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

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

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25 October 2018 (25.10.2018)

(15) Information about Correction:
see Notice of 25 October 2018 (25.10.2018)

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(54) Title: METHODS FOR DETERMINING CAR-T CELLS DOSING

(57) Abstract: Provided are methods of determining dosing of cells engineered with a recombinant receptor, such as a T cell receptor (TCR) or chimeric antigen receptor (CAR). In some embodiments, the methods include determining a therapeutic range for dosing by the estimated probabilities of risk of developing a toxicity and estimated probabilities of response to the engineered cells when administered.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61K39/44 A61K39/00
ADD.

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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 X	GARFALL ALFRED L ET AL: "Posterior Reversible Encephalopathy Syndrome (PRES) after Infusion of Anti-Bcma CAR T Cells (CART-BCMA) for Multiple Myeloma: Successful Treatment with Cyclophosphamide", BLOOD; 58TH ANNUAL MEETING AND EXPOSITION OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH), AMERICAN SOCIETY OF HEMATOLOGY, US; SAN DIEGO, CA, USA , vol. 128, no. 22 2 December 2016 (2016-12-02), page 5702, XP009503773, ISSN: 0006-4971 Retrieved from the Internet: URL:www.bloodjournal.org/content/128/22/5702 paragraph [0004] -/--	1-14, 21-41, 43,44, 51-62, 91-127

[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
4 September 2018	

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hix, Rebecca

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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	BATLEVI C L ET AL: "Novel immunotherapies in lymphoid malignancies", NATURE REVIEWS CLINICAL ONCOLOGY 20160101 NATURE PUBLISHING GROUP GBR, vol. 13, no. 1, 1 January 2016 (2016-01-01), pages 25-40, XP009503771, ISSN: 1759-4774 page 31, left-hand column, paragraph 2	1-14, 21-41, 43,44, 51-62, 91-127
A	WO 2016/064929 A1 (JUNO THERAPEUTICS INC [US]) 28 April 2016 (2016-04-28) paragraph [0024] paragraph [0531] paragraph [0535] paragraph [0544]	1-14, 21-41, 43,44, 51-62, 91-127
A	US 2016/185861 A1 (BEDOYA FELIPE [US] ET AL) 30 June 2016 (2016-06-30) paragraph [0442] - paragraph [0443]	1-14, 21-41, 43,44, 51-62, 91-127
X,P	BRANDON R. SHANK ET AL: "Chimeric Antigen Receptor T Cells in Hematologic Malignancies", PHARMACOTHERAPY : THE JOURNAL OF HUMAN PHARMACOLOGY AND DRUG THERAPY, vol. 37, no. 3, 1 March 2017 (2017-03-01), pages 334-345, XP055471941, US ISSN: 0277-0008, DOI: 10.1002/phar.1900 the whole document	16-41, 43,44, 51-62, 91-107
X	WO 2014/011984 A1 (UNIV PENNSYLVANIA [US]; PHILADELPHIA CHILDREN HOSPITAL [US]) 16 January 2014 (2014-01-16) pages 4, 33; figure 4	16-41, 43,44, 51-62, 91-107

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INTERNATIONAL SEARCH REPORT

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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	M. L. DAVILA ET AL: "Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia", SCIENCE TRANSLATIONAL MEDICINE, vol. 6, no. 224, 19 February 2014 (2014-02-19), pages 224ra25-224ra25, XP055234425, US ISSN: 1946-6234, DOI: 10.1126/scitranslmed.3008226 the whole document	16-41, 43,44, 51-62, 91-107
X	MAUDE SHANNON L ET AL: "Managing cytokine release syndrome associated with novel T cell-engaging therapies.", CANCER JOURNAL (SUDBURY, MASS.), vol. 20, no. 2, March 2014 (2014-03), pages 119-122, XP002780801, ISSN: 1540-336X the whole document	16-41, 43,44, 51-62, 91-107
X	MARCO L. DAVILA ET AL: "CD19-Targeted T Cells for Hematologic Malignancies : Clinical Experience to Date", CANCER JOURNAL, vol. 21, no. 6, 1 January 2015 (2015-01-01), pages 470-474, XP055377589, US ISSN: 1528-9117, DOI: 10.1097/PPO.0000000000000153 the whole document	16-41, 43,44, 51-62, 91-107
X	JENNIFER N. BRUDNO ET AL: "Toxicities of chimeric antigen receptor T cells: recognition and management", BLOOD, vol. 127, no. 26, 20 May 2016 (2016-05-20) , pages 3321-3330, XP055442400, US ISSN: 0006-4971, DOI: 10.1182/blood-2016-04-703751 the whole document	16-41, 43,44, 51-62, 91-107

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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	FREY NOELLE V ET AL: "Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia", HEMATOLOGY / THE EDUCATION PROGRAM OF THE AMERICAN SOCIETY OF HEMATOLOGY, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 2016, no. 1, 2 December 2016 (2016-12-02), pages 567-572, XP008184859, ISSN: 1520-4383, DOI: 10.1182/ASHEDUCATION-2016.1.567 the whole document -----	16-41, 43,44, 51-62, 91-107
X	R. J. BRENTJENS ET AL: "CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia", SCIENCE TRANSLATIONAL MEDICINE, vol. 5, no. 177, 20 March 2013 (2013-03-20), pages 177ra38-177ra38, XP055234457, US ISSN: 1946-6234, DOI: 10.1126/scitranslmed.3005930 the whole document -----	16-41, 43,44, 51-62, 91-107
X	WO 2012/062596 A1 (MICROMET GMBH [DE]; ZUGMAIER GERHARD [DE]; NAGORSEN DIRK [DE]; SCHEELE) 18 May 2012 (2012-05-18) paragraph [0030] - paragraph [0032] -----	16-41, 43,44, 51-62, 91-107
X,P	WO 2017/165571 A1 (SEATTLE CHILDREN'S HOSPITAL [US]) 28 September 2017 (2017-09-28) the whole document -----	16-41, 43,44, 51-62, 91-107

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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.:
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 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.:

1-14, 16-41, 43, 44, 51-62, 91-127

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-14, 108-127(completely); 21-41, 43, 44, 51-62, 91-107(partially)

A method of treatment, the method comprising:(a) administering, to a subject having a disease or condition, a dose of genetically engineered cells comprising T cells expressing a chimeric antigen receptor (CAR) for treating the disease or condition;(b) after administering the dose of genetically engineered cells, monitoring CAR+ T cells in the blood of the subject to assess if the cells are within a therapeutic range, and(c) if the genetically engineered cells are not within the therapeutic range, administering an agent to the subject capable of modulating, optionally increasing or decreasing, CAR+ T cell expansion or proliferation, in the subject, wherein the therapeutic range is:(i) based upon the range of peak CD3+ CAR+ T cells, or a CD8+CAR+ T cell subset thereof, in the blood among one or more subjects previously treated with the genetically engineered cells that is associated with an estimated probability of response of greater than or greater than about 65% and an estimated probability of a toxicity of less than or about 30%; or(ii) peak CD3+CAR+ T cells in the blood, following administration of the genetically engineered cells, that is between or between about 10 cells per microliter and 500 cells per microliter; or(iii) peak CD8+CAR+ T cells in the blood, following administration of the genetically engineered cells, that is between or between about 2 cells per microliter and 200 cells per microliter. A kit comprising CAR-T cells. A kit comprising an agent capable of modulating CAR-T cells.

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2. claims: 15(completely); 17-41, 43, 44, 51-62, 91-107(partially)

A method of modulating activity of engineered cells, the method comprising:(a) selecting a subject in which the level, amount or concentration of a volumetric measure of tumor burden or an inflammatory marker in a sample from the subject is at or above a threshold level, wherein the sample does not comprise genetically engineered T cells expressing a chimeric antigen receptor (CAR) and/or is obtained from the subject prior to receiving administration of genetically engineered T cells expressing a CAR; and(b) administering to the selected subject an agent that is capable of decreasing expansion or proliferation of genetically engineered T cells expressing a CAR.

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3. claims: 16(completely); 17-41, 43, 44, 51-62, 91-107(partially)

A method of modulating activity of engineered cells, the method comprising administering to a subject an agent that

is capable of decreasing expansion or proliferation of genetically engineered T cells expressing a chimeric antigen receptor (CAR) in a subject, wherein the subject is one in which the level, amount or concentration of a volumetric measure of tumor burden or an inflammatory marker in a sample from the subject is at or above a threshold level.

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4. claims: 42, 45-50(completely); 43, 44, 51-62, 91-101, 103-107(partially)

A method of dosing a subject, the method comprising administering, to a subject having a disease or condition, a dose of genetically engineered cells comprising T cells expressing a chimeric antigen receptor (CAR), wherein the dose comprises a number of the genetically engineered cells that is sufficient to achieve peak CAR+ cells in the blood within a determined therapeutic range in the subject, or in a majority of subjects so treated by the method or in greater than 75% of the subjects so treated by the method, wherein the therapeutic range is:(i) based upon the range of peak CD3+ CAR+ T cells, or a CD8+CAR+ T cell subset thereof, in the blood among one or more subjects previously treated with the genetically engineered cells that is associated with an estimated probability of response of greater than or greater than about 65% and an estimated probability of a toxicity of less than or about 30%; or(ii) peak CD3+CAR+ T cells in the blood, following administration of the genetically engineered cells, that is between or between about 10 cells per microliter and 500 cells per microliter; or(iii) peak CD8+CAR+ T cells in the blood, following administration of the genetically engineered cells, that is between or between about 2 cells per microliter and 200 cells per microliter.

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5. claims: 63-66(completely); 68-101, 103-107(partially)

A method of assessing likelihood of a durable response, the method comprising:(a) detecting, in a biological sample from a subject, peak levels of one or more inflammatory marker and/or peak levels of genetically engineered cells comprising T cells expressing a chimeric antigen receptor (CAR), wherein the subject has been previously administered a dose of the genetically engineered cells for treating a disease or condition; and(b) comparing, individually, the peak levels to a threshold value, thereby determining a likelihood that a subject will achieve a durable response to the administration of the genetically engineered cells.

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6. claims: 67(completely); 68-101, 103-107(partially)

A method of treatment, comprising;(a) selecting a subject having received administration of genetically engineered

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

cells comprising T cells expressing a chimeric antigen receptor (CAR) in which:peak levels of one or more inflammatory markers in a sample from the subject is above a threshold value; and/orpeak level of T cells comprising a chimeric antigen receptor (CAR) in a sample from the subject is below a lower threshold value or is above an upper threshold value; and(b) administering to the subject a therapeutic agent or alternative therapeutic treatment other than the genetically engineered cells.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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