

subtypes in patients with previously untreated DLBCL from MAIN, a phase III trial that evaluated bevacizumab plus R-CHOP (NCT 00486759).

Challa-Malladi (Cancer Cell 20, 2011, 728-40) discloses that combined genetic inactivation of β 2-Microglobulin and CD58 reveals frequent escape from immune recognition in DLBCL.

Despite previous success in the treatment of DLBCL (for example due to the advances with R, in particular R-CHOP), however, there is still a high unmet medical need for some DLBCL patients (cf. NCCN clinical practice guidelines in oncology; non-Hodgkin's lymphoma, v 2.2015) for an improved treatment (cf. Sehn, loc. cit.).

Therefore, the technical problem underlying the present invention is to provide an improved treatment of DLBCL in certain patients.

The solution to said technical problem is provided herein below and characterized in the appended claims.

Summary

~~In one aspect, the present disclosure refers to the use of a humanized Type II anti CD20 antibody comprising (a) a heavy chain variable region as depicted in SEQ ID NO:1 or as comprised in SEQ ID NO:5 (amino acid residues 1 to 119) and a light chain variable region as depicted in SEQ ID NO:2 or as comprised in SEQ ID NO:6 (amino acid residues 1 to 115); or (b) a heavy chain variable region that is encoded by a nucleic acid sequence which is at least 80% identical to SEQ ID NO:3 or SEQ ID NO:7 and a light chain variable region that is encoded by a nucleic acid sequence which is at least 80% identical to SEQ ID NO:4 or SEQ ID NO:8, wherein said antibody is capable of causing an increased antibody-dependent cellular cytotoxicity (ADCC) as compared to rituximab, is capable of causing an increased antibody-dependent cellular phagocytosis (ADCP) as compared to rituximab and/or has an increased affinity for Fc γ RIII receptors as compared to rituximab, in the manufacture of a medicament for treating diffuse large B-cell lymphoma (DLBCL) in a patient which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab, wherein said patient is (i) a patient with one or more mutation(s) in one or more of the gene(s) selected from the group consisting of *GREBBP*, *EP300*, *MEF2B*, *MYC*, *EZH2* and *TNFRSF14*;~~

~~(ii) a patient with (a) genetic mutation(s) in CD58 and/or with a low expression of CD58 that corresponds to $\log_2(\text{normalized Reads Per Kilobase Million (nRPKM)}) \leq 5.2$; (iii) a patient with a cell-of-origin (COO) subtype of DLBCL being germinal-center B-cell-like (GCB) DLBCL as defined by a Linear Predictor Score (LPS) <1141 (strong-GCB DLBCL); and/or (iv) a BCL2-translocated DLBCL patient and/or a DLBCL patient with high BCL2 expression wherein $\geq 50\%$ of the tumor cells express BCL2.~~

In ~~another one~~ aspect, the present disclosure refers to an *in vitro* method for identifying a DLBCL patient (patient with/suffering from DLBCL) which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab, said method comprising determining whether a patient is ~~(i) a patient with one or more mutation(s) in one or more of the gene(s) selected from the group consisting of CREBBP, EP300, MEF2B, MYC, EZH2 and TNFRSF14; (ii) a patient with (a) genetic mutation(s) in CD58 and/or with a low expression of CD58 that corresponds to $\log_2(\text{normalized Reads Per Kilobase Million (nRPKM)}) \leq 5.2$; (iii) a patient with a cell-of-origin (COO) subtype of DLBCL being germinal-center B-cell-like (GCB) DLBCL as defined by a Linear Predictor Score (LPS) <1141 (strong-GCB DLBCL); and/or (iv) a BCL2-translocated DLBCL patient and/or a DLBCL patient with high BCL2 expression wherein $\geq 50\%$ of the tumor cells express BCL2.~~ a patient as defined herein.

In ~~yet~~ another aspect, the present disclosure refers to an *in vitro* method for diagnosing in a patient a form of DLBCL which can be treated with obinutuzumab so that an improved clinical outcome as compared to a treatment with rituximab is reached, said method comprising determining whether a patient is a patient as defined herein, and diagnosing said form of DLBCL if the patient is a patient as defined herein.

~~In yet another aspect, the present disclosure refers to the use of a humanized Type II anti-CD20 antibody comprising a heavy chain variable region as depicted in SEQ ID NO:1 or as comprised in SEQ ID NO:5 (amino acid residues 1 to 119) and a light chain variable region as depicted in SEQ ID NO:2 or as comprised in SEQ ID NO:6 (amino acid residues 1 to 115) in the manufacture of a medicament for treating DLBCL in a patient which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab, wherein (i) said patient has been identified according to the method as defined herein, or wherein (ii) a form of DLBCL has been diagnosed in said patient according to the method as defined herein.~~

It was surprisingly found in the context of the invention that, of all DLBCL patients, some patients respond to a treatment with obinutuzumab (in particular in combination with a chemotherapy, more particular in combination with a CHOP chemotherapy) by an improved clinical outcome, in particular as compared to a treatment with rituximab (in particular in combination with a chemotherapy, more particular in combination with a CHOP chemotherapy). It was also surprisingly found in the context of the invention that subgroups of DLBCL patients can be identified/determined which respond to a treatment with obinutuzumab (in particular in combination with a chemotherapy, more particular in combination with a CHOP chemotherapy) by an improved clinical outcome, in particular as compared to a treatment with rituximab (in particular in combination with a chemotherapy, more particular in combination with a CHOP

CLAIMS

1. ~~Use of a humanized Type II anti-CD20 antibody comprising~~
 - ~~(a) a heavy chain variable region as depicted in SEQ ID NO:1 or as comprised in SEQ ID NO:5 (amino acid residues 1 to 119) and a light chain variable region as depicted in SEQ ID NO:2 or as comprised in SEQ ID NO:6 (amino acid residues 1 to 115); or~~
 - ~~(b) a heavy chain variable region that is encoded by a nucleic acid sequence which is at least 80% identical to SEQ ID NO:3 or SEQ ID NO:7 and a light chain variable region that is encoded by a nucleic acid sequence which is at least 80% identical to SEQ ID NO:4 or SEQ ID NO:8,~~

~~wherein said antibody is capable of causing an increased antibody-dependent cellular cytotoxicity (ADCC) as compared to rituximab, is capable of causing an increased antibody-dependent cellular phagocytosis (ADCP) as compared to rituximab and/or has an increased affinity for FcγRIII receptors as compared to rituximab,~~

~~in the manufacture of a medicament for treating diffuse large B-cell lymphoma (DLBCL) in a patient which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab, wherein said patient is~~

 - ~~(i) a patient with one or more mutation(s) in one or more of the gene(s) selected from the group consisting of *CREBBP*, *EP300*, *MEF2B*, *MYC*, *EZH2* and *TNFRSF14*;~~
 - ~~(ii) a patient with (a) genetic mutation(s) in *CD58* and/or with a low expression of *CD58* that corresponds to $\log_2(\text{normalized Reads Per Kilobase Million (nRPKM)}) \leq 5.2$;~~
 - ~~(iii) a patient with a cell-of-origin (COO) subtype of DLBCL being germinal-center B-cell-like (GCB) DLBCL as defined by a Linear Predictor Score (LPS) < 1141 (strong GCB DLBCL); and/or~~
 - ~~(iv) a *BCL2* translocated DLBCL patient and/or a DLBCL patient with high *BCL2* expression wherein $\geq 50\%$ of the tumor cells express *BCL2*.~~
2. ~~The use according to claim 1, wherein said clinical outcome is progression free survival (PFS), overall survival (OS) and/or event free survival (EFS).~~
3. ~~The use according to claim 1 or 2, wherein said patient is:~~

- (i) ~~— a patient as defined in claim 1(i); and~~
 - (ii) ~~— a patient as defined in claim 1(ii).~~
4. ~~The use according to any one of claims 1 to 3, in particular according to claim 3(i), wherein said patient is~~
- ~~— (i) — a patient as defined in claim 1(iii); and~~
 - ~~(ii) — a patient as defined in claim 1(iv).~~
5. ~~The use according to any one of claims 1 to 4, in particular according to claim 1(iii) or 4(i), wherein said patient is identified by determining the expression of a set of genes comprising one or more (preferably all) of the genes *TNFRSF13B*, *LIMD1*, *IRF4*, *CREB3L2*, *PIM2*, *CYB5R2*, *RAB7L1*, and *CCDC50*; and *MME*, *SERPINA9*, *ASB13*, *MAML3*, *ITPKB*, *MYBL1*, and *S1PR2*.~~
6. ~~The use according to claim 4(i) or 5, wherein said patient with strong-GCB DLBCL is a patient having a tumor with a weighted expression of a set of genes comprising one or more (preferably all) of the genes *TNFRSF13B*, *LIMD1*, *IRF4*, *CREB3L2*, *PIM2*, *CYB5R2*, *RAB7L1*, and *CCDC50*; and *MME*, *SERPINA9*, *ASB13*, *MAML3*, *ITPKB*, *MYBL1*, and *S1PR2* resulting in a Linear Predictor Score (LPS) < 1141.~~
7. ~~The use according to claim 5 or 6, wherein said set of genes further comprises one or more (preferably all) of the genes *R3HDM1*, *WDR55*, *ISY1*, *UBXN4*, and *TRIM56*.~~
8. ~~The use according to any one of claims 5 to 7, wherein the expression of said one or more genes as defined in claims 5 or 6 is normalized to the expression of one or more (preferably all) genes as defined in claim 7.~~
9. ~~The use according to any one of claims 1 to 8, wherein said LPS is the weighted sum of the expression of (said) genes calculated according to the following formula (formula I):~~

$$LPS(X) = \sum_j a_j X_j,$$

- ~~— wherein X_j is the gene expression for gene j and a_j is the coefficient for gene j .~~

- ~~10. The use according to any one of claims 1 to 9, wherein the expression of (said) genes is determined by the NanoString Research Use Only Lymphoma Subtyping Test (LST) (NanoString Technologies, Inc., Seattle, WA, USA).~~
- ~~11. The use according to any one of claims 1 to 10, wherein said LPS is ≤ 1100 .~~
- ~~12. The use according to any one of claims 1 to 11, wherein said LPS is ≤ 749 .~~
- ~~13. The use according to any one of claim 1 to 12, wherein said LPS is ≤ 725 .~~
- ~~14. The use according to any one of claims 1 to 13, wherein said antibody comprises a glycoengineered Fc region.~~
- ~~15. The use according to claim 14, wherein said antibody has an increase in the fraction of non-fucosylated oligosaccharides attached to said glycoengineered Fc region.~~
- ~~16. The use according to claim 14 or 15, wherein said antibody has an increase in the fraction of bisected, non-fucosylated oligosaccharides attached to said glycoengineered Fc region.~~
- ~~17. The use according to any one of claims 1 to 16, in particular according to claim 14, wherein said antibody has significantly higher levels of binding to human FcγRIII receptors relative to the non-glycoengineered antibody and/or relative to rituximab.~~
- ~~18. The use according to any one of claims 1 to 17, in particular according to claim 14, wherein said antibody has significantly higher levels of ADCC activity relative to the non-glycoengineered antibody and/or relative to rituximab.~~
- ~~19. The use according to any one of claims 1 to 18, wherein said antibody is obinutuzumab (Gazyva™/Gazyvaro™; GA101).~~
- ~~20. The use according to any one of claims 1 to 19, wherein one or more additional other cytotoxic or chemotherapeutic agent(s) or ionizing radiation enhancing the effects of such agent(s), is (are) to be administered.~~
- ~~21. The use according to any one of claims 1 to 20, wherein said antibody is to be administered in combination with a CHOP chemotherapy.~~

~~22. The use according to any one of claims 1 to 21, wherein said antibody is comprised in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.~~

123. An *in vitro* method for identifying a diffuse large B-cell lymphoma (DLBCL) patient (patient with/suffering from DLBCL) which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab,

said method comprising determining whether a patient is ~~a patient as defined in any one of claims 1 to 13~~(i) a patient with one or more mutation(s) in one or more of the gene(s) selected from the group consisting of *CREBBP*, *EP300*, *MEF2B*, *MYC*, *EZH2* and *TNFRSF14*;

(ii) a patient with (a) genetic mutation(s) in *CD58* and/or with a low expression of *CD58* that corresponds to $\log_2(\text{normalized Reads Per Kilobase Million (nRPKM)}) \leq 5.2$;

(iii) a patient with a cell-of-origin (COO) subtype of DLBCL being germinal-center B-cell-like (GCB) DLBCL as defined by a Linear Predictor Score (LPS) < 1141 (strong-GCB DLBCL); and/or

(iv) a *BCL2*-translocated DLBCL patient and/or a DLBCL patient with high *BCL2* expression wherein $\geq 50\%$ of the tumor cells express *BCL2*.

2. The *in vitro* method according to claim 1, wherein said clinical outcome is progression free survival (PFS), overall survival (OS) and/or event free survival (EFS).

3. The *in vitro* method according to claim 1 or 2, wherein said patient is:

(i) a patient as defined in claim 1(i); and

(ii) a patient as defined in claim 1(ii).

4. The *in vitro* method according to any one of claims 1 to 3, in particular according to claim 3(i), wherein said patient is

(i) a patient as defined in claim 1(iii); and

(ii) a patient as defined in claim 1(iv).

5. The *in vitro* method according to any one of claims 1 to 4, in particular according to claim 1(iii) or 4(i), wherein said patient is identified by determining the expression of a set of genes comprising one or more (preferably all) of the genes *TNFRSF13B*, *LIMD1*, *IRF4*, *CREB3L2*, *PIM2*, *CYB5R2*, *RAB7L1*, and

CCDC50; and MME, SERPINA9, ASB13, MAML3, ITPKB, MYBL1, and S1PR2.

6. The *in vitro* method according to claim 4(i) or 5, wherein said patient with strong-GCB DLBCL is a patient having a tumor with a weighted expression of a set of genes comprising one or more (preferably all) of the genes *TNFRSF13B*, *LIMD1*, *IRF4*, *CREB3L2*, *PIM2*, *CYB5R2*, *RAB7L1*, and *CCDC50*; and *MME*, *SERPINA9*, *ASB13*, *MAML3*, *ITPKB*, *MYBL1*, and *S1PR2* resulting in a Linear Predictor Score (LPS) < 1141.
7. The *in vitro* method according to claim 5 or 6, wherein said set of genes further comprises one or more (preferably all) of the genes *R3HDM1*, *WDR55*, *ISY1*, *UBXN4*, and *TRIM56*.
8. The *in vitro* method according to any one of claims 5 to 7, wherein the expression of said one or more genes as defined in claims 5 or 6 is normalized to the expression of one or more (preferably all) genes as defined in claim 7.
9. The *in vitro* method according to any one of claims 1 to 8, wherein said LPS is the weighted sum of the expression of (said) genes calculated according to the following formula (formula I):

$$LPS(X) = \sum_j a_j X_{j\pm}$$

wherein X_j is the gene expression for gene j and a_j is the coefficient for gene j .

10. The *in vitro* method according to any one of claims 1 to 9, wherein the expression of (said) genes is determined by the NanoString Research Use Only Lymphoma Subtyping Test (LST) (NanoString Technologies, Inc., Seattle, WA, USA).
11. The *in vitro* method according to any one of claims 1 to 10, wherein said LPS is ≤ 1100 .
12. The *in vitro* method according to any one of claims 1 to 11, wherein said LPS is ≤ 749 .
13. The *in vitro* method according to any one of claim 1 to 12, wherein said LPS is

≤ 725.-

124. An *in vitro* method for diagnosing in a patient a form of DLBCL which can be treated with obinutuzumab so that an improved clinical outcome as compared to a treatment with rituximab is reached, said method comprising determining whether a patient is a patient as defined in any one of claims 1 to 13, and diagnosing said form of DLBCL if the patient is a patient as defined in any one of claims 1 to 13.
125. ~~The use of a humanized Type II anti-CD20 antibody comprising a heavy chain variable region as depicted in SEQ ID NO:1 or as comprised in SEQ ID NO:5 (amino acid residues 1 to 119) and a light chain variable region as depicted in SEQ ID NO:2 or as comprised in SEQ ID NO:6 (amino acid residues 1 to 115) in the manufacture of a medicament for treating DLBCL in a patient which responds to a treatment with obinutuzumab by reaching an improved clinical outcome as compared to a treatment with rituximab, according to any one of claims 1 to 22, wherein (i) it has been determined whether said patient is a patient as defined in any one of claims 1 to 13, wherein (ii) said patient has been identified according to the method of any one of claims 231 to 13, or wherein (iii) a form of DLBCL has been diagnosed in said patient according to the method of claim 2414.~~
216. The use according to ~~any one of claims 1 to 22 and 2515~~, wherein said treatment comprises the step of (i) ~~determining whether the patient to be treated is a patient as defined in any one of claims 1 to 13~~, (ii) identifying a DLBCL patient according to the method of any one of claims 1 to 13-23, or (iii) diagnosing in the patient a form of DLBCL according to the method of claim 124.
17. The use according to claim 15 or 16, wherein said antibody comprises a glycoengineered Fc region.
18. The use according to claim 17, wherein said antibody has an increase in the fraction of non-fucosylated oligosaccharides attached to said glycoengineered Fc region.
19. The use according to claim 17 or 18, wherein said antibody has an increase in the fraction of bisected, non-fucosylated oligosaccharides attached to said glycoengineered Fc region.

20. The use according to any one of claims 15 to 19, in particular according to claim 17, wherein said antibody has significantly higher levels of binding to human FcγRIII receptors relative to the non-glycoengineered antibody and/or relative to rituximab.
21. The use according to any one of claims 15 to 20, in particular according to claim 17, wherein said antibody has significantly higher levels of ADCC activity relative to the non-glycoengineered antibody and/or relative to rituximab.
22. The use according to any one of claims 15 to 21, wherein said antibody is obinutuzumab (Gazyva™/Gazyvaro™; GA101).
23. The use according to any one of claims 15 to 22, wherein one or more additional other cytotoxic or chemotherapeutic agent(s) or ionizing radiation enhancing the effects of such agent(s), is (are) to be administered.
24. The use according to any one of claims 15 to 23, wherein said antibody is to be administered in combination with a CHOP chemotherapy.
25. The use according to any one of claims 15 to 24, wherein said antibody is comprised in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.