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(71) Applicants: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US). **MEDIMMUNE LIMITED** [GB/GB]; Milstein Building, Granta Park Cambridgeshire CB21 6GH (GB).

(72) Inventors: **CHAO, Bo Hua**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **LEE, Sang Min**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(74) Agent: **GARCIA, Carlos A.** et al.; ELI LILLY AND COMPANY, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

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(54) Title: COMBINATIONS OF EGFR INHIBITORS AND ANTI-HUMAN VEGFR-2 ANTIBODIES

(57) Abstract: The present invention relates to a combination of anti-human VEGFR-2 antibodies and human EGFR tyrosine kinase inhibitors for the treatment of T790M-positive EGFR-mutant non-small cell lung cancer.

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COMBINATIONS OF EGFR INHIBITORS AND ANTI-HUMAN VEGFR-2 ANTIBODIES

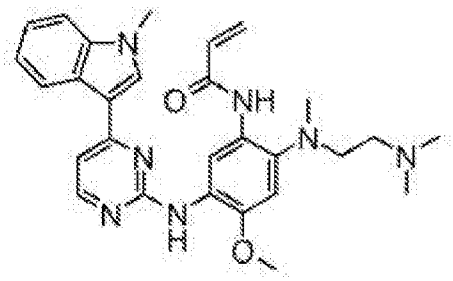
The present invention relates to a combination of anti-human VEGFR-2 antibodies and EGFR tyrosine kinase inhibitors for the treatment of T790M-positive EGFR-mutant non-small cell lung cancer.

Epidermal growth factor receptor (EGFR) tyrosine kinse inhibitors (TKIs) typically prolong the progression-free survival of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors display activating mutation(s) in the EGFR gene. However, many such patients eventually develop resistance to EGFR TKIs after treatment. One important mechanism of acquired resistance is the T790M EGFR mutation in exon 20 of the EGFR gene. This acquired resistance has led to the development of further TKIs such as osimertinib. Osimertinib 80-mg once-daily table has been approved in the United States and the European Union for the treatment of patients with metastic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy. However, some tumours may develop further resistance and thus a need exists for additional treatments for overcoming these resistance mechanisms.

The first generation TKI, erlotinib, in combination with bevacizumab has been shown to improve progression free survival, but not overall survival, in patients who have previously received a first-line chemotherapy regimen for the treatment of NSCLC (Johnson, B.E., et al., *Journal of Clinical Oncology* 2013; 31 (31): 3926-3934). RELAY, a Phase 3 randomized study of erlotinib with or without ramucirumab as first-line therapy for patients with EGFR-mutant NSCLC is also ongoing (NCT02411448).

The inventions described herein derive, in part, from Study I4T-MC-JVDL, an open-label, multicenter Phase 1 study with expansion cohorts to evaluate the safety and preliminary efficacy of ramucirumab in combination with osimertinib.

Osimertinib is a third-generation EGFR inhibitor with selectivity against certain mutant forms of EGFR. Osimertinib may be useful for the treatment of cancers which are, or have become, resistant to treatment with the EGFR inhibitors: gefinitib, erlotinib, and/or afatinib. Osimertinib has the structure:



and may be known by the chemical name: *N*-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(l-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide. Osimertinib and pharmaceutically acceptable salts thereof are disclosed in WO2013/014448. A non-limiting example of a pharmaceutically acceptable salt of osimertinib is a mesylate salt. A non-limiting example of osimertinib is TAGRISSO®.

Ramucirumab is an anti-human VEGFR-2 antibody produced in mammalian cells, wherein the antibody comprises two light chains, each of the light chains having the amino acid sequence of SEQ ID NO: 3, and two heavy chains, each of the heavy chains having the amino acid sequence of SEQ ID NO: 4. The light chain variable region of ramucirumab is that given in SEQ ID NO: 1. The heavy chain variable region of ramucirumab is that given in SEQ ID NO: 2. A non-limiting example of ramucirumab is CYRAMZA®. Ramucirumab is a human IgG1 monoclonal antibody directed against human vascular endothelial growth factor receptor 2 (VEGFR-2). Ramucirumab and methods of making and using ramucirumab are disclosed in WO2003/075840.

As used herein, the term "human VEGFR-2" refers to Human Vascular Endothelial Growth Factor Receptor 2, having the amino acid sequence of SEQ ID NO: 5. VEGFR-2 is also known as KDR.

As used herein, the term "human EGFR" refers to human epidermal growth factor receptor.

As used herein, "about" means a deviation from a given value by no more or less than 10%, by weight. As a non-limiting example, "about 100 mg" denotes a range from 90 mg (inclusive) to 110 mg (inclusive).

The term "antibody" as used herein refers to a polypetide complex having two heavy chains (HC) and two lights chains (LC) such that the heavy chains and light chains are interconnected by disulfide bonds; wherein the antibody is an IgG subclass antibody.

As used herein, the term "light chain variable region" or "LCVR" refers to a portion of a light chain of an antibody molecule that includes the amino acid sequences of the complementarity-determining regions ("CDRs") and framework regions (FRs).

As used herein, the term "heavy chain variable region" or "HCVR" refers to a portion of a heavy chain of an antibody molecule that includes the amino acid sequences of the CDRs and FRs.

As used herein, the terms "treating," "treat," or "treatment" refer to restraining, slowing, lessening, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease, or ameliorating clinical symptoms of a condition. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of the extent of a disease or disorder, stabilization of a disease or disorder (i.e., where the disease or disorder does not worsen), delay or slowing of the progression of a disease or disorder, amelioration or palliation of the disease or disorder, and remission (whether partial or total) of the disease or disorder, whether detectable or undetectable. Treatment can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the disease. In some examples, the present invention can be used as a medicament.

As used herein, the term "patient" refers to a mammal, preferably a human.

As used herein, the term "cancer" refers to or describes the physiological condition in patients that is typically characterized by unregulated cellular proliferation. Included in this definition are benign and malignant cancers.

Currently approved tests for EGFR T790M-positive NSCLC that are currently recommended for the use of osimertinib include those listed below. In the US, as approved by the Food and Drug Administration, the cobas® *EGFR* Mutation Test Version 2 is a real-time polymerase chain reaction test for the qualitative detection of defined mutations of the *EGFR* gene in DNA derived from formalin-fixed paraffin-embedded tumor tissue from NSCLC patients. The test is intended to aid in identifying patients with NSCLC whose tumors have defined *EGFR* mutations and for whom safety and efficacy of a drug have been established as follows: (a) Tarceva® (erlotinib) - Exon 19 deletions and L858R mutations and (b) Tagrisso® (osimertinib) - T790M mutations.

In the EU, according to the currently approved Summary of Product Characteristics (SmPC) for osimertinib as a treatment for locally advanced or metastatic NSCLC, a validated test is recommended to determine *EGFR* T790M mutation status. As indicated in the SmPC, the mutation status should be tested using either tumor DNA derived from a tissue sample or circulating tumor DNA (ctDNA) obtained from a plasma sample. Only robust, reliable, and sensitive tests with demonstrated utility for the determination of T790M mutation status of tumor-derived DNA (from a tissue or a plasma sample) should be used. Positive determination of T790M mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with osimertinib. If a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

The presence of the EGFR activating mutations such as the deletion of exon 19 and the L858R mutation in exon 21 can be determined by known methods, a non-limiting example of which is the cobas® EGFR Mutation Test v2 (Roche Molecular Diagnostics).

The study population for Study I4T-MC-JVDL is as follows. Patients are eligible to be included in the study only if they meet all of the following criteria: [1] Have a diagnosis of NSCLC with at least 1 measurable lesion assessable using standard techniques by the Response Evaluation Criteria In Solid Tumors Version 1.1 (Eisenhauer, E.A. et al., *Eur. J. Cancer*: 2009; 45(2): 228-247); [2] Have locally advanced or metastatic NSCLC not amenable to curative therapy; [3] Have lung cancer with documented evidence of one of the 2 common *EGFR* mutations known to be associated with *EGFR* TKI sensitivity (Ex19del, L858R); [4] Have disease progression immediately following first-line *EGFR* TKI treatment (with disease control as the best response to the first-line *EGFR* TKI treatment) regardless of prior chemotherapy; [5] Have T790M-positive status using a test validated and performed locally after disease progression on *EGFR* TKI treatment; [6] Tumor tissue from a biopsy taken after disease progression on the most recent *EGFR* TKI treatment is required. Patients for whom newly obtained samples cannot be obtained (for example, inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor; [7] Have Eastern Cooperative Oncology Group Performance Status of 0 or 1 at the time of enrollment (Oken, M.M. et al., *Am. J. Clin. Oncol.* 1982; 5:649-655); [8] Have provided signed

informed consent and are amenable to compliance with protocol schedules and testing; [9] Have serum albumin that is ≥25 g/L at the time of enrollment; [10] Have urinary protein that is <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <2 g of protein in 24 hours to allow participation in the study; [11] Have adequate organ function with all screening labs performed within 7 days of treatment initiation; [12] Be at least 18 years old at the time of signing informed consent; [13] Have a life expectancy of ≥3 months; [14] Have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 by NCI CTCAE Version 4.0; [15] For male patients, are sterile (including vasectomy confirmed by postvasectomy semen analysis) or agree to use a highly effective method of contraception, and to not donate sperm starting with the first dose of study therapy, during the study, and for at least 6 months following the last dose of study therapy or country requirements, whichever is longer; [16] For female patients, are surgically sterile, postmenopausal, or agree to use a highly effective method of contraception during the study, and for 6 months following the last dose of study treatment or country requirements, whichever is longer; [17] For female patients and of child-bearing potential, must have a negative serum or urine pregnancy test within 7 days prior to enrollment, and should not be breast feeding.

For the Study I4T-MC-JVDL, paitents will be excluded from the study if they meet any of the following criteria: [18] Previous treatment with an *EGFR* mAb (except for past treatment for squamous cell carcinoma of head and neck or mCRC); [19] Previous treatment with an *EGFR* TKI (for example, erlotinib or gefitinib) within 8 days or approximately 5x half-life, whichever is longer, of the first dose of study treatment (If sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration and time to reversibility of drug-related AEs could be agreed upon by the Sponsor and the investigator); [20] Previous treatment with osimertinib or other third-generation *EGFR* TKIs; [21] Patients with symptomatic or growing brain metastases less than 4 weeks prior to enrollment. Patients with asymptomatic and stable brain metastases, such as those who have completed radiotherapy for brain metastases at least 4 weeks prior to receiving treatment and

requiring no steroids or anticonvulsants for at least 2 weeks prior to receiving treatment, are eligible; [22] Have a serious concomitant illness or medical condition(s) including, but not limited to, the following: Active infection including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection (screening for chronic conditions is not required), active or uncontrolled clinically serious infection, active substance abuse disorders, history of drug-induced interstitial lung disease (ILD), ILD, or radiation pneumonitis requiring treatment with steroid prior to study enrollment, or any evidence of clinically active ILD, known allergy or hypersensitivity reaction to any of the treatment components; [23] Have history of another malignancy in 3 years, EXCEPT: adequately treated nonmelanomatous skin cancer, curatively treated cervical carcinoma in situ, other noninvasive carcinoma or in situ neoplasm, or prostate cancer that is not expected to impact patient survival; [24] Have a significant bleeding disorder or vasculitis or had a Grade ≥3 bleeding episode within 12 weeks prior to enrollment. Patients with a history of gross hemoptysis (defined as bright red blood of ≥1/2 teaspoon) within 2 month prior to enrollment are excluded; [25] Have experienced any arterial thrombotic event or arterial thromboembolic event, including myocardial infarction, unstable angina (history or evidence of current clinically relevant coronary artery disease of current ≥Class III as defined by Canadian Cardiovascular Society Angina Grading Scale or congestive heart failure of current ≥Class III as defined by the New York Heart Association), cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment; [26] Have a history of deep vein thrombosis, pulmonary embolism, or any other significant venous thromboembolism (venous catheter thrombosis or superficial venous thrombosis not considered “significant”) during the 3 months prior to study enrollment. Patients with venous thromboembolism occurring 3 to 6 months prior to study enrollment are allowed, if being treated with low molecular weight heparin; [27] Have a history of GI perforation and/or fistula within 6 months prior to Enrollment; [28] Have a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn’s disease, ulcerative colitis, or chronic diarrhea; [29] Have uncontrolled hypertension, as defined in CTCAE Version 4.0, prior to initiating study treatment, despite antihypertensive intervention. CTCAE Version 4.0 defines uncontrolled

hypertension as Grade >2 hypertension; clinically, the patient continues to experience elevated blood pressure (systolic >160 mmHg and/or diastolic >100 mmHg) despite medications; [30] Are receiving chronic therapy with any of the following medications within 7 days prior to enrollment: a. nonsteroidal anti-inflammatory agents (NSAIDs; such as indomethacin, ibuprofen, naproxen, or similar agents) b. other antiplatelet agents (such as clopidogrel, ticlopidine, dipyridamole, or anagrelide) Aspirin use at doses up to 325 mg/day is permitted; [31] Have had a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment; [32] Have an elective or a planned major surgery during the course of the trial; [33] Have undergone major surgery within 28 days prior to enrollment, or minor surgical procedure such as central venous access device placement within 7 days prior to enrollment; [34] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study (except in the setting of *EGFR* TKI as detailed above). Patients participating in surveys or observational studies are eligible to participate in this study; [35] Are pregnant, or breastfeeding [36] Have radiologically documented evidence of major blood vessel invasion or encasement by cancer; [37] Have radiographic evidence of pulmonary intratumor cavitation, regardless of tumor histology; [38] Are receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemoembolization, or targeted therapy or radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks prior to enrollment (except in the setting of *EGFR* TKI as detailed above); [39] Are currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inducers of CYP3A4; [40] Have any of the following cardiac abnormal findings: Mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTc value, any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG; for example, complete left bundle branch block, third-degree heart block, or second-degree heart block, any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history

of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval, have a history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest; [41] Have undergone chest irradiation within 2 weeks prior to study drug administration, have not recovered from all radiation-related toxicities, or requires corticosteroids. A 2-week washout is permitted for focal palliative radiation to non-central nervous system disease; [42] Have refractory nausea and vomiting, inability to swallow the formulated product, or previous significant bowel resection that would preclude absorption; [43] Have any other serious uncontrolled medical disorders or psychological conditions that would, in the opinion of the investigator, limit the patient's ability to complete the study or sign an informed consent document; [44] Have liver cirrhosis at a level of Child-Pugh B (or worse) or liver cirrhosis (any degree) and a history of hepatic encephalopathy or clinical meaningful ascites resulting from cirrhosis.

Ramucirumab and osimertinib will be administered as follows. Ramucirumab may be be administered at a dose of 10 mg/kg via intravenous administration over 60 minutes on Day 1 of a two-week cycle in combination with 80 mg of osimertinib administered once daily. A patient may continue to receive ramucirumab in combination with osimertinib at the assigned dose level until he/she meets one or more of the specified reasons for discontinuation such as the observation of a dose-limiting toxicity.

The ramucirumab dose may be delayed and/or reduced to 8 mg/kg if the patient experiences an adverse event. Doses may be delayed to allow time for the patient to recover from the event. Certain adverse events require immediate and permanent discontinuation of study treatment. If administration of ramucirumab is delayed for more than 4 weeks (2 cycles) after Day 1 of the most recent treatment cycle, the patient should be discontinued from ramucirumab treatment. Any patient who requires a dose reduction to less than 6 mg/kg of ramucirumab will have ramucirumab discontinued. Such patients may continue with osimertinib as a single agent.

ORR (objective response rate) and DCR (disease control rate) (according to RECIST 1.1), and the corresponding confidence intervals, will be provided for each

cohort, respectively. Time-to-event variables, such as time to response, DOR (duration of response), PFS (progression free survival), and OS (overall survival), will be estimated by Kaplan-Meier methodology for each cohort, respectively. Presentations of efficacy may include patients enrolled in the Dose-Finding Portion with the same treatment schedule. All patients who receive at least 1 dose of ramucirumab or osimertinib will be evaluated for safety and toxicity. Adverse event (AE) terms and severity grades will be assigned by the investigator using CTCAE Version 4.0. Safety analyses will include summaries of the following: (a) DLTs: the number of patients who experienced any DLTs during DLT observation period will be summarized by dose schedule in the Dose-Finding Portion for each arm; (b) AEs, including severity and possible relationship to study drug; c) AEs by Medical Dictionary for Regulatory Activities® System Organ Class (SOC) by decreasing frequency of Preferred Term within SOC; (d) Laboratory and nonlaboratory AEs by CTCAE term and maximum CTCAE grade (regardless of causality and at least possibly related to study treatment).

The objective response rate (ORR) is the proportion of enrolled patients who have received any amount of either study drug, have at least 1 postbaseline tumor image, and achieve a best overall response of complete response (CR) or partial response (PR).

Duration of response (DOR) is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

Disease Control Rate (DCR) is defined as the proportion of enrolled patients who have a best overall response of CR, PR, or stable disease. Progression-free survival (PFS) is defined as the time from the date of first study treatment until the date of the first observed radiographically documented PD or death due to any cause, whichever is earlier. The censoring is taken in the following order: - if a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,- if a patient is not known to have died or have

objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date. ORR, DOR, DCR, and PFS will be assessed based on RECIST 1.1 (Eisenhauer, E.A. et al., *Eur. J. Cancer*: 2009; 45(2): 228-247).

Overall survival (OS), including 1- and 2- year survival rates, is determined from the date of first study treatment until death due to any cause. If the patient was alive at the data inclusion cutoff date for the analysis (or was lost to follow-up), OS will be censored on the last date the patient was known to be alive.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the heavy chain has the amino acid sequence of SEQ ID NO: 4 and the light chain has the amino acid sequence of SEQ ID NO: 3.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a

pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the antibody is administered by intravenous administration.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the patient has previously received treatment with gefitinib, erlotinib, or afatinib prior to receiving the antibody.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and a L858R mutation in exon 21.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of 6 mg/kg to 10 mg/k on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering

to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of 6 mg/kg to 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 8 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 8 mg/kg to 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg on day 1 of a 14 day cycle, combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

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to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of 6 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 8 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of 8 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of 10 mg/kg

on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of 80 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6

mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of 40 mg.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the patient is administered a mesylate salt of osimertinib.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; optionally, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 8 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; optionally, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 8 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 80 mg; optionally, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of 80 mg; wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.

The present disclosure provides a method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 in combination with osimertinib or a pharmaceutically acceptable salt thereof, wherein the cancer has metastasized to the central nervous system.

The present disclosure provides a method of treating metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab in combination with osimertinib or a pharmaceutically acceptable salt thereof; wherein the cancer has metastasized to the central nervous system.

The present disclosure provides a method of treating metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab in combination with osimertinib or a pharmaceutically acceptable salt thereof; wherein the cancer has metastasized to the central nervous system, wherein ramucirumab is administered at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle.

The present disclosure provides a method of treating metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab in combination with osimertinib or a pharmaceutically acceptable salt thereof; wherein the cancer has metastasized to the central nervous system, wherein osimertinib or a pharmaceutically acceptable salt thereof is administered orally at a daily dose of about 40 mg to about 80 mg.

The present disclosure provides an anti-human VEGFR-2 (SEQ ID NO: 5) antibody for use in simultaneous, separate, or sequential combination with osimertinib or a pharmaceutically acceptable salt thereof in the treatment of patients with metastatic EGFR T790M-positive non-small cell lung cancer.

The present disclosure provides an anti-human VEGFR-2 (SEQ ID NO: 5) antibody for use in simultaneous, separate, or sequential combination with osimertinib or a pharmaceutically acceptable salt thereof in the treatment of patients with metastatic EGFR T790M-positive non-small cell lung cancer; wherein the antibody comprises a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1; wherein the cancer has metastasized to the central nervous system, alternatively wherein the antibody is ramucirumab.

The present disclosure provides the use of an anti-human VEGFR2 (SEQ ID NO:5) antibody for the manufacture of a medicament for the treatment of metastatic EGFR T790M-positive non-small cell lung cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with osimertinib or a pharmaceutically acceptable salt; wherein the cancer has metastasized to the central nervous system.

The present disclosure provides the use of an anti-human VEGFR2 (SEQ ID NO:5) antibody for the manufacture of a medicament for the treatment of metastatic EGFR T790M-positive non-small cell lung cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with osimertinib or a pharmaceutically acceptable salt; wherein the cancer has metastasized to the central nervous system; wherein the antibody comprises a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1; wherein the cancer has metastasized to the central nervous system, alternatively wherein the antibody is ramucirumab.

In some embodiments of the invention, the patient has received treatment with gefitinib, erlotinib, or afatinib prior to receiving the antibody. In some embodiments of the invention, the cancer further comprises at least one additional EGFR activating

mutation selected from the group consisting of a deletion of exon 19 and a L858R mutation in exon 21. In some embodiments of the invention, the patient is administered 6 mg/kg to 10 mg/kg of the antibody. In some embodiments of the invention, the patient is administered 8 mg/kg to 10 mg/kg of the antibody. In some embodiments of the invention, the patient is administered 6 mg/kg of the antibody. In some embodiments of the invention, the patient is administered 8 mg/kg of the antibody. In some embodiments of the invention, the patient is administered 10 mg/kg of the antibody. In some embodiments of the invention, the patient is administered 80 mg of osimertinib or a pharmaceutically acceptable salt thereof. In some embodiments of the invention, the patient is administered 40 mg of osimertinib or a pharmaceutically acceptable salt thereof. In some embodiments of the invention, the patient is administered a mesylate salt of osimertinib.

In embodiments that refer to a method of treatment as described herein, such embodiments are also further embodiments provided for the corresponding combination of anti-human VEGFR2 antibodies such as ramucirumab in combination with osimertinib and pharmaceutically acceptable salts thereof, for use in that treatment, or alternatively for the use of the combination for the manufacture of a medicament for use in that treatment.

STUDY RESULTS

Eligible patients with advanced EGFR T790M-positive NSCLC and naïve to third-generation EGFR TKIs who progressed after EGFR TKI therapy were enrolled. In the dose-finding portion, following a dose de-escalation design, patients received daily oral osimertinib (80 mg) and 10 mg/kg intravenous (IV) of ramucirumab on day 1 (D1) every two weeks (Arm A). In both dose-finding and expansion portions, patients received study treatment until progressive disease or meeting discontinuation criteria. Primary objective of the study is to assess the safety and tolerability of ramucirumab combined with osimertinib, whereas secondary objectives include preliminary efficacy.

Three patients were treated in the completed dose-finding portionfor the combination of ramucirumab and osimertinib. The expansion cohort for ramucirumab/osimertinib is fully enrolled with 22 patients. No dose-limiting toxicities

(DLTs) have beenobserved. After the DLT observation period, an unrelated serious AE of Grade 2 diverticulitis (unrelated to study treatment) was observed. Expansion cohort for ramucirumab/osimertinib is fully enrolled with 22 patients. Safety data is available for 18 our of the 22 patients. Grade ≥ 3 TEAEs were reported in 4 patients, including dyspnea (unrelated [n = 1]), decreased appetite (unrelated [n = 1]), hypertension (related [n =2]). Three patients reported serious adverse events (none related to study treatment): Grade 3 dyspnea and Grade 2 pyrexia, Grade 2 dyspnea, and Grade 2 urinary tract infection. No deaths were reported in patients in the dose-finding portion, and one death unrelated to study teatement was report in the expansion cohort. The recommended dose for the expansion cohort is 10 mg/kg of ramucirumab IV every two weeks with oral 80 mg of osimertinib.

Patients (N=25) were 45-80 years (median 64) with ECOG-PS 0 (n=3) or 1 (n=22) and 10 patients had central nervous system (i.e. CNS) metastasis at enrollment while 15 never had CNS metastasis. Patients with CNS metastasis could have had prior radiotherapy (n=7) or no radiotherapy (n=3) to the CNS. Median follow-up time was 7.23 months. Fifteen patients remained on study treatment (five with CNS metastasis, ten without). TEAEs of interest (CNS metastasis, no CNS metastasis), such as headache (4/10, 5/15), vomiting (3/10, 4/15), and nausea (2/10, 4/15), were observed with comparable rates in patients with or without CNS metastasis. One patient developed TEAE of cerebral hemorrhage (Grade 1), related to CNS metastasis, but unrelated to study treatment, according to the investigator. Another patient with CNS metastasis developed Grade 5 TRAE of subdural hemorrhage, unrelated to CNS metastasis, ~7 weeks after the last dose of Ram. Only one patient with CNS metastasis had measurable CNS lesions (tumor shrinkage of 24% [SD] as best response). The other nine patients with CNS metastasis had non-measurable CNS lesions, one of whom had a CNS complete response; his systemic best response was SD. The rest of patients had CNS non-CR/non-PD. To date, one patient (1/25) developed CNS progression (due to new CNS lesion); and their CNS best response was SD. These results demonstrate that the combination of ramucirumab and osimertinib displays antitumor activity in the CNS. Patients with CNS metastasis, with/without prior radiotherapy, appeared to tolerate this combination similarly to patients without CNS metastasis.

As of March 2nd, 2018, the safety profile of the combination of ramucirumab and osimertinib was consistent with the safety profile for each drug as a monotherapy, with no additive toxicities. Two patients died from adverse events: one death due to cadiogenic pulmonary edema reported as unrelated to study treatment and one death due to Grade 5 subdural hemorrhage reported as related to study treatment (~7 weeks after ramucirumab discontinuation). Encouraging antitumor active was demonstrated with this combination. The tables below further summarize the results from the ongoing trial.

Table 1: Overview of Adverse Events

	Ram 10 mg/kg + Osi 80 mg (N = 25)	
	TEAE, n (%)	TRAE, n (%)
Any Grade AE	25 (100)	25 (100)
Grade ≥ 3 AE	10 (40)	4 (16)
Serious AE	8 (32)	1 (4)
Discountinued study due to AE	1 (4)[a]	1 (4)[a]
AE leading to death	1 (4)[b]	0

Abbreviations: AE=adverse event; N=number of treated patients from the dose-finding Arm A and expansion Cohort A; Osi=osimertinib; Ram=ramucirumab; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event. [a]Ram discontinued for Grade 3 congestive heart failure in a 76-year-old patient with adenocarcinoma of lung, who subsequently experienced Grade 5 subdural hemorrhage ~7 weeks after the last dose of Ram. [b]Death due to cardiogenic pulmonary edema reported as unrelated to study treatment.

Table 2: Decreased Tumor Burden in Treated Patients

Ram 10 mg/kg + Osi 80 mg (N = 25)	
	Confirmed Best Overal Response N (%)
Complete Response (CR)	1 (4)
Partial Response (PR)	18 (72)
Stable Disease (SD)	4 (16)

Progressive Disease (PD)	1 (4)
Non-evaluable	1 (4)
Objective response rate (CR/PR)	19 (76)
Disease control rate (CR/PR/SD)	23 (92)
Median Duration of Response (90% CI)	NR (NR, NR)
6-month Duration of Response Rate (90% CI)	83.3 (62.4, 93.2)
12-month Duration of Response Rate (90% CI)	75.0 (50.9, 88.5)

Abbreviation: NR means not reached.

Table 3: Progression-Free Survival

Ram 10 mg/kg + Osi 80 mg (N = 25)	
Patients/events	25/10
Median PFS (90% CI)	NR (5.49, NR)
6-month PFS rate (90% CI)	66.9 (48.6, 80.0)
12-month PFS rate (90% CI)	57.5 (38.9, 72.3)
Patients censored, n (%)	15 (60)

Abbreviations: N=number of treated patients from the dose-finding ARM A and expansion Cohort A; NR=not reached; PFS=progression-free survival; Osi=osimertinib; Ram=ramucirumab.

SEQUENCE LISTING

SEQ ID NO: 1 (Anti-Human VEGFR-2 Antibody, LCVR) (Artificial Sequence)

DIQMTQSPSSVSASIGDRVTITCRASQGIDNWLGWYQQKPGKAPKLLIYDASNLD
TGVPSRFSGSGSGTYFTLTISSLQAEDFAVYFCQQAKAFPPTFGGGTKVDIK

SEQ ID NO: 2 (Anti-Human VEGFR-2 Antibody, HCVR) (Artificial Sequence)

EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSS
SYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVTDAFDIWGQG
TMVTVSS

SEQ ID NO: 3 (Anti-Human VEGFR-2 Antibody, LC) (Artificial Sequence)

DIQMTQSPSSVSASIGDRVTITCRASQGIDNWLGWYQQKPGKAPKLLIYDASNLD
TGVPSRFSGSGSGTYFTLTISSLQAEDFAVYFCQQAKAFPPTFGGGTKVDIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 4 (Anti-Human VEGFR-2 Antibody, HC) (Artificial Sequence)

EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSS
SYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVTDAFDIWGQG
TMVTVSSASTKGPSVLPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK

SEQ ID NO: 5 (Human VEGFR-2) (Homo Sapiens)

MQSKVLLAVALWLCVETRAASVGLPSVSLDLPRLSIQKDILTIKANTTLQITCRGQ
RDLDWLWPNNQSGSEQRVEVTECSDGLFCKTLTIPKVIGNDTGAYKCFYRETDL

ASVIYVYVQDYRSPFIASVSDQHGVVYITENKNKTVVIPCLGSISNLNVSLCARYP
EKRFVPDGNRISWDSKKGFTIPSYMISYAGMVFCEAKINDESYQSIMYIVVVVGY
RIYDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKPFVA
FGSGMESLVEATVGERVRIPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVLTIME
VSERDTGNYTVILTNPISKEKQSHVVSLVVYVPPQIGEKSLISPVDSYQYGTTQTL
TCTVYAIPPPHHIHWYWQLEEECANEPSQAVSVTNPYPCEEWRSVEDFQGGNKIE
VNKNQFALIEGKNKTVSTLVIQAANVSALYKCEAVNKVGRGERVISFHVTRGPEI
TLQPDMQPTEQESVSLWCTADRSTFENLTWYKLGPQPLPIHVGELPTPVCKNLDT
LWKLNATMFSNSTNDILIMELKNASLQDQGDYVCLAQDRKTKKRHCVVRQLTV
LERVAPTITGNLENQTTSIGESIEVSCTASGNPPPQIMWFKDNETLVEDSGIVLKDG
NRNLTIRRVRKEDEGLYTCQACSVLGCAKVEAFFIIEGAQEKTNLEIIILVGTAVIA
MFFWLLLVIILRTVKRANGGELKTGYLSIVMDPDELPLDEHCERLPYDASKWEFP
RDRLKLGKPLGRGAFGQVIEADAFGIDKTATCRTVAVKMLKEGATHSEHRALMS
ELKILIHIGHHLNVVNLLGACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVPYKT
KGARFRQGKDYVGAIPVDLKRRLDSITSSQSSASSGFVEEKSLSDVEEEEAPEDLY
KDFLTLEHLICYSFQVAKGMEFLASRKCIHRDLAARNILLSEKNVVKICDFGLAR
DIYKDPDYVRKGDARLPLKWMAPETIFDRVYTIQSDVWSFGVLLWEIFSLGASPY
PGVKIDEEFCRRLKEGTRMRAPDYTTPEMYQTMLDCWHGEPSQRPTFSELVEHL
GNLLQANAQQDGKDYIVLPISETLSMEEDSGLSLPTSPVSCMEEEEVCDPKFHYD
NTAGISQYLQNSKRKSRPVSVKTFEDIPLEEPEVKVIPDDNQTDSGMVLASEELKT
LEDRTKLSPSFGGMVPSKSRESVASEGSNQTSGYQSGYHSDDTDTTVYSSEEAEL
LKLIEIGVQTGSTAQILQPDSGTTLSSPPV

WE CLAIM:

1. A method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient an antibody comprising a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1 at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg.
2. The method of claim 1, wherein the heavy chain has the amino acid sequence of SEQ ID NO: 4 and the light chain has the amino acid sequence of SEQ ID NO: 3.
3. The method of claim 1, wherein the patient has received treatment with gefitinib, erlotinib, or afatinib prior to receiving the antibody.
4. The method of claim 1, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and a L858R mutation in exon 21.
5. The method of claim 1, wherein the patient is administered 6 mg/kg to 10 mg/kg of the antibody.
6. The method of claim 1, wherein the patient is administered about 8 mg/kg to about 10 mg/kg of the antibody.
7. The method of claim 1, wherein the patient is administered 8 mg/kg to 10 mg/kg of the antibody.
8. The method of claim 1, wherein the patient is administered about 6 mg/kg of the antibody.
9. The method of claim 1, wherein the patient is administered 6 mg/kg of the antibody.
10. The method of claim 1, wherein the patient is administered about 8 mg/kg of the antibody.
11. The method of claim 1, wherein the patient is administered 8 mg/kg of the antibody.

12. The method of claim 1, wherein the patient is administered about 10 mg/kg of the antibody.
13. The method of claim 1, wherein the patient is administered 10 mg/kg of the antibody.
14. The method of claim 1, wherein the patient is administered about 80 mg of osimertinib or a pharmaceutically acceptable salt thereof.
15. The method of claim 1, wherein the patient is administered 80 mg of osimertinib or a pharmaceutically acceptable salt thereof.
16. The method of claim 1, wherein the patient is administered about 40 mg of osimertinib or a pharmaceutically acceptable salt thereof.
17. The method of claim 1, wherein the patient is administered 40 mg of osimertinib or a pharmaceutically acceptable salt thereof.
18. The method of claim 1, wherein the patient is administered a mesylate salt of osimertinib.
19. The method of any one of claims 1-18, wherein the cancer has metastasized to the central nervous system.
20. A method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of about 40 mg to about 80 mg; wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.
21. A method of treating advanced or metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab at a dose of about 10 mg/kg on day 1 of a 14 day cycle, in combination with osimertinib or a pharmaceutically acceptable salt thereof administered orally at a daily dose of 80 mg; wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and an a L858R mutation in exon 21.

22. A method of treating metastatic EGFR T790M-positive non-small cell lung cancer in a human patient comprising administering to the patient ramucirumab in combination with osimertinib or a pharmaceutically acceptable salt thereof; wherein the cancer has metastasized to the central nervous system.
23. The method of claim 22, wherein ramucirumab is administered at a dose of about 6 mg/kg to about 10 mg/kg on day 1 of a 14 day cycle.
24. The method of claim 23, wherein osimertinib or a pharmaceutically acceptable salt thereof is administered orally at a daily dose of about 40 mg to about 80 mg.
25. An anti-human VEGFR-2 (SEQ ID NO: 5) antibody for use in simultaneous, separate, or sequential combination with osimertinib or a pharmaceutically acceptable salt thereof in the treatment of patients with metastatic EGFR T790M-positive non-small cell lung cancer; wherein the cancer has metastasized to the central nervous system.
26. The antibody for use of claim 25, wherein the antibody comprises a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1.
27. The antibody for use of any one of claims 25-26, wherein the antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 4 and a light chain having the amino acid sequence of SEQ ID NO: 3.
28. The antibody for use of any one of claims 25-27, wherein the patient has received treatment with gefitinib, erlotinib, or afatinib prior to receiving the antibody.
29. The antibody for use of any one of claims 25-28, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and a L858R mutation in exon 21.
30. The antibody for use of any one of claims 25-29, wherein the patient is administered 6 mg/kg to 10 mg/kg of the antibody.
31. The antibody for use of any one of claims 25-29, wherein the patient is administered 8 mg/kg to 10 mg/kg of the antibody.
32. The antibody for use of any one of claims 25-29, wherein the patient is administered 6 mg/kg of the antibody.

33. The antibody for use of any one of claims 25-29, wherein the patient is administered 8 mg/kg of the antibody.
34. The antibody for use of any one of claims 25-29, wherein the patient is administered 10 mg/kg of the antibody.
35. The antibody for use of any one of claims 25-34, wherein the patient is administered 80 mg of osimertinib or a pharmaceutically acceptable salt thereof.
36. The antibody for use of any one of claims 25-34, wherein the patient is administered 40 mg of osimertinib or a pharmaceutically acceptable salt thereof.
37. The antibody for use of any one of claims 25-36, wherein the patient is administered a mesylate salt of osimertinib.
38. Use of an anti-human VEGFR2 (SEQ ID NO:5) antibody for the manufacture of a medicament for the treatment of metastatic EGFR T790M-positive non-small cell lung cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with osimertinib or a pharmaceutically acceptable salt; wherein the cancer has metastasized to the central nervous system.
39. The antibody for use of claim 38, wherein the antibody comprises a heavy chain having a heavy chain variable region having the amino acid sequence of SEQ ID NO: 2 and a light chain having a light chain variable region having the amino acid sequence of SEQ ID NO: 1.
40. The antibody for use of any one of claims 38-39, wherein the antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 4 and a light chain having the amino acid sequence of SEQ ID NO: 3.
41. The antibody for use of any one of claims 38-40, wherein the patient has received treatment with gefitinib, erlotinib, or afatinib prior to receiving the antibody.
42. The antibody for use of any one of claims 38-41, wherein the cancer further comprises at least one additional EGFR activating mutation selected from the group consisting of a deletion of exon 19 and a L858R mutation in exon 21.
43. The antibody for use of any one of claims 38-42, wherein the patient is administered 6 mg/kg to 10 mg/kg of the antibody.
44. The antibody for use of any one of claims 38-42, wherein the patient is administered 8 mg/kg to 10 mg/kg of the antibody.

45. The antibody for use of any one of claims 38-42, wherein the patient is administered 6 mg/kg of the antibody.
46. The antibody for use of any one of claims 38-42, wherein the patient is administered 8 mg/kg of the antibody.
47. The antibody for use of any one of claims 38-42, wherein the patient is administered 10 mg/kg of the antibody.
48. The antibody for use of any one of claims 38-47, wherein the patient is administered 80 mg of osimertinib or a pharmaceutically acceptable salt thereof.
49. The antibody for use of any one of claims 38-47, wherein the patient is administered 40 mg of osimertinib or a pharmaceutically acceptable salt thereof.
50. The antibody for use of any one of claims 38-49, wherein the patient is administered a mesylate salt of osimertinib.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/047031

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

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2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/047031

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61K31/00 C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SULLIVAN I ET AL: "Osimertinib in the treatment of patients with epidermal growth factor receptor T790M mutation-positive metastatic non-small cell lung cancer: Clinical trial evidence and experience", THERAPEUTIC ADVANCES IN RESPIRATORY DISEASE 20161201 SAGE PUBLICATIONS LTD GBR, vol. 10, no. 6, 1 December 2016 (2016-12-01), pages 549-565, XP002786876, ISSN: 1753-4658 Pages 553 and 558 ----- -/--	1-50

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2018	11/12/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sitch, David

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Planchard et al: "P2.06-005Phase 1 Study of Ramucirumab orNecitumumab in Combination withOsimertinib (AZD9291) in AdvancedT790M-Positive EGFR-Mutant NSCLC", , January 2017 (2017-01), XP002786877, Retrieved from the Internet: URL:https://www.jto.org/article/S1556-0864(16)32739-3/pdf [retrieved on 2018-11-27] abstract	1
A	COBO M ET AL: "Spotlight on ramucirumab in the treatment of nonsmall cell lung cancer: Design, development, and clinical activity", LUNG CANCER: TARGETS AND THERAPY 20170712 DOVE MEDICAL PRESS LTD. NZL, vol. 8, 12 July 2017 (2017-07-12), pages 57-66, XP002786878, ISSN: 1179-2728	1
A	WO 2015/134242 A1 (LILLY CO ELI [US]) 11 September 2015 (2015-09-11) Page 1, paragraph 1 page 35 - page 39; example 1	1
X,P	AKAMATSU H ET AL: "Osimertinib With Ramucirumab in EGFR-mutated, T790M-positive Patients With Progression During EGFR-TKI Therapy: Phase Ib Study", CLINICAL LUNG CANCER 20181101 ELSEVIER INC. USA, vol. 19, no. 6, 22 August 2018 (2018-08-22), pages e871-e874, XP002786879, ISSN: 1525-7304 the whole document	1-50
X,P	DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1 November 2017 (2017-11-01), YU H: "Osimertinib with ramucirumab or necitumumab in advanced T790M-positive EGFR-mutant NSCLC: Preliminary PH1 study results", XP002786880, Database accession no. EMB-620148327 abstract	1-50

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& YU H: "Osimertinib with ramucirumab or necitumumab in advanced T790M-positive EGFR-mutant NSCLC: Preliminary PH1 study results", JOURNAL OF THORACIC ONCOLOGY 20171101 ELSEVIER INC. NLD, vol. 12, no. 11, Supplement 2, 1 November 2017 (2017-11-01), pages S1972 CONF 20171015 to 20171018 Yokohama-18th Worl, ISSN: 1556-1380	

X,P	DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1 October 2018 (2018-10-01), PAZ-ARES L: "CNS Activity of Ramucirumab in Combination with Osimertinib in Patients with Advanced T790M-Positive EGFR-Mutant NSCLC", XP002786881, Database accession no. EMB-002001207981 abstract & PAZ-ARES L: "CNS Activity of Ramucirumab in Combination with Osimertinib in Patients with Advanced T790M-Positive EGFR-Mutant NSCLC", JOURNAL OF THORACIC ONCOLOGY - IASLC 19TH WORLD CONFERENCE ON LUNG CANCER 20181001 ELSEVIER INC. NLD, vol. 13, no. 10, Supplement, 1 October 2018 (2018-10-01), pages S453 20180923 to 20180926 Toronto-S454 CONF, ISSN: 1556-0864	1-50

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/047031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2937024 A1	11-09-2015
		CN 106068126 A	02-11-2016
		EP 3113845 A1	11-01-2017
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