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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, 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.
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[Continued on next page]

(54) Title: METHODS USING MONOVALENT ANTIGEN BINDING CONSTRUCTS TARGETING HER2

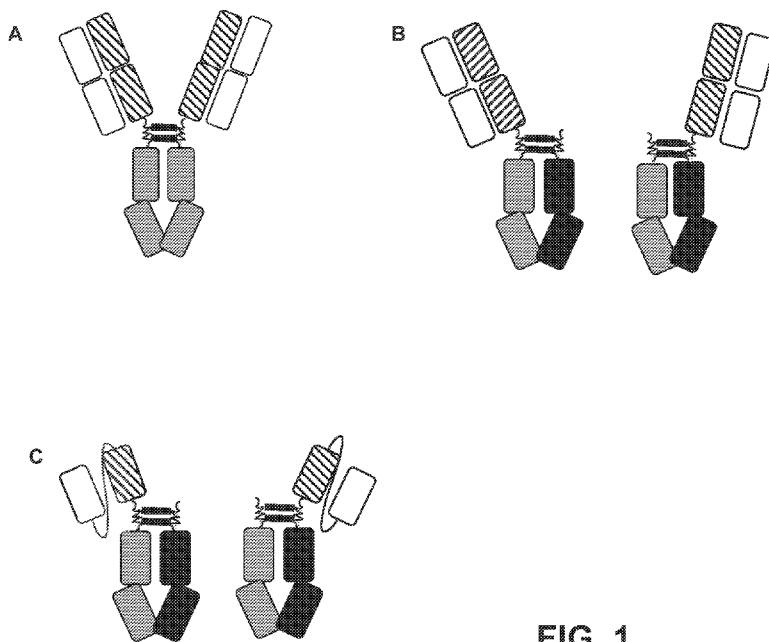


FIG. 1

(57) Abstract: Provided herein are methods of use and treatment using a first or a first and second monovalent antigen-binding constructs targeting HER2. The monovalent antigen-binding constructs can include at least one antigen-binding polypeptide comprising a heavy chain variable domain, wherein the antigen-bind polypeptide specifically binds HER2; and a heterodimeric Fc, the Fc comprising at least two CH3 sequences, wherein the Fc is coupled, with or without a linker, to the antigen-binding polypeptide.





**Declarations under Rule 4.17:**

— *of inventorship (Rule 4.17(iv))*

**Published:**

— *with international search report (Art. 21(3))*

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

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

29 October 2015

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US2014/065571

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC(8) - A61K-39/395 (2015.01)  
 CPC - A61K-39/39558 (2015.01)  
 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)  
 IPC(8) - A61K 39/395; C07K 14/705, 16/00, 16/30; C12P 21/08 (2015.01)  
 USPC - 424/133.1, 138.1, 178.1; 506/9; 536/23.53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 CPC - A61K 39/39558, 2039/505; C07K 16/00, 2317/64, 2317/526, 2317/732 (2015.01) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 Orbit, Google Patents, Google Scholar, Google  
 Search terms used: monovalent, antigen-binding construct, polypeptide, dimeric Fc, extracellular domain, HER2, cancer, human epidermal growth factor

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category*    | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.                              |
|--------------|---|--|
| X<br>--<br>Y | US 2009/0226466 A1 (FONG et al) 10 September 2009 (10.09.2009) entire document  | 1-14, 37, 40-42, 45, 46<br>-----<br>38, 39, 43, 44 |
| Y            | MOORE et al. "A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens," MAbs, 01 November 2011 (01.11.2011), Vol. 3, No. 6, Pgs. 546-557. entire document | 38, 43   |
| Y            | TROISE et al. "Differential binding of human immunoagents and Herceptin to the ErbB2 receptor," FEBS Journal, 15 September 2008 (15.09.2008), Vol. 275, No. 20, Pgs. 4967-4979. entire document                             | 39, 44   |

Further documents are listed in the continuation of Box C.

|   |  |
|---|--|
| * Special categories of cited documents:  | "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  |
| "A" document defining the general state of the art which is not considered to be of particular relevance  | "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   |
| "E" earlier application or patent but published on or after the international filing date   | "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 |
| "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) | "&" document member of the same patent family  |
| "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  |  |

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| Date of the actual completion of the international search<br>29 January 2015 | Date of mailing of the international search report<br><b>19 FEB 2015</b> |
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| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Blaine R. Copenheaver<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |
|---|---|

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/065571

**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.: 15-36  
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 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.