

WHAT IS CLAIMED IS:

1. Use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein

the IL-15/IL-15R α heterodimeric Fc fusion protein comprises:

a) a first monomer comprising, from N- to C-terminal:

i) an IL-15 receptor alpha (IL-15R α) sushi domain;

ii) a first domain linker; and

iii) a first variant Fc domain comprising CH2-CH3; and

b) a second monomer comprising from N- to C-terminal:

i) a variant IL-15 domain comprising the amino acid sequence of SEQ ID NO:2 and any one of the amino acid substitutions selected from the group consisting of N4D/N65D, D30N/N65D, and D30N/E64Q/N65D;

ii) a second domain linker; and

iii) a second variant Fc domain comprising CH2-CH3;

wherein the first and second variant Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering; and

wherein the checkpoint blockade antibody is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-TIGIT antibody, an anti-LAG3 antibody, and an anti-CTLA-4 antibody.

2. Use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of medicament for inducing T cell expansion in a patient,

wherein the protein comprises:

a) a first monomer comprising, from N- to C-terminal:

i) an IL-15 receptor alpha (IL-15R α) sushi domain;

ii) a first domain linker; and

iii) a first variant Fc domain comprising CH2-CH3; and

b) a second monomer comprising from N- to C-terminal:

i) a variant IL-15 domain comprising the amino acid sequence of SEQ ID NO:2 and any one of the amino acid substitutions selected from the group consisting of N4D/N65D, D30N/N65D, and D30N/E64Q/N65D;

ii) a second domain linker; and

iii) a second variant Fc domain comprising CH2-CH3;

wherein the first and second variant Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S :

S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K;

L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering; and

wherein the checkpoint blockade antibody is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-TIGIT antibody, an anti-LAG3 antibody, and an anti-CTLA-4 antibody.

3. The use according to claim 1 or 2, wherein the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/E64Q/N65D.

4. The use according to any previous claim, wherein the IL-15R α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

5. The use according to any previous claim, wherein the first and second variant Fc domains have S364K/E357Q : L368D/K370S substitutions.

6. The use according to any previous claim, wherein the first variant Fc domain has S364K/E357Q substitutions and the second variant Fc domain L368D/K370S substitutions.

7. The use according to any previous claim, wherein the first and second variant Fc domains each comprise M428L/N434S substitutions.

8. The use according to any previous claim, wherein the first and second variant Fc domains each comprise E233P/L234V/L235A/G236del/S267K substitutions.

9. The use according to any previous claim, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein and the checkpoint blockade antibody are administered concomitantly or sequentially.

10. The use according to any previous claim, wherein the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.
11. The use according to any previous claim, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 or XENP24045.
12. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is nivolumab.
13. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is pembrolizumab.
14. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is pidilizumab.
15. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24045 (SEQ ID NO:XX) and the anti-PD-1 antibody is nivolumab.
16. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24045 (SEQ ID NO:XX) and the anti-PD-1 antibody is pembrolizumab.
17. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24045 (SEQ ID NO:XX) and the anti-PD-1 antibody is pidilizumab.
18. The use according to any previous claim, wherein the cancer is metastatic cancer.
19. The use according to any previous claim, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, colon cancer, ovarian cancer, melanoma cancer, bladder cancer, renal cancer, kidney cancer, liver cancer, head and

neck cancer, colorectal cancer, melanoma, pancreatic cancer, gastric carcinoma cancer, esophageal cancer, mesothelioma, prostate cancer, leukemia, lymphoma, and myeloma.

20. The use according to any previous claim, wherein the method results in a minimal level of vascular leakage in the patient.

21. The use according to claim 20, wherein the level of vascular leakage ranges from a 20% reduction or less in serum albumin in the patient following administration.

22. The use according to any one of claims 2 to 21, wherein the T cell expansion is at least a 2-fold increase in T cells.

23. The use according to any one of claims 2 to 22, wherein the T cell expansion ranges from a 2-fold to a 15-fold increase in T cells.

24. The use according to any one of claims 1 to 23, wherein the method does not increase the likelihood of inducing hypoalbuminemia.

25. The use according to any one of claims 2 to 24, wherein the T cells comprise tumor infiltrating lymphocytes.

26. A combination therapy comprises an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody selected from an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-TIGIT antibody, an anti-LAG3 antibody, and an anti-CTLA-4 antibody,

wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises:

a) a first monomer comprising, from N- to C-terminal:

i) an IL-15 receptor alpha (IL-15R α) sushi domain;

ii) a first domain linker; and

iii) a first variant Fc domain comprising CH2-CH3; and

b) a second monomer comprising from N- to C-terminal:

i) a variant IL-15 domain comprising the amino acid sequence of SEQ ID NO:2 and any one of the amino acid substitutions selected from the group consisting of N4D/N65D, D30N/N65D, and D30N/E64Q/N65D;

ii) a second domain linker; and

iii) a second variant Fc domain comprising CH2-CH3;

the first and second variant Fc domains have a set of amino acid substitutions selected from the group consisting of S267K/L368D/K370S : S267K/S364K/E357Q; S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q, according to EU numbering.