

Claims

1. An interleukin-2/interleukin-15 receptor $\beta\gamma$ (IL-2/IL-15R $\beta\gamma$) agonist for use in treating or managing cancer or infectious diseases, wherein the IL-2/IL-15R $\beta\gamma$ agonist is to be administered to a human patient using a cyclical administration regimen, wherein the cyclical administration regimen comprises:
 - (a) a first period of x days during which the IL-2/IL-15R $\beta\gamma$ agonist is 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-2/IL-15R $\beta\gamma$ 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-15R $\beta\gamma$ 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 or 21 days.
2. The IL-2/IL-15R $\beta\gamma$ agonist for use of claim 1, wherein the IL-2/IL-15R $\beta\gamma$ agonist is to be administered to a human patient using a cyclical administration regimen, wherein the cyclical administration regimen comprises:
 - (a) a first period of x days during which the IL-2/IL-15R $\beta\gamma$ agonist is 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-2/IL-15R $\beta\gamma$ agonist, wherein x is 5, 6, 7, 8 or 9 days, preferably, 6, 7 or 8 days, more preferably 7 days, and y is 2, 3 or 4 days, preferably 2 or 3 days, more preferably 2 days;
 - (b) repeating the first period at least once; and
 - (c) a second period of z days without administration of the IL-2/IL-15R $\beta\gamma$ agonist, wherein z is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 days, preferably 7 or 14 days, more preferably 7 days.

3. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 or 2, 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.
4. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 to 3, wherein the daily dose is 0.1 $\mu\text{g/kg}$ to 50 $\mu\text{g/kg}$, preferably 0.25 $\mu\text{g/kg}$ to 25 $\mu\text{g/kg}$, more preferably 3 $\mu\text{g/kg}$ to 20 $\mu\text{g/kg}$, even
5 more preferably 6 to 12 $\mu\text{g/kg}$.
5. The IL-2/IL-15R $\beta\gamma$ agonist for use of claim 4, wherein the daily dose selected within the dose range of 0.1 to 50 $\mu\text{g/kg}$ is not substantially increased during the administration regimen, preferably wherein the dose is maintained during the administration regimen.
6. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 to 3, wherein the daily dose is a fixed
10 dose independent of body weight of 7 μg to 3500 μg , preferably 17.5 μg to 1750 μg , more preferably 42 μg to 700 μg and especially 140 μg to 700 μg .
7. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 to 4 or 6, wherein the daily dose is increased during the administration regimen, preferably wherein the daily dose is increased after each period of x days, more preferably wherein the daily dose is increased by 20% to
15 100%, especially by 30% to 50% after each period of x days.
8. The IL-2/IL-15R $\beta\gamma$ agonist for use of claim 7, wherein the daily dose is increased once after the first period of x days.
9. The IL-2/IL-15R $\beta\gamma$ agonist for use of claim 8, wherein the daily dose is increased by 20% to 100%, preferably by 30% to 50% after the first period of x days.
- 20 10. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 to 9, wherein the daily dose is to be administered in a single injection.
11. The IL-2/IL-15R $\beta\gamma$ agonist for use of any of claims 1 to 9, wherein the daily dose is split into 2 or 3 individual doses that are to be administered within one day, wherein the time interval between administration of the individual doses is at least about 4 h and preferably not more
25 than 14 h, more preferably wherein the daily dose is split into 3 individual doses that are to be administered within one day, wherein the time interval between administration of the individual doses is about 5 to about 7 h, especially about 6 h, or wherein the daily dose is split into 2 individual doses that are to be administered within one day, wherein the time interval between administration of the individual doses is about 6 h to about 10 h, especially about 8 h.

12. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 11, wherein the IL-2/IL-15R $\beta\gamma$ agonist is to be administered subcutaneously (s.c.) or intraperitoneally (i.p.), preferably s.c..
13. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 12, wherein administration of the IL-2/IL-15R $\beta\gamma$ agonist in step (a) results in
 - (1) an increase of the % of Ki-67⁺ NK of total NK cells in comparison to no administration of the IL-2/IL-15R $\beta\gamma$ agonist, and wherein administration of the IL-2/IL-15R $\beta\gamma$ agonist in step (b) results in a Ki-67⁺ NK cell level that is at least 70% of the of the Ki-67⁺ NK cells of step (a), or
 - (2) maintenance of NK cell numbers or preferably an increase of NK cell numbers to at least 110% as compared to no administration of IL-2/IL-15R $\beta\gamma$ agonist after at least one repetition of the first period, preferably after at least two repetitions of the first period, and/or
 - (3) NK cell numbers of at least 1.1×10^3 NK cells/ μ l after at least one repetition of the first period, preferably after at least two repetitions of the first period.
14. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 13, wherein the cyclic administration is repeated over at least 3 cycles, preferably 5 cycles, more preferably at least 10 cycles and even more preferably until disease progression.
15. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 14, wherein the IL-2/IL-15R $\beta\gamma$ agonist has an *in vivo* half-life of 30 min to 24 h, preferably 1 h to 12 h, more preferably of 2 h to 6 h.
16. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 15, wherein the IL-2/IL-15R $\beta\gamma$ agonist is an interleukin 15 (IL-15)/interleukin-15 receptor alpha (IL-15R α) complex, preferably a fusion protein comprising the human IL-15R α sushi domain or derivative thereof, a flexible linker and the human IL-15 or derivative thereof, preferably wherein the human IL-15R α 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-15R α complex is SEQ ID NO: 9.
17. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 1 to 16, wherein a further therapeutic agent is to be administered in combination with the IL-2/IL-15R $\beta\gamma$ agonist, preferably wherein the further therapeutic agent and the IL-2/IL-15R $\beta\gamma$ agonist are to be administered on the same days and/or on different days.

18. The IL-2/IL-15R $\beta\gamma$ agonist for use according to claim 17, wherein the further therapeutic agent is selected from a checkpoint inhibitor, preferably an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-LAG-3 antibody, an anti-TIM-3 antibody, an anti-CTLA4 antibody or an anti-TIGIT antibody, more preferably an anti-PD-L1 antibody or an anti-PD-1 antibody, or a therapeutic antibody, preferably an anti-CD38 antibody, an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD30 antibody, an anti-CD33 antibody, an anti-CD52 antibody, an anti-CD79B antibody, an anti-EGFR antibody, an anti-HER2 antibody, an anti-VEGFR2 antibody, an anti-GD2 antibody, an anti-Nectin 4 antibody and an anti-Trop-2 antibody, more preferably an anti-CD38 antibody, especially wherein in weeks with anti-CD38 antibody administration, the anti-CD38 antibody is to be administered on the 1st day or the 3rd day of the week.
19. The IL-2/IL-15R $\beta\gamma$ agonist for use according to claim 18, wherein the checkpoint inhibitor or therapeutic antibody is to be administered at the beginning of the first period (a) of each cycle.
20. The IL-2/IL-15R $\beta\gamma$ agonist for use according to claim 18 or claim 19, wherein the x days and z days are adapted that an integral multiple of x days + z days equal the days of one treatment cycle of the checkpoint inhibitor or the therapeutic antibody, or if the treatment cycle of the checkpoint inhibitor or the therapeutic antibody changes over time, equal to each individual treatment cycle of the checkpoint inhibitor or the therapeutic antibody.
21. An IL-2/IL-15R $\beta\gamma$ agonist for use in treating or managing cancer or infectious diseases, wherein the IL-2/IL-15R $\beta\gamma$ agonist is to be administered according to the following administration regimen
- (i) administration of the IL-2/IL-15R $\beta\gamma$ agonist to a human patient at a daily dose on a first number of consecutive days; and
 - (ii) a second number of days without administration of the IL-2/IL-15R $\beta\gamma$ agonist,
- wherein the first number is 2, 3 or 4 days and the second number is 3, 4, or 5 days, wherein the first number and second add up to 7 days, preferably wherein the first number is 2 days and the second number is 5 days,

wherein the administration regimen is repeated at least once, preferably at least twice, more preferably at least 4 times, most preferably until disease progression.

22. The IL-2/IL-15R $\beta\gamma$ agonist for use of claim 21, wherein the daily dose is 0.1 to 50 $\mu\text{g/kg}$, preferably wherein the dose of 0.1 to 50 $\mu\text{g/kg}$ is not substantially increased during the administration regimen, preferably wherein the dose is maintained during the administration regimen.
23. The IL-2/IL-15R $\beta\gamma$ agonist for use according to claim 21 or claim 22, wherein administration of the IL-2/IL-15R $\beta\gamma$ agonist in step (i) results in
 - (1) an increase of the % of Ki-67⁺ NK of total NK cells in comparison to no administration of the IL-2/IL-15R $\beta\gamma$ agonist, and wherein administration of the IL-2/IL-15R $\beta\gamma$ agonist after the first repetition results in a Ki-67⁺ NK cell level that is at least 70% of the of the Ki-67⁺ NK cells of step (i),
 - (2) maintenance of NK cell numbers or preferably an increase of NK cell numbers to at least 110% as compared to no administration of IL-2/IL-15R $\beta\gamma$ agonist after at least one repetition of the period (i), preferably after at least two repetitions of the period (i), and/or
 - (3) NK cell numbers of at least 1.1×10^3 NK cells/ μl after at least one repetition of the period (i), preferably after at least two repetitions of the first period.
24. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of the claims 21 to 23, wherein the IL-2/IL-15R $\beta\gamma$ agonist has an *in vivo* half-life of 30 min to 24 h, preferably 1 h to 12 h, more preferably of 2 h to 6 h.
25. An IL-2/IL-15R $\beta\gamma$ agonist for use according to any of the claims 21 to 24, wherein the IL-2/IL-15R $\beta\gamma$ agonist is an IL-15/interleukin-15 receptor alpha (IL-15R α) complex, preferably wherein the IL-15/IL-15R α complex is a fusion protein comprising the human IL-15R α sushi domain or derivative thereof, a flexible linker and the human IL-15 or derivative thereof, preferably wherein the human IL-15R α 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-15R α complex is SEQ ID NO: 9.
26. The IL-2/IL-15R $\beta\gamma$ agonist for use according to any of claims 21 to 25, wherein a further therapeutic agent is to be administered in combination with the IL-2/IL-15R $\beta\gamma$ agonist, preferably wherein the further therapeutic agent and the IL-2/IL-15R $\beta\gamma$ agonist are to be administered on the same days and/or on different days.

27. The IL-2/IL-15R $\beta\gamma$ agonist for use according to claim 26, wherein the further therapeutic agent is selected from (i) a checkpoint inhibitor, preferably an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-LAG-3 antibody, an anti-TIM-3 antibody, an anti-CTLA4 antibody or an anti-TIGIT antibody, more preferably an anti-PD-L1 antibody or an anti-PD-1 antibody, or
- 5 (ii) a therapeutic antibody, preferably an anti-CD38 antibody, an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD30 antibody, an anti-CD33 antibody, an anti-CD52 antibody, an anti-CD79B antibody, an anti-EGFR antibody, an anti-HER2 antibody, an anti-VEGFR2 antibody, an anti-GD2 antibody, an anti-Nectin 4 antibody and an anti-Trop-2 antibody, more
- 10 preferably an anti-CD38 antibody.