Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies

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Ethical review	Approved WMO
Status	Completed
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON48940

Source
ToetsingOnline

Brief title
CA209-908 Pediatric Primary CNS

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Brain Cancer, CNS Malignancies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CNS, Ipilimumab, Nivolumab, Pediatric

Outcome measures

Primary outcome

For safety lead in: To estimate the safety and tolerability of study treatments (firstly nivolumab alone, and then nivolumab in combination with ipilimumab) in pediatric participants with primary high- grade CNS tumors.

For expansion: To investigate efficacy of the study treatments (as assessed by Overall Survival and Progressive Free survival), individually in each of pediatric cohorts, as follows:

Cohort 1: OS in newly diagnosed DIPG

Cohort 2: PFS in recurrent or progressive HGG

Cohort 3: PFS in Progressive medulloblastoma

Cohort 4: PFS in Recurrent or progressive ependymoma

Cohort 5: PFS in Recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, embryonic CNS tumors)

Secondary outcome

To describe any observed anti-tumor activity of study treatment in pediatric primary high grade CNS tumors.

To estimate the safety of study therapy in all cohorts by incidence of

laboratory abnormalities, AEs, SAEs, drug-related AEs, AEs leading to

discontinuation, and death.

To further characterise the efficacy of the study treatment in each cohort by

rates of progression free survival at 6 months and overall survival at 12

months.

Study description

Background summary

CA209-908 is a multicentre, phase 1b/2 study involving investigational drugs called nivolumab and ipilimumab, in children and young adults (aged from at least 6 months to 22 years old) with certain types of brain cancer.

The patients will be included in one of five groups (or cohorts), depending on their tumour type. The five cohorts include patients with:
Diffuse intrinsic pontine glioma (DIPG) that was never treated before (Cohort 1)
Recurrent or progressive supratentorial high-grade gliomas (HGG) previously treated by surgical resection and radiotherapy (with or without chemotherapy) (Cohort 2)
Medulloblastoma that is recurrent or progressive after prior therapy (Cohort 3)
Ependymoma that is recurrent or progressive after prior therapy (Cohort 4)
Other recurrent or progressive tumour types after prior therapy (Cohort 5)

Collectively, the above primary CNS tumours comprise the most common malignancy in children of 0 - 19 years of age.

Some types of CNS tumours, such as medulloblastoma, ependymoma, and germ cell tumors, are associated with a reasonably good prognosis at diagnosis, however existing standard of care treatments can cause delayed complications including neurocognitive impairment, hearing loss, endocrine abnormalities, cerebrovascular disease and secondary malignancies with profound effects on the quality of life in survivors. Other tumour types (such as diffuse intrinsic pontine glioma (DIPG) and high-grade astrocytoma) do not have any curative treatment options. The median life expectancy of children diagnosed with a DIPG is less than one year and pediatric patients with high-grade astrocytoma also suffer from an extremely poor prognosis.

Cancer immunotherapy is based on the knowledge that tumours can be recognized as foreign rather than as self and can be effectively attacked by an activated

immune system. Nivolumab and ipilimumab are types of immunotherapy drugs called monoclonal antibodies that work by blocking inhibitory signalling pathways in the immune response. This results in stimulation of the body*s own immune system to help attack the cancer cells.
Nivolumab has demonstrated clinical activity and been approved for the treatment of several tumour types, including melanoma, advanced renal cell cancer and advanced NSCLC. Ipilimumab is approved for the treatment of melanoma (alone or in combination with nivolumab).

Study objective

Firstly, the objective of the study is to estimate the safety and tolerability of study treatments (firstly nivolumab alone, and then nivolumab in combination with ipilimumab) in pediatric participants with primary high-grade CNS tumors. Secondly, the study will investigate the efficacy of the study treatments (as assessed by Overall Survival and Progressive Free survival), individually in each of pediatric cohorts (1-5).

Study design

This is an open-label, sequential arm Phase 1b/2 study that is designed to evaluate safety and efficacy of nivolumab monotherapy, as well as nivolumab combined with ipilimumab in common pediatric high grade brain tumours. Because it is likely that the different tumour subtypes (different molecular genetics & natural disease history, survival benefit) will have a different response to study therapy, patients will be enrolled to histologically-defined Cohorts (1-5).

Subjects will undergo screening tests and assessments to determine eligibility including a review of medical history, physical examination, blood and CSF collections, MRI imaging, and submission of a tumour sample for central testing (except patients with DIPG). Those eligible for the study will be assigned to a treatment Module (dependent on the time at which they enter the study).

Patients will attend the hospital for their treatment, and various assessments will be performed during these visits. These include a physical exam, vitals (weight, blood pressure, heart rate, and temperature), performance status and a review of medications and any side effects, blood collections and tumour assessment by MRI.
Patients will be reimbursed for reasonable travel expenses incurred for attending study visits.

After stopping study treatment, patients will be asked to return to the clinic after 1 month and then again after another 2 months. Patients will be asked the same questions regarding their medical condition, side effects, medications etc. Also, the procedures/samples performed and/or collected while they were

taking study treatment may be repeated at one or more of the visits.

Follow-up for Survival (after follow-up visit 2) will commence 12 weeks after the second follow-up visit. These visits will occur approximately every 3 months and can take place by telephone. The patient will be asked the same questions regarding their medical condition as described previously. MRI scanning will continue every 8 weeks for patients that do not have confirmed progression. Additional blood, CSF or tissue samples may be taken upon confirmed disease progression (optional).

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations.

Intervention

Treatments are defined by Module:
Module A: nivolumab 3 mg/kg every 2 weeks, as monotherapy, and
Module B: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

Enrolment to Module A will open in parallel for all cohorts, with the first 6 treated patients in Cohort 1 and 10 patients in Cohorts 2-5 (combined) to be evaluated for safety. Based on determination of adequate safety, enrolment will re-open for evaluation of efficacy to complete the planned number of participants for each cohort in Module A expansion. Enrolment will begin in Module B, by cohort, based on completion of planned accrual in Module A or a decision of the study steering committee. Accrual will not open in parallel for Module B.

For Module B, the first 10 participants treated and DLT-evaluable in all cohorts combined will be evaluated for safety by the study before additional participants are enrolled, after which cohorts will be re-opened for full accrual in the expansion.

A total of 160 patients will be treated (80 per treatment Module). Patients will continue treatment until confirmed progression, unacceptable toxicity, or withdrawal of consent.

Study burden and risks

The study is intensive in terms of patient visits. Patients need to present to the clinic for each treatment, which will be administered by intravenous (IV) infusion. The treatment schedule is detailed in Section 2 of the protocol and in the Patient Information sheet.

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential), regular imaging by MRI and monitoring for adverse events. Blood will be collected at certain visits for research purposes (PK and biomarker studies). If there is no archive tumour tissue available, patients will be required to have a biopsy in order to participate. Some patients (Cohorts 3,4,5) will need to have a CSF collection by lumbar puncture (unless clinically contraindicated) during screening.

New Immune system targeted therapy (immunotherapies) such as Nivolumab and Ipilimumab could potentially provide clinical benefit and improvements in the outcome for pediatric patients with high grade CNS malignancies. However, with all experimental drugs and clinical trials, there are known and unknown risks. Risks of taking the study medication and study procedures are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study. Because nivolumab, as monotherapy or immediately after RT or in combination with ipilimumab has not been studied in paediatric participants with CNS tumors previously, a safety lead-in will be implemented. The Study Steering Committee will review safety information in order to determine closure and re-opening of enrolment by Cohort.

To assure an ongoing favourable risk/benefit assessment for participants enrolled onto CA209908, high grade treatment-related AEs will be closely monitored throughout the conduct of the trial. The medical monitor will be responsible for reviewing, on a systematic and continuous basis, the safety of participants on this study. This includes a review of serious and non-serious AEs.
The numbers assigned to most cohorts and module are based on statistical calculations and are the smallest number of subjects required to evaluate safety and enable a clinically meaningful comparison to historical controls.

Contacts

Public
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Scientific
Bristol-Myers Squibb

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Prior to study participation, written informed consent from participants, or in the case of minors, written permission (informed consent) from parents or legally acceptable representatives.
• Males and Females, ages >= 6 months to < 22 years old
• Participants must have received standard of care therapy, and there must be no potentially-curative treatment available, in one of the following cohorts:
1. newly diagnosed (by MRI or histology) DIPG that has been treated with radiation therapy (RT) (Cohort 1)
2. histologically confirmed recurrent or progressive non-brainstem HGG previously treated with surgical resection and RT (with or without chemotherapy) (Cohort 2)
3. histologically confirmed medulloblastoma that has relapsed or is resistant to at least one line of prior therapy including surgery, RT, and chemotherapy (regardless of age) (Cohort 3)
4. histologically confirmed ependymoma that has relapsed or is resistant to at least one line of prior therapy including surgical resection and RT (regardless of age) (Cohort 4)
5. histologically-confirmed other high grade CNS malignancy which is recurrent or progressive after at least one line of prior therapy (Cohort 5)
• If first recurrence of the CNS tumor is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either histopathologic confirmation of recurrent tumor, or new enhancement on MRI outside of the radiotherapy treatment field (Cohorts 2-5).

• A tumor sample must be available (from resection at time of recurrence, or otherwise archive sample from previous resection) for submission to central laboratory. This is not required for DIPG (Cohort 1).
• Substantial recovery (ie, no ongoing safety issues) from surgical resection prior to first dose of study therapy.
• Adequate wash-out interval since last administration of other treatment for CNS malignancies
• Able to taper (preferably discontinue) steroids. Participants must be receiving not more than 0.05 mg/kg dexamethasone per day (or equivalent) for intracranial mass effect at study entry.
• Participants who have received high-dose chemotherapy with autologous hematopoietic cell transplantation must be at least 6 months post-hematopoietic cell transplantation and they must have a CD4 count of at least 200.
• Lansky play score (LPS) for =< 16 years of age or Karnofsky performance scale (KPS) for > 16 years of age must be >= 60.
• Women of child-bearing potential must have a negative pregnancy test within 24 hours of starting treatment, and should not be breastfeeding. Women of childbearing potential, or male subjects who are sexually active with women of child-bearing potential must agree to the contraceptive requirements of the study.

Exclusion criteria

• Participants with active, known, or suspected autoimmune disease.
• Participants with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration.
• Participants who cannot undergo magnetic resonance imaging (MRI) with contrast enhancement.
• Specific blood test results indicating impaired haematological, liver or kidney function
• Participants cannot test positive for Hepatitis B/C
• Participants must not have HIV or AIDs
• Unable to taper steroids due to ongoing mass effect
• Participants with low-grade gliomas or tumors of unknown malignant potential
• Evidence of > Grade 1 recent CNS hemorrhage on the baseline MRI scan.
• Participants with bulky tumor on imaging are ineligible; bulky tumor is defined as:
i) Tumor with any evidence of uncal herniation or severe midline shift
ii) Tumor with diameter of > 6 cm in one dimension on contrast-enhanced MRI
iii) Tumor that in the opinion of the investigator, shows significant mass effect.
• Prior treatment with any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
• Prior allogeneic hematopoietic cell transplantation (unless MM approval in advance).
• Participants who are receiving any other anti-cancer or investigational drug therapy or non-palliative radiation therapy.
• Any serious or uncontrolled medical disorder that may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

• Patients cannot be incarcerated or detained for a psychiatric or physical illness
• History of allergy or hypersensitivity to study drug components or to any monoclonal antibody.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-12-2017
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	01-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	07-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2021

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2016-004441-82-NL
ClinicalTrials.gov	NCT03130959
CCMO	NL61450.078.17

Study results

Date completed:	17-01-2021
Results posted:	15-07-2022

First publication
01-01-1900