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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.

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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))

(88) Date of publication of the international search report:

27 December 2012

(54) Title: USE OF INHIBITORS OF EGFR-FAMILY RECEPTORS IN THE TREATMENT OF HORMONE REFRACTORY BREAST CANCERS

(57) Abstract: Provided are methods of suppressing growth of hormone refractory breast tumors by contacting tumor cells with an ErbB3 inhibitor, preferably an anti-ErbB3 antibody. Also provided are methods for treating hormone refractory breast cancer in a patient by administering to the patient an inhibitor of heregulin binding to ErbB3 or to ErbB2/ErbB3 heterodimer, which inhibitor is an anti-ErbB3 antibody or an anti-ErbB2 antibody. The treatment methods can further comprise selecting a patient having a hormone refractory breast cancer and then administering the inhibitor to the patient. The treatment methods may also comprise administering an estrogen receptor antagonist, or an aromatase inhibitor to the patient and may at further comprise administering to the patient at least one additional anti-cancer agent that is not an ErbB3 inhibitor, an estrogen receptor antagonist, or an aromatase inhibitor to the patient in combination with the ErbB3 inhibitor.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/32 A61K39/395 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K A61K

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

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

EPO-Internal, WPI Data, EMBASE, BIOSIS, 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	NIE LIN ET AL: "Efficacy of MM121 in ER+ and triple negative breast cancer studies", PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 51, 17 April 2010 (2010-04-17), page 436, XP001537417, ISSN: 0197-016X	1-28,44, 50,53, 54,57-60
Y	abstract	48,49,52
X	WO 2008/100624 A2 (MERRIMACK PHARMACEUTICALS INC [US]; SCHOEBERL BIRGIT [US]; NIELSEN ULR) 21 August 2008 (2008-08-21)	44,50, 53,54, 57-60
Y	claims 2,44,45; example 8	1-28
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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

16 October 2012

Date of mailing of the international search report

07/11/2012

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/028792

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHOEBERL BIRGIT M ET AL: "Computational modeling and simulation lead to the development of MM-121, a human monoclonal antibody ErbB3 antagonist", PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 49, 1 April 2008 (2008-04-01), page 386, XP009125511, ISSN: 0197-016X	44,50, 53,54, 57-60
Y	abstract	1-28
X	SCHOEBERL BIRGIT M ET AL: "MM-121: a human monoclonal antibody ErbB3 antagonist", PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 49, 1 April 2008 (2008-04-01), page 944, XP009125512, ISSN: 0197-016X	44,50, 53,54, 57-60
Y	abstract	1-28
X,P	WO 2011/112953 A2 (MERRIMACK PHARMACEUTICALS INC [US]; MOYO VICTOR [US]; GARCIA GABRIELA) 15 September 2011 (2011-09-15) claims 1, 6, 7, 16, 17, 22-30	1-28,44, 50,53, 54,57-60
X	J. BASELGA ET AL: "Phase II Trial of Pertuzumab and Trastuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer That Progressed During Prior Trastuzumab Therapy", JOURNAL OF CLINICAL ONCOLOGY, vol. 28, no. 7, 1 February 2010 (2010-02-01), pages 1138-1144, XP55029441, ISSN: 0732-183X, DOI: 10.1200/JCO.2009.24.2024 the whole document	45,46, 50,51, 53,54, 57-60
X	HUHALOV ALEXANDRA ET AL: "MM-111: A novel ErbB3 antagonist with potent antitumor activity in ErbB2 over-expressing malignancies", PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AACR, US, vol. 50, 1 April 2009 (2009-04-01), page 1320, XP009145435, ISSN: 0197-016X	44,45, 47,50, 53,54, 56-60
Y	abstract	48,49,52
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/028792

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DENLINGER C.S. ET AL: "A phase I/II and pharmacologic study of MM-111 in patients with advanced refractory (HER2+) cancers", JOURNAL OF CLINICAL ONCOLOGY, vol. 28, no. 15, 20 May 2010 (2010-05-20), XP002684948,	1-28,44, 45,47, 50,53, 54,56-60
Y	the whole document	48,49,52
X	HARMS BRIAN D ET AL: "Application of computational modeling to guide the development of MM-111, a bispecific antibody targeting ErbB3 in ErbB2 overexpressing tumors", PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AACR, US, vol. 50, 1 April 2009 (2009-04-01), page 797, XP009145434, ISSN: 0197-016X abstract	44,45, 47,50, 53,54, 56-60
A	WO 2010/059315 A1 (MERRIMACK PHARMACEUTICALS INC [US]; MCDONAGH CHARLOTTE [US]; FELDHAUS) 27 May 2010 (2010-05-27) sequence 16	56
A	HOLBRO THOMAS ET AL: "The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation.", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 100, no. 15, 22 July 2003 (2003-07-22), pages 8933-8938, XP002684949, ISSN: 0027-8424 the whole document	29-60
T	MCDONAGH CHARLOTTE F ET AL: "Antitumor Activity of a Novel Bispecific Antibody That Targets the ErbB2/ErbB3 Oncogenic Unit and Inhibits Heregulin-Induced Activation of ErbB3", MOLECULAR CANCER THERAPEUTICS, vol. 11, no. 3, March 2012 (2012-03), pages 582-593, XP002684950, ISSN: 1535-7163 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)

☒

 on paper
 - ☒

 in electronic form
 - b. (time)

☐

 in the international application as filed
 - ☐

 together with the international application in electronic form
 - ☒

 subsequently to this Authority for the purpose of search
2.

☒

 In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/028792

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.:

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/US2012/028792

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008100624	A2	21-08-2008	
		AU 2008216600 A1	21-08-2008
		CA 2678181 A1	21-08-2008
		CN 101674846 A	17-03-2010
		CO 6231000 A2	20-12-2010
		CR 11029 A	29-12-2009
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		NZ 579644 A	25-05-2012
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		CN 102282168 A	14-12-2011
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		KR 20110112301 A	12-10-2011
		US 2011059076 A1	10-03-2011
		US 2012003221 A1	05-01-2012
		WO 2010059315 A1	27-05-2010

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

Claims relating to ErbB3 inhibitors, in particular ErbB3 inhibitory antibodies for the treatment of hormone refractory breast cancers

2. claims: 29-60

Claims relating to antibodies inhibiting the binding of heregulin to ErbB2/ErbB3 for the treatment of hormone refractory estrogen-receptor positive cancers
