WE CLAIM:

1. A method of treating a tumor in a subject comprising: selecting a subject having a tumor comprising a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 ; administering talimogene laherparepvec to the subject; and administering pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof to the subject.

2. The method of claim 1, wherein the tumor expresses lower levels of two, three, four or five interferon gamma (IFNγ) signature genes prior to administering compared to a prespecified threshold of a control panel of signature genes selected from the group consisting of IFNγ, signal transducer and activator of transcription 1 (STAT1), C-C chemokine receptor type 5 (CCR5), chemokine (C-X-C motif) ligand 9 (CXCL9), perforin 1 (PRF1), HLA-DRA, chemokine (C-X-C motif) ligand 10 (CXCL10), chemokine (C-X-C motif) ligand 11 (CXCL11), indoleamine 2,3-dioxygenase 1 (IDO1) and granzyme A (GZMA).

3. The method of claim 1, wherein the tumor expresses no IFNγ signature genes prior to administering the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigen-binding fragment thereof.

4. The method of claim 1, wherein the tumor has a programmed death-ligand 1 (PD-L1) status of less than about 50% prior to administering the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigen-binding fragment thereof.

5. The method of claim 1, wherein the tumor has a PD-L1 status of less than about 1% prior to administering the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigen-binding fragment thereof.

6. The method of claim 1, wherein the talimogene laherparepvec is administered to the subject prior to the administration of the pembrolizumab or the antigen-binding fragment thereof.

7. The method of claim 1, wherein the subject has a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

8. The method of claim 7, wherein: the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; the breast cancer is HER2+ breast cancer, HER2- HR+ breast cancer, or triplenegative breast cancer; the prostate cancer is castration-resistant prostate cancer; the bladder cancer is transitional cell cancer or urothelial cancer; the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck; and/or the sarcoma is soft tissue sarcoma or bone sarcoma.

9. The method of claim 1, wherein the tumor comprises a CD8+ T-cell infiltration density of fewer than about 1000 cells / mm2 .

10. A method of treating a tumor in a subject that is poorly responsive to or nonresponsive to monotherapy with pembrolizumab, a pembrolizumab variant or an antigenbinding fragment thereof comprising: administering talimogene laherparepvec to the subject; and administering pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof to the subject.

11. The method of claim 10, wherein: the tumor comprises a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 prior to administering; the tumor expresses lower levels of two, three, four or five interferon gamma (IFNγ) signature genes prior to administering than a pre-specified threshold of a control panel of 95 signature genes selected from the group consisting of IFNγ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA; and/or the tumor has a PD-L1 status of less than about 50% prior to administering the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigenbinding fragment thereof.

12. A method of treating a tumor in a subject that progressed during monotherapy with pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof, comprising: administering talimogene laherparepvec to the subject; and administering pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof to the subject.

13. The method of claim 12, wherein: the tumor comprises a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 prior to administering; the tumor expresses lower levels of two, three, four or five interferon gamma (IFNγ) signature genes prior to administering than a pre-specified threshold of a control panel of signature genes selected from the group consisting of IFNγ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA; and/or the

tumor has a PD-L1 status of less than about 50% prior to administering the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigenbinding fragment thereof.

14. A method of treating a tumor having a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 comprising contacting the tumor with talimogene laherparepvec and pembrolizumab, a pembrolizumab variant or an antigenbinding fragment thereof.

15. The method of claim 14, wherein the tumor is from a subject having a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, 96 colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

16. The method of claim 15, wherein: the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; and/or the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck.

17. The method of claim 14, wherein the tumor expresses lower levels of two, three, four or five interferon gamma (IFNɣ) signature genes prior to contacting than a pre-specified threshold of a control panel of signature genes selected from the group consisting of IFNɣ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA.

18. The method of claim 14, wherein the tumor has a PD-L1 of less than about 50% prior to contacting with the talimogene laherparepvec and the pembrolizumab, the pembrolizumab variant or the antigen-binding fragment thereof.

19. A method of treating a tumor expressing lower levels of two, three, four or five interferon gamma (IFNɣ) signature genes prior to treatment than a pre-specified threshold of a control panel of signature genes elected from the group consisting of IFNɣ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA, comprising contacting the tumor with talimogene laherparepvec and pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof.

20. The method of claim 19, wherein the tumor is from a subject having a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric

cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

21. The method of claim 20, wherein: 97 the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; and/or the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck.

22. The method of claim 19, wherein the tumor has a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 prior to contacting.

23. The method of claim 19, wherein the tumor has a PD-L1 status of less than about 50% prior to contacting with the talimogene laherparepvec and the pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof.

24. A method of treating a tumor having a PD-L1 status of less than about 50% prior to treatment, comprising contacting the tumor with talimogene laherparepvec and pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof.

25. The method of claim 24, wherein the tumor is from a subject having a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

26. The method of claim 25, wherein: the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; and/or the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck.

27. The method of claim 24, wherein the tumor has a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 prior to contacting.

28. The method of claim 24, wherein the tumor expresses lower levels of two, three, four or five interferon gamma (IFNγ) signature genes prior to contacting than a pre-specified threshold of a control panel of signature genes selected from the group consisting of IFNγ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA.

29. A method of treating a tumor having a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 and expressing lower levels of five or fewer interferon gamma (IFNɣ) signature genes prior to treatment than a pre-specified threshold of a control panel of signature genes selected from the group consisting of IFNɣ, STAT1, CCR5, CXCL9, PRF1, HLA-DRA, CXCL10, CXCL11, IDO1 and GZMA, comprising contacting the tumor with talimogene laherparepvec and pembrolizumab, a pembrolizumab variant or an-antigen-binding fragment thereof.

30. The method of claim 29, wherein the tumor is from a subject having a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

31. The method of claim 30, wherein: the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; and/or the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck.

32. The method of claim 29, wherein the tumor has a PD-L1 status of less than about 50% prior to contacting with the talimogene laherparepvec and the pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof.

33. A method of treating a previously pembrolizumab-, pembrolizumab variant- or antigen-binding fragment thereof-resistant tumor in a subject subsequently exposed to 99 talimogene laherparepvec comprising administering to the subject pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof.

34. The method of claim 33, wherein the subject has a cancer selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, sarcoma, renal cell cancer, gastric cancer, esophageal cancer, anal canal cancer, biliary tract cancer and pancreatic cancer.

35. The method of claim 34, wherein: the melanoma is cutaneous melanoma, metastatic melanoma, or uveal melanoma; and/or the head and neck cancer is recurrent or metastatic squamous cell carcinoma of the head and neck.

36. A method of rendering a tumor that is resistant to monotherapy with pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof in a subject sensitive to pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof, comprising contacting the tumor with talimogene laherparepvec.

37. The method of claim 36, wherein a sample of the tumor taken from the subject after contacting the tumor with talimogene laherparepvec has an increased level of one or any combination of CD8+ T-cells, CD4+ T-cells, IFNγ, CD20+ B-cells, memory T-cells, regulatory T-cells and CD56+ cells relative to a sample of the tumor taken prior to the contacting the tumor with talimogene laherparepvec.

38. The method of claim 36, wherein the tumor has a CD8+ T-cell infiltration density of greater than 1000 cells / mm2 after contacting with talimogene laherparepvec.

39. A method of treating a tumor in a subject comprising: selecting a subject having a tumor comprising a CD8+ T-cell infiltration density of fewer than about 1500, about 1400, about 1300, about 1200, about 1100, about 1000, about 900, about 800, about 700, about 600, or about 500 cells / mm2 ; 100 administering talimogene laherparepvec to the subject intratumorally as an initial dose followed by one or more secondary doses; and administering pembrolizumab, a pembrolizumab variant or an antigen-binding fragment thereof to the subject systemically as an initial dose followed by one or more secondary doses.

Dated this 18th day of October, 2019