negative regulation of Th1 type responses, Th2 polarization and polarization of macrophages to the M2 phenotype. This work also includes studies that have shown that Galectin-9 participates in direct inactivation of T cells through interactions with the T-cell immunoglobulin and mucin protein 3 (TIM-3) receptor (Dardalhon et al., *J Immunol.,* 2010, 185, 1383-1392; Sanchez-Fueyo et al., *Nat Immunol.,* 2003, 4, 1093-1101).

Galectin-9 has also been found to play a role in polarizing T cell differentiation into tumor suppressive phenotypes), as well as promoting tolerogenic macrophage programming and adaptive immune suppression (Daley et al., *Nat Med.,* 2017, 23, 556-567). In mouse models of pancreatic ductal adenocarcinoma (PDAC), blockade of the checkpoint interaction between Galectin-9 and the receptor Dectin-1 found on innate immune cells in the tumor microenvironment (TME) has been shown to increase anti-tumor immune responses in the TME and to slow tumor progression (Daley et al., *Nat Med., 2017, 23, 556-567*). Galectin-9 also has been found to bind to CD206, a surface marker of M2 type macrophages, resulting in a reduced secretion of CVL22 (MDC), a macrophage derived chemokine which has been associated with longer survival and lower recurrence risk in lung cancer (Enninga et al, J Pathol. 2018 Aug;245(4):468-477).

SUMMARY

The present disclosure is based on the unexpected discovery that a synergistic effect is observed in combined therapies involving both an exemplary anti-galectin 9 antibody (*e.g.*, G9.2-17(IgG4)) and chemotherapeutics such as gemcitabine and paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel or nab-paclitaxel) in an animal model. Alternatively or in addition, the present disclosure is based, at least in part, on the unexpectedly discovery that an anti-Galectin 9 antibody G9.2-17 (IgG4) has a quicker clearance rate in human subjects as compared with other antibody therapeutics. Accordingly, a treatment regimen comprising a dosing schedule of once every week was developed to ensure a suitable plasma concentration, e.g., a therapeutic systemic exposure level, of the anti-Galectin 9 antibody (anti-Gal-9 antibody) for achieving therapeutic effects. In one aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) and one or more chemotherapeutics in the manufacture of a medicament for combination therapy to treat a solid tumor in a human patient; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of

SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

In another aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a first medicament and use of one or more chemotherapeutics in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a human patient; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

In another aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a human patient, wherein said medicament is to be administered in combination with one or more chemotherapeutics; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid

sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

In another aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) and one or more chemotherapeutics in the manufacture of a medicament for combination therapy to treat a solid tumor in a human patient; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; wherein the anti-Gal9 antibody is at a dose of t 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

In another aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a first medicament and use of one or more chemotherapeutics in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a human patient; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a

heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; wherein the subject has one or more of the following features: (i) has no infection by SARS-CoV-2; and (ii) has no active brain or leptomeningeal metastasis; and wherein the anti-Gal9 antibody is at a dose of 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

In a further aspect, the present disclosure provides a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a human patient, wherein said medicament is to be administered in combination with one or more chemotherapeutics; wherein the anti-Gal-9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; wherein the subject has one or more of the following features: (i) has no infection by SARS-CoV-2; and (ii) has no active brain or leptomeningeal metastasis; and wherein the anti-Gal9 antibody is at a dose of 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

Accordingly, provided herein are methods for treating a solid tumor involving the co-use of an anti-galectin-9 antibody (*e.g.*, G9.2-17 or a functional variant thereof) and one or more chemotherapeutics (e.g., gemcitabine, paclitaxel such as paclitaxel protein-bound (*e.g.*, nab-paclitaxel or Abraxane®), or a combination thereof). In some instances, the anti-Gal-9 antibody disclosed herein such as G9.2-17(IgG4) may be administered at a once per week dosing schedule.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal-9 antibody). The anti-Gal-9 antibody may have the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17. The subject may be undergoing an anti-cancer therapy comprising one or more chemotherapeutics.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal-9 antibody) and an effective amount of one or more chemotherapeutics. The anti-Gal-9 antibody may have the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of one or more chemotherapeutics. The subject may be undergoing a therapy comprising an antibody that binds human galectin-9 (anti-Gal-9 antibody), which has the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17.

Any of the methods disclosed herein may be applied for treating a metastatic solid tumor. In some examples, the solid tumor is pancreatic ductal adenocarcinoma (PDAC), for example, metastatic PDAC.

In some examples, the subject to be treated by any of the methods disclosed herein may have one or more of the following features: (i) has no resectable cancer; (ii) has no infection by SARS-CoV-2; and (iii) has no active brain or leptomeningeal metastasis. In some examples, the solid tumor is pancreatic ductal adenocarcinoma (PDAC), and the subject has no locally advanced PDAC without distant organ metastatic deposits.

In some examples, the one or more chemotherapeutics involved in any of the methods disclosed herein may comprise an antimetabolite (e.g., a nucleoside analog), a microtubule inhibitor, or a combination thereof. In some examples, the nucleoside analog is gemcitabine and/or the tubulin inhibitor is paclitaxel, for example, nanoparticle albumin-bound paclitaxel (*e.g.*, Abraxane®).

In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose of about 0.2 mg/kg to about 32 mg/kg (*e.g.*, about 0.2 mg/kg to about 16 mg/kg, 0.5 mg/kg to about 16 mg/kg, about 2 mg/kg to about 32 mg/kg or about 2 mg/kg to about 16 mg/kg, or about 0.2 mg/kg to about 15 mg/kg. or about 0.2 to about 16 mg/kg or higher).

In some examples, the anti-Gal-9 antibody is administered to the subject once a week. In some examples, the anti-Gal-9 antibody may be administered to the subject at a dose of about 0.2 mg/kg to about 32 mg/kg once every week. In some examples, the anti-Gal-9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. Alternatively, the anti-Gal-9 antibody disclosed herein, such as G9.2-17 (IgG4) may be administered to the subject at a dose of about 650 mg to about 1120 mg once every week. For example, the anti-Gal-9 antibody can be administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of about 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody can be administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of about 1040-1120 mg once every week.

In some examples, the anti-Gal-9 antibody is administered to the subject once every 2 or 3 weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 0.2 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 2 mg/kg, 4 mg/kg, 6 mg/kg, 6.3 mg/kg, 8 mg/kg, 10 mg/kg, 12 mg/kg, or 16 mg/kg or higher. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 2 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, or 16 mg/kg or higher. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 0.2 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 2 mg/kg, 4 mg/kg, 6 mg/kg, 6.3 mg/kg, 10 mg/kg, or 16 mg/kg or higher. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 0.2 mg/kg, 0.63 mg/kg, 2 mg/kg, 4 mg/kg, 6 mg/kg, 6.3 mg/kg, 8 mg/kg, 10 mg/kg, 12 mg/kg, or 16 mg/kg once every 2 weeks. In some examples, the antibody is administered once every 2 weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 2 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, or 16 mg/kg or higher once every 2 weeks. In some examples, the antibody is administered once every 2 weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 0.2 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 2 mg/kg , 4 mg/kg, 6 mg/kg, 6.3 mg/kg, 10 mg/kg, or 16 mg/kg or higher once every 2 weeks.

In some examples, the anti-Gal-9 antibody such as G9.2-17 (IgG4) may be administered to a subject at a dose of about 650 mg to about 1120 mg once every 2-6 weeks, for example, once every 2 weeks, once every 3 weeks, or once every 4 weeks. In some examples, the anti-Gal-9 antibody is administered to a subject at a dose of about 650 mg to about 700 mg once every 2-6 weeks, for example, once every 2 weeks, once every 3 weeks, or once every 4 weeks. In other examples, the anti-Gal-9 antibody is administered to a subject at a dose of about 1040 mg to about 1120 mg once every 2-6 weeks, for example, once every 2

weeks, once every 3 weeks, or once every 4 weeks.

In some examples, the anti-Gal-9 antibody is administered once every 2 weeks for one cycle, once every 2 weeks for two cycles, once every 2 weeks for 3 cycles, once every 2 weeks for 4 cycles, or once every 2 weeks for more than 4 cycles. In some examples, the duration of treatment is 0-3 months, 0-6 months, 3-6 months, 6-12 months, 12-24 months or longer. In some examples, the duration of treatment is 12-24 months or longer. In some examples, the cycles extend for a duration of 3 months to 6 months, or 6 months to 12 months or 12 months to 24 months or longer. In some examples, the cycle length is modified, e.g., temporarily or permanently to a longer duration, e.g., 3 weeks or 4 weeks or 6 weeks.

In some examples, the anti-Gal-9 antibody is administered to the subject by intravenous infusion. In some examples, the cancer is PDAC. In some examples, the cancer is metastatic cancer. In some examples, the subject can be administered multiple doses of the anti-Galectin 9 antibody and a later dose is higher than an earlier dose.

In some examples, the anti-Gal-9 antibody can be administered to the subject at a dose of about 0.5 mg/kg to about 32 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody can be administered to the subject at a dose of about 0.2 mg/kg to about 32 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 0.5 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody can be administered to the subject at a dose of about 2 mg/kg to about 16 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody can be administered to the subject at a dose of about 0.2 mg/kg to about 16 mg/kg or higher once every two weeks by intravenous injection. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 0.2 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 0.6 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of about 0.63 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 2 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of about 4 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 6 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of

about 6.3 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 8 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of about 10 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 12 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of about 16 mg/kg or higher once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody is administered to the subject at a dose of about 32 mg/kg once every two weeks by intravenous infusion. In some examples, the anti-Gal-9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week.

In any of the methods disclosed herein, the one or more chemotherapeutics comprise an antimetabolite, a microtubule inhibitor, or a combination thereof. For example, the antimetabolite may be gemcitabine. Alternatively or in addition, the microtubule inhibitor may be paclitaxel. In some instances, the paclitaxel is a protein-bound paclitaxel, for example, a nanoparticle albumin-bound paclitaxel. In some examples, the one or more chemotherapeutics comprise a combination of gemcitabine and paclitaxel.

In some examples, the method comprises a cycle of 28 days, in which the anti-Gal9 antibody is administered to the subject on day 1 and day 15 and gemcitabine and paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) are administered to the subject on day 1, day 8, and day 15. In some examples, the paclitaxel is administered to the subject at 125 mg/m^2 intravenously. In some examples, the gemcitabine is administered to the subject at 1000 mg/m^2.

In some instances, the method disclosed herein may comprise a cycle of 28 days, in which the anti-Gal-9 antibody is administered to the subject on day 1, day 8, day 15, and day 22 and the gemcitabine and paclitaxel are administered to the subject on day 1, day 8, and day 15. In some examples, the paclitaxel is administered to the subject at 125 mg/m^2 intravenously. Alternatively or in addition, the gemcitabine is administered to the subject at 1000 mg/m^2.

In some examples, the anti-Galectin-9 antibody comprises a light chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) set forth as SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) set forth as SEQ ID NO: 3 and/or comprises a heavy chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) set forth as SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) set forth as SEQ ID NO: 6.

In some examples, the anti-Gal9 antibody may comprise a heavy chain variable region (V_H) that comprises the amino acid sequence of SEQ ID NO: 7; and a light chain variable region (V_L) that comprises the amino acid sequence of SEQ ID NO: 8. In some examples, the anti-Gal9 antibody can be an IgG molecule, for example, an IgG4 molecule. In specific examples, the anti-Gal9 antibody may comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 19 and a light chain that comprises the amino acid sequence of SEQ ID NO: 15.

In some examples, the one or more chemotherapeutics can be administered to the subject on a day when the subject receives the anti-Galectin 9 antibody. Alternatively, the administration of the one or more chemotherapeutics and the administration of the anti-Galectin 9 antibody can be performed on two consecutive days. In some examples, the administration of the one or more chemotherapeutics can be performed prior to the administration of the anti-Gal- 9 antibody, *e.g.*, on the first dosing day and the anti-Galectin 9 antibody is administered on the subsequent day.

In any of the methods disclosed herein, the subject may be a human patient. In some examples, the subject may comprise galectin-9 positive cancer cells or immune cells. In some instances, the subject may have an elevated level of galectin-9 relative to a control value. For example, the subject may have an elevated serum or plasma level of galectin-9 relative to the control value.

In some examples, the subject may have received at least one line of systemic anti-cancer therapy. In other examples, the subject may be free of prior therapy involving gemcitabine and/or paclitaxel or had a prior therapy involving gemcitabine and/or paclitaxel at least six months before administration of the anti-Gal-9 antibody.

In some instances, the subject is examined for one or more of the following features before, during, and/or after the treatment: (a) one or more tumor markers in tumor biopsy samples from the subject, optionally wherein the one or more tumor markers comprise CA15-3, CA-125, CEA, CA19-9, and/or alpha fetoprotein, and any other tumor -type specific tumor markers; (b) cytokine profile; and (c) galectin 9 serum/plasma levels, d) peripheral blood mononuclear cell immunophenotyping, e) tumor tissue biopsy/excisional specimen multiplex immunophenotyping, f) tumor tissue biopsy/excisional specimen galectin-9 expression levels and pattern, g) any other immune score test such as: PDL-1 immunohistochemistry, tumor mutational burden (TMB), tumor microsatellite instability status, as well as panels such as: Immunoscore®- HalioDx, ImmunoSeq- Adaptive Biotechnologies, TIS, developed on the NanoString nCounter® gene expression system, 18-gene signature, PanCancer IO 360™ assay

(NanoString Technologies) etc. Other suitable biomarkers specific to the target tumor may also be examined.

Any of the methods disclosed herein may further comprise monitoring occurrence of one or more adverse effects in the subject. In some instances, the one or more adverse effects comprise hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity, gastrointestinal toxicity, or a combination thereof.

In some examples, the method may further comprise reducing the dose of the anti-Gal9 antibody, the dose of the one or more chemotherapeutics, or both when an adverse effect is observed. For example, when moderate to severe hepatic impairment is observed in a subject, the method may further comprise reducing the dose of the anti-Gal-9 antibody, the dose of gemcitabine, the dose of paclitaxel, or a combination thereof. In one specific example, an anti-Gal-9 antibody dose reduction as per clinician's assessment or at least by 30% is implemented. In another example, a reduction level of 30 or 50% of the previous dose level is implemented. If required, one more dose reduction by 30% of dose level -1 (the level at first dose reduction) is implemented (dose level -2, the level at second dose reduction). In another example, one more dose reduction by 50% of dose level -1 is implemented (dose level -2). In some examples, one or more dose reductions by about 10% to about 80% of a previous dose level are implemented. In some examples, one or more dose reductions by about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, or about 70% to about 80% of previous levels are implemented. In some examples, one or more dose reductions by 10% to 20%, 20% to 30%, 30% to 40%, 40% to 50%, 50% to 60%, or 70% to 80% of previous levels are implemented. In some examples, one or more dose reductions by about 10%, by about 20%, by about 30%, by about 40%, by about 50%, by about 60%, by about 70%, or by about 80% of previous levels are implemented. In some examples, one or more dose reductions by 10%, by 20%, by 30%, by 40%, by 50%, by 60%, by 70%, or by 80% of previous levels are implemented. In some instances, administration of the paclitaxel is withheld when the subject has a level of aspartate transaminase (AST) greater than 10x upper limit of normal (ULN), a level of bilirubin greater than 5x ULN, or both.

In some instances, the method may further comprise reducing the dose of the anti-Gal-9 antibody, the dose of the gemcitabine, the dose of the paclitaxel, or a combination thereof, when moderate to severe hepatic impairment is observed. In other instances, the method may further comprise reducing the dose or terminating administration of the anti-Gal-9 antibody, the gemcitabine, the paclitaxel, or a combination thereof, when severe hematologic toxicity,

neurologic toxicity, cutaneous toxicity, and/or gastrointestinal toxicity is observed. In some examples, the dose of the paclitaxel is reduced to 100 mg/m^2 – 75 mg/m^2. In other examples, the dose of the gemcitabine is reduced to 800 mg/m^2 – 600 mg/m^2.

Also within the scope of the present disclosure are pharmaceutical compositions for use in treating a solid tumor (*e.g.*, those described herein and including metastatic solid tumors), and uses of any of the anti-Galectin-9 antibodies for manufacturing a medicament for treating the solid tumor, in combination with one or more chemotherapeutic agents as also disclosed herein.

The details of one or more examples of the disclosure are set forth in the description below. Other features or advantages of the present disclosure are to be apparent from the following drawing and detailed description of several examples, and also from the appended claims.

BRIEF DESCRIPTION OF DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to the drawing in combination with the detailed description of specific embodiments presented herein.

Figs. 1A-1D include graphs showing Kaplan-Meier survival curves and log rank tests for orthotopic mPA6115 pancreatic cancer xenograft mouse models grouped by treatment regimens. Group 1 = untreated; Group 2 = chemo vehicle control, saline; Group 3 = Isotype IgG1 mouse; Group 4 = Anti-Gal9 mAb; Group 5= Gemcitabine/Abraxane; and Group 6 = Anti-Gal9 mAb and Gemcitabine/Abraxane. **Fig. 1A** shows survival curves for all six groups. **Fig. 1B** shows survival curves for Groups 1, 5, and 6. **Fig. 1C** shows survival curves for Groups 1, 4, and 6. **Fig. 1D** shows survival curves for Groups 1, 4, 5, and 6.

Fig. 2 includes a graph showing hazard ratios (HR) and their 95% confidence interval (%95CI) of group 4-6 against group 1, group 2 and group 3 respectively calculated from cox-regression analysis where group 1 = untreated orthotopic mPA6115 mice; group 2 = chemo vehicle control, saline treated orthotopic mPA6115 mice; group 3 = Isotype IgG1 mouse treated orthotopic mPA6115 mice; group 4 = Anti-Gal9 mAb treated orthotopic mPA6115 mice; group 5= Gemcitabine/Abraxane treated orthotopic mPA6115 mice; and group 6 = Anti-Gal9 mAb and Gemcitabine/Abraxane treated orthotopic mPA6115 mice.

Fig. 3 includes a graph the mean body weight of each treatment group as measured twice a week for the study duration where group 1 = untreated orthotopic mPA6115 mice;

What Is Claimed Is:

1. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) and one or more chemotherapeutics in the manufacture of a medicament for combination therapy to treat a solid tumor in a human patient;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

2. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a first medicament and use of one or more chemotherapeutics in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a human patient;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid

sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

3. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a human patient, wherein said medicament is to be administered in combination with one or more chemotherapeutics;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-Galectin-9 antibody is at a dose of 10 mg/kg to 16 mg/kg once every week; or at a dose of 650 mg to 1120 mg once every week.

4. The use of any one of claims 1 to 3, wherein the anti-Gal-9 antibody is at a dose of 10 mg/kg or 16 mg/kg once every week, or at a dose of 650 mg to 700 mg once every week, or 1040 to 1120 mg once every week.

5. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) and one or more chemotherapeutics in the manufacture of a medicament for combination therapy to treat a solid tumor in a human patient;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6;

wherein the anti-Gal9 antibody is at a dose of t 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

6. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a first medicament and use of one or more chemotherapeutics in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a human patient;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6;

wherein the subject has one or more of the following features:

(i) has no infection by SARS-CoV-2; and

(ii) has no active brain or leptomeningeal metastasis; and

wherein the anti-Gal9 antibody is at a dose of 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

7. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a human patient, wherein said medicament is to be administered in combination with one or more chemotherapeutics;

wherein the anti-Gal-9 antibody comprises:

(a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6;

wherein the subject has one or more of the following features:

(i) has no infection by SARS-CoV-2; and

(ii) has no active brain or leptomeningeal metastasis; and

wherein the anti-Gal9 antibody is at a dose of 0.2 mg/kg to 32 mg/kg once every two weeks to once every 6 weeks; optionally once every two weeks.

8. The use of any one of claims 5-7, wherein the anti-Gal9 antibody is at a dose of about 0.2 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 2 mg/kg, about 4 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 8 mg/kg, about 10 mg/kg, about 12 mg/kg, or about 16 mg/kg once every two weeks to once every six weeks, optionally once every two weeks;

wherein the anti-Gal9 antibody is at a dose of 650 mg to 1120 mg once every two weeks to once every six weeks, optionally once every two weeks; or

wherein anti-Gal9 antibody is at a dose of 650 mg to 700 mg once every two weeks to once every six weeks, optionally once every two weeks, or at a dose of 1040 mg to 1120 mg once every two weeks to once every six weeks, optionally once every two weeks.

9. The use of any one of claims 1-3 or 5-7, wherein the solid tumor is a metastatic solid tumor.

10. The use of claim 9, wherein the solid tumor is pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CAA), renal cell carcinoma (RCC), urothelial cancer, head and neck cancer, breast cancer, lung cancer, or a gastrointestinal (GI) solid tumors.

11. The use of any one of claims 1-3 or 5-7, wherein the anti-Gal-9 antibody is formulated for intravenous infusion.

12. The use of any one of claims 1-3 or 5-7, wherein the V_L of the anti-Gal-9 antibody comprises the amino acid sequence of SEQ ID NO: 8 and/or

wherein the V_H of the anti-Gal-9 antibody comprises the amino acid sequence of SEQ ID NO: 7.

13. The use of any one of claims 1-3 or 5-7, wherein the anti-Gal-9 antibody is a full-length antibody, which is an IgG1 or IgG4 molecule.

14. The use of claim 13, wherein the anti-Gal-9 antibody is a human IgG4 molecule having a modified Fc region relative to the wildtype human IgG4 counterpart;

wherein the modified Fc region comprises the amino acid sequence of SEQ ID NO: 14.

15. The use of any one of claims 1-3 or 5-7, wherein the anti-Gal-9 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 15.

16. The use of any one of claims 1-3 or 5-7, wherein the one or more chemotherapeutics comprise an antimetabolite, a microtubule inhibitor, or a combination thereof.

17. The use of claim 16, wherein the chemotherapeutics comprise gemcitabine and paclitaxel.

18. The use of claim 17, wherein the paclitaxel is a protein-bound paclitaxel or a nanoparticle albumin-bound paclitaxel.

19. The use of claim 17, wherein the use comprises a cycle of 28 days, in which the anti-Gal-9 antibody is to be administered to the human patient on day 1 and day 15 and the gemcitabine and paclitaxel are to be administered to the human patient on day 1, day 8, and day 15; or

wherein the use comprises a cycle of 28 days, in which the anti-Gal9 antibody is to be administered to the human patient on day 1, day 8, day 15, and day 22 and the gemcitabine and paclitaxel are to be administered to the human patient on day 1, day 8, and day 15.

20. The use of claim 17, wherein the paclitaxel is to be administered to the human patient at 125 mg/m^2 intravenously; and/or

wherein the gemcitabine is to be administered to the human patient at 1000 mg/m^2.

21. The use of any one of claims 1-3 or 5-7, wherein the human patient has an elevated serum or plasma level of galectin-9 relative to a control value.

22. The use of any one of claims 1-3 or 5-7, wherein the human patient received at least one line of systemic anti-cancer therapy; or

wherein the human patient is free of prior therapy involving gemcitabine and/or paclitaxel or had a prior therapy involving gemcitabine and/or paclitaxel at least six months before administration of the anti-Gal9 antibody.

23. The use of any one of claims 1-3 or 5-7, wherein the human patient is examined for one or more of the following features before, during, and/or after the treatment:

(a) one or more tumor markers in tumor biopsy samples from the subject, optionally wherein the one or more tumor markers comprise CA15-3, CA-125, CEA, CA19-9, and/or alpha fetoprotein;

(b) cytokine profile; and

(c) galectin 9 levels.

24. The use of any one of claims 1-3 or 5-7, wherein the dose of the anti-Gal9 antibody, the dose of the one or more chemotherapeutics, or both are to be reduced, when an adverse effect is observed; and wherein the adverse effect comprises hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity, gastrointestinal toxicity, or a combination thereof.

25. The use of claim 17, wherein use of the paclitaxel is withheld when the human patient has a level of aspartate transaminase (AST) greater than 10x upper limit of normal (ULN), a level of bilirubin greater than 5x ULN, or both;

wherein the dose of the anti-Galectin-9 antibody, the dose of the gemcitabine, the dose of the paclitaxel, or a combination thereof, when moderate to severe hepatic impairment is observed; or

wherein the dose of the anti-Gal9 antibody, the gemcitabine, the paclitaxel, or a combination thereof, when severe hematologic toxicity, neurologic toxicity, cutaneous toxicity, and/or gastrointestinal toxicity is observed.

26. The use of claim 25, wherein the dose of the paclitaxel is reduced to 100 mg/m^2 – 75 mg/m^2; and/or

wherein the dose of the gemcitabine is reduced to 800 mg/m^2 – 600 mg/m^2.