Nivolumab plus ipilimumab plus chemo vs pembrolizumab plus chemo in PD-L1 negative metastatic NSCLC patients: comparative effectiveness using the target trial emulation framework.

First published: 30/10/2026

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Study Planned

Administrative details

EU PAS number

EUPAS1000001143

Study ID

1000001143

DARWIN EU® study

No

Study countries

Netherlands

Study description

This retrospective new user active comparator cohort study adapting the target trial emulation frameowrk enables the head-to-head comparison of nivolumab plus ipilimumab plus platinum doublet chemotherapy (CheckMate 9LA)with pembrolizumab plus platinum doublet chemotherapy (KEYNOTE-189 and KEYNOTE-407) in adults with metastatic stage IV NSCLC; using data from the Dutch Medication Audit (DMA) and the Dutch Lung Cancer Audit - lungcarcinoma (DLCA-L) from the Dutch Institute for Clinical Auditing (DICA).

At the time of writing the protocol, the authors became aware of the planned study EUPAS1000000987, part of the TARGET-EU project. However, this study protocol has been designed and will be executed independently from the TARGET-EU team, and will make use of a different observational data source. As a result, this study provides additional knowledge on the head-to-head effectiveness on top of the original KEYNOTE and CheckMate trials and the TARGET-EU study, and provide knowledge on how to design and execute trial emulations of randomized controlled trials for lung cancer using the estimand framework (to allow for independent comparison with the TARGET-EU study).

Moreover, as secondary analyses in this study, cost-effectiveness will be assessed for both therapies (Track A) and different estimands for the effectiveness will be studied to see their methodological implications (Track B).

Study status

Planned

Research institutions and networks

Institutions

University of Groningen

Netherlands

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Institution | Educational Institution

University Medical Center Groningen

Dutch Institute for Clinical Auditing, Medicines Evaluation Board.

Contact details

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 02/03/2026

Study start date
Planned: 01/09/2026

Data analysis start date
Planned: 01/11/2026

Date of interim report, if expected
Planned: 31/12/2026

Date of final study report
Planned: 01/02/2027

Sources of funding

- EU institutional research programme

More details on funding

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Study protocol

EUPAS1000001143_study_protocol.pdf (1.15 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Method development or testing

Data collection methods:

Secondary use of data

Study design:

Retrospective new user active comparator cohort study

Main study objective:

To estimate the difference in average overall survival (OS) if all adults with stage IV, PD-L1 < 1% NSCLC had initiated nivolumab, ipilimumab and chemotherapy compared to if they all had initiated pembrolizumab and chemotherapy.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

NIVOLUMAB

IPILIMUMAB

PEMBROLIZUMAB

CARBOPLATIN

CISPLATIN

PACLITAXEL

PEMETREXED

Anatomical Therapeutic Chemical (ATC) code

(L01FF01) nivolumab

nivolumab

(L01FX04) ipilimumab

ipilimumab

(L01FF02) pembrolizumab

pembrolizumab

(L01XA02) carboplatin

carboplatin

(L01XA01) cisplatin

cisplatin

(L01CD01) paclitaxel

paclitaxel

(L01BA04) pemetrexed

pemetrexed

Medical condition to be studied

Non-small cell lung cancer stage IV

Population studied

Short description of the study population

Adults with newly diagnosed metastatic NSCLC and PD-L1<1%

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)

- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Study design details

Setting

Adults (≥18 years) with newly diagnosed metastatic NSCLC, a PD-L1<1%, ECOG PS ≤ 1, no prior systemic anticancer therapy, prior radiotherapy to the lung within 6 months of trial-treatment initiation, and no major surgery or traumatic injury within 21 days before enrollment -
who are registered in both the Dutch Medication Audit (DMA) and Dutch Lung Cancer Audit (lungcarcinoma) DLCA-L - will be followed from the moment of first administration of either the exposure (nivolumab+ipilimumab+chemotherapy) or the comparator (pembrolizumab+chemotherapy) until the outcome or the end of their observed data, whichever occured first.

Comparators

(pembrolizumab plus carboplatin + paclitaxel) OR (pembrolizumab plus cisplatin or carboplatin + pemetrexed)

Outcomes

Primary: Death, Secondary: time to next treatment, treatment duration, healthcare utilization.

Data analysis plan

Primary analysis.
A flexible parametric survival model will be used, due to their ease-of-use when it comes to confounding adjustment and predicting the counterfactuals (using

the g-formula) to estimate the restricted mean survival time (RMST) from treatment initiation to death up to 3 years, with supplementary cutoffs at 4 and 5 years. Secondary, a Cox proportional hazards model will be used to estimate the proportional hazards over time.
When excluding the unobserved confounders, the adjustment set exists of the following covariates: age, sex, smoking history, ECOG PS, histology, the treating hospital, TNM stage, and the presence of CNS, bone and liver metastases. These will be used in the parametric Royston-Parmar model and semi-parametric Cox Proportional Hazards regression. There are two censoring events: (1) last observation / L2FU (indistinguishable) and (2) end of data collection. These censoring events are assumed to be administrative, therefore no IPCW is required.

For details regarding missing data methods, see the study protocol. For secondary and exploratory analyses, see the study protocol.

Summary results

Not available.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Dutch Medication Audit (DMA);

Dutch Lung Cancer Audit - Lungcarcinoma (DLCA-L).

Data sources (types)

Cancer registry

Disease registry

Drug registry

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown