COMBINATIONS OF IADADEMSTAT FOR CANCER THERAPY

FIELD

The present invention relates to combinations of iadademstat for cancer therapy, in particular combinations with immune checkpoint inhibitors as defined herein.

BACKGROUND

Cancer immunotherapy, also referred to as immuno-oncology, is the artificial stimulation of the immune system to treat cancer. Checkpoint inhibitor therapy is a form of cancer immunotherapy that targets immune checkpoints, key regulators of the immune system that stimulate or inhibit its actions, which tumors can use to protect themselves from attacks by the immune system. Checkpoint therapy can block inhibitory checkpoints, restoring immune system function. In particular, PD(L)1 inhibitors are a group of immune checkpoint inhibitors that act to inhibit the association of programmed cell death protein 1 (PD-1, also called PDCD1 or CD279) to its ligands, programmed death-ligand 1 (PD-L1, also known as CD274) and programmed death-ligand 2 (PD-L2, also known as CD273). The interaction of these cell surface proteins is involved in the suppression of the immune system and occurs following infection to limit the killing of bystander host cells and prevent autoimmune disease, but also in different types of cancer.

By recruiting the immune system against cancer cells, PD(L)1 inhibitor therapy holds promise to achieve long-lasting responses in several malignant conditions, and several PD-1 inhibitors and PD-L1 inhibitors have already been approved as a treatment for several types of cancer. However, a therapeutic response to immune checkpoint inhibitors such as PD-1 or PD-L1 inhibitors is observed only in a small subset of cancer patients. The low mutational burden of “cold” tumors enables them to stay undetected from the host inflammatory response (innate resistance). Also, cancer cells develop a number of coping strategies in response to the selective pressure applied by the treatment with immune checkpoint inhibitors (recruitment of regulatory cells, defective antigen presentation, immunosuppressant mediators, reduced costimulation, and T cell apoptosis).

There is thus a need for improved methods and compositions for the treatment of cancer that address the problem of resistances and lack of responsiveness to immune checkpoint inhibitors, particularly to PD(L)1 inhibitors.

SUMMARY

The disclosure is based on the unexpected finding that the combination of iadademstat with immune checkpoint inhibitors, particularly PD(L)1 inhibitors (as defined herein), exhibits outstanding activity in inhibiting the growth of cancer cells as compared to treatment with the immune checkpoint inhibitor alone. Iadademstat can thus be used to sensitize tumors to PD(L)1 inhibitors and improve the responsiveness of tumors to PD(L)1 inhibitor therapy.

Thus, the instant disclosure relates to combinations of iadademstat, or a pharmaceutically acceptable salt or solvate thereof, with PD(L)1 inhibitors (as defined herein).

Accordingly, in one aspect, the present disclosure provides a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor. In another aspect, the present disclosure provides a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for use in therapy. In yet another aspect, the present disclosure provides a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for use in the treatment of a disease.

The present disclosure further provides a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for use in the treatment of cancer.

The present disclosure further provides a method for treating cancer in a patient (preferably a human) in need thereof, comprising administering to the patient a therapeutically effective amount of a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor.

The present disclosure further provides a method for treating cancer in a patient (preferably a human) in need thereof, comprising administering to the patient a therapeutically effective amount of iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a therapeutically effective amount of a PD(L)1 inhibitor.

In one aspect, the present disclosure further provides the use of iadademstat, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of cancer to be used in combination with a PD(L)1 inhibitor. In another aspect, the present disclosure provides use of a PD(L)1 inhibitor for the manufacture of a medicament for the treatment of cancer to be used in combination with iadademstat or a pharmaceutically acceptable salt or solvate thereof. In yet another aspect, the present disclosure provides use of a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for the manufacture of a medicament for the treatment of cancer.

The present disclosure further provides the use of a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of treatment with a combination of iadademstat (referred to as “ORY-1001”) and a PD(L)1 inhibitor (triangles) in comparison with treatment with the PD(L)1 inhibitor alone (squares) on tumor volume in the mice B16F10 melanoma model, as explained in more detail in Example 1. Data is represented as mean± standard error of the mean (SEM); p=0.004.

Figure 2 shows the effect of treatment with a combination of iadademstat (“ORY-1001”) and a PD(L)1 inhibitor (triangles) in comparison with treatment with the PD(L)1 inhibitor alone (squares) on tumor weight in the same mice B16F10 melanoma model, as explained in more detail in Example 1. Data is represented as mean± standard error of the mean (SEM); p=0.001.

DETAILED DESCRIPTION OF THE INVENTION

As indicated above, the present invention is based on the discovery that the combination of iadademstat with PD(L)1 inhibitors exhibits outstanding anticancer activity, with superior anticancer efficacy as compared to treatment with the PD(L)1 inhibitor alone. The combined treatment with iadademstat and a PD(L)1 inhibitor causes a significant increase in the antitumor effect as compared to treatment with the PD(L)1 inhibitor alone, as illustrated in Example 1 and in Figures 1 and 2 using an *in vivo* murine melanoma model. Treatment with the combination produces statistically significant reductions in both the tumor volume and tumor weight compared

CLAIMS

1. A combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor.
2. A combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for use in therapy.
3. A combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for use in the treatment of a disease.
4. Use of iadademstat, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of cancer to be used in combination with a PD(L)1 inhibitor.
5. Use of a PD(L)1 inhibitor for the manufacture of a medicament for the treatment of cancer to be used in combination with iadademstat or a pharmaceutically acceptable salt or solvate thereof.
6. Use of a combination comprising iadademstat, or a pharmaceutically acceptable salt or solvate thereof, and a PD(L)1 inhibitor for the manufacture of a medicament for the treatment of cancer.
7. The combination according to claim 1, the combination for use according to claim 2 or 3, or the use according to any one of claims 4 to 6, wherein the PD(L)1 inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor.
8. The combination according to claim 1 or 7, the combination for use according to any one of claims 2, 3 or 7, or the use according to any one of claims 4 to 7, wherein the PD(L)1 inhibitor is selected from the group consisting of Pembrolizumab, Nivolumab, Cemiplimab, Camrelizumab, Tislelizumab, Sintilimab, Toripalimab, Spartalizumab, AGEN-2034, AK-103, AK-104, AK-105, AK-112, AK-123, AM-0001, AMP-224, AT16201, BCD-100, BH-2950, BH-2996h, BI-754091, BMS-1001, BMS-1166, CS-1003, CX-188, ENUM-244C8, GLS-010, hAb21, HLX-10, IKT-202, JNJ-63723283, JTX-4014, KN0-46, MEDI-0680, MGA-012, MGD-013, PF-06801591, PRS-332, RO7121661, STI-A1110, TSR-042, XmAb-20717, Atezolizumab, Avelumab, Durvalumab, AK-106, APL-502, AVA-004, BGB-A333, BH-2996h, BMS-936559, CA-170, CA-327, CBA-0710, CK-301, CS-1001, CX-072, FAZ-053, FS-118, GR1405, HLX-20, IKT-201, JS-003, KD033, KN-035, KY-1003, LY3300054, M-7824, MCLA-145, MSB-2311, and SHR-1316.
9. The combination according to any one of claims 1, 7 or 8, the combination for use according to any one of claims 2, 3, 7 or 8, or the use according to any of claims 4 to 8, wherein the PD(L)1 inhibitor is selected from the group consisting of Pembrolizumab, Nivolumab, Cemiplimab, Atezolizumab, Avelumab and Durvalumab.
10. The combination according to claim 1 or 7, the combination for use according to any one of claims 2, 3 or 7, or the use according to any one of claims 4 to 7, wherein the PD(L)1 inhibitor is a PD-1 inhibitor.
11. The combination according to claim 10, the combination for use according to claim 10, or the use according to claim 10, wherein the PD-1 inhibitor is selected from the group consisting of Pembrolizumab, Nivolumab, Cemiplimab, Camrelizumab, Tislelizumab, Sintilimab, Toripalimab,

Spartalizumab, AGEN-2034, AK-103, AK-104, AK-105, AK-112, AK-123, AM-0001, AMP-224, AT16201, BCD-100, BH-2950, BH-2996h, BI-754091, BMS-1001, BMS-1166, CS-1003, CX-188, ENUM-244C8, GLS-010, hAb21, HLX-10, IKT-202, JNJ-63723283, JTX-4014, KN0-46, MEDI-0680, MGA-012, MGD-013, PF-06801591, PRS-332, RO7121661, STI-A1110, TSR-042, and XmAb-20717.

12. The combination according to claim 10 or 11, the combination for use according to claim 10 or 11, or the use according to claim 10 or 11, wherein the PD-1 inhibitor is selected from the group consisting of Pembrolizumab, Nivolumab and Cemiplimab.
13. The combination according to claim 1 or 7, the combination for use according to any one of claims 2, 3 or 7, or the use according to any one of claims 4 to 7, wherein the PD(L)1 inhibitor is a PD-L1 inhibitor.
14. The combination according to claim 13, the combination for use according to claim 13, or the use according to claim 13, wherein the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, AK-106, APL-502, AVA-004, BGB-A333, BH-2996h, BMS-936559, CA-170, CA-327, CBA-0710, CK-301, CS-1001, CX-072, FAZ-053, FS-118, GR1405, HLX-20, IKT-201, JS-003, KD033, KN-035, KY-1003, LY3300054, M-7824, MCLA-145, MSB-2311, and SHR-1316.
15. The combination according to claim 13 or 14, the combination for use according to claim 13 or 14, or the use according to claim 13 or 14, wherein the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab and Durvalumab.
16. The combination according to claim 1, the combination for use according to claim 2 or 3, or the use according to any one of claims 4 to 6, wherein the PD(L)1 inhibitor is a PD-L2 inhibitor.
17. The use according to any one of claims 4 to 16, wherein the cancer is selected from the group consisting of melanoma, small cell lung cancer, non-small cell lung cancer (NSCLC), head and neck cancer, renal cell carcinoma, Hodgkin lymphoma, urothelial carcinoma, colorectal cancer, hepatocellular cancer, cutaneous squamous cell carcinoma, ovarian cancer, gastric cancer, gastroesophageal cancer, Merkel cell carcinoma, nasopharyngeal cancer, breast cancer, and esophageal squamous cell carcinoma.
18. The use according to claim 17, wherein the cancer is melanoma.
19. The use according to claim 17, wherein the cancer is small cell lung cancer.
20. The use according to any one of claims 4 to 19, wherein the cancer is a cancer that is refractory, non-responsive or relapsed to PD(L)1 inhibitor therapy.
21. The combination according to any one of claims 1 or 7 to 16, the combination for use according to any one of claims 2, 3 or 7 to 16, or the use according to any one of claims 4 to 20, wherein iadademstat or a pharmaceutically acceptable salt or solvate thereof is iadademstat di-hydrochloride.
22. The combination for use according to any one of claims 2, 3, 7 to 16 or 21, or the use according to any one of claims 4 to 21, wherein iadademstat or the pharmaceutically acceptable salt or solvate thereof is administered orally.

23. The combination for use according to any one of claims 2, 3, 7 to 16, 21 or 22, or the use according to any one of claims 4 to 22, wherein iadademstat or the pharmaceutically acceptable salt or solvate thereof and the PD(L)1 inhibitor are administered using separate formulations.
24. The combination for use according to any one of claims 2, 3, 7 to 16 or 21 to 23, or the use according to any one of claims 4 to 23, wherein iadademstat or the pharmaceutically acceptable salt or solvate thereof and the PD(L)1 inhibitor are administered as a simultaneous regimen.
25. The combination for use according to any one of claims 2, 3, 7 to 16 or 21 to 23, or the use according to any one of claims 4 to 23, wherein iadademstat or the pharmaceutically acceptable salt or solvate thereof and the PD(L)1 inhibitor are administered as a sequential regimen.