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- (71) **Applicant:** REGENERON PHARMACEUTICALS, INC. [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).
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- (74) **Agent:** COTTINGHAM, Frank; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (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, 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, PA, 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))
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- with sequence listing part of description (Rule 5.2(a))

- (88) **Date of publication of the international search report:**  
27 June 2013



WO 2013/048883 A3

(54) **Title:** ANTI-ERBB3 ANTIBODIES AND USES THEREOF

(57) **Abstract:** The present invention provides antibodies that bind to ErbB3 and methods of using same. According to certain embodiments of the invention, the antibodies are fully human antibodies that bind to human ErbB3. In certain embodiments, the antibodies of the present invention block the interaction of ErbB3 with an ErbB3 ligand such as neuregulin 1. The antibodies of the invention are useful for the treatment of various cancers.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2012/056446

A. CLASSIFICATION OF SUBJECT MATTER  
 INV. C07K16/32 A61K39/395  
 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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 2007/077028 A2 (U3 PHARMA AG [DE] ; AMGEN INC [US] ; ROTHE MI KE [DE] ; TREDER MARTIN [DE] ) 12 July 2007 (2007-07-12)	1,4, 14-17 , 19,20, 22-24, 26,27
Y	the whole document -----	5,6
X	wo 2008/100624 A2 (MERRIMACK PHARMACEUTICALS INC [US] ; SCHOEBERL BI RGIT [US] ; NI ELSEN ULR) 21 August 2008 (2008-08-21)	1, 14-17 , 19,20, 22-24, 26,27
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X	wo 2011/044311 A2 (MERCK SHARP & DOHME [US] ; ZHANG NINGYAN [US] ; HUBER HANS [US] ) 14 April 2011 (2011-04-14)	1, 14-17 , 19,20, 22-24, 26,27
Y	the whole document -----	5,6

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 <b>29 April 2013</b>	Date of mailing of the international search report <b>07/05/2013</b>
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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 <b>Perez-Mato, Isabel</b>
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/056446

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	wo 2011/076683 AI (ROCHE GLYCART AG [CH] ; BOSSENMAI ER BI RGIT [DE] ; DIMOUDIS NI KOLAOS [DE] ) 30 June 2011 (2011-06-30) the whol e document	5,6
Y	SCH0EBERL BI RGIT ET AL: "An ErbB3 anti body, MM-121, is acti ve in cancers with ligand-dependent acti vati on" , CANCER RESEARCH , AACR, US PHI LADELPHIA, PA, vol . 70, no. 6, 15 March 2010 (2010-03-15) , pages 2485-2494, XP002581703 , ISSN: 1538-7445 , DOI : 10.1158/0008-5472 .CAN-09-3145 [retri eved on 2010-03-09] the whol e document	5,6
Y	G SALA ET AL: "An ErbB-3 anti body, MP-RM-1, inhi bits tumor growth by blocki ng ligand-dependent and independent acti vati on of ErbB-3/Akt signal ing" , ONCOGENE, vol . 31, no. 10, 8 August 2011 (2011-08-08) , pages 1275-1286, XP055042235 , ISSN: 0950-9232 , DOI : 10.1038/onc. 2011 .322 the whol e document	5,6
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/056446

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	<p>AURISICCHIO L. , MARRA E. , ROSCILLI G. ,  MANCINI R. , CI LIBERTO G. : "The promi se of  anti -ErbB3 mono cl onal s as new cancer  therapeuti cal s" ,  ONCOTARGET,  vol . 3, no. 8, 10 August 2012 (2012-08-10)  , pages 744-758, XP002690058,  the whol e document</p> <p style="text-align: center;">-----</p>	<p>1,4-6,  14-17 ,  19,20,  22-24,  26,27</p>
Y, P	<p>w0 2011/136911 A2 (AVEO PHARMACEUTICALS  INC [US] ; VINCENT SYLVIE [US] ; WINSTON  WILLIAM M) 3 November 2011 (2011-11-03)</p> <p>the whol e document</p> <p style="text-align: center;">-----</p>	<p>1,4-6,  14-17 ,  19,20,  22-24,  26,27</p>
Y, P	<p>LUIGI AURISICCHIO ET AL: "Novel  anti -ErbB3 mono cl onal anti bodi es show  therapeuti c effi cacy i n xenografted and  spontaneous mouse tumors" ,  JOURNAL OF CELLULAR PHYSIOLOGY,  29 December 2011 (2011-12-29) , pages  n/a-n/a, XP055017238,  ISSN: 0021-9541 , DOI : 10. 1002/jcp. 24037  the whol e document</p> <p style="text-align: center;">-----</p>	<p>1,4-6,  14-17 ,  19,20,  22-24,  26,27</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2012/056446

## 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. :

I (completely) ; 4-6, 14-17, 19, 20, 22-24, 26, 27 (partially)

### 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 (completely) ; 4-6, 14-17 , 19, 20, 22-24, 26, 27 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3 and blocks its binding to NRG1 with an IC50 of less than 30  $\mu$ M in an ELISA at 25°C.

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2. claims : 2 (completely) ; 4-6, 14-17 , 19, 20, 22-24, 26, 27 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3 and inhibits at least 65% of NRG1-induced phosphorylation of Akt in tumor cells in vitro.

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3. claims : 3 (completely) ; 4-6, 14-17 , 19, 20, 22-24, 26, 27 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3 and reduces NRG1-induced tumor cell growth in vitro by at least 60% when combined with an inhibitor of EGFR2 or ErbB2.

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4. claims : 7-28 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3, wherein said antibody or fragment compete for binding to ErbB3 with an antibody of SEQ ID NOs:306 and 314.

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5. claims : 7-28 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3, wherein said antibody or fragment compete for binding to ErbB3 with an antibody of SEQ ID NOs:322 and 330.

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- 6-967 . claims : 9-28 (partially)

directed to an isolated antibody or antigen-binding fragment thereof that specifically binds ErbB3, wherein said antibody or fragment comprises (a) the CDRs of the heavy chain variable region having a sequence of SEQ ID NOs: 2, 8, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 466 and 482: and (b) the CDRs of a light chain variable region having an amino acid sequence selected from the group

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122,  
138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314,  
330, 346, 362, 378, 394, 410, 428, 442, 458, 474 and 490, in  
all their possible combinations

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/056446

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/056446

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