J. Endocrino. (2011) 211, 17-25. On the other hand, it has been reported that agents blocking the GR signaling pathway can potentiate chemotherapy in killing breast cancer cells. See U.S. Pat. No. 9,149,485. Mifepristone, a steroidal, non-selective agent that blocks the GR signaling pathway and other steroidal signaling pathways (including progesterone-receptor signaling pathway), has been suggested for treatment of cervical cancer (US Pat. Publ. No. 2004/0102422). However, GR signaling is believed to have the opposite effect in some other cancers. For example, the prevailing view regarding pancreatic cancer is that glucocorticoid, e.g., dexamethasone, can relieve side effects of the chemotherapeutic agent and should be co-administered with chemotherapeutic agents in treating pancreatic cancer. Zhang et al., BMC Cancer, 2006 March 15 6: 61. Further, it has been reported that dexamethasone, a glucocorticoid receptor agonist, inhibits pancreatic cancer cell growth. See, Normal et al., J. Surg. Res. 1994 Jul; 57(1): 33-8. Thus, the reposts in the literature are often contradictory, and it remains unclear whether or not glucocorticoid signaling will have an effect on a cancer, and whether such an effect may be a positive or a negative effect.

[0006] Accordingly, in view of the lack of good treatments options for many cancer patients, improved treatments for cancerous tumors, including cervical cancer, are desired.

SUMMARY

[0006a] In one aspect, the present disclosure refers to a use of a non-steroidal selective glucocorticoid receptor modulator (SGRM), in the manufacture of a medicament for treating a subject hosting a cancerous tumor, wherein an effective amount of a chemotherapeutic agent and an effective amount of the medicament are to be administered to the subject to reduce the tumor load of the cancerous tumor.

[0007] Disclosed herein are novel methods for treating a subject hosting a cancerous tumor, such as a cervical cancer tumor or other cancerous tumor (e.g., breast cancer, ovarian cancer, prostate cancer). The present application provides novel and surprising combination therapies that employ non-steroidal compounds that inhibit GR signaling to treat patients suffering from cancer, including patients suffering from cervical cancer and other cancers. The methods comprise administering to the subject an effective amount of a chemotherapeutic agent and an effective amount of a non-steroidal selective glucocorticoid receptor modulator (SGRM) to

reduce the tumor load of the cancerous tumor in the subject. In some cases, the cancerous tumor is a cervical cancer tumor.

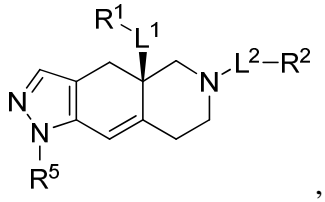
[0008] In some cases, the chemotherapeutic agent is selected from the group consisting of antimicrotubule agents, alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors and combinations thereof. In some cases, the

chemotherapeutic agent is a taxane. In some cases, the chemotherapeutic agent is selected from the group consisting of nab-paclitaxel, 5-fluorouracil (5-FU), gemcitabine, cisplatin and capecitabine.

[0009] In some cases, the glucocorticoid receptor modulator is orally administered. In some cases, the glucocorticoid receptor modulator is administered by transdermal application, by a nebulized suspension, or by an aerosol spray.

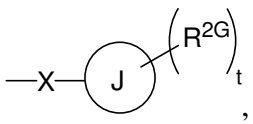
[0010] In some cases, the effective amount of the SGRM is a daily dose of between 1 and 100 mg/kg/day, wherein the SGRM is administered with at least one chemotherapeutic agent. In some examples, the daily dose of the SGRM is 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 30, 40, 50 60, 70, 80, 90 or 100 mg/kg/day. In some cases, the glucocorticoid receptor modulator is administrated for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 weeks.

[0009] In some cases, the glucocorticoid receptor modulator backbone is a fused azadecalin. In some cases, the fused azadecalin is a compound having the following formula:



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wherein L^1 and L^2 are members independently selected from a bond and unsubstituted alkylene; R^1 is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, $-OR^{1A}$, $NR^{1C}R^{1D}$, $-C(O)NR^{1C}R^{1D}$, and $-C(O)OR^{1A}$, wherein R^{1A} is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl, R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl, wherein R^{1C} and R^{1D} are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen; R^2 has the formula:



,

WHAT IS CLAIMED IS:

1. Use of a non-steroidal selective glucocorticoid receptor modulator (SGRM), in the manufacture of a medicament for treating a subject hosting a cancerous tumor, wherein an effective amount of a chemotherapeutic agent and an effective amount of the medicament are to be administered to the subject to reduce the tumor load of the cancerous tumor.

2. The use of claim 1, wherein the cancerous tumor is a cervical cancer tumor.

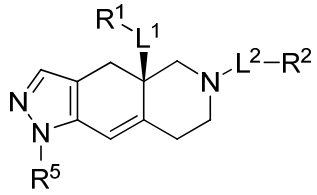
3. The use of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of taxanes, alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors and combinations thereof.

4. The use of claim 3, wherein the chemotherapeutic agent is a taxane.

5. The use of claim 3, wherein the chemotherapeutic agent is selected from the group consisting of nab-paclitaxel, 5-fluorouracil (5-FU), gemcitabine, cisplatin and capecitabine.

6. The use of claim 1, wherein the glucocorticoid receptor modulator backbone is a fused azadecalin.

7. The use of claim 6, wherein the fused azadecalin is a compound having the following formula:



wherein

L^1 and L^2 are members independently selected from a bond and unsubstituted alkylene;

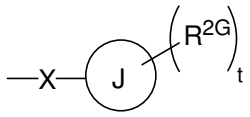
R^1 is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, $-OR^{1A}$, $NR^{1C}R^{1D}$, $-C(O)NR^{1C}R^{1D}$, and $-C(O)OR^{1A}$, wherein

R^{1A} is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl,

R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl,

wherein R^{1C} and R^{1D} are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen;

R^2 has the formula:



wherein

R^{2G} is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, -CN, and -CF_3;

J is phenyl;

t is an integer from 0 to 5;

X is -$S(O_2)$-; and

R^5 is phenyl optionally substituted with 1-5 R^{5A} groups, wherein

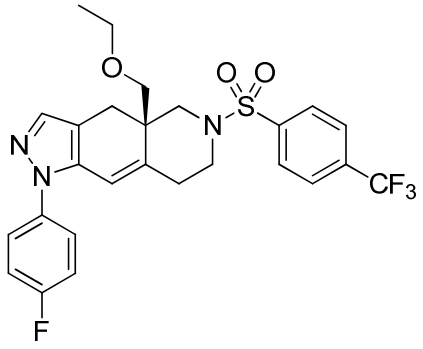
R^{5A} is a member selected from hydrogen, halogen, -OR^{5A1}, $S(O_2)NR^{5A2}R^{5A3}$, -CN, and unsubstituted alkyl, wherein

R^{5A1} is a member selected from hydrogen and unsubstituted alkyl, and

R^{5A2} and R^{5A3} are members independently selected from hydrogen and unsubstituted alkyl,

or salts and isomers thereof.

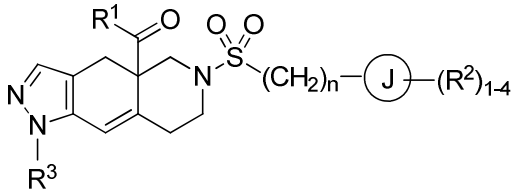
8. The use of claim 6, wherein the fused azadecalin is:



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9. The use of claim 6, wherein the glucocorticoid receptor modulator backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin.

10. The use of claim 9, wherein the heteroaryl ketone fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, N-oxide, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, $C_{1\ 6}$ haloalkyl, $C_{1\ 6}$ alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8}

heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R^{2c} groups;

alternatively, two R^2 groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two R^2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2d} groups;

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{2c} is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, and $NR^{2a}R^{2b}$;

each R^{2d} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, or two R^{2d} groups attached to the same ring atom are combined to form (=O);

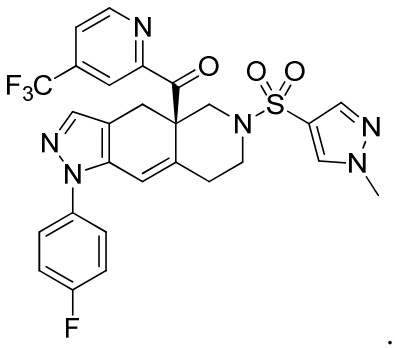
R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups;

each R^{3a} is independently selected from the group consisting of hydrogen, halogen, and C_{1-6} haloalkyl; and

subscript n is an integer from 0 to 3;

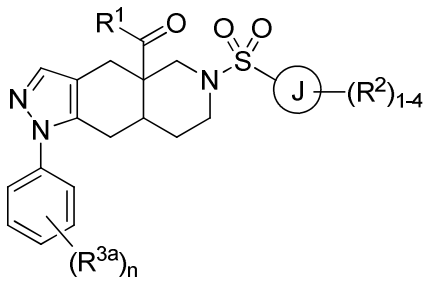
or salts and isomers thereof.

11. The use of claim 9, wherein the heteroaryl-ketone fused azadecalin is



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12. The use of claim 9, wherein the octahydro fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, N-oxide, and C_{3-8} cycloalkyl;

ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S;

alternatively, two R^2 groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2c} groups;

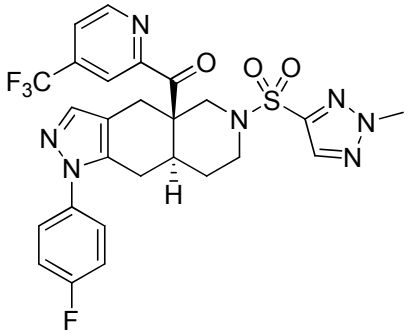
R^{2a}, R^{2b} and R^{2c} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{3a} is independently halogen; and

subscript n is an integer from 0 to 3,

or salts and isomers thereof.

13. The use of claim 9, wherein the octahydro fused azadecalin has the formula:



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