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

(72) Inventor; and

(71) Applicant : **CZIBERE, Akos** [DE/US]; 4 Mead Street, Boston, MA 02134 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ONSUM, Matthew, David** [US/US]; 90 Bynner Street, Jamaica Plain, MA 02130 (US). **NIYIKIZA, Clet** [US/US]; 326 Overlook Lane, Gulph Mills, PA 19428 (US). **MOYO, Victor** [ZW/US]; 1694 Main Street, Apt. #5, Concord, MA 01742 (US). **KUBASEK, William** [US/US]; 165 Fairview Ave., Belmont, MA 02478 (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, 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.

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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))

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27 December 2012

(54) Title: METHODS FOR PREVENTING TOXIC DRUG-DRUG INTERACTIONS IN COMBINATION THERAPIES COMPRISING ANTI-ERBB3 AGENTS

(57) Abstract: Methods are disclosed for preventing toxic drug-drug interactions during combination cancer therapy with a drug that is an anti-ErbB3 agent, such as an anti-ErbB3 antibody, together with a drug that is a tyrosine kinase inhibitor and/or a drug that binds to alpha-1 acid glycoprotein (e.g., erlotinib). Health care practitioners obtaining any one of the drugs are warned that when co-administering the drug that is an anti-ErbB3 agent with either or both of a drug that is a tyrosine kinase inhibitor and a drug that binds to alpha-1 acid glycoprotein, at least one of the co-administered drugs should be administered using a reduced dosage to prevent toxicity. In a reduced dosage, the amount of drug administered per unit time is reduced as compared to a dose that would be administered if the drug was administered as monotherapy. The reduced dosage can be, for example, a reduced drug dose or a reduced drug dosing frequency, or both. Compositions useful in practicing the disclosed methods are also provided.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/036619**A. CLASSIFICATION OF SUBJECT MATTER*****A61K 39/395(2006.01)i, A61K 38/16(2006.01)i, A61K 38/17(2006.01)i, A61P 35/00(2006.01)i***

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 39/395; C07K 16/00; A61K 31/4745; A61K 31/5377

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)
eKOMPASS(KIPO internal) & Keywords: drug-drug interaction, tyrosine kinase inhibitor (TKI), ErbB3 inhibitor, alpha 1-acid glycoprotein binder, MM-121, AMG888, erlotinib, gefitinib**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIRGIT SCHOEBERL et al. 'An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation' Cancer Research, 2010, Vol. 70, No. 6, pp. 2485-2494, ISSN 0008-5472. See abstract; p. 2492.	1-5,9,10,13-20
A	US 2010-0266584 A1 (BIRGIT SCHOEBERL et al.) 21 October 2010 See abstract; paragraphs [0155] and [0234]; claims 1, 12, 13, 17, 20, and 24.	1-5,9,10,13-20
A	US 2006-0293323 A1 (WILLIAM LEON ELLIOTT et al.) 28 December 2006 See abstract; paragraphs [0017], [0024], and [0093].	1-5,9,10,13-20

☐ 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 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

25 OCTOBER 2012 (25.10.2012)

Date of mailing of the international search report

29 OCTOBER 2012 (29.10.2012)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan
City, 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

Choi Sung Hee

Telephone No. 82-42-481-8740



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/036619**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.: 21-46, 49, 50
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 21-46, 49, and 50 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☒ Claims Nos.: 12, 35, 36, 41-45
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:
Claims 12, 35, 36, and 41-45 are unclear, since they refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a).
3. ☒ Claims Nos.: 6-8, 11, 33, 34, 37-40, 46-51
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:

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 fee, this Authority did not invite payment of any additional fee.
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.:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/036619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0266584 A1	21.10.2010	AU 2008-216600 A1 CA 2678181 A1 CN 101674846 A EP 2129396 A2 JP 2010-518820 A KR 10-2010-0014426 A US 2009-0291085 A1 US 2010-0056761 A1 US 2011-0123523 A1 US 7846440 B2	21.08.2008 21.08.2008 17.03.2010 09.12.2009 03.06.2010 10.02.2010 26.11.2009 04.03.2010 26.05.2011 07.12.2010
US 2006-0293323 A1	28.12.2006	US 2004-0067942 A1	08.04.2004