

stability over months to years under conditions typical for storage of drugs for self-administration, *i.e.* at refrigerator temperature in a syringe, resulting in a long shelf-life for the corresponding drug product.

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SUMMARY

The present disclosure provides formulations of anti-LAG3 antibodies or antigen binding fragments. Applicants discovered certain excipients that mitigate the phase separation of anti-LAG3 in solution. The disclosure provides one or more of an excipient selected from the group consisting of histidine, aspartate, glutamine, glycine, proline, methionine, arginine or a pharmaceutically acceptable salt thereof, NaCl, KCl, LiCl, CaCl₂, MgCl₂, ZnCl₂, and FeCl₂, at a total concentration of 10-1000 mM, and a buffer at pH about 5-8. The present disclosure provides a formulation comprising an anti-LAG3 antibody or antigen binding fragment thereof and a buffer at pH about 5-8, and one or more of arginine, histidine or a pharmaceutically acceptable salt thereof, or NaCl at a total concentration of 15-250 mM. In one example, the formulation comprises an anti-LAG3 antibody or antigen-binding fragment thereof, a sugar or polyol; a non-ionic surfactant, a buffer at pH about 5-8, 25-200 mM arginine or a pharmaceutically acceptable salt thereof. In a further example, the formulation comprises about 25 mg/mL anti-LAG3 antibody; about 50 mg/mL sucrose; about 0.2 mg/mL polysorbate 80; about 10 mM L-histidine buffer at about pH 5.8-6.0; about 70 mM L-Arginine-HCl thereof; and optionally about 10 mM L-methionine. The formulation optionally comprises an anti-PD-1 antibody.

The disclosure provides a co-formulation of anti-LAG3 antibodies or antigen binding fragments and anti-PD-1 antibodies or antigen binding fragments with arginine or a pharmaceutically acceptable salt thereof at a total concentration of 10-1000 mM, and a buffer at pH about 5-8, and optionally 3-100 mM of methionine. In one example, the formulation comprises about 25 mg/mL anti-LAG3 antibody and about 25 mg/ml anti-PD-1 antibody; about 50 mg/mL sucrose; about 0.2 mg/mL polysorbate 80; about 10 mM L-histidine buffer at pH about 5.8-6.0; about 70 mM L-Arginine-HCl thereof; and about 10 mM L-methionine. Surprisingly, the anti-LAG3/anti-PD-1 co-formulations shows better

stability than the individual antibody formulations. The formulations can be lyophilized for reconstitution or in liquid form.

5 In another aspect, the present disclosure provides a formulation comprising an anti-LAG3 antibody at a concentration of 10-250 mg/ml and comprises a variable light chain region comprising CDRL1 of SEQ ID NO: 39, CDRL2 of SEQ ID NO: 40, CDRL3 of SEQ ID NO: 41 and a variable heavy chain region comprising CDRH1 of SEQ ID NO: 42, CDRH2 of SEQ ID NO: 59, CDRH3 of SEQ ID NO: 44, one or more of an excipient selected from the group consisting of histidine, aspartate, glutamine, glycine, proline, methionine, arginine or pharmaceutically acceptable salt thereof, NaCl, KCl, LiCl at a total concentration of 15-300 mM,
10 and 1-30 mM of a histidine, acetate or citrate buffer at pH 5.0-6.5.

The present disclosure also provides a method of treating cancer or infection, comprising administering the reconstituted or liquid formulation (solution formulation) to a subject in need thereof. In further examples the formulation is used in treating chronic

infection. Also contemplated is the use of the solution or lyophilized formulation in the manufacture of a medicament for treating cancer or infection.

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BREIF DESCRIPTON OF THE DRAWINGS

Figure 1: Number of particles per container $\geq 10 \mu\text{m}$ as measured by mHIAC for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 2: Number of particles per container $\geq 25 \mu\text{m}$ as measured by mHIAC for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

10 Figure 3: Potency as measured by ELISA for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 4: Monomer (%) by UP-SEC for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

15 Figure 5: High molecular weight species (%) by UP-SEC for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 6: Acidic Variants (%) by HP-IEX for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 7: Total Main Peak (%) by HP-IEX for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

20 Figure 8: Basic Variants (%) by HP-IEX for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 9: Purity Heavy Chain + Light Chain (%) by CE-SDS Reducing for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

25 Figure 10: Purity Intact IgG (%) by CE-SDS Non-Reducing for anti-LAG3 drug product samples that were stored at -80°C , -20°C , 5°C , 25°C , and 40°C .

Figure 11: Homology model of anti-LAG3 antibody Ab6 showing Tryptophan surface exposure. Trp102 is surface exposed as measured by accessible surface area ($85.25\text{\AA}^2$) calculated using a homology model.

30 Figure 12: Reduction of self-interaction (KD) and improvement of colloidal stability (OD350) and relative solubility (%PEGmid-point) of anti-LAG3 antibody in the presence of salt (50 mM NaCl) and in the presence of L-arginine hydrochloride (40 mM) in 10 mM histidine buffer pH 5.6.

Figure 13: Effect of L-arginine hydrochloride on the diffusion interaction parameter (KD) and turbidity (OD350 at 50 mg/mL) of the anti-LAG3 antibody in 10 mM histidine buffer at pH 5.8 and at pH 6.0.

CLAIMS

WHAT IS CLAIMED IS:

1. A formulation comprising an anti-LAG3 antibody at a concentration of
5 10-250 mg/ml and comprises a variable light chain region comprising CDRL1 of SEQ ID NO: 39, CDRL2 of SEQ ID NO: 40, CDRL3 of SEQ ID NO: 41 and a variable heavy chain region comprising CDRH1 of SEQ ID NO: 42, CDRH2 of SEQ ID NO: 59, CDRH3 of SEQ ID NO: 44, one or more of an excipient selected from the group consisting of histidine, aspartate, glutamine, glycine, proline, methionine, arginine or pharmaceutically acceptable salt thereof,
10 NaCl, KCl, LiCl at a total concentration of 15-300 mM, and 1-30 mM of a histidine, acetate or citrate buffer at pH 5.0-6.5.
2. The formulation of claim 1, wherein the excipient is L-arginine or a pharmaceutically acceptable salt thereof at a concentration of 15-250 mM, or wherein the excipients are NaCl and L-arginine or a pharmaceutically acceptable salt thereof with total
15 concentration of 20-250 mM, or wherein the excipient is L-histidine, L-aspartate, L-glutamine, or L-glycine at 15-200 mM.
3. The formulation of claim 1, wherein the excipient is L-arginine or a pharmaceutically acceptable salt thereof at a concentration of 40-150 mM.
4. The formulation of claim 1, wherein the
20 excipient is a combination of NaCl and L-arginine or a pharmaceutically acceptable salt thereof with a total concentration of 70-100 mM.
5. The formulation of claim 1, wherein the excipient is NaCl, KCl or LiCl at 40-150 mM.
6. The formulation of claim 1, wherein the excipient is L-histidine at
25 40-100 mM.
7. The formulation of any one of claims 1-4 further comprising a non-reducing disaccharide or polyol, or a non-ionic surfactant, or a combination thereof.
8. The formulation of claim 7, wherein the non-reducing disaccharide is trehalose or sucrose, or a combination thereof.
9. The formulation of claim 7, wherein the polyol is
30 selected from the group consisting of mannitol, sorbitol, glycerol and polyethylene glycol.
10. The formulation of any one of claims 7 to 9, wherein the non-reducing disaccharide or polyol is at a concentration of 10-200 mg/ml.
11. The formulation of claim 7, wherein the non-ionic surfactant is a
35 polysorbate.

12. The formulation of any one of claims 1 to 6, further comprising a surfactant selected from polysorbate 20 and polysorbate 80, and a sugar selected from sucrose and trehalose, or a combination thereof.
13. The formulation of any one of claims 1 to 6 further comprising
5 10-250 mg/mL sucrose, trehalose, mannitol, sorbitol, polyethylene glycol or glycerol; 0.005-2.0 mg/mL polysorbate 80 or 20.
14. The formulation of any one of claims 1 to 6 further comprising 30-120 mg/mL sucrose or trehalose; 0.05-1.5 mg/mL polysorbate 80 or 20; and wherein the buffer is 1-30 mM L-histidine, acetate or citrate buffer at pH 5.0 -6.5.
- 10 15. The formulation of any one of claims 1 to 6, further comprising 50-90 mg/mL sucrose or trehalose; 0.05-1.0 mg/mL polysorbate 80; and wherein the buffer is 5-30 mM L-histidine, acetate or citrate buffer at pH 5.0 -6.5.
16. The formulation of claim 1 comprising 20-220 mg/mL of the anti-LAG3 antibody; 50-90 mg/mL sucrose or trehalose; 0.05-1.0 mg/mL
15 polysorbate 80 or 20; 5-20 mM L-histidine, acetate or citrate buffer at pH 5.0 - 6.5; and 40-150 mM L-arginine or a pharmaceutically acceptable salt thereof.
17. The formulation of claim 1 comprising 20-220 mg/mL of the anti-LAG3 antibody; 20-200 mg/mL glycerol, sorbitol or PEG400; 0.05-1.0 mg/mL polysorbate 80 or 20; 3-150 mM L-histidine, acetate or citrate buffer at pH 5.0 - 6.5; and
20 40-150 mM L-arginine or a pharmaceutically acceptable salt thereof.
18. The formulation of claim 1 comprising 20-220 mg/mL of the anti-LAG3 antibody; 20-150 mM L-glutamine, L-glycine, L-proline or L-methionine; 0.05-1.0 mg/mL polysorbate 80 or 20; 1-30 mM L-histidine, acetate or citrate buffer at pH 5.0 - 6.5; and 40-150 mM L-arginine or a pharmaceutically acceptable salt thereof.
- 25 19. The formulation of claim 1 comprising 20-220 mg/mL of the anti-LAG3 antibody; 0.05-1.0 mg/mL polysorbate 80 or 20; 1-30 mM L-histidine, acetate or citrate buffer at pH 5.0 - 6.5; and 40-150 mM NaCl or a pharmaceutically acceptable salt thereof.
20. The formulation of claim 1, comprising 25 mg/mL of the anti-LAG3
30 antibody; 50 mg/mL sucrose; 0.2 mg/mL polysorbate 80; 10 mM L-histidine buffer at pH 5.8; 70 mM L-arginine or a pharmaceutically acceptable salt thereof; and 10 mM L-methionine, or comprising 25 mg/mL of the anti-LAG3 antibody; 50 mg/mL sucrose; 0.2 mg/mL polysorbate 80; 10 mM L-histidine buffer at pH 5.8-6.0; and 70 mM L-arginine or L-arginine-HCl.
21. The formulation of any one of claims 1-20 that is a liquid formulation.
- 35 22. The formulation of any one of claims 1-20 that is a reconstituted

solution from a lyophilized formulation.

23. The formulation of any one of claims 1-22, wherein the anti-LAG3 antibody comprises: a light chain variable region sequence of SEQ ID NO: 37 and a heavy chain variable region sequence of SEQ ID NO: 58.

5 24. The formulation of any one of claims 1-23, wherein the anti-LAG3 antibody comprises a light chain sequence of SEQ ID NO: 35 and a heavy chain sequence of SEQ ID NO: 57.

10 25. The formulation of any one of claims 1-24, further comprising an anti-PD-1 antibody that comprises a variable light chain region comprising CDRL1 of SEQ ID NO: 1, CDRL2 of SEQ ID NO: 2, and CDRL3 of SEQ ID NO: 3, and a variable heavy chain region comprising CDRH1 of SEQ ID NO: 6, CDRH2 of SEQ ID NO: 7, and CDRH3 of SEQ ID NO: 8.

15 26. The formulation of claim 25, wherein the anti-PD-1 antibody comprises a heavy chain variable region of SEQ ID NO: 9 and a light chain variable region of SEQ ID NO: 4.

27. The formulation of claim 25, wherein the anti-PD-1 antibody comprises a heavy chain sequence of SEQ ID NO: 10 and a light chain sequence of SEQ ID NO: 5.

28. The formulation of claim 27, wherein the molar ratio of anti-LAG3 antibody and anti-PD-1 antibody is 1:1, 2:1, 3:1 or 3.5:1.

20 29. The formulation of claim 27, comprising 10-120 mg/mL of the anti-LAG3 antibody and 10-120 mg/mL of the anti-PD-1 antibody.

25 30. The formulation of claim 25 comprising 10-120 mg/mL of an anti-LAG3 antibody; 10-120 mg/mL of an anti-PD-1 antibody; 30-120 mg/mL of a non-reducing disaccharide; 0.05-2.0 mg/mL polysorbate 80 or 20; 1-30 mM histidine or acetate buffer at pH 5.0 - 6.5; and 40-150 mM L-arginine or a pharmaceutically acceptable salt thereof; wherein the anti-LAG3 antibody comprises a light chain sequence of SEQ ID NO: 35 and a heavy chain sequence of SEQ ID NO: 57, and the anti-PD-1 antibody comprises a heavy chain sequence of SEQ ID NO: 10 and a light chain sequence of SEQ ID NO: 5.

30 31. The formulation of claim 27 comprising 20-30 mg/mL of the anti-LAG3 antibody; 20-30 mg/mL of the anti-PD-1 antibody; 50-90 mg/mL sucrose or trehalose; 0.05-1.0 mg/mL polysorbate 80 or 20; 3-30 mM histidine buffer at pH 5.0 - 6.5; and 40-100 mM L-arginine or a pharmaceutically acceptable salt thereof.

32. The formulation of any one of claims 1-31, further comprising 3-100 mM L-methionine.

35 33. The formulation of any one of claims 1-31, further comprising

5-15 mM L-methionine.

34. The formulation of any one of claims 1-33, wherein at 5 °C, the % monomer of the anti-LAG3 antibody is $\geq 95\%$ after 3 months as measured by size exclusion chromatography.

5 35. The formulation of any one of claims 1-34, wherein at 5 °C, the % acidic variant of the anti-LAG3 antibody is less than 15% after 3 months as measured by ion exchange chromatography.