(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2012 (14.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/079093 A2

(51) International Patent Classification:
A61K 39/395 (2006.01) *A61K 47/48* (2006.01)

(21) International Application Number:
PCT/US2011/064496

(22) International Filing Date:
12 December 2011 (12.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/421,992 10 December 2010 (10.12.2010) US

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(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, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: DOSAGE AND ADMINISTRATION OF BISPECIFIC SCFV CONJUGATES

(57) **Abstract**: Disclosed are methods for the therapeutic administration of bispecific scFv conjugates as single doses at at least weekly intervals. In certain embodiments the conjugate is MM-111 and is administered at intervals of every two weeks or every three weeks. In other embodiments a single loading dose of MM-111 is administered to a human patient followed at at least weekly intervals by a least a single maintenance dose of MM- 111. The loading dose is larger than the maintenance dose.

WO 2012/079093 A2

DOSAGE AND ADMINISTRATION OF BISPECIFIC SCFV CONJUGATES

FIELD OF THE INVENTION

Provided are methods for the administration of therapeutic bispecific scFv conjugates in which a mutated human serum albumin linker is covalently bonded to distinct amino and carboxy terminal single-chain Fv molecules (scFvs).

BACKGROUND OF THE INVENTION

Antibody-like binding moieties (including those in intact antibodies, antibody fragments, and engineered antibody fragments such as scFvs) are often used for therapeutic applications. Antibody fragments such as scFvs generally exhibit shorter serum half lives than intact antibodies, and in some therapeutic applications increased in vivo half lives would be desirable for therapeutic agents possessing the functionality of such fragments / scFvs.

Human serum albumin (HSA) is a protein of about 66,500 kD and is comprised of 585 amino acids including at least 17 disulphide bridges. As with many of the members of the albumin family, human serum albumin plays an important role in human physiology and is located in virtually every human tissue and bodily secretion. HSA has the ability to bind and transport a wide spectrum of ligands throughout the circulatory system, including the long-chain fatty acids, which are otherwise insoluble in circulating plasma.

A bispecific scFv HSA conjugate designated MM-111 (also referred to as B2B3-1) is described in copending US patent application 12/757,801, and PCT publication number WO2009/126920, each of which is incorporated herein by reference in its entirety. MM-111 is currently undergoing clinical trials, including an open-label Phase 1-2 and pharmacologic study of MM-111 in patients with advanced, refractory HER2 positive cancers, and an open-label Phase 1-2 trial of MM-111 in combination with trastuzumab (HERCEPTIN) in patients with advanced HER2 positive breast cancer. The ErbB2/ErbB3 (ErbB2/3) oncogenic heterodimer is the most potent ErbB receptor pairing with respect to strength of interaction, impact on receptor tyrosine phosphorylation, and effects on downstream signaling through mitogen activated protein kinase and phosphoinositide-3 kinase pathways. ErbB3 signaling has become recognized as an important mechanism of resistance to ErbB2 (HER-2) targeted agents (such as trastuzumab) in clinical use. In ErbB2 HIGH disease states resistance to directed therapies is driven by heregulin/ErbB3 signaling. Current ErbB2-targeted therapies do not effectively inhibit heregulin activated ErbB2/3. Preclinically combinations of MM-111 (inhibiting heregulin activation of ErbB2/3 without blocking ErbB2) with trastuzumab (targeting ErbB2) provide complete inhibition.

MM-111 specifically targets the ErbB2/ErbB3 heterodimer and abrogates ligand binding. In preclinical models of HER-2+ gastric, breast, ovarian and lung cancers, MM-111 inhibits ligand-induced ErbB3 phosphorylation, cell cycle progression, and tumor growth.

SUMMARY OF THE INVENTION

Provided are methods of administering bispecific scFv conjugates in which an bispecific scFv is covalently bonded to amino and carboxy terminal binding moieties that are first and second single-chain Fv molecules (scFvs). An exemplary bispecific scFv conjugate of this type is MM-111 (B2B3-1). MM-111 is a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:1. MM-111 comprises first and second binding moieties that are single-chain Fv molecules: the first binding moiety specifically binds ErbB3 and the second binding moiety specifically binds ErbB2. Dosage units comprising fixed amounts of MM-111 are also provided. In accordance with the invention, bispecific scFv conjugates such as MM-111 are administered at at least weekly intervals (e.g., weekly or biweekly) at a dose of at least 20 mg/kg. In certain embodiments an initial loading dose that is equal to or greater than 120% of the weekly or biweekly dose is administered at the onset of therapeutic treatment with the bispecific scFv conjugate.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows MM-111 serum concentration levels obtained in patients treated with 3, 6, 12, or 20 mg/kg of MM-111. A preclinical PK/PD model relating [drug] to tumor growth inhibition was used to select the EC80 as a target clinical trough level (Cmin). A clinical population-PK model indicates that a 20 mg/kg maintenance dose reaches or exceeds this target in 80% of the patients by week 3 of treatment. A loading dose of 25 mg/kg is predicted to achieve the target in week 1. X Axis =Serum concentration (mg/L). Y axis = Weeks 0, 2, 4, and 6.

Figure 2 shows a clinical trial enrollment and response summary.

Figure 3 shows MM-111 cardiac safety data in the form of a graph showing changes in mid-ejection fraction (n=8) as determined from ECGs. No clinically significant abnormalities were observed.

DETAILED DESCRIPTION

Methods and Compositions

Provided are methods of administering MM-111.

In certain aspects a first method is provided for the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, comprising administering an effective amount MM-111 to the patient at an interval measured in days, the method comprising: administering to the patient a single loading dose of at least 20 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a single maintenance dose of MM-111, wherein the maintenance dose is smaller than the loading dose. In other aspects the preceding method is one wherein the maintenance dose is at least 5 mg/kg less than

the loading dose. In other aspects the preceding methods are methods wherein the at least seven day intervals are intervals of every 10 days. In other aspects the preceding methods are methods wherein the at least seven day intervals are intervals of every 14 days. In other aspects the preceding methods are methods wherein the at least seven day intervals are intervals of every 18 days. In other aspects the preceding methods are methods wherein the at least seven day intervals are intervals of every 21 days.

In certain aspects the first method is one wherein the at least seven day intervals are intervals of a number of days indicated by a top number, the loading dose of at least 20 mg/kg of MM-111 is a dose in mg/kg indicated by a middle number, and the maintenance dose of MM-111 smaller than the loading dose is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

In certain aspects a second method is provided for the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, comprising administering an effective amount MM-111 to the patient, the method comprising: administering to the patient a single initial dose of at least 15 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a subsequent dose of MM-111 which is the same as the initial dose. In other aspects the preceding second method is one wherein the dose is about 20 mg/kg. In other aspects the preceding second method is one wherein the dose is about 30 mg/kg. In other aspects the preceding second method is one wherein the dose is about 44 mg/kg. In other aspects the preceding second method is one wherein the dose is about 75 mg/kg. In other aspects the preceding second method is one wherein the dose is about 105 mg/kg.

In certain aspects the second method is one wherein the at least seven day intervals are intervals of a number of days indicated by a top number and the dose of at least 15 mg/kg of MM-111 is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

In certain aspects a composition A is provided for use in the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, said composition comprising MM-111 for administration to the patient at an interval measured in days, as a single loading dose of at least 20 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a single maintenance dose of MM-111, wherein the maintenance dose is smaller than the loading dose. In certain aspects a composition B is provided which is composition A wherein the maintenance dose is at least 5 mg/kg less than the loading dose. In certain aspects composition A or composition B is one wherein the at least seven day intervals

are intervals of every 10 days. In certain aspects composition A or composition B is one wherein the at least seven day intervals are intervals of every 14 days.

In certain aspects composition A or composition B is one wherein the at least seven day intervals are intervals of every 18 days. In certain aspects composition A or composition B is one wherein the at least seven day intervals are intervals of every 21 days.

In certain aspects composition A is a composition wherein the at least seven day intervals are intervals of a number of days indicated by a top number, the loading dose of at least 20 mg/kg of MM-111 is a dose in mg/kg indicated by a middle number, and the maintenance dose of MM-111 smaller than the loading dose is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

In an additional aspect, a composition C is provided for use in the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, said composition comprising MM-111 for administration to the patient at an interval measured in days as a single initial dose of at least 15 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a subsequent dose of MM-111 which is the same as the initial dose. In an additional aspect of composition C, the dose is about 20 mg/kg. In an additional aspect of composition C, the dose is about 30 mg/kg. In an additional aspect of composition C, the dose is about 44 mg/kg. In an additional aspect of composition C, the dose is about 75 mg/kg. In an additional aspect of composition C, the dose is about 105 mg/kg.

In an additional aspect of composition C, the at least seven day intervals are intervals of a number of days indicated by a top number and the dose of at least 15 mg/kg of MM-111 is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

Kits and Unit Dosage Forms

Further provided are kits that include a pharmaceutical composition containing MM-111 including a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods. The kits include instructions to allow a practitioner (e.g., a physician, nurse, or patient) to administer the composition contained therein to treat an ErbB2 expressing cancer.

Preferably, the kits include multiple packages of the single-dose pharmaceutical composition(s) containing an effective amount of MM-111 for a single administration in accordance with the methods provided above. Optionally, instruments or devices necessary for administering the pharmaceutical composition(s) may be included in the kits. For instance, a kit

may provide one or more pre-filled syringes containing an amount of MM-111 that is about 100 times the dose in mg/kg indicated for administration in the above methods. Such unit dosage forms preferably contain about 2g, about 3g, about 4.4g, about 7.5g or about 10.5g.

Furthermore, the kits may also include additional components such as instructions or administration schedules for a patient suffering from a disease or condition (e.g., a cancer, autoimmune disease, or cardiovascular disease) to use the pharmaceutical composition(s) containing an bispecific scFv, or any binding, diagnostic, and/or therapeutic agent conjugated thereto.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, methods, and kits of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

EXAMPLES

The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

Example 1: *Mode of Administration of MM-111*

MM-111 is prepared as a formulation containing 25 mg/ml MM-111 in a sterile aqueous solution comprising 20 mM L-histidine hydrochloride, 150 mM sodium chloride, pH 6.5, which is stored at 2-8°C.

MM-111 must be brought to room temperature prior to administration. Containers (e.g., vials) of MM-111 must not be shaken. The appropriate quantity of MM-111 is removed from the container, diluted in 250 mL of 0.9% normal saline and administered as an infusion using a low protein binding in-line filter (preferably a 0.22 micrometer filter).

MM-111 is initially administered over about 90 minutes (first administration). In the absence of an infusion reaction, subsequent doses are administered over about 60 minutes.

A patient's body weight at the start of a dosing cycle is to be used to calculate the dose used throughout the cycle. Should a patient's body weight change by more than 10%, a new total dose is calculated to reflect this change.

Example 2: *Dosage and Administration of MM-111*

Preferred plasma concentrations of MM111 achieved during treatment are at least 106 mg/L. It has now been discovered that certain combinations of dose frequency and dosage will achieve and maintain this plasma concentration during the course of treatment in at least half, and preferably in more than 60%, 70% or 80% of treated patients.

In certain embodiments a higher initial dose (loading dose - LD) is given, followed as defined intervals by at least one maintenance dose (MD). Intervals of dosing in days are typically indicated as QxD, wherein x represents an integer, so that a QxD of 7 indicates dosing every 7 days. Table 1A, Table 1B, and Table 1C below show doses and dosing intervals of the invention. In Table 1A, Table 1B, and Table 1C the indicated loading doses are optional – initial doses are preferably made at the indicated loading dose (LD), but may (e.g., as directed or at the physician's discretion) be made at the maintenance dose (MD). Table 1A provides a set of exemplary dosing intervals, loading doses and maintenance doses. Table 1B provides a variation of Table 1A allowing for dosage variability (indicated as "about") of up to +/- 3 mg/mL. Table 1C appears below and provides a more extensive set of exemplary dosing intervals, loading doses and maintenance doses. In each cell of Table 1A, Table 1B, and Table 1C, the top figure is the integer x in the interval QxD (e.g., 18 as the top figure in a cell indicates a dosing interval of Q18D or every 18 days), the middle figure represents the (optional) loading dose (LD) in mg/kg, and the bottom figure represents the maintenance dose (MD) in mg/kg. Thus the top cell in Table 1A indicates a dosing interval (QxD) of once every seven days, a loading dose (optional) of 25 mg per kg of patient body weight, and a maintenance dose of 20 mg per kg of patient body weight; while the cell furthest to the right on the top row of Table 1C indicates a dosing interval (QxD) of once every seven days, a loading dose (optional) of 30 mg per kg of patient body weight, and a maintenance dose of 15 mg per kg of patient body weight.

Table 1A

7 25 20
7 40 30
14 60 45
14 90 75
21 120 105

Table 1B

7 about 25 about 20
7 about 40 about 30
14 about 60 about 44
14 about 90 about 75
21 about 120 about 105

Table 1C

7 10 5	7 15 5	7 20 5	7 25 5	7 30 5	7 15 10	7 20 10	7 25 10	7 30 10	7 35 10	7 20 15	7 25 15	7 30 15
7 35 15	7 40 15	7 25 20	7 30 20	7 35 20	7 40 20	7 45 20	7 30 25	7 35 25	7 40 25	7 45 25	7 50 25	7 55 25
7 60 25	7 65 25	14 35 30	14 40 30	14 45 30	14 50 30	14 55 30	14 60 30	14 65 30	14 70 30	14 75 30	14 40 35	14 45 35
14 50 35	14 55 35	14 60 35	14 65 35	14 70 35	14 75 35	14 45 40	14 50 40	14 55 40	14 60 40	14 65 40	14 70 40	14 75 40
14 50 45	14 55 45	14 60 45	14 65 45	14 70 45	14 75 45	14 55 50	14 60 50	14 65 50	14 70 50	14 75 50	14 60 55	14 65 55
14 70 55	14 75 55	14 65 60	14 70 60	14 75 60	14 70 65	14 75 65	14 75 70	21 60 55	21 65 55	21 70 55	21 65 60	21 70 60
21 75 60	21 70 65	21 75 70	21 80 75	21 85 80	21 90 85							

Example 3: *Clinical Trial of MM-111*

A first-in-human phase 1-2 study evaluates the safety and tolerability of MM-111 and preliminarily explores efficacy in HER-2+ advanced breast cancer (ABC). The safety data obtained during the Phase 1 dose escalation portion of this study provide the basis of this report.

Methods: Patients (pts) with histologically confirmed HER-2+ advanced solid tumors progressing or recurring on standard therapy; aged ≥ 18 years; ECOG PS < 2 and adequate organ function were eligible for Phase I. Pts with stable CNS lesions were also eligible. A Modified Fibonacci schema was used for dose escalation in Phase I. Primary endpoints for Phase 1 were determination of maximum tolerated dose/maximum feasible dose while secondary endpoints included determination of dose-limiting toxicity, adverse events, and pharmacokinetic (PK) and immunogenicity profiles of MM-111. MM-111 was administered intravenously weekly in 4-week cycles.

Example 4: *Clinical Trial Results - Overview*

12 patients (11 ABC and 1 gastric cancer) were treated: median age 59 (range 36-82), median PS 1 (range 0-1), 11♀:1♂, median number of prior therapies 7 (3-12). A total 19 courses (median 2; range 1-2) of therapy was administered at 4 dose-levels (3 mg/kg, 6 mg/kg, 12 mg/kg and 20 mg/kg respectively). Adverse events (see Example 3) assessed as being at least possibly related to MM-111 included pain (n=1), fatigue (n=3), dyspepsia (n=1), muscle spasms (n=1), heartburn (n=1), infusion reaction (n=1) and nail changes (n=1). There were no treatment interruptions due to adverse events. No dose limiting toxicities were observed and there has been no evidence of cardiotoxicity or immunogenicity to date. PK data indicate dose proportionality at the dose-levels explored and support weekly dosing.

Example 5: *Clinical Trial Results - Safety and Pharmacokinetics*

Patients (pts) with histologically confirmed HER-2+ advanced solid tumors progressing or recurring on standard therapy; aged ≥ 18 years; ECOG PS < 2 and adequate organ function were eligible for Phase I. Pts with stable CNS lesions were also eligible. A Modified Fibonacci schema was used for dose escalation in Phase I. Primary endpoints for Phase 1 were determination of maximum tolerated dose/maximum feasible dose while secondary endpoints included determination of dose-limiting toxicity, adverse events, and pharmacokinetic (PK) and immunogenicity profiles of MM-111. MM-111 was administered intravenously weekly in 4-week cycles.

Primary objectives: Phase 1: To determine the Phase 2 dose based upon either the maximum tolerated dose (MTD) or the maximum feasible dose with HER2-positive solid tumors. Phase 2: To estimate Progression-Free Survival (PFS) in patients with HER2-positive breast cancer progressing on trastuzumab and/or lapatinib

Secondary objectives:

- To describe the dose limiting toxicity of MM-111
- To determine the adverse event profile of MM-111
- To determine the objective response rate of MM-111 in patients with HER2-positive breast cancer in Phase 2
- To determine the Clinical Benefit Rate in Phase 2
- To determine the pharmacokinetic (PK) parameters and immunogenicity of MM-111

Study Design:

- Phase I: standard "3 + 3" design
- 4 dosing cohorts (Amended to include a 5th cohort with loading dose, ongoing)
- Dose escalation decisions are made following a 4-week DLT evaluation period.
- MTD defined as highest dose level in which a DLT is experienced by < 2 patients in a cohort
- Patients receive MM-111 weekly in four week cycles
- Phase II: Dosing at MTD or optimal biologic dose
- Adverse events during Phase 1 and Phase 2 will be graded according to CTCAE v3.0
- Responses will be assessed according to RECIST v1.1

Eligibility:

- Histologically confirmed advanced cancer that is HER2+
- Non-measurable (Phase 1 only) or measurable or disease
- ECOG Performance Status 0 or 1
- Phase 2 only: Prior trastuzumab or lapatinib therapy with progressive disease on or after treatment
- Stable CNS disease requiring no therapy is acceptable
- Normal LVEF
- Normal renal and hepatic function

Table 2. – Results as of May 2011: Demographics

N	**18**
Male/Female	**2/16**
Median Age (Range)	**62 (36-82)**
Tumor types	**Breast = 16** **Gastric = 1** **Lung = 1**
Median # prior systemic therapies (range)	**6 (2-9)**

Table 3 – Results as of May 2011: Dose Levels

Dose (mg/Kg)	Number of Patients
3 mg/kg	3
6mg/kg	3
12mg/kg	3
20 mg/kg	3
25 mg/kg (L) **20 mg/kg (M)**	6

Summary of Adverse Events:

Twelve patients were enrolled at doses up to 20 mg/kg. Six patients were enrolled at a loading dose (L) of 25 mg/kg and a maintenance dose (M) of 20 mg/kg No DLTs have been identified and a Maximum Tolerated Dose has not been reached.

There were no apparent trends in AEs, lab values, ECGs vital signs or effect on cardiac ejection fraction in any of the cohorts, and overall the safety profile has been consistent with the patient population. Twelve patients were tested for the presence of anti-MM-111 and anti-HSA antibodies, and all samples were negative.

Table 4 - Summary of Serious Adverse Events as of May 2011

System Organ Class	Total N = 18 # Patients	# of Patients with ≥ Grade 3 Event
Musculoskeletal and connective tissue disorders	10	1
Gastrointestinal disorders	8	1
General disorders and administration site conditions	10	
Metabolism and nutrition disorders	7	1
Infections and infestations	3	
Injury, poisoning and procedural complications	3	
Neoplasms benign	4	
Nervous system disorders	5	
Investigations	3	
Ear and labyrinth disorders	1	
Blood and lymphatic system disorders	3	
Psychiatric disorders	1	
Renal and urinary disorders	1	
Respiratory	4	1
Skin and subcutaneous tissue disorders	7	

Table 5 – Summary of adverse events assessed as related to MM-111

Event Term	CTCAE Grade	Relationship	Total N = 12 # Patients
Dyspepsia	1	Possible	1
Fatigue	2	Possible	3
Pain	1	Possible	1
Muscle Spasms	1	Possible	1
Heartburn	1	Possible	1
Infusion Reaction	2	Probable	1
Nail Changes	1	Definite	1

5

Table 6 - MM-111 Serum Concentration Levels

COHORT	Value	Cmax (ng/ml)	Tmax (H)	T1/2 (H)	AUC ( )
	N	3	3	3	3
3mg/kg	Median	62.6	1.50	48.78	3269.05
	Min;Max	47.50 : 67.10	1.50:2.00	47.34: 71.18	3060.27 :4753.0
	CV%	17.4	17.3	24.0	25.0
6mg/kg	Median	129.00	2.00	88.75	9751.35
	Min;Max	93.3 : 166.0	1.50 :2.00	53.50: 142.66	5453.63: 12002.1
	CV%	28.1	15.7	47.3	36.7
12mg/kg	Median	288.00	2.00	100.39	20274.60
	Min;Max	184.0 :304.0	1.50 :2.00	97.95: 116.61	11597.80: 23785.
	CV%	25.2	15.7	9.7	33.8
20mg/kg	Median	348.00	4.00	104.34	38216.25
	Min;Max	344.0-522.0	1.5:8.0	103.61-107.95	35136.75 : 48518.
	CV%	25.1	72.9	2.2	17.3
25 mg/kg	N	5	5	5	5
	Median	6.72E+05	1	90	7.69E+07
	Min	5.66E+05	1	84	6.44E+07
	Max	9.80E+05	4	155	1.51E+08

Example 6: *Administration of MM-111 at greater than weekly intervals*

The foregoing results indicate that effective administration of MM-111 can be achieved with dosing at greater than weekly intervals.

Those skilled in the art will recognize, and will be able to ascertain and implement 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 combinations of the embodiments disclosed in the dependent claims are contemplated to be within the scope of the disclosure.

All publications, patent applications, and patents mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication, patent application, or patent was specifically and individually indicated to be incorporated by reference. In particular, U.S. Serial No. 61/421,992 in hereby incorporated by reference in its entirety.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention; can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

What is claimed is:

CLAIMS

1. A method for the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, comprising administering an effective amount MM-111 to the patient at an interval measured in days, the method comprising: administering to the patient a single loading dose of at least 20 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a single maintenance dose of MM-111, wherein the maintenance dose is smaller than the loading dose.

2. The method of claim 1 wherein the maintenance dose is at least 5 mg/kg less than the loading dose.

3. The method of claim 1 or claim 2 wherein the at least seven day intervals are intervals of every 14 days.

4. The method of claim 1 or claim 2 wherein the at least seven day intervals are intervals of every 21 days.

5. A method for the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, comprising administering an effective amount MM-111 to the patient, the method comprising: administering to the patient a single initial dose of at least 10 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a subsequent dose of MM-111 which is the same as the initial dose.

6. The method of claim 5 wherein the dose is about 15 mg/kg.

7. The method of claim 5 wherein the dose is about 20 mg/kg.

8. The method of claim 5 wherein the dose is about 25 mg/kg.

9. The method of claim 5 wherein the dose is about 30 mg/kg.

10. The method of claim 5 wherein the dose is about 35 mg/kg.

11. The method of claim 5 wherein the dose is about 40 mg/kg.

12. The method of claim 5 wherein the dose is about 45 mg/kg.

13. The method of claim 5 wherein the dose is about 50 mg/kg.

14. The method of claim 1 wherein the at least seven day intervals are intervals of a number of days indicated by a top number, the loading dose of at least 20 mg/kg of MM-111 is a dose in mg/kg indicated by a middle number, and the maintenance dose of MM-111 smaller than the loading dose is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

15. The method of claim 5 wherein the at least seven day intervals are intervals of a number of days indicated by a top number and the dose of at least 15 mg/kg of MM-111 is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

16. A composition for use in the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, said composition comprising MM-111 for administration to the patient at an interval measured in days, as a single loading dose of at least 20 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a single maintenance dose of MM-111, wherein the maintenance dose is smaller than the loading dose.

17. The composition of claim 16 wherein the maintenance dose is at least 5 mg/kg less than the loading dose.

18. The composition of claim 16 or claim 17 wherein the at least seven day intervals are intervals of every 10 days.

19. The composition of claim 16 or claim 17 wherein the at least seven day intervals are intervals of every 14 days.

20. The composition of claim 16 or claim 17 wherein the at least seven day intervals are intervals of every 21 days.

21. A composition for use in the treatment of a human patient diagnosed with cancer characterized by expression of ErbB2 receptor, said composition comprising MM-111 for administration to the patient at an interval measured in days as a single initial dose of at least 5 mg/kg of MM-111 followed at at least seven day intervals by at least one administration of a subsequent dose of MM-111 which is the same as the initial dose.

22. The composition of claim 21 where in the dose is about 10 mg/kg.

23. The composition of claim 21 wherein the dose is about 15 mg/kg.

24. The composition of claim 21 wherein the dose is about 20 mg/kg.

25. The composition of claim 21 wherein the dose is about 25 mg/kg.

26. The composition of claim 21 wherein the dose is about 30 mg/kg.

27. The composition of claim 21 wherein the dose is about 35 mg/kg.

28. The composition of claim 21 wherein the dose is about 40 mg/kg.

29. The composition of claim 21 wherein the dose is about 45 mg/kg.

30. The composition of claim 21 wherein the dose is about 50 mg/kg.

31. The composition of claim 16 wherein the at least seven day intervals are intervals of a number of days indicated by a top number, the loading dose of at least 20 mg/kg of MM-111 is a dose in mg/kg indicated by a middle number, and the maintenance dose of MM-111 smaller than the loading dose is a dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

32. The composition of claim 21 wherein the at least seven day intervals are intervals of a number of days indicated by a top number and the dose of at least 5 mg/kg of MM-111 is a

dose in mg/kg indicated by a bottom number in a cell of Table 1C selected from any populated cell of Table 1C.

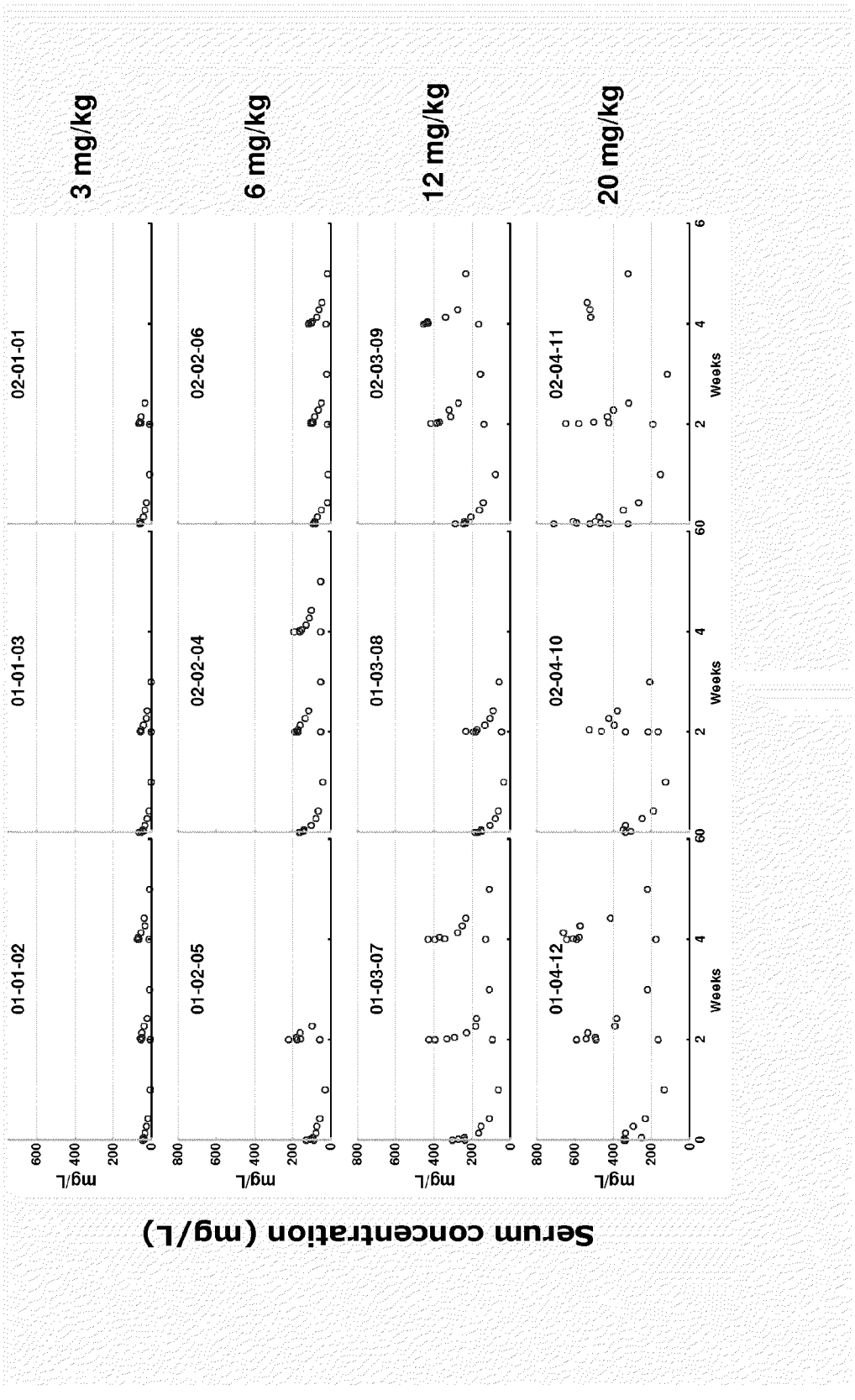
3 mg/kg
6 mg/kg
12 mg/kg
20 mg/kg
01-01-02
01-01-03
02-01-01
01-02-05
02-02-04
02-02-06
01-03-07
01-03-08
02-03-09
01-04-12
02-04-10
02-04-11
Serum concentration (mg/L)
mg/L
Weeks

Figure 1

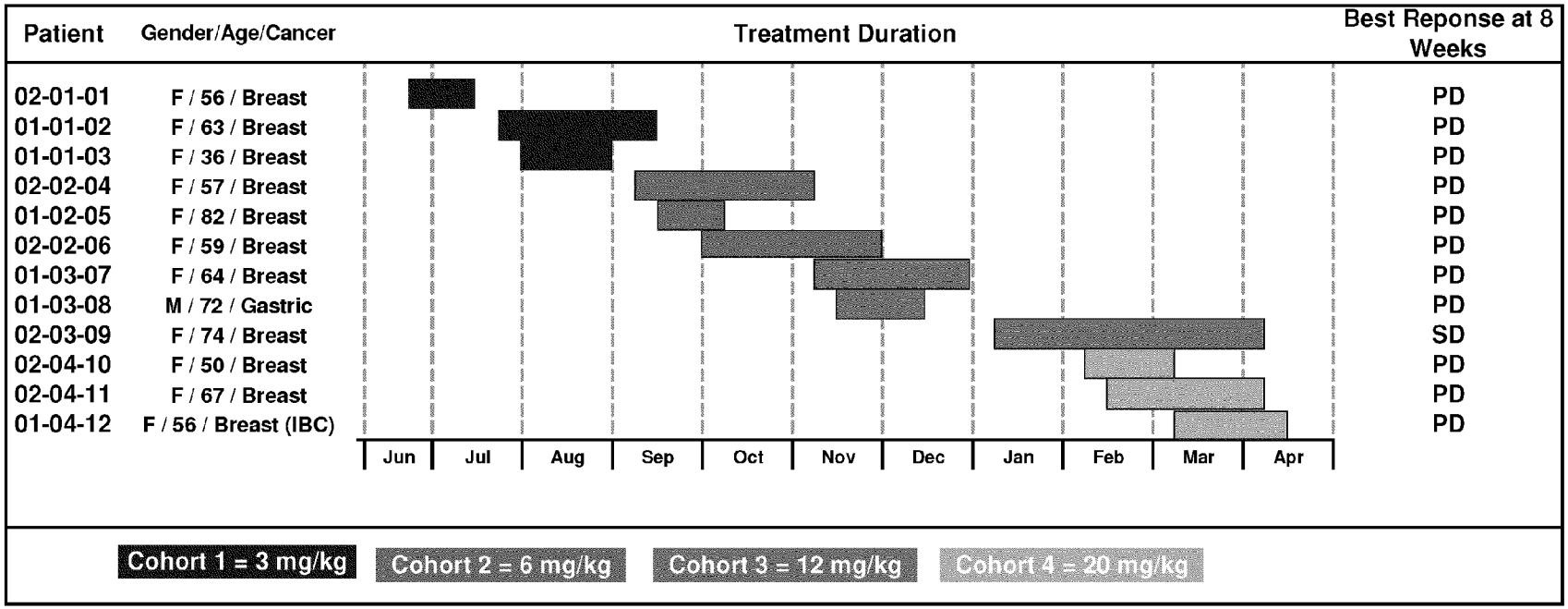

Figure 2

WO 2012/079093 PCT/US2011/064496

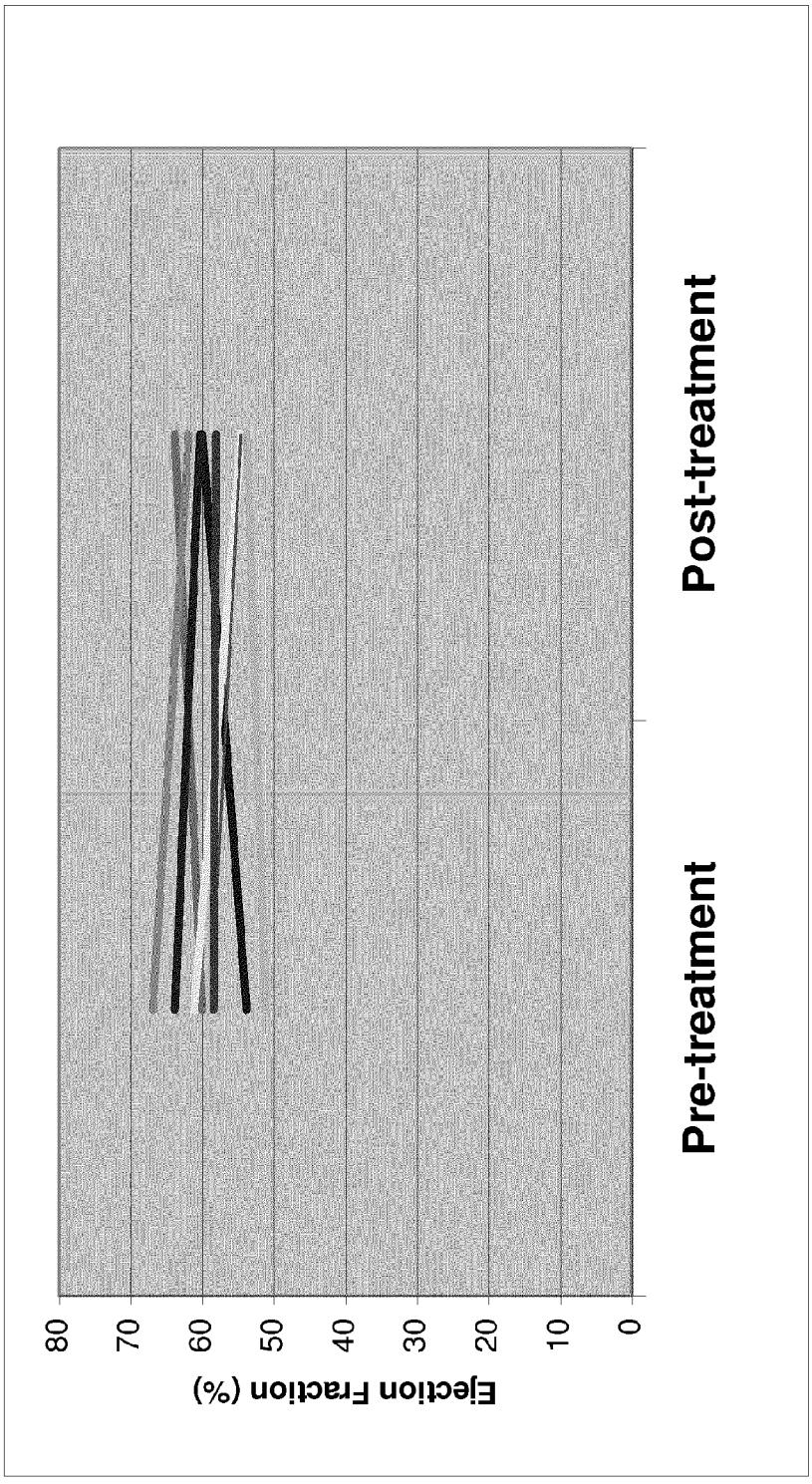
Ejection Fraction (%)
80
70
60
50
40
30
20
10
0
Pre-treatment
Post-treatment

Figure 3

SEQUENCE LISTING

<110> Merrimack Pharmaceuticals, Inc. et al.

<120> DOSAGE AND ADMINISTRATION OF BISPECIFIC SCFV CONJUGATES

<130> 06727/032WO2

<150> 61/421,992
<151> 2010-12-10

<160> 1

<170> PatentIn version 3.5

<210> 1
<211> 1095
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 1

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20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Arg Asp Gly Ser Ala Ser Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Val Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Phe Val Ser Trp Tyr Gln Gln
165 170 175

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His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asp Arg
            180                 185                 190

Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205

Ala Ser Leu Ile Ile Ser Gly Leu Gln Ala Asp Asp Glu Ala Asp Tyr
    210                 215                 220

Tyr Cys Ser Ser Tyr Gly Ser Ser Ser Thr His Val Ile Phe Gly Gly
225                 230                 235                 240

Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ser Asp Ala His Lys Ser
                245                 250                 255

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
            260                 265                 270

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe Glu
        275                 280                 285

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
    290                 295                 300

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
305                 310                 315                 320

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
                325                 330                 335

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
            340                 345                 350

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
        355                 360                 365

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
    370                 375                 380

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
385                 390                 395                 400

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
                405                 410                 415

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
            420                 425                 430

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
        435                 440                 445
```

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
450 455 460

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
465 470 475 480

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
485 490 495

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
500 505 510

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
515 520 525

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
530 535 540

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
545 550 555 560

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
565 570 575

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
580 585 590

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
595 600 605

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
610 615 620

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
625 630 635 640

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
645 650 655

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
660 665 670

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
675 680 685

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
690 695 700

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
705 710 715 720

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
725 730 735

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
740 745 750

Phe Gln Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
755 760 765

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
770 775 780

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
785 790 795 800

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
805 810 815

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
820 825 830

Ala Leu Gly Leu Ala Ala Ala Leu Gln Val Gln Leu Val Gln Ser Gly
835 840 845

Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly
850 855 860

Ser Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Ala Trp Val Arg Gln Met
865 870 875 880

Pro Gly Lys Gly Leu Glu Tyr Met Gly Leu Ile Tyr Pro Gly Asp Ser
885 890 895

Asp Thr Lys Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Val
900 905 910

Asp Lys Ser Val Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Pro
915 920 925

Ser Asp Ser Ala Val Tyr Phe Cys Ala Arg His Asp Val Gly Tyr Cys
930 935 940

Thr Asp Arg Thr Cys Ala Lys Trp Pro Glu Trp Leu Gly Val Trp Gly
945 950 955 960

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Ser Gly
965 970 975

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro
980 985 990

```
Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly
        995                1000                1005

Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp Tyr Gln Gln
    1010                1015                1020

Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asp His Thr Asn
    1025                1030                1035

Arg Pro Ala Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly
    1040                1045                1050

Thr Ser Ala Ser Leu Ala Ile Ser Gly Phe Arg Ser Glu Asp Glu
    1055                1060                1065

Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Tyr Thr Leu Ser Gly Trp
    1070                1075                1080

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
    1085                1090                1095
```