antibodies only. WO 2005/046657 relates to the treatment of inflammatory bowel disease by anti-CSF-1-antibodies. US 2002/0141994 relates to inhibitors of colony stimulating factors. WO 2006/096489 relates to the treatment of rheumatoid arthritis by anti-CSF-1-antibodies. WO 2009/026303 and WO 2009/112245 relate to certain anti-CSF-1R antibodies binding to CSF-1R within the first three subdomains (D1 to D3) of the Extracellular Domain (CSF-1R-ECD). WO2011/123381(A1) relates to antibodies against CSF-1R.

Summary

~~In a first aspect, t~~The disclosure comprises an antibody binding to human CSF-1R, characterized in binding to the (dimerization) domains D4 to D5 (SEQ ID No: 85) of the extracellular domain of human CSF-1R for use in

a) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R expressing tumor cells;

b) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;

c) the inhibition of cell survival (in CSF-1R ligand-dependant and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or

d) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages,

wherein the anti-CSF-1R antibody is administered in combination with a chemotherapeutic agent, radiation, and/or cancer immunotherapy.

This combination therapy with antibodies binding to human CSF-1R, characterized in binding to the (dimerization) domains D4 to D5, has valuable properties like less activation potential to CSF-1R activation and in consequence reduced toxitcity and no stimulation of CSF-1R receptor (e.g.compared to a combination therapy with antibodies binding to human CSF-1R, characterized in binding to the domains D1 to D3).

The term "ligand dependent" as used herein refers to a ligand-independent signaling through the extracellular ECD (and does not include the ligand independent signaling mediated by activating point mutations in the intracellular kinase domain). In one embodiment CSF-1R ligand in this context refers a CSF-1R ligand selected from human CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)).

~~In a second aspect, the disclosure comprises an antibody binding to human CSF-1R, characterized in binding to the domains D4 to D5 (SEQ ID No: 85) of the extracellular domain of human CSF-1R for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand wherein the anti-CSF-1R antibody is administered in combination with a chemotherapeutic agent, radiation and/or cancer immunotherapy.~~

The disclosure comprises an antibody binding to human CSF-1R, antibody binding to human CSF-1R, characterized in binding to the (dimerization) domains D4 to D5 (SEQ ID No: 85) of the extracellular domain of human CSF-1R for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand (in one embodiment the CSF-1R ligand is selected from human CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)) (detectable in serum, urine or tumor biopsies),

wherein the anti-CSF-1R antibody is administered in combination with a chemotherapeutic agent, radiation and/or cancer immunotherapy. The term "increase of CSF-1R ligand" refers to the overexpression of human CSF-1R ligand (in one embodiment the CSF-1R ligand is selected from human CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)) (compared to normal tissue) before treatment or overexpression of human CSF-1R ligand induced by treatment with anti-CSF-1R antibody (and compared to the expression levels before treatment). In certain embodiments, the term "increase" or "above" refers to a level above the reference level or to an overall increase of 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%,

~~In a third aspect, the disclosure comprises an antibody binding to human CSF-1R, for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand wherein the anti-CSF-1R antibody is administered in combination with a cancer immunotherapy, wherein the cancer immunotherapy is selected from the group of:~~

~~a) T cell engaging agents selected from agonistic antibodies which bind to human OX40, to GITR, to CD27, or to 4-1BB, und T-cell bispecific antibodies (e.g. T cell-engaging BiTE™ antibodies CD3-CD19, CD3-EpCam, CD3-EGFR), IL-2 (Proleukin), Interferon (IFN) alpha, antagonizing antibodies which bind to human CTLA-4 (e.g. ipilimumab), to PD-1, to PD-L1, to TIM-3, to BTLA, to VISTA, to LAG-3, or to CD25,~~

~~b) targeting immunosuppression: antibodies or small molecules targeting STAT3 or NFkB signaling, blocking IL-6, IL-17, IL-23,TNFa function,~~

~~c) cancer vaccines/enhance dendritic cell function: OncoVex (oncolytic virus secreting GM-CSF), an agonistic CD40 antibody, Toll-like receptor (TLR) ligands, TLR agonists, recombinant fusion protein encoding MAGE-A3, PROSTVAC; or~~

~~d) adoptive cell transfer: GVAX(prostate cancer cell line expressing GM-CSF), dendritic cell vaccine, adoptive T cell therapy, adoptive CAR T cell therapy.~~

The disclosure further relates to the combination therapy of an antibody binding to human CSF-1R for use in the treatment of cancer (including

CSF-1R recombinant cells are able to form spheroids independent of the CSF-1 ligand. Furthermore these antibodies inhibit (both) human and cynomolgous macrophage differentiation, as they inhibit survival of human and cynomolgous monocytes.

Further antibodies binding to the binding to the (dimerization) domains D4 to D5 can be selected by screening for antibodies that bind to the complete extracellular domain of human CSF-1R (SEQ ID NO: 64) (including domains D1 to D5), and not binding to the domains D1 to D3 (SEQ ID NO: 66) of the extracellular domain of human CSF-1R.

~~In a fourth aspect, the disclosure relates to a method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:~~

~~- ex vivo or in vitro determining in vitro the level of one or more of the following markers: CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), and Ki67 and other markers like e.g. immuninfiltrates; in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and~~

~~- wherein a change in the level of one or more of CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density) and Ki67 and other markers like e.g. immuninfiltrates (e.g. T cells (e.g. CD4 and/or CD8 T cells), as compared with to the corresponding level in an individual not suffering from cancer, is indicative that the subject is a candidate for the anti-CSF-1R antibody based cancer treatment regimen.~~

~~In a fifth aspect, the disclosure relates to a method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:~~

~~- ex vivo or in vitro determining in vitro the level of one or more of the following markers: CSF-1, Trap5b, sCD163, IL-34; in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and~~

~~- wherein a change in the level of one or more of CSF-1, Trap5b, sCD163, IL-34, as compared with to the corresponding level in an individual not suffering from~~

~~cancer, is indicative that the subject is a candidate for the anti-CSF-1 R antibody-based cancer treatment regimen.~~

~~In a sixth aspect, the disclosure relates to a method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:~~

~~- ex vivo or in vitro determining in vitro the level of one or more of the following markers: IFNγ, TNFα , IL-1β, IL-4, IL-6 , IL-8 , IL-10, IL-13, GM-CSF, VEGF, MCP-1, CCL18, CCL22, MIP-1 , Galectin 3, IL1Ra, TGF alpha; in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and~~

~~- wherein a change in the level of one or more of IFNγ, TNFα , IL-1β, IL-4, IL-6 , IL-8 , IL-10, IL-13, GM-CSF, VEGF, MCP-1, CCL18, CCL22, MIP-1, Galectin 3, IL1Ra, TGF alpha, as compared with to the corresponding level in an individual not suffering from cancer, is indicative that the subject is a candidate for the anti-CSF-1 R antibody-based cancer treatment regimen.~~

In ~~a seventh~~one aspect, the disclosure relates to use of an antibody binding to human CSF-1R in the manufacture of a medicament for ~~use in~~ the treatment of cancer, wherein the antibody is to be administered in combination with a bispecific ANG-2-VEGF antibody

In ~~a eighth~~another aspect, the disclosure relates to use of an antibody binding to human CSF-1R in the manufacture of a medicament for ~~use in~~ the treatment of cancer, wherein the anti-CSF-1R antibody is to be administered in combination with an agonistic CD40 antibody.

Description of the Figures

Figure 1 Growth inhibition of BeWo tumor cells in 3D culture under treatment with different anti-CSF-1R monoclonal antibodies at a concentration of 10µg/ml.
X axis: viability normalized mean relative light units (RLU) corresponding to the ATP-content of the cells (CellTiterGlo assay).
Y axis: tested probes: Minimal Medium (0.5% FBS), mouse IgG1 (mIgG1, 10µg/ml), mouse IgG2a (mIgG2a 10µg/ml), CSF-1 only, Mab 2F11, Mab 2E10, Mab2H7, Mab1G10 and SC 2-4A5.
Highest inhibition of CSF-1 induced growth was observed with the anti-CSF-1R antibodies according to the invention.

~~Patent Claims~~

~~1. An antibody binding to human CSF-1R, characterized in binding to the (dimerization) domains D4 to D5 (SEQ ID No: 85) of the extracellular domain of human CSF-1R for use in~~

~~a) the inhibition of cell proliferation in CSF-1R ligand-dependant and/or CSF-1R ligand-independant CSF-1R expressing tumor cells;~~

~~b) the inhibition of cell proliferation of tumors with CSF-1 ligand-dependant and/or CSF-1 ligand-independant CSF-1R expressing macrophage infiltrate;~~

~~c) the inhibition of cell survival (in CSF-1R ligand-dependant and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or~~

~~d) the inhibition of cell differentiation (in CSF-1R ligand-dependant and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;~~

~~wherein the anti-CSF-1R antibody is administered in combination with a chemotherapeutic agent, radiation, and/or cancer immunotherapy.~~

~~2. An antibody binding to human CSF-1R, characterized in binding to the domains D4 to D5 (SEQ ID No: 85) of the extracellular domain of human CSF-1R for use in~~

~~the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand~~

~~wherein the anti-CSF-1R antibody is administered in combination with a chemotherapeutic agent, radiation and/or cancer immunotherapy.~~

~~3. The antibody according to claims 1 or 2, wherein the chemotherapeutic agent is selected from the group consisiting of taxanes (paclitaxel (Taxol), docetaxel (Taxotere), modified paclitaxel (Abraxane and Opaxio)), doxorubicin, modified doxorubicin (Caelyx or Doxil)), sunitinib (Sutent),~~

sorafenib (Nexavar), and other multikinase inhibitors, oxaliplatin, cisplatin, carboplatin, etoposide, gemcitabine, and vinblastine.

4. The antibody or use according to claims 1 or 2, wherein the cancer immunotherapy is selected from the group of:

a) T cell engaging agents selected from agonistic antibodies which bind to human OX40, TO GITR, TO CD27, OR TO 4-1BB, und T-cell bispecific antibodies (e.g. T cell-engaging BiTE™ antibodies CD3-CD19, CD3-EpCam, CD3-EGFR), IL-2 (Proleukin), Interferon (IFN) alpha, antagonizing antibodies which bind to human CTLA-4, to PD-1, to PD-L1, to TIM-3, to BTLA, to VISTA, to LAG-3, or to CD25,

b) targeting immunosuppression: antibodies or small molecules targeting STAT3 or NFkB signaling, blocking IL-6, IL-17, IL-23,TNFa function,

c) cancer vaccines/enhance dendritic cell function: oncolytic virus secreting GM-CSF (OncoVex), an agonistic CD40 antibody, Toll-like receptor (TLR) ligands, TLR agonists, recombinant fusion protein encoding MAGE-A3, PROSTVAC; or

d) adoptive cell transfer: GVAX(prostate cancer cell line expressing GM-CSF), dendritic cell vaccine, adoptive T cell therapy, adoptive CAR T cell therapy.

5. The antibody or use according to claim 4, wherein the cancer immunotherapy is an agonistic CD40 antibody.

6. The antibody according to claims 1 or 2, wherein the chemotherapeutic agent is selected from the group of taxanes (docetaxel or paclitaxel or a modified paclitaxel (Abraxane or Opaxio)), doxorubicin, capecitabine and/or bevacizumab for the treatment of breast cancer.

7. The antibody according to claims 1 or 2, wherein the chemotherapeutic agent is selected from the group of carboplatin, oxaliplatin, cisplatin, paclitaxel, doxorubicin (or modified doxorubicin (Caelyx or Doxil)), or topotecan (Hycamtin) for the treatment of ovarian cancer.

8. The antibody according to claims 1 or 2,wherein the chemotherapeutic agent is selected from the group of a multi-kinase inhibitor (sunitinib

(Sutent), sorafenib (Nexavar) or motesanib diphosphate (AMG 706) and/or doxorubicin for treatment of kidney cancer.

9. The antibody according to claims 1 or 2,, wherein the chemotherapeutic agent is selected from the group of oxaliplatin, cisplatin, and/or radiation for the treatment of squamous cell carcinoma.

10. The antibody according to claims 1 or 2, wherein the chemotherapeutic agent is selected from the group of taxol and/or carboplatin for the treatment of lung cancer.

11. The antibody according any one of the preceding claims, wherein the antibody is characterized in that the antibody does not bind to human CSF-1R fragment delD4 (SEQ ID NO: 65).

12. The antibody according any one of the preceding claims, wherein the antibody is characterized in that

the antibody binds to human CSF-1R fragment delD4 (SEQ ID NO: 65) and to human CSF-1R Extracellular Domain (SEQ ID NO: 64) with a ratio of 1:50 or lower.

13. The antibody according any one of the preceding claims, characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,

b) the heavy chain variable domain is SEQ ID NO:15 and the light chain variable domain is SEQ ID NO:16;

c) the heavy chain variable domain is SEQ ID NO:75 and the light chain variable domain is SEQ ID NO:76;

d) the heavy chain variable domain is SEQ ID NO:83 and the light chain variable domain is SEQ ID NO:84;

or a humanized version thereof.

~~14. The antibody according any one of the preceding claims, characterized in that~~

~~a) the heavy chain variable domain is SEQ ID NO:23 and the light chain variable domain is SEQ ID NO:24, or~~

~~b) the heavy chain variable domain is SEQ ID NO:31 and the light chain variable domain is SEQ ID NO:32, or~~

~~c) the heavy chain variable domain is SEQ ID NO:39 and the light chain variable domain is SEQ ID NO:40, or~~

~~d) the heavy chain variable domain is SEQ ID NO:47 and the light chain variable domain is SEQ ID NO:48, or~~

~~e) the heavy chain variable domain is SEQ ID NO:55 and the light chain variable domain is SEQ ID NO:56.~~

~~15. The antibody according any one of the preceding claims, characterized in that~~

~~a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6, or~~

~~b) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 9, a CDR2 region of SEQ ID NO: 10, and a CDR1 region of SEQ ID NO: 11, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:12, a CDR2 region of SEQ ID NO: 13, and a CDR1 region of SEQ ID NO: 14, or~~

~~c) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 17, a CDR2 region of SEQ ID NO: 18, and a CDR1 region of SEQ ID NO:19, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 20, a CDR2 region of SEQ ID NO:21, and a CDR1 region of SEQ ID NO:22, or~~

~~d) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 25, a CDR2 region of SEQ ID NO: 26, and a CDR1 region of SEQ ID NO: 27, and the light chain variable domain comprises a CDR3 region~~

~~of SEQ ID NO:28, a CDR2 region of SEQ ID NO: 29, and a CDR1 region of SEQ ID NO: 30, or~~

~~e) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 33, a CDR2 region of SEQ ID NO: 34, and a CDR1 region of SEQ ID NO: 35, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:36, a CDR2 region of SEQ ID NO: 37, and a CDR1 region of SEQ ID NO: 38, or~~

~~f) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:41, a CDR2 region of SEQ ID NO: 42, and a CDR1 region of SEQ ID NO:43, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 44, a CDR2 region of SEQ ID NO:45, and a CDR1 region of SEQ ID NO:46, or~~

~~g) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:52, a CDR2 region of SEQ ID NO: 53, and a CDR1 region of SEQ ID NO: 54; or~~

~~h) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:69, a CDR2 region of SEQ ID NO: 70, and a CDR1 region of SEQ ID NO:71, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 72, a CDR2 region of SEQ ID NO:73, and a CDR1 region of SEQ ID NO:74, or~~

~~i) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 77, a CDR2 region of SEQ ID NO: 78, and a CDR1 region of SEQ ID NO: 79, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:80, a CDR2 region of SEQ ID NO: 81, and a CDR1 region of SEQ ID NO: 82.~~

~~16. The antibody according any one of the preceding claims, characterized in that said antibody is of human IgG1 subclass or is of human IgG4 subclass.~~

~~17. An antibody binding to human CSF-1R, for use in~~

~~the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand~~

~~wherein the anti-CSF-1R antibody is administered in combination with a cancer immunotherapy,~~

~~wherein the cancer immunotherapy is selected from the group of:~~

~~a) T cell engaging agents selected from agonistic antibodies which bind to human OX40, to GITR, to CD27, or to 4-1BB, und T-cell bispecific antibodies (e.g. T cell-engaging BiTE™ antibodies CD3-CD19, CD3-EpCam, CD3-EGFR), IL-2 (Proleukin), Interferon (IFN) alpha, antagonizing antibodies which bind to human CTLA-4 (e.g. ipilimumab), to PD-1, to PD-L1, to TIM-3, to BTLA, to VISTA, to LAG-3, or to CD25,~~

~~b) targeting immunosuppression: antibodies or small molecules targeting STAT3 or NFkB signaling, blocking IL-6, IL-17, IL-23,TNFa function,~~

~~c) cancer vaccines/enhance dendritic cell function: OncoVex (oncolytic virus secreting GM-CSF), an agonistic CD40 antibody, Toll-like receptor (TLR) ligands, TLR agonists, recombinant fusion protein encoding MAGE-A3, PROSTVAC; or~~

~~d) adoptive cell transfer: GVAX(prostate cancer cell line expressing GM-CSF), dendritic cell vaccine, adoptive T cell therapy, adoptive CAR T cell therapy.~~

~~18. The antibody according to claim 17~~

~~wherein the cancer immunotherapy is selected from the group of:~~

~~cancer vaccines/enhance dendritic cell function: OncoVex (oncolytic virus secreting GM-CSF), an agonistic CD40 antibody, Toll-like receptor (TLR) ligands, TLR agonists, recombinant fusion protein encoding MAGE-A3, PROSTVAC.~~

~~19. The antibody or use according to claim 17, wherein the cancer immunotherapy is an agonistic CD40 antibody.~~

~~20. A method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:~~

~~ex vivo or in vitro determining in vitro the level of one or more of the following markers:~~

~~CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density), and Ki67 and other markers like e.g. immuninfiltrates;~~

~~in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and~~

~~wherein a change in the level of one or more of CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density) and Ki67 and other markers like e.g. immuninfiltrates (e.g. T cells (e.g. CD4 and/or CD8 T cells), as compared with to the corresponding level in an individual not suffering from cancer, is indicative that the subject is a candidate for the anti -CSF-1 R antibody-based cancer treatment regimen.~~

~~21. The method of claim 20, wherein the antibody used in said regimen is an antibody according to any of the preceding claims.~~

~~22. The method of claims 20 or 21 wherein in this method the change in the level of CSF-1R, CD68/CD163, CD68/MHC class II, CD31 (microvessel density) and Ki67 and other markers like e.g. immuninfiltrates (e.g. T cells (e.g. CD4- and/or CD8 T cells), as compared to the level in an individual not suffering from cancer is an increase in the level of one or more of these markers.~~

~~23. A method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:~~

~~ex vivo or in vitro determining in vitro the level of one or more of the following markers:~~

~~CSF-1, Trap5b, sCD163, IL-34 ;~~

in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and

wherein a change in the level of one or more of CSF-1, Trap5b, sCD163, IL-34, as compared with to the corresponding level in an individual not suffering from cancer, is indicative that the subject is a candidate for the anti-CSF-1 R antibody-based cancer treatment regimen.

24. The method of claim 23, wherein the antibody used in said regimen is an antibody according to any of the preceding claims.

25. The method of claims 23 or 24 wherein in this method the change in the level of CSF-1, Trap5b, sCD163, IL-34, as compared to the level in an individual not suffering from cancer is an increase in the level of one or more of these markers.

26. The method of any of claims 23 to 25 wherein in this method ex vivo or in vitro the level and change of the level of sCD163 is determined.

27. A method for determining whether a subject having a cancer is a candidate for an anti-CSF-1R antibody-based cancer treatment regimen, the method comprising:

ex vivo or in vitro determining in vitro the level of one or more of the following markers:

IFNγ, TNFα , IL-1β, IL-4, IL-6 , IL-8 , IL-10, IL-13, GM-CSF, VEGF, MCP-1, CCL18, CCL22, MIP-1 , Galectin 3, IL1Ra, TGF-alpha;

in a sample of the subject, wherein the sample is selected from the group consisting of tissue, blood, serum, plasma, tumor cells and circulating tumor cells; and

wherein a change in the level of one or more of IFNγ, TNFα , IL-1β, IL-4, IL-6 , IL-8 , IL-10, IL-13, GM-CSF, VEGF, MCP-1, CCL18, CCL22, MIP-1, Galectin 3, IL1Ra, TGF-alpha, as compared with to the corresponding level in an individual not suffering from cancer, is indicative that the subject is a candidate for the anti-CSF-1 R antibody-based cancer treatment regimen.

~~28. The method of claim 27, wherein the antibody used in said regimen is an antibody according to any of the preceding claims.~~

~~29. The method of claims 27 or 28 wherein in this method the change in the level of IFNγ, TNFα , IL-1β, IL-4, IL-6 , IL-8 , IL-10, IL-13, GM-CSF, VEGF, MCP-1, CCL18, CCL22, MIP-1 , Galectin 3, IL1Ra, TGF alpha, as compared to the level in an individual not suffering from cancer is an increase in the level of one or more of these markers.~~

Patent Claims

~~30~~1. Use of an ~~An~~ antibody binding to human CSF-1R in the manufacture of a medicament for ~~use in~~ the treatment of cancer, wherein the antibody is to be administered in combination with a bispecific ANG-2-VEGF antibody.

~~31~~2. Use of an ~~An~~ antibody binding to human CSF-1R in the manufacture of a medicament for ~~use in~~ the treatment of cancer, wherein the anti-CSF-1R antibody is to be administered in combination with an agonistic CD40 antibody.

~~32~~3. The use ~~antibody binding to human CSF-1R~~ according to claim ~~31~~2, i) wherein the anti-CSF-1R antibody comprises (a) a heavy chain variable domain amino acid sequence of SEQ ID NO:39 and (b) a light chain variable domain amino acid sequence of SEQ ID NO:40; and ii) wherein the agonistic CD40 antibody comprises (a) a heavy chain variable domain amino acid sequence of SEQ ID NO: 88 and (b) a light chain variable domain amino acid sequence of SEQ ID NO: 89.

~~33~~4. The use ~~antibody binding to human CSF-1R~~ according to claim ~~31~~2, wherein the anti-CSF-1R antibody comprises (a) a heavy chain variable domain amino acid sequence of SEQ ID NO:39 and (b) a light chain variable domain amino acid sequence of SEQ ID NO:40; and wherein the agonistic CD40 antibody is dacetuzumab.

~~34~~5. The use ~~antibody binding to human CSF-1R~~ according to claim ~~31~~2, i) wherein the anti-CSF-1R antibody comprises (a) a heavy chain variable domain amino acid sequence of SEQ ID NO:39 and (b) a light chain variable domain amino acid sequence of SEQ ID NO:40; and ii) wherein the agonistic CD40 antibody comprises (a) a heavy chain variable domain amino acid sequence of SEQ ID NO: 90 and (b) a light chain variable domain amino acid sequence of SEQ ID NO: 91.