antibodies, it is thus clear that not all patients even within the subsets of immunotherapy-responsive cancers demonstrate tumour regression.

Therefore, there is still a need to identify additional pathways that provide either agonism or additional inhibition to existing immune checkpoint inhibitors pathways.

SUMMARY

In one aspect, the present disclosure provides use of a combination comprising an anti-progastrin (anti-hPG) monoclonal antibody and an immune checkpoint inhibitor, in the manufacture of a medicament for treating colorectal cancer, wherein said anti-hPG antibody comprises: a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively, and wherein said immune checkpoint inhibitor is an anti-PD1 antibody.

In yet another aspect, the present disclosure provides use of an anti-progastrin (anti-hPG) monoclonal antibody in the manufacture of a first medicament, and use of an immune checkpoint inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination with a pharmaceutical acceptable vehicle and/or an excipient for treating colorectal cancer.

DESCRIPTION

The present inventors have shown that the combination of a molecule binding to progastrin and an immune checkpoint inhibitor results in greater therapeutic efficacy against cancer. Notably, the inventors showed that administering an anti-progastrin monoclonal antibody in combination with an immune checkpoint inhibitor such as an anti-PD-1 antibody significantly increases the survival of colorectal cancer cell lines xenografted mice. This is illustrated by a median survival time which is significantly increased compared to each of the therapies alone. Moreover, the combination of said anti-progastrin monoclonal antibody and immune checkpoint inhibitor leads to a level of expression of interferon γ which is more than doubled.

In a first aspect, the present invention relates to a combination comprising a progastrin-binding molecule and an immune checkpoint inhibitor. Preferably, the invention relates to a combination of a progastrin-binding molecule and an immune checkpoint inhibitor.

Immune checkpoint inhibitors

As used herein, a “checkpoint inhibitor” refers to a molecule, such as e.g., a small molecule, a soluble receptor, or an antibody, which targets an immune checkpoint and blocks the function of said immune checkpoint. More specifically, a “checkpoint inhibitor” as used herein is a molecule, such as e.g., a small molecule, a soluble receptor, or an antibody, that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. Such proteins, the “immune checkpoints” or “immune checkpoint proteins” as used herein, regulate T cell function in the immune system. Notably, they help keep immune responses in check and can keep T cells from killing cancer cells. Said immune checkpoint proteins achieve this result by interacting with specific ligands which send a signal into the T cell and essentially switch off or inhibit T cell function. Inhibition of these proteins results in restoration of T cell function and an immune response to the cancer cells.

CLAIMS

1. Use of a combination comprising an anti-progastrin (anti-hPG) monoclonal antibody and an immune checkpoint inhibitor, in the manufacture of a medicament for treating colorectal cancer,

wherein said anti-hPG antibody comprises:

- a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and
- a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively, and

wherein said immune checkpoint inhibitor is an anti-PD1 antibody.

2. The use of claim 1, wherein said anti-hPG antibody is selected among single chain antibodies, camelised antibodies, chimeric antibodies, IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies.

3. The use of claim 1 or 2, wherein said anti-hPG antibody is a C-terminal anti-progastrin antibody.

4. The use of any one of claims 1 to 3, wherein said anti-hPG antibody is a neutralising antibody.

5. The use of any one of claims 1 to 4, wherein said anti-hPG antibody is a monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°49 and a light chain of amino acid sequence SEQ ID N°50.

6. The use of any one of claims 1 to 4, wherein said anti-hPG antibody is a humanised antibody.

7. The use of claim 6, wherein said anti-hPG antibody is a humanised antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°69 and 71, and a light chain variable region of amino acid sequence selected between SEQ ID N°70 and 72, wherein said antibody also comprises constant regions of the light-chain and the heavy-chain derived from a human antibody.

8. The use of claim 6 or 7, wherein said anti-hPG antibody comprises a heavy chain variable region of amino acid sequence SEQ ID N°71 and a light chain variable region of amino acid sequence SEQ ID N°72, said antibody also comprising constant regions of the light-chain and the heavy-chain derived from a human antibody.

9. The use of any one of claims 6 to 8, wherein said anti-hPG antibody comprises a heavy chain of amino acid sequence SEQ ID N°73 and a light chain of amino acid sequence SEQ ID N°74.

10. The use of any one of claims 1 to 9, wherein said anti-PD1 antibody is pembrolizumab, nivolumab, cemiplimab, or pidilizumab.

11. Use of an anti-progastrin (anti-hPG) monoclonal antibody in the manufacture of a first medicament, and use of an immune checkpoint inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination with a pharmaceutical acceptable vehicle and/or an excipient for treating colorectal cancer.

12. The use of claim 11, wherein the first medicament and the second medicament are for simultaneous, separate or sequential use.