A Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Anti-PD-1 Antibody), Platinum based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients With Advanced or Metastatic Non-Small Cell Lung Cancer With Tumors Expressing PD-L1 >=50%

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The primary objective of the study is to compare the progression-free survival (PFS) of REGN2810 (cemiplimab) plus ipilimumab combination therapy (hereinafter referred to as REGN2810/ipi) and REGN2810 plus 2 cycles only of platinum-based doublet...

Ethical review	Approved WMO
Status	Suspended
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON46388

Source
ToetsingOnline

Brief title
0456/0145 REG (R2810-ONC-16111)

Condition

- Miscellaneous and site unspecified neoplasms benign
- Respiratory tract neoplasms

Synonym
lung cancer; lung tumours

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Inc.
Source(s) of monetary or material Support: Regeneron Pharmaceuticals Inc.

Intervention

Keyword: comparison, lung cancer, progression-free survival, REGN2810

Outcome measures

Primary outcome

The primary endpoint is PFS as assessed by a blinded Independent Review

Committee (IRC) based on RECIST 1.1 assessments.

Secondary outcome

The key secondary endpoints will be OS and ORR.

Other secondary endpoints will include the following:

• The safety and tolerability of REGN2810/ipi and REGN2810/chemo/ipi measured

by the incidence of treatment-emergent adverse events (TEAEs), dose-limiting

toxicities (DLTs), serious adverse events (SAEs), deaths, and laboratory

abnormalities

• Overall survival at 12 months and 18 months

• Quality of life as measured by the European Organization for Research and

Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and

European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)

• Tumor mutation burden as assessed by the Foundation Medicine *FoundationOne®*

panel, sample permitting

Study description

Background summary

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%). The majority of patients with NSCLC are found to have advanced cancer at the time of diagnosis. With chemotherapy, these patients have a median overall survival (OS) of up to 12 to 18 months and a 5-year survival rate of approximately 18%.

Systemic treatment with platinum based doublet regimens, with or without maintenance treatment, has been, until recently, the standard first line treatment for all patients with advanced NSCLC whose tumors do not have an epidermal growth factor receptor (EGFR) mutation, an anaplastic lymphoma kinase (ALK) mutation, or a c-ros oncogene 1 receptor tyrosine kinase (ROS1) fusion. Despite initial treatment with platinum based doublet regimens, the disease often progresses, and additional treatment options have been limited.

The hypothesis of this study is that REGN2810 and ipilimumab for up to 4 cycles of combination therapy (REGN2810/ipi) or REGN2810 plus platinum-based doublet chemotherapy for 2 cycles and ipilimumab for up to 4 cycles of combination therapy (REGN2810/chemo/ipi) will prolong median progressive-free survival (PFS) compared with standard-of-care pembrolizumab monotherapy in the first line treatment of patients with advanced or metastatic NSCLC whose tumors express PD L1 in >=50% of tumor cells.

Study objective

The primary objective of the study is to compare the progression-free survival (PFS) of REGN2810 (cemiplimab) plus ipilimumab combination therapy (hereinafter referred to as REGN2810/ipi) and REGN2810 plus 2 cycles only of platinum-based doublet chemotherapy plus ipilimumab combination therapy (hereinafter referred to as *REGN2810/chemo/ipi*) with standard-of-care pembrolizumab monotherapy in

the first line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD L1) in >=50% of tumor cells.

Study design

This is a phase 3, randomized, global, open-label, pivotal, study of the efficacy and safety of REGN2810/ipi versus REGN2810/chemo/ipi versus pembrolizumab monotherapy in patients with stage IIIB or stage IV squamous or non squamous NSCLC whose tumors express PD L1 in >=50% of tumor cells and who have received no prior systemic treatment for their advanced disease.
The study will consist of the following 3 periods: screening, treatment, and follow-up.

Intervention

• Treatment Arm A: pembrolizumab monotherapy 200 mg Q3W for 108 weeks
• Treatment Arm B: REGN2810 350 mg Q3W for 108 weeks plus ipilimumab 50 mg Q6W for up to 4 doses (REGN2810/ipi)
• Treatment Arm C: REGN2810 350 mg Q3W for 108 weeks plus platinum-based doublet chemotherapy Q3W for 2 cycles and ipilimumab 50 mg Q6W for up to 4 doses (REGN2810/chemo/ipi)

Study burden and risks

This study is a randomized, open-label, phase 3 study evaluating the efficacy of REGN2810/ipi or REGN2810/chemo/ipi compared with pembrolizumab monotherapy in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD L1 in >=50% of tumor cells and who have received no prior systemic treatment for their advanced disease. This study will be open-label because the differences in administration and known distinct toxicities of the therapies do not lend themselves to blinding.
Because this is the first study to evaluate the combination of REGN2810 and ipilimumab and the combination or platinum doublet chemotherapy and ipilimumab, there will be an early review of data to ensure patient safety after the first 10 patients in the REGN2810/ipi and the first 10 patients in the REGN2810/chemo/ipi treatment arm have completed 4 weeks of follow-up following the first dose of REGN2810/ipi or REGN2810/chemo/ipi respectively. An additional safety review will be performed by the Independent Data Monitoring Committee (IDMC) after the first 10 patients in the REGN2810/ipi and REGN2810/chemo/ipi regimen have received all 4 doses of ipilimumab and have been followed for at least 6 weeks after the last dose. This analysis will include all patients who have been exposed to the combination treatment.
The study population is limited to previous and current smokers as the benefit of PD-1 blockade has not been shown to the same extent in non-smokers likely

due to the lower mutational burden in this population

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

1. Men and women >=18 years of age.
2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB disease who are not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease if they have not received prior systemic treatment for recurrent or metastatic NSCLC.
3. Availability of an archival or on-study obtained formalin-fixed, paraffin embedded tumor tissue sample
4. Expression of PD L1 in >=50% of tumor cells determined by a commercially available assay.

5. At least 1 radiographically measureable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.
6. ECOG performance status of <=1.
7. Anticipated life expectancy of at least 3 months.

Exclusion criteria

1. Patients who have never smoked, defined as smoking <=100 cigarettes in a lifetime.
2. Active or untreated brain metastases or spinal cord compression. Patients are eligible if central nervous system (CNS) metastases are adequately treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. Patients must be off (immunosuppressive doses of) corticosteroid therapy (see exclusion criterion 7 for details on timing of discontinuation of corticosteroid therapy).
3. Patients with tumors tested positive for EGFR gene mutations, ALK gene translocations, or ROS1 fusions. All patients will have tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions.
4. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
5. History of interstitial lung disease (eg, idiopathic pulmonary fibrosis or organizing pneumonia), of active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management, or of pneumonitis within the last 5 years. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved >=6months prior to enrollment.
6. Ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk of immune-related treatment-emergent adverse events (irTEAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
7. Patients with a condition requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of randomization. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

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:	Suspended
Start date (anticipated):	17-07-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin 10mg/ml concentrate for solution for infusion
Generic name:	carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin 1mg/ml Concentrate for Solution for Infusion
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine 2g Powder for Solution for Infusion
Generic name:	gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not yet known
Generic name:	cemiplimab
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-03-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-10-2018
Application type:	First submission
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
EudraCT	EUCTR2017-001041-27-NL
CCMO	NL64676.056.18