Study Report

P2-C3-003

DARWIN EU® – Overall survival in patients with locally advanced or metastatic non-small cell lung cancer treated with selected immunotherapies as first line of treatment

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Version 5.0

Contents

Study Title	DARWIN EU® – Overall survival in patients with locally advanced or metastatic non-small cell lung cancer treated with selected immunotherapies as first line of treatment
Study Report Version	V5.0
Date	02/05/2025
EU PAS number	EUPAS1000000112
Active substance	- Pembrolizumab - Nivolumab - Atezolizumab - Cemiplimab - Durvalumab - Ipilimumab - Chemotherapies (reference cohort for comparisons): cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine
Medicinal product	Keytruda, Opdivo, Tecentriq, Libtayo, Imfinzi, Yervoy
Research question and objectives	The **aim** of this study was to assess the overall survival of patients with locally advanced or metastatic non-small cell cancer (NSCLC) who initiate first-line treatment with selected immunotherapies (pembrolizumab, atezolizumab, cemiplimab, nivolumab, durvalumab and ipilimumab) and how it compares to the survival of locally advanced or metastatic NSCLC patients treated with chemotherapies as first line. The **specific objectives** of this study were: 1) To characterise patients at the time of initiating first line therapy as well as treatments received by patients with locally advanced or metastatic NSCLC, including treatment combinations. 2) To estimate the overall survival rates of patients with locally advanced or metastatic NSCLC **who initiated treatment** with immunotherapies (Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Ipilimumab) and also with chemotherapies (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine) given **as monotherapy or in combination (as per the label) and as first line of treatment**, regardless of treatment discontinuation or treatment switch. 3) To compare the overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of chemotherapy (reference cohort).
Country(-ies) of study	France, Spain, The Netherlands
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1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Talita Duarte-Salles	Erasmus MC
Epidemiologists	Julieta Politi Anton Barchuk* Berta Raventós**	
Data Scientist	Maarten van Kessel Ross Williams	
Data Partner* **	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Miguel-Angel Mayer	PSMAR - IMASIS
	Angela Leis	PSMAR - IMASIS
	Juan Manuel Ramirez	PSMAR - IMASIS
	Peter Prinsen	Netherlands Cancer Registry
	Jelle Evers	Netherlands Cancer Registry
	Ronald Damhuis	Netherlands Cancer Registry
	Romain Griffier	University of Bordeaux - CDWBordeaux
	Guillaume Verdy	University of Bordeaux - CDWBordeaux

*Included in the study team on the 12th of April 2024.
**Included in the study team on the 8th of August 2024.
***Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

2. DATA SOURCES

This study was conducted using routinely collected data from 3 databases in 3 European countries. The databases were selected based on their ability to identify patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), cancer treatments, staging, and date of death. All databases were previously mapped to the OMOP CDM.

At the time of writing the study protocol, these were the databases for this study identified from the network of data partners of DARWIN EU®:

1. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
2. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
3. Netherlands Cancer Registry (NCR), The Netherlands

Information on selected data sources is described in **Table 2.1**.

Table 2.1. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CDWBordeaux	Covers secondary care setting, database has information on cancer treatment, mortality and other outcomes for in-house patients.	Secondary care (in and outpatients)	EHR	1.9 million	12/2023
Spain	IMASIS	Covers secondary care setting, database has information on cancer treatment, mortality and other outcomes for in-house patients.	Secondary care (in and outpatients)	EHR	0.6 million	12/2023
The Netherlands	NCR	Cancer registry data with high quality information on cancer diagnoses, mortality, and cancer treatment.	Cancer registry	Registry	3.5 million	10/01/2024 with incident cancer patients included up to 31/12/2022

CDWBordeaux = Clinical Data Warehouse of Bordeaux university hospital, IMASIS = Institut Municipal Assistència Sanitària Information System, NCR = Netherlands Cancer Registry.

3. ABSTRACT

Title

DARWIN EU® – Overall survival in patients with locally advanced or metastatic non-small cell lung cancer treated with selected immunotherapies as first line of treatment

Rationale and Background

Over the last decade, a better understanding of the molecular mechanism of lung cancer has led to the development of new therapies resulting in improvement in overall survival, mostly driven by advances in the treatment of non-small cell lung cancer (NSCLC). NSCLC has been recognised as a set of multiple diseases; therefore, numerous approved targeted therapies are now available in driver mutation-positive NSCLC, and immunotherapies in the form of an immune checkpoint inhibitor(s) (ICIs) are indicated in patients without a driver mutation.

While there is evidence of the clinical efficacy of these immunotherapies, there is still uncertainty about the benefits on a more diverse patient population treated outside clinical trials. A better understanding of the effectiveness of these medicines in real world settings, which was the aim of this study, can help inform health technology assessment. This is particularly important considering the high costs of these immunotherapies, their increasing widespread use and population ageing coupled with high incidence in older age groups.

Research Question and Objectives

The **overall aim** of this study was to assess the overall survival of patients with locally advanced or metastatic NSCLC who initiated first-line treatment with selected immunotherapies (pembrolizumab, atezolizumab, cemiplimab, nivolumab, durvalumab, and ipilimumab) and compare it to the survival of locally advanced or metastatic NSCLC patients treated with chemotherapies as first-line.

The **specific objectives** of this study were:

1) To characterise patients at the time of initiating the first line therapy as well as to characterise treatments received by patients with locally advanced or metastatic NSCLC, including treatment combinations.

2) To estimate the overall survival rates of patients with locally advanced or metastatic NSCLC **who initiated treatment** with immunotherapies (Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Ipilimumab) and also with chemotherapies (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine) given **as monotherapy or in combination (as per the label) and as first line of treatment**, regardless of treatment discontinuation or treatment switch.

3) To compare the overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of chemotherapy (reference cohort).

Research Methods

Study design

- Descriptive study: To address objective 1, a large-scale characterisation study was performed of locally advanced or metastatic NSCLC patients at time of start of treatment. We also performed treatment pattern analysis to provide a description of treatments and treatment combinations received among these patients as first-line.
- New user matched cohort study.

An interim analysis was conducted to address objective 1. The results informed the specific cohorts to be considered for objectives 2 (characterisation of overall survival) and 3 (comparative survival analysis).

Population

Patients aged 18 or above with locally advanced or metastatic NSCLC who initiated first-line treatment with any of the therapies listed above between 01/01/2016 and 31/12/2022.

One cohort was created for each new user of immunotherapy treatment (including treatment given in combination with other immunotherapies or with chemotherapies) and a cohort of new users of chemotherapies alone.

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
2. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
3. Netherlands Cancer Registry (NCR), The Netherlands

Exposures

Initiation of the following first-line treatments after diagnosis of locally advanced or metastatic NSCLC: pembrolizumab, nivolumab, atezolizumab, cemiplimab, durvalumab, ipilimumab and chemotherapy (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine).

Primary outcome of interest

For objective 1, demographic and clinical characteristics at the time of starting treatment as well as therapies received.

For objectives 2 and 3, overall survival since the start of therapy for locally advanced or metastatic NSCLC.

Follow-up

For objective 1, patients were followed for 42 days after the date of start of first-line therapy.

For objectives 2 and 3, patients were followed in each cohort from the date of therapy initiation until the date of death, loss to follow-up, end of study period or end of data availability in each database.

Data analyses

All analyses were conducted separately for each database and were carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

First, we executed cohort diagnostics to evaluate data availability and quality in terms of identifying locally advanced or metastatic NSCLC and recording cancer treatments of interest.

A minimum cell count of 5 was used when reporting results, with any smaller counts between 1 and 4 reported as "<5" to comply with the database's privacy protection regulations. All analyses were reported by database, overall and stratified by age and sex when possible (i.e., when the minimum cell count was reached).

For objective 1, the characterisation of patients at the time of initiating first-line therapy was conducted for those starting immunotherapy and/or chemotherapy as a group. The number and percentage of patients receiving each of the pre-specified NSCLC treatment/s as monotherapy/combinations was described at the time of starting first line of therapy (index date) and including all treatments up to 42 days following index date, representing the first-line treatment.

For objective 2, overall survival was calculated for each study cohort with sufficient counts (determined after carrying out objective 1) using data on time at risk of death from any cause since start of therapy and the Kaplan-Meier method. Results were reported as plots of the estimated survival curves as well as the estimated median survival, restricted mean survival time (RMST), and the probability of survival at years 1, 2, and 3.

For objective 3, we used a propensity score-matched cohort design, where patients in the selected immunotherapy and chemotherapies cohorts were matched 1:1 based on propensity scores (PS). PS were estimated as the probability of exposure to the selected immunotherapy (target cohort) conditional on available covariates in the database, i.e., age, sex, index year, stage of tumour, and WHO performance status (WHO-PS). PS was estimated using Lasso regression. Hazard Ratios (HR) and 95% confidence intervals for overall survival were estimated using Cox proportional hazards models comparing the target vs comparator (reference) cohorts after PS matching. An additional analysis was conducted using multivariate adjustment by the available covariates. Kaplan-Meier plots and/or cumulative incidence plots were used to illustrate the probability of survival over time. A supplementary analysis was performed to estimate the difference in RMST between first-line therapy groups.

Results

We identified 1,229, 321 and 38,957 patients with locally advanced or metastatic NSCLC with no prior history of cancer in CDWBordeaux, IMASIS, and NCR, respectively. From these, 10%, 51%, and 38% were treated with chemotherapy and/or immunotherapy as first-line within the study period, respectively.

Characterisation

Among individuals that received treatment, male predominance was observed across all databases, ranging between 55.3% (NCR) to 76.2% (IMASIS). The median age was similar across databases, ranging from 63 (IMASIS) to 66 (NCR) years. By age group, in CDWBordeaux and IMASIS, most patients were within the 18-64 age group (56.1% and 53.0%, respectively), while in NCR, 52.5% fell within the 65-79 age group.

History of comorbidities and medications among treated patients was only available in CDWBordeaux (N=123) and IMASIS (N=164). In both databases, conditions directly reflecting malignancy diagnosis of NSCLC were the most frequently recorded entries, and tobacco/nicotine dependence was among the most common entry not directly related to the malignancy diagnosis. In CDWBordeaux, other notable diagnoses included abnormal findings on diagnostic imaging of the lung (29.8%), cough (27.9%), and dyspnoea (27.9%). In IMASIS, other entries not directly related to the malignancy diagnosis included essential hypertension (15.7%), and hyperlipidaemia (13.8%). Notably, in IMASIS, COVID-19 was reported in 12.6% of individuals.

In CDWBordeaux, the most frequently prescribed medication the year prior to the index date was acetaminophen as oral formulation (42.3%), followed by enoxaparin (30.8%). In IMASIS, the most prescribed medications were omeprazole (as oral formulation: 32.1% and injectable solution: 16%) and different formulations of acetaminophen. In both databases, other commonly prescribed medications include pain relievers (e.g. tramadol, fentanyl, dipyrone), and drugs used for anxiety (e.g., lorazepam, hydroxyzine).

Chemotherapies were the most frequently prescribed first-line treatments in CDWBordeaux and IMASIS, while in NCR, immunotherapies were more frequently prescribed as first-line treatment than chemotherapies. Overall, pembrolizumab was the most frequently prescribed first-line immunotherapy treatment in all databases (39 to 42 patients in CDWBordeaux, 68 to 74 patients in IMASIS, and 8,005 to 8,044 patients in NCR), followed by nivolumab (<5 in CDWBordeaux, <5 to 12 in IMASIS, and 143 to 161 in NCR).

Regarding treatment combinations or monotherapies, the most frequent first-line treatment was the combination of two chemotherapies in CDWBordeaux and chemotherapy as monotherapy in IMASIS. In NCR, most frequent first-line treatments consisted of combination of two chemotherapies or combinations of 3 or more treatments including both chemotherapies and immunotherapies

Survival rates

In NCR only, overall survival was estimated for the following treatments: chemotherapy (n=5,425), pembrolizumab (n=7,992), nivolumab (n=213), and nivolumab and ipilimumab combination (n=62). Among all locally advanced (stage 3b) and metastatic (stage 4) NSCLC patients, median overall survival varied by treatment type. The highest median survival (years) was observed for nivolumab and ipilimumab combination (16.16 months (95%CI: 11.53, 35.74)), followed by pembrolizumab (13.11 months (12.58, 13.63)), nivolumab (12.19 months (9.43, 14.59)), and chemotherapy (9.96 months (9.56, 10.41)). When looking into the RMST (4-years follow-up), it was 20.86 months (15.21, 26.55) for nivolumab and ipilimumab combination, 20.14 months (19.71, 20.60) for pembrolizumab, 17.25 months (16.79, 17.71) for chemotherapy, and 16.92 months (14.49, 19.32) for nivolumab.

The 3-year survival probabilities were 20.19% (19.04, 21.40) for chemotherapy, 26.95% (25.74, 28.22) for pembrolizumab, 17.56% (12.26, 25.16) for nivolumab, and 22.80% (10.84, 47.95) for the combination of nivolumab and ipilimumab.

By age group, survival decreased with increasing age for all treatments. Results also differed by sex for all treatments, with females having higher survival estimates than males.

Regarding PD-L1 expression by treatment, the highest proportion of patients with PD-L1 >=50% was observed in the pembrolizumab cohort (45.6%), while the other treatments, the proportion of patients with PD-L1 >=50% was lower (<15%). Overall, survival varied by PD-L1 expression and treatment type. However, across all treatments, higher PD-L1 expression corresponded with improved survival estimates. That said, for nivolumab and the nivolumab and ipilimumab combination cohort, not all PD-L1 expression categories were estimated due to the small sample size.

By tumour stage, survival estimates were lower in stage 4 compared to stage 3b, across all treatment cohorts.

Survival comparison

We compared overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy (pembrolizumab, nivolumab, and the nivolumab and ipilimumab combination) to that of exclusive chemotherapy (reference cohort) as first-line treatment in two analyses: 1) using 1:1 PS matching with the available covariates in NCR (age, sex, index year, stage of tumour, and WHO-PS), and 2) by adjusting models for the same variables included in the PS matching.

Only the model using PS matching for pembrolizumab compared to exclusive chemotherapy as first-line treatment passed diagnostics. A total of 3,003 patients with locally advanced or metastatic NSCLC treated with pembrolizumab (i.e. target cohort) were matched to 3,003 patients treated with chemotherapy exclusively as first-line treatment (i.e. reference or comparator cohort). The number of observed events in each cohort was 1,966 and 2,332, respectively. The HR and 95%CI estimated using Cox proportional hazards models after PS matching was 0.66 (0.62-0.70).

We additionally estimated RMST difference as a supplemental analysis. The RMST difference between chemotherapy and the target first-line therapy groups were: 6.54 months (95%CI: 5.63, 7.46) for pembrolizumab, 1.24 (-2.24, 4.72) for nivolumab, and 5.81 (-2.21, 13.84) for nivolumab and ipilimumab.

Discussion

In this study, we have provided results on the large-scale characterisation of locally advanced or metastatic NSCLC patients at the time of start of treatment and a description of treatments and treatment combinations as first-line in three European databases. Sample size constraints limited the value of CDWBordeaux and IMASIS to address objectives 2 and 3, which were only conducted in NCR.

In NCR, we were able to provide an estimation of overall survival among patients treated with chemotherapy, pembrolizumab, nivolumab, and nivolumab and ipilimumab combination as first-line therapies. Overall survival varied by treatment type, with pembrolizumab showing the highest 3-year survival rates. Differences in survival were also observed across age, sex, and PD-L1 expression, with younger patients, female sex, and those with higher PD-L1 expression generally exhibiting higher survival.

We were unable to compare overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of chemotherapy by using a target trial emulation design due to limited number of patients in IMASIS and CDWBordeaux, and the lack of information on patient history of comorbidities and medications in NCR, which did not allow for LSPS matching or negative control outcome analysis. However, in the PS matched model using only age, sex, stage of tumour, WHO-PS, and index year, pembrolizumab showed a survival benefit over chemotherapy exclusively as first-line therapy in locally advanced or metastatic NSCLC patients.

4. LIST OF ABBREVIATIONS

Abbreviation	Name
ALK	Anaplastic Lymphoma Kinase
CDM	Common Data Model
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CI	Confidence Interval
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DOI	Declaration Of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Record
EMA	European Medicines Agency
GDPR	General Data Protection Regulation
HR	Hazard Ratios
ICI	Immune checkpoint inhibitor
ICD-9-CM	International Classification of Diseases
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IRB	Institutional Review Board
LSPS	Large-scale propensity scores
NCR	Netherlands Cancer Registry
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PD-L1	Programmed Death-Ligand 1
PS	Propensity Score
PSMar	Parc Salut Mar
RMST	Restricted Mean Survival Time
ROS1	C-ros oncogene 1
SD	Standard deviation
SMD	Standardised Mean Difference

Abbreviation	Name
SNOMED	Systematized Nomenclature of Medicine
TNM	Tumour, nodes, metastasis
WHO	World Health Organisation
WHO-PS	WHO Performance Status
UICC	Union for International Cancer Control

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timeline (planned)	Timeline (actual)
Draft Study Protocol	18/01/2024	18/01/2024
Final Study Protocol	25/06/2024	February 2024
Creation of Analytical code	February-March 2024	July/September 2024
Execution of Analytical Code on the data	April/May 2024	August/October 2024
Interim Study Report	May/June 2024	29/10/2024
Draft Study Report	January 2025	05/03/2025
Final Study Report	February 2025	02/05/2025

7. RATIONALE AND BACKGROUND

Over the last decade, a better understanding of the molecular mechanism of lung cancer has led to the development of new therapies resulting in improvement in overall survival, mostly driven by advances in the treatment of non-small cell lung cancer (NSCLC) (1, 2). NSCLC has been recognised as a set of multiple diseases; therefore, numerous approved targeted therapies are now available in driver mutation positive NSCLC (2), and immunotherapies in the form of immune checkpoint inhibitor(s) (ICIs) are indicated in patients without a driver mutation (2).

The first ICIs used in treatment of lung cancer was in the form of programmed cell death ligand-1 (PD-L1) inhibitor nivolumab as second-line therapy for patients with advanced NSCLC. Randomised phase III trials showed higher objective response rate and overall survival with nivolumab compared to docetaxel in patients with advanced squamous and non-squamous NSCLC following progression on platinum-based chemotherapy (2-4). Thereafter, another PD-L1 inhibitor pembrolizumab and PD-L1 inhibitor atezolizumab were approved for the same indication, based on higher efficacy of these agents compared to docetaxel in second-line setting (2, 5, 6).

The success of ICIs in second-line settings led to their use in first-line treatment of advanced NSCLC. Several phase III clinical trials showing durable responses and improvement in overall survival with ICI or ICI plus platinum-based chemotherapy compared to chemotherapy alone have rapidly expanded first-line treatment options for patients with advanced NSCLC not harbouring sensitising EGFR mutations or ALK translocations (2). These options include pembrolizumab (7), atezolizumab (8), cemiplimab (9), nivolumab (10, 11), and durvalumab (12), which are indicated as monotherapy or in combination with other treatments and/or platinum-based chemotherapy (See **Appendix I Table 1**).

While there is evidence on the clinical efficacy of these immunotherapies, there is still uncertainty on the benefits for a more diverse patient population treated outside clinical trials (13, 14), as well as the potential differences in effectiveness by immunotherapies related to important effect modifiers (15). A better understanding of the effectiveness of these medicines in real-world settings, which is the aim of this study, can help inform health technology assessment. This is particularly important considering the high costs of these immunotherapies, their increasing widespread use and population aging coupled with high incidence in older age groups.

8. RESEARCH QUESTION AND OBJECTIVES

The **overall aim** of this study was to assess the overall survival of patients with locally advanced or metastatic NSCLC who initiate first-line treatment with selected immunotherapies (Pembrolizumab, Atezolizumab, Cemiplimab, Nivolumab, Durvalumab, Ipilimumab) and how it compares to the survival of locally advanced or metastatic NSCLC patients treated with chemotherapies as first line.

The **specific objectives** of this study were:

1) To characterise patients at the time of initiating the first-line therapy as well as to characterise treatments received by patients with locally advanced or metastatic NSCLC, including treatment combinations.

2) To estimate the overall survival rates of patients with locally advanced or metastatic NSCLC who initiated treatment with immunotherapies (Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Ipilimumab) and also with chemotherapies (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel,

gemcitabine, and vinorelbine) given **as monotherapy or in combination (as per the label) and as the first line of treatment**, regardless of treatment discontinuation or treatment switch.

3) To compare the overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of chemotherapy (reference cohort).

9. RESEARCH METHODS

9.1 Study type and study design

Table 9.1. Description of potential study types and related study designs.

Study type	Study design	Study classification
Comparative effectiveness studies	New user cohorts	Complex

At the time of launching the study, there was uncertainty around the availability of data for the specific immunotherapies that could be considered for objectives 2 and 3. To address this issue, an interim analysis was conducted to address objective 1, and the results from these analyses were used to decide the specific cohorts of immunotherapies to be included in objectives 2 and 3. In particular, sample size was the main driver to select the concrete immunotherapies for characterisation of overall survival and comparison with chemotherapies (see section 9.7 for more details).

To address objective 1, a large-scale characterisation study was performed of locally advanced or metastatic NSCLC patients at time of start of treatment. We also performed treatment pattern analysis to provide a description of treatments and treatment combinations received among these patients as first-line.

Based on results obtained for objective 1, the database and cohorts with sufficient counts were selected for a target trial emulation approach which was used to address objectives 2 and 3. The estimand of the target trial was defined as per the following attributes:

- Population: Patients with locally advanced or metastatic NSCLC.
- Treatments:
    - Pembrolizumab
    - Nivolumab
    - Nivolumab and Ipilimumab
    - Chemotherapies (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine)

  given as first line of treatment.
- Variable/outcome: overall survival, i.e. time from initiation of treatment to death from any cause.
- Summary measure: The hazard ratio was used for comparison between immunotherapy and chemotherapy treatment groups.
- Intercurrent events: treatment discontinuation and treatment switch. Both were dealt with a 'treatment policy strategy', i.e. the interest lies on effectiveness of the above treatments regardless of treatment discontinuation and treatment switch.

Based on the above attributes, the estimand (precise research question of interest) targeted with objective 3 can be described as follows: what is the hazard ratio of time to death from any cause in selected

immunotherapies given as the first line of treatment compared to chemotherapies given without chemotherapy as first line of treatment regardless of treatment discontinuation or switch?

9.2 Study setting and data sources

This study was conducted using routinely collected data from 3 databases in 3 European countries. The databases were selected based on their ability to identify patients with locally advanced or metastatic NSCLC, cancer treatments, cancer staging, and date of death. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

The selected databases from the network of data partners of DARWIN EU® were:

1. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
2. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
3. Netherlands Cancer Registry (NCR), The Netherlands

Data Selection

These databases fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for population level descriptive epidemiology while covering different regions of Europe. Detailed information on the selected data sources is described in **Table 2.1** above**Error! Reference source not found.**.

When it comes to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the Achilles tool, (16) which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, data density. Data density includes information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source), 2) measurement value distribution (i.e. min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provides more objective checks (see Section D1.3.5.2 on Complete Data Quality Assurance Package) on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of databases was based on the availability of data on the selected conditions (advanced or metastatic NSCLC), the treatments and the outcome of interest (date of death) to perform the described analyses. The DARWIN EU® portal as well as information from the onboarding documents were used to assess whether databases have information on use of treatments and indications of interest. Data within the DARWIN EU® portal is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time covered by each released database, as this can vary across different domains. To facilitate this, the *CDMOnboarding* (and *Achilles*) packages (16) contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows to get insights when data collection started, when new sources of data were added and until when data was included. In addition, at time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *CohortDiagnostics* (17) have been developed. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts and index event misclassification. Upon finalisation of the study protocol and creation of the disease cohorts of

interest by DARWIN EU Coordination Centre, this package was executed in each data sources by each data partners.

A detailed description of each database participating in this study can be found below.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymised relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry. It contains structured data related to diagnosis, procedures, drug administration, and laboratory tests and clinical annotations in a free-text format.

Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The Bordeaux University Hospital serves as the primary public health facility for the entire population of the Bordeaux metropolitan area. Additionally, it functions as a referral and expertise centre for the Nouvelle Aquitaine region. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in and out-hospital deaths). Deaths in this database have two sources. First, this database retrieves in-hospital deaths. Second, patient records are regularly linked to data from the national death registry (every six months) using probabilistic algorithms based on search engines and machine learning strategies, with satisfactory results (18). Still, some deaths could go undetected, thus producing an underestimation of the event, given that records are not matched by using a common identifier between the two data sources, such as the social security number.

Netherlands Cancer Registry (NCR), The Netherlands

The NCR compiles clinical data of all individuals newly diagnosed with cancer in the Netherlands. Cancer registration clerks register newly diagnosed cancer patients since 1989 on a national basis, with 3 million patients included. Over the past 35 years, this registry has provided clinicians and researchers with a wealth of clinical data (e.g., patient and tumour characteristics, primary treatment, outcome) on cancer patients of all ages. Specifically, it also comprises information on tumour staging (according to the TNM-classification developed and maintained by the Union for International Cancer Control (UICC)), tumour site (topography) and morphology (histology) (according to the WHO International Classification of Diseases for Oncology (ICD-O-3)), co-morbidity at diagnosis and treatment received directly after diagnosis (first line). Overall, patients are followed up for less than one year, with the exception of death which is collected any time after diagnosis. See https://iknl.nl/en for more information.

9.3 Study period

The study period was between 01/01/2016 and 31/12/2022 for the inclusion of cases. Follow-up was extended until the last date of data availability in each database.

9.4 Follow-up

The index date used for this study is specified in **Table 9.2**.

For objective 1: a minimum time of data availability of 30 days post-treatment initiation was applied to allow time to capture treatments.

For objectives 2 and 3: Participants were followed in each cohort from therapy initiation date until date of death (from any cause), loss to follow-up, end of study date, or end of data availability, whichever occurred first, in each database. A minimum of one year of potential follow-up time was required (e.g.: individuals could only be included to the study one year prior to the end of data availability).

Table 9.2. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type	Diagnosis position	Incident with respect to…
Adult patients with locally advanced or metastatic NSCLC who initiated first-line treatment with any of the therapies of interest	Date of initiation (i.e., first prescription) of the first-line treatments after diagnosis of locally advanced or metastatic NSCLC	Single entry	Incident	[-∞, ID]	IP and OT	RxNorm	N/A	Specific medication

[1] ID: index date; IP: inpatient; OT: other; N/A: not applicable.

9.5 Study population with in and exclusion criteria

Patients aged 18 years or older with locally advanced or metastatic NSCLC who initiated first-line treatment with any of the therapies of interest between 01/01/2016 and 31/12/2022 were included. For the description of treatments (objective 1), only one cohort was created including all locally advanced or metastatic NSCLC.
For objectives 2 and 3, one cohort was created for each immunotherapy treatment (target cohorts) as well as a cohort of new users of chemotherapies (comparator cohort). The specific treatment cohorts were determined based on the results from the first study objective.

Inclusion criteria

Inclusion criteria were the following:

- Patients aged 18 years or older.
- Primary diagnosis of NSCLC, including the following morphological types: adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and all subtypes.
- Initial presentation with locally advanced or metastatic disease based on AJCC/UICC TNM classification (3b or 4 stage).
- Patients with specific drug treatments for NSCLC registered within the 6 months following NSCLC diagnosis.
- A minimum of 30 days of follow-up post-diagnosis of locally advanced or metastatic NSCLC.
- For objectives 2 and 3, a minimum of one year of potential follow-up time was required, meaning that individuals were only included one year before end of data availability. This ensured a minimum time of data availability to identify outcomes.

The code lists used to identify locally advanced and metastatic NSCLC are available in Appendix I (**Table 2**). For patients with more than one TNM measurement recorded, we selected the measurement recorded closest and prior to the date of start of first-line treatment (**Figure 1**). Any TNM recorded during the first two months after the diagnosis of NSCLC was considered.

Exclusion criteria

Exclusion criteria were the following:

- Primary diagnosis of small-cell lung cancer.
- Stage 1-3a lung cancer.
- Any cancer diagnosis (except non-melanoma skin cancer or except lung cancer in the prior 2 months) prior to date of NSCLC diagnosis.
- Patients with no drug treatment registered within the 6 months following NSCLC diagnosis

Operational definitions of Inclusion and Exclusion Criteria are provided in **Tables 9.3** and **9.4.**

Table 9.3. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
Age	Age in years defined by (time 0 – year of birth)/365	Before index date	N/A	N/A	Years	N/A	All individuals within the selected databases
Locally advanced or metastatic NSCLC	See definition of locally advanced, metastasis and NSCLC in section 9.5	Before index date	2016-2022	IP and OT	SNOMED and TNM	N/A	
Initiation of immunotherapy	Pembrolizumab, nivolumab, atezolizumab, cemiplimab, durvalumab, ipilimumab	At and after index date	At index and within 6 months post index	IP and OT	RXNorm	N/A	
Initiation of chemotherapy	Cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine	At and after index date	At index and within 6 months post index	IP and OT	RXNorm	N/A	
Minimum time period	A minimum period of 30 days post-diagnosis of locally advanced or	It is counted after diagnosis of locally	30 days	IP and OT	N/A	N/A	All individuals within the selected databases

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
	metastatic NSCLC was applied to allow time to capture treatments	advanced or metastatic NSCLC					
Minimum potential follow-up time	Only participants with a treatment initiated one year prior to end of data availability in the database were included	After index date	1 year	IP and OT	N/A	N/A	All individuals within the selected databases

[1] IP = inpatient, OT = other, n/a = not applicable

Table 9.4. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
History of cancer diagnosis	Patients were excluded if they had a diagnosis of small cell lung cancer or another primary tumour prior to their NSCLC diagnosis	Before index date	Any time prior to locally advanced or metastatic NSCLC diagnosis	IP and OT	SNOMED	N/A	All study population

[1] IP = inpatient, OT = other, n/a = not applicable

9.6 Variables

9.6.1 Exposure

Initiation of the following first-line treatments (index date) after diagnosis of locally advanced or metastatic NSCLC given as monotherapy or in combination (as per the label) and as first line of treatment, regardless of treatment discontinuation or treatment switch: pembrolizumab, nivolumab, atezolizumab, cemiplimab, durvalumab, ipilimumab, and chemotherapy alone (cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine). The code lists for all exposures are available in **Appendix I**.

The drug treatment of cancer is usually based on the administration of more than one antineoplastic drug administered during a time-frame of a theoretical maximum of 21 days (i.e., one treatment cycle) repeated over several cycles, and is considered as the first-line treatment regimen. However, hospital-based databases rarely record first-line regimens as such, making it difficult to ascertain the initial treatment regimen from treatment switches or modifications due to disease progression. In turn, when first-line treatment is not recorded as such within databases, we defined first-line treatment regimens as all treatments that were started between the first treatment day (index date) and including all additional therapies started within the following 42 days (which is the time for two cycles of standard chemotherapy to be completed, and after which the initial assessment of treatment effect is usually performed) (See **Figure 1**). Only treatments initiated within 6 months of initial NSCLC diagnosis were considered.

Operational definitions of exposures are provided in **Table 9.5.**

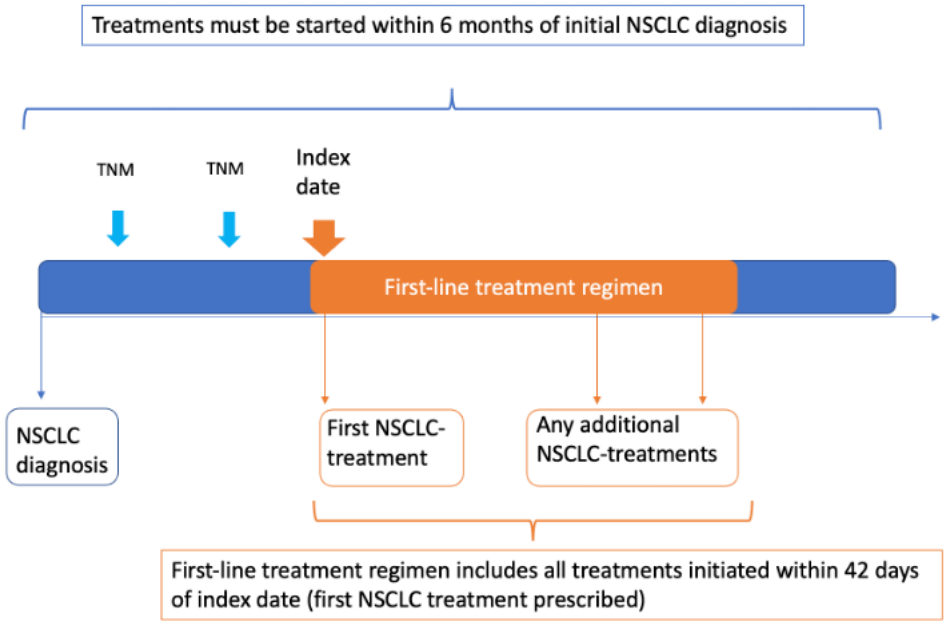


Figure 1. Timeline from NSCLC diagnosis to index date, and first-line treatment definition.

Table 9.5. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to…
Immunotherapies cohorts	The code lists provided in Table 3 of Appendix I	N/A	At index and 42 days post index date	IP and OT	RxNorm	N/A	All study population	Locally advanced or metastatic NSCLC
Chemotherapies cohorts	The code lists provided in Table 3 of Appendix I	N/A	At index and 42 days post index date	IP and OT	RxNorm	N/A	All study population	Locally advanced or metastatic NSCLC

[1] IP = inpatient, OT = other, n/a = not applicable

9.6.2 Outcome

The primary outcome of interest was overall survival, estimated from start of first-line treatment for locally advanced or metastatic NSCLC, and calculated based on date of death (**Table 9.6**). Individuals contributed to survival time as per the follow-up described in section 9.4.

Table 9.6. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations:
Overall survival	Overall survival since date of start of first-line treatment	Yes	Time to event	N/A	IP and OP	Date of Death	N/A	All study individuals

[1] IP = inpatient, OT = other, n/a = not applicable

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Demographics: age at the index date following the first treatment for locally advanced or metastatic NSCLC and sex (male/ female) were described. The following age grouping was used: 18-64; 65-80; 80 or over.

Health conditions: history of the co-morbidities was identified over four time periods: 1) 30 days prior to one day before index date, 2) 365 days prior to 31 days before index date, 3) all available days observed up to one day prior to index date, and 4) at index date.

Medications: pre-existing medication use was identified using different time windows defined as: 1) 365 days to 31 days prior to index date, 2) 30 days to 1 day prior to index date, 3) at index date, 4) 1 to 30 days post-index, 5) 1 to 90 days post-index, and 6) 1 to 365 days post-index date.

Other information: Eastern Cooperative Oncology Group (ECOG)/WHO Performance Status (WHO-PS, concept_ids 4190931, 4161577, 4161578, 4162590, 4161579) and programmed death-ligand 1 (PD-L1) expression (concept_id 718584) at index date was available in NCR only.

Operational definitions of covariates are provided in **Table 9.7.**

Table 9.7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations
Demographics	Age at index date and sex		Numeric, binary	At index date [0]	IP and OT	N/A	All study population
Health conditions	Conditions prior to index date		Binary	[-365,-31], [-30 –1], All history prior to index date At index date [0]	IP and OT	SNOMED	
Medication use	Drug prescriptions prior to index date		Binary	[-365,-31], [-30 –1] At index date [0] [1-30] [1-90] [1-365]	IP and OT	RxNorm	
Other information	ECOG/WHO Performance Status and PD-L1 expression which are available in NCR only	Categorical, binary	At NSCLC diagnosis	IP and OT	N/A	N/A	

[1] IP = inpatient, OT = other, n/a = not applicable

9.7 Study size

For each database, all individuals satisfying the eligibility criteria for a study cohort were included.

For objective 1, which is descriptive, no sample size calculation was performed. Based on exploratory feasibility counts, the total number of subjects with lung cancer across the three data sources was expected at 253,000 subjects.

For objective 3, **Table 9.8** provides some information on the precision (based on the width of the 95% confidence intervals (CI)) for the effect size comparing treatment groups for mortality. Because there is no closed-form sample size formula available related to the width of a CI for a hazard ratio (HR), calculations were done for the mortality rate ratio (MRR) as proxy for the HR. These calculations were based on assumptions of a MRR comparing immunotherapy versus chemotherapy of 0.74 (19) and a more conservative MRR of 0.85 which might be expected in real-world data. With a median survival in the chemotherapy group of 1.17 years (14 months) and assuming an exponential distribution of survival times, the mortality rate (MR) in the chemotherapy group was set to 0.59. The relative precision was defined as the difference between the upper limit of the 95% CI of the MRR and the estimated MRR, as percentage of the estimated MRR. Person-years needed in the immunotherapy group were calculated (20) and subsequently numbers of deaths. The sample size needed for the immunotherapy group was calculated based on participants surviving contributing on average 2.5 years of follow-up and participants dying contributing on average 1.42 years (17 months) of follow-up. The total sample size needed was twice the sample size in the immunotherapy group because the two comparison groups would be of equal size, as a result of the 1:1 PS matching.

The numbers found for objective 1 were used to assess the feasibility of establishing the comparison groups.

Table 9.8. Sample size needed for different levels of precision for assumed mortality rate ratios (MRR).

Mortality Rates			95% CI			Relative precision (%)	Person-years in immuno	Deaths in immuno	Sample size in immuno	Sample size total
Assumed MRR	Chemotherapy	Immunotherapy	Lower limit	Upper limit	Ratio					
0.74	0.59	0.44	0.70	0.78	1.12	5.7	4,923	2,164	2,907	5,814
0.74	0.59	0.44	0.65	0.84	1.30	13.8	904	397	534	1,068
0.74	0.59	0.44	0.60	0.91	1.52	23.3	346	152	205	410
0.74	0.59	0.44	0.55	1.00	1.81	34.5	173	76	103	206
0.85	0.59	0.51	0.80	0.90	1.13	6.3	3,829	1,934	2,370	4,740
0.85	0.59	0.51	0.75	0.96	1.28	13.3	898	453	556	1,112
0.85	0.59	0.51	0.70	1.03	1.47	21.4	373	188	231	462
0.85	0.59	0.51	0.65	1.11	1.71	30.8	196	99	122	244

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a simulated set of patients and quality control checks were performed. These quality control checks examined the efficiency of the code and the plausibility of the generated results. After all the tests were passed, the final study code was released in the version-controlled Study Repository for execution against all the participating data sources. Study code for objectives 2 and 3 was only executed in NCR. The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the results. The study results of all data sources were checked after they were made available to the DARWIN EU® Coordination Centre. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical methods

All analyses were conducted separately for each database and carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

First, we ran Cohort Diagnostics to evaluate data availability and data quality in terms of identification of locally advanced or metastatic NSCLC as well as recording of cancer treatments of interest.

Before sharing the study package (study code to run), test runs of the analytics were performed on simulated data and quality control checks were performed. After all the tests were passed (see section 10 Quality Control), the final package was released in a version-controlled study repository for execution against all the participating data sources.

Data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the default aggregated results. Results were then made available to the Principal Investigators and study team in a secure online repository (Data Transfer Zone). All results were locked and timestamped for reproducibility and transparency.

A minimum cell count of 5 was used when reporting results, with any smaller counts between 1 and 4 reported as “<5” to comply with the database’s privacy protection regulations. All analyses were performed by database, overall and stratified by age and sex when possible (minimum cell count reached). Results from objective 1 were further stratified by calendar year, when possible.

9.9.1 Main summary measures

For each analysis, summary descriptive analyses were conducted including age, sex, key variables for matching and conditions and medication pre-index date for characterisation.

9.9.2 Main statistical methods

The analyses in this study were in line with the D1.3.8.1 Draft Catalogue of Data Analysis, for a Comparative Effectiveness Study, as shown in **Table 9.9.**

Table 9.9. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Comparative Effectiveness Studies	Complex	New cohort design: - Large-scale characterisation of participants in the target and comparator cohorts - Large-scale propensity scores (LSPS) estimated - Incidence rate/s of each of the outcomes of interest in the target and comparator cohorts - Diagnostic/s: Covariate balance, Equipoise, residual confounding/systematic error (optional) - Rate Ratios or Hazard Ratio/s and 95% confidence intervals using Poisson or Cox models, respectively

Objective 1: To characterise patients at the time of initiating the first-line therapy as well as to characterise treatments received by patients with locally advanced or metastatic NSCLC, including treatment combinations and sequences.

Large-scale patient-level characterisation was conducted (objective 1). Age and sex at the time of NSCLC diagnosis were described for each generated study cohort. The index date was the date of first-line treatment initiation for NSCLC, following each patient's initial diagnosis of locally advanced or metastatic NSCLC. Medical history was assessed for any time –and up to 1 day before the index date, between 365 to 31 days before the index date, between 30 to 1 day before the index date, and at the index date. Medication use history was reported for the period between 365 and 31 days before the index date, between 30 and 1 day before, and at the index date. We also reported medication use for 1 to 30, 1 to 90, and 1 to 365 days post-index date. These time windows were defined based on the options currently available in the standard analytical tools that were used for this project. Covariates presented in the summary baseline characteristics table were pre-defined as described in section 9.6.3. and **Table 9.7**. When sample size allowed, results were further stratified by calendar year to describe treatments before and after approval of immunotherapies (year 2017).

The number and percentage of patients receiving each of the pre-specified NSCLC treatment/s as monotherapy/combinations were described at index date and including all treatments up to 42 days following index date, representing the first-line treatment.

The results from this objective were used to inform and evaluate sample size and feasibility of conducting objectives 2 and 3.

Objective 2: To estimate the overall survival rates of patients who initiated treatments of interest given as monotherapy or in combination and as first line of treatment, regardless of treatment discontinuation or treatment switch.

Overall survival from the time of therapy initiation was estimated for each study cohort using data on time at risk of death from any cause and the Kaplan-Meier method. Results were reported as plots of the estimated survival curves as well as the overall and median estimated probability of survival with 95% confidence intervals (95%CI) at years 1, 2 and 3. When sample size allowed, results were stratified by histology and PD-L1 expression (in NCR only), in addition to age groups and sex.

We also estimated restricted mean survival time (RMST) in the different treatment cohorts. The RMST was calculated restricted to the first 4 years after initiating first-line therapy. The RMST was estimated using the *survfit* and *summary.survfit* functions from the *survival* package in R to compute the area under the Kaplan-Meier curve.

Objective 3: To compare the overall survival under each immunotherapy to that of chemotherapy (reference cohort).

The analysis results for objective 1 provided additional information to inform the feasibility and extent of analysis for objective 3. We used a propensity score-matched cohort design, where target and comparator cohort participants were matched to 1:1 based on propensity scores. Propensity score matching was conducted using nearest neighbour matching with a calliper width of 0.2.

Propensity scores were estimated as the probability of exposure to the selected immunotherapy (target cohort) conditional on all covariates available in NCR which included: age, sex, stage of tumour, WHO-PS (21). Propensity scores were estimated using Lasso regression. Hazard Ratios (HR) and 95%CI were estimated using Cox proportional hazards models comparing the selected immunotherapy vs chemotherapies cohorts after PS matching. All time at risk of patients in the cohorts was used regardless of treatment discontinuation and switch. An additional analysis was conducted using multivariate adjustment by the available covariates instead of PS matching. Kaplan-Meier plots were used to summarise survival over time. Log-log plots were visually inspected to identify potential violation of the proportional hazards assumption and were reported.

In this study, we applied a comprehensive set of diagnostics before running the comparative effectiveness analysis. The covariate balance between treatment groups was assessed using standardised mean differences (SMD) (22). A threshold of maximum SMD < 0.1 was applied to both covariate and shared covariate balance to ensure comparable characteristics across groups. To evaluate the feasibility of non-randomized comparisons, we assessed empirical equipoise using the preference score approach (23), which identifies treatment settings where alternative therapies are used as if interchangeably in routine practice. A threshold of 20% within a preference range of 0.3 to 0.7 indicated sufficient overlap in treatment assignment. We adopted a lower empirical equipoise threshold (20% of subjects having propensity scores between 0.3 and 0.7) due to the limited available covariates for propensity score matching. Typically, in observational studies, an empirical equipoise threshold of at least 50% would be preferred. However, given the limited variable availability, achieving higher empirical equipoise was practically infeasible; the actual empirical equipoise proportion was reported along with the results and considered in the limitations. Finally, to assess generalizability, we compared the distribution of baseline covariates before and after propensity score adjustment using the standardised mean difference (SMD) as the primary metric (24). A threshold SMD of < 1 was used to define adequate generalizability. Only results that satisfied all diagnostic criteria - including thresholds for covariate balance, equipoise, and generalizability - were reported.

A supplementary analysis was performed to estimate the difference in RMST between first-line therapy groups. For this analysis we used the same matched cohorts generated in the cohort analysis. The RMST difference was estimated using *rmst_two_arm* function of the *simitrial* package in R.

9.9.3 Missing values

Methods for characterisation implicitly assume missing data on patient demographic and clinical characteristics occurred completely at random.

For objectives 2 and 3, individuals who were lost to follow-up prior to the end of the study period were non-administratively censored. The methods employed in the analyses implicitly assume censoring occurred at random.

9.9.4 Sensitivity analysis

No sensitivity analysis was performed.

10. DATA MANAGEMENT

10.1 Data management

All databases were previously mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and returned the results set, which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from EU member states processed personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

The output files were stored in the DARWIN Digital Research Environment (DRE). These output files did not contain any data that allowed identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining metastatic or locally advanced NSCLC, a systematic search of possible codes for inclusion were identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and queries the vocabulary tables of the OMOP CDM to find potentially relevant codes. The codes returned were then reviewed by clinical epidemiologists to consider their relevance. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a consideration of the validity of the defined study cohorts in each of the included databases and inform decisions around whether multiple definitions were required.

The study code was based on four R packages previously developed to (1) characterise demographic characteristics of study cohorts (PatientProfiles;https://cran.r-project.org/web/packages/PatientProfiles/index.html), (2) characterise treatments received by patients and their sequences (TreatmentPatterns; https://CRAN.R-project.org/package=TreatmentPatterns), (3) estimate the overall survival rates of patients who initiate different treatments (CohortSurvival; https://CRAN.R-project.org/package=CohortSurvival), and (4) estimate differences in overall survival between the different study cohorts (CohortMethod; https://ohdsi.github.io/CohortMethod/). These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

12. RESULTS

All results are available in a web application (“Shiny app”) at https://data.darwin-eu.org/EUPAS1000000112/Characterisation/ and https://data.darwin-eu.org/EUPAS1000000112/Survival/.

12.1 Study population

Table 12.1 shows the number of individuals with locally advanced or metastatic NSCLC included in the study across the three databases. We identified 1,229, 321 and 38,957 patients with locally advanced or metastatic NSCLC with no prior history of cancer in CDWBordeaux, IMASIS, and NCR, respectively. From these, 10%, 51%, and 38% were treated with chemotherapy and/or immunotherapy as first-line within the study period, respectively.

Table 12.1. Number of individuals with locally advanced or metastatic NSCLC included in the study, by database.

	CDWBordeaux	IMASIS	NCR
Qualifying initial records[1]	4,956	772	76,374
NSCLC stage 3b and above	1,952	417	45,454
No prior history of cancer	1,229	321	38,957
Any selected treatments started within 6 months of advanced or metastatic NSCLC diagnosis	123	164	14,936

[1] Refers to age (>=18), study period for patient inclusion (2016-2022), and NSCLC diagnosis. CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR=Netherlands Cancer Registry; NSCLC = non-small cell lung cancer.

12.2 Patient characteristics

Table 12.2 shows the demographic characteristics of the study population that started cancer treatment across the three databases. Male predominance was observed across all databases, ranging between 55.3% (NCR) and 76.2% (IMASIS). The median age was similar across databases, ranging from 63 (IMASIS) to 66 (NCR) years. By age group, in CDWBordeaux and IMASIS, most patients were within the 18-64 age group (56.1% and 53.0%, respectively), while in NCR, 52.5% fell within the 65-79 age group.

Table 12.2. Demographic characteristics of individuals with locally advanced or metastatic NSCLC undergoing selected treatments, by database.

		CDWBordeaux (N=123)	IMASIS (N=164)	NCR (N=14,936)
Female	N (%)	44 (35.8%)	39 (23.8%)	6,673 (44.7%)
Male	N (%)	79 (64.2%)	125 (76.2%)	8,263 (55.3%)
Age	Median [Q25 - Q75]	64 [58 - 71]	63 [56 - 71]	66 [60 - 72]
	Mean (SD)	64.03 (10.32)	63.46 (9.81)	65.73 (9.25)
	Range	40 - 88	39 - 84	22 - 95
Age group				
18-64	N (%)	69 (56.1%)	87 (53.0%)	6,344 (42.5%)
65-79	N (%)	44 (35.8%)	69 (42.1%)	7,838 (52.5%)
>=80	N (%)	10 (8.1%)	8 (4.9%)	754 (5.0%)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR = Netherlands Cancer Registry; SD = standard deviation.

Table 12.3 summarises the demographic characteristics of individuals by WHO Performance Status (WHO-PS) in NCR. The total number of subjects in each group decreased with increasing WHO-PS, and 89.1% of individuals had a PS 1 or PS 0. Male predominance was observed across all groups, highest in WHO-PS 3 (58.5%). Median age increased slightly with increasing WHO-PS, going from 65 years in WHO-PS 0 to 67 years in WHO-PS 3.

Table 12.3. Demographic characteristics of individuals with locally advanced or metastatic NSCLC undergoing selected treatments, by WHO Performance Status (PS) in NCR.

Variable	Estimate	WHO-PS 0	WHO-PS 1	WHO-PS 2	WHO-PS 3
Number subjects	N	5,245	5,988	1,217	217
Female	N (%)	2,379 (45.4%)	2,598 (43.4%)	548 (45.0%)	90 (41.5%)
Male	N (%)	2,866 (54.6%)	3,390 (56.6%)	669 (55.0%)	127 (58.5%)
Age	Median [Q25 - Q75]	65 [59 - 71]	67 [61 - 73]	68 [61 - 74]	67 [59 - 73]
Age group					
18-64	N (%)	2,475 (47.2%)	2,342 (39.1%)	411 (33.8%)	95 (43.8%)
65-79	N (%)	2,567 (48.9%)	3,299 (55.1%)	718 (59.0%)	111 (51.2%)
>=80	N (%)	203 (3.9%)	347 (5.8%)	88 (7.2%)	11 (5.1%)

NCR = Netherlands Cancer Registry; WHO-PS = World Health Organization performance status.

Table 12.4 shows the demographic characteristics of the study population across the three databases in those who started chemotherapy and/or immunotherapy. In IMASIS and NCR, the chemotherapy and immunotherapy groups had a similar distribution in terms of sex and age. In CDWBordeaux, the chemotherapy group had a higher percentage of males (64.0%) compared to the immunotherapy group (55.3%).

Across all WHO-PS categories in NCR, distribution by sex was similar in both treatment groups, with a slightly higher median age among immunotherapy-treated compared to chemotherapy in the WHO-PS 2 and 3 (**Table 12.5**). Overall, the distribution of WHO-PS levels was similar between treatment groups, with similar proportions of patients in each category.

Table 12.4. Demographic characteristics of individuals with locally advanced or metastatic NSCLC undergoing selected treatments by database and treatment type (chemotherapy/immunotherapy*).

		CDWBordeaux (N=123)		IMASIS (N=164)		NCR (N=14,936)	
Variable	**Estimate**	**Chemotherapy***	**Immunotherapy***	**Chemotherapy***	**Immunotherapy***	**Chemotherapy***	**Immunotherapy***
Number subjects	N	100	47	123	93	11,968	9,287
Female	N (%)	36 (36.00%)	21 (44.68%)	31 (25.20%)	25 (26.88%)	5,262 (43.97%)	4,209 (45.32%)
Male	N (%)	64 (64.00%)	26 (55.32%)	92 (74.80%)	68 (73.12%)	6,706 (56.03%)	5,078 (54.68%)
Age	Median [Q25 - Q75]	64 [58 - 70]	64 [58 - 70]	63 [56 - 70]	63 [58 - 72]	66 [59 - 72]	66 [60 - 73]
	Mean (SD)	63.87 (9.59)	63.28 (11.34)	62.92 (9.85)	64.77 (9.41)	65.31 (9.20)	65.72 (9.31)
	Range	41 to 82	40 to 88	39 to 84	41 to 84	22 to 92	22 to 95
Age group							
18-64	N (%)	56 (56.00%)	29 (61.70%)	65 (52.85%)	50 (53.76%)	5,274 (44.07%)	3,918 (42.19%)
65-79	N (%)	38 (38.00%)	14 (29.79%)	53 (43.09%)	36 (38.71%)	6,190 (51.72%)	4,884 (52.59%)
>=80	N (%)	6 (6.00%)	-	5 (4.07%)	7 (7.53%)	504 (4.21%)	485 (5.22)
Observation time post-index (days)							
	Median [Q25-Q75]	124 [86 - 239]	93 [76 - 202]	483 [214 - 830]	427 [162 - 776]	293 [132 - 607]	298 [123 - 622]
	Mean (SD)	363.60 (587.65)	295.66 (472.41)	667.59 (618.89)	556.78 (521.78)	447.49 (443.01)	439.50 (420.81)
	Range	60 to 2,487	61 to 2,260	17 to 2,574	5 to 2,429	0 to 2,548	0 to 2,413

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR=Netherlands Cancer Registry.

* Categories are not mutually exclusive as a patient might be prescribed with both therapies concurrently.

Table 12.5. Demographic characteristics of individuals with locally advanced or metastatic NSCLC undergoing selected treatments by WHO Performance Status (PS) and stratified by treatment (chemotherapy/immunotherapy*) in NCR.

		WHO-PS 0		WHO-PS 1		WHO-PS 2		WHO-PS 3	
Variable	**Estimate**	**Chemotherapy***	**Immunotherapy***	**Chemotherapy***	**Immunotherapy***	**Chemotherapy***	**Immunotherapy***	**Chemotherapy***	**Immunotherapy***
Number subjects	N	4,310	3,288	4,723	3,905	897	728	148	140
Female	N (%)	1,929 (44.76%)	1,512 (45.99%)	2,000 (42.35%)	1,709 (43.76%)	395 (44.04%)	327 (44.92%)	62 (41.89%)	60 (42.86%)
Male	N (%)	2,381 (55.24%)	1,776 (54.01%)	2,723 (57.65%)	2,196 (56.24%)	502 (55.96%)	401 (55.08%)	86 (58.11%)	80 (57.14%)
Age	Median [Q25 - Q75]	65 [59 - 71]	65 [59 - 71]	67 [60 - 73]	67 [60 - 73]	67 [61 - 73]	69 [62 - 75]	64 [58 - 72]	67 [59 - 74]
	Mean (SD)	64.54 (9.23)	64.52 (9.27)	66.08 (8.99)	66.43 (9.11)	66.45 (9.34)	67.81 (9.38)	64.51 (9.43)	66.29 (9.77)
	Range	23 to 92	23 to 92	22 to 89	31 to 95	24 to 90	37 to 90	38 to 86	36 to 84
Age group									
18-64	N (%)	2,057 (47.73%)	1,569 (47.72%)	1,925 (40.76%)	1,535 (39.31%)	330 (36.79%)	235 (32.28%)	74 (50.00%)	55 (39.29%)
65-79	N (%)	2,099 (48.70%)	1,599 (48.63%)	2,563 (54.27%)	2,136 (54.70%)	517 (57.64%)	437 (60.03%)	71 (47.97%)	74 (52.86%)
>=80	N (%)	154 (3.57%)	120 (3.65%)	235 (4.98%)	234 (5.99%)	50 (5.57%)	56 (7.69%)	-	11 (7.86%)
Observation time post-index (days)									
	Median [Q25 - Q75]	370 [175 - 737]	375 [172 - 724]	274 [129 - 556]	277 [117 - 578]	161 [65 - 355]	181 [61 - 396]	120 [50 - 257]	111 [49 - 250]
	Mean (SD)	521.69 (465.16)	505.46 (434.92)	415.35 (407.80)	412.24 (399.07)	281.94 (330.00)	313.35 (362.98)	220.81 (315.99)	224.15 (313.35)
	Range	0 to 2,548	0 to 2,313	1 to 2,394	1 to 2,364	1 to 2,043	1 to 1,854	4 to 2,297	4 to 1,986

NCR = Netherlands Cancer Registry; WHO-PS = World Health Organization performance status.

* Categories are not mutually exclusive as a patient might be prescribed with both therapies concurrently.

12.2.1 Large-scale characterisation of treated patients

Period anytime to 1 day prior to the index date (presented for conditions only)

In **Table 12.6** we describe the top 10 conditions recorded during the period ranging from anytime to 1 day prior to the index date (date of start of first treatment) in CDWBordeaux and IMASIS. No results are presented for NCR since data on the prior history of comorbidities and treatments are not recorded in this database.

In CDWBordeaux (N=123) and IMASIS (N=164), entries directly reflecting malignancy diagnosis of NSCLC were the most frequent. Entries not directly related to the malignancy diagnosis for CDWBordeaux were tobacco dependence in remission in 51.22% of individuals. Other conditions included cough (44.72%), dyspnoea (51.22%) and fatigue (43.9%). In IMASIS, entries not directly related to the malignancy diagnosis included essential hypertension (32.93%), COVID-19 (26.83), and tobacco dependence syndrome (23.17%).

Table 12.6. Number and % of ten most frequently recorded conditions (anytime to 1 day) prior to index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Primary adenocarcinoma of lung	87 (70.73)	Primary malignant neoplasm of respiratory tract	119 (72.56)
Malignant adenomatous neoplasm	86 (69.92)	Essential hypertension	54 (32.93)
Dyspnea	63 (51.22)	Malignant neoplasm of upper lobe of lung	49 (29.88)
Tobacco dependence in remission	63 (51.22)	Adenocarcinoma, NOS, of upper lobe, lung	48 (29.27)
Primary malignant neoplasm of respiratory tract	61 (49.59)	COVID-19	44 (26.83)
Cough	55 (44.72)	Tobacco dependence syndrome	38 (23.17)
Fatigue	54 (43.9)	Hyperlipidaemia	33 (20.12)
General problem AND/OR complaint	52 (42.28)	Nicotine dependence	33 (20.12)
Secondary malignant neoplasm of bone	50 (40.65)	Carcinoma, NOS, of upper lobe, lung	28 (17.07)
Anaemia in neoplastic disease	47 (38.21)	Neoplasm of intrathoracic lymph nodes	21 (12.8)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.
* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.

Period 365 to 31 days prior to the index date

In **Table 12.7** we describe the top 10 conditions recorded during the period ranging from 365 to 31 days prior to the index date (date of start of first treatment) in CDWBordeaux and IMASIS. No results are presented for NCR since data on the prior history of comorbidities and treatments are not recorded in this database.

In CDWBordeaux (N=123) and IMASIS (N=164), entries directly reflecting malignancy diagnosis of NSCLC were also the most frequent. Entries not directly related to the malignancy diagnosis for CDWBordeaux were tobacco dependence in remission, affecting 30.8% of individuals. Other notable conditions included abnormal findings on diagnostic imaging of the lung (29.8%), cough (27.9%),

and dyspnoea (27.9%). In IMASIS, entries not directly related to the malignancy diagnosis included essential hypertension (15.7%), nicotine dependence (14.5%), and hyperlipidaemia (13.8%). Notably, in IMASIS, COVID-19 was reported in 12.6% of individuals.

Table 12.7. Number and % of ten most frequently recorded conditions (365 to 31 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Malignant adenomatous neoplasm	42 (40.38)	Primary malignant neoplasm of respiratory tract	69 (43.4)
Primary adenocarcinoma of lung	38 (36.54)	Essential hypertension	25 (15.72)
Tobacco dependence in remission	32 (30.77)	Nicotine dependence	23 (14.47)
Primary malignant neoplasm of respiratory tract	32 (30.77)	Hyperlipidaemia	22 (13.84)
Abnormal findings on diagnostic imaging of lung	31 (29.81)	Malignant neoplasm of upper lobe of lung	22 (13.84)
Cough	29 (27.88)	Adenocarcinoma, NOS, of upper lobe, lung	21 (13.21)
Dyspnoea	29 (27.88)	COVID-19	20 (12.58)
Primary malignant neoplasm of lung	25 (24.04)	Pleural effusion	13 (8.18)
Essential hypertension	24 (23.08)	Neoplasm of intrathoracic lymph nodes	13 (8.18)
Tobacco dependence, continuous	23 (22.12)	Tobacco dependence syndrome	12 (7.55)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.
* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.

Table 12.8 presents the top ten most frequently prescribed medications during the 365 to 31 days prior the start of treatment (index date). This was only available in CDWBordeaux and IMASIS. In CDWBordeaux, the most frequently prescribed medication was acetaminophen as oral formulation (42.3%), followed by enoxaparin (30.8%). In IMASIS, the most prescribed medications were omeprazole (as oral formulation: 32.1% and injectable solution: 16%) and different formulations of acetaminophen. In both databases, the most commonly prescribed medications include pain relievers (e.g. tramadol, fentanyl, dipyrone), and drugs used for anxiety (e.g., lorazepam, hydroxyzine).

Table 12.8. Number and % of ten most frequent medications prescribed (365 to 31 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Sodium 9 MG/ML Injectable Solution	45 (43.27)	omeprazole 20 MG Delayed Release Oral Capsule	51 (32.08)
acetaminophen 1000 MG Oral Tablet	44 (42.31)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	43 (27.04)
enoxaparin sodium 100 MG/ML Injectable Solution	32 (30.77)	acetaminophen 1000 MG Oral Tablet	39 (24.53)

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
acetaminophen 10 MG/ML Injection	26 (25)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	30 (18.87)
prednisolone 20 MG Disintegrating Oral Tablet	19 (18.27)	Omeprazole 40 MG Injectable Solution Box of 50	26 (16.35)
tramadol hydrochloride 50 MG Disintegrating Oral Tablet	16 (15.38)	0.4 ML Enoxaparin 100 MG/ML Prefilled Syringe [Clexane] Box of 50 by Sanofi	24 (15.09)
Glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe	16 (15.38)	2 ML Dexketoprofen 25 MG/ML Injectable Solution	23 (14.47)
hydroxyzine hydrochloride 25 MG Oral Tablet	15 (14.42)	lorazepam 1 MG Oral Tablet	21 (13.21)
lauromacrogols / Potassium / Sodium Oral Powder	15 (14.42)	dipyrone 400 MG/ML Injectable Solution	21 (13.21)
nefopam 10 MG/ML Injectable Solution	15 (14.42)	Fentanyl 0.05 MG/ML Injectable Solution	20 (12.58)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.
* Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.

Period 30 to 1 days prior to the index date

Table 12.9 presents the 10 most frequent recorded conditions observed from 31 to 1 days prior to index date, which were only available for CDWBordeaux and IMASIS. In the CDWBordeaux (N=123) and IMASIS (N=164), the most frequent diagnoses during this time window were related to NSCLC (malignancy, histopathology, and location).

In terms of entries not directly reflecting malignancy diagnosis, in CDWBordeaux, dyspnoea affected 39.8% of individuals, alongside fatigue (33.3%) and tobacco dependence in remission (37.4%). Additionally, anaemia in neoplastic disease (30.9%) and general problems or complaints (30.1%) were also frequent. In IMASIS, COVID-19 was recorded in 17.7% of the patients.

Table 12.9. Number and % of ten most frequently recorded conditions (30 to 1 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Malignant adenomatous neoplasm	72 (58.54)	Primary malignant neoplasm of respiratory tract	76 (46.34)
Primary adenocarcinoma of lung	62 (50.41)	Malignant neoplasm of upper lobe of lung	32 (19.51)
Primary malignant neoplasm of respiratory tract	50 (40.65)	COVID-19	29 (17.68)
Dyspnoea	49 (39.84)	Adenocarcinoma, NOS, of upper lobe, lung	27 (16.46)
Secondary malignant neoplasm of bone	47 (38.21)	Carcinoma, NOS, of upper lobe, lung	19 (11.59)
Tobacco dependence in remission	46 (37.4)	Adenocarcinoma, NOS, of lower lobe, lung	11 (6.71)
Fatigue	41 (33.33)	Squamous cell carcinoma, NOS, of upper lobe, lung	10 (6.1)

Primary malignant neoplasm of lung	38 (30.89)	Primary adenocarcinoma of lung	10 (6.1)
Anaemia in neoplastic disease	38 (30.89)	Primary malignant neoplasm of main bronchus	9 (5.49)
General problem AND/OR complaint	37 (30.08)	Neoplasm of intrathoracic lymph nodes	9 (5.49)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.

* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.

Medications prescribed during this time window are shown in **Table 12.10** (only available for CDWBordeaux and IMASIS). For CDWBordeaux, acetaminophen use was high (43.9%), followed by enoxaparin (39.8%). Other frequently reported medications include folic acid (35.0%) and prednisolone (31.7%). In IMASIS, the most frequently recorded medication was omeprazole (31.1%), followed by folic acid (19.5%), different formulations of acetaminophen, and lorazepam (14.0%).

Table 12.10. Number and % of ten most frequent medications prescribed (30 to 1 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Sodium 9 MG/ML Injectable Solution	60 (48.78)	omeprazole 20 MG Delayed Release Oral Capsule	51 (31.1)
acetaminophen 1000 MG Oral Tablet	54 (43.9)	folic acid 5 MG Oral Tablet	32 (19.51)
enoxaparin sodium 100 MG/ML Injectable Solution	49 (39.84)	acetaminophen 1000 MG Oral Tablet	28 (17.07)
folic acid 0.4 MG Oral Tablet	43 (34.96)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	27 (16.46)
prednisolone 20 MG Disintegrating Oral Tablet	39 (31.71)	lorazepam 1 MG Oral Tablet	23 (14.02)
vitamin B12 0.5 MG/ML Injectable Solution	32 (26.02)	morphine sulfate 10 MG/ML Injectable Solution	20 (12.2)
metoclopramide	27 (21.95)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	19 (11.59)
Sodium Chloride 9 MG/ML Inhalant Solution	26 (21.14)	0.4 ML Enoxaparin 100 MG/ML Prefilled Syringe [Clexane] Box of 50 by Sanofi	16 (9.76)
lauromacrogols / Potassium / Sodium Oral Powder	24 (19.51)	dexamethasone 4 MG Oral Tablet	15 (9.15)
glucose 50 MG/ML Injectable Solution	23 (18.7)	vitamin B12 1 MG/ML Injectable Solution	14 (8.54)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.

* Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.

Period - at the index date

Entries at the index date were present for CDWBordeaux and IMASIS, although counts were generally low for IMASIS (**Table 12.11**). In CDWBordeaux, diagnosis reflected cancer-related codes, fatigue, and tobacco dependence as the most frequent entries recorded.

Table 12.11. Number and % of ten most frequently recorded conditions at index date by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments*.

CDWBordeaux (N=123)		IMASIS (N=164)	
Most frequent entries	**n (%)**	**Most frequent entries**	**n (%)**
Malignant adenomatous neoplasm	33 (26.83)	Primary malignant neoplasm of respiratory tract	8 (4.88)
Fatigue	23 (18.7)	Primary malignant neoplasm of main bronchus	<5
Tobacco dependence in remission	21 (17.07)	Primary malignant neoplasm of supraglottis	<5
Secondary malignant neoplasm of bone	20 (16.26)	Essential hypertension	<5
Secondary malignant neoplasm of brain	19 (15.45)	Seizure	<5
Primary malignant neoplasm of lung	17 (13.82)	Concussion with no loss of consciousness	<5
Primary malignant neoplasm of respiratory tract	16 (13.01)	Hyperlipidaemia	<5
Essential hypertension	16 (13.01)	Alcohol dependence	<5
Primary malignant neoplasm of lower lobe, bronchus or lung	16 (13.01)	Cocaine dependence	<5
Secondary malignant neoplasm of intrathoracic lymph nodes	15 (12.2)	Disturbance of temperature regulation of newborn	<5

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.
* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.
A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5".

Table 12.12 shows the most frequent recorded medications at index date (date of start of cancer treatment). In CDWBordeaux, cancer-related treatments such as pemetrexed, paclitaxel, carboplatin, and pembrolizumab were commonly recorded, alongside supportive medications such as ondansetron, methylprednisolone, and folic acid. In IMASIS, pembrolizumab, cisplatin, carboplatin, and pemetrexed were the most frequently recorded cancer treatments. In NCR, the prevalence of recording for each cancer-related treatment was higher than in other databases, and the most frequently used medications were carboplatin, pembrolizumab, pemetrexed, and cisplatin.

Table 12.12. Number and % of ten most frequent medications by database in individuals with locally advanced or metastatic NSCLC undergoing selected treatments (at index date)*.

CDWBordeaux (N=123)		IMASIS (N=164)		NCR (N=14,936)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)	**Most frequent entries**	n (%)
ondansetron 8 MG Injectable Solution	48 (39.02)	4 ML pembrolizumab 25 MG/ML Injectable Solution [Keytruda] Box of 1 by Merck	63 (38.41)	carboplatin	7,909 (52.95)

pemetrexed 500 MG Injection	46 (37.4)	100 ML Cisplatin 1 MG/ML Injectable Solution Box of 1	47 (28.66)	pembrolizumab	7,788 (52.14)
methylprednisolone Injectable Solution	43 (34.96)	60 ML Carboplatin 10 MG/ML Intravenous Solution [CARBOPLATINE ACCORD] Box of 1 by Accord	43 (26.22)	pemetrexed	7,464 (49.97)
folic acid 0.4 MG Oral Tablet	43 (34.96)	20 ML pemetrexed 25 MG/ML Injectable Solution Box of 1	41 (25)	cisplatin	3,879 (25.97)
Paclitaxel 6 MG/ML Injection	41 (33.33)	50 ML Cisplatin 1 MG/ML Injectable Solution Box of 1	18 (10.98)	gemcitabine	1,555 (10.41)
aprepitant 125 MG Oral Capsule	40 (32.52)	paclitaxel	14 (8.54)	etoposide	1,152 (7.71)
Carboplatin 10 MG/ML Injection	39 (31.71)	vinorelbine 30 MG Oral Capsule [Navelbine] Box of 1 by Pierre Fabre	6 (3.66)	paclitaxel	1,134 (7.59)
Sodium 9 MG/ML Injectable Solution	38 (30.89)	10 ML nivolumab 10 MG/ML Intravenous Solution [Opdivo] Box of 1 by Bristol Myers Squibb	5 (3.05)	docetaxel	170 (1.14)
pembrolizumab 25 MG/ML Injection	36 (29.27)	levetiracetam	<5	vinorelbine	133 (0.89)
prednisolone 20 MG Disintegrating Oral Tablet	30 (24.39)	Paclitaxel 100 MG Intravenous Suspension Box of 1	<5	nivolumab	131 (0.88)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR=Netherlands Cancer Registry.
*Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.
A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5".

Post-index windows (presented for medications only)

Table 12.13 shows the top ten most frequently recorded medications in 1 to 30 days, 1 to 90 days and 1 to 365 days post-index time per database.

In CDWBordeaux, prednisolone, enoxaparin, and metoclopramide were consistently prescribed in 30-, 90- and 365-days post-index time. Other frequently used medications in all 3 windows included antiemetic agents, such as aprepitant and ondansetron, acetaminophen and folic acid.

In IMASIS, omeprazole was the most frequently prescribed drug in 30-, 90- and 365-days post-index time. Dexamethasone and acetaminophen were also commonly prescribed, with increasing prevalence in the longer time windows. Morphine and lorazepam had a high prevalence of use after the 90-day post-index

window. As for cancer-specific treatments, pembrolizumab was present in all three windows among the ten most frequent medications. Carboplatin and cisplatin were among the ten most frequent medications in the 1-30 and up to 90-day windows. Pemetrexed was only observed in the 1-30 days window.

In NCR, large-scale characterisation only displays cancer-specific treatments. For the 1-30 window, the proportion of users for any treatment was low, and carboplatin was the most frequently used medicine. The proportion of users by therapy increased with longer time windows, and pemetrexed and pembrolizumab were the most frequently used in the 1-90 days and the 1-365 days' time windows.

Table 12.13. Number and % of ten most frequent medications in individuals with locally advanced or metastatic NSCLC in 1 to 30 days, 1 to 90 days and 1 to 365 days post-index time per database*.

CDWBordeaux (N=123)					
1-30	n (%)	**1-90**	n (%)	**1-365**	n (%)
Sodium 9 MG/ML Injectable Solution	60 (48.78)	Sodium 9 MG/ML Injectable Solution	75 (60.98)	Sodium 9 MG/ML Injectable Solution	82 (66.67)
prednisolone 20 MG Disintegrating Oral Tablet	58 (47.15)	prednisolone 20 MG Disintegrating Oral Tablet	65 (52.85)	prednisolone 20 MG Disintegrating Oral Tablet	65 (52.85)
metoclopramide	47 (38.21)	enoxaparin sodium 100 MG/ML Injectable Solution	52 (42.28)	enoxaparin sodium 100 MG/ML Injectable Solution	60 (48.78)
folic acid 0.4 MG Oral Tablet	45 (36.59)	metoclopramide	49 (39.84)	glucose 50 MG/ML Injectable Solution	52 (42.28)
enoxaparin sodium 100 MG/ML Injectable Solution	44 (35.77)	glucose 50 MG/ML Injectable Solution	47 (38.21)	metoclopramide	51 (41.46)
acetaminophen 1000 MG Oral Tablet	41 (33.33)	folic acid 0.4 MG Oral Tablet	47 (38.21)	acetaminophen 1000 MG Oral Tablet	50 (40.65)
aprepitant 80 MG Oral Capsule	40 (32.52)	acetaminophen 1000 MG Oral Tablet	47 (38.21)	folic acid 0.4 MG Oral Tablet	48 (39.02)
metoclopramide 10 MG Oral Tablet	40 (32.52)	aprepitant 80 MG Oral Capsule	41 (33.33)	metoclopramide 10 MG Oral Tablet	43 (34.96)

glucose 50 MG/ML Injectable Solution	35 (28.46)	metoclopramide 10 MG Oral Tablet	41 (33.33)	aprepitant 80 MG Oral Capsule	41 (33.33)
ondansetron 8 MG Injectable Solution	34 (27.64)	ondansetron 8 MG Injectable Solution	35 (28.46)	lauromacrogols / Potassium / Sodium Oral Powder	39 (31.71)
IMASIS (N=164)					
1-30	**n (%)**	**1-90**	**n (%)**	**1-365**	**n (%)**
omeprazole 20 MG Delayed Release Oral Capsule	61 (37.2)	omeprazole 20 MG Delayed Release Oral Capsule	87 (53.05)	omeprazole 20 MG Delayed Release Oral Capsule	128 (78.05)
4 ML pembrolizumab 25 MG/ML Injectable Solution [Keytruda] Box of 1 by Merck	50 (30.49)	4 ML pembrolizumab 25 MG/ML Injectable Solution [Keytruda] Box of 1 by Merck	55 (33.54)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	91 (55.49)
dexamethasone 4 MG Oral Tablet	46 (28.05)	dexamethasone 4 MG Oral Tablet	53 (32.32)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	86 (52.44)
folic acid 5 MG Oral Tablet	37 (22.56)	acetaminophen 1000 MG Oral Tablet	47 (28.66)	acetaminophen 1000 MG Oral Tablet	84 (51.22)
fosaprepitant	37 (22.56)	60 ML Carboplatin 10 MG/ML Intravenous Solution [CARBOPLATINE ACCORD] Box of 1 by Accord	46 (28.05)	dexamethasone 4 MG Oral Tablet	74 (45.12)
60 ML Carboplatin 10 MG/ML Intravenous Solution [CARBOPLATINE	35 (21.34)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	45 (27.44)	lorazepam 1 MG Oral Tablet	68 (41.46)

ACCORD] Box of 1 by Accord					
20 ML pemetrexed 25 MG/ML Injectable Solution Box of 1	35 (21.34)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	44 (26.83)	morphine sulfate 10 MG/ML Injectable Solution	65 (39.63)
100 ML Cisplatin 1 MG/ML Injectable Solution Box of 1	33 (20.12)	folic acid 5 MG Oral Tablet	43 (26.22)	Omeprazole 40 MG Injectable Solution Box of 50	62 (37.8)
acetaminophen 1000 MG Oral Tablet	28 (17.07)	100 ML Cisplatin 1 MG/ML Injectable Solution Box of 1	41 (25)	4 ML pembrolizumab 25 MG/ML Injectable Solution [Keytruda] Box of 1 by Merck	60 (36.59)
500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	27 (16.46)	fosaprepitant	40 (24.39)	folic acid 5 MG Oral Tablet	55 (33.54)
NCR (N=14,936)					
1-30	n (%)	**1-90**	n (%)	**1-365**	n (%)
carboplatin	541 (3.62)	pemetrexed	1,268 (8.49)	pembrolizumab	2,247 (15.05)
pemetrexed	271 (1.81)	pembrolizumab	1257 (8.42)	pemetrexed	2,116 (14.17)
etoposide	242 (1.62)	carboplatin	957 (6.41)	durvalumab	1,115 (7.47)
cisplatin	220 (1.47)	durvalumab	439 (2.94)	carboplatin	1,091 (7.3)
pembrolizumab	174 (1.17)	etoposide	280 (1.87)	etoposide	294 (1.97)
docetaxel	115 (0.77)	cisplatin	269 (1.8)	cisplatin	283 (1.89)
gemcitabine	90 (0.6)	gemcitabine	166 (1.11)	docetaxel	252 (1.69)
		docetaxel	156 (1.04)	gemcitabine	204 (1.37)
		paclitaxel	74 (0.5)	nivolumab	157 (1.05)
				paclitaxel	104 (0.7)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR = Netherlands Cancer Registry.

*Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.

12.2.2 Large-scale characterisation by treatment type

This section describes large-scale characterisation on conditions and medications used in locally advanced or metastatic NSCLC by treatment type. Results are only presented for the 365 to 31 prior to index date time window for simplicity. Complete information on other windows is available in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Characterisation/).

Chemotherapy

Chemotherapy-treated patients totalled 100 in CDWBordeaux, 123 in IMASIS, and 11,968 in NCR.

Table 12.14 shows the 10 most frequently recorded conditions in CDWBordeaux and IMASIS from 365 to 31 days prior to the index date among those patients treated with chemotherapy as monotherapy or in combination with other treatments. Conditions related to the diagnosis of NSCLC were the most frequent in CDWBordeaux and IMASIS. Conditions unrelated to the malignancy for CDWBordeaux were tobacco dependence in remission and abnormal findings on diagnostic imaging of the lung, affecting each 28.6% of the patients, followed by cough (21%). In IMASIS, non-cancer-related conditions included hyperlipidaemia (16.7%), followed by COVID-19 (15.0%), and hypertension (14.2%).

Table 12.14. Number and % of ten most frequently recorded conditions (365 to 31 days prior) to index date by database in individuals with locally advanced or metastatic NSCLC treated with chemotherapy*.

CDWBordeaux (N=100)		IMASIS (N=123)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Primary adenocarcinoma of lung	32 (38.1)	Primary malignant neoplasm of respiratory tract	52 (43.33)
Malignant adenomatous neoplasm	31 (36.9)	Hyperlipidaemia	20 (16.67)
Abnormal findings on diagnostic imaging of lung	24 (28.57)	COVID-19	18 (15)
Tobacco dependence in remission	24 (28.57)	Essential hypertension	17 (14.17)
Primary malignant neoplasm of respiratory tract	23 (27.38)	Nicotine dependence	14 (11.67)
Cough	18 (21.43)	Malignant neoplasm of upper lobe of lung	12 (10)
Primary malignant neoplasm of lung	17 (20.24)	Adenocarcinoma, NOS, of upper lobe, lung	12 (10)
Dyspnoea	17 (20.24)	Tobacco dependence syndrome	11 (9.17)
Tobacco dependence syndrome	17 (20.24)	Pleural effusion	9 (7.5)
Loss of appetite	17 (20.24)	Chronic obstructive lung disease	9 (7.5)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.

* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.

Table 12.15 shows the top 10 most frequent medications recorded from 365 to 31 days prior to index date in patients treated with chemotherapy. In CDWBordeaux, the most frequently prescribed medications were different presentations of acetaminophen, enoxaparin, and prednisolone. In IMASIS, omeprazole was the

most frequently prescribed medication, followed by different formulations of acetaminophen, lorazepam, and insulin.

Table 12.15. Number and % of ten most frequent medications (365 to 31 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC treated with chemotherapy*.

CDWBordeaux (N=100)		IMASIS (N=123)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Sodium 9 MG/ML Injectable Solution	34 (40.48)	omeprazole 20 MG Delayed Release Oral Capsule	34 (28.33)
acetaminophen 1000 MG Oral Tablet	31 (36.9)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	29 (24.17)
enoxaparin sodium 100 MG/ML Injectable Solution	26 (30.95)	acetaminophen 1000 MG Oral Tablet	26 (21.67)
acetaminophen 10 MG/ML Injection	18 (21.43)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	20 (16.67)
prednisolone 20 MG Disintegrating Oral Tablet	13 (15.48)	2 ML Dexketoprofen 25 MG/ML Injectable Solution	15 (12.5)
nefopam 10 MG/ML Injectable Solution	12 (14.29)	0.4 ML Enoxaparin 100 MG/ML Prefilled Syringe [Clexane] Box of 50 by Sanofi	15 (12.5)
tramadol hydrochloride 50 MG Disintegrating Oral Tablet	12 (14.29)	lorazepam 1 MG Oral Tablet	14 (11.67)
Glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe	12 (14.29)	insulin, regular, human Injectable Solution	14 (11.67)
hydroxyzine hydrochloride 25 MG Oral Tablet	10 (11.9)	Omeprazole 40 MG Injectable Solution Box of 50	14 (11.67)
lauromacrogols / Potassium / Sodium Oral Powder	10 (11.9)	dipyrone 400 MG/ML Injectable Solution	13 (10.83)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System, NCR=Netherlands Cancer Registry.

* Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.

Immunotherapy

Immunotherapy-treated patients were 47 in CDWBordeaux, 93 in IMASIS, and 9,287 in NCR.

Table 12.16 shows the 10 most frequently recorded conditions in CDWBordeaux and IMASIS from 365 to 31 days prior to the index date among those patients treated with immunotherapy as monotherapy or in combination with other treatments. Conditions related to the diagnosis of NSCLC were the most frequent in both databases. Conditions related to the diagnosis of NSCLC were the most frequent in both databases. The four most prevalent conditions not reflecting cancer diagnosis were dyspnoea (40.0%), tobacco dependence in remission (37.5%), cough (37.5%), and abnormal findings on diagnostic imaging of the lung (29.1%) in CDWBordeaux; while in IMASIS, were COVID-19 (20.0%), and essential hypertension and nicotine dependence (18.9%), and hyperlipidaemia (12.2%).

Table 12.16. Number and % of ten most frequently recorded conditions (365 to 31 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC treated with immunotherapy*.

CDWBordeaux (N=47)		IMASIS (N=93)	
Most frequent entries	n (%)	**Most frequent entries**	n (%)
Malignant adenomatous neoplasm	21 (52.5)	Primary malignant neoplasm of respiratory tract	52 (57.78)
Dyspnoea	16 (40)	Malignant neoplasm of upper lobe of lung	23 (25.56)
Primary malignant neoplasm of respiratory tract	16 (40)	COVID-19	18 (20)
Cough	15 (37.5)	Adenocarcinoma, NOS, of upper lobe, lung	18 (20)
Tobacco dependence in remission	15 (37.5)	Essential hypertension	17 (18.89)
Primary malignant neoplasm of lung	13 (32.5)	Nicotine dependence	17 (18.89)
Primary adenocarcinoma of lung	13 (32.5)	Primary adenocarcinoma of lung	12 (13.33)
Abnormal findings on diagnostic imaging of lung	11 (27.5)	Hyperlipidaemia	11 (12.22)
Anaemia in neoplastic disease	11 (27.5)	Carcinoma, NOS, of upper lobe, lung	11 (12.22)
General problem AND/OR complaint	11 (27.5)	Neoplasm of intrathoracic lymph nodes	9 (10)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.

* Categories are not mutually exclusive as a patient might have recorded several conditions concurrently.

Table 12.17 shows the top 10 most frequent medications recorded from 365 to 31 days prior to index date in those patients treated with immunotherapy. In CDWBordeaux, different formulations of acetaminophen were the most prescribed medication, followed by enoxaparin and prednisolone. In IMASIS, omeprazole was the most frequent medication, followed by different formulations of acetaminophen. Other common medications were dexamethasone, lorazepam and dipyrone.

Table 12.17. Number and % of ten most frequent medications (365 to 31 days) prior to index date by database in individuals with locally advanced or metastatic NSCLC treated with immunotherapy*.

CDWBordeaux (N=47)		IMASIS (N=93)	
Most frequent entries*	n (%)	Most frequent entries*	n (%)
acetaminophen 1000 MG Oral Tablet	21 (52.50)	omeprazole 20 MG Delayed Release Oral Capsule	45 (50.00)
Sodium 9 MG/ML Injectable Solution	18 (45.00)	acetaminophen 1000 MG Oral Tablet	34 (37.78)

enoxaparin sodium 100 MG/ML Injectable Solution	12 (30.00)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	33 (36.67)
acetaminophen 10 MG/ML Injection	12 (30.00)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	24 (26.67)
prednisolone 20 MG Disintegrating Oral Tablet	10 (25.00)	Omeprazole 40 MG Injectable Solution Box of 50	22 (24.44)
glucose 50 MG/ML Injectable Solution	8 (20.00)	dexamethasone 4 MG Oral Tablet	20 (22.22)
lauromacrogols / Potassium / Sodium Oral Powder	8 (20.00)	dipyrone 400 MG/ML Injectable Solution	20 (22.22)
Potassium Chloride 600 MG Oral Capsule	7 (17.50)	lorazepam 1 MG Oral Tablet	19 (21.11)
metoclopramide	6 (15.00)	0.4 ML Enoxaparin 100 MG/ML Prefilled Syringe [Clexane] Box of 50 by Sanofi	19 (21.11)
aspirin 75 MG Oral Tablet	6 (15.00)	morphine sulfate 10 MG/ML Injectable Solution	18 (20.00)

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System.

* Categories are not mutually exclusive as a patient might be prescribed with several medications concurrently.

12.2.3 PD-L1 classification

Table 12.18 shows PD-L1 classification according to the ingredients received as first-line therapy in NCR. For this table, treatments are assessed at the ingredient level, regardless of whether they are administered as monotherapy or in combination.

Table 12.18. Number of patients (%) treated according to PD-L1 classification using different thresholds in NCR*.

Ingredient	Threshold 1, n(%)		Threshold 2, n(%)		Threshold 3, n(%)		
	PD-L1<1%	PD-L1 >=1%	PD-L1 <5%	PD-L1 >=5%	PD-L1 <50%	PD-L1 >=50%	No record, n(%)
Atezolizumab	52 (46.02)	61 (53.98)	58 (51.33)	55 (48.67)	77 (68.14)	36 (31.86)	0 (0)
Carboplatin	5,096 (46.65)	5,764 (52.77)	5,922 (54.22)	4,938 (45.21)	8,257 (75.59)	2,603 (23.83)	63 (0.58)
Cemiplimab	<5 (100)	0 (0)	<5 (100)	0 (0)	<5 (100)	0 (0)	0 (0)
Cisplatin	2,124 (43.6)	2,733 (56.1)	2,418 (49.63)	2,439 (50.06)	3,444 (70.69)	1,413 (29)	15 (0.31)

Docetaxel	317 (46.48)	365 (53.52)	352 (51.61)	330 (48.39)	483 (70.82)	199 (29.18)	0 (0)
Durvalumab	553 (34.61)	1,030 (64.46)	689 (43.12)	894 (55.94)	1,033 (64.64)	550 (34.42)	15 (0.96)
Gemcitabine	989 (45.6)	1,162 (53.57)	1,157 (53.34)	994 (45.83)	1,673 (77.13%)	478 (22.04)	18 (0.84)
Ipilimumab	49 (60.49)	32 (39.51)	52 (64.2)	29 (35.8)	59 (72.84)	22 (27.16)	0 (0)
Nivolumab	195 (55.71)	155 (44.29)	213 (60.86)	137 (39.14)	277 (79.14)	73 (20.86)	0 (0)
Paclitaxel	795 (49.53)	795 (49.53)	936 (58.32)	654 (40.75)	1314 (81.87)	276 (17.2%)	15 (0.94)
Pembrolizumab	2,879 (30.01)	6,700 (69.84)	3,422 (35.67)	6,157 (64.18)	4,945 (51.54)	4,634 (48.30)	15 (0.16)
Pemetrexed	4,222 (47.4)	4,670 (52.43)	4,857 (54.53)	4,035 (45.3)	6,792 (76.25)	2,100 (23.58)	15 (0.17)
Vinorelbine	45 (48.39)	48 (51.61)	48 (51.61)	45 (48.39)	64 (68.82)	29 (31.18)	0 (0)

* Percentages have been calculated for each threshold separately, considering missing values.

12.3 First-line treatments

12.3.1 Overall first-line therapies

We have identified 123, 164, and 14,936 patients with first-line therapy in CDWBordeaux, IMASIS and NCR, respectively. Results for most frequent types of first-line therapies are presented in **Table 12.19**. The most frequent first-treatment line was combination of two chemotherapies in CDWBordeaux and chemotherapy as monotherapy in IMASIS. In NCR, most frequent first-line treatments consisted of combination of two or more chemotherapy drugs and combinations of one immunotherapy drug and chemotherapy. Two immunotherapy drugs were rarely used in NCR and not used in CDWBordeaux and IMASIS.

Table 12.19. Number of patients observed in each database according to the number of treatments and treatment types observed*.

Treatment type	First-line treatments[1]	CDWBordeaux (N=123)		IMASIS (N=164)		NCR (N=14,936)	
		Minimun[1]	Maximum[2]	Minimun[1]	Maximum[2]	Minimun[1]	Maximum[2]
Chemotherapy	Monotherapy	15	18	72	75	1,312	1,322
	Two and more drugs	57	72	22	38	6,847	6,877
Immunotherapy (one drug)	One immunotherapy drug	20	26	39	45	2,992	2,992
	Two immunotherapy drugs	0	0	<5	<5	32	32

Immunotherapy with chemotherapy	One immunotherapy drug and chemotherapy	21	24	32	41	5,182	5,236
	Two immunotherapy drug and chemotherapy	0	0	0	0	32	47

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System; NCR=Netherlands Cancer Registry. *Counts were derived from the results of the description of first-line treatments (as monotherapy or combinations) shown in table 12.20. Please note that only the most frequent first-line treatments are shown in table 12.20.[1] Minimum count were calculated assuming that the number of patients in cohorts with <5 patients were equal to 1. [2] Maximum counts were calculated assuming that the number of patients in cohorts with <5 patients were equal to 4.

Results for the most frequent first-line therapies are presented in **Table 12.20**. It must be noted that treatments are recorded as unique combinations within the first 42 days of initiating therapy. First-line therapies involving a single treatment include patients who received only one treatment during this time window and do not include counts for patients who received this medication as part of a treatment combination, which is presented as separate first-line treatment. **Table 12.20** describes combinations with counts exceeding 50 patients across any of the three databases. Complete information on treatment combinations with lower counts can be found in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Characterisation/

The most frequent first-line treatments were carboplatin+paclitaxel in CDWBordeaux (n=27) and cisplatin in IMASIS (n=43). Carboplatin+pembrolizumab+pemetrexed was the most frequent first-line treatment captured in NCR (n=3,401), and the second most frequent in CDWBordeaux (n=20). Pembrolizumab was among the three most frequent treatments captured across databases (n=18 in CDWBordeaux, n=37 in IMASIS, n=2,902 in NCR).

No first-line treatments with pemetrexed (alone or in combination) were found in IMASIS. Cemipilimab was not captured as first-line treatment (alone or in combination) in any of the databases considered. Durvalumab was only captured in NCR.

Table 12.20. Most frequent first-line treatments with number of patients observed in each database.

First-line treatments[1]	CDWBordeaux	IMASIS	NCR
Carboplatin+pembrolizumab+pemetrexed	20	0	3,401
Pembrolizumab	18	37	2,902
Carboplatin+pemetrexed	17	0	1,866
Cisplatin+pemetrexed	8	0	1,325
Carboplatin+gemcitabine	<5	<5	904
Carboplatin+paclitaxel+pembrolizumab	0	5	895
Cisplatin	0	43	803
Cisplatin+pembrolizumab+pemetrexed	<5	0	559
Carboplatin	<5	12	473
Cisplatin+gemcitabine	0	<5	466
Carboplatin+cisplatin+pemetrexed	<5	0	167
Carboplatin+paclitaxel	27	11	149
Cisplatin+docetaxel	0	0	131
Carboplatin+cisplatin+pembrolizumab+ pemetrexed	0	0	85

Carboplatin+cisplatin+gemcitabine	0	0	85
Cisplatin+vinorelbine	<5	7	73
Carboplatin+cisplatin	0	<5	67

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System, NCR=Netherlands Cancer Registry. [1] Treatment combinations with total counts > 50 across any database.

Chemotherapies were the most frequently prescribed first-line treatments in CDWBordeaux and IMASIS, while in NCR, immunotherapies were more frequently prescribed as first-line treatment than chemotherapies (**Table 12.21**). Overall, pembrolizumab was the most frequently prescribed first-line immunotherapy treatment in all databases (39 to 42 patients in CDWBordeaux, 68 to 74 patients in IMASIS, and 8005 to 8044 patients in NCR), followed by nivolumab (<5 in CDWBordeaux, <5 to 12 in IMASIS, and 135 to 153 in NCR).

Table 12.21. Most frequent first-line treatments with number of patients observed in each database independently of treatment combination*.

Treatment group	CDWBordeaux		IMASIS		NCR	
	Minimun[1]	Maximum[2]	Minimun[1]	Maximum[2]	Minimun[1]	Maximum[2]
Pembrolizumab	39	42	68	74	8,005	8,044
Nivolumab	<5	<5	<5	12	135	153
Atezolizumab	0	0	<5	<5	59	71
Cemiplimab	0	0	0	0	0	0
Durvalumab	0	0	0	0	43	55
Ipilimumab	<5	<5	<5	<5	60	63
Chemotherapies	73	101	94	109	6,850	6,889

CDWBordeaux = Bordeaux University Hospital; IMASIS = Institut Municipal Assistència Sanitària Information System, NCR=Netherlands Cancer Registry. *Counts were derived from the results of the description of first-line treatments (as monotherapy or combinations) shown in table 12.20. Please note that only the most frequent first-line treatments are shown in table 12.20. The exact counts for patients in the pembrolizumab, nivolumab, nivolumab and ipilimumab, and chemotherapies are shown for NCR only in table 12.26. [1] Minimum count were calculated assuming that the number of patients in cohorts with <5 patients were equal to 1. [2] Maximum counts were calculated assuming that the number of patients in cohorts with <5 patients were equal to 4.

12.3.1 First-line therapies stratified by covariates of interest

In this section, we describe first-line therapies stratified by covariates of interest in NCR only. We have only described the most frequent line therapies (with >50 counts across stratification groups). Due to limited sample sizes, we did not report stratified results for CDWBordeaux and IMASIS. All results can be found in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Characterisation/).

Stratification by age groups

First-line treatments stratified by age groups in NCR can be found in **Table 12.22**.

Table 12.22. Most frequent first-line treatments with number of patients observed in NCR stratified by age groups.

First-line treatments	17-65 years	65-79 years	80+ years
Carboplatin+pembrolizumab+pemetrexed	1,655	1,661	95
Pembrolizumab	1,163	1,540	199
Carboplatin+pemetrexed	806	991	74
Cisplatin+pemetrexed	824	485	18
Carboplatin+gemcitabine	254	577	73
Carboplatin+paclitaxel+pembrolizumab	330	534	38
Cisplatin	468	320	15
Cisplatin+pembrolizumab+pemetrexed	358	199	<5
Cisplatin+gemcitabine	205	259	9
Carboplatin	192	262	12
Carboplatin+cisplatin+pemetrexed	97	79	0
Carboplatin+paclitaxel	80	68	<5
Cisplatin+docetaxel	61	66	<5
Carboplatin+cisplatin+gemcitabine	38	52	<5
Carboplatin+cisplatin+pembrolizumab+ pemetrexed	54	32	<5
Cisplatin+vinorelbine	43	30	0
Carboplatin+cisplatin	25	42	0

NCR=Netherlands Cancer Registry.

Stratification by sex

Counts of most frequent first-line treatments stratified by sex in NCR can be found in **Table 12.23**.

Table 12.23. Most frequent first-line treatments with number of patients observed in NCR stratified by sex.

First-line treatments[1]	Females	Males
Carboplatin+pembrolizumab+pemetrexed	1,609	1,802
Pembrolizumab	1,369	1,533
Carboplatin+pemetrexed	882	989
Cisplatin+pemetrexed	665	661
Carboplatin+gemcitabine	294	615
Carboplatin+paclitaxel+pembrolizumab	272	626

Cisplatin	367	436
Cisplatin+pembrolizumab+pemetrexed	271	293
Cisplatin+gemcitabine	163	310
Carboplatin	202	264
Carboplatin+cisplatin+pemetrexed	97	78
Carboplatin+paclitaxel	62	87
Cisplatin+docetaxel	62	69
Carboplatin+cisplatin+pembrolizumab+ pemetrexed	52	34

NCR=Netherlands Cancer Registry.

Stratification by calendar year

First-line treatments stratified by calendar year can be found in **Table 12.24**. In this report, we have only described results for three specific years (2016, 2019 and 2022). Additional results can be found in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/).

Table 12.24. Most frequent first-line treatments with number of patients observed in NCR stratified by calendar year.

First-line treatments[1]	2016	2019	2022
Carboplatin+pembrolizumab+pemetrexed	0	656	927
Pembrolizumab	0	524	524
Carboplatin+pemetrexed	72	308	242
Cisplatin+pemetrexed	90	255	79
Carboplatin+paclitaxel+pembrolizumab	0	128	267
Cisplatin	28	199	96
Carboplatin+gemcitabine	35	153	112
Cisplatin+pembrolizumab+pemetrexed	0	165	104
Carboplatin	<5	77	120
Cisplatin+gemcitabine	15	100	38
Carboplatin+cisplatin+pemetrexed	7	41	<5
Carboplatin+paclitaxel	<5	24	22

NCR=Netherlands Cancer Registry. [1] Treatment combinations with total counts > 100 across databases considering 2016, 2019 and 2022.

Stratification by WHO performance status (WHO-PS)

First-line treatments stratified by WHO-PS can be found in **Table 12.25**. This stratification is available in NCR only.

Table 12.25. Most frequent first-line treatments with number of patients observed in NCR stratified by WHO performance status.

First-line treatments[1]	WHO-PS 0	WHO-PS 1	WHO-PS 2	WHO-PS 3
Carboplatin+pembrolizumab+pemetrexed	1,139	1,464	248	57
Pembrolizumab	908	1,255	319	70
Carboplatin+pemetrexed	525	679	213	27
Cisplatin+pemetrexed	589	449	47	10
Carboplatin+paclitaxel+pembrolizumab	302	397	85	15
Carboplatin+gemcitabine	251	384	119	17
Cisplatin	375	265	25	5
Cisplatin+pembrolizumab+pemetrexed	269	210	25	10
Carboplatin	144	223	41	13
Cisplatin+gemcitabine	214	158	27	5
Carboplatin+cisplatin+pemetrexed	86	58	<5	0
Carboplatin+paclitaxel	53	49	17	<5
Cisplatin+docetaxel	54	60	6	0
Carboplatin+cisplatin+gemcitabine	29	42	10	0
Carboplatin+cisplatin+pembrolizumab+pemetrexed	31	34	10	0
Carboplatin+cisplatin	29	30	<5	<5
Cisplatin+vinorelbine	41	21	<5	0

NCR=Netherlands Cancer Registry, WHO-PS = World Health Organization performance status. [1] Treatment combinations with total counts > 100 across databases.

12.4 Survival rates

Overall survival since the start of first-line therapy for locally advanced or metastatic NSCLC was estimated as part of objective 2. The results described in the following subsections correspond to the combined analysis of all patients with locally advanced (stage 3b) and metastatic (stage 4) NSCLC. All results can be found in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Survival/). This analysis was only conducted in NCR where sufficient counts were observed for the following first-line therapies: chemotherapy alone (as monotherapy or in combination with other chemotherapies, but not in combination with immunotherapies), pembrolizumab, nivolumab, and the nivolumab and ipilimumab combination, with all three immunotherapies possibly given in combination with chemotherapies (as per the approved indication).

12.4.1 Overall comparison

The overall survival analysis by treatment type is summarised in **Table 12.26** and **Figure 2**.

A total of 5,425 individuals were treated with chemotherapy, from which 4,134 deaths were observed. Median survival was 9.96 months (9.56, 10.41), the RMST (restricted to 4 years follow-up) was estimated at 17.25 months (16.79, 17.71) and the 1-year, 2-year, and 3-year survival probability were 44.06% (95%CI: 42.72, 45.44), 27.04% (25.82, 28.33), and 20.19% (19.04, 21.40), respectively.

For pembrolizumab, a total of 7,992 treated individuals were identified, from which 4,906 deaths were observed. The median survival was 13.11 months (12.58, 13.63), the RMST was estimated at 20.14 months (19.71, 20.60) and the 1-year, 2-year, and 3-year survival probability were 52.15% (51.01, 53.32), 34.77% (33.59, 35.99), and 26.95% (25.74, 28.22), respectively.

A total of 213 individuals were treated with nivolumab, from which 147 deaths were observed. Median survival was 12.19 months (9.43, 14.59), the RMST was estimated at 16.92 months (14.49, 19.32) and the 1-year, 2-year, and 3-year survival probability were 50.00% (43.26, 57.81), 25.04% (19.07, 32.89), and 17.56% (12.26, 25.16), respectively. However, caution should be exercised when interpreting given the high uncertainty around these estimates.

A total of 62 individuals were treated with nivolumab and ipilimumab combination, and 27 deaths were observed. Median survival was 16.16 months (11.53, 35.74). The RMST was estimated at 20.86 months (15.21, 26.55). The 1-year, 2-year, and 3-year survival probability was 62.04% (48.20, 79.86), 28.50% (15.63, 51.96), and 22.80% (10.84, 47.95), respectively. However, caution should be exercised when interpreting given the high uncertainty around these estimates.

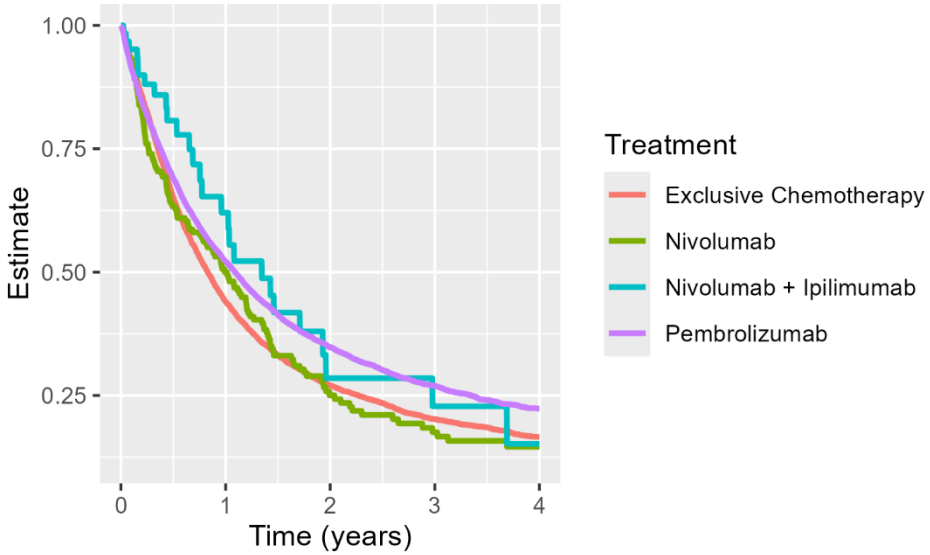
Table 12.26. Overall survival (in months) by treatment in NCR*.

Treatment	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	5,425	4,134	9.96 (9.56, 10.41)	17.25 (16.79, 17.71)	44.06 (42.72, 45.44)	27.04 (25.82, 28.33)	20.19 (19.04, 21.40)
Pembrolizumab	7,992	4,906	13.11 (12.58, 13.63)	20.14 (19.71, 20.60)	52.15 (51.01, 53.32)	34.77 (33.59, 35.99)	26.95 (25.74, 28.22)
Nivolumab	213	147	12.19 (9.43, 14.59)	16.92 (14.49, 19.32)	50.00 (43.26, 57.81)	25.04 (19.07, 32.89)	17.56 (12.26, 25.16)
Nivolumab + ipilimumab	62	27	16.16 (11.53, 35.74)	20.86 (15.21, 26.55)	62.04 (48.20, 79.86)	28.50 (15.63, 51.96)	22.80 (10.84, 47.95)

NCR=Netherlands Cancer Registry.

*Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the chemotherapy cohort were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

a) All treatments



b) By treatment and with 95%CI

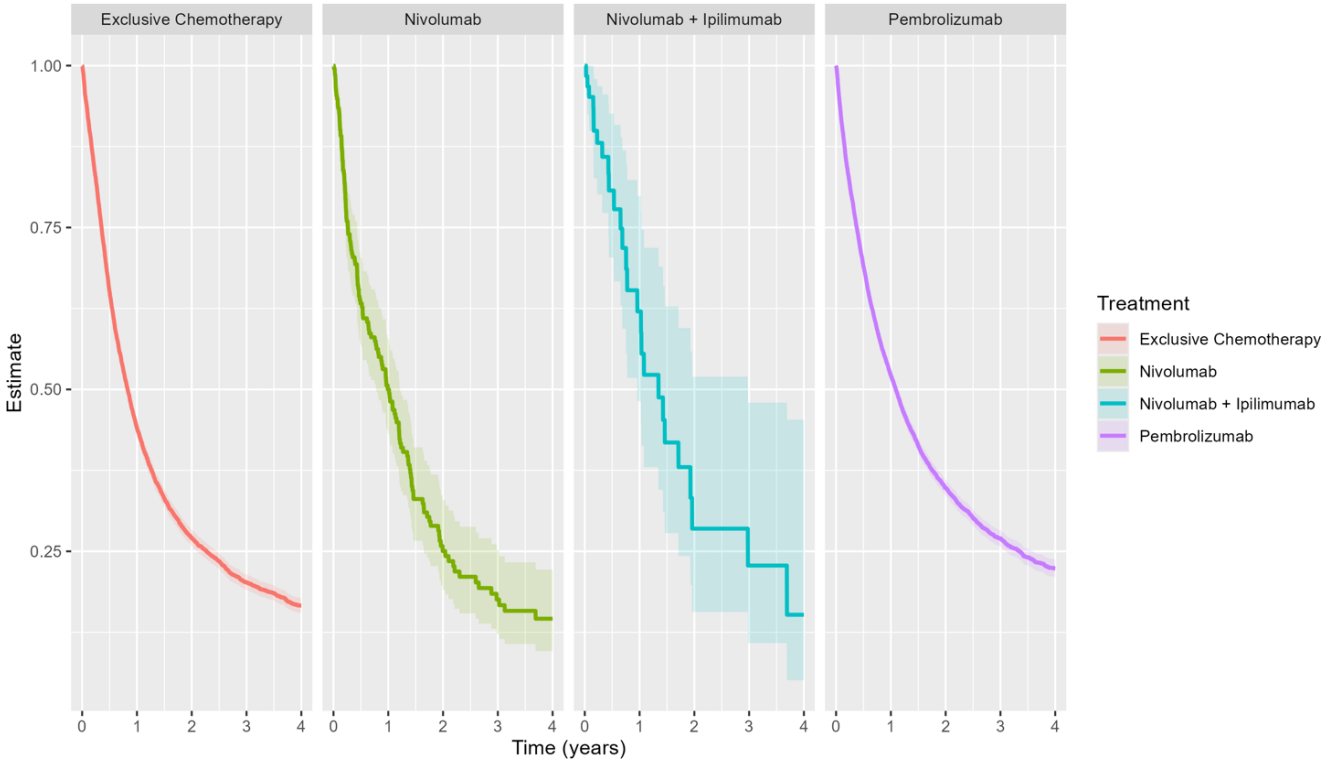


Figure 2. Overall survival of patients with locally advanced or metastatic NSCLC by treatment type in NCR.

12.4.2 Survival rates by age and sex

Survival rates stratified by age group and sex are shown in **Table 12.27** and **Table 12.28**.

For all therapies, the median survival was highest in the 18-64 age group, followed by the 65-79 and the >=80 age groups. For chemotherapy, median survival ranged from 10.41 months (9.66, 11.11) among the 18-64 age group to 9.69 months (8.61, 11.14) among the >=80 age group. For pembrolizumab, median survival for these age groups (in the same order) ranged from 14.52 (13.54, 15.41) to 9.82 (8.41, 11.27). For nivolumab, median survival was 16.16 (11.47, 21.29) among the 18-64 age group and 9.30 (5.91, 13.60) among the 65-79 age group. Counts for nivolumab were low (n<5) for the >=80 age group while no cases in this age group were observed for nivolumab and ipilimumab. Median survival was not estimated for nivolumab and ipilimumab due to low counts of patients when stratified by age group.

In general, the 1-, 2-, and 3-year survival decreased with increasing age. For chemotherapy, the 1-year survival was similar across age groups at approximately 42%–45%. Differences by age were observed for 3-year survival, where estimates were 22.65% (20.86, 24.59) in the 18-64 age group and 16.47% (12.11, 22.41) in the >=80 age group. For pembrolizumab, 1-year survival was 54.99% (53.25, 56.80) in the 18-64 age group, and 43.65% (39.06, 48.79) in the >=80 age group. When assessed at 3 years, survival rates in these age groups were 30.95% (29.09, 32.93) and 14.48% (10.84, 19.35), respectively. For patients receiving nivolumab or nivolumab and ipilimumab, estimates of 1-, 2-, and 3-year survival among the 18-64 age group were numerically higher than those obtained among the 64-75 age group.

Survival estimates differed by sex also for all therapies, with females showing a higher median survival than males. For chemotherapy, median survival was 11.53 months (10.81, 12.45) among females and 8.84 (8.41, 9.36) among males. Corresponding figures (in the same order) were 14.95 (14.06, 16.00) and 11.50 (10.94, 12.32) for pembrolizumab, and 16.16 (12.19, 21.03) and 9.07 (5.58, 12.98) for nivolumab. Differences by sex were also observed in the 1-, 2-, and 3-year survival estimates. For chemotherapies, 1-year survival was 48.83% (46.79, 50.95) among females and 40.43% (38.69, 42.25) among males, and decreased to 23.81% (21.99, 25.79) and 17.42% (16.00, 18.97), respectively, for 3-year survival. For pembrolizumab, 1-year survival was 56.11% (54.43, 57.85) among females and 48.89% (47.36, 50.48) among males, and decreased to 31.47% (29.62, 33.44) and 23.24% (21.69, 24.90) when estimated for 3-year survival. Results for nivolumab and nivolumab and ipilimumab also showed numerical differences by sex.

Table 12.27. Overall survival (in months) stratified by age group in NCR, per first-line therapy*.

First-line therapy	Age (years)	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	18 - 64	2,306	1,711	10.41 (9.66, 11.11)	18.14 (17.41, 18.89)	45.80 (43.76, 47.93)	29.33 (27.43, 31.36)	22.65 (20.86, 24.59)
	65 - 79	2,856	2,212	9.72 (9.20, 10.32)	16.59 (15.97, 17.22)	42.76 (40.93, 44.67)	25.47 (23.81, 27.23)	18.48 (16.95, 20.13)
	>= 80	263	211	9.69 (8.61, 11.14)	16.16 (14.19, 18.14)	42.84 (37.17, 49.36)	23.89 (19.00, 30.03)	16.47 (12.11, 22.41)
Pembrolizumab	18 - 64	3,309	1,954	14.52 (13.54, 15.41)	21.72 (21.03, 22.44)	54.99 (53.25, 56.80)	37.97 (36.15, 39.88)	30.95 (29.09, 32.93)
	65 - 79	4,228	2,627	12.42 (11.66, 13.27)	19.35 (18.76, 19.94)	50.81 (49.24, 52.43)	33.27 (31.65, 34.98)	24.98 (23.32, 26.76)
	>= 80	455	325	9.82 (8.41, 11.27)	15.57 (13.96, 17.15)	43.65 (39.06, 48.79)	24.36 (20.13, 29.47)	14.48 (10.84, 19.35)
Nivolumab	18 - 64	108	73	16.16 (11.47, 21.29)	19.02 (15.64, 22.41)	57.35 (48.19, 68.25)	31.35 (22.68, 43.33)	18.55 (11.33, 30.35)
	65 - 79	102	71	9.30 (5.91, 13.60)	15.01 (11.50, 18.50)	43.77 (34.42, 55.65)	18.81 (11.59, 30.54)	17.10 (10.18, 28.75)
	>= 80	<5	<5	-	NA	-	-	-
Nivolumab and ipilimumab	18 - 64	31	11	-	27.01 (18.50, 35.55)	69.24 (50.84, 94.30)	46.16 (26.23, 81.23)	36.93 (18.06, 75.50)
	65 - 79	31	16	-	-	54.79 (36.40, 82.46)	9.74 (1.66, 57.19)	-
	>= 80	-	-	-	-	-	-	-

NCR=Netherlands Cancer Registry. "-"= Not estimated. NA= Not available due to confidentiality restrictions. *Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the chemotherapy cohort were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

Table 12.28. Overall survival (in months) stratified by sex in NCR, per first-line therapy*.

First-line therapy	Sex	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	Females	2,349	1,702	11.53 (10.81, 12.45)	19.02 (18.30, 19.78)	48.83 (46.79, 50.95)	30.74 (28.81, 32.80)	23.81 (21.99, 25.79)
	Males	3,076	2,432	8.84 (8.41, 9.36)	15.87 (15.28, 16.49)	40.43 (38.69, 42.25)	24.24 (22.69, 25.90)	17.42 (16.00, 18.97)
Pembrolizumab	Females	3,617	2,072	14.95 (14.06, 16.00)	22.01 (21.36, 22.70)	56.11 (54.43, 57.85)	39.59 (37.81, 41.46)	31.47 (29.62, 33.44)
	Males	4,375	2,834	11.50 (10.94, 12.32)	18.63 (18.04, 19.19)	48.89 (47.36, 50.48)	30.80 (29.26, 32.42)	23.24 (21.69, 24.90)
Nivolumab	Females	88	54	16.16 (12.19, 21.03)	20.34 (16.30, 24.38)	61.34 (51.42, 73.17)	29.36 (19.98, 43.15)	24.99 (16.01, 39.02)
	Males	125	93	9.07 (5.58, 12.98)	14.55 (11.60, 17.48)	41.73 (33.24, 52.37)	21.76 (14.73, 32.13)	12.69 (7.21, 22.34)
Nivolumab and ipilimumab	Females	24	9	-	25.89 (16.07, 35.71)	72.75 (54.10, 97.83)	38.19 (17.92, 81.39)	38.19 (17.92, 81.39)
	Males	38	18	-	17.2 (11.00-23..30)	54.26 (36.42, 80.83)	21.10 (8.08, 55.09)	10.55 (1.95, 56.93)

NCR=Netherlands Cancer Registry. "-"= Not estimated. *Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the chemotherapy cohort were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

12.4.3 Survival rates by PD-L1 expression

Survival rates stratified by PD-L1 expression are shown in **Table 12.29**.

For chemotherapy (n=5,425), 1,881 patients had a PD-L1 expression of <1%, 216 patients had a PD-L1 expression between >=1% and 4%, 772 patients had a PD-L1 expression between >=5% and 49%, and 783 had a PD-L1 expression of >50%. Survival estimates were worse for patients with PD-L1 expression <1%, for which the 3-year survival was 13.18% (95%CI: 11.58, 15.00). For patients with PD-L1 between 5% to 49%, or >=50%, the 3-year survival estimates were 17.85% (15.08, 21.12) and 28.82% (25.48, 32.60), respectively.

In the pembrolizumab cohort (n=7,992), the highest number of patients was observed in the group of PD-L1 expression >=50% (n=3,648), followed by PD-L1 expression <1 (n=2,287). Survival estimates were higher for patients with higher PD-L1 expression. The 3-year survival was 14.97% (13.03, 17.20) for patients with PD-L1 expression <1%, 20.09 (15.10, 27.74) for patients with expression between >1% and 4%, 25.57% (95%CI: 23.43, 30.13) for patients with expression between >=5% and 49%, and 33.86 (32.05, 35.77) for patients with expression >=50%.

In the nivolumab cohort (n=213), most patients had a PD-L1 expression of <1% (n=81). There were 7 patients with PD-L1 expression between 1% and 4%, 28 patients with PD-L1 expression >=5%-49%, and 25 patients with PD-L1 expression >=50%. Survival estimates for the >=1% and <5% were not estimated due to the small sample size. Overall, 3-year survival in other subgroups ranged from 4.69% (0.7, 31.34) in PD-L1 >=5% to 49%, to 27.71% (14.08, 54.54) in the >=50%.

In the nivolumab and ipilimumab cohort (n=62), most patients had a PD-L1 expression of <1% (n=30), and there were 8 patients in the >=50% group. Survival estimates for the >=1% and <5% and >=5% and <50% were not estimated due to the small sample size. Overall, 3-year survival was 19.88% (4.07, 97.13) in the <1% group and 37.50% (15.33, 91.74) in patients with PD-L1 expression >=50%.

Table 12.29. Overall survival (in months) stratified by PD-L1 expression in NCR, per first-line therapy*.

First-line therapy	PD-L1, %	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	<1	1,881	1,543	7.85 (7.23, 8.35)	13.86 (13.18, 14.59)	35.58 (33.41, 37.89)	19.05 (17.23, 21.06)	13.18 (11.58, 15.00)
	1 - 4	216	151	9.20 (8.05, 11.66)	16.49 (14.03, 18.92)	41.54 (35.13, 49.12)	23.73 (18.14, 31.03)	21.38 (15.94, 28.66)
	5 - 49	772	601	10.09 (9.20, 11.30)	16.72 (15.54, 17.91)	44.05 (40.59, 47.80)	26.47 (23.36, 29.99)	17.85 (15.08, 21.12)
	>= 50	783	518	13.47 (11.30, 15.61)	20.83 (19.45, 22.18)	51.58 (48.08, 55.34)	34.48 (31.07, 38.27)	28.82 (25.48, 32.60)
	Missing	1,773	1,321	11.96 (11.11, 12.91)	19.52 (18.66, 20.37)	49.90 (47.59, 52.33)	32.67 (30.47, 35.03)	24.76 (22.69, 27.01)
Pembrolizumab	<1	2,287	1,56	9.40 (8.84, 10.09)	15.34 (14.62, 16.10)	41.94 (39.82, 44.18)	22.40 (20.40, 24.60)	14.97 (13.03, 17.20)
	1 - 4	430	268	10.74 (9.36, 13.14)	18.04 (16.16, 19.91)	46.69 (41.91, 52.02)	29.74 (24.96, 35.44)	20.09 (15.10, 26.74)
	5 - 49	1,222	724	14.03 (12.95, 15.47)	20.50 (19.35, 21.62)	55.62 (52.75, 58.64)	34.71 (31.68, 38.02)	26.57 (23.43, 30.13)
	>= 50	3,648	2,106	16.76 (15.57, 18.00)	22.77 (22.11, 23.46)	57.39 (55.75, 59.09)	42.21 (40.47, 44.03)	33.86 (32.05, 35.77)
	Missing	405	248	14.23 (12.09, 17.35)	21.22 (19.25, 23.20)	55.20 (50.34, 60.54)	35.14 (30.23, 40.84)	29.25 (24.29, 35.23)
Nivolumab	<1	81	51	7.36 (5.58, 14.36)	-	42.26 (31.57, 56.57)	18.54 (10.01, 34.32)	11.12 (4.33, 28.60)
	1 - 4	7	<5	-	NA	NA	NA	NA
	5 - 49	28	24	3.72 (2.28, 12.36)	-	28.14 (14.87, 53.24)	9.38 (2.56, 34.38)	4.69 (0.70, 31.34)
	>= 50	25	18	-	21.82 (14.85, 28.78)	63.33 (46.82, 85.66)	33.25 (18.71, 59.08)	27.71 (14.08, 54.54)
	Missing	72	50	-	20.70 (16.49, 24.90)	59.91 (49.13, 73.06)	34.69 (24.36, 49.38)	24.05 (14.89, 38.84)
Nivolumab and ipilimumab	<1	30	10	-	-	53.01 (31.35, 89.62)	39.76 (18.37, 86.03)	19.88 (4.07, 97.13)
	1 - 4	<5	<5	-	NA	NA	-	-

First-line therapy	PD-L1, %	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
	5 - 49	<5	<5	-	NA	NA	-	-
	>= 50	8	6	-	-	75.00 (50.27, 100.00)	37.50 (15.33, 91.74)	37.50 (15.33, 91.74)
	Missing	18	7	-	22.11 (11.47, 32.76)	64.93 (41.44, 100.00)	21.64 (4.54, 100.00)	21.64 (4.54, 100.00)

NCR=Netherlands Cancer Registry; PD-L1 = Programmed Death-Ligand 1. "-"= Not estimated. NA= Not available due to confidentiality restrictions.
*Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the cohort of chemotherapy were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

12.4.4 Survival rates by tumour stage

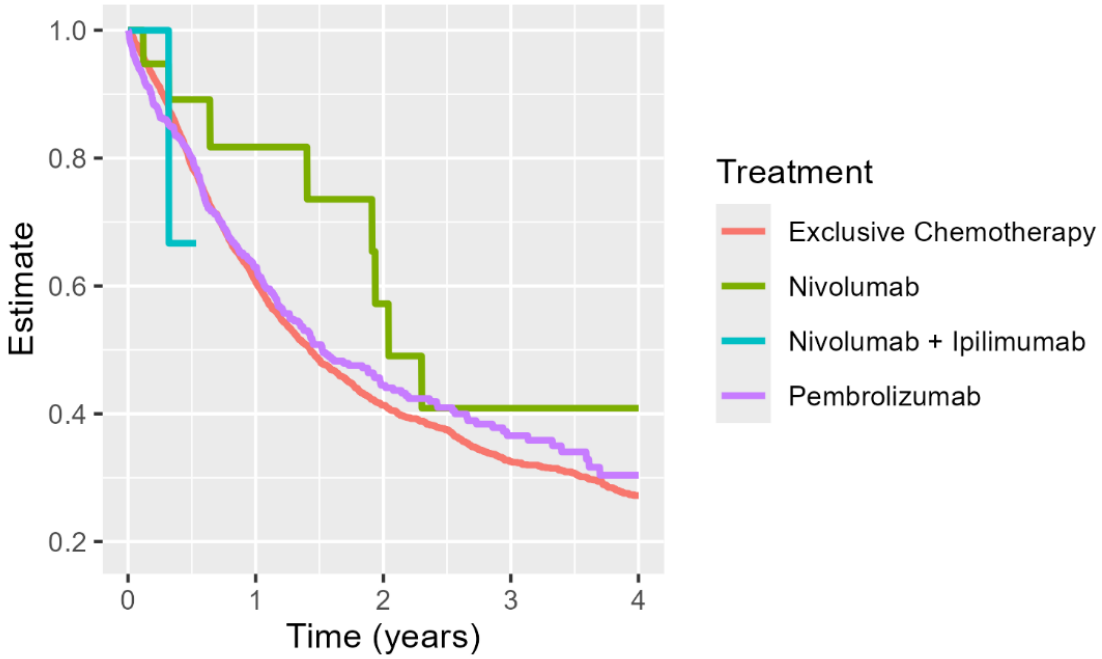
Among the study population of locally advanced and metastatic NSCLC included in the survival analysis in NCR, 2,624 patients had stage 3b, while 11,109 had stage 4. Survival estimates (**Table 12.30, Figure 3** [stage 3b], and **Figure 4** [stage 4]) were lower in stage 4 compared to stage 3b NSCLC patients across all treatment cohorts (**Table 12.30**). In both stages 3b and 4, the 3-year survival was higher in patients who received pembrolizumab (36.58% (31.51, 42.48) and 26.32% (25.09, 27.62), respectively) than patients who received chemotherapy (32.48% (30.27, 34.85) and 13.11% (11.93, 14.41)). Among stage 4 patients, the 3-year overall survival in nivolumab and nivolumab and ipilimumab groups were 15.36% (10.16, 23.23) and 23.07% (10.97, 48.51), respectively.

Table 12.30. Overall survival (in months) stratified by stage of tumour in NCR, per first-line therapy*.

First-line therapy	Stage of tumour	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	Stage 3b	2,047	1,285	17.15 (15.84, 18.59)	23.56 (22.74, 24.41)	60.75 (58.59, 62.98)	41.33 (39.09, 43.69)	32.48 (30.27, 34.85)
	Stage 4	3,396	2,861	7.36 (7.03, 7.88)	13.57 (13.04, 14.09)	34.26 (32.67, 35.93)	18.76 (17.43, 20.20)	13.11 (11.93, 14.41)
Pembrolizumab	Stage 3b	552	268	18.27 (16.03, 23.79)	24.61 (22.77, 26.45)	62.94 (58.72, 67.46)	44.46 (39.70, 49.80)	36.58 (31.51, 42.48)
	Stage 4	7,463	4,650	12.75 (12.16, 13.34)	19.84 (19.38, 20.30)	51.38 (50.20, 52.58)	34.10 (32.89, 35.35)	26.32 (25.09, 27.62)
Nivolumab	Stage 3b	20	9	-	29.90 (21.22, 38.57)	81.73 (64.72, 100.00)	57.21 (35.83, 91.37)	40.87 (21.07, 79.25)
	Stage 4	193	138	11.43 (7.85, 13.83)	15.70 (13.24, 18.14)	46.97 (39.98, 55.20)	22.16 (16.28, 30.17)	15.36 (10.16, 23.23)
Nivolumab and ipilimumab	Stage 3b	5	<5	-	NA	-	-	-
	Stage 4	57	26	16.16 (11.53, 35.74)	21.06 (15.31, 26.81)	62.77 (48.77, 80.79)	28.83 (15.82, 52.56)	23.07 (10.97, 48.51)

NCR=Netherlands Cancer Registry. "-"= Not estimated. NA= Not available due to confidentiality restrictions.
*Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the chemotherapy cohort were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

a) All treatments



b) By treatment and with 95%CI

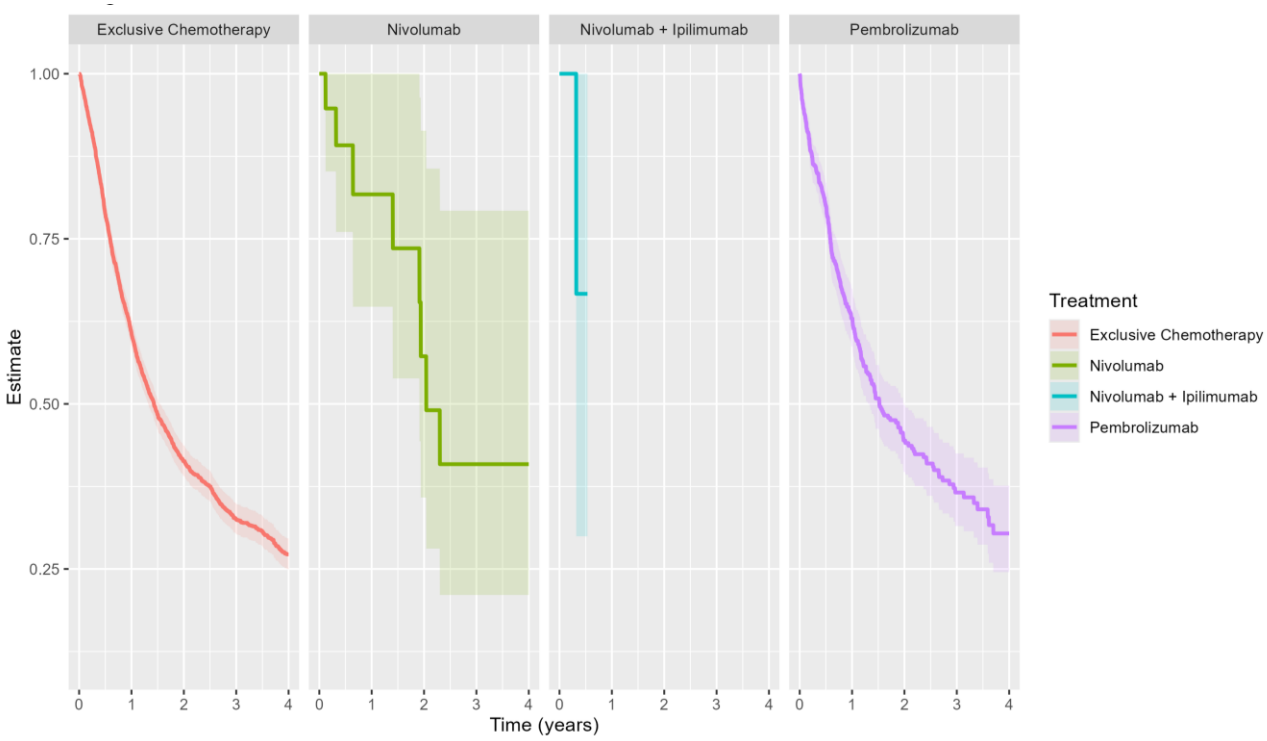
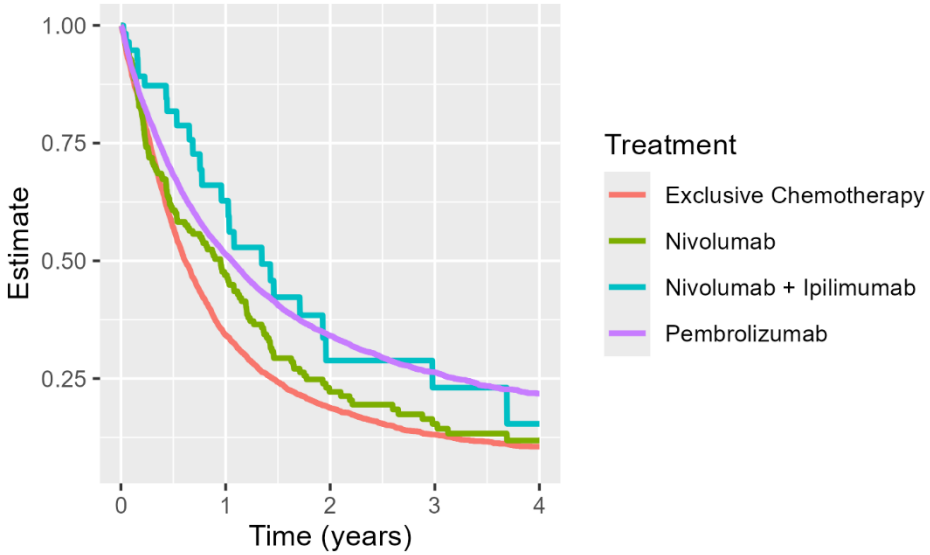


Figure 3. Overall survival of patients with locally advanced NSCLC (stage 3b) by treatment type in NCR.

a) All treatments



b) By treatment and with 95%CI

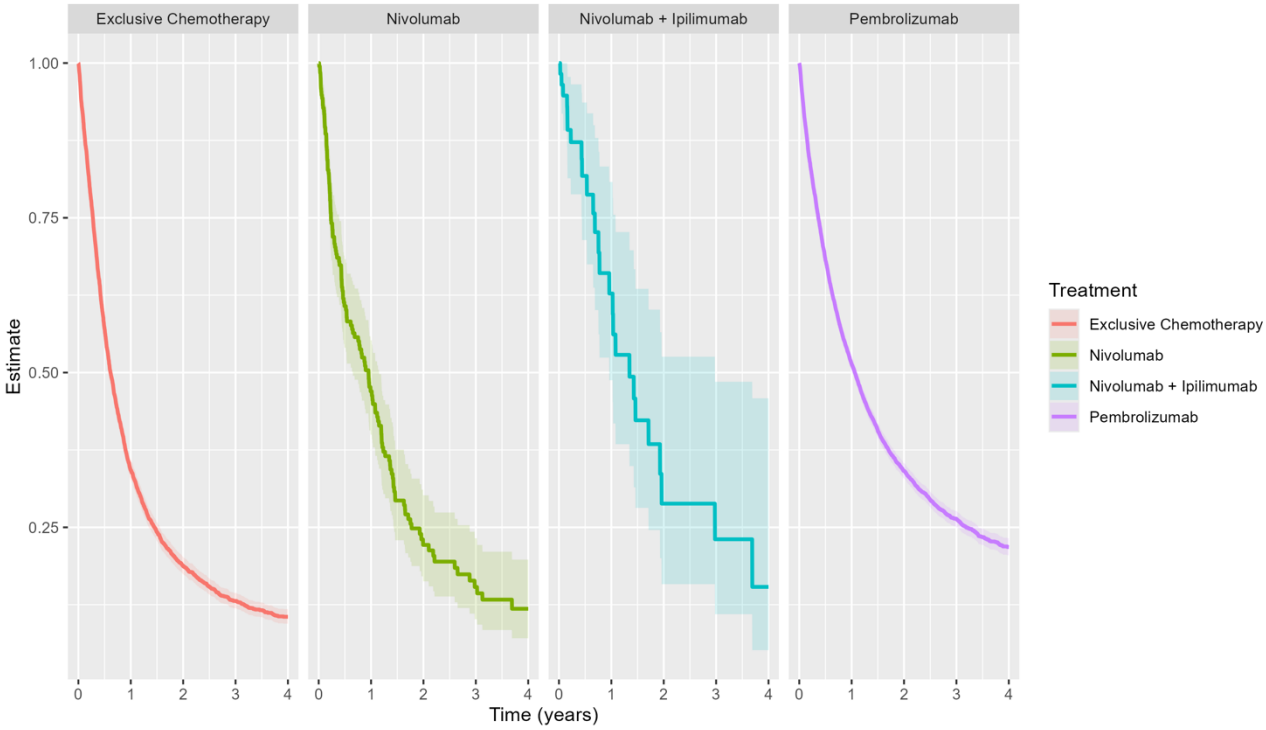


Figure 4. Overall survival of patients with metastatic NSCLC (stage 4) by treatment type in NCR.

12.5 Survival comparative analysis

This analysis was conducted only in the NCR data source in which sufficient counts were observed for the following first-line therapies: chemotherapy (exclusive), pembrolizumab, nivolumab, and the nivolumab and ipilimumab combination. Here we show the results derived from the CohortMethod R package which includes a comparison in overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of exclusive chemotherapy (reference cohort) as first-line treatment. All results are available in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Survival/).

In this section we report only results from models that passed diagnostics (covariate balance and equipoise). The complete results also describing analyses that failed diagnostics are available in the Shiny App (https://data.darwin-eu.org/EUPAS1000000112/Survival/) and in **Appendix II Table 1**. We conducted one analysis using PS matching with the available covariates in NCR (age, sex, index year, stage of tumour, and WHO-PS), and another analysis adjusting for the same variables. We have also added model log-log figures to **Appendix II Figures 1-3**. Only the model using PS matching for pembrolizumab compared to exclusive chemotherapy as first-line treatment passed diagnostics. Please see **Appendix II Table 3** for the results on model diagnostics.

From 7,993 patients in the pembrolizumab cohort, PS matching with patients in the chemotherapy cohort was possible for 3,003 patients. For pembrolizumab, population characteristics before and after propensity score adjustment are provided in **Figure 5 and Appendix II Table 2**. The SMD values of all included covariates were less than 0.1 after PS matching, which implies that the difference in the standardized means of available covariates between the two groups after PS matching was low. Please see the “15.2 Limitations of the research methods” for important considerations when interpreting these results.

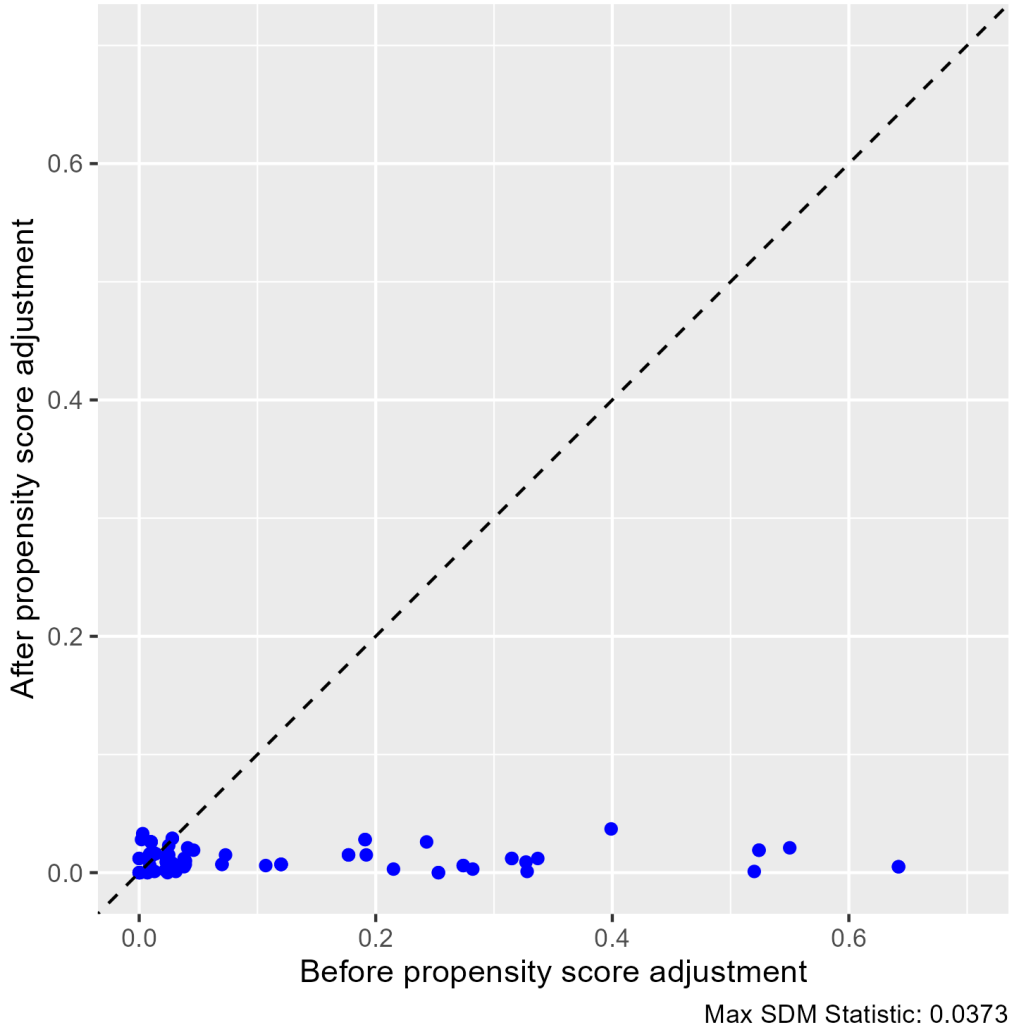


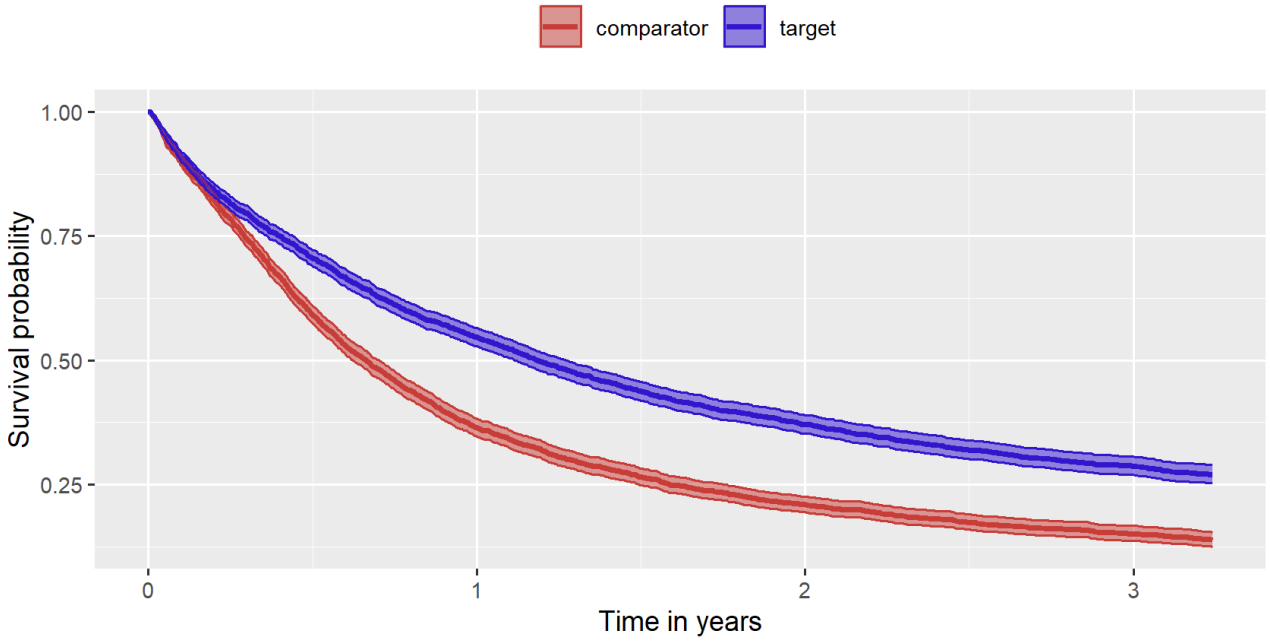
Figure 5. Covariate balance before and after propensity score adjustment (target cohort Pembrolizumab – stage 3b and 4). Each dot represents the standardized difference of means for a single covariate before and after propensity score adjustment on the propensity score. The maximum absolute standardized difference of the mean (Max SDM) is given at the bottom of the figure.

Results for PS matching models that passed diagnostics are shown in **Table 12.31**. A total of 3,003 patients with locally advanced or metastatic NSCLC treated with pembrolizumab (i.e. target cohort) were matched to 3,003 patients treated with chemotherapy exclusively as first-line treatment (i.e. reference or comparator cohort). The number of observed events in each cohort was 1,966 and 2,332, respectively. The Kaplan-Meier curves for the target and comparator matched cohorts are shown in **Figure 6**. The HR and 95%CI estimated using Cox proportional hazards models after PS matching was 0.66 (0.62-0.70).

Table 12.31. Comparison of overall survival of patients with locally advanced or metastatic NSCLC under pembrolizumab to that of exclusive chemotherapy as first-line treatment in NCR after propensity score matching.

Target cohort	Target patients (n)	Target events (n)	Comparator	Comparator patients (n)	Comparator events (n)	Hazard Ratio	95% CI
Pembrolizumab	3,003	1,966	Chemotherapy	3,003	2,332	0.66	0.62-0.70

Propensity score matching was conducting including the following list of covariates: age, sex, index year, stage of tumour, and WHO-PS. The target cohort corresponds to patients with advanced or metastatic NSCLC under each immunotherapy to that of exclusive chemotherapy (reference cohort, comparator) as first-line treatment.



time (years)	0	1	2	3	4
target	3,003	1410	785	481	255
comparator	3,003	945	425	226	101

Figure 6. Kaplan Meier plot, showing survival as a function of time for the target (Pembrolizumab) and comparator (Chemotherapy only) cohorts. The shaded area denotes the 95% CI.

From 213 patients in the nivolumab cohort, 212 were matched 1:1 to patients in the chemotherapy cohort using PS. For nivolumab and ipilimumab, all patients (n=62) were matched to patients in the chemotherapy cohort using PS. Models for both cohorts did not pass diagnostics, with SMD values >0.1 for several

covariates after PS matching (**Appendix II Figures 4 and 5**). Results from the models that failed diagnostics are shown in **Appendix II Table 1**.

We additionally estimated RMST difference at 4 years as a supplemental analysis (**Table 12.32**). The RMST difference between chemotherapy and the target first-line therapy groups were: 6.54 months (95%CI: 5.63, 7.46) for pembrolizumab, 1.24 (-2.24, 4.72) for nivolumab, and 5.81 (-2.21, 13.84) for nivolumab and ipilimumab.

Table 12.32. Restricted mean survival time (RMST) difference at 4 years by treatment group in NCR*.

First-line therapy group	N patients	N deaths	RMST at 4 years (95% CI) (months)	RMST difference (95% CI) (months) versus chemotherapy
Chemotherapy	3003	2,322	14.48 (13.90, 15.08)	
Pembrolizumab	3003	1,939	21.03 (20.34, 21.73)	6.54 (5.63, 7.46)
Chemotherapy	212	148	15.67 (13.17, 18.16)	
Nivolumab	212	145	16.91 (14.48, 19.34)	1.24 (-2.24, 4.72)
Chemotherapy	62	38	15.10 (9.52, 20.67)	
Nivolumab+Ipilimumab	62	27	20.90 (15.13, 26.68)	5.81 (-2.21, 13.84)

NCR=Netherlands Cancer Registry.
* Cut-off time is restricted to a maximum of 4 years. Chemotherapies included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine. Patients in the chemotherapy cohort were given chemotherapies exclusively as first-line therapy, while patients in the immunotherapy cohorts (pembrolizumab, nivolumab, nivolumab and ipilimumab) could also be given chemotherapies as first-line therapy.

13. DEVIATIONS FROM PROTOCOL

Since the last publication of the protocol, this has been amended to incorporate the following changes:

1. The exclusion criteria “Any cancer diagnosis (except non-melanoma skin cancer) prior to date of NSCLC diagnosis” was modified. This exclusion criterion was implemented with additional knowledge obtained after running CohortDiagnostics in the three databases. In hospital databases such as IMASIS and CDWBordeaux, broader concepts were recorded for initial cancer diagnosis and later, more specific concepts were recorded to include information to confirm NSCLC histologically. To account for that, a selection of broad concepts representing the initial broad diagnosis of lung cancer was allowed for two months prior to the final diagnosis.

2. Treatment sequences were not described; Sunburst plots and Sankey diagrams were not created since we were only describing treatments recorded in a period of 42 days.

3. For objective 1, the initial proposal was to describe patient characteristics stratified by time period (before and after 2017) to describe treatments before and after approval of immunotherapies. However, we finally provided results stratified by calendar year instead.

4. For Objective 2, overall survival rates of patients with locally advanced or metastatic NSCLC **who initiated treatment** with immunotherapies are presented individually for the following treatments: Pembrolizumab, Nivolumab, and Nivolumab with Ipilimumab combination, irrespective of whether these included chemotherapy as part of the first-line treatment, instead of an overall immunotherapy. Chemotherapies, which included cisplatin, carboplatin, pemetrexed, paclitaxel, docetaxel, gemcitabine, and vinorelbine, are presented as a group and include treatments given **as monotherapy or in combination with other chemotherapies and without exposure to immunotherapies as first line of treatment.**

5. For objective 2, additional stratification by stage of tumour (3b or 4) was added to help informing the potential for matching in objective 3.

6. For objective 3, large scale propensity matching (LSPS) and use of negative control outcomes were not possible because only NCR had sufficient number of patients in the cohorts of interest to conduct the comparative effectiveness analyses, and no data on history of co-morbidities and medications was available in this database. For this reason, matching was limited to age, sex, WHO-PS, tumour stage and year of index date, and no negative control outcome analysis was performed.

7. For objective 3, exact matching on year of birth and calendar year of index date was not performed. With the limited number of patients in the target and comparator cohorts, exact matching would most likely result into empty, or very small groups. We therefore chose to use these covariates in the PS matching models instead in order to allow the inclusion of the maximum number of patients in the target and comparator cohorts.

14. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, did not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there would have been a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

15. DISCUSSION

15.1 Key results

We identified 1,229, 321 and 38,957 patients with locally advanced or metastatic NSCLC with no prior history of cancer in CDWBordeaux, IMASIS, and NCR, respectively. From these, 10%, 51%, and 38% were treated with chemotherapy and/or immunotherapy as first-line within the study period in each database, respectively.

Among patients that initiated treatment, male predominance was observed across all databases, ranging between 55.3% (NCR) to 76.2% (IMASIS). The median age was similar across databases, ranging from 63 (IMASIS) to 66 (NCR) years. By age group, in CDWBordeaux and IMASIS, most patients were within the 18-64 age group (53.1% and 56.1%, respectively), while in NCR, 52.5% fell within the 65-79 age group.

WHO-PS was only available in NCR and 88.7% of individuals had a WHO-PS <=1. The median age increased with increasing WHO-PS, from 65 years in WHO-PS 0 to 67 years in WHO-PS 3.

In IMASIS and NCR, the chemotherapy and immunotherapy groups had a similar distribution in terms of sex and age. In CDWBordeaux, the chemotherapy group had a higher percentage of males (64.0%) compared to the immunotherapy group (55.3%). Across all WHO-PS categories in NCR, distribution by sex was similar in both treatment groups, with a slightly higher median age among immunotherapy-treated compared to chemotherapy in the WHO-PS 2 and 3. Overall, the distribution of WHO-PS levels was similar between treatment groups, with a similar proportion of patients in each category.

History of comorbidities and medications among treated patients was only available in CDWBordeaux (N=123) and IMASIS (N=164). In both databases, conditions directly reflecting malignancy diagnosis of NSCLC were the most frequently recorded entries, and tobacco/nicotine dependence was among the most common entry not directly related to the malignancy diagnosis. In CDWBordeaux, other notable diagnoses included abnormal findings on diagnostic imaging of the lung (29.8%), cough (27.9%), and dyspnoea (27.9%). In IMASIS, other entries not directly related to the malignancy diagnosis included essential hypertension (15.7%), and hyperlipidaemia (13.8%). Notably, in IMASIS, COVID-19 was reported in 12.6% of individuals.

The number of patients who started chemotherapy and/or immunotherapy within 6 months after the diagnosis of locally advanced or metastatic NSCLC was 123 in CDWBordeaux and 164 in IMASIS , with counts below 100 when stratified by treatment type (monotherapy, combinations, etc.). The number of patients with locally advanced or metastatic NSCLC that were treated was 14,936 in NCR .

In CDWBordeaux, the most frequently prescribed medication the year prior to the index date was acetaminophen as oral formulation (42.3%), followed by enoxaparin (30.8%). In IMASIS, the most prescribed medications were omeprazole (as oral formulation: 32.1% and injectable solution: 16%) and different formulations of acetaminophen. In both databases, other commonly prescribed medications include pain relievers (e.g. tramadol, fentanyl, dipyrone), and drugs used for anxiety (e.g., lorazepam, hydroxyzine.

Chemotherapies were the most frequently prescribed first-line treatments in CDWBordeaux and IMASIS, while in NCR, immunotherapies were more frequently prescribed as first-line treatment than chemotherapies. Overall, pembrolizumab was the most frequently prescribed first-line immunotherapy treatment in all databases (39 to 42 patients in CDWBordeaux, 68 to 74 patients in IMASIS, and 8,005 to 8,044 patients in NCR), followed by nivolumab (<5 in CDWBordeaux, <5 to 12 in IMASIS, and 143 to 161 in NCR).

Regarding treatment combinations or monotherapies, the most frequent first-line treatment was the combination of two chemotherapies in CDWBordeaux and chemotherapy as monotherapy in IMASIS. In NCR, most frequent first-line treatments consisted of combination of two chemotherapies or combinations of 3 or more treatments including both chemotherapies and immunotherapies.

Survival analysis

In NCR, overall survival was estimated for the following treatments: chemotherapy (n=5,425), pembrolizumab (n=7,992), nivolumab (n=213), and nivolumab and ipilimumab combination (n=62). Among all locally advanced (stage 3b) and metastatic (stage 4) NSCLC patients, median overall survival varied by treatment type. The highest median survival (years) was observed for nivolumab and ipilimumab combination (16.16 months (95%CI: 11.53, 35.74)), followed by pembrolizumab (13.11 months (12.58, 13.63)), nivolumab (12.19 months (9.43, 14.59)), and chemotherapy (9.96 months (9.56, 10.41)). When looking into the RMST (4-years follow-up), it was 20.86 months (15.21, 26.55) for nivolumab and

ipilimumab combination, 20.14 months (19.71, 20.60) for pembrolizumab, 17.25 months (16.79, 17.71) for chemotherapy, and 16.92 months (14.49, 19.32) for nivolumab.

The 1-year survival probability was highest for the nivolumab and ipilimumab combination-treated, followed by pembrolizumab, nivolumab and chemotherapy. The 3-year survival probabilities were highest for pembrolizumab (26.95%, (25.74, 28.22)), followed by the nivolumab and ipilimumab combination (22.80%, (10.84, 47.95)), chemotherapy (20.19%, (19.04, 21.40)), and were lowest for nivolumab (17.56%, (12.26, 25.16)). It should be noted that caution should be exercised when interpreting given the low precision of estimates for the 3-year survival probabilities of nivolumab and ipilimumab combination.

By age group, survival generally decreased with increasing age for all treatments. Results also differed by sex for all treatments, with females having higher survival estimates than males.

Regarding PD-L1 expression by treatment, the highest proportion of patients with PD-L1 >=50% was observed in the pembrolizumab cohort (45.6%), while the other treatments, the proportion of patients with PD-L1 >=50% was lower (<35%).

In terms of survival, estimates varied by both PD-L1 expression levels and treatment type. However, across all treatments, higher PD-L1 expression corresponded with improved survival estimates. The 3-year survival estimates for PD-L1 >=50% were 27.71 for nivolumab, 28.82% (25.48, 32.60) for chemotherapy, 33.86% (32.05, 35.77) for pembrolizumab, and 37.50% (15.33, 91.74)for nivolumab and ipilimumab combination. Survival estimates for PD-L1 expression <1% were 13.18% (11.58, 15.00) for chemotherapy, 14.97% (13.03, 17.20) for pembrolizumab, and 19.88% (4.07, 97.13) for the nivolumab and ipilimumab combination and 11.12% (4.33, 28.60) for nivolumab alone.

For nivolumab and the nivolumab and ipilimumab combination cohort, survival estimates were not estimable for all PD-L1 expression categories, due to the small sample size.

By tumour stage, survival estimates were lower in stage 4 compared to stage 3b, across all treatment cohorts. For each stage (3b and 4, individually), pembrolizumab showed superior survival estimates compared to chemotherapy.

Survival comparative analysis

We compared overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy (pembrolizumab, nivolumab, and the nivolumab and ipilimumab combination) to that of exclusive chemotherapy (reference cohort) as first-line treatment in two analyses: 1) using 1:1 PS matching with the available covariates in NCR (age, sex, index year, stage of tumour, and WHO-PS), and 2) by adjusting models for the same variables included in the PS matching.

Only the model using PS matching for pembrolizumab compared to exclusive chemotherapy as first-line treatment passed diagnostics (covariate balance and equipoise). A total of 3,003 patients with locally advanced or metastatic NSCLC treated with pembrolizumab (i.e. target cohort) were matched to 3,003 patients treated with chemotherapy exclusively as first-line treatment (i.e. reference or comparator cohort). The number of observed deaths in each cohort was 1,966 and 2,332, respectively. The HR and 95%CI estimated using Cox proportional hazards models after PS matching was 0.66 (0.62-0.70) in the pembrolizumab cohort in comparison to the chemotherapy cohort.

Finally, the RMST difference between chemotherapy and the target first-line therapy groups were: 6.54 months (95%CI: 5.63, 7.46) for pembrolizumab, 1.24 (-2.24, 4.72) for nivolumab, and 5.81 (-2.21, 13.84) for nivolumab and ipilimumab.

15.2 Limitations of the research methods

General considerations

This study was being conducted following several assumptions that must be considered. While the nature of the data may not be able to reflect patient characteristics to ascertain the adequateness of each treatment, there was interest in describing any patient with locally advanced or metastatic NSCLC treated with these therapies.

It must be noted that information on specific mutations that are known to affect both survival and treatment options (such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1)) were not available in the data sources included in the study and therefore, some patients with these mutations might have been included in the survival analysis in NCR.

Defining first-line treatment as medications administered within 42 days of the index date may introduce some degree of misclassification. However, it is unlikely that second-line therapy would be initiated as early as six weeks after diagnosis in real-world clinical practice. Typically, the effectiveness of initial therapy is assessed after two treatment cycles, which often spans six weeks in many chemotherapy regimens. For immunotherapy, this period may be even longer, as indicated by tumour assessment guidelines. Additionally, second-line treatment should not be present in NCR due to coding regulations, irrespective of the 42 days criterion.

Because some drugs are used for treatment for first- and second-line treatments, some residual misclassification between first-line and second-line therapy may be present. However, strict inclusion and exclusion criteria, together with the definition of first-line treatments, have likely mitigated this risk. Still, this should be taken into account when interpreting the results.

Because surgical procedures were not assessed, some misclassification could arise from individuals with a lower clinical stage who were included following a surgical procedure. However, this misclassification is expected to occur at random.

Finally, the lack of pathology data for some patients might result in an underestimation of NSCLC cases. However, data on confirmation of tumour morphology was used, which might have avoided misclassification of the study population.

Data sources

It should be noted that among data partners, there was a different use of concept IDs related to AJCC/UICC staging (6th, 7th and 8th versions). We have adopted site-specific staging classification versions used by each data partner. However, this may have led to possible misclassification issues related to the use of different versions, which should be considered.

There may be incomplete capture of treatment exposure in NCR. This is because data on cancer treatments administered as part of a clinical trial cannot be shared for research in this database.

The recording of co-morbidities and medications pre-index may vary across databases. In NCR, no history of health conditions or non-cancer treatments is available. Therefore, the use of large-scale patient-level characterisation and large-scale propensity score matching were not possible in this database.

In the IMASIS database, there is an established linkage between the electronic health records and the hospital Cancer Registry, facilitating the integration of pertinent data such as TNM staging, histology and dates of death. However, it should be noted that while in-hospital deaths are captured in IMASIS in real-time, this database currently lacks a direct connection with the population death registry which allows capturing out-of-hospital deaths. However, this is likely mitigated by the linkage between IMASIS and the

hospital Cancer Registry, since the Cancer Registry is periodically linked to the death registry. Still, absence of direct linkage may result in potential delays in accurately reflecting mortality status updates for some patients within the system.

In CDWBordeaux, death is recorded through two sources. First, this database retrieves in-hospital deaths. Second, patient records are regularly linked to data from the national death registry (every six months) using probabilistic algorithms based on search engines and machine learning strategies, with satisfactory results (18). Still, some deaths could go undetected, thus producing an underestimation of the event, given that records are not matched by using a common identifier between the two data sources, such as the social security number.

Only 14% of patients with advanced NSCLC in NCR and 23% in IMASIS were excluded from the analysis due to a prior history of cancer. In contrast, this proportion was 37% in CDWBordeaux. The proportion of patients with multiple primary tumours in lung cancer reaches 10-18%, according to various studies.(25, 26) Still, a figure of 37% does not seem realistic and likely reflects both the specific study population in the hospital settings and the data collection method specific to the hospital database. Some of these patients might encompass broad, non-specific recorded diagnosis that denote specific lung cancer diagnosis captured early in the diagnostic process but not specified as such. For this reason, some patients eligible for the study in CDWBordeaux may have been excluded from the analysis, but this is likely non-differential. Future studies might benefit from a further review of primary health records to differentiate patients with multiple primary cancers from those with single cancer diagnoses captured multiple times in hospital records. Finally, only 10% of patients in CDWBordeaux initiated treatments of interest within 6 months, as specified in the inclusion criteria, in contrast to 51% in IMASIS and 38% in NCR. This may also relate to patient characteristics and their care in hospital settings. Even patients with advanced NSCLC may be admitted for palliative surgical procedures rather than drug therapy, which may be provided in outpatient or less specialised settings. The difference in this proportion between IMASIS and NCR could be attributed to the higher likelihood of NCR capturing patients with advanced diseases who do not receive treatment.

Survival rates

These results should be interpreted with caution due to the following limitations. First, results were estimated using only one (NCR) of the three participating databases, as sample sizes in the other participating databases were insufficient for analysis. Additionally, some strata remained small, limiting the precision of subgroup-specific estimates. Second, we defined first-line treatment as all therapies initiated within 42 days of the first recorded treatment, which may have been insufficient to capture all treatments in some cases.

Survival comparative analysis

For the comparative effectiveness analyses, we planned to use LSPS to minimize measured confounding, and negative control outcomes to assess potential residual confounding. However, this analysis was only possible in NCR for which no data on patient history of co-morbidities and medications pre-index were available. Propensity score matching was conducted based on available covariates, and was limited to age, sex, index year, stage of tumour, and WHO-PS. The only model that passed diagnostics still had equipoise less than 50%, suggesting that positivity assumption may be violated and there is limited overlap between groups compared. LSPS matching was not possible, and therefore, we cannot rule out residual confounding. This limits the interpretation of results which may be subject to bias due to unmeasured confounding. Consequently, the estimated treatment effects may not accurately reflect the true causal relationships, and caution is needed when drawing conclusions from these findings. Future studies should aim to include more comprehensive data, including patient history of co-morbidities and medications, to improve the validity of the analyses and better control for confounding factors.

15.3 Interpretation

The proportion of locally advanced or metastatic NSCLC that received treatment (irrespective of chemotherapy and/or immunotherapy) was 10%, 51%, and 38% in CDWBordeaux, IMASIS, and NCR, respectively. While our assessment did not include all treatment options, this proportion is low. In Europe, it is estimated that approximately 35% of patients with advanced NSCLC receive no systemic treatment.(27) Reasons to forgo treatment can be related to the advanced stage of the disease, older age, poor performance status, or concerns about treatment-related harms outweighing the potential clinical benefits.(28) In hospital-based databases, the low proportion of treated patients may also indicate that patients seek treatment at other centres.

Among individuals that underwent treatment, male predominance for locally advanced or metastatic NSCLC was observed across all databases, ranging from 55% (NCR) to 76% (IMASIS). While the incidence of lung cancer has increased in women and decreased in men, in Europe and globally, in the last decades, lung cancer remains more common in men. (29, 30) From the perspective of managing advanced disease, adenocarcinoma,(29) which is more prevalent in women, is more likely to be treated with tyrosine kinase inhibitors compared to other morphological types that are typically treated with conventional chemotherapy or immunotherapy. That could also partially explain male predominance in our study.

Patients in NCR were slightly older than patients in IMASIS and CDWBordeaux, underscoring the ability of cancer registries to capture the full scope of patients, including older patients with advanced disease who are less likely to be referred to specialised medical facilities. This observation is also supported by the demographic characteristics of individuals based on WHO-PS in NCR. Patients with WHO-PS 0 were younger than those with WHO-PS 1 and 2. This trend did not continue for WHO-PS 3, which likely represents a subset of patients with aggressive morphological forms that can be diagnosed at a younger age.

Patients who received chemotherapy as first-line therapy had a similar distribution in terms of age and sex compared to patients who received immunotherapy in IMASIS and NCR databases, while a higher percentage of males was observed among chemotherapy-treated patients in CDWBordeaux. However, these results are challenging to interpret due to the small sample size in CDWBordeaux. Across all WHO-PS categories in NCR, distribution by sex was similar in both treatment groups, with a slightly higher median age among immunotherapy-treated compared to chemotherapy in the WHO-PS 2 and 3. The overall distribution of WHO-PS levels was similar between treatment groups, with similar proportions of patients in each category.

Large-scale characterisation identified the conditions in locally advanced or metastatic NSCLC patients before and at diagnosis in CDWBordeaux and IMASIS. As expected, tobacco dependence, both in remission and continuously, as well as tobacco dependence syndrome and nicotine dependency, occurring one year to one month before diagnosis, represent the typical risk groups for lung cancer diagnosis. Common conditions recorded in CDWBordeaux up to the index date included dyspnoea and fatigue, which are common symptoms of lung cancer presentation. Notably, in IMASIS, COVID-19 was a prevalent condition not directly related to the NSCLC diagnosis, present in 13% of cases one year to one month prior and 18% one month to one day before diagnosis. Medications received before diagnosis were not specific; however, cancer treatment was most prevalent at the index date. Following the index date, medications in CDWBordeaux and IMASIS reflected supplementary drugs used in cancer treatment regimens and supportive care: steroids, solutions used in intravenous infusions, antiemetics, pain management, folates, and low molecular weight heparins. In NCR, only anticancer treatments were recorded. No notable differences were observed on patient characteristics (history of conditions and medication use) by cancer treatment subgroups.

Concerning PD-L1 status, most patients who received pembrolizumab and durvalumab exhibited PD-L1 expression levels greater than 1%—70% and 64%, respectively. In contrast, less than 60% of patients with PD-L1 expression above 1% were given chemotherapy. For pembrolizumab, 45% of patients had PD-L1 expression more than 50%, representing the highest proportion among all other treatment groups (compared to <35% in all other therapies). This suggests a selection of treatment based on PD-L1 expression, in line with indications for first line pembrolizumab – monotherapy for locally advanced or metastatic NSCLC, according to treatment guidelines.(31) The combination of pembrolizumab with chemotherapy is the treatment of choice for PD-L1 >50%, although it is sometimes given for PD-L1 expression <50%, in case of a more prognostically unfavourable disease.(32, 33) In the cases of ipilimumab and nivolumab, the clinical benefit in clinical trials was observed to be independent of PD-L1 expression,(10) and could have likely been used in combination with radiotherapy and possibly surgery during the period, as country-specific guidelines (the Netherlands) suggest their use in combination with chemotherapy for locally advanced or metastatic NSCLC with a PD-L1 expression <1%.(31, 34, 35) Meanwhile, for durvalumab, a PD-L1 expression above 1% was noted in the approval granted in 2021.

Different chemotherapy schemes, whether as doublet or monotherapy, were the most common treatment in CDWBordeaux, IMASIS, and NCR. Additionally, the combination of chemotherapy and immunotherapy was almost as common as using chemotherapy doublets in NCR. Focusing on specific regimens, a majority of advanced NSCLC patients in NCR received a combination of carboplatin, pemetrexed, and pembrolizumab, followed by pembrolizumab monotherapy and platinum-based doublets (cisplatin/carboplatin alongside pemetrexed or gemcitabine). This reflects national practices and guidelines that favour combining immunotherapy with chemotherapy or opting for pembrolizumab monotherapy. The use of other immunotherapy agents was considerably low in NCR. Some combinations represented unexpected treatment patterns, such as monotherapies with cisplatin or carboplatin, which are not recommended in current clinical guidelines and may reflect physician discretion based on individual patient characteristics, limitations in available treatment options, or potential data capture issues. Some regimens, such as cisplatin, cisplatin with docetaxel, or cisplatin with vinorelbine, are sometimes used together with radiotherapy during stage 3. Carboplatin and cisplatin are unlikely to be used in combination, and these likely represent switches related to toxicity. It must be noted that systemic treatments can be part of chemoradiation in stage 3, which we did not assess.

Pembrolizumab remained the most utilised immunotherapeutic drug. Notably, in 2016, no treatments with pembrolizumab (monotherapy or in combination) were identified, mirroring the approval timeline for this specific indication—first-line therapy. In NCR, a higher proportion of patients with WHO-PS 2 and 3 were treated with pembrolizumab monotherapy, while those with WHO-PS 0 and 1 were more likely to receive pembrolizumab in combination with chemotherapy, in accordance with local guidelines.(31)

Due to the small sample size in CDWBordeaux and IMASIS, the survival analysis focused only on treated patients in NCR.

Overall survival was higher for the pembrolizumab cohort compared to exclusive chemotherapy, although the absolute crude differences for the 2-year survival, 3-year survival were modest, at approximately 8% (35% versus 27%) and 7% (27% versus 20%), respectively. Similarly, the overall survival for pembrolizumab, while in line with results from clinical trials, yielded slightly lower probabilities than those reported in the first clinical trial. For instance, in KEYNOTE-024, the efficacy of pembrolizumab was investigated in previously untreated metastatic NSCLC with a PD-L1 expression >50% and no EGFR or ALK mutations. The 3-year survival estimates were 43.7% and 24.7% for the pembrolizumab and chemotherapy groups, respectively.(36) In contrast, the KEYNOTE-189 study included previously untreated patients with metastatic non-squamous NSCLC, no EGFR or ALK mutations, and no PD-L1 expression level was required. This trial investigated the efficacy of pembrolizumab in combination with chemotherapy, compared to

chemotherapy plus placebo. (37) The 3-year survival rates were 31.3% with pembrolizumab plus chemotherapy vs. 17.4% with chemotherapy alone, showing a survival benefit, though less pronounced than in KEYNOTE-024, likely related to differences in inclusion criteria.(36) The KEYNOTE-042 investigated the efficacy of pembrolizumab (monotherapy) compared to chemotherapy in previously untreated locally advanced or metastatic NSCLC and a PD-L1 expression >1%.(38) Overall survival outcomes favoured pembrolizumab (vs. chemotherapy) regardless of PD-L1 % expression, with 5-year survival estimates of 21.9%, 19.4%, and 16.6%, for PD-L1 expression of >50%, >20%, and >1%, respectively.

In the comparative effectiveness analyses, Cox proportional hazards models after PS matching by age, sex, index year, stage of tumour, and WHO-PS showed a HR of 0.66 (95%CI: 0.62-0.70) in the pembrolizumab cohort in comparison to the chemotherapy cohort. Consistent results were found in the estimated RMST difference analyses which showed higher survival in the pembrolizumab vs chemotherapy therapy group, with a RMST difference of 6.54 months (5.63, 7.46). The estimated HRs are in line with the KEYNOTE-189 clinical trial (37) which found a HR of 0.60 (0.50, 0.72), and the KEYNOTE-042 clinical trial (38) where HRs were 0.68 (0.57, 0.81), 0.75 (0.64, 0.87), and 0.79 (0.70, 0.89) for PD-L1 expression of >50%, >20%, and >1%, respectively, for pembrolizumab vs chemotherapy overall survival after 5 years follow-up.

In line with our findings, a nationwide study in Norway investigated the overall survival for pembrolizumab and chemotherapy in advanced NSCLC. Although median survival for patients treated with pembrolizumab (monotherapy=13.8 months, combination=12.8 months) was lower in clinical practice compared to clinical trials, the survival benefit identified in this study relative to chemotherapy was similar.(39) Survival of patients with metastatic NSCLC treated with chemotherapy or targeted therapy in real-world practice has been noted to be shorter than for patients included in trials, likely related to poor performance status, earlier discontinuation, and fewer subsequent lines of treatment.(40)

Less pronounced difference in survival estimates between pembrolizumab and chemotherapy cohorts compared to clinical trials could be related to comparing overall survival for first-line treatments without accounting for the effects of second-line therapy, which, in many instances, could be immunotherapy for patients in the chemotherapy cohort. Unfortunately, NCR does not explicitly capture information on the second-line treatment for all patients. Another point for consideration which could lead to less pronounced differences between pembrolizumab and chemotherapy, is that the use of these treatments varies based on other factors not accounted for in this study, such as EGFR- and ALK-expression mutations, ROS1 rearrangements, and more detailed staging classifications within each stage, or specific tumour histology, which limits the comparability of treatments concerning PD-L1 expression, staging, and survival outcomes.

Differences between immunotherapy and chemotherapy, especially for stage 3b, may be underestimated since our study did not account for local therapies, such as radiation. The combination of systemic chemotherapy and radiation has been associated with improvements in local tumour control and long-term survival, and, notably, concomitant radio-chemotherapy has been shown to improve overall survival to 15% at five years, but at the cost of significant toxicity. (41, 42)

The survival improvement observed for pembrolizumab over chemotherapy in the survival analysis was also observed in PS-matched model (matched on age, sex, stage of tumour, WHO-PS, and index year), supporting a clinical benefit from pembrolizumab when accounting for baseline differences. However, the variables used for adjustment were limited and residual confounding cannot be ruled out. Additionally, this study only assessed first line of treatment and further treatment lines may have influenced our estimates, especially second-line immunotherapy taking into account the PD-L1 status.

15.4 Generalisability

This study included data from 3 databases from 3 different European countries/regions (France, The Netherlands, Spain/Catalonia). Data came from secondary care (IMASIS and CDWBordeaux) and a cancer registry (NCR). However, not all data sources could inform all objectives, with objectives 2 and 3 being informed by NCR only. The lack of data availability on history of co-morbidities and medications in this database was an important limitation advising caution in interpretation. While we consider results largely representative of individuals newly diagnosed with locally advanced and metastatic NSCLC in The Netherlands, results should not be generalised to the whole of Europe as differences in population characteristics, treatments and survival may vary by country.

16. CONCLUSION

In this study, we have provided results on the large-scale characterisation of locally advanced or metastatic NSCLC patients at the time of start of treatment and a description of treatments and treatment combinations as first-line in three European databases. Sample size constraints limited the value of CDWBordeaux and IMASIS to address objectives 2 and 3, which were only conducted in NCR.

In NCR, we were able to provide an estimation of overall survival among patients treated with chemotherapy, pembrolizumab, nivolumab, and nivolumab and ipilimumab combination as first-line therapies. Overall survival varied by treatment type, with pembrolizumab showing the highest 3-year survival rates. Differences in survival were also observed across age, sex, tumour stage and PD-L1 expression, with younger patients, female sex, locally advanced NSCLC (stage 3b) and those with higher PD-L1 expression generally exhibiting higher survival.

We were unable to compare overall survival of patients with locally advanced or metastatic NSCLC under each immunotherapy to that of chemotherapy by using a target trial emulation design due to limited number of patients in IMASIS and CDWBordeaux, and the lack of information on patient history of comorbidities and medications in NCR, which did not allow for LSPS matching or negative control outcome analysis. However, in the PS matched model using only age, sex, stage of tumour, WHO-PS, and index year, pembrolizumab showed a survival benefit over chemotherapy exclusively as first-line therapy in locally advanced or metastatic NSCLC patients.

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18. ANNEXES

Appendix I. Dates of EMA approvals and code list definitions.

Table 1. Dates of EMA approval (any indication and study-site specific) and indications for selected immunotherapies for first-line treatment of locally advanced NSCLC in Europe.

EMA (https://www.ema.europa.eu/en/homepage)	Pembrolizumab	Nivolumab	Ipilimumab	Atezolizumab	Cemiplimab	Durvalumab	*Tremelimumab*
	KEYTRUDA	Nivolumab BMS / Opdivo	Yervoy	Tecentriq	Libtayo	Imfinzi	*Tremelimumab AstraZeneca / IMJUDO*
Initial approval for any indication (CHMP)	29-7-2015	23-4-2015	19-5-2011	20-7-2017	26-4-2019	26-7-2018	*15-12-2022*
Indication	KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	Opdivo as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	"Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy"	"Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible (see section 5.1). Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.	Libtayo as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation	Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.	*IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR*

EMA (https://www.ema.europa.eu/en/homepage)	Pembrolizumab	Nivolumab	Ipilimumab	Atezolizumab	Cemiplimab	Durvalumab	*Tremelimumab*
				Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq."			*mutations or ALK positive mutations.*
Approval for study site specific indication (CHMP) (if different)	23-6-2016	21/5/2015 - 30/11/2015	17-9-2020	20-7-2017	20-5-2021	26-7-2018	*15-12-2022*
Indication	"KEYTRUDA is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these	Nivolumab BMS is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults".	YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	"Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible (see section 5.1). Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic	Libtayo as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: • locally advanced NSCLC who are not candidates for definitive chemoradiation, or • metastatic NSCLC.	Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.	*IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer*

EMA (https://www.ema.europa.eu/en/homepage)	Pembrolizumab	Nivolumab	Ipilimumab	Atezolizumab	Cemiplimab	Durvalumab	*Tremelimumab*
	mutations prior to receiving KEYTRUDA."			non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq."			*(NSCLC) with no sensitising EGFR mutations or ALK positive mutations.*
Approval for study objective specific indication (CHMP) (if different)	**15-12-2016**	**17-9-2020**	**17-9-2020**	**31-1-2019**	**20-5-2021**	**26-7-2018**	***15-12-2022***
Indication	KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations"	OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in	Libtayo as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: • locally advanced NSCLC who are not candidates for definitive	Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.	*IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is*

EMA (https://www.ema.europa.eu/en/homepage)	Pembrolizumab	Nivolumab	Ipilimumab	Atezolizumab	Cemiplimab	Durvalumab	*Tremelimumab*
				combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies	chemoradiation, or • metastatic NSCLC.		*indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations.*

Table 2. Code list for advanced and metastatic NSCLC.

Concept Id	Concept Name
44501357	Acinar cell carcinoma of lower lobe, lung
44505032	Acinar cell carcinoma of lung, NOS
36560845	Acinar cell carcinoma of main bronchus
44501585	Acinar cell carcinoma of middle lobe, lung
36531338	Acinar cell carcinoma of overlapping lesion of lung
44502549	Acinar cell carcinoma of upper lobe, lung
36567582	Acinar cell cystadenocarcinoma of lower lobe, lung
36552952	Acinar cell cystadenocarcinoma of lung, NOS
36561283	Acinar cell cystadenocarcinoma of main bronchus
36564508	Acinar cell cystadenocarcinoma of middle lobe, lung
36520679	Acinar cell cystadenocarcinoma of overlapping lesion of lung
36541364	Acinar cell cystadenocarcinoma of upper lobe, lung
36546742	Adenocarcinoid tumour of lower lobe, lung
36554343	Adenocarcinoid tumour of lung, NOS
36551562	Adenocarcinoid tumour of main bronchus
36530898	Adenocarcinoid tumour of middle lobe, lung
36518168	Adenocarcinoid tumour of overlapping lesion of lung
36544100	Adenocarcinoid tumour of upper lobe, lung
4112738	Adenocarcinoma of lung
44499889	Adenocarcinoma of lung, mixed mucinous and non-mucinous of lower lobe, lung
44505023	Adenocarcinoma of lung, mixed mucinous and non-mucinous of lung, NOS
36560716	Adenocarcinoma of lung, mixed mucinous and non-mucinous of main bronchus
36520748	Adenocarcinoma of lung, mixed mucinous and non-mucinous of middle lobe, lung
36552385	Adenocarcinoma of lung, mixed mucinous and non-mucinous of overlapping lesion of lung
44502334	Adenocarcinoma of lung, mixed mucinous and non-mucinous of upper lobe, lung
44502623	Adenocarcinoma of lung, mucinous of lower lobe, lung
44505022	Adenocarcinoma of lung, mucinous of lung, NOS
36517902	Adenocarcinoma of lung, mucinous of main bronchus
36553787	Adenocarcinoma of lung, mucinous of middle lobe, lung
36528862	Adenocarcinoma of lung, mucinous of overlapping lesion of lung
44500448	Adenocarcinoma of lung, mucinous of upper lobe, lung
36543615	Adenocarcinoma with apocrine metaplasia of lower lobe, lung
36539915	Adenocarcinoma with apocrine metaplasia of lung, NOS
36548825	Adenocarcinoma with apocrine metaplasia of main bronchus
36543960	Adenocarcinoma with apocrine metaplasia of middle lobe, lung
36551818	Adenocarcinoma with apocrine metaplasia of overlapping lesion of lung
36542106	Adenocarcinoma with apocrine metaplasia of upper lobe, lung
36527609	Adenocarcinoma with cartilaginous and osseous metaplasia of lower lobe, lung

Concept Id	Concept Name
36548193	Adenocarcinoma with cartilaginous and osseous metaplasia of lung, NOS
36551189	Adenocarcinoma with cartilaginous and osseous metaplasia of main bronchus
36526019	Adenocarcinoma with cartilaginous and osseous metaplasia of middle lobe, lung
36549979	Adenocarcinoma with cartilaginous and osseous metaplasia of overlapping lesion of lung
36518654	Adenocarcinoma with cartilaginous and osseous metaplasia of upper lobe, lung
44502466	Adenocarcinoma with mixed subtypes of lower lobe, lung
44505024	Adenocarcinoma with mixed subtypes of lung, NOS
44501795	Adenocarcinoma with mixed subtypes of main bronchus
44502703	Adenocarcinoma with mixed subtypes of middle lobe, lung
36548626	Adenocarcinoma with mixed subtypes of overlapping lesion of lung
44500414	Adenocarcinoma with mixed subtypes of upper lobe, lung
36530431	Adenocarcinoma with neuroendocrine differentiation of lower lobe, lung
36564925	Adenocarcinoma with neuroendocrine differentiation of lung, NOS
36518010	Adenocarcinoma with neuroendocrine differentiation of main bronchus
36556919	Adenocarcinoma with neuroendocrine differentiation of middle lobe, lung
36532026	Adenocarcinoma with neuroendocrine differentiation of overlapping lesion of lung
44503034	Adenocarcinoma with neuroendocrine differentiation of upper lobe, lung
36535086	Adenocarcinoma with spindle cell metaplasia of lower lobe, lung
36567502	Adenocarcinoma with spindle cell metaplasia of lung, NOS
36553794	Adenocarcinoma with spindle cell metaplasia of main bronchus
36551342	Adenocarcinoma with spindle cell metaplasia of middle lobe, lung
36533348	Adenocarcinoma with spindle cell metaplasia of overlapping lesion of lung
36555776	Adenocarcinoma with spindle cell metaplasia of upper lobe, lung
36530839	Adenocarcinoma with squamous metaplasia of lower lobe, lung
36521617	Adenocarcinoma with squamous metaplasia of lung, NOS
36529004	Adenocarcinoma with squamous metaplasia of main bronchus
36552086	Adenocarcinoma with squamous metaplasia of middle lobe, lung
36536903	Adenocarcinoma with squamous metaplasia of overlapping lesion of lung
44502784	Adenocarcinoma with squamous metaplasia of upper lobe, lung
36546635	Adenocarcinoma, intestinal type of lung, NOS
42511919	Adenocarcinoma, intestinal type of upper lobe, lung
44501404	Adenocarcinoma, NOS, of lower lobe, lung
44505016	Adenocarcinoma, NOS, of lung, NOS
44500290	Adenocarcinoma, NOS, of main bronchus
44502329	Adenocarcinoma, NOS, of middle lobe, lung
36518742	Adenocarcinoma, NOS, of overlapping lesion of lung
44499882	Adenocarcinoma, NOS, of upper lobe, lung
1553230	Adenoid basal carcinoma of lung, NOS
44502769	Adenoid cystic carcinoma of lower lobe, lung
44505018	Adenoid cystic carcinoma of lung, NOS

Concept Id	Concept Name
36536437	Adenoid cystic carcinoma of main bronchus
44499686	Adenoid cystic carcinoma of middle lobe, lung
36531120	Adenoid cystic carcinoma of overlapping lesion of lung
36545242	Adenoid cystic carcinoma of upper lobe, lung
44503098	Adenosquamous carcinoma of lower lobe, lung
44505033	Adenosquamous carcinoma of lung, NOS
44502961	Adenosquamous carcinoma of main bronchus
44502885	Adenosquamous carcinoma of middle lobe, lung
36535081	Adenosquamous carcinoma of overlapping lesion of lung
44499900	Adenosquamous carcinoma of upper lobe, lung
36538056	Alveolar adenocarcinoma of lower lobe, lung
36558877	Alveolar adenocarcinoma of lung, NOS
36525316	Alveolar adenocarcinoma of main bronchus
44503152	Alveolar adenocarcinoma of middle lobe, lung
36559892	Alveolar adenocarcinoma of overlapping lesion of lung
44501794	Alveolar adenocarcinoma of upper lobe, lung
3654297	Anaplastic lymphoma kinase fusion oncogene negative non-small cell lung cancer
3654352	Anaplastic lymphoma kinase fusion oncogene positive non-small cell lung cancer
36566849	Basal cell adenocarcinoma of lower lobe, lung
36534932	Basal cell adenocarcinoma of lung, NOS
36560457	Basal cell adenocarcinoma of main bronchus
36523265	Basal cell adenocarcinoma of middle lobe, lung
36566204	Basal cell adenocarcinoma of overlapping lesion of lung
36549769	Basal cell adenocarcinoma of upper lobe, lung
36548902	Basaloid carcinoma of lower lobe, lung
36540691	Basaloid carcinoma of lung, NOS
36558592	Basaloid carcinoma of main bronchus
36555136	Basaloid carcinoma of middle lobe, lung
36536720	Basaloid carcinoma of overlapping lesion of lung
36524040	Basaloid carcinoma of upper lobe, lung
44503010	Basaloid squamous cell carcinoma of lower lobe, lung
44505013	Basaloid squamous cell carcinoma of lung, NOS
44502436	Basaloid squamous cell carcinoma of main bronchus
44501567	Basaloid squamous cell carcinoma of middle lobe, lung
36541713	Basaloid squamous cell carcinoma of overlapping lesion of lung
44500287	Basaloid squamous cell carcinoma of upper lobe, lung
44503018	Bronchiolo-alveolar carcinoma, non-mucinous of lower lobe, lung
44505021	Bronchiolo-alveolar carcinoma, non-mucinous of lung, NOS
36561810	Bronchiolo-alveolar carcinoma, non-mucinous of main bronchus
44500790	Bronchiolo-alveolar carcinoma, non-mucinous of middle lobe, lung

Concept Id	Concept Name
36531901	Bronchiolo-alveolar carcinoma, non-mucinous of overlapping lesion of lung
44499688	Bronchiolo-alveolar carcinoma, non-mucinous of upper lobe, lung
36547511	Carcinoma simplex of lower lobe, lung
36546260	Carcinoma simplex of lung, NOS
36529246	Carcinoma simplex of main bronchus
36529404	Carcinoma simplex of middle lobe, lung
36563697	Carcinoma simplex of overlapping lesion of lung
36536126	Carcinoma simplex of upper lobe, lung
36529581	Carcinoma with osteoclast-like giant cells of lower lobe, lung
36525643	Carcinoma with osteoclast-like giant cells of lung, NOS
36520147	Carcinoma with osteoclast-like giant cells of main bronchus
36548953	Carcinoma with osteoclast-like giant cells of middle lobe, lung
36561916	Carcinoma with osteoclast-like giant cells of overlapping lesion of lung
36551697	Carcinoma with osteoclast-like giant cells of upper lobe, lung
44499676	Carcinoma, anaplastic, NOS, of lower lobe, lung
36545372	Carcinoma, anaplastic, NOS, of lung, NOS
36565111	Carcinoma, anaplastic, NOS, of main bronchus
44501179	Carcinoma, anaplastic, NOS, of middle lobe, lung
36542965	Carcinoma, anaplastic, NOS, of overlapping lesion of lung
36543187	Carcinoma, anaplastic, NOS, of upper lobe, lung
44504995	Carcinoma, NOS, of lower lobe, lung
44505001	Carcinoma, NOS, of lung, NOS
44504988	Carcinoma, NOS, of main bronchus
44500629	Carcinoma, NOS, of middle lobe, lung
36530830	Carcinoma, NOS, of overlapping lesion of lung
44502676	Carcinoma, NOS, of upper lobe, lung
44502764	Carcinoma, undifferentiated, NOS, of lower lobe, lung
44505003	Carcinoma, undifferentiated, NOS, of lung, NOS
36567740	Carcinoma, undifferentiated, NOS, of main bronchus
44500114	Carcinoma, undifferentiated, NOS, of middle lobe, lung
36558543	Carcinoma, undifferentiated, NOS, of overlapping lesion of lung
44503538	Carcinoma, undifferentiated, NOS, of upper lobe, lung
36548325	Carcinosarcoma, embryonal of lower lobe, lung
36549830	Carcinosarcoma, embryonal of lung, NOS
36519168	Carcinosarcoma, embryonal of main bronchus
36531839	Carcinosarcoma, embryonal of middle lobe, lung
36565772	Carcinosarcoma, embryonal of overlapping lesion of lung
36561424	Carcinosarcoma, embryonal of upper lobe, lung
44501740	Carcinosarcoma, NOS, of lower lobe, lung
44505037	Carcinosarcoma, NOS, of lung, NOS

Concept Id	Concept Name
36549254	Carcinosarcoma, NOS, of main bronchus
36553640	Carcinosarcoma, NOS, of middle lobe, lung
36550205	Carcinosarcoma, NOS, of overlapping lesion of lung
44503111	Carcinosarcoma, NOS, of upper lobe, lung
44502949	Clear cell adenocarcinoma, NOS, of lower lobe, lung
44505026	Clear cell adenocarcinoma, NOS, of lung, NOS
44499508	Clear cell adenocarcinoma, NOS, of main bronchus
36556614	Clear cell adenocarcinoma, NOS, of middle lobe, lung
36567491	Clear cell adenocarcinoma, NOS, of overlapping lesion of lung
44499915	Clear cell adenocarcinoma, NOS, of upper lobe, lung
36567589	Cloacogenic carcinoma of lower lobe, lung
36544737	Cloacogenic carcinoma of lung, NOS
36561467	Cloacogenic carcinoma of main bronchus
36558610	Cloacogenic carcinoma of middle lobe, lung
36538830	Cloacogenic carcinoma of overlapping lesion of lung
36526155	Cloacogenic carcinoma of upper lobe, lung
36560854	Cribriform carcinoma, NOS, of lower lobe, lung
36519384	Cribriform carcinoma, NOS, of lung, NOS
36547678	Cribriform carcinoma, NOS, of main bronchus
36534747	Cribriform carcinoma, NOS, of middle lobe, lung
36565786	Cribriform carcinoma, NOS, of overlapping lesion of lung
36558515	Cribriform carcinoma, NOS, of upper lobe, lung
42511851	Cystadenocarcinoma, NOS, of lower lobe, lung
36535031	Enterochromaffin cell carcinoid of lower lobe, lung
44505020	Enterochromaffin cell carcinoid of lung, NOS
36549665	Enterochromaffin cell carcinoid of main bronchus
36520819	Enterochromaffin cell carcinoid of middle lobe, lung
36559151	Enterochromaffin cell carcinoid of overlapping lesion of lung
36529692	Enterochromaffin cell carcinoid of upper lobe, lung
36561922	Enterochromaffin-like cell tumour of lower lobe, lung
36527049	Enterochromaffin-like cell tumour of lung, NOS
36561609	Enterochromaffin-like cell tumour of main bronchus
36566155	Enterochromaffin-like cell tumour of middle lobe, lung
36537900	Enterochromaffin-like cell tumour of overlapping lesion of lung
36541362	Enterochromaffin-like cell tumour of upper lobe, lung
4140471	Epidermal growth factor receptor negative non-small cell lung cancer
4143825	Epidermal growth factor receptor positive non-small cell lung cancer
36545324	Epithelial-myoepithelial carcinoma of lower lobe, lung
36539299	Epithelial-myoepithelial carcinoma of lung, NOS
36552502	Epithelial-myoepithelial carcinoma of main bronchus

Concept Id	Concept Name
36550225	Epithelial-myoepithelial carcinoma of middle lobe, lung
36538432	Epithelial-myoepithelial carcinoma of overlapping lesion of lung
36553379	Epithelial-myoepithelial carcinoma of upper lobe, lung
36537690	Epithelioma, malignant of lower lobe, lung
36556677	Epithelioma, malignant of lung, NOS
36566002	Epithelioma, malignant of main bronchus
36517557	Epithelioma, malignant of middle lobe, lung
36525101	Epithelioma, malignant of overlapping lesion of lung
36525066	Epithelioma, malignant of upper lobe, lung
42512326	Foetal adenocarcinoma of lower lobe, lung
44505027	fatal adenocarcinoma of lung, NOS
42512311	foetal adenocarcinoma of main bronchus
42512102	fatal adenocarcinoma of middle lobe, lung
42512167	foetal adenocarcinoma of overlapping lesion of lung
42512758	fatal adenocarcinoma of upper lobe, lung
36517234	Giant cell and spindle cell carcinoma of lower lobe, lung
36552199	Giant cell and spindle cell carcinoma of lung, NOS
36529740	Giant cell and spindle cell carcinoma of main bronchus
36539842	Giant cell and spindle cell carcinoma of middle lobe, lung
36537196	Giant cell and spindle cell carcinoma of overlapping lesion of lung
36529691	Giant cell and spindle cell carcinoma of upper lobe, lung
44502320	Giant cell carcinoma of lower lobe, lung
44500541	Giant cell carcinoma of lung, NOS
44503539	Giant cell carcinoma of main bronchus
36544137	Giant cell carcinoma of middle lobe, lung
36532996	Giant cell carcinoma of overlapping lesion of lung
44500573	Giant cell carcinoma of upper lobe, lung
36560499	Glassy cell carcinoma of lower lobe, lung
36536786	Glassy cell carcinoma of lung, NOS
36555815	Glassy cell carcinoma of main bronchus
36545406	Glassy cell carcinoma of middle lobe, lung
36563276	Glassy cell carcinoma of overlapping lesion of lung
36541263	Glassy cell carcinoma of upper lobe, lung
36560910	Goblet cell carcinoid of lower lobe, lung
36527952	Goblet cell carcinoid of lung, NOS
36534372	Goblet cell carcinoid of main bronchus
36527622	Goblet cell carcinoid of middle lobe, lung
36543118	Goblet cell carcinoid of overlapping lesion of lung
36562068	Goblet cell carcinoid of upper lobe, lung
36518085	Granular cell carcinoma of lower lobe, lung

Concept Id	Concept Name
36532368	Granular cell carcinoma of lung, NOS
36567179	Granular cell carcinoma of main bronchus
36562795	Granular cell carcinoma of middle lobe, lung
36563562	Granular cell carcinoma of overlapping lesion of lung
36519172	Granular cell carcinoma of upper lobe, lung
36537768	Hepatoid adenocarcinoma of lower lobe, lung
36549522	Hepatoid adenocarcinoma of lung, NOS
36545761	Hepatoid adenocarcinoma of main bronchus
36562863	Hepatoid adenocarcinoma of middle lobe, lung
36558400	Hepatoid adenocarcinoma of overlapping lesion of lung
36557699	Hepatoid adenocarcinoma of upper lobe, lung
4110589	Large cell carcinoma of lung
4314040	Large cell carcinoma of lung, TNM stage 1
4307118	Large cell carcinoma of lung, TNM stage 2
4312768	Large cell carcinoma of lung, TNM stage 3
4313751	Large cell carcinoma of lung, TNM stage 4
44503537	Large cell carcinoma with rhabdoid phenotype of lower lobe, lung
36550921	Large cell carcinoma with rhabdoid phenotype of lung, NOS
36524261	Large cell carcinoma with rhabdoid phenotype of main bronchus
36560935	Large cell carcinoma with rhabdoid phenotype of middle lobe, lung
36526440	Large cell carcinoma with rhabdoid phenotype of overlapping lesion of lung
44502426	Large cell carcinoma with rhabdoid phenotype of upper lobe, lung
44501124	Large cell carcinoma, NOS, of lower lobe, lung
44500971	Large cell carcinoma, NOS, of lung, NOS
44500918	Large cell carcinoma, NOS, of main bronchus
44500183	Large cell carcinoma, NOS, of middle lobe, lung
36565647	Large cell carcinoma, NOS, of overlapping lesion of lung
44500841	Large cell carcinoma, NOS, of upper lobe, lung
44499863	Large cell neuroendocrine carcinoma of lower lobe, lung
44501059	Large cell neuroendocrine carcinoma of lung, NOS
44500480	Large cell neuroendocrine carcinoma of main bronchus
44500048	Large cell neuroendocrine carcinoma of middle lobe, lung
36561693	Large cell neuroendocrine carcinoma of overlapping lesion of lung
44501388	Large cell neuroendocrine carcinoma of upper lobe, lung
44500359	Lepidic adenocarcinoma of lower lobe, lung
44499741	Lepidic adenocarcinoma of lung, NOS
36565633	Lepidic adenocarcinoma of main bronchus
44500356	Lepidic adenocarcinoma of middle lobe, lung
36535558	Lepidic adenocarcinoma of overlapping lesion of lung
44501438	Lepidic adenocarcinoma of upper lobe, lung

Concept Id	Concept Name
36531398	Lymphoepithelial carcinoma of lower lobe, lung
36533051	Lymphoepithelial carcinoma of lung, NOS
36535188	Lymphoepithelial carcinoma of main bronchus
44499730	Lymphoepithelial carcinoma of middle lobe, lung
36520546	Lymphoepithelial carcinoma of overlapping lesion of lung
44501617	Lymphoepithelial carcinoma of upper lobe, lung
36545284	Malignant tumour, clear cell type of lower lobe, lung
36527781	Malignant tumour, clear cell type of lung, NOS
36522516	Malignant tumour, clear cell type of main bronchus
36522910	Malignant tumour, clear cell type of middle lobe, lung
36566035	Malignant tumour, clear cell type of overlapping lesion of lung
36518733	Malignant tumour, clear cell type of upper lobe, lung
36524292	Malignant tumour, giant cell type of lower lobe, lung
36550795	Malignant tumour, giant cell type of lung, NOS
36530810	Malignant tumour, giant cell type of main bronchus
36559936	Malignant tumour, giant cell type of middle lobe, lung
36535659	Malignant tumour, giant cell type of overlapping lesion of lung
36567622	Malignant tumour, giant cell type of upper lobe, lung
36540207	Malignant tumour, spindle cell type of lower lobe, lung
36552710	Malignant tumour, spindle cell type of lung, NOS
36523996	Malignant tumour, spindle cell type of main bronchus
36554594	Malignant tumour, spindle cell type of middle lobe, lung
36546341	Malignant tumour, spindle cell type of overlapping lesion of lung
36526134	Malignant tumour, spindle cell type of upper lobe, lung
44499898	Medullary carcinoma, NOS, of lower lobe, lung
36526857	Medullary carcinoma, NOS, of lung, NOS
36540041	Medullary carcinoma, NOS, of main bronchus
36555685	Medullary carcinoma, NOS, of middle lobe, lung
36529915	Medullary carcinoma, NOS, of overlapping lesion of lung
36564670	Medullary carcinoma, NOS, of upper lobe, lung
36565803	Metaplastic carcinoma, NOS, of lower lobe, lung
36526753	Metaplastic carcinoma, NOS, of lung, NOS
36549552	Metaplastic carcinoma, NOS, of main bronchus
36547828	Metaplastic carcinoma, NOS, of middle lobe, lung
36548970	Metaplastic carcinoma, NOS, of overlapping lesion of lung
36522427	Metaplastic carcinoma, NOS, of upper lobe, lung
36684857	Metastatic non-small cell lung cancer
42512265	Micropapillary carcinoma, NOS, of lower lobe, lung
42512505	Micropapillary carcinoma, NOS, of lung, NOS
42512456	Micropapillary carcinoma, NOS, of main bronchus

Concept Id	Concept Name
42511962	Micropapillary carcinoma, NOS, of middle lobe, lung
42512801	Micropapillary carcinoma, NOS, of overlapping lesion of lung
42512752	Micropapillary carcinoma, NOS, of upper lobe, lung
42512246	Minimally invasive adenocarcinoma, mucinous of lower lobe, lung
42512620	Minimally invasive adenocarcinoma, mucinous of lung, NOS
42512222	Minimally invasive adenocarcinoma, mucinous of main bronchus
42512380	Minimally invasive adenocarcinoma, mucinous of middle lobe, lung
42512616	Minimally invasive adenocarcinoma, mucinous of overlapping lesion of lung
42512867	Minimally invasive adenocarcinoma, mucinous of upper lobe, lung
42512859	Minimally invasive adenocarcinoma, non-mucinous of lower lobe, lung
42512336	Minimally invasive adenocarcinoma, non-mucinous of lung, NOS
42512569	Minimally invasive adenocarcinoma, non-mucinous of main bronchus
42511979	Minimally invasive adenocarcinoma, non-mucinous of middle lobe, lung
42511673	Minimally invasive adenocarcinoma, non-mucinous of overlapping lesion of lung
42511853	Minimally invasive adenocarcinoma, non-mucinous of upper lobe, lung
44500933	Mixed adenoneuroendocrine carcinoma of lower lobe, lung
36550952	Mixed adenoneuroendocrine carcinoma of lung, NOS
36537376	Mixed adenoneuroendocrine carcinoma of main bronchus
36544341	Mixed adenoneuroendocrine carcinoma of middle lobe, lung
36559841	Mixed adenoneuroendocrine carcinoma of overlapping lesion of lung
44501493	Mixed adenoneuroendocrine carcinoma of upper lobe, lung
36532293	Mixed cell adenocarcinoma of lower lobe, lung
36529938	Mixed cell adenocarcinoma of lung, NOS
36563834	Mixed cell adenocarcinoma of main bronchus
36563105	Mixed cell adenocarcinoma of middle lobe, lung
36537460	Mixed cell adenocarcinoma of overlapping lesion of lung
36567546	Mixed cell adenocarcinoma of upper lobe, lung
44501411	Mucin-producing adenocarcinoma of lower lobe, lung
44503093	Mucin-producing adenocarcinoma of lung, NOS
44500302	Mucin-producing adenocarcinoma of main bronchus
44500303	Mucin-producing adenocarcinoma of middle lobe, lung
36530069	Mucin-producing adenocarcinoma of overlapping lesion of lung
44502876	Mucin-producing adenocarcinoma of upper lobe, lung
44502341	Mucinous adenocarcinoma of lower lobe, lung
44505030	Mucinous adenocarcinoma of lung, NOS
44502952	Mucinous adenocarcinoma of main bronchus
44502543	Mucinous adenocarcinoma of middle lobe, lung
36556450	Mucinous adenocarcinoma of overlapping lesion of lung
44500072	Mucinous adenocarcinoma of upper lobe, lung
36520186	Mucinous cystadenocarcinoma, NOS, of lower lobe, lung

Concept Id	Concept Name
44505029	Mucinous cystadenocarcinoma, NOS, of lung, NOS
44500201	Mucinous cystadenocarcinoma, NOS, of upper lobe, lung
44501086	Mucoepidermoid carcinoma of lower lobe, lung
44505028	Mucoepidermoid carcinoma of lung, NOS
36565274	Mucoepidermoid carcinoma of main bronchus
44502109	Mucoepidermoid carcinoma of middle lobe, lung
36530344	Mucoepidermoid carcinoma of overlapping lesion of lung
44502238	Mucoepidermoid carcinoma of upper lobe, lung
36539178	Myoepithelial carcinoma of lower lobe, lung
44505038	Myoepithelial carcinoma of lung, NOS
36533557	Myoepithelial carcinoma of main bronchus
36524452	Myoepithelial carcinoma of middle lobe, lung
36564894	Myoepithelial carcinoma of overlapping lesion of lung
36526943	Myoepithelial carcinoma of upper lobe, lung
44504994	Neoplasm, malignant of lower lobe, lung
44504998	Neoplasm, malignant of lung, NOS
44504985	Neoplasm, malignant of main bronchus
44499479	Neoplasm, malignant of middle lobe, lung
36530340	Neoplasm, malignant of overlapping lesion of lung
44504990	Neoplasm, malignant of upper lobe, lung
44503150	Neuroendocrine carcinoma, NOS, of lower lobe, lung
44502105	Neuroendocrine carcinoma, NOS, of lung, NOS
44499502	Neuroendocrine carcinoma, NOS, of main bronchus
44501887	Neuroendocrine carcinoma, NOS, of middle lobe, lung
36523843	Neuroendocrine carcinoma, NOS, of overlapping lesion of lung
44502938	Neuroendocrine carcinoma, NOS, of upper lobe, lung
44501408	Neuroendocrine tumour, grade 2 of lower lobe, lung
44503017	Neuroendocrine tumour, grade 2 of lung, NOS
44501264	Neuroendocrine tumour, grade 2 of main bronchus
44502106	Neuroendocrine tumour, grade 2 of middle lobe, lung
36532214	Neuroendocrine tumour, grade 2 of overlapping lesion of lung
44500647	Neuroendocrine tumour, grade 2 of upper lobe, lung
44500865	Neuroendocrine tumour, NOS, of lower lobe, lung
44499438	Neuroendocrine tumour, NOS, of lung, NOS
44502936	Neuroendocrine tumour, NOS, of main bronchus
44502772	Neuroendocrine tumour, NOS, of middle lobe, lung
36556766	Neuroendocrine tumour, NOS, of overlapping lesion of lung
44500726	Neuroendocrine tumour, NOS, of upper lobe, lung
44500188	Non-small cell carcinoma of lower lobe, lung
44505008	Non-small cell carcinoma of lung, NOS

Concept Id	Concept Name
4310703	Non-small cell carcinoma of lung, TNM stage 1
4314172	Non-small cell carcinoma of lung, TNM stage 2
4311997	Non-small cell carcinoma of lung, TNM stage 3
4308479	Non-small cell carcinoma of lung, TNM stage 4
44500713	Non-small cell carcinoma of main bronchus
44501471	Non-small cell carcinoma of middle lobe, lung
36551824	Non-small cell carcinoma of overlapping lesion of lung
44499422	Non-small cell carcinoma of upper lobe, lung
4115276	Non-small cell lung cancer
45766129	Non-small cell lung cancer with mutation in epidermal growth factor receptor
45766131	Non-small cell lung cancer without mutation in epidermal growth factor receptor
605821	Non-small cell lung carcinoma with NRG1 fusion
4208307	Nonsquamous nonsmall cell neoplasm of lung
42512043	Nuclear protein in testis (NUT)-associated carcinoma of lower lobe, lung
42512060	Nuclear protein in testis (NUT)-associated carcinoma of lung, NOS
42511764	Nuclear protein in testis (NUT)-associated carcinoma of main bronchus
42512203	Nuclear protein in testis (NUT)-associated carcinoma of middle lobe, lung
42512108	Nuclear protein in testis (NUT)-associated carcinoma of overlapping lesion of lung
42511775	Nuclear protein in testis (NUT)-associated carcinoma of upper lobe, lung
44500415	Papillary adenocarcinoma, NOS, of lower lobe, lung
44505025	Papillary adenocarcinoma, NOS, of lung, NOS
44500730	Papillary adenocarcinoma, NOS, of main bronchus
44502943	Papillary adenocarcinoma, NOS, of middle lobe, lung
36555703	Papillary adenocarcinoma, NOS, of overlapping lesion of lung
44502176	Papillary adenocarcinoma, NOS, of upper lobe, lung
44499007	Papillary carcinoma, NOS, of lower lobe, lung
44503004	Papillary carcinoma, NOS, of lung, NOS
44500343	Papillary carcinoma, NOS, of main bronchus
36522300	Papillary carcinoma, NOS, of middle lobe, lung
36533515	Papillary carcinoma, NOS, of overlapping lesion of lung
44500577	Papillary carcinoma, NOS, of upper lobe, lung
44501061	Papillary squamous cell carcinoma of lower lobe, lung
44505010	Papillary squamous cell carcinoma of lung, NOS
44501394	Papillary squamous cell carcinoma of main bronchus
36561274	Papillary squamous cell carcinoma of middle lobe, lung
36560118	Papillary squamous cell carcinoma of overlapping lesion of lung
44501613	Papillary squamous cell carcinoma of upper lobe, lung
44499866	Pleomorphic carcinoma of lower lobe, lung
44505004	Pleomorphic carcinoma of lung, NOS
44500843	Pleomorphic carcinoma of main bronchus

Concept Id	Concept Name
44501558	Pleomorphic carcinoma of middle lobe, lung
36519829	Pleomorphic carcinoma of overlapping lesion of lung
44501926	Pleomorphic carcinoma of upper lobe, lung
36561699	Polygonal cell carcinoma of lower lobe, lung
36539661	Polygonal cell carcinoma of lung, NOS
44502006	Polygonal cell carcinoma of main bronchus
36539223	Polygonal cell carcinoma of middle lobe, lung
36523297	Polygonal cell carcinoma of overlapping lesion of lung
36529321	Polygonal cell carcinoma of upper lobe, lung
36712707	Primary adenocarcinoma of lower lobe of left lung
36712709	Primary adenocarcinoma of lower lobe of right lung
45768916	Primary adenocarcinoma of lung
602150	Primary adenocarcinoma of middle lobe of right lung
36712708	Primary adenocarcinoma of upper lobe of left lung
36717017	Primary adenocarcinoma of upper lobe of right lung
45768928	Primary adenoid cystic carcinoma of lung
45768881	Primary adenosquamous carcinoma of lung
46272955	Primary clear cell adenocarcinoma of lung
45768879	Primary foetal adenocarcinoma of lung
45768930	Primary mixed mucinous and non-mucinous bronchiolo-alveolar carcinoma of lung
45768880	Primary mixed subtype adenocarcinoma of lung
45768917	Primary mucinous adenocarcinoma of lung
45768932	Primary mucinous bronchiolo-alveolar carcinoma of lung
45769034	Primary mucinous cystadenocarcinoma of lung
45772939	Primary mucoepidermoid carcinoma of lung
45768927	Primary myoepithelial carcinoma of lung
45768931	Primary non-mucinous bronchiolo-alveolar carcinoma of lung
609080	Primary non-small cell carcinoma of left lung
609079	Primary non-small cell carcinoma of right lung
45768886	Primary papillary adenocarcinoma of lung
45768929	Primary salivary gland type carcinoma of lung
45768885	Primary solid carcinoma of lung
44499947	Pseudosarcomatous carcinoma of lower lobe, lung
44505006	Pseudosarcomatous carcinoma of lung, NOS
44501560	Pseudosarcomatous carcinoma of main bronchus
44499623	Pseudosarcomatous carcinoma of middle lobe, lung
36517425	Pseudosarcomatous carcinoma of overlapping lesion of lung
44500710	Pseudosarcomatous carcinoma of upper lobe, lung
36561198	Pulmonary blastoma of lower lobe, lung
36568076	Pulmonary blastoma of lung, NOS

Concept Id	Concept Name
36530883	Pulmonary blastoma of main bronchus
36531963	Pulmonary blastoma of middle lobe, lung
36567381	Pulmonary blastoma of overlapping lesion of lung
44500809	Pulmonary blastoma of upper lobe, lung
3654301	Reactive oxygen species 1 negative non-small cell lung cancer
36716426	Reactive oxygen species 1 positive non-small cell lung cancer
36523412	Schneiderian carcinoma of lower lobe, lung
36538057	Schneiderian carcinoma of lung, NOS
36530722	Schneiderian carcinoma of main bronchus
36538858	Schneiderian carcinoma of middle lobe, lung
36556624	Schneiderian carcinoma of overlapping lesion of lung
36556267	Schneiderian carcinoma of upper lobe, lung
36541038	Scirrhous adenocarcinoma of lower lobe, lung
36539497	Scirrhous adenocarcinoma of lung, NOS
36521066	Scirrhous adenocarcinoma of main bronchus
36549175	Scirrhous adenocarcinoma of middle lobe, lung
36526433	Scirrhous adenocarcinoma of overlapping lesion of lung
36525052	Scirrhous adenocarcinoma of upper lobe, lung
44499513	Signet ring cell carcinoma of lower lobe, lung
44505031	Signet ring cell carcinoma of lung, NOS
44500458	Signet ring cell carcinoma of main bronchus
36539786	Signet ring cell carcinoma of middle lobe, lung
36536832	Signet ring cell carcinoma of overlapping lesion of lung
44502711	Signet ring cell carcinoma of upper lobe, lung
44502390	Solid carcinoma, NOS, of lower lobe, lung
44505019	Solid carcinoma, NOS, of lung, NOS
36541699	Solid carcinoma, NOS, of main bronchus
36545286	Solid carcinoma, NOS, of middle lobe, lung
36531543	Solid carcinoma, NOS, of overlapping lesion of lung
44500061	Solid carcinoma, NOS, of upper lobe, lung
44502856	Spindle cell carcinoma, NOS, of lower lobe, lung
44505005	Spindle cell carcinoma, NOS, of lung, NOS
44499621	Spindle cell carcinoma, NOS, of main bronchus
36528414	Spindle cell carcinoma, NOS, of middle lobe, lung
36538391	Spindle cell carcinoma, NOS, of overlapping lesion of lung
44501559	Spindle cell carcinoma, NOS, of upper lobe, lung
36557771	Squamous cell carcinoma with horn formation of lower lobe, lung
36557751	Squamous cell carcinoma with horn formation of lung, NOS
36541027	Squamous cell carcinoma with horn formation of main bronchus
36538464	Squamous cell carcinoma with horn formation of middle lobe, lung

Concept Id	Concept Name
36531136	Squamous cell carcinoma with horn formation of overlapping lesion of lung
36556975	Squamous cell carcinoma with horn formation of upper lobe, lung
36545785	Squamous cell carcinoma, adenoid of lower lobe, lung
36561870	Squamous cell carcinoma, adenoid of lung, NOS
36522039	Squamous cell carcinoma, adenoid of main bronchus
36548201	Squamous cell carcinoma, adenoid of middle lobe, lung
36566369	Squamous cell carcinoma, adenoid of overlapping lesion of lung
36525571	Squamous cell carcinoma, adenoid of upper lobe, lung
44500239	Squamous cell carcinoma, clear cell type of lower lobe, lung
44505014	Squamous cell carcinoma, clear cell type of lung, NOS
36531347	Squamous cell carcinoma, clear cell type of main bronchus
36554751	Squamous cell carcinoma, clear cell type of middle lobe, lung
36567060	Squamous cell carcinoma, clear cell type of overlapping lesion of lung
44500855	Squamous cell carcinoma, clear cell type of upper lobe, lung
44500190	Squamous cell carcinoma, keratinizing, NOS, of lower lobe, lung
44501707	Squamous cell carcinoma, keratinizing, NOS, of lung, NOS
44501188	Squamous cell carcinoma, keratinizing, NOS, of main bronchus
44502921	Squamous cell carcinoma, keratinizing, NOS, of middle lobe, lung
36567522	Squamous cell carcinoma, keratinizing, NOS, of overlapping lesion of lung
44503136	Squamous cell carcinoma, keratinizing, NOS, of upper lobe, lung
44503138	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of lower lobe, lung
44499726	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of lung, NOS
44500433	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of main bronchus
44501709	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of middle lobe, lung
36520827	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of overlapping lesion of lung
44499794	Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of upper lobe, lung
44500348	Squamous cell carcinoma, microinvasive of lower lobe, lung
36554642	Squamous cell carcinoma, microinvasive of lung, NOS
36567972	Squamous cell carcinoma, microinvasive of main bronchus
36549159	Squamous cell carcinoma, microinvasive of middle lobe, lung
36541640	Squamous cell carcinoma, microinvasive of overlapping lesion of lung
36552939	Squamous cell carcinoma, microinvasive of upper lobe, lung
44499488	Squamous cell carcinoma, NOS, of lower lobe, lung
44505011	Squamous cell carcinoma, NOS, of lung, NOS
44501335	Squamous cell carcinoma, NOS, of main bronchus
44499010	Squamous cell carcinoma, NOS, of middle lobe, lung
36531819	Squamous cell carcinoma, NOS, of overlapping lesion of lung
44500984	Squamous cell carcinoma, NOS, of upper lobe, lung
44501516	Squamous cell carcinoma, spindle cell of lower lobe, lung
36543984	Squamous cell carcinoma, spindle cell of lung, NOS

Concept Id	Concept Name
36567150	Squamous cell carcinoma, spindle cell of main bronchus
44502457	Squamous cell carcinoma, spindle cell of middle lobe, lung
36535903	Squamous cell carcinoma, spindle cell of overlapping lesion of lung
44501310	Squamous cell carcinoma, spindle cell of upper lobe, lung
37109576	Squamous non-small cell lung cancer
36532437	Superficial spreading adenocarcinoma of lower lobe, lung
36537250	Superficial spreading adenocarcinoma of lung, NOS
36561009	Superficial spreading adenocarcinoma of main bronchus
36546410	Superficial spreading adenocarcinoma of middle lobe, lung
36521546	Superficial spreading adenocarcinoma of overlapping lesion of lung
36518808	Superficial spreading adenocarcinoma of upper lobe, lung
36525385	Transitional cell carcinoma, NOS, of lower lobe, lung
44500587	Transitional cell carcinoma, NOS, of lung, NOS
36550929	Transitional cell carcinoma, NOS, of main bronchus
36554307	Transitional cell carcinoma, NOS, of middle lobe, lung
36557711	Transitional cell carcinoma, NOS, of overlapping lesion of lung
44503204	Transitional cell carcinoma, NOS, of upper lobe, lung
36564290	Tumour cells, malignant of lower lobe, lung
36568204	Tumour cells, malignant of lung, NOS
36568135	Tumour cells, malignant of main bronchus
36527742	Tumour cells, malignant of middle lobe, lung
36529129	Tumour cells, malignant of overlapping lesion of lung
36547553	Tumour cells, malignant of upper lobe, lung
36402618	Tumorlet, malignant of main bronchus
36526133	Urothelial carcinoma, sarcomatoid of lower lobe, lung
36564406	Urothelial carcinoma, sarcomatoid of lung, NOS
36565366	Urothelial carcinoma, sarcomatoid of main bronchus
36546625	Urothelial carcinoma, sarcomatoid of middle lobe, lung
36532630	Urothelial carcinoma, sarcomatoid of overlapping lesion of lung
36549209	Urothelial carcinoma, sarcomatoid of upper lobe, lung
36538987	Verrucous carcinoma, NOS, of lower lobe, lung
36538582	Verrucous carcinoma, NOS, of lung, NOS
36537230	Verrucous carcinoma, NOS, of main bronchus
36559186	Verrucous carcinoma, NOS, of middle lobe, lung
36531433	Verrucous carcinoma, NOS, of overlapping lesion of lung
36562727	Verrucous carcinoma, NOS, of upper lobe, lung
44501791	Vipoma of lower lobe, lung
1635230	AJCC/UICC 7th pathological Stage 4
1635745	AJCC/UICC 7th pathological Stage 4A
1634537	AJCC/UICC 7th pathological Stage 4A1

Concept Id	Concept Name
1633372	AJCC/UICC 7th pathological Stage 4A2
1634472	AJCC/UICC 7th pathological Stage 4B
1634492	AJCC/UICC 7th pathological Stage 4C
1633697	AJCC/UICC 8th pathological Stage 4
1634005	AJCC/UICC 8th pathological Stage 4A
1633786	AJCC/UICC 8th pathological Stage 4A1
1633298	AJCC/UICC 8th pathological Stage 4A2
1634487	AJCC/UICC 8th pathological Stage 4B
1634551	AJCC/UICC 8th pathological Stage 4C
1634688	AJCC/UICC pathological Stage 4
1635232	AJCC/UICC pathological Stage 4A
1635365	AJCC/UICC pathological Stage 4A1
1634063	AJCC/UICC pathological Stage 4A2
1633577	AJCC/UICC pathological Stage 4B
1635567	AJCC/UICC pathological Stage 4C
1635336	AJCC/UICC 7th pathological M1 Category
1634268	AJCC/UICC 7th pathological M1a Category
1635008	AJCC/UICC 7th pathological M1b Category
1634188	AJCC/UICC 7th pathological M1c Category
1634325	AJCC/UICC 7th pathological M1d Category
1634891	AJCC/UICC 8th pathological M1 Category
1635097	AJCC/UICC 8th pathological M1a Category
1634712	AJCC/UICC 8th pathological M1b Category
1634657	AJCC/UICC 8th pathological M1c Category
1634526	AJCC/UICC 8th pathological M1d Category
1635505	AJCC/UICC pathological M1 Category
1634312	AJCC/UICC pathological M1a Category
1634093	AJCC/UICC pathological M1b Category
1635338	AJCC/UICC pathological M1c Category
1635373	AJCC/UICC pathological M1d Category
1635530	AJCC/UICC 7th clinical T4 Category
1634522	AJCC/UICC 7th clinical T4a Category
1634120	AJCC/UICC 7th clinical T4b Category
1634046	AJCC/UICC 7th clinical T4c Category
1635768	AJCC/UICC 7th clinical T4d Category
1634641	AJCC/UICC 7th clinical T4e Category
1634576	AJCC/UICC 7th T4 Category
1634724	AJCC/UICC 7th T4a Category
1634162	AJCC/UICC 7th T4b Category
1634476	AJCC/UICC 7th T4c Category

Concept Id	Concept Name
1635275	AJCC/UICC 7th T4d Category
1633604	AJCC/UICC 7th T4e Category
1634973	AJCC/UICC 8th clinical T4 Category
1634963	AJCC/UICC 8th clinical T4a Category
1634854	AJCC/UICC 8th clinical T4b Category
1633767	AJCC/UICC 8th clinical T4c Category
1635022	AJCC/UICC 8th clinical T4d Category
1635648	AJCC/UICC 8th clinical T4e Category
1635242	AJCC/UICC 8th T4 Category
1633411	AJCC/UICC 8th T4a Category
1634318	AJCC/UICC 8th T4b Category
1633399	AJCC/UICC 8th T4c Category
1634582	AJCC/UICC 8th T4d Category
1634096	AJCC/UICC 8th T4e Category
1635558	AJCC/UICC clinical T4 Category
1634192	AJCC/UICC clinical T4a Category
1634291	AJCC/UICC clinical T4b Category
1634877	AJCC/UICC clinical T4c Category
1635368	AJCC/UICC clinical T4d Category
1634561	AJCC/UICC clinical T4e Category
1634654	AJCC/UICC T4 Category
1635222	AJCC/UICC T4a Category
1634436	AJCC/UICC T4b Category
1635526	AJCC/UICC T4c Category
1633909	AJCC/UICC T4d Category
1634193	AJCC/UICC T4e Category
1633276	AJCC/UICC 7th clinical M1 Category
1635878	AJCC/UICC 7th clinical M1a Category
1635302	AJCC/UICC 7th clinical M1b Category
1635461	AJCC/UICC 7th clinical M1c Category
1633666	AJCC/UICC 7th clinical M1d Category
1633696	AJCC/UICC 7th M1 Category
1634775	AJCC/UICC 7th M1a Category
1635747	AJCC/UICC 7th M1b Category
1635843	AJCC/UICC 7th M1c Category
1633866	AJCC/UICC 7th M1d Category
1633974	AJCC/UICC 8th clinical M1 Category
1635149	AJCC/UICC 8th clinical M1a Category
1633375	AJCC/UICC 8th clinical M1b Category
1633784	AJCC/UICC 8th clinical M1c Category

Concept Id	Concept Name
1633799	AJCC/UICC 8th clinical M1d Category
1633498	AJCC/UICC 8th M1 Category
1634082	AJCC/UICC 8th M1a Category
1634661	AJCC/UICC 8th M1b Category
1634975	AJCC/UICC 8th M1c Category
1634259	AJCC/UICC 8th M1d Category
1635085	AJCC/UICC clinical M1 Category
1633777	AJCC/UICC clinical M1a Category
1635090	AJCC/UICC clinical M1b Category
1635255	AJCC/UICC clinical M1c Category
1634048	AJCC/UICC clinical M1d Category
1635142	AJCC/UICC M1 Category
1635100	AJCC/UICC M1a Category
1634463	AJCC/UICC M1b Category
1635519	AJCC/UICC M1c Category
1634064	AJCC/UICC M1d Category

Table 3. List of medication codes.

	Concept name	Concept id*
1	Pembrolizumab	45775965
2	Nivolumab	45892628
3	Atezolizumab	42629079
4	Cemiplimab	35200783
5	Durvalumab	1594034
6	Ipilimumab	40238188
7	Cisplatin	1397599
8	Carboplatin	1344905
9	Pemetrexed	1304919
10	Paclitaxel	1378382
11	Docetaxel	1315942
12	Gemcitabine	1314924
13	Vinorelbine	1343346

*Including all descendants.

Appendix II. Supplementary results

Table 1. Comparison of overall survival of patients with locally advanced or metastatic NSCLC under pembrolizumab to that of exclusive chemotherapy as first-line treatment in NCR after propensity score matching and covariate adjustment.

Target cohort	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Hazard Ratio	95% CI
PS matching								
Pembrolizumab	3,003	1,966	Chemotherapy	3,003	2,332	PASS	0.66	0.62-0.70
Nivolumab	212	212	Chemotherapy	147	49	FAIL	0.91	0.72-1.14
Nivolumab and ipilimumab	62	27	Chemotherapy	62	38	FAIL	0.53	0.32-0.87
Covariate adjustment								
Pembrolizumab	7,993	4,907	Chemotherapy	5,309	4,029	FAIL	0.63	0.60-0.63
Nivolumab	213	147	Chemotherapy	5,387	4,099	FAIL	0.84	0.71-1.00
Nivolumab and ipilimumab	62	27	Chemotherapy	5,316	4,037	FAIL	0.57	0.37-0.82

Propensity score matching was conducting including the following list of covariates: age, sex, index year, stage of tumour, and ECOG/WHO performance status. Models were adjusted for age, sex, index year, stage of tumour, and ECOG/WHO performance status.

Table 2. Characteristics before and after propensity score matching, showing the (weighted) percentage of subjects with the characteristics in the target (*Pembrolizumab*) and comparator (*Chemotherapy*) cohort, as well as the standardised difference of the means in NCR.

covariateName	Before Matching MeanTreated	Before Matching MeanComparator	absBefore Matching StdDiff	After Matching MeanTreated	After Matching MeanComparator	absAfter Matching StdDiff
Age group (years)						
20 - 24	-0,001	-0,001	0,007	0	-0,002	0
25 - 29	-0,001	-0,001	0,007	-0,002	-0,002	0
30 - 34	0,002	0,001	0,001	0,002	0,002	0
35 - 39	0,004	0,005	0,014	0,003	0,004	0,016
40 - 44	0,012	0,011	0,009	0,012	0,01	0,016
45 - 49	0,03	0,031	0,008	0,028	0,031	0,014
50 - 54	0,074	0,064	0,038	0,069	0,066	0,012
55 - 59	0,119	0,126	0,022	0,127	0,126	0,002
60 - 64	0,174	0,186	0,031	0,179	0,179	0,001
65 - 69	0,206	0,196	0,023	0,196	0,201	0,013
70 - 74	0,194	0,204	0,025	0,207	0,198	0,023

covariateName	Before Matching MeanTreated	Before Matching MeanComparator	absBefore Matching StdDiff	After Matching MeanTreated	After Matching MeanComparator	absAfter Matching StdDiff
75 - 79	0,129	0,126	0,009	0,124	0,129	0,015
80 - 84	0,048	0,042	0,028	0,043	0,044	0,008
85 - 89	0,008	0,006	0,024	0,008	0,008	0
90 - 94	0,001	-0,001	0,025	-0,002	-0,002	0,015
95 - 99	-0,001	0	0	-0,002	0	0
Age in years	65,941	65,819	0,013	65,917	65,91	0,001
Gender						
FEMALE	0,453	0,433	0,039	0,442	0,437	0,01
MALE	0,547	0,567	0,039	0,558	0,563	0,01
Index year						
2016	-0,001	0,046	0,337	-0,002	-0,002	0,012
2017	0,025	0,124	0,399	0,068	0,077	0,037
2018	0,09	0,299	0,55	0,239	0,23	0,021
2019	0,19	0,185	0,012	0,227	0,22	0,017
2020	0,217	0,124	0,243	0,154	0,164	0,026
2021	0,244	0,115	0,328	0,161	0,161	0,001
2022	0,233	0,107	0,327	0,151	0,148	0,009
measurement during day -180 through 0 days relative to index						
AJCC/UICC 8th pathological Stage 4A	0,003	0,008	0,07	0,008	0,008	0,007
AJCC/UICC 7th clinical Stage 3B	-0,001	0,013	0,177	-0,002	-0,002	0,015
AJCC/UICC 7th clinical Stage 4	-0,001	0,041	0,315	-0,002	-0,002	0,012
AJCC/UICC 8th clinical Stage 3C	0,03	0,087	0,253	0,081	0,081	0
AJCC/UICC 8th clinical Stage 4	-0,001	0,001	0,028	-0,002	0,002	0,029
AJCC/UICC 8th clinical Stage 4A	0,352	0,264	0,191	0,367	0,354	0,028
AJCC/UICC 8th clinical Stage 4B	0,581	0,319	0,524	0,454	0,463	0,019
AJCC/UICC 8th pathological Stage 3B	0,001	0,034	0,274	0,003	0,003	0,006
measurement during day -30 through 0 days						

covariateName	Before Matching MeanTreated	Before Matching MeanComparator	absBefore Matching StdDiff	After Matching MeanTreated	After Matching MeanComparator	absAfter Matching StdDiff
relative to index						
AJCC/UICC 7th clinical Stage 3B	0	0,007	0	0	0	0
AJCC/UICC 7th clinical Stage 4	-0,001	0,016	0,192	-0,002	-0,002	0,015
AJCC/UICC 8th clinical Stage 3B	0,02	0,158	0,52	0,054	0,054	0,001
AJCC/UICC 8th clinical Stage 3C	0,018	0,057	0,215	0,049	0,049	0,003
AJCC/UICC 8th clinical Stage 4A	0,169	0,13	0,107	0,171	0,169	0,006
AJCC/UICC 8th clinical Stage 4B	0,278	0,159	0,282	0,222	0,224	0,003
AJCC/UICC 8th pathological Stage 3B	-0,001	0,003	0,073	-0,002	-0,002	0,015
AJCC/UICC 8th pathological Stage 4A	0,001	-0,001	0,003	0,002	-0,002	0,029
AJCC/UICC 8th pathological Stage 4B	-0,001	0	0	-0,002	0	0
measurement during day -365 through 0 days relative to index						
AJCC/UICC 8th clinical Stage 3B	0,036	0,245	0,642	0,096	0,095	0,005
AJCC/UICC 8th pathological Stage 4B	0,001	0,002	0,027	0,002	0,002	0,008
condition_era during day -30 through 0 days relative to index						
WHO performance status grade 1	0,216	0,207	0,023	0,209	0,21	0,002
WHO performance status grade 3	0,008	0,008	0,002	0,008	0,01	0,028
condition_occurrence during day -180						

covariateName	Before Matching MeanTreated	Before Matching MeanComparator	absBefore Matching StdDiff	After Matching MeanTreated	After Matching MeanComparator	absAfter Matching StdDiff
through 0 days relative to index						
WHO performance status grade 1	0,429	0,37	0,12	0,396	0,399	0,007
WHO performance status grade 2	0,086	0,089	0,01	0,107	0,099	0,026
condition_occurrence during day -30 through 0 days relative to index						
WHO performance status grade 0	0,162	0,176	0,038	0,16	0,162	0,005
WHO performance status grade 1	0,206	0,202	0,009	0,201	0,203	0,006
WHO performance status grade 2	0,042	0,05	0,041	0,057	0,052	0,021
WHO performance status grade 3	0,008	0,008	0,003	0,007	0,01	0,033
WHO performance status grade 4	0,001	-0,001	0	-0,002	-0,002	0,012
WHO performance status grade 0	0,337	0,349	0,024	0,34	0,335	0,009
WHO performance status grade 3	0,017	0,014	0,024	0,017	0,019	0,015
WHO performance status grade 4	0,002	0,001	0,01	0,003	0,002	0,014

Table 3. Diagnostics of propensity score (PS) matching and covariate adjustment models.

Target cohort	Covariate Balance Max SDM (<= 0.1)	Shared Covariate Balance Max SDM (<= 0.1)	Equipoise (>=0.2)	MDRR (<=10)	Generalizability Max SDM (<=1)
PS matching					
Pembrolizumab	0.037	0.037	0.293	1.089	0.521
Nivolumab	0.167	0.167	0.428	1.385	0.024
Nivolumab and ipilimumab	0.274	0.274	0.416	2.003	0.000

Target cohort	Covariate Balance Max SDM (<= 0.1)	Shared Covariate Balance Max SDM (<= 0.1)	Equipoise (>=0.2)	MDRR (<=10)	Generalizability Max SDM (<=1)
Covariate adjustment					
Pembrolizumab	0.656	0.656	-	1.062	0.063
Nivolumab	0.446	0.446	-	1.252	0.029
Nivolumab and ipilimumab	1.232	1.232	-	1.509	0.091

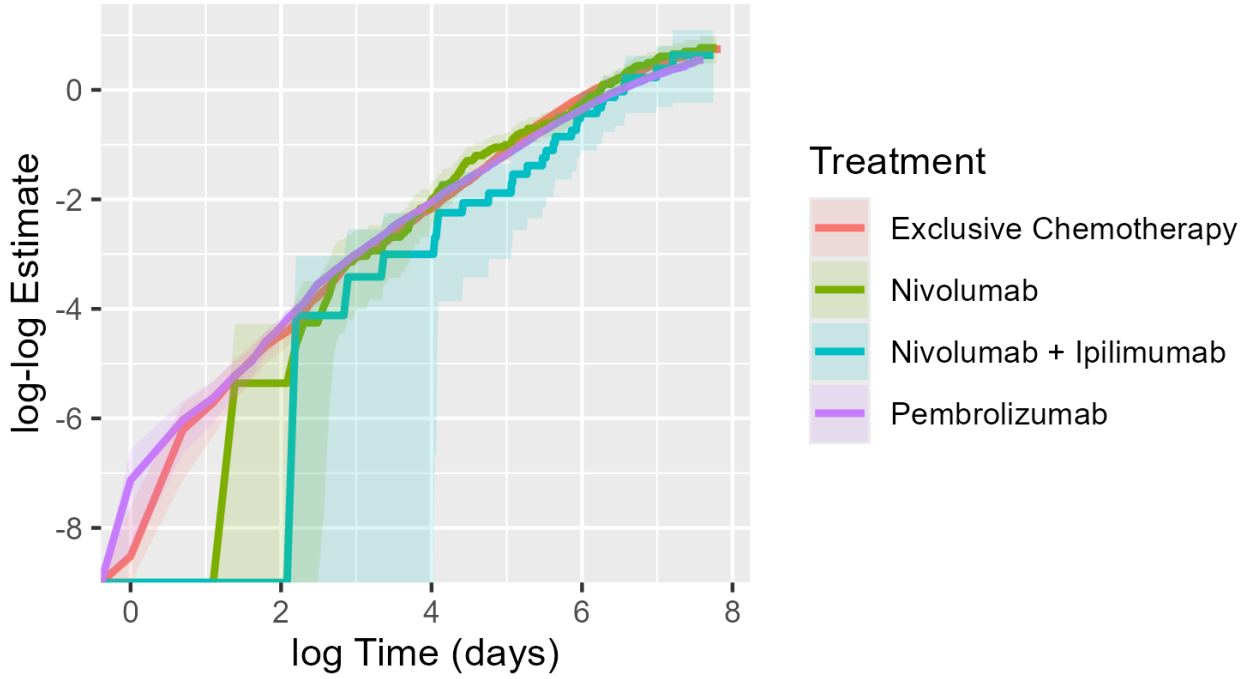

Figure 1. Model log-log estimate for locally advanced or metastatic NSCLC (stages 3b or 4).

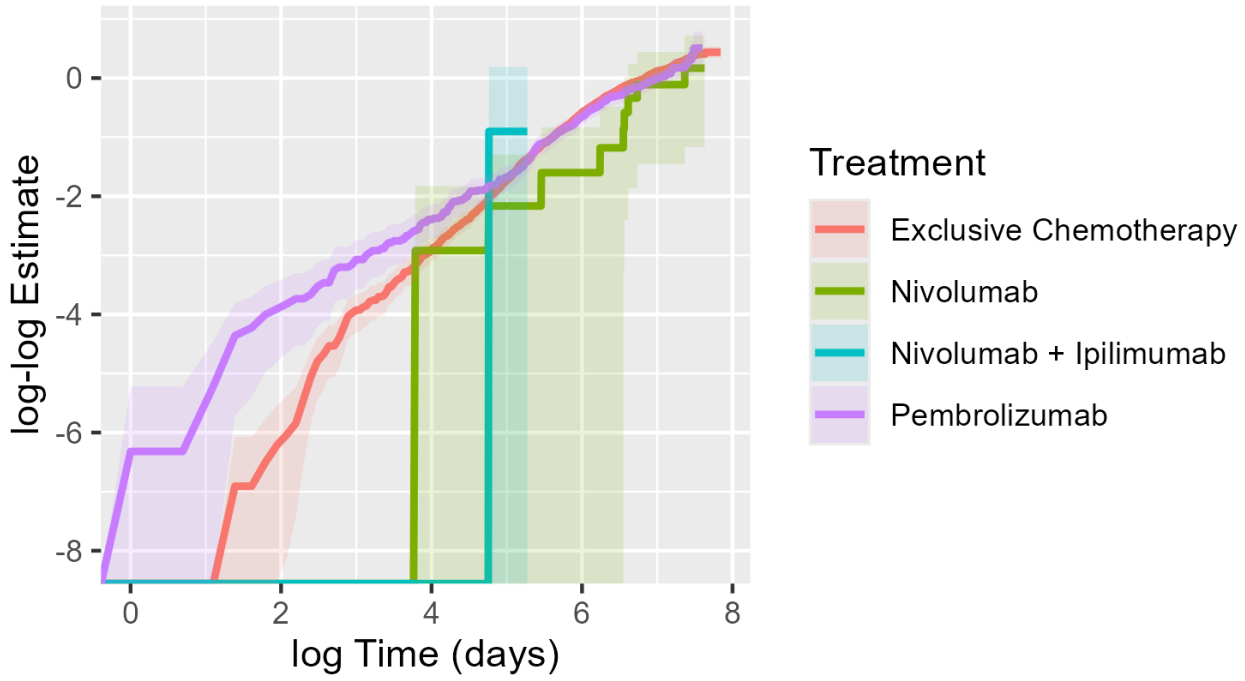

Figure 2. Model log-log estimate for locally advanced NSCLC (stage 3b).

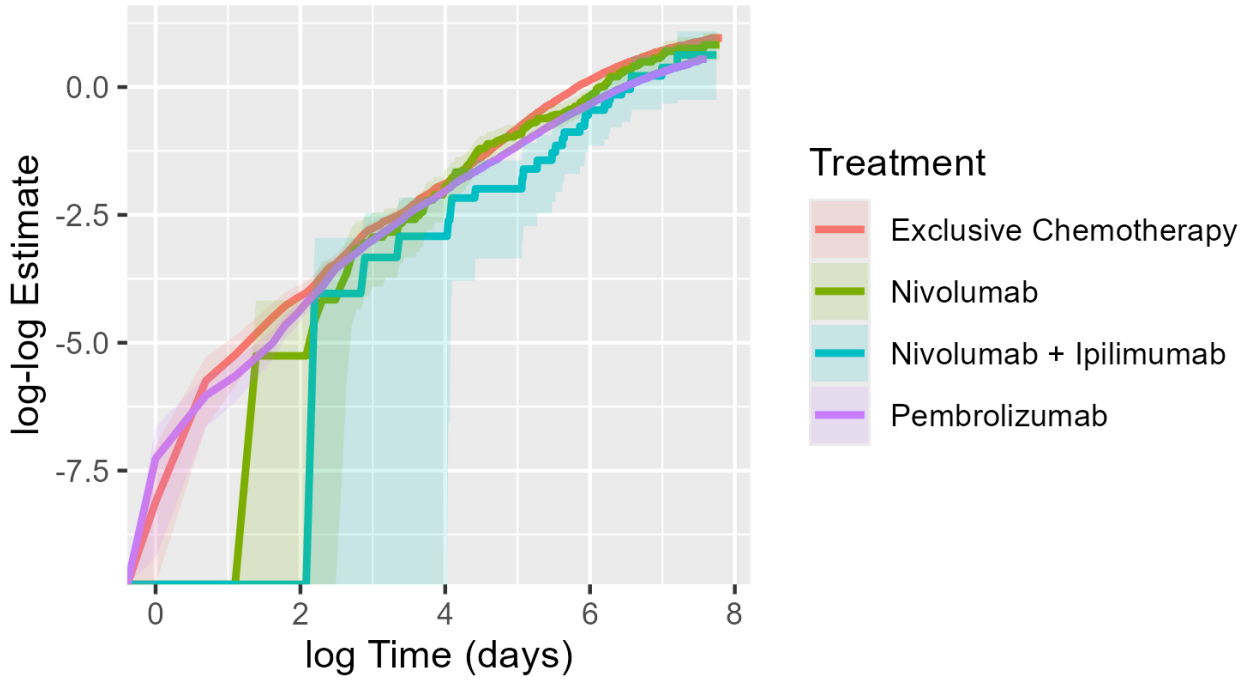

Figure 3. Model log-log estimate metastatic NSCLC (stage 4).

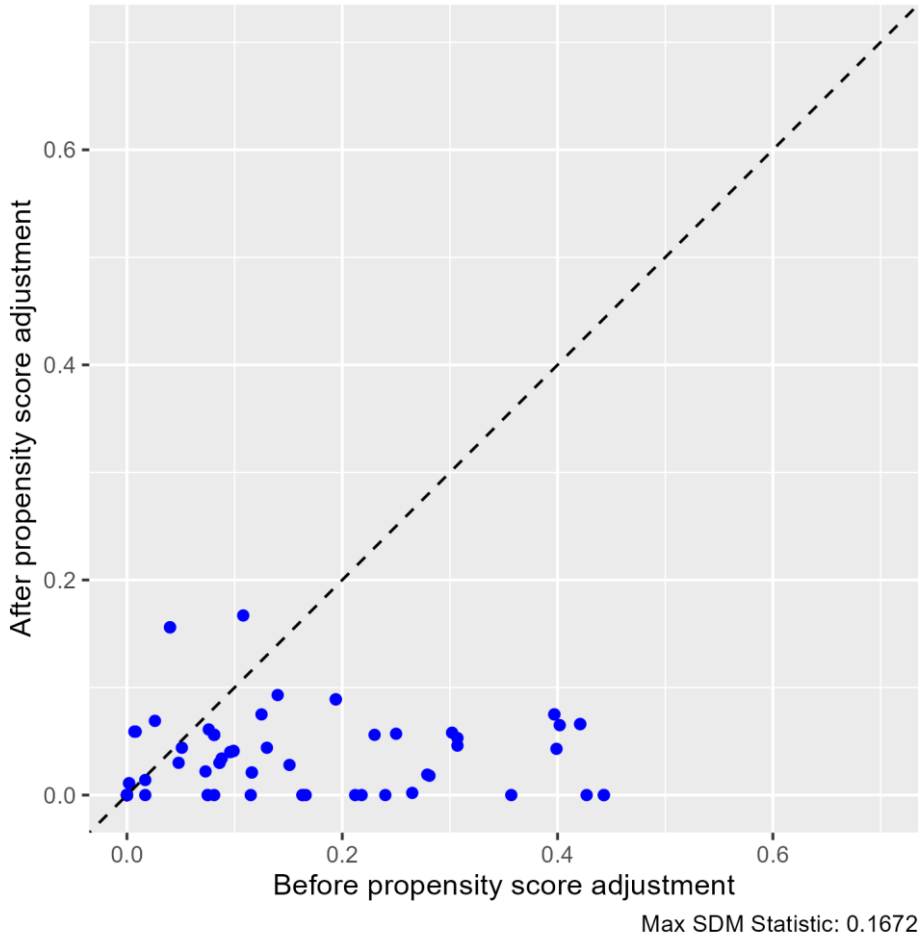

Figure 4. Covariate balance before and after propensity score adjustment (target cohort Nivolumab – stage 3b and 4). Each dot represents the standardised difference of means for a single covariate before and after propensity score adjustment on the propensity score. The maximum absolute standardised difference of the mean (Max SDM) is given at the bottom of the figure.

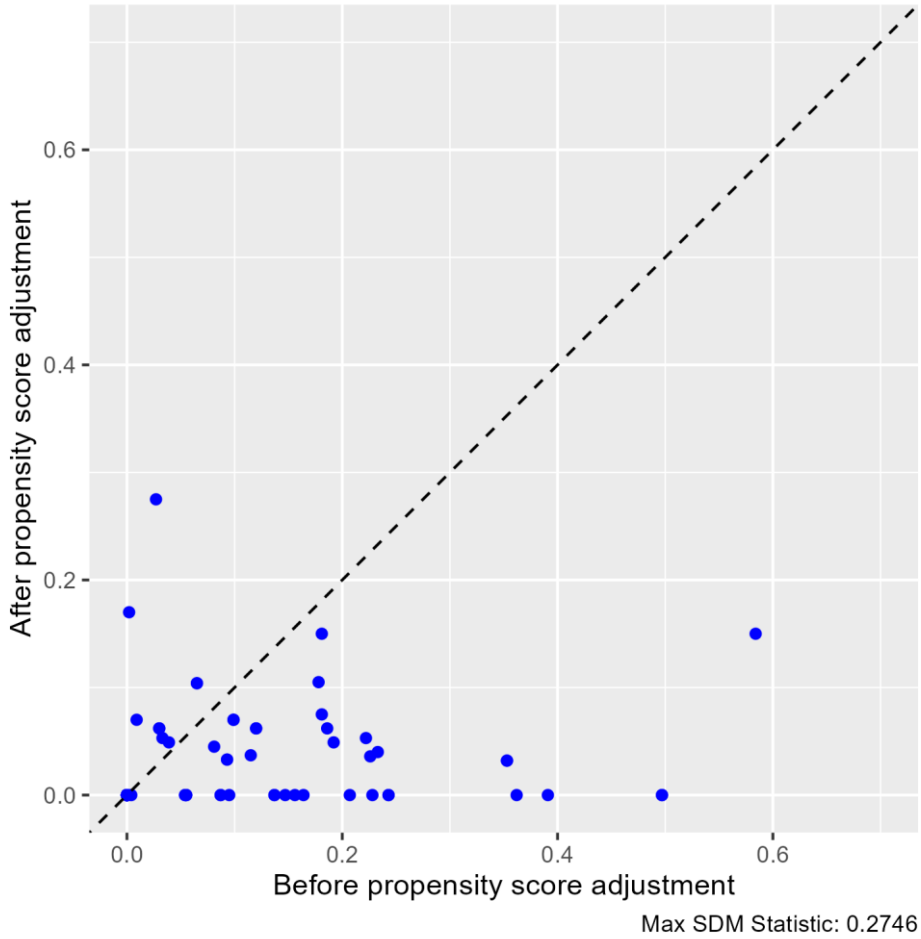

Figure 5. Covariate balance before and after propensity score adjustment (target cohort Nivolumab and ipilimumab– stage 3b and 4). Each dot represents the standardised difference of means for a single covariate before and after propensity score adjustment on the propensity score. The maximum absolute standardised difference of the mean (Max SDM) is given at the bottom of the figure.