KURZPROTOKOLL
ATLANTIC

Öffentlicher Titel	Phase II Studie mit dem PD-L1-Antikörper MEDI4736 bei nicht-kleinzelligem Lungenkarzinom
Wissenschaftl. Titel	Eine nicht vergleichende, offene, multizentrische, internationale Phase-II-Studie bzgl. MEDI4736 bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom (Stadium IIIB-IV),die mindestens zwei vorangegangene systemische Behandlungen, eischließlich einer Platin-basierten Chemotherapie, erhalten haben (D4191C00003).
Kurztitel	ATLANTIC
Studienart	multizentrisch, prospektiv, einarmig, einfach verblindet
Studienphase	Phase II
Erkrankung	Lunge: Lungenkrebs: Nicht kleinzelliges Lungenkarzinom (NSCLC) - Zweitlinie oder höher
Einschlusskriterien	- 1. Provision of signed, written and dated informed consent prior to any study specific procedures - 2. Male or female aged 18 years or older - 3. Patients must have EITHER - Histologically- or cytologically-documented NSCLC who present with Stage IIIB/ Stage IV disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology]), OR - Recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease) - 4. Patients must have received at least 2 prior systemic treatment regimens for treatment of NSCLC - 5. Patients must have experienced disease progression or recurrence after both a platinum-based chemotherapy regimen and at least 1 additional systemic therapy - Patients with tumours with activating EGFR TK mutations must have received an EGFR TKI and patients with tumours that are ALK fusion positive must have received an ALK TKI, given before or after the platinum-based chemotherapy regimen - Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy - platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease is considered first-line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Patients with recurrent disease >6 months must also have progressed after a subsequent platinum -based chemotherapy regimen given to treat the recurrence. - 6. Patient’s tumour sample must be PD-L1 positive (>=25% of tumour cells with membrane staining [Cohorts 1 and 2]) or PD-L1 positive with >=90% of tumour cells with membrane staining (Cohort 3): either recent or archival sample) based on central assessment. Sample requirements as follows: - A mandatory provision of a recent (3 months) tumour biopsy taken following the completion of the most recent systemic anti-cancer therapy, except if technically not feasible and after discussion with the study physician (for collection and processing procedures, refer to Section 6.6.1 and the Laboratory Manual). Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease AND - Provision of an archived tumour tissue block (or at least 10 newly cut unstained slides) where such samples exist in a quantity sufficient to allow for analysis (refer to Section 6.6.1 and the Laboratory Manual for details).

- 7. Patients must have measurable disease, at least 1 lesion, not previously irradiated,which can be accurately measured at baseline as 10 mm in the longest diameter (except lymph nodes that must have short axis 15 mm) with CT or MRI and which is suitable for accurate repeated measurements per RECIST v1.1 guidelines
- 8. Life expectancy >=12 weeks at Day 1
- 9. World Health Organisation (WHO) Performance Status of 0 or 1
- 10. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women <50 years old would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
- Women >=50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, radiation-induced oophorectomy with last menses >1 year ago, chemotherapy-induced menopause with >1 year interval since last menses, or surgical sterilisation (bilateral oophorectomy or hysterectomy11. Adequate organ and marrow function as defined below:
- Absolute neutrophil count >1.5 x 109/L (1500 per mm3)
- Platelets >100 x 109/L (100,000 per mm3)
- Haemoglobin >=9.0 g/dL (5.59 mmol/L).
- Serum creatinine CL >40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:
- Males: Creatinine CL (mL/min) = Weight (kg) x (140 – Age)/ 72 x serum creatinine (mg/dL)
- Females: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) x 0.85/ 72 x serum creatinine (mg/dL)
- Serum bilirubin <=1.5 x upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert’s syndrome (persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology) who will be allowed in consultation with their physician.
- In patients with no liver metastasis: AST and ALT <=2.5 x ULN
- In patients with liver metastasis: AST or ALT <=5 x ULN.
- Treatment through PD After completion of the first period of treatment with MEDI4736, retreatment in the next 12 months would be offered on the basis of objective RECIST 1.1. progression with or without confirmation.

- For all patients who are treated through progression (including patients who achieve disease control [ie, CR, PR, or SD] and restart treatment upon evidence of PD during follow-up) the investigator should ensure patients still meet all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to treatment. This consent document will specify that treatment beyond initial evidence of PD is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible for continuing MEDI4736.)For patients who achieve and maintain disease control through to the end of the 12-moMEDI4736 treatment period and restart treatment with MEDI4736 upon evidence of PD, with or without confirmation, during follow-up, the patient must not have received an intervening systemic anti-cancer therapy post-MEDI4736 discontinuation.
- Genetics research study (optional)
- For inclusion in the optional (DNA) genetics research study patients must fulfil the following criteria:
- Provide informed consent for the genetic sampling and analyses.
- If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

Ausschlusskriterien

- Patients should not enter the study if any of the following exclusion criteria are fulfilled:
- 1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca/MedImmune staff and/or staff at the study site)
- 2. Previous drug assignment in the present study
- 3. Participation in another clinical study with an investigational product during the last 4 weeks
- 4. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
- 5. Mixed small cell and NSCLC histology
- 6. Receipt of any investigational drug within 4 weeks prior to the first dose of MEDI4736
- 7. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolisation, monoclonal antibodies) <=21 days prior to the first dose of MEDI4736 (<=14 days prior to the first dose of MEDI4736 for patients who have received prior TKIs [eg, erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C). If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator.
- 8. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaledcorticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
- 9. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody
- 10. Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (eg, hearing loss) after consultation with the AstraZeneca/MedImmune study physician.

- 11. Any prior Grade 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- 12. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- 13. Receipt of radiation therapy within 4 weeks prior to starting MEDI4736. Limited field of radiation for palliation within 2 weeks of the first dose of study treatment is allowed, provided:
- The lung is not in the radiation field
- Irradiated lesion(s) cannot be used as target lesions.
- 14. Recent major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access) that would prevent administration of investigational product
- 15. Active or prior documented autoimmune disease within the past 2 years. NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
- 16. Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)
- 17. History of primary immunodeficiency
- 18. History of allogeneic organ transplant
- 19. History of hypersensitivity to MEDI4736 or any excipient
- 20. Brain metastases or spinal cord compression unless asymptomatic, treated and stable off steroids and anti-convulsants for at least 1 month prior to entry into the study
- 21. History of leptomeningeal carcinomatosis
- 22. Mean QT interval corrected for heart rate (QTc) 470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction
- 23. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any patient known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent
- 24. Known history of previous clinical diagnosis of tuberculosis
- 25. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving MEDI4736
- 26. History of another primary malignancy except for: Malignancy treated with curative intent and with no known active disease >=5 years before the first dose of study drug and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ.
- 27. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
- 28. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of patient safety or study results.
- 29. Absence of a tumour sample (archival and recent).

	- Genetics research study (optional) - Exclusion criteria for participation in the optional (DNA) genetics research component of the study: - Previous allogeneic bone marrow transplant - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection - Procedures for withdrawal of incorrectly enrolled patients are provided in Section 5.3.
Alter	18 Jahre und älter
Prüfzentren	**Innere Medizin 2** (Nachbeobachtung) Hämatologie / Medizinische Onkologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Allg. Ansprechpartner der Abteilung Häma/Onko
Sponsor	Astra Zeneca
Förderer	Astra Zeneca
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02087423 EudraCT 2013-005427-16