HDAC inhibitor vorinostat in resistant BRAF V600 mutated advanced melanoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47107

Source
ToetsingOnline

Brief title
Vorinostat in advanced BRAF V600 melanoma

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W,ERC grant en in aanvraag Oncode

Intervention

Keyword: BRAF resistance, BRAF V600 melanoma, Vorinostat

Outcome measures

Primary outcome

The primairy aim of this proof of principle (POP) and pharmacological study is to demonstrate significant anti-tumor activity of short term treatment with vorinostat in advanced BRAF V600 melanoma progressing under treatment with BRAFi or combined BRAFi and MEKi with a response rate of at least 30%.

Secondary outcome

-To demonstrate that emerging resistant clones with a secondary mutation in the MAPK pathway can be detected by ctDNA analysis and purged by short term treatment with vorinostat

-To characterize the safety and tolerability of intermittent treatment of vorinostat before and after treatment with BRAFi/MEKi in this population, assessed by the incidence and severity of adverse events

-To determine progression free survival and overall survival of intermittent treatment with vorinostat and BRAFi/MEKi

-To determine the pharmacokinetic profile of vorinostat, as measured by plasma concentrations of vorinostat and relevant metabolites

-To explore pharmacodynamics of vorinostat,especially levels of phosphorylation of selected MAPK-proteins, such as MEK and ERK

-To explore the genetic determinants of resistance and response to vorinostat.

Study description

Background summary

Activating mutations in the BRAF gene are present in about 50% of human melanomas. BRAF inhibitors (BRAFi) inhibit the serine-threonine protein kinase BRAF, which plays a dominant role in the MAPK pathway influencing cell growth. MEK inhibitors (MEKi) inhibit MEK1 and MEK2, two regulatory proteins downstream of BRAF. The clinical benefit of this treatment is limited due to development of drug resistance in 6-8 months for treatment with BRAFi and 9-14 months for treatment with BRAFi in combination with MEKi.(1, 2) This is often associated with secondary mutations in the MAPK pathway leading to re-activation of the pathway.(3, 4) Withholding from treatment with BRAFi and/or MEKi leads to a reversible hyperactivation of the MAPK pathway, causing a transient growth arrest. Chronic proliferation and growth arrest occur when there is a persistent hyperactivation of the MAPK pathway. Treatment of BRAFi and/or MEKi resistant melanoma with vorinostat, a histone deacetylase inhibitor (HDACi), leads to persistent hyperactivation of the pathway and a state of growth arrest with hallmarks of oncogene induced senescence.(4) In these studies in mice with BRAFi resistant BRAF V600 mutated melanoma switch from a BRAFi to the HDACi vorinostat resulted in complete disappearance of the tumor after two months of treatment.(4)The first treated patients in this proof of concept study revealed mixed responses at the first tumor evaluation. Importantly however, tumor biopsies showed newly developed secondary MAPK pathway mutations at baseline and a complete absence of these resistance mutations after 2 weeks of vorinostat treatment. Based on these clinical results we postulate that BRAFi-resistant BRAF V600 mutant melanoma cells can be eliminated by a short treatment with the HDAC inhibitor (HDACi) vorinostat due to killing of tumor cells harboring a secondary mutation in the MAPK-pathway. This mechanism is confirmed in cell line experiments.

Vorinostat is approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have progressive, persistent or recurrent disease on or following two systemic therapies. It is a HDACi with specific action on the enzymatic activity of HDACs 1,2,3 and 6 by interacting with the catalytic site of these HDACs. Vorinostat causes the accumulation of acetylated histones and this leads to apoptosis and cell cycle arrest, in vitro. However, the mechanism of antineoplastic effect of vorinostat has not yet been fully characterized.
The registered posology is 400 mg vorinostat oral once daily (QD), continuously to be taken as 4 capsules of 100 mg each. The newly developed capsules used in this study contain 90 mg vorinostat per capsule. The daily dose will be 360 mg, slightly lower than registered for treatment of CTCL for safety reasons.

Study objective

The primary aim of this proof of principle (POP) and pharmacological study is to demonstrate significant anti-tumor activity of vorinostat in advanced resistant BRAF V600 melanoma and secondary aims are to explore the safety, pharmacokinetics and pharmacodynamics of vorinostat.

Study design

This is a phase I, single-center, single-arm, non-randomized, open-label, clinical pharmacological proof of principal study to determine the safety of vorinostat as anti-tumor therapy in patients with advanced resistant BRAF V600 mutated melanoma. A total of 20 evaluable patients with BRAF V600 mutated melanoma who developed resistance to BRAFi and/or BRAFi+MEKi after at least 4 weeks of PR or CR response will be enrolled in this study. Vorinostat will be given at a single daily dose of 360 mg derived from the established and registered dose for treatment of cutaneous T-cell lymphoma. Treatment will be continuous and doses will be reduced in steps of 90 mg per dose-reduction in case of unacceptable safety concerns.

Intervention

Continuously treatment with a single daily dose of 360 mg vorinostat

Study burden and risks

- Blood will be drawn for pharmacokinetic, pharmacodynamic and pharmacogenetic research
- Tumor biopsies will be taken pre-, upon and at end of treatment for histological analyses of biomarkers, genetics and immune infiltration
- Patients will be asked to keep a diary and note daily what they ate voor breakfast

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. Histological proof of advanced melanoma with BRAF V600 mutation;
2. Progression of disease, according to RECIST 1.1 or clinical progression, while on treatment with BRAFi, such as vemurafenib or dabrafenib, or the combination of BRAFi and MEKi such as vemurafenib plus cobimetinib or dabrafenib plus trametinib;
3. At least one progressive target lesion according to RECIST 1.1;
4. Previous documented response of at least 4 weeks to treatment with the BRAFi and/or BRAFi+MEKi;
5. Start with vorinostat treatment within a maximuminimum period of 3 days after discontinuation of BRAFi and/or BRAFi+MEKi. The BRAFi and/or BRAFi+MEKi can be continued after progression to provide sufficient time to perform baseline assessments;
6. Age * 18 years;
7. Able and willing to give written informed consent;
8. WHO performance status of 0, 1 or 2;
9. Able and willing to undergo blood sampling for PK and PD analysis;
10. Life expectancy * 3 months allowing adequate follow up of toxicity evaluation and antitumor activity;
11. Evaluable Measurable disease according to RECIST 1.1;
12. Minimal acceptable safety laboratory values
a. ANC of * 1.5 x 109 /L
b. Platelet count of * 100 x 109 /L
c. Hemoglobin * 6.0 mmol/L
d. Hepatic function as defined by serum bilirubin * 1.5 x ULN, ALAT and ASAT * 2.5 x ULN, or in case of liver metastases ALAT and ASAT * 5 x ULN
e. Renal function as defined by serum creatinine * 1.5 x ULN or creatinine clearance * 50

ml/min (by Cockcroft-Gault formula, or MDRD)
13. Negative pregnancy test (urine/serum) within 72 hours before receiving the first dose of study medication for female patients with childbearing potential;
14. Able and willing to undergo fresh histological tumor sampling of progressive target lesion prior to start, upon treatment and upon progression of vorinostat if technically possible.

Exclusion criteria

1. Any treatment with investigational drugs within 28 days prior to receiving the first dose of investigational treatment; or 21 days for standard chemotherapy and immunotherapy;
2. Patients who have had previous treatment with vorinostat or other HDACi;
3. Leptomeningeal disease;
4. Symptomatic brain metastasis. Patients previously treated or untreated for the conditions who are asymptomatic in the absence of corticosteroid therapy are allowed to enroll. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening demonstrating no current evidence of progressive brain metastases). Patients are not permitted to receive enzyme inducing anti-epileptic drugs or corticosteroids;
5. Woman who are pregnant or breast feeding;
6. Unreliable contraceptive methods. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms)
7. Radiotherapy within the last 4 weeks prior to receiving the first dose of investigational treatment; except 1x8 Gy for pain palliation;
8. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients
9. Patients with a known history of hepatitis B or C;
10. Recent myocardial infarction (< 6 months) or unstable angina

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-07-2016
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	.
Generic name:	vorinostat

Ethics review

Approved WMO Date:	13-04-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-05-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2020
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	EUCTR2015-005840-33-NL
CCMO	NL56358.031.16

Study results

Date completed:	08-11-2023
Actual enrolment:	33