THERAPY

Field of the Invention

The present invention is concerned with identifying cancer patients for which treatment with PD-1/PD-L1 antibodies will be particularly effective. The present invention is further concerned with ways to increase the effectiveness of PD-1/PD-L1 antibody treatment for a given group of cancer patients. The present invention is also concerned with compositions and methods for treating cancer.

Background of the Invention

The discovery of the immune check points, CTLA-4 and PD-1, and the subsequent introduction of immune checkpoint inhibitors (ICIs) have revolutionized the treatment and prognosis of several cancers (Robert, C., *Nat. Commun.* **11**, (2020)). However, not all cancers are sensitive to ICI, for example, pancreatic cancer (PC) remains highly refractory to ICI. Several trials that investigated the ICI in patients with advanced pancreatic cancer failed to demonstrate clinically relevant efficacy (Brahmer, J. R. *et al., N. Engl. J. Med.* **366**, 2455–2465 (2012); O'Reilly, E. M. *et al.*, *JAMA Oncol.* **5**, 1431–1438 (2019); and Royal, R. E. *et al., J. Immunother*. **33**, 828–833 (2010)).

Recently, a phase II trial in patients with refractory metastatic pancreatic cancer (CheckPAC) investigated a PD-1 antibody Nivolumab with, or without, Ipilimumab, combined with radiotherapy (Chen, I. M. *et al.,. J. Clin. Oncol.* **71**, (2022)). A clinical benefit rate of 37.2% was observed in the combination group, however only 14% of patients achieved a partial response. There is therefore an ongoing need for improved approaches for treating cancers that are refractory to PD-1/PD-L1 antibody treatment and particularly for pancreatic cancer.

Summary

Embodiments of the present disclosure provide a way to improve treatment with PD-1/PD-L1 antibodies, particularly for cancer types that are refractory to treatment with such antibodies. Embodiments of the present disclosure are based on the finding that the presence or absence of a TGF-beta specific T cell response is indicative of how effective treatment with PD-1/PD-L1 antibody will be and also, if such a response is present, the magnitude of the response is also indicative of how effective treatment will be. Embodiments of the present

disclosure therefore identify a patient group for which treatment with PD-1/PD-L1 antibody will be particularly effective. It also allows for the use of TGFbeta or immunogenic peptides from TGFbeta to stimulate, or boost, a TGF-beta T cell response and hence increase the likely efficacy of PD-1/PD-L1 antibody treatment for cancer.

Embodiments of the present disclosure are particularly effective for cancers that are refractory to treatment with PD-1/PD-L1 antibody such as pancreatic cancer. A PD-1/PD-L1 antibody which may be employed in embodiments of the present disclosure is Nivolumab. Hence, in an embodiment the antibody is Nivolumab and the cancer is pancreatic cancer. A particularly useful indicator is the presence, and size if present, of a T cell response against the TGFbeta-15 peptide sequence of SEQ ID NO: 28.

Accordingly, embodiments of the present disclosure provide a PD-1/PD-L1 antibody for use in a method of treating a cancer in a patient, wherein the method comprises administering the PD-1/PD-L1 antibody to said patient, wherein the patient has been previously identified as having a TGFbeta-specific T cell response.

Embodiments of the present disclosure further provide a method of treating cancer in a patient, the method comprising administering a PD-1/PD-L1 antibody to said patient, wherein the patient has been previously identified as having a TGFbeta-specific T cell response.

According to one aspect, there is provided a method of stratifying a patient with cancer into one of at least two treatment groups, the method comprising:

i. performing an assay on a sample previously obtained from the patient to detect the presence or absence of a TGFb-specific T cell response;

ii. allocating the patient to a first treatment group if a TGFb-specific response is present or stratifying the patient into a second treatment group if a TGFb-specific response is absent;

wherein if the patient is allocated to the first treatment group they are to be administered with a PD-1/PD-L1 antibody.

Embodiments of the present disclosure also provide a method of stratifying a patient with cancer into one of at least two treatment groups, the method comprising:

i. performing an assay on a sample previously obtained from the patient to detect the level of a TGFb-specific T cell response, if present;

ii. allocating the patient to a first treatment group if the TGFb-specific T cell response is at least a threshold value for a TGFb-specific T cell and stratifying the patient into a second treatment group if a TGFb-specific response is below the threshold value;

wherein if the patient is allocated to the first treatment group they are to be administered with a PD-1/PD-L1 antibody.

Embodiments of the present disclosure also provide a PD-1/PD-L1 antibody for use in a method of treating cancer, wherein the method comprises:

(i) administering to a patient an immunogenic fragment of human transforming growth factor (TGFb) which comprises or consists of a sequence of at least 9 consecutive amino acids of SEQ ID NO: 1; and

(ii) administering the PD-1/PD-L1 antibody.

Embodiments of the present disclosure further provide an immunogenic fragment of human transforming growth factor b (TGFb) for use in a method of treating a cancer in a patient, the method comprising

(i) administering to the patient the immunogenic fragment of human transforming growth factor b (TGFb), wherein the immunogenic fragment comprises or consists of a peptide sequence of at least 9 consecutive amino acids of SEQ ID NO: 1; and

(ii) administering to the patient a PD-1/PD-L1 antibody.

According to one aspect, there is provided a programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibody for use in the treatment of a cancer in a patient, wherein the PD-1/PD-L1 antibody is to be administered to said patient, wherein the patient has been previously identified as having a transforming growth factor beta (TGFb)-specific T cell response.

According to another aspect, there is provided a PD-1/PD-L1 antibody for the use as disclosed herein, wherein the patient is also being administered with radiotherapy.

According to another aspect, there is provided a method of stratifying a patient with cancer into one of at least two treatment groups, the method comprising:

i. performing an assay on a sample previously obtained from the patient to detect the level of a TGFb-specific T cell response, if present;

ii. allocating the patient to a first treatment group if the TGFb-specific T cell response is at least a threshold value for a TGFb-specific T cell and stratifying the patient into a second treatment group if a TGFb-specific response is below the threshold value;

wherein if the patient is allocated to the first treatment group they are to be administered with a PD-1/PD-L1 antibody, optionally wherein the threshold value is the median baseline TGFb-specific T cell response for cancer patients with the same type of

cancer and preferably wherein the threshold value is 75% of the baseline TGFb-specific T cell response in cancer patients with the same cancer type.

According to another aspect, there is provided a PD-1/PD-L1 antibody for use in the treatment of cancer, wherein:

(i) an immunogenic fragment of human TGFb which comprises or consists of a sequence of at least 9 consecutive amino acids of SEQ ID NO: 1 is to be administered to a patient; and

(ii) the PD-1/PD-L1 antibody is to be administered to the patient.

According to another aspect, there is provided an immunogenic fragment of human TGFb for use in the treatment of a cancer in a patient, wherein

(i) the immunogenic fragment of human TGFb, which comprises or consists of a peptide sequence of at least 9 consecutive amino acids of SEQ ID NO: 1 is to be administered to the patient; and

(ii) a PD-1/PD-L1 antibody is to be administered to the patient.

According to another aspect, there is provided a use of a PD-1/ PD-L1 antibody in the manufacture of a medicament for the treatment of a cancer in a patient, wherein the PD-1/PD-L1 antibody is to be administered to said patient, wherein the patient has been previously identified as having a transforming growth factor beta (TGFb)-specific T cell response.

Brief Description of the Figures

Figure 1: TGFb-15 specific responses in pancreatic cancer (PC) patients. A. Peripheral blood mononuclear cells (PBMCs) from pancreatic cancer patients were stimulated once *in vitro* with TGFb-15 peptide and IL-2, and incubated for 14 days before plating in interferon-gamma enzyme-linked immunosorbent spots (IFNγ ELISPOTs) at a concentration of 2 x10^5 cells/well with overnight incubation. The experiments were performed in triplicates with negative control wells left unstimulated. The responses were characterized in 32 samples isolated at baseline (left) and in 31 samples isolated after 4 series of treatment (right). **B.** Representative pictures of a response at baseline (top) and a response after 4 series of treatment. **C.** Normalized counts of the data from A comparing the amplitude of response in patients with clinical benefit and response in patients with progressive disease. Normalization was performed by subtracting the mean spot count of the control wells from the mean spot count of peptide stimulated wells. Error bars in A and C depict standard error of the mean and statistics were performed using a paired T-test. Statistics were made using Mann-Whitney test.

Figure 2. The amplitude of TGFb-15 specific immune responses fluctuates over time. A. Normalized counts at baseline were compared to counts after 4 series of treatment (i.e.