

CLAIMS

1. Use of a therapeutically effective amount of a heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the medicament is formulated for use in combination with an immuno-oncology agent,

and wherein the heterotandem bicyclic peptide complex comprises:

(a) a first peptide ligand which binds to a component present on a cancer cell; conjugated via a linker to

(b) one or more CD137 binding peptide ligands;

wherein each of said peptide ligands comprise a polypeptide comprising at least three reactive groups, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the reactive groups of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

2. Use of a therapeutically effective amount of a heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the medicament is used with an immuno-oncology agent,

and wherein the heterotandem bicyclic peptide complex comprises:

(a) a first peptide ligand which binds to a component present on a cancer cell; conjugated via a linker to

(b) one or more CD137 binding peptide ligands;

wherein each of said peptide ligands comprise a polypeptide comprising at least three reactive groups, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the reactive groups of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

3. Use of a therapeutically effective amount of a heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, and an immuno-oncology agent, in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the heterotandem bicyclic peptide complex comprises:

(a) a first peptide ligand which binds to a component present on a cancer cell; conjugated via a linker to

(b) one or more CD137 binding peptide ligands;

wherein each of said peptide ligands comprise a polypeptide comprising at least three reactive groups, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the reactive groups of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

4. The use of any one of claims 1-3, wherein:

(i) the reactive groups are cysteine residues; and/or

(ii) the heterotandem bicyclic peptide complex comprises two or more CD137 binding peptide ligands.

5. The use of any one of claims 1-4, wherein a CD137 binding peptide ligand comprises an amino acid sequence selected from:

C_iIEEGQYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 5);

C_i[tBuAla]PE[D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 6);

C_iIEEGQYC_{ii}F[D-Ala]DPY[Nle]C_{iii} (SEQ ID NO: 7);

C_i[tBuAla]PK[D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 8);

C_i[tBuAla]PE[D-Lys]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 9);

C_i[tBuAla]P[K(PYA)][D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 10);

C_i[tBuAla]PE[D-Lys(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 11);

(SEQ ID NO: 11)-A (herein referred to as BCY14601);

C_iIEE[D-Lys(PYA)]QYC_{ii}FADPY(Nle)C_{iii} (SEQ ID NO: 12);

C_i[tBuAla]PE[dK]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 60);

C_i IEE[dK(PYA)]QYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 61);
 C_i [tBuAla]EE(dK)PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 62);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 63);
 C_i [tBuAla]EE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 64);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FANPY[Nle]C_{iii} (SEQ ID NO: 65);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FAEPY[Nle]C_{iii} (SEQ ID NO: 66);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FA[Aad]PY[Nle]C_{iii} (SEQ ID NO: 67);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FAQPY[Nle]C_{iii} (SEQ ID NO: 68);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle][Cysam]_{iii} (SEQ ID NO: 69);
[MerPro]_i[tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 70; herein referred to as BCY12353);
[MerPro]_i[tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle][Cysam]_{iii} (SEQ ID NO: 71; herein referred to as BCY12354);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 72);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 73);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 74; herein referred to as BCY12372);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FAD[NMeAla]Y[Nle]C_{iii} (SEQ ID NO: 75);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FAD[NMeDAla]Y[Nle]C_{iii} (SEQ ID NO: 76);
 C_i [tBuAla]P[K(PYA)][dA]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 77);
 C_i [tBuAla]PE[dK(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 78);
 C_i [tBuAla]PE[dK(Me,PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 79);
 C_i [tBuAla]PE[dK(Me,PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 80); and
[MerPro]_i[tBuAla]EE[dK]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 81; herein referred to as BCY13137);
wherein [MerPro]_i, C_i , C_{ii} , C_{iii} and [Cysam]_{iii} represent first (i), second (ii) and third (iii) reactive groups which are selected from cysteine, MerPro and Cysam, Nle represents norleucine, tBuAla represents t-butyl-alanine, PYA represents 4-pentynoic acid, Aad represents alpha-L-amino adipic acid, MerPro represents 3-mercaptopropionic acid and

Cysam represents cysteamine, NMeAla represents N-methyl-alanine, or a pharmaceutically acceptable salt thereof.

6. The use of any one of claims 1-5, wherein a CD137 binding peptide ligand comprises an amino acid sequence which is:

$C_i[tBuAla]PE[D-Lys(PYA)]PYC_{ii}FADPY[Nle]C_{iii}$ (SEQ ID NO: 11);

wherein C_i , C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively, tBuAla represents t-butyl-alanine, PYA represents 4-pentynoic acid, Nle represents norleucine, or a pharmaceutically acceptable salt thereof.

7. The use of any one of claims 1-6, wherein a CD137 binding bicyclic peptide ligand comprises N- and C-terminal modifications and comprises a peptide sequence selected from:

Ac-A-(SEQ ID NO: 5)-Dap (herein referred to as BCY7732);

Ac-A-(SEQ ID NO: 5)-Dap(PYA) (herein referred to as BCY7741);

Ac-(SEQ ID NO: 6)-Dap (herein referred to as BCY9172);

Ac-(SEQ ID NO: 6)-Dap(PYA) (herein referred to as BCY11014);

Ac-A-(SEQ ID NO: 7)-Dap (herein referred to as BCY8045);

Ac-(SEQ ID NO: 8)-A (herein referred to as BCY8919);

Ac-(SEQ ID NO: 9)-A (herein referred to as BCY8920);

Ac-(SEQ ID NO: 10)-A (herein referred to as BCY8927);

Ac-(SEQ ID NO: 11)-A (herein referred to as BCY8928);

Ac-A-(SEQ ID NO: 12)-A (herein referred to as BCY7744);

Ac-(SEQ ID NO: 60)-Dap(PYA) (herein referred to as BCY11144);

Ac-A-(SEQ ID NO: 61)-K (herein referred to as BCY11613);

Ac-(SEQ ID NO: 62)-Dap(PYA) (herein referred to as BCY12023);

Ac-(SEQ ID NO: 63) (herein referred to as BCY12149);

Ac-(SEQ ID NO: 64) (herein referred to as BCY12143);

Ac-(SEQ ID NO: 65) (herein referred to as BCY12147);

Ac-(SEQ ID NO: 66) (herein referred to as BCY12145);

Ac-(SEQ ID NO: 67) (herein referred to as BCY12146);

Ac-(SEQ ID NO: 68) (herein referred to as BCY12150);
Ac-(SEQ ID NO: 69) (herein referred to as BCY12352);
Ac-(SEQ ID NO: 72)-[1,2-diaminoethane] (herein referred to as BCY12358);
[Palmitic Acid]-[yGlu]-[yGlu]-(SEQ ID NO: 73) (herein referred to as BCY12360);
Ac-(SEQ ID NO: 75) (herein referred to as BCY12381);
Ac-(SEQ ID NO: 76) (herein referred to as BCY12382);
Ac-(SEQ ID NO: 77)-K (herein referred to as BCY12357);
Ac-(SEQ ID NO: 78)-[dA] (herein referred to as BCY13095);
[Ac]-(SEQ ID NO: 78)-K (herein referred to as BCY13389);
Ac-(SEQ ID NO: 79)-[dA] (herein referred to as BCY13096); and
Ac-(SEQ ID NO: 80) (herein referred to as BCY13097);

wherein Ac represents an acetyl group, Dap represents diaminopropionic acid and PYA represents 4-pentynoic acid, or a pharmaceutically acceptable salt thereof.

8. The use of any one of claims 1-7, wherein a CD137 binding bicyclic peptide ligand comprises N- and C-terminal modifications and comprises:

Ac-(SEQ ID NO: 11)-A (herein referred to as BCY8928);

wherein Ac represents an acetyl group, or a pharmaceutically acceptable salt thereof.

9. The use of any one of claims 1-8 wherein the heterotandem bicyclic peptide complex comprises two CD137 binding peptide ligands, wherein both of said two CD137 binding peptide ligands have the same peptide sequence which comprises Ac-(SEQ ID NO: 11)-A (herein referred to as BCY8928), wherein Ac represents an acetyl group, or a pharmaceutically acceptable salt thereof.

10. The use of any one of claims 1-9, wherein the component present on a cancer cell is Nectin-4, and wherein:

- (i) the first peptide ligand comprises a Nectin-4 binding bicyclic peptide ligand;
- (ii) the first peptide ligand comprises a Nectin-4 binding bicyclic peptide ligand and the Nectin-4 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

C_iP[1Nal][dD]C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 1; herein referred to as BCY8116);

C_iP[1Nal][dK](Sar₁₀-(B-Ala))C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 3);

C_iPFGC_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 4; herein referred to as BCY11414);

C_iP[1Nal][dK]C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 14);

[MerPro]_iP[1Nal][dK]C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 15; herein referred to as BCY12363);

C_iP[1Nal][dK]C_{ii}M[HArg]DWSTP[HyP]W[Cysam]_{iii} (SEQ ID NO: 16);

[MerPro]_iP[1Nal][dK]C_{ii}M[HArg]DWSTP[HyP]W[Cysam]_{iii} (SEQ ID NO: 17; herein referred to as BCY12365);

C_iP[1Nal][dK]C_{ii}M[HArg]HWSTP[HyP]WC_{iii} (SEQ ID NO: 18);

C_iP[1Nal][dK]C_{ii}M[HArg]EWSTP[HyP]WC_{iii} (SEQ ID NO: 19);

C_iP[1Nal][dE]C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 20; herein referred to as BCY12368);

C_iP[1Nal][dA]C_{ii}M[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 21; herein referred to as BCY12369);

C_iP[1Nal][dE]C_{ii}L[HArg]DWSTP[HyP]WC_{iii} (SEQ ID NO: 22; herein referred to as BCY12370); and

C_iP[1Nal][dE]C_{ii}M[HArg]EWSTP[HyP]WC_{iii} (SEQ ID NO: 23; herein referred to as BCY12384);

wherein [MerPro]_i, C_i, C_{ii}, C_{iii} and [Cysam]_{iii} represent first (i), second (ii) and third (iii) reactive groups which are selected from cysteine, MerPro and Cysam, 1Nal represents 1-naphthylalanine, HArg represents homoarginine, HyP represents trans-4-hydroxy-L-proline, Sar₁₀ represents 10 sarcosine units, B-Ala represents beta-alanine, MerPro represents 3-mercaptopropionic acid and Cysam represents cysteamine, or a pharmaceutically acceptable salt thereof;

(iii) the first peptide ligand comprises a Nectin-4 binding bicyclic peptide ligand and the Nectin-4 binding bicyclic peptide ligand comprises N-terminal modifications and comprises a peptide sequence selected from:

SEQ ID NO: 1 (herein referred to as BCY8116);
[PYA]-[B-Ala]-[Sar₁₀]- (SEQ ID NO: 1) (herein referred to as BCY8846);
[PYA]- (SEQ ID NO: 1) (herein referred to as BCY11015);
[PYA]-[B-Ala]- (SEQ ID NO: 1) (herein referred to as BCY11016);
[PYA]-[B-Ala]-[Sar₁₀]- (SEQ ID NO: 2) (herein referred to as BCY11942);
Ac- (SEQ ID NO: 3) (herein referred to as BCY8831);
SEQ ID NO: 4 (herein referred to as BCY11414);
[PYA]-[B-Ala]- (SEQ ID NO: 14) (herein referred to as BCY11143);
Palmitic-yGlu-yGlu- (SEQ ID NO: 14) (herein referred to as BCY12371);
Ac- (SEQ ID NO: 14) (herein referred to as BCY12024);
Ac- (SEQ ID NO: 16) (herein referred to as BCY12364);
Ac- (SEQ ID NO: 18) (herein referred to as BCY12366); and
Ac- (SEQ ID NO: 19) (herein referred to as BCY12367);

wherein PYA represents 4-pentynoic acid, B-Ala represents beta-alanine, Sar₁₀ represents 10 sarcosine units, or a pharmaceutically acceptable salt thereof; and/or

(iv) the first peptide ligand comprises a Nectin-4 binding bicyclic peptide ligand and the Nectin-4 binding bicyclic peptide ligand comprises SEQ ID NO: 1 (herein referred to as BCY8116).

11. The use of claim 10, wherein the heterotandem bicyclic peptide complex is selected from those listed in Tables A and B, such as BCY11027, BCY11863 and BCY11864, or a pharmaceutically acceptable salt thereof.

12. The use of any one of the preceding claims, wherein the heterotandem bicyclic peptide complex is BCY11863, or a pharmaceutically acceptable salt thereof.

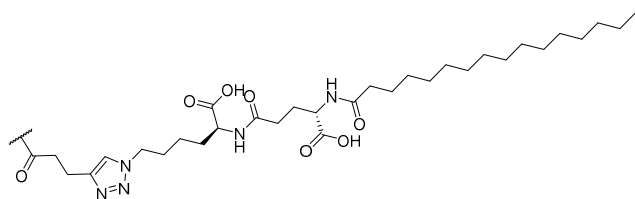
13. The use of any one of claims 1-9, wherein the component present on a cancer cell is EphA2, and wherein:

- (i) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand;
- (ii) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the EphA2 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

C_i[HyP]LVNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 24);
C_iLWDPTPC_{ii}ANLHL[HArg]C_{iii} (SEQ ID NO: 25);
C_i[HyP]LVNPLC_{ii}L[K(PYA)]P[dD]W[HArg]C_{iii} (SEQ ID NO: 26);
C_i[HyP][K(PYA)]VNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 27);
C_i[HyP]LVNPLC_{ii}[K(PYA)]HP[dD]W[HArg]C_{iii} (SEQ ID NO: 28);
C_i[HyP]LVNPLC_{ii}LKP[dD]W[HArg]C_{iii} (SEQ ID NO: 29);
C_i[HyP]KVNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 30);
C_i[HyP]LVNPLC_{ii}KHP[dD]W[HArg]C_{iii} (SEQ ID NO: 31);
C_i[HyP]LVNPLC_{ii}LHP[dE]W[HArg]C_{iii} (SEQ ID NO: 32);
C_i[HyP]LVNPLC_{ii}LEP[dD]W[HArg]C_{iii} (SEQ ID NO: 33);
C_i[HyP]LVNPLC_{ii}LHP[dD]WTC_{iii} (SEQ ID NO: 34);
C_i[HyP]LVNPLC_{ii}LEP[dD]WTC_{iii} (SEQ ID NO: 35);
C_i[HyP]LVNPLC_{ii}LEP[dA]WTC_{iii} (SEQ ID NO: 36);
C_i[HyP]LVNPLC_{ii}L[3,3-DPA]P[dD]WTC_{iii} (SEQ ID NO: 37; herein referred to as BCY12860);
C_i[HyP][Cba]VNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 38);
C_i[HyP][Cba]VNPLC_{ii}LEP[dD]WTC_{iii} (SEQ ID NO: 39);
C_i[HyP][Cba]VNPLC_{ii}L[3,3-DPA]P[dD]WTC_{iii} (SEQ ID NO: 40);
C_i[HyP]LVNPLC_{ii}L[3,3-DPA]P[dD]W[HArg]C_{iii} (SEQ ID NO: 41);
C_i[HyP]LVNPLC_{ii}LHP[d1Nal]W[HArg]C_{iii} (SEQ ID NO: 42);
C_i[HyP]LVNPLC_{ii}L[1Nal]P[dD]W[HArg]C_{iii} (SEQ ID NO: 43);
C_i[HyP]LVNPLC_{ii}LEP[d1Nal]WTC_{iii} (SEQ ID NO: 44);
C_i[HyP]LVNPLC_{ii}L[1Nal]P[dD]WTC_{iii} (SEQ ID NO: 45; herein referred to as BCY13119);
C_i[HyP][Cba]VNPLC_{ii}LEP[dA]WTC_{iii} (SEQ ID NO: 46);
C_i[HyP][hGlu]VNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 47);

$C_i[\text{HyP}]\text{LVNPLC}_{ii}[\text{hGlu}]\text{HP}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 48);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{hGlu}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 49);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{LHP}[\text{dNle}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 50);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{Nle}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 51);
 $[\text{MerPro}]_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[3,3\text{-DPA}]\text{P}[\text{dD}]\text{WTC}_{iii}$ (SEQ ID NO: 154);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{LHP}[\text{dD}]\text{W}[\text{HArg}][\text{Cysam}]_{iii}$ (SEQ ID NO: 155);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{His3Me}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 156);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{His1Me}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 157);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[4\text{ThiAz}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 158);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{LFP}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 159);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{Thi}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 160);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[3\text{Thi}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 161);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{LNP}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 162);
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{LQP}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 163); and
 $C_i[\text{HyP}]\text{LVNPLC}_{ii}\text{L}[\text{K(PYA-(Palmitoyl-Glu-LysN}_3\text{))}]\text{P}[\text{dD}]\text{W}[\text{HArg}]\text{C}_{iii}$ (SEQ ID NO: 164);

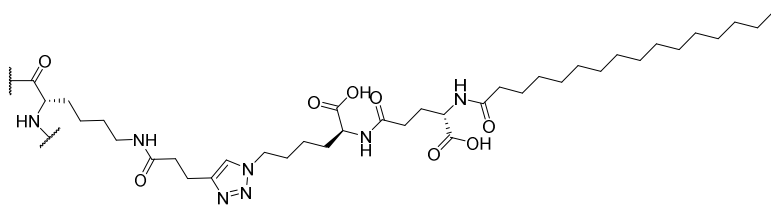
wherein $[\text{MerPro}]_i$, C_i , C_{ii} , C_{iii} and $[\text{Cysam}]_{iii}$ represent first (i), second (ii) and third (iii) reactive groups which are selected from cysteine, MerPro and Cysam, HyP represents trans-4-hydroxy-L-proline, HArg represents homoarginine, PYA represents 4-pentynoic acid, 3,3-DPA represents 3,3-diphenylalanine, Cba represents β -cyclobutylalanine, 1Nal represents 1-naphthylalanine, hGlu represents homoglutamic acid, Thi represents thienyl-alanine, 4ThiAz represents beta-(4-thiazolyl)-alanine, His1Me represents N1-methyl-L-histidine, His3Me represents N3-methyl-L-histidine, 3Thi represents , Palmitoyl-Glu-LysN₃[PYA] represents:



(Palmitoyl-Glu-LysN₃)[PYA]

, $[\text{K(PYA-(Palmitoyl-Glu-LysN}_3\text{))}]$

represents:



[K(PYA(Palmitoyl-Glu-LysN3))]

, Nle represents norleucine,

MerPro represents 3-mercaptopropionic acid and Cysam represents cysteamine, or a pharmaceutically acceptable salt thereof;

(iii) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the EphA2 binding bicyclic peptide ligand comprises an amino acid sequence which is:



wherein C_i , C_{ii} , C_{iii} and represent first (i), second (ii) and third (iii) cysteine groups, HyP represents trans-4-hydroxy-L-proline, HArg represents homoarginine, or a pharmaceutically acceptable salt thereof;

(iv) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the EphA2 binding bicyclic peptide ligand comprises an amino acid sequence which is:



wherein C_i , C_{ii} , C_{iii} and represent first (i), second (ii) and third (iii) cysteine groups, HyP represents trans-4-hydroxy-L-proline, 1Nal represents 1-naphthylalanine, or a pharmaceutically acceptable salt thereof;

(v) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the EphA2 binding bicyclic peptide ligand comprises N-terminal modifications and comprises a peptide sequence selected from:

A-[HArg]-D-(SEQ ID NO: 24) (herein referred to as BCY9594);

[B-Ala]-[Sar₁₀]-A-[HArg]-D-(SEQ ID NO: 24) (herein referred to as BCY6099);

[PYA]-A-[HArg]-D-(SEQ NO: 24) (herein referred to as BCY11813);

Ac-A-[HArg]-D-(SEQ ID NO: 24)-[K(PYA)] (herein referred to as BCY11814);

Ac-A-[HArg]-D-(SEQ ID NO: 24)-K (herein referred to as BCY12734);

[NMeAla]-[HArg]-D-(SEQ ID NO: 24) (herein referred to as BCY13121);

[Ac]-(SEQ ID NO: 24)-L[dH]G[dK] (herein referred to as BCY13125);

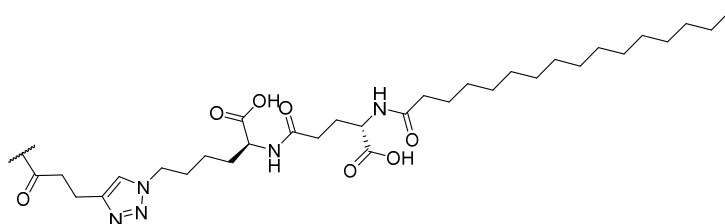
[PYA]-[B-Ala]-[Sar₁₀]-VGP-(SEQ ID NO: 25) (herein referred to as BCY8941);

Ac-A-[HArg]-D-(SEQ ID NO: 26) (herein referred to as BCY11815);
Ac-A-[HArg]-D-(SEQ ID NO: 27) (herein referred to as BCY11816);
Ac-A-[HArg]-D-(SEQ ID NO: 28) (herein referred to as BCY11817);
Ac-A-[HArg]-D-(SEQ ID NO: 29) (herein referred to as BCY12735);
(Palmitoyl-Glu-LysN₃)[PYA]A[HArg]D-(SEQ ID NO: 29) (hereinafter known as BCY14327);

Ac-A-[HArg]-D-(SEQ ID NO: 30) (herein referred to as BCY12736);
Ac-A-[HArg]-D-(SEQ ID NO: 31) (herein referred to as BCY12737);
A-[HArg]-D-(SEQ ID NO: 32) (herein referred to as BCY12738);
A-[HArg]-E-(SEQ ID NO: 32) (herein referred to as BCY12739);
A-[HArg]-D-(SEQ ID NO: 33) (herein referred to as BCY12854);
A-[HArg]-D-(SEQ ID NO: 34) (herein referred to as BCY12855);
A-[HArg]-D-(SEQ ID NO: 35) (herein referred to as BCY12856);
A-[HArg]-D-(SEQ ID NO: 35)-[dA] (herein referred to as BCY12857);
(SEQ ID NO: 35)-[dA] (herein referred to as BCY12861);
[NMeAla]-[HArg]-D-(SEQ ID NO: 35) (herein referred to as BCY13122);
[dA]-ED-(SEQ ID NO: 35) (herein referred to as BCY13126);
[dA]-[dA]-D-(SEQ ID NO: 35) (herein referred to as BCY13127);
AD-(SEQ ID NO: 35) (herein referred to as BCY13128);
A-[HArg]-D-(SEQ ID NO: 36) (herein referred to as BCY12858);
A-[HArg]-D-(SEQ ID NO: 37) (herein referred to as BCY12859);
Ac-(SEQ ID NO: 37)-[dK] (herein referred to as BCY13120);
A-[HArg]-D-(SEQ ID NO: 38) (herein referred to as BCY12862);
A-[HArg]-D-(SEQ ID NO: 39) (herein referred to as BCY12863);
[dA]-[HArg]-D-(SEQ ID NO: 39)-[dA] (herein referred to as BCY12864);
(SEQ ID NO: 40)-[dA] (herein referred to as BCY12865);
A-[HArg]-D-(SEQ ID NO: 41) (herein referred to as BCY12866);
A-[HArg]-D-(SEQ ID NO: 42) (herein referred to as BCY13116);
A-[HArg]-D-(SEQ ID NO: 43) (herein referred to as BCY13117);
A-[HArg]-D-(SEQ ID NO: 44) (herein referred to as BCY13118);

[dA]-[HArg]-D-(SEQ ID NO: 46)-[dA] (herein referred to as BCY13123);
[d1Nal]-[HArg]-D-(SEQ ID NO: 46)-[dA] (herein referred to as BCY13124);
A-[HArg]-D-(SEQ ID NO: 47) (herein referred to as BCY13130);
A-[HArg]-D-(SEQ ID NO: 48) (herein referred to as BCY13131);
A-[HArg]-D-(SEQ ID NO: 49) (herein referred to as BCY13132);
A-[HArg]-D-(SEQ ID NO: 50) (herein referred to as BCY13134);
A-[HArg]-D-(SEQ ID NO: 51) (herein referred to as BCY13135);
(SEQ ID NO: 154)-[dK] (herein referred to as BCY13129);
A[HArg]D-(SEQ ID NO: 155) (herein referred to as BCY13133);
A[HArg]D-(SEQ ID NO: 156) (herein referred to as BCY13917);
A[HArg]D-(SEQ ID NO: 157) (herein referred to as BCY13918);
A[HArg]D-(SEQ ID NO: 158) (herein referred to as BCY13919);
A[HArg]D-(SEQ ID NO: 159) (herein referred to as BCY13920);
A[HArg]D-(SEQ ID NO: 160) (herein referred to as BCY13922);
A[HArg]D-(SEQ ID NO: 161) (herein referred to as BCY13923);
A[HArg]D-(SEQ ID NO: 162) (herein referred to as BCY14047);
A[HArg]D-(SEQ ID NO: 163) (herein referred to as BCY14048); and
A[HArg]D-(SEQ ID NO: 164) (herein referred to as BCY14313);

wherein PYA represents 4-pentynoic acid, B-Ala represents beta-alanine, Sar₁₀ represents 10 sarcosine units, HArg represents homoarginine, NMeAla represents N-methyl-alanine, 1Nal represents 1-naphthylalanine, Palmitoyl-Glu-LysN₃[PYA] represents:



(Palmitoyl-Glu-LysN₃)[PYA]

, or a pharmaceutically

acceptable salt thereof; and/or

(vi) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the EphA2 binding bicyclic peptide ligand comprises N-terminal modifications and comprises:

A-[HArg]-D-(SEQ ID NO: 24) (herein referred to as BCY9594);
wherein HArg represents homoarginine, or a pharmaceutically acceptable salt thereof;
and/or
(vii) the first peptide ligand comprises an EphA2 binding bicyclic peptide ligand and the
EphA2 binding bicyclic peptide ligand comprises N-terminal modifications and comprises:
A-[HArg]-D-(SEQ ID NO: 44) (herein referred to as BCY13118);
wherein HArg represents homoarginine, or a pharmaceutically acceptable salt thereof.

14. The use of claim 13, wherein the heterotandem bicyclic peptide complex is selected
from those listed in Table C, such as BCY12491, BCY12730, BCY13048, BCY13050,
BCY13053 and BCY13272, or a pharmaceutically acceptable salt thereof.

15. The use of any one of claims 1-9 or 13-14, wherein the heterotandem bicyclic peptide
complex is BCY13272, or a pharmaceutically acceptable salt thereof.

16. The use of any one of the preceding claims, wherein the molecular scaffold is 1,1',1''-
(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA).

17. The use of any one of the proceeding claims, wherein the immuno-oncology agent
is:

- (i) a small molecule, antibody or biologic;
- (ii) a checkpoint inhibitor;
- (iii) a checkpoint inhibitor and the checkpoint inhibitor is an antibody; and/or
- (iv) an antagonist of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9,
CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48,
GARP, PD1H, LAIR1, TIM-1, or TIM-4.

18. The use of claim 17, wherein the immuno-oncology agent is checkpoint inhibitor
and the checkpoint inhibitor is:

- (i) an antagonist of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, or TIGIT;
- (ii) a PD-1 antagonist;
- (iii) an anti-PD-1 antibody;
- (iii) an anti-PD-1 antibody and the anti-PD-1 antibody is pembrolizumab or nivolumab;
- (iv) an anti-PD-L1 antibody;
- (v) an anti-PD-L1 antibody and the anti-PD-L1 antibody is durvalumab or atezolizumab;
- (vi) an anti-CTLA-4 antibody; or
- (vii) an anti-CTLA-4 antibody and the anti-CTLA-4 antibody is ipilimumab.

19. The use of any of the preceding claims, wherein:

- (i) the heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, and the immuno-oncology agent are formulated for administration simultaneously or sequentially;
- (ii) the heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, and the immuno-oncology agent are formulated for administration within 1, 2, 3, 4, 5, 6, or 7 days from one another;
- (iii) the heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, is formulated for administration by an intravenous infusion; and/or
- (iv) the heterotandem bicyclic peptide complex, or a pharmaceutically acceptable salt thereof, is formulated for administration at a frequency of once a week or twice a week.

20. The use of any of claims 1-12 or 16-19, wherein BT7480, or a pharmaceutically acceptable salt thereof, is formulated for administration at a dose of about 0.1-75 mg/kg.

21. Use of BT7480, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is formulated for use in combination with a checkpoint inhibitor.

21. The use of any one of claims 1-12 or 16-20, wherein the cancer is high Nectin-4 expressing.
22. The use of any one of claims 1-12 or 16-21, wherein:
- (i) the cancer is a solid tumor;
 - (ii) the cancer is a solid tumor and the solid tumor is sarcoma, carcinoma, or lymphoma; and/or
 - (iii) the cancer is colon cancer.
24. Use of BT7455, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is used in combination with a checkpoint inhibitor.
25. The use of any one of claims 1-9, 13-19, or 24, wherein the cancer is high EphA2 expressing.