In another aspect, the present disclosure provides a use of a cathepsin S inhibitor in the manufacture of a medicament for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent is a biologic.

In another aspect, the present disclosure provides a use of a cathepsin S inhibitor in the manufacture of a kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit further comprises instructions for using the cathepsin S inhibitor in a method of treatment comprising the administration of an effective amount of the cathepsin S inhibitor and the therapeutic agent to said subject, wherein the therapeutic agent is a biologic.

One of the early steps in the cycle of anti-tumor immunity is the capture and presentation of tumor-associated antigens by dendritic cells in the context of MHC-I or MHC-II molecules. Therefore, for cancer immunotherapy (CIT), it sounds counterintuitive to use a compound supressing MHC-II maturation and antigen presentation. Nevertheless, recent studies have shown that the cathepsins upregulated in a wide range of cancers are

Claims

1. Use of a cathepsin S inhibitor in the manufacture of a medicament for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent is a biologic.

2. Use of a cathepsin S inhibitor in the manufacture of a kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit further comprises instructions for using the cathepsin S inhibitor in a method of treatment comprising the administration of an effective amount of the cathepsin S inhibitor and the therapeutic agent to said subject, wherein the therapeutic agent is a biologic.

3. The use according to claim 2, wherein the kit comprises:

   (a) a therapeutic agent;

   (b) a cathepsin S inhibitor; and

   (c) instructions for using the therapeutic agent and the cathepsin S inhibitor in a method of treatment comprising the administration of an effective amount of said therapeutic agent and said cathepsin S inhibitor to a patient in need thereof.

4. The use according to any one of claims 1 to 3, wherein the first dose of the cathepsin S inhibitor is to be administered to the subject before the first dose of the therapeutic agent.

5. The use according to any one of claims 1 to 4, wherein the reducing or preventing or the instructions comprises:

   (a) a first effective dose of the cathepsin S inhibitor to be administered to the subject;

   (b) optionally the administration of the cathepsin S inhibitor is to be continued before the therapeutic agent is administered to the subject;

   (c) a first effective dose of the therapeutic agent is to be administered to the subject; and

(d) the administration of the cathepsin S inhibitor and/or the therapeutic agent to the subject is to be continued.

6. The use according to any one of claims 1 to 5, wherein the first dose of the cathepsin S inhibitor is to be administered to the subject prior to the first dose of the therapeutic agent, in particular between at least 1 day and 2 weeks before the first dose of the therapeuthic agent, in particular between at least 1 day and 1 week before the first dose of the therapeutic agent, more particularly 1 week before the first dose of the therapeutic agent.

7. The use according to any one of claims 1 to 6, wherein the therapeutic agent does not rely on MHC-II antigen presentation.

8. The use according to any one of claims 1 to 7, wherein the ADA are produced through a T-cell dependent immune response.

9. The use according to any one of claims 1 to 8, wherein the ADA are produced through a T-helper cell dependent immune response.

10. The use according to any one of claims 1 to 9, wherein the ADA are produced by a MHC-II dependent immune response.

11. The use according to any one of claims 1 to 10, wherein the therapeutic agent is an antibody.

12. The use according to any one of claims 1 to 11, wherein the therapeutic agent is a biologic which induces, enhances or suppresses an immune response.

13. The use according to any one of claims 1 to 12, wherein the therapeutic agent is a biologic, in particular a protein, more particularly a polypeptide, an antibody, more particularly a bispecific antibody, in particular a T-cell bispecific antibody, an antibody fragment, an antibody-drug conjugate, a BiTE, a cytokine or a vector, for example a gene therapy vector.

14. The use according to any one of claims 1 to 13, wherein the therapeutic agent is a monoclonal antibody, in particular a monoclonal antibody selected from alemtuzumab (LEMTRADA®), atezolizumab (TECENTRIQ®), bevacizumab (AVASTIN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), pertuzumab (OMNITARG®, 2C4), trastuzumab (HERCEPTIN®), tositumomab (Bexxar®), abciximab (REOPRO®), adalimumab (HUMIRA®), apolizumab,

aselizumab, atlizumab, bapineuzumab, basiliximab (SIMULECT®), bavituximab, belimumab (BENLYSTA®) briankinumab, canakinumab (ILARIS®), cedelizumab, certolizumab pegol (CIMZIA®), cidfusituzumab, cidtuzumab, cixutumumab, clazakizumab, crenezumab, daclizumab (ZENAPAX®), dalotuzumab, denosumab (PROLIA®, XGEVA®), eculizumab (SOLIRIS®), efalizumab, emicizumab (HEMLIBRA®), epratuzumab, erlizumab, felvizumab, fontolizumab, golimumab (SIMPONI®), ipilimumab, imgatuzumab, infliximab (REMICADE®), labetuzumab, lebrikizumab, lexatumumab, lintuzumab, lucatumumab, lulizumab pegol, lumretuzumab, mapatumumab, matuzumab, mepolizumab, mogamulizumab, motavizumab, motovizumab, muronomab, natalizumab (TYSABRI®), necitumumab (PORTRAZZA®), nimotuzumab (THERACIM®), nolovizumab, numavizumab, obinutuzumab (GAZYVA®/GAZYVARO®), ocrelizumab (OCREVUS®), olokizumab, omalizumab (XOLAIR®), onartuzumab (also known as MetMAb), palivizumab (SYNAGIS®), pascolizumab, pecfusituzumab, pectuzumab, pegylated interferon (PEGAZYS®), pembrolizumab (KEYTRUDA®), pexelizumab, priliximab, ralivizumab, ranibizumab (LUCENTIS®), reslivizumab, reslizumab, resyvizumab, rituximab (MABTHERA®), robatumumab, rontalizumab, rovelizumab, ruplizumab, sarilumab, secukinumab, seribantumab, sifalimumab, sibrotuzumab, siltuximab (SYLVANT®) siplizumab, sontuzumab, tadocizumab, talizumab, tefibazumab, tocilizumab (ACTEMRA®), toralizumab, trastuzumab emtansine (KADCYLA®), tucusituzumab, umavizumab, urtoxazumab, ustekinumab (STELARA®), vedolizumab (ENTYVIO®), visilizumab, zanolimumab and zalutumumab.

15. The use according to any one of claims 1 to 14, wherein the therapeutic agent is a recombinant fusion protein comprised of a human monoclonal antibody directed against fibroblast activation protein-alpha (FAP) linked to an engineered variant form of interleukin-2 (IL-2v).

16. The use according to any one of claims 1 to 15, wherein the therapeutic agent is cergutuzumab amunaleukin.

17. The use according to any one of claims 1 to 16, wherein the therapeutic agent is an anti-TNFalpha antibody.

18. The use according to any one of claims 1 to 17, wherein the therapeutic agent is infliximab (REMICADE®) or adalimumab (HUMIRA®).

19. The use according to any one of claims 1 to 18, wherein the cathepsin S inhibitor is

(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; or

(2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

or a pharmaceutically acceptable salt thereof.

20. The use according to any one of claims 1 to 19, wherein the cathepsin S inhibitor is to be administered in an amount that is sufficient to reduce or prevent the formation of ADA against the therapeutic agent.

21. The use according to any one of claims 1 to 20, wherein the cathepsin S inhibitor is to be administered at dose of between 50 mg/kg/day and 400 mg/kg/day, in particular between 75 mg/kg/day and 250 mg/kg/day, more particularly at 100 mg/kg/day or 200 mg/kg/day.

22. The use according to any one of claims 1 to 21, wherein the cathepsin S inhibitor is to be administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d.

***