Similarly, PD-1 expression on tumor infiltrating lymphocytes was found to mark dysfunctional T cells in breast cancer and melanoma (Ghebeh *et al*, *BMC Cancer*. 2008 8:5714-15 (2008); Ahmadzadeh *et al*., *Blood* 114: 1537-1544 (2009)) and to correlate with poor prognosis in renal cancer (Thompson *et al*., *Clinical Cancer Research* 15: 1757-1761(2007)). Thus, it has been proposed that PD-L1 expressing tumor cells interact with PD-1 expressing T cells to attenuate T cell activation and evasion of immune surveillance, thereby contributing to an impaired immune response against the tumor.

Immune checkpoint therapies targeting the PD-1 axis have resulted in groundbreaking improvements in clinical response in multiple human cancers (Brahmer *et al*., *N Engl J Med* 2012, 366: 2455-65; Garon *et al*. *N Engl J Med* 2015, 372: 2018-28; Hamid *et al*., *N Engl J Med* 2013, 369: 134-44; Robert *et al*., *Lancet* 2014, 384: 1109-17; Robert *et al*., *N Engl J Med* 2015, 372: 2521-32; Robert *et al*., *N Engl J Med* 2015, 372: 320-30; Topalian *et al*., *N Engl J Med* 2012, 366: 2443-54; Topalian *et al*., *J Clin Oncol* 2014, 32: 1020-30; Wolchok *et al*., *N Engl J Med* 2013, 369: 122-33). Immune therapies targeting the PD-1 axis include monoclonal antibodies directed to the PD-1 receptor (KEYTRUDA™ (pembrolizumab), Merck and Co., Inc., Kenilworth, NJ, USA and OPDIVO™ (nivolumab), Bristol-Myers Squibb Company, Princeton, NJ, USA) and also those that bind to the PD-L1 ligand (MPDL3280A; TECENTRIQ™ (atezolizumab), Genentech, San Francisco, CA, USA; IMFINZI™ (durvalumab), AstraZeneca Pharmaceuticals LP, Wilmington, DE; BAVENCIO™ (avelumab), Merck KGaA, Darmstadt, Germany). Both therapeutic approaches have demonstrated anti-tumor effects in numerous cancer types.

It would be beneficial to develop additional dosing schedules that allow for the administration of a safe and effective dose of an anti-PD-1 antibody that is more convenient for patients.

SUMMARY

The present disclosure provides alternative, less frequent, dosing regimens for treating a cancer patient with an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the dosing schedule is expected to provide a safe and effective dose of the anti-PD-1 antibody, or antigen-binding fragment thereof. Specifically, the disclosure provides a method of treating cancer in a human patient comprising administering about 400 mg of an anti-PD-1 antibody or antigen binding fragment thereof to the patient every six weeks, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises (a) light chain complementarity determining regions (CDRs) comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3 and heavy chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8; or (b) light chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 11, 12 and 13 and heavy chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 14, 15 and 16. In preferred examples of the disclosure, the antibody or antigen-binding fragment is pembrolizumab.

In examples of the disclosure, the amount of anti-PD-1 antibody or antigen-binding fragment thereof administered to the patient is from about 350 mg to about 450 mg. In further examples, the amount of antibody or antigen-binding fragment is about 400 mg. In further examples, the amount of antibody or antigen-binding fragment is 400 mg.

In one aspect, there is provided use of an anti-PD-1 antibody, or antigen binding fragment thereof in the manufacture of a medicament for treating cancer in a human patient, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises:

(a) light chain complementarity determining regions (CDRs) comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3 and heavy chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8; or

(b) light chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 11, 12 and 13 and heavy chain CDRs comprising a sequence of amino acids as set forth in SEQ ID NOs: 14, 15 and 16, and

wherein about 400 mg of the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered to the patient every approximately six weeks.

In another aspect, there is provided a composition comprising about 400 mg of pembrolizumab and a pharmaceutically acceptable carrier.

In another aspect, there is provided a kit for treating a patient with cancer, the kit comprising:

(a) about 400 mg of an anti-PD-1 antibody or antigen binding fragment thereof, and

(b) instructions for using the anti-PD-1 antibody or antigen binding fragment thereof, in the use as defined herein.

In another aspect, there is provided use of the composition as defined herein in the manufacture of a medicament for treating an individual suffering from cancer.

In all of the above treatment methods, compositions and uses herein, the PD-1 antibody or antigen-binding fragment inhibits the binding of PD-L1 to PD-1, and preferably also inhibits the binding of PD-L2 to PD-1. In some preferred examples of the treatment methods, compositions and uses of the disclosure, the PD-1 antibody or antigen-binding fragment is a monoclonal antibody, which specifically binds to PD-1 and blocks the binding of PD-L1 to PD-1. In one particular example, the anti-PD-1 antibody comprises a heavy chain and a light chain, and wherein the heavy and light chains comprise the amino acid sequences shown in Figure 1 (SEQ ID NO:5 and SEQ ID NO:10).

In some examples of any of the above treatment methods, compositions and uses, the cancer expresses one or both of PD-L1 and PD-L2. In some examples, PD-L1 expression is elevated in the cancer.

In certain examples of any of the methods described herein, the anti-PD-1 antibody or antigen binding fragment is administered to a patient subcutaneously.

In alternative examples of any of the methods described herein, the anti-PD-1 antibody or antigen binding fragment is administered to a patient intravenously.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows amino acid sequences of the light chain and heavy chain for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:5 and 10, respectively). Light chain and heavy chain variable regions are underlined (SEQ ID NO's 4 and 9) and CDRs are bold and boxed.

FIGURE 2 shows that pembrolizumab Cmax at steady state for 400 mg Q6W lies within the range from 2 mg/kg Q3W and 200 mg Q3W to 10 mg/kg Q2W.

FIGURE 3 shows that pembrolizumab exposures (Cavg and Cmin) at steady state are similar for 400 mg Q6W relative to 2 mg/kg Q3W and 200 mg Q3W.

FIGURE 4A and 4B show the pembrolizumab pharmacokinetic profiles at steady state for the 400 mg Q6W dosing regimen compared to the 200 mg, Q3W, flat dosing regimen (top), the Q3W, 2 mg/kg weight-based dosing regimen (middle), and the Q2W, 10 mg/kg weight-based dosing regimen (bottom). Results are provided for log scale concentrations (FIG. 4A) and linear scale concentrations (FIG. 4B).

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

As used throughout the specification and appended claims, the following abbreviations apply: