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(71) Applicant: **BAYER AKTIENGESELLSCHAFT** [DE/DE]; Kaiser-Wilhelm-Allee 1, 51373 Leverkusen (DE).

(72) Inventors: **WENGNER, Antje, Margret**; Borkumstr. 12 e, 13189 Berlin (DE). **SIEMEISTER, Gerhard**; Reimerswalder Steig 26, 13503 Berlin (DE). **LIU, Li**; 11 Hillside Drive, East Hanover, 07936 NJ (US).

(74) Agent: **BIP PATENTS**; Alfred-Nobel-Str. 10, 40789 Monheim am Rhein (DE).

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(54) Title: PREDICTIVE MARKERS FOR ATR KINASE INHIBITORS

(57) Abstract: The present invention covers an ATR kinase inhibitor, particularly 2-[(3R)-3-methylmorpholin-4-yl]- 4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine ("Compound A"), for use in the treatment of a hyper-proliferative disease in a subject, wherein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

Predictive markers for ATR kinase inhibitors

The present invention covers an inhibitor of ATR kinase, particularly of 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (in the following called "Compound A") for use in the treatment of a hyper-proliferative disease in a subject, wherein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

Background

The integrity of the genome of eukaryotic cells is secured by complex signalling pathways, known as DNA damage response (DDR). Recognition of DNA damage activates DDR pathways resulting in cell cycle arrest, suppression of general translation, induction of DNA repair, and, finally, in cell survival or cell death. Proteins that directly recognize aberrant DNA structures recruit and activate kinases of the DDR pathway, such as ATR. ATR responds to a broad spectrum of DNA damage, including double-strand breaks and lesions derived from interference with DNA replication as well as increased replication stress that is observed in oncogene-driven tumor cells (e.g. Ras mutation/ upregulation, Myc upregulation, CyclinE overexpression).

ATR kinase inhibitors are specifically or generically disclosed in the following publications: J. Med. Chem. 2013, 56, 2125-2138; Exp. Rev. Mol. Med. 16, e10, 2014; WO2010054398A1; WO2010071837A1; WO2010073034A1; WO2011143399A1; WO2011143419A1; WO2011143422A1; WO2011143423A2; WO2011143425A2; WO2011143426A1; WO2011154737A1; WO2011163527A1; WO2012138938A1; WO2012178123A1; WO2012178124A1; WO2012178125A1; WO2013049719A1; WO2013049720A1; WO2013049722A1; WO2013049859A1; WO2013071085A1; WO2013071088A1; WO2013071090A1; WO2013071093A1; WO2013071094A1; WO2013152298A1; WO2014062604A1; WO2014089379A1; WO2014143240; WO 2014143241; WO 2014143242; ACS Med. Chem. Lett. 2015. 6, 37-41; ACS Med. Chem. Lett. 2015. 6, 42-46, WO 2015085132, WO 2015187451.

2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (in the following called "Compound A") is a new ATR kinase inhibitor, which is described in International Patent Application WO2016020320. Identification of one or more biomarkers that predict sensitivity to Compound A could result in more effective biomarker-driven targeted therapy for hyper-proliferative diseases.

No predictive markers for ATR kinase inhibitors have been identified yet in the clinical setting. However, preclinical evidence suggests a number of candidate predictive biomarkers for ATR kinase inhibitors VE-821, VX-970 and AZD6738: Williamson et al. suggest that ATR kinase inhibitors could have potential as single-agent treatments for ARID1A defective cancers (Nature Communications 7:13837 | DOI: 10.1038/ncomms13837, (2016)). According to Mohni et al. ATR pathway inhibition is synthetically lethal in VE-821 treated cancer cells with ERCC1 deficiency and loss of the structure-specific endonuclease ERCC1-XPF (ERCC4) is synthetic lethal with ATR pathway inhibitors (Cancer Res. 74, (2014), 2835-2845). ATR inhibition by VE-821 also seems to synergize with loss of ERCC1, ATM and XRCC1 (Mohni et al., PLOS ONE | DOI:10.1371/journal.pone.0125482 May 12, 2015). According to Hocke et al. (Oncotarget Vol. 7, No. 6, (2016), 7080-7095) POLD1 deficiency might represent a predictive marker for treatment response towards ATR inhibitors. Flynn et al. (Science 347, (2015), 273–277) suggest that ATR kinase inhibitors may be useful for treatment of ALT-positive cancers. According to the data described by Menezes et al. (Mol. Cancer. Res. 13(1), (2015), 120-129) single-agent ATR inhibitors may have therapeutic utility in the treatment of mantle cell lymphoma with ATM loss-of-function. Middleton et al. (Oncotarget, Vol.6, No. 32, (2015), 32396- 32409) suggest that defects in ATM, BRCA2, XRCC3 and XRCC1 and high DNA-PKcs expression conferred sensitivity to VE-821 monotherapy.

According to Jones et al. (Cancer Research (2017), Author Manuscript Published OnlineFirst on October 16, 2017; DOI: 10.1158/0008-5472.CAN-17-2056) in Synovial sarcoma SS18-SSX1 or SS18-SSX2 fusion proteins induce ATR kinase inhibitor sensitivity. Nieto-Soler et al. (Oncotarget. 2016; 7:58759-58767) suggest that expression of EWS-FLI1 (also called EWSR1-FLI1) or EWS-ERG (also called EWSR1-ERG oncogenic translocations sensitizes non-ES cells to ATR inhibitors.

Remi-Buisson et al. (Cancer Res 77(17), (2017), 4567-4578) describe that APOBEC3A and APOBEC3B activities confer susceptibility to ATR kinase inhibitors.

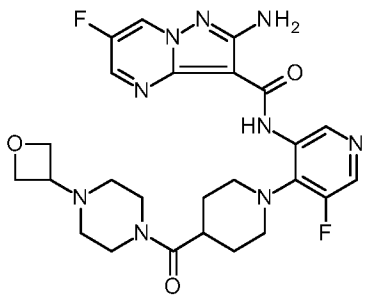
The object of the present invention is to provide one or more biomarker(s) for the treatment of one or more hyper-proliferative disease(s) with an ATR kinase inhibitor, particularly with Compound A, as described herein, in a subject.

DETAILED DESCRIPTION of the INVENTION

Definitions of terms used in the context of the present invention:

The term "ATR kinase inhibitor" or the term "inhibitor of ATR kinase" as used herein means any compound that inhibits ATR kinase. Examples of ATR kinase inhibitors which may be used in context with the present invention include VX-803, VX-970, AZD-6738 and preferably Compound A (described infra), particularly Compound A.

In context with the present invention the term "VX-803" means 2-amino-6-fluoro-N-[5-fluoro-4-(4-{[4-(oxetan-3-yl)piperazin-1-yl]carbonyl}piperidin-1-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide. VX-803 has the following structure



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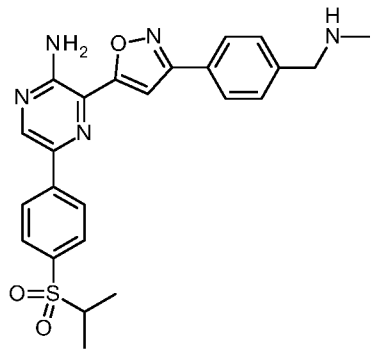
In context with the present invention the term "VX-970" means 3-(3-{4-[(methylamino)methyl]phenyl}-1,2-oxazol-5-yl)-5-[4-(propan-2-ylsulfonyl)phenyl]pyrazin-2-amine. VX-970 has the structure



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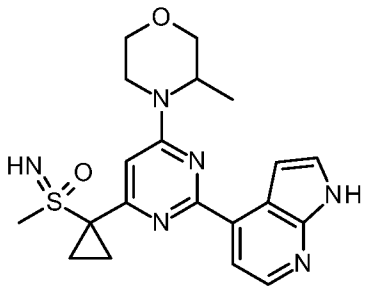
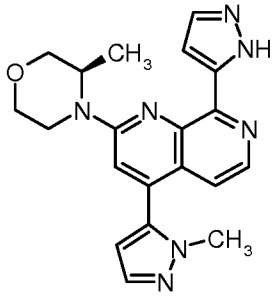
In context with the present invention the term "AZD-6738" means 4-{4-[(3R)-3-methylmorpholin-4-yl]-6-[1-(S-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1H-pyrrolo[2,3-b]pyridine. AZD-6738 has the structure



The term "Compound A" as used herein means 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine of structure:



Compound A.

The expression "gene/protein" means one gene or one protein. The expression "gene(s)/protein(s) means one or more gene(s) or one or more protein(s). The expression "gene(s)" means one gene or more genes. The expression "protein(s)" means one protein or more proteins.

The term "hyper-proliferative disease" includes but is not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), as well as malignant neoplasia. Examples of malignant neoplasia treatable with an ATR kinae inhibitor, particularly Compound A, include solid and hematological tumors. Solid tumors can be exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervous system, colon, anum, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. In addition, malignant neoplasias include primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Hematological tumors can be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well

as AIDS related malignancies.
Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ, particularly with bone metastases.
Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.
Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.
Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.
Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.
Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.
Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.
Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.
Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.
Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.
Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.
Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.
Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

In particular, the present invention covers the treatment of lung cancer, colorectal cancer, cervical cancer, bladder cancer, breast cancer, melanoma, B-cell lymphoma, particularly diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, prostate cancer, gliomas, ovarian cancer, glioblastoma, neuroblastoma, chronic lymphocytic leukemia (CLL), fibrosarcoma, gastric cancer, esophageal cancer, pancreatic cancer,

chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma (MM) and T-cell lymphoma, endometrial cancer, vaginal cancer, and vulvar cancer, as well as sarcoma of the uterus.

Preferably, the present invention covers the treatment of prostate cancer, B-cell lymphoma, particularly diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, melanoma, particularly malignant melanoma, ovarian, particularly, ovarian adenocarcinoma, colorectal cancer, lung, particularly non-small cell lung carcinoma, cervical cancer, and breast cancer, particularly triple-negative mammary carcinoma, pancreatic cancer, fibrosarcoma.

The term "biomarker(s)" as used herein means one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

Particularly, the term biomarker(s) as used herein means one or more biomarker(s), wherein the biomarker comprise(s)

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

A preferred biomarker of the present invention is RBBP8 gene/protein, which is characterized by one or more deleterious mutation(s).

The term "functional mutation" as used herein means a mutation of a gene which results in an altered function of the gene, its corresponding RNA or its corresponding protein compared to the function of the respective wildtype gene, corresponding wildtype RNA or corresponding wildtype protein.

The term "altered function" as used herein means either reduced or increased function of the gene, its corresponding RNA or its corresponding protein compared to the function of the respective wildtype gene, corresponding wildtype RNA or corresponding wildtype protein. The term "altered function" also includes

the complete loss of the function or the gain of a new function of the gene, its corresponding RNA or its corresponding protein compared to the function of the respective wildtype gene, corresponding wildtype RNA or corresponding wildtype protein.

The functional mutation of the gene/protein can be a "deleterious mutation" or an "activating mutation".

The term "deleterious mutation" as used herein means a mutation of the gene which has a deleterious effect on the function of said gene, its corresponding RNA or its corresponding protein compared to the function of the respective wildtype gene/RNA/protein.
For example, the deleterious mutation of the gene may result in a reduced gene expression level of said gene, a reduced amount or a reduced activity of the protein corresponding to said gene, or it may result in a nonfunctional gene/protein ("loss-of-function") compared to the respective wildtype gene/protein.
Examples of a deleterious mutation include but are not limited to the following:
The deleterious mutation can be a nonsense mutation, which is a point mutation in the respective gene, resulting in a premature stop codon, or a nonsense codon in the transcribed mRNA, and in a truncated, incomplete, and nonfunctional protein corresponding to the respective gene.
The deleterious mutation can be a missense mutation, which is a point mutation in the respective gene, resulting in the production either of a nonfunctional protein (complete loss of function) or in a protein with partial loss of function compared to the respective wildtype protein.
The deleterious mutation can also result in a frameshift mutation, which is a genetic mutation in the respective gene caused by insertions or deletions of one or more nucleotides in such gene, wherein the number of nucleotides is not divisible by three, and resulting in a (sometimes truncated) nonfunctional protein corresponding to the respective gene.
The deleterious mutation can also be a large rearrangement mutation, for example a deletion of one or more exons disrupting the reading frame or a critical functional domain of the corresponding protein. Another example for a large rearrangement mutation is a duplication of one or more non-terminal exons disrupting the reading frame or a critical functional domain of the corresponding protein.
The deleterious mutation can also be a splice site mutation, which is a genetic mutation that inserts, deletes or changes a number of nucleotides in the specific site at which splicing takes place during the processing of precursor messenger RNA into mature messenger RNA. Splice site consensus sequences that drive exon recognition are located at the very termini of introns. The deletion of the splicing site results in one or more introns remaining in mature mRNA thereby resulting in the production of a nonfunctional protein corresponding to the respective gene.
The deleterious mutation can also be a copy number variant (CNV), particularly a decrease of the gene copy

number (e.g. a homozygous or heterozygous deletion) compared to the normal gene copy number of the respective wildtype gene.

The term "activating mutation" as used herein means a mutation of the gene which changes said gene, its corresponding RNA and/or its corresponding protein in such a way, that its effects (e.g. the amount of corresponding RNA/protein, or the protein activity) get stronger compared to the respective wildtype gene/RNA/protein. The term "activating mutation" also includes a mutation of a gene, in which the protein corresponding to said gene gets a new function compared to the function of the corresponding wildtype protein. Examples of activating mutations include but are not limited to the following: The activating mutation can be a substitution of one amino acid residue by another that confers a new or higher activity upon the protein.
The activating mutation can be a copy number variant (CNV), particularly an increase of the gene copy number compared to the normal gene copy number of the respective gene.
The activating mutation can also be a fusion gene or fusion protein, e.g. occurring as a result of translocation, interstitial deletion or chromosomal inversion.

The respective wildtype gene is characterized by a reference nucleotide sequence of the cDNA of said gene, which is described under SEQ ID Nos 1 to 7 and SEQ ID Nos 15 to 19, particularly by the coding sequence of said cDNA described under SEQ ID Nos 1 to 7 and SEQ ID Nos 15 to 19. The reference amino acid sequence of the respective wildtype protein is described under SEQ ID Nos 8 to 14 and SEQ ID Nos 20 to 24.

The term "stratification method" as used herein means the method by which one or more of the functional mutation(s) as defined herein, particularly of the deleterious mutations, the activating mutations and/or the expression of the fusion – proteins is (are) determined. Preferably, the stratification method is an in-vitro method. Examples of stratification methods, which can be used in context with the present inventions, are described infra.

The term "sample" as used herein means the sample from the subject, preferably an in vitro sample, which is used in the stratification method (as defined herein), *e.g.* a sample of tumor cells or of tumor tissue, a blood sample, particularly a sample of tumor tissue containing tumor cells.

The term "therapeutically effective amount" of an inhibitor of ATR kinase, particularly of Compound A means an amount of said compound, or a pharmaceutically acceptable salt, isomer, polymorph,

metabolite, hydrate, solvate or ester thereof, which is effective to treat the hyperproliferative disease.

Aspects of the present invention:

Use(s) of the present invention

The present invention covers an inhibitor of ATR kinase, particularly 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (in the following called "Compound A") or a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, particularly Compound A, for use in the treatment of a hyper-proliferative disease in a subject, wherein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

The present invention also covers an inhibitor of ATR kinase, particularly 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (in the following called "Compound A") or a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject, wherein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment of the use of the present invention the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment of the use of the present invention the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

In another embodiment of the use of the present invention the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in RBBP8 gene/protein.

The present invention therefore also covers an inhibitor of ATR kinase, particularly Compound A, or a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, preferably Compound A, for use in the treatment of a hyper-proliferative disease in a subject, wherein said subject or hyper-proliferative disease is or has been characterized by one or more deleterious mutation(s) in the RBBP8 gene/protein.

In another embodiment of the use of the present invention the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5.

In another embodiment of the use of the present invention the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) the expression of a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2.

In another embodiment of the present invention the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and one or more deleterious mutation(s) in in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

In another embodiment of the present invention the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment of the present invention the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s) comprising one or more functional mutation(s) of the gene(s)/protein(s), particularly deleterious and/or activating mutations, as described in Table 1 and/or in Table 2 infra.

Table 1: Deleterious mutations - examples

Gene	Short insertions/ deletions (INDELs)	Substitution-Nonsense	Copy Number Variant (CNV)
RBBP8			decrease of the gene copy number
ERCC1			decrease of the gene copy number
HUS1			decrease of the gene copy number
POLD1	c337delG, p.P116fs*53	c.733G>T, p.E245*	decrease of the gene copy number

Table 2: Activating mutations - examples

Gene	Alteration
APOBEC3A	Increase of gene copy number / upregulation of gene/protein expression
APOBEC3B	Increase of gene copy number / upregulation of gene/protein expression
PGBD5	Increase of gene copy number / upregulation of gene/protein expression

Further examples of deleterious/activating mutations of the gene(s) mentioned herein are described in publically available databases, such as e.g. ClinVar (Landrum MJ, Lee JM, Riley GR, et al., "ClinVar: public archive of relationships among sequence variation and human phenotype", Nucleic Acids Res. 2014;42:D980–5; https://www.ncbi.nlm.nih.gov/clinvar), HGMD (the Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php; Stenson PD, Mort M, Ball EV, et al., "The human gene mutation database: 2008 update.", Genome Med. 2009;1:13) or in "The Human Variome Project" (http://www.humanvariomeproject.org; Timothy D Smith and Mauno Vihinen, "Standard development at the Human Variome Project", Database 2015, 2015), which has curated a gene-/disease- specific databases to collect the sequence variants and genes associated with diseases.

Further examples of deleterious/activating mutations of the gene(s), which may be used in context with the method(s)/use(s)/kit(s)/pharmaceutical composition(s) of the present invention, are described in COSMIC database (www.cancer.sanger.ac.uk; "COSMIC: exploring the world's knowledge of somatic mutations in human cancer", Forbes et al., Nucleic Acids Res. 2015, Jan; 43 (Database issue):D805-11. doi: 10.1093/nar/gku1075. Epub 2014 Oct 29), particularly in release 79 of COSMIC (COSMIC v79), which was released on 14th November 2016.

Examples of EWSR1-ERG fusion gene/protein, which may be used as biomarkers in context with the method(s)/use(s)/kit(s)/pharmaceutical composition(s) of the present invention, are described for example in Sorensen et al. (Nature Genetics 6(2), (1994), 146-151), Dockhorn-Dworniczak et al. (Klinische Pädiatrie 209(4), (1997), 156-164), Giovannini et al. (The Journal of Clinical Investigation 94(2), 489-496), Peter et al. (International Journal of Cancer 67(3), (1996), 339-342) and Bielack et al. (The New England Journal of Medicine 350(13), (2004), 1364-1365).

Examples of EWSR1-FLI1 fusion gene/protein, which may be used as biomarkers in context with the method(s)/use(s)/kit(s)/pharmaceutical composition(s) of the present invention, are described for example in Delattre et al. (Nature 359, (1992), 162-165), Zucman et al. (The EMBO Journal 12(12), (1993), 4481-4487), Giovannini et al. (The Journal of Clinical Investigation 94(2), 489-496), Dockhorn-Dworniczak et al. (Klinische Pädiatrie 209(4), (1997), 156-164), Zoubek et al. (British Journal of Cancer 70(5), (1994), 908-913), de Alava et al. (Journal of Clinical Oncology 16(4), (1998), 1248-1255) and van Doorninc et al. (Journal of Clinical Oncology 28(12), (2010), 1989-1994).

Examples of SS18-SSX1 fusion gene/protein, which may be used as biomarkers in context with the method(s)/use(s)/kit(s)/pharmaceutical composition(s) of the present invention, are described for example in Nilsson et al. (Cancer research; 59(13); 1999; 3180-4), Amary et al. (Histopathology; 51(4); 2007; 559-61), O'Sullivan et al. (The Journal of molecular diagnostics: JMD; 4(3); 2002; 178-80), Wei Y et al. (Oncogene; 22(14); 2003; 2215-22), Crew et al. (The EMBO journal;14(10); 1995; 2333-40), Safar et al. (Diagnostic molecular pathology: the American journal of surgical pathology, part B;7(5); 1998; 283-7), Sanders et al. (Molecular diagnosis: a journal devoted to the understanding of human disease through the clinical application of molecular biology; 4(1); 1999; 65-70), Panagopoulos et al. (Genes, chromosomes & cancer; 31(4); 2001; 362-72) and de Leeuw et al. (Human molecular genetics;4(6); 1995; 1097-9).

Examples of SS18-SSX2 fusion gene/protein, which may be used as biomarkers in context with the method(s)/use(s)/kit(s)/pharmaceutical composition(s) of the present invention, are described for example in Nilsson et al. (Cancer research; 59(13); 1999; 3180-4), Wei et al. (Oncogene; 22(14); 2003; 2215-22),

Crew et al. (The EMBO journal;14(10); 1995; 2333-40), Otsuka et al. (Cancer genetics and cytogenetics; 167(1); 2006; 82-8), Fligman et al.(The American journal of pathology; 147(6); 1995; 1592-9) and Panagopoulos et al. (Genes, chromosomes & cancer; 31(4); 2001; 362-72).

In another embodiment of the present invention the subject or the hyper-proliferative disease is characterized by one or more biomarker(s) comprising the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 fusion gene/protein, particularly fusion genes and their corresponding fusion proteins described in Table 3 infra.

Table 3: Fusion genes encoding fusion proteins - examples

5' Partner Gene				3' Partner Gene			
Gene Name	**Last Observed Exon**	**Inferred Break-point**	**Inserted Sequence**	**Gene Name**	**First Observed Exon**	**Inferred Break-point**	**Inserted Sequence**
EWSR1	7	1112	-	ERG	8	967	-
EWSR1	7	1112	-	ERG	11	1141	-
EWSR1	7	1112	-	ERG	9	1036	-
EWSR1	10	1364	-	ERG	8	967	-
EWSR1	7	1112	-	ERG	10	1093	-
EWSR1	7	1112	-	FLI1	6	920	-
EWSR1	7	1112	-	FLI1	5	854	-
EWSR1	10	1364	-	FLI1	6	920	-
EWSR1	10	1364	-	FLI1	5	854	-
EWSR1	7	1112	-	FLI1	8	1046	-
EWSR1	7	1112	-	FLI1	7	986	-
EWSR1	10	1364	-	FLI1	8	1046	-
EWSR1	9	1331	-	FLI1	4	650	-
EWSR1	9	1331	-	FLI1	7	986	-
EWSR1	7	1112	-	FLI1	9	1094	-
EWSR1	10	1364	-	FLI1	7	986	-
EWSR1	8	1293	-	FLI1	7	986	-
EWSR1	8	1293	-	FLI1	6	920	-
SS18	10	1286	-	SSX1	6	467	-
SS18	10	1286	-	SSX1	5	417	-

SS18	10	1286	-	SSX1	6	467-103	-
SS18	10	1286+8793	-	SSX1	6	467-?	-
SS18	9	1152	-	SSX1	4	321	-
SS18	10	1286+1941	-	SSX1	6	467-1313	-
SSX1	5	466+575	-	SS18	11	1287-12019	-
SS18	9	1152	-	SSX1	5	417	-
SS18	10	1286	6 bp insertion (Sanders et al., (1999), supra)	SSX1	4	321	-

In another embodiment of the present invention the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s) selected from one or more functional mutation(s) of the gene(s)/protein(s) which are described in the Experimental Section infra.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the RBBP8 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype RBBP8 gene (having no deleterious mutation) is described under SEQ ID No. 1. A reference amino acid sequence of the wildtype RBBP8 protein is described under SEQ ID No. 8.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly activating mutation(s), of the APOBEC3A gene/protein. A reference nucleotide sequence of the cDNA of the wildtype APOBEC3A gene (having no activating mutation) is described under SEQ ID No. 2. A reference amino acid sequence of the wildtype APOBEC3A protein is described under SEQ ID No. 9.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly activating mutation(s), of the APOBEC3B gene/protein. A reference nucleotide sequence of the cDNA of the wildtype APOBEC3B gene (having no activating mutation) is described under SEQ ID No. 3. A reference amino acid sequence of the wildtype APOBEC3A protein is described under SEQ ID No. 10.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the CLSPN gene/protein. A reference nucleotide sequence of the cDNA of the

wildtype CLSPN gene (having no deleterious mutation) is described under SEQ ID No. 15. A reference amino acid sequence of the wildtype CLSPN protein is described under SEQ ID No. 20.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the ERCC1 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype ERCC1 gene (having no deleterious mutation) is described under SEQ ID No. 4. A reference amino acid sequence of the wildtype wildtype ERCC1 protein is described under SEQ ID No. 11.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the HUS1 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype HUS1 gene (having no deleterious mutation) is described under SEQ ID No. 5. A reference amino acid sequence of the wildtype HUS1 protein is described under SEQ ID No. 12.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the MAD2L2 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype MAD2L2 gene (having no deleterious mutation) is described under SEQ ID No. 16. A reference amino acid sequence of the wildtype MAD2L2 protein is described under SEQ ID No. 21.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly activating mutation(s), of the PGBD5 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype PGBD5 gene (having no activating mutation) is described under SEQ ID No. 6. A reference amino acid sequence of the wildtype PGBD5 protein is described under SEQ ID No. 13.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the POLD1 gene/protein. A reference nucleotide sequence of the cDNA of the wildtype POLD1 gene (having no deleterious mutation) is described under SEQ ID No. 7. A reference amino acid sequence of the wildtype POLD1 protein is described under SEQ ID No. 14.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the RAD1 gene/protein. A reference nucleotide sequence of the cDNA of the

wildtype RAD1 gene (having no deleterious mutation) is described under SEQ ID No. 17. A reference amino acid sequence of the wildtype RAD1 protein is described under SEQ ID No. 22.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the TIMELESS gene/protein. A reference nucleotide sequence of the cDNA of the wildtype TIMELESS gene (having no deleterious mutation) is described under SEQ ID No. 18. A reference amino acid sequence of the wildtype TIMELESS protein is described under SEQ ID No. 23.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) one or more functional mutation(s), particularly deleterious mutation(s), of the TIPIN gene/protein. A reference nucleotide sequence of the cDNA of the wildtype TIPIN gene (having no deleterious mutation) is described under SEQ ID No. 19. A reference amino acid sequence of the wildtype TIPIN protein is described under SEQ ID No. 24.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) the expression of a EWSR1-ERG fusion gene encoding a EWSR1-ERG fusion protein.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) the expression of a EWSR1-FLI1 fusion gene encoding a EWSR1-FLI1 fusion protein.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) the expression of a SS18-SSX1 fusion gene encoding a SS18-SSX1 fusion protein.

In another embodiment the subject or the hyper-proliferative disease is or has been characterized by one or more biomarker(s), wherein the biomarker comprise(s) the expression of a SS18-SSX2 fusion gene encoding a SS18-SSX2 fusion protein.

In another embodiment of the use of the present invention a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, is administered to the subject.

The present invention also covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject, said method comprising the steps:

a) determining or having determined if one or more of the biomarker(s) defined herein are present in a

sample, preferably in an in vitro sample, of the subject;

b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly Compound A to the subject, if one or more of the biomarker(s) determined by or according to step a) is (are) present in the sample.

The present invention also covers an inhibitor of ATR kinase, particularly Compound A for use in a method of treating a hyper-proliferative disease in a subject said method comprising the steps:

a) determining or having determined if one or more of the biomarker(s) selected from

(i) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

(ii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;

are present in a sample, preferably in an in vitro sample, of the subject;

b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly Compound A to the subject, if one or more of the biomarker(s) determined by or according to any one of steps a)(i) and/or a)(ii) is (are) present in the sample.

The present invention also covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject said method comprising the steps:

a) determining or having determined if one or more of the biomarker(s) selected from one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8 is (are) present in a sample, preferably in an in vitro sample, of the subject;

b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step a) is (are) present in the sample.

The present invention also covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject said method comprising the steps:

a) determining or having determined if the biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein are present in a sample, preferably in an in vitro sample, of the subject;

b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of

Compound A, to the subject, if the biomarker(s) determined by or according to step a) is (are) present in the sample.

In another embodiment of the use of an inhibitor of ATR kinase, particularly Compound A, in a method of treating a hyper-proliferative disease in a subject according to the present invention said method comprising the steps:

a) assaying or having assayed a sample, preferably an in vitro sample, from the subject, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more of the biomarker(s) defined herein are present in the sample;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step b) is (are) present in the sample.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly Compound A, in a method of treating a hyper-proliferative disease in a subject said method comprising the steps:

a) assaying or having assayed a sample, preferably an in vitro sample, from the subject, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more of the biomarker(s) defined in (i) and/or (ii) are present in the sample:
    (i) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN gene/protein; and/or
    (ii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to any one of steps (b)(i) and/or (b)(ii) is (are) present in the sample.

In another embodiment the present invention covers an inhibitor of ATR kinase, particularly Compound A for use in a method of treating a hyper-proliferative disease in a subject, wherein said subject is or has been selected by having one or more biomarker(s) defined herein.

In another embodiment the present invention covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject, wherein said subject is or has been selected by having one or more of the biomarker(s) selected from

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment the present invention covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject, wherein said subject is or has been selected by having one or more of the biomarker(s) selected from one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8.

The present invention also covers an inhibitor of ATR kinase, particularly Compound A, for use in a method of treating a hyper-proliferative disease in a subject, wherein said hyper-proliferative disease is or has been characterized by

a) one or more functional mutation(s) in one or more gene(s)/protein(s) as defined herein; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment the present invention also covers an inhibitor of ATR kinase, particularly Compound A, for the use in a method of treating a subject diagnosed with a hyper-proliferative disease, said method comprising the steps:

a) assaying or having assayed a sample, preferably an in vitro sample, from the subject, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more of the biomarker(s) defined herein are present in the sample;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step b) is (are) present in the sample.

In another embodiment the present invention also covers an inhibitor of ATR kinase, particularly Compound A, for the use in a method of treating a subject diagnosed with a hyper-proliferative disease,

said method comprising the steps:

a) assaying or having assayed a sample, preferably an in vitro sample, from the subject, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein is (are) present in the sample;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step b) is (are) present in the sample.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly of Compound A, for the preparation of a medicament for treating a hyper-proliferative disease in a subject, wherein said subject or said hyper-proliferative disease is or has been characterized by one or more biomarker(s) defined herein.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly of Compound A, for the preparation of a medicament for treating a hyper-proliferative disease in a subject, wherein said subject or said hyper-proliferative disease is or has been characterized by one or more biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment of the use of an inhibitor of ATR kinase, particularly of Compound A, in the manufacture of a medicament for treating a hyper-proliferative disease in a subject according to the invention the one or more functional mutation(s) and/or the expression of a fusion gene is (are) determined or has (have) been determined by one or more of the stratification method(s) described herein.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly of Compound A, in the manufacture of a medicament for a method of treating a hyper-proliferative disease in a subject, said method comprising the steps:

a) assaying or having assayed a sample from the subject for the presence of the biomarker(s) defined herein, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more of the biomarker(s) defined herein are present in the sample;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step (b) is (are) present in the sample.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly of Compound A, in the manufacture of a medicament for a method of treating a hyper-proliferative disease in a subject, said method comprising the steps:

a) determining or having determined if one or more of the biomarker(s) defined herein are present in a sample of said subject;
b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step a) is (are) determined positively.

In another embodiment the present invention covers the use of an inhibitor of ATR kinase, particularly of Compound A, in the manufacture of a medicament for a method of treating a hyper-proliferative disease in a subject, said method comprising the steps:

a) determining or having determined if one or more of the biomarker(s) comprising one or more deleterious mutation(s) of the RBBP8 gene/protein are present in a sample of said subject;
b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step a) is (are) present in the sample.

Method(s) of the present invention

In another embodiment the present invention covers a method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, particularly of Compound A, wherein said subject or said hyper-proliferative disease is or has been characterized by one or more biomarker(s) defined herein.

In another embodiment the present invention covers a method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, particularly of Compound A, wherein said subject is or has been characterized by

a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-

FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment the present invention covers a method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, particularly of Compound A, wherein said subject is or has been characterized by

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment the present invention covers a method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, particularly of Compound A, wherein said hyper-proliferative disease or subject is or has been characterized by one or more biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment of the method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, particularly of Compound A, the one or more functional mutation(s) and/or the expression of the fusion protein(s) defined herein is (are) or has/have been determined by one or more of the stratification method(s) described herein.

The present invention also covers a method of treatment of a subject diagnosed with a hyper-proliferative disease comprising the steps

a) assaying or having assayed a sample from the subject, preferably an in vitro sample from the subject, particularly by one or more of the stratification method(s) described herein;
b) determining or having determined if one or more of the biomarker(s) defined herein are present in the sample;
c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to step b) is (are) present.

The present invention also covers a method of treatment of a subject diagnosed with a hyper-proliferative

disease comprising the steps

a) assaying or having assayed a sample from the subject, particularly by one or more of the stratification method(s) described herein;

b) determining or having determined if one or more of the biomarker(s) defined in (i), (ii) and/or (iii) are present in the sample:

(i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

(ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

(iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;

c) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, if one or more of the biomarker(s) determined by or according to any one of steps (b)(i), (b)(ii) and/or (b)(iii) is (are) present in the sample.

The present invention also covers a method of treatment of a hyper-proliferative disease characterized by one or more biomarker(s) in a subject comprising administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, wherein the one or more biomarker(s) comprise(s)

a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

The present invention also covers a method of treatment of a hyper-proliferative disease characterized by one or more biomarker(s) in a subject comprising administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, wherein the one or more biomarker(s) comprise(s)

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

The present invention also covers a method of treatment of a hyper-proliferative disease characterized by one or more biomarker(s) in a subject comprising administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to the subject, wherein the one or more biomarker(s) comprise(s) one or more deleterious mutation(s) in RBBP8 gene/protein.

The present invention also covers a method of treatment of a hyper-proliferative disease in a subject comprising:

a) determining or having determined that said hyper-proliferative disease of said subject is characterized by one or more biomarker(s), wherein the one or more biomarker(s) comprise(s)
   (i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   (ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
   (iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein; and
b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to said subject.

The present invention also covers a method of treatment of a hyper-proliferative disease in a subject comprising:

a) determining or having determined that said hyper-proliferative disease of said subject is characterized by one or more biomarker(s), wherein the one or more biomarker(s) comprise(s) one or more deleterious mutation(s) in RBBP8 gene/protein; and
b) administering a therapeutically effective amount of an inhibitor of ATR kinase, particularly of Compound A, to said subject.

The present invention also concerns a method for identifying a subject having a hyper-proliferative disease disposed to respond favorably to an inhibitor of ATR kinase, particularly to Compound A, wherein the method comprises the detection of one or more of the biomarker(s) defined herein in a

sample of said subject. Preferably the detection of one or more biomarker(s) is performed in vitro, particularly in a sample of tumor cells, tumor tissue or blood.

The present invention also concerns a method for identifying a subject having a hyper-proliferative disease disposed to respond favorably to an inhibitor of ATR kinase, particularly to Compound A, wherein the method comprises the detection of one or more of the biomarker(s) selected from:

(i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

(ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

(iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein; in a sample of said subject.

Preferably the detection of one or more biomarker(s) is performed in vitro, particularly in a sample of tumor cells, tumor tissue or blood.

The present invention also concerns a method for identifying a subject having a hyper-proliferative disease disposed to respond favorably to Compound A, wherein the method comprises the detection of one or more of the biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment the one or biomarker(s) defined herein is (are) or has/have been determined by one or more of the stratification method(s) described herein.

The present invention also concerns a method for identifying a subject with a hyper-proliferative disease who is more likely to respond to a therapy comprising an inhibitor of ATR kinase, particularly Compound A, than other subjects, the method comprising

a) determining or having determined in a sample from said subject one or more of the biomarker(s) defined herein;

b) identifying those subjects for whom in step a) one or more of the biomarker(s) is (are) present in the sample.

The present invention also concerns a method for identifying a subject with a hyper-proliferative disease who is more likely to respond to a therapy comprising an inhibitor of ATR kinase, particularly Compound A, than other subjects, the method comprising

a) determining or having determined in a sample from said subject the biomarker(s) selected from:
   (i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   (ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
   (iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;
b) identifying those subjects for whom one or more of the biomarker(s) of any one of a)(i), a)(ii) or a)(iii) is (are) present in the sample.

The present invention also concerns a method for identifying a subject with a hyper-proliferative disease who is more likely to respond to a therapy comprising an inhibitor of ATR kinase, particularly Compound A, than other subjects, the method comprising

a) determining or having determined in a sample from said subject one or more of the biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein;
b) identifying those subjects for whom in step a) one or more of the biomarker(s) is (are) present in the sample.

Preferably the determination of one or more biomarker(s) is performed in vitro, particularly in a sample of said subject selected from tumor cells, tumor tissue or blood.

The present invention also concerns a method of determining whether a subject having a hyper-proliferative disease will respond to the treatment with an inhibitor of ATR kinase, particularly with Compound A, wherein the method comprises the detection of one or more of the biomarker(s) defined herein in a sample of said subject. Preferably the sample is a sample of tumor cells or of tumor tissue of said subject. Particularly, the biomarker(s) is (are) or has/have been determined by one or more of the stratification method(s) described herein.

The present invention also concerns a method of determining the likelihood that a subject with a hyper-proliferative disease benefits from treatment with an inhibitor of ATR kinase, particularly with

Compound A, the method comprising the detection of one or more of the biomarker(s) defined herein in a sample of said subject and identifying the subject being more likely to respond to said treatment with Compound A when the one or more biomarker(s) is (are) present in the sample.

The present invention also covers a method of predicting whether a subject with a hyper-proliferative disease will respond to the treatment with an inhibitor of ATR kinase, particularly with Compound A, wherein the method comprises the detection of one or more of the biomarker(s) defined herein in a sample of said subject.

The present invention also covers a method of predicting whether a subject with a hyper-proliferative disease will respond to the treatment with an inhibitor of ATR kinase, particularly with Compound A, wherein the method comprises the detection of one or more of the biomarker(s) selected from

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;

in a sample of said subject.

Preferably the detection of one or more biomarker(s) is performed in vitro, particularly in a sample of said subject selected from tumor cells, tumor tissue or blood.

The present invention also covers a method of diagnosing a subject with a hyper-proliferative disease as being disposed to respond favorably to an inhibitor of ATR kinase, particularly to Compound A, comprising:

a) detecting or having detected if one or more of the biomarker(s) defined in (i), (ii) and/or (iii) are present in the sample:

(i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
(ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

(iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein; and

b) diagnosing the subject to respond favourably to Compound A when the one or more of the biomarker(s) detected in step a) are present in the sample.

Preferably the measurement of one or more biomarker(s) is performed in vitro, particularly in a sample of said subject selected from tumor cells, tumor tissue or blood.

The present invention also covers a method of treating a subject with a hyper-proliferative disease, wherein the subject is disposed to respond favorably to an inhibitor of ATR kinase, particularly to Compound A, comprising:

a) detecting or having detected if one or more of the biomarker(s) (i), (ii) and/or (iii) are present in the sample:

(i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

(ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

(iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;

b) diagnosing or having diagnosed the subject to respond favourably to Compound A when the one or more of the biomarker(s) detected in step a) are present in the sample; and

c) treating the diagnosed subject 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.

The present invention also covers the use of one or more of the biomarker(s) defined herein for identifying a subject with a hyper-proliferative disease who is disposed to respond favorably to an inhibitor of ATR kinase, particularly to Compound A.

Kit(s) and pharmaceutical composition(s) of the present invention

The present invention also covers a kit comprising an inhibitor of ATR kinase, particularly Compound A, together with means, preferably a detecting agent, to detect in a sample from a subject one or more of the biomarker(s) comprising:

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

The present invention also covers a kit comprising an inhibitor of ATR kinase, particularly Compound A, together with means, preferably a detecting agent, to detect, particularly in a sample from a subject, one or more of the biomarker(s) defined herein.

The present invention also covers a kit comprising an inhibitor of ATR kinase, particularly Compound A, together with means, preferably a detecting agent, to detect, particularly in a sample from a subject, one or more of the biomarker(s) comprising one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

The present invention also covers a kit comprising an inhibitor of ATR kinase, particularly Compound A, together with means, preferably a detecting agent, to detect in a sample from a subject one or more of the biomarker(s) comprising one or more deleterious mutation(s) in RBBP8 gene/protein.

The present invention also covers a kit comprising an inhibitor of ATR kinase, particularly Compound A, together with means, preferably a detecting agent, to detect, particularly in a sample from a subject, one or more of the biomarker(s) comprising one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5.

The present invention further covers the use of pharmaceutical compositions which comprise an inhibitor of ATR kinase, particularly Compound A, together with one or more, preferably inert, nontoxic,

pharmaceutically suitable excipients, for use in any of the method(s)/use(s) for treating a hyper-proliferative disease in a subject comprising one or more of the biomarker(s) described herein.

The present invention further covers the use of pharmaceutical compositions which comprise an inhibitor of ATR kinase, particularly Compound A, together with one or more, preferably inert, nontoxic, pharmaceutically suitable excipients, for use in any of the method(s)/use(s) for the treatment of a hyper-proliferative disease in a subject comprising one or more of the biomarker(s) described herein.

Biomarker(s) of the hyper-proliferative-disease or subject

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)

a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in one or more

gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and PGBD5.

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

In another embodiment of the use(s)/method(s)/pharmaceutical composition(s)/kit(s) of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment of the use/method/pharmaceutical composition/kit of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

In another embodiment of the use/method/pharmaceutical composition/kit of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and one or more deleterious mutation(s) in RBBP8 gene/protein.

In another embodiment of the use/method/pharmaceutical composition/kit of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and one or more activating mutation(s) in one or more gene(s)/protein(s) selected from

APOBEC3A, APOBEC3B and/or PGBD5.

In another embodiment of the use/method/pharmaceutical composition/kit of the invention described herein the hyper-proliferative disease or the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s) one or more deleterious mutation(s) in TP53 gene/protein and the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

Compound A can act systemically and/or locally. For this purpose, it can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival, otic route, or as an implant or stent. Compound A can be administered in administration forms suitable for these administration routes.

Suitable administration forms for oral administration are those which deliver Compound A in a rapid and/or modified manner, and contain Compound A in crystalline and/or amorphous and/or dissolved form, for example tablets (uncoated or coated tablets, for example with enteric or retarded-dissolution or insoluble coatings which control the release of Compound A, tablets or films/wafers which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.
Parenteral administration can be accomplished with avoidance of an absorption step (for example by an intravenous, intraarterial, intracardial, intraspinal or intralumbal route) or with inclusion of an absorption (for example by an intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal route). Suitable administration forms for parenteral administration include injection and infusion formulations in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.
For the other administration routes, suitable examples are pharmaceutical forms for inhalation or inhalation medicaments (including powder inhalers, nebulizers), nasal drops, solutions or sprays; tablets, films/wafers or capsules for lingual, sublingual or buccal administration, films/wafers or capsules, suppositories, ear or eye preparations (for example eye baths, ocular insert, ear drops, ear powders, ear-rinses, ear tampons), vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (for example patches), milk, pastes, foams, dusting powders, implants, intrauterine coils, vaginal rings or stents.
Compound A can be converted to the administration forms mentioned. This can be done in a manner known per se, by mixing with pharmaceutically suitable excipients.

These excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecylsulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants, for example ascorbic acid), dyes (e.g. inorganic pigments, for example iron oxides) and flavour and/or odour correctants.

Pharmaceutically acceptable excipients are non-toxic, preferably they are non-toxic and inert. Pharmaceutically acceptable excipients include, inter alia: fillers and excipients (for example cellulose, microcrystalline cellulose, such as, for example, Avicel®, lactose, mannitol, starch, calcium phosphate such as, for example, Di-Cafos®),

- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat)
- solvents (for example water, ethanol, Isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyle sulphate, lecithin, phospholipids, fatty alcohols such as, for example, Lanette®, sorbitan fatty acid esters such as, for example, Span®, polyoxyethylene sorbitan fatty acid esters such as, for example, Tween®, polyoxyethylene fatty acid glycerides such as, for example, Cremophor®, polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers such as, for example, Pluronic®),
- buffers and also acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine)
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas)
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidon, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids such as, for example, Carbopol®, alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate such as, for example, Explotab®, cross- linked polyvinylpyrrolidon, croscarmellose-sodium such as, for example, AcDiSol®),
- flow regulators, lubricants, glidant and mould release agents (for example magnesium stearate,

stearic acid, talc, highly-disperse silicas such as, for example, Aerosil®),

- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones such as, for example, Kollidon®, polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates such as, for example, Eudragit®, polyvinylpyrrolidones such as, for example, Kollidon®, polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative diseases by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 50 mg/kg body

weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

In spite of this, it may be necessary to deviate from the amounts specified, specifically depending on body weight, administration route, individual behaviour towards the active ingredient, type of formulation, and time or interval of administration. For instance, less than the aforementioned minimum amount may be sufficient in some cases, while the upper limit mentioned has to be exceeded in other cases. In the case of administration of greater amounts, it may be advisable to divide them into several individual doses over the day.

For example, an inhibitor of ATR kinase, particularly Compound A, may be combined with known antihyperproliferative, cytostatic or cytotoxic substances for treatment of cancers. Examples of suitable antihyperproliferative, cytostatic or cytotoxic combination active ingredients include:
131I-chTNT, abarelix, abiraterone, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib,

aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, blinatumomab, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine, carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, Iasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neridronic acid, netupitant/palonosetron, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab,

nimustine, nintedanib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, roniciclib, samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Stratification Methods

Various stratification methods can be used in context of the present invention to identify

a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein;

in a sample.

Functional mutation(s)

The determination of functional mutations, particularly of deleterious and activating mutations, of gene(s)/protein(s) is known to the person skilled in the art. Deleterious mutations and activating mutations can be, for example, determined by one or more of the following stratification methods: Next generation sequencing (NGS) (Metzker ML, "Sequencing technologies—the next generation", Nat Rev Genet. 2010;11:31–46); Sanger sequencing and other first generation sequencing methods (Lilian T. C. Franca, Emanuel Carrilho and Tarso B. L. Kist, A review of DNA sequencing techniques, Quarterly Reviews of Biophysics 35, 2 (2002), pp. 169–200); PCR, particularly multiplex PCR; Fluorescence in situ hybridization (FISH); array comparative genomic hybridization (array CGH); single nucleotide polymorphism microarray (SNP microarrays), in particular to determine copy number variants (CNVs); or immunohistochemistry (IHC), in particular to determine the loss or overexpression of the respective protein.

The term ''NGS'' does not denote a single technique; rather, it refers to a diverse collection of post-Sanger sequencing technologies developed in the last decade. These methods include sequencing-by-synthesis (Ronaghi M et al., "A sequencing method based on real-time pyrophosphate", Science. 1998;281:363–365), sequencing-by-ligation (Shendure J et al., "Accurate multiplex polony sequencing of an evolved bacterial genome", Science. 2005;309:1728–32.16), ion semiconductor sequencing (Rothberg JM et al., "An integrated semiconductor device enabling non-optical genome sequencing.", Nature. 2011;475:348–52.17), and others.

Bioinformatics approaches are used for detecting and analyzing the sequence variants from NGS data (Teng S, "NGS for Sequence Variants.", Adv Exp Med Biol. 2016;939:1-20). NGS variant detection consists of quality control (to remove potential artifacts and bias from data), sequence alignment (reads are mapped to positions on a reference genome), and variant calling (which is performed by comparing the aligned reads with known reference sequences to find which segments are different with the reference genomes).

The sequence variants detected from NGS can be classified to single nucleotide variants (SNVs), small insertions and deletions (INDELs), and large structural variants (SVs) based on their sequences in length. SNVs, the most common type of sequence variants, are single DNA basepair differences in individuals. INDELs are defined as small DNA polymorphisms including both insertions and deletions ranging from 1 to 50 bp in length. SVs are large genomic alterations (>50 bp) including unbalanced variants (deletions, insertions, or duplications) and balanced changes (translocations and inversions). Copy number variants (CNVs), a large category of unbalanced SVs, are DNA alterations that result in the abnormal number of copies of particular DNA segments.

Variant analysis includes variant annotation which can be used to determine the effects of sequence variants on genes and proteins and filter the functional important variants from a background of neutral polymorphisms.

Variant association analyses connects the functional important variants with complex diseases or clinical traits. The disease-related casual variants can be identified by combining these approaches. Results of these variant analysis are stored in public databases, such as for example COSMIC (the Catalogue Of Somatic Mutations In Cancer, www. cancer.sanger.ac.uk), ClinVar (Landrum MJ, Lee JM, Riley GR, et al., "ClinVar: public archive of relationships among sequence variation and human phenotype.", Nucleic Acids Res. 2014;42:D980–5), HGMD (Stenson PD, Mort M, Ball EV, et al., "The human gene mutation database: 2008 update.", Genome Med. 2009;1:13) or "The Human Variome Project" (http://www.humanvariomeproject.org/), which has curated the gene-/disease- specific databases to collect the sequence variants and genes associated with diseases.

As described above, public data bases, relevant literatures and ongoing evidences associated with the recurrence and function of the gene are used to determine the reportable status of an alteration found from NGS data for the genes of interest. Functional mutations can be classified by any one of the following reportable status: deleterious mutation(s) and activation mutation(s).

Expression of a fusion gene encoding a fusion protein

EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 fusion genes and their corresponding fusion proteins can be detected by the methods known to the person skilled in the art, which are for example described in Latysheva and Babu, Nucleic Acid Research 44 (10), (2016), 4487-4503), Davare and Tognon (Biol. Cell 107, (2015), 111-129) and Surace et al. (Lab Invest. 84(9), (2004);1185-92).

Experimental Section

Preparation of Compound A

Compound A was prepared according to the procedure described in example 111 of International Patent Application WO2016020320.

Example 1

Treatment of isogenic DT40 chicken lymphoma cell lines with Compound A

DT40 cells from isogenic cell lines (see Table 4: Test systems) were seeded in 40 µl of growth medium (RPMI 1640 medium containing stabilized glutamine (#FG1215, Merck/Biochrom), supplemented with 10% fetal calf serum, 1% chicken serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 5E-05M ß-mercaptoethanol) at 200 cells/well in 384-well white microtiter plates ((#6007680; Perkin Elmer Life Sciences) and incubated for 24 h at 37°C. Compound A was added using a digital dispenser (Tecan) to the cells in the test plates and incubated continuously for 3 days at 37°C. To determine cell viability (corresponding to cell number) 10 µl/well of CTG solution (Promega Cell Titer Glo solution, # G755B and G756B) was added. After incubation for further 10 min luminescence was measured using a PHERAstar FSX (BMG Labtech) equipment. All measurements were done in quadruplicates. The percentage change of cell viability was calculated by normalization with respect to the luminescence reading (cell number) at the beginning of treatment of cells (a reference plate was measured at the time point of compound application to the measurement plates) and the luminescence reading (cell number) of the untreated control group. Half-maximal growth inhibition (IC_{50}) was determined as compound concentration, which was required to achieve 50% inhibition of cellular growth using a 4-parameter fit.

To evaluate the relative cellular sensitivity of the isogenic DT40 cell lines towards Compound A the mean IC_{50} of each mutant cell line was divided by the mean IC_{50} of wild-type cells, and then the quotient was converted into logarithmic scale (base 2). Log_2 ratios of ≤ -1 or $\geq +1$, corresponding to a 2-fold change in sensitivity relative to wild-type cells, were considered as particularly relevant.

Results

The activity of Compound A was tested in an isogenic DT40 cell line deficient in the gene RBBP8 (Table 3) derived from DT40 chicken lymphoma cells, which do not express TP53 (Takao et al., Oncogene 1999;

18: 7002-7009). Relative sensitivities against Compound A were calculated for the mutant DT40 cell line versus the parental wild-type DT40 cell line (Table 5).
The results indicate that cells deficient in the gene RBBP8 (copy number reduced from 3 to 1) encoding CtIP protein are more than 2-fold more sensitive towards Compound A as compared to wild-type cells. The result demonstrates that deleterious mutations in the RBBP8 gene sensitize tumor cells to treatment with Compound A.

Table 4: DT40 isogenic mutant cell lines. All cell lines were obtained from Kyoto University, Japan.

Cell line	Gene	Function of deleted (mutated) gene(s), and annotation	Reference
CtIP+/-/-	RBBP8	Heterozygous knockout of CtIP gene	1
CtIPs/-/-	RBBP8	Removal of Top1cc and Top2cc by its endonuclease activity (S322A mutation)	1

[1] Nakamura K, Kogame T, Oshiumi H, Shinohara A, Sumitomo Y, Agama K, et al. Collaborative action of Brca1 and CtIP in elimination of covalent modifications from double-strand breaks to facilitate subsequent break repair. PLoS Genet 2010;6:e1000828.

Table 5: Inhibition of proliferation of isogenic DT40 cells by Compound A and relative sensitivities (log_2 ratios).

Cell line	Gene	IC_{50} (M)	log_2 (ratio)
Wild-type		1.3E-07	0.00
CtIP+/-/-	RBBP8	3.4E-08	-1.93
CtIPs/-/-	RBBP8	6.8E-08	-0.93

Claims

1. An ATR kinase inhibitor for use in the treatment of a hyper-proliferative disease in a subject, wherein the subject is or has been characterized by one or more biomarker(s), wherein the biomarker(s) comprise(s)
   a) one or more functional mutations in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

2. The use according to claim 1, wherein the biomarker(s) comprise(s)
   a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
   c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

3. The use according to claims 1 or 2, wherein the biomarker comprises one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN.

4. The use according to claims 1 or 2, wherein the biomarker comprises one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5.

5. The use according to claims 1 or 2, wherein the biomarker comprises the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

6. The use according to claims 1, 2 or 3, wherein the biomarker comprises one or more deleterious mutation(s) in RBBP8 gene/protein.

7. The use of any one of claims 1 to 6, wherein the ATR kinase inhibitor 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.

8. A method of treatment of a hyper-proliferative disease characterized by one or more biomarker(s) in a subject comprising administering a therapeutically effective amount of an inhibitor of ATR kinase to the subject, wherein the one or more biomarker(s) comprise(s)
   a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

9. The method of treatment according to claim 8, wherein the biomarker(s) comprise(s)
   a) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or
   b) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or
   c) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

10. The method of treatment according to claims 8 or 9, wherein the biomarker comprises one or more deleterious mutation(s) in RBBP8 gene/protein.

11. The method of treatment according to claims 8, 9 or 10, 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.

12. A method of treatment of a hyper-proliferative disease in a subject comprising:
   a) determining or having determined that said hyper-proliferative disease of said subject is characterized by one or more biomarker(s), wherein the one or more biomarker(s) comprise(s)
      (i) one or more deleterious mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, CLSPN, ERCC1, HUS1, MAD2L2, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

(ii) one or more activating mutation(s) in one or more gene(s)/protein(s) selected from APOBEC3A, APOBEC3B and/or PGBD5; and/or

(iii) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein; and

b) administering a therapeutically effective amount of an inhibitor of ATR kinase to said subject.

13. The method of treatment according to claim 12, wherein the biomarker comprises one or more deleterious mutation(s) in RBBP8 gene/protein.

14. The method of treatment according to claims 12 or 13, 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.

15. A method for the treatment of a hyper-proliferative disease in a subject using an effective amount of an inhibitor of ATR kinase, wherein said subject is or has been characterized by

a) one or more functional mutation(s) in one or more gene(s)/protein(s) selected from RBBP8, APOBEC3A, APOBEC3B, CLSPN, ERCC1, HUS1, MAD2L2, PGBD5, POLD1, RAD1, TIMELESS and/or TIPIN; and/or

b) the expression of a fusion gene encoding a fusion protein selected from EWSR1-ERG, EWSR1-FLI1, SS18-SSX1 and/or SS18-SSX2 gene/protein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/083486

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2018/153968 A1 (BAYER AG [DE]; BAYER PHARMA AG [DE]) 30 August 2018 (2018-08-30) claims 1-16,19 page 2, paragraph 3 - page 3, paragraph 1	1-10, 12-15
X	WO 2017/118734 A1 (THE INST OF CANCER RESEARCH: ROYAL CANCER HOSPITAL [GB]; BREAST CANCER) 13 July 2017 (2017-07-13)	1-3,5,8, 9,12,15
Y	page 2, paragraph 1 page 5, paragraph 3-4 examples 1,2	7,11,14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2019	11/02/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bruma, Anja

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SANDRA HOCKE ET AL: "A synthetic lethal screen identifies ATR-inhibition as a novel therapeutic approach for POLD1-deficient cancers", ONCOTARGET, vol. 7, no. 6, 9 February 2016 (2016-02-09), XP055549975, DOI: 10.18632/oncotarget.6857	1-3,5,8, 9,12,15
Y	the whole document	7,11,14

X	WO 2012/138938 A1 (VERTEX PHARMA [US]; CHARRIER JEAN-DAMIEN [GB]; MACCORMICK SOMHAIRLE [G) 11 October 2012 (2012-10-11)	1-3,6, 8-10,12, 13,15
Y	claims 78-99 paragraphs [0147] - [0166], [0176], [0181]	7,11,14

X	RÉMI BUISSON ET AL: "APOBEC3A and APOBEC3B Activities Render Cancer Cells Susceptible to ATR Inhibition", CANCER RESEARCH, vol. 77, no. 17, 11 July 2017 (2017-07-11) , pages 4567-4578, XP055549997, US ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-16-3389	1,4,8,9, 12,15
Y	the whole document	7,11,14

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Y	claims 1-7,68,70-72 paragraphs [0140], [0144], [0163], [0172], [0177]	7,11,14

Y	WO 2016/020320 A1 (BAYER PHARMA AG [DE]) 11 February 2016 (2016-02-11) example 156 claim 1	7,11,14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/083486

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