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(54) Title: COMBINATION THERAPY

(57) Abstract: The invention provides for the treatment of diseases or disorders characterized by cells expressing the CD40 membrane glycoprotein. The invention provides methods for the treatment of various diseases or disorders characterized by cells expressing CD40 with a combination of an agent causes the depletion of cells expressing CD40 and a second agent which causes the depletion of cells expressing the CD20 membrane antigen. Pharmaceutical compositions and articles of manufacture such as kits comprising the agents and combinations thereof are also provided.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/08057

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/00, 39/395

US CL : 424/133.1, 138.1, 143.1, 181.1

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)

U.S. : 424/133.1, 138.1, 143.1, 181.1

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)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YE D et al. Augmentation of a humanized anti-HER2 mAb 4D5 induced growth inhibition by a human-mouse chimeric anti-EGF receptor mAb C225. Oncogene. 1999, Vol. 18, pages 731-738.	1-5 and 9-19
Y	MURPHY WJ et al. Antibodies to CD40 prevent Epstein-Barr virus-mediated human B-cell lymphomagenesis in severe combined immune deficient mice given human peripheral blood lymphocytes. Blood. 01 September 1995, Vol. 86, No. 5, pages 1946-1953.	1-5 and 9-19
Y	ILLIDGE T et al. Radioimmunotherapy in the pi-BCL1 B cell lymphoma model: efficacy depends on more than targeted irradiation alone. Cancer Biother Radiopharm. December 2000, Vol. 15 , No. 6, pages 581-591.	1-5 and 9-19
Y	JAKOBSON E et al. Agonistic propeties of anti-B cell antibodies purified on staphylococcal protein A may be due to contaminating protein A. J Immunol Methods. 31 July 1992, Vol. 152, No. 1, pages 49-57.	1-5 and 9-19
T	OTTAIANO A et al. CD40 activation as potential tool in malignant neoplasms. Tumori. September-October 2002, Vol. 88, No. 5, pages 361-366.	1-5 and 9-19

☒ 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 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	Date of mailing of the international search report
07 February 2003 (07.02.2003)	19 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Stephen L. Rawlings, Ph.D. Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZIEBOLD JL et al. Differential effects of CD40 stimulation on normal and neoplastic cell growth. Arch Immunol Ther Exp (Warsz). 2000, Vol. 48, No. 4, pages 225-233.	1-5 and 9-19
Y	Zhou ZH et al. An agonist anti-human CD40 monoclonal antibody that induces dendritic cell formation and maturation and inhbits proliferation of a myeloma cell line. Hybridoma. December 1999, Vol 18, No. 6, pages 471-478.	1-5 and 9-19
Y	Maloney DG et al. IDEC-C2B8: results of a phase I mulitple-does trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Invest. October 1997, Vol. 15, No. 10, pages 3266-3274.	1-5 and 9-19

Continuation of B. FIELDS SEARCHED Item 3:
MEDLINE, WEST: anti-CD20, anti-CD40, C2B8, S2C6, apoptosis, immunotherapy, antibody-mediated therapy, non-Hodgkins lymphoma, synergy, combination therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/08057

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim 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. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation 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 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.: 1-5 and 9-19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-19, drawn to a method for treating a mammal having a neoplastic disorder, wherein said method comprises administering to said mammal a combination of a CD40 specific agent and a CD20 specific agent, and a composition comprising said combination.

Group II, claim(s) 20, drawn to a kit.

Group III, claim(s) 21-30, drawn to a method for a method for treating a mammal having an autoimmune disorder, wherein said method comprises administering to said mammal a combination of a CD40 specific agent and a CD20 specific agent, and a composition comprising said combination.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Claims 1 and 2 are generic to a plurality of distinct species of invention, wherein said neoplastic disease or disorder is selected from the group consisting of (a) lymphoma, (b) myeloma, and (c) leukemia, as set forth in claims 4 and 5, 6 and 7, and 8, respectively.

Claim 21 is generic to a plurality of distinct species of invention, wherein said autoimmune disease or disorder is selected from the group consisting of (d) rheumatoid arthritis and (e) systemic lupus erythrematosus, as set forth in claims 22 and 23, respectively.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of group I is the treatment of mammal having a neoplastic disease by a process comprising administering to the mammal a composition comprising a combination of two agents specific for either CD40 or CD20.

The special technical feature of group II is a kit.

The special technical feature of group III is the treatment of mammal having a autoimmune disease by a process comprising administering to the mammal a composition comprising a combination of two agents specific for either CD40 or CD20.

Accordingly, groups I-III are not linked by the same or corresponding special technical feature so as to form a single general inventive concept.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The special technical feature of each species of invention differs as each disease has a different etiology and pathology, and therefore the species are not so linked as to form a single general inventive concept.