

Claims

1. ~~Use of An~~ inhibitor of ATR kinase, in the manufacture of a medicament for use in a method of treating a hyper-proliferative disease in a subject, wherein said subject or the hyper-
5 proliferative disease is characterized by one or more biomarker(s) selected from
- a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from BRCA1, APC, ATG5, ARID1A, ATM, ATR, ATRIP, ATRX, BAP1, BARD1, BLM, BRAF, BRCA2, BRIP1, CCND1, CCNE1, CCNE2, CDC7, CDK12, CHEK1, CHEK2, DCLRE1A, DCLRE1B, DCLRE1C, DYRK1A, EGFR, ERBB2, ERBB3, ERCC2, ERCC3, ERCC4, ERCC5, FAM175A,
10 FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXO18, FBXW7, FEN1, GEN1, HDAC2, H2AFX, HRAS, KRAS, LIG4, MDC1, MLH1, MLH3, MRE11A, MSH2, MSH3, MSH6, MYC, NBN, NRAS, PALB2, PARP1, PARP2, PARP3, PARP4, PCNA, PIK3CA, PMS2, POLA1, POLB, POLH, POLL, POLN, POLQ, PRKDC, PTEN, RAD9A, RAD17, RAD18, RAD50, RAD51, RAD52, RAD54B, RAD54L, RB1, REV3L, RPA1,
15 RPA2, SLX4, TDP1, TDP2, TMRSS2, TMRSS2-ERG, TOPBP1, TOP2A, TOP2B, TP53, TP53BP1, TRRAP, UBE2N, UIMC1, USP1, WDR48, WRN, XPA, XRCC1, XRCC2, XRCC3, XRCC4 and/or XRCC6 gene/protein; and/or
- b) the activation of the ALT pathway; and/or
- c) microsatellite instability.
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2. The ~~inhibitor of ATR kinase for use according to claim 1, which wherein the inhibitor of ATR~~
kinase is 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-
1,7-naphthyridine or a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof.
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3. The ~~inhibitor of ATR kinase for use according to claims 1 or 2, wherein the subject or the~~
hyper-proliferative disease is characterized by one or more biomarker(s), which comprise(s) one
or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from BRCA1, APC,
ARID1A, ATG5, ATM, ATR, ATRIP, ATRX, BAP1, BARD1, BLM, BRCA2, BRIP1, CDK12,
30 CHEK1, CHEK2, DCLRE1A, DCLRE1B, DCLRE1C, ERCC2, ERCC3, ERCC4, ERCC5, FAM175A, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXO18, FBXW7, FEN1, GEN1, H2AFX, HDAC2, LIG4, MDC1, MLH1, MLH3, MRE11A, MSH2, MSH3, MSH6, NBN, PALB2, PARP1, PARP2, PARP3, PARP4, PMS2, POLA1, POLB, POLH, POLN, POLN, POLQ, PRKDC, PTEN, RAD17, RAD18, RAD50,
35 RAD51, RAD52, RAD54B, RAD54L, RAD9A, RB1, REV3L, RPA1, RPA2, SLX4, TDP1, TDP2, TP53, TP53BP1, TRRAP, UBE2N, UIMC1, USP1, WDR48, WRN, XPA, XRCC1, XRCC2, XRCC3, XRCC4 and/or XRCC6.

4. The ~~inhibitor of ATR kinase for use~~ according to claims 1 or 2, wherein the subject or the hyper-proliferative disease is characterized by one or more biomarker(s), which comprise(s) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from BRCA1, ATM, BLM, BRCA2, ERCC5, FEN1, FANCD2, FANCG, H2AFX, PARP1, PCNA, POLL, POLB/POLL, RAD9A, RAD17, RAD52, REV3L, TDP2, TP53BP1, UBE2N, XPA.
5. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is (are) selected from BRCA1, ATM, BLM, ERCC5, FEN1, FANCD2, H2AFX, PARP1, PCNA, RAD9A, RAD17, REV3L, TP53BP1, UBE2N.
6. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is (are) selected from BRCA1, ATM, FANCD2, H2AFX, RAD17, UBE2N.
7. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is (are) selected from BRCA1, ATM, FEN1, H2AFX, PCNA.
8. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is BRCA1.
9. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is ATM.
10. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is FANCD2.
11. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is H2AFX.
12. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is RAD17.
13. The ~~inhibitor of ATR kinase for use~~ according to claim 4, wherein the one or more gene(s)/protein(s) is UBE2N.
14. The ~~inhibitor of ATR kinase for use~~ according to any one of claims 1 to 13, ~~wherein the method of treating a hyper-proliferative disease comprises the steps:~~
determining if wherein the medicament is to be administered to the subject if the one or more of

the biomarker(s) defined in any one of claims 1 to 13 has been positively determined to be~~are~~
present in a sample ~~of~~obtained from the subject;
administering a therapeutically effective amount of the inhibitor of ATR kinase, preferably of 2-
[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-
5 naphthyridine or a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable
salt, to the subject, if one or more of the biomarker(s) determined by step (b) is (are) determined
positively.

15. The ~~inhibitor of ATR kinase for use according to claim 14, wherein the sample of the subject~~
10 is an in vitro sample.

16. Use of one or more of the biomarker(s) defined in any one of claims 1 to 13 for identifying a
subject with a hyper-proliferative disease who is disposed to respond favorably to 2-[(3R)-3-
methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine or a
15 tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt~~Compound A.~~

17. A kit comprising 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-
pyrazol-5-yl)-1,7-naphthyridine or a tautomer, an N-oxide, a hydrate, a solvate, or a
pharmaceutically acceptable salt together with means to detect one or more of the biomarker(s)
20 defined in any one of claims 1 to 13.

18. A method for identifying a subject having a hyper-proliferative disease disposed to respond
favorably to an inhibitor of ATR kinase, ~~preferably to 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-~~
~~methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine or a tautomer, an N-oxide, a~~
25 ~~hydrate, a solvate, or a pharmaceutically acceptable salt thereof~~, wherein the method comprises
the detection of one or more of the biomarker(s) defined in any one of claims 1 to 13 in a sample
obtained from ~~of~~ the subject.

19. A method of determining whether a subject having a hyper-proliferative disease will respond
30 to the treatment with an inhibitor of ATR kinase, ~~preferably with 2-[(3R)-3-methylmorpholin-4-~~
~~yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine or a tautomer, an N-~~
~~oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof~~, wherein the method
comprises the detection of one or more of the biomarker(s) defined in any one of claims 1 to 13 in
a sample obtained from ~~of~~ the subject.

20. The method of claim 18 or 19, wherein the inhibitor of ATR kinase is 2-[(3R)-3-
methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine or a

tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof.