Real-World Costs of Adverse Events in First-Line Treatment of Metastatic Non-Small Cell Lung Cancer

Nicole M. Engel-Nitz, PhD; Michael P. Johnson, MS; Scott H. Bunner, MPH; and Kellie J. Ryan, MPH

ABSTRACT

BACKGROUND: Non-small cell lung cancer (NSCLC) is the most common form of lung cancer in the United States. Immunotherapies and cytotoxic chemotherapies used to treat advanced NSCLC carry a substantial risk of adverse events (AEs), but real-world data on the incidence and costs associated with the unique AE profiles of these treatments are sparse.

OBJECTIVE: To examine the AE incidence and costs among patients initiating non–driver mutation-targeted first-line therapy for metastatic NSCLC (mNSCLC) in clinical practice.

METHODS: This was a retrospective administrative claims study conducted among commercial and Medicare Advantage health plan members who initiated first-line, nontargeted systemic anti-NSCLC therapy between January 1, 2008, and February 28, 2018. Patients were assigned to mutually exclusive treatment cohorts (cytotoxic chemotherapy [CHEM], immuno-oncology agents [IO], or immuno-oncology + cytotoxic chemotherapy [IO-CHEM]) and were observed from the index date (start of first-line therapy) through the earliest of health plan disenrollment, death, or March 31, 2018. AE incidence rates and associated health care costs were measured from the index date through the earliest of the start of a new therapy, 180 days after the end of first-line therapy, or the end of the study period. The factors influencing whether patients incurred high AE-related health care costs were assessed using multivariable models adjusted for patient demographic and clinical characteristics.

RESULTS: The final study population (mean [SD] age 68.6 [9.5] years, 53.9% male) included 8,818 in the CHEM cohort, 482 in the IO cohort, and 412 in the IO-CHEM cohort. Overall, 74.4% had at least 1 AE during follow-up. The AE incidence rate was lowest for the IO cohort, with incidence rate ratios (95% CI) of 1.4 (1.3-1.6) for the CHEM cohort and 1.4 (1.2-1.6) for the IO-CHEM cohort. Mean AE-related costs were lowest for the IO cohort ($16,319) and highest for the CHEM cohort ($23,009; $P<0.001$). In the multivariable analysis, the odds of incurring any AE costs were similar for the IO and IO-CHEM cohorts compared with the CHEM cohort (OR = 0.82; $P=0.135$ and OR = 0.98; $P=0.888$, respectively). Among patients who incurred AE costs, those in the IO cohort were less likely than those in the CHEM cohort to have high costs (OR = 0.60; $P=0.030$); the difference between the IO-CHEM and CHEM cohorts was not statistically significant.

CONCLUSIONS: Among real-world patients initiating nontargeted first-line therapy for mNSCLC, those receiving immunotherapy experienced fewer AEs and had lower total AE-related costs than those treated with cytotoxic chemotherapy. Immunotherapy-treated patients were no more likely than chemotherapy-treated patients to incur AE-related costs and were less likely to have high AE costs if they incurred any at all. These findings indicate that immunotherapy-related AEs are not a differentiating factor in cost of care for this patient population in clinical practice.

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What is already known about this subject

- Immunotherapies and cytotoxic chemotherapies used to treat metastatic non-small cell lung cancer (mNSCLC) are associated with improved survival but also carry a substantial risk of adverse events (AEs).
- Real-world data on the AE incidence and AE-related costs of current mNSCLC treatments are sparse.

What this study adds

- Patients with first-line immunotherapy-treated mNSCLC had less frequent AEs, lower total AE costs, and lower odds of incurring high AE costs than those treated with cytotoxic chemotherapy.
- Patients with previous infections or neurological disorders had a higher likelihood of incurring high AE costs during first-line therapy.

Lung cancer is the leading cause of cancer mortality in the United States, with an estimated 228,150 new diagnoses and 142,670 deaths in 2019.[1] It is also among the costliest cancers; total expenditures associated with lung cancer care in 2018 were estimated at more than $14 billion nationally, and the total cost of treatment has been found to surpass $100,000 per patient.[2,3]

Surgical resection is potentially curative for localized non-small cell lung cancer (NSCLC); however, 40% of patients with NSCLC already have stage IV disease at diagnosis.[4] While platinum-based chemotherapy was long the primary option for first-line treatment of advanced NSCLC, the arsenal of available treatments expanded substantially with the development of drugs targeted toward specific driver mutations or the programmed cell death receptor-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) pathways.[5] Today, NSCLC treatment options for patients with metastatic tumors overexpressing PD-L1 and without driver mutations include not only traditional cytotoxic chemotherapy but also immunotherapy with immune checkpoint inhibitors such as pembrolizumab, nivolumab, and atezolizumab.[6]

Although current first-line therapies for advanced NSCLC are associated with improved survival, they also carry a substantial risk of adverse events (AEs).[7] Immunotherapies are associated with lower rates of some toxicities common to classical chemotherapy,[8-11] but they may cause unique

immune-related AEs that can be severe and affect multiple organ systems, sometimes requiring hospitalization and/or treatment with steroids.[12] While it is recognized that AEs of NSCLC treatment can reduce quality of life,[13] real-world data on the incidence and costs associated with the unique AE profiles of these therapies are sparse. Much of our understanding about the extent of AEs experienced by patients treated for advanced NSCLC comes from clinical trials,[14] which use highly selected patient samples that may differ substantially from real-world patient populations.[15] Cost studies conducted among real-world patients with NSCLC have shown a high economic burden but did not differentiate between immunotherapy and conventional chemotherapy,[16] did not specifically examine AE-related costs,[3] or use data collected before the approval of first-line immunotherapy.[17,18] The present study was conducted to address these knowledge gaps by examining the incidence and costs associated with selected AEs among patients initiating nontargeted first-line chemotherapy or immunotherapy for metastatic NSCLC (mNSCLC) in clinical practice.

Methods

Study Design and Data Sources

This was a retrospective study conducted using commercial and Medicare Advantage administrative claims data from the Optum Research Database (ORD) from January 1, 2007, through March 31, 2018 (study period). Mortality information was sourced from claims and Social Security Administration data as available. The ORD is geographically diverse across the United States and contains deidentified medical and pharmacy claims data and linked member enrollment information. Medical claims include diagnosis and procedure codes from the *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM); Current Procedural Terminology or Healthcare Common Procedure Coding System codes; site of service codes; and paid amounts. Pharmacy claims include drug name, National Drug Code number, dosage form, drug strength, fill date, number of days supply, and financial information for outpatient pharmacy services. Because no identifiable protected health information was accessed in the conduct of this study, institutional review board approval or waiver of approval was not required.

Patient Selection and Observation Periods

The study included patients from the ORD with evidence of NSCLC who initiated first-line, non–driver mutation-targeted systemic anticancer therapy between January 1, 2008, and February 28, 2018 (identification period). Inclusion criteria were at least 1 claim for National Comprehensive Cancer Network (NCCN)-recommended, nontargeted therapy for NSCLC (based on September 2017 guidelines) during the identification period (cisplatin, carboplatin, gemcitabine, pemetrexed, docetaxel, paclitaxel, etoposide, vinorelbine, vinblastine, bevacizumab, atezolizumab, nivolumab, pembrolizumab, and ramucirumab)[19]; continuous health plan enrollment with medical and pharmacy benefits for at least 6 months before and at least 1 month after the first qualifying claim for NSCLC therapy (index date); aged ≥ 18 years as of the index date; at least 1 nondiagnostic claim for lung cancer (ICD-9-CM 162.xx or ICD-10-CM C34.xx) in the 6 months before the index date (6-month baseline period); and evidence of metastasis or unresectable locally advanced disease (at least 1 nondiagnostic claim for metastatic disease during the 6-month baseline period or within 30 days after the index date, or evidence of concurrent chemoradiation between 7 days before and up to 30 days after the index date). The period of continuous enrollment before the index date back to January 1, 2007, was the variable baseline period. The period of continuous enrollment from the index date through the earliest of health plan disenrollment, death, or March 31, 2018, was the follow-up period. At least 1 month of follow-up was required unless the patient had died.

Patients were excluded if they had evidence of lung cancer-specific surgery (not including biopsy) during the 6-month baseline period, any claim for systemic anticancer therapy (not including hormone therapies or radiopharmaceutical therapies) during the period 12 months before the index date, any claim for targeted therapy (Figure 1 footnote a) during the variable baseline period or follow-up period, 2 or more nondiagnostic claims at least 30 days apart with diagnosis codes for other cancers in position 1 or 2 during the variable baseline period, or any claim for drugs associated primarily with small cell lung cancer (Figure 1 footnote b) during the variable baseline period or follow-up period.

Cohort Assignments and Line of Therapy Definitions

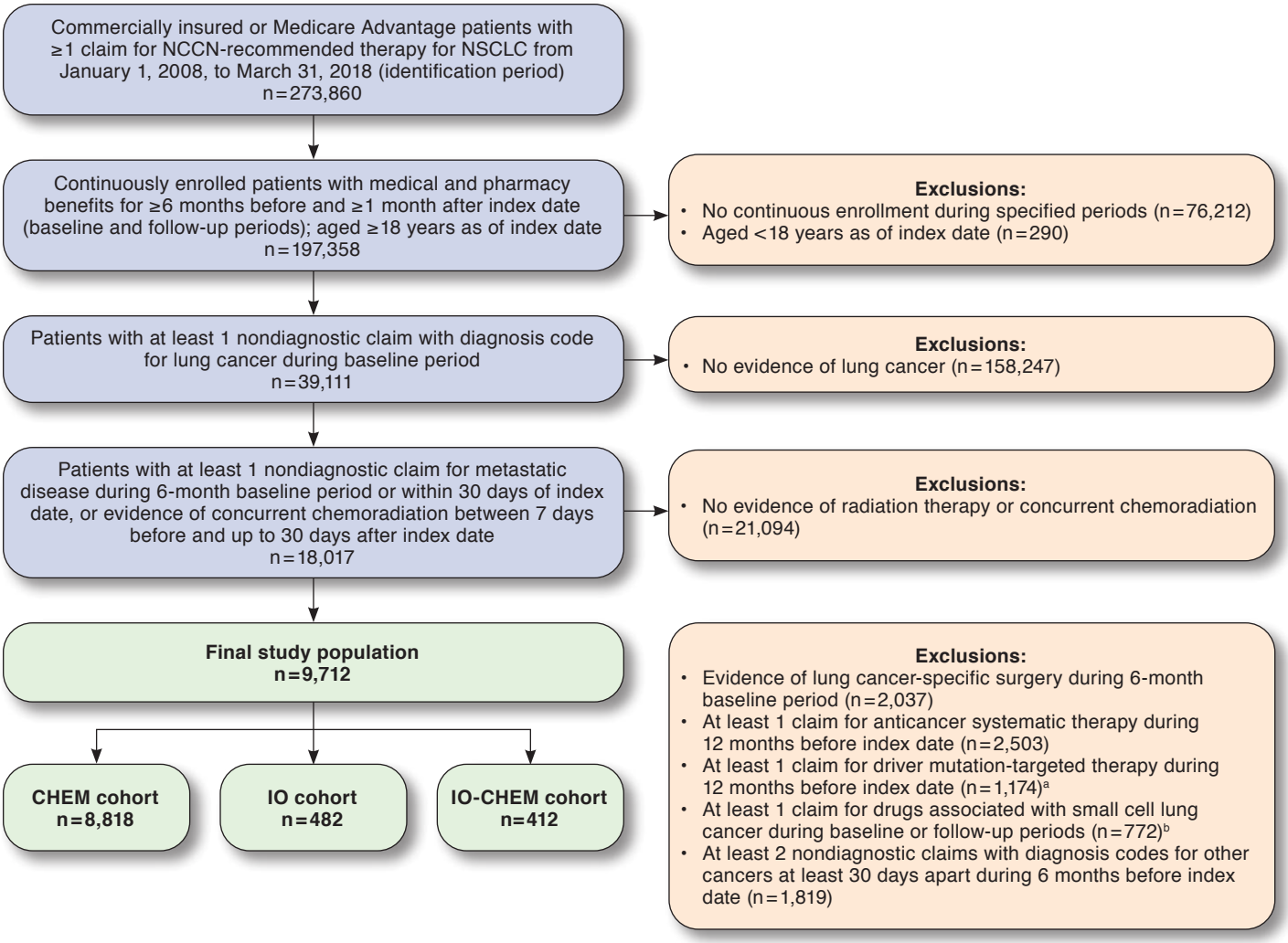
Patients were assigned to mutually exclusive treatment cohorts (cytotoxic chemotherapy [CHEM], immuno-oncology agents [IO], or immuno-oncology + cytotoxic chemotherapy [IO-CHEM]) based on the first observed line of therapy (LOT), which by definition began on the index date (date of the first infusion or fill for a systemic anticancer agent). The first LOT included all agents received within 30 days following the index date and ended on the earliest of any of the following: addition or substitution of a new agent, treatment gap of at least 60 days after the run-out date of all agents in the LOT, death, health plan disenrollment, or end of the study period.

Study Measures

Patient demographic characteristics were assessed as of the index date. Baseline Quan-Charlson Comorbidity Index scores were assessed during the 6-month baseline period.[20] Study outcomes were assessed during the follow-up period.

Selected AEs were measured during the AE observation period, which began on the index date (start of LOT1) and

FIGURE 1 Patient Selection and Attrition



[a]*Afatinib, alectinib, brigatinib, crizotinib, ceritinib, erlotinib, gefitinib, trastuzumab,vandetanib, cabozantinib, ado-trastuzumab emtansine, dasatinib, imbrutinib, vemarafenib, osimertinib, dabrafenib, trametinib, and cetuximab.*

[b]*Topotecan, temozolomide, cyclophosphamide, doxorubicin, vincristine, and bendamustine.*

CHEM = cytotoxic chemotherapy; IO = immuno-oncology agents = IO-CHEM, immuno-oncology + cytotoxic chemotherapy; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer.

ended on the earliest of the start of a new LOT; 180 days after the end of LOT1; or at the end of the study period. AEs measured in this study included those with a prevalence of at least 10% according to the drug labels for NCCN-recommended therapies and some AEs that were less prevalent but were selected by a clinical expert because of severity and/or clinical relevance to immunotherapy. AEs other than infusion reactions were identified on the basis of claims with a relevant ICD-9/10-CM diagnosis code in position 1 or 2 or a relevant procedure code on a medical claim. Infusion reactions were identified on the basis of codes for specified conditions (hypertension, hypertensive crises associated with neurological signs and symptoms, wheezing, oxygen desaturation, chest pain, headaches, rigors, hypotension, and diaphoresis) occurring in position 1 or 2 on claims within 2 days of an infusion (defined as the dates of medical claims for chemotherapy or immunotherapy during the LOT). Conditions were not considered as infusion reactions if the patient had a claim with a diagnosis for that condition in the 7 days before the infusion. Blood disorders (anemia, thrombocytopenia, leukopenia)

TABLE 1 Patient Characteristics

Characteristic	Total (N = 9,712)		CHEM (n = 8,818)		IO (n = 482)		IO-CHEM (n = 412)		*P* Value CHEM vs. IO	*P* Value IO-CHEM vs. IO
Age, years, mean (SD)	68.6	(9.5)	68.4	(9.4)	72.2	(9.9)	69.5	(9.5)	<0.001	<0.001
Follow-up time, months, mean (SD)	163.7	(122.5)	164.3	(122.2)	173.4	(142.3)	139.3	(100.9)	0.170	<0.001
Baseline CCI score category, n (%)										
1-2	163	(1.7)	147	(1.7)	12	(2.5)	4	(1.0)	0.175	0.088
3-4	401	(4.1)	373	(4.2)	16	(3.3)	12	(2.9)	0.331	0.728
5+	9,148	(94.2)	8,298	(94.1)	454	(94.2)	396	(96.1)	0.936	0.185
Sex, male, n (%)	5,239	(53.9)	4,795	(54.4)	225	(46.7)	219	(53.2)	<0.001	0.054
Insurance type, n (%)									<0.001	0.001
Commercial	3,469	(35.7)	3,267	(37.1)	89	(18.5)	113	(27.4)		
Medicare Advantage	6,243	(64.3)	5,551	(63.0)	393	(81.5)	299	(72.6)		
Geographic region									0.222	0.470
Northeast	1,514	(15.6)	1,364	(15.5)	87	(18.1)	63	(15.3)		
Midwest	3,265	(33.6)	2,966	(33.6)	156	(32.4)	143	(34.7)		
South	4,058	(41.8)	3,684	(41.8)	205	(42.5)	169	(41.0)		
West	875	(9.0)	804	(9.1)	34	(7.1)	37	(9.0)		

CCI = Charlson Comorbidity Index; CHEM = cytotoxic chemotherapy; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy; SD = standard deviation.

were calculated separately as well as presented as a group. AE incidence was calculated only among patients without the selected AE during the variable baseline period. Incidence rates were calculated by dividing the number of patients with the AE during the AE observation period by the total patient-years of observation up to the occurrence of the AE.

Health care costs associated with selected AEs were calculated as the combined health plan-paid amounts plus patient-paid amounts during the AE observation period, adjusted to 2017 U.S. dollars using the annual medical care component of the Consumer Price Index.[21] Total costs for each AE were calculated as the sum of costs on each claim associated with the AE. For claims that contained codes for more than 1 AE, costs were attributed separately to the total costs of each AE. For AE costs associated with inpatient stays, the costs of the entire stay were attributed to the AE. Pharmacy costs associated with each AE were calculated on the basis of all pharmacy claims with dates between the first and last medical claims associated with the AE. In addition to total AE costs over the AE period, population-level per patient per month (PPPM) costs were estimated.

Statistical Analysis

Analytic dataset creation was conducted using SAS software version 9.4 (SAS Institute, Cary, NC). All study variables were analyzed descriptively. Results were stratified by treatment cohort and compared using statistical tests appropriate for the distribution of the measure (e.g., t-test, Mann-Whitney U-test, chi-square test). Incidence rate ratios (IRRs) were calculated to compare the risks of selected AEs among treatment cohorts; chi-square testing was performed, with 95% confidence intervals (CIs) derived using 10,000 bootstrapped samples for the composite measures of any AE and blood condition, and standard binomial CIs for the remaining AEs. *P* values ≤ 0.05 were considered to indicate statistical significance.

The factors influencing whether patients had high AE-related health care costs were assessed using logistic regressions adjusted for insurance type, geographic region, sex, baseline Charlson score, baseline metastatic disease, and baseline AEs. Because a substantial number of patients had zero AE costs, 1 model estimated the probability of incurring any AE cost, and a separate model estimated the probability of having high costs (defined as the 90th percentile) among patients incurring > $0 AE costs.[22] Odds ratios (ORs), 95% CIs, and *P* values are presented for each covariate included in the logistic models.

Results

Patient Characteristics

Of 273,860 patients with at least 1 claim for nontargeted, NCCN-recommended therapy for NSCLC during the identification period, 9,712 met the remaining study criteria (Figure 1). The final study population included 8,818 in the CHEM cohort, 482 in the IO cohort, and 412 in the IO-CHEM cohort. In the total population, mean (standard deviation; SD) age was 68.6 (9.5) years, 53.9% were male, and 64.3% had Medicare Advantage insurance. Most patients (94.2%) had a baseline Charlson comorbidity score of 5 or more (Table 1).

Patient characteristics were similar among the 3 cohorts, with a few exceptions (Table 1). The IO cohort had a higher mean age compared with the CHEM and IO-CHEM cohorts

TABLE 2 Incidence Rates of Selected AEs During the AE Period

Event	Incidence Rate[a] per 1,000 Person-Years				Incidence Rate Ratio (95% CI)[b]	
	Total (N = 9,712)	CHEM (n = 8,818)	IO (n = 482)	IO-CHEM (n = 412)	CHEM vs. IO	IO-CHEM vs. IO
Any selected AE	9,135	9,327	6,499	8,843	**1.4 (1.2-1.7)**	**1.4 (1.1-1.7)**
Blood disorders	1,403	1,527	327	806	**4.7 (3.5-6.0)**	**2.5 (1.7-3.5)**
Anemia	774	826	145	589	**5.7 (4.0-8.4)**	**4.1 (2.6-6.4)**
Infusion reactions	767	752	842	1,051	0.9 (0.8-1.1)	1.2 (0.9-1.7)
Gastrointestinal disorders	922	952	501	854	**1.9 (1.5-2.4)**	**1.7 (1.3-2.3)**
Infections	761	811	417	505	**1.9 (1.6-2.5)**	1.2 (0.9-1.7)
Leukopenia	448	493	22	126	**22.3 (9.5-68.7)**	**5.7 (2.1-19.5)**
Neurological disorders	305	308	259	283	1.2 (0.9-1.6)	1.1 (0.7-1.7)
Hemorrhage	253	260	195	175	1.3 (0.97-1.9)	0.9 (0.5-1.5)
Kidney injury	208	209	186	233	1.1 (0.8-1.6)	1.3 (0.8-2.1)
Thrombocytopenia	140	149	40	81	**3.7 (1.9-8.1)**	2.0 (0.8-5.4)
Hypothyroidism	70	55	284	180	**0.2 (0.1-0.3)**	0.6 (0.4-1.1)
Pneumonitis	55	53	70	75	0.8 (0.5-1.4)	1.1 (0.5-2.5)
Ocular disorders	32	32	32	26	1.0 (0.5-2.6)	0.8 (0.2-3.2)
Hepatitis	21	23	4	6	5.1 (0.9-204.2)	1.5 (0.0-114.8)
Type 1 diabetes	17	18	14	20	1.3 (0.4-6.5)	1.5 (0.2-11.2)
Myositis	15	16	4	0	3.7 (0.6-147.5)	0.0 (0.0-56.8)
Hyperthyroidism	8	6	36	33	**0.2 (0.1-0.4)**	0.9 (0.2-3.2)

[a]Rates are calculated among patients without the selected AE during the variable baseline period.
[b]Bold type indicates P ≤ 0.05.
AE = adverse event; CHEM = cytotoxic chemotherapy; CI = confidence interval; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy.

(72.2 years vs. 68.4 years and 69.5 years, respectively; $P < 0.001$ for both) and a higher percentage of patients with Medicare Advantage insurance (81.5% vs. 63.0% and 72.6%, respectively; $P < 0.001$ for CHEM vs. IO; $P = 0.001$ for IO-CHEM vs. IO). In addition, the IO cohort had a shorter follow-up time compared with the IO cohort (139.3 days vs. 173.4 days; $P < 0.001$) and a lower percentage of men compared with the CHEM cohort (46.7% vs. 54.4%; $P < 0.001$).

Among NCCN-recommended agents, the most common cytotoxic chemotherapies (used by > 10% of patients) were carboplatin (73.7%), pemetrexed (29.7%), paclitaxel (22.4%), etoposide (22.2%), and bevacizumab (11.5%). The prevalence of immuno-oncology agent use (as monotherapy or part of combination therapy) was 6.9% for pembrolizumab, 1.5% for nivolumab, and 0.1% for atezolizumab.

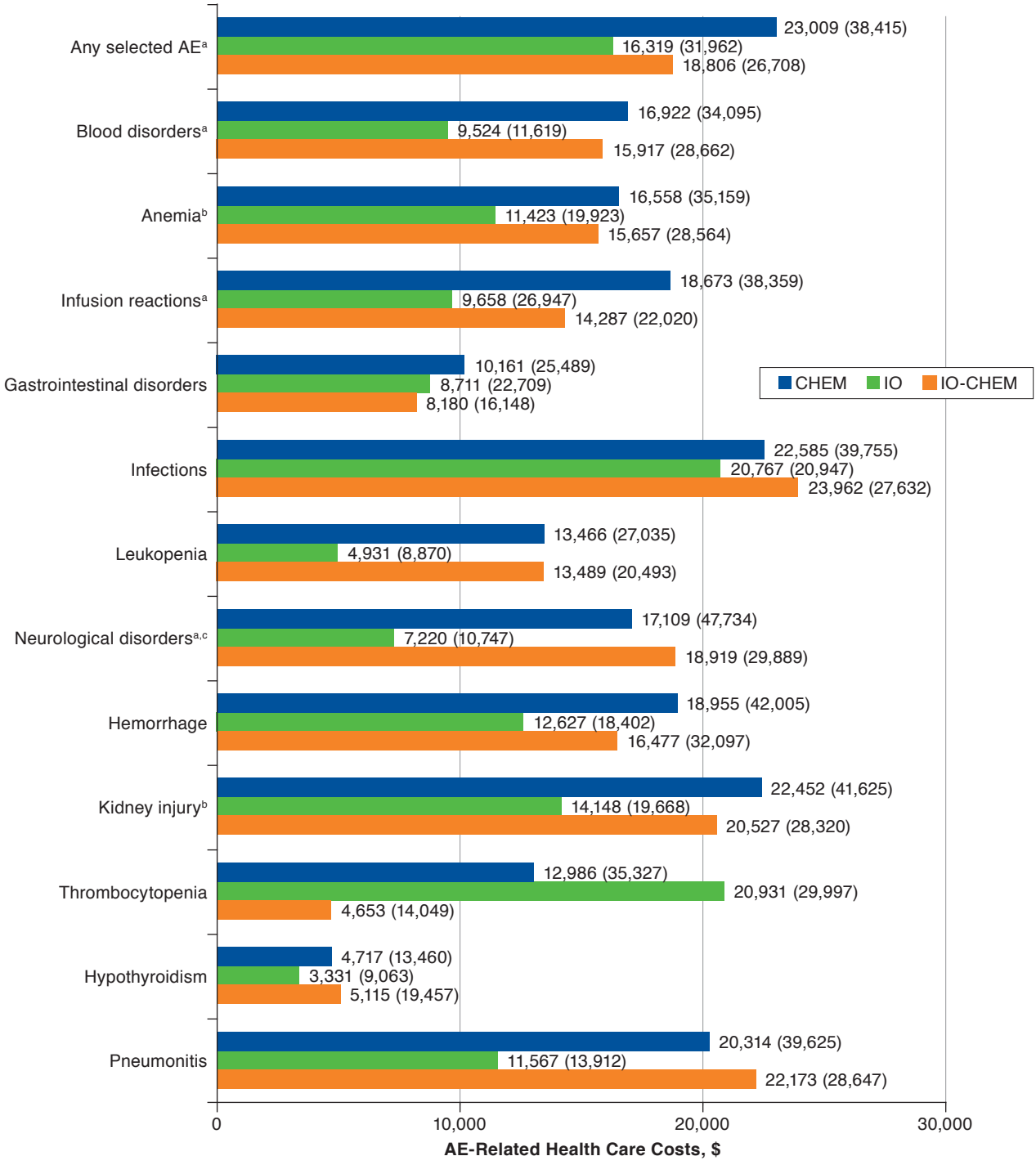
Incidence of Selected Adverse Events

AE incidence during the AE observation period is presented for patients who did not have evidence of that AE during the baseline period. Overall, 74.4% of the study population had ≥ 1 AE during follow-up (Appendix A, available in online article); compared with the IO cohort, IRRs (95% CI) were 1.4 (1.2-1.7) for the CHEM cohort and 1.4 (1.1-1.7) for the IO-CHEM cohort (Table 2). Common AEs across all treatment cohorts in the total study population included blood disorders (43.0%), gastrointestinal (GI) disorders (31.6%), and infections (28.5%; Appendix A). IRRs that were significantly higher for the other cohorts compared with the IO cohort included anemia (IRR = 5.7 CHEM, IRR = 4.1 IO-CHEM), GI disorders (IRR = 1.9 CHEM, IRR = 1.7 IO-CHEM), leukopenia (IRR = 22.3 CHEM, IRR = 5.7 IO-CHEM), and thrombocytopenia (IRR = 3.7 CHEM). The CHEM cohort had lower rates versus the IO cohort for hypothyroidism (IRR = 0.2 CHEM) and hyperthyroidism (IRR = 0.2 CHEM; Table 2).

Health Care Costs Related to Adverse Events

Total cost of AEs varied across the cohorts: mean AE-related costs were highest for the CHEM cohort ($23,009) and lowest for the IO cohort ($16,319; $P<0.001$; Figure 2). Although the mean cost for the IO-CHEM cohort ($18,806) was higher than that for the IO cohort, the difference was not statistically significant. When examined as a PPPM measure, total AE-related costs were significantly lower for the IO cohort ($4,259) compared with the CHEM cohort ($6,323; $P < 0.001$) or the IO-CHEM cohort ($6,269; $P = 0.020$). With a few exceptions, the mean cost per patient for a specific AE (among patients with that AE during follow-up but not in the baseline period) did not differ across the systemic therapy cohorts, whether measured as a total cost or as a PPPM cost across the AE period (Figure 2 and Appendix B, available in online article). Mean AE costs were significantly higher for the CHEM cohort versus the IO cohort for blood disorders ($16,922 vs. $9,524; $P < 0.001$),

FIGURE 2 Total AE-Related Health Care Costs Per Patient During the AE Period



Note: AEs occurring in >2% of patients are shown, listed in order of incidence rate from highest (any selected AE) to lowest (pneumonitis). Costs presented are among patients without the selected AE during the variable baseline period and exclude zero costs. AE-related health care costs are represented as mean (SD) in U.S. dollars.

[a]P<0.001 for CHEM vs. IO.

[b]P<0.05 for CHEM vs. IO.

[c]P<0.05 for IO-CHEM vs. IO.

AE = adverse event; CHEM = cytotoxic chemotherapy; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy; SD = standard deviation.

TABLE 3 Logistic Models of AE-Related Costs

Independent Variable	Positive AE-Related Costs[a]			High AE-Related Costs Among Patients Incurring Any AE Costs[b,c]		
	Odds Ratio (95% CI)	*P* Value	Predicted Value	Odds Ratio (95% CI)	*P* Value	Predicted Value
Cohort						
CHEM	reference	–	0.877	reference	–	0.102
IO	0.82 (0.63-1.06)	0.135	0.854	0.60 (0.38-0.95)	0.030	0.065
IO-CHEM	0.98 (0.73-1.32)	0.888	0.875	0.79 (0.51-1.20)	0.263	0.083
Insurance type						
Commercial	reference	–		reference	–	
Medicare Advantage	1.32 (1.16-1.50)	<0.001		0.27 (0.24-0.32)	<0.001	
Geographic region						
Northeast	1.17 (0.97-1.42)	0.097		1.57 (1.27-1.93)	<0.001	
Midwest	1.05 (0.91-1.20)	0.521		0.91 (0.76-1.09)	0.304	
South	reference	–		reference	–	
West	1.10 (0.88-1.38)	0.391		1.25 (0.98-1.59)	0.073	
Sex						
Female	reference	–		reference	–	
Male	1.00 (0.88-1.13)	0.996		0.98 (0.84-1.14)	0.773	
Baseline CCI score category						
1-2	reference	–		reference	–	
3-4	1.03 (0.57-1.86)	0.932		0.94 (0.50-1.76)	0.841	
5+	1.25 (0.70-2.22)	0.446		1.35 (0.75-2.41)	0.315	
Baseline metastatic disease	0.61 (0.45-0.84)	0.002		0.62 (0.47-0.82)	<0.001	
Baseline conditions						
Gastrointestinal disorders	0.92 (0.78-1.09)	0.330		1.04 (0.85-1.27)	0.701	
Hepatitis	1.06 (0.60-1.86)	0.848		1.37 (0.81-2.33)	0.239	
Hyperthyroidism	1.30 (0.52-3.28)	0.578		1.01 (0.39-2.61)	0.987	
Hypothyroidism	1.24 (0.96-1.60)	0.096		0.95 (0.71-1.28)	0.736	
Infections	1.40 (1.22-1.60)	<0.001		1.17 (1.01-1.36)	0.036	
Kidney injury	1.51 (1.17-1.95)	0.001		1.09 (0.84-1.42)	0.512	
Myositis	1.92 (1.11-3.33)	0.020		1.04 (0.67-1.62)	0.855	
Neurological disorders	1.02 (0.83-1.23)	0.833		1.51 (1.21-1.89)	<0.001	
Ocular disorders	1.58 (0.89-2.81)	0.118		0.92 (0.52-1.64)	0.787	
Pneumonitis	1.19 (0.86-1.65)	0.302		1.13 (0.81-1.59)	0.474	
Type 1 diabetes	1.74 (0.94-3.23)	0.080		0.68 (0.35-1.32)	0.257	
Blood disorders	1.13 (0.95-1.33)	0.160		1.15 (0.96-1.38)	0.122	

[a]*Likelihood ratio: chi-square = 106.446, DF = 22, P < 0.001.*

[b]*High AE-related costs are defined as those in the 90th percentile (≥ $49,402 during the AE period).*

[c]*Likelihood ratio: chi-square = 371.467, DF = 22, P < 0.001.*

AE = adverse event; CCI = Charlson Comorbidity Index; CHEM = cytotoxic chemotherapy; CI = confidence interval; DF = degrees of freedom; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy.

anemia ($16,558 vs. $11,423; $P < 0.05$), infusion reactions ($18,673 vs. $9,658; $P < 0.001$), neurological disorders ($17,109 vs. $7,220; $P < 0.001$), and kidney injury ($22,452 vs. $14,148; $P < 0.05$; Figure 2). Mean AE costs were significantly higher for the IO-CHEM cohort ($18,919) versus the IO cohort for neurological disorders ($P < 0.05$; Figure 2).

Multivariable Analysis of AE-Related Costs and Descriptive Analysis of High-Cost and Lower-Cost Cohorts

Patients with AE-related costs were stratified into high-cost (90th percentile, ≥ $49,402; n = 745) and lower-cost (n = 7,763) cohorts on the basis of total AE costs. Compared with the CHEM cohort, the IO and IO-CHEM cohorts were not statistically significantly different in their odds of having any AE costs; the predicted proportions of patients incurring costs were 87.7% for the CHEM cohort, 85.4% for the IO cohort, and 87.5% for the IO-CHEM cohort (Table 3). However, the odds of having AE costs were higher for Medicare Advantage enrollees (OR = 1.32; $P < 0.001$) and patients with baseline infections (OR = 1.40; $P < 0.001$), kidney injury (OR = 1.51; $P = 0.001$), or myositis (OR = 1.92; $P = 0.020$) and lower for those with a code for metastatic disease during the 6-month baseline period (OR = 0.61; $P = 0.002$).

Descriptive analysis of the high-cost versus lower-cost cohorts showed that patients in the high-cost cohort were slightly younger (mean age 64.8 years vs. 69.2 years; $P<0.001$), but there were no statistically significant differences in baseline Charlson comorbidity scores (mean 7.3 vs. 7.2; $P=0.224$) or the percentage of patients with baseline metastatic disease (86.3% vs. 88.6%; $P=0.061$). A higher percentage of high-cost patients had inpatient stays (91.9% vs. 44.6%; $P<0.001$), intensive care unit (ICU) admissions (37.1% vs. 8.1%; $P<0.001$), and emergency department (ED) visits (67.7% vs. 55.8%; $P<0.001$) during the AE period. Mean (SD) follow-up time was longer for the high-cost cohort than the lower-cost cohort (196.3 [137.6] days vs. 167.7 [124.0] days). When prevalence rate ratios for high-cost versus lower-cost patients were examined to account for variable follow-up time, high-cost patients were found to have lower rates of ED visits (rate ratio = 0.84, 95% CI = 0.75-0.93) and ICU admissions (rate ratio = 0.72, 95% CI = 0.62-0.83), and the difference in rates of inpatient stays was not statistically significant (rate ratio = 1.02, 95% CI = 0.94-1.12).

Among patients who incurred AE-related costs, those in the IO cohort were less likely than those in the CHEM cohort to have high costs (OR = 0.60, 95% CI = 0.38-0.95; $P=0.030$; Table 3), but the difference between the IO-CHEM and CHEM cohorts was not statistically significant. The predicted proportions of patients falling in the high-cost group were 10.2% for the CHEM cohort, 6.5% for the IO cohort, and 8.3% for the IO-CHEM cohort. Patients with AE-related costs were more likely to be in the high-cost group if they lived in the Northeast (OR=1.57, 95% CI=1.27-1.93; $P<0.001$) or had baseline infections (OR= 1.17, 95% CI = 1.01-1.36; $P=0.036$) or neurological disorders (OR = 1.51, 95% CI = 1.21-1.89; $P<0.001$), and were less likely to be in the high-cost group if they were Medicare Advantage enrollees (OR = 0.27, 95% CI = 0.24-0.32; $P<0.001$) or had a code for metastatic disease during the baseline period (OR = 0.62, 95% CI = 0.47-0.82; $P<0.001$).

Discussion

In this study of real-world patients initiating nontargeted first-line therapy for mNSCLC, AEs were less frequent and total AE costs were significantly lower for those treated with immunotherapy compared with those treated with cytotoxic chemotherapy either alone or in combination with immuno-oncology agents. While the odds of incurring any AE-related costs were similar among cohorts, patients in the IO cohort who had AE costs were less likely to have high costs compared with patients in the CHEM cohort. These findings suggest that IO-related AEs are not a substantial driver of cost of care during first-line treatment of mNSCLC.

AEs were common in this study population, with 74% of patients having at least 1 selected AE during the follow-up period. This prevalence is consistent with randomized clinical trials (RCTs). A meta-analysis of 7 RCTs including 2,122 patients with advanced NSCLC and 1,328 with advanced melanoma showed that the percentage experiencing any AE ranged from 67.6% for those treated with PD-1/PD-L1 inhibitors to 82.9% for those treated with conventional chemotherapy.[14] In addition, we found that AE incidence was 1.4 times higher among patients in the CHEM and IO-CHEM cohorts compared with the IO cohort. This is also congruent with RCTs, in which AE prevalence has consistently been lower among patients in immunotherapy arms compared with those in chemotherapy arms (relative risk = 0.82 for any AE, according to the meta-analysis).[14] As in RCTs, blood disorders, GI disorders, and neurological disorders in the present study were all significantly more common among patients receiving conventional chemotherapy, whereas patients receiving IO alone were more likely to experience immune-related AEs such as hypothyroidism, hyperthyroidism, and pneumonitis.[14]

Our study is the first to our knowledge to examine the unique AE profiles of both chemotherapy and immunotherapy treatment and their costs among real-world patients with mNSCLC. In another recent retrospective database study of patients with NSCLC treated with PD(L)-1 inhibitors, Cathcart-Rake et al. (2018) noted that hypothyroidism and blood disorders were the most frequent AEs (9.2% and 5.7% prevalence, respectively).[23] However, comparability with our results is limited, as the Cathcart-Rake study did not examine patients treated with cytotoxic chemotherapy alone and was not limited to first-line treatment; many patients had received conventional chemotherapy before immunotherapy.[23]

Previous retrospective studies have shown high AE-related costs among real-world patients with NSCLC[16-18,23]; however, the present study is the first to our knowledge to compare AE-related costs for NSCLC treatment with immuno-oncology agents versus conventional chemotherapy. We found that mean AE costs were significantly lower for the IO cohort than for the CHEM cohort, whether assessed as total costs ($13,887 vs. $20,783; $P<0.001$) or PPPM ($4,259 vs. $6,323; $P<0.001$). Moreover, among patients who incurred AE costs, those in the IO cohort were 40% less likely to have high costs (defined as the 90th percentile) than those in the CHEM cohort. Given that larger proportions of high-cost versus lower-cost patients had inpatient stays, ICU admissions, and ED visits during the AE period, our findings suggest that high AE costs may have been driven by hospitalizations and ED visits, similar to what was seen in previous studies.[2,3,16,18]

The lower prevalence rate ratios for ED visits and ICU admissions observed among high-cost versus lower-cost patients may have been due to the longer mean follow-up period in the high-cost cohort. PPPM AE costs in our analysis were substantially higher than those in the only other similar U.S. real-world studies to date. Bittoni et al. (2018) and Arunachalam et al. (2018) found mean total PPPM AE-related costs of $1,084

for first-line therapy and $1,036 for second-line therapy,[17,24] respectively. However, these earlier analyses were conducted in Medicare-only populations, included only costs related to AEs coded as the primary diagnosis on a claim, and adjusted costs to 2013 U.S. dollars, all of which likely contributed to this discrepancy.

We found that AE costs were not significantly different between the IO-CHEM and CHEM cohorts; this was unexpected, as the combination of therapies might be hypothesized to have a cumulative effect on AEs. The reasons for this finding cannot be determined with certainty from our data. However, given that our analysis did not account for chemotherapy strength or treatment duration, it may have been due to lower chemotherapy strength in the IO-CHEM cohort or to a longer follow-up period in the CHEM cohort (resulting in more time for AEs to be observed). In addition, it is possible that patients in the IO-CHEM cohort had been selected by their physicians as being more likely to tolerate combination therapy and therefore experienced fewer and/or less severe AEs.

Although the high cost of immuno-oncology agents has led to concerns regarding the potential economic burden of treatment with these drugs,[25] little research had been conducted until recently to elucidate the real-world costs involved. Our findings demonstrate that AE-related costs are actually lower among patients receiving IO treatment alone compared with conventional chemotherapy alone, and that AE costs are not substantially changed by the addition of IO treatment to chemotherapy. Interestingly, Korytowsky et al. (2018) found that total cost of care, hospitalizations, and ED visits were each significantly lower in the period after approval of IO treatment for NSCLC compared with the preapproval period.[3] Taken together, the current evidence raises the possibility that IO treatment of patients with NSCLC could favorably affect total health care costs despite higher drug costs.

Limitations

This study faced several limitations. Certain variables that influence the choice of NSCLC therapy, such as performance status, were not available in the database; this may have resulted in unmeasured confounding. Mortality may have been underestimated as not all deaths are identified in claims or Social Security data. The IO cohort had a higher mean age than the other cohorts, suggesting that patients who are more frail may have been channeled to the IO cohort; however, the IO cohort was still less likely to experience AEs.

It was not possible to differentiate the cost of individual AEs for patients who had claims with codes for more than 1 AE. For these patients, costs were counted separately toward the total costs of both AEs, which may have caused slight overestimation of costs for some AEs. Overlap between infections and other AEs was particularly common, with 61.3% of patients hospitalized with infection also having evidence of another AE during the hospitalization. In a subanalysis, costs for hospitalizations that included both infection and another AE were higher than those for hospitalizations for either infection or the other AE independently (data not shown).

This study relied on diagnosis codes to identify mNSCLC and determine the presence of each AE; therefore, any coding errors may have resulted in misclassification of patients with NSCLC or AEs of interest, and medical claims may not have captured all AEs that occurred. Furthermore, because causality cannot be determined using claims data, the presence of a diagnosis code occurring after a cancer therapy does not guarantee that the associated condition was caused by the therapy. The effect of this limitation was minimized by looking for diagnosis codes for specific AEs known to be related to the therapies in our study.

Finally, because this analysis was conducted in a managed care population, the results may not be generalizable to other populations (e.g., patients who are uninsured).

Conclusions

Among real-world patients initiating nontargeted first-line therapy for mNSCLC, those receiving immunotherapy experienced fewer AEs and had lower total AE-related costs than those treated with cytotoxic chemotherapy. Furthermore, patients treated with immunotherapy were no more likely than patients treated with chemotherapy to incur AE-related costs and, in fact, were less likely to have high AE costs if they incurred any at all. These findings indicate that IO-related AEs are not a differentiating factor in cost of care for patients receiving first-line treatment for mNSCLC in clinical practice.

Authors

NICOLE M. ENGEL-NITZ, PhD; MICHAEL P. JOHNSON, MS; and SCOTT H. BUNNER, MPH, Optum, Eden Prairie, Minnesota.
KELLIE J. RYAN, MPH, AstraZeneca, Gaithersburg, Maryland.

AUTHOR CORRESPONDENCE: Nicole Engel-Nitz, Optum, 11000 Optum Cir., MN101-E300, Eden Prairie, MN 55344. Tel.: 952.205.7770; E-mail: nicole.engel-nitz@optum.com.

DISCLOSURES

This study was sponsored by AstraZeneca. Ryan is an employee of AstraZeneca. Engel-Nitz, Johnson, and Bunner are employees of Optum, which was contracted by AstraZeneca to conduct this study, and shareholders in UnitedHealth Group. Engel-Nitz has also worked on cancer-related studies for which Optum received funding from Bayer AG, Clovis Oncology, Eli Lilly, EMD Serono, Exact Sciences, Janssen, and Novartis. Johnson worked on cancer-related studies for which Optum received funding from Eli Lilly, Medtronic, Sanofi, and UnitedHealthcare. Bunner has worked on cancer-related studies for which Optum received funding from Celgene and Incyte.

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APPENDIX A Incidence of Selected AEs During the AE Period

Event	Total (N = 9,712)[a]	CHEM (n = 8,818)[a]	IO (n = 482)[a]	IO-CHEM (n = 412)[a]	*P* Value	
					CHEM vs. IO	IO-CHEM vs. IO
Any selected AE, %	74.4	75.2	64.9	69.2	<0.001	0.003
Blood disorders[b]	43.0	45.5	14.3	26.1	<0.001	<0.001
Gastrointestinal disorders	31.6	32.4	20.3	27.1	<0.001	0.028
Infections	28.5	30.1	18.0	18.1	<0.001	0.961
Anemia	27.9	29.5	6.6	19.6	<0.001	<0.001
Infusion reactions	26.3	26.0	29.3	29.6	0.117	0.907
Leukopenia	17.1	18.6	1.0	4.6	<0.001	0.001
Neurological disorders	12.6	12.8	11.6	10.2	0.457	0.538
Hemorrhage	10.7	11.0	8.8	6.5	0.150	0.235
Kidney injury	8.9	8.9	8.4	8.4	0.688	0.981
Thrombocytopenia	6.0	6.4	1.9	3.0	<0.001	0.295
Hypothyroidism	3.0	2.4	12.2	6.5	<0.001	0.006
Pneumonitis	2.4	2.4	3.2	2.8	0.228	0.703
Ocular disorders	1.4	1.4	1.5	1.0	0.895	0.506
Hepatitis	0.9	1.0	0.2	0.2	0.082	0.910
Type 1 diabetes	0.8	0.8	0.6	0.8	0.710	0.831
Myositis	0.7	0.7	0.2	0.0	0.188	0.355
Hyperthyroidism	0.4	0.3	1.7	1.2	<0.001	0.582

[a]*Incidences are calculated among patients without the selected AE during the variable baseline period.*
[b]*Includes anemia, leukopenia, and thrombocytopenia.*
AE = adverse event; CHEM = cytotoxic chemotherapy; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy.

APPENDIX B Population Mean Per Patient Per Month AE-Related Health Care Costs During the AE Period

Event	Total (N = 9,712)	CHEM (n = 8,818)	IO (n = 482)	IO-CHEM (n = 412)	*P* Value	
					CHEM vs. IO	IO-CHEM vs. IO
Any selected AE						
n	7,135	6,543	309	283		
Total follow-up months	41,467	38,111	1,959	1,398		
Cost PPPM	3,880	3,950	2,574	3,808	<0.001	0.010
U.S. $ (95% CI)	(3,719-4,042)	(3,779-4,121)	(1,991-3,156)	(3,082-4,534)		
Blood disorders[a]						
n	3,071	2,933	53	85		
Total follow-up months	18,528	17,762	371	395		
Cost PPPM	2,779	2,794	1,360	3,427	<0.001	0.011
U.S. $ (95% CI)	(2,568-2,990)	(2,577-3,011)	(777-1,943)	(1,971-4,882)		
Anemia						
n	2,175	2,077	28	70		
Total follow-up months	12,956	12,419	201	337		
Cost PPPM	2,764	2,769	1,594	3,254	0.011	0.071
U.S. $ (95% CI)	(2,504-3,024)	(2,502-3,036)	(732-2,456)	(1,712-4,797)		
Infusion reactions						
n	2,529	2,268	140	121		
Total follow-up, months	15,961	14,264	1,013	684		
Cost PPPM	2,846	2,969	1,334	2,527	<0.001	0.018
U.S. $ (95% CI)	(2,604-3,089)	(2,704-3,234)	(715-1,954)	1,770-3,285)		
Gastrointestinal disorders						
n	2,522	2,349	77	96		
Total follow-up months	15,430	14,369	564	497		
Cost PPPM	1,641	1,661	1,189	1,580	0.206	0.434
U.S. $ (95% CI)	(1,475-1,808)	(1,486-1,836)	(479-1,900)	(917-2,244)		

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APPENDIX B Population Mean Per Patient Per Month AE-Related Health Care Costs During the AE Period *(continued)*

Event	Total (N = 9,712)	CHEM (n = 8,818)	IO (n = 482)	IO-CHEM (n = 412)	*P* Value	
					CHEM vs. IO	IO-CHEM vs. IO
Infections						
n	1,676	1,537	75	64		
Total follow-up months	9,951	9,222	467	262		
Cost PPPM	3,799	3,764	3,334	5,852	0.470	0.032
U.S. $ (95% CI)	(3,449-4,149)	(3,396-4,133)	(2,226-4,443)	(3,876-7,828)		
Leukopenia						
n	1,596	1,573	4	19		
Total follow-up months	9,427	9,317	23	87		
Cost PPPM	2,276	2,274	859	2,947	0.039	0.168
U.S. $ (95% CI)	(2,042-2,511)	(2,037-2,510)	(-464 to 2,182)	(540-5,354)		
Neurological disorders						
n	1,071	985	48	38		
Total follow-up months	7,035	6,497	351	187		
Cost PPPM	2,547	2,594	987	3,848	< 0.001	0.017
U.S. $ (95% CI)	(2,108-2,986)	(2,124-3,063)	(514-1,459)	(1,613-6,082)		
Hemorrhage						
n	888	827	37	24		
Total follow-up months	5,804	5,433	270	101		
Cost PPPM	2,849	2,885	1,729	3,915	0.043	0.229
U.S. $ (95% CI)	(2,403-3,296)	(2,416-3,355)	(716-2,743)	(591-7,240)		
Kidney injury						
n	773	706	35	32		
Total follow-up months	4,818	4,436	237	146		
Cost PPPM	3,529	3,574	2,092	4,501	0.024	0.094
U.S. $ (95% CI)	(3,023-4,035)	(3,034-4,113)	(928-3,256)	(2,018-6,985)		
Thrombocytopenia						
n	563	543	8	12		
Total follow-up months	3,671	3,567	32	72		
Cost PPPM	1,982	1,977	5,316	772	0.313	0.216
U.S. $ (95% CI)	(1,521-2,443)	(1,507-2,447)	(-1,156 to 11,788)	(-583 to 2,128)		
Hypothyroidism						
n	269	192	53	24		
Total follow-up months	2,259	1,606	466	188		
Cost PPPM	533	564	379	654	0.288	0.610
U.S. $ (95% CI)	(337-729)	(324-804)	(138-620)	(-362 to 1,670)		
Pneumonitis						
n	221	196	14	11		
Total follow-up months	1,510	1,307	131	72		
Cost PPPM	2,906	3,045	1,241	3,408	0.004	0.201
U.S. $ (95% CI)	(2,097-3,716)	(2,133-3,957)	(436-2,045)	(399-6,417)		

Note: Population cost estimates represent total AE-related costs divided by the total person-time during the AE period. AEs occurring in >2% of patients are shown, listed in order of incidence rate from highest (any selected AE) to lowest (pneumonitis). Costs presented are among patients without the selected AE during the variable baseline period, and exclude zero costs.

[a]*Includes anemia, leukopenia, and thrombocytopenia.*

AE = adverse event; CHEM = cytotoxic chemotherapy; CI = confidence interval; IO = immuno-oncology agents; IO-CHEM = immuno-oncology + cytotoxic chemotherapy; PPPM = per patient per month.