

Trial record 1 of 1 for: NCT02902029

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Evaluating the Efficacy and Safety of a Sequencing Schedule of Cobimetinib Plus Vemurafenib Followed by Immunotherapy With an Anti- PD-L1 Antibody in Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma (ImmunoCobiVem)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified December 2016 by University Hospital, Essen

Sponsor:

University Hospital, Essen

Information provided by (Responsible Party):

Prof. Dr. med. Dirk Schadendorf, University Hospital, Essen

ClinicalTrials.gov Identifier:

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[History of Changes](#)

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[No Study Results Posted](#)

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Purpose

Most patients with locally advanced or metastatic tumors succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic melanoma. Targeting the the Ras/Raf signalling pathway by BRAF and MEK inhibition as well as targeting immunologic checkpoint control with an antiPD-L1 antibody have emerged as treatment option.

In this study the best timing for sequential use of both treatment options (BRAF/MEK inhibition and antiPD-L1 antibody) in patients with unresectable or metastatic BRAFV600 mutant melanoma will be assessed.

Condition	Intervention	Phase
Malignant Melanoma	Drug: Vemurafenib Drug: Cobimetinib Drug: Atezolizumab	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment

Masking: Open Label

Primary Purpose: Treatment

Official Title: A Phase II, Open-label, Randomized-controlled Trial Evaluating the Efficacy and Safety of a Sequencing Schedule of Cobimetinib Plus Vemurafenib Followed by Immunotherapy With an Anti- PD-L1 Antibody Atezolizumab for the Treatment in Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma

Resource links provided by NLM:

[MedlinePlus](#) related topics: [Melanoma](#)

[Drug Information](#) available for: [Vemurafenib](#) [Cobimetinib](#) [Atezolizumab](#)

[Genetic and Rare Diseases Information Center](#) resources: [Carcinoid Tumor](#) [Neuroepithelioma](#)

[U.S. FDA Resources](#)

Further study details as provided by University Hospital, Essen:

Primary Outcome Measures:

- Time to Second Objective Disease Progression [Time Frame: 4 years] [Designated as safety issue: No]

Time to Second Objective Disease Progression (PFS2) defined as time from start of run-in phase (date of first intake of study drug) to second objective disease progression according to RECIST v. 1.1. (PD2) following randomization or death from any cause

Secondary Outcome Measures:

- Adverse events according to CTCAE Version 4.0 criteria (Safety / Toxicity) [Time Frame: Until 90 days of discontinuation of dosing of the investigational product] [Designated as safety issue: Yes]
All adverse events according to CTCAE Version 4.0 criteria, that are related to the administration of the investigational agents will be assessed
- Overall survival [Time Frame: 4 years] [Designated as safety issue: No]
Overall Survival (OS) of a patient defined as the time from start of run-in phase (date of first intake of study drug) until documented date of death
- Overall survival 12 months [Time Frame: 1 year] [Designated as safety issue: No]
Overall survival rate at 12 months defined as the rate of patients alive 12 months after start of run-in phase (date of first intake of study drug)
- Overall survival 24 months [Time Frame: 2 years] [Designated as safety issue: No]
Overall survival rate at 24 months defined as the rate of patients alive 24 months after start of run-in phase (date of first intake of study drug)
- 12-months disease control rate (DCR) [Time Frame: 1 year] [Designated as safety issue: No]
DCR is defined as the rate of patients showing complete response (CR) or partial response (PR) or stable disease (SD) at 12 months after start of run-in phase (date of first intake of study drug).
- 24-months disease control rate (DCR). [Time Frame: 2 years] [Designated as safety issue: No]
DCR is defined as the rate of patients showing complete response (CR) or partial response (PR) or stable disease (SD) at 24 months after start of run-in phase (date of first intake of study drug).
- Rate of patients with progressive disease who could not cross-over to subsequent line of therapy due to deterioration of ECOG status and/or brain metastases [Time Frame: 4 years] [Designated as safety issue: Yes]
 - From run-in phase (vemurafenib + cobimetinib) to study treatment in Arm A or Arm B
 - From vemurafenib + cobimetinib to atezolizumab (Arm A)
 - From atezolizumab to vemurafenib + cobimetinib (Arm B)

Estimated Enrollment: 176
 Study Start Date: November 2016
 Estimated Study Completion Date: June 2020
 Estimated Primary Completion Date: March 2020 (Final data collection date for primary outcome measure)

<u>Arms</u>	<u>Assigned Interventions</u>
<p>Experimental: Arm A</p> <p>After a 3 months run-in period with vemurafenib and cobimetinib [960 mg vemurafenib twice daily (BID), 28/0; 60 mg cobimetinib daily (QD), 21/7], all patients who do not show disease progression or definite treatment interruption (e.g. due to unacceptable toxicity) for more than 28 days will be randomized.</p> <p>Further treatment with vemurafenib and cobimetinib (960 mg vemurafenib BID, 28/0; 60 mg cobimetinib QD, 21/7).</p> <p>After progression of disease patients in Arm A will subsequently receive atezolizumab treatment (1200 mg/ q3w).</p>	<p>Drug: Vemurafenib 960 mg vemurafenib BID until progression or unacceptable toxicity develops</p> <p>Drug: Cobimetinib 60 mg cobimetinib QD, 21/7 until progression or unacceptable toxicity develops</p> <p>Drug: Atezolizumab 1200 mg atezolizumab administered intravenously on day 1 of each 21 day-cycle. Will be given until progression or unacceptable toxicity develops</p>
<p>Experimental: Arm B</p> <p>After a 3 months run-in period with vemurafenib and cobimetinib (960 mg vemurafenib BID, 28/0; 60 mg cobimetinib QD, 21/7), all patients who do not show disease progression or definite treatment interruption (e.g. due to unacceptable toxicity) for more than 28 days will be randomized.</p> <p>Further treatment with atezolizumab. Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on day 1 of each 21 day-cycle.</p> <p>After progression of disease patients in Arm B will cross back to vemurafenib and cobimetinib treatment (960 mg vemurafenib BID, 28/0; 60 mg cobimetinib QD, 21/7).</p>	<p>Drug: Vemurafenib 960 mg vemurafenib BID until progression or unacceptable toxicity develops</p> <p>Drug: Cobimetinib 60 mg cobimetinib QD, 21/7 until progression or unacceptable toxicity develops</p> <p>Drug: Atezolizumab 1200 mg atezolizumab administered intravenously on day 1 of each 21 day-cycle. Will be given until progression or unacceptable toxicity develops</p>

Detailed Description:

At this time there is no experience concerning the sequencing strategy when using the two effective therapeutical approaches as targeting the Ras/Raf signalling pathway by BRAF and MEK inhibition or targeting immunologic checkpoint control with an antiPD-L1 antibody.

This is a prospective, open, multicenter, randomized phase II study in patients with unresectable or metastatic BRAFV600 mutant melanoma. In this study the scheduling of the treatment with a combined BRAF/MEK inhibition and the treatment with an anti-PD-L1 antibody will be assessed.

After a 3 months run-in period with vemurafenib and cobimetinib, all patients who did not show disease progression or treatment interruption for more than 28 days during run-in phase will be randomized in a 1:1 ratio:

- either to proceed vemurafenib and cobimetinib until disease progression and subsequently cross-over to atezolizumab treatment until disease progression (Arm A).
- or to receive the anti-PD-L1 antibody atezolizumab until disease progression and subsequently cross-back to vemurafenib and cobimetinib until disease progression (Arm B). In a translational research program tumor tissue, blood plasma and peripheral blood mononuclear cell will be analyzed to evaluate the biologic effects of treatment sequence on the molecular profile and biomarker expression in tissue and plasma.

▶ Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)

Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Be willing and able to provide written informed consent for the trial.
- Male or female patient being ≥ 18 years of age on day of signing informed consent.
- Histologically confirmed diagnosis of locally advanced, unresectable or metastatic melanoma AJCC (unresectable stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c) without active or untreated brain metastases; all known CNS lesions must have been treated with stereotactic therapy or surgery at least 4 weeks prior to the first dose of trial treatment AND the patient must be without evidence of clinical or radiographic disease progression in the CNS for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms must have returned to baseline, the patient must have no evidence of new or enlarging brain metastases, and the patient must not have used steroids for at least 3 weeks prior to trial treatment.
- No previous therapy for the advanced or metastatic stage. Prior adjuvant therapy is permitted (e.g. Interferon, Interleukin-2-therapy, chemo- or radiotherapy). Prior adjuvant therapy has to be terminated (last dose) at least 28 days before enrolment. Patients who are in follow-up period of a clinical trial in adjuvant setting and progressing may be enrolled / randomized.
- Measurable disease, i.e., present with at least one measurable lesion per RECIST, version 1.1, for the definition of a measurable lesion.
- Presence of BRAF mutation (V600) in tumor tissue.
- Performance status of 0 or 1 on the ECOG Performance Scale.
- Adequate organ function.
- Adequate cardiac function.
- Able to take oral medications.
- Female subject of childbearing potential should have a negative pregnancy test within 72 hours prior to receiving the first dose of study medication.
- Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use a highly effective form of contraception according to CTFG during the course of this study and for at least 6 months after completion of study therapy.

Exclusion Criteria:

- Use of any investigational or non-registered product within the 30 days before registration.
- Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study Day 1.
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Prior therapy with a BRAF inhibitor (including but not limited to vemurafenib, dabrafenib, encorafenib and / or MEK inhibitor
- Prior major surgery.
- Known additional malignancy that is progressing or requires active treatment within 5 years prior to the study.
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- History of leptomeningeal metastases.
- History or current evidence of central serous retinopathy (CSR) or retinal vein occlusion (RVO) or predisposing factors to RVO or CSR.
- History of retinal degenerative disease.
- History of allogenic bone marrow transplantation or organ transplantation.
- History of Gilbert's syndrome.
- Impaired cardiovascular function or clinically significant cardiovascular diseases.
- Uncontrolled arterial hypertension despite medical treatment.
- Impairment of gastrointestinal function or gastrointestinal disease.
- Evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Active infection requiring systemic therapy.

- Positive test for Human Immunodeficiency Virus (HIV).
- Positive test for Hepatitis B or Hepatitis C.
- Known hypersensitivity reaction to any of the components of study treatment.
- Medical, psychiatric, cognitive or other conditions, including known alcohol or drug abuse.
- Patients having received a live, attenuated vaccine within 4 weeks prior to the first dose of trial treatment.
- Legal incapacity or limited legal capacity.

▶ Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT02902029

Contacts

Contact: Dirk Schadendorf, Prof. Dr. dirk.schadendorf@uk-essen.de

Locations

Germany

SLK-Kliniken Heilbronn GmbH Heilbronn, Baden-Wuerttemberg, Germany, 74078 Contact: Uwe Martens, Prof. Dr. uwe.martens@slk-kliniken.de Principal Investigator: Uwe Martens, Prof. Dr. Sub-Investigator: Jamil Akkad	Not yet recruiting
University Hospital Mannheim, Clinic for Dermatology Mannheim, Baden-Wuerttemberg, Germany, 68167 Contact: Jochen Utikal, Prof. Dr. jochen.utikal@umm.de Principal Investigator: Jochen Utikal, Prof. Dr. Sub-Investigator: Christoffer Gebhardt, Dr. med.	Recruiting
National Centre for Tumour Diseases (NCT) Heidelberg, BW, Germany, 69120 Contact: Jessica Hassel, Dr. med. jessica.hassel@med.uni-heidelberg.de Principal Investigator: Jessica Hassel, Dr. med. Sub-Investigator: Martin Hartmann, Dr. med	Not yet recruiting
University Hospital Essen, Department of Dermatology, Skin Cancer Center Essen, North Rhine-Westphalia, Germany, 45122 Contact: Dirk Schadendorf, Prof. Dr. dirk.schadendorf@uk-essen.de Principal Investigator: Dirk Schadendorf, Prof. Dr. Sub-Investigator: Bastian Schilling, PD Dr.	Not yet recruiting
HELIOS Klinikum Erfurt Erfurt, Thuringia, Germany, 99089 Contact: Rudolf Herbst, Prof. Dr. rudolf.herbst@helios-kliniken.de Principal Investigator: Rudolf Herbst, Prof. Dr. Sub-Investigator: Ivonne Kellner, Dr. med.	Recruiting
Medizinische Hochschule Hannover Hannover, Germany, 30625 Contact: Ralf Gutzmer, Prof. Dr. gutzmer.ralf@mh-hannover.de Principal Investigator: Ralf Gutzmer, Prof. Dr. Sub-Investigator: Imke Satzger, Pd Dr.	Not yet recruiting

Sponsors and Collaborators

University Hospital, Essen

Investigators

Principal Investigator: Dirk Schadendorf, Prof. Dr. University Hospital, Essen

▶ More Information

Responsible Party: Prof. Dr. med. Dirk Schadendorf, Prof. Dr. med., University Hospital, Essen
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 Other Study ID Numbers: ImmunoCobiVem_2015
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Health Authority: Germany: Paul-Ehrlich-Institut

Individual Participant Data

Plan to Share IPD: No

Keywords provided by University Hospital, Essen:
unresectable stage IIIB, IIIC, IV melanoma

Additional relevant MeSH terms:

Melanoma

Neuroendocrine Tumors

Neuroectodermal Tumors

Neoplasms, Germ Cell and Embryonal

Neoplasms by Histologic Type

Neoplasms

Neoplasms, Nerve Tissue

Nevi and Melanomas

Antibodies

Antibodies, Monoclonal

Immunologic Factors

Physiological Effects of Drugs

ClinicalTrials.gov processed this record on December 30, 2016