

models of pancreatic ductal adenocarcinoma (PDA), 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

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.

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 one aspect, the present disclosure provides a use of (a) an antibody that binds human galectin-9 (anti-Gal9 antibody), and (b) one or more chemotherapeutics in the manufacture of a medicament for combination therapy to treat a solid tumor, 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 the one or more chemotherapeutics comprise gemcitabine, paclitaxel, or a combination thereof.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal9 antibody). The anti-Galectin-9 antibody may have the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17. The subject may be undergoing an anti-cancer therapy comprising one or more chemotherapeutics.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of an antibody that binds human galectin-9 (anti-Gal9 antibody) and an effective amount of one or more

chemotherapeutics. The anti-Gal9 antibody may have the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17.

In some examples, the method for treating a solid tumor disclosed herein may comprise administering to a subject in need thereof an effective amount of one or more chemotherapeutics. The subject may be undergoing a therapy comprising an antibody that binds human galectin-9 (anti-Gal9 antibody), which has the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as antibody G9.2-17.

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

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

In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose of about 0.5 mg/kg to about 32 mg/kg (e.g., about 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). In some examples, the anti-Galectin-9 antibody is administered to the subject once a week. In some examples, the anti-Galectin-9 antibody is administered to the subject once every 2 or 3 weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 2 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, or 16 mg/kg. In some examples, the antibody is administered once every 2 weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject at a dose selected from 2 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, or 16 mg/kg once every 2 weeks. In some examples, the anti-Galectin-9 antibody is administered once every 2 weeks for one cycle, once every 2 weeks for two cycles, once every 2 weeks for 3 cycles, once every 2 weeks for 4 cycles, or once every 2 weeks for more than 4 cycles. In some examples, the duration of treatment is 0-3 months, 0-6 months, 3-6 months, 6-12 months, 12-24 months or longer. In some examples, the duration of treatment is 12-24 months or longer. In some examples, the cycles extend for a duration of 3 months to 6 months, or 6 months to 12 months or 12 months to 24 months or longer. In some examples, the cycle length is modified, e.g., temporarily or permanently to a longer duration, e.g., 3 weeks or 4 weeks. In any of these examples, the anti-Galectin-9 antibody is administered to

the subject once a week, once every two weeks, once every three weeks, or once every four weeks. In some examples, the anti-Galectin-9 antibody is administered to the subject by intravenous infusion. In some examples, the cancer is PDA. In some examples, the cancer is metastatic cancer.

5 In some examples, the anti-Gal9 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 injection. 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 injection. In some examples, the anti-Gal9 antibody can be administered to the subject at a dose of about 2 mg/kg to about 16 mg/kg
10 once every two weeks by intravenous injection. 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 injection. 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 injection. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 8 mg/kg once every two weeks
15 by intravenous injection. 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 injection. 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 injection. In some examples, the anti-Gal9 antibody is administered to the subject at a dose of about 32 mg/kg once every two weeks by intravenous
20 injection.

In some examples, the method comprises a cycle of 28 days, in which the anti-Gal9 antibody is administered to the subject on day 1 and day 15 and gemcitabine and paclitaxel (e.g., nanoparticle albumin-bound paclitaxel) are administered to the subject on day 1, day 8, and day 15. In some examples, the paclitaxel is administered to the subject at 125 mg/m²
25 intravenously. In some examples, the gemcitabine is administered to the subject at 1000 mg/m².

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

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

In some examples, the subject to be treated by any of the methods disclosed herein can be a human patient. In some examples, the subject has galectin-9 positive cancer cells or immune cells. Such galectin-9 positive cancer cells or immune cells may be detected in tumor organoids derived from the subject. In some examples, the subject may have an elevated level of galectin-9 relative to a control value. For example, the subject may have an elevated serum or plasma level of galectin-9 relative to the control value.

In some examples, the subject may have received at least one line of systemic anti-cancer therapy. Alternatively or in addition, the subject may be free of prior therapy involving gemcitabine and/or paclitaxel. In some examples, the subject may have received a prior therapy involving gemcitabine and/or paclitaxel at least six months before administration of the anti-Gal9 antibody.

In any of the methods disclosed herein, 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 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 may also be examined.

Any of the methods disclosed herein may further comprise monitoring occurrence of one or more adverse effects in the subject. Exemplary adverse effects include, but are not limited to, hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity,

gastrointestinal toxicity, or a combination thereof. When one or adverse effects are observed, the method disclosed herein may further comprise reducing the dose of the anti-Gal9 antibody, the dose of the one or more chemotherapeutics, or both. For example, when moderate to severe hepatic impairment is observed in a subject, the method may further
5 comprise reducing the dose of the anti-Gal9 antibody, the dose of gemcitabine, the dose of paclitaxel, or a combination thereof.

In some examples, administration of the paclitaxel is withheld when the subject has a level of aspartate transaminase (AST) greater than 10x upper limit of normal (ULN), a level of bilirubin greater than 5x ULN, or both. In some examples, the method may further
10 comprise reducing the dose or terminating administration of the anti-Gal9 antibody, gemcitabine, 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 may be reduced to $100 \text{ mg/m}^2 - 75 \text{ mg/m}^2$. Alternatively or in addition, the dose of gemcitabine is reduced to $800 \text{ mg/m}^2 - 600 \text{ mg/m}^2$.
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Also within the scope of the present disclosure are pharmaceutical compositions comprising any of the anti-Gal9 antibodies and the one or more chemotherapeutics for use in treating a solid tumor such as PDAC, as well as uses of a combination of the anti-Gal9 antibody and the one or more chemotherapeutic agents for manufacturing a medicament for
20 use in treating the solid tumor.

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

25 BRIEF DESCRIPTION OF DRAWINGS

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

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

Anti-Gal9 mAb and Gemcitabine/Abraxane. *Fig. 1A* shows survival curves for all six groups. *Fig. 1B* shows survival curves for Groups 1, 5, and 6. *Fig. 1C* shows survival curves for Groups 1, 4, and 6. *Fig. 1D* shows survival curves for Groups 1, 4, 5, and 6.

5 **Fig. 2** includes a graph showing hazard ratios (HR) and their 95% confidence interval (%95CI) of group 4-6 against group 1, group 2 and group 3 respectively calculated from cox-regression analysis where group 1 = untreated orthotopic mPA6115_ mice; group 2 = chemo

What Is Claimed Is:

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

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

the one or more chemotherapeutics comprise gemcitabine, paclitaxel, or a combination thereof.

2. The use of claim 1, wherein the solid tumor is a metastatic solid tumor.

3. The use of claim 1 or claim 2, wherein the solid tumor is pancreatic ductal adenocarcinoma (PDAC).

4. The use of any one of claims 1-3, wherein the anti-Gal9 antibody is to 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 injection.

5. The use of any one of claims 1-3, wherein the anti-Gal9 antibody is to be administered to the subject at a dose of about 2 mg/kg to about 16 mg/kg once every two weeks by intravenous injection.

6. The use of claim 5, wherein the anti-Gal9 antibody is to be administered to the subject at a dose of about 2 mg/kg, about 4 mg/kg, about 8 mg/kg, about 12 mg/kg, or about 16 mg/kg once every two weeks by intravenous injection.

7. The use of any one of 1-6, wherein the use comprises a cycle of 28 days, in which the anti-Gal9 antibody is to be administered to the subject on day 1 and day 15 and the gemcitabine and paclitaxel are to be administered to the subject on day 1, day 8, and day 15.

8. The use of claim 7, wherein the paclitaxel is a protein-bound paclitaxel, which preferably is a nanoparticle albumin-bound paclitaxel.

9. The use of claim 7 or claim 8, wherein the paclitaxel is to be administered to the subject at 125 mg/m² intravenously.

10. The use of any one of claims 1-9, wherein the gemcitabine is to be administered to the subject at 1000 mg/m².

11. The use of any one of claims 1-10, wherein 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.

12. The use of any one of claims 1-11, wherein the anti-Gal9 antibody comprises 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.

13. The use of any one of claims 1-12, wherein the anti-Gal9 antibody is an IgG4 molecule.

14. The use of claim 13, wherein the anti-Gal9 antibody comprises 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.

15. The use of any one of claims 1-14, wherein the subject is a human patient.

16. The use of any one of claims 1-15, wherein the subject comprises galectin-9 positive cancer cells or immune cells.

17. The use of claim 16, wherein galectin-9 positive cancer cells or immune cells are detected in tumor organoids derived from the subject.

18. The use of any one of claims 1-17, wherein the subject has an elevated level of galectin-9 relative to a control value, optionally

wherein the subject has an elevated serum or plasma level of galectin-9 relative to the control value.

19. The use of any one of claims 1-18, wherein the subject received at least one line of systemic anti-cancer therapy; or

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. The use of any one of claims 1-19, 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;

(b) cytokine profile; and

(c) galectin 9 levels.

21. The use of any one of claims 1-20, wherein the use further comprises monitoring occurrence of one or more adverse effects in the subject.

22. The use of claim 21, wherein the one or more adverse effects comprise hepatic impairment, hematologic toxicity, neurologic toxicity, cutaneous toxicity, gastrointestinal toxicity, or a combination thereof.

23. The use of claim 21 or claim 22, 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.

24. The use of claim 23, 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.

25. The use of claim 24, wherein the use further comprises reducing the dose of the anti-Gal9 antibody, the dose of the gemcitabine, the dose of the paclitaxel, or a combination thereof, when moderate to severe hepatic impairment is observed; or.

wherein the use further 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.

26. The use of claim 25, wherein the dose of the paclitaxel is reduced to 100 mg/m²– 75 mg/m²; and/or

wherein the dose of the gemcitabine is reduced to 800 mg/m²– 600 mg/m².

27. The use of any one of claims 1-3 and 7-26, wherein the anti-Gal9 antibody is to be administered to the subject once every week.