of autologous SCT as acceptable options for patients who achieve a CR following frontline therapy (Dearden 2011; NCCN 2013).

[0008] The clinical safety and activity of brentuximab vedotin 1.8 mg/kg administered every 3 weeks were evaluated in a pivotal phase 2 study of patients with relapsed or refractory sALCL (Study SG035-0004). In this study, all patients had previously received at least 1 prior regimen of multiagent systemic chemotherapy with curative intent. The majority of patients had a diagnosis of ALK-negative disease (72%); relative to the most recent therapy, 50% of patients were refractory. Additionally, approximately 60% of patients had primary refractory disease, defined as failure to achieve a complete remission (CR) with frontline therapy or progression within 3 months of completing frontline therapy, and 22% of patients had never achieved a response with any previous therapy. In this study of highly refractory patients, the objective response (CR + PR) rate was 86%, with 57% of patients achieving a CR (Pro 2012). The median duration of response was 12.6 months, and in the subset of patients who achieved a CR, the median duration of response was 13.2 months. Brentuximab vedotin was generally well tolerated, with manageable side effects.

SUMMARY

[0009] The present disclosure provides improved methods for administering an anti-CD30 antibody-drug conjugate and reducing adverse events in subject having a mature T cell lymphoma and receiving anti-CD30 antibody drug conjugate therapy. In one aspect, the present disclosure refers to the use of a granulopoiesis stimulating factor in the manufacture of a medicament for use in combination therapy for treating a mature T cell lymphoma in a subject, wherein the medicament is to be administered in a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) and prophylactically administering a granulopoiesis stimulating factor, wherein the medicament is to be administered with the initiation of the combination therapy.

[0009a] In another aspect, the present disclosure refers to the use of a granulopoiesis stimulating factor in the manufacture of a medicament or use in combination therapy for reducing the incidence of neutropenia in a subject having mature T cell lymphoma and receiving a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), wherein the use comprises that the medicament is to be administered to the subject, wherein the medicament is to be administered with initiation of the combination therapy.

[0009b] In yet another aspect, the present disclosure refers to the use of a granulopoiesis stimulating factor in the manufacture of a medicament for use in combination therapy for decreasing the incidence of infection in a subject having mature T cell lymphoma and receiving a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), wherein the use comprises that the medicament is to be administered to the subject in an amount effective to reduce infections, wherein the medicament is to be administered with the initiation of the combination therapy.

[0009c] In some examples, the anti-CD30 antibody-drug conjugate is administered in combination with a chemotherapy regimen. It is contemplated that the therapeutic regimen may include chemotherapeutics known in the field of cancer treatment. Exemplary chemotherapeutics are disclosed in greater detail in the Detailed Description. In various examples, the methods herein include treatment comprising a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP). In some examples, side effects such as peripheral neuropathy are reduced by adjusting the amount and/or timing of anti-CD30 antibody drug conjugate. In other examples, side effects including neutropenia, febrile neutropenia or infection are reduced by co-administration of the anti-CD30 antibody drug conjugate with a granulopoiesis stimulating factor.

[0010] In one example, the disclosure provides a method of administering an anti-CD30 drug conjugate, e.g., brentuximab vedotin, to a subject having a mature T cell lymphoma at a dose of 1.8 mg/kg, administered, e.g., every three weeks. The mature T cell lymphoma may be more particularly diagnosed as, for example, peripheral T cell lymphoma (PTCL), PTCL entities typically manifesting as nodal involvement, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphomas, peripheral T-cell lymphoma-not otherwise specified, subcutaneous

What is Claimed:

1. Use of a granulopoiesis stimulating factor in the manufacture of a medicament for use in combination therapy for treating a mature T cell lymphoma in a subject, wherein the medicament is to be administered in a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) and prophylactically administering a granulopoiesis stimulating factor, wherein the medicament is to be administered with the initiation of the combination therapy.

2. The use of claim 1 wherein the medicament is to be

i) administered from 1 day to 7 days, or from 2 days to 5 days, after the initiation of the combination therapy; and/or

ii) administered from 1 day to 7 days after a second, or subsequent, administration of the combination therapy; or

iii) administered from 2 days to 5 days after a second, or subsequent, administration of the combination therapy.

3. The use of any one of claims 1 to 2 wherein the granulopoiesis stimulating factor is to be administered to a subject that has not received an anti-CD30 antibody drug conjugate therapy previously.

4. Use of a granulopoiesis stimulating factor in the manufacture of a medicament for use in combination therapy for reducing the incidence of neutropenia in a subject having mature T cell lymphoma and receiving a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), wherein the use comprises that the medicament is to be administered to the subject, wherein the medicament is to be administered with initiation of the combination therapy.

5. The use of any one of claims 1 to 4 wherein the granulopoiesis stimulating factor in the medicament is a granulocyte-colony stimulating factor (GCSF), optionally wherein the GCSF is a long-acting GCSF or a non long-acting GCSF.

6. The use of claim 5 wherein the GCSF is long-acting GCSF, and is to be administered 1 day or 2 days after the initiation of the combination therapy.

7. The use of claim 5 wherein the GCSF is not long acting, and is to be administered 1, 2, 3, 4, 5, 6 or 7 days after the initiation of the combination therapy.

8. The use of any one of claims 1 to 7 wherein the combination therapy is to be administered every 3 weeks, or every 2 weeks.

9. The use of claim any one of claims 1 to 8 wherein the combination therapy is to be administered on day 1 of a 21 day cycle.

10. The use of claim 9 wherein the combination therapy is to be administered for no more than six to eight cycles.

11. The use of claim 10 wherein the subject receives single-agent anti-CD30 antibody drug conjugate for eight to 10 additional cycles for a total of 16 cycles.

12. The use of any one of claims 1 to 11 wherein the anti-CD30 antibody drug conjugate is brentuximab vedotin and is to be administered at 1.8 mg/kg, cyclophosphamide is to be administered at 750 mg/m^2, doxorubicin is to be administered at 50 mg/m^2, and prednisone is to be administered at 100 mg on days 1 to 5 of a 21 day cycle.

13. The use of any one of claims 1 to 12 wherein the granulopoiesis stimulating factor is to be administered in a dose range from 5 to 10 mcg/kg/day, or 300 to 600 mcg/day, or 6 mg/dose.

14. The use of any one of claims 1 to 13 wherein the granulopoiesis stimulating factor is to be given intravenously or subcutaneously.

15. The use of any one of claims 1 to 14 wherein the granulopoiesis stimulating factor is to be given in a single dose or multiple doses.

16. The use of any one of claims 1 to 15 wherein the subject is suffering from a mature T cell lymphoma selected from the group consisting of peripheral T cell lymphoma (PTCL), PTCL entities typically manifesting as nodal involvement, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphomas, peripheral T-cell lymphoma-not otherwise specified, subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic gamma delta T-cell lymphoma, enteropathy-type intestinal T-cell lymphoma, and extranodal T-cell lymphoma-nasal type.

17. The use of claim 16, wherein the mature T cell lymphoma is PTCL and wherein the PTCL is selected from the group consisting of systemic anaplastic large cell lymphoma (sALCL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma-not otherwise

specified (PTCL-NOS), Adult T-Cell Leukemia/Lymphoma (ATLL), Enteropathy-associated T-cell lymphoma (EATL) and Hepatosplenic T-cell lymphoma.

18. The use of claim 17 wherein the PTCL is a sALCL and wherein the sALCL is selected from the group consisting of anaplastic lymphoma kinase positive (ALK+) sALCL and anaplastic lymphoma kinase negative (ALK-) sALCL.

19. The use of claim 18 wherein the sALCL is an ALK+ sALCL.

20. The use of claim 17 wherein the PTCL is selected from the group consisting of angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), Adult T-Cell Leukemia/Lymphoma (ATLL), Enteropathy-associated T-cell lymphoma (EATL) and Hepatosplenic T-cell lymphoma.

21. The use of any one of claims 17, wherein the subject has i) not previously been treated for a hematologic cancer; or

ii) previously been treated for a hematologic cancer and the cancer has relapsed or is refractory.

22. The use of any one of claims 17, wherein the PTCL is a stage III or stage IV PTCL.

23. The use of any one of claims 17 to 22 wherein the PTCL is a CD30-expressing PTCL, optionally wherein the CD30 expression is ≥10%.

24. The use of any one of claims 17 to 23 wherein when the mature T cell lymphoma is PTCL, and wherein if the subject is diagnosed with Grade 2 or greater peripheral motor neuropathy after starting treatment with a combination therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg every three weeks in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), the dose of anti-CD30 antibody drug conjugate is reduced to 1.2 mg/kg.

25. Use of a granulopoiesis stimulating factor in the manufacture of a medicament for use in combination therapy for decreasing the incidence of infection in a subject having mature T cell lymphoma and receiving a combination therapy comprising an anti-CD30 antibody drug conjugate comprising monomethyl auristatin E (MMAE) in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), wherein the use comprises that the medicament is to be administered to the subject in an amount effective to reduce infections, wherein the medicament is to be administered with the initiation of the combination therapy.

26. The use of claim 25 wherein the medicament is to be

i) administered from 1 day to 7 days after, or from 2 days to 5 days, after the initiation of the combination therapy;

ii) administered from 1 day to 7 days after a second, or subsequent, administration of the combination therapy; and/or

iii) administered from 2 days to 5 days after the a second, or subsequent, administration of the combination therapy.

27. The use of any one of claims 25 to 26 wherein the medicament is to be administered to a subject that has not received an anti-CD30 antibody drug conjugate therapy previously.

28. The use of any one of claims 25 to 27 wherein the subject has not experienced treatment-emergent grade 3-4 neutropenia after administration of the combination therapy.

29. The use of any one of claims 25 to 28 wherein the granulopoiesis stimulating factor is a granulocyte-colony stimulating factor GCSF, optionally wherein the GCSF is a long-acting GCSF or a non long-acting GCSF.

30. The use of claim 29 wherein the GCSF is long-acting, and is to be administered 1 day or 2 days after the initiation of the combination therapy.

31. The use of claim 29 wherein the GCSF is not long acting, and is to be administered 1, 2, 3, 4 or up to 7 days after the initiation of the combination therapy.

32. The use of any one of claims 25 to 31 wherein the combination therapy is to be administered every 3 weeks, or every 2 weeks.

33. The use of claim 32 wherein the antibody is to be administered on day 1 of a 21-day cycle.

34. The use of claim 32 or 33 wherein the combination therapy is to be administered for no more than six to eight cycles.

35. The use of claim 34 wherein the subject receives single-agent anti-CD30 antibody drug conjugate for eight to 10 additional cycles for a total of 16 cycles.

36. The use of any one of claims 1-35 wherein the anti-CD30 antibody of the anti-CD30 antibody drug conjugate comprises

i) a heavy chain CDR1 set out in SEQ ID NO: 4, a heavy chain CDR2 set out in SEQ ID NO: 6, a heavy chain CDR3 set out in SEQ ID NO: 8; and

ii) a light chain CDR1 set out in SEQ ID NO: 12, a light chain CDR2 set out in SEQ ID NO: 14, and a light chain CDR13 set out in SEQ ID NO: 16.

37. The use of any one of claims 1 to 36 wherein the anti-CD30 antibody of the anti-CD30 antibody drug conjugate comprises

i) an amino acid sequence at least 85% identical to a heavy chain variable region set out in SEQ ID NO: 2 and

ii) an amino acid sequence at least 85% identical to a light chain variable region set out in SEQ ID NO: 10.

38. The use of any one of claims 1-37 wherein the anti-CD30 antibody of the anti-CD30 antibody drug conjugate is a monoclonal anti-CD30 antibody.

39. The use of any one of claims 1-38 wherein the anti-CD30 antibody of the anti-CD30 antibody drug conjugate is a chimeric AC10 antibody.

40. The use of any one of claims 1-39 wherein the antibody drug conjugate comprises monomethyl auristatin E and a protease-cleavable linker.

41. The use of claim 40 wherein the protease cleavable linker i) comprises a thiolreactive spacer and a dipeptide; and/or ii) consists of a thiolreactive maleimidocaproyl spacer, a valine–citrulline dipeptide, and a p-amino-benzyloxycarbonyl spacer.

42. The use of any one of claims 1-41 wherein the anti-CD30 antibody drug conjugate is brentuximab vedotin.

43. The use of claim 42 wherein the anti-CD30 antibody drug conjugate is brentuximab vedotin and is to be administered at 1.8 mg/kg, cyclophosphamide is to be administered at 750 mg/m^2, doxorubicin is to be administered at 50 mg/m^2, and prednisone is to be administered at 100 mg on days 1 to 5 of a 21 day cycle.

44. The use of any one of claims 1-43 wherein the medicament is to be administered in a dose range from 5 to 10 mcg/kg/day, or 300 to 600 mcg/day, or 6 mg/dose.

45. The use of any one of claims 1-44 wherein the medicament is to be given intravenously or subcutaneously.

46. The use of any one of claims 1-44 wherein the medicament is to be given in a single dose or multiple doses.

47. The use of any one of claims 1-46 wherein the mature T cell lymphoma is selected from the group consisting of peripheral T cell lymphoma (PTCL), PTCL entities typically manifesting as nodal involvement, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphomas, peripheral T-cell lymphoma-not otherwise specified, subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic gamma delta T-cell lymphoma, enteropathy-type intestinal T-cell lymphoma, and extranodal T-cell lymphoma-nasal type.

48. The use of claim 47, the mature T cell lymphoma is PTCL.

49. The use of claim 48 wherein the PTCL is selected from the group consisting of systemic anaplastic large cell lymphoma (sALCL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), Adult T-Cell Leukemia/Lymphoma (ATLL), Enteropathy-associated T-cell lymphoma (EATL) and Hepatosplenic T-cell lymphoma.

50. The use of claim 48 or 49 wherein the PTCL is a sALCL.

51. The use of claim 50 wherein the sALCL is selected from the group consisting of anaplastic lymphoma kinase positive (ALK+) sALCL and anaplastic lymphoma kinase negative (ALK-) sALCL.

52. The use of claim 51 wherein the sALCL is an ALK+ sALCL.

53. The use of claim 48 or 49 wherein the PTCL is selected from the group consisting of angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), Adult T-Cell Leukemia/Lymphoma (ATLL), Enteropathy-associated T-cell lymphoma (EATL) and Hepatosplenic T-cell lymphoma.

54. The use of claim 48 or 49 wherein the PTCL is selected from the group consisting of systemic anaplastic large cell lymphoma (sALCL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), Adult T-Cell Leukemia/Lymphoma (ATLL), Enteropathy-associated T-cell lymphoma (EATL) and Hepatosplenic T-cell lymphoma.

55. The use of any one of claims 48 to 54, wherein the subject i) has not previously been treated for a hematologic cancer; or

ii) has previously been treated for a hematologic cancer and the cancer has relapsed or is refractory.

56. The use of any one of claims 48 to 55, wherein the PTCL is a stage III or stage IV PTCL.

57. The use of any one of claims 48 to 56 wherein the PTCL is a CD30-expressing PTCL, optionally wherein the CD30 expression is ≥10%.

58. The use of any one of claims 48 to 57, wherein the medicament is to be administered from 1 to 8 days after initiation of the combination therapy.