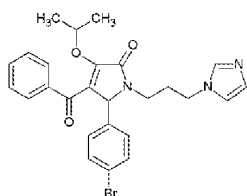


CLAIMS:

1. An MDM2 antagonist for use in a method of treating a cancer, wherein the cancer is BAP1 depleted.
2. An MDM2 antagonist for use according to claim 1, wherein the cancer:
5 is CDKN2A depleted; and/or
shows increased expression of one, two, three, four, five or more interferon signature genes.
3. An MDM2 antagonist for use according to claim 2, wherein the interferon signature genes are
10 CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1.
4. An MDM2 antagonist for use according to any of claims 1 to 3, wherein a sample of patient
15 tissue is tested to determine the cancer expression profile prior to treatment.
5. An MDM2 antagonist for use according to claim 4, wherein the sample comprises cancer DNA, ctDNA, or cancer cells.
6. An MDM2 antagonist for use according to claim 4 or claim 5, wherein the testing comprises an assay to detect protein, mRNA and/or ctDNA.
- 20 7. An MDM2 antagonist for use according to claim 6, wherein (i) protein is detected using an immunoassay, a protein-binding assay, an antibody-based assay, an antigen-binding protein-based assay, a protein-based array, an enzyme-linked immunosorbent assay (ELISA), flow cytometry, a protein array, a blot, a Western blot, nephelometry, turbidimetry, chromatography, mass spectrometry, enzymatic activity, a radioimmunoassay, immunofluorescence,
25 immunochemiluminescence, immunoelectrochemiluminescence, immunoelectrophoretic, a competitive immunoassay, or immunoprecipitation; and/or (ii) wherein mRNA is detected using RT-PCR or a quantitative gene expression assay.
8. An MDM2 antagonist for use according to any of claims 4 to 7 wherein the patient is selected for treatment based on the determined expression profile.
- 30 9. An MDM2 antagonist for use according to any preceding claim, wherein the cancer is:
(i) non-small-cell lung carcinoma, mesothelioma, glioblastoma or kidney renal clear Cell carcinoma; or
(ii) brain, clear cell renal cell carcinoma (ccRCC), esophageal cancer or melanoma.
10. An MDM2 antagonist for use according to any preceding claim, wherein the cancer is P53
35 wild-type.
11. An MDM2 antagonist for use according to any preceding claim, wherein the cancer cells undergo apoptosis following the treatment step.
12. An MDM2 antagonist for use according to any preceding claim, wherein activated caspase-3 is induced by the MDM2 antagonist in at least a proportion of the cancer cells.

13. An MDM2 antagonist for use according to claim 12, wherein activated caspase-3 is induced by the MDM2 antagonist in at least 40% of the cancer cells or at least 60% of the cancer cells.
14. An MDM2 antagonist for use according to any preceding claim, wherein the cancer shows increased expression, relative to a control, of one, two, three, four, five or more of: CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1 and WARS.
15. An MDM2 antagonist for use according to claim 14, wherein the cancer shows increased expression of CXCL10 or CXCL11.
16. An MDM2 antagonist for use according to any preceding claim, wherein the cancer shows increased expression of one, two, three, four, five or more of IRF7, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, IRF9, FLI1 and BRCA1.
17. An MDM2 antagonist for use according to any preceding claim, wherein the MDM2 antagonist is a compound of formula (I^o) or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof as defined herein, for example (2*S*,3*S*)-3-(4-chlorophenyl)-3-[(1*R*)-1-(4-chlorophenyl)-7-fluoro-5-[(1*S*)-1-hydroxy-1-(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1*H*-isoindol-2-yl]-2-methylpropanoic acid or a tautomer, pharmaceutically acceptable salt or solvate thereof.
18. An MDM2 antagonist for use according to any preceding claim, wherein the MDM2 antagonist is selected from the group consisting of idasanutlin (RG-7388), HDM-201, KRT-232 (AMG-232), ALRN-6924, MI-773 (SAR405838), CGM-097, milademetan tosylate, APG-115, BI-907828, LE-004, DS-5272, SJ-0211, BI-0252, AM-7209, SP-141, SCH-1450206, NXN-6, ADO-21, CTX-50 - CTX-1, ISA-27, RO-8994, RO-6839921, ATSP-7041, SAH-p53-8, PM-2, K-178, MMRI-64 and



, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof.

19. Use of the expression level of BAP1 and optionally the expression levels of one or more of:
CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1;

in a cancer cell sample of a human patient, as a biomarker or biomarkers for assessing whether the cancer is susceptible to treatment with an MDM2 antagonist, for example wherein the MDM2 antagonist is a compound of formula (I^o) or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof as defined herein, for example (2*S*,3*S*)-3-(4-chlorophenyl)-3-[(1*R*)-1-(4-chlorophenyl)-7-fluoro-5-[(1*S*)-1-hydroxy-1-(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-

dihydro-1H-isoindol-2-yl]-2-methylpropanoic acid or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof.

20. A method for prognosing or assessing the responsiveness of a human cancer patient to treatment with an MDM2 antagonist, comprising assessing the expression level in a sample
5 from a cancer patient of BAP1 and optionally one or more of:
CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1,
10 COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1;
and determining whether the tested expression level indicates that the cancer should be treated with an MDM2 antagonist.
21. A method according to claim 20, wherein the assessment step comprises comparing the expression level with the expression level (i) associated with responsiveness or non-
15 responsiveness to treatment with an MDM2 antagonist or (ii) from a healthy non-cancer cell of the same type.
22. A method according to claim 20 or claim 21, wherein the patient is classified into a group based on the biomarker profile, optionally wherein the groups comprise or consist of:
(iii) responders and non-responders; or
20 (iv) strong responders.
23. A method according to any of claims 20 to 22, wherein a patient is identified as particularly suitable for treatment when 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the following markers are expressed at a higher level than in a patient identified as not suitable for treatment: CXCL10,
25 CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1.
24. A method according to any of claims 20 to 23, wherein the patient is identified for treatment with the MDM2 antagonist when decreased BAP1 expression and/or decreased CDKN2A
30 expression is detected, relative to the expression level (i) associated with non-responsiveness to treatment with an MDM2 antagonist or (ii) from a healthy non-cancer cell of the same type.
25. A method according to any of claims 20 to 24, comprising the step of detecting the expression level of the biomarkers in a sample of cancer cells from said human patient.
- 35 26. A method according to claim 25, wherein the detection is carried out using an *in vitro* detection assay.
27. A method of determining the susceptibility of a human cancer patient to treatment with an MDM2 antagonist, comprising detecting in a sample of cancer cells from the patient the expression of BAP1 and optionally one or more of:

CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPST11, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1;

and assessing whether the cancer in the patient is likely to respond to treatment with a MDM2 antagonist on the basis of the expression level of the biomarkers in the sample.

28. A method of detecting the expression of BAP1 and optionally one or more of:

CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPST11, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1;

in a human patient suffering from cancer.

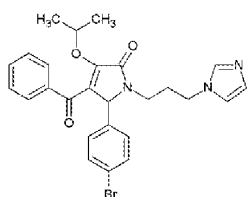
29. A method according to claim 28, comprising the steps of:

(a) obtaining a sample of cancer cells from a human patient; and

(b) detecting whether said biomarkers are expressed in the sampled cancer cells by contacting the sample with one or more reagents for detecting expression of the biomarkers.

30. A method according to any of claims 20 to 29, wherein the MDM2 antagonist is a compound of formula (I^o) or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof as defined herein, for example (2*S*,3*S*)-3-(4-chlorophenyl)-3-[(1*R*)-1-(4-chlorophenyl)-7-fluoro-5-[(1*S*)-1-hydroxy-1-(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1*H*-isoindol-2-yl]-2-methylpropanoic acid or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof.

31. A method according to any of claims 20 to 29, wherein the MDM2 antagonist is selected from the group consisting of idasanutlin, HDM-201, KRT-232 (AMG-232), ALRN-6924, MI-773 (SAR405838), CGM-097, milademetan tosylate, APG-115, BI-907828, LE-004, DS-5272, SJ-0211, BI-0252, AM-7209, SP-141, SCH-1450206, NXN-6, ADO-21, CTX-50 - CTX-1, ISA-27, RO-8994, RO-6839921, ATSP-7041, SAH-p53-8, PM-2, K-178, MMRI-64 and



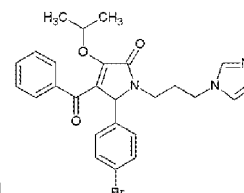
- 30 , or a tautomer or a solvate or a pharmaceutically acceptable salt thereof.

32. A method according to any of claims 20 to 31, further comprising the step of treating the cancer in the patient by administering an MDM2 antagonist.

33. A method according to claim 32, wherein the MDM2 antagonist is a compound of formula (I^o) or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof as defined herein, for example (2*S*,3*S*)-3-(4-chlorophenyl)-3-[(1*R*)-1-(4-chlorophenyl)-7-fluoro-5-[(1*S*)-1-hydroxy-1-

(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1H-isoindol-2-yl]-2-methylpropanoic acid or a tautomer, *N*-oxide, pharmaceutically acceptable salt or solvate thereof.

34. A method according to claim 32, wherein the MDM2 antagonist is selected from the group consisting of idasanutlin, HDM-201, KRT-232 (AMG-232), ALRN-6924, MI-773 (SAR405838), CGM-097, milademetan tosylate, APG-115, BI-907828, LE-004, DS-5272, SJ-0211, BI-0252, AM-7209, SP-141, SCH-1450206, NXN-6, ADO-21, CTX-50 - CTX-1, ISA-27, RO-8994, RO-



6839921, ATSP-7041, SAH-p53-8, PM-2, K-178, MMRi-64 and , or a tautomer or a solvate or a pharmaceutically acceptable salt thereof.

35. A method according to any one of claims 32 to 34, wherein the treatment is provided to the patient based on the outcome of the method.
36. A kit or device for detecting the expression level of at least one biomarker for sensitivity to MDM2 inhibition in a sample from a human patient, comprising a detection reagent for detecting BAP1 and optionally detection reagents for detecting one or more of:

CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1.

37. A system for determining the suitability of a human cancer patient for treatment with an MDM2 antagonist, comprising a storage memory for storing data associated with a sample from the patient comprising data associated with a panel of biomarkers indicating biomarker expression levels in the sample from the subject, the panel of biomarkers comprising BAP1 and optionally one or more of:

CDKN2A, CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1; and

a processor communicatively coupled to the storage memory for classifying the patient.

38. An MDM2 antagonist for use in a method of treating a cancer, wherein the cancer:
- is BAP1 depleted; and/or
 - is CDKN2A depleted; and/or
 - shows increased expression of one, two, three, four, five or more of: CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1,

- WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1.
39. An MDM2 antagonist for use in a method of treating a cancer, wherein the cancer is characterised by one or more, or two or more of the following:
- 5 is BAP1 depleted; and/or
 is CDKN2A depleted; and/or
 shows increased expression of one, two, three, four, five or more of: CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58,
- 10 TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1.
40. An MDM2 antagonist for use, use, method, kit or system according to any preceding claim, wherein the cancer shows BAP1 loss.
- 15 41. An MDM2 antagonist for use, use, method, kit or system according to any preceding claim, wherein the cancer shows CDKN2A loss.
42. An MDM2 antagonist for use, use, or method according to any of claims 1 to 35 or 38 to 41, wherein the MDM2 antagonist is part of a combination therapy with a second therapeutic agent.
43. An MDM2 antagonist for use in a method of treating a cancer, wherein the cancer:
- 20 has BAP1 present at a normal or high level; and/or
 has CDKN2A present at a normal or high level; and/or
 shows decreased expression of one, two, three, four, five or more of the interferon signature genes: CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1,
- 25 USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1;
- in combination with an agent to induce sensitivity to an MDM2 antagonist for example to lower the levels of BAP1 and/or CDKN2A, or increase levels of interferon signature genes.
- 30 44. A method of treating cancer in a patient wherein said method comprises the steps of selecting a patient:
- (a) having normal or high levels of BAP1 and/or CDKN2A, and/or low levels of interferon signature genes, within a biological sample obtained from said patient; and
- (b) administering a therapeutically effective amount of an MDM2 antagonist and an agent
- 35 to induce sensitivity to an MDM2 antagonist for example by lowering the levels of BAP1 and/or CDKN2a, and/or to increasing levels of interferon signature genes, to said patient selected in step (a).
45. A method according to claim 43 or claim 44, wherein the agent to induce sensitivity to an MDM2 antagonist is ASTX660.

46. A pharmaceutical composition comprising an MDM2 inhibitor, wherein the MDM2 inhibitor is a compound of formula (I^o) or a tautomer, N-oxide, pharmaceutically acceptable salt or solvate thereof, for example (2S,3S)-3-(4-chlorophenyl)-3-[(1R)-1-(4-chlorophenyl)-7-fluoro-5-[(1S)-1-hydroxy-1-(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1H-isoindol-2-yl]-2-methylpropanoic acid or a tautomer, N-oxide, pharmaceutically acceptable salt or solvate thereof, for use in the treatment of cancer in a patient, wherein the cancer is as defined in any of claims 1 to 3.
47. An MDM2 antagonist for use in a method of treating a patient with cancer, wherein the method comprises:
- (i) determining that a sample from the patient:
- is BAP1 depleted; and/or
 - is CDKN2A depleted; and/or
 - shows increased expression of one, two, three, four, five or more of: CXCL10, CXCL11, RSAD2, MX1, BATF2, IFI44L, IFITM1, ISG15, CMPK2, IFI27, CD74, IFIH1, CCRL2, IFI44, HERC6, ISG20, IFIT3, HLA-C, OAS1, IFI35, IRF9, EPSTI1, USP18, BST2, CSF1, C1S, DHX58, TRIM14, OASL, IRF7, LGALS3BP, DDX60, LAP3, LAMP3, PARP12, PARP9, SP110, PLSCR1, WARS, IRF7, STAT1, IRF3, IRF5, MSC, JUN, SPI1, IRF1, COMMD3-BMI1, STAT2, RUNX3, SREBF1, FLI1 and BRCA1; and
- (ii) administering an effective amount of the MDM2 antagonist to the patient.