



(51) International Patent Classification:

C07K 16/28 (2006.01) *A61K 45/06* (2006.01)
C07K 16/30 (2006.01) *A61P 35/00* (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:

PCT/US2015/030870

(22) International Filing Date:

14 May 2015 (14.05.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/996,819 14 May 2014 (14.05.2014) US
62/005,401 30 May 2014 (30.05.2014) US

(71) Applicant: **MERRIMACK PHARMACEUTICALS, INC.** [US/US]; One Kendall Square, Suite B7201, Cambridge, MA 02139 (US).

(72) Inventors: **KEARNS, Jeffrey, David**; 42 Everett St., #2, Arlington, MA 02474-6902 (US). **WOLF, Beni, B.**; 29 Fairbanks Road, Lexington, MA 02421 (US).

(74) Agents: **REMILLARD, Jane, E.** et al.; Nelson Mullins Riley & Scarborough LLP, One Post Office Square, Boston, MA 02109-2127 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: DOSAGE AND ADMINISTRATION ANTI-EGFR THERAPEUTICS

(57) Abstract: Methods for optimizing a therapeutic response in a patient (e.g., a cancer patient) to an anti-EGFR therapy, and methods for preventing or ameliorating infusion reactions in a patient receiving an anti-EGFR therapy are disclosed.



WO 2015/175827 A1

DOSAGE AND ADMINISTRATION OF ANTI-EGFR THERAPEUTICS

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 12, 2015, is named MMJ-046PC_SL.txt and is 9,885 bytes in size.

BACKGROUND

Appropriate dosing of parenteral medications such as antibody preparations is a critical factor in their administration to patients. One aspect of the requirement for safe and effective dosing schemes is that infusion reactions are occasionally associated with administration of antibody preparations to patients. In the field of anticancer therapy, infusion reactions have been reported in association with the administration of several antibody-targeted therapeutics, including rituximab, trastuzumab, bevacizumab, cetuximab and panitumumab. Such infusion reactions include chills, pyrexia and dizziness, which are often associated with hypersensitivity and allergic symptoms such as urticaria. Severe infusion reactions may be life-threatening and include anaphylactoid symptoms such as dyspnea, bronchospasm, hypotension, loss of consciousness and shock, or even myocardial infarction or cardiac arrest in some patients. Infusion related reactions are assigned grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.0) as follows. Grade 1 includes a mild transient reaction, wherein interruption of infusion and/or interventions is not indicated. Grade 2 includes reactions that indicate the therapy or infusion should be interrupted, but the reaction responds promptly to symptomatic treatment (e.g., NSAIDS, narcotics, or intravenous (i.v.) fluids). In such cases, prophylactic medications are indicated for up to 24 hours at the discretion of the physician or staff. Grade 3 reactions include prolonged infusion related reactions (e.g., reactions not rapidly responsive to symptomatic medication and/or a brief interruption of infusion), a recurrence of symptoms following initial improvement, and hospitalization indicated for clinical sequelae. Grade 4 includes infusion related reactions with

life-threatening consequences, and urgent intervention indicated as well as cessation of infusion. Grade 5 includes infusion related reactions causing the death of the patient.

Anti-EGFR antibodies provide beneficial therapy for various cancers, but may be ineffective or lose effectiveness over time. Newer EGFR inhibitory antibody preparations are in development, including oligoclonal mixtures of anti-EGFR monoclonal antibodies. Oligoclonal anti-EGFR antibody mixtures represent a recent advance in anti-EGFR cancer therapy and have been shown preclinically to provide superior anti-cancer therapeutic effects. MM-151 and Sym004 are oligoclonal mixtures of antibodies that bind to the extracellular domain of EGFR and inhibit EGFR activity. MM-151 comprises a formulation in a pharmaceutically acceptable carrier of a triple combination of monoclonal antibody P1X, monoclonal antibody P2X, and monoclonal antibody P3X at a P1X:P2X:P3X molar ratio of 2:2:1. These experimental therapies are designed to be more potent than first generation anti-EGFR monoclonal antibodies, and thus require specially adapted dosing and administration schedules and procedures.

Thus, there is an unmet need to develop and implement methods of safely and effectively administering novel antibody-comprising therapeutics, including methods for preventing and ameliorating infusion reactions in patients, e.g., cancer patients receiving such therapeutics. The following disclosure provides such methods and confers additional advantages.

SUMMARY

Disclosed herein are compositions and methods designed to safely and effectively administer oligoclonal anti-EGFR antibody preparations such as MM-151 and Sym004 and to prevent and ameliorate infusion reactions in patients receiving treatment such antibody-based therapeutics.

In one aspect, a method is provided for treating a cancer in a human patient by administering an oligoclonal mixture of anti-EGFR antibodies to the patient, wherein the method comprises intravenously administering the oligoclonal mixture of anti-EGFR antibodies in at least one treatment cycle, the at least one cycle comprising:

an initial two week treatment cycle consisting of a first week and a second week, wherein a first dose of the an oligoclonal mixture of anti-EGFR antibodies is administered during the first week administered at a rate of X mg/hour for a first $\frac{1}{2}$ hour, immediately followed by a rate of $2X$ mg/hour for a second $\frac{1}{2}$ hour, immediately followed by a rate of $4X$ mg/hour until all of the

first dose has been administered and a second dose, that is greater than or equal to the first dose, is administered during the second week; wherein administration, at each rate subsequent to the first $\frac{1}{2}$ hour, is optionally one or more of: delayed, altered or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate. In one embodiment, if the patient exhibits an adverse reaction to the administration of the anti-EGFR antibodies at the preceding rate (i.e., the rate at which the adverse reaction was observed) and the alteration comprises an interruption of administration, i) the patient is treated for symptoms of the adverse reaction at the discretion of an attending clinician, and ii) following treatment of the symptoms, the administration is resumed at a rate lower than or equal to the rate at which the administration was interrupted. In one embodiment, the administration is resumed at half the rate at which the administration was interrupted.

In another formulation of this aspect, provided herein is use of an oligoclonal mixture of anti-EGFR antibodies (for the manufacture of a medicament) for treating a cancer in a human patient by intravenous administration of the medicament to the patient in at least one treatment cycle, the at least one cycle comprising: an initial two week treatment cycle consisting of a first week and a second week, wherein a first dose of the an oligoclonal mixture of anti-EGFR antibodies is administered during the first week administered at a rate of X mg/hour for a first $\frac{1}{2}$ hour, immediately followed by a rate of $2X$ mg/hour for a second $\frac{1}{2}$ hour, immediately followed by a rate of $4X$ mg/hour until all of the first dose has been administered and a second dose, that is greater than or equal to the first dose, is administered during the second week.

In one embodiment, the second dose is administered at a rate of X mg/hour for a first $\frac{1}{2}$ hour, immediately followed by a rate of $2X$ mg/hour for a second $\frac{1}{2}$ hour, immediately followed by a rate of $4X$ mg/hour for a third $\frac{1}{2}$ hour, immediately followed by a rate of $8X$ mg/hour until all of the second dose has been administered, wherein administration at each rate of the second dose is optionally either delayed or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate or of the preceding dose.

In another embodiment, if the patient tolerates the initial cycle, the at least one cycle further comprises at least one subsequent treatment cycle, each treatment cycle comprising at least one administration of the oligoclonal mixture of anti-EGFR antibodies at a third dose. In another embodiment, the third dose is greater than or equal to the second dose and is greater than the first dose.

In another embodiment, if the third dose of the oligoclonal mixture of anti-EGFR antibodies is administered, it is administered at a rate of 2X mg/hour for a first ½ hour, immediately followed by a rate of 4X mg/hour for a second ½ hour, immediately followed by a rate of 8X mg/hour for a third ½ hour, immediately followed by a rate of 16X mg/hour until all of the third dose has been administered. In one embodiment, X is 25.

In one embodiment, the first dose of the oligoclonal mixture of anti-EGFR antibodies is about 225 mg or is about 3 mg/kg. In another embodiment, the second dose is about 450 mg or is about 6 mg/kg.

In one embodiment, the at least one subsequent treatment cycle is three weeks or four weeks.

In another embodiment, the at least one subsequent treatment cycle is four weeks, and, if administered, the third dose is administered on day 1 of each week of the four week treatment cycle. In yet another embodiment, the at least one subsequent treatment cycle is four weeks, and, if administered, the third dose is administered during the first week and the third week of each four week cycle.

In one embodiment, the at least one subsequent treatment cycle is three weeks, and, if administered, the third dose of the oligoclonal mixture of anti-EGFR antibodies is administered during week 1 of each three week cycle. In another embodiment, the oligoclonal mixture of anti-EGFR antibodies consists of two or more anti-EGFR antibodies.

In one embodiment, the oligoclonal mixture of anti-EGFR antibodies consists of anti-EGFR antibodies that specifically bind to two or more different epitopes of the extracellular domain of EGFR.

In one embodiment, the two or more different epitopes is three different epitopes.

In one embodiment, the two or more anti-EGFR antibodies is three anti-EGFR antibodies. In another embodiment, the three anti-EGFR antibodies is MM-151bio or optionally MM-151. In yet another embodiment, the three anti-EGFR antibodies comprise a first antibody with a heavy chain comprising SEQ ID NO:1 and a light chain comprising SEQ ID NO:2; a second antibody with a heavy chain comprising SEQ ID NO:3 and a light chain comprising SEQ ID NO:4; and a third antibody with a heavy chain comprising SEQ ID NO:5 and a light chain comprising SEQ ID NO:6. In another embodiment, the three anti-EGFR antibodies comprise a first antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 7, 8 and 9

respectively, and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 10, 11 and 12 respectively; a second antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 13, 14 and 15 respectively, and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 16, 17, and 18 respectively; and a third antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 19, 20 and 21 respectively, and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 22, 23 and 24 respectively.

In another embodiment, the antibodies are IgG antibodies, optionally IgG1 antibodies.

In another embodiment, the third dose (and optionally each subsequent dose) of the oligoclonal mixture of anti-EGFR antibodies is about 4.5 mg/kg, about 6 mg/kg, about 7.5 mg/kg, about 9 mg/kg, about 10 mg/kg, about 10.5 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 18 mg/kg, or about 20 mg/kg, and is administered weekly, bi-weekly or tri-weekly. In one embodiment, the third dose of the oligoclonal mixture of anti-EGFR antibodies is 10.5 mg/kg. In one embodiment, the 10.5 mg/kg is administered weekly.

In another aspect, provided are methods for treating a patient having a cancer, comprising co-administration of a topoisomerase inhibitor and the oligoclonal mixture of anti-EGFR antibodies. In one embodiment, the at least one dose of a topoisomerase inhibitor is administered at least during the initial two week treatment cycle, optionally wherein, if the patient tolerates the initial cycle, the at least one cycle further comprises at least one subsequent treatment cycle, each subsequent treatment cycle comprising at least one administration of the oligoclonal mixture of anti-EGFR antibodies at a third dose. In one embodiment, the topoisomerase inhibitor is administered during the initial two week treatment cycle prior to administration of the oligoclonal mixture of anti-EGFR antibodies. In another embodiment, the topoisomerase inhibitor is additionally administered during the at least one subsequent treatment cycle, and during each subsequent cycle is coadministered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

In one embodiment, the topoisomerase inhibitor is a topoisomerase I inhibitor. In one embodiment, the topoisomerase I inhibitor is a camptothecin. In one embodiment, the camptothecin is irinotecan HCl or liposomal irinotecan (e.g., liposomal irinotecan sucrosfate).

In one embodiment, each cycle of the at least one subsequent treatment cycle is a four week treatment cycle and the third dose of the oligoclonal mixture of anti-EGFR antibodies and

the topoisomerase inhibitor are each administered during day one of week one and day one of week three of the four week treatment cycle, optionally wherein, in each cycle of co-administration, the topoisomerase inhibitor is administered prior to administration of the oligoclonal mixture of anti-EGFR antibodies. In another embodiment, each cycle of the at least one subsequent treatment cycle is a four week treatment cycle and the topoisomerase inhibitor is administered on day one of week one of each four week treatment cycle and the anti-EGFR inhibitor is administered weekly. In one embodiment, in each cycle of co-administration, the topoisomerase inhibitor is administered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

In one aspect, provided is a method for ameliorating and/or preventing infusion reactions in a patient having a cancer comprising administering to the patient anti-inflammatory treatments prior to administering an oligoclonal mixture of anti-EGFR antibodies and/or irinotecan. Such method comprises a pretreatment comprising an effective amount of each of 1) drug 1: a histamine H1 blocker; and one or both of: 2) drug 2: an anti-inflammatory steroid; and 3) drug 3: acetaminophen, which is administered to the patient. In one embodiment, the one or both of 2) and 3) are both of 2) and 3); which pretreatment is administered to the patient prior to each infusion of the oligoclonal mixture of anti-EGFR antibodies. In another embodiment, the effective amount of each of 1) and one or both of 2) and 3) are all administered to the patient 30-60 minutes prior to the administration of the oligoclonal mixture of anti-EGFR antibodies. In one embodiment, 2) is dexamethasone or methylprednisolone. In another embodiment, the dexamethasone is administered to the patient at a dose of 5, 10, 15, 20 or 25 mg, or the methylprednisolone is administered to the patient at a dose of 25, 50, 75, 100, or 125 mg. In one embodiment, 2) is methylprednisolone. In another embodiment, 1) is diphenhydramine. In another embodiment, the diphenhydramine is administered at a dose of 25 mg to 50 mg. In one embodiment, the 25 mg to 50 mg is 25 mg or 50 mg.

In one embodiment, if the patient develops an infusion reaction in response to a cycle of administration of the oligoclonal mixture of anti-EGFR antibodies, an effective amount of 1) and/or 2) and/or 3) is re-administered during the cycle. In one embodiment, an effective amount of one or both of 1) and 2) is re-administered when the infusion reaction is observed. In some embodiments, administration of the anti-EGFR antibodies may be interrupted while the effective

amount of 2) is re-administered, and then resumed when 2) has been administered. In another embodiment, the administration of the pretreatment is repeated prior to each subsequent cycle.

In various embodiments, treatment of the patient in accordance with the disclosed methods results in a response classified as PR or CR, or in an SD response.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a graphic representation of the changes in infusion rate associated with the data set forth in Table III and Table IV plotted in comparison to constant infusion.

Figure 1B is a graphic representation of the variations in cumulative drug (mg of MM-151) dosed over time for the data set forth in Table III and Table IV plotted in comparison to constant infusion.

Figure 2A is a graphic representation of the changes in infusion rate associated with the data set forth in Table V and Table VI for the first infusion (“Priming Week 1”) and for the second infusion (“Priming Week 2”).

Figure 2B is a graphic representation of the variations in cumulative drug (mg of MM-151) dosed over time for the data set forth in Table V and Table VI for the first infusion (“Priming Week 1”) and for the second infusion (“Priming Week 2”).

Figure 2C is a graphic representation of the changes in infusion rate associated with the data set forth in Table V and Table VI for the first full dose and for the second full dose (and subsequent full doses).

Figure 2D is a graphic representation of the variations in cumulative drug (mg of MM-151) dosed over time for the data set forth in Table V and Table VI for the first full dose and for the second full dose (and subsequent full doses).

Figure 3 summarizes data from patients that received MM-151 according to the following regimens: Top row of pie charts: 0.25 to 9 mg/kg MM-151 infusion on a standard schedule (no rate optimization or premedication, top line). Middle row of pie charts: 9 mg/kg MM-151 on Modified Schedule 1 (slower than usual infusion, middle line). Bottom row of pie charts: data patients treated with MM-151 monotherapy comprising two priming doses, one of 225 mg and one of 450 mg, followed by two full doses (as opposed to priming doses) of ≥ 10.5 mg/kg on Modified Schedule 2 (with premedication, bottom line).

Figure 4 summarizes data from patients that received MM-151 following the generation of the data presented in Figure 3, including 65 patients included in Figure 3 and 41 additional patients administered MM-151 according to Modified Schedule 2 in the clinical trial. Some of these 41 additional patients were administered MM-151 in combination with irinotecan with a

MM-151 dose of 4.5, 6, 7.5, or 9 mg/kg (these data were combined because no effect was seen of irinotecan co-administration on the frequency or severity of IRRs).

DETAILED DESCRIPTION

Oligoclonal anti-EGFR antibody mixtures represent a recent advance in anti-EGFR cancer therapy. MM-151 and Sym004 (SYMPHOGEN) are each oligoclonal mixtures of antibodies that bind to the extracellular domain of EGFR and inhibit EGFR activity. MM-151 comprises a formulation in a pharmaceutically acceptable carrier of a triple combination of P1X + P2X + P3X at a P1X:P2X:P3X molar ratio of 2:2:1. While MM-151 comprises P1X, P2X and P3X, variants of P1X, P2X and P3X have been prepared that comprise V_H and V_L sequences closely related to those of SEQ ID NOs 1-6; see, e.g., U.S. patent publications Nos. 20110287002 and 20140127207. Related variants may preserve a sufficient degree of functional similarity to provide bioequivalent pharmacokinetics, safety and efficacy. Closely related variants of P1X V_H and V_L , P2X V_H and V_L , and P3X V_H and V_L may each include one, two or all three of the complementarity determining regions (CDRs) of each variable region. Such variants may be combined (e.g., at a P1X analog:P2X analog:P3X analog molar ratio of about 2:2:1 in a pharmaceutically acceptable carrier), and, where closely enough related to P1X, P2X and P3X, may thereby form a variant preparation biosimilar to MM-151. As used in this specification, and in the claims, “MM-151bio” is meant to include MM-151 and such MM-151 biosimilar preparations.

Provided herein are methods for treating a cancer with an anti-EGFR antibody therapeutic. In particular, disclosed herein are specific dosages and regimens for administering an oligoclonal anti-EGFR antibody therapeutic preparation to a human patient having a cancer, such dosages and regimens being designed to increase a patient's tolerance of the therapeutic, decrease the likelihood of infusion-related reactions (IRRs), and maximize the amount of dose that may be administered to the patient safely so as to safely achieve maximum anti-cancer benefits. Previous attempts to mitigate IRR cause by administration of antibody-based anti-EGFR therapeutics have resulted in very long infusion times, e.g., 6-9 hours in some cases, depending on body weight. Infusion times longer than 5 hours may be impractical in a clinical

setting. Other attempts to address infusion reactions require patients to come to the clinic for treatment two or more days in a row. In order to avoid these difficulties, a regimen was designed that reduces or prevents infusion reactions, avoids long infusions, and avoids split-day treatments, thus allowing administration of higher doses of oligoclonal anti-EGFR therapy to patients, which higher doses may provide more effective therapy.

Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. For example, human antibodies may be administered once or twice weekly by intravenous injection or once or twice monthly by intravenous injection.

It is especially advantageous to formulate parenteral compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of antibodies, e.g., a quantity calculated to provide an amount sufficient for a single cycle of administration.

Oligoclonal antibody mixtures

P1X is a human IgG1 having a heavy chain variable region (V_H) comprising SEQ ID NO: 1 and a light chain variable region (V_L) comprising SEQ ID NO: 2;

P2X is a human IgG1 having a V_H comprising SEQ ID NO: 3 and a V_L comprising SEQ ID NO: 4; and

P3X is a human IgG1 having a V_H comprising SEQ ID NO: 5 and a V_L comprising SEQ ID NO: 6.

In various embodiments, P1X, P2X and P3X are each expressed in recombinant cell protein expression systems. Such protein expression systems include commercially available systems using bacterial cells (e.g., *E. coli* with PET vector), insect cells (e.g., Sf9 cells with pIB/V5-Histidine vector) and mammalian cells (e.g., HEK 293 cells with pLOC vector). A preferred expression host cell is a Chinese hamster ovary (CHO) cell. A preferred expression vector is a commercially available mammalian expression vector that is suitable for expression

of IgG heavy and light chains in a CHO cell, e.g., one from SELEXIS, LONZA, or GE HEALTHCARE.

Table I: Exemplary Antibody Variable Regions

P1X V _H	MGFGLSWLFLVAILKGVQC QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAISWVRQA PGQGLEWMGSIPIFGTVNY AQKFQGRVTITADESTSTAY MELSSLRSEDVAVYYCARDP SVNLYWYFDLWGRGTLVTVSS	SEQ ID NO: 1
P1X V _L	MGTPAQLLFLLLWLPDITG DIQMTQSPSTLSASVGDRVT ITCRASQSISSWWAWYQQK GKAPKLLIYDASSLESGVPS RFGSGSGTEFTLTISLQ DDFATYYCQYHAHPTTFGG GTKVEIK	SEQ ID NO: 2
P2X V _H	MGFGLSWLFLVAILKGVQC QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAISWVRQA PGQGLEWMGSIPIFGAANP AQKSQGRVTITADESTSTAY MELSSLRSEDVAVYYCAKMG RGKVAFDIWGGTMVTVSS	SEQ ID NO: 3
P2X V _L	MGTPAQLLFLLLWLPDITG DIVMTQSPDSLAVSLGERAT INCKSSQSVLYSPNNKNYLA WYQQKPGQPPKLLIYWASTR ESGVPDRFSGSGGTDFLT ISSLQAEDVAVYYCQYYGS PITFGGGTKVEIK	SEQ ID NO: 4
P3X V _H	MGFGLSWLFLVAILKGVQC QVQLVQSGAEVKKPGASVKV SCKASGYAFTSYGINWVRQA PGQGLEWMGWISAYNGNTYY AQKLRRGVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDL GGYGSGLVFPDPWGQGTLVTVSS	SEQ ID NO: 5
P3X V _L	MGTPAQLLFLLLWLPDITG EIVMTQSPATLSVSPGERAT LSCRASQSVSSNLAWYQQK GQAPRLLIYGASTRATGIPA	SEQ ID NO: 6

	RFSGSGSGTEFTLTISSLQS EDFAVYYCQDYRTWPRRVFG GGTKVEIK	
--	--	--

Table II: Exemplary Antibody CDRs

P1X V _H CDR1	SYAIS	SEQ ID NO: 7
P1X V _H CDR2	IIPIFGTVNY	SEQ ID NO: 8
P1X V _H CDR3	DPSVNL	SEQ ID NO: 9
P1X V _L CDR1	QSISSWWA	SEQ ID NO: 10
P1X V _L CDR2	DASSL	SEQ ID NO: 11
P1X V _L CDR3	QQYHAHP	SEQ ID NO: 12
P2X V _H CDR1	SYAIS	SEQ ID NO: 13
P2X V _H CDR2	IIPIFGAANP	SEQ ID NO: 14
P2X V _H CDR3	MGRGKV	SEQ ID NO: 15
P2X V _L CDR1	QSVLYSPNNKNYLA	SEQ ID NO: 16
P2X V _L CDR2	WASTR	SEQ ID NO: 17
P2X V _L CDR3	QQYYGSP	SEQ ID NO: 18
P3X V _H CDR1	SYGIN	SEQ ID NO: 19
P3X V _H CDR2	ISAYNGNTYY	SEQ ID NO: 20
P3X V _H CDR3	DLGGYGSGS	SEQ ID NO: 21
P3X V _L CDR1	QSVSSNLA	SEQ ID NO: 22
P3X V _L CDR2	GASTR	SEQ ID NO: 23
P3X V _L CDR3	QDYRTWPR	SEQ ID NO: 24

Dosage of oligoclonal antibody mixtures

In one embodiment, the oligoclonal antibody mixture is formulated for intravenous administration. In particular embodiments, the oligoclonal antibody mixture is administered at a dose selected from: priming doses of from 100 to 1000 mg, e.g., 225 mg or 450 mg, or 3 mg/kg or 6 mg/kg; and full doses of from 1 to 20 mg/kg, e.g., 3 mg/kg, 6 mg/kg, 7.5 mg/kg, 9 mg/kg, 10.5 mg/kg, 12 mg/kg, 15 mg/kg or 18 mg/kg or 20 mg/kg. In one embodiment, the dose of the oligoclonal antibody mixture is varied over time. For example, the antibody may be initially administered at a low dose and increased over time.

Camptothecin Topoisomerase I Inhibitors

Irinotecan hydrochloride (HCl) is marketed as CAMPTOSAR® (irinotecan hydrochloride injection). Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class that is a derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. Camptothecin and its derivatives are referred to as camptothecins, and irinotecan is a camptothecin. The chemical name for irinotecan is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-

hydroxy-3,14-dioxo1H pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. Irinotecan HCl is a monohydrochloride trihydrate that is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is slightly soluble in water and organic solvents. Irinotecan HCl is also known as CPT-11. Other camptothecin topoisomerase I inhibitors include 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, irinotecan, topotecan, lurtotecan, silatecan, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin.

Pharmaceutical Compositions

Pharmaceutical compositions suitable for administration to a patient are typically in forms suitable for parenteral administration, e.g., in a liquid carrier, or suitable for reconstitution into liquid solution or suspension, for intravenous administration.

In general, compositions typically comprise a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable" means approved by a government regulatory agency or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the antibodies are administered. Such pharmaceutical carriers can be sterile liquids, typically water and aqueous solutions such as saline and aqueous sucrose or dextrose and glycerol solutions, which may also contain excipients such as emulsifiers (e.g., a polysorbate), buffering agents (e.g. phosphate buffers or amino acids). Liquid compositions for parenteral administration can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and subcutaneous. In one embodiment, an oligoclonal mixture of anti-EGFR antibodies and irinotecan are administered intravenously (e.g., separately or together, each, e.g., for MM-151, over the course of 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, or 360 minutes).

MM-151 may be formulated for intravenous infusion as a clear liquid that may be supplied in sterile, single-use vials containing 10mL of MM-151 (with an extractable volume of

9.5mL) at a total protein concentration of 25 mg/mL in 20mM histidine, 10% sucrose, 0.02% polysorbate 80, pH 6.0. MM-151 Drug Product thus formulated should be stored at 2-8°C.

Irinotecan HCl is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes in brown glass vials: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Irinotecan is also available in three single-dose sizes in amber-colored polypropylene CYTOSAFE vials: 2 mL-fill vials contain 40 mg irinotecan hydrochloride, 5 mL-fill vials contain 100 mg irinotecan hydrochloride and 15 mL-fill vials contain 300 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Patient Populations

Provided herein are effective methods for treating solid tumors (e.g., that are advanced and/or EGFR dependent) in a human patient using an oligoclonal mixture of anti-EGFR antibodies, or using a combination of such an oligoclonal mixture and irinotecan.

In one embodiment, a human patient for treatment of a cancer in accordance with the methods provided herein has not been previously been treated for the cancer with an antineoplastic medication. In another embodiment, a human patient for treatment using the subject methods and compositions has evidence of recurrent or persistent disease following primary chemotherapy. In one embodiment, the human patient suffers from colorectal cancer, head and neck cancer (e.g., head and neck squamous cell carcinoma), non-small cell lung cancer, gastric cancer, breast cancer, endometrial cancer, ovarian cancer, cervical cancer, bladder cancer (and related urothelial cancers), esophageal cancer, brain cancer (e.g., glioblastoma multiforme) liver cancer (e.g., hepatoma), pancreatic cancer, and squamous cell carcinoma. In one embodiment, the patient has a pathologically documented, definitively diagnosed colorectal adenocarcinoma that is locally advanced or metastatic and surgically unresectable.

In another embodiment, a patient has shown evidence of recurrent or persistent disease following treatment with at least 1 and no more than 2 treatment regimens for locally advanced

or metastatic disease. In one embodiment, if the patient is to receive combination therapy comprising irinotecan, the patient should have received only 1 prior treatment containing irinotecan.

In one embodiment, patients must have received no prior therapy with EGFR-targeted therapeutics. In another embodiment, patients must have received prior therapy with one or more EGFR-targeted therapeutics and have become refractory to such therapy.

Combination Therapies

The methods provided herein are useful for both anti-EGFR monotherapy and combination therapy with other anti-cancer therapies, e.g. chemotherapeutics (e.g., irinotecan, 5-FU/leucovorin, oxaliplatin (and combinations of the foregoing such as FOLFOX and FOLFIRI), MM-398 (alone or in combination with 5-FU/leucovorin), targeted small molecules, e.g., trametinib, selumetinib, binimetinib, cobimetinib, afatinib, sunitinib, sorafenib, pazopanib, imatinib, vemurafenib, dabrafenib, erlotinib, gefitinib, and lapatinib, or monoclonal antibodies such as seribantumab, MM-141, MM-131, MM-111, ipilimumab, nivolumab, pembrolizumab, pidilizumab, trastuzumab, pertuzumab, ado-trastuzumab emtansine. Each of these anti-cancer therapies is preferably co-administered at the manufacturer's recommended dose, unless such a dose causes an adverse reaction when administered in combination with MM-151 (or MM-151bio), in which case a reduced dose is preferred.

In one embodiment, an oligoclonal mixture of anti-EGFR antibodies is administered concomitantly with irinotecan, to effect improvement in subjects having a solid tumor. In one embodiment, the oligoclonal mixture of anti-EGFR antibodies is MM-151 or MM-151bio.

As used herein, adjunctive or combined administration (co-administration) includes simultaneous administration of the compounds in the same or different dosage form, or separate administration of the compounds (e.g., sequential administration). For example, the oligoclonal antibody mixture can be simultaneously administered with irinotecan, wherein both the antibody and the irinotecan are formulated together. Alternatively, the oligoclonal antibody mixture can be administered in combination with irinotecan, wherein both the antibody mixture and the irinotecan are formulated for separate administration and are administered concurrently or sequentially. For example, the irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the oligoclonal antibody mixture, or vice versa.

Such concurrent or sequential administration beneficially results in both the oligoclonal antibody mixture and irinotecan being simultaneously present in treated patients.

In one embodiment, the oligoclonal antibody mixture is administered as a monotherapy prior to the combination therapy. In another embodiment, the oligoclonal antibody mixture is administered as a monotherapy following the combination therapy.

Outcomes

Responses to therapy may include:

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. 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.

In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of cancer. In one embodiment, the patient so treated exhibits CR, PR; in another embodiment the patient exhibits SD.

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, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: 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.

In other embodiments, such improvement is 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. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In some embodiments, administration of effective amounts of the oligoclonal anti-EGFR antibody mixture, e.g., MM-151 or MM-151bio, and optionally irinotecan according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of combination treatment produce a comparable clinical benefit rate ($\text{CBR} = \text{CR} + \text{PR} + \text{SD} \geq 6 \text{ months}$) better than that achieved by the oligoclonal anti-EGFR antibody mixture, e.g., MM-151 or MM-151bio, or irinotecan alone, or the combination of cetuximab and irinotecan. In other embodiments, the improvement of clinical benefit rate is about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more compared to cetuximab or irinotecan alone or the combination of cetuximab and irinotecan.

Kits and Unit Dosage Forms

Also provided are kits that include a pharmaceutical composition containing an oligoclonal mixture of anti-EGFR antibodies, such as MM-151 or MM-151bio, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods.

The kits can optionally also include instructions, e.g., comprising administration parameters including dosages and infusion rates, to allow a practitioner (e.g., a physician, nurse, or patient) to administer the composition contained therein to a patient having cancer in accordance with the methods disclosed herein. In one embodiment, the kit further comprises irinotecan. Optionally, the kit may comprise a preparation of oligoclonal anti-EGFR antibodies (e.g., MM-151, MM-151bio or Sym004) and/or irinotecan in a desired unit dosage form for administration.

Pretreatments

Prior to infusion of oligoclonal anti-EGFR antibodies (e.g., 30-60 minutes before each infusion), one or more drugs may be administered to reduce the incidence and severity of infusion reactions. A histamine H1 antagonist (antihistamine) may be administered. Exemplary antihistamines for this pre-treatment include diphenhydramine, chlorpheniramine, and brompheniramine. In one embodiment, diphenhydramine is administered orally (p.o.) or intravenously (i.v.) at a dose of 25-50 mg. Acetaminophen may be administered, e.g., at a dose of 650 mg p.o. or i.v. Additionally, an anti-inflammatory steroid may be administered. Exemplary steroids for this purpose include dexamethasone and methylprednisolone. In one embodiment, methylprednisolone is administered intravenously (i.v.) at a dose of 25-125 mg (e.g., 25, 50, 75, 100, or 125 mg). In another embodiment, dexamethasone is administered p.o. or i.v. at a dose of 5-25 mg (e.g., 5, 10, 15, 20 or 25 mg). Pretreatment may optionally be reduced or discontinued after the first full dose (i.e., dose other than a priming dose) of oligoclonal anti-EGFR antibodies, particularly if no infusion reactions are observed. Pretreatment may optionally be resumed at a later dosing visit, particularly to reduce the incidence of infusion reactions in patients that did not receive drug on one or more preceding visits.

EXAMPLES

The present invention is further illustrated by the following Examples, which should not be construed as further limiting. These Examples incorporate results obtained during a Phase I clinical trial of MM-151. In this trial, patients who received a relatively high dose of MM-151 at the beginning of the first infusion were much more likely to develop a rapidly presenting infusion reaction (e.g., hypersensitivity) at the beginning of the dosing, requiring a stoppage in

treatment, than were patients who received a relatively lower dose of MM-151. In addition, patients who received higher doses during the first infusion of MM-151 and didn't exhibit a hypersensitivity reaction tended to develop cytokine-driven infusion reactions about three to six hours after the beginning of the drug infusion. Finally, patients who received anti-inflammatory treatments prior to the first infusion of MM-151 exhibited fewer infusion reactions than patients who did not receive anti-inflammatory treatments prior to MM-151 infusion.

Surprisingly, patients were much less likely to develop an infusion reaction in subsequent infusions compared to the first infusion, indicating that patients experience fewer side effects with each subsequent administration of MM-151.

As presented in the tables below "FD" (full dose), may be, e.g., 4.5, 6, 7, 7.5, 8, 9, 10, 10.5, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg. In those Tables relating to combination therapy comprising irinotecan, "180" indicates 180 mg/m² of irinotecan HCl, which is preferably administered prior to MM-151 administration. The amounts of either or both of 1) each full dose of MM-151 or 2) of each full dose of the combination therapy, may be reduced during the course of treatment at the discretion of the treating physician, such as in response to an adverse event.

Example 1: Pre-Treatment

In all patients not treated with the Standard Schedule described below, premedication with methylprednisolone i.v. at a dose of 25-125 mg, diphenhydramine p.o. or i.v. at a dose of 25 or 50 mg, and acetaminophen p.o. or i.v. at a dose of 650 mg is administered to each patient prior to the initial infusion of MM-151 and premedication is preferably continued before each subsequent infusion of MM-151, but may be altered at the treating physician's discretion.

Example 2: A priming phase with escalating rate of infusion and subsequent dosing for MM-151 monotherapy administration

In the following clinical trial, the first 37 patients to be treated received MM-151 according to the Standard Schedule, i.e., by constant infusion (approximately 60-90 minutes in duration). These patients frequently exhibited infusion-related reactions that were sometimes severe. In some cases, administration of MM-151 to patients who exhibited infusion-related reactions was terminated prematurely and not restarted (i.e. the intended dose of MM-151 was not administered). In some cases, patients who exhibited infusion-related reactions were

withdrawn from the trial due to the severity of their reactions. The trial design was then modified to enable the determination of whether MM-151 would be better tolerated with pre-medication and with modified infusion protocols involving administration via a slow first infusion, followed by increased rates on subsequent infusions. Two such modified infusion protocols are set forth below as Modified Schedule 1 and Modified Schedule 2.

Administration Details of Modified Schedule 1

In Modified Schedule 1, administration of MM-151 was initiated at a low infusion rate for one hour and the rate was then escalated as described below in the following paragraph. Table III below gives an exemplary dosing schedule for patients getting treatment with a full dose of MM-151 on a weekly basis (QW), every other week (Q2W), or every three weeks (Q3W). Any pretreatment is given before each administration. Herein, this infusion schedule is termed as “Modified Schedule 1.”

In Modified Schedule 1, the rates of infusion of MM-151 are carefully controlled to reduce or prevent hypersensitivity reactions (e.g., allergic reactions). Modified Schedule 1 is set forth in Table IV below, and provides a rate escalation schedule for the first two infusions at dose level of 10.5 mg/kg to an 85 kg patient. The infusion rate for Cycle 1 Week 1 begins at 10 mg/hour (1X) for the first 60 minutes followed by an escalation of six subsequent rates for 30 min each—20 mg/hour (2X), 40 mg/hour (4X), 60 mg/hour (6X), 100 mg/hour (10X), 150 mg/hour (15X), and finally 200 mg/hour (20X). The final 200 mg/hour rate is continued until the full dose is delivered (all of these escalation steps occurring over the course of approximately seven hours in total). The infusion rate for Cycle 1 Week 2 and subsequent administrations begins at 50 mg/hour (5X) for the first 60 minutes followed by an escalation of seven subsequent rates for 30 min each—100 mg/hour (10X), 150 mg/hour (15X), 200 mg/hour (20X), 250 mg/hour (25X), 300 mg/hour (30X), 350 mg/hour (35X), and finally 400 mg/hour (40X). The final 200 mg/hour rate is continued until the full dose is delivered (all of these escalation steps occurring over the course of approximately 4.5 hours in total). If a patient experienced an infusion reaction during an infusion, the next full dose was optionally (at the treating physician’s discretion) administered with the slower Cycle 1 Week 1 schedule. If a patient did not experience an infusion reaction during an infusion, the next full dose was administered (at the treating physician’s discretion) at the faster Cycle 1 Week 2 schedule.

Particular embodiments of this infusion schedule (“Modified Schedule 1”) are shown as line plots in Figures 1A – 1B. Figure 1A depicts the rate escalation schedules for Cycle 1 Week 1 and the subsequent full dose administration(s) and Figure 1B shows the cumulative amount of drug administered during these administrations.

Table III: Dosage and Administration of MM-151 Monotherapy (“Modified Schedule 1”)

Schedule	Cycle 1				Subsequent Cycles			
	W1	W2	W3	W4	W1	W2	W3	W4
QW	FD	FD	FD	FD	FD	FD	FD	FD
Q2W	FD	–	FD	–	FD	–	FD	–
Q3W	FD	–	–	n/a	FD	–	–	n/a

Table IV: Example of MM-151 administration with an alternative infusion schedule (“Modified Schedule 1”) at 10.5 mg/kg for an 85 kg patient

Infusion	Rate (mg/hour)	Duration (hr)	Drug Infused (mg)	Cumulative Drug Infused (mg)	Cumulative Time (hr)
1 st Infusion (Cycle 1 Week 1)	10	1.0	10	10	1.0
	20	0.5	10	20	1.5
	40	0.5	20	40	2.0
	60	0.5	30	70	2.5
	100	0.5	50	120	2.0
	150	0.5	75	195	3.5
	200	3.5	697.5	892.5	7.0
Subsequent Infusions (Cycle 1 Week 2, et seq.)	50	1.0	50	50	1.0
	100	0.5	50	100	1.5
	150	0.5	75	175	2.0
	200	0.5	100	275	2.5
	250	0.5	125	400	3.0
	300	0.5	150	550	3.5
	350	0.5	175	725	4.0
	400	0.4	167.5	892.5	4.42

Administration Details of Modified Schedule 2

Three issues arose during the trial in which Modified Schedule 1 was employed. Firstly, the slow infusion schedule required extended administration times (administration of the first full dose of MM-151 extended to two days for almost all patients). Secondly, the large number of rate escalation steps during administration in accordance with Modified Schedule 1 created a significant burden for nursing staff, particularly when infusion reactions occurred, as they required rate de-escalation, resulting in highly complex administration patterns. Thirdly,

Modified Schedule 1, while reducing the severity of infusion reactions, did not adequately reduce the frequency with which they occurred – this is believed to have been due to cytokine mediated inflammatory events. Modified Schedule 2 was invented to address these issues.

In Modified Schedule 2, a priming phase designed to enhance the safety and ease of MM-151 administration precedes Cycle 1. The priming phase consists of two weekly fixed doses of 225 mg (Priming Week 1) and 450 mg (Priming Week 2) given prior to Cycle 1. Safety data support the fixed 225 mg and 450 mg doses as they equate to approximately 2.7 mg/kg (2.1 to 3.7, \pm S.D) and approximately 5.4 mg/kg (4.2 to 7.4, \pm S.D) for the average patient enrolled in this study at the time the clinical trial was modified to include Modified Schedule 2 (84 ± 23 kg (mean \pm S.D), range 48-169 kg, N=55). Table V below gives an exemplary dosing schedule for patients getting treatment on a weekly basis (QW), every other week (Q2W), or every three weeks (Q3W). Any pretreatment is given before each administration.

In Modified Schedule 2, the rates of infusion of MM-151 are carefully controlled to reduce or prevent both hypersensitivity reactions (e.g., allergic reactions) and cytokine-mediated infusion reactions. Table VI below gives a rate escalation schedule for the first four infusions and includes the Priming Phase and the first two full doses. The infusion rate for Priming Week 1 (W1) begins at 25 mg/hour (1X) for the first 30 minutes, followed by a rate of 50 mg/hour (2X) for the second 30 minutes, and finally followed by 100 mg/hour (4X) until the full dose is delivered at slightly less than three hours. The infusion rate for Priming Week 2 (W2) begins at 1X for the first 30 minutes, followed by a rate of 2X for the second 30 minutes, followed by the rate of 4X for the next 30 minutes, and finally by the rate of 8X until the full dose is delivered at approximately 3 ½ hours. Similarly, the first full dose is administered at the beginning of Cycle 1 beginning with an infusion rate of 50 mg/hour (2X) for the first 30 minutes, and then advanced at the discretion of the treating medical professional, for example, followed by a rate of 4X for the next 30 minutes, followed by a rate of 8X for the next 30 minutes, and finally followed by a rate of 16X until the full dose is administered to the patient. If a patient experiences an infusion reaction on one or both Priming Phase infusions, the first full dose may be administered with a slower schedule beginning with an infusion rate of 50 mg/hour (2X) for the first 30 minutes, and then advanced at the discretion of the treating medical professional, for example, followed by a rate of 4X for the next 30 minutes, followed by a rate of 8x until the full dose is administered to the patient.

Particular embodiments of this infusion schedule (“Modified Schedule 2”) are shown as line plots in Figures 2A – 2D. Figure 2A depicts the rate escalation schedules for Priming Week 1 and Priming Week 2. Figure 2B shows the cumulative amount of drug administered during Priming Week 1 and Priming Week 2. Figure 2C depicts the rate escalation schedules for Cycle 1 Week 1 and the subsequent full dose administration(s) and Figure 2D shows the cumulative amount of drug administered during these administrations.

Table V: Dosage and Administration of MM-151 Monotherapy (“Modified Schedule 2”)

Schedule	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
QW	225 mg	450 mg	FD	FD	FD	FD	FD	FD	FD	FD
Q2W	225 mg	450 mg	FD	–	FD	–	FD	–	FD	–
Q3W	225 mg	450 mg	FD	–	–	n/a	FD	–	–	n/a

¹DLT evaluation period will consist of both the Priming Phase and cycle 1

Table VI: MM-151 administration with the optimized infusion schedule (“Modified Schedule 2”) at 10.5 mg/kg for an 85 kg patient

Infusion	Rate (mg/hour)	Time (hr)	Drug Infused (mg)	Cumulative Drug Infused (mg)	Cumulative Time (hr)
1 st Infusion (Priming Week 1)	25	0.5	12.5	12.5	0.5
	50	0.5	25.0	37.5	1.0
	100	1.875	187.5	225.0	2.88
2 nd Infusion (Priming Week 2)	25	0.5	12.5	12.5	0.5
	50	0.5	25.0	37.5	1.0
	100	0.5	50.0	87.5	1.5
	200	1.81	362.5	450	3.31
3 rd Infusion (1 st Full Dose ¹)	50	0.5	25	25	0.5
	100	0.5	50	75	1.0
	200	0.5	100	175	1.5
	400	1.794	717.5	892.5	3.29
4 th Infusion (2 nd Full Dose ¹)	100	0.5	50	50	0.5
	400	0.5	200	250	1.0
	600	1.07	642.5	892.5	2.07

¹For this embodiment, a Full Dose is 10.5 mg/kg (892.5 mg for an 85 kg patient)

Results of administration of MM-151 by constant infusion, “Modified Schedule 1” and “Modified Schedule 2”

Results are shown as pie charts in Figure 3 for patients who were administered MM-151 by three infusion schedules—constant infusion over 60 to 90 min (“Standard Schedule”),

Modified Schedule 1, or Modified Schedule 2. As shown in the figure, patients receiving MM-151 via Modified Schedule 1 (middle row) had fewer Grade 3 infusion reactions, but a similar frequency of Grade 2 infusion reactions at the first visit, and no infusion reactions at all by the time of the fourth visit, even though these patients received a greater dose of drug (up to 9 mg/kg for some patients) than the patients on the Standard Schedule. As also shown in the figure, patients receiving MM-151 via Modified Schedule 2 (bottom row) had no Grade 3 infusion reactions, had fewer Grade 2 infusion reactions than patients in the other groups at the first visit, and no infusion reaction at all by the time of the fourth visit, even though these patients received a greater dose of drug (up to 15 mg/kg for some patients) in the third and fourth administrations than patients in the other groups. In Figure 3, patients who missed a visit but continued therapy were recorded as missing for the pie chart corresponding to the missed visit.

Additional results are shown as pie charts in Figure 4 and include 41 additional patients administered MM-151 according to Modified Schedule 2 in the clinical trial following the generation of the data presented in Figure 3, including patients administered MM-151 in combination with irinotecan. As shown in the figure, patients receiving MM-151 via the optimized infusion schedule (bottom line) had no Grade 3 infusion reactions and had fewer Grade 2 infusion reactions than patients in the other groups, even though these patients received a greater dose of drug (up to 20 mg/kg for some patients) in the third and fourth administrations than patients in the other groups. In Figure 4, patients who missed a visit but continued therapy were recorded as present for the next numbered visit, so that the data shown are for the first four administrations, regardless of gaps between visits.

Example 3: Dosage and administration of MM-151 + Irinotecan combination therapy (with MM-151 administered according to “Modified Schedule 2” at weekly or biweekly dosing intervals)

Table VIIa: Dosage of MM-151 + Irinotecan

	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
MM-151	225 mg	450 mg	FD	FD	FD	FD	FD	FD	FD	FD
Irinotecan	180	–	180	–	180	–	180	–	180	–

¹DLT evaluation period will consist of both the Priming Phase and cycle 1

Table VIIb: MM-151 + Irinotecan Combination Dose Escalation – Q2W dosing, 2 week Priming Phase, Fixed Dosing

	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
MM-151	225 mg	450 mg	FD	–	FD	–	FD	–	FD	–
Irinotecan	180	–	180	–	180	–	180	–	180	–

¹DLT Evaluation Period = Priming phase + Cycle 1

Example 4: Alternative dosing schedule for MM-151

The following tables highlight alternative MM-151 monotherapy and MM-151 + irinotecan infusion schemas. The schedule set forth in Table VIII is less preferred because it requires multiple days for initial infusions of MM-151.

Table VIII: MM-151 Monotherapy Dose Escalation – 2 Day First Infusion

Schedule	Cycle n			
	W1	W2	W3	W4
QW	D0 - 25-50% ¹ D1 - 50-75%	FD	FD	FD
Q2W	D0 - 25-50% D1 - 50-75%	–	FD	–

¹ D0 = Day 0 – administer 25-50% of current MM-151 mg/kg dose level;

D1 = Day 1 – administer remaining MM-151 at 50-75% of current dose level; MM-151 administration over 2 subsequent days occurs only for the first MM-151 dose in cycle 1

Example 5: Alternative dosing schedules for MM-151 “Modified Schedule 3”

Modified Schedule 3 uses the rate escalation scheme set forth in Modified Schedule 2 with dosing set in terms of mg/kg (body weight based dosing) rather than mg/patient (fixed dose per patient). The 225 mg fixed dose of Modified Schedule 2 is replaced with a 3 mg/kg dose in Modified Schedule 3, and the 450 mg fixed dose of Modified Schedule 2 is replaced with a 6 mg/kg dose in Modified Schedule 3. Following the 2-week priming phase, full doses (FD) of MM-151 are administered QW, Q2W, or Q3W as indicated.

Table IX: MM-151 Monotherapy Dose Escalation – 2 week Priming Phase, mg/kg Dosing

Schedule	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
QW	3	6	FD	FD	FD	FD	FD	FD	FD	FD
Q2W	3	6	FD	–	FD	–	FD	–	FD	–
Q3W	3	6	FD	–	–	–	FD	–	–	–

¹Priming phase only precedes cycle 1; Subsequent cycles have no priming phase;

DLT Evaluation Period = Priming phase + Cycle 1

Table X: MM-151 + Irinotecan Combination Dose Escalation – 2 week Priming Phase, mg/kg Dosing

	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
MM-151	3	6	FD	FD	FD	FD	FD	FD	FD	FD
Irinotecan	180	–	180	–	180	–	180	–	180	–

¹ DLT Evaluation Period = Priming phase + Cycle 1

Table XI: MM-151 + Irinotecan Combination Dose Escalation – Q2W dosing, 2 week Priming Phase, mg/kg Dosing

	Priming Phase ¹		Cycle 1				Subsequent Cycles			
	W1	W2	W1	W2	W3	W4	W1	W2	W3	W4
MM-151	3	6	FD	–	FD	–	FD	–	FD	–
Irinotecan	180	–	180	–	180	–	180	–	180	–

¹ DLT Evaluation Period = Priming phase + Cycle 1

Example 6: Adjustment of administration of MM-151 if an infusion-related reaction occurs

The following schema highlights the management of infusion reactions that may occur during the administration of MM-151. This schema incorporates the grading of infusion-related reactions as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.0; as described in the Background above).

If a patient experiences a Grade 1 infusion-related reaction (lowest severity), the infusion may proceed according to the infusion schedule and the symptoms should be monitored by the treating physician (or nurse or other medical staff). At the discretion of the treating physician, additional medication may be administered, preferably one or both of a histamine H1 blocker and an anti-inflammatory steroid.

If a patient experiences a Grade 2 infusion-related reaction (moderate severity), the infusion of MM-151 should be interrupted and additional medication administered, preferably one or both of a histamine H1 blocker and an anti-inflammatory steroid. If the infusion-related

reaction symptoms resolve during the interruption, the infusion may be resumed at a rate equal to or lower than the rate at the time of the interruption. In one embodiment, the infusion may resume at a rate that is approximately (or exactly) 50% of the rate at the time of the interruption. In another embodiment, the infusion rate is initially lowered and is subsequently escalated, optionally until it reaches or exceeds the rate at the time of the interruption. Preferably, the remaining steps set forth in the infusion rate schedule for the dosing visit will be carried out to effect the rate escalation.

If a patient experiences a Grade 3 or a Grade 4 infusion-related reaction (severe), the infusion of MM-151 should be terminated and additional medication administered, preferably one or both of a histamine H1 blocker and an anti-inflammatory steroid. Additional medication such as one or both of a bronchodilator and epinephrine should be administered. The patient should be monitored by the treating physician for worsening of symptoms and treated accordingly. If a patient experiences a Grade 3 infusion-related reaction, the administration of MM-151 may resume at the next scheduled dosing visit at the discretion of the treating physician. If a patient experiences a Grade 4 infusion-related reaction, MM-151 should not be administered to the patient at any subsequent visit.

An exemplary embodiment of this schema is set forth below and highlights the activities that the treating physician may undertake if a patient exhibits an infusion-related reaction. These guidelines may be altered at the discretion of the treating physician and/or by the guidelines in place at the medical institution where the administration of MM-151 is being performed.

If a patient exhibits a Grade 1 infusion-related reaction:

- Maintain the infusion rate unless progression of symptoms to \geq Grade 2; if symptoms worsen, refer to the guidelines below.
- Consider treating the patient with additional medication with diphenhydramine 25-50 mg p.o. or i.v. and/or methylprednisolone 125 mg (or equivalent) i.v.
- Monitor the patient every 15 minutes for worsening of condition.

If a patient exhibits a Grade 2 infusion-related reaction:

- Interrupt the infusion and, at the discretion of the treating clinician, disconnect the infusion tubing from the patient.

- Administer additional medication with diphenhydramine 25-50 mg p.o. or i.v. and/or methylprednisolone 125 mg (or equivalent) i.v.
- Monitor the patient every 15 minutes for worsening of condition (preferably until symptoms resolve).
- After recovery from symptoms, resume the infusion rate at 50% of the previous rate and if no further symptoms appear, increase rate stepwise until the infusion is completed.
- If Grade 2 symptoms recur, disconnect the infusion tubing from patient and do not restart the infusion.
- If all symptoms have resolved after 7 days, the patient may be administered MM-151 at the next scheduled dosing visit.
- If symptoms worsen to \geq Grade 3 at any time, follow the guidelines below.

If a patient exhibits a Grade 3 infusion-related reaction:

- Interrupt the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine 25-50 mg i.v.
- Administer 1) normal saline 2) epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) subcutaneous (s.q.) or intramuscular (i.m.) and 3) bronchodilators (nebulized albuterol 2.5-5 mg in 3 mL of saline), as medically indicated.
- Consider additional medication with methylprednisolone 125 mg (or equivalent) i.v.
- Monitor the patient every 15 minutes for worsening of condition (preferably until symptoms resolve).
- If the symptoms improve and the patient is discharged, advise patient to seek emergency treatment and notify the treating clinician if the infusion reaction symptoms recur after discharge from the clinic.
- Depending on the severity and persistence of the reaction, the treating physician may consider administration of MM-151 at the next scheduled dosing visit.

If a patient exhibits a Grade 4 infusion-related reaction:

- Interrupt the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine 50 mg i.v.

- Administer 1) normal saline 2) epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) s.q. or i.m. and 3) bronchodilators (nebulized albuterol 2.5-5 mg in 3 mL of saline), as medically indicated.
- Consider additional medication with methylprednisolone (or equivalent) i.v. up to 0.5 mg/kg Q 6h) to prevent recurrent or ongoing reactions.
- Monitor the patient every 15 minutes for worsening of condition (preferably until symptoms resolve).
- Consider hospital admission for observation.
- Do not re-administer MM-151 to the patient.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims. Any combination of the embodiments disclosed in the any plurality of the dependent claims or Examples is contemplated to be within the scope of the disclosure.

INCORPORATION BY REFERENCE

The disclosure of each and every U.S. and foreign patent and pending patent application and publication referred to herein is specifically incorporated herein by reference in its entirety, as are the contents of Sequence Listing and Figures.

.

CLAIMS

What is claimed is:

1. A method of treating a cancer in a human patient, the method comprising administering an oligoclonal mixture of anti-EGFR antibodies to the patient, wherein the method comprises intravenously administering the oligoclonal mixture of anti-EGFR antibodies in at least one treatment cycle, the at least one cycle comprising:

an initial two week treatment cycle consisting of a first week and a second week, wherein a first dose of the oligoclonal mixture of anti-EGFR antibodies is administered during the first week at a rate of X mg/hour for a first ½ hour, immediately followed by a rate of 2X mg/hour for a second ½ hour, immediately followed by a rate of 4X mg/hour until all of the first dose has been administered and a second dose, that is greater than or equal to the first dose, is administered during the second week;

wherein administration, at each rate subsequent to the first ½ hour, is optionally one or more of: delayed, altered or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate.

2. The method of claim 1, wherein the patient exhibits an adverse reaction to the administration at the preceding rate and the alteration comprises an interruption of administration, and:

- i) the patient is treated for symptoms of the adverse reaction at the discretion of an attending clinician, and
- ii) following treatment of the symptoms, the administration is resumed at a rate lower than or equal to the rate at which the administration was interrupted.

3. The method of claim 2, wherein, in ii) the administration is resumed at half the rate at which the administration was interrupted.

4. The method of any of claims 1-3, wherein the second dose is administered at a rate of X mg/hour for a first ½ hour, immediately followed by a rate of 2X mg/hour for a second ½ hour,

immediately followed by a rate of 4X mg/hour for a third $\frac{1}{2}$ hour, immediately followed by a rate of 8X mg/hour until all of the second dose has been administered;

wherein administration at each rate of the second dose is optionally either delayed or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate or of the preceding dose.

5. The method of claim 4, wherein, if the patient tolerates the initial cycle, the at least one cycle further comprises at least one subsequent treatment cycle, each subsequent treatment cycle comprising at least one administration of the oligoclonal mixture of anti-EGFR antibodies at a third dose.

6. The method of claim 5, wherein the third dose is greater than or equal to the second dose and is greater than the first dose.

7. The method of claim 6, wherein the third dose of the oligoclonal mixture of anti-EGFR antibodies is administered at a rate of 2X mg/hour for a first $\frac{1}{2}$ hour, immediately followed by a rate of 4X mg/hour for a second $\frac{1}{2}$ hour, immediately followed by a rate of 8X mg/hour for a third $\frac{1}{2}$ hour, immediately followed by a rate of 16X mg/hour until all of the third dose has been administered;

wherein administration at each rate of the third dose is optionally either delayed or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate or of the preceding dose.

8. The method of claim 7, wherein X is 25.

9. The method of claim 1, wherein the first dose is about 225 mg or is about 3 mg/kg.

10. The method of claim 1, wherein the second dose is about 450 mg or is about 6 mg/kg.

11. The method of claim 5, wherein the at least one subsequent treatment cycle has a duration of three weeks or four weeks.

12. The method of claim 11, wherein the at least one subsequent treatment cycle has a duration of four weeks, and the third dose is administered on day 1 of each week of the four week treatment cycle.

13. The method of claim 11, wherein the at least one subsequent treatment cycle has a duration of four weeks, and the third dose is administered during the first week and the third week of each four week cycle.

14. The method of claim 11, wherein the at least one subsequent treatment cycle has a duration of three weeks, and the third dose of the oligoclonal mixture of anti-EGFR antibodies is administered during week 1 of each three week cycle.

15. The method of claim 1, wherein the oligoclonal mixture of anti-EGFR antibodies consists of anti-EGFR antibodies that specifically bind to two or more different epitopes of the extracellular domain of EGFR.

16. The method of claim 15, wherein the two or more different epitopes is three different epitopes.

17. The method of claim 16, wherein the oligoclonal mixture of anti-EGFR antibodies that specifically bind to three different epitopes of the extracellular domain of EGFR is MM-151bio, optionally MM-151.

18. The method of claim 17, wherein the oligoclonal mixture of anti-EGFR antibodies comprises 3 anti-EGFR antibodies, wherein the 3 anti-EGFR antibodies comprise a first antibody with a heavy chain comprising SEQ ID NO:1 and a light chain comprising SEQ ID NO:2; a second antibody with a heavy chain comprising SEQ ID NO:3 and a light chain comprising SEQ ID NO:4; and a third antibody with a heavy chain comprising SEQ ID NO:5 and a light chain comprising SEQ ID NO:6.

19. The method of claim 18, wherein the third dose of the oligoclonal mixture of anti-EGFR antibodies is 4.5 mg/kg, 6 mg/kg, 7.5 mg/kg, 9 mg/kg, 10 mg/kg, 10.5 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 18 mg/kg, and 20 mg/kg; and is administered weekly, bi-weekly or tri-weekly.

20. The method of claim 17, further comprising co-administration of at least one dose of a topoisomerase inhibitor during the initial two week treatment cycle, optionally wherein, if the patient tolerates the initial cycle, the at least one cycle further comprises at least one subsequent treatment cycle, each subsequent treatment cycle comprising at least one administration of the oligoclonal mixture of anti-EGFR antibodies at a third dose.

21. The method of claim 20, wherein the topoisomerase inhibitor is co-administered during the initial two week treatment cycle, and during that cycle is co-administered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

22. The method of claim 21, wherein the topoisomerase inhibitor is administered during the at least one subsequent treatment cycle, and during each subsequent cycle is coadministered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

23. The method of claim 20, wherein the topoisomerase inhibitor is a topoisomerase I inhibitor.

24. The method of claim 23, wherein the topoisomerase I inhibitor is a camptothecin.

25. The method of claim 24, wherein the camptothecin is irinotecan HCl or liposomal irinotecan, optionally liposomal irinotecan sucrosolate.

26. The method of claim 20, wherein each cycle of the at least one subsequent treatment cycle is a four week treatment cycle and the third dose of the oligoclonal mixture of anti-EGFR antibodies and the topoisomerase inhibitor are each administered during day one of week one and day one of week three of the four week treatment cycle, optionally wherein, in each cycle of

co-administration, the topoisomerase inhibitor is administered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

27. The method of claim 20, wherein each cycle of the at least one subsequent treatment cycle is a four week treatment cycle and the topoisomerase inhibitor is administered on day one of week one of each four week treatment cycle and the third dose of the oligoclonal mixture of anti-EGFR antibodies is administered weekly.

28. The method of claim 27, wherein, in each cycle of co-administration, the topoisomerase inhibitor is administered prior to administration of the oligoclonal mixture of anti-EGFR antibodies.

29. A method of treating a cancer in a human patient, the method comprising one or more administrations by infusion of an oligoclonal mixture of anti-EGFR antibodies to the patient, wherein, prior to each administration of the oligoclonal mixture of anti-EGFR antibodies, a pretreatment comprising an effective amount of:

1) drug 1: a histamine H1 blocker,

and an effective amount of one, or of each of both, of:

2) drug 2: an anti-inflammatory steroid, and

3) drug 3: acetaminophen,

is administered to the patient.

30. The method of claim 29, wherein the one or both of 2) and 3) are both of 2) and 3)

31. The method of claim 29, wherein the effective amount of each of 1) and one or both of 2) and 3) are all administered to the patient 30-60 minutes prior to the infusion of the oligoclonal mixture of anti-EGFR antibodies.

32. The method of claim 29, wherein 2) is dexamethasone or methylprednisolone.

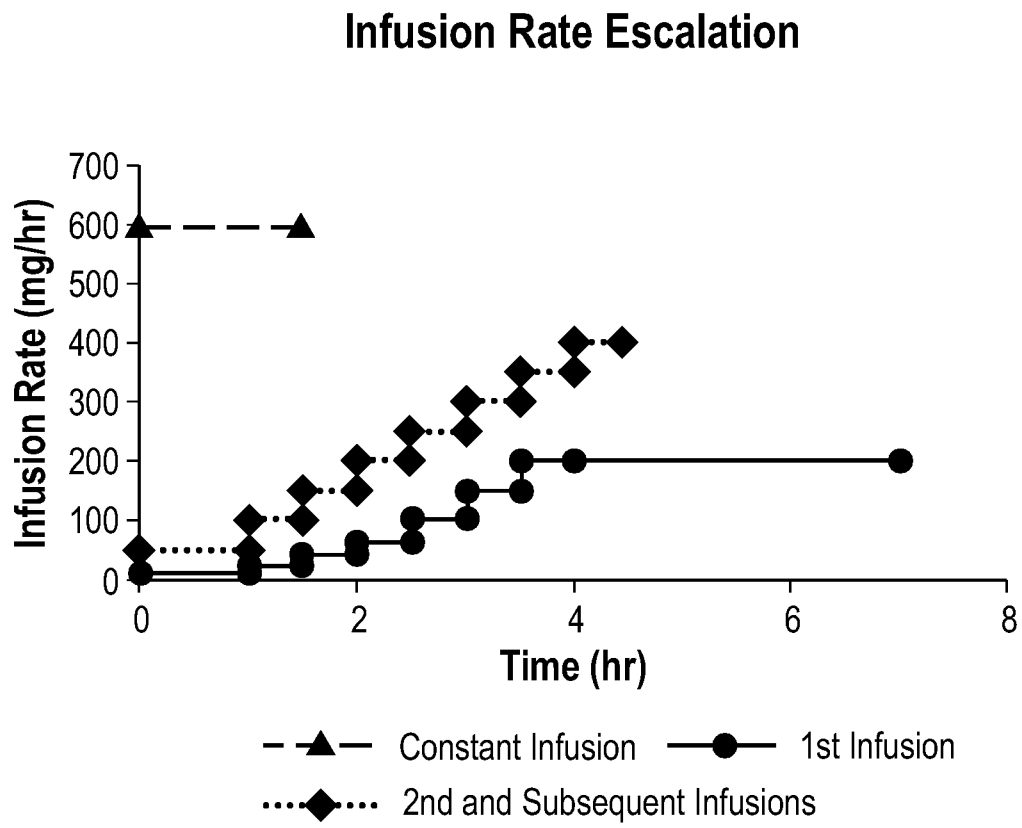
33. The method of claim 32, wherein the dexamethasone is administered to the patient at a dose of 5, 10, 15, 20 or 25 mg, or the methylprednisolone is administered to the patient at a dose of 25, 50, 75, 100, or 125 mg.
34. The method of claim 33, wherein 2) is methylprednisolone.
35. The method of claim 29, wherein 1) is diphenhydramine.
36. The method of claim 35, wherein the diphenhydramine is administered at a dose of 25 mg to 50 mg.
37. The method of claim 36, wherein the 25 mg to 50 mg is 25 mg or 50 mg.
38. The method of any one of claims 29 to 37, wherein, if the patient develops an infusion reaction in response to an infusion of the oligoclonal mixture of anti-EGFR antibodies, an effective amount of one or both of 1) and 2) is re-administered when the infusion reaction is observed.
39. The method of any one of claims 1-28, wherein the treatment of the patient results in a response classified as PR or CR.
40. The method of any one of claims 1-28, wherein the treatment of the patient results in a response classified as SD.
41. The method of claim 17, wherein the oligoclonal mixture of anti-EGFR antibodies comprises 3 anti-EGFR antibodies, wherein the 3 anti-EGFR antibodies comprise:
- i) a first antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 7, 8 and 9 respectively, and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 10, 11 and 12 respectively;
 - ii) a second antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 13, 14 and 15 respectively and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 16, 17, and 18 respectively; and

iii) a third antibody comprising heavy chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 19, 20 and 21 respectively, and light chain CDRs 1, 2 and 3 set forth in SEQ ID NOs: 22, 23 and 24 respectively.

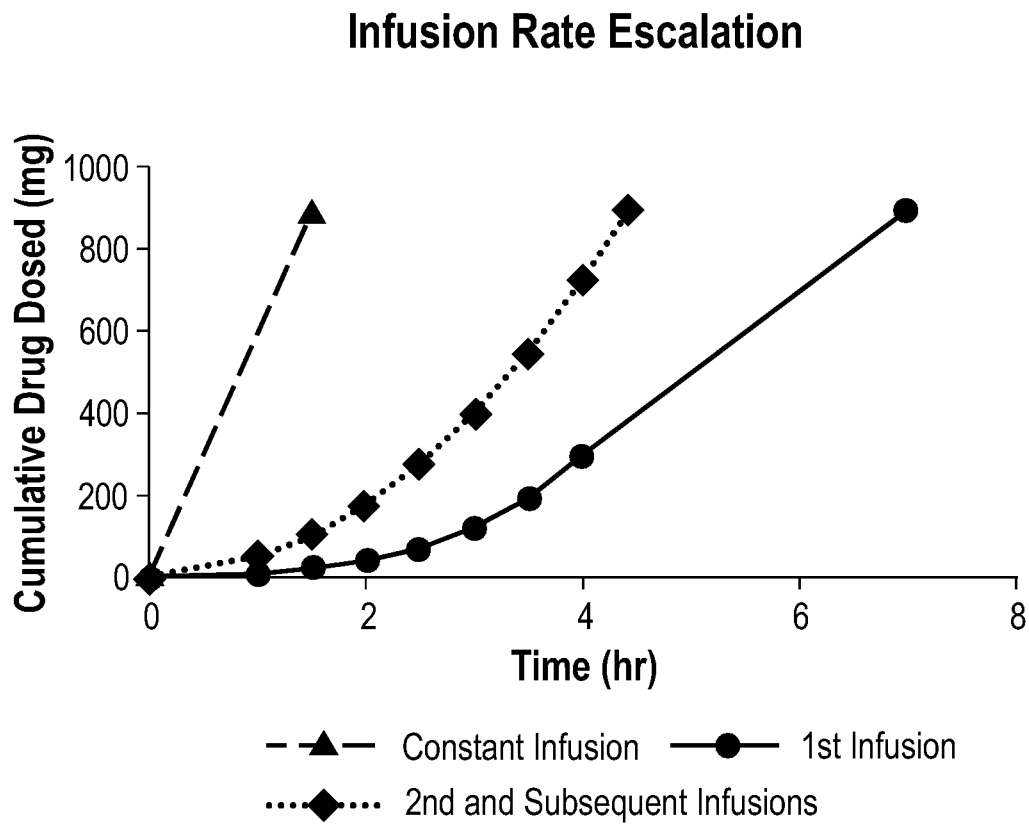
42. The method of claim 18 or 41, wherein the antibodies are IgG antibodies, optionally IgG1 antibodies.

43. The method of claim 41, wherein the antibodies bind the extracellular domain of EGFR.

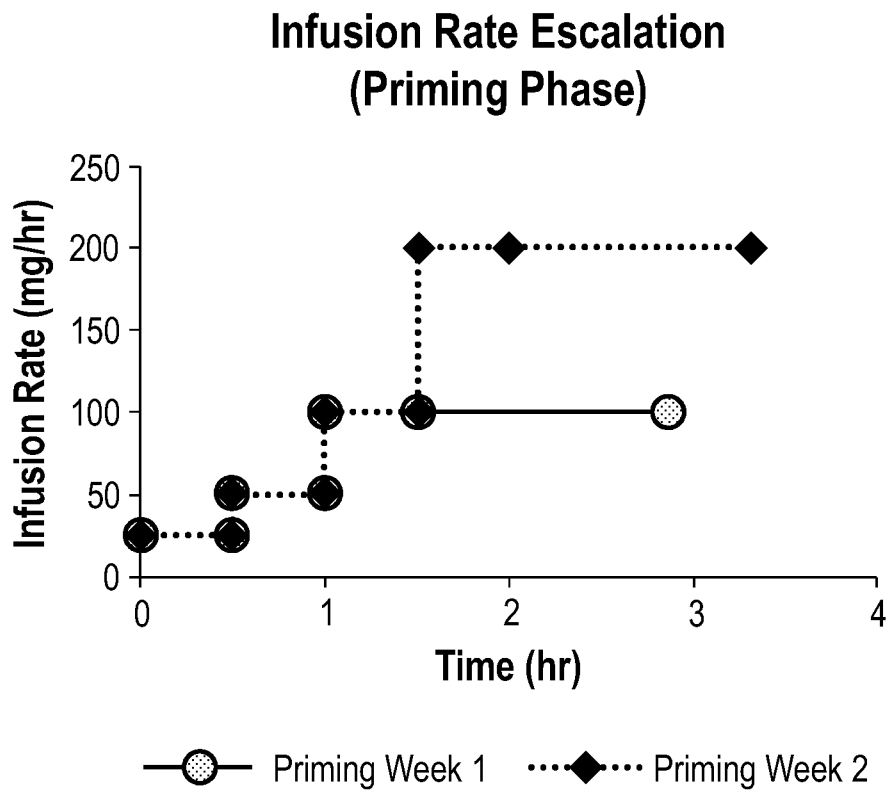
1/8

**Figure 1A**

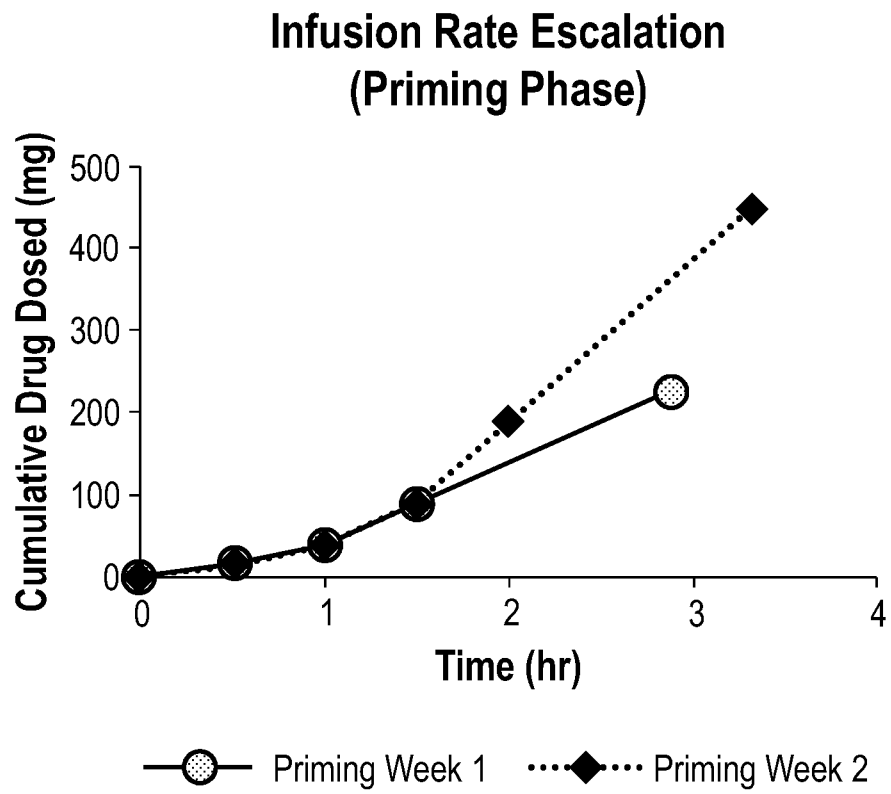
2/8

**Figure 1B**

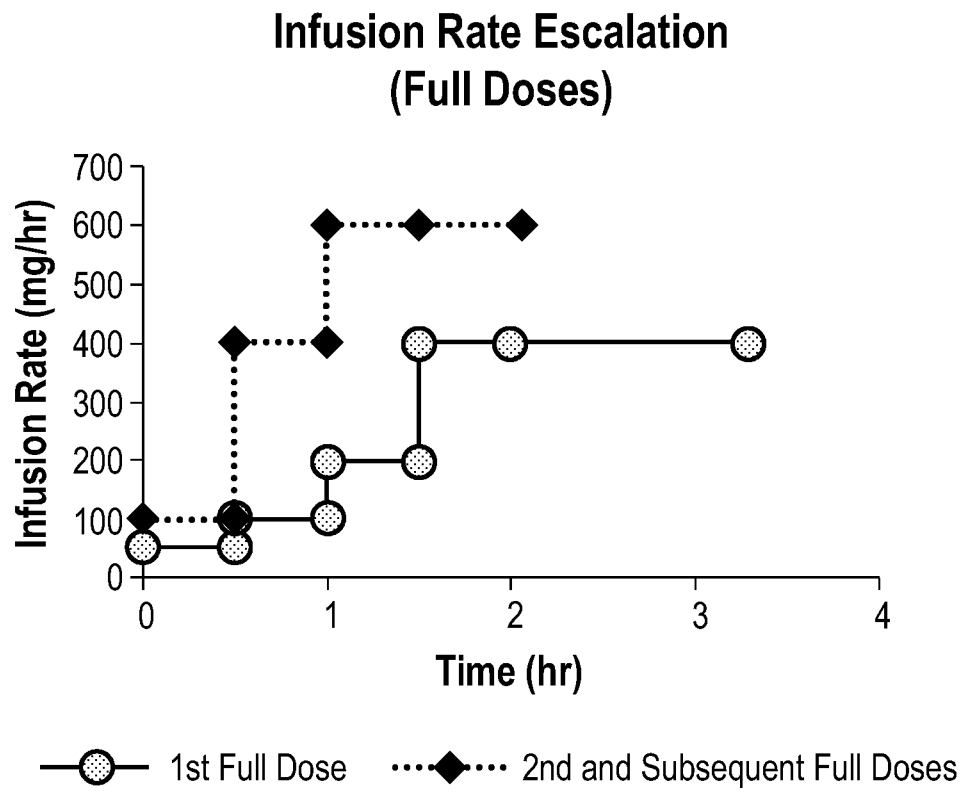
3/8

**Figure 2A**

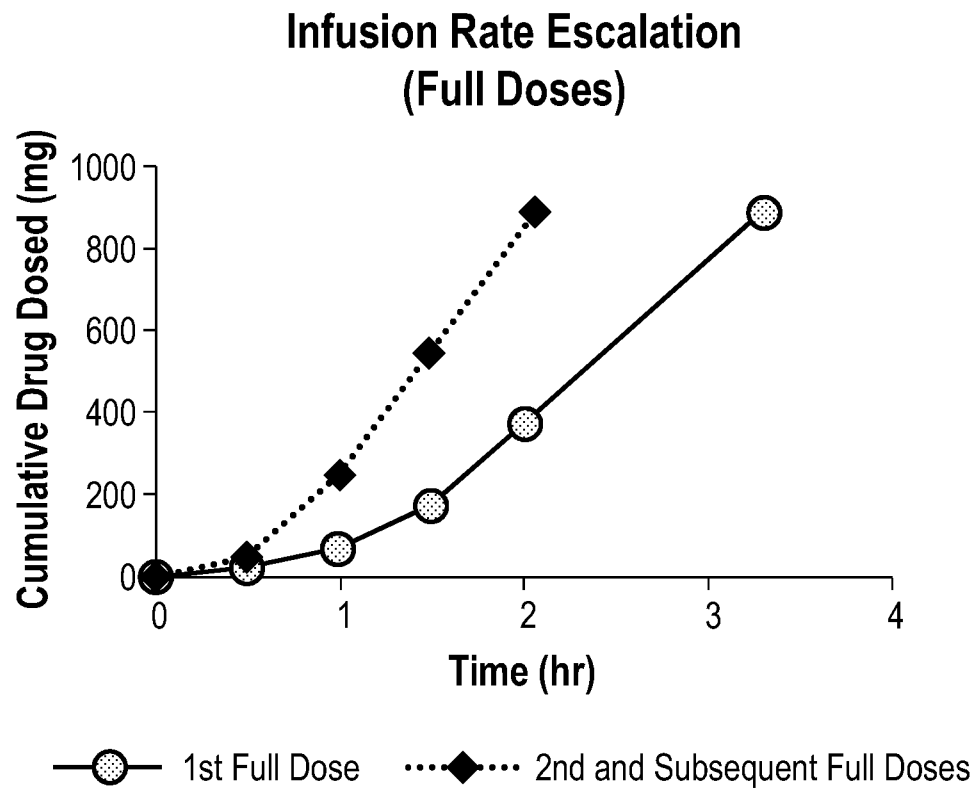
4/8

**Figure 2B**

5/8

**Figure 2C**

6/8

**Figure 2D**

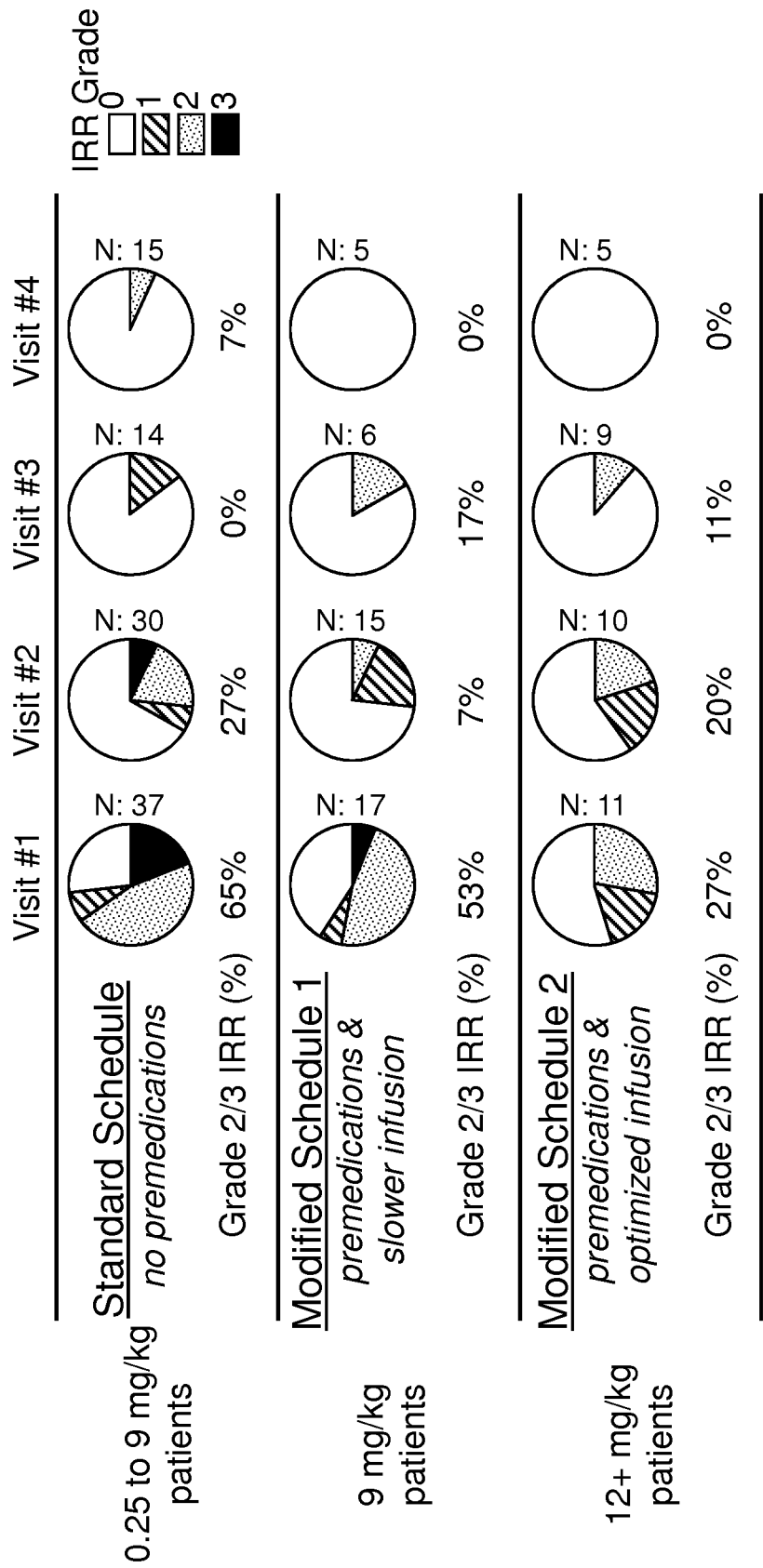
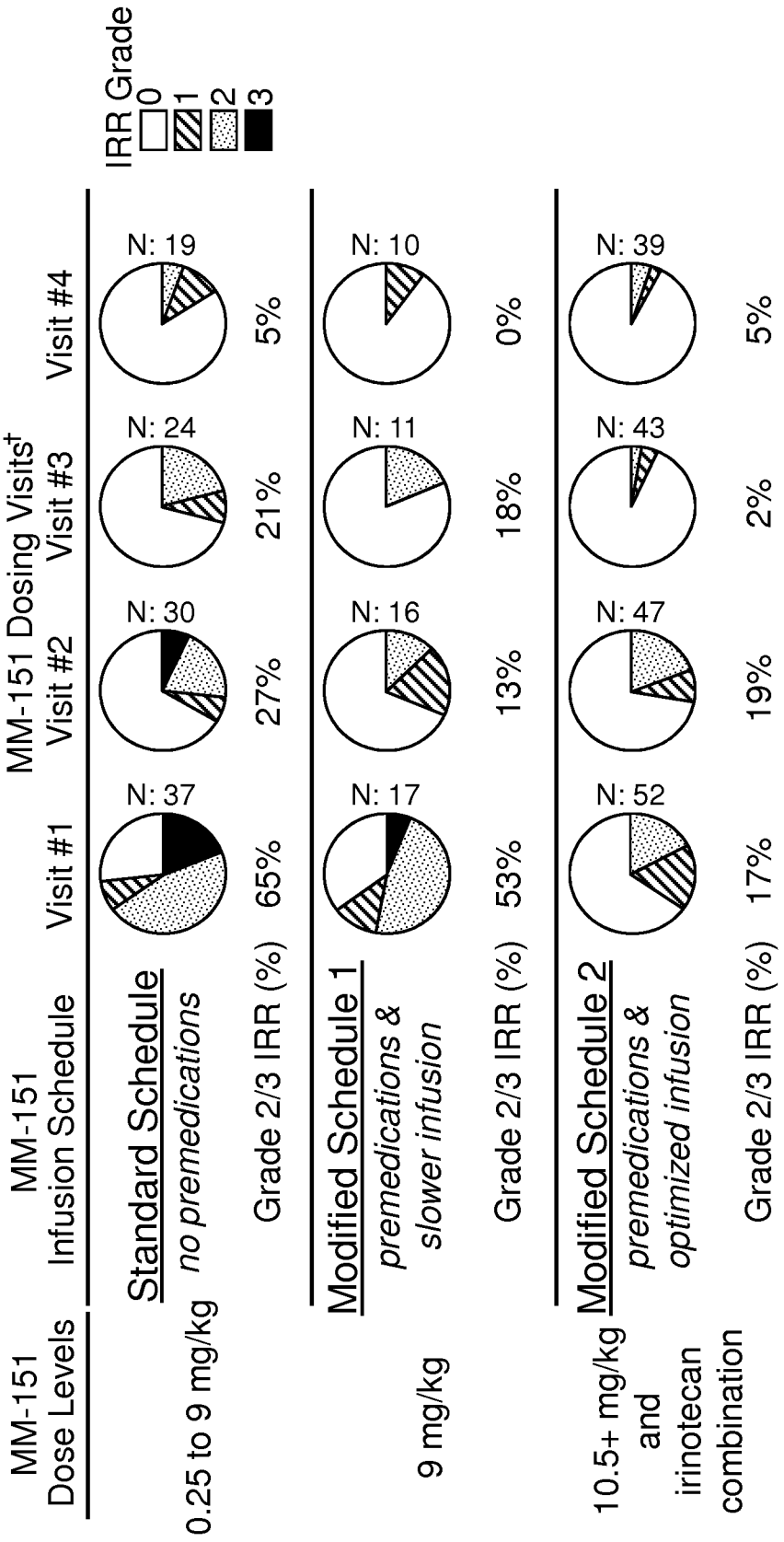


Figure 3



[†]If MM-151 was not administered on a scheduled dosing visit, that visit is not counted in the numbering of visits #2-4.

Figure 4

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/030870

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/28 C07K16/30 A61K39/395 A61K45/06 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 C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NIAL TEBBUTT ET AL: "Targeting the ERBB family in cancer: couples therapy", NATURE REVIEWS CANCER, vol. 13, 1 September 2013 (2013-09-01), pages 663-673, XP055204985,	1-17
Y	page 670-671, section "Combination of two or more antibodies"; Table 3 -----	18-28
X	R. DIENSTMANN ET AL: "Phase I trial of the first-in-class EGFR antibody mixture, Sym004, in patients with advanced solid tumors.", J CLIN ONCOL, vol. 29, no. suppl, 1 January 2011 (2011-01-01), page 3089, XP055205005,	1-17
Y	the whole document ----- -/--	18-28



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 July 2015

Date of mailing of the international search report

12/10/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Luyten, Kattie

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/030870

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L. G. PAZ-ARES ET AL: "Phase I Pharmacokinetic and Pharmacodynamic Dose-Escalation Study of RG7160 (GA201), the First Glycoengineered Monoclonal Antibody Against the Epidermal Growth Factor Receptor, in Patients With Advanced Solid Tumors", JOURNAL OF CLINICAL ONCOLOGY, vol. 29, no. 28, 1 October 2011 (2011-10-01), pages 3783-3790, XP055205026, ISSN: 0732-183X, DOI: 10.1200/JCO.2011.34.8888 whole document, especially the Abstract; page 3784, right-hand column, first full paragraph	1-28
Y	----- DORTE L. NIELSEN ET AL: "Re-treatment with cetuximab in patients with severe hypersensitivity reactions to cetuximab. Two case reports.", ACTA ONCOLOGICA, vol. 45, no. 8, 1 January 2006 (2006-01-01), pages 1137-1138, XP055205065, ISSN: 0284-186X, DOI: 10.1080/02841860600871764 whole document, especially Table 1	1-28
Y	----- WO 2013/006547 A2 (MERRIMACK PHARMACEUTICALS INC [US]; ADIMAB LLC [US]; BUKHALID RAGHIDA) 10 January 2013 (2013-01-10) page 38, lines 38-43; SEQ ID NOs 19-24	1-28
X,P	----- M. BEERAM ET AL: "329 A first-in-human study evaluating the safety and pharmacology of MM-151, a novel oligoclonal anti-EGFR antibody combination in patients with refractory solid tumors", EUROPEAN JOURNAL OF CANCER, vol. 50, 1 November 2014 (2014-11-01), page 107, XP055204873, ISSN: 0959-8049, DOI: 10.1016/S0959-8049(14)70455-1	1-17, 20-28
Y,P	the whole document	18,19
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/030870

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	M. Beeram ET AL: "329 A first-in-human study evaluating the safety and pharmacology of MM-151, a novel oligoclonal anti-EGFR antibody combination in patients with refractory solid tumors", 26th EORTC - NCI - AACR Symposium on Molecular Targets and Cancer Therapeutics, 20 November 2014 (2014-11-20), XP055204976, Retrieved from the Internet: URL: http://www.merrimackpharma.com/sites/default/files/documents/MM151Ph1EORTC2014.pdf [retrieved on 2015-07-28]	1-17, 20-28
Y,P	whole document, especially the Abstract; section "Management of Infusion Related Reactions" -----	18,19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/030870

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-28

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-28

A method of treating a cancer in a human patient, the method comprising administering an oligoclonal mixture of anti-EGFR antibodies to the patient, wherein the method comprises intravenously administering the oligoclonal mixture of anti-EGFR antibodies in at least one treatment cycle, the at least one cycle comprising: an initial two week treatment cycle consisting of a first week and a second week, wherein a first dose of the oligoclonal mixture of anti-EGFR antibodies is administered during the first week at a rate of X mg/hour for a first 1/2 hour, immediately followed by a rate of 2X mg/hour for a second 1/2 hour, immediately followed by a rate of 4X mg/hour until all of the first dose has been administered and a second dose, that is greater than or equal to the first dose, is administered during the second week; wherein administration, at each rate subsequent to the first 1/2 hour, is optionally one or more of: delayed, altered or not carried out if the patient exhibits an adverse reaction to the administration at the preceding rate.

2. claims: 29-43

A method of treating a cancer in a human patient, the method comprising one or more administrations by infusion of an oligoclonal mixture of anti-EGFR antibodies to the patient, wherein, prior to each administration of the oligoclonal mixture of anti-EGFR antibodies, a pretreatment comprising an effective amount of: 1) drug 1: a histamine H1 blocker, and an effective amount of one, or of each of both, of: 2) drug 2: an anti-inflammatory steroid, and 3) drug 3: acetaminophen, is administered to the patient.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/030870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013006547 A2	10-01-2013	AU 2012279132 A1	14-03-2013
		CA 2840088 A1	10-01-2013
		CN 103781494 A	07-05-2014
		EP 2729172 A2	14-05-2014
		HK 1197071 A1	02-01-2015
		JP 2014522850 A	08-09-2014
		KR 20140048230 A	23-04-2014
		TW 201313739 A	01-04-2013
		US 2012308576 A1	06-12-2012
		US 2014127207 A1	08-05-2014
		US 2014170668 A1	19-06-2014
		US 2014234314 A1	21-08-2014
		WO 2013006547 A2	10-01-2013

摘要

本申请公开了一种优化患者(如癌症患者)对抗-EGFR 疗法的治疗反应的方法，以及患者通过接受抗-EGFR 疗法预防或改善输液反应的方法。