An Open-label, Randomized, Phase I/II Trial Investigating the Safety and Efficacy of IO102 in Combination with Pembrolizumab, with or without Chemotherapy, as First-line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer

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Primary Objectivea) Phase I (Safety Run-in) The primary objective of the Phase I Safety Run-in part is to investigate the safety of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy (carboplatin and pemetrexed)…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON46066

Source
ToetsingOnline

Brief title
IO102 with pembrolizumab, with or without chemotherapy for NSCLC

Condition

- Metastases

Synonym
Lung Cancer, Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: IO Biotech Aps
Source(s) of monetary or material Support: IO Biotech Aps

Intervention

Keyword: IO102, NSCLC, pembrolizumab

Outcome measures

Primary outcome

Phase I (Safety Run-in)

Objective: The primary objective is to investigate the safety of IO102 in combination either with pembrolizumab alone or pembrolizumab and chemotherapy (carboplatin and pemetrexed) in patients with metastatic NSCLC, that are eligible for pembrolizumab treatment as first-line therapy for stage IV disease.

Hypothesis: IO102 will show acceptable safety and tolerability profile when co administered with pembrolizumab in patients with metastatic NSCLC without prior treatment for the metastatic disease, without worsening the known safety profile of pembrolizumab alone or in combination with chemotherapy in this disease condition as compared to pembrolizumab or pembrolizumab in combination with chemotherapy.

Phase II

The primary objectives include:

Primary Efficacy Objective

Objective: To investigate the efficacy of IO102 in combination with either

pembrolizumab alone or pembrolizumab and chemotherapy versus pembrolizumab alone or pembrolizumab in combination with chemotherapy in patients with metastatic NSCLC, that are eligible for pembrolizumab treatment as first-line therapy.

Hypothesis: IO102 improves the objective response rate (ORR) when co-administered with either pembrolizumab alone or pembrolizumab and chemotherapy in patients with metastatic NSCLC without prior treatment for the metastatic disease assessed by RECIST 1.1 when compared to pembrolizumab alone, or with pembrolizumab and a platimum-based doublet chemotherapeutic regimen as observed in the control arms and using historical data from Merck KN-024, KN-021, KN-189 and KN-042 trials.

Secondary outcome

Secondary Objectives

The secondary objectives of the trial include:

Safety Objective:

To investigate the safety of IO102 in combination with pembrolizumab with or without chemotherapy (carboplatin and pemetrexed) in patients with metastatic NSCLC, that are eligible for pembrolizumab treatment, with or without chemotherapy, as first-line therapy for stage IV disease.

Hypothesis: IO102 will show acceptable safety and tolerability profile when co administered with pembrolizumab alone or in combination with chemotherapy in patients with metastatic NSCLC without prior treatment for the metastatic disease, without worsening the known safety profile of pembrolizumab with or without chemotherapy in this disease condition.

Secondary efficacy objectives:

To investigate DCR, time to event parameters of response including duration of

objective response, PFS, OS, and tumour shrinkage with IO102 in combination

with pembrolizumab alone or pembrolizumab in combination with chemotherapy

Study description

Background summary

Lung cancer is the leading cause of cancer-related death worldwide in men and women, causing 1.56 million deaths annually as of 2012. The main types are NSCLC (85%) and small-cell lung cancer (SCLC, 15%). The two main sub-types of NSCLC are adenocarcinoma (50%) and squamous-cell carcinoma (30-40%). Treatment options for patients with NSCLC are limited, and it is this population of patients this trial is focused on.
The trial medication IO102 will be given in combination with standard treatment, which includes pembrolizumab (a drug that is licensed for advanced lung cancer) with or without chemotherapy (carboplatin and pemetrexed). IO102 is a novel treatment designed to activate the patients* own immune cells to fight the cancer and stop the cancer cells from escaping from the body*s immune system. The drug is hence expected to act in two ways: 1. Direct killing of cancer cells and 2. Removal of the body*s immune suppressive cells which are cells that prevent the immune system from fighting the cancer. By making the cancer cells more visible/recognisable to the immune system it is hoped that this trial drug will enhance existing treatments available.

Study objective

Primary Objective
a) Phase I (Safety Run-in) The primary objective of the Phase I Safety Run-in part is to investigate the safety of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy (carboplatin and pemetrexed) in patients with metastatic NSCLC, that are eligible for pembrolizumab treatment as first-line therapy for stage IV disease.
b) Phase II
The primary objectives of the Phase II part include:
Primary Efficacy Objective
To assess the efficacy of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy versus either pembrolizumab alone or pembrolizumab and chemotherapy as measured by objective response rate (ORR) per investigator assessment in patients with metastatic NSCLC, that are eligible

for pembrolizumab treatment as first-line therapy.

Study design

This is a Phase I/II, multi-center, international, open-label, randomized trial investigating the safety and efficacy of two parallel cohorts of IO102 (Cohort A and Cohort B) in combination with pembrolizumab alone or pembrolizumab in combination with chemotherapy as first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) who have not received prior systemic therapy for their metastatic disease.
This clinical trial consists of two parts; a Phase I Safety Run-in part and a Phase II part with two parallel randomized cohorts (A and B) where patients are randomized based on the level of programmed cell death ligand 1 (PD-L1) expression. Treatment will be administered for up to 35 cycles of treatment (where 1 cycle is 3 weeks).

Intervention

Not applicable

Study burden and risks

The safety and efficacy of IO102 has been explored in a number of clinical trials, e.g., as a single agent in Non-Small Cell Lung Cancer (NSCLC) (as the shorter peptide, IO101) and as combination therapy with ipilimumab in melanoma, in a small number of subjects. During these trials, the majority of subjects have experienced mild to moderate injection site reactions (i.e., redness, swelling, or itching) which were controlled by local treatment with steroid ointments and or antihistamines. In addition, dyspepsia, abdominal pain, and diarrhoea could be related to the vaccine treatment, as Indoleamine 2,3-dioxygenase (IDO) is expressed in the epithelial cells in the gastrointestinal tract.

The safety and efficacy data generated to date provide a favourable benefit-risk assessment for the use of pembrolizumab in advanced/metastatic NSCLC. The important identified risks for pembrolizumab are of an immune-mediated nature, the majority being mild to moderate in severity, manageable with appropriate care, and rarely requiring discontinuation of therapy. In addition, two important potential risks have been identified, although the data available thus far for these events does not provide sufficient evidence of a causal relationship to pembrolizumab* myasthenic syndrome and an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with Programmed cell death 1 (PD-1) inhibitors. The published results of both the NSCLC pembrolizumab trials KN001 and KN024 showed treatment was associated with

Adverse Events (AEs) of fatigue, pruritus, decreased appetite, diarrhoea, and fatigue (all grades) and more severe AEs of dyspnoea, pneumonitis, anaemia, diarrhoea and fatigue (Grade 3 to 5 AEs).

This Phase I/II trial will involve a SMC that will closely monitor the combination of IO102 and pembrolizumab, during the entire trial. The frequency of trial visits, every 3 weeks, will also provide an appropriate level of monitoring from the investigator. No trial procedures are considered to be an unnecessary risk to participating patients.The inclusion of a tumour biopsy to determine PD-L1 status ensures compliance of the patient population recruited with the current license for pembrolizumab in this treatment setting.

Contacts

Public
IO Biotech Aps

Ole Maaløsvej 3 .
Copenhagen N DK-2200
NL
Scientific
IO Biotech Aps

Ole Maaløsvej 3 .
Copenhagen N DK-2200
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with histologically or cytologically confirmed metastatic NSCLC (Cohort A) or non squamous NSCLC (Cohort B), who have not received prior systemic treatment for their metastatic disease.
a. No known sensitizing EGFR or ALK mutations.
b. Solitary metastases must be biopsied to confirm the diagnosis metastasis from NSCLC
2. PD-L1 tumor expression of greater than or equal to 50% (Cohort A) or below 50% (Cohort B). PD-L1 tumour expression should be confirmed prior to randomization using the DAKO 22C3 assay, using local/central services.
3. A male participant able to father a child must agree to use contraception starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy.
Note: See section 6.7.2 of the protocol for details on contraception
4. A female participant is eligible to participate if she is not pregnant not breastfeeding, and at least one of the following conditions applies:
a. Not a woman of childbearing potential (WOCBP)
b. A WOCBP who agrees to follow contraceptive guidance starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy.
Note: A WOCBP i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Note: See section 6.7.2 of the protocol for details on contraception.
5. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial in accordance with ICH-GCP and local legislation prior to admission to the trial.
6. Be equal to or over 18 years of age on day of signing informed consent.
7. Have measurable disease per RECIST 1.1 as assessed by local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Have provided a blood sample and archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides.
Note: If archival tissue is available, it is preferred this is obtained within 90 days prior to randomization. If using unstained cut slides, newly cut slides should be used for the testing, within 14 days from the date slides are cut.
9. Have an ECOG performance status of 0 to 1.
10. Have adequate organ function as defined in the following Table 3. Specimens must be collected within 10 days prior to the start of trial treatment.

Exclusion criteria

1. A WOCBP who has a positive urine pregnancy test (e.g., within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor and was discontinued from that treatment due to a Grade 3 or higher immune-related AE (irAE).
3. Has received prior systemic anti-cancer therapy in the first line setting for the participant's metastatic disease.
Note: Participants must have recovered from all AEs due to previous therapies to *Grade 1 or baseline. Participants with *Grade 2 neuropathy may be eligible.
Note: If participant received major surgery, they must have recovered adequately from the adverse events and/or complications from the intervention prior to starting trial treatment.
4. Has received prior radiotherapy to the lung >30 Gy within 6 months of start of trial treatment. Participants must have recovered from all radiation-related adverse events, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (*2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
5. Has received a live vaccine within 30 days prior to the first dose of trial treatment. Seasonal influenza vaccines for
injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
6. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 6 months prior to the first dose of trial treatment.
Note: Participants who have entered the follow-up phase of an investigational trial may participate as long as it has been 6 months after the last dose of the previous investigational agent.
7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial treatment.
8. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.
Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during trial screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.
10. Has severe hypersensitivity (*Grade 3) to IO102, pembrolizumab, carboplatin, pemetrexed and/or any of its excipients.
11. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement

therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
15. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (HCV) (defined as HCV ribonucleic acid *RNA* [qualitative] is detected) infection.
Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial.
18. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days for cohort A and 180 days for cohort B after last dose of trial treatment.
19. Has had an allogenic tissue/solid organ transplant.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-09-2018
Enrollment:	16

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:	IO102
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	PEMBROLIZUMAB
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-11-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2018-000139-28-NL
CCMO	NL67943.000.18