

CLAIMS

1. Use of an anti-PD-1 or anti-PD-L1 antibody in the manufacture of a medicament for treating a bladder cancer or a squamous cell carcinoma of the head and neck (SCCHN) in a human subject in need thereof, wherein the medicament is to be administered to the subject in combination with an indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor,

wherein the subject is identified as exhibiting prior to the administering of the medicament a combined biomarker comprising (a) a high *IFN* γ inflammatory signature score, which is characterized by an *IFN* γ inflammatory signature score that is greater than an average *IFN* γ inflammatory signature score, and (b) a low tryptophan 2,3-dioxygenase 2 (*TDO2*) gene expression score, which is characterized by a *TDO2* gene expression that is smaller than an average *TDO2* gene expression score;

wherein the *IFN* γ inflammatory signature score is determined by measuring the expression of a panel of inflammatory genes comprising interferon gamma (*IFN* γ) related genes ("*IFN* γ inflammatory gene panel") in a tumor tissue biopsy sample obtained from the subject;

wherein the inflammatory genes comprise *IFN* γ , *CXCL10*, *CXCL9*, *HLA-DRA*, *IDO1*, *STAT1*, *CCR5*, *CXCL11*, *GZMA*, and *PRF1*; and

wherein the IDO1 inhibitor comprises linrodostat mesylate ((2R)-N-(4-chlorophenyl)-2-(cis-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanamide), linrodostat, indoximod, p-(3-benzofuranyl)-DL-alanine, p-[3-benzo(b)thienyl]-DL-alanine, 6-nitro-L-tryptophan, or any combination thereof.

2. The use of claim 1, wherein the average *IFN* γ inflammatory signature score is determined by averaging the expression of the genes of the *IFN* γ inflammatory gene panel in cancer samples obtained from a population of subjects afflicted with the cancer.

3. The use of claim 2, wherein the average *IFN* γ inflammatory signature score is of a reference sample, which comprises a non-tumor tissue of the subject, a corresponding non-tumor tissue of the subject, or the corresponding tissue of subjects without a tumor.

4. The use of any one of claims 1 to 3, wherein the high *IFN* γ inflammatory signature score is characterized by an *IFN* γ inflammatory signature score that is at least 25% higher than an average *IFN* γ inflammatory signature score.

5. The use of claim 4, wherein the *IFN* γ high inflammatory signature score is characterized by an *IFN* γ inflammatory signature score that is at least 50% higher than the average *IFN* γ inflammatory signature score.

6. The use of claim 4, wherein the high *IFN* γ inflammatory signature score is characterized by an *IFN* γ inflammatory signature score that is at least 75% higher than the average *IFN* γ inflammatory signature score.

7. The use of any one of claims 1 to 6, wherein the average *TDO2* gene expression score is determined by averaging the expression of the *TDO2* gene in cancer samples obtained from a population of subjects afflicted with the cancer.

8. The use of any one of claims 1 to 7, wherein the average *TDO2* gene expression score is of a reference sample, which comprises a non-tumor tissue of the subject, a corresponding non-tumor tissue of the subject, or the corresponding tissue of subjects without a tumor.

9. The use of claim 8, wherein the low *TDO2* gene expression score is characterized by a *TDO2* gene expression score that is at least 25% lower than the average *TDO2* gene expression score.

10. The use of claim 9, wherein the low *TDO2* gene expression score is characterized by a *TDO2* gene expression score that is at least 50% lower than the average *TDO2* gene expression score.

11. The use of claim 9, wherein the low *TDO2* gene expression score is characterized by a *TDO2* gene expression score that is at least 75% lower than the average *TDO2* gene expression score.

12. The use of any one of claims 1 to 11, wherein the cancer comprises a bladder cancer.

13. The use of any one of claims 1 to 11, wherein the cancer comprises a squamous cell carcinoma of the head and neck (SCCHN).

14. The use of any one of claims 1 to 13, wherein the tumor tissue biopsy sample is obtained from the stroma of a tumor.

15. The use of any one of claims 1 to 14, wherein the tumor tissue biopsy sample is a formalin-fixed paraffin-embedded tissue or a fresh-frozen tissue.

16. The use of any one of claims 1 to 15, wherein the expression of the genes in the IFN γ inflammatory gene panel and/or *TDO2* gene expression is determined by detecting the presence of mRNA encoded by the gene, the presence of a protein encoded by the gene, or both.

17. The use of claim 16, wherein the presence of mRNA encoded by the genes in the IFN γ inflammatory gene panel and/or the *TDO2* gene is determined using reverse transcriptase PCR.

18. The use of claim 17, wherein the presence of the protein encoded by the genes in the IFN γ inflammatory gene panel and/or the *TDO2* gene is determined using an immunohistochemical (IHC) assay.

19. The use of claim 18, wherein the IHC assay is an automated IHC assay.

20. The use of any one of claims 1 to 19, wherein the medicament comprises an anti-PD-1 antibody.

21. The use of claim 20, wherein the anti-PD-1 antibody is a chimeric, humanized or human monoclonal antibody or a portion thereof.

22. The use of claim 20 or 21, wherein the anti-PD-1 antibody comprises a heavy chain constant region which is of a human IgG1 or IgG4 isotype.

23. The use of any one of claims 20 to 22, wherein the anti-PD-1 antibody comprises nivolumab, pembrolizumab, cemiplimab, or an antigen-binding portion thereof.

24. The use of any one of claims 20 to 22, wherein the anti-PD-1 antibody is nivolumab or an antigen-binding portion thereof.

25. The use of any one of claims 1 to 24, wherein the medicament comprises an anti-PD-L1 antibody.

26. The use of claim 25, wherein the anti-PD-L1 antibody comprises avelumab, atezolizumab, durvalumab, or an antigen-binding portion thereof.

27. The use of claim 25, wherein the anti-PD-L1 antibody is avelumab, atezolizumab, or durvalumab.

28. The use of any one of claims 20 to 24, wherein the anti-PD-1 antibody is to be administered at a dose from 0.1 mg/kg to 10.0 mg/kg body weight once every 1, 2 or 3 weeks.

29. The use of claim 28, wherein the anti-PD-1 antibody is to be administered at a dose of 3 mg/kg body weight once every 2 weeks.

30. The use of any one of claims 20 to 24, wherein the anti-PD-1 antibody is to be administered at a flat dose.

31. The use of claim 30, wherein the anti-PD-1 antibody is to be administered at a flat dose of 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500 or 550 mg.

32. The use of claim 31, wherein the anti-PD-1 antibody is to be administered at a flat dose of 240 mg.

33. The use of claim 31, wherein the anti-PD-1 antibody is to be administered at a flat dose of 480 mg.

34. The use of any one of claims 30 to 33, wherein the anti-PD-1 antibody is to be administered at a flat dose once every 1, 2, 3 or 4 weeks.

35. The use of claim 32, wherein the anti-PD-1 antibody is to be administered at a flat dose of 240 mg once every two weeks.

36. The use of claim 33, wherein the anti-PD-1 antibody is to be administered at a flat dose of 480 mg once every four weeks.

37. The use of any one of claims 25 to 27, wherein the anti-PD-L1 antibody is to be administered at a dose from 0.1 mg/kg to 10.0 mg/kg body weight once every 1, 2 or 3 weeks.

38. The use of any of any one of claims 1 to 37, wherein the anti-PD-1 or anti-PD-L1 antibody is to be administered for as long as clinical benefit is observed or until unmanageable toxicity or disease progression occurs.

39. The use of any one of claims 1 to 38, wherein the anti-PD-1 or anti-PD-L1 antibody is formulated to be administered intravenously.

40. The use of any one of claims 1 to 38, wherein the IDO1 inhibitor is formulated to be administered orally.

41. The use of any one of claims 1 to 40, wherein the IDO1 inhibitor is to be administered at a flat dose of 100 mg.

42. The use of any one of claims 1 to 40, wherein the IDO1 inhibitor is to be administered at a flat dose of 200 mg.

43. The use of any one of claims 1 to 40, wherein the IDO1 inhibitor is to be administered at a flat dose of 100 mg every day.

44. The use of any one of claims 1 to 40, wherein the IDO1 inhibitor is to be administered at a flat dose of 200 mg every day.

45. The use of any one of claims 1 to 19, wherein the anti-PD-1 antibody comprises nivolumab or an antigen-binding portion thereof to be administered intravenously at a 240 mg every two weeks or 480 mg dose every four weeks, and the IDO1 inhibitor is to be administered orally at a 100 mg or 200 mg dose every day.

46. The use of claim 45, wherein the IDO1 inhibitor comprises linrodostat mesylate.

47. The use of any one of claims 1 to 46, wherein the cancer is relapsed.

48. The use of any one of claims 1 to 47, wherein the cancer is refractory.

49. The use of any one of claims 1 to 48, wherein the PD-1 or anti-PD-L1 antibody is to be administered before the IDO1 inhibitor.

50. The use of any one of claims 1 to 48, wherein the PD-1 or anti-PD-L1 antibody is to be administered after the IDO1 inhibitor.

51. The use of any one of claims 1 to 48, wherein the PD-1 or anti-PD-L1 antibody is to be administered concurrently with the IDO1 inhibitor.

52. The use of any one of claims 1 to 51, wherein the cancer is refractory following at least one prior therapy comprising of at least one anticancer agent.

53. The use of claim 52, wherein the at least one anticancer agent comprises a standard of care therapy.

54. The use of claim 52 or 53, wherein the at least one anticancer agent comprises an immunotherapy.

55. The use of any one of claims 1 to 54, wherein the cancer is locally advanced.

56. The use of any one of claims 1 to 55, wherein the cancer is metastatic.