Synopsis

Sponsor:

University of Essen, Hufelandstr. 55, D-45147 Essen, Germany
Represented by Prof. Dr. med. Dirk Schadendorf

Investigational medicinal products: Vargatef® / Placebo / Taxomedac®

Drug substance: Nintedanib / Placebo / Paclitaxel

Registration: ClinicalTrials.gov Identifier: NCT02308553

Study title:

A phase I/II, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of nintedanib/vargatef in combination with paclitaxel chemotherapy for treatment of patients with BRAF wildtype metastatic melanoma

Study protocol version:

V1.4 2016-06-21, including Amendment 01 (previous protocol V 1.3 2014-10-14)

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First patient in: 17 MAR 2015 **Last patient out:** 17 OCT 2019	**Phase:** I / II

Study objective(s):

The objectives of this study were to characterize the safety and to estimate the efficacy of nintedanib when combined with paclitaxel chemotherapy compared with paclitaxel chemotherapy alone in patients with BRAF wildtype metastatic melanoma not previously treated with taxanes or kinase inhibitors.

Primary objective of Phase I:

To define the Maximum Tolerable Dose (MTD) of the nintedanib/paclitaxel combination treatment.

Primary objective of Phase II:

To evaluate the progression-free survival (PFS) according to RECIST v1.1

Secondary objectives:

- To evaluate the overall survival (OS)
- To evaluate safety and toxicity (graded according to CTCAE, Version 4.0)
- To evaluate Quality of Life (EORTC QLQ-C30) during therapy (i.e. until end of treatment visit)

Objective of translational research project:

To identify and evaluate prognostic and predictive biomarkers by analysis of tumor tissue and serum samples

Trial design:

Nipawilma was a multicenter, randomized, double-blind, placebo-controlled phase I/II trial designed to characterize the safety and estimate the efficacy of nintedanib when combined with paclitaxel chemotherapy compared with paclitaxel chemotherapy alone in patients with BRAF wildtype metastatic melanoma not previously treated with taxanes or kinase inhibitors.

Methods:

The **phase I-par**t of the trial was designed as a Run-in Phase based on acceptable safety data for nintedanib monotherapy. A classical 3+3, open-label, single arm design was used. Enrolled patients were planned to be treated with the predefined dose levels of 150 mg (dose level 1) and 200 mg (dose level 2) nintedanib, twice daily (BID) p.o., in combination with paclitaxel 90 mg/m^2 given as iv infusion on day 1, 8, 15, q28.

A cohort of three patients was treated in each dose level and toxicity was assessed in the first treatment cycle (28 days + 1-week washout). In case of no dose limiting toxicity (DLT), the dose was increased by one dose level.

In case of one DLT, up to three further patients were recruited into the same dose level.

If >1 DLT occurred in one dose level in up to six patients, this dose level was not further evaluated.

The highest dose level with ≤1 DLT out of six patients was defined as MTD and was evaluated in the second part of the trial after approval of the sponsor.

In the **phase II-part**, patients were randomized 1:1 to be either treated with nintedanib (MTD of phase I) [Arm A] or placebo [Arm B] p.o. BID in combination with paclitaxel (90 mg/m², iv, day 1, 8, 15, q28) for 6 cycles. Thereafter, nintedanib / placebo monotherapy could be continued for a maximum of 48 weeks after initial dosing or until unacceptable toxicity or disease progression, whichever occurred first.

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Number of patients (planned and analyzed)

Phase I:
Planned number of patients to be enrolled into phase I part was ≥6.
A total of 10 patients was enrolled into phase I-part. Of these, 1 patient violated an exclusion criterion, thus 9 patients could be analyzed.

Phase II:
Planned number of patients to be enrolled into phase II part was 120. However, only 24 patients were randomized within the planned recruitment period. Recruitment period was not extended and thus the study was terminated according to the planned timelines in the protocol. Of the 24 patients, 2 were randomized by mistake and therefore, only 22 patients could be analyzed.

Diagnosis and key inclusion criteria:

Patients with advanced (unresectable stage III or IV) BRAF V600 wildtype cutaneous malignant melanoma.

Inclusion criteria:

1. Histologically confirmed, (surgically incurable or unresectable) stage III or IV, BRAF V600 wildtype metastatic cutaneous malignant melanoma.
2. Written informed consent must be obtained from the patient prior to performing any study-related procedures.
3. A minimum of 1 measurable lesion according to RECIST v1.1 criteria.
4. ECOG performance status of 0-1.
5. Adequate hematologic, renal and liver function as defined by laboratory values performed within 14 days prior to initiation of dosing:
    - Hematologic
        - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
        - Hemoglobin ≥9 g/dL (5.6 mmol/L; Subjects may not have had a transfusion within 7 days of screening assessment)
        - Platelets: ≥100 x 10^9/L
    - Hepatic
        - Total bilirubin: ≤1.0 x ULN
        - AST and ALT: ≤1.5 x ULN (In the case of liver metastases: 2.5 x ULN)
    - Renal
        - Serum creatinine: ≤1.5 mg/dL (133 µmol/L) or, if greater than 1.5 mg/dL: Calculated creatinine clearance: ≥50 mL/min
6. Women of childbearing potential (WOCBP) should be using an effective method of contraception (Pearl-Index <1) to avoid pregnancy for at least 6 months after completion of paclitaxel treatment and for at least 3 months after completion of nintedanib/placebo monotherapy as directed by their physician. Women will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years. WOCBP must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) up to 28 days prior to commencement of dosing.
7. Men should use an effective method of contraception during treatment and for at least 6 months after completion of paclitaxel treatment and for at least 3 months after completion of nintedanib/placebo monotherapy as directed by their physician.
8. Patients must have recovered from all prior treatment-related toxicities to NCI CTCAE (v4.0) Grade of 0 or 1, except for toxicities not considered a safety risk such as alopecia.
9. Male or female, aged 18 years or older
10. Life expectancy at least 3 months

Exclusion criteria:

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1. Prior systemic therapy with taxanes or kinase inhibitors. Any prior therapy for metastatic disease must have been discontinued at least 4 weeks prior to initiation of dosing.
2. Major surgery or radiation therapy within 4 weeks of starting the study treatment (minor surgical procedures such as biopsies are allowed, however patients must have recovered).
3. Known inherited predisposition to bleeding or thrombosis and therapeutic anticoagulation (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid <325 mg per day)
   Patients with the following coagulation parameters will be excluded:
   - International normalised ratio (INR) >2
   - Prothrombin time (PT) and partial thromboplastin time (PTT): >50% of deviation of institutional ULN
4. History of clinically significant haemorrhagic or thromboembolic event in the past 6 months
5. NCI CTCAE (V4.0) grade 3 hemorrhage within 4 weeks of starting the study treatment.
6. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization.
7. Serious, non-healing wound, ulcer, or bone fracture.
8. Known central nervous system (CNS) disease:
   - Previous Grade 2 or higher sensory neuropathy.
   - History of or known spinal cord compression, or carcinomatous meningitis, or evidence of active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month before randomization) or leptomeningeal disease on screening CT or MRI scan.
9. Any of the following within the 6 months prior to enrolment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism.
10. New York Heart Association (NYHA) Grade II or greater congestive heart failure.
11. Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.0 grade ≥2.
12. Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure >100 mmHg on antihypertensive medications).
13. Symptomatic peripheral vascular disease.
14. Proteinuria at screening as demonstrated by urine dipstick for proteinuria ≥2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤1g of protein in 24 hours to be eligible).
15. Known hypersensitivity reaction to any of the components of study treatment (e.g. contrast media) or other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.
16. Previous cancer (unless a recurrence free survival (RFS) interval of at least 5 years) with the exception of surgically cured carcinoma in-situ of the cervix and basal or squamous cell carcinoma of the skin.
17. Known clinically uncontrolled infectious disease including HIV positivity or AIDS-related illness and active or chronic hepatitis C and/or B infection.
18. Pregnancy (absence to be confirmed by ß-hCG test) or lactation period.
19. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule
20. Active alcohol or drug abuse
21. Treatment with other investigational drugs or treatments in another clinical trial within the past four weeks before start of therapy or concomitantly with this trial.
22. Legal incapacity or limited legal capacity

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23. Significant weight loss (>10% of body weight) within past 6 months prior to inclusion into the trial.

Investigational medicinal product (dosage, method of administration, batch number)

Nintedanib was provided as soft gelatin capsules with 100 mg and 150 mg of substance. In phase I-part nintedanib is provided open label. To ensure blinding in phase II-part, nintedanib and placebo capsules were identical in appearance. Boxes were labelled with unique medication numbers. Neither the investigator nor the patient knew the content.

150 mg or 200 mg nintedanib was taken p.o. twice daily yielding a total daily dose of 300 or 400 mg. Nintedanib capsules should not be taken on days of paclitaxel administration.

Paclitaxel treatment was open label. Paclitaxel was administered intravenously with a dose of 90 mg/m^2 over a period of one hour on day 1, 8, and 15 during 4-week cycles. A total of 6 cycles should be given in combination with nintedanib/placebo.

Duration of treatment:

Nintedanib/placebo could be taken for a maximum of 48 weeks after initial dosing until unacceptable toxicity or disease progression, whichever occurred first. During the first 24 weeks nintedanib/placebo was administered in combination with paclitaxel (6 cycles), subsequently as monotherapy.

Reference product (dosage, method of administration, batch number)

Placebo was provided as soft gelatin capsules with 100 mg and 150 mg of substance. To ensure blinding nintedanib and placebo capsules were identical in appearance. Boxes were labelled with unique medication numbers. Neither the investigator nor the patient knew the content.

150 mg or 200 mg placebo was taken p.o. twice daily yielding a total daily dose of 300 or 400 mg. Placebo capsules should not be taken on days of paclitaxel administration.

First reference drug:
Second reference drug:

Unblinding:

The investigator was able to unblind each patient enrolled by his site into phase II electronically via the eCRF. Unblinding should only be conducted if medically imperative for diagnostic or therapeutic decisions to know what the patient was receiving. Reason of unblinding had to be documented by the investigator into the eCRF and date of unblinding was automatically included after saving. If electronic unblinding was not possible, the investigator received a set of sealed envelopes, one for each randomization number containing information on the patient's trial medication. Date and reason for opening a sealed envelope had to be documented. The investigator was not allowed to open the randomization envelopes at the end of the trial. The envelopes were collected by the monitor at the final visit.

Efficacy evaluation:

To compare PFS according to RECIST v1.1 and OS between treatment groups

Safety evaluation:

To compare the rate and severity of adverse events during study treatment between treatment groups. Adverse events were recorded according to NCI CTC v4.0.

Statistical methods:

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Progression-free survival and overall survival were analyzed using Kaplan-Meier methods. Additionally, PFS- and OS-rates were given at 6, 12, 18 and 24 months. Patients with event but unknown date of event will not be considered in the respective analysis. For patients with unknown date the query-log was be presented.

For categorical variables the number of observations and their percentage were shown, with missing values forming one category. For continuous variables mean, standard deviation, median, minimum and maximum as well as number of missing values were presented.

Quality of life was analyzed according to the corresponding manual.

Results of phase I were presented for the subgroups 'Dose level 1' vs. 'Dose level 2'.

Results of phase II were presented for the subgroups 'patients treated with paclitaxel plus nintedanib' vs. 'patients treated with paclitaxel plus placebo'.

Since the study was prematurely discontinued all analyses were purely descriptive, there was no testing and hence no p-values.

Summary of results:

Efficacy:
Primary efficacy objective was PFS determined according to RECIST v1.1 criteria by the respective trial site. Mean PFS (in months) from start of therapy until progression or death of any cause, whatever occurred first, was 6.94 months for phase I patients and 3.07 months for phase II patients. Considering only phase II patients, mean PFS was 3.16 months for Arm A and 3.00 months for Arm B. Thus, mean values were in the same range for nintedanib-arm and placebo-arm. Regarding median PFS values, these were higher for nintedanib-arm compared to placebo-arm, namely 3.47 and 1.64 months, respectively; however, statistically significance of difference was not addressed because the planned 120 patients could not be randomized and the low number of actually analyzed patients is prone to distortion and bias.
PFS rate for Arm A and Arm B was 0.0% and 9.1% at months 6. After 12 months, PFS rate was 0.0% for both treatment arms. Regarding median OS, this was in the same range for Arm A-patients compared to Arm B-patients, 20.6 months vs. 19.3 months. Mean values amounted to 16.59 months and 13.75 months for nintedanib-arm and placebo-arm, respectively.
OS rate at 6, 12, 18 and 24 months was at each time point higher in Arm A than in Arm B: 83.3% vs. 80.8%, 83.3% vs.60.6%, 65.5% vs. 60.6% and 31.2% vs. 20.2%, respectively.
Regarding QoL by use of EORTC QLQ-C30, the functional scores as well as the global health status remained stable during combination treatment.
Thus, there seems to be a positive effect by adding nintedanib to paclitaxel chemotherapy, however, due to low analyzed patient number no statistical comparison between both treatment arms was performed.

Tolerability:
The safety profile observed in this trial was in line with the published safety profile. All patients had at least 1 AE; most AEs were of NCI CTCAE grade 1 and 2 and were reported as single events only. All patients in Arm A and 92.3% of patients in Arm B experienced treatment-related AEs. The great majority of AEs was recovered at the end of the trial.
Patients in Arm A reported more AEs than patients in Arm B, namely 122 and 92 AEs, respectively, and more frequently experienced AEs belonging to SOCs 'Gastrointestinal disorders', 'General disorders and administration site conditions', 'Nervous system disorders' and 'Skin and subcutaneous tissue disorders' than patients in Arm B. 13 patients, 2 in phase I and 11 in phase II, reported a total of 19 SAEs which were mainly assessed by the investigator as being not treatment-related. No SAR occurred in phase I-patients. SARs of Arm A patient were 'AST increased' and 'ALT increased' and both events were assessed as related to nintedanib/placebo. SARs of Arm B patients (2 patients with anaphylactic reaction and 1 patient with arthralgia) were documented as related to paclitaxel.
In 3 patients, study treatment was discontinued prematurely due to severe toxicities.1 patient in Arm A (11%) reported severe hematological toxicity leading to study termination after the first week of cycle 1.

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2 patients in Arm B (15%) experienced an anaphylactic reaction, which was in both cases assessed by the investigator as related to paclitaxel and which led to discontinuation of study treatment after first paclitaxel infusion. In summary, no unexpected or unusual safety issues were observed. The treatment with nintedanib and paclitaxel was well tolerated. **Conclusion(s):** In conclusion, nintedanib-paclitaxel combination therapy was well tolerated but due to small patient number did not show statistically relevant improvement in PFS and OS compared to paclitaxel chemotherapy alone in patients with metastatic BRAF wildtype cutaneous melanoma**.**
Date of report: 21 JUL 2020