

CLAIMS

1. Use of ficlatuzumab in the manufacture of a medicament for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in a subject having recurrent or metastatic HNSCC that is identified as human papillomavirus (HPV) negative, wherein the medicament is for use in combination with cetuximab and wherein the treatment comprises (i) administering to the subject the medicament comprising an effective amount of ficlatuzumab, and (ii) administering to the subject an effective amount of cetuximab on the same day.
2. The use of claim 1, wherein if the subject has recurrent or metastatic HNSCC that is HPV positive, the subject is not treated.
3. The use of claims 1 or 2, wherein an HPV status of the HNSCC is determined (i) by p16 immunohistochemistry, wherein the HNSCC is HPV negative when the HNSCC is classified as p16 negative, or the HNSCC is primary oral, laryngeal, or hypopharyngeal HNSCC, and wherein the HNSCC is HPV positive when the HNSCC is classified as p16 positive, or (ii) by tumoral DNA analysis and the HNSCC is HPV negative based on the absence of HPV DNA in the tumor.
4. The use of any one of claims 1-3, wherein the HNSCC in the subject has not been treated previously with cetuximab, wherein the HNSCC in the subject was treated previously with PD-1 or PD-L1 immunotherapy, and/or wherein the HNSCC is PD-1 or PD-L1 immunotherapy-resistant, and wherein the immunotherapy is selected from pembrolizumab, nivolumab, cemiplumab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab or tisotumab.
5. The use of any one of claims 1-4, wherein the HNSCC in the subject was treated previously with platinum chemotherapy comprising carboplatin, cisplatin, nedaplatin, oxaliplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin, and/or wherein the HNSCC is platinum-resistant, or wherein the subject is ineligible for platinum chemotherapy.
6. The use of any one of claims 1-5, wherein the HNSCC in the subject was previously treated (i) with 5 -fluorouracil or another antimetabolite chemotherapy, or (ii) with

pembrolizumab, with or without platinum, and with or without 5 -fluorouracil as a first line therapy, and wherein treating the HNSCC with cetuximab and ficlatuzumab is a second line therapy.

7. The use of any one of claims 1-6, wherein the HNSCC is from a primary site in the oral cavity, pharynx, or larynx, and wherein the HNSCC is hypopharyngeal cancer, laryngeal cancer, lip or oral cavity cancer, nasopharyngeal cancer, oropharyngeal cancer, paranasal sinus or nasal cavity cancer, or salivary gland cancer.

8. The use of any one of claims 1-7, wherein the dose of ficlatuzumab is 10 mg/kg to 100 mg/kg, 10 mg/kg to 50 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg.

9. The use of any one of claims 1-8, wherein the dose of ficlatuzumab is administered every two weeks or every two weeks +/- 3 days by intravenous administration.

10. The use of any one of claims 1-9, wherein the dose of cetuximab is 250 to 700 mg/m², 300 to 500 mg/m², 500 mg/m², 400 mg/m², or 300 mg/m².

11. The use of any one of claims 1-10, wherein the dose of cetuximab is administered every two weeks or every two weeks +/- 3 days by intravenous administration.

12. The use of any one of claims 1-11, wherein the dose of cetuximab and the dose of ficlatuzumab are administered simultaneously or sequentially by intravenous administration.

13. The use of any one of claims 1-12, wherein the subject is administered cetuximab and ficlatuzumab until progression of the HNSCC, development of a new metastasis, or the subject experiences unacceptable toxicity.

14. A method of identifying a subject with a recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that is suitable for a combination therapy with ficlatuzumab and cetuximab, the method comprising assessing whether the HNSCC is human papillomavirus (HPV)-negative or HPV-positive, wherein the subject is identified as suitable for the combination therapy if the HNSCC is human papillomavirus (HPV)-negative, and wherein the combination therapy comprises (i) administering to the subject an effective amount of

ficlatuzumab, and (ii) administering to the subject an effective amount of cetuximab on the same day that the effective amount of ficlatuzumab is administered.

15. The method of claim 14, wherein if the subject is HPV positive, the subject is not suitable for the combination therapy.

16. The method of claim 15, wherein the combination therapy is a second line therapy and wherein the subject is identified as suitable for the combination therapy if the HNSCC is platinum-resistant or the subject is ineligible for platinum chemotherapy and wherein platinum is carboplatin or cisplatin.

17. The method of any one of claims 14-16, wherein the subject is identified as suitable for the combination therapy if (a) the HNSCC is not responsive to immunotherapy with a PD-1 or PD-L1 inhibitor, or (b) the HNSCC is platinum-resistant and not responsive to immunotherapy with a PD-1 or PD-L1 inhibitor and wherein platinum is carboplatin or cisplatin; and,

wherein the immunotherapy is pembrolizumab, nivolumab, cemiplumab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab or tisotumab.

18. The method of any one of claims 14-17, wherein an HPV status of the HNSCC is determined by (a) p16 immunohistochemistry, wherein the HNSCC is HPV negative when the HNSCC is classified as p16 negative and/or the HNSCC is primary site oral, laryngeal, or hypopharyngeal HNSCC, and wherein the HNSCC is HPV positive when the HNSCC is classified as p16 positive; and/or (b) tumoral DNA analysis and the HNSCC is HPV negative based on the absence of HPV DNA in the tumor or HPV positive based on the presence of HPV DNA in the tumor.

19. The method of any one of claims 14-18, wherein the HNSCC is from a primary site in the oral cavity, pharynx, or larynx, and HNSCC is from a primary site in the oral cavity, pharynx, or larynx.

20. The method of any one of claims 14-19, wherein the combination therapy comprises administering a dose of ficlatuzumab that is 10 mg/kg to 100 mg/kg, 10 mg/kg to 50 mg/kg, 20 mg/kg, 15 mg/kg, or 10 mg/kg.

21. The method of any one of claims 14-20, wherein the combination therapy comprises administering a dose of ficlatuzumab and cetuximab every two weeks, or cetuximab every two weeks +/- 3 days by intravenous administration.
22. The method of any one of claims 14-21, wherein the combination therapy comprises administering a dose of cetuximab that is 250 to 700 mg/m², 300 to 500 mg/m², or 500 mg/m².
23. The method of any one of claims 14-22, wherein the combination therapy comprises administering a dose of cetuximab and a dose of ficlatuzumab either simultaneously or sequentially, by intravenous administration.
24. Use of an anti-HGF antibody in the manufacture of a medicament for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in a subject having recurrent or metastatic HNSCC that is identified as human papillomavirus (HPV) negative, wherein the medicament is for use in combination with an anti-EGFR antibody and wherein the treatment comprises (i) administering to the subject a therapeutically effective amount of the anti-HGF antibody and (ii) administering to the subject a therapeutically effective amount of the anti-EGFR antibody on the same day.
25. The use of claim 24, wherein the anti-HGF antibody comprises: (i) an immunoglobulin heavy chain variable region comprising a CDRH1 comprising the amino acid sequence of SEQ ID NO: 1, a CDRH2 comprising the amino acid sequence of SEQ ID NO: 2, and a CDRH3 comprising the amino acid sequence of SEQ ID NO: 3; and (ii) an immunoglobulin light chain variable region comprising a CDRL1 comprising the amino acid sequence of SEQ ID NO: 4, a CDRL2 comprising the amino acid sequence of SEQ ID NO: 5, and a CDRL3 comprising the amino acid sequence of SEQ ID NO: 6; and, wherein the anti-EGFR antibody comprises: (i) an immunoglobulin heavy chain variable region comprising a CDRH1 comprising the amino acid sequence of SEQ ID NO: 9, a CDRH2 comprising the amino acid sequence of SEQ ID NO: 10, and a CDRH3 comprising the amino acid sequence of SEQ ID NO: 11; and (ii) an immunoglobulin light chain variable region comprising a CDRL1 comprising the amino acid sequence of SEQ ID NO: 12, a CDRL2 comprising the amino acid sequence of SEQ ID NO: 13, and a CDRL3 comprising the amino acid sequence of SEQ ID NO: 14.

26. The use of claim 25, wherein the anti-HGF antibody comprises: (i) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 or 17; and (ii) an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or 18, and wherein the anti-EGFR antibody comprises: (i) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 15 or 19; and (ii) an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 16 or 20.

27. The use of any one of claims 24-26, wherein the anti-HGF antibody is ficlatuzumab and the anti-EGFR antibody is cetuximab.

28. The use of any one of claims 24-27, wherein the anti-HGF antibody and the anti-EGFR antibody are administered concurrently or sequentially for at least one cycle of treatment.

29. The use of any one of claims 24-28, wherein the anti-HGF antibody is administered after the anti-EGFR antibody for at least one cycle of treatment.

30. The use of any one of claims 24-29, wherein the anti-HGF antibody and the anti-EGFR antibody are each administered about every week, about every two weeks, about every three weeks, or about every four weeks.

31. The use of any one of claims 24-30, wherein the anti-HGF antibody is administered at about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, or about 25 mg/kg, and wherein the anti-EGFR antibody is administered at about 200 mg/m², about 250 mg/m², about 300 mg/m², about 400 mg/m², about 500 mg/m², about 600 mg/m², about 700 mg/m², or about 800 mg/m².

32. The use of any one of claims 24-31, wherein the anti-HGF antibody and the anti-EGFR antibody are administered by intravenous infusion.

33. The use of any one of claims 24-32, wherein the treatment comprises administering to the subject (i) 20 mg/kg ficlatuzumab, and (ii) 500 mg/m² cetuximab every two weeks.