A Randomized Phase 3 Multicenter Open-label Study to Compare the Efficacy of TAK-788 as First-line Treatment Versus Platinum-Based Chemotherapy in Patients With Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54828

Source
ToetsingOnline

Brief title
TAK-788-3001

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
longkanker, Non-small cell lung cancer

Research involving

Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: sponsor

Intervention

Keyword: Non-Small Cell Lung Cancer, TAK-788

Outcome measures

Primary outcome

- To compare the efficacy of TAK-788 as first-line treatment with that of platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations, as evidenced by progression-free survival (PFS) as assessed by blinded independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

- To assess the safety and tolerability of TAK-788 in comparison with platinum-based chemotherapy.

Secondary outcome

• To compare secondary measures of clinical efficacy of TAK-788 to that of platinum-based chemotherapy, as evidenced by confirmed objective response rate (ORR), time to response, duration of response, disease control rate (DCR) per IRC and the investigator, and overall survival (OS) per the investigator.

• To compare patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of

Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module, QLQ LC13, in patients treated with TAK 788 compared with those treated with platinum-based chemotherapy.

• To collect pharmacokinetics (PK) of TAK 788 and its active metabolites, AP32960 and AP32914, to contribute to population PK and exposure-response analyses (TAK-788 group only).

Study description

Background summary

Of the 2 main histologic types of lung cancer (small cell lung cancer and non-small cell lung cancer [NSCLC]), NSCLC represents over 85% of all lung cancers. The majority of patients with NSCLC present with either locally advanced or metastatic disease, with 70% to 80% of patients presenting with potentially inoperable, later-stage disease, thereby contributing to a 5-year overall survival (OS) rate of approximately 15% to 17%. NSCLC with EGFR (Epidermal Growth Factor Receptor) exon 20 insertion mutations is a life-threatening disease involving rare mutations for which there is currently no approved or adequate therapy available, and constitutes a distinct, well-defined patient population with urgent unmet medical needs, regardless of prior treatment history. Several different EGFR TKIs (eg, erlotinib, gefitinib, afatinib, osimertinib) have been tested nonclinically and clinically with limited clinical benefit observed in patients with EGFR exon 20 insertion mutations. Given the limited treatment options, new target therapy more specifically inhibiting EGFR exon 20 insertion mutations while sparing WT EGFR inhibition will bring tremendous hope for this underserved patient population.
TAK-788 is an irreversible TKI that forms a covalent bond with cysteine 797 in EGFR, which results in increased selectivity/potency and sustained inhibition of EGFR signaling. TAK-788 was designed to address the limitations of current EGFR TKIs. It has superior potency against EGFR exon 20 insertion mutations, which has been improved using iterative, structure-guided design. It has enhanced potency for mutant EGFR over WT EGFR, which is intended to reduce dose-limiting, class-related toxicities (eg, rash and diarrhea). TAK-788 is being evaluated in 1 ongoing global phase 1/2 clinical efficacy and safety study (Study AP32788-15-101) in patients with NSCLC and multiple ongoing clinical pharmacology studies.

Study objective

Given the limited effectiveness of available EGFR TKIs in patients with NSCLC with EGFR exon 20 insertion mutations, this subset patient population is routinely treated with chemotherapy, similar to patients with no driver mutations (ie, WT EGFR). However, the benefits of the standard chemotherapy are limited with typical safety concerns related to chemotherapy treatment. TAK-788 has shown promising activity in refractory NSCLC with EGFR exon 20 insertion mutations at 160 mg QD orally in the analysis of Parts 1 and 2 (dose escalation and expansion phases) of Study AP32788-15-101 with a tolerable safety profile. The effectiveness and safety of TAK-788 as a first-line treatment in patients with NSCLC with EGFR exon 20 insertion mutations will be examined in this randomized and controlled study, in which the standard-of-care (platinum-doublet chemotherapy) will be used as the active comparator.

Study design

This study is an open-label, multicenter, phase 3, randomized, active-comparator study of TAK-788 in adult patients with NSCLC with EGFR exon 20 insertion mutations. The patient population will consist of adults diagnosed with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and who have not previously received systemic treatment for locally advanced or metastatic disease. It is expected that approximately 318 patients will be randomized in this study. Determination of EGFR mutation status for enrollment will be on the basis of a local test; confirmation of EGFR mutation status in the tumor specimen will be performed retrospectively on the basis of a central laboratory test analytically validated for the detection of EGFR exon 20 insertion mutations and will not be required for enrollment. Patients who are not centrally confirmed to have EGFR exon 20 insertion mutations may continue to receive study drug if they are receiving clinical benefit at the discretion of the investigator and with the sponsor*s approval; these patients will continue in the study and continue study assessments per the schedule of events. Once a patient has met all eligibility criteria, the patient will be randomized in a 1:1 fashion to either TAK-788 orally (N = 159) or platinum-based chemotherapy intravenously (IV) (investigator*s choice of either pemetrexed/cisplatin or pemetrexed/carboplatin) (N = 159). Patients will be stratified by the presence of CNS metastases at baseline (yes vs no) and race (Asian vs non-Asian). Each treatment cycle is defined as 3 weeks (21 days). For the TAK-788 group (Arm A), TAK-788 will be administered at 160 mg orally QD. Patients will continue to be treated with TAK-788 until they experience PD as assessed by the IRC, intolerable toxicity, or another discontinuation criterion. Treatment with TAK-788 may be continued after PD, at the discretion of the investigator and with the sponsor*s approval, if there is still evidence of clinical benefit. For the chemotherapy group (Arm B), platinum-based chemotherapy will be administered IV on Day 1 of each cycle, followed by a rest period of 20 days. Pemetrexed/cisplatin or pemetrexed/carboplatin will be repeated every 3 weeks for 4 cycles followed by maintenance treatment with pemetrexed on Day 1 of each 21-day cycle thereafter. Treatment will continue until PD, as assessed by the IRC, intolerable toxicity,

or another discontinuation criterion. Treatment with chemotherapy may be continued after PD, at the discretion of the investigator and with the sponsor*s approval, if there is still evidence of clinical benefit. At the discretion of the investigator with the sponsor*s approval, patients in the chemotherapy group may cross over to treatment with TAK-788 after IRC-assessed PD is documented and crossover eligibility criteria (Section 8.1.2.1) are met. All patients who cross over to TAK-788 must have a washout period of at least 7 days between treatments and will start TAK-788 within 28 days after IRC-assessed PD.
Patients who permanently discontinue study drug without IRC-assessed PD will continue efficacy assessments in the posttreatment follow-up phase. The posttreatment follow-up phase will continue until IRC-assessed PD, start of new anticancer therapy, withdrawal of consent for further disease assessments, loss to follow-up, death, pregnancy, or study termination by the sponsor. After the posttreatment follow-up phase, patients may either cross over to TAK-788 (if originally randomized to the chemotherapy group, IRC-assessed PD is documented, and crossover eligibility criteria are met) or enter the survival follow-up phase. Patients who discontinue study drug will enter either the posttreatment follow-up phase (if patient discontinued without IRC-assessed PD) to continue efficacy assessments or the survival follow-up phase to be followed for survival; subsequent anticancer therapy; subsequent disease assessment outcome until the first disease progression on a subsequent anticancer therapy; and patient-reported health status (EQ-5D-5L) until death, loss to follow-up, withdrawal of consent for survival follow-up, or the end of the study.
Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] with contrast, unless contrast media is contraindicated) will be employed to assess the status of the patient*s underlying disease. Laboratory values, vital signs, electrocardiograms (ECGs), and AEs will be obtained to evaluate the safety and tolerability of study drug. AEs will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective 27 November 2017 [34]. Blood samples for PK of TAK-788 and its active metabolites, including, but not limited to, AP32960 and AP32914, will be collected at prespecified time points for patients in the TAK-788 group as described in the schedule of events (Appendix A). Tumor tissue harvested either from the primary or a metastatic site and blood samples will be obtained for central confirmation of EGFR mutation status and/or for molecular profiling and exploratory biomarker studies as described in the schedule of events (Appendix A). PROs will be collected by administering paper questionnaires or questionnaires via an interactive voice response system or other electronic method (Section 9.4.8) at prespecified time points according to the schedule of events (Appendix A).

Intervention

TAK-788 group (Arm A): TAK-788 160 mg QD with or without a low-fat meal
Chemotherapy group (Arm B): Investigator*s choice of either:
• Pemetrexed/cisplatin: pemetrexed (500 mg/m2) plus cisplatin (75 mg/m2), on

Day 1 of a 21-day cycle.
• Pemetrexed/carboplatin: pemetrexed (500 mg/m2) plus carboplatin, at a dose calculated to produce an area under the curve (AUC) of 5 mg·min/mL, on Day 1 of a 21-day cycle. The same calculated AUC should be used for all carboplatin doses.
Pemetrexed/cisplatin or pemetrexed/carboplatin will be repeated every 3 weeks for 4 cycles then followed by maintenance treatment with pemetrexed (500 mg/m2), on Day 1 of a 21-day cycle thereafter.

Study burden and risks

Clinical investigation of the potential benefit of TAK-788 is ongoing through a comprehensive and global development plan that involves Study AP32788-15-101 (see Section 4.1.3.2). The current investigator*s brochure describes the known safety profile of TAK-788. The known safety profile indicates that the types of adverse events (AEs) reported with TAK-788 are generally manageable and reversible. While some of these potential toxicities may be serious, they can be managed by clinical monitoring and standard medical intervention or dose modifications. Overall, the benefit-risk assessment for TAK-788 based on the available experience is expected to be favorable.

Contacts

Public
Millenium Pharmaceuticals

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Scientific
Millenium Pharmaceuticals

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Male or female adult patients (aged 18 years or older, or as defined per local regulations).
• Histologically or cytologically confirmed nonsquamous cell locally advanced not suitable for definitive therapy, recurrent, or metastatic (Stage IV) NSCLC.
• A documented EGFR in-frame exon 20 insertion mutation sometimes referred to as duplication (including A763_Y764insFQEA, V769_D770insASV [ASV duplication], D770_N771insNPG, D770_N771insSVD [SVD duplication], H773_V774insNPH [NPH duplication], or any other in-frame exon 20 insertion mutation) assessed by a Clinical Laboratory Improvements Amendment-certified (United States [US] sites) or an accredited (outside of the US) local laboratory. The local molecular testing reports may be required by the sponsor to confirm the exon 20 insertion mutation status. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations except EGFR mutations for which there are approved EGFR tyrosine kinase inhibitors (ie, exon 19 del, L858R, T790M, L861Q, G719X, or S768I, where X is any other amino acid).
• Adequate tumor tissue available, either from primary or metastatic sites, for central laboratory confirmation of EGFR in-frame exon 20 insertion mutation. Note: confirmation of central test positivity is not required before randomization.
• At least 1 measurable lesion per RECIST version 1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy.
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
• Adequate organ and hematologic function, as determined by the following:
-- Blood transfusions are permitted with a recommended >=14-day washout period before blood samples are obtained for Cycle 1 Day 1 laboratory evaluations. This washout period may be shortened if deemed medically necessary by the principal investigator (but it must not be <7 days).
- Alanine aminotransferase/aspartate aminotransferase <=2.5 times the upper limit of the normal range (ULN; <=5 times the ULN is acceptable if liver metastases are present).
- Total serum bilirubin <=1.5 times the ULN (<=3.0 times the ULN for patients with Gilbert syndrome or if liver metastases are present).
- Estimated creatinine clearance >=45 mL/min (calculated by using the Cockcroft-Gault equation).
- Serum albumin >=2 g/dL.
- Serum lipase <=1.5 times the ULN.

- Serum amylase <=1.5 times the ULN unless the increased serum amylase is due to salivary isoenzymes.
- Absolute neutrophil count >=1500/µL.
- Platelets >=100,000/µL.
- Hemoglobin >=9 g/dL.
- Serum electrolytes within normal ranges (ie, calcium, magnesium, potassium, and sodium) based on local laboratory testing.

Exclusion criteria

• Received prior systemic treatment for locally advanced or metastatic disease (with the exception below):
Neoadjuvant or adjuvant chemotherapy/immune therapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >6 months before the development of metastatic disease.
• Received radiotherapy <=14 days before randomization or has not recovered from radiotherapy-related toxicities. Palliative radiation administered outside the chest and brain, stereotactic radiosurgery, and stereotactic body radiotherapy are allowed up to 7 days before randomization.
• Received a moderate or strong cytochrome P450 (CYP)3A inhibitor or moderate or strong CYP3A inducer within 10 days before randomization.
• Had major surgery within 28 days before randomization. Minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed.
• Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated nonmelanoma skin cancer or cervical cancer in situ; definitively treated nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
• Have known active brain metastases (have either previously untreated intracranial central nervous system [CNS] metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before randomization and have no evidence of new or enlarging brain metastases.
• Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
• Currently being treated with medications known to be associated with the development of torsades de pointes.
• Currently have or have had a history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.
• Have an ongoing or active infection including, but not limited to, the requirement for intravenous antibiotics, or a known history of HIV. Testing for

HIV is not required in the absence of history.
Note: Hepatitis B surface antigen-positive patients are allowed to enroll if hepatitis B virus DNA is below 1000 copies/mL in the plasma. Patients who are positive for anti-hepatitis C virus antibody can be enrolled but must not have detectable hepatitis C virus RNA in the plasma.
• Received a live vaccine within 4 weeks before randomization per SmPCs for pemetrexed, cisplatin,and carboplatin.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin-Losung-Ribosepharm
Generic name:	Cisplatin

Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ribocarbo
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TAK-788
Generic name:	TAK-788

Ethics review

Approved WMO Date:	14-01-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-04-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-001845-42-NL
CCMO	NL72252.028.19
Other	WHO UTN: U1111-1232-6059