# A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants Whose Disease has Remained Stable or Responded to First-Line Platinum-Based Chemotherapy with Pembrolizumab for Stage IIIB/IIIC or IV Non-Small Cell Lung Cancer (ZEAL-1L)

Published: 02-10-2020
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2023-508443-40-00 check the CTIS register for the current data. Dual Primary Objectives:• To compare progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR) using...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Respiratory tract neoplasms |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54238

**Source**
ToetsingOnline

**Brief title**
213400 - ZEAL-1L

## Condition

- Respiratory tract neoplasms

**Synonym**
non small cell lung cancer (NSCLC); lung cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** GlaxoSmithKline
**Source(s) of monetary or material Support:** GlaxoSmithKline B.V.

## Intervention

**Keyword:** Niraparib, Non-Small Cell Lung Cancer (NSCLC), Pembrolizumab, Standard of care First-Line

## Outcome measures

### Primary outcome

OS is one of the dual primary endpoints for the study; it is defined as the

time from randomization to the date of death due to any cause. Participants who

are alive will be censored at the date of last contact.

### Secondary outcome

The following key secondary efficacy endpoint will be evaluated:

• PFS in NSQ population defined as per primary PFS endpoint

• PFS in CR/PR population defined as per primary PFS endpoint

• OS in NSQ population defined as per primary OS endpoint

• OS in the CR/PR population

• TTP in the CNS is defined as the time from the date of randomization until

the earliest date of documented PD in the CNS. CNS progression is defined as

progression in the CNS due to new CNS lesion or progression of baseline CNS

lesion, as assessed by BICR per RANO-BM criteria.

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

• PFS as assessed by the Investigator using RECIST v1.1

• PFS, per RECIST v1.1 based on BICR, and OS by PD-L1 status (PD-L1 TC <1% and NE

versus >=1%)

• TTD, defined as the time from randomization to meaningful deterioration on a composite

endpoint of dyspnea, chest pain, and cough, on the EORTC QLQ-LC13

• Change from baseline in the EORTC QLQ-C30 and EORTC QLQ-LC13 domains

Safety Analysis (Secondary and Exploratory Endpoints)

Safety will be evaluated based on the incidence of AEs, SAEs, and AESIs, the incidence of treatment discontinuations, dose interruptions, and dose reductions due to AEs, SAEs, or AESIs, changes in ECOG performance status, changes in clinical laboratory results (hematology, chemistry, thyroid function, and urinalysis), vital sign measurements, observations during physical examination, and use of concomitant medications

# Study description

**Background summary**

Development of more efficacious treatment options for patients with NSCLC remains a high unmet need. Novel combination therapy regimens are needed with acceptable safety profiles that deliver clinically meaningful improvement in PFS and OS when administered in the maintenance setting for patients with advanced/metastatic NSCLC whose disease did not progress with frontline pembrolizumab/platinum-based therapy.

This study will evaluate the efficacy of niraparib in combination with pembrolizumab in comparison to pembrolizumab plus placebo as maintenance therapy in participants with Stage IIIB, IIIC or IV NSCLC (both squamous and non-squamous histology) who have achieved SD, PR, or CR in response to standard of care induction with 4 to 6 cycles of platinum doublet chemotherapy and pembrolizumab. Patients with asymptomatic brain metastases (BM) will be allowed to enrol in this study given the high potential of lung cancer patients to have or develop BM during treatment. If the participant did not have a CNS magnetic resonance imaging (MRI) at the beginning of standard of care induction therapy, the presence of BM at first screening scan will not be considered evidence of progression in the absence of other factors, such as new CNS symptoms.

**Study objective**

This study has been transitioned to CTIS with ID 2023-508443-40-00 check the CTIS register for the current data.

Dual Primary Objectives:

• To compare progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the overall population.
• To compare overall survival (OS) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the overall population.

Key Secondary Objectives:
• To evaluate and compare the time to progression (TTP) in the central nervous system (CNS) as assessed by BICR using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria
• To compare PFS as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the nonsquamous (NSQ) population
• To compare PFS as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in best response to standard of care induction chemotherapy with complete and partial response (CR/PR) population
• To compare OS of niraparib plus pembrolizumab versus placebo plus

pembrolizumab as maintenance therapy in the NSQ population
• To compare OS of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the best response to standard of care induction chemotherapy with CR/PR population

Secondary Objectives:
• To evaluate CNS PFS as assessed by BICR using RANO-BM
• To evaluate PFS as assessed by the Investigator using RECIST v1.1
• To evaluate PFS as assessed by BICR using RECIST v1.1 and OS by programmed cell deathligand
1 (PD-L1) status (PD-L1 tumor cells [TCs] <1% versus >=1%)
• To evaluate and compare time to deterioration in lung symptoms (TTD), defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the European Organisation for Research and Treatment of Cancer Quality of Life
Questionnaire 13-item lung cancer-specific module (EORTC QLQ-LC13)
• To evaluate changes from baseline in health-related quality of life (HRQoL) and symptoms as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) and the EORTC QLQ-LC13 total and
domain scores
• To evaluate safety and tolerability in participants treated with niraparib plus pembrolizumab compared to placebo plus pembrolizumab
• To describe the exposure of niraparib when given in combination with pembrolizumab

Exploratory Objectives:
• To further evaluate safety and tolerability in participants treated with niraparib plus pembrolizumab compared to placebo plus pembrolizumab
• To evaluate time from randomization to progression or death from any cause in the absence of progression, whichever comes first, on subsequent anticancer treatment following maintenance therapy (progression-free survival 2 [PFS2])
- To evaluate ORR and DOR as verified by BICR per RECIST v1.1 and RANO-BM in participants with evidence of disease at baseline
• To evaluate PFS as assessed by BICR using RECIST v1.1 and OS by homologous recombination deficiency (HRD) status (positive or negative)
• To evaluate PFS as assessed by BICR using RECIST v1.1 and OS by tumor mutational burden (TMB) status (high versus low)
• To evaluate frequency and severity of symptomatic adverse events (AEs) based on the Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events (PRO-CTCAE) and the Functional Assessment of Cancer Therapy - General Population (FACT-GP5)
• To evaluate change from baseline in overall symptom severity on the Patient Global Impression of Severity/Change (PGIS/PGIC)
• To evaluate change from baseline as assessed by the European Quality of Life 5-Dimensions 3-Level Scale (EQ-5D-3L)
• To explore the impact of niraparib exposure on efficacy and safety endpoints

• To evaluate circulating tumor DNA (ctDNA) burden in blood from baseline and on-treatment samples
• To explore potential mechanisms of either de novo or treatment-emergent resistance
- To explore the effect of statins on the efficacy of niraparib

**Study design**

Participants may be randomized directly after completing the standard of care induction period or, under the Investigator*s discretion, they may use an optional recovery period and be randomized within 6 weeks of the last dose of chemotherapy. If the 6-week recovery period is used, pembrolizumab, in the absence of chemotherapy, must continue in the cycle immediately following the last cycle of standard of care induction and in accordance with standard prescribing directions.

In order to be a candidate for this study, participants must have SD, PR, or CR, as assessed by the Investigator per RECIST v1.1 criteria, following 4-6 cycles standard of care treatment. In addition, a tumor specimen must be submitted for central PD-L1 testing and stratification.

For all participating EU countries (including UK), the Ventana PD-L1 SP263 assay will be performed at Q Squared Solutions laboratory in West Lothian, Scotland, United Kingdom. The Ventana PD-L1 SP263 assay is CE-marked for its analytical performance in formalin-fixed, paraffin-embedded (FFPE) tissue specimens.

Participants who have achieved SD, PR, or CR following the standard of care induction treatment and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive niraparib plus pembrolizumab or placebo plus pembrolizumab as maintenance therapy. The proportion of participants with SD will be carefully monitored at the time of randomization, and a cap will be applied at SD enrolment threshold of 50% of total sample size to prevent the proportion of participants entering the study to differ significantly from the proportions observed in the KEYNOTE-189 and KEYNOTE-407 studies (approximately 35% to 40%).

Participants will be stratified by:
• histology (squamous versus non-squamous),
• PD-L1 status (TC <1%/NE versus >=1%), and
• best response to standard of care induction chemotherapy (CR/PR versus SD)

Participants will continue to receive their assigned treatment until radiographic PD is documented (and reviewed by BICR), unacceptable toxicity, death, withdrawal of consent, or becoming lost to follow-up, whichever comes first.

Treatment with pembrolizumab will continue for up to a total maximum of 35 cycles from the beginning of standard of care induction therapy (ie, approximately 92 weeks from randomization). Treatment with niraparib/placebo will continue until radiographic PD or other treatment discontinuation criterion is met, or for up to 3 years.

Follow-up assessments will occur as indicated in the Schedule of Activities (Table 1) of the study protocol.

An Independent Data Monitoring Committee (IDMC) will be established to provide independent review and assessment of the efficacy and safety data. An interim safety analysis will be assessed by the IDMC when approximately 120 participants total across both treatment arms have completed at least 2 cycles of maintenance therapy. IDMC periodic data safety reviews will be performed as specified in the IDMC charter.

Approximately 650 participants are expected to be randomized in the study.

**Intervention**

Niraparib/Placebo:
Niraparib/placebo will be administered orally once daily (2-3 tablets) throughout each 21-day cycle until radiographic PD or another treatment discontinuation criterion is met, or for up to 3 years.

(Standard treatment)
Pembrolizumab:
Pembrolizumab will be administered in accordance with the product*s standard prescribing instructions as an IV infusion over approximately 30 minutes each 21-day cycle for up to a maximum of 35 cycles from the beginning of standard of care induction therapy.

**Study burden and risks**

Side effects considered very common (may affect more than 1 in 10 people):
Decrease in the number of blood platelets, the number of red blood cells, the number of white blood cells, the number and the number of neutrophils
High blood pressure, the heart skipping beats or beating harder than usual, painful and frequent urination (urinary tract infection), shortness of breath, runny or stuffy nose, cough, headache, dizziness, feeling weak, lack of energy, difficulty in sleeping, joint pain, back pain, stomach pain, indigestion, feeling sick, vomiting , frequent watery stools, constipation and decreased appetite.

These side effects are considered common (may affect up to 1 in 10 people):
Infection due to low white blood cell counts, bronchitis

fast heart beat
swelling of lower legs and feet (edema)
muscle pain
rash, decrease in weight
feelings of sadness
depressed, feelings of worry
nervousness or unease
inflammation of the eye (conjunctivitis)
nose bleed
sore, red mouth, swelling or irritation of the lining of the mouth, throat, esophagus, stomach or intestines (mucosal inflammation/mucositis)
abnormal taste in mouth
dry mouth
increased sensitivity of the skin to sunlight
decrease in potassium in the blood
increased level of creatinine in your blood (blood creatinine increase), which may be a sign of kidney damage
increased levels of substances in the blood produced by the liver

These side effects are considered uncommon (may affect up to 1 in 100 people):
• Fever with low white blood cell count (febrile neutropenia)
• Decrease in all types of blood cells (pancytopenia)

These side effects are considered rare (may affect up to 1 in 1000 people):
• Severe life-threatening infection due to low white cell counts (associated with low blood pressure and possible organ failure (for example, heart, kidney and/or liver) (neutropenic sepsis)
• Severe increase in blood pressure.
• A brain condition with symptoms including seizures, headache, confusion and changes in vision

In addition to the above, the side effects below were reported by patients who were prescribed niraparib by their doctors:
• Allergic reaction (hypersensitivity, including anaphylaxis).
• Life-threatening allergic reaction (such as difficulty breathing, rash, localized swelling, such as tongue, throat or lips) (anaphylaxis)
• Confusion
• Disorientation
• Hallucination
• Impaired concentration, understanding, memory and thinking
• Inflammation of the (pneumonitis)

Niraparib belongs to the group known as PARP inhibitors. These class effects are potential risks for the group of drugs, but have not yet been identified as side effects for niraparib.
Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML):
• PARP inhibitors may cause blood cancers known as myelodysplastic syndrome

(MDS) and acute myeloid leukemia (AML).
• MDS/AML, including cases with a fatal outcome have been reported in a small number of patients who took niraparib or placebo (i.e., sugar pill). In 2 studies comparing niraparib to placebo, the likelihood of getting MDS/AML in patients who took niraparib was similar to those in patients who took placebo.
Second Primary Malignancy:
• PARP inhibitors may also cause a new primary cancer (that is, a cancer other than the one for which you have been treated). In 2 studies comparing niraparib to placebo, the likelihood of getting a new primary cancer in patients who took niraparib was similar to those in patients who took placebo.
Risks associated with study procedures
• Blood draws: mild pain, bruising, irritation or redness from the needle.
• CT scans: The cumulative radiation exposure from the tests is considered small and is not likely to adversely affect the subject. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease.
• MRI: Some people cannot have an MRI because they have some type of metal in their body. For instance, if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, they cannot have an MRI. During this test, you will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise.

## Contacts

**Public**
GlaxoSmithKline

Van Asch van Wijckstraat 55H
Amersfoort 3811 LP
NL
**Scientific**
GlaxoSmithKline

Van Asch van Wijckstraat 55H
Amersfoort 3811 LP
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Male or female, age 18 years and above.
Diagnosis of NSCLC
Advanced or metastatic NSCLC
Completion of 4-6 cycles of platinum-based standard of care first-line induction chemotherapy with pembrolizumab
Participants must have SD, PR, or CR of their NSCLC per Investigator*s assessment
ECOG performance status 0-1.
Life expectancy of at least 12 weeks.
Adequate organ and bone marrow function
Participants must submit FFPE tumor specimens
Toxicity from induction therapy must have recovered to a level of organ and bone marrow function as defined by Inclusion Criteria #8 (see protocol) and no ongoing toxicity with grade 3 or higher.
Able to swallow and retain orally administered study treatment.
Contraception guidelines for females and males should be followed

## Exclusion criteria

Mixed small cell lung cancer or sarcomatoid variant NSCLC.
Received prior PARP inhibitor(s) in prior lines of treatment.
A systolic BP >140 mmHg or diastolic BP >90 mmHg.
A clinically significant gastrointestinal abnormalities that may alter absorption.
Leptomeningeal disease, carcinomatous meningitis, symptomatic BM, or radiographic signs of CNS hemorrhage.
Received colony-stimulating factors within 4 weeks prior to the first dose of

study treatment.
Active or previously documented autoimmune or inflammatory disorder
Receiving chronic systemic steroids (prednisone >20 mg per day).
Participants with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
Previously or currently participating in a treatment study with IP within 4 weeks of the first dose of standard of care first-line induction therapy.
Received prior systemic cytotoxic chemotherapy, biological therapy or hormonal therapy for cancer, or received thoracic radiation therapy of >30 Gy within 6 months of the first dose of the start of standard of care first-line induction therapy.
Received live vaccine within 30 days of planned start of study randomization.
Known hypersensitivity to the components of niraparib, placebo, or pembrolizumab or their formulation excipients.
Major surgery within 4 weeks of starting the first dose of study treatment or have not recovered from any effects of any major surgery.
Active concomitant malignancy that warrants systemic, biologic or hormonal therapy.
Pregnant, breastfeeding or expecting to conceive children while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
Presence of hepatitis B or hepatitis C

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 07-04-2023 |

| | |
|---|---|
| Enrollment: | 25 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Keytruda |
| Generic name: | Pembrolizumab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Zejula |
| Generic name: | Niraparib |
| Registration: | Yes - NL outside intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 08-10-2020 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 18-12-2020 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 11-02-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-02-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO | |

| | |
|---|---|
| Date: | 07-05-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 09-05-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 12-08-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 19-08-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 12-01-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 19-01-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 21-07-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 22-07-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United |

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|---|---|
| | (Nieuwegein) |
| Approved WMO Date: | 25-03-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 03-05-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 02-08-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 04-09-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# 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 | CTIS2023-508443-40-00 |

| Register | ID |
| --- | --- |
| EudraCT | EUCTR2020-002202-20-NL |
| CCMO | NL75207.100.20 |
| Other | www.gskclinicalstudyregister.com, nummer 213400 |