Combination of targeted therapy (encorafenib and binimetinib) followed by combination of immunotherapy (ipilimumab and nivolumab) vs immediate combination of immunotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation : an EORTC randomized phase II study (EBIN)

Published: 22-10-2018
Last updated: 25-09-2024

This study has been transitioned to CTIS with ID 2023-505376-30-00 check the CTIS register for the current data. The primary objective is to prospectively assess whether a sequential approach with an induction period of 12 weeks with encorafenib +…

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

Summary

ID

NL-OMON55892

Source
ToetsingOnline

Brief title
EORTC 1612 (EBIN) study

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
Metastatic melanoma;

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Bristol-Myers Squibb,EORTC (European Organisation for Research and Treatment of Cancer),Pierre Fabre

Intervention

Keyword: BRAF, Immunotherapy, Melanoma, Targeted therapy

Outcome measures

Primary outcome

Progression-free survival (PFS): defined as the time from the date of

randomization until the first date of progression, or until date of death

(whatever the cause), whichever occurs first. For patients who remain alive and

whose disease has not progressed, PFS will be censored on the date of last

visit/contact when a disease assessment was performed. PFS will be based on the

disease assessment or date of death provided by the local investigator

Secondary outcome

-* Overall survival (OS): defined as the time from the date of randomization to

the date of death, whatever the cause. The follow-up of patients still alive

will be censored at the moment of last visit/contact

-* CR rate, time to CR and duration of CR

-* Best overall objective response (CR+PR) rate (ORR), time to best objective

reponse (OR) and duration of OR

- Toxicity grades are in accordance with National Cancer Institute Common

Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

Study description

Background summary

In recent years, the approval of immunomodulatory agents and targeted agents for treatment of advanced or metastatic melanoma has dramatically changed the landscape and is leading to a potential broad range of applications for combinations therapies.
However, there are no trials that have assessed which is the best treatment sequence and presently, there is no consensus on the optimal first line treatment for patient with BRAF mutant metastatic melanoma.

Study objective

This study has been transitioned to CTIS with ID 2023-505376-30-00 check the CTIS register for the current data.

The primary objective is to prospectively assess whether a sequential approach with an induction period of 12 weeks with encorafenib + binimetinib followed by an immunotherapy combination with nivolumab + ipilimumab improves Progression Free Survival (PFS) compared to an immunotherapy combination nivolumab + ipilimumab alone as first line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The secondary objectives are:
-* To prospectively assess whether a sequential approach with an induction period of 12 weeks with encorafenib + binimetinib followed by combination immunotherapy with nivolumab + ipilimumab improves Overall Survival (OS) as compared to combination immunotherapy nivolumab + ipilimumab alone.
-* To prospectively assess in both treatment groups:
-* Complete response (CR) rate, time to CR and duration of CR
-* Best overall response (CR+PR) rate (ORR), time to best response and duration of response
-* To prospectively assess adverse event (AE) profiles (AE, grade 3-4 AE rate and Serious Adverse Event) between patients receiving the sequential approach versus patients receiving combination immunotherapy alone.

The exploratory objectives are:
-* To assess the iRECIST tumor response in both treatment groups.
-* To assess PFS2 in both treatment arms.
-* To assess response to second line by RECIST 1.1
-* To compare Quality of Life between the two arms.
-* To collect biological material for translational research projects to explore the biology of melanoma and in parallel assessing the prognostic and/or predictive value of potential biomarkers.

Study design

This is a multicenter, 2-arm open-label, randomized comparative phase II study.

Intervention

A total of approximately 270 patients with unresectable or metastatic (7th edition AJCC stage IIIC/IV) melanoma will be centrally randomized at the EORTC Headquarters to receive one of the 2 treatment arms.

- Arm A: nivolumab 3 mg/kg q3w + ipilimumab 1 mg/kg q3w for 4 injections followed by nivolumab 480 mg IV q4w until completion of 2 years total treatment or progression. Then treatment will be left at the investigator choice and continued until the 2nd progression.

- Arm B: encorafenib 450 mg QD + binimetinib 45 mg BID orally for 12 weeks followed, after a week of pause, by nivolumab 3 mg/kg q3w + ipilimumab 1mg/kg q3w for 4 injections, followed by nivolumab 480 mg IV q4w until completion of 2 years total treatment or progression. Then patients will be rechallenged with encorafenib 450 mg QD + binimetinib 45 mg BID orally continuously until the 2nd progression.

Study burden and risks

To date, there are no trials that have assessed which is the best treatment sequence and presently, there is no consensus on the optimal first line treatment for patient with BRAF mutant metastatic melanoma.
There is evidence suggesting that targeted agents can provide not only additive effects to immunotherapy, but also can sensitize the tumor cells to immune attacks, increasing antigen expression, and improve the effector function of immune cells.
Preclinical and clinical data support the rationale for intermittent regimens with BRAF inhibitors, showing that the development of resistance could be delayed with intermittent therapy.
A phase I study has shown a high rate of liver toxicity with the combination of ipilimumab plus vemurafenib (Ref. 20). This suggests caution is needed when combining target and immunomodulatory agents and that sequencing these

different combinations would be a more explorable strategy.
Indeed, a sequential approach could merge the high response rate of target therapy with the peculiarity of immunotherapy to achieve long-term durable responses, prior to secondary resistance occurrence to the targeted therapy. It has been shown that BRAF inhibitors alone or combined with MEK inhibitors lead to an increased expression of tumor antigens and an increased immune infiltrate (Ref. 17). At the same time, BRAF or BRAF/MEK leads to an increased expression of TIM-3 and PD-L1, which are markers of T cell exhaustion and form the target for anti-PD-1 immunotherapy treatment.

If these patients would not participate in this study, they would also receive immunotherapie as a standard of care, with all accessory visits. Thus, the extra burden of participating is mainly due to extra screeningexaminations and the biopsies and blood taken for translational research.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

• Histologically or cytologically confirmed unresectable stage III/ IV cutaneous or mucosal melanoma • Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrolment as per local assessment • Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. This can be an archived sample if obtained at maximum 3 months prior to randomization and if the patient did not receive treatment since then. • Measurable disease per RECIST 1.1 criteria by computed tomography (CT) or magnetic resonance imaging (MRI) of Chest/Abdomen/Pelvis and brain CT/MRI performed within 28 days prior to randomization • Patients >= 18 years of age • Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 • Patients must be able to swallow and retain oral tablets • Adequate organ function within 14 days prior to randomization: • Absolute neutrophil count (ANC) >= 1.5 x 109/L (>= 1500 per mm3) • Lymphocyte count >= 1.0 x 109/L (>= 1000 per mm3) • Platelet count >= 100 x 109/L (>= 100,000 per mm3) • Hemoglobin >= 9.0 g/dL (>= 5.59 mmol/l) • Total bilirubin <= 1.5 x institutional upper limit of normal (ULN) or direct bilirubin <= ULN for patients with total bilirubin levels > 1.5 x ULN. • AST (SGOT)/ALT (SGPT) <= 2.5 x institutional upper limit of normal (< 5x ULN in case of liver metastases) • Lipase < 2.0 x the ULN and no radiologic or clinical evidence of pancreatitis • Serum phosphorus, calcium, magnesium and potassium within normal ranges as per local lab values • Creatinine <= 1.5 x ULN or calculated creatinine clearance >= 60 mL/min for patient with creatinine levels > 1.5 x institutional laboratory value (according to Cockroft-Gault, Appendix D in protocol); • International Normalized Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) <= 1.5 x ULN Note: patients receiving anticoagulant therapy (have to be shifted to low molecular weight heparin (LMWH) before treatment start; as warfarin and related 4-hydroxycoumarin-containing molecules are not permitted) are eligible if their PT or INR or PTT is within the recommended range for the desired level of anticoagulation. • Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement can be included. • Adequate cardiac function: • left ventricular ejection fraction (LVEF) >= 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram, • 12-lead ECG (in triplicate [2-5 minutes apart]). Single ECG should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position on which QTcF must be <470 ms. • Women of child bearing potential (WOCBP) must have a negative serum (preferred) or urine pregnancy test within 72 hours prior to registration.Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e. females who have had evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is

possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.• Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and after the study treatment: • for at least 5 months for a woman and 7 months for a man after the last study treatment (nivolumab and ipilimumab or nivolumab alone). • for a period of at least 2 months after last dose of encorafenib and binimetinib Note: A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Such methods include: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner • Sexual abstinence Note: for patient that will receive ENCO: there is a potential for ENCO to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. • Female patients must not be breast feeding during the trial treatment and for a period of at least 5 months after treatment discontinuation. • Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. • Before patient registration/randomization and before any related study activity, written informed consent must be given according to ICH/GCP, and national/local regulations}e* *8@ Changes are the following (ref. prot v3.0 and v4.0 tracked changes) : - Serum phosphorus, total calcium, total magnesium and potassium within normal ranges as per local lab values; in case of small variation (+/-10%) in phosphorus, calcium or magnesium, the patient may be considered eligible and the decision will be left to the investigator - Serum total bilirubin <= 1.5 x institutional upper limit of normal (ULN) or direct bilirubin <= ULN for patients with total bilirubin levels > 1.5 x ULN. - AST (SGOT)/ALT (SGPT) <= 2.5 x ULN (< 5x ULN in case of liver metastases) - Creatinine <= 1.5 x ULN or calculated creatinine clearance >= 60 mL/min for patient with creatinine levels > 1.5 x ULN (according to Cockroft-Gault formula, Appendix D);

Exclusion criteria

• Uveal melanoma • Any symptomatic brain or leptomeningeal disease. Subjects with brain metastases are eligible if these have been locally treated and there is no magnetic resonance imaging (MRI) evidence of progression 4 weeks after end of treatment. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. • Any prior treatment for advanced disease including treatment with an anti-programmed death receptor-1 (PD-1), anti-programmed death-1 ligand-1 (PD-L1), anti-PD-L2, anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody, anti-LAG-3, anti-TIM-3,

anti-IDO, etc or BRAF or MEK inhibitors. • History of hypersensitivity to study drugs or any excipient (refer to Investigator's brochures for binimetinib and encorafenib and SmPCs for ipilimumab and nivolumab). • Prior adjuvant melanoma therapy with IFN, anti-PD1, anti-PDL1 or anti-CTLA-4 or any other systemic treatment is permitted if completed at least 1 year prior to randomization and all related adverse events have returned to grade <= 1. • Concomitant administration of strong inducers and inhibitors of P-gp, glucuronidation, CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John*s Wort [hypericin]) • Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin) • Live vaccines within 30 days prior to the first dose of study therapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, BCG, and typhoid vaccine. • Current participation or treatment with other investigational agent or use of an investigational device within 4 weeks of the first dose of study treatment • Child-Pugh B/C and patients with history of acute or chronic pancreatitis • Known history or current evidence of active Hepatitis B (e.g., HBsAg reactive) or C (e.g., HCV RNA [qualitative] is detected) • History of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies) • Chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 2 weeks prior to the first dose of study treatment • Corticosteroid use as premedication for IV contrast allergies/reactions is allowed • Conditions requiring systemic treatment with <10 mg daily prednisone equivalents or equivalent doses of any other corticosteroid are allowed • History of interstitial lung disease (ILD) OR pneumonitis (other than chronic obstructive pulmonary disease (COPD) exacerbation) that has required oral or IV steroids are allowed • Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed • Autoimmune paraneoplastic syndrome requiring immunosuppressive or dedicated treatment. A specific attention should be given in order to detect any minor myasthenia signs at enrolment; acetylcholine receptor antibodies will be systematically tested when symptoms are suggestive of a myasthenia • History of any other hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. A patient with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible, for example cervical cancer in situ or pT1a incidental prostate cancer • Previous allogeneic tissue/solid organ transplant • Active infection requiring therapy • Major surgery or trauma within 12 weeks prior to first dose of treatment or presence of any non-healing wound. Complete wound healing from major surgery must have occurred one month before the first dose of study treatment. • Minor surgery (including uncomplicated tooth extractions) within 28 days before randomization with complete wound healing at least 10 days before randomization is permitted. • Any anticancer treatment within 4 weeks before randomization e.g. radiation, surgery, systemic therapy. • Patients with clinically relevant ongoing complications from prior anticancer

therapies. • Severe or uncontrolled systemic disease or any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the study, or which would jeopardize compliance with the protocol • History or current evidence of retinal vein occlusion (RVO) or current risk factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); an ophthalmological assessment is mandatory within 28 days from the first dose of study treatment. • History of retinal degenerative disease. Changes are the following (ref. prot v3.0 and v4.0 tracked changes) : - Prior adjuvant melanoma therapy with IFN, anti-PD1, anti-PDL1 or anti-CTLA-4 or any other systemic treatment is permitted if completed at least 6 months prior to randomization and all related adverse events have returned to grade <= 1. - History of interstitial lung disease (ILD) OR pneumonitis (other than chronic obstructive pulmonary disease (COPD) exacerbation) that has required oral or IV steroids are not allowed

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):	22-11-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Binimetinib

Generic name:	Binimetinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Encorafenib
Generic name:	Encorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ipilimumab
Generic name:	Ipilimumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-10-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
EU-CTR	CTIS2023-505376-30-00
EudraCT	EUCTR2017-002887-42-NL
ClinicalTrials.gov	NCT03235245
CCMO	NL67202.031.18