

We claim:

1. Use of an antibody or antigen-binding fragment thereof that specifically binds programmed death 1 (PD-1) a programmed death 1 (PD-1) inhibitor in the manufacture of a medicament for treating or inhibiting the growth of a tumor in a patient with cutaneous squamous cell carcinoma (CSCC)-a skin cancer, wherein the patient has completed surgery and/or radiation therapy to treat the CSCC-skin cancer; and a therapeutically effective amount of the antibody or antigen-binding fragment thereof PD-1 inhibitor is to be subsequently administered to the patient as an adjuvant treatment;

wherein the antibody or antigen-binding fragment thereof comprises three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) of a heavy chain variable region (HCVR) and three CDRs (LCDR1, LCDR2, and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8; and

wherein the patient has at least one of the following high risk features:

- (i) nodal disease with extracapsular extension and at least 1 node >20 mm;
- (ii) in-transit metastases (ITM);
- (iii) T4 lesion;
- (iv) perineural invasion (PNI); and
- (v) recurrent CSCC plus at least one of the following additional features: ≥N2b disease associated with a recurrent lesion; nominal ≥T3; and ≥20 mm diameter of recurrent lesion.

2. The use ~~of~~ according to claim 1, wherein the patient has completed surgery and optionally, post-surgery radiation therapy.

3. ~~The use according to claim 1 or 2, wherein the skin cancer is cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC), Merkel cell carcinoma, or melanoma.~~

4. ~~The use according to any one of claims 1-3, wherein the skin cancer is CSCC.~~

5. ~~The use according to any one of claims 1-4, wherein the patient is at high risk of CSCC recurrence or has suffered at least one incident of recurrence.~~

~~6. The use according to claim 5, wherein the patient has at least one of the following high-risk features:~~

- ~~(a) nodal disease with extracapsular extension and at least 1 node >20 mm;~~
- ~~(b) in-transit metastases (ITM);~~
- ~~(c) T4 lesion;~~
- ~~(d) perineural invasion (PNI); and~~
- ~~(e) recurrent CSCC plus at least one of the following additional features:~~
 - ~~(i) $\geq$ N2b disease associated with a recurrent lesion;~~
 - ~~(ii) nominal $\geq$ T3; and~~
 - ~~(iii) $\geq$ 20 mm diameter of recurrent lesion.~~

~~7.3. The use according to claim 1 or 2 any one of claims 1-6, wherein the therapeutically effective amount comprises 5 mg to 500 mg of the antibody or antigen-binding fragment thereof PD-1 inhibitor.~~

~~8.4. The use according to claim 3 any one of claims 1-6, wherein the therapeutically effective amount comprises 350 mg of the antibody or antigen-binding fragment thereof PD-1 inhibitor.~~

~~9.5. The use according to any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof PD-1 inhibitor is to be administered as one or more doses, wherein each dose is to be administered 2 to 12 weeks, preferably 3 weeks after the immediately preceding dose.~~

~~10.6. The use of claim 59, wherein each dose comprises 5 mg to 500mg, preferably 350 mg of the antibody or antigen-binding fragment thereof PD-1 inhibitor.~~

~~11.7. The use according to any one of claims 1-610, wherein the antibody or antigen-binding fragment thereof PD-1 inhibitor is to be administered intravenously.~~

~~12.8. The use according to any one of claims 1-711, wherein the antibody or antigen-binding fragment thereof ~~step (b) occurs~~ is to be administered to the patient 2 to 6 weeks after completion of ~~the~~ radiation therapy.~~

~~13.9. The use according to any one of claims 1-812, wherein ~~administration of the~~ antibody or antigen-binding fragment thereof to be administered PD-1 inhibitor leads to reduced risk of subsequent skin cancer recurrence or zero incidence of subsequent skin cancer recurrence.~~

~~14.10.~~ The use according to any one of claims ~~1-812~~, wherein ~~administration of the~~ antibody or antigen-binding fragment thereof to be administered ~~PD-1 inhibitor~~ leads to at least ~~about~~ 10% lower incidence of subsequent skin cancer recurrence as compared to a patient after completion of surgery and radiation therapy without adjuvant ~~skin cancer~~ treatment.

~~15.11.~~ The use according to any one of claims ~~1-1014~~, further comprising wherein the administration of an additional therapeutic agent is to be administered to the patient, wherein the additional therapeutic is selected from a chemotherapeutic, a corticosteroid, an anti-inflammatory drug, and ~~or~~ combinations thereof.

~~16.~~ The use according to any one of claims ~~1-15~~, wherein the PD-1 inhibitor is selected from the group consisting of an anti-PD-1 antibody or antigen-binding fragment thereof, an anti-PD-L1 antibody or antigen-binding fragment thereof, and an anti-PD-L2 antibody or antigen-binding fragment thereof.

~~17.~~ The use according to any one of claims ~~1-16~~, wherein the PD-1 inhibitor is an anti-PD-1 antibody or antigen-binding fragment thereof that comprises three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three CDRs (LCDR1, LCDR2, and LCDR3) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.

~~18.~~ The use according to claim ~~17~~, wherein: HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8.

~~19.12.~~ The use according to any one of claims 1-11 ~~claim 17 or 18~~, wherein the ~~anti-PD-1~~ antibody or antigen-binding fragment thereof comprises a HCVR having an amino acid sequence of SEQ ID NO: 1 and a LCVR having an amino acid sequence of SEQ ID NO: 2 ~~a HCVR/LCVR sequence pair of SEQ ID NOs: 1/2~~.

~~20.13.~~ The use according to any one of claims ~~1-12-17-19~~, wherein the ~~anti-PD-1~~ antibody comprises a heavy chain and a light chain, wherein the heavy chain has an amino acid sequence of SEQ ID NO: 9.

~~21.14.~~ The use according to any one of claims ~~1-12-17-19~~, wherein the ~~anti-PD-1~~ antibody comprises a heavy chain and a light chain, wherein the light chain has an amino acid sequence of SEQ ID NO: 10.

~~22.15.~~ The use according to any one of claims ~~1-12-17-19~~, wherein the ~~anti-PD-1~~ antibody comprises a heavy chain and a light chain, wherein the heavy chain has an amino acid sequence of SEQ ID NO: 9 and ~~for~~ the light chain has an amino acid sequence of SEQ ID NO: 10.

~~23.16.~~ The use according to any one of claims 1-~~15~~16, wherein the antibody ~~PD-1 inhibitor~~ is cemiplimab or a bioequivalent thereof.

~~24.~~—The use according to any one of claims 1-16, wherein the PD-1 inhibitor is an anti-PD-1 antibody selected from the group consisting of cemiplimab, nivolumab, pembrolizumab, pidilizumab, MEDI0608, BI 754091, PF-06801591, spartalizumab, camrelizumab, JNJ-63723283, and MCLA-134.

~~25.~~—The use according to any one of claims 1-16, wherein the PD-1 inhibitor is an anti-PD-L1 antibody selected from the group consisting of H1H8314N, avelumab, atezolizumab, durvalumab, MDX-1105, LY3300054, FAZ053, STI-1014, CX-072, KN035, and CK-301.

~~26.17.~~ AUse of a pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof that specifically binds a programmed death 1 (PD-1) ~~inhibitor for use in the manufacture of a medicament for an~~ adjuvant treatment of a patient with skin cancer-cutaneous squamous cell carcinoma (CSCC) after the patient has completed ~~completion of surgery and post-surgery radiation.~~

wherein the antibody or antigen-binding fragment thereof comprises three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) and three CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR), wherein HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8; and

wherein the patient has at least one of the following high risk features:

- (i) nodal disease with extracapsular extension and at least 1 node >20 mm;

- (ii) in-transit metastases (ITM);
- (iii) T4 lesion;
- (iv) perineural invasion (PNI); and

(v) recurrent CSCC plus at least one of the following additional features: $\geq$ N2b disease associated with a recurrent lesion; nominal $\geq$ T3; and $\geq$ 20 mm diameter of recurrent lesion.

~~27. The pharmaceutical composition of claim 26, wherein the PD-1 inhibitor is an anti-PD-1 antibody or antigen-binding fragment thereof comprising three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three CDRs (LCDR1, LCDR2, and LCDR3) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.~~

~~28. The pharmaceutical composition of claim 27, wherein: HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8.~~

~~29-18. The use according to pharmaceutical composition of claim 17-28 wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a HCVR having an amino acid sequence of SEQ ID NO: 1 and a LCVR having an amino acid sequence of SEQ ID NO: 2. HCVR/LCVR sequence pair of SEQ ID NOs: 1/2.~~

~~30-19. The pharmaceutical composition use according to any one of claims 17-18-26-29, comprising wherein the pharmaceutical composition comprises 5 mg to 500 mg of the the antibody or antigen-binding fragment thereof PD-1 inhibitor.~~

~~31-20. The pharmaceutical composition use according to any one of claims 17-19-26-30, comprising wherein the pharmaceutical composition comprises 350 mg of the antibody or antigen-binding fragment thereof PD-1 inhibitor.~~

~~32. The pharmaceutical composition according to any one of claims 26-31, wherein the skin cancer is CSCC.~~

~~33. Use of a programmed death 1 (PD-1) inhibitor in the manufacture of a medicament for treating or inhibiting the growth of a tumor in a patient with a skin cancer for which surgical~~

~~removal is planned, wherein a therapeutically effective amount of the PD-1 inhibitor is administered to the patient as a neoadjuvant treatment prior to the surgical removal.~~

~~34. The use according to claim 33, wherein the skin cancer is cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC), Merkel cell carcinoma, or melanoma.~~

~~35. The use according to claim 33 or 34, wherein the skin cancer is CSCC.~~

~~36. The use according to any one of claims 33-35, wherein the patient is at high risk of CSCC recurrence.~~

~~37. The use according to claim 36, wherein the patient has at least one of the following high-risk features:~~

- ~~(a) nodal disease with extracapsular extension and at least 1 node >20 mm;~~
- ~~(b) in-transit metastases (ITM);~~
- ~~(c) T4 lesion;~~
- ~~(d) perineural invasion (PNI); and~~
- ~~(e) recurrent CSCC plus at least one of the following additional features:~~
 - ~~(i) $\geq$ N2b disease associated with a recurrent lesion;~~
 - ~~(ii) nominal $\geq$ T3; and~~
 - ~~(iii) $\geq$ 20 mm diameter of recurrent lesion.~~

~~38. The use according to any one of claims 33-37, wherein the therapeutically effective amount comprises 5 mg to 500 mg of the PD-1 inhibitor administered as a neoadjuvant.~~

~~39. The use according to any one of claims 33-38, wherein the therapeutically effective amount comprises 350 mg of the PD-1 inhibitor administered as the neoadjuvant.~~

~~40. The use according to any one of claims 33-38, wherein one or more doses of the PD-1 inhibitor are to be administered as neoadjuvant treatment, wherein each dose is administered 2 to 12 weeks, preferably 3 weeks after the immediately preceding dose.~~

~~41. The use according to claim 40, wherein each dose comprises 5 mg to 500 mg, preferably 350 mg of the PD-1 inhibitor.~~

~~42. The use according to any one of claims 33-41, further comprising: (c) subsequent to the neoadjuvant treatment, surgical removal of the skin cancer.~~

~~43. — The use according to claim 42, further comprising administration to the patient of an adjuvant treatment comprising a therapeutically effective amount of a PD-1 inhibitor after step (c), wherein the adjuvant PD-1 inhibitor may be the same as or different from the neoadjuvant PD-1 inhibitor.~~

~~44. — The use according to claim 43, wherein the adjuvant treatment comprises administration of 5 mg to 500 mg of the PD-1 inhibitor.~~

~~45. — The use according to claim 43 or 44, wherein the adjuvant treatment comprises administration of 350 mg of the PD-1 inhibitor.~~

~~46. — The use according to any one of claims 33-42, wherein the PD-1 inhibitor is to be administered intravenously.~~

~~47. — The use according to any one of claims 33-46, wherein administration of the PD-1 inhibitor leads to reduced risk of subsequent skin cancer recurrence or zero incidence of subsequent skin cancer recurrence.~~

~~48. — The use according to any one of claims 33-46, wherein administration of the PD-1 inhibitor leads to at least about 10% lower incidence of subsequent skin cancer recurrence as compared to a patient after completion of surgery and radiation therapy without adjuvant skin cancer treatment.~~

~~49. — The use according to any one of claims 33-46, further comprising administration of an additional therapeutic agent selected from a chemotherapeutic, a corticosteroid, an anti-inflammatory drug, and/or combinations thereof.~~

~~50. — The use according to any one of claims 33-49, wherein the PD-1 inhibitor is selected from the group consisting of an anti-PD-1 antibody or antigen-binding fragment thereof, an anti-PD-L1 antibody or antigen-binding fragment thereof, and an anti-PD-L2 antibody or antigen-binding fragment thereof.~~

~~51. — The use according to any one of claims 33-50, wherein the PD-1 inhibitor is an anti-PD-1 antibody or antigen-binding fragment thereof that comprises three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three CDRs (LCDR1, LCDR2, and~~

~~LCDR3) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.~~

~~52. The use according to claim 51, wherein: HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8.~~

~~53. The use according to claim 51 or 52, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a HCVR/LCVR sequence pair of SEQ ID NOs: 1/2.~~

~~54. The use according to any one of claims 51-53, wherein the anti-PD-1 antibody comprises a heavy chain and a light chain, wherein the heavy chain has an amino acid sequence of SEQ ID NO: 9.~~

~~55. The use according to any one of claims 51-53, wherein the anti-PD-1 antibody comprises a heavy chain and a light chain, wherein the light chain has an amino acid sequence of SEQ ID NO: 10.~~

~~56. The use according to any one of claims 51-53, wherein the anti-PD-1 antibody comprises a heavy chain and a light chain, wherein the heavy chain has an amino acid sequence of SEQ ID NO: 9 and the light chain has an amino acid sequence of SEQ ID NO: 10.~~

~~57. The use according to any one of claims 33-50, wherein the PD-1 inhibitor is cemiplimab or a bioequivalent thereof.~~

~~58. The use according to any one of claims 33-50, wherein the PD-1 inhibitor is an anti-PD-1 antibody selected from the group consisting of cemiplimab, nivolumab, pembrolizumab, pidilizumab, MEDI0608, BI 754048, PF-06371548, spartalizumab, camrelizumab, JNJ-63313240, and MCLA-134.~~

~~59. The use according to any one of claims 33-50, wherein the PD-1 inhibitor is an anti-PD-L1 antibody selected from the group consisting of H1H8314N, avelumab, atezolizumab, durvalumab, MDX-1105, LY3300054, FAZ053, STI-1014, CX-031, KN035, and CK-301.~~

~~60. — A pharmaceutical composition comprising a therapeutically effective amount of a programmed death 1 (PD-1) inhibitor for use in a neoadjuvant treatment prior to planned surgery for treating skin cancer.~~

~~61. — The pharmaceutical composition of claim 60, wherein the PD-1 inhibitor is an anti-PD-1 antibody or antigen-binding fragment thereof comprising three complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three CDRs (LCDR1, LCDR2, and LCDR3) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.~~

~~62. — The pharmaceutical composition of claim 61, wherein: HCDR1 has an amino acid sequence of SEQ ID NO: 3; HCDR2 has an amino acid sequence of SEQ ID NO: 4; HCDR3 has an amino acid sequence of SEQ ID NO: 5; LCDR1 has an amino acid sequence of SEQ ID NO: 6; LCDR2 has an amino acid sequence of SEQ ID NO: 7; and LCDR3 has an amino acid sequence of SEQ ID NO: 8.~~

~~63. — The pharmaceutical composition of claim 62, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a HCVR/LCVR sequence pair of SEQ ID NOs: 1/2.~~

~~64. — The pharmaceutical composition according to any one of claims 60-63, comprising 5 mg to 500 mg of the PD-1 inhibitor.~~

~~65. — The pharmaceutical composition according to any one of claims 60-63, comprising 350 mg of the PD-1 inhibitor.~~

~~66. — The pharmaceutical composition according to any one of claims 60-65, wherein the skin cancer is CSCC.~~