

COMBINATION OF ANTI-GALECTIN-9 ANTIBODIES AND CHEMOTHERAPEUTICS FOR USE IN CANCER THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 63/182,519, filed April 30, 2021, U.S. Provisional Application No. 63/193,381, filed May 26, 2021, and U.S. Provisional Application No. 63/313,882, filed February 25, 2022, the contents of each of which are incorporated by reference herein in their entirety.

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SEQUENCE LISTING

 The instant application contains a Sequence Listing which has been filed electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 25, 2022, is named 112174-0212-NP010WO1_SEQ.txt and is
15 89,162 bytes in size.

BACKGROUND OF INVENTION

 Galectin-9 is a tandem-repeat lectin consisting of two carbohydrate recognition domains (CRDs) and was discovered and described for the first time in 1997 in patients suffering from
20 Hodgkin's lymphoma (HL) (Tureci et al., J. Biol. Chem. 1997, 272, 6416–6422). Three isoforms exist, and can be located within the cell or extracellularly. Elevated Galectin-9 levels have been observed in a wide range of cancers, including melanoma, Hodgkin's lymphoma, hepatocellular, pancreatic, gastric, colon and clear cell renal cell cancers (Wdowiak et al. Int. J. Mol. Sci. 2018, 19, 210). In renal cancer, patients with high Galectin-9 expression showed
25 more advanced progression of the disease with larger tumor size (Kawashima et al.; BJU Int. 2014;113:320–332). In melanoma, Galectin-9 was expressed in 57% of tumors and was significantly increased in the plasma of patients with advanced melanoma compared to healthy controls (Enninga et al., Melanoma Res. 2016 Oct; 26(5): 429–441). A number of studies have shown utility for Galectin-9 as a prognostic marker, and more recently as a potential new drug
30 target (Enninga et al., 2016; Kawashima et al. BJU Int 2014; 113: 320–332; Kageshita et al., Int J Cancer. 2002 Jun 20;99(6):809-16, and references therein).

 Galectin-9 has been described to play an important role in a number of cellular processes such as adhesion, cancer cell aggregation, apoptosis, and chemotaxis. Recent studies have shown a role for Galectin-9 in immune modulation in support of the tumor, e.g., through

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 CCL22 (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 OF INVENTION

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.

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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-Gal-9 antibody is administered to the subject once a week. In some embodiments, 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 embodiments, 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 embodiments, the anti-Gal-9 antibody is administered to the subject once every 2 or 3 weeks. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the antibody is administered once every 2 weeks. In some embodiments, 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 embodiments, the antibody is administered once every 2 weeks. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the duration of treatment is 0-3 months, 0-6 months, 3-6 months, 6-12 months, 12-24 months or longer. In some embodiments, the duration of treatment is 12-24 months or longer. In some embodiments, 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 embodiments, 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 embodiments, the anti-Gal-9 antibody is administered to the subject by intravenous infusion. In some embodiments, the cancer is PDAC. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the one or more chemotherapeutics comprise a combination of gemcitabine and paclitaxel.

In some embodiments, 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/m² intravenously. In some examples, the gemcitabine is administered to the subject at 1000 mg/m².

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/m² intravenously. Alternatively or in addition, the gemcitabine is administered to the subject at 1000 mg/m².

In some embodiments, 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 embodiments, 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
5 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 embodiments, 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
10 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.

15 In any of the methods disclosed herein, the subject may be a human patient. In some embodiments, 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.

20 In some embodiments, the subject may have received at least one line of systemic anti-cancer therapy. In other embodiments, 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
25 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
30 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
5 comprise hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity, gastrointestinal toxicity, or a combination thereof.

In some embodiments, 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,
10 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)
15 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 embodiments, one or more dose reductions by about 10% to about 80% of a previous dose level are implemented. In some embodiments, 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%
20 to about 60%, or about 70% to about 80% of previous levels are implemented. In some embodiments, 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 embodiments, 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.
25 In some embodiments, 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.

30 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 $100 \text{ mg/m}^2 - 75 \text{ mg/m}^2$. In other examples, the dose of the gemcitabine is reduced to $800 \text{ mg/m}^2 - 600 \text{ mg/m}^2$.

Also within the scope of the present disclosure are pharmaceutical compositions for use
 5 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 embodiments of the invention are set forth in the description
 10 below. Other features or advantages of the present invention are to be apparent from the following drawing and detailed description of several embodiments, and also from the appended claims.

BRIEF DESCRIPTION OF DRAWINGS

The following drawings form part of the present specification and are included to
 15 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
 20 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-
 25 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
 30 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;

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.

5 **Fig. 4** is a schematic depicting an exemplary study scheme. CRM: reassessment method; RP2D: recommended Phase 2 dose; PK: pharmacokinetics; PD: pharmacodynamics; PDAC: pancreatic ductal adenocarcinoma; CRC: colorectal cancer; CCA: cholangiocarcinoma; TBD: to be decided.

Fig. 5 includes a graph showing the effect of G2.9-17 on TGF-beta1 secretion
10 measurements in whole blood of an exemplary healthy human donor. TGF-beta1 release from donor cryopreserved macrophages incubated in the presence of M2 polarization cocktails. IgG4 isotype is a negative control antibody. Data represent mean + SEM of triplicate measures. Significance was determined by two-way ANOVA with Dunnett's multiple comparison test. * $p < 0.05$

15 **Fig. 6** includes a graph showing the effect of G2.9-17 on IL-10 secretion in whole blood of an exemplary healthy human donor. IL-10 release from donor cryopreserved macrophages incubated in the presence of M2 polarization cocktails (IL-4/IL-13 or Gal-9). IgG4 isotype is a negative control antibody. Data represent the mean ($\pm$ SEM) of triplicate. Significance was determined by two-way ANOVA with Tukey's multiple comparisons test, * $P < 0.05$.

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DETAILED DESCRIPTION OF INVENTION

 Provided herein are methods of co-using anti-Galectin-9 antibodies, *e.g.*, G9.2-17, and chemotherapeutics such as gemcitabine and paclitaxel (*e.g.*, protein-bound paclitaxel such as nanoparticle albumin-conjugated paclitaxel, for example, Abraxane[®]) for treating solid tumors,
25 for example, pancreatic ductal adenocarcinoma (PDAC). In some embodiments, the solid tumors are metastatic. In some embodiments, the methods disclosed herein provide specific doses and/or dosing schedules. In some instances, the methods disclosed herein target specific patient populations, for example, patients who have undergone prior treatment and show disease progression through the prior treatment, or patients who are resistant (*de novo* or
30 acquired) to the prior treatment.

 In some embodiments, the methods disclosed herein provide specific doses and/or dosing schedules of the anti-Gal-9 antibody disclosed herein (*e.g.*, G9.2-17(IgG4)) in combination with the chemotherapeutic agents also disclosed herein (*e.g.*, gemcitabine and paclitaxel), for example, 0.2 mg/kg to 16 mg/kg of the antibody once every week to once every

4 weeks (e.g., 0.2 mg/kg, 0.63 mg/kg, 2 mg/kg, 6.3 mg/kg, 10 mg/kg, or 16 mg/kg once every week or once every two weeks). In some examples, the dosing schedule for the anti-Gal9 antibody such as G9.2-17(IgG4) may be 10 mg/kg or 16 mg/kg once every week. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10
5 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 flat dose, for example, about 650 mg to about 1120 mg (e.g., about 650-700 mg or about 1040-1120 mg) once every week to once every 4 weeks, e.g., once every week or once every two weeks. It was discovered that G9.2-17 (IgG4) has an
10 unexpectedly quick clearance rate in human subjects as compared with conventional antibody therapeutics. Accordingly, a treatment regimen comprising a dosing schedule of once very week was developed to ensure a systemic exposure level of the anti-Gal-9 antibody that achieves therapeutic effect.

Galectin-9, a tandem-repeat lectin, is a beta-galactoside-binding protein, which has been
15 shown to have a role in modulating cell-cell and cell-matrix interactions. It is found to be strongly overexpressed in Hodgkin's disease tissue and in other pathologic states. It has in some instances also been found circulating in the tumor microenvironment (TME).

Galectin-9 interacts with Dectin-1, an innate immune receptor which is highly expressed on macrophages in PDAC, as well as on cancer cells (Daley, et al. *Nat Med.*
20 2017;23(5):556-6). Regardless of the source of Galectin-9, disruption of its interaction with Dectin-1 has been shown to lead to the reprogramming of CD4⁺ and CD8⁺ cells into indispensable mediators of anti-tumor immunity. Thus, Galectin-9 serves as a valuable therapeutic target for blocking the signaling mediated by Dectin-1. Accordingly, in some embodiments, the anti-Galectin-9 antibodies describe herein disrupt the interaction between
25 Galectin-9 and Dectin-1.

Galectin-9 also interacts with TIM-3, a type I cell surface glycoprotein expressed on the surface of leukemic stem cells in all varieties of acute myeloid leukemia (except for M3 (acute promyelocytic leukemia)), but not expressed in normal human hematopoietic stem cells (HSCs). TIM-3 signaling resulting from Galectin-9 ligation has been found to have a
30 pleiotropic effect on immune cells, inducing apoptosis in Th1 cells (Zhu et al., *Nat Immunol.*, 2005, 6:1245-1252) and stimulating the secretion of tumor necrosis factor- α (TNF- α), leading to the maturation of monocytes into dendritic cells, resulting in inflammation by innate immunity (Kuchroo et al., *Nat Rev Immunol.*, 2008, 8:577-580). Further Galectin-9/TIM-3 signaling has been found to co-activate NF- κ B and β -catenin signaling, two pathways that

promote LSC self-renewal (Kikushige et al., *Cell Stem Cell*, 2015, 17(3):341-352). An anti-Galectin-9 antibody that interferes with Galectin-9/TIM-3 binding could have a therapeutic effect, especially with respect to leukemia and other hematological malignancies. Accordingly, in some embodiments, the anti-Galectin-9 antibodies described herein disrupt the interaction

5 between Galectin-9 and TIM-3.

Further, Galectin-9 interacts with CD206, a mannose receptor highly expressed on M2 polarized macrophages, thereby promoting tumor survival (Enninga et al., *J Pathol.* 2018 Aug;245(4):468-477). Tumor-associated macrophages expressing CD206 are mediators of tumor immunosuppression, angiogenesis, metastasis, and relapse (see, e.g., Scodeller et al., *Sci*

10 *Rep.* 2017 Nov 7;7(1):14655, and references therein). Specifically, M1 (also termed classically activated macrophages) are triggered by Th1-related cytokines and bacterial products, express high levels of IL-12, and are tumoricidal. By contrast, M2 (so-called alternatively activated macrophages) are activated by Th2-related factors, express high level of anti-inflammatory cytokines, such as IL-10, and facilitate tumor progression (Biswas and Mantovani; *Nat*

15 *Immunol.* 2010 Oct; 11(10):889-96). The pro-tumoral effects of M2 include the promotion of angiogenesis, advancement of invasion and metastasis, and the protection of the tumor cells from chemotherapy-induced apoptosis (Hu et al., *Tumour Biol.* 2015 Dec; 36(12): 9119–9126, and references therein). Tumor-associated macrophages are thought be of M2-like phenotype and have a protumor role. Galectin-9 has been shown to mediate myeloid cell differentiation

20 toward an M2 phenotype (Enninga et al., *Melanoma Res.* 2016 Oct;26(5):429-41). It is possible that Galectin-9 binding CD206 may result in reprogramming TAMs towards the M2 phenotype, similar to what has been previously shown for Dectin. Without wishing to be bound by theory, blocking the interaction of Galectin-9 with CD206 may provide one mechanism by which an anti-Galectin-9 antibody, e.g., a G9.2-17 antibody, can be therapeutically beneficial.

25 Accordingly, in some embodiments, the anti-Galectin-9 antibodies described herein disrupt the interaction between Galectin-9 and CD206.

Galectin-9 has also been shown to interact with protein disulfide isomerase (PDI) and 4-1BB (Bi S, et al. *Proc Natl Acad Sci U S A.* 2011;108(26):10650-5; Madireddi et al. *J Exp Med.* 2014;211(7):1433-48).

30 Anti-Galectin-9 antibodies can serve as therapeutic agents for treating diseases associated with Galectin-9 (e.g., those in which a Galectin-9 signaling plays a role). Without being bound by theory, an anti-Galectin-9 antibody may block a signaling pathway mediated by Galectin-9. For example, the antibody may interfere with the interaction between Galectin-9 and its binding partner (e.g., Dectin-1, TIM-3 or CD206), thereby blocking the signaling

triggered by the Galectin-9/Ligand interaction. Alternatively, or in addition, an anti-Galectin-9 antibody may also exert its therapeutic effect by inducing blockade and/or cytotoxicity, for example, ADCC, CDC, or ADCP against pathologic cells that express Galectin-9. A pathologic cell refers to a cell that contributes to the initiation and/or development of a disease, either
5 directly or indirectly. See, e.g., WO2019/084553, WO2020/198390, WO2020/0223702, and WO2021022256, the relevant disclosures of each of which are incorporated by reference for the subject matter and purpose referenced herein.

The anti-Galectin-9 antibodies disclosed herein are capable of suppressing the signaling mediated by Galectin-9 (*e.g.*, the signaling pathway mediated by Galectin-9/Dectin-1 or
10 Galectin-9/Tim-3) or eliminating pathologic cells expressing Galectin-9 via, *e.g.*, ADCC. Accordingly, the anti-Galectin-9 antibodies described herein can be used for inhibiting any of the Galectin-9 signaling and/or eliminating Galectin-9 positive pathologic cells, thereby benefiting treatment of diseases associated with Galectin-9. See, *e.g.*, WO2019/084553, PCT/US2020/024767, and PCT/US2020/031181, the relevant disclosures of each of which are
15 incorporated by reference for the purpose and subject matter referenced herein.

As reported herein, combined therapy of a representative anti-Gal9 antibody (G9.2-17 such as G9.2-17 (IgG4)) and chemotherapeutics (gemcitabine and nab-paclitaxel) successfully prolonged survival in an animal model as disclosed herein. A synergistic effect of the representative anti-Gal9 antibody and gemcitabine and nab-paclitaxel on time of survival was
20 observed in the animal model. These results demonstrate that the anti-tumor methods disclosed herein, involving the combination of an anti-Galectin-9 antibody and chemotherapeutics such as those disclosed herein, would achieve superior therapeutic efficacy than the antibody or chemotherapy alone against the target solid tumors.

Accordingly, described herein are therapeutic uses of anti-Galectin-9 antibodies and
25 chemotherapeutics for treating certain solid tumors as disclosed herein.

Antibodies Binding to Galectin-9

The present disclosure provides anti-Gal-9 antibody G9.2-17 and functional variants thereof for use in the treatment methods disclosed herein.

30 An antibody (interchangeably used in plural form) is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term “antibody”, *e.g.*, anti-Galectin-9 antibody, encompasses not only intact (*e.g.*, full-length) polyclonal or monoclonal antibodies,

but also antigen-binding fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain (scFv), mutants thereof, fusion proteins comprising an antibody portion, humanized antibodies, chimeric antibodies, diabodies, nanobodies, linear antibodies, single chain antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. An antibody, *e.g.*, anti-Galectin-9 antibody, includes an antibody of any class, such as IgD, IgE, IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

A typical antibody molecule comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), which are usually involved in antigen binding. The V_H and V_L regions can be further subdivided into regions of hypervariability, also known as “complementarity determining regions” (“CDR”), interspersed with regions that are more conserved, which are known as “framework regions” (“FR”). Each V_H and V_L is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the Chothia definition, the AbM definition, the EU definition, the “Contact” numbering scheme, the IMGT numbering scheme, the “AHO” numbering scheme, and/or the contact definition, all of which are well known in the art. See, *e.g.*, Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, Chothia *et al.*, (1989) *Nature* 342:877; Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917, Al-lazikani *et al.* (1997) *J. Molec. Biol.* 273:927-948; Edelman *et al.*, *Proc Natl Acad Sci U S A.* 1969 May;63(1):78-85; and Almagro, *J. Mol. Recognit.* 17:132-143 (2004); MacCallum *et al.*, *J. Mol. Biol.* 262:732-745 (1996), Lefranc M P *et al.*, *Dev Comp Immunol*, 2003 January; 27(1):55-77; and Honegger A and Pluckthun A, *J Mol Biol*, 2001 Jun. 8; 309(3):657-70. See also hgmp.mrc.ac.uk and

bioinf.org.uk/abs).

In some embodiments, the anti-Galectin-9 antibody described herein is a full-length antibody, which contains two heavy chains and two light chains, each including a variable domain and a constant domain. Alternatively, the anti-Galectin-9 antibody can be an antigen-binding fragment of a full-length antibody. Examples of binding fragments encompassed within the term “antigen-binding fragment” of a full length antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a F(ab')₂ fragment, a bivalent fragment including two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR) that retains functionality. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain Fv (scFv). See *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883.

Any of the antibodies described herein, *e.g.*, anti-Galectin-9 antibody, can be either monoclonal or polyclonal. A “monoclonal antibody” refers to a homogenous antibody population and a “polyclonal antibody” refers to a heterogeneous antibody population. These two terms do not limit the source of an antibody or the manner in which it is made.

Reference antibody G9.2-17 refers to an antibody capable of binding to human Galectin-9 and comprises a heavy chain variable region of SEQ ID NO:7 and a light chain variable domain of SEQ ID NO:8, both of which are provided below. In some embodiments, the anti-Galectin-9 antibody for use in the methods disclosed herein is the G9.2-17 antibody. In some embodiments, the anti-Galectin-9 antibody for use in the methods disclosed herein is an antibody having the same heavy chain complementarity determining regions (CDRs) as reference antibody G9.2-17 and/or the same light chain complementarity determining regions as reference antibody G9.2-17. Two antibodies having the same V_H and/or V_L CDRs means that their CDRs are identical when determined by the same approach (*e.g.*, the Kabat approach, the Chothia approach, the AbM approach, the Contact approach, or the IMGT approach as known in the art. See, *e.g.*, bioinf.org.uk/abs/).

The heavy and light chain CDRs of reference antibody G9.2-17 is provided in **Table 1** below (determined using the Kabat methodology):

Table 1. Heavy and Light Chain CDRs of G9.2-17

G9.2-17	V _L CDR1	RASQSVSSAVA	SEQ ID NO:1
	V _L CDR2	SASSLYS	SEQ ID NO:2
	V _L CDR3	QQSSTDPIIT	SEQ ID NO:3
	V _H CDR1	FTVSSSSIH	SEQ ID NO:4
	V _H CDR2	YISSSSGYTTYADSVKG	SEQ ID NO:5
	V _H CDR3	YWSYPSWWPYRGMDY	SEQ ID NO:6

In some examples, the anti-Galectin-9 antibody for use in the methods disclosed herein may comprise (following the Kabat scheme) 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 and/or may comprise 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. The anti- Galectin-9 antibody, including the reference antibody G9.2-17, can be in any format as disclosed herein, for example, a full-length antibody or a Fab. The term “G9.2-17(Ig4)” used herein refers to a G9.2-17 antibody which is an IgG4 molecule. Likewise, the term “G9.2-17 (Fab)” refers to a G9.2-17 antibody, which is a Fab molecule.

In some embodiments, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NOs: 1, 2, and 3, respectively. In some embodiments, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 4, 5, and 6, respectively.

Additional Galectin-9 antibodies, *e.g.*, which bind to the CRD1 and/or CRD2 region of Galectin-9 are described in co-owned, co-pending US Patent Application 16/173,970 and in

co-owned, co-pending International Patent Applications PCT/US18/58028 and PCT/US2020/024767, the contents of each of which are herein incorporated by reference in their entireties.

In some embodiments, the anti-Galectin-9 antibody disclosed herein comprises light chain CDRs that have at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs of reference antibody G9.2-17. Alternatively or in addition, in some embodiments, the anti-Galectin-9 antibody comprises heavy chain CDRs that have at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_H CDRs of reference antibody G9.2-17.

The “percent identity” of two amino acid sequences is determined using the algorithm of Karlin and Altschul Proc. Natl. Acad. Sci. USA 87:2264-68, 1990, modified as in Karlin and Altschul Proc. Natl. Acad. Sci. USA 90:5873-77, 1993. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. J. Mol. Biol. 215:403-10, 1990. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the protein molecules of the invention. Where gaps exist between two sequences, Gapped BLAST can be utilized as described in Altschul et al., Nucleic Acids Res. 25(17):3389-3402, 1997. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used.

In other embodiments, the anti-Galectin-9 antibody described herein comprises a V_H that comprises the HC CDR1, HC CDR2, and HC CDR3, which collectively contain up to 8 amino acid residue variations (8, 7, 6, 5, 4, 3, 2, or 1 variations(s), including additions, deletions, and/or substitutions) relative to the HC CDR1, HC CDR2, and HC CDR3 of reference antibody G9.2-17. Alternatively or in addition, in some embodiments, the anti-Galectin-9 antibody described herein comprises a V_H that comprises the LC CDR1, LC CDR2, and LC CDR3, which collectively contain up to 8 amino acid residue variations (8, 7, 6, 5, 4, 3, 2, or 1 variations(s) including additions, deletions, and/or substitutions) relative to the LC CDR1, LC CDR2, and LC CDR3 of reference antibody G9.2-17.

In one example, the amino acid residue variations are conservative amino acid residue substitutions. As used herein, a “conservative amino acid substitution” refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering

polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, *e.g.*, Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made among amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

In some embodiments, the anti-Galectin-9 antibodies disclosed herein, having the heavy chain CDRs disclosed herein, contains framework regions derived from a subclass of germline V_H fragment. Such germline V_H regions are well known in the art. See, *e.g.*, the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php. Examples include the IGHV1 subfamily (*e.g.*, IGHV1-2, IGHV1-3, IGHV1-8, IGHV1-18, IGHV1-24, IGHV1-45, IGHV1-46, IGHV1-58, and IGHV1-69), the IGHV2 subfamily (*e.g.*, IGHV2-5, IGHV2-26, and IGHV2-70), the IGHV3 subfamily (*e.g.*, IGHV3-7, IGHV3-9, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-33, IGHV3-43, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-66, IGHV3-72, and IGHV3-73, IGHV3-74), the IGHV4 subfamily (*e.g.*, IGHV4-4, IGHV4-28, IGHV4-31, IGHV4-34, IGHV4-39, IGHV4-59, IGHV4-61, and IGHV4-B), the IGHV subfamily (*e.g.*, IGHV5-51, or IGHV6-1), and the IGHV7 subfamily (*e.g.*, IGHV7-4-1).

Alternatively or in addition, in some embodiments, the anti-Galectin-9 antibody, having the light chain CDRs disclosed herein, contains framework regions derived from a germline V_K fragment. Examples include an IGKV1 framework (*e.g.*, IGKV1-05, IGKV1-12, IGKV1-27, IGKV1-33, or IGKV1-39), an IGKV2 framework (*e.g.*, IGKV2-28), an IGKV3 framework (*e.g.*, IGKV3-11, IGKV3-15, or IGKV3-20), and an IGKV4 framework (*e.g.*, IGKV4-1). In other instances, the anti-Galectin-9 antibody comprises a light chain variable region that contains a framework derived from a germline V_λ fragment. Examples include an IGλ1 framework (*e.g.*, IGλV1-36, IGλV1-40, IGλV1-44, IGλV1-47, IGλV1-51), an IGλ2 framework (*e.g.*, IGλV2-8, IGλV2-11, IGλV2-14, IGλV2-18, IGλV2-23), an IGλ3 framework (*e.g.*, IGλV3-1, IGλV3-9, IGλV3-10, IGλV3-12, IGλV3-16, IGλV3-19, IGλV3-21, IGλV3-25, IGλV3-27), an IGλ4 framework (*e.g.*, IGλV4-3, IGλV4-60, IGλV4-69), an IGλ5 framework (*e.g.*, IGλV5-39, IGλV5-45), an IGλ6 framework (*e.g.*, IGλV6-57), an IGλ7 framework (*e.g.*, IGλV7-43, IGλV7-46), an IGλ8 framework (*e.g.*, IGλV8-61), an IGλ9 framework (*e.g.*, IGλV9-49), or an IGλ10 framework (*e.g.*, IGλV10-54).

In some embodiments, the anti-Galectin-9 antibody for use in the method disclosed herein can be an antibody having the same heavy chain variable region (V_H) and/or the same light chain variable region (V_L) as reference antibody 69.2-17, the V_H and V_L region amino acid sequences are provided below:

5

V_H:

EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVAY**ISSSSGYTTYADSVKGR**FT
ISADTSKNTAYLQMNSLRAEDTAVYYCARY**WSYPSWWPYRGMDY**WGQGTTLVTVSS (SEQ ID NO:
7)

10 **V_L:**

DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGT
DFTLTISLQPEDFATYYC**QSSSTDPIT**FGQGTKVEIKR (SEQ ID NO: 8)

15 In some embodiments, the anti-Galectin-9 antibody has at least 80% sequence identity (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to the heavy chain variable region of SEQ ID NO: 7. Alternatively or in addition, the anti-Galectin-9 antibody has at least 80% sequence identity (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to the light chain variable region of SEQ ID NO: 8.

20 In some instances, the anti-Galectin-9 antibody disclosed herein is a functional variant of reference antibody G9.2-17. A functional variant can be structurally similar as the reference antibody (e.g., comprising the limited number of amino acid residue variations in one or more of the heavy chain and/or light chain CDRs as G9.2-17 as disclosed herein, or the sequence identity relative to the heavy chain and/or light chain CDRs of G9.2-17, or the V_H and/or V_L of G9.2-17 as disclosed herein) with substantially similar binding affinity (e.g., having a K_D value in the same order) to human Galectin-9.

25 In some embodiments, the anti-Galectin-9 antibody as described herein can bind and inhibit the activity of Galectin-9 by at least 20% (e.g., 31%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). The apparent inhibition constant (K_i^{app} or K_{i,app}), which provides a measure of inhibitor potency, is related to the concentration of inhibitor required to reduce enzyme activity and is not dependent on enzyme concentrations.

30 The inhibitory activity of an anti-Galectin-9 antibody described herein can be determined by routine methods known in the art.

The K_i^{app} value of an antibody may be determined by measuring the inhibitory effect of different concentrations of the antibody on the extent of the reaction (e.g., enzyme activity);

fitting the change in pseudo-first order rate constant (v) as a function of inhibitor concentration to the modified Morrison equation (Equation 1) yields an estimate of the apparent K_i value. For a competitive inhibitor, the K_i^{app} can be obtained from the y-intercept extracted from a linear regression analysis of a plot of K_i^{app} versus substrate concentration.

5

$$v = A \cdot \frac{([E] - [I] - K_i^{app}) + \sqrt{([E] - [I] - K_i^{app})^2 + 4[E] \cdot K_i^{app}}}{2} \quad (\text{Equation 1})$$

Where A is equivalent to v_o/E , the initial velocity (v_o) of the enzymatic reaction in the absence of inhibitor (I) divided by the total enzyme concentration (E). In some embodiments, the anti-Galectin-9 antibody described herein has a K_i^{app} value of 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50, 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5 pM or less for the target antigen or antigen epitope. In some embodiments, the anti-Galectin-9 antibody has a lower K_i^{app} for a first target (*e.g.*, the CRD2 of Galectin-9) relative to a second target (*e.g.*, CRD1 of the Galectin-9). Differences in K_i^{app} (*e.g.*, for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold. In some examples, the anti-Galectin-9 antibody inhibits a first antigen (*e.g.*, a first protein in a first conformation or mimic thereof) greater relative to a second antigen (*e.g.*, the same first protein in a second conformation or mimic thereof; or a second protein). In some embodiments, any of the anti-Galectin-9 antibodies is further affinity matured to reduce the K_i^{app} of the antibody to the target antigen or antigenic epitope thereof.

In some embodiments, the anti-Galectin-9 antibody suppresses Dectin-1 signaling, *e.g.*, in tumor infiltrating immune cells, such as macrophages. In some embodiments, the anti-Galectin-9 antibody suppresses Dectin-1 signaling triggered by Galectin-9 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods, such as routine assays. Alternatively or in addition, the anti-Galectin-9 antibody suppresses the T cell immunoglobulin mucin-3 (TIM-3) signaling initiated by Galectin-9. In some embodiments, the anti-Galectin-9 antibody suppresses the T cell immunoglobulin mucin-3 (TIM-3) signaling, *e.g.*, in tumor infiltrating immune cells, *e.g.*, in some embodiments by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods, such as routine assays.

In some embodiments, the anti-Galectin-9 antibody suppresses the CD206 signaling,

e.g., in tumor infiltrating immune cells. In some embodiments, the anti-Galectin-9 antibody suppresses the CD206 signaling triggered by Galectin-9 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods, such as routine assays. In some

5 embodiments, the anti-Galectin-9 antibody blocks or prevents binding of Galectin-9 to CD206 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods, such as routine assays.

 In some embodiments, the anti-Galectin-9 antibody induces cell cytotoxicity, such as

10 ADCC, in target cells expressing Galectin-9, *e.g.*, wherein the target cells are cancer cells or immune suppressive immune cells. In some embodiments, the anti-Galectin-9 antibody induces apoptosis in immune cells, such as T cells, or cancer cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods, such as routine assays. In some

15 embodiments, any of the anti-Galectin-9 antibodies described herein induce cell cytotoxicity such as complement-dependent cytotoxicity (CDC) against target cells expressing Galectin-9.

 Antibody-dependent cell-mediated phagocytosis (ADCP) is an important mechanism of action for antibodies that mediate part or all of their action through phagocytosis. In that case, antibodies mediate uptake of specific antigens by antigen presenting cells. ADCP can be

20 mediated by monocytes, macrophages, neutrophils, and dendritic cells, through FcγRIIa, FcγRI, and FcγRIIIa, of which FcγRIIa (CD32a) on macrophages represent the predominant pathway.

 In some embodiments, the anti-Galectin-9 antibody induces cell phagocytosis of target cells, *e.g.*, cancer cells or immune suppressive immune cells expressing Galectin-9 (ADCP). In

25 some embodiments, the anti-Galectin-9 antibody increases phagocytosis of target cells, *e.g.*, cancer cells or immune suppressive immune cells, by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

 In some embodiments, the anti-Galectin-9 antibody described herein induces cell cytotoxicity such as complement-dependent cytotoxicity (CDC) against target cells, *e.g.*,

30 cancer cells or immune suppressive immune cells. In some embodiments, the anti-Galectin-9 antibody increases CDC against target cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

 In some embodiments, the anti-Galectin-9 antibody induces T cell activation, *e.g.*, in tumor infiltrating T cells, *i.e.*, suppress Galectin-9 mediated inhibition of T cell activation,

either directly or indirectly. In some embodiments, the anti-Galectin-9 antibody promotes T cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). T cell activation can be determined by conventional methods, such as assays (*e.g.*, measurement of CD44, TNF alpha, IFNgamma, and/or PD-1). In

5 some embodiments, the anti-Galectin-9 antibody promotes CD4+ cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces CD44 expression in CD4+ cells. In some embodiments, the anti-Galectin-9 antibody increases CD44 expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%,

10 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces IFNgamma expression in CD4+ cells. In some embodiments, the anti-Galectin-9 antibody increases IFNgamma expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces TNFalpha expression in CD4+ cells.

15 In some embodiments, the anti-Galectin-9 antibody increases TNFalpha expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

In some embodiments, the anti-Galectin-9 antibody promotes CD8+ cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater), including

20 any increment therein). In a non-limiting example, the anti-Galectin antibody induces CD44 expression in CD8+ cells. In some embodiments, the anti-Galectin-9 antibody increases CD44 expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces IFNgamma expression in CD8+ cells. In some embodiments, the anti-

25 Galectin-9 antibody increases IFNgamma expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces TNFalpha expression in CD8+ cells. In some embodiments, the anti-Galectin-9 antibody increases TNFalpha expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater,

30 including any increment therein).

In some embodiments, an anti-Galectin-9 antibody as described herein has a suitable binding affinity for the target antigen (*e.g.*, Galectin-9) or antigenic epitopes thereof. As used herein, "binding affinity" refers to the apparent association constant or K_A . The K_A is the reciprocal of the dissociation constant (K_D). The anti-Galectin-9 antibody described herein may

have a binding affinity (K_D) of at least 10^{-5} , 10^{-6} , 10^{-7} , 10^{-8} , 10^{-9} , 10^{-10} M, or lower for the target antigen or antigenic epitope. An increased binding affinity corresponds to a decreased K_D .

Binding affinity (or binding specificity) can be determined by a variety of methods including equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon resonance, or spectroscopy (*e.g.*, using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH7.4, 150 mM NaCl, 0.005% (v/v) Surfactant P20).

These techniques can be used to measure the concentration of bound binding protein as a function of target protein concentration. Under certain conditions, the fractional concentration of bound binding protein ($[Bound]/[Total]$) is generally related to the concentration of total target protein ($[Target]$) by the following equation:

$$[Bound]/[Total] = [Target]/(K_d + [Target])$$

It is not always necessary to make an exact determination of K_A , though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, *e.g.*, determined using a method such as ELISA or FACS analysis, is proportional to K_A , and thus can be used for comparisons, such as determining whether a higher affinity is, *e.g.*, 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, *e.g.*, by activity in a functional assay, *e.g.*, an *in vitro* or *in vivo* assay. In some cases, the *in vitro* binding assay is indicative of *in vivo* activity. In other cases, the *in vitro* binding assay is not necessarily indicative of *in vivo* activity. In some cases, tight binding is beneficial, but in other cases tight binding is not as desirable *in vivo*, and an antibody with lower binding affinity is more desirable.

In some embodiments, the heavy chain of any of any of the anti-Galectin-9 antibodies as described herein further comprise a heavy chain constant region (CH) or a portion thereof (*e.g.*, CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can be of any suitable origin, *e.g.*, human, mouse, rat, or rabbit. In one specific example, the heavy chain constant region is from a human IgG (a gamma heavy chain) of any IgG subfamily as described herein.

In some embodiments, the heavy chain constant region of the antibodies described herein comprise a single domain (*e.g.*, CH1, CH2, or CH3) or a combination of any of the single domains, of a constant region (*e.g.*, SEQ ID NOs: 10, 12-14, and 21). In some embodiments, the light chain constant region of the antibodies described herein comprise a

single domain (*e.g.*, CL), of a constant region. Exemplary light and heavy chain sequences are listed below. Exemplary light and heavy chain sequences are listed below. The hIgG1 LALA sequence includes two mutations, L234A and L235A (EU numbering), which suppress FcγR binding as well as a P329G mutation (EU numbering) to abolish complement C1q binding, thus abolishing all immune effector functions. The hIgG4 Fab Arm Exchange Mutant sequence includes a mutation to suppress Fab Arm Exchange (S228P; EU numbering). An IL2 signal sequence (MYRMQLLSIALSLALVTNS; SEQ ID NO: 9) can be located N-terminally of the variable region. It is used in expression vectors, which is cleaved during secretion and thus not in the mature antibody molecule. The mature protein (after secretion) starts with "EVQ" for the heavy chain and "DIM" for the light chain. Amino acid sequences of exemplary heavy chain constant regions are provided below:

hIgG1 Heavy Chain Constant Region (SEQ ID NO: 10)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK*

hIgG1 LALA Heavy Chain Constant Region (SEQ ID NO: 12)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAAGGPSVFLFPPKPKDTLMI
SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
KVSNAKALGAPAEIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK*

hIgG4 Heavy Chain Constant Region (SEQ ID NO: 13)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGKTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPAEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
NKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVSCSVMHEALHNHYTQKSLSLSPGK*

hIgG4 Heavy Chain Constant Region (SEQ ID NO: 20)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGKTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPAEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
NKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVSCSVMHEALHNHYTQKSLSLSPGK*

hIgG4 mut Heavy Chain Constant Region (SEQ ID NO: 14)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGKTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPAEFLGGPSVFLFPPKPKDTLMISRT

PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSPGK*

5 **hIgG4 mut Heavy Chain Constant Region (SEQ ID NO: 21)**

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPKSNTKVDKRVESKYGPPCP**P**CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSPGK*

In some instances, the heavy chain constant region in an anti-Galectin-9 antibody disclosed herein (*e.g.*, G9.2-17) may have the C-terminal Lysine (K) residue removed for, *e.g.*, manufacturing purposes. The corresponding amino acid sequences of those having no terminal

15 K residue are provided below:

hIgG1 Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 24)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPKSNTKVDKRVESKYGPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHREALHNHYTQKSLSLSPG*

25 **hIgG1 LALA Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 25)**

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPKSNTKVDKRVESKYGPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**G**APIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHREALHNHYTQKSLSLSPG*

hIgG4 Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 26)

35 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPKSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSPG*

hIgG4 Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 27)

45 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPKSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPFVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSPG*

hIgG4 mut Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 28)

50

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
 TVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE
 VTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG
 LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 5 VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSPG*

hIgG4 mut Heavy Chain Constant Region with No C-Terminal Lysine (SEQ ID NO: 29)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
 10 TVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE
 VTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG
 LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLG*

15 In some embodiments, anti-Galectin-9 antibodies having any of the above heavy
 chain constant regions are paired with a light chain having the following light chain constant
 region:

Light Chain Constant Region (SEQ ID NO: 11)

20 TVAAPSVEIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
 STLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Exemplary full length anti-Galectin-9 antibodies are provided below:

25 G9.2-17 hIgG1 Heavy Chain (SEQ ID NO: 16)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
 TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLA
 PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
 YICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
 30 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
 KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
 GSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK*

G9.2-17 hIgG1 Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 30)

35 EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
 ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLAPS
 SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC
 NVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
 40 AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
 SKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPG*

G9.2-17 hIgG1 LALA Heavy Chain (SEQ ID NO: 17)

45 EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
 TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLA
 PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
 YICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPEEAGGPSVFLFPPKPKDTLMISRTPEVTCVVD

VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK*

5 **G9.2-17 hIgG1 LALA Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 31)**

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLVTVSSASTKGPSVFPLAPS
SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
10 NVNHKPSNTKVDKKEVEPKSCDKHTHTCPPCPAPEAAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLY
SKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK*

15 **G9.2-17 hIgG4 Heavy Chain (SEQ ID NO: 18)**

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLVTVSSASTKGPSVFPLA
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT
YTCNVDHKPSNTKVDKRVEVKYGPCCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQ
20 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

25 **G9.2-17 hIgG4 Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 32)**

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLVTVSSASTKGPSVFPLAPC
SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTC
NVDHKPSNTKVDKRVEVKYGPCCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPE
30 VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

35 **G9.2-17 hIgG4 Heavy Chain (SEQ ID NO: 22)**

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLVTVSSASTKGPSVFPLA
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT
YTCNVDHKPSNTKVDKRVEVKYGPCCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQ
40 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

45 **G9.2-17 hIgG4 Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 33)**

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLVTVSSASTKGPSVFPLAPC
SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTC
NVDHKPSNTKVDKRVEVKYGPCCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPE
50 VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

G9.2-17 hIgG4 Fab Arm Exchange mut Heavy Chain (SEQ ID NO: 19)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
 TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLA
 PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKT
 5 YTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ
 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
 SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF
 FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

10 G9.2-17 hIgG4 Fab Arm Exchange mut Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 34)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
 ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLAPC
 15 SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKT
 YTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ
 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
 SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF
 FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPG*

20

G9.2-17 hIgG4 Fab Arm Exchange mut Heavy Chain (SEQ ID NO: 23)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRF
 TISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLA
 PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKT
 25 YTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ
 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
 SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF
 FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

30 G9.2-17 hIgG4 Fab Arm Exchange mut Heavy Chain with No C-terminal Lysine Residue (SEQ ID NO: 35)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTTYADSVKGRFT
 ISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLLTVTVSSASTKGPSVFPLAPC
 35 SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKT
 YTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ
 EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
 SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF
 FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG*

40

Any of the above heavy chain can be paired with a Light Chain of (SEQ ID NO: 15)

shown below:

DIQMTQSPSSLSASVGRVTITCRASQSVSSAVAWYQQKPKAPKLLIYSASSLYSGVPSRFSGRSG
 TDFTLTISSLQPEDFATYYCQQSSTDPITFGQGTKVEIKRTVAAPSVEIFPPSDEQLKSGTASVVCLL
 45 NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLSP
 VTKSFNRGEC*

In some embodiments, the anti-Galectin-9 antibody comprises a heavy chain IgG1
 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,

50 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 10. In one

embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region comprising SEQ ID NO: 13. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 10.

- 5 In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 13. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 13. In one embodiment, the anti-Galectin-9 antibody comprises a
10 heavy chain IgG4 constant region consisting of SEQ ID NO: 13.

- In some embodiments, the constant region is from human IgG4. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 20. In one embodiment, the anti-Galectin-
15 9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 20. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 20.

- In any of these embodiments, the anti-Galectin-9 antibody comprises a light chain constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
20 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 11. In some embodiments, the anti-Galectin-9 antibody comprises a light chain constant region comprising SEQ ID NO: 11. In some embodiments, the anti-Galectin-9 antibody comprises a light chain constant region consisting of SEQ ID NO: 11.

- In some embodiments, the IgG is a mutant with minimal Fc receptor engagement. In one example, the constant region is from a human IgG1 LALA. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 12. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region comprising SEQ ID NO: 12. In one
25 embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region consisting of SEQ ID NO: 12.
30

 In some embodiments, the anti-Galectin-9 antibody comprises a modified constant region. In some embodiments, the anti-Galectin-9 antibody comprise a modified constant region that is immunologically inert, *e.g.*, does not trigger complement mediated lysis, or does

not stimulate antibody-dependent cell mediated cytotoxicity (ADCC). ADCC activity can be assessed using methods disclosed in U.S. Pat. No. 5,500,362. In other embodiments, the constant region is modified as described in *Eur. J. Immunol.* (1999) 29:2613-2624; PCT Application No. PCT/GB99/01441; and/or UK Patent Application No. 9809951.8. In some
 5 embodiments, the IgG4 constant region is a mutant with reduced heavy chain exchange. In some embodiments, the constant region is from a human IgG4 Fab Arm Exchange mutant S228P.

 In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%,
 10 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 14. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 14. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 14.

15 In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 21. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 21. In one embodiment, the anti-Galectin-9 antibody comprises a
 20 heavy chain IgG4 constant region consisting of SEQ ID NO: 21.

 In some embodiments, the anti-Galectin -9 antibody has chains corresponding to SEQ ID NO: 15 for the light chains; and the amino acid sequences of exemplary heavy chains correspond to SEQ ID NOs: 10 (hIgG1); 12 (hIgG1 LALA); 13 (hIgG4); 20 (hIgG4); 14 (hIgG4 mut); and 21 (hIgG4 mut).

25 In some embodiments, the anti-Galectin-9 antibody has a light chain comprising, consisting essentially of, or consisting of SEQ ID NO: 15. In some embodiments, the anti-Galectin-9 antibody has a heavy chain comprising, consisting essentially of, or consisting of any one of the sequences selected from the group consisting of SEQ ID NO: 16-19, 22 and 23. In some embodiments, the anti-Galectin-9 antibody has a light chain comprising, consisting
 30 essentially of, or consisting of SEQ ID NO: 15 and a heavy chain comprising, consisting essentially of, or consisting of any one of the sequences selected from the group consisting of SEQ ID NO: 16-19. In some embodiments, the anti-Galectin-9 antibody has a light chain comprising SEQ ID NO: 15 and a heavy chain comprising any one of the sequences selected from the group consisting of SEQ ID NO: 16-19, 22 and 23. In some embodiments, the anti-

Galectin-9 antibody has a light chain consisting essentially of SEQ ID NO: 15 and a heavy chain consisting essentially of any one of the sequences selected from the group consisting of SEQ ID NO: 16-19, 22 and 23. In some embodiments, the anti-Galectin-9 antibody has a light chain consisting of SEQ ID NO: 15 and a heavy chain consisting of any one of the sequences
5 selected from the group consisting of SEQ ID NO: 16-19, 22 and 23. In one specific embodiment, the anti-Galectin-9 antibody has a light chain consisting essentially of SEQ ID NO: 15 and a heavy chain consisting essentially of SEQ ID NO: 19. In another specific embodiment, the anti-Galectin-9 antibody has a light chain consisting essentially of SEQ ID NO: 15 and a heavy chain consisting essentially of SEQ ID NO: 20.

10 In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 16. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 16. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ
15 ID NO: 16.

In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 17. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 17. In one
20 embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ ID NO: 17.

In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 18. In one embodiment, the
25 anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 18. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ ID NO: 18.

In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or
30 99% and any increment therein) sequence identity to SEQ ID NO: 22. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 22. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ ID NO: 22.

In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence

having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 19. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 19. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ ID NO: 19.

In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 23. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence comprising SEQ ID NO: 23. In one embodiment, the anti-Galectin-9 antibody comprises a heavy chain sequence consisting of SEQ ID NO: 23.

In any of these embodiments, the anti-Galectin-9 antibody comprises a light chain sequence having at least 80% (e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% and any increment therein) sequence identity to SEQ ID NO: 15. In some embodiments, the anti-Galectin-9 antibody comprises a light chain sequence comprising SEQ ID NO: 15. In some embodiments, the anti-Galectin-9 antibody comprises a light chain sequence consisting of SEQ ID NO: 15.

In specific examples, the anti-Galectin-9 antibody used in the treatment methods disclosed herein has a heavy chain of SEQ ID NO:19 and a light chain of SEQ ID NO:15. In some embodiments, the anti-Galectin-9 antibody used in the treatment methods disclosed herein is G9.2-17 IgG4. In some examples, such an anti-Galectin-9 antibody does not have the C-terminal lysine residue in its heavy chain.

Preparation of Anti-Galectin-9 Antibodies

Antibodies capable of binding Galectin-9 as described herein can be made by any method known in the art, including but not limited to, recombinant technology. One example is provided below.

Nucleic acids encoding the heavy and light chain of an anti-Galectin-9 antibody as described herein can be cloned into one expression vector, each nucleotide sequence being in operable linkage to a suitable promoter. In one example, each of the nucleotide sequences encoding the heavy chain and light chain is in operable linkage to a distinct promoter. Alternatively, the nucleotide sequences encoding the heavy chain and the light chain can be in operable linkage with a single promoter, such that both heavy and light chains are expressed from the same promoter. When necessary, an internal ribosomal entry site (IRES) can be

inserted between the heavy chain and light chain encoding sequences.

In some examples, the nucleotide sequences encoding the two chains of the antibody are cloned into two vectors, which can be introduced into the same or different cells. When the two chains are expressed in different cells, each of them can be isolated from the host cells
5 expressing such and the isolated heavy chains and light chains can be mixed and incubated under suitable conditions allowing for the formation of the antibody.

Generally, a nucleic acid sequence encoding one or all chains of an antibody can be cloned into a suitable expression vector in operable linkage with a suitable promoter using methods known in the art. For example, the nucleotide sequence and vector can be contacted,
10 under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of a gene. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector. The selection of expression vectors/promoter would depend on the type of host cells for use in
15 producing the antibodies.

A variety of promoters can be used for expression of the antibodies described herein, including, but not limited to, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the *Rous sarcoma* virus LTR, HIV-LTR, HTLV-1 LTR, the simian virus 40 (SV40) early promoter, *E. coli* lac UV5 promoter, and the herpes simplex tk virus promoter.

20 Regulatable promoters can also be used. Such regulatable promoters include those using the lac repressor from *E. coli* as a transcription modulator to regulate transcription from lac operator-bearing mammalian cell promoters [Brown, M. et al., *Cell*, 49:603-612 (1987)], those using the tetracycline repressor (tetR) [Gossen, M., and Bujard, H., *Proc. Natl. Acad. Sci. USA* 89:5547-5551 (1992); Yao, F. et al., *Human Gene Therapy*, 9:1939-1950 (1998); Shockelt, P.,
25 et al., *Proc. Natl. Acad. Sci. USA*, 92:6522-6526 (1995)]. Other systems include FK506 dimer, VP16 or p65 using estradiol, RU486, diphenol murislerone, or rapamycin. Inducible systems are available from Invitrogen, Clontech and Ariad.

Regulatable promoters that include a repressor with the operon can be used. In one embodiment, the lac repressor from *E. coli* can function as a transcriptional modulator to
30 regulate transcription from lac operator-bearing mammalian cell promoters (M. Brown et al., *Cell*, 49:603-612 (1987); Gossen and Bujard (1992); M. Gossen et al., *Natl. Acad. Sci. USA*, 89:5547-5551 (1992)) combined the tetracycline repressor (tetR) with the transcription activator (VP 16) to create a tetR-mammalian cell transcription activator fusion protein, tTa (tetR-VP 16), with the tetO-bearing minimal promoter derived from the human

cytomegalovirus (hCMV) major immediate-early promoter to create a tetR-tet operator system to control gene expression in mammalian cells. In one embodiment, a tetracycline inducible switch is used. The tetracycline repressor (tetR) alone, rather than the tetR-mammalian cell transcription factor fusion derivatives can function as potent trans-modulator to regulate gene expression in mammalian cells when the tetracycline operator is properly positioned downstream for the TATA element of the CMVIE promoter (Yao et al., *Human Gene Therapy*, 10(16):1392-1399 (2003)). One particular advantage of this tetracycline inducible switch is that it does not require the use of a tetracycline repressor-mammalian cells transactivator or repressor fusion protein, which in some instances can be toxic to cells (Gossen et al., *Natl. Acad. Sci. USA*, 89:5547-5551 (1992); Shockett et al., *Proc. Natl. Acad. Sci. USA*, 92:6522-6526 (1995)), to achieve its regulatable effects.

Additionally, the vector can contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; internal ribosome binding sites (IRESes), versatile multiple cloning sites; and T7 and SP6 RNA promoters for *in vitro* transcription of sense and antisense RNA. Suitable vectors and methods for producing vectors containing transgenes are well known and available in the art.

Examples of polyadenylation signals useful to practice the methods described herein include, but are not limited to, human collagen I polyadenylation signal, human collagen II polyadenylation signal, and SV40 polyadenylation signal.

One or more vectors (*e.g.*, expression vectors) comprising nucleic acids encoding any of the antibodies may be introduced into suitable host cells for producing the antibodies. The host cells can be cultured under suitable conditions for expression of the antibody or any polypeptide chain thereof. Such antibodies or polypeptide chains thereof can be recovered by the cultured cells (*e.g.*, from the cells or the culture supernatant) via a conventional method, *e.g.*, affinity purification. If necessary, polypeptide chains of the antibody can be incubated under suitable conditions for a suitable period of time allowing for production of the antibody.

In some embodiments, methods for preparing an antibody described herein involve a recombinant expression vector that encodes both the heavy chain and the light chain of an anti-Galectin-9 antibody, as also described herein. The recombinant expression vector can be introduced into a suitable host cell (*e.g.*, a dhfr- CHO cell) by a conventional method, *e.g.*,

calcium phosphate-mediated transfection. Positive transformant host cells can be selected and cultured under suitable conditions allowing for the expression of the two polypeptide chains that form the antibody, which can be recovered from the cells or from the culture medium.

When necessary, the two chains recovered from the host cells can be incubated under suitable
5 conditions allowing for the formation of the antibody.

In one example, two recombinant expression vectors are provided, one encoding the heavy chain of the anti-Galectin-9 antibody and the other encoding the light chain of the anti-Galectin-9 antibody. Both of the two recombinant expression vectors can be introduced into a suitable host cell (*e.g.*, dhfr- CHO cell) by a conventional method, *e.g.*, calcium phosphate-
10 mediated transfection. Alternatively, each of the expression vectors can be introduced into a suitable host cells. Positive transformants can be selected and cultured under suitable conditions allowing for the expression of the polypeptide chains of the antibody. When the two expression vectors are introduced into the same host cells, the antibody produced therein can be recovered from the host cells or from the culture medium. If necessary, the polypeptide chains
15 can be recovered from the host cells or from the culture medium and then incubated under suitable conditions allowing for formation of the antibody. When the two expression vectors are introduced into different host cells, each of them can be recovered from the corresponding host cells or from the corresponding culture media. The two polypeptide chains can then be incubated under suitable conditions for formation of the antibody.

20 Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recovery of the antibodies from the culture medium. For example, some antibodies can be isolated by affinity chromatography with a Protein A or Protein G coupled matrix.

Any of the nucleic acids encoding the heavy chain, the light chain, or both of an anti-
25 Galectin-9 antibody as described herein, vectors (*e.g.*, expression vectors) containing such; and host cells comprising the vectors are within the scope of the present disclosure.

Anti-Galectin-9 antibodies thus prepared can be characterized using methods known in the art, whereby reduction, amelioration, or neutralization of Galectin-9 biological activity is detected and/or measured. For example, in some embodiments, an ELISA-type assay is suitable
30 for qualitative or quantitative measurement of Galectin-9 inhibition of Dectin-1 or TIM-3 signaling.

The bioactivity of an anti-Galectin-9 antibody can verified by incubating a candidate antibody with Dectin-1 and Galectin-9, and monitoring any one or more of the following characteristics: (a) binding between Dectin-1 and Galectin-9 and inhibition of the signaling

transduction mediated by the binding; (b) preventing, ameliorating, or treating any aspect of a solid tumor; (c) blocking or decreasing Dectin-1 activation; (d) inhibiting (reducing) synthesis, production or release of Galectin-9. Alternatively, TIM-3 can be used to verify the bioactivity of an anti-Galectin-9 antibody using the protocol described above. Alternatively, CD206 can be used to verify the bioactivity of an anti-Galectin-9 antibody using the protocol described above.

In some embodiments, bioactivity or efficacy is assessed in a subject, e.g., by measuring peripheral and intra-tumoral T cell ratios, T cell activation, or by macrophage phenotyping.

Additional assays to determine bioactivity of an anti-Galectin-9 antibody include measurement of CD8+ and CD4+ (conventional) T-cell activation (in an in vitro or in vivo assay, e.g., by measuring inflammatory cytokine levels, e.g., IFN γ , TNF α , CD44, ICOS granzymeB, Perforin, IL2 (upregulation); CD26L and IL-10 (downregulation)); measurement of reprogramming of macrophages (in vitro or in vivo), e.g., from the M2 to the M1 phenotype (e.g., increased MHCII, reduced CD206, increased TNF- α and iNOS), Alternatively, levels of ADCC can be assessed, e.g., in an in vitro assay, as described herein.

Combined Cancer Therapy

The present disclosure provides methods for treating solid tumors, such as pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CAA), renal cell carcinoma (RCC), urothelial, head and neck, breast cancer, lung cancer, or other GI solid tumors, using any of the anti-Galectin antibodies, for example G9.2-17 (e.g., G9.2-17(IgG4)), in combination with one or more chemotherapeutics such as gemcitabine and/or paclitaxel (e.g., Abraxane[®]).

Without being bound by theory, it is thought that anti-Galectin-9 antibodies, through their inhibition of Dectin-1, can reprogram immune responses against tumor cells *via*, e.g., inhibiting the activity of $\gamma\delta$ T cells infiltrated into tumor microenvironment, and/or enhancing immune surveillance against tumor cells by, e.g., activating CD4+ and/or CD8+ T cells. Thus, combined use of an anti-Galectin-9 antibody and one or more chemotherapeutics such as those described herein would be expected to significantly enhance anti-tumor efficacy.

(A) Exemplary Target Solid Tumors for Treatment

In some aspects, the present disclosure provides methods of treating a solid tumor, for example, PDAC, CRC, HCC, cholangiocarcinoma, renal cell carcinoma (RCC), urothelial cancer, head and neck cancer, breast cancer, lung cancer, or other GI solid tumors. The

treatment methods disclosed herein involve the combined therapy of an anti-Gal9 antibody such as G9.2-17(IgG4) and one or more chemotherapeutics (*e.g.*, gemcitabine and paclitaxel as disclosed herein).

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with few long-term survivors (Yadav et al., *Gastroenterology*, 2013, 144, 1252-1261). Inflammation is paramount in PDAC progression as oncogenic mutations alone, in the absence of concomitant inflammation, are insufficient for tumorigenesis (Guerra et al., *Cancer Cell*, 2007, 11, 291-302). Innate and adaptive immunity cooperate to promote tumor progression in PDAC. In particular, specific innate immune subsets within the tumor microenvironment (TME) are apt at educating adaptive immune effector cells towards a tumor-permissive phenotype. Antigen presenting cell (APC) populations, including M2-polarized tumor-associated macrophages (TAMs) and myeloid dendritic cells (DC), induce the generation of immune suppressive Th2 cells in favor of tumor-protective Th1 cells (Ochi et al., *J of Exp Med.*, 2012, 209, 1671-1687; Zhu et al., *Cancer Res.*, 2014, 74, 5057-5069). Similarly, it has been shown that myeloid derived suppressor cells (MDSC) negate anti-tumor CD8⁺ cytotoxic T-Lymphocyte (CTL) responses in PDAC and promote metastatic progression (Connolly et al., *J Leuk Biol.*, 2010, 87, 713-725; Pylayeva-Gupta et al., *Cancer Cell*, 2012, 21, 836-847; Bayne et al., *Cancer Cell*, 2012, 21, 822-835).

Colorectal cancer (CRC), also known as bowel cancer, colon cancer, or rectal cancer, is any cancer affecting the colon and the rectum. CRC is known to be driven by genetic alterations of tumor cells and is also influenced by tumor-host interactions. Recent reports have demonstrated a direct correlation between the densities of certain T lymphocyte subpopulations and a favorable clinical outcome in CRC, supporting a major role of T-cell-mediated immunity in repressing tumor progression of CRC.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection. HCC is usually accompanied by cirrhotic liver with extensive lymphocyte infiltration due to chronic viral infection. Many studies have demonstrated that tumor-infiltrating effector CD8⁺ T cells and T helper 17 (Th17) cells correlate with improved survival after surgical resection of tumors. However, tumor-infiltrating effector T cells fail to control tumor growth and metastasis (Pang et al., *Cancer Immunol Immunother* 2009;58:877-886).

Cholangiocarcinoma is a group of cancers that begin in the bile ducts. Cholangiocarcinoma is commonly classified by its location in relation to the liver. For

example, intrahepatic cholangiocarcinoma, accounting for less than 10% of all cholangiocarcinoma cases, begins in the small bile ducts within the liver. In another example, perihilar cholangiocarcinoma (also known as a Klatskin tumor), accounting for more than half of the cholangiocarcinoma cases, begins in hilum, where two major bile ducts join and leave the liver. Others are classified as distal cholangiocarcinomas, which begin in bile ducts outside the liver.

In some embodiments, the methods of the present disclosure increase anti-tumor activity (e.g., reduce cell proliferation, tumor growth, tumor volume, and/or tumor burden or load or reduce the number of metastatic lesions over time) by at least about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or more as compared to levels prior to treatment or in a control subject. In some embodiments, reduction is measured by comparing cell proliferation, tumor growth, and/or tumor volume in a subject before and after administration of the pharmaceutical composition. In some embodiments, the method of treating or ameliorating a cancer in a subject allows one or more symptoms of the cancer to improve by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more. In some embodiments, before, during, and after the administration of the pharmaceutical composition, cancerous cells and/or biomarkers in a subject are measured in a biological sample, such as blood, serum, plasma, urine, peritoneal fluid, and/or a biopsy from a tissue or organ. In some embodiments, the methods include administration of the compositions of the invention to reduce tumor volume, size, load or burden in a subject to an undetectable size, or to less than about 1%, 2%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, or 90% of the subject's tumor volume, size, load or burden prior to treatment. In other embodiments, the methods include administration of the compositions of the invention to reduce the cell proliferation rate or tumor growth rate in a subject to an undetectable rate, or to less than about 1%, 2%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, or 90% of the rate prior to treatment. In other embodiments, the methods include administration of the compositions of the invention to reduce the development of or the number or size of metastatic lesions in a subject to an undetectable rate, or to less than about 1%, 2%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, or 90% of the rate prior to treatment.

The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which are depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” can mean within an acceptable standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to $\pm 20\%$, preferably up to $\pm 10\%$, more

preferably up to $\pm 5\%$, and more preferably still up to $\pm 1\%$ of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated, the term “about” is implicit and in this context means within an acceptable error range for the particular value.

As used herein, the term “treating” refers to the application or administration of a composition including one or more active agents to a subject, who has a target disease or disorder, a symptom of the disease/disorder, or a predisposition toward the disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disorder, a symptom of the disease or disorder, or the predisposition toward the disease or disorder.

Alleviating a target disease/disorder includes delaying the development or progression of the disease, or reducing disease severity or prolonging survival. Alleviating the disease or prolonging survival does not necessarily require curative results. As used therein, “delaying” the development of a target disease or disorder means to defer, hinder, slow, retard, stabilize, and/or postpone progression of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated. A method that “delays” or alleviates the development of a disease, or delays the onset of the disease, is a method that reduces probability of developing one or more symptoms of the disease in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a number of subjects sufficient to give a statistically significant result.

“Development” or “progression” of a disease means initial manifestations and/or ensuing progression of the disease. Development of the disease can be detectable and assessed using standard clinical techniques as well known in the art. However, development also refers to progression that may be undetectable. For purpose of this disclosure, development or progression refers to the biological course of the symptoms. “Development” includes occurrence, recurrence, and onset. As used herein “onset” or “occurrence” of a target disease or disorder includes initial onset and/or recurrence.

(B) Exemplary Patient Population for Treatment

A subject having a target solid tumor as disclosed herein, for example, PDAC, can be identified by routine medical examination, *e.g.*, laboratory tests, organ functional tests, genetic tests, interventional procedure (biopsy, surgery) any and all relevant imaging modalities,. In

some embodiments, the subject to be treated by the method described herein is a human cancer patient who has undergone or is subjecting to an anti-cancer therapy, for example, chemotherapy, radiotherapy, immunotherapy, tumor-treating fields (TTFields), or surgery.

5 In some embodiments, subjects have received prior immune-modulatory anti-tumor agents. Non-limiting examples of such immune-modulatory agents include, but are not limited to as anti-PD1, anti-PD-L1, anti-CTLA-4, anti-OX40, anti-CD137, anti-TIGIT, anti-PVRIG, platinum-based agent, etc. Non-limiting examples of platinum-based agents include cisplatin, carboplatin, oxaliplatin, nedaplatin, and lobaplatin. In some embodiments, the subject shows disease progression through the treatment. In other embodiments, the subject is resistant to the
10 treatment (either de novo or acquired). In some embodiments, such a subject is demonstrated as having advanced malignancies (*e.g.*, inoperable or metastatic). Alternatively, or in addition, in some embodiments, the subject has no standard therapeutic options available or ineligible for standard treatment options, which refer to therapies commonly used in clinical settings for treating the corresponding solid tumor.

15 Tumor-treating fields (TTFields) are a cancer treatment modality that uses alternating electric fields of intermediate frequency (~100-500 kHz) and low intensity (1-3 V/cm) to disrupt cell division. In any of the embodiments described herein, the anti-Galectin-9 antibody in combination with a chemotherapeutic agent described herein may be administered prior to, concurrent with, or after a tumor-treating fields (TTFields) regimen. In any of the embodiments
20 described herein, the anti-Galectin-9 antibody, in combination with a chemotherapeutic agent described herein, may be administered prior to, concurrent with, or after a reverse-thermal hydrogel technology-based therapy, *e.g.*, reverse-thermal hydrogel chemotherapy.

In some instances, the subject may be a human patient having a refractory disease, for example, a refractory PDAC. As used herein, “refractory” refers to the tumor that does not
25 respond to or becomes resistant to a treatment. In some instances, the subject may be a human patient having a relapsed disease, for example, a relapsed PDAC. As used herein, “relapsed” or “relapses” refers to the tumor that returns or progresses following a period of improvement (*e.g.*, a partial or complete response) with treatment.

In some embodiments, the human patient to be treated by the methods disclosed herein
30 may meet one or more of the inclusion and exclusion criteria disclosed in Example 2 below. For example, the human patient may be older than 18 and have histologically confirmed unresectable metastatic cancer (*e.g.*, adenocarcinomas and squamous cell carcinomas). The patient may have measurable disease, according to RECIST v. 1.1. In some instances, the human patient may have recent archival tumor sample (*e.g.*, obtained within 5 years) available

for biomarker analyses (*e.g.*, galectin-9 tumor tissue expression, which may be assessed by IHC). In some instances, the human patient is a PDAC patient who has received at least one line of systemic therapy in the metastatic cancer setting. Such a patient may either be gemcitabine-containing regimen naïve or at least 6 months out of having been treated using a gemcitabine-containing regimen. The patient may have Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and/or Karnofsky score > 70 . The patient may also have adequate hematologic and end organ function, *e.g.*, neutrophil count $\geq 1 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, for HCC in Part 1 $\geq 50 \times 10^9/L$; hemoglobin ≥ 9.0 g/dL without transfusion in the previous week, Creatinine $\leq 1.5 \times$ ULN, AST (SGOT) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or hepatic metastases are present), ALT (SGPT) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or hepatic metastases present), Bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's disease may have a bilirubin $\leq 3.0 \times$ ULN), Albumin ≥ 3.0 g/dL, INR and PTT $\leq 1.5 \times$ ULN; and/or amylase and lipase $\leq 1.5 \times$ ULN. In some instances, the human patient shows no evidence of active infection or infections requiring parenteral antibiotics, and no serious infection within 4 weeks before the treatment starts. Pancreatic, biliary, or enteric fistulae allowed, provided they are controlled with an appropriate non-infected and patent drain.

Alternatively or in addition, the human patient subject to any treatment disclosed herein may be free of: (i) metastatic cancer of an unknown primary, (ii) clinically significant, active uncontrolled bleeding, any bleeding diathesis (*e.g.*, active peptic ulcer disease); (iii) radiation therapy within 4 weeks of the first dose of the treatment, (iv) with fungating tumor masses or locally advanced PDAC; (v) $\geq$ CTCAE grade 3 toxicity (except alopecia and vitiligo) due to prior cancer therapy; (vi) history of second malignancy, (vii) evidence of severe or uncontrolled systemic diseases, congestive cardiac failure $>$ New York Heart Association (NYHA) class 2, or myocardial infarction (MI) within 6 months, (viii) serious non-healing wound, active ulcer, or untreated bone fracture; (ix) uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures; (x) history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins; (xi) significant vascular disease (*e.g.*, aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of the treatment, history of pulmonary embolism, stroke or transient ischemic attack within 3 months prior to the treatment, and/or history of abdominal fistula or gastrointestinal perforation within 6 months prior to the treatment; (xii) active autoimmune disorder (except type I diabetes, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia); (xiii) requires systemic immunosuppressive treatment; (xiv) tumor-related pain ($>$ grade 3) unresponsive to broad analgesic interventions (oral and/or

patches); (xiii) uncontrolled hypercalcemia, despite use of bisphosphonates; (xiv) received organ transplant(s).

In some instances, the subject is a human patient having an elevated level of Galectin-9 as relative to a control level. The level of Galectin-9 can be a plasma or serum level of
 5 Galectin-9 in the human patient. In other examples, the level of Galectin-9 can be the level of cell-surface Galectin-9, for example the level of Galectin-9 on cancer cells. In one example, the level of Galectin-9 can be the level of surface Galectin-9 expressed on cancer cells in patient-derived organotypic tumor spheroids (PDOT), which can be prepared by, *e.g.*, the method disclosed in Examples below. A control level may refer to the level of Galectin-9 in a matched
 10 sample of a subject of the same species (*e.g.*, human) who are free of the solid tumor. In some examples, the control level represents the level of Galectin-9 in healthy subjects.

To identify such a subject, a suitable biological sample can be obtained from a subject who is suspected of having the solid tumor and the biological sample can be analyzed to determine the level of Galectin-9 contained therein (*e.g.*, free, cell-surface expressed, or total)
 15 using conventional methods, *e.g.*, ELISA or FACS. In some embodiments, organoid cultures are prepared, *e.g.*, as described herein, and used to assess Galectin-9 levels in a subject. Single cells derived from certain fractions obtained as part of the organoid preparation process are also suitable for assessment of Galectin-9 levels in a subject. In some instances, an assay for measuring the level of Galectin-9, either in free form or expressed on cell surface, involves the
 20 use of an antibody that specifically binds the Galectin-9 (*e.g.*, specifically binds human Galectin-9). Any of the anti-Galectin-9 antibodies known in the art can be tested for suitability in any of the assays described above and then used in such assays in a routine manner. In some embodiments, an antibody described herein (*e.g.*, a G9.2-17 antibody) can be used in such as assay. In some embodiments, an antibody described co-pending US Patent Application
 25 16/173,970 and in co-owned, co-pending International Patent Application PCT/US18/58028, the relevant disclosures of each of which are incorporated by reference for the purpose and subject matter referenced herein. In some examples, the anti-Galectin-9 antibody is a Fab molecule. Assay methods for determining Galectin-9 levels as disclosed herein are also within the scope of the present disclosure.

30 (C) Exemplary Treatment Conditions

In some embodiments, the antibodies described herein, *e.g.*, G9.2-17 such as its IgG4 form, are administered to a subject in need of the treatment at an amount sufficient to inhibit the activity of Galectin-9 (and/or Dectin-1 or TIM-3 or CD206) in immune suppressive

immune cells in a tumor by at least 20% (*e.g.*, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) *in vivo*. In other embodiments, the antibodies described herein, *e.g.*, G9.2-17, are administered in an amount effective in reducing the activity level of Galectin-9 (and/or Dectin-1 or TIM-3 or CD206) in immune suppressive immune cells in a tumor by at least 20% (*e.g.*,
5 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) (as compared to levels prior to treatment or in a control subject). In some embodiments, the antibodies described herein, *e.g.*, G9.2-17, are administered to a subject in need of the treatment at an amount sufficient to promote M1-like programming in TAMs by at least 20% (*e.g.*, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) *in vivo* (as compared to levels prior to treatment or in a control subject).

10 Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical composition to the subject, depending upon the type of disease to be treated or the site of the disease. In some embodiments, the anti-Galectin-9 antibody can be administered to a subject by intravenous infusion.

Injectable compositions may contain various carriers such as vegetable oils,
15 dimethylactamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, and polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like). For intravenous infusion, water soluble antibodies can be administered by the drip method, whereby a pharmaceutical formulation containing the antibody and a physiologically acceptable excipient is infused. Physiologically acceptable excipients may include, for
20 example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable excipients. Intramuscular preparations, *e.g.*, a sterile formulation of a suitable soluble salt form of the antibody, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

In some embodiments, the methods are provided, the anti-Galectin-9 antibody is
25 administered concurrently with the one or more chemotherapeutics. In some embodiments, the anti-Galectin-9 antibody is administered before or after the one or more chemotherapeutics. In some embodiments, the one or more chemotherapeutics are administered systemically. In some embodiments, the one or more chemotherapeutics is administered locally. In some
30 embodiments, the one or more chemotherapeutics is administered by intravenous administration, *e.g.*, as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-arterial, intra-articular, intravesical, intrasynovial, intrathecal, intratumoral, sub-urothelial, oral, inhalation or topical routes. In one embodiment, the one or more chemotherapeutics is administered to the subject by intravenous infusion. In some embodiments, the anti-Galectin-9 antibody described herein is

administered to a patient who is currently on or has been previously on an anti-cancer therapy, e.g., a chemotherapy.

An effective amount of the pharmaceutical composition described herein can be administered to a subject (*e.g.*, a human) in need of the treatment via a suitable route, systemically or locally. In some embodiments, the anti-galectin-9 antibodies are administered by intravenous administration, *e.g.*, as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-arterial, intra-articular, intrasynovial, intrathecal, intravesical, intratumoral, sub-urothelial, oral, inhalation or topical routes. In one embodiment, the anti-galectin-9 antibody is administered to the subject by intravenous infusion. In one embodiment, the anti-galectin-9 antibody is administered to the subject intraperitoneally. As used herein, “an effective amount” refers to the amount of each active agent required to confer therapeutic effect on the subject, either alone or in combination with one or more other active agents. In some embodiments, the therapeutic effect is reduced Galectin-9 activity and/or amount/expression, reduced Dectin-1 signaling, reduced TIM-3 signaling, reduced CD206 signaling, or increased anti-tumor immune responses in the tumor microenvironment. Non-limiting examples of increased anti-tumor responses include increased activation levels of effector T cells, or switching of the TAMs from the M2 to the M1 phenotype. In some cases, the anti-tumor response includes increased ADCC responses. Determination of whether an amount of the antibody achieved the therapeutic effect would be evident to one of skill in the art. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment.

Empirical considerations, such as the half-life, generally contribute to the determination of the dosage. For example, antibodies that are compatible with the human immune system, such as humanized antibodies or fully human antibodies, are in some instances used to prolong half-life of the antibody and to prevent the antibody being attacked by the host's immune system. Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily, based on treatment and/or suppression and/or

amelioration and/or delay of a target disease/disorder. Alternatively, sustained continuous release formulations of an antibody may be appropriate. Various formulations and devices for achieving sustained release are known in the art.

In one example, dosages for an antibody as described herein are determined empirically in individuals who have been given one or more administration(s) of the antibody. Individuals are given incremental dosages of the antagonist. To assess efficacy of the antagonist, an indicator of the disease/disorder can be followed.

Anti-Galectin-9 Antibody Treatment

Any of the anti-Galectin-9 antibodies described herein can be used in any of the methods described herein. In some embodiments, the anti-Galectin-9 antibody is G9.2-17. The G9.2-17 antibody may be an IgG4 molecule (G9.2-17(IgG4)) as disclosed herein. In specific examples, the anti-Galectin-9 antibody (G9.2-17) used herein has a heavy chain of SEQ ID NO:19 and a light chain of SEQ ID NO:15. The anti-Gal9 antibody may be formulated as disclosed herein and given to a subject in need of the treatment via a suitable route, for example, intravenous infusion.

In some instances, the anti-Galectin-9 antibody as disclosed herein (*e.g.*, G9.2-17 such as G9.2-17(IgG4)) can be administered to a subject at a suitable dose, for example, about 0.2 to about 32 mg/kg. Examples include 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 2 mg/kg to 3 mg/kg, 3 mg/kg to 4 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, 4 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12 mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (*e.g.*, 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 6.3 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any incremental doses within these ranges. In some embodiments, the antibody is administered at a dose of about 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 2 mg/kg to 4 mg/kg, about 4 mg/kg to 8 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, about 8 mg/kg to 12 mg/kg, about 12 mg/kg to 16 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (*e.g.*, about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6

mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) or any incremental doses within these ranges.

In some embodiments, the anti-Gal-9 antibody such as G9.2-17(IgG4) is administered at 0.2 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 0.6 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 0.63 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 2 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 4 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 6 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 6.3 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 8 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 10 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 12 mg/kg. In some embodiments, the anti-Gal-9 antibody is administered at 16 mg/kg. In some instances, multiple doses of the anti-Galectin-9 antibody can be administered to a subject at a suitable interval or cycle, for example, once every week, once every two to four weeks (*e.g.*, every two, three, or four weeks). The treatment may last for a suitable period, for example, up to 3 months, up to 6 months, or up to 12 months or up to 24 months or longer. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Gal-9 antibody is administered to the subject at a dose of 10 mg/kg once every week. Alternatively, the anti-Gal-9 antibody is administered to the subject at a dose of 16 mg/kg once every week.

In some instances, the anti-Gal-9 antibody such as G9.2-17(IgG4) disclosed herein may be administered to a subject at a flat dose, *e.g.*, about 650 mg to about 1120 mg, once every week to once every 4 weeks. In some examples, the anti-Gal-9 antibody is administered to a subject at a about 650 mg to about 700 mg once every week. In some examples, the anti-Gal-9 antibody is administered to a subject at a about 650 mg to about 700 mg once every two weeks. In some examples, the anti-Gal-9 antibody is administered to a subject at a about 1040 mg to about 1120 mg once every week. In some examples, the anti-Gal-9 antibody is administered to a subject at a about 1040 mg to about 1120 mg once every two weeks.

In some examples, the anti-Gal-9 antibody such as G9.2-17(IgG4) antibody is

administered to a human patient having a solid tumor as disclosed herein (*e.g.*, PDAC) at a dose of about 3 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 15 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 0.2 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 0.6 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 0.63 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 2 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 4 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 6 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 6.3 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 8 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 10 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 12 mg/kg once every two weeks via intravenous infusion. In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose of about 16 mg/kg or higher dose level once every two weeks via intravenous infusion.

In other examples, the anti-Galectin-9 antibody is administered to the human patient having the target solid tumor at a dose 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, and 16 mg/kg or higher dose level once every two weeks via intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the

anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some examples, about 2 mg/kg to 16 mg/kg anti-Gal9 antibody (*e.g.*, G9.2-17 in IgG4 form) may be given to a subject in need of the treatment once every two weeks. In some
5 examples, about 0.2 mg/kg to 16 mg/kg anti-Gal9 antibody (*e.g.*, G9.2-17 in IgG4 form) may be given to a subject in need of the treatment once every two weeks. In some examples, the anti-Gal9 antibody (*e.g.*, G9.2-17 in IgG4 form as disclosed herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15) is administered to the subject at a dose of about 0.5 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4
10 mg/kg, about 5 mg/kg, about 6 mg/kg, 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein, once every two weeks by intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10
15 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some examples, the anti-Gal9 antibody (*e.g.*, G9.2-17 in IgG4 form as disclosed
20 herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15) 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-Gal9 antibody is administered to the subject at a dose of about 0.63 mg/kg once every two
25 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-Gal9 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
30 infusion. In some examples, the anti-Gal9 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-Gal9 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-Gal9 antibody is administered to the subject at a dose of about 16 mg/kg once every two weeks by intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Gal9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Gal9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some examples, the anti-Gal9 antibody (e.g., G9.2-17 in IgG4 form as disclosed herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15) is administered to the subject at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 3 mg/kg to 4 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, about 4 mg/kg to 8 mg/kg, about 8 mg/kg to 10 mg/kg, about 8 mg/kg to 12 mg/kg, about 10 mg/kg to 12 mg/kg, about 12 mg/kg to 16 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (e.g., about 0.2 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) any increment therein, once a week by intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Gal9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Gal9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some examples, the anti-Gal9 antibody (e.g., G9.2-17 in IgG4 form as disclosed herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15) is administered to the subject at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 3 mg/kg to 4 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, 4 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12

mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (e.g., 0.2 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 0.5 mg/kg, 1 mg/kg, 2mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 6.3 mg/kg, about 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any incremental doses within these ranges or any incremental doses within these ranges, once a week by intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some examples, the anti-Gal9 antibody (e.g., G9.2-17 in IgG4 form as disclosed herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15) is administered to the subject at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein, once a week by intravenous infusion. In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In specific examples, the anti-Galectin-9 antibody such as G9.2-17 (IgG4) may be administered to a human patient at a suitable dose (e.g., the doses disclosed herein) once every week. For example, 2.0 mg/kg of G9.2-17(IgG4) may be administered to the human patient once every week. For example, 6.3 mg/kg of G9.2-17(IgG4) may be administered to the human patient once every week. In another example, 10 mg/kg of G9.2-17(IgG4) may be administered to the human patient once every week. Alternatively, 12 mg/kg of G9.2-17(IgG4) may be administered to the human patient once every week. In yet another example, 16 mg/kg of G9.2-17(IgG4) may be administered to the human patient once every week.

In some instances, the anti-Galectin-9 antibody may be given to the human patient for at least 2 cycles, at least 3 cycles, at least 4 cycles, at least 5 cycles, at least 6 cycles, or more. In some instances, the treatment period may be 6 months to 12 months. In other instances, the treatment period may be 12 months to 24 months. In other instances, the treatment period may be longer than 24 months.

In some embodiments, the anti-Galectin 9 antibody disclosed herein (*e.g.*, G9.2-17 IgG4) is administered *via* a 30-minute to 6 hours infusion period intravenously. In some examples the intravenous infusion of the anti-Galectin 9 antibody may be performed for 30 minutes to 2 hours. In other examples, the anti-Galectin 9 antibody may be administered *via* a long infusion period, for example, about 2-6 hours, *e.g.*, about 2-4 hours or about 4-6 hours. In specific examples, examples anti-Galectin 9 antibody may be infused intravenous in a period of about 3 hours, about 4 hours, about 5 hours, or about 6 hours.

In specific embodiments, the interval or cycle is 1 week. In specific embodiments, the interval or cycle is 2 weeks. In some embodiments, the regimen is once every 2 weeks for one cycle, once every 2 weeks for two cycles, once every 2 weeks for three cycles, once every 2 weeks for four cycles, or once every 2 weeks for more than four cycles. In some embodiments, the treatment is once every 2 weeks for 1 to 3 months, once every 2 weeks for 3 to 6 months, once every 2 weeks for 6 to 12 months, or once every 2 weeks for 12 to 24 months, or longer.

In specific embodiments, the interval or cycle is 3 weeks. In some embodiments, the regimen is once every 3 weeks for one cycle, once every 3 weeks for two cycles, once every 3 weeks for three cycles, once every 3 weeks for four cycles, or once every 3 weeks for more than four cycles. In some embodiments, the treatment is once every 3 weeks for 1 to 3 months, once every 3 weeks for 3 to 6 months, once every 3 weeks for 6 to 12 months, or once every 3 weeks for 12 to 24 months, or longer.

In specific embodiments, the interval or cycle is 4 or more weeks. In some embodiments, the regimen is once every 4 or more weeks for one cycle, once every 4 or more weeks for two cycles, once every 4 or more weeks for three cycles, once every 4 or more weeks for four cycles, or once every 4 or more weeks for more than four cycles. In some embodiments, the treatment is once every 4 or more weeks for 1 to 3 months, once every 4 or more weeks for 3 to 6 months, once every 4 or more weeks for 6 to 12 months, or once every 4 or more weeks for 12 to 24 months, or longer. In some embodiments, the treatment is a combination of treatment at various time, *e.g.*, a combination of 2 weeks, 3 weeks, 4 or more 4 weeks. In some embodiments, the treatment interval is adjusted in accordance with the patient's response to treatment. In some embodiments, the dosage(s) is adjusted in accordance with the

patient's response to treatment. In some embodiments, the dosages are altered between treatment intervals. In some embodiments, the treatment may be temporarily stopped. In some embodiments, anti-Galectin-9 therapy is temporarily stopped. In some embodiments, chemotherapy is temporarily stopped. In some embodiments, both are temporarily stopped. In any of these embodiments, the anti-Gal9 antibody may be G9.2-17 in IgG4 form as disclosed herein, having a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 15).

Alternatively, a human patient may start with a low dose of the anti-Galectin-9 antibody such as G9.2-17 (IgG4) disclosed herein, for example, 0.2 mg/kg, 0.63 mg/kg, or 2 mg/kg. When no adverse effects are observed, the dose of the antibody may be elevated, for example, to 6.3 mg/kg, 10 mg/kg, or 16 mg/kg.

Chemotherapy

The one or more chemotherapeutics may comprise an antimetabolite, a microtubule (e.g., tubulin) inhibitor, a platinum agent, or a combination thereof. Antimetabolites include, for example, folic acid antagonist (e.g., methotrexate) and nucleotide analogs such as pyrimidine antagonist (e.g., 5-fluorouracil, foxuridine, cytarabine, capecitabine, and gemcitabine), purine antagonist (e.g., 6-mercaptopurine and 6-thioguanine), and adenosine deaminase inhibitor (e.g., cladribine, fludarabine and pentostatin). Microtubule inhibitors (MIT) include, for example, paclitaxel (e.g., Taxol®), docetaxel, vinblastine, vincristine, and vinorelbine.

In some examples, the antimetabolites used in the methods disclosed herein is gemcitabine, which may be given by intravenous infusion. The amount of gemcitabine to be given to a subject depends on many factors, including height and weight, general health or other health problems, and the type of cancer to be treated, which would be within the knowledge of a medical practitioner following guidance provided by the Food and Drug Administration (e.g., see the drug labels of approved gemcitabine products). In some examples, a subject may be administered gemcitabine by intravenous infusion at a dose of 1000 mg/m² optionally over 30 minutes once weekly for up to 7 weeks, followed by one week rest from the treatment. Subsequent cycles may consist of infusion once weekly for three consecutive weeks out of every four weeks. If one or more adverse effects occur, the dose of gemcitabine may be reduced or the treatment may be withheld. More details for managing adverse effects associated with gemcitabine treatment are provided in Example 2 below.

Microtubule inhibitors are a class of compounds that inhibit the formation of cellular microtubules, thereby blocking cell proliferation. In some examples, the microtubule inhibitor

is a stabilizing agent that promotes polymerization of microtubules. Examples include taxanes and epothilones. In other examples, the microtubule inhibitor is a destabilizing agent that promotes depolymerization of microtubules. Examples include vinca alkaloids. In some examples, the microtubule inhibitor used in the methods disclosed herein is paclitaxel. In some instances, the paclitaxel is in free form. In other instances, the paclitaxel is conjugated to a protein, for example, albumin. In specific examples, the paclitaxel is Abraxane[®], which is nanoparticle albumin-conjugated paclitaxel.

The amount of paclitaxel, *e.g.*, protein-bound paclitaxel such as nab-paclitaxel, to be given to a subject depends on many factors, including height and weight, general health or other health problems, and the type of cancer to be treated, which would be within the knowledge of a medical practitioner following guidance provided by the Food and Drug Administration (*e.g.*, see the drug labels of approved paclitaxel products). For example, when nanoparticle albumin-conjugated paclitaxel (nab-paclitaxel, *e.g.*, Abraxane[®]), it can be given to a subject by intravenous infusion at 260 mg/m² over 30 minutes every 3 weeks. The dose of paclitaxel may be reduced if severe adverse effects (*e.g.*, neutropenia or severe sensory neuropathy) are observed. In some instances, the dose of nab-paclitaxel may be reduced to 180 mg/m². When in combination with the anti-Gal9 antibody, the dose of paclitaxel may be 125 mg/m². If needed, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m². More details for managing side effects associated with paclitaxel are provided in Example 2 below.

In some instances, the chemotherapeutic agents to be co-used with the anti-Gal-9 antibody can comprise a platinum agent, for example, cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.

Combined Therapy

The combined therapy provided herein comprises any of the anti-Galectin-9 antibody therapy disclosed herein (*e.g.*, involving the antibody of G9.2-17(IgG4)) and any of the chemotherapy disclosed herein (*e.g.*, involving the combination of gemcitabine and paclitaxel).

In some specific examples, the anti-Gal9 antibody (*e.g.*, G9.2-17 in IgG4 form), gemcitabine, and paclitaxel (*e.g.*, nanoparticle albumin-conjugated paclitaxel or Abraxane[®]) may be administered to a subject in need of the treatment following the treatment regimen and dosing schedules provided in Example 2 below. For example, the treatment may comprise one or more cycles, each consisting of 28 days. In each cycle, the anti-Gal9 antibody (*e.g.*, G9.2-17(IgG4)) is given to the subject (*e.g.*, a human patient having PDAC) once every two weeks (*e.g.*, on Day 1 and Day 15) at a dose of about 2 mg/kg to 16 mg/kg (*e.g.*, about 2 mg/kg,

about 4 mg/kg, about 8 mg/kg, about 12 mg/kg, or about 16 mg/kg) *via* intravenous infusion. In some embodiments, in each cycle, the anti-Gal9 antibody (*e.g.*, G9.2-17(IgG4)) is given to the subject (*e.g.*, a human patient having PDAC) once every two weeks (*e.g.*, on Day 1 and Day 15) at a dose of about 0.2 mg/kg to 16 mg/kg (*e.g.*, 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 10 mg/kg, or about 16 mg/kg) *via* intravenous infusion. Gemcitabine and paclitaxel (*e.g.*, protein-bound paclitaxel such as Abraxane[®]) can be administered to the subject once every week for three weeks followed by one week without treatment (*e.g.*, on Day 1, Day 8, and Day 15 in the 28-day cycle), using the dosage and dosing scheduled as approved by the FDA. For example, gemcitabine may be given to the subject once every week at 1000 mg/m² in each cycle *via* intravenous infusion and paclitaxel may be given to the subject once every week at 125 mg/m². When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method for treating a solid tumor (*e.g.*, PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1 and day 15 (*i.e.*, once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg to about 32 mg/kg *via* intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (*e.g.*, intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (*e.g.*, intravenous infusion). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (*i.e.*, once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg to 0.5 mg/kg, about 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 3 mg/kg to 4 mg/kg, about 4 mg/kg to 8 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, about 6 mg/kg to 8 mg/kg, about 6.3 mg/kg to 8 mg/kg, about 8 mg/kg to 12 mg/kg, about 8 mg/kg to 10 mg/kg, about 10 mg/kg to 12 mg/kg, about 12 mg/kg to 16 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (*e.g.*, about 0.2 mg/kg, about 0.5 mg/kg, about 0.63 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about

- 2mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) or any increment therein via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous injection). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m²,
- (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 3 mg/kg to 4 mg/kg, 4 mg/kg to 8 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12 mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (e.g., 0.2 mg/kg, 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, 1 mg/kg, 2mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 6.3 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any increment therein, via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous injection). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m²,
- (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the

subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method for treating a solid tumor (e.g., PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 2 mg/kg to about 16 mg/kg via intravenous infusion 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 embodiments, the method for treating a solid tumor (e.g., PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg to about 16 mg/kg via intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (e.g., intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method for treating a solid tumor (e.g., PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein, via intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (e.g., intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,

wherein

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg to 0.5 mg/kg, about 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 3 mg/kg to 4 mg/kg, about 4 mg/kg to 8 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, about 6 mg/kg to 8 mg/kg, about 6.3 mg/kg to 8 mg/kg, about 8 mg/kg to 12 mg/kg, about 8 mg/kg to 10 mg/kg, about 10 mg/kg to 12 mg/kg, about 12 mg/kg to 16 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (e.g., about 0.2 mg/kg, about 0.5 mg/kg, about 0.63 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) any increment therein, via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 3 mg/kg to 4 mg/kg, 4 mg/kg to 8 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12 mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (e.g., 0.2 mg/kg, 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 6.3 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14

mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any increment therein, via intravenous infusion,

- 5 (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

10 In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) or any increment therein, via intravenous infusion,
- 15 (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 20 (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).
- 25

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg,
- 30

about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein,
via intravenous infusion,

(2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose
of 1000 mg/m² intravenously (e.g., intravenous infusion),

5 (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the
subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g.,
intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,
wherein:

10 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (*i.e.*, once
every 2 weeks (q2w)) at a dose of about 0.2 mg/kg via intravenous infusion,

(2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose
of 1000 mg/m² intravenously (e.g., intravenous infusion),

15 (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the
subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g.,
intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,
wherein:

20 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (*i.e.*, once
every 2 weeks (q2w)) at a dose of about 0.6 mg/kg via intravenous infusion,

(2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose
of 1000 mg/m² intravenously (e.g., intravenous infusion),

25 (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the
subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g.,
intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,
wherein:

30 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (*i.e.*, once
every 2 weeks (q2w)) at a dose of about 0.63 mg/kg via intravenous infusion,

(2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose
of 1000 mg/m² intravenously (e.g., intravenous infusion),

(3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the
subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g.,
intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 2 mg/kg via intravenous infusion,
- 5 (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

10 In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 4 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 15 (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 6 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 25 (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- 30 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 6.3 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the

subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- 5 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 8 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 10 (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- 15 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 10 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 20 (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more cycle(s) treatment of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 12 mg/kg via intravenous infusion,
- 25 (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

30 In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 16 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose

of 1000 mg/m² intravenously (e.g., intravenous infusion),

- (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

5 In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 32 mg/kg via intravenous infusion,
- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 1000 mg/m² intravenously (e.g., intravenous infusion),
- 10 (3) paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 125 mg/m² intravenously (e.g., intravenous infusion).

In any of the above administration method embodiments, when needed, the dose of

15 gemcitabine may be reduced to 800 mg/m² or 600 mg/m², and alternatively or in addition, the dose of paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) may be reduced to 100 mg/m² or 75 mg/m².

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days, wherein:

- 20 (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg to 0.5 mg/kg, about 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 3 mg/kg to 4 mg/kg, about 4 mg/kg to 8 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, about 6mg/kg to 8 mg/kg, about 6.3 mg/kg to 8 mg/kg, about 8 mg/kg to 12 mg/kg,
- 25 about 8 mg/kg to 10 mg/kg, about 10 mg/kg to 12 mg/kg, about 12 mg/kg to 16 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (e.g., about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about
- 30 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg,

about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) or any increment therein, via intravenous infusion,

- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 800 mg/m², 600 mg/m², or 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 100 mg/m², 75 mg/m² or 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,

wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 3 mg/kg to 4 mg/kg, 4 mg/kg to 8 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12 mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (e.g., 0.2 mg/kg, 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 6.3 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any incremental doses within these ranges or any incremental doses within these ranges, or any increment therein, via intravenous infusion,

- (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 800 mg/m², 600 mg/m², or 1000 mg/m² intravenously (e.g., intravenous infusion),

- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the subject on day 1, day 8, and day 15 at a dose of 100 mg/m², 75 mg/m² or 125 mg/m² intravenously (e.g., intravenous infusion).

In some embodiments, the method comprises one or more treatment cycle(s) of 28 days,

wherein:

- (1) anti-Gal9 antibody is administered to the subject on day 1 and day 15 (i.e., once every 2 weeks (q2w)) at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 1

- mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein, via intravenous infusion,
- 5 (2) gemcitabine is administered to the subject on day 1, day 8, and day 15 at a dose of 800 mg/m², 600 mg/m², or 1000 mg/m² intravenously (e.g., intravenous infusion),
- (3) paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) is administered to the
- 10 subject on day 1, day 8, and day 15 at a dose of 100 mg/m², 75 mg/m² or 125 mg/m² intravenously (e.g., intravenous infusion).

In any of the above administration methods, treatment cycles may continue over a period of 12-24 months.

- In any of the method embodiments described herein, the anti-galectin-9 antibody can be
- 15 administered (alone or in combination with one or more chemotherapeutic agents, e.g., gemcitabine and nab-paclitaxel, e.g., at the doses described herein) once a week, once every 2 weeks for one cycle, once every 2 weeks for two cycles, once every 2 weeks for three cycles, once every 2 weeks for four cycles, or once every 2 weeks for more than four cycles. In some
- 20 embodiments, the treatment is 1 to 3 months, 3 to 6 months, 6 to 12 months, 12 to 24 months, or longer. In some embodiments, the treatment is once every 2 weeks for 1 to 3 months, once every 2 weeks for 3 to 6 months, once every 2 weeks for 6 to 12 months, or once every 2 weeks for 12 to 24 months, or longer.

- In some embodiments, the method for treating a solid tumor (e.g., PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is
- 25 administered to the subject on day 1, day 7, day 15, and day 21 (i.e., once weekly (q1w)) at a dose of about 0.2 mg/kg to 0.5 mg/kg, about 0.5 mg/kg to 1 mg/kg, about 1 mg/kg to 2 mg/kg, about 3 mg/kg to 4 mg/kg, about 4 mg/kg to 8 mg/kg, about 4 mg/kg to 6 mg/kg, about 4 mg/kg to 6.3 mg/kg, about 6 mg/kg to 8 mg/kg, about 6.3 mg/kg to 8 mg/kg, about 8 mg/kg to 12 mg/kg, about 8 mg/kg to 10 mg/kg, about 10 mg/kg to 12 mg/kg, about 12 mg/kg to 16
- 30 mg/kg, about 16 mg/kg to 20 mg/kg, about 20 mg/kg to 24 mg/kg, about 24 mg/kg to 28 mg/kg, or about 28 mg/kg to 32 mg/kg (e.g., about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg,

about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, or about 32 mg/kg) or any increment therein, via intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (e.g., intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) may be reduced to 100 mg/m² or 75 mg/m². In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some embodiments, the method for treating a solid tumor (e.g., PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1, day 7, day 15, and day 21 (i.e., once weekly (q1w)) at a dose of 0.2 mg/kg to 0.5 mg/kg, 0.5 mg/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 3 mg/kg to 4 mg/kg, 4 mg/kg to 8 mg/kg, 4 mg/kg to 6 mg/kg, 4 mg/kg to 6.3 mg/kg, 6 mg/kg to 8 mg/kg, 6.3 mg/kg to 8 mg/kg, 8 mg/kg to 12 mg/kg, 8 mg/kg to 10 mg/kg, 10 mg/kg to 12 mg/kg, 12 mg/kg to 16 mg/kg, 16 mg/kg to 20 mg/kg, 20 mg/kg to 24 mg/kg, 24 mg/kg to 28 mg/kg, or 28 mg/kg to 32 mg/kg (e.g., about 0.2 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.63 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, about 6.3 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, or 32 mg/kg) or any incremental doses within these ranges or any incremental doses within these ranges, via intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (e.g., intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (e.g., intravenous infusion). When needed, the dose of gemcitabine

may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) may be reduced to 100 mg/m² or 75 mg/m². In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some embodiments, the method for treating a solid tumor (*e.g.*, PDAC) described herein comprises one or more treatment cycle(s) of 28 days, wherein the anti-Gal9 antibody is administered to the subject on day 1, day 7, day 15, and day 21 (*i.e.*, once weekly (q1w)) at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.63 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 6.3 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg or any increment therein, via intravenous infusion 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, paclitaxel is administered to the subject at 125 mg/m² intravenously (*e.g.*, intravenous infusion). In some examples, gemcitabine is administered to the subject at 1000 mg/m² intravenously (*e.g.*, intravenous infusion). When needed, the dose of gemcitabine may be reduced to 800 mg/m² or 600 mg/m². Alternatively or in addition, the dose of paclitaxel (*e.g.*, nanoparticle albumin-bound paclitaxel) may be reduced to 100 mg/m² or 75 mg/m². In some embodiments, the anti-Gal9 antibody may be administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week. For example, the anti-Galectin-9 antibody is administered to the subject at a dose of 10 mg/kg once every week or at a flat dose of 650-700 mg once every week. Alternatively, the anti-Galectin-9 antibody is administered to the subject at a dose of 16 mg/kg once every week or at a flat dose of 1040-1120 mg once every week.

In some instances, Gal-9 antibody treatment may be initiated concomitantly with chemotherapy (*e.g.*, gemcitabine and nab-paclitaxel). Alternatively, Gal-9 antibody treatment may be initiated after a chemotherapeutic regimen (*e.g.*, gemcitabine and nab-paclitaxel) has already started. In some instances, Gal-9 antibody treatment is administered concomitantly with chemotherapy (*e.g.*, gemcitabine and nab-paclitaxel), and subsequently chemotherapy is discontinued. In some instances, in which the chemotherapy is stopped, administration of anti-

Gal-9 antibody treatment regimen may be continued.

In any of the above embodiments, the interval or cycle may be once every week. In any of the above embodiments, the interval or cycle may be once every 2 weeks. In some embodiments, the regimen may be once every 2 weeks for one cycle, once every 2 weeks for two cycles, once every 2 weeks for three cycles, once every 2 weeks for four cycles, or once every 2 weeks for more than four cycles. In some embodiments, the treatment may be once every 2 weeks for 1 to 3 months, once every 2 weeks for 3 to 6 months, once every 2 weeks for 6 to 12 months, or once every 2 weeks for 12 to 24 months, or longer.

In any of the above embodiments, the interval or cycle may be 3 weeks. In some embodiments, the regimen may be once every 3 weeks for one cycle, once every 3 weeks for two cycles, once every 3 weeks for three cycles, once every 3 weeks for four cycles, or once every 3 weeks for more than four cycles. In some embodiments, the treatment may be once every 3 weeks for 1 to 3 months, once every 3 weeks for 3 to 6 months, once every 3 weeks for 6 to 12 months, or once every 3 weeks for 12 to 24 months, or longer.

In any of the above embodiments, the interval or cycle may be 4 or more weeks. In some embodiments, the regimen is once every 4 or more weeks for one cycle, once every 4 or more weeks for two cycles, once every 4 or more weeks for three cycles, once every 4 or more weeks for four cycles, or once every 4 or more weeks for more than four cycles. In some embodiments, the treatment may be once every 4 or more weeks for 1 to 3 months, once every 4 or more weeks for 3 to 6 months, once every 4 or more weeks for 6 to 12 months, or once every 4 or more weeks for 12 to 24 months, or longer. In some embodiments, the treatment may be a combination of treatment at various time, e.g., a combination of 2 weeks, 3 weeks, 4 or more 4 weeks. In some embodiments, the treatment interval may be adjusted in accordance with the patient's response to treatment. In some embodiments, the dosage(s) is adjusted in accordance with the patient's response to treatment. In some embodiments, the dosages are altered between treatment intervals. In some embodiments, the treatment may be temporarily stopped. In some embodiments, anti-Galectin-9 therapy is temporarily stopped. In some embodiments, chemotherapy is temporarily stopped. In some embodiments, both are temporarily stopped.

In any of the combined treatment methods disclosed herein, the one or more chemotherapeutic agents (e.g., gemcitabine and nab-paclitaxel) and the anti-Galectin-9 antibody (e.g., G9.2-17 IgG4) may have the same day administration. In that case, the one or more chemotherapeutic agents can be administered to the subject prior to the administration of the anti-Galectin-9 antibody. In other examples, the one or more chemotherapeutic agents

(e.g., gemcitabine and nab-paclitaxel) and the anti-Galectin-9 antibody (e.g., G9.2-17 IgG4) may be administered to the subject on two consecutive days. The chemotherapeutic agents can be administered on the first day of dosing and the anti-Galectin-9 antibody can be administered on the following day.

5 In other instances, the checkpoint inhibitor such as any of the chemotherapeutic agents disclosed herein (e.g., gemcitabine and nab-paclitaxel) may be administered about 1-7 days (e.g., 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days) prior to administration of the anti-Galectin 9 antibodies disclosed herein such as G9.2-17.

10 In some examples, the anti-Galectin 9 antibody can be administered to a subject prior to administration of the chemotherapeutic agent. In other instances, the administration of the anti-Galectin 9 antibody and the administration of the chemotherapeutic agent are performed on two consecutive days. The anti-Galectin-9 antibody may be administered to the subject on the first day of dosing and chemotherapeutic agent can be administered to the subject on the subsequent day. In other instances, the anti-Galectin-9 antibodies disclosed herein, such as G9.2-17, may
15 be administered about 1-7 days (e.g., 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days) prior to administration of the chemotherapeutic agent, such as gemcitabine and nab-paclitaxel.

 In some embodiments, methods are provided herein, wherein an anti-gal-9 antibody is administered in combination with chemotherapy (e.g., gemcitabine and nab-paclitaxel), for improving the overall response (e.g., at 3, 6 or 12 months), e.g., as compared to a baseline level
20 prior to initiation of treatment. In some embodiments, methods are provided herein for achieving a complete response, a partial response or stable disease (e.g., as measured at 3 months, 6 months or 12 months, or at a later time according to RECIST or iRECIST criteria). Such a response can be temporary over a certain time period or permanent. In some
25 embodiments, the methods may improve the likelihood of a complete response, a partial response or stable disease (e.g., as measured at 3 months, 6 months or 12 months), e.g., as compared to a baseline level prior to initiation of treatment. Such a response can be temporary over a certain time period or permanent.

 In some embodiments, treating can result in longer survival or greater likelihood of survival, e.g., at a certain time, e.g., at 6 or 12 months or at a later time point.

30 In any of the methods described herein, partial response, stable disease, complete response, a partial response, stable disease, progressive disease, disease progressing (e.g., as measured at 3 months, 6 months or 12 months, or at a later time), can be assessed according to RECIST criteria or iRECIST criteria. A response to treatment, e.g., a treatment of a solid tumor as described herein, can be assessed according to RECIST or the RECIST 1.1 criteria and/or

irRC, irRECIST, iRECIST, imRECISTPDAC, as described in Eisenhower et al., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); European Journal Of Cancer 45 (2009) 228 – 247; or Borcoman et al., Annals of Oncology 30: 385–396, 2019; Nishino et al., Clin Cancer Res 2013; 19(14): 3936–3943, the contents of each
 5 of which is herein incorporated by reference in its entirety.

In some embodiments, methods are described herein to improve quality of life and symptom control as compared to baseline prior to initiation of treatment (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). In some embodiments, improvements can be measured on the ECOG scale described in Example 2 herein.

10 In some embodiments, the disclosure provides methods for reducing or maintaining tumor size in a subject, including a human subject, (e.g., as measured at 3 months, 6 months or 12 months, or at a later time) either permanently or over a minimum time period, relative to a baseline tumor size prior to initiation of the treatment in the subject, the method comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody
 15 as disclosed herein. In some embodiments, the disclosure provides methods for improving the likelihood of reducing or maintaining tumor size in a subject, including a human subject, either permanently or over a minimum time period, (e.g., as measured at 3 months, 6 months or 12 months, or at a later time), e.g., as compared to a baseline level prior to initiation of treatment. In some embodiments, the disclosure provides methods for reducing or maintaining a tumor
 20 burden, in a subject, including a human subject (e.g., as measured at 3 months, 6 months or 12 months, or at a later time), as compared to baseline levels prior to initiation of the treatment. Accordingly, in some embodiments, tumor size and/or burden is measured in regularly scheduled restaging scans (e.g., CT with contrast, MRI with contrast, PET-CT (diagnostic CT) and/or X-ray).

25 In some embodiments, methods are provided herein, for increasing the time to disease progression or increase the time in progression-free survival (e.g., as measured at 6 months), comprising administering an anti-gal-9 antibody in combination with chemotherapy (e.g. gemcitabine and nab-paclitaxel). In some embodiments, the methods can result in a greater likelihood of progression free survival (e.g., as measured at 3 months, 6 months or 12 months,
 30 or at a later time post initiation of treatment). In some embodiments, methods are provided herein for improving duration and depth of response according to RECIST 1.1 criteria, (e.g., as measured at 3 months, 6 months or 12 months, or at a later time post initiation of treatment), comprising administering an anti-gal-9 antibody in combination with chemotherapy (e.g. gemcitabine and nab-paclitaxel).

In some embodiments, the methods provided herein, wherein an anti-gal-9 antibody is administered in combination with chemotherapy (e.g., gemcitabine and nab-paclitaxel), may improve quality of life and/or improving symptom control (e.g., as measured at 1 month, 3 months, 6 months or 12 months, or at a later time using ECOG scale) as compared to baseline prior to initiation.

Alternatively or in addition, the anti-Galectin-9 antibody may be used in combination with a regimen comprising UGN-102, UGN-201, or UGN-302. In one embodiment, UGN-102, UGN-201, or UGN-302 are formulated in a hydrogel e.g., a reverse-thermal hydrogel technology-based hydrogel. In some examples, the anti-Galectin-9 antibody can be administered prior to UGN-102, UGN-201, or UGN-302. In some examples, the anti-Galectin-9 antibody can be administered concurrently with UGN-102, UGN-201, or UGN-302. In some examples, the anti-Galectin-9 antibody may be administered after UGN-102, UGN-201, or UGN-302.

(iv) Monitoring Treatment Responses

A patient's responses to any of the treatments disclosed herein may be monitored via routine practice or as disclosed herein.

In some embodiments, response to treatment can also be characterized by immunophenotype in blood and tumors, cytokine profile (serum), soluble galectin-9 levels in blood (serum or plasma), galectin-9 tumor tissue expression levels and pattern of expression by immunohistochemistry (tumor, stroma, immune cells), tumor mutational burden (TMB), PDL-1 expression (e.g., by immunohistochemistry), mismatch repair status, or tumor markers relevant for the disease (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). Non-limiting examples of such tumor markers include Ca15-3, CA-125, CEA, CA19-9, alpha fetoprotein. These parameters can be compared to baseline levels prior to initiation of treatment.

In any of the methods disclosed herein, the subject may be examined for one or more of the following features before, during, and/or after the treatment: (a) one or more tumor markers in blood 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 such as

5 PDAC may also be used.

Accordingly, in some embodiments, methods of modulating treatment conditions are contemplated herein based on one or more of the features disclosed herein.

In some embodiments, an increase in an overall immune response, e.g., an increase in an overall inflammatory immune response, is determined by a reduction in tumor weight, tumor

10 size or tumor burden or any RECIST criteria described herein. In some embodiments an increase in an overall immune response is determined by increased level(s) of one or more proinflammatory cytokine(s), e.g., including two or more, three or more, or a majority of proinflammatory cytokines (one or more, two or more, or a majority of anti-inflammatory and/or immune suppressive cytokines and/or one or more of the most potent anti-inflammatory

15 or immune suppressive cytokines either decrease or remain constant). In some embodiments an increase in an overall immune response is determined by increased levels of one or more of the most potent proinflammatory cytokines (one or more anti-inflammatory and/or immune suppressive cytokines including one or more of the most potent cytokines either decrease or remain constant). In some embodiments an increase in an overall immune response is

20 determined by decreased levels of one or more, including a majority of, immune suppressive and/or anti-inflammatory cytokines (the levels of one or more, or a majority of, proinflammatory cytokines, including e.g., the most potent proinflammatory cytokines, either increase or remain constant). In some embodiments, an increase in an overall immune response is determined by increased levels of one or more of the most potent anti-inflammatory and/or

25 immune suppressive cytokines (one or more, or a majority of, proinflammatory cytokines, including, e.g., the most potent proinflammatory cytokines either increase or remain constant). In some embodiments an increase in an overall immune response is determined by a combination of any of the above. Also, an increase (or upregulation) of one type of immune response parameter can lead to a corresponding decrease (or downregulation) in another type of

30 immune response parameter. For example, an increase in the production of certain proinflammatory cytokines can lead to the downregulation of certain anti-inflammatory and/or immune suppressive cytokines and *vice versa*.

(D) Modulating Immune Responses

In some embodiments, methods described herein, wherein a Gal-9 antibody is administered with a chemotherapy, e.g., gemcitabine and nab-paclitaxel, may modulate levels of immune cells and immune cell markers in the blood or in tumors. Such changes can be measured in patient blood and tissue samples using methods known in the art, such as

5 multiplex flow cytometry and multiplex immunohistochemistry. For example, a panel of phenotypic and functional PBMC immune markers can be assessed at baseline prior to commencement of the treatment and at various time point during treatment. **Table 2** lists non-limiting examples of markers useful for these assessment methods. Flow cytometry (FC) is a fast and highly informative method of choice technology to analyze cellular phenotype and

10 function and has gained prominence in immune phenotype monitoring. It allows for the characterization of many subsets of cells, including rare subsets, in a complex mixture such as blood, and represents a rapid method to obtain large amounts of data. Advantages of FC are high speed, sensitivity, and specificity. Standardized antibody panels and procedures can be used to analyze and classify immune cell subtypes. Multiplex IHC is a powerful investigative

15 tool which provides objective quantitative data describing the tumor immune context in both immune subset number and location and allows for multiple markers to be assessed on a single tissue section. Computer algorithms can be used to quantify IHC-based biomarker content from whole slide images of patient biopsies, combining chromogenic IHC methods and stains with digital pathology approaches.

20 **Table 2. PBMC phenotyping markers**

	PBMC phenotyping markers		PBMC phenotyping markers
CD3	Total T cells	CD16	NK cells
CD4	CD4+ T cells	CD11b	Monocytes/macrophages
CD8	CD8+ T cells	CD11c	Monocytes/macrophages, DCs
CD25	Treg activation	CD14	Monocyte subsets, macrophages
CD27	T cell maturation; B cell naïve/memory	CD33	Total myeloid cells
CD38	T cell maturation; B cell naïve/memory	FcεR1 a	Antigen presenting DC cells
CD45RA	Naïve/memory cells	CD19	Total B cells
CD45RO	Naïve/memory cells	T-bet	T cells subsets
CD56	NKT/NK cells (T cell subset)	gdTCR	Gamma delta T cells
CD127	T cell subsets	CD274 (PDL-1)	Checkpoint
CD152 (CLTA-4)	Checkpoint	Tim-3	Checkpoint
CD279 (PD-1)	Checkpoint	TCRVa24-Ja18	iNKT cells
FoxP3	Treg cells	Live/dead	General
HLA-DR	Activation/Antigen presentation	CD45	General

In some embodiments, the disclosure provides methods for modulating an immune

response (e.g., as measured at 3 months, 6 months or 12 months, or at a later time) in a subject, including a human subject, comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody as disclosed herein. In some embodiments, the disclosure provides methods for modulating levels of immune cells and immune cell markers, including but not limited to those described herein in **Table 2**, e.g., as compared to baseline levels prior to initiation of treatment, in the blood or in tumors of a subject, including a human subject, comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody as disclosed herein. In some embodiments, the overall result of modulation is upregulation of proinflammatory immune cells and/or down regulation of immune-suppressive immune cells.

Accordingly, in some embodiments, the methods described herein, wherein an anti-gal9 antibody is administered in combination with a chemotherapy, may modulate immune activation markers such as those in **Table 2**. In some embodiments, the methods described herein, wherein an anti-gal9 antibody is administered alone or in combination with a checkpoint inhibitor therapy, results in one or more of (1) an increase in more CD8 cells in plasma or tumor tissue, (2) a reduction in T regulatory cells (Tregs) in plasma or tumor tissue, (3) an increase in M1 macrophages in plasma or tumor tissue and (4) a decrease in MDSCs in plasma or tumor tissue, and (5) a decrease in M2 macrophages in plasma or tumor tissue (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). In some embodiments, the markers that are assessed using the techniques described above or known in the art are selected from CD4, CD8 CD14, CD11b/c, and CD25. These parameters can either be compared to baseline levels prior to initiation of treatment.

In some embodiments, treating as described herein results in changes in proinflammatory and anti-inflammatory cytokines. In some embodiments, methods are provided herein for one or more of (1) increasing levels of IFNgamma in plasma or tumor tissue; (2) increasing levels of TNFalpha in plasma or tumor tissue; (3) decreasing levels of IL-10 in plasma or tumor tissue (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). These parameters can be compared to baseline levels prior to initiation of treatment.

In some embodiments, changes in cytokines or immune cells may be assessed between a pre dose 1 tumor biopsy and repeat biopsy conducted at a feasible time. In some embodiments, changes in cytokines or immune cells may be assessed between 2 repeat biopsies. In some embodiments, methods are described herein of modulating levels one or more of soluble galectin-9 levels in blood (serum or plasma), or galectin-9 tumor tissue expression levels and pattern of expression by immunohistochemistry (tumor, stroma, immune cells),

(e.g., as measured at 3 months, 6 months or 12 months, or at a later time). In some embodiments, methods are described herein for decreasing of one or more of soluble galectin-9 levels in blood (serum or plasma), or in galectin-9 tumor tissue expression levels and pattern of expression by immunohistochemistry (tumor, stroma, immune cells) decrease. (e.g., as
5 measured at 2 weeks, 4 weeks, 1 month, 3 months, 6 months or 12 months, or at a later time). These galectin-9 levels can be compared to baseline levels prior to initiation of treatment. In some embodiments, measurements are taken at 2 months.

In some embodiments, methods are described herein for modulating levels of PD-L1 expression, e.g., as assessed by immunohistochemistry. In some embodiments, the disclosure
10 provides methods for modulating PDL-1 expression, e.g., as assessed by immunohistochemistry (e.g., as measured at 2 weeks, 4 weeks, 1 month, 3 months, 6 months or 12 months, or at a later time), comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody as disclosed herein. In some embodiments of the methods, PDL-1 expression, e.g., as assessed by immunohistochemistry, remains
15 unchanged. PD-L1 levels can either be compared to baseline levels prior to initiation of treatment. In some embodiments, the methods provided herein decrease PDL-1 expression, e.g., as assessed by immunohistochemistry. PD-L1 levels may be measured using routine methods known in the art. In one non-limiting example, PD-L1 (SP263) can be used for detection of PD-L1 in cancer tissues using immunohistochemistry. In some embodiments,
20 methods are provided herein for modulating one or more tumor markers (increase or decrease) relevant for the disease (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). Non-limiting examples of such tumor markers include Ca15-3, CA-125, CEA, CA19-9, alpha fetoprotein. These parameters can be compared to baseline levels prior to initiation of treatment. In some embodiments, the methods provided herein decrease the occurrence of one
25 or more tumor markers relevant for the disease.

In some embodiments, the disclosure provides methods for modulating PDL-1 expression, e.g., as assessed by immunohistochemistry (e.g., as measured at 2 weeks, 4 weeks,
1 month, 3 months, 6 months or 12 months, or at a later time), comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody as disclosed herein. In
30 some embodiments of the methods, PDL-1 expression, e.g., as assessed by immunohistochemistry, remains unchanged. PD-L1 levels can be compared to baseline levels prior to initiation of treatment. In some embodiments, the methods provided herein decrease PDL-1 expression, e.g., as assessed by immunohistochemistry.

In some embodiments, the disclosure provides methods for modulating one or more

biomarkers (increasing or decreasing) relevant for the disease (e.g., as measured at 2 weeks, 4 weeks, 1 month, 3 months, 6 months or 12 months, or at a later time), comprising administering to the subject a therapeutically effective amount of an anti-Galectin-9 antibody as disclosed herein. Levels of biomarkers in clinical tissues from patients can be measured using routine
5 methods, such as multiplex Immunofluorescence (mIF) technology, as described herein in the examples. An exemplary panel of biomarkers may include CD3, CD4, CD8, CD45RO, FoxP3, CD11b, CD14, CD15, CD16, CD33, CD68, CD163, HLA-DR, Arginase1, Granzyme B, Ki67, PD1, PD-L1, F4/80, Ly6G/C and PanCK.

These markers can be compared to baseline levels prior to initiation of treatment (e.g.,
10 at certain intervals, e.g., at 3 months, 6 months or 12 months). In some embodiments, cytokine profiles are modulated.

In some embodiments, the disclosure provides methods of modulating an immune response in a subject. The immune response may be T cell-mediated and/or B cell-mediated immune responses that are influenced by modulation of immune cell activity, for example, T
15 cell activation. In one embodiment of the disclosure, an immune response is T cell mediated. As used herein, the term “modulating” means changing or altering, and embraces both upmodulating and downmodulating. For example, “modulating an immune response” means changing or altering the status of one or more immune response parameter(s). Exemplary parameters of a T cell mediated immune response include levels of T cells (e.g., an increase or
20 decrease in effector T cells) and levels of T cell activation (e.g., an increase or decrease in the production of certain cytokines). Exemplary parameters of a B cell mediated immune response include an increase in levels of B cells, B cell activation and B cell mediated antibody production.

When an immune response is modulated, some immune response parameters may
25 decrease and others may increase. For example, in some instances, modulating the immune response causes an increase (or upregulation) in one or more immune response parameters and a decrease (or downregulation) in one or more other immune response parameters, and the result is an overall increase in the immune response, e.g., an overall increase in an inflammatory immune response. In another example, modulating the immune response causes
30 an increase (or upregulation) in one or more immune response parameters and a decrease (or downregulation) in one or more other immune response parameters, and the result is an overall decrease in the immune response, e.g., an overall decrease in an inflammatory response.

In some embodiments, methods are provided herein, comprising administering an anti-gal9 antibody in combination with a chemotherapy, for modulating soluble galectin-9 levels in

blood (serum or plasma), or galectin-9 tumor tissue expression levels and pattern of expression by immunohistochemistry (tumor, stroma, immune cells) in a subject, (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). Galectin-9 levels in a subject can be compared to baseline levels prior to initiation of treatment.

5 In some embodiments, methods are provided herein for decreasing of one or more of soluble galectin-9 levels in blood (serum or plasma), or in galectin-9 tumor tissue expression levels and pattern of expression by immunohistochemistry (tumor, stroma, immune cells) decrease. (e.g., as measured at 3 months, 6 months or 12 months, or at a later time).

10 In some embodiments, methods are provided herein, comprising administering an anti-gal9 antibody in combination with a chemotherapy, for modulating one or more tumor markers (increase or decrease) relevant for the disease (e.g., as measured at 3 months, 6 months or 12 months, or at a later time). Non-limiting examples of such tumor markers include Ca15-3, CA-125, CEA, CA19-9, alpha fetoprotein. These parameters can be compared to baseline levels prior to initiation of treatment.

15

Kits for Use in Combined Therapy of Solid Tumors

20 The present disclosure also provides kits for use in treating or alleviating a solid tumor, for example, PDA, CRC, HCC, or cholangiocarcinoma, and others described herein. Such kits can include one or more containers comprising an anti-Galectin-9 antibody, *e.g.*, any of those described herein (*e.g.*, G9.2-17(IgG4)), and optionally one or more chemotherapeutics (*e.g.*, a gemcitabine and/or paclitaxel) to be co-used with the anti-Galectin-9 antibody, which is also described herein.

25 In some embodiments, the kit can comprise instructions for use in accordance with any of the methods described herein. The included instructions can comprise a description of administration of the anti-Galectin-9 antibody, and the one or more chemotherapeutics, to treat, delay the onset, or alleviate a target disease as those described herein. In some embodiments, the kit further comprises a description of selecting an individual suitable for treatment based on
30 identifying whether that individual has the target disease, *e.g.*, applying the diagnostic method as described herein. In still other embodiments, the instructions comprise a description of administering an antibody to an individual at risk of the target disease.

The instructions relating to the use of an anti-Galectin-9 antibody and the one or more chemotherapeutics generally include information as to dosage, dosing schedule, and route of

administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical
5 storage disk) are also acceptable.

The label or package insert indicates that the composition is used for treating, delaying the onset and/or alleviating the solid tumor. In some embodiments, instructions are provided for practicing any of the methods described herein.

The kits of this invention are in suitable packaging. Suitable packaging includes, but is
10 not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (e.g., an atomizer) or an infusion device such as a minipump. In some embodiments, a kit has a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection
15 needle). In some embodiments, the container also has a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-Galectin-9 antibody as those described herein.

Kits may optionally provide additional components such as buffers and interpretive
20 information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container. In some embodiments, the invention provides articles of manufacture comprising contents of the kits described above.

General Techniques

25 The practice of the present invention are employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook, et al., 1989) Cold Spring Harbor Press; Oligonucleotide
30 Synthesis (M. J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J. E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R. I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J. P. Mather and P. E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J. B. Griffiths, and D. G. Newell, eds., 1993-8) J. Wiley and Sons; Methods in Enzymology (Academic Press,

Inc.); Handbook of Experimental Immunology (D. M. Weir and C. C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J. M. Miller and M. P. Calos, eds., 1987); Current Protocols in Molecular Biology (F. M. Ausubel, et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis, et al., eds., 1994); Current Protocols in Immunology (J. E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C. A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995).

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference for the purposes or subject matter referenced herein.

EXAMPLES

While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit, and scope of the present disclosure. All such modifications are intended to be within the scope of the disclosure.

Example 1. In Vivo Study of Anti-Galectin-9 Antibody in Combination with Chemotherapeutics for Cancer Treatment in a Pancreatic Cancer Mouse Model

Preclinical assessment of an anti-galectin-9 IgG4 fully human antibody (G9.2-17(IgG4)) for the treatment of difficult to treat solid tumors – as a single agent or in combination with other systemic chemotherapeutic anti-cancer modalities – was performed in a mouse model of pancreatic cancer.

The specific animal used was the orthotopic mPA6115 pancreatic cancer xenograft model in female C57BL/6 mice. To generate this model, first, tumors were sourced from mPA6115 mice, a mouse homograft model of pancreatic ductal adenocarcinoma (PDAC) that retains morphological similarity to human PDAC. The mPA6115 mouse strain carried the

conditional mutant Kras (Kras^{LSL-G12D/WT}), a constitutive deletion of Trp53 (P53KO/KO) and a Cre driven by the promotor of Pdx1 gene and developed severe PDAC tumors at the age of 8 weeks.

At that time, mPA6115 mice with palpable tumors were sacrificed, and their pancreatic tumors were collected. The collected tumor tissue was cut into small fragments (~2 mm³) and transplanted subcutaneously (SC) to the syngeneic recipients, C57BL/6 mice. These seed tumors were maintained subcutaneously in the C57BL/6 mice until the volume of seed tumor reached 700~1000 mm³. Once seed tumors reached the desired volume, the tumors were collected and cut into pieces of about 2 mm³ in diameter. Tumors then were washed with ice cold Roswell Park Memorial Institute (RPMI) 1640 medium (without serum) to remove the adjacent non-tumor tissues. Then the tumor pieces were placed in ice cold RPMI 1640 medium until orthotopic implantation. The same day that seed tumors were collected, 6-7 week old female C57BL/6 mice were subjected to pancreatic orthotopic implantation. Specifically, after animals were fully anesthetized, a small longitudinal incision below the left lower rib cage was made to expose the spleen and the pancreas underneath the spleen. One seed tumor piece per mouse was sewn into the pancreas with 6-0 silk suture. Then the tissue surrounding the tumor piece was sutured with 6-0 silk suture, and the tumor piece was wrapped with pancreas tissue. The abdomen was then closed with a 4-0 silk suture. After tumor implantation, animals were kept in a warm cage, and subsequently returned to the animal room after full recovery from the anesthesia.

On the day when implantation was performed, implemented mice were randomly grouped into 6 groups based on their body weight where randomization was performed based on the "Matched distribution" method (StudyDirector™ software, version 3.1.399.19). The date of randomization was denoted as day 0. Three days after implantation, animals began a dosing regimen according to group number. The dosing regimen for each group is provided below in **Table 3**.

Table 3. Study Dosing Schedule

Group No.	Treatment	Dose level (mg/kg)	Dosing Solution (mg/ml)	Dosing Volume (μL/g)	Route of Admin.	Dosing Frequency & Duration
1	Untreated	-	-	-	-	-
2	chemo vehicle control saline	-	-	10	i.p.	QW*5
3	Isotype IgG1 mouse	200 ug/mouse	2	100 μL/mouse	i.p.	Q4D*8

4	Anti-Gal9 mAb	200 ug/mouse	2	100 μL/mouse	i.p.	Q4D*14
5	Gemcitabine	50	5	10	i.p.	QW*6
	Abraxane	15	1.5	10	i.v.	QW*6
6	Anti-Gal9 mAb	200 ug/mouse	2	100 μL/mouse	i.p.	Q4D*16
	Gemcitabine	50	5	10	i.p.	QW*10
	Abraxane	15	1.5	10	i.v.	QW*10
7	10 non-tumor bearing mice for blood sampling					

i.p. = intraperitoneal; i.v. = intravenous; QW = once a week; Q4D = once every four days

- For these studies, an anti-galectin-9 mouse IgG1 was used. This antibody, referred to as Anti-Gal9 mAb, was the mouse IgG1 version of the human G9.2-17 antibody, which binds the same carbohydrate binding domain 2 (CRD2) on galectin-9 as G9.2-17 and has the same VH and VL regions as G9.2-17. Thus, resulting data using Anti-Gal9 mAb is correlative to human efficacy of G9.2-17. In addition to treating mice with only Anti-Gal9 mAb (group 4), groups 5 and 6 of implanted mice were also treated with a standard of care chemotherapy (a gemcitabine/abraxane regimen), or a combination of Anti-Gal9 mAb and chemotherapy.
- After pancreatic orthotopic implantation, the mice in groups 1-7 were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss, eye/hair matting and any other abnormalities. Body weights and tumor volumes measured twice per week after randomization using StudyDirector™ software (version 3.1.399.19). Measurements and monitoring were collected as described from day 0 until day 66 when the last mouse was found dead. Blood, plasma, spleen, and tumors were collected from each mouse at end of life. **Table 4** below shows the average life span of the mice by experiment group. The longest survival in all of the control arms (Groups 1, 2 and 3) was day 33, while the last mouse died on day 55, 41, and 66, in Group 4 (anti-galectin-9 IgG1), 5 (gemcitabine/abraxane), 6 (combination therapy), respectively.

Table 4. Average life span for mice per group

Group No.	Treatment	median, days	day, when the last mouse died/euthanized	mean survival day
Group 1	Untreated	27	33	27
Group 2	chemo vehicle control, saline	26	33	28

Group 3	Isotype IgG1 mouse	31	33	28
Group 4	Anti-Gal9 mAb	27	55	32
Group 5	Gemcitabine/ Abraxane	31	41	28
Group 6	Anti-Gal9 mAb/ Gemcitabine/ Abraxane	31	66	34

The primary endpoint of survival in animals engrafted with orthotopic KPC tumors was assessed by estimating survival curves for each group, considered separately, using the Kaplan-Meier method and compared statistically using the log rank test. Specifically, Kaplan-Meier survival curves/Log Rank test (SPSS 18) were used. The Kaplan-Meier survival curves and log rank test are shown in **Figs. 1A-1D**. Results of log rank test are provided in **Table 5**.

Table 5. Log rank test

Log rank test	Group No.	P value
Group 1 VS	2	0.663
	3	0.233
	4	0.069
	5	0.134
	6	0.051
Group 2 VS	3	0.826
	4	0.091
	5	0.515
	6	0.156
Group 3 VS	4	0.094
	5	0.791
	6	0.193
Group 4 VS	5	0.349
	6	0.733
Group 5 VS	6	0.220

*, p<0.05; **, p<0.01; ***, p<0.001; ns, p≥0.05

Cox-regression analysis (coxph function of survival R package) was used to calculate hazard ratios (HR) and their 95% confidence interval (%95CI) of group 4-6 against group 1, group 2 and group 3 respectively. We also used cox-regression analysis to calculate hazard ratios (HR) and their 95% confidence interval (%95CI) of group 5 and 6 against group 4.

- 5 Finally, we used cox-regression analysis to calculate hazard ratio (HR) and its 95% confidence interval (%95CI) of group 6 against group 5. Results of the cox regression analysis are shown in **Fig. 2** and **Table 6**.

Table 6. Cox regression analysis

Group	Compared against	p. value	HR	HR (95% CI)
Group 4	Group 1	0.017	0.348	(0.146 , 0.83)
Group 5	Group 1	0.262	0.624	(0.274 , 1.422)
Group 6	Group 1	0.015	0.336	(0.14 , 0.806)
Group 4	Group 2	0.052	0.427	(0.181 , 1.009)
Group 5	Group 2	0.525	0.767	(0.339 , 1.738)
Group 6	Group 2	0.045	0.413	(0.173 , 0.982)
Group 4	Group 3	0.091	0.477	(0.202 , 1.125)
Group 5	Group 3	0.707	0.856	(0.379 , 1.932)
Group 6	Group 3	0.079	0.460	(0.193 , 1.094)
Group 5	Group 4	0.166	1.795	(0.784 , 4.109)
Group 6	Group 4	0.933	0.966	(0.424 , 2.198)
Group 6	Group 5	0.149	0.538	(0.232 , 1.248)
Group 2	Group 1	0.615	0.813	(0.364 , 1.818)
Group 3	Group 1	0.445	0.730	(0.325 , 1.639)
Group 3	Group 2	0.790	0.897	(0.402 , 2.002)

*, p<0.05; **, p<0.01; ***, p<0.001; ns, p≥0.05

For the cox regression analysis that used group 1 as the reference, group 4 and group 6 had significant lower hazard ratio than group 1, whereas group 2 and group 3 did not have significant different hazard ratios with group 1. In the cox regression analysis that used group 2 as the reference, group 6 had a significant lower hazard ratio than group 2; however, group 3 did not have significant different hazard ratios with group 2. For the cox regression analysis that used group 3 as the reference, groups 4, 5, and 6 did not have significant different hazard

ratios with group 3. In the cox regression analysis that used group 4 as the reference, groups 5 and 6 did not have significant different hazard ratios with group 4. Finally, the cox regression analysis that used group 5 as the reference showed that group 6 did not have significant different hazard ratios with group 5.

5 These data demonstrated that the combination of the anti-galectin-9 antibody and gemcitabine/abraxane is well tolerated, can be administered over prolonged periods of time (max administered 16 doses for the anti-galectin-9 IgG1 antibody (mouse IgG1 version) and 10 doses for gemcitabine/abraxane), and delivered survival benefit over untreated animals (Group 6 vs Group 1: Cox analysis, HR=0.336, HR(95%CI)= (0.14 , 0.806), p=0.015; as well as p = 0.051 LogRank test for mean survival). Anti-galectin-9 IgG1 alone delivered survival benefit over untreated animals (Group 4 vs Group 1: Cox analysis, HR=0.348, HR(95%CI)= (0.146 , 0.83), p=0.017).

15 No tumor was found in the pancreas from the last mouse in Group 6 on day 66 when the mouse was found dead, terminating the study. Based on the historical data, the take rate of orthotopic mPA6115 model in vehicle groups were 100%. As such, the last mouse in Group 6 was a complete responder to the combination anti-galectin-9/gemcitabine/abraxane regimen.

20 Body weights were measured in mice engrafted with orthotopic KPC tumors twice per week after implantation/randomization (day 0) until all mice were euthanized or died. **Fig. 3** shows the body weight measurements collected for the duration of the study period measured by using StudyDirector™ software (version 3.1.399.19). The last mouse in Group 4 was moribund and euthanized on day 55 with the tumor weight of 2544.6 mg (TV=1877.07 mm³). From day 51 to 55, there was only one last mouse in Group 4 with body weight change from 12.36% to -2.25% compared with the weight at the first day of treatment. The body weight loss was most likely be correlated to the condition induced by tumor growth.

25 Overall, the data in this example confirmed the safety and efficacy of the anti-galectin-9 regimen and the combination anti-galectin-9/gemcitabine/abraxane regimen in the orthotopic Pancreatic Cancer Xenograft Model mPA6115.

Example 2: A Phase 1/2 Open-label, Multi-center Study of the Safety, Pharmacokinetics, and Anti-tumor Activity of Anti-Galectin-9 Monoclonal Antibody Alone and in Combination with Chemotherapy in Patients with Metastatic Solid Tumors

30 Galectin-9 is a molecule overexpressed by many solid tumors, including those in pancreatic cancer, colorectal cancer, and hepatocellular carcinoma. Moreover, Galectin-9 is expressed on tumor-associated macrophages, as well as intra-tumoral immunosuppressive

gamma delta T cells, thereby acting as a potent mediator of cancer-associated immunosuppression.

5 G9.2-17 (IgG4) is a fully human IgG4 monoclonal antibody (mAb) targeting galectin-9 (-gal-9) protein. Gal-9 functions as an immuno-suppressor, conferring immune privilege to tumor cells and disabling immune mediated cancer attack by regulating macrophages, T-cells, myeloid derived suppressor cells as well as cancer cell susceptibility to cytotoxic T-cell-induced death. Based on the available data, G9.2-17 (IgG4) blockade of gal-9 interferes with the immunosuppressive functions of gal-9 resulting in effective immune activation and tumor growth inhibition across multiple preclinical models.

10 Gal-9 can be overexpressed and/or secreted in many solid tumor types including pancreatic adenocarcinoma, cholangiocarcinoma (CCA), colorectal cancer (CRC), breast cancer, bladder cancer, ovarian cancer, non-small cell and small cell lung cancer, nasopharyngeal cancer, malignant melanoma, ovarian cancer etc., and high levels of tissue and/or circulating gal-9 correlate with aggressive tumor features and adverse survival outcome.

15 Therefore, the target indications of G9.2-17 (IgG4) are relapsed or refractory, metastatic solid tumors, where G9.2-17 (IgG4) is investigated both as a single agent and in combination with a checkpoint inhibitor (a programmed cell death 1 [PD 1] antibody).

Dose escalation (Part 1) is conducted in all common solid tumors types in order to establish the safety and tolerability profile of G9.2-17 (IgG4), assess its immunogenicity potential, establish the pharmacokinetic (PK) and pharmacodynamic (PD) profile, and arrive at the recommended Phase 2 dose (RP2D). This may be the maximal tolerated dose (MTD). The expansion cohorts (Part 2) are planned in: first line metastatic pancreatic ductal adenocarcinoma (PDAC), in combination with gemcitabine/nab-paclitaxel; as well as CRC and CCA, e.g., as a single agent.

25 No other therapies targeting gal-9 are currently known to be approved or in clinical trials for any indication.

In nonclinical studies conducted to-date, no significant toxicities have been observed at doses that are ~500-fold above those intended for human administration. Furthermore, G9.2-17 (IgG4) has been shown to be highly specific for gal-9 and has been demonstrated to be efficacious in multiple animal models of cancer. The patient populations targeted for enrollment are at late stages in their disease and have failed at standard of care treatments prior to enrollment in this study. G9.2-17 (IgG4), either taken alone or in combination with one or more chemotherapeutic agents such as gemcitabine and paclitaxel as disclosed herein would be expected to benefit treatment of malignant tumors such as malignant solid tumors.

Objectives and Endpoints**Part 1: Dose Escalation**

OBJECTIVES	ENDPOINTS
Primary	
To establish the safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) for G9.2-17 (IGG4)	- Evaluation of safety parameters including adverse events, vital sign measurements, clinical safety laboratory tests, 12-lead ECG, echocardiography/cardiac ultrasound (ECHO), physical examinations - Evaluation of dose-limiting toxicities (DLTs) - Determination of RP2D
Secondary	
To characterize the pharmacokinetic (PK) profile of G9.2-17 (IgG4)	Evaluation of PK parameters of G9.2-17 (IGG4) (including but not limited to area under the curve from time zero until 336 h [AUC_{0-336h}], maximum observed serum concentration [C_{max}], time to reach C_{max} [T_{max}], estimated half-life [$t_{1/2}$])
To assess the pharmacodynamics (PD) of G9.2-17 (IGG4)	- Peripheral blood mononucleocyte (PBMC) immunophenotyping by flow cytometry - Pre-specified cytokine profile (serum) by ELISA - Soluble gal-9 levels in blood (serum) by ELISA - Gal-9 tumor tissue expression levels, and pattern of expression by IHC (expression on tumor cells and immune cells as well as a combined score) - Tumor tissue multiplex immunophenotyping - Programmed death ligand-1 (PD-L1) expression by IHC - Mismatch repair (MMR) status by IHC
To assess the immunogenicity of G9.2-17 (IgG4)	Evaluation of ADA
Exploratory	
To evaluate preliminary efficacy of G9.2-17 (IgG4)	- Evaluation of confirmed objective response rate (ORR) - Evaluation of disease control rate (DCR) - Evaluation of duration of response (DoR) - Evaluation of progression-free survival (PFS) - Evaluation of overall survival (OS)

5 **Part 2: Cohort Expansion**

Objectives	Endpoints
Primary	
To establish the safety and tolerability of G9.2-17 (IgG4) as single treatment and in combination with gemcitabine/nab-paclitaxel	Evaluation of safety parameters including adverse events, vital sign measurements, clinical safety laboratory tests, 12-lead ECG, ECHO, physical examinations

	• Evaluation of DLTs
To assess the ORR in patients with CRC or CCA treated with G9.2-17 (IgG4) alone	Evaluation of the confirmed ORR-3 in patients with CRC or CCA
To assess PFS in patients with PDAC treated with G9.2-17 (IgG4) in combination with gemcitabine/nab-paclitaxel	Evaluation of PFS-6 in patients with PDAC
Secondary	
To characterize the pharmacokinetic (PK) profile of G9.2-17 (IgG4)	Evaluation of PK parameters of G9.2-17 (IgG4)
To assess the pharmacodynamics (PD) of G9.2-17 (IgG4)	• PBMC immunophenotyping by flow cytometry • Cytokine profile (serum) by ELISA • Soluble gal-9 levels in blood (serum) by ELISA • Gal-9 tumor tissue expression levels, and pattern of expression by IHC (expression on tumor cells and immune cells as well as a combined score) • Tumor tissue multiplex immunophenotyping • PD-L1 expression by IHC • MMR status by IHC • TMB in tissue
To assess the immunogenicity of G9.2-17 (IGG4)	Evaluation of ADA
To evaluate efficacy of G9.2-17 (IgG4)	• Confirmed ORR • PFS • DCR • DoR • OS

Study Design

5 This is an open-label, uncontrolled, multicenter Phase 1/2 study with a dose escalation phase (Part 1) and a cohort expansion phase (Part 2) in patients with relapsed/refractory metastatic solid tumors. This study is conducted at up to 20 sites in the United States. The study duration is estimated to be 12-24 months. Follow-up for survival continues for up to 2 years. A study schema is presented in **Fig. 4**.

Treatment Duration and Treatment Periods

Treatment Duration

Study drug administration continues until progression of disease, unacceptable toxicity, or withdrawal from the study. Patients who discontinue the study drug prior to disease progression and are not being treated with other systemic anti-cancer therapy(ies), are followed on the study until the time of disease progression.

5 Treatment Periods

The study consists of the following periods in both Part 1 and Part 2:

Screening period: up to 4 weeks prior to first dose (Day -28 to Day -1)

Treatment period: 28-day treatment cycles as presented in the Schedule of Assessments (SoA; **Table 13** and **Table 14**)

10 Post-treatment period: 30 days after last treatment (End of Treatment Visit/Early Termination Visit)

Follow-up period: Long-term follow-up for up to 2 years (visits every 3 months) for patients discontinuing treatment due to reasons other than progression of disease, and not receiving additional systemic anticancer treatments

15

Part 1: Dose Escalation Phase

A dose-finding study is conducted using a continuous reassessment method (CRM) (O'Quigley et al., 1990) to establish DLTs and the RP2D. Two to six patients per treatment cohort 1-6 are assigned to receive sequentially higher IV injections of G9.2-17 (IgG4) every two weeks (Q2W) on Day 1 and Day 15 of each 28-day cycle, starting at a dose of 0.2 mg/kg. Patients assigned to a specific dose escalation cohort receive the corresponding study dose for that cohort. They receive study drug at one of 8 dose levels until progression of disease, unacceptable toxicity, or withdrawal from the study for other reasons. Patients who withdraw for reasons other than toxicity or tolerability issues during the first treatment cycle only are replaced.

25

For cohorts 1-6, two patients at a time are dosed under the CRM design. Dose escalations are based on analysis of patient safety data focusing on occurrences of DLTs at previous dose levels and other relevant safety and dosing data from previous cohorts. Dose escalations may occur after a minimum of 28 days (1 cycle). No dose level skipping is allowed.

30

Following the completion of cohort 6 under the CRM design, a once weekly (QW) G9.2-17 (IgG4) dosing schema is evaluated, provided the RP2D has not been reached within the CRM design. Cohorts 7 and 8 are not evaluated with the CRM design. Patients are only allowed to enter Cohort 7 once no DLT has been identified.

For cohorts 7 and 8, four patients at a time are dosed per cohort. Four patients per dose level in cohorts 7 and 8 are assigned to receive sequentially higher IV injections of G9.2-17 (IGG4) every week (QW) on Days 1, 8, 15, and 22 of each 28-day cycle. Starting with the first four patients in cohort 7, dose escalations to the next cohort only occur if no DLTs are identified. If a single DLT is documented in cohort 7, no further patients are dosed within that cohort and cohort 8 is not activated.

Part 1, cohorts 1-8 enroll approximately 36 patients. A total of 6 dosage levels are evaluated within the CRM design:

- Dose Escalation Cohort 1 = 0.2 mg/kg Q2W
- Dose Escalation Cohort 2 = 0.63 mg/kg Q2W
- Dose Escalation Cohort 3 = 2 mg/kg Q2W
- Dose Escalation Cohort 4 = 6.3 mg/kg Q2W
- Dose Escalation Cohort 5 = 10 mg/kg Q2W
- Dose Escalation Cohort 6 = 16 mg/kg Q2W

Additional 2 dosage levels are included for the consideration of RP2D:

- Dose Escalation Cohort 7 = 10 mg/kg QW
- Dose Escalation Cohort 8 = 16 mg/kg QW

Patients treated in early cohorts prior to identification of the RP2D are allowed to dose escalate up to the highest dose level cleared. After a complete cycle, dose escalations may occur after a minimum of 28 days (1 cycle). Dose escalations may not occur in the middle of a cycle. Patients can continue to dose escalate to the highest approved dose level until they are discontinued for toxicity or disease progression, or for other reasons (e.g., a patient elects to discontinue from the study).

Dose escalations are based on the development of DLTs in patients treated at previous dose levels. For each dose cohort, prior DLT probabilities are specified from GLP-compliant toxicity studies as well as from preclinical models. For the specified target DLT rate and total number of dose levels, the skeleton for a power model $d^{\exp(a)}$ is generated according to the approach of Lee and Cheung, using a prior MTD adjusted by PK/PD data, located at the median dose level and a spacing measure of $\delta = 0.05$ (Lee and Cheung, 2011). The prior distribution on the parameter “a” has a mean zero normal distribution with the least informative prior variance. The trial is stopped for safety if the lower limit of an Agresti and Coull binomial

confidence interval (CI) for the lowest study dose level exceeds the target DLT rate (Agresti and Coull, 1998). The RP2D is the MTD dose derived from Part 1.

If a DLT occurs in any patient during the first 28 days of treatment, that patient is permanently discontinued from study drug administration.

- 5 For patients who experience toxicities (including IMARs) outside of the DLT window, dose reduction is allowed only if clinical benefit is expected and may continue to be derived with lower doses of G9.2-17 (IgG4). The dose of G9.2-17 (IgG4) is initially reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in **Table 7**. No further dose reductions are allowed.

10

Table 7. Recommended Dose Modifications for G9.2-17 (IgG4) (AEs outside the DLT window and other than IMARs)

Adverse Reaction	Severity	G9.2-17 (IgG4) Dose Modification
Non-hematologic and hematologic toxicities	≥Grade 4	Permanently discontinue treatment with G9.2-17 (IgG4).
Hematologic toxicities	Grade 3	- Withhold treatment until toxicity resolves to ≤ Grade 2. - Resume G9.2-17 (IgG4) at 50% reduction from previous dose. - If recurs again at ≥ Grade 3 severity, hold until resolved to ≤ Grade 2 and implement a further 50% dose reduction. - No further dose reductions are allowed.
- Non-hematologic toxicities (except those listed in Appendix 4, Management of Immune-Mediated Adverse Reactions (IMARs) Caused by G9.2-17 (IgG4))	Grade 3	- Withhold treatment until toxicity resolves to ≤ Grade 2. - Resume G9.2-17 (IgG4) at 50% reduction from previous dose. - If recurs again at ≥ Grade 3 severity, hold until resolved to ≤ Grade 2 and implement a further 50% dose reduction. - No further dose reductions are allowed.
Gastrointestinal (Nausea, Vomiting)	- Grade 3 - Not requiring hospitalization or parenteral nutrition support; managed by supportive care	- Withhold G9.2-17 (IgG4) until toxicity reverses to ≤ Grade 2 - Resume G9.2-17 (IgG4) with no dose reduction
Electrolyte Abnormalities	Grade 3 corrected to ≤ Grade 2 within 24 hours	If recurrent, withhold G9.2-17 (IgG4) until toxicity reverses to ≤ Grade 2
- Electrolyte Abnormalities	≥Grade 3 lasting <24-72 hours - Not clinically complicated; resolves spontaneously or responds to conventional medical interventions	- Then resume G9.2-17 (IgG4) at a 50% reduction from the previous dose - If recurrent, withhold G9.2-17 (IgG4) until toxicity reverses to ≤ Grade 2 - Resume G9.2-17 (IgG4) at an additional 50% dose reduction

Adverse Reaction	Severity	G9.2-17 (IgG4) Dose Modification
Amylase or Lipase Elevation	• $\geq$ Grade 3 • Not associated with symptoms or clinical manifestations of pancreatitis	• No further dose reductions are allowed

Part 1 completion

Part 1 is completed when up to six patients have received the dose that has been identified as RP2D. The RP2D is based, in part, on the continual reassessment method (CRM) study design, PK and PD data parameters, additional safety and efficacy data and any other factors to be considered.

Backfill cohorts

The purpose of backfill cohorts is to assess the safety, tolerability, and the biological effect of G9.2-17 (IGG4) in patients whose tumors are gal-9 positive. The gal-9 status of the RP2D cohort is retrospectively determined. If fewer than 6 patients with gal-9 positive tumors are treated at the RP2D, patients designated for the backfill cohort require prospective assessment of gal-9 tumor status by IHC. Up to 6 additional patients, whose tumors are gal-9 positive, may be enrolled to backfill cohorts at the RP2D dose level.

Part 2: Cohort Expansion Phase

The second part of the protocol adopts a Simon's two-stage optimal design and includes approximately 223 patients. It is planned to expand cohorts for PDAC, CRC and CCA and/or potentially other solid tumor types which are based on implementing tumor-specific consideration for expansion cohorts and clinical trial endpoints. The rationale behind this approach is to ensure recruitment feasibility, as well as to capture the clinical need for specific indications.

CRC and CCA patients receive one of two treatments (4 treatment arms total):

- G9.2-17(IgG4) as a single agent

PDAC patients receive G9.2-17 (IGG4) in combination with gemcitabine/nab-paclitaxel.

For all patients receiving a combination treatment (gemcitabine/nab-paclitaxel + G9.2-17 (IgG4)), treatments can be administered on the same day. Gemcitabine/nab-paclitaxel should be administered prior to G9.2-17 (IgG4). If for any reason same-day administration cannot be accomplished, gemcitabine/nab-paclitaxel should be administered on the first day, and G9.2-17 (IgG4) on the subsequent day.

Patients with CRC and CCA

Treatment of single agent cohorts or combination agent cohorts for CRC and CCA patients may be executed in parallel.

G9.2-17 (IgG4) single treatment

5 The starting dose of G9.2-17 (IgG4) in the single treatment is the RP2D identified in Part 1. For the CRC and CCA single treatment arms, the optimal two-stage design (Stages I and II) are used to test the null hypothesis that the ORR3 is $\leq 5\%$ versus the alternative hypothesis that the ORR3 is $\geq 15\%$ within the single-agent arms.

10 After testing the investigational drug on 23 patients in Stage I, this trial arm is terminated if ≤ 1 patient responds. If the trial goes on to the Stage II of Simon's optimal design, approximately 33 patients are treated additionally in each of the single-agent arms. If the total number of responding patients is ≤ 5 , the investigational drug within that arm is rejected. If ≥ 6 patients have a confirmed ORR 3, the Part 3 expansion cohort for that arm is activated and described in an amendment to the protocol.

15 Dose reduction is allowed only if the clinical benefit is expected and may continue to be expected to derive with lower doses of G9.2-17 (IgG4). The dose of G9.2-17 (IgG4) is initially reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in the protocol. No further dose reductions are allowed.

20 Patients with PDAC

 The Part 2 cohort for patients with metastatic PDAC entails combination treatment of G9.2-17 (IgG4) and gemcitabine/nab-paclitaxel in the first line metastatic setting.

 The dose of G9.2-17 (IgG4) is the RP2D-1 dose, which is the dose level in the cohort immediately preceding the RP2D dose identified in Part 1. To ensure patient safety, a safety
25 run-in is performed in which the first 8 patients are dosed and that arm is continued only if ≤ 2 patients develop a DLT, which is below the target toxicity level (TTL) of 25%. If 3 or more patients develop a DLT, this combination treatment arm is terminated. In this combination treatment run-in cohort, patients who withdraw for reasons other than toxicity or tolerability issues during the first treatment cycle only are replaced. If a DLT occurs, in any of the 8 safety
30 run in patients, during the first 28 days of treatment, that patient is permanently discontinued from study drug administration.

 For patients who experience toxicities outside of the DLT window, dose reduction is allowed when clinical benefit is expected and may continue to be derived with lower doses of G9.2-17 (IgG4). The dose of G9.2-17 (IgG4) is initially reduced by 50%, and potentially by a

further 50%. No further dose reductions are allowed. Dose modifications of gemcitabine and/or nab-paclitaxel are allowed.

If an IMAR occurs/recurs that is not managed by dose reduction of either agent, both study medications must be discontinued.

- 5 The primary efficacy endpoint is patient PFS6. In the 1st line metastatic setting using gemcitabine/nab-paclitaxel, the PFS6 was reported to be 50% (von Hoff et al., 2013). After testing the G9.2-17 (IGG4)/chemotherapy combination in 11 patients in the first stage of the Simon two-stage design, the trial is terminated if 6 or fewer patients exhibit $PFS \geq 6$ months. If the trial goes on to the second stage of the Simon's two-stage design, approximately 14 patients
10 are treated additionally. If the total number of responding patients with PFS-6 is ≤ 16 , the study arm is rejected.

Part 2 completion

- Completion of Part 2 is dependent upon patient ORR 3 for CRC and CCA patients, and
15 PFS 6 for PDAC.

Part 3: Expansion

- If a promising efficacy signal is identified within one or more of the trial arms that is attributable to the tumor type, an expansion cohort is launched to confirm the finding as
20 described above. The sample size for each of the expansion arms is determined based on the point estimates determined in Part 2, in combination with a predetermined level of precision for the 95% CI around the ORR/OS and PFS. A protocol amendment is submitted with details around the expansion population, treatment regimen, and statistical analysis plan prior to initiating Part 3.

25

Dose-limiting Toxicity Criteria

- Dose-limiting toxicities assessed in this trial are defined as a clinically significant hematologic and/or non-hematologic AE or abnormal laboratory value assessed as unrelated to metastatic tumor disease progression, intercurrent illness, or concomitant medications and is
30 possibly related or related to the study drug and occurring during the first cycle (28 days) on study. Any patient that experiences a DLT in Part 1 or Part 2 during the first 28 days of treatment is permanently discontinued from study drug administration.

A DLT is a toxicity that meets any of the following criteria:

- Any death not clearly due to the underlying disease or extraneous causes

- Indications of potential drug induced liver injury (Hy's Law cases) as follows:
 - o ALT or AST >3 x the upper limit of normal (ULN) with confirmation by repeat testing 24 hours later, AND
 - o Serum total bilirubin (TBL) > 2 x ULN with confirmation by repeat testing 24 hours later
 - o No other explanation can be found for the elevated TBL and/or ATs, such as viral hepatitis (A, B or C), alcoholic or autoimmune hepatitis, pre-existing or acute liver disease, gall bladder obstruction or bile duct disease, Gilbert syndrome, disease progression, or another medication capable of causing the observed effect.
- All Grade 4 non-hematologic and hematological toxicities of any duration
- All Grade 3 non-hematologic and hematological toxicities. Exceptions are as follow:
 - o Grade 3 nausea, vomiting and diarrhea that does not require hospitalization or total parenteral nutrition support and can be managed with supportive care to $\leq$ Grade 2 within 48 h.
 - o Grade 3 electrolyte abnormalities that are corrected to $\leq$ Grade 2 within 24 h.
 - o Grade 3 electrolyte abnormality that lasts <24 -72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
 - o $\geq$ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.

25 ***End of Study Definition***

End of study for Part 1 of the study is defined at the point when the RP2D has been identified and all patients have been treated with G9.2-17 (IGG4) until confirmed disease progression.

- 30 End of study for Part 2 of the study is defined for each of the three tumor types following the completion of Simon's two-stage optimal design and all enrolled patients have been treated with G9.2-17 (IGG4) (alone or in combination) until confirmed disease progression.

In both Part 1 and Part 2 patients are followed for OS for up to 2 years following the last dose of G9.2-17 (IgG4) if they discontinue treatment due to reasons other than progression of disease and they not receiving additional systemic anticancer treatments.

The end of the study is defined as the date of the last patient's last visit.

5

Trial Stopping Rules

Part 1

The trial is stopped for safety if the lower limit of an Agresti and Coull binomial CI for the lowest study dose level exceeds the target DLT rate (Agresti and Coull, 1998).

10

Part 2

After testing the investigational drug on 23 patients in Stage I of Simon's optimal design for CRC and CCA single treatment arms, the respective trial arm is stopped if ≤ 1 patient responds. If the trial goes on to the Stage II of Simon's optimal design, a trial arm is stopped if the total number of responding patients is ≤ 5 within that arm.

15

For the PDAC G9.2-17 (IgG4) + gemcitabine/nab-paclitaxel combination treatment arm, Simon's optimal design guides trial stopping as well. After testing the G9.2-17 (IgG4)/chemotherapy combination on 11 patients in Stage I, the trial arm is stopped if ≤ 6 patients exhibit PFS ≥ 6 months. If the trial goes on to Stage II, the trial arm is stopped if the total number of responding patients with PFS of ≥ 6 months is ≤ 16 .

20

To ensure patient safety in both combination treatment arms, a safety run-in is performed in which the first 8 patients are dosed. For each cancer type (*e.g.*, CCA, CRC, and/or PDAC) enrollment continues only if ≤ 2 patients develop a DLT, which is below the target toxicity level (TTL) of 25%. If 3 or more patients with a given cancer type develop a DLT in a combination treatment arm, enrollment for that cancer type in that arm is terminated.

25

Study Population

Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

30

Part 1 and Part 2

1. Written Informed Consent (mentally competent patient, able to understand and willing to sign the informed consent form)
2. Age ≥ 18 years, male or non-pregnant female

3. Histologically confirmed unresectable metastatic cancer (adenocarcinomas and squamous cell carcinomas allowed). Patients with resectable disease are excluded.
4. Able to comply with the study protocol
5. Life expectancy > 3 months
- 5 6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
7. Coronavirus SARS-CoV-2 (COVID-19) negative patients
8. Patient able and willing to undergo pre- and on/post-treatment biopsies. The planned biopsies should not expose the patient to substantially increased risk of complications. Every effort is made that the same lesion is biopsied on repeat biopsies.
- 10 9. Measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Note that lesions intended to be biopsied should not be target lesions.
- 10 Adequate hematologic and end organ function, defined by the following laboratory results obtained prior to first dose of study drug treatment:
 - a. neutrophil count $\geq 1 \times 10^9/L$
 - 15 b. platelet count $\geq 100 \times 10^9/L$; for hepatocellular carcinoma (HCC) in Part 1 $\geq 50 \times 10^9/L$
 - c. hemoglobin ≥ 9.0 g/dL without transfusion in the previous week
 - d. creatinine $\leq 1.5 \times$ upper limit of normal (ULN)
 - e. aspartate aminotransferase AST (SGOT) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or
 - 20 hepatic metastases are present)
 - f. alanine aminotransferase (ALT [SGPT]) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or hepatic metastases present)
 - g. bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's disease may have a bilirubin $\leq 3.0 \times$ ULN)
 - 25 h. albumin ≥ 3.0 g/dL
 - i. international normalized ratio (INR) and partial thromboplastin time (PTT) $\leq 1.5 \times$ ULN
 - j. amylase and lipase $\leq 1.5 \times$ ULN
11. No evidence of active infection or infections requiring parenteral antibiotics, and no
- 30 serious infection within 4 weeks before study start
12. Women of child-bearing potential must have a negative pregnancy test within 72 h prior to start of treatment. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use contraceptive methods that result in a

failure rate of < 1% per year during the treatment period and for at least 180 days after the last study treatment.

- A woman is of childbearing potential if she is post-menarche, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.

13. Four (4) weeks or 5 half-lives (whichever is shorter) since the last dose of anti-cancer therapy before the first G9.2-17 (IgG4) administration

14. Continuation of bisphosphonate treatment (*e.g.*, zoledronic acid) or denosumab for bone metastases, which have been stable for at least 6 months before C1D1, is allowed

15. Biliary or gastric outlet obstruction allowed, provided it is effectively drained by endoscopic, operative, or interventional means

16. Pancreatic, biliary, or enteric fistulae allowed, provided they are controlled with an appropriate non-infected and patent drain (if any drains or stents are in situ, patency needs to be confirmed before study start)

Additionally, for Part 1 only:

17. Patients:

a. who have already received at least one prior line of systemic therapy for metastatic disease, or

b. who have a tumor type for which there are no available standard of care options.

Additionally, for Part 2 only:

18. PDAC expansion cohort: 1st line metastatic patients who are either gemcitabine-containing regimen naïve or at least 3 months out of having been treated using a

gemcitabine-containing regimen previously in a neoadjuvant or adjuvant/locally advanced setting

19. CRC and CCA expansion cohorts – patients who have received at least one prior line of therapy in the metastatic setting

5

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patient unwilling or unable to follow protocol requirements
2. Patient diagnosed with metastatic cancer of an unknown primary
- 10 3. Prior or current illicit drug addiction (medical and recreational marijuana/cannabidiol (CBD)/Tetrahydrocannabinol (THC) would not be considered “illicit”)
4. Clinically significant, active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease). Prophylactic or therapeutic use of anticoagulants is allowed.
- 15 5. Pregnant and/or lactating females
6. Receiving any other investigational agents or participating in any other clinical trial involving another investigational agent for treatment of solid tumors within 4 weeks or 5 half-lives of the administered drug (whichever is shorter) prior to Cycle 1, Day 1 of the study, or other investigational therapy or major surgery within 4 weeks of the date of consent, or
- 20 planned surgery within 4 weeks of envisaged study start (this includes dental surgery).
7. Radiation therapy within 4 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass, and which does not jeopardize required measurable lesions for response assessment (RECIST v1.1).
- 25 8. Patients with fungating tumor masses
9. Patients with locally advanced PDAC without distant organ metastatic deposits
10. Grade 4 immune-mediated toxicities with a prior checkpoint inhibitor. Grade 2 or Grade 3 pneumonitis or any other Grade 3 checkpoint inhibitor-related toxicity that led to immunotherapy treatment discontinuation. Low-grade (< Grade 3) toxicities, such as
- 30 neuropathy from prior treatments, manageable electrolyte abnormalities and lymphopenia, alopecia and vitiligo are allowed.
11. History of second malignancy, except those treated with curative intent more than five years previously without relapse or low likelihood of recurrence (for example, non-

melanotic skin cancer, cervical carcinoma in situ, early (or localized) prostate cancer, or superficial bladder cancer)

12. Active brain or leptomeningeal metastases. Patients with brain metastases are eligible provided they have shown clinically and radiographically stable disease (SD) for at least 4 weeks after definitive therapy and have not used steroids (> 10 mg/day of prednisone or equivalent) for at least 4 weeks prior to the first dose of study drug

13. Evidence of severe or uncontrolled systemic diseases, congestive heart failure $>$ New York Heart Association (NYHA) class 2, myocardial infarction (MI) within 6 months, or laboratory finding that makes it undesirable for the patient to participate in the trial

14. Any medical condition that is considered significant to compromise the safety of the patient or that impairs the interpretation of G9.2-17 (IgG4) toxicity assessment

15. Serious non-healing wound, active ulcer, or untreated bone fracture

16. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. For the purposes of this study, "recurrent" is defined as ≥ 3 drains in the previous 30 days.

17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

18. Significant vascular disease (*e.g.*, aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of Cycle 1, Day 1

19. History of pulmonary embolism, stroke or transient ischemic attack within 3 months prior to Cycle 1, Day 1

20. History of abdominal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1

21. Active auto-immune disorder (except type I/II diabetes, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia areata)

22. Requires systemic immunosuppressive treatment, including, but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents. Patients who have received or are receiving acute, low dose systemic immunosuppressant medications (*e.g.*, ≤ 10 mg/day of prednisone or equivalent) may be enrolled. Replacement therapy (*e.g.*, thyroxine, insulin, physiologic corticosteroid replacement therapy [*e.g.*, ≤ 10 mg/day of prednisone equivalent] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone), topical steroids, intranasal steroids, intra-articular, and ophthalmic steroids is allowed.

23. Severe tumor-related pain ($\geq$ Grade 3, per the Common Terminology Criteria for Adverse Events, (CTCAE) v.5.0) unresponsive to broad analgesic interventions (oral and/or patches)

24. Hypercalcemia (Grade 3 per CTCAE v 5.0), despite use of bisphosphonates

5 25. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk of treatment complications

26. Received organ transplant(s)

10 27. Patients undergoing dialysis

28. For Part 1, hormonal androgen deprivation therapy is allowed to continue for patients with metastatic castration-resistant prostate cancer.

29. Any ablative therapy (Radio Frequency Ablation or Percutaneous Ethanol Injection) for HCC < 6 weeks prior trial entry

15 30. Hepatic encephalopathy or severe liver adenoma

31. Child-Pugh score ≥ 7

Additionally, for Part 2 only:

20 32. Hypersensitivity to the active substance or to any of the excipients of gemcitabine/nab-paclitaxel

Study Drug and Other Interventions

Study intervention(s) is/are defined as any investigational agent(s), marketed product(s), placebo, or medical device(s) intended to be administered/used to/in a study participant
25 according to the study protocol.

Agents administered in combination with G9.2-17 (IgG4)

Gemcitabine plus Nab-Paclitaxel

Gemcitabine is a nucleoside metabolic inhibitor indicated for treatment of multiple cancer types, both alone and in combination with other therapies. Nab-paclitaxel (Abraxane[®]; a
30 protein-bound form of paclitaxel) is a microtubule inhibitor also indicated for treatment of multiple tumor types. Specifically, Nab-paclitaxel is indicated as a first line treatment for metastatic PDAC in combination with gemcitabine. Gemcitabine is administered as a 1000 mg/m² dose over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Nab-paclitaxel is

administered as a 125 mg/m² dose over 3-40 minutes on Days 1, 8 and 15 of each 28-day cycle.

The adverse events that are attributed to the combination of gemcitabine + nab-paclitaxel are shown below in **Table 8**.

5

Table 8. Adverse Events Reported for Gemcitabine + Nab-Paclitaxel in the Treatment of Pancreatic Cancer, According to Frequency

Common: AEs occurring in >30% of patients			
Neutropenia	Thrombocytopenia	Peripheral neuropathy	Nausea
Alopecia	Peripheral edema	Diarrhea	Vomiting
Pyrexia	Decreased appetite	Rash	Fatigue
Less Common: AE's occurring in 10-29% of patients			
Asthenia	Mucositis	Dysgeusia	Headache
Dehydration	Hypokalemia	Cough	Epistaxis
Urinary tract infections	Pain in extremity	Arthralgia	Myalgia
Depression			
Rare AEs occurring in <10% of patients			
Oral candidiasis	Hypertension	Pneumonitis	
Cystoid macular edema	Pneumonia	Tachycardia	
Congestive cardiac failure			
Most Common Serious Adverse Reactions (>1%)			
Pyrexia (6%)		Dehydration (5%)	
Pneumonia (4%)		Vomiting (4%)	

10 Limiting infusion of nab-paclitaxel to 30 minutes reduces the likelihood of infusion-related reactions.

Premedication to prevent hypersensitivity reactions is generally not needed prior to administration of nab-paclitaxel. Gemcitabine is contraindicated in patients with a hypersensitivity to gemcitabine.

15 Abraxane causes myelosuppression and should not be used when neutrophil counts are <1,500 cells/mm³. Severe hypersensitivity reactions have been known to occur with Abraxane. Gemcitabine should not be administered to patients with known sensitivity to gemcitabine.

Tables 9-11 below provide recommended dose modifications for gemcitabine + Nab-Paclitaxel in PDAC patients.

Table 9. Dose Level Reduction for Gemcitabine and Nab-Paclitaxel

Dose Level	Nab-Paclitaxel (mg/m ²)	Gemcitabine (mg/m ²)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

5

Table 10. Dose Recommendations and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle

10

Cycle Day	ANC (cells/mm ³)		Platelet count (cells/mm ³)	Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Table 11. Dose Modifications for Other Adverse Reactions

Adverse Reaction	Severity*	Dose Modification	
		Nab-Paclitaxel	Gemcitabine
Neutropenia	Grade 3 or 4	- Withhold until fever resolves and ANC ≥ 1,500 - Resume at next lower dose level.	
Peripheral Neuropathy	Grade 3 or 4	- Withhold until improves to ≤ Grade 1; - Resume at next lower dose level	No dose reduction
Cutaneous toxicity	Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists.	
Gastrointestinal toxicity	Grade 3 mucositis or diarrhea	- Withhold until improves to ≤ Grade 1; - Resume at next lower dose level	
Sepsis	Fever, regardless of ANC	- Initiate treatment with broad spectrum antibiotics; - Withhold until fever resolves and ANC ≥ 1,500; - Resume at next lower dose level.	

Adverse Reaction	Severity*	Dose Modification	
		Nab-Paclitaxel	Gemcitabine
Pneumonitis	Any	• Withhold during evaluation. Upon diagnosis of pneumonitis, permanently discontinue treatment	
Hypersensitivity	Severe	• Permanently discontinue	

* Toxicity was graded per NCI CTCAE V5.

Study Intervention Administration

All patients receive G9.2-17 (IgG4). G9.2-17 (IgG4) is administered via IV infusion, weekly, or every 2 weeks, until progression of disease, unacceptable toxicity, or withdrawal of consent.

In Part 1, patients receive G9.2-17 (IgG4) alone at sequentially increasing doses starting at 0.2 mg/kg.

In Part 2, patients receive the RP2D of G9.2-17 (IgG4) (as determined in Part 1) as a single agent or the G9.2-17 (IgG4) RP2D-1 in combination with gemcitabine/nab-paclitaxel as follows:

- Patients with CRC or CCA
 - o G9.2-17 (IgG4) in CRC
 - o G9.2-17 (IgG4) in CCA
- Patients with PDAC
 - o G9.2-17 (IgG4) + gemcitabine/nab-paclitaxel
- Other solid tumor types (based on data from Part 1)
 - o G9.2-17 (IgG4) as a single agent and/or in combination with a checkpoint inhibitor or chemotherapy that is determined based on each tumor type

See **Table 12** for a summary description of each study intervention.

Patients who experience a DLT in Part 1 do not resume treatment. Patients who experience a DLT in Part 2 have their treatment interrupted. Their treatment may resume at the same or reduced dose of G9.2-17 (IgG4) if they are experiencing a clinical benefit.

Table 12. Summary Characteristics of Study Interventions

Arm Name	G9.2-17 (IgG4)	G9.2-17 (IgG4) + gemcitabine/nab-paclitaxel (Abraxane)
Intervention Name	G9.2-17 (IgG4)	gemcitabine/nab-paclitaxel
Intervention Type	Biologic	Drugs
Dose Formulation	Vial	Vial(s)

Arm Name	G9.2-17 (IgG4)	G9.2-17 (IgG4) + gemcitabine/nab-paclitaxel (Abraxane)
Unit Dose Strength(s)	30 mg/mL	Nab-paclitaxel: 5 mg/mL powder for suspension for infusion. Gemcitabine: 200 mg or 1 g lyophilized powder in single-dose vials for reconstitution
Dosage Level(s)	Part 1: increasing doses starting at Q2W 0.2 mg/kg with a maximum dose of QW 16 mg/kg Part 2: RP2D for single agent G9.2-17 (IGG4) or RP2D-1 for G9.2-17 (IGG4) in combination with chemotherapy	Part 2 only: Nab-paclitaxel: 125 mg/m ² Gemcitabine: 1000 mg/m ²
Frequency of Administration	Q2W: Days 1 and 15 of each 28-day cycle (Part 1, Cohorts 1-6) QW: Days 1, 8, 15, and 22 of each 28-day cycle (Part 1, Cohorts 7-8 and Part 2)	Days 1, 8, and 15 of each 28-day cycle
Route of Administration	IV infusion	IV infusion
Use	experimental	standard of care
IMP and non-IMP	IMP	non-IMP
Sourcing	Provided centrally	Provided locally by the trial site, subsidiary, or designee.
Packaging and Labeling	Study Intervention is provided in appropriate configurations; each is labeled as required per country requirement	Study Intervention is provided locally according to approved label

Preparation of G9.2-17 (IgG4)

Manufacture and packaging of the investigational medicinal product (IMP) G9.2-17 (IgG4) is in accordance with applicable current Good Manufacturing Practice (cGMP) and the product meets applicable criteria for use in humans.

G9.2-17 (IgG4) drug product is diluted to the target dose prior to administration. All dilutions should be performed in a controlled and sterile environment (patient dose is prepared for and delivered via an approximately 60 minutes IV infusion).

G9.2-17 (IgG4) is a sterile liquid and is stored at 2°C to 8°C and protected from light.

Dose De-escalation

Dose Continuation for G9.2-17 (IgG4) for patients in the G9.2-17 (IgG4) +gemcitabine/nab-paclitaxel cohort

If a patient is experiencing clinical benefit from G9.2-17 (IgG4), and protocol efficacy assessment criteria, and the patient is experiencing adverse reactions that are not attributed to G9.2-17 (IgG4), then treatment with G9.2-17 (IgG4) alone may continue while the gemcitabine/nab-paclitaxel is modified/discontinued.

- 5 G9.2-17 (IgG4) may be continued if:
- the patient's clinical status is not deteriorating rapidly; AND
 - the combination agent is discontinued due to AEs that are attributed to the combination agent only.

If an IMAR occurs/recurs that is not managed by dose reduction of either agent, both
10 study medications must be discontinued.

Nab-paclitaxel is not recommended in patients who have total bilirubin $>5 \times \text{ULN}$ or AST $>10 \times \text{ULN}$. In addition, Nab-paclitaxel is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin $>1.5 \times \text{ULN}$ and AST $\leq 10 \times \text{ULN}$). The starting dose should be reduced for patients
15 with moderate or severe hepatic impairment.

Discontinuation of Study Intervention

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued due to reasons other than
20 disease progression, and the patient is not being treated with other anti-cancer therapy(ies), the patient continues to be evaluated for disease progression for up to 2 years. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Every effort must be made by study personnel to keep patients on study treatment until
25 one of the reasons for study treatment termination are met (disease progression, toxicity related to the study drug, withdrawal of consent). If the patient has radiographic progression but no unequivocal clinical progression and alternate treatment is not initiated, the patient may continue on study treatment. However, if patients have unequivocal clinical progression without radiographic progression, study treatment should be stopped, and patients advised
30 regarding available treatment options.

A patient may be discontinued prior to disease progression for any of the following reasons:

- A DLT per definition in Section 3.4.4.

• An AE occurs/recurs outside of the DLT window that requires discontinuation of study treatment(s)

- An IMAR occurs/recurs that requires discontinuation of study treatment(s)
- Termination of the study by PureTech Health, LLC

5 • Intercurrent illness or medical condition that prevents further administration of treatment or may jeopardize the patient's safety if they continue on study treatment

- Pregnancy
- Use of a non-protocol anti-cancer therapy

Patients may also be discontinued prior to disease progression for any of the following reasons:

- Significant deviation from protocol on the part of the patient (includes lack of compliance)

The explanation of why the patient is discontinuing study treatment should be documented in the case report form (CRF). If the patient discontinues study treatment due to toxicity, "Dose-Limiting Toxicity" or "Adverse Event" is recorded as the primary reason for withdrawal. If a patient is prematurely discontinued from the study at any time due to an AE or SAE, the patient must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of the underlying disease.

20 ***Concomitant Therapy***

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- 25 • Dates of administration including start and end dates
- Dosage information including dose and frequency

Permitted Medications

The following concomitant medications are allowed:

- 30 • Any standard of care pre-medication for patients on a combination treatment regimen.
- Continuation of bisphosphonate treatment (e.g., zoledronic acid) or denosumab for bone metastases, which have been stable for at least 6 months before treatment (C1D1),

- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone), topical steroids, intranasal steroids, intra-articular, and ophthalmic steroids
 - Prophylactic or therapeutic use of anticoagulants
 - Vaccination for COVID-19, common flu and/or other common clinically
- 5 required indications (e.g. tetanus, pneumococcus, HBV, etc.) is allowed before or during the study period. The timing and type of vaccine must be recorded.

Prohibited Medications

Following medications are not allowed while on this study:

- 10 • Concomitant administration of other investigational agents, other than G9.2-17 (IGG4), for any indication.
- Systemic immunosuppressive treatment, including, but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents. However, patients are allowed to take acute, low dose systemic immunosuppressant
- 15 medications (e.g., ≤ 10 mg/day of prednisone or equivalent).
- Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy [eg, ≤ 10 mg/day of prednisone equivalent] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

20 Supportive Care

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with institutional guidelines

SCHEDULE OF ASSESSMENTS
Table 13. Schedule of Assessments for Cohorts 1-6

	Pre-Dose	Treatment Phase												Post Treatment				
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 (28 days)				Cycle 4 (28 days) and beyond		End of Treatment or Early Termination	IMAR Follow -Up ^T	Long Term Follow -Up ^U Every 3 mons
		1	2	8	15	1	8	15	1	2	8	15	1	8	15	30 days after last dose	90 days after last dose	
Cycle Day		C1 D1	C1 D2	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C3 D2	C3 D8	C3 D15	CX D1	CX D8	CX D15	--	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	7	n/a
Study drug administration ^A		X		X	X	X	X	X	X		X	X	X	X	X			
Study Procedures & Examinations																		
Eligibility assessment and written informed consent	X																	
Demographics ^B	X																	
Medical history ^C	X																	
Previous and concomitant medications ^D	X	X	X	X	X			X	X	X	X	X	X		X	X		
Adverse events ^E		X	X	X	X	X	X	X	X	X	X	X	X		X	X		
ECHO/MUGA ^F	X												X					
12-lead ECG (QTcF)	X	X					X		X				X					
Physical exam ^G	X	X			X	X	X	X	X	X	X	X	X		X	X	X	

[illegible]

- ADA: anti-drug antibodies; AE: adverse event; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; C: cycle; CPK: creatine phosphokinase; COVID19: Coronavirus SARS-CoV-2; CRP: C-reactive protein; CT: computed tomography; D or d: day(s); ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ECHO: echocardiography/cardiac ultrasound; FSH: follicle-stimulating hormone; IMAR: immune-mediated adverse reaction; INR: international normalized ratio; LDH: lactate dehydrogenase; LH: luteinizing hormone; min: minute(s); MUGA: multigated acquisition scan; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PTH: parathyroid hormone; PTT: partial thromboplastin time; QTcF: QT interval, Fridericia's Correction Formula; RBC: red blood cell count; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; TSH: thyroid stimulating hormone; WBC: white blood cell count.
- A) Study drug administration: G9.2-17 (IGG4) treatment is administered, on CID1 and CID15 on every cycle. In Part 2, on Day 8 in every cycle, gemcitabine and nab-paclitaxel is administered to PDAC patients on the G9.2-17 (IGG4) combination regimen. Study drug may be administered on Days 1, 8 and 15 +/- 3 days from C2 onwards.
- B) Demographics: Data include age, gender, race, and ethnicity.
- C) Medical history: In addition to general medical history, data collection also includes oncology history, surgical/transplant and radiation therapy history and COVID-19 history and testing.
- D) Previous and concomitant medications (including vaccines and complementary treatments/supplements): Data to include name, indication, dose, route, start and end dates for each. Allergies and intolerances, dose modifications while on study, schedule of dosing changes and reasons for them should also be obtained.
- E) Adverse events: Any AEs starting or worsening after study drug administration is recorded. AEs should be followed until resolved to one of the following: baseline, stabilized, or deemed irreversible. All SAEs are to be collected until 30 days after last dose of study medication. All study-procedure-related SAEs must be collected from the date of patient's written consent.
- F) ECHO/MUGA: This assessment of heart function is conducted at Screening and repeated on Day 1 of Cycle 4; the assessment window is +/- 5 days. It should be conducted more frequently when clinically indicated and once every 3 months.
- G) Physical exam: Include height at screening for determination of body surface area. Include weight at all scheduled exam times. A Neurological exam is conducted only on patients who have stable and/or pre-treated brain metastases.
- H) Vital Signs: temperature, heart rate, blood pressure, respiratory rate.
- I) Pregnancy test (blood or urine): Only for women of childbearing potential with uterus in situ. Test results must be available before scheduled dosing.
- J) Hematology: Analysis includes complete blood count, differential, platelets, hemoglobin. Collect blood samples pre-dose.
- K) Serum chemistry: Analysis includes albumin, alkaline phosphatase, bilirubin (total, direct), blood urea nitrogen, calcium, CPK, creatinine, electrolytes (sodium, potassium, chloride, magnesium, phosphorus), gamma glutamyl transferase (gamma GT), glucose, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), LDH, SGPT (ALT) or SGOT (AST), total protein. Fasting glucose to be assessed only if clinically indicated. Collect blood samples pre-dose.
- L) Blood Coagulation: Collect blood samples pre-dose. Analysis includes APTT, PT, PTT, and INR (if on allowable anti-coagulants), CRP, and troponin.
- M) Urinalysis: Analysis includes color, appearance, dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, pH. (Urine culture and sensitivity to be run only if patient is clinically symptomatic.)
- N) Tumor imaging assessment: For screening, the assessment must be performed within the 28-day screening period. On study, assessments are done every 8 weeks +/- 7 days (ie, C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the previous 4-6 weeks. Assessments may be performed more frequently if clinically indicated. If an objective response is seen on a scan, a confirmation scan is done 4 weeks (+7 d) later. After this confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks +/- 7 days from the date of the confirmatory scan.
- O) Tumor biopsies: If patient MMR/MSI status is unknown at screening, the test should be run at the local laboratory. In Part 2, TMB tissue analysis is performed. The on-study biopsy is scheduled for C3D15 +/- 7 days and should occur only after the tumor imaging scan in Cycle 3. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to perform biopsy on-treatment should be discussed with the Medical Monitor.
- P) Tumor type-relevant biomarkers: Blood samples are to be collected at screening and every cycle pre-dose administration as appropriate for the tumor type. Blood sampling may be decreased to every 3rd cycle after 6 months of treatment.

Q) PD blood sampling: Blood samples are collected pre-dose administration on dosing days. May be decreased to every 3rd cycle after 6 months of treatment.

R) PK blood sampling: Cycle 1 and Cycle 3 Day 1: blood samples are collected pre-dose and at end of study drug infusion (EOI), 2 and 4 h ($\pm$ 30 min) post-study drug administration. Cycle 1 and Cycle 3 Day 15, blood samples are collected pre-dose and at EOI only. Cycle 1 and Cycle 3 Day 2 and 8 (non-dosing days), PK blood samples are collected at only one time point. Cycle 2 and Cycle 4: blood samples are collected Day 1 only and should occur pre-dose and at EOI. Blood samples for PK are collected every 2 cycles thereafter (i.e., C6D1, C8D1, etc.) pre-dose and at EOI.

S) ADA blood sampling: Blood samples are collected Day 1 of Cycles 1-4, blood samples are collected every 2 cycles, Day 1, pre-dose (ie, C6D1, C8D1, etc.).

U) Long-Term Follow-up: Tumor imaging should continue, where possible, for patients discontinuing treatment due to reasons other than progression of disease and not receiving additional systemic anticancer treatments. Survival data is collected at a minimum every 3 months. It can be collected more frequently to support data cleaning or regulatory submission efforts. Follow-up can be conducted by telephone, electronic messaging or chart review and will continue for up to 2 years after the patient has the End of Treatment/Early Termination visit.

Table 14. Schedule of Assessments for Cohorts 7 and 8

	Pre-Dose	Treatment Phase														Post Treatment						
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 (28 days)						Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up ^T	Long Term Follow-Up ^U Every 3 mons
Study Day	-28 to -1	1	3	8	15	22	1	8	15	22	1	3	8	15	22	1	8	15	22	30 days after last dose	90 days after last dose	
Cycle Day		C1 D1	C1 D3	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C3 D3	C3 D8	C3 D15	C3 D22	CX D1	CX D8	CX D15	CC D22	--	--	
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	7	n/a
Study drug administration ^A		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X			
Study Procedures & Examinations																						
Eligibility assessment and written	X																					

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ADA: anti-drug antibodies; AE: adverse event; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; C: cycle
CPK: creatine phosphokinase; COVID19: Coronavirus SARS-CoV-2; CRP: C-reactive protein; CT: computed tomography; D or d: day(s); ECG: electrocardiogram;
ECOG: Eastern Cooperative Oncology Group; ECHO: echocardiography/cardiac ultrasound; FSH: follicle-stimulating hormone; IMAR: immune-mediated adverse
reaction; INR: international normalized ratio; LDH: lactate dehydrogenase; LH: luteinizing hormone; min: minute(s); MUGA: multigated acquisition scan; PD:
pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PTH: parathyroid hormone; PTT: partial thromboplastin time; QTcF: QT interval, Fridericia's
Correction Formula; RBC: red blood cell count; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; TSH: thyroid
stimulating hormone; WBC: white blood cell count.

A) Study drug administration: G9.2-17 (IGG4) treatment is administered, on CXD1, CXD8, CXD15, and CXD22 on every weekly cycle (Cohorts 7-8). In Part 2, on Day 8 in every cycle, gemcitabine and nab-paclitaxel is administered to PDAC patients on the G9.2-17 (IGG4) combination regimen. Study drug may be administered on Days 1, 8 and 15 +/- 3 days from C2 onwards.

B) Demographics: Data include age, gender, race, and ethnicity.

C) **Demographics:** Data include age, gender, race, and ethnicity.

DD) Previous and concomitant medications (including vaccines and complementary treatments/supplements): Data to include name, indication, dose, route, start and end dates for each. Allergies and intolerances, dose modifications while on study, schedule of dosing changes and reasons for them should also be obtained.

(E) Adverse events: Any AEs starting or worsening after study drug administration is recorded. AEs should be followed until resolved to one of the following: baseline, stabilized, or deemed irreversible. All SAEs are to be collected until 30 days after last dose of study medication. All study-procedure-related SAEs must be collected from the date of patient's written consent.

from the date of patient's written consent. This assessment of heart function is conducted at Screening and repeated on Day 1 of Cycle 4; the assessment window is ± 5 days. It should be conducted more frequently when clinically indicated and once every 3 months.

Physical exam: Include height at screening for determination of body surface area. Include weight at all scheduled exam times. A Neurological exam is conducted only on patients who have stable and/or pre-treated brain metastases.

H) Vital Signs: temperature, heart rate, blood pressure, respiratory rate.

D) Pregnancy test (blood or urine): Only for women of childbearing potential with uterus in situ. Test results must be available before scheduled dosing.

- J) Hematology: Analysis includes complete blood count, differential, platelets, hemoglobin. Collect blood samples pre-dose.
- K) Serum chemistry: Analysis includes albumin, alkaline phosphatase, bilirubin (total, direct), blood urea nitrogen, calcium, CPK, creatinine, electrolytes (sodium, potassium, chloride, magnesium, phosphorus), gamma glutamyl transferase (gamma GT), glucose, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), LDH, SGPT (ALT) or SGOT (AST), total protein. Fasting glucose to be assessed only if clinically indicated. Collect blood samples pre-dose.
- L) Blood Coagulation: Collect blood samples pre-dose. Analysis includes APTT, PT, PTT, and INR (if on allowable anti-coagulants), CRP, and troponin.
- M) Urinalysis: Analysis includes color, appearance, dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, pH. (Urine culture and sensitivity to be run only if patient is clinically symptomatic.)
- N) Tumor imaging assessment: For screening, the assessment must be performed within the 28-day screening period. On study, assessments are done every 8 weeks $\pm$ 7 days (ie, C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the previous 4-6 weeks. Assessments may be performed more frequently if clinically indicated. If an objective response is seen on a scan, a confirmation scan is done 4 weeks (+7 d) later. After this confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks $\pm$ 7 days from the date of the confirmatory scan.
- O) Tumor biopsies: If patient MMR/MSI status is unknown at screening, the test should be run at the local laboratory. In Part 2, TMB tissue analysis is performed. The on-study biopsy is scheduled for C3D15 $\pm$ 7 days and should occur only after the tumor imaging scan in Cycle 3. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to perform biopsy on-treatment should be discussed with the Medical Monitor.
- P) Tumor type-relevant biomarkers: Blood samples are to be collected at screening and every cycle pre-dose administration as appropriate for the tumor type. Blood sampling may be decreased to every 3rd cycle after 6 months of treatment.
- Q) PD blood sampling: Blood samples are collected pre-dose administration on dosing days. May be decreased to every 3rd cycle after 6 months of treatment.
- R) PK blood sampling: Cycle 1 and Cycle 3 Day 1: blood samples are collected pre-dose, end of study drug infusion (EOI) and 1 h ($\pm$ 15 min) post-study drug administration. Cycle 1 and Cycle 3 Day 3, blood samples are collected at one time point, any time. Cycle 1 and Cycle 3 Day 8, Day 15, and Day 22, blood samples are collected pre-dose and at EOI only. Cycle 2 and every even cycle thereafter: blood samples are collected Day 1 only and should occur pre-dose and at EOI. Blood samples for PK will not be collected on every odd cycle after Cycle 3.
- S) ADA blood sampling: Blood samples are collected Day 1 and Day 15 of Cycles 1 and 2, pre-dose. Thereafter, it is collected every cycle, Day 1, pre-dose (ie, C3D1, C4D1, etc.).
- U) Long-Term Follow-up: Tumor imaging should continue, where possible, for patients discontinuing treatment due to reasons other than progression of disease and not receiving additional systemic anticancer treatments. Survival data is collected at a minimum every 3 months. It can be collected more frequently to support data cleaning or regulatory submission efforts. Follow-up can be conducted by telephone, electronic messaging or chart review and will continue for up to 2 years after the patient has the End of Treatment/Early Termination visit.

Study Assessments and Procedures

A signed, written ICF approved by an Institutional Review Board (IRB) must be obtained from the potential patient before he/she can participate in any study-specific procedures, including study-specific screening procedures.

5 Patients are entered in the study once all screening procedures have been completed and it is determined that they meet all eligibility criteria.

• Study procedures and their respective timing for Part 1, Cohorts 1-6 are summarized in the SoA (**Table 13**). Study procedures and their respective timing for Part 1, Cohorts 7 and 8 are summarized in the SoA (**Table 14**) Protocol waivers or exemptions are not
10 allowed.

• Adherence to all study requirements, including those specified in the SoA, is essential and required for study conduct.

• Immediate safety concerns should be discussed immediately upon occurrence or awareness to determine the need for intervention or study discontinuation.

15 • All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. A screening log is maintained to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

• Procedures conducted as part of the participant's routine clinical management (e.g.,
20 blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Assessments by Visit

25 The SoA (**Table 13** and **Table 14**) provides a list of assessments to be performed during the screening period (up to 28 days), the treatment period (presented as 28-day cycles), the End of Treatment/Early Termination period, IMAR follow-up and the long-term follow-up period. Optional visits are allowed during each treatment cycle if medically indicated, during which any of the study assessments may be performed.

30 During the COVID-19 pandemic many governments require citizens to practice social distancing, and more vulnerable populations are advised to self-isolate. These types of constraints

may affect the ability to run this clinical study as originally intended. Planned site visits can be adapted so that the study can safely continue during the pandemic. Possible modifications may include:

- visit and/or study procedure postponement
- replacement with telephone/video call(s)
- replacement with home visits
- visits performed at an alternative clinical location
- visits performed by a health-care provider outside the study team
- visit and/or study procedure completely cancelled.

10

Screening Period (between Day -28 and Day -1)

The following procedures must be conducted within 4 weeks of initiating treatment:

Study Procedures & Examinations

- Written informed consent
- Verify inclusion and exclusion criteria for patient eligibility
- Patient demographics
- Medical history
- Previous and concomitant medications
- ECHO/multigated acquisition scan (MUGA)
- 12-lead ECG (QT interval corrected using Fridericia's formula [QTcF])
- Physical examination - in patients with stable and pre-treated brain metastases, perform a neurological exam
- ECOG performance status
- Vital signs
- Tumor imaging assessment (computed tomography [CT] or magnetic resonance imaging (MRI), with or without contrast; or positron emission tomography (PET)-CT; CT with contrast is preferred)

25

Clinical Labs

- Pregnancy test for women of childbearing potential (WOCBP)
- Hematology
- Serum chemistry

30

- Thyroid stimulating hormone (TSH), free T4 or thyroxine (fT4), serum lipase, amylase, parathyroid hormone (PTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), free cortisol
- Blood coagulation
- Urinalysis

Pharmacodynamics and Pharmacokinetics

- Tumor biopsy
 - o Biopsy can be omitted if it is deemed that the procedure is a risk to the patient.
 - o If a biopsy is unavailable, site will make every effort to obtain an archival tumor tissue sample available as a formalin-fixed paraffin-embedded (FFPE) block. Acceptable archival samples include those obtained via a core needle biopsy or excisional surgery within the last five years.
- dMMR-MSI-H status (if the MMR and MSI status of the patients has not been previously determined, the test must be run at the local laboratory)
- Tumor type-relevant biomarkers

Treatment Period

- Each treatment cycle has a duration of 28 days.

Treatment Procedures for Day 1 of each cycle (CXD1; ± 2 days beginning Cycle 2)

The following procedures are performed on Day 1 of each treatment cycle.

Study Procedures and Examinations

- Concomitant medications
- AEs
- 12-lead ECG (QTcF)
- Physical examination
- ECOG performance status
- Vital signs

Clinical Labs

- Pregnancy test for WOCBP

- Hematology
 - Serum chemistry
 - TSH, fT4, lipase, amylase, PTH, FSH, LH, free cortisol
 - Blood coagulation
 - 5 • Urinalysis
- PK/PD Assessments
- PD blood sampling
 - PK blood sampling
 - ADA blood sampling
 - 10 • Tumor type-relevant biomarkers
- Study drug administration
- Administered only after all pre-dose assessments and procedures are completed.
- Additionally, beginning on Day 1 of Cycle 3, the following assessment is performed every 8 weeks:
- 15 • Tumor imaging assessment (CT or MRI, with or without contrast; or PET-CT; CT with contrast is preferred)
- Furthermore, beginning on Day 1 of Cycle 4, the following assessment is performed every 3 months:
- ECHO/MUGA
 - 20
- Cohorts 1-6: Treatment Procedures for Days 2 and 8 of Cycle 1 and Cycle 3 (CXD2 $\pm$ 1 day and CXD8 $\pm$ 1 day)
- Study Procedures and Examinations
- 25 • Concomitant medications
 - AEs
- PK/PD Assessments
- PD blood sampling
 - PK blood sampling
 - 30
- Cohorts 1-6: Treatment Procedures for Day 15 of each Cycle (CXD15 $\pm$ 1 day for Cycle 1 and $\pm$ 2 days for beginning Cycle 2)

The following procedures are performed on Day 15 of each treatment cycle.

Study Procedures and Examinations

- Concomitant medications
- AEs
- 5 • Physical examination
- ECOG performance status
- Vital signs

Clinical Labs

- Hematology
- 10 • Serum chemistry
- Blood coagulation
- Urinalysis

PK/PD Assessments

- PD blood sampling on C1D15 and C3D15 only
- 15 • PK blood sampling on C1D15 and C3D15 only
- Tumor type-relevant biomarkers
- Tumor biopsy on C3D15 ± 7 days (Cycle 3 ONLY; can be eliminated if it is deemed too risky for the patient)

Study drug administration

- 20 • Administered only after all pre-dose assessments and procedures are completed.

Cohorts 7 and 8: Treatment Procedures for Day 3 of Cycle 1 and Cycle 3 (C1D3 ± 1 day and C3D3 ± 1 day)

25 Study Procedures and Examinations

- Concomitant medications
- AEs

PK/PD Assessments

- PD blood sampling
- 30 • PK blood sampling

Cohorts 7 and 8: Treatment Procedures for Day 8 of each Cycle (CXD8 ± 1 day)

	Study Procedures and Examinations
5	• Concomitant medications • AEs • Physical examination • ECOG performance status • Vital signs
	Clinical Labs
10	• Hematology • Serum chemistry • Blood coagulation • Urinalysis
	PK/PD Assessments
15	• PD blood sampling • PK blood sampling for odd numbered Cycles only
	Study drug administration
	• Administered only after all pre-dose assessments and procedures are completed.
20	<u>Cohorts 7 and 8: Treatment Procedures for Days 15 and 22 of each Cycle (CXD15 ±1 day for Cycle 1 and ±2 days for beginning Cycle 2)</u>
	The following procedures are performed on Days 15 and 22 of each treatment cycle.
	Study Procedures and Examinations
25	• Concomitant medications • AEs • Physical examination • ECOG performance status • Vital signs
	Clinical Labs
30	• Hematology • Serum chemistry • Blood coagulation • Urinalysis

PK/PD Assessments

- PD blood sampling on C1D15 and C3D15 only
- PK blood sampling on odd numbered Cycles only
- Tumor type-relevant biomarkers
- 5 • Tumor biopsy on C3D15 ± 7 days (Cycle 3 ONLY; can be eliminated if it is deemed too risky for the patient)
- ADA blood sampling on C1D15 and C2D15 only

Study drug administration

- Administered only after all pre-dose assessments and procedures are completed.

10

Additional Treatment beyond Cycle 4

Treatment cycles beyond Cycle 4 can be repeated as indicated in the SoA (**Table 13** and **Table 14**). If the patient is experiencing clinical benefit, even in the event of radiological progression, the patient can continue on treatment.

15

End of Treatment or Early Termination Procedures

The following procedures are done 30 days (± 3 days) after the last dose, including patients who have discontinued treatment early.

Study Procedures and Examinations

- 20 • Concomitant medications
- AEs
- Physical examination
- ECOG
- Vital signs
- 25 • Tumor imaging assessment: Confirmatory scan if end of study is > 8 weeks after previous scan.

Clinical Labs

- Pregnancy test for WOCBP
- Hematology
- 30 • Serum chemistry
- TSH, fT4, lipase, amylase, PTH, FSH, LH, free cortisol
- Blood coagulation

- Urinalysis

PD Assessments

- PD blood sampling
- ADA blood sampling
- Tumor type-relevant biomarkers

5

Long-Term Follow-Up

OS is assessed every 3 months for up to 2 years after the patient has the End of Treatment/Early Termination. Tumor imaging assessment continues, where possible, for patients discontinuing treatment due to reasons other than progression of disease and not receiving additional systemic anticancer treatments.

10

Survival data as well as information on any new anticancer therapy initiated after disease progression is collected at a minimum every 3 months. It can be collected more frequently to support data cleaning or regulatory submission efforts. Follow-up may be performed by telephone interview, electronic messaging or chart review and is reported on the CRF. During the Follow-Up Period, deaths, regardless of causality are collected and reported within 24 h of discovery or notification of the event.

15

RECIST v1.1 Criteria for Tumor Assessment

At the screening tumor assessment, tumor lesions/lymph nodes are categorized as measurable or non-measurable with measurable tumor lesions recorded according to the longest diameter in the plane of measurement (except for pathological lymph nodes, which are measured in the shortest axis). When more than one measurable lesion is present at screening all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter). A sum of the diameters for all target lesions is calculated and reported as the baseline sum diameters.

20

25

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at screening. Measurements are not required, and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'.

30

Tumor target lesions are assessed according to the RECIST v1.1 Guidelines (Eisenhauer et al., 2009) using the following disease response measures:

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions:

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-progressive disease (non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

A summary is provided in **Table 15** below.

Table 15. Evaluation of Overall Timepoint Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

CR: Complete Response, Non-PD: Non-progressive Disease, PR: Partial Response, SD: Stable Disease, NE: Non-evaluable

*When target lesions show SD/PR and some subset of non-target lesions is non-evaluable, a careful decision must be made whether to call the overall response at this timepoint SD/PR or NE. This is based on whether the non-evaluable lesions, if they showed growth, could cause an overall response of progressive disease in the context of the other lesion responses seen. If the non-evaluable non-target lesions comprise a significant proportion of the overall disease burden, the appropriate timepoint response is NE.

- 5 The disease response measures at different timepoints allow for the calculation of the following:
- Disease control rate (DCR), defined as percentage of patients who have achieved CR, PR and SD.
 - Objective response rate (ORR), defined as the proportion of patients with tumor size reduction of a predefined amount (tumor shrinkage of $\geq 30\%$).
 - Progression-free survival (PFS), defined as the time from study drug treatment initiation to disease progression (tumor growth by $\geq 30\%$).
 - Duration of response (DoR), defined as the length of time that a tumor continues to respond to treatment without the cancer growing or spreading.
 - Overall survival (OS) defined as the time from study drug treatment initiation to death from any cause.

Safety Assessment

Physical Examinations

Medical and physical examinations must be performed by a qualified physician, nurse practitioner, or physician assistant, and should include a thorough review of all body systems. Additionally, height (at screening only) and weight are measured.

5 Vital Signs

Vital signs are measured in a post-supine position after 5 minutes rest and include temperature, blood pressure (systolic and diastolic), heart rate, and respiratory rate.

Electrocardiograms

12-lead ECG is obtained as outlined in the SoA (see **Table 13** and **Table 14**) using an ECG
10 machine that automatically calculates the heart rate and measures heart rate, PR interval, QRS duration, distance in time on the ECG tracing from the start of the QRS complex to the end of T-wave (QT) interval, and QTcF intervals.

Clinical Safety Laboratory Assessments

Patients have blood samples collected for routine clinical laboratory testing (approximately
15 5 mL at each timepoint), according to the SoA (**Table 13** and **Table 14**); additional tests may be performed at any time during the study as determined necessary.

The clinical laboratory parameters are analyzed at the site's local laboratory. Laboratory assessments completed include hematology and serum chemistry and is defined as following:

- Serum Chemistry: Includes glucose, total protein, albumin, electrolytes [sodium,
20 potassium, chloride, magnesium, phosphorus], calcium, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, gamma glutamyl transferase (gamma GT), lactate dehydrogenase (LDH), creatinine, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), blood urea nitrogen, creatine phosphokinase (CPK)
 - o TSH, fT4, lipase, amylase, PTH, FSH, LH, free cortisol additionally at
25 specified visits
 - o Fasting glucose is assessed only if clinically indicated
- Hematology: Includes complete blood count, differential, platelets, hemoglobin
- Coagulation: Includes prothrombin time (PT) and PTT, activated partial
thromboplastin time (APTT) and INR (if on allowable anti-coagulants) C-reactive protein
30 (CRP), and troponin

- Urinalysis: Patients have urine samples collected for routine urinalysis. The urinalysis includes color, appearance, and dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, white blood cell count (WBC), red blood cell count (RBC), and pH, and urine culture (if patient is clinically symptomatic).

5 • If clinically significant values do not return to normal/baseline or Grade 1 within a period of time judged reasonable, the etiology should be identified.

- All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA (**Table 13** and **Table 14**).

10 • If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant (e.g., SAE or AE or dose modification), then the results must be recorded.

Pregnancy Testing

15 WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

Additional pregnancy testing should be performed during the treatment period and at the End of Treatment/Early Termination visit according to the SoA (**Table 13** and **Table 14**), and as required locally.

20 Pregnancy testing is performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

If the patient has prior history of bilateral salpingo-oophorectomy and/or hysterectomy, record these surgical procedures; a pregnancy test is not required for these patients.

Pharmacokinetics Assessments

25 The following serum PK parameters are calculated for G9.2-17 (IGG4), if possible:

- AUC_{0-336h}
- C_{max}
- T_{max}
- $t_{1/2}$
- 30 • serum concentration vs. time profiles

Blood samples of approximately 5 mL are collected and processed to serum at each timepoint as specified in the SoA (**Table 13** and **Table 14**).

PK schedule for Cohorts 1-6:

Cycle 1 and Cycle 3 Day 1

- 5
- Pre-dose
 - At the End of Infusion (EOI)
 - 2 h ($\pm$ 30 min) after EOI
 - 4 h ($\pm$ 30 min) after EOI

Cycle 1 and Cycle 3 Day 15

- 10
- Pre-dose
 - At EOI

Cycle 1 and Cycle 3 Day 2 and 8 (non-dosing days)

- Any point during the visit

Cycle 2 and Cycle 4 Day 1

- 15
- Pre-dose
 - At EOI

Every 2 Cycles beyond Cycle 4 on Day 1 (i.e., C6D1, C8D1 etc.)

- Pre-dose
- At EOI

20 PK schedule for Cohorts 7 and 8:

Every odd numbered Cycle Day 1 (i.e., C1D1, C3D1, etc.)

- Pre-dose
- At the End of Infusion (EOI)
- 1 h ($\pm$ 15 min) after EOI

25 Every odd numbered Cycle Day 3 (i.e., C1D3, C3D3, etc.)

- Any point during the visit

Odd numbered Cycle Days 8, 15, and 22 (i.e. C1D8, C3D8, etc.)

- Pre-dose
- At EOI

30 Even numbered Cycle Day 1 (i.e., C2D1, C4D1, etc.)

- Pre-dose

- At EOI

If the dose of study drug is determined to be interrupted, additional PK and safety assessments are collected upon resumption of dosing; additional PK assessments may be performed during the interruption. If the dose of study drug is reduced, additional PK assessments are collected pre-administration of the reduced dose (within 2 h pre-dosing), and 2 to 4 h after starting the reduced study drug dose. Additional PK, and other blood assessments may be taken if clinically indicated. Centers that are not able to hold patients more than 2 h post-dose due to COVID-19 restrictions, contribute samples at EOI and 2 h post-dose only.

Instructions for the collection and handling of biological samples are provided. The actual date and time (24-h clock time) of each sample are recorded.

Samples are used to evaluate the serum concentration levels of total G9.2-17 (IGG4) and free/partially free G9.2-17 (IGG4) by a designated laboratory. Concentrations are determined using validated assays. A minimum of two 50 µL aliquots of serum are needed to determine total G9.2-17 (IGG4) concentrations. A minimum of two 100 µL aliquots of serum are needed to determine free and partially free G9.2-17 (IGG4) concentrations and residual serum in a third aliquot. Samples collected for analyses of G9.2-17 (IGG4) plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses is not performed on these blood samples. Participant confidentiality is maintained. At visits during which blood samples for the determination of PD, ADA, safety lab of G9.2-17 (IGG4) is taken, one sample of sufficient volume can be used.

Genetics

Genetics are not evaluated in this study.

Pharmacodynamic Biomarkers

Planned time points for biomarker assessments are provided in the SoA (**Table 13** and **Table 14**); sampling may be decreased to every 3rd cycle after 6 months of treatment.

Collection of biological samples for other biomarker research is also part of this study. The following samples for biomarker research are required and are collected from all participants in this study as specified in the SoA:

- Blood samples, to be collected prior to study drug administration (approximately 15 mL pre-dose)
- Tumor biopsy (tissue sample)

Samples are tested for PD biomarkers (by flow cytometry, ELISA, IHC, or multiplex phenotyping) to evaluate their association with the observed clinical responses to G9.2-17 (IGG4) using validated assays.

The following biomarkers are assessed for this study:

- 5 • Tumor markers (blood): CA15-3, CA-125, carcinoembryonic antigen (CEA), CA19-9, alpha fetoprotein, neuron-specific enolase (NSE), cytokeratin-fragment-21 (CYFRA-21) to be assessed every cycle pre-dose administration as needed per tumor type. This may be decreased to every 3 cycles after 6 months of treatment, following the same schedule as tumor imaging assessments, as appropriate.
- 10 • PBMC phenotype (blood): e.g., CD3, CD4, CD8, CD45RO, forkhead-box-protein P3 (FOXP3), CD11B, CD14, CD15, CD16, CD33, CD68, human leukocyte antigen (HLA) DR, CD163, arginase 1, granzyme B, KI67, PD-1, PD L1, pan cytokeratin (PAN CK)
- Cytokines (blood): eg, interferon gamma (IFN γ), IL 10, IL 12p70, IL 13, IL 1 β , IL 2, IL 4, IL 6, IL 8, TNF α , MIP-1b, monocyte chemoattractant protein 1 (MCP-1), MIP-1a,
- 15 IL 17a, IL 5, TGF β
- Gal-9 in blood and tumor tissue
- PD-L1 (tissue)
- Mismatch repair status (tissue)
- Tumor Mutational Burden (TMB)

20 Exploratory biomarker changes, if any, are correlated with safety and response outcomes.

Samples may be stored for a maximum of 2 years (or according to local regulations) following the last patient's last visit for the study at a facility selected to enable further analysis of the effect of G9.2-17 (IGG4) on pharmacodynamic biomarkers.

Immunogenicity Assessments

25 Blood samples (approximately 3 mL) are collected from all participants according to the SoA (**Table 13** and **Table 14**) and processed to serum. Additionally, serum samples should also be collected at the end of treatment/early termination visit from patients who discontinued study intervention or were withdrawn from the study.

Cohorts 1-6: Cycle 1 to Cycle 4 Day 1

- 30 • Pre-dose

Cohorts 1-6: Every 2 cycles beyond Cycle 4 on Day 1 (i.e., C6D1, C8D1 etc.):

- Pre-dose

Cohorts 7 and 8: Every Cycle Day 1

- Pre-dose

Cohorts 7 and 8: Cycle 1 Day 15 and Cycle 2 Day 15 only

- 5 • Pre-dose

A minimum of two aliquots of 500 µL serum each, with residual serum in a third tube are obtained. Samples are shipped to a lab designated for analysis using a validated assay. These samples are tested.

10 Serum samples are screened for antibodies binding to G9.2-17 (IgG4) (ADA) and the titer of confirmed positive samples is reported. Other analyses may be performed to verify the stability of antibodies to G9.2-17 (IgG4) and/or further characterize the immunogenicity of G9.2-17 (IgG4).

The detection and characterization of antibodies to G9.2-17 (IgG4) is performed using a validated assay method. All samples collected for detection of antibodies to study intervention are evaluated for G9.2-17 (IgG4) serum concentration to enable interpretation of the antibody data.

15 Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention. Samples may be stored for a maximum of 2 years (or according to local regulations) following the last patient's last visit for the study at a suitable facility to enable further analysis of immune responses to G9.2-17 (IgG4).

20 ***Other Assessments***

Demographics

At Screening, patient demographic data is collected. These include age, gender, race, and ethnicity.

25 **Medical History**

The medical history includes oncology history, surgical/transplant history radiation therapy history, and COVID 19 history and testing.

- 30 • Personal medical history, including prior treatments/surgeries, record of any implants in situ or past implants, prior and/or current use of medical devices, concomitant medications (name, indication, dose, route, start and end dates dose modifications if any and reason), pre-existing symptoms, and AEs), hereditary diseases at risk of based on family history and complete family history to the best knowledge of the patient

- Record of any dental work performed in the past 12 months
- For patients with previously resected pancreatic adenocarcinoma, record whether the primary tumor was localized to the head of pancreas, pancreatic body or the pancreatic tail.

- 5
- Bowel habits/ typical frequency and consistency
 - Record any dietary requirements or preferences (for example, practice of a particular diet regimen: intermittent fasting, keto diet etc.)
 - Record and allergies past and present (allergen, severity)

10 Prior and Concomitant Medications

Prior and concomitant medications, including vaccines and complementary treatments/supplements, are documented for each patient at each scheduled visit (**Table 13** and **Table 14**).

Tumor Imaging Assessments

- 15 Tumor assessments are performed using CT or MRI with or without contrast; a PET-CT is performed.

CT with contrast is the preferred modality (MRI, PET-CT, or other imaging modalities instead of, or in addition to, the CT scan, if CT is not feasible or appropriate, given location of the disease). Assessment should include the chest/abdomen/pelvis at a minimum and should include
 20 other anatomic regions as indicated, based on the patient's tumor type and/or disease history. Imaging scans must be de-identified and archived in their native format as part of the patient study file. While the type of scan obtained, as appropriate for the disease, the same method should be used for the duration of the study.

On study, assessments are done every 8 weeks $\pm$ 7 days according to the SoA (i.e., C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the last 4-6 weeks.
 25 Assessments may be performed more frequently if clinically indicated. For Part 2 only, if an objective response is seen on a scan, a confirmation scan is done 4 weeks (+7 days) later. After a confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks ($\pm$ 7 days) from the date of the confirmatory scan.

30 Tumor Biopsies

Pre- and on-treatment biopsies are collected. A pre-treatment biopsy is collected during

screening. If a pre-treatment biopsy is unobtainable as per the reasons outlined in the inclusion criteria, and the patient is enrolled in the study, an archival tumor tissue specimen from that patient is collected from a primary tumor and/or a metastatic deposit. Excisional or core biopsy (FFPE tissue block(s) OR fresh tissue in formalin) obtained currently or within 5 years before study start
 5 from the primary tumor lesion or a metastatic deposit. If both primary and metastatic tissues are available, use of metastatic deposit tissue is prioritized. If information of treatment(s) received before and after tissue acquisition are available, this is collected as well.

The on-treatment biopsy is scheduled for C3D15 $\pm$ 7 days and should occur only after the tumor imaging scan in Cycle 3. In instances where the procedure cannot be performed within the
 10 protocol-specified timeframe, alternatives may be permitted but must be discussed with the Study Director/Medical Monitor. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to complete biopsy on-treatment should be discussed with the Medical Monitor.

15 ECHO/MUGA

ECHO and/or MUGA are obtained at the timepoints indicated in the SoA (**Table 13** and **Table 14**). If clinically indicated, the assessment is to be repeated once every 3 months.

ECOG

20 ECOG performance status is assessed at the timepoints indicated in the SoA (**Table 13** and **Table 14**) using the following grading (Oken et al., 1982).

- Grade 0: Fully active, able to carry on all pre-disease performance without restriction
- Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry
 25 out work of a light or sedentary nature, e.g., light housework, office work
- Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 30 • Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- Grade 5: Dead

Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

An AE is defined in the ICH Guideline for GCP as “any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.”

This definition of AEs is broadened in this study to include any such occurrence (e.g., sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a patient has signed informed consent to the time of initiation of the investigational drug. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches, gout, hypertension, etc.) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Serious Adverse Events

A SAE is defined as an AE that:

- Results in death;
- Is life threatening (places the patient at immediate risk of death);
- Requires in-patient hospitalization or prolongation of existing hospitalization;

A hospitalization meeting the definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgeries (as outpatient/same day/ambulatory procedures), or social admission (eg, patient has no place to sleep).

- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include anaphylaxis and allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Relatedness

For all AEs, enough information should be obtained to determine the causality of the AE (e.g., study drug or other illness). The relationship of the AE to the study treatment is assessed following the definitions below:

- 5 • Unrelated: any event that does not follow a reasonable temporal sequence from administration of study drug AND that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- Unlikely Related: any event that does not follow a reasonable temporal sequence from administration of study drug OR that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- 10 • Possibly Related: any reaction that follows a reasonable temporal sequence from administration of study drug OR that follows a known response pattern to the suspected drug AND that could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- Related: any reaction that follows a reasonable temporal sequence from
15 administration of study drug AND that follows a known response pattern to the suspected drug AND that recurs with re-challenge, AND/OR is improved by stopping the drug or reducing the dose.

Adverse Event Management

20 AEs are not recorded prior to the administration of the first dose of study medication. AEs that start, or symptoms related to medical history that worsen after study drug administration are recorded. AEs should be followed until they are either resolved, have returned to baseline, or are determined to be a stable or chronic condition. All SAEs are collected until 30 days after the last dose of study medication. All study-procedure-related SAEs must be collected from the date of
25 patient's written consent.

Immune-Mediated Adverse Reactions

The specific IMARs noted are:

- Immune-Mediated Hepatitis
- Immune-Mediated Nephritis
- 30 • Immune-Mediated Pneumonitis
- Immune-Mediated Pneumonitis

- Immune-Mediated Colitis and Diarrhea Immune-Mediated Endocrinopathies
- Immune-Mediated Skin Reactions
- Other Immune-Mediated Adverse Reactions: arthritis, encephalitis, rhabdomyolysis, myositis, myocarditis, pancreatitis, and uveitis.

5 The monitoring plan is intended to limit the severity and duration of IMARs that occur during combination drug development, and encompass: scheduled visits for a physical exam, vital signs, safety laboratory assessments including blood hematology, biochemistry, assessing endocrine functions each Day 1 of a new dosing cycle (pre-dose), assessing coagulation status and urine analyses. The Schedule of Assessments (**Table 13** and **Table 14**) also encompasses assessing

10 the ejection fraction once every three months and conducting regular ECGs.

A summary of management of IMARs caused by G9.2-17 (IgG4), either alone or in combination with other therapeutic agents, is provided in **Table 16** below.

Table 16. Management of Immune-Mediated Adverse Reactions (IMARs) Caused by G9.2-17 (IgG4)

15

IMAR	Guidance for Management
Immune-mediated pneumonitis	• Monitor patients for signs with radiographic imaging and for clinical symptoms of pneumonitis. • Withhold G9.2-17 (IGG4) for moderate and permanently discontinue for severe or life-threatening pneumonitis. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. • Withhold G9.2-17 (IGG4) until resolution to < Grade 2. For moderate (Grade 2) pneumonitis. Resume treatment at a 50% dose reduction. • Upon recurrence of Grade 2 pneumonitis at the reduced dose of G9.2-17 (IGG4), permanently discontinue G9.2-17 (IGG4).
Immune-mediated colitis	• Monitor patients for signs and symptoms of colitis. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration. • If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. • When initial Grade 2 colitis resolves to < Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction.

IMAR	Guidance for Management
	• If $\geq$ Grade 2 colitis recurs, withhold G9.2-17 (IGG4) until colitis resolves to $<$ Grade 2. Resume G9.2-17 (IGG4) at an additional 50% dose reduction. No further dose reductions for G9.2-17 (IGG4) are allowed. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life threatening (Grade 4) colitis. • When Grade 3 colitis resolves to $\leq$ Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • Permanently discontinue G9.2-17 (IGG4) for life-threatening (Grade 4) or for recurrent colitis of $\geq$ Grade 2 upon re-initiation of G9.2-17 (IGG4).
Immune-mediated hepatitis	• Monitor for changes in liver function. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. • Withhold G9.2-17 (IGG4) for moderate (Grade 2) immune-mediated hepatitis. When resolved to $<$ Grade 2 resume G9.2-17 (IGG4) at a 50% dose reduction. • If $\geq$ Grade 2 hepatitis recurs, permanently discontinue G9.2-17 (IGG4). • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. • Permanently discontinue G9.2-17 (IGG4) for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis.
Immune-mediated endocrinopathies: Hypophysitis	• Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. • Withhold G9.2-17 (IGG4) for moderate (Grade 2) or severe (Grade 3) and when resolved to $<$ Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • If $\geq$ Grade 2 toxicity recurs, permanently discontinue G9.2-17 (IGG4). • Permanently discontinue G9.2-17 (IGG4) for life-threatening (Grade 4) hypophysitis.
Adrenal insufficiency	• Monitor patients for signs and symptoms of adrenal insufficiency.

IMAR	Guidance for Management
	• Withhold G9.2-17 (IGG4) for moderate (Grade 2) and once resolved to < Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • If ≥ Grade 2 toxicity recurs, permanently discontinue G9.2-17 (IGG4). • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. • Permanently discontinue G9.2-17 (IGG4) for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency, or for recurrent colitis of ≥ Grade 2 upon re-initiation of G9.2-17 (IGG4).
Hypothyroidism and Hyperthyroidism	• Administer hormone-replacement therapy for hypothyroidism. • Initiate medical management for control of hyperthyroidism. • There are no recommended dose adjustments of G9.2-17 (IGG4) for < Grade 3 hypothyroidism or hyperthyroidism • Discontinue G9.2-17 (IGG4) for ≥ Grade 3 hypothyroidism or hyperthyroidism
Type 1 Diabetes Mellitus	• Withhold G9.2-17 (IGG4) in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. • Upon resolution to ≤ Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • If ≥ Grade 2 toxicity recurs, permanently discontinue G9.2-17 (IGG4). • Permanently discontinue G9.2-17 (IGG4) for life-threatening (Grade 4) hyperglycemia.

IMAR	Guidance for Management
Immune-mediated nephritis and renal dysfunction (Defined as renal dysfunction or $\geq$ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology)	• Monitor patients for elevated serum creatinine prior to and periodically during treatment. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. • Withhold G9.2-17 (IGG4) for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. When resolved to $<$ Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • If $\geq$ Grade 2 toxicity recurs, permanently discontinue G9.2-17 (IGG4). • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. • Permanently discontinue G9.2-17 (IGG4) for life-threatening (Grade 4) increased serum creatinine.
Immune-mediated skin adverse reactions (Immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN))	• Withhold for severe and permanently discontinue for life-threatening rash. • For symptoms or signs of SJS or TEN, withhold G9.2-17 (IGG4) and refer the patient for specialized care for assessment and treatment. • If SJS or TEN is confirmed, permanently discontinue G9.2-17 (IGG4). • For immune-mediated rash $\geq$ Grade 2, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. • Withhold G9.2-17 (IGG4) for moderate (Grade 2) and severe (Grade 3) rash and when resolved to $<$ Grade 2, resume G9.2-17 (IGG4) at a 50% dose reduction. • If $\geq$ Grade 2 rash recurs, withhold G9.2-17 (IGG4) until resolved to $<$ Grade 2 and resume G9.2-17 (IGG4) at an additional 50% dose reduction. No further dose reductions are allowed. • Permanently discontinue G9.2-17 (IGG4) for life threatening (Grade 4) rash.
Immune-mediated encephalitis	• Monitor for changes in neurologic function. • Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. • Withhold G9.2-17 (IGG4) in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out

IMAR	Guidance for Management
	infectious or other causes of moderate to severe neurologic deterioration. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. • Permanently discontinue G9.2-17 (IGG4) for immune-mediated encephalitis.
Other Immune-Mediated Adverse Reactions (May include: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.)	• If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, and may require treatment with systemic steroids to reduce the risk of permanent vision loss. • For any suspected immune-mediated adverse reactions, exclude other causes. • Based on the severity (Grade) of the adverse reaction, permanently discontinue or withhold G9.2-17 (IGG4), administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. • Consider restarting G9.2-17 (IGG4) after completion of corticosteroid taper based on the severity of the event, resuming at a 50% dose reduction.

Dose-Reduction Procedure for Adverse Event Management

In the event where dose-reduction is used for AE management in Part 2 of the study, two dose reductions of 50% each are allowed. Dose reductions are pursued when clinical benefit is expected and may continue to be derived.

Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (eg, clinical chemistry, hematology, and urinalysis) or other abnormal assessments (eg, ECGs or vital signs) that are judged as clinically significant are recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at screening and significantly worsen following the start of the study are reported as

AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

- 5 Laboratory measurements that deviate clinically significantly from previous measurements may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

Time Period and Frequency for Collecting AE and SAE Information

- 10 All AEs and SAEs are collected from the start of intervention until the follow-up visit at the time points specified in the SoA (**Table 13** and **Table 14**).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent are recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs are recorded and reported immediately and under no circumstance should this exceed 24 h.

15

Follow-up of AEs and SAEs

After the initial AE/SAE report, it is required to proactively follow each participant at subsequent visits/contacts. All SAEs are followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

20 **Statistical Considerations**

The study is completed when the last patient has had their last visit. The database is locked for the primary analysis after the last patient has had their primary endpoint event. A final study analysis is performed after study completion.

25 ***Statistical Hypotheses***

The current study is designed to identify the MTD of G9.2-17 (IgG4) (Part 1) by assessing DLTs, followed by an assessment of drug activity (alone or in combination) in the three disease types using Simon's two-stage optimal design. Study hypotheses for Part 2 are detailed below.

CRC and CCA G9.2-17 (IgG4) single agent treatment arms

30

- Null hypothesis: ORR 3 is $\leq 5\%$
- Alternative hypothesis: ORR 3 is $\geq 15\%$.

PDAC G9.2-17 (IgG4) + gemcitabine/nab-paclitaxel combination treatment

In the 1st line metastatic setting using gemcitabine/nab-paclitaxel, the PFS 6 was reported to be 50% (Von Hoff et al., 2013). This study tests the following:

- Null hypothesis: PFS 6 is $\leq 50\%$
- Alternative hypothesis: PFS 6 is 75%.

5 ***Analysis Sets***

The intent-to-treat (ITT) population is defined as those patients who received at least one dose of the study drug, unless otherwise specified. The primary efficacy analyses are performed for the ITT. Patient disposition is performed for the ITT.

10 The Efficacy Population is defined as all patients in the ITT and having at least one measurable ORR 3 or PFS 6 assessment. This population is used for a sensitivity analysis.

The per-protocol (PP) Population is defined as any patient who received at least one full cycle of G9.2-17 (IGG4) and without major protocol deviations.

The safety population (SAF) is defined as all patients who receive at least one dose of the study drug. The safety analyses are performed for the SAF.

15 The PK/PD population is defined as those patients who have received at least one full cycle of G9.2-17 (IGG4).

Primary Endpoint(s)

Safety Analysis – Part 1 and Part 2

20 All safety analyses are made on the SAF unless otherwise specified.

Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events that occur on or after the first dose of study medication. The MedDRA coding dictionary is used for the coding of AEs. TEAEs, serious or CTCAE Grade 3 or Grade 4 TEAEs, and TEAEs related to treatment are
25 summarized overall and by system organ class and preferred term by treatment group. These summarize the number of events and the number and percent of patients with a given event. In addition, the number and percent of patients with TEAEs are provided by maximum severity. A summary of all TEAEs by system organ class and preferred term occurring in $\geq 5\%$ of patients in either treatment group is provided.

30 DLTs, the MTD and the RP2D are summarized.

Laboratory Assessments

All laboratory-based data is presented as listings of all values as well as of abnormal results judged to be clinically significant, which is reported as AEs. Numeric summaries of all observed findings and changes from baseline screening laboratory evaluations are provided by visit and treatment group, including chemistry, hematology, and urinalysis results. No inferential
5 comparisons are planned.

Vital Signs

Numeric summaries of all observed findings and changes from baseline screening vital signs are provided by time point and treatment group, including blood pressure, heart rate, respiratory rate, and temperature. No inferential analyses are planned for vital signs.

10 *ECGs, ECHO/MUGA, and Physical Examination*

Physical examination data and changes are presented as listings. ECG results are presented as listings and summarized by treatment group and visit, based on incidence of clinically significant abnormalities. No inferential comparisons across treatment groups are planned.

15 Primary Efficacy Analysis - Part 2

Disease response is assessed according to RECIST v1.1 and is summarized descriptively for the ITT, PP, and Efficacy Populations.

The primary efficacy endpoints are:

- ORR 3 for CRC and CCA
- 20 • PFS 6 for PDAC

Secondary Endpoint(s)

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

PK, PD, and immunogenicity are summarized descriptively for the PK/PD population in
25 both Part 1 and Part 2.

Secondary Efficacy Analysis - Part 2

Disease response (ORR, PFS, DCR, DoR, and OS) is assessed according to RECIST v1.1 and is summarized descriptively for the ITT, PP, and Efficacy Populations.

30

Exploratory Endpoints

Analysis of exploratory endpoints is detailed in the SAP.

Other Analysis

Other collected data not specifically mentioned is presented in patient listings.

Disposition, Demographics, Baseline Characteristics, and Medical History

5 Disposition information is summarized including the number of enrolled patients, screening failures, treated patients, and the number of patients withdrawn by reason.

Demographics, baseline characteristics, and medical history is summarized by treatment group and overall using descriptive statistics for the ITT and PP.

Prior and Concomitant Medications

10 Number and percentage of patients taking prior and concomitant medications is summarized by treatment group and overall for the ITT and PP.

Example 3. A non-GLP Single-Dose, Range-Finding Intravenous Toxicity Study in Male Sprague Dawley Rats with 1- and 3-Week Postdose Observation Periods

15 This study evaluated the anatomical endpoints of G9.2-17 IgG4 following a single intravenous bolus administration to Sprague Dawley rats followed by 1-week (terminal) and 3-week (recovery) necropsies on Days 8 and 22. All animals survived to the scheduled necropsies. There were no test article-related macroscopic findings, organ weight changes, or microscopic findings in either the terminal or recovery necropsy animals on this study.

20 The objective of this non-GLP exploratory, single-dose, range finding, intravenous toxicity study was to identify and characterize the acute toxicities of G9.2-17 IgG4 following intravenous bolus administration over 2 minutes to Sprague Dawley rats followed by 1-week (terminal) and 3-week (recovery) postdose observation periods.

This non-GLP single dose toxicity study was conducted in 24 Sprague Dawley male rats to
25 determine the toxicokinetics and potential toxicity of G9.2-17 IgG4 at different doses in a single administration. Animals were administered either vehicle or 10 mg/kg, 30 mg/kg or 70 mg/kg G9.2-17 IgG4 by slow bolus intravenous infusion for at least 2 minutes on Day 1 followed by either a 1-week (terminal, Day 8) or 3-week (recovery, Day 22) period after the dose. Study endpoints included mortality, clinical observations, body weights, and food consumption, clinical
30 pathology (hematology, coagulation, clinical chemistry and urinalysis), toxicokinetic parameters,

ADA evaluation and anatomic pathology (gross necropsy, organ weights, and histopathology).

Summaries of the experimental design is provided in **Table 17** below.

Table 17. Experimental Design

Group Number	Treatment	Dosage Level (mg/kg)	Number of Males ^a
1	Vehicle ^b	0	6
2	G9.2-17 IgG4	10	6
3	G9.2-17 IgG4	30	6
4	G9.2-17 IgG4	70	6

^a 3 animals/sex/group were euthanized at the Day 8 terminal necropsy; the remaining 3 animals/sex/group were euthanized at the Day 22 recovery necropsy.

^b The vehicle was Formulation Buffer (20mM Tris, 150mM NaCl, pH 8.0 ±0.05).

5 All surviving animals were submitted for necropsy on Day 8 or Day 22. Complete postmortem examinations were performed and organ weights were collected. The organs were weighed from all animals at the terminal and recovery. Tissues required for microscopic evaluation were trimmed, processed routinely, embedded in paraffin, and stained with hematoxylin and eosin.

10 There were no unscheduled deaths during the course of this study. All animals survived to the terminal or recovery necropsies. Histological changes noted were considered to be incidental findings or related to some aspect of experimental manipulation other than administration of the test article. There was no test article related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations. No G9.2-17 IgG4-related findings were noted in clinical observations, body weights, food consumption, clinical pathology or anatomic pathology.

15 In conclusion, the single intravenous administration of 10, 30, and 70 mg/kg G9.2-17 IgG4 to Sprague Dawley rats was tolerated with no adverse findings. Therefore, under the conditions of this study the NOEL was 70 mg/kg.

Example 4. A non-GLP Single-Dose, Range-Finding Intravenous Infusion Toxicity Study of G9.2-17 IgG4 in Cynomolgus Monkeys with a 3-Week Post-Dose Observation Period

20 This non-GLP single-dose toxicity study was conducted in 8 cynomolgus monkeys to identify and characterize the acute toxicities of G9.2-17 IgG4 administered at different doses as a single dose. Animals (1 male [M]/1 female [F]/group) were administered either vehicle or 30

mg/kg, 100 mg/kg, or 200 mg/kg G9.2-17 IgG4 by 30-minute intravenous (IV) infusion followed by a 3 week post-dose observation period. Study endpoints included: mortality, clinical observations, body weights, and qualitative food consumption; clinical pathology (hematology, coagulation, clinical chemistry, immunophenotyping and galectin 9 expression on leukocyte subsets, and cytokine analysis); toxicokinetic parameters; serum collection for possible anti-drug antibody evaluation (ADA); and soluble galectin-9 analyses; and anatomic pathology (gross necropsy, organ weights, and histopathology).

No G9.2-17 IgG4-related findings were noted in clinical observations, body weights, food consumption, clinical pathology (hematology, clinical chemistry, coagulation, or cytokine analysis), immunophenotyping, galectin-9 expression on leukocyte subsets, soluble galectin-9 or anatomic pathology.

In conclusion, the single intravenous infusion administration of 30, 100, and 200 mg/kg G9.2-17 IgG4 to cynomolgus monkeys was tolerated with no adverse findings. Therefore, under the conditions of this study the No-observed-Adverse-Effect-Level (NOAEL) was 200 mg/kg, the highest dose level evaluated. The study design is shown in **Table 18**.

Table 18. Experimental Design

Group No.	Treatment	Dose Level (mg/kg)		Adjusted Dose Concentration (mg/mL)		Dose Volume (mL/kg)		Animal No.
					Males	Necropsy Day	Females	Necropsy Day
1	Vehicle	0	0	20	1001	22	1501	22
2	G9.2-17 IgG4	30	1.5	20	2001	22	2501	22
3	G9.2-17 IgG4	100	5	20	3001	22	3501	22
4 ^a	G9.2-17 IgG4	200	10	20	4001	22	4501	22

^a Group 4 was administered 1 week after administration of Groups 1 through 3.

Group No.	Treatment	Dose Level (mg/kg)	Adjusted Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Animal No.			
					Males	Necropsy Day	Females	Necropsy Day
1	Vehicle	0	0	20	1001	22	1501	22
2	G9.2-17 IgG4	30	1.5	20	2001	22	2501	22
3	G9.2-17 IgG4	100	5	20	3001	22	3501	22
4 ^a	G9.2-17 IgG4	200	10	20	4001	22	4501	22

^a Group 4 was administered 1 week after administration of Groups 1 through 3.

The vehicle and test article were administered once via IV infusion for 30 minutes during the study via a catheter percutaneously placed in the saphenous vein. The dose levels were 30, 100, and 200 mg/kg and administered at a dose volume of 20 mL/kg. The control group received the vehicle in the same manner as the treated groups.

The animals were placed in sling restraints during dosing. The vehicle or test article were based on the most recent body weights and administered using an infusion pump and sterile disposable syringes. The dosing syringes were filled with the appropriate volume of vehicle or test article (20 mL/kg with 2 mL extra). At the completion of dosing, the animals were removed from the infusion system. The weight of each dosing syringe was recorded prior to the start and end of each infusion to determine dose accountability.

Detailed clinical observations

The animals were removed from the cage, and a detailed clinical examination of each animal was performed at 1 and 4.5 hours post-start of infusion (SOI) on Day 1 and once daily thereafter during the study. The animals were removed from the cage, and a detailed clinical examination of each animal was performed at 1 and 4.5 hours post-start of infusion (SOI) on Day 1 and once daily thereafter during the study. Body weights for all animals were measured and recorded at transfer, prior to randomization, on Day -1, and weekly during the study.

Clinical pathology evaluations (hematology, coagulation, and clinical chemistry) were conducted on all animals pretest and on Days 1 (prior to dosing), 3, 8, and 21. Additional samples

for the determination of hematology parameters and peripheral blood lymphocyte and cytokine analysis samples were collected at 30 minutes (immediately after the end of infusion) and 4.5, 8.5, 24.5, and 72.5 hours post-SOI (relative to Day 1). Bone marrow smears were collected and preserved.

- 5 Blood samples (approximately 0.5 mL) were collected from all animals via the femoral vein for determination of the serum concentrations of the test article (see **Table 19**) (for a deviation, see Appendix 1). The animals were not fasted prior to blood collection, with the exception of the intervals that coincided with fasting for clinical pathology collections.

Table 19. Bioanalysis Sample Collection Schedule

Group No.	Sample Collection Time Points (Time Post-SOI) relative to Day 1												
	Predose	0.583 hr ^a	1 hr	2.5 hr	4.5 hr	8.5 hr	24.5 hr (Day 2)	48.5 hr (Day 3)	72.5 hr (Day 4)	120.5 hr (Day 6)	168.5 hr (Day 8)	360.5 hr (Day 16)	504.5 hr (Day 22)
1 - 4	X	X	X	X	X	X	X	X	X	X	X	X	X

X = Sample was collected.

^a: Only the 0.583 hr post-SOI timepoint from Group 1 animals was analyzed for test article content. Additional timepoints may be analyzed at the discretion of the Study Director.

- 10 For processing, blood samples were collected in non-additive barrier free microtubes and centrifuged at controlled room temperature within 1 hour of collection. The resulting serum was divided into 2 approximately equal aliquots in pre labeled cryovials. All aliquots were stored frozen at -60°C to -90°C within 2 hours of collection.

- 15 Postmortem study evaluations were performed on all animals euthanized at the scheduled necropsy.

- 20 Necropsy examinations were performed under procedures approved by a veterinary pathologist. The animals were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any subcutaneous masses were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities. The organs were removed, examined, and, where required, placed in fixative. All designated tissues were fixed in neutral buffered formalin (NBF), except for the eyes (including the optic nerve) and testes. The eyes (including the optic nerve) and testes were placed in a modified Davidson's fixative, and then transferred to 70% ethanol for up to three days prior to final placement in NBF. Formalin was infused into the lung via the trachea. A full

complement of tissues and organs was collected from all animals.

Body weights and protocol-designated organ weights were recorded for all animals at the scheduled necropsy and appropriate organ weight ratios were calculated (relative to body and brain weights). Paired organs were weighed together. A combined weight for the thyroid and parathyroid glands was collected.

Results

All animals survived to the scheduled necropsy on Day 22. No test article-related clinical or veterinary observations were noted in treated animals. No test article-related effects on body weight were observed in treated animals during the treatment or recovery period. There were no G9.2-17 IgG4-related effects on hematology endpoints in either sex at any dose level at any interval.

There were no G9.2-17 IgG4-related effects on coagulation times (i.e., activated partial thromboplastin times [APTT] and prothrombin times) or fibrinogen concentrations in either sex at any dose level at any interval. All fluctuations among individual coagulation values were considered sporadic, consistent with biologic and procedure-related variation, and/or negligible in magnitude, and not related to G9.2-17 IgG4 administration.

There were no G9.2-17 IgG4-related effects on clinical chemistry endpoints in either sex at any dose level at any interval. All fluctuations among individual clinical chemistry values were considered sporadic, consistent with biologic and procedure-related variation, and/or negligible in magnitude, and not related to G9.2-17 IgG4 administration.

There were no G9.2-17 IgG4-related effects on cytokine endpoints in either sex at any dose level at any interval. All fluctuations among individual cytokine values were considered sporadic, consistent with biologic and procedure-related variation, and/or negligible in magnitude, and not related to G9.2-17 IgG4 administration.

Review of the gross necropsy observations revealed no findings that were considered to be test article related. There were no organ weight alterations that were considered to be test article-related. There were no test article-related changes.

In conclusion, the single intravenous infusion administration of 30, 100, and 200 mg/kg G9.2-17 IgG4 to cynomolgus monkeys was tolerated with no adverse findings. Therefore, under the conditions of this study the No-observed-Adverse-Effect-Level (NOAEL) was 200 mg/kg, the highest dose level evaluated.

The animals were removed from the cage, and a detailed clinical examination of each animal was performed at 1 and 4.5 hours post-start of infusion (SOI) on Day 1 and once daily thereafter during the study.

5 Example 5. Intravenous Infusion Study of G9.2-17 in Cynomolgus Monkeys

The objective of this study was to further characterize the toxicity and toxicokinetics of the test article, G9.2-17 (a hIgG4 Monoclonal Antibody which binds to Galectin-9) at different doses, following once weekly 30-minute intravenous (IV) infusion for 5 weeks in cynomolgus monkeys, and to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 3-week recovery period.

Experimental Design

Table 20 summarizes the study design.

Table 20. Experimental Design

Group No.	Test Material	Dose Level (mg/kg/dose)	Dose Volume ^a (mL/kg)	Dose Concentration (mg/mL)	Main Study		Recovery Study	
					No. of Males	No. of Females	No. of Males	No. of Females
1	Vehicle	0	10	0	3	3	2	2
2	G9.2-17	100	10	10	3	3	2	2
3	G9.2-17	300	10	30	3	3	2	2

^a Based on the most recent practical body weight measurement.

Animals (cynomolgus monkeys) used in the study were assigned to study groups by a standard, by weight, randomization procedure designed to achieve similar group mean body weights. Males and females were randomized separately. Animals assigned to study had body weights within $\pm 20\%$ of the mean body weight for each sex.

The formulations lacking G9.2-17 (“vehicle”) or encompassing G9.2-17 (“test article”) were administered to the animals once weekly for 5 weeks (Days 1, 8, 15, 22, and 29) during the study via 30-minute IV infusion. The dose levels were 0, 100 and 300 mg/kg/dose and administered at a dose volume of 10 mL/kg. The control animals group received the vehicle in the same manner as the treated groups. Doses were administered via the saphenous vein via a percutaneously placed catheter and a new sterile disposable syringe was used for each dose. Dose accountability was measured and recorded prior to dosing and at the end of dosing on toxicokinetic

sample collection days (Days 1, 15, and 29) to ensure a $\pm 10\%$ target dose was administered. Individual doses were based on the most recent body weights. The last dose site was marked for collection at the terminal and recovery necropsies. All doses were administered within 8 hours of test article preparation.

5 In-life procedures, observations, and measurements were performed on the animals as exemplified below.

Electrocardiographic examinations were performed on all animals. Insofar as possible, care was taken to avoid causing undue excitement of the animals before the recording of electrocardiograms (ECGs) in order to minimize extreme fluctuations or artifacts in these
10 measurements. Standard ECGs (10 Lead) were recorded at 50 mm/sec. Using an appropriate lead, the RR, PR, and QT intervals, and QRS duration were measured and heart rate was determined. Corrected QT (QTc) interval was calculated using a procedure based on the method described by Bazett (1920). All tracings were evaluated and reported by a consulting veterinary cardiologist.

To aid in continuity and reliability, functional observational battery (FOB) evaluations
15 were conducted by two independent raters for all occasions and consisted of a detailed home cage and open area neurobehavioral evaluation (Gauvin and Baird, 2008). Each technician scored the monkey independently (without sharing the results with each other) for each home cage and out of cage observational score, and then the individual scores were assessed for agreement with their partner's score after the completion of the testing. FOB evaluations were conducted on each
20 animal predose (on Day -9 or Day 8) to establish baseline differences and at 2 to 4 hours from the start of infusion on Days 1 and 15, and prior to the terminal and recovery necropsies. The observations included, but were not limited to, evaluation of activity level, posture, lacrimation, salivation, tremors, convulsions, fasciculations, stereotypic behavior, facial muscle movement, palpebral closure, pupil response, response to stimuli (visual, auditory, and food), body
25 temperature, Chaddock and Babinski reflexes, proprioception, paresis, ataxia, dysmetria, and slope assessment, movement, and gait.

Blood pressure of each animal was measured and recorded and consisted of systolic, diastolic, and mean arterial pressure. Blood pressure measurements are reported using three readings that have the Mean Arterial Pressure (MAP) within 20 mmHg.

30 Respiratory rates of each animal were measured and recorded 3 times per animal/collection interval by visual assessment per Testing Facility SOP. The average of the 3 collections is the

reported value.

Clinical pathology evaluations (*e.g.*, immunophenotyping and cytokine evaluations) were conducted on all animals at predetermined intervals. Bone marrow smears were collected and preserved. Blood samples (approximately 0.5 mL) were collected from all animals via the femoral vein for determination of the serum concentrations of the test article. The animals were not fasted prior to blood collection, with the exception of the intervals that coincided with fasting for clinical pathology collections. At the conclusion of the study (day 36 or day 50), animals were euthanized and tissues for histology processing and microscopic evaluation were collected.

Soluble galectin-9 was evaluated as follows. Blood samples (approximately 1 mL) were collected from all animals via the femoral vein for determination of the serum for soluble galectin 9 predose and 24 hours from the start of infusion on Days 1, 8, 15, and 29, and prior to the terminal and/or recovery necropsies. The animals were not fasted prior to blood collection, with the exception of the intervals that coincided with fasting for clinical pathology collections.

Soluble galectin-9 samples were processed as follows. Blood samples were collected in non-additive, barrier free tubes, allowed to clot at ambient temperature, and centrifuged at ambient temperature. The resulting serum was divided into 2 aliquots (100 µL in Aliquot 1 and remaining in Aliquot 2) in pre labeled cryovials. All aliquots were flash frozen on dry ice within 2 hours of collection and stored frozen at -60°C to 90°C.

All results presented in the tables of the report were calculated using non-rounded values as per the raw data rounding procedure and may not be exactly reproduced from the individual data presented.

Results

• Mortality

All animals survived to the scheduled terminal necropsy on Day 36 and recovery necropsy on Day 50.

• Detailed Clinical and Veterinary Observations

No test article-related clinical or veterinary observations were noted in treated animals during the treatment or recovery periods.

• Functional Observational Battery

No test article-related FOB observations were noted in treated animals during the treatment or recovery periods.

- **Body Weight and Body Weight Gains**

5 No test article-related effects in body weight and body weight gain were noted in treated animals during the treatment or recovery periods.

- **Ophthalmology Examinations**

No test article-related effects in ophthalmology examinations were noted in treated animals during the treatment or recovery periods.

- **Blood Pressure Values**

10 No test article-related effects in blood pressure values were noted in treated animals during the treatment or recovery periods.

- **Respiratory Rate Values**

No test article-related effects in respiratory rate values were noted in treated animals during the treatment or recovery periods.

15

- **Electrocardiology**

No test article-related effects in electrocardiographic evaluations were noted in treated animals during the treatment or recovery periods.

- **Hematology**

20 There were no G9.2-17-related effects among hematology parameters in either sex at any dose level at any timepoint.

- **Coagulation**

There were no G9.2-17-related effects among coagulation parameters in either sex at any dose level at any timepoint.

- **Clinical Chemistry**

25 There were no G9.2-17-related effects among clinical chemistry parameters in either sex at any dose level at any timepoint.

- **Urinalysis**

No G9.2-17-related alterations were observed among urinalysis parameters in either sex at any dose level at the 13-week interim.

- **Cytokine**

5 No definitive G9.2-17-related effects on cytokines were seen at any dose level or timepoint.

- **Peripheral Blood Leukocyte Analysis (PBLA)**

There were no G9.2-17-related effects on PBLA endpoints in either sex at any dose level at any time point.

10 • **Bioanalysis, Galectin-9, and Toxicokinetic Evaluation**

G9.2-17 was quantifiable in all cynomolgus monkey samples from all G9.2-17-dosed animals after dose administration. No measurable amount of G9.2-17 was detected in control cynomolgus monkey samples. Soluble galectin-9 was quantifiable in all cynomolgus monkey samples from all animals. G9.2-17 serum concentrations were below the bioanalytical limit of quantitation (LLOQ < 0.04 ug/mL) in all serum samples obtained predose from most G9.2-17
15 treated animals on Day 1 and from control animals on Days 1 and 29.

- **Gross Pathology and Organ Weight**

There were no definitive test article-related macroscopic observations in main study or recovery animals. There were also no test article-related organ weight changes for main study or
20 recovery animals.

- **Histopathology**

There were no definitive test article-related microscopic observations.

In conclusion, once weekly intravenous infusion administration of 100 and 300 mg/kg of G9.2-17 for 5-weeks to cynomolgus monkeys was tolerated with no adverse findings.

25

Example 6. Intravenous Infusion Study of G9.2-17 in Sprague Dawley Rats

The objective of this study was to evaluate potential toxicity of G9.2-17, an IgG4 human monoclonal antibody directed against galectin-9 at different doses, when administered by

intravenous infusion to Sprague Dawley Rats once weekly for 4 consecutive weeks followed by a 3-week post dose recovery period. In addition, the toxicokinetic characteristics of G9.2-17 were determined.

5 Experimental Design

Table 21 summarizes the study design.

Table 21: Study Design

Group	Test Material	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume ^a (mL/kg)	Terminal		Recovery		TK/Gal-9/Cyto	
					M	F	M	F	M	F
1	Control	0	0	10	10	10	5	5	12	12
2	G9.2-17	100	10	10	10	10	5	5	12 +6 ^b	12+6 ^b
3	G9.2-17	300	30	10	10	10	5	5	12+6 ^b	12+6 ^b

^a Individual dose volumes were calculated based on the most recent body weight.

^b SSD animals: 3 animals/sex/group for TK collections only following a single dose administration on Day 1.

10

One hundred eighty-six animals (Sprague Dawley rats) were assigned to treatment groups randomly by body weight. Control Article/Vehicle, Formulation Buffer for Test Article, and test article, G9.2-17, were administered via a single IV injection in a tail vein at dose levels of 0, 100, and 300 mg/kg once on Days 1, 8, 15, 22, and 29. Test article was administered at dose levels of 100 and 300 mg/kg once on Day 1 to animals assigned to the SSD subgroup.

15

Clinical observations were performed once daily prior to room cleaning in the morning, beginning on the second day of acclimation. A mortality check was conducted twice daily to assess general animal health and wellness. Food consumption was estimated by weighing the supplied and remaining amount of food in containers once weekly. The average gram (g)/animal/day was calculated from the weekly food consumption. Body weights were taken prior to randomization, on Day -1, then once weekly throughout the study, and on the day of each necropsy. Functional Observation Battery (FOB) observations were recorded for SSB animals approximately 24 hours post dose administrations on Days 1, 35 and 49. Urine was collected overnight using metabolic

20

cages. Samples were obtained on Days 36 and 50.

Animals were fasted overnight prior to each series of collections that included specimens for serum chemistry. In these instances, associated clinical pathology evaluations were from fasted animals. Blood was collected from a jugular vein of restrained, conscious animals or from the vena cava of anesthetized animals at termination.

Parameters assessed during the In-life examinations of the study included clinical observations, food consumption, body weights, functional observational battery. Blood samples were collected at selected time points for clinical pathology (hematology, coagulation, and serum chemistry) analyses. Urine samples were collected for urinalysis. Blood samples were also collected at selected time points for toxicokinetic (TK), immunogenicity (e.g., anti-drug antibody or ADA), and cytokine analyses. Animals were necropsied on Days 36 and 50. At each necropsy, gross observations and organ weights were recorded, and tissues were collected for microscopic examination.

Results

In-life Examinations

Mortality: There were no abnormal clinical observations or body weight changes noted for this animal during the study.

Clinical Observations: There were no G9.2-17-related clinical observations noted during the study.

Food Consumption/ Body Weights: There were no G9.2-17-related changes in food consumption, body weights or body weight gain noted during the study.

Clinical Pathology: There were no G9.2-17-related changes noted in clinical pathology parameters.

Cytokine Analysis: There were no G9.2-17-related changes in serum concentrations of IL-2, IL-4, IFN- γ , IL-5, IL-6, IL-10, and/or TNF- α , MCP-1 and MIP-1b.

Gross Pathology: There were no G9.2-17-related gross observations. Further, there were no G9.2-17-related changes in absolute or relative organ weights.

Histopathology: There were no G9.2-17-related histologic findings.

In conclusion, intravenous G9.2-17 administration to Sprague Dawley rats once weekly for

a total of 5 doses was generally well tolerated. There were no G9.2-17-related changes in clinical observations, food consumption, body weights, FOB parameters, clinical pathology, cytokine, gross observations, or organ weights.

5 **Example 7. Inhibition of Polarization and Repolarization of M2 Macrophages**

Macrophages play an indispensable role in the immune system with decisive functions in both innate and acquired immunity. M1 macrophages are generally considered potent effector cells which can kill tumor cells, while M2 polarized macrophages express a series of cytokines, chemokines, and proteases to promote angiogenesis, lymphangiogenesis, tumor growth, metastasis, and immunosuppression (Sica et al., 2008; Semin. Cancer Biol. 2008;18: 349–355). In M2 macrophages, production of anti-inflammatory cytokines, such as TGF- β and IL-10, is enhanced (Martinez et al., Front Biosci. 2008 Jan 1;13:453-61., Mantovani et al., Trends Immunol 2002 Nov;23(11):549-55.; Zhang et al., J Hematol Oncol 10, 58 (2017)). Given that macrophages comprise a key component of the host immune response, inhibition of polarization or repolarization of M2 macrophages is an important therapeutic consideration in oncological immunotherapy (Poh and Ernst, Front Oncol. 2018 Mar 12; 8:49).

Whole blood from three healthy human donors was used to isolate CD14+ monocytes. The monocytes were allowed to differentiate to macrophages in X-VIVO-15 media (Lonza) in a 10 cm tissue culture dish for 7 days. The differentiated macrophages were either used directly for assessing inhibition of polarization, or they were cryopreserved and used at a later time for repolarization assays. Prior to use in an assay, the M0 macrophages were phenotyped.

Two different polarization cocktails were used to evaluate macrophage polarization: one with a mixture of IL-4 and IL-13, and a second containing only gal-9. The effect of G9.2-17 on M2 polarization was tested via its direct addition to one of these cocktails, and incubation with macrophages for 48 hours. The effect of G9.2-17 on repolarization of M2 macrophages was tested via addition to the M2-polarized macrophages.

The state of polarization was identified by the measurement of secretion of either IL-10 (repolarization) or TGF-beta1 (inhibition of polarization and repolarization). These factors were quantified in cell culture supernatants using CytoMetric Bead Arrays following the manufacturer's protocol.

Representative data from one donor showing the effect of G9.2-17 on polarization of fresh

monocyte-derived macrophages is in **Fig. 5**. All donor macrophages showed similar results, with a decrease in TGF-beta1 secretion following incubation with G9.2-17 compared to the isotype matched control or untreated cells. **Fig. 5** shows the effect on TGF-beta1 secretion by previously frozen macrophages following incubation with G9.2-17 or an isotype matched control. Treatment with 20 ng/mL of polarization cocktail significantly induced TGF- β 1 secretion, while G9.2-17 treatment abolished the IL-4/IL-13-dependent increase of TGF- β 1 secretion. **Fig. 6** shows the effects on IL-10 secretion on repolarization of cryopreserved macrophages. Treatment with G9.2-17 led to a reduction of secreted IL-10 and TGF-b1 levels in all donors compared to untreated and IgG4 isotype control antibody controls, in the presence of both types of polarization cocktails.

This assay confirms that G9.2-17 can potently inhibit TGF-beta1 and IL-10 at the concentration of 20 μ g/ml.

Example 8. Measurement of Biomarkers

A multiplex Immunofluorescence (mIF) technology, is performed on clinical tissues from patients. The mIF assay consists of 10 rounds of staining with two biomarkers stained and imaged per round for a total of ten rounds. For every round, one antibody is conjugated to one of two fluorescent dyes that will allow imaging of the biomarker such that two biomarkers are imaged each round. Biomarkers are stained, imaged, and then the signal is quenched to allow for further staining and imaging rounds to occur without bleed-through of competing signal. When the staining and imaging of the entire 19-marker panel is complete, positivity of each biomarker on cells is classified by deep learning algorithms that are trained to detect positive signal. When analysis is complete, various data is generated, including density and raw counts of positive cells for each biomarker and co-expression of interest. Biomarkers include CD3, CD4, CD8, CD45RO, FoxP3, CD11b, CD14, CD15, CD16, CD33, CD68, CD163, HLA-DR, Arginase1, Granzyme B, Ki67, PD1, PD-L1, F4/80, Ly6G/C and PanCK.

Example 9. Evaluating Mouse Galectin-9 in Plasma by ELISA

This study evaluated galectin-9 in plasma of orthotopic pancreatic cancer xenograft model mPA6115 in female C57BL/6 mice (same mouse model as in Example 1 above). Mice were assigned to multiple groups and treated following the study design illustrated in Table 3 above. As per the protocol, plasma samples were collected from retro orbital sinus on day 3 before the 1st

dose for all mice from Group 1-6 engrafted with tumors (pre-dose) and 10 non-tumor bearing mice in Group 7 (tumor implantation was on day 0) and by cardiac puncture at termination for euthanized mice which were moribund (post-dose).

Levels of galectin-9 in the plasma samples were analyzed by ELISA following the below procedure:

1. Brought all reagents and samples to room temperature (18 - 25°C) before use. It was recommended that all standards and samples be run at least in duplicate.
2. Labeled removable 8-well strips as appropriate for your experiment.
3. Added 100 µl of each standard and prepared samples into appropriate wells.
- 10 Covered wells and incubate for 2.5 hours at room temperature with gentle shaking.
4. Discarded the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with Wash Buffer (300 µl) using a multi-channel Pipette or autowasher. Complete removal of liquid at each step was essential to good performance. After the last wash, removed any remaining Wash Buffer by aspirating or decanting. Inverted the plate and blot it against clean
- 15 paper towels.
5. Added 100 µl of 1X prepared biotinylated antibody (Reagent Preparation step 3) to each well. Incubated for 1 hour at room temperature with gentle shaking.
6. Discarded the solution. Repeat the wash as in step 4.
7. Added 100 µl of prepared Streptavidin solution to each well. Incubated for 45
- 20 minutes at room temperature with gentle shaking.
8. Discarded the solution. Repeat the wash as in step 4.
9. Added 100 µl of TMB One-Step Substrate Reagent to each well. Incubated for 30 minutes at room temperature in the dark with gentle shaking.
10. Added 50 µl of Stop Solution to each well. Read at 450 nm immediately.

25

The results demonstrated that galectin-9 serum levels increased in the mPA6115 mouse model once tumors were orthotopically engrafted, which was aligned with observations in pancreatic adenocarcinoma cancer patients. This study demonstrated that galectin-9 serum levels increased significantly in animals where pancreatic ductal adenocarcinomas were growing

30 orthotopically. This implies that the source of such galectin-9 is indeed the tumor tissue, further supporting the therapeutic approach of blocking galectin-9 in this disease context.

EQUIVALENTS

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, 5 can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

While several inventive embodiments have been described and illustrated herein, those of ordinary skill in the art are readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages 10 described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art are readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations are depend upon the specific application or applications for which the inventive 15 teachings is/are used. Those skilled in the art are recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive 20 embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

25 All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

All references, patents and patent applications disclosed herein are incorporated by reference with respect to the subject matter for which each is cited, which in some cases may 30 encompass the entirety of the document.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims,

unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, *i.e.*, elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, *i.e.*, “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, *i.e.*, the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” are refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (*i.e.*, “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including

elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

- 5 It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

What Is Claimed Is:

1. A method for treating a solid tumor, comprising administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal9 antibody) and an effective amount of one or more chemotherapeutics; wherein the anti-Gal9 antibody has the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17, and wherein the subject has 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.
2. The method of claim 1, wherein the anti-Gal9 antibody is administered to the subject at a dose of about 0.2 mg/kg to about 32 mg/kg once every two weeks to once every 6 weeks, optionally once every two weeks.
3. The method of claim 2, wherein the anti-Gal9 antibody is administered to the subject at a dose of about 0.2 mg/kg to about 16 mg/kg once every two weeks to once every six weeks, optionally once every two weeks.
4. The method of claim 3, wherein the anti-Gal9 antibody is administered to the subject 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.
5. The method of claim 1, wherein the anti-Gal9 antibody is administered to the subject at a dose of about 650 mg to about 1120 mg once every two weeks to once every six weeks, optionally once every two weeks.
6. The method of claim 5, wherein anti-Gal9 antibody is administered to the subject at a dose of about 650 mg to about 700 mg once every two weeks to once every six weeks,

optionally once every two weeks, or at a dose of about 1040 mg to about 1120 mg once every two weeks to once every six weeks, optionally once every two weeks.

7. A method for treating a solid tumor, comprising administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal9 antibody) and an effective amount of 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 administered to the subject at a dose of about 0.2-32 mg/kg once every week, optionally wherein the anti-Galectin-9 antibody is administered to the subject at a dose of about 10 mg/kg to about 16 mg/kg once every week.

8. The method of claim 7, wherein the anti-Gal-9 antibody is administered to the subject at a dose of 10 mg/kg or 16 mg/kg once every week.

9. The method of claim 8, wherein the anti-Gal-9 antibody is administered to the subject at a dose of about 650 mg to about 1120 mg once every week.

10. The method of claim 9, wherein the anti-Gal9 antibody is administered to the subject at a dose of about 650 mg to about 700 mg once every week, or about 1040 to about 1120 mg once every week.

11. The method of any one of claims 1-10, wherein the solid tumor is a metastatic solid tumor.

12. The method of claim 11, wherein the solid tumor is pancreatic ductal
5 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.

13. The method of claim 12, wherein the subject has no locally advanced PDAC
10 without distant organ metastatic deposits.

14. The method of any one of claims 1-13, wherein the anti-Gal-9 antibody is administered to the subject by intravenous infusion.

15. The method of any one of claims 1-4, wherein the V_L of the anti-Gal-9 antibody comprises the amino acid sequence of SEQ ID NO: 8.

16. The method of any one of claims 1-15, wherein the V_H of the anti-Gal-9 antibody comprises the amino acid sequence of SEQ ID NO: 7.
20

17. The method of any one of claims 1-16, wherein the anti-Gal-9 antibody is a full-length antibody.

18. The method of claim 17, wherein the anti-Gal-9 antibody is an IgG1 or IgG4
25 molecule.

19. The method of claim 18, wherein the anti-Gal-9 antibody is a human IgG4 molecule having a modified Fc region relative to the wildtype human IgG4 counterpart.

20. The method of claim 19, wherein the modified Fc region comprises the amino acid sequence of SEQ ID NO: 14.
30

21. The method of any one of claims 1-20, 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.

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22. The method of any one of claims 1-21, wherein the one or more chemotherapeutics comprise an antimetabolite, a microtubule inhibitor, or a combination thereof.

23. The method of claim 22, wherein the antimetabolite is gemcitabine, the microtubule inhibitor is paclitaxel, or a combination thereof.

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24. The method of claim 23, wherein the paclitaxel is a protein-bound paclitaxel.

25. The method of claim 24, wherein the paclitaxel is a nanoparticle albumin-bound paclitaxel.

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26. The method of any one of claims 1-6 and 11-25, wherein the method comprises a cycle of 28 days, in which the anti-Gal-9 antibody is administered to the subject on day 1 and day 15 and the gemcitabine and paclitaxel are administered to the subject on day 1, day 8, and day 15.

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27. The method of any one of claims 7-25, wherein the method comprises a cycle of 28 days, in which the anti-Gal9 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.

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28. The method of any one of claims 23-27, wherein the paclitaxel is administered to the subject at 125 mg/m² intravenously.

29. The method of claim 28, wherein the gemcitabine is administered to the subject at 1000 mg/m².

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30. The method of any one of claims 1-29, wherein the subject is a human patient.

31. The method of any one of claims 1-30, wherein the subject comprises galectin-9
5 positive cancer cells or immune cells.

32. The method of any one of claims 1-31, wherein the subject has an elevated level of
galectin-9 relative to a control value.

10 33. The method of claim 32, wherein the subject has an elevated serum or plasma level
of galectin-9 relative to the control value.

34. The method of any one of claims 1-33, wherein the subject received at least one line
of systemic anti-cancer therapy.

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35. The method of any one of claims 1-34, wherein the subject 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.

20 36. The method of any one of claims 1-35, wherein 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;
- 25 (b) cytokine profile; and
- (c) galectin 9 levels.

37. The method of any one of claims 1-36, wherein the method further comprises
monitoring occurrence of one or more adverse effects in the subject.

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38. The method of claim 37, wherein the one or more adverse effects comprise hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity, gastrointestinal toxicity, or a combination thereof.

5 39. The method of claim 37 or 38, further comprising reducing the dose of the anti-Gal9 antibody, the dose of the one or more chemotherapeutics, or both, when an adverse effect is observed.

10 40. The method of claim 39, wherein 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.

15 41. The method of claim 40, wherein the method comprises reducing 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.

20 42. The method of claim 41, wherein the method comprises reducing the dose or terminating administration 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.

43. The method of claim 41 or 42, wherein the dose of the paclitaxel is reduced to 100 mg/m² – 75 mg/m².

25 44. The method of any one of claims 41-43, wherein the dose of the gemcitabine is reduced to 800 mg/m² – 600 mg/m².

30 45. The method of any one of claims 1-44, wherein the subject is administered multiple doses of the anti-Gal 9 antibody and a later dose is higher than an earlier dose.

46. The method of any one of claims 1-44, wherein the subject is administered multiple doses of the anti-Gal-9 antibody and a later dose is lower than an earlier dose.