# ENDOXIFEN FOR TREATMENT OF CANCERS

## BACKGROUND

## CROSS-REFERENCE

**[0001]** The present application claims the benefit of U.S. Provisional Application No. 63/272,869, entitled "ENDOXIFEN FOR TREATMENT OF CANCERS," filed on October 28, 2021, which application is herein incorporated by reference in its entirety for all purposes.

**[0002]** While cancer survival rates have been increasing over the last few decades, cancer remains the second leading cause of death in the United States. Despite extensive research into treatments and prevention, drug resistance and relapse remain limiting factors in developing cancer cures. To combat these and other factors, there is a need for cancer therapies capable of overcoming drug resistance and preventing relapse.

## SUMMARY

**[0002a]** In an aspect, there is provided the use of a therapeutically effective amount of an oral formulation of (Z)-endoxifen in the manufacture of a medicament for treating a cancer in a subject in need thereof.

**[0003]** In various examples, the present disclosure provides a method of treating a gastrointestinal cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of endoxifen, thereby treating the gastrointestinal cancer.

**[0004]** In some examples, the gastrointestinal cancer is a colorectal cancer, a gastric cancer, a pancreatic cancer, an esophageal cancer, a rectal cancer, a biliary cancer, a cholangiocarcinoma, or a combination thereof. In some examples, the gastrointestinal cancer is a carcinoma. In some examples, the gastrointestinal cancer is an adenocarcinoma. In some examples, the gastrointestinal cancer is a colorectal cancer. In some examples, the gastrointestinal cancer is a colon cancer. In some examples, the colon cancer is sigmoid colon cancer, adenocarcinoma of the colon, stage III colorectal cancer, stage IV colorectal cancer, or descending colon cancer. In some examples, the colorectal cancer is colon cancer, sigmoid colon cancer, adenocarcinoma of the colon, stage III colorectal cancer, stage IV colorectal cancer, or descending colon cancer.

**[0005]** In some examples, the gastrointestinal cancer is a gastric cancer. In some examples, the gastrointestinal cancer is a pancreatic cancer. In some examples, the

pancreatic cancer is pancreatic ductal adenocarcinoma, metastatic pancreatic ductal adenocarcinoma, or stage III metastatic pancreatic ductal adenocarcinoma.

**[0006]** In some examples, the gastrointestinal cancer is an esophageal cancer. In some examples, the esophageal cancer is esophageal adenocarcinoma or metastatic esophageal cancer. In some examples, the gastrointestinal cancer is a rectal cancer. In some examples, the rectal cancer is rectum adenocarcinoma. In some examples, the gastrointestinal cancer is a cholangiocarcinoma. In some

examples, the cholangiocarcinoma is metastatic cholangiocarcinoma. In some examples, the gastrointestinal cancer is metastatic. In some examples, the gastrointestinal cancer is recurrent.

**[0007]** In various examples, the present disclosure provides a method of treating a skin cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of endoxifen, thereby treating the skin cancer.

**[0008]** In some examples, the skin cancer is a melanoma. In some examples, the melanoma is acral melanoma, recurrent acral melanoma, or anorectal melanoma. In some examples, the skin cancer is metastatic. In some examples, the skin cancer is recurrent.

**[0009]** In various examples, the present disclosure provides a method of treating neuroblastoma in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of endoxifen, thereby treating the neuroblastoma.

**[0010]** In some examples, the neuroblastoma is metastatic. In some examples, the neuroblastoma is recurrent.

**[0011]** In some examples, the endoxifen is (Z)-endoxifen. In some examples, the (Z)-endoxifen has an isomeric purity of at least 90%. In some examples, the endoxifen administered orally, topically, rectally, intravenously, intra-arterially, parenterally, transdermally, or via inhalation. In some examples, the endoxifen is administered orally. In some examples, the endoxifen is formulated as a sustained-release composition or a delayed release composition. In some examples, the endoxifen is formulated as a capsule or a tablet. In some examples, the endoxifen is administered topically or transdermally. In some examples, the endoxifen is formulated is a cream, a gel, a cream, an emulsion, a lotion, an ointment, a solution, a paste, a patch, or an oil.

**[0012]** In some examples, the method comprises administering the endoxifen to the subject daily. In some examples, the method comprises administering the endoxifen to the subject at a dose of no less than 1 mg and no more than 160 mg per day. In some examples, the method comprises administering the endoxifen to the subject at a dose of no less than 1 mg and no more than 40 mg per day. In some examples, the method comprises administering the endoxifen to the subject at a dose of no less than 1 mg and no more than 10 mg per day. In some examples, the method comprises administering the endoxifen to the subject at a dose of no less than 2 mg and no more than 5 mg per day. In some examples, the method comprises administering the endoxifen 1, 2, 3, or 4 times per day. In some examples, the method comprises administering the endoxifen for at least 7, at least 14, at least 21, or at least 28 days.

**[0013]** In some examples, the administering achieves a systemic endoxifen $C_{max}$ of between about 0.01 and about 50 μM in the subject. In some examples, the administering achieves a systemic endoxifen $C_{max}$ of between about 1 and about 10 μM in the subject. In some examples, the

administering maintains a systemic endoxifen concentration of at least 1 μM for at least one week in the subject

**[0014]** In some examples, the method further comprises administering an additional therapeutic agent. In some examples, the additional therapeutic agent comprises an anti-cancer agent. In some examples, the anti-cancer agent is selected from the group consisting of bicalutamide, enzalutamide, trastuzumab, atezolizumab, alpelisib, olaparib, talazoparib, ribociclib, neratinib, an antineoplastic, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, pegylated liposomal doxorubicin, epirubicin, fluorouracil, gemcitabine, methotrexate, paclitaxel, protein-bound paclitaxel, vinorelbine, eribulin, ixabepilone, an immune checkpoint inhibitor, a PD1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, and an ATP-cassette binding protein inhibitor. In some examples, the additional therapeutic agent comprises a selective serotonin reuptake inhibitor. In some examples, the selective serotonin reuptake inhibitor comprises citalopram, escitalopram, fluoxetine, paroxetine, sertraline, or vilazodone.

**[0015]** In some examples, the method further comprises surgical tumor removal. In some examples, the administering the therapeutically effective amount of endoxifen is concurrent with, subsequent to, or concurrent with and subsequent to the surgical tumor removal. In some examples, the method further comprises radiotherapy. In some examples, the administering the therapeutically effective amount of endoxifen is concurrent with, subsequent to, or concurrent with and subsequent to the radiotherapy.

## INCORPORATION BY REFERENCE

**[0016]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee. The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

**[0018] FIG. 1** shows a histogram depicting the number of samples derived from patients diagnosed with various cancer types, including Breast Cancer (BRST), Cervical Carcinoma (CC), Cholangiocarcinoma (CHOL), Colorectal Cancer (CRC), Esophageal Adenocarcinoma

## CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of an oral formulation of (Z)-endoxifen in the manufacture of a medicament for treating a cancer in a subject in need thereof.

2. The use of claim 1, wherein the cancer is a skin cancer.

3. The use of claim 2, wherein the skin cancer is a melanoma.

4. The use of claim 3, wherein the melanoma is acral melanoma, recurrent acral melanoma, or anorectal melanoma.

5. The use of any one of claims 2-4, wherein the skin cancer is metastatic.

6. The use of any one of claims 2-5, wherein the skin cancer is recurrent.

7. The use of claim 1, wherein the cancer is a neuroblastoma.

8. The use of claim 7, wherein the neuroblastoma is metastatic.

9. The use of claim 7 or claim 8, wherein the neuroblastoma is recurrent.

10. The use of claim 1, wherein the cancer is a gastrointestinal cancer.

11. The use of claim 10, wherein the gastrointestinal cancer is a colorectal cancer, a gastric cancer, a pancreatic cancer, an esophageal cancer, a rectal cancer, a biliary cancer, a cholangiocarcinoma, or a combination thereof.

12. The use of claim 10 or claim 11, wherein the gastrointestinal cancer is a carcinoma.

13. The use of any one of claims 10-12, wherein the gastrointestinal cancer is an adenocarcinoma.

14. The use of any one of claims 10-13, wherein the gastrointestinal cancer is a colorectal cancer.

15. The use of any one of claims 10-14, wherein the gastrointestinal cancer is a colon cancer.

16. The use of claim 15, wherein the colon cancer is sigmoid colon cancer, adenocarcinoma of the colon, stage III colorectal cancer, stage IV colorectal cancer, or descending colon cancer.

17. The use of any one of claims 11-16, wherein the colorectal cancer is colon cancer, sigmoid colon cancer, adenocarcinoma of the colon, stage III colorectal cancer, stage IV colorectal cancer, or descending colon cancer.

18. The use of any one of claims 10-13, wherein the gastrointestinal cancer is a gastric cancer.

19. The use of any one of claims 10-13, wherein the gastrointestinal cancer is a pancreatic cancer.

20. The use of claim 19, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma, metastatic pancreatic ductal adenocarcinoma, or stage III metastatic pancreatic ductal adenocarcinoma.

21. The use of any one of claims 10-13, wherein the gastrointestinal cancer is an esophageal cancer.

22. The use of claim 21, wherein the esophageal cancer is esophageal adenocarcinoma or metastatic esophageal cancer.

23. The use of any one of claims 10-13, wherein the gastrointestinal cancer is a rectal cancer.

24. The use of claim 23, wherein the rectal cancer is rectum adenocarcinoma.

25. The use of any one of claims 10-13, wherein the gastrointestinal cancer is a cholangiocarcinoma.

26. The use of claim 25, wherein the cholangiocarcinoma is metastatic cholangiocarcinoma.

27. The use of any one of claims 10-26, wherein the gastrointestinal cancer is metastatic.

28. The use of any one of claims 10-27, wherein the gastrointestinal cancer is recurrent.

29. The use of any one of claims 1-28, wherein the (Z)-endoxifen has an isomeric purity of at least 90%.

30. The use of claim 29, wherein the (Z)-endoxifen is formulated as a sustained-release composition or a delayed release composition.

31. The use of claim 30, wherein the (Z)-endoxifen is formulated as a capsule or a tablet.

32. The use of any one of claims 1-31, comprising the (Z)-endoxifen to be administered to the subject daily.

33. The use of any one of claims 1-32, comprising the (Z)-endoxifen to be administered to the subject at a dose of no less than 1 mg and no more than 160 mg per day.

34. The use of any one of claims 1-33, comprising the (Z)-endoxifen to be administered to the subject at a dose of no less than 1 mg and no more than 40 mg per day.

35. The use of any one of claims 1-34, comprising the (Z)-endoxifen to be administered to the subject at a dose of no less than 1 mg and no more than 10 mg per day.

36. The use of any one of claims 1-35, comprising the (Z)-endoxifen to be administered to the subject at a dose of no less than 2 mg and no more than 5 mg per day.

37. The use of any one of claims 1-36, comprising the (Z)-endoxifen to be administered 1, 2, 3, or 4 times per day.

38. The use of any one of claims 1-37, comprising the (Z)-endoxifen to be administered for at least 7, at least 14, at least 21, or at least 28 days.

39. The use of any one of claims 1-38, wherein the administering achieves a systemic (Z)-endoxifen $C_{max}$ of between about 0.01 and about 50 μM in the subject.

40. The use of any one of claims 1-39, wherein the administering achieves a systemic (Z)-endoxifen $C_{max}$ of between about 1 and about 10 μM in the subject.

41. The use of any one of claims 1-40, wherein the administering maintains a systemic (Z)-endoxifen concentration of at least 1 μM for at least one week in the subject.

42. The use of any one of claims 1-41, further comprising an additional therapeutic agent to be administered.

43. The use of claim 42, wherein the additional therapeutic agent comprises an anti-cancer agent.

44. The use of claim 43, wherein the anti-cancer agent is selected from the group consisting of bicalutamide, enzalutamide, trastuzumab, atezolizumab, alpelisib, olaparib, talazoparib,

ribociclib, neratinib, an antineoplastic, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, pegylated liposomal doxorubicin, epirubicin, fluorouracil, gemcitabine, methotrexate, paclitaxel, protein-bound paclitaxel, vinorelbine, eribulin, ixabepilone, an immune checkpoint inhibitor, a PD1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, and an ATP-cassette binding protein inhibitor.

45. The use of claim 42, wherein the additional therapeutic agent comprises a selective serotonin reuptake inhibitor.

46. The use of claim 45, wherein the selective serotonin reuptake inhibitor comprises citalopram, escitalopram, fluoxetine, paroxetine, sertraline, or vilazodone.

47. The use of any one of claims 1-46, further comprising surgical tumor removal.

48. The use of claim 47, wherein the administering the therapeutically effective amount of (Z)-endoxifen is concurrent with, subsequent to, or concurrent with and subsequent to the surgical tumor removal.

49. The use of any one of claims 1-48, further comprising radiotherapy.

50. The use of claim 49, wherein the therapeutically effective amount of (Z)-endoxifen is to be administered concurrent with, subsequent to, or concurrent with and subsequent to the radiotherapy.