

**COMBINATIONS OF STAT-INHIBITORS AND IMMUNE CHECKPOINT
INHIBITORS FOR THE TREATMENT AND/OR MANAGEMENT OF CANCER
CROSS-REFERENCE**

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/268,897, filed March 4, 2022, which is incorporated by reference in its entirety herein.

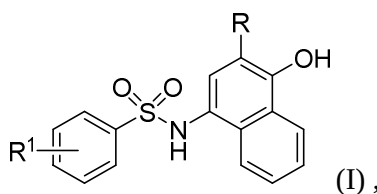
BACKGROUND

[0002] Immune checkpoints are inhibitory pathways that help maintain self-tolerance and modulate the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage. Tumors co-opt certain immune checkpoint pathways as a mechanism of immune resistance, particularly against T-cells that are specific for tumor antigens. The development of checkpoint blocking antibodies that target or are directed against, for example, programmed death 1 receptor (PD-1), can facilitate the treatment of cancers. Immunotherapies, such as anti-PD-1 or anti-PD-L1 antibody therapies, have led to improvements in treating cancers; however, there are still many patients who do not respond readily or lose responsiveness to the treatment over time. Thus, there is a need to improve cancer treatments by combining different therapies.

SUMMARY

[0003] Provided herein, in certain examples, are combinations (e.g., combinations of compounds described herein, e.g., a STAT3 inhibitor and an immune checkpoint inhibitor), which can be used, for example, in methods of treating a cancer in a subject in need thereof.

[0004] In certain examples, provided herein are methods of treating a cancer in a subject in need thereof, comprising a) orally administering to the subject an effective amount of a compound of Formula (I):

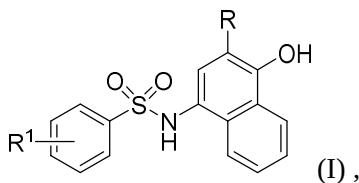


or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of hydrogen, phenylsulfanyl, 2-hydroxy-naphthalen-1-yl, quinolin-8-ylsulfanyl, triazol-3-yl sulfanyl, and benzothiazol-2-ylsulfanyl; R¹ is selected from the group consisting of hydrogen, methyl, chloro, bromo, methoxy, ethoxy, tert-butyl, nitro, methyl ester, acetamide, 1,4 dioxine, fluoro, trifluoro methoxy, acetyl, trifluoro methyl, propyl,

cyclohexene, methoxy-phenoxy, chloro phenoxy, tolyloxy, and phenoxy; and b) administering to the subject an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (I) is N-(1',2-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide, N-(3,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(4,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(5,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(6,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(7,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(8,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, 4-Bromo-N-(1,6'-dihydroxy-[2,2']binaphthalenyl-4'-yl)-benzenesulfonamide, or 4-Bromo-N-[4-hydroxy-3-(1H-[1,2,4]triazol-3-ylsulfanyl)naphthalen-1-yl]-benzenesulfonamide, or a pharmaceutically acceptable salt thereof. In some examples, the compound of Formula (I) is N-(1',2-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide. In some examples, the immune checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104, AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (I). In some examples, after three weeks or more of administration of the compound of Formula (I) and the immune checkpoint inhibitor, the subject has at least a partial remission. In some examples, after six weeks or more of administration of the compound of Formula (I) and the immune checkpoint inhibitor, the subject has complete

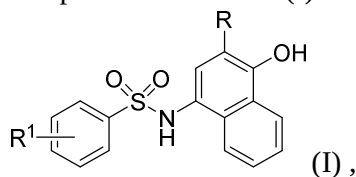
remission. In some examples, the methods described herein reduce tumor size by at least 20% more within six weeks of administration relative to a subject administered immune checkpoint inhibitor alone.

[0004a] In one aspect, the present disclosure refers to use of a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of hydrogen, phenylsulfanyl, 2-hydroxy-naphthalen-1-yl, quinolin-8-ylsulfanyl, triazol-3-yl sulfanyl, and benzothiazol-2-ylsulfanyl; R¹ is selected from the group consisting of hydrogen, methyl, chloro, bromo, methoxy, ethoxy, tert-butyl, nitro, methyl ester, acetamide, 1,4 dioxine, fluoro, trifluoro methoxy, acetyl, trifluoro methyl, propyl, cyclohexene, methoxy-phenoxy, chloro phenoxy, tolyloxy, and phenoxy, in the manufacturing of a medicament for treating, reducing the risk of recurrence of, or preventing recurrence of cancer in a subject in need thereof, wherein the use further comprises an immune checkpoint inhibitor, and wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof is for oral administration.

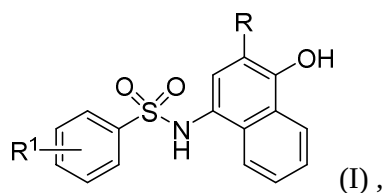
[0005] Further provided herein, in certain examples, are methods of reducing the risk of recurrence of a cancer in a subject in need thereof, comprising a) orally administering to the subject an effective amount of a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of hydrogen, phenylsulfanyl, 2-hydroxy-naphthalen-1-yl, quinolin-8-ylsulfanyl, triazol-3-yl sulfanyl, and benzothiazol-2-ylsulfanyl; R¹ is selected from the group consisting of hydrogen, methyl, chloro, bromo, methoxy, ethoxy, tert-butyl, nitro, methyl ester, acetamide, 1,4 dioxine, fluoro, trifluoro methoxy, acetyl, trifluoro methyl, propyl, cyclohexene, methoxy-phenoxy, chloro phenoxy, tolyloxy, and phenoxy; and b) administering to the subject an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (I) is N-(1',2'-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide, N-(3,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, N-(4,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, N-(5,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, N-(6,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, N-(7,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, N-(8,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxy-benzenesulfonamide, 4-Bromo-N-(1,6'-dihydroxy-[2,2']binaphthalenyl-4-yl)-benzenesulfonamide, or 4-Bromo-N-[4-hydroxy-3-(1H-[1,2,4]triazol-3-ylsulfanyl)-naphthalen-1-yl]-benzenesulfonamide, or a pharmaceutically acceptable salt thereof. In some examples, the compound of Formula (I) is N-(1',2'-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide. In some examples, the immune checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104,

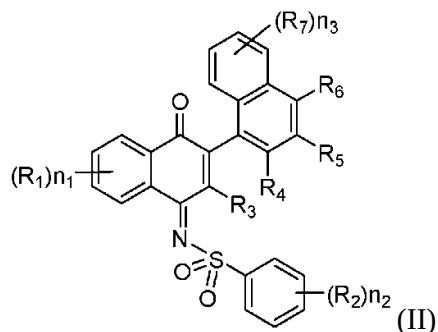
AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (I).

[0006] Also provided herein, in certain examples, are methods of preventing recurrence of a cancer in a subject in need thereof, comprising a) orally administering to the subject an effective amount of a compound of Formula (I):



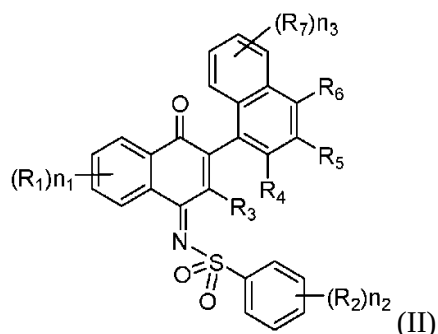
or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of hydrogen, phenylsulfanyl, 2-hydroxy-naphthalen-1-yl, quinolin-8-ylsulfanyl, triazol-3-yl sulfanyl, and benzothiazol-2-ylsulfanyl; R¹ is selected from the group consisting of hydrogen, methyl, chloro, bromo, methoxy, ethoxy, tert-butyl, nitro, methyl ester, acetamide, 1,4 dioxine, fluoro, trifluoro methoxy, acetyl, trifluoro methyl, propyl, cyclohexene, methoxy-phenoxy, chloro phenoxy, tolyloxy, and phenoxy; and b) administering to the subject an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (I) is N-(1',2'-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide, N-(3,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(4,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(5,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(6,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(7,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, N-(8,1'-Dihydroxy-[1,2']binaphthalenyl-4'-yl)-4-methoxybenzenesulfonamide, 4-Bromo-N-(1,6'-dihydroxy-[2,2']binaphthalenyl-4-yl)-

benzenesulfonamide, or 4-Bromo-N-[4-hydroxy-3-(1H-[1,2,4]triazol-3-ylsulfanyl)-naphthalen-1-yl]-benzenesulfonamide, or a pharmaceutically acceptable salt thereof. In some examples, the compound of Formula (I) is N-(1',2'-dihydroxy-1,2'-binaphthalen-4'-yl)-4-methoxybenzenesulfonamide. In some examples, the immune checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104, AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (I). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (I). **[0007]** Provided herein, in certain examples, are methods of treating a cancer in a subject in need thereof, comprising administering to the subject a) an effective amount of a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein, and b) an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (II) is administered orally. In some examples, the immune

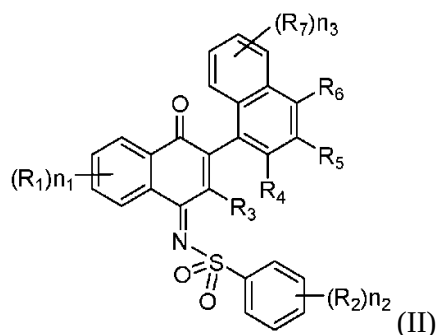
checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104, AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolelimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (II). **[0008]** Further provided herein, in certain examples, are methods of reducing the risk of recurrence of a cancer in a subject in need thereof, comprising administering to the subject a) an effective amount of a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein, and b) an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (II) is administered orally. In some examples, the immune checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab,

sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104, AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (II).

[0009] Also provided herein, in certain examples, are methods of preventing recurrence of a cancer in a subject in need thereof, comprising administering to the subject a) an effective amount of a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein, and b) an effective amount of an immune checkpoint inhibitor. In some examples, the compound of Formula (II) is administered orally. In some examples, the immune checkpoint inhibitor is administered parenterally. In some examples, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some examples, the PD-1 inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, sasanlimab, retifanlimab, tebotelimab, ABBV-181, AK104, AK105, BCD-100, BI-754091, CBT-501, CC-90006, GLS-010, HLX10, IBI-308, JNJ-3283, JS001, LZM009, MEDI0680 (AMP-514), REGN-2810, SHR-1210, Sym021, TSR-042, or XmAb20717. In some examples, the anti-PD-1 antibody is

pembrolizumab. In some examples, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, envafolimab, FS118, BCD-135, BGB-A333, BGBA-317, CBT-502, CK-301, CS1001, FAZ053, MDX-1105, MSB2311, SHR-1316, M7824, LY3415244, CA-170, or CX-072. In some examples, the immune checkpoint inhibitor is administered prior to administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered concomitantly with administration of the compound of Formula (II). In some examples, the immune checkpoint inhibitor is administered subsequently to administration of the compound of Formula (II).

[0010] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description, Examples, and Claims**.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Various features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0012] FIG. 1 shows the in vivo efficacy results of TTI-101 ± anti-PD-1 in the syngeneic H22 liver cancer model through Day 21 of administration.

[0013] FIG. 2 shows the in vivo efficacy results of TTI-101 ± anti-PD-1 in the syngeneic H22 liver cancer model through Day 47 of administration. and Day 47.

[0014] FIG. 3 illustrates the result of a tumor rechallenge study with H22 liver cancer cells following treatment with TTI-101 and anti-PD-1 combination.

[0015] FIG. 4 illustrates the PK properties upon oral dosing of TTI-101 in SD rats.

[0016] FIG. 5 illustrates percent change in tumor volume when TTI-101 is administered PO vs. IP in murine H22 liver cancer model.

DETAILED DESCRIPTION

[0017] As generally described herein, the present disclosure provides methods of treating a cancer in a subject in need thereof or preventing recurrence of a cancer in a subject in need thereof, comprising administering to the subject an effective amount of a signal transducer and activator of transcription 3 (STAT3) inhibitor and an effective amount of an immune checkpoint inhibitor, such as PD-1 inhibitor or an PD-L1 inhibitor.