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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, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
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KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))
— with sequence listing part of description (Rule 5.2(a))

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

26 July 2018 (26.07.2018)

(54) Title: METHODS AND COMPOSITIONS FOR USE OF THERAPEUTIC T CELLS IN COMBINATION WITH KINASE
INHIBITORS

(57) Abstract: The present disclosure relates to methods, compositions and uses involving immunotherapies and inhibitors of a target
protein tyrosine kinase in which the kinase is not IL-2-inducible T cell kinase (ITK) and/or is selected from Bruton's tyrosine kinase
(BTK), tec protein tyrosine kinase (TEC), BMX non-receptor tyrosine kinase (Etk), TXK tyrosine kinase (TXK) and/or receptor tyro-
sine-protein kinase ErbB4 (ErbB4). The provided methods, compositions and uses include administration of one or more such inhibitor
with another agent, such as an immunotherapeutic agent targeting T cells and/or genetically engineered T cells, such as CAR-expressing
T cells. Also provided are methods of manufacturing engineered cells, cells, compositions, methods of administration, nucleic acids,
articles of manufacture and kits. In some aspects, features of the methods and cells provide for improved activity, efficacy, persistence,
expansion and/or proliferation of T cells for adoptive cell therapy or endogenous T cells recruited by immunotherapeutic agents.



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A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K35/00 C07K14/00 C07K16/28 A61K45/06 A61K31/505
 A61K31/506
 ADD. A61K39/395 A61K35/17
 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 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 practicable, search terms used)
 EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUELLA M ET AL: "The Addition of the BTK Inhibitor Ibrutinib to Anti-CD19 Chimeric Antigen Receptor T Cells (CART19) Improves Responses against Mantle Cell Lymphoma", CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 22, no. 11, 1 June 2016 (2016-06-01), pages 2684-2696, XP002764049, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-15-1527 [retrieved on 2016-01-27]	1-123
Y	the whole document ----- -/--	1-123

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 23 March 2018	Date of mailing of the international search report 20/06/2018
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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 Lechner, Oskar
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PETER SIDAWAY: "Haematological cancer: Ibrutinib supercharges CAR T cells", NATURE REVIEWS CLINICAL ONCOLOGY, vol. 13, no. 4, 16 February 2016 (2016-02-16), pages 204-204, XP055281214, NY, US ISSN: 1759-4774, DOI: 10.1038/nrclinonc.2016.28	1-123
Y	the whole document	1-123
X	M RUELLA ET AL: "Kinase inhibitor ibrutinib to prevent cytokine-release syndrome after anti-CD19 chimeric antigen receptor T cells (CART) for B cell neoplasms", LEUKEMIA., 28 September 2016 (2016-09-28), XP055462077, US ISSN: 0887-6924, DOI: 10.1038/leu.2016.262	1-123
Y	the whole document	1-123
X	Joseph A Fraietta ET AL: "Regular Article IMMUNOBIOLOGY Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia", Blood, 3 March 2016 (2016-03-03), XP055449528, DOI: 10.1182/blood-2015-11-Retrieved from the Internet: URL:http://www.bloodjournal.org/content/bloodjournal/127/9/1117.full.pdf?sso-checked=true [retrieved on 2018-02-08]	1-123
Y	abstract	1-123
X	ANAS YOUNES: "Promising Novel Agents for Aggressive B-Cell Lymphoma", HEMATOLOGY - ONCOLOGY CLINICS OF NORTH AMERICA, vol. 30, no. 6, 1 December 2016 (2016-12-01), pages 1229-1237, XP055462100, US ISSN: 0889-8588, DOI: 10.1016/j.hoc.2016.07.007	1-123
Y	p 1231, 1234-1235	1-123
X	WO 2016/164580 A1 (NOVARTIS AG [CH]; UNIV PENNSYLVANIA [US]; ANGST DANIELA [CH]; BYRD JOH) 13 October 2016 (2016-10-13)	1-123
Y	claims 1-10	1-123
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/064362

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>JOHN C. BYRD ET AL: "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia", NEW ENGLAND JOURNAL OF MEDICINE, THE - NEJM -, 7 December 2015 (2015-12-07), XP055245199, US ISSN: 0028-4793, DOI: 10.1056/NEJMoal509981 abstract</p>	1-123
Y	<p>JAE H. PARK ET AL: "CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date", BLOOD, vol. 127, no. 26, 20 May 2016 (2016-05-20) , pages 3312-3320, XP055449358, US ISSN: 0006-4971, DOI: 10.1182/blood-2016-02-629063 the whole document</p>	1-123
Y	<p>WO 2016/020901 A1 (ACERTA PHARMA BV [NL]) 11 February 2016 (2016-02-11) paragraphs [0022], [0073] - [0075]; claims 1, 11; figures 31-33</p>	1-123
Y	<p>WO 2015/083008 A1 (ACERTA PHARMA BV [NL]) 11 June 2015 (2015-06-11) claims 1, 4, 23, 38</p>	1-123

INTERNATIONAL SEARCH REPORT

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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.: **1-123(partially)**
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 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.:
1-123(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: 1-123(partially)

- a)
T cells that specifically bind to CD19 in combination with
 - b) an inhibitor of a target protein tyrosine kinase comprising ibrutinib or a compound of formula II , or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof (claim 15).
 - c)
for use in the treatment of a cancer selected from the group consisting of sarcomas, carcinomas, lymphomas, non-Hodgkin lymphomas (NHLs), diffuse large B cell lymphoma (DLBCL), leukemia, CLL, ALL, AML and myeloma (claim 26).
-

2. claims: 1-123(partially)

- a)
T cells that specifically bind to ROR1 in combination with
 - b) an inhibitor of a target protein tyrosine kinase comprising ibrutinib or a compound of formula II , or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof (claim 15).
 - c)
for use in the treatment of a cancer selected from the group consisting of sarcomas, carcinomas, lymphomas, non-Hodgkin lymphomas (NHLs), diffuse large B cell lymphoma (DLBCL), leukemia, CLL, ALL, AML and myeloma (claim 26).
-

3. claims: 1-123(partially)

- group of inventions
- a)
T cells that specifically bind to one of the other searchable molecules identifies in claim 28 with the exception of CD19 and ROR1 in combination with
 - b) an inhibitor of a target protein tyrosine kinase comprising ibrutinib or a compound of formula II, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof (claim 15).
 - c)
for use in the treatment of a cancer selected from the group consisting of sarcomas, carcinomas, lymphomas, non-Hodgkin lymphomas (NHLs), diffuse large B cell lymphoma (DLBCL), leukemia, CLL, ALL, AML and myeloma (claim 26).
-

4. claims: 1-123(partially)

Inventions claimed but not covered by any of inventions 1-3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-123(partially)

In reply to a request for clarification what has to be searched the Applicants informed the International Search Authority (ISA) that they would like to have searched:

In response, the Applicant identifies the following subject matter to be searched: A method of treatment involving administration, to a subject having a cancer, T cells comprising a recombinant antigen receptor that specifically binds to an antigen associated with the cancer or to a tag comprised by a therapeutic agent targeted to the cancer and an inhibitor that comprises the compound of Formula (II), or an enantiomer, pharmaceutically acceptable salt, solvate, hydrate, co-crystal, polymorph or prodrug thereof.

The above-described subject matter would be encompassed by at least claims 17-20 (completely), and 21-26, 28-41 and 45-75 (partially). If the Searching Authority further requires identification of a particular cancer for search, the Applicant requests search of cancers as recited in claim 26.

The ISA had indicated that in view of extensive clarity (Art. 6 PCT) and insufficiency issues (Art 5 PCT), the examiner is unable to search the subject matter as covered by the independent claims 1-3, 8-10, 17-19, 76, 87-89 113, 117.

Based on the indications provided by the Applicants, the ISA defines the searchable subject matter for claims 1-123 as:

a)

T cells that specifically bind to an antigen selected from those listed in claim 28 with the exception of an antigen associated with a universal tag, pathogen-specific antigen, NKG2D ligands [no limitation concerning the nature of said molecules] in combination with

b) an

inhibitor of a target protein tyrosine kinase comprising a compound of formula II, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof (claim 15).

[Co-crystal and prodrugs of compound II were not a subject of the search given that the scope encompassed by said terms is unclear and also insufficiently disclosed compounds and thus not searchable.]

c)

for use in the treatment of a cancer selected from the group consisting of sarcomas, carcinomas, lymphomas, non-Hodgkin lymphomas (NHLs), diffuse large B cell lymphoma (DLBCL), leukemia, CLL, ALL, AML and myeloma (claim 26).

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 Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/064362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016164580	A1	13-10-2016	EP 3280795 A1 14-02-2018
			US 2018140602 A1 24-05-2018
			WO 2016164580 A1 13-10-2016

WO 2016020901	A1	11-02-2016	AR 101476 A1 21-12-2016
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			TW 201705959 A 16-02-2017
			US 2017143712 A1 25-05-2017
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			WO 2017025814 A1 16-02-2017

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			CA 2931431 A1 11-06-2015
			CN 105979948 A 28-09-2016
			EA 201691169 A1 30-09-2016
			EP 3076974 A1 12-10-2016
			JP 2016540053 A 22-12-2016
			KR 20160093062 A 05-08-2016
			WO 2015083008 A1 11-06-2015
