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(54) Title: COMBINATION THERAPY FOR CANCER WITH EXON 14 SKIPPING MUTATION(S) OR EXON 14 SKIPPING  
PHENOTYPE

(57) Abstract: The present invention provides preparation of medicaments for use in treating and methods of treating cancer with  
tumors with MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype with emibetuzumab, in combination, as described  
herein, with merestinib.



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## COMBINATION THERAPY FOR CANCER WITH EXON 14 SKIPPING MUTATION(S) OR EXON 14 SKIPPING PHENOTYPE

The present invention relates to combinations of a ligand neutralizing and MET  
5 receptor internalizing bivalent anti-human MET antibody, preferably, emibetuzumab,  
with an anti-human MET kinase inhibitor, preferably, merestinib, or a pharmaceutically  
acceptable salt thereof, and to methods of using the combinations to treat certain  
disorders, such as lung cancer and gastric cancer, in patients with tumors bearing MET  
exon 14 skipping(s) or MET exon 14 skipping phenotype.

10 Overexpression and activation of MET tyrosine receptor kinase can be an  
oncogenic driver of tumor growth in many types of cancer. The MET signaling pathway  
regulates a wide variety of normal cellular functions that can be subverted to support  
neoplasia, including cell proliferation, survival, apoptosis, scattering and motility,  
invasion, and angiogenesis. MET over-expression (with or without gene amplification),  
15 aberrant autocrine or paracrine ligand production, and missense MET mutations are  
mechanisms that lead to activation of the MET pathway in tumors and are associated with  
poor prognostic outcome. Combinations of MET inhibitors and MET antibodies have  
been contemplated in the art. *See*, US 20140037625 and WO 2012031027.

Different genomic changes may occur in the intronic and/or exonic segments of  
20 MET and can lead to an alternatively spliced transcript of MET where exon 14 is skipped  
(i.e., exon 14 is largely or entirely deleted). MET exon 14 skipping mutations result in a  
protein missing the Y1003 phosphorylation site, the binding site for the ubiquitin ligase  
CBL, which targets MET for degradation. Additionally, a single point mutation at  
Y1003, D1002 or R1004 will also result in an inability of the ubiquitin ligase CBL to  
25 bind to the MET receptor without skipping of exon 14 (i.e., MET exon 14 skipping  
phenotype). This results in a MET protein with increased stability and oncogenic  
potential. MET exon 14 skipping mutations or an exon 14 skipping phenotype has been  
observed in adenosquamous, adenocarcinoma, sarcomatoid, squamous cell, large cell, and  
small cell histologies. Specifically, MET exon 14 skipping has been detected in lung  
30 adeonocarcinoma, as well as in neuroblastoma, gastric, and colon cancer cell lines.

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Tumors with MET exon 14 skipping mutations have been reported to be responsive to treatment with MET inhibitors in clinical case reports and series.

MET exon 14 skipping mutation (s) or exon 14 skipping phenotype are targetable mutations in lung cancer and is reported in approximately 3 to 6 % of non-small cell lung cancer (NSCLC) patients. Lung cancer remains the third most prevalent cancer in the United States and is the leading cause of cancer death in both men and women throughout the world. The two main types of lung cancer are small cell lung cancer and NSCLC. The majority of patients with lung cancer have advanced and/or metastatic disease at diagnosis and the majority of patients treated with curative intent develop recurrence.

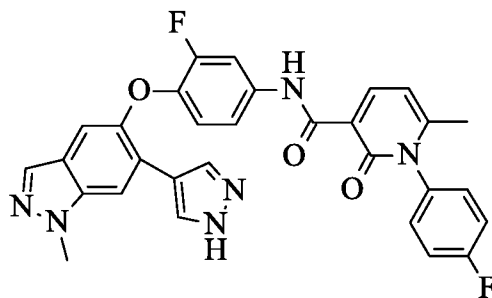
These patients present with advanced, inoperable stage cancer for which there is no prospect of cure. Treatment is provided to improve symptoms, optimize quality of life, and prolong survival.

MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype are also targetable mutations in gastric cancer, a malignant tumor that originates in the stomach lining. Gastric cancers are classified according to the type of tissue from which they originate, with the most common type being adenocarcinoma and accounts for over 90% of all stomach cancers. Adenocarcinoma of the esophagus including carcinoma of the gastroesophageal junction (GEJ) is one of the fastest rising malignancies and is associated with a poor prognosis. Other forms of gastric cancer include lymphomas and sarcomas. Gastric cancer may be cured if it is found and treated at an early stage, but unfortunately, it is often found at a later stage.

There remains a need for the treatment of cancers with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype. Tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype can have a response to MET inhibitors. Thus, a combination of an anti-human MET inhibitor, preferably, merestinib, or a pharmaceutically acceptable salt thereof, with an anti-human MET neutralizing and internalizing bivalent antibody, preferably, emibetuzumab, may provide a treatment option for cancer patients who have tumors bearing MET exon 14 skipping mutations or MET exon 14 skipping phenotype.

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*N*-(3-Fluoro-4-(1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (CAS # 1206799-15-6), also known as merestinib and represented by the structural formula (I) below, is a small molecule type II MET kinase inhibitor. Merestinib and methods of making and using this compound and pharmaceutically acceptable salts thereof including for the treatment of neoplastic diseases such as solid and non-solid tumors are disclosed in WO 2010/011538. Furthermore, merestinib is currently being evaluated in Phase 2 clinical studies for patients in NSCLC and solid tumors (see ClinicalTrials.gov NCT02920996).



Formula (I)

Anti-human MET monoclonal antibodies, including, but not limited to, C8-H241 antibodies, were previously disclosed in WO 2010/059654. Emibetuzumab is a C8-H241-IgG4 antibody comprising: two light chains, each of whose amino acid sequence is that given in SEQ ID NO: 5, and two heavy chains, each of whose amino acid sequence is that given in SEQ ID NO: 7 (see, WHO Drug Information, *Proposed International Nonproprietary Names (INN) List 111*, Volume 28, No. 2, July 2014). Emibetuzumab has high neutralization and internalization activities resulting in inhibition of both HGF-dependent and HGF-independent (e.g., MET amplified) MET pathway activation and tumor growth in xenograft models. Emibetuzumab is currently being evaluated in Phase 2 clinical studies in combination with erlotinib in NSCLC patients (see, ClinicalTrials.gov NCT01900652, NCT01897480).

The present invention provides methods of treating cancer with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype by using a novel

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combination of emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, as part of a specific treatment regimen that provides unexpected beneficial therapeutic effects from the combined activity of these therapeutic agents in some cancer patients as compared to the therapeutic effects provided by either agent alone. Preferably, the cancer is lung, neuroblastoma, gastric, or colon cancer. More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is lung cancer. Most preferably, the cancer is non-small cell lung cancer.

Accordingly, the present invention provides a method of treating cancer with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype in a patient, comprising administering to a cancer patient in need of such treatment an effective amount of emibetuzumab in combination with an effective amount of an anti-MET inhibitor. In a further embodiment, the anti-MET inhibitor is merestinib, or a pharmaceutically acceptable salt thereof. Preferably, the cancer in the aforementioned methods is lung, neuroblastoma, gastric, or colon cancer. More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is carcinoma of the gastroesophageal junction. Even more preferably, the cancer is lung cancer. Most preferably, the cancer in the aforementioned methods is non-small cell lung cancer.

The invention further provides a pharmaceutical composition comprising emibetuzumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, in combination with a pharmaceutical composition of an anti-MET inhibitor with one or more pharmaceutically acceptable carriers, diluents, or excipients. In a further embodiment, the anti-MET inhibitor is merestinib, or a pharmaceutically acceptable salt thereof.

In addition, the invention provides a kit comprising emibetuzumab in combination with an anti-MET inhibitor. The invention also provides a kit comprising emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof. The invention further provides a kit comprising a pharmaceutical composition comprising emibetuzumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical composition comprising an anti-MET inhibitor, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The invention also provides

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a kit comprising a pharmaceutical composition comprising emibetuzumab, with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical composition comprising merestinib, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

5           The invention also provides a kit comprising an effective amount of emibetuzumab in combination with an effective amount of merestinib, or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use in the treatment of cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype. In a further embodiment of the invention, the cancer is lung,  
10   neuroblastoma, gastric, or colon cancer. More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is carcinoma of the gastroesophageal junction. Even more preferably, the cancer is lung cancer. Most preferably, the cancer in the aforementioned methods is non-small cell lung cancer.

          The invention further provides a combination comprising emibetuzumab and  
15   merestinib, or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use in the treatment of cancer with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype. In a further embodiment of the invention, the cancer is lung, neuroblastoma, gastric, or colon cancer. More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is carcinoma of the  
20   gastroesophageal junction. Even more preferably, the cancer is lung cancer. Most preferably, the cancer in the aforementioned methods is non-small cell lung cancer.

          The invention further provides the use of a combination comprising emibetuzumab and meresitnib, or a pharmaceutically acceptable salt thereof, for use in therapy. The invention also provides a combination comprising emibetuzumab and  
25   merestinib, or a pharmaceutically acceptable salt thereof. A further embodiment of the invention is the use of the combination comprising emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, for treating cancer with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype. In a further embodiment of the invention, the cancer is lung, neuroblastoma, gastric, or colon cancer.  
30   More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is

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carcinoma of the gastroesophageal junction. Even more preferably, the cancer is lung cancer. Most preferably, the cancer in the aforementioned methods is non-small cell lung cancer.

The invention further provides the use of a combination comprising  
5 emibetuzumab and an anti-MET inhibitor for the manufacture of a medicament for the treatment of cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype. In a further embodiment of the invention, the cancer is lung, neuroblastoma, gastric, or colon cancer. More preferably, the cancer is gastric or lung cancer. Even more preferably, the cancer is carcinoma of the gastroesophageal junction. Even more  
10 preferably, the cancer is lung cancer. Most preferably, the cancer in the aforementioned methods is non-small cell lung cancer.

Another aspect of the present invention is a method of treating cancer with tumors bearing MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype in a patient, comprising administering to a patient in need of such treatment wherein  
15 merestinib, or a pharmaceutically acceptable salt thereof, is administered at a dose between about 60 mg to about 160 mg daily on a 28-day cycle and emibetuzumab is administered at a dose between about 500 mg to about 2500 mg on about day 1 and about day 15 of the 28-day cycle of merestinib dosing. More preferably, merestinib, or a pharmaceutically acceptable salt thereof, is administered at a dose between about 80 mg  
20 to about 120 mg daily of a 28-day cycle and emibetuzumab is administered at a dose of about 750 mg on about day 1 and about day 15 of the 28-day cycle of the merestinib dosing. In yet a further embodiment, merestinib is administered orally and emibetuzumab is administered intravenously.

Each of the embodiments described herein envisions within its scope  
25 pharmaceutically acceptable salts of the compounds referenced or described herein. Accordingly, the phrase "or a pharmaceutically acceptable salt thereof" is implicit in the references to or descriptions of all compounds herein.

The phrase "MET exon 14 skipping mutation", "exon 14 skipping mutation",  
"MET exon 14 skipping", "exon 14 skipping", or grammatical versions thereof, as used  
30 herein, refer to somatic mutations in the gene for MET, which, upon translation of the

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mRNA transcripts expressed thereby, result in cellular expression of MET polypeptides wherein exon 14 is largely or entirely deleted.

The phrases “MET exon 14 skipping phenotype”, “exon 14 skipping phenotype”, or grammatical versions thereof, as used herein refer to any single somatic point mutation in the gene for MET which, upon translation of the mRNA transcripts expressed thereby, result in cellular expression of MET polypeptides mutated at Y1003, D1002 or R1004 and which have a diminished ability to bind the ubiquitin ligase CBL, resulting in a MET protein with increased stability and oncogenic potential.

The term “ $K_D$ ”, as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen or antibody fragment-antigen interaction.

The phrase “specifically binds” as used herein in reference to the affinity of an antibody, or antigen-binding fragment thereof, for the MET-ECD is intended to mean, unless indicated otherwise, a  $K_D$  of less than about  $1 \times 10^{-8}$  M, preferably, less than about  $1 \times 10^{-9}$  M as determined by common methods known in the art, including by use of a surface plasmon resonance (SPR) biosensor at 25°C (for MET-ECD).

As used herein, the term “C8-H241 antibody” or “C8-H241 Ab” refers to an antibody comprising: a LCVR whose amino acid sequence is that given in SEQ ID NO: 1, and a HCVR whose amino acid sequence is that given in SEQ ID NO: 3, wherein that C8-H241 Ab specifically binds to MET-ECD. In some embodiments, a C8-H241 Ab is a C8-H241-IgG4 Ab, an antibody comprising: a LC whose amino acid sequence is that given in SEQ ID NO: 5, and a HC whose amino acid sequence is that given in SEQ ID NO: 7 and that specifically binds to MET-ECD.

As used herein, the term “emibetuzumab” refers to a C8-H241-IgG4 antibody comprising: two light chains, each of whose amino acid sequence is that given in SEQ ID NO: 5, and two heavy chains, each of whose amino acid sequence is that given in SEQ ID NO: 7 and that specifically binds to MET-ECD (see, WHO Drug Information, *Proposed International Nonproprietary Names (INN) List 111*, Volume 28, No. 2, July 2014).

In certain embodiments, a C8-H241 Ab or a C8-H241-IgG4 Ab, including, but not limited to, emibetuzumab binds MET-ECD with a  $K_D$  value of between about 100 nM to about 1 pM, preferably, between about 10 nM to about 10 pM, more preferably, between

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about 10 nM to about 100 pM, more preferably, between about 2.5 nM to about .5 nM, and most preferably about 1 nM, as determined by a surface plasmon resonance (SPR) based assay (such as the BIAcore assay as described in PCT Application Publication No. WO 2005/012359) conducted at 25 °C. Antibody affinities may also be determined by ELISA; and competition assays (e.g., a RIA), for example.

The terms “MET polypeptide”, “MET receptor”, “MET”, “HGF receptor” or “HGFR” are used interchangeably herein and, unless otherwise indicated, are intended to refer to the human receptor tyrosine kinase, as well as functionally active, mutated forms thereof, that bind human hepatocyte growth factor. Specific examples of MET include, e.g., a human polypeptide encoded by the nucleotide sequence provided in GenBank accession no. NM\_000245, or the human protein encoded by the polypeptide sequence provided in GenBank accession no. NP\_000236.

The extracellular domain of MET has the amino acid sequence shown in, for example, SEQ ID NO: 9. However, amino acids 1-24 of SEQ ID NO: 9 comprise the signal sequence. Therefore, unless stated otherwise, the term “MET-ECD” as used herein means the protein beginning and ending at amino acids 25 and 932, respectively, of SEQ ID NO: 9 (*i.e.*, SEQ ID NO: 10). The SEMA domain consists of approximately 500 amino acid residues at the N-terminus of MET, and contains the  $\alpha$ -chain (amino acid residues 25-307 of SEQ ID NO: 9 (*i.e.*, SEQ ID NO: 11) and part of the  $\beta$ -chain (amino acid residues 308-519 of SEQ ID NO: 18 (*i.e.*, SEQ ID NO: 12)).

Unless indicated otherwise, the term “antibody” refers to an immunoglobulin molecule comprising two heavy chains and two light chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100 to about 110 amino acids primarily responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

As used herein, the term “antigen-binding fragment” refers to any antibody fragment that retains the ability to bind to its antigen. Such “antigen-binding fragments” can be selected from the group consisting of Fv, scFv, Fab, F(ab')<sub>2</sub>, Fab', scFv-Fc fragments and diabodies. An antigen-binding fragment of an antibody will typically

comprise at least one variable region. Preferably, an antigen-binding fragment comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR). More preferably, an antigen-binding fragment as used herein comprises a HCVR and a LCVR which confers antigen-binding specificity to MET-ECD (i.e., a “MET-ECD binding  
5 fragment”).

As used herein, the term “light chain variable region (LCVR)” refers to a portion of a LC of an antibody molecule that includes amino acid sequences of Complementarity Determining Regions (CDRs; i.e., LCDR1, LCDR2, and LCDR3), and Framework Regions (FRs).

10 As used herein, the term “heavy chain variable region (HCVR)” refers to a portion of a HC of an antibody molecule that includes amino acid sequences of Complementarity Determining Regions (CDRs; i.e., HCDR1, HCDR2, and HCDR3), and Framework Regions (FRs).

As used herein, the terms “complementarity determining region” and “CDR”,  
15 refer to the non-contiguous antigen combining sites found within the variable region of LC and HC polypeptides of an antibody or an antigen-binding fragment thereof. These particular regions have been described by others including Kabat, *et al.*, *Ann. NY Acad. Sci.* 190:382-93 (1971); Kabat *et al.*, *J. Biol. Chem.* 252:6609-6616 (1977); Kabat, *et al.*, *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of  
20 Health and Human Services, NIH Publication No. 91-3242 (1991); Chothia, *et al.*, *J. Mol. Biol.* 196:901-917 (1987); MacCallum, *et al.*, *J. Mol. Biol.*, 262:732-745 (1996); and North, *et al.*, *J. Mol. Biol.*, 406, 228-256 (2011), where the definitions include overlapping or subsets of amino acid residues when compared against each other.

The CDRs are interspersed with regions that are more conserved, termed  
25 framework regions (“FR”). Each LCVR and HCVR is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The three CDRs of the light chain are referred to as “LCDR1, LCDR2, and LCDR3” and the three CDRs of the HC are referred to as “HCDR1, HCDR2, and HCDR3.” The CDRs contain most of the residues which form  
30 specific interactions with the antigen. The numbering and positioning of CDR amino acid

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residues within the LCVR and HCVR regions is in accordance with known conventions (e.g., Kabat (1991), Chothia (1987), and/or North (2011)). In different embodiments of the invention, the FRs of the antibody may be identical to the human germline sequences, or may be naturally or artificially modified.

5           In certain embodiments, C8-H241 antibodies, including C8-H241-IgG4 antibodies or emibetuzumab, for the methods and/or uses of the present invention may be altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or  
10       removed.

          Where a C8-H241 antibody, including, but not limited to, emibetuzumab, comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain  
15       of the Fc region (see, e.g., Wright et al. TIBTECH 15:26-32 (1997)). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the “stem” of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody  
20       variants with certain improved properties.

          In some embodiments, the C8-H241 antibody, including, but not limited to, emibetuzumab may have a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of  
25       fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycosyl structures attached to Asn297 (e.g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues);  
30       however, Asn297 may also be located about  $\pm 3$  amino acids upstream or downstream of

position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function (see, US Patent Publication Nos. US 2003/0157108 and US 2004/0093621, for example).

Examples of publications related to “defucosylated” or “fucose-deficient” antibody

5 variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; and Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. Arch. Biochem. Biophys. 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1; and WO 2004/056312 A1),  
10 and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004); Kanda, Y. et al., Biotechnol. Bioeng., 94(4):680-688 (2006); and WO 2003/085107).

Unless indicated otherwise, when referring to an amino acid residue in an antibody by a number, the EU numbering system is used herein as it is conventionally  
15 used in the art (see, Kabat, *et al.*, *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (1991), for example).

As used herein, the term “kit” refers to a package comprising at least two separate containers, wherein a first container contains a C8-H241 antibody, preferably,  
20 emibetuzumab, and a second container contains an anti-MET inhibitor. As used herein, the term “kit” also refers to a package comprising at least two separate containers, wherein a first container contains emibetuzumab, and a second container contains merestinib, or a pharmaceutically acceptable salt thereof. A “kit” may also include instructions to administer all or a portion of the contents of these first and second  
25 containers to a cancer patient, preferably, a gastric cancer patient, a patient having carcinoma of the GEJ, a lung cancer patient, or a NSCLC patient and preferably a cancer patient with tumors with MET exon 14 skipping mutation(s) or MET exon 14 skipping phenotype.

As used herein, the terms “treating,” “to treat,” or “treatment” refers to restraining, slowing, stopping, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

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

5 As used herein, the terms “cancer” and “cancerous” refer to or describe the physiological condition in patients that is typically characterized by unregulated cell proliferation. Included in this definition are benign and malignant cancers. By “early stage cancer” or “early stage tumor” is meant a cancer that is not advanced or metastatic or is classified as a Stage 0, I, or II cancer. Examples of cancer include, but are not  
10 limited to, gastric cancer, preferably, carcinoma of the gastroesophageal junction, and lung cancer, preferably NSCLC.

In some embodiments of the present invention, the cancer patients are selected for treatment with a combination therapy disclosed herein on the basis of having a tumor in which MET is expressed or overexpressed. Preferably, the MET expression status of a  
15 cancer patient’s tumor is determined by using an immunohistochemistry (IHC) assay, PCR assay, gene sequencing assay and/or fluorescence in-situ hybridization (FISH) assay suitable for the detection of MET or MET gene amplification. More preferably, an IHC method for determining whether a cancer patient’s tumor expresses or overexpresses MET is performed essentially as described in Example 7 of PCT International Publication  
20 WO 2013/169532 using an anti-MET antibody, or an antigen-binding fragment thereof, disclosed therein that specifically binds to MET-ECD, wherein said anti-MET antibody comprises a LC and a HC, wherein the amino acid sequence of the LC and HC is that given in SEQ ID NO: 13 and SEQ ID NO: 14, respectively. In some embodiments, a patient is selected for treatment with the combination therapies of the present invention  
25 after a sample of a cancer patient’s tumor has been determined expressed or overexpress MET by use of an IHC assay wherein the assay comprises the step of contacting the sample with a MET antibody, or antigen-binding fragment thereof, wherein the antibody, or fragment thereof, comprises a LC and a HC, wherein the amino acid sequence of the LC and HC is that given in SEQ ID NO: 13 and SEQ ID NO: 14, respectively. In various  
30 embodiments of the methods of the present invention, the aforementioned IHC assay of

the patient's tumor is performed using a formalin-fixed and paraffin-embedded sample of the patient's tumor.

In some embodiments of the present invention, the cancer patients are selected for treatment with a combination therapy disclosed herein on the basis of having a tumor with MET exon 14 skipping mutations or MET exon 14 phenotype. Preferably, the MET exon 14 skipping mutation status of a cancer patient's tumor is determined by next generation gene sequencing methodologies. More preferably, the MET exon 14 skipping mutations or MET exon 14 phenotype of a cancer patient's tumor is determined by using Hybridization-captured Next Generation Sequencing (see., *e.g.*, Schrock, A. B., *et al.*, J Thoracic Oncology 2016, 9(11): 1493-1502). More preferably, the MET exon 14 phenotype of a cancer patient's tumor is determined by using the nCounter Analysis System (NANOSTRING<sup>®</sup> Technologies), a fluorescence-based platform for multiplexed digital mRNA profiling without amplification or generation of cDNA (see., *e.g.*, Geiss, G. K., *et al.*, Nature Biotechnology 2008, 26: 317-325).

A main advantage of the combination treatments of the invention is the ability of producing marked anti-cancer effects in a patient without causing significant toxicities or adverse events, so that the patient benefits from the combination treatment method overall. The efficacy of the combination treatment of the invention can be measured by various endpoints commonly used in evaluating cancer treatments, including but not limited to, tumor regression, tumor weight or size shrinkage, time to progression, overall survival, progression free survival, overall response rate, duration of response, and quality of life. The therapeutic agents used in the invention may cause inhibition of metastatic spread without shrinkage of the primary tumor, may induce shrinkage of the primary tumor, or may simply exert a tumoristatic effect. Because the invention relates to the use of a combination of unique anti-tumor agents, novel approaches to determining efficacy of any particular combination therapy of the present invention can be optionally employed, including, for example, measurement of plasma or urinary markers of angiogenesis and measurement of response through radiological imaging.

As used herein, the term "effective amount" refers to the amount or dose of a C8-H241 antibody, preferably, emibetuzumab, and/or to the amount or dose of an anti-MET

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inhibitor, preferably, merestinib, which, upon single or multiple dose administration to the patient, optionally in combination with one or more other active agents, as the case may be, provides an effective response in the patient under diagnosis or treatment. As used herein, the term “effective amount” also refers to the amount or dose of a C8-H241

5 antibody, preferably, emibetuzumab, and to the amount or dose of merestinib, or a pharmaceutically acceptable salt thereof, which, upon single or multiple dose administration to the patient, optionally, in combination with one or more other active agents, provides an effective response in the patient under diagnosis or treatment. It is understood that a combination therapy of the present invention is carried out by  
10 administering a C8-H241 antibody, preferably, emibetuzumab, together with an anti-MET inhibitor in any manner which provides effective levels of the C8-H241 antibody, preferably, emibetuzumab, and the anti-MET inhibitor, preferably, merestinib, in the body. It is also understood that a combination therapy of the present invention is carried out by administering emibetuzumab together with merestinib, or a pharmaceutically  
15 acceptable salt thereof, in any manner which provides effective levels of emibetuzumab and merestinib in the body.

As used herein, the terms “effective response” of a patient or a patient's “responsiveness” to treatment with a combination of agents, or “therapeutic effect” refers to the clinical or therapeutic benefit(s) imparted to a patient upon administration of i) a  
20 combination of a C8-H241 antibody, preferably, emibetuzumab, and an anti-MET inhibitor, or ii) emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof. Such benefit(s) include any one or more of: extending survival (including overall survival and progression free survival); resulting in an objective response (including a complete response or a partial response); tumor regression, tumor weight or size  
25 shrinkage, longer time to disease progression, increased duration of survival, longer progression free survival, improved overall response rate, increased duration of response, and improved quality of life and/or improving signs or symptoms of cancer, etc.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained  
30 under analogous circumstances. In determining the effective amount for a patient, a

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number of factors are considered by the attending diagnostician, including, but not limited to: the species of patient; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

Emibetuzumab is generally effective over a wide dosage range in the combination of the present invention. For example, dosages normally are given on days one and fifteen of a 28-day treatment cycle and each dose falls within the range of about 500 mg to about 2500 mg, preferably about 750 mg to about 2000 mg, and most preferably about 750 mg. In addition, an anti-MET inhibitor, preferably merestinib, or a pharmaceutically acceptable salt thereof, is generally effective over a wide dosage range in the combination of the present invention. For example, dosages per 28-day cycle normally fall within the range of daily dosing of about 60 to 160 mg, preferably about 80 to about 120 mg, and most preferably 120 mg. In some instances dosage levels below the lower limit of the aforesaid ranges for emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, may be more than adequate, while in other cases smaller or still larger doses may be employed with acceptable side effects, and therefore the above dosage range is not intended to limit the scope of the invention in any way. When given in combination with an anti-MET inhibitor, for example, over a 28-day cycle, emibetuzumab, is administered on days one and fifteen within the range of about 500 mg to about 2500 mg and an anti-MET inhibitor, preferably, merestinib, or a pharmaceutically acceptable salt thereof, is administered daily within the range of about 60 to 120 mg. When given in combination, for example, over a 28-day cycle, emibetuzumab is administered on day one and day fifteen within the range of about 750 mg to about 2000 mg and an anti-MET inhibitor, preferably, merestinib, or a pharmaceutically acceptable salt thereof, is administered on day one and day fifteen within the range of about 80-120 mg. Optionally, a 21-day cycle may be employed with dose given daily the dosage of merestinib, or a pharmaceutically acceptable salt thereof, within the range of about 60-120 mg, more preferably, 80-120 mg

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and the dosage of emibetuzumab in the range of about 750 mg to about 200 mg, more preferably, 1000 mg given on day one and day 21.

Emibetuzumab, and an anti-MET inhibitor, preferably, merestinib, or a pharmaceutically acceptable salt thereof, are preferably formulated as pharmaceutical compositions administered by any route which makes the compound bioavailable. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver. Preferably, an anti-MET inhibitor, more preferably, merestinib, or a pharmaceutically acceptable salt thereof, compositions are for oral administration, although parenteral administration, including intravenous or subcutaneous administration, may be used. (See, *e.g.*, Remington: The Science and Practice of Pharmacy (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006.) Pharmaceutical compositions of emibetuzumab are for parenteral administration, such as intravenous or subcutaneous administration. More preferably, emibetuzumab compositions comprise about 10 to about 20 mg/ml of emibetuzumab, about 10 to about 20 mM histidine buffer, pH 5.5-6.0, about 75 mM to about 150 mM sodium chloride, about 0.01% to about 0.06% polysorbate 80, and, optionally, about 100 mM to about 150 mM glycine. Preferably, emibetuzumab compositions are formulated for intravenous administration and comprise about 20 mg/ml of emibetuzumab, about 10 mM histidine buffer, pH 5.5, about 150 mM sodium chloride, and about 0.06% polysorbate 80. Such pharmaceutical compositions and processes for preparing same are well known in the art. (See, *e.g.*, Remington: The Science and Practice of Pharmacy (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006.)

As used herein, the term “in combination with” refers to the administration of an anti-MET inhibitor, preferably merestinib, or a pharmaceutically acceptable salt thereof, and emibetuzumab either separately, simultaneously, or sequentially in any order, such as for example, at repeated intervals as during a standard course of treatment for a single cycle or more than one cycle, such that one agent can be administered prior to, at the same time, or subsequent to the administration of the other agent, or any combination thereof. It can also mean that one drug is given alone first until patients progress before the second drug is being added on.

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A main advantage of the combination treatments of the invention is the ability of producing marked anti-cancer effects in a patient without causing significant toxicities or adverse events, so that the patient benefits from the combination treatment method overall. The efficacy of the combination treatment of the invention can be measured by various endpoints commonly used in evaluating cancer treatments, including but not limited to, tumor regression, tumor weight or size shrinkage, time to progression, overall survival, progression free survival, overall response rate, duration of response, and quality of life. The therapeutic agents used in the invention may cause inhibition of metastatic spread without shrinkage of the primary tumor, may induce shrinkage of the primary tumor, or may simply exert a tumoristatic effect. Because the invention relates to the use of a combination of unique anti-tumor agents, novel approaches to determining efficacy of any particular combination therapy of the present invention can be optionally employed, including, for example, measurement of plasma or urinary markers of angiogenesis and/or cell cycle activity, tissue-based biomarkers for angiogenesis and/or cell cycle activity and/or circulating levels of MET exon 14 skipping polypeptides and/or MET mutations leading to MET exon 14 skipping or exon 14 skipping phenotype, and measurement of response through radiological imaging.

The following examples illustrate the unexpected benefit of the present combinations.

### Example 1

#### **Evaluation of the combination of merestinib (LY2801653) and emibetuzumab (LY2875358) in a xenograft tumor model bearing MET exon 14 skipping mutation(s)**

To determine the efficacy of merestinib, in combination with emibetuzumab, in an Hs746t-derived xenograft mouse model of human gastric carcinoma and to compare the combination effect to that of either monotherapy, studies conducted essentially as described below may be performed. Hs746t is a gastric cancer cell line known to have MET exon 14 skipping mutation(s) and MET amplification (Asaoka *et al.*, Biochem Biophys Res Commun 394:1042-1046).

*Study Designs and Methods:*

Female athymic nude mice (Envigo) are used for this study. Food and water are available ad libitum. Animals are acclimated for 1 week prior to any experimental manipulation. The study is performed in accordance with AAALAC accredited institutional guidelines.

Merestinib is formulated as a solution in 10% PEG 400/90% (20% Captisol in water). Emibetuzumab is diluted in phosphate buffered saline (PBS). Solutions are freshly prepared every 7 days.

Obtain Hs746t cells from ATCC (American Type Culture Collection) and maintain in RPMI 1640 with 10% fetal bovine serum at 37 °C in 5% CO<sub>2</sub>. Expand cells in culture, harvest, and wash in Hank's Balanced Salt Solution (HBSS, GIBCO®). Implant sub-confluent MKN45 cells into 60 female *nu/nu* mice at a concentration of  $1 \times 10^7$  cells in 0.2 ml HBSS subcutaneously into the hind flank of the animal. Randomize the animals when tumors reach an average volume of 350 mm<sup>3</sup> by tumor volume into four treatment groups ( $n = 7$ ): PBS vehicle control; merestinib (at 6 mg/kg or 12 mg/kg), qd orally; emibetuzumab, at 10 mg/kg, IP, qw; merestinib (at 6 mg/kg or 12 mg/kg) qd orally and emibetuzumab at 10 mg/kg, IP, qw.

Administer merestinib by oral gavage at either 6 mg/kg or 12 mg/kg in a dose volume of 0.2 mL in 10% polyethylene glycol 400/ 90% of a mixture of 20% Captisol in water, and antibody treatments by intraperitoneal injection (IP) starting on day 12 after tumor cell implantation when average tumor volume of 350 mm<sup>3</sup> and ending on Day 33. Inject animals IP in a dosing volume of 10 mg/kg. After 14 days of dosing (Study Day 27), the animals in the control group are sacrificed because of tumor volumes exceeding >2000 mm<sup>3</sup>. After the 28-day dosing period, animals in the single agent arms are sacrificed. Tumors in the animals in the combination treatment groups are observed for an additional 2 weeks.

In both studies, animals are sacrificed using CO<sub>2</sub> and cervical dislocation when tumors grow larger than 2000 mm<sup>3</sup>, or at the end of study.

Dose animals in treatment group 4, with merestinib first, followed by emibetuzumab, 30 – 45 minutes later. Record tumor growth and body weight changes at least twice a week. Body weight measurement during the course of the study, is a general indicator of tolerability.

- 5           Measure tumor growth with calipers and record body weights twice weekly. Calculate tumor volumes by the formula  $Volume (mm^3) = L \times W^2 (\pi/6)$  where  $L$  represents the larger diameter and  $W$  the smaller diameter. Calculate T/C% using the formula  $T/C\% = 100 \times \Delta T / \Delta C$ . Where  $\Delta T$  = mean tumor volume of the drug-treated group on the final day of the study – mean tumor volume of the drug-treated group on the initial day of the dosing and  $\Delta C$  = mean tumor volume of the control group on the final day of the study – mean tumor volume of the control group on the initial day of the dosing. Calculate changes in body weight by the formula  $(Weight\ on\ observation\ day - Weight\ on\ day\ 12) / Weight\ on\ Day\ 12 \times 100$ . Calculate test for significant differences between treatment groups by *RM ANOVA* using the JMP (v.9.0.3) statistical package (SAS Institute Inc., 15 Cary, NC, USA).

#### *Results:*

- Merestinib inhibits Hs746t cell proliferation with  $IC_{50}=34nM$  and totally eliminates pMET at 65-100nM. Emibetuzumab slightly inhibits Hs746t cell proliferation ( $IC_{50}>100nM$ ), reduces 10-20% cell surface MET, and shows no effect on pMET expression (at 130-650nM).

- In the Hs746t xenograft model, merestinib (12 mg/kg) treatment results in 91.8% tumor regression after 21 day dosing, while 6 mg/kg merestinib provides transient tumor regression followed by re-growth while on treatment with T/C=18.3% after 21 day dosing. No tumor regrowth is observed in 6/7 mice in the 12mg/kg merestinib cohort during the 5 weeks post-treatment. Emibetuzumab treatment provides transient tumor regression (37.7%) after 3 doses, but tumors are observed to regrow while on treatment. Combination of 6 mg/kg merestinib and 10 mg/kg emibetuzumab results in 85% tumor regression for the duration of the 28 day

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dosing period and the treatment is well tolerated. Regrowth of tumors in animals is observed upon termination of this combination treatment.

All animals are shown to have survived the dosing and observation period. No loss in body weight is observed in the combination treatment group. All mice in the vehicle control group display disease progression.

To assess the effect of the combination of merestinib and emibetuzumab, a repeated measures ANOVA model is fit on log transformed tumor volume using the mixed procedure in SAS software (version 9.3, Cary, NC) followed by a 2x2 interaction test to test for statistical significance of the combination of the two single agents. The observed percent reduction of the combination on day 28 is 83.1%. The expected percent reduction of the combination on day 28 is 81.5%. The p-value from the 2x2 interaction test on day 28 is not significant at  $p=0.654$ . All pairwise comparisons between the combination group and each single agent group on day 33 are also statistically significant. By inspection of the means, these results indicate that the combination group is statistically smaller than each single agent group. Full statistical analysis is not feasible as the animals in the vehicle control groups were removed after 14 days of dosing as the animals are sacrificed due to tumor burden.

The data of Example 1 indicates that the combination of merestinib and emibetuzumab results in tumor regression.

## Example 2

### **Evaluation of sequential and concurrent administration of merestinib (LY2801653) and emibetuzumab (LY2875358) in a xenograft tumor model bearing MET exon 14 skipping mutation(s)**

To determine the efficacy of low-dose merestinib, in sequential and concurrent combination with emibetuzumab, in an Hs746t-derived xenograft mouse model of human gastric carcinoma, and to compare the combination effect to that of higher-dose emibetuzumab monotherapy, studies conducted essentially as described below may be performed.

*Study Designs and Methods:*

Female athymic nude mice (Envigo) are used for this study. Food and water are available ad libitum. Animals are acclimated for 1 week prior to any experimental manipulation. The study is performed in accordance with AAALAC accredited institutional guidelines.

Merestinib is formulated as a solution in 10% PEG 400/90% (20% Captisol in water). Emibetuzumab and IgG control are diluted in PBS. Solutions are freshly prepared every 7 days.

Obtain, maintain, expand, harvest, and wash Hs746t cell as in Example 1. Implant cells into 36 female *nu/nu* mice at a concentration of  $2 \times 10^6$  cells in 0.2 ml HBSS subcutaneously into the hind flank of the animal. Randomize the animals (N=36) when tumors reach an average volume of  $350 \text{ mm}^3$  by tumor volume into five treatment groups ( $n = 6$ ): combined vehicle control of 10% PEG 400/90% (20% Captisol in water) administered by oral gavage qd, and IgG control at 10 mg/kg administered via IP injection qw; emibetuzumab (10 mg/kg and 20 mg/kg) administered via IP injections qw for 4 cycles; emibetuzumab (10 mg/kg) administered via IP qw for 7 cycles with concurrent administration of merestinib (6 mg/kg) administered orally qd for 50 days; and merestinib (6mg/kg), administered orally qd for 17 days, as single agent, with sequential combination administration of emibetuzumab (10 mg/kg) administered via IP qw for 6 cycles starting on day 37 (whereupon tumor regression and regrowth to  $500 \text{ mm}^3$  after single agent merestinib (day 37) is observed), for a total of 58 days of merestinib dosing. After the 28-day dosing period, animals in the single agent arms are sacrificed. Tumors in the animals in the combination treatment groups are monitored for continued growth or regrowth of tumors.

In these studies, animals are sacrificed using  $\text{CO}_2$  and cervical dislocation when tumors grow larger than  $2000 \text{ mm}^3$ , or at the end of study.

Measure tumor volumes and body weight at least twice weekly. Body weight measurement during the course of the study, is a general indicator of tolerability.

Measure tumor growth with calipers and record body weights twice weekly.

Calculate tumor volumes by the formula  $Volume (\text{mm}^3) = L \times W^2 (\pi/6)$  where  $L$  represents

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the larger diameter and  $W$  the smaller diameter. Calculate  $T/C\%$  using the formula  $T/C\% = 100 \times \Delta T / \Delta C$ . Where  $\Delta T$  = mean tumor volume of the drug-treated group on the final day of the study – mean tumor volume of the drug-treated group on the initial day of the dosing and  $\Delta C$  = mean tumor volume of the control group on the final day of the study – mean tumor volume of the control group on the initial day of the dosing. Calculate changes in body weight by the formula  $(Weight\ on\ observation\ day - Weight\ on\ day\ 12) / Weight\ on\ Day\ 12 \times 100$ . Calculate test for significant differences between treatment groups by *RM ANOVA* using the JMP (v.9.0.3) statistical package (SAS Institute Inc., Cary, NC, USA).

Transform tumor volume to the log scale to equalize variance across time and treatment groups. Analyze the log volume data with a two-way repeated measures analysis of variance by time and treatment using the MIXED procedures in SAS software (Version 9.3). The correlation model for the repeated measures is spatial power. Compare treated groups to the control group at each time point. The MIXED procedure is also used separately for each treatment group to calculate adjusted means and standard errors at each time point. Both analyses account for the autocorrelation within each animal and the loss of data that occurs when animals are removed or lost before the end of the study. The adjusted means and standard errors are plotted for each treatment group versus time. Full statistical analysis is not feasible as the animals in the vehicle control groups were removed after 17 days of dosing (study day 37), as half the animals from the vehicle group are removed and sacrificed due to tumor burden (tumor volume >2000 mm<sup>3</sup>).

### *Results:*

In the Hs746t xenograft model, merestinib (6 mg/kg qd for 58 days) results in transient tumor regression, with maximal regression (30.2%) occurring on Day 27 (7 days of dosing), followed by re-growth while on treatment; by Day 37, tumor volumes approach about 500 mm<sup>3</sup>. Sequential addition of emibetuzumab (10 mg/kg qw for 6 cycles) to merestinib treatment on Day 37 results in tumor regression in 5/6 animals, with complete regression and no tumor regrowth over a 26 day observation period after dosing

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completion in 2/6 animals. Transient tumor regression with slow regrowth during post-treatment observation is evident in an additional 2/6 animals. In an additional animal, tumor regression occurs to about 50 mm<sup>3</sup> with slow regrowth during the post-treatment observation. In the one non-responding animal, tumor size on day 37 is notably the largest (approximately 1200 mm<sup>3</sup>) in the entire cohort, when emibetuzumab treatment is initiated.

Concurrent treatment with merestinib (6 mg/kg qd for 50 days) and emibetuzumab (10 mg/kg qw for 7 cycles) results in initial tumor regression (87.5% on day 37), but regression proved transient, with slow tumor regrowth over the course of treatment. Tumor size approaches pre-treatment volumes by Day 70, and additional monitoring for a week post-treatment results in tumor size doubling in volume in 4/6 animals.

Single-agent emibetuzumab treatment (10 mg/kg and 20 mg/kg qw 28 days) results in transient tumor regression at both doses. In the 10 mg/kg cohort, maximum regression (16.0%) is observed on Day 27, with maximum regression (58.9%) in the 20 mg/kg cohort occurring on Day 37. Tumor volumes from both cohorts were not statistically significant ( $p = 0.129$ ).

In these studies, body weight measurements provide an indication of the tolerability of the various treatments. There were no significant decreases in body weight observed in any group.

The data of Example 2 indicates that the concurrent combination of low-dose merestinib and emibetuzumab results in transient tumor regression, with sequential combination of emibetuzumab to low-dose merestinib resulting in longer duration of treatment response.

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## SEQUENCE LISTING

## &lt;SEQ ID NO: 1; PRT1; Artificial Sequence&gt; Emibetuzumab LCVR

5

DIQMTQSPSSLSASVGDRVTTITCSVSSSVSSIYHLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSG  
SGSGTDFTLTISSLQPEDFATYYCQVYSGYPLTFGGGTKVEIK

## &lt;SEQ ID NO: 2; DNA; Artificial Sequence&gt; Emibetuzumab DNA LCVR

10

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAC  
TTGCAGTGTCTCAGCTCAAGTGTATCCTCCATTACTTGCAGTGGTATCAGCAGAAACCAGGGAAAG  
CCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCATCAAGGTTCAAGTGGC  
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTA  
CTACTGTCAAGTCTACAGTGGTTACCCGCTCACGTTCCGGCGGAGGGACCAAGGTGGAGATCAAA

15

## &lt;SEQ ID NO: 3; PRT1; Artificial Sequence&gt; Emibetuzumab HCVR

20

QVQLVQSGAEVKKPGASVKVSCKASGYTFDYYMHWVRQAPGQGLEWMGRVNPNNRRGTTYNQKFE  
GRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARANWLDYWGQGTITVTVSS

## &lt;SEQ ID NO: 4; DNA; Artificial Sequence&gt; Emibetuzumab DNA HCVR

25

CAGGTTCAAGTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAAGGTCTCCTG  
CAAGGCTTCTGGTTACACCTTTACCGACTACTACATGCACTGGGTGCGTCAGGCCCCCTGGTCAAG  
GTCTTGAGTGGATGGGTGCGTGTAAATCCTAACCGGAGGGGTACTACCTACAACCAGAAATTCGAG  
GGCCGTGTCAACATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGCGTAGCCTGCG  
TTCTGACGACACGCGGTGTATTACTGTGCGCGTGCAGAACTGGCTTGACTACTGGGGCCAGGGCA  
CCACCGTCACCGTCTCC

30

## &lt;SEQ ID NO: 5; PRT1; Artificial Sequence&gt; Emibetuzumab LC

35

DIQMTQSPSSLSASVGDRVTTITCSVSSSVSSIYHLHWYQQKPGKAPKLLIYSTSNLASGVPSRFSG  
SGSGTDFTLTISSLQPEDFATYYCQVYSGYPLTFGGGTKVEIKRTVAAPSVFI FPPSDEQLKSGT  
ASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSTLTLSKADYEKHKVYAC  
EVTHQGLSSPVTKSFNRGEC

## &lt;SEQ ID NO: 6; DNA; Artificial Sequence&gt; Emibetuzumab DNA LC

40

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAC  
TTGCAGTGTCTCAGCTCAAGTGTATCCTCCATTACTTGCAGTGGTATCAGCAGAAACCAGGGAAAG  
CCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCATCAAGGTTCAAGTGGC  
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTA  
CTACTGTCAAGTCTACAGTGGTTACCCGCTCACGTTCCGGCGGAGGGACCAAGGTGGAGATCAAA  
GAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA  
GCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGGTGGA  
TAACGCCCTCCAATCGGGTAACCTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCT  
ACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC  
GAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

45

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## &lt;SEQ ID NO: 7; PRT1; Artificial Sequence&gt; Emibetuzumab HC

5 QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWMGR  
VNPNNRGTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARAN  
WLDYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE  
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV  
10 DHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISR  
TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV  
LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQ  
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFF  
LYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLG

## &lt;SEQ ID NO: 8; DNA; Artificial Sequence&gt; Emibetuzumab HC

15 CAGGTTTCAGCTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAA  
GGTCTCCTGCAAGGCTTCTGGTTACACATTCAGTACTACTACATGCACTGGGTGCG  
TCAGGCCCTGGTCAAGGTCTTGAGTGGATGGGTCGTGTTAATCCTAACCGGAGGG  
20 GTACTACCTACAACCAGAAATTCGAGGGCCGTGTCACCATGACCACAGACACATC  
CACGAGCACAGCCTACATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGT  
ATTACTGTGCGCGTGCGAACTGGCTTGACTACTGGGGCCAGGGCACCACCGTCACC  
GTCTCCTCCGCTCCACCAAGGGCCCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGG  
AGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG  
AACC GG TGACGGTGTCGTGGAAC TCAGGCGCCCTGACCAGCGGCGTGACACCTT  
25 CCCGGCTGTCTTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGC  
CCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCCCAG  
CAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCACCC  
TGCCCAGCACCTGAGGCCGCCGGGGGACCATCAGTCTTCTGTTCCTCCCTCCAAACC  
CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTGGTGGACG  
30 TGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGT  
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGT  
GGTCAGCGTCTCACCCTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAG  
TGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAGC  
CAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA  
35 GATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCTACCCAGC  
GACATCGCCGTGGAGTGGGAAAGCAATGGGCAGCCGAGAGCAACTACAAGACC  
ACGCCCTCCCGTGGTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTG  
GACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGG  
40 CTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGT

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**<SEQ ID NO: 9; PRT; Homo sapiens> Extracellular domain of MET**

MKAPAVLAPGIIIVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHEH  
 HIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPCQDCSSKANLSGGVWVDNINMAL  
 VVDITYDDQLISCGSVNRGTCQRHVFPNNHTADIQSEVHCIFSPQIEEPSQCPDCVVSAL  
 5 GAKVLSSVKDRFINFFVGNTINSSYFPDHPLHSISVRRLKETKDGMFLTDQSYIDVLPE  
 FRDSYPIKYVHAFESNNFIYFLTVQRETLDQTFHTRIIRFCSINSGLHSEMPLECEIL  
 TEKRKKRSTKKEVFNILQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRS  
 AMCAFPIKYVNDFFNKIVNKNVRCLOHFYGNHEHCFNRTLRLNSSGCEARRDEYRTEF  
 10 TTALQVRDLFMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSRGPSTPHVNFL  
 LDSPVSPPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW  
 CHDKCVRSEECLESGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNKFDLKK  
 TRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVIT  
 SISPKYGPMAGGTLTLTGNYLNSGNSRHISIGGKTCTLKSVNSILECYTPAQTISTEF  
 15 AVKLKIDLANRETSIFSYPREDPIVYEIHPKTSFISGGSTITGVGKNLNSVSVPRMVINVH  
 EAGRNFTVACQHRNSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNVP  
 FKPFEKPVISMGNENVLEIKGNDIDPEAVKGEVLKVGKNKSCENIHLHSEAVLCTVPNDL  
 LKLNSLNIWQKQAISSTVLGKIVIVQPDQNT

**<SEQ ID NO: 10; PRT; Homo sapiens> Mature MET-ECD**

20 ECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHEH  
 HIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPCQDCSSKANLSGGVWVDNINMAL  
 VVDITYDDQLISCGSVNRGTCQRHVFPNNHTADIQSEVHCIFSPQIEEPSQCPDCVVSAL  
 GAKVLSSVKDRFINFFVGNTINSSYFPDHPLHSISVRRLKETKDGMFLTDQSYIDVLPE  
 25 FRDSYPIKYVHAFESNNFIYFLTVQRETLDQTFHTRIIRFCSINSGLHSEMPLECEIL  
 TEKRKKRSTKKEVFNILQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRS  
 AMCAFPIKYVNDFFNKIVNKNVRCLOHFYGNHEHCFNRTLRLNSSGCEARRDEYRTEF  
 TTALQVRDLFMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSRGPSTPHVNFL  
 LDSPVSPPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW  
 30 CHDKCVRSEECLESGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNKFDLKK  
 TRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVIT  
 SISPKYGPMAGGTLTLTGNYLNSGNSRHISIGGKTCTLKSVNSILECYTPAQTISTEF  
 AVKLKIDLANRETSIFSYPREDPIVYEIHPKTSFISGGSTITGVGKNLNSVSVPRMVINVH  
 EAGRNFTVACQHRNSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNVP  
 35 FKPFEKPVISMGNENVLEIKGNDIDPEAVKGEVLKVGKNKSCENIHLHSEAVLCTVPNDL  
 LKLNSLNIWQKQAISSTVLGKIVIVQPDQNT

**<SEQ ID NO: 11; PRT; Homo sapiens>  $\alpha$ -chain of MET**

40 ECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHEHHIFLGATNYIYVLNEEDLQKVAEY  
 KTGPVLEHPDCFPCQDCSSKANLSGGVWVDNINMALVVDITYDDQLISCGSVNRGTCQRH  
 VFPNNHTADIQSEVHCIFSPQIEEPSQCPDCVVSALGAKVLSSVKDRFINFFVGNTINSS  
 YFPDHPLHSISVRRLKETKDGMFLTDQSYIDVLPEFRDSYPIKYVHAFESNNFIYFLTV  
 QRETLDQTFHTRIIRFCSINSGLHSEMPLECEILTEKRKKR  
 45

**<SEQ ID NO: 12; PRT; Homo sapiens>  $\beta$ -chain of MET**

STKKEVFNILQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPI  
 KYVNDFFNKIVNKNVRCLOHFYGNHEHCFNRTLRLNSSGCEARRDEYRTEFTTALQVR

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DLFMGQFSEVLLTSISTFIKGLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLLDSHPVS  
PEVIVEHTLNQNGYTLVITGKKITKIPLNGLG

**<SEQ ID NO: 13; PRT; Artificial Sequence> MET Dx Ab LC**

5    EIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQRKQGRSPQLLVYNAKPLAEGVPSRFSGS  
     GSGTQFSLKINSLQPEDFGTYQCQHHYGTPFTFGSGTRLEIKRADAAPTVSIFFPSSEQLTSGGA  
     SVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCE  
     ATHKTSTSPIVKSFNRNEC

10   **<SEQ ID NO: 14; PRT; Artificial Sequence> MET Dx Ab HC**

     EVQLQQSGTVLARPGASVKMSCKASGYSTSYWYVWKQRPQGQLEWIGGFHPRNSGTNYNQKFK  
     GKAKLTAVTSASTAYMELSSLTNEDSAVYYCTRGYYDGSFTYWGQGLTVTVSAAKTTPPSVYPL  
     APGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWP  
     SETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLTTITLTPKVTCTVVV  
15   DISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFP  
     APIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNT  
     QPIMDTDGSYFVYSKLVNQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK

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## WE CLAIM:

1. A method of treating cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype in a patient, comprising administering to a patient in need of such treatment an effective amount of merestinib, or a pharmaceutically acceptable salt thereof in combination with an effective amount of emibetuzumab.
2. The method according to Claim 1 wherein merestinib, or a pharmaceutically acceptable salt thereof, is administered at a dose of between about 60 mg to about 160 mg daily on a 28-day cycle and emibetuzumab is administered at a dose of about 500 mg to about 2000 mg on about day 1 and about day 15 of the 28-day cycle of merestinib dosing.
3. The method according to Claim 2 wherein merestinib, or a pharmaceutically acceptable salt thereof, is administered at a dose of between about 80 mg to about 120 mg daily on a 28-day cycle and emibetuzumab is administered at a dose of about 750 mg on about day 1 and about day 15 of the 28-day cycle of merestinib dosing.
4. The method according to Claims 2 or 3 wherein merestinib, or a pharmaceutically acceptable salt thereof, is administered orally and emibetuzumab is administered intravenously.
5. The method according to any one of Claims 1 to 4 wherein the cancer is gastric cancer or lung cancer.
6. The method according to any one of Claims 1 to 5 wherein the cancer is lung cancer.
7. The method according to Claim 6 wherein the cancer is non-small cell lung cancer.

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8. A kit comprising an an effective amount of emibetuzumab in combination with an effective amount of the compound merestinib, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype.
9. The kit for use according to Claim 8 wherein the cancer is gastric cancer or lung cancer.
10. The kit for use according to Claims 8 or 9 wherein the cancer is lung cancer.
11. The kit for use according to Claim 10 wherein the cancer is non-small cell lung cancer.
12. A combination comprising emibetuzumab and meristinib, or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use in the treatment of cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype.
13. The combination for use according to Claim 12 wherein the cancer is gastric cancer or lung cancer.
14. The combination for use according to Claims 12 or 13 wherein the cancer is lung cancer.
15. The combination for use according to Claim 14 wherein the cancer is non-small cell lung cancer.
16. The use of the combination comprising emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, in therapy.

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17. The use of the combination comprising emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, for treating cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype.
- 5 18. The use of the combination comprising emibetuzumab and merestinib, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer with tumors bearing MET exon 14 skipping or MET exon 14 skipping phenotype.
- 10 19. The use according to any of Claims 16 to 18 wherein the cancer is gastric or lung cancer.
20. The use according to any of Claims 16 to 18 wherein the cancer is lung cancer.
- 15 21. The use according to any of Claims 16 to 18 wherein the cancer is non-small cell lung cancer.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/061028

### 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. ☒ forming part of the international application as filed:
    - ☒ 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.
  - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
    - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
    - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
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/US2017/061028

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K31/435 A61K39/395 A61P35/00  
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 A61P

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, WPI Data, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
L	SAU-CHI BETTY YAN ET AL: "Abstract #528: Evaluation of single agent merestinib (LY2801653) or emibetuzumab (LY2875358) and the combination in a xenograft tumor model bearing MET exon 14 skipping", PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 58, 1 April 2017 (2017-04-01), page 132, XP055390405, the whole document  -----  -/-	1-21



Further documents are listed in the continuation of Box C.



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

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"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

9 February 2018

Date of mailing of the international search report

07/03/2018

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/061028

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>REUNGWETWATTANA THANYANAN ET AL: "The race to targetMETexon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable", LUNG CANCER, vol. 103, 15 November 2016 (2016-11-15), pages 27-37, XP029863831, ISSN: 0169-5002, DOI: 10.1016/J.LUNGCAN.2016.11.011 page 32, column 2, paragraph 4 - paragraph 5; table 2 page 33, column 2, paragraph 2 abstract</p>	1-21
A	<p>-----</p> <p>ASSUNTA SGAMBATO ET AL: "The c-Met inhibitors: a new class of drugs in the battle against advanced nonsmall-cell lung cancer.", CURRENT PHARMACEUTICAL DESIGN, vol. 18, no. 37, 1 January 2012 (2012-01-01), pages 6155-6168, XP055087133, ISSN: 1381-6128, DOI: 10.2174/138161212803582478 page 6157, column 1, paragraph 5 - column 2, paragraph 2 page 6165, column 1, paragraph 5</p>	1-21
A	<p>-----</p> <p>L. LIU ET AL: "LY2875358, a Neutralizing and Internalizing Anti-MET Bivalent Antibody, Inhibits HGF-Dependent and HGF-Independent MET Activation and Tumor Growth", CLINICAL CANCER RESEARCH, vol. 20, no. 23, 17 September 2014 (2014-09-17), pages 6059-6070, XP055425191, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-14-0543 the whole document</p> <p>-----</p>	1-21