based on the Mayo four stage prognostic staging system discussed in Kumar et al., 2012 (Kumar et al., Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements, J Clin Oncol 30:989-995 2012), with the outcome for Stage IV patients being quite dire.

Current treatment of patients with AL amyloidosis is aimed at reducing or eliminating the bone marrow disorder, *i.e*. the plasma cells that are responsible for producing the light chains, thereby limiting or halting the production of amyloid. The most aggressive treatment options include stem cell transplant and high-dose chemotherapy for those patients who can tolerate it. Other treatment regimens include combinations of drugs often used to treat hematological malignancies, such as melphalan, prednisone, dexamethasone and proteosome inhibitors such as bortezomib, in an attempt to reduce light chain production. There are no currently approved treatments for AL amyloidosis, and none that directly target potentially toxic forms of the amyloidogenic proteins. While some treatment options may ameliorate some of the morbidity associated with AL amyloidosis, few if any have been demonstrated to improve the prognosis in patients. Furthermore, Mayo Stage IV patients with AL amyloidosis represent a patient subset with a very high burden of morbidity and mortality, with no currently approved treatments, and population estimates of approximately 2,760 patients in the U.S., and from 6,900 to 10,350 patients in the U.S. and the European Union combined.

Thus, there is an unmet need for therapies that improve health status, including reducing the risk of mortality or enhancing the quality of life in patients with AL amyloidosis.

SUMMARY

The present disclosure relates to methods of treating certain AL amyloidosis patients.

In one aspect, provided herein is a use of an antibody ~~which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105),~~ comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5, in the manufacture of a medicament for treating a patient having AL amyloidosis, wherein the patient has been previously selected as having (a) Mayo Stage

IV AL amyloidosis, (b) a 6 minute walk distance (6MWD) ≥ 150 meters and EF > 50% at baseline.~~%,~~ (c) Mayo Stage IV AL amyloidosis and an EF > 50% at baseline, or (d) Mayo Stage IV AL amyloidosis, ~~and~~ a 6MWD ≥ 150 meters, and EF > 50% at baseline.~~%.~~

~~In one aspect, provided herein is a use of an antibody which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105) in the manufacture of medicament for treating a patient with AL amyloidosis who has a demonstrated 6 minute walk distance (6MWD) of greater than or equal to 150 meters and an ejection fraction (EF) of more than 50%.~~

~~In one aspect, provided herein is a use of an antibody which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105),~~ In one aspect, provided herein is a use of an antibody comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5, in the manufacture of a medicament for reducing the risk of mortality in a patient with AL amyloidosis by at least 45%, wherein the patient has been previously selected as having: (a) Mayo Stage IV AL amyloidosis, (b) a ~~and/or has a demonstrated~~ 6 minute walk distance (6MWD) of greater than or equal to 150 meters and an ejection fraction (EF) of more than 50% at baseline,~~%,~~ or (c)~~the patient has~~ Mayo Stage IV AL amyloidosis and an EF of > 50% at baseline. ~~%.~~

In one aspect, provided herein is a use of an antibody ~~which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105)~~ comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5 in the manufacture of a medicament for improving a 6 minute walk distance (6MWD) in a patient having AL amyloidosis, wherein the patient has been previously selected as having a 6MWD of greater than or equal to 150 meters, and EF > 50% at baseline.

Provided herein are methods of treating a patient having AL amyloidosis, comprising determining the Mayo Stage of the patient's AL amyloidosis, and/or the 6 minute walk distance (6MWD) and ejection fraction (EF) of the patient, or determining the Mayo Stage

and EF of the patient, selecting the patient for treatment with an antibody which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to human kappa (κ) or lambda light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105) if the patient has Mayo Stage IV AL amyloidosis, has a 6MWD ≥ 150 meters and an EF > 50% at baseline, has Mayo Stage IV and EF > 50% at baseline, or has Mayo Stage IV, a 6MWD ≥ 150 meters and an EF > 50% at

CLAIMS

What is claimed is:

1. Use of an antibody comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5~~which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105)~~, in the manufacture of a medicament for treating a patient having AL amyloidosis, wherein the patient has been previously selected as having (a) Mayo Stage IV AL amyloidosis, (b) a 6 minute walk distance (6MWD) ≥ 150 meters and EF > 50% at baseline, (c) Mayo Stage IV AL amyloidosis and an EF > 50% at baseline, or (d) Mayo Stage IV AL amyloidosis, ~~and~~ a 6MWD ≥ 150 meters, and EF > 50% at baseline.

2. The use of claim 1, wherein the patient has been previously selected as having Mayo Stage IV AL amyloidosis.

3. The use of claim 1, wherein the patient has been previously selected as having a 6MWD ≥ 150 meters and an EF > 50% at baseline.

4. The use of claim ~~2~~1, wherein the patient has been previously selected as having Mayo Stage IV AL amyloidosis, a 6MWD ≥ 150 meters and an EF > 50% at baseline.

5. The use of claim ~~2~~1, wherein the patient has been previously selected as having Mayo Stage IV amyloidosis and an EF > 50% at baseline.

~~6. The use of any of the preceding claims, wherein the antibody comprises a light chain variable region comprising three complementarity determining regions of 2A4, 7D8 or 11-1F4, and a heavy chain variable region comprising three complementarity determining regions of 2A4, 7D8 or 11-1F4, respectively.~~

~~7. The use of any of the preceding claims, wherein the antibody is a humanized version of 2A4.~~

~~8. The use of any of claims1-6, wherein the antibody is a humanized or chimeric version of 11-1F4.~~

~~9. The use of any of claims1-5, wherein the antibody comprises a light chain variable region comprising three complementarity determining regions set forth as SEQ ID NOs: 3, 4 and 5, or SEQ ID NOs: 16, 17, and 18, and a heavy chain variable region comprising three complementarity determining regions set forth as SEQ ID NOs: 6, 7 and 8, or SEQ ID NOs: 19, 20, and 21.~~

6. The use of any one of claims 1-5, wherein the antibody is a humanized antibody.

~~10~~7. The use of any one of claims1-~~5~~6, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1~~ or 14~~.

~~11~~8. The use of any one of claims 1-~~5~~6, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2~~ or 15~~.

~~12~~9. The use of any one of claims 1-~~5~~6, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1~~ or 14~~, and the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2~~ or 15~~.

~~13. The use of any of claims1-5, wherein the antibody comprises a light chain comprising the amino acid sequence set forth as SEQ ID NO:10, and a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 11, 12 or 13.~~

~~14. The use of any of claims1-5, wherein the antibody comprises a light chain comprising the amino acid sequence set forth as SEQ ID NO:10, and a heavy chain comprising the amino acid sequence set forth as SEQ ID NO:12.~~

~~15~~10. The use of any one of claims 1-~~5~~6, wherein the antibody is birtamimab.

~~16~~11. The use of any one of ~~the preceding~~ claims 1-10, wherein the patient is newly diagnosed and AL amyloidosis treatment naïve.

~~17~~12. The use of any one of claims1-~~5~~10, wherein the patient previously received or concomitantly receives treatment with melphalan, prednisone, dexamethasone, bortezomib, cyclophosphamide, lenalidomide, doxorubicin, doxycycline, daratumumab, autologous transplant, or a combination thereof.

13. The use of any one of claims 1-10, wherein the patient previously received or concomitantly receives treatment with cyclophosphamide, bortezomib, and dexamethasone (CyBorD).

~~18. The use of any of claims2 or 4, wherein the patient's risk of mortality is reduced by at least about 35%.~~

~~19. Use of an antibody which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105) in the manufacture of medicament for treating a patient with AL amyloidosis who has a demonstrated 6 minute walk distance (6MWD) of greater than or equal to 150 meters and an ejection fraction (EF) of more than 50%.~~

~~20~~14. Use of an antibody comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5~~which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105)~~, in the manufacture of a medicament for reducing the risk of mortality in a patient with AL amyloidosis by at least 45%, wherein the patient has been previously selected as having: (a) Mayo Stage IV AL amyloidosis, (b) a ~~and/or has a demonstrated~~ 6 minute walk distance (6MWD) of greater than or equal to 150

meters and an ejection fraction (EF) of more than 50% at baseline, or (c) ~~the patient has~~ Mayo Stage IV AL amyloidosis and an EF of > 50% at baseline.

15. The use of claim 14, wherein the patient has been previously selected as having Mayo Stage IV AL amyloidosis.

16. The use of claim 14, wherein the patient has been previously selected as having a 6MWD of greater than or equal to 150 meters and EF of > 50% at baseline.

17. The use of claim 14, wherein the patient has been previously selected as having Mayo Stage IV AL amyloidosis and an EF of > 50% at baseline.

~~21~~18. The use of any one of claims 14-17~~claim 20~~, wherein the risk of mortality is of all-cause mortality.

~~22. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 48.9%.~~

~~23. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 50%.~~

~~24. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 50.2%.~~

~~25. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 60%.~~

~~26. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 70%.~~

~~27. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 79.9%.~~

~~28. The use of claim 21, wherein the risk of all-cause mortality is reduced by at least about 81.5%.~~

~~29~~19. The use of any one of claims 14-17~~claim 20~~, wherein the risk of mortality is of cardiac mortality.

~~30. The use of claim 29, wherein the risk of cardiac mortality is reduced by at least about 75%.~~

~~31. The use of 29, wherein the risk of cardiac mortality is reduced by at least about 62.2%.~~

20. The use of any one of claims 14-19, wherein the antibody is a humanized antibody.

21. The use of any one of claims 14-20, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1.

22. The use of any one of claims 14-20, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2.

23. The use of any one of claims 14-20, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1, and the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2.

~~32~~24. The use of any of claims ~~19-31~~14-20, wherein the antibody is birtamimab.

~~33~~25. The use of any one of ~~the preceding~~ claims 14-24, wherein the patient exhibits improvement in the 36-Item Short Form Survey Physical Component Score (SF-36 PCS) or SF-36v2 following treatment with the antibody.

~~34. The use of claim 33, wherein after nine months of treatment the change in the patient's score on the SF-36 PCS or SF-36v2 is at least 5 points higher relative to a different patient at the same time point who has not been administered the antibody.~~

~~35. The use of any of the preceding claims, wherein an effective dosage of the antibody is to be administered from a pharmaceutical formulation comprising the antibody at a concentration within the range from about 1mg/mL to about 100 mg/mL.~~

~~36. The use of any of the preceding claims, wherein a dosage is from about 0.5 mg/kg to about 30 mg/kg and the antibody is to be administered intravenously or subcutaneously at a frequency of from about weekly to about quarterly.~~

~~37. The use of claim 35, wherein the antibody is present at a concentration of about 50 mg/mL.~~

~~38. The use of any of claims 35-37, wherein the dosage is to be administered intravenously following the transfer of an amount of the formulation required for the dosage from a vial to an intravenous bag containing a liquid.~~

~~39. The use of any claims 41-43, wherein the dosage is about 24 mg/kg and the antibody is to be administered intravenously every 28 days.~~

~~40. The use of any of the preceding claims, wherein the duration of the treatment is at least 9 months.~~

~~41. The use of claim 24, wherein the duration of the treatment is at least 12 months.~~

~~42. The use of any of the preceding claims, wherein the duration is effective to achieve or maintain at least about a 3 point increase from baseline in SF-36 PCS or SF-36v2.~~

~~43. The use of any of the preceding claims, wherein the antibody is a Fab, Fab', F(ab')$_2$, F(ab)c, Dab, nanobody, or Fv.~~

~~44~~26. Use of an antibody comprising a heavy chain variable region comprising heavy chain CDRs of SEQ ID NOs: 6, 7, and 8 and a light chain variable region comprising light chain CDRs of SEQ ID NOs: 3, 4, and 5~~which competes for binding to human amyloid A peptide or human kappa or lambda light chain immunoglobulin with 2A4 (ATCC Accession Number PTA-9662) or 7D8 (ATCC Accession Number PTA-9468), or competes for binding to kappa light chain immunoglobulin with 11-1F4 (ATCC Accession Number PTA-105)~~ in the manufacture of a medicament for improving a 6 minute walk distance (6MWD) in a patient having AL amyloidosis, wherein the patient has been previously selected as having a 6MWD of greater than or equal to 150 meters, and EF > 50% at baseline.

~~45. The use of claim 44, wherein the AL amyloidosis is Mayo Stage IV AL amyloidosis.~~

~~46. The use of claim 44 or claim 45, wherein an ejection fraction (EF) of the patient is > 50%.~~

27. The use of claim 26, wherein the antibody is a humanized antibody.

28. The use of claim 26 or 27, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1.

29. The use of claim 26 or 27, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2.

30. The use of claim 26 or 27, wherein the light chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 1, and the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 2.

~~47~~31. The use of claim 26 or 27~~any of claims 44-46~~, wherein the antibody in birtamimab.

32. The use of any one of claims 1-31, wherein an effective dosage of the antibody is to be administered from a pharmaceutical formulation comprising the antibody at a concentration within the range from 1 mg/mL to 100 mg/mL.

33. The use of any one of claims 1-32, wherein a dosage is from 0.5 mg/kg to 30 mg/kg and the antibody is to be administered intravenously or subcutaneously at a frequency of from weekly to quarterly.

34. The use of claim 32 or 33, wherein the antibody is present at a concentration of 50 mg/mL.

35. The use of claim 33 or 34, wherein the dosage is 24 mg/kg and the antibody is to be administered intravenously every 28 days.