not carry germline BRCA1 or BRCA2 mutations and would therefore not derive benefit from treatment with a PARP inhibitor (O'Shaughnessy et al. 2014).

[005] In the preclinical setting, combinatorial strategies hold the promise of sensitizing BRCA-proficient tumors to PARP inhibitors and new data has been generated with some bromodomain and extra-terminal domain (BET) inhibitors. BET proteins are epigenetic readers and exhibit high selectivity for acetylated lysine residues in histones and other proteins. They function as transcription regulators via association with many gene promoters or enhancers. Early clinical trials with BET inhibitors (BETi) showed limited single-agent activity in patients with hematologic malignancies (Berthon et al. 2016), NUT carcinoma (Stathis et al. 2016) and very recently in solid tumors (Aftimos et al. 2017). However, there is promise for BETi in combinations with other agents as they modulate resistance mechanisms and confer sensitivity to various agents. Several explorative combination clinical trials are ongoing with BETi including combination with checkpoint monoclonal antibodies, androgen receptor antagonists, estrogen modulators, BCL2 inhibitors, and others.

[006] However, at this time, it is unclear which, BET inhibitors will combine synergistically with a PARP inhibitor; what level of synergy is required; and which PARP inhibitor will be the best combination partner for each BET inhibitor, resulting in clinical benefit when administered to patients with TNBC. In addition to a clinical benefit, the combination also has to be safe and well tolerated at the efficacious doses. It cannot be predicted from the art which combinations will show the best overall profile.

SUMMARY

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

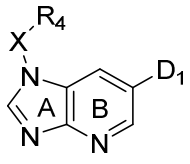
[008] In some examples, the BET bromodomain inhibitor is administered simultaneously with the second therapeutic agent. In some examples, the BET bromodomain inhibitor is administered sequentially with the second therapeutic agent. In some examples, the BET bromodomain inhibitor is administered in a 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.

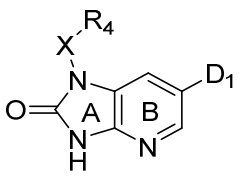
[0010] In some examples, the second therapeutic agent is a PARP inhibitor.

[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,

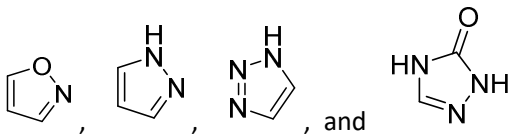
wherein:

Ring A and **Ring B** may be optionally substituted with groups independently selected from hydrogen, deuterium, -NH_2, amino, heterocycle(C_4-C_6), carbocycle(C_4-C_6), halogen, -CN, -OH, -CF_3, alkyl (C_1-C_6), thioalkyl (C_1-C_6), alkenyl (C_2-C_6), and alkoxy (C_1-C_6);

X is selected from –NH-, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2CH_2O-, -CH_2CH_2NH-, -CH_2CH_2S-, -C(O)-, -C(O)CH_2-, -C(O)CH_2CH_2-, -$CH_2C(O)$-, -$CH_2CH_2C(O)$-, -C(O)NH-, -C(O)O-, -C(O)S-, -C(O)$NHCH_2$-, -C(O)OCH_2-, -C(O)SCH_2-, wherein one or more hydrogen may independently be replaced with deuterium, hydroxyl, methyl, halogen, -CF_3, ketone, and where S may be oxidized to sulfoxide or sulfone;

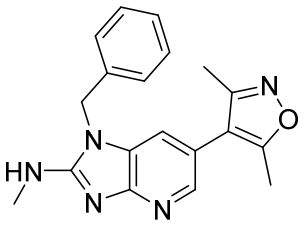
R_4 is selected from optionally substituted 3-7 membered carbocycles and heterocycles; and

D_1 is selected from the following 5-membered monocyclic heterocycles:



which are optionally substituted with deuterium, alkyl (C_1-C_4), alkoxy (C_1-C_4), amino, halogen, amide, -CF_3, -CN, -N_3, ketone (C_1-C_4), -S(O)Alkyl(C_1-C_4), -SO_2alkyl(C_1-C_4), -thioalkyl(C_1-C_4), -COOH, and/or ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0013] In some examples, the BET bromodomain inhibitor for use in the combination therapies of the invention is a compound of Formula Ia. In some examples, the compound of Formula Ia is 1-benzyl-6-(3,5-dimethylisoxazol-4-yl)-N-methyl-1H-imidazo[4,5-b]pyridine-2-amine (“Compound I”), which has the following formula:



(Compound I)

[0014] In some examples, the BET bromodomain inhibitor of Formula Ia is a pharmaceutically acceptable salt or co-crystal of Compound I. In some examples, the BET bromodomain inhibitor is a mesylate salt/co-crystal of Compound I in crystalline form I.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 shows the effect of Compound I, talazoparib, and the combination of Compound I and talazoparib on cell viability of TNBC HCC1937 cells (mutant BRCA1).

[0016] FIG. 2 shows the effect of Compound I, olaparib, and the combination of Compound I and olaparib on cell viability of TNBC HCC1937 cells (mutant BRCA1).

[0017] FIG. 3 shows the effect of Compound I, veliparib, and the combination of Compound I and veliparib on cell viability of TNBC cell line HCC1937 (BRCA1 mutant).

[0018] FIG. 4 shows the effect of Compound I, olaparib, and the combination of Compound I and olaparib on cell viability of TNBC HCC1599 cells (mutant BRCA2).

[0019] FIG. 5 shows the effect of Compound I, talazoparib, and the combination of Compound I and talazoparib on cell viability of TNBC BT549 cells (wild-type BRCA1 and BRCA2).

[0020] FIG. 6 shows the effect of Compound I, veliparib, and the combination of Compound I and veliparib on cell viability of TNBC BT549 cells (wild-type BRCA1 and BRCA2).

[0021] FIG. 7 shows the effect of Compound I, olaparib, and the combination of Compound I and olaparib on cell viability of TNBC BT549 cells (wild-type BRCA1 and BRCA2).

[0022] FIG. 8 shows the effect of Compound I, niraparib, and the combination of Compound I and niraparib on cell viability of HCC-70 cells (wild-type BRCA-1 and BRCA-2).

[0023] FIG. 9 shows an X-ray powder diffractogram (XRPD) of a mesylate salt/co-crystal of Compound I.

[0024] FIG. 10 shows a differential scanning calorimeter (DSC) curve of a mesylate salt/co-crystal of Compound I.

[0025] FIG. 11 shows a thermogravimetric analysis (TGA) of a mesylate salt/co-crystal of Compound I.

Claims

What is claimed is:

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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