Title	Nivolumab plus ipilimumab plus chemo vs pembrolizumab plus chemo in PD-L1 negative metastatic NSCLC patients: comparative effectiveness using the target trial emulation framework.
Research question & Objectives	This study primary aims to compare the overall survival between nivolumab plus ipilimumab plus chemo and pembrolizumab plus chemo in patients with PD-L1 negative, metastatic NSCLC.
Protocol version	V1
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Study registration	**Site:** University Medical Center Groningen **Identifier:** n/a
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Conflict of interest	S. Verweij received funding from the Medicines Evaluation Board for his PhD. C. Boersma has received consultation fees, paid expert testimony, funding or grants, speaking and lecture fees, and travel reimbursement from various medical- and pharmaceutical companies and public institutes via Health-Ecore B.V. (advisory company), and has stock ownership in Health-Ecore B.V., Digital Health Link B.V., SensUR Health B.V., Digital Health Inform Holding B.V., and Pharmecore Holding B.V. O. Schuurbiers has received travel reimbursement from Johnsen & Johnsen and is chair of the Dutch Lung Cancer Audit – Lung Oncology (DLCA-L) registry. W. van Geffen is a Fiduciary Officer for the NVALT (Dutch Society of Respiratory Physicians), a medical advisor for the Netherlands Comprehensive Cancer Organisation (IKNL), and a site investigator for trials run by his department funded by Roche, Pfizer, Novartis, Novocure and MSD, BMS, Taiho, Abbvie, Mirati, Amgen. All other authors have no competing interests to declare.

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2. Abstract

Background: In the Netherlands, nivolumab plus ipilimumab plus platinum-doublet chemotherapy and pembrolizumab plus platinum-doublet chemotherapy are both used in the first line in patients with PD-L1 negative metastatic non-small cell lung cancer (NSCLC). [1] Nivolumab plus ipilimumab plus chemotherapy is considered potentially more effective than pembrolizumab plus chemotherapy, based on the 5-year overall survival (OS) in PD-L1-negative patients (22% vs 10-11%, respectively) reported in the CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407 studies. [2–4] However, uncertainty remains regarding which schedule is most effective, as a direct head-to-head comparison is lacking in the trials supporting their registration. [5]

Objectives: In this study, we will compare nivolumab and ipilimumab plus platinum doublet chemotherapy with pembrolizumab plus platinum doublet chemotherapy in patients with PD-L1 negative, stage IV, NSCLC for the first three years of follow-up, aiming to reproduce the original trial results to assess effectiveness in the real world. Longer follow-up data is limited and will therefore be considered as exploratory analysis.

Methods: We will use observational (non-randomized) data from Dutch clinical practice, using registry data from the Dutch Institute for Clinical Auditing. Newly diagnosed stage IV, PD-L1 negative, adult (>18 years) NSCLC patients receiving nivolumab plus ipilimumab plus chemotherapy or pembrolizumab plus chemotherapy will be included. The primary estimand this study targets is the difference in average OS, expressed as the absolute difference in restricted mean survival time (RMST) up to three years. RMST will be estimated by calculating the area under the survival curve, with t_{cut} set at three years. The g-formula will be applied to account for baseline differences between treatment groups. OS will also be estimated using Kaplan-Meier techniques and Cox regression. Our secondary estimand is the difference in average time-to-next treatment and treatment duration, as a proxy for progression-free survival (PFS). Another secondary estimand includes incremental cost-effectiveness, which will be calculated for life years and QALYs using a Markov model (track A). As an exploratory objective, different estimands for the OS and PFS will be estimated to gain methodological knowledge on the definitions of estimands in observational studies. A hypothetical strategy will be used for the intercurrent event of treatment discontinuation due to toxicity (track B).

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
19 October 2026	V1	All	Completed protocol	Finalized protocol and send out to contributors for approval of submission to RWD catalogues.

4. Milestones

Table 1 Milestones

Milestone	Date
Finalize protocol	19 October 2026
Upload protocol to EMA's RWD catalogue	29 October 2026
Data access	1 July 2026
Finish data analysis	1 December 2026
Finish first version of the manuscript	1 January 2027
Publication submitted	1 February 2027

5. Rationale and background

What is known about the condition: In 2024, lung cancer was estimated to have the highest incidence and mortality rates among all cancer types worldwide.[6] Of all lung cancer cases, approximately 87% are non-small cell lung cancer (NSCLC). [7] Of all patients with NSCLC in the Netherlands, nearly half (49%) were diagnosed with stage IV (metastatic) disease in 2023. [8] Non-squamous NSCLC is more likely to contain genetic mutations that drive cancer growth (e.g., EGFR, ALK, and KRAS) compared to squamous NSCLC. [9] These mutations allow the use of targeted therapies.[9] Tumors without these genetic mutations rely more heavily on chemotherapy and immunotherapy. All non-oncogene-addicted metastatic NSCLC cases (squamous and non-squamous) are recommended for programmed death-ligand 1 (PD-L1) immuno-histochemistry testing, as these allow for immunotherapy monotherapy (e.g., pembrolizumab monotherapy for PD-L1>50%). [10]

What is known about the exposure of interest: Nivolumab, ipilimumab and pembrolizumab are checkpoint inhibiters. Nivolumab and pembrolizumab bind to the programmed death-1 (PD-1) receptor, a cell receptor that is a negative regulator of T-cells, and thus Nivolumab and pembrolizumab potentiates T-cell responses, including anti-tumor responses. [11,12] Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumor cells. [13] These immune therapies are often combined with chemotherapy. [10]

In the Netherlands, nivolumab plus ipilimumab plus platinum-doublet chemotherapy, and pembrolizumab plus platinum-doublet chemotherapy are both used in the first line in PD-L1 negative patients with metastatic (stage IV) NSCLC. [1] They have been approved in the EU since September 2020 and July 2018, respectively. [14,15] Nivolumab plus ipilimumab plus chemotherapy is considered potentially more effective than pembrolizumab plus chemotherapy, based on the five-year overall survival (OS) in PD-L1-negative patients (22% vs 10-11%, respectively) reported in the CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407 studies, in which nivolumab plus ipilimumab plus chemotherapy was compared to chemotherapy alone (CheckMate 9LA), and pembrolizumab plus chemotherapy was compared to chemotherapy alone (KEYNOTE-189 and KEYNOTE-407). [2–4]

Gaps in knowledge: A well powered direct head-to-head comparison of nivolumab plus ipilimumab plus platinum doublet chemotherapy and pembrolizumab plus platinum doublet chemotherapy is missing.

What is the expected contribution of this study? This study enables the head-to-head comparison of nivolumab plus ipilimumab plus platinum doublet chemotherapy and pembrolizumab plus platinum doublet chemotherapy. At the time of writing the protocol, the authors became aware of the planned study EUPAS1000000987, [16] part of the TARGET-EU project. However, this study protocol has been developed independently from the TARGET-EU study and will use a different observational data source. As a result, this proposed study will provide additional knowledge on top of the original trials and the TARGET-EU study on the effectiveness of nivolumab plus ipilimumab plus chemotherapy, pembrolizumab plus chemotherapy, and how to design and execute emulations of randomized controlled trials for lung cancer. Moreover, in the study proposed

below, cost-effectiveness will be assessed (Track A), and different estimands for the effectiveness will be studied to see their methodological implications (Track B).

What knowledge gap(s) will remain?

As nivolumab plus ipilimumab plus chemotherapy was approved by the European Medicines Agency (EMA) on the 17th of September 2020, it is expected that not enough follow-up data is available yet to estimate the five-years overall survival. This emulation protocol therefore primarily focuses on the three-years overall survival with the aim to replicate the original trial results over the first three years of follow-up as closely as possible to assess effectiveness in the real world, while also acknowledging that an expected meaningful, and statistically significant clinical difference (in context of the superiority design) between nivolumab plus ipilimumab plus chemotherapy and pembrolizumab plus chemotherapy may not be observed over these first three years. This emulation protocol thereby deviates from the hypothetical target trial protocol in Appendix 1, which was designed with the ideal trial in mind, assuming five-years of follow-up.

6. Research question and objectives

Table 2 Primary and secondary research questions and objective

A. **Primary research question and objective:** *Overall Survival*

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.
Hypothesis:	The OS of adults with stage IV, PD-L1 < 1% NSCLC treated with nivolumab, ipilimumab and chemotherapy is superior to those treated with pembrolizumab and chemotherapy.
Population ***(mention key inclusion-exclusion criteria):***	Adults with newly diagnosed, metastatic, PD-L1 <1% NSCLC, to be eligible for treatment.
Exposure:	Nivolumab plus ipilimumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed.
Comparator:	Pembrolizumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed
Outcome:	Overall survival
Time ***(when follow up begins and ends):***	From the day of initiation of the exposure until the event (death), loss to follow-up, or end of data collection (31-05-2026); whichever occurred first. Study start date is 26-07-2018, the date pembrolizumab was first approved in the EU (for non-squamous NSCLC).
Setting:	All (both outpatient and inpatient)
Main measure of effect:	Time to first event (death)

B. **Secondary research question and objective 1:** *Time-to-next treatment (TTNT) and treatment duration (TD) (as proxies for Progression Free Survival)*

Objective:	To estimate the difference in average Time-to-next treatment (TTNT) and treatment duration (TD) 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.
Hypothesis:	The Time-to-next treatment (TTNT) and treatment duration (TD) of adults with stage IV, PD-L1<1% NSCLC treated with nivolumab, ipilimumab and chemotherapy is superior to those treated with pembrolizumab and chemotherapy.
Population ***(mention key inclusion-exclusion criteria):***	Adults with newly diagnosed, metastatic, PD-L1 <1% NSCLC, to be eligible for treatment.
Exposure:	Nivolumab plus ipilimumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed.
Comparator:	Pembrolizumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed
Outcome:	Time-to-next treatment (TTNT) and treatment duration (TD)
Time ***(when follow up begins and ends):***	From the day of initiation of the exposure until the event (TTNT/TD) or death, loss to follow-up, or end of data-collection (31-05-2026); whichever occurred first. Study start date is 26-07-2018, the date pembrolizumab was first approved in the EU (for non-squamous NSCLC).
Setting:	All (both outpatient and inpatient)
Main measure of effect:	Time to first event

C. Secondary research question and objective 2: *Cost-Effectiveness (track A)*

Objective:	To estimate the difference in effectiveness, costs and incremental cost-effectiveness 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.
Hypothesis:	n/a
Population *(mention key inclusion-exclusion criteria):*	Adults with newly diagnosed, metastatic, PD-L1 <1% NSCLC, to be eligible for treatment.
Exposure:	Nivolumab plus ipilimumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed.
Comparator:	Pembrolizumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed
Outcome:	Overall survival, Quality of life, Healthcare resource utilization and costs
Time *(when follow up begins and ends):*	From the day of initiation of the exposure until the event, end of data collection, loss to follow-up, or end of data-collection (31-05-2026); whichever occurred first. Study start date is 26-07-2018, the date pembrolizumab was first approved in the EU (for non-squamous NSCLC).
Setting:	All (both outpatient and inpatient)
Main measure of effect:	Difference in Life Years (LYs) and Quality of Life (Quality Adjusted Life Years; QALYs) as effect measure, difference in healthcare resource utilization and costs, and the incremental cost-effectiveness ratio (ICER) presented in cost per QALY and cost per LY gained.

D. Exploratory research question and objective 1: *OS if nobody discontinued due to toxicity (Track B)*

Objective:	To estimate the marginal difference in 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; and if in both exposure and comparator, nobody discontinued due to toxicity.
Hypothesis:	The marginal overall survival if nobody discontinued due to toxicity of adults with stage IV, PD-L1<1% NSCLC treated with nivolumab, ipilimumab and chemotherapy is superior to those treated with pembrolizumab and chemotherapy.
Population ***(mention key inclusion-exclusion criteria):***	Adults with newly diagnosed, metastatic, PD-L1 <1% NSCLC, to be eligible for treatment.
Exposure:	Nivolumab plus ipilimumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed.
Comparator:	Pembrolizumab plus platinum-doublet chemotherapy: *Squamous histology:* Carboplatin + paclitaxel *Non-squamous histology:* Carboplatin + pemetrexed, or cisplatin + pemetrexed
Outcome:	Overall survival
Time ***(when follow up begins and ends):***	From the day of initiation of the exposure until the event, loss to follow-up, end of data-collection (31-05-2026), or discontinuation due to toxicity; whichever occurred first. Study start date is 26-07-2018, the date pembrolizumab was first approved in the EU (for non-squamous NSCLC).
Setting:	All (both outpatient and inpatient)
Main measure of effect:	Time to first event

7. Research methods

7.1. Components of the target trial and the emulation

For the full definition of the hypothetical target trial, see the target trial protocol in Appendix 1 of this protocol.

Table 3 Components of the target trial and the emulation

	Hypothetical Target trial	Target Trial Emulation	Comments
Eligibility	Patients diagnosed with histologically confirmed IV NSCLC (both squamous and non-squamous): 1. aged ≥ 18 years of age, 2. PD-L1<1% 3. ECOG PS ≤ 1, 4. Life expectancy ≥ 3 months, 5. No prior systemic anti-cancer therapy given as primary therapy, 6. Prior radiotherapy to the lung within 6 months of trial-treatment initiation, 7. Prior (neo)adjuvant chemotherapy completed at least 12 months before enrollment, 8. No prior systemic cytotoxic chemotherapy for metastatic disease, 9. No prior targeted or biological antineoplastic therapy, 10. No known EGFR mutations, 11. No known ALK translocations, 12. No major surgery or traumatic injury within 21 days before enrollment, 13. No previous malignancies, unless complete remission was achieved at least 2 years prior to enrollment, 14. No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody. 15. No symptomatic central nervous system metastases 16. Negative hepatitis B and C tests within 28 days	Patients newly diagnosed with histologically confirmed IV NSCLC (both squamous and non-squamous): 1. aged ≥ 18 years of age, 2. PD-L1<1% 3. ECOG PS≤ 1, 4. n/a 5. No prior systemic anti-cancer therapy given 6. Prior radiotherapy to the lung within 6 months of trial-treatment initiation, 7. idem item 5, 8. Idem item 5 9. idem item 5 10. No known EGFR mutations (assumption), 11. No known ALK translocations (assumption), 12. No major surgery or traumatic injury within 21 days before enrollment, 13. n/a 14. idem item 5 15. n/a 16. n/a 17. n/a 18. n/a 19. n/a	**Not feasible:** 4: Life expectancy ≥ 3 months is not collected in this study, however, ECOG PS 0-1 would correspond to life expectancy ≥ 3 months. 5, 7-9, 14: We only included patients receiving first-line systemic treatment, as defined by first-line treatment status in the expensive medicines (add-on) dataset of the DMA. Therefore, items 5, 7-9, and 14 are all captured, but applied more broadly to all chemotherapy, immunotherapy, and targeted therapies. This is limited to expensive medicines administered in the same hospital, as we cannot follow individual patients across multiple centers (see Section 8. Limitations of the methods, point 1, for details). 13: Previous malignancies are treated in routine clinical practice, therefore, these patients are likely to be included in our population. Nevertheless, impact on our results will be limited as patients are more likely to die of stage IV NSCLC. 15: Symptomatic central nervous system metastases are not available in our RWD. Nevertheless, this remains relevant to our research question, as it corresponds to

	17. Not receiving corticosteroids (prednisone>10mg/day) or immunosuppressive treatment within 2 weeks 18. No carcinomatous meningitis, symptomatic interstitial lung disease, HIV, AIDS, or previous malignancy (except non-melanoma skin cancers and in situ cancers) within 2 years 19. No history of noninfectious pneumonitis that required the use of glucocorticoids		Dutch clinical practice. See section *8. Limitations* for more details. **Assumptions:** 10, 11: '… no ALK or EGFR mutations' is part of the therapeutic indications in the SmPC of both pembrolizumab + chemotherapy, [12] and nivolumab + ipilimumab + chemotherapy,[13] therefore it is assumed that all patients treated with these medicines in the Netherlands do not have EGFR mutations and/or ALK translocations 16-19: These criteria are not available in our RWD, however, wo do not expected this to influence our results, as these patients are very rare and / or unlikely to receive our exposure or comparator treatments: 16: Hepatitis B and C are not routinely tested in clinical practice, when liver function is normal, as this is very rare 17: Prednisone needs to be below 10 mg/day for patients to receive treatment in routine clinical practice. 18: Carcinomatous meningitis is very rare, and interstitial lung disease is a contraindication to receiving treatment. 19: A history of pneumonitis is a relative contraindication, therefore, it is very rare in this population.
Treatment strategy	Nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg IV every 6 weeks), continued until disease progression, unacceptable toxicity, or completion per protocol (2 years). + *Squamous* histology: Carboplatin (AUC: 6 mg /mL/min) plus paclitaxel (200 mg/m2), (IV every 3 weeks for two cycles). *Non-squamous* histology: Carboplatin (AUC 5 or 6 mg /mL/min) plus pemetrexed (500 mg/m2) or cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2), (IV every 3 weeks for two cycles).	Nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg IV every 6 weeks), continued until disease progression, unacceptable toxicity, or completion per protocol (2 years). + *Squamous* histology: Carboplatin (AUC: 6 mg /mL/min) plus paclitaxel (200 mg/m2), (IV every 3 weeks for two cycles). *Non-squamous* histology: Carboplatin (AUC 5 or 6 mg /mL/min) plus pemetrexed (500 mg/m2) or cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2), (IV every 3 weeks for two cycles).	Carboplatin is not part of the add-on data (DMA data), therefore, it is assumed that when nivolumab + ipilimumab + paclitaxel/pemetrexed or pembrolizumab + paclitaxel/pemetrexed is found in the dataset, carboplatin is administered as well. AUC, m2, length, and weight are not part of the dataset. Only the provided dose per administration is collected, therefore, dose in mg/m2 and mg/ml/min (AUC)

	Alternative dosing of nivolumab is allowed. OR 200 mg pembrolizumab IV, every 3 weeks for up to 35 cycles. + *Squamous* histology: carboplatin (AUC: 6 mg /mL/min)) on day 1 and paclitaxel (200 mg /m2) on day 1 or paclitaxel (100 mg/m2) on days 1, 8, and 15. (IV every 3 weeks for 4 cycles). *Non-squamous* histology: Cisplatin (75 mg /m2) or carboplatin (AUC: 5 mg /mL/min) plus pemetrexed (500 mg /m2), (IV every 3 weeks for 4 cycles). Followed by pemetrexed maintenance (500 mg /m2) every 3 weeks. Alternative dosing of pembrolizumab is allowed. Maintenance without pemetrexed is allowed.	Alternative dosing of nivolumab is allowed. OR 200 mg pembrolizumab IV, every 3 weeks for up to 35 cycles. + *Squamous* histology: carboplatin (AUC: 6 mg /mL/min)) on day 1 and paclitaxel (200 mg /m2) on day 1 or paclitaxel (100 mg/m2) on days 1, 8, and 15. (IV every 3 weeks for 4 cycles). *Non-squamous* histology: Cisplatin (75 mg /m2) or carboplatin (AUC: 5 mg /mL/min) plus pemetrexed (500 mg /m2), (IV every 3 weeks for 4 cycles). Followed by pemetrexed maintenance (500 mg /m2) every 3 weeks. Alternative dosing of pembrolizumab is allowed. Maintenance without pemetrexed is allowed.	cannot be checked. For patient inclusion, we assume that chemotherapy doses conform to the doses in the hypothetical target trial, as these doses are used in Dutch clinical practice.
Treatment assignment	Randomization (1:1), Double blinded Stratified by • tumor histology, • sex • smoking status	Randomization cannot be directly emulated. G-formula will be applied to account for baseline differences between treatment groups. The treatment groups will be unbalanced in numbers, as more patients treated with pembrolizumab plus chemotherapy are available.	For a trial, 1:1 would be most efficient. However, we have relatively more pembrolizumab plus chemotherapy patients. For the emulation, we will therefore add more pembrolizumab patients in an unbalanced ratio, as this will increase precision.
Follow-up	Event driven follow-up design. From date of randomization up to experiencing the primary outcome or loss-to-follow-up.	Study start is July 26, 2018. From date of treatment initiation up to experiencing the primary outcome, loss-to-follow-up or end of data-collection (31-05-2026).	Retrospective, so not event driven. For more information on the study start date, see section *7.6.3 Context and rationale for follow up*.
Outcomes	*Primary endpoint:* OS defined as time between date of randomization and death due to any cause. *Secondary endpoint:* • PFS • *(track A):* Quality of life (PROMs: EQ-5D): Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter	*Primary endpoint:* OS defined as time between date of initiation of treatment and death due to any cause. *Secondary endpoint:* • Time to next treatment (TTNT) defined as time between date of initiation of treatment and initiation of the subsequent line of therapy or death • Treatment duration (TD) defined as time between	PFS is not collected in the dataset, therefore TTNT and TD are used as a proxy for PFS, as these are associated. [17,18] More details in section *8. Limitations*. Quality of life using PROMs (EQ-5D) is not collected within the study, therefore quality of life will be estimated based on

	for the remainder of the treatment period. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-Up phase, then every 6 months thereafter. • *(track A):* Healthcare resource utilization (HCRU) *Exploratory endpoint:* Effect of co-mutations (TP53, KEAP1, STK11) on efficacy	date of initiation of treatment and the date of last dose plus x weeks corresponding to treatment interval (3 or 6 weeks) or death • *(track A):* Quality of life (health state utility obtained from literature, using disutilities / utilities per event / health state) • *(track A):* Healthcare resource utilization (HCRU)	health state utilities identified using literature. TP53 mutations are not registered, whereas KEAP1 and STK11 mutations have been registered since 01-01-2025, although no patients with these mutations have been identified in our population.
Causal contrast	ITT For the OS, different estimands will be estimated. The primary estimand will be a treatment policy estimand where the key intercurrent events (discontinuation due to any reason, and start of new treatment due to any reason) will be handled with a treatment policy strategy. For track B, a hypothetical strategy for the intercurrent event discontinuation due to toxicity will be used, assuming toxicity is only related to immune response. For all other intercurrent events, the treatment policy strategy will be followed. For PFS, the same ICEs will be considered. A more detailed rationale for the estimands can be found in Table 4.	ITT For the OS, different estimands will be estimated. The primary estimand will be a treatment policy estimand where the key intercurrent events (discontinuation due to any reason, and start of new treatment due to any reason) will be handled with a treatment policy strategy. For track B, a hypothetical strategy for the intercurrent event discontinuation due to toxicity will be used, assuming toxicity is only related to immune response. For all other intercurrent events, the treatment policy strategy will be followed. For TTNT (proxy PFS), the same ICEs will be considered. A more detailed rationale for the estimands can be found in Table 4.	Track B: Estimating the hypothetical estimand for discontinuation due to toxicity in PFS is only feasible in the emulation when considering time until next treatment as a proxy for PFS. Time-on-treatment or treatment duration cannot be used as proxies for PFS, because treatment discontinuation due to toxicity and treatment discontinuation due to progression both result in the end of follow-up, as they are both part of the outcome.
Identifying assumptions		• Conditional exchangeability: Assumes that individuals from both exposure groups can be exchanged without influencing the outcome. • Positivity: For every combination of the adjustment variables, there is a nonzero (>0) probability of receiving both treatment strategies at each point in time. • Consistency: Assumes that the outcome under the observed exposure is the same as if the exposure was hypothetically assigned. treatment strategies are sufficiently well-defined	For the violation of positivity assumption, more details can be found in section *7.6.3 Context and rationale of the follow-up*.
Statistical analysis	<u>OS</u> Estimated using KM techniques. RMST will be estimated by	<u>OS</u> Estimated using KM techniques. RMST will be estimated by calculating the area under the survival	Because of insufficient follow-up data, a 5-year OS analysis is not feasible. The emulation will therefore focus on 3-year

	calculating the area under the survival curve. T_{cut} is set at 5 years. Besides that, Stratified Cox model with Efron's tie handling method, including stratified factors, histology and sex. **Subgroup** analysis for OS on • Age categorization (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, and ≥65) • Sex (male vs. female) • ECOG PS (0, 1) • Smoking status (current/former, never smoked, unknown) • CNS Metastasis (yes vs. no) • Liver Metastasis (yes vs. no) • Bone Metastasis (yes vs. no). • Tumor histology (squamous, non-squamous)	curve. T_{cut} is set at 3 years. Additionally, t_{cut} at 4 and 5 years. Besides that, Stratified Cox model with Efron's tie handling method, including stratified factors histology and sex. G-formula will be applied. **Subgroup** analysis for OS on • Age categorization (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, and ≥65) • Sex (male vs. female) • ECOG PS (0, 1) • Smoking status (current/former, never smoked, unknown) • CNS Metastasis (yes vs. no) • Liver Metastasis (yes vs. no) • Bone Metastasis (yes vs. no). • Tumor histology (squamous, non-squamous)	OS. Follow-up beyond 3 years is limited, so the 4-year and 5-year analyses will be considered exploratory.
	PFS RMST will be estimated by calculating the area under the time-to-event curve. T_{cut} is set at 1 year. Additionally, t_{cut} is set at 2 years. Besides that, stratified Cox proportional hazards model, with treatment as the sole covariate. Ties will be handled using the exact method. **Subgroup** analysis: same subgroups as for OS calculation.	**Time-to-next treatment (TTNT) and treatment duration (TD)** RMST will be estimated by calculating the area under the time-to-event curve. T_{cut} is set at 1 year. Additionally, t_{cut} is set at 2 years. Besides that, stratified Cox proportional hazards model, with treatment as the sole covariate. Ties will be handled using the exact method. G-formula will be applied. **Subgroup** analysis: same subgroups as for OS calculation.	
	Cost-effectiveness (Track A): **General considerations** Cost-effectiveness will be estimated using methods following the Dutch guidelines for economic evaluations in healthcare. 1. Analytic model: Markov 2. Effectiveness: life years and QALY 3. Cost input: both direct and indirect	Cost-effectiveness (Track A): **General considerations** Cost-effectiveness will be estimated using methods following the Dutch guidelines for economic evaluations in healthcare. 1. Analytic model: Markov 2. Effectiveness: life years and QALY 3. Cost input: both direct and indirect	**Cost analysis** 1. Treatment costs: Carboplatin is not collected in the dataset: assumption: carboplatin is administered as often as paclitaxel/pemetrexed. Dose is based on KEYNOTE/CheckMate-9LA

	4. Time horizon: lifetime 5. Discount rates: 3% costs, 1.5% health outcomes 6. Cost perspective: societal perspective 7. Sensitivity analysis: both deterministic sensitivity and probabilistic sensitivity analyses. The estimated range of each parameter will be based on the 95% CI in the studies. Outcomes of the sensitivity analysis will be presented in a tornado diagram, a cost-effectiveness plane, and a cost-effectiveness acceptability curve. 8. Scenario analysis will be conducted for the following scenarios: no discounting, healthcare perspective, alternative lengths of the time horizon, distributions for extrapolation of time-to-event data, and subgroup analyses. **Cost analysis** 1. Treatment costs: actual consumption valued by Z-index 2026 2. Hospital activities: actual consumption valued by: (A) independent cost price research and literature, (B) financial records within healthcare organizations, (C) NZa tariffs, (D) market prices, and (E) DBC tariffs. 3. Indirect costs: e.g. productivity losses: Friction cost method	4. Time horizon: lifetime 5. Discount rates: 3% costs, 1.5% health outcomes 6. Cost perspective: societal perspective 7. Sensitivity analysis: both deterministic sensitivity and probabilistic sensitivity analyses. The estimated range of each parameter will be based on the 95% CI in the studies. Outcomes of the sensitivity analysis will be presented in a tornado diagram, a cost-effectiveness plane, and a cost-effectiveness acceptability curve. 8. Scenario analysis will be conducted for the following scenarios: no discounting, healthcare perspective, alternative lengths of the time horizon, distributions for extrapolation of time-to-event data, and subgroup analyses. **Cost analysis** 1. Treatment costs: actual consumption valued by Z-index 2026 2. Hospital activities: actual consumption valued by: (A) independent cost price research and literature, (B) financial records within healthcare organizations, (C) NZa tariffs, (D) market prices, and (E) DBC tariffs. 3. Indirect costs: e.g. productivity losses: Friction cost method	2. Hospital activities: The costs of hospital activities can only be determined for 1 hospital, as we cannot follow individual patients across multiple centers (see Section *8. Limitations* for details).
	Effect of co-mutations of efficacy Same as for OS and PFS, stratified for co-mutations (TP53, KEAP1, STK11).	n/a	TP53 mutations are not registered, whereas KEAP1 and STK11 mutations have been registered since 01-01-2025, although no patients with these mutations have been identified in our population.

PS, performance status; PD-L1, programmed death-ligand 1; OS, overall survival; PFS, progression-free survival; CNS, central nervous system; QALY, Quality Adjusted Life Years; Nza, Dutch Healthcare Authority; DBC, diagnosis treatment combinations; RMST, restricted mean survival time.

7.2. Estimand table

The population-level summary measure was defined as the difference in restricted mean survival time (RMST) from t=0 to five years in the hypothetical target trial protocol (Appendix 1), as the survival curves are expected to diverge after three years. However, in the emulation protocol, the t_{cut} was set at three years due to limited follow-up data for the nivolumab plus ipilimumab plus chemotherapy cohort. The four- and five-year time points were added to further characterize this divergence, albeit with more limited follow-up data available. As the survival curves are expected to diverge after three years based on the clinical trials, we do not expect to show superiority in RMST at three years. Nevertheless, we believe the results at three years are still relevant, as our assumptions from the clinical trials may deviate in the real world.

Contrary to what has been stated in the hypothetical target trial protocol (see Appendix 1), for the crossover to the alternative treatment arm intercurrent event, a 'treatment policy' strategy will be considered, as it is expected that the number of patients switching to the crossover therapy is limited (<10). Thus, (A) fitting a reliable model on this limited number of events within the g-formula is impossible, (B) the effect on the outcome estimates is assumed to be negligible, and (C) bias due to informative censoring is therefore also assumed to be negligible.

In contrast to the estimand table in the hypothetical target trial protocol (see Appendix 1), the exploratory estimand assessing the effect of co-mutations (TP53, KEAP1, and STK11) on treatment efficacy has been removed, as insufficient data are available. TP53 mutations are not registered, whereas KEAP1 and STK11 mutations have been registered since 01-01-2025, although no patients with these mutations have yet been identified in our population. The changes made for emulation are detailed in Table 3.

Table 4 Components of the estimand

Elements of the estimand						
Population (who and at what time)	**Contrasted treatments (what, when, and how)**	**Endpoint (what, when, and how)**	**Intercurrent events (what and corresponding strategy)**	**Population-level summary measure**	**Estimand started as a research question**	**Example of a treatment decision to be informed by the estimand**
Primary estimand (OS) (see Table 2A)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	Three-years overall survival: time from start treatment to death (due to any cause)	●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*start new treatment (crossover)* treatment policy approach.	Main interest is difference in restricted mean survival time (RMST), using a three-year cutoff. Additionally, cutoffs at four and five years. Besides that, the hazard ratio.	What would be the difference in mean survival time up to three years if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, regardless of tumor progression, discontinuation of the treatment or start of new treatment?	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%
Secondary estimand 1 (TTNT and TD) (see Table 2B)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab +	●Time-to-next treatment (TTNT), defined as time between date of initiation of treatment and initiation of the subsequent line of therapy or death	<u>TTNT:</u> ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach.	Main interest is difference in restricted mean survival time (RMST), with cutoff at one year. Additionally, cutoff at two years. Besides that, hazard ratio.	What would be the difference in average TTNT and TD up to one year if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, regardless of discontinuation or	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%

	chemo with any dosing regimen	●Treatment duration (TD), defined as time between date of initiation of treatment and the date of last dose plus x weeks corresponding to treatment interval (3 or 6 weeks) or death			start of new treatment?	
Secondary estimand 2 (Cost-effectiveness) – Track A (see Table 2C)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	●Overall survival ●Quality of life ●Healthcare resource utilization	<u>Overall survival:</u> ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* treatment policy approach <u>Quality of life:</u> Idem as overall survival, plus: ●*Death* while-alive approach. <u>Healthcare resource utilization:</u> ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* treatment policy approach,	●Incremental cost-effectiveness ratio (ICER) for LYs and QALYs ●Difference in healthcare resource utilization and costs ●Difference in effectiveness (LYs and QALYs)	What would be the difference in effectiveness, costs and incremental cost-effectiveness if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo?	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%

			●*Death* while-alive approach.			
Exploratory estimand 1 (OS if nobody discontinued due to toxicity) – Track B (see Table 2D)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	Three-years overall survival: time from start treatment to death (death due to any cause)	●*Treatment discontinuation due to toxicity (for some period or for entire period)* hypothetical, ●*Treatment discontinuation due to any other reason (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* treatment policy approach.	Main interest is difference in restricted mean survival time, using a three-year cutoff. Additionally, cutoffs at four and five years. Besides that, the hazard ratio.	What would be the difference in average overall survival if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo *if nobody discontinued due to toxicity*?	NA

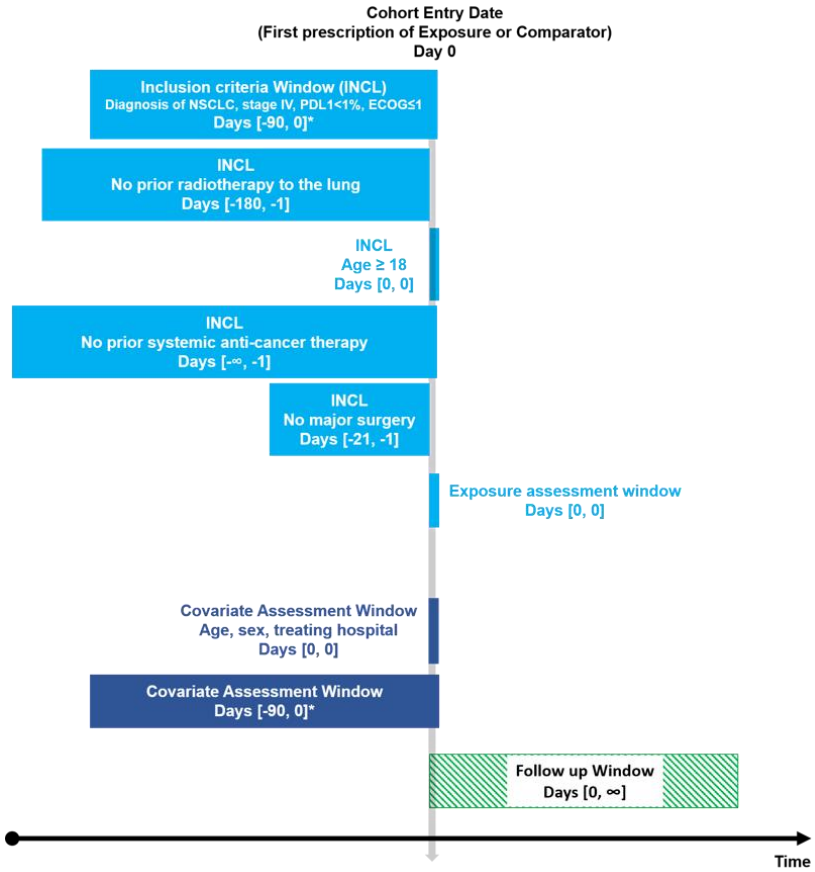
Abbreviations: NSCLC: non-small cell lung cancer, PD-L1: programmed death-ligand, OS: overall survival, QALY: Quality Adjusted Life Years, LY: life years.

7.3. Study design

Research design (e.g. cohort, case-control, etc.): Retrospective new user active comparator cohort study

Rationale for study design choice: This study design reduces the risk of bias from unmeasured time-varying confounding by indication (such as depletion of susceptibles, immortal time bias, and adjustment for causal intermediates) and fits neatly into the target trial framework. Patients need to be followed from the start of treatment until censoring (death or other event of interest, treatment failure, end of follow-up, or end of data collection) (Table 9). Individual-patient data are retrieved from the Dutch Institute for Clinical Auditing (DICA) registries and documented as encounters from various sources, including diagnoses, drug dispensing of nivolumab plus ipilimumab plus chemotherapy, or pembrolizumab plus chemotherapy, the outcomes, and baseline covariates. It is arranged in *days* from the index date (time 0).

7.4. Study design diagram



*For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.

7.5. Setting

7.5.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

The start of the follow-up, also known as time 0, is the day of initiation of therapy.

Table 5 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 (day)	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure: nivolumab, ipilimumab and chemotherapy	Date of first-time use of nivolumab, ipilimumab, and chemotherapy (time 0)	Single	Incident	[-∞, -1]	Any	ATC	n/a	Drug Nivolumab + ipilimumab + chemo or pembrolizumab + chemo	No validation study	n/a
Control: pembrolizumab and chemotherapy	Date of first-time use of pembrolizumab and chemotherapy (time 0)	Single	Incident	[-∞, -1]	Any	ATC	n/a	Drug Nivolumab + ipilimumab + chemo or pembrolizumab + chemo	No validation study	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.5.2 Context and rationale for study in- and exclusion criteria:

Newly diagnosed stage IV, PD-L1 negative, adult (>18y) NSCLC patients receiving 1) nivolumab + ipilimumab + chemotherapy or 2) pembrolizumab + chemotherapy. Newly diagnosed as these therapies are used in the first line and mitigate selection bias. PD-L1 negative, as nivolumab + ipilimumab + chemotherapy is only recommended in Dutch guidelines for PD-L1 negative patients.

For the assessment window, the date of first visit will be used as a proxy for the date of confirmed diagnosis, TNM stage, the PD-L1 test result, and the determination of ECOG performance status (PS). In reality, the date of first visit will be earlier than the date of confirmation of these criteria. The date of clinical TNM stage and ECOG PS are predefined is the variable definition of the DLCA-L registry, see Table 6 for the details.

Table 6. Operational Definitions of In- and exclusion Criteria

Criterion	Details	Order of application	Assessment window (day)	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm	Data source
Histologically confirmed non-small cell lung cancer (NSCLC)	Histopathological NSCLC	Before selection of index date	[-90, 0]	Any	n/a	n/a	Exposure Control	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
Stage IV	Clinical TNM stage, 8th edition, at the time of the last multidisciplinary team meeting before start treatment	Before selection of index date	[-90, 0]	Any	n/a	n/a	Control	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
Age ≥18 years old	(time 0 – year of birth)/365	Before selection of index date	[0, 0]	Any	n/a	n/a	Exposure Control	n/a		DMA
PD-L1 < 1%	n/a	Before selection of index date	[-90, 0]	Any	n/a	n/a	Control	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
ECOG PS ≤ 1	ECOG performance status at the time of the multidisciplinary team meeting at which the treatment was decided	Before selection of index date	[-90, 0]	Any	n/a	n/a	Exposure Control	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
No prior systemic anti-cancer therapy given	n/a	Before selection of index date	[-∞, -1]	Any	ATC	n/a	Exposure Control	DLCA-L checks: first line	active_*ingredient* prior time 0	DMA: Add-on data

								treatment is recorded		
Prior radiotherapy to the lung within 6 months of trial-treatment initiation,		Before selection of index date	[-180, -1]	Any	n/a	n/a	Exposure Control	DLCA-L checks: first line treatment (incl. radiotherapy) is recorded		DMA: DBC activity codes + DLCA-L
No major surgery or traumatic injury within 21 days before enrollment	Open surgical procedure	Before selection of index date	[-21, -1]	Any	n/a	n/a	Exposure Control			DMA: DBC activity codes

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable, DBC = diagnosis treatment combinations
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
Note: Care setting and Code type are deleted as this is not relevant for our dataset.

7.6. Variables

7.6.1 Context and rationale for exposure(s) of interest

Diagnosis position is any as registered in the DMA, i.e., pembrolizumab could, for example. be prescribed for a different cancer type within the population of stage IV NSCLC patients. A two-day discrepancy between initiation of first therapy (e.g., pembrolizumab) and co-therapies (e.g., chemotherapy) is allowed and assumed to be an administration error, the assessment window therefore remains the index date (time 0). Carboplatin is not part of the dataset therefore, it is assumed that when nivolumab + ipilimumab + paclitaxel/pemetrexed or pembrolizumab + paclitaxel/pemetrexed is found in the dataset, carboplatin is administered as well.

Algorithm to define duration of exposure effect:

n/a, only first administration (time 0) is considered.

Table 7. Operational Definitions of Exposure and Comparator

Nivo+ipi group	Details	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm	Data source
Nivolumab	First administration of Nivolumab	[0, 0]	Any	ATC	Any	Exposure	Any NSCLC treatments	No validation study	n/a	DMA: add-on data
Ipilimumab	At least one administration of ipilimumab	[0, 0]	Any	ATC	Any	Exposure	Any NSCLC treatments	No validation study	n/a	DMA: add-on data
Chemotherapy	At least one administration of Carboplatin + paclitaxel OR carboplatin + pemetrexed OR cisplatin + pemetrexed	[0, 0]	Any	ATC	Any	Exposure	Any NSCLC treatments	No validation study	Carboplatin is not part of the dataset: paclitaxel OR pemetrexed OR cisplatin + pemetrexed	DMA: add-on data

Pembro group	Details	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm	Data source
Pembrolizumab	At least one administration of pembrolizumab	[0, 0]	Any	ATC	Any	Comparator	Any NSCLC treatments	No validation study	n/a	DMA: add-on data
Chemotherapy	Carboplatin + paclitaxel *or* cisplatin or carboplatin + pemetrexed	[0, 0]	Any	ATC	Any	Comparator	Any NSCLC treatments	No validation study	Carboplatin is not part of the dataset: paclitaxel OR pemetrexed OR cisplatin + pemetrexed	DMA: add-on data

7.6.2 Context and rationale for outcome(s) of interest

Table 8. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm	Data source
Death	Date of death registered in DBC, Vektis, and/or DLCA-L	Yes	Time-to-event	n/a	Any	n/a	n/a	Exposure Comparator	No validation study	n/a	DMA: DBC data or DLCA-L, including Vektis
Time to next treatment	Time between date of initiation of treatment and initiation of the subsequent line of therapy or death	No	Time-to-event	n/a	Any	ATC	n/a	Exposure Comparator	No validation study	n/a	DMA: add-on data
Treatment duration	Time between date of initiation of treatment and the date of last dose plus 3 or 6 weeks corresponding to treatment interval or death	No	Time-to-event	n/a	Any	ATC	n/a	Exposure Comparator	No validation study	n/a	DMA: add-on data
Healthcare utilization (track A)	All activities within the hospital	No	n/a	n/a	Any	n/a	n/a	Exposure Comparator	No validation study	n/a	DMA: add-on data + DBC activity data

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable, DBC = diagnosis treatment combinations
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.6.3 Context and rationale for follow up

Study start date is July 26, 2018, the date pembrolizumab plus chemotherapy was first approved in the European Union (for non-squamous NSCLC). The indexdate for each patient (time 0 or baseline) is the first registered prescription of exposure or control therapy for this patient after the study start date. While the combination therapy of nivolumab and ipilimumab was approved by the European Medicines Agency (EMA) on the 17th of September 2020, the impact of violation in positivity of treatment assignment is assumed to be negligible, since we expect those that initiated pembrolizumab for metastatic NSCLC prior to 17-09-2020 to be biologically similar to patients initiating treatment after 17-09-2020, and, therefore, hypothetically could have had nivolumab and ipilimumab (see Table 13, with the sensitivity analyses, and section *8. Limitations*). The end of observation in the DLCA-L data is 31-12-2025, meaning that patients diagnosed up to this date, including information on patient characteristics (e.g., ECOG PS, PD-L1), will be included. The end of observation in the DMA data is 31-05-2026, meaning that data on treatment, outcomes, and activities are available up to this date.

Table 9. Operational Definitions of Follow Up

Follow up start	Day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	Date of the outcome in dd-mm-yyyy. Outcome as described in Table 7
Date of death	Yes	According to DBC, Vektis, and/or DLCA-L which are all linked together
End of observation in data	Yes	Data end is 31-12-2025 in DLCA-L and 31-05-2026 in DMA
Day X following index date *(specify day)*	No	No end of follow-up is specified.
End of study period (specify date)	No	No end of follow-up is specified.
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	Follow-up will continue after end of exposure until event of interest.
Date of switch from exposure *(specify algorithm)*	No	Switches are not considered in the follow-up definition, as this ICE follows a treatment policy estimand (see section 7.2)
Date of crossover	No	The date of initiating the crossover therapy is not considered the end of follow-up due to the limited number of crossovers expected (see section 7.2).

Other date *(specify)*	*NA*	*NA*

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.6.4 Context and rationale for covariates

A Directed Acyclic Graph (DAG) was constructed to identify potential confounders and effect modifiers, and guide covariate adjustment (Figure 1). These variables were identified from the KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA study protocols and trial results. [19–21] Confounding variables include age, sex, smoking history, ECOG PS, histology, the treating hospital, TNM stage, and the presence of CNS, bone and liver metastases. By conditioning on these variables alone, all possible backdoor paths are closed when dismissing the unobserved variables "Immunosuppressant usage" and "Prior malignancies". Their backdoor paths cannot be closed due to being unobserved and having both a direct effect on Exposure and on Death, unlike the unobserved variable "TP53 mutation", see Figure 1. KEAP1 and/or STK11 mutations are considered as an ancestor of the exposure, i.e., a covariate only influencing the exposure and not the outcome. The Dutch guidelines indicate that nivolumab plus ipilimumab plus chemotherapy is more likely to yield greater benefit compared to pembrolizumab plus chemotherapy in patients with KEAP1 and/or STK11 mutations, aged ≤ 75 years, with a smoking history, and without liver metastases. [1] Consequently, these patients are more likely to receive nivolumab plus ipilimumab plus chemotherapy in clinical practice. This is attributable to the fact that KEAP1 and/or STK11 mutations adversely affect the efficacy of pembrolizumab plus chemotherapy. Furthermore, the CheckMate 9LA trial demonstrated the greatest benefit of nivolumab plus ipilimumab plus chemotherapy over chemotherapy alone in patients aged ≤ 75 years with a smoking history, whereas patients with liver metastases derived less benefit. [19] No effect modifiers are considered.

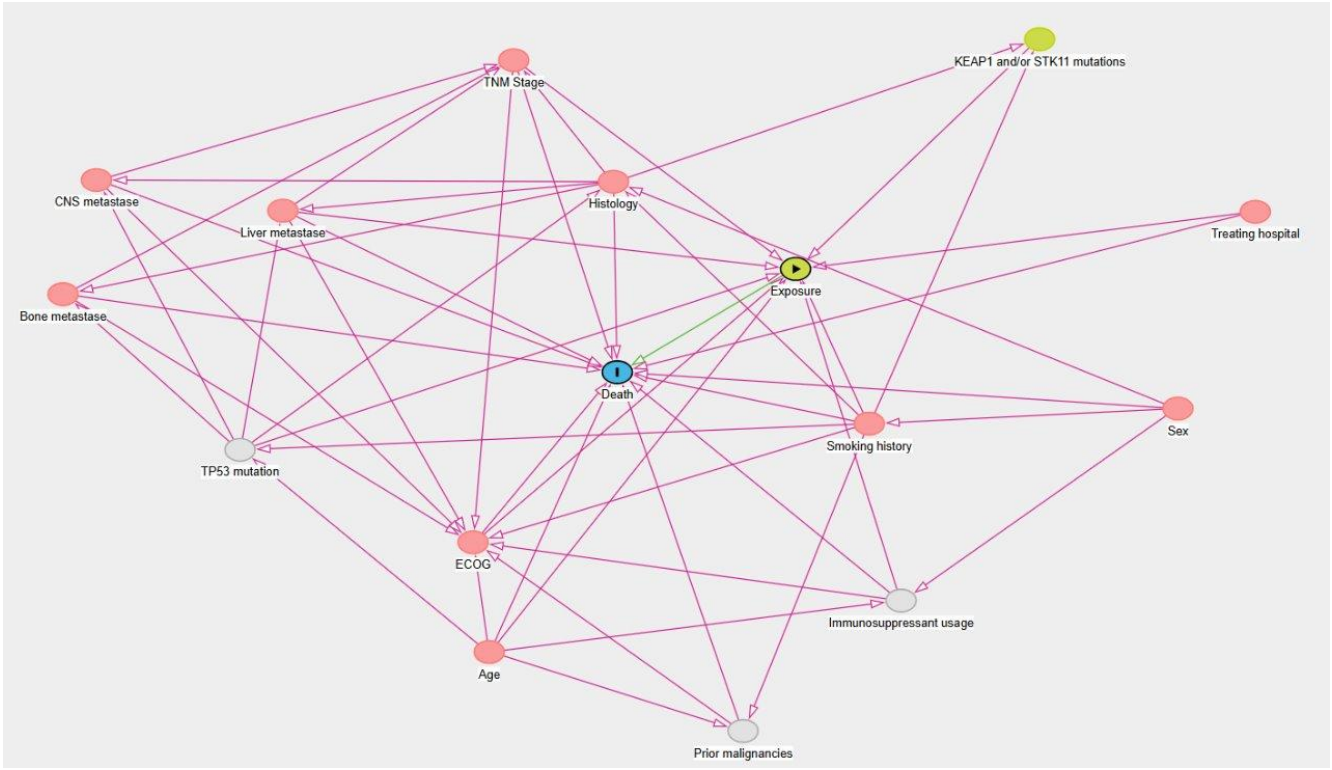


Figure 1. Directed Acyclic Graph. Grey nodes depict unobserved variables, all other colored nodes are observed. The blue node "**I**" depicts the outcome of interest. The green node "▶" depicts the exposures of interest (either the pembrolizumab treatment strategy or nivolumab + ipilimumab strategy). The other green node depicts a variable that influences the exposure, but not the outcome. Pink nodes depict confounding variables influencing both exposure and outcome. The edges (arrows) depict the causal relationship of node X on node Y.

Table 10. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm	Data source
KEAP1 / STK11 mutation	KEAP1 mutation/fusion, STK11 mutation/fusion, no KEAP1 or STK11 mutation, no molecular diagnostics, unknown.	Categorical	[-90, 0]	Any	n/a	Primary	Exposure Comparator	n/a	**DLCA-L variables:** 1.mutandtrans = 15 --> STK11 mutation 2.mutandtrans = 16 --> KEAP1 mutation 3.moleculair == 1 AND mutandtrans =NIET 15 /16 -->no KEAP1 or STK11 mutation 4.moleculair ==2 (Yes, but not successful) -->no molecular diagnostics 5.moleculair == NA / 9 (unknown) -->unknown For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	Registered from 01-01-2025 in DLCA-L
Age	time 0 – year of birth)/365	Continuous	[0, 0]	Any	n/a	n/a	Exposure Comparator	n/a	n/a	DMA: DBC data
Smoking history	Current smoker, former smoker, never smoker, unknown	Categorical	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a	DLCA-L

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm	Data source
									proxy for (date of) confirmed diagnosis.	
Liver metastases	Yes, no	Binary	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
ECOG PS	ECOG PS (0, 1) as determined at the multidisciplinary team meeting at which the treatment was established.	Categorical	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
Histology	squamous, non-suqamous	Categorical	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
Sex	Female, male, unknown	Categorical	[0, 0]	Any	n/a	n/a	Exposure Comparator	n/a	n/a	DMA: DBC data
Bone metastases	Yes, no	Binary	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date	DLCA-L

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm	Data source
									of first visit will be used as a proxy for (date of) confirmed diagnosis.	
CNS metastases	Yes, no, not assessed	Categorical	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L
Treating hospital	Pseudonimized hospital ID and hospital type (Academic, teaching hospital, and general hospital)	Categorical	[0, 0]	Any	ATC	n/a	Exposure Comparator	n/a	n/a	DMA: DBC data
TNM stage	IVA, IVB, unknown. Clinical stage according to the 8th edition of the TNM classification	Categorical	[-90, 0]	Any	n/a	n/a	Exposure Comparator	n/a	For the assessment window, the date of first visit will be used as a proxy for (date of) confirmed diagnosis.	DLCA-L

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable, DBC = diagnosis treatment combinations
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
PS=performance status

7.7. Intercurrent Events (Track B)

In track B, a different estimand will be studied as compared to the primary analysis (Table 4). Here we specifically describe the intercurrent events for the primary analysis (Table 11a) and Track B (Table 11b).

Table 11. Intercurrent events

A. Operational Definitions of intercurrent events for the primary analysis

ICE	Details	Type of ICE	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations	Measurment validation	Source for algorithm	Data source
Discontinues treatment due to toxicity	Discontinuation of treatment before completing the full treatment schedule due to experiencing toxicity	Treatment policy	[0, ∞]	Any	n/a	n/a	Exposure, Control	No validation study	In DLCA-L look at toxicity side effect ≥ grade 3 (y/n/NA) + Stopping treatment early in DMA	DLCA-L + DMA: add-on data
Discontinues treatment due to any other reason	Discontinuation of treatment before completing the full treatment schedule due to any other reason than toxicity (e.g., L2FU, withdrawing consent, etc.)	Treatment policy	[0, ∞]	Any	n/a	n/a	Exposure, Control	No validation study	In DMA: those that stop treatment prematurely + In DLCA-L those that did not report toxicity	DLCA-L + DMA add-on data
Start new treatment (no crossover)	Use of new anticancer therapy	Treatment policy	[0, ∞]	Any	ATC	n/a	Exposure, Control	No validation study	In DMA those that start new treatment	DMA: add-on data
Start new treatment (Crossover)	Use of the other study drug (either pembrolizumab or nivolumab + ipilimumab)	Treatment policy	[0, ∞]	Any	ATC	n/a	Exposure, Control	No validation study	In DMA those that start the comparator treatment	DMA: add-on data

B. Operational Definitions of intercurrent events for the Exploratory research question and objective 1: *OS if nobody discontinued due to toxicity (Track B)*

ICE	Details	Type of ICE	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations	Measurment validation	Source for algorithm	Data source
Discontinues treatment due to toxicity	To estimate the effect of treatment if nobody discontinued due to toxicity, where toxicity is assumed to happen solely because of strong immune response, and not because of frailty.	Hypothetical	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*
Discontinues treatment due to any other reason	Discontinuation of treatment before completing the full treatment schedule due to any other reason than toxicity (e.g., L2FU, withdrawing consent, etc.)	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*
Start new treatment (no crossover)	Use of new anticancer therapy	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*
Start new treatment (Crossover)	Use of the other study drug (either pembrolizumab or nivolumab + ipilimumab)	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*	*Same as Table 11A*

7.8. Data analysis

7.8.1 Context and rationale for analysis plan

Table 12. Primary, secondary, and subgroup analysis specification

A. Primary analysis (OS)

Hypothesis:	Exposure to Nivolumab plus ipilimumab plus chemotherapy decreases risk of death relative to pembrolizumab plus chemotherapy with the upper bound of the 95% confidence interval for the hazard ratio below 1.0.
Exposure contrast:	Exposure (Nivolumab plus ipilimumab plus chemotherapy), comparator (pembrolizumab plus chemotherapy)
Outcome:	Death
Analytic software:	R
Model(s): ***(provide details or code)***	**Primary outcome model RMST:** 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). *Endpoint*: Mean restricted survival time from treatment initiation to death up to 3 years. Supplementary cutoff at 4 and 5 years. *Example of R-code used:* `# Fit Royston-Parmar model to observed data` `fit <- flexsurvspline(` `  Surv(time, outcome) ~ exposure + covariates,  # Covariates listed below in Confounding adjustment method` `  data = df, # df is our dataset` `  k = 4,` `  scale = "hazard"` `# create counterfactuals` `df1 <- df0 <- df # copy data` `df1$exposure = 1 # counterfactual df of what would happen if everyone initiated nivolumab + ipilimumab` `df0$exposure = 0 # counterfactual df of what would happen if everyone initiated pembrolizumab` `# Predict survival outcomes for the counterfactuals` `times <- seq(0, 3, by = 0.01)  # 3 year cut-off for RMST` `pred_1 <- predict(fit, newdata = df1, type = "survival", times = times )` `pred_0 <- predict(fit, newdata = df0, type = "survival", times = times )` `...`

	Supplementary outcome model HR: A Cox proportional hazards model will be used to estimate the proportional hazards over time *Endpoint*: Hazards ratio *Example of R-code used: # see R-code for primary outcome, but instead of a flexsurvspline(), a coxph() model will be used*
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Covariates All potential confounders are described in Figure 1 (*7.6.4 Context and rationale for covariates*). 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. **Censoring** 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.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Missingness will be assessed by comparing complete vs. incomplete cases on their exposure status, outcome values and patient characteristics. By default, variables in the DCLA-L and DMA that contain missingness are assumed to be missing at random (MAR). However, these variables will be discussed with a pulmonologist and the registry owners regarding the possibility of missing not at random (MNAR). **MAR:** For the variables that contain missingness assumed to be MAR, multiple imputation of chained equations (MICE) will be performed using all complete variables, including exposure and outcome variables. For each variable that contains missingness, its predictor-correlation will be determined using expert knowledge. For MAR variables with *strong predictors* up to 70% missingness will be allowed for imputation. For MAR with medium to weak predictors, missingness up to 30% will be allowed. In case missingness for a given variable is higher than the previously mentioned thresholds, it may be decided to drop the variable. **MNAR:** For the variables that contain missingness assumed to be MNAR, the potential impact of assumptions will be estimated using sensitivity analyses to assess robustness. **Additional missing data assumptions:** 1. Patients with missing age or sex are excluded. 2. Patients with no information on exposure will be excluded. 3. Patients that could not be linked (see 7.9 Data sources) will be excluded. 4. Missing exposure data after treatment initiation is assumed to be treatment discontinuation 5. While technically not part of the missing data methods, PD-L1 status prior to its introduction to the registry (2020) will be simulated using model-based extrapolation based on observed PD-L1 and its predictors post-introduction to the registry. See 8. Limitations.

Subgroup Analyses	***List all subgroups***
	• Age categorization (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, and ≥65) • Sex (male vs. female) • ECOG PS (0, 1) • Smoking status (current/former, never smoked, unknown) • CNS Metastasis (yes vs. no) • Liver Metastasis (yes vs. no) • Bone Metastasis (yes vs. no) • Tumor histology (squamous, non-squamous) • TNM stage (IVA, IVB)

B. Secondary Analysis 1 (TTNT and TD)

Hypothesis:	Exposure to Nivolumab plus ipilimumab plus chemotherapy decreases time to next treatment and treatment duration relative to pembrolizumab plus chemotherapy with the upper bound of the 95% confidence interval for the hazard ratio below 1.0.
Exposure contrast:	Exposure (Nivolumab plus ipilimumab plus chemotherapy), comparator (pembrolizumab plus chemotherapy)
Outcome:	TTNT and TD
Analytic software:	Same as for primary analysis
Model(s): ***(provide details or code)***	Same as for primary analysis, except using an estimator to estimate TD or TTNT instead of survival: `fit <- glm(` `  treatment_duration ~ treatment + covariates,` `  data = df,` `  family = Gamma(link="log")` `  )`
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Same as for primary analysis
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Same as for primary analysis
Subgroup Analyses	***List all subgroups***
	Same as for primary analysis

C. Secondary Analysis 2 (Cost-effectiveness – track A)

Hypothesis:	Aim: What would be the incremental cost-effectiveness, costs, and difference in effectiveness if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo?
Exposure contrast:	Exposure (Nivolumab plus ipilimumab plus chemotherapy), comparator (pembrolizumab plus chemotherapy)
Outcome:	Overall survival, Quality of life, Death, and healthcare resource utilization
Analytic software:	R
Model(s): ***(provide details or code)***	Outcome model: Markov model Effectiveness: LYs and QALY Cost input: both direct and indirect Time horizon: lifetime Discount rates: 3% costs, 1.5% health outcomes. Cost perspective: societal perspective
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Same as for primary analysis
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Same as for primary analysis
Subgroup Analyses	***List all subgroups***
	Same as for primary analysis

D. Exploratory analysis 1 (OS if nobody discontinued due to toxicity – Track B)

Hypothesis:	See primary analysis (A)
Exposure contrast:	See primary analysis (A)
Outcome:	See primary analysis (A)
Analytic software:	See primary analysis (A)
Model(s): *(provide details or code)*	See primary analysis (A)
Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.*
	See primary analysis (A)
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	See primary analysis (A) See 8. Limitations. Patients having their toxicity registered to the DLCA-L as "No" while, according to the DMA, still being on treatment after registration to the DLCA-L will be switched to having unknown status of toxicity.
Subgroup Analyses	*List all subgroups*
	See primary analysis (A)

Table 13. Sensitivity analyses – rationale, strengths and limitations

Sensitivity analysis	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Including ECOG PS > 1 patients	Dropping the ECOG PS≤1 inclusion criteria	To estimate the effectiveness of the study treatments on the outcome for patients with more severe disease status (ECOG PS>1)	Novel real-world evidence of the effectiveness of study treatments for previously neglected subpopulations.	Deviation from the target trial, introducing more heterogeneity in the study population.
Study start date set to 17-09-2020	The study start date is changed from the date the first study treatment was first authorized in the EU for metastatic NSCLC (i.e., pembrolizumab, 26-07-2018) to the date all study treatments were authorized in the EU (i.e., the date where the combination therapy of nivolumab and ipilimumab was authorized as first line treatment for metastatic NSCLC), 17-09-2020.	Positivity violation as it was not possible for patients to receive the nivolumab and ipilimumab as combination therapy for metastatic NSCLC prior to 17-09-2020. Outcomes of patients treated before September 2020 could differ from those of patients treated after September 2020, due to improvements in cancer care (e.g., diagnostics, protocol changes, targeted treatment options).	Possible bias introduced due to the violation of positivity is avoided.	By changing the study start date to a later point in time, we will exclude all patients that initiated pembrolizumab prior to 17-09-2020 and also lose pembrolizumab patients that potentially have long follow-up times; reducing the power.
Univariate deterministic sensitivity analysis: cost-effectiveness (track A)	Each model parameter will be varied one at a time across its 95% CI. Outcomes will be presented in a tornado diagram.	Identifies which individual parameters have the greatest influence on the ICER, helping to pinpoint key drivers of model uncertainty.	n/a	n/a
Probabilistic sensitivity analysis: cost-effectiveness (track A)	All parameters are varied simultaneously using a Monte Carlo simulation (1,000 iterations). Costs are assigned a Gamma distribution, probabilities a PERT distribution, and utilities a Beta distribution. Outcomes will be presented in a cost-effectiveness plane.	Captures the combined effect of uncertainty across all parameters simultaneously, providing an overall picture of model robustness.	More comprehensive analysis, as it reflects the joint uncertainty of all parameters simultaneously rather than relying on point estimates.	n/a
Scenario analyses: cost-effectiveness (track A)	Additional scenarios are tested: no discounting, healthcare perspective, alternative lengths of the time horizon, distributions for extrapolation of time-to-event data, and subgroup analyses	To test the impact of the assumptions, we assessed whether the findings held across varying parameter inputs.	Improves generalizability of the findings.	n/a

7.9. Data sources

Data will be used from a data linkage of the Dutch Medication Audit (DMA) registry and the Dutch Lung Cancer Audit – Lung Oncology (DLCA-L) registry from the Dutch Institute for Clinical Auditing (DICA). This data linkage will be performed at the patient level and includes 74% of all Dutch hospitals. The DMA and DLCA-L registries provide insights into the use and real-world outcomes of systemic therapies to participating Dutch hospitals, offering a nearly complete representation of Dutch oncological lung cancer treatment. The DMA registry includes medical claims data from high-cost drugs (add-on data) and diagnosis treatment combinations (DBC) data. The DLCA-L registry manually collects data on patient- and tumor characteristics and is linked to the national claims database, Vektis, which is used in this study to collect the date of death. A detailed description of the dataset construction and linkage of DMA and DLCA-L are described elsewhere. [22,23] In this study, we included patients based on DMA data (patients with NSCLC receiving exposure or comparator treatment in the first line). We then linked DLCA-L data to this population, resulting in a linkage rate of 80%. This is demonstrated in Figure 2.

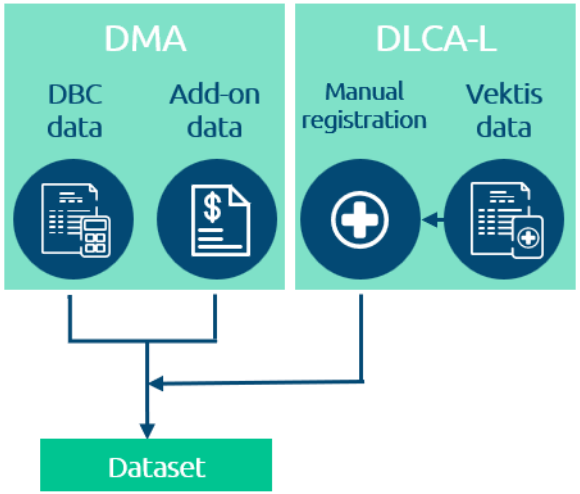


Figure 2. Data sources and linkage between the Dutch Medication Audit (DMA) registry and the Dutch Lung Cancer Audit – Lung Oncology (DLCA-L) registry. Diagnosis treatment combinations (DBC)

7.6.1 Context and rationale for data sources

Reason for selection: The DMA registry includes medical claims data from high-cost drugs and diagnosis treatment combinations (DBC). The DLCA-L registry manually collects data on patient- and tumor characteristics.

Strengths of data source(s): Linking the DMA and DLCA-L enables effectiveness and safety analyses of these treatments on certain tumor characteristics. Moreover, medicine data is collected over multiple time-points, making time-varying analyses and handling intercurrent events possible.

Limitations of data source(s): Due to the manual registration of data in the DLCA-L registry, fields may contain various degrees of missingness.

Data source provenance/curation: DICA

Table 14. Metadata about data sources and software

Study period: For DMA data: 01-01-2017 until 31-05-2026, which mainly includes exposures and follow-up. DLCA-L: 01-01-2015 until 31-12-2025, which mainly includes inclusion criteria and covariates.
Eligible cohort entry period: 26-07-2018 until 31-05-2026, 26-07-2018 was chosen as start date for patients entering the study, as the first treatment was available on European market (EMA authorization of pembrolizumab plus chemotherapy for patients with metastatic non-squamous NSCLC). [15]
Data linkage: The DLCA-L data is linked to DMA data at the patient level, using the hospital patient identification number. When a patient could not be linked using the hospital patient identification number, probabilistic linkage was performed based on year of birth, sex, and date of first outpatient visit.

	Data 1	**Data 2**
Data Source(s):	DMA	DLCA-L
Study Period:	01-01-2017 until 31-05-2026	01-01-2015 until 31-12-2025
Eligible Cohort Entry Period:	26-07-2018 until 31-05-2026	26-07-2018 until 31-12-2025
Data Version (or date of last update):	June 2026	June 2026
Data sampling/extraction criteria:		
Data linkage:	To DLCA-L	To DMA
Conversion to CDM*:	no	no
Software for data management:		

*CDM = Common Data Model

7.10. Data management

In this study the data will be collected, processed, and archived following the DICA quality registry governance, which is in accordance with the General Data Protection Regulation (GDPR) and the FAIR (Findable, Accessible, Interoperable, Reusable) principles under the responsibility of DICA.

DICA operates under the Dutch agreement model which states that quality registration holders must be separate from the data processor. For the collection of data in the Netherlands, DICA collaborates with the data processor MRDM.[24] Strict agreements have been established between DICA, MRDM, and the participating hospitals (including the seven hospitals within this study). This means that DICA receives pseudonymised data from MRDM based on the EHR data and medical claims data, delivered by hospitals to MRDM. Data from the registries can only be shared externally on an aggregated level and only if agreed upon by authorised members of the registry itself. DICA offers participant hospitals in its clinical audits the opportunity of submitting an application to receive data from clinical audits for the purpose of scientific research under strict conditions. These applications are assessed at several levels. In the participation agreement between DICA and the participant hospitals in clinical audits, to which the DICA Regulations also apply, further conditions are set for the use of data for scientific research. These conditions include that only pseudonymised or anonymised data that cannot (directly) be traced back to individual patients can be made available. The parties also agree that, in accordance with the applicable laws and regulations, the participants will set up a system of no-objection that offers the patient the possibility to explicitly object to the use of his/her data for scientific research in advance. In this way, the patient's privacy will be protected as much as possible.

The pseudonymized aggregated data will be archived at the University Medical Center Groningen (UMCG) network for 15 years, complying with strict UMCG security and back-up policy.

7.11. Quality control

The DMA registry includes financial and administrative healthcare data on high-cost drugs and medical claims data described in diagnosis treatment combinations (DBCs), which are considered highly reliable as they form the basis for reimbursement and funding processes of hospitals in the Netherlands. These data undergo monthly standardized validation procedures, including checks on data completeness, consistency, plausibility, and overall data quality. Any discrepancies identified during the validation process, including missing, inconsistent, or unexpected values, are systematically investigated and resolved with the hospital to ensure the robustness, reliability, and validity of the dataset.

The DLCA-L registry includes manually collected data from electronic health records. The data quality of the DLCA-L is assured by using precise definitions for the variables in the registry, and data collection is performed by trained data managers, supervised by medical specialists. Moreover, data verification is performed by comparing DLCA-L data with administrative healthcare data every three years to ensure data quality.

7.12. Study size and feasibility

The sample size calculations as performed in the hypothetical target trial protocol (Appendix 1) are not applicable, as five-year OS is not feasible. We will therefore provide sample size calculations for the three-year OS for RMST. However, if we obtain a smaller sample size in the observational data as compared to what is reported here in the protocol, the study will still be continued under a lower power.

A sample size calculation based on RMST was performed. To detect an expected HR of 0.85 with a change point at 12 months and a cut-off at 36 months (3-years), with a one-sided α level of 0.025 and 80% power, a total of 7468 patients would be required. A HR of 0.85 is chosen instead of 0.7 as used in the five-year sample size calculation (Appendix 1), as a smaller difference is expected after three years than after five years. See Table 15 for summary details and the theoretical overall survival curves are shown in Figure 3.

We expect around 309 patients in the exposure group (nivolumab plus ipilimumab plus chemotherapy) and 1790 patients in the comparator group (pembrolizumab plus chemotherapy). According to the RMST sample size calculation for three-year OS, this number of patients is insufficient to assess superiority. Although this number is still reasonable, as it is in line with the number of patients included in the KEYNOTE-189, KEYNOTE-407 and CheckMate 9LA clinical trials [19–21], a subsequent study with a longer follow-up period (5-year OS) and/or a larger number of patients may be needed to obtain conclusive results on OS.

Table 15. Power and sample size

Hazard ratio (HR)	Alpha	Power	change points (months)	ta (months)	lambda0	lambda1	kappa0	kappa1	Pi	RMSTd	Number of patients
0.85	0.025	80%	12	36	(0.0431,0.0431)	(0.0431,0.0366)	(1,1)	(1,1)	0	0.815	12866

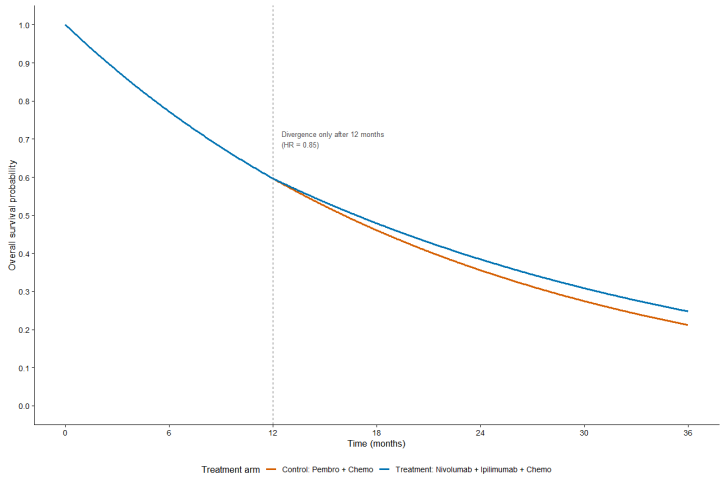


Figure 3 Theoretical overall survival curves for treatment: nivolumab + ipilimumab + chemotherapy (blue line), and control: pembrolizumab + chemotherapy (orange line), using a Piecewise Weibull model, HR = 0.85 after 12 months.

8. Limitation of the methods

1. Although the registry contains data from multiple centers, on an individual level (i.e., for each individual) we cannot follow patients across multiple centers and, therefore, data is only registered from a single center (one hospital). Academic hospitals might have a higher percentage of patients who are referred before or after index date to another hospital and nivolumab plus ipilimumab plus chemotherapy might be overrepresented in academic hospitals, as not every hospital is allowed to provide nivolumab plus ipilimumab plus chemotherapy.
    a. Eligibility criteria: prior anti-cancer therapy / surgery given are only visible within the hospital, so potentially missing prior treatment in a different hospital. As both exposure and comparator therapy are indicated and recommended as first line therapy, we assume no prior treatments are given to this population. Moreover, the indication text, available for each administration, mentions ‘first line treatment’.
    b. Cost-effectiveness: healthcare utilization is lower when patients are referred (e.g. emergency department, radiotherapy). (track A)
2. In this study, only newly diagnosed NSCLC patients with stage IV metastatic disease will be included. Reoccurring disease of any stage will be excluded. This is a deviation from the KEYNOTE and CheckMate trials where patients with stage IV disease were eligible after having remission of stage III or lower.

3. For the secondary objective of estimating PFS, both TTNT and TD will be used as proxies, assuming that treatment is discontinued / new treatment is started due to progression. In reality, toxicity induces this as well. Nevertheless, studies have shown that PFS and TTNT / TD are associated. [17,18]
4. Proxies are used (date first visit) for dates of confirmation of diagnosis and ECOG PS, used for the washout windows.
5. The study start date was set at July 26, 2018, to maximize the number of eligible patients and follow-up data. However, a violation of positivity may have been introduced , as the study start date is prior to the authorization date of nivolumab and ipilimumab as combination therapy for metastatic NSCLC (September 17, 2020). Therefore, robustness was assessed using sensitivity analysis (Table 13).
6. PD-L1 was introduced to the DLCA-L in 2020. Therefore, model-based extrapolation has been performed to simulate PD-L1 values prior to 2020.
7. Toxicity is registered in the DLCA-L, specified as: Was there toxicity as a result of the administered systemic treatment? No, or less than grade 3 (< 3, according to CTC); Yes, grade 3 or higher (3+, according to CTC); Unknown. The time window in which toxicity occurs is not specified. The DLCA-L requires that all patients diagnosed in a given calendar year have all their DLCA-L data, including toxicity and other covariates, registered (retrospectively) before mid-February of the following year. Due to this process, patients diagnosed in January may be more likely to have their toxicity captured, as they have a longer follow-up period for registration, and thus a higher chance of toxicity being observed. Patients diagnosed on 31 December, in contrast, have only 1.5 months of follow-up time to register toxicity (13.5 vs. 1.5 months, respectively). (track B)
    a. Patients still on treatment after the mid-February in the year succeeding their registration to the DLCA-L may still experience toxicity, but this will not be registered anymore.

9. Protection of human subjects

A detailed description of the dataset construction and linkage of DMA and DLCA-L are described in section *7.9*. Data management is described in section *7.10*. In compliance with Dutch regulations, no patient informed consent or formal ethical approval were necessary for secondary use of the data collected in the registries from Dutch Institute for Clinical Auditing. This study was assessed and approved for the use of DICA data for scientific research by the privacy and methodology department of DICA and by authorized members of the registry itself (clinical audit boards of DMA and scientific committee of DLCA-L), application number DMA-DLCA-L-2025-132 and DMA-DLCA-L-2025-133.

In this way, the patient's privacy will be protected as much as possible.

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11. Appendices

11.1. Appendix 1 – hypothetical target trial protocol

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

Hypothetical target trial Protocol

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Introduction

In the Netherlands, nivolumab plus ipilimumab plus platinum-doublet chemotherapy and pembrolizumab plus platinum-doublet chemotherapy are both used in the first line in PD-L1 negative patients with metastatic non-small cell lung cancer (NSCLC). [1] Nivolumab plus ipilimumab plus chemotherapy is considered potentially more effective than pembrolizumab plus chemotherapy, based on the 5-year OS in PD-L1-negative patients (22% vs 10-11%, respectively) reported in the CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407 studies, in which nivolumab plus ipilimumab plus chemotherapy was compared to chemotherapy alone (CheckMate 9LA), and pembrolizumab plus chemotherapy was compared to chemotherapy alone (KEYNOTE-189 and KEYNOTE-407). [2–4] However, uncertainty remains regarding which schedule is most effective, as a direct head-to-head comparison is lacking in the trials supporting their registration. [5]

One phase 3 clinical trial from Japan compared nivolumab plus ipilimumab plus chemotherapy with pembrolizumab plus chemotherapy, however, this study was insufficiently powered, with too few events and insufficient follow-up (median follow-up of 15.3 months). [6] In addition, some small observational studies (N<60 in nivolumab plus ipilimumab, PD-L1<1% group) in which nivolumab plus ipilimumab has been compared with pembrolizumab, with or without chemotherapy. [7–12] These studies have yielded conflicting conclusions: nivolumab plus ipilimumab significantly improves overall survival (OS) in PD-L1<1% patients, [8] pembrolizumab is significantly better for PFS, [9] or no significant differences were observed. [6,7,11,12] These conflicting findings are likely attributable to the small sample sizes in these studies, with only 22-58 PD-L1<1% patients in the nivolumab plus ipilimumab plus chemotherapy group. A larger study with adequate follow-up and a more robust design could potentially resolve this uncertainty.

Nivolumab plus ipilimumab plus chemotherapy is also considered to be more toxic than pembrolizumab plus chemotherapy. [5] The Dutch National Health Care Institute performed a post-hoc calculation (Bucher) to estimate the risk ratios for the incidence of severe adverse events, resulting in higher, albeit statistically non-significant risk ratios for nivolumab, ipilimumab, and chemotherapy compared with pembrolizumab and chemotherapy for both CheckMate 9LA vs KEYNOTE-189 (1.15; 95% CI 0.94–1.42) and CheckMate 9LA vs KEYNOTE-407 (1.22; 95% CI 0.98–1.54). [13] Furthermore, based on list prices and excluding chemotherapy costs, medication costs per patient for one year (assuming standard dosing for an 80 kg patient) are higher for nivolumab plus ipilimumab than for pembrolizumab (€130,982 versus €99,439, respectively). [14] A formal cost-effectiveness analysis comparing these two regimens in clinical practice, incorporating both direct and indirect costs, is therefore warranted (track A).

As this study will use observational (non-randomized) data from Dutch clinical practice, we will employ a target trial emulation approach to study the head-to-head comparison in clinical practice, where we will first define the hypothetical target trial as stated in this protocol. A separate emulation protocol will be formalized from the hypothetical target trial and published before performing our epidemiological analyses, thereby mitigating biases often seen in observational research and ensuring transparency over the a priori defined design choices. The CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407 studies will inform the design of the hypothetical target trial. [15–17]

Concluding, our study will compare nivolumab and ipilimumab plus platinum doublet chemotherapy with pembrolizumab plus platinum doublet chemotherapy in PD-L1 negative patients with stage IV NSCLC, using real-world data in the Dutch setting. A superiority design was chosen because nivolumab plus ipilimumab plus chemotherapy is considered potentially more effective and more

toxic than pembrolizumab and chemotherapy. As a secondary objective, this study aims to assess the cost-effectiveness of nivolumab plus ipilimumab plus chemotherapy compared to pembrolizumab plus chemotherapy (track A). As an exploratory objective, different estimands for the OS and progression-free survival (PFS) will be estimated to gain methodological knowledge on the definitions of estimands in observational studies (track B).

Methods

We will employ a target trial emulation approach. First, we will define the target trial protocol (part I), here we will describe the estimands and the hypothetical trial protocol. After finalizing part I, we will select a suitable RWD source, e.g. registry data.

Second, we will define the target trial emulation protocol to make changes transparent, and this study protocol will be written following the HARPER template (part II). [18] This will be based on data availability (e.g. variables, missing data, and number of patients) within the available dataset. This target trial emulation protocol, together with the target trial protocol (part I), will be uploaded to the HMA-EMA Catalogues of RWD studies before starting with part III.

Third, the study will be performed following the target trial emulation protocol, and results will be published in a peer-reviewed journal (part III).

Estimands

Expressing our analysis as intention-to-treat (ITT) or per-protocol is not detailed enough to fully describe and interpret the causal effect estimated. We will therefore describe the causal effect according to the estimand framework ICH E9R1. [19] As we expect to observe different intercurrent events (according to ICH E9R1), we propose different strategies to handle them. [19] The primary estimand this study targets is the difference in average OS, expressed as the absolute difference in restricted mean survival time up to five years, if all adults with newly diagnosed metastatic NSCLC and PD-L1<1% had initiated nivolumab, ipilimumab, and chemotherapy compared to if they had initiated pembrolizumab and chemotherapy, regardless of tumor progression, treatment discontinuation or start of new treatment.

Our secondary estimand is the difference in average progression-free survival, as this is also considered a clinically relevant endpoint. [20] Another secondary estimand includes incremental cost-effectiveness. (Track A) The effect of co-mutations (TP53, KEAP1, and STK11) on treatment efficacy will be assessed as an exploratory objective, as previous studies have shown that these mutations are prognostic factors for outcomes of immunotherapy in NSCLC. KEAP1 and STK11 mutations have been shown to have a negative impact on the effectiveness of anti-PD-(L)1 therapy and may therefore indicate greater benefit from nivolumab plus ipilimumab plus chemotherapy, [21,22] as also described in the Dutch guidelines. [1] TP53 mutations modulate the ability of cancer cells to proliferate, escape apoptosis, invade and metastasize. [23] The prognostic impact of TP53 mutations in patients with NSCLC treated with chemo-immunotherapy is not well understood. [24] Therefore, our study aims to investigate the prognostic impact of TP53 mutations on treatment with nivolumab plus ipilimumab plus chemotherapy compared with pembrolizumab plus chemotherapy. The components of the primary estimand, together with those of the secondary and exploratory estimands can be found in Table S1.

For the intercurrent event of crossover treatment switching, we will follow the hypothetical strategy (ICH E9 [19]), as for survival analyses, it is assumed that future (unobserved) risk is the same as

in people who were not censored. Treatment policy is not suitable, as this may limit the interpretation of the effect of the experimental treatment to directly assess the effect of the experimental treatment on OS compared to control. [20]

The population was defined according to the Dutch guidelines for nivolumab plus ipilimumab plus chemotherapy. [1]

Overall survival and progression-free survival will be analyzed using Kaplan-Meier methods. For OS and PFS, the main interest of population-level summary measure is restricted mean survival time (RMST), because under non-proportional hazards with late separation of the survival curves, RMST has a more valid interpretation than the HR does. [25] Based on the OS results from the clinical trials and an indirect comparison, [2–4,26] and the delayed yet durable effects of immunotherapies, the survival curves are expected to take time to diverge, with separation anticipated after three to four years, and differences in treatment effect are expected to become apparent in the tail of the survival curve (i.e., among long-term survivors). Therefore, treatment effects are expected to not be proportional, and the HR estimate may be difficult to interpret clinically. Consequently, RMST will be defined as the area under the survival curve from t=0 to five years, as the survival curves are expected to diverge after three years and a clinically relevant difference is expected after five years. The t_{cut} for PFS will be set at 1 year, as the curves are expected to diverge after 1 year. Additionally, t_{cut} will be set at 2 years. Supplementary, hazard ratios (HRs) will be estimated using Cox regression, as this is in line with CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407. [15–17]

Table S1. Elements of the estimands. Specifications applicable only to track A are highlighted in blue, and those applicable only to track B are highlighted in purple.

Elements of the estimands						
Population (who and at what time)	**Contrasted treatments (what, when, and how)**	**Endpoint (what, when, and how)**	**Intercurrent events (what and corresponding strategy)**	**Population-level summary measure**	**Estimand started as a research question**	**Example of a treatment decision to be informed by the estimand**
Primary estimand (OS)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	Overall survival: time from start treatment to death (due to any cause)	●Tumor progression treatment policy, ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*start new treatment (crossover)* hypothetical strategy.	Main interest is difference in restricted mean survival time (RMST), using a five-year cutoff. Besides that, the hazard ratio.	What would be the difference in overall survival up to 5 years if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, *if nobody switched to crossover therapy*, regardless of tumor progression, discontinuation of the treatment or start of new treatment due to any reason except switch to or start of crossover therapy?	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%
Secondary estimand 1 (PFS)						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab	PFS (time from start treatment to death from any cause or tumor progression)	●*Treatment discontinuation for other reasons than tumor progression (for some period or for entire period)* treatment policy approach ●*Start any new treatment for other reasons than tumor progression (except crossover)* treatment policy approach, ●*start new treatment for other reasons than tumor progression (crossover)* hypothetical strategy.	Main interest is difference in restricted mean survival time (RMST), with cutoff at one year. Additionally, cutoff at two years. Besides that, hazard ratio.	What would be the difference in average progression free survival up to 1 year if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, *if nobody switched to crossover therapy*, regardless of discontinuation or start of new treatment except switch	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%

	+ chemo with any dosing regimen				to or start of crossover therapy, with both treatment assignments due to reasons other than tumor progression?	
Secondary estimand 2 (Cost-effectiveness) – Track A						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	●Overall survival ●Quality of life ●Healthcare resource utilization	Overall survival: ●*Tumor progression* treatment policy approach, ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* hypothetical strategy. Quality of life: Idem as overall survival, plus: ●*Death* while-alive approach. Healthcare resource utilization: ●*Tumor progression* treatment policy approach, ●*Treatment discontinuation (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* treatment policy approach, ●*Death* while-alive approach.	●Incremental cost-effectiveness ratio (ICER) for LYs and QALYs ●Difference in healthcare resource utilization and costs ●Difference in effectiveness (LYs and QALYs)	What would be the difference in effectiveness, costs and incremental cost-effectiveness if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, *if nobody switched to crossover therapy*, regardless of tumor progression, discontinuation of the treatment or start of new treatment due to any reason except switch to or start of crossover therapy?	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%

Exploratory estimand 1 (OS if nobody discontinued due to toxicity) – Track B						
Adults with newly diagnosed metastatic NSCLC and PD-L1<1%	Initiation of first line Nivolumab + Ipilimumab + chemo with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	Overall survival: time from start treatment to death (due to any cause)	●*Tumor progression* treatment policy approach ●*Treatment discontinuation due to toxicity (for some period or for entire period)* hypothetical, ●*Treatment discontinuation due to any other reason (for some period or for entire period)* treatment policy approach, ●*Start any new treatment (except crossover)* treatment policy approach, ●*Start new treatment (crossover)* hypothetical strategy.	Main interest is difference in restricted mean survival time, using a five-year cutoff. Besides that, the hazard ratio.	What would be the difference in average overall survival if all adults with NSCLC had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo *if nobody discontinued due to toxicity and nobody switched to crossover therapy* of regardless of tumor progression, discontinuation of the treatment or start of new treatment due to any other reason except switch to or start of crossover therapy?	NA
Exploratory estimand 2 (Effect of co-mutations on OS and PFS)						
Adults with newly diagnosed metastatic NSCLC and, PD-L1<1%	Initiation of first line nivo+ipi+chemo scheme with any dosing regimen versus initiation of first line pembrolizumab + chemo with any dosing regimen	Overall survival: time from start treatment to death (due to any cause) PFS (time from start treatment to death from any cause or tumor progression)	*See intercurrent events for OS and PFS*	*See population-level summary measure for OS and PFS.* Overall survival and PFS will be analyzed stratified according to co-mutations (TP53, KEAP1, STK11)	What would be the difference in average overall survival and PFS for adults with NSCLC and either the co-mutation tp53, KEAP1 or STK11 if all had initiated nivolumab + ipilimumab + chemo, compared to if they had initiated pembrolizumab + chemo, *if nobody switched to crossover therapy,* regardless of tumor progression, discontinuation of the treatment or start of new treatment due to any other reason except switch to or start of crossover therapy?	Advising on treatment initiation in the population of adults with NSCLC, PD-L1<1%

Abbreviations: NSCLC: non-small cell lung cancer, PD-L1: programmed death-ligand, OS: overall survival, PFS: progression-free survival, QALY: Quality Adjusted Life Years, LY: life years.

Hypothetical target trial specifications

The hypothetical target trial specifications are based on the study designs of CheckMate 9LA, KEYNOTE-189, and KEYNOTE-407. [2–4] CheckMate 9LA compared nivolumab plus ipilimumab plus chemotherapy with chemotherapy alone in patients with metastatic NSCLC, while the KEYNOTE trials compared pembrolizumab plus chemotherapy with chemotherapy alone in patients with metastatic non-squamous NSCLC (KEYNOTE-189) and metastatic squamous NSCLC (KEYNOTE-407). In Table S2, the components of the target trial protocol are specified in accordance with the TARGET statement. [27]

Differences between the hypothetical RCT and Checkmate 9LA & KEYNOTE

Some changes have been made in our target trial protocol compared to the protocols of the KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA studies to align with the standard of care in the current Dutch setting. In our study, only patients with PD-L1<1% will be included, whereas KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA included patients irrespective of PD-L1 status. Only patients with PD-L1<1% will be included, as nivolumab plus ipilimumab plus chemotherapy is only administered to patients with PD-L1<1% in the Dutch setting, [1] while pembrolizumab plus chemotherapy is administered to patients with either PD-L1<1% or PD-L1 1-50%. [28] This is a result of the Dutch guidelines for first line immunotherapy in metastatic NSCLC patients. [1,5] Some changes have been made in the dosing regimens to be consistent with the standard of care in the current Dutch setting. Alternative dosing of pembrolizumab and nivolumab is allowed, as this does not impact relevant outcomes and is used in Dutch clinical practice. [29–31] Alternative dosing for pembrolizumab includes weight-based dosing (100, 150, or 200 mg Q3W or 200, 300, or 400 mg Q6W), compared with the standard doses of 200mg Q3W or 400mg Q6W. [31] Alternative dosing for nivolumab includes weight-based dosing (160, 180, 200, 220, 240, 260, 280, 300, 320, 340, or 360 mg), compared with the standard dose of 360mg Q3W. [31] Maintenance therapy without pemetrexed is permitted in the pembrolizumab plus pemetrexed group, as this does not impact OS and is used in Dutch clinical practice. [32]

For the outcomes, some endpoints were removed as this is not within the aim of our study. OS is the primary endpoint, as this is the most convincing outcome to assess the benefits in anticancer medicines. [20] PFS is a secondary outcome as quality of life and OS may be affected by PFS. Moreover, secondary outcomes include quality of life and healthcare resource utilization to be able to assess cost-effectiveness. (Track A)

Economic evaluation was not prespecified within the protocol of KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA. Therefore, it has been newly developed in this target trial protocol. (Track A)

Table S2. Target trial specifications, informed by clinical trial protocols from KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA. Deviations from these protocols in the target trial specifications are highlighted in red (deletions), green (additions). Additional commentary is marked in grey. Specifications applicable only to track A are highlighted in blue, and those applicable only to track B are highlighted in purple.

	KEYNOTE-189 and KEYNOTE-407	CheckMate 9LA	Hypothetical Target trial
Eligibility	Patients diagnosed with pathologically confirmed IV non-squamous NSCLC (KEYNOTE-189) and squamous NSCLC (KEYNOTE-407): • aged ≥ 18 years of age, • [DEL]~~tissue available to assess PD-L1 expression levels~~ • ECOG ≤ 1, • Life expectancy ≥ 3 months, • No prior systemic anti-cancer therapy given as primary therapy, • Prior radiotherapy to the lung within 6 months of trial-treatment initiation, • Prior (neo)adjuvant chemotherapy completed at least 12 months before enrollment, • No prior systemic cytotoxic chemotherapy for metastatic disease, • No prior targeted or biological antineoplastic therapy, • No known EGFR mutations (KEYNOTE-189), • No known ALK translocations (KEYNOTE-189), • No major surgery or traumatic injury within 21 days before enrollment, • No previous malignancies, unless curative treatment with no evidence of disease recurrence in [DEL]~~5 years~~ of initiating said therapy, *COMMENT: Since the life expectancy of metastatic NSCLC is probably worse than that of other malignancies, 2 years is sufficient (CheckMate 9LA).* • No prior treatment with anti-PD-1, PD-L1 or PD-L2 agent, • No symptomatic central nervous system metastases • Not receiving systemic immunosuppressive treatment	Patients diagnosed with histologically confirmed IV NSCLC (both squamous and non-squamous): • aged ≥ 18 years of age, • [DEL]~~had provided a tumor sample for determination of PD-L1 status~~ • ECOG ≤ 1, • Life expectancy ≥ 3 months, • No prior systemic anti-cancer therapy given as primary therapy, • Prior definitive chemoradiation occurred at least 6 months prior to enrollment, • Prior (neo)adjuvant chemotherapy completed at least 6 months before enrollment, • *Non-squamous:* No known EGFR mutations, • *Non-squamous:* No known ALK translocations, • No major surgery or traumatic injury within [DEL]~~14 days~~ before enrollment, *COMMENT: 14 days is considered too short for undergoing these therapies* • No previous malignancies, unless complete remission was achieved at least 2 years prior to enrollment, • No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody. • No symptomatic central nervous system metastases • Negative hepatitis B and C tests within 28 days • Not receiving corticosteroids (prednisone>10mg/day) or	Patients diagnosed with histologically confirmed IV NSCLC (both squamous and non-squamous): • aged ≥ 18 years of age, • [NEW] PD-L1<1% *COMMENT:* Dutch setting • ECOG ≤ 1, • Life expectancy ≥ 3 months, • No prior systemic anti-cancer therapy given as primary therapy, • Prior radiotherapy to the lung within 6 months of trial-treatment initiation, • Prior (neo)adjuvant chemotherapy completed at least 12 months before enrollment, • No prior systemic cytotoxic chemotherapy for metastatic disease, • No prior targeted or biological antineoplastic therapy, • No known EGFR mutations, • No known ALK translocations, • No major surgery or traumatic injury within 21 days before enrollment, • No previous malignancies, unless complete remission was achieved at least 2 years prior to enrollment, • No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody. • No symptomatic central nervous system metastases • Negative hepatitis B and C tests within 28 days • Not receiving corticosteroids (prednisone>10mg/day) or

	• No history of non-infectious pneumonitis that required the use of glucocorticoids	immunosuppressive treatment within 2 weeks • No carcinomatous meningitis, symptomatic interstitial lung disease, HIV, AIDS, or previous malignancy (except non-melanoma skin cancers and in situ cancers) within 2 years	immunosuppressive treatment within 2 weeks • No carcinomatous meningitis, symptomatic interstitial lung disease, HIV, AIDS, or previous malignancy (except non-melanoma skin cancers and in situ cancers) within 2 years • No history of noninfectious pneumonitis that required the use of glucocorticoids
Treatment strategy	200 mg pembrolizumab IV, every 3 weeks for up to 35 cycles. + **KEYNOTE-407** (*Squamous* histology): carboplatin (AUC: 6 mg /mL/min)) on day 1 and [DEL]~~either~~ paclitaxel (200 mg /m2) on day 1 [DEL]~~or nab-paclitaxel (100 mg/m2) on days 1, 8, and 15. (IV every 3 weeks for 4 cycles)~~. *COMMENT: Nab-paclitaxel is no longer used in Dutch clinical practice* **KEYNOTE-189** (*Non-squamous* histology): Cisplatin (75 mg /m2) or carboplatin (AUC: 5 mg /mL/min) plus pemetrexed (500 mg /m2), (IV every 3 weeks for 4 cycles). Followed by pemetrexed maintenance (500 mg /m2) every 3 weeks. [DEL]~~*OR* Placebo + chemotherapy~~	Nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg IV every 6 weeks), continued until disease progression, unacceptable toxicity, or completion per protocol (2 years). + *Squamous* histology: Carboplatin (AUC: 6 mg /mL/min) plus paclitaxel (200 mg/m2), (IV every 3 weeks for two cycles). *Non-squamous* histology: Carboplatin (AUC 5 or 6 mg /mL/min) plus pemetrexed (500 mg/m2) or cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2), (IV every 3 weeks for two cycles). [DEL]~~*OR* Placebo + chemotherapy~~	Nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg IV every 6 weeks), continued until disease progression, unacceptable toxicity, or completion per protocol (2 years). + *Squamous* histology: Carboplatin (AUC: 6 mg /mL/min) plus paclitaxel (200 mg/m2), (IV every 3 weeks for two cycles). *Non-squamous* histology: Carboplatin (AUC 5 or 6 mg /mL/min) plus pemetrexed (500 mg/m2) or cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2), (IV every 3 weeks for two cycles). [NEW] alternative dosing of nivolumab is allowed, as this does not impact OS and is used in Dutch clinical practice. [30. 31] OR 200 mg pembrolizumab IV, every 3 weeks for up to 35 cycles. + *Squamous* histology: carboplatin (AUC: 6 mg /mL/min)) on day 1 and paclitaxel (200 mg /m2) on day 1 (IV every 3 weeks for 4 cycles). *Non-squamous* histology: Cisplatin (75 mg /m2) or carboplatin (AUC: 5 mg /mL/min) plus pemetrexed (500 mg /m2), (IV every 3 weeks for 4 cycles). Followed by pemetrexed maintenance (500 mg /m2) every 3 weeks. [NEW] alternative dosing of pembrolizumab is allowed, as this does not impact OS and is used in Dutch clinical practice. [29,30] [NEW] maintenance without pemetrexed is allowed, as this does not impact OS and is used in Dutch clinical practice. [32]

Treatment assignment	Randomization [DEL]~~(2:1)~~, Double blinded Stratified by • [DEL]~~PD-L1 expression (≤1% vs. ≥1%),~~ *COMMENT: only patients with PD-L1<1% are included* • [DEL]~~chemotherapy (cisplatin vs. carboplatin,~~ • [DEL]~~paclitaxel vs. nab-paclitaxel~~), • smoking status (KEYNOTE-189) • [DEL]~~region (KEYNOTE-407).~~ *COMMENT: Patients only included within in the Netherlands*	Randomization (1:1), Double blinded Stratified by • tumor histology, • sex • [DEL]~~PD-L1 expression (≤1% vs. ≥1%).~~ *COMMENT: only patients with PD-L1<1% are included*	Randomization (1:1), Double blinded Stratified by • tumor histology, • sex • smoking status
Follow-up	Event driven follow-up design. From date of randomization to - PFS: initiating a non-study cancer treatment; or - experiencing progression or death; or - withdrawing consent; or - becoming lost to follow-up whichever occurred first.	Event driven follow-up design From date of randomization up to experiencing the primary outcome (death due to any cause) or loss-to-follow-up (whichever occurred first).	Event driven follow-up design From date of randomization up to experiencing the primary outcome, loss-to-follow-up, [NEW] or treatment switch to crossover (whichever occurred first).
Outcomes	- *Primary endpoint:* • [NEW]*Secondary endpoint (track A):* PFS (RECIST 1.1) • OS [DEL]~~where the trial is considered positive if the hypothesis for either one of these endpoints is successful.~~ *Secondary endpoint:* • [DEL]~~ORR~~ • [DEL]~~response duration~~ • [DEL]~~safety.~~ *Exploratory endpoint:* • [DEL]~~Effect of PD-L1 expression on efficacy~~ • [NEW]*Secondary endpoint (track A):* Quality of life (PROMs: EORTC QLQ-C30, QLQ-LC13, EQ-5D)	*Primary endpoint:* OS defined as time between date of randomization and death due to any cause. *Secondary endpoint:* • PFS • [DEL]~~ORR~~ • [DEL]~~overall survival, progression free survival, and objective response rate by PD-L1 expression level~~ • [DEL]~~efficacy by tumor mutational burden~~ • [DEL]~~progression-free survival after next line of treatment~~ *Exploratory endpoint:* • [NEW]*Secondary endpoint (track A):* Quality of life (PROMs: EQ-5D): Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-Up phase, then every 6 months thereafter.	*Primary endpoint:* OS defined as time between date of randomization and death due to any cause. *Secondary endpoint:* • PFS • *(track A):* Quality of life (PROMs: EQ-5D): Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-Up phase, then every 6 months thereafter. • *(track A):* Healthcare resource utilization (HCRU) *[NEW] Exploratory endpoint:* • Effect of co-mutations (TP53, KEAP1, STK11) on efficacy

		• [NEW]*Secondary endpoint (track A):* Healthcare resource utilization (HCRU)	
Causal contrast	ITT	ITT	ITT [NEW]*Track B: Estimands* For the OS, different estimands will be estimated. The primary estimand will be a treatment policy estimand where the key intercurrent events (ICE) (discontinuation due to any reason not being toxicity or switch to crossover therapy, and start of new treatment due to any reason not being toxicity or start of crossover therapy) will be handled with a treatment policy strategy. Discontinuation due to switch to crossover therapy, or start of crossover therapy will be estimated using hypothetical strategy. For track B, a hypothetical strategy for the intercurrent event discontinuation due to toxicity will be used, assuming toxicity is only related to immune response. For all other intercurrent events, the treatment policy strategy will be followed. For PFS, the same ICEs will be considered. A more detailed rationale for the estimands will be provided in the HARPER emulation protocol.
Statistical analysis	**OS** Stratified Cox model with Efron's tie handling method, including stratified factors [DEL]~~PD-L1 expression (≤1% vs. ≥1%)~~, chemotherapy (cisplatin vs. carboplatin, [DEL]~~paclitaxel vs. nab-paclitaxel~~), and smoking status (never vs. former or current) (KEYNOTE-189) or [DEL]~~geographic region of enrollment (East Asia vs. the rest of the world)~~ (KEYNOTE-407). **Subgroup** analysis for OS on • Age category (≤65, >65 years) • Sex (female, male)	**OS** Estimated using KM techniques. A two-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method. OS rates at fixed timepoints (e.g. 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. Analyses were stratified by [DEL]~~PD-L1 expression~~, sex, and histology. **Subgroup** analysis for OS on • Age categorization (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, and ≥65) • Sex (male vs. female)	**OS** Estimated using KM techniques. [NEW] RMST will be estimated by calculating the area under the survival curve. T_{cut} is set at 5 years. Besidat that, stratified Cox model with Efron's tie handling method, including stratified factors, histology and sex. **Subgroup** analysis for OS on • Age categorization (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥75, and ≥65) • Sex (male vs. female)

	• ECOG Performance Scale (0, 1) • Smoking status (never, former/ current) • [DEL]~~PD-L1 expression (unknown, TPS TPS ≥1%, or TPS ≥50%)~~ • Brain metastasis status at baseline (yes, no) • [DEL]~~Taxane chemotherapy (paclitaxel, nab-paclitaxel) (KEYNOTE-407)~~ • [DEL]~~Platinum based drug (Carboplatin vs Cisplatin) (KEYNOTE-189)~~ *COMMENT: Not relevant, as also not included in CheckMate 9LA* • Race (white, -non-white)	• ECOG performance (0, ≥1) • Smoking status (current/former, never smoked, unknown) • [DEL]~~PD-L1 subgroups (<1%, ≥1%, 1-49%, ≥50%)~~ •CNS Metastasis (yes vs. no) • Liver Metastasis (yes vs. no) • Bone Metastasis (yes vs. no). • Tumor histology (squamous, non-squamous)	• ECOG performance status (0, 1) • Smoking status (current/former, never smoked, unknown) •CNS Metastasis (yes vs. no) • Liver Metastasis (yes vs. no) • Bone Metastasis (yes vs. no). • Tumor histology (squamous vs non-squamous)
	PFS Stratified Cox model with Efron's tie handling method, including stratified factors [DEL]~~PD-L1 expression (≤1% vs. ≥1%~~), chemotherapy (cisplatin vs. carboplatin), and smoking status (KEYNOTE-189) or [DEL]~~region (KEYNOTE-407)~~. **Subgroup** analysis: same subgroups as for OS calculation.	**PFS** Stratified Cox proportional hazards model, with treatment as the sole covariate. Ties will be handled using the exact method. **Subgroup** analysis: same subgroups as for OS calculation.	**PFS** [NEW] RMST will be estimated by calculating the area under the time-to-event curve. T_{cut} is set at 1 year. Additionally, t_{cut} is set at 2 years. Besides that, stratified Cox proportional hazards model, with treatment as the sole covariate. Ties will be handled using the exact method. **Subgroup** analysis: same subgroups as for OS calculation.
	Cost-effectiveness NA		[NEW] Track A: **Cost-effectiveness (Track A)**: **General considerations** Cost-effectiveness will be estimated using methods following the Dutch guidelines for economic evaluations in healthcare. [33] • Analytic model: Markov • Effectiveness: life years and QALY • Cost input: both direct and indirect • Time horizon: lifetime • Discount rates: 3% costs, 1.5% health outcomes [33] • Cost perspective: societal perspective • Sensitivity analysis: both deterministic sensitivity and probabilistic sensitivity analyses. The estimated range of each parameter will be based on the 95% CI in the studies. Outcomes of the sensitivity

		analysis will be presented in a tornado diagram, a cost-effectiveness plane, and a cost-effectiveness acceptability curve. • Scenario analysis will be conducted for the following scenarios: no discounting, healthcare perspective, alternative lengths of the time horizon, distributions for extrapolation of time-to-event data, and subgroup analyses. [33] Cost analysis • Treatment costs: actual consumption valued by Z-index 2026 • Hospital activities: actual consumption valued by: (A) independent cost price research and literature, (B) financial records within healthcare organizations, (C) NZa tariffs, (D) market prices, and (E) DBC tariffs. [34] • Indirect costs: e.g. productivity losses: Friction cost method
		[NEW] Effect of co-mutations of efficacy Same as for OS and PFS, stratified for co-mutations (TP53, KEAP1, STK11).

PS, performance status; PD-L1, programmed death-ligand 1; OS, overall survival; PFS, progression-free survival; CNS, central nervous system; QALY, Quality Adjusted Life Years; Nza, Dutch Healthcare Authority; DBC, diagnosis treatment combinations.

Sample size calculation

A sample size calculation based on RMST was considered to assess whether there is a sufficient patient sample size. The cutoff time of five years is used in the primary RMST analysis, therefore, ta (cutoff time) is set at 60 months. Lambda0 is calculated using the median OS of 16.1 months of pembrolizumab in the KEYNOTE-189 and KEYNOTE-407 studies. Sample size was calculated using a Piecewise Weibull model from the R script from Li et al. [35] Kappa is set at 1.0, one-sided α level of 0.025 and 80% power. Two scenarios were calculated based on the survival results of nivolumab plus ipilimumab plus chemotherapy compared to pembrolizumab plus chemotherapy in the clinical trials (KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA). [2–4]. Scenario 1: to detect an expected HR of 0.70 (after 12 months), a total of 1472 patients would be required. The theoretical overall survival curves are shown in Figure S1. Scenario 2: to detect an expected HR of 0.2 (after 36 months), a total of 4103 patients would be required (Figure S2). Input variables are shown in Table S3.

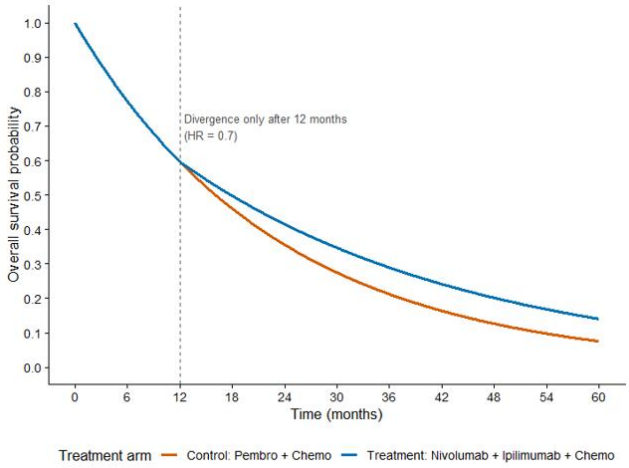


Figure S1 Theoretical overall survival curves for treatment: nivolumab + ipilimumab + chemotherapy (blue line), and control: pembrolizumab + chemotherapy (orange line), using a Piecewise Weibull model, HR = 0.7 after 12 months.

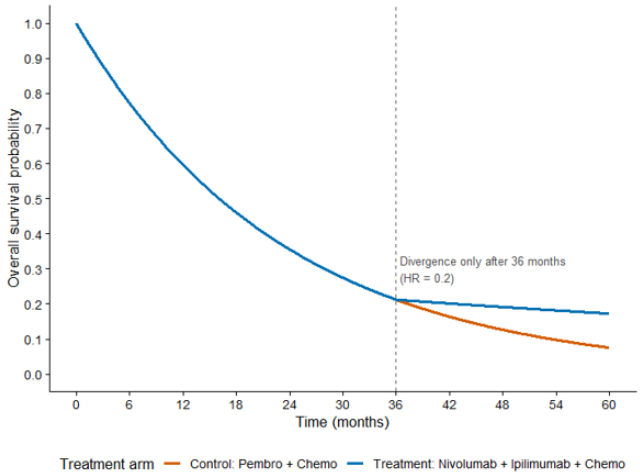


Figure S2 Theoretical overall survival curves for treatment: nivolumab + ipilimumab + chemotherapy (blue line), and control: pembrolizumab + chemotherapy (orange line), using a Piecewise Weibull model, HR = 0.2 after 36 months.

Table S3 Input variables for RMST sample size calculation

Hazard ratio (HR)	change points (months)	ta (months)	lambda0	lambda1	kappa0	kappa1	Pi	RMSTd	Number of patients
0.70	12	60	(0.0431,0.0431)	(0.0431,0.0301)	(1,1)	(1,1)	0	3.405	**1472**
0.20	36	60	(0.0431,0.0431)	(0.0431,0.0086)	(1,1)	(1,1)	0	2.037	**4103**

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