Synopsis

Sponsor:

University Hospital Essen, Hufelandstraße 55, 45122 Essen Germany

Represented by Prof. Dr. Dirk Schadendorf

Investigational medicinal product: Opdivo®, Yervoy®

Drug substance: Nivolumab, Ipilimumab

Registration: ClinicalTrials.gov Identifier: NCT02523313

Study title:

A Phase II Randomized, Double-Blind Trial of Immunotherapy with Nivolumab or Nivolumab plus Ipilimumab versus Double-Placebo Control as a Post-Surgical/Post-Radiation Treatment for Stage IV Melanoma with No Evidence of Disease

National Coordinating Investigator:

Prof. Dr. Dirk Schadendorf, Department of Dermatology, Skin Cancer Center, Comprehensive Cancer Center Essen, Hufelandstraße 55, 45122 Essen, Germany

Study sites: 20 sites in Germany

Publication: Zimmer L et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020 May 16;395(10236):1558-1568.

First patient in: 02 September 2015 **Last patient out:** 27 June 2021	**Phase:** II

Study objective(s):

The primary objective of this trial was to estimate the efficacy of adjuvant immunotherapy with nivolumab alone or in combination with ipilimumab therapy in stage IV melanoma patients with no evidence of disease (NED), i.e., the primary endpoint was recurrence-free survival (RFS).

Secondary objectives:

- Overall survival (OS)
- Time to recurrence (TTR)
- Progression-/recurrence-free survival 2 (PRFS2) for crossover patients of arm C
- Safety/toxicity (i.e., assessment of all adverse events ≥ grade 3 according to CTCAE version 4.0 that are related to the administration of the investigational agents)

Trial design:

This was a prospective, double-blind placebo-controlled, multicenter, randomized phase II trial testing the adjuvant immunotherapy with nivolumab plus ipilimumab placebo or nivolumab plus ipilimumab versus double placebo control as a post-surgical/post-radiation treatment for stage IV melanoma with NED.

Methods:

Patients fulfilling all inclusion and exclusion criteria were enrolled and randomized (1:1:1). Nivolumab was applied as monotherapy plus ipilimumab placebo (arm A) or in combination with ipilimumab (arm B). In the control group, nivolumab placebo was applied together with ipilimumab placebo (arm C). One cycle of treatment was defined as 12 weeks. Dose modifications (reductions or escalations) were not permitted. Dose delays could be performed in case of drug-related adverse events.

Arm A - Nivolumab monotherapy plus ipilimumab placebo:

Patients received nivolumab 3 mg/kg body weight (BW) by intravenous (IV) infusion every two weeks (+ ipilimumab placebo in week 1, 4, 7 and 10 and nivolumab placebo in week 4 and 10) and thereafter as maintenance therapy every two weeks for up to one year after initial dosing or until recurrence of disease, whichever occurred first.

Arm B - Nivolumab plus ipilimumab combination:

Patients received nivolumab 1 mg/kg BW and ipilimumab 3 mg/kg BW by IV infusion every three weeks for four doses. Both study drugs were administered on the same day over the first 12 weeks (+ nivolumab placebo in week 3, 5, 9 and 11). After week 12, nivolumab was given as maintenance therapy at a dose of 3 mg/kg BW every two weeks for up to one year after initial dosing (of the combination) or until recurrence of disease, whichever occurred first.

Arm C - Double placebo control:

Patients received nivolumab placebo and ipilimumab placebo by IV infusion every three weeks for four doses. Both placebos were administered on the same day over the first 12 weeks (+ nivolumab placebo in week 3, 5, 9 and 11). After week 12, nivolumab placebo was given as maintenance therapy at a dose of 3 mg/kg BW every two weeks for up to one year after initial dosing (of the combination) or until recurrence of disease.

Upon documented recurrence of disease, patients could receive nivolumab 3 mg/kg BW monotherapy every two weeks for up to one year or until subsequent progression, whichever occurred first (cross-over option).

Number of patients (planned and analyzed): 159 patients were planned to be randomized (53 per arm); 167 patients were randomized (59 in arm A, 56 in arm B and 52 in arm C) and included in the intent-to-treat population (of 237 screened patients).

Diagnosis and key inclusion criteria:

Stage IV melanoma with NED after surgery or radiation therapy

Inclusion criteria:

1. Stage IV melanoma arising from a primary cutaneous site or metastatic from an unknown primary site with NED after surgery or radiation therapy (conducted within eight weeks before enrolment)
2. Signed written informed consent
3. Men and women, aged 18 to 80 years
4. Known BRAF status
5. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study
6. Minimum life expectancy of five years excluding their melanoma diagnosis
7. ECOG performance status of 0 or 1
8. Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L 1 expression classification (positive (≥ 5% tumor cells expressing PD-L1) or negative (< 5% tumor cells expressing PD-L1)). If an insufficient amount of tumor tissue from the resected site is provided for analysis, acquisition of additional archived tumor tissue (block and/or slides) for the biomarker analyses is required.
9. Prior radiotherapy must have been completed at least two weeks prior to study drug administration
10. Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:
    - WBC ≥ 2000/µL
    - Neutrophils ≥ 1500/µL
    - Platelets ≥ 100 x103/µL
    - Hemoglobin ≥ 9.0 g/dL
    - Serum creatinine ≤ 1.5xUL
    - Creatinine clearance (CrCl) ≥ 40mL/min if using the Cockcroft-Gault formula

Female CrCl =

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 0.85}{72 \times \text{serum creatinine [mg/dL]}}$$

Male CrCl =

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.00}{72 \times \text{serum creatinine [mg/dL]}}$$

- AST/ALT ≤ 3 x ULN
- Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who may have total bilirubin < 3.0 mg/dL)

11. Negative pregnancy test for female subjects and effective contraception (Pearl-Index < 1) for both male and female subjects if the risk of conception exists

Exclusion criteria:

1. History of primary uveal or mucosal melanoma
2. Prior therapy with CTLA4 or PD1 antibodies
3. The patient has psychiatric or addictive disorders that may compromise his/her ability to give informed consent or to comply with the trial procedures
4. Lack of availability for clinical follow-up assessments
5. Any immunosuppressive therapy given within the past 30 days prior to study drug administration (excluding physiologic steroid hormone replacement)
6. Other malignancies within the past five years requiring treatment except basal or squamous skin carcinomas or carcinoma in situ of the cervix
7. Serious cardiac, gastrointestinal, hepatic or pulmonary disease reducing life expectancy to less than five years
8. Patients with serious intercurrent illness requiring hospitalization
9. Other serious illnesses, e.g., serious infections requiring antibiotics or bleeding disorders
10. The patient is known to be positive for Human Immunodeficiency Virus (HIV) or other chronic infections (HBV, HCV) or has another confirmed or suspected immunosuppressive or immunodeficient condition
11. Known hypersensitivity reaction to any of the components of study treatment
12. Pregnancy (absence to be confirmed by ß-HCG serum test, minimum sensitivity 25 IU/L or equivalent units of HCG)) or lactation period
13. Women of childbearing potential (WOCBP): Refusal or inability to use effective means of contraception (Pearl-Index <1). WOCBP will be instructed to adhere to contraception until 31 weeks after the last dose of investigational product
14. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year (Pearl-Index < 1). Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception until 31 weeks after the last dose of investigational product
15. Known alcohol or drug abuse
16. Participation in another clinical study and use of any investigational or non-registered product (drug or vaccine) within the 30 days before registration
17. Significant disease or condition which, in the investigator's opinion, would exclude the patient from the study
18. Legal incapacity or limited legal capacity

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

Nivolumab: 100 mg/vial (packed in cartons with five vials); each ml of concentrate for solution for infusion contained 10 mg of nivolumab. Nivolumab was administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug could be diluted with 0.9% sodium chloride injection at a final concentration of at least 0.35 mg/ml. For the first 12 weeks of treatment, the nivolumab dose was 3 mg/kg BW every two weeks

in arm A, and 1 mg/kg BW every three weeks in arm B. After week 12, the nivolumab maintenance dose was 3 mg/kg every two weeks (in both arms).

Batch numbers: CLI8066 (4G79023), CLI8368 (AAD9141), CLI8368/CLI8401 (AAD9141), CLI8401 (AAD9141), CLI8496 (AAG8273), CLI8505 (AAH8854), CLI8739 (AAM0095), AAJ0125, AAK4700, AAK5719, AAK8179

Ipilimumab: 200 mg/vial (packed in boxes with four vials); each ml of concentrate for solution for infusion contained 5 mg ipilimumab. Ipilimumab was administered as a 90-minute IV infusion with a low-protein-binding in-line filter. The drug could be diluted with 0.9% sodium chloride injection or 5% dextrose injection at a final concentration of 1–4 mg/ml. The ipilimumab dose was 3 mg/kg BW every three weeks for the first 12 weeks of treatment (arm B).

Batch numbers: CLI8066 (4G82323), CLI8368 (AAD9835), CLI8854 (AAN4303), CLI8513 (AAG4174)

When both study drugs were administered on the same day, nivolumab was administered first, followed by ipilimumab.

Duration of treatment: Up to one year (patients of arm C who crossed over to nivolumab monotherapy could also receive nivolumab for up to one year)

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

N/A

First reference drug: N/A

Second reference drug: N/A

Unblinding: Upon recurrence of disease and treatment discontinuation of each patient, investigators were unblinded to each patient's treatment assignment to determine the appropriate subsequent treatment.

Efficacy evaluation: Tumor assessments using CT or MRI scans and classification of the response according to RECIST v1.1 were performed at the beginning of each treatment cycle (12-weekly).

Safety evaluation: Safety was evaluated for all treated patients, who received at least one dose of nivolumab and/or ipilimumab and/or placebo, using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://ctep.cancer.gov). Safety assessments were based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

All (S)AEs that occurred within 90 days of discontinuation of the investigational product(s) had to be reported, except in cases where a study participant had started a new anti-neoplastic therapy (after the start of a new anti-neoplastic therapy, SAEs suspected to be related to the investigational product(s) were still supposed to be reported).

With version 3.0 of the study protocol (dated 05 Sep 2019), AEs associated with the disease being studied or its relapse or progression, signs, or symptoms of the disease being studied did not meet the AE definition anymore, unless they were more severe than expected for the participant's condition.

Statistical methods: Efficacy endpoints were analyzed in the intention-to-treat (ITT) set (i.e., all randomly assigned patients) and safety in the safety (SAF) set (i.e., all patients who received at least one dose of study drug).

The following hypothesis was formulated: RFS of patients treated with nivolumab monotherapy or nivolumab combined with ipilimumab is better than that of patients treated with placebo. All other parameters were evaluated in an explorative manner.

The probability of remaining free of recurrence (i.e., RFS) or alive (i.e., OS) over time was estimated using the Kaplan-Meier method. RFS, OS and time to recurrence were compared

between each treatment group and placebo using the log-rank test. Two-sided 95% CIs were calculated for all outcomes and IQRs for medians. In addition, HRs and 97.5% CIs were calculated for the primary outcome. The trial design was not powered for a comparison between the nivolumab plus ipilimumab group versus the nivolumab group, but exploratory analyses without formal hypothesis testing were done between the nivolumab-containing groups at any point in time. HRs for disease recurrence or death for the following prespecified subgroups were estimated: age, sex, stage IV melanoma subgroups, ECOG grade, cerebral metastases, PD-L1 status, melanoma type, BRAF status, NRAS status, adjuvant therapy, prior systemic therapy (stage IV metastatic), and prior radiotherapy. Furthermore, forest plots were produced, and a test of interaction between each variable and the trial group in a Cox model was done.

Summary of results: Between 02 SEP 2015 and 20 NOV 2018, 167 (of 237 screened) patients were randomly assigned to receive nivolumab (arm A, n=59), nivolumab plus ipilimumab (arm B, n=56), or placebo (arm C, n=52) and included in the ITT set. Of these, 5 patients (3 in arm A and 1 each in arm B and C) did not receive the assigned treatment. Thus, 162 patients were included in the safety set. The final analysis was done two years after the last patient had ended treatment. The median follow-up was 49.2 months (IQR 34.9–58.1): 53.8 months (IQR 35.4–59.1) in the nivolumab group, 45.6 months (28.6–55.2) in the nivolumab plus ipilimumab group, and 50.7 months (41.6–58.1) in the placebo group.

Efficacy: In the ITT set, the 1-year RFS rates were 51.7% (95% CI 37.98–63.83) in the nivolumab group, 75.3% (61.10–84.88) in the nivolumab plus ipilimumab group, and 32.2% (19.81–45.32) in the placebo group. Two-year RFS rates were 36.9% (24.46–49.46) in the nivolumab group, 66.5% (51.58–77.81) in the nivolumab plus ipilimumab group, and 15.0% (6.68–26.56) in the placebo group. Median RFS was not yet reached in the nivolumab plus ipilimumab group, whereas it was 12.3 months (95% CI 5.30–23.85) in the nivolumab group, and 6.3 months (3.26–9.61) in the placebo group. The risk of disease recurrence was lower with nivolumab (HR 0.60, 97.5% CI 0.36–1.00; p=0.0236) or with nivolumab plus ipilimumab (HR 0.25, 97.5% CI 0.13–0.48; p<0.0001) than with placebo. The additional exploratory analysis comparing the nivolumab plus ipilimumab group versus the nivolumab group identified a HR for relapse of 0.41 (97.5% CI 0.22–0.78; p=0.0013), suggesting higher efficacy of the nivolumab plus ipilimumab regimen in the trial population.

The 6-month TTR rates were 60.7% (95% CI 46.71–72.10) in the nivolumab group, 83.6% (70.84–91.14) in the nivolumab plus ipilimumab group, and 50.9% (36.53–63.59) in the placebo group. The 12-month TTR rates were 55.2% (41.25–67.09) in the nivolumab group, 75.3% (61.10–84.88) in the nivolumab plus ipilimumab group, and 32.2% (19.81–45.32) in the placebo group. Median TTR was not yet reached in the nivolumab plus ipilimumab group, whereas it was 15.2 months (95% CI 5.30–33.26) in the nivolumab group, and 6.3 months (4.87–9.61) in the placebo group. Median PRFS2 for cross-over patients of the placebo group (n=19) was not yet reached. The risk of disease recurrence (local or distant metastasis) or melanoma-related death was lower with nivolumab (HR 0.57, 95% CI 0.36–0.90; p=0.0137) or with nivolumab plus ipilimumab (HR 0.26, 95% CI 0.15–0.45; p<0.0001) than with placebo. The comparison of both immunotherapy groups in the additional exploratory analysis identified a lower risk for the nivolumab plus ipilimumab combination (HR 0.44, 95% CI 0.25–0.77; p=0.0034) than with nivolumab alone.

The 1-year OS rates were 92.2% (95% CI 80.44–96.98) in the nivolumab group, 95.7% (84.02–98.92) in the nivolumab plus ipilimumab group, and 93.9% (82.31–98.00) in the placebo group. Two-year OS rates were 81.7% (67.81–90.07) in the nivolumab group, 91.2% (78.16–96.60) in the nivolumab plus ipilimumab group, and 87.3% (73.87–94.10) in the placebo group. Median OS was not yet reached in either of the study groups. The risk of death was lower with nivolumab plus ipilimumab (HR 0.41, 95% CI 0.17–0.99; p=0.0396) than with placebo. The HR for death for nivolumab versus placebo was 0.75 (95% CI 0.36–1.56; p=0.4423), and - according to the additional exploratory analysis - for the combination of nivolumab plus ipilimumab versus nivolumab alone 0.55 (95% CI 0.22–1.38; p=0.1969).

Tolerability: Treatment-related AEs were reported for 130 (80.2%) patients of the SAF: for 47 (83.9%) patients receiving nivolumab, for 53 (96.4%) patients receiving nivolumab plus ipilimumab, and for 30 (58.8%) patients receiving placebo. The proportion of grade 3 or 4

treatment-related AEs was higher in the nivolumab plus ipilimumab group than in the nivolumab group (70.9% vs 28.6%) or the placebo group (5.9%). No grade 5 AEs were reported. Treatment-related AEs led to discontinuation of the study treatment in 42 (25.9%) patients of the SAF: in 7 (12.5%) patients in the nivolumab group, in 34 (61.8%) patients in the nivolumab plus ipilimumab group, and in 1 (2.0%) patient in the placebo group.

Conclusion(s):

Adjuvant therapy with nivolumab alone or in combination with ipilimumab increased RFS significantly compared with placebo in patients with stage IV melanoma with NED. Moreover, the comparison of both immunotherapy groups identified higher RFS rates with the combination immunotherapy versus nivolumab alone. Although this study was not designed for a formal comparison between the two active treatment groups, the large separation of the RFS curves suggests superior RFS of the combination of nivolumab plus ipilimumab over nivolumab. Additionally, OS was markedly improved for patients receiving nivolumab plus ipilimumab compared with placebo. Use of subsequent anti-PD-1 therapy was high in placebo patients and most likely impacted the OS comparison of nivolumab alone vs placebo. The rate of grade 3–4 treatment-related AEs was also substantially higher in the combination immunotherapy group. In both active treatment groups, the rates of grade 3–4 treatment-related AEs were higher than the rates reported in previous pivotal trials done in advanced melanoma with measurable disease.

In conclusion, high toxicity but substantial efficacy of combined nivolumab plus ipilimumab treatment as adjuvant therapy for stage IV melanoma with NED suggests superior efficacy when compared with placebo and with nivolumab monotherapy, which might support a change of practice in the treatment of stage IV melanoma patients with NED.

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Amendments to the study protocol

There were three substantial amendments to the protocol with implications in the study design and statistical analysis. Respective changes included the following:

With **amendment 1** (and protocol version 1.6), the participating countries changed from Germany and Switzerland to Germany and Austria. The exclusion criterion on pregnancy (EC 12) was adapted. Absence of pregnancy had to be confirmed by ß-HCG serum instead of urine test. A serum pregnancy test was only required at baseline and no longer prior to every infusion. It was also decided that recruitment will not be stopped during the first interim analysis since no SUSAR occurred during the first year of treatment according to the first DSUR. The deliverable quantity of study drugs was changed (nivolumab: changed from ten to five vials per carton; ipilimumab: changed from five to four vials per box), and the dilution of ipilimumab was updated according to the current IB and SmPC (final concentration ranging from 1–4 mg/dl instead of from 1–2 mg/dl). The dose that was previously given for the placebos was deleted.

With **amendment 2** (and protocol version 2.0), the recruitment period was extended by three months (from 36 to 39 months), and the number of planned patients was adapted according to a new calculation based on recent findings from study CA209-238.

With **amendment 3** (and protocol version 3.0), the follow-up period was extended (after the treatment period of approx. one year, all patients are followed-up for a maximum of five years or until end of study, i.e., 24 months after end of treatment of last patient). The new assumed end of study was QIII 2021. Moreover, two more secondary objectives (TTR, PFS2/RFS2 for crossover patients of arm C) were added. AE reporting was further specified with respect to the event of the start of a new anti-neoplastic therapy as well as the AE definition (the disease being studied or its relapse or progression, signs, or symptoms of the disease being studied, unless more severe than expected for the participant's condition did not meet the AE definition anymore because recurrence/progression of melanoma is assessed as outcome data and therefore analyzed as such). Statistical methods (section 11 of the study protocol) were revised. Major changes included the following: For the primary variable, PFS was replaced by RFS as the study included patients with NED and redefined as time from randomization (instead of time from first study treatment) to time of first recurrence, new primary melanoma or death from any cause, whichever occurred first. The calculation of RFS rates at 6, 12, 18 and 24 months as well as median RFS was added. The definition of the secondary variable OS was changed from time from randomization (instead of time from first study treatment) to death. The calculation of OS rates at 12 and 24 months as well as median OS was added. The definitions of the newly added secondary objectives were added. Moreover, the definitions of the examined study populations were adapted. Statistical methods were adapted accordingly, and the analysis of efficacy was now primary based on the ITT set.