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 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 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 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 yet another aspect, the present disclosure refers to the use of an anti-CD30 antibody drug conjugate in the manufacture of a medicament for use in combination therapy for treating a subject having a mature T cell lymphoma that has exhibited Grade 2 or greater peripheral neuropathy, wherein the subject is to be administered the medicament at a dose between 0.9 mg/kg to 1.2 mg/kg, 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).

[0009d] 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

panniculitis-like T-cell lymphoma, hepatosplenic gamma delta T-cell lymphoma, enteropathy-type intestinal T-cell lymphoma, and extranodal T-cell lymphoma-nasal type.

[0011] In various examples, the disclosure provides a method for treating a subject having a mature T cell lymphoma that has exhibited Grade 2 or greater peripheral neuropathy after starting treatment with a combination therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) every three weeks, comprising administering anti-CD30 antibody drug conjugate at a dose of 0.9 mg/kg to 1.2 mg/kg. In various examples, the subject exhibits Grade 2 or Grade 3 peripheral neuropathy.

[0012] In various examples, when the subject exhibits Grade 3 neuropathy, the administration of anti-CD30 antibody drug conjugate is withheld until peripheral neuropathy decreases to Grade 2 or less and then 0.9 mg/kg to 1.2 mg/kg anti-CD30 antibody drug conjugate is administered. In various examples, when the subject exhibits Grade 3 neuropathy, the administration of anti-CD30 antibody drug conjugate is reduced, optionally to 0.9 to 1.2 mg/kg, until peripheral neuropathy decreases to Grade 2 or less and then 0.9 mg/kg to 1.2 mg/kg anti-CD30 antibody drug conjugate is administered or maintained.

[0013] In various examples, the subject exhibited Grade 2 or 3 peripheral neuropathy after starting anti-CD30 antibody drug conjugate therapy at a dose of 1.8 mg/kg in combination with a chemotherapy consisting essentially of cyclophosphamide (C), doxorubicin (H) and prednisone (P) therapy, preferably the anti-CD30 antibody drug conjugate is brentuximab vedotin, administered every three weeks.

[0014] In various examples, the dose of anti-CD30 antibody drug conjugate is increased from 0.9 to 1.2 mg/kg to 1.8 mg/kg or 1.2 mg/kg after the Grade 2 or Grade 3 peripheral neuropathy improves to Grade 1 or less. In various examples, when the anti-CD30 antibody drug conjugate administration is at 1.2 mg/kg, the administration may be every two weeks, up to a maximum of 120 mg every two weeks.

[0015] In various examples, the disclosure provides a method for treating a subject having a mature T cell lymphoma that has exhibited Grade 2 or greater peripheral neuropathy after starting treatment with a therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg, comprising administering anti-CD30 antibody drug conjugate at a dose of 0.9 mg/mg to 1.2 mg/kg. In various examples, the subject exhibits Grade 2 or Grade 3 peripheral neuropathy.

[0016] In various examples, when the subject exhibits Grade 3 neuropathy, the administration of anti-CD30 antibody drug conjugate is withheld until peripheral neuropathy decreases to Grade 2 or less and then 0.9 mg/kg to 1.2 mg/kg anti-CD30 antibody drug conjugate is administered. In various examples, when the subject exhibits Grade 3 neuropathy, the administration of anti-CD30 antibody drug conjugate is reduced, optionally to 0.9 to 1.2 mg/kg, until peripheral neuropathy decreases to Grade 2 or less and then 0.9 mg/kg to 1.2 mg/kg anti-CD30 antibody drug conjugate is administered.

[0017] In various examples, the dose of anti-CD30 antibody drug conjugate is increased from 0.9 to 1.2 mg/kg to 1.8 mg/kg or 1.2 mg/kg after the Grade 2 or Grade 3 peripheral neuropathy improves to Grade 1 or less, wherein if the dose is increased to 1.8 mg/kg, the administration optionally is in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone therapy, preferably the anti-CD30 antibody drug conjugate is brentuximab vedotin, administered every three weeks.

[0018] In various examples, the mature T cell lymphoma is peripheral T cell lymphoma (PTCL). In various examples, 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.

[0019] In various examples, when the mature T cell lymphoma is peripheral T cell lymphoma, and wherein if the subject is diagnosed with Grade 3 or greater peripheral sensory 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.

[0020] In various examples, 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.

[0021] In various examples, the PTCL is a sALCL. In various examples, the sALCL is selected from the group consisting of anaplastic lymphoma kinase positive (ALK+) sALCL and

anaplastic lymphoma kinase negative (ALK-) sALCL. In various examples, the sALCL is an ALK+ sALCL. In various examples, the sALCL is an ALK- sALCL.

[0022] In various examples, the PTCL is not a sALCL. In various examples, 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.

[0023] In various examples, the PTCL is not an AITL. In various examples, 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.

[0024] In various examples, the subject has an International Prognostic Index (IPI) score of 0 or 1. In various examples, the subject has an International Prognostic Index (IPI) score ≥ 2. In various examples, the subject has an International Prognostic Index (IPI) score of 2 or 3. In various examples, the subject has an International Prognostic Index (IPI) score ≥ 4. In various examples, the subject has an International Prognostic Index (IPI) score of 4 or 5.

[0025] In various examples, the subject has a Baseline ECOG Status of 0 or 1. In various examples, the subject has a Baseline ECOG Status of 2.

[0026] In various examples, the subject is newly diagnosed with PTCL and/or has not previously been treated for a hematologic cancer. In various examples, the subject has previously been treated for a hematologic cancer. In various examples, the cancer has relapsed or is refractory.

[0027] In various examples, the PTCL is a stage III or stage IV PTCL.

[0028] In various examples, the PTCL is a CD30-expressing PTCL tumor. In various examples, the PTCL is a CD30-expressing PTCL and the CD30 expression is ≥10% of lymphoma cells.

[0029] In various examples, the CD30 expression is measured by a FDA approved test. Exemplary tests include local pathology assessment in a CD30-qualified laboratory; CD30 positivity confirmed in diagnostic biopsy using immunohistochemistry. The 3 following criteria are used to determine CD30 positivity:

1) CD30 detected in 10% or greater of neoplastic cells (in cases where enumeration of neoplastic cells was not possible, total lymphocytes may have been used).

2) CD30 staining at any intensity above background, and

3) Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.

[0030] In various examples, the neuropathy is measured periodically using standard assays known in the art.

[0031] In various examples, doses of anti-CD30 antibody drug conjugate may be reduced if the patient experiences renal or hepatic impairment. In various examples, if the subject experiences mild hepatic impairment (Child-Pugh A) the dose is reduced to approximately 1.2 mg/kg and is administered every 2 weeks, up to a maximum of 120 mg (depending on weight of patient) administered every 2 weeks.

[0032] In various examples, if the anti-CD30 antibody drug conjugate (ADC) is administered at 1.8 mg/kg with CHP combination therapy, the combination therapy is administered every three weeks. In various examples, the combination therapy is administered on day 1 of a 21 day cycle. In various examples, the ADC + CHP combination therapy is administered for no more than eight cycles. In various examples, the ADC +CHP combination therapy is administered for six to eight cycles. In various examples, the A+CHP therapy is administered for 4, 5, 6, 7 or 8 cycles. Optionally, the subject receives single-agent anti-CD30 antibody drug conjugate, e.g., brentuximab vedotin, for eight to 10 additional cycles for a total of 16 cycles.

[0033] In various examples, the ADC or combination therapy is administered until a PET scan determines there is no tumor or progression of tumor.

[0034] In various examples, the neuropathy is peripheral motor neuropathy or peripheral sensory neuropathy. In various examples, the ADC or combination therapy reduces one or more symptoms of peripheral neuropathy selected from the group consisting of paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy.

[0035] In various examples, the dose of anti-CD30 antibody drug conjugate is delayed by one week or two weeks if peripheral neuropathy appears, and ADC or combination therapy is continued when the neuropathy is resolved or determined to be Grade 2 or less, or Grade 1 or less.

[0036] In a second example, the disclosure provides a method for treating a mature T cell lymphoma in a subject comprising co-administering an anti-CD30 antibody drug conjugate,

optionally with a chemotherapy, with a granulopoiesis stimulating factor at the initiation of, or first administration of, the antibody drug conjugate therapy, e.g. as primary prophylaxis. In various examples, the granulopoiesis stimulating factor can be used also in combination with any standard or modified chemotherapeutic regimen, e.g., as a frontline therapy. For example, treatment at initiation of therapy, e.g., as primary prophylaxis, includes wherein the granulopoiesis stimulating factor is administered from within 1 day to within 7 days after the initiation of or first administration of the therapy, e.g., ADC or combination therapy. In various examples, the granulopoiesis stimulating factor is administered from within 2 days to within 5 days after the initiation of or first administration of the therapy, e.g., ADC or combination therapy. In some examples, the granulopoiesis stimulating factor is administered on the same day as the ADC or combination therapy.

[0037] In various examples, provided herein is a method for treating a mature T cell lymphoma in a subject comprising administering a combination therapy comprising an anti-CD30 antibody drug conjugate in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) and prophylactically administering a granulopoiesis stimulating factor, wherein the granulopoiesis stimulating factor is administered with the initiation of the combination therapy.

[0038] Also described herein is amethod for reducing the incidence of neutropenia or febrile neutropenia in a subject having mature T cell lymphoma and receiving therapy comprising anti-CD30 antibody drug conjugate, optionally in combination with a chemotherapy. In various examples, the disclosure provides a method 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 in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) comprising administering to the subject a granulopoiesis stimulating factor, wherein the granulopoiesis stimulating factor is administered with initiation of the combination therapy.

[0039] Also described herein is a method for decreasing the incidence of infection, or for decreasing the incidence of other adverse events, in a subject having mature T cell lymphoma and receiving therapy comprising anti-CD30 antibody drug conjugate, optionally in combination with a chemotherapy. In various examples, the disclosure provides a method 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 in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) comprising

administering to the subject a granulopoiesis stimulating factor in an amount effective to reduce infections, wherein the granulopoiesis stimulating factor is administered with the initiation of the combination therapy.

[0040] In various examples, it is contemplated that the anti-CD30 antibody drug conjugate is brentuximab vedotin.

[0041] In various examples, the granulopoiesis stimulating factor is administered from 1 day to 7 days, or from 1 day to 5 days, or from 2 days to 5 days, after a second or subsequent, administration of the therapy. In some examples, the granulopoiesis stimulating factor is administered on the same day as the second or subsequent administration of the ADC or combination therapy.

[0042] In various examples, the granulopoiesis stimulating factor is administered to a subject that has not received an anti-CD30 antibody drug conjugate therapy previously, or to a subject before the subject has experienced treatment-emergent neutropenia. In various examples, the subject has not experienced treatment-emergent grade 3-4 neutropenia after administration of the ADC or combination therapy.

[0043] In various examples, the granulopoiesis stimulating factor is granulocyte colony stimulating factor (GCSF). In various examples, the GCSF is a long-acting GCSF or is not long-acting GCSF. In various examples, the granulopoiesis stimulating factor is granulocyte monocyte colony stimulating factor (GM-CSF). In various examples, the GCSF is long-acting, and is administered in a single dose 1, 2 or 3 days after initiation of the ADC or combination therapy. In various examples, the stimulating factor is GMCSF, or the GCSF is not long acting, and is administered in multiple doses (e.g. multiple daily doses) starting at 1, 2, 3, 4, 5, 6, or 7 days after the initiation of the therapy for a duration of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more days. In various examples, the granulopoiesis stimulating factor is pegfilgrastim or filgrastim.

[0044] In various examples, the anti-CD30 antibody drug conjugate, optionally in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP), is administered every 3 weeks.

[0045] In various examples, anti-CD30 antibody drug conjugate is administered on day 1 of a 21-day cycle. In various examples, the method further comprises administering a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP)

as a combination therapy, preferably the anti-CD30 antibody drug conjugate is brentuximab vedotin, on the same day as the anti-CD30 antibody drug conjugate.

[0046] In various examples, 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.

[0047] In various examples, the anti-CD30 antibody of the anti-CD30 antibody drug conjugate also 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. It is contemplated that the amino acid variable region sequence can be 90%, 95%, 96% 97%, 98% or 99% identical to either SEQ ID NO: 2 or SEQ ID NO: 10.

[0048] In various examples, the anti-CD30 antibody of the anti-CD30 antibody drug conjugate is a monoclonal anti-CD30 antibody. In various examples, the anti-CD30 antibody of the anti-CD30 antibody drug conjugate is a chimeric AC10 antibody.

[0049] In various examples, the antibody drug conjugate comprises monomethyl auristatin E and a protease-cleavable linker. In various examples, the protease cleavable linker is comprises a thiolreactive spacer and a dipeptide. In various examples, the protease cleavable linker consists of a thiolreactive maleimidocaproyl spacer, a valine–citrulline dipeptide, and a p-amino-benzyloxycarbonyl spacer.

[0050] In various examples, the antibody is an IgG antibody, preferably an IgG1 antibody.

[0051] In various examples, the anti-CD30 antibody drug conjugate is brentuximab vedotin.

[0052] In various examples, the subject is also receiving a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) as a combination therapy. In various examples, the cyclophosphamide is administered at 750 mg/m^2, doxorubicin is administered at 50 mg/m^2, and prednisone is administered at 100 mg on days 1 to 5 of a 21 day cycle.

[0053] In various examples, the anti-CD30 antibody drug conjugate is brentuximab vedotin and is administered at 1.8 mg/kg, cyclophosphamide is administered at 750 mg/m^2, doxorubicin is administered at 50 mg/m^2, and prednisone is administered at 100 mg on days 1 to 5 of a 21 day cycle.

[0054] In various examples, the granulopoiesis stimulating factor, e.g., G-CSF, is administered in a dose range from 5 to 10 mcg/kg/day, or 300 to 600 mcg/day. In various examples, the granulopoiesis stimulating factor is administered at a dose of 6 mg/dose.

[0055] In various examples, the granulopoiesis stimulating factor is given intravenously or subcutaneously. In various examples, the granulopoiesis stimulating factor is given in a single dose or multiple doses, for example, a long-acting GCSF may be administered in a single dose or multiple doses on the same day, and a non-long-acting GCSF may be given in multiple doses over multiple days.

[0056] In any of the examples disclosed herein, the subject is suffering from a mature T cell lymphoma (MTCL) 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.

[0057] In various examples, the mature T cell lymphoma is peripheral T cell lymphoma (PTCL). In various examples, 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.

[0058] In various examples, the PTCL is a sALCL. In various examples, the sALCL is selected from the group consisting of anaplastic lymphoma kinase positive (ALK+) sALCL and anaplastic lymphoma kinase negative (ALK-) sALCL. In various examples, the sALCL is an ALK+ sALCL. In various examples, the sALCL is an ALK- sALCL.

[0059] In various examples, the PTCL is not a sALCL. In various examples, 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.

[0060] In various examples, the PTCL is not an AITL. In various examples, 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.

[0061] In various examples, the subject has an International Prognostic Index (IPI) score of 0 or 1. In various examples, the subject has an International Prognostic Index (IPI) score ≥ 2. In various examples, the subject has an International Prognostic Index (IPI) score of 2 or 3. In various examples, the subject has an International Prognostic Index (IPI) score ≥ 4. In various examples, the subject has an International Prognostic Index (IPI) score of 4 or 5.

[0062] In various examples, the subject has a Baseline ECOG Status of 0 or 1. In various examples, the subject has a Baseline ECOG Status of 2.

[0063] In various examples, the subject is newly diagnosed with PTCL and/or has not previously been treated for a hematologic cancer. In various examples, the subject has previously been treated for a hematologic cancer. In various examples, the cancer has relapsed or is refractory.

[0064] In various examples, the PTCL is a stage III or stage IV PTCL.

[0065] In various examples, the PTCL is a CD30-expressing PTCL tumor. In various examples, the PTCL is a CD30-expressing PTCL and the CD30 expression is ≥10% of lymphoma cells.

[0066] In various examples, the CD30 expression is measured by a FDA approved test. Exemplary tests include local pathology assessment in a CD30-qualified laboratory; CD30 positivity confirmed in diagnostic biopsy using immunohistochemistry. The 3 following criteria are used to determine CD30 positivity:

1) CD30 detected in 10% or greater of neoplastic cells (in cases where enumeration of neoplastic cells was not possible, total lymphocytes may have been used).

2) CD30 staining at any intensity above background, and

3) Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.

[0067] In various examples, when the lymphoma is peripheral T cell lymphoma, the granulopoiesis stimulating factor can be administered from 1 to 8 days after anti-CD30 antibody drug conjugate administration.

[0068] In a third example, the disclosure provides a method of treating a subject having mature T cell lymphoma comprising administering as frontline treatment an effective amount of a composition comprising bretuximab vedotin (A) in combination with chemotherapy consisting

of cyclophosphamide, doxorubicin and prednisone (CHP), wherein the brentuximab vedotin is administered at 1.8 mg/kg every two weeks, cyclophosphamide is administered at 750 mg/m^2 on day 1 of a 21 day cycle, doxorubicin is administered at 50 mg/m^2 on day 1 of a 21 day cycle, and prednisone is administered at 100 mg on days 1 to 5 of a 21 day cycle, until a maximum of eight cycles, and wherein the brentuximab vedotin is administered within about 1 hour after administration of the CHP therapy; optionally the subject is characterized by one or more of the following: (1) ALK-positive sALCL with an IPI score greater than or equal to 2, ALK-negative sALCL, PTCL-NOS, AITL, Adult T-cell leukemia/lymphoma (ATLL; acute and lymphoma types only, must be positive for human T-cell leukemia virus 1), Enteropathy-associated T-cell lymphoma (EATL), Hepatosplenic T-cell lymphoma; (2) Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT, or (3) an Eastern Cooperative Oncology Group (ECOG) performance status prior to therapy of 2 or less. The methods herein further provide that progression free survival (PFS) of the subject after therapy is maintained for greater than 1 year. In various examples, the progression free survival (PFS) of the subject after therapy is maintained for approximately 2 years. In certain examples, after six to eight cycles of A+CHP therapy the subject has a Deauville score of 3 or less, or 2 or less.

[0069] In another example, the disclosure provides an anti-CD30 antibody drug conjugate for use in treating a subject that has exhibited Grade 2 or greater peripheral neuropathy after starting treatment with a combination therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) every three weeks, wherein said patient is administered anti-CD30 antibody drug conjugate at a dose of 0.9 mg/kg to 1.2 mg/kg.

[0070] In a further example, contemplated herein is an anti-CD30 antibody drug conjugate for use in treating a mature T cell lymphoma in a subject comprising administering a combination therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg in combination with a chemotherapy consisting essentially of cyclophosphamide, doxorubicin and prednisone (CHP) every three weeks and prophylactically administering a granulopoiesis stimulating factor, wherein the stimulating factor is administered with the initiation of the combination therapy, e.g., from 1 day to 7 days after the initiation of the combination therapy.

[0071] In a related example, also contemplated is an anti-CD30 antibody drug conjugate for use in reducing the incidence of neutropenia, infection or other adverse events in a subject comprising administering a combination therapy comprising an anti-CD30 antibody drug conjugate at a dose of 1.8 mg/kg in combination with a chemotherapy consisting essentially of

cyclophosphamide, doxorubicin and prednisone (CHP) every three weeks and prophylactically administering a granulopoiesis stimulating factor, wherein the stimulating factor is administered with the initiation of the combination therapy, e.g., from 1 day to 7 days after the initiation of the combination therapy. In various examples, when the mature T cell lymphoma is PTCL, the granulopoiesis stimulating factor is administered from 1 to 8 days after initiation of the combination therapy.

[0072] It is specifically provided herein that all examples of the disclosure described above with the methods of treatment are applicable to the anti-CD30 antibody drug conjugate for use in any of the indications described above.

[0073] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the disclosure and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as “one embodiment”, “some embodiments”, “certain embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the disclosure. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

DETAILED DESCRIPTION

[0074] The present disclosure provides methods for improving adverse events associated with treatment of mature T Cell Lymphomas with an anti-CD30 antibody drug conjugate, optionally in combination with a chemotherapeutic regimen. The regimens described herein are

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 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 method 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 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 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 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 method 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 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 given intravenously or subcutaneously.

46. The use of any one of claims 1-44 wherein the medicament is 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 method 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.

59. Use of an anti-CD30 antibody drug conjugate in the manufacture of a medicament for use in combination therapy for treating a subject having a mature T cell lymphoma that has exhibited Grade 2 or greater peripheral neuropathy, wherein the subject is to be administered the medicament at a dose between 0.9 mg/kg to 1.2 mg/kg, 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).