

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 pharmaceutical composition comprising an amyloid light chain antibody and a CD38 antibody.

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. A pharmaceutical composition comprising an amyloid light chain antibody and a CD38 antibody.
2. The pharmaceutical composition of claim 1, wherein the amyloid light chain antibody is a humanized antibody.
3. The 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.
4. The 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.
5. The 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.
6. The 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.
7. The pharmaceutical 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.
8. The pharmaceutical composition of claim 7, 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.
9. The pharmaceutical composition of claim 7, wherein the amyloid light chain antibody is birtamimab.

10. The pharmaceutical composition of any one of 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.
11. The pharmaceutical composition of any one of 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.
12. The pharmaceutical composition of any one of claims 1-9, 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.
13. The pharmaceutical composition of any one of claims 1-9, 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.
14. The pharmaceutical composition of any one of claims 1-9, 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: 20, 21, and 22, respectively, and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 23, 24, and 25, respectively.
15. The pharmaceutical composition of any one of claims 1-9, 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: 26, 27, and 28, respectively, and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively.

16. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2, 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, and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 33.
17. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2, 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, and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 35.
18. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2, 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, and CDR3 sequences from the antibody comprising the amino acid sequences set forth in SEQ ID NO: 37.
19. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody comprises a heavy chain variable region comprising CDR1, CDR2, 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.
20. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody is daratumumab.
21. The pharmaceutical composition of any one of claims 1-9, 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.
22. The pharmaceutical composition of any one of claims 1-9, wherein the CD38 antibody is isatuximab.

23. The pharmaceutical composition of any one of claims 1-9, 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.
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.