An exploratory tumor biopsy-driven study to understand the relationship between biomarkers and indicators of clinical response in immunomodulatory treatment naïve unresectable stage III/IV melanoma patients receiving REGN2810 (anti-PD-1)

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The primary objective of the exploratory study is to characterize the types and dynamics of changes in the tumor microenvironment that occur following programmed-death-1 (PD-1) receptor blockade with REGN2810 and to assess their relationship to the...

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

Summary

ID

NL-OMON49259

Source
ToetsingOnline

Brief title
Regeneron R2810-ONC-1606
(0456/0086)

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign
- Skin neoplasms malignant and unspecified

Synonym
unresectable melanoma; skin cancer

Health condition

melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Melanoma Stage III/IV, Phase 1b, REGN2810

Outcome measures

Primary outcome

The correlation between changes in the tumor microenvironment and the change in

tumor volume following REGN2810 treatment versus baseline.

The changes in tumor microenvironment that will be correlated to the change in

tumor volume may include:

* Changes in number of immune cells in the tumor microenvironment:

o Changes in the number of tumor infiltrating lymphocytes (TILs) focusing on

CD8+ T cells, CD4+ T cells, Tregs and myeloid cells

o Changes in cell type representation in the immune cell infiltrate (normalized

against total number of TILs)

* Fold-change in tumor gene expression focusing on the top 10 genes

differentially affected in responders compared to non-responders (changes in expression of additional genes of interest may be evaluated as part of the exploratory analyses)

* Changes in positive and negative immune checkpoint modulator expression focusing on LAG3, TIM3, and GITR (other molecules of interest may be evaluated as part of the exploratory analyses):
o Changes in overall expression level (assessed by RNASeq) and in situ expression (assessed by RNAScope)

* Changes in number of cells expressing molecule of interest.

Secondary outcome

* Correlation between baseline tumor characteristics and the change in tumor volume following treatment in REGN2810.
o Tumor gene expression as assessed by tumor RNASeq
o Tumor mutational load as assessed by whole-exome DNA sequencing and comparison between somatic and germline DNA

* Adverse Event (AEs) in patients treated with REGN2810.

* Concentrations of REGN2810 in serum and anti-REGN2810 antibody levels

* The overall response rate (ORR) and progression-free survival (PFS) in

patients treated with REGN2810.

Study description

Background summary

This is an exploratory study with a limited sample size and the analysis in this study will be descriptive and hypothesis generating. The primary hypotheses the study explores are:

* There are changes in the tumor microenvironment that occur following PD-1 blockade with REGN2810.
* There is a correlation in the tumor microenvironment that occur following PD-1 blockade with REGN2810 and clinical response as defined by changes in tumor volume.

A fixed sample size of 30 patients was initially selected based on clinical and feasibility considerations. With 30 patients, the (In order to obtain a better representation of patients with non-acral cutaneous subtype(s) of melanoma in this study, the overall sample size will be increased up to 50 patients). The precision of correlation between changes in tumor microenvironment and changes in tumor volume can be estimated using FISHER Z transformation. The primary analysis set includes all patients who have passed screening and deemed to be eligible for this study. Eligible patients are defined as patients with a tumor assessment at screening and at least one post-baseline tumor assessment. Additionally, patients must have biomarker data that meet QC criteria at baseline and at least one post treatment assessment. For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category. In general, the biomarker data will be transformed prior to relating fold change from baseline to clinical endpoints.

Secondary endpoints will be analyzed using the similar methods described in analysis of primary endpoint.
Baseline characteristic and adverse events will be summarized using descriptive statistics.

Due to exploratory nature of the study, uncertainty in measurability and variability of biomarker variables and no formal hypothesis testing, the multiplicity control is not applicable to this study.

Study objective

The primary objective of the exploratory study is to characterize the types and dynamics of changes in the tumor microenvironment that occur following programmed-death-1 (PD-1) receptor blockade with REGN2810 and to assess their relationship to the clinical response as defined by changes in tumor volume.

Specific techniques will include:
* Changes in immune cell infiltrates (as measured by RNASeq, RNAScope in situ hybridization and/or immunohistochemistry (IHC), if needed and available) to determine number, subset ratios, and geographic distribution of CD8+ T cells and other immune cells (for example, CD4+ T cells, B cells, NK cells, myeloid-derived suppressor cells, etc.).
* Changes in positive and negative immune checkpoint modulator expression (as assessed by RNASeq, in situ gene expression by RNAScope in situ hybridization and/or protein levels by IHC, if needed and available), of LAG3, TIM3, GITR, and other molecules of interest.

The secondary objectives of the exploratory study are:
* To assess the correlative relationship between baseline tumor characteristics and the changes in tumor volume following treatment with REGN2810.
* To assess the safety and tolerability of REGN2810.
* To measure drug concentrations during treatment.
* To assess immunogenicity of REGN2810.
* To assess the overall response rate (ORR) and progression-free survival (PFS) of melanoma patients treated with REGN2810.

For the additional exploratory objectives refer to the protocol.

Study design

This is a single-arm, multicenter, biomarker-driven trial evaluating the relationship between tumor and immune-related biomarkers and clinical response in immunomodulatory treatment-naïve unresectable stage III/IV melanoma patients receiving REGN2810 (anti-PD-1).

After a screening period of up to 28 days, patients will receive treatment with REGN2810 every 2 weeks up to 24 doses (48 weeks).

Each patient will receive 3 mg/kg REGN2810 given as a 30-minute infusion. Tumor assessments will be made every 8 weeks by imaging. Extensive safety evaluations will occur every 8 weeks; routine safety evaluations will be conducted at each REGN2810 dosing visit.

A patient will receive treatment until the 48-week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response (CR). Patients with confirmed CR after a minimum of 24 weeks of treatment may elect to discontinue treatment.

Patients with a single tumor assessment of PD (without prior partial response [PR]/CR) may continue treatment with the experimental regimen until the next tumor assessment, at the discretion of the investigator, based on the clinical state of the patient. Patients with confirmed and increasing PD per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (2 radiologic assessments of PD at least 4 weeks apart), or patients who are rapidly progressing and/or experiencing significant clinical deterioration or study drug toxicity, should discontinue study treatment.

Patients who discontinue study treatment will be followed for survival approximately every 3 months until death, lost to follow-up, or study termination by the sponsor.

Intervention

Each patient will receive 3 mg/kg REGN2810 given as a 30-minute infusion. Maximum of 24 doses.

Study burden and risks

The emerging safety profile of REGN2810 is consistent with that described in the clinical literature for other antibodies directed against PD-1.

In the dose-escalation cohort of R2810-ONC-1423 study, REGN2810 was well-tolarated; no DLTs were reported when administered to patients with advanced solid tumors at doses of 1,3, or 10 mg/kg either as monotheprapy or in combination with hypofractionated radiation and/or cyclophosphamide. In this heavily pre-treated phase 1 population of patients with solid malignancies, including tumor types known to respond poorly to PD-1/PD-L1 blockade, an overall response rate of 18.3% indicates that REGN2810 is a clinically active inhibitor of the PD-1 pathway. In study R1979-ONC-1504, the emerging data show that REGN2810 is well-tolerated in patients with lymphoma.

The benefit-risk profile continues to be positive in both solid tumors and lymphomas supporting further study of REGN2810.

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. Histologically confirmed diagnosis of stage III (unresectable) or stage IV cutaneous (non-acral lentiginous) with at least 1 lesion that is measurable by RECIST 1.1 criteria and accessible for biopsies. , 2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work)., 3. *18 years old, 4. Hepatic function:, a. Total bilirubin *1.5 x upper limit of normal, b. Transaminases *3 x ULN, c. Alkaline phosphatase (ALP) *2.5 x ULN, 5. Serum creatinine *1.5 x ULN or estimated glomerular filtration rate >50 mL/min/1.73m^2, 6. Bone marrow function:, a. Hemoglobin *9.0 g/dL, b. Absolute neutrophil count (ANC) *1.5 x 10^9/L, c. Platelet count *75 x 10^9/L, 7. Willing and able to comply with clinic visits and study-related procedures, 8. Provide signed informed consent, 9. Able to understand and complete study-related questionnaires, 10. Anticipated life expectancy >12 weeks

Exclusion criteria

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs., 2. Prior treatment with an agent that blocks

the PD-1/PD-L1 pathway., 3. Prior treatment with other immune modulating anti-cancer agents., 4. Untreated or active brain metastases or spinal cord compression. , 5. Immunosuppressive corticosteroid doses, 6. History of human immunodeficiency virus (HIV)., 7. Uncontrolled chronic hepatitis B or C., 8. History of pneumonitis within the last 5 years., 9. Grade 3 or 4 hypercalcemia at time of enrollment., 10. Any systematic anticancer treatment, investigational or standard of care, within 30 days of the initial administration of REGN2810 or planned to occur during the study period (Patients receiving bisphosphonates or denosumab are not excluded)., 11. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments., 12. Known allergy to doxycycline or tetracycline, 13. Concurrent malignancy other than melanoma and/or history of malignancy other than
melanoma within 3 years of date of first planned dose of REGN2810, except for tumors
with negligible risk of metastasis or death, such as adequately treated basal cell
carcinoma (BCC) of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ
of the breast, or history of prostate adenocarcinoma treated with curative intent at least
3 years prior and with undetectable PSA for at least 3 years prior to enrollment. Patients
with hematologic malignancies (e.g., chronic lymphocytic leukemia, CLL) are excluded., 14. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make
the patient ineligible for participation., 15. Patients with a history of solid organ transplant., 16. Any medical co-morbidity, clinical laboratory finding, or concomitant medication that, in the opinion of the investigator, renders the patient an unsuitable candidate for tumor biopsies due to high safety risks., 17. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study., 18. Inability to undergo any response assessment by contrast-enhanced radiologic imaging., 19. Pregnant or breastfeeding women, 20. Sexually active men or women of childbearing potential who are unwilling to practice
highly effective contraception prior to the initial dose, during the study, and for at least 6
months after the last dose. , 21. Prior treatment with idelalisib, 22. Radiation therapy within 2 weeks prior to enrollment and not recovered to baseline from
any AE due to radiation., See protocol section 6.2.2. for more detailed information

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):	07-03-2018
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cemiplimab
Generic name:	SUB179369

Ethics review

Approved WMO Date:	21-11-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-05-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	30-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	30-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-002755-16-NL
CCMO	NL59275.091.16