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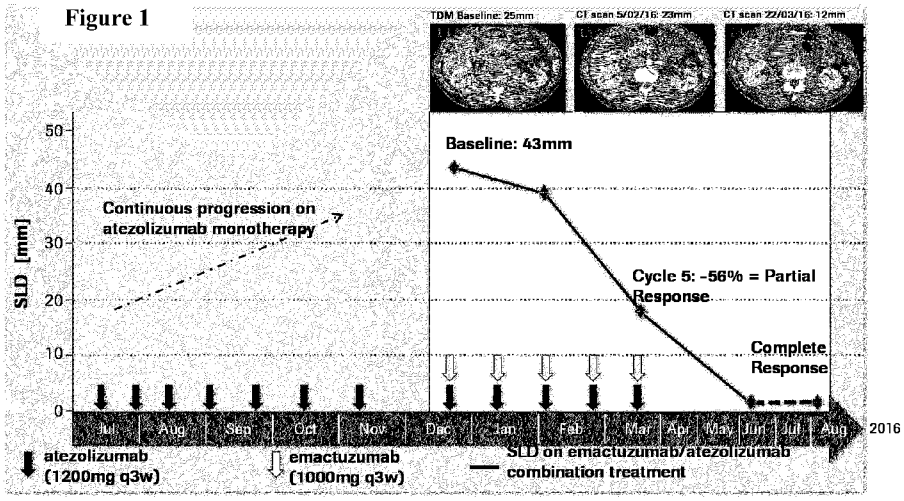
(54) Title: TREATMENT OF TUMORS WITH AN ANTI-CSF-1R ANTIBODY IN COMBINATION WITH AN ANTI-PD-L1 ANTIBODY AFTER FAILURE OF ANTI-PD-L1/PD1 TREATMENT

Figure 1



(57) Abstract: The current disclosure relates to the combination therapy of an anti-CSF-1R antibody (especially a CSF-1R dimerization inhibitor) in combination with an anti-PD-L1 antibody after PD1/PD-L1 inhibitor treatment failure, corresponding pharmaceutical compositions or medicaments using such combination therapy.

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Treatment of tumors with an anti-CSF-1R antibody in combination with an anti-PD-L1 antibody after failure of anti-PD-L1/PD1 treatment

The current invention relates to the combination therapy of an anti-CSF-1R antibody (especially a CSF-1R dimerization inhibitor) in combination with an anti-PD-L1 antibody after disease progression on PD1/PD-L1 inhibitor treatment, corresponding pharmaceutical compositions or medicaments using such combination therapy.

Background of the Invention

CSF-1R and CSF-1R antibodies

The human CSF-1 receptor (CSF-1R; colony stimulating factor 1 receptor; synonyms: M-CSF receptor; Macrophage colony-stimulating factor 1 receptor, Fms proto-oncogene, c-fms) is known since 1986 (Coussens, L., et al., Nature 320 (1986) 277-280). CSF-1R is a growth factor and encoded by the c-fms proto-oncogene (reviewed e.g. in Roth, P., and Stanley, E.R., Curr. Top. Microbiol. Immunol. 181 (1992) 141-167).

CSF-1R is the receptor for CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage colony-stimulating factor) and mediates the biological effects of this cytokine (Sherr, C.J., et al., Cell 41 (1985) 665-676). The cloning of the colony stimulating factor-1 receptor (CSF-1R) (also called c-fms) was described for the first time in Roussel, M.F., et al., Nature 325 (1987) 549-552. In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee, P.S., et al., Embo J. 18 (1999) 3616-3628). Recently a second ligand for CSF-1R termed interleukin-34 (IL-34) was identified (Lin, H., et al, Science 320 (2008) 807-811).

Currently two CSF-1R ligands that bind to the extracellular domain of CSF-1R are known. The first one is CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage; SEQ ID NO: 28) and is found extracellularly as a disulfide-linked homodimer (Stanley, E.R. et al., Journal of Cellular Biochemistry 21 (1983) 151-159; Stanley, E.R. et al., Stem Cells 12 Suppl. 1 (1995) 15–24). The second one is IL-34 (Human IL-34; SEQ ID NO: 29) (Hume, D. A. , et al, Blood 119 (2012)

1810-1820). The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of hematopoietic precursor cells to the macrophage lineage (including osteoclast). Activation of CSF-1R is mediated by its CSF-1R ligands, CSF-1 (M-CSF) and IL-34. Binding of CSF-1 (M-CSF) to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Li, W. et al, EMBO Journal.10 (1991) 277-288; Stanley, E.R., et al., Mol. Reprod. Dev. 46 (1997) 4-10).

The biologically active homodimer CSF-1 binds to the CSF-1R within the subdomains D1 to D3 of the extracellular domain of the CSF-1 receptor (CSF-1R-ECD). The CSF-1R-ECD comprises five immunoglobulin-like subdomains (designated Dl to D5). The subdomains D4 to D5 of the extracellular domain (CSF-1R-ECD) are not involved in the CSF-1 binding (Wang, Z., et al Molecular and Cellular Biology 13 (1993) 5348-5359). The subdomain D4 is involved in dimerization (Yeung, Y-G., et al Molecular & Cellular Proteomics 2 (2003) 1143–1155; Pixley, F. J., et al., Trends Cell Biol. 14 (2004) 628-638).

Further signaling is mediated by the p85 subunit of PI3K and Grb2 connecting to the PI3K/AKT and Ras/MAPK pathways, respectively. These two important signaling pathways can regulate proliferation, survival and apoptosis. Other signaling molecules that bind the phosphorylated intracellular domain of CSF-1R include STAT1, STAT3, PLCy, and Cbl (Bourette, R.P. and Rohrschneider, L.R., Growth Factors 17 (2000) 155-166).

CSF-1R signaling has a physiological role in immune responses, in bone remodeling and in the reproductive system. The knockout animals for either CSF-1 (Pollard, J.W., Mol. Reprod. Dev. 46 (1997) 54-61) or CSF-1R (Dai, X.M., et al., Blood 99 (2002) 111-120) have been shown to have osteopetrotic, hematopoietic, tissue macrophage, and reproductive phenotypes consistent with a role for CSF-1R in the respective cell types.

Sherr, C.J., et al., Blood 73 (1989) 1786-1793 relates to some antibodies against CSF-1R that inhibit the CSF-1 activity. Ashmun, R.A., et al., Blood 73 (1989) 827-837 relates to CSF-1R antibodies. Lenda, D., et al., Journal of Immunology 170 (2003) 3254-3262 relates to reduced macrophage recruitment, proliferation, and activation in CSF-1-deficient mice results in decreased tubular apoptosis during renal inflammation. Kitaura, H., et al., Journal of Dental Research 87 (2008) 396-400 refers to an anti-CSF-1 antibody which inhibits orthodontic tooth movement.

WO 2001/030381 mentions CSF-1 activity inhibitors including antisense nucleotides and antibodies while disclosing only CSF-1 antisense nucleotides. WO 2004/045532 relates to metastases and bone loss prevention and treatment of metastatic cancer by a CSF-1 antagonist disclosing as antagonist anti-CSF-1-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). WO 2011/123381, WO 2011/140249, WO 2012/110360 relate to antibodies against CSF-1R. WO 2011/070024 relate to certain anti-CSF-1R antibodies binding to CSF-1R within the dimerization domain (D4 to D5).

WO 2013/132044, and WO 2015/036511 relate inter alia to the combination therapy of anti-CSF-1R antibodies with cancer immunotherapies.

It has now been found surprisingly that a combination therapy of anti-CSF1R antibodies and anti-PDL1 antibodies is highly effective for tumors with anti-PD-L1/PD1 axis treatment failure.

Summary of the Invention

Combination of cancer immunotherapies to harness the amplifying cytotoxic T cells to fight cancer has become a major focus in the treatment of patients. CSF-1R blocking agents that eliminate T cell suppressive tumor-associated macrophages (TAM) in tumors, represent a novel player for combinatorial immunotherapies.

Surprisingly, we found that that a combination therapy of anti-CSF1R antibodies and anti-PDL1 antibodies is highly effective for tumors with prior treatment failure on or after anti-PD-L1/PD1 axis treatment.

One aspect of the invention is an antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

In one embodiment of the invention CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

In one embodiment of the invention the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

In one embodiment of the invention the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

In one embodiment of the invention the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

In one embodiment of the invention in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab.

In one embodiment of the invention in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab.

In one embodiment of the invention anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

In one embodiment of the invention the prior treatment which failed was a atezolizumab or durvalumab treatment.

In one embodiment of the invention the prior treatment which failed was a atezolizumab treatment

In one embodiment of the invention the prior treatment which failed was a durvalumab treatment.

One embodiment of the invention is the described anti-CSF-1R antibody for use in one of the above treatments, wherein the combined therapy is for use in treating or delaying progression of an immune related disease such as tumor immunity.

One embodiment of the invention is the described anti-CSF-1R antibody for use in one of the above treatments, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

Description of the Figures

Figure 1: Emactuzumab in combination with atezolizumab after treatment failure with atezolizumab monotherapy: Readout according to RECIST 1.1. criteria. Sum of the longest diameters (SLD) are shown. A complete response could be determined in an UBC (urinary bladder cancer) patient previously progressive on atezolizumab monotherapy.

Figure 2: Emactuzumab in combination with atezolizumab after treatment failure with an anti-PD-L1 antibody (not further specified): Readout according to RECIST 1.1. criteria. Sum of the longest diameters (SLD) are shown. A partial response could be determined in a urinary bladder cancer patient previously progressive on anti-PD-L1 monotherapy (not further specified).

Figure 3: Emactuzumab in combination with atezolizumab after treatment failure with nivolumab monotherapy: Readout according to RECIST 1.1. criteria. Sum of the longest diameters (SLD) are shown. A partial response could be determined in a non-small cell lung cancer patient previously progressive on nivolumab monotherapy.

Figure 4: Emactuzumab in combination with atezolizumab after treatment failure with pembrolizumab monotherapy: Readout according to RECIST 1.1. criteria. Sum of the longest diameters (SLD) are shown. A partial response could be determined in a non-small cell lung cancer patient previously progressive on pembrolizumab monotherapy.

Detailed Description of the Invention

The term "wherein a prior treatment of the cancer … failed" as used herein refers to the situation wherein the cancer showed disease progression (e.g. when the Overall Response is a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment. The term "wherein a prior treatment of the patient (suffering from a cancer) failed" as used herein refers to the situation wherein the patient (suffering from cancer) showed disease progression (e.g. a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment. Such patients suffering from cancer or such cancers are non-responsive to the prior treatment.

A "tumor with CSF-1R expressing macrophage infiltrate" refers to a heterogeneous tumor comprising tumor cells and infiltrating CSF-1R-expressing tumor-associated macrophages (TAMs) or tissue resident macrophages.

According to these RECIST 1.1 criteria, tumor response for solid tumors (Eisenhauer E.A., et al, Eur. J. Cancer 45 (2009) 228-247) is categorized in

dependency of the volume progression or regression of the tumors and lesions (e.g. measured via CT) into four levels: complete response (CR) or partial response (PR), stable disease (SD) and progressive disease (PD).

CSF-1R is a protein encoded by the CSF-1R gene. It controls the production, differentiation, and function of M2 macrophages, which, in turn, support tumor growth and metastasis formation and secrete immunosuppressive cytokines, leading to a poor prognosis in patients. Furthermore, presence of CSF-1R positive macrophages in several human cancers (such as ovarian and breast carcinoma) has been shown to correlate not only with increased vascular density but also worse clinical outcome. CSF-1R inhibitors, which selectively inhibit M2-like TAMs, have demonstrated activity in preclinical models (DeNardo, D. et al., Cancer Discovery 1 (2011) 54-67; Lin, E. et al., J. Exp. Med. 193 (2001) 727-740). Blockade of CSF-1R activity results in reduced recruitment of TAMs and, in combination with chemotherapy, a synergistic action results in reduced tumor growth and metastatic burden. Recent data have shown that in patients with PVNS and TGCT, overexpression of the CSF-1 is detected and is in part mediated by a translocation of the CSF-1R gene (West, R.B. et al., Proc. Natl. Acad. Sci. USA 3 (2006) 690-695). In breast cancer the presence of a CSF-1 response gene signature predicts risk of recurrence and metastasis (Beck, A. et al., Clin. Cancer Res. 3 (2009) 778-787).

Many tumors are characterized by a prominent immune cell infiltrate, including macrophages. Initially, the immune cells were thought to be part of a defense mechanism against the tumor, but recent data support the notion that several immune cell populations including macrophages may, in fact, promote tumor progression. Macrophages are characterized by their plasticity. Depending on the cytokine microenvironment, macrophages can exhibit so-called M1 or M2-subtypes. M2 macrophages are engaged in the suppression of tumor immunity. They also play an important role in tissue repair functions such as angiogenesis and tissue remodeling which are coopted by the tumor to support growth. In contrast to tumor promoting M2 macrophages, M1 macrophages exhibit antitumor activity via the secretion of inflammatory cytokines and their engagement in antigen presentation and phagocytosis (Mantovani, A. et al., Curr. Opin. Immunol. 2 (2010) 231-237).

By secreting various cytokines such as colony stimulating factor 1 (CSF-1) and IL-10, tumor cells are able to recruit and shape macrophages into the M2- subtype,

whereas cytokines such as granulocyte macrophage colony stimulating factor (GM-CSF), IFN-gamma program macrophages towards the M1 subtype. Using immunohistochemistry, it is possible to distinguish between a macrophage subpopulation co-expressing CD68 and CD163, which is likely to be enriched for M2 Macrophages, and a subset showing the CD68+/MHC II+, or CD68+/CD80+ immunophenotype, likely to include M1 macrophages. Cell shape, size, and spatial distribution of CD68 and CD163 positive macrophages is consistent with published hypotheses on a tumor-promoting role of M2 macrophages, for example by their preferential location in tumor intersecting stroma, and vital tumor areas. In contrast, CD68+/MHC class II+ macrophages are ubiquitously found. Their hypothetical role in phagocytosis is reflected by clusters of the CD68+/MHC class II+, but CD163- immunophenotype near apoptotic cells and necrotic tumor areas.

The subtype and marker expression of different macrophage subpopulations is linked with their functional state. M2 macrophages can support tumorigenesis by:

a) enhancing angiogenesis via the secretion of angiogenic factors such as VEGF or bFGF,
b) supporting metastasis formation via secretion of matrix metalloproteinases(MMPs), growth factors and migratory factors guiding the tumor cells to the blood stream and setting up the metastatic niche (Wyckoff, J. et al., Cancer Res. 67 (2007) 2649-2656),
c) playing a role in building an immunosuppressive milieu by secreting immunosuppressive cytokines such as IL-4, Il-13, IL-1ra and IL-10, which in turn regulate T regulatory cell function. Conversely CD4 positive T cells have been shown to enhance the activity of tumor promoting macrophages in preclinical models (Mantovani, A. et al., Eur. J. Cancer 40 (2004) 1660-1667; DeNardo, D. et al., Cancer Cell 16 (2009) 91-102).

Accordingly, in several types of cancer (e.g. breast, ovarian, Hodgkin's lymphoma) the prevalence of M2 subtype tumor associated macrophages (TAMs) has been associated with poor prognosis (Bingle, L. et al., J. Pathol. 3 (2002) 254-265; Orre, M., and Rogers, P.A., Gynecol. Oncol. 1 (1999) 47-50; Steidl, C. et al., N. Engl. J. Med. 10 (2010) 875-885). Recent data show a correlation of CD163 positive macrophage infiltrate in tumors and tumor grade (Kawamura, K. et al., Pathol. Int. 59 (2009) 300-305). TAMs isolated from patient tumors had a tolerant phenotype and were not cytotoxic to tumor cells (Mantovani, A. et al., Eur. J. Cancer 40

(2004) 1660-1667). However, infiltration of TAMs in the presence of cytotoxic T cells correlates with improved survival in non small cell lung cancer and hence reflects a more prominent M1 macrophage infiltrate in this tumor type (Kawai, O. et al., Cancer 6 (2008) 1387-1395).

CSF-1R belongs to the class III subfamily of receptor tyrosine kinases and is encoded by the c-fms proto-oncogene. Binding of CSF-1 or IL-34 induces receptor dimerization, followed by autophosphorylation and activation of downstream signaling cascades. Activation of CSF-1R regulates the survival, proliferation and differentiation of monocytes and macrophages (Xiong, Y. et al., J. Biol. Chem. 286 (2011) 952-960).

In addition to cells of the monocytic lineage and osteoclasts, which derive from the same hematopoietic precursor as the macrophage, CSF-1R/c-fms has also been found to be expressed by several human epithelial cancers such as ovarian and breast cancer and in leiomyosarcoma and TGCT/PVNS, albeit at lower expression levels compared to macrophages. As with TGCT/PVNS, elevated levels of CSF-1, the ligand for CSF-1R, in serum as well as ascites of ovarian cancer patients have been correlated with poor prognosis (Scholl, S. et al., Br. J. Cancer 62 (1994) 342-346; Price, F. et al., Am. J. Obstet. Gynecol. 168 (1993) 520-527). Furthermore, a constitutively active mutant form of CSF 1R is able to transform NIH3T3 cells, one of the properties of an oncogene (Chambers, S., Future Oncol 5 (2009) 1429-1440).

As surrogate for the tumor associated macrophages (TAMs) the precursor human CD14+CD16+ (positive) monocytes in blood serum are measured, as the recovery of this blood monocytes correlates with the subsequent recovery of the tumor associated macrophages (TAMs). The term "after a significant recovery of CD14+CD16+ positive monocytes in blood serum (in one embodiment the recovery is more than 60%, in one embodiment more than 80%)" as used herein refers to the a reproduction of CD14+CD16+ positive monocytes in blood serum after they have been depleted first by the anti-CSFR antibody treatment and after, when there is a time when no more anti-CSFR antibody treatment is administered (anti-CSF-1R drug holiday) the cell population of CD14+CD16+ positive monocytes in blood serum grows again towards more than 50% percent (in one embodiment the recovery is more than 60%, in one embodiment more than 80%) of the value this population had before anti-CSFR antibody treatment. A pharmacodynamic model can been fitted to the human CD14+CD16+ monocyte

data. Based on preliminary population analysis, a dose of 750 mg administered Q6W shows significant recovery of CD14+CD16+ monocytes.

In one embodiment different treatment schedules can be applied. E.g. as the first treatment with the anti-CSF-1R antibody leads to a strong reduction/depletion of tumor associated macrophages (TAMs) and their precursor human CD14+CD16+ (positive) monocytes in blood serum, the length of an treatment cycle can be chosen to provide enough time that a significant recovery of the of this human CD14+CD16+ (positive) monocytes blood monocytes correlating with the subsequent recovery of the tumor associated macrophages (TAMs), so that the TAMs are not continuously depleted. And the combination treatment with the PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody can exert its strong synergistic anti-tumor efficacy.

The human CSF-1R (CSF-1 receptor; synonyms: M-CSF receptor; Macrophage colony-stimulating factor 1 receptor, Fms proto-oncogene, c-fms, SEQ ID NO: 24)) is known since 1986 (Coussens, L., et al., Nature 320 (1986) 277-280). CSF-1R is a growth factor and encoded by the c-fms proto-oncogene (reviewed e.g. in Roth, P. and Stanley, E.R., Curr. Top. Microbiol. Immunol. 181 (1992) 141-167).

CSF-1R is the receptor for the CSF-1R ligands CSF-1 (macrophage colony stimulating factor, also called M-CSF) (SEQ ID No.: 28) and IL-34 (SEQ ID No.: 29) and mediates the biological effects of these cytokines (Sherr, C.J., et al., Cell 41 (1985) 665-676; Lin, H., et al., Science 320 (2008) 807-811). The cloning of the colony stimulating factor-1 receptor (also called c-fms) was described for the first time in Roussel, M.F., et al., Nature 325 (1987) 549-552. In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee, P.S., et al., Embo J. 18 (1999) 3616-3628).

CSF-1R is a single chain, transmembrane receptor tyrosine kinase (RTK) and a member of the family of immunoglobulin (Ig) motif containing RTKs characterized by 5 repeated Ig-like subdomains D1-D5 in the extracellular domain (ECD) of the receptor (Wang, Z., et al Molecular and Cellular Biology 13 (1993) 5348-5359). The human CSF-1R Extracellular Domain (CSF-1R-ECD) (SEQ ID NO: 12) comprises all five extracellular Ig-like subdomains D1 –D5. The human CSF-1R fragment D1-D3 (SEQ ID NO: 13) comprises the respective subdomains

D1-D3. The sequences are listed without the signal peptide. The human CSF-1R fragment D4-D5 (SEQ ID NO: 14) comprises the respective subdomains D4-D5. The human CSF-1R fragment delD4 (SEQ ID NO: 15) comprises the ECD subdomains D1, D2, D3 and D5.

Currently two CSF-1R ligands that bind to the extracellular domain of CSF-1R are known. The first one is CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage; human CSF-1, SEQ ID NO: 16) and is found extracellularly as a disulfide-linked homodimer (Stanley, E.R. et al., Journal of Cellular Biochemistry 21 (1983) 151-159; Stanley, E.R. et al., Stem Cells 12 Suppl. 1 (1995) 15–24). The second one is IL-34 (human IL-34; SEQ ID NO: 17) (Hume, D. A., et al, Blood 119 (2012) 1810-1820). Thus in one embodiment the term "CSF-1R ligand" refers to human CSF-1 (SEQ ID NO: 16) and/or human IL-34 (SEQ ID NO: 17).

For experiments often the active 149 amino acid (aa) fragment of human CSF-1 (aa 33-181 of SEQ ID NO: 16) is used. This active 149 aa fragment of human CSF-1 (aa 33-181 of SEQ ID NO: 16) is contained in all 3 major forms of CSF-1 and is sufficient to mediate binding to CSF-1R (Hume, D. A., et al, Blood 119 (2012) 1810-1820).

The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of hematopoietic precursor cells to the macrophage lineage (including osteoclast). Activation of CSF-1R is mediated by its CSF-1R ligands, CSF-1 (M-CSF) and IL-34. Binding of CSF-1 (M-CSF) to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Li, W. et al, EMBO Journal.10 (1991) 277-288; Stanley, E.R., et al., Mol. Reprod. Dev. 46 (1997) 4-10).

As used herein, "binding to human CSF-1R" or "specifically binding to human CSF-1R" or "which binds to human CSF-1R" or "anti-CSF-1R antibody" refers to an antibody specifically binding to the human CSF-1R antigen with a binding affinity of KD-value of 1.0 x 10^{-8} mol/l or lower, in one embodiment of a KD-value of 1.0 x10^{-9} mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BIAcore®, GE-Healthcare Uppsala, Sweden). Thus an "antibody binding to human CSF-1R" as used herein refers to an antibody specifically binding to the human CSF-1R antigen with a binding affinity of KD 1.0 x 10^{-8} mol/l or lower (in one embodiment 1.0 x

10^{-8} mol/l - 1.0 x 10^{-13} mol/l), in on embodiment of a KD 1.0 x10^{-9} mol/l or lower (in one embodiment 1.0 x 10^{-9} mol/l - 1.0 x 10^{-13} mol/l).

In one embodiment the antibody which binds to human CSF-1R used in the combination therapy described herein is selected from the group consisting of

hMab 2F11-c11, hMab 2F11-d8 , hMab 2F11-e7 , hMab 2F11-f12 , and hMab 2F11-g1. These antibodies are described in WO 2011/070024.

In one embodiment the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab and is characterized in comprising the following VH and VL sequences as described herein:

Table 1:

anti-CSF-1R antibody	amino acid sequence of the heavy chain variable domain VH, SEQ ID NO:	amino acid sequence of the light chain variable domain VL, SEQ ID NO:
emactuzumab	1	2

These anti-CSF-1R antibodies described in the invention bind to the extracellular domain of human CSF-1R. In one preferred embodiment the anti-CSF-1R antibody binds to the membrane proximal domains D4 and D5 which constitute the receptor dimerization interface. So an antibody which binds to CSF-1R and binds to domains D4 and D5 of the extracellular domain (ECD) of human CSF-1R is characterized in that the anti-CSF1R antibody does not bind to the domains D1, D2 and D3 of the extracellular domain (ECD) of human CSF-1R.

In another embodiment the anti-CSF1R antibody binds to the domains D1 to D3. In one embodiment, the antibody which binds to human CSF-1R used in the combination therapy described herein is disclosed in WO 2009/026303, WO 2009/112245, WO 2011/123381 and US8263079, WO 2011/140249, and WO 2012/110360, (which all are incorporated by reference).

The anti-CSF-1R antibodies described in the invention block CSF-1, IL-34 mediated as well as ligand-independent activation of the receptor resulting in induction of apoptosis of M2-like macrophages differentiated in vitro in the presence of CSF-1 while sparing the M1-like GM-CSF differentiated macrophages.

In human breast cancer tissue, M2 (CD68+/CD163+) macrophages and CSF 1R-expressing macrophages are co-localized.

PD-1/PD-L1/PD-L2 pathway:

An important negative co-stimulatory signal regulating T cell activation is provided by programmed death – 1 receptor (PD-1)(CD279), and its ligand binding partners PD-L1 (B7-H1, CD274; SEQ ID NO: 18) and PD-L2 (B7-DC, CD273). The negative regulatory role of PD-1 was revealed by PD-1 knock outs (Pdcd1-/-), which are prone to autoimmunity. Nishimura et al., Immunity 11: 141-51 (1999); Nishimura et al., Science 291: 319-22 (2001). PD-1 is related to CD28 and CTLA-4, but lacks the membrane proximal cysteine that allows homodimerization. The cytoplasmic domain of PD-1 contains an immunoreceptor tyrosine-based inhibition motif (ITIM, V/IxYxxL/V). PD-1 only binds to PD-L1 and PD-L2. Freeman et al., J. Exp. Med. 192: 1-9 (2000); Dong et al., Nature Med. 5: 1365-1369 (1999); Latchman et al., Nature Immunol. 2: 261-268 (2001); Tseng et al., J. Exp. Med. 193: 839-846 (2001).

PD-1 can be expressed on T cells, B cells, natural killer T cells, activated monocytes and dendritic cells (DCs). PD-1 is expressed by activated, but not by unstimulated human CD4+ and CD8+ T cells, B cells and myeloid cells. This stands in contrast to the more restricted expression of CD28 and CTLA-4. Nishimura et al., Int. Immunol. 8: 773-80 (1996); Boettler et al., J. Virol. 80: 3532-40 (2006). There are at least 4 variants of PD-1 that have been cloned from activated human T cells, including transcripts lacking (i) exon 2, (ii) exon 3, (iii) exons 2 and 3 or (iv) exons 2 through 4. Nielsen et al., Cell. Immunol. 235: 109-16 (2005). With the exception of PD-1 Δex3, all variants are expressed at similar levels as full length PD-1 in resting peripheral blood mononuclear cells (PBMCs). Expression of all variants is significantly induced upon activation of human T cells with anti-CD3 and anti-CD28. The PD-1 Δex3 variants lacks a transmembrane domain, and resembles soluble CTLA-4, which plays an important role in autoimmunity. Ueda et al., Nature 423: 506-11 (2003). This variant is enriched in the synovial fluid and sera of patients with rheumatoid arthritis. Wan et al., J. Immunol. 177: 8844-50 (2006).

The two PD-1 ligands differ in their expression patterns. PD-L1 is constitutively expressed on mouse T and B cells, CDs, macrophages, mesenchymal stem cells and bone marrow-derived mast cells. Yamazaki et al., J. Immunol. 169: 5538-45

(2002). PD-L1 is expressed on a wide range of nonhematopoietic cells (e.g., cornea, lung, vascular epithelium, liver nonparenchymal cells, mesenchymal stem cells, pancreatic islets, placental synctiotrophoblasts, keratinocytes, etc.) [Keir et al., Annu. Rev. Immunol. 26: 677-704 (2008)], and is upregulated on a number of cell types after activation. Both type I and type II interferons IFN's) upregulate PD-L1. Eppihimer et al., Microcirculation 9: 133-45 (2002); Schreiner et al., J. Neuroimmunol. 155: 172-82 (2004). PD-L1 expression in cell lines is decreased when MyD88, TRAF6 and MEK are inhibited. Liu et al., Blood 110: 296-304 (2007). JAK2 has also been implicated in PD-L1 induction. Lee et al., FEBS Lett. 580: 755-62 (2006); Liu et al., Blood 110: 296-304 (2007). Loss or inhibition of phosphatase and tensin homolog (PTEN), a cellular phosphatase that modified phosphatidylinositol 3-kinase (PI3K) and Akt signaling, increased post-transcriptional PD-L1 expression in cancers. Parsa et al., Nat. Med. 13: 84-88 (2007).

PD-L2 expression is more restricted than PD-L1. PD-L2 is inducibly expressed on DCs, macrophages, and bone marrow-derived mast cells. PD-L2 is also expressed on about half to two-thirds of resting peritoneal B1 cells, but not on conventional B2 B cells. Zhong et al., Eur. J. Immunol. 37: 2405-10 (2007). PD-L2+ B1 cells bind phosphatidylcholine and may be important for innate immune responses against bacterial antigens. Induction of PD-L2 by IFN-gamma is partially dependent upon NF- κB. Liang et al., Eur. J. Immunol. 33: 2706-16 (2003). PD-L2 can also be induced on monocytes and macrophages by GM-CF, IL-4 and IFN-gamma. Yamazaki et al., J. Immunol. 169: 5538-45 (2002); Loke et al., PNAS 100:5336-41 (2003).

PD-1 signaling typically has a greater effect on cytokine production than on cellular proliferation, with significant effects on IFN-gamma, TNF-alpha and IL-2 production. PD-1 mediated inhibitory signaling also depends on the strength of the TCR signaling, with greater inhibition delivered at low levels of TCR stimulation. This reduction can be overcome by costimulation through CD28 [Freeman et al., J. Exp. Med. 192: 1027-34 (2000)] or the presence of IL-2 [Carter et al., Eur. J. Immunol. 32: 634-43 (2002)].

Evidence is mounting that signaling through PD-L1 and PD-L2 may be bidirectional. That is, in addition to modifying TCR or BCR signaling, signaling may also be delivered back to the cells expressing PD-L1 and PD-L2. While treatment of dendritic cells with a naturally human anti-PD-L2 antibody isolated

from a patient with Waldenstrom's macroglobulinemia was not found to upregulate MHC II or B7 costimulatory molecules, such cells did produce greater amount of proinflammatory cytokines, particularly TNF-alpha and IL-6, and stimulated T cell proliferation. Nguyen et al., J. Exp. Med. 196: 1393-98 (2002). Treatment of mice with this antibody also (1) enhanced resistance to transplanted b16 melanoma and rapidly induced tumor-specific CTL. Radhakrishnan et al., J. Immunol. 170: 1830-38 (2003); Radhakrishnan et al., Cancer Res. 64: 4965-72 (2004); Heckman et al., Eur. J. Immunol. 37: 1827-35 (2007); (2) blocked development of airway inflammatory disease in a mouse model of allergic asthma. Radhakrishnan et al., J. Immunol. 173: 1360-65 (2004); Radhakrishnan et al., J. Allergy Clin. Immunol. 116: 668-74 (2005).

Further evidence of reverse signaling into dendritic cells ("DC's") results from studies of bone marrow derived DC's cultured with soluble PD-1 (PD-1 EC domain fused to Ig constant region – "s-PD-1"). Kuipers et al., Eur. J. Immunol. 36: 2472-82 (2006). This sPD-1 inhibited DC activation and increased IL-10 production, in a manner reversible through administration of anti-PD-1.

Additionally, several studies show a receptor for PD-L1 or PD-L2 that is independent of PD-1. B7.1 has already been identified as a binding partner for PD-L1. Butte et al., Immunity 27: 111-22 (2007). Chemical crosslinking studies suggest that PD-L1 and B7.1 can interact through their IgV-like domains. B7.1:PD-L1 interactions can induce an inhibitory signal into T cells. Ligation of PD-L1 on CD4+ T cells by B7.1 or ligation of B7.1 on CD4+ T cells by PD-L1 delivers an inhibitory signal. T cells lacking CD28 and CTLA-4 show decreased proliferation and cytokine production when stimulated by anti-CD3 plus B7.1 coated beads. In T cells lacking all the receptors for B7.1 (i.e., CD28, CTLA-4 and PD-L1), T cell proliferation and cytokine production were no longer inhibited by anti-CD3 plus B7.1 coated beads. This indicates that B7.1 acts specifically through PD-L1 on the T-cell in the absence of CD28 and CTLA-4. Similarly, T cells lacking PD-1 showed decreased proliferation and cytokine production when stimulated in the presence of anti-CD3 plus PD-L1 coated beads, demonstrating the inhibitory effect of PD-L1 ligation on B7.1 on T cells. When T cells lacking all known receptors for PD-L1 (i.e., no PD-1 and B7.1), T cell proliferation was no longer impaired by anti-CD3 plus PD-L1 coated beads. Thus, PD-L1 can exert an inhibitory effect on T cells either through B7.1 or PD-1.

The direct interaction between B7.1 and PD-L1 suggests that the current understanding of costimulation is incomplete, and underscores the significance to the expression of these molecules on T cells. Studies of PD-L1-/- T cells indicate that PD-L1 on T cells can downregulate T cell cytokine production. Latchman et al., Proc. Natl. Acad. Sci. USA 101: 10691-96 (2004). Because both PD-L1 and B7.1 are expressed on T cells, B cells, DCs and macrophages, there is the potential for directional interactions between B7.1 and PD-L1 on these cells types. Additionally, PD-L1 on non-hematopoietic cells may interact with B7.1 as well as PD-1 on T cells, raising the question of whether PD-L1 is involved in their regulation. One possible explanation for the inhibitory effect of B7.1:PD-L1 interaction is that T cell PD-L1 may trap or segregate away APC B7.1 from interaction with CD28.

As a result, the antagonism of signaling through PD-L1, including blocking PD-L1 from interacting with either PD-1, B7.1 or both, thereby preventing PD-L1 from sending a negative co-stimulatory signal to T-cells and other antigen presenting cells is likely to enhance immunity in response to infection (e.g., acute and chronic) and tumor immunity. An exemplary PD-L1 antagonist is the anti-PD-L1 antibody atezolizumab.

In another embodiment, the anti-PD-L1/PD1 interaction can blocked by antagonist anti-PD-1 like the anti-PD1 antibodies pembrolizumab or nivolumab.

The term “human PD-L1” refers to the human protein PD-L1 (SEQ ID NO: 18, PD-1 signaling typically). As used herein, "binding to human PD-L1” or "specifically binding to human PD-L1” or “which binds to human PD-L1” or “anti-PD-L1 antibody” or “antagonistic anti-PD-L1” refers to an antibody specifically binding to the human PD-L1 antigen with a binding affinity of KD-value of 1.0 x 10^{-8} mol/l or lower, in one embodiment of a KD-value of 1.0 x10^{-9} mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BIAcore®, GE-Healthcare Uppsala, Sweden). Thus an “antibody binding to human PD-L1” as used herein refers to an antibody specifically binding to the human PD-L1 antigen with a binding affinity of KD 1.0 x 10^{-8} mol/l or lower (in one embodiment 1.0 x 10^{-8} mol/l - 1.0 x 10^{-13} mol/l), in on embodiment of a KD 1.0 x10^{-9} mol/l or lower (in one embodiment 1.0 x 10^{-9} mol/l - 1.0 x 10^{-13} mol/l).

The term “human PD1” refers to the human protein PD1 (SEQ ID NO: 19, PD-1 signaling typically). As used herein, "binding to human PD1” or "specifically binding to human PD1” or “which binds to human PD1” or “anti- PD1 antibody” or “antagonistic anti-PD1” refers to an antibody specifically binding to the human PD1 antigen with a binding affinity of KD-value of 1.0×10^{-8} mol/l or lower, in one embodiment of a KD-value of 1.0×10^{-9} mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BIAcore®, GE-Healthcare Uppsala, Sweden). Thus an “antibody binding to human PD1” as used herein refers to an antibody specifically binding to the human PD1 antigen with a binding affinity of KD 1.0×10^{-8} mol/l or lower (in one embodiment 1.0×10^{-8} mol/l - 1.0×10^{-13} mol/l), in on embodiment of a KD 1.0×10^{-9} mol/l or lower (in one embodiment 1.0×10^{-9} mol/l - 1.0×10^{-13} mol/l).

In one embodiment the antibody which binds to human PD-L1 used in the combination therapy described herein is atezolizumab or durvalumab and is characterized in comprising the following VH and VL sequences as described herein:

Table 2:

anti-PD-L1 antibody	amino acid sequence of the heavy chain variable domain VH, SEQ ID NO:	amino acid sequence of the light chain variable domain VL, SEQ ID NO:
atezolizumab	3	4
durvalumab	5	6

In one preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4, or

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab, or durvalumab.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab.

In one preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4, or

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6,

and the prior treatment of the cancer which failed was with an antagonistic PD-L1 antibody.

In one preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4, or

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6,

and the prior treatment of the cancer which failed, was with an antagonistic PD1 antibody.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4;

and the prior treatment of the cancer which failed was with an antagonistic PD-L1 antibody (in one embodiment with atezolizumab).

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4;

and the prior treatment of the cancer which failed, was with an antagonistic PD1 antibody.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab, or durvalumab; and the prior treatment of the cancer which failed was with an antagonistic PD-L1 antibody.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab; and the prior treatment of the cancer which failed was with an antagonistic PD-L1 antibody (in one embodiment with atezolizumab or durvalumab).

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab, or durvalumab; and the prior treatment of the cancer which failed was with an antagonistic PD1 antibody.

In another preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is emactuzumab, and the antibody which binds to human PD-L1 used in the combination therapy is atezolizumab; and the prior treatment of the cancer

which failed was with an antagonistic PD1 antibody (in one embodiment with pembrolizumab or nivolumab).

The term "epitope" denotes a protein determinant capable of specifically binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually epitopes have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

The "variable domain" (light chain variable domain VL, heavy chain variable domain VH) as used herein denotes each of the pair of light and heavy chain domains which are involved directly in binding the antibody to the antigen. The variable light and heavy chain domains have the same general structure and each domain comprises four framework (FR) regions whose sequences are widely conserved, connected by three "hypervariable regions" (or complementary determining regions, CDRs). The framework regions adopt a beta-sheet conformation and the CDRs may form loops connecting the beta-sheet structure. The CDRs in each chain are held in their three-dimensional structure by the framework regions and form together with the CDRs from the other chain the antigen binding site. The antibody's heavy and light chain CDR3 regions play a particularly important role in the binding specificity/affinity of the antibodies according to the invention and therefore provide a further object of the invention.

The term "antigen-binding portion of an antibody" when used herein refer to the amino acid residues of an antibody which are responsible for antigen-binding. The antigen-binding portion of an antibody comprises amino acid residues from the "complementary determining regions" or "CDRs". "Framework" or "FR" regions are those variable domain regions other than the hypervariable region residues as herein defined. Therefore, the light and heavy chain variable domains of an antibody comprise from N- to C-terminus the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Especially, CDR3 of the heavy chain is the region which contributes most to antigen binding and defines the antibody's properties. CDR and FR regions are determined according to the standard definition of Kabat et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991) and/or those residues from a "hypervariable loop".

The terms "nucleic acid" or "nucleic acid molecule", as used herein, are intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "amino acid" as used within this application denotes the group of naturally occurring carboxy alpha-amino acids comprising alanine (three letter code: ala, one letter code: A), arginine (arg, R), asparagine (asn, N), aspartic acid (asp, D), cysteine (cys, C), glutamine (gln, Q), glutamic acid (glu, E), glycine (gly, G), histidine (his, H), isoleucine (ile, I), leucine (leu, L), lysine (lys, K), methionine (met, M), phenylalanine (phe, F), proline (pro, P), serine (ser, S), threonine (thr, T), tryptophan (trp, W), tyrosine (tyr, Y), and valine (val, V).

The "Fc part" of an antibody is not involved directly in binding of an antibody to an antigen, but exhibit various effector functions. A "Fc part of an antibody" is a term well known to the skilled artisan and defined on the basis of papain cleavage of antibodies. Depending on the amino acid sequence of the constant region of their heavy chains, antibodies or immunoglobulins are divided in the classes: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG1, IgG2, IgG3, and IgG4, IgA1, and IgA2. According to the heavy chain constant regions the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively. The Fc part of an antibody is directly involved in ADCC (antibody-dependent cell-mediated cytotoxicity) and CDC (complement-dependent cytotoxicity) based on complement activation, C1q binding and Fc receptor binding. Complement activation (CDC) is initiated by binding of complement factor C1q to the Fc part of most IgG antibody subclasses. While the influence of an antibody on the complement system is dependent on certain conditions, binding to C1q is caused by defined binding sites in the Fc part. Such binding sites are known in the state of the art and described e.g. by Boackle, R.J., et al., Nature 282 (1979) 742-743; Lukas, T.J., et al., J. Immunol. 127 (1981) 2555-2560; Brunhouse, R., and Cebra, J.J., Mol. Immunol. 16 (1979) 907-917; Burton, D.R., et al., Nature 288 (1980) 338-344; Thommesen, J.E., et al., Mol. Immunol. 37 (2000) 995-1004; Idusogie, E.E., et al., J. Immunol.164 (2000) 4178-4184; Hezareh, M., et al., J. Virology 75 (2001) 12161-12168; Morgan, A., et al., Immunology 86 (1995) 319-324; EP 0 307 434. Such binding sites are e.g. L234, L235, D270, N297, E318, K320, K322, P331 and P329 (numbering according to EU index of Kabat, E.A., see below). Antibodies of subclass IgG1, IgG2 and IgG3 usually show complement activation and C1q and C3 binding, whereas IgG4 do not activate the complement system and do not bind C1q and C3.

In one embodiment the antibody according to the invention comprises an Fc part derived from human origin and preferably all other parts of the human constant regions. As used herein the term "Fc part derived from human origin" denotes a Fc part which is either a Fc part of a human antibody of the subclass IgG1, IgG2, IgG3 or IgG4, preferably a Fc part from human IgG1 subclass, a mutated Fc part from human IgG1 subclass (in one embodiment with a mutation on L234A + L235A), a Fc part from human IgG4 subclass or a mutated Fc part from human IgG4 subclass (in one embodiment with a mutation on S228P). In one preferred embodiment the human heavy chain constant region of human IgG1 subclass, in another preferred embodiment the human heavy chain constant region is of human IgG1 subclass with mutations L234A, L235A and P329, in another preferred embodiment the human heavy chain constant region is of human IgG4 subclass, and in another preferred embodiment the human heavy chain constant region is of human IgG4 subclass with mutation S228P. In one embodiment said antibodies have reduced or minimal effector function. In one embodiment the minimal effector function results from an effectorless Fc mutation. In one embodiment the effectorless Fc mutation is L234A/L235A or L234A/L235A/P329G or N297A or D265A/N297A. In one embodiment the effectorless Fc mutation is selected for each of the antibodies independently of each other from the group comprising (consisting of) L234A/L235A, L234A/L235A/P329G, N297A and D265A/N297A.

In one embodiment the antibodies described herein are of human IgG class (i.e. of IgG1, IgG2, IgG3 or IgG4 subclass).

In a preferred embodiment the antibodies described herein are of human IgG1 subclass or of human IgG4 subclass. In one embodiment the described herein are of human IgG1 subclass. In one embodiment the antibodies described herein are of human IgG4 subclass.

In one embodiment the antibody described herein is characterized in that the constant chains are of human origin. Such constant chains are well known in the state of the art and e.g. described by Kabat, E.A., (see e.g. Johnson, G. and Wu, T.T., Nucleic Acids Res. 28 (2000) 214-218). For example, a useful human heavy chain constant region comprises an amino acid sequence of SEQ ID NO: 21. For example, a useful human light chain constant region comprises an amino acid sequence of a kappa-light chain constant region of SEQ ID NO: 20.

The invention comprises a method for the treatment of a patient in need of therapy, characterized by administering to the patient a therapeutically effective amount of an antibody according to the invention.

The invention comprises the use of an antibody according to the invention for the described therapy.

One embodiment of the invention are the CSF-1R antibodies described herein in for use in the treatment of cancer in combination with an antagonistic PD-L1 antibody as described herein.

The term "cancer" as used herein may be, for example, lung cancer, non small cell lung (NSCL) cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. In one preferred embodiment such cancer is a breast cancer, colorectal cancer, melanoma, head and neck cancer, lung cancer or prostate cancer. In one preferred embodiment such cancer is a breast cancer, ovarian cancer, cervical cancer, lung cancer or prostate cancer. In another preferred embodiment such cancer is breast cancer, lung cancer, colon cancer, ovarian cancer, melanoma cancer, bladder cancer, renal cancer, kidney cancer, liver cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric carcinoma cancer, esophageal cancer, mesothelioma, prostate cancer, leukemia, lymphoma, myelomas. In one preferred embodiment such cancers are further characterized by CSF-1 or CSF-1R expression or overexpression. One further embodiment the invention are the CSF-1R antibodies of the present invention for

use in the simultaneous treatment of primary tumors and new metastases. Thus another embodiment of the invention are the CSF-1R antibodies of the present invention for use in the treatment of periodontitis, histiocytosis X, osteoporosis, Paget's disease of bone (PDB), bone loss due to cancer therapy, periprosthetic osteolysis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, psioratic arthritis, osteoarthritis, inflammatory arthridities, and inflammation.

In one preferred embodiment of the invention the cancer is a lymphoma (preferably B-cell Non-Hodgkin's lymphomas (NHL)) and lymphocytic leukemias. Such lymphomas and lymphocytic leukemias include e.g. a) follicular lymphomas, b) Small Non-Cleaved Cell Lymphomas/ Burkitt's lymphoma (including endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma and Non-Burkitt's lymphoma) c) marginal zone lymphomas (including extranodal marginal zone B cell lymphoma (Mucosa-associated lymphatic tissue lymphomas, MALT), nodal marginal zone B cell lymphoma and splenic marginal zone lymphoma), d) Mantle cell lymphoma (MCL), e) Large Cell Lymphoma (including B-cell diffuse large cell lymphoma (DLCL), Diffuse Mixed Cell Lymphoma, Immunoblastic Lymphoma, Primary Mediastinal B-Cell Lymphoma, Angiocentric Lymphoma-Pulmonary B-Cell Lymphoma) f) hairy cell leukemia, g) lymphocytic lymphoma, waldenstrom's macroglobulinemia, h) acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukemia, i) plasma cell neoplasms, plasma cell myeloma, multiple myeloma, plasmacytoma j) Hodgkin's disease.

In one further embodiment, the cancer is a B-cell Non-Hodgkin's lymphomas (NHL). In further embodiment, the cancer is a Mantle cell lymphoma (MCL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), B-cell diffuse large cell lymphoma (DLCL), Burkitt´s lymphoma, hairy cell leukemia, follicular lymphoma, multiple myeloma, marginal zone lymphoma, post transplant lymphoproliferative disorder (PTLD), HIV associated lymphoma, waldenstrom's macroglobulinemia, or primary CNS lymphoma.

In one preferred embodiment the cancer is a Non-Hodgkin lymphoma, in one embodiment a B-cell diffuse large cell lymphoma (DLCL). In one embodiment, the method comprises administering to an individual having DLBLC an effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-

L1 antibody or an antagonistic PD1 antibody failed. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. In one embodiment, the one or more additional therapeutic agents are selected from rituximab, obinituzumab, cyclophosphamide, doxorubicin, vincristine, prednisolone, methylprednisolone, ifosfamide, carboplatin, etoposide, dexamethasone, high-dose cytarabine, cisplatin, and bendamustine.

In another preferred embodiment of the invention the cancer is a multiple myeloma. In one embodiment, the method comprises administering to an individual having multiple myeloma an effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

In another preferred embodiment of the invention the cancer is a solid tumor.

In another preferred embodiment of the invention the cancer is a melanoma, urinary bladder cancer (UCB), or lung cancer (e.g. non small cell lung (NSCL) cancer). In another preferred embodiment of the invention the cancer is a Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

In another preferred embodiment of the invention the cancer is urinary bladder cancer (UCB). In a further aspect, the invention provides a method for treating a bladder cancer or urothelial carcinoma, such as a transitional cell carcinoma (TCC), by administering an effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In a further aspect of the embodiment, the bladder cancer is a squamous cell carcinoma. In a further aspect, the bladder cancer is selected from the group consisting of adenocarcinoma, small cell carcinoma and sarcoma. In one embodiment, the method comprises administering to an individual having a bladder cancer an effective amount of the CSF-1R antibodies described herein in combination with an

antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from gemcitabine, cisplatin, methotrexate, vinblastine, doxorubicin, carboplatin, vinflunine, paclitaxel and docetaxel may be co-administered.

In another preferred embodiment of the invention the cancer is melanoma. In further aspects, the invention provides methods for treating melanoma by administering to a patient in need thereof a therapeutically effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib and cobimetinib) for BRAF-mutated melanomas. (e.g. V600 mutant melanoma) may be co-administered.

In another preferred embodiment of the invention the cancer is lung cancer. In one embodiment the lung cancer is Small Cell Lung Cancer (SCLC). In one embodiment, the SCLC is a small cell carcinoma (oat cell cancer), mixed small cell/large cell carcinoma or combined small cell carcinoma. In further aspects, the invention provides methods for treating Small Cell Lung Cancer (SCLC) by administering to a patient in need thereof a therapeutically effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In one such embodiment, the method further

comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from etoposide, a platinum compound (cisplatin or carboplatin), irinotecan, topotecan, vinca alkaloids (vinblastine, vincristine, or vinorelbine), alkylating agents (cyclophosphamide or ifosfamide), doxorubicin, taxanes (docetaxel or paclitaxel), and gemcitabine may be co-administered. In one embodiment the lung cancer is Non-Small Cell Lung Cancer (NSCLC). In one embodiment, the SCLC is a small cell carcinoma (oat cell cancer), mixed small cell/large cell carcinoma or combined small cell carcinoma. In further aspects, the invention provides methods for treating Non-Small Cell Lung Cancer (NSCLC) by administering to a patient in need thereof a therapeutically effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from cisplatin, carboplatin, paclitaxel, paclitaxel protein bound, docetaxel, gemcitabine, vinorelbine, etoposide, nintedanib, vinblastine, and pemetrexed, afatinib, bevacizumab, cabozantinib, ceritinib, crizotinib, erlotinib hydrochloride, osimertinib, ramucirumab, gefitinib, necitumumab, alectinib, trastuzumab, cetuximab, ipilimumab, trametinib, dabrafenib, vemurafenib, dacomitinib, tivantinib, onartuzumab, especially EGFR tyrosine kinase inhibitors like e.g. erlotinib for EGFR positive cancers, and ALK inhibitors like e.g. critozinib, alectinib, for ALK positive cancers, may be co-administered.

In another preferred embodiment of the invention the cancer is Head and Neck Squamous Cell Carcinoma (HNSCC). In further aspects, the invention provides methods for treating Head and Neck Squamous Cell Carcinoma (HNSCC) by administering to a patient in need thereof a therapeutically effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1

antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from methotrexate, cetuximab, cisplatin, carboplatin, paclitaxel, paclitaxel protein bound, docetaxel and 5-fluorouracil may be co-administered.

In another preferred embodiment of the invention the cancer is Renal cell carcinoma (RCC) In one embodiment, the method comprises administering to an individual having Renal cell carcinoma (RCC) an effective amount of the CSF-1R antibodies described herein in combination with an antagonistic PD-L1 antibody as described herein wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed. The CSF-1R antibodies in combination with an antagonistic PD-L1 antibody as described herein can be used either as anti-CSF-1R/anti-PD-L1 combination alone or in addition in combination with other agents in a therapy. For instance, one or more additional therapeutic agents selected from e.g. bevacizumab may be co-administered.

The antibodies described herein are preferably produced by recombinant means. Such methods are widely known in the state of the art and comprise protein expression in prokaryotic and eukaryotic cells with subsequent isolation of the antibody polypeptide and usually purification to a pharmaceutically acceptable purity. For the protein expression nucleic acids encoding light and heavy chains or fragments thereof are inserted into expression vectors by standard methods. Expression is performed in appropriate prokaryotic or eukaryotic host cells, such as CHO cells, NS0 cells, SP2/0 cells, HEK293 cells, COS cells, yeast, or E. coli cells, and the antibody is recovered from the cells (from the supernatant or after cells lysis).

Recombinant production of antibodies is well-known in the state of the art and described, for example, in the review articles of Makrides, S.C., Protein Expr. Purif. 17 (1999) 183-202; Geisse, S., et al., Protein Expr. Purif. 8 (1996) 271-282;

Kaufman, R.J., Mol. Biotechnol. 16 (2000) 151-161; Werner, R.G., Drug Res. 48 (1998) 870-880.

The antibodies may be present in whole cells, in a cell lysate, or in a partially purified, or substantially pure form. Purification is performed in order to eliminate other cellular components or other contaminants, e.g. other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis, and others well known in the art. See Ausubel, F., et al., ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

Expression in NS0 cells is described by, e.g., Barnes, L.M., et al., Cytotechnology 32 (2000) 109-123; Barnes, L.M., et al., Biotech. Bioeng. 73 (2001) 261-270. Transient expression is described by, e.g., Durocher, Y., et al., Nucl. Acids. Res. 30 (2002) E9. Cloning of variable domains is described by Orlandi, R., et al., Proc. Natl. Acad. Sci. USA 86 (1989) 3833-3837; Carter, P., et al., Proc. Natl. Acad. Sci. USA 89 (1992) 4285-4289; Norderhaug, L., et al., J. Immunol. Methods 204 (1997) 77-87. A preferred transient expression system (HEK 293) is described by Schlaeger, E.-J. and Christensen, K., in Cytotechnology 30 (1999) 71-83, and by Schlaeger, E.-J., in J. Immunol. Methods 194 (1996) 191-199.

The heavy and light chain variable domains according to the invention are combined with sequences of promoter, translation initiation, constant region, 3' untranslated region, polyadenylation, and transcription termination to form expression vector constructs. The heavy and light chain expression constructs can be combined into a single vector, co-transfected, serially transfected, or separately transfected into host cells which are then fused to form a single host cell expressing both chains.

The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, enhancers and polyadenylation signals.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is

positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The monoclonal antibodies are suitably separated from the culture medium by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. DNA and RNA encoding the monoclonal antibodies are readily isolated and sequenced using conventional procedures. The hybridoma cells can serve as a source of such DNA and RNA. Once isolated, the DNA may be inserted into expression vectors, which are then transfected into host cells such as HEK 293 cells, CHO cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of recombinant monoclonal antibodies in the host cells.

As used herein, the expressions “cell”, “cell line”, and “cell culture” are used interchangeably and all such designations include progeny. Thus, the words “transformants” and “transformed cells” include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Variant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

In another aspect, the present invention provides a composition, e.g. a pharmaceutical composition, containing one or a combination of monoclonal antibodies, or the antigen-binding portion thereof, of the present invention, formulated together with a pharmaceutically acceptable carrier.

As used herein, “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption/resorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for injection or infusion.

A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. In addition to water, the carrier can be, for example, an isotonic buffered saline solution.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient (effective amount). The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

The term "a method of treating" or its equivalent, when applied to, for example, cancer refers to a procedure or course of action that is designed to reduce or eliminate the number of cancer cells in a patient, or to alleviate the symptoms of a cancer. "A method of treating" cancer or another proliferative disorder does not necessarily mean that the cancer cells or other disorder will, in fact, be eliminated, that the number of cells or disorder will, in fact, be reduced, or that the symptoms of a cancer or other disorder will, in fact, be alleviated. Often, a method of treating cancer will be performed even with a low likelihood of success, but which, given the medical history and estimated survival expectancy of a patient, is nevertheless deemed to induce an overall beneficial course of action.

The terms “administered in combination with” or “co-administration”, “co-administering”, “combination therapy“ or “combination treatment” refer to the

administration of the anti-CSF-1R as described herein, and the antagonistic PD-L1 antibody, as described herein e.g. as separate formulations/applications (or as one single formulation/application). The co-administration can be simultaneous or sequential in either order, wherein there is a time period while both (or all) active agents simultaneously exert their biological activities. The co-administration is either simultaneously or sequentially (e.g. intravenous (i.v.) through a continuous infusion. In one embodiment the co-administration is simultaneously. In one embodiment the co-administration is sequentially. The co-administration is either simultaneously or sequentially (e.g. intravenous (i.v.) through a continuous infusion.

It is self-evident that the antibodies are administered to the patient in a "therapeutically effective amount" (or simply "effective amount") which is the amount of the respective compound or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The amount of co-administration and the timing of co-administration will depend on the type (species, gender, age, weight, etc.) and condition of the patient being treated and the severity of the disease or condition being treated. Said anti-CSF-1R antibody and further agent are suitably co-administered to the patient at one time or over a series of treatments e.g. on the same day or on the day after.

In one embodiment such additional chemotherapeutic agents, which may be administered with the anti-CSF-1R antibody as described herein and the antagonistic PD-L1 antibody, as described herein , include, but are not limited to, anti-neoplastic agents including alkylating agents including: nitrogen mustards, such as mechlorethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas, such as carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU); Temodal(TM) (temozolamide), ethylenimines/methylmelamine such as thriethylenemelamine (TEM), triethylene, thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC); antimetabolites including folic acid analogs such as methotrexate and trimetrexate, pyrimidine analogs such as 5-fluorouracil (5FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'-difluorodeoxycytidine, purine analogs such as 6-merca.rho.topurine, 6-thioguamne, azathioprine, T-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine

phosphate, and 2- chlorodeoxyadenosine (cladribine, 2-CdA); natural products including antimitotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorelbine, taxotere, estramustine, and estramustine phosphate; pipodophylotoxins such as etoposide and teniposide; antibiotics such as actinomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycin C, and actinomycin; enzymes such as L-asparaginase; biological response modifiers such as interferon-alpha, IL-2, G-CSF and GM-CSF; miscellaneous agents including platinum coordination complexes such as oxaliplatin, cisplatin and carboplatin, anthracenediones such as mitoxantrone, substituted urea such as hydroxyurea, methylhydrazine derivatives including N- methylhydrazine (MIH) and procarbazine, adrenocortical suppressants such as mitotane (o, p-DDD) and aminoglutethimide; hormones and antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide; Gemzar(TM) (gemcitabine), progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate; estrogen such as diethylstilbestrol and ethinyl estradiol equivalents; antiestrogen such as tamoxifen; androgens including testosterone propionate and fluoxymesterone/equivalents; antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide; and non-steroidal antiandrogens such as flutamide. Therapies targeting epigenetic mechanism including, but not limited to, histone deacetylase inhibitors, demethylating agents (e.g., Vidaza) and release of transcriptional repression (ATRA) therapies can also be combined with the antigen binding proteins. In one embodiment the chemotherapeutic agent is selected from the group consisting of taxanes (like e.g. paclitaxel (Taxol), docetaxel (Taxotere), modified paclitaxel (e.g., Abraxane and Opaxio), doxorubicin, sunitinib (Sutent), sorafenib (Nexavar), and other multikinase inhibitors, oxaliplatin, cisplatin and carboplatin, etoposide, gemcitabine, and vinblastine. In one embodiment the chemotherapeutic agent is selected from the group consisting of taxanes (like e.g. taxol (paclitaxel), docetaxel (Taxotere), modified paclitaxel (e.g. Abraxane and Opaxio). In one embodiment, the additional chemotherapeutic agent is selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, or oxaliplatin. In one embodiment the chemotherapeutic agent is 5-fluorouracil, leucovorin and irinotecan (FOLFIRI). In one embodiment the chemotherapeutic agent is 5-fluorouracil, and oxaliplatin (FOLFOX).

In one preferred embodiment, no additional chemotherapeutic agent is administered together with the anti-CSF-1R antibody in combination with the PD1/PD-L1 inhibitor.

Description of the amino acid sequences

SEQ ID NO: 1	heavy chain variable domain, anti-CSF-1R antibody emactuzumab
SEQ ID NO: 2	light chain variable domain, anti-CSF-1R antibody emactuzumab
SEQ ID NO: 3	heavy chain variable domain of anti-PD-L1 antibody atezolizumab
SEQ ID NO: 4	light chain variable domain of anti-PD-L1 antibody atezolizumab
SEQ ID NO: 5	heavy chain variable domain of anti-PD-L1 antibody durvalumab
SEQ ID NO: 6	light chain variable domain of anti-PD-L1 antibody durvalumab
SEQ ID NO: 7	heavy chain variable domain of anti-PD1 antibody pembrolizumab
SEQ ID NO: 8	light chain variable domain of anti-PD1 antibody pembrolizumab
SEQ ID NO: 9	heavy chain variable domain of anti-PD1 antibody nivolumab
SEQ ID NO: 10	light chain variable domain of anti-PD1 antibody nivolumab
SEQ ID NO: 11	exemplary human CSF-1R (wt CSF-1R)
SEQ ID NO: 12	human CSF-1R Extracellular Domain (domains D1-D5)
SEQ ID NO: 13	human CSF-1R fragment domains D1-D3
SEQ ID NO: 14	human CSF-1R fragment domains D4-D5
SEQ ID NO: 15	human CSF-1R fragment delD4 (domains 1,2,3 and 5 of the Extracellular Domain)
SEQ ID NO: 16	exemplary human CSF-1
SEQ ID NO: 17	exemplary human IL-34
SEQ ID NO: 18	exemplary human PD-L1
SEQ ID NO: 19	exemplary human PD1
SEQ ID NO: 20	human kappa light chain constant region
SEQ ID NO: 21	human heavy chain constant region derived from IgG1

SEQ ID NO: 22	human heavy chain constant region derived from IgG1 mutated on L234A and L235A
SEQ ID NO: 23	human heavy chain constant region derived from IgG4
SEQ ID NO: 24	human heavy chain constant region derived from IgG4 mutated on S228P
SEQ ID NO: 25	heavy chain variable domain, anti-CSF-1R antibody 1 of US8263079
SEQ ID NO: 26	light chain variable domain, anti-CSF-1R antibody 1 of US8263079
SEQ ID NO: 27	heavy chain, anti-CSF-1R antibody 1 of US8263079
SEQ ID NO: 28	light chain, anti-CSF-1R antibody 1 of US8263079
SEQ ID NO: 29	heavy chain of anti-PD-L1 antibody avelumab
SEQ ID NO: 30	light chain of anti-PD-L1 antibody avelumab

In the following, specific embodiments of the invention are described:

1A. An antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

1B. An antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein the cancer showed disease progression (in one embodiment a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment of the

cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein the patient (suffering from cancer) showed disease progression on (and/or after) the prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody.

2. The anti-CSF-1R antibody for use in the treatment according to embodiment 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The anti-CSF-1R antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The anti-CSF-1R antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

7. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

8. The anti-CSF-1R antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab or avelumab treatment (In one embodiment a atezolizumab or durvalumab or avelumab monotherapy).

10. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment (In one embodiment a atezolizumab monotherapy).

11. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a durvalumab or avelumab treatment (In one embodiment a durvalumab or avelumab monotherapy).

12. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment (In one embodiment a pembrolizumab or nivolumab monotherapy).

13. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 12, wherein the antagonistic PD-L1 antibody used in combination .is administered at a dose of 1100-1300 mg (in one embodiment at a dose of 1200 mg) at each cycle.

14. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg (in one embodiment at a dose of 1000 mg) at each cycle.

15. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth (or of an immune related disease such as tumor immunity).

16. The anti-CSF-1R antibody for use in the treatment according to any one of embodiments 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

In the following, specific embodiments of the invention are described:

1A. A pharmaceutical composition or medicament comprising an antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

1B. A pharmaceutical composition or medicament comprising an antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein the cancer showed disease progression (in one embodiment a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein the patient (suffering from cancer) showed disease progression on (and/or after) the prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody.

2. The pharmaceutical composition or medicament according to embodiment 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The pharmaceutical composition or medicament according to any one of embodiments 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The pharmaceutical composition or medicament according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The pharmaceutical composition or medicament according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The pharmaceutical composition or medicament according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

7. The pharmaceutical composition or medicament according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

8. The pharmaceutical composition or medicament according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The pharmaceutical composition or medicament according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab or avelumab treatment (In one embodiment a atezolizumab or durvalumab or avelumab monotherapy).

10. The pharmaceutical composition or medicament according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment (In one embodiment a atezolizumab monotherapy).

11. The pharmaceutical composition or medicament according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a durvalumab or avelumab treatment (In one embodiment a durvalumab or avelumab monotherapy).

12. The pharmaceutical composition or medicament according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment (In one embodiment a pembrolizumab or nivolumab monotherapy).

13. The pharmaceutical composition or medicament according to any one of embodiments 1 to 12, wherein the antagonistic PD-L1 antibody used in combination .is administered at a dose of 1100-1300 mg (in one embodiment at a dose of 1200 mg) at each cycle.

14. The pharmaceutical composition or medicament according to any one of embodiments 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg (in one embodiment at a dose of 1000 mg) at each cycle.

15. The pharmaceutical composition or medicament according to any one of embodiments 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth (or of an immune related disease such as tumor immunity).

16. The pharmaceutical composition or medicament according to any one of embodiments 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

17. The pharmaceutical composition or medicament according to any one of embodiments 1 to 16, wherein the cancer is melanoma, urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

18. The pharmaceutical composition or medicament according to any one of embodiments 1 to 16, wherein the cancer is urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

19. The pharmaceutical composition or medicament according to any one of embodiments 1 to 16, wherein the cancer is Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

In the following, specific embodiments of the invention are described:

1A. Use of an antibody which binds to human CSF-1R in the manufacture of a medicament for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

1B. Use of an antibody which binds to human CSF-1R in the manufacture of a medicament for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein the cancer showed disease progression (in one embodiment a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein the patient (suffering from cancer) showed disease progression on (and/or after) the prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody.

2. The use according to embodiment 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The use according to any one of embodiments 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The use according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The use according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The use according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

7. The use according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

8. The use according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The use according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab or avelumab treatment (In one embodiment a atezolizumab or durvalumab or avelumab monotherapy).

10. The use according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment (In one embodiment a atezolizumab monotherapy).

11. The use according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a durvalumab or avelumab treatment (In one embodiment a durvalumab or avelumab monotherapy).

12. The use according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment (In one embodiment a pembrolizumab or nivolumab monotherapy).

13. The use according to any one of embodiments 1 to 12, wherein the antagonistic PD-L1 antibody used in combination .is administered at a dose of 1100-1300 mg (in one embodiment at a dose of 1200 mg) at each cycle.

14. The use according to any one of embodiments 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg (in one embodiment at a dose of 1000 mg) at each cycle.

15. The use according to any one of embodiments 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth (or of an immune related disease such as tumor immunity).

16. The use according to any one of embodiments 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

17. The use according to any one of embodiments 1 to 16, wherein the cancer is melanoma, urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

18. The use according to any one of embodiments 1 to 16, wherein the cancer is urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

19. The use according to any one of embodiments 1 to 16, wherein the cancer is Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

In the following, specific embodiments of the invention are described:

1A. A method of treatment, the method comprising administering (an effective amount of) an antibody which binds to human CSF-1R, for

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

1B. A method of treatment, the method comprising administering (an effective amount of) an antibody which binds to human CSF-1R, for

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein the cancer showed disease progression (in one embodiment a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein the patient (suffering from cancer) showed disease progression on (and/or after) the prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody.

2. The method according to embodiment 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The method according to any one of embodiments 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The method according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6

or c) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The method according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The method according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

7. The method according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

8. The method according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The method according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab or avelumab treatment (In one embodiment a atezolizumab or durvalumab or avelumab monotherapy).

10. The method according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment (In one embodiment a atezolizumab monotherapy).

11. The method according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a durvalumab or avelumab treatment (In one embodiment a durvalumab or avelumab monotherapy).

12. The method according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment (In one embodiment a pembrolizumab or nivolumab monotherapy).

13. The method according to any one of embodiments 1 to 12, wherein the antagonistic PD-L1 antibody used in combination .is administered at a dose of 1100-1300 mg (in one embodiment at a dose of 1200 mg) at each cycle.

14. The method according to any one of embodiments 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg (in one embodiment at a dose of 1000 mg) at each cycle.

15. The method according to any one of embodiments 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth (or of an immune related disease such as tumor immunity).

16. The method according to any one of embodiments 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

17. The method according to any one of embodiments 1 to 16, wherein the cancer is melanoma, urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

18. The method according to any one of embodiments 1 to 16, wherein the cancer is urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

19. The method according to any one of embodiments 1 to 16, wherein the cancer is Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

In the following, specific embodiments of the invention are described:

1A. An antagonistic PD-L1 antibody, for use in

a) the treatment of cancer in combination with an antibody which binds to human CSF-1R, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antibody which binds to human CSF-1R, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

1B. An antagonistic PD-L1 antibody, for use in

a) the treatment of cancer in combination with an antibody which binds to human CSF-1R, wherein the cancer showed disease progression (in one embodiment a Progressive Disease (PD) according to the RECIST1.1 criteria for solid tumors) on (and/or after) the prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antibody which binds to human CSF-1R, wherein the patient (suffering from cancer) showed disease progression on (and/or after) the prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody.

2. The antagonistic PD-L1 antibody for use in the treatment according to embodiment 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The antagonistic PD-L1 antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The antagonistic PD-L1 antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

7. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 5, wherein in the combination treatment the anti-

CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab or avelumab.

8. The antagonistic PD-L1 antibody for use in the treatment according to embodiment 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab or avelumab treatment (In one embodiment a atezolizumab or durvalumab or avelumab monotherapy).

10. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment (In one embodiment a atezolizumab monotherapy).

11. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a durvalumab or avelumab treatment (In one embodiment a durvalumab or avelumab monotherapy).

12. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment (In one embodiment a pembrolizumab or nivolumab monotherapy).

13. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 12, wherein the antagonistic PD-L1 antibody used in combination .is administered at a dose of 1100-1300 mg (in one embodiment at a dose of 1200 mg) at each cycle.

14. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg (in one embodiment at a dose of 1000 mg) at each cycle.

15. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth (or of an immune related disease such as tumor immunity).

16. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

17. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 16, wherein the cancer is melanoma, urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

18. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 16, wherein the cancer is urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

19. The antagonistic PD-L1 antibody for use in the treatment according to any one of embodiments 1 to 16, wherein the cancer is Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

Examples

Determination of the binding of anti-CSF-1R antibodies to human CSF-1R fragment delD4 and to human CSF-1R Extracellular Domain (CSF-1R-ECD)

The binding of anti-CSF-1R antibodies to human CSF-1R fragment delD4 (SEQ ID NO: 15) and to human CSF-1R Extracellular Domain (CSF-1R-ECD) (SEQ ID NO: 12) was measured as described in Example 4 of WO 2011/070024. Results of the binding signal in Relative Units (RU) are shown below.

Table:

Binding of <CSF-1R> MAbs to human CSF-1R fragment delD4 and CSF-1R-ECD, measured by SPR

	Binding to delD4 [RU]	Binding to CSF-1R-ECD [RU]
emactuzumab	0	237

Anti-CSF-1R emactuzumab showed binding to the human CSF-1R Extracellular Domain (CSF-1R-ECD); however no binding was detected to CSF-1R fragment delD4.

Determination of the binding of anti-CSF-1R antibodies to human CSF-1R fragment D1-D3

The binding of anti-CSF-1R antibodies to f anti-CSF-1R antibodies to human CSF-1R fragment D1-D3 (SEQ ID NO:13) was measured as described in Example 10 of WO2011/070024. Results are shown below.

Table:

Binding of human CSF-1R fragment D1-D3 measured by SPR

CSF-1R Mab	**Sub domain**	**K_D (nM)**
emactuzumab	D1-D3	no binding

Combination of anti-CSF-1R antibody and an antagonistic anti-PD-L1 antibody after PD1/PD-L1 treatment failure:

Clinical efficacy in the sense of anti-tumor activity was/will be assessed as follows:

Best overall response.

Overall response rate (ORR), defined as partial response rate plus complete response rate, confirmed by repeated assessments ≥ 4 weeks after initial documentation.

Progressive-free survival (PFS), defined as the time from first study treatment to the first occurrence of disease progression or death, whichever occurs first.

Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to the time of progression or death from any cause, whichever occurs first.

Clinical benefit rate (CBR), defined as partial response rate plus complete response rate plus stable disease rate.

Best overall response, objective response and disease progression will be determined by Investigator assessment and by central review using both conventional RECIST v1.1 and modified RECIST criteria. Optional submission of the latest (not older than 6 months prior to Cycle 1 Day 1) pre-study computed tomography (CT) scans (historical CT scans) is highly encouraged if available. This scan will be compared to those collected during the study to determine longitudinal tumor-growth kinetics.

Example 1.1: Combination of anti-CSF-1R antibody and anti-PDL1 antibody after anti-PDL1 antibody treatment failure in urothelial bladder cancer (UBC)

The example presents the case of a 52y/o male patient diagnosed with UBC in Oct 2013. The patient had received 6 cycles of methotrexate, vinblastine, adriamycine and CDDP.

Because of progressive disease under this treatment, the patient was included in the clinical trial GO29294 (IMvigor211) and received a total of seven infusions of the anti-PD-L1 antibody atezolizumab (TECENTRIQ) (1200mg every 3 weeks). The patient showed continuous disease progression (Progressive Disease (PD) according to RECIST 1.1) and treatment was discontinued. The patient then entered clinical study BP29428 and received combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200mg) every 3 weeks. Under this regimen the patient, previously unresponsive to anti-PD-L1 monotherapy, showed initially a partial response (PR according to RECIST 1.1) followed by a complete response (CR). Results are shown in Figure 1.

Example 1.2: Combination of anti-CSF-1R antibody and anti-PDL1 antibody after anti-PDL1 antibody treatment failure in urothelial bladder cancer (UBC)

The example presents the case of a 64y/o female patient diagnosed with UBC in Feb 2013. The patient had received 3 cycles of neoadjuvant treatment with gemcitabine and cisplatine; subsequent curative cystectomy and lymph node removal; adjuvant radiotherapy of the bladder (total cumulative dose: 45 Gy); 6 cycles of methotrexate as first line treatment for metastatic disease (best RECIST response: unknown); and 25 cycles of an anti-PD-L1 antibody (not further specified) as a second line treatment for metastatic disease under which the patient experienced a complete response (CR according to RECIST 1.1) but ultimately developed progressive disease.

The patient then entered clinical study BP29428 and received combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200mg) every 3 weeks. Under this regimen the patient showed initially a stable disease (SD) which further improved to a PR during subsequent tumor assessments. As of today the patient is still ongoing on Study BP29428. Results are shown in Figure 2.

The patient then entered clinical study BP29428 and received combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200mg) every 3 weeks. Under this regimen the patient showed initially a SD which further improved to a PR during subsequent tumor assessments. As of today the patient is still ongoing on Study BP29428. Results are shown in Figure 4.

Example 2: Combination of anti-CSF-1R antibody and anti-PD-L1 antibody after anti-PD-L1 antibody treatment failure in melanoma

Analogously as described in Examples 1 to 4, patients suffering from a melanoma which show progression (progressive disease PD according to RECIST 1.1) under anti-PD-L1 treatment (atezolizumab (1200 mg every 3 weeks)), receive a combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200 mg) every 3 weeks. Responses are determined as described in Examples 1.

Example 3: Combination of anti-CSF-1R antibody and anti-PD-L1 antibody after anti-PD-L1 antibody treatment failure in urinary bladder cancer (UBC), lung cancer or melanoma

Analogously as described in Examples 1 to 4, patients suffering from urinary bladder cancer (UBC), lung cancer or melanoma which show progression (progressive disease PD according to RECIST 1.1) under anti-PD-L1 treatment (durvalumab or avelumab), receive a combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200 mg) every 3 weeks. Responses are determined as described in Examples 1 to 2.

Example 4: Combination of anti-CSF-1R antibody and anti-PD-L1 antibody after anti-PD1 antibody treatment failure in urinary bladder cancer (UBC), lung cancer or melanoma

Analogously as described in Examples 1 to 4, patients suffering from urinary bladder cancer (UBC), lung cancer or melanoma which show progression (progressive disease PD according to RECIST 1.1) under anti-PD1 treatment (pembrolizumab or nivolumab), receive a combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200 mg) every 3 weeks. Responses are determined as described in Examples 1 to 3.

Example 4.1: Combination of anti-CSF-1R antibody and anti-PDL1 antibody after anti-PD1 antibody treatment failure in non-small cell lung cancer (NSCLC)

The example presents the case of a 62y/o male patient diagnosed with NSCLC in Jan 2016. The patient had received 6 cycles of cisplatine or carboplatine together with gemcitabine as first line treatment for metastatic disease (best RECIST response: PR); and 12 cycles of nivolumab as a second line treatment for metastatic disease under which the patient experienced a SD but ultimately developed progressive disease.

The patient then entered clinical study BP29428 and received combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200mg) every 3 weeks. Under this regimen the patient showed a PR. Results are shown in Figure 3.

Example 4.2: Combination of anti-CSF-1R antibody and anti-PDL1 antibody after anti-PD1 antibody treatment failure in non-small cell lung cancer (NSCLC)

The example presents the case of a 62y/o female patient diagnosed with NSCLC in Jun 2014. Initially, the patient received radiotherapy of the brain and lung. The patient then received 16 cycles of carboplatine and pemetrexed and another 14 cycles of pemetrexed only as first line treatment for metastatic disease (best RECIST response: SD); and 12 cycles of pembrolizumab as a second line treatment for metastatic disease under which the patient experienced a SD but ultimately developed progressive disease. The patient also received palliative radiosurgery for brain metastases.

Example 5: Combination of anti-CSF-1R antibody and anti-PD-L1 antibody after anti-PD-L1 antibody treatment failure in Renal cell carcinoma (RCC), Head and Neck Squamous Cell Carcinoma (HNSCC), or lymphomas (e.g. B-cell diffuse large cell lymphoma (DLCL))

Analogously as described in Examples 1 to 4, patients suffering from renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), or lymphomas (e.g. B-cell diffuse large cell lymphoma (DLCL) which show progression under anti-PD-L1 treatment (atezolizumab or durvalumab or avelumab), receive a combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200 mg) every 3 weeks. Responses are determined as described in Examples 1 to 4.

Example 6: Combination of anti-CSF-1R antibody and anti-PD-L1 antibody after anti-PD1 antibody treatment failure in Renal cell carcinoma (RCC), Head and Neck Squamous Cell Carcinoma (HNSCC), or lymphomas (e.g. B-cell diffuse large cell lymphoma (DLCL))

Analogously as described in Examples 1 to 4, patients suffering from renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), or lymphomas (e.g. B-cell diffuse large cell lymphoma (DLCL) which show progression under anti-PD1 treatment (pembrolizumab or nivolumab), receive a combination treatment of anti-CSF1R antibody emactuzumab (1000 mg) and atezolizumab (1200 mg) every 3 weeks. Responses are determined as described in Examples 1 to 5.

Patent Claims

1. An antibody which binds to human CSF-1R, for use in

a) the treatment of cancer in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the cancer with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed,

or

b) the treatment of a patient suffering from a cancer with CSF-1R expressing macrophage infiltrate in combination with an antagonistic PD-L1 antibody, wherein a prior treatment of the patient with a PD-L1/PD1 inhibitor selected from the group of an antagonistic PD-L1 antibody or an antagonistic PD1 antibody failed.

2. The anti-CSF-1R antibody for use in the treatment according to claim 1, wherein the CSF-1R antibody binds to domain D4 or D5 of the extracellular domain (ECD) of CSF-1R.

3. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 6, wherein the anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2.

4. The anti-CSF-1R antibody for use in the treatment according to claim 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4 or b) a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

5. The anti-CSF-1R antibody for use in the treatment according to claim1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:1 and a light chain variable domain VL of SEQ ID NO:2, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:3 and a light chain variable domain VL of SEQ ID NO:4.

6. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab.

7. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 5, wherein in the combination treatment the anti-CSF-1R antibody is emactuzumab and the antagonistic PD-L1 antibody is atezolizumab or durvalumab.

8. The anti-CSF-1R antibody for use in the treatment according to claim 1,

wherein anti-CSF-1R antibody comprises

a heavy chain variable domain VH of SEQ ID NO:25 and a light chain variable domain VL of SEQ ID NO:26, and

the antagonistic PD-L1 antibody comprises

a heavy chain variable domain VH of SEQ ID NO:5 and a light chain variable domain VL of SEQ ID NO:6.

9. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 8, wherein the prior treatment which failed was a atezolizumab or durvalumab treatment.

10. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 8, wherein the prior treatment which failed was a atezolizumab treatment

11. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 8, wherein the prior treatment which failed was a durvalumab treatment.

12. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 8, wherein the prior treatment which failed was a pembrolizumab or nivolumab treatment.

13. The anti-CSF-1R antibody for use in the according to any one of claims 1 to 12, wherein the antagonistic PD-L1 antibody used in combination is administered at a dose of 1100-1300 mg at each cycle.

14. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 13, wherein the anti-CSF-1R antibody is administered at a dose of 900-1100 mg at each cycle.

15. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 14, wherein the combined therapy is for use in treating or delaying progression of tumor growth.

16. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 14, wherein the combined therapy is for use in stimulating an immune response or function, such as T cell activity.

17. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 16, wherein the cancer is melanoma, urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

18. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 16, wherein the cancer is urinary bladder cancer (UCB), or non small cell lung (NSCL) cancer.

19. The anti-CSF-1R antibody for use in the treatment according to any one of claims 1 to 16, wherein the cancer is Renal cell carcinoma (RCC) or Head and Neck Squamous Cell Carcinoma (HNSCC).

Figure 1

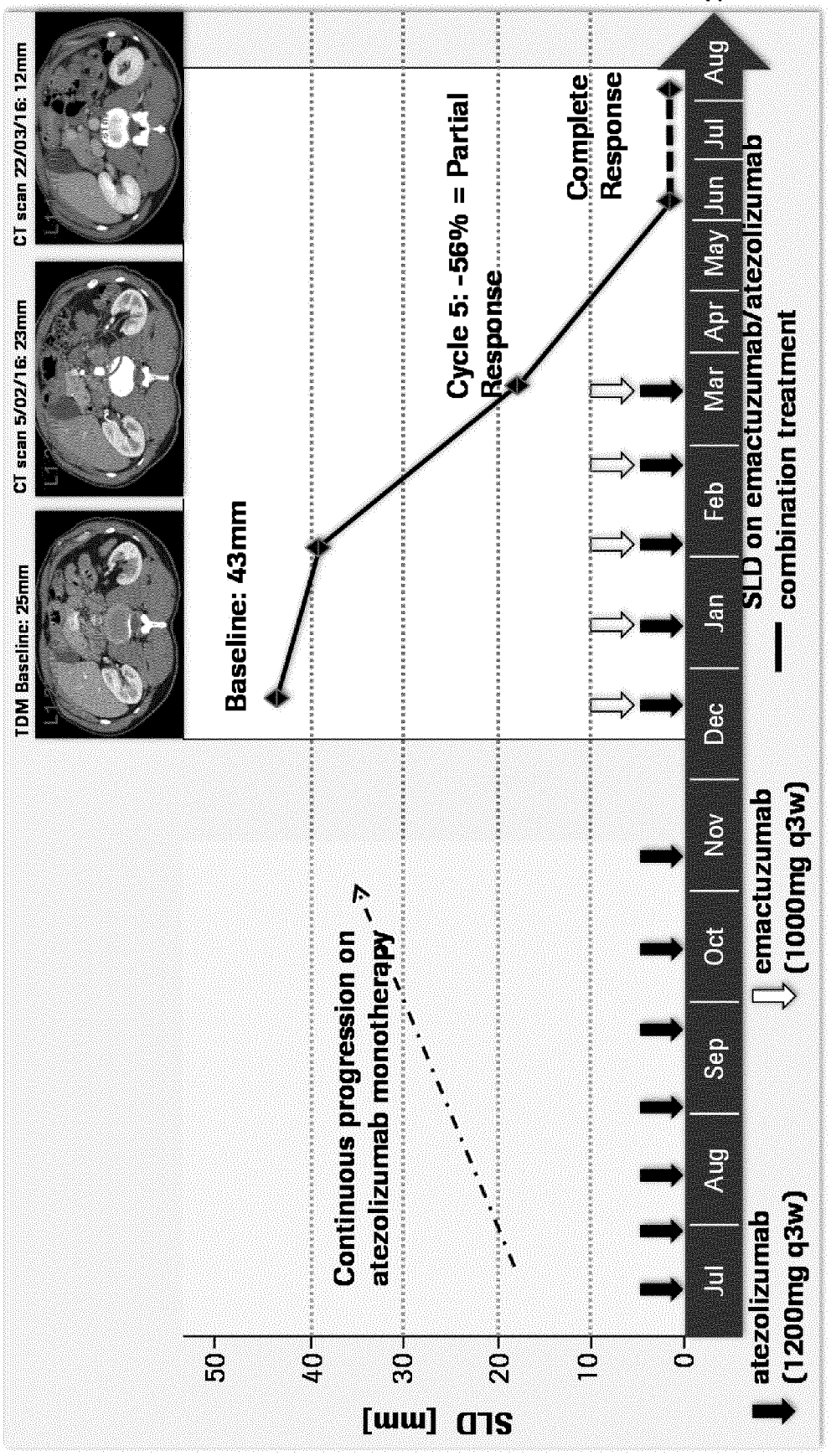

TDM Baseline: 25mm
CT scan 5/02/16: 23mm
CT scan 22/03/16: 12mm
Baseline: 43mm
Cycle 5: -56% = Partial Response
Complete Response
Continuous progression on atezolizumab monotherapy
SLD [mm]
0
10
20
30
40
50
Jul
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
2016
atezolizumab (1200mg q3w)
emactuzumab (1000mg q3w)
SLD on emactuzumab/atezolizumab combination treatment

Figure 2

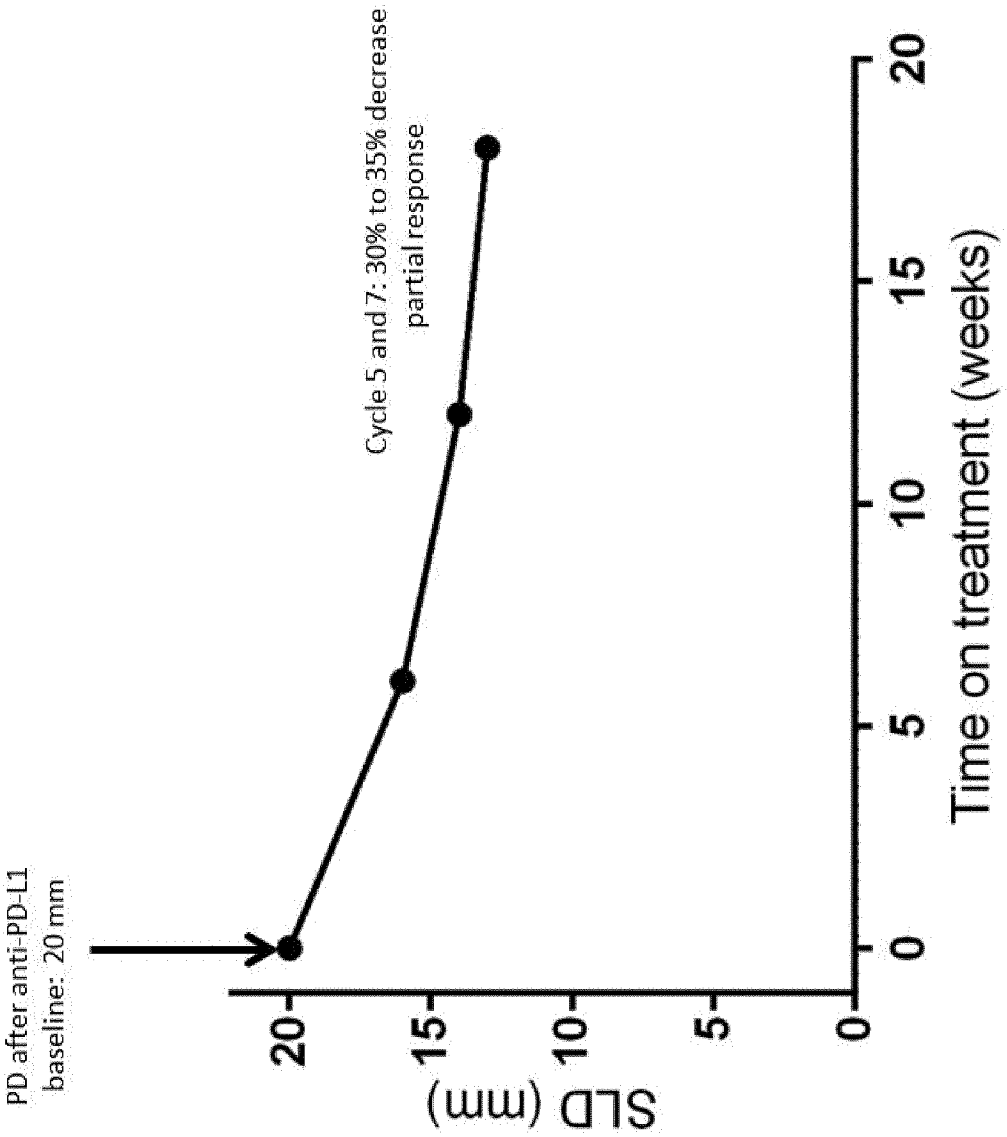

PD after anti-PD-L1
baseline: 20 mm
Cycle 5 and 7: 30% to 35% decrease
partial response
SLD (mm)
20
15
10
5
0
0
5
10
15
20
Time on treatment (weeks)

Figure 3

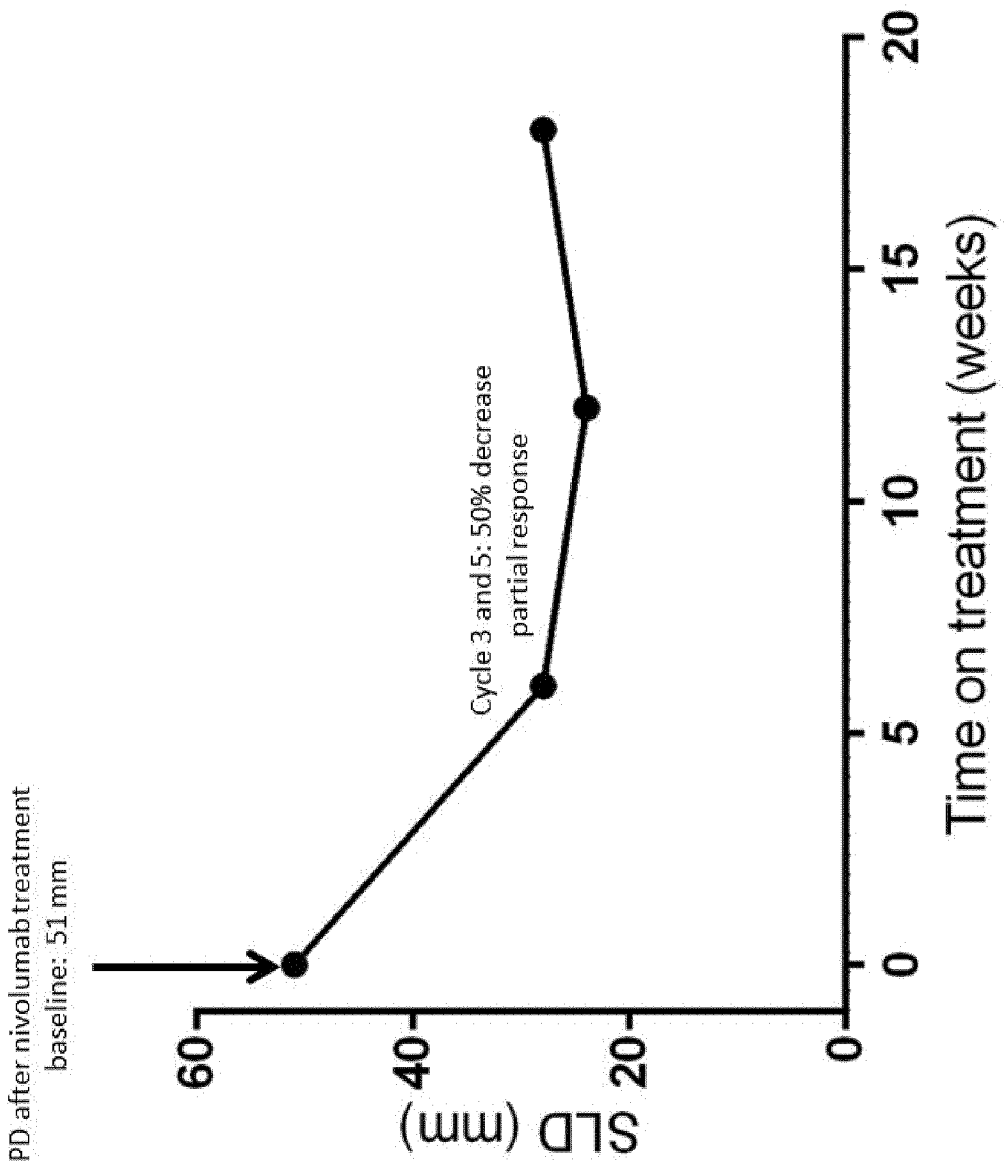
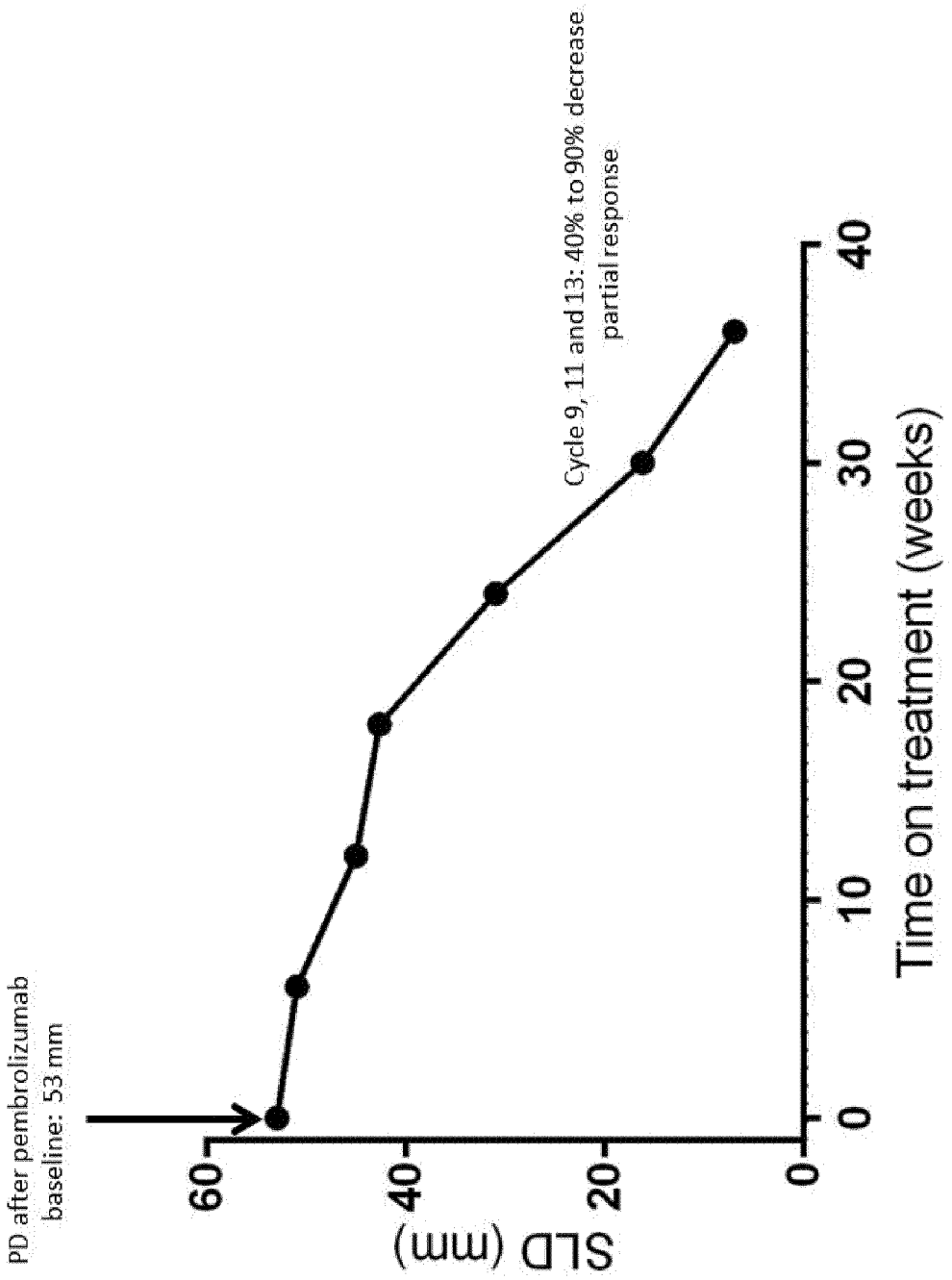

PD after nivolumab treatment
baseline: 51 mm
Cycle 3 and 5: 50% decrease
partial response
SLD (mm)
60
40
20
0
0
5
10
15
20
Time on treatment (weeks)

Figure 4


PD after pembrolizumab
baseline: 53 mm
Cycle 9, 11 and 13: 40% to 90% decrease
partial response
SLD (mm)
60
40
20
0
0
10
20
30
40
Time on treatment (weeks)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/083696

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/28 A61P35/00
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)
C07K A61K A61P

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, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/036511 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 19 March 2015 (2015-03-19) cited in the application whole document, especially Example 8; Table 6; Figure 4; paragraph bridging pages 36-37	1-19

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2018	19/02/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Luyten, Kattie

1

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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.
Y	Anonymous: "NCT02452424 on 2016_12_18: A Combination Clinical Study of PLX3397 and Pembrolizumab To Treat Advanced Melanoma and Other Solid Tumors", , 18 December 2016 (2016-12-18), pages 1-7, XP055374604, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT02452424/2016_12_18 [retrieved on 2017-05-19] whole document; especially paragraph bridging pages 1-2	1-19
Y	Anonymous: "NCT02323191 on 2016_10_03: A Study of RO5509554 and MPDL3280A Administered in Combination in Patients With Advanced Solid Tumors", , 3 October 2016 (2016-10-03), pages 1-5, XP055374638, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT02323191/2016_10_03 [retrieved on 2017-05-19] the whole document	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/083696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 2014320355 A1	18-02-2016
		CA 2916826 A1	19-03-2015
		CN 105473617 A	06-04-2016
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		RU 2016113757 A	17-10-2017
		SG 11201601881R A	28-04-2016
		TW 201522376 A	16-06-2015
		US 2015073129 A1	12-03-2015
		US 2017051065 A1	23-02-2017
		WO 2015036511 A1	19-03-2015