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U.S. prevalence of endocrine therapy–naïve locally advanced or metastatic breast cancer
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ABSTRACT
Background Variations in treatment choice, or late stage at first diagnosis, mean that, despite guideline recommendations, not all patients with hormone receptor (HR)–positive locally advanced or metastatic breast cancer (LA/mBCa) will have received endocrine therapy before disease progression. In the present study, we aimed to estimate the proportion of women with postmenopausal HR-positive LA/mBCa in the United States who are endocrine therapy-naïve.

Methods Women in the Optum Electronic Health Record (EHR) database with a breast cancer (BCa) diagnosis (January 2008–March 2015) were included. Patient and malignancy characteristics were identified using structured data fields and natural-language processing of free-text clinical notes. The proportion of women with postmenopausal HR-positive, human epidermal growth factor 2 (HER2)–negative (or unknown) LA/mBCa who had not received prior endocrine therapy was determined. Results were extrapolated to the entire U.S. population using the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results database. Results are presented descriptively.

Results In the EHR database, 11,831 women with BCa had discernible information on postmenopausal status, HR status, and disease stage. Of those women, 1923 (16.3%) had postmenopausal HR-positive, HER2-negative (or unknown) LA/mBCa, and 70.7% of those 1923 patients (n = 1360) had not received prior endocrine therapy, accounting for 11.5% of the overall population. Extrapolating those estimates nationally suggests an annual incidence of 14,784 cases, and a 5-year limited duration prevalence of 50,638 cases.

Conclusions A substantial proportion of women with postmenopausal HR-positive LA/mBCa in the United States could be endocrine therapy–naïve.

Key Words Breast cancer, advanced; breast cancer, metastatic; electronic health records; endocrine therapy; hormone receptor–positive disease

INTRODUCTION
Most breast cancers (BCAs) are hormone receptor (HR)–positive [estrogen receptor (ER)– or progesterone receptor (PR)–positive, or both] and HER2 (human epidermal growth factor 2)–negative at diagnosis. Standard adjuvant treatment for women with postmenopausal HR-positive BCa includes endocrine therapy with tamoxifen or an aromatase inhibitor (letrozole, anastrozole, or exemestane). Fulvestrant, a selective estrogen receptor degrader, was recently approved by the U.S. Food and Drug Administration for use in patients who have received no prior endocrine therapy. Because most BCa is detected at an early stage, patients with postmenopausal HR-positive locally advanced or metastatic BCa (LA/mBCa) are likely to have received prior endocrine therapy for their BCa. Patients who have not received prior endocrine therapy could include those with a primary diagnosis of LA/mBCa (that is, those patients who have not been treated for early BCa), or less commonly, those with a previous diagnosis of early BCa who, because of variability in real-world treatment decisions, did not receive adjuvant endocrine therapy.

Previous estimates of the size of the patient population with a primary diagnosis of HR-positive advanced BCa...
have ranged from 13% to 17% of patients with a known hr status. However, uncertainty about that estimate arises because of the limited generalizability of the findings of those small retrospective cohort studies. Understanding the prevalence of hr-positive advanced bca in patients not having received prior endocrine therapy is important to confirm the extent to which newer treatments, such as fulvestrant, could address a treatment gap in patients with bca.

In the present study, we aimed to estimate the proportion of patients in the United States with a diagnosis of postmenopausal hr-positive, her2-negative La/mbc who did not receive prior endocrine therapy (including patients with a primary diagnosis of hr-positive, her2-negative La/mbc, and patients with prior early bca or La/mbc who did not receive prior endocrine therapy) and to extrapolate the findings to estimate the size of that population nationally.

METHODS

Study Population
This observational study relied on retrospectively analyzed data from the Optum Electronic Health Record (ehr) database, which documents patient care across various provider groups and health care settings in the United States, including approximately 43.3 million patients as of 30 June 2014. As the data are sourced from multiple provider groups, they are converted into a consistent format before use. Information from structured fields within the ehr and through natural language processing (nlp) of free-text clinical notes was used, as previously reported.

The cohort evaluated for the present study included women more than 40 years of age who had received a diagnosis of bca between 1 January 2008 and 31 March 2015. To reduce the number of false-positive cases identified, patients were required to have had at least 2 encounters with a bca diagnosis, coded according to the International Classification of Diseases (9th or 10th edition, or both), that were between 30 and 180 days apart and to have at least 1 year of coverage in the ehr database (figure 1). The index date was defined as the earliest date at which a patient met those criteria. A subset of that population was designated the target population, defined as women with postmenopausal hr-positive, her2-negative (or unknown) La/mbc (figure 1). Patients without a baseline prescription record and without at least 1 physician office visit record in the 12 months before the index date were excluded to limit the population to patients with regular health care utilization within participating ehr systems and, therefore, to patients with a more complete record of health characteristics.

Patient characteristics (including demographics, ehr characteristics, health care utilization, and risk factors) were based on information obtained from encounters occurring in the baseline period of 12 months before and including the index date. Prior use of endocrine therapy and previous cancer diagnoses were defined in a baseline period of at least 12 months, but up to 5 years before the index date, when data were available. Prior use of endocrine therapy was determined using prescription data and medication orders. Endocrine therapies included aromatase inhibitors, androgens, er antagonists, gonadotropin-releasing hormone agonists, gonadotropin-releasing hormone antagonists, luteinizing hormone-releasing agonists, and luteinizing hormone-releasing antagonists.

Postmenopausal status, hr status, her2 status, and cancer TNM stage were obtained from the nlp of free-text clinical notes within the ehrs. We used a generalized nlp approach that relied on feature-based context-free grammar recognition developed specifically for clinical notes. That generalized approach is validated for the identification of clinical concepts, features (for example, lists, tables, sentences), and grammar rules (used to provide sentiment and attributes of the clinical concepts). In women 40–55 years of age, postmenopausal status was based on the presence of postmenopausal diagnostic codes or nlp-identified documentation of a patient’s postmenopausal status before the index date. Women more than 55 years of age were considered postmenopausal unless specifically contradicted by nlp-identified information in free-text notes. Hormone receptor status was described in terms of hr or pgr status, or both. In addition to nlp-identified information from the free-text notes, hr status was established using International Classification of Diseases (9th edition) diagnostic codes and treatment history.

In our analysis, locally advanced bca was defined as a subset of stage iiB (T3N0M0) and all stage iii disease. For the purpose of the guidelines developed at the Second International Consensus Guidelines for Advanced Breast
Cancer\textsuperscript{11,12}, the definition of locally advanced BCa has been revised to include only inoperable locally advanced disease that has not yet spread to distant sites. Thus, for locally advanced malignancies, observed cases were excluded from the target population if a surgical procedure for mastectomy or lumpectomy occurred within 6 months of the diagnosis date. Metastatic BCa was defined as cases meeting stage IV criteria. Cases were identified by using NLP to search the free-text notes to identify specific TNM stage and related attributes for BCa within the 6 months preceding and up to 6 months after the index date. As a supplement to TNM staging, we identified attributes of BCa mentions that could be mapped to locally advanced or metastatic malignancies (for example, explicit mention of “metastatic” or “locally advanced” in the absence of TNM staging).

Diagnosis records—or records of chemotherapy, radiotherapy, or endocrine therapy—were used to establish whether cases were considered primary LA/mBCa (that is, the first recorded diagnosis of cancer) or LA/mBCa with a prior BCa diagnosis. Incident cases were defined as those with no evidence of a BCa diagnosis, chemotherapy, or radiotherapy from a minimum of 12 months and up to 5 years before the index date. Individuals with evidence of a BCa diagnosis, chemotherapy, or radiotherapy within 5 years before the index date were considered prevalent cases (recurrence of early BCa or progression of LA/mBCa).

Data Analysis

To compare aspects of patient care in a variety of settings, estimates of the size of the target population were stratified by region and year of diagnosis. Results are presented descriptively; no formal statistical comparisons are made.

Sensitivity analyses were performed to assess the influence of missing data on proportion estimates. Those analyses included patients with confirmed HER2-negative status only, or with imputed values for missing HR status in the target population. Hormone receptor status was singly imputed, relying on a fully conditional specification with logistic imputation of ER and PR status. That imputation was performed using the SAS multiple imputation for missing data procedure (SAS Institute, Cary, NC, U.S.A.), with missing HR status predicted based on all assessed covariates (patient characteristics comprising demographics, EHR characteristics, health care utilization, and risk factors). Assuming that the observed covariates explain differences between observed and missing values, a comparison of the original and imputed data tables allowed for quantification of bias attributable to missing data.

The proportion of the target population—patients with postmenopausal HR-positive, HER2-negative (or unknown) LA/mBCa—in this sample who did not receive prior endocrine therapy was extrapolated using data from the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database to estimate the size of the target population at the national level\textsuperscript{13}.

For prevalence estimates, the extrapolation approach multiplied the 2015 SEER national estimate of 5-year prevalence ($N_{SEER}$) by the SEER estimate of the proportion of prevalent BCa for patients who were 55 years of age or older with HR-positive, HER2-negative LA/mBCa (target population, $TP_{SEER}$) and by the observed EHR-based estimate of the proportion of prevalent cases in the target population without prior endocrine therapy ($Untreated / TP_{EHR}$). Similarly, the incidence estimate multiplied the 2015 SEER national estimate of BCa cases by the SEER estimate of the proportion of incident BCa cases in the target population and by the observed EHR-based estimate of the proportion of the incident cases in the target population without prior hormone therapy:

$$\text{Extrapolated } N = N_{SEER} \times TP_{SEER} \times \text{Untreated} / TP_{EHR}$$

RESULTS

Patient Populations

Overall, 63,962 women more than 40 years of age in the Optum EHR database were diagnosed with BCa during the study period (Table 1). Discriminable information on postmenopausal status, HR status, and disease stage (Table 1) was available for 11,831 patients. In all, the subset of patients with postmenopausal HR-positive, HER2-negative (or unknown) LA/mBCa (the target population) comprised 1923 patients. More than half those patients (54.1%, 1040 of 1923) had a primary diagnosis of LA/mBCa, and 45.9% (883 of 1923) had LA/mBCa after a prior BCa diagnosis. Figure 2 compares the proportions of patients with a diagnosis of LA/mBCa or of early BCa at the index date for incident cases (no prior BCa diagnosis) and prevalent cases (with a prior BCa diagnosis).

The target population tended to be older: only 3.4% of the target population (66 of 1923) was between 40 and 54 years of age, compared with 22.2% of the overall cohort (14,189 of 63,962). In addition, compared with the overall cohort, the target population was more likely to have received prior chemotherapy [10.2% (196 of 1923) vs. 4.7% (3019 of 63,962)].

Endocrine Therapy

Prior endocrine therapy had not been administered to 70.7% of patients with postmenopausal HR-positive, HER2-negative (or unknown) LA/mBCa [95% confidence interval (CI): 63.8% to 77.7%; 1360 of 1923]. Of patients in the target population without a record of prior BCa, 88.5% (95% CI: 86.4% to 90.3%; 920 of 1040) had not received prior endocrine therapy within the 5 years preceding the index date. Among prevalent BCa cases in the target population, 49.8% (95% CI: 46.5% to 53.1%; 440 of 883) had no record of prior endocrine therapy. With imputation of missing HR status, those estimates were slightly higher: within the imputed target population, 91.1% of incident cases and 77.2% of all cases had not received prior endocrine therapy.

Within the overall cohort, 11.5% of patients with BCa and a discernible postmenopausal status, HR status, and disease stage (95% CI: 10.8% to 12.1%; 1360 of 11,831) satisfied the definition of the target population and had not received prior endocrine therapy. That proportion ranged from 8.5% in the South (95% CI: 7.5% to 9.5%; 299 of 3527) to 13.7% in the West (95% CI: 11.7% to 15.8%; 199 of 1448). Restricting the study population to incident cases with available postmenopausal status, HR status, and disease stage, the proportion of patients with a primary diagnosis of HR-positive, HER2-negative (or unknown) LA/mBCa without prior endocrine therapy was 16.2% (95% CI: 15.1% to 17.4%; 920 of 5671).
A sensitivity analysis that imputed data for patients with missing HR information was performed. Of all eligible women with bca, the proportion of patients with postmenopausal la/mbc, discernible HR status (imputed), and no prior endocrine therapy was 11.2% (95% CI: 10.7% to 11.8%; 1624 of 14,448). That proportion declined to 6.7% (95% CI: 6.3% to 7.2%; 798 of 11,831) when patients with unknown HR status were excluded from the target population. Consequently, the national extrapolations of the proportion of the overall bca population who met the definition for the untreated target population. Given that HER2 status was unknown for a large proportion of the patients (69.5%), excluding those patients (a proportion of whom would have been HER2-negative) without changing the denominator represents the lower bound of the estimate with HER2-negative cases. However, we did not observe a notable difference in the estimate of the proportion of the target population without prior endocrine therapy in the analyses with and without imputation (77.2% vs. 75.9% respectively). Consequently, the national extrapolations are expected to be minimally affected by biases resulting from missing HR or HER2 status within the EHR database.

### Extrapolation to the U.S. Population

Extrapolation of the observed proportion of patients in this target population without prior endocrine therapy in the study sample to SEER national estimates of patients with postmenopausal HR-positive, HER2-negative LA/mBCa estimated an annual incidence of 14,784 patients and a 5-year limited duration prevalence of 50,638 patients (Table III). 

### DISCUSSION

The present study of real-world data provides an estimate of the number of patients with postmenopausal HR-positive, HER2-negative (or unknown) LA/mBCa in the United States who have not received prior endocrine therapy.

Approximately half the patients in this study with a prior bca diagnosis (49.8%), and most without a prior bca diagnosis (88.5%), had not received endocrine therapy as of the study’s cohort entry date. Extrapolating those percentages to the U.S. population, we estimated an annual incidence of approximately 15,000 women with postmenopausal HR-positive, HER2-negative LA/mBCa who have not received prior endocrine therapy.

Sensitivity analyses were conducted to assess the potential effect of missing HR status data (imputation of missing values) and unknown HER2 status (exclusion of patients with uncertain values). Relative to analyses of patients with a known HR or HER2 status, analyses with imputed values for missing HR status yielded a higher estimate of the proportion of the overall bca population who met the definition for the untreated target population. Given that HER2 status was unknown for a large proportion of the patients (69.5%), excluding those patients (a proportion of whom would have been HER2-negative) without changing the denominator represents the lower bound of the estimate with HER2-negative cases. However, we did not observe a notable difference in the estimate of the proportion of the target population without prior endocrine therapy in the analyses with and without imputation (77.2% vs. 75.9% respectively). Consequently, the national extrapolations are expected to be minimally affected by biases resulting from missing HR or HER2 status within the EHR database.
TABLE II  Disease characteristics for the overall breast cancer study cohort

| Characteristic                                      | Incident cases (n=35,600) | Prevalent cases (n=28,362) | All cases (n=63,962) |
|-----------------------------------------------------|---------------------------|---------------------------|----------------------|
| Postmenopausal status                               |                           |                           |                      |
| Yes                                                 | 27,707 (77.8)             | 22,164 (78.1)             | 49,871 (78.0)        |
| No                                                  | 7,893 (22.2)              | 6,198 (21.9)              | 14,091 (22.0)        |
| Hormone receptor status                             |                           |                           |                      |
| ER-positive, PgR-positive                           | 12,072 (33.9)             | 5,515 (19.4)              | 17,587 (27.5)        |
| ER-positive, PgR-negative                           | 1,406 (3.9)               | 726 (2.6)                 | 2,132 (3.3)          |
| ER-positive, PgR uncertain                          | 1,599 (4.5)               | 1,221 (4.3)               | 2,820 (4.4)          |
| ER-negative, PgR-positive                           | 444 (1.2)                 | 89 (0.3)                  | 533 (0.8)            |
| ER-negative, PgR-negative                           | 2,025 (5.7)               | 1,154 (4.1)               | 3,179 (5.0)          |
| ER-negative, PgR uncertain                          | 328 (0.9)                 | 207 (0.7)                 | 535 (0.8)            |
| ER uncertain, PgR-positive                          | 1,075 (3.0)               | 497 (1.8)                 | 1,572 (2.5)          |
| ER uncertain, PgR-negative                          | 325 (0.9)                 | 215 (0.8)                 | 540 (0.8)            |
| ER uncertain, PgR uncertain                         | 16,326 (45.9)             | 18,738 (66.1)             | 35,064 (54.8)        |
| HER2 status                                         |                           |                           |                      |
| Positive                                            | 4,606 (12.9)              | 1,931 (6.8)               | 6,537 (10.2)         |
| Negative                                            | 8,359 (24.0)              | 4,392 (15.5)              | 12,951 (20.2)        |
| Uncertain                                           | 22,435 (63.0)             | 22,039 (77.7)             | 44,474 (69.5)        |
| Disease stage at index date                         |                           |                           |                      |
| Early                                               | 14,005 (39.3)             | 7,298 (25.7)              | 21,303 (33.3)        |
| Locally advanced                                    | 2,202 (6.2)               | 1,858 (6.6)               | 4,060 (6.3)          |
| Metastatic                                          | 559 (1.6)                 | 639 (2.3)                 | 1,198 (1.9)          |
| Uncertain                                           | 18,834 (52.9)             | 18,567 (65.5)             | 37,401 (58.5)        |
| First time diagnosed as locally advanced or metastatic|                           |                           |                      |
| Yes                                                 | 713 (2.0)                 | 1,801 (6.4)               | 2,514 (3.9)          |
| No                                                  | 3,201 (9.0)               | 4,936 (17.4)              | 8,137 (12.7)         |
| Uncertain                                           | 31,686 (89.0)             | 21,625 (76.2)             | 53,311 (83.4)        |
| Prior endocrine therapy                             |                           |                           |                      |
| Yes                                                 | 1,870 (5.3)               | 5,774 (20.4)              | 7,644 (12.0)         |
| No                                                  | 33,730 (94.7)             | 22,588 (79.6)             | 56,318 (88.0)        |

ER = estrogen receptor; PgR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

FIGURE 2  Proportion of patients with breast cancer by primary diagnosis. EHR = electronic health record.
Despite treatment guidelines3–5,14,15, many patients with prevalent HR-positive, HER2-negative (or unknown) LA/mBCa had not received prior endocrine therapy. Reasons for that observation might include prescriber preference for treatments such as chemotherapy or radiotherapy (or both) over endocrine therapy or a consideration that the risk of recurrence was sufficiently low in some patients to offset the potential side effects of adjuvant endocrine therapy. In an analysis of patients with HR-positive advanced BCa, Bonotto et al.16 determined that 38% of patients received first-line chemotherapy instead of endocrine therapy, with the choice being driven by age and site of metastases (endocrine therapy was preferentially provided to older patients, and in the case of bone metastases only). Patient preference and contraindications might also be contributing factors. In addition, it is possible that the EHR data might have underestimated the number of patients who received prior endocrine therapy. The median baseline period available for patients within this EHR-based cohort was 3.2 years. Because the median recurrence-free survival time for BCa is approximately 3.5 years17, prior endocrine therapy for early BCa outside the limit of our study might not have been captured. Furthermore, patients could have relocated and received care at nonparticipating institutions, where the treatment received would have been unknown.

It could be expected that, in all incident cases of BCa, patients would not have received prior endocrine therapy. However, 11.5% of incident cases of LA/mBCa in the present study had a record of prior endocrine therapy. It is possible that some patients in the study were prescribed endocrine therapy for prevention rather than for treatment of BCa. For example, in the present study, raloxifene (generally used for prevention of BCa) was used in 14.2% of patients with incident HR-positive LA/mBCa who had received prior endocrine therapy. In addition, as mentioned previously, endocrine therapy might have been recorded for cancer diagnoses that were outside the available capture of EHR encounters in the study database and thus might actually reflect endocrine therapy for prevalent patients.

The results of the present study are specific to the United States; however, the same patient population might be common in developing countries, where patients are more likely to present with advanced BCa18. Furthermore, this patient population might be more relevant to community practices (where patients are more likely to receive initial diagnosis and treatment) than to specialist referral centres, where encountering such patients could be less likely.

The observed distributions of disease stage and HR status in the present study were largely consistent with SEER-published values, although they were sometimes higher than expected. The proportion of LA/mBCa cases in this EHR sample was 16.5% of incident cases with discernible status (2761 of 16,766); in comparison, approximately 13% of incident BCa cases were identified as stage III or IV within the 2010 SEER data19. However, it could be expected that the SEER and EHR estimates are not identical, given that some cases of stage III BCa were included in the EHR-based estimate, but not in the SEER estimate. In addition, the proportion of patients receiving a primary diagnosis of LA/mBCa in our study was similar (18.2%) to that in other published real-world-evidence studies6–9,20.

According to the American Cancer Society, 84% of BCa is HR-positive1. When the present study took into account diagnostic codes, prior hormonal treatment, and NLP of free-text clinical notes, HR-positive status was reported for 91% of patients. That increased proportion might reflect recording practices in EHR data systems. For instance, clinicians might be more likely to record positive than negative HR status or advanced-stage results within free notes, which would then influence the denominator in the calculation of prevalence. Alternatively, the distribution of HR status varies by patient characteristics, with higher
rates of ER-positive bca in older patient populations than in younger patient populations, and thus the elevated estimate of HR-positive bca in the ehr data might be attributable, in part, to the focus of our study on a postmenopausal patient population.

Interpretation of our study results is subject to certain limitations. Data residing in ehr systems are intended to document patient care and to ensure continuity of information across providers and are not designed for research purposes. As a result, those data should be interpreted with caution and recognition of what they represent. A large number of providers in the United States are not included in the Optum ehr database, and furthermore, patient care received through encounters with health care providers outside the Optum ehr systems would be captured only when documented in the notes of participating provider systems.

The incident cases identified in the present study might not necessarily be newly diagnosed cases, because inclusion in the study was based on the time of a patient’s earliest qualifying diagnosis. Accordingly, incident cases are likely to be somewhat overestimated in the Optum ehr cohort compared with the seer database, and the results of the extrapolation calculations should therefore be interpreted with that potential in mind.

Several recent publications have presented efficacy and safety data from phase iii randomized trials evaluating various treatments in this patient population (postmenopausal HR-positive LA/mbca without prior endocrine therapy). Fulvestrant is a selective ER degrader that is currently approved as monotherapy, or in combination with the cyclin-dependent kinase 4/6 inhibitor palbociclib, for the treatment of HR-positive, HER2-negative LA/mbca in postmenopausal women with disease progression after prior endocrine therapy. Results of the recently completed phase iii FALCON study (NCT01602380 at http://ClinicalTrials.gov/) indicated that fulvestrant monotherapy (500 mg) was superior to anastrozole as first-line treatment for HR-positive LA/mbca in patients who had received no prior endocrine therapy. Fulvestrant was recently approved by the U.S. Food and Drug Administration for use in that patient population. The FALCON trial included women with confirmed HR-positive LA/mbca who had not received prior hormonal treatment for bca. The trial was restricted to patients with a World Health Organization performance status of 0–2, one or more measurable or non-measurable lesions, and no life-threatening metastatic visceral disease; further restrictions were also placed on receipt of prior therapies for bca. Results of the present real-world evidence study have defined the size of the patient population to whom the results of the FALCON study would be most applicable.

Furthermore, PALOMA-2 (NCT01740427) and MONALEESA-2 (NCT01958021) demonstrated that the combination of a cyclin-dependent kinase 4/6 inhibitor (palbociclib and ribociclib respectively) with letrozole was more effective than letrozole alone as first-line treatment for HR-positive LA/mbca. Although patients could have received prior adjuvant endocrine therapy, both studies included a substantial proportion of patients who had not received prior endocrine therapy (43.7% and 48.2% respectively). A consistent treatment effect was observed between the subgroups with and without prior endocrine therapy.

It is important to note that, to optimize outcomes, decisions about treatment should be made on an individual patient basis. Based on recent data, monotherapy with fulvestrant could be considered for the patient population described in the present study. Endocrine therapy in combination with a targeted treatment such as a cyclin-dependent kinase 4/6 inhibitor could also be an option in patients for whom those therapies are available.

CONCLUSIONS

In the present study, we have defined the specific population of patients who have not received prior endocrine therapy, which represents a significant proportion of patients with postmenopausal HR-positive LA/mbca in the United States.

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The results published here were presented at the 2016 San Antonio Breast Cancer Symposium, and the corresponding abstract is published online. The results were also presented as a poster at the 33rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; Montreal, QC; 26–30 August 2017.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: TD, JL, and NJ are employees of, and receive a salary from, AstraZeneca; APN, CL, EG, MD, and JDS are employees of Optum Epidemiology, which conducted this research under a contract with AstraZeneca; APN and JDS also own stock in United Health Group; TD owns stock in Achillion Pharmaceuticals, AstraZeneca, Bristol–Myers Squibb, Gilead, Inovio Pharmaceuticals, and Roche. WJG has no conflicts to disclose.

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