- Targeted oral bioavailability for the parent drug between 75 to 90%
- Targeted bioavailability for the metabolite between 120 and 140%
- The half-life values for parent drug and metabolite after oral administration closely match those after intravenous administration
- The appearance of metabolite after oral administration closely matches that of intravenous administration
- The C_{max} after oral administration for the parent drug up to 80% of C_{max} for intravenous administration
- Comparable to the intravenous (IV) formulation with respect to both C_{max} and AUC for parent drug
- Formulation of metabolite reasonably comparable between oral and IV
- To permit once a day dosing if bioavailability (F) is >80%
- To permit twice a day dosing (BID) if bioavailability is >50% but <80%

The present invention addresses the above-discussed need. It is hence an object of the invention to provide novel and/or improved oral formulations of bendamustine, particularly oral bendamustine formulations meeting the criteria set out above.

In the context of the present invention, it has surprisingly been found that oral formulations of bendamustine with specific modified cyclodextrins, such as methyl-β-cyclodextrin, exhibit a greatly improved oral bioavailability, which renders these formulations highly advantageous for therapeutic use by oral administration, including in the treatment of cancer.

In an aspect of the present disclosure, there is provided an oral pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein said modified cyclodextrin is selected from methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and a combination thereof.

In another aspect, there is provided the oral pharmaceutical composition as defined above for use in the treatment of cancer.

In another aspect, there is provided the oral pharmaceutical composition as defined above for use in the treatment of an autoimmune disease/disorder, rheumatoid arthritis, multiple sclerosis, lupus erythematosus, or a neurodegenerative disease/disorder, or for the use in immunomodulatory therapy.

In another aspect, there is provided a use of bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin for the preparation of a medicament for oral administration, wherein said modified cyclodextrin is selected from methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and a combination thereof.

Accordingly, the present ~~invention~~ disclosure provides a composition for use as a medicament, wherein the composition comprises bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein the composition is to be administered orally, and wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ thus provides a composition for use in therapy, wherein the composition comprises bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein the composition is to be administered orally, and wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is

substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

In other words, the present disclosure~~invention~~ provides a pharmaceutical composition for oral administration, wherein the pharmaceutical composition comprises bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ likewise provides an oral pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ further provides an oral pharmaceutical formulation comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ also provides a pharmaceutical composition which is formulated (or adapted) for oral administration, wherein the pharmaceutical composition comprises bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, and wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

Moreover, the present disclosure~~invention~~ relates to the use of bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin for the preparation of a medicament for oral administration, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said

α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ also relates to the use of bendamustine or a pharmaceutically acceptable salt or solvate thereof and a modified cyclodextrin for the preparation of a medicament which is formulated (or adapted) for oral administration, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The present disclosure~~invention~~ furthermore refers to the use of bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin for the preparation of an oral medicament (or an oral pharmaceutical composition) for the treatment of a disease or disorder, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The disclosure~~invention~~ likewise provides a method of treating a disease or disorder (e.g., cancer) in a subject/patient (e.g., a human) in need thereof, the method comprising orally administering a pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin to the subject/patient, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof. In particular, the method comprises the oral administration of a therapeutically effective amount of the pharmaceutical composition. Examples of the disease or disorder to be treated are described further below.

Moreover, the present disclosure~~invention~~ provides a method of enhancing the oral bioavailability of bendamustine or a pharmaceutically acceptable salt or solvate thereof, the method comprising orally administering a pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin to a subject/patient (e.g., a human) in need thereof, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

The ~~invention~~ disclosure further relates to a method of delivering bendamustine or a pharmaceutically acceptable salt or solvate thereof to a subject/patient (e.g., a human) in need thereof, the method comprising orally administering a pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin to the subject/patient, wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof. The method particularly comprises the oral administration of a therapeutically effective amount of the pharmaceutical composition.

The composition (or pharmaceutical composition, formulation or medicament) according to the present invention can be used for the treatment of various diseases or disorders, including in particular cancer (Darwish M et al., *Cancer Chemother Pharmacol*, 2015, 75(6), 1143-1154; Mundt M et al., *Beilage zu Onkologie*, Band 24, Heft 3, Juni 2001 (doi:10.1159/000055100); Cheson BD et al., *J Clin Oncol*, 2009, 27(9), 1492-1501), but also non-cancerous diseases/disorders (Faivre G et al., *Neurology*, 2014, 82(10 Supplement), P7.261 (May 01, 2014 Poster Session VII Neuro-oncology: Primary CNS Lymphoma and Other Hematologic Malignancies), http://www.neurology.org/content/82/10_Supplement/P7.261). For example, bendamustine has been shown to induce the production of interleukin-10, which suppresses inflammation, in studies with human B cells, and has thus been found to exert anti-inflammatory activity (see, e.g., Lu L et al., *Int Immunopharmacol*, 2016, 39, 273-279); the composition (or pharmaceutical composition, formulation or medicament) according to the invention is hence considered to be effective in the treatment of autoimmune diseases/disorders, such as, e.g., systemic lupus erythematosus.

The cancer to be treated in accordance with the invention is preferably a hematological cancer. The hematological cancer may, for example, be selected from lymphoma, Hodgkin lymphoma, nodular sclerosing Hodgkin lymphoma, mixed-cellularity Hodgkin lymphoma, lymphocyte-rich Hodgkin lymphoma, lymphocyte-depleted Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, non-Hodgkin lymphoma, follicular non-Hodgkin lymphoma, diffuse non-Hodgkin lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, mycosis fungoides, Sézary's disease, T-zone lymphoma, lymphoepithelioid lymphoma, Lennert's lymphoma, lymphosarcoma, a malignant immunoproliferative disease, Waldenström's macroglobulinemia, alpha heavy chain disease, gamma heavy chain disease, Franklin's disease, an immunoproliferative small intestinal disease, Mediterranean lymphoma, multiple myeloma,

CLAIMS

~~1. A composition for use as a medicament, wherein the composition comprises bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein the composition is to be administered orally, and wherein said modified cyclodextrin is selected from α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, dihydroxy-C_{1-4}-alkyl, -CO(C_{1-4}-alkyl), or any combination thereof.~~

~~2~~1. An oral pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin, wherein said modified cyclodextrin is selected from methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and a ~~α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, dihydroxy-C_{1-4}-alkyl, -CO(C_{1-4}-alkyl), or any~~ combination thereof.

~~3~~2. The ~~composition for use according to claim 1 or the~~ oral pharmaceutical composition of claim ~~2~~1, wherein the composition comprises bendamustin hydrochloride.

~~4~~3. The ~~composition for use according to claim 1 or the~~ oral pharmaceutical composition of claim ~~2~~1, wherein the composition comprises bendamustin hydrochloride monohydrate.

~~5. The composition for use according to any one of claims 1, 3 or 4 or the oral pharmaceutical composition of any one of claims 2 to 4, wherein the modified cyclodextrin is β-cyclodextrin which is substituted with methyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl, hydroxybutyl, acetyl, or any combination thereof.~~

~~6. The composition for use according to any one of claims 1 or 3 to 5 or the oral pharmaceutical composition of any one of claims 2 to 5, wherein the modified cyclodextrin is selected from methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, dihydroxypropyl-β-cyclodextrin, hydroxybutyl-β-cyclodextrin, acetyl-~~

β-cyclodextrin, and a β-cyclodextrin substituted with at least two different groups selected from methyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl, hydroxybutyl, and acetyl.

7. The composition for use according to any one of claims 1 or 3 to 6 or the oral pharmaceutical composition of any one of claims 2 to 6, wherein the modified cyclodextrin is methyl-β-cyclodextrin.

8. The composition for use according to any one of claims 1 or 3 to 6 or the oral pharmaceutical composition of any one of claims 2 to 6, wherein the modified β-cyclodextrin is hydroxypropyl-β-cyclodextrin.

9. The composition for use according to any one of claims 1 or 3 to 8 or the oral pharmaceutical composition of any one of claims 2 to 8, wherein the composition comprises an inclusion complex of said modified cyclodextrin and said bendamustine or the pharmaceutically acceptable salt or solvate thereof, wherein the inclusion complex is obtainable by kneading, physically mixing, co-evaporating, freeze-drying, or spray-drying said modified cyclodextrin and said bendamustine or the pharmaceutically acceptable salt or solvate thereof.

10. The composition for use according to any one of claims 1 or 3 to 9 or the oral pharmaceutical composition of any one of claims 2 to 91, wherein the composition comprises said bendamustine or the pharmaceutically acceptable salt or solvate thereof and said modified cyclodextrin at a molar ratio of about 1:10 to about 1:0.5.

11. The composition for use according to any one of claims 1 or 3 to 10 or the oral pharmaceutical composition of any one of claims 2 to 101, wherein said composition is provided in the form of a solid oral dosage form, preferably in the form of a pill, a tablet, a mini-tablet, a capsule, a lozenge, a troche, a pellet, a powder, granules, or a film;
and wherein the solid oral dosage form optionally has an enteric coating, wherein the enteric coating is preferably made from a material selected from methyl acrylate-methacrylic acid copolymer, ethyl acrylate-methylacrylic acid copolymer, methyl methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, shellac,

~~cellulose acetate trimellitate, carboxymethyl cellulose, sodium alginate, zein, amylose, starch, and dextrins~~.

~~12~~6. ~~A~~ The oral pharmaceutical composition as defined in any one of claims 1 to ~~11~~ 5 for use in the treatment of cancer~~, wherein the composition is to be administered orally~~.

~~13~~7. The oral pharmaceutical composition ~~for use~~ according to claim ~~12~~6, wherein said cancer is a hematological cancer~~ which is preferably selected from lymphoma, Hodgkin lymphoma, nodular sclerosing Hodgkin lymphoma, mixed-cellularity Hodgkin lymphoma, lymphocyte-rich Hodgkin lymphoma, lymphocyte-depleted Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, non-Hodgkin lymphoma, follicular non-Hodgkin lymphoma, diffuse non-Hodgkin lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, mycosis fungoides, Sézary's disease, T-zone lymphoma, lymphoepithelioid lymphoma, Lennert's lymphoma, lymphosarcoma, a malignant immunoproliferative disease, Waldenström's macroglobulinemia, alpha heavy chain disease, gamma heavy chain disease, Franklin's disease, an immunoproliferative small intestinal disease, Mediterranean lymphoma, multiple myeloma, Kahler's disease, myelomatosis, leukemia, plasma cell leukemia, lymphoid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, subacute lymphocytic leukemia, prolymphocytic leukemia, hairy-cell leukemia, leukemic reticuloendotheliosis, adult T-cell leukemia, myeloid leukemia, acute myeloid leukemia, chronic myeloid leukemia, subacute myeloid leukemia, myeloid sarcoma, chloroma, granulocytic sarcoma, acute promyelocytic leukemia, acute myelomonocytic leukemia, a chronic BCR-ABL negative myeloproliferative disorder, polycythaemia vera, essential thrombocythemia, idiopathic myelofibrosis, monocytic leukemia, acute erythraemia, erythroleukemia, acute erythraemic myelosis, Di Guglielmo's disease, chronic erythraemia, Heilmeyer-Schöner disease, acute megakaryoblastic leukemia, mast cell leukemia, acute panmyelosis, acute myelofibrosis, and Letterer-Siwe disease~~.

~~14~~8. The oral pharmaceutical composition ~~for use~~ according to claim ~~12~~6, wherein said cancer is a solid cancer~~ which is preferably selected from breast cancer, lung cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, bladder cancer, prostate cancer, head and/or neck cancer, and soft-tissue sarcoma~~.

~~15~~9. ~~A~~ The oral pharmaceutical composition as defined in any one of claims 1 to ~~11~~ 5 for use in the treatment of an autoimmune disease/disorder, rheumatoid arthritis, multiple sclerosis, lupus erythematosus, or a neurodegenerative disease/disorder, or for the use in immunomodulatory therapy~~, wherein the composition is to be administered orally~~.

~~16~~10. The oral pharmaceutical composition ~~for use~~ according to any one of claims ~~12~~ 6 to ~~14~~8, wherein the composition is to be administered in combination with a further anticancer agent and/or radiotherapy~~,~~

~~wherein said further anticancer agent is preferably selected from etoposide, fludarabine, mitoxantrone, methotrexate, prednisone, vincristine, and an anti-CD20 monoclonal antibody, and wherein said further anticancer agent is more preferably an anti-CD20 monoclonal antibody selected from rituximab, ocrelizumab, ofatumumab, obinutuzumab, and ibritumomab tiuxetan~~.

~~17~~11. The oral pharmaceutical composition ~~for use~~ according to any one of claims ~~12~~ 6 to ~~15~~9, wherein the composition is to be administered in combination with rituximab.

~~18~~12. The oral pharmaceutical composition ~~for use~~ according to any one of claims ~~12~~ 6 to ~~17~~11, wherein the composition is to be administered in combination with an antiemetic agent~~,~~

~~wherein said antiemetic agent is preferably selected from alosetron, azasetron, bemesetron, cilansetron, clozapine, dazopride, dolasetron, granisetron, lerisetron, metoclopramide, mianserin, mirtazapine, olanzapine, ondansetron, palonosetron, quetiapine, ramosetron, ricasetron, tropisetron, zatosetron, clozapine, cyproheptadine, hydroxyzine, olanzapine, risperidone, ziprasidone, dronabinol, nabilone, tetrahydrocannabinol, alizapride, bromopride, chlorpromazine, clebopride, domperidone, haloperidol, hydroxyzine, itopride, metoclopramide, metopimazine, prochlorperazine, thiethylperazine, trimethobenzamide, cyclizine, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine, atropine, diphenhydramine, hyoscyamine, scopolamine, aprepitant, casopitant, ezlopitant, fosaprepitant, maropitant, netupitant, rolapitant, vestipitant, cerium oxalate, dexamethasone, lorazepam, midazolam, propofol, and a combination thereof~~.

1913. The composition for use according to any one of claims 1 or 3 to 17 or the oral pharmaceutical composition of any one of claims 2 to 111, wherein the composition is to be administered orally to a human subject.

2014. Use of bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin for the preparation of a medicament for oral administration, wherein said modified cyclodextrin is selected from methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin and aα-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

21. A method of treating a disease or disorder in a subject in need thereof, the method comprising orally administering a pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin to the subject, wherein said modified cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.

22. A method of delivering bendamustine or a pharmaceutically acceptable salt or solvate thereof to a subject in need thereof, the method comprising orally administering a pharmaceutical composition comprising bendamustine or a pharmaceutically acceptable salt or solvate thereof in combination with a modified cyclodextrin to the subject, wherein said modified cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, and wherein said α-cyclodextrin, said β-cyclodextrin or said γ-cyclodextrin is substituted with C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, dihydroxy-C_{1-4} alkyl, -CO(C_{1-4} alkyl), or any combination thereof.