Pembrolizumab alone versus pembrolizumab-chemotherapy in first line NSCLC

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This study has been transitioned to CTIS with ID 2024-516581-11-00 check the CTIS register for the current data. Primary Objective:- to assess the effect of chemotherapy given concurrently with pembrolizumab on overall response rate (ORR) in NSCLC...

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

Summary

ID

NL-OMON55042

Source
ToetsingOnline

Brief title
PAULIEN

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Paulien van Deutekom Foundation

Intervention

Keyword: Chemotherapy, NSCLC, PD-L1, Pembrolizumab

Outcome measures

Primary outcome

1. ORR, as defined by partial response (PR) and complete response (CR) at week 6

2. Disease control rate (DCR), as defined by stable disease (SD) and PR and CR at week 6

Secondary outcome

1. PFS, as determined using Response Evaluation Criteria in Solid Tumors (RECIST1.1) and defined as time to the development of new lesions, progression of existing lesions, or death, whichever comes first.

2. PFS-2, as defined by the PFS on second line chemotherapy in arm 1.

3. ORR-2, as defined by the ORR on second line chemotherapy in arm 1.

4. Overall Survival (OS). Time frame: Baseline until death.

5. Safety defined as the percentage of patients with adverse events. Adverse events will be defined as described in the Common Terminology Criteria for Adverse Events (CTCAE).

Study description

Background summary

Lung cancer is the leading cause of cancer mortality. Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers. Historically, platinum-based doublet chemotherapy was the standard first-line treatment for metastatic NSCLC in the absence of targetable alterations. Chemotherapy alone

produces response rates ranging only between 15-30%. Since the introduction of immunotherapy, the treatment landscape for patients with NSCLC has fundamentally changed. Monoclonal antibodies targeting programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) have received regulatory approval for first-line treatment in patient with non-small cell lung cancer (NSCLC). Pembrolizumab (a PD-1 monoclonal antibody) significantly improved progression-free survival (PFS) and overall survival (OS) compared with platinum-based chemotherapy in patients with a PD-L1 tumor proportion score of 50% or greater. In addition; adding pembrolizumab to standard chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone regardless of PD-L1 expression. Therefore, the combination of pembrolizumab with chemotherapy has replaced cytotoxic chemotherapy as the first-line treatment of choice in patients with a tumor PD-L1 of less than 50%. In patients with PD-L1 >=50%, however, both pembrolizumab monotherapy and pembrolizumab combined with chemotherapy can be given as a first line option. In these patients, usually pembrolizumab monotherapy is chosen as it has less toxicities as compared to pembro-chemotherapy.

In the population of patient with a high tumor burden it may be assumed that the combination of pembrolizumab and chemotherapy will result in a higher response rate and may lead to an improvement in progression free survival and possibly overall survival.

The aim of this project is to determine whether patients with high tumor burden and high PD-L1 expression respond better to the combination of pembrolizumab with platinum-based chemotherapy rather than to pembrolizumab alone.

Study objective

This study has been transitioned to CTIS with ID 2024-516581-11-00 check the CTIS register for the current data.

Primary Objective:
- to assess the effect of chemotherapy given concurrently with pembrolizumab on overall response rate (ORR) in NSCLC patients with high PD-L1 and high tumor burden

Secondary Objectives:
- to examine the effect of chemotherapy given concurrently with pembrolizumab on progression free sur-vival (PFS) and overall survival (OS) in patients with high PD-L1 and high tumor burden as compared to pembrolizumab monotherapy followed by chemotherapy at progression
- to compare the PFS of concurrent chemo-pembrolizumab with sequential pembrolizumab followed by chemotherapy at progression (i.e. PFS-1 plus PFS-2)

Exploratory Objectives: The tumor biopsy prior to start of therapy and additional blood samples will be used for translational research.

- If sufficient tumor material is available, tumor mutational burden will be performed.
- Immunoprofiling of tumor micro-environment will be performed on the tumor biopsy using multiplex immunohistochemistry panels.
- Blood samples obtained at baseline and after 6 weeks of therapy will be analyzed for markers associated with tumor inflammation, immune system activation and exhaustion and circulating tumor DNA.

Study design

A phase 3, multicenter, randomized controlled trial.
Patients will be evaluated for study end points with follow-up at 6, 12 weeks and subsequently 3 month intervals with history and physical examination, imaging including CT of the chest and/or abdomen, and laboratory testing including complete blood cell counts and/or comprehensive metabolic panels as needed.

Intervention

Treatment regimen (Arm 1): Sequential pembrolizumab followed by chemo at progression
- Pembrolizumab monotherapy in first line
• Pembrolizumab monotherapy 3 or 6-weekly until progression at fixed dose of 200mg IV.
- Chemotherapy, subsequently in second line after PD
In non-squamous cell:
• Chemotherapy will be given using platinum/pemetrexed (4 cycles 3-weekly), followed by pemetrexed monotherapy 3 or 6-weekly until progression.
• Platinum: either carboplatin ([Glomerular Filtration Rate (ml/min) + 25] x (5 mg/ml x min) IV) on day 1 of each cycle or cisplatin 75 (or80) mg/m2 administered IV on day 1 according to local protocol. Pre-hydration and post hydration schedule is mandatory as described by local proto-col with NaCl 2.5 or 0.9%.
• Pemetrexed (500 mg/m2 IV) on day 1 of each cycle. Pemetrexed cycles will be repeated until progression, unacceptable toxicity or patient withdrawal.
• Dexamethasone (8 mg IV) on day 1 of each cycle to prevent allergic reactions to pemetrexed.
• Patients will receive folate (500 µg 1x/day orally) and hydroxocobalamin (1000 µg 1x/9weeks intramuscularly) during the whole course of pemetrexed therapy.
In squamous cell:
• Chemotherapy will be given using carboplatin/paclitaxel (4 cycles 3-weekly)
• Carboplatin ([Glomerular Filtration Rate (ml/min) + 25] x (5 mg/ml x min) IV) on day 1 of each cycle
• Paclitaxel 200 mg/m2 administered IV on day 1.of each cycle.

Treatment regimen (Arm 2): Concurrent pembrolizumab and chemotherapy
- Pembrolizumab plus chemotherapy
• In non-squamous cell: combination of Platinum/pemetrexed and pembrolizumab (4 cycles 3-weekly), followed by pemetrexed/pembrolizumab monotherapy 3-weekly until progression
• In squamous cell: combination of Platinum/paclitaxel and pembrolizumab (4 cycles 3-weekly), followed by pembrolizumab monotherapy 3 or 6-weekly until progression
• Dosing as described above

Study burden and risks

Patients will undergo one of two accepted routine first line therapies. As such, there are no additional risks nor is there an additional benefit associated with participation in this study, other than the benefit for future patients that will derived from the knowledge gained in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Histologically confirmed NSCLC, negative for EGFR and ALK mutations
• WHO PS 0-2
• No prior systemic therapy
• High PD-L-1 expression (>=50% TPS)
• High tumor burden (metastases (M1)) and not amenable for local consolidative therapies

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Patients amenable for local consolidative therapies
• Use of steroids equivalent to >10 mg prednisolon per day prior to start of study
• Untreated brain metastases
• Adequate bone marrow and organ functions (renal and liver)
• Uncontrolled active infections, HIV
• Autoimmune diseases and interstitial lung diseases are to be excluded depending on physicians decision

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-02-2020
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2020
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2021
Application type:	Amendment

Review commission: METC Amsterdam UMC

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	CTIS2024-516581-11-00
EudraCT	EUCTR2019-002743-26-NL
CCMO	NL70714.029.19