SUMMARY

[0007] Applicant discloses herein methods of normalizing neutrophil-to-lymphocyte ratio (NLR). For cancer patients, an NLR that is higher than normal (greater than 3) is predictive of poorer prognosis. Decreasing NLR has been correlated with improved cancer treatment outcomes. Reducing the NLR in cancer patients to a normal value (i.e., less than about 3) improves the prognoses of those patients, improves their response to cancer treatment, improves the outcomes of cancer therapies, can reduce tumor load and promote tumor elimination. As noted above, mifepristone does not alter neutrophil or lymphocyte abundance in healthy subjects, and so does not affect NLR in healthy subjects (Laue, 1990). Surprisingly, as disclosed herein, administration of a nonsteroidal GRA was effective to reduce NLR in cancer patients receiving cancer treatment.

[0008] The methods disclosed herein include selecting cancer patients who have an NLR of greater than 3 and administering a nonsteroidal glucocorticoid receptor antagonist (GRA) such as, e.g., relacorilant, in combination with a cancer treatment to normalize (reduce) NLR in cancer patients with high NLR and receiving cancer treatment. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a cancer treatment to treat cancer patients with high NLR. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a cancer treatment to enhance the response to cancer treatment in cancer patients with high NLR and receiving cancer treatment. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a cancer treatment to reduce tumor load in cancer patients having a tumor or tumors and with high NLR and receiving cancer treatment. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a cancer treatment to promote tumor elimination in cancer patients with high NLR and receiving cancer treatment. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a cancer treatment to improve the health of cancer patients with high NLR. The methods disclosed herein include administering a nonsteroidal GRA such as, e.g., relacorilant, in combination with a taxane, such as nab-paclitaxel, to a cancer patient with high NLR to lower the NLR, to improve the response of the patient to the taxane, and to improve the health of the cancer patient.

[0008a] In one aspect of the present disclosure, there is provided a use of a nonsteroidal selective glucocorticoid receptor antagonist (GRA) in the manufacture of a medicament for reducing the neutrophil-to-lymphocyte ratio (NLR) in a cancer patient having a tumor and having a NLR greater than 3,

wherein an effective amount of the nonsteroidal selective glucocorticoid receptor antagonist (GRA) is to be administered to said cancer patient,

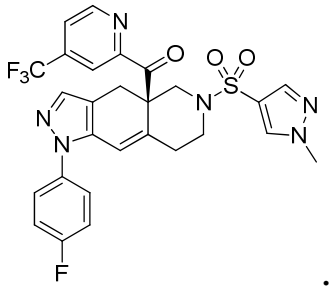
whereby the NLR of said cancer patient is reduced.

[0009] In ~~embodiment~~example**s**, the cancer treatment may include administration of a chemotherapeutic agent (e.g., a taxane, such as nab-paclitaxel, gemcitabine, or other

chemotherapeutic agent). In ~~embodiment~~examples, the cancer treatment may include administration of an immunotherapeutic agent (e.g., a checkpoint inhibitor, such as an antibody directed to a protein target selected from PD-1, PD-L1, CTKA4, LAG3, B7-H3, B7-H4, OX-40, CD-137, and TIM3, or other immunotherapy. In ~~embodiment~~examples, the cancer treatment may include administration of radiotherapy (e.g., direction of ionizing radiation to a tumor, infusion of a radioactive pharmaceutical composition, implantation of a radiation source, or other radiotherapy). Cancer treatment may include surgery and other cancer treatments, and may include combinations of these cancer treatments.

[0010] In ~~embodiment~~examples of the methods disclosed herein, the nonsteroidal GRA is a nonsteroidal compound comprising a fused azadecalin structure. In ~~embodiment~~examples, the compound comprising a fused azadecalin structure is a compound described and disclosed in U.S. Patent 7,928,237 and in U.S. Patent 8,461,172. In ~~embodiment~~examples, the compound comprising a heteroaryl-ketone fused azadecalin structure is a compound described and disclosed in U.S. Patent 8,859,774. In ~~embodiment~~examples, the compound comprising an octahydro fused azadecalin structure is a compound described and disclosed in U.S. Patent 10,047,082. The entire contents of these patents, and all patents, patent applications, patent publications, and publications discussed herein, both *supra* and *infra*, are hereby incorporated by reference in their entireties.

[0011] In ~~embodiment~~examples, for example, the nonsteroidal GRA is a heteroaryl-ketone fused azadecalin compound (e.g., a compound disclosed in a U.S. Patent 8,859,774). In particular ~~embodiment~~examples, the nonsteroidal GRA is (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, also known as "relacorilant" and as "CORT125134" (Example 18 of U.S. 8,859,774), which has the following structure:



[0012] Relacorilant is chemically distinct from the steroidal compound mifepristone. Unlike mifepristone, relacorilant does not antagonize the progesterone receptor. Thus relacorilant

(and other fused azadecalin compounds disclosed, e.g., in U.S. 8,859,774, U.S. 7,928,237, U.S. 8,461,172, and in U.S. Patent 10,047,082 and other patents cited herein) provides a means of selectively antagonizing the glucocorticoid receptor. The effect of relacorilant on the NLR has not been described.

[0013] In some cases, the selective nonsteroidal GRA is orally administered. In some cases, the selective nonsteroidal GRA is administered by injection, infusion, transdermal application, by a nebulized suspension, or by an aerosol spray.

[0014] In some cases, the effective amount of the nonsteroidal selective GRA is a daily dose of between 1 and 100 mg/kg/day. In some ~~embodiment~~examples, the dose of the nonsteroidal selective GRA is a daily dose of 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 GRA 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, 80 weeks, or until the cancer becomes worse (disease progression).

[0015] The present methods provide improved methods of normalizing (reducing) NLR in cancer patients with high NLR and receiving cancer treatment; of enhancing the response to cancer treatment in cancer patients with high NLR and receiving cancer treatment (e.g., improving the response of a cancer patient with high NLR to taxane (e.g., nab-paclitaxel) chemotherapy); of reducing tumor load in cancer patients having a tumor or tumors and with high NLR and receiving cancer treatment; of promoting tumor elimination in cancer patients with high NLR and receiving cancer treatment; and improving the health of cancer patients with high NLR and receiving cancer treatment. The present methods provide advantages to patients by improving and enhancing cancer treatments, delaying disease progression, improving patient longevity and survival, quality of life, and other beneficial health outcomes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1A. Effect of relacorilant on neutrophil-to-lymphocyte ratio (NLR) of healthy subjects. Dosing and assessment schedule for healthy subject study. (A) Single ascending dose (SAD) prednisone-challenge design.

[0017] Figure 1B. Effect of relacorilant on neutrophil-to-lymphocyte ratio (NLR) of healthy subjects. Dosing and assessment schedule for healthy subject study. (B) Multiple ascending dose (MAD) prednisone-challenge design.

WE CLAIM:

1. Use of a nonsteroidal selective glucocorticoid receptor antagonist (GRA) in the manufacture of a medicament for ~~A method of~~ reducing the neutrophil-to-lymphocyte ratio (NLR) in a cancer patient having a tumor and having a NLR greater than 3, ~~the method comprising:~~

wherein ~~administering~~ an effective amount of ~~a~~the nonsteroidal selective glucocorticoid receptor antagonist (GRA) is to be administered to said cancer patient,

w~~W~~hereby the NLR of said cancer patient is reduced.

2. The ~~A method~~ use of claim 1, ~~reducing the neutrophil-to-lymphocyte ratio (NLR) in a cancer patient having a tumor and having a NLR greater than 3, the method comprising:~~

wherein ~~administering~~ an effective amount of a cancer treatment and an effective amount of a nonsteroidal selective glucocorticoid receptor antagonist (GRA) is to be administered to said cancer patient,

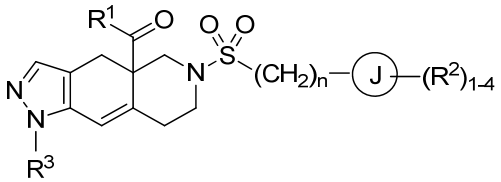
~~W~~whereby the NLR of said cancer patient is reduced.

3. The ~~method~~ use of claim 1 or claim 2, wherein said neutrophil-to-lymphocyte ratio (NLR) of said cancer patient is reduced to about 3 or less.

4. The ~~method~~ use of claim 2 or claim 3, wherein the use ~~said administration of a cancer treatment and administration of a nonsteroidal selective GRA~~ is effective to reduce the tumor load of the patient.

5. The ~~method~~ use of any of claims 1 to 4, wherein said neutrophil-to-lymphocyte ratio (NLR) of said cancer patient is reduced to about 3 or less~~the nonsteroidal selective GRA comprises a fused azadecalin structure~~.

6. The ~~method~~ use of any of claims 1 to 4, wherein the nonsteroidal selective GRA is a compound comprising a heteroaryl-ketone fused azadecalin structure, said GRA having 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);

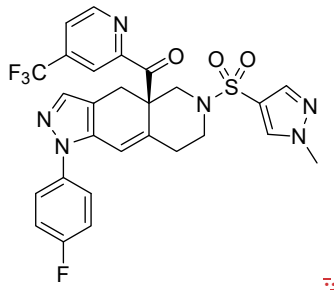
R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups;

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;

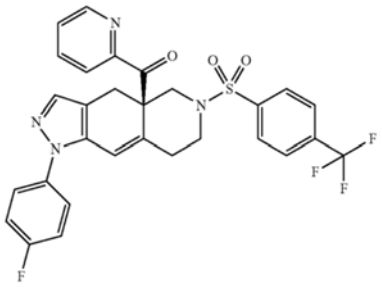
or salts and isomers thereof.

7. The ~~method~~ use of claim 6, wherein the nonsteroidal selective GRA is (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the structure:



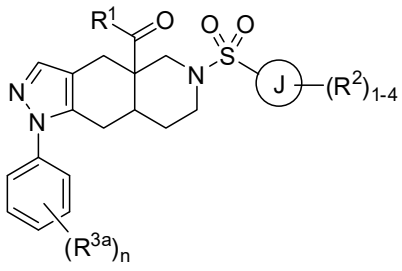
~~.~~, or

~~8. The method of claim 6, wherein the nonsteroidal selective GRA~~ is (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo 3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone, which has the structure:



.

~~9~~8. The ~~method~~ use of any of claims 1 to 4, wherein the nonsteroidal selective GRA comprises an octahydro fused azadecalin structure, said GRA having the formula:



(I)

wherein

R^1 is selected from the group consisting of pyridine and thiazole, 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 phenyl, pyridine, pyrazole, and triazole;

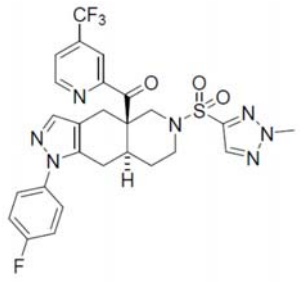
each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and -CN;

R^{3a} is F;

subscript n is an integer from 0 to 3;

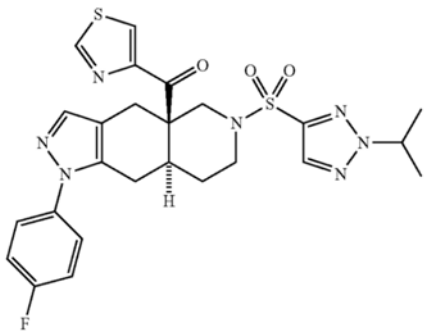
or salts and isomers thereof.

~~10~~9. The ~~method~~ use of claim ~~9~~8, wherein the nonsteroidal selective GRA is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the structure:



~~.~~, or

~~11. The method of claim 9, wherein the nonsteroidal selective GRA~~ is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-4-yl)methanone, which has the structure:



.

~~12~~10. The ~~method~~ use of any of claims 2 to 4, wherein the cancer treatment comprises ~~administration of~~ a chemotherapeutic agent or an immunotherapeutic agent.

~~13~~11. The ~~method~~ use of claim ~~12~~10, wherein 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~~.~~, and

~~14. The method of claim 12, wherein the chemotherapeutic agent is an antimicrotubule agent selected from plinabulin and a taxane.~~

~~15. The method of claim 14, wherein the chemotherapeutic agent is nab-paclitaxel.~~

~~16. The method of any of claims 2 to 4, wherein the cancer treatment comprises administration of an immunotherapeutic agent.~~

~~17. The method of claim 16, wherein~~ the immunotherapeutic agent comprises ~~administration of~~ an antibody directed against a protein target selected from PD-1, PD-L1, CTKA4, LAG3, B7-H3, B7-H4, OX-40, CD137, and TIM3.

~~18~~12. The ~~method~~ use of claim 2~~any of claims 2 to 4~~, wherein the cancer treatment comprises one or more of cancer radiation therapy, ~~administration of~~ growth factor inhibitors, and ~~administration of~~ anti-angiogenesis factors.

~~19~~13. The ~~method~~ use of any of claims 2 to ~~18~~12, wherein said reducing NLR is effective to enhance the response to cancer treatment in a cancer patient receiving cancer treatment and having a neutrophil-to-lymphocyte ratio of greater than 3, wherein said enhancing is as compared to the response in the absence of the present ~~method~~use, wherein the use comprises~~the method comprising~~:

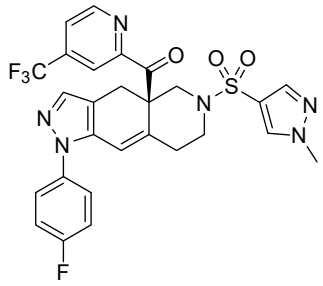
~~administering~~ an effective amount of a cancer treatment and an effective amount of a nonsteroidal selective glucocorticoid receptor antagonist (GRA) to be administered to said cancer patient,

~~W~~whereby the cancer patient's NLR is reduced and the cancer patient's response to cancer treatment is enhanced.

~~20. The method of claim 19, wherein the nonsteroidal selective GRA comprises a fused azadecalin structure.~~

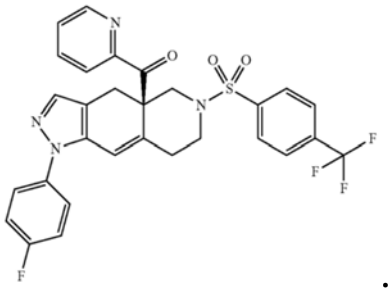
~~21~~14. The ~~method~~ use of claim 13~~19 or claim 20~~, wherein the nonsteroidal selective GRA comprises a heteroaryl-ketone fused azadecalin structure.

~~22~~15. The ~~method~~ use of claim ~~21~~14, wherein the nonsteroidal selective GRA is (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the structure:



~~.~~, or

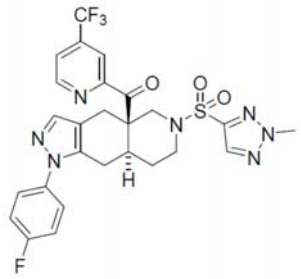
~~23. The method of claim 21, wherein the nonsteroidal selective GRA~~ is (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo 3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone, which has the structure:



.

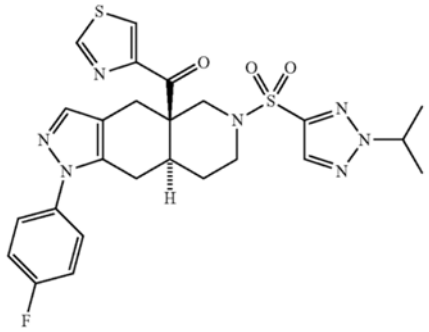
~~24~~16. The ~~method~~ use of claim 13~~19 or claim 20~~, wherein the nonsteroidal selective GRA comprises an octahydro fused azadecalin structure.

~~25~~17. The ~~method~~ use of claim ~~24~~16, wherein the nonsteroidal selective GRA is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the structure:



-, or

~~26. The method of claim 24, wherein the nonsteroidal selective GRA~~ is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-4-yl)methanone, which has the structure:



.

~~27~~18. The ~~method~~ use of claim 13~~19 or claim 20~~, wherein the cancer treatment comprises ~~administration of~~ a chemotherapeutic agent or an immunotherapeutic agent.

~~28~~19. The ~~method~~ use of claim ~~27~~18, wherein 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 and the immunotherapeutic agent comprises an antibody directed against a protein target selected from PD-1, PD-L1, CTKA4, LAG3, B7-H3, B7-H4, OX-40, CD137, and TIM3.

~~29. The method of claim 27, wherein the chemotherapeutic agent is an antimicrotubule agent selected from plinabulin and a taxane.~~

~~30. The method of claim 29, wherein the chemotherapeutic agent is nab-paclitaxel.~~

~~31. The method of claim 19 or claim 20, wherein the cancer treatment comprises administration of an immunotherapeutic agent.~~

~~32. The method of claim 31, wherein the immunotherapeutic agent comprises administration of an antibody directed against a protein target selected from PD-1, PD-L1, CTKA4, LAG3, B7-H3, B7-H4, OX-40, CD137, and TIM3.~~

~~33~~20. The ~~method~~ use of claim 13~~19 or claim 20~~, wherein the cancer treatment comprises one or more of cancer radiation therapy, ~~administration of~~ growth factor inhibitors, and ~~administration of~~ anti-angiogenesis factors.

~~34. The method of any of claims 12 to 15 and 27 to 30, wherein the chemotherapeutic agent is an antimetabolite.~~

~~35. The method of claim 34, wherein the chemotherapeutic agent is gemcitabine.~~

~~36~~21. The ~~method~~ use of any of claims 13 to 20~~19 to 35~~, wherein the patient exhibits a partial response to the cancer treatment and GRA treatment, wherein said partial response is an improvement as compared to the patient's response to the cancer treatment alone,

~~W~~whereby the cancer patient's NLR is reduced and the cancer patient's response to cancer treatment is enhanced.

~~37~~22. The ~~method~~ use of any of claims 13 to 20~~19 to 35~~, wherein the patient exhibits a complete response to the cancer treatment and GRA treatment, wherein said complete response is an improvement as compared to the patient's response to the cancer treatment alone,

~~W~~whereby the cancer patient's NLR is reduced and the cancer patient's response to cancer treatment is enhanced.

~~38. The method of any of claims 1 to 37, wherein said NLR of said cancer patient is reduced after at least 7 days of administration of said nonsteroidal selective GRA.~~