PASS Information

Title	Comparing Common Safety Outcomes in Locally Advanced or Metastatic Non-small Cell Lung Cancer Patients Treated with Various First-line Platinum-containing Combination Regimens
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Active substance	Pemetrexed L01BA04 Paclitaxel L01CD01 Docetaxel L01CD02 Cisplatin L01XA01 Carboplatin L01XA02 Bevacizumab L01XC07
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Research question and objectives	To evaluate the safety outcomes among Stage IIIB/IV NSCLC patients treated with Pemetrexed+Cisplatin, Pemetrexed+Carboplatin, Pemetrexed+Bevacizumab+Carboplatin, Paclitaxel+Carbopltain, Paclitaxel+Bevacizumab+Carboplatin, or Docetaxel+Carboplatin
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Electronically Approved by Lilly on date provided below.

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2. List of Abbreviations

Term	Definition
CDER	The Center for Drug Evaluation and Research
CI	confidence interval
Doc/Carbo	docetaxel + carboplatin
EMR	electronic medical records
FDA	United States Food and Drug Administration
HCP	health care provider
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD-9-CM	international classification of diseases, 9th revision, clinical modification
ICD-O-3	international classification of diseases for oncology, 3rd revision
NSCLC	non-small cell lung cancer
Pac/Bev/Carbo	paclitaxel + bevacizumab + carboplatin
Pac/Carbo	paclitaxel + carbopltain
Pem/Bev/Carbo	pemetrexed + bevacizumab + carboplatin
Pem/Carbo	pemetrexed + carboplatin
Pem/Cis	pemetrexed + cisplatin
SD	standard deviation
US	United States

3. Responsible Parties

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4. Abstract

Title: Safety Outcomes in Locally Advanced or Metastatic Non-small Cell Lung Cancer Patients Treated with Various First-line Platinum-containing Combination Regimens

Version: 1.0. **Date:** 18 June 2015

Rationale and background: Pemetrexed was approved for locally advanced and metastatic non-small cell lung cancer (NSCLC) in the first line treatment and maintenance treatment. Clinical trials showed that in advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine in the first-line therapy (Scagliotti et al. 2008), and that pemetrexed continuation maintenance therapy after induction is well-tolerated and offers superior overall survival compared with placebo (Paz-Ares et al. 2013). However, the safety outcomes of pemetrexed/platinum combinations in the first-line treatment of locally advanced and metastatic NSCLC patients compared to other frequently used chemotherapies in the real world is not well established.

Study design: A retrospective cohort study is proposed. The study will use information from a United States (US) database that contains oncology clinics electronic medical records, combined with medical claims and pharmacy data, to assess the incidence of haematological and non-haematological safety outcomes among Stage IIIB/IV NSCLC patients treated with Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo.

Population: The study population is the Stage IIIB/IV NSCLC patients with who received one of the selected chemotherapy regimens on or after the date of NSCLC diagnosis. From 26 September 2008 (the date that Pemetrexed was first approved for first-line treatment of NSCLC by the FDA in the US) and 30 November 2014 (1 month before the last date that the data are available in the database), among all patients with only one primary tumor type and valid age information, those who meet the following criteria will be included in the study:

1) Patients were diagnosed with lung cancer as a primary cancer (at least one ICD-9-CM code indicating lung cancer, or a TUMOR TYPE value of "Lung Cancer") with at least an ICD-O-3 code indicating non-small cell histology (Howlader et al. 2014), *or* a cancer subtype recorded as "NSCLC" records in the IMS Oncology electronic medical records (EMR); ***and***
2) The staging information indicating locally advanced ***or*** metastatic disease
3) Patients initiated the first-line treatment including Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo after the lung cancer diagnosis. The date of any of the above first-line treatment initiation is the index date; ***and***
4) Patients must be 18 years of age or older on the index date; ***and***
5) Patient's oncology practice must be stable between the index date and end of record in the database, or 31 December 2014, whichever comes first.

Variables:

Exposure variable is first-line platinum-containing combination therapies of Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo after the NSCLC diagnosis.

Patient characteristics include patients' demographic characteristics (age and gender) and comorbidity conditions identified in the six months prior to the index date. The comorbidity conditions to be considered include: Diabetes, diabetes with chronic complications, cardiovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, renal disease, and mild, moderate or severe liver disease.

Other medications include medications prescribed or administered, including systemic anti-cancer treatments and all other medications by drug class, recorded up to three months prior to the index date (index date not included), and concomitant medications during the index therapy on-treatment period will be reported. Patients who received systemic anti-cancer treatments at any time prior to the index date will be excluded.

Study outcomes are the safety endpoint events that occurred on or after the index date. The safety outcomes to be assessed include:

Anemia, neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, anorexia, constipation, diarrhea, mucositis/stomatitis, taste disturbance/dysgeusia/taste alteration, fatigue/asthenia/lethargy/malaise, nausea, vomiting, alopecia, neuropathy sensory, lacrimation disorders (watery eye), ototoxicity, peripheral edema, thromboembolic events, conjunctivitis, renal failure, infection, dyspepsia/heartburn, pain, cardiovascular events, hypertension, bleeding/hemorrhage.

Data sources: The present study will use a US-based oncology clinics based electronic medical record and medical claim database: IMS Oncology Database.

Study size: A feasibility assessment to determine the sample size and study power has been conducted. 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 (Pac/Carbo) with around 80% power, at 95% two-sided confidence interval. 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 Pac/Carbo group have the study outcome.

Data analysis: The primary analysis of this protocol is to describe the incident safety outcomes after index date in patients who were administered at least one of the selected chemotherapy regimens. If sample size allows, adjusted incidence rates, rate difference and hazard ratios will be estimated among the comparable patients with the application of the propensity score stratification method.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned Date
Start of data analysis	15 January 2016
End of data analysis	30 April 2016
Final report of study results	31 May 2016

7. Rationale and Background

Alimta® (pemetrexed) was approved for locally advanced and metastatic non-small cell lung cancer (NSCLC) in the first line treatment and maintenance treatment. Clinical trials showed that in advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine in the first-line therapy (Scagliotti et al. 2008), and that pemetrexed continuation maintenance therapy after induction is well tolerated and offers superior overall survival compared with placebo (Paz-Ares et al. 2013). However, in the real world, the safety outcomes of pemetrexed/platinum combinations in the first-line treatment of locally advanced and metastatic NSCLC patients compared to other commonly used chemotherapy regimens is not well established.

This study will contribute to the understanding of the safety of various commonly used first-line chemotherapies recommended by treatment guidelines to treat patients with NSCLC in the real-world setting, and to provide additional subgroup analyses in populations which there is limited clinical trial data i.e. elderly patients. The study will be conducted using a US-based database of electronic medical records from oncology clinics and medical claims. Although Alimta (pemetrexed) was previously approved as a second-line treatment for NSCLC, this study will limit the analysis to the first-line patients.

Lilly intends to disseminate its findings from this study by including the results in a manuscript submitted to an appropriate journal and/or through poster or podium presentations, as appropriate. In addition, Lilly intends to make the results available to health care providers (HCPs) who may request such information on an unsolicited basis in a manner that is acceptable under applicable local regulations. The results of this study will not be used to establish recommendations for clinicians on one chemotherapy regimen over another.

8. Research Question and Objectives

The purpose of this study is to evaluate the occurrence of safety outcomes of locally advanced/metastatic NSCLC patients treated with first line Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo chemotherapies.

8.1. Primary Objectives

1) To estimate the crude incidence proportions and incidence rates of the safety outcomes among the NSCLC patients receiving first line treatment with the selected chemotherapy regimens
2) To describe demographic and clinical characteristics of the NSCLC patients receiving first-line treatment with the selected chemotherapy regimens
3) If sample size allows, to estimate the incidence rate, rate difference and hazard ratio (HR) of safety outcomes among the NSCLC patients receiving first-line treatment with the selected chemotherapy regimens, using the Pac/Carbo group as a reference and adjusting for patients' demographic and clinical characteristics. The null hypothesis is that there is no difference in the rate of safety outcomes between the chemotherapy regimens.

8.2. Secondary Objectives

If sample size allows, to conduct subgroup analyses to further examine the safety profiles of the NSCLC patients treated with the regimens in those who were below 70 and who were 70 years or older. The null hypothesis is that there is no difference in the rate of safety outcomes between the patients aged below or greater than 70 years.

9. Research Methods

9.1. Study Design

This will be a retrospective cohort study design using IMS Oncology Database, a US oncology clinic database including electronic medical records, inpatient/outpatient medical claims, and pharmacy claims. The exposure groups will include: patients with evidence of first-line treatment with Pemetrexed (ATC L01BA04) + Cisplatin (ATC L01CD02) (Pem/Cis), Pemetrexed + Carboplatin (ATC L01XA02) (Pem/Carbo), Pemetrexed + Bevacizumab (ATC L01XC07) + Carboplatin (Pem/Bev/Carbo), Paclitaxel (ATC L01CD01) + Carboplatin (Pac/Carbo), Paclitaxel + Bevacizumab + Carboplatin (Pac/Bev/Carbo), and Docetaxel (ATC L01CD02) + Carboplatin (Doc/Carbo) after the NSCLC diagnosis. The exposure groups were selected based on feasibility counts of the eligible patients in the database. The index date will be the date of the first evidence of any of the above treatments after the NSCLC diagnosis. Therapies with more than 100 eligible patients were included in the study. Chemotherapies such as Paclitaxel + Cisplatin and Docetaxel + Cisplatin were not included due to the small number of eligible patients in the database. For each patient, the baseline period will be defined as the six months prior to the index date for baseline characteristics and comorbidities and for the three months prior to the index date for co-prescribed medication. For each study endpoint, the follow-up begins on the date the first qualifying treatment was initiated (that is, index date) and continues until the first occurrence of the study end point, end of on-treatment period (defined as 30 days after the last dose of the study regimen before treatment discontinuation, see Section 9.3.1), an administration/prescription record indicating a switch from the study medicines to another systemic treatment, the last record in the database, or 31 December 2014, whichever comes first. Sensitivity analyses with additional thresholds of end of follow up (3, 6, and 9 months after the index date in addition to the overall follow-up requirement) will be conducted. The study contains descriptive analysis to present the frequencies and proportions for the patient baseline characteristics and study endpoints, and if sample size allows to conduct an adjusted comparative analysis to present HRs and incidence rate difference of the study endpoints, with the null hypothesis that there is no difference between each exposure groups in comparison to the Pac/Carbo treatment group (the most commonly used platinum-containing combination therapy in NSCLC in the US). While there is no *a priori* hypothesis about the confounders to be included or the difference in safety profile occurrence among the exposure groups, some patient characteristics may be adjusted for, such as age and gender.

9.2. Setting

Of all IMS Oncology patients (male and female), those who meet the following criteria will be included in the study:

1) Patients were diagnosed with lung cancer as a primary cancer (at least one ICD-9-CM code in 162.2, 162.3, 162.4, 162.5, 162.8, or162.9, or a TUMOR TYPE value of "Lung Cancer") with
    a. At least an ICD-O-3 code indicating non-small cell histology (8003-8004, 8012-8015, 8021-8022, 8030-8035, 8046, 8050-8052, 8070-8076, 8078, 8082-8084,

8090, 8094, 8120, 8123, 8140-8141, 8143-8145, 8147, 8190, 8200-8201, 8211, 8240-8241, 8243-8246, 8249-8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8430, 8440, 8470-8471, 8480-8481, 8490, 8503, 8507, 8525, 8550, 8560, 8562, 8570-8572, 8574-8576) (Howlader et al. 2014), ***or***

b. A cancer subtype recorded as "NSCLC" records in the IMS Oncology EMR;

and

2) The staging information indicating
   a. Locally advanced (T1-2 N3 M0; T3 N3 M0; T4 N2-3 M0) ***or***
   b. Metastatic disease (a STAGE value of "Stage IV" or "Stage 4"; M value >=1 such as M1, M2; a tumor type of "Secondary malignant neoplasm"; a secondary cancer diagnosis code [ICD-9-CM: 196.x, 197.x (except 197.0), 198.x, or 199.0]).
3) Patients initiated the first-line treatment including Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo after the lung cancer diagnosis. The date of any of the above treatment initiation is the index date. The index date was between 26 September 2008 and 30 November 2014; ***and***
4) Patients must be 18 years of age or older on the index date; ***and***
5) Patient's oncology practice must be stable between the index date and end of record in the database, or 31 December 2014, whichever comes first.

The exclusion criteria are a history of any other primary tumor, missing information on patient age, patients younger than 18 years at the index date, patients whose oncology practice is not stable in the IMS oncology database for the duration of the study, small cell lung cancer patients, patients who have NSCLC which is node negative and/or non-metastatic, or staging information is not available, patients who did not receive one of the selected chemotherapy regimens and patients who had received any systemic chemotherapy prior to the index date.

9.3. Variables

9.3.1. Exposure

The exposure variable is first-line Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo treatment after the diagnosis of NSCLC. Administration of chemotherapy regimens and administration dates will be abstracted from the electronic medical records. Medication is classified by generic name in the database. The on-treatment period begins on the day of the first dose of the study treatment and continues to 30 days after the last treatment cycle or a switch in chemotherapy regimen, whichever comes first. Treatment discontinuation is defined as a gap in continuous study medication coverage exceeding 42 days (2 cycles).

9.3.2. Patient Characteristics

Baseline characteristics include patients' demographic characteristics (age, gender, body weight, and race/ethnicity) and comorbid conditions within the 6 months prior to the index date and patients' medication use up to three months prior to the index date. The comorbidity conditions

to be considered include: diabetes, diabetes with chronic complications, cardiovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, renal disease, and mild, moderate or severe liver disease. 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 is all cancer patients, cancer characteristics will be described separately. The comorbidity conditions will be identified through ICD-9-CM diagnosis codes suggested by Deyo et al. (1992). Medications prescribed or administered (at the drug group level) recorded up to 3 months prior to the index date (index date not included) will be reported. All systemic anti-cancer treatments and all other medications will be identified, and patients who received systemic anti-cancer treatment within at any time prior to the index date will be excluded.

Concomitant medications during the study chemotherapy on-treatment period will also be reported.

9.3.3. Study Outcomes

The study outcomes are the safety endpoint events that occurred on or after the index date during the defined on-treatment period. EMR and in-patient and outpatient claims will be used to identify the events of interest and the date on which they occurred. If sample size allows, the safety endpoints to be assessed include:

- Hematological outcomes including anemia, neutropenia, febrile neutropenia, leukopenia, and thrombocytopenia, and
- Non-hematological outcomes including anorexia, constipation, diarrhea, mucositis/stomatitis, taste disturbance/dysgeusia/taste alteration, fatigue/asthenia/lethargy/malaise, nausea, vomiting, alopecia, neuropathy sensory, lacrimation disorders (watery eye), ototoxicity, peripheral edema, thromboembolic events, conjunctivitis, renal failure, infection, dyspepsia/heartburn, pain, cardiovascular events, hypertension, and bleeding/hemorrhage.

The safety outcomes will be identified through ICD-9-CM diagnosis codes recorded in the electronic medical records, medical claims and hospital admission diagnoses records.

For each safety endpoint, the observation period begins when the first-line therapies of Pem/Cis, Pem/Carbo, Pem/Bev/Carbo, Pac/Carbo, Pac/Bev/Carbo, or Doc/Carbo are first administered to the patient (index date) and last until the end of follow-up (defined in Section 9.3.1). Patients with certain comorbidities in the baseline (such as cardiovascular outcomes) may be excluded for the specific outcome as they are at higher risk for repeat outcomes.

9.4. Data Sources

IMS Oncology is a private-practice database 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. The IMS pharmacy claims database, established in 2001, includes claims (National Council for Prescription Drug Programs [NCPDP] version 5.2)

for more than 2 billion prescriptions dispensed annually. The IMS medical claims database, established in 1999, includes more than one billion annual claims (CMS 1500 forms) containing diagnosis and visit information and represents activity of more than 865,000 physicians per month. The IMS CDM database contains patient hospital-visit records for approximately 9 million in-patient and 96 million out-patient visits annually.

The IMS Oncology EMR data consist primarily of medium and large community-based oncology practices. Each practice utilizes an Electronic Medical Record system capturing detailed, patient-level clinical data which is then de-identified, assigned a synthetic identification, and integrated into the warehouse. IMS receives data-feeds from Medical Oncology Practices and Comprehensive Cancer Centers in the US. More than 500,000 cancer patients are in this dataset, representing 344 locations from 37 states. This encompasses about 550 treating providers. Approximately 60,000 patients are observed in this database every month. Detailed clinical data are available for these EMR patients. Data features include but are not limited to: diagnostic information (and includes non-oncology as well as oncology diagnoses), cancer Staging, TNM Values, patient demographics, laboratory results and vital signs, injectables and oral medications including chemotherapy and hormonal drugs, dosing, and drug regimens and treatment intervals. Facility information (type, state) is also included. In addition, for a small subset of patients, available patient social history (for example, smoking, alcohol use), and blood transfusion data at an administration level are provided. The data time period is from January 1997 to December 2014, although the data are more robust from 2004 onward.

9.5. Study Size

A feasibility assessment was conducted to determine the sample size using IMS Oncology data. All first-line regimens in NSCLC patients were identified between 26 September 2008 and 30 November 2014, and from this analysis the 6 most commonly used combination regimens were selected for this study. The results of the feasibility study identified the following groups of patients receiving first-line treatment with the selected chemotherapy regimens with more than 100 patients in each group (Table 1).

Table 1. Feasibility Assessment Results, Patients Receiving the Most Commonly Used Platinum Combinations for First-line Treatment of NSCLC

Chemotherapy	N
Pem/Cis	272
Pem/Carbo	1195
Pem/Bev/Carbo	509
Pac/Carbo	2417
Pac/Bev/Carbo	414
Doc/Carbo	263

Abbreviations: Bev = bevacizumab; Carbo = carboplatin; Cis = cisplatin; Doc = docetaxel; N = number of patients; NSCLC = non-small cell lung cancer; Pac = paclitaxel; Pem = pemetrexed.

These first-line chemotherapies are selected because they are most commonly used by the patients in the IMS Oncology database, each with more than 100 eligible patients. A first-line regimen will not be included in the analysis if it has less than 100 eligible patients. 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 (Pac/Carbo) with around 80% power, at 95% two-sided confidence interval (CI). Based on the feasibility counts, the available samples size will have 80% power to detect a statistically significant risk ratio ≥ 2 in any of the comparison therapies if 10% or more of the Pac/Carbo group have the study outcome. In some of the comparison therapies, i.e. Pem/Carbo, Pem/Bev/Carbo and Pac/Bev/Carbo, if a safety outcome occurs in 5% of the Pac/Carbo group, then this analysis will have sufficient statistical power, however in the other comparison arms, with fewer patients there will not be sufficient power. This is presented in Table 2.

The risk ratio value of 2 was selected based on the suggestion from OMOP: "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).

Table 2. Power and Sample Size Estimation of Primary Retrospective Cohort Study, with 2-sided Confidence Level of 95% (>= 0.05) (numbers in bold indicate scenarios where the analysis will have sufficient statistical power)

Outcome in Pac/ Carbo Group		80% Power Ratio Pac/Carbo: Comparison Therapies					
		1:1	1:0.5	1:0.4	1:0.3	1:0.2	1:0.1
1%	Pac/Carbo	2319	3620	4267	5342	7488	13910
	Other therapies	2319	1810	1707	1603	1498	1391
5%	Pac/Carbo	**435**	**677**	**797**	**997**	**1395**	2587
	Other therapies	**435**	**339**	**319**	**229**	**279**	259
10%	Pac/Carbo	**199**	**309**	**363**	**453**	**633**	**1171**
	Other therapies	**199**	**155**	**146**	**136**	**127**	**118**
15%	Pac/Carbo	**121**	**186**	**218**	**272**	**379**	**771**
	Other therapies	**121**	**93**	**88**	**82**	**76**	**78**
20%	Pac/Carbo	**82**	**125**	**146**	**182**	**252**	**463**
	Other therapies	**82**	**63**	**59**	**55**	**51**	**47**
25%	Pac/Carbo	**58**	**88**	**103**	**127**	**176**	**321**
	Other therapies	**58**	**44**	**41**	**38**	**36**	**33**

Abbreviations: Carbo = carboplatin; Pac = paclitaxel.

9.6. Data Management

Datasets and analytic programs will be kept on a secure server and archived per Lilly record retention procedures. SAS ® Proprietary Software 9.2 will be utilized for data management; the

relevant commands such as proc datasets, proc format, proc sql, etc., will be used to access the raw data, manage the analytical dataset, and process the integrated analytical datasets.

9.7. Data Analysis

All data programming and analysis will be carried out using SAS (version 9.2). Specific objectives will be addressed as described below.

Objective 1: To describe baseline demographic and clinical characteristics of the NSCLC patients receiving first-line treatment with the selected chemotherapy regimens

For each chemotherapy group, the demographic characteristics at index, baseline cancer characteristics (that is, tumour staging information), comorbidities during the 6 months prior to the index date, and other medications during 3 months prior to the index will be assessed using descriptive statistics. Concomitant medications during the on-treatment period will also be summarized for each group. The demographic and clinical characteristics will be summarized using counts and frequencies for categorical variables and mean/SD/median/min/max for continuous variables. Subgroup comparison will be performed within each chemotherapy group for patients aged below 70 years vs aged 70 years or older. The statistical significance of differences between age subgroups in patient demographic and clinical characteristics, as well as concomitant medications will be assessed using t-tests or chi-square tests as appropriate.

Objective 2: To estimate the crude incidence rates of the safety outcomes among the NSCLC patients receiving first line treatment with the selected chemotherapy regimens

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

Objective 3: If sample size allows, to estimate the incidence rates, rate difference, and HR of treatment-emergent safety outcomes among the NSCLC receiving first-line treatment with the selected chemotherapy regimens separately, using Pac/Carbo as the reference group and with adjustment for patients' demographic and clinical characteristics using propensity score methods. In the event that the incidence of some outcomes is low, some similar outcomes, i.e. nausea and vomiting, may be grouped for the purposes of having a sufficiently powered analysis.

Propensity score stratification will be used to adjust for differences in the distribution of baseline characteristics between each chemotherapy and Pac/Carbo, separately. Propensity score stratification, instead of propensity score matching, is used because propensity score matching would result in the exclusion of a substantial number of patients in the Pac/Carbo reference group. Stratification does not compromise generalizability.

For each comparison pair (Pem/Carbo, Pem/Bev/Carbo, Pem/Cis, Pac/Bev/Carbo, or Doc/Carbo in comparison to Pac/Carbo), propensity score stratification will be performed in 2 steps, and the propensity score models will be assessed and finalized before the assessment of outcome data. First, for all eligible patients, unconditional logistic regression will be used to estimate the

probability of initiating the comparison chemotherapy treatment given their baseline demographic characteristics, baseline comorbidities and medications used during 3 months prior to the index date. Patients will then be classified into strata determined by quintiles of the propensity score, to produce comparable cohorts with similar baseline characteristics within each stratum. Adjusted estimates of the safety outcome incidence rates and rate differences will be calculated by taking a weighted average of the stratum-specific estimates where the weights equalled the number of comparison chemotherapy treated patients in each stratum divided by the total number of comparison chemotherapy patients. Because the strata will be constructed based on quintiles of the comparison chemotherapy group, the weights will be 0.2 for each stratum (Greenland et al. 1999; Sato et al. 2003; Stuart 2010).

Given that propensity score stratification has better generalizability while propensity score matching is more advantaged in terms of bias control, propensity score matching will be applied as a sensitivity analysis. Appropriate sensitivity analysis may also be conducted to evaluate the robustness of various assumptions, for example unmeasured confounding.

Cox proportional hazards regression models will be used to compare time-to-event between Pac/Carbo and each comparison group, with Pac/Carbo serving as the reference group, stratified by propensity score quintiles. Statistical significance will be determined using 95% CIs and two-tailed p-values ($p<0.05$). Incidence rates and rate differences will be estimated.

Objective 4: If sample size allows, the Cox proportional hazards regression models will be applied to the subgroups within each chemotherapy group defined by age (<70 years, ≥70 years) to assess the potential effect modification by age, adjusted by propensity score quintiles.

No multiplicity adjustments will be conducted in the study.

Number and proportion of missing data for each pertinent variable will be reported.

9.8. Quality Control

The study will use an existing database, which have been used primarily for research, fully HIPAA compliant. The study programs for data management or statistical analyses will be validated by individual(s) outside the study team to ensure data integrity and accuracy. All study programs, log files, and output files will be 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 would be reviewed by 2 experienced clinicians to ensure the accuracy of the diagnosis and decrease the misclassification.

9.9. Limitations of the Research Methods

EMR and medical claims data are extremely valuable for the efficient and effective examination of disease outcome and treatment patterns; however, these data are collected for the purpose of administration and payment, instead of pharmacoepidemiology research. Therefore, there are limitations associated with the use of these data.

First, information about the medical conditions is to be collected using ICD-9 disease classification coding system in the EMR or medical claims; thus the conditions captured will be

the severe conditions that need medical attention, but not the less severe ones. Caution needs to be taken that the pattern of less severe conditions may not be reflected by the study results.

Second, some important information are not well populated in the EMR database, such as certain lab results and Eastern Cooperative Oncology Group performance status, to assess how a patient's disease is progressing and determine appropriate treatment and prognosis. However, the study does include a number of pre-treatment covariates in the propensity score method to balance and minimize the differences between the selected chemotherapy cohorts.

Third, the presence or absence of disease may not be completely accurate, because the diagnostic code may be incorrectly coded or included as rule-out criteria rather than actual disease, especially in the medical claims.

According to the feasibility analysis, and sample size calculation, the study is powered to detect a statistically significant risk ratio ≥ 2 with 80% power, at 95% two-sided CI in any of the comparison arms if 10% or more of the group have the study outcome. If a study endpoint occurs in 5% of the Pac/Carbo group, then the available sample size will have 80% power to detect a statistically significant risk ratio ≥ 2 only in some of the larger comparison arms. This is a limitation of the available data.

If sample size allows, the current study will adopt an existing propensity score stratification methodology to preserve the generalizability of the results to all eligible NSCLC patients receiving first line treatment with the selected chemotherapy regimens (in comparison to Pac/Carbo) and minimize biases due to the unequal distributions of important baseline characteristics between the varies patient groups, given the non-randomization property of observational database. Since random assignment is impossible, this approach offers robust control for confounding because it enables tailoring of the covariates selection based on pretreatment characteristics of the two treatment groups and the events of interest. If sample size allows, propensity score matching will be conducted as a sensitivity analysis. However, given the nature of the data, which was addressed above, residual confounding could be a possibility.

9.10. Other Aspects

None

10. Protection of Human Subjects

All information about this observational study and individual medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. This study will be conducted in accordance with applicable laws and regulations of the region, country or countries where the study is being conducted, as appropriate.

11. Management and Reporting of Adverse Events/ Adverse Reactions

During the course of retrospective observational research, information pertaining to adverse reactions will not be discovered as the study does not involve identifiable patient data associated with a Lilly drug. The data in this study are only being analysed in aggregate, study data sets do not include safety measures, and there will be no medical chart review or review of free text data fields.

12. Plans for Disseminating and Communicating Study Results

Lilly intends to disseminate its findings from this study by including the results in a manuscript submitted to an appropriate journal and/or through poster or podium presentations, as appropriate. In addition, Lilly intends to make the results available to HCPs who may request such information on an unsolicited basis in a manner that is acceptable under applicable local regulations. The results of this study effort will not be used to establish recommendations for clinicians on one regimen of pemetrexed or platinum-based chemotherapy over another.

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Not applicable.

Annex 3. Additional Information

Not applicable

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