of infection with COVID-19.

Although cancer providers have been challenged with navigating infection prevention, staffing shortages, and resource limitations during the pandemic, postponing or delaying chemotherapy may not be in the best long-term interest of patients receiving treatment for curative intent.[5] Sharing of best practices has been important to optimize clinical care while reducing risk of transmission among patients and lessening demand on hospitals. To that end, there has been renewed focus in further reducing the risk of FN for patients with cancer. Improving FN outcomes also aligns with value-based care efforts (eg, the Oncology Care Model [OCM]) that have occurred over the past few years.

Recently, ASCO and the National Comprehensive Cancer Network issued temporary recommendations for the use of CSFs in patients with cancer during the COVID-19 pandemic. Specifically, the threshold for the use of CSF prophylaxis was lowered from only high-risk patients (> 20% risk of FN) to intermediate- (10%-20% risk of FN) or high-risk patients.[6,7] This expansion of CSF prophylaxis is aimed at mitigating the risks associated with COVID-19 for patients with cancer while benefiting facilities by potentially increasing the number of beds available to treat patients of the pandemic.

Considering these new recommendations during the pandemic and the general trend toward value-based care in oncology, we compared the different CSF prophylaxis strategies from a clinical and economic perspective by assessing the cost-effectiveness of PP versus SP using a biosimilar filgrastim (specifically filgrastim-sndz) in patients with breast cancer, non–small-cell lung cancer (NSCLC), and non-Hodgkin lymphoma (NHL) receiving potentially curative chemotherapy.

## METHODS

### Model Structure

Building on previously published cost-effectiveness analyses in FN, a Markov cycle tree–based model was constructed in Microsoft Excel to evaluate the cost-effectiveness of PP versus SP with a biosimilar filgrastim (specifically filgrastim-sndz) from the US payer perspective.[8,9] The model evaluated CSF prophylaxis strategies for the most common intermediate-risk chemotherapy regimens in patients with breast cancer (adjuvant docetaxel), NSCLC (adjuvant carboplatin and paclitaxel), and NHL (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). Because of the novelty of COVID-19, the rapidity of change, and the underlying complexities of its care patterns, characteristics surrounding the complications of infection with COVID-19 were not incorporated into the model.

The general model structure diagram for breast cancer, NSCLC, and NHL is presented in Appendix Figure A1, online only. The model structure for each analysis was adapted to the specific number of cycles for each cancer type. The first cycle of each regimen was represented as a decision tree with the two arms to pursue either a PP or SP strategy. Based on the risk of FN during the first cycle, patients either developed FN or completed the cycle without FN.

A Markov cycle tree was employed to represent the remainder of chemotherapy. Patients were tracked to determine their history of FN and repeated the Markov cycle until completing up to the maximum number of cycles. In each cycle, patients with a history of FN (*v* patients without a history of FN) experienced a higher FN risk based on a value cited in previously published economic evaluations. If FN occurred, patients were treated in an inpatient or an outpatient setting and either died from FN or survived to the next cycle of chemotherapy. All deaths during chemotherapy were assumed to be FN-related and to occur at the end of each cycle.

The postchemotherapy phase of the model followed 1-year Markov cycles. Initially, patients were stratified into two groups based on the risks of receiving a suboptimal chemotherapy dose with and without a history of FN. In accordance with previous clinical and cost-effectiveness research, patients with suboptimal chemotherapy delivery were at higher annual risk of cancer-related death. 20 years post-chemotherapy, mortality reverted to standard age- and sex-related rates. The primary outcomes of the analysis were incremental costs per FN event avoided, per life year (LY) gained, and per quality-adjusted life year (QALY) gained. Cost-effectiveness was assessed at the commonly cited willingness-to-pay (WTP) thresholds of $50,000 in US dollars (USD), $100,000 USD, and $150,000 USD, using a biosimilar filgrastim (specifically filgrastim-sndz) SP as the reference comparator.

### Model Parameters

All model inputs are presented in Table 1. In each analysis, the age at which patients entered the cohort varied according to their cancer type. Similarly, the baseline FN risks for each cancer type were selected to reflect the real world and focus on intermediate risk. Baseline FN risk for breast cancer was derived from patients having at least one FN risk factor based on the premise that patients received doxorubicin plus cyclophosphamide before docetaxel.[2] Baseline FN risk for NSCLC was also based on patients having at least one risk factor given that more than 90% of patients with NSCLC receiving carboplatin plus paclitaxel have at least one risk factor.[10] For NHL, no additional FN

**TABLE 1.** Model Parameters

| Parameter | Base-Case Value (Range for PSA)[a] | Distribution | Reference |
|---|---|---|---|
| General population and treatment inputs | | | |
| Discount rate | 0.030 (0.010-0.050) | Beta | Assumption |
| Patient sex (% male)[b] | BRCA: 0.000 (0.000-0.000)<br>NSCLC: 0.650 (0.585-0.715)<br>NHL: 0.516 (0.464-0.567) | Beta | Assumption<br>Strauss et al[24]<br>Lyman et al[11] |
| Patient weight (kg) | BRCA: 60.6 (54.5-66.7)<br>NSCLC: 70.3 (63.3-77.4)<br>NHL: 75.0 (67.5-82.5) | Normal | Weycker et al[25]<br>Criss et al[26]<br>Fust et al[9] |
| Baseline FN risk (over all cycles)[c] | BRCA: 0.160 (0.100-0.200)<br>NSCLC: 0.180 (0.100-0.200)<br>NHL: 0.180 (0.100-0.200) | Beta | Sparano et al[27]<br>Weycker et al[10]<br>Lyman et al[11] |
| Probability and effectiveness inputs | | | |
| RR of FN in cycles 2+ and no history of FN (*v* cycle 1) | 0.21 (0.16-0.29) | Lognormal | Whyte et al,[28] Fust et al[9] |
| RR of FN in cycles 2+ and history of FN (*v* no history) | 9.09 (6.19-13.35) | Lognormal | Whyte et al,[28] Fust et al[9] |
| RDI < X% and no history of FN | BRCA (85%): 0.309 (0.278-0.340)<br>NSCLC (85%): 0.250 (0.225-0.275)<br>NHL (90%): 0.408 (0.367-0.449) | Beta | Veitch et al[29]<br>Crawford et al[30]<br>Pettengell et al[31] |
| RDI < X% and history of FN | BRCA (85%): 0.488 (0.371-0.649)<br>NSCLC (85%): 0.383 (0.345-0.421)<br>NHL (90%): 0.706 (0.635-0.777) | Beta | Veitch et al[29]<br>Crawford et al[30]<br>Pettengell et a[31]<br>Shayne et al[32] |
| RR of FN for filgrastim (*v* no CSF) | 0.42 (0.30-0.57) | Lognormal | Wang et al[33] |
| Resource utilization inputs | | | |
| % of patients self-administering CSF | 0.200 (0.000-0.400) | Beta | Fust et al[9] |
| % of FN events requiring hospitalization | BRCA: 0.832 (0.795-0.863)<br>NSCLC: 0.832 (0.795-0.863)<br>NHL: 0.754 (0.679-0.829) | Beta | Weycker et a[34]<br>Weycker et al[34]<br>Chrischilles et al,[35] Lyman et al[11] |
| LOS for FN hospitalization, PP (days) | BRCA: 2.6 (2.0-3.4)<br>NSCLC: 4.3 (3.3-5.6)<br>NHL: 3.1 (0.0-7.7) | Normal | Clark et al,[36] Kawatkar et al[20]<br>Clark et al,[36] Kawatkar et al[20]<br>Chrischilles et al[35] |
| LOS for FN hospitalization, SP (days) | BRCA: 4.1 (3.7-4.5)<br>NSCLC: 6.8 (5.7-8.3)<br>NHL: 8.2 (6.7-10.3) | Normal | Kawatkar et al[20]<br>Kawatkar et al[20]<br>Chrischilles et al[35] |
| Pharmacy and medical cost inputs, 2020 USD | | | |
| Filgrastim-sndz (per mcg) | 0.43 (0.39-0.47) | Gamma | CMS ASP July 2020[12] |
| CSF administration by clinician[d] | 38 (34-42) | Gamma | CMS Physician Fee Schedule 2020[37] |
| FN event requiring hospitalization (per day) | BRCA: 5,019 (4,649-5,508)<br>NSCLC: 5,075 (4,231-6,170)<br>NHL: 5,075 (4,248-6,056) | Gamma | Kawatkar et al,[20] BLS[13] |
| FN event treated in outpatient setting | BRCA: 2,815 (2,671-2,977)<br>NSCLC: 3,797 (3,179-4,600)<br>NHL: 3,417 (3,064-3,830) | Gamma | Kawatkar et al,[20] BLS[13] |
| Health utility inputs | | | |
| During chemotherapy | BRCA: 0.55 (0.50-0.61)<br>NSCLC: 0.57 (0.51-0.63)<br>NHL: 0.61 (0.49-0.73) | Beta | Cámara et al[38]<br>Bezjak et al[39]<br>Hill et al,[8] Fust et al[9] |
| During FN hospitalization | 0.33 (0.27-0.40) | Beta | Hill et al,[8] Fust et al[9] |
| After chemotherapy (year 1) | BRCA: 0.66 (0.59-0.73)<br>NSCLC: 0.72 (0.65-0.79)<br>NHL: 0.79 (0.62-0.92) | Beta | Cámara et al[38]<br>Bezjak et al[39]<br>Hill et al,[8] Fust et al[9] |

(continued on following page)

**TABLE 1.** Model Parameters (continued)

| Parameter | Base-Case Value (Range for PSA)[a] | Distribution | Reference |
|---|---|---|---|
| After chemotherapy (year > 1) | BRCA: 0.86 (0.77-0.95)<br>NSCLC: 0.69 (0.62-0.76)<br>NHL: 0.89 (0.79-0.96) | Beta | Whyte et al[26]<br>Bezjak et al[39]<br>Hill et al,[8] Fust et al[9] |
| Mortality inputs | | | |
| Cancer-related 1-year mortality[e] | BRCA: 0.0300 (0.0270-0.0330)<br>NSCLC: 0.0600 (0.0540-0.0660)<br>NHL: 0.0652 (0.0587-0.0717) | Beta | NCI Cancer Stat Facts[40]<br>Strauss et al[24]<br>NCI SEER NHL[41] |
| Mortality during FN event (inpatient) | BRCA: 0.0560 (0.0480-0.0630)<br>NSCLC: 0.1120 (0.1010-0.1230)<br>NHL: 0.0580 (0.0000-0.0890) | Beta | Dulisse et al[42]<br>Cupp et al[43]<br>Lyman et al,[19] Fust et al[9] |
| Mortality during FN event (outpatient) | BRCA: 0.0000 (0.0000-0.0000)<br>NSCLC: 0.0000 (0.0000-0.0000)<br>NHL: 0.0050 (0.0000-0.0100) | Beta | Rolston et al[44]<br>Rolston et al[44]<br>Lyman et al[19] |
| HR for mortality and RDI < X% (*v* RDI ≥ X%) | BRCA (85%): 1.002 (0.657-1.527)<br>NSCLC (85%): 2.004 (1.159-3.463)<br>NHL (90%): 2.080 (1.190-3.700) | Lognormal | Veitch et al,[29] Cespedes Feliciano et al[45]<br>Ramsden et al[46]<br>Fust et al[9] |

Abbreviations: ASP, average sales price; BLS, Bureau of Labor Statistics; BRCA, breast cancer; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CPT, Current Procedural Terminology; CSF, colony-stimulating factor; FN, febrile neutropenia; HR, hazard ratio; LOS, length of stay; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PP, primary prophylaxis; RDI, relative dose intensity; RR, relative risk; SP, secondary prophylaxis.

[a]Unless otherwise specified, the parameter values presented apply to all three models.

[b]Low and high values are based on 90% and 110% of the base-case value, respectively.

[c]For BRCA, value is based on the FN rate for docetaxel every 3 weeks. For NSCLC, value is based on the FN risk over the treatment course in patients receiving carboplatin and paclitaxel for nonmetastatic NSCLC and with ≥ 1 risk factor for FN. In the analysis, 97.3% of such patients had ≥ 1 risk factor and only 12.3% received CSF prophylaxis in the first cycle. For NHL, value is based on the cumulative probability of FN over 126 days of CHOP therapy for patients with 2 risk factors.

[d]Based on national payment amount for CPT code 99211 (office visit) plus CPT code 96372 (subcutaneous injection).

[e]For BRCA and NHL, value is based on % survival over 5 years with the respective cancer, and the 1-year probability for death was calculated by first converting the 5-year probability to the instantaneous rate using the following equation: $r = -[\ln(1 - P)]/t$.

risk factors were the basis of the baseline risk, as patients receiving R-CHOP have a baseline FN risk of approximately 18% and additional risk factors would place patients above intermediate risk.[11]

As the risk for FN over the entire course of chemotherapy is greatest in the first cycle, baseline cycle–specific FN risk was calculated as the risk in patients without a history of FN and without CSF prophylaxis. This baseline risk was decreased in patients who received CSF prophylaxis. History of FN increased the likelihood of subsequent FN events. Patients who experienced FN events received treatment in the inpatient or outpatient setting and had an increased likelihood of receiving reduced doses of chemotherapy.

Biosimilar filgrastim costs were based on the average sales price of filgrastim-sndz as of July 2020.[12] Other costs included CSF administration, inpatient FN management, and outpatient FN management and were adjusted to 2020 USD.[13] Chemotherapy costs were excluded from the analysis as they were assumed to be equivalent between patients receiving PP and SP. Similarly, the difference in chemotherapy costs for patients receiving low versus high relative dose intensity was assumed to be negligible. Postchemotherapy costs were assumed to be unaffected by prophylaxis strategy and were also excluded.

QALYs were calculated by applying utility weights to the estimated LYs. We accounted for quality of life during chemotherapy, during FN hospitalization, and after chemotherapy. The improvement in quality of life experienced 1 year after chemotherapy was assumed to remain constant until death. Mortality during chemotherapy was FN-related. Cancer-related mortality subsequently affected patients until 20 years after chemotherapy, after which standard US death rates applied.[14]

### Sensitivity Analyses

Alternative parameter values were tested via a one-way sensitivity analysis to evaluate the impact of each parameter on the models' outcomes. In addition, a probabilistic sensitivity analysis (PSA) accounted for joint uncertainty among all model parameters and assessed the likelihood of cost-effectiveness of PP over a range of WTP thresholds. The PSA simulated 1,000 iterations, with parameter values sampled simultaneously from their individual distributions.

## RESULTS

The base-case results for the breast cancer, NSCLC, and NHL analyses are presented in Table 2. Over all three cancer types, biosimilar filgrastim (using filgrastim-sndz) as PP versus SP provided an additional 0.102-0.144 LYs and

**TABLE 2.** Base-Case and PSA Results by Cancer Type

| Comparator | Costs | FN Events Avoided | LYs | QALYs | ICER ($/FN Event Avoided) | ICER ($/LY) | ICER ($/QALY) |
|---|---|---|---|---|---|---|---|
| Base-case results: BRCA | | | | | | | |
| PP | $5,364 USD | 0.138 | 13.625 | 11.515 | $19,677 USD | $31,077 USD | $35,563 USD |
| SP | $3,359 USD | 0.036 | 13.560 | 11.458 | Reference | Reference | Reference |
| Base-case results: NSCLC | | | | | | | |
| PP | $6,704 USD | 0.157 | 8.623 | 5.940 | $5,660 USD | $5,123 USD | $7,213 USD |
| SP | $6,053 USD | 0.042 | 8.496 | 5.850 | Reference | Reference | Reference |
| Base-case results: NHL | | | | | | | |
| PP | $9,186 USD | 0.173 | 8.368 | 7.284 | $20,806 USD | $17,146 USD | $18,971 USD |
| SP | $6,723 USD | 0.055 | 8.224 | 7.154 | Reference | Reference | Reference |

| Comparator | Mean Costs | Mean FN Events Avoided | Mean LYs | Mean QALYs | ICER ($/FN Event Avoided) | ICER ($/LY) | ICER ($/QALY) |
|---|---|---|---|---|---|---|---|
| PSA results: BRCA | | | | | | | |
| PP | $5,391 USD | 0.137 | 13.720 | 11.570 | $20,808 USD | $32,751 USD | $37,543 USD |
| 95% CI | $4,671 to $6,185 USD | 0.079 to 0.216 | 10.911 to 16.423 | 8.888 to 14.112 | $6,653 to $43,079 USD | $9,831 to $86,298 USD | $11,258 to $100,062 USD |
| SP | $3,353 USD | 0.037 | 13.655 | 11.513 | Reference | Reference | Reference |
| 95% CI | $2,336 to $4,620 USD | 0.015 to 0.074 | 10.855 to 16.331 | 8.848 to 14.047 | | | |
| PSA Results: NSCLC | | | | | | | |
| PP | $6,766 USD | 0.158 | 8.666 | 5.972 | $6,399 USD | $5,947 USD | $8,272 USD |
| 95% CI | $5,711 to $8,159 USD | 0.094 to 0.237 | 7.259 to 10.202 | 4.861 to 7.146 | −$10,098 to $27,385 USD | −$9,500 to $26,055 USD | −$13,199 to $36,128 USD |
| SP | $6,119 USD | 0.044 | 8.539 | 5.882 | Reference | Reference | Reference |
| 95% CI | $4,058 to $8,859 USD | 0.020 to 0.079 | 7.124 to 10.086 | 4.786 to 7.047 | | | |
| PSA results: NHL | | | | | | | |
| PP | $9,189 USD | 0.175 | 8.476 | 7.378 | $21,476 USD | $18,024 USD | $19,738 USD |
| 95% CI | $7,564 to $11,168 USD | 0.104 to 0.273 | 6.801 to 10.520 | 5.789 to 9.286 | −$2,405 to $54,655 USD | −$2,439 to $67,331 USD | −$2,640 to $76,839 USD |
| SP | $6,730 USD | 0.057 | 8.335 | 7.250 | Reference | Reference | Reference |
| 95% CI | $4,435 to $9,730 USD | 0.025 to 0.107 | 6.666 to 10.422 | 5.656 to 9.239 | | | |

Abbreviations: BRCA, breast cancer; FN, febrile neutropenia; ICER, incremental cost-effectiveness ratio; LY, life year; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PP, primary prophylaxis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SP, secondary prophylaxis.

0.065-0.130 QALYs at an incremental cost ranging from $650 to $2,463 USD. The incremental cost-effectiveness ratios (ICERs) ranged from $5,660 to $20,806 USD per FN event avoided, $5,123 to $31,077 USD per LY gained, and $7,213 to $35,563 USD per QALY gained, with NSCLC reflecting the lowest ICERs.

According to the one-way sensitivity analysis results on cost per QALY gained, for breast cancer, variation in baseline FN risk, mortality hazard ratio for low relative dose intensity, and the relative risk of FN with filgrastim versus no CSF exerted the greatest influence over the results. For NSCLC and NHL, the most influential parameters were baseline FN risk, mean length of stay for hospitalization (SP), and the cost of an FN event requiring hospitalization.

When the baseline FN risk was adjusted to 10%-20% for the breast cancer model, the results ranged from $86,573 to $18,995 USD per QALY gained, respectively. When similar adjustments were made in the NSCLC model, the results ranged from $53,670 to $1,467 USD per QALY gained. Finally, for the NHL model, the results ranged from

$67,238 to $12,884 USD per QALY gained when adjusting the baseline FN risk to 10% and 20%, respectively.

Adjusting the average sales price of filgrastim-sndz by 90%-110% of baseline had less of an impact on the model results than baseline FN risk. For breast cancer, the results varied from $30,056 to $41,070 USD cost per QALY gained, whereas for NSCLC and NHL, the results ranged from $3,250 to $11,177 USD and $14,593 to $23,349 USD, respectively.

The results of the three PSAs are presented as cost-effectiveness acceptability curves ranging from WTP thresholds per QALY gained of $0 to $150,000 USD (Fig 1). For breast cancer, the likelihood of cost-effectiveness at a WTP threshold of $50,000 USD per QALY gained was 73.6%. For NSCLC and NHL, the likelihood of cost-effectiveness at a WTP threshold of $50,000 USD per QALY gained was 99.4% and 91.8%, respectively.

## DISCUSSION

Based on our analysis, using a biosimilar filgrastim (specifically filgrastim-sndz) as PP is a cost-effective approach to avoid FN events, which reduces the need for patients to receive hospital or outpatient care. This is especially important for reducing transmission of SARS-CoV-2 among patients with cancer, who are highly susceptible to the complications of COVID-19.[5] By mitigating the risk of FN in patients receiving chemotherapy with intermediate to high FN risk, the expanded use of CSF further contributes to efficient care management given facility, resource, and staffing labor constraints during the COVID-19 pandemic, while maximizing curative potential.[5]

As SARS-CoV-2 is expected to be endemic,[15] the cost-effectiveness of biosimilar filgrastim in intermediate FN risk regimens raises the possibility that this should be a standing recommendation within practice guidelines. There is historical precedent for re-evaluating risk thresholds informing the use of PP against FN. In 2006, ASCO lowered the definition of high risk for FN, the risk at which PP is recommended, from 40% to 20%.[16,17] Although the recommendation was informed primarily by clinical efficacy data for CSF in patients with an FN risk of approximately 20%, an economic analysis published before the guideline update illustrated that the added costs of more widespread CSF use at the lower threshold were offset by reductions in hospitalization costs.[18]

The introduction of biosimilar CSFs has led to the reduction in drug prices for historically expensive therapies. The availability of biosimilar CSFs makes this cost-effectiveness analysis more relevant, as previously published US cost-effectiveness analyses focused only on the originator products and therefore do not reflect the present US market for CSFs.[8,19] The present analysis supports the use of CSFs in patients receiving intermediate-risk chemotherapy in addition to currently available clinical trial data that show benefit of PP for chemotherapy regimens in solid tumors and NHL.

Before COVID-19, utilization of CSF PP was relatively low in patients receiving chemotherapy regimens at intermediate risk of FN. For example, PP with either filgrastim or pegfilgrastim was provided to only about 20.7% of patients and SP to 45.7% of patients receiving R-CHOP-21.[20] These real-world prophylaxis rates suggest that a significant portion of patients are at risk for FN and subsequent hospitalization and increased mortality because of this potentially preventable adverse event.

Especially in the current environment where value for money is an urgent focus of providers, governments, and manufacturers, the expanded use of PP also has the potential to contribute to value-based care. In 2016, the Centers for Medicare & Medicaid Services launched the OCM, a system that incentivizes practice advancements and value-based care in oncology. OCM-participating practices must reduce drug costs and meet certain quality measures, including reducing emergency department visits that do not lead to hospital admission.[21] Expanding the PP use of CSF has the potential to reduce emergency department visits and hospital admissions. As the OCM transitions toward the Oncology Care First Model, it will continue to focus on the concept of value-based care by expanding on the enhanced services provided to beneficiaries. Oncology Care First Model is seen as a likely intermediate step toward an oncology bundled payment structure where reimbursement for all services during an episode will be based on a prospective payment system.[22] Under this model, practices will have more incentive to reduce their drug costs and provide the most cost-effective therapies to their patients.

Our study has some limitations. First, in the absence of data for each cancer type, some inputs were based on studies that examined patients with different cancer types. However, we believe the data used in this analysis represent reasonable and conservative estimates of reality. The structure of the analyses likely represents a simplification of the complex interplay between disease, treatments, and costs. The models assumed only one episode of FN per cycle, and no adverse events were included. The analyses also only evaluated short-acting CSFs, whereas long-acting agents are more commonly used for prophylaxis. Furthermore, the inputs for the percentage of patients requiring hospitalization to treat FN were derived from data that predated more recent guidance that emphasizes outpatient management of FN. These are areas of need for future research. Finally, because of the velocity of new information regarding COVID-19 and its novelty, we did not consider how infection introduced through FN management might affect the results. During the time of the COVID-19 pandemic, these results may be viewed as conservative estimates for the cost-effectiveness of using biosimilar filgrastim

(specifically filgrastim-sndz) as a PP strategy. Real-world evidence studies should be conducted to evaluate the impact of these recommendations on population-based outcomes. In the future, the use of machine learning may be viable for reducing the uncertainty within complex health economic models, but this is still in its infancy and not yet the preferred approach by health technology assessment organizations.[23]

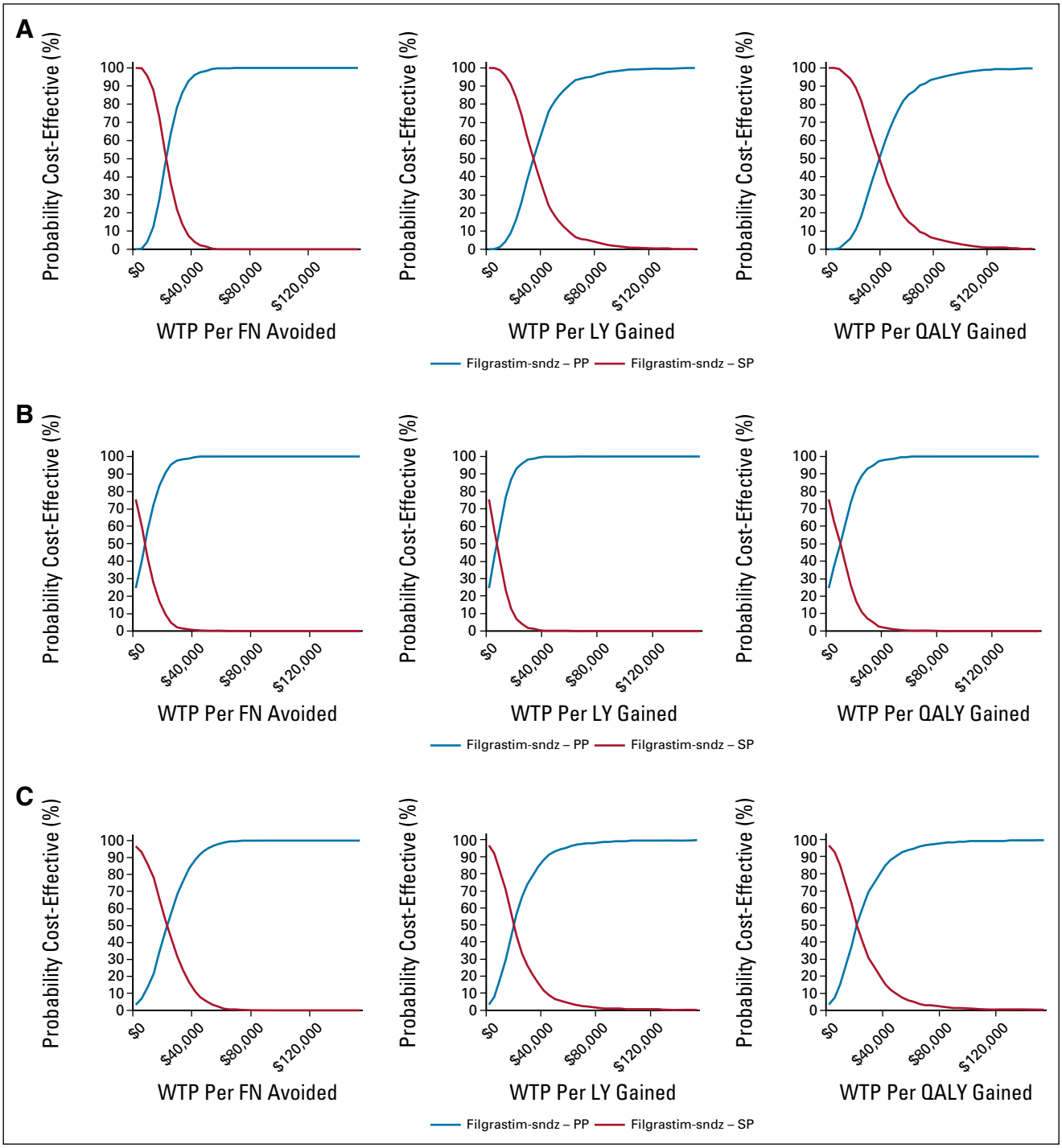


**FIG 1.** PSA cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves illustrating the probability of PP with biosimilar filgrastim being cost-effective relative to SP across a range of WTP thresholds for cost per FN avoided, cost per LY gained, and cost per QALY gained. Curves are shown for (A) breast cancer, (B) NSCLC, and (C) NHL. FN, febrile neutropenia; LY, life year; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PP, primary prophylaxis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SP, secondary prophylaxis; WTP, willingness to pay.

In conclusion, PP with biosimilar filgrastim is cost-effective in patients receiving intermediate-risk, curative chemotherapy regimens for breast cancer, NSCLC, and NHL. In the era of COVID-19 and value-based care, the use of biosimilar filgrastim has valuable potential to reduce complications associated with unnecessary contact with the health care system among patients undergoing potentially curative chemotherapy. This analysis supports the expanded use of PP with biosimilar filgrastim and should be more strongly considered, if not recommended, by patients and providers to improve long-term outcomes.


## AFFILIATIONS

[1]Sandoz, Inc, Princeton, NJ
[2]Xcenda, LLC, Palm Harbor, FL
[3]Fred Hutchinson Cancer Research Center, Seattle, WA

## CORRESPONDING AUTHOR

Edward Li, PharmD, MPH, Sandoz Inc, 100 College Rd W, Princeton, NJ 08540; e-mail: edward-1.li@sandoz.com.



## PRIOR PRESENTATION

Presented in part at the ASCO 2019 Quality Care Symposium, San Diego, CA, September 6-7, 2019; the 2020 ASCO 2020 Virtual Scientific Program, May 29-31, 2020; and the ASCO 2020 Virtual Quality of Care Symposium, October 9-10, 2020.

## SUPPORT

Supported by Sandoz, Inc.


## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.20.01047.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Edward Li, Dylan J. Mezzio, Kim Campbell, Gary H. Lyman
**Collection and assembly of data:** Edward Li, Dylan J. Mezzio, David Campbell, Kim Campbell
**Data analysis and interpretation:** All authors
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## REFERENCES


1. Smith TJ, Bohlke K, Lyman GH, et al: Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 33:3199-3212, 2015
2. Becker PS, Griffiths EA, Alwan LM, et al: NCCN guidelines insights: Hematopoietic growth factors, version 1.2020. J Natl Compr Canc Netw 18:12-22, 2020
3. Kuderer NM, Choueiri TK, Shah DP, et al: Clinical impact of COVID-19 on patients with cancer (CCC19): A cohort study. Lancet 395:1907-1918, 2020
4. Zhang L, Zhu F, Xie L, et al: Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol 31:894-901, 2020
5. Ueda M, Martins R, Hendrie PC, et al: Managing cancer care during the COVID-19 pandemic: Agility and collaboration toward a common goal. J Natl Compr Canc Netw 18 1-4, 2020
6. American Society of Clinical Oncology (ASCO): COVID-19 Patient Care Information, Cancer Treatment & Supportive Care. https://www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care
7. Griffiths EA, Alwan LM, Bachiashvili K, et al: Considerations for use of hematopoietic growth factors in patients with cancer related to the COVID-19 pandemic. J Natl Compr Canc Netw 1:1-4, 2020
8. Hill G, Barron R, Fust K, et al: Primary versus secondary prophylaxis with pegfilgrastim for the reduction of febrile neutropenia risk in patients receiving chemotherapy for non-Hodgkin's lymphoma: Cost-effectiveness analyses. J Med Econ 17:32-42, 2014
9. Fust K, Li X, Maschio M, et al: Cost-effectiveness analysis of prophylaxis treatment strategies to reduce the incidence of febrile neutropenia in patients with early-stage breast cancer or non-Hodgkin lymphoma. Pharmacoeconomics 35:425-438, 2017
10. Weycker D, Li X, Barron R, et al: Importance of risk factors for febrile neutropenia among patients receiving chemotherapy regimens not classified as high-risk in guidelines for myeloid growth factor use. J Natl Compr Canc Netw 13:979-986, 2015
11. Lyman GH, Morrison VA, Dale DC, et al: Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 44:2069-2076, 2003
12. Centers for Medicare & Medicaid Services (CMS): July 2020 ASP Pricing Schedule. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files
13. Bureau of Labor Statistics: CPI—All urban consumers—U.S. medical care services. https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SAM2
14. Arias E, Xu JQ: United States Life Tables, 2015. National Vital Statistics Reports (Table 2-3), Volume 7. Hyattsville, MD, National Center for Health Statistics. 2018
15. Tabish SA: COVID-19 pandemic: Emerging perspectives and future trends. J Public Health Res 9:1786, 2020
16. Calhoun EA, Schumock GT, McKoy JM, et al: Granulocyte colony—Sstimulating factor for chemotherapy-induced neutropenia in patients with small cell lung cancer: The 40% rule revisited. Pharmacoeconomics 23:767-775; 2005
17. Smith TJ, Khatcheressian J, Lyman GH, et al: 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 24:3187-3205, 2006
18. Lyman GH, Kuderer NM: The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. Crit Rev Oncol Hematol 50: 129-146, 2004
19. Lyman G, Lalla A, Barron R, et al: Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. Curr Med Res Opin 25:401-411, 2009

20. Kawatkar AA, Farias AJ, Chao C, et al: Hospitalizations, outcomes, and management costs of febrile neutropenia in patients from a managed care population. Support Care Cancer 25:2787-2795, 2017
21. Centers for Medicare & Medicaid Services (CMS): Innovation Models, Oncology Care Model. https://innovation.cms.gov/innovation-models/oncology-care
22. Young G, Schleicher SM, Dickson NR, et al: Insights from the oncology care first proposal-where we've been and where we're going in value-based care. JCO Oncol Pract 16:151-153, 2020
23. Chen Y, Chirikov VV, Marston XL, et al: Machine learning for precision health economics and outcomes research (P-HEOR): Conceptual review of applications and next steps. J Health Econ Outcomes Res 7:35-42, 2020
24. Strauss GM, Herndon JE II, Maddaus MA, et al: Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 26: 5043-5051, 2008
25. Weycker D, Barron R, Edelsberg J, et al: Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. Breast Cancer Res Treat 133:301-310, 2012
26. Criss SD, Mooradian MJ, Sheehan DF, et al: Cost-effectiveness and budgetary consequence analysis of durvalumab consolidation therapy vs no consolidation therapy after chemoradiotherapy in stage III non-small cell lung cancer in the context of the US health care system. JAMA Oncol 5:358-365, 2019
27. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-1671, 2008 [Erratum: N Engl J Med 359:106, 2008. N Engl J Med 360:1685, 2009]
28. Whyte S, Cooper KL, Stevenson MD, et al: Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. Value Health 14:465-474, 2011
29. Veitch Z, Khan OF, Tilley D, et al: Impact of cumulative chemotherapy dose on survival with adjuvant FEC-D chemotherapy for breast cancer. J Natl Compr Canc Netw 17:957-967, 2019
30. Crawford J, Dale DC, Kuderer NM, et al: Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: The results of a prospective nationwide study of oncology practice. J Natl Compr Canc Netw 6:109-118, 2008
31. Pettengell R, Bosly A, Szucs T, et al: INC-EU prospective observational European neutropenia study: Preliminary Hodgkin and non-Hodgkin lymphoma results. Poster presented at: 11th Congress of the European Hematology Association, Amsterdam, the Netherlands, June 15-18, 2006
32. Shayne M, Culakova E, Poniewierski MS, et al: Dose intensity and hematologic toxicity in older cancer patients receiving systemic chemotherapy. Cancer 110: 1611-1120, 2007
33. Wang L, Baser O, Kutikova L, et al: The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: A systematic review and meta-analysis of randomized controlled trials. Support Care Cancer 23:3131-3140, 2015
34. Weycker D, Barron R, Kartashov A, et al: Incidence, treatment, and consequences of chemotherapy-induced febrile neutropenia in the inpatient and outpatient settings. J Oncol Pharm Pract 20:190-198, 2014
35. Chrischilles E, Delgado DJ, Stolshek BS, et al: Impact of age and colony-stimulating factor use on hospital length of stay for febrile neutropenia in CHOP-treated non-Hodgkin's lymphoma. Cancer Control 9:203-211, 2002
36. Clark OA, Lyman GH, Castro AA, et al: Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. J Clin Oncol 23:4198-4214, 2005
37. Centers for Medicare & Medicaid Services (CMS): Physician Fee Schedule Look-Up. https://www.cms.gov/apps/physician-fee-schedule/overview.aspx, 2020
38. Cámara RJA, Schwentner L, Friedl TWP, et al: Quality of life during and after adjuvant anthracycline-taxane-based chemotherapy with or without Gemcitabine in high-risk early breast cancer: Results of the SUCCESS A trial. Breast Cancer Res Treat 175:627-635, 2019
39. Bezjak A, Lee CW, Ding K, et al: Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: Results from a randomized trial, JBR.10. J Clin Oncol 26:5052-5059, 2008
40. National Cancer Institute: SEER Cancer Stat Facts: Female Breast Cancer. https://seer.cancer.gov/statfacts/html/breast.html
41. National Cancer Institute: SEER Cancer Stat Facts: Non-Hodgkin Lymphoma. https://seer.cancer.gov/statfacts/html/nhl.html
42. Dulisse B, Li X, Gayle JA, et al: A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. J Med Econ 16:720-735, 2013
43. Cupp J, Culakova E, Poniewierski MS, et al: Analysis of factors associated with in-hospital mortality in lung cancer chemotherapy patients with neutropenia. Clin Lung Cancer 19:e163-e169, 2018
44. Rolston KV, Frisbee-Hume SE, Patel S, et al: Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. Support Care Cancer 18:89-94, 2010
45. Cespedes Feliciano EM, Chen WY, Lee V, et al: Body composition, adherence to anthracycline and taxane-based chemotherapy, and survival after non-metastatic breast cancer. JAMA Oncol 6:264-270, 2020
46. Ramsden K, Laskin J, Ho C: Adjuvant chemotherapy in resected stage II non-small cell lung cancer: Evaluating the impact of dose intensity and time to treatment. Clin Oncol (R Coll Radiol) 27:394-400, 2015

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Primary Prophylaxis With Biosimilar Filgrastim for Patients at Intermediate Risk for Febrile Neutropenia: A Cost-Effectiveness Analysis**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

**Edward Li**
**Employment:** Sandoz
**Stock and Other Ownership Interests:** Novartis

**Dylan J. Mezzio**
**Employment:** Xcenda, Gilead Sciences
**Stock and Other Ownership Interests:** Gilead Sciences
**Consulting or Advisory Role:** Xcenda
**Research Funding:** Xcenda, Gilead Sciences
**Travel, Accommodations, Expenses:** Gilead Sciences

**David Campbell**
**Employment:** Xcenda
**Research Funding:** Xcenda

**Kim Campbell**
**Employment:** Sandoz-Novartis
**Stock and Other Ownership Interests:** Novartis
**Travel, Accommodations, Expenses:** Novartis

**Gary H. Lyman**
**Consulting or Advisory Role:** G1 Therapeutics, Sandoz-Novartis, Samsung Bioepis, BeyondSpring Pharmaceuticals, Teva
**Research Funding:** Amgen
**Travel, Accommodations, Expenses:** Bayer

No other potential conflicts of interest were reported.

## APPENDIX

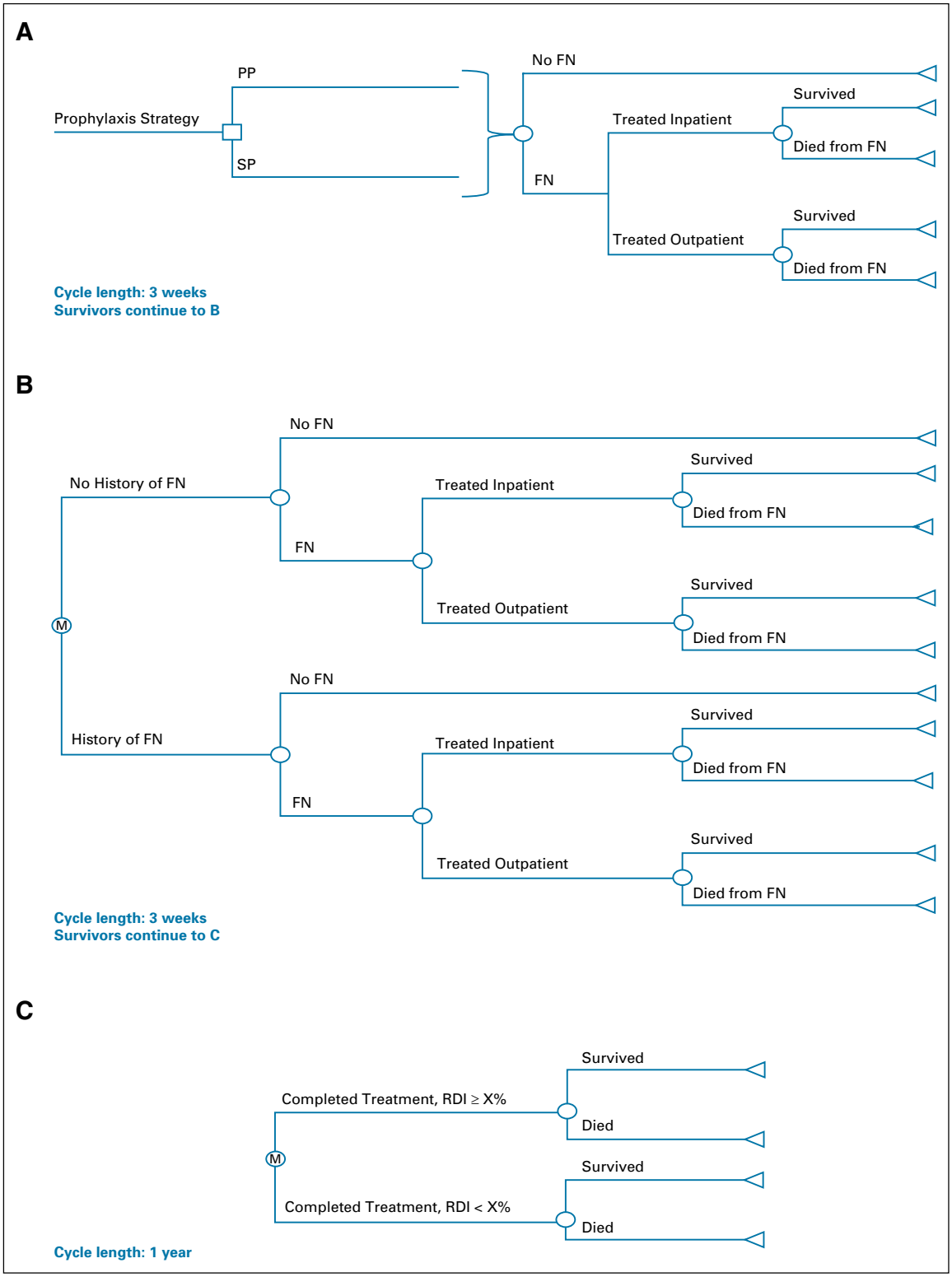


**FIG A1.** General model structure. In addition to health care costs, the model was designed to evaluate the total number of FN events avoided, total LYs, and total QALYs over (A) the first cycle of chemotherapy, (B) subsequent cycles of chemotherapy, and (C) postchemotherapy over a lifetime horizon. The RDI threshold (X% in figure) was 90% for NHL and 85% for breast cancer and NSCLC. FN, febrile neutropenia; LY, life year; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; QALY, quality-adjusted life year; RDI, relative dose intensity.