Open Label Phase 2 Study Neo-Adjuvant BRAF/MEK Inhibition Followed by Surgery and Adjuvant BRAF/MEK Inhibition in In-transit Melanoma Metastases (NASAM)

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Encorafenib/binimetinb combination therapy can possibly reduce tumor size and thus making surgical treatment less comprehensive. In addition, the treatment can potentially improve recurrence-free survival, overall survival, and distant metastases-...

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

Summary

ID

NL-OMON52356

Source
ToetsingOnline

Brief title
NASAM

Condition

- Skin neoplasms malignant and unspecified

Synonym
in transit metastases melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Pierre-Fabre stelt encorafenib/binimetinib voor 28 ptn in de studie beschikbaar en vergoedt het extra doen van een MUGA-scan

Intervention

Keyword: (Neo)-Adjuvant, BRAF/MEK Inhibition, In-transit Melanoma Metastases, Surgery

Outcome measures

Primary outcome

Primary study endpoint is to determine efficacy of neo-adjuvant BRAF/MEK inhibition with encorafenib/binimetinib in patients with histologically confirmed in-transit melanoma metastases, measured as partial-, complete- or no response. In the biopsy at week 0 the viability will be judged and will be graded according to the amount of tumor necrosis: >50% tumor necrosis with <50% viable tumor cells, <50% necrosis with >50% viable tumor cells and 100% necrosis without viable tumor cells. Partial response is defined as a decrease of at least 50% of the viable tumor cells, compared to the baseline measurement, week 0, and complete response as 100% decrease of tumor cells, whereas no response is defined as more than 50% of viable tumor cells present.

Secondary outcome

Secondary endpoints/parameters are: toxicity according to CTCAE v 5.0, recurrence free survival (RFS); defined as the time from inclusion into the study to recurrence of disease (local and/or distant), distant metastasis free survival (DMS) defined as the moment from inclusion into the study to recurrence event (distant) and overall survival (OS); defined as moment of

inclusion into the study up to the last moment alive.

Study description

Background summary

In-transit metastases of cutaneous melanoma is a unique form of locoregional disease occurrence in the dermal and subdermal tissue[1]. The clinical presentation of in-transit metastases can vary largely, with involvement of 1 to 100 subcutaneous metastatic nodules, and nodules too can differ significantly in size, ranging from 1mm to 5cm[2]. In-transit melanoma metastases occurring without lymph node and or distant metastases involvement is classified as stage IIIB or IIIC, depending on primary tumor characteristics, according to the American Joint Committee on Cancer (AJCC) 8th Edition[3]. Interestingly, patients diagnosed solely with in-transit melanoma metastases, so called N1c positive patients, have similar overall survival rates as compared to stage IIIA melanoma patients, however with a lower quality of life due to a relatively high tumor burden, which poses the significant impact this disease can have[4].
Primary therapy for in-transit melanoma is complete resection of the tumor. However, patients who have undergone complete resection of in-transit metastases have a high rate of locoregional disease recurrence, which justifies the need for additional adjuvant therapy[1, 5, 6]. Even though adjuvant therapy is warranted, no consensus exists on adjuvant therapy for these patients, as only a small subgroup of pN1c patients were included in adjuvant trials investigating the efficacy of nivolumab and dabrafenib/trametinib[7, 8]. Currently, FDA approved adjuvant approaches for resected in-transit metastases include anti-programmed death 1 agent nivolumab and adjuvant BRAF/MEK inhibition with dabrafenib/trametinib, a therapy eligible for patients harboring the oncogenic BRAFV600E/K mutation[9].

Since the disease can be widespread, complete surgical excision of the tumor can become challenging and form a heavy burden for the patient. Neo-adjuvant therapy can be of aid in in reducing tumor size and thus making surgical intervention less comprehensive[10]. Recently conducted studies investigating the combination therapy of nivolumab and ipilimumab, an anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody, in neo-adjuvant setting for in-transit melanoma have achieved radiological and pathological disease responses, despite limitations in sample size[11, 12]. As for targeted therapy, neo-adjuvant BRAF/MEK inhibition with dabrafenib/trametinib, has shown to decrease tumor size and induce pathological responses in patients with resectable stage III melanoma, however conducted studies included few in-transit metastases patients[13, 14]. An equivalent therapy to dabrafenib/trametinib is the combination therapy encorafenib/binimetinib with a

more favorable toxicity profile, which is FDA and EMA approved as systemic therapy for advanced melanoma[15]. Despite this, encorafenib/binimetinib has not been studied in the (neo)adjuvant setting yet.
Since dabrafenib/trametinib and encorafenib/binimetinib have a similar working mechanism but with a more favorable toxicity profile for encorafenib/binimetinib, we propose the following trial: Neo-Adjuvant encorafenib/binimetinib in patients with in-transit melanoma metastases, followed by Surgical excision and subsequently Adjuvant encorafenib/binimetinib (NASAM).

Furthermore, a pooled data analysis from the Neoadjuvant Melanoma Consortium Group observed a (near) complete pathological response in 33% in neo-adjuvant immunotherapy treated patients and 47% in patients who received neoadjuvant BRAF/MEK inhibition. The one-year recurrence free survival was 96% in the neoadjuvant immunotherapy cohort and 88% in the neoadjuvant BRAF/MEK-treated patients. Interestingly, in patients with a partial response, the two-year recurrence free survival was significantly higher in the neoadjuvant treated immunotherapy group as compared to the neoadjuvant BRAF/MEK cohort with 13% versus 64%, respectively. This underlines the importance of attaining a pathologic (near) complete response in targeted therapy treated patients, whereas partial response to immunotherapy might be sufficient to achieve improved recurrence free survival.
Rresults of the NeoAdjuvant melanoma Consortium has demonstrated that patients who develop a (near) complete pathological response to BRAF/MEK inhibition have an improved recurrence free survival. This underlines the potential of neoadjuvant BRAF/MEK inhibition in patients with locoregional in-transit disease, especially as response to therapy can be fast and might come with less therapy related adverse events. More specifically, trials investigating the efficacy of neo-adjuvant BRAF/MEK inhibition with dabrafenib/trametinib, showed to significantly improve event-free survival versus standard of care in patients with high-risk surgically resectable clinical stage III-IV melanoma[13, 14]. Moreover, the NeoCombi study demonstrated promising results: 35 stage IIIB/IIIC BRAFV600E/V600K mutated of which 7 (20%) stage patients with in-transit metastases only, received neo- adjuvant BRAF/MEK inhibition with dabrafenib/trametinib, followed by surgical resection leading to a pathological response in 30 (86%) patients[14]. In addition, a study conducted by Ameria and colleagues, revealed that 9 (75%) patients with stage III or oligometastatic stage IV melanoma, treated with neo-adjuvant BRAF/MEK inhibition achieved a pathological response[13]. Taken these promising study results together, we hypothesize that neo- adjuvant BRAF/MEK inhibition can contribute to reducing locoregional tumor burden, consequently surgery will become less comprehensive, thus forming a smaller burden for the patient.

Study objective

Encorafenib/binimetinb combination therapy can possibly reduce tumor size and thus making surgical treatment less comprehensive. In addition, the treatment

can potentially improve recurrence-free survival, overall survival, and distant metastases-free survival, implying the benefit the study potentially has.

Study design

Phase 2 open-label single arm intervention study administering encorafenib/binimetinib in neo-adjuvant setting followed by surgery and subsequent adjuvant encorafenib/binimetinib in patients with a (near) complete pathological response to neo-adjuvant encorafenib/binimetinib.
Patient with partial respons or no respons to neo-adjuvant BRAF/MEKi will receive adjuvant anti-PD-1 therapy.

Intervention

Patients diagnosed with in-transit melanoma metastases will receive encorafenib/binimetinib in the neo-adjuvant setting for 8 weeks according to the schedule depicted below. Additionally, patients will undergo extra blood drawings in the context of translational research. Upon completion of neo-adjuvant therapy, patients will undergo surgery. Patients with a (near) complete response will receive adjuvant encorafenib/binimetinib for 44 weeks. Patients with a partial respons or no respons to neo-adjuvant encorafenib/binimetinib, will receive adjuvant anti-PD-1 (nivolumab) for 52 weeks.

Study burden and risks

The combination of encorafenib/binimetinib has been FDA and EMA approved as standard therapy for BRAF V600E/V600K mutated cutaneous melanoma in the advanced setting, based on progression free survival and overall survival results from the randomized phase 3 trial COLUMBUS[15]. In addition, the COLUMBUS trial demonstrated that encorafenib/binimetinib has a favorable side-effect profile as compared to other BRAF/MEK inhibition therapies such as dabrafenib/trametinib and vemurafenib/cobimetinib[16, 17]. Important to outline is, that encorafenib/binimetinib has not been investigated yet in the neo-adjuvant nor in the adjuvant setting for melanoma.
Despite the current lack of information regarding the efficacy of encorafenib/binimetinib in both neo-adjuvant and adjuvant setting, we hypothesize that encorafenib/binimetinib is effective in the neo-adjuvant setting, since this regimen has shown to be effective in treating melanoma in the advanced setting, and encorafenib/binimetinib has a similar working mechanism as FDA and EMA approved adjuvant BRAF/MEK inhibition with dabrafenib/trametinib.

Patients who will enroll in our study, are at risk of receiving an ineffective therapy for the treatment of in-transit metastases, despite available evidence regarding the systematic efficacy of encorafenib/binimetinib in the metastatic

setting. Furthermore, patients will be at risk of developing treatment related adverse events. An additional burden in this trial is extra blood drawings that will be performed at the beginning, during and at the end of treatment. Considered as standard care, the mandated 4-monthly PET-CT and MRI scan at start with hospital visit is a burden for the patient. Patients are mandated to undergo surgery upon completing neo-adjuvant treatment, and surgery can potentially have complications, such as uncontrolled bleeding, infection, thrombosis, nerve damage and shock.
Despite the named burdens of this trial, important is to underline the benefit the trial potentially has for the patients. Encorafenib/binimetinb combination therapy can possibly reduce tumor size and thus making surgical treatment less comprehensive. In addition, the treatment can potentially improve recurrence-free survival, overall survival, and distant metastases-free survival, implying the benefit the study potentially has.

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. Age over 18 years old
2. World Health Organization (WHO) Performance Status 0 or I
3. Primary cutaneous melanoma or unknown primary melanoma with pathologically confirmed in-transit metastatic melanoma
4. Histologically confirmed presence of BRAFV600E/K mutation in primary tumor tissue
5. Patients must have undergone complete disease staging including: PET-CT scan and MRI scan
6. Patients must be medically fit to undergo surgery
7. Patients must be able to take oral medication
8 No prior anticancer systemic treatment (including chemotherapy, immunotherapy, oncolytic viral therapy, other systemic therapies)
9. No prior radiotherapy to site of interest (surgical therapy is allowed; in order to obtain pathological information of the melanoma)
10. Screening laboratory values must meet the following criteria: WBC >= 2.0x109/L, Neutrophils >= 1.0x109/L, Platelets >= 100 x109/L, Hemoglobin >= 6.5 mmol/L, AST <= 2.5 x ULN, ALT <= 2.5 x ULN, Total bilirubin <= 1.5 X ULN, INR and PTT in normal range, LDH < 2xULN. Serum creatinine <= 1.5 × ULN; or calculated creatinine clearance >= 50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m2.
11. Absence of additional severe and/or uncontrolled concurrent disease
12. Patients known to be human immunodeficiency virus (HIV) positive are eligible if they have undetectable HIV viral load and stable and adequate CD4 counts (>= 500 mm^3) on screening labs provided they meet all other protocol criteria for participation and that there are no high-risk drug interactions

Exclusion criteria

1. Presence of regional lymph node metastases
2. Presence of distant metastases
3. Current treatment with antiretroviral drugs, herbal remedies and drugs that are strong inhibitors or inducers of CYP3A and CYP2C8
4. Patients with active bacterial infections with systemic manifestations (malaise, fever, leukocytosis) are not eligible until completion of appropriate therapy
5. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study treatment hazardous or obscure the interpretation of toxicity determination or adverse events
6. History of congestive heart failure, active cardiac conditions, including unstable coronary syndromes (unstable or severe angina, recent myocardial infarction), significant arrhythmias and severe valvular disease must be

evaluated for risks of undergoing general anesthesia. Furthermore, enlarged QTc interval, uncontrolled hypertension, poor left ventricular function (< 50%, as determined by MUGA scan) and recent thromboembolic or cerebral event.
7. History of central serous retinopathy or retinal vein occlusion
8. Active intestinal disease interfering with oral drug absorption
9. Patients who are unable to be temporally removed from chronic anti-coagulation therapy
10. Other malignancy within 2 years prior to entry into the study, except for treated non-melanoma skin cancer and in situ cervical carcinoma
11. Patient must not have active hepatitis B, and/or active hepatitis C infection given concerns for drug interactions or increased toxicities. Testing is not required
12. Patient must not have any known history of acute or chronic pancreatitis
13. Patient must not have any concurrent neuromuscular disorder that is associated with elevated creatine kinase (CK) (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy
14. Pregnancy or nursing

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):	21-03-2022
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	braftovi

Generic name:	encorafenib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	mektovi
Generic name:	binimetinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-08-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-12-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2021-002285-40-NL
CCMO	NL77905.058.21

Study results

Date completed: 01-08-2024

Actual enrolment: 6

Summary results
Trial ended prematurely