Claims

1. Use of nutlin-3 in the manufacture of a medicament for treating cancer in a patient, wherein said nutlin-3 is to be administered with VX-680,

   wherein said nutlin-3 is to be administered prior to administration of said VX-680, and wherein said medicament selectively targets a p53-deficient cancer cell.

2. The use according to claim 1, wherein said cancer is selected from the group consisting of leukemia; lymphoma; myeloma; skin cancer such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma; breast cancer; head and neck cancer, such as brain cancer; colorectal cancer; colon cancer; rectal cancer; lung cancer, such as non small cell lung cancer; ovarian cancer; renal cancer; prostate cancer; liver cancer; and HPV- associated cancer such as cervical cancer.

3. The use according to claim 1, wherein said nutlin-3 is to be administered 12, 16, 18, 24, 36, 48 or 72 hours prior to administration of said VX-680.

4. A pharmaceutical combination for use in selectively targeting a p53-deficient cancer cell, in a patient suffering from cancer, comprising nutlin-3 and VX-680,

   wherein said nutlin-3 is provided in a form suitable for administration prior to administration of said VX-680.

5. The combination according to claim 4, wherein said cancer is selected from the group consisting of leukemia; lymphoma; myeloma; skin cancer such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma; breast cancer; head and neck cancer, such as brain cancer; colorectal cancer; colon cancer; rectal cancer; lung cancer, such as non small cell lung cancer; ovarian cancer; renal cancer; prostate cancer; liver cancer; and HPV- associated cancer such as cervical cancer.

6. A method of identifying a cancer patient that is likely or not to respond to a therapy, comprising determining whether a cell or tissue sample isolated from the patient is p53-positive or p53-deficient, wherein determination that the cell or tissue sample is p53-deficient identifies the patient as likely to respond to the therapy, and wherein the therapy comprises administering to a patient nutlin-3 and VX-680,

wherein said nutlin-3 is to be administered prior to administration of said VX-680.

7. Use of nutlin-3 in the manufacture of a medicament for treating a cancer patient, wherein said nutlin-3 is to be administered with VX-680, wherein the patient is one who has been identified as likely to respond to the therapy, wherein the patient is identified by a method comprising determining whether a cell or tissue sample isolated from the patient is p53-positive or p53 deficient, wherein determination that the cell or tissue sample is p53 deficient identifies the patient as likely to respond to the therapy, and

wherein said nutlin-3 is to be administered prior to administration of said VX-680.

8. A kit for use in selectively targeting p53-deficient cancer cells, in a patient suffering from cancer, the kit comprising:

i) nutlin-3,

ii) VX-680, and

iii) instructions to administer said nutlin-3 prior to administration of said VX-680.

9. A method for screening to identify a compound that selectively targets a first cell type or a second cell type, wherein the first cell type is a p53-deficient cell and wherein the second cell type is a p53-positive cell, and wherein the first cell type is labelled with a first detectable marker and wherein the second cell type is labelled with a second detectable marker, the method comprising:

(i) contacting said first and second cell types with the compound; and

(ii) determining the relative amounts of the first and second detectable markers,

wherein the first and second detectable marker are independently detectable and wherein a relative increase in the amount of the first marker in comparison to the amount of the second marker is indicative of a compound selectively targeting a p53-

positive cell and wherein a relative increase in the amount of the second marker is indicative of a compound selectively targeting a p53-deficient cell.

10. The method according to claim 9, wherein said detectable marker is selected from the group consisting of a fluorescent compound, a radioisotope compound, a non-radioisotope compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator compound, a chromogenic compound, an X-radiographic compound, and an enzyme.

11. The method according to claim 10, wherein said fluorescent compound is selected from the group consisting of a Green Fluorescent Protein (GFP), Red Fluorescent Protein (RFP), fluorescein, rhodamine, phycoerytherin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine.

12. The method according to claim 11, wherein said first cell type is labeled with RFP and said second cell type is labeled with GFP.

13. The method according to claim 9, wherein said cell types are contacted with the compound *in vitro, ex vivo* or *in vivo*.

14. The method of claim 9, wherein said relative amounts of the first and second marker are determined using fluorescence-activated cell sorting (FACS) or quantitative imaging microscopy.

15. An oral dosage form for use in cancer therapy, wherein said oral dosage form comprises

(i) a first composition comprising nutlin-3 for inducing cell cycle arrest in a p53-positive cell; and

(ii) a second composition comprising VX-680,

wherein said first composition is formulated for immediate release on contact with aqueous media and wherein said second composition is formulated for modified release on contact with aqueous media.

16. An oral dosage form as claimed in claim 15, wherein the first and second compositions are multiparticulates.

17. An oral dosage form as claimed in claim 16, wherein the multiparticulates comprising the first composition are uncoated and wherein the multiparticulates comprising the second composition have an enteric coat.

18. An oral dosage form as claimed in 16, wherein the multiparticulates are filled into a capsule.

19. An oral dosage form as claimed in claim 15 which takes the form of a tablet in which the first and second compositions are arranged in two or more separate layers.

20. An oral dosage form as claimed in claim 15, wherein the modified release comprises delayed and/or sustained release.

21. An oral dosage form as claimed in claim 15 in which the second composition is coated with an enteric coat.

Claims

1. A method of selectively targeting a p53-deficient cancer cell, comprising administering to a patient suffering from cancer:

(i) a reversible cell cycle arrest-inducing agent for inducing cell cycle arrest in a p53-positive cell; and

(ii) an aurora kinase inhibitor,

wherein said reversible cell cycle arrest-inducing agent is administered prior to administration of said aurora kinase inhibitor.

2. The method according to claim 1, wherein said cancer is selected from the group consisting of leukemia; lymphoma; myeloma; skin cancer such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma; breast cancer; head and neck cancer, such as brain cancer; colorectal cancer; colon cancer; rectal cancer; lung cancer, such as non small cell lung cancer; ovarian cancer; renal cancer; prostate cancer; liver cancer; and HPV- associated cancer such as cervical cancer.

3. The method according to claim 1, wherein said reversible cell cycle arrest-inducing agent is selected from the group consisting of nutlin-1, nutlin-2, nutlin-3 and nutlin 3a.

4. The method according to claim 1, wherein said aurora kinase inhibitor is selected from the group consisting of VX-680, AZD1152, ZM44739 and Hesperadin.

5. The method according to claim 1, wherein said reversible cell cycle arrest-inducing agent is nutlin-3 and said aurora kinase inhibitor is VX-680.

6. The method according to claim 1, wherein said reversible cell cycle arrest-inducing agent is administered 12, 16, 18, 24, 36, 48 or 72 hours prior to administration of said aurora kinase inhibitor.

7. A pharmaceutical combination for use in selectively targeting a p53-deficient cancer cell, in a patient suffering from cancer, comprising:

i) a reversible cell cycle arrest-inducing agent for inducing cell cycle arrest in a p53-positive cell; and

ii) an aurora kinase inhibitor,

wherein said reversible cell cycle arrest-inducing agent is provided in a form suitable for administration prior to administration of said aurora kinase inhibitor.

8. The combination according to claim 7, wherein said cancer is selected from the group consisting of leukemia; lymphoma; myeloma; skin cancer such as

basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma; breast cancer; head and neck cancer, such as brain cancer; colorectal cancer; colon cancer; rectal cancer; lung cancer, such as non small cell lung cancer; ovarian cancer; renal cancer; prostate cancer; liver cancer; and HPV- associated cancer such as cervical cancer.

9. The combination according to claim 7, wherein said reversible cell cycle arrest-inducing agent is selected from the group consisting of nutlin-1, nutlin-2 and nutlin-3.

10. The combination according to claim 7, wherein said aurora kinase inhibitor is selected from the group consisting of VX-680, AZD1152, ZM44739 and Hesperadin.

11. The combination according to claim 7, wherein said reversible cell cycle arrest-inducing agent is nutlin-3 and said aurora kinase inhibitor is VX-680.

12. A method of identifying a cancer patient that is likely or not to respond to a therapy, comprising determining whether a cell or tissue sample isolated from the patient is p53-positive or p53 deficient, wherein determination that the cell or tissue sample is p53 deficient identifies the patient as likely to respond to the therapy, and wherein the therapy comprises administering to a patient:

(i) a reversible cell cycle arrest-inducing agent; and

(ii) an aurora kinase inhibitor,

and wherein said reversible cell cycle arrest-inducing agent is administered prior to administration of said aurora kinase inhibitor.

13. A method of treating a cancer patient identified as likely to respond to a therapy, wherein the patient is identified by a method comprising determining whether a cell or tissue sample isolated from the patient is p53-positive or p53 deficient, wherein determination that the cell or tissue sample is p53 deficient identifies the patient as likely to respond to the therapy, and wherein the method of treatment comprises administering to the patient:

(i) a reversible cell cycle arrest-inducing agent; and

(ii) an aurora kinase inhibitor,

wherein said reversible cell cycle arrest-inducing agent is administered prior to administration of said aurora kinase inhibitor.

14. A kit for use in selectively targeting p53-deficient cancer cells, in a patient suffering from cancer, the kit comprising:

i) a reversible cell cycle arrest-inducing agent for inducing cell cycle arrest in a p53-positive cell; and

ii) an aurora kinase inhibitor,

iii) instructions to administer said reversible cell cycle arrest-inducing agent prior to administration of said aurora kinase inhibitor.

15. A method for screening to identify a compound that selectively targets a first cell type or a second cell type, wherein the first cell type is a p53-deficient cell and wherein the second cell type is a p53-positive cell, and wherein the first cell type is labelled with a first detectable marker and wherein the second cell type is labelled with a second detectable marker, the method comprising:

(i) contacting said first and second cell types with the compound; and

(ii) determining the relative amounts of the first and second detectable markers,

wherein the first and second detectable marker are independently detectable and wherein a relative increase in the amount of the first marker in comparison to the amount of the second marker is indicative of a compound selectively targeting a p53-positive cell and wherein a relative increase in the amount of the second marker is indicative of a compound selectively targeting a p53-deficient cell.

16. The method according to claim 15, wherein said detectable marker is selected from the group consisting of a fluorescent compound, a radioisotope compound, a non-radioisotope compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator compound, a chromogenic compound, an X-radiographic compound, and an enzyme.

17. The method according to claim 16, wherein said fluorescent compound is selected from the group consisting of a Green Fluorescent Protein (GFP), Red Fluorescent Protein (RFP), fluorescein, rhodamine, phycoerytherin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine.

18. The method according to claim 17, wherein said first cell type is labeled with RFP and said second cell type is labeled with GFP.

19. The method according to claim 15, wherein said cell types are contacted with the compound *in vitro, ex vivo* or *in vivo*.

20. The method of claim 15, wherein said relative amounts of the first and second marker are determined using fluorescence-activated cell sorting (FACS) or quantitative imaging microscopy.

21. An oral dosage form comprising

(i) a first composition comprising a reversible cell cycle arrest-inducing agent for inducing cell cycle arrest in a p53-positive cell; and

(ii) a second composition comprising an aurora kinase inhibitor,

wherein said first composition is formulated for immediate release on contact with aqueous media and wherein said second composition is formulated for modified release on contact with aqueous media.

22. An oral dosage form as claimed in claim 21, wherein the first and second compositions are multiparticulates.

23. An oral dosage form as claimed in claim 22, wherein the multiparticulates comprising the first composition are uncoated and wherein the multiparticulates comprising the second composition have an enteric coat.

24. An oral dosage form as claimed in 22, wherein the multiparticulates are filled into a capsule.

25. An oral dosage form as claimed in claim 21 which takes the form of a tablet in which the first and second compositions are arranged in two or more separate layers.

26. An oral dosage form as claimed in claim 21, wherein the modified release comprises delayed and/or sustained release.

27. An oral dosage form as claimed in claim 21 in which the second composition is coated with an enteric coat.