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AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
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KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU,
RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
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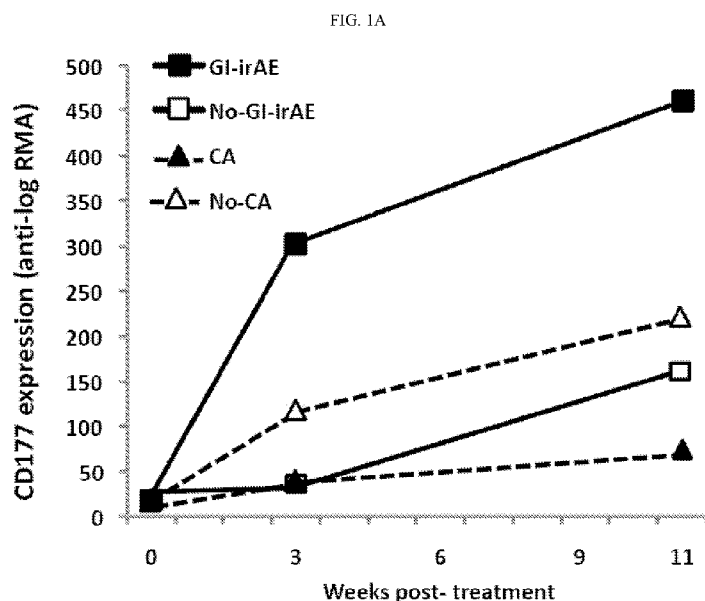
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ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

[Continued on next page]

(54) **Title:** METHODS FOR PREDICTING GASTROINTESTINAL IMMUNE - RELATED ADVERSE EVENTS (GI-IRAE) IN
PATIENTS TREATED WITH CO - STIMULATORY PATHWAY MODULATORS



(57) **Abstract:** The invention described herein
relates to diagnostic and therapeutic methods
and compositions useful for predicting the
likelihood a cancer patient will experience a
gastrointestinal immune-related adverse event
(GI-irAE) after administration of a pharma-
ceutically acceptable amount of an activator of
the immune system.



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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/031985

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/574 C07K16/28
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)
G01N C07K

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/061487 A1 (ALLIGATOR BIOSCIENCE AB [SE]) 26 May 2011 (2011-05-26) abstract page 16, lines 1-5 page 32, lines 4-17 page 33, lines 8-19 example B claims 1-60	1-16
A	WO 2011/146382 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 24 November 2011 (2011-11-24) abstract paragraphs [0068] - [0071], [0135] - [0136] figures 13,14 claims 1-14	4-6, 10-16

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

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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.
A	BERMAN D. ET AL.: "Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma.", CANCER IMMUN., vol. 10, P. 11, 24 November 2010 (2010-11-24), pages 1-10, XP002709661, abstract page 6, column 2	1-16
A	----- YUAN J. ET AL.: "CTLA-4 blockade enhances polyfunctional NY-ESO-1 specific T cell responses in metastatic melanoma patients with clinical benefit", PROC. NAT. ACAD. SCI., vol. 105, no. 51, 23 December 2008 (2008-12-23), pages 20410-20415, XP55073916, abstract page 20411, column 1, last paragraph page 20412, column 2, paragraph 2 table S1	1-16
X	----- JI R.-R. ET AL.: "An immune-active tumor microenvironment favors clinical response to ipilimumab", CANCER IMMUNOL., vol. 61, no. 7, 7 December 2011 (2011-12-07), pages 1019-1031, XP035074379, abstract	16
A	page 1029, column 1, paragraph 3	1-15
A	----- GRAZIANI G. ET AL.: "Ipilimumab: A novel immunostimulatory monoclonal antibody for the treatment of cancer", PHARMACOL. RES., vol. 65, no. 1, January 2012 (2012-01), pages 9-22, XP028445663, [retrieved on 2011-09-10] abstract page 13, paragraph 5	1-16
X,P	----- SHAHABI V. ET AL.: "Gene expression profiling of whole blood in ipilimumab-treated patients for identification of potential biomarkers of immune-related gastrointestinal adverse events", J. TRANSL. MED., vol. 11, no. 1, 75, 22 March 2013 (2013-03-22), pages 1-11, XP021145564, the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011061487 A1	26-05-2011	CA 2781181 A1	26-05-2011
		CN 102803961 A	28-11-2012
		EP 2502071 A1	26-09-2012
		US 2013004483 A1	03-01-2013
		WO 2011061487 A1	26-05-2011

WO 2011146382 A1	24-11-2011	EP 2571577 A1	27-03-2013
		US 2013064831 A1	14-03-2013
		WO 2011146382 A1	24-11-2011
