Claims

1. An interleukin-2/interleukin-15 receptor βγ (IL-2/IL-15Rβγ) agonist for use in the treatment of squamous cell carcinoma in a human patient.

2. The IL-2/IL-15Rβγ agonist for the use of claim 1, whereas the squamous cell carcinoma is selected from the group consisting of skin squamous cell carcinoma, non-small-cell lung carcinoma (NSCLC), especially squamous-cell carcinoma of the lung (SCC), squamous cell thyroid carcinoma, head and neck squamous cell carcinoma (HNSCC), oral squamous cell carcinoma, oropharyngeal squamous cell carcinoma, and laryngeal squamous cell carcinoma, esophageal squamous cell carcinoma, esophageal and gastro-esophageal junction cancer squamous cell carcinoma, vaginal squamous-cell carcinoma, penile squamous cell carcinoma, anal squamous cell carcinoma, prostate squamous cell carcinoma, and bladder squamous cell carcinoma, especially skin squamous cell carcinoma.

3. The IL-2/IL-15Rβγ agonist for the use of claim 1 or claim 2, whereas the patient is resistant or refractory to at least one immune checkpoint inhibitor treatment.

4. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 3, wherein the IL-2/IL-15Rβγ agonist is not administered in combination with an immune checkpoint inhibitor.

5. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 3, wherein the IL-2/IL-15Rβγ agonist is not administered in combination with a PD-1 antagonist.

6. The IL-2/IL-15Rβγ agonist for the use of claim 3, wherein the IL-2/IL-15Rβγ agonist is not administered in combination with the immune checkpoint inhibitor the patient is refractory or resistant to, preferably wherein the immune checkpoint inhibitor the patient is refractory or resistant to and that is not administered in combination is a PD-1 antagonist.

7. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 3, wherein the IL-2/IL-15Rβγ agonist is administered in combination with an immune checkpoint inhibitor.

8. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 3 and 7, wherein the IL-2/IL-15Rβγ agonist is administered in combination with a PD-1 antagonist.

9. The IL-2/IL-15Rβγ agonist for the use of any one of claims 3, 7 and 8, wherein the IL-2/IL-15Rβγ agonist is administered in combination with the immune checkpoint inhibitor the patient is refractory or resistant to, preferably wherein the immune checkpoint inhibitor the patient is refractory or resistant to and that is administered in combination is a PD-1 antagonist.

10. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 9, wherein the treatment of the cancer results in at least about 30% size reduction of the tumor present prior to the treatment, preferably about 30% size reduction within 16 weeks of the treatment, preferably about 50% size reduction within 16 weeks of the treatment.

11. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 10, wherein the response to the IL-2/IL-15Rβγ agonist is mediated by the innate immune response mediated by NK cells.

12. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 11, whereas the IL-2/IL-15Rβγ agonist is administered according to a cyclical administration regimen, wherein the cyclical administration regimen comprises:

(a) a first period of x days during which the IL-2/IL-15Rβγ agonist is administered at a daily dose on y consecutive days at the beginning of the first period followed by x-y days without administration of the IL-2/IL-15Rβγ agonist,
wherein x is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days, preferably, 7 or 14 days, and y is 2, 3 or 4 days, preferably 2 or 3 days;

(b) repeating the first period at least once; and

(c) a second period of z days without administration of the IL-2/IL-15Rβγ agonist,
wherein z is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, 35, 42, 49, 56, 63 or 70 days, preferably 7, 14, 21 or 56 days, more preferably 7, 14 or 21 days.

13. The IL-2/IL-15Rβγ agonist for the use of claim 12, wherein x is 7 days, y is 2, 3 or 4 days and z is 7 days, preferably wherein y is 2 days and z is 7 days.

14. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 13, wherein the daily dose of the IL-2/IL-15Rβγ agonist is 0.1 µg/kg to 50 µg/kg, preferably 0.25 µg/kg to 25 µg/kg, more preferably 0.6 µg/kg to 12 µg/kg and even more preferably 2 µg/kg to 12 µg/kg, preferably 3 µg/kg to 20 µg/kg, more preferably 6 to 12 µg/kg.

15. The IL-2/IL-15Rβγ agonist for the use of any one of claims 1 to 14, wherein the IL-2/IL-15Rβγ agonist is an interleukin-15 (IL-15)/interleukin-15 receptor alpha (IL-15Rα) complex, preferably a fusion protein comprising the human IL-15Rα sushi domain or derivative thereof, a

~~flexible linker and the human IL-15 or derivative thereof, preferably wherein the human IL-15Rα sushi domain comprises the sequence of SEQ ID NO: 6, and wherein the human IL-15 comprises the sequence of SEQ ID NO: 4, more preferably wherein the IL-15/IL-15Rα complex is SEQ ID NO: 9.~~

Claims

1. ~~An~~ Use of an interleukin 15 (IL-15)/interleukin-15 receptor alpha (IL-15Rα) complex ~~for use~~ in the manufacture of a medicament for the treatment of squamous cell carcinoma in a human patient, wherein the patient is resistant or refractory to at least one immune checkpoint inhibitor treatment.

2. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 1, whereas the squamous cell carcinoma is selected from the group consisting of skin squamous cell carcinoma, non-small-cell lung carcinoma (NSCLC), especially squamous-cell carcinoma of the lung (SCC), squamous cell thyroid carcinoma, head and neck squamous cell carcinoma (HNSCC), oral squamous cell carcinoma, oropharyngeal squamous cell carcinoma, and laryngeal squamous cell carcinoma, esophageal squamous cell carcinoma, esophageal and gastro-esophageal junction cancer squamous cell carcinoma, vaginal squamous-cell carcinoma, penile squamous cell carcinoma, anal squamous cell carcinoma, prostate squamous cell carcinoma, and bladder squamous cell carcinoma, especially skin squamous cell carcinoma.

3. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 1 or claim 2, wherein the IL-15/IL-15Rα complex is not ~~administered~~to be administered in combination with an immune checkpoint inhibitor.

4. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 1 or claim 2, wherein the IL-15/IL-15Rα complex is not ~~administered~~to be administered in combination with a PD-1 antagonist.

5. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 1, wherein the IL-15/IL-15Rα complex is not ~~administered~~to be administered in combination with the immune checkpoint inhibitor the patient is refractory or resistant to, preferably wherein the immune checkpoint inhibitor the patient is refractory or resistant to and that is not ~~administered~~to be administered in combination is a PD-1 antagonist.

6. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 1 or claim 2, wherein the IL-15/IL-15Rα complex is ~~administered~~to be administered in combination with an immune checkpoint inhibitor.

7. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1-, 2 and 6, wherein the IL-15/IL-15Rα complex is ~~administered~~to be administered in combination with a PD-1 antagonist.

8. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1, 6 and 7, wherein the IL-15/IL-15Rα complex is ~~administered~~to be administered in combination with the immune checkpoint inhibitor the patient is refractory or resistant to, preferably wherein the immune checkpoint inhibitor the patient is refractory or resistant to and that is ~~administered~~to be administered in combination is a PD-1 antagonist.

9. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1 to 8, wherein the treatment of the cancer results in at least about 30% size reduction of the tumor present prior to the treatment, preferably about 30% size reduction within 16 weeks of the treatment, preferably about 50% size reduction within 16 weeks of the treatment.

10. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1 to 9, wherein the response to the IL-15/IL-15Rα complex is mediated by the innate immune response mediated by NK cells.

11. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1 to 10, whereas the IL-15/IL-15Rα complex is ~~administered~~to be administered according to a cyclical administration regimen, wherein the cyclical administration regimen comprises:
    (a) a first period of x days during which the IL-15/IL-15Rα complex is ~~administered~~to be administered at a daily dose on y consecutive days at the beginning of the first period followed by x-y days without administration of the IL-15/IL-15Rα complex, wherein x is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days, preferably, 7 or 14 days, and y is 2, 3 or 4 days, preferably 2 or 3 days;
    (b) repeating the first period at least once; and
    (c) a second period of z days without administration of the IL-15/IL-15Rα complex, wherein z is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, 35, 42, 49, 56, 63 or 70 days, preferably 7, 14, 21 or 56 days, more preferably 7, 14 or 21 days.

12. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of claim 11, wherein x is 7 days, y is 2, 3 or 4 days and z is 7 days, preferably wherein y is 2 days and z is 7 days.

13. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1 to 12, wherein the daily dose of the IL-15/IL-15Rα complex is 0.1 µg/kg to 50 µg/kg, preferably 0.25 µg/kg to 25 µg/kg, more preferably 0.6 µg/kg to 12 µg/kg and even more preferably 2 µg/kg to 12 µg/kg, preferably 3 µg/kg to 20 µg/kg, more preferably 6 to 12 µg/kg.

14. ~~The IL-15/IL-15Rα complex for the use~~Use of the IL-15/IL-15Rα complex of any one of claims 1 to 13, wherein the IL-15/ IL-15Rα complex is a fusion protein comprising the human IL-15Rα sushi domain or derivative thereof, a flexible linker and the human IL-15 or derivative thereof, preferably wherein the human IL-15Rα sushi domain comprises the sequence of SEQ ID NO: 6, and wherein the human IL-15 comprises the sequence of SEQ ID NO: 4, more preferably wherein the IL-15/IL-15Rα complex is SEQ ID NO: 9.