# A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS)

Published: 21-10-2015
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-509137-39-00 check the CTIS register for the current data. Primary/dualco-primary. To prospectively investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery (...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Respiratory and mediastinal neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53053

**Source**
ToetsingOnline

**Brief title**
PEARLS

### Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

**Synonym**
non-small cell lung cancer / lung cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Merck Sharp & Dohme (MSD)
**Source(s) of monetary or material Support:** farmaceutische industrie

## Intervention

**Keyword:** NSCLC, Pembrolizumab

## Outcome measures

### Primary outcome

Primary/ dual -primary endpoints

* DFS in the PD-L1 strong positive sub-group;

* DFS in the overall population .

Timepoint(s) of evaluation of this end point:

1. Every 12 weeks (± 2 weeks) during the 1st year after randomization,every 6 months (± 4 weeks) for the 2nd and 3rd year, yearly (± 4 weeks) for year 4 and 5. Thereafter at least yearly up to year 10.
2. Every 12 weeks (± 2 weeks) during the 1st year after randomization,every 6 months (± 4 weeks) for the 2nd and 3rd year, yearly (± 4 weeks) for year 4 and 5. Thereafter at least yearly up to year 10.

### Secondary outcome

Secondary endpoints

* DFS in the PD-L1 positive population;

* OS in the overall population;

* OS in the PD-L1 strong positive subgroup;

* OS in the PD-L1 positive population;

* LCSS in the overall population;

* Toxicity according to CTCAE version 4.0.

Exploratory endpoints

* Health-Related Quality of Life (HRQOL);

* Pharmacokinetics (PK) of pembrolizumab;

* ADA serum titers against pembrolizumab;

* Exploratory assessment of predictive biomarkers and immune dynamics

Timepoint(s) of evaluation of this end point:

1. Every 12 weeks (± 2 weeks) during the 1st year after randomization,every 6 months (± 4 weeks) for the 2nd and 3rd year, yearly (± 4 weeks) for year 4 and 5. Thereafter at least yearly up to year 10.
2. OS will be measured from the date of randomization until the date ofdeath.
3. OS will be measured from the date of randomization until the date ofdeath.
4. OS will be measured from the date of randomization until the date ofdeath.
5. LCSS will be measured from the date of randomization until the dateof death (due to lung cancer specifically).
6. Every 3 weeks during treatment and at 12 weeks after the last treatment.

# Study description

**Background summary**

Please refer to page 23 in the protocol.

Lung Cancer is the leading cause of cancer-related death world-wide; in 2012, 313,000 new cases have been estimated in Europe and 1,825,000 worldwide with 268,000 and 1,590,000 deaths respectively.
Non Small Cell Lung Cancer (NSCLC) accounts for 80-85% of all lung cancers, about 20% of cases being diagnosed at an early stage when the disease is still curable by surgery.

Surgical resection is the standard treatment for operable patients with resectable stage I to IIIA .

Despite the recent advances in staging, post operative support and adjuvant chemotherapy, 40% of patients with stage I, 66% of stage II, and 75% of stage IIIA will still develop recurrence and die as a result of their disease within 5 years of resection.
Residual micrometastases are believed to be the cause of disease recurrence. In an effort to eradicate micrometastases and improve overall survival (OS), numerous clinical trials have evaluated adjuvant and neoadjuvant chemotherapy.

Adjuvant chemotherapy is the standard treatment for patients with completely resected stage II or III NSCLC.

PD-L1 expression was described in many cancer types and in particular in lung cancer where up to 50% of NSCLCs are reported to express PD-L1. High expressers of PD-L1 on immunohistochemistry of tumor samples appear to get the best benefit from PD-1 or PD-L1 inhibitors although the benefit is not exclusive to this group.

Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

**Study objective**

This study has been transitioned to CTIS with ID 2023-509137-39-00 check the CTIS register for the current data.

Primary/dualco-primary.
To prospectively investigate whether adjuvant treatment with pembrolizumab

after completion of radical surgery (lobectomy/pneumonectomy) with or without standard adjuvant chemotherapy for stage IB (T >= 4 cm) -II-IIIA NSCLC patients improves Disease Free Survival (DFS), as assessed locally by the investigator, compared to placebo in the PD-L1 strong positive subgroup (TPS>=50%) or overall population.
Note: TNM stage (according to the 7th edition of the TNM classification for lung cancer)
Secondaries.
To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population;
To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population (TPS>=1%);
To prospectively determine and compare OS in the PD-L1 strong positive and overall population;
To prospectively determine and compare OS in the PD-L1 positive population;
To prospectively determine and compare OS in overall population;
To prospectively determine and compare the Lung Cancer Specific Survival (LCSS) in the whole population irrespective of PD-L1 status;
To prospectively assess the safety of pembrolizumab after radical surgery followed by standard adjuvant chemotherapy.
Exploratory.
To assess outcome according to stratification factors and other prognostic and predictive markers for NSCLC;
To evaluate these treatments in the elderly (age >=70 years old);
To prospectively study the influence of dose and duration of adjuvant chemotherapy on outcome;
To prospectively assess genetic alterations and biomarkers of immunological pathways with outcome;
To prospectively assess DNA mutational burden and nanostring RNA analysis with outcome;
To prospectively assess EQ-5D health state profiles at pre-specified time points;
To prospectively assess Health-Related Quality of Life (HRQOL);
To evaluate the pharmacokinetics (PK) of pembrolizumab in this patient population to determine the pembrolizumab exposure -response relationships for measures of effectiveness, toxicity, and pharmackodynamic biomarkers in the study population;
To evaluate the development of anti-drug antibiodies (ADA) against pembrolizumab (immunogenicity evaluation);
To assess and describe the quality assurance for surgery.

**Study design**

This is an international, triple-blinded, placebo-controlled, randomized phase III trial, which will be conducted in multiple countries (region Western Europe versus Eastern Europe versus Rest of the world versus Asia)

### Intervention

The study treatment will be triple-blind. The treatment will either be study medication (pembrolizumab) or placebo.

### Study burden and risks

- The use of study medication pembrolizumab can cause side effects;
- Some medication cannot be taken next to the study medication, because they can affect treatment with the study medication;
- If subjects are randomized into the placebo group, their condition is not being treated and can therefore remain unchanged or even worsen;
- The usual risks associated with blood draw;
- The usual risks associated with intravenous infusion (for admission of the study medication or placebo)

## Contacts

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US
**Scientific**
Merck Sharp & Dohme (MSD)

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07065 NJ
US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Patient enrollment will follow a three- steps procedure as illustrated in Section 4 (step 1 registration, step 2 central confirmation of PD-L1 status, step 3 randomization). Patients must meet all of the criteria described in Sections 3.1, 3.2 and 3.3 to be eligible for randomization in step 3.
1) Registration - step 1 (ORTA step 1)
Before patient registration, written informed consent for tumor testing must be given according to ICH/GCP and national/local regulations. For patients that accept to participate in the translational research, we recommend the informed consent for translational research be signed before registration step 1;
Pathological diagnosis of NSCLC confirmed at surgery, any histology is eligible;
Confirmed UICC v7 stage IB with T >= 4 cm, II-IIIA NSCLC after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) as documented in the pathology report;
(Note: TNM stage according to the 7th edition of the TNM classification for lung cancer)
Resection margins proved microscopically free (R0); Resection margins should must be considered to beare evaluated at the bronchial, venous and arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or of additionally resected tissue;
A systematic complete mediastinal lymph node dissection or a lobe-specific mediastinal lymph node dissection (Appendix K) is recommended. At a minimum, the pathology and/or operative report must include the examination of at least two different mediastinal lymph node (N2) levels, one of which is the subcarinal (level 7) and the second of which is lobe-specific;
A systematic nodal dissection is recommended or at least a lobe-specific systematic nodal dissection. However, the intraoperative lymph node evaluation can be accepted if no lymph nodes are found in those area and there is clear documentation in the operative report by the surgeon of exploration of the required lymph node areas. At minimum, the pathology and/or operative report should include the examination of at least two different mediastinal nodal (N2) station with one being subcarinal (level 7);
In the uncommon clinical situation where the surgeon thoroughly examines a particular mediastinal lymph node level and does not find any lymph nodes, that mediasintal lymph node level may be counted among the minimum two required levels. However, the surgeon must clearly document in the operative report or in a separate written statement that the lymph node level was explored and no lymph nodes were present. Normal appearing lymph nodes, if present, must be biopsied or/removed;
No extracapsular nodal extension of the tumor in resected mediastinal (N2) lymph nodes. Extracapsular tumor extension is permitted in resected N1 lymph nodes;

The highest mediastinal node removed can be positive for malignancy;.
Carcinoma in situ can be present at bronchial margin;.
Patients with two synchronous primary non-small cell lung cancers are excluded from the study;
Availability of tumor sample obtained at surgical resection for PD-L1 Immunohistochemistry (IHC) expression assessment. Patients must submit the tumor sample during screening for PD-L1 IHC expression testing at a central pathology laboratory. Patients will be eligible to participate regardless of the level of PD-L1 status, however tissue must be considered satisfactory for characterization of PD-L1 status. Patients whose samples are inadequate for PD-L1 determination will not be randomized;.
Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should must be freshly cut and submitted to the central testing laboratory;
At least 18 years;
Before patient registration, written informed consent for PD-L1 IHC testing must be given according to ICH/GCP, and national/local regulations.
2) Central confirmation of PD-L1 status - step 2
This central confirmation through EORTC is required for enrolling the patient in step 3.
3) Randomization - step 3 (ORTA step 2)
Before patient randomization, written informed consent (*Main Study*) for participation in the study must be given according to ICH/GCP, and national/local regulations;
No evidence of disease (NED) at clinical examination and/or baseline baseline radiological assessment duringon baseline assessment as documented by contrast enhanced chest/upper abdomen CT scan, brain CT/MRI and clinical examination within 128 weeks prior to the randomization date;
Note: In screening phase, if a patient cannot have a CT with contrast, the patient is not eligible.
Adjuvant chemotherapy is not mandatory but considered for patients with stage IB (T >= 4 cm) and strongly recommended for stage II and IIIA, and will be administered according to national and local guidelines. Patients who received more than 4 cycles of adjuvant therapy are not eligible;
Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date.
Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of the surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle).
ECOG Performance status 0-1;
Adequate organ function performed within 10 days of treatment initiation;
No prior or foreseen planned neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy is allowed;
Note: Prior radiotherapy for another malignancy (breast cancer/lymphoma/germ cell tumors, etc.) is not an exclusion criterion, the same applies for prior anti-cancer systemic chemotherapy.

No prior treatment with an anti-PD-1, anti-PD-L1/2, anti- CD137, CTLA-4 modulatorss or any other immune-modulating agents ; patients receiving live vaccine within 30 days prior to the first dose infusion of study treatment are not eligible;
No current participation in a interventional clinical trial or treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose infusion of study treatment;
No known history of Human Immunodeficiency Virus (HIV) (known HIV 1/2 antibodies positive). No known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg results. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay;
No chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 3 days prior to the first dose infusion of trial treatment: Corticosteroid use on study for management of ECIs (pembrolizumab Event of Clinical Interest), as pre-medication for the administration of chemotherapies, and/or a premedication for IV contrast allergies/reactions is allowed;
Daily prednisone at doses of 5-7.5 mg is allowed as an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy;
No history of interstitial lung disease (ILD) OR a history of (non-infectious) pneumonitis that required oral or IV steroids (other than COPD exacerbation) or current pneumonitis;
No active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Any replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement are also allowed;.
No history of a hematologic or primary solid tumor malignancy, unless in remission for at least 5 years.

### Exclusion criteria

Please refer to D4a. All eligibility criteria are listed in this section.

## Study design

### Design

Study phase: 3

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 12-04-2017 |
| Enrollment: | 50 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | pembrolizumab |
| Generic name: | pembrolizumab |
| Registration: | Yes - NL outside intended use |

## Ethics review

Approved WMO

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|---|---|
| Date: | 21-10-2015 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

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|---|---|
| Date: | 01-03-2016 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

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|---|---|
| Date: | 15-03-2016 |
| Application type: | First submission |

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|---|---|
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-01-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-02-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-05-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-07-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-11-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-09-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-10-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 04-02-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-03-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 12-08-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-10-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-12-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-02-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-04-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-06-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

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| | (Assen) |
| Approved WMO Date: | 07-07-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-08-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-10-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-12-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-04-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 26-11-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-09-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-09-2022 |

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| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-12-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-04-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-12-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-01-2024 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2023-509137-39-00 |
| EudraCT | EUCTR2015-000575-27-NL |
| CCMO | NL54953.056.15 |