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(54) Title: ANTICANCER COMBINATION THERAPY

(57) Abstract: The present invention relates to a bromodomain and extra-terminal protein (BET) inhibitor in combination with a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor for use in the treatment of cancer.

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ANTICANCER COMBINATION THERAPY

FIELD OF THE INVENTION

The present invention relates to a combination therapy in the treatment of cancer using a bromodomain and extra-terminal (BET) protein inhibitor and a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

BACKGROUND

Bromodomains are found in a variety of mammalian DNA-binding proteins. The bromodomain, which is the conserved structural module in chromatin-associated proteins and histone acetyltransferases, is known to recognize acetyl-lysine residues on proteins. The two bromodomains of BRD4, a member of the bromodomain and extra terminal domain protein (BET) family which consists of the four members, BRD2, BRD3, BRD4 and BRDT, bind selectively to acetylated lysine residues on histone H3 and H4. BRD4 mediates the release of kinase-inactive P-TEFb from a ribonucleoprotein complex, and finally enables transcription elongation. Bromodomain proteins thus regulate gene expression.

The bromodomain and extra-terminal subfamily of bromodomain-containing proteins have been implicated in disease processes including cancer and are investigated as a target group in oncology. BET inhibitors are a class of drugs presently being investigated for therapeutic applications in anti-cancer therapies. These molecules reversibly bind the bromodomains of BET proteins BRD2, BRD3, BRD4, and BRDT, and prevent protein-protein interaction between BET proteins and acetylated histones and transcription factors. BET inhibitors showed promising antitumor efficacy in a number of preclinical cancer models and led to clinical studies focusing on the treatment of solid tumors and hematological malignancies.

Cancers have been shown responsive to BET inhibitor therapy *in vitro* and *in vivo*, and the efficacy of BET inhibitors has been shown to be improved in combination strategies with further inhibitors such as histone acetyltransferase p300 (p300)/CREB binding protein (CBP) inhibitors. CBP (CREB (cyclic adenosine monophosphate (cAMP) responsive element binding protein) binding protein) and p300 (adenovirus E1A-associated 300kD-protein), which also is denoted EP300, are two closely related and evolutionary conserved histone acetyltransferases (HATs). A synergistic effect of an acetyl-lysine competitive protein-protein interaction inhibitor, I-CBP112, that targets the p300/CBP bromodomains and BET bromodomain inhibitor JQ1 in leukemia cell lines already was reported (Picaud et al., Cancer Res., 2015;75(23):5106-5119). A novel small-molecule inhibitor of the p300/CBP conserved bromodomain, denoted CCS1477, was recently shown to provide *in vivo* evidence for anti-tumor activity in prostate cancer cell lines (Welti et al., Cancer Discov. 2021, CD-20-0751. doi: 10.1158/2159-8290.CD-20-0751).

WO 2020/023768 A1 describes a method of treating cancer by administering AKT inhibitors (also known as Protein Kinase B (PKB) inhibitors), cyclin-dependent kinase (CDK) inhibitors, and/or one or more p300/CBP inhibitors in combination with one or more BET inhibitors for the treatment of cancer resistant to a treatment with BET inhibitors alone. WO 2020/093162 A1 describes the treatment of BET inhibitor-resistant cancers using BET and p300/CBP inhibition co-therapy. Co-treatment is described using BET inhibitors and p300/CBP inhibitors as well as compounds having dual BET and p300/CBP inhibition activity. WO 2016/044694 A1 describes the use of p300/CBP inhibitors in combination with BET inhibitors for the treatment of cancer. Synergistic effects of p300/CBP inhibitor G272 and BET inhibitor JQ1 are described for leukemia and breast cancer cell lines. Further, mono-therapy using p300/CBP inhibitors has been suggested. For example, WO 2015/054642 describes a use of p300/CBP bromodomain inhibitors for the treatment of cancer. WO 2014/076237 describes BET inhibitors belonging to the class of triazolopyrazine derivatives.

Nuclear protein of the testis (NUT) carcinoma, formerly denoted NUT midline carcinoma (NMC), is a rare and highly aggressive form of undifferentiated squamous cell carcinoma. NUT carcinoma is defined by chromosomal rearrangement of the *NUT* gene, most commonly to the bromodomain and extraterminal domain (BET) gene *BRD4*, forming a *BRD4-NUT* fusion oncogene. NUT carcinoma is described as one of the most therapy-resistant tumors. In the treatment of NUT carcinoma, a combined inhibition of p300/CBP and BET using the p300/CBP histone acetyltransferase (HAT) inhibitor A-485 in combination with BET inhibitor JQ1 showed synergistic effects (Zhang et al., Oncogene, 2020, 39, pages 4770–4779). A combination of p300/CBP and BET bromodomain inhibitors, GNE-781 and OTX015, respectively, was shown to synergistically inhibit growth of NMC cells *in vitro*, while a dual compound combining p300/CBP and BET bromodomain-selective inhibition showed growth inhibition of NMC cells *in vitro* and in NMC xenograft models *in vivo* (Morrison-Smith et al., 2020, Mol Cancer Ther., 19(7):1406-1414).

Despite the above described treatments of cancer, and although various combination therapies have been suggested, there is still need for new and efficient therapeutic concepts and specific combinations for the treatment of cancer diseases, in particular solid tumors, which show advantages over standard therapies. Specifically there is need for additional treatment options for highly aggressive forms such as NUT carcinoma.

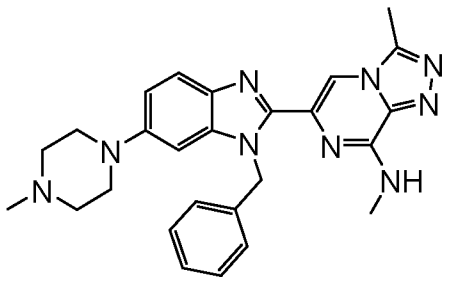
It is thus an object of the present invention to provide a combination treatment that shows advances over treatments known in the prior art.

SUMMARY

In *in-vitro* experiments in NUT cancer cell lines as well as in *in-vivo* NUT xenografts it has been found that inhibition of cell proliferation and reduction of relative tumor volume, respectively, resulting from the combined use of the BET inhibitor BI-BET and a p300/CBP

bromodomain inhibitor is more effective than the effect resulting from the single use of each compound.

According to a first aspect is provided a bromodomain and extra-terminal protein (BET) inhibitor for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein the BET inhibitor is administered in combination with a p300 (histone acetyltransferase p300)/CBP (CREB binding protein) inhibitor. The BET inhibitor is BI-BET according to formula (1) below, or a pharmaceutically acceptable salt thereof



(1)

and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

In embodiments, the p300/CBP bromodomain inhibitor is selected from the group consisting of CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and GNE-781, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

In a preferred embodiment, the p300/CBP bromodomain inhibitor is CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

In embodiments, the p300/CBP CH1 domain inhibitor is INTH-454, or a pharmaceutically acceptable salt thereof or a hydrate thereof.
In embodiments, the oncological and/or hyperproliferative disease is a cancer selected from the group consisting of prostate cancer (including but not limited to castration-resistant prostate cancer (CRPC)), bladder cancer, breast cancer (including but not limited to ductal

breast cancer), cancers of the gastrointestinal tract (including but not limited to colon cancer, colorectal cancer, gastric cancer, pancreatic cancer (including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma), oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer), head and neck cancer (including but not limited to nasopharyngeal cancer), brain cancer (including but not limited to glioblastoma, medulloblastoma and astrocytoma), neuroblastoma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, liver cancer (including but not limited to hepatocellular carcinoma), neuroendocrine cancer, melanoma (including but not limited to uveal melanoma), lung cancer (including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), NUT carcinoma, lymphoma (including but not limited to diffuse large B-cell lymphoma (DLBCL), leukemias (including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL)), (primary) myelofibrosis (PMF), multiple myeloma (MM), leiomyosarcoma, rhabdomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, salivary gland adenocarcinoma, osteosarcoma, adenoid cystic carcinoma, ependymoma, acinic cell carcinoma and merkel cell carcinoma.

In preferred embodiments, the oncological and/or hyperproliferative disease is NUT carcinoma.

Another aspect relates to a pharmaceutical combination comprising as active ingredients a BET inhibitor and a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined herein or a pharmaceutically acceptable salt thereof and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

In embodiments, the pharmaceutical combination is for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer.

Another aspect relates to a kit comprising in one or more containers:
(i) a first pharmaceutical composition or dosage form comprising a BET inhibitor, wherein the BET inhibitor is BI-BET as defined herein, or a pharmaceutically acceptable salt thereof, and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles;
(ii) a second pharmaceutical composition or dosage form comprising a p300/CBP inhibitor, wherein the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles; and
(iii) optionally a package insert comprising instructions.

In embodiments, the kit is for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer.

Another aspect relates to a method of treating an oncological and/or hyperproliferative disease, in particular cancer, the method comprising administering to a patient a therapeutically effective amount of a BET inhibitor in combination with a therapeutically effective amount of a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined herein, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

Another aspect relates to a use of a BET inhibitor for the manufacture of a medicament for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein the BET inhibitor is to be used in combination with a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined herein, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

In an embodiment of all aspects disclosed herein, the p300/CBP bromodomain inhibitor is selected from the group consisting of CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and GNE-781, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

In an embodiment of all aspects disclosed herein, the the p300/CBP CH1 domain inhibitor is INTH-454, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

In another embodiment of all aspects disclosed herein, the oncological and/or hyperproliferative disease is a cancer selected from the group consisting of prostate cancer (including but not limited to castration-resistant prostate cancer (CRPC)), bladder cancer, breast cancer (including but not limited to ductal breast cancer), cancers of the gastrointestinal tract (including but not limited to colon cancer, colorectal cancer, gastric cancer, pancreatic cancer (including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma), oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer), head and neck cancer (including but not limited to nasopharyngeal cancer), brain cancer (including but not limited to glioblastoma, medulloblastoma and astrocytoma), neuroblastoma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, liver cancer (including but not limited to hepatocellular carcinoma), neuroendocrine cancer, melanoma (including but not limited to uveal melanoma), lung cancer (including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), NUT carcinoma, lymphoma (including but not limited to diffuse large B-cell lymphoma (DLBCL), leukemias (including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL)), (primary) myelofibrosis (PMF), multiple myeloma (MM), leiomyosarcoma, rhabdomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, salivary gland adenocarcinoma, osteosarcoma, adenoid cystic carcinoma, ependymoma, acinic cell carcinoma and merkel cell carcinoma.

In a preferred embodiment of all aspects disclosed herein, the cancer is NUT carcinoma.

In a preferred embodiment of all aspects disclosed herein, the p300/CBP bromodomain inhibitor is CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor CCS1477 in Ty-82 NUT carcinoma cell line.

Figure 2 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor GNE-781 in Ty-82 NUT carcinoma cell line.

Figure 3 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor CCS1477 in Ty-82 NUT carcinoma cell line.

Figure 4 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor CCS1477 in 10-15 NUT carcinoma cell line.

Figure 5 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor CCS1477 in 14169 NUT carcinoma cell line.

Figure 6 Synergistic effect of BI-BET and p300/CBP bromodomain inhibitor CCS1477 in 10326 NUT carcinoma cell line.

Figure 7 Tumor growth kinetics of human NUT carcinoma cell line Ty-82 (BRD4-NUT) grown as subcutaneous xenografts in NOG mice. Ty-82 tumor-bearing mice were treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Median tumor volumes are plotted over time. Day 1 was the first day, day 17 the last day of the experiment.

Figure 8 Change of body weight over time of Ty-82 tumor-bearing mice treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Median body weight changes are plotted over time.

Figure 9 Absolute tumor volume at the end of treatment (day 17) of Ty-82 tumor-bearing mice treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Each symbol represents one individual tumor. The horizontal lines represent the median tumor volumes.

Figure 10 Tumor growth kinetics of human NUT carcinoma cell line 10326 (BRD3-NUT) grown as subcutaneous xenografts in NOG mice. Ty-82 tumor-bearing mice were treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Median tumor volumes are plotted over time. Day 1 was the first day, day 21 the last day of the experiment.

Figure 11 Change of body weight over time of 10326 tumor-bearing mice treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Median body weight changes are plotted over time.

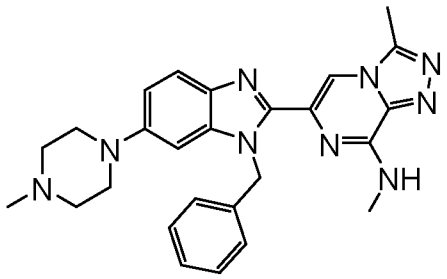
Figure 12 Absolute tumor volume at the end of treatment (day 21) of 10326 tumor-bearing mice treated with vehicle (control), 2 mg/kg BI-BET, 5 or 10 mg/kg CCS1477 or their combinations. Each symbol represents one individual tumor. The horizontal lines represent the median tumor volumes.

DETAILED DESCRIPTION

BET inhibitor and p300/CBP inhibitors

As used herein, the term "BET" refers to all members of the BET family, including BRD2, BRD3, BRD4, and BRDT. As used herein, the term "BET inhibitor" refers to a compound that inhibits the binding of bromodomains to acetylated lysines on histone H3 and H4. BET inhibitors thus act as important regulators of gene transcription. BET inhibitors belonging to different compound classes are known.

The BET inhibitor denoted herein "BI-BET" is a small-molecule BET bromodomain inhibitor according to formula (1) below, or a pharmaceutically acceptable salt thereof



(1).

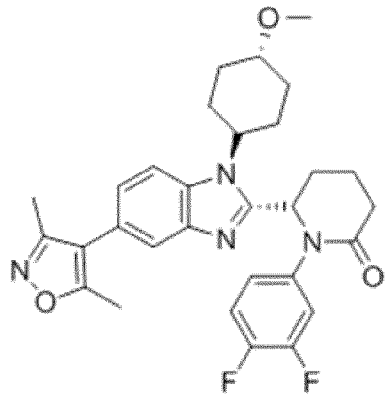
The term "BI-BET" as used herein also encompasses the tautomers and pharmaceutically acceptable salts and all other solid forms of the compound. The compound denoted BI-BET herein is disclosed in WO 2014/076237 as example compound III-13. WO 2014/076237 describes triazolopyrazine derivatives such as BI-BET as BET inhibitors and provides the synthesis procedure. Properties of the compound BI-BET and evidence for anti-tumor activity in acute myeloid leukemia (AML) in combination therapy further are disclosed in WO 2019/145410 A1.

As used herein, the term "p300/CBP inhibitor" refers to a compound that binds to any domain of p300 and/or CBP and inhibits and/or reduces a biological activity of p300 and/or CBP. A p300/CBP inhibitor, in general, may bind to and inhibit a p300/CBP bromodomain and/or p300/CBP HAT domain and/or a p300/CBP CH1 domain. A p300/CBP inhibitor usable together with BI-BET for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, is an inhibitor of the p300/CBP bromodomains and/or the p300/CBP CH1 domain.

The term "bromodomain" as used herein refers an approximately 110 amino acid protein domain that recognizes acetylated lysine residues, such as those on the *N*-terminal tails of histones. Bromodomains thus are responsible in transducing the signal carried by acetylated lysine residues and translating it into various normal or abnormal phenotypes.

As used herein, the term "p300/CBP bromodomain inhibitor" refers to a compound that binds to the p300 bromodomain and/or CBP bromodomain and inhibits and/or reduces a biological activity of p300 and/or CBP. In embodiments, the p300/CBP bromodomain inhibitor does not bind to the HAT domain of CBP and/or p300.

In embodiments, the p300/CBP bromodomain inhibitor is CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof. Embodiments, where the p300/CBP bromodomain inhibitor is CCS1477 are preferred embodiments in respect of the nature of the p300/CBP bromodomain inhibitor. The compound denoted CCS1477 is a small-molecule inhibitor of the p300/CBP bromodomain according to formula (2) or a pharmaceutically acceptable salt thereof or a hydrate thereof

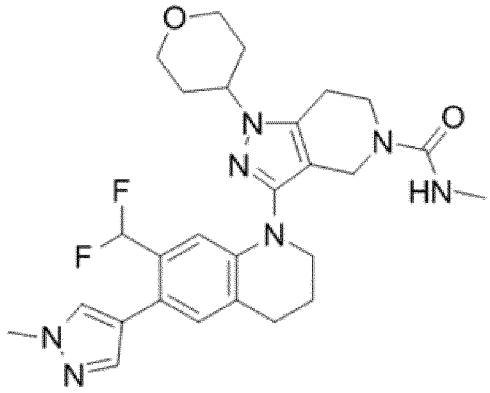


(2).

The term "CCS1477" as used herein also encompasses the tautomers of the compound, as well as the solvates, including hydrates and solvates of pharmaceutically acceptable salts thereof. International Patent Application WO 2018/073586 A1 describes a processes for synthesizing CCS1477. Properties of the compound CCS1477 and *in vivo* evidence for anti-tumor activity in prostate cancer cell lines further are disclosed in Welti et al., Cancer Discov. 2021, CD-20-0751. CCS1477 is an orally bioavailable inhibitor.

In embodiments, the p300/CBP bromodomain inhibitor is GNE-781, or a pharmaceutically acceptable salt thereof or a hydrate thereof. The compound denoted GNE-781 is a small-

molecule inhibitor of the p300/CBP bromodomain according to formula (3) or a pharmaceutically acceptable salt thereof or a hydrate thereof



(3).

The term "GNE-781" as used herein also encompasses the tautomers of the compound, as well as the solvates, including hydrates and solvates of pharmaceutically acceptable salts thereof. GNE-781 is a potent and selective bromodomain inhibitor of p300/CBP. GNE-781 is an orally bioavailable inhibitor. The compound is commercially available.

The term "CH1 domain" as used herein refers to the cysteine/histidine-rich region 1 (CH1 domain) of the protein interaction domains of the p300/CBP protein.

As used herein, the term "p300/CBP CH1 domain inhibitor" refers to to a compound that binds to the CH1 domain of p300 and/or CBP and inhibits and/or reduces a biological activity of p300 and/or CBP. An example for a CH1 domain inhibitor is the compound denoted "INTH-454" as described in Cattori et al., AACR; Mol Cancer Ther 2019;18(12 Suppl):Abstract no. C040. doi:10.1158/1535-7163.TARG-19-C040.

The term "pharmaceutically acceptable salts" as used herein includes both acid and base addition salts. Pharmaceutically acceptable acid addition salts refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids or organic acids. Pharmaceutically acceptable base addition salts include salts derived from inorganic bases or

organic nontoxic bases. The term "solvate" as used herein refers to an association or complex of one or more solvent molecules and a compound of the present invention. Examples of solvents include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term "hydrate" refers to a complex where the solvent molecule is water.

To be used for treatment, the BET inhibitor and the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor, separately or jointly, may be included into pharmaceutical compositions appropriate to facilitate administration. The compounds thus may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, excipients and/or vehicles appropriate for each route of administration. Typical pharmaceutical compositions for administering the BET inhibitor and the p300/CBP bromodomain inhibitors and/or the p300/CBP CH1 domain inhibitors, separately or jointly, include for example tablets, capsules, suppositories, solutions, e.g. solutions for injection and infusion, elixirs, emulsions or dispersible powders. Dosage forms and formulations of active ingredients are known in the art.

The BET inhibitor BI-BET may be administered by oral routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, excipients and vehicles appropriate for each route of administration. Likewise, the p300/CBP bromodomain inhibitors and/or the p300/CBP CH1 domain inhibitors, such as the p300/CBP bromodomain inhibitors CCS1477 and GNE-781 or the p300/CBP CH1 domain inhibitor INTH-454, may be administered by oral routes of administration and may be formulated, alone or in combination, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, excipients and vehicles appropriate for each route of administration. Although oral administration may be preferred in view of compliance, routes of administration for the BET inhibitor BI-BET and/or p300/CBP bromodomain inhibitors such as CCS1477 and GNE-781

and/or the p300/CBP CH1 domain inhibitors such as INTH-454 as described herein, are not limited to oral administration, but the compounds may be administered parenterally, e.g. intramuscular, intraperitoneal, intravenous, transdermal or subcutaneous injection or by implant, or enterical, nasal, vaginal, rectal, or topical administration.

Combination therapy

It is a purpose of the present invention to provide novel therapies for treating various oncological and/or diseases, in particular solid cancers, and specifically NUT carcinoma.

It was surprisingly discovered that the use of BET inhibitor BI-BET in combination with a p300/CBP bromodomain inhibitor such as CCS1477 or GNE-781, has the potential to improve clinical outcome compared to the use of a BET inhibitor or a p300/CBP bromodomain inhibitor such as CCS1477 or GNE-781 alone.

Specifically, combination treatment with BET inhibitor BI-BET and p300/CBP bromodomain inhibitors CCS1477 or GNE-781 reduced cell proliferation more than each single treatment in several NUT carcinoma cell lines *in vitro*. Further, anti-tumor activity of BI-BET in combination with p300/CBP bromodomain inhibitor CCS1477 was demonstrated *in vivo*.

Although various combination therapies are known in the art, satisfying therapeutic concepts for the treatment of cancer diseases, in particular highly aggressive NUT carcinoma are still lacking.

The surprising results shown in the examples described herein indicate that the combination of BET inhibitor BI-BET with p300/CBP bromodomain inhibitors CCS1477 or GNE-781 resulted in a synergistic, i.e. more than additive, interaction of the two compounds. Particularly *in vivo* results in NUT carcinoma xenografts provide for superior results in that

significant anti-tumor activity compared to monotherapies with BI-BET or CCS1477 in BRD4-NUT carcinoma xenografts and in BRD3-NUT carcinoma xenografts was obtainable.

Thus, the invention relates to BET inhibitor BI-BET in combination with p300/CBP bromodomain inhibitors and/or p300/CBP CH1 domain inhibitors, such as the p300/CBP bromodomain inhibitors CCS1477 or GNE-781 or the p300/CBP CH1 domain inhibitor INTH-454, as described herein, for use in anti-cancer therapy. Such a combined treatment may include that the BET inhibitor and the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor can be administered formulated either dependently, such as formulated together into one composition, or independently, such as formulated as separate compositions. In other words, the BET inhibitor and the p300/CBP bromodomain inhibitor and/or p300/CBP CH1 domain inhibitor may be administered either as part of the same pharmaceutical composition or dosage form or, preferably, in separate pharmaceutical compositions or dosage forms.

One aspect relates to a pharmaceutical combination comprising as active ingredients BET inhibitor BI-BET as described herein and a p300/CBP bromodomain inhibitor and/or p300/CBP CH1 domain inhibitor, such as the p300/CBP bromodomain inhibitors CCS1477 and GNE-781 or the p300/CBP CH1 domain inhibitor INTH-454 as described herein, and optionally pharmaceutically acceptable carrier, excipients, and/or vehicles.

The term "pharmaceutically acceptable carrier, excipients and/or vehicles" refers to a non-toxic carrier, excipient or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, excipients or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate , partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such

as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, polyvinyl pyrrolidone, cellulose-based substances, sodium carboxymethylcellulose, or polyethylene glycol.

As used herein, the term "active ingredient" refers to a component that is intended to furnish pharmacological activity or other direct effect.

The BET inhibitor and p300/CBP bromodomain inhibitor and/or p300/CBP CH1 domain inhibitor may be administered at therapeutically effective amounts or be included in a pharmaceutical composition, dosage form or pharmaceutical combination in a therapeutically effective amount. A therapeutically effective amount refers to an amount effective at dosages and for periods of time necessary to achieve a desired therapeutic result and is the minimum amount necessary to prevent, ameliorate, or treat a disease or disorder, or which any toxic or detrimental effects of the compound is outweighed by the therapeutically beneficial effects.

As used herein, the term "pharmaceutical combination" may refer to either a fixed combination in one pharmaceutical composition or dosage unit form, or, preferably, a kit of parts for the combined administration where the BET inhibitor may be administered independently of the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor at the same time or separately within time intervals. The compounds of the pharmaceutical combination can be together or separate. This means that the pharmaceutical combination of BI-BET and a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor refers to use, application or formulations of the separate partners with or without instructions for combined use or to combination products. The combination partners may thus be administered entirely separately or be entirely separate pharmaceutical dosage forms. The combination partners may be pharmaceutical compositions that are also sold independently of each other and where just instructions for their combined use are provided in the package equipment, e.g. leaflet or the like, or in other information e.g. provided to

physicians and medical staff (e.g. oral communications, communications in writing or the like), for simultaneous or sequential use for being jointly active. The terms "co-administration" or "combined administration" or "combined use" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the active ingredients are not necessarily administered by the same route of administration and/or at the same time.

Another aspect relates to a kit comprising in one or more containers:
(i) a first pharmaceutical composition or dosage form comprising a BET inhibitor, wherein the BET inhibitor is BI-BET as described herein, or a pharmaceutically acceptable salt thereof, and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles;
(ii) a second pharmaceutical composition or dosage form comprising a p300/CBP inhibitor, wherein the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor, e. g. p300/CBP bromodomain inhibitors CCS1477 or GNE-781 or p300/CBP CH1 domain inhibitor INTH-454 as described herein, and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles; and
(iii) optionally a package insert comprising instructions.

The terms "first" and "second" with respect to pharmaceutical compositions, as used herein, is solely intended to indicate that these compositions are two different compositions. Thus, these terms shall not be understood to refer to the order or sequence of administration.

Preferably, the package insert comprises printed instructions for simultaneous, concurrent, sequential, successive, alternate or separate use in the treatment of a hyperproliferative disease, in particular cancer, as described herein, in a patient in need thereof.

The BET inhibitor and the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor, the pharmaceutical compositions and combination, as well as all formulations of BET inhibitor and the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor as disclosed herein, can be administered simultaneously, concurrently, sequentially, successively, alternately or separately.

The term "simultaneous" refers to the administration of both compounds/compositions at substantially the same time. The term "concurrent" refers to administration of the active ingredients within the same general time period, for example on the same day(s) but not necessarily at the same time. The term "sequential" administration includes administration of one active ingredient during a first time period, for example over the course of a few hours, days or a week, using one or more doses, followed by administration of the other active ingredient during a second time period, for example over the course of a few hours, days or a week, using one or more doses. An overlapping schedule may also be employed, which includes administration of the active ingredients on different days over the treatment period, not necessarily according to a regular sequence. The term "successive" administration, alternatively, refers to an administration where the second administration step is carried out immediately once the administration of the first compounds has been finished. Alternate administration includes administration of one active ingredient during a time period, for example over the course of a few hours, days or a week, followed by administration of the other active ingredient during a subsequent period of time, for example over the course of a few hours, days or a week, and then repeating the pattern for one or more cycles, wherein the overall number of repeats depends on the chosen dosage regimen.

Variations of these general administration forms may also be employed. In some embodiments, BET inhibitor and the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor may be administered simultaneously or concurrently. In embodiments,

the BET inhibitor and/or the p300/CBP bromodomain inhibitor and/or the p300/CBP CH1 domain inhibitor may be administered sequentially.

Oncological and/or hyperproliferative diseases

The combinations, compositions, kits, uses, methods and compounds for use according to the present invention are usable for the treatment of oncological and/or hyperproliferative disorders, in particular cancer.

According to an aspect is provided a BET inhibitor for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein BI-BET as described herein is administered in combination with a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

Another aspect refers to the aforementioned pharmaceutical combination or kit for use in a method of treating an oncological or hyperproliferative disease, preferably cancer, as described herein.

Another aspect relates to a method of treating an oncological and/or hyperproliferative disease, in particular cancer, the method comprising administering to a patient a therapeutically effective amount of a BET inhibitor in combination with a therapeutically effective amount of a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined herein, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

Another aspect relates to a use of a BET inhibitor for the manufacture of a medicament for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein the BET inhibitor is to be used in combination with a p300/CBP inhibitor, where the

BET inhibitor is BI-BET as defined herein, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

As used herein, the term "hyperproliferative disease" refers to conditions wherein cell growth is increased over normal levels. Hyperproliferative diseases include malignant diseases, such as cancers, and non-malignant diseases. In preferred embodiments, the hyperproliferative disorder is cancer. As used herein, the term "oncological disease" refers to a disease or medical condition associated with cancer or cancer indication. Cancers are classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body, where the cancer first developed.

In embodiments, the oncological and/or hyperproliferative disease is a cancer selected from the group consisting of prostate cancer (including but not limited to castration-resistant prostate cancer (CRPC)), bladder cancer, breast cancer (including but not limited to ductal breast cancer), cancers of the gastrointestinal tract (including but not limited to colon cancer, colorectal cancer, gastric cancer, pancreatic cancer (including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma), oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer), head and neck cancer (including but not limited to nasopharyngeal cancer), brain cancer (including but not limited to glioblastoma, medulloblastoma and astrocytoma), neuroblastoma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, liver cancer (including but not limited to hepatocellular carcinoma), neuroendocrine cancer, melanoma (including but not limited to uveal melanoma), lung cancer (including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), NUT carcinoma, lymphoma (including but not limited to diffuse large B-cell lymphoma (DLBCL), leukemias (including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL)), (primary) myelofibrosis (PMF),

multiple myeloma (MM), leiomyosarcoma, rhabdomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, salivary gland adenocarcinoma, osteosarcoma, adenoid cystic carcinoma, ependymoma, acinic cell carcinoma and merkel cell carcinoma.

In some embodiments, the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, pancreatic cancer, including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma, oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer, lung cancer, including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) and NUT carcinoma.

In further embodiments, the cancer harbours a NUT fusion, including but not limited to BRD4-NUT, BRD3-NUT and NSD3-NUT.

In preferred embodiments, the cancer is NUT carcinoma. NUT carcinoma (NC), formerly also known as NUT midline carcinoma, is a rare, genetically defined, aggressive human cancer defined by rearrangements of the gene NUT. In the majority of NCs most of the coding sequence of NUT is fused to BRD4 or BRD3, creating chimeric genes that encode BRD-NUT fusion proteins. As used herein, the term "NUT carcinoma" is to be understood to encompass all forms of NUT carcinoma. NUT carcinoma presents as a poorly differentiated carcinoma originating from midline locations such as the head, neck or mediastinum. Frequently, NUT carcinoma is found in the head and neck area, lungs or thorax.

In some embodiments, the NUT carcinoma harbours a NUT fusion, including but not limited to BRD4-NUT, BRD3-NUT and NSD3-NUT. In another embodiment, the cancer is selected from the group consisting of

- a cancer harbouring a BET fusion;
- a cancer showing MYC overexpression;

- a cancer with amplification and/or high copy number gain of MYC;
- a cancer with amplification and/or high copy number gain of MYCN;
- a cancer with a translocation involving MYC;
- a cancer with a translocation involving MYCN;
- a cancer with a translocation involving BRD3; and
- a cancer with a translocation involving BRD4.

Unless otherwise defined, the technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The examples which follow serve to illustrate the invention in more detail but do not constitute a limitation thereof.

Example 1

Effects of BET inhibitor BI-BET in combination with p300/CBP bromodomain inhibitors CCS1477 and GNE-781 in NUT carcinoma cell lines *in vitro*

The efficacy of BI-BET, of p300/CBP bromodomain inhibitors CCS1477 and GNE-781 and their respective combinations was tested in several NUT carcinoma cell lines harbouring fusions of BRD4-NUT or BRD3-NUT.

Cells:

Ty-82 is a human NUT carcinoma cell line (JCRB (Japanese Collection of Research Bioresources) Cell Bank Japan No. 1330) with a fusion of BRD4-NUT.

10-15 is a is a NUT carcinoma cell line (in-licensed from French, Brigham & Women`s Hospital) with a fusion of BRD4-NUT.

14169 is a NUT carcinoma cell line (in-licensed from French, Brigham & Women`s Hospital) with a fusion of BRD4-NUT.
10326 is a NUT carcinoma cell line (in-licensed from French, Brigham & Women`s Hospital) with a fusion of BRD3-NUT.

10-15, 10326 and 14169 cell lines were grown in T-75 flasks using DMEM medium (Sigma #D6429) supplemented with 10 % fetal calf serum and Glutamax™ (Gibco™). Ty-82 was grown in RPMI (Gibco #61870-010) supplemented with 10 % fetal calf serum. Cultures were incubated at 37 °C and 5 % CO_2 in a humidified atmosphere.

Assay:
For the IncuCyte live cell imaging assays, cells were plated in Poly-D-Lysine 96-well assay plates (Corning® BioCoat™ #354640) and were incubated with the respective compounds (BI-BET, CCS1477 or GNE-781), either alone or in combination. Results were analysed with the IncuCyte® S3 2019A software.
The analysis was done by the Essen BioScience IncuCyte® S3 live cell imaging system. It enables observation and quantification of cell behavior over time by automatically gathering and analyzing images around the clock. This live-cell, non-perturbating imaging approach yields kinetic data, all generated within the controlled environment of a standard cell incubator.

Results:
The figures 1 to 6 show analysis of cell growth in NUT carcinoma cell lines over time for control, treatment with the indicated concentration of BI-BET, the indicated concentration of CCS1477 or GNE-781 and the combination of both. In particular, the figures 1 and 2 show analysis of cell growth in Ty-82 NUT carcinoma cell lines over time for control, treatment with 1.2 nM of BI-BET, 37 nM of CCS1477 or 12 nM of GNE-781, respectively, and the combination of both. Figures 3 to 6 show analysis of cell growth over time for control, for

treatment with 1.2 nM of BI-BET and 12 nM of CCS1477, and the combination of both in Ty-82, 10-15, 14169 and 10326 NUT carcinoma cell lines.

Cell growth of BET inhibitor treated cells was reduced in comparison to DMSO control treated cells. Cell growth of CCS1477 or GNE-781 treated cells was reduced in comparison to DMSO control treated cells. Combination of BET inhibitor plus CCS1477 or GNE-781 treatment reduced cell proliferation more than each single treatment.

Synergy was monitored by Bliss score

For the combination assays, Ty-82 cells were plated in 96-well plates (Corning® #3599) and were incubated with the respective compounds (BI-BET, CCS1477 or GNE-781), either alone or in combination. After 96 hours of compound incubation, Alamar Blue was added for 6 hours and was measured in Wallac Victor 500/305, Fluorescence Alamar (Ex530 / Em 590).

The following tables 1 and 2 summarize the results of the 96h cell proliferations assays for Ty-82 NUT carcinoma cell line incubated with BI-BET and CCS1477 or GNE-781. Values for cell growth inhibition (CGI) are given in percentage, where a CGI < 100% indicates cell growth, CGI of 100% indicates stasis and a CGI > 100% CGI indicates cell death.

Table 1: CGI_m of Ty-82 NUT carcinoma cell line incubated with BI-BET and CCS1477

BI-BET [nmol/l]	CGI_m					
100	113	148	169	176	184	189
33.3	99	114	148	165	173	181
11.1	91	101	128	144	158	163
3.7	84	92	98	122	139	147
1.12	50	70	84	93	100	117
0		37	52	72	86	93
	0	12.3	37	111	333	1000
	CCS1477 [nmol/l]					

Table 2: CGI_m of Ty-82 NUT carcinoma cell line incubated with BI-BET and GNE-781

BI-BET [nmol/l]	CGI_m					
100	101	169	180	179	183	180
33.3	100	156	170	170	173	173
11.1	92	135	158	155	155	155
3.7	74	103	122	121	129	132
1.12	31	83	92	93	98	95
0		48	70	74	79	84
	0	12.3	37	111	333	1000
	GNE-781 [nmol/l]					

Example 2

Anti-tumor activity of BET inhibitor BI-BET in combination with p300/CBP bromodomain inhibitor CCS1477 in NUT carcinoma xenografts *in vivo*

The efficacy of BI-BET in combination with p300/CBP bromodomain inhibitor CCS1477 was tested in a subcutaneous xenograft mouse model derived from the human NUT carcinoma cells in NOG (NOD/Shi-*scid*/IL-2Rγ^{null}) mice (CIEA, Central Institute for Experimental Animals). Human NUT carcinoma cell line Ty-82 (BRD4-NUT) was grown as subcutaneous xenografts in the NOG mice.

Cells:

Ty-82 (JCRB Japan No. 1330) were cultured in T75 culture flasks at 37°C and 5% CO_2. The medium used was RPMI 1640 supplemented with 10% fetal calf serum (FCS). (Thermo Fisher scientific #61870010). Cells were split twice weekly with a ratio of 1:2.

Mice:

Mice were 8 to 10 week-old female CIEA NOG purchased from Taconic, Denmark (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug}/JicTac). After arrival at the animal facility, mice were allowed to adjust to conditions at least for 5 days before they were used for the experiment. They were

housed in Macrolon® type III cages in groups of 8 to 10 under standardized conditions at 21.5 ± 1.5 °C temperature and 55 ± 10 % humidity. Standardized diet (PROVIMI KLIBA) and autoclaved tap water were provided ad libitum. Subcutaneous microchips implanted under isoflurane anesthesia were used to identify each mouse.

Establishment of tumors, randomization:

To establish subcutaneous tumors, Ty-82 cells were harvested by centrifugation, washed and resuspended in PBS + 5 % FCS at 5 x 10^7 cells/ml. 100 µl cell suspension containing 5 x 10^6 cells was injected subcutaneously into the right flank of the mice (1 site per mouse). Mice were randomly distributed between the treatment and the vehicle control group (26 days after cell injection) when tumors were well established and had reached volumes of 89 to 177 mm^3.

Administration of test compounds:

BI-BET and CCS1477 were suspended in 0.5 % Natrosol and administered intragastrally by gavage needle with a volume of 10 ml/kg body weight. The suspensions were used for a maximum of 4 days.

Monitoring of tumor growth and side effects:

Tumor diameters were measured three times a week with a caliper. The volume of each tumor [in mm^3] was calculated according to the formula "tumor volume = length * $diameter^2$ * π/6". To monitor side effects of treatment, mice were inspected daily for abnormalities and body weight was determined three times a week. Animals were sacrificed when the median tumor volume of the group reached a size of approximately 1000 mm^3. In addition, animals with tumor sizes exceeding 1500 mm^3 in diameter, with ulcerating tumors or 18 % body weight loss were euthanized for ethical reasons. The statistical evaluation of the tumor volume and the body weight was conducted on day 17.

Results:

Figures 7 and 9 show that treatment with a combination of 2 mg/kg BI-BET qd with 10 mg/kg CCS1477 qd was significantly different to the monotherapy with 2 mg/kg BI-BET qd (median TGI = 107 % versus 5 %, p <0.0002) and 10 mg/kg CCS1477 (median TGI = 107 % versus 29 %, p <0.0002). In the combination group all 8 tumors showed clear regressions, while no tumor regressions could be observed in both monotherapy groups. Also treatment with a combination of 2 mg/kg BI-BET qd with 5 mg/kg CCS1477 qd was significantly different to the monotherapy with 2 mg/kg BI-BET qd (median TGI = 94 % versus 5 %, p <0.0002) and 5 mg/kg CCS1477 (median TGI = 94 % versus 11 %, p <0.0002). Figure 8 shows that on day 17, the body weight loss in the combination groups was not significantly different compared to the monotherapy with BI-BET and CCS1477.

Table 3 shows the TGI (Tumor growth inhibition, calculated to the formula: TGI =100 x {1-[($treated_{final\ day}$– $treated_{day\ 1}$) / ($control_{final\ day}$– $control_{day\ 1}$)]}) at day 17 for each treatment group.

Table 3: TGI at day 17 for each treatment group

	dose [mg/kg]	schedule	route	TGI @ d17 [%]	Mortality [x/y]	P value @ d17	P value @ d17	P value @ d17
Control	-	qd	p.o.	-	0/10	*		
BI-BET	2	qd	p.o.	5	0/8	0.5148	0.0004	0.0004
CCS1477	10	qd	p.o.	29	0/8	0.4731	0.0004	
CCS1477	5	qd	p.o.	11	0/8	0.5148		0.0004
BI-BET + CCS1477	2 + 10	qd qd	p.o. p.o.	107	0/8	0.0005	*	
BI-BET + CCS1477	2 + 5	qd qd	p.o. p.o.	94	0/8	0.0005		*

* indicates reference group for comparison

The results demonstrated a synergistic effect of the combined administration compared to the single treatments. Combination of BI-BET with the p300/CBP bromodomain inhibitor

CCS1477 showed significant anti-tumor activity compared to the control and compared to the respective monotherapies, with tumor regressions in all mice of the 10 mg/kg combination group and tumor stasis in the 5 mg/kg combination group, demonstrating clear synergy. All doses were well tolerated.

Example 3

Anti-tumor activity of BET inhibitor BI-BET in combination with p300/CBP bromodomain inhibitor CCS1477 in BRD3-NUT carcinoma xenografts *in vivo*

The efficacy of BI-BET in combination with p300/CBP bromodomain inhibitor CCS1477 was tested in a second subcutaneous xenograft mouse model derived from human NUT carcinoma cells in NOG mice (CIEA). In these NOG mice human NUT carcinoma cell line 10326 (BRD3-NUT) was grown as subcutaneous xenografts.

For BRD3-NUT carcinoma xenografts, 10326 cells (French, Brigham & Women`s Hospital) were cultured in T75 culture flasks at 37°C and 5% CO_2. The medium used was DMEM medium (Sigma #D6429) supplemented with 10 % fetal calf serum and Glutamax™ (Gibco™). Mice were as described in Example 2. Also establishment of tumors, randomization, administration of test compounds, and monitoring of tumor growth and side effects was performed as described in example 2.

Results:

Figures 10 and 12 show that also in BRD3-NUT carcinoma xenografts treatment with a combination of 2 mg/kg BI-BET qd with 5 or 10 mg/kg CCS1477qd significantly different to the monotherapy with 5 or 10 mg/kg CCS1477 and was more pronounced compared to the monotherapy with 2 mg/kg BI-BET qd. Table 4 shows the TGI at day 21 for each treatment group.

Table 4: TGI at day 21 for each treatment group in BRD3-NUT 10326 xenografts

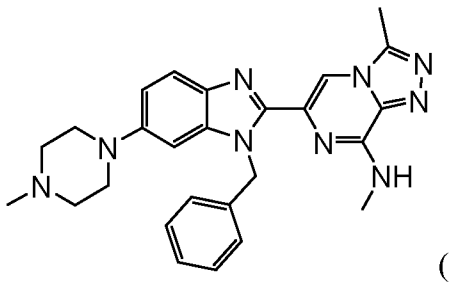
	dose [mg/kg]	schedule	route	TGI @ d21 [%]	mortality [x/y]	P value @ d21	P value @ d21	P value @ d21
Control	-	qd/q7d	p.o./i.v.		0/10	*		
BI-BET	2	qd	p.o.	99	0/10	< 0.0005		
CCS1477	10	qd	p.o.	88	0/10	< 0.0005	<0.0002	
CCS1477	5	qd	p.o.	65	0/10	0.0026		<0.0002
BI-BET + CCS1477	2 + 10	qd qd	p.o. p.o.	107	2/10	< 0.0005	*	
BI-BET + CCS1477	2 + 5	qd qd	p.o. p.o.	108	0/10	< 0.0005		*

* indicates reference group for comparison

The results demonstrated a synergistic effect of the combined administration compared to the single treatments also in BRD3-NUT 10326 xenografts. All mice in both combination groups showed tumour regression (TGI 107% in the 2 mg/kg BI-BET and 10 mg/kg CCS1477 combination group and TGI 108% in the 2 mg/kg BI-BET and 5 mg/kg CCS1477 combination group). Two animals of the 2 mg/kg BI-BET and 10 mg/kg CCS1477 combination group had to be sacrificed due to body weight loss.

Claims

1. A bromodomain and extra-terminal protein (BET) inhibitor for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein the BET inhibitor is administered in combination with a p300 (histone acetyltransferase p300)/CBP (CREB binding protein) inhibitor, characterized in that the BET inhibitor is BI-BET according to formula (1) below, or a pharmaceutically acceptable salt thereof



(1)

and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

2. The BET inhibitor for use according to claim 1, wherein the p300/CBP bromodomain inhibitor is selected from the group consisting of CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and GNE-781, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and/or wherein the p300/CBP CH1 domain inhibitor is INTH-454 or a pharmaceutically acceptable salt thereof or a hydrate thereof.

3. The BET inhibitor for use according to any one of claim 1 or 2, wherein the p300/CBP bromodomain inhibitor is CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

4. The BET inhibitor for use according to any one of claims 1 to 3, wherein the oncological and/or hyperproliferative disease is a cancer selected from the group consisting of prostate cancer (including but not limited to castration-resistant prostate cancer (CRPC)), bladder cancer, breast cancer (including but not limited to ductal breast cancer), cancers of the gastrointestinal tract (including but not limited to colon cancer, colorectal cancer, gastric cancer, pancreatic cancer (including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma), oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer), head and neck cancer (including but not limited to nasopharyngeal cancer), brain cancer (including but not limited to glioblastoma, medulloblastoma and astrocytoma), neuroblastoma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, liver cancer (including but not limited to hepatocellular carcinoma), neuroendocrine cancer, melanoma (including but not limited to uveal melanoma), lung cancer (including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), NUT carcinoma, lymphoma (including but not limited to diffuse large B-cell lymphoma (DLBCL), leukemias (including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL)), (primary) myelofibrosis (PMF), multiple myeloma (MM), leiomyosarcoma, rhabdomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, salivary gland adenocarcinoma, osteosarcoma, adenoid cystic carcinoma, ependymoma, acinic cell carcinoma and merkel cell carcinoma.

5. The BET inhibitor for use according to any one of claims 1 to 4, wherein the oncological and/or hyperproliferative disease is NUT carcinoma.

6. A pharmaceutical combination comprising as active ingredients a BET inhibitor and a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined in claim 1 or a

pharmaceutically acceptable salt thereof and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

7. The pharmaceutical combination according to claim 6, for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer.

8. A kit comprising in one or more containers:
(i) a first pharmaceutical composition or dosage form comprising a BET inhibitor, wherein the BET inhibitor is BI-BET as defined in claim 1, or a pharmaceutically acceptable salt thereof, and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles;
(ii) a second pharmaceutical composition or dosage form comprising a p300/CBP inhibitor, wherein the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor and, optionally, pharmaceutically acceptable carriers, excipients and/or vehicles; and
(iii) optionally a package insert comprising instructions.

9. The kit according to claim 8, for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer.

10. A method of treating an oncological and/or hyperproliferative disease, in particular cancer, the method comprising administering to a patient a therapeutically effective amount of a BET inhibitor in combination with a therapeutically effective amount of a p300/CBP inhibitor, wherein the BET inhibitor is BI-BET as defined in claim 1, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

11. Use of a BET inhibitor for the manufacture of a medicament for use in the treatment of an oncological and/or hyperproliferative disease, in particular cancer, wherein the BET inhibitor is to be used in combination with a p300/CBP inhibitor, characterized in that the BET inhibitor is BI-BET as defined in claim 1, or a pharmaceutically acceptable salt thereof, and the p300/CBP inhibitor is a p300/CBP bromodomain inhibitor and/or a p300/CBP CH1 domain inhibitor.

12. The pharmaceutical combination according to any one of claim 6 or 7, the kit according to any one of claim 8 or 9, the method of claim 10, or the use of claim 11, wherein the p300/CBP bromodomain inhibitor is selected from the group consisting of CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and GNE-781, or a pharmaceutically acceptable salt thereof or a hydrate thereof, and/or the p300/CBP CH1 domain inhibitor is INTH-454, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

13. The pharmaceutical combination according to claim 7, the kit according to claim 9, the method of claim 10, or the use of claim 11, wherein the oncological and/or hyperproliferative disease is a cancer selected from the group consisting of prostate cancer (including but not limited to castration-resistant prostate cancer (CRPC)), bladder cancer, breast cancer (including but not limited to ductal breast cancer), cancers of the gastrointestinal tract (including but not limited to colon cancer, colorectal cancer, gastric cancer, pancreatic cancer (including but not limited to pseudopapillary pancreatic carcinoma and pancreatic ductal adenocarcinoma), oesophageal cancer, cholangiocarcinoma, small bowel cancer, duodenal cancer), head and neck cancer (including but not limited to nasopharyngeal cancer), brain cancer (including but not limited to glioblastoma, medulloblastoma and astrocytoma), neuroblastoma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, liver cancer (including but not limited to hepatocellular carcinoma),

neuroendocrine cancer, melanoma (including but not limited to uveal melanoma), lung cancer (including but not limited to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), NUT carcinoma, lymphoma (including but not limited to diffuse large B-cell lymphoma (DLBCL), leukemias (including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL)), (primary) myelofibrosis (PMF), multiple myeloma (MM), leiomyosarcoma, rhabdomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, salivary gland adenocarcinoma, osteosarcoma, adenoid cystic carcinoma, ependymoma, acinic cell carcinoma and merkel cell carcinoma.

14. The pharmaceutical combination according to claim 7, the kit according to claim 9, the method of claim 10, or the use of claim 11, wherein the cancer is NUT carcinoma.

15. The pharmaceutical combination according to any one of claim 6 or 7, the kit according to to any one of claim 8 or 9, the method of claim 10, or the use of claim 11, wherein the p300/CBP bromodomain inhibitor is CCS1477, or a pharmaceutically acceptable salt thereof or a hydrate thereof.

Fig. 1

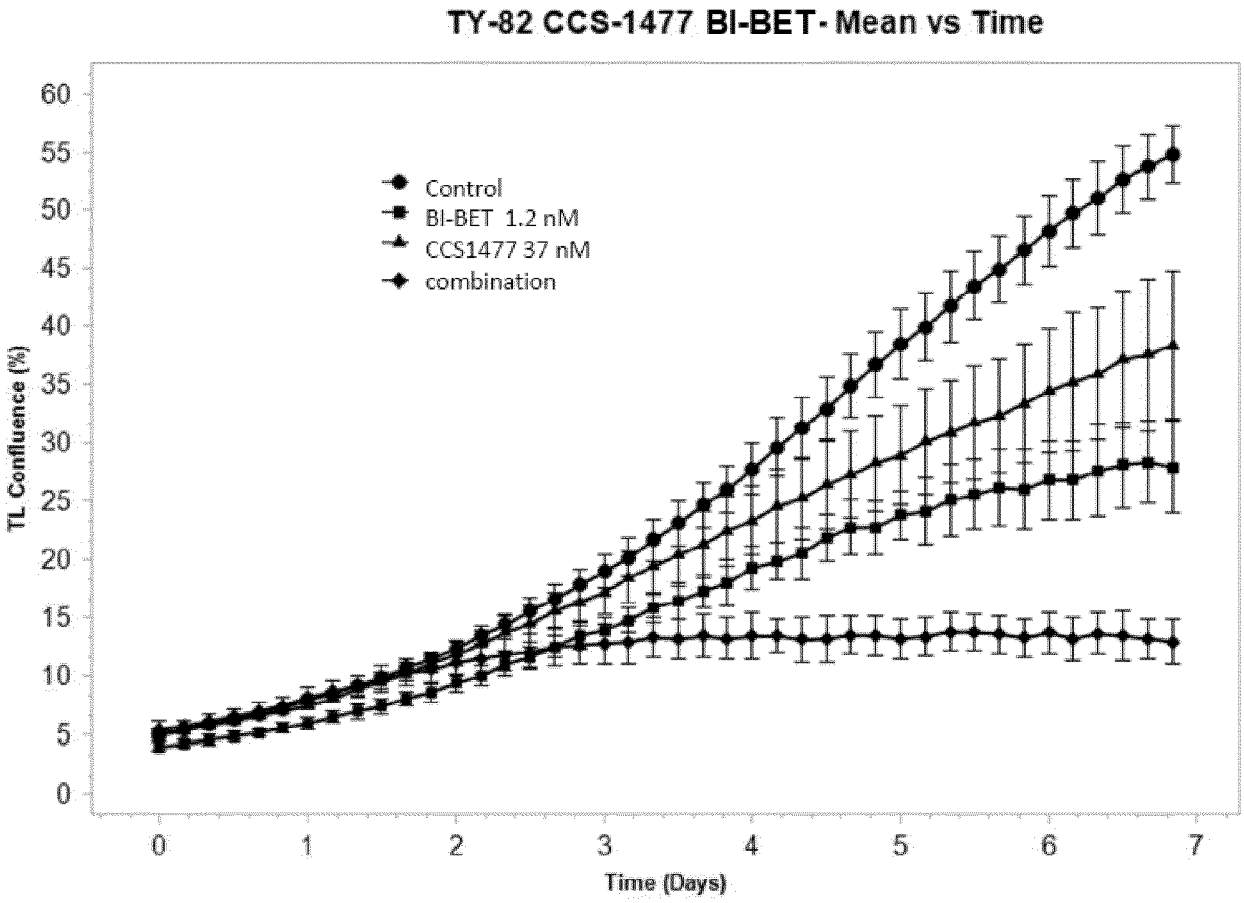

TY-82 CCS-1477 BI-BET - Mean vs Time
Control
BI-BET 1.2 nM
CCS1477 37 nM
combination
TL Confluence (%)
Time (Days)
0
5
10
15
20
25
30
35
40
45
50
55
60
0
1
2
3
4
5
6
7

Fig. 2

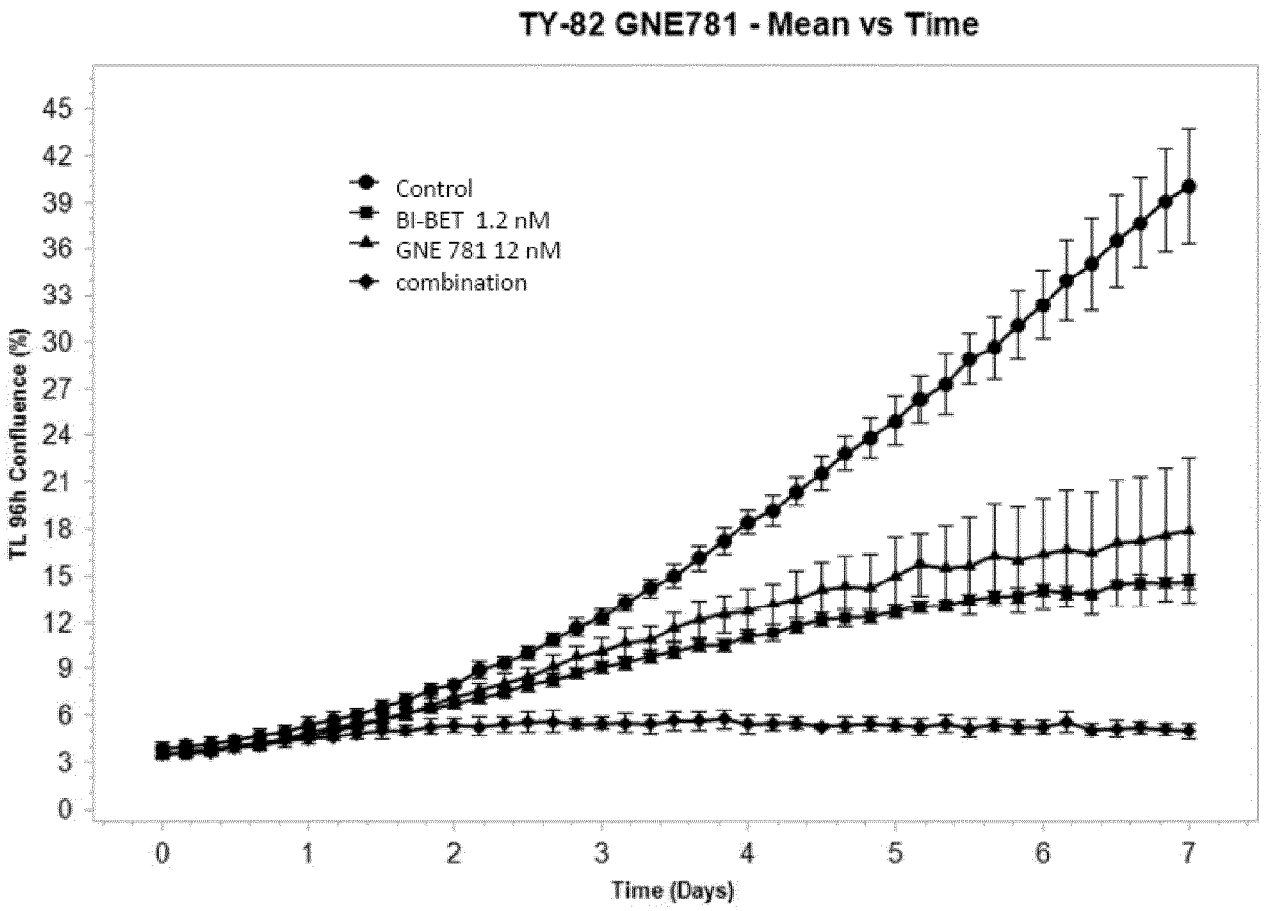

TY-82 GNE781 - Mean vs Time
Control
BI-BET 1.2 nM
GNE 781 12 nM
combination
TL 96h Confluence (%)
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
0
1
2
3
4
5
6
7
Time (Days)

Fig. 3

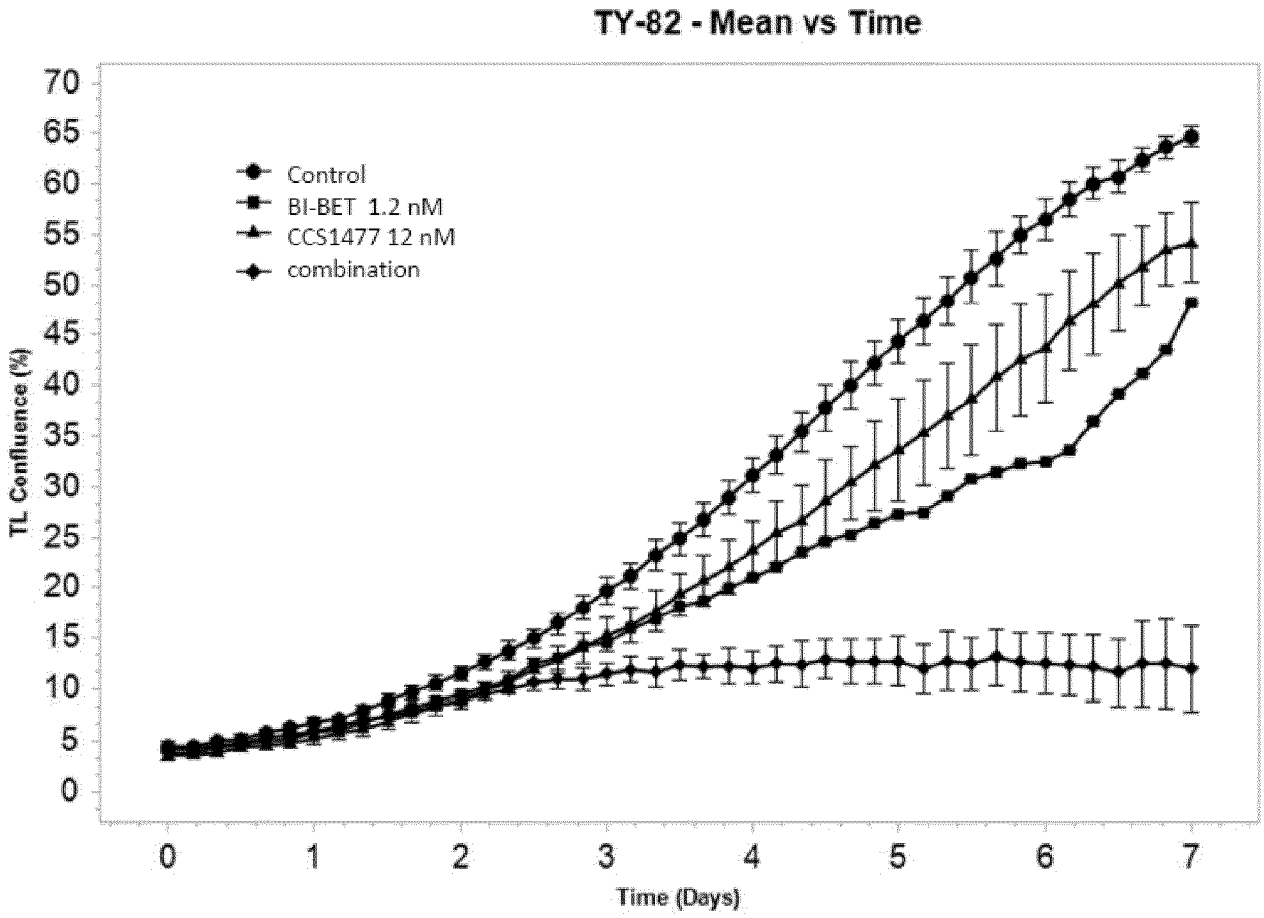

TY-82 - Mean vs Time
Control
BI-BET 1.2 nM
CCS1477 12 nM
combination
TL Confluence (%)
Time (Days)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
0
1
2
3
4
5
6
7

Fig. 4

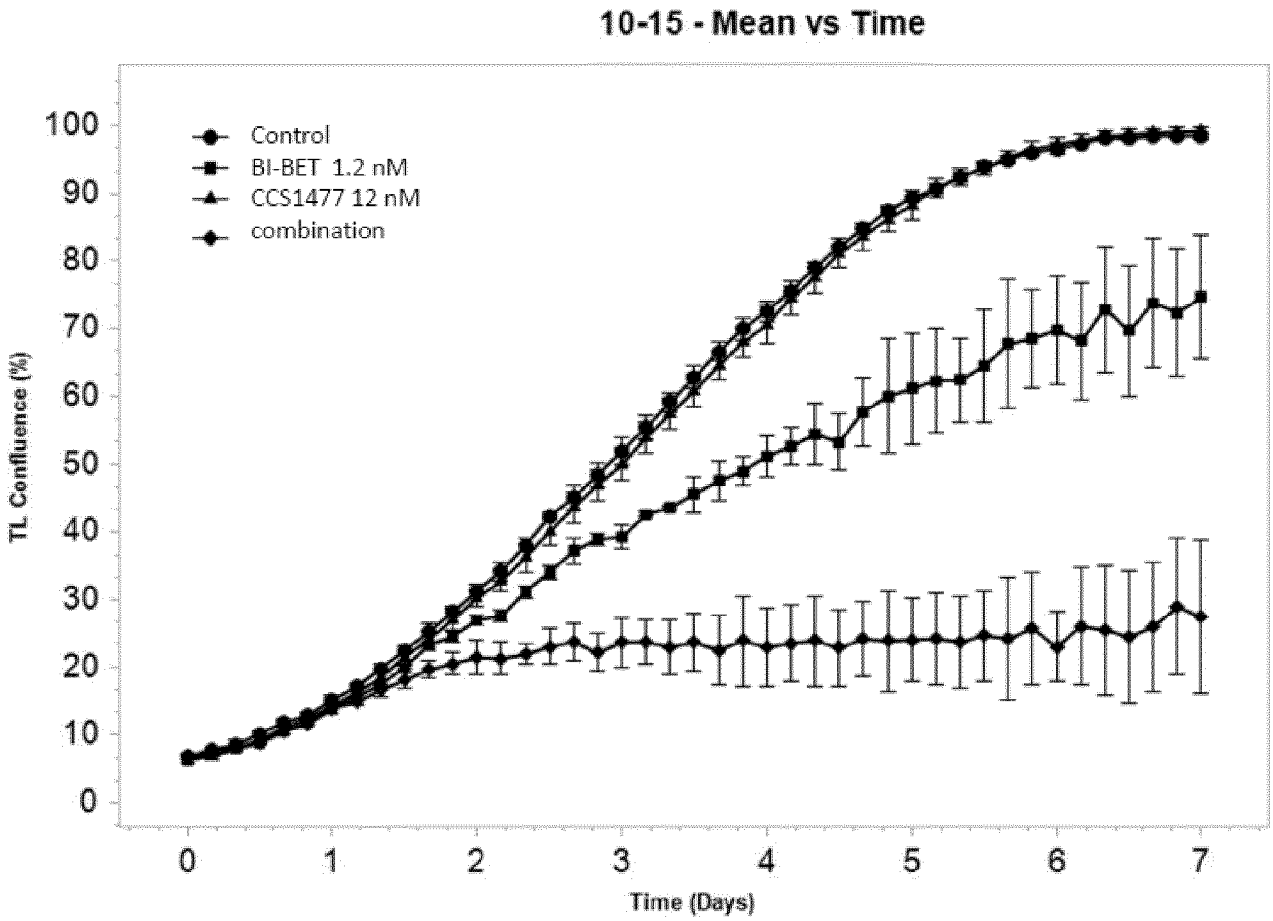

10-15 - Mean vs Time
Control
BI-BET 1.2 nM
CCS1477 12 nM
combination
TL Confluence (%)
Time (Days)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7

Fig. 5

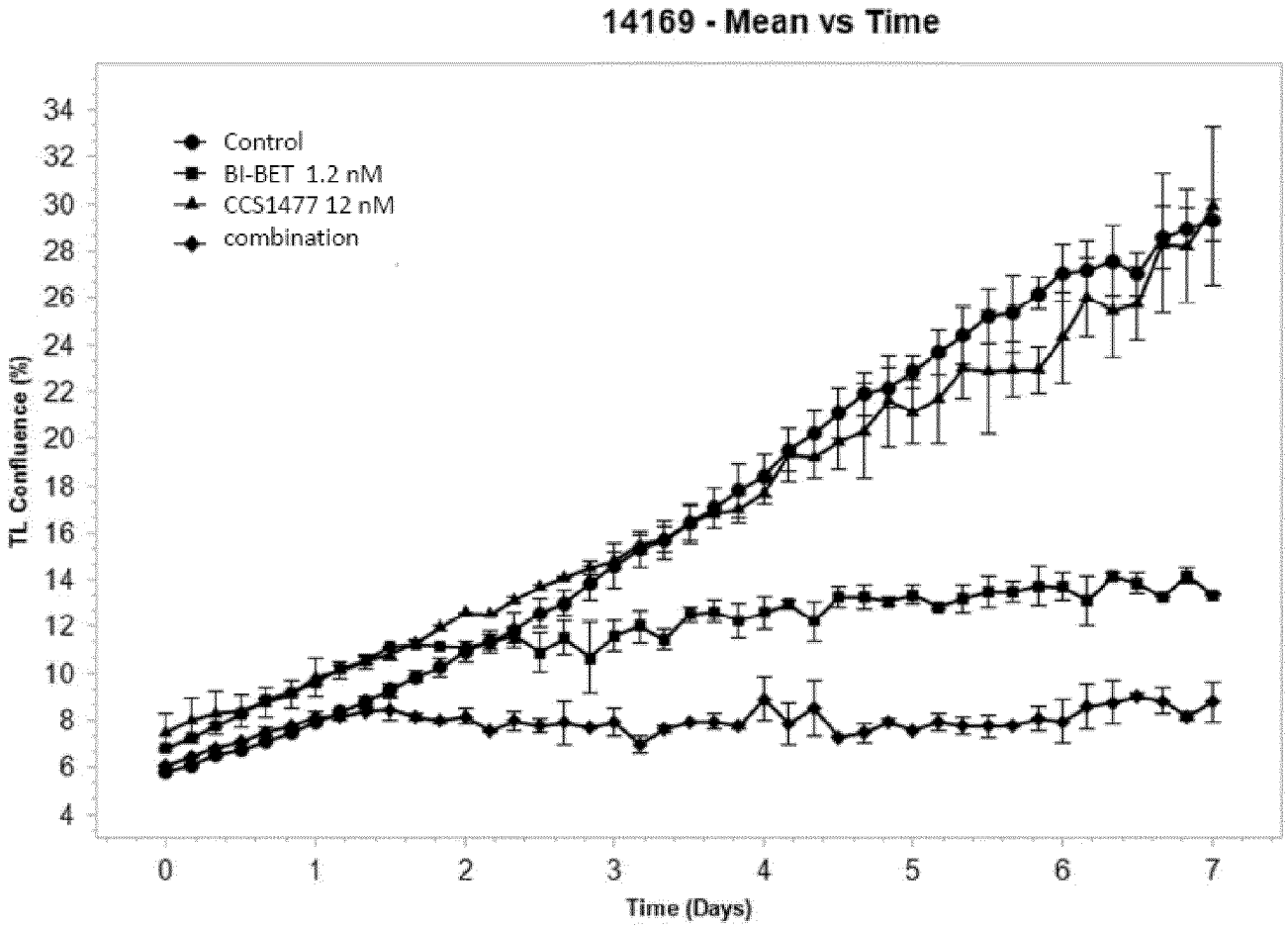

14169 - Mean vs Time
Control
BI-BET 1.2 nM
CCS1477 12 nM
combination
TL Confluence (%)
Time (Days)
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
0
1
2
3
4
5
6
7

Fig. 6

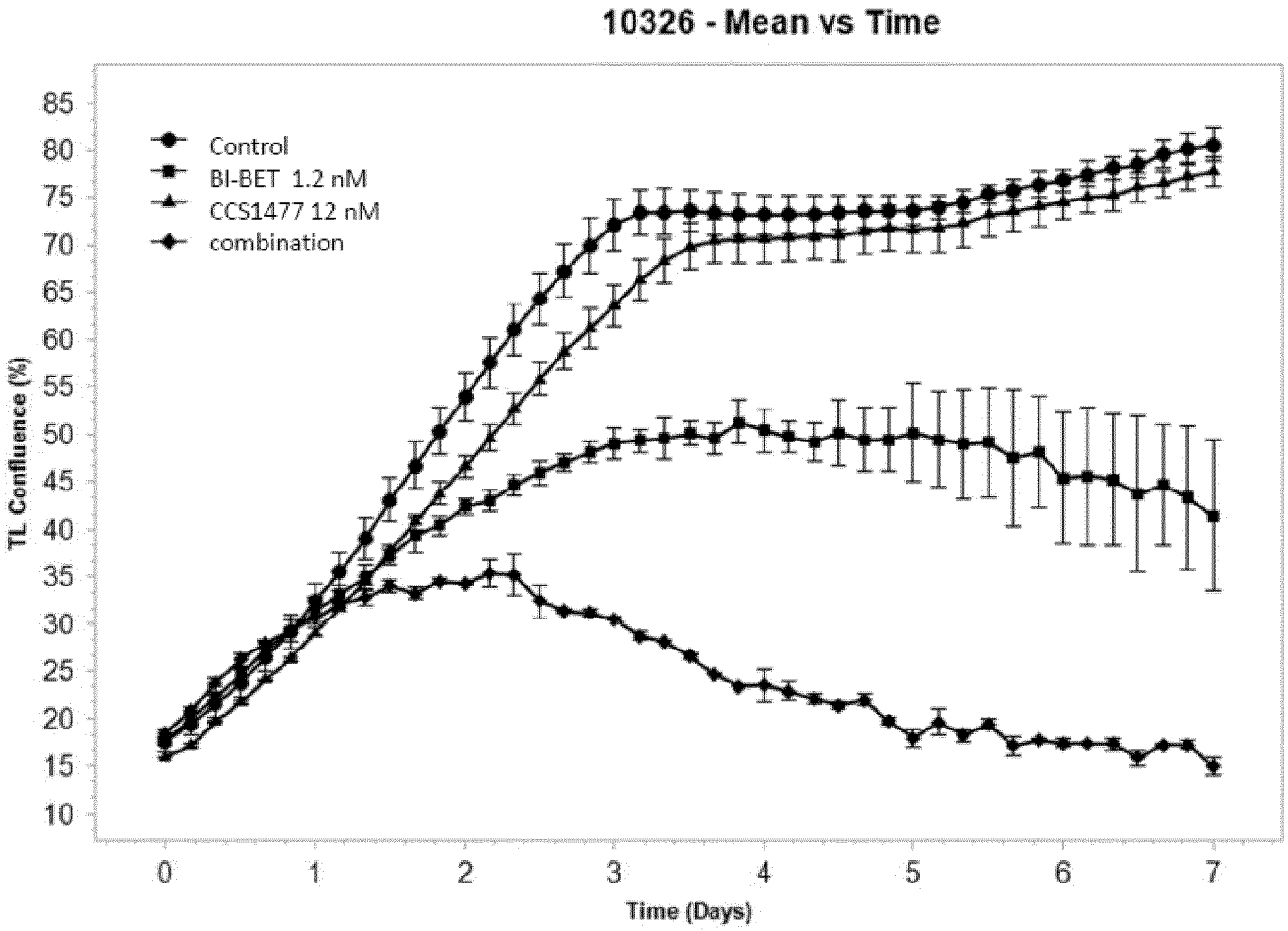

10326 - Mean vs Time
Control
BI-BET 1.2 nM
CCS1477 12 nM
combination
TL Confluence (%)
Time (Days)
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
0
1
2
3
4
5
6
7

Fig. 7

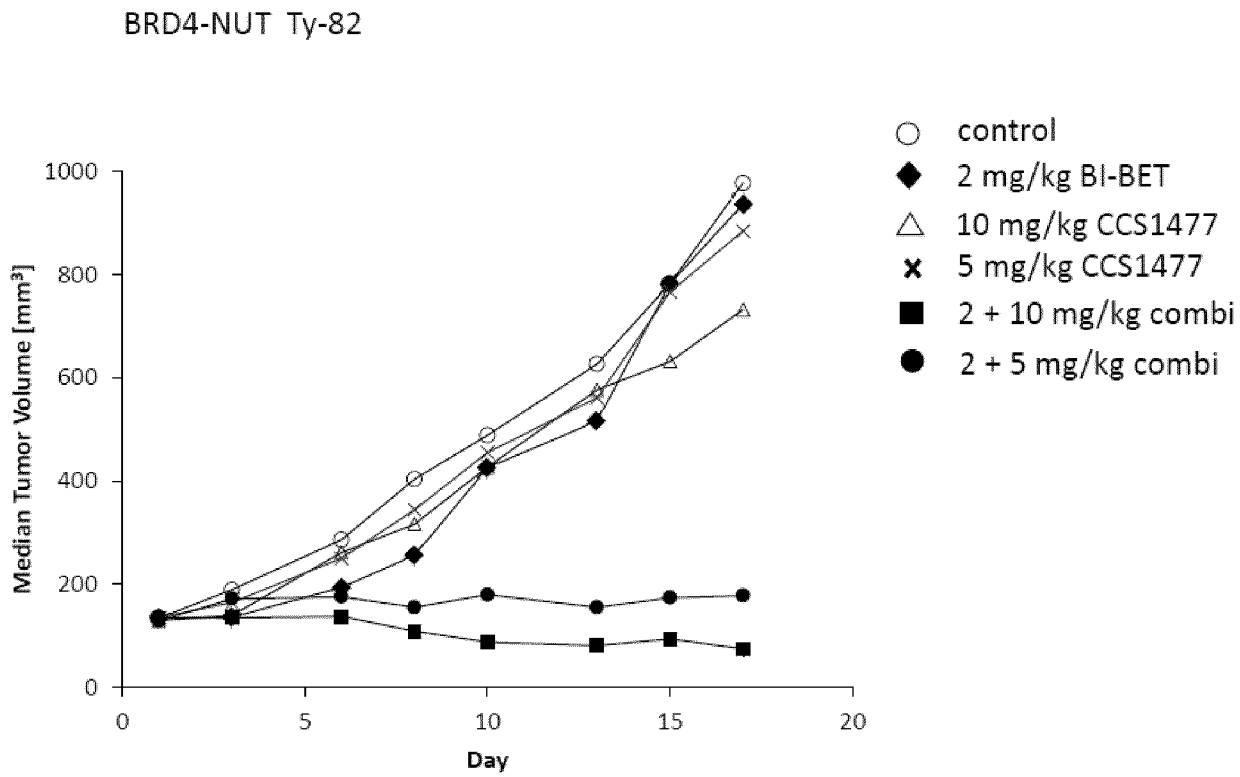

BRD4-NUT Ty-82
Median Tumor Volume [mm³]
1000
800
600
400
200
0
0
5
10
15
20
Day
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

Fig. 8

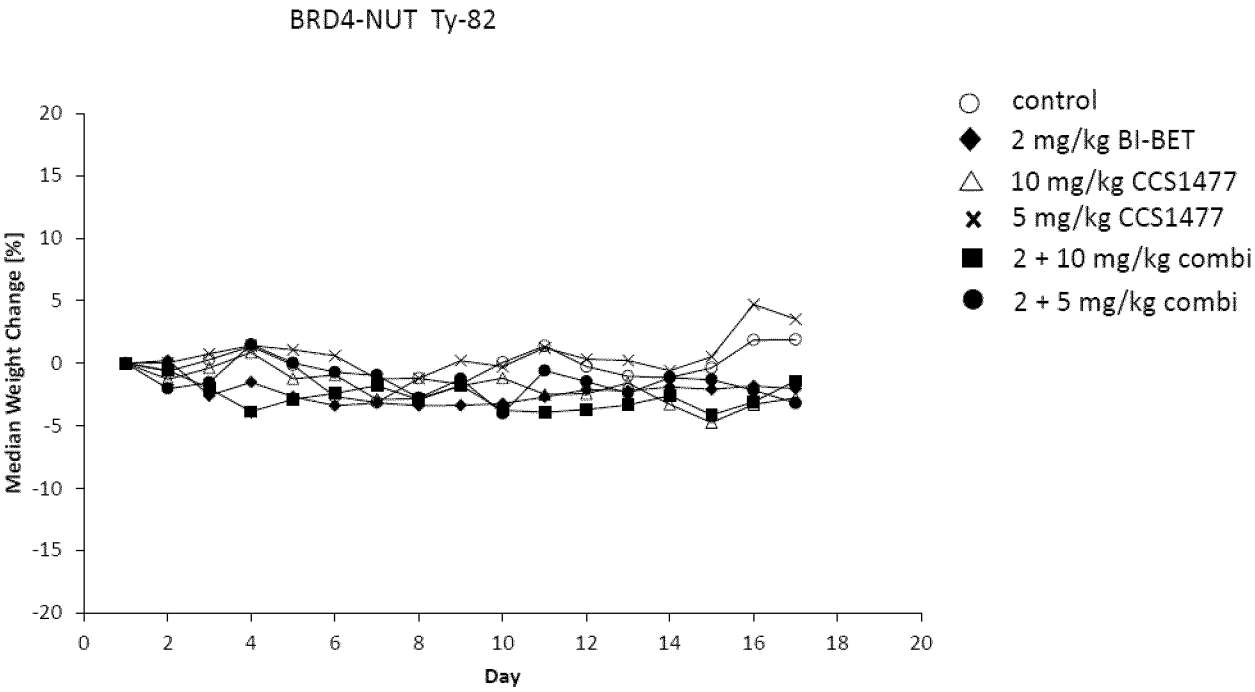

BRD4-NUT Ty-82
Median Weight Change [%]
20
15
10
5
0
-5
-10
-15
-20
0
2
4
6
8
10
12
14
16
18
20
Day
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

Fig. 9

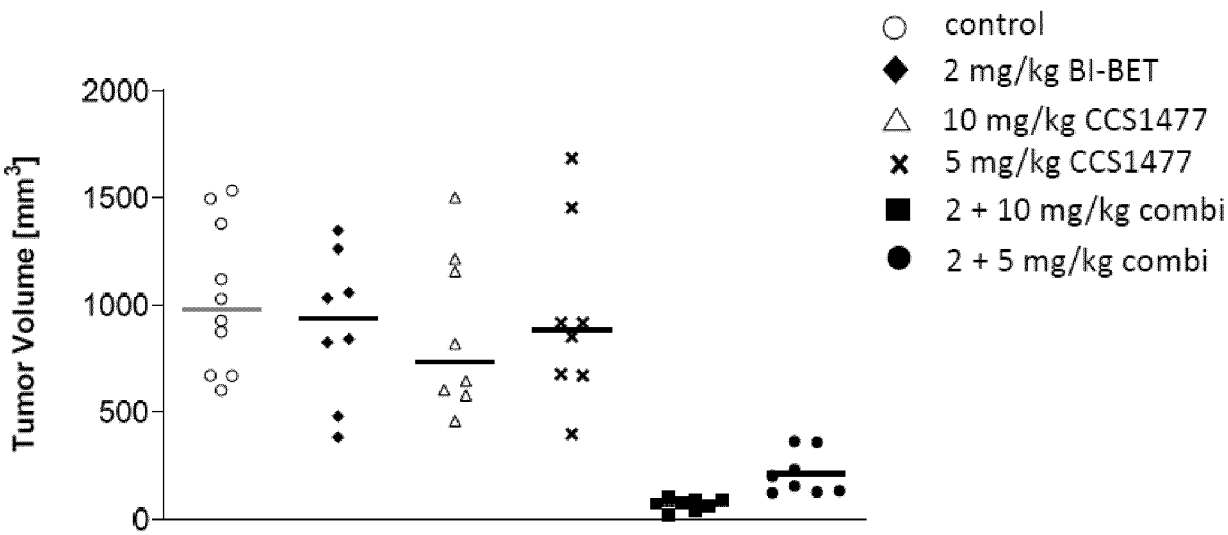

Tumor Volume [mm3]
2000
1500
1000
500
0
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

Fig. 10

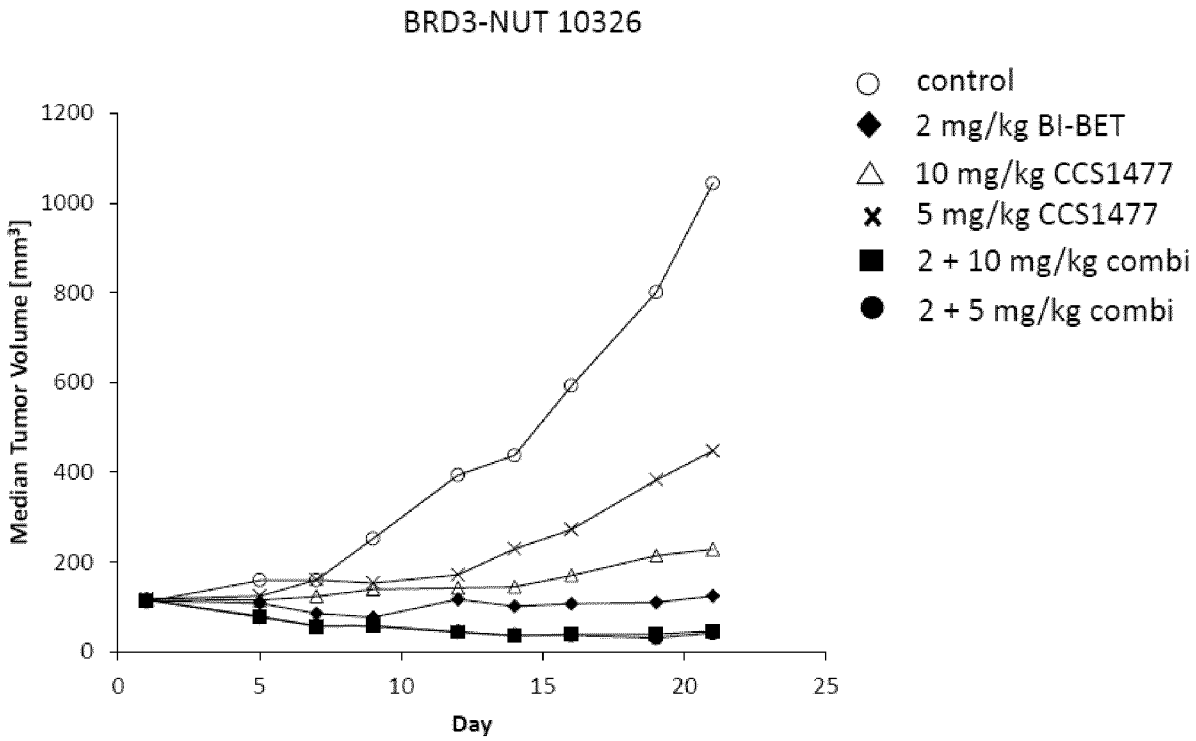

BRD3-NUT 10326
Median Tumor Volume [mm³]
1200
1000
800
600
400
200
0
0
5
10
15
20
25
Day
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

Fig. 11

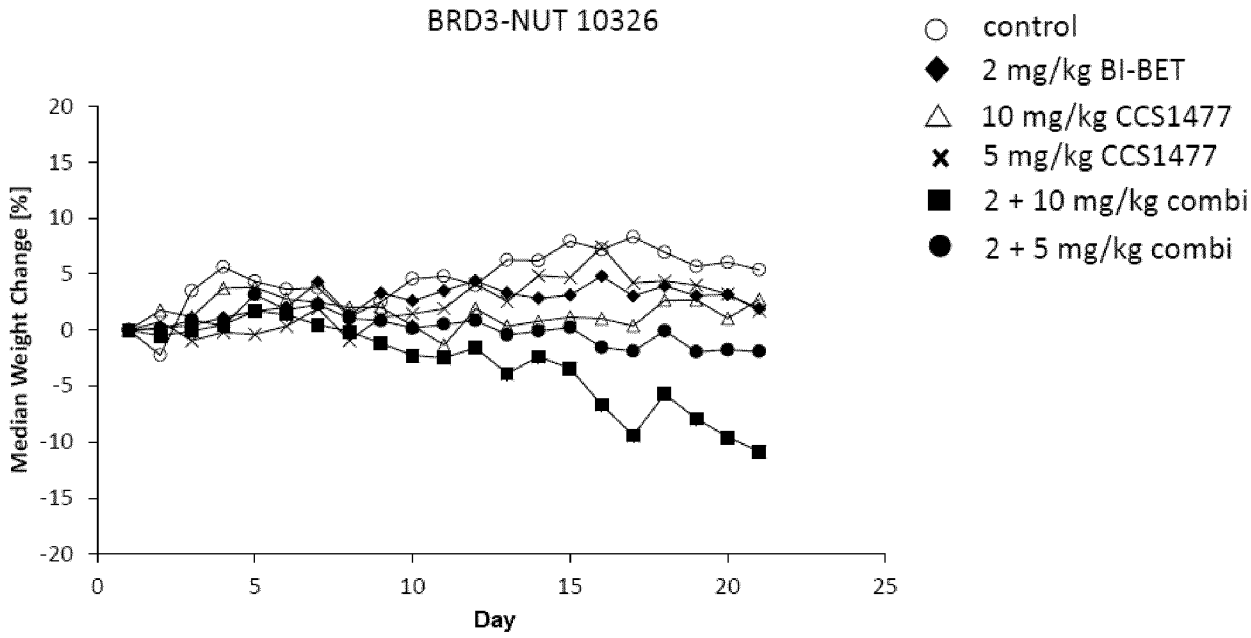
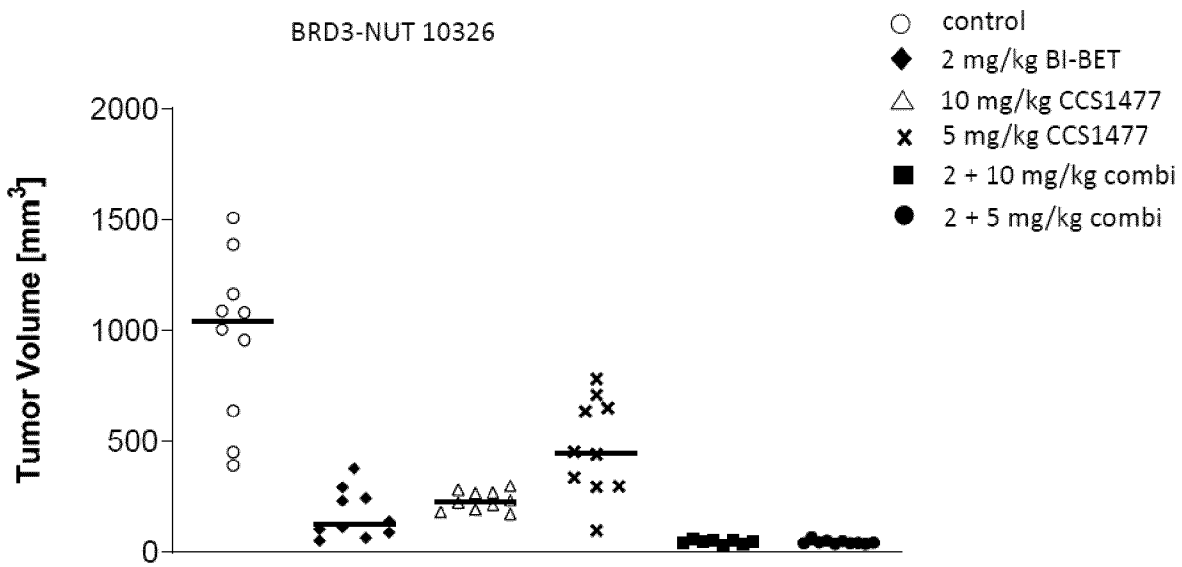

BRD3-NUT 10326
Median Weight Change [%]
Day
20
15
10
5
0
-5
-10
-15
-20
0
5
10
15
20
25
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

Fig. 12


BRD3-NUT 10326
Tumor Volume [mm3]
2000
1500
1000
500
0
control
2 mg/kg BI-BET
10 mg/kg CCS1477
5 mg/kg CCS1477
2 + 10 mg/kg combi
2 + 5 mg/kg combi

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/055043

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4184 A61K31/4196 A61K31/496 A61K31/4985 A61P35/00
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/145410 A1 (BOEHRINGER INGELHEIM INT [DE]) 1 August 2019 (2019-08-01) claim 7; compound 5	1-15
Y	WO 2016/044694 A1 (GENENTECH INC [US]; CONSTELLATION PHARMACEUTICALS INC [US]) 24 March 2016 (2016-03-24) claims 1, 13, 14; examples 1-5; compounds I, II, III, IV	1-15
A	US 2014/142098 A1 (ENGELHARDT HARALD [AT] ET AL) 22 May 2014 (2014-05-22) compounds III-13	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2022	31/05/2022

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	Scheid, Günther

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/055043

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		MA 38099 A1	31-01-2018
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