Non-Comparative, Open-Label, Multiple Cohort Phase 1/2 Study of Nivolumab and Nivolumab plus Ipilimumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors

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

Summary

ID

NL-OMON47503

Source
ToetsingOnline

Brief title
CA209 358

Condition

- Other condition

Synonym
virus positive and virus negative solid tumors

Health condition

neoplasms squamous cell carcinoma head and neck, merkel cell carcioma, nasopharygeal carcinoma, carcinoma of cervix vigina or vulva, gastric carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: metastatic, neoadjuvant, Nivolumab, virus positive

Outcome measures

Primary outcome

In the neoadjuvant cohort, to investigate the safety and tolerability of

neoadjuvant nivolumab administration in the following tumor types:

HPV-positive SCCHN

HPV-negative SCCHN

Merkel Cell Carcinoma

Cervical, vaginal, or vulvar cancers

In the metastatic/recurrent cohort, to evaluate the investigator-assessed

objective response rate (ORR) with monotherapy or combination therapy in

subjects with the following diseases:

Metastatic or recurrent nasopharyngeal carcinoma (NPC)

Metastatic or Recurrent EBV related gastric

Metastatic or Recurrent Merkel Cell Carcinoma

Metastatic or Recurrent Cervical, vaginal, or vulvar cancers

Metastatic or Recurrent HPV positive Squamous Cell cancer of the Head and Neck

(SCCHN)

Secondary outcome

Neoadjuvant cohort: To determine the percent change from baseline of immune cells and the percent change from baseline of select immune activation/inhibitory molecules of viral specific T cells in tumor specific subsets of nivolumab treated subjects.

Metastatic cohort: To evaluate the duration of response, progression-free survival and overall survival in subjects with monotherapy or combination therapy.

Study description

Background summary

CA209-358 is a multicentre, phase 1/2 study involving an investigational drug called Nivolumab given alone in patients with neoadjuvant Squamous Cell Carcinoma of Head and Neck (SCCHN), or neoadjuvant Cervical, Vaginal, Vulvar carcinoma (GYN) or Merkel cell carcinoma (MCC); or patients with viral positive metastatic SCCHN, gastric cancer (GC), GYN, MCC or Nasopharyngeal carcinoma (NPC).
For patients with metastatic disease treatment options are limited. For gastric carcinoma there is a poor survival prognosis for Stage II-III tumors and advanced and metastatic gastric cancer with current treatment options.
For nasopharyngeal carcinoma there is poor overall survival and no established standard of care for patients who progress after first line of chemotherapy in the recurrent or metastatic setting.
For SCC head and neck there is no effective standard of care that provides survival benefits beyond 4 - 6 months in second line platinum refractory recurrent or metastatic SCCHN.
For the GYN carcinomas after first line chemotherapy, there is no standard of care that has demonstrated improved benefit over best supportive care.
For metastatic MCC the disease is incurable with chemotherapy with very poor overall survival (<10%).

Therefore, for all these cancers there is classed to be an unmet medical need.

It has been established that virus associated tumors express PD-1 ligands. The hypothesis of this study is that these tumor types may be more likely to respond to nivolumab which blocks the interaction of PDL-1/PD-L2 and PD-1, in two settings, a neoadjuvant or window of opportunity cohort in patients with resectable disease and a cohort of patients with metastatic disease who have progressed after one line of therapy or refused standard of care.

Nivolumab and ipilimumab has been shown to have survival benefit in patients across a number of tumor types.

Approximately 84 neoadjuvant and 400 metastatic patients will take part globally.

Study objective

In patients with neoadjuvant disease the purpose of the study is to define the safety and tolerability of the drug. In patients with metastatic disease the purpose is to determine if treatment with Nivolumab or Nivolumab and ipilimumab will lead to clinical benefit in patients in those tumour types.

Study design

This is an Non-Comparative, Open-Label, Multiple Cohort Phase 1/2 Study of Nivolumab and Nivolumab plus Ipilimumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors
The first cohort, a neoadjuvant treatment regimen of 84 subjects in 3 tumor types, has the following major goal:
Investigate the safety and tolerability of neoadjuvant nivolumab administration, which is the primary objective of this cohort;

Enrollment for each tumor type in the neoadjuvant cohort will pause after the first 10 subjects are enrolled to assess safety and determine the number of subjects with chemotherapy/radiation (GYN patients where appropriate) or surgical (SCCHN, MCC, and GYN patients) delays beyond 4 weeks from the planned date. If * 3 of the first 10 subjects for a single tumor type have delays beyond 4 weeks from the planned surgery date or planned start date for chemoradiation due to a nivolumab immune-related adverse event(s) specified in the label, that specific tumor cohort will close. The remaining tumor types in the neoadjuvant cohort will not close enrollment should a tumor type(s) close due to a delay in surgery due to nivolumab. If the first 8 patients for a single tumor type experience no delay, a pause in enrollment will not be required.
The Neoadjuvant Cohort will enroll 3 tumor types: HPV positive and negative SCCHN, HPV-positive cervical/vaginal/vulvar cancers, and

polyomavirus-associated Merkel Cell carcinoma. The SCCHN tumor types will require virus testing prior to study drug assignment. Twenty-one virus positive and 21 virus negative SCCHN subjects will be enrolled. The other tumor types will not require prospective virus testing for entry, given the high (> 85%) infection rate. The virus negative group will serve as a control group for the biological analysis. Subjects will have an initial biopsy, receive 2 doses of nivolumab, followed by a surgical resection or chemotherapy/radiation. No other pre-surgical therapy is allowed.

The second cohort, a treatment regimen of 400 subjects in the recurrent/metastatic setting in 5 tumor types, has the following major goal: Evaluate the investigator-assessed objective response rate (ORR) of nivolumab monotherapy or nivolumab/ipilimumab combination, which is the primary objective of this cohort

The Metastatic Cohort will enroll subjects in the metastatic or recurrent setting with their disease. This cohort will be comprised of the 5 following tumor types: EBV-related Gastric, EBV-related nasopharyngeal, HPV-positive SCCHN, HPV-positive cervical/vulvar/vaginal, and polyomavirus-associated Merkel Cell carcinoma. The SCCHN and gastric tumor types will require virus testing to ensure positivity prior to treatment. Nivolumab will be administered until unacceptable toxicity or disease progression as defined by RECIST 1.1.

Intervention

The investigational product is: nivolumab (BMS-936558) and ipilimumab (BMS-734016).

Neoadjuvant Cohort subjects will receive two doses of nivolumab administered at 240 mg IV on Day 1 and on Day 15.

Metastatic Cohort subjects will receive treatment depending on study arm (see protocol).

Subjects who complete the neoadjuvant portion of the study and complete standard of care treatment who develop unresectable recurrent or metastatic disease within 1 year of surgical resection or completion of standard of care (whichever is later) may receive treatment with nivolumab on Day 1 of a treatment cycle every 2 weeks (14 days), if eligible.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements including oxygen saturation levels, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for

adverse events. For patients in the neoadjuvant cohort they will be required to provide a biopsy after nivolumab dosing though this may form part of their surgical resection. For patients in the metastatic cohort, every 8 weeks (from week 9 onwards) patients will undergo radiographic assessment of their tumour(s) (by Spiral CT or MRI) through the first year, then every 12 weeks until disease progression or treatment discontinuation whichever occurs later. An additional PET scan would be required to confirm complete response.

Blood samples will be collected at certain visits for research purposes (PK and immunogenicity) including Biomarker samples. The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard over care. These procedures are carried out by trained medical professionals and every effort will be made to minimize any risks or discomfort to the patient. Treatment for cancer often have side effects, including some that are life-threatening. Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.

The clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC)
assessed objective response rate (ORR) will be utilized.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Histopathologic confirmation of the following tumor types (please refer to protocol for full details pertaining to eligible tumor types):, • Merkel Cell Carcinoma, • Gastric or Gastro-Esophageal junction carcinoma, • Nasopharyngeal Carcinoma, • Squamous cell carcinoma of the cervix, vagina, or vulva, • Squamous cell carcinoma of the Head and Neck, -Measurable disease by CT or MRI, -Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, -Subject willing to comply to provide tumor tissue (archival or fresh biopsy specimen), -Men and women of age 18 or older.

Exclusion criteria

-Active brain metastases or leptomeningeal metastases, -Subjects with active, known or suspected autoimmune disease, -Subjects with a condition requiring systemic treatment with either corticosteroids, -Subjects with hepatitis;Subjects with HIV, -Pregnant or breastfeeding women

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-936558
Generic name:	Nivolumab
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-07-2015
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	29-09-2015
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	13-11-2015
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	01-03-2016
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	12-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	11-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	24-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	22-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-000230-29-NL
CCMO	NL53828.031.15

Study results

Results posted: 18-10-2023

First publication
01-01-1900