PASS Information

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Research question and objectives	To describe the safety profiles among NSCLC patients treated with Pem/Carbo AUC5 and the Pem/Carbo AUC6
Country(-ies) of study	United States of America
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Table of Contents

Section **Page**

1. Abstract

Title: Safety Profile of Pemetrexed+Carboplatin AUC5 and Pemetrexed+Carboplatin AUC6 for Patients with Non-Small Cell Lung Cancer

Keywords: pemetrexed; carboplatin; non-small cell lung cancer; observational study; safety

Rationale and background: Pemetrexed in combination with carboplatin chemotherapy (Pem/Carbo) is widely recognized and endorsed by local and regional treatment guidelines (e.g., NCCN 2015) and is broadly used in clinical practice to treat patients with nonsquamous NSCLC in various countries around the world. Systemic carboplatin doses that are most widely used in the clinic are area under the concentration-time curve (AUC) of 5 and 6 mg/mL•min. There is a lack of information summarizing the safety profiles of patients treated with these two regimens in real-world settings, which are in need by health care professional (HCPs).

Research question and objectives: The objective of this study is to evaluate the safety profiles of NSCLC patients treated with Pem/Carbo AUC5 (PCb5) and Pem/Carbo AUC6 (PCb6).

Study design: An observational, cohort study utilizing secondary data from the IMS Oncology US clinic-based, longitudinal, patient-level electronic medical records (EMR) including patients with NSCLC on PCb5 or PCb6 regimens initiated concomitantly on or after the diagnosis of lung cancer during 2004-2014.

Setting: Electronic medical records collected in the routine clinical practice setting were used for this study with secondary data use.

Subjects and study size, including dropouts: A total of 820 NSCLC patients receiving PCb5 (N=636) or PCb6 (N=184) were included in the analyses. Adult (18 years or older) NSCLC patients were included if: 1) PCb5 or PCb6 regimens were initiated concomitantly on or after the diagnosis of lung cancer between 04 February 2004 and 31 May 2014, with the date of therapy initiation as the index date; 2) there were valid records for age, sex, body weight and the carboplatin dose prescribed at the index date, and at least one serum creatinine test result from 7 days prior to until 7 days after the index date; and 3) patients were under the care of an oncology practice that was a stable provider of EMR data in every month from the index date to the last record in the data, 30 days after the last dose of PCb5 or PCb6 treatment, or 30 June 2014, whichever earlier. Patients with squamous histology were excluded given that pemetrexed is indicated for the treatment of non-squamous NSCLC.

Variables and data sources:

Exposure variable is PCb5 or PCb6. Carboplatin AUC value is calculated based on recorded Carboplatin dose, patient's gender, age, weight, and serum creatinine concentration.

Patient characteristics include patients' demographic characteristics (age and gender) and comorbidity conditions identified before the index date.

Other medications include medications prescribed or administered, including systemic anti-cancer treatments and all other medications by drug class, recorded up to 3 months prior to the

index date (index date not included), and concomitant medications during the Pem/Carbo ontreatment period.

Study outcomes are the adverse events (AEs) that occurred on or after the index date. The haematological outcomes to be assessed include: neutropenia, leukopenia, thrombocytopenia, anemia, and febrile neutropenia. The non-haematological outcomes include: alopecia, anorexia, constipation, diarrhea, fatigue, mucositis/stomatitis, nausea, rash, vomiting, peripheral sensory neuropathy, and renal failure.

Results: 636 NSCLC patients receiving PCb5 (37% age ≥70 years) and 184 patients receiving PCb6 (34% age ≥70 years) who met the inclusion criteria were identified in the EMR. Patients receiving PCb5 had a higher proportion to have comorbidities. Anemia (PCb5 vs. PCb6: 12.1% vs. 19.0%) and neutropenia (7.7% vs. 4.9%) were the most common AEs diagnosed in the two cohorts. Overall incidence rates (IRs) per 100 person-years were similar for neutropenia in both cohorts, were significantly higher for anemia (IR: 43.6 vs. 101.0) and thrombocytopenia (IR: 1.5 vs. 17.9), and were numerically lower for nausea (IR:14.4 vs. 9.9) in the PCb6 compared to the PCb5 cohort. Within the PCb6 cohort, the IR per 100 person-years was higher for neutropenia for ≥70 year-old patients (IR: 41.1) compared to <70 year-old patients (IR: 14.5). After propensity score stratification, adjusted IRs showed similar patterns.

Discussion: Results from this real-world analysis add to existing evidence from randomized clinical trials about PCb safety profiles in the overall NSCLC population and in elderly patients. Limitations included lack of power for AEs other than anemia given the nature of EMR. These results may help guide physicians when making treatment decisions.

Marketing Authorisation Holder(s): Eli Lilly and Company

Names and affiliations of principal investigators: PPD

2. List of abbreviations

Term	Definition
AE	adverse events
AUC	area under the concentration-time curve
CI	confidence interval
CSF	Colony Stimulating Factors
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic medical records
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD	International Classification of Diseases
IR	incidence rate
NSCLC	Non-small cell lung cancer
PCb	Pemetrexed plus carboplatin
PCb5	Pemetrexed plus carboplatin AUC 5
PCb6	Pemetrexed plus carboplatin AUC 6
Pem/Carbo	Pemetrexd plus carboplatin
PS	performance status
US	United States

3. Investigators

Not applicable.

4. Other responsible parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 April 2015	15 September 2015	
End of data collection	31 September 2015	30 November 2016	
Final report of study results	31 December 2015	22 February 2018	

6. Rationale and background

Platinum-based doublet chemotherapy, with cisplatin as the preferred platinum, is considered the standard of care as first-line treatment of advanced non-small cell lung cancer (NSCLC) patients with good performance status (PS) who are not eligible for additional targeted treatment, according to treatment guidelines[1,2]. However, carboplatin-based doublets are considered more feasible in certain patients who may have worse than expected outcomes (patients with an Eastern Cooperative Oncology Group [ECOG] PS >1 or elderly patients with comorbidities)[3,4]. In addition to its ease of administration, carboplatin has a more favorable toxicity profile than cisplatin in terms of digestive, neurological, and nephrotoxicity, although it is generally associated with more myelosuppression[5,6]. Pemetrexed, a multitargeted antifolate, is indicated in combination with cisplatin as first-line treatment for patients with advanced nonsquamous NSCLC, and has a well-established safety profile when administered in combination with cisplatin or as a single agent during maintenance therapy[2,6-9]. Pemetrexed was shown to be tolerable in combination with carboplatin in phase II studies in patients with advanced NSCLC, and the pemetrexed-carboplatin (PCb) doublet is a frequently used first-line treatment in United States (US) clinical practice[5,10,11], as recommended by the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines[1,2]. Systemic carboplatin doses that are most widely used in the clinic are area under the concentration-time curve (AUC) of 5 and 6 mg/mL•min[3-5].

A recent meta-analysis of clinical trial data from five studies[5,12-15] reported a better safety profile among nonsquamous NSCLC patients treated with PCb5 than PCb6 in the first-line setting[16]. However, there is limited evidence about the safety profiles of these two treatment regimens in the real-world setting. The purpose of this analysis was to examine the safety profile, and patient and disease characteristics of a NSCLC population treated with either the PCb5 or PCb6 regimen under real-world disease conditions to further support widespread clinical use.

7. Research question and objectives

The purpose of this study was to evaluate the safety profiles of NSCLC patients treated with PCb5 and PCb6.

The primary objectives included:

1) To describe demographic and clinical characteristics of the NSCLC patients treated with PCb5 or PCb6;

2) To estimate the crude incidence proportions and incidence rates (IRs) of the adverse events (AEs) among the NSCLC patients treated with PCb5 or PCb6;

3) If data allow, to estimate the incidence rate, rate difference, and hazard ratio (HR) of the AEs among the NSCLC patients treated with PCb5 or PCb6, adjusted for patients' demographic and clinical characteristics.

If data allowed, the secondary objectives included conducting subgroup analysis to further examine the safety profiles of the NSCLC patients treated with the 2 regimens in those who were below 70 and who were 70 years or older.

8. Amendments and updates

Not applicable.

9. Research methods

9.1. Study design

This was a retrospective cohort study with secondary use of data, IMS Oncology electronic medical records (EMR), to assess the selected AEs in the NSCLC patients receiving PCb5 and PCb6 in the routine clinical practice setting. The 2 exposure groups were patients with evidence of PCb5 or PCb6 treatment after the NSCLC diagnosis.

The primary objectives were to describe the patient characteristics and incidence of selected AEs in the two treatment cohorts. The descriptive analysis showed the frequencies and proportions for the patient characteristics and the selected AEs in each treatment cohort. The study also included adjusted comparative analysis to present HRs and incidence rate difference of the study endpoints, with the null hypothesis that there was no difference between the 2 exposure groups. While there was no a priori hypothesis about the confounders to be included or the difference in safety profile occurrence among the 2 exposure groups, patient demographic and clinical characteristics were adjusted for by calculating propensity score.

Subgroup analyses by age (<70 years or ≥70 years) were conducted to further assess the AEs of interest among the elderly patients that were insufficiently represented in clinical trials due to exclusion criteria of clinical trials.

9.2. Setting

The study used secondary data that were EMR from mid-to-large size US oncology clinics between 01 January 2000 and 30 June 2014. The index date was the date of the first evidence of PCb5 or PCb6 treatment after the NSCLC diagnosis. Carboplatin dose was calculated using Calvert Formula[17]. For each patient, the baseline period was defined as the period from the first record in the database until the index date. For each study endpoint, the follow-up began on the date of the first qualifying treatment initiation and continued until the occurrence of the study end point, end of on-treatment period (defined as 30 days after the last dose of the study medicine before treatment discontinuation, see Section 9.4.1), an administration/prescription record indicating a switch from the study medicines to another carboplatin AUC value in combination with pemetrexed, the last record in the database, or 30 June 2014, whichever came first.

9.3. Subjects

The two patient cohorts were patients treated with pemetrexed 500 mg/m2 and carboplatin AUC5 (PCb5) after NSCLC diagnosis or patients treated with pemetrexed 500 mg/m2 and carboplatin AUC6 (PCb6) after NSCLC diagnosis. Adult (18 years or older) NSCLC patients were included if: 1) PCb5 or PCb6 regimens were initiated concomitantly on or after the diagnosis of lung cancer between 04 February 2004 (date of Food and Drug Administration [FDA] approval for premetrexed in treating NSCLC) and 31 May 2014, with the date of therapy initiation as the index date; 2) there were valid records for age, sex, body weight and the carboplatin dose prescribed at the index date, and at least one serum creatinine test result from 7

days prior to until 7 days after the index date; and 3) patients were under the care of an oncology practice that was a stable provider of EMR data in every month from the index date to the last record in the data, 30 days after the last dose of PCb5 or PCb6 treatment, or 30 June 2014, whichever earlier. Specific histology was not an inclusion criterion given no clinically relevant differences in adverse reactions were seen in patients based on histology. Patients with squamous histology were excluded given that pemetrexed is indicated for the treatment of non-squamous NSCLC. Patients who received supportive care drugs before starting chemotherapy were also excluded because their data are considered unreliable.

9.4. Variables

9.4.1. Exposure

The exposure variables were PCb5 or PCb6 treatment after the diagnosis of NSCLC. Carboplatin AUC values were calculated as a function of carboplatin dose and glomerular filtration rate (GFR) based on Calvert formula. In this study, calculated creatinine clearance was used as surrogate for GFR by using the Cockcroft-Gault formula[16]. The on-treatment period begins on the day of the first dose of the study treatment and continues to 30 days after the treatment discontinuation. Treatment discontinuation was defined as a gap in continuous study medication coverage exceeding 42 days (2 cycles), or an administration record indicating a switch from the study medication to another treatment, whichever came first. The administration of Pemetrexed and Carboplatin and patients' gender, age, weight, and serum creatinine were abstracted from the electronic medical records.

9.4.2. Patient Characteristics

Baseline characteristics included patients' demographic characteristics (age and gender) and comorbidity conditions identified on or before the index date, and patients' medication use up to 3 months prior to the index date. Comorbidities were selected and modified based on Charlson's comorbidity index (Charlson et al. 1987; Deyo et al. 1992; Simon et al. 2012). Given that the study cohort consisted of all cancer patients, cancer characteristics were described separately. The comorbidity conditions were identified through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD)-9-CM diagnoses codes suggested by Deyo et al. (1992). Medications prescribed or administered recorded up to 3 months prior to the index date (index date not included) and during treatment were identified by class. All systemic anti-cancer treatments prior to the index date were identified.

9.4.3. Study Outcomes

The study outcomes are the selected AEs that occurred on or after the index date during the on-treatment period. The selected AEs to be assessed included neutropenia, leukopenia, thrombocytopenia, anaemia, febrile neutropenia, alopecia, anorexia, constipation, diarrhoea, fatigue, mucositis/stomatitis, nausea, rash, vomiting, peripheral sensory neuropathy, and renal failure. The AEs were identified using ICD-9-CM diagnoses codes from the EMR.

For each AE, the observation period began when PCb5 or PCb6 treatments was first administered to the patient (index date) and lasted until the occurrence of the AE of interest; end of on-treatment period (defined as 30 days after the last dose of the study drugs before treatment discontinuation); an administration/prescription record indicating a switch to another carboplatin AUC value in combination with pemetrexed; the last record in the database; or 30 June 2014, whichever occurred first. We did not censor for death, or admission to hospice care or a nursing home, because those data were not available from the EMR.

Common Terminology Criteria for Adverse Events (CTCAE) Grade is not available in the EMR and blood transfusion is not properly captured since it is primarily administered in the hospital setting and not in the community oncology practice setting, the latter being the source of IMS Oncology EMR. American Society of Clinical Oncology guidelines for use of Colony Stimulating Factors (CSF) recommend the use of CSF when the risk of febrile neutropenia is in the range of 20% or higher (generally associated to grade ≥3 neutropenia)[17]. Thus, the use of CSFs among patients with neutropenia was characterized to infer the severity of this AE.

9.5. Data sources

Data for this retrospective, observational, cohort study were extracted from IMS's private-practice databases of longitudinal, patient-level EMR, hospital charge data, and medical and pharmacy claims collected from physicians and other healthcare providers across the 50 states in the United States. Patient-level EMR were collected from about 550 treating providers, representing 344 locations from 37 States in the US. Data in the databases are de-identified, and the databases are certified as being compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was exempt from institutional review board approval because it did not involve any intervention or new data collection, and used anonymized existing data.

9.6. Bias

Grade or severity of disease was not recorded in the EMR. Considering the nature of EMR, conditions that were less severe or might be managed by over-the-counter products might not be recorded.

9.7. Study size

The analyses finally included 636 patients in the PCb5 cohort and 184 patients in the PCb6 cohort from the IMS Oncology data after applying the inclusion and exclusion criteria. Study power was calculated using Epi Info 7. Sample size for the retrospective cohort study was estimated to detect a statistically significant risk ratio ≥2 based on the assumption of proportion of the safety outcomes in the unexposed group or reference group (Pem/Carbo AUC5) with around 80% power, at 95% two-sided confidence interval (CI). The risk ratio value of 2 was selected based on the suggestion from Observational Medical Outcomes Partnership: "You need a relative risk >2 to have confidence in result…detecting effects smaller than 2 will incur higher risk of false positives" (FDA Science Board Subcommittee, Review of the FDA/CDER Pharmacovigilance Program, 06 May 2011).

Based on the feasibility counts, the available samples size will have 80% power to detect a statistically significant risk ratio ≥ 2 if 10% or more of the Pem/Carbo AUC5 group have the study outcome.

Table 9.1. Power and Sample Size Estimation of Primary Retrospective Cohort Study, with 2 - sided Confidence Level of 95% (α = 0.05)

% Outcome in Unexposed Group	*Power = 1- β (type II error)*							
	Pem/Carbo AUC5				Pem/Carbo AUC6			
	60	70	80	90	60	70	80	90
Unexposed: Exposed Ratio = 3:1								
1	2,419	3,048	3,876	5,188	807	1,016	1,292	1,730
5	460	579	736	986	154	193	246	329
10	215	271	**344**	460	72	91	**115**	154
15	133	168	213	285	45	56	71	95
20	92	116	148	198	31	39	50	66
25	68	85	108	145	23	29	36	49

9.8. Data transformation

SAS ® Proprietary Software 9.2 was utilized for data management; the relevant comments such as proc datasets, proc format, proc sql, etc., were used to access the raw data, manage the analytical dataset, and process the integrated analytical datasets. Datasets and analytic programs were kept on a secure server and archived per Lilly record retention procedures.

9.9. Statistical methods

9.9.1. Main summary measures

For each group, the demographic characteristics, cancer characteristics, comorbidities during pre-index period, and other systemic cancer treatments and other medications during 3 months prior to the index date were assessed using descriptive statistics. The demographic and clinical characteristics were summarized using counts and frequencies with 95% CI for categorical variables and mean/standard deviation/median/min/max for continuous variables. The statistical significance of differences in patient demographic and clinical characteristics, and prior and concomitant medications were assessed using t-tests or chi-square tests as appropriate. Stratified analyses were performed by patient's age (<70 or ≥70 years).

For the incidence estimation, only the first occurrence of the safety outcomes occurred on or after the index date were count. The IRs with 95% CIs were estimated using the counts of the first occurrence of the events and the exposure follow-up time. The frequency of the safety outcomes during the follow-up was summarized as counts and percentages with 95% CIs.

9.9.2. Main statistical methods

Propensity score stratification was used to adjust for differences in the distribution of baseline characteristics for AEs that occurred at least once in each of the treatment cohort. Propensity score stratification, instead of propensity score matching, was used because there were more than 3 times as many Pem/Carbo AUC5 as Pem/Carbo AUC6 patients eligible for study inclusion and propensity score matching would have led to the exclusion of a substantial number of Pem/Carbo AUC5-treated patients, thereby not compromising generalizability.

Propensity score stratification was performed in 2 steps, and the propensity score models were assessed and finalized before the assessment of outcome data. First, for all eligible patients, unconditional logistic regression were used to estimate the probability of initiating Pem/Carbo AUC6 treatment given their baseline demographic characteristics, baseline comorbidities, and medications used during 3 months prior to the index date. Patients were then classified into strata determined by quintiles of the propensity score in the Pen/Carbo AUC6 cohort, to produce cohorts with similar baseline characteristics within each stratum. Adjusted estimates of the safety outcome incidence rates and rate differences were calculated by taking a weighted average of the stratum-specific estimates where the weights equaled the number of Pem/Carbo AUC6 patients in each stratum divided by the total number of Pem/Carbo AUC6 patients. Because the strata were constructed based on quintiles of the Pem/Carbo AUC6 cohort, the weights were 0.2 for each stratum (Greenland et al. 1999; Sato and Matsuyama 2003; Stuart 2010).

Cox regression models were used to compare time-to-event between the Pem/Carbo AUC5 and Pem/Carbo AUC6 cohorts, with Pem/Carbo AUC5 serving as reference. Statistical significance was determined using 95% CIs and two-tailed p-values ($p<0.05$). Adjusted IRs and rate differences were also estimated.

9.9.3. Missing values

Number and proportion of missing data for each pertinent variable were reported. Missing data were not imputed.

9.9.4. Sensitivity analyses

Given that propensity score stratification has better generalizability while propensity score matching is more advantaged in terms of bias control, adjusted safety outcome incidence rates and rate differences were also estimated applying the propensity score matching method.

9.9.5. Amendments to the statistical analysis plan

Not applicable.

9.10. Quality Control

The study used an existing database, which have been used primarily for research, fully HIPAA compliant. The study programs for data management or statistical analyses were validated by individual(s) outside the study team to ensure data integrity and accuracy. All study programs, log files, and output files were stored on the secure sever, and archiving any statistical

programming performed to generate the results. In addition, the diagnosis criteria for comorbidity and safety outcome endpoints were adjudicated by 2 experienced clinicians to ensure the accuracy of the diagnosis and decrease the misclassification.

10. Results

10.1. Participants

Within the study period, 4279 NSCLC patients initiating pemetrexed and carboplatin with a valid age, gender and weight on the index data were identified from the IMS Oncology EMR from 04 February 2004 to 31 May 2014, among whom 1399 had a valid serum creatinine test during the required period allowing the calculation of carboplatin AUC. Of those, 832 patients were treated with PCb5 or PCb6. After further restricting patients to those receiving care from stable providers of EMR and not having squamous histology or supportive care drugs before starting chemotherapy, a total of 820 NSCLC patients receiving PCb5 (N=636) or PCb6 (N=184) were included in the analyses.

10.2. Descriptive data

The statistical tests for the difference in demographic characteristics between the distributions in the two cohorts were not significant. Therefore, the comparisons of the demographics between the two cohorts would only be numerical. There were more female patients in the PCb6 cohort. Compared to the PCb5 cohort, the PCb6 cohort had a smaller proportion of patients with one or more comorbidities before the index date (2.2% vs. 4.9%). A slightly higher proportion of patients in the PCb6 versus PCb5 cohort received prior chemotherapy (16.8% vs. 21.2%) or supportive care drugs; however, fewer patients in the PCb6 cohort had received prior biologics (8.7% vs. 12.9% (Table 10.1). The median treatment duration was 1.68 months in both cohorts of all ages (mean of 2.2 months), and were 1.68 months and 2.07 months in the PCb5 cohort and in the PCb6 cohort respectively among the elderly (≥70 years). The proportion of patients who received any prior systemic therapy (chemotherapy and/or biologics) was similar in the two cohorts (PCb5: 25.8% vs. PCb6: 26.1%). When analyzed by age (≥70 years and <70 years), the elderly in each treatment group were more likely to have one or more comorbidities prior to the index date and fewer prior medications than the non-elderly (Table 10.1).

Table 10.1. Baseline Characteristics at the Index Date, and Comorbidities and Medications (Class)[a] Prior to the Index Date

	Overall		≥70 years		<70 years	
Baseline Characteristics	**PCb5 (*N*=636)**	**PCb6 (*N*=184)**	**PCb5 (*N*=235)**	**PCb6 (*N*=62)**	**PCb5 (*N*=401)**	**PCb6 (*N*=122)**
Age at index, mean yrs (SD)	65.4 (9.7)	64.1 (9.9)	75.1 (3.3)	74.3 (2.6)	59.8 (7.5)	58.9 (8.0)
Gender, *n* (%)						
Male	339 (53.3)	85 (46.2)	123 (52.3)	27 (43.5)	216 (53.9)	58 (47.5)
Female	297 (46.7)	99 (53.8)	112 (47.7)	35 (56.5)	185 (46.1)	64 (52.5)
Stage, *n* (%)						
IA-IIIA	60 (9.4)	14 (7.6)	26 (11.1)	4 (6.5)	34 (8.5)	10 (8.2)
IIIB/IV	207 (32.5)	48 (26.1)	72 (30.6)	19 (30.6)	135 (33.7)	29 (23.8)
Unknown/missing	369 (58.0)	122 (66.3)	137 (58.3)	39 (62.9)	232 (57.9)	83 (68.0)
Comorbidities, *n* (%)						
Patients with ≥1 comorbidity	31 (4.9)	4 (2.2)	17 (7.2)	2 (3.2)	14 (3.5)	2 (1.6)
Cerebrovascular Disease	3 (0.5)	0	2 (0.9)	0	1 (0.3)	0
Chronic Pulmonary Disease	17 (2.7)	2 (1.1)	8 (3.4)	1 (1.6)	9 (2.2)	1 (0.8)
Congestive Heart Failure	2 (0.3)	0	0	0	2 (0.5)	0
Peptic Ulcer Disease	1 (0.2)	1 (0.5)	1 (0.4)	0	0	1 (0.8)
Peripheral Vascular Disease	3 (0.5)	0	3 (1.3)	0	0	0
Renal Disease	4 (0.6)	0	2 (0.9)	0	2 (0.5)	0
Rheumatologic Disease	3 (0.5)	0	3 (1.3)	0	0	0
Type 2 Diabetes	8 (1.3)	1 (0.5)	4 (1.7)	1 (1.6)	4 (1)	0
Medications (class) up to 3 months prior to index date, *n* (%)						
Patients with ≥1 chemotherapy and/or biologic drug	164 (25.8)	48 (26.1)	51 (21.7)	14 (22.6)	113 (28.2)	34 (27.9)
Patients with ≥1 biologic drug	82 (12.9)	16 (8.7)	28 (11.9)	4 (6.5)	54 (13.5)	12 (9.8)
Patients with ≥1 chemotherapy drug	107 (16.8)	39 (21.2)	29 (12.3)	12 (19.4)	78 (19.5)	27 (22.1)
Patients receiving ≥1 supportive care drug	78 (12.3)	31 (16.8)	19 (8.1)	7 (11.3)	59 (14.7)	24 (19.7)

Abbreviations: PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Medications prescribed or administered recorded up to 3 months prior to the index date (index date not included) were reported. All systemic anti-cancer treatments and all other medications were identified. Among the eligible patients, biologics recorded up to 3 months prior to the index date included: bevacizumab and cetuximab; chemotherapy medications recorded up to 3 months prior to the index date included: bortezomib, carboplatin, cisplatin, docetaxel, erlotinib, etoposide, gemcitabine, paclitaxel, paclitaxel protein-bound particles, pemetrexed, vinorelbine, and vorinostat. The most common prior chemotherapies were paclitaxel plus carboplatin, pemetrexed plus cisplatin, and pemetrexed alone. The vast majority of patients who received prior biological therapy were treated with bevacizumab, either alone or in combination with chemotherapy (data not shown).

10.3. Outcome data

The counts of the first occurrence of the AEs in NSCLC patients treated with PCb5 or PCb6 are shown in Table 10.2 (all ages), Table 10.3 (70 years or older) and Table 10.4 (younger than 70 years). Anemia (77 in the PCb5 group, 35 in the PCb6 group), neutropenia (49 in the PCb5 group and 9 in the PCb6 group) and nausea (27 in the PCb5 group and 4 in the PCb6 group) were the three most commonly diagnosed AEs in each treatment group. Alopecia, mucositis stomatitis and peripheral sensory neuropathy were not diagnosed in any group. Only 1 patient was observed to have a diagnosis for leukopenia.

10.4. Main results

The crude incidence proportions and IRs per 100 person-years of selected AEs, including hematologic toxicities, gastrointestinal toxicities (nausea and vomiting), and fatigue, in NSCLC patients treated with PCb5 or PCb6 are shown in Table 10.2 (all ages), Table 10.3 (70 years or older) and Table 10.4 (younger than 70 years). In the overall population and across age groups, the IRs of anemia and thrombocytopenia were numerically higher whereas the IRs of nausea were numerically lower in the PCb6 cohort compared to the PCb5 cohort. In particular, the IR of anemia in the PCb6 cohort was more than double that in the PCb5 group. The IR of neutropenia in the PCb5 cohort was similar between the two age groups (IR=28.0 per 100 person-years in patients ≥70 years; IR=29.1 per 100 person-years in patients <70 years), but in the PCb6 cohort it was higher for older patients (IR=41.1 per 100 person-years) compared to younger patients (IR=14.5 per 100 person-years) (Table 10.3 and Table 10.4). Among those who were diagnosed with neutropenia, 77.6% of patients in the PCb5 cohort received CSFs compared to 55.6% in the PCb6 cohort. Among elderly population (≥70 years) with neutropenia, the proportions of patients receiving CSF were 82.4% and 40% in the PCb5 and PCb6 cohorts, respectively; while in the non-elderly patients, the proportions were 75% in both cohorts.

After propensity score stratification, adjusted IRs showed similar patterns as the unadjusted results (Table 10.5). In the overall population and in patients <70 years, the adjusted analysis showed an increased risk of anemia and thrombocytopenia in patients treated with PCb6 compared with those treated with PCb5, which was statistically significant (p<0.05) for the overall population and numerically higher for the non-elderly. However, the adjusted HR for thrombocytopenia had a relatively wide CI, likely due to the small number (3 patients in the PCb5 cohort) of patients with thrombocytopenia. In the elderly population (≥70 years), besides the increased risk of anemia and thrombocytopenia, there was a numerically higher risk of neutropenia in the PCb6 cohort compared to the PCb5 cohort.

Table 10.2. Incidence Proportions and Incidence Rates per 100 Person-Years of Selected AEs[a,b] in NSCLC Patients (all ages) Treated with PCb5 or PCb6 in the US-Based Oncology Database during the Observation Period

	PCb5 (*N*=636)					PCb6 (*N*=184)				
Variables	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**
Alopecia	0	0.0%	---	0	---	0	0.0%	---	0	---
Anemia	77	12.1%	(0.096, 0.146)	43.62	(33.88, 53.36)	35	19.0%	(0.133, 0.247)	101.01	(67.55, 134.47)
Anorexia	2	0.3%	(0, 0.007)	1.03	(0, 2.46)	0	0.0%	---	0	---
Constipation	2	0.3%	(0, 0.007)	1.03	(0, 2.46)	0	0.0%	---	0	---
Diarrhea	2	0.3%	(0, 0.007)	1.03	(0, 2.46)	0	0.0%	---	0	---
Fatigue	11	1.7%	(0.007, 0.027)	5.73	(2.34, 9.12)	4	2.2%	(0, 0.044)	9.84	(0.2, 19.48)
Leukopenia	1	0.2%	(0, 0.006)	0.51	(0, 1.51)	0	0.0%	---	0	---
Mucositis stomatitis	0	0.0%	---	0	---	0	0.0%	---	0	---
Nausea	27	4.2%	(0.026, 0.058)	14.42	(8.97, 19.87)	4	2.2%	(0, 0.044)	9.85	(0.19, 19.51)
Neutropenia	49	7.7%	(0.055, 0.099)	28.71	(20.67, 36.75)	9	4.9%	(0.018, 0.08)	22.68	(7.86, 37.5)
Peripheral sensory neuropathy	0	0.0%	---	0	---	0	0.0%	---	0	---
Rash desquamation	1	0.2%	(0, 0.006)	0.51	(0, 1.51)	0	0.0%	---	0	---
Renal failure	1	0.2%	(0, 0.006)	0.51	(0, 1.51)	0	0.0%	---	0	---
Thrombocytopenia	3	0.5%	(0, 0.011)	1.54	(0, 3.28)	7	3.8%	(0.011, 0.065)	17.88	(4.63, 31.13)
Vomiting	13	2.0%	(0.008, 0.032)	6.77	(3.09, 10.45)	4	2.2%	(0, 0.044)	9.85	(0.19, 19.51)

Abbreviations: AEs = adverse events; CSF = colony stimulating factor; IP = incidence proportions; IRs = incidence rates; NSCLC = non-small cell lung cancer; PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Electronic medical records and inpatient and outpatient claims were used to identify the medical conditions using ICD-9-CM diagnosis codes.

Table 10.3. Incidence Proportions and Incidence Rates per 100 Person-Years of Selected AEs[a,b] in NSCLC Patients 70 Years or Older Treated with PCb5 or PCb6 in the US-Based Oncology Database during the Observation Period

	PCb5 (*N*=235)					PCb6 (*N*=62)				
Variables	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**
Alopecia	0	0.0%	---	0	---	0	0.0%	---	0	---
Anemia	33	14.0%	(0.095, 0.185)	53.77	(35.42, 72.12)	13	21.0%	(0.108, 0.312)	141.15	(64.42, 217.88)
Anorexia	0	0.0%	---	0	---	0	0.0%	---	0	---
Constipation	0	0.0%	---	0	---	0	0.0%	---	0	---
Diarrhea	0	0.0%	---	0	---	0	0.0%	---	0	---
Fatigue	4	1.7%	(0.001, 0.033)	5.9	(0.12, 11.68)	1	1.6%	(0, 0.047)	7.76	(0, 22.97)
Leukopenia	1	0.4%	(0, 0.012)	1.43	(0, 4.23)	0	0.0%	---	0	---
Mucositis stomatitis	0	0.0%	---	0	---	0	0.0%	---	0	---
Nausea	11	4.7%	(0.02, 0.074)	16.56	(6.78, 26.34)	1	1.6%	(0, 0.047)	7.7	(0, 22.79)
Neutropenia	17	7.2%	(0.039, 0.105)	28.03	(14.7, 41.36)	5	8.1%	(0.012, 0.15)	41.08	(5.07, 77.09)
Peripheral sensory neuropathy	0	0.0%	---	0	---	0	0.0%	---	0	---
Rash desquamation	0	0.0%	---	0	---	0	0.0%	---	0	---
Renal failure	1	0.4%	(0, 0.012)	1.42	(0, 4.2)	0	0.0%	---	0	---
Thrombocytopenia	0	0.0%	---	0	---	5	8.1%	(0.012, 0.15)	42.12	(5.19, 79.05)
Vomiting	5	2.1%	(0.003, 0.039)	7.2	(0.89, 13.51)	1	1.6%	(0, 0.047)	7.7	(0, 22.79)

Abbreviations: AEs = adverse events; IP = incidence proportions; IR = incidence rates; NSCLC = non-small cell lung cancer; PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Electronic medical records and inpatient and outpatient claims were used to identify the medical conditions using ICD-9-CM diagnosis codes.

Table 10.4. Incidence Proportions and Incidence Rates per 100 Person-Years of Selected AEs[a,b] in NSCLC Patients Younger Than 70 Years Treated with PCb5 or PCb6 in the US-Based Oncology Database During the Observation Period

	PCb5 (*N*=401)					PCb6 (*N*=122)				
Variables	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**	**n**	**IP**	**95% CI**	**IR Per 100 person-years**	**95% CI**
Alopecia	0	0.0%	---	0	---	0	0.0%	---	0	---
Anemia	44	11.0%	(0.079, 0.141)	38.2	(26.91, 49.49)	22	18.0%	(0.111, 0.249)	86.48	(50.34, 122.62)
Anorexia	2	0.5%	(0, 0.013)	1.61	(0, 3.84)	0	0.0%	---	0	---
Constipation	2	0.5%	(0, 0.013)	1.61	(0, 3.84)	0	0.0%	---	0	---
Diarrhea	2	0.5%	(0, 0.013)	1.61	(0, 3.84)	0	0.0%	---	0	---
Fatigue	7	1.7%	(0.005, 0.029)	5.64	(1.47, 9.81)	3	2.5%	(0, 0.052)	10.81	(0, 23.04)
Leukopenia	0	0.0%	---	0	---	0	0.0%	---	0	---
Mucositis stomatitis	0	0.0%	---	0	---	0	0.0%	---	0	---
Nausea	16	4.0%	(0.02, 0.06)	13.24	(6.75, 19.73)	3	2.5%	(0, 0.052)	10.86	(0, 23.15)
Neutropenia	32	8.0%	(0.053, 0.107)	29.08	(19.01, 39.15)	4	3.3%	(0.002, 0.064)	14.54	(0.29, 28.79)
Peripheral sensory neuropathy	0	0.0%	---	0	---	0	0.0%	---	0	---
Rash desquamation	1	0.2%	(0, 0.006)	0.81	(0, 2.4)	0	0.0%	---	0	---
Renal failure	0	0.0%	---	0	---	0	0.0%	---	0	---
Thrombocytopenia	3	0.7%	(0, 0.015)	2.42	(0, 5.16)	2	1.6%	(0, 0.038)	7.33	(0, 17.48)
Vomiting	8	2.0%	(0.006, 0.034)	6.52	(1.99, 11.05)	3	2.5%	(0, 0.052)	10.86	(0, 23.15)

Abbreviations: AEs = adverse events; IP = incidence proportions; IR = incidence rates NSCLC = non-small cell lung cancer; PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Electronic medical records and inpatient and outpatient claims were used to identify the medical conditions using ICD-9-CM diagnosis codes.

Table 10.5. Incidence Rate Difference and Hazard Ratio of the AEs[a,b] Comparing Patients Treated with PCb6 to Patients Treated with PCb5 after Propensity Score Stratification

Age Group	AEs During Observation Period	PCb5 *n*	PCb6 *n*	Incidence Rate Difference per 100 Patient-years	95% CI	Adjusted HR	95% CI
Overall		**(*N*=636)**	**(*N*=184)**				
	Anemia	77	35	15.3	(12.48, 18.16)	1.59*	(1.07, 2.38)
	Fatigue	11	4	0.8	(0.39, 1.21)	1.22	(0.39, 3.84)
	Nausea	27	4	-2.8	(-3.78, -1.82)	0.50	(0.18, 1.43)
	Neutropenia	49	9	-3.9	(-4.85, -2.85)	0.60	(0.30, 1.23)
	Thrombocytopenia	3	7	4.7	(1.77, 7.57)	8.33*	(2.15, 32.22)
	Vomiting	13	4	0.1	(0.04, 0.08)	1.04	(0.34, 3.19)
≥70 years		**(*N*=235)**	**(*N*=62)**				
	Anemia	33	13	20.9	(14.87, 26.99)	1.57	(0.83, 2.99)
	Fatigue	4	1	1.8	(0.21, 3.35)	1.02	(0.11, 9.18)
	Nausea	11	1	-3.3	(-5.21, -1.45)	0.34	(0.04, 2.60)
	Neutropenia	17	5	2.4	(1.39, 3.39)	1.09	(0.40, 2.96)
	Thrombocytopenia	0	5	12.9	(1.58, 24.12)	---	---
	Vomiting	5	1	-0.03	(-0.05, -0.01)	0.76	(0.09, 6.53)
<70 years		**(*N*=401)**	**(*N*=122)**				
	Anemia	44	22	15.0	(11.39, 18.65)	1.64	(0.98, 2.73)
	Fatigue	7	3	0.7	(0.29, 1.19)	1.37	(0.35, 5.31)
	Nausea	16	3	-1.8	(-2.64, -1.00)	0.60	(0.18, 2.07)

Neutropenia	32	4	-6.0	(-7.96, -4.04)	0.39	(0.14, 1.10)
Thrombocytopenia	3	2	1.2	(0.15, 2.19)	2.19	(0.37, 13.10)
Vomiting	8	3	0.7	(0.29, 1.15)	1.21	(0.32, 4.57)

Abbreviations: AEs = adverse events; CI = confidence interval; HR = hazard ratio; PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Electronic medical records and inpatient and outpatient claims were used to identify the medical conditions using ICD-9-CM diagnosis codes.

[b] AEs that were not diagnosed in any of the two cohort were not included in this table.

$^{*}p<0.05$.

10.5. Other analyses

Sensitivity analyses was conducted by adjusting the patient characteristics using 1:1 propensity score matching (Annex 2.Table.1). Although by the nature of 1:1 matching, the sensitivity analysis had a smaller sample size, the pattern of the risk estimates were generally consistent with the primary analyses with propensity score stratification (see Annex 2.Table.1).

10.6. Adverse events/adverse reactions

During the course of secondary use of data in observational research, information pertaining to ARs will not be discovered because the study does not involve identifiable patient data associated with a Lilly product. Data in this study are being analyzed in aggregate only and there will be no medical chart review or review of free text data fields. No unknown risks were identified based on aggregate evaluation of data.

11. Discussion

11.1. Key results

In a real-world setting, this study examined IMS Oncology, a large US-based oncology EMR database for demographic, clinical characteristics, and preselected AEs in NSCLC patients treated with either PCb5 (N=636) or PCb6 (N=184). The results showed that in routine clinical practice more patients with comorbidities received PCb5 than PCb6. Although the proportion of patients who received any prior systemic therapy (chemotherapy and/or biologics) was similar in the two cohorts (PCb5: 25.8% vs. PCb6: 26.1%), patients in the PCb5 cohort had a lower percentage to have had prior chemotherapy. These patterns were consistent in the age groups of elderly and non-elderly patients. In addition, as expected, elderly patients had more comorbidities and fewer prior treatments than younger patients. Altogether these results suggest that a more fragile, less fit patient population, especially among the elderly, is being treated with PCb5. These data may contribute to understanding the rationale behind choosing PCb5 versus PCb6 regimens in the real world and may help guide treatment decisions based on safety, which is a major concern for physicians in a palliative setting.

11.2. Limitations

A few limitations of the study warrant careful consideration.

Grade or severity of disease as well as patients' performance status were not recorded in the database. Given the nature of EMR, captured medical conditions are considered severe enough to require medical attention; less severe conditions may not have been recorded. The observed prevalence of CSF use in patients with neutropenia would support this assumption. In addition, the EMR reflected the routine clinical practice with a focus on medically managing patients instead of a complete scientific assessment. It was observed that only 1 patient had a diagnosis of leukopenia given 58 patients had diagnoses for neutropenia, which could be explained by that in the routine clinical practice neutropenia are more likely to be recorded than leukopenia because neutrophil count is the most important indicator of infection risk.

The requirement of serum creatinine test results within the specific time frame for the carboplatin AUC value calculation restricted the number of patients eligible for the study. The small number of patients with records of AEs other than anemia further limited the study power.

The EMR data for this study does not contain accurate death dates which prevented this study to evaluate treatment-related deaths or to assess the survival benefit of the two regimens.

11.3. Interpretation

Both the crude and adjusted analyses showed that across age groups, with a median treatment duration of 3 cycles in each of the 2 cohorts, patients exposed to PCb6 had an increased risk of having anemia, thrombocytopenia, and other safety outcomes except for nausea and neutropenia. These findings are consistent with outcomes reported from a clinical trial meta-analysis in which PCb6-treated patients had higher incidence of anemia and thrombocytopenia and similar neutropenia compared to PCb5-treated patients[19].

Approximately one-third of patients in either treatment group in the study were 70 years of age or older. The sub-group analyses were conducted by age to further assess the patients in the elderly (≥70 years) age group. This age-group analysis provided results that are generally unavailable from clinical trials in which elderly patients are frequently underrepresented (in a meta-analysis, only 14% of patients enrolled in four phase III pemetrexed clinical trials in NSCLC were ≥70[26]), despite the fact that the elderly comprise a large proportion (approximately 50%) of newly diagnosed cases of NSCLC[27]. The results suggest that elderly patients treated with PCb6 are at higher risk of experiencing hematologic toxicities of anemia, neutropenia, and thrombocytopenia than younger patients; with PCb5, however, only the risk of experiencing anemia was higher in the elderly. This observation is consistent with findings from Gridelli et al. (2014) of maintenance pemetrexed in the PARAMOUNT trial, which reported that elderly patients had a higher incidence of hematologic toxicities, including grade 3/4 anemia and neutropenia, whereas the remaining safety profile of pemetrexed maintenance therapy was comparable between the two age subgroups (<70 years and ≥70 years) [28].

09 dose was safer than PCb6[29]. None of the 4 elderly patients enrolled in the PCb5 cohort experienced grade ≥3 toxicities, whereas 3/6 (50%) patients experienced neutropenia grade ≥3 and 4/6 (67%) patients experienced thrombocytopenia grade ≥3 in the PCb6 cohort[29].

Although the AE severity is not captured in IMS EMR database, for neutropenia we tried to infer it from the use of CSFs, recommended for patients at risk of developing febrile neutropenia. A majority of patients in the PCb5 cohort (78%) and 56% of patients in PCb6 cohort who experienced neutropenia received CSFs. This suggests that a majority of events of neutropenia captured in IMS EMR may correspond to grade ≥3 CTCAEs. The higher proportion of patients in the PCb5 cohort receiving CSFs, especially among the elderly population, may be due in part to a more fragile baseline condition of those patients compared to the PCb6 treated patients, as suggested by a higher load of comorbidities. However, since frailty or ECOG performance scores are not available in the data source we cannot fully confirm this hypothesis.

11.4. Generalisability

The IMS Oncology EMR data consists primarily of medium and large community-based oncology practices. The patients included in this data better represent the advanced cancer patients. The external validity of the data source has been established by a wide range of publications, including peer-reviewed journal articles, based on these data, as well as acceptance of the data for the FDA REMS, FDA Oncology Drugs Advisory Committee, and National Coverage Decisions by CMS.

12. Other information

Not applicable.

13. Conclusion

In conclusion, these results from a real-world database add to the limited evidence available from randomized clinical trials about the safety profile of pemetrexed in combination with the most commonly used carboplatin doses in US clinical practice, in the overall NSCLC population and in elderly patients. The occurrence of anemia and thrombocytopenia was more common in patients treated with the PCb6 regimen in all age groups, with a higher incidence of neutropenia only in the elderly subgroup. The additional risk of AEs with PCb6 may explain the practice of treating less healthy patients (e.g., with more comorbidities) with the PCb5 regimen. Acknowledging its limitations, the results of this observational study may help guide physicians when making treatment decisions by providing answers relevant to patient safety and routine patient care.

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Annex 1. List of standalone documents

Not applicable.

Annex 2. Additional information

Annex 2 Table 1. Incidence Rate Difference and Hazard Ratio of the AEs[a,b] Comparing Patients Treated with PCb6 to Patients Treated with PCb5 After Propensity Score Matching

Age Group	AEs During Observation Period	PCb5 *n*	PCb6 *n*	Incidence Rate Difference per 100 Patient-years	95% CI	Adjusted HR	95% CI
Overall		**(*N*=184)**	**(*N*=184)**				
	Anemia	28	35	7.25	(5.47, 9.03)	1.25	(0.76, 2.06)
	Fatigue	6	4	-1.56	(-2.52, -0.6)	0.65	(0.18, 2.29)
	Nausea	5	4	-0.91	(-1.5, -0.32)	0.79	(0.21, 2.94)
	Neutropenia	16	9	-5.92	(-8.23, -3.61)	0.54	(0.24, 1.21)
	Vomiting	3	4	0.59	(0.16, 1.02)	1.32	(0.3, 5.91)
≥70 years		**(*N*=62)**	**(*N*=62)**				
	Anemia	6	13	23.99	(13.21, 34.77)	2.43	(0.92, 6.4)
	Fatigue	2	1	-0.94	(-2, 0.12)	0.52	(0.05, 5.72)
	Nausea	2	1	-0.88	(-1.88, 0.12)	0.49	(0.04, 5.44)
	Neutropenia	7	5	0	(0, 0)	0.72	(0.23, 2.26)
	Vomiting	1	1	0.64	(-0.24, 1.52)	1.03	(0.06, 16.44)
<70 years		**(*N*=120)**	**(*N*=120)**				
	Anemia	12	22	14.93	(9.91, 19.95)	1.78	(0.88, 3.6)
	Fatigue	2	3	1.04	(0.12, 1.96)	1.43	(0.24, 8.55)
	Nausea	5	3	-2.23	(-3.78, -0.68)	0.56	(0.13, 2.35)

Neutropenia	10	4	-7.46	(-11.36, -3.56)	0.36	(0.11, 1.15)
Vomiting	2	3	1.06	(0.14, 1.98)	1.44	(0.24, 8.62)

Abbreviations: AEs = adverse events; CI = confidence interval; HR = hazard ratio; PCb5 = pemetrexed plus carboplatin area under the concentration-time curve of 5 mg/mL•min; PCb6 = pemetrexed plus carboplatin area under the concentration-time curve of 6 mg/mL•min.

[a] Electronic medical records and inpatient and outpatient claims were used to identify the medical conditions using ICD-9-CM diagnosis codes.

[b] AEs that were not diagnosed in any of the two cohort were not included in this table.

[*] $p<0.05$.