Title: COMBINATIONS OF AN ANTI-HER2 ANTIBODY-DRUG CONJUGATE AND CHEMOTHERAPEUTIC AGENTS, AND METHODS OF USE

Abstract: Combinations of the antibody-drug conjugate trastuzumab-MCC-DM1 and chemotherapeutic agents, including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, are useful for inhibiting tumor cell growth, and for treating disorders such as cancer mediated by HER2 and KDR (VEGFR receptor 1). Methods of using such combinations for in vitro, in situ, and in vivo diagnosis, prevention or treatment of such disorders in mammalian cells, or associated pathological conditions, are disclosed.
**INTERNATIONAL SEARCH REPORT**

**PCT/US2009/036608**

### A. CLASSIFICATION OF SUBJECT MATTER

|-------|------------|------------|------------|------------|------------|------------|------------|------------|-----------|

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

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>US 2005/276812 A1 (EBENS ALLEN J JR [US] ET AL) 15 December 2005 (2005-12-15) cited in the application paragraphs [007], [018], [010], [0353], [0469], [0470], [0471]; claims 11-55</td>
<td>1-22, 24-29</td>
</tr>
</tbody>
</table>


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 document 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 of 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

- "I" later document published after the international filing date or priority data 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.
- "B" document member of the same patent family

**Date of the actual completion of the international search**

2 February 2010

**Date of mailing of the international search report**

12/03/2010

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 740-2040, Fax: (+31-70) 740-2016

Authorized officer

Leherte, Chantal
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<tr>
<td>X,P</td>
<td>JUNNILA T ET AL: &quot;515 POSTER Trastuzumab-mertansine (T-DM1) retains all the mechanisms of action (MOA) of trastuzumab and is extremely effective in combination with docetaxel&quot; EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 6, no. 12, 1 October 2008 (2008-10-01), page 163, XP025534579 ISSN: 1359-6349 [retrieved on 2008-10-01] the whole document</td>
<td>1, 8, 24</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

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 fee, 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.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a HER2 dimerization inhibitor antibody.

2. claims: 3(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of an anti-VEGF antibody.

3. claims: 4(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of 5-FU.

4. claim: 5
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of carboplatin.

5. claims: 6(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of lapatinib.

6. claims: 7(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of ABT-869.

7. claims: 8(completely); 1, 11-29(partially)
   a therapeutic combination comprising a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of docetaxel.

8. claim: 9
a therapeutic combination comprising a therapeutically
effective amount of trastuzumab-MCC-DM1, and a
therapeutically effective amount of GDC-0941.

9. claims: 10(completely); 1, 11-29(partially)

a therapeutic combination comprising a therapeutically
effective amount of trastuzumab-MCC-DM1, and a
therapeutically effective amount of GNE-390.

10. claims: 30-32

A method for determining compounds to be used in combination
for the treatment of cancer.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
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<td>US 2009202536 A1</td>
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<td>US 2002001587 A1</td>
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<td>US 2008226659 A1</td>
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