CLAIMS

What it claimed is:

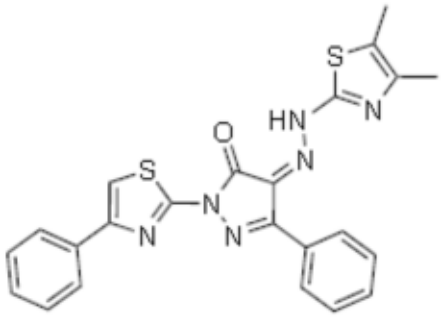
1. A pharmaceutical combination, comprising:

a B-cell lymphoma 2 associated X protein (BAX) activating compound; and

an anti-apoptotic protein inhibiting compound.

2. The pharmaceutical combination of claim 1, wherein the anti-apoptotic protein inhibiting compound is a BCL-XL inhibiting compound, a BCL-2 inhibiting compound, a BCL-w inhibiting compound, a BFL-1 inhibiting compound or a MCL-1 inhibiting compound.

3. The pharmaceutical combination of claim 1 or 2, wherein the BAX activating compound is a compound having a structure of BTSA1.2, or a pharmaceutically acceptable salt thereof



BTSA 1.2.

4. The pharmaceutical combination of claim 1 or claim 2, wherein the anti-apoptotic protein inhibiting compound comprises navitoclax or venetoclax.

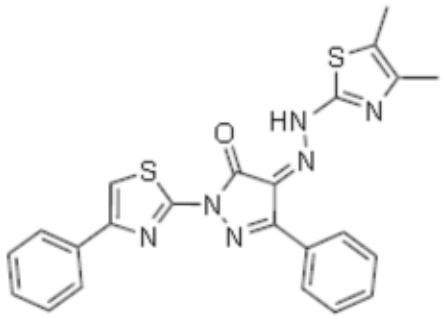
5. The pharmaceutical combination of claim 1 or 2, wherein the anti-apoptotic protein inhibiting compound is ABT-737, navitoclax, venetoclax, AMG 176, AMG 397, AZD-4320, AZD-0466, AZD-5991, VU661013, S65487, MIK665, sabutoclax, gambogic acid, obatoclax mesylate, APG1252, DT2216 or a combination of any of the foregoing.

6. A pharmaceutical composition comprising the pharmaceutical combination of any of claims 1-3, and a pharmaceutically acceptable carrier.

7. Use of a B-cell lymphoma 2 associated X protein (BAX) activating compound in the manufacturing of a pharmaceutical composition for treating a cancer in a subject in

combination with a B-cell lymphoma-extra large protein (BCL-XL) inhibiting compound, a BCL-2 inhibiting compound, a BCL-w inhibiting compound, a BFL-1 inhibiting compound or a MCL-1 inhibiting compound in an amount effective to treat the cancer in the subject.

8. The use of claim 7, wherein the BAX activating compound is a compound having a structure of BTSA1.2, or a pharmaceutically acceptable salt thereof.



BTSA1.2

9. The use of claim 7 or 8, wherein the anti-apoptotic protein inhibiting compound comprises Navitoclax or Venetoclax.

10. The use of any of claims 7-9, wherein the cancer is a hematological cancer or a solid tumor.

11. The use of any of claims 7-10, wherein the cancer is breast cancer, prostate cancer, lymphoma, skin cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, melanoma, malignant melanoma, ovarian cancer, brain or spinal cord cancer, primary brain carcinoma, medulloblastoma, neuroblastoma, glioma, head-neck cancer, glioma, glioblastoma, liver cancer, bladder cancer, stomach cancer, kidney cancer, placental cancer, cancer of the gastrointestinal tract, non-small cell lung cancer (NSCLC), head or neck carcinoma, breast carcinoma, endocrine cancer, eye cancer, genitourinary cancer, cancer of the vulva, ovary, uterus or cervix, hematopoietic cancer, myeloma, leukemia, lymphoma, ovarian carcinoma, lung carcinoma, small-cell lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, bladder carcinoma, pancreatic carcinoma, stomach carcinoma, colon carcinoma, prostatic carcinoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, myeloma, multiple myeloma, adrenal carcinoma, renal cell carcinoma, endometrial carcinoma, adrenal cortex carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoides, malignant hypercalcemia, cervical hyperplasia, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic granulocytic leukemia,

acute granulocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, polycythemia vera, essential thrombocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, soft tissue cancer, soft-tissue sarcoma, osteogenic sarcoma, sarcoma, primary macroglobulinemia, central nervous system cancer and retinoblastoma.

12. The use of any of claims 7-11, wherein the cancer is colon cancer, rectal cancer, or colorectal cancer.

13. The use of any of claims 7-12, wherein a route of the administering comprises oral, rectal, sublingual, buccal, intravenous, intramuscular, transdermal, cutaneous, subcutaneous, intrathecal, nasal, vaginal, or a combination thereof.

14. The use of any of claims 7-13, wherein the route of the administering is oral.

15. Use of a combination of an anticancer agent comprising a B-cell lymphoma 2 associated X protein (BAX) activating compound and an anti-apoptotic inhibiting compound for the manufacture of a medicament for treating cancer in a subject, in which the cancer is determined to be:

(i) a cancer in which detectable level of BAX:anti-apoptotic protein complexes can be immunoprecipitated from the cancer cells, and/or

(ii) a cancer comprising cancer cells that are anti-apoptotic protein dependent or unprimed to apoptosis.

16. The use of claim 15, wherein the anti-apoptotic protein inhibiting compounds is a BCL-XL inhibiting compound, a BCL-2 inhibiting compound, a BCL-w inhibiting compound, a BFL-1 inhibiting compound or a MCL-1 inhibiting compound.

17. The use of claim 15, wherein the BAX:anti-apoptotic protein complexes are formed by co-immunoprecipitating BAX and the anti-apoptotic protein from the cancer cells.

18. The use of claim 17, wherein the BAX: anti-apoptotic protein complex is BAX:BCL-XL and the anti-apoptotic protein is BCL-XL; the BAX: anti-apoptotic protein complex is BAX:BCL-2 and the anti-apoptotic protein is BCL-2; the BAX: anti-apoptotic protein complex is BAX:BCL-w and the anti-apoptotic protein is BCL-w; the BAX: anti-

apoptotic protein complex is BAX:BFL-1 and the anti-apoptotic protein is BFL-1 or the BAX: anti-apoptotic protein complex is BAX:MCL-1 and the anti-apoptotic protein is MCL-1.

19. The use of claim 17 or claim 18, wherein the cancer is further a cancer in which the cancer cells are determined to be sensitive to the anticancer agent by detecting a level of BAX:BCL-XL, BAX:BCL-2, BAX:BCL-w, BAX:BFL-1 or BAX:MCL-1 complexes in the cancer cells that is increased as compared to normal cells of the same type.

20. The use of any of claims 16-19, wherein the cancer cells are determined to be anti-apoptotic BCL-XL, BCL-2, BCL-w, BFL-1 or MCL-1 dependent or unprimed to apoptosis by BH3 profiling.

21. The use of claim 20, wherein the BH3-profiling comprises contacting the cancer cells with a BH3 domain peptide, measuring the amount of BH3 domain peptide induced mitochondrial depolarization in the cancer cells, and comparing the amount of BH3 domain peptide induced mitochondrial depolarization in the cancer cells to a control cell population of the same type.

22. Use of a combination of an anticancer agent comprising a B-cell lymphoma 2 associated X protein (BAX) activating compound and an anti-apoptotic protein inhibiting compound for the manufacture of a medicament for treating cancer, wherein the cancer is a cancer expressing a detectable level of a gene comprising MUC13, EPS8L3, IGFBP7, or a combination thereof.

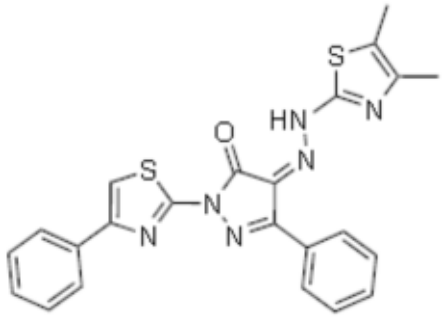
23. The use of claim 22, wherein the anti-apoptotic protein inhibiting compound is a BCL-XL inhibiting compound, a BCL-2 inhibiting compound, a BCL-w inhibiting compound, a BFL-1 inhibiting compound or a MCL-1 inhibiting compound.

24. The use of claim 23, wherein the cancer is a cancer expressing a level of the gene MUC13, EPS8L3, IGFBP7, or a combination thereof a the biological sample of the cancer that is increased as compared to a control sample.

25. The use of claim 24, wherein the biological sample comprises cancer cells and the control sample comprises normal cells of the same type.

26. The use of any of claims 23-25, wherein quantitative reverse transcription PCR is used to determine the level of gene messenger RNA in the biological sample.

27. The use of any one of claims 15-26, wherein the BAX activating compound is a compound having a structure of BTSA1.2, or a pharmaceutically acceptable salt thereof.



BTSA1.2

28. The use of any one of 15-27, wherein the anti-apoptotic inhibiting compound comprises Navitoclax or Venetoclax.