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(56) References Cited:

WO-A1-2011/051307
WO-A1-2007/068354
WO-A1-99/54440
US-A1- 2007 224 191
WO-A1-2012/055961
WO-A1-2006/114115

VIARDOT A. et al.: "Treatment of patients with non-hodgkin lymphoma (NHL) with CD 19/ CD 3 bispecific antibody blinatumomab (MT103): Double-step dose increase to continuous infusion of 60 µg/m2/d is tolerable and highly effective", Blood, vol. 116, no. 21, 2010, pages 1186-1187, DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2010 (2010-11), VIARDOT ANDREAS ET AL: "Treatment of Patients with Non-Hodgkin Lymphoma (NHL) with CD19/CD3 Bispecific Antibody Blinatumomab (MT103): Double-Step Dose Increase to Continuous Infusion of 60 mu g/m(2)/d Is Tolerable and Highly Effective", XP002667646, Database accession no. PREV201100425423 & BLOOD, vol. 116, no. 21, November 2010 (2010-11), pages 1186-1187, 52ND ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH); ORLANDO, FL, USA; DECEMBER 04 -07, 2010 ISSN: 0006-4971(print) -& Viardot et al.: "Treatment of Patients With Non-Hodgkin Lymphoma With CD19/CD3Bispecific Antibody Blinatumomab (MT103)", Micromet , 6 December 2010 (2010-12-06), XP002667647, Retrieved from the Internet: URL:http://www.micromet.com/Assets/Micromet_Viardot_poster_6DEC2010.aspx [retrieved on 2012-01-19]

DIRK NAGORSEN ET AL: "Immunotherapy of lymphoma and leukemia with T-cell engaging BiTE antibody blinatumomab", LEUKEMIA AND LYMPHOMA, vol. 50, no. 6, 1 January 2009 (2009-01-01), pages 886-891, XP008128752, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH ISSN: 1042-8194, DOI: 10.1080/10428190902943077

GOEBELER et al.: "CD3/CD19 BISPECIFIC BITE (R) ANTIBODY BLINATUMOMAB TREATMENT OF NON-HODGKIN LYMPHOMA (NHL) PATIENTS: 60 mu G/M-2/D BY CONTINUOUS INFUSION IS TOLERABLE AND RESULTS IN DURABLE RESPONSES", HAEMATOLOGICA, vol. 95, no. Suppl 2, 10 June 2010 (2010-06-10), page 230,

ALLEN SHIH et al.: "Role of Corticosteroids in Palliative Care", Journal of Pain & Palliative Care Pharmacotherapy, vol. 21, no. 4, 2007, pages 69-76,

KLINGER, MATTHIAS: "Wirkmechanismus des bispezifischen anti- CD 19 x anti- CD 3 BiTE-Antikorpers MT103 in Patienten mit rezidivem indolenten B-Zell-Non-Hodgkin-Lymphom", dissertation (doctor's thesis, 2009,

BAEUERLE P A ET AL: "BiTE: a new class of antibodies that recruit T-cells", DRUGS OF THE FUTURE, vol. 33, no. 2, February 2008 (2008-02), pages 137-147, XP002667644, ISSN: 0377-8282

WOLF ET AL: "BiTEs: bispecific antibody constructs with unique anti-tumor activity", DRUG DISCOVERY TODAY, vol. 10, no. 18, 15 September 2005 (2005-09-15), pages 1237-1244, XP005103829, ELSEVIER, RAHWAY, NJ, US ISSN: 1359-6446, DOI: 10.1016/S1359-6446(05)03554-3

HOFFMANN PATRICK ET AL: "Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct", INTERNATIONAL JOURNAL OF CANCER, vol. 115, no. 1, 20 May 2005 (2005-05-20), pages 98-104, XP002335808, JOHN WILEY & SONS, INC, UNITED STATES, SWITZERLAND, GERMANY ISSN: 0020-7136, DOI: 10.1002/IJC.20908

DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2009 (2009-11), NAGORSEN DIRK ET AL: "Confirmation of Safety, Efficacy and Response Duration in Non-Hodgkin Lymphoma Patients Treated with 60 mu g/m(2)/d of BiTE (R) Antibody Blinatumomab.", XP002668994, Database accession no. PREV201000353716 & NAGORSEN DIRK ET AL: BLOOD, vol. 114, no. 22, November 2009 (2009-11), page 1066, 51ST ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 05 -08, 2009 -& Nagorsen et al.: "Confirmation of Safety, Efficacy and Response Duration in Non-Hodgkin Lymphoma Patients treated with 60 microg/m^2/d of BiTE® Antibody Blinatumomab", Micromet - ASH Poster , 7 December 2009 (2009-12-07), XP002667643, Retrieved from the Internet: URL:http://www.micromet.com/Assets/ASH_pos ter_final_Dec_7_2009.aspx [retrieved on 2012-01-19]

CHRISTIAN BRANDL ET AL: "The effect of dexamethasone on polyclonal T cell activation and redirected target cell lysis as induced by a CD19/CD3-bispecific single-chain antibody construct", CANCER IMMUNOLOGY, IMMUNOTHERAPY, vol. 56, no. 10, 20 February 2007 (2007-02-20), pages 1551-1563, XP019539092, SPRINGER, BERLIN, DE ISSN: 1432-0851, DOI: 10.1007/S00262-007-0298-Z

GOEBELER M ET AL: "CD3/CD19 BISPECIFIC BITE (R) ANTIBODY BLINATUMOMAB TREATMENT OF NON-HODGKIN LYMPHOMA (NHL) PATIENTS: 60 mu G/M-2/D BY CONTINUOUS INFUSION IS TOLERABLE AND RESULTS IN DURABLE RESPONSES", HAEMATOLOGICA-THE HEMATOLOGY JOURNAL, vol. 95, no. Suppl. 2, 10 June 2010 (2010-06-10), - 13 June 2010 (2010-06-13), page 230, XP002667641, & 15TH ANNUAL MEETING OF THE EUROPEAN-HEMATOLOGY-ASSOCIATION; BARCELONA, SPAIN
R. Bargou: "1Blinatumomab (CD3/CD19 BiTE antibody) results in a high response rate in patients with relapsed non-hodgkin lymphoma (NHL) including MCL and DLBCL", , June 2011 (2011-06), XP002667645, 11th International Conference on Malignant Lymphoma, Lugano Switzerland, June 15-18, 2011 Retrieved from the Internet: URL:http://www.micromet.com/Assets/FN_Micr omet_ICML-NHL-Oral-15June.aspx [retrieved on 2012-01-18]

Patentkrav

1. Glukokortikoid (GC) for bruk i en fremgangsmåte av profylakse av bivirkninger forårsaket av administrasjonen av et CD3-bindingsdomene, hvori GC administreres før administrasjonen av den første dosen av CD3- bindingsdomenet og før administrasjonen av den andre dosen og/eller den tredje dosen av CD3-bindingsdomenet, hvori en første dose av CD3-bindingsdomenet administreres for en første tidsperiode og fortløpende en andre dose av CD3-bindingsdomenet administreres for en andre tidsperiode, hvori den andre dosen overskrider den første dosen, hvori GC er deksametason, hvori den nevrologiske bivirkningen er én eller flere av sanseforstyrrelser, anfall, encefalopati, cerebralt ødem, forvirring, ataksi, apraksi, taleforstyrrelse, parese, skjelving eller desorientering, hvori CD3-bindingsdomenet er et CD19 x CD3-bispesifikt enkeltkjedet antistoff.

2. Glukokortikoidet for bruken ifølge krav 1, hvori etter en første og andre dose av CD3-bindingsdomenet i en første og andre tidsperiode, en tredje dose av CD3-bindingsdomenet administreres, hvori den tredje dosen overstiger den første og andre dosen.

3. Glukokortikoidet for bruken ifølge krav 1, hvori CD3-bindingsdomenet administreres kontinuerlig.

4.Glukokortikoidet for bruken ifølge krav 1, hvori ovennevnte CD19 x CD3 bispesifikke enkelkjede antistoffet er MT103.

5. Glukokortikoidet for bruken ifølge hvilket som helst av de foregående kravene, hvori ovennevnte pasient er et menneske.

6. Glukokortikoidet for bruken ifølge hvilket som helst av de foregående kravene, hvori ovennevnte pasient **karakteriseres ved** et B/T-celleforhold på mindre enn 1:5.

7. Glukokortikoidet for bruken ifølge hvilket som helst av krav 1 til 6, hvori ovennevnte CD3-bindingsdomene binder til menneskelig CD3-epsilon.