

What is claimed is: Claims

1. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 706, 707 and 708, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 714, 715 and 716, respectively;

(ii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 728, 729 and 730, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 736, 737 and 738, respectively;

(iii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 750, 751 and 752, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 758, 759 and 760, respectively; and

(iv) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 772, 773 and 774, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 780, 781 and 782, respectively.

2. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

— (i) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 709, 710 and 711, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 717, 718 and 719, respectively;

(ii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 731, 732 and 733, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 739, 740 and 741, respectively;

(iii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 753, 754 and 755, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 761, 762 and 763, respectively; and

(iv) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 775, 776 and 777, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 783, 784 and 785, respectively.~~

31. An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 706, 707 and 708, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 714, 715 and 716, respectively.

4. ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 728, 729 and 730,, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 736, 737 and 738, respectively.~~

5. ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 750, 751 and 752,, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 758, 759 and 760, respectively.~~

6. ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 772, 773 and 774, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 780, 781 and 782, respectively.~~

7. ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting~~

of SEQ ID NOs: 712, 734, 756 and 778; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 720, 742, 764 and 786.

8. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences selected from the group consisting of:

- (i) — SEQ ID NO: 712 and 720, respectively;
- (ii) — SEQ ID NO: 734 and 742, respectively;
- (iii) — SEQ ID NO: 756 and 764, respectively; and
- (iv) — SEQ ID NO: 71775 and 786, respectively.

9. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 712, 734, 756 and 778; and wherein the light chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 720, 742, 764 and 786.

10. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

- (i) — SEQ ID NO: 712 and 720, respectively;
- (ii) — SEQ ID NO: 734 and 742, respectively;
- (iii) — SEQ ID NO: 756 and 764, respectively; and
- (iv) — SEQ ID NO: 778 and 786, respectively.

11. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 712 and 720, respectively.

~~123.~~ An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 712 and 720, respectively.

~~13. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 734 and 742, respectively.~~

~~14. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 734 and 742, respectively.~~

~~15. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 756 and 764, respectively.~~

~~16. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 756 and 764, respectively.~~

~~17. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 778 and 786, respectively.~~

~~18. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising~~

amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 778 and 786, respectively.

19. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 722, 744, 766 and 788; and wherein the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 724, 746, 768 and 790.~~

20. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 722, 744, 766 and 788; and wherein the light chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 724, 746, 768 and 790.~~

21. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 726, 748, 770 and 792; and wherein the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 724, 746, 768 and 790.~~

22. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 726, 748, 770 and 792; and wherein the light chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 724, 746, 768 and 790.~~

23. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 722 and 724, respectively;~~
- ~~(ii) — SEQ ID NO: 744 and 746, respectively;~~
- ~~(iii) — SEQ ID NO: 766 and 768, respectively; and~~
- ~~(iv) — SEQ ID NO: 788 and 790, respectively.~~

24. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 722 and 724, respectively;~~
- ~~(ii) — SEQ ID NO: 744 and 746, respectively;~~
- ~~(iii) — SEQ ID NO: 766 and 768, respectively; and~~
- ~~(iv) — SEQ ID NO: 788 and 790, respectively.~~

25. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 726 and 724, respectively;~~
- ~~(ii) — SEQ ID NO: 748 and 746, respectively;~~
- ~~(iii) — SEQ ID NO: 770 and 768, respectively; and~~
- ~~(iv) — SEQ ID NO: 792 and 790, respectively.~~

26. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 726 and 724, respectively;~~
- ~~(ii) — SEQ ID NO: 748 and 746, respectively;~~

(iii) — SEQ ID NO: 770 and 768, respectively; and

(iv) — SEQ ID NO: 792 and 790, respectively.

27. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences set forth in SEQ ID NO: 722 and 724, respectively.

28. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 722 and 724, respectively.

29. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences set forth in SEQ ID NO: 744 and 746, respectively.

30. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 744 and 746, respectively.

31. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences set forth in SEQ ID NO: 766 and 768, respectively.

32. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 766 and 768, respectively.

33. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences set forth in SEQ ID NO: 788 and 790, respectively.~~

34. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 788 and 790, respectively.~~

35. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences set forth in SEQ ID NO: 726 and 724, respectively.~~

36. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 726 and 724, respectively.~~

37. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences set forth in SEQ ID NO: 748 and 746, respectively.~~

38. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 748 and 746, respectively.~~

39. — ~~An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences set forth in SEQ ID NO: 770 and 768, respectively.~~

~~40. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 770 and 768, respectively.~~

~~41. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences set forth in SEQ ID NO: 792 and 790, respectively.~~

~~42. — An isolated monoclonal antibody, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 792 and 790, respectively.~~

43. A pharmaceutical composition comprising an isolated monoclonal antibody or antigen binding portion thereof, of any one of the preceding claims, and a pharmaceutically acceptable carrier.

~~44~~5. A nucleic acid comprising a nucleotide sequence encoding the light chain, heavy chain, or both light and heavy chains of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-~~42~~3.

~~45~~6. An expression vector comprising the nucleic acid of claim ~~44~~5.

~~46~~7. A cell transformed with an expression vector of claim ~~45~~6.

~~47. — A method for producing a monoclonal antibody that specifically binds human IL-27, or an antigen binding portion thereof, the method comprising maintaining a cell according to claim 46 under conditions permitting expression of the monoclonal antibody or antigen binding portion thereof.~~

48.— The method of claim 47, further comprising obtaining the monoclonal antibody or antigen binding portion thereof.

49.— A method to inhibit or reduce STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.

50.— A method to inhibit or reduce inhibition of CD161 expression in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell.

51.— A method to inhibit or reduce PD-L1 and/or TIM-3 expression in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42, wherein the antibody, or antigen binding portion thereof, inhibits or PD-L1 and/or TIM-3 expression in a cell.

52.— A method to induce or enhance secretion of one or more cytokines from a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.

53.— A method of stimulating an immune response in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43.

54.— A method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43.

55. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell, thereby stimulating the immune response, or treating the cancer.~~

56. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces inhibition of CD161 expression in a cell, thereby stimulating the immune response, or treating the cancer.~~

57. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces PD-L1 and/or TIM-3 expression on a cell, thereby stimulating the immune response, or treating the cancer.~~

58. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one of claims 1-42 or the pharmaceutical composition of claim 43, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition induces or enhances PD-1-mediated secretion of one or more cytokines from a cell, thereby stimulating the immune response, or treating the cancer.~~

59. — ~~The method of any one of claims 54-58, wherein the cancer is chosen from lung cancer (e.g., non-small cell lung cancer), sarcoma, testicular cancer, ovarian cancer, pancreas cancer, breast cancer (e.g., triple-negative breast cancer), melanoma, head and neck cancer (e.g., squamous~~

~~head and neck cancer), colorectal cancer, bladder cancer, endometrial cancer, prostate cancer, thyroid cancer, hepatocellular carcinoma, gastric cancer, brain cancer, lymphoma (e.g., DL-BCL), leukemia (e.g., AML) or renal cancer (e.g., renal cell carcinoma, e.g., renal clear cell carcinoma).~~

~~60. — A method of enhancing one or more activities of an anti PD-1 antibody (e.g., enhances PD-1 mediated cytokine secretion; enhances anti PD-1 mediated TNF α secretion; enhances anti PD-1 mediated IL-6 secretion from a cell exposed to anti PD-1 antibodies), the method comprising exposing a cell to an antibody, or antigen binding portion thereof, of any one of claims 1-42, concurrently with or sequentially to an anti PD-1 antibody, thereby to enhance one or more activities of anti PD1 antibodies.~~

~~618. A pharmaceutical composition comprising an anti-PD-1 antibody and an antibody, or antigen binding portion thereof, of any one of claims 1-423, and a pharmaceutically acceptable carrier.~~

~~629. A kit comprising an anti-PD-1 antibody and an antibody, or antigen binding portion thereof, of any one of claims 1-423, for concurrent or sequential administration, and instructions for its use.~~

~~63. — The method of any one of claims 53-59, wherein the isolated monoclonal antibody, or antigen binding portion thereof, is administered in combination with one or more additional therapeutic agents or procedure, wherein the second therapeutic agent or procedure is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.~~

~~64. — The method of claim 63, wherein the one or more additional therapeutic agents is a PD-1 antagonist, a PD-L1 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, a CTLA-4 inhibitor, a CD73~~

inhibitor, a CD39 inhibitor, an A2AR inhibitor, an IDO inhibitor, peg IL-2, peg IL-10, a CD40 agonist, or a combination thereof.

65. — The method of claim 64, wherein the one or more additional therapeutic agents is a PD-1 antagonist.

66. — The method of claim 65, wherein the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, AMP-224, AB122, and JTX-4014.

67. — The method of claim 64, wherein the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.

68. — The method of claim 64, wherein the one or more additional therapeutic agents is selected from the group consisting of sunitinib (Sutent[®]), Cabozantinib (Cabometyx[®]), Axitinib (Inlyta[®]), Lenvatinib (Lenvima[®]), Everolimus (Afinitor[®]), Bevacizumab (Avastin[®]), epacadostat, NKTR-214 (CD-122 biased agonist), tivozanib (Fotivda[®]), abexinostat, Ipilimumab (Yervoy[®]), tremelimumab, Pazopanib (Votrient[®]), Sorafenib (Nexavar[®]), Temsirolimus (Torisel[®]), Ramucirumab (Cyramza[®]), niraparib, savolitinib, vorolanib (X-82), Regorafenib (Stivargo[®]), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab (Cyramza[®]), apatinib (YN968D1), encapsulated doxorubicin (Thermodox[®]), Tivantinib (ARQ197), ADI-PEG-20, binimetinib, apatinib mesylate, nintedanib, lirilumab, Nivolumab (Opdivo[®]), Pembrolizumab (Keytruda[®]), Atezolizumab (Tecentriq[®]), Avelumab (Bavencio[®]), Durvalumab (Imfinzi[®]), cemiplimab-rwlc (Libtayo[®]), tislelizumab, and spartalizumab.

69. — The method of claim 64, wherein the one or more additional therapeutic agents is a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is MGB453 or TSR-022.

70. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033.~~

71. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a TIGIT inhibitor.~~

72. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a CD112R inhibitor.~~

73. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a TAM (Axl, Mer, Tyro) inhibitor.~~

74. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a 4-1BB agonist.~~

75. — ~~The method of claim 64, wherein the one or more additional therapeutic agents is a Tyrosine Kinase Inhibitor (TKI).~~

76. — ~~A method of treating a cancer in a subject, the method comprising administering to the patient a therapeutically effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, comprising heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 161, 162 and 163, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 169, 170 and 171, respectively, wherein the isolated monoclonal antibody, or antigen binding portion thereof, is administered in combination with one or more additional therapeutic agents or procedures, selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, a cellular immunotherapy, and a combination thereof.~~

77. — A method of detecting IL-27 or EBI3 or p28 in a sample from a subject, the method comprising the steps of (a) contacting a sample from the subject with a detection antibody under conditions to permit the detection antibody to form a detection antibody-EBI3 complex or a detection antibody-p28 complex, if IL-27 or EBI3 or p28 is present in the sample, wherein the detection antibody is an antibody, or antigen binding fragment thereof, according to any one of claims 1-42 or Table 12; and (b) detecting the presence of the complex, if any, produced in step (a).

78. — A method of detecting an IL-27 associated cancer in a subject, the method comprising the steps of: (a) contacting a sample from a subject suspected of having an IL-27 associated cancer with a detection antibody under conditions to permit the detection antibody to form a detection antibody-EBI3 complex or a detection antibody-p28 complex, if IL-27 or EBI3 or p28 is present in the sample, wherein the detection antibody is an antibody, or antigen binding portion thereof, according to any one of claims 1-42 or Table 12; and (b) detecting the presence of the complex, if any, produced in step (a).

79. — The method of claims 77 or 78, wherein the detection antibody is coupled to a detectable label.

80. — The method of any one of claims 77-79, wherein the method further comprises contacting the sample with a capture antibody to produce a complex comprising IL-27 or EBI3 and the capture antibody, if IL-27 or EBI3 is present in the sample, wherein the capture antibody is an antibody, or antigen binding portion thereof, according to any one of claims 1-42.

81. The method of claim 80, wherein the capture antibody has one or more CDRs of Ab7, optionally is Ab7.

82. — The method of claim 80, wherein the capture antibody is immobilized on a solid support.

83. — The method of any one of claims 77-82, wherein the sample is contacted with the capture antibody before the detection antibody.

~~84. The method of any one of claims 77-82, wherein the sample is a body fluid sample.~~

~~85. The method of claim 84, wherein the fluid sample is blood, serum, plasma, cell lysates or tissue lysates.~~

~~86. The method of any one of claims 76-85, wherein the cancer is selected from renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), lung cancer, gastroesophageal cancer, ovarian cancer, endometrial cancer, melanoma, leukemia and lymphoma.~~

~~87. The method of claim 86, wherein the cancer is renal cell carcinoma (RCC).~~

~~88. The method of claim 86, wherein the cancer is hepatocellular carcinoma (HCC).~~

~~89. The method of claim 86, wherein the cancer is selected from leukemia and lymphoma.~~

~~90. The method of claim 86, wherein the cancer is ovarian cancer.~~

~~91. Use of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-42 or the pharmaceutical composition of claim 43 for stimulating an immune response in a subject, or for treating cancer in a subject, optionally for use in combination with one or more additional therapeutic agents or procedure.~~

~~92. A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-42 or the pharmaceutical composition of claim 43 and instructions for use in stimulating an immune response in a subject, or treating cancer in a subject, optionally with instructions for use in combination with one or more additional therapeutic agents or procedure.~~

~~93~~10. A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-~~42~~3 and instructions for use in detecting IL-27 in a sample from a subject, optionally with instructions for use to detect an IL-27-associated cancer in a subject.

~~94~~11. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims ~~1-42~~3, wherein the antibody or antigen binding portion thereof antagonizes IL-27.

~~95~~12. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims ~~1-42~~3, wherein the antibody or antigen binding portion thereof inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.

~~96~~13. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~95~~12, wherein the cell is an immune cell.

~~97~~14. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~95~~12, wherein the cell is a cancer cell.

~~98~~15. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims ~~1-42~~3, wherein the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell.

~~99~~16. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~98~~15, wherein the cell is an immune cell.

~~100~~17. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims ~~1-42~~3, wherein the antibody or antigen binding portion thereof inhibits or reduces PD-L1 and/or TIM-3 expression in a cell.

~~101~~18. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~100~~17, wherein the cell is an immune cell.

~~102~~19. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~101~~18, wherein the cell is a cancer cell.

~~103~~20. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~101~~18, wherein the cell is a cancer cell, wherein the antibody or antigen binding portion thereof inhibits or reduces PD-L1 expression in a cancer cell.

~~104~~21. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-~~42~~3, wherein the antibody or antigen binding portion thereof induces or enhances the PD-1-mediated secretion of one or more cytokines from a cell.

~~105~~22. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~104~~21, wherein the one or more cytokines is IFN γ , TNF α or IL-6.

~~106~~23. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~105~~22, wherein the one or more cytokines is IFN γ , IL-17, TNF α or IL-6.

~~107~~24. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~105~~22, wherein the one or more cytokines is TNF α .

~~108~~. — ~~The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 104-107, wherein the cell is an immune cell.~~

~~109~~25. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-~~42~~3, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1 an IgA2, an IgD, and an IgE antibody.

~~110~~26. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim ~~109~~25, wherein the antibody is an IgG1 antibody or an IgG4 antibody.

~~111~~27. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim ~~110~~26, wherein the antibody comprises a wild type IgG1 heavy chain constant region.

~~112~~28. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim ~~110~~26, wherein the antibody comprises a wild type IgG4 heavy chain constant region.

~~113~~29. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-~~42~~3, wherein the antibody comprises an Fc domain comprising at least one mutation.

~~114~~30. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~113~~29, wherein the antibody comprises a mutant IgG1 heavy chain constant region.

~~115~~31. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~113~~29, wherein the antibody comprises a mutant IgG4 heavy chain constant region.

~~116~~32. The isolated monoclonal antibody, or antigen binding portion thereof, of claim ~~115~~31, wherein the mutant IgG4 heavy chain constant region comprises any one of the substitutions S228P, L235E, L235A, or a combination thereof, according to EU numbering.

~~117~~33. An isolated monoclonal antibody, or antigen binding portion thereof, that binds to substantially the same epitope as the antibody, or antigen binding portion thereof, according to any one of claims 1-~~42~~3.

~~118~~34. An isolated monoclonal antibody, or antigen binding portion thereof, that binds to at least one of the amino acid residues bound by the antibody, or antigen binding portion thereof, according to any one of claims 1-~~42~~3.

~~119~~35. An isolated monoclonal antibody, or antigen binding portion thereof, wherein a mutation of the epitope bound by the antibody or antigen binding portion thereof inhibits, reduces, or blocks binding to both the antibody or antigen binding portion thereof and to the antibody or antigen binding portion thereof according to any one of claims 1-~~42~~3.

120. — An isolated monoclonal antibody, or antigen binding portion thereof, that binds to an epitope on IL-27, wherein the epitope is the same or is similar to the epitope bound by an antibody molecule described in Table 12.

121. — An isolated monoclonal antibody that specifically binds to and antagonizes human WSX-1, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 802, 803 and 804, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 805, 806 and 807, respectively.

122. — An isolated monoclonal antibody that specifically binds human WSX-1, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences selected from the group consisting of SEQ ID NO: 794 and 796, respectively.

123. — An isolated monoclonal antibody that specifically binds human WSX-1, or antigen binding portion thereof, comprises a light chain constant region, wherein the light chain constant region comprises the amino acid sequence set forth in SEQ ID NO: 798.

124. — An isolated monoclonal antibody that specifically binds human WSX-1, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs at least 90% identical to the group consisting of heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 802, 803 and 804, respectively, and at least 90% identical to the group consisting of light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 805, 806 and 807, respectively.

125. — An isolated monoclonal antibody that specifically binds human WSX-1, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions at least 90% identical to the group consisting of SEQ ID NO: 794 and 796, respectively.

126. — ~~An isolated monoclonal antibody that specifically binds human WSX-1, or antigen binding portion thereof, comprises a light chain constant region, wherein the light chain constant region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 798.~~

127. — ~~A pharmaceutical composition comprising an isolated monoclonal antibody or antigen binding portion thereof, of any one of claims 121-126, and a pharmaceutically acceptable carrier.~~

128. — ~~A nucleic acid comprising a nucleotide sequence encoding the light chain, heavy chain, or both light and heavy chains of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 121-126.~~

129. — ~~An expression vector comprising the nucleic acid of claim 128.~~

130. — ~~A cell transformed with an expression vector of claim 129.~~

131. — ~~A method for producing a monoclonal antibody that specifically binds human WSX-1, or an antigen binding portion thereof, the method comprising maintaining a cell according to claim 130 under conditions permitting expression of the monoclonal antibody or antigen binding portion thereof.~~

132. — ~~A method of detecting WSX-1 in a sample from a subject, the method comprising the steps of (a) contacting a sample from the subject with a detection antibody under conditions to permit the detection antibody to form a detection antibody-WSX-1 complex, if WSX-1 is present in the sample, wherein the detection antibody is an antibody, or antigen binding fragment thereof, according to any one of claims 121-126; and (b) detecting the presence of the complex, if any, produced in step (a).~~

133. — ~~A method of detecting a WSX-1 associated cancer in a subject, the method comprising the steps of: (a) contacting a sample from a subject suspected of having a WSX-1 associated cancer with a detection antibody under conditions to permit the detection antibody to form a detection antibody-WSX-1 complex, if WSX-1 is present in the sample, wherein the detection antibody is~~

an antibody, or antigen binding portion thereof, according to any one of claims 121-126; and (b) detecting the presence of the complex, if any, produced in step (a).

~~134. — Use of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 121-126 or the pharmaceutical composition of claim 127 for stimulating an immune response in a subject, or for treating cancer in a subject, optionally for use in combination with one or more additional therapeutic agents or procedure.~~

~~135. — A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 121-126 or the pharmaceutical composition of claim 127 and instructions for use in stimulating an immune response in a subject, or treating cancer in a subject, optionally with instructions for use in combination with one or more additional therapeutic agents or procedure.~~

~~136. The isolated monoclonal antibody of claims 1-423, wherein the isolated monoclonal antibody specifically binds to human IL-27.~~

~~137. The isolated monoclonal antibody of claims 1, 2, 4, 6-10, 13, 14, 17, 18-26, 29, 30, 33, 34, 37, 38, 41, and 42, wherein the isolated monoclonal antibody specifically antagonizes human IL-27.~~

~~138. — The method of claim 76, wherein the one or more additional therapeutic agents is a PD-1 antagonist, a PD-L1 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, a CTLA-4 inhibitor, a CD73 inhibitor, a CD39 inhibitor, an A2AR inhibitor, an IDO inhibitor, peg IL-2, peg IL-10, a CD40 agonist, or a combination thereof.~~

~~139. — The method of claim 138, wherein the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, AMP-224, AB122, and JTX-4014.~~