KURZPROTOKOLL
CA209401

Öffentlicher Titel	Phase IIIb Studie zu Nivolumab mit Ipilimumab als Erstlinienbehandlung bei Melanompatienten
Wissenschaftl. Titel	Clinical Trial of Nivolumab (BMS-936558) Combined With Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects With Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma CheckMate 401: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 401
Kurztitel	CA209401
Studienart	multizentrisch, prospektiv, Therapiestudie, offen/unverblindet, zweiarmig
Studienphase	Phase III
Erkrankung	Haut: Hautkrebs: Schwarzer Hautkrebs (Malignes Melanom) - Erstlinie

Einschlusskriterien

- Subjects must have signed and dated an IRB/IEC-approved written informed consent form in accordance with regulatory and local guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
- Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory tests, including completion of quality of life questionnaires and other requirements of the study.
- Subjects with histologically-confirmed unresectable stage III or stage IV melanoma as per AJCC 2010 staging system, including mucosal and ocular melanoma, regardless of BRAF mutation status
- Subjects are included if they are newly diagnosed with advanced/metastatic disease and have not received prior systemic treatment for their advanced disease. NOTE: Prior adjuvant or neoadjuvant melanoma therapy (except anti-CTLA-4, anti-PD- 1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, such as anti-CD-137) is permitted if it was completed at least 6 weeks prior to study entry, and all related AEs have either returned to baseline or stabilized.
- Although lesions measured by physical exam (calipers) can be considered measurable, at least one target lesion must be measurable disease by CT or MRI per RECIST 1.150
- Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drug
- Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 2 weeks after treatment is complete and within 6 weeks of first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Screening laboratory values must meet the following criteria and should be obtained prior to commencement of treatment: (1) White blood counts (WBC) >= 2000/L; (2) Neutrophils >=1500/L; (3) Platelets >= 100 X 10^3/L; (4) Hemoglobin >= 9.0 g/dL; (5) Creatinine serum creatinine <= 1.5 x upper limit of normal [ULN] or creatinine clearance (CrCL) > 40 mL/minute (using Cockcroft/Gault formula); (a) Female CrCl= [(140- age in years) weight in kg X 0.85) ÷ (72 x serum creatinine in mg/ dL)]; (b) Male CrCl= [(140- age in years) x weight in kg x 1.00) ÷ (72 x serum creatinine in mg/ dL)]; (6) AST <= 3 x ULN; (7) ALT <=3 x ULN; (7) Total bilirubin <= 1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)
- Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, has not been treated). If re-enrolled, the subject must be re-consented.
- Men and women, aged >=18 years

- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug
- Women must not be breastfeeding
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 5 half-lives (5 times the half-life = 125 days [nivolumab]; 5 times the half-life = 90 days [ipilimumab) plus 30 days (duration of ovulatory cycle). Because the half-life of nivolumab is longer than that of ipilimumab, subjects must agree to continue contraception for a total of 155 days or 23 weeks (nivolumab) post-treatment completion.
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the study drug (125 days nivolumab; 90 days for ipilimumab) plus 90 days (duration of sperm turnover). Because the half-life of nivolumab is longer than that of ipilimumab, subjects must agree to continue contraception for a total of 31 weeks post-treatment completion.
- Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.
- Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.
- At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below: (1) HIGHLY EFFECTIVE METHODS OF CONTRACEPTION: (a) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject’s WOCBP partner. Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods ofcontraception since they will not be receiving study drug.; (b) Nonhormonal IUDs, such as ParaGard; (c) Tubal ligation; (d) Vasectomy; (e) Complete abstinence; NOTE: Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.; (2) LESS EFFECTIVE METHODS OF CONTRACEPTION: (a) Diaphragm with spermicide; (b) Cervical cap with spermicide; (c) Vaginal sponge; (d) Male condom without spermicide; (e) Progestin only pills by WOCBP subject or male subject’s WOCBP partner; (f) Female condom; Note: A male and female condom must not be used together

Ausschlusskriterien

- Active (symptomatic) and not treated brain metastases or leptomeningeal metastases.
- Subjects who received prior therapy with an anti-CTLA-4, anti-PD-1, anti PD-L1 or anti-PD-L2, anti-CD-137 agents (or any other antibody or drug specifically targeting T -cell costimulation or checkpoint pathways) as adjuvant, neo-adjuvant, or advanced melanoma
- Subjects who are expected to require any form of systemic antineoplastic therapy while receiving study drug(s)

- Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions
- Subjects with previous malignancies (except non-melanoma skin cancer and the
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
- Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy
- All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug
- As of Amendment 02, this criterion is no longer applicable
- Any positive test result for hepatitis B virus or hepatitis C virus during screening indicating acute or chronic infection
- As of Amendment 01, this criterion is no longer applicable.
- History of severe hypersensitivity reactions to other monoclonal antibodies
- History of allergy or intolerance (unacceptable AEs) to study drug components or Polysorbate-80-containing infusions
- WOCBP who are pregnant or breastfeeding
- Women with a positive pregnancy test at enrollment or prior to administration of study medication
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Alter	18 Jahre und älter
Sponsor	Bristol-Myers Squibb
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02599402 EudraCT 2015-001274-17