administered in combination with a second therapeutic agent, wherein the second therapeutic agent is a PARP inhibitor. The present invention discloses methods of treating triple-negative breast cancer by co-administration of a BET bromodomain inhibitor of Formula Ia or Formula Ib, or a pharmaceutically acceptable salt or co-crystal thereof, and a second therapeutic agent to a subject in need thereof.

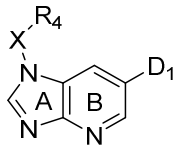
[008] In some examples, the BET bromodomain inhibitor is administered simultaneously with the second therapeutic agent. In some examples, the BET bromodomain inhibitor is administered sequentially with the second therapeutic agent. In some examples, the BET bromodomain inhibitor is administered in a single pharmaceutical composition with the second therapeutic agent. In some examples, the BET bromodomain inhibitor and the second therapeutic agent are administered as separate compositions. In some examples, the BET bromodomain inhibitor and the second therapeutic agent are administered in combination with a checkpoint inhibitor.

[009] In some examples the second therapeutic agent is an agent used to treat breast cancer. In some examples, the breast cancer is TNBC.

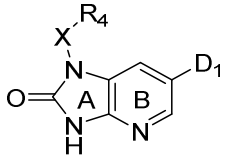
[0010] In some examples, the second therapeutic agent is a PARP inhibitor.

[0011] In some examples, the BET bromodomain inhibitor and the PARP inhibitor are administered in combination with a checkpoint inhibitor.

[0012] The BET bromodomain inhibitor used in the combination therapies of the invention is a compound of Formula Ia or Formula Ib



(Formula Ia)



(Formula Ib)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or co-crystal thereof,

Claims

1. Use of a BET bromodomain inhibitor selected from 1-benzyl-6-(3,5-dimethylisoxazol-4-yl)-N-methyl-1H-imidazo[4,5-b]pyridin-2-amine (Compound I), 1-benzyl-6-(3,5-dimethylisoxazol-4-yl)-1H-imidazo[4,5-b]pyridin-2-amine, and pharmaceutically acceptable salts/co-crystals thereof, in the manufacture of a medicament for use in combination therapy for treating breast cancer, wherein the medicament is to be administered in combination with a second therapeutic agent, wherein the second therapeutic agent is a PARP inhibitor.

2. The use of claim 1, wherein the BET bromodomain inhibitor is Compound I.

3. The use of claim 1 or claim 2, wherein the BET bromodomain inhibitor is the mesylate salt/co-crystal of Compound I Form I.

~~4. The use according to any one of claims 1-3, wherein the second therapeutic agent is a PARP inhibitor.~~

~~5.~~4. The use according to claim ~~4~~1, further comprising a checkpoint inhibitor to be administered.

~~6.~~5. The use according to any one of claims 1-3, wherein the second therapeutic agent is talazoparib.

~~7.~~6. The use according to any one of claims 1-~~6~~5, wherein the breast cancer is triple-negative breast cancer (TNBC).

~~8.~~7. The use according to any one of claims 1-~~7~~6, wherein the subject previously has been treated with a breast cancer therapy.

~~9.~~8. The use according to any one of claims ~~8~~7, wherein the breast cancer therapy is chemotherapy.

~~10.~~9. The use according to any one of claims ~~8~~7, wherein the breast cancer therapy is immunotherapy.

~~11.~~10. The use according to any one of claims 1-~~10~~9, wherein the subject previously has shown disease progression on treatment with a PARP inhibitor.

~~12.~~11. The use according to any one of claims 1-~~11~~10, wherein the subject is a human.

~~13.~~12. The use according to any one of claims 1-~~12~~11, wherein the subject with breast cancer has one or both germline mutations BRCA1 and BRCA2.

~~14.~~13. The use according to any one of claims 1-11~~12~~, wherein the subject with breast cancer does not carry germline mutations BRCA1 or BRCA2.

~~15.~~14. The use according to any one of claims 1-11~~12~~, wherein the subject with breast cancer has somatic mutations to either BRCA1 or BRCA2.

~~16.~~15. The use according to any one of claims 1-11~~12~~, wherein the subject with breast cancer has one or more somatic mutations to homologous recombination (HR) genes, including ATM, CHEK2, NBN, PALB2, ATR, RAD51, RAD54, DSS1, RPA1, CHK1, FANCD2, FANCA, FANCC, FANCM, BARD1, RAD51C, RAD51D, RIF1, and BRIP1.

~~17.~~16. The use according to any one of claims 1-11~~12~~, wherein the subject with breast cancer has one or more germline mutations to homologous recombination (HR) genes, including ATM, CHEK2, NBN, PALB2, ATR, RAD51, RAD54, DSS1, RPA1, CHK1, FANCD2, FANCA, FANCC, FANCM, BARD1, RAD51C, RAD51D, RIF1, and BRIP1.

~~18.~~17. The use according to any one of claims 1-11~~12~~, wherein the subject has a tumor characterized as homologous recombination (HR)-proficient.

~~19.~~18. The use according to any one of claims 1-11~~12~~, wherein the subject has a tumor characterized as homologous recombination deficient (HRD).

~~20.~~19. The use according to claim 1, wherein a compound selected from 1-benzyl-6-(3,5-dimethylisoxazol-4-yl)-N-methyl-1H-imidazo[4,5-b]pyridin-2-amine (Compound I) and 1-benzyl-

6-(3,5-dimethylisoxazol-4-yl)-1H-imidazo[4,5-b]pyridin-2-amine and pharmaceutically acceptable salts or co-crystals thereof, is to be dosed with a PARP inhibitor without resulting in thrombocytopenia as a dose-limiting toxicity.

~~21.~~20. The use according to claim ~~20~~19, wherein the PARP inhibitor is talazoparib.