

Patent claims

1. An isolated heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein:
 - 5 (a) the HVR-H1 sequence is GYTFTX₁YP;
 - (b) the HVR-H2 sequence is INTNTGNP;
 - (c) the HVR-H3 sequence is ARX₂GX₃X₄X₅X₆X₇X₈X₉X₁₀X₁₁X₁₂X₁₃;
 further wherein: X₁ is S or A; X₂ is V or T; X₃ is G or Y; X₄ is Y, S or F; X₅ is S, G or T; X₆ is V, S or G; X₇ is D, Y or P; X₈ is E, D or Y; X₉ is Y or W; X₁₀ is A, F or S; X₁₁ is F or D;

10 X₁₂ is D or P; X₁₃ is V, I or absent.

2. The polypeptide of Claim 1 wherein X₁ is S or A; X₂ is V or T; X₃ is G or Y; X₄ is Y or S; X₅ is S or G; X₆ is V or S; X₇ is D or Y; X₈ is E; X₉ is Y; X₁₀ is A or F; X₁₁ is F; X₁₂ is D; X₁₃ is V or I.

15

3. The polypeptide of Claim 1 wherein wherein X₁ is S; X₂ is V or T; X₃ is G; X₄ is Y; X₅ is S or G; X₆ is V; X₇ is D or Y; X₈ is E; X₉ is Y; X₁₀ is A; X₁₁ is F; X₁₂ is D; X₁₃ is V or I.

4. The polypeptide of Claim 1 wherein X₁ is S; X₂ is V; X₃ is G; X₄ is Y; X₅ is S; X₆ is V;

20 X₇ is D; X₈ is E; X₉ is Y; X₁₀ is A; X₁₁ is F; X₁₂ is D; X₁₃ is V.

5. The polypeptide of any one of Claims 1-4 further comprising variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-

25 (HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4).

6. The polypeptide of Claim 5 wherein the heavy chain framework sequences are derived from human consensus framework sequences.

- 30 7. The polypeptide of Claim 5 wherein the heavy chain framework sequences are derived from human germline framework sequences.

8. The polypeptide of Claim 5 wherein one or more of the heavy chain framework sequences is the following:
HC-FR1 is QVQLVQSGSELKKPGASVKVSCAKS;
5 HC-FR2 is MNWVRQAPGQGLEWMGW;
HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYC;
HC-FR4 is WGQGTLVTVSS.
9. The polypeptide of any one of Claims 5-8 further comprising at least a C_H1 domain.
10
10. The polypeptide of Claim 9 further comprising a C_H2 and a C_H3 domain.
11. The isolated heavy chain polypeptide of any one of Claims 1-10 in combination with a variable region light chain comprising an HVR-L1, HVR-L2 and HVR-L3, wherein:
15 (a) the HVR-L1 sequence is QGISY;
(b) the HVR-L2 sequence is AAS;
(c) the HVR-L3 sequence is X₁₄QX₁₅X₁₆X₁₇X₁₈X₁₉X₂₀;
further wherein X₁₄ is Q, G or H; X₁₅ is L, V or T; X₁₆ is N, S, I or M; X₁₇ is S, R or F; X₁₈ is Y or R; X₁₉ is P or L; X₂₀ is T or A.
20
12. The polypeptide of Claim 11 wherein X₁₄ is Q or G; X₁₅ is L or V; X₁₆ is N or S; X₁₇ is S or R; X₁₈ is Y; X₁₉ is P; X₂₀ is T.
13. The polypeptide of Claim 11 wherein X₁₄ is Q; X₁₅ is L; X₁₆ is S; X₁₇ is S; X₁₈ is Y;
25 X₁₉ is P; X₂₀ is T.
14. The polypeptide of any of Claims 11-13 further comprising variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-
30 L2)-(LC-FR3)-(HVR-L3)-(LC-FR4).

15. The polypeptide of Claim 14 wherein the light chain framework sequences are derived from human consensus framework sequences.
16. The polypeptide of Claim 14 wherein the light chain framework sequences are derived from human germline framework sequences.
17. The polypeptide of Claim 14 wherein the light chain framework sequences are kappa light chain sequences.
18. The polypeptide of Claim 14 wherein one or more of the light chain framework sequences is the following:
 LC-FR1 is DIQLTQSPSFLSASVGDRVITICRAS;
 LC-FR2 is LAWYQQKPGKAPKLLIY;
 LC-FR3 is TLQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYC;
 LC-FR4 is FGGGTKVEIK.
19. The polypeptide of any one of Claims 14-18 further comprising a C_L domain.
20. An isolated anti-TIGIT antibody or antigen binding fragment thereof comprising a heavy chain and a light chain variable region sequence, wherein:
- (a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein further: (i) the HVR-H1 sequence is GYTFTX₁YP; (ii) the HVR-H2 sequence is INTNTGNP; (iii) the HVR-H3 sequence is ARX₂GX₃X₄X₅X₆X₇X₈X₉X₁₀X₁₁X₁₂X₁₃;
- (b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further: (iv) the HVR-L1 sequence is QGISSY; (v) the HVR-L2 sequence is AAS; (vi) the HVR-L3 sequence is X₁₄QX₁₅X₁₆X₁₇X₁₈X₁₉X₂₀;
- wherein further X₁ is S or A; X₂ is V or T; X₃ is G or Y; X₄ is Y, S or F; X₅ is S, G or T; X₆ is V, S or G; X₇ is D, Y or P; X₈ is E, D or Y; X₉ is Y or W; X₁₀ is A, F or S; X₁₁ is F or D; X₁₂ is D or P; X₁₃ is V, I or absent; X₁₄ is Q, G or H; X₁₅ is L, V or T; X₁₆ is N, S, I or M; X₁₇ is S, R or F; X₁₈ is Y or R; X₁₉ is P or L; X₂₀ is T or A.

21. The antibody or antibody fragment of Claim 20 wherein X₁ is S or A; X₂ is V or T; X₃ is G or Y; X₄ is Y or S; X₅ is S or G; X₆ is V or S; X₇ is D or Y; X₈ is E; X₉ is Y; X₁₀ is A or F; X₁₁ is F; X₁₂ is D; X₁₃ is V or I; X₁₄ is Q or G; X₁₅ is L or V; X₁₆ is N or S; X₁₇ is S or R; X₁₈ is Y; X₁₉ is P; X₂₀ is T.

5

22. The antibody or antibody fragment of Claim 20 wherein X₁ is S; X₂ is V or T; X₃ is G; X₄ is Y; X₅ is S or G; X₆ is V; X₇ is D or Y; X₈ is E; X₉ is Y; X₁₀ is A; X₁₁ is F; X₁₂ is D; X₁₃ is V or I; X₁₄ is Q; X₁₅ is L; X₁₆ is S; X₁₇ is S; X₁₈ is Y; X₁₉ is P; X₂₀ is T.

10 23. The antibody or antibody fragment of Claim 20 wherein X₁ is S; X₂ is V; X₃ is G; X₄ is Y; X₅ is S; X₆ is V; X₇ is D; X₈ is E; X₉ is Y; X₁₀ is A; X₁₁ is F; X₁₂ is D; X₁₃ is V; X₁₄ is Q; X₁₅ is L; X₁₆ is S; X₁₇ is S; X₁₈ is Y; X₁₉ is P; X₂₀ is T.

24. The antibody or antibody fragment of Claim 20, wherein

- 15 (a) the HVR-H1 sequence is GYTFTSYP,
 (b) the HVR-H2 sequence is INTNTGNP,
 (c) the HVR-H3 sequence is ARVGGYSVDEYAFDV;
 and wherein
 (d) the HVR-L1 sequence is QGISSY,
 20 (e) the HVR-L2 sequence is AAS,
 (f) the HVR-L3 sequence is QQLSSYPT.

25. The antibody or antibody fragment of any of Claims 20 – 24 further comprising:

- (a) variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and
 25 HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and
 (b) variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4).

30

26. The antibody or antibody fragment of Claim 25 wherein the framework sequences are derived from human consensus framework sequences.

27. The antibody or antibody fragment of Claim 25 wherein the framework sequences
5 are derived from human germline framework sequences.

28. The antibody or antibody fragment of Claim 25 wherein one or more of the framework sequences is the following:

HC-FR1 is QVQLVQSGSELKKPGASVKVSCAS;

10 HC-FR2 is MNWVRQAPGQGLEWMGW;

HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISLKAEDTAVYYC;

HC-FR4 is WGQGTLVTVSS.

29. The antibody or antibody fragment of Claim 25 wherein one or more of the framework
15 sequences is the following:

LC-FR1 sequence is DIQLTQSPSFLSASVGDRVITICRAS;

LC-FR2 sequence is LAWYQQKPGKAPKLLIY;

LC-FR3 sequence is TLQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYC;

LC-FR4 sequence is FGGGTKVEIK.

20

30. The antibody or antibody fragment of Claim 25 wherein:

(a) the variable heavy chain framework sequences are the following:

(i) HC-FR1 is QVQLVQSGSELKKPGASVKVSCAS;

(ii) HC-FR2 is MNWVRQAPGQGLEWMGW;

25 (iii) HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISLKAEDTAVYYC;

(iv) HC-FR4 is WGQGTLVTVSS; and

(b) the variable light chain framework sequences are the following:

(i) LC-FR1 sequence is DIQLTQSPSFLSASVGDRVITICRAS;

(ii) LC-FR2 sequence is LAWYQQKPGKAPKLLIY;

30 (iii) LC-FR3 sequence is TLQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYC;

(iv) LC-FR4 sequence is FGGGTKVEIK.

31. An isolated anti-TIGIT antibody or antigen binding fragment thereof, having the HC-FR and LC-FR sequences of claim 30, selected from the following:
- i) an antibody, wherein the HVR-H1, HVR-H2, HVR-H3 sequences are selected from one of the ID's shown in Table 2, and wherein
 - (a) the HVR-L1 sequence is QGISSY,
 - (b) the HVR-L2 sequence is AAS,
 - (c) the HVR-L3 sequence is QQLNSYPT;
 - ii) an antibody wherein the HVR-L1, HVR-L2, HVR-L3 sequences are selected from one of the ID's shown in Table 3, and wherein
 - (a) the HVR-H1 sequence is GYTFTSYP,
 - (b) the HVR-H2 sequence is INTNTGNP,
 - (c) the HVR-H3 sequence is ARVGGYSVDEYAFDV; or
 - iii) an antibody chosen from Table 4.
32. The antibody or antibody fragment of any one of Claims 25-31 further comprising at least a C_{H1} domain.
33. The antibody or antibody fragment of Claim 32 further comprising a C_{H2} and a C_{H3} domain.
34. The antibody or antibody fragment of any one of Claims 25-33 further comprising a C_L domain.
35. The antibody of Claim 34, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.
36. The antibody of Claim 35 wherein the constant region is IgG1.
37. The antibody or antibody fragment of any one of the preceding Claims which is a fully human antibody.

38. An isolated anti-TIGIT antibody or antigen binding fragment thereof comprising a heavy chain variable region sequence and a light chain variable region sequence, wherein:

- 5 (a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence:

QVQLVQSGSELKKPGASVKVSCASGYTFTSYPMNWRQAPGQGLEWMGWINTNTG
NPTYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARVGGYSVDEYAFDVWGQ
GTLTVSS, and

- 10 (b) the light chain sequence has at least 85% sequence identity to the light chain sequence:

DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASLTQSGVP
SRFSGSGSGTEFTLTISLQPEDFATYYCQQLSSYPTFGGGTKVEIK.

- 15 39. The antibody or antigen binding fragment of Claim 38, wherein the sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or is 100%.

40. The antibody or antigen binding fragment of Claim 39, wherein the sequence identity
20 is 100%.

41. An isolated anti-TIGIT antibody wherein the heavy chain is:
QVQLVQSGSELKKPGASVKVSCASGYTFTSYPMNWRQAPGQGLEWMGWINTNTG
NPTYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARVGGYSVDEYAFDVWGQ
25 GTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVWTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD
30 SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG, and
(b) the light chain is:

DIQLTQSPSFLSASVGDRVITICRASQGISSYLAWYQQKPGKAPKLLIYAASLTQSGVP
 SRFSGSGSGTEFTLTISSLQPEDFATYYCQQLSSYPTFGGGTKVEIKRTVAAPSVFIFPP
 SDEQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
 TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

5

42. The antibody of any one of Claims 20-41 wherein the antibody is capable of binding to human and cynomolgus monkey TIGIT.

10

43. The antibody of any one of Claims 20-20 wherein the antibody is capable of blocking the interaction between human, or cynomolgus monkey TIGIT and the respective human, or cynomolgus monkey PVR.

15

44. The antibody of any of Claims 20-43 wherein the antibody binds to human TIGIT with a K_D of 10×10^{-9} M or less.

45. An isolated anti-TIGIT antibody or antigen binding fragment thereof which binds to a functional epitope comprising residues Q53, T55, Y113 and P114 of human TIGIT.

20

46. The isolated anti-TIGIT antibody or antigen binding fragment of claim 45 wherein the functional epitope further comprises residues Q56, N70, and H111 of human TIGIT.

25

47. An isolated anti-TIGIT antibody or antigen binding fragment thereof which binds to a conformational epitope comprising residues T51, A52, Q53, T55, Q56, N70, D72, H111, T112, Y113, P114, and G116 of human TIGIT.

48. An isolated anti-TIGIT antibody or antigen binding fragment thereof wherein the antibody cross-competes for binding to TIGIT with an antibody or antigen binding fragment of any of Claims 20-42.

30

49. A pharmaceutical composition comprising the anti-TIGIT antibody or antigen binding fragment of any of Claims 20-48 and at least one pharmaceutically acceptable carrier.

50. An isolated nucleic acid encoding a polypeptide of any one of Claims 1-41.

51. An isolated nucleic acid encoding the light chain or a heavy chain sequence of an
5 anti-TIGIT antibody or antigen binding fragment of any one of Claims 20-41.

52. An isolated nucleic acid encoding the heavy chain according to Claim 41, which nucleic acid has the following sequence:

ATGGAAACAGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGCTCCA
10 CAGGCCAGGTGCAGCTGGTGCAGTCCGGCTCCGAGCTGAAGAAACCCGGCGCCT
CCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACACCTTCACCTCCTACCCCATGAA
CTGGGTGAGGCAGGCTCCTGGCCAGGGAAGTGGAGTGGATGGGCTGGATCAACAC
CAACACCGGCAACCCTACCTACGCCAGGGCTTCACCGGCAGGTTCTGTGTTCTCC
CTGGACACCAGCGTGTCCACCGCCTACCTGCAGATCTCCTCCCTGAAGGCCGAGG
15 ACACCGCCGTGTACTACTGCGCCAGGGTGGGAGGCTACTCCGTGGACGAGTACG
CCTTCGACGTGTGGGGCCAGGGCACCCCTGGTGACCGTGTCTCCGCTAGCACCAA
GGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACA
GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTG
TGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGT
20 CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG
CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAGAGTTGAGCCCAAATCTTGTGACAAACTCACACATGCCCACCGTGCCCAGC
ACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCC AAAACCCAAGGAC
ACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCC
25 ACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAG
GTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAG
GGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCACGGGAGGAGATGA
30 CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAACAACACTACAAGACCACGCC

TCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGT.

- 5 53. An isolated nucleic acid encoding the light chain according to Claim 41, which nucleic acid has the following sequence:
- ATGAGGGCCCTGCTGGCTAGACTGCTGCTGTGCGTGCTGGTCGTGTCCGACAGCA
AGGGCGACATCCAGCTGACCCAGTCCCCCTCCTTCCTGTCCGCTTCCGTGGGCGA
CAGGGTGACCATCACTTGTGCTGCCTCCAGGGCATCTCCTCCTACCTGGCCTGG
10 TACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCTTCCACAC
TGCAGTCCGGCGTGCCCTCCAGGTTTTCCGGATCCGGCTCCGGCACCGAGTTCAC
CCTGACCATCTCCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAG
CTGTCCTCCTACCCACCTTCGGCGGCGGCACAAAGGTGGAGATCAAGCGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
15 ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAG
CAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT.
- 20
54. A vector comprising the nucleic acid of any of claims 50-53.
55. A host cell comprising the vector of Claim 54.
- 25 56. The host cell of Claim 55 which is eukaryotic.
57. The host cell of Claim 56 which is mammalian.
58. The host cell of Claim 57 which is a Chinese Hamster Ovary (CHO) cell, preferably
30 CHO-K1SV.

59. A process for making an anti-TIGIT antibody or antigen binding fragment thereof comprising culturing the host cell of any one of Claims 55-58 under conditions suitable for the expression of the vector encoding the anti-TIGIT antibody or antigen binding fragment, and recovering the antibody or fragment.

5

60. A method of treating cancer comprising administering to a subject in need thereof an effective amount of an anti-TIGIT antibody of any one of claims 20-48, or the pharmaceutical composition of Claim 49, which induces antibody dependent cell-mediated cytotoxicity (ADCC).

10

61. A method of treating cancer comprising administering to a subject in need thereof an effective amount of an anti-TIGIT antibody of any one of claims 20-48, or the pharmaceutical composition of Claim 49.

15

62. The method of Claims 60 or 61 wherein the cancer is selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

20

63. A method of treating a T-cell dysfunctional disorder comprising administering a therapeutically effective amount of an anti-TIGIT antibody of any one of claims 20-48 or the pharmaceutical composition of Claim 47, to a subject in need thereof.

25

64. The method of Claim 63, wherein the T-cell dysfunctional disorder is tumor immunity.

30

65. The method of Claim 64, wherein the tumor immunity results from a cancer selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

66. The method of any one of Claims 60-65, wherein the method further comprises the application of a treatment regimen selected from the group consisting of: radiation therapy, surgery, chemotherapy, gene therapy, DNA therapy, viral therapy, RNA therapy, immunotherapy, bone marrow transplantation, nanotherapy, monoclonal antibody therapy, adjuvant therapy, neoadjuvant therapy, hormonal therapy, angiogenesis inhibitor, palliative care.
67. The method of any one of Claims 60-66, further comprising the administration of at least one anti-cancer agent.
68. A kit of parts comprising the pharmaceutical composition of Claim 49 and a package insert comprising instructions for using the pharmaceutical composition for the treatment according to any one of Claims 60-66.
69. A kit of parts comprising the pharmaceutical composition of Claim 49, at least one further anti-cancer agent, and a package insert comprising instructions for using the at least one anti-cancer agent in combination with the pharmaceutical composition for the treatment according to any one of Claims 60-67.