Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 2997406 A1 2017/06/15

(21) 2 997 406

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2016/12/06
(87) Date publication PCT/PCT Publication Date: 2017/06/15
(85) Entrée phase nationale/National Entry: 2018/03/05
(86) N° demande PCT/PCT Application No.: EP 2016/079800
(87) N° publication PCT/PCT Publication No.: 2017/097723
(30) Priorités/Priorities: 2015/12/09 (EP15198715.3); 2016/06/02 (EP16172739.1); 2016/10/10 (EP16193151.4)

(51) Cl.Int./Int.Cl. *C07K 16/28* (2006.01), *A61K 39/395* (2006.01), *C07K 16/30* (2006.01)

(71) Demandeur/Applicant:
F.HOFFMANN-LA ROCHE AG, CH

(72) Inventeurs/Inventors:
BACAC, MARINA, CH;
EVERS, STEFAN, CH;
KLEIN, CHRISTIAN, CH;
PISA, PAVEL, CH;
ROSSMANN, EVA, CH;
SARO, JOSE, CH;
UMANA, PABLO, CH

(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : METHODE DE TRAITEMENT
(54) Title: TREATMENT METHOD

(57) Abrégé/Abstract:
The present invention relates to methods of treating a disease, and methods for reduction of the formation of anti-drug antibodies (ADAs) in response to the administration of a therapeutic agent. The invention further relates to methods of treating a disease, particularly a B-cell proliferative disorder, and methods for reduction of adverse effects in response to the administration of a therapeutic agent, particularly a T-cell activating therapeutic agent.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2017 (15.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/097723 A3

(51) **International Patent Classification**:
C07K 16/28 (2006.01) ***C07K 16/30*** (2006.01)
A61K 39/395 (2006.01)

(21) **International Application Number**:
PCT/EP2016/079800

(22) **International Filing Date**:
6 December 2016 (06.12.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

15198715.3	9 December 2015 (09.12.2015)	EP
16172739.1	2 June 2016 (02.06.2016)	EP
16193151.4	10 October 2016 (10.10.2016)	EP

(71) **Applicant** *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) **Applicant** *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road, 8th Floor, Suite 8 - Legal Department, Little Falls, New Jersey 07424 (US).

(72) **Inventors**: **BACAC, Marina**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH). **EVERS, Stefan**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH). **KLEIN, Christian**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH). **PISA, Pavel**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH). **ROSSMANN, Eva**; c/o F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel (CH). **SARO, Jose**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH). **UMAÑA, Pablo**; c/o Roche Glycart AG, Wagistrasse 18, 8952 Schlieren (CH).

(74) **Agent**: **CUENI, Leah**; Grenzacherstrasse 124, 4070 Basel (CH).

(81) **Designated States** *(unless otherwise indicated, for every 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, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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**:
31 August 2017

WO 2017/097723 A3

(54) **Title**: TYPE II ANTI-CD20 ANTIBODY FOR REDUCING FORMATION OF ANTI-DRUG ANTIBODIES

(57) **Abstract**: The present invention relates to methods of treating a disease, and methods for reduction of the formation of anti-drug antibodies (ADAs) in response to the administration of a therapeutic agent. The invention further relates to methods of treating a disease, particularly a B-cell proliferative disorder, and methods for reduction of adverse effects in response to the administration of a therapeutic agent, particularly a T-cell activating therapeutic agent.

Claims

1. A Type II anti-CD20 antibody for use in a method of treating a disease in a subject, the method comprising a treatment regimen comprising

(i) administration to the subject of the Type II anti-CD20 antibody,

and consecutively after a period of time

(ii) administration to the subject of a therapeutic agent,

wherein the period of time between the administration of the Type II anti-CD20 antibody and the administration of the therapeutic agent is sufficient for reduction of the number of B-cells in the subject in response to the administration of the Type II anti-CD20 antibody.

2. The Type II anti-CD20 antibody of claim 1, wherein the treatment regimen effectively reduces the formation of anti-drug antibodies (ADAs) in the subject in response to the administration of the therapeutic agent as compared to a corresponding treatment regimen without the administration of the anti-CD20 antibody.

3. The Type II anti-CD20 antibody of claim 1 or 2, wherein the treatment regimen effectively reduces cytokine release associated with the administration of the therapeutic agent in the subject as compared to a corresponding treatment regimen without the administration of the Type II anti-CD20 antibody.

4. The Type II anti-CD20 antibody of claim 3, wherein the therapeutic agent is a T cell activating therapeutic agent.

5. A Type II anti-CD20 antibody for use in a method for (i) reducing the formation of anti-drug antibodies (ADAs) against a therapeutic agent in a subject and/or (ii) reducing cytokine release associated with the administration a therapeutic agent, particularly a T-cell activating therapeutic agent, in a subject, comprising administration of the Type II anti-CD20 antibody to the subject prior to administration of the therapeutic agent.

6. The Type II anti-CD20 antibody of claim 5, wherein the period of time between the administration of the Type II anti-CD20 antibody and administration of the therapeutic agent is sufficient for reduction of the number of B-cells in the subject in response to the administration of the Type II anti-CD20 antibody.

7. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the anti-CD20 antibody comprises a heavy chain variable region comprising the heavy chain CDR (HCDR) 1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, and the HCDR3 of SEQ ID NO: 6; and a light chain variable region comprising the light chain CDR (LCDR) 1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9.

8. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the anti-CD20 antibody comprises the heavy chain variable region sequence of SEQ ID NO: 10 and the light chain variable region sequence of SEQ ID NO: 11.

9. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the anti-CD20 antibody is an IgG antibody, particularly an IgG_1 antibody, and wherein at least about 40% of the N-linked oligosaccharides in the Fc region of the anti-CD20 antibody are non-fucosylated.

10. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the anti-CD20 antibody is obinutuzumab.

11. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the therapeutic agent comprises a polypeptide.

12. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the therapeutic agent comprises an antibody.

13. The Type II anti-CD20 antibody of claim 12, wherein the antibody comprised in the therapeutic agent specifically binds to carcinoembryonic antigen (CEA).

14. The Type II anti-CD20 antibody of claim 13, wherein the antibody comprised in the therapeutic agent comprises

(i) a heavy chain variable region comprising the heavy chain CDR (HCDR) 1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, and the HCDR3 of SEQ ID NO: 16; and a light chain variable region comprising the light chain CDR (LCDR) 1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19; or

(ii) a heavy chain variable region sequence of SEQ ID NO: 20 and a light chain variable region sequence of SEQ ID NO: 21.

15. The Type II anti-CD20 antibody of claim 12, wherein the antibody comprised in the therapeutic agent specifically binds to CD3, particularly CD3ε.

16. The Type II anti-CD20 antibody of claim 15, wherein the antibody comprised in the therapeutic agent comprises

(i) a heavy chain variable region comprising the heavy chain CDR (HCDR) 1 of SEQ ID NO: 32, the HCDR2 of SEQ ID NO: 33, and the HCDR3 of SEQ ID NO: 34; and a light chain variable region comprising the light chain CDR (LCDR) 1 of SEQ ID NO: 35, the LCDR2 of SEQ ID NO: 36 and the LCDR3 of SEQ ID NO: 37; or

(ii) a heavy chain variable region sequence of SEQ ID NO: 38 and a light chain variable region sequence of SEQ ID NO: 39.

17. The Type II anti-CD20 antibody of claim 12, wherein the antibody comprised in the therapeutic agent specifically binds to CD20.

18. The Type II anti-CD20 antibody of claim 15, wherein the antibody comprised in the therapeutic agent comprises

(i) a heavy chain variable region comprising the heavy chain CDR (HCDR) 1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, and the HCDR3 of SEQ ID NO: 6; and a light chain variable region comprising the light chain CDR (LCDR) 1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9; or

(ii) a heavy chain variable region sequence of SEQ ID NO: 10 and a light chain variable region sequence of SEQ ID NO: 11.

19. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the therapeutic agent comprises a cytokine, particularly interleukin-2.

20. The Type II anti-CD20 antibody of claim 19, wherein the cytokine is a mutant human IL-2 polypeptide comprising the amino acid substitutions F42A, Y45A and L72G (numbering relative to the human IL-2 sequence SEQ ID NO: 12).

21. The Type II anti-CD20 antibody of any one of the preceding claims, wherein the therapeutic agent comprises an immunoconjugate comprising an antibody as defined in claim 14, and a cytokine as defined in claim 20.

22. The Type II anti-CD20 antibody of any one of claims 1 to 16, wherein the therapeutic agent comprises a bispecific antibody comprising an antibody as defined in claim 14 and an antibody as defined in claim 16.

23. The Type II anti-CD20 antibody of any one of claims 1 to 12 and 16 to 18, wherein the therapeutic agent comprises a bispecific antibody comprising an antibody as defined in claim 16 and an antibody as defined in claim 20.