

inhibitors such as bortezomib, in an attempt to reduce light chain production. CD38 antibodies such as daratumumab (DARZALEX®) and Isatuximab have been developed for the treatment of multiple myeloma. Daratumumab attaches to CD38 present on the surface of myeloma cells. It is thought to work both by killing tumor cells directly and by stimulating an immune response against cancer cells.

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 achieve high rates of hematologic and cardiac responses in patients.

Thus, there is a need for therapies that improve the outcome of patients with AL amyloidosis.

SUMMARY

In one aspect, the present disclosure provides a ~~use of pharmaceutical composition comprising~~ an amyloid light chain antibody ~~in the manufacture of a first medicament and use of a CD38 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a patient with AL amyloidosis, wherein an effective dosage of the amyloid light chain antibody in combination with the CD38 antibody are to be administered to the patient.~~

~~In another aspect, the present disclosure provides a use of an amyloid light chain antibody in the manufacture of a first medicament, use of a CD38 antibody in the manufacture of a second medicament, and use of a plasma cell therapy in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combination therapy to treat a plasma cell dyscrasia in a patient, wherein the patient is to be first treated with a combination therapy of the amyloid light chain antibody and the CD38 antibody prior to receiving the plasma cell therapy.~~

~~In another aspect, the present disclosure provides a combination of an amyloid light chain antibody and a CD38 antibody for use in treatment of AL amyloidosis.~~

~~In yet another aspect, the present disclosure provides a use of a CD38 antibody in the manufacture of a first medicament and use of NEOD0001 in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to improve cardiac function in an AL patient unresponsive to treatment with NEOD001, wherein an effective dosing regimen of the CD38 antibody in combination with NEOD0001 are to be added to the patient's treatment.~~

The present disclosure relates to methods of treating patients with AL amyloidosis with antibodies that target different proteins associated with AL amyloidosis or a plasma cell dyscrasia and provides a method of treating a patient with AL amyloidosis, comprising administering an effective dosage of an antibody which specifically binds to amyloid light chains and an antibody that specifically binds to CD38, for example, a chimeric or humanized monoclonal antibody to CD38. Typically, the dosage is effective to achieve an improvement in hematologic or cardiac or other organ function. The dosage can be effective to achieve an improvement in both hematologic and organ function, for example, cardiac function. In some methods, the amyloid light chain antibody or the CD38 antibody is a Fab, Fab', F(ab')₂, F(ab)c, Dab, nanobody or Fv.

In some of the methods disclosed herein, the amyloid light chain antibody competes for binding to human amyloid A peptide or human kappa or human lambda light chain immunoglobulin with antibody 2A4 (ATCC Accession Number 9662) or 7D8 (ATCC Accession Number PTA-9468) or binds to the same epitope as or competes for binding to human kappa or human lambda light chain immunoglobulin with 11-1F4. In some methods, the amyloid light chain antibody is a humanized version of 2A4 or 7D8. In some methods, the antibody is a humanized bispecific or multispecific version containing combinations of 11-1F4, 2A4, and/or 7D8.

In some of the methods disclosed herein, the amyloid light chain antibody comprises a light chain variable region comprising three complementarity determining regions set forth as

CLAIMS

What is claimed is:

1. ~~Use of A pharmaceutical composition comprising~~ an amyloid light chain antibody ~~in the manufacture of a first medicament and use of a CD38 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a patient with AL amyloidosis, wherein an effective dosage of the amyloid light chain antibody in combination with the CD38 antibody are to be administered to the patient.~~

2. ~~The use of claim 1, wherein the amyloid light chain antibody competes for binding to human amyloid A peptide or human kappa or human lambda light chain immunoglobulin with antibody 2A4 (ATCC Accession Number 9662) or 7D8 (ATCC Accession Number PTA-9468) or binds to the same epitope as competes for binding to human kappa or human lambda light chain immunoglobulin with 11-1F4.~~

3.2. ~~The use pharmaceutical composition~~ of claim ~~2~~1, wherein the amyloid light chain antibody is a humanized ~~version of 2A4 antibody~~.

4.3. ~~The use pharmaceutical composition~~ of claim 1, wherein the amyloid light chain antibody comprises a light chain variable region comprising three complementarity determining regions set forth as SEQ ID NOs: 3, 4, and 5, and a heavy chain variable region comprising three complementarity determining regions set forth as SEQ ID NOs: 6, 7, and 8.

5.4. ~~The use pharmaceutical composition~~ of claim 1, wherein the light chain variable region of the amyloid light chain antibody comprises the amino acid sequence set forth as SEQ ID NO: 1.

6.5. ~~The use pharmaceutical composition~~ of claim 1, wherein the heavy chain variable region of the amyloid light chain antibody comprises the amino acid sequence set forth as SEQ ID NO: 2.

7.6. ~~The use pharmaceutical composition~~ of claim 1, wherein the light chain variable region of the amyloid light chain antibody comprises the amino acid sequence set forth as SEQ ID NO: 1 and the heavy chain variable region of the amyloid light chain antibody comprises the amino acid sequence set forth as SEQ ID NO: 2.

~~8.7.~~ The ~~usepharmaceutical composition~~ of claim 1, wherein the amyloid light chain 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.

~~9.8.~~ The ~~usepharmaceutical composition~~ of claim ~~87~~, wherein the amyloid light chain 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.

~~10.9.~~ The ~~usepharmaceutical composition~~ of claim ~~87~~, wherein the amyloid light chain antibody is birtamimab.

~~11.10.~~ The ~~usepharmaceutical composition~~ of any one of ~~the preceding~~ claims 1-9, wherein the CD38 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 14 or 15.

~~12.11.~~ The ~~usepharmaceutical composition~~ of any one of ~~the preceding~~ claims 1-10, wherein the CD38 antibody comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 17 or 18.

~~13.12.~~ The ~~usepharmaceutical composition~~ of any one of claims 1-109, wherein the CD38 antibody comprises heavy and light chain variable region amino acid sequences as set forth in (a) SEQ ID NOs: 14 and 17, respectively; (b) SEQ ID NOs: 15 and 18, respectively; (c) SEQ ID NOs: 16 and 19, respectively; (d) SEQ ID NOs: 43 and 44, respectively; (e) SEQ ID NOs: 53 and 54, respectively; (f) SEQ ID NOs: 57 and 58, respectively; (g) SEQ ID NOs: 59 and 60, respectively; (h) SEQ ID NOs: 61 and 62, respectively; or (i) SEQ ID NOs: 63 and 64, respectively.

~~14.13.~~ The ~~usepharmaceutical composition~~ of any one of claims 1-109, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 47, 48, and 49, respectively, and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 50, 51, and 52, respectively.

~~15.14.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 20, 21_a and 22, respectively, and a light chain variable region comprising CDR1, CDR2_a and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 23, 24_a and 25, respectively.

~~16.15.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 26, 27_a and 28, respectively, and a light chain variable region comprising CDR1, CDR2_a and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 29, 30_a and 31, respectively.

~~17.16.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequence set forth in SEQ ID NO: 32, and a light chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 33.

~~18.17.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequence set forth in SEQ ID NO: 34, and a light chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 35.

~~19.18.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequence set forth in SEQ ID NO: 36, and a light chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 37.

~~20.19.~~ The ~~use~~pharmaceutical composition of any one of claims 1-~~109~~, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2_a and CDR3 sequences from the antibody comprising the amino acid sequence set forth in SEQ ID NO: 38,

and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 39.

21.20. The ~~use~~pharmaceutical composition of any one of claims 1-~~409~~, wherein the CD38 antibody is daratumumab.

22.21. The ~~use~~pharmaceutical composition of any one of claims 1-~~409~~, wherein the CD38 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 43, and a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 44.

23.22. The ~~use~~pharmaceutical composition of any one of claims 1-~~409~~, wherein the CD38 antibody is isatuximab.

24.23. The ~~use~~pharmaceutical composition of any one of claims 1-~~409~~, wherein the CD38 antibody comprises a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 53, and a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 54.

~~25. The use of any of the preceding claims, wherein the patient previously received treatment with ixazomib, venetoclax, melphalan, prednisone, dexamethasone, bortezomib, carfilzomib, cyclophosphamide, thalidomide, pomalidomide, lenalidomide, doxorubicin, doxycycline, daratumumab, autologous transplant or a combination thereof.~~

~~26. The use of any of the preceding claims, wherein the patient had not responded to therapy with bortezomib.~~

~~27. The use of any of the preceding claims, wherein the amyloid light chain antibody and the CD38 antibody are to be administered to the patient by intravenous infusions separated by two days.~~

24. The pharmaceutical composition of any one of claims 1-23, wherein the pharmaceutical composition further comprises a buffer.

25. The pharmaceutical composition of claim 24, wherein the buffer is a histidine buffer.

- ~~28. The use of claim 27, wherein the amyloid light chain antibody is to be administered first.~~
- ~~29. The use of claim 27, wherein the CD38 antibody is to be administered first.~~
- ~~30. The use of any of the preceding claims, wherein the patient achieved greater VGPR after treatment relative to a patient receiving the CD38 antibody alone.~~
- ~~31. The use of any of the preceding claims, wherein the patient achieved a hematologic response in a shorter time after treatment relative to a patient receiving the CD38 antibody alone.~~
- ~~32. The use of any of the preceding claims, wherein the patient achieved a cardiac response in a shorter time after treatment relative to a patient receiving the CD38 antibody alone.~~
- ~~33. The use of any of the preceding claims, wherein the patient achieved a greater reduction in NT-proBNP after treatment relative to a patient receiving the CD38 antibody alone.~~
- ~~34. The use of any of the preceding claims, wherein the dosage of the amyloid light chain antibody is from about 0.5 mg/kg to about 30 mg/kg and the amyloid light chain antibody is administered intravenously or subcutaneously at a frequency of from about weekly to about quarterly.~~
- ~~35. The use of any of the preceding claims, wherein the effective dosage of an amyloid light chain antibody is to be administered as a formulation comprising:~~
- ~~a) the amyloid light chain antibody at a concentration of about 50 mg/mL;~~
 - ~~b) the histidine buffer at a concentration of about 25 mM;~~
 - ~~c) the trehalose at a concentration of about 230 mM;~~
 - ~~d) the polysorbate 20 at a concentration of about 0.2 g/L; and~~
- ~~wherein the pH is about 6.5.~~
- ~~36. The use of any of the preceding claims, wherein the amyloid light chain antibody or the CD38 antibody is a Fab, Fab', F(ab')₂, F(ab)c, Dab, nanobody or Fv.~~
- ~~37. The use of any preceding claim, wherein prior to receiving treatment with either the amyloid light chain antibody and a CD38 antibody, the patient was treatment naïve.~~

~~38. — Use of an amyloid light chain antibody in the manufacture of a first medicament, use of a CD38 antibody in the manufacture of a second medicament, and use of a plasma cell therapy in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combination therapy to treat a plasma cell dyscrasia in a patient, wherein the patient is to be first treated with a combination therapy of the amyloid light chain antibody and the CD38 antibody prior to receiving the plasma cell therapy.~~

~~39. — The use of claim 38, wherein the patient is to receive the plasma cell therapy after achieving a reduction in NT-proBNP levels relative to the patient's NT-proBNP levels prior to receiving the combination therapy of an amyloid light chain antibody and a CD38 antibody.~~

~~40. — A combination of an amyloid light chain antibody and a CD38 antibody for use in treatment of AL amyloidosis.~~

~~41. — Use of a CD38 antibody in the manufacture of a first medicament and use of NEOD0001 in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to improve cardiac function in an AL patient unresponsive to treatment with NEOD001, wherein an effective dosing regimen of the CD38 antibody in combination with NEOD0001 are to be added to the patient's treatment.~~

~~42. — The use of claim 41, wherein the unresponsiveness of the patient to NEOD001 treatment is determined by NT-proBNP levels in the patient during a period following NEOD001 treatment greater than or equal to the NT-proBNP levels in the patient prior to NEOD001 treatment.~~

~~43. — The use of claim 42, wherein the NT pro-BNP levels are greater than the NT-proBNP levels prior to NEOD001 treatment.~~

~~44. — The use of any of claims 41-43, wherein the period following NEOD001 treatment is at least two months.~~

~~45. — The use of any of claims 41-44, wherein the patient has received at least two doses of NEOD001 before receiving the CD38 antibody.~~

~~46. — The use of any of claims 41-44, wherein the patient has received at least three doses of NEOD001 before receiving the CD38 antibody.~~

- ~~47. The use of any of claims 41-46, wherein the CD38 antibody is to be administered after an increase of more than about 6,000 pg/mL NT-proBNP in the patient.~~
- ~~48. The use of any of claims 41-46, wherein the CD38 antibody is to be administered after an increase of more than about 12,000 pg/mL NT-proBNP in the patient.~~
- ~~49. The use of any of claims 41-48, wherein the CD38 antibody is to be administered after the levels of NT-proBNP levels increase at least about 100%.~~
- ~~50. The use of any of claims 41-48, wherein the CD38 antibody is to be administered after the levels of NT-proBNP levels increase at least about 200%.~~
- ~~51. The use of any of claims 41-48, wherein the CD38 antibody is to be administered after the levels of NT-proBNP levels increase at least about 300%.~~
- ~~52. The use of any of claims 41-51, wherein the AL patient has been previously been receiving NEOD001 and CyBorD.~~
- ~~53. The use of any of claims 41-51, wherein the CD38 antibody is daratumumab or isatuximab.~~
- ~~54. The use of claim 53, wherein the CD38 antibody is daratumumab.~~
- ~~55. The use of claim 54, wherein daratumumab is to be administered to the patient at 16 mg/kg every 28 days.~~
- ~~56. The use of any of claims 41-55, wherein NEOD001, when administered in combination with the CD38 antibody, is to be administered to the patient at 24 mg/kg every 28 days.~~
- ~~57. The use of any of claims 41-56, wherein the duration of treatment with the CD38 antibody is effective to reduce the patient's NT-proBNP levels at least to the levels prior to receiving NEOD001 treatment.~~
- ~~58. The use of claim 57, wherein the duration is effective to reduce the patient's NT-proBNP levels below the levels prior to receiving NEOD001 treatment.~~

- ~~59. — The use of claim 57, wherein the treatment comprises at least one dose of the CD38 antibody.~~
- ~~60. — The use of claim 57, wherein the treatment comprises at least two doses of the CD38 antibody.~~
- ~~61. — The use of claim 57, wherein the treatment comprises at least three doses of the CD38 antibody.~~
- ~~62. — The use of claim 57, wherein the duration is at least nine months.~~
- ~~63. — The use of claim 57, wherein the duration is at least twelve months.~~
- ~~64. — The use of any one of claims 1-36, wherein the patient is to be treated with the combination of an amyloid light chain antibody and a CD38 antibody to stabilize or improve the patient's health prior to receiving plasma cell therapy.~~
- ~~65. — The use of claim 63, wherein the plasma cell therapy comprises one or more of ixazomib, venetoclax, melphalan, prednisone, dexamethasone, bortezomib, carfilzomib, cyclophosphamide, thalidomide, pomalidomide, lenalidomide, doxorubicin and/or doxycycline, thereby enhancing the ability of the patient to tolerate the side effects of the plasma cell therapy.~~
- ~~66. — The use of claim 64, wherein the stabilization or improvement in the patient's health is measured by VGPR and/or NT-proBNP levels.~~
- ~~67. — The use of claim 64, wherein stabilizing or improving the patient's health includes stabilizing or improving the patient's cardiac function.~~
- ~~68. — The use of claim 67, wherein the patient receives the plasma cell therapy after achieving a reduction in NT-proBNP relative to the patient's NT-proBNP levels prior to receiving treatment with the combination of the amyloid light chain antibody and the CD38 antibody.~~
- ~~69. — The use of claim 68, wherein the reduction in NT-proBNP is at least 55%.~~
- ~~70. — The use of any of claims 64, wherein the amyloid light chain antibody is birtamimab.~~

~~71. The use of any of claims 64, wherein the CD38 antibody is daratumumab.~~

~~72. The use of any of claims 64, wherein the plasma cell therapy is bortezomib.~~