Targeting Both Tumor and Stroma Cells to Treat Melanoma: NIPAWILMA

**Efficacy and Safety of Nintedanib Combined with Paclitaxel Chemotherapy for Patients with BRAF wt Metastatic Melanoma (NIPAWILMA)**

**Condition**
Cutaneous Malignant Melanoma

**ClinicalTrials.gov Identifier**
NCT02308553

**EudraCT Number**
2013–004458–34

**Study Design**

*Study Type:* Interventional  
*Study Phase:* I/II  
*Endpoint Classification:* Safety/Efficacy Study  
*Allocation:* Randomized  
*Intervention Model:* Parallel Assignment  
*Masking:* Double Blind (Subject, Caregiver, Investigator)  
*Primary Purpose:* Treatment  
*Estimated Enrollment:* 126 patients

**Intervention**

*Drug:* Nintedanib + Paclitaxel  
*Drug:* Nintedanib-Placebo + Paclitaxel

**Study Arm A (Experimental):** Nintedanib (150 or 200 mg bid) for up to 48 weeks combined with paclitaxel 90 mg/m² BSA day 1, 8, 15 q28 days for a maximum of 6 courses  
**Study Arm B (Placebo Comparator):** Nintedanib-Placebo (150 or 200 mg bid) for up to 48 weeks combined with paclitaxel 90 mg/m² BSA day 1, 8, 15 q28 days for a maximum of 6 courses

**Primary Outcome Measure**
Progression-free survival (PFS) (time frame: 12 months after LPI)

**Secondary Outcome Measures**
Overall survival (time frame: 12 months after LPI)  
Safety and toxicity (graded according to CTCAE, Version 4.0) (time frame: 12 months after LPI)  
Quality of Life (EORTC QLQ-C30) (time frame: 12 months after LPI)

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

**Collaborators**
Boehringer Ingelheim  
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**Contacts**
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**Description**

Study phase I: Run-in-phase based on acceptable safety data for nintedanib monotherapy, a rapid dose finding will be conducted in a classical 3 + 3 design. Predefined dose levels are 150 mg (dose level 1) and 200 mg (dose level 2) nintedanib, twice daily, with weekly paclitaxel 90 mg/m².

Study phase II: Patients with advanced (unresectable stage III or IV) BRAf V600 wild type melanoma (n = 120) will be randomized (1:1) to receive either nintedanib (150 or 200 mg BID depending on results of phase I) in combination with paclitaxel or placebo in combination with paclitaxel.

Total study duration per patient: approximately 12 months of therapy + follow up until end of study.

All patients enrolled in either phase I or phase II will be treated according to the following treatment plan:

- Week 1–24: Chemotherapy with paclitaxel combined with nintedanib/placebo
- Week 25–48: Extended monotherapy with nintedanib/placebo
- Week 52 (or approximately 4 weeks after last treatment dose): End-of-treatment visit.

Follow up: After end of treatment the survival, disease status and further therapies of each patient will be assessed every 3 months until death, progression of disease or end of study, whichever occurs first.
**Eligibility Criteria**

- Ages eligible for study: 18 years and older
- Genders eligible for study: both
- Accepts healthy volunteers: no

**Inclusion Criteria**

- Histologically confirmed, (surgically incurable or unresectable) stage III or IV, BRAF V600 wildtype metastatic cutaneous malignant melanoma
- Written informed consent
- Adequate hematologic, renal and liver function within 14 days prior to initiation of dosing:
  - Hematologic: absolute neutrophil count (ANC) ≥1.5 x 10⁹/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 10⁹/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 or serum creatinine: ≤ 1.5 mg/dl (133 μmol/l) or, if greater than 1.5 mg/dl; calculated creatinine clearance; ≥ 50 ml/min
- Effective method of contraception for at least 3 months after completion of nintedanib/placebo monotherapy as directed by their physician
- 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
- Women of childbearing potential must demonstrate negative results for a pregnancy test and use an effective method of contraception for at least 6 months after completion of nintedanib/placebo monotherapy as directed by their physician and must demonstrate
- 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
- Life expectancy at least 3 months

**Exclusion Criteria**

- 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
- 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)
- Known inherited predisposition to bleeding or thrombosis and therapeutic anticogulation (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous device) 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; history of clinically significant haemorrhagic or thromboembolic event in the past 6 months; NCI CTCAE (v4.0) grade 3 hemorrhage within 4 weeks of starting the study treatment
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization
- Serious, non-healing wound, ulcer, or bone fracture
- Known 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
- 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
- New York Heart Association (NYHA) grade II or greater congestive heart failure
- Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.0 grade ≥ 2.
- Inadequately controlled hypertension (defined as systolic blood pressure > 150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)
- Symptomatic peripheral vascular disease
- 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-h urine collection and must demonstrate ≤ 1 g of protein in 24 h to be eligible)
- 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
- Previous cancer (unless a 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
- Known clinically uncontrolled infectious disease including HIV positivity or AIDS-related illness and active or chronic hepatitis C and/or B infection
- Pregnancy (absence to be confirmed by a-hCG test) or lactation period
- Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule
- Active alcohol or drug abuse
- Treatment with other investigational drugs or treatments in another clinical trial within the past 4 weeks before start of therapy or concomitantly with this trial
- Legal incapacity or limited legal capacity
- Significant weight loss (> 10% of body weight) within past 6 months prior to inclusion into the trial
Selective inhibition of the MAPK pathway by specific BRAF\textsuperscript{V600E} and MEK inhibitors has led to great advances in the therapy of BRAF-mutated melanoma and therefore this treatment has become standard treatment for BRAF-mutated melanoma next to immune checkpoint blocking antibodies. However, only about 50% of cutaneous melanomas harbor a respective mutation in BRAF\textsuperscript{[1]}. The underlying pathogenetics of BRAF wt melanoma are not yet completely understood. Activation of the Ras-Raf-MEK-ERK pathway via aberrant expression of growth factor receptors like fibroblast growth factor (FGF) receptor or the receptors for vascular endothelial growth factor (VEGF) as well as activation of other pathways like the PI3K-AKT-PTEN pathway seem to be involved in such cases\textsuperscript{[2, 3]}. Besides the well-known function of VEGF signaling, also signals from platelet-derived growth factor (PDGF)\textsuperscript{[4]} and FGF\textsuperscript{[5]} are relevant for tumor angiogenesis. Moreover, these factors are involved in the modulation of stromal cells in the tumor microenvironment. Since signaling via PDGF, and FGF receptors constitute important escape mechanisms from sole VEGF pathway inhibition\textsuperscript{[6]}, simultaneous inhibition of the VEGF, PDGF, and FGF pathways may offer a promising therapeutic approach for BRAF wt melanoma.

Nintedanib is an oral triple kinase inhibitor targeting VEGF, PDGF, and FGF receptors. After showing a significant increase in PFS and OS in combination with docetaxel compared to docetaxel alone\textsuperscript{[7]}, it was approved by the EMA for the second-line treatment of advanced and metastatic non-small cell lung cancer in 2014.

The German NIPAWILMA study analyzes the safety and efficacy of a combination of nintedanib with chemotherapy in patients with unresectable stage III or IV BRAF\textsuperscript{V600} wt cutaneous malignant melanoma. Currently, the dose-finding phase I involving 10 patients is completed revealing a well-tolerated treatment regimen. The randomized, placebo-controlled phase II analyzing nintedanib + paclitaxel vs. placebo + paclitaxel is now open for recruitment. Besides safety and efficacy parameters, one focus of the study is on translational research. To this purpose tumor tissue and serum samples of the patients taken at defined time points will be analyzed in a highly experienced central laboratory for the identification and evaluation of prognostic and predictive biomarkers in this multi-targeted approach.

References