TITLE PAGE

CLINICAL STUDY REPORT - SYNOPSIS

A Phase II Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab Maintenance Following First-Line Platinum Based Chemotherapy in Patients with Metastatic Squamous - Non-Small Cell Lung Cancer (sNSCLC)

Protocol Number: AIO-TRK-0115-Study

EudraCT number: 2015-001123-22

Name of Product/Test Drug/IMP:	KEYTRUDA
Phase of Development:	Phase II
Date of First Patient In:	01-MAR-2016
Date of Last Patient Out:	16-DEC-2020
Indication:	Metastatic squamous non-small cell lung cancer
Design:	Randomized, double-blind, placebo-controlled study
Sponsor:	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin, Germany Phone: +49-30-322932931 Fax: +49-30-322932926
Coordinating Investigator:	PD Dr. Martin Reck LungenClinic Grosshansdorf Wöhrendamm 80 22927 Grosshansdorf Germany
Name of Sponsor Signatory:	Ralph Keller
Date of Report (FINAL 1.0):	09-Jun-2022

This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and other applicable regulatory.

SYNOPSIS

Name of Company: AIO-Studien-gGmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Keytruda		
Name of Active Ingredient: Pembrolizumab 200 mg fixed *(MK-3475)*		

Title of Study:

A Phase II Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab Maintenance Following First-Line Platinum Based Chemotherapy in Patients with Metastatic Squamous - Non-Small Cell Lung Cancer (sNSCLC)

Eine doppelblinde, randomisierte, Placebo-kontrollierte Phase II Studie zur Untersuchung einer Erhaltungstherapie durch Pembrolizumab nach einer platinbasierten Erstlinientherapie bei Patienten mit metastasierten, nicht-kleinzelligen Plattenepithelkarzinom der Lunge

Trial sites / Investigators:

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Publication (reference):

2022 World Conference on Lung Cancer, Tracking Number: 2022-RA-1140-WCLC

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Study Dates: First Patient Treated: 10-Mar-2016 Last Patient Completed: 16-Dec-2020	**Phase of Development:** Phase II

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Objectives:

Primary Objective:

To investigate the efficacy of Pembrolizumab vs. placebo in terms of progression-free survival in patients with metastatic squamous, non-small cell lung cancer

Secondary Objectives:

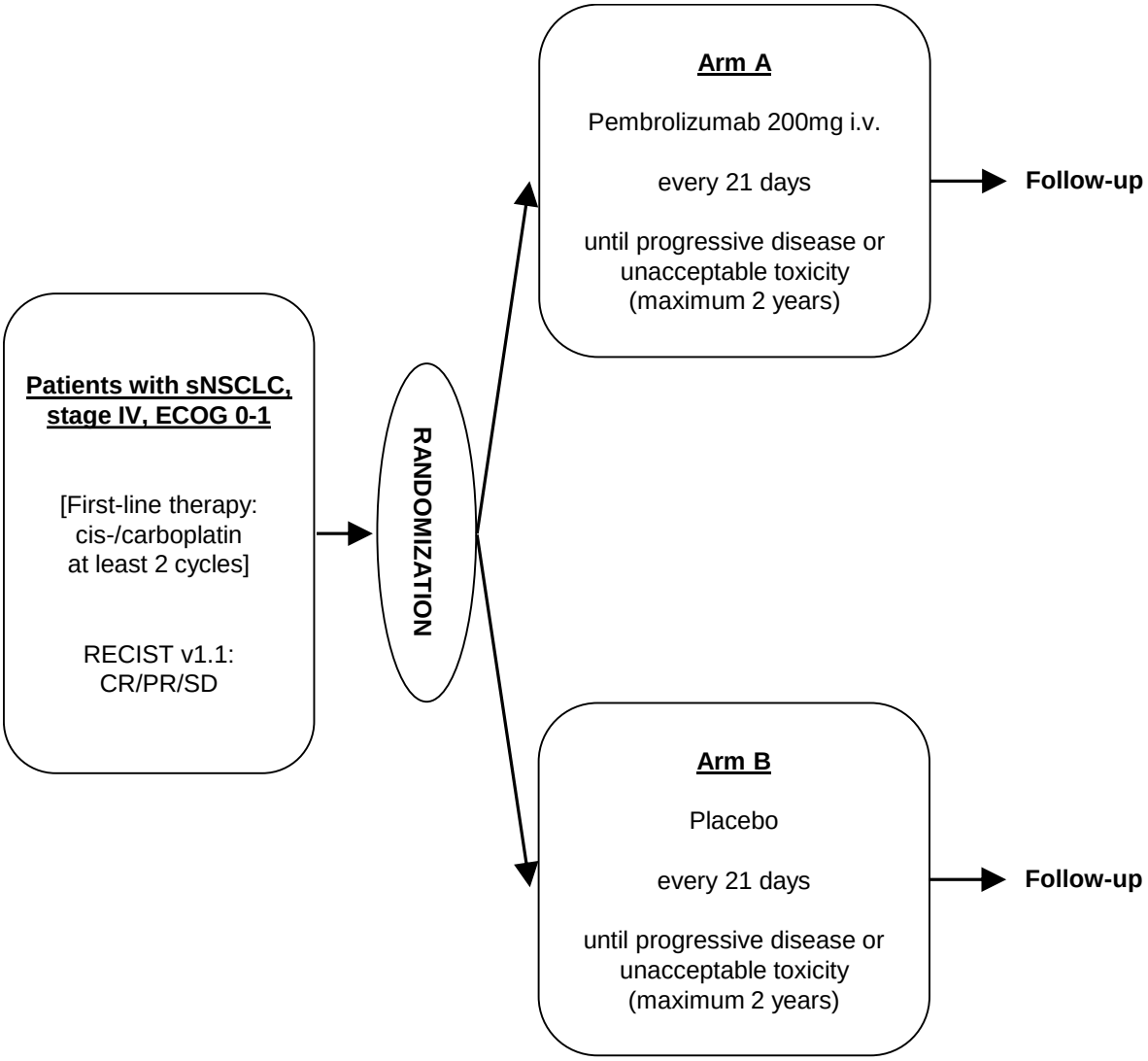
To evaluate tumor response, survival, tolerability and safety as well as quality of life of patients receiving Pembrolizumab

Methodology:

A Phase II Randomized, Double-Blind, Placebo-Controlled Study

Study Design:

Figure 1 Study Design



Planned number of patients: 65 patients per treatment arm, 130 patients total

Actual number of patients: 41 patients total (Arm A: 16 patients, Arm B: 18 patients, not randomized: 7 patients)

Analyzed: 34 patients (Arm A: 16 patients, Arm B: 18 patients)

Main Criteria for Inclusion:

1. Male or female patient, age ≥ 18 years
2. Signed informed consent
3. Ability to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations
4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
5. At least one measurable tumor lesion according to RECIST 1.1
6. Histologically or cytologically confirmed diagnosis of stage IV (AJCC Version 7) squamous non-small cell lung carcinoma
7. Complete response, partial response or stable disease after at least 2 cycles of first-line chemotherapy with cisplatin or carboplatin
8. Last administration of platinum based first-line chemotherapy ≥3 weeks and ≤ 8 weeks prior first dose of study treatment
9. Tumor specimen available for central PD-L1 testing. Tumor specimen must be a tumor block not pre-cut slides.
10. Adequate bone-marrow and organ function:
    a. Absolute neutrophil count ≥ 1.5 x 109/L and
    b. Thrombocytes ≥ 100 x 109/L and
    c. Hemoglobin ≥ 9 g/dL
    d. INR ≤ 1.5 and PTT ≤ 1.5 x upper limit during the last 7 days before therapy
    e. Bilirubin < 1.5 x ULN and
    f. AST (GOT) and ALT (GPT) < 3 x ULN (5 x ULN in case of liver metastases)
    g. Creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 45 mL/min (after first line chemotherapy)
11. In female patients of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months), a negative pregnancy test at screening
12. Female patients of childbearing potential and male patients with female partners of childbearing potential must agree to use 2 adequate barrier methods of contraception during study treatment and for 120 days after last administration of study drug.

Main Criteria for Exclusion:

1. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start. It was permissible that a patient participates in a follow-up phase of any previous study.
2. Patient received systemic steroid therapy within three days prior to the first dose of study treatment (however an upper limit 10mg prednisolone or prednisolone equivalent is acceptable) or received any other form of immunosuppressive medication
3. History of allogeneic tissue/solid organ transplant
4. History of pneumonitis or interstitial lung disease that has required oral or i.v. steroids
5. Radiotherapy of target lesion ≤ 28 days prior first dose of study treatment
6. Major surgery ≤ 28 days prior first dose of study treatment
7. Minor surgery (e.g. venous catheter) ≤ 24 hours prior first dose of study treatment
8. Cardiovascular or cerebrovascular disease of clinical relevance: e.g. acute myocardial infarction or stroke during the last 6 months, unstable angina, relevant and unstable dysrhythmia (controlled TAA allowed).
9. Severe wound healing disorders, active ulcus ventriculi/duodenal ulcer, bone fracture

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10. Known active HBV, HCV or HIV infection
11. Has any other active infection requiring systemic therapy.
12. Patients with active tuberculosis
13. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
14. Female patient pregnant or breastfeeding, or expecting to conceive or father children during the study and through 120 days after last administration of study drug
15. Indications of a neurological or other disease, which may influence the feasibility of the study or may seriously disturb tolerability
16. A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 3 days prior to the first dose of trial treatment.
17. Patient has had a prior monoclonal antibody, which does significantly interfere with the immune system or which does have a systemic therapeutic impact on the tumor within 4 weeks prior to study Day 1.
18. Patient has not recovered (i.e., ≤ Grade 1 or at baseline) from side effects due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.]
19. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
20. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome were not excluded from the study.
21. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
22. Has known hypersensitivity to pembrolizumab or any of its insipients.
23. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.

Test Product, Dose and Mode of Administration, Batch Number:

Pembrolizumab (MK-3475) was administered as an i.v. infusion with 200 mg fixed dose corresponding to 4 vials (50 mg/vial) for Arm A. Batch Number DL00020035, 6SNL82001, M049224, N011848, S010583

Duration of Treatment:

approximately 7 months

Reference Therapy, Dose, and Mode of Administration, Batch Number:

Placebo (Arm B) Normal saline was used as placebo and was administered using the same i.v. bags as for Arm A. Batch Number n.a.

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Criteria for Evaluation:

Primary:

- Progression-free survival

Secondary:

- Overall response rate
- Overall survival
- Tolerability and safety
- Quality of life (FACT-L, LCSS)

Statistical Methods:

Sample Size Estimation:

With a total number of 112 events (progressions or deaths), a log-rank test for testing superiority of progression-free survival with a 5% one-sided significance level has 80% power to reject the null-hypothesis if the true median progression-free survival times in patients treated with placebo and Pembrolizumab are 2.5 and 4 months, respectively. Assuming exponential distribution of PFS, this treatment effect translates to a treatment-specific hazard ratio of 0.625. With a recruitment rate of 7.3 patients per month and a lost-to-follow-up rate of 5% per year, the required number of events can be expected to be observed within a study duration of roughly 35 months with a maximum of 130 randomized patients.

Statistical Analysis Outline:

An observed cases approach was applied, and missing data were not imputed. A significance level of 10% two-sided (corresponding to 5% one-sided) was generally applied. Efficacy analysis was primarily evaluated within the per-protocol analysis population. PFS and OS were analyzed descriptively using the Kaplan-Meier method. Objective response rates were compared between arms using Fisher's exact test.

Adverse Events were summarized overall, by type, by term and by severity; 90% confidence intervals for event rates were calculated.

Summary of Results:

Safety Results:

A total of eight SAEs were reported from seven patients in this study. Five of these SAEs were reported from four (25%) patients of Arm A. Of these five SAEs four events reported in three patients (18.8%, CI95% 7.8%-38.8%) were related to study treatment. In Arm B three non related SAEs were reported.

Efficacy Results:

An objective response was observed in 2 (12.5%) patients of Arm A and in 3 (16.7%) patients of Arm B. The difference in objective response rate between Arm A and Arm B did not reach statistical significance.

The median OS was 24.0 months for Arm A (95%-CI 17.0-26.7) and 10.9 months for Arm B (95%-CI 5.4-39.7).

The median PFS for Arm A was 9.5 months (95% CI 2.0-19.8 months) and for Arm B was 4.8 months (95% CI 3.4-6.2 months).

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Conclusions:

Adverse event rates and response rates were comparable in both study arms, as far as this can be concluded for such small sample size. The experimental arm showed seemingly prolonged survival and PFS, although no statistically significant difference was investigated due to the small sample size.

Maintenance therapy with Pembrolizumab compared to placebo in patients with advanced squamous cell NSCLC pretreated with platinum based chemotherapy did show an enhanced clinical activity. Further confirmation of this encouraging signal would be warranted. No new safety signals were observed.

Date of Report: 09-Jun-2022