Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in childeren and adolescent patients with BRAF V600 mutation positive low grade glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)

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This study aims to demonstrate the effectiveness of dabrafenib with trametinib in pediatric patients with BRAF V600 mutant relapsed refractory HGG.This study aims to demonstrate the effectiveness of dabrafenib with trametinib compared to...

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

Summary

ID

NL-OMON50503

Source
ToetsingOnline

Brief title
DRB436G2201

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
braintumor, glioma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BRAF V600, dabrafenib, HGG, LGG, trametinib

Outcome measures

Primary outcome

The primary objective for HGG cohort is: to evaluate the anti-tumor activity of dabrafenib in combination with trametinib as measured by overall response rate (ORR) to the combination therapy by investigator assessment using the RANO criteria.

The primary objective for LGG cohort is: Compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria.

Secondary outcome

For HGG: 1. Evaluate ORR by central independent review

2. Evaluate duration of response (DOR) by investigator and central independent review

3. Evaluate time to response (TTR) by investigator and central independent review

4. Evaluate progression free survival (PFS) by investigator and central

independent review

5. Evaluate overall survival (OS)

6. Evaluate the safety profile of dabrafenib in combination with trametinib in the study population

7. To characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population

For LGG: 1. ORR by central independent review assessment per RANO criteria

2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.

3. PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria

4. TTR, calculated as the time from the start date of study treatment to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria

5. OS, defined as the time from first dose of study treatment to death due to any cause

6. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO.

7. To characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population

For both cohorts LGG and HGG: Plasma concentration-time profiles of dabrafenib,

its metabolites and trametinib and PK parameters

Study description

Background summary

HGG typically arise from cells within the glial lineage and are classified by the World Health Organization (WHO) as either grade III or IV meaning that they are highly aggressive tumors with characteristic pathological findings. HGGs are rare tumors in the pediatric population, and comprise approximately 8-12% of all primary, pediatric central nervous system (CNS) tumors. Approximately 350-400 new cases of pediatric HGG are diagnosed in Europe yearly.
Current therapies for children with HGGs are limited and the long-term outcomes are poor despite aggressive multimodality therapy and improvements in neurosurgery, radiotherapy, and chemotherapy. The majority of patients do develop recurrent disease. The EMA suggested after a pediatric research expert meeting that pediatric patients with relapsed, refractory, and or resistant HGGs should consider experimental treatments available in clinical trials.
The prognostic role of BRAF V600 mutation in pediatric HGG is unclear, but available data suggest that BRAF V600 mutation may be prognostically favourable in pediatric HGG. For this reason, the historical RR in BRAF V600 mutant pediatric relapsed refractory HGG may be higher than that observed in unselected populations, where the RR is less than 12%. The combination of dabrafenib with trametinib in adults with BRAF V600 mutant melanoma, NSCLC and other tumors have resulted in improved efficacy over dabrafenib monotherapy and suggests that greater efficacy may also be seen in the pediatric setting such as patients with relapsed refractory BRAF V600 mutant HGG. Given the high unmet medical need in pediatric HGG, the encouraging efficacy of dabrafenib monotherapy in pediatric patients with BRAF V600 mutant HGG, and the improved efficacy seen in adult cancer studies upon the addition of trametinib to dabrafenib, this study aims to demonstrate the effectiveness of dabrafenib with trametinib in pediatric patients with BRAF V600 mutant relapsed refractory HGG.

Low grade glioma (LGG) also represents a diverse group of histologically distinct tumor types, including pilocytic astrocytoma, ganglioglioma, and astrocytoma and others. They are distinguished from HGG generally by their lower apparent mitotic rates. Although LGGs are also rare pediatric tumor types, they are approximately 2 times as common(incidence 1.68 cases per 100,000) as HGG.
Treatment goals generally are to prolong overall and progression free survival while minimizing morbidity of treatment. Surgical removal, when practical. The extent of resection is predictive of progression free interval. Most patients

will eventually experience progression of their disease and require post-surgical therapy like chemotherapy with carboplatin and vincristine.
The BRAF V600 mutation is identified in about 17% of pediatric LGG tumors. Research revealed that those patients whose tumor harbored the BRAF V600 mutation had worse PFS and OS than those with tumors with wild type sequence at BRAF V600. This research also revealed a lower ORR for these patients when treated with chemotherapy with apparent 11% PR+CR rate.
Pediatric patients with LGG harboring a BRAF V600 mutation have a poorer prognosis than those without this mutation, and require improved treatment options

Study objective

This study aims to demonstrate the effectiveness of dabrafenib with trametinib in pediatric patients with BRAF V600 mutant relapsed refractory HGG.
This study aims to demonstrate the effectiveness of dabrafenib with trametinib compared to chemotherapy (vincristin and carboplatine) in pediatric patients with BRAF V600 mutant LGG.

Study design

This is a multi-center, global, single arm, open-label, phase II study evaluating the effect of dabrafenib in combination with trametinib in children and adolescent patients with LGG BRAF V600 positive mutation and BRAF V600 mutation positive relapsed, refractory, high grade gliomas (HGG). Approximately 142 patients will be enrolled into the study, of which 40 patients with HGG and 102 patients with LGG. All patients with HGG and two third of the patient with LGG will receive oral dabrafenib twice daily and trametinib once daily based on weight, age and appropriate dose level. One third of the patients with LGG will receive chemotherapy.
Patients may continue study treatment until disease progression or loss of clinical benefit as determined by the investigator, occurrence of unacceptable toxicity, withdrawal of consent or lost to follow-up, or sponsor termination of the study. Patients with LGG who have progressed after receiving chemotherapy do have the possiblity to start with treatment of dabrafenib and trametinib.
All patients will be followed for survival for at least 2 years after the last study treatment (except if consent is withdrawn, patient death, lost to follow-up or study is discontinued). An interim analysis for futility will be implemented to allow possible termination of recruitment and the study in the event that there is insufficient efficacy.

Intervention

Childeren with HGG will be treated with dabrafenib (capsules or oral solution), twice daily and trametinib (tablets or oral solution), once daily based onbased

on weight, age and appropirate dose level.
Two third of the childeren with LGG will be treated with dabrafenib (capsules or oral solution), twice daily and trametinib (tablets or oral solution), once daily based onbased on weight, age and appropirate dose level.
One third of the childeren with LGG wil be treated with chemotherapy (vincristin and carboplatine). If they progress they can cross-over to treatment with dabrafenib and trametinib.

Study burden and risks

The risks of dabrafenib and trametinib.
The risks and discomforts of the research assessments (scans, x ray, blood drawn, biopsy, opthalmic examinations, ECG and ECHO, physical exam, use of anticonception)
Keep a diary and the amount of visits to the hospital.

Contacts

Public
Novartis

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Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Male or female >= 1 and <18 years of age.
- HGG cohort only: Relapsed, progressed, or failed to respond to frontline therapy.
- LGG cohort: progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment
- Histologically confirmed diagnosis of High Grade Glioma (Grade III or IV glioma as defined by WHO histological classification system, revised 2016), including anaplastic pleomorphic xanthoastrocytoma (aPXA) and anaplastic ganglioglioma.
- LGG defined by WHO histological classification system
- BRAF V600 mutation-positive tumor
- confirmed measurable disease.
- Tumor tissue (archival or newly obtained) must be provided for testing HGG histopathology and HGG and LGG BRAF mutational status.
- Karnofsky/Lansky performance score of >=50%.
- Adequate bone marrow function in the absence of growth factor support.
- Adequate renal function, liver function, and cardiac function.
- If receiving glucocorticoids, patient must be on a stable or weaning dose for at least 7 days prior to first dose of study treatment.

Exclusion criteria

- Malignancy OTHER than BRAF V600 mutant HGG and LGG.
- Previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor.
- HGG: Cancer therapy or investigational drugs within 3 weeks preceding the first dose of study treatment.
- LGG: Any systemic anticancer therapy or investigational drugs prior to enrollment.
- HGG: Radiotherapy to CNS glioma lesions within 3 months prior to first dose of study treatment, unless there is clear evidence of radiologic progression outside of the field of radiation.
- LGG: Radiotherapy to CNS glioma lesions at any point prior to enrollment.
- History of malignancy with confirmed activating RAS mutation or with BRAF fusion such as BRF-KIAA1549.
- Current use of a prohibited medication or herbal preparation or requires any of these medications during the study. See Section 6.4 for details of the protocol.
- Unresolved toxicity greater than NCI CTCAE v 4.03 grade 2 from previous

anti-cancer therapy,
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib, trametinib and their excipients. LGG also history
of allergic reactions or contraindications to the use of carboplatin or vincristine.
- Autologous or allogeneic stem cell transplant within 3 months prior to the first dose of study treatment
- History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study
- Uncontrolled medical conditions, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol.
- Presence of active GI disease or other condition that will interfere significantly with the absorption of drugs.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-04-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Mekinist
Generic name:	trametinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	dabrafenib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vincristine Sulfate
Generic name:	Vincristine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2023
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	EUCTR2015□004015□20-NL
CCMO	NL62996.078.17