

## MALIGNANT NEOPLASIS TREATMENT USING PD-1 ANTIBODY COMBINATION

### Field of the invention

[001] The present invention relates to the field of medicine, specifically to methods for treating a malignant neoplasm, comprising administering an antibody to PD-1, in particular prololigimab, in combination with a chemotherapeutic agent.

### Background of the invention

[002] Programmed death 1 (PD-1) protein is an inhibitor member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA. PD-1 is expressed by activated B cells, T cells, and myeloid cells (Agata et al., supra; Okazaki et al. (2002) *Curr. Opin. Immunol.* 14: 391779-82; Bennet et al. (2003) *J Immunol* 170:711-8). The initial members of the family, CD28 and ICOS, were discovered by functional effect on augmenting T cell proliferation following the addition of monoclonal antibodies (Hutloff et al. (1999) *Nature* 397:263-266; Hansen et al. (1980) *Immunogenetics* 10:247-260). PD-1 was discovered through screening for differential expression in apoptotic cells (Ishida et al. (1992) *EMBO J* 11:3887-95). The other members of the family, CTLA-4 and BTLA, were discovered through screening for differential expression in cytotoxic T lymphocytes and TH1 cells, respectively. CD28, ICOS and CTLA-4 all have an unpaired cysteine residue allowing for homodimerization. In contrast, PD-1 is suggested to exist as a monomer, lacking the unpaired cysteine residue characteristic in other CD28 family members.

[003] PD-1 is a 55 kDa type I transmembrane protein that is part of the Ig gene superfamily (Agata et al. (1996) *Int Immunol* 8:765-72). PD-1 comprises a membrane proximal immunoreceptor tyrosine-based inhibitory motif (ITIM) and a membrane distal tyrosine-based switch motif (ITSM) (Thomas, M.L. (1995) *J Exp Med* 181:1953-6; Vivier, E and Daeron, M (1997) *Immunol Today* 18:286-91). Although structurally similar to CTLA-4, PD-1 lacks the MYPPPY motif that is critical for B7-1 and B7-2 binding. Two ligands for PD-1 have been identified, PD-L1 and PD-L2, that have been shown to downregulate T cell activation upon binding to PD-1 (Freeman et al. (2000) *J Exp Med* 192:1027-34; Latchman et al. (2001) *Nat Immunol* 2:261-8; Carter et al. (2002) *Eur J Immunol* 32:634-43). Both PD-L1 and PD-L2 are B7 homologs that bind to PD-1, but do not bind to other CD28 family members.

[004] One ligand for PD-1, PD-L1, is abundant in a variety of human cancers (Dong et al. (2002) *Nat. Med.* 8:787-9). The interaction between PD-1 and PD-L1 results in a decrease in tumor infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and immune evasion by the cancerous cells (Dong et al. (2003) *J. Mol. Med.* 81:281-7; Blank et al. (2005) *Cancer Immunol. Immunother.* 54:307-314; Konishi et al. (2004) *Clin. Cancer Res.* 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1, and

the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99:12293-7; Brown et al. (2003) J. Immunol. 170:1257-66).

[005] PD-1 is an inhibitory member of the CD28 family expressed on activated B cells, T cells, and myeloid cells (Agata et al., supra; Okazaki et al. (2002) Curr Opin Immunol 14: 391779-82; Bennett et al. (2003) J Immunol 170:711-8). PD-1 deficient animals develop various autoimmune phenotypes, including autoimmune cardiomyopathy and a lupus-like syndrome with arthritis and nephritis (Nishimura et al. (1999) Immunity 11:141-51; Nishimura et al. (2001) Science 291:319-22). Furthermore, PD-1 has been found to play a role in autoimmune encephalomyelitis, systemic lupus erythematosus, graft-versus-host disease (GVHD), type I diabetes, and rheumatoid arthritis (Salama et al. (2003) J Exp Med 198:71-78; Prokunina and Alarcon-Riquelme (2004) Hum Mol Genet 13:R143; Nielsen et al. (2004) Lupus 13:510). In a murine B cell tumor line, the ITSM of PD-1 was shown to be essential to block BCR-mediated Ca<sup>2+</sup>-flux and tyrosine phosphorylation of downstream effector molecules (Okazaki et al. (2001) PNAS 98:13866-71).

[006] To date, known are a number of antibodies against PD-1, for example, nivolumab (BMS), pembrolizumab (Merck), which are human monoclonal antibodies of the IgG4 isotype.

[007] Further known is a novel antibody to PD-1 prolgolimab (also known as BCD-100), which is a human monoclonal antibody of the IgG1 isotype with effectorless mutations L234A, L235A. Prolgolimab has shown increased affinity for PD-1, increased aggregation stability in comparison with antibodies of the IgG4 isotype. Furthermore, prolgolimab is currently under clinical trials for various types of malignant neoplasms, including melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer; cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment.

[008] Therapy of malignant neoplasms may combine immunotherapy and chemotherapy. Such therapy may be more effective than immunotherapy or chemotherapy alone.

[009] Thus, there is currently a need to develop novel methods for treating malignant neoplasms, including administering an antibody to PD-1, in particular prolgolimab, in combination with chemotherapeutic agents (chemotherapy).

### **Description of the invention**

#### **Definitions**

[0010] The terms used in this description generally have their ordinary meanings in the art within the context of the invention, and in the specific context where each term is used. Certain terms that are used to describe the invention are discussed below, or elsewhere in the description,

to provide additional guidance to the practitioner regarding the description of the invention. Synonyms for certain terms are provided. A recital of one or more synonyms does not exclude the use of other synonyms. The use of examples anywhere in this description, including examples of any terms discussed herein, is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. The invention is not limited to various embodiments given in this description.

[0011] Furthermore, unless otherwise required by context, singular terms shall include plural terms, and the plural terms shall include the singular terms.

[0012] As used in the present description and claims that follow, unless otherwise dictated by the context, the words "have", "include," and "comprise" or variations thereof such as "has", "having," "includes", "including", "comprises," or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

[0013] The term "pharmaceutical composition" refers to a composition and/or formulation containing a therapeutically effective amount of the antibody according to the invention plus excipients or auxiliary substances (carriers, diluents, vehicles, solvents and other excipients).

[0014] The term "aqueous composition" as used herein refers to a water-based composition, the water in the composition may be: water, water for injections, physiologic saline (0.9%-1.0% aqueous solution of sodium chloride).

[0015] The term "parenteral administration" refers to administration regimens, typically using injection, and includes, in particular intravenous, intramuscular, intraarterial, intratracheal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, intraarticular, subcapsular, subarchnoid, intraspinal, epidural and intrasternal injection or infusion.

[0016] The term "use" applies to the possibility to use the antibody of the present invention or a pharmaceutical composition containing thereof to treat, relief the course of the disease, expedite the remission, reduce the recurrence rate following the diseases or disorders mediated by receptors with which the antibody of the present invention can bind. Examples of diseases are, without limitation, malignant neoplasms, including melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer, non-squamous cell non-small cell lung cancer, squamous cell lung cancer, small cell lung cancer, including inoperable/metastatic small cell lung cancer, early stage lung cancer before and after definitive treatment; cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment, head and neck cancers, including head and neck squamous cell carcinoma, Hodgkin's lymphoma, gastrointestinal cancer, metastatic esophageal squamous

cell carcinoma, bladder cancer, including metastatic urothelial carcinoma, kidney cancer, endometrial cancer, including metastatic endometrial cancer, early stages of endometrial cancer before and after definitive treatment, breast cancer, including metastatic breast cancer, early stages of endometrial cancer before and after definitive treatment, liver cancer, including metastatic or inoperable liver cancer, early stages of liver cancer before and after definitive treatment, inoperable or metastatic solid tumor, including inoperable or metastatic solid tumor with evidence of microsatellite instability.

[0017] The term "method of treatment" refers to the possibility to use the antibody of the invention or pharmaceutical composition containing same to treat, relieve the course of the disease, expedite the remission, reduce the recurrence rate following the diseases or disorders associated with PD1 activity. "Treat" or "treatment" of a disease, disorder or condition may comprise the prevention or delay of the onset of clinical symptoms of a disease, disorder or condition developing in human, the inhibition of a disease, disorder or condition, i.e. stop, reduction or delay of the development of a disease or a relapse thereof (in case of maintenance therapy) or at least one clinical or subclinical symptom thereof, or the alleviation or easement of a disease, i.e. the causing of regression of a disease, disorder or condition. Examples of diseases are, without limitation, malignant neoplasms, including melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive surgical treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer.

[0018] A "chemotherapeutic agent" is a chemical compound useful in the treatment of a malignant neoplasm. Examples of chemotherapeutic agents include alkylating agents such as thiotepea and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylmelamine; acetogenins (e.g. bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scoplectin, and 9-aminocamptothecin); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (e.g. cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such

as the enediyne antibiotics (e.g. calicheamicin, e.g. calicheamicin gamma II and calicheamicin omega II (see, e.g. Agnew, Chem. Intl. Ed. Engl., 33: 183-186 (1994)); dynemicin, including dynemicin A; esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXOL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamideglycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitogazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (e.g., T-2 toxin, verracurin A, roridin A and anguidine); urethan; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, e.g., paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE®), and docetaxel (TAXOTERE®); chlorambucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin, and carboplatin; vinca alkaloids, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®), FILDESIN®, and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid, including bexarotene (TARGRETIN®); biphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE- 58095,

zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAJX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, e.g. those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g. LURTOTECAN®); rmRH (e.g., ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (Pfizer); perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteasome inhibitor (e.g. PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (811577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); tyrosine kinase inhibitors (see definition below); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin.

[0019] Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors, such as anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVTSTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs), such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal aromatase inhibitors, such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors, such as anastrozole (AREVIIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors including vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, imidazole; lutenizing hormone-releasing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and triptorelin; sex steroids, including progestins, such as megestrol acetate and medroxyprogesterone acetate, estrogens, such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretinoic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens, such as flutamide, nilutamide and bicalutamide; testolactone; and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

[0020] The subject of treatment, or patient, is a mammal, preferably a human subject. Said subject may be either male or female, of any age.

## Abbreviations

AUC — area under the pharmacokinetic "concentration-time" curve ("area under the curve")

AUMC — the total area under the curve prepared when product concentration in the organism is multiplied by time

Cl — Total clearance

C<sub>max</sub> — Maximum concentration

CTCAE — Common Toxicity Criteria for Adverse Events by the U.S. National Cancer Institute

ECOG — Eastern Cooperative Oncology Group

GCP — Good Clinical Practice

HBV — hepatitis B virus

HCV — hepatitis C virus

ICH — International Conference on Harmonization

irRC — immune-related Response Criteria

T<sub>1/2</sub> — Half-life

T<sub>max</sub> — Time to maximum concentration

TNM — (tumor, node, metastasis) system for staging malignant tumors

SPD — sum of the product of the perpendicular diameters for multiple lesions

LDi — longest transverse diameter of a lesion

SDi — short axis perpendicular to LDi

Q2W — once in 2 weeks

Q3W — once in 3 weeks

PPD — product of LDi and perpendicular diameter

TPS (Tumor Proportion Score) — the percentage of PD-L1-expressing viable tumor cells (with complete or partial membrane staining of any intensity relative to the total tumor cells

CPS (Combined Positive Score) — the number of PD-L1 stained cells (tumor and lymphoid cells) in relation to total viable tumor cells multiplied by 100

ALT — alanine aminotransferase

AST — aspartate aminotransferase

ANC — absolute neutrophil count

HIV — Human immunodeficiency virus

G-CSF — granulocyte colony-stimulating factor

GOST — State standard

JSC — Joint stock company

IHC — immunohistochemical study

IRC — individual registration card

ELISA — Enzyme immunoassay

RC — research center

kDa — kilodalton

CT — computed tomography

INN — International nonproprietary name

NSCLC — non-small cell lung cancer

IDMC- Independent Data Monitoring Committee

AE — adverse event

RCC — renal cell cancer

RF — Russian Federation

CC — cervical cancer

SAE — serious adverse event

FN — febrile neutropenia

ChT — chemotherapy

AP — alkaline phosphatase

ECG — electrocardiography

Echo-CG — echocardiography

#### **Summary of the invention**

[0021] The present invention discloses methods for treating a malignant neoplasm in a subject in need thereof, comprising administering a therapeutically effective amount of antibody to PD-1, in particular prolgolimab, in combination with at least one chemotherapeutic agent, in particular paclitaxel, carboplatin or cisplatin. The present invention discloses methods for treating a malignant neoplasm in a subject in need thereof, comprising administering a therapeutically effective amount of antibody to PD-1 prolgolimab in combination with antibody to VEGF, in particular bevacizumab, and at least one chemotherapeutic agent, in particular paclitaxel, carboplatin or cisplatin.

[0022] As disclosed in international patent application WO/2018/013017 incorporated herein by reference, the anti-PD-1 antibody prolgolimab that is a human IgG1 monoclonal antibody with effectorless mutations L234A, L235A (referred herein as "antibody of the invention") has shown to have improved aggregation stability, increased affinity and improved pharmacokinetic parameters, such as  $t_{1/2\beta}$  (hour) or  $C_{max}$  ( $\mu\text{g/ml}$ ) when compared to known anti-PD-1 antibodies that are based on human IgG4 antibody, such as nivolumab. Prolgolimab has a weight average molecular weight around 146 kDa and is specific for human PD-1. Prolgolimab has a heavy chain that contains 459 amino acids (SEQ ID NO: 1), and has a human light chain containing 214 amino acids (SEQ ID NO: 2), the constant portion (Fc) of prolgolimab comprises mutations L234A, L235A.

[0023] In one aspect, the present invention relates to the use of the antibody to PD-1 in combination with at least one chemotherapeutic agent for treating a malignant neoplasm in a subject in need thereof.

[0024] In one aspect, the present invention relates to a method for treating a malignant neoplasm in a subject in need thereof, including administering a therapeutically effective amount of the antibody to PD-1 in combination with at least one chemotherapeutic agent.

[0025] The therapeutically effective amount of the antibody to PD-1 according to the present invention depends on the condition to be treated, the severity of the condition, the previous therapy and the patient's history and response to the therapeutic agent. A suitable dose can be adjusted by the decision of the attending physician so that it can be administered to the patient once or through several injections.

[0026] In some embodiments of the invention, the therapeutically effective amount of the antibody to PD-1 per dose for the patient is from about 0.01 to 10 mg/kg of body weight, or about 1 to 10 mg/kg of body weight, or about 0.05 mg/kg of body weight, or about 0.25 mg/kg of body weight, or about 0.5 mg/kg of body weight, or about 1 mg/kg of body weight, or about 2 mg/kg of body weight, or about 3 mg/kg of body weight, or about 4 mg/kg of body weight, or about 5 mg/kg of body weight, or about 6 mg/kg of body weight, or about 7 mg/kg of body weight, or about 8 mg/kg of body weight, or about 9 mg/kg of body weight, or about 10 mg/kg of body weight.

[0027] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 1 mg/kg or 3 mg/kg of body weight.

[0028] In some embodiments of the invention, the antibody to PD-1 is administered at a fixed dose (in mg). An acceptable dose of the antibody to PD-1 may contain 5-450 mg/dose, or may contain 40 mg, or 50 mg, or 60 mg per dose; or may contain 70 mg, or 80 mg, or 90 mg, or 100 mg per dose; or may contain 110 mg, or 120 mg, or 130 mg, or 140 mg per dose; or may contain 150 mg, or 160 mg, or 170 mg, or 180 mg per dose; or may contain 190 mg, or 200 mg, or 210 mg, or 220 mg per dose; or may contain 230 mg, or 240 mg, or 250 mg, or 260 mg per dose; or may contain 270 mg, or 280 mg, or 290 mg per dose, or may contain 300 mg, or 310 mg, or 320 mg, or 330 mg, or 340 mg, or 350 mg per dose; or may contain 360 mg, or 370 mg, or 380 mg, or 390 mg, or 400 mg, or 410 mg, or 420 mg, or 430 mg, or 440 mg, or 450 mg per dose.

[0029] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 100-400 mg.

[0030] The frequency of dosing may be normally about once per week, or about once every 2 weeks, or about once every 3 weeks, or about once every 4 weeks.

[0031] In some embodiments of the invention, the antibody to PD-1 is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

[0032] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 1 mg/kg of body weight every 2 weeks or every 3 weeks.

[0033] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 3 mg/kg of body weight every 2 weeks or every 3 weeks.

[0034] In some embodiments of the invention, the antibody to PD-1 is prolgolimab.

[0035] In some embodiments of the invention, prolgolimab is administered parenterally.

[0036] In some embodiments of the invention, said parenteral administration may be intravenous, subcutaneous or intramuscular administration.

[0037] In some embodiments of the invention, prolgolimab may be administered intravenously as an infusion.

[0038] In some embodiments of the invention, prolgolimab may be administered intravenously as an infusion over 60 minutes; in case of good tolerability, the infusion time may be shortened to 30 minutes.

[0039] In some embodiments of the invention, the chemotherapeutic agent is selected from a group comprising taxane, a platinum agent.

[0040] In some embodiments of the invention, the chemotherapeutic agent is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

[0041] In some embodiments of the invention, taxane is selected from paclitaxel, docetaxel.

[0042] In some embodiments of the invention, paclitaxel is administered at a dose of 135-175 mg/m<sup>2</sup>.

[0043] In some embodiments of the invention, paclitaxel is administered at a dose of 135 or 175 mg/m<sup>2</sup>.

[0044] In some embodiments of the invention, paclitaxel is administered at a dose of 175 mg/m<sup>2</sup> as a 3-hour intravenous (IV) infusion.

[0045] In some embodiments of the invention, paclitaxel is administered at a dose of 135 mg/m<sup>2</sup> as a 24-hour IV infusion.

[0046] In some embodiments of the invention, the platinum agent is selected from carboplatin, cisplatin.

[0047] In some embodiments of the invention, cisplatin is administered at a dose of 50-100 mg/m<sup>2</sup>.

[0048] In some embodiments of the invention, cisplatin is administered at a dose of 50 mg/m<sup>2</sup>, 100 mg/m<sup>2</sup>.

[0049] In some embodiments of the invention, cisplatin is administered at a dose of 50-100 mg/m<sup>2</sup> as an IV infusion every 3 or every 4 weeks.

[0050] In some embodiments of the invention, carboplatin is administered at a dose of AUC 5-7.

[0051] In some embodiments of the invention, carboplatin is administered at a dose of AUC 5, AUC 6, AUC 7.

[0052] The dose of carboplatin is calculated by using the Calvert's formula (AUC 5-7). AUC (area under the curve) is a statistical measure, the area limited to a certain curve of drug plasma concentration versus the x-axis (time).

[0053] In some embodiments of the invention, paclitaxel is administered at a dose of 175 mg/m<sup>2</sup> as a 3-hour intravenous (IV) infusion followed by administration of cisplatin every 3 weeks.

[0054] In some embodiments of the invention, paclitaxel is administered at a dose of 135 mg/m<sup>2</sup> as a 24-hour IV infusion followed by administration of cisplatin every 3 weeks.

[0055] Further, in the course of treatment of the subject, it is possible to reduce the dose of any chemotherapeutic agent, in particular, paclitaxel, carboplatin, cisplatin. Dose reduction may be, for example, 50% or 25%.

[0056] In some embodiments of the invention, an antibody to VEGF is further administered.

[0057] In some embodiments of the invention, the antibody to VEGF is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

[0058] In some embodiments of the invention, the antibody to VEGF is bevacizumab.

[0059] In some embodiments of the invention, bevacizumab is administered at a dose of 15 mg/kg of body weight.

[0060] In one aspect, the present invention relates to the use of the antibody to PD-1 in combination with paclitaxel and carboplatin or cisplatin for treating a malignant neoplasm in a subject in need thereof.

[0061] In one aspect, the present invention relates to a method for treating a malignant neoplasm in a subject in need thereof, including administering a therapeutically effective amount of the antibody to PD-1 in combination with paclitaxel and carboplatin or cisplatin.

[0062] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 1 mg/kg or 3 mg/kg of body weight.

[0063] In some embodiments of the invention, paclitaxel is administered at a dose of 175 mg/m<sup>2</sup>.

[0064] In some embodiments of the invention, carboplatin is administered at a dose of AUC 5 or cisplatin is administered at a dose of 50 mg/m<sup>2</sup>.

[0065] In some embodiments of the invention, the antibody to PD-1 in combination with paclitaxel and carboplatin or cisplatin are administered every 2 weeks or every 3 weeks.

[0066] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg of body weight is administered in combination with paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 or cisplatin at a dose of 50 mg/m<sup>2</sup> every 2 weeks or every 3 weeks.

[0067] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks.

[0068] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks.

[0069] In some embodiments of the invention, the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks.

[0070] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

[0071] In some embodiments of the invention, the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

[0072] In some embodiments of the invention, therapy may include one or more cycles of dose administration. For example, the therapy may include no more than 6 cycles of dose administration, or exactly 6 cycles of dose administration. A cycle as used in the present invention refers to the repetition of previously administered doses of active substances over a certain period of time (every 2 weeks, 3 weeks, 4 weeks, etc.).

[0073] In some embodiments of the invention, maintenance therapy is further performed following the above main therapy (antibody to PD-1 in combination with at least one chemotherapeutic agent). Maintenance therapy involves administration of the antibody to PD-1 at a dose of 1 mg/ml or 3 mg/ml every 2 or every 3 weeks. Maintenance therapy is performed until progression.

[0074] In some embodiments of the invention, the antibody to PD-1 in combination with paclitaxel and carboplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 every 2 or every 3 weeks until progression.

[0075] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel and cisplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 every 2 or every 3 weeks until progression.

[0076] The doses of antibody to PD-1, paclitaxel, carboplatin and cisplatin may be those indicated above.

[0077] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg every 2 or every 3 weeks until progression.

[0078] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg every 2 or every 3 weeks until progression.

[0079] In some embodiments of the invention, the antibody to PD-1 is prolgolimab.

[0080] In one aspect, the present invention relates to the use of the antibody to PD-1 in combination with bevacizumab, paclitaxel, carboplatin or cisplatin for treating a malignant neoplasm in a subject in need thereof.

[0081] In one aspect, the present invention relates to a method for treating a malignant neoplasm in a subject in need thereof, including administering a therapeutically effective amount of the antibody to PD-1 in combination with bevacizumab, paclitaxel, carboplatin or cisplatin.

[0082] In some embodiments of the invention, the antibody to PD-1 is administered at a dose of 1 mg/kg or 3 mg/kg of body weight.

[0083] In some embodiments of the invention, bevacizumab is administered at a dose of 15 mg/kg of body weight.

[0084] In some embodiments of the invention, paclitaxel is administered at a dose of 175 mg/m<sup>2</sup>.

[0085] In some embodiments of the invention, carboplatin is administered at a dose of AUC 5 or cisplatin is administered at a dose of 50 mg/m<sup>2</sup>.

[0086] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel, carboplatin or cisplatin is administered every 2 weeks or every 3 weeks.

[0087] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg of body weight is administered in combination with bevacizumab at a dose of 15 mg/kg of body weight, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 or cisplatin at a dose of 50 mg/m<sup>2</sup> every 2 weeks or every 3 weeks.

[0088] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2

weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks.

[0089] In some embodiments of the invention, the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks.

[0090] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

[0091] In some embodiments of the invention, the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

[0092] In some embodiments of the invention, the antibody to PD-1 is prolgolimab.

[0093] In some embodiments of the invention, therapy may include one or more cycles of dose administration until progression. For example, the therapy may include no more than 6 cycles of dose administration, or exactly 6 cycles of dose administration. A cycle as used in the present invention refers to the repetition of previously administered doses of active substances over a certain period of time (every 2 weeks, 3 weeks, 4 weeks, etc.).

[0094] In some embodiments of the invention, maintenance therapy is further performed following the above main therapy (antibody to PD-1 in combination with at least one chemotherapeutic agent). Maintenance therapy involves administration of the antibody to PD-1 at a dose of 1 mg/ml or 3 mg/ml every 2 or every 3 weeks. Maintenance therapy is performed until progression.

[0095] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel and carboplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 every 2 or every 3 weeks until progression.

[0096] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel and carboplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 and bevacizumab every 3 weeks until progression.

[0097] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel and cisplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 every 2 or every 3 weeks until progression.

[0098] In some embodiments of the invention, the antibody to PD-1 in combination with bevacizumab, paclitaxel and cisplatin is administered for no more than 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 and bevacizumab every 3 weeks until progression.

[0099] The doses of antibody to PD-1, bevacizumab, carboplatin and cisplatin may be those as indicated above.

[00100] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg every 2 or every 3 weeks until progression.

[00101] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg and bevacizumab at a dose of 15 mg/kg every 3 weeks until progression.

[00102] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg every 2 or every 3 weeks until progression.

[00103] In some embodiments of the invention, the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg in combination with bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> is administered for 6 cycles every 3 weeks, followed by administration of the antibody to PD-1 at a dose of 1 mg/kg or 3 mg/kg and bevacizumab at a dose of 15 mg/kg every 3 weeks until progression.

[00104] In some embodiments of the invention, the antibody to PD-1 is prolgolimab.

[00105] In some embodiments of the invention, the malignant neoplasm is selected from the group including melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer, non-squamous cell non-small cell lung cancer, squamous cell lung cancer, small cell lung cancer, including inoperable/metastatic small cell lung cancer, early stage lung cancer before and after definitive treatment; cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment, head and neck cancers, including head and neck squamous cell carcinoma, Hodgkin's lymphoma,

gastrointestinal cancer, metastatic esophageal squamous cell carcinoma, bladder cancer, including metastatic urothelial carcinoma, kidney cancer, endometrial cancer, including metastatic endometrial cancer, early stages of endometrial cancer before and after definitive treatment, breast cancer, including metastatic breast cancer, early stages of endometrial cancer before and after definitive treatment, liver cancer, including metastatic or inoperable liver cancer, early stages of liver cancer before and after definitive treatment, inoperable or metastatic solid tumor, including inoperable or metastatic solid tumor with evidence of microsatellite instability.

[00106] In some embodiments of the invention, the malignant neoplasm is cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment.

[00107] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

- (a) prolgolimab at a concentration from 15 mg/ml to 40 mg/ml as an antibody;
- (b) trehalose dihydrate at a concentration from 80 mg/ml to 110 mg/ml;
- (c) sodium acetate trihydrate at a concentration from 0.2 mg/ml to 2.5 mg/ml; and
- (d) acetic acid to pH from 4.5 to 5.5.

[00108] In some embodiments of the invention, said prolgolimab may be present at a concentration from 15 mg/ml to 25 mg/ml.

[00109] In some embodiments of the invention, said prolgolimab may be present at a concentration of 20 mg/ml.

[00110] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration from 95 mg/ml to 105 mg/ml.

[00111] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration of 100 mg/ml.

[00112] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration from 1.6 mg/ml to 1.9 mg/ml.

[00113] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration from 1.7 mg/ml to 1.8 mg/ml.

[00114] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration of 1.742 mg/ml.

[00115] In some embodiments of the invention, said acetic acid may be added to pH 5.0.

[00116] In some embodiments of the invention, said acetic acid may be present at a concentration from 0.04 mg/ml to 0.77 mg/ml.

[00117] In some embodiments of the invention, said acetic acid may be present at a concentration from 0.40 mg/ml to 0.50 mg/ml.

[00118] In some embodiments of the invention, said acetic acid may be present at a concentration of 0.43 mg/ml.

[00119] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

- (a) prolgolimab at a concentration from 90 mg/ml to 150 mg/ml as an antibody;
- (b) trehalose dihydrate at a concentration from 50 mg/ml to 110 mg/ml;
- (c) sodium acetate trihydrate at a concentration from 0.2 mg/ml to 2.5 mg/ml; and
- (d) acetic acid to pH from 4.5 to 5.5.

[00120] In some embodiments of the invention, said prolgolimab may be present at a concentration from 90 mg/ml to 110 mg/ml.

[00121] In some embodiments of the invention, said prolgolimab may be present at a concentration of 100 mg/ml.

[00122] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration from 75 mg/ml to 85 mg/ml.

[00123] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration of 80 mg/ml.

[00124] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration from 1.6 mg/ml to 1.9 mg/ml.

[00125] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration from 1.7 mg/ml to 1.8 mg/ml.

[00126] In some embodiments of the invention, said sodium acetate trihydrate may be present at a concentration of 1.742 mg/ml.

[00127] In some embodiments of the invention, said acetic acid may be added to pH from 5.0 to 5.5.

[00128] In some embodiments of the invention, said acetic acid may be added to pH 5.0.

[00129] In some embodiments of the invention, said acetic acid may be present at a concentration from 0.045 mg/ml to 0.77 mg/ml.

[00130] In some embodiments of the invention, said acetic acid may be present at a concentration from 0.40 mg/ml to 0.50 mg/ml.

[00131] In some embodiments of the invention, said acetic acid may be present at a concentration from 0.43 mg/ml.

[00132] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

- (a) prolgolimab at a concentration of 20 mg/ml as an antibody;
- (b) trehalose dihydrate at a concentration of 100 mg/ml;

(c) sodium acetate trihydrate at a concentration of 1.742 mg/ml; and

(d) acetic acid to pH 5.0

[00133] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

(a) prolgolimab at a concentration of 100 mg/ml as an antibody;

(b) trehalose dihydrate at a concentration of 80 mg/ml;

(c) sodium acetate trihydrate at a concentration of 1.742 mg/ml; and

(d) acetic acid to pH from 5.0 to 5.5.

[00134] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

(a) prolgolimab at a concentration from 5 mg/ml to 150 mg/ml as an antibody;

(b) trehalose dihydrate at a concentration from 70 mg/ml to 110 mg/ml;

(c) L-histidine at a concentration from 0.2 to 2.5 mg/ml; and

(d) L-histidine hydrochloride at a concentration from 0.2 to 3.5 mg/ml.

[00135] In some embodiments of the invention, said prolgolimab may be present at a concentration from 15 mg/ml to 40 mg/ml.

[00136] In some embodiments of the invention, said prolgolimab may be present at a concentration from 15 mg/ml to 25 mg/ml.

[00137] In some embodiments of the invention, said prolgolimab may be present at a concentration of 20 mg/ml.

[00138] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration from 95 mg/ml to 105 mg/ml.

[00139] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration of 100 mg/ml.

[00140] In some embodiments of the invention, said L-histidine may be present at a concentration from 0.7 mg/ml to 1.0 mg/ml.

[00141] In some embodiments of the invention, said L-histidine may be present at a concentration of 0.92 mg/ml.

[00142] In some embodiments of the invention, said L-histidine hydrochloride may be present at a concentration from 2.8 mg/ml to 3.3 mg/ml.

[00143] In some embodiments of the invention, said L-histidine hydrochloride may be present at a concentration of 2.96 mg/ml.

[00144] In some embodiments of the invention, said composition may have pH from 5.5 to 6.5.

[00145] In some embodiments of the invention, said composition may have pH 5.5.

[00146] In some embodiments of the invention, said prolgolimab may be present at a concentration from 90 mg/ml to 110 mg/ml.

[00147] In some embodiments of the invention, said prolgolimab may be present at a concentration of 100 mg/ml.

[00148] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration from 75 mg/ml to 85 mg/ml.

[00149] In some embodiments of the invention, said trehalose dihydrate may be present at a concentration of 80 mg/ml.

[00150] In some embodiments of the invention, said L-histidine may be present at a concentration from 0.7 mg/ml to 1.0 mg/ml.

[00151] In some embodiments of the invention, said L-histidine may be present at a concentration of 0.92 mg/ml.

[00152] In some embodiments of the invention, said L-histidine hydrochloride may be present at a concentration from 2.8 mg/ml to 3.3 mg/ml.

[00153] In some embodiments of the invention, said L-histidine hydrochloride may be present at a concentration of 2.96 mg/ml.

[00154] In some embodiments of the invention, said composition may have pH from 5.5 to 6.5.

[00155] In some embodiments of the invention, said composition may have pH from 5.5 to 6.0.

[00156] In some embodiments of the invention, said composition may have pH 5.5.

[00157] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

- (a) prolgolimab at a concentration of 20 mg/ml as an antibody;
- (b) trehalose dihydrate at a concentration of 100 mg/ml;
- (c) L-histidine at a concentration of 0.92 mg/ml; and
- (d) L-histidine hydrochloride at a concentration of 2.96 mg/ml;
- (e) wherein said composition has pH 5.5.

[00158] In some embodiments of the invention, prolgolimab may be administered as an aqueous pharmaceutical composition comprising:

- (a) prolgolimab at a concentration of 100 mg/ml as an antibody;
- (b) trehalose dihydrate at a concentration of 80 mg/ml;
- (c) L-histidine at a concentration of 0.92 mg/ml; and
- (d) L-histidine hydrochloride at a concentration of 2.96 mg/ml;
- (e) wherein said composition has pH from 5.5 to 6.0.

[00159] In some embodiments of the invention, said aqueous pharmaceutical composition may further comprise a suitable solubilizer.

[00160] In some embodiments of the invention, said solubilizer may be Poloxamer 188.

[00161] In some embodiments of the invention, said Poloxamer 188 may be present in an amount greater than 0 mg/ml but equal to or less than 1 mg/ml.

[00162] In some embodiments of the invention, said Poloxamer 188 may be present in an amount of 0 mg/ml, 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, 0.5 mg/ml, 0.6 mg/ml, 0.7 mg/ml, 0.8 mg/ml, 0.9 mg/ml, 1.0 mg/ml.

[00163] In some embodiments of the invention, the use of said aqueous pharmaceutical composition of prolgolimab may comprise administering said composition parenterally.

[00164] In some embodiments of the invention, said parenteral administration may be intravenous, subcutaneous or intramuscular administration.

[00165] In some embodiments of the invention, the use of said aqueous pharmaceutical composition of anti-PD-1 antibody prolgolimab may comprise administering said composition intravenously as an infusion.

[00166] In some embodiments, the aqueous pharmaceutical composition of anti-PD-1 antibody prolgolimab of the invention may be administered intravenously as an infusion over 60 minutes; in case of good tolerability, the infusion time may be shortened to 30 minutes.

### **Examples**

[00167] The use of prolgolimab (BCD-100) for treating patients in combination with platinum-containing chemotherapy and bevacizumab in first-line therapy in female patients with recurrent/persistent or metastatic cervical cancer, phase II trial, BCD-100-4/CAESURA.

### **Trial design**

[00168] Trial no. BCD-100-4/CAESURA (CAESURA, NCT03912402) in terms of design thereof is an open-label, single-arm study of efficacy and safety of the BCD-100 product (JSC "BIOCAD", Russia) in combination with platinum-containing chemotherapy (ChT) and bevacizumab (BEV) in first-line therapy in female patients with recurrent/persistent or metastatic cervical cancer (CC). The trial is carried out in 2 stages. At the first stage, the female patients received BCD-100 + ChT + BEV therapy for up to 6 cycles, either until they developed intolerable toxicity events, or until disease progression. The female patients who demonstrated a positive antitumor effect (stabilization of the disease, partial or complete response) and who had no signs of intolerable toxicity were transferred to the second stage of the trial, the maintenance therapy stage.

[00169] The data of the 1st stage of the trial was obtained and analyzed.

[00170] Within the framework of this trial, a combination therapy modality including platinum, taxanes, bevacizumab and prolgolimab products is studied for the first time. To date,

there is no literature data on the efficacy and safety of adding immunotherapy to standard first-line therapy in the population of female patients with recurrent/persistent or metastatic cervical cancer.

### **Treatment**

#### **First stage**

[00171] The female patients received combination therapy including:

- BCD-100 3 mg/kg as a 1-hour infusion once every 3 weeks (Q3W);
- Bevacizumab 15 mg/kg as a 1-hour Q3W infusion;
- Paclitaxel 175 mg/m<sup>2</sup> as a 3-hour Q3W infusion;
- Cisplatin 50 mg/m<sup>2</sup> as a 1-hour Q3W infusion or Carboplatin AUC 5 mg/ml/min as a

1-hour Q3W infusion (the choice of Carboplatin or Cisplatin was left to the discretion of the Study Physician based on the risk/benefit ratio for a particular female patient).

[00172] Modification of the therapeutic regimen within the first stage was not envisaged, except in cases of intolerant toxicity described in the Protocol of the present trial. After the use of said combination therapy for 18 weeks (6 cycles of BCD-100 + ChT + BEV), in case of achieving a positive antitumor effect (stabilization of the disease, partial or complete response) and provided there is no intolerable toxicity, in the interests of the female patient, therapy could be continued as part of the second stage of the trial. If the female patient received less than 6 cycles of therapy as part of the first stage due to intolerant toxicity, in the interests of the patient, therapy could be continued according to a regimen envisaged as part of the second stage of the trial.

#### **Second stage**

[00173] This stage of the trial consists of maintenance therapy, which is conducted in female patients who have achieved a positive antitumor effect. Maintenance therapy regimen:

- BCD-100 3 mg/kg as a 1-hour Q3W infusion;
- Bevacizumab 15 mg/kg as a 1-hour Q3W infusion

[00174] Therapy as part of the second stage of the trial is conducted until disease progression or until development of intolerable toxicity events, but for not more than 12 cycles inclusive. Within the framework of trial no. BCD-100-EXT, the therapy of the female patients may be continued when stabilization or response to therapy is achieved and provided that there are no intolerable toxicity events.

#### **Efficacy study**

[00175] The antitumor effect of combination therapy with BCD-100 was evaluated based on the results of computed tomography (CT) 9 and 18 weeks following beginning of therapy according to the RECIST 1.1 and iRECIST criteria (standard criteria for evaluation of tumor dynamics by CT). If a positive antitumor effect was achieved (stabilization of the disease, partial or complete response) against the background of 6 cycles of administration of the BCD-100 product in combination with platinum-containing chemotherapy and bevacizumab, the female

patient could be transferred to the second stage of the trial by the decision of the Study Physician. At the second stage, the female patient could further receive up to 12 cycles (inclusive) of the BCD-100 product in combination with bevacizumab (further therapy could continue as part of another trial BCD-100-EXT). Evaluation of efficacy at the second stage of the trial had an ancillary character. The female patients underwent a CT scan every 12 weeks, and unscheduled study was further contemplated if disease progression was suspected.

#### **Safety and immunogenicity study**

[00176] Safety was assessed on the basis of data on the registration of adverse events and serious adverse events, as well as data from general examination and determination of physiological parameters, results of general and biochemical blood tests and other tests.

[00177] The immunogenicity study was part of the mandatory procedures for monitoring the safety of the therapeutic product and was performed prior to the first administration of the product and then every 42 days of product therapy until the end of the first stage of the trial. The female patients who were transferred to the second stage of the trial, for mandatory safety monitoring, were subject to sampling to evaluate the immunogenicity of BCD-100.

#### **Results of trial**

##### **Summary of characteristics of patient population**

[00178] 59 patients were enrolled aged 18 and older. The population included female patients with histologically verified (all histological types) primary metastatic cervical cancer, or recurrent/persistent cervical cancer, with the presence of measurable control tumor foci (at least 1 focus), according to the RECIST 1.1 criteria (confirmed by central revision), having a general condition corresponding to a score of 0-1 according to ECOG scale (Table 1).

[00179] This population included female patients who took the place of those who discontinued prior to first administration of BCD-100, or of those who discontinued as a result of serious deviations from the protocol. The resulting modified ITT population of female patients who received at least one dose of BCD-100 included 58 female patients.

[00180] The population per protocol (PP) included 42 patients who received all 6 cycles of therapy at the first stage. Administration of at least one of the four combination therapy products (i.e. prolgorimab, bevacizumab, paclitaxel, cisplatin/carboplatin) was assumed as a therapy cycle.

**Table 1 – Main characteristics of the disease, in mITT population**

| Parameter                                                   | Statistics | N = 58     |
|-------------------------------------------------------------|------------|------------|
| Stage of disease according to FIGO at the time of diagnosis |            |            |
| Stage IA                                                    | n (%)      | 1 (1.72)   |
| Stage IB                                                    | n (%)      | 6 (10.34)  |
| Stage II                                                    | n (%)      | 4 (6.90)   |
| Stage IIA                                                   | n (%)      | 4 (6.90)   |
| Stage IIB                                                   | n (%)      | 15 (25.86) |

| Parameter                                                                     | Statistics   | N = 58     |
|-------------------------------------------------------------------------------|--------------|------------|
| Stage III                                                                     | n (%)        | 3 (5.17)   |
| Stage IIIA                                                                    | n (%)        | 1 (1.72)   |
| Stage IIIB                                                                    | n (%)        | 17 (29.31) |
| Stage IV                                                                      | n (%)        | 3 (5.17)   |
| Stage IVB                                                                     | n (%)        | 4 (6.90)   |
| Duration of disease at the time of screening (months)                         |              |            |
|                                                                               | Mean         | 34.29      |
|                                                                               | Median       | 14.50      |
|                                                                               | Minimum      | 0.2        |
|                                                                               | Maximum      | 279.7      |
|                                                                               | L. quartile  | 8.10       |
|                                                                               | Up. quartile | 26.30      |
|                                                                               | St. Dev.     | 54.735     |
|                                                                               | CV (%)       | 159.6      |
| Disease status at the time of screening                                       |              |            |
| Metastatic                                                                    | n (%)        | 42 (72.41) |
| Recurrent                                                                     | n (%)        | 15 (25.86) |
| Persistent                                                                    | n (%)        | 1 (1.72)   |
| Presence of distant metastases at the time of screening                       |              |            |
| Yes                                                                           | n (%)        | 47 (81.03) |
| No                                                                            | n (%)        | 11 (18.97) |
| Proportion of patients with different number of organs with metastatic lesion |              |            |
| 0                                                                             | n (%)        | 11 (18.97) |
| 1                                                                             | n (%)        | 22 (37.93) |
| 2                                                                             | n (%)        | 11 (18.97) |
| 3 or more                                                                     | n (%)        | 14 (24.14) |
| Number of organs with distant metastases                                      |              |            |
|                                                                               | Mean         | 1.6        |
|                                                                               | Median       | 1.0        |
|                                                                               | Minimum      | 0          |
|                                                                               | Maximum      | 5          |
|                                                                               | L. quartile  | 1.0        |
|                                                                               | Up. quartile | 2.0        |
|                                                                               | St. Dev.     | 1.31       |
|                                                                               | CV (%)       | 80.76      |
| Tumor volume at screening (mm)                                                |              |            |
|                                                                               | Mean         | 65.4       |
|                                                                               | Median       | 48.0       |
|                                                                               | Minimum      | 12         |
|                                                                               | Maximum      | 208        |
|                                                                               | L. quartile  | 37.0       |
|                                                                               | Up. quartile | 96.0       |
|                                                                               | St. Dev.     | 44.27      |
|                                                                               | CV (%)       | 67.71      |
| Proportion of patients with risk factors                                      | n (%)        | 12 (20.69) |
| Tumor invasion to vaginal wall, uterus                                        | n (%)        | 6 (10.34)  |
| Tumor invasion to hollow organ wall                                           | n (%)        | 4 (6.90)   |

| Parameter                                                                                | Statistics | N = 58     |
|------------------------------------------------------------------------------------------|------------|------------|
| Tumor invasion (involvement in tumor conglomerate) to large vessels                      | n (%)      | 2 (3.45)   |
| Local recurrence of tumor in an area which was previously treated with radiation therapy | n (%)      | 1 (1.72)   |
| Tumor extension only to lesser pelvis                                                    |            |            |
| Yes                                                                                      | n (%)      | 7 (12.07)  |
| No                                                                                       | n (%)      | 51 (87.93) |
| Histological type                                                                        |            |            |
| Squamous cell cancer                                                                     | n (%)      | 50 (86.21) |
| Adenocarcinoma                                                                           | n (%)      | 7 (12.07)  |
| Mixed type                                                                               | n (%)      | 1 (1.72)   |
| PD-L1 expression status according to TPS                                                 |            |            |
| TPS < 1%                                                                                 | n (%)      | 11 (18.97) |
| TPS ≥ 1%                                                                                 | n (%)      | 42 (72.41) |
| Unknown                                                                                  | n (%)      | 5 (8.62)   |
| PD-L1 expression status according to CPS                                                 |            |            |
| CPS < 1                                                                                  | n (%)      | 6 (10.34)  |
| CPS ≥ 1                                                                                  | n (%)      | 45 (77.59) |
| Unknown                                                                                  | n (%)      | 7 (12.07)  |
| Prior therapy                                                                            |            |            |
| Yes                                                                                      | n (%)      | 47 (81.03) |
| No                                                                                       | n (%)      | 11 (18.97) |
| Type of prior therapy                                                                    |            |            |
| Chemotherapy                                                                             |            | 21 (36.21) |
| Neoadjuvant chemotherapy                                                                 |            | 5 (8.62)   |
| Adjuvant chemotherapy                                                                    |            | 4 (6.90)   |
| Chemoradiotherapy                                                                        |            | 11 (18.97) |
| Therapy of metastatic disease                                                            |            | 1 (1.72)   |
| Other chemotherapy                                                                       |            | 1 (1.72)   |
| Radiation therapy (including chemoradiotherapy)                                          |            | 42 (72.41) |
| Surgical treatment                                                                       |            | 18 (31.03) |
| Chemotherapeutic agents of prior therapy                                                 |            |            |
| Cisplatin                                                                                | n (%)      | 6 (10.34)  |
| Carboplatin                                                                              | n (%)      | 3 (5.17)   |
| Paclitaxel                                                                               | n (%)      | 2 (3.45)   |
| Fluorouracil                                                                             | n (%)      | 2 (3.45)   |
| Irinotecan                                                                               | n (%)      | 2 (3.45)   |
| Gemcitabine                                                                              | n (%)      | 1 (1.72)   |

N: number of patients in the mITT population; n: number of observations; Percentages were calculated as 100 x n/N.

Summary of clinical efficacy obtained during trial no. BCD-100-4/CAESURA.

[00181] Tumor response to therapy was evaluated in two patient populations (mITT and PP) according to both RECIST 1.1 and iRECIST criteria. Data analysis was performed based on data of independent central CT review and based on data of local evaluation. The main analysis was the analysis of efficacy parameters based on data of independent central revision according to RECIST 1.1 criteria in the mITT population.

[00182] In the mITT population, the overall response rate against the background of combination therapy with prolgolimab was 50.00% in accordance with RECIST 1.1 evaluation criteria and 65.52% in accordance with iRECIST evaluation criteria. The table below shows detailed data on the response rate in the mITT population according to RECIST 1.1 and iRECIST criteria based on data of central revision.

**Table 2 - Response rate in the mITT population according to RECIST 1.1 and iRECIST criteria based on data of central revision**

| Evaluation criteria Evaluation                                                                                     | Statistics | N = 58     |
|--------------------------------------------------------------------------------------------------------------------|------------|------------|
| <b>RECIST 1.1</b>                                                                                                  |            |            |
| Complete response (CR)                                                                                             | n (%)      | 2 (3.45)   |
| Partial response (PR)                                                                                              | n (%)      | 27 (46.55) |
| Stabilization (SD)                                                                                                 | n (%)      | 13 (22.41) |
| Disease progression (PD)                                                                                           | n (%)      | 7 (12.07)  |
| Not evaluated (NE)                                                                                                 | n (%)      | 1 (1.72)   |
| No response evaluation at the time of analysis                                                                     | n (%)      | 8 (13.79)  |
| Control over disease (CR+PR+SD)                                                                                    | n (%)      | 42 (72.41) |
| Overall response rate (CR+PR)                                                                                      | n (%)      | 29 (50.00) |
| <b>iRECIST</b>                                                                                                     |            |            |
| Complete response (iCR)                                                                                            | n (%)      | 2 (3.45)   |
| Partial response (iPR)                                                                                             | n (%)      | 36 (62.07) |
| Stabilization (iSD)                                                                                                | n (%)      | 7 (12.07)  |
| Unconfirmed disease progression (iUPD)                                                                             | n (%)      | 4 (6.90)   |
| Confirmed disease progression (iCPD)                                                                               | n (%)      | 0          |
| Not evaluated (NE)                                                                                                 | n (%)      | 1 (1.72)   |
| No response evaluation at the time of analysis                                                                     | n (%)      | 8 (13.79)  |
| Control over disease (iCR+iPR+iSD)                                                                                 | n (%)      | 45 (77.59) |
| Overall response rate (iCR+iPR)                                                                                    | n (%)      | 38 (65.52) |
| N: number of patients in the mITT population; n: number of observations; Percentages were calculated as 100 x n/N. |            |            |

[00183] Over the analyzed period, 29 patients achieved response to therapy, which exceeds the preset critical value ( $r = 24$ ) for the number of positive responses in the therapy group necessary to confirm the reliable antitumor effect of the test therapy (relative to the literature data on the efficacy of standard therapy). The trial reached its primary endpoint, thus allowing to conclude that the test therapy regimen is sufficiently effective.

[00184] According to the central revision evaluation, the overall response rate in the PP population against the background of combination therapy with prolgolimab was 59.52% in accordance with RECIST 1.1 evaluation criteria and 80.95% in accordance with iRECIST evaluation criteria. The frequency of achieving disease control was 88.10% in accordance with RECIST 1.1 evaluation criteria and 95.24% in accordance with iRECIST evaluation criteria. It should be noted that the indicators of therapy efficacy in the population of female patients who

received all 6 therapy cycles are greater as compared to those in the mITT population, thus suggesting a more favorable prognosis in this subgroup of female patients.

[00185] The median time to achieve response to therapy according to all estimates was about 2.2 months, which corresponds to the time frame of the first control CT study. The median duration of response to therapy was not achieved by any of the evaluations.

[00186] The resulting data suggests sufficient efficacy of combination therapy with prolgolimab with standard first-line therapy in female patients with recurrent/persistent or metastatic cervical cancer.

#### **Summary of clinical safety obtained during trial no. BCD-100-4/CAESURA**

[00187] Safety analysis includes all patients included in the trial and who received at least 1 administration of the test product (mITT).

[00188] Over the analyzed period, the prolgolimab exposure was 126 days or greater in 68.97% (40 out of 58) of patients. Median (l. quartile; up. quartile) infusions was 6 (5; 6) infusions. Most of the female patients received 6 prolgolimab injections, according to the therapy regimen planned in the protocol (considering the time frame of data segment). Exposure to complete combination of test therapy (all chemotherapy drugs, including bevacizumab and prolgolimab) was 126 days or more in 74.14% (43 out of 58) of patients. Most of the female patients received a full course of therapy with all products of the test combination.

[00189] Over the analyzed period, most of the female patients (98.28%) had at least one adverse event. Further, causal relationship between the development of these AEs and prolgolimab therapy, according to the investigators, was observed in 35 patients out of 58 (60.34%).

[00190] Grade 3-4 adverse events according to CTCAE 5.0 were observed in 30 (51.72%) female patients. The grade 3-4 adverse events observed in 10 patients (17.24%), according to the investigators, had causal relationship with prolgolimab therapy.

[00191] Adverse events meeting the severity grades were observed in 20 patients (34.48%) out of 58. According to the investigators, only 2 of the registered SAEs had direct relationship with prolgolimab therapy.

[00192] Grade 5 adverse events were observed in 7 (12.07%) female patients. According to an investigator, only 1 case of grade 5 adverse event was associated with prolgolimab therapy.

[00193] Over the analyzed period of therapy, imAEs were observed in 17 out of 58 patients (29.31%). In the vast majority of cases, these imAEs corresponded to severity grades 1 and 2 according to CTCAE 5.0. Grade 3-4 imAEs were observed in 5 patients (8.62%).

[00194] Therapy was prematurely discontinued due to development of an adverse event (intolerable toxicity) in 10 (17.24%) patients, and 3 (5.17%) patients discontinued therapy with fatal outcome.

[00195] Table 3 shows data on primary main safety parameters.

**Table 3 – Main safety parameters in mITT population**

| Parameter                                                                                                                                      | N = 58<br>n (%) |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Proportion of patients with adverse events, including serious adverse events                                                                   | 57 (98.28)      |
| Proportion of patients with adverse events, including serious adverse events, associated, according to the investigator, with the test product | 35 (60.34)      |
| Proportion of patients with serious adverse events                                                                                             | 20 (34.48)      |
| Proportion of patients with serious adverse events associated, according to the investigator, with the test product                            | 2 (3.45)        |
| Proportion of patients with grade 3-4 adverse events                                                                                           | 30 (51.72)      |
| Proportion of patients with grade 3-4 adverse events, associated, according to the investigator, with the test product                         | 10 (17.24)      |
| Proportion of patients with grade 5 adverse events                                                                                             | 7 (12.07)       |
| Proportion of patients with grade 5 adverse events, associated, according to the investigator, with the test product                           | 1 (1.72)        |
| Proportion of patients who developed immuno-mediated adverse events                                                                            | 17 (29.31)      |
| Proportion of patients who developed grade 3-4 immuno-mediated adverse events                                                                  | 5 (8.62)        |
| N: number of patients in the mITT population; n: number of observations;<br>Percentages were calculated as $100 \times n/N$ .                  |                 |

[00196] Considering the fact that the test therapy regimen suggests addition of prolgolimab to the standard of CC treatment, it is important to note that, according to the literature (Avastin Extension of indication variation assessment report 26 February 2015 EMA/CHMP/205694/2015), the platinum-containing chemotherapy regimen in combination with bevacizumab is characterized by safety parameters similar to those obtained in the present trial. Thus, the standard therapy regimen in a similar population of patients was characterized by the development of AEs with an incidence of 100%, by the development of SAEs in 45.9% of patients, by the development of grade 3/4/5 AEs in 78.0% of patients, by the discontinuation of therapy due to the development of AEs in 33.0% of patients. Thus, we may conclude that the addition of prolgolimab to standard therapy was associated with the development of immunotherapy-specific adverse events, i.e. immuno-mediated AEs, that were not observed against the background of standard therapy, but did not lead to a significant deterioration in the safety profile of the combined therapy regimen as compared to treatment standard.

[00197] Based on total analysed safety parameters, it can be noted that the safety profile of combination therapy supplemented with prolgolimab corresponds to the literature data relating to the safety of the standard regimen of platinum-containing chemotherapy in combination with

bevacizumab. Further, the addition of prolgolimab to standard therapy was associated with the development of immunotherapy-specific adverse events, i.e. immuno-mediated AEs, that were not observed (according to literature data) against the background of standard therapy, but did not lead to a significant deterioration in the safety profile of the combined therapy regimen as compared to treatment standard.

### **Immunogenicity**

[00198] Immunogenicity analysis included data from 55 patients who received at least one prolgolimab administration with no omitted/lost/spoiled blood serum sample taken on day 1 of week 0, as well as at least one of the samples taken at one of the subsequent visits. The immunogenicity study did not reveal the formation of binding antibodies to prolgolimab in any of the patients.

### **Conclusion**

[00199] Within the framework of this trial, a combination therapy modality including platinum, taxanes, bevacizumab and prolgolimab products is studied for the first time. Currently, there is no literature data on the efficacy and safety of adding immunotherapy to standard first-line therapy in the population of female patients with recurrent/persistent or metastatic cervical cancer.

[00200] The study was conducted on a representative population, which was balanced by the main demographic parameters and characteristics of the disease, and which was close to the target population of patients with recurrent/persistent or metastatic cervical cancer.

[00201] The obtained data on efficacy and safety are sufficient to rationalize the use of the product in combination with platinum-containing chemotherapy and bevacizumab.

[00202] Within the framework of the multicenter, open-label, phase II trial no. BCD-100-4/CAESURA in a population of patients with primary metastatic cervical cancer or recurrent/persistent cervical cancer, a significant therapeutic effect of the use of prolgolimab in combination with platinum-containing chemotherapy and bevacizumab was demonstrated. Taking into account the efficacy indicators under a satisfactory safety profile obtained in the trial, the use of prolgolimab in combination with platinum-containing chemotherapy and bevacizumab provides the risk-benefit balance in the given population of patients.

**Claims**

1. Use of antibody to PD-1 in combination with at least one chemotherapeutic agent for treating a malignant neoplasm.
2. The use according to claim 1, wherein the antibody to PD-1 is administered at a dose of 0.5-10 mg/kg of body weight or at a dose of 100-400 mg.
3. The use according to claim 1, wherein the antibody to PD-1 is administered at a dose of 1 mg/kg or 3 mg/kg of body weight.
4. The use according to claim 1, wherein the antibody to PD-1 is administered every 2 weeks, or every 3 weeks, or every 4 weeks.
5. The use according to claim 1, wherein the antibody to PD-1 is administered at a dose of 1 mg/kg of body weight every 2 weeks or at a dose of 3 mg/kg of body weight every 3 weeks.
6. The use according to claim 1, wherein the antibody to PD-1 is prolgolimab.
7. The use according to claim 1, wherein the chemotherapeutic agent is selected from the group comprising taxane, a platinum agent.
8. The use according to claim 1, wherein the chemotherapeutic agent is administered every 2 weeks, or every 3 weeks, or every 4 weeks.
9. The use according to claim 7, wherein taxane is selected from paclitaxel, docetaxel.
10. The use according to claim 9, wherein paclitaxel is administered at a dose of 135-175 mg/m<sup>2</sup>.
11. The use according to claim 9, wherein paclitaxel is administered at a dose of 135 or 175 mg/m<sup>2</sup>.
12. The use according to claim 7, wherein the platinum agent is selected from carboplatin, cisplatin.
13. The use according to claim 12, wherein cisplatin is administered at a dose of 50-100 mg/m<sup>2</sup>.
14. The use according to claim 12, wherein cisplatin is administered at a dose of 50 mg/m<sup>2</sup>.
15. The use according to claim 12, wherein carboplatin is administered at a dose of AUC 5-7.
16. The use according to claim 12, wherein carboplatin is administered at a dose of AUC 5.
17. The use according to claim 1, further being in combination with antibody to VEGF.

18. The use according to claim 17, wherein the antibody to VEGF is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

19. The use according to claim 17, wherein the antibody to VEGF is bevacizumab.

20. The use according to claim 19, wherein bevacizumab is administered at a dose of 15 mg/kg of body weight.

21. Use of antibody to PD-1 in combination with paclitaxel and carboplatin or cisplatin for treating a malignant neoplasm.

22. The use according to claim 21, wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

23. The use according to claim 21, wherein the antibody to PD-1 is prolololimab.

24. Use of antibody to PD-1 in combination with bevacizumab, paclitaxel, carboplatin or cisplatin for treating a malignant neoplasm.

25. The use according to claim 24, wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

26. The use according to claim 24, wherein the antibody to PD-1 is prolgolimab.

27. The use according to any of claims 1-26, wherein the malignant neoplasm is selected from the group comprising melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer, non-squamous cell non-small cell lung cancer, squamous cell lung cancer, small cell lung cancer, including inoperable/metastatic small cell lung cancer, early stage lung cancer before and after definitive treatment; cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment, head and neck cancers, including head and neck squamous cell carcinoma, Hodgkin's lymphoma, gastrointestinal cancer, metastatic esophageal squamous cell carcinoma, bladder cancer, including metastatic urothelial carcinoma, kidney cancer, endometrial cancer, including metastatic endometrial cancer, early stages of endometrial cancer before and after definitive treatment, breast cancer, including metastatic breast cancer, early stages of endometrial cancer before and after definitive treatment, liver cancer, including metastatic or inoperable liver cancer, early stages of liver cancer before and after definitive treatment, inoperable or metastatic solid tumor, including inoperable or metastatic solid tumor with evidence of microsatellite instability.

28. A method for treating a malignant neoplasm in a subject in need thereof, comprising administering a therapeutically effective amount of antibody to PD-1 in combination with at least one chemotherapeutic agent.

29. The method of treatment according to claim 28, wherein the antibody to PD-1 is administered at a dose of 0.5-10 mg/kg of body weight or at a dose of 100-400 mg.

30. The method of treatment according to claim 28, wherein the antibody to PD-1 is administered at a dose of 1 mg/kg or 3 mg/kg of body weight.

31. The method of treatment according to claim 28, wherein the antibody to PD-1 is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

32. The method of treatment according to claim 28, wherein the antibody to PD-1 is administered at a dose of 1 mg/kg of body weight every 2 weeks or at a dose of 3 mg/kg of body weight every 3 weeks.

33. The method of treatment according to claim 28, wherein the antibody to PD-1 is prolgolimab.

34. The method of treatment according to claim 28, wherein the chemotherapeutic agent is selected from the group comprising taxane, a platinum agent.

35. The method of treatment according to claim 28, wherein the chemotherapeutic agent is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

36. The method of treatment according to claim 34, wherein taxane is selected from paclitaxel, docetaxel.

37. The method of treatment according to claim 36, wherein paclitaxel is administered at a dose of 135-175 mg/m<sup>2</sup>.

38. The method of treatment according to claim 36, wherein paclitaxel is administered at a dose of 135 or 175 mg/m<sup>2</sup>.

39. The method of treatment according to claim 36, wherein the platinum agent is selected from carboplatin, cisplatin.

40. The method of treatment according to claim 39, wherein cisplatin is administered at a dose of 50-100 mg/m<sup>2</sup>.

41. The method of treatment according to claim 39, wherein cisplatin is administered at a dose of 50 mg/m<sup>2</sup>.

42. The method of treatment according to claim 39, wherein carboplatin is administered at a dose of AUC 5-7.

43. The method of treatment according to claim 39, wherein carboplatin is administered at a dose of AUC 5.

44. The method of treatment according to claim 28, further comprising administration of antibody to VEGF.

45. The method of treatment according to claim 44, wherein the antibody to VEGF is administered every 2 weeks, or every 3 weeks, or every 4 weeks.

46. The method of treatment according to claim 44, wherein the antibody to VEGF is bevacizumab.

47. The method of treatment according to claim 46, wherein bevacizumab is administered at a dose of 15 mg/kg of body weight.

48. A method for treating a malignant neoplasm in a subject in need thereof, comprising administering a therapeutically effective amount of antibody to PD-1 in combination with paclitaxel and carboplatin or cisplatin.

49. The method of treatment according to claim 48, wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight is administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

50. The method of treatment according to claim 48, wherein the antibody to PD-1 is prolgolimab.

51. A method for treating a malignant neoplasm in a subject in need thereof, comprising administering a therapeutically effective amount of antibody to PD-1 in combination with bevacizumab, paclitaxel, carboplatin or cisplatin.

52. The method of treatment according to claim 51, wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and carboplatin at a dose of AUC 5 are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 1 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks; or

wherein the antibody to PD-1 at a dose of 3 mg/kg of body weight and bevacizumab at a dose of 15 mg/kg of body weight are administered every 2 weeks or every 3 weeks, paclitaxel at a dose of 175 mg/m<sup>2</sup> and cisplatin at a dose of 50 mg/m<sup>2</sup> are administered every 3 weeks.

53. The method of treatment according to claim 51, wherein the antibody to PD-1 is prolgolimab.

54. The method of treatment according to any of claims 28-53, wherein the malignant neoplasm is selected from the group comprising melanoma, including inoperable/metastatic melanoma, early stages of melanoma before and after definitive treatment; lung cancer, non-small cell lung cancer (NSCLC), including inoperable/metastatic non-small cell lung cancer, non-squamous cell non-small cell lung cancer, squamous cell lung cancer, small cell lung cancer, including inoperable/metastatic small cell lung cancer, early stage lung cancer before and after definitive treatment; cervical cancer, including metastatic cervical cancer, recurrent cervical cancer, progressive cervical cancer, persistent cervical cancer, early stages of cervical cancer before and after definitive treatment, head and neck cancers, including head and neck squamous

cell carcinoma, Hodgkin's lymphoma, gastrointestinal cancer, metastatic esophageal squamous cell carcinoma, bladder cancer, including metastatic urothelial carcinoma, kidney cancer, endometrial cancer, including metastatic endometrial cancer, early stages of endometrial cancer before and after definitive treatment, breast cancer, including metastatic breast cancer, early stages of endometrial cancer before and after definitive treatment, liver cancer, including metastatic or inoperable liver cancer, early stages of liver cancer before and after definitive treatment, inoperable or metastatic solid tumor, including inoperable or metastatic solid tumor with evidence of microsatellite instability.