

CLAIMS

1. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising measuring the Nectin-4, SDHC and/or DDR2 DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient, and selecting a patient having an elevated Nectin-4, SDHC and/or DDR2 DNA copy number in the tumor tissue.
2. The method of claim 1, wherein the step of measuring the Nectin-4, SDHC and/or DDR2 DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient comprises using Next-generation sequencing (NGS) technologies or an array-based sequence capture.
3. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in a tumor tissue, comprising measuring the Nectin-4, SDHC and/or DDR2 DNA copy number of a patient using Next-generation sequencing (NGS) technologies or an array-based sequence capture, and selecting a patient who has an elevated Nectin-4 DNA copy number.
4. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising measuring the SDHC DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient, and selecting a patient having an elevated SDHC DNA copy number in the tumor tissue.
5. The method of claim 4, wherein the step of measuring the SDHC DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient comprises using Next-generation sequencing (NGS) technologies or an array-based sequence capture.
6. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising measuring the SDHC DNA copy number of a patient using Next-generation sequencing (NGS) technologies or an array-based sequence capture, and selecting a patient who has an elevated SDHC DNA copy number.
7. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising measuring the DDR2 DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient, and selecting a patient having an elevated DDR2 DNA copy number in the tumor tissue.
8. The method of claim 7, wherein the step of measuring the DDR2 DNA copy number in tumor tissue or in circulating tumor DNA (ctDNA) of a patient comprises using Next-generation sequencing (NGS) technologies or an array-based sequence capture.
9. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising measuring the DDR2 DNA copy number of a patient using Next-generation sequencing (NGS) technologies or an array-based sequence capture, and selecting a patient who has an elevated DDR2 DNA copy number.
104. The method of any one of claims 1-93, wherein the patient has pancreatic cancer, stomach cancer, bladder cancer, head & neck cancer, non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or ovarian cancer.

115. The method of any one of claims 1-3, wherein the patient selected has a Nectin-4, SDHC and/or DDR2 Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

12. The method of any one of claims 4-6, wherein the patient selected has an SDHC Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

13. The method of any one of claims 7-9, wherein the patient selected has a DDR2 Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

146. Use of a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the manufacture of a medicament for A method of treating a cancer in a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue, comprising administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

157. The method-use of claim 146, wherein a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue refers to a patient having a Nectin-4, SDHC and/or DDR2 Log2(CN ratio), as measured in tumor tissue or in circulating tumor DNA (ctDNA) of said patient, of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

16. The method of claim 14, wherein a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue refers to a patient having an SDHC Log2(CN ratio)), as measured in tumor tissue or in circulating tumor DNA (ctDNA) of said patient, of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

17. The method of claim 14, wherein a patient having an elevated Nectin-4 protein and/or RNA expression level in tumor tissue refers to a patient having a DDR2 Log2(CN ratio)), as measured in tumor tissue or in circulating tumor DNA (ctDNA) of said patient, of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more.

188. Use of a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the manufacture of a medicament for A method of treating a cancer in a patient, comprising selecting a wherein the patient having has a Nectin-4, SDHC and/or DDR2 Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more in tumor tissue or in circulating tumor DNA (ctDNA) as determined by Next generation sequencing (NGS) technologies or an array-based sequence capture, and administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

~~19. A method of treating a cancer in a patient, comprising selecting a patient having an SDHC Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more in tumor tissue or in circulating tumor DNA (ctDNA) as determined by Nextgeneration sequencing (NGS) technologies or an array-based sequence capture, and administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.~~

~~20. A method of treating a cancer in a patient, comprising selecting a patient having a DDR2 Log2(CN ratio) of about 0.1 or more, about 0.2 or more, about 0.3 or more, about 0.4 or more, about 0.5 or more, about 0.6 or more, about 0.7 or more, about 0.8 or more, about 0.9 or more, or about 1.0 or more in tumor tissue or in circulating tumor DNA (ctDNA) as determined by Nextgeneration sequencing (NGS) technologies or an array-based sequence capture, and administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.~~

~~219. The method-use of any one of claims 14-206-8, wherein the cancer is pancreatic cancer, stomach cancer, bladder cancer, head & neck cancer, non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or ovarian cancer.~~

~~2210. The method-use of any one of claims 14-216-9, further comprising administering an immuno-oncology agent, optionally-~~

~~23. The method of claim 22, wherein the immune-oncology agent is a PD-1 antagonist optionally-~~

~~24. The method of claim 23, wherein the PD-1 antagonist is an antagonistic PD-1 antibody, optionally-~~

~~25. The method of claim 24, wherein the antagonistic PD-1 antibody is selected from nivolumab, pembrolizumab, MEDI-0680, pidilizumab, AMP-224, atezolizumab, durvalumab, BMS-936559, avelumab, or cemiplimab.~~

~~2611. The method-use of any one of claims 146-2510, wherein the Bicycle toxin conjugate specific for Nectin-4 is BT8009 or the Bicycle TICA is BT7480.~~

~~2712. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in a tumor tissue, comprising measuring Nectin-4 protein level in a tumor tissue of a patient, and selecting a patient having an elevated Nectin-4 protein level in the tumor tissue.~~

~~2813. The method of claim 2712, wherein the step of measuring Nectin-4 protein level in a tumor tissue of a patient comprises using a Nectin-4 multiplexed immunofluorescence (mIF) assay.~~

~~2914. A method of identifying or selecting a patient having an elevated Nectin-4 protein and/or RNA expression level in a tumor tissue, comprising measuring staining intensity in a tumor tissue section of a patient using a Nectin-4 mIF assay, and selecting a patient who is staining positive in the Nectin-4 mIF assay.~~

~~30~~15. The method of any one of claims ~~27~~12-2914, wherein the patient has pancreatic cancer, stomach cancer, esophageal cancer, bladder cancer, head & neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or ovarian cancer.

~~31~~16. The method of claim ~~28~~13 or ~~29~~14, wherein the Nectin-4 mIF assay uses a rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD) of Nectin-4, optionally.

~~32~~. The method of claim ~~31~~, wherein the rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD) of Nectin-4 is rabbit monoclonal a-Nectin-4 primary antibody YMW-1-58.

~~33~~17. The method of claim ~~29~~14, wherein staining positive in the Nectin-4 mIF assay refers to:
(i) an H-score of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in the Nectin-4 mIF assay;

(ii) ~~34. The method of claim 29, wherein staining positive in the Nectin-4 mIF assay refers to an H-score for tumor cell membrane of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in the Nectin-4 mIF assay; or~~

~~35. The method of claim 29, wherein staining positive in the Nectin-4 mIF assay refers to~~ (iii) an H-score for tumor cell cytoplasm of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in the Nectin-4 mIF assay.

~~36~~18. Use of a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the manufacture of a medicament for A method of treating a cancer in a patient having an elevated Nectin-4 protein and/or RNA expression level in a tumor tissue, comprising administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

~~37~~19. The method use of claim ~~36~~18, wherein a patient having an elevated Nectin-4 protein and/or RNA expression level in a tumor tissue refers to a patient having an H-score of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in a Nectin-4 mIF assay.

~~38~~20. Use of a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the manufacture of a medicament for A method of treating a cancer in a patient, comprising selecting a wherein the patient having has an H-score of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in an Nectin-4 mIF assay,

and administering to the patient a Bicycle toxin conjugate or Bicycle TICA specific for Nectin-4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

~~39. The method of any one of claims 36-38, wherein the cancer is pancreatic cancer, stomach cancer, esophageal cancer, bladder cancer, head & neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or ovarian cancer.~~

~~40. The method of claim 37 or 38, wherein the Nectin-4 mIF assay uses a rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD) of Nectin-4.~~

~~41. The method of claim 40, wherein the rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD) of Nectin-4 is rabbit monoclonal a-Nectin-4 primary antibody YMW-1-58.~~

~~4221. The method-use of claim 3820, wherein the H-score refers to an H-score for tumor cell membrane or an H-score for tumor cell cytoplasm.~~

~~4322. Use of BT8009 or BT7480, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the manufacture of a medicament for A method of treating a cancer in a patient, comprising selecting a wherein the patient having has an H-score for tumor cell membrane of about 15 or more, about 20 or more, about 30 or more, about 40 or more, about 50 or more, about 75 or more, about 100 or more, about 125 or more, or about 150 or more in a tumor tissue section in a Nectin-4 mIF assay, and administering to the patient BT8009 or BT7480, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.~~

~~4423. The method-use of any one of claims 4318-20 or 22, wherein the cancer is pancreatic cancer, stomach cancer, esophageal cancer, bladder cancer, head & neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or ovarian cancer.~~

~~4524. The method-use of any one of claims 19, 20 or 22-43, wherein the Nectin-4 mIF assay uses a rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD), optionally -~~

~~46. The method of claim 45, wherein the rabbit monoclonal a-Nectin-4 primary antibody selectively binding to the extracellular domain (ECD) of Nectin-4 is rabbit monoclonal a-Nectin-4 primary antibody YMW-1-58.~~