KURZPROTOKOLL
SCORES

Öffentlicher Titel	Phase Ib/II Studie zu MEDI4736 mit AZD9L50 oder AZD5069 bei rezidiviert/refraktärem oder metastasiertem Plattenepithelkarzinom an Kopf und Hals
Wissenschaftl. Titel	A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety' Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of MEDI4736 in Combination With AZD9L50 or AZD5069 in Patients With Advanced Solid Malignancies and Subsequently Comparing AZD9150 and AZD5069 Both as Monotherapy and in Combination With MEDI4736 as Second Line Treatment in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck
Kurztitel	SCORES
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, mehrarmig
Studienphase	Phase I/II
Erkrankung	Kopf-Hals: Kopf-Hals-Tumoren: Zweitlinie oder höher
Ziele	- Dose-escalation Part A: The primary objective of the dose-escalation phase is to determine the MTDs or recommended doses for dose-expansion and to determine the safety profiles of either AZD9150 or AZD5069 in combination with MEDI4736 in patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists. - Dose-expansion Part B: The primary objective of the dose-expansion phase is to evaluate the ORR of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 in the second-line treatment of patients with RM-SCCHN. - Dose-escalation Part A: - The secondary objectives of the dose-escalation phase are to: - Assess the PK of AZD9150, AZD5069, and MEDI4736 in the selected dose combinations - Determine the IM of MEDI4736 in combination with AZD9150 or AZD5069 - Determine the IM of AZD9150 in combination with MEDI4736 - Assess pharmacodynamic response in blood for AZD9150 (STAT3 knockdown) and MEDI4736 (sPD-L1) - Assess baseline circulating MDSCs and effect of treatment on circulating MDSCs - Evaluate the antitumor activity of AZD9150 or AZD5069 in combination with MEDI4736 - Dose-expansion Part B: - The secondary objectives of the dose-expansion phase are to: - Evaluate the safety and tolerability of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 - Assess secondary measures of efficacy (DCR at 2, 4, 6, and 12 months; duration of overall response [DOR], PFS, OS; and proportion of patients alive at 12 months - Assess the PK of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 - Assess the effect of food on AZD5069 PK in monotherapy - Assess the urinary PK of AZD9150 - Assess the PK of MEDI4736 in combination with AZD9150 or AZD5069 - Determine the IM of AZD9150 alone or in combination with MEDI4736 - Determine the IM of MEDI4736 in combination with AZD9150 or AZD5069 - Assess pharmacodynamic response in blood for AZD9150 (STAT3 knockdown) and MEDI4736 (sPD-L1) - Assess tumor cell pharmacodynamics (STAT3 knockdown)

- Assess baseline circulating MDSCs and effect of treatment on circulating MDSCs
- Evaluate baseline tumor PD-L1 expression for potential correlation with drug activity or the ability to prospectively identify patients likely to respond to treatment

Einschlusskriterien

- 1. The patient or legal representative (legal representative not permitted to consent in Germany) must be able to read and understand the informed consent form (ICF) and must have been willing to give written informed consent and any locally required authorisation (eg, Health Insurance Portability and Accountability Act in the USA; European Union Data Privacy Directive in the EU) before any study-specific procedures, including screening evaluations, sampling, and analyses.
- 2. For inclusion in the optional genetic research, patients must provide a separate ICF for genetic research.
- Male and female patients must be at least 18 years of age.
- Has an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1.
- Has measurable disease, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with a minimum size of 10 mm by computerised tomography (CT) scan, except lymph nodes which must have minimum short axis size of 15 mm (CT scan slice thickness no greater than 5 mm in both cases). Indicator lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented progression after therapy.
- Has undergone 3 previous regimens of cytoreductive therapies including, but not limited to, platinum-based compounds, taxanes, or 5-fluorouracil.
- Adequate organ and marrow function as defined below. Transfusions intended to elevate any parameters below solely for the intent of meeting study eligibility are not permitted. - Leukocytes 3000 mcL - Absolute neutrophil count 1500 mcL - Platelets 100 000 mcL - Haemoglobin 9 g/dL - Total bilirubin 1.5 x ULN; total bilirubin 3×ULN in patients with documented Gilbert’s Syndrome (unconjugated hyperbilirubinaemia) or in the presence of liver metastases - ALT and AST 2.5×ULN if no demonstrable liver metastases or 5×ULN in the presence of liver metastases - Creatinine within normal limits OR, for patients with levels above institutional normal: - Creatinine clearance measured by 24-hour urine collection 60 mL/min, OR Calculated corrected creatinine clearance 60 mL/min/1.73 m2 using the Cockcroft-Gault formula (Cockcroft and Gault 1976) corrected for the body surface area (see Section 8.3).
- 8. Women of childbearing potential and men who are sexually active with a female partner of childbearing potential must be surgically sterilised, practicing abstinence, or agree to use 2 birth control methods before study entry, for the duration of study participation, and for 20 weeks after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician. Women of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). Section 5.1.1 Table 10 lists the methods of contraception considered adequate; note that 2 methods must be combined. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- 9. Women of childbearing potential also may not be breast feeding and must have a negative serum or urine pregnancy test within 72 hours before the start of study treatment.

- 10. The patient or legal representative (legal representative not permitted to consent in Germany) must be willing to provide written consent for collection of formalin fixed paraffin-embedded blocks or slides from archival diagnostic histology samples, where available. Additional inclusion criteria - Dose-escalation Part A 1. Has a histological confirmation of a solid malignancy (other than HCC) that is refractory to standard therapy or for which no standard of care regimen currently exists. Additional inclusion criteria - Dose-expansion Part B For inclusion into the dose-expansion Part B of the study, each patient must fulfil all of the following criteria listed in Section 4.1.1 as well as the following conditions: 1. Has histologically and/or cytologically confirmed SCCHN that is RM and not amendable to curative therapy by surgery or radiation. Squamous cell carcinoma of the head and neck originating from the following sites is eligible: oral cavity, oropharynx, larynx, or hypopharynx. Not eligible are: - Patients with squamous cell carcinoma of any other primary anatomic location in the head and neck (eg, paranasal cavity) - Patients with squamous cell carcinoma of unknown primary - Patients with nonsquamous histologies of head and neck tumors 2. Has at least 1 SCCHN tumor lesion (TL) amenable to biopsy and must be medically fit and willing to undergo a biopsy during screening and, unless clinically contraindicated, at the end of Cycle 1. (In the event of PD, biopsies at the end of treatment are optional but encouraged.) Tumor lesions used for biopsy should not be lesions used as RECIST TLs, unless there are no other lesions suitable for biopsy. If a RECIST TL is used for biopsy, the lesion must be 2 cm in longest diameter. 3. Must have failed, refused, or has been found to be ineligible for least 1 prior platinum-based chemotherapy for RM-SCCHN. Additional inclusion criteria - Dose-expansion Part B: treatment arms B1 and B2 1. Has had prior exposure to any anti-PD-(L)1 antibody.

Ausschlusskriterien

- Spinal cord compression unless asymptomatic and not requiring steroids for at least 4 weeks before the start of study treatment. - Presently has a second malignancy other than SCCHN, or history of treatment for invasive cancer other than SCCHN in the past 3 years. Exceptions are
- 2. Presently has a second malignancy other than SCCHN, or history of treatment for invasive cancer other than SCCHN in the past 3 years. Exceptions are: - Previously treated in-situ carcinoma (ie, noninvasive) - Cervical carcinoma stage 1B or less - Noninvasive basal cell and squamous cell skin carcinoma - Radically treated prostate cancer (prostatectomy or radiotherapy) with normal prostate-specific antigen, and not requiring ongoing antiandrogen hormonal therapy
- 3. Patients must have completed any previous cancer-related treatments before enrolment. Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic, or hormonal therapy for cancer excludes the patient (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable). The following intervals between the end of the prior treatment and first dose of study drug must be observed: - Port-a-cath placement: No waiting is required. - Minor surgical procedures (as defined by the Investigator): 7 postoperative days - Major surgery (as defined by the Investigator): 4 weeks - Radiotherapy: 4 weeks - Chemotherapy: 4 weeks - Immunotherapy or investigational anticancer therapy with agents other than mAbs: 4 weeks - Immunotherapy or investigational anticancer therapy with mAbs: 6 weeks - Immunosuppressive medication: 4 weeks with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
- 4. Is still experiencing toxicity related to prior treatment and assessed as CTCAE grade >1. Exceptions are alopecia and/or anorexia. The eligibility of patients who are still experiencing irreversible toxicity that is not reasonably expected to be exacerbated by the study drugs in this study (eg, hearing loss) must be reviewed and approved by both the Principal Investigator and Medical Monitor.
- 5. Has experienced immune-related AEs (irAEs) while receiving prior immunotherapy (including anti-CTLA4 treatment) and assessed as CTCAE grade 3

- 6. Has active or prior documented autoimmune disease within the past 2 years with the exceptions of vitiligo, Grave's disease, and/or psoriasis not requiring systemic treatment
- 7. Has active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)
- 8. Has a history of primary immunodeficiency
- 9. Has undergone an organ transplant that requires use of immunosuppressive treatment
- 10. Has any of the following cardiac criteria: - Any abnormalities in rhythm, conduction or morphology of resting 12-lead ECG that in the opinion of the Investigator render the patient unsuitable for participation in the study - Mean resting corrected QT interval (QTc) calculated using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females according to local assessment and obtained from 3 ECGs within 5 minutes - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, or family history of long QT syndrome, or unexplained sudden death under 40 years of age
- 11. Is unable to take oral medications and/or has a clinical or radiological diagnosis of bowel obstruction. Patient may not have a percutaneous endoscopic gastrostomy tube and may not be receiving total parenteral nutrition.
- 12. Has a history of allergic reactions attributed to the study treatments (AZD9150, AZD5069, or MEDI4736), their compounds, or agents of similar chemical or biologic composition (eg, antibody therapeutics)
- 13. Suffers from a comorbidity that in the opinion of the Investigator renders the patient unsuitable for participation in the study. Such comorbidity may include, but is not limited to, uncontrolled intercurrent illness such as active infection, severe active peptic ulcer disease or gastritis, myocardial infarction within 6 months before entry, congestive heart failure, symptomatic congestive heart failure, active cardiomyopathy, unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension, or psychiatric illness/social situations that would limit compliance with study requirements.
- 14. As judged by the Investigator, has any evidence of severe or uncontrolled diseases such as active bleeding diatheses, or has an active viral infection for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV)
- 15. Has a known history of tuberculosis
- 16. Has a condition that, in the opinion of the Investigator, would interfere with the evaluation of the study drugs or the interpretation of patient safety or study results
- 17. Has received a live attenuated vaccine within 28 days before the first dose of study drug

- 18. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements Additional exclusion criteria - Dose-escalation Part A 1. Patients with clinically active brain metastases (known or suspected) are excluded unless the brain metastases have been previously treated and are considered stable. Stable brain metastases are defined as no change on CT scan or magnetic resonance imaging (MRI) scan for a minimum of 2 months AND no change in steroid dose for a minimum of 4 weeks, unless change due to intercurrent infection or other acute event. 2. Has had prior exposure to AZD9150, AZD5069, MEDI4736, or any other anti-PD-(L)1 antibody. Additional exclusion criteria - Dose-expansion Part B 1. Patients with brain metastases (known or suspected) are excluded. Additional exclusion criteria - Dose-expansion Part B: treatment arms B3, B4, B5, and B6 1. Has had prior exposure to AZD9150, AZD5069, MEDI4736, or any other anti-PD-(L)1 antibody. Additional exclusion criteria - Optional genetic research A patient must not be included in the optional genetic research if any of the following exclusion criteria are fulfilled. 1. Patients who have previously received an allogeneic bone marrow transplant are excluded from the optional genetic research. 2. Patients who have received nonleukocyte depleted whole blood transfusion(s) within 120 days before the date of the genetic sample collection are excluded from the optional genetic research.

Alter	18 Jahre und älter
Fallzahl	147
Sponsor	Astra Zeneca (Hauptsponsor)
Förderer	Astra Zeneca
Registrierung in anderen Studienregistern	EudraCT 2015-002525-19