

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/103676 A3

(51) International Patent Classification⁷: **A61K 31/5377**,
A61P 35/00

(21) International Application Number:
PCT/US2003/017565

(22) International Filing Date: 4 June 2003 (04.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/386,622 5 June 2002 (05.06.2002) US

(71) Applicant: **CEDARS-SINAI MEDICAL CENTER**
[US/US]; 8700 Beverly Boulevard, Los Angeles, CA
90048-1865 (US).

(72) Inventor: **AGUS, David, B.**; 522 North Crescent Drive,
Beverly Hills, CA 90210 (US).

(74) Agents: **LEVY, Seth, D.** et al.; Pillsbury Winthrop LLP,
Suite 2800, 725 South Figueroa Street, Los Angeles, CA
90017-5406 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
25 March 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: METHOD OF TREATING CANCER USING KINASE INHIBITORS

(57) **Abstract:** Described herein are methods for treating cancer and other disease conditions in individuals who have either devel-
oped a resistance to conventional tyrosine kinase inhibitor (TKI) therapy or who are non-responsive *ab initio* to conventional TKI
therapy. In various embodiments, the methods include administering to a patient a resistance-surmounting quantity of a TKI on a
weekly or semi-weekly basis. Alternate embodiments of the present invention include a diagnostic method for assessing an indi-
vidual's probability of being resistant to TKI therapy, based upon an expression level of epithelial membrane protein-1 (EMP-1);
one of the genes believed to be responsible for TKI resistance. The methods of the present invention may be particularly useful in
the treatment of lung, breast, prostate, ovarian, brain and colon cancers. The methods of the present invention may be effective in
blocking the HER-2 kinase domain either in addition to or in lieu of blocking the EGFR kinase domain.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/17565

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5377 A61P35/00

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 7 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, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/032155 A (BUNDRED NIGEL JAMES ;UNIV MANCHESTER (GB)) 10 May 2001 (2001-05-10)	2-6, 11, 12, 16-23, 26, 27
Y	page 11, line 17 - line 24 page 26, line 14 - line 16	2-6, 11, 12, 16-23, 26, 27
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 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.

Z document member of the same patent family

Date of the actual completion of the international search

3 September 2003

Date of mailing of the international search report

22 01. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Taylor, G.M.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/17565

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KELLY H C ET AL: "ZD1839 ('IRESSA'), AND ORAL EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR (EGFR-TKI): PHARMACOKINETICS IN A PHASE I STUDY OF PATIENTS WITH ADVANCED CANCER" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 41, March 2000 (2000-03), page 612, XP001011263 ISSN: 0197-016X abstract	2-6,11, 12, 16-23, 26,27
Y		2-6,11, 12, 16-23, 26,27
X	----- SIROTNAK F M ET AL: "EFFICACY OF CYTOTOXIC AGENTS AGAINST HUMAN TUMOR XENOGRAFTS IS MARKEDLY ENHANCED BY COADMINISTRATION OF ZD1839 (IRESSA), AN INHIBITOR OF EGFR TYROSINE KINASE" CLINICAL CANCER RESEARCH, THE ASSOCIATION, DENVER, NJ, US, vol. 6, no. 12, December 2000 (2000-12), pages 4885-4892, XP001014739 ISSN: 1078-0432 abstract	2-6,11, 12, 16-23, 26,27
Y		2-6,11, 12, 16-23, 26,27
P,X	----- SIRONTAK, F M; SHE, Y; LEE, F; CHEN, J; SCHER, H I: "Studies with CWR22 Xenografts in Nude Mice Suggest That ZD1839 May Have a Role in the Treatment of Both Androgen-Dependent and Androgen-independent Human Prostate Cancer" CLINICAL CANCER RESEARCH, vol. 8, no. 12, 2002, pages 3870-3876, XP002253303 abstract	2-6,11, 12, 16-23, 26,27
P,X	----- LORUSSO P M: "Phase I Studies of ZD1839 in Patients With Common Solid Tumours" SEMINARS IN ONCOLOGY, vol. 30, no. I(1), February 2003 (2003-02), pages 21-29, XP009016714 abstract -----	2-6,11, 12, 16-23, 26,27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/17565

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claims 1-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,7-10, 15, 22-25
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:

see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

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 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.:

2-6, 11, 12, 16-23, 26, 27

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 7-10, 15, 22-25

Present claims 1, 7-10, 15 and 22-25 relate to products/methods defined by reference to desirable characteristics or properties, namely

"the treatment of a patient resistant or non-responsive to conventional kinase therapy" (claims 1 and 15);

"a resistance-surmounting quantity of the kinase inhibitor" (claims 1 and 15);

"a pharmaceutically acceptable equivalent thereof" (claims 7 and 22);

"an amount sufficient to block HER-2 kinase in the patient" (claims 8 and 23);

"an amount sufficient to yield a serum concentration of at least about 800 micro-M in the patient" (claims 9 and 24);

"an amount sufficient to block a kinase receptor in the patient other than EGFR or HER-2" (claims 10 and 25).

The claims cover all products/methods having this characteristic or property, whereas the application provides support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT for only a very limited number of such products/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the products/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the treatment of cancer comprising the administration of a kinase inhibitor selected from the named drugs disclosed in claim 7 in the amounts defined in claims 3-5.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 2-6,11,12,16-23,26,27

The use of high-dose kinase inhibitors in the treatment of cancer.

2. claims: 13,14

Screening methods for detecting individuals who are sensitive to kinase inhibitor therapy.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/17565

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0132155	A	10-05-2001	AU 1155901 A	14-05-2001
			BR 0015194 A	18-06-2002
			CA 2389411 A1	10-05-2001
			CN 1387437 T	25-12-2002
			EP 1272188 A2	08-01-2003
			WO 0132155 A2	10-05-2001
			JP 2003513035 T	08-04-2003
			NO 20022065 A	24-06-2002
			ZA 200203431 A	09-12-2002
