A PHASE IB STUDY OF THE SAFETY AND PHARMACOLOGY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) ADMINISTERED WITH IPILIMUMAB, INTERFERON-ALPHA, OR OTHER IMMUNE-MODULATING THERAPIES IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

Published: 11-09-2014
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Primary ObjectivesThe primary objectives for this study are as follows:* To evaluate the safety and tolerability of atezolizumab and ipilimumab when administered in combination in patients with advanced or metastatic non-small cell lung cancer (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON47714

Source
ToetsingOnline

Brief title
GO29322

Condition

- Renal disorders (excl nephropathies)
- Lower respiratory tract disorders (excl obstruction and infection)

- Skin neoplasms malignant and unspecified

Synonym
Colorectal cancer, Head and Neck Squamous cell carcinoma, Non Small cell lung Cancer, renal cancer and melanoma (skin cancer)

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann-La Roche Ltd.
Source(s) of monetary or material Support: F. Hoffmann - La Roche Ltd.

Intervention

Keyword: Atezolizumab plus interferon alpha, Atezolizumab plus ipilimumab, Atezolizumab plus other immune modulating therapies, Locally advanced or metastatic solid tumors

Outcome measures

Primary outcome

Safety Outcome Measures

The safety outcome measures for this study are as follows:

* Nature and frequency of dose limiting toxicities (DLTs)

* Nature, frequency, and severity of adverse events, per the National Cancer

Institute Common Terminology Criteria for Adverse Events, Version 4.0

* Changes in vital signs, physical findings, and clinical laboratory test

results during and following atezolizumab administration

* Incidence of anti-atezolizumab antibodies during the study relative to the

incidence at baseline

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

* Progression free survival (PFS), defined as the time from first study

treatment to the first occurrence of disease progression or death, whichever

occurs first

* Objective response (PR plus CR), confirmed by repeat assessments * 4 weeks after initial documentation

* Best overall response

* Duration of objective response, defined as the time from the first occurrence of a documented objective response to the time of progression or death from any cause, whichever occurs first

* Overall survival, defined as the time from first study treatment to death from any cause

Best overall response, objective response, and disease progression will be determined by investigator assessment using conventional RECIST v1.1 and immune modified RECIST criteria.

Secondary outcome

Pharmacokinetic Outcome Measures

The PK outcome measures for the combination study are as follows:

* Serum atezolizumab concentrations: Predose, maximum (Cmax), treatment discontinuation, and follow-up visit * 90 days after the last dose.

* Serum ipilimumab concentrations: Predose, maximum (Cmax), treatment discontinuation, and follow-up visit * 90 days after the last dose.

* Serum bevacizumab concentrations: Predose, maximum (Cmax), treatment discontinuation, and follow-up visit * 90 days after the last dose.

* Serum obinutuzumab concentrations: Predose, maximum (Cmax), treatment discontinuation, and follow-up visit * 90 days after the last dose.

Note: Assays may be generated at a later date to characterize the pharmacokinetics and immunogenicity of interferon alfa-2b and PEG-interferon alfa-2a.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

* Identification and profiling of exploratory biomarkers in plasma, serum, or blood (e.g., T-cell markers, interferon-gamma [IFN-*], and other markers)
* Changes in immune-related markers (including but not limited to CD8, granzyme B, and other exploratory markers) in archival and fresh tumor tissue prior to and during combination atezolizumab treatment

The following exploratory predictive biomarker endpoints will be assessed when appropriate:

* PD-L1 status by immunohistochemistry or quantitative PCR in archival tissues and/or fresh biopsies
* Status of other exploratory biomarkers related to PD-L1 or immune cell biology (including but not limited to CD8 or PD-1) and tumor biology (e.g., tumor mutation status) in archival tissues and/or fresh biopsies

Study description

Background summary

see pages 88-104 of the protocol (1. Background)

Study objective

Primary Objectives
The primary objectives for this study are as follows:
* To evaluate the safety and tolerability of atezolizumab and ipilimumab when administered in combination in patients with advanced or metastatic non-small cell lung cancer (NSCLC) or melanoma
* To evaluate the safety and tolerability of atezolizumab and interferon alfa-2b when administered in combination in patients with advanced or metastatic renal cell carcinoma (RCC) or melanoma
* To identify a recommended Phase II dose (RP2D) and schedule for atezolizumab plus ipilimumab
* To identify a RP2D for atezolizumab plus interferon alfa-2b
* To evaluate the safety and tolerability of atezolizumab and polyethylene glycol (PEG)-interferon alfa-2a when administered in combination in patients with advanced or metastatic solid tumors
* To evaluate the safety and tolerability of atezolizumab in combination with PEG-interferon alfa-2a and bevacizumab in patients with advanced or metastatic solid tumors
* To evaluate the safety and tolerability of atezolizumab and obinutuzumab when administered in combination in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

Secondary Objectives
The efficacy objectives of this study are as follows:
* To make a preliminary assessment of the anti-tumor activity of atezolizumab and ipilimumab when administered in combination
* To make a preliminary assessment of the anti-tumor activity of atezolizumab and interferon alfa-2b when administered in combination
* To make a preliminary assessment of the anti-tumor activity of atezolizumab and PEG-interferon alfa-2a when administered in combination
* To make a preliminary assessment of the anti-tumor activity of atezolizumab, PEG-interferon alfa-2a, and bevacizumab when administered in combination
* To make a preliminary assessment of the anti-tumor activity of atezolizumab and obinutuzumab when administered in combination

The pharmacokinetic (PK) objectives of this study are as follows:
* To characterize the pharmacokinetics of atezolizumab and ipilimumab when administered in combination
* To characterize the pharmacokinetics of atezolizumab when administered in combination with interferon alfa-2b.
* To characterize the pharmacokinetics of atezolizumab when administered in combination with PEG-interferon alfa-2a.
* To characterize the pharmacokinetics of atezolizumab when administered with bevacizumab and PEG-interferon alfa-2a.
* To characterize the pharmacokinetics of atezolizumab and obinutuzumab when administered in combination.

The immunogenicity objective of this study is as follows:

* To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab, ipilimumab, bevacizumab, and obinutuzumab and to assess their potential relationship with relevant outcome markers

Assays may be generated at a later date to characterize the pharmacokinetics and immunogenicity of interferon alfa-2b and PEG-interferon alfa-2a.
Exploratory Objectives
The exploratory objectives for this study are as follows:
* To assess whether biomarkers, including but not limited to serum, plasma, tumor tissue, RNA, or other sources, are predictive of response to atezolizumab in combination with ipilimumab, interferon alfa-2b, PEG-interferon alfa-2a ± bevacizumab or with obinutuzumab (i.e., predictive biomarkers), of susceptibility to developing adverse events or progression to a more severe disease state (i.e., prognostic biomarkers), can act as pharmacodynamic indicators of anti-tumor activity of combination drug therapy (i.e., pharmacodynamics biomarkers), can provide evidence of combination drug activity, or can increase the knowledge and understanding of therapeutic mode of action and/or disease biology (i.e., mechanism of action biomarkers)
* To assess the relationship between somatic mutations, identified through whole genome sequencing (WGS) and/or next-generation sequencing (NGS) performed on DNA extracted from tissue and blood, and safety, PK, activity, immunogenicity, or other biomarker endpoints

For treatment Arm E (atezolizumab + obinutuzumab), analysis of B cell depletion and regulatory B cell gene signature will be evaluated for tumor tissues.

Study design

Description of Study
This is a Phase Ib, open-label, multicenter, global study designed to assess the safety and tolerability of atezolizumab in combination with other immune-modulating therapies. Approximately 200 patients may be enrolled in this study at approximately 8 sites worldwide.
This study will have five treatment arms. For each treatment arm, the study will consist of a Screening Period (Days -28 to -1), a Treatment Period, a Treatment Discontinuation Visit (occurring * 30 days after the last dose of study medication), and a Survival Follow-Up period. Day 1 (baseline) will be defined as the first day a patient receives atezolizumab.
Treatment Arms A and B will have two stages (dose escalation and expansion). In both treatment arms, a serial tissue biopsy cohort and a separate cohort evaluating patients previously treated with immune-modulating therapy (programmed death-ligand 1 [PD-L1] programmed death-1[PD-1]) will open during the Expansion Stage.
* Arm A: atezolizumab plus ipilimumab
Dose-Escalation Stage: Patients with NSCLC
Expansion Stage: Patients with NSCLC
Mandatory biopsy cohort: Patients with NSCLC or melanoma

Prior atezolizumab-treated cohort: Patients with NSCLC or melanoma
* Arm B: atezolizumab plus interferon alfa-2b
Dose-Escalation Stage: Patients with RCC or melanoma
Expansion Stage: Patients with RCC or melanoma
Mandatory biopsy cohort: Patients with RCC or melanoma
Prior immunotherapy-treated cohort: Patients with RCC or melanoma who were previously treated with PD-L1/PD-1 therapy within 6 months prior to study enrollment. Patients must have demonstrated radiologic evidence of disease progression after having derived stable disease for at least 6 months, or partial response (PR) or complete response (CR) of any duration. Patients with melanoma who were previously treated with anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) therapy may also be enrolled.

There will be no dose-escalation stage for treatment Arms C, D, and E. Arms C and D, will have a separate cohorts evaluating patients who were previously treated with immune-modulating therapy (PD-L1/PD-1).
* Arm C: atezolizumab plus PEG-interferon alfa-2a
Cohort 1: Patients with RCC
Cohort 2: Patients with locally advanced or metastatic solid tumor (e.g., NSCLC, RCC, or melanoma) who were previously treated with PD-L1/PD-1 therapy within 6 months prior to study enrollment. Patients must have demonstrated radiologic evidence of disease progression after having derived stable disease for at least 6 months, or PR or CR of any duration. Patients with melanoma who were previously treated with anti-CTLA-4 therapy may also be enrolled. Patients with other solid tumors may be considered for enrollment into Cohort 2.
* Arm D: atezolizumab plus PEG-interferon alfa-2a and bevacizumab
Cohort 1: Patients with first-line (1L) metastatic RCC
Cohort 2: Patients with locally advanced or metastatic non squamous NSCLC or CRC
Cohort 3: Patients with locally advanced or metastatic solid tumor (e.g., NSCLC, RCC, or melanoma) who were previously treated with PD-L1/PD-1 therapy within 6 months prior to study enrollment. Patients with melanoma who were previously treated with anti-CTLA-4 therapy may also be enrolled. Patients must have demonstrated radiologic evidence of disease progression after having derived stable disease for at least 6 months, or PR or CR of any duration. Patients with other solid tumors may be considered for enrollment into Cohort 3.
Preliminary safety and tolerability data from Arm B of this study indicate that intermittent interferon alfa-2b dosing regimen is relatively well tolerated when combined with atezolizumab. The combination of interferon-alpha with bevacizumab has been approved for 1L RCC. Furthermore, the safety, tolerability, and PK variability of the combination of atezolizumab with bevacizumab at the dose level and schedule indicated for Arm D have been studied in patients with metastatic CRC in a Phase Ib study (Study GP28328), demonstrating tolerability without exacerbation of bevacizumab-associated adverse events. Because the safety profile for PEG-interferon alfa-2a is reported to be consistent with that of interferon-alpha therapies, differences in safety events for this combination therapy is not expected. However,

special caution will be taken by implementing a 21-day safety evaluation period for the first 6 patients enrolled in Arm C. Completion of enrollment into Arm C and opening of Arm D will occur upon conclusion of the safety evaluation window and only if the combination is deemed to be tolerable.
* Arm E: atezolizumab ± obinutuzumab
Cohort 1: Atezolizumab + obinutuzumab in patients with R/M HNSCC
Cohort 2: Atezolizumab monotherapy in patients with R/M HNSCC

The safety, tolerability, and PK of the combination of atezolizumab with obinutuzumab at the dose level indicated for Arm E has been studied in patients with hematological cancers in a Phase Ib study (Study GO29383), demonstrating tolerability without exacerbation of atezolizumab- or obinutuzumab-associated adverse events. As a result, formal escalation and de-escalation will not be used for Arm E.
Patients receiving atezolizumab will continue to receive study drug as long as they experience clinical benefit in the opinion of the investigator or until unacceptable toxicity or symptomatic deterioration attributed to disease progression (e.g., pain secondary to disease or unmanageable ascites) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Intervention

See K2. Studydesign

Study burden and risks

An overview of the risks can be found in the informed consent form for Arm A, B, C, D and E appendix 2.

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

Patients must meet the following criteria for study entry:
* Signed Informed Consent Form
* Age * 18 years
* Able to comply with the study protocol, in the investigator*s judgment
* Histologically or cytologically documented locally advanced or metastatic solid tumors meeting the following study drug-specific criteria
* Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
* Life expectancy * 12 weeks
* Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
* Adequate hematologic and end organ function, defined by the following laboratory test results obtained within 14 days prior to the first study treatment:
ANC * 1500 cells/µL (without granulocyte colony stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
WBC counts > 2500 cells/µL
Lymphocyte count * 250 cells/µL
Serum albumin * 2.5 g/dL
Platelet count * 100,000 cells/µL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
Hemoglobin * 9.0 g/dL
Patients may be transfused or receive erythropoietic treatment to meet this criterion.
AST, ALT, and alkaline phosphatase * 2.5 × upper limit of normal (ULN), with the following exceptions:
Patients with documented liver or bone metastases: alkaline phosphatase * 5 × ULN
Serum bilirubin * 1.5 × ULN
Patients with known Gilbert disease who have serum bilirubin level * 3 × ULN may be enrolled.
INR and aPTT * 1.5 × ULN
This applies only to patients who are not receiving therapeutic anticoagulation; patients

receiving therapeutic anticoagulation should be on a stable dose.
Creatinine clearance * 30 mL/min
Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration, or Modification of Diet in Renal Disease formulae may be used for creatinine clearance calculation. Note that 24-hour urine collection is not required.
* For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for > 90 days after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 18 months after the last dose of obinutuzumab.
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (* 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
* For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for * 6 months after the last dose of bevacizumab. Men must refrain from donating sperm during this same period.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
* Archival tumor tissue
A representative formalin-fixed paraffin embedded (FFPE) tumor specimen collected at first diagnosis and/or subsequent tumor recurrence(s) consistent with the patient*s diagnosis is required for participation in this study (FFPE block [preferred] or a minimum of 15 unstained serial sections). This specimen must be accompanied by the associated pathology report. The tumor sample and associated pathology report must be confirmed to be available prior to any study-specific screening procedures. Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression and is therefore not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.
For samples not meeting minimum requirements for size/slide number, contact the Medical Monitor via your site contact with information on tissue size and tumor content/number of slides to determine eligibility.
Alternatively, or if the archival tumor sample does not meet minimum requirements, the patient may be offered the option of undergoing a pre-treatment procedure (excisional or core tumor biopsy) to obtain an adequate tumor sample. Acceptable samples include core needle biopsies for deep tumor tissue (minimum 3 cores) or excisional, incisional, punch, or

forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression and is therefore not acceptable. Patients having additional tissue samples from procedures performed at different times during the course of their cancer will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.;Detailed information about the specific inclusion criteria for Arm A, B, C, D and E can be found on pages 76-78 of the protocol.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
Cancer-Specific Exclusions
* NSCLC with sensitizing mutations in EGFR or ALK rearrangements
* Melanoma with BRAF mutations
* Active or untreated CNS metastases as determined by computed tomography (CT) scan or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments; patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
Measureable disease outside the CNS
No metastases to midbrain, pons, or medulla
No history of intracranial or spinal cord hemorrhage
No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
No evidence of interim progression * 4 weeks between the completion of CNS-directed therapy and the screening radiographic study
* Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for * 2 weeks prior to screening
* Leptomeningeal disease
* Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
Patients with indwelling catheters (e.g., PleurX®) are allowed.
* Uncontrolled tumor-related pain
Patients requiring pain medication must be on a stable regimen at study entry.
Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.
Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
* Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent

skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use and receive a bisphosphonate instead while on study.
* History of other malignancy within 2 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent, or other cancers with a similar outcome;General Medical Exclusions
* Pregnant and lactating women
* Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment, with the following exceptions:
Hormone-replacement therapy or oral contraceptives
Tyrosine kinase inhibitors (TKIs) that have been discontinued > 7 days prior to Cycle 1, Day 1; baseline scans must be obtained after discontinuation of prior TKIs.
* Investigational therapy within 28 days prior to initiation of study treatment
* History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
* Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the atezolizumab formulation
* History of or active autoimmune disease including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener*s granulomatosis, Sjögren*s syndrome, Bell*s palsy, Guillain Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
Patients with autoimmune thyroid disease or vitiligo may be eligible following consultation with the Medical Monitor.
Patients with controlled Type I diabetes mellitus on a stable insulin regimen may be eligible for this study.
* History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), risk of pulmonary toxicity, or evidence of active pneumonitis on screening chest CT scan
History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
* Prior allogeneic bone marrow transplantation or prior solid organ transplantation
* History of HIV (tested prior to inclusion into the study if not in contradiction with local legislation)
* Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)
Patients with past/resolved hepatitis B virus (HBV) infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1.
Note: For patients in Arm E, patients with past/resolved HBV infection are eligible provided they are willing to undergo regular monthly DNA testing and be placed on prophylactic anti-viral therapy for the duration of obinutuzumab treatment and for 12 months after the last dose of obinutuzumab. Patients who have protective titers of HBsAg after vaccination or prior but cured hepatitis B are eligible.
* Patients with active hepatitis C
Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain

reaction (PCR) is negative for HCV RNA.
* Active tuberculosis
* Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
* Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
* Received therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
*Patients with a history of confirmed progressive multifocal leukoencephalopathy
* Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months prior to study treatment, unstable arrhythmias, or unstable angina
* Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the study other than for diagnosis
* Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study and within 90 days after the last dose of atezolizumab
Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study and within 5 months after the last dose of atezolizumab.
* History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator*s judgment
* Any serious medical condition, physical examination finding, or abnormality in clinical laboratory tests that, in the investigator*s judgment, precludes the patient*s safe participation in and completion of the study;Exclusion Criteria Related to Medications
* Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies, or any other antibody or drug targeting T-cell co stimulation, with the following exceptions:
Note: Patients enrolled in the prior anti-PD-L1/PD-1 treated cohorts with melanoma may have received prior anti-CTLA-4 treatment or other immunotherapies.
* Treatment with systemic immunostimulatory agents (including but not limited to interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
Note: Prior exposure to alpha-interferons, including Roferon A®, Intron A®, and pegylated interferons, is allowed if the above criteria are met.
* Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Cycle 1, Day 1
Patients who have received acute and/or low-dose systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of * 10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Medical Monitor.
The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.;Detailed information about the specific exclusion criteria for Arm A, B, C, D and E can be found on page 81 of the protocol.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2015
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IntronA 18 MIU
Generic name:	IntronA 18 MIU
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	IntronA25 MIU
Generic name:	IntronA25 MIU
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	na
Generic name:	Atezolizumab
Product type:	Medicine
Brand name:	Pegasys 180 µg
Generic name:	Pegasys 180 µg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy 50 mg

Generic name:	Yervoy 50 mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-09-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-11-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-06-2016
Application type:	Amendment
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Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2019
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014-000812-33-NL
CCMO	NL49791.031.14