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(54) Title: RADIOPROTECTION BY INHIBITION OF SUPEROXIDE DISMUTASE 1

(57) Abstract: The present invention relates to an inhibitor of intracellular copper-zinc-superoxide dismutase for use in protecting a subject from injury by a radiation burst. The present invention also relates to a kit comprising an SOD1 inhibitor and a radiosensitizer of cancer cells, to an in vitro use of an SOD1 inhibitor for protecting non-cancer cells from ionizing radiation, and to methods, compositions, and uses related thereto.

Radioprotection by inhibition of superoxide dismutase 1

The present invention relates to an inhibitor of intracellular copper-zinc-superoxide dismutase for use in protecting a subject from injury by a radiation burst. The present invention also relates to a kit comprising an SOD1 inhibitor and a radiosensitizer of cancer cells, to an in vitro use of an SOD1 inhibitor for protecting non-cancer cells from ionizing radiation, and to methods, compositions, and uses related thereto.

Ionizing radiation may have, depending on its dose, profound effects on living cells. Direct effects are caused by radiation directly interacting with genetic material, e.g. DNA, or some other cellular component critical to the survival of the cell. The probability of radiation interacting with the genetic material is low, however, since genetic material only represents a small fraction of the biological molecules constituting a cell. Indirect effects, in contrast, are mainly caused by interaction of radiation with water, producing radicals such as hydroxyl radicals, superoxide ions, and the like. These radicals cause the breakdown of biological molecules and, depending on intensity of breakdown, cause destruction of the cell and the symptoms of radiation injury known in the art.

Since free radicals are also produced as inevitable by-products of oxidative metabolism, protective enzymes catalyzing degradation of radicals to non- or at least less toxic products have evolved, such as catalase, catalyzing the conversion of hydrogen peroxide (H_2O_2) to water and oxygen, and superoxide dismutase (SOD), which dismutates superoxide ions (O_2^-) to oxygen and hydrogen peroxide. In mammals, three SODs are known: SOD1 (Pfam PF00080), also known as copper-zinc-SOD, is mostly found in the cytoplasm; SOD2 (PFAM PF02777), also known as Manganese-SOD, is located in the mitochondria, and SOD3, which is also a copper-zinc enzyme, is located extracellularly. Inhibitors of SODs were proposed as anti-cancer agents, e.g. tetrathiomolybdate comprising compounds (Donate et al. (2008), Br J Cancer 98:776).

Ionizing radiation has long been an important modality in cancer treatment, since high doses of radiation can kill cancer cells; however, simultaneously, toxicity is induced in surrounding non-malignant tissues, which causes adverse events and may affect compliance with recommended protocols by patients.

US 10 722 526 B2 taught radioprotection or radiomitigation with respect to radiation-induced damage by compounds like 2-methoxyestradiol. Milas et al. (1984), Int J Rad Oncol Biol Phys 10(12):2335 reported radioprotective activity of diethyldithiocarbamate (DDC) and suggested inhibition of superoxide dismutase as an explanation; this was, however, in open contradiction with earlier findings that DDC only weakly inhibits superoxide dismutase and only with very slow kinetics (Misra et al. (1979), JBC 254(22):11623). Evans et al. (1985), Int J Rad Oncol Biol Phys 11(6):1163 reported tumor radiosensitization with concomitant bone marrow radioprotection in mice by DDC, assuming a direct radical scavenging effect mediated by the thiol compound. Mashiba et al. (1991), Life Sciences 49:1419, described enhanced radiosensitization in tumor cells by a combination of RK28 with DDC. Trapp et al. (2009), Melanoma Res 19(6):350 described antimelanoma activity of ATN-224.

In accordance with the role of antioxidant enzymes in protection of cells from ionizing radiation, one suggestion to improve radiation therapy was to inhibit antioxidant enzymes, in order to increase radiation damage to cancer cells (Jiang et al. (2018), Cancer Lett 438:154, Che et al. (2016), Drug Discovery Today 21(1), 143).

The standard dose rate delivered during a radiotherapy treatment typically is in the range of from 0.5–20 Gy/min, depending on the irradiation technology used. In recent years, protocols were developed which provide ultra-high dose rate (FLASH) radiation several orders of magnitude higher than what is used in conventional clinical radiotherapy. Such treatments were surprisingly found to strongly reduce adverse effects and effects on normal tissue surrounding a tumor, while being essentially as effective as conventional radiation therapy on the tumor itself (reviewed e.g. in Vozenin et al. (2022), Nat Rev Clin Oncol19:791). Thus, FLASH radiation has been considered a major improvement of radiation therapy, since it enables treatment of cancer tumors with significantly lower radiation toxicity. The limiting factor for wide implementation of FLASH radiotherapy is the need of high doses (of at least 6 Gy) per

beam and very high dose rates (of at least 40 Gy/s) to achieve the FLASH protection, which requires special equipment which is not widely available.

Thus there is still a need for improved cancer treatments, in particular by radiotherapy. The technical problem underlying the present invention can be seen as the provision of means and methods for complying with the aforementioned needs. The technical problem is solved by the embodiments characterized in the claims and herein below.

In accordance, the present invention relates to an inhibitor of intracellular copper-zinc-superoxide dismutase (SOD1 inhibitor) for use in protecting a subject from injury by a radiation burst (radiation burst injury).

In general, terms used herein are to be given their ordinary and customary meaning to a person of ordinary skill in the art and, unless indicated otherwise, are not to be limited to a special or customized meaning. As used in the following, the terms “have”, “comprise” or “include” or any arbitrary grammatical variations thereof are used in a non-exclusive way. Thus, these terms may both refer to a situation in which, besides the feature introduced by these terms, no further features are present in the entity described in this context and to a situation in which one or more further features are present. As an example, the expressions “A has B”, “A comprises B” and “A includes B” may both refer to a situation in which, besides B, no other element is present in A (i.e. a situation in which A solely and exclusively consists of B) and to a situation in which, besides B, one or more further elements are present in entity A, such as element C, elements C and D or even further elements. Also, as is understood by the skilled person, the expressions "comprising a" and "comprising an" preferably refer to "comprising one or more", i.e. are equivalent to "comprising at least one". In accordance, expressions relating to one item of a plurality, unless otherwise indicated, preferably relate to at least one such item, more preferably a plurality thereof; thus, e.g. identifying "a cell" relates to identifying at least one cell, preferably to identifying a multitude of cells.

Further, as used in the following, the terms "preferably", "more preferably", "most preferably", "particularly", "more particularly", "specifically", "more specifically" or similar terms are used in conjunction with optional features, without restricting further possibilities. Thus, features introduced by these terms are optional features and are not intended to restrict the scope of the

claims in any way. The invention may, as the skilled person will recognize, be performed by using alternative features. Similarly, features introduced by "in an embodiment" or similar expressions are intended to be optional features, without any restriction regarding further embodiments of the invention, without any restrictions regarding the scope of the invention and without any restriction regarding the possibility of combining the features introduced in such way with other optional or non-optional features of the invention.

The methods specified herein below, preferably, are in vitro methods. The method steps may, in principle, be performed in any arbitrary sequence deemed suitable by the skilled person, but preferably are performed in the indicated sequence; also, one or more, preferably all, of said steps may be assisted or performed by automated equipment. Moreover, the methods may comprise steps in addition to those explicitly mentioned above.

As used herein, if not otherwise indicated, the term "about" relates to the indicated value with the commonly accepted technical precision in the relevant field, preferably relates to the indicated value ± 20%, more preferably ± 10%, most preferably ± 5%. Further, the term "essentially" indicates that deviations having influence on the indicated result or use are absent, i.e. potential deviations do not cause the indicated result to deviate by more than ± 20%, more preferably ± 10%, most preferably ± 5%. Thus, “consisting essentially of” means including the components specified but excluding other components except for materials present as impurities, unavoidable materials present as a result of processes used to provide the components, and components added for a purpose other than achieving the technical effect of the invention. For example, a composition defined using the phrase “consisting essentially of” encompasses any known acceptable additive, excipient, diluent, carrier, and the like. Preferably, a composition consisting essentially of a set of components will comprise less than 5% by weight, more preferably less than 3% by weight, even more preferably less than 1% by weight, most preferably less than 0.1% by weight of non-specified component(s).

The degree of identity (e.g. expressed as "%identity") between two biological sequences, preferably DNA, RNA, or amino acid sequences, can be determined by algorithms well known in the art. Preferably, the degree of identity is determined by comparing two optimally aligned sequences over a comparison window, where the fragment of sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the

sequence it is compared to for optimal alignment. The percentage is calculated by determining, preferably over the whole length of the polynucleotide or polypeptide, the number of positions at which the identical residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman (1981), by the homology alignment algorithm of Needleman and Wunsch (1970), by the search for similarity method of Pearson and Lipman (1988), by computerized implementations of these algorithms (e.g. BLAST, GAP, BESTFIT, PASTA, or TFASTA), or by visual inspection. Given that two sequences have been identified for comparison, GAP and BESTFIT are preferably employed to determine their optimal alignment and, thus, the degree of identity. Preferably, the default values of 5.00 for gap weight and 0.30 for gap weight length are used. More preferably, the Basic Local Alignment Search Tool (BLAST) implementation is used with default parameter values for alignment. In the context of biological sequences referred to herein, the term "essentially identical" indicates a %identity value of at least 80%, preferably at least 90%, more preferably at least 98%, most preferably at least 99%. As will be understood, the term essentially identical includes 100% identity. The aforesaid applies to the term "essentially complementary" mutatis mutandis.

The term “polypeptide”, as used herein, refers to a molecule consisting of several, typically at least 20 amino acids that are covalently linked to each other by peptide bonds. Molecules consisting of less than 20 amino acids covalently linked by peptide bonds are usually considered to be "peptides". Preferably, the polypeptide comprises of from 50 to 1000, more preferably of from 75 to 1000, still more preferably of from 100 to 500, most preferably of from 110 to 400 amino acids. Preferably, the polypeptide is comprised in a fusion polypeptide and/or a polypeptide complex.

The term "intracellular copper-zinc-superoxide dismutase", which may also be referred to as "superoxide dismutase 1" or "SOD1", is known to the skilled person. Preferably, the term relates to a cytosolic superoxide dismutase of a eukaryotic cell, preferably a mammal, more preferably a human. SOD1 preferably is a homodimeric enzyme and comprises and requires copper and zinc ions for activity. Preferably, SOD1 comprises an amino acid sequence as shown in SEQ ID NO:1 (Genbank Acc No. AAB05662.1) or a sequence at least 70% identical thereto, more

preferably a sequence at least 90% identical thereto. Thus, SOD1 preferably is a mammalian SOD1, more preferably a human SOD1. Activity of SOD1 can be measured by methods known in the art, e.g. from Vonk et al, (2010), JBC 285(37):2891; corresponding kits are commercially available.

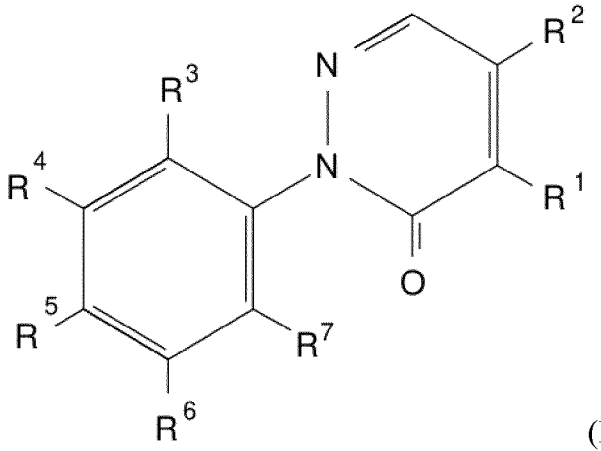
The term "inhibitor of copper-zinc-superoxide dismutase", also referred to as "SOD1 inhibitor" is understood by the skilled person to relate to a chemical compound inhibiting SOD1 activity. Preferably, the SOD1 inhibitor is a direct SOD1 inhibitor, i.e., preferably, is a compound directly interacting with SOD1 or at least one of its components and, thereby, inhibits SOD1 activity. The SOD1 inhibitor may be an unspecific superoxide dismutase inhibitor, but preferably is a specific superoxide dismutase inhibitor, more preferably is a specific SOD1 inhibitor. Methods for identifying SOD inhibitors, in particular SOD1 inhibitors, are known to the skilled person. Preferably, an SOD1 inhibitor is a compound inhibiting SOD1 activity in cultured host cells by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50% at a concentration of at most 1 mM, preferably at most 0.1 mM, more preferably at most 0.01 mM, still more preferably at most 0.001 mM. Preferably, an SOD1 inhibitor is a compound inhibiting SOD1 activity in cultured host cells by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50% at a concentration causing cell death in at most 25%, preferably at most 10%, more preferably at most 5%, still more preferably at most 1%, of said cultured cells. Also preferably, an SOD1 inhibitor is a compound inhibiting SOD1 activity in vivo in a subject by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%, at a dose causing at most Grade 1 (mild) or Grade 2 (moderate) adverse events as specified in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE of 09 August 2006).

Preferably, the SOD1 inhibitor is a low-molecular mass compound, preferably with a molecular mass of at most 1 kDa, more preferably at most 0.5 kDa. Preferably, the SOD1 inhibitor comprises a copper complexant. Also preferably, the SOD1 inhibitor comprises tetrathiomolybdate ions, 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol, and/or cyanide ions.

Preferably, the SOD1 inhibitor comprises tetrathiomolybdate ions. The terms "tetrathiomolybdate" and "tetrathiomolybdate ions" are known to the skilled person. The

molecular formula of tetrathiomolybdate is MoS_4^{2-}(CAS No. 16330-92-0). Tetrathiomolybdate ions may be provided by any compound deemed appropriate by the skilled person, e.g. its acid H_2MoS_4 or a, preferably pharmaceutically acceptable, salt thereof, e.g. bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0), diammonium tetrathiomolybdate, disodium tetrathiomolybdate, or dipotassium tetrathiomolybdate. Preferably, the SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0).

Also preferably, the SOD1 inhibitor is a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one. Thus, preferably, the SOD1 inhibitor has the chemical structure of formula (I):



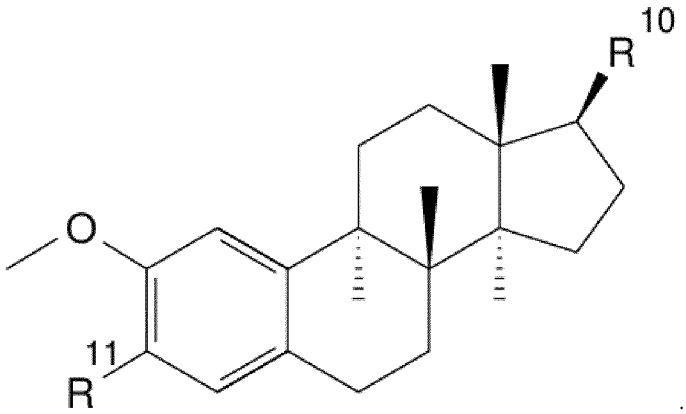
(I),

wherein R^1 and R^2 are independently selected from -Cl, -Br, -I, and -F, preferably wherein R^1 and R^2 are -Cl or are -Br;

wherein R^3 to R^7 are independently selected from -H, $-CH_3$, $-CH_2CH_3$, -Cl, -Br, -I, and -F, preferably wherein R^4 is $-CH_3$ and R^3 and R^5 to R^7 are -H; or R^5 and R^7 are -Cl and R^3, R^4, and R^6 are -H. Thus, preferably, the 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one is 4,5-dichloro-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1, CAS No. 41931-13-9), 4,5-dibromo-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1.28, CAS No. 1035450-90-8), or 4,5-dichloro-2(2,4-dichlorophenyl)pyridazin-3(2H)-one (LCS-1.34, CAS No. 24725-65-3).

Also preferably, the SOD1 inhibitor is 2-methoxyestradiol ((8R,9S,13S,14S,17S)-2-Methoxy-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol, Cas No. 362-07-2) or a derivative or prodrug thereof. A "prodrug" of 2-methoxyestradiol, as the term is used herein, relates to a chemical compound having a chemical structure different from 2-methoxyestradiol, but being metabolized to 2-methoxyestradiol in the body of a subject. A "derivative" of 2-methoxyestradiol, as referred to herein, is a compound having a similar, but non-identical, structure compared to 2-methoxyestradiol and having the property of being an

SOD1 inhibitor. Preferably, a derivative is a compound obtainable from 2-methoxyestradiol by at most three, preferably at most two, more preferably by one derivatization steps known to the skilled person. More preferably, a derivative is a compound obtainable from 2-methoxyestradiol by at most three, preferably at most two, more preferably by one derivatization step selected from (i) alkylation, preferably O- alkylation, preferably methylation, ethylation, propylation, or isopropylation; (ii) esterification, preferably of -OSO_2NH, -COOH and/or -OPO_3H_2 groups, preferably sulfamatylation, acetylation, propionylation, iso-propionylation, or succinylation; (iii) reduction, preferably of C=C and/or hydroxyl; (iv); oxidation, preferably of hydroxyl, C-H, and/or C-C groups. Preferably, the 2-methoxyestradiol derivative or prodrug has a structure according to formula (II)



wherein R^{10} and R^{11} are independently selected from -OSO_2NH, -OH, -OSO_3,OCH_3, -OCH_2CH_3, -NH_2, with the provisio that R^{10} and R^{11} are not both -OH; preferably wherein R^{10} and R^{11} are -OSO_2NH. Thus, the 2-methoxyestradiol derivative preferably is 2-methoxyestradiol disulfamate ([(8R,9S,13S,14S,17S)-2-methoxy-13-methyl-3-sulfamoyloxy-6,7,8,9,11,12,14, 15,16,17-decahydrocyclopenta[a]phenanthren-17-yl] sulfamate, CAS No.401600-86-0).

Also preferably, the SOD1 inhibitor N,N'-Bis(2-aminoethyl)-2 ethanediamine (Triethylentetramin, CAS No. 112-24-3) or one of its salts, preferably its dihydrochloride (Trientine hydrochloride, CAS No. 38260-01-4).

Further preferably, the SOD1 inhibitor comprises cyanide ions (CAS No. 57-12-5. Thus, the SOD1 inhibitor preferably is hydrogen cyanide or any salt thereof deemed appropriate by the skilled person, e.g. sodium cyanide or potassium cyanide. In view of the well-known toxicity of cyanides to living subjects, they are preferably used as SOD1 inhibitors in vitro, e.g. on

cultured cells, and/or also preferably are not used in vivo in a subject, in particular in case the subject is a human.

The term "subject", as used herein, relates to an animal, preferably a vertebrate animal, more preferably a mammal, most preferably a human. Preferably the subject is known or suspected experience a radiation burst, preferably radiotherapy. Preferably, the subject is suffering from cancer. As used herein, the term "host cell" relates to any cell comprising an SOD, preferably an SOD1. Preferably, the cell is a eukaryotic cell, preferably a yeast cell, e.g. a cell of a strain of baker's yeast, or is an animal cell. More preferably, the host cell is an animal cell, preferably an insect cell or a mammalian cell, in particular a mouse or rat cell. Most preferably, the host cell is a human cell.

The term "radiation" is understood by the skilled person. Preferably, radiation is radiation interacting with, preferably causing damage to, biological material, in particular cells. Preferably, radiation comprises, preferably is, particulate radiation, in particular radiation comprising helium ions (alpha radiation), carbon ions, oxygen ions, and/or neutrons; or comprises, preferably is, electron radiation, in particular beta radiation, or comprises, preferably is, photon radiation, in particular gamma radiation. Preferably, the radiation is a type of radiation used in radiotherapy, in particular radiotherapy of cancer.

The term "radiation burst", as used herein, relates to a, preferably foreseeable or predictable, short term increase in radiation, the term "short-term" preferably relating to a time frame of at most 12 hours, preferably at most 6 hours, more preferably at most 2 hours, still more preferably at most 0.5 hours, most preferably at most one minute. Corresponding radiation bursts are known in the art, e.g. radiation bursts caused by solar flares typically last for several hours, a planned radiation burst experienced by a radiation worker may last for a few minutes or hours, while e.g. a radiotherapy session may be finished within minutes or even less than a minute. As the skilled person will understand in view of the description herein, the time frame (duration) of a radiation burst is preferably measured as starting at the time at which radiation intensity increases significantly beyond background radiation and preferably ends at the time when radiation intensity returns to values non-significantly above the background. radiation. Preferably, a radiation burst causes a radiation dose of from 1 Gy to 100 Gy, preferably of from 2 Gy to 25 Gy in a subject or part thereof. In accordance with the above, the radiation burst

causes the aforesaid radiation dose within at most 12 hours, preferably at most 6 hours, more preferably within 2 hours, still more preferably within 0.5 hours, most preferably within less than one minute.

Preferably, the radiation burst is radiotherapy, more preferably is cancer radiotherapy. The term "radiotherapy" is understood by the skilled person and preferably relates to the use of ionizing radiation to kill or control an undesirable cell population in a subject, wherein said undesirable cell population preferably comprises cancer cells. As referred to herein, radiotherapy includes curative radiotherapy as well as adjunctive radiotherapy. Preferably the radiation burst is administered to the subject as a radiotherapy session. In such case, the radiation burst may be radiotherapy with a dose rate of at most 10 Gy/s, preferably at most 0.5 Gy/s, even more preferably at most 0.05 Gy/s. Thus, radiotherapy preferably is radiotherapy with conventional dose rates. It is, however, also envisaged that radiotherapy with higher dose rates is administered, e.g. with a dose rate of more than 10 Gy/s, preferably more than 50 Gy/s, even more preferably more than 100 Gy/s. The dose per treatment, i.e. dose per session preferably is of from 0.1 Gy to 10 Gy, preferably of from 1 Gy to 5 Gy. However, depending on the subject, disease, in particular cancer type, organ or organ system treated, and other factors known to the skilled person, also higher or lower doses may be administered by radiotherapy. Thus, preferably, radiotherapy is radiotherapy with a dose per treatment of from 10 Gy to 100 Gy, preferably of from 20 Gy to 50 Gy. As the skilled person understands, the aforesaid doses indicated herein in Gy are doses of absorbed radiation energy per kilogram. Thus, the aforesaid doses may be body doses or organ or organ system doses. Also preferably, said doses are topical doses at the site of radiotherapy. The skilled person knows how to adjust radiotherapy doses in dependence of relevant parameters, and appropriate guidelines for radiotherapy are available. In accordance with the above, the SOD1 inhibitor may in particular be for use in protecting a subject from radiation burst injury in treating a subject by radiotherapy, in particular treating and/or preventing cancer by radiotherapy,

The term "cancer", as used herein, relates to a disease of an animal, including man, characterized by uncontrolled growth by a group of body cells (cancer cells). This uncontrolled growth may be accompanied by intrusion into and destruction of surrounding tissue (infiltration) and possibly spread of cancer cells to other locations in the body (metastasis). Preferably, also included by the term cancer is a recurrence of a cancer (relapse). Thus,

preferably, the cancer is a solid cancer, a metastasis, or a relapse thereof. Preferably, the cancer is of stage 0 to stage III. Preferably, the cancer is selected from the list consisting of acute myeloid leukemia (AML), acute lymphoblastic leukemia, adrenocortical carcinoma, aids-related lymphoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, brain stem glioma, breast cancer, burkitt lymphoma, carcinoid tumor, cerebellar astrocytoma, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal stromal tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, hepatocellular cancer, hodgkin lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, kaposi sarcoma, laryngeal cancer, medulloblastoma, medulloepithelioma, melanoma, merkel cell carcinoma, mesothelioma, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sézary syndrome, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, waldenström macroglobulinemia, and wilms tumor. More preferably, the cancer is a cancer of the brain, skin, lung, liver, pancreas, intestines, esophagus, heart, kidney, prostate, breast, head&neck, bone, bone marrow, reproductive organs, and/or spinal cord pedicles, preferably as indicated herein above.

The terms "treating" and “treatment” refer to an amelioration of a disease or disorder referred to herein or the symptoms accompanied therewith to a significant extent; as used herein, the term includes prevention of deterioration of a disease, disorder, or symptoms associated therewith. Said treating as used herein also includes an entire restoration of health with respect

to the diseases or disorders referred to herein. It is to be understood that treating, as the term is used herein, may not be effective in all subjects to be treated. However, the term shall require that, preferably, a statistically significant portion of subjects suffering from a disease or disorder referred to herein can be successfully treated. Whether a portion is statistically significant can be determined without further ado by the person skilled in the art using various well known statistic evaluation tools, e.g., determination of confidence intervals, p-value determination, Student´s t-test, Mann-Whitney test etc. Preferred confidence intervals are at least 90%, at least 95%, at least 97%, at least 98% or at least 99 %. The p-values are, preferably, 0.1, 0.05, 0.01, 0.005, or 0.0001. Preferably, the treatment shall be effective for at least 10%, at least 20% at least 50% at least 60%, at least 70%, at least 80%, or at least 90% of the subjects of a given cohort or population. Preferably, treating comprises inhibiting proliferation, more preferably killing, of cancer cells. Preferably, treating cancer is reducing tumor and/or cancer cell burden in a subject. As will be understood by the skilled person, effectiveness of treatment of e.g. cancer is dependent on a variety of factors including, e.g. cancer stage and cancer type. Also preferably, cancer treatment further comprises at least one of chemotherapy, immunotherapy, surgery, and radiotherapy. Preferably, treating comprises treating a relapse. Also preferably, treating comprises treating an advanced stage cancer.

The terms “preventing” and "prevention" refer to retaining health with respect to the diseases or disorders referred to herein for a certain period of time in a subject. It will be understood that said period of time may be dependent on the radiation dose and number of radiation therapy sessions which are administered, as well as individual factors of the subject. It is to be understood that prevention may not be effective in all subjects treated as specified herein. However, the term requires that, preferably, a statistically significant portion of subjects of a cohort or population are effectively prevented from suffering from a disease or disorder referred to herein or its accompanying symptoms. Preferably, a cohort or population of subjects is envisaged in this context which normally, i.e. without preventive measures according to the present invention, would develop a disease or disorder as referred to herein. Whether a portion is statistically significant can be determined without further ado by the person skilled in the art using various well known statistic evaluation tools discussed elsewhere in this specification. In the context of cancer treatment, preventing in particular relates to preventing cancer development, preventing metastasis formation, and/or preventing relapse, preferably relates to preventing metastasis formation and/or preventing relapse.

As will be understood by the skilled person, radiotherapy may be accompanied or complemented by other treatment modalities, such as chemotherapy, surgery, and/or immunotherapy. The terms ""chemotherapy" and "surgery" are understood by the skilled person. Appropriate standard treatment protocols are available in the art. The term "immunotherapy", as used herein, relates to the treatment and/or prevention of disease, preferably cancer, by modulation of the immune response of a subject. Said modulation may be inducing, enhancing, or suppressing said immune response, e.g. by administration of at least one immune checkpoint modulator and/or cytokine. Preferably, the cytokine is an interferon, an interleukin, or a chemokine in such case. The immunotherapy may also comprise administration of T cells, e.g. CAR T cells and/or recombinant T cell receptor T cells, and/or at least one T cell engager, i.e. a molecule tethering a T cell to a target cell; corresponding T cell engagers, e.g. bispecific T cell engagers (BiTEs) such as bispecific antibodies, are known in the art. Furthermore, radiotherapy, in particular radiotherapy of cancer, may be accompanied by administration of at least one radiosensitizer, i.e. of a chemical compound increasing sensitivity of target cells such as cancer cells to ionizing radiation. Preferably, said radiosensitizer is a compound increasing the damage of radiation on DNA. Thus, preferred radiosensitizers are selected from the list consisting of temozolomide, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium and efaproxiral, all of which are as such known to the skilled, as are their uses as radiosensitizers.

The term "injury by a radiation burst", which may also be referred to as "radiation burst injury" is understood by the skilled person in the light of the description herein. Preferably, the radiation burst injury is at least one disease or disorder or symptom thereof caused by a dose of radiation in a subject or a host cell. Preferably, the radiation burst injury is an acute radiation injury or a chronic radiation injury; the skilled person is aware that the terms "acute" and "chronic" injury are used in the context of radiation injury as relating to the timing between radiation and injury, not to the duration of radiation. Thus, preferably, an acute radiation injury is a reaction to irradiation occurring within minutes, hours, or within at most 7 days after irradiation, while a chronic radiation injury is a reaction to irradiation occurring more than 7 days after irradiation. Typical radiation injuries, grouped by the organ system they occur most frequently, are summarized in Table 1 below.

Table 1: Acute and chronic radiation injuries of organs and organ systems.

organ system	acute radiation injury	chronic radiation injury
skin	burn, ulceration	scarring fibrosis
bone	delayed fracture healing	osteoporosis, osteomalacia, bone mineral loss
bone marrow	reduced blood cell counts, reduced white blood cells, reduced platelets	fibrosis, marrow failure
intestines	enteritis, nausea, vomiting	strictures, fistulae, sinus formation
brain	swelling, seizure	cognitive deficits
esophagus	dysphagia, ulcerations	stricture
lung	inflammation pneumonitis	fibrosis
heart	blood vessel swelling	fibrosis, blood vessel damage, heart attack
liver	hepatitis	fibrosis, liver failure
kidney	nephritis, hemorhage	renal failure
reproductive organs	reduced reproductive capacity	reduced reproductive capacity

Thus, an acute radiation injury is preferably selected from the list consisting of burn, ulceration, delayed fracture healing, reduced blood cell counts, reduced white blood cells, reduced platelets, enteritis, nausea, vomiting, swelling, seizure, dysphagia, ulcerations, inflammation pneumonitis, blood vessel swelling, hepatitis, nephritis, hemorhage, and reduced reproductive capacity. Also preferably, a chronic radiation injury is selected from the list consisting of fibrosis, osteoporosis, osteomalacia, bone mineral loss, bone marrow failure, strictures, fistulae, sinus formation, cognitive deficits, blood vessel damage, heart attack, liver failure, renal failure, and reduced reproductive capacity. In case of radiotherapy of cancer, in addition to the above, radiation injury may be cell death of non-cancer cells, scarring at a treated site, ulceration, moist desquamation, erythema, and/or dry desquamation, all preferably at a treated site. Preferably, the radiation burst injury is not a mutagenesis-related injury, i.e. preferably is not an injury caused by a direct effect of ionizing radiation on genetic material, in particular DNA.

The term "protecting from radiation burst injury" is understood by the skilled person in view of the disclosure herein, in particular herein above and the Examples. Preferably, said protecting is reducing the extent or frequency of at least one symptom of radiation burst injury by at least

at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%. More preferably, at least one radiation burst injury, in particular a chronic radiation burst injury, is prevented by at least 75%, more preferably at least 90%. As is understood by the skilled person, the extent of radiation burst injury is a measure of the intensity at which a given radiation burst injury occurs; thus, the extent of radiation burst injury may be measured in a single individual and compared to a reference of control subjects. The extent of radiation burst injury may, however, also be determined over a multitude of subjects, e.g. by calculating a mean, or a similar statistically relevant parameter. As will also be understood, a frequency of radiation burst injury is a measure of how many subjects in a plurality of subjects have a given radiation burst injury after a radiation burst, preferably at a predetermined extent. In accordance, the extent of radiation burst injury will preliminarily be a measure of severity of radiation burst injury, while the frequency of radiation burst injury will primarily be a measure of how frequently a radiation burst injury occurs in a predetermined population. As referred to herein, protecting from radiation burst injury may be reducing the extent of radiation burst injury, may be reducing the frequency of radiation burst injury, or may be both.

Preferably, the radiation burst is radiotherapy and protecting a subject is protecting non-cancer cells from radiotherapy. In such case, the SOD1 inhibitor is preferably administered topically, e.g. in the vicinity of an irradiated site. The SOD1 inhibitor may, however, also be administered systemically, in particular in case an intracorporal site is irradiated or in case of large area or whole-body irradiation.

In view of the description herein above, preferably, the radiation burst is a radiotherapy, in particular a radiotherapy session; also preferably, protecting a subject is protecting non-cancer cells from radiotherapy. Thus, preferably, the present invention relates to an inhibitor of copper-zinc-superoxide dismutase (SOD1 inhibitor) for use in protecting non-cancer cells from radiotherapy of cancer in a subject. Also in such case, protecting non-cancer cells preferably comprises reduction of non-cancer cell death after radiotherapy by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%; and/or comprises reduction of scarring by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%. Also preferably, protecting non-cancer cells comprises avoiding necrosis and/or blistering at the treated site; and/or comprises avoiding ulceration and/or moist desquamation at the treated site. Further preferably, protecting non-cancer cells

comprises at most development of erythema and/or dry desquamation at the treated site as radiation adverse effect(s).

According to the present invention, the SOD1 inhibitor is for use in protecting a subject from radiation burst injury. Thus, the SOD1 inhibitor preferably is for medical use in a subject, preferably for preventing radiation burst injury; in case the radiation burst is radiotherapy e.g. of cancer, the effect of radiotherapy preferably is treatment of cancer, while, also preferably, the effect of SOD1 inhibitor administration is protection of non-cancer cells. Thus, by performing radiotherapy in the presence of at least one SOD1 inhibitor in non-cancer cells, cancer cells are killed or inhibited, while non-cancer cells are protected from the effects of radiation. Thus, preferably, said use comprises administration of said SOD1 inhibitor in a time frame of from 1 min to 12 h, preferably 1 min to 6 h, more preferably 1 min to 3 h, still more preferably 1 min to 2 h, before start of said radiation burst. Also preferably, said use comprises administration of said SOD1 inhibitor in a time frame of from 5 min to 60 min, preferably 5 min to 45 min, more preferably 5 min to 30 min, before start of said radiation burst. In view of the description herein, the skilled person understands that it is preferred that SOD1 is inhibited over the whole duration of the radiation burst; thus, in case of extended duration radiation bursts, repeated and/or continuous administration of the SOD1 inhibitor may be envisaged. Preferably, the dose of the SOD1 inhibitor is adjusted such that SOD1 activity in the areas, tissue, organ, or subject is inhibited by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably by at least 50%, preferably over the whole duration of the radiation burst. However, higher doses of the SOD1 inhibitor may be envisaged, e.g. to achieve further reduction of radiation burst injury. Appropriate doses of SOD1 inhibitors are in principle known in the art and can be adjusted by the skilled person by measuring SOD1 activity and/or superoxide ion concentration.

Preferably, the SOD inhibitor is comprised in a pharmaceutical composition, said pharmaceutical composition preferably further comprising a pharmaceutically acceptable carrier. The terms "medicament" and "pharmaceutical composition" are used essentially interchangeably herein and are, in principle, known to the skilled person. As referred to herein, the terms relate to any composition of matter comprising the specified active agent(s) as pharmaceutically active compound(s) and, optionally, one or more excipient. The pharmaceutically active compounds can be present in liquid or dry, e.g. lyophilized, form. It

will be appreciated that the form and character of the pharmaceutical acceptable excipient, e.g. carrier or diluent, is dictated by the amount of active ingredient with which it is to be combined, the route of administration, and other well-known variables. The excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and being not deleterious to the recipient thereof. The excipient employed may include a solid, a gel, or a liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are phosphate buffered saline solution, physiological saline, Ringer's solutions, dextrose solution, and Hank's solution, syrup, oil, water, emulsions, various types of wetting agents, and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax. Said suitable carriers comprise those mentioned above and others well known in the art, see, e.g., Remington´s Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania. The excipient(s) is/are selected so as not to affect the biological activity of the combination. The excipient may, however, also be selected to improve uptake of the active agent into a cell, in particular a non-cancer cell.

The SOD1 inhibitor and/or medicament preferably is administered systemically, preferably orally or parenterally, e.g. by intravenous administration, or is administered topically, preferably intra-tumorally; in case of cancer radiotherapy, topical administration may be peritumoral, and/or topical at a site of radiotherapy. Administration may, however, also be into a blood vessel, typically an artery, afferent to an intended site of effect, such as a peritumoral region. However, depending on the nature of the formulation and the desired therapeutic application, the SOD1 inhibitor and/or medicament may be administered by other routes as well.

A therapeutically effective dose refers to an amount of the active compound which protects a subject from radiation burst injury. Therapeutic efficacy and toxicity of a drug can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50. The dosage regimen will be determined by the attending physician and by clinical factors takin into account in particular

parameters described herein above. As is well known in the medical arts, dosages for any one patient may depend upon many factors, including the patient's size, age, the particular formulation of the medicament to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. The medicament referred to herein is, preferably, administered at least once, e.g. as a bolus. However, the medicament may be administered more than one time and, preferably, at least twice, e.g. permanently or periodically after defined time windows. SOD1 inhibition can be monitored by periodic assessment. Dosage recommendations may be indicated in the prescriber or user instructions in order to anticipate dose adjustments depending on the considered recipient. As will be understood by the skilled person, appropriate doses for the pharmaceutically active compounds described herein are known in the art for single use of said compounds. Thus, a dose may be in particular such a dose known in the art.

The medicament according to the present invention may comprise further active agents in addition to the aforementioned active agent(s). Preferably, the pharmaceutically active compounds according to the invention are to be applied together with at least one further drug and, thus, may be formulated together with this at least one further drug as a medicament. More preferably, in case of cancer treatment, said at least one further active agent is a chemotherapeutic agent or an immunotherapeutic agent, such as a T cell or an immune checkpoint modulator, or is a radiosensitizer, all preferably as specified herein above. Also, it is to be understood that the formulation of a pharmaceutical composition preferably takes place under GMP standardized conditions or the like in order to ensure quality, pharmaceutical safety, and effectiveness of the medicament.

Advantageously, it was found in the work underlying the present invention that administration of an SOD1 inhibitor before radiation exposure can strongly reduce injury of non-cancer cells normally caused by such radiation. Thus, the methods proposed herein enable significant reduction of radiation injury, in particular of non-cancer cells, during exposure of a subject to irradiation, such as e.g. in radiotherapy. Moreover, the means and methods of the present invention also allow performing high-dose radiotherapy with reduced or at least not increased radiation injury compared to conventional dose therapy. In particular, the present invention enables mimicking FLASH radiotherapy while using radiotherapy at conventional dose rates. Moreover, it was found that combining the methods and compounds of the present invention

with FLASH radiotherapy further reduced radiation injury compared to the effect caused by switching from conventional radiotherapy to FLASH radiotherapy; i.e., the compounds and methods of the present invention provide further protection even in FLASH radiation applications compared to FLASH alone.

The definitions made above apply mutatis mutandis to the following. Additional definitions and explanations made further below also apply for all embodiments described in this specification mutatis mutandis.

The present invention preferably also relates to the combined preparation as specified herein above for use in medicine; and for use in treating and/or preventing cancer. The present invention further relates to a use of an SOD1 inhibitor for the manufacture of a medicament for protecting non-cancer cells from radiotherapy of cancer and/or for reducing or avoiding adverse effects of radiotherapy mediated by effects of ionizing radiation on non-cancer cells. The present invention further relates to a method for protecting non-cancer cells in radiotherapy of a subject comprising administering a SOD1 inhibitor to said subject before said radiotherapy. Said method preferably is an in vivo method; preferably, said method further comprises administration of radiotherapy to said subject, preferably within a time frame as specified herein above. Thus, the present invention also relates to a method for treating and/or preventing cancer in a subject by radiotherapy, said method comprising (a) administering at least one SOD1 inhibitor to said subject, (b) administering radiotherapy to said subject; and (c) thereby treating and/or preventing cancer in said subject.

The present invention also relates to a kit comprising an SOD1 inhibitor and a radiosensitizer of cancer cells, preferably comprised in a common housing.

The term “kit”, as used herein, refers to a collection of the aforementioned compounds, means or reagents which may or may not be packaged together. The components of the kit may be comprised by separate vials (i.e. as a kit of separate parts) or provided in a single vial, e.g. as a pharmaceutical composition as specified herein above. The housing of the kit preferably allows translocation of the compounds of the kit, in particular common translocation; thus, the housing may in particular be a transportable container comprising all specified components. Moreover, it is to be understood that the kit of the present invention may be used for practicing the methods

referred to herein. It is preferably envisaged that all components are provided in a ready-to-use manner for practicing the methods referred to above. Further, the kit preferably contains instructions for carrying out said methods. The instructions can be provided by a user's manual on paper or in electronic form. Preferably, the kit is adapted for use in a method of the present invention, more preferably is adapted to comprise all reagents required to perform said method or methods. Also preferably, the kit comprises the compounds as specified in single doses, i.e. comprises the compounds in amounts corresponding to a single dose to be administered to a subject.

Preferably, the compounds in the kit are for separate or for combined administration. "Separate administration", as used herein, relates to an administration wherein at least two of the pharmaceutically active compounds of the present invention are administered via different routes and/or at different parts of the body of a subject. E.g. one compound may be administered by enteral administration (e.g. orally), whereas a second compound is administered by parenteral administration (e.g. intravenously). Preferably, in such case the kit comprises at least two physically separated preparations for separate administration, wherein each preparation contains at least one pharmaceutically active compound; said alternative is preferred e.g. in cases where the pharmaceutically active compounds of the combined preparation have to be administered by different routes, e.g. parenterally and orally, due to their chemical or physiological properties. Conversely, "combined administration" relates to an administration wherein the pharmaceutically active compounds of the present invention are administered via the same route, e.g. orally or, preferably, intravenously. Thus, in such case, the kit may comprise a preparation comprising at least two, preferably all, pharmaceutically active compounds in a single preparation. Thus, the kit may preferably comprise a combined preparation as specified herein above.

Also preferably, the compounds in the kit are for simultaneous or for sequential administration. "Simultaneous administration", as used herein, relates to an administration wherein the pharmaceutically active compounds of as specified are administered at the same time, i.e., preferably, administration of the pharmaceutically active compounds starts within a time interval of less than 15 minutes, more preferably, within a time interval of less than 5 minutes. Most preferably, administration of the pharmaceutically active compounds starts at the same time, e.g. by swallowing a tablet comprising the pharmaceutically active compounds, or by

swallowing a tablet comprising one of the pharmaceutically active compounds and simultaneous injection of the second compound, or by applying an intravenous injection of a solution comprising one pharmaceutically active compound and injecting second compound in different part of the body. Conversely, "sequential administration", as used herein, relates to an administration of the pharmaceutically active compounds such that effective concentrations are present in relevant tissue(s) during at least part of the duration of a radiation burst, but which, preferably, is not a simultaneous administration as specified herein above. Preferably, sequential administration is an administration wherein administration of the pharmaceutically active compounds, preferably all pharmaceutically active compounds, starts within a time interval of 12 hours, still more preferably within a time interval of 4 hours, even more preferably within a time interval of one hour, most preferably within a time interval of 5 minutes. As the skilled person understands, sequential administration may in particular be envisaged in cases where two pharmaceutically active compounds have significantly different pharmacokinetic properties.

Also, the present invention relates to a use of an SOD1 inhibitor for protecting non-cancer cells from ionizing radiation. Said use preferably is an in vitro use. Preferably said use comprises inducing mutations in the genomes of said non-cancer cells.

In view of the above, the following embodiments are specifically envisaged:

Embodiment 1: An inhibitor of intracellular copper-zinc-superoxide dismutase (SOD1 inhibitor) for use in protecting a subject from injury by a radiation burst (radiation burst injury).

Embodiment 2: The SOD1 inhibitor for use of embodiment 1, wherein said SOD1 inhibitor comprises a copper complexant.

Embodiment 3: The SOD1 inhibitor for use of embodiment 1 or 2, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions, a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol or a derivative or prodrug thereof, and/or cyanide ions.

Embodiment 4: The SOD1 inhibitor for use of any one of embodiments 1 to 3, wherein said SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0), 4,5-

dichloro-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1, CAS No. 41931-13-9), 4,5-dibromo-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1.28, CAS No. 1035450-90-8), 4,5-dichloro-2(2,4-dichlorophenyl)pyridazin-3(2H)-one (LCS-1.34, CAS No. 24725-65-3), or N,N'-Bis(2-aminoethyl)-2 ethanediamine (Trientine, CAS No. 112-24-3).

Embodiment 5: The SOD1 inhibitor for use of any one of embodiments 1 to 4, wherein said subject is a mammal.

Embodiment 6: The SOD1 inhibitor for use of any one of embodiments 1 to 5, wherein said subject is a human.

Embodiment 7: The SOD1 inhibitor for use of any one of embodiments 1 to 6, wherein said SOD1 comprises an amino acid sequence as shown in SEQ ID NO:1 (Genbank Acc No. AAB05662.1) or a sequence at least 70% identical thereto.

Embodiment 8: The SOD1 inhibitor for use of embodiment 6, wherein said SOD1 comprises an amino acid sequence as shown in SEQ ID NO:1 or a sequence at least 90% identical thereto.

Embodiment 9: The SOD1 inhibitor for use of any one of embodiments 1 to 8, wherein said use comprises administration of said SOD1 inhibitor in a time frame of from 1 min to 12 h, preferably 1 min to 6 h, more preferably 1 min to 3 h, still more preferably 1 min to 2 h, before start of said radiation burst.

Embodiment 10: The SOD1 inhibitor for use of any one of embodiments 1 to 9, wherein said use comprises administration of said SOD1 inhibitor in a time frame of from 5 min to 60 min, preferably 5 min to 45 min, more preferably 5 min to 30 min, before start of said radiation burst.

Embodiment 11: The SOD1 inhibitor for use of any one of embodiments 1 to 10, wherein said radiation burst causes a radiation dose of from 1 Gy to 100 Gy, preferably of from 2 Gy to 25 Gy.

Embodiment 12: The SOD1 inhibitor for use of any one of embodiments 1 to 11, wherein said radiation burst causes said radiation dose within at most 12 hours, preferably at most 6 hours, more preferably within 2 hours, still more preferably within 0.5 hours, most preferably within less than one minute.

Embodiment 13: The SOD1 inhibitor for use of any one of embodiments 1 to 12, wherein said dose is a body dose or an organ dose.

Embodiment 14: The SOD1 inhibitor for use of any one of embodiments 1 to 13, wherein said radiation comprises particulate radiation, in particular radiation comprising helium ions (alpha radiation), carbon ions, oxygen ions, and/or neutrons; electron radiation, in particular beta radiation, or photon radiation, in particular gamma radiation.

Embodiment 15: The SOD1 inhibitor for use of any one of embodiments 1 to 14, wherein said radiation burst injury is an acute radiation injury or a chronic radiation injury.

Embodiment 16: The SOD1 inhibitor for use of any one of embodiments 1 to 15, wherein said radiation burst injury is an acute radiation injury selected from the list consisting of burn, ulceration, delayed fracture healing, reduced blood cell counts, reduced white blood cells, reduced platelets, enteritis, nausea, vomiting, swelling, seizure, dysphagia, ulcerations, inflammation pneumonitis, blood vessel swelling, hepatitis, nephritis, hemorhage, and reduced reproductive capacity.

Embodiment 17: The SOD1 inhibitor for use of any one of embodiments 1 to 16, wherein said radiation burst injury is a chronic radiation injury selected from the list consisting of fibrosis, osteoporosis, osteomalacia, bone mineral loss, bone marrow failure, strictures, fistulae, sinus formation, cognitive deficits, blood vessel damage, heart attack, liver failure, renal failure, and reduced reproductive capacity.

Embodiment 18: The SOD1 inhibitor for use of any one of embodiments 1 to 17, wherein said radiation burst injury is not a mutagenesis-related injury.

Embodiment 19: The SOD1 inhibitor for use of any one of embodiments 1 to 18, wherein protecting from radiation burst injury is reducing a severity of at least one symptom of at least one radiation burst injury by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%.

Embodiment 20: The SOD1 inhibitor for use of any one of embodiments 1 to 19, wherein said radiation burst is radiotherapy.

Embodiment 21: The SOD1 inhibitor for use of any one of embodiments 1 to 20, wherein said protecting is protecting non-cancer cells from radiotherapy of cancer.

Embodiment 22: The SOD1 inhibitor for use of any one of embodiments 1 to 22, wherein said use comprises topical administration of said SOD1 inhibitor to said non-cancer cells.

Embodiment 23: The SOD1 inhibitor for use of any one of embodiments 1 to 22, wherein said radiation is radiotherapy with a dose rate of at most 10 Gy/s, preferably at most 0.5 Gy/s, even more preferably at most 0.05 Gy/s.

Embodiment 24: The SOD1 inhibitor for use of any one of embodiments 1 to 23, wherein said radiotherapy is radiotherapy with a dose rate of more than 10 Gy/s, preferably more than 50 Gy/s, even more preferably more than 100 Gy/s.

Embodiment 25: The SOD1 inhibitor for use of any one of embodiments 1 to 24, wherein said radiotherapy is radiotherapy with a dose per treatment of from 0.1 Gy to 10 Gy, preferably of from 1 Gy to 5 Gy.

Embodiment 26: The SOD1 inhibitor for use of any one of embodiments 1 to 25, wherein said radiotherapy is radiotherapy with a dose per treatment of from 10 Gy to 100 Gy, preferably of from 20 Gy to 50 Gy.

Embodiment 27: The SOD1 inhibitor for use of any one of embodiments 1 to 26, wherein said dose is a topical dose at the site of radiotherapy.

Embodiment 28: The SOD1 inhibitor for use of any one of embodiments 1 to 27, wherein protecting non-cancer cells comprises reduction of non-cancer cell death after radiotherapy by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%.

Embodiment 29: The SOD1 inhibitor for use of any one of embodiments 1 to 28, wherein protecting non-cancer cells comprises reduction of scarring by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%.

Embodiment 30: The SOD1 inhibitor for use of any one of embodiments 1 to 29, wherein protecting non-cancer cells comprises avoiding necrosis and/or blistering at the treated site.

Embodiment 31: The SOD1 inhibitor for use of any one of embodiments 1 to 30, wherein protecting non-cancer cells comprises avoiding ulceration and/or moist desquamation at the treated site.

Embodiment 32: The SOD1 inhibitor for use of any one of embodiments 1 to 31, wherein protecting non-cancer cells comprises at most erythema and/or dry desquamation at the treated site as radiation adverse effect(s).

Embodiment 33: The SOD1 inhibitor for use of any one of embodiments 1 to 32, wherein said cancer is a solid cancer.

Embodiment 34: The SOD1 inhibitor for use of embodiment 33, wherein said cancer is stage 0 to stage III.

Embodiment 35: The SOD1 inhibitor for use of any one of embodiments 1 to 34, wherein said cancer is a cancer of the brain, skin, lung, liver, pancreas, intestines, esophagus, heart, kidney, prostate, breast, head&neck, bone, bone marrow, reproductive organs, and/or spinal cord pedicles.

Embodiment 36: An SOD1 inhibitor for use in protecting non-cancer cells from radiotherapy of cancer in a subject.

Embodiment 37: An SOD1 inhibitor for use in radiotherapy of cancer, wherein said radiotherapy comprises protecting non-cancer cells from radiotherapy.

Embodiment 38: An SOD1 inhibitor for use in radiotherapy of cancer, wherein said radiotherapy comprises reducing or avoiding adverse effects of radiotherapy mediated by effects of ionizing radiation on non-cancer cells.

Embodiment 39: The SOD inhibitor for of any one of embodiments 36 to 38, further having a feature of any one of embodiments 1 to 35.

Embodiment 40: Use of an SOD1 inhibitor for the manufacture of a medicament for protecting non-cancer cells from radiotherapy of cancer and/or for reducing or avoiding adverse effects of radiotherapy mediated by effects of ionizing radiation on non-cancer cells.

Embodiment 41: A method for protecting non-cancer cells in radiotherapy of a subject comprising administering a SOD1 inhibitor to said subject before said radiotherapy.

Embodiment 42: A method for treating and/or preventing cancer in a subject by radiotherapy, said method comprising
(a) administering at least one SOD1 inhibitor to said subject,
(b)administering radiotherapy to said subject; and
(c) thereby treating and/or preventing cancer in said subject.

Embodiment 43: A kit comprising an SOD1 inhibitor and a radiosensitizer of cancer cells.

Embodiment 44: The kit of embodiment 43, wherein said radiosensitizer is not said SOD1 inhibitor.

Embodiment 45: The kit of embodiment 43 or 44, wherein said radiosensitizer is selected from the list consisting of temozolomide, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium and efaproxiral.

Embodiment 46: The kit of any one of embodiments 43 to 46, wherein said SOD1 inhibitor is an SOD1 inhibitor as specified in any one of embodiments 1 to 4.

Embodiment 47: Use of an SOD1 inhibitor for protecting non-cancer cells from ionizing radiation.

Embodiment 48: The use of embodiment 48, wherein said use is an in vitro use.

Embodiment 49: The use of embodiment 47 or 48, wherein said use comprises inducing mutations in the genomes of said non-cancer cells.

Embodiment 50: A compound comprising tetrathiomolybdate ions, a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol or a derivative or prodrug thereof, and/or cyanide ions.

Embodiment 51: A composition comprising a compound selected from the list consisting of bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0), 4,5-dichloro-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1, CAS No. 41931-13-9), 4,5-dibromo-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1.28, CAS No. 1035450-90-8), 4,5-dichloro-2(2,4-dichlorophenyl)pyridazin-3(2H)-one (LCS-1.34, CAS No. 24725-65-3), and N,N'-Bis(2-aminoethyl)-2 ethanediamine (Trientine, CAS No. 112-24-3).

Embodiment 52: The compound of embodiment 50 or the composition of embodiment 51, wherein said compound is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0).

Embodiment 53: The compound or composition of any one of embodiments 50 to 52 for use in protecting a subject from injury by a radiation burst (radiation burst injury).

Embodiment 54: The compound or composition for use of embodiment 53 further having a feature of any one of embodiments 5 to 35.

Embodiment 55: Use of the compound of embodiment 50 or the composition of embodiment 51 for the manufacture of a medicament for protecting non-cancer cells from

radiotherapy of cancer and/or for reducing or avoiding adverse effects of radiotherapy mediated by effects of ionizing radiation on non-cancer cells.

Embodiment 56: A method for protecting non-cancer cells in radiotherapy of a subject comprising administering the compound of embodiment 50 or the composition of embodiment 51 to said subject before said radiotherapy.

Embodiment 57: A method for treating and/or preventing cancer in a subject by radiotherapy, said method comprising
(a) administering at least one compound of embodiment 50 and/or at least one composition of embodiment 51 to said subject,
(b) administering radiotherapy to said subject; and
(c) thereby treating and/or preventing cancer in said subject.

Embodiment 58: A kit comprising (i) the compound of embodiment 50 or the composition of embodiment 51 and (ii) a radiosensitizer of cancer cells.

Embodiment 59: The kit of embodiment 58, wherein said radiosensitizer is selected from the list consisting of temozolomide, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium and efaproxiral.

Embodiment 60: Use of the compound of embodiment 50 or the composition of embodiment 51 for protecting non-cancer cells from ionizing radiation.

Embodiment 61: The use of embodiment 60, wherein said use is an in vitro use.

Embodiment 62: The use of embodiment 60 or 61, wherein said use comprises inducing mutations in the genomes of said non-cancer cells.

All references cited in this specification are herewith incorporated by reference with respect to their entire disclosure content and the disclosure content specifically mentioned in this specification.

Figure Legends

Fig. 1: Conventional and FLASH irradiation in the presence or absence of ATN-224 or NaCN, fractions of cells surviving the indicated doses. Control: non-irradiated cells (survival=1); Control Conv: cells after irradiation at conventional dose rates; Control Flash: cells after irradiation at high dose rates; ATN-224: cells (non-irradiated) in the presence of ATN-224; ATN Conv: cells after irradiation at conventional dose rates in the presence of ATN-224; ATN Flash: cells after irradiation at high dose rates in the presence of ATN-224; NaCN: cells (non-irradiated) in the presence of NaCN; NaCN conv: cells after irradiation at conventional dose rates in the presence of NaCN; cells after irradiation at high dose rates in the presence of NaCN. Y-axis: fraction of surviving cells relative to non-irradiated cells.

The following Examples shall merely illustrate the invention. They shall not be construed, whatsoever, to limit the scope of the invention.

Example 1

1.1 Cell culture

Human non-small lung cells (H460) were cultured in RPMI 1640 medium (Thermo Fischer Scientific) supplemented with Fetal Bovine Serum 10% (Thermo Fischer Scientific) and Pen/Strep 1% (Thermo Fischer Scientific) and maintained at 37 °C in a humidified 5% CO2 atmosphere.

1.2 Clonogenic Assay

A clonogenic assay experimental setting was used to study the impact of ATN 224 after radiation treatment with different dose rates. A day before the treatment, 400 000 H460 cells were seeded into 35 mm petri dishes (Greiner) and incubated overnight. Cells were treated before irradiation using 60 µM of ATN-224 for 30 minutes; incubation was performed in the same conditions as cell culture. After incubation, cells were irradiated using a MultiRad225 X-ray source (Faxitron Bioptics) with 10 Gy using a conventional dose rate (conv) of 2.15 Gy/s and a high dose rate (HDR) of approximately 10 Gy/s. After irradiation, cells were detached, collected, and plated at a density of 400 000 per flask in duplicate. Two non-irradiated controls were prepared in the same way (with and without ATN-224 treatment) were plated at a density

of 1200 cells per flask in quadruplicate. All samples were plated in T175 flasks. The clonogenic assay was stopped 10 days after irradiation. All samples were fixed in 100% ethanol, stained with Crystal violet, scanned, and counted using an in-house Image J macro tool.

1.3 Dosimetry

To achieve HDR, the petri dishes were placed very close to the source. The dosimetry was performed using EBT XD (Ashland) radiochromic films (RF) only for irradiation using HDR by placing a RF in the bottom of the petri dishes. A previous study allowed us to determine the dose delivered inside the dish for the used experimental setup.

1.4 SOD1 activity

SOD1 activity was measured with the superoxide dismutase assay manufactured by Sigma-Aldrich (order No. CS0009), according to manufacturer's instructions.

1.4 Results

Results of SOD1 activity measurements are shown in Table 2 below.

Table 2: SOD activities after indicated treatments; sd: standard deviation.

	Activity [U/ml]	sd		Normalized Activity	sd
Control NaCN	11,37	0,55		1,000	0,068
NaCN 4 mM / 1 hr	5,05	0,15		0,444	0,025
Control ATN	21,75	0,84		1,000	0,054
ATN 60 µM/ 30 min	12,72	0,33		0,585	0,027
Control HU 2	5,74	0,47		1,000	0,116
HU 2	7,75	0,42		1,349	0,132

Results of the clonogenic assay are shown in Fig. 1. Using non-irradiated cells as positive control (survival fraction=1), it was found that conventional irradiation with a dose of 10 Gy killed more than 99.95% of the cells, while HDR at essentially the same dose killed between 99 and 99.9% of the cells. Pretreatment of the cells with ATN-224 or sodium cyanide led to significantly increased survival rates, which were, in particular with ATN-224, similar to those with HDR.

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Claims

1. An inhibitor of intracellular copper-zinc-superoxide dismutase (SOD1 inhibitor) for use in protecting a subject from injury by a radiation burst (radiation burst injury).

2. The SOD1 inhibitor for use of claim 1, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions, a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol or a derivative or prodrug thereof, and/or cyanide ions.

3. The SOD1 inhibitor for use of claim 1 or 2, wherein said SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0), 4,5-dichloro-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1, CAS No. 41931-13-9), 4,5-dibromo-2-(m-tolyl)-pyridazin-3(2H)-one (LCS-1.28, CAS No. 1035450-90-8), 4,5-dichloro-2(2,4-dichlorophenyl)pyridazin-3(2H)-one (LCS-1.34, CAS No. 24725-65-3), or N,N'-Bis(2-aminoethyl)-2 ethanediamine (Trientine, CAS No. 112-24-3).

4. The SOD1 inhibitor for use of any one of claims 1 to 3, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions.

5. The SOD1 inhibitor for use of any one of claims 1 to 4, wherein said SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0).

6. The SOD1 inhibitor for use of any one of claims 1 to 5, wherein said subject is a human.

7. The SOD1 inhibitor for use of any one of claims 1 to 6, wherein said use comprises administration of said SOD1 inhibitor in a time frame of from 1 min to 12 h, preferably 1 min to 6 h, more preferably 1 min to 3 h, still more preferably 1 min to 2 h, before start of said radiation burst.

8. The SOD1 inhibitor for use of any one of claims 1 to 7, wherein said use comprises administration of said SOD1 inhibitor in a time frame of from 1 min to 2 h before start of said radiation burst

9. The SOD1 inhibitor for use of any one of claims 1 to 8, wherein said radiation burst causes a radiation dose of from 1 Gy to 100 Gy, preferably of from 2 Gy to 25 Gy in said subject.

10. The SOD1 inhibitor for use of any one of claims 1 to 9, wherein said radiation burst causes a radiation dose of from 2 Gy to 25 Gy in said subject.

11. The SOD1 inhibitor for use of any one of claims 1 to 10, wherein said radiation burst injury is an acute radiation injury selected from the list consisting of burn, ulceration, delayed fracture healing, reduced blood cell counts, reduced white blood cells, reduced platelets, enteritis, nausea, vomiting, swelling, seizure, dysphagia, ulcerations, inflammation pneumonitis, blood vessel swelling, hepatitis, nephritis, hemorhage, and reduced reproductive capacity.

12. The SOD1 inhibitor for use of any one of claims 1 to 11, wherein said radiation burst injury is a chronic radiation injury selected from the list consisting of fibrosis, osteoporosis, osteomalacia, bone mineral loss, bone marrow failure, strictures, fistulae, sinus formation, cognitive deficits, blood vessel damage, heart attack, liver failure, renal failure, and reduced reproductive capacity.

13. The SOD1 inhibitor for use of any one of claims 1 to 12, wherein protecting from radiation burst injury is reducing a severity of at least one symptom of at least one radiation burst injury by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%.

14. The SOD1 inhibitor for use of any one of claims 1 to 13, wherein said radiation burst is radiotherapy and wherein said protecting is protecting non-cancer cells from radiotherapy of cancer.

15. The SOD1 inhibitor for use of claim 14, wherein said radiotherapy is radiotherapy with a dose rate of at most 10 Gy/s, preferably at most 0.5 Gy/s, even more preferably at most 0.05 Gy/s.

16. The SOD1 inhibitor for use of any one of claims 1 to 15, wherein protecting non-cancer cells comprises reduction of non-cancer cell death after radiotherapy by at least 20%, preferably at least 30%, more preferably at least 40%, still more preferably at least 50%.

17. The SOD1 inhibitor for use of any one of claims 1 to 16, wherein said cancer is a cancer of the brain, skin, lung, liver, pancreas, intestines, esophagus, heart, kidney, prostate, breast, head&neck, bone, bone marrow, reproductive organs, and/or spinal cord pedicles.

18. A kit comprising an SOD1 inhibitor and a radiosensitizer of cancer cells, preferably wherein said radiosensitizer is selected from the list consisting of temozolomide, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium, and efaproxiral.

19. The kit of claim 18, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions, a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol or a derivative or prodrug thereof, and/or cyanide ions.

20. The kit of claim 18 or 19, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions.

21. The kit of any one of claims 18 to 20, wherein said SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0).

22. In vitro use of an SOD1 inhibitor for protecting non-cancer cells from ionizing radiation.

23. The in vitro use of claim 22, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions, a 4,5-dihalogeno-2-aryl-pyridazin-3(2H)-one, 2-methoxyestradiol or a derivative or prodrug thereof, and/or cyanide ions.

24. The in vitro use of claim 22 or 23, wherein said SOD1 inhibitor comprises tetrathiomolybdate ions.

25. The in vitro use of any one of claims 22 to 24, wherein said SOD1 inhibitor is bis-choline tetrathiomolybdate (ATN-224, CAS No. 649749-10-0).

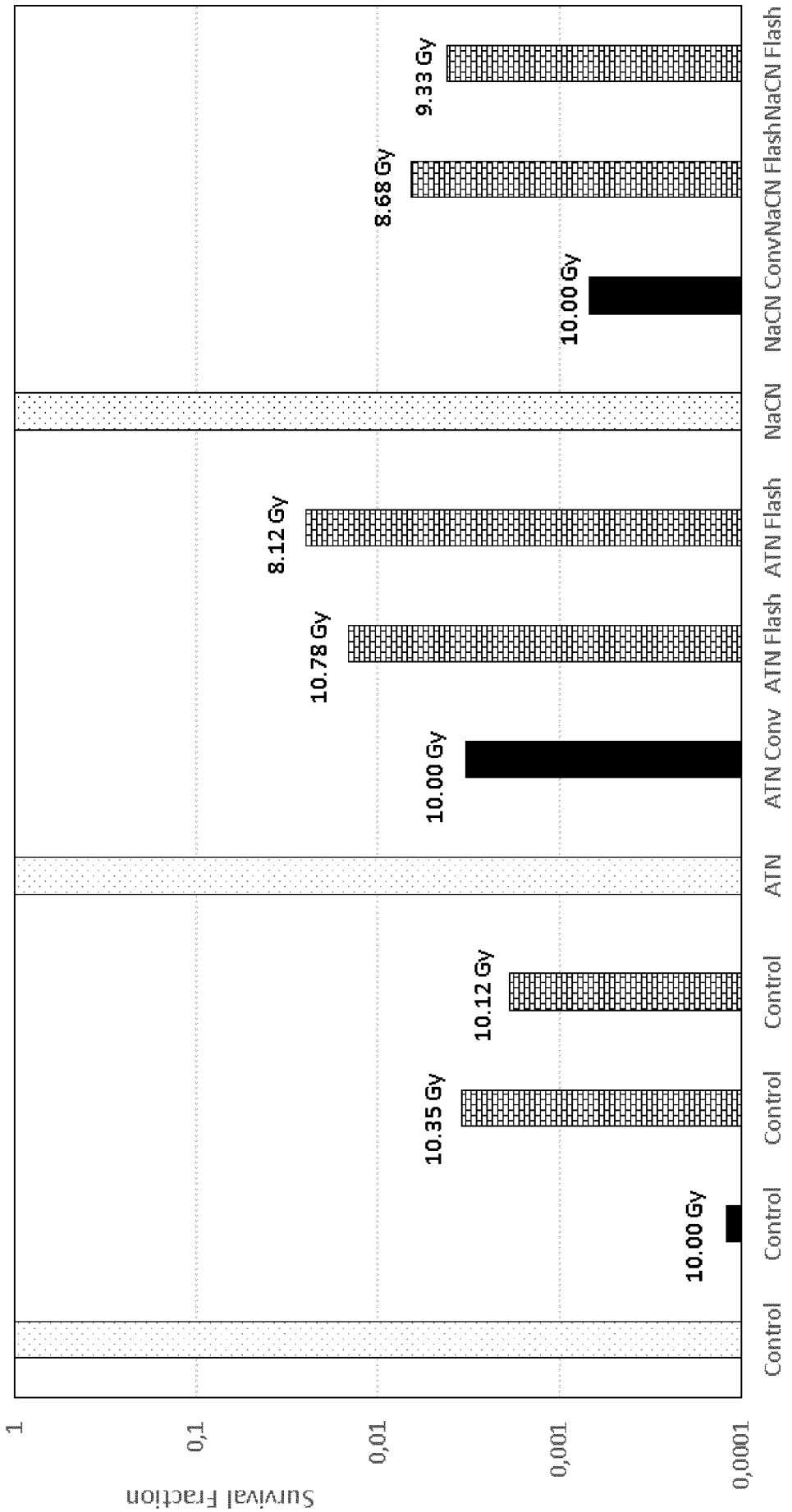
Survival Fraction
1
0,1
0,01
0,001
0,0001
Control
Control Conv
Control Flash
Control Flash
ATN
ATN Conv
ATN Flash
ATN Flash
NaCN
NaCN Conv
NaCN Flash
NaCN Flash
10.00 Gy
10.35 Gy
10.12 Gy
10.00 Gy
10.78 Gy
8.12 Gy
10.00 Gy
8.68 Gy
9.33 Gy

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/058942

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/14 A61K33/24 A61P39/00 A61P39/04
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)
A61K A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 10 722 526 B2 (KOREA INST RADIOLOGICAL & MEDICAL SCIENCES [KR]) 28 July 2020 (2020-07-28)	1,2, 6-17,22, 23
Y	column 3, line 47 - column 4, line 6 column 6, lines 10-24 column 9, lines 52-58 examples	3

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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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"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
13 June 2024	21/06/2024

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	Gradassi, Giulia

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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.
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Y	page 2236, left-hand column, paragraph 2 - right-hand column, paragraph 3 page 2237, left-hand column, paragraph 4 - page 2239, right-hand column, paragraph 2	3
X	EVANS ET AL: "Tumor radiosensitization with concomitant vone marrow radioprotection: A study in mice using diethyldithiocarbamate (DDC) under oxygenated and hypoxic conditions", INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS, PERGAMON PRESS, USA, vol. 11, no. 6, 1 June 1985 (1985-06-01), pages 1163-1169, XP026842413, ISSN: 0360-3016 [retrieved on 1985-06-01]	1,6-8, 11-14, 16,17
Y	abstract; page 1164 left-hand column paragraphs 2-5; page 1165 left-hand column paragraph 2 to 1166 right-hand column paragraph 1	3
X	TRAPP V ET AL: "Redox-related antimelanoma activity of ATN-224", MELANOMA RESEARCH 2009 LIPPINCOTT WILLIAMS AND WILKINS GBR, vol. 19, no. 6, December 2009 (2009-12), pages 350-360, XP009547631, ISSN: 0960-8931 abstract page 352, left-hand column, paragraph 3-5	18-21

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/058942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASHIBA H ET AL: "Enhancement of radiosensitizing effect of the nitroimidazole derivative RK28 on the proliferation of MethA tumor cells in combined use with diethyldithiocarbamate", LIFE SCIENCE, PERGAMON PRESS, OXFORD, GB, vol. 49, no. 19, 1 January 1991 (1991-01-01), pages 1419-1425, XP025566691, ISSN: 0024-3205, DOI: 10.1016/0024-3205(91)90394-Q [retrieved on 1991-01-01] page 1420, paragraph 2-7	18
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Y	WO 97/26791 A1 (UNIV CALIFORNIA [US]; BURNHAM INST [US] ET AL.) 31 July 1997 (1997-07-31) claim 2	3

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2024/058942

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/058942

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