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(54) Title: COMBINATION TREATMENTS WITH SERIBANTUMAB

(57) Abstract: Compositions and methods for treating a cancer in a selected human patient are provided, comprising administering to the patient a combination of an anti-ErbB3 antibody (e.g., Seribantumab) and a second anti-cancer therapeutic. A cancer to be treated by the methods and compositions disclosed herein includes cancers that are heregulin (HRG) positive cancers.

# COMBINATION TREATMENTS WITH SERIBANTUMAB

## RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 62/149,271 filed April 17, 2015, the contents of which are hereby incorporated by reference.

## BACKGROUND

Non-Small-Cell Lung Cancer (NSCLC)

Lung cancer is one the leading causes of cancer-related deaths worldwide. There were estimated to be 224,410 new cases diagnosed in 2014 alone, making up approximately 13% of all cancer diagnoses. For cases diagnosed during the period of 2003-2009, the 1- and 5-year survival rates were 43% and 17% respectively ("American Cancer Society Facts and Figures 2014"). Over 80% of lung cancers are non-small cell lung cancers (NSCLC), and nearly two thirds of these are diagnosed at an advanced stage. A platinum-based doublet regimen with a "third-generation" agent (paclitaxel, docetaxel, gemcitabine, vinorelbine, or pemetrexed) is considered standard of care worldwide for the treatment of advanced NSCLC. However, only one third of patients that receive this regimen reach an objective response during first-line therapy, and another 20-30% achieves stabilization of disease. Unfortunately, almost all such patients ultimately see progression of their disease.

Current Treatments for NSCLC

Three agents that are currently approved for treatment of refractory (recurrent, i.e., second-line treatment) advanced NSCLC are docetaxel, pemetrexed, and erlotinib.

Docetaxel, brand names TAXOTERE®, DOCECAD® - IUPAC name 1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}, is an anti-mitotic taxane anti-cancer therapeutic that is typically administered via a one-hour infusion every three weeks over ten or more cycles. The approved dose of docetaxel in the second-line treatment of NSCLC is 75 $mg/m^2$ intravenously over 60 minutes once every 3 weeks. Docetaxel should be administered prior to seribantumab dosing.

Pemetrexed, brand name ALIMTA® - IUPAC name (2S)-2-{[4-[2-(2-amino-4-oxo-1,7-dihydro pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]amino}pentanedioic acid), is a folate antimetabolite currently approved for the treatment of pleural mesothelioma and non-small cell lung cancer. It is typically administered at a dose of 500 $mg/m^2$ intravenously over 10 minutes on day 1 of each 21-day cycle.

Ovarian cancer

Ovarian cancer, including epithelial ovarian cancer is a leading cause of cancer-related death in women, as are primary peritoneal carcinoma and fallopian tube carcinoma. Since ovarian cancer is relatively asymptomatic at its early stages, it often remains undiagnosed until the disease has reached an advanced stage. The standard treatment for advanced ovarian cancer includes surgery followed by chemotherapy with a platinum-based chemotherapeutic agent, e.g., cisplatin, carboplatin, oxaliplatin, and satraplatin, or with an antimicrotubule agent such as paclitaxel. Other drugs used to treat ovarian cancer include bevacizumab, carboplatin, cyclophosphamide, doxorubicin, gemcitabine, olaparib, and topotecan. Although standard treatments are often successful, many patients suffer a recurrence of the disease, often with expression of resistance to platinum-based regimens.

Seribantumab, an anti-ErbB3 monoclonal antibody therapeutic

Seribantumab (previously MM-121 or Ab #6) is an human monoclonal anti-ErbB3 IgG2; see, e.g., U.S. Patent Nos. 7,846,440; 8,691,771 and 8,961,966; 8,895,001, U.S. Patent Publication Nos., 20110027291, 20140127238, 20140134170, and 20140248280), as well as international Publication Nos. WO/2013/023043, WO/2013/138371, WO/2012/103341, and U.S. Patent Application serial No. 14/967,158.

Seribantumab is a recombinant human IgG2 mAb that binds an epitope on human ErbB3 with high specificity. The complete tetrameric structure of the IgG2 molecule is composed of 2 heavy chains (445 amino acids each) and 2 lambda light chains (217 amino acids each) held together by intrachain and interchain disulfide bonds. The amino acid sequence (see below) predicts a molecular weight of 143 kDa for the intact nonglycosylated monomer IgG2. Glycosylation analysis demonstrates N-linked glycosylation of seribantumab, which is predicted to contribute approximately 2.9 kDa to the molecular weight of the intact glycosylated seribantumab monomer. The predicted molecular weight of intact glycosylated seribantumab, 146 kDa, is within 0.2% of the actual molecular weight as experimentally determined by mass spectroscopy. The isolectric point of seribantumab is approximately 8.6 (major isoform as determined by isoelectric focusing electrophoresis).

Seribantumab is administered by intravenous infusion (e.g., over the course of one hour) and is supplied as a clear liquid solution in sterile, single-use vials containing 10.1 ml of seribantumab at a concentration of 25 mg/ml in an aqueous solution of 20mM histidine, 150mM sodium chloride, at a pH of about 6.5 (in the range of 6.2 to 6.8), to be stored at 2-8°C. Seribantumab comprises a heavy chain having the amino acid sequence of SEQ ID NO:7 and a light chain having the amino acid sequence of SEQ ID NO:8. Seribantumab comprises a heavy chain variable region (VH) and a light

chain variable region (VL) encoded by the nucleic acid sequences set forth in SEQ ID NOs:9 and 11, respectively. Seribantumab comprises VH and VL regions comprising the amino acid sequences set forth in SEQ ID NOs:10 and 12, respectively. Seribantumab comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3).

Evaluation of Treatment Outcomes

Treatment outcomes for NSCLC, ovarian cancer, primary peritoneal carcinoma and fallopian tube carcinoma are evaluated using standard measures for tumor response. TARGET LESION (tumor) responses to therapy are classified as:

*Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm;

*Partial Response (PR):* At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters;

*Progressive Disease (PD:* At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression); and

*Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or less that does not increase the sum of the diameters by 5 mm or more is coded as stable disease). To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

NON-TARGET LESION responses to therapy are classified as:

*Complete Response (CR):* Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis). If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response;

*Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits; and

*Progressive Disease (PD):* Either or both of appearance of one or more new lesions and unequivocal progression of existing non-target lesions. In this context, unequivocal progression must be representative of overall disease status change, not a single lesion increase.

OTHER EXEMPLARY POSITIVE RESPONSES

Patients treated with these methods may experience improvement in at least one sign of NSCLC or ovarian cancer, primary peritoneal carcinoma and fallopian tube carcinoma. Response may also be measured by a reduction in the quantity and/or size of measurable tumor lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as >10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target lesions, e.g., pathological lymph nodes can also be measured for improvement. Lesions can be measured using, e.g., x-ray, CT, or MRI images. Microscopy, cytology or histology can be also used to evaluate responsiveness to a therapy. An effusion that appears or worsens during treatment when a measurable tumor has otherwise met criteria for response or stable disease can be considered to indicate tumor progression, but only if there is cytological confirmation of the neoplastic origin of the effusion.

Although the currently approved treatments for NSCLC ovarian cancer, primary peritoneal carcinoma and fallopian tube carcinoma provide some benefit, there is still much room for improvement, particularly for patients with advanced or metastatic disease. Thus more effective treatments for patients with advanced NSCLC, ovarian cancer, primary peritoneal carcinoma and fallopian tube carcinoma are needed. The present invention addresses this need and provides additional benefits.

## SUMMARY

Provided are compositions and methods for treating a cancer in a selected human patient, comprising administering to the patient a combination of an anti-ErbB3 antibody and a second anti-cancer therapeutic.

The cancer may be a non-small cell lung cancer (NSCLC) e.g., nonsquamous NSCLC, and the second anti-cancer therapeutic may be, e.g., docetaxel or pemetrexed, wherein the combination is administered (or is for administration) according to a particular clinical dosage regimen (i.e., at a particular dose amount and according to a specific dosing schedule). The cancer may instead be an ovarian cancer (e.g., persistent, recurrent, resistant, or refractory ovarian cancer) or the cancer may be primary peritoneal carcinoma or fallopian tube carcinoma and, for each of these the second anti-cancer therapeutic may be, e.g., paclitaxel, gemcitabine, irinotecan, liposomal irinotecan (e.g., nal-

IRI) or liposomal doxorubicin, e.g., DOXIL®. In one embodiment, the cancer is a locally advanced or metastatic NSCLC that has progressed (i.e., is treatment refractory) after prior therapy with an organoplatinum agent. In one embodiment, the NSCLC is squamous cell carcinoma. In another embodiment, the cancer is EGFR wild-type.

In one aspect, a method of treating a cancer in an adult human patient is provided, the method comprising administering to the patient an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3), wherein the anti-ErbB3 antibody is administered as a first single dose of 3000 mg, regardless of patient body mass. In one embodiment, the first single dose is followed by at least one additional single dose, each of which at least one additional dose is administered three weeks after the immediately prior dose and is administered at a dosage of 3000 mg, regardless of patient body mass.

In a second aspect a method of treating a cancer patient who has a NSCLC tumor; and has progressed following treatment with no more than two systemic therapies for locally advanced or metastatic disease, of which one if which therapies was a platinum-based regimen is provided; the method comprising administering to the patient an effective amount of each of (1) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3), and (2) docetaxel or pemetrexed.

In a third aspect a composition for treating a cancer in an adult human patient is provided, the composition comprising an antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3), wherein the composition is for administration as a first single dose of 3000 mg, regardless of patient body mass. In one embodiment, the composition is for administration as a first single dose of 3000 mg, regardless of patient body mass, followed by at least one additional single dose, each of which at least one additional dose is administered three weeks after the immediately prior dose and is administered at a dosage of 3000 mg, regardless of patient body mass.

In one embodiment, the cancer is non-small cell lung cancer (NSCLC). In another embodiment, the cancer is ovarian cancer.

In one embodiment, the patient has progressed following treatment with no more than two systemic therapies for locally advanced or metastatic disease, of which one was a prior platinum-based regimen. In another embodiment, the patient has progressed following treatment with no more than three systemic therapies for locally advanced or metastatic disease, of which one was a prior platinum-based regimen. In another embodiment, the human patient is treated following disease progression or recurrence after prior treatment with antineoplastic therapy (*e.g.,* anti-cancer agent). In another embodiment, the human patient is treated after failure of an antineoplastic therapy. In another embodiment, the cancer is identified as a cancer that has acquired resistance to antineoplastic therapy.

In exemplary embodiments of any of the above aspects, the methods disclosed herein further comprise coadministration of an effective amount of a second anti-cancer therapeutic with the anti-ErbB3 antibody. In one embodiment, the second anti-cancer therapeutic is docetaxel, and wherein the effective amount of docetaxel is 75 mg/m$^2$. In another embodiment the second anti-cancer therapeutic is pemetrexed, and wherein the effective amount is 500 mg/m$^2$. In one embodiment, the effective amount of the docetaxel or pemetrexed is co-administered at least 30 minutes before the administration of the antibody.

In a fourth aspect, a composition for treating a cancer in an adult human patient is provided, the composition comprising an antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3), wherein the composition is for administration as a first single dose of 3000 mg, regardless of patient body mass. In one embodiment, the composition is for administration as a first single dose of 3000 mg, regardless of patient body mass, followed by at least one additional single dose, each of which at least one additional dose is administered three weeks after the immediately prior dose and is administered at a dosage of 3000 mg, regardless of patient body mass. In another embodiment, the composition is for administration at a dose of 20 mg/kg. In one embodiment, the ovarian cancer is persistent, recurrent, resistant, or refractory ovarian cancer.

In a fifth aspect, a method of treating a cancer patient who has an ovarian tumor is provided, a primary peritoneal carcinoma or a fallopian tube carcinoma, the method comprising administering to the patient an effective amount of each of (1) an anti-ErbB3 antibody comprising CDRH1,

CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3), and (2) paclitaxel, irinotecan, or gemcitabine.

In exemplary embodiments of any of the above aspects, the anti-ErbB3 antibody is seribantumab.

In one embodiment the treatment methods described herein comprise administering seribantumab in combination with one or more other antineoplastic agents (*e.g.*, other chemotherapeutics, other anti-cancer agents, or other small molecule drugs).

In one embodiment, no more than three other anti-cancer therapeutics are administered within a treatment cycle. In another embodiment, no more than two other anti-cancer therapeutics are administered in combination with seribantumab within the treatment cycle. In another embodiment, no more than one other anti-cancer therapeutic is administered in combination with seribantumab within the treatment cycle. In another embodiment, no other anti-cancer therapeutic is administered in combination with seribantumab within the treatment cycle. In another embodiment, the other anti-cancer therapeutics may be administered either simultaneously or before or after administration of seribantumab.

A cancer to be treated by the methods and compositions disclosed herein includes cancers that are heregulin (HRG) positive cancers, optionally wherein HRG positivity is determined by a HRG RNA-ISH assay or a quantitative RT-PCR assay. In such assay a sample is determined to be positive if such assay reveals at least 1-3 dots per cell, wherein the cells are from patient tumor samples. In one embodiment, HRG positivity is based on an FDA-approved test. In one embodiment, the cancer is non-small cell lung cancer (NSCLC). In another embodiment, the cancer is locally advanced or metastatic. In another embodiment, the patient has progressed following treatment with no more than two systemic therapies for locally advanced or metastatic disease, one of which systemic therapies comprised a platinum-based regimen.

In one embodiment, the treatment of a cancer comprising the compositions and/or methods of any of the above aspects produces at least one therapeutic effect selected from the group consisting of: reduction in size of a tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** shows that the capacity of heregulin (HRG) to induce proliferation in a panel of NSCLC cell lines *in vitro* is indicative of single-agent response to seribantumab *in vivo*. Nine out of 25 EGFR wild-type NSCLC cell lines are responsive to HRG; they exhibit increased cell proliferation in response to exogenously added HRG, as measured by CellTiter-Glo® (CTG) using 3D spheroid cultures.

**Figures 2A-2D** are four graphs showing that cells responsive to HRG *in vitro* responded to seribantumab *in vivo*, while cell lines not responsive to HRG *in vitro* did not respond to seribantumab *in vivo*. HRG-responsive cell lines A549 (Figure 2A) and H322M (Figure 2B) as well as HRG non-responsive cell lines H460 (Figure 2C) and HOP-92 (Figure 2D) are shown.Tumor volume over time is shown as indicative of seribantumab response.

**Figures 3A-3D** are four graphs showing that 5nM HRG induces resistance to docetaxel (111nM, Figure 3A) and pemetrexed (1111nM, Figure 3B) in a 3D spheroid proliferation assay in multiple cell lines after 96hrs; Figure 3C and Figure 3D show that treatment with seribantumab (1μM, "MM-121") restores sensitivity to docetaxel (Figure 3C) and pemetrexed (Figure 3D) in NSCLC cell lines (A549, EKVX, H358, H322M, Calu-3, H661, H441, H1355, H430).

**Figure 4** is a set of graphs showing HRG mRNA expression levels across different indications based on the TCGA data set.

**Figures 5A and 5B** are two graphs shows HRG mRNA expression across NSCLC tissue samples from both the MM-121-01-101 phase II Study (Figure 5A) and commercially-sourced biopsy specimens (Figure 5B).

**Figures 6A-6C** are a set of box and whisker plots (indicating interquartile ranges and outliers) showing seribantumab pharmacokinetics for weight-based and fixed dosing regimens by doses and intervals. Figure 6A shows seribantumab maximum concentration (Cmax, mg/L), Figure 6B shows seribantumab minimum concentration (Cmin, mg/L), and Figure 6C shows seribantumab average concentration (AvgConc, mg/L). Weight-based and fixed doses are indicated along the y-axis.

**Figures 7A-7C** are a set of graphs showing that heregulin mediates resistance to treatment regardless of the class of chemotherapy, and that co-administration with seribantumab ("MM-121") abrogates this resistance. In a mouse OVCAR8 xenograft model of ovarian cancer, tumor-bearing mice were treated with paclitaxel (Figure 7A), irinotecan (Figure 7B), or gemcitabine (Figure 7C), either alone as monotherapies or with a fixed dose of seribantumab. In each case, the tumors treated with paclitaxel, irinotecan, gemcitabine monotherapy began to

progress over time, whereas this effect was greatly reduced when the chemotherapeutics were co-administered with seribantumab. Control mice received PBS alone.

**DETAILED DESCRIPTION**

Provided herein are methods for effective treatment of platinum refractory NSCLC (e.g., a locally advanced or metastatic NSCLC) in a human patient using a combination of seribantumab and either a taxane, (e.g., docetaxel) or a folate antimetabolite (e.g., pemetrexed). I. Patient Selection

A NSCLC patient selected for treatment is an adult patient who has failed at least one, but not more than three, systemic therapies for locally advanced or metastatic NSCLC, one which failed systemic therapies must have been a platinum-based therapy (e.g., a doublet therapy). In another aspect, the NSCLC patient has one or more NSCLC tumors that are positive for heregulin (HRG) mRNA as assessed by an RNA-ISH assay, as described in the Examples below. In one embodiment, the NSCLC tumor is positive for HRG as assessed by an FDA-approved test.

In another aspect, the invention provides methods for effective treatment of cancer (*e.g.*, NSCLC) in a human patient in need thereof who previously received antineoplastic therapy and developed resistance to the antineoplastic therapy. For example, in one embodiment, the method comprises treating cancer in a human patient in need thereof who previously received antineoplastic therapy and developed resistance to the antineoplastic therapy by administering seribantumab and either a taxane, (e.g., docetaxel) or a folate antimetabolite (e.g., pemetrexed).

II. Combination Therapies

Seribantumab is to be co-administered with a taxane (e.g., docetaxel) or a folate antimetabolite (e.g., pemetrexed), to a selected subject with NSCLC. In another embodiment, seribantumab is to be co-administered with paclitaxel, irinotecan, or gemcitabine to a selected subject with an ovarian cancer, primary peritoneal carcinoma or fallopian tube carcinoma.

"Co-administer" refers to simultaneous or sequential administration of the seribantumab and the taxane or folate antimetabolite. When sequential, co-administration must occur within a timespan that is short enough so that both the seribantumab and the taxane or folate antimetabolite are simultaneously present in treated patients.

In one embodiment, seribantumab is co-administered with the taxane docetaxel. Docetaxel is approved for single agent use in treating breast cancer and NSCLC (post-platinum therapy), and in combination therapy for treatment of hormone refractory prostate cancer, NSCLC (in combination with cisplatin), gastric adenocarcinoma, and squamous cell carcinoma of

the head and neck. The approved dose regimen of docetaxel for the treatment of NSCLC is 75 $mg/m^2$, given intravenously over 1 hour, once every 3 weeks.

In another embodiment, seribantumab is co-administered with the folate antimetabolite pemetrexed, also marketed under the trade name ALIMTA®. ALIMTA is approved for combination therapy treatment of non-squamous cell NSCLC and mesothelioma. The recommended dose of ALIMTA is 500 $mg/m^2$ i.v. on Day 1 of each 21-day cycle. Dose reductions may be needed if toxicity is observed in combination therapy regimens, and may be adjusted in subsequent cycles.

In another embodiment, no more than three other anti-cancer therapeutics are administered in combination with seribantumab within a treatment cycle. In another embodiment, no more than two other anti-cancer therapeutics are administered in combination with seribantumab within the treatment cycle. In another embodiment, no more than one other anti-cancer therapeutic is administered in combination with seribantumab within the treatment cycle. In another embodiment, no other anti-cancer therapeutic is administered in combination with seribantumab within the treatment cycle. In another embodiment, the other anti-cancer therapeutics may be administered either simultaneously or before or after administration of seribantumab.

As used herein, "antineoplastic agent" refers to agents that have the functional property of inhibiting a development or progression of a neoplasm in a human, particularly a malignant (cancerous) lesion, such as a carcinoma, sarcoma, lymphoma, or leukemia. Inhibition of metastasis is frequently a property of antineoplastic agents.

III. Treatment Protocols

A selected patient having advanced or metastatic NSCLC is treated on day 1 of at least one 21-day treatment cycle. Prior to the first treatment cycle, the patient undergoes a pre-treatment regimen. The regimen is specific to the upcoming chemotherapeutic treatment (e.g., pemetrexed or docetaxel) and is designed to mitigate pemetrexed- or docetaxel-related toxicity. Docetaxel pre-treatment comprises premedication with a corticosteroid such as dexamethasone (e.g., 8 mg twice daily) for three days, starting one day prior to docetaxel administration. Pemetrexed pre-treatment comprises premedication with a low-dose oral folic acid preparation (or multivitamin containing folic acid) on a daily basis, starting at least seven days before the start of the first 21-day cycle. On day 1 of each 21-day cycle, the patient will receive a standard dose of docetaxel or pemetrexed intravenously at least 30 minutes prior to the administration of seribantumab. Seribantumab is then administered intravenously over 90 minutes (on day 1 of the first 21-day cycle) or 60 minutes (on day 1 of any subsequent 21-day cycle).

As used herein, the term "fixed dose" (also known as a "flat dose" or a "flat-fixed dose") is used refer to a measured dose that is administered to an adult patient without regard for the weight or body surface area (BSA) of the patient. The fixed dose is therefore not provided as a mg/kg (weight-based) dose, or as a mg/m$^2$ (BSA) dose, but rather as an absolute amount of an agent (*e.g.*, mgs of the anti-ErbB3 antibody) to be administered to an adult patient in a single administration.

IV. Outcomes

A patient treated in accordance with the disclosed protocols may exhibit CR, PR, or SD with respect to target lesions. In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, tumor cell proliferation is reduced or inhibited. Alternately, one or more of the following can indicate a beneficial response to treatment: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent. Other indications of a favorable response include reduction in the quantity and/or size of measurable tumor lesions or of non-target lesions.

V. Kits and Unit Dosage Forms

Also provided are kits that include, in an inner container (e.g., a vial) contained within an outer container (e.g., a bag, clamshell or box), a composition comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO:1 (CDRH1) SEQ ID NO:2 (CDRH2) and SEQ ID NO:3 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:4 (CDRL1) SEQ ID NO:5 (CDRL2) and SEQ ID NO:6 (CDRL3) and a pharmaceutically acceptable carrier, in a therapeutically effective unit dosage form (e.g., as a single dose) for use in the preceding methods. Optionally, the anti-ErbB3 antibody is seribantumab. Unit dosage forms will typically comprise an amount of drug, optionally slightly above the dosage amount (e.g., 3000 mg) to facilitate removal of the required amount from the inner container. This dosage amount may comprise multiple vials, e.g., 12x 10.1 mL vials or 6x 20 mL vials. Each vial in a kit should comprise the same lot number. The kits can optionally also include instructions, comprising, e.g., administration parameters and schedules, to allow a practitioner (e.g., a physician or nurse) to administer the antibody composition (and other drugs, if any) contained therein to NSCLC patients in accordance with the

methods taught herein. In one embodiment, the kit further comprises docetaxel and/or pemetrexed, e.g., each in a separate container, optionally in single dose unit dosage form. The kit may further contain diluents, instruments, or devices necessary for administering the pharmaceutical composition(s) e.g., one or more of a container of sterile diluent, e.g., saline or dextrose solution for injection; a syringe or syringes (e.g. pre-filled syringes); a catheter, a hypodermic (IV) needle, an IV infusion set.

The following examples are merely illustrative and should not be construed as limiting the scope of this disclosure in any way as many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

All patents, patent applications and publications cited herein are incorporated herein by reference in their entireties.

## EXAMPLES

### Methods

Heregulin (HRG) RNA-ISH is performed as described below and in pending international application No. PCT/US2014/072594, "Biomarker Profiles for Predicting Outcomes of Cancer Therapy with ErbB3 Inhibitors and/or Chemotherapies," filed 29 December, 2014, with the exception of the core needle biopsy analysis in Example 3.

#### RNA-ISH Assay

In this assay, FFPE tumor samples are scored for HRG RNA levels using the following variant of an Advanced Cell Diagnostics® ("ACD" Hayward, California) RNAscope® assay. Specifically, cells are permeabilized and incubated with a set of oligonucleotide "Z" probes (see, e.g., US Patent No. 7,709,198) specific for HRG. Using "Z" probes, as well as using multiple sets of probes per transcript, increases the specificity of the assay over standard ISH methods. One HRG probe set that can be used in this assay is ACD Part Number 311181. Another HRG probe set prepared by ACD (and used in RNAscope® assays) includes 62 probes (31 pairs), each 25 bases in length, that target a 1919 base long region of the HRG transcript comprising nucleotides 442-2977 of SEQ ID NO:42 and that together detect 15 separate HRG isoforms (α, β1, β1b, β1c, β1d, β2, β2b, β3, β3b, γ, γ2, γ3, ndf43, ndf34b, and GGF2). Following Z probe incubation, a pre-amplifier is added that can only hybridize to a pair of adjacent Z probes bound to the target transcript. This minimizes amplification of non-specific binding. Several sequential amplification steps are then performed based on sequence-specific hybridization to the pre-amplifier, followed by enzyme-mediated

chromogenic detection that enables semi-quantitative measurement of HRG RNA levels in the tumor tissue.

**Step 1**: FFPE tissue sections are deparaffinized and pretreated to block endogenous phosphatases and peroxidases and to unmask RNA binding sites. **Step 2**: Target-specific double Z probes are applied, which specifically hybridize to the target RNA at adjacent sequences. **Step 3**: Targets are detected by sequential applications of a preamplifier oligonucleotide, amplifier oligonucleotides, a final HRP-conjugated oligonucleotide, and DAB. **Step 4**: Slides are visualized using a light microscope and scored by a pathologist.

To score the assay, a reference tissue microarray (TMA) of four cell lines is stained alongside the tumor sample. These cell lines express different levels of HRG, ranging from low to high. A pathologist then assigns the patient sample a score based on a visual comparison with the reference TMA.

1. Sample Preparation and Staining

Patient sample preparation and pathologist review procedures are similar to qIHC assays. Upon biopsy or surgical resection, patient tumor samples are immediately placed in fixative (10% neutral buffered formalin) typically for 20-24 hours at room temperature. Samples are then transferred to 70% ethanol and embedded in paraffin as per standard hospital procedures. Before the assay is performed, 4-μm sections of the sample are prepared and mounted on positively charged 75 x 25 mm glass slides. These are baked for improved tissue adhesion (10-30 min at 65°C), dipped in paraffin for tissue preservation, and stored at room temperature under nitrogen. One of the sections is used for routine H&E staining, which a pathologist reviews for tumor content, quality, and clinical diagnosis. The pathologist differentiates areas of tumor, stroma, and necrosis. Following this review, an adjacent or nearby tissue section (within 20 μm of the H&E section) is used for the assay.

Pretreat solutions, target probes, and wash buffers for RNAscope® assays are obtained from ACD. The assay can be run manually, or using a VENTANA autostainer (Discovery XT). For the manual assay, 40°C incubations are performed in a metal slide tray inside a HybEZ oven (ACD). For the automated assay, incubation temperatures are controlled by the autostainer. ACD software is usede to run the RNAscope® assays on the VENTANA autostainer.

To begin the assay, samples are deparaffinized by baking at 65°C for 30 min, followed by sequential immersion in xylenes (2 × 20 min) and 100% ethanol (2 × 3 min). After air-drying, tissues are covered with Pretreat1 solution, which blocks endogenous enzymes (phosphatases and peroxidases which would produce background with chromogenic detection reagents), incubated for 10 min at room temperature, then rinsed twice by immersion in $dH_2O$. Slides are then

incubated in boiling Pretreat2 solution for 15 min, which unmasks binding sites, and transferred immediately to containers of $dH_2O$.

After washing by immersion in $dH_2O$ (2 × 2 min), tissue is covered with Pretreat3 solution and incubated in a HybEZ oven at 40°C for 30 min. Pretreat3 solution contains a protease, which strips the RNA transcripts of protein and exposes them to the target probes. After washing the slides 2 × 2 min in $dH_2O$, the tissues are covered with the 15 isoform-detecting HRG RNAscope® probes described above. Serial tissue sections are incubated with positive control probes (protein phosphatase 1B (PP1B) ACD Part Number 313901), negative control probes (bacterial gene DapB - ACD Part Number 310043), or HRG probes for 2 h at 40°C. Slides are washed (2 × 2 min) with 1× RNAscope® wash buffer before incubating with Amp1 reagent. Amp1 incubation conditions (30 min, 40°C) favor binding only to pairs of adjacent probes bound to RNA transcripts. Slides are washed by immersion in RNAscope® wash buffer before incubating with subsequent amplification reagents.

For signal amplification, each of the sequentially applied reagents binds to the preceding reagent and amplifies the signal present at the previous step. Amplification steps may include Amp2 (15 min, 40°C), Amp3 (30 min, 40°C), Amp4 (15 min, 40°C), Amp5 (30 min, room temperature), and Amp6 (15 min, room temperature). The final reagent, Amp6, can be conjugated to horseradish peroxidase (HRP). To visualize the transcripts, the slides are then incubated with the ACD staining reagent, which contains diaminobenzidine (DAB), for 10 min at room temperature. Chromogen development is stopped by rinsing with $dH_2O$. Nuclei are then counterstained with hematoxylin, which is blued with dilute ammonium chloride. Stained slides are immersed in 80% ethanol (2 × 5 min), 100% ethanol (2 × 5 min), and xylenes (2 × 5 min) before coverslipping with Cytoseal non-aqueous mounting medium (Thermo Scientific, 8312-4).

2. Generation of Biomarker Values

The biomarker values to be generated are a composite of pathologist scores. To score the assay, a TMA comprising plugs of four different cell lines is included in each staining run. Cell line plugs are prepared prior to generating a TMA. Cultured cells grown to a sub-confluent density are harvested by trypsinization, rinsed in PBS, and fixed for 16-24hr at 4°C before rinsing in PBS and resuspending in 70% ethanol. Cells are then centrifuged for 1-2 minutes at approximately 12,000rpm to produce a dense cell pellet, which is then coated with low-melting point agarose. The agarose pellets are stored in 70% ethanol at 4°C, and embedded in paraffin before constructing the TMA.

The arrays are constructed, e.g., using a Manual Tissue Arrayer (MTA-1, Beecher Instruments), with which a 0.6 mm punch is used to take a portion of the cell pellet and plug it

into an empty recipient paraffin block. The pathologist uses the images of the TMA to provide a score ranging from 0 (undetectable) to 4 (high). The pathologist provides two scores for the top two populations of tumor cells, and one score for the top population of stromal cells (when available), along with the percentage of cells in each population. So, for example, a patient sample may have 20% tumor with a score of 3, 40% tumor with a score of 2, and 60% stroma with a score of 2. Scores are provided for the target probe (HRG), as well as the positive control probe (PP1B) and the negative control probe (DapB).

Example 1: Seribantumab shows *in vitro* and *in vivo* single agent activity against growth of lung cancer cell lines that are responsive to heregulin (HRG)

RNA-ISH assays and biomarker analysis are performed as described above. These studies indicate that 9 out of 25 EGFR wild-type NSCLC cell lines are responsive to HRG: they exhibit increased cell proliferation in response to exogenously added HRG, as measured by a CellTiter Glo® luminescent cell viability assay (Promega) using 3D spheroid cultures (Figure 1).

Two HRG-responsive cell lines and two non-responsive cell lines were selected to assess the single agent activity of seribantumab in subcutaneous mouse xenografts. The mice were dosed with 300 μg seribantumab every three days (Q3D). As shown in Figure 2A and 2B, the HRG-responsive cell lines(A549 and H322M, respectively) responded to seribantumab as a single agent *in vivo*. In contrast, H460 and Hop92, which were not responsive to HRG *in vitro*, did not respond to seribantumab *in vivo* (Figure 2C and 2D, respectively). High tissue HRG mRNA levels were measured in the seribantumab-responsive xenograft tumors. Interestingly, both human HRG mRNA, indicative of autocrine HRG signaling, and mouse HRG mRNA, indicative of stroma-derived paracrine signaling, were observed in the HRG-responsive tumors. These data indicate that a subset of EGFR wild-type NSCLC cell lines are responsive to HRG, that these cell lines elicit the production of HRG, and that the presence of HRG in tissue appears to be necessary for seribantumab response *in* vivo, further supporting exclusion of patients whose tumors do not express HRG.

Example 2: Seribantumab treatment can overcome HRG-induced resistance to pemetrexed and docetaxel in lung cancer cell lines

As depicted in Figure 3A-3D, HRG induces resistance to pemetrexed and docetaxel in a panel of 9 lung cancer cell lines. HRG-driven ErbB3 signaling mediates survival signaling through the PI3K/AKT pathway and has been implicated as a general mechanism that imparts insensitivity to cytotoxic chemotherapy. As shown in Figure 3A and 3B, HRG induces resistance to pemetrexed and docetaxel in a subset of EGFR wild-type NSCLC cell lines. Proliferation was measured, in the

presence or absence of HRG, in a panel of nine cell lines using 3D spheroid cultures. Full dose response curves were obtained but results are only shown for a single relevant dose of chemotherapy. In three of these cell lines – those most responsive to HRG – inhibition of cell viability by both docetaxel and pemetrexed was decreased upon the addition of HRG. In fact, HRG induced proliferation even in the presence of chemotherapy, as noted by the negative values for % inhibition. Importantly, when seribantumab was added in addition to HRG, sensitivity to both docetaxel and pemetrexed was restored in these cell lines (Figure 3C and 3D).

Example 3: HRG mRNA expression levels in NSCLC tissue samples

Analysis of tumor samples from previous randomized phase II clinical trials of seribantumab in breast and ovarian cancer indicated that a CT level of HRG expression of -5 relative to reference genes as measured by quantitative RT-PCR (per PCT/US2014/072594, discussed above) was a threshold value for seribantumab activity. In patients with HRG expression at or above the threshold (≥-5), increased PFS was observed in patients treated with seribantumab co-administered with standard-of-care therapy. Since this threshold roughly corresponds to the presence of detectable HRG-encoding RNA, The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov/) dataset was analyzed to determine the prevalence of detectable HRG expression in a wide variety of solid tumors (Figure 4). The data suggest that NSCLC is an indication in which HRG-driven ErbB3 signaling is particularly prevalent.

In addition, HRG expression was assessed using an RNA *in situ* hybridization (RNA-ISH) assay (also per PCT/US2014/072594) in pre-treatment core needle biopsies obtained from patients enrolled in a study of seribantumab in EGFR wild-type NSCLC (MM-121-01-101). Overall, 54% of the samples scored 1+ (i.e., 1-3 dots/cell (visible at 20-40X magnification) or higher (Figure 5A). Furthermore, the analysis was expanded and an additional 53 archival lesions and biopsies were analyzed that were procured from Cureline, Inc. (San Francisco, CA) (Figure 5B). Comparable to the findings in the MM-121-01-101 lung study, the prevalence of HRG mRNA by RNA-ISH with a score of >1+ was found to be between 44-54%, and correlated with increased PFS from the addition of seribantumab.

Example 4: Determination of a seribantumab dose for combination with docetaxel or pemetrexed

Population pharmacokinetic (PK) analyses support using a fixed dosing regimen for seribantumab.

**Analysis by simulation:** To evaluate optimal dosing regimens, population analysis was used to estimate the point estimates and variabilities of pharmacokinetic parameters, and to evaluate the

source of the variabilities, including their relationships with body weight. The resulting estimates were used to compare fixed dosing and weight-based dosing regimens. For fixed dosing strategies, comparable dose is simulated by assuming the weight-based dose times the median of weight in the population (72kg), rounded to the next 500mg (vial size). The simulation results show comparable variability between both fixed-dosing and weight-based dosing regimens, suggesting no benefits of reduced PK variability with weight-based dosing (higher concentrations are predicted for the dose regimens of 10mg/kg equivalent only because of rounding up doses to the next 500mg). For example, a weight-based dosing of 20 mg/kg Q2W and a corresponding fixed dose of 1.5 g Q2W have comparable maximum, minimum, and average steady-state concentration levels and variability. This result can be explained as a consequence that clearance increased less than proportionally to weight (i.e., the estimated proportionality between $\log_{10}$ of clearance and weight was 0.203). This proportionality results in higher-weight patients being overdosed by a weight-based regimen (which assumed a proportionality constant of one between $\log_{10}$ of clearance and weight).

A simulation study, conducted by comparing the simulated pharmacokinetics (averaged and minimum concentration) at different dose intervals, indicates an every 3 week regimen is optimal. A dose regimen of 3g Q3W is predicted to have: 1) comparable maximum concentration (Cmax) to 40mg/kg Q3W; 2) comparable minimum concentration (Cmin) to 20mg/kg Q2W; and 3) average steady-state concentration in between 20mg/kg Q2W (the dose studied in previous NSCLC study) and 20mg/kg Q1W (the dose studied in previous ovarian and breast cancer studies). Therefore, this simulation study suggests that a seribantumab dose regimen of 3g Q3W should improve compliance and convenience while maintaining the pharmacokinetic levels within the bounds of the exposures observed from previously studied effective seribantumab doses (40mg/kg loading + 20mg/kg Q1W or +20mg/kg Q2W). To evaluate the contribution of loading dose, concentration trajectories of simulated dose regimens with and without loading dose are compared. The loading dose is limited to a maximum of 3g (a corresponding fixed dose for a 40mg/kg). The results show comparable pharmacokinetics with and without a loading dose, and therefore, support the regimen without loading dose.

**Experimental:** The pharmacokinetics of seribantumab were evaluated using population pharmacokinetic analysis from 499 patients who had been treated with seribantumab. 4925 data points from the combined phase I and phase II studies of seribantumab were analyzed. These pharmacokinetic data were described using a two-compartment model, with estimated parameters provided in Table 1. Covariate selection evaluated potential relationships between baseline covariates (sex, race, age, weight, intended-dose, and study/indication) and volume of distribution and clearance. The results indicated significant relationships between weight, sex, and clearance,

with the final parameter estimates provided in Table 1. The model assumed a proportional relationship between the log of clearance (CL) and weight, and obtained an estimated proportionality constant of 0.203. In the presence of the relationship between weight and clearance, no significant relationship between volume (V) and weight (WT) were observed.

**Table 1: Final parameter estimates from population PK analysis of seribantumab**

| Parameters | (Estimated) values |
|---|---|
| Number of patients | 499 |
| **Fixed effects** | |
| CL (L/wk) | 3.15 |
| V (L) | 3.23 |
| Q (L/wk) | 2.92 |
| V2 (L) | 2.68 |
| | |
| | |
| | |
| | |
| | |

| Parameters | (Estimated) values |
|---|---|
| **Random effects** | |
| Omega CL (%) | 36% |
| Cov CL and V (%) | 27% |
| Omega V (%) | 37% |
| **Sigma** | |
| Additive | 25.18 |
| Proportional | 0.23 |
| **Covariate selection** | |
| WT-CL | 0.203 |
| SEX-CL | 0.255 |
| WT-V | 0.002 |

To evaluate the benefit of weight-based dosing, a simulation study was conducted by comparing pharmacokinetics with weight-based and fixed-dose regimens. Post-hoc estimates of PK parameters from each of the 499 patients were used in the simulation. The simulated dose for the fixed dosing regimen was chosen by rounding up to the closest 500 mg dose unit. The simulation results showed comparable variability between both fixed-dosing and weight-based dosing regimens, suggesting no benefits of the reduced PK variability with weight-based dosing (Figures 6A-6C). For example, a weight-based dosing of 20 mg/kg Q2W and a corresponding fixed dose of 1.5 g Q2W have comparable maximum, minimum, and average steady-state concentration levels and variability. The result can be explained in that estimated proportionality between log of CL and weight is 0.203, and therefore, a weight-based regimen (which assumed a proportionally constant of one between log of CL and weight) would tend to overdose higher-weight patients. To evaluate the optimization of seribantumab dosing regimens for improved compliance and simplicity, a simulation study was conducted by comparing the simulation pharmacokinetics (averaged and minimum concentration) by different dose intervals. The results showed the potential to optimize the dosing frequency to once every 3 weeks. A dose regimen of 3000 mg Q3W is predicted to have: 1) a comparable maximum

concentration (Cmax) to 40 mg/kg Q3W, a dose level previously used as a loading dose for weight-based and weekly seribantumab dosing regimens; 2) a comparable minimum concentration (Cmin) to 20 mg/kg Q2W which was the dose used in the previous seribantumab study in NSCLC in combination with 100 mg erlotinib; and 3) an average steady-state concentration that is in between 20 mg/kg Q2W and 20 mg/kg Q1W which is the previously studied regular dose for seribantumab following the 40 mg/kg loading dose in combination with chemotherapy. Therefore, this simulation study suggests that a seribantumab dose regimen of 3000 mg Q3W has a potential to improve compliance while maintaining the pharmacokinetic levels within the bounds of the exposures observed from previously studied seribantumab doses (40mg/kg + 20 mg/kg Q1W and 20mg/kg Q2W). In addition, no MTD was identified when seribantumab was co-administered with standard doses of pemetrexed, paclitaxel or cabazitaxel. In these studies, seribantumab was co-administered with full doses of the chemotherapy agents (pemetrexed, paclitaxel or cabazitaxel) at 40 mg/kg as a loading dose followed by weekly doses of 20 mg/kg. The loading dose of 40 mg/kg equals 3000 mg in an average patient weighing 75kg. As such, the cumulative seribantumab dose proposed for this study, 3000 mg seribantumab Q3W as a fixed dose, does not exceed previously tested dose regimens for seribantumab in combination with pemetrexed.

Accordingly, seribantumab will be administered at a fixed dose of 3g/3000 mg on day 1 of each 21-day cycle in sync with the chemotherapy regimens outlined in the study below.

Example 5: Study Design for treatment of NSCLC

This study is a randomized, open-label, international, multi-center, phase II study in adult patients with NSCLC that has progressed following no more than two systemic therapies for locally advanced or metastatic disease, of which one must have been a platinum-based doublet therapy.

Following signing informed consent and evaluation of initial eligibility criteria, all patients will provide a tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual) to a central lab facility for HRG testing. It is important that no systemic therapy is administered between the date of acquisition of the tissue sample and screening for this study in order to accurately assess a patient's HRG status. If adequate tissue is not available, patients should undergo a fine needle aspirate (FNA) or core needle biopsy (CNB) to acquire the necessary tissue for HRG testing. For these procedures, investigators are asked to choose an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location of the core needle biopsy or FNA has an established serious complication rate of >2% at the institution completing the

procedure, this is considered a high risk procedures and should be avoided. Upon receipt of a tissue sample at the central lab, the investigational site will be informed of the results within 7 days. Patients with a positive HRG status will be eligible for the interventional study population. Patients with tumors that show no staining for HRG will not continue further screening procedures and will be eligible for the observational group as outlined below.

**Observational Group**

Baseline data will be collected which includes demographics, disease characteristics and previous treatments. In addition, data regarding subsequent anti-cancer therapies received and OS will be collected. Patients are free to participate in any study and seek any care suitable.

**Interventional Group**

By the time all screening procedures have been completed and determination of eligibility for treatment randomization (HRG positive, interventional group), the investigator must select the chemotherapy backbone (docetaxel or pemetrexed) most appropriate for each patient based on current presentation and medical history. Patients will be randomized in a 2:1 ratio (experimental arm versus comparator arm) using an Interactive Web Response System (IWRS). Randomization will be stratified based on the chemotherapy backbone (docetaxel or pemetrexed) and number of prior systemic therapies for locally advanced or metastatic disease (1 or 2). Within the interventional group, patients will be assigned to Arm A or Arm B:

**Interventional Arm A (Experimental Arm)**:

Seribantumab: fixed dose of 3000 mg (12 x 10.1 mL vials; 6 x 20 mL vials) intravenously (IV) on day 1 of each 21-day cycle

Docetaxel: 75 mg/m$^2$ IV on day 1 of each 21-day cycle

**OR**

Seribantumab: fixed dose of 3000 mg (12 x 10.1 mL vials; 6 x 20 mL vials) IV on day 1 of each 21-day cycle

Pemetrexed: 500 mg/m$^2$ IV on day 1 of each 21-day cycle

**Interventional Arm B (Comparator Arm):**

Docetaxel: 75 mg/m$^2$ IV on day 1 of each 21-day cycle

**OR**

Pemetrexed: 500 mg/m$^2$ IV on day 1 of each 21-day cycle

Treatment must start within 7 days following randomization. Patients are expected to be treated until investigator-assessed progressive disease or unacceptable toxicity. Tumor assessments will be measured and recorded by the local radiologist every 6 weeks (+/- 1 week)

and evaluated using the RECIST guidelines (version 1.1). All patients, including any patient that comes off treatment for reasons other than RECIST 1.1 assessed progressive disease, should have an additional scan 6 weeks (+/- 1 week) following treatment termination. In addition, an independent central review of scans will be conducted to support secondary efficacy objectives. All images for patients in the interventional group will be submitted to a central imaging facility for this purpose and will be assessed by independent reviewers in accordance with the Imaging Charter. After patients come off treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first.

Safety has been established for the combination of seribantumab + pemetrexed, and seribantumab has been administered in combination with taxanes (paclitaxel and cabazitaxel) at the standard doses with no maximum tolerated dose (MTD) reached. However, as no data is available for the combination of seribantumab and docetaxel, enrollment into this backbone will be paused after the twelfth patient has been randomized to docetaxel or seribantumab + docetaxel and completed one full cycle of treatment, and the emerging safety data on both arms will be reviewed by investigators, medical monitors and representatives from the sponsor. Additional input may be gathered from the DMC before continuing enrollment. The DMC will continue to monitor safety data in accordance with the DMC Charter on a quarterly basis.

Inclusion Criteria

For inclusion in the trial, all patients will have/be: cytologically or histologically confirmed NSCLC, with either metastatic disease (stage IV); Stage IIIB disease not amenable to surgery with curative intent; disease progression or evidence of recurrent disease documented by radiographic assessment following the last systemic therapy; received one prior platinum-based regimen for the management of primary or recurrent disease; clinically eligible for intended chemotherapy, docetaxel or pemetrexed, once every three weeks per the investigator's judgment; available recent tumor specimen, collected following completion of most recent therapy; a lesion amenable to either core needle biopsy or fine needle aspiration; greater than or equal to eighteen years of age; and able to provide informed consent or have a legal representative able to do so. To be included in the interventional group, patients will have/be: a positive *in situ* hybridization (ISH) test for heregulin with a score of $\geq$1+, as determined by centralized testing; measureable disease in accordance with RECIST v1.1; ECOG performance status (PS) of 0 or 1; Screening ECG without clinically significant abnormalities; Adequate bone marrow reserve as evidenced by ANC > 1,500/µl, platelet count > 100,000/µl, and hemoglobin > 9 g/dL; adequate renal function as evidenced by a serum/plasma creatinine < 1.5 x ULN for patients receiving docetaxel and a

creatinine clearance ≥ 45 mL/min for patients receiving pemetrexed; for patients receiving pemetrexed: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤5 x ULN is acceptable if liver metastases are present); for patients receiving docetaxel: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT ) ≤ 1.5 x ULN, Alkaline phosphatase (AP) < 2.5 ULN and serum/plasma total bilirubin within normal institutional limits. Women of childbearing potential, as well as fertile men and their partners, must be willing to abstain from sexual intercourse or to use an effective form of contraception during the study (an effective form of contraception is an oral contraceptive or a double barrier method) and for 90 days following the last dose of study drug(s), or greater, as in accordance with the label requirements or institutional guidelines for docetaxel/pemetrexed.

Exclusion Criteria

Patients will meet all the inclusion criteria listed above and none of the following exclusion criteria:

a) Known Anaplastic Lymphoma Kinase (ALK) gene rearrangement or presence of exon 19 deletion or exon 21 (L858R) substitution of the EGFR gene

b) Pregnant or lactating

c) Prior radiation therapy to >25% of bone marrow-bearing areas

d) Received >2 prior systemic anti-cancer drug regimen for locally advanced disease

• Maintenance therapy with pemetrexed following first-line treatment for Stage IIIB or Stage IV disease is counted as one line of therapy

e) Patients who have received prior docetaxel for advanced/ metastatic disease are not eligible for the docetaxel-containing chemotherapy backbone

f) Patients who have received prior pemetrexed for advanced/ metastatic disease and/or maintenance therapy are not eligible for the pemetrexed-containing chemotherapy backbone

g) Received other recent antitumor therapy including:

• Investigational therapy administered within the 28 days or 5 half-lives, whichever is shorter, prior to the first scheduled day of dosing in this study

• Radiation or other standard systemic therapy within 14 days prior to the first scheduled dose in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation

h) CTCAE grade 3 or higher peripheral neuropathy

i) Presence of an unexplained fever > 38.5°C during screening visits that does not resolve prior

to the first day of dosing. If the fever and active infection have resolved prior to randomization, the patient will be eligible. At the discretion of the investigator, patients with tumor fever may be enrolled.

j) Symptomatic CNS metastases or CNS metastases requiring steroids

k) Use of strong CYP3A4 inhibitors for patients considered for the docetaxel backbone.

l) Any other active malignancy requiring systemic therapy

m) Known hypersensitivity to any of the components of MM-121 or previous hypersensitivity reactions to fully human monoclonal antibodies

n) History of severe allergic reactions to docetaxel or pemetrexed

o) Known hypersensitivity to polysorbate (Tween®) 80 or arginine

p) Clinically significant cardiac disease, including: symptomatic congestive heart failure, unstable angina, acute myocardial infarction within 1 year months of planned first dose, or unstable cardiac arrhythmia requiring therapy (including torsades de pointes)..

q) Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals, known human immunodeficiency virus (HIV) infection, or active B or C infection.

r) Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator.

Example 6: Co-administration of seribantumab and chemotherapeutics abrogates HRG-mediated resistance to said chemotherapeutics in an ovarian cancer mouse xenograft model.

The anti-tumor efficacy of seribantumab and a chemotherapeutic agent (e.g. irinotecan, gemcitabine, or paclitaxel) either alone (*i.e.*, as a monotherapy) or in combination, in tumor-bearing mice was evaluated using human ovarian epithelial carcinoma OVCAR8 cells (NCI) implanted as xenografts in nu/nu nude, Crl:NU-*Foxn1*$^{nu}$ mice. In these xenograft studies, the mice were obtained from Charles River Laboratories. The mice were housed in Tecniplast® Individually Ventilated polycarbonate (Makrolon®) Cages (IVC) set in climate-controlled rooms and had free access to food and acidified water. A cell suspension of 8 x $10^6$ cells/mouse, mixed 1:1 in reduced growth factor Matrigel™ (BD Biosciences, Cat # 354230) and PBS was implanted by subcutaneous injection into the left flank of female, 4-5 week old nu/nu nude, Crl:NU-*Foxn1*$^{nu}$ mice. Tumors were allowed to reach 250 $mm^3$ in size before randomization.

*Combination Therapy Study*

A combination therapy study was performed to demonstrate the effects of various combinations of a fixed dose of seribantumab, irinotecan HCl, gemcitabine, and paclitaxel.

Mice were randomized as above into 8 groups of 10 mice each. Five groups were treated with i.p. doses of a single agent alone, as follows: (1) seribantumab (300 µg Q3D), (2) irinotecan HCl (6.25 mg/kg Q7D), (3) gemcitabine (25mg/kg Q7D), (4) paclitaxel (10mg/kg Q7D), or (5) PBS (Q3D) alone (Control). Three groups were treated with a combination therapy of (1) seribantumab and paclitaxel, (2) seribantumab and irinotecan HCl, and (3) seribantumab and gemcitabine, with the doses described above. Treatment continued for three weeks. Tumors were measured twice weekly and tumor volume calculated.

As shown in Figures 7A-7C (seribantumab ("MM-121" in the figure) mouse dose; 300 µg Q3D), seribantumab as a single agent significantly suppressed tumor growth in a dose-dependent manner *in vivo* in this model of ovarian cancer. Moreover, while irinotecan HCl, gemcitabine, and paclitaxel alone each inhibited tumor growth *in vivo*, combination treatments with seribantumab and paclitaxel (Figure 7A), irinotecan HCl (Figure 7B), or gemcitabine (Figure 7C) exhibited an additive effect on tumor growth inhibition, as compared to tumor growth inhibition observed with each of the individual agents.

**Endnotes**

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein. The disclosure of each and every US, international, or other patent or patent application or publication referred to herein is hereby incorporated herein by reference in its entirety.

## SEQUENCE SUMMARY

| SEQ ID NO: | DESIGNATION | | SEQUENCE |
|---|---|---|---|
| 1 | Heavy Chain CDR1 (CDRH1) of Seribantumab | Human CDRH 1 Protein | His Tyr Val Met Ala |
| 2 | Heavy Chain CDR2 (CDRH2) | Human CDRH | Ser Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr Ala Asp Ser Val Lys Gly |

| | | | |
|---|---|---|---|
| | of Seribantumab | 2<br><br>Protein | |
| 3 | Heavy Chain CDR3 (CDRH3) of Seribantumab | Human CDRH 3<br><br>Protein | Gly Leu Lys Met Ala Thr Ile Phe Asp Tyr |
| 4 | Light Chain CDR1 (CDRL1) of Seribantumab | Human CDRL1<br><br>Protein | Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Val Val Ser |
| 5 | Light Chain CDR2 (CDRL2) of Seribantumab | Human CDRL2<br><br>Protein | Glu Val Ser Gln Arg Pro Ser |
| 6 | Light Chain CDR3 (CDRL3) of Seribantumab | Human CDRL3<br><br>Protein | Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val Ile |
| 7 | Heavy Chain of Antibody Seribantumab | Human Heavy Chain<br><br>Protein | 1 EVQLLESGGG LVQPGGSLRL SCAASGFTFS HYVMAWVRQA PGKGLEWVSS<br>51 ISSSGGWTLY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCTRGL<br>101 KMATIFDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD<br>151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY<br>201 TCNVDHKPSN TKVDKTVERK CCVECPPCPA PPVAGPSVFL FPPKPKDTLM<br>251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV<br>301 VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP<br>351 PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG<br>401 SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK |
| 8 | Light Chain of Seribantumab | Human Light Chain<br><br>Protein | 1 QSALTQPASV SGSPGQSITI SCTGTSSDVG SYNVVSWYQQ HPGKAPKLII<br>51 YEVSQRPSGV SNRFSGSKSG NTASLTISGL QTEDEADYYC CSYAGSSIFV<br>101 IFGGGTKVTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL VSDFYPGAVT<br>151 VAWKADGSPV KVGVETTKPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCRV<br>201 THEGSTVEKT VAPAECS |
| 9 | Heavy Chain Variable Region | Human VH | gaggtgcagc tgctggagag cggcggaggg ctggtccagc caggcggcag cctgaggctg |

| | | | |
|---|---|---|---|
| | (VH) of Seribantumab | DNA | tcctgcgccg ccagcggctt caccttcagc cactacgtga tggcctgggt gcggcaggcc ccaggcaagg gcctggaatg ggtgtccagc atcagcagca gcggcggctg gaccctgtac gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcac caggggcctg aagatggcca ccatcttcga ctactggggc cagggcaccc tggtgaccgt gagcagc |
| 10 | Heavy Chain Variable Region (VH) of Seribantumab | Human VH Protein | Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr Val Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Thr Arg Gly Leu Lys Met Ala Thr Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser |
| 11 | Light Chain Variable Region (VL) of Seribantumab | Human VL DNA | cagtccgccc tgacccagcc cgccagcgtg agcggcagcc caggccagag catcaccatc agctgcaccg gcaccagcag cgacgtgggc agctacaacg tggtgtcctg gtatcagcag caccccggca aggcccccaa gctgatcatc tacgaggtgt cccagaggcc cagcggcgtg agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg cagaccgagg acgaggccga ctactactgc tgcagctacg ccggcagcag catcttcgtg atcttcggcg gagggaccaa ggtgaccgtc cta |
| 12 | Light Chain Variable Region (VL) of Seribantumab | Human VL Protein | Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Val Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Glu Val Ser Gln Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val Ile Phe Gly Gly Gly Thr Lys Val Thr Val Leu |
| 13 | Human ErbB3 | Human Protein | Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser His |

| | | | |
|---|---|---|---|
| | | | Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu<br>Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile<br>Glu Lys Asn Asp Lys Leu Cys His Met Asp<br>Thr Ile Asp Trp Arg Asp Ile Val Arg Asp<br>Arg Asp Ala Glu Ile Val Val Lys Asp Asn<br>Gly Arg Ser Cys Pro Pro Cys His Glu Val<br>Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser<br>Glu Asp Cys Gln Thr Leu Thr Lys Thr Ile<br>Cys Ala Pro Gln Cys Asn Gly His Cys Phe<br>Gly Pro Asn Pro Asn Gln Cys Cys His Asp<br>Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln<br>Asp Thr Asp Cys Phe Ala Cys Arg His Phe<br>Asn Asp Ser Gly Ala Cys Val Pro Arg Cys<br>Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr<br>Phe Gln Leu Glu Pro Asn Pro His Thr Lys<br>Tyr Gln Tyr Gly Gly Val Cys Val Ala Ser<br>Cys Pro His Asn Phe Val Val Asp Gln Thr<br>Ser Cys Val Arg Ala Cys Pro Pro Asp Lys<br>Met Glu Val Asp Lys Asn Gly Leu Lys Met<br>Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys<br>Ala Cys Glu Gly Thr Gly Ser Gly Ser Arg<br>Phe Gln Thr Val Asp Ser Ser Asn Ile Asp<br>Gly Phe Val Asn Cys Thr Lys Ile Leu Gly<br>Asn Leu Asp Phe Leu Ile Thr Gln Gly Asp<br>Pro Trp His Lys Ile Pro Ala Leu Asp Pro<br>Glu Lys Leu Asn Val Phe Arg Thr Val Arg<br>Glu Ile Thr Gly Tyr Leu Asn Ile Gln Ser<br>Trp Pro Pro His Met His Asn Phe Ser Val<br>Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg<br>Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu<br>Ile Met Lys Asn Leu Asn Val Thr Ser Leu<br>Gly Phe Arg Ser Leu Lys Glu Ile Ser Ala<br>Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln<br>Leu Cys Tyr His His Ser Leu Asn Trp Thr<br>Lys Val Leu Arg Gly Pro Thr Glu Glu Arg<br>Leu Asp Ile Lys His Asn Arg Pro Arg Arg<br>Asp Cys Val Ala Glu Gly Lys Val Cys Asp<br>Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly<br>Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg<br>Asn Tyr Ser Arg Gly Gly Val Cys Val Thr<br>His Cys Asn Phe Leu Asn Gly Glu Pro Arg<br>Glu Phe Ala His Glu Ala Glu Cys Phe Ser<br>Cys His Pro Glu Cys Gln Pro Met Glu Gly<br>Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp<br>Thr Cys Ala Gln Cys Ala His Phe Arg Asp<br>Gly Pro His Cys Val Ser Ser Cys Pro His<br>Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr<br>Lys Tyr Pro Asp Val Gln Asn Glu Cys Arg<br>Pro Cys His Glu Asn Cys Thr Gln Gly Cys<br>Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly<br>Gln Thr Leu Val Leu Ile Gly Lys Thr His<br>Leu Thr Met Ala Leu Thr Val Ile Ala Gly<br>Leu Val Val Ile Phe Met Met Leu Gly Gly<br>Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile<br>Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu<br>Glu Arg Gly Glu Ser Ile Glu Pro Leu Asp<br>Pro Ser Glu Lys Ala Asn Lys Val Leu Ala |

| | | | |
|---|---|---|---|
| | | | Arg Ile Phe Lys Glu Thr Glu Leu Arg Ser<br>Leu Lys Val Leu Gly Ser Gly Val Phe Gly<br>Thr Val His Lys Gly Val Trp Ile Pro Glu<br>Gly Glu Ser Ile Lys Ile Pro Val Cys Ile<br>Lys Val Ile Glu Asp Lys Ser Gly Arg Gln<br>Ser Phe Gln Ala Val Thr Asp His Met Leu<br>Ala Ile Gly Ser Leu Asp His Ala His Ile<br>Val Arg Leu Leu Gly Leu Cys Pro Gly Ser<br>Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro<br>Leu Gly Ser Leu Leu Asp His Val Arg Gln<br>His Arg Gly Ala Leu Gly Pro Gln Leu Leu<br>Leu Asn Trp Gly Val Gln Ile Ala Lys Gly<br>Met Tyr Tyr Leu Glu Glu His Gly Met Val<br>His Arg Asn Leu Ala Ala Arg Asn Val Leu<br>Leu Lys Ser Pro Ser Gln Val Gln Val Ala<br>Asp Phe Gly Val Ala Asp Leu Leu Pro Pro<br>Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala<br>Lys Thr Pro Ile Lys Trp Met Ala Leu Glu<br>Ser Ile His Phe Gly Lys Tyr Thr His Gln<br>Ser Asp Val Trp Ser Tyr Gly Val Thr Val<br>Trp Glu Leu Met Thr Phe Gly Ala Glu Pro<br>Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro<br>Asp Leu Leu Glu Lys Gly Glu Arg Leu Ala<br>Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr<br>Met Val Met Val Lys Cys Trp Met Ile Asp<br>Glu Asn Ile Arg Pro Thr Phe Lys Glu Leu<br>Ala Asn Glu Phe Thr Arg Met Ala Arg Asp<br>Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu<br>Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu<br>Pro His Gly Leu Thr Asn Lys Lys Leu Glu<br>Glu Val Glu Leu Glu Pro Glu Leu Asp Leu<br>Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn<br>Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu<br>Ser Leu Pro Val Gly Thr Leu Asn Arg Pro<br>Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser<br>Ser Gly Tyr Met Pro Met Asn Gln Gly Asn<br>Leu Gly Glu Ser Cys Gln Glu Ser Ala Val<br>Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro<br>Val Ser Leu His Pro Met Pro Arg Gly Cys<br>Leu Ala Ser Glu Ser Ser Glu Gly His Val<br>Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys<br>Val Ser Met Cys Arg Ser Arg Ser Arg Ser<br>Arg Ser Pro Arg Pro Arg Gly Asp Ser Ala<br>Tyr His Ser Gln Arg His Ser Leu Leu Thr<br>Pro Val Thr Pro Leu Ser Pro Pro Gly Leu<br>Glu Glu Glu Asp Val Asn Gly Tyr Val Met<br>Pro Asp Thr His Leu Lys Gly Thr Pro Ser<br>Ser Arg Glu Gly Thr Leu Ser Ser Val Gly<br>Leu Ser Ser Val Leu Gly Thr Glu Glu Glu<br>Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn<br>Arg Arg Arg Arg His Ser Pro Pro His Pro<br>Pro Arg Pro Ser Ser Leu Glu Glu Leu Gly<br>Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu<br>Ser Ala Ser Leu Gly Ser Thr Gln Ser Cys<br>Pro Leu His Pro Val Pro Ile Met Pro Thr<br>Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu<br>Tyr Met Asn Arg Gln Arg Asp Gly Gly Gly |

| | | | |
|---|---|---|---|
| | | | Pro Gly Gly Asp Tyr Ala Ala Met Gly Ala<br>Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu<br>Met Arg Ala Phe Gln Gly Pro Gly His Gln<br>Ala Pro His Val His Tyr Ala Arg Leu Lys<br>Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser<br>Ala Phe Asp Asn Pro Asp Tyr Trp His Ser<br>Arg Leu Phe Pro Lys Ala Asn Ala Gln Arg<br>Thr |

# CLAIMS

We claim:

1. A method of treating a patient having heregulin (HRG) positive non-small cell lung cancer (NSCLC), the method comprising administering to the patient once on day 1 of a 21-day treatment cycle an anti-neoplastic therapy consisting of:

i. a dose of 3000 mg seribantumab; and

ii. a dose of 75 mg/m$^2$ docetaxel,

to treat the NSCLC in the patient.

2. The method of claim 1, wherein the cancer is positive for HRG mRNA as measured by RNA in-situ hybridization (RNA-ISH), wherein the HRG RNA-ISH results in a score of $\geq$ 1+.

3. The method of claim 1, wherein the cancer is positive for HRG as measured by quantitative RT-PCR.

4. The method of claim 1, wherein the patient has failed at least one systemic therapy for locally advanced and/or metastatic NSCLC.

5. The method of claim 1, wherein the patient has progressed following treatment with no more than three systemic therapies for locally advanced or metastatic disease, one of which systemic therapies comprised a platinum-based regimen.

6. The method of claim 1, wherein docetaxel is co-administered at least 30 minutes before administration of seribantumab.

7. The method of claim 1, wherein the anti-neoplastic therapy is administered intravenously.

8. The method of claim 1, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction in size of a tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response.

9. The method of claim 1, wherein the NSCLC is EGFR wild-type.

10. The method of claim 1, wherein the NSCLC is a squamous cell carcinoma.

11. A method of treating a patient having HRG positive non-small cell lung cancer (NSCLC, the method comprising administering to the patient once on day 1 of a 21-day treatment cycle an anti-neoplastic therapy consisting of:

i. a dose of 3000 mg seribantumab; and

ii. a dose of 500 mg/$m^2$ pemetrexed,

to treat the NSCLC in the patient.

12. The method of claim 10, wherein the tumor is positive for HRG mRNA as measured by RNA *in-situ* hybridization (RNA-ISH), wherein the HRG RNA-ISH results in a score of $\geq$ 1+.

13. The method of claim 11, wherein the cancer is positive for HRG as measured by quantitative RT-PCR.

14. The method of claim 11, wherein the patient has failed at least one systemic therapy for locally advanced and/or metastatic NSCLC.

15. The method claim 11, wherein the patient has progressed following treatment with no more than two systemic therapies for locally advanced or metastatic disease, one of which systemic therapies comprised a platinum-based regimen.

16. The method of claim 11, wherein the pemetrexed is co-administered at least 30 minutes before the administration of seribantumab.

17. The method of claim 11, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction in size of a tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response.

18. The method of claim 11, wherein the NSCLC is EGFR wild-type.

19. The method of a claim 11, wherein the NSCLC is a squamous cell carcinoma.

20. The method of claim 11, wherein the antineoplastic therapy is administered intravenously.

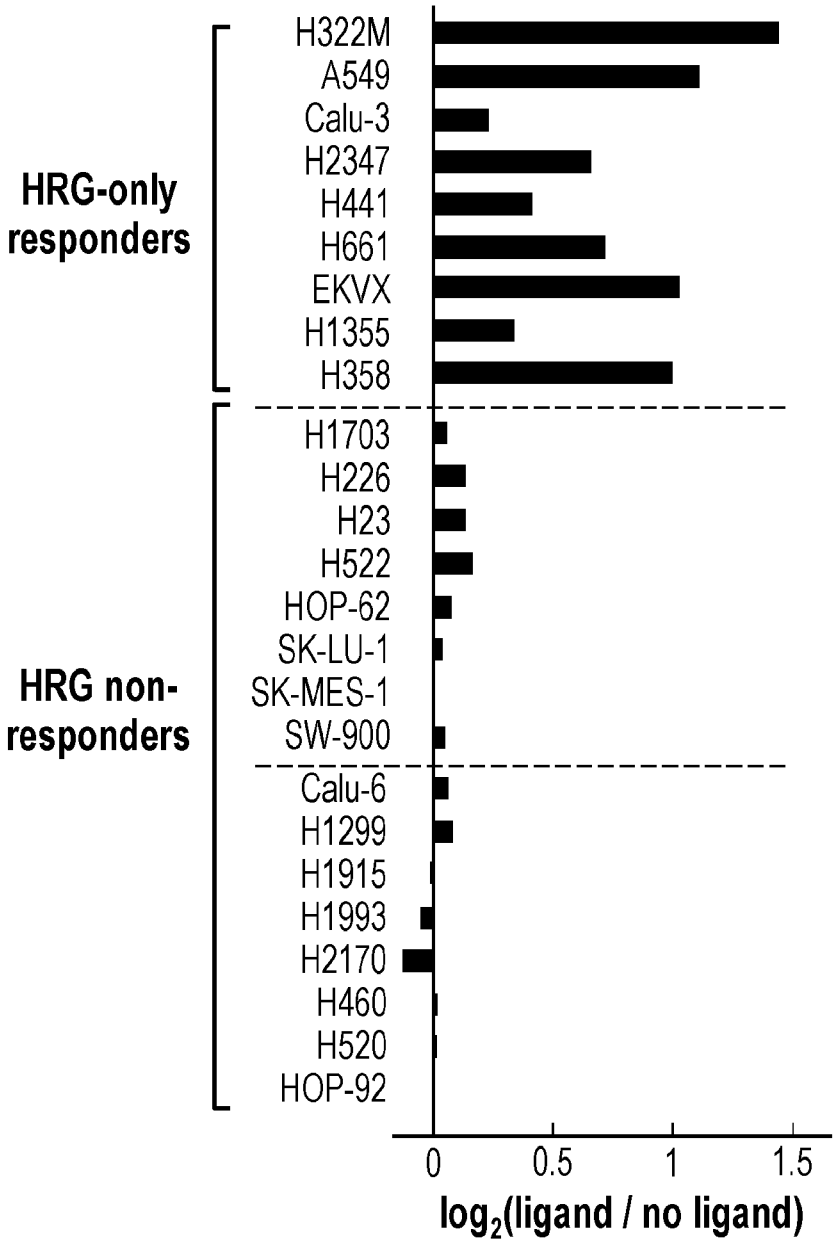
HRG-only responders
HRG non-responders
H322M
A549
Calu-3
H2347
H441
H661
EKVX
H1355
H358
H1703
H226
H23
H522
HOP-62
SK-LU-1
SK-MES-1
SW-900
Calu-6
H1299
H1915
H1993
H2170
H460
H520
HOP-92
0
0.5
1
1.5
log2(ligand / no ligand)

FIG. 1

A549

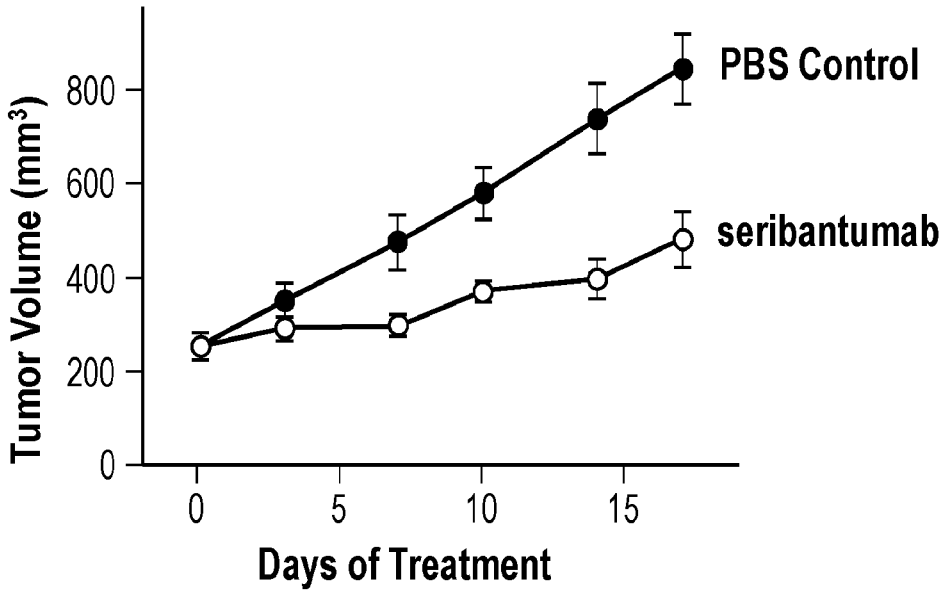


FIG. 2A

H322M

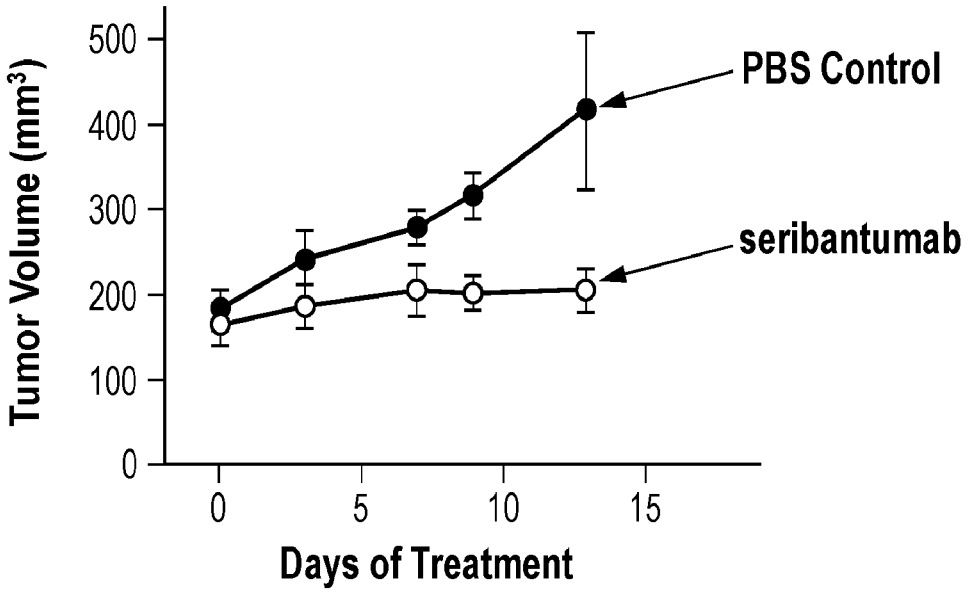


FIG. 2B

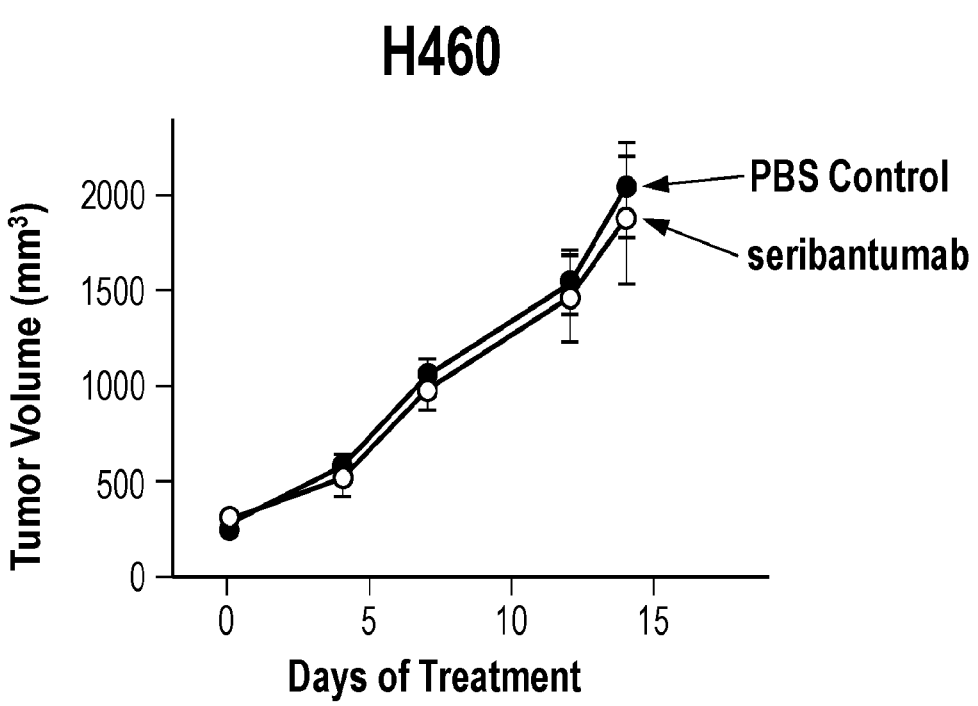
H460
Tumor Volume (mm3)
2000
1500
1000
500
0
0
5
10
15
Days of Treatment
PBS Control
seribantumab

FIG. 2C

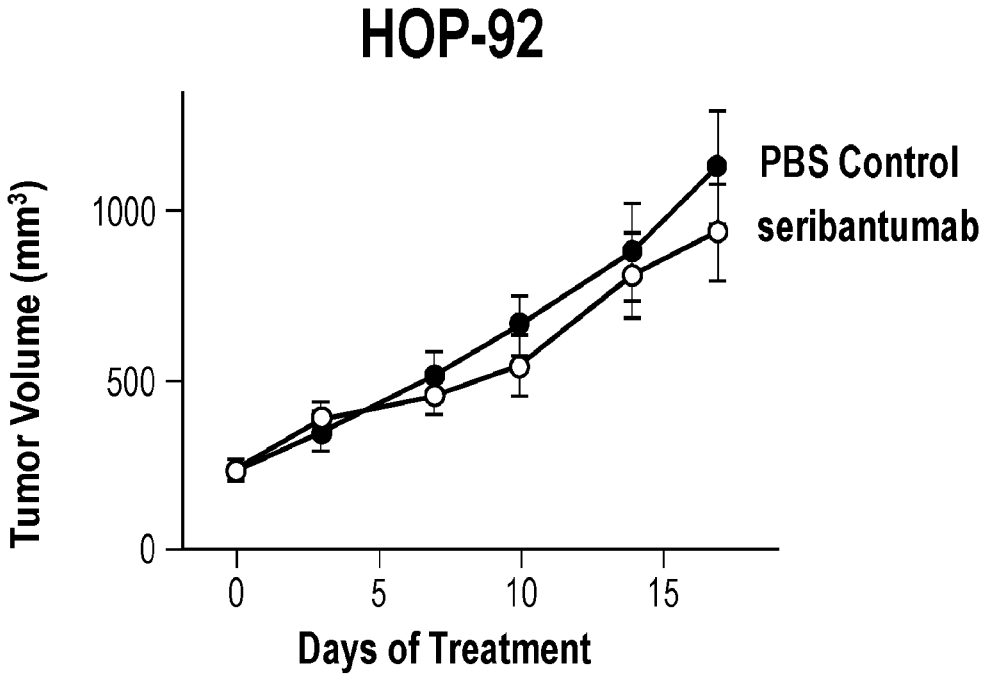
HOP-92
Tumor Volume (mm3)
1000
500
0
0
5
10
15
Days of Treatment
PBS Control
seribantumab

FIG. 2D

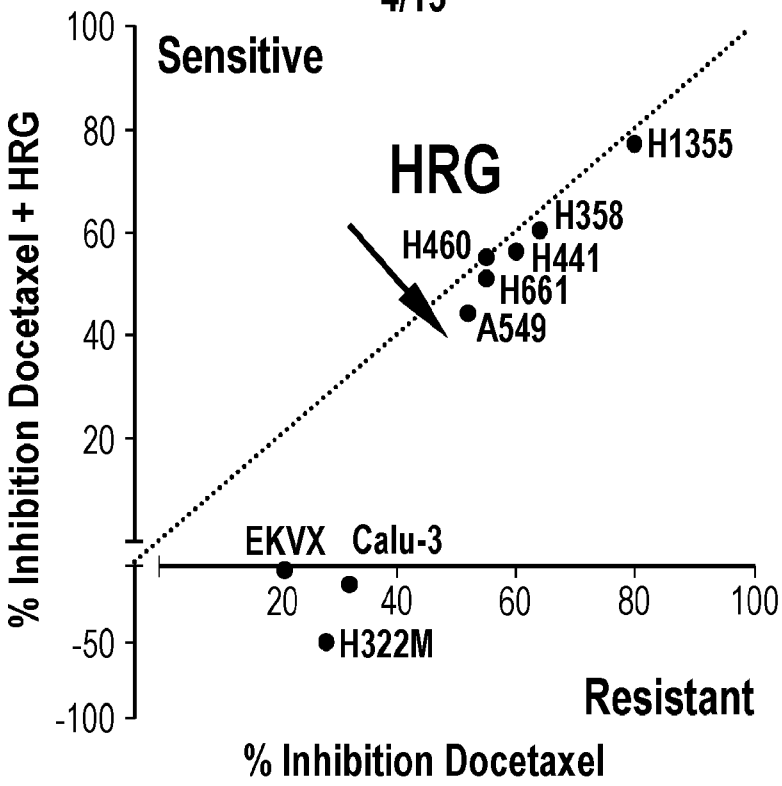
Sensitive
HRG
H1355
H358
H460
H441
H661
A549
EKVX
Calu-3
H322M
Resistant
% Inhibition Docetaxel + HRG
% Inhibition Docetaxel
100
80
60
40
20
-50
-100
20
40
60
80
100

FIG. 3A

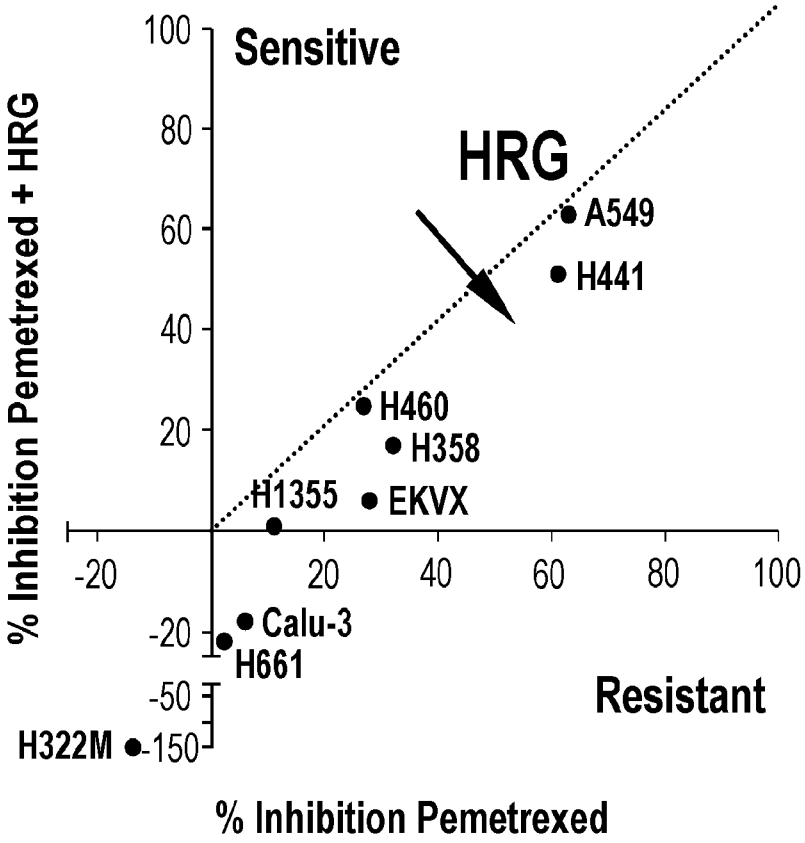
Sensitive
HRG
A549
H441
H460
H358
H1355
EKVX
Calu-3
H661
H322M
Resistant
% Inhibition Pemetrexed + HRG
% Inhibition Pemetrexed
100
80
60
40
20
-20
-50
-150
-20
20
40
60
80
100

FIG. 3B

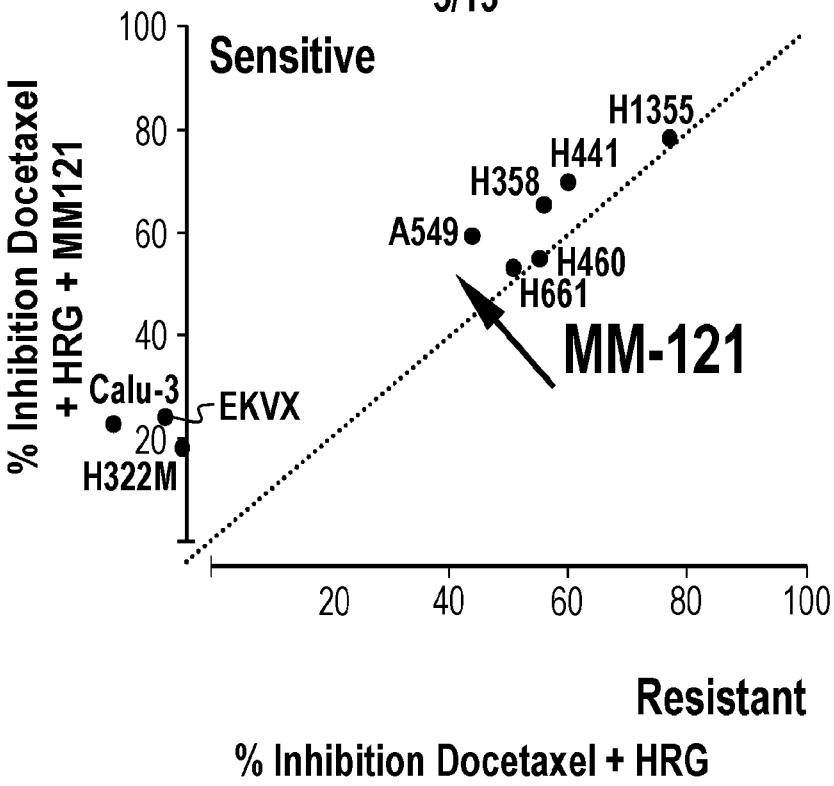
Sensitive
Resistant
% Inhibition Docetaxel + HRG + MM121
% Inhibition Docetaxel + HRG
100
80
60
40
20
20
40
60
80
100
H1355
H441
H358
A549
H460
H661
MM-121
Calu-3
EKVX
H322M

FIG. 3C

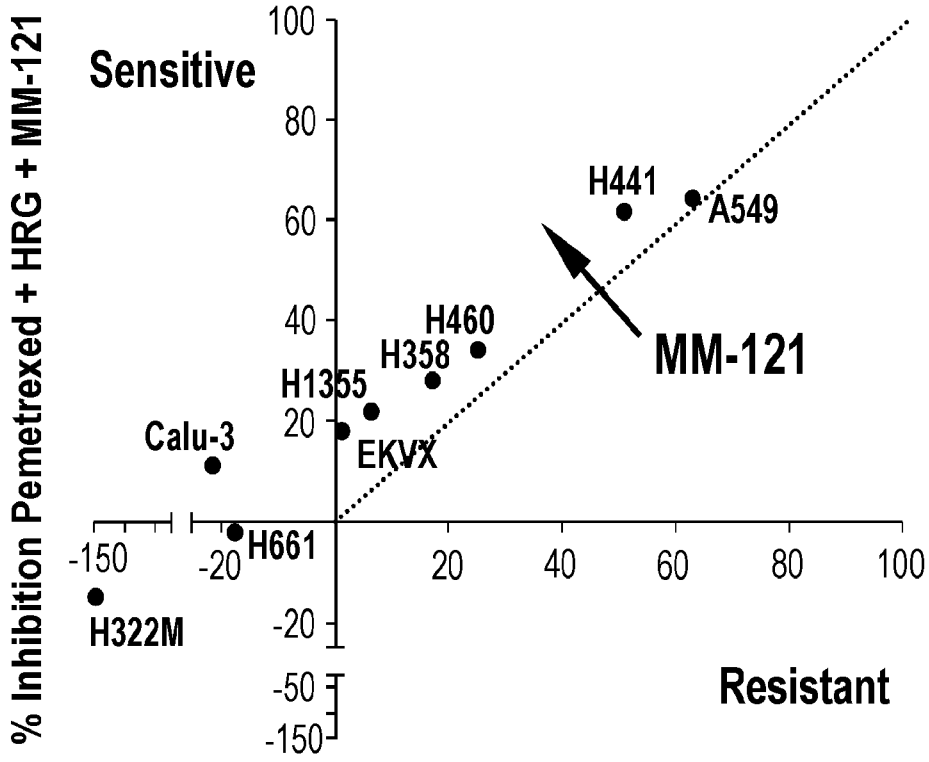
Sensitive
Resistant
% Inhibition Pemetrexed + HRG + MM-121
% Inhibition Pemetrexed + HRG
100
80
60
40
20
-20
-50
-150
-150
-20
20
40
60
80
100
H441
A549
H460
H358
H1355
MM-121
Calu-3
EKVX
H661
H322M

FIG. 3D

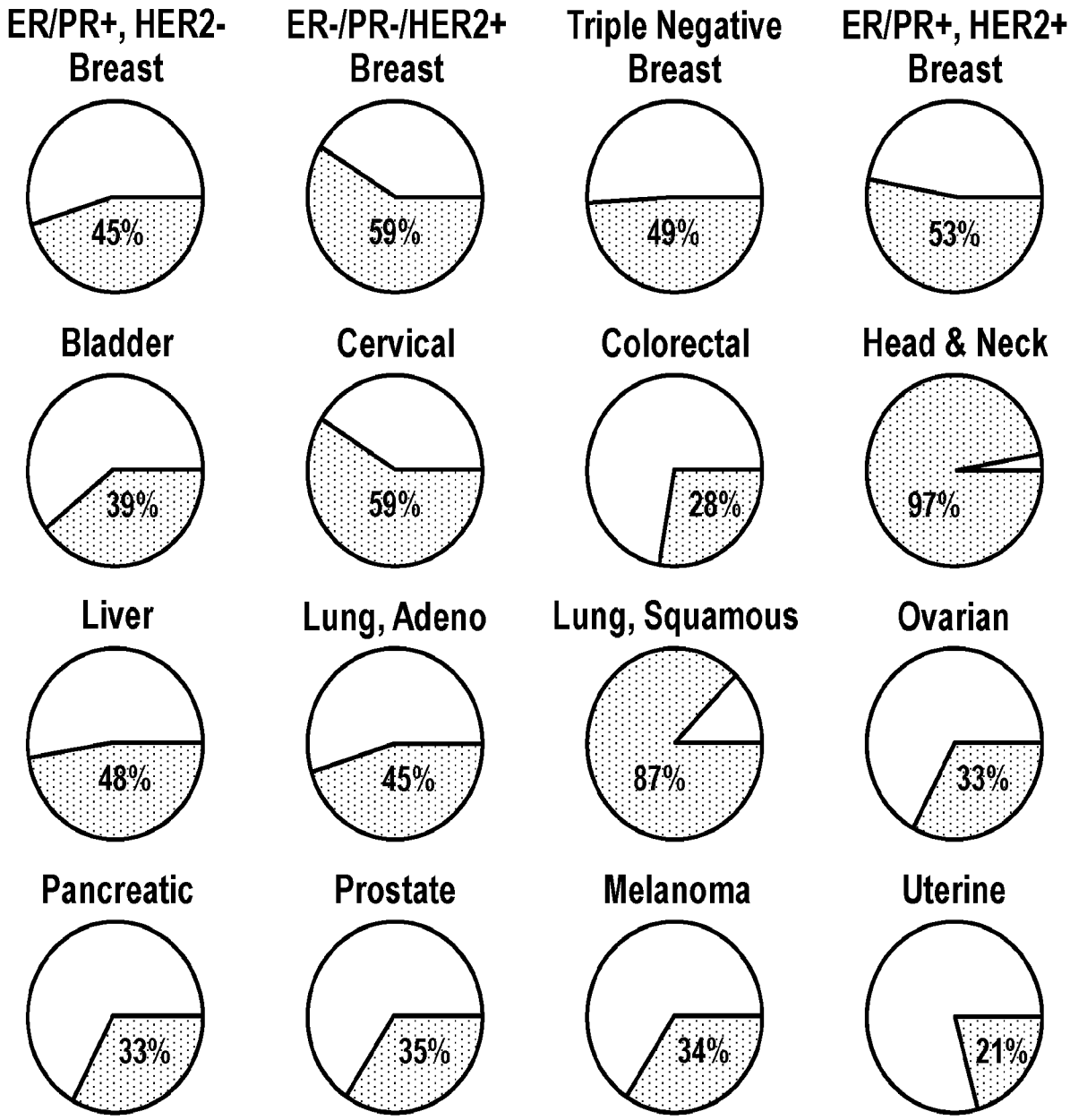
ER/PR+, HER2- Breast
45%
ER-/PR-/HER2+ Breast
59%
Triple Negative Breast
49%
ER/PR+, HER2+ Breast
53%
Bladder
39%
Cervical
59%
Colorectal
28%
Head & Neck
97%
Liver
48%
Lung, Adeno
45%
Lung, Squamous
87%
Ovarian
33%
Pancreatic
33%
Prostate
35%
Melanoma
34%
Uterine
21%

FIG. 4

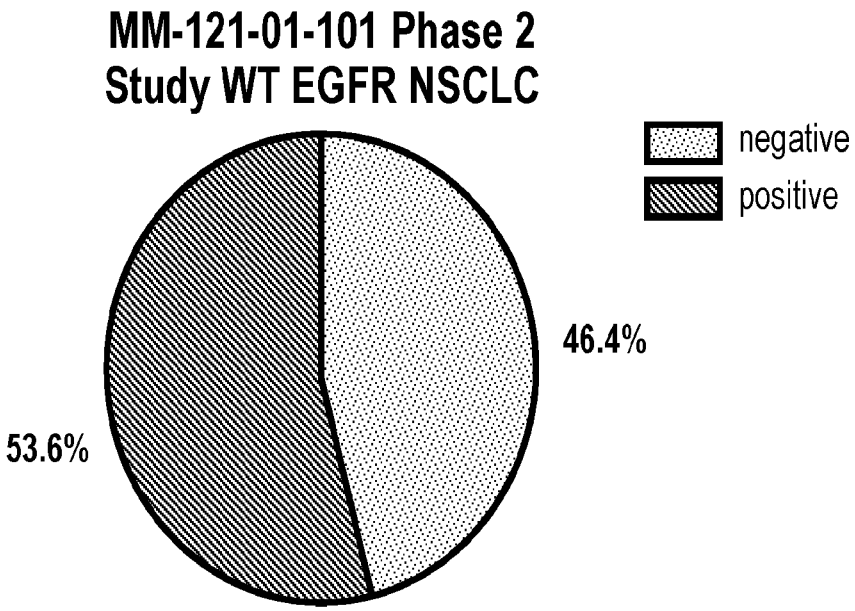
MM-121-01-101 Phase 2
Study WT EGFR NSCLC
negative
positive
46.4%
53.6%

FIG. 5A

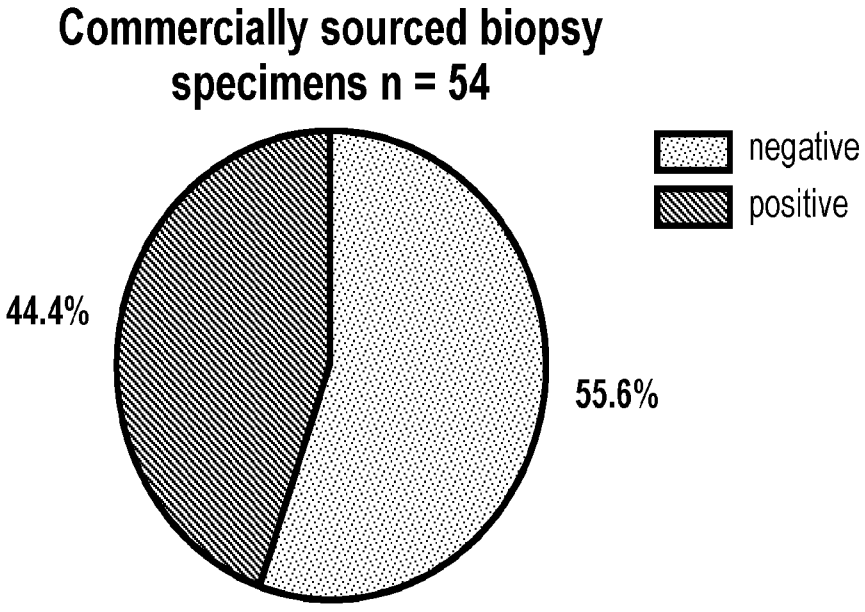
Commercially sourced biopsy
specimens n = 54
negative
positive
44.4%
55.6%

FIG. 5B

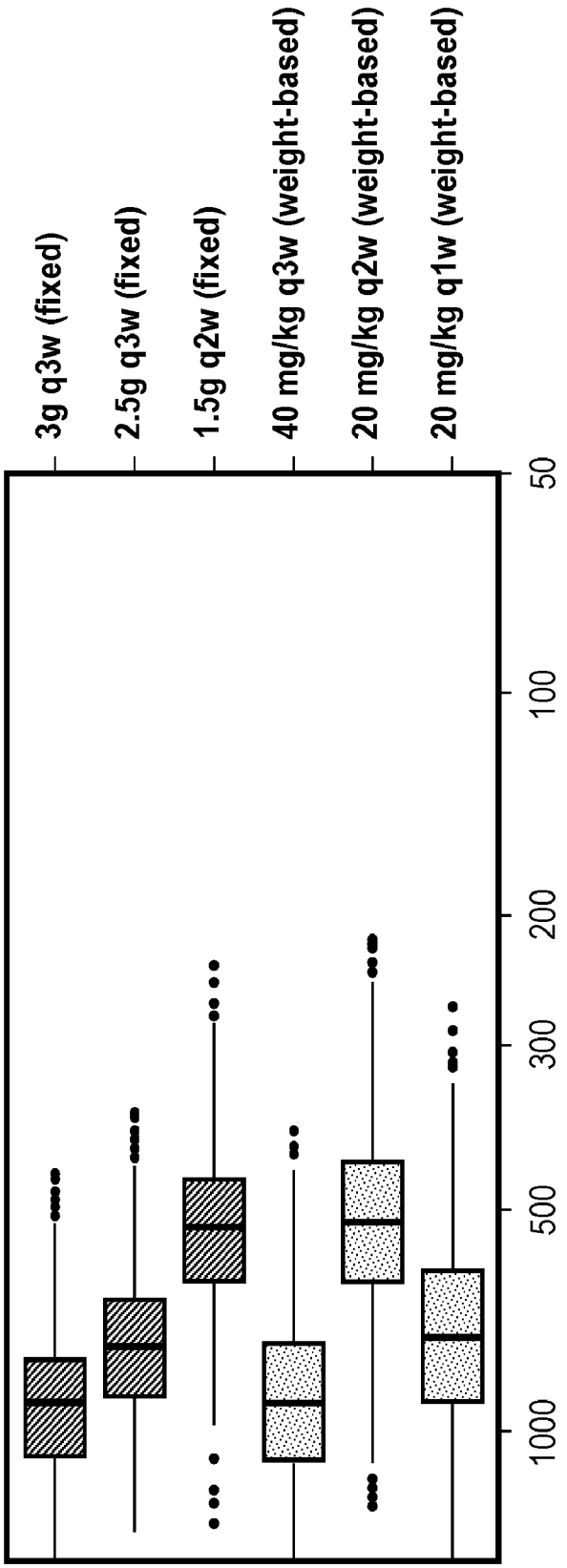
3g q3w (fixed)
2.5g q3w (fixed)
1.5g q2w (fixed)
40 mg/kg q3w (weight-based)
20 mg/kg q2w (weight-based)
20 mg/kg q1w (weight-based)
50
100
200
300
500
1000
Seribantumab Cmax
(mg/L)

FIG. 6A

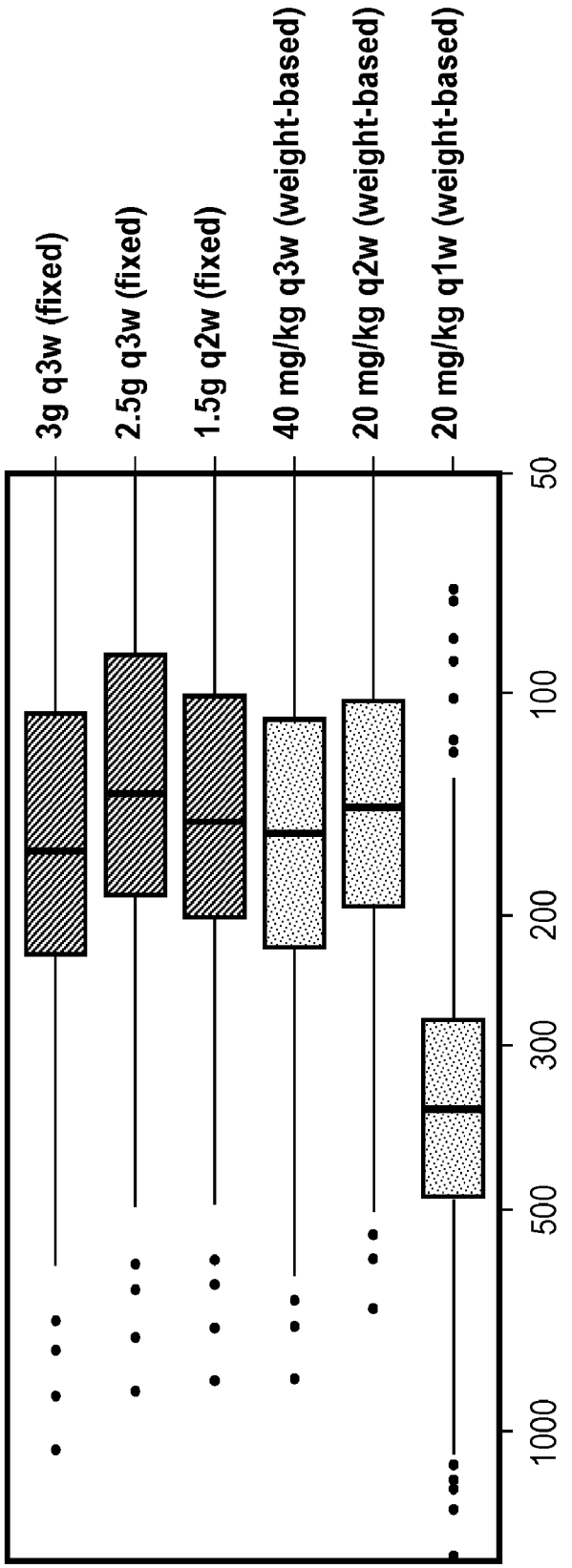
3g q3w (fixed)
2.5g q3w (fixed)
1.5g q2w (fixed)
40 mg/kg q3w (weight-based)
20 mg/kg q2w (weight-based)
20 mg/kg q1w (weight-based)
50
100
200
300
500
1000
Seribantumab Cmin
(mg/L)

FIG. 6B

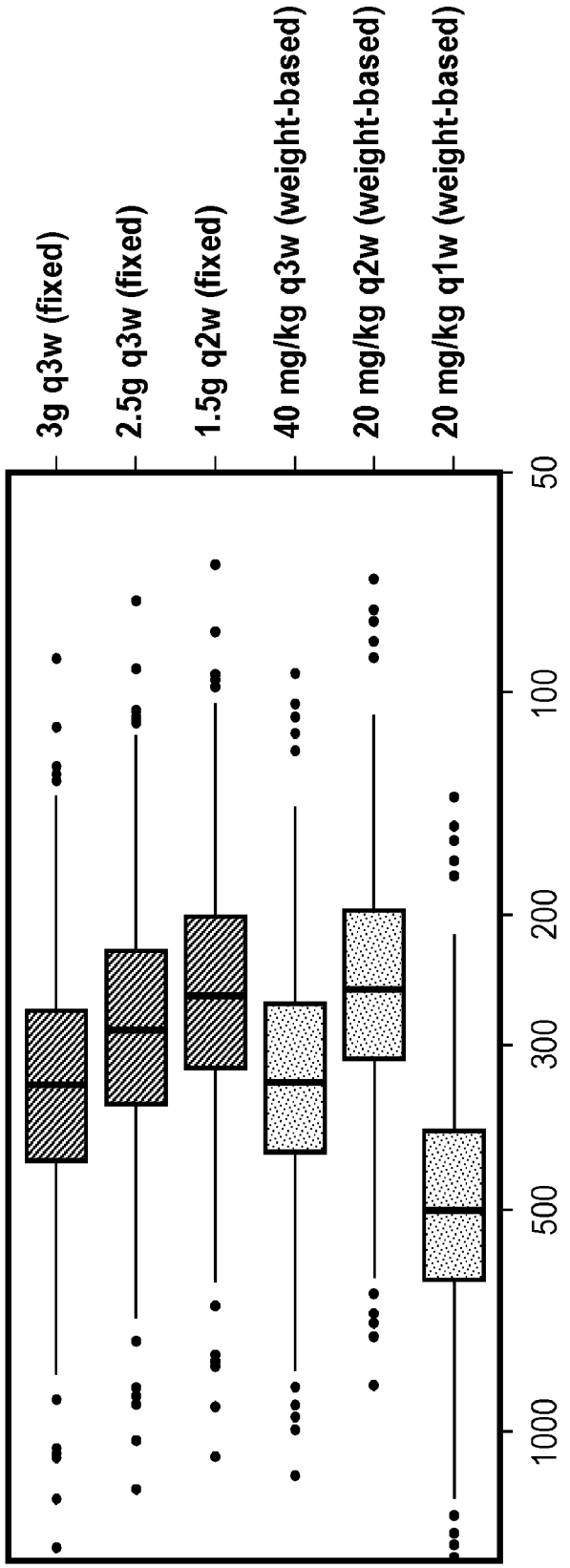
3g q3w (fixed)
2.5g q3w (fixed)
1.5g q2w (fixed)
40 mg/kg q3w (weight-based)
20 mg/kg q2w (weight-based)
20 mg/kg q1w (weight-based)
50
100
200
300
500
1000
Seribantumab Avg Conc
(mg/L)

FIG. 6C

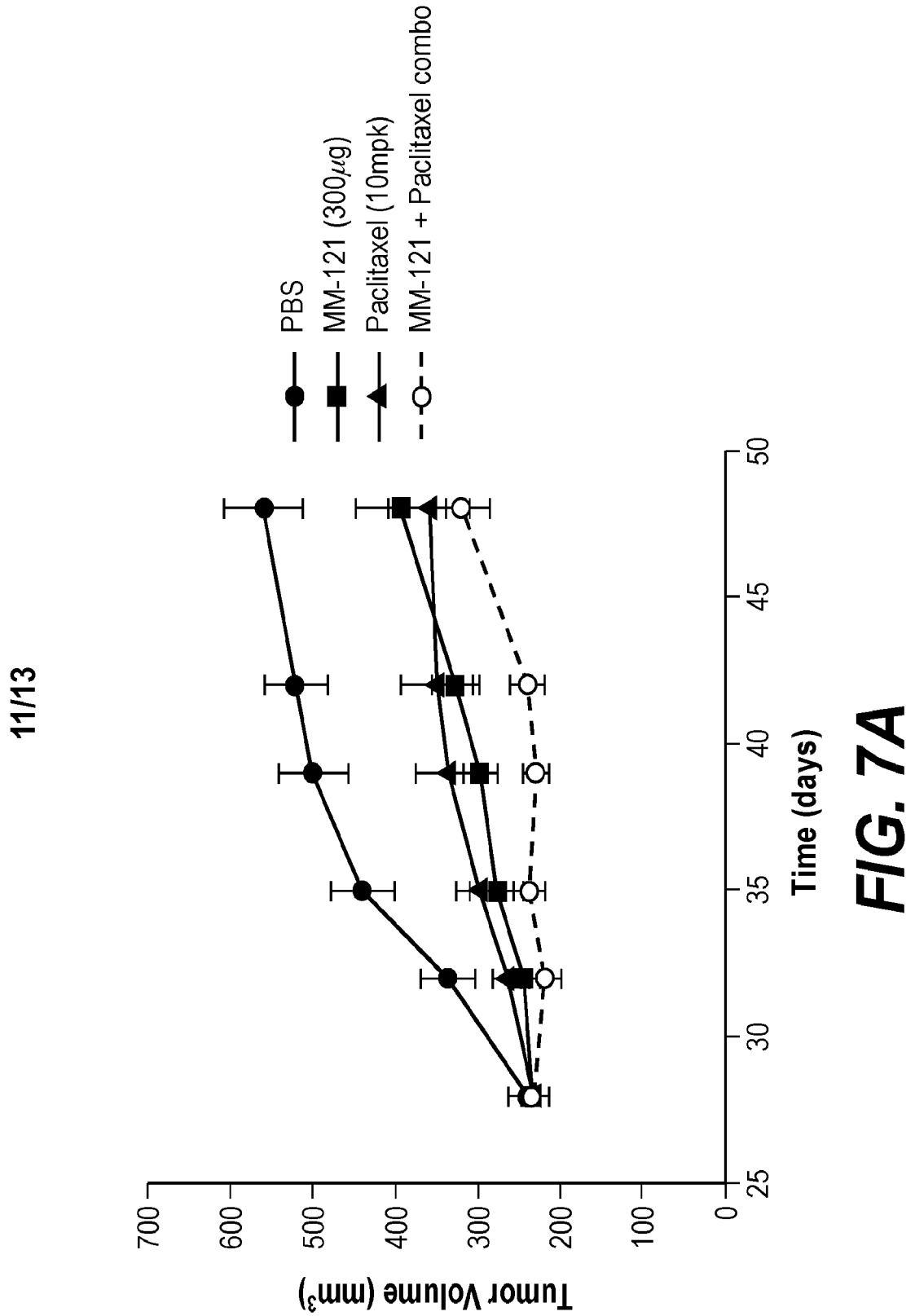
11/13
PBS
MM-121 (300μg)
Paclitaxel (10mpk)
MM-121 + Paclitaxel combo
Tumor Volume (mm³)
Time (days)
0
100
200
300
400
500
600
700
25
30
35
40
45
50

FIG. 7A

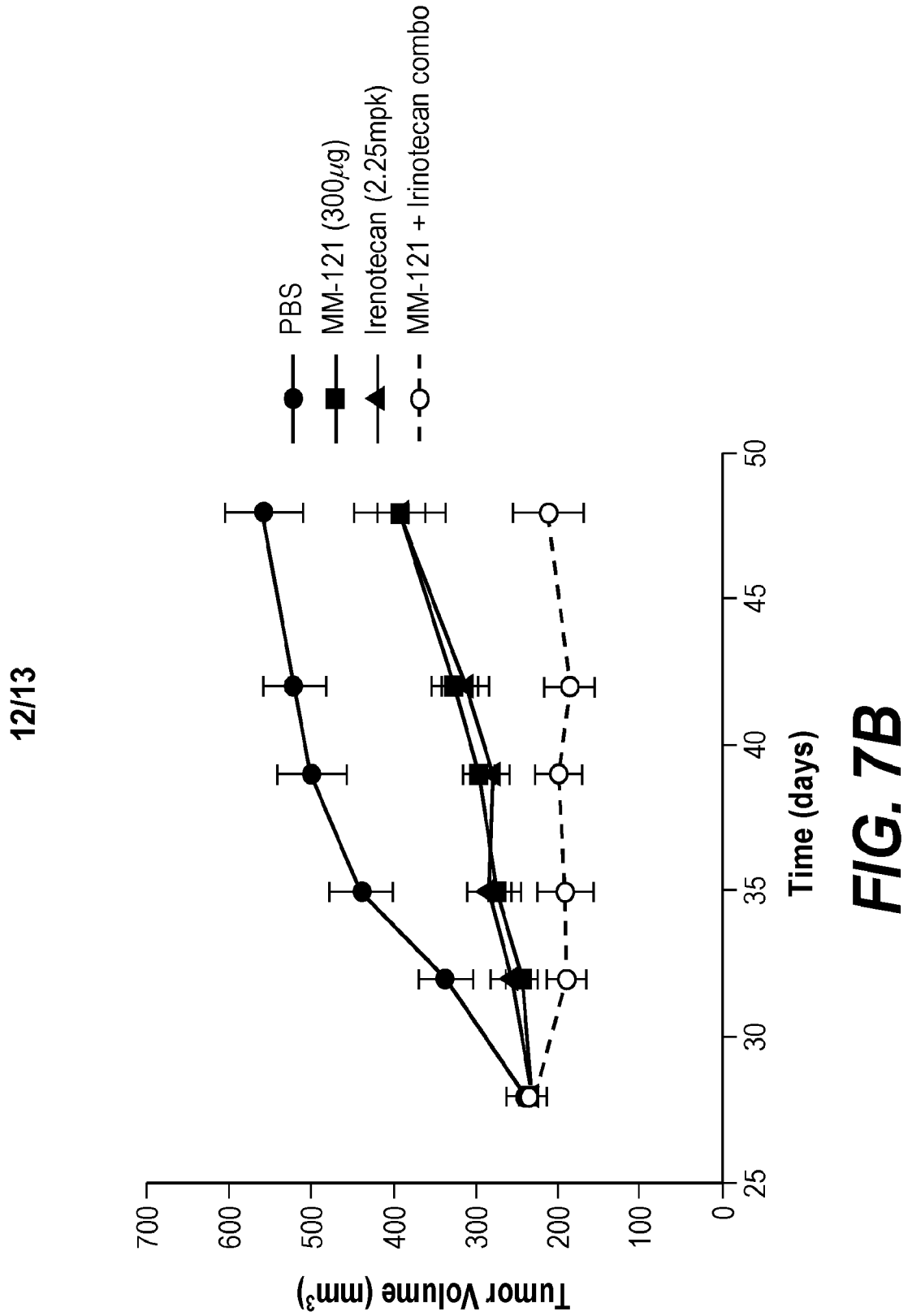
12/13
PBS
MM-121 (300μg)
Irenotecan (2.25mpk)
MM-121 + Irinotecan combo
Tumor Volume (mm³)
700
600
500
400
300
200
100
0
25
30
35
40
45
50
Time (days)

FIG. 7B

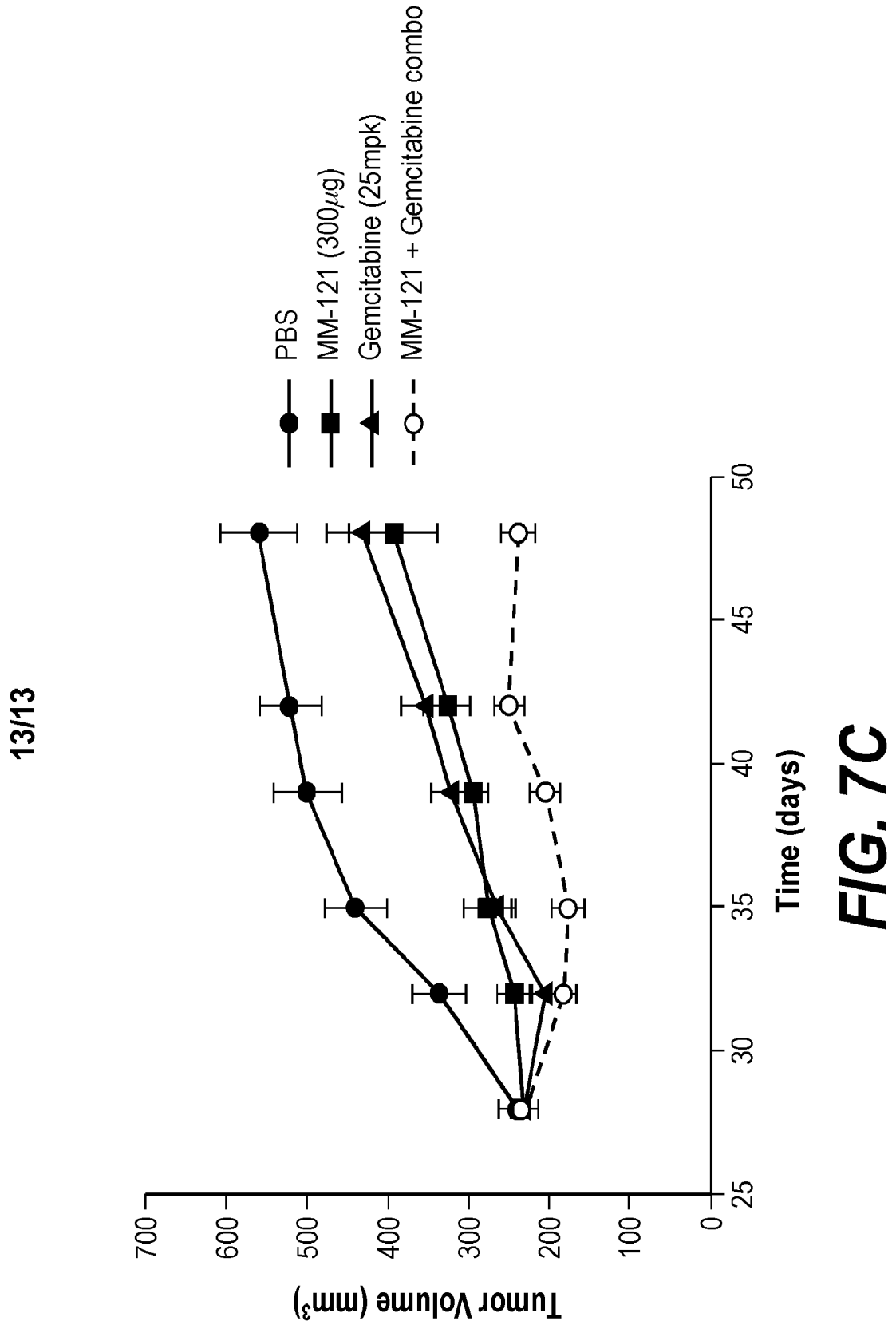
13/13
PBS
MM-121 (300μg)
Gemcitabine (25mpk)
MM-121 + Gemcitabine combo
Tumor Volume (mm³)
Time (days)
0
100
200
300
400
500
600
700
25
30
35
40
45
50

FIG. 7C

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/027933

**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. [X] furnished subsequent to the international filing date for the purposes of international search only:

      [X] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [X] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [X] 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/US2016/027933

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/337 A61K39/395 A61K31/519 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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | G MACBEATH ET AL: "A META-ANALYSIS OF BIOMARKERS IN THREE RANDOMIZED, PHASE 2 STUDIES OF MM-121, A LIGAND-BLOCKING ANTI-ERBB3 ANTIBODY, IN PATIENTS WITH OVARIAN, LUNG, AND BREAST CANCERS", ANNALS OF ONCOLOGY, vol. 25, no. S4, 1 September 2014 (2014-09-01), pages 313-47, XP055180759, DOI: 10.1093/annonc/mdu326.79 abstract<br>-----<br>-/-- | 1-20 |

[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

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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

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"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 |
|---|---|
| 15 June 2016 | 24/06/2016 |

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

2

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. |
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| Y | WO 2012/125864 A2 (MERRIMACK PHARMACEUTICALS INC [US]; GARCIA GABRIELA [US]; KUBASEK WILL) 20 September 2012 (2012-09-20) page 21, paragraph 2 - page 23, paragraph 2 figures 2,3 | 1-20 |
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| | | WO 2015100459 A2 | 02-07-2015 |

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*A61P 35/00*(2006.01)
*A61K 31/519*(2006.01)
*A61K 31/337*(2006.01)

权利要求书2页 说明书21页 附图13页

(54)发明名称

借助塞里班土单抗的组合治疗

(57)摘要

提供用于治疗选择的人类患者的癌症的组合物和方法,包含向所述患者投予抗ErbB3抗体(例如塞里班土单抗)和第二抗癌治疗剂的组合。通过本文公开的方法和组合物治疗的癌症包括作为调蛋白(HRG)阳性癌症的癌症。

CN 107750165 A

1.一种治疗患有调蛋白(HRG)阳性非小细胞肺癌(NSCLC)的患者的方法,所述方法包括在21天治疗周期的第1天向所述患者给予由以下组成的抗肿瘤疗法一次:

i.3000mg剂量的塞里班土单抗;和

ii.75mg/$m^2$剂量的多西他赛,

以治疗所述患者的所述NSCLC。

2.根据权利要求1所述的方法,其中所述癌症对于HRG mRNA为阳性,如通过RNA原位杂交(RNA-ISH)所测量,其中所述HRG RNA-ISH产生≥1+的评分。

3.根据权利要求1所述的方法,其中所述癌症对于HRG为阳性,如通过定量RT-PCR所测量。

4.根据权利要求1所述的方法,其中所述患者经历过至少一种失败的针对局部晚期和/或转移性NSCLC的系统性疗法。

5.根据权利要求1所述的方法,其中所述患者在用不多于三种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展,所述系统性疗法中的一种包含基于铂的治疗方案。

6.根据权利要求1所述的方法,其中多西他赛在给予塞里班土单抗之前至少30分钟共同给予。

7.根据权利要求1所述的方法,其中所述抗肿瘤疗法静脉内给予。

8.根据权利要求1所述的方法,其中所述治疗产生选自以下的至少一个治疗效果:肿瘤大小的减小、癌转移的降低、完全缓解、部分缓解、稳定疾病、整体应答率的提高或病理性完全应答。

9.根据权利要求1所述的方法,其中所述NSCLC为EGFR野生型。

10.根据权利要求1所述的方法,其中所述NSCLC为鳞状细胞癌。

11.一种治疗患有HRG阳性非小细胞肺癌(NSCLC)的患者的方法,所述方法包括在21天治疗周期的第1天向所述患者给予由以下组成的抗肿瘤疗法一次:

i.3000mg剂量的塞里班土单抗;和

ii.500mg/$m^2$剂量的培美曲塞,

以治疗所述患者的所述NSCLC。

12.根据权利要求10所述的方法,其中所述肿瘤对于HRG mRNA为阳性,如通过RNA原位杂交(RNA-ISH)所测量,其中所述HRG RNA-ISH产生≥1+的评分。

13.根据权利要求11所述的方法,其中所述癌症对于HRG为阳性,如通过定量RT-PCR所测量。

14.根据权利要求11所述的方法,其中所述患者经历过至少一种失败的用于局部晚期和/或转移性NSCLC的系统性疗法。

15.根据权利要求11所述的方法,其中所述患者在用不多于两种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展,所述系统性疗法中的一种包含基于铂的治疗方案。

16.根据权利要求11所述的方法,其中所述培美曲塞在给予塞里班土单抗之前至少30分钟共同给予。

17.根据权利要求11所述的方法,其中所述治疗产生选自以下的至少一个治疗效果:肿瘤大小的减小、癌转移的降低、完全缓解、部分缓解、稳定疾病、整体应答率的提高或病理性完全应答。

18.根据权利要求11所述的方法,其中所述NSCLC为EGFR野生型。

19.根据权利要求11所述的方法,其中所述NSCLC为鳞状细胞癌。

20.根据权利要求11所述的方法,其中所述抗肿瘤疗法静脉内给予。

# 借助塞里班土单抗的组合治疗

[0001] 相关申请

[0002] 本申请要求2015年4月17日提交的美国临时申请第62/149,271号的权益，其内容在此以引用方式并入。

## 背景技术

[0003] 非小细胞肺癌(NSCLC)

[0004] 肺癌是在世界范围内癌症相关死亡的一个首要原因。单独在2014年估计存在诊断的224,410个新病例，占全部癌症诊断的大约13％。对于在2003年到2009年的时间段期间诊断的病例，1年和5年存活率分别为43％和17％(“美国癌症学会事实和数字2014(American Cancer Society Facts and Figures 2014)”)。超过80％的肺癌为非小细胞肺癌(NSCLC)，并且这些的几乎三分之二诊断为晚期。具有“第三代”药剂(太平洋紫杉醇(paclitaxel)、多西他赛(docetaxel)、吉西他滨(gemcitabine)、长春瑞宾(vinorelbine)或培美曲塞(pemetrexed))的基于铂的双重方案被认为是在世界范围内用于治疗晚期NSCLC的护理标准。然而，仅三分之一的接收此方案的患者在一线疗法期间达到目标应答，并且另外20％到30％实现疾病的稳定性。不利的是，几乎所有这类患者最终看出疾病进展。

[0005] 当前对于NSCLC的治疗

[0006] 当前批准用于治疗顽固性(复发性，即，第二线治疗)晚期NSCLC的三种药剂为多西他赛、培美曲塞和埃罗替尼。

[0007] 多西他赛，商品名TAXOTERE®、DOCECAD®-IUPAC名称1,7β,10β-三羟基-9-氧代-5β,20-环氧基紫杉-11烯-2α,4,13α-三基4-乙酸2-苯甲酸酯13-{(2R,3S)-3-[(叔丁氧基羰基)氨基]-2-羟基-3-苯基丙酸酯}为抗有丝分裂紫杉烷抗癌治疗剂，其通常经由在十个或更多个循环内每三周一小时输液投予。在NSCLC的第二线治疗中批准的多西他赛剂量为每3周一次在60分钟内静脉内75mg/$m^2$。多西他赛应在塞里班土单抗(seribantumab)给药之前投予。

[0008] 培美曲塞，商品名ALIMTA®-IUPAC名称(2S)-2-{[4-[2-(2-氨基-4-氧代-1,7-二氢吡咯并[2,3-d]嘧啶-5-基)乙基]苯甲酰基]氨基}戊二酸)，为当前批准用于治疗胸膜间皮瘤和非小细胞肺癌的叶酸抗代谢产物。其通常在每个21天周期的第1天在10分钟内以500mg/$m^2$的剂量静脉内投予。

[0009] 卵巢癌

[0010] 卵巢癌(包括上皮卵巢癌)为妇女的与癌症相关的死亡的首要原因，与原发性腹膜癌瘤和输卵管癌瘤一样。因为卵巢癌在其早期相对无症状，所以通常得不到诊断直到疾病已达到晚期。用于晚期卵巢癌的标准治疗包括手术随后用基于铂的化疗剂(例如，顺铂、卡铂、奥沙利铂和赛特铂)，或用抗微管剂如太平洋紫杉醇的化疗。用于治疗卵巢癌的其它药物包括贝伐单抗、卡铂、环磷酰胺、阿霉素、吉西他滨、奥拉帕尼和拓朴替康。虽然标准治疗通常成功，但是许多患者经历疾病的复发，通常伴随对基于铂的方案的耐受性的表达。

[0011] 塞里班土单抗，抗ErbB3单克隆抗体治疗剂

[0012] 塞里班土单抗(先前MM-121或Ab#6)为人类单克隆抗ErbB3IgG2;参见例如美国专利第7,846,440号;第8,691,771号和第8,961,966号;第8,895,001,美国专利公开第20110027291号、第20140127238号、第20140134170号,和第20140248280号),以及国际公开第WO/2013/023043号、第WO/2013/138371号、第WO/2012/103341号,和美国专利申请第14/967,158号。

[0013] 塞里班土单抗为高特异性地结合在人类ErbB3上的表位的重组型人类IgG2mAb。IgG2分子的完整四聚结构由通过链内和链间二硫键保持在一起的2个重链(每个445个氨基酸)和2个λ轻链(每个217个氨基酸)构成。氨基酸序列(参见下文)预测完好非糖基化单体IgG2的143kDa的分子量。糖基化分析展现塞里班土单抗的N-连接糖基化,预测其为完整的糖基化塞里班土单抗单体的分子量贡献大约2.9kDa。预测的完整的糖基化塞里班土单抗的分子量(146kDa)在实际分子量(如通过质谱法以实验方式测定)的0.2%内。塞里班土单抗的等电位点为大约8.6(如通过等电点聚焦电泳测定的主要同功异型物)。

[0014] 塞里班土单抗通过静脉内输液投予(例如在一小时的过程内)并且作为在灭菌的单次使用式小瓶中的澄清液体溶液供应,其含有10.1mL的塞里班土单抗,在20mM组胺酸、150mM氯化钠的水溶液中浓度为25mg/ml,pH为约6.5(在6.2到6.8的范围内),存储在2℃到8℃下。塞里班土单抗包含具有SEQ ID NO:7的氨基酸序列的重链和具有SEQ ID NO:8的氨基酸序列的轻链。塞里班土单抗包含分别由阐述于SEQ ID NO:9和SEQ ID NO:11中的核酸序列编码的重链可变区(VH)和轻链可变区(VL)。塞里班土单抗包含包含分别阐述于SEQ ID NO:10和SEQ ID NO:12中的氨基酸序列的VH和VL区。塞里班土单抗包含包含阐述于SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列,和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列。

[0015] 治疗后果的评估

[0016] 使用用于肿瘤应答的标准度量评估对于NSCLC、卵巢癌、原发性腹膜癌瘤和输卵管癌瘤的治疗后果。目标病变(肿瘤)对治疗的应答分类为:

[0017] 完全应答(CR):所有目标病变的消失。任何病理性淋巴结(无论目标或非目标)必须具有到<10mm的短轴缩减;部分应答(PR):将基线总和直径用作参考,目标病变的直径的总和减小至少30%;

[0018] 进行性疾病(PD:将研究的最小总和(如果其为研究的最小,那么这包括基线总和)用作参考,目标病变的直径总和增大至少20%。除20%的相对增大之外,总和还必须展现至少5mm的绝对增大。(注意:一个或多个新病变的出现也视为进展);和

[0019] 稳定疾病(SD):将在研究时的最小总和直径用作参考,既没有足够的收缩以认定PR也没有足够的增大以认定PD。(注意:不使直径的总和增大5mm或更多的20%或更少的改变编码为稳定疾病)。被指定为稳定疾病的状态,量测值必须在研究以6周的最小间隔进行之后已满足稳定疾病标准至少一次。

[0020] 非目标病变对治疗的应答分类为:

[0021] 完全应答(CR):所有非目标病变的消失和肿瘤标记水平级的标准化。所有淋巴结必须在大小上是非病理性的(<10mm短轴)。如果肿瘤标记物初始地高于正常上限,那么它们必须对于患者归一化以被认为是完全临床应答;

[0022] 非CR/非PD:一个或多个非目标病变的持续和/或肿瘤标记水平维持高于正常界限值;和

[0023] 进行性疾病(PD):一个或多个新病变的出现和现有非目标病变的明确进展中的任一者或两者。在此情形下,明确进展必须表示整体疾病状态改变,非单个病变增大。

[0024] 其它示例性阳性应答

[0025] 用这些方法治疗的患者可经历NSCLC或卵巢癌、原发性腹膜癌瘤和输卵管癌瘤的至少一个迹象的改善。应答还可通过可测量肿瘤病变的量和/或大小的降低来测量。可测量的病变被定义为通过CT扫描(CT扫描片层厚度不超过5mm)在至少一个维度上(将记录最长直径)可精确测量为>10mm,通过临床测验10mm卡尺测量结果或通过胸部X射线>20mm的那些。非目标病变的大小,例如病理性淋巴结还可测量改善。病变可使用例如x射线、CT或MRI图像测量。显微法、细胞学或组织结构也可用于评估对疗法的应答性。当可测量肿瘤已另外满足应答或稳定疾病的标准时,在治疗期间出现或恶化的渗出性可被视为指示肿瘤进展,但是仅当存在渗出性的赘生性来源的细胞学确认时。

[0026] 虽然当前批准的用于NSCLC卵巢癌、原发性腹膜癌瘤和输卵管癌瘤的治疗提供一些益处,但是仍然存在大大改善的空间,尤其对于患有晚期或转移性疾病的患者。因此需要对于患有晚期NSCLC、卵巢癌、原发性腹膜癌瘤和输卵管癌瘤的患者更有效的治疗。本发明解决此需要并且提供附加益处。

## 发明内容

[0027] 提供用于治疗选择的人类患者的癌症的组合物方法,包含向患者投予抗ErbB3抗体和第二抗癌治疗剂的组合。

[0028] 癌症可为非小细胞肺癌(NSCLC),例如非鳞状NSCLC,并且第二抗癌治疗剂可为例如多西他赛或培美曲塞,其中组合根据特定临床给药方案(即,以特定剂量量和根据具体给药时程)投予(或用于投予)。癌症可替代地为卵巢癌(例如永久、复发性、抗性或顽固性卵巢癌)或癌症可为原发性腹膜癌瘤或输卵管癌瘤,并且对于这些中的每个,第二抗癌治疗剂可为例如太平洋紫杉醇、吉西他滨、伊立替康、脂质体伊立替康(例如nal-IRI)或脂质体阿霉素,例如DOXIL®。在一个实施例中,癌症为在用有机铂药剂的之前疗法之后已进展的局部晚期或转移性NSCLC(即,治疗顽固性)。在一个实施例中,NSCLC为鳞状细胞癌。在另一个实施例中,癌症为EGFR野生型。

[0029] 在一方面,提供治疗成年人类患者的癌症的方法,方法包含向患者投予抗ErbB3抗体,所述抗ErbB3抗体包含包含阐述于SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列,和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列,其中抗ErbB3抗体作为3000mg的第一单次剂量投予,不管患者体重如何。在一个实施例中,第一单次剂量后跟着至少一个附加单次剂量,至少一个附加剂量中的每个在紧接着之前剂量之后三周投予,并且以3000mg的剂量投予,不管患者体重如何。

[0030] 在第二方面,提供治疗患有NSCLC肿瘤;和在用不多于两种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展的癌症患者的方法,其中一种为基于铂的方案;方法包含向患者投予的有效量以下中的每个:(1)抗ErbB3抗体,所述抗ErbB3抗体包含包含阐述于

SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列,和(2)多西他赛或培美曲塞。

[0031] 在第三方面,提供用于治疗成年人类患者的癌症的组合物,组合物包含抗体,所述抗体包含包含阐述于SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列,和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列,其中组合物作为3000mg的第一单次剂量用于投予,不管患者体重如何。在一个实施例中,组合物作为3000mg的第一单次剂量用于投予,不管患者体重如何,随后至少一个附加单次剂量,至少一个附加剂量中的每个在紧接着之前剂量之后三周投予,并且以3000mg的剂量投予,不管患者体重如何。

[0032] 在一个实施例中,癌症为非小细胞肺癌(NSCLC)。在另一个实施例中,癌症为卵巢癌。

[0033] 在一个实施例中,患者在用不多于两种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展,其中一个为之前基于铂的方案。在另一个实施例中,患者在用不多于三种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展,其中一种为之前基于铂的方案。在另一个实施例中,人类患者在用抗肿瘤疗法(例如抗癌剂)的之前治疗之后疾病进展或复发之后治疗。在另一个实施例中,人类患者在抗肿瘤疗法失败之后治疗。在另一个实施例中,癌症被鉴定为已获得对抗肿瘤疗法的耐受性的癌症。

[0034] 在以上方面中的任一个的示例性实施例中,本文公开的方法进一步包含有效量的第二抗癌治疗剂与抗ErbB3抗体的共投予。在一个实施例中,第二抗癌治疗剂为多西他赛,并且其中多西他赛的有效量为75mg/$m^2$。在另一个实施例中,第二抗癌治疗剂为培美曲塞,并且其中有效量为500mg/$m^2$。在一个实施例中,有效量的多西他赛或培美曲塞在投予抗体之前至少30分钟共投予。

[0035] 在第四方面,提供用于治疗成年人类患者的癌症的组合物,组合物包含抗体,所述抗体包含包含阐述于SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列,和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列,其中组合物作为3000mg的第一单次剂量用于投予,不管患者体重如何。在一个实施例中,组合物作为3000mg的第一单次剂量用于投予,不管患者体重如何,随后至少一个附加单次剂量,至少一个附加剂量中的每个在紧接着之前剂量之后三周投予,并且以3000mg的剂量投予,不管患者体重如何。在另一个实施例中,组合物以20mg/kg的剂量投予。在一个实施例中,卵巢癌为永久、复发性、抗性或顽固性卵巢癌。

[0036] 在第五方面,提供治疗患有卵巢肿瘤、原发性腹膜癌瘤或输卵管癌瘤的癌症患者的方法,方法包含向患者投予的有效量以下中的每个:(1)抗ErbB3抗体,所述抗ErbB3抗体包含包含阐述于SEQ ID NO:1(CDRH1)SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列,和(2)太平洋紫杉醇、伊立替康或吉西他滨。

[0037] 在以上方面中的任一个的示例性实施例中，抗ErbB3抗体为塞里班土单抗。

[0038] 在一个实施例中，本文所述的治疗方法包含投予与一种或多种其它抗肿瘤剂(例如其它化学治疗剂、其它抗癌剂或其它小分子药物)组合的塞里班土单抗。

[0039] 在一个实施例中，在治疗周期内投予不多于三种其它抗癌疗治疗剂。在另一个实施例中，在治疗周期内不多于两种其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，在治疗周期内不多于一种其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，在治疗周期内无其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，其它抗癌治疗剂可与投予塞里班土单抗同时或在其之前或在其之后投予。

[0040] 待通过本文公开的方法和组合物治疗的癌症包括作为调蛋白(HRG)阳性癌症的癌症，任选地其中HRG阳性通过HRG RNA-ISH检验或定量RT-PCR检验测定。在这类检验中，如果这类检验每个细胞显示至少1到3个，那么样本测定为阳性，其中细胞来自患者肿瘤样本。在一个实施例中，HRG阳性基于FDA批准的测试。在一个实施例中，癌症为非小细胞肺癌(NSCLC)。在另一个实施例中，癌症为局部晚期或转移性的。在另一个实施例中，患者在用不多于两种用于局部晚期或转移性疾病的系统性疗法治疗之后已进展，系统性疗法中的一种包含基于铂的方案。

[0041] 在一个实施例中，包含以上方面中的任一个的组合物和/或方法的癌症的治疗产生选自以下组成的组的至少一个治疗效果：肿瘤大小的减小、癌转移的降低、完全缓解、部分缓解、稳定疾病、整体应答率的提高或病理性完全应答。

## 附图说明

[0042] 图1示出调蛋白(HRG)诱导在一组体外NSCLC细胞系中增殖的能力指示对体内塞里班土单抗的单一药剂应答。25个EGFR野生型NSCLC细胞系中的九个应答于HRG；它们呈现应答于外源添加HRG提高的细胞增殖，如通过使用3D球形培养物的CellTiter-Glo®(CTG)所测量。

[0043] 图2A到图2D为示出应答于体外HRG的细胞应答于体内塞里班土单抗的四个曲线，同时不应答于体外HRG的细胞系不应答于体内塞里班土单抗。示出HRG-应答性细胞系A549(图2A)和H322M(图2B)以及HRG非应答性细胞系H460(图2C)和HOP-92(图2D)。随时间的肿瘤体积示出为指示塞里班土单抗应答。

[0044] 图3A到3D为示出在96h之后在多个细胞系中的3D球形增殖检验中5nM HRG诱导对多西他赛(111nM，图3A)和培美曲塞(1111nM，图3B)的耐受性；图3C和图3D示出在NSCLC细胞系(A549、EKVX、H358、H322M、Calu-3、H661、H441、H1355、H430)中用塞里班土单抗(1μM，“MM-121”)治疗恢复对多西他赛(图3C)和培美曲塞(图3D)的敏感性。

[0045] 图4为示出基于TCGA数据组在不同适应症上的HRG mRNA表达水平的一组曲线。

[0046] 图5A和5B为示出在来自MM-121-01-101II期研究(图5A)和商业来源的活检试样(图5B)两者的NSCLC组织样本上HRG mRNA的两个曲线。

[0047] 图6A到6C为示出对于通过剂量和时间间隔的基于重量的和固定给药方案的塞里班土单抗药代动力学的一组盒须曲线(表明四分位范围和离群值)。图6A示出了塞里班土单抗最大浓度(Cmax，mg/L)，图6B示出了塞里班土单抗最小浓度(Cmin，mg/L)，并且图6C示出了塞里班土单抗平均浓度(AvgConc，mg/L)。基于重量和固定剂量沿y轴指示。

[0048] 图7A到7C为示出调蛋白调节对不管化疗的类别的治疗的耐受性和与塞里班土单抗(“MM-121”)共投予消除此耐受性的一组曲线。在卵巢癌的小鼠OVCAR8异种移植模型中，荷瘤小鼠用太平洋紫杉醇(图7A)、伊立替康(图7B)或吉西他滨(图7C)单独(如单一疗法)或与固定剂量的塞里班土单抗一起治疗。在每种情况下，用太平洋紫杉醇、伊立替康、吉西他滨单一疗法治疗的肿瘤开始随时间进展，而当化学治疗剂与塞里班土单抗共投予时此影响大大降低。对照小鼠仅接收PBS。

## 具体实施方式

[0049] 本文提供用于使用塞里班土单抗和紫杉烷(例如多西他赛)或叶酸抗代谢产物(例如培美曲塞)的组合有效治疗人类患者的铂顽固性NSCLC(例如局部晚期或转移性NSCLC)的方法。

[0050] I.患者选择

[0051] 选择用于治疗的NSCLC患者为经历过至少一种但不多于三种失败的针对局部晚期或转移性NSCLC的系统性疗法的成年患者，失败的一种系统性疗法必须已经为基于铂的疗法(例如双重疗法)。在另一方面，NSCLC患者患有对于调蛋白(HRG)mRNA为阳性的一种或多种NSCLC肿瘤，如通过如描述于下文实例中的RNA-ISH检验评定。在一个实施例中，NSCLC肿瘤对于HRG为阳性，如通过FDA批准的测试评定。

[0052] 在另一方面，本发明提供用于有效治疗先前接收抗肿瘤疗法并且发展对抗肿瘤疗法的耐受性的有需要的人类患者的癌症(例如NSCLC)的方法。举例来说，在一个实施例中，方法包含通过投予塞里班土单抗和紫杉烷(例如多西他赛)或叶酸抗代谢产物(例如培美曲塞)中任一者治疗先前接收抗肿瘤疗法并且发展对抗肿瘤治疗的耐受性的有需要的人类患者的癌症。

[0053] II.组合疗法

[0054] 塞里班土单抗与紫杉烷(例如多西他赛)或叶酸抗代谢产物(例如培美曲塞)向患有NSCLC的选择的受试者共投予。在另一个实施例中，塞里班土单抗与太平洋紫杉醇、伊立替康或吉西他滨向患有卵巢癌、原发性腹膜癌瘤或输卵管癌瘤的选择的受试者共投予。

[0055] “共投予”是指塞里班土单抗和紫杉烷或叶酸抗代谢产物的同时或依次投予。当依次时，共投予必须在足够短的时间跨度内发生，使得塞里班土单抗和紫杉烷或叶酸抗代谢产物两者同时存在于治疗的患者体内。

[0056] 在一个实施例中，塞里班土单抗与紫杉烷多西他赛共投予。多西他赛被批准用于在治疗乳癌和NSCLC(铂疗法后)中使用的单一药剂，和与用于治疗激素顽固性前列腺癌、NSCLC(与顺铂组合)、胃腺癌和头部和颈部的鳞状细胞癌的组合疗法。用于治疗NSCLC的多西他赛的批准剂量方案为75mg/$m^2$，每3周一次在1小时内静脉内给予。

[0057] 在另一个实施例中，塞里班土单抗与叶酸抗代谢产物培美曲塞(也以商品名ALIMTA®出售)共投予。ALIMTA被批准用于非鳞状细胞NSCLC和间皮瘤的组合疗法治疗。ALIMTA的推荐剂量为在每个21天周期的第1天静脉内500mg/$m^2$。如果在组合疗法方案中观察到毒性，那么可需要剂量减少，在后续周期中可调节。

[0058] 在另一个实施例中，在治疗周期内不多于三种其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，在治疗周期内不多于两种其它抗癌治疗剂与塞里班土单抗组

合投予。在另一个实施例中，在治疗周期内不多于一种其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，在治疗周期内无其它抗癌治疗剂与塞里班土单抗组合投予。在另一个实施例中，其它抗癌治疗剂可与投予塞里班土单抗同时或在其之前或在其之后投予。

[0059] 如本文所用，“抗肿瘤剂”是指具有抑制人类肿瘤(尤其恶性(癌)病变，如癌瘤、肉瘤、淋巴瘤或白血病)的发展或进展的功能特性的药剂。癌转移的抑制经常为抗肿瘤剂的特性。

[0060] III.治疗协定

[0061] 患有晚期或转移性NSCLC的选择的患者在至少一个21天治疗周期的第1天治疗。在第一治疗周期之前，患者经历预治疗方案。方案特定于即将来临化疗治疗(例如培美曲塞或多西他赛)并且被设计成缓解与培美曲塞或多西他赛相关的毒性。多西他赛预治疗包含用皮质类固醇(如地塞米松)前驱用药(例如每天两次8mg)三天，在多西他赛投予之前一天开始。培美曲塞预治疗包含用低剂量口服叶酸制剂(或含叶酸的多种维生素)在每天基础上前驱用药，在第一21天周期开始之前至少七天开始。在每个21天周期的第1天，患者将在塞里班土单抗投予之前至少30分钟静脉内接收标准剂量的多西他赛或培美曲塞。塞里班土单抗随后在90分钟(在第一21天周期的第1天)或60分钟(在任何后续21天周期的第1天)内静脉内投予。

[0062] 如本文所使用，使用术语“固定剂量”(也被称作“均一剂量”或“均一固定剂量”)是指不考虑患者的重量或体表面积(BSA)向成年患者投予的经测量的剂量。因此固定剂量不以mg/kg(基于重量)剂量，或以mg/$m^2$(BSA)剂量提供，而是实际上在单次投予中以药剂的绝对量(例如抗ErbB3抗体的mg)向成年患者投予。

[0063] IV.后果

[0064] 根据所公开的协定治疗的患者可相对于目标病变呈现CR、PR或SD。在另一个实施例中，如此治疗的患者经历肿瘤收缩和/或增长率的减小，即，抑制肿瘤生长。在另一个实施例中，降低或抑制肿瘤细胞增殖。可替代地，以下一种或多种可指示对治疗的有益应答：可减少癌细胞数目；可减小肿瘤大小；可抑制、延迟、减缓或停止癌细胞浸润到周边器官中；可减缓或抑制肿瘤转移；可抑制肿瘤生长；可阻止或延迟肿瘤的复发；可在一定程度上解除与癌症相关联的一个或多个症状。有利应答的其它指示包括减小可测量肿瘤病变或非目标病变的量和/或大小。

[0065] V.试剂盒和单位剂型

[0066] 还提供容纳在外容器(例如袋，贝壳掀盖式或盒子)内的内容器(例如小瓶)中包括包含抗ErbB3抗体的组合物的试剂盒，所述抗ErbB3抗体包含包含阐述于SEQ ID NO:1(CDRH1)、SEQ ID NO:2(CDRH2)和SEQ ID NO:3(CDRH3)中的氨基酸序列的CDRH1、CDRH2和CDRH3序列和包含阐述于SEQ ID NO:4(CDRL1)SEQ ID NO:5(CDRL2)和SEQ ID NO:6(CDRL3)中的氨基酸序列的CDRL1、CDRL2和CDRL3序列和药学上可接受的载剂，其以治疗有效单位剂型(例如为单一剂量)用于前述方法。任选地，抗ErbB3抗体为塞里班土单抗。单位剂型将通常包含任选地略微高于剂量量(例如3000mg)药物量，以有助于从内容器取出所需要的量。此剂量量可包含多个小瓶，例如12×10.1mL小瓶或6×20mL小瓶。在试剂盒中每个小瓶应包含相同批号。试剂盒可任选地另外包括说明书，包含例如投予参数和时程，以允许执业医生

(例如医生或护士)根据在本文中教导的方法向NSCLC患者投予其中所含的抗体组合物(和其它药物,如果存在的话)。在一个实施例中,试剂盒进一步包含多西他赛和/或培美曲塞,例如各自在单独容器中,任选地以单一剂量单位剂型。试剂盒可进一步含有投予(一种或多种)医药组合物所必需的稀释液、仪器或装置,例如一个或多个灭菌稀释剂的容器,例如用于注射的盐水或葡萄糖溶液;一个或多个注射器(例如预填充的注射器);导管、皮下(IV)针、IV输液器。

[0067] 以下实例仅为说明性的并且应不被理解为以任何方式限制本公开的范围,因为在阅读本公开,许多变化形式和等效物对于本领域的技术人员将变得显而易见。

[0068] 在本文中引用的所有专利、专利申请和公开以全文引用的方式并入本文中。

[0069] 实例

[0070] 方法

[0071] 调蛋白(HRG)RNA-ISH如以下和在2014年12月29日提交的未决国际申请第PCT/US2014/072594号“用于用ErbB3抑制剂和/或化学疗法预测癌症疗法的后果的生物标记曲线(Biomarker Profiles for Predicting Outcomes of Cancer Therapy with ErbB3 Inhibitors and/or Chemotherapies)”中所描述执行,除实例3中的穿刺活检分析之外。

[0072] RNA-ISH检验

[0073] 在此检验中,使用Advanced Cell Diagnostics®(加利福尼亚哈沃德的“ACD”(“ACD”Hayward,California))RNAscope®检验的以下变型对FFPE肿瘤样本进行HRG RNA水平评分。具体地说,细胞经渗透并且与对HRG具有特异性的一组寡核苷酸“Z”探针一起培育(参见例如美国专利第7,709,198号)。使用“Z”探针以及每个转录物使用多组探针,在标准ISH方法内提高检验的特异性。可用于此检验的一个HRG探针组为ACD零件编号311181。通过ACD制备(并且用于RNAscope®检验中)的另一个HRG探针组包括62个探针(31对),在长度上每个为25个碱基,其以包含SEQ ID NO:42的核苷酸442-2977的HRG转录物的1919个碱基长区域为目标,并且一起检测15个单独HRG同功异型物(α、β1、β1b、β1c、β1d、β2、β2b、β3、β3b、γ、γ2、γ3、ndf43、ndf34b和GGF2)。在Z探针培育之后,添加可仅与结合到目标转录物的一对相邻Z探针杂交的预扩增剂。这最小化非特异性结合的扩增。然后基于对预扩增剂序列的特异杂交执行若干依次扩增步骤,随后是实现在肿瘤组织中HRG RNA水平的半定量测量的酶介导的显色检测。

[0074] 步骤1:FFPE组织切片经去石蜡并且预处理以阻断内源性磷酸酶和过氧化酶并且使RNA结合位点暴露。步骤2:施用目标特异性双Z探针,其在相邻序列特异性地与目标RNA杂交。步骤3:目标通过依次施用预扩增剂寡核苷酸、扩增剂寡核苷酸、最终HRP-共轭的寡核苷酸和DAB来检测。步骤4:使用光学显微镜观测切片并且由病理学家评分。

[0075] 为了对检验评分,四个细胞系的参考组织微阵列(TMA)与肿瘤样本在一起染色。这些细胞系表达不同水平的HRG,在从低到高范围内。然后病理学家基于与参考TMA的视觉比较分配患者样本评分。

[0076] 1.样品制备和染色

[0077] 患者样本制备和病理学家检查程序类似于qIHC检验。一旦活检或手术切除,就将患者肿瘤样本立即放置于固定液(10%中性缓冲的福尔马林)中通常在室温下维持20到24小时。然后按照标准医院程序将样本转移到70%乙醇并且嵌入石蜡中。在执行检验之前,制

备4μm切片的样本并且封固在带正电的75×25mm载玻片上。烘烤这些用于改善组织粘连(在65℃下10到30min),在石蜡中浸渍用于组织防腐,并且在氮气下在室温下存储。切片中的一个用于常规H&E染色,病理学家检查肿瘤内容物、质量和临床诊断。病理学家将区分肿瘤、基质和坏死的区域。在此检查之后,相邻或附近组织切片(在H&E切片的20μm内)用于检验。

[0078] 用于RNAscope®检验的预处理溶液、目标探针和洗涤缓冲液从ACD获得。检验可手动地,或使用VENTANA自动染色仪(Discovery XT)运行。对于手动检验,在HybEZ烘箱(ACD)内的金属滑动托盘中执行40℃培育。对于自动检验,通过自动染色仪控制培育温度。ACD软件用于在VENTANA自动染色仪上运行RNAscope®检验。

[0079] 为了开始检验,样本通过在65℃下烘烤30min去石蜡,随后依次浸入二甲苯(2×20min)和100%乙醇(2×3min)中。在空气干燥之后,组织用预处理1溶液覆盖,其阻断内源性酶(将生成具有显色检测试剂背景的磷酸酶和过氧化酶),在室温下培育10min,然后通过浸入dH2O中冲洗两次。切片然后在沸腾的预处理2溶液中培育15min,其使结合位点暴露,并且立即转移到dH2O的容器。

[0080] 在通过浸入dH2O(2×2min)中洗涤之后,组织用预处理3溶液覆盖并且在40℃下在HybEZ烘箱中培育30min。预处理3溶液含有蛋白酶,其剥去蛋白的RNA转录物物并且使其暴露于目标探针。在dH2O中洗涤切片2×2min之后,组织用上文所述的15种检测同功异型物的HRGRNAscope®探针覆盖。连续组织切片与阳性对照探针(蛋白磷酸酶1B(PP1B)ACD零件编号313901)、阴性对照探针(细菌基因DapB-ACD零件编号310043)或HRG探针在40℃下一起培育2h。切片在与Amp1试剂一起培育之前用1×RNAscope®洗涤缓冲液洗涤(2×2min)。Amp1培育条件(30min,40℃)促进仅与结合到RNA转录物的探针对结合。切片通过在与后续扩增试剂以前培育之前浸入RNAscope®洗涤缓冲液中洗涤。

[0081] 对于信号扩增,依次施用的试剂中的每一种结合到前述试剂并且扩增存在于先前步骤中的信号。扩增步骤可包括Amp2(15min,40℃)、Amp3(30min,40℃)、Amp4(15min,40℃)、Amp5(30min,室温)和Amp6(15min,室温)。最终试剂(Amp6)可共轭到辣根过氧化酶(HRP)。为了观察转录物,切片然后在室温下与ACD染色试剂(其含有二氨基联苯胺(DAB))一起培育10min。通过用dH2O冲洗停止色原体显影。细胞核然后用苏木精对比染色,其用稀释氯化铵染成蓝色。经染色的切片在用Cytoseal非水封固剂(赛默科技(Thermo Scientific)8312-4)盖片之前浸入80%乙醇(2×5min)、100%乙醇(2×5min)和二甲苯(2×5min)中。

[0082] 2.生成生物标记值

[0083] 将生成的生物标记值为病理学家评分的复合。为了对检验评分,包含四个不同细胞系的插塞的TMA包括在每个染色运行中。细胞系插塞在生成TMA之前制备。生长到亚汇合密度的经培养细胞通过胰蛋白酶消化收获,在PBS中冲洗,并且在PBS中冲洗和再悬浮于70%乙醇中之前在4℃下固定16到24h。细胞然后以大约12,000rpm离心1到2分钟,以产生致密细胞团,其然后用低熔点琼脂糖涂布。琼脂糖团粒在4℃下存储在70%乙醇中,并且在构建TMA之前嵌入石蜡中。

[0084] 例如使用手动组织阵列仪(MTA-1,Beecher仪器(Beecher Instruments))构造阵列,其中0.6mm冲头用于获得细胞团的一部分并且将其塞入空受体石蜡块中。病理学家使用TMA的图像以提供在0(不可检测)到4(高)范围内的评分。病理学家提供用于肿瘤细胞的最高两个群体的两个评分,并且一个评分用于基质细胞(当可获得时)的最高群体,连同在每

个群体中的细胞的百分比。因此，例如患者样本可具有评分为3的20％肿瘤，评分为2的40％肿瘤和评分为2的60％基质。为目标探针(HRG)以及阳性对照探针(PP1B)和阴性对照探针(DapB)提供评分。

[0085] 实例1：塞里班土单抗示出对应答于调蛋白(HRG)的肺癌细胞系的生长的体外和体内单一药剂活性

[0086] 如上所述执行RNA-ISH检验和生物标记分析。这些研究表明25个EGFR野生型NSCLC细胞系中的9个应答于HRG：它们呈现应答于外源添加的HRG提高的细胞增殖，如通过使用3D球形培养物的CellTiterGlo®发光细胞活力检验(普洛麦格(Promega))所测量(图1)。

[0087] 选择两个HRG-应答性细胞系和两个非应答性细胞系以评定在皮下小鼠异种移植中塞里班土单抗的单一药剂活性。小鼠以每三天(Q3D)300μg塞里班土单抗给药。如图2A和2B所示，HRG-应答性细胞系(分别A549和H322M)应答于作为体内单一药剂的塞里班土单抗。相比之下，H460和Hop92(其不应答于体外HRG)不应答于体内塞里班土单抗(分别图2C和2D)。在塞里班土单抗-应答性异种移植肿瘤中测量到高组织HRG mRNA水平。令人感兴趣的是，在HRG-应答性肿瘤中观察到指示自分泌HRG信号传导的人类HRG mRNA和指示基质-衍生旁分泌信号传导的小鼠HRG mRNA两者。这些数据表明EGFR野生型NSCLC细胞系的子集应答于HRG，这些细胞系引起产生HRG，并且在组织中存在HRG好像是体内塞里班土单抗应答必需的，进一步支持肿瘤不表达HRG的患者的排斥。

[0088] 实例2：塞里班土单抗治疗可克服在肺癌细胞系中HRG-诱导的对培美曲塞和多西他赛的耐受性

[0089] 如图3A到3D所描绘，在一组9个肺癌细胞系中HRG诱导对培美曲塞和多西他赛的耐受性。HRG-驱动的ErbB3信号传导介导通过PI3K/AKT路径的存活率信号传导并且已暗指为赋予对细胞毒素化疗不灵敏性的一般机制。如图3A和3B所示，在EGFR野生型NSCLC细胞系的子集中，HRG诱导对培美曲塞和多西他赛的耐受性。在存在或不存在HRG下，在一组九个细胞系中使用3D球形培养物测量增殖。获得全剂量应答曲线，但是结果仅示出用于单一相关剂量的化疗。在添加HRG后，在这些细胞系中的三个(那些大多数应答于HRG)中，通过多西他赛和培美曲塞两者的细胞活力的抑制降低。实际上，甚至在存在化疗的情况下，HRG诱导增殖，如由用于抑制％的负值所指出。重要的是，当除了HRG之外添加塞里班土单抗时，在这些细胞系中对多西他赛和培美曲塞两者的敏感性恢复(图3C和3D)。

[0090] 实例3：在NSCLC组织样本中的HRG mRNA表达水平

[0091] 来自在乳房和卵巢癌中的先前随机II期临床试验的塞里班土单抗的肿瘤样本的分析指示相对于参考基因的-5的HRG表达的CT水平，如通过定量RT-PCR测量(根据PCT/US2014/072594，上文所论述)，为塞里班土单抗活性的阈值。在具有处于或高于阈值(≥-5)的HRG表达的患者中，在用塞里班土单抗与标准的护理疗法共投予治疗的患者中观察到提高的PFS。因为此阈值粗略地对应于存在可检测HRG-编码RNA，所以分析癌症基因组图谱(The Cancer Genome Atlas)(TCGA;http://cancergenome.nih.gov/)数据集以确定在广泛多种实体肿瘤中可检测HRG表达的发病率(图4)。数据表明NSCLC为其中HRG-驱动ErbB3信号传导尤其流行的病症。

[0092] 此外，在从参与在EGFR野生型NSCLC(MM-121-01-101)中的塞里班土单抗的研究的患者获得的预治疗穿刺活检中使用RNA原位杂交(RNA-ISH)检验(同样根据PCT/US2014/

072594)评定HRG表达。总体上,54%的样本评分1+(即,1到3个点/细胞(在20到40X放大下可见)或更高(图5A)。此外,延伸分析并且分析附加53种存档病变和活检,其从Cureline公司(加利福尼亚州旧金山(San Francisco,CA))取得(图5B)。与在MM-121-01-101肺研究中的发现相当,发现通过RNA-ISH具有>1+评分的HRG mRNA的发病率在44%到54%之间,并且与由于添加塞里班土单抗的提高的PFS相关。

[0093] 实例4:测定与多西他赛或培美曲塞组合的塞里班土单抗剂量

[0094] 群体药物代谢动力学(PK)分析支持使用对于塞里班土单抗的固定给药方案。

[0095] 通过模拟分析:为了评估理想给药方案,群体分析用于估计药物动力学参数的点估计值和变化性,并且用于评估变化性的来源,包括其与体重的关系。所得估计值用于比较固定给药和基于体重的给药方案。对于固定给药策略,相当的剂量通过假设基于体重的剂量乘以在群体中的体重的中值(72kg)来模拟,四舍五入成接下来500mg(小瓶大小)。模拟结果示出在固定给药和基于体重的给药方案两者之间相当的变化,表明在基于体重的给药的情况下降低PK变化无益处(对于10mg/kg等效的剂量方案,预测较高的浓度,仅由于舍入成接下来500mg)。举例来说,20mg/kg Q2W的基于体重的给药和相对应的1.5g Q2W的固定剂量具有相当的最大、最小和平均稳态浓度水平和变化。此结果可因此解释提高的清除率小于与体重成比例(即,在$\log_{10}$的清除率和体重之间的估计比例为0.203)。此比例产生通过基于体重的方案剂量过度给药的较高重量患者(这假设在$\log_{10}$的清除率和体重之间的比例常数为一)。

[0096] 通过以不同剂量时间间隔比较模拟药代动力学(平均和最小浓度)进行的模拟研究指示每3周方案为理想的。3g Q3W的剂量方案预测具有:1)相当的最大浓度(Cmax)为40mg/kg Q3W;2)相当的最小浓度(Cmin)为20mg/kg Q2W;和3)在20mg/kg Q2W(在先前NSCLC研究中研究的剂量)和20mg/kg Q1W(在先前卵巢癌和乳癌研究中研究的剂量)之间的平均稳态浓度。因此,此模拟研究表明3g Q3W的塞里班土单抗剂量方案应改善顺从性和便利性,同时将药物代谢动力学水平维持在从先前研究有效塞里班土单抗剂量观察到的暴露的界限内(40mg/kg负载+20mg/kg Q1W或+20mg/kg Q2W)。为了评估负载剂量的贡献,在有负载剂量和无负载剂量的情况下比较模拟剂量方案的浓度轨迹。负载剂量限于3g的最大值(对于40mg/kg的相对应的固定剂量)。结果示出在具有和没有负载剂量的情况下相当的药代动力学,并因此支持在没有负载剂量的情况下的方案。

[0097] 实验:使用来自已用塞里班土单抗治疗的499个患者的群体药物代谢动力学分析评估塞里班土单抗的药代动力学。分析来自塞里班土单抗的组合I期和II期研究的4925个数据点。这些药物代谢动力学数据使用二室模型描述,其中估计的参数在表1中提供。共变量选择评估在基线共变量(性别、人种、年龄、体重、预期剂量和研究/适应症)和分布体积和清除率之间的可能关系。结果指示在体重、性别和清除率之间的显著关系,其中最终参数估计在表1中提供。模型假设在清除率的log(CL)和体重之间的成比例关系,并且获得0.203的估计的比例常数。在存在在体重和清除率之间的关系的情况下,观察到在体积(V)和体重(WT)之间无显著关系。

[0098] 表1:来自塞里班土单抗的群体PK分析的最终参数估计值

[0099]

| 参数 | （估计）值 |
|---|---|
| 患者数 | 499 |
| **固定效果** | |
| CL（L/wk） | 3.15 |
| V（L) | 3.23 |
| Q（L/wk） | 2.92 |
| V2（L） | 2.68 |
| | |
| | |
| | |
| | |
| | |

| 参数 | （估计）值 |
|---|---|
| **随机效果** | |
| ω CL（%） | 36% |
| Cov CL 和 V（%） | 27% |
| ω V（%） | 37% |
| **σ** | |
| 累加 | 25.18 |
| 比例 | 0.23 |
| **共变量选择** | |
| WT-CL | 0.203 |
| SEX-CL | 0.255 |
| WT-V | 0.002 |

[0100] 为了评估基于体重的给药的益处，通过比较在基于体重的和固定剂量方案的情况下的药代动力学进行模拟研究。来自499个患者中的每个的PK参数的事后估计值用于模拟中。通过舍入到最接近的500mg剂量单位选来择用于固定给药方案的模拟剂量。模拟结果示出在固定给药和基于体重的给药方案两者之间相当的变化，表明在基于体重的给药的情况下降低PK变化无益处(图6A到6C)。举例来说，20mg/kg Q2W的基于体重的给药和相对应的1.5g Q2W的固定剂量具有相当的最大、最小和平均稳态浓度水平和变化。结果可解释为在CL的log和体重之间的估计比例为0.203，并且因此基于体重的方案(假设在CL的log和体重之间的比例常数为一)将趋于过度给药较高体重患者。为了评估用于改善的顺从性和简单性的塞里班土单抗给药方案的优化，通过不同剂量时间间隔比较模拟药代动力学(平均和最小浓度)进行模拟研究。结果示出将给药频率优化成每3周一次的可能性。预测3000mg Q3W的剂量方案具有：1)相当的最大浓度(Cmax)为40mg/kg Q3W，先前用作用于基于体重和每周塞里班土单抗给药方案的负载剂量的剂量水平；2)相当的最小浓度(Cmin)为20mg/kg Q2W，其为在与100mg埃罗替尼组合的NSCLC中用于先前塞里班土单抗研究的剂量；和3)在20mg/kg Q2W和20mg/kg Q1W中间的平均稳态浓度，其为在与化疗组合的40mg/kg负载剂量之后用于塞里班土单抗的先前研究普通剂量。因此，此模拟研究表明3000mg Q3W的塞里班土单抗剂量方案具有改善顺从性同时将药物代谢动力学水平维持在从先前研究的塞里班土单抗剂量观察到的暴露的界限内(40mg/kg负载+20mg/kg Q1W或+20mg/kg Q2W)的可能性。此外，当塞里班土单抗与标准剂量的培美曲塞、太平洋紫杉醇或卡巴他赛共投予时，未识别出MTD。在这些研究中，塞里班土单抗以作为负载剂量的40mg/kg与全剂量的化疗剂(培美曲塞、太平洋紫杉醇或卡巴他赛)共投予，随后20mg/kg的每周剂量。40mg/kg的负载剂量等于在平均体重75kg的患者中3000mg。因而，累积塞里班土单抗剂量建议用于此研究，3000mg塞里班土单抗Q3W作为固定剂量，不超过先前测试的用于与培美曲塞组合的塞里班土单抗的剂量方案。

[0101] 因此，塞里班土单抗将与用在下文研究中概述的化疗方案同步在每个21天周期的第1天以3g/3000mg的固定剂量投予。

[0102] 实例5：用于治疗NSCLC的研究设计

[0103] 本研究为患有在不多于两种用于局部晚期或转移性疾病的系统性疗法之后进展

的NSCLC的成年患者中的随机、开放标示、国际、多中心、II期研究，其中一种系统性疗法必须已经为基于铂的双重疗法。

[0104] 在签名知情同意和初始合格标准的评估之后，所有患者将向中心实验室机构提供组织样本(其满足如在研究实验指南中概述的收集和处理的要求)用于HRG测试。重要的是在获取组织样本和筛选用于此研究的日期之间不投予系统性疗法，以便精确评估患者的HRG状态。如果未得到足够组织，那么患者应进行针抽吸(FNA)或穿刺活检(CNB)以获得对于HRG测试的必需组织。对于这些程序，要求研究员选择容易可获得肿瘤病变以最小化与组织的收集相关联的任何可能风险。作为普通准则，如果穿刺活检或FNA的所选择程序位置在完成程序的机构具有>2％的确立的严重并发症比率，那么这视为高风险程序并且应避免。一旦在中心实验室接收组织样本，研究性部位将在7天内告知结果。患有阳性HRG状态的患者将符合干预研究群体的条件。患有示出对于HRG无染色的肿瘤的患者将不继续进一步筛选程序，并且将符合用于如下文概述的观测组的条件。

[0105] 观测群组

[0106] 将收集基线数据，包括人口统计资料、疾病特征和先前治疗。此外，接收关于后续抗癌疗法的数据并且将收集OS。患者自由参与任何研究并且寻求任何合适的护理。

[0107] 干预群组

[0108] 到所有筛选程序已经完成并且确定治疗随机分组合格(HRG阳性，干预群组)的时候，研究员必须基于当前呈递和病史选择最适合于每个患者的化疗主结构(多西他赛或培美曲塞)。患者将使用交互的万维网应答系统(IWRS)以2:1比率(实验组对比较剂组)的随机分组。随机分组将基于化疗主结构(多西他赛或培美曲塞)和用于局部晚期或转移性疾病的之前系统性疗法的数量(1或2)分级。在干预群组内患者将被指派到组A或组B：

[0109] 干预组A(实验组)：

[0110] 塞里班土单抗：在每个21天周期的第1天3000mg的固定剂量(12×10.1mL小瓶;6×20mL小瓶)静脉内(IV)

[0111] 多西他赛：在每个21天周期的第1天75mg/$m^2$IV

[0112] 或

[0113] 塞里班土单抗：在每个21天周期的第1天3000mg的固定剂量(12×10.1mL小瓶;6×20mL小瓶)IV

[0114] 培美曲塞：在每个21天周期的第1天500mg/$m^2$IV

[0115] 干预组B(比较剂组)：

[0116] 多西他赛：在每个21天周期的第1天75mg/$m^2$IV

[0117] 或

[0118] 培美曲塞：在每个21天周期的第1天500mg/$m^2$IV

[0119] 治疗必须在随机分组之后7天内开始。期望治疗患者直到研究员-评定进行性疾病或不可接受的毒性。将测量肿瘤评定并且每6周(+/-1周)由本地放射学家记录，并且使用RECIST指南(版本1.1)评估。所有患者，包括出于除RECIST 1.1评定的进行性疾病的原因之外停用治疗的任何患者，应在治疗终止之后具有附加扫描6周(+/-1周)。此外，将进行扫描的独立中心检查以支持第二功效目标。出于此目的，在干预群组中的患者的所有图像将提交到中心成像机构，并且将由独立审阅人根据成像章程(Imaging Charter)评定。在患者停

用治疗之后，将收集存活率信息和关于后续疗法的信息直到死亡或研究关闭，无论哪个首先出现。

[0120] 对于塞里班土单抗+培美曲塞的组合已确立安全性，并且塞里班土单抗已与紫杉烷(太平洋紫杉醇和卡巴他赛)在不达到最大耐受剂量(MTD)的情况下以标准剂量组合投予。然而，因为无数据可用于塞里班土单抗和多西他赛的组合，所以入选此主结构将在第十二个患者已随机分组到多西他赛或塞里班土单抗+多西他赛并且完成一个全周期治疗之后暂停，两组出来的安全数据将由研究员、医疗监测员和来自发起者的代表审查。附加输入可在继续入选之前从DMC聚集。DMC将在季度基础上根据DMC章程继续监测安全数据。

[0121] 纳入标准

[0122] 为纳入在试验中，所有患者将具有/为：细胞学上或组织学上确认的NSCLC，具有任一转移性疾病(阶段IV)；未经受治愈目的的手术的阶段IIIB疾病；在最后一个系统性疗法之后通过放射评定记录的疾病进展或复发性疾病的证据；接收一个之前基于铂的方案用于处理原发性或复发性疾病；根据研究员的判断，临床上符合每三周一次的预期化疗、多西他赛或培美曲塞的条件；可获得的最近肿瘤试样，在最近疗法完成之后收集；经受穿刺活检或细针抽吸的病变；大于或等于十八岁的年龄；和能够提供知情同意或具有能够如此做的法律代表性。为被包括在干预群组中，患者将具有/为对调蛋白的阳性原位杂交(ISH)测试具有≥1+的评分，如通过集中测试测定；根据RECIST v1.1可测量的疾病；0或1的ECOG性能表现状态(PS)；没有临床上显著异常的筛选ECG；足够骨髓储留，如通过ANC>1,500/μl、薄片计数>100,000/μl和血红蛋白>9g/dL证明；足够肾功能，如对于接收多西他赛的患者，通过血清/血浆肌酸酐<1.5×ULN，并且对于接收培美曲塞的患者，肌酸酐清除率≥45mL/min证明；对于接收培美曲塞的患者：天冬氨酸转氨酶(AST)和丙氨酸转氨酶(ALT)≤2.5×ULN(如果存在肝癌转移，那么≤5×ULN为可接受)；对于接收多西他赛的患者：天冬氨酸转氨酶(AST)和丙氨酸转氨酶(ALT)≤1.5×ULN，碱性磷酸酶(AP)<2.5ULN，并且血清/血浆总共胆红素在正常机构界限值内。生育可能性的女性以及可育男性和其伴侣必须愿意放弃性交，或在研究期间使用有效形式的避孕(一种有效形式的避孕为口服避孕药或双阻隔方法)，并且在(一个或多个)研究药物的最后一个剂量之后持续90天或更久，如根据多西他赛/培美曲塞的标示要求或机构指南。

[0123] 排除标准

[0124] 患者将满足上文所列的所有纳入标准并且没有以下排除标准：

[0125] a)已知退行性淋巴瘤激酶(ALK)基因重组或存在EGFR基因的外显子19缺失或外显子21(L858R)取代

[0126] b)怀孕或哺乳期

[0127] c)之前放疗到>25％的带有骨髓的区域

[0128] d)接收>2个用于局部晚期疾病的之前系统性抗癌药物方案

[0129] •在用于阶段IIIB或阶段IV疾病的一线治疗之后用培美曲塞的维持疗法计为一个治疗线

[0130] e)已接收用于晚期/转移性疾病之前多西他的赛患者不符合含多西他赛化疗主结构的条件

[0131] f)已接收用于晚期/转移性疾病的之前培美曲塞维持治疗的患者不符合含培美曲

塞的化疗主结构的条件

[0132] g)接收包括以下的其它最近抗肿瘤疗法：

[0133] •在本研究中的给药的第一安排日之前的28天或5个半衰期(无论哪个更短)内投予研究性疗法

[0134] •在本研究中的第一安排剂量之前14天内放射或其它标准系统性疗法，此外(若需要)包括用于解除来自这类放射的任何实际或预期毒性的时间范围

[0135] h)CTCAE等级3或更高外周神经病

[0136] i)在给药第一天之前，在筛选未分辨的就诊期间存在不可解释的>38.5℃发热。如果发热和活跃感染在随机分组之前已分辨，那么患者将符合条件。在研究员的断定下，具有肿瘤发热的患者可入选。

[0137] j)需要类固醇的症状性CNS癌转移或CNS癌转移

[0138] k)使用对于患者视为多西他赛主结构的强CYP3A4抑制剂。

[0139] l)需要系统性疗法的任何其它活跃恶性肿瘤

[0140] m)已知对MM-121的组分中的任一种过敏或对完全人类单克隆抗体的先前过敏反应

[0141] n)对多西他赛或培美曲塞严重过敏反应的病史

[0142] o)已知对聚山梨醇酯(Tween®)80或精氨酸过敏

[0143] p)临床上显著心脏疾病，包括：症状性充血性心脏衰竭、不稳定心绞痛、在规划的第一剂量的1年月数内急性心肌梗塞或需要疗法的不稳定心律不整(包括扭转型心动过速)。

[0144] q)需要IV抗生素、抗病毒剂或抗真菌剂的不受控感染，已知人类免疫缺陷病毒(HIV)感染或活跃B或C感染。

[0145] r)出于任何其它原因，如研究员认为的不是参与此临床研究的适当候选员的患者。

[0146] 实例6：在卵巢癌小鼠异种移植模型中，塞里班土单抗和化学治疗剂的共投予消除HRG-介导的对所述化学治疗剂的耐受性。

[0147] 使用作为在nu/nu裸Crl:NU-Foxn1$^{nu}$小鼠中异种移植植入的人类卵巢上皮癌瘤OVCAR8细胞(NCI)评估在荷瘤小鼠中塞里班土单抗和化疗剂(例如伊立替康、吉西他滨或太平洋紫杉醇)单独(即，如单一疗法)或组合的抗肿瘤功效。在这些异种移植研究中，小鼠从查尔斯河实验室(Charles River Laboratories)获得。小鼠容纳于在气候控制的房间中的Tecniplast®单独地供氧聚碳酸酯(Makrolon®)笼子(IVC)组中并且自由获取食物和酸化水。$8\times10^6$个细胞/小鼠的细胞悬浮液，1:1混合在降低的成长因子Matrigel™(碧迪生物科学公司(BD Biosciences)，目录号354230)中，并且PBS通过皮下注射植入雌性4到5周龄nu/nu裸Crl:NU-Foxn1$^{nu}$小鼠的左侧腹。在随机分组之前，允许肿瘤在大小上达到250mm$^3$。

[0148] 组合疗法研究

[0149] 执行组合疗法研究以展现固定剂量的塞里班土单抗、伊立替康HCl、吉西他滨和太平洋紫杉醇的多种组合的作用。

[0150] 小鼠如上随机分组到每组10个小鼠的8组。五组单独用腹膜内剂量的单一药治疗，如下：(1)塞里班土单抗(300μg Q3D)，(2)伊立替康HCl(6.25mg/kg Q7D)，(3)吉西他滨

(25mg/kg Q7D)，(4)太平洋紫杉醇(10mg kg Q7D)，或(5)单独PBS(Q3D)(对照)。三组用(1)塞里班土单抗和太平洋紫杉醇，(2)塞里班土单抗和伊立替康HCl和(3)塞里班土单抗和吉西他滨的组合疗法治疗，其中剂量在上文描述。治疗继续三周。每周测量肿瘤两次并且计算肿瘤体积。

[0151] 如图7A到7C(塞里班土单抗(在图中“MM-121”)小鼠剂量;300μg Q3D)所示，在此卵巢癌模型中，作为单一药剂的塞里班土单抗以剂量依赖性方式显著遏制体内肿瘤生长。此外，虽然仅伊立替康HCl、吉西他滨和太平洋紫杉醇各自单独抑制体内肿瘤生长，但是如与用各独药剂中的每种观察到的肿瘤生长抑制相比，用塞里班土单抗和太平洋紫杉醇(图7A)、伊立替康HCl(图7B)或吉西他滨(图7C)的组合治疗呈现对肿瘤生长抑制的附加作用。

[0152] 尾注

[0153] 虽然已结合其具体实施例描述了本发明，但是应理解，能够另外修改，并且本申请旨在涵盖一般来说根据本发明的原理的本发明的任何变化形式、用途或改编，并且包括在本发明所说领域内已知或惯用实践内出现的并且可应用于在本文中阐述的主要特征的与本公开的这类偏离。在本文中参考的每个和每一个US、国际或其它专利或专利申请或公开的公开内容在此以全文引用的方式并入本文中。

[0154] 序列汇总

[0155]

| SEQ ID NO: | 名称 | | 序列 |
|---|---|---|---|
| 1 | 塞里班土单抗的重链 CDR1（CDRH1） | 人类 CDRH1 蛋白质 | His Tyr Val Met Ala |
| 2 | 塞里班土单抗的重链 CDR2（CDRH2） | 人类 CDRH2 蛋白质 | Ser Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr Ala Asp Ser Val Lys Gly |
| 3 | 塞里班土单抗的重链 CDR3（CDRH3） | 人类 CDRH3 蛋白质 | Gly Leu Lys Met Ala Thr Ile Phe Asp Tyr |
| 4 | 塞里班土单抗的轻链 CDR1（CDRL1） | 人类 CDRL1 蛋白质 | Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Val Val Ser |
| 5 | 塞里班土单抗的轻链 CDR2（CDRL2） | 人类 CDRL2 蛋白质 | Glu Val Ser Gln Arg Pro Ser |
| 6 | 塞里班土单抗的轻链 CDR3（CDRL3） | 人类 CDRL3 蛋白质 | Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val Ile |
| 7 | 抗体塞里班土单抗的重链 | 人类重链 蛋白质 | 1 EVQLLESGGG LVQPGGSLRL SCAASGFTFS HYVMAWVRQA PGKGLEWVSS<br>51 ISSSGGWTLY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCTRGL<br>101 KMATIFDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD<br>151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY<br>201 TCNVDHKPSN TKVDKTVERK CCVECPPCPA PPVAGPSVFL FPPKPKDTLM<br>251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV<br>301 VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP<br>351 PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG<br>401 SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK |
| 8 | 塞里班土单抗的轻链 | 人类轻链 蛋白质 | 1 QSALTQPASV SGSPGQSITI SCTGTSSDVG SYNVVSWYQQ HPGKAPKLII<br>51 YEVSQRPSGV SNRFSGSKSG NTASLTISGL QTEDEADYYC CSYAGSSIFV<br>101 IFGGGTKVTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL VSDFYPGAVT<br>151 VAWKADGSPV KVGVETTKPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCRV<br>201 THEGSTVEKT VAPAECS |

[0156]

| | | | |
|---|---|---|---|
| 9 | 塞里班土单抗的重链可变区（VH） | 人类VH DNA | gaggtgcagc tgctggagag cggcggaggg<br>ctggtccagc caggcggcag cctgaggctg<br>tcctgcgccg ccagcggctt caccttcagc<br>cactacgtga tggcctgggt gcggcaggcc<br>ccaggcaagg gcctggaatg ggtgtccagc<br>atcagcagca gcggcggctg gaccctgtac<br>gccgacagcg tgaagggcag gttcaccatc<br>agcagggaca acagcaagaa caccctgtac<br>ctgcagatga acagcctgag ggccgaggac<br>accgccgtgt actactgcac caggggcctg<br>aagatggcca ccatcttcga ctactggggc<br>cagggcaccc tggtgaccgt gagcagc |
| 10 | 塞里班土单抗的重链可变区（VH） | 人类VH蛋白质 | Glu Val Gln Leu Leu Glu Ser Gly Gly Gly<br>Leu Val Gln Pro Gly Gly Ser Leu Arg Leu<br>Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser<br>His Tyr Val Met Ala Trp Val Arg Gln Ala<br>Pro Gly Lys Gly Leu Glu Trp Val Ser Ser<br>Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr<br>Ala Asp Ser Val Lys Gly Arg Phe Thr Ile<br>Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr<br>Leu Gln Met Asn Ser Leu Arg Ala Glu Asp<br>Thr Ala Val Tyr Tyr Cys Thr Arg Gly Leu<br>Lys Met Ala Thr Ile Phe Asp Tyr Trp Gly<br>Gln Gly Thr Leu Val Thr Val Ser Ser |
| 11 | 塞里班土单抗的轻链可变区（VL） | 人类VL DNA | cagtccgccc tgacccagcc cgccagcgtg<br>agcggcagcc caggccagag catcaccatc<br>agctgcaccg gcaccagcag cgacgtgggc<br>agctacaacg tggtgtcctg gtatcagcag<br>caccccggca aggcccccaa gctgatcatc<br>tacgaggtgt cccagaggcc cagcggcgtg<br>agcaacaggt tcagcggcag caagagcggc<br>aacaccgcca gcctgaccat cagcggcctg<br>cagaccgagg acgaggccga ctactactgc<br>tgcagctacg ccggcagcag catcttcgtg<br>atcttcggcg gagggaccaa ggtgaccgtc cta |
| 12 | 塞里班土单抗的轻链可变区（VL） | 人类VL蛋白质 | Gln Ser Ala Leu Thr Gln Pro Ala Ser Val<br>Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile<br>Ser Cys Thr Gly Thr Ser Ser Asp Val Gly<br>Ser Tyr Asn Val Val Ser Trp Tyr Gln Gln<br>His Pro Gly Lys Ala Pro Lys Leu Ile Ile<br>Tyr Glu Val Ser Gln Arg Pro Ser Gly Val<br>Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly<br>Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu<br>Gln Thr Glu Asp Glu Ala Asp Tyr Tyr Cys<br>Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val<br>Ile Phe Gly Gly Gly Thr Lys Val Thr Val<br>Leu |
| 13 | 人类ErbB3 | 人类蛋白质 | Ser Glu Val Gly Asn Ser Gln Ala Val Cys<br>Pro Gly Thr Leu Asn Gly Leu Ser Val Thr<br>Gly Asp Ala Glu Asn Gln Tyr Gln Thr Leu<br>Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val |

[0157]

| | | | |
|---|---|---|---|
| | | | Met Gly Asn Leu Glu Ile Val Leu Thr Gly<br>His Asn Ala Asp Leu Ser Phe Leu Gln Trp<br>Ile Arg Glu Val Thr Gly Tyr Val Leu Val<br>Ala Met Asn Glu Phe Ser Thr Leu Pro Leu<br>Pro Asn Leu Arg Val Val Arg Gly Thr Gln<br>Val Tyr Asp Gly Lys Phe Ala Ile Phe Val<br>Met Leu Asn Tyr Asn Thr Asn Ser Ser His<br>Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu<br>Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile<br>Glu Lys Asn Asp Lys Leu Cys His Met Asp<br>Thr Ile Asp Trp Arg Asp Ile Val Arg Asp<br>Arg Asp Ala Glu Ile Val Val Lys Asp Asn<br>Gly Arg Ser Cys Pro Pro Cys His Glu Val<br>Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser<br>Glu Asp Cys Gln Thr Leu Thr Lys Thr Ile<br>Cys Ala Pro Gln Cys Asn Gly His Cys Phe<br>Gly Pro Asn Pro Asn Gln Cys Cys His Asp<br>Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln<br>Asp Thr Asp Cys Phe Ala Cys Arg His Phe<br>Asn Asp Ser Gly Ala Cys Val Pro Arg Cys<br>Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr<br>Phe Gln Leu Glu Pro Asn Pro His Thr Lys<br>Tyr Gln Tyr Gly Gly Val Cys Val Ala Ser<br>Cys Pro His Asn Phe Val Val Asp Gln Thr<br>Ser Cys Val Arg Ala Cys Pro Pro Asp Lys<br>Met Glu Val Asp Lys Asn Gly Leu Lys Met<br>Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys<br>Ala Cys Glu Gly Thr Gly Ser Gly Ser Arg<br>Phe Gln Thr Val Asp Ser Ser Asn Ile Asp<br>Gly Phe Val Asn Cys Thr Lys Ile Leu Gly<br>Asn Leu Asp Phe Leu Ile Thr Gln Gly Asp<br>Pro Trp His Lys Ile Pro Ala Leu Asp Pro<br>Glu Lys Leu Asn Val Phe Arg Thr Val Arg<br>Glu Ile Thr Gly Tyr Leu Asn Ile Gln Ser<br>Trp Pro Pro His Met His Asn Phe Ser Val<br>Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg<br>Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu<br>Ile Met Lys Asn Leu Asn Val Thr Ser Leu<br>Gly Phe Arg Ser Leu Lys Glu Ile Ser Ala<br>Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln<br>Leu Cys Tyr His His Ser Leu Asn Trp Thr<br>Lys Val Leu Arg Gly Pro Thr Glu Glu Arg<br>Leu Asp Ile Lys His Asn Arg Pro Arg Arg<br>Asp Cys Val Ala Glu Gly Lys Val Cys Asp<br>Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly<br>Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg<br>Asn Tyr Ser Arg Gly Gly Val Cys Val Thr<br>His Cys Asn Phe Leu Asn Gly Glu Pro Arg<br>Glu Phe Ala His Glu Ala Glu Cys Phe Ser<br>Cys His Pro Glu Cys Gln Pro Met Glu Gly<br>Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp<br>Thr Cys Ala Gln Cys Ala His Phe Arg Asp |

[0158]

| | | | |
|---|---|---|---|
| | | | Gly Pro His Cys Val Ser Ser Cys Pro His<br>Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr<br>Lys Tyr Pro Asp Val Gln Asn Glu Cys Arg<br>Pro Cys His Glu Asn Cys Thr Gln Gly Cys<br>Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly<br>Gln Thr Leu Val Leu Ile Gly Lys Thr His<br>Leu Thr Met Ala Leu Thr Val Ile Ala Gly<br>Leu Val Val Ile Phe Met Met Leu Gly Gly<br>Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile<br>Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu<br>Glu Arg Gly Glu Ser Ile Glu Pro Leu Asp<br>Pro Ser Glu Lys Ala Asn Lys Val Leu Ala<br>Arg Ile Phe Lys Glu Thr Glu Leu Arg Ser<br>Leu Lys Val Leu Gly Ser Gly Val Phe Gly<br>Thr Val His Lys Gly Val Trp Ile Pro Glu<br>Gly Glu Ser Ile Lys Ile Pro Val Cys Ile<br>Lys Val Ile Glu Asp Lys Ser Gly Arg Gln<br>Ser Phe Gln Ala Val Thr Asp His Met Leu<br>Ala Ile Gly Ser Leu Asp His Ala His Ile<br>Val Arg Leu Leu Gly Leu Cys Pro Gly Ser<br>Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro<br>Leu Gly Ser Leu Leu Asp His Val Arg Gln<br>His Arg Gly Ala Leu Gly Pro Gln Leu Leu<br>Leu Asn Trp Gly Val Gln Ile Ala Lys Gly<br>Met Tyr Tyr Leu Glu Glu His Gly Met Val<br>His Arg Asn Leu Ala Ala Arg Asn Val Leu<br>Leu Lys Ser Pro Ser Gln Val Gln Val Ala<br>Asp Phe Gly Val Ala Asp Leu Leu Pro Pro<br>Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala<br>Lys Thr Pro Ile Lys Trp Met Ala Leu Glu<br>Ser Ile His Phe Gly Lys Tyr Thr His Gln<br>Ser Asp Val Trp Ser Tyr Gly Val Thr Val<br>Trp Glu Leu Met Thr Phe Gly Ala Glu Pro<br>Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro<br>Asp Leu Leu Glu Lys Gly Glu Arg Leu Ala<br>Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr<br>Met Val Met Val Lys Cys Trp Met Ile Asp<br>Glu Asn Ile Arg Pro Thr Phe Lys Glu Leu<br>Ala Asn Glu Phe Thr Arg Met Ala Arg Asp<br>Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu<br>Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu<br>Pro His Gly Leu Thr Asn Lys Lys Leu Glu<br>Glu Val Glu Leu Glu Pro Glu Leu Asp Leu<br>Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn<br>Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu<br>Ser Leu Pro Val Gly Thr Leu Asn Arg Pro<br>Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser<br>Ser Gly Tyr Met Pro Met Asn Gln Gly Asn<br>Leu Gly Glu Ser Cys Gln Glu Ser Ala Val<br>Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro<br>Val Ser Leu His Pro Met Pro Arg Gly Cys<br>Leu Ala Ser Glu Ser Ser Glu Gly His Val |

[0159]

| | | | |
|---|---|---|---|
| | | | Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn Ala Gln Arg Thr |

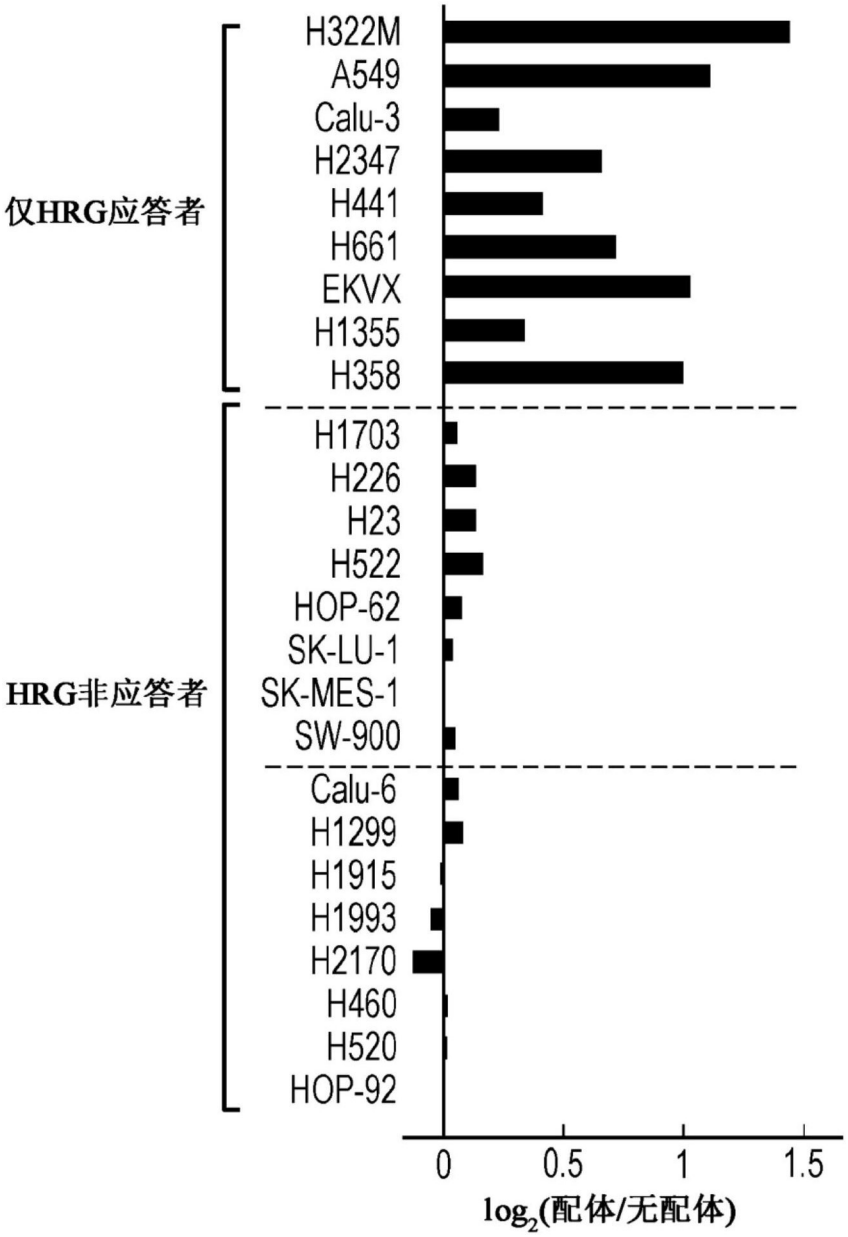
仅HRG应答者
H322M
A549
Calu-3
H2347
H441
H661
EKVX
H1355
H358
HRG非应答者
H1703
H226
H23
H522
HOP-62
SK-LU-1
SK-MES-1
SW-900
Calu-6
H1299
H1915
H1993
H2170
H460
H520
HOP-92
0
0.5
1
1.5
log2(配体/无配体)

图1

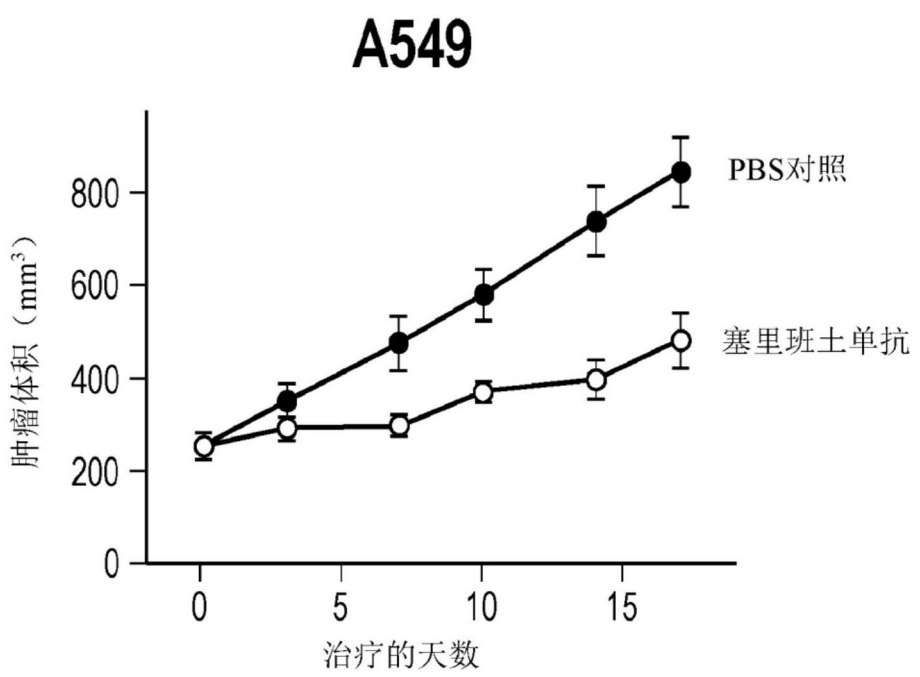
A549
PBS对照
塞里班土单抗
肿瘤体积（mm³）
800
600
400
200
0
0
5
10
15
治疗的天数

图2A

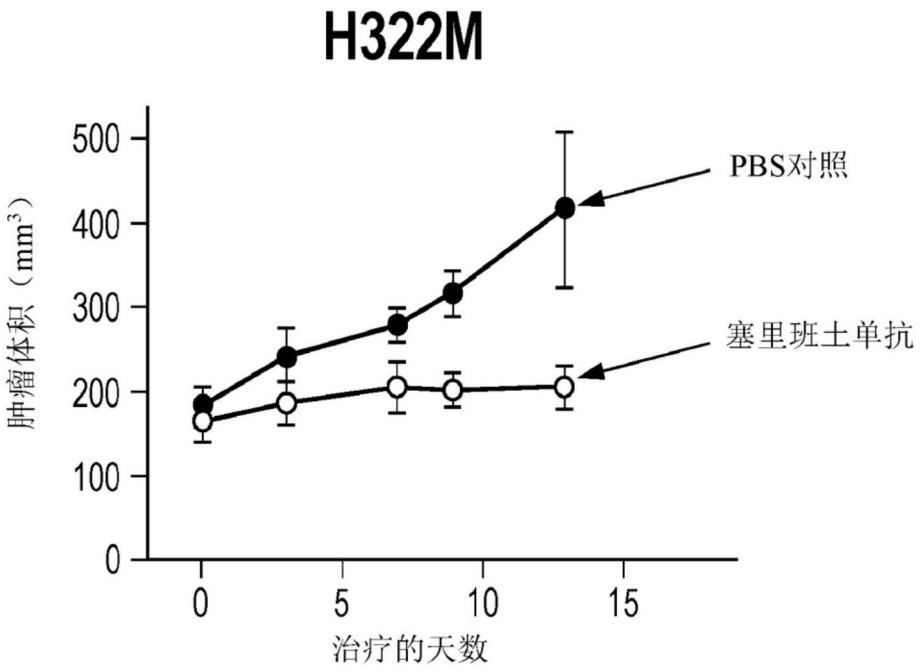
H322M
PBS对照
塞里班土单抗
肿瘤体积（mm³）
500
400
300
200
100
0
0
5
10
15
治疗的天数

图2B

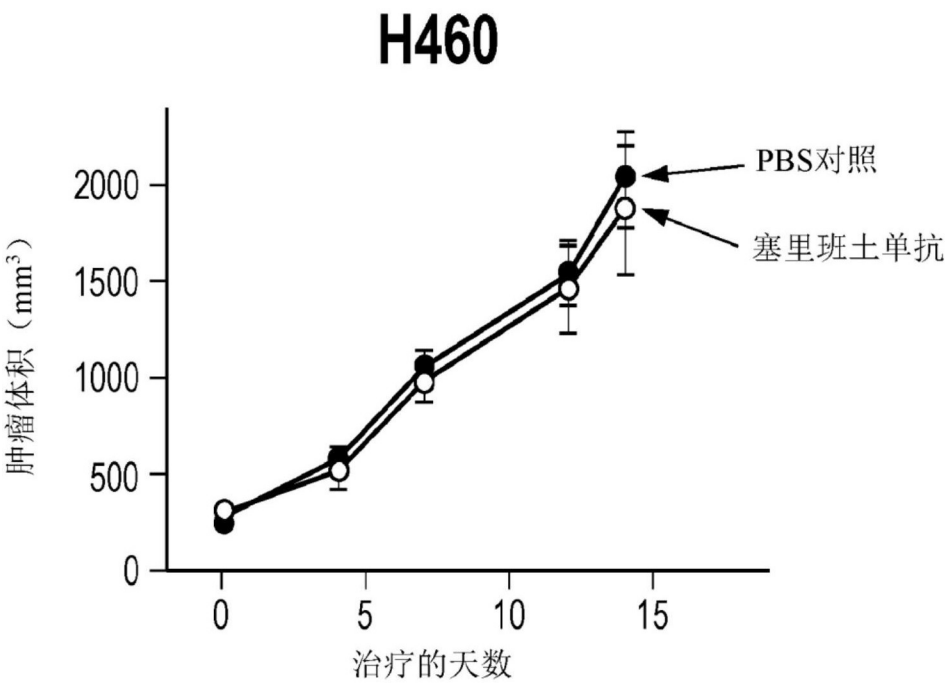
H460
PBS对照
塞里班土单抗
肿瘤体积（mm³）
2000
1500
1000
500
0
0
5
10
15
治疗的天数

图2C

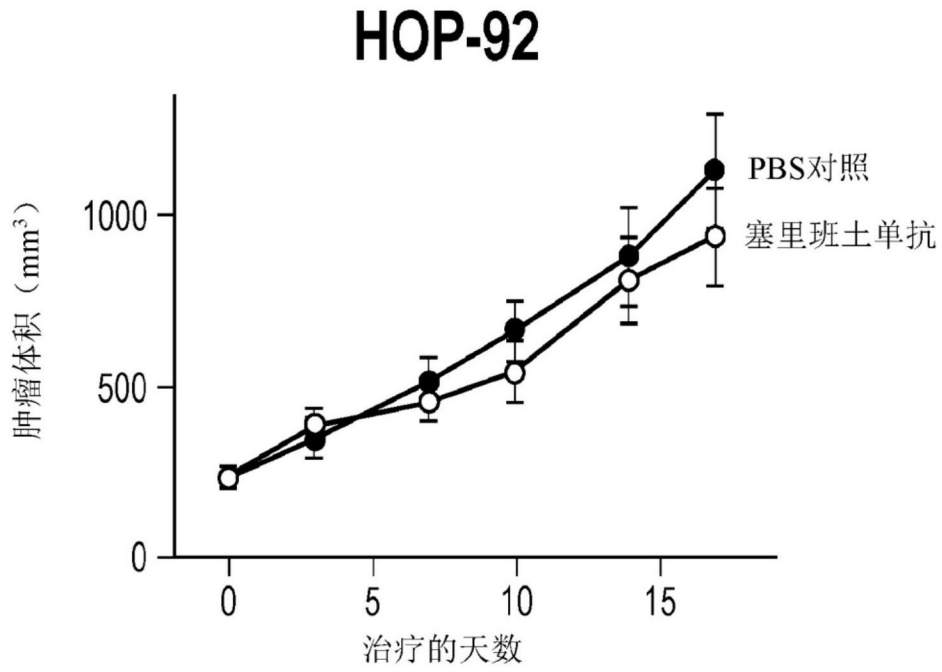
HOP-92
PBS对照
塞里班土单抗
肿瘤体积（mm³）
1000
500
0
0
5
10
15
治疗的天数

图2D

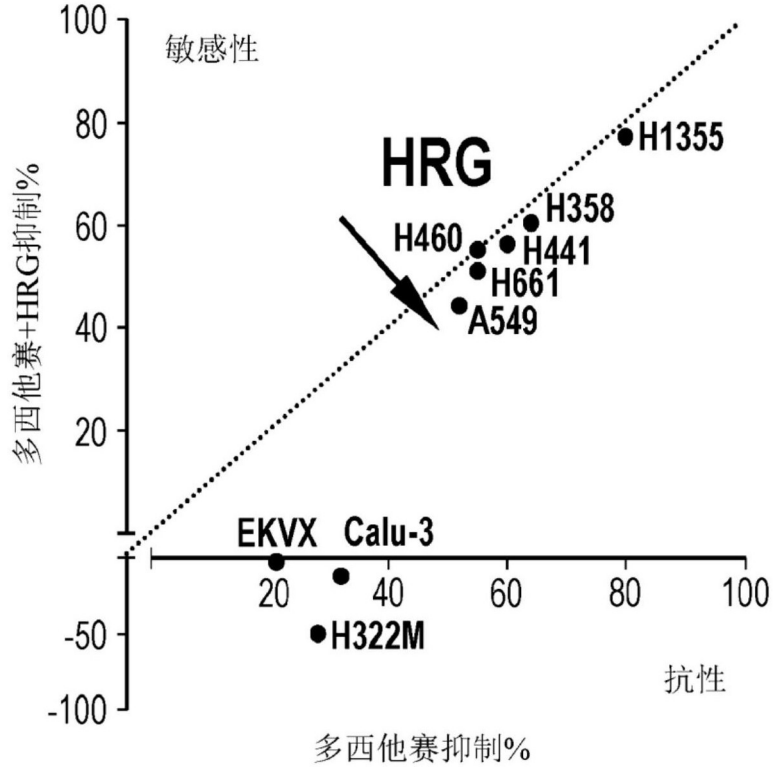
敏感性
HRG
H1355
H358
H460
H441
H661
A549
EKVX
Calu-3
H322M
多西他赛+HRG抑制%
多西他赛抑制%
抗性
100
80
60
40
20
-50
-100
20
40
60
80
100

图3A

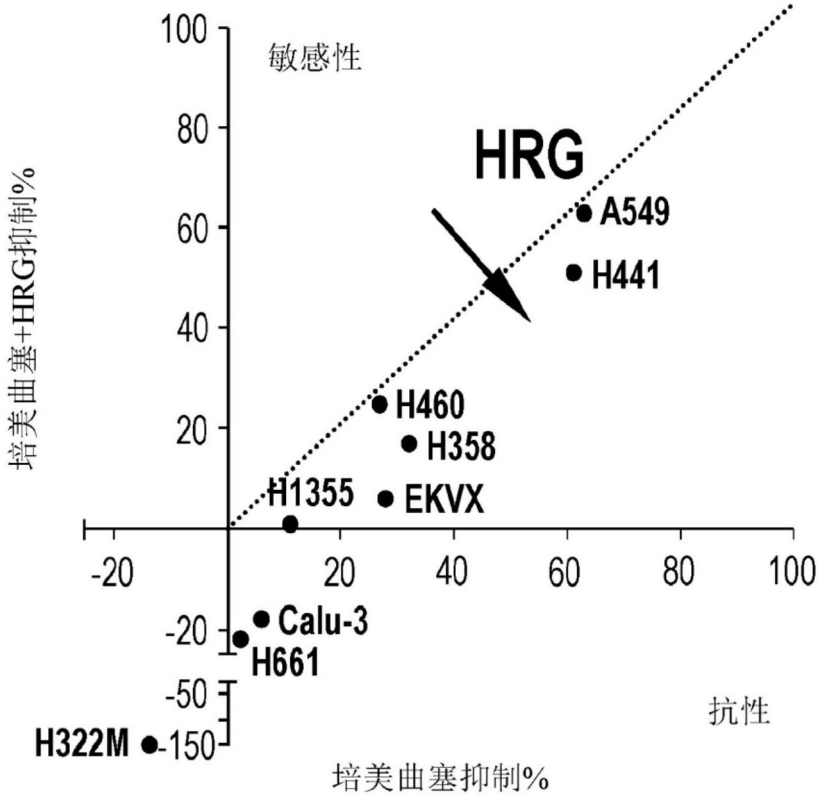
敏感性
HRG
A549
H441
H460
H358
H1355
EKVX
Calu-3
H661
H322M
培美曲塞+HRG抑制%
培美曲塞抑制%
抗性
100
80
60
40
20
-20
-50
-150
-20
20
40
60
80
100

图3B

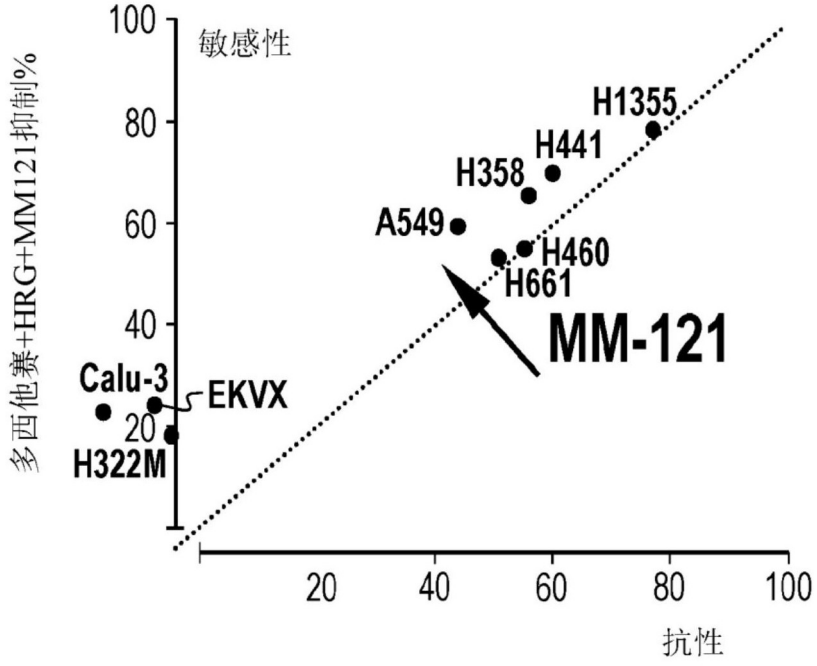
敏感性
多西他赛+HRG+MM121抑制%
100
80
60
40
20
H1355
H441
H358
A549
H460
H661
MM-121
Calu-3
EKVX
H322M
20
40
60
80
100
抗性
多西他赛+HRG抑制%

图3C

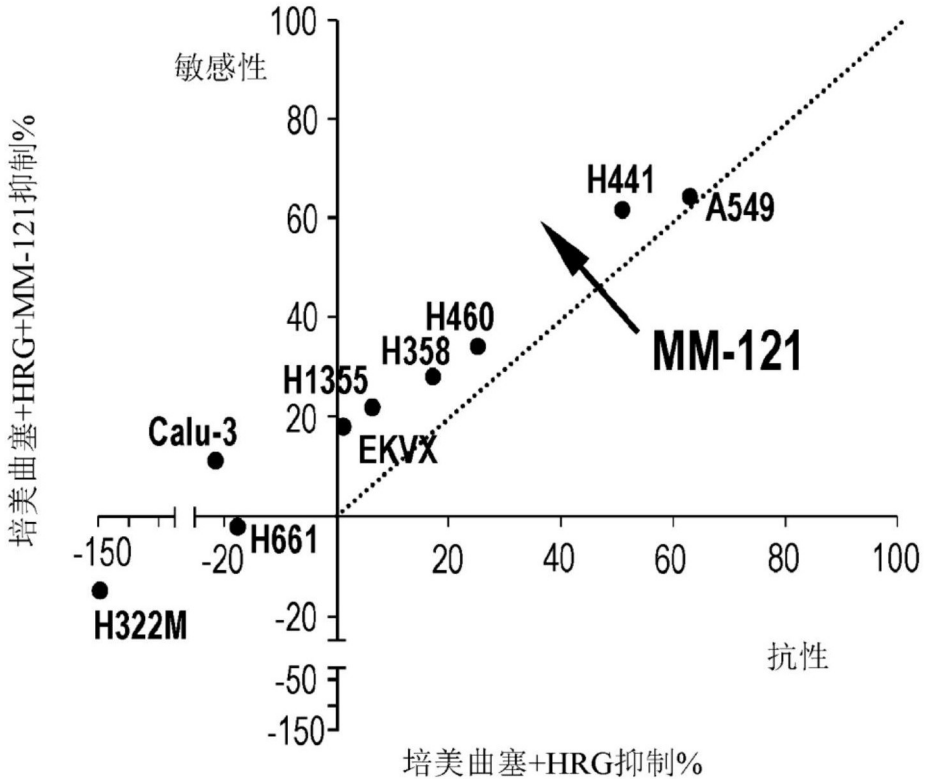
敏感性
培美曲塞+HRG+MM-121抑制%
100
80
60
40
20
-20
-50
-150
H441
A549
H460
H358
MM-121
H1355
Calu-3
EKVX
H661
H322M
-150
-20
20
40
60
80
100
抗性
培美曲塞+HRG抑制%

图3D

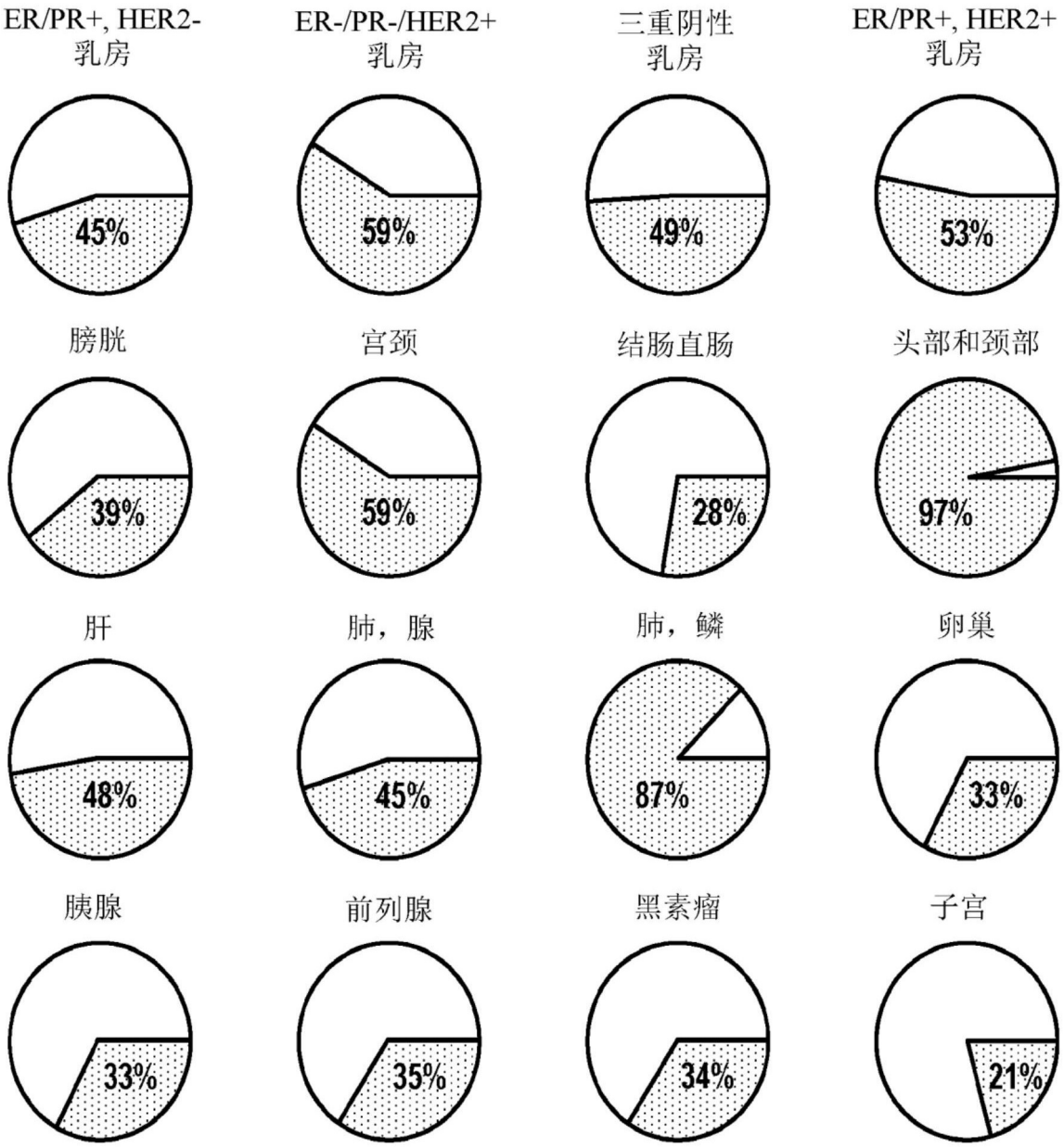
ER/PR+, HER2-
乳房
45%
ER-/PR-/HER2+
乳房
59%
三重阴性
乳房
49%
ER/PR+, HER2+
乳房
53%
膀胱
39%
宫颈
59%
结肠直肠
28%
头部和颈部
97%
肝
48%
肺，腺
45%
肺，鳞
87%
卵巢
33%
胰腺
33%
前列腺
35%
黑素瘤
34%
子宫
21%

图4

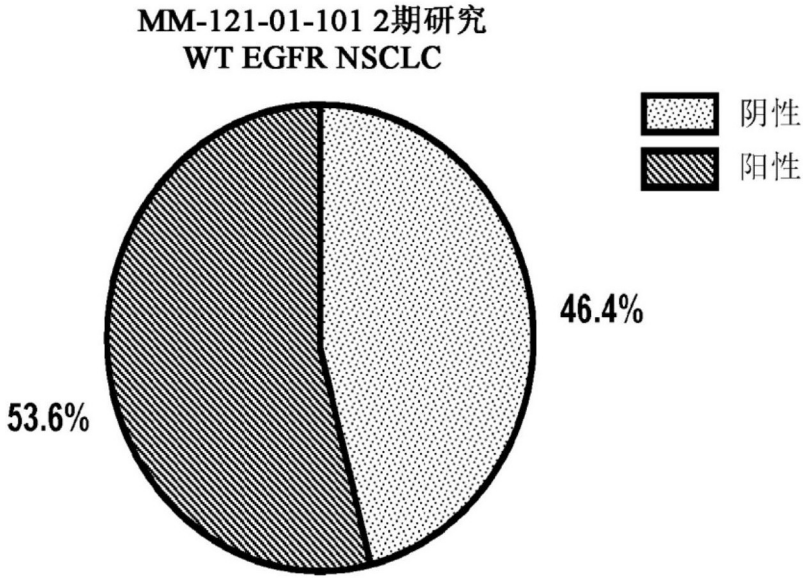
MM-121-01-101 2期研究
WT EGFR NSCLC
阴性
阳性
46.4%
53.6%

图5A

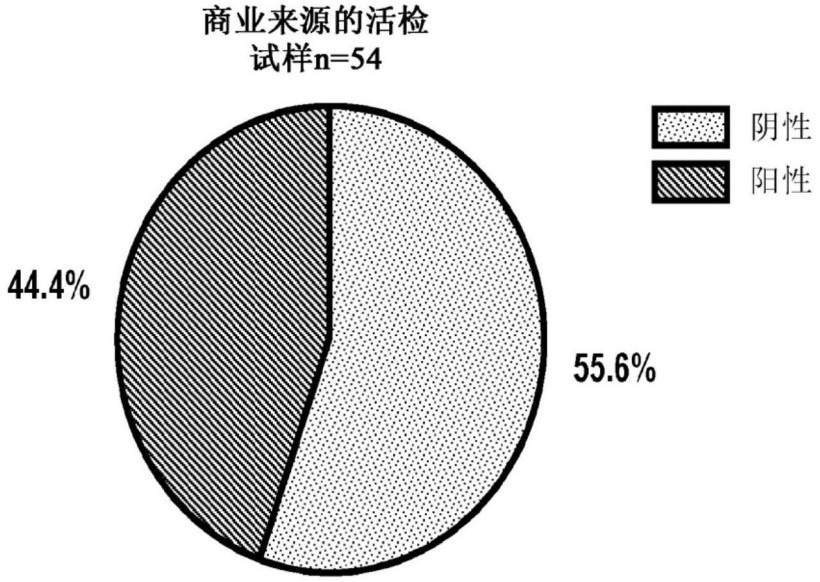
商业来源的活检
试样n=54
阴性
阳性
44.4%
55.6%

图5B

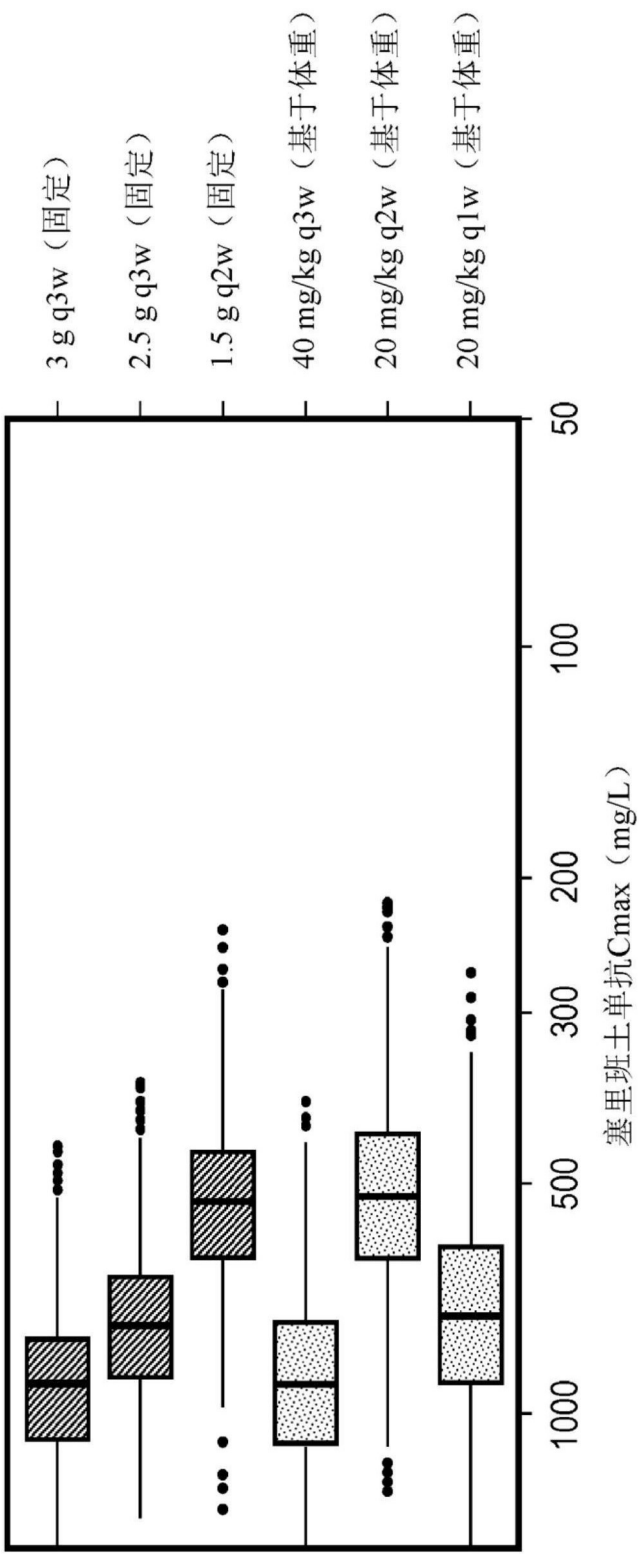
3 g q3w（固定）
2.5 g q3w（固定）
1.5 g q2w（固定）
40 mg/kg q3w（基于体重）
20 mg/kg q2w（基于体重）
20 mg/kg q1w（基于体重）
50
100
200
300
500
1000
塞里班士单抗Cmax（mg/L）

图6A

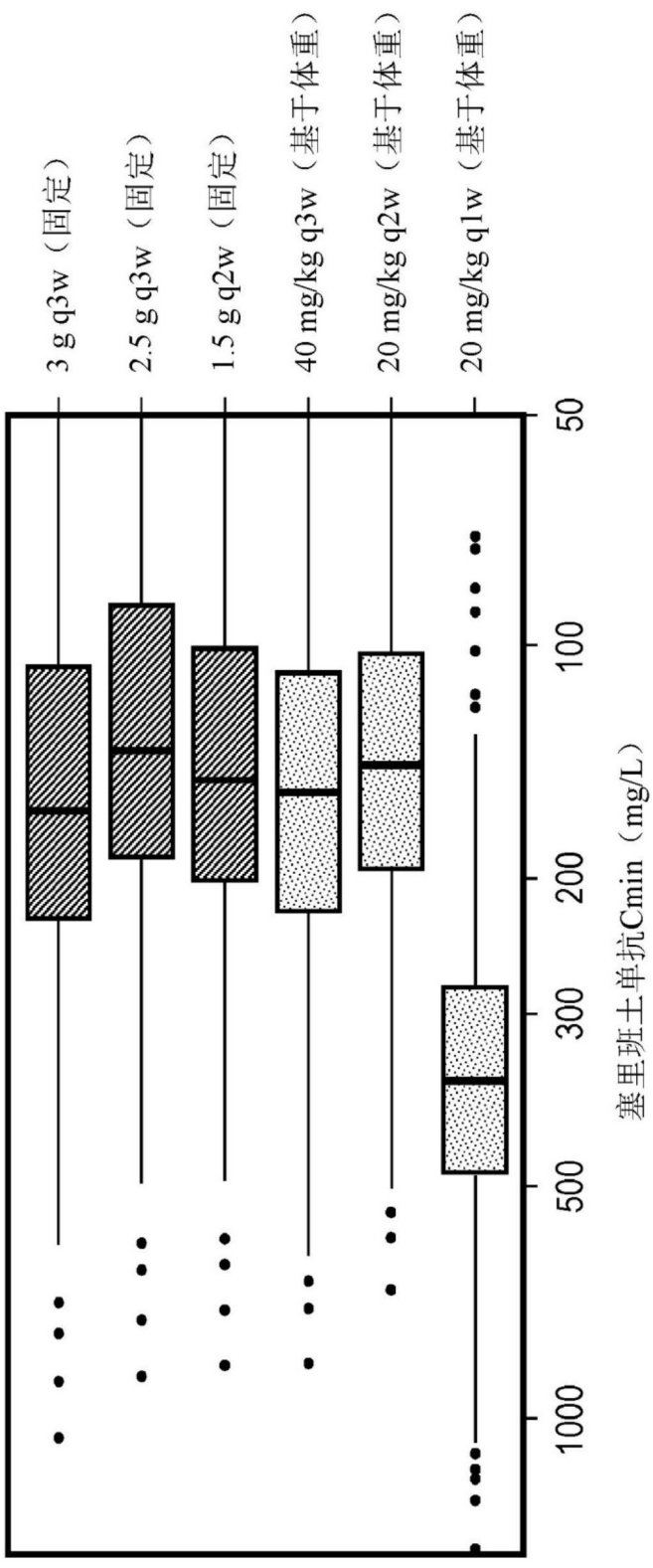
3 g q3w（固定）
2.5 g q3w（固定）
1.5 g q2w（固定）
40 mg/kg q3w（基于体重）
20 mg/kg q2w（基于体重）
20 mg/kg q1w（基于体重）
50
100
200
300
500
1000
塞里班士单抗Cmin（mg/L）

图6B

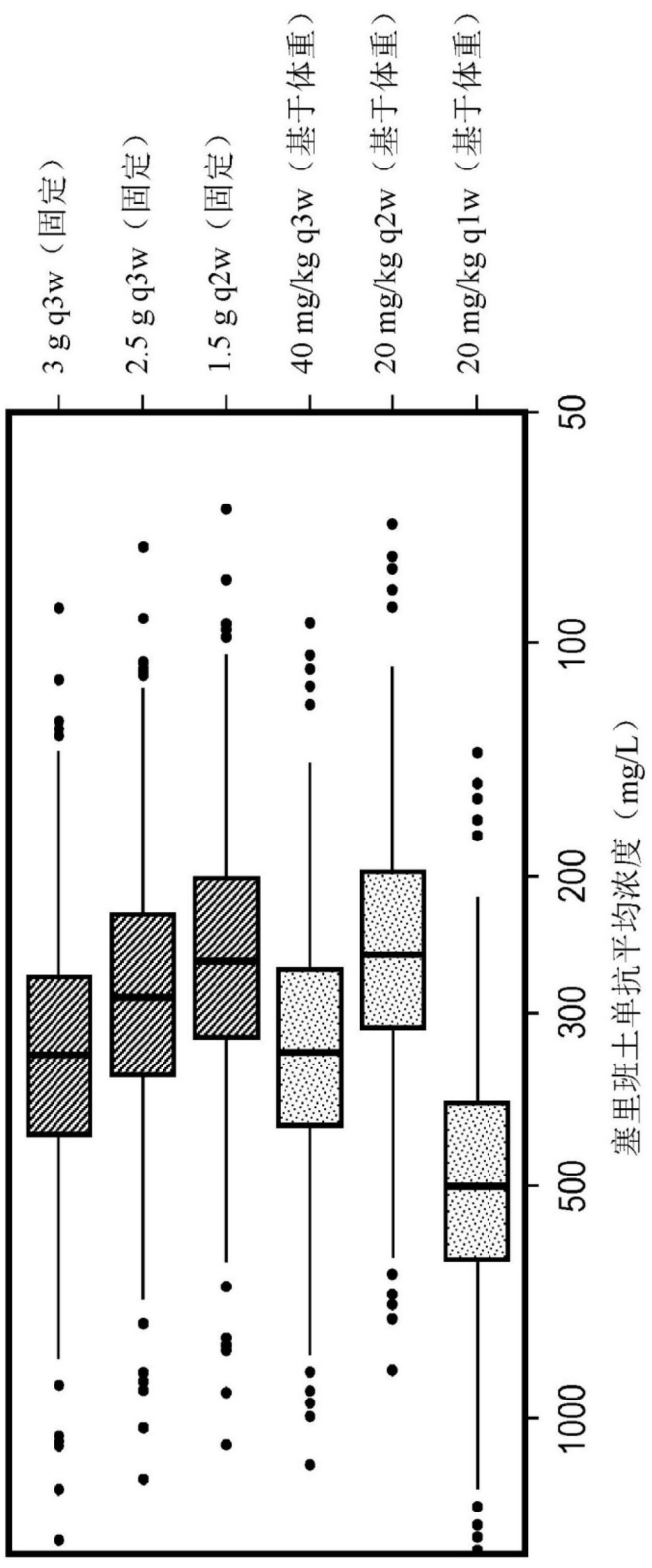
3 g q3w（固定）
2.5 g q3w（固定）
1.5 g q2w（固定）
40 mg/kg q3w（基于体重）
20 mg/kg q2w（基于体重）
20 mg/kg q1w（基于体重）
50
100
200
300
500
1000
塞里班土单抗平均浓度（mg/L）

图6C

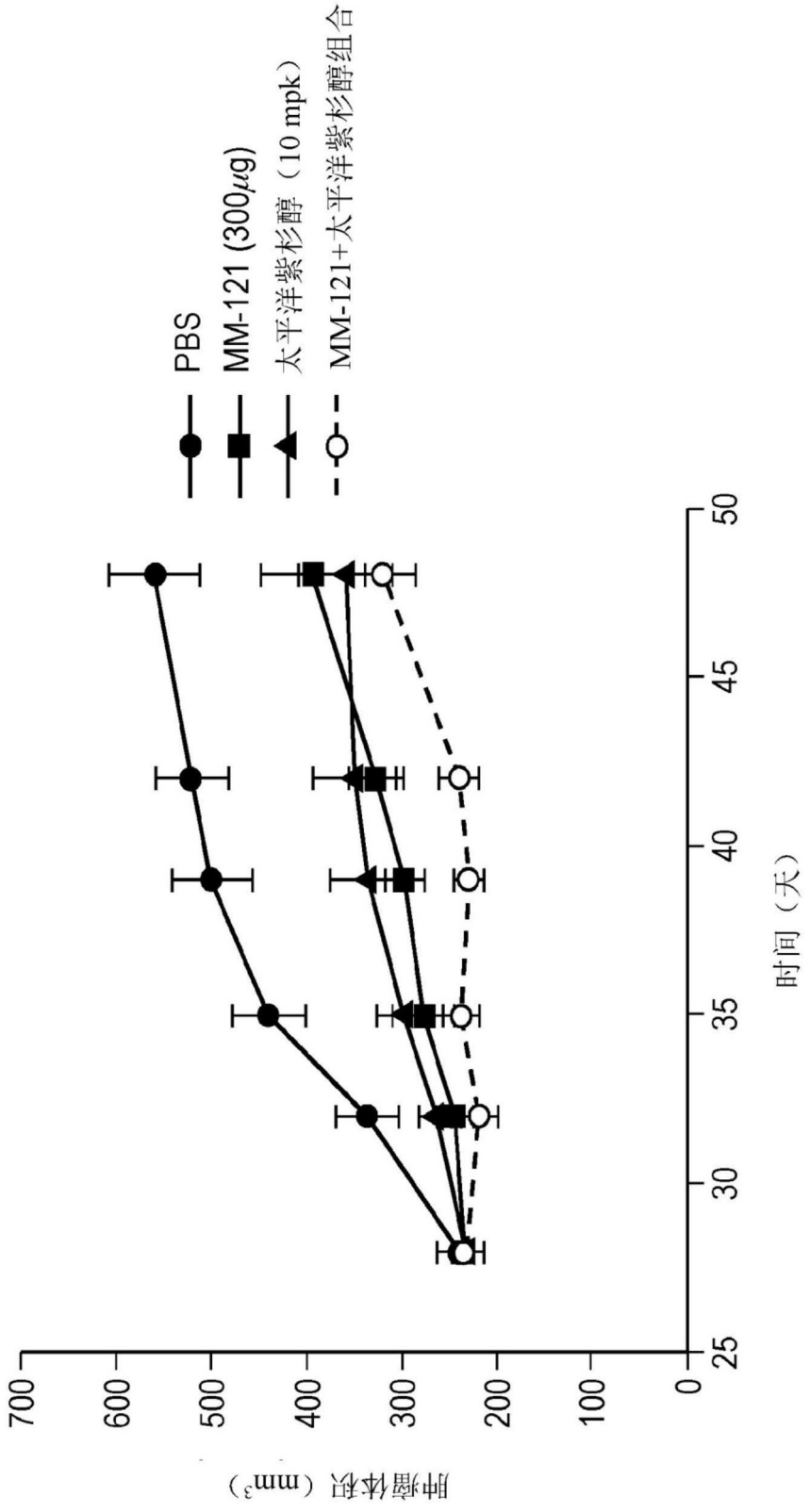
PBS
MM-121 (300μg)
太平洋紫杉醇（10 mpk）
MM-121+太平洋紫杉醇组合
肿瘤体积（mm³）
700
600
500
400
300
200
100
0
25
30
35
40
45
50
时间（天）

图7A

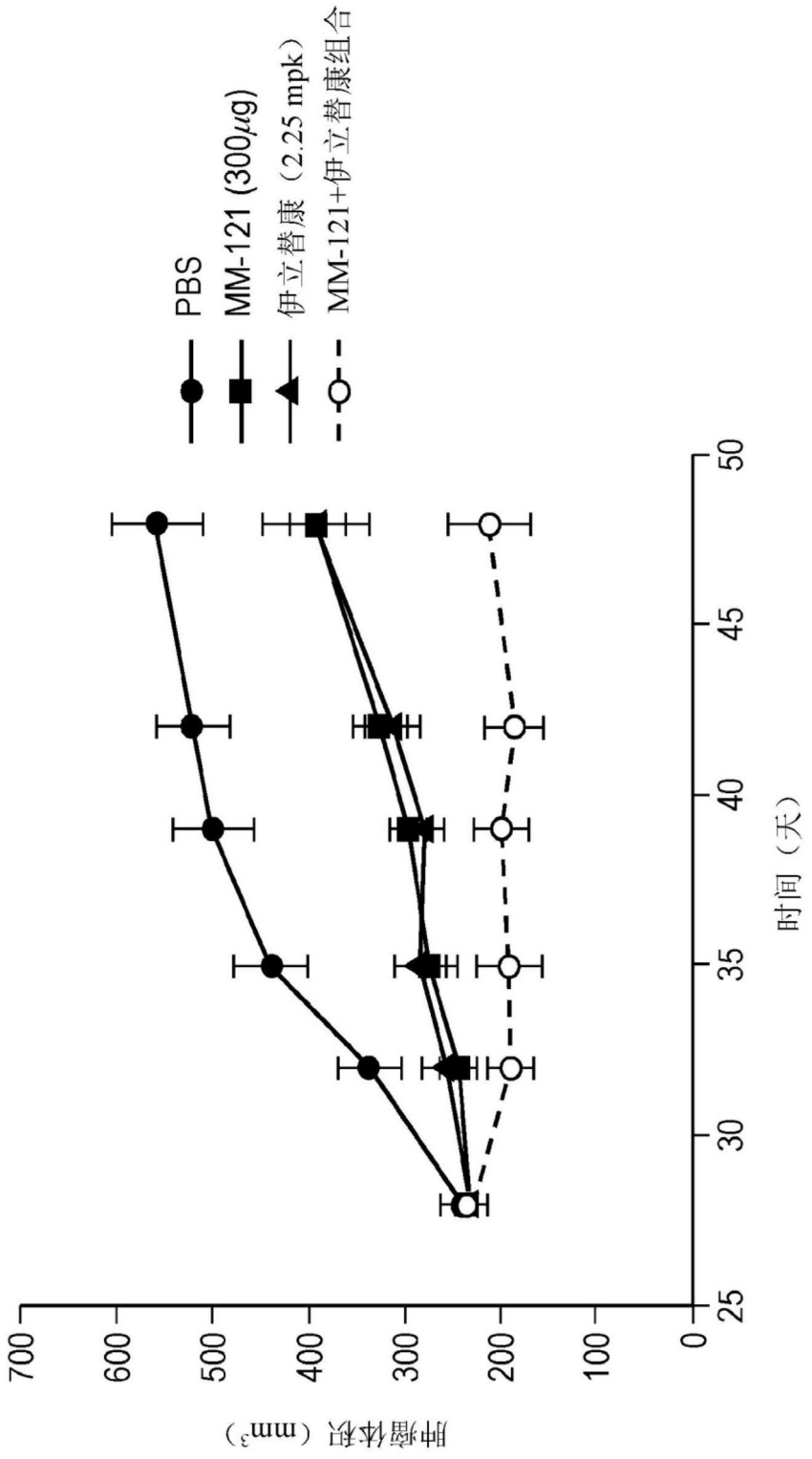
PBS
MM-121 (300μg)
伊立替康（2.25 mpk）
MM-121+伊立替康组合
肿瘤体积（mm³）
700
600
500
400
300
200
100
0
25
30
35
40
45
50
时间（天）

图7B

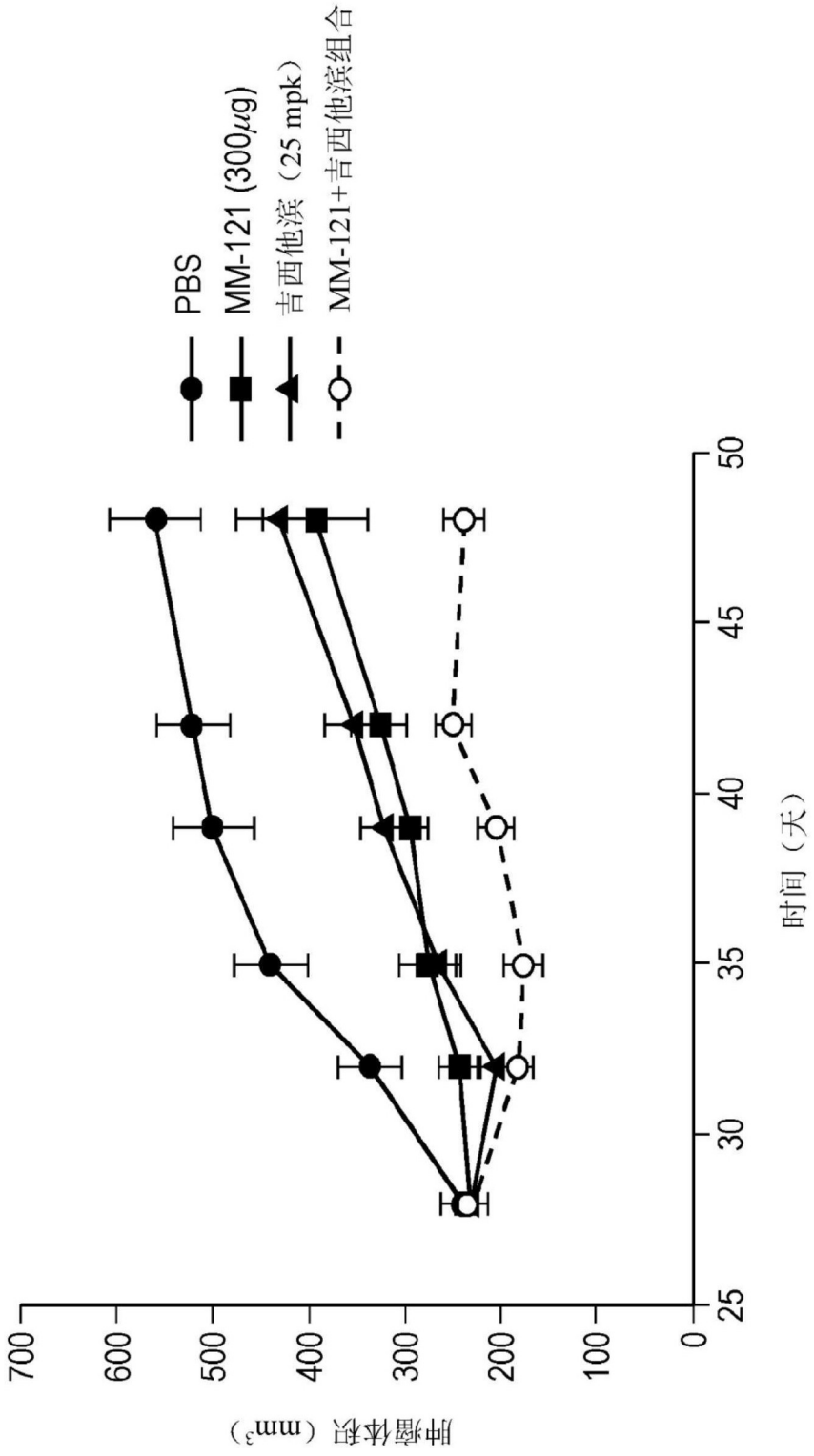
PBS
MM-121 (300μg)
吉西他滨（25 mpk）
MM-121+吉西他滨组合
肿瘤体积（mm³）
700
600
500
400
300
200
100
0
25
30
35
40
45
50
时间（天）

图7C