

in tumor-infiltrating lymphocytes (TILs), and immune checkpoint ligands are overexpressed on tumor cells, contributing to immune escape by tumor cells. De-repression of TILs by blockade of immune checkpoint interactions by drugs such as Opdivo® (nivolumab) and Keytruda® (pembrolizumab) have proven highly effective in treatment of cancer. Despite the promise of checkpoint blockade therapies such as nivolumab and pembrolizumab, many patients still fail to achieve sufficient response to checkpoint blockade alone.

[0005] Therefore, there remains an unmet need in oncology treatment for therapeutic strategies with cytokines which do not require high doses and are targeted to tumors to avoid systemic toxicity. Further, there is a need to identify additional therapeutic modalities to stack with checkpoint blockade that could increase patient response rate. The present invention addresses these needs and caveats by providing reduced potency IL-15/R α -Fc fusion proteins with enhanced pharmacokinetics and pharmacodynamics, and which synergistically combine with checkpoint blockade antibodies.

BRIEF SUMMARY OF THE INVENTION

[0006] The present ~~invention~~disclosure is directed to administering a novel IL-15/IL-15R α heterodimeric Fc fusion protein in combination with a checkpoint blockade antibody. In some ~~embodiment~~examples, the checkpoint blockade antibody 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.

[0006a] In one aspect, the present disclosure refers to the 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.

[0006b] In another aspect, the present disclosure refers to the 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.

[0006c] In another aspect, the present disclosure refers to the use of an IL15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of a medicament for combination therapy to treat cancer in a patient in need thereof, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLES GDASIHDTVQDLIILA NNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQMFIN TSGGGGSEPKSSDKTHTCPPCPAPPVA GPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVS GFYPSDIAVEWESDGPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYT QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes ITCPPPMSEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCI RGGG GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006d] In another aspect, the present disclosure refers to the use of an IL15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of a medicament for combination therapy to induce T-cell expansion in a patient, wherein the protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLES GDASIHDTVQDLIILA NNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQMFIN TSGGGGSEPKSSDKTHTCPPCPAPPVA GPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVS GFYPSDIAVEWESDGPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYT QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide

that encodes

ITCPPPMSEVHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIIRGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPOVY
TLPPSREQMTKNQVKLTCLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQOGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006e] In another aspect, the present disclosure refers to a combination therapy comprising 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.

[0006f] In another aspect, the present disclosure refers to the use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a patient in need thereof, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes NWVNISDLKKIEDLIQSMHIDATLYTESNVHPSCVTAMKCFLELQVISLESGDASIHDTVQDLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHVHVMFINTSGGGGSEPKSSDKTHTCPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPOVYTLPPSREEMTKNQVSLTCDVS
GFYPSDIAVEWESDGPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFCSVLHEALHSHYT
QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

ITCPPPMSEVHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIIRGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPOVY
TLPPSREQMTKNQVKLTCLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQOGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006g] In another aspect, the present disclosure refers to the use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of a medicament for combination therapy to treat 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.

[0006h] In another aspect, the present disclosure refers to the use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of medicament for combination therapy to induce 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.

[0006i] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a patient in need thereof, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESQDASIHDTVQDLIILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHVQMFINTSGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFCVSLHEALHSHYTQKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes ITCPPPMSEVHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIIRGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCVSLHEALHSHYTQKSLSLSPGK; 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.

[0006j] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to induce T-cell expansion in a patient, wherein the protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLES GDASIHD TVQDLIILA
NNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQMFINTSGGGGSEPKSSDKTHTCPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVS
GFYPSDIAVEWESDGPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDV FSCSVLHEALHSHYT
QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

ITCPPPMSEVHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQENNYKTTTPVLDS DGSFFLYSKLTVDKSR
WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006k] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat 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.

[0006l] In another aspect, the present disclosure refers to the use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to induce 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.

[0006m] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for treating cancer in a patient in need thereof, wherein said medicament is to be administered in combination with a checkpoint blockade antibody, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLES GDASIHDTVQDLIILA
NNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGGGSEPKSSDKTHTCPPCPAPPVA
GPSVFLFPPKPKDTLMISRTP E V T C V V V D V K H E D P E V K F N W Y V D G V E V H N A K T K P R E E E Y N S T Y R V V
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVS
GFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYT
QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

ITCPPPMSEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTP E V T C V V V D V K H E D P E V K F N W Y V D G V
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006n] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for inducing T-cell expansion in a patient, wherein said medicament is to be administered in combination with a checkpoint blockade antibody, wherein the protein comprises: a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLES GDASIHDTVQDLIILA
NNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGGGSEPKSSDKTHTCPPCPAPPVA
GPSVFLFPPKPKDTLMISRTP E V T C V V V D V K H E D P E V K F N W Y V D G V E V H N A K T K P R E E E Y N S T Y R V V
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVS
GFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYT
QKSLSLSPGK; and b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

ITCPPPMSEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTP E V T C V V V D V K H E D P E V K F N W Y V D G V
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

[0006o] In another aspect, the present disclosure refers to of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for treating cancer in a patient in need thereof, wherein said medicament is to be administered in combination with a checkpoint blockade 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; 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.

[0006p] In yet another aspect, the present disclosure refers to the use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for inducing T-cell expansion in a patient, wherein said medicament is to be administered in combination with a checkpoint blockade antibody, 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.

[0007] In some [aspectexamples](#), provided herein is a method of treating cancer in a patient in need thereof comprising administering:

a therapeutically effective amount of an IL-15/IL-15R α heterodimeric Fc fusion protein comprising:

- 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

a therapeutically effective amount of a checkpoint blockade antibody 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.

[0008] In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/E64Q/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/N65D. In some [embodimentexample](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions N4D/N65D.

[0009] In some [embodimentexamples](#), the IL-15R α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

[0010] In some [embodimentexamples](#), the first and second variant Fc domains have S364K/E357Q : L368D/K370S substitutions. In some [embodimentexamples](#), the first variant Fc domain has S364K/E357Q substitutions and the second variant Fc domain L368D/K370S substitutions.

[0011] In some [embodimentexamples](#), the first and second variant Fc domains each comprise M428L/N434S substitutions.

[0012] In some [embodimentexample](#), the first and second variant Fc domains each comprise E233P/L234V/L235A/G236del/S267K substitutions.

[0013] In some [embodimentexamples](#), the IL-15/IL-15R α heterodimeric Fc fusion protein and the checkpoint blockade antibody are administered concomitantly or sequentially.

[0014] In some [embodimentexamples](#), the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.

[0015] In some [embodimentexamples](#), the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 or XENP24045.

[0016] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0017] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0018] In some [embodimentexamples](#), the cancer is metastatic cancer. In some [embodimentexamples](#), 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.

[0019] In some [embodimentexamples](#), the method of treating cancer outlined herein results in a minimal level of vascular leakage in the patient.

[0020] In some [embodimentexamples](#), the level of vascular leakage ranges from a 20% reduction or less in serum albumin in the patient following administration.

[0021] In some [aspectexamples](#), provided herein is a method of treating cancer in a patient, the method comprising administering a combination therapy comprising an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody to the patient, wherein the IL-15/IL-15R α heterodimeric Fc fusion 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 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.

[0022] In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/E64Q/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions N4D/N65D.

[0023] In some [embodimentexamples](#), the IL-15R α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

[0024] In some [embodimentexamples](#), the first and second variant Fc domains have S364K/E357Q : L368D/K370S substitutions. In some [embodimentexamples](#), the first variant Fc domain has S364K/E357Q substitutions and the second variant Fc domain L368D/K370S substitutions.

[0025] In some [embodimentexamples](#), the first and second variant Fc domains each comprise M428L/N434S substitutions.

[0026] In some [embodimentexamples](#), the first and second variant Fc domains each comprise E233P/L234V/L235A/G236del/S267K substitutions.

[0027] In some [embodimentexamples](#), the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.

[0028] In some [embodimentexamples](#), the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) or XENP24045 (SEQ ID NO:XX).

[0029] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0030] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0031] In some [embodimentexamples](#), the cancer is metastatic cancer. In some [embodimentexamples](#), 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.

[0032] In some [embodiment examples](#), the method of treating cancer described herein results in a minimal level of vascular leakage in the patient.

[0033] In some [embodiment examples](#), the level of vascular leakage ranges from a 20% reduction or less in serum albumin in the patient following administration.

[0034] In some [aspect examples](#), provided herein is a method of inducing T cell expansion in a patient comprising administering:

a therapeutically effective amount of an IL-15/IL-15R α heterodimeric Fc fusion protein comprising:

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

a therapeutically effective amount of a checkpoint blockade antibody 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.

[0035] In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/E64Q/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/N65D. In some [embodimentexample](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions N4D/N65D.

[0036] In some [embodimentexamples](#), the IL-15 α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

[0037] In some [embodimentexamples](#), the first and second variant Fc domains have S364K/E357Q : L368D/K370S substitutions. In some [embodimentexamples](#), the first variant Fc domain has S364K/E357Q substitutions and the second variant Fc domain L368D/K370S substitutions.

[0038] In some [embodimentexamples](#), the first and second variant Fc domains each comprise M428L/N434S substitutions.

[0039] In some [embodimentexample](#), the first and second variant Fc domains each comprise E233P/L234V/L235A/G236del/S267K substitutions.

[0040] In some [embodimentexamples](#), the IL-15/IL-15 α heterodimeric Fc fusion protein and the checkpoint blockade antibody are administered concomitantly or sequentially.

[0041] In some [embodimentexample](#), the e anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab. In some [embodimentexamples](#), the the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) or XENP24045 (SEQ ID NO:XX).

[0042] In some [embodimentexamples](#), the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is nivolumab. In some [embodimentexample](#), the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is pembrolizumab. In some [embodimentexamples](#), the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) and the anti-PD-1 antibody is pidilizumab.

[0043] In some [embodimentexamples](#), the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24045 (SEQ ID NO:XX) and the anti-PD-1 antibody is

nivolumab. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0044] In some [embodimentexamples](#), the patient has cancer. In some [embodimentexamples](#), the cancer is metastatic cancer. In some [embodimentexamples](#), 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.

[0045] In some [embodimentexamples](#), the T cell expansion is at least a 2-fold increase in T cells. In some [embodimentexamples](#), the T cell expansion ranges from a 2-fold to a 15-fold increase in T cells.

[0046] In some [embodimentexamples](#), the method does not increase the likelihood of inducing hypoalbuminemia.

[0047] In some [embodimentexamples](#), the T cells comprise tumor infiltrating lymphocytes.

[0048] In some [aspectexamples](#), the present [inventiondisclosure](#) provides a combination therapy comprising 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. In some [embodimentexamples](#), 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.

[0049] In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/E64Q/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions D30N/N65D. In some [embodimentexamples](#), the variant IL-15 domain comprises the amino acid sequence of SEQ ID NO:2 and the amino acid substitutions N4D/N65D.

[0050] In some [embodimentexamples](#), the IL-15R α sushi domain comprises the amino acid sequence of SEQ ID NO:4.

[0051] In some [embodimentexamples](#), the first and second variant Fc domains have S364K/E357Q : L368D/K370S substitutions. In some [embodimentexamples](#), the first variant Fc domain has S364K/E357Q substitutions and the second variant Fc domain L368D/K370S substitutions.

[0052] In some [embodimentexamples](#), the first and second variant Fc domains each comprise M428L/N434S substitutions.

[0053] In some [embodimentexamples](#), the first and second variant Fc domains each comprise E233P/L234V/L235A/G236del/S267K substitutions.

[0054] In some [embodimentexample](#), the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.

[0055] In some [embodimentexamples](#), the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequence of XENP24306 (SEQ ID NO:XX) or XENP24045 (SEQ ID NO:XX).

[0056] In some [embodimentexamples](#), the 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.

[0057] In some [embodimentexamples](#), 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.

[0058] In some [embodimentexamples](#), 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.

[0059] In some [embodimentexamples](#), 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.

[0060] In some [embodimentexamples](#), 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.

[0061] In some [embodimentexamples](#), 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0062] Figure 1 depicts the structure of IL-15 in complex with its receptors IL-15R α (CD215), IL-15R β (CD122), and the common gamma chain (CD132).

[0063] Figure 2A and Figure 2B depict the sequences for IL-15 and its receptors.

[0064] Figure 3A- Figure 3E depict useful pairs of Fc heterodimerization variant sets (including skew and pI variants). On Figure 3D and Figure 3E, there are variants for which there are no corresponding “monomer 2” variants; these are pI variants which can be used alone on either monomer.

[0065] Figure 4 depict a list of isosteric variant antibody constant regions and their respective substitutions. pI_() indicates lower pI variants, while pI_(+) indicates higher pI

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-15 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-15 α heterodimeric Fc fusion protein and the checkpoint blockade antibody are to be 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 sequences of XENP024306 or XENP024045,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

12. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the anti-PD-1 antibody is nivolumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

13. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the anti-PD-1 antibody is pembrolizumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVCLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

14. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the anti-PD-1 antibody is pidilizumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG

KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

15. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the anti-PD-1 antibody is nivolumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
QPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

16. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045- and the anti-PD-1 antibody is pembrolizumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

17. The use according to claim 11, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the anti-PD-1 antibody is pidilizumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

18. The use according to any one of claims 1 or 2, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the checkpoint blockade antibody is atezolizumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

19. The use according to any one of claims 1 or 2, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the checkpoint blockade antibody is atezolizumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD

GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

20. Use of an IL15/IL-15R α heterodimeric Fc fusion protein and a
checkpoint blockade antibody in the manufacture of a medicament for combination therapy to
treat cancer in a patient in need thereof,

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

a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCCKVTAMKCFLELQ
VISLESGDASIHTVQDLIILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and

b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK; 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.

21. Use of an IL15/IL-15R α heterodimeric Fc fusion protein and a checkpoint blockade antibody in the manufacture of a medicament for combination therapy to induce T-cell expansion in a patient,

wherein the protein comprises:

a) a first monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQ
VISLESGDASIHDTVQDLILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and

b) a second monomer comprising an amino acid sequence encoded by a polynucleotide that encodes

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVK
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

~~48~~22. The use according to any previous claim, wherein the cancer is metastatic cancer.

~~49~~23. 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~~24. The use according to any previous claim, wherein the ~~method~~use results in a minimal level of vascular leakage in the patient.

~~21~~25. The use according to claim ~~20~~24, wherein the level of vascular leakage ranges from a 20% reduction or less in serum albumin in the patient following administration.

~~22~~26. The use according to any one of claims 2 to ~~21~~25, wherein the T cell expansion is at least a 2-fold increase in T cells.

~~23~~27. The use according to any one of claims 2 to ~~22~~26, wherein the T cell expansion ranges from a 2-fold to a 15-fold increase in T cells.

~~24~~28. The use according to any one of claims 1 to ~~23~~27, wherein the ~~method~~use does not increase the likelihood of inducing hypoalbuminemia.

~~25~~29. The use according to any one of claims 2 to ~~24~~28, wherein the T cells comprise tumor infiltrating lymphocytes.

~~26~~30. A combination therapy comprising 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.

31. The combination therapy according to claim 30, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 or XENP024045,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

32. The combination therapy according to claim 31, wherein the IL-15/IL-
15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306
and the anti-PD-1 antibody is nivolumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTEGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

33. The combination therapy according to claim 31, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the anti-PD-1 antibody is pembrolizumab.

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDFVSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

34. The combination therapy according to claim 31, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the anti-PD-1 antibody is pidilizumab.

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDFVSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHW
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVVKLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVLHEALHSHYTQKSLSLSPGK.

35. The combination therapy according to claim 31, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the anti-PD-1 antibody is nivolumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQVISLES
GDASIHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHW
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVVKLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMH EALHNHYTQKSLSLSPGK.

36. The combination therapy according to claim 31, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the anti-PD-1 antibody is pembrolizumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREQMTKNQVCLTKLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

37. The combination therapy according to claim 31, wherein the IL-15/IL-15 α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the anti-PD-1 antibody is pidilizumab.

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG

KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK.

38. The combination therapy according to claim 30, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024306 and the checkpoint blockade antibody is atezolizumab,

wherein the amino acid sequences of XENP024306 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFIN TSGGG
GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSL
SLSPGK

and

ITCPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK.

39. The combination therapy according to claim 30, wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises the amino acid sequences of XENP024045 and the checkpoint blockade antibody is atezolizumab,

wherein the amino acid sequences of XENP024045 are:

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDAS
IHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFIN TSGGG

GSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPE
VKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESD
GOPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDFVSCSVMHEALHNHYTQKS
LSLSPGK

and

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWT
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGOPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFCFSVMH
EALHNHYTQKSLSLSPGK.

40. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the
manufacture of a first medicament and use of a checkpoint blockade antibody in the
manufacture of a second medicament, wherein the first and second medicaments are to be
used in combination therapy to treat cancer in a patient in need thereof,

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

_____ a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQ
VISLESGDASIHTVQDLIILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGOPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDFVSCSVLHEALH
SHYTQKSLSLSPGK; and

_____ b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVK

LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

41. Use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint
blockade antibody in the manufacture of a medicament for combination therapy to treat
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.

42. Use of an IL-15/IL-15R α heterodimeric Fc fusion protein and a checkpoint
blockade antibody in the manufacture of medicament for combination therapy to induce 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.

43. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the
manufacture of a first medicament and use of a checkpoint blockade antibody in the
manufacture of a second medicament, wherein the first and second medicaments are to be
used in combination therapy to treat cancer in a patient in need thereof,

wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises:
a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCCKVTAMKCFLELQ
VISLESGDASIHDTVQDLILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and

b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVK
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

44. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the
manufacture of a first medicament and use of a checkpoint blockade antibody in the
manufacture of a second medicament, wherein the first and second medicaments are to be
used in combination therapy to induce T-cell expansion in a patient,

wherein the protein comprises:

a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQ
VISLESGDASIHTVQDLILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and

b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHW
TPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK; 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.

45. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat 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.

46. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a first medicament and use of a checkpoint blockade antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to induce 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.

47. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the
manufacture of a medicament for combinatorial therapy for treating cancer in a patient in
need thereof, wherein said medicament is to be administered in combination with a
checkpoint blockade antibody,

wherein the IL-15/IL-15R α heterodimeric Fc fusion protein comprises:
a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCCKVTAMKCFLELQ
VISLESGDASIHDTVQDLILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and
b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVK
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

48. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the
manufacture of a medicament for combinatorial therapy for inducing T-cell expansion in a
patient, wherein said medicament is to be administered in combination with a checkpoint
blockade antibody,

wherein the protein comprises:

a) a first monomer comprising an amino acid sequence encoded by a
polynucleotide that encodes

NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLELQ
VISLESGDASIHTVQDLILANNSLSSNGNVTESGCKECELEEKNIKEFLQSFVHIVQ
MFINTSGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSD
IAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALH
SHYTQKSLSLSPGK; and

b) a second monomer comprising an amino acid sequence encoded by
a polynucleotide that encodes

ITCPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIRGGGGSEPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVK
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK; 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.

49. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for treating cancer in a patient in need thereof, wherein said medicament is to be administered in combination with a checkpoint blockade 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;

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.

50. Use of an IL15/IL-15R α heterodimeric Fc fusion protein in the manufacture of a medicament for combinatorial therapy for inducing T-cell expansion in a patient, wherein said medicament is to be administered in combination with a checkpoint blockade antibody,

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.