entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0009] Provided herein is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a human PD-1 axis binding antagonist and an anti-HER2 antibody. In one aspect, provided herein is use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-L1 binding antagonist is to be administered with a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3.

[0010] Also provided herein is a method of enhancing immune function in an individual having cancer comprising administering an effective amount of a PD-1 axis binding antagonist and an anti-HER2 antibody. In one aspect, provided herein is use of a PD-L1 binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PD-L1 binding antagonist is to be administered with a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3.

[0011] In another aspect, provided herein is use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with a composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier.

[0012] In another aspect, provided herein is use of a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the bispecific anti-HER2 antibody and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with a composition comprising a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier.

[0013] In another aspect, provided herein is a composition comprising a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the composition is to be administered in combination with a second composition, wherein the second composition comprises a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier.

[0014] In another aspect, provided herein is a composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier.

[0015] In another aspect, provided herein is a kit comprising a medicament comprising a PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions indicating that the medicament is to be administered in combination with a composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier for treating or delaying progression of a cancer in an individual.

[0016] In another aspect, provided herein is a kit comprising a first medicament comprising a PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier. In some embodiments, the kit further comprises a package insert comprising instructions for administration of the first medicament and the second medicament for treating or delaying progression of cancer in an individual.

[0017] In another aspect, provided herein is a kit comprising a medicament comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions indicating that the medicament is to be administered in combination with a composition comprising a PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

[0018] In some embodiments of the methods, uses, compositions, and kits described above and herein, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist. In some embodiments, the PD-1 axis binding antagonist is an antibody. In some embodiments, the antibody is a humanized antibody, a chimeric antibody or a human antibody. In some embodiments, the antibody is an antigen binding fragment. In some embodiments, the antigen-binding fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$, and Fv.

[0019] In some embodiments, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. In some embodiments, the PD-1 binding antagonist is an antibody. In some embodiments, the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (pembrolizumab, lambrolizumab), CT-011 (pidilizumab), and AMP-224.

[0020] In some embodiments, the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In some embodiments, the PD-L1 binding antagonist inhibits the binding of PD-

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-L1 binding antagonist is to be administered with a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3.

2. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

3. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

4. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

5. The use of any one of claims 1-4, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.

6. The use of claim 1, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

7. The use of claim 5, wherein the anti-PD-L1 antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:19, HVR-H2 sequence of SEQ ID NO:20, and HVR-H3 sequence of SEQ ID NO:21; and a light chain comprising HVR-L1 sequence of SEQ ID NO:22, HVR-L2 sequence of SEQ ID NO:23, and HVR-L3 sequence of SEQ ID NO:24.

8. The use of claim 5, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 or 26 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.

9. The use of claim 1, wherein the first antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HHER2) and a light chain variable region (V_LHER2), and the second antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HCD3) and a light chain variable region (V_LCD3).

10. The use of claim 9, wherein the first antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HHER2) comprising HVR-H1

sequence of SEQ ID NO:38, HVR-H2 sequence of SEQ ID NO:50, and HVR-H3 sequence of SEQ ID NO:40; and a light chain variable region (V_LHER2) comprising HVR-L1 sequence of SEQ ID NO:41, HVR-L2 sequence of SEQ ID NO:42, and HVR-L3 sequence of SEQ ID NO:43.

11. The use of claim 10, wherein the heavy chain variable region (V_HHER2) of the anti-HER2 bispecific antibody comprises the amino acid sequence of SEQ ID NO:34 and a light chain variable region (V_LHER2) of the anti-HER2 bispecific antibody comprises the amino acid sequence of SEQ ID NO:35.

12. The use of any one of claims 1-11, wherein the second antigen binding domain binds to a human CD3 polypeptide.

13. The use of claim 12, wherein the CD3 polypeptide is a human CD3ε polypeptide or a human CD3γ polypeptide.

14. The use of claim 13, wherein the second antigen binding domain of the anti-HER2 bispecific antibody binds to a human CD3ε polypeptide or a human CD3 γ polypeptide in a native T-cell receptor (TCR) complex in association with other TCR subunits.

15. The use of any one of claims 9-14, wherein the bispecific antibody is a single-chain bispecific antibody comprising the first antigen binding domain and the second antigen binding domain.

16. The use of claim 15, wherein the single-chain bispecific antibody comprises variable regions, as arranged from N-terminus to C-terminus, selected from the group consisting of (1) V_HHER2-V_LHER2-V_HCD3-V_LCD3, (2) V_HCD3-V_LCD3-V_HHER2-V_LHER2, (3) V_HCD3-V_LCD3-V_LHER2-V_HHER2, (4) V_HHER2-V_LHER2-V_LCD3-V_HCD3, (5) V_LHER2-V_HHER2-V_HCD3-V_LCD3, or (6) V_LCD3-V_HCD3-V_HHER2-V_LHER2.

17. The use of any one of claims 9-14, wherein (a) the first antigen binding domain of the anti-HER2 bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 ($CH1_1$) domain, a first CH2 ($CH2_1$) domain, a first CH3 ($CH3_1$) domain; and (b) the second antigen binding domain of the anti-HER2 bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a second CH1 ($CH1_2$) domain, second CH2 ($CH2_2$) domain, and a second CH3 ($CH3_2$) domain.

18. The use of claim 17, wherein at least one of the one or more heavy chain constant domains of the first antigen binding domain of the anti-HER2 bispecific antibody is paired with another heavy chain constant domain of the second antigen binding domain of the anti-HER2 bispecific antibody.

19. The use of claim 18, wherein the $CH3_1$ and $CH3_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH3_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH3_2$ domain.

20. The use of claim 19, wherein the $CH3_1$ and $CH3_2$ domains meet at an interface between said protuberance and cavity.

21. The use of any one of claims 17-20, wherein the $CH2_1$ and $CH2_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH2_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH2_2$ domain.

22. The use of claim 21, wherein the $CH2_1$ and $CH2_2$ domains meet at an interface between said protuberance and cavity.

23. The use of any one of claims 1-22, wherein the bispecific anti-HER2 antibody comprises an aglycosylation site mutation.

24. The use of claim 23, wherein the aglycosylation site mutation is a substitution mutation.

25. The use of claim 24 wherein the substitution mutation is at amino acid residue N297, L234, L235, and/or D265 (EU numbering).

26. The use of claim 25, wherein the substitution mutation is selected from the group consisting of N297G, N297A, L234A, L235A, and D265A.

27. The use of claim 26, wherein the substitution mutation is a D265A mutation and an N297G mutation.

28. The use of any one of claims 24-27, wherein the aglycosylation site mutation reduces effector function of the bispecific anti-HER2 antibody.

29. The use of any one of claims 1-28, wherein the cancer is a HER2-positive cancer.

30. The use of claim 29, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, or prostate cancer.

31. The use of any one of claims 1-30, wherein the individual has cancer or has been diagnosed with cancer.

32. The use of claim 31, wherein cancer cells in the individual express PD-L1.

33. The use of claim 31 or 32, wherein the individual has cancer that is resistant to a HER2 targeted therapy.

34. The use of claim 31 or 32, wherein the individual is refractory to a HER2 targeted therapy.

35. The use of claim 33 or 34, wherein the HER2 targeted therapy is a treatment with an

anti-HER2 antibody or an inhibitor of the HER2 pathway.

36. The use of claim 35, wherein the HER2 targeted therapy is treatment with trastuzumab, pertuzumab, ado-trastuzumab emtansine, or lapatinib.

37. The use of any one of claims 1-36, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

38. The use of any one of claims 1-37, wherein the bispecific anti-HER2 antibody is to be administered before the PD-L1 binding antagonist, simultaneous with the PD-L1 binding antagonist, or after the PD-L1 binding antagonist.

39. Use of a PD-L1 binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PD-L1 binding antagonist is to be administered with a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3.

40. The use of claim 39, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation, and/or cytolytic activity relative to prior to the administration of the PD-L1 binding antagonist and the bispecific anti-HER2 antibody.

41. The use of claim 39, wherein the number of CD8 T cells is elevated relative to prior to the administration of the combination.

42. The use of claim 41, wherein the CD8 T cell is an antigen-specific CD8 T cell.

43. The use of claim 39, wherein Treg function is suppressed relative to prior to the administration of the combination.

44. The use of claim 39, wherein T cell exhaustion is decreased relative to prior to the administration of the combination.

45. The use of any one of claims 39-44, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

46. The use of any one of claims 39-44, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

47. The use of any one of claims 39-44, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

48. The use of any one of claims 39-47, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.

49. The use of any one of claims 39-44, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

50. The use of claim 48, wherein the anti-PD-L1 antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:19, HVR-H2 sequence of SEQ ID NO:20, and

HVR-H3 sequence of SEQ ID NO:21; and a light chain comprising HVR-L1 sequence of SEQ ID NO:22, HVR-L2 sequence of SEQ ID NO:23, and HVR-L3 sequence of SEQ ID NO:24.

51. The use of claim 48, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 or 26 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.

52. The use of claim 1, wherein the first antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HHER2) and a light chain variable region (V_LHER2), and the second antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HCD3) and a light chain variable region (V_LCD3).

53. The use of claim 52, wherein the first antigen binding domain of the anti-HER2 bispecific antibody comprises a heavy chain variable region (V_HHER2) comprising HVR-H1 sequence of SEQ ID NO:38, HVR-H2 sequence of SEQ ID NO:50, and HVR-H3 sequence of SEQ ID NO:40; and a light chain variable region (V_LHER2) comprising HVR-L1 sequence of SEQ ID NO:41, HVR-L2 sequence of SEQ ID NO:42, and HVR-L3 sequence of SEQ ID NO:43.

54. The use of claim 52, wherein the heavy chain variable region (V_HHER2) of the anti-HER2 bispecific antibody comprises the amino acid sequence of SEQ ID NO:34 and the light chain variable region (V_LHER2) of the anti-HER2 bispecific antibody comprises the amino acid sequence of SEQ ID NO:35.

55. The use of any one of claims 39-54, wherein the second antigen binding domain of the anti-HER2 bispecific antibody binds to a human CD3 polypeptide.

56. The use of claim 55, wherein the CD3 polypeptide is a human CD3ε polypeptide or a human CD3γ polypeptide.

57. The use of claim 55, wherein the second antigen binding domain of the anti-HER2 bispecific antibody binds to a human CD3ε polypeptide or a human CD3γ polypeptide in a native T-cell receptor (TCR) complex in association with other TCR subunits.

58. The use of any one of claims 39-57, wherein the bispecific antibody is a single-chain bispecific antibody comprising the first antigen binding domain and the second antigen binding domain.

59. The use of claim 58, wherein the single-chain bispecific antibody comprises variable regions, as arranged from N-terminus to C-terminus, selected from the group consisting of (1) V_HHER2-V_LHER2-V_HCD3-V_LCD3, (2) V_HCD3-V_LCD3-V_HHER2-V_LHER2, (3) V_HCD3-

V_LCD3-V_LHER2-V_HHER2, (4) V_HHER2-V_LHER2-V_LCD3-V_HCD3, (5) V_LHER2-V_HHER2-V_HCD3-V_LCD3, or (6) V_LCD3-V_HCD3-V_HHER2-V_LHER2.

60. The use of any one of claims 39-57, wherein (a) the first antigen binding domain of the anti-HER2 bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 ($CH1_1$) domain, a first CH2 ($CH2_1$) domain, a first CH3 ($CH3_1$) domain; and (b) the second antigen binding domain of the anti-HER2 bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a second CH1 ($CH1_2$) domain, second CH2 ($CH2_2$) domain, and a second CH3 ($CH3_2$) domain.

61. The use of claim 60, wherein at least one of the one or more heavy chain constant domains of the first antigen binding domain of the anti-HER2 bispecific antibody is paired with another heavy chain constant domain of the second antigen binding domain of the anti-HER2 bispecific antibody.

62. The use of claim 61, wherein the $CH3_1$ and $CH3_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH3_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH3_2$ domain.

63. The use of claim 62, wherein the $CH3_1$ and $CH3_2$ domains meet at an interface between said protuberance and cavity.

64. The use of any one of claims 60-63, wherein the $CH2_1$ and $CH2_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH2_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH2_2$ domain.

65. The use of claim 64, wherein the $CH2_1$ and $CH2_2$ domains meet at an interface between said protuberance and cavity.

66. The use of any one of claims 39-65, wherein the bispecific anti-HER2 antibody comprises an aglycosylation site mutation.

67. The use of claim 66, wherein the aglycosylation site mutation is a substitution mutation.

68. The use of claim 67, wherein the substitution mutation is at amino acid residue N297, L234, L235, and/or D265 (EU numbering).

69. The use of claim 68, wherein the substitution mutation is selected from the group consisting of N297G, N297A, L234A, L235A, and D265A.

70. The use of claim 68, wherein the substitution mutation is a D265A mutation and an N297G mutation.

71. The use of any one of claims 66-70, wherein the aglycosylation site mutation reduces

effector function of the bispecific anti-HER2 antibody.

72. The use of any one of claims 39-71, wherein the cancer is a HER2-positive cancer.

73. The use of claim 72, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, or prostate cancer.

74. The use of any one of claims 39-73, wherein cancer cells in the individual express PD-L1.

75. The use of any one of claims 39-74, wherein the individual has cancer that is resistant to a HER2 targeted therapy.

76. The use of any one of claims 39-74, wherein the individual is refractory to a HER2 targeted therapy.

77. The use of claim 75 or 76, wherein the HER2 targeted therapy is a treatment with an anti-HER2 antibody or an inhibitor of the HER2 pathway.

78. The use of claim 77, wherein the HER2 targeted therapy is a treatment with trastuzumab, pertuzumab, ado-trastuzumab emtansine, or lapatinib.

79. The use of any one of claims 1-78, wherein the PD-L1 binding antagonist and/or the bispecific anti-HER2 antibody are administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

80. The use of any one of claims 1-79, wherein the medicament is to be administered with a chemotherapeutic agent for treating or delaying progression of cancer.

81. Use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with a composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier.

82. Use of a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the bispecific anti-HER2 antibody and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with a composition comprising a human PD-L1 binding antagonist and an

optional pharmaceutically acceptable carrier.

83. A composition comprising a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the composition is to be administered in combination with a second composition, wherein the second composition comprises a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3_and an optional pharmaceutically acceptable carrier.

84. A composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier.

85. A kit comprising a medicament comprising a PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions indicating that the medicament is to be administered in combination with a composition comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3 and an optional pharmaceutically acceptable carrier for treating or delaying progression of a cancer in an individual.

86. A kit comprising a first medicament comprising a PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3_and an optional pharmaceutically acceptable carrier.

87. The kit of claim 86, wherein the kit further comprises a package insert comprising instructions indicating that the first medicament and the second medicament are to be administered for treating or delaying progression of cancer in an individual.

88. A kit comprising a medicament comprising a bispecific anti-HER2 antibody that comprises a first antigen binding domain that binds to HER2, and a second antigen binding domain that binds to CD3_and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions indicating that the medicament is to be administered in combination with a composition comprising a PD-L1 binding antagonist and an optional

pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.