Signaling through the epidermal growth factor receptor (EGFR) pathway is a major driver of HNSCC (4). EGFR is overexpressed in up to 90% of all HNSCC (5, 6). EGFR inhibition with cetuximab has proven to be a successful therapeutic strategy, albeit with somewhat limited long-term clinical benefits due to intrinsic or acquired resistance (7). Tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and lapatinib, that target EGFR and or HER2 have been investigated in clinical studies of HNSCC but have not demonstrated a survival advantage in randomized trials (8-10).

NRG1 autocrine signaling has been shown to regulate lung epithelial cell proliferation (Jinbo, et al., Am. J. Respir. Cell Mol. Biol. 27 : 306-313 (2002) and to play a role in human lung development (Patel, et al, Am. J. Resp Cell Mol Bio, 22: 432-440 (2000)) and has been implicated in insensitivity of NSCLC to EGFR inhibitors (Zhou, et al. , Cancer cell 10:39-50 (2006)). Preclinical studies suggested that certain cancer cell lines are driven by an autocrine-signaling loop in which NRG1 promotes malignancy by engaging the HER2 kinase. (Wilson, et al., Cancer Cell, 20:158-173(2011)).

Summary ~~of the Invention~~

In one aspect, there is provided the use of a therapeutically effective amount of a HER3 inhibitor in the manufacture of a medicament for treating a type of cancer in a patient, wherein the patient, prior to administration of the HER3 inhibitor, was diagnosed with a cancer which overexpresses NRG1.

One ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method of treating a type of cancer in a patient comprising administering a therapeutically effective amount of a HER3 inhibitor to the patient, where the patient, prior to administration of the HER3 inhibitor, was diagnosed with a cancer which overexpresses NRG1. NRG1 overexpression is indicative of therapeutic responsiveness by the subject to the HER3 inhibitor. In one embodiment, the patient was diagnosed with a cancer expressing NRG1 at a level higher than the median level for NRG1 expression in the cancer type. In certain embodiments, the patient was diagnosed with a cancer expressing NRG1 at a level which is at the 60th percentile or higher, 75th percentile or higher, or 80th percentile or higher for NRG1 expression in the cancer type. In one embodiment, the type of cancer is one which exhibits a bimodal expression profile consisting of an overexpression mode and a lack of overexpression mode. In one embodiment, the inflection point of the bimodal expression profile is 1.5 as measured on a linear scale. In one embodiment, the type of cancer is one which exhibits autocrine neuregulin-induced signaling, such HNSCC.

In one embodiment, the HER3 inhibitor inhibits NRG1 binding to HER3. In one embodiment, the HER3 inhibitor is an antibody. In one embodiment, the HER3 inhibitor is a bispecific HER3/EGFR inhibitor. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the bispecific antibody comprises the HVR sequences of the heavy chain

variable domain of SEQ ID NO: 1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2.

In one embodiment, the diagnosis comprised determining the expression level of NRG1 in a sample from the patient's cancer and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

In one aspect, there is provided the use of a therapeutically effective amount of a bispecific HER3/EGFR inhibitor in the manufacture of a medicament for treating head and neck squamous cell carcinoma (HNSCC) in a patient, wherein the patient, prior to administration of the bispecific HER3/EGFR inhibitor, was diagnosed with a HNSCC which overexpresses NRG1

Another ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method of treating head and neck squamous cell carcinoma (HNSCC) in a patient comprising administering a therapeutically effective amount of a bispecific HER3/EGFR inhibitor to the patient, wherein the patient, prior to administration of the bispecific HER3/EGFR inhibitor, was diagnosed with a HNSCC which overexpresses NRG1. NRG1 overexpression is indicative of therapeutic responsiveness by the subject to the bispecific HER3/EGFR inhibitor. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the bispecific antibody comprises the HVR sequences of the heavy chain variable domain of SEQ ID NO: 1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2.

~~Another aspect of the invention~~In one aspect, there is provided~~s~~ a method for selecting a therapy for a patient with a type of cancer which exhibits autocrine neuregulin-induced signaling comprising determining neuregulin 1 (NRG1) expression in a cancer sample from the patient and selecting a HER3 inhibitor for therapy if the cancer sample overexpresses NRG1. In one embodiment, the cancer sample expresses NRG1 at a level higher than the median level for NRG1 expression in the cancer type. In certain embodiments, the cancer sample expresses NRG1 at a level which is at the 60th percentile or higher, 75th percentile or higher, or 80th percentile or higher for NRG1 expression in the cancer type. In one embodiment, the type of cancer is one which exhibits a bimodal expression profile consisting of an overexpression mode and a lack of overexpression mode. In one embodiment, the inflection point of the bimodal expression profile is 1.5 as measured on a linear scale. In one embodiment, the type of cancer is one which exhibits autocrine neuregulin-induced signaling, such HNSCC. In one embodiment, the method further comprises administering a therapeutically effective amount of the HER3 inhibitor to the patient. In one embodiment, the type of cancer is HNSCC. In one embodiment, the HER3 inhibitor inhibits NRG binding to HER3. In one embodiment, the HER3 inhibitor is an antibody. In one embodiment, the HER3 inhibitor is a bispecific HER3/EGFR inhibitor. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the

bispecific antibody comprises the HVR sequences of the heavy chain variable domain of SEQ ID NO: 1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2.

In one embodiment, the determination of NRG1 expression comprises determining the

expression level of NRG1 in a sample from the patient's cancer and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

Another ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method for selecting a therapy for a patient with a head and neck squamous cell carcinoma (HNSCC) comprising determining neuregulin 1 (NRG1) expression in a HNSCC sample from the patient and selecting a bispecific HER3/EGFR inhibitor as the therapy if the HNSCC sample overexpresses NRG1. In one embodiment, the method further comprises administering a therapeutically effective amount of the bispecific HER3/EGFR inhibitor inhibitor to the patient. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the bispecific antibody comprises the HVR sequences of the heavy chain variable domain of SEQ ID NO: 1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the determination of NRG1 expression comprises determining the expression level of NRG1 in a sample from the patient's cancer and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

Another ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method for advertising a HER3 inhibitor or a pharmaceutically acceptable composition thereof comprising promoting, to a target audience, the use of the HER3 inhibitor or pharmaceutical composition thereof for treating a patient population with a type of cancer, where the patient's cancer overexpresses NRG1. In one embodiment, the HER3 inhibitor inhibits NRG binding to HER3. In one embodiment, the HER3 inhibitor is an antibody. In one embodiment, the HER3 inhibitor is a bispecific HER3/EGFR inhibitor. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the bispecific antibody comprises the HVR sequences of the heavy chain variable domain of SEQ ID NO: 1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2.

Another ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method for advertising a bispecific HER3/EGFR inhibitor or a pharmaceutically acceptable composition thereof comprising promoting, to a target audience, the use of the bispecific HER3/EGFR inhibitor or pharmaceutical composition thereof for treating a patient population with a HNSCC, where the patient's HNSCC overexpresses NRG1. In one embodiment, the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR. In one embodiment, the bispecific antibody comprises the HVR sequences of the heavy chain variable domain of SEQ ID NO:

1 and the HVR sequences of the light chain variable domain sequence of SEQ ID NO: 2. In one embodiment, the bispecific antibody comprises the heavy chain variable domain of SEQ ID NO: 1 and the light chain variable domain sequence of SEQ ID NO: 2.

In one aspect, there is provided a method of quantifying NRG1 expression level in a cancer sample comprising :

determining the expression level of NRG1 in the sample, and

quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

Another ~~aspect~~ embodiment of the ~~invention~~ disclosure provides a method of quantifying NRG1 expression level in a cancer sample comprising determining the expression level of NRG1 in the sample, and quantifying the expression level of NRG1 in the sample relative to the expression level of an internal reference gene or genes in the sample. In one embodiment, the reference gene or genes is one or both of AL-137727 and VPS33B. In one embodiment, the sample is from a cancer that exhibits autocrine neuregulin-induced signaling, such as head and neck squamous cell carcinoma (HNSCC). In one specific embodiment, of this method, the expression level of NRG1 and the expression level of the one or both of AL-137727 and VPS33B is determined using polymerase chain reaction (PCR). In one embodiment, the PCR used in the method is quantitative real time polymerase chain reaction (qRT-PCR). In another embodiment, the expression level of NRG1 is determined using immunohistochemistry (IHC) or ELISA. In another embodiment, the expression level of NRG1 is determined using immunohistochemistry (IHC) or ELISA. In another embodiment, the expression level of NRG1 is determined by direct RNA sequencing. In another embodiment, the expression level of NRG1 is determined using RNA in situ hybridization.

In one aspect, there is provided a HER3 inhibitor for use in the treatment of a type of cancer which overexpresses NRG1.

Brief Description of the Drawings

Figure 1 is a graph demonstrating that the MEHD7945A antibody binds to both HER3-ECD and EGFR-ECD.

Figure 2A and B are graphs demonstrating that MEHD7945A inhibits EGFR and HER2/HER3-dependent signaling.

Figure 3 is a graph showing inhibition of tumor growth in FaDu cancer model by MEHD7945A.

Figure 4 is a summary of the tumor growth inhibitory effect of MEHD7945A compared to cetuximab or anti-HER3 in numerous murine xenograft models.

Figure 5 shows NRG1 (A) and HER3 (B) expression levels in cancer types as determined by qRT-PCR.

Figure 6 shows the biomodal distribution of NRG1expression in HNSCC as compared to other cancer types.

Figure 7 shows the bimodal distribution of NRG1 expression in HNSCC when plotted on a $\log_{10}$ scale. The dotted line indicates the inflection point between the overexpression and lack of overexpression modes of NRG1 expression in HNSCC, which is set at 0.3689 on the logarithm scale, corresponding to approximately 1.50 on the linear scale.

WHAT IS CLAIMED IS:

1. ~~A method of treating a type of cancer in a patient comprising administering~~Use of a therapeutically effective amount of a HER3 inhibitor in the manufacture of a medicament for treating a type of cancer in a ~~to the~~ patient, wherein the patient, prior to administration of the HER3 inhibitor, was diagnosed with a cancer which overexpresses NRG1.

2. The ~~method~~ use of claim 1, wherein the patient was diagnosed with a cancer expressing NRG1 at a level higher than the median level for NRG1 expression in the cancer type.

3. The ~~method~~ use of claim 2, wherein the patient was diagnosed with a cancer expressing NRG1 at a level which is the 60th percentile or higher for NRG1 expression in the cancer type.

4. The ~~method~~ use of claim 2, wherein the patient was diagnosed with a cancer expressing NRG1 at a level which is the 75th percentile or higher for NRG1 expression in the cancer type.

5. The ~~method~~ use of claim 2, wherein the patient was diagnosed with a cancer expressing NRG1 at a level which is the 80th percentile or higher for NRG1 expression in the cancer type.

6. The ~~method~~ use of claim 1, wherein the type of cancer is one which exhibits a bimodal expression profile consisting of an overexpression mode and a lack of overexpression mode.

7. The ~~method~~ use of any of claims 1-6, wherein the type of cancer exhibits autocrine neuregulin-induced signaling.

8. The ~~method~~ use of any of claims 1-7, wherein the type of cancer is head and neck squamous cell carcinoma (HNSCC).

9. The ~~method~~ use of any of claims 1-8, wherein the HER3 inhibitor inhibits NRG1 binding to HER3.

10. The ~~method~~ use of any of claims 1-9, wherein the HER3 inhibitor is an antibody.

11. The ~~method~~ use of any of claims 1-10, wherein the HER3 inhibitor is a bispecific HER3/EGFR inhibitor.

12. The ~~method~~ use of claim 11, wherein the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR.

13. The ~~method~~ use of claim 12, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises

a HVR-H1 comprising the amino acid sequence LSGDWIH (SEQ ID NO: 3),

a HVR-H2 comprising the amino acid sequence VGEISAAGGYTD (SEQ ID NO: 4),

a HVR-H3 comprising the amino acid sequence ARESRVSFEAAMDY (SEQ ID NO: 5), and

a HVR-L1 comprising the amino acid sequence NIATDVA (SEQ ID NO: 6),

a HVR-L2 comprising the amino acid sequence SASF (SEQ ID NO: 7), and

a HVR-L3 comprising the amino acid sequence SEPEPYT (SEQ ID NO: 8).

14. The ~~method~~ use of claim 13, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises a heavy chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 2.

15. The ~~method~~ use of claim 12, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises a heavy chain variable domain of SEQ ID NO: 1 and a light chain variable domain of SEQ ID NO: 2.

16. The ~~method~~ use of any of claims 1-15, wherein the diagnosis comprised determining the expression level of NRG1 in a sample from the patient's cancer and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

17. ~~A method of treating head and neck squamous cell carcinoma (HNSCC) in a patient comprising administering~~Use of a therapeutically effective amount of a bispecific HER3/EGFR inhibitor in the manufacture of a medicament for treating head and neck squamous cell carcinoma (HNSCC) in a~~to the~~ patient, wherein the patient, prior to administration of the bispecific HER3/EGFR inhibitor, was diagnosed with a HNSCC which overexpresses NRG1.

18. The ~~method~~ use of claim 17, wherein the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR.

19. The ~~method~~ use of claim 17, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises

a HVR-H1 comprising the amino acid sequence LSGDWIH (SEQ ID NO: 3),

a HVR-H2 comprising the amino acid sequence VGEISAAGGYTD (SEQ ID NO: 4), and

a HVR-H3 comprising the amino acid sequence ARESRVSFEAAMDY (SEQ ID NO: 5),

and

a HVR-L1 comprising the amino acid sequence NIATDVA (SEQ ID NO: 6),

a HVR-L2 comprising the amino acid sequence SASF (SEQ ID NO: 7), and

a HVR-L3 comprising the amino acid sequence SEPEPYT (SEQ ID NO: 8).

20. The ~~method~~ use of claim 19, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises a heavy chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 2.

21. The ~~method~~ use of claim 18, wherein the the antigen binding domain that specifically binds to HER3 and EGFR comprises a heavy chain variable domain of SEQ ID NO: 1 and a light chain variable domain sequence of SEQ ID NO: 2.

22. The ~~method~~ use of any of claims 17-21, wherein the diagnosis comprised determining the expression level of NRG1 in a sample from the patient's HNSCC and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

23. A method for selecting a therapy for a patient with a type of cancer which exhibits autocrine neuregulin-induced signaling comprising determining neuregulin 1 (NRG1) expression in a cancer sample from the patient and selecting a HER3 inhibitor for therapy if the cancer sample overexpresses NRG1.

24. The method of claim 23, wherein the cancer sample expresses NRG1 at a level higher than the median level for NRG1 expression in the cancer type.

25. The method of claim 24, wherein the cancer sample expresses NRG1 at a level which is the 60th percentile or higher for NRG1 expression in the cancer type.

26. The method of claim 24, wherein the cancer sample expresses NRG1 at a level which is the 75th percentile or higher for NRG1 expression in the cancer type.

27. The method of claim 24, wherein the cancer sample expresses NRG1 at a level which is the 80th percentile or higher for NRG1 expression in the cancer type.

28. The method of claim 23, wherein the type of cancer is one which exhibits a bimodal expression profile consisting of an overexpression mode and a lack of overexpression mode.

29. The method of any of claims 23-28, wherein the type of cancer is head and neck squamous cell carcinoma (HNSCC)

30. The method of any of claims 23-29, wherein the HER3 inhibitor inhibits NRG1 binding to HER3.

31. The method of any of claims 23-30, wherein the HER3 inhibitor is an antibody.

32. The method of claim 31, wherein the HER3 inhibitor is a bispecific HER3/EGFR inhibitor.

33. The method of claim 32, wherein the bispecific HER3/EGFR inhibitor is a bispecific antibody which comprises an antigen binding domain that specifically binds to HER3 and EGFR.

34. The method of claim 33, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises

a HVR-H1 comprising the amino acid sequence LSGDWIH (SEQ ID NO: 3),

a HVR-H2 comprising the amino acid sequence VGEISAAGGYTD (SEQ ID NO: 4), and

a HVR-H3 comprising the amino acid sequence ARESRVSFEAAMDY (SEQ ID NO: 5),

and

a HVR-L1 comprising the amino acid sequence NIATDVA (SEQ ID NO: 6),

a HVR-L2 comprising the amino acid sequence SASF (SEQ ID NO: 7), and

a HVR-L3 comprising the amino acid sequence SEPEPYT (SEQ ID NO: 8).

35. The method of claim 34, wherein the antigen binding domain that specifically binds to HER3 and EGFR comprises a heavy chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 2.

36. The method of claim 33, wherein the bispecific antibody comprises a heavy chain variable domain of SEQ ID NO: 1 and a light chain variable domain sequence of SEQ ID NO: 2.

37. The method of any of claims 23-36, wherein NRG1 expression has been determined using polymerase chain reaction (PCR).

38. The method of claim 37, wherein the PCR is quantitative real time polymerase chain reaction (qRT-PCR).

39. The method of any of claims 23-36, wherein NRG1 expression has been determined using IHC.

40. The method of any of claims 23-39, wherein the determining the NRG1 expression in the HNSCC sample comprises determining the expression level of NRG1 in the sample and quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

41. The method of any of claims 23-40, ~~further comprising administering~~wherein a therapeutically effective amount of the HER3 inhibitor is to be administered to the patient.

42. A method of quantifying NRG1 expression level in a cancer sample comprising :

determining the expression level of NRG1 in the sample, and

quantifying the expression level of NRG1 in the sample relative to the expression level of one or both of AL-137727 and VPS33B in the sample.

43. The method of claim 42, wherein the cancer exhibits autocrine neuregulin-induced signaling.

44. The method of claim 42 or 43, wherein the cancer is head and neck squamous cell carcinoma (HNSCC).

45. The method of any of claims 42-44, wherein the expression level of NRG1 and the expression level of the one or both of AL-137727 and VPS33B is determined using polymerase chain reaction (PCR).

46. The method of claim 45, wherein the PCR is quantitative real time polymerase chain reaction (qRT-PCR).

47. The method of any of claims 42-44, wherein the expression level of NRG1 and the expression level of the one or both of AL-137727 and VPS33B is determined using immunohistochemistry (IHC).

48. A HER3 inhibitor for use in the treatment of a type of cancer which overexpresses NRG1.