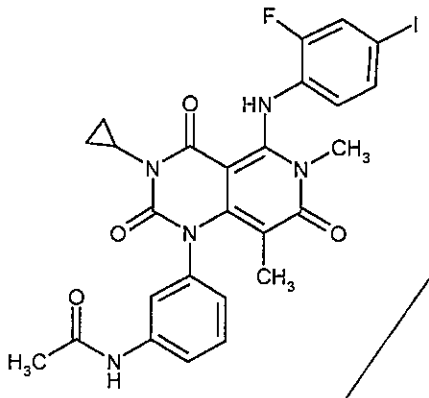
We claim:

1. A combination comprising:

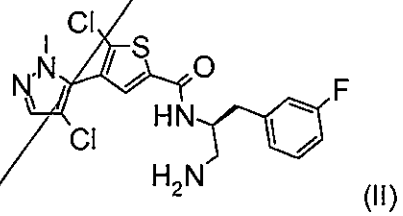
(i) a compound of Structure (I):



(I);

or a pharmaceutically acceptable salt or solvate thereof; and

(ii) a compound of Structure (II):



(II)

or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 where the compound of Structure (I) is in the form of a dimethyl sulfoxide solvate and the compound of Structure (II) is in the form of a hydrochloride salt.

3. A combination kit comprising a combination according to claim 1 or claim 2 together with a pharmaceutically acceptable carrier or carriers.

4. A combination according to any one of claims 1 to 3 where the amount of the compound of Structure (I) is an amount selected from 0.125mg to 10mg, and the amount of the compound of Structure (II) is an amount selected from 5mg to 500mg.

5. Use of a combination according to any of claims 1 to 4 in the manufacture of a medicament or medicaments for the treatment of cancer or pre-cancerous syndromes.

6. A method of treating cancer in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, to such human,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

7. A method according to claim 6 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.125mg to about 10mg, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, is selected from about 10mg to about 300mg.

8. A method according to claim 7 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.25mg to about 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, is selected from about 10mg to about 300mg, and that amount is administered once per day.

9. A method according to claim 8 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

10. A method treating a cancer selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the <u>in vivo</u> administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, to such human,

wherein the combination is administered within a specified period, and wherein the combination is administered for a duration of time.

11. A method according to claim 10 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.125mg to about 10mg, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg.

12. A method according to claim 11 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.25mg to about 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg, and that amount is administered once per day.

13. A method according to claim 12 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

14. A method according to claim 10 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

15. A method according to claim 11 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

16. A method according to claim 12 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

17. A method according to claim 13 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

18. A method of treating a cancer that is either wild type or mutant for Ras/Raf and either wild type or mutant for PI3K/PTEN in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride to such human,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

19. A method according to claim 18 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.125mg to about 10mg, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg.

20. A method according to claim 19 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.25mg to about 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg, and that amount is administered once per day.

21. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-

1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

22. A method according to claim 18 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

23. A method according to claim 19 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

24. A method according to claim 20 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

25. A method according to claim 21 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

26. A method treating a cancer selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride to such human,

wherein the compounds of the combination are administered sequentially.

27. A method according to claim 26 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.125mg to about 10mg, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg.

28. A method according to claim 27 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.25mg to about 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg, and that amount is administered once per day.

29. A method according to claim 28 wherein *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered for from 1 to 21 consecutive days, followed by an optional drug holiday of from 1 to 14 days, followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-

tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 1 to 21 days.

30. A method according to claim 26 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

31. A method according to claim 27 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

32. A method according to claim 28 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

33. A method according to claim 29 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

34. A method of treating a cancer that is either wild type or mutant for Ras/Raf and either wild type or mutant for PI3K/PTEN in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride to such human,

wherein the compounds of the combination are administered sequentially.

35. A method according to claim 34 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 0.125mg to about 10mg, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg.

36. A method according to claim 35 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-

2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from about 1mg to about 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is selected from about 10mg to about 300mg, and that amount is administered once per day.

37. A method according to claim 36 wherein *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered for from 1 to 21 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 1 to 21 days.

38. A method according to claim 34 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

39. A method according to claim 35 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

40. A method according to claim 36 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

41. A method according to claim 37 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

42. A method according to claim 37 wherein *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered for from 2 to 21 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 2 to 21 days.

43. A method according to claim 42 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

44. A method according to claim 29 wherein *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered for from 2 to 21 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 2 to 21 days.

45. A method according to claim 44 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

46. A method according to claim 9 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

47. A method according to claim 8 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing.

48. A method according to claim 13 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

49. A method according to claim 12 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing.

50. A method according to claim 21 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

51. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-

fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing.

52. A method according to claim 8 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

53. A method according to claim 12 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

54. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-

yl]phenyl}acetamide dimethyl sulfoxide for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

55. A method of treating pre-cancerous syndromes in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride to such human,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

56. The method of claim 56 wherein the pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammapathy of unknown significance (MGUS), myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithleial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

57. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 days over a 14 day period, and during the other days of the 14 day period N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing.

58. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-

thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone, optionally followed by one or more cycles of repeat dosing.

59. A method according to claim 20 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 days over a 14 day period, and during the other days of the 14 day period *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone, optionally followed by one or more cycles of repeat dosing.

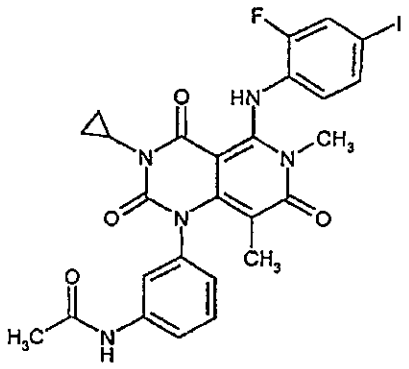
60. A method according to claim 20 wherein the compound N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound.

61. A method according to claim 20 wherein the compound *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound.

Claims

1. A combination comprising:

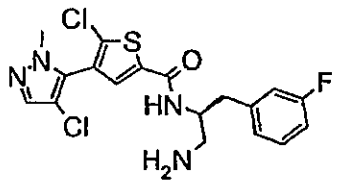
(i) a compound of Structure (I):



(I);

or a pharmaceutically acceptable salt or solvate thereof; and

(ii) a compound of Structure (II):



(II)

or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 where the compound of Structure (I) is in the form of a dimethyl sulfoxide solvate and the compound of Structure (II) is in the form of a hydrochloride salt.

3. A combination kit comprising a combination according to claim 1 or claim 2 together with a pharmaceutically acceptable carrier or carriers.

4. Use of a combination according to claim 1 or claim 2 or of a combination kit according to claim 3 in the manufacture of a medicament or medicaments for the treatment of cancer or pre-cancerous syndromes.

5. A combination or combination kit as claimed in any one of claims 1 to 3 for use in the treatment of cancer or pre-cancerous syndromes.

6. A combination or combination kit for use in the treatment of cancer or pre-cancerous syndromes, comprising a therapeutically effective amount of a combination of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

7. A combination or combination kit for use according to claim 6 wherein the amount of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is selected from 0.25mg to 9mg, and that amount is administered once per day, and the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, is selected from 10mg to 300mg, and that amount is administered once per day.

8. A combination or combination kit for use according to claim 6 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

9. A combination or combination kit for use according to claim 6 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

10. A combination or combination kit for use according to claim 6 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period: either N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing; or *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone, optionally followed by one or more cycles of repeat dosing.

11. A combination or combination kit for use according to claim 6 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for at least 7 consecutive days.

12. A combination or combination kit for use according to claim 6 wherein N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each

other for 5 days over a 14 day period, and during the other days of the 14 day period: either N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is administered alone, optionally followed by one or more cycles of repeat dosing; or *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone, optionally followed by one or more cycles of repeat dosing.

13. A combination or combination kit for use according to claim 6 or claim 7 wherein the compound N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound; and/or the compound *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound.

14. A use according to claim 4, or a combination or combination kit for use according to any one of claims 5 to 13, wherein the cancer is either wild type or mutant for Ras/Raf and either wild type or mutant for PI3K/PTEN.

15. A use according to claim 4, or a combination or combination kit for use according to any one of claims 5 to 13, wherein the cancer is selected from ovarian, breast, pancreatic and prostate.