CLAIMS

What it claimed is:

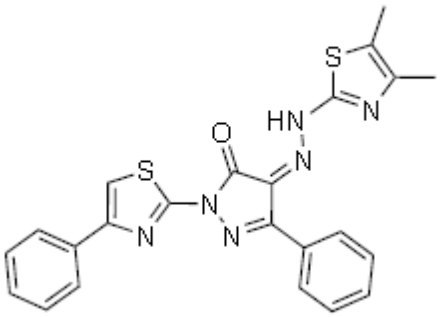
1. A pharmaceutical combination, comprising:

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.

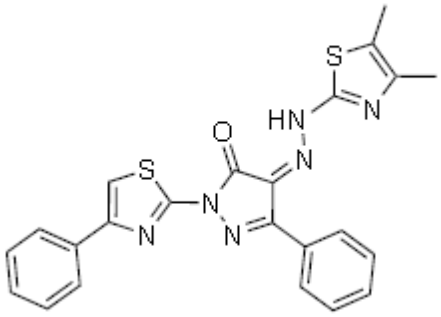
4. The pharmaceutical combination of claim 1 or claim 2, wherein the anti-apoptotic protein inhibiting compound comprises navitoclax or venetoclax.

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 ~~A method of~~ for treating a cancer in a subject ~~comprising administering to the subject a B-cell lymphoma 2 associated X protein (BAX) activating compound~~ 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 ~~method~~ 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 ~~method~~ use of claim 7 or 8, wherein the anti-apoptotic protein inhibiting compound comprises Navitoclax or Venetoclax.

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

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

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

~~15. A method of treating cancer in a subject in need thereof, the method comprising:~~

~~obtaining a biological sample comprising cancer cells from the subject;~~

~~detecting a level of BAX:anti-apoptotic protein complexes immunoprecipitated from the cancer cells and/or detecting that the cancer cells are anti-apoptotic protein-dependent or unprimed to apoptosis; and~~

~~administering to the subject an anticancer agent comprising a B-cell lymphoma 2 associated X protein (BAX) activating compound and an anti-apoptotic inhibiting compound in an amount effective to treat the cancer.~~

~~16. The method 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 method 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 method 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 method of claim 17 or claim 18, wherein the method further comprises determining the cancer cells are sensitive to the anticancer agent when the level of BAX:BCL-XL, BAX:BCL-2, BAX:BCL-w, BAX:BFL-1 or BAX:MCL-1 complexes in the cancer cells is increased as compared to normal cells of the same type.

20. The method of any of claims 16-19, wherein the detecting that the cancer cells are anti-apoptotic BCL-XL, BCL-2, BCL-w, BFL-1 or MCL-1 dependent or unprimed to apoptosis comprises BH3 profiling.

21. The method 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. A method of treating cancer in a subject in need thereof, the method comprising:

obtaining a biological sample from the subject;

measuring expression level of at least one gene in the biological sample, wherein the gene comprises MUC13, EPS8L3, IGFBP7, or a combination thereof; and

administering to the subject an anticancer agent comprising a B-cell lymphoma 2 associated X protein (BAX) activating compound and an anti-apoptotic protein inhibiting compound in an amount effective to treat the cancer.

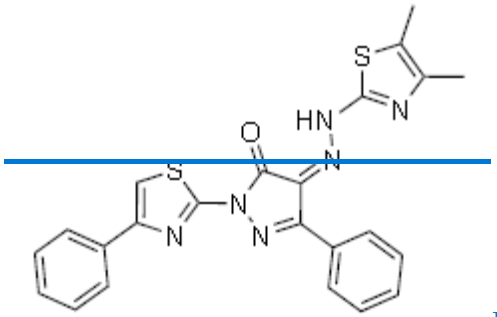
~~23. The method of claim 22, wherein the anti-apoptotic protein inhibiting compound is a BCL-XL inhibiting compound, a BCL-2 inhibiting compound, a BCL-w inhibiting compound, a BFL-1 inhibiting compound or a MCL-1 inhibiting compound.~~

~~24. The method of claim 23, the method further comprises determining that the expression level of the gene MUC13, EPS8L3, IGFBP7, or a combination thereof in the biological sample is increased as compared to a control sample prior to administering the sample and the anti-apoptotic protein inhibiting compound is a BCL-XL inhibiting compound.~~

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

~~26. The method of any of claims 23-25, wherein the detecting comprises quantitative reverse transcription PCR to determine the level of gene messenger RNA in the biological sample.~~

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