(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 September 2017 (21.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/157418 A1

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61K 31/337* (2006.01)
A61K 31/5025 (2006.01) *A61K 35/00* (2006.01)

(21) International Application Number:
PCT/EP2016/055499

(22) International Filing Date:
15 March 2016 (15.03.2016)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: COMBINATION OF MKNK1-INHIBITORS

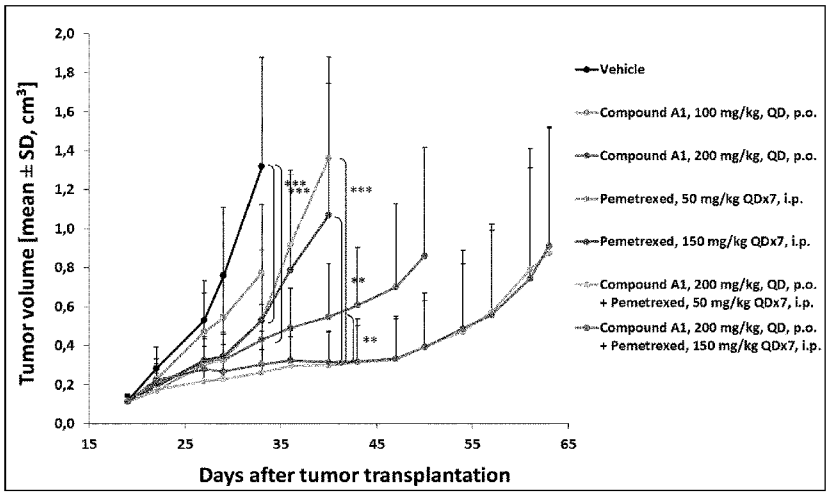

Figure 7

(57) Abstract: The present invention relates to combinations of at least two components, component A and component B, component A being a MKNK1-inhibitor of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, and component B being an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof, and pemetrexed. Another aspect of the present invention relates to the use of such combinations as described supra for the preparation of a medicament for the treatment or prophylaxis of a disease, particurlarly for the treatment of cancer and/or metastases thereof.

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Combination of MKNK1-Inhibitors

The present invention relates to combinations of at least two components, component A and component B, component A being a MKNK1 inhibitor of general formula (I) as described herein, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same,
and component B being an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:
- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

Another aspect of the present invention relates to the use of such combinations as described herein for the preparation of a medicament for the treatment or prophylaxis of a disease, particularly for the treatment of cancer, particularly Non-Small Cell Lung Cancer (NSCLC) and/or metastases thereof.

Yet another aspect of the present invention relates to methods of treatment or prophylaxis of a cancer in a subject, comprising administering to said subject a therapeutically effective amount of a combination as described herein.

Further, the present invention relates to a kit comprising a combination of:
- one or more components A, as defined herein, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof ;
- a component B, as defined *supra*, or a solvate or hydrate thereof ; and optionally
- one or more pharmaceutical agents C;

in which optionally either or both of said components A and B are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

Another aspect of the present invention relates to a combination as defined herein, for use in the treatment or prophylaxis of a cancer and/or metastases thereof, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof, and pemetrexed.

BACKGROUND

Cancer is the second most prevalent cause of death in the United States, causing 450,000 deaths per year. While substantial progress has been made in identifying some of the likely environmental and hereditary causes of cancer, there is a need for additional therapeutic modalities that target cancer and related diseases. In particular there is a need for therapeutic methods for treating diseases associated with dysregulated growth / proliferation.
Cancer is a complex disease arising after a selection process for cells with acquired functional capabilities like enhanced survival / resistance towards apoptosis and a limitless proliferative potential. Thus, it is preferred to develop drugs for cancer therapy addressing distinct features of established tumors.
The present invention relates to chemical compounds that inhibit MKNK1 kinase (also known as MAP Kinase interacting Kinase, Mnk1).

Human MKNKs comprise a group of four proteins encoded by two genes (Gene symbols: MKNK1 and MKNK2) by alternative splicing. MKNK, a target at the junction of the Ras-Raf-MEK-ERK and PI3K-AKT-mTor pathways, modulates the function of eIF4E through phosphorylation of a conserved serine residue (Ser209). In addition to eIF4E, MKNKs mediate phosphorylation of several other target proteins such as Sprouty2, hnRNPA1 (heterogenous nuclear ribonucleoprotein A1), PSF (polypyrimidine tract-binding protein-associated splicing factor) and cPLA2 (cytosolic phospholipase A2) and therefore, play a key role in oncogenic progression, drug resistance, production of proinflammatory cytokines and cytokine signaling in cancer [Buxade M et al., Frontiers in Bioscience 5359-5374, May 1, 2008]. MKNK activity is tightly

regulated and is mediated by ERK (extracellular regulated kinase) and p38 MAPK binding.

eIF4E is an oncogene and critical for malignant transformation by regulating protein translation of so-called “weak” mRNAs. These weak mRNAs are usually less efficiently translated due to their long and complex 5´UTR region and they encode proteins that play significant roles in all aspects of malignancy including VEGF, FGF-2, c-Myc, cyclin D1, survivin, BCL-2, MCL-1, MMP-9, heparanase, etc. Expression and function of eIF4E is elevated in multiple human cancers and directly related to disease progression [Konicek et al., Cell Cycle 7:16, 2466-2471, 2008].

While the MKNK-dependent phosphorylation of eIF4E is necessary for oncogenic transformation, the kinase activity of MKNK appears to be dispensable for normal development as the MKNK1/MKNK2 double knock-out mice are viable, fertile, and develop normally Ueda et al., Mol Cell Biol 24, 6539-6549, 2004]. Furthermore, it has been demonstrated that MKNK1 is responsible for the inducible phosphorylation of eIF4E in response to MAPK activation, whereas MKNK2 mainly contributes to basal, constitutive eIF4E phosphorylation. Evidence from basic research supports the anti-tumor efficacy and tolerability of pharmacological inhibition of MKNK1 and renders this kinase a therapeutic target for treating cancer [Diab et al., Chem. Biol. 24;21(4):441-52, 2014]: Increased eIF4E phosphorylation predicts poor prognosis in non-small cell lung cancer patients [Yoshizawa et al., Clin Cancer Res. 16(1):240-8, 2010]. Further data point to a functional role of MKNK1 in carcinogenesis, as overexpression of constitutively active MKNK1, but not of kinase-dead MKNK1, in mouse embryo fibroblasts accelerates tumor formation [Chrestensen C. A. et al., Genes Cells 12, 1133–1140, 2007]. Moreover, increased phosphorylation and activity of MKNK proteins correlate with overexpression of HER2 in breast cancer [Chrestensen, C. A. et al., J. Biol. Chem. 282, 4243–4252, 2007]. Constitutively active, but not kinase-dead, MKNK1 also accelerated tumor growth in a model using Eμ-Myc transgenic hematopoietic stem cells to produce tumors in mice.

In summary, eIF4E phosphorylation through MKNK protein activity can promote cellular proliferation and survival and is critical for malignant transformation. Thus, developing MKNK1 inhibitors for treatment in mono- and combination therapy is a promising strategy to treat cancer and overcome cancer treatment resistance.

MKNK1 inhibitors represent valuable compounds that should complement therapeutic options not only as single agents but also in combination with other drugs, e.g. anti-hyperproliferative, cytotoxic, cytostatic and/or DNA targeting agents and radiation therapy, which are currently used as standard of care in the treatment of cancer and/or metastases thereof, particularly the standard of care drugs used for the treatment of NSCLC and/or metastases thereof.

Lung cancer is the leading cause of cancer death and the second most common cancer among both men and women in the United States. Despite considerable improvements in surgical techniques, diagnostics, there is still an acute medical need for additional therapeutic options for the treatment of lung cancer, particularly NSCLC, more particularly when treatment with standard of care drugs does not prove adequate/sufficient.

Different MKNK1 inhibitors are disclosed in, for example, WO 2012/156367, WO 2012/163942, WO 2012/175591, WO 2013/041634, WO 2013/034570, WO 2013/087581, WO 2013/144189, WO 2014/076162, WO 2013/149909, WO 2014/128093.

However, the state of the art does not disclose the combinations of the present invention comprising an inhibitor of MKNK1 kinase of general formula (I) as described herein, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same,

and an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:

- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

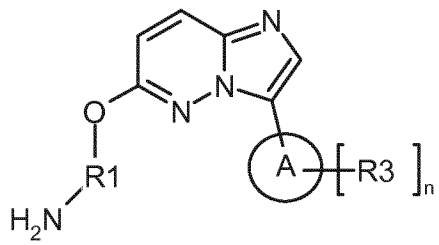
SUMMARY of the INVENTION

Surprisingly it was observed that by administering a MKNK1 kinase of general formula (I) as described herein, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same,

in combination with an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof, and pemetrexed, a significant effect on tumor growth inhibition was obtained over the respective monotherapies, particularly the combinations of the present invention have shown surprising therapeutic advantages in cancer models, which are resistant/insensitive to treatment with the standard of care drugs. Such advantages include improved anti-tumor efficacy of the combination of the present invention over the respective monotherapies, particularly when:

- standard of care drugs provide partial and/or incomplete anti-tumor response, and/or
- tumor progression/regrowth is not stopped or not delayed due to (acquired or intrinsic) resistance of the tumor to standard of care drugs.

Therefore, in accordance with a first aspect, the present invention provides combinations of at least two components, component A and component B, component A being an inhibitor of MKNK1 of general formula (I),



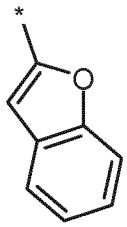
(I)

in which :

R1 represents a linear C_2-C_6-alkyl-, a linear C_1-C_6-alkyl-O-linear C_1-C_6-alkyl-, a branched C_3-C_6-alkyl-, a C_3-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_3-C_6-cycloalkyl- or a C_3-C_6-cycloalkyl-linear C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl-, aryl which is optionally substituted one or more times independently from each other with R, heteroaryl-, heteroaryl- which is optionally substituted one or more times independently from each other with R, $-C(=O)NH_2$, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', $-NH_2$, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)S(=O)R', -N(R')S(=O)R', $-N(H)S(=O)_2R'$, $-N(R')S(=O)_2R'$, -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', $-OC(=O)NH_2$, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', $-S(=O)_2R'$, $-S(=O)_2NH_2$, $-S(=O)_2NHR'$, $-S(=O)_2N(R')R''$ group ;

A represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, -C(=O)R', $-C(=O)NH_2$, -C(=O)N(H)R',-C(=O)N(R')R'', $-NH_2$, -NHR', -N(R')R'',

-N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', -S(=O)(=NR')R'' group ;

R represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

and component B being an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:

- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

The combinations comprising at least two components, component A and component B, as decribed and defined herein, are also referred to as “combinations of the present invention”.

Further, the present invention relates to :

a kit comprising a combination of :

Component A: one or more MKNK1-kinase inhibitors as described herein, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof ;

Component B : one or more anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:

- a taxane, such as docetaxel or paclitaxel; or combinations thereof, and
- pemetrexed,

and, optionally,

Component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation/composition which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with another aspect, the present invention covers the combinations as described herein for the treatment or prophylaxis of a cancer, particularly NSCLC and/or metastases thereof.

In accordance with another aspect, the present invention covers the use of such combinations as described herein for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly NSCLC and/or metastases thereof.

In accordance with another aspect, the present invention covers methods of treatment or prophylaxis of a cancer, particularly NSCLC and/or metastases thereof in a subject, comprising administering to said subject a therapeutically effective amount of a combination as described herein.

In accordance with another aspect, the present invention covers compositions containing a combination as described herein together with pharmaceutically acceptable ingredients.

In accordance with another aspect, the present invention covers a combination as described herein, for use in the treatment or prophylaxis of a cancer and/or metastases thereof, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof.

In accordance with another aspect, the present invention covers a combination as described herein, for use in the treatment or prophylaxis of a cancer and/or metastases thereof, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from pemetrexed.

In accordance with an embodiment the cancer is NSCLC and/or metastases thereof.

In accordance with an embodiment the cancer is resistant and/or insensitive to treatment with docetaxel.

In accordance with an embodiment the cancer is resistant and/or insensitive to treatment with paclitaxel.

In accordance with an embodiment the cancer is resistant and/or insensitive to treatment with pemetrexed.

In accordance with another aspect, the present invention covers the use of a combination as described herein, for the manufacture of a medicament for the treatment or prophylaxis of a cancer and/or metastases thereof, such as NSCLC

and/or metastases thereof, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from:
- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

In accordance with another aspect, the present invention covers a method of treatment or prophylaxis of a cancer and/or metastases thereof, such as NSCLC and/or metastases thereof, in a subject, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from:
- a taxane, such as docetaxel or paclitaxel, or combinations thereof,, and
- pemetrexed,

comprising administering to said subject a therapeutically effective amount of a combination as described herein.

DETAILED DESCRIPTION

A. Definitions

The terms as mentioned in the present text have preferably the following meanings :

The term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom, preferably a fluorine, chlorine, bromine or iodine atom. In accordance with an embodiment, the term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine atom. In accordance with an embodiment, the term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a chlorine atom.

The term “C_1-C_6-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl,

1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group.

The term "linear C_2-C_6-alkyl-" is to be understood as preferably meaning a linear, saturated, monovalent hydrocarbon group having 2, 3, 4, 5, or 6 carbon atoms, *e.g.* an ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl. Particularly, said group has 2, 3, 4 or 5 carbon atoms ("linear C_2-C_5-alkyl"), *e.g.* an ethyl, n-propyl, n-butyl or n-pentyl group. Alternatively, said group has 2, 3 or 4 carbon atoms ("linear C_2-C_4-alkyl"), *e.g.* an ethyl, n-propyl or n-butyl group. Alternatively, said group has 2 or 3 carbon atoms ("linear C_2-C_3-alkyl"), *e.g.* an ethyl or n-propyl group.

The term "branched C_3-C_6-alkyl-" is to be understood as preferably meaning a branched, saturated, monovalent hydrocarbon group having 3, 4, 5, or 6 carbon atoms, *e.g.* a iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 3, 4 or 5 carbon atoms ("branched C_3-C_5-alkyl"), *e.g.* an iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl. Particularly, said group has 3 or 4 carbon atoms ("branched C_3-C_4-alkyl"), *e.g.* an iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 3 carbon atoms (branched "C_3-alkyl"), *e.g.* an iso-propyl group.

The term "halo-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-

C_6-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. In accordance with an embodiment, said halogen atom is F. Said halo-C_1-C_6-alkyl group is, for example, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, or $-CH_2CF_3$. In accordance with an embodiment, said halogen atom is Cl. Said halo-C_1-C_6-alkyl group is, for example, $-CCl_3$, $-CCl_2CCl_3$, or $-CH_2CCl_3$.

The term "C_1-C_6-alkoxy" is to be understood as preferably meaning a linear, branched or cyclic, saturated, monovalent, hydrocarbon group of formula –O-alkyl, in which the term "alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, cyclo-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, cylco-butoxy pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy group is, for example, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$.

The term "C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a C_1-C_6-alkoxy group, as defined *supra*, *e.g.* methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, in which the term "C_1-C_6-alkyl" is defined *supra*, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy-C_1-C_6-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is

replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy-C_1-C_6-alkyl group is, for example, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, or $-CH_2CH_2OCH_2CF_3$.

The term "C_2-C_6-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, homoallyl, (E)-but-2-enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl, (E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl, (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl, (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl, (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl, (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl, (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl, (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-enyl, (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl, (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-

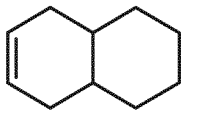
enyl, (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl, (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl, (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl, (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl, (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl, (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl, (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or allyl.

The term "C_2-C_6-alkynyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkynyl"). Said C_2-C_6-alkynyl group is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-inyl, hex-3-inyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-inyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-inyl.

The term "C_3-C_{10}-cycloalkyl" is to be understood as meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms ("C_3-C_{10}-cycloalkyl"). Said C_3-C_{10}-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, or a bicyclic hydrocarbon ring, *e.g.* a perhydropentalenylene or decalin ring. Particularly, said group has 3, 4, 5, or 6 carbon atoms ("C_3-C_6-cycloalkyl"), *e.g.*

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. Particularly, said group has 4, 5, or 6 carbon atoms ("C_4-C_6-cycloalkyl"), *e.g.* cyclobutyl, cyclopentyl, cyclohexyl.

The term "C_4-C_{10}-cycloalkenyl" is to be understood as preferably meaning a monovalent, mono-, or bicyclic hydrocarbon ring which contains 4, 5, 6, 7, 8, 9 or 10 carbon atoms and one, two, three or four double bonds, in conjugation or not, as the size of said cycloalkenyl ring allows. Said C_4-C_{10}-cycloalkenyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclobutenyl, cyclopentenyl, or cyclohexenyl or a bicyclic hydrocarbon, e.g. :



The term "3- to 10-membered heterocycloalkyl", is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NRa, in which R^a represents a hydrogen atom, or a C_1-C_6-alkyl- or halo-C_1-C_6-alkyl- group ; it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

Particularly, said 3- to 10-membered heterocycloalkyl can contain 2, 3, 4, or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "3- to 6-membered heterocycloalkyl"), more particularly said heterocycloalkyl can contain 4 or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "5- to 6-membered heterocycloalkyl").

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidinyl, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, pyrrolidinonyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, or a 6-membered ring, such as tetrahydropyranyl,

piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example. Optionally, said heterocycloalkyl can be benzo fused.

Said heterocyclyl can be bicyclic, such as, without being limited thereto, a 5,5-membered ring, e.g. a hexahydrocyclopenta[c]pyrrol-2(1H)-yl ring, or a 5,6-membered bicyclic ring, e.g. a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl ring.

As mentioned *supra*, said nitrogen atom-containing ring can be partially unsaturated, *i.e.* it can contain one or more double bonds, such as, without being limited thereto, a 2,5-dihydro-1H-pyrrolyl, 4H-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl ring, for example, or, it may be benzo-fused, such as, without being limited thereto, a dihydroisoquinolinyl ring, for example.

The term "4- to 10-membered heterocycloalkenyl", is to be understood as meaning an unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NRa, in which R^a represents a hydrogen atom, or a C_1-C_6-alkyl- or halo-C_1-C_6-alkyl- group ; it being possible for said heterocycloalkenyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom. Examples of said heterocycloalkenyl may contain one or more double bonds, *e.g.* 4H-pyranyl, 2H-pyranyl, 3H-diazirinyl, 2,5-dihydro-1H-pyrrolyl, [1,3]dioxolyl, 4H-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl group, or, it may be benzo fused.

The term "aryl" is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 9, 10, 11, 12, 13 or 14 carbon atoms (a "C_6-C_{14}-aryl" group), particularly a ring having 6 carbon atoms (a "C_6-aryl" group), *e.g.* a phenyl group; or a biphenyl group, or a ring having 9 carbon atoms (a "C_9-aryl" group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a "C_{10}-aryl" group), *e.g.* a

tetralinyl, dihydronaphthyl, or naphthyl group, or a ring having 13 carbon atoms, (a "C_{13}-aryl" group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a "C_{14}-aryl" group), *e.g.* an anthranyl group.

The term "heteroaryl" is understood as preferably meaning a monovalent, monocyclic- , bicyclic- or tricyclic aromatic ring system having 5, 6, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a "5- to 14-membered heteroaryl" group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.

In general, and unless otherwise mentioned, the heteroarylic or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylene, pyridin-3-yl, pyridin-3-ylene, pyridin-4-yl and pyridin-4-ylene; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl and thien-3-ylene.

The term "C_1-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-alkoxy", or "C_1-C_6-haloalkoxy" is to be understood as meaning a hydrocarbon group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_1-C_6" is to be interpreted as any sub-range

comprised therein, *e.g.* C_1-C_6 , C_2-C_5 , C_3-C_4 , C_1-C_2 , C_1-C_3 , C_1-C_4 , C_1-C_5 ; particularly C_1-C_2 , C_1-C_3 , C_1-C_4 , C_1-C_5, C_1-C_6; more particularly C_1-C_4 ; in the case of "C_1-C_6-haloalkyl" or "C_1-C_6-haloalkoxy" even more particularly C_1-C_2.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.* in the context of the definitions of "C_2-C_6-alkyl-", "linear C_2-C_6-alkyl-", "C_2-C_6-alkenyl" and "C_2-C_6-alkynyl", is to be understood as meaning a hydrocarbon group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6 , C_3-C_5 , C_3-C_4 , C_2-C_3 , C_2-C_4 , C_2-C_5 ; particularly C_2-C_3.

Further, as used herein, the term "C_3-C_6", as used throughout this text, *e.g.* in the context of the definition of "branched C_3-C_6-alkyl-", "C_3-C_6-cycloalkyl", is to be understood as meaning a hydrocarbon group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C_3-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_3-C_6 , C_4-C_5 , C_3-C_5 , C_3-C_4 , C_4-C_6, C_5-C_6 ; particularly C_3-C_6.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, particularly one,

two, three or four times, more particularly one, two or three times, even more particularly one or two times".

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

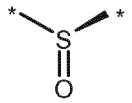
The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{129}I and ^{131}I, respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^{3}H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

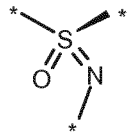
Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of this invention may contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

The compounds of the present invention may contain sulphur atoms which are asymmetric, such as an asymmetric sulphoxide or sulphoximine group, of structure:





, for example,

in which * indicates atoms to which the rest of the molecule can be bound.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

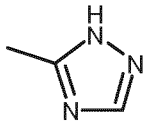
The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of

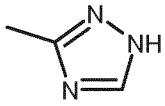
diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

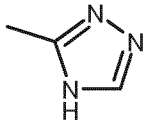
In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* R- or S- isomers, or E- or Z-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, namely :


1H-tautomer


2H-tautomer


4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term “pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention.

For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. **1977**, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

As used herein, the term "*in vivo* hydrolysable ester" is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.* pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkoxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl ; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

As defined herein the term “standard of care drug(s)” is meant to be understood a drug selected from:
- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

The term " resistant” or “insensitive” to “treatment with stardard of care drugs” is meant to define a cancer disease, particularly NSCLC, in which the treatment with a drug selected from:
- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed,

is not therapeutically effective, for failing to:
- reduce the growth of a tumor and/or metastasis thereof or even eliminate the tumor and/ or metastasis thereof,
- prevent regrowth of a tumor after initial response,
- provide for a longer survival time, and/or
- provide a longer time for tumor progression.

The resistance and/or insensitivity may be intrinsic (to the patient) or acquired.

The methods, combinations, uses and kits of the present invention cover both intrinsic and acquired resistance and/or insensitivity to standard of care drugs as defined herein.

Component A of the Combination

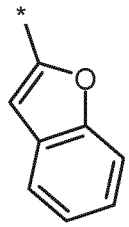
Component A can be selected from the group of MKNK1 inhibitors generically or specifically disclosed in WO 2013/034570, which are incorporated by reference herein.

In another embodiment, the component A being an inhibitor of MKNK1 is selected from the group of compounds of general formula (I) supra, wherein:

R1 represents a linear C_2-C_6-alkyl-, a linear C_1-C_6-alkyl-O-linear C_1-C_6-alkyl-, a branched C_3-C_6-alkyl-, a C_3-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_3-C_6-cycloalkyl- or a C_3-C_6-cycloalkyl-linear C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl-, aryl which is optionally substituted one or more times independently from each other with R, heteroaryl-, heteroaryl- which is optionally substituted one or more times independently from each other with R, $-C(=O)NH_2$, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', $-NH_2$, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)S(=O)R', -N(R')S(=O)R', $-N(H)S(=O)_2R'$, $-N(R')S(=O)_2R'$, -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', $-OC(=O)NH_2$, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', $-S(=O)_2R'$, $-S(=O)_2NH_2$, $-S(=O)_2NHR'$, $-S(=O)_2N(R')R''$ group ;

A represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy- group ;

R represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=$O)_2$R', -N(R')S(=$O)_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=$O)_2$R', -S(=$O)_2$$NH_2$, -S(=$O)_2$NHR', -S(=$O)_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

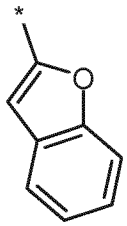
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In another embodiment, the component A being an inhibitor of MKNK1 is selected from the group of compounds of general formula (I) supra, wherein:

R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-linear C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl-, aryl which is optionally substituted one or more times independently from each other with R, heteroaryl-, heteroaryl- which is optionally substituted one or more times independently from each other with R, -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'' group ;

(A) represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy- group ;

R represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -

N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

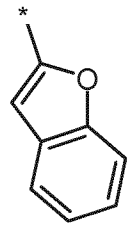
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In another embodiment, the component A being an inhibitor of MKNK1 is selected from the group of compounds of general formula (I) supra, wherein:

R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

an -NH_2, C_1-C_6-alkyl-, a C_2-C_6-alkenyl-, a C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl- group, aryl which is optionally substituted one or more times independently from each other with R, a heteroaryl-, or a heteroaryl- which is optionally substituted one or more times independently from each other with R ;

A represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy- group ;

R represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

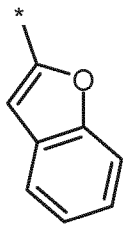
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In another embodiment, the component A being an inhibitor of MKNK1 is selected from the group of compounds of general formula (I) supra, wherein:

R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

an -NH_2, C_2-C_6-alkenyl-, a C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl, aryl which is optionally substituted one or more times independently from each other with R, a heteroaryl- group, or a heteroaryl- which is optionally substituted one or more times independently from each other with R ;

(A) represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, C_1-C_6-alkoxy- group, C_1-C_6-alkyl- group ;

R represents a substituent selected from :

a halogen atom, a C_1-C_6-haloalkyl-, C_1-C_6-alkoxy- ;

n represents an integer of 0 or 1 ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In other embodiment, said component A is a compound of general formula (I) selected from the group consisting of:
4-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}butan-1-amine ;

trans-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine ;

cis-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine ;

3-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

2-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

2-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

(2*S*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine ;

4-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}butan-1-amine ;

3-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-methylbutan-1-amine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

(2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;
4-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylbutan-2-amine ;

(2*R*)-2-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

(2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-phenylethan-amine ;

(1*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethan-amine ;

(1*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethan-amine ;

(1*S*)-2-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethanamine ;

1-(*trans*-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutyl)-methanamine ;

2-(2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethoxy)ethanamine ;

trans-3-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclobutanamine ;

(1*R*,2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclohexanamine;

(1*S*,2*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclopentanamine;

(1*S*,2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclopentanamine salt with formic acid

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-phenylpropan-1-amine salt with formic acid

1-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclobutanamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}hex-5-en-1-amine;

1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylpropan-2-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-cyclopropylethanamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(morpholin-4-yl)-propan-1-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-(tetrahydro-2*H*-pyran-4-yl)ethanamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-4-methylpentan-1-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propane-1,3-diamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-(tetrahydrofuran-3-yl)ethanamine;

trans-3-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylpropan-1-amine;

1-Cyclopropyl-2-{[3-(4-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine;

(2*R*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

(2*R*)-1-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

1-[3-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)oxetan-3-yl]methanamine;

(2*S*)-1-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

(1*S*)-2-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethanamine;

(2*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*R*)-2-{[3-(7-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*R*)-2-{[3-(5-Methyl-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*S*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-phenylpropan-2-amine;

1-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclopropan-amine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-phenylpropan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(4-fluorophenyl)-propan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(pyridin-4-yl)propan-1-amine ;

(2R)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(pyridin-3-yl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(4-fluorophenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(pyridin-2-yl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(3-isopropoxyphenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-[3-(trifluoromethyl)phenyl]ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(2,4-difluorophenyl)ethanamine ;

(1S)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(4-fluorophenyl)ethanamine ;

(1S)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(4-chlorophenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(pyridin-3-yl)ethanamine ; and

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(pyridin-3-yl)ethanamine,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In a preferred embodiment of the aspects of the present invention, said component A is (2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

In a preferred embodiment of the aspects of the present invention, said component A is (2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine, or a pharmaceutically acceptable salt thereof, or a mixture of same.

In a more preferred embodiment of the aspects of the present invention, component A is (2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine.

In other embodiment, component A is selected from the group of MKNK1 inhibitors disclosed in WO 2012/156367, WO 2012/163942, WO 2012/175591, WO 2013/041634, WO 2013/087581, WO 2013/144189, WO 2014/076162, WO 2013/149909, WO 2014/128093, which are incorporated herein by reference in their entirety.

Compounds of formula (I) as described and defined herein can be prepared according to the preparation methods contained in WO 2013/034570, which is incorporated herein by reference in its entirety.

The MKNK1-inhibitors mentioned in the prior art as well as in the lists above have been disclosed for the treatment or prophylaxis of different diseases, especially cancer.

The specific compounds of the lists as disclosed above are preferred as being component A of the combination, most preferred is the compound used in the experimental section.

The combination of the present invention is demonstrated herein with one of the MKNK1 inhibitors specifically disclosed in the Examples section, as example 13, of WO 2013/034570, referrred to as Compound A1 (or as Compd A1) below.

In another aspect a combination of the present invention comprises a compound of general formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, as described above, and a taxane, such as docetaxel or paclitaxel, or a combination thereof. Particularly, the taxane is selected from docetaxel and paclitaxel or a combination thereof. More particularly, the taxane is docetaxel or paclitaxel.

In another aspect a combination of the present invention comprises a compound of general formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, as described above, and docetaxel.

In another aspect a combination of the present invention comprises a compound of general formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, as described above, and paclitaxel.

In another aspect a combination of the present invention comprises a compound of general formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, as described above, and pemetrexed.

In addition, a combination of the present invention comprising Compound A1 or a pharmaceutically acceptable salt thereof, as mentioned above and a taxane, such as docetaxel or paclitaxel, is a preferred aspect of the invention.

Particularly preferred is a combination of the present invention comprising Compound A1 as mentioned above and docetaxel. Particularly preferred is a combination of the present invention comprising Compound A1 as mentioned above and paclitaxel.

In another aspect a combination of the present invention comprises Compound A1 or a pharmaceutically acceptable salt thereof as mentioned above and a taxane, such as docetaxel or paclitaxel, or a combination thereof.

In another aspect a combination of the present invention comprises Compound A1 or a pharmaceutically acceptable salt thereof as mentioned above and paclitaxel.

In another aspect a combination of the present invention comprises Compound A1 or a pharmaceutically acceptable salt thereof and docetaxel.

It is to be understood that the present invention relates also to any combination of the embodiments of component A described above.

In addition, a combination of the present invention comprising Compound A1 or a pharmaceutically acceptable salt thereof, as mentioned above and pemetrexed is a preferred aspect of the invention.

Component A may be administered by the oral, intravenous, topical, local installations, intraperitoneal or nasal route. In accordance with a preferred embodiment, the component A is administered by the oral route.

Component B of the Combination

Component B is an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof.

Suitable dose(s), administration regime(s) and administration route(s) for taxanes include those described in the NCCN Clinical Practice Guidelines in

Oncology (NCCN guidelines), in particular in the NCCN Guidelines for Non-Small Cell Lung Cancer version 2.2013, which are included herein by reference in its entirety.

Therefore, certain aspects of the invention as described herein provide embodiments wherein, Component B is an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from a taxane, such as docetaxel and paclitaxel, or combinations thereof.

Alternatively, Component B is an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from pemetrexed.

Therefore, certain aspects of the invention as described herein provide embodiments wherein, Component B is an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from pemetrexed.

Suitable dose(s), administration regime(s) and administration route(s) for pemetrexed include those described in the NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines), in particular in the NCCN Guidelines for Non-Small Cell Lung Cancer version 2.2013, which are included herein by reference in its entirety.

The term “cytotoxic” refers to an agent which can be administered to kill or eliminate a cancer cell. The term “cytostatic” refers to an agent which can be administered to restrain tumor proliferation rather than induce cytotoxic cytoreduction yielding an elimination of the cancer cell from the total viable cell population of the patient. The term “anti-hyperproliferative” refers to an agent which can inhibit the survival or multiplication of the tumor cells with high proliferation rate.

The chemotherapeutic agents described herein, e.g., pemetrexed, docetaxel and paclitaxel are considered cytotoxic, cytostatic agent, or anti-hyper-

proliferative agents depending on individual tumor types. These anti-hyperproliferative, cytotoxic and cytostatic agents have gained wide spread use as chemotherapeutics in the treatment of various cancer types and are well known.

Component B may be administered by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

Docetaxel is sold under the tradename Taxotere® by Sanofi-Aventis (1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}, CAS No. 114977-28-5). Docetaxel belongs to the taxanes chemotherapy drug class and is a semi-synthetic analogue of paclitaxel (Taxol®). It is an anti-mitotic chemotherapy medication that works by interfering with cell division. While not bound by a theory, the cytotoxic activity of docetaxel is believed to be exerted by promoting and stabilising microtubule assembly, while preventing physiological microtubule depolymerisation/disassembly in the absence of GTP. This leads to a significant decrease in free tubulin, needed for microtubule formation and results in inhibition of mitotic cell division between metaphase and anaphase, preventing further cancer cell progeny. Because microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell and cause initiation of apoptosis. Docetaxel is administered by intravenous injection or by other appropriate infusion techniques.

Paclitaxel is sold under the tradename Taxol® by the Bristol-Myers Squibb Company. Paclitaxel ((2α,4α,5β,7β,10β,13α)-4,10-bis(acetyloxy)-13-{[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}- 1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate – CAS No: 33069-62-4) has the empirical formula C47H51NO14 and a molecular weight of 853.9. It is highly lipophilic in water. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubles from tubulin dimers and stabilizes microtubules by preventing depolymerization. While not bound by a theory, it is believed that this stability results in the inhibition in the normal dynamic reorganization of the microtubule network that is

essential for vital interphase and mitotic cellular functions. Also, paclitaxel is believed to induce abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. Paclitaxel is administered by intravenous injection or by other appropriate infusion techniques.

Protein-bound paclitaxel (Tradename: Abraxane®) is an injectable formulation of paclitaxel, a mitotic inhibitor drug used in the treatment of breast cancer, lung cancer (NSCLC) and pancreatic cancer. In this formulation, paclitaxel is bonded to albumin as a delivery vehicle. It is also called nab-paclitaxel (with the "nab" syllable derived from "nanoparticle albumin–bound") or paclitaxel albumin-bound.

For the purpose of the present invention the term “paclitaxel” is meant to include paclitaxel and protein-bound paclitaxel.

In an embodiment of all aspects of the present invention the term “paclitaxel” means paclitaxel.

In an embodiment of all aspects of the present invention the term “paclitaxel” means protein-bound paclitaxel.

Pemetrexed [(2*S*)-2-{[4-[2-(2-amino-4-oxo-1,7-dihydropyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]amino}pentanedioic acid] is sold under the tradename Alimta® by Eli Lilly. Pemetrexed belongs to the class of chemotherapy drugs called folate antimetabolites. It works by inhibiting three enzymes used in purine and pyrimidine synthesis—thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA, which are required for the growth and survival of both normal cells and cancer cells. Pemetrexed is administered by intravenous injection or by other appropriate infusion techniques. Patients on pemetrexed therapy may take folic acid and vitamin B_{12}

supplement even if levels are normal. It may also be recommended for some patients to be administered a steroid (e.g., dexamethasone 4 mg twice daily) on the day prior, day of, and day after pemetrexed infusion.

Therefore, according to a particular embodiment, component C is folic acid and/or vitamin B_{12}.

According to another embodiment, component C is a steroid (e.g. dexamethasone 4 mg twice daily)

Pemetrexed may be used in combination with platinum compounds for the treatment of NSCLC (as described, for example, in the NCCN Guidelines for Non-Small Cell Lung Cancer version 2.2013 or in Journal of Experimental & Clinical Cancer Research201029:38, J Thorac Oncol. 2013 Oct;8(10):1308-16, Clin Lung Cancer. 2013 May;14(3):215-23, Clin Cancer Res. 2005 Jan 15;11(2 Pt 1):690-6, Semin Oncol. 2005 Apr;32(2 Suppl 2):S5-8, which are incoportated herein by reference). Carboplatin is generally preferred in view of a more favorable toxicity profile.

Therefore, according to a particular embodiment, component C is a platinum compound, such as cisplatin, carboplatin, and oxaliplatin. Preferably, the platinum compound is carboplatin.

These and other anti-hyperproliferative/cytotoxic/cytostatic agents may be administered in the conventional formulations and regimens in which they are known for use in monotherapy or in combinations thereof.

In a particular embodiment, the present invention relates to a combination of a component A with a component B, optionally with a component C, as mentioned in the Examples Section herein.

Further, the present invention relates to :

a kit comprising a combination of :

component A: one or more MKNK1-kinase inhibitors, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : one or more anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:
- a taxane, such as docetaxel or paclitaxel; or combinations thereof, and
- pemetrexed

and, optionally,

component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

Such kit can be used to treat a patient with a MKNK1 stimulated cancer as well as cancers not stimulated through MKNK1 kinase. Particularly such kit can be used to treat NSCLC and/or metastases thereof.

The term “component C” being at least one pharmaceutical agent includes the effective compound itself as well as its pharmaceutically acceptable salts, solvates, hydrates or stereoisomers as well as any composition or pharmaceutical formulation comprising such effective compound or its pharmaceutically acceptable salts, solvates, hydrates or stereoisomers. A list of such readily available agents is being provided further below.

The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

Component A is administered intravenously, intraperitoneally, preferably it is administered orally.

Component B preferably is administered by the more appropriate route within the knowledge of the skilled person. Suitable route(s) are included in NCCN Guidelines for NSCLC Version 2.2013, which is included herein by reference in its entirety.

Component C being administered as the case may be.

The term “pharmaceutically acceptable” is used synonymously to the term “physiologically acceptable”.

The term “pharmaceutically or physiologically acceptable salt" of component A refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chorine salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of a component A of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate,

methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Components of this invention can be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending

agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

Components of this invention can also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions can be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs can be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may

also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

Components of this invention can also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the component in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions can be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents

and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

Components of the invention can also be administered in the form of suppositories for rectal administration of the drug. These components can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It can be desirable or necessary to introduce a component of the present invention to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific

anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al,* "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* 1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters,

saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilized powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or

effervescent components to produce porous matrices intended for immediate release, without the need of water.

Commercial utility

Component A

The compounds of formula (I) and the stereoisomers thereof according to the combination as referred to above are components A. The compounds according to the combination have valuable pharmaceutical properties, which make them commercially utilizable. In particular, they inhibit the MKNK1 kinase and block eIF4E phosphorylation thus inducing apoptosis and suppressing proliferation. They are expected to be commercially applicable in the therapy of diseases (e.g. diseases dependent on overactivated MKNK1 or dependent on overexpression of phosphorylated eIF4E). In summary, eIF4E phosphorylation through MKNK1 protein activity can promote cellular proliferation and survival and is critical for malignant transformation. Inhibition of MKNK activity may provide a tractable cancer therapeutic approach.

Component B

Due to the mechanism as discussed above component B is especially suitable to have effects on tumor diseases.

Combination

The combinations of the present invention thus can be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof,

e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

One embodiment relates to the use of a combination as described herein (e.g. according to any one of claims 1 to 8) for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly NSCLC and/or metastases thereof.

In an embodiment the invention relates to combinations comprising component A or a pharmaceutically acceptable salt thereof and Component B being an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:
- a taxane, such as docetaxel or paclitaxel; or combinations thereof, and
- pemetrexed,
for use in the treatment of cancer indications, particularly NSCLC and/or metastases thereof.

Such cancer types include, but are not limited to, NSCLC and/or metastases thereof.

Such cancer types include, but are not limited to, advanced or recurrent NSCLC and/or metastases thereof.

In an embodiment the invention relates to a method of treatment or prophylaxis of a cancer, particularly NSCLC and/or metastases thereof, in a subject, comprising administering to said subject a therapeutically effective amount of a combination according to any one of claims 1 to 8.

Preferred uses of the combinations of the invention are for the treatment of NSCLC and/or metastases thereof.

Preferred uses of the combinations of the invention are for the treatment of advanced or recurrent NSCLC and/or metastases thereof.

In an embodiment of all aspects of the present invention the cancer is NSCLC and/or metastases thereof.

In an embodiment of all aspects of the present invention the cancer is recurrent NSCLC and/or metastases thereof.

In an embodiment of all aspects of the present invention the cancer is advanced NSCLC and/or metastases thereof.

In an embodiment of all aspects of the present invention the cancer is NSCLC and/or metastases thereof at any stage as defined in The Revised International System for Staging Lung Cancer, adopted in 2010 by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111 (6): 1710-7, 1997 ; Lung. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 253-70., which are included herein by reference in their entirety).

In an embodiment of all aspects the cancer is resistant and/or insensitive to treatment with standard of care drugs.

Techniques and methods to determine whether a cancer is resistant and/or insensitive to treatment with standard of care drugs are readily available to the skilled person, such as the methods provided in the Experimental Section of the present application. It is within the knowledge of the skilled person how to readily adapt/modify such methods to test different tumor models for the same or different indications in order to determine whether a cancer is resistant and/or insensitive to treatment with standard of care drugs. Suitable techniques include *in vitro* and *in vivo* methods.

The term "inappropriate" within the context of the present invention, in particular in the context of "inappropriate cellular immune responses, or inappropriate cellular inflammatory responses", as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

Combinations of the present invention might be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis.

This invention includes a method comprising administering to a mammal in need thereof, including a human, an amount of a component A and an amount of component B of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder.

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

neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.,* the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Combinations of the present invention might also be used for treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related

macular degeneration [AMD ; see, Lopez et al. Invest. Opththalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, combinations of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

Dose and administration

Component A

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

The total amount of the active ingredients to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day.

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

Component B

The hyper-proliferative, cytotoxic or cytostatic agent taxane, such as docetaxel or paclitaxel, or combinations thereof, can be administered to a patient at a dosage which can range from about 0.1 to about 300 mg/kg of total body weight. Also, the agents can also be administered in conventional amounts routinely used in cancer chemotherapy, particularly in NSCLC and advanced or recurrent NSCLC and/or metastases thereof.

The specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compounds employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition

thereof can be ascertained by those skilled in the art using conventional treatment tests.

Suitable dose(s), administration regime(s) and administration route(s) for taxanes, such as docetaxel or paclitaxel; or combinations thereof include those described in the NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines), in particular in the NCCN Guidelines for NSCLC Version 2.2013 which is included herein by reference in its entirety. Further, suitable dose(s), administration regime(s) and administration route(s) for taxanes, such as docetaxel or paclitaxel; or combinations thereof may be readily determined by standard techniques known to the skilled person.

The dose(s), administration regime(s) and administration route(s) may have to be adapted according to, inter alia, the indication, the indication stage, the patient age and/or the patient gender, among other factors. Such adaptations can be readily determined by standard techniques known to the skilled person.

Suitable dose(s), administration regime(s) and administration route(s) for pemetrexed include those described in the NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines), in particular in the NCCN Guidelines for NSCLC Version 2.2013 which is included herein by reference in its entirety. Further, suitable dose(s), administration regime(s) and administration route(s) for pemetrexed may be readily determined by standard techniques known to the skilled person.

The dose(s), administration regime(s) and administration route(s) may have to be adapted according to, inter alia, the indication, the indication stage, the patient age and/or the patient gender, among other factors. Such adaptations can be readily determined by standard techniques known to the skilled person.

For both the MKNK1 inhibitor of general formula (I) and the hyper-proliferative, cytotoxic or cytostatic agent, selected from a taxane, such as docetaxel or paclitaxel, or combinations thereof, and pemetrexed, the administered dosage of the compound(s) may be modified depending on any superior or unexpected results which may be obtained as routinely determined with this invention.

The hyper-proliferative, cytotoxic or cytostatic agent can be administered to a patient orally, topically, parenterally, rectally, by inhalation, and by injection. Administration by injection includes intravenous, intramuscular, subcutaneous, and parenterally as well as by infusion techniques. The agents can be administered by any of the conventional routes of administration for these compounds. The preferred route of administration for the hyper-proliferative/cytotoxic/cytostatic agents using this invention is typically by injection which is the same route of administration used for the agent alone. Any of the hyper-proliferative, cytotoxic or cytostatic agents can be administered in combination with an MKNK1 inhibitor of general formula (I) by any of the mentioned routes of administration.

For administering the MKNK1 inhibitor of general formula (I) and the hyper-proliferative/cytotoxic/cytostatic agent(s), by any of the routes of administration herein discussed, the MKNK1 inhibitor of general formula (I) can be administered simultaneously with the hyper-proliferative, cytotoxic or cytostatic agent. This can be performed by administering a single formulation which contains both the MKNK1 inhibitor of general formula (I) and the hyper-proliferative/cytotoxic/cytostatic agent or administering the MKNK1 inihibitor of general formula (I) compound and the hyperproliferative/cytotoxic/cytostatic agents in independent formulations at the same time to a patient.

Alternatively, the MKNK1 inhibitor of general formula (I) can be administered in tandem with the hyper-proliferative/cytotoxic/cytostatic agent. The MKNK1 inihbitor of general formula (I) can be administered prior to the hyper-proliferative/cytotoxic/cytostatic agent. For example, the MKNK1 inihibitor of general formula (I) can be administered once or more times per day up to 28 consecutive days, or once or more times per week up to 4 consecutive weeks followed by administration of the hyper-proliferative, cytotoxic or cytostatic agent. Also, the hyper-proliferative, cytotoxic or cytostatic agent can be administered first followed by adminstration of the MKNK1 inihibitor of general formula (I). The choice of sequence administration of the MKNK1 inihibitor of general formula (I) relative to the hyper-proliferative/cytotoxic/cytostatic agent may vary for different agents. Also, the hyper-proliferative/cytotoxic or cytostatic

agent can be administered using any regimen which is conventionally used for these agents.

In another regimen of administration, the MKNK1 inihibitor of general formula (I) and the hyper-proliferative/cytotoxic/cytostatic agent can be administered once or more times per day on the day of administration.

Any of the routes and regimens of administration may be modified depending on any superior or unexpected results which may be obtained as routinely determined with this invention.

Combinations of the present invention

The combinations of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth, more especially on NSCLC and/or metastases thereof.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The combinations of component A and component B of this invention can be administered as the sole pharmaceutical agent or in combination with one or more further pharmaceutical agents C (i.e. component C) where the resulting combination of components A, B and C causes no unacceptable adverse effects. For example, the combinations of components A and B of this invention can be combined with component C, *i.e.* one or more further pharmaceutical agents, such as known anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

Component C, can be one or more pharmaceutical agents such as 131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate,amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib , crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin,

levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan,

tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin or combinations thereof.

Alternatively, said component C can be one or more further pharmaceutical agents selected from gemcitabine, paclitaxel, oxaliplatin, cisplatin, carboplatin, sodium butyrate, 5-FU, doxirubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α-glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

Optional anti-hyper-proliferative agents which can be added as component C to the combination of components A and B of the present invention include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use as component C with the combination of components A and B of the present invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages

1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel (when component B is not itself docetaxel), erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel (when component B is not itself paclitaxel), pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use as component C with the combination of components A and B of the present invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Generally, the use of cytotoxic and/or cytostatic agents as component C in combination with a combination of components A and B of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor and/or metastasis or even eliminate the tumor and/ or metastasis as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(8) provide a longer time for tumor progression, and/or

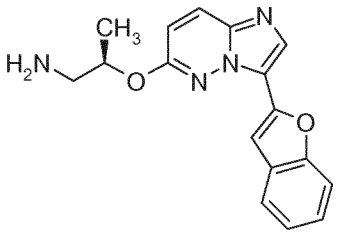
(9) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXPERIMENTAL SECTION

The schemes and procedures described in the art as cited in the present application (see introductory part) disclose general synthetic routes and specific procedures within their experimental sections to arrive at the MKNK1-compounds which are preferred components A of the present combination.

Compound A1 is a MKNK1 inhibitor as disclosed in the experimental section of WO 2013/034570 in example 13 ((2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine), which is incorporated herein by reference.



Compound A1

Component B is available from commercial sources. Alternatively Component B may be prepared using any of the methods available in the art.

Examples demonstrating monotherapy activity of component A and the effect of the combinations of components A and B of the present invention

Example 1: Compound A1 and docetaxel combination therapy demonstrates enhanced efficacy in the human A549 NSCLC xenograft model

This study was designed to determine the anti-tumor efficacy and tolerability of Compound A1 in monotherapy as well as in combination with docetaxel in the human A549 NSCLC (non-small cell lung cancer) xenograft model to test the opportunity for the combination treatment of patients with NSCLC tumors.

1. Test system, study design and methods

Female, 5-6 weeks old NMRI nu/nu mice (20-22 g) from Taconic M&B A/S (Denmark) were used for the human xenograft studies.

Experiments were initiated after an acclimatization period of at least 7 days. Animals were kept in a 12 hours light/dark cycle, food and water was available ad libitum and housing temperature was 23 °C. All animal experiments were conducted in accordance with the German animal welfare law and approved by local authorities.

A549 human colorectal adenocarcinoma cells were cultured as previously described according to ATCC protocol. Cells were harvested for transplantation in a subconfluent (70%) state. Animals were subcutaneously injected with tumor cells suspended in 50% Matrigel/50% Medium into the left inguinal region of female nude mice on day 0.

When tumors reached a predetermined size of 35-40 mm2, animals were randomized into treatment and control group (n=10 animals/group) and treatment with Compound A1 (p.o.) and/or Docetaxel (i.v.) started. Both, the oral and intravenous application volume were 10 ml/kg for mice.

Tumor response was assessed by determination of the tumor area (product of the longest diameter and its perpendicular) using a caliper. The animal body weight was monitored as a measure for treatment-related toxicity. Measurements of tumor area and body weight were performed three times weekly.

Animals were sacrificed when showing signs of toxicity (>20% body weight loss) or when tumors reached a size of approximately 120 mm². At the end of the experiment, animals were sacrificed, tumors were excised and tumor wet weights were determined. Tumors were then cut in two pieces and snap frozen in liquid nitrogen for a) PK and PD analysis or b) in vivo mode of action (pathway inhibition) analysis. Additionally, plasma was sampled for determination of unbound compound concentration/exposition.

Tumor growth inhibition is presented as T/C ratio (treatment / control) calculated with tumor areas and tumor weights at study end. Relative tumor growth inhibition based on tumor area (relative T/C) was calculated by the formula [(tumor area of treatment group at day x) - (tumor area of treatment group at day before first treatment)] / [(tumor weight vehicle group at day x) - (tumor area of vehicle group at day before first treatment)]. Furthermore, treatment responses were evaluated by means of the clinically-used RECIST criteria (complete response, partial response, stable disease and progressive disease) and response rates were calculated accordingly (RR = number of animals with complete and partial response). [Eisenhauer EA et.al. EJ;45:228-247, 2009]

Statistical analysis was assessed using GraphPad Prism 6.0 software. A one-way analysis of variance was performed and differences to the control were compared by a pair-wise comparison procedure (post hoc test; Dunnett´s multiple comparison method). Combination therapy groups were analysed by unpaired t-test to determine significance vs. the respective control/monotherapy groups.

2. Results

Compound A1 was administered at 200 mg/kg (QD, p.o.). Docetaxel was administered at 30 mg/kg, once weekly (Q7D) by intravenous (i.v.) injection. In all experimental groups, treatment was initiated when tumors were approximately 35-40 mm² in size, i.e. on day 12 after tumor cell inoculation and animal body weight and tumor size were determined three times weekly. The study was terminated when tumors in the control groups were ~120 mm2 in size, i.e. 33 days after tumor cell inoculation. At sacrifice, plasma samples and tumors were collected and final tumor weight was determined.

In this study, Compound A1 administered at 200 mg/kg (QD) resulted in significant antitumor activity with a final T/Carea of 0.63 and T/Cweight of 0.63 as compared to vehicle control. Similarly, docetaxel administered at 30 mg/kg (Q7D) resulted in significantly reduced tumor growth with a T/Cweight of 0.21. Compound A1 and docetaxel combination treatment resulted in significantly improved anti-tumor efficacy in comparison to the respective monotherapies with a final T/Cweight of 0.12 and a response rate of 50% (Figure 1 and Tables 1, 2). Overall, treatments were well tolerated. Mice in the combination therapy groups suffered from increased body weight loss (> -10%) approximately 2 weeks after treatment initiation but recovered quickly after a dose holiday of 3 days. This study demonstrates that the MKNK1 inhibitor Compound A1 clearly improves antitumor efficacy in combination with docetaxel in the KRAS mutant NSCLC xenograft model. Therefore, Compound A1 represents a strong candidate for chemotherapy combination in KRAS mutant NSCLC clinical trials and could potentiate anti-tumor efficacy and/or overcome chemotherapy resistance.

Example 2: Dose-dependent anti-tumor efficacy of Compound A1 in combination with docetaxel in the A549 human NSCLC human xenograft model

In Example 1, Compound A1 combination therapy with docetaxel was found to exhibit more potent anti-tumor efficacy than either of the respective monotherapies in A549 human NSCLC model in nude mice. In this study, the dose-dependent therapeutic effects and tolerability of Compound A1 in combination with docetaxel was assessed in the same NSCLC model.

Female, 5-6 weeks old NMRI nu/nu mice (20-22 g) from Taconic M&B A/S (Denmark) were used for the human xenograft studies.
Experiments were initiated after an acclimatization period of at least 7 days. Animals were kept in a 12 hours light/dark cycle, food and water was available ad libitum and housing temperature was 23 °C. All animal experiments were conducted in accordance with the German animal welfare law and approved by local authorities.

A549 human colorectal adenocarcinoma cells were cultured as previously described according to ATCC protocol. Cells were harvested for transplantation in a subconfluent (70%) state. Animals were subcutaneously injected with tumor cells suspended in 50% Matrigel/50% Medium into the left inguinal region of female nude mice on day 0.

When tumors reached a predetermined size of 25-30 mm2, animals were randomized into treatment and control group (n=12 animals/group) and treatment with Compound A1 (p.o.) and/or docetaxel (i.v.) started. Both, the oral and intravenous application volume were 10 ml/kg for mice.

Tumor response was assessed by determination of the tumor area (product of the longest diameter and its perpendicular) using a caliper. The animal body weight was monitored as a measure for treatment-related toxicity. Measurements of tumor area and body weight were performed three times weekly.

Animals were sacrificed when showing signs of toxicity (>20% body weight loss) or when tumors reached a size of approximately 120 mm^2. At the end of the experiment, animals were sacrificed, tumors were excised and tumor wet weights were determined. Tumors were then cut in two pieces and snap frozen in liquid nitrogen for a) PK and PD analysis or b) in vivo mode of action (pathway inhibition) analysis. Additionally, plasma was sampled for determination of unbound compound concentration/exposure.

Tumor growth inhibition is presented as T/C ratio (treatment / control) calculated with tumor areas and tumor volume. Tumor growth inhibition based on tumor area (T/C) was calculated by the formula [(tumor area of treatment group at day x)/ (tumor weight vehicle group at day x)]. Furthermore, treatment responses were evaluated by means of the clinically-used RECIST criteria (complete response, partial response, stable disease and progressive disease) and response rates were calculated accordingly (RR = number of animals with complete and partial response).

Statistical analysis was assessed using GraphPad Prism 6.0 software. A one-way analysis of variance was performed and differences to the control were compared by a pair-wise comparison procedure (post hoc test; Dunnett´s multiple comparison method). Combination therapy groups were analysed by

unpaired t-test to determine significance vs. the respective control/monotherapy groups.
(p- values: * $p<0.05$, ** $p<0.01$, ***$p<0.001$)

Compound A1 was administered at 200 mg/kg (QD, p.o.) or 100 mg/kg (BID, p.o.) and docetaxel was administered at 15 mg/kg (Q7D, i.v.). The docetaxel dose was reduced to 10 mg/kg Q7D 32 days post tumor transplantation for the remainder of the study. To analyze dose-dependent anti-tumor efficacy in combination therapies, Compound A1 was administered at 12.5, 25, 50, 100 and 200 mg/kg, QD. In all experimental groups, treatment was initiated when tumors were approximately 25-30 mm^2 in size, i.e. on day 11 after tumor cell inoculation.
Mice in the vehicle groups as well as Compound A1 monotherapy groups were sacrificed on day 39 post tumor inoculation when the control group had reached termination criteria (tumor sizes ~120 mm2). Mice treated with docetaxel were sacrificed on day 88 (docetaxel alone or in combination with Compound A1 at 12.5, 25, 50 mg/kg) or on day 105 (docetaxel in combination with Compound A1 at 100 and 200 mg/kg) post tumor cell inoculation. Treatment with Compound A1 at 200 mg/kg QD and 100 mg/kg BID resulted in significant anti-tumor activity in monotherapy with a final T/Carea of 0.45/0.53 and T/Cweight of 0.36/0.43, respectively (Tables 3,4). No significant difference in efficacy was observed between the 2 different dosing schedules (QD vs. BID). Docetaxel administered at 15/10 mg/kg (Q7D, i.v.) showed good efficacy with a T/C area of 0.28 (on day 40 post tumor inoculation) (Figure 2).
Compound A1 and docetaxel combination therapy resulted in significantly improved antitumor efficacy in comparison to the docetaxel monotherapy; with response rates of up to 25% (Table 4). A clear dose-dependent effect on tumor growth inhibition was observed in the combination therapy. Importantly, highly significant results with regard to disease stabilization over the whole study period (105 days) was observed with Compound A1 at 100 mg/kg QD and 200 mg/kg QD in combination with docetaxel. Overall, treatments were well tolerated. Animals in the high-dose combination therapy group (Compound A1 at

200 mg/kg QD + docetaxel) showed transient body weight loss ~ 10% but quickly recovered after a dose holiday of three days (see Figure 2). This study demonstrates, that the MKNK1 inhibitor Compound A1 clearly improves antitumor efficacy in combination therapy with docetaxel in a dose-dependent manner.

Example 3: Evaluation of Compound A1 in combination with docetaxel in Lu7166, Lu7187, Lu7558 and Lu7700 patient-derived NSCLC xenograft models

The anti-tumor efficacy of Compound A1 in combination with docetaxel was further evaluated in four patient-derived NSCLC xenograft models (all transplanted on nude mice). The primary human xenografts Lu7166, Lu7187, Lu7558 and Lu7700 were derived from patients with lung cancer and were used as xenotransplantation models established by the EPO Berlin-Buch GmbH.

The primary human xenografts Lu7166, Lu7187, Lu7558 and Lu7700 were derived from patients with lung cancer and were used as xenotransplantation model in immunodeficient male NMRI:nu/nu mice. The tumor model was established by the EPO Berlin-Buch GmbH [Fichtner I, et.al., Clin Cancer Res.;14(20):6456-68. Oct 15 2008]. The tumors were propagated in vivo and tumor tissue from one in vivo passage was used for s.c. implantation in the inguinal region of male nude mice. After an acclimatization time of 4 days, for the study, tumor fragments (2x2mm/mouse) from an *in vivo* passage were transplanted subcutan (s.c.) into nude mice at day 0.

After removal of the tumors from donor mice, the tumors were cut into fragments (2-3 mm diameter) and placed in RPMI 1640 culture medium until s.c. implantation. The mice were anaesthetized with Radenarkon (Etomidate). A small incision was made in the skin of right flank. The tumor fragments (one fragment/mouse) were transplanted with tweezers.

Nude-mice are routinely used for this tumor model. Usually, a tumor take rate between 80-100 % is to be expected by using the above mentioned method. Treatment was started when the tumors were approximately 0.11 cm^3 in size on day 5. At this time animals were randomly distributed to treatment and control

groups. Treatment of each animal was based on individual body weight. Body weight was determined 2x/week and all animals were checked daily for treatment-related toxicity. The decrease in body weight provides a measure of treatment-related toxicity.

Tumor diameters were measured two times weekly with a calliper. Tumor volumes were calculated according to $V = (length \times (width)^2)/2$. For calculation of the relative tumor volume (RTV) the volumes at each measurement day were related to the day of first treatment. At each measurement day the median and mean tumor volumes per group and also the treated to control (T/C) values in percent were calculated.

Groups were ended when tumor volumes reached a weight of >10% of the animal's normal body weight (typically a mean s.c. flank diameter of 17 mm in a 25 g mouse). At this time mice are sacrificed and analyzed for tumors and metastases. Plasma and tumor samples were cryoconserved. The animal experiment was performed in accordance with the UKCCCR regulations for the Welfare of Animals and of the German Animal protection Law and approved by the local responsible authorities.

Animals were randomly assigned to 4 experimental groups. At treatment initiation the ears of the animals were marked and each cage was labelled with the cage number, study number and animal number per cage.

Treatment started on day 5 after tumor implantation. The administered volume was 0.2 ml/20 g mouse body weight. Doses and schedules for Compound A1 and Docetaxel were derived from previous studies in which they were administered with similar schedules. Detailed doses and schedules are shown in the summary tables.

Individual body weights of mice were determined twice weekly and mean body weight per group was related to the initial value in percent (body weight change, BWC), see tables in appendix.

On the day of necropsy mice were sacrificed by cervical dislocation and inspected for gross organ changes and metastases. Tumors were taken and tumor weigh was determined. From all mice tumor material and plasma were cryopreserved for further investigations.

Descriptive statistics were performed on the data of tumor volume. These data are reported in tables as median values, means and standard deviations. For the comparison whether the differences in tumor volume between the groups are statistically significant, post tests following repeated-measures two-way ANOVA using the Bonferroni method were performed.

2. Results

Compound A1 and docetaxel combination therapy demonstrates enhanced efficacy in Lu7166 PDX model

In this study, the Lu7166 patient-derived tumors were found to be sensitive to Compound A1 and docetaxel treatments. Monotherapies resulted in significant tumor growth inhibition at the end of the experiment as compared to the vehicle-treated control group with final T/CVol values of 0.44 and 0.55 for docetaxel and Compound A1, respectively. Importantly, Compound A1 and docetaxel combination therapy resulted in improved anti-tumor efficacy with a final T/CVol of 0.26 (Figure 3, Tables 5,6).

In summary, in this Lu7166 tumor model, combination therapy provided improved therapeutic effects and short-term tumor stabilization. However, a slight increase in tumor growth was observed after 2-3 weeks.

Compound A1 and docetaxel combination therapy demonstrates prolonged anti-tumor efficacy in Lu7187 PDX model

In this study, the patient-derived Lu7187 tumors were found to partially respond to docetaxel but not Compound A1 monotherapy. As the tumors in the docetaxel monotherapy group initially continued to grow, the response was classified as disease progression according to the RECIST criteria.

Compound A1 and docetaxel combination provided superior tumor volume reduction over docetaxel monotherapy group in this model and temporary tumor stabilization. Surprisingly, combination treatment clearly improved responses in comparison to the docetaxel monotherapy with a final T/CVol of 0.10 vs. 0.25 (Tables 7,8),respectively, leading to a stabilization of tumor growth for 9 weeks, particularly in view of the lack of response to Compound A1 monotherapy. After

10 weeks the tumors developed resistance to Compound A1 and continued to grow (see Figure 4), but tumor volume was still inferior to the docetaxel monotherapy group, which is again surprising, particularly in view of the lack of response to Compound A1 monotherapy.

The second treatment cycle of Compound A1 and docetaxel combination therapy demonstrates efficacy in Lu7558 PDX model

In the Lu7558 lung cancer model, mice were exposed to two cycles of treatment; the first docetaxel cycle was continued for 4 treatments (Q7D, over 28 days) and Compound A1 treatment was continued until day 58.

The Lu7558 tumors were found to be sensitive to docetaxel treatment, demonstrating a significant decrease in tumor growth in comparison to the vehicle-treated control group (Figure 5). In contrast, Lu7558 tumors did not respond to Compound A1 monotherapy. Surprisingly, Compound A1 and docetaxel combination therapy provided superior tumor volume reduction over docetaxel monotherapy group in this model with a final T/CVol of 0.16 vs. 0.51 in docetaxel monotherapy and longterm tumor stabilization (Tables 9,10), particularly in view of the lack of response to Compound A1 monotherapy. Both treatments (docetaxel monotherapy and docetaxel/ Compound A1 combination) induced partial tumor regression according to the RECIST criteria. While tumors in the docetaxel only-treated mice showed tumor progression, surprisingly the tumors in the combination therapy group remained in remission as long as treatment with Compound A1 was continued, particularly in view of the lack of response to Compound A1 monotherapy.

The second treatment cycle with docetaxel and Compound A1 (from day 70 on) was effective, leading again to a partial regression of all tumors (Figure 5). However, during the second chemotherapy cycle, animals in the combination group developed clear side effects and treatments were suspended. Although, tumor regrowth was observed shortly after the treatments were stopped, there was a clear delay in this process in the docetaxel/ Compound A1 combination group, which is again surprising, particularly in view of the lack of response to Compound A1 monotherapy.

Compound A1 demonstrates minor anti-tumor efficacy compared to docetaxel in Lu7700 PDX model

In this study, the Lu7700 tumors responded well to docetaxel monotherapy and exhibited significantly reduced tumor growth and disease stabilization in comparison to tumors in the vehicle-treated control group (Figure 6, Tables 11, 12). Compound A1 monotherapy resulted in only minor effects characterized as delayed tumor growth and RECIST criteria of disease progression. The combination did not provide additive effects on tumor growth inhibition as the Lu7700 model showed very high sensitivity to the docetaxel monotherapy treatment alone.

Example 4: Evaluation of Compound A1 in combination with pemetrexed in the Lu7462 patient-derived NSCLC human xenograft model.

The anti-tumor efficacy of Compound A1 in combination with pemetrexed was evaluated in a patient-derived NSCLC xenograft model (transplanted on nude mice). The primary human xenograft Lu7462 was derived from a patient with lung cancer and was used as a subcutaneous xenotransplantation model established by the EPO Berlin-Buch GmbH.

1. Test system, study design and methods

The primary human xenograft Lu7462 is derived from a patient with lung cancer and was used as xenotransplantation model in immunodeficient female NMRI:nu/nu mice. The tumor model was established by the EPO Berlin-Buch GmbH [Fichtner I, et.al., Clin Cancer Res.;14(20):6456-68. Oct 15 2008]. The tumor was propagated in vivo and tumor tissue from one in vivo passage was used for s.c. implantation in the inguinal region of male nude mice. After an acclimatization time of 4 days, tumor fragments (2x2mm/mouse) from an in vivo passage were transplanted subcutaneously (s.c.) into female nude mice for the study (day 0): After removal of the tumors from donor mice, the tumors were cut into fragments (2-3 mm diameter) and placed in RPMI 1640 culture medium until s.c. implantation. The mice were anaesthetized with Radenarkon (Etomidate). A

small incision was made in the skin of right flank. The tumor fragments (one fragment/mouse) were transplanted with tweezers. Nude-mice are routinely used for this tumor model. Usually, a tumor take rate between 80-100 % is to be expected by using the above mentioned method.

Treatment was started when the tumors were approximately 0.11 cm^3 in size on day 19. At this time animals were randomly distributed to treatment and control groups. Treatment of each animal was based on individual body weight. Body weight was determined twice per week and all animals were checked daily for treatment-related toxicity. The decrease in body weight provides a measure of treatment-related toxicity.

Tumor diameters were measured two times weekly with a calliper. Tumor volumes were calculated according to V = (length x (width)2)/2. For calculation of the relative tumor volume (RTV) the volumes at each measurement day were related to the day of first treatment. At each measurement day the median and mean tumor volumes per group and also the treated to control (T/C) values in percent were calculated.

Groups were ended when tumor volumes reached a weight of >10% of the animal's normal body weight (typically a mean s.c. flank diameter of 17 mm in a 25 g mouse). At this time mice were sacrificed and analyzed for tumors and metastases. Plasma and tumor samples were cryoconserved.

The animal experiment was performed in accordance with the UKCCCR regulations for the Welfare of Animals and of the German Animal protection Law and approved by the local responsible authorities.

Animals were randomly assigned to the experimental groups. At treatment initiation the ears of the animals were marked and each cage was labelled with the cage number, study number and animal number per cage.

Treatment started on day 19 after tumor implantation. The administered volume was 0.2 ml/20 g mouse body weight. Doses and schedules for Compound A1 and Pemetrexed were derived from previous studies in which they were administered with similar schedules. Detailed doses and schedules are shown in the summary tables.

On the day of necropsy mice were sacrificed at 3, 7, 24h after the last treatment and inspected for gross organ changes and metastases. Tumors were taken and tumor weight was determined. From all mice tumor material and plasma were cryopreserved for further investigations.

Descriptive statistics were performed on the data of tumor volume. These data are reported in tables as median values, means and standard deviations (see appendix). For the comparison whether the differences in tumor volume between the groups are statistically significant, post tests following repeated-measures two-way ANOVA using the Bonferroni method were performed.

2. Results

Treatment with either Compound A1 or Pemetrexed resulted in an inhibition of tumor growth in comparison to the vehicle treated control group. The tumor growth inhibition was significant in comparison to the control group.

Reported final T/CVol values are 0.59 and 0.33 for Compound A1 (100 and 200 mg/kg, QD) and 0.40 for Pemetrexed (50 and 150 mg/kg, QDx7) respectively (see table 14).

Therefore, Compound A1 shows a clear dose-dependent anti-tumor activity in this tumor model. In contrast, dosing of 50 mg/kg QDx7 Pemetrexed already resulted in maximal anti-tumor activity of this chemotherapeutic agent in Lu7462 and further increased dosing of Pemetrexed (150 mg/kg QDx7) did not lead to further improved anti-tumor activity in monotherapy.

Importantly, combination therapy of Compound A1 with Pemetrexed resulted in significantly improved anti-tumor efficacy with a final T/CVol of 0.20 and 0.23 (see Figure 7, Tables 13,14).Furthermore, the combination provided tumor growth stabilization when compared to the chemotherapy single agent groups.

In summary, this study demonstrates, that Compound A1 shows good anti-tumor activity in the patient-derived NSCLC model Lu7462 and significantly improves efficacy in combination with Pemetrexed, compared to Pemetrexed alone.

Description of the Figures

Figure 1

Anti-tumor efficacy of Compound A1 in monotherapy and in combination with docetaxel in human A549 non-small cell lung cancer (NSCLC) xenograft model in mice.

A549 human NSCLC cells were implanted s.c. into nude mice on day 0. Treatment with the indicated doses was started on day 12 when tumors had reached a mean size of approximately 35-40 mm^2. Compound A1 was administered at 200 mg/kg (QD, p.o.). Tumor growth was monitored by caliper measurements three times weekly. Time course of tumor growth is shown (mean ± SD). (** equals $p < 0.01$ and *** equals $p < 0.001$)

Figure 2

Response of A549 human non-small cell lung cancer (NSCLC) xenografts to Compound A1 mono- and combination therapy with docetaxel.

A549 human NSCLC cells were implanted s.c. into nude mice on day 0. Treatment was started on day 11 when tumors had reached a size of approximately 25-30 mm^2. Compound A1 was administered orally (p.o.) upon 200 mg/kg once daily (QD) or 100 mg/kg bi-daily (2QD). In addition, combination therapy with docetaxel was tested . To evaluate dose-dependency of the combination therapy, different doses of Compound A1 (12.5, 25, 50, 100, 200 mg/kg QD) were tested in combination with a fixed dose of docetaxel (15/10 mg/kg Q7D; dose reduction from 15 to 10 at day 32). Tumor growth was monitored by determination of the tumor area using caliper measurement three times weekly. Time course of tumor growth is shown.

Figure 3

Anti-tumor efficacy of Compound A1 in comparison and in combination with docetaxel in Lu7166 human NSCLC patient-derived xenograft model in mice.

Lu7166 human NSCLC tumor fragments were implanted s.c. into male NMRI nu/nu mice on day 0. Treatment was started when the tumors were approximately 0.09 cm^3 in size on day 15. Compound A1 was administered at

200 mg/kg (QD, p.o.) and docetaxel at 12.5 mg/kg (Q7D, i.v.). Tumor growth was monitored twice weekly by caliper measurements of tumor volume. Graph represents time course of tumor growth. Mean and standard deviations are presented. Asterisks indicate statistical significance in comparison to the vehicle group (*** $p < 0.001$).

Figure 4

Anti-tumor efficacy of Compound A1 in comparison and in combination with docetaxel in Lu7187 human non-small cell lung cancer (NSCLC) patient-derived xenograft model in mice

Lu7187 human NSCLC tumor fragments were implanted s.c. into male NMRI nu/nu mice on day 0. Treatment was started when the tumors were approximately 0.12 cm^3 in size on day 20 with Compound A1 at 200 mg/kg (QD, p.o.) and on day 22 with docetaxel at 12.5 mg/kg (Q7D, i.v.). Tumor growth was monitored twice weekly by caliper measurements of tumor volume. Graph represents time course of tumor growth. Mean and standard deviations are presented.

Figure 5

Anti-tumor efficacy of Compound A1 in comparison and in combination with docetaxel in Lu7558 human non-small cell lung cancer (NSCLC) patient-derived xenograft model in mice.

Lu7558 human NSCLC tumor fragments were implanted s.c. into male NMRI nu/nu mice on day 0. Treatment was started when the tumors were approximately 0.11 cm^3 in size on day 6. Compound A1 was administered at 200 mg/kg (QD, p.o.) and docetaxel at 12.5 mg/kg (Q7D, i.v.) for four weeks. A second treatment cycle with docetaxel consisting of five consecutive once weekly administrations was initiated on day 70. Tumor growth was monitored twice weekly by caliper measurements of tumor volume. Graph represents time course of tumor growth. Mean and standard deviations are presented. Asterisks indicate statistical significance (* $p < 0.05$ on day 68 and ** $p < 0.01$ on day 140) between combination treatment and docetaxel monotherapy.

Figure 6

Anti-tumor efficacy of Compound A1 in comparison to and in combination with docetaxel in a Lu7700 human NSCLC patient-derived xenograft model.

Lu7700 human NSCLC tumor fragments were implanted s.c. into male NMRI nu/nu mice on day 0. Treatment was started when the tumors were approximately 0.11 cm^3 in size on day 8. Compound A1 was administered at 200 mg/kg once daily (QD, p.o.) and docetaxel at 12.5 mg/kg once weekly (Q7D). Tumor growth was monitored twice weekly by caliper measurements of tumor volume. Time course of tumor growth. Mean and standard deviations are presented. Asterisks indicate statistical significance when compared to the vehicle group at the end of the experiment. (* $p < 0.05$, *** $p < 0.001$).

Figure 7

Anti-tumor efficacy of Compound A1 in comparison to and in combination with Pemetrexed in a Lu7462 human NSCLC patient-derived xenograft model.

Lu7462 human NSCLC tumor fragments were implanted s.c. into female NMRI nu/nu mice on day 0. Treatment was started when the tumors were approximately 0.11 cm^3 in size on day 19. Compound A1 was administered orally at 100 or 200 mg/kg once daily (QD, p.o.) and Pemetrexed at 50 or 150 mg/kg once daily for 7 consecutive days (QDx7, i.p.). Tumor growth was monitored twice weekly by caliper measurements of tumor volume. Time course of tumor growth. Mean and standard deviations are presented. Asterisks indicate statistical significance when compared to the vehicle group or to the respective monotherapy treatment as indicated by brackets. (** $p < 0.01$, *** $p < 0.001$).

Description of Tables

Table 1

Efficacy of Compound A1 and docetaxel in the xenogeneic A549 human NSCLC mouse model. Measured data; tumor area +/-SD (referring to Figure 1).

Results tumor area

Mean

Measure	1	2	3	4	5	6	9	11	12	13
Date	02.12.2013	04.12.2013	06.12.2013	09.12.2013	11.12.2013	13.12.2013	16.12.2013	18.12.2013	20.12.2013	23.12.2013
Days after transpl.	12	14	16	19	21	23	26	28	30	33
Days after start of therapy	0	2	4	7	9	11	14	16	18	21
Vehicle 1 (PEG400:EtOH 90:10)	37,43	51,61	62,69	75,18	78,57	84,05	86,54	96,04	105,48	107,64
Vehicle 2 (0.9% NaCl)	37,69	50,83	63,89	73,66	79,97	86,73	92,39	101,41	115,46	121,81
Compound A1, 200 mg/kg, QD, p.o.	37,65	43,03	46,21	49,51	54,58	54,38	63,73	63,72	63,04	67,64
Docetaxel, 30 mg/kg, Q7D, i.v.	37,72	45,88	52,39	52,96	56,66	53,17	44,90	47,30	44,40	39,19
Compound A1, 200 mg/kg, QD, p.o. + docetaxel, 30 mg/kg, Q7D, i.v.	37,99	43,71	44,71	39,66	41,68	35,89	34,05	30,13	29,25	25,64

SD

Measure	1	2	3	4	5	6	9	11	12	13
Date	02.12.2013	04.12.2013	06.12.2013	09.12.2013	11.12.2013	13.12.2013	16.12.2013	18.12.2013	20.12.2013	23.12.2013
Days after transpl.	12	14	16	19	21	23	26	28	30	33
Days after start of therapy	0	2	4	7	9	11	14	16	18	21
Vehicle 1 (PEG400:EtOH 90:10)	6,73	10,48	12,46	15,92	16,15	14,07	18,41	15,26	25,51	29,80
Vehicle 2 (0.9% NaCl)	6,32	11,99	10,01	14,23	15,96	16,07	16,86	17,61	26,29	22,25
Compound A1, 200 mg/kg, QD, p.o.	6,25	7,84	8,98	13,12	14,61	16,19	15,95	17,93	17,65	17,00
Docetaxel, 30 mg/kg, Q7D, i.v.	6,26	8,04	4,97	6,28	7,84	4,84	4,03	6,51	7,87	7,09
Compound A1, 200 mg/kg, QD, p.o. + docetaxel, 30 mg/kg, Q7D, i.v.	6,73	10,61	7,46	7,49	8,87	9,14	9,32	7,46	6,21	6,32

Table 2

Efficacy of Compound A1 and docetaxel in the xenogeneic A549 human NSCLC mouse model. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Area[a]	Max. Body Weight Loss[b]	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle 1	Equal volume QD, p.o.	1.00	1.00	1%	0/10	0%	0	0	0	10
Vehicle 2	Equal volume QD, i.v.	1.27	1.13	1%	0/10	0%	0	0	0	10
Compound A1	200 QD, p.o.	0.63*	0.63*	1%	0/10	0%	0	0	1	9
Docetaxel	30 Q7D, i.v.	0.21*	0.36*	7%	0/10	0%	0	0	9	1
Compound A1+ Docetaxel	200, QD, p.o. 30, Q7D, i.v.	0.12*	0.24*	12%	0/10	50%	0	5	5	0

*statistically significant *vs.* vehicle control ($p < 0.05$)
a) T/C = Treatment/Control ratio, calculated from mean tumor areas or final tumor weights at study end.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response: PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Table 3

Dose-dependent efficacy of Compound A1 in combination with docetaxel in the xenogeneic A549 human NSCLC mouse model. Measured data; tumor area +/-SD (referring to Figure 2).

Results tumor area											
Mean											
Measure	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**14**	**17**
Date	**19.05.14**	**21.05.14**	**23.05.14**	**26.05.14**	**28.05.14**	**30.05.14**	**03.06.14**	**06.06.14**	**10.06.14**	**13.06.14**	**16.06.14**
Days after transpl.	**11**	**13**	**15**	**18**	**20**	**22**	**26**	**29**	**33**	**36**	**39**
Days after start of therapy	**0**	**2**	**4**	**7**	**9**	**11**	**15**	**18**	**22**	**25**	**28**
vehicles	27,87	43,65	49,65	59,04	63,60	67,18	76,44	87,24	97,55	109,51	118,79
Docetaxel, 15/10 mg/kg QW	27,09	38,58	34,35	43,39	43,81	42,71	38,88	38,20	35,28	37,95	33,65
Compd. A1 , **200 mg/kg QD**	27,68	31,22	28,20	35,45	35,92	38,89	44,27	44,86	50,16	54,43	53,13
Compd. A1 , **100 mg/kg BID**	27,35	34,31	35,13	36,50	38,44	40,76	47,13	48,72	56,23	62,63	63,13
Compd. A1 , **12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	27,87	43,50	39,20	46,13	42,64	40,10	38,72	35,61	32,68	35,31	35,13
Compd. A1 , **25 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	27,05	35,76	32,62	34,42	33,84	30,74	28,52	26,58	24,89	28,81	28,08
Compd. A1 , **50 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	27,76	35,61	34,45	32,98	35,27	30,83	29,59	25,83	25,88	25,52	27,05
Compd. A1 , **100 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	27,90	30,89	29,40	30,22	29,51	28,23	29,32	25,08	25,88	26,14	28,25
Compd. A1 , **200 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	27,76	27,58	25,42	31,75	28,23	27,76	29,08	24,95	26,60	25,59	25,99
SD											
Measure	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**14**	**17**
Date	**19.05.14**	**21.05.14**	**23.05.14**	**26.05.14**	**28.05.14**	**30.05.14**	**03.06.14**	**06.06.14**	**10.06.14**	**13.06.14**	**16.06.14**
Days after transpl.	**11**	**13**	**15**	**18**	**20**	**22**	**26**	**29**	**33**	**36**	**39**
Days after start of therapy	**0**	**2**	**4**	**7**	**9**	**11**	**15**	**18**	**22**	**25**	**28**
vehicles	2,91	5,60	7,51	9,34	13,34	14,42	16,56	23,22	25,68	28,39	30,44
Docetaxel, 15/10 mg/kg QW	2,34	6,66	8,17	6,14	8,56	8,34	7,80	6,95	9,91	9,37	8,74
Compd. A1 , **200 mg/kg QD**	3,10	5,29	5,44	5,84	6,39	8,34	11,03	11,79	14,31	15,57	15,40
Compd. A1 , **100 mg/kg BID**	2,41	5,73	6,75	9,19	8,96	8,95	11,93	14,10	18,48	18,30	18,79
Compd. A1 , **12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	4,46	9,59	11,02	13,54	12,44	13,25	13,58	12,64	13,98	12,74	13,93
Compd. A1 , **25 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	4,19	6,97	7,52	9,77	7,63	6,80	7,83	7,87	6,29	7,79	8,00
Compd. A1 , **50 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	3,95	7,72	8,95	8,43	10,11	9,75	8,11	5,92	6,27	6,78	6,95
Compd. A1 , **100 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	2,57	6,99	7,15	7,65	8,06	8,06	10,82	9,84	10,21	8,28	7,75
Compd. A1 , **200 mg/kg QD + Docetaxel, 15/10 mg/kg QW**	3,27	4,91	4,09	8,03	5,95	5,65	8,56	7,63	11,68	9,54	9,60

Results tumor area

Mean

Measure	18	19	20	21	22	23	24	25	26
Date	19.06.14	23.06.14	30.06.14	07.07.14	10.07.14	14.07.14	18.07.14	22.07.14	25.07.14
Days after transpl.	42	46	53	60	63	67	71	75	78
Days after start of therapy	31	35	42	49	52	56	60	64	67
vehicles									
Docetaxel, 15/10 mg/kg QW	31,59	31,26	35,94	44,19	49,55	55,15	57,21	63,21	69,27
Compd. A1 , 200 mg/kg QD									
Compd. A1 , 100 mg/kg BID									
Compd. A1 , 12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW	34,13	33,26	36,82	37,56	40,27	46,58	50,39	59,51	68,27
Compd. A1 , 25 mg/kg QD + Docetaxel, 15/10 mg/kg QW	27,27	26,89	29,88	30,27	33,01	39,20	42,75	43,41	44,04
Compd. A1 , 50 mg/kg QD + Docetaxel, 15/10 mg/kg QW	27,99	27,81	33,51	33,71	34,96	38,20	44,29	47,79	45,23
Compd. A1 , 100 mg/kg QD + Docetaxel, 15/10 mg/kg QW	27,99	28,16	25,80	26,35	25,92	29,38	31,33	29,58	30,00
Compd. A1 , 200 mg/kg QD + Docetaxel, 15/10 mg/kg QW	27,12	26,44	25,92	24,17	23,07	23,74	24,70	24,67	24,95

SD

Measure	18	19	20	21	22	23	24	25	26
Date	19.06.14	23.06.14	30.06.14	07.07.14	10.07.14	14.07.14	18.07.14	22.07.14	25.07.14
Days after transpl.	42	46	53	60	63	67	71	75	78
Days after start of therapy	31	35	42	49	52	56	60	64	67
vehicles									
Docetaxel, 15/10 mg/kg QW	8,80	8,26	10,45	13,40	15,28	16,48	18,11	18,03	19,88
Compd. A1 , 200 mg/kg QD									
Compd. A1 , 100 mg/kg BID									
Compd. A1 , 12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW	14,58	14,84	19,31	22,49	26,54	30,37	32,83	27,97	33,00
Compd. A1 , 25 mg/kg QD + Docetaxel, 15/10 mg/kg QW	7,29	7,37	8,08	8,10	7,42	11,84	11,05	9,65	9,27
Compd. A1 , 50 mg/kg QD + Docetaxel, 15/10 mg/kg QW	8,31	8,11	10,88	12,03	12,99	15,05	17,34	17,20	15,58
Compd. A1 , 100 mg/kg QD + Docetaxel, 15/10 mg/kg QW	8,77	8,34	9,12	8,90	9,18	8,91	9,80	10,58	9,33
Compd. A1 , 200 mg/kg QD + Docetaxel, 15/10 mg/kg QW	10,49	10,58	13,13	11,67	10,99	12,56	12,46	12,02	12,87

Results tumor area

Mean

Measure	27	28	29	30	31	32	35	36	38	39	40
Date	29.07.14	01.08.14	04.08.14	08.08.14	12.08.14	15.08.14	18.08.14	19.08.14	21.08.14		
Days after transpl.	82	85	88	92	96	99	102	103	105	0	0
Days after start of therapy	71	74	77	81	85	88	91	92	94		
vehicles											
Docetaxel, 15/10 mg/kg QW	75,66	78,77	77,74								
Compd. A1 , 200 mg/kg QD											
Compd. A1 , 100 mg/kg BID											
Compd. A1 , 12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW	71,77	79,30	82,38								
Compd. A1 , 25 mg/kg QD + Docetaxel, 15/10 mg/kg QW	45,44	45,55	45,95								
Compd. A1 , 50 mg/kg QD + Docetaxel, 15/10 mg/kg QW	47,57	50,34	50,54								
Compd. A1 , 100 mg/kg QD + Docetaxel, 15/10 mg/kg QW	30,76	29,98	30,70	41,27	39,62	43,95		38,56	43,51		
Compd. A1 , 200 mg/kg QD + Docetaxel, 15/10 mg/kg QW	24,89	26,47	24,50	26,88	25,10	29,36		29,10	28,60		

SD

Measure	27	28	29	30	31	32	35	36	38	39	40
Date	29.07.14	01.08.14	04.08.14	08.08.14	12.08.14	15.08.14	18.08.14	19.08.14	21.08.14		
Days after transpl.	82	85	88	92	96	99	102	103	105	0	0
Days after start of therapy	71	74	77	81	85	88	91	92	94		
vehicles											
Docetaxel, 15/10 mg/kg QW	24,35	26,46	27,70								
Compd. A1 , 200 mg/kg QD											
Compd. A1 , 100 mg/kg BID											
Compd. A1 , 12.5 mg/kg QD + Docetaxel, 15/10 mg/kg QW	36,92	40,80	44,49								
Compd. A1 , 25 mg/kg QD + Docetaxel, 15/10 mg/kg QW	9,25	11,03	8,82								
Compd. A1 , 50 mg/kg QD + Docetaxel, 15/10 mg/kg QW	17,98	19,42	20,68								
Compd. A1 , 100 mg/kg QD + Docetaxel, 15/10 mg/kg QW	10,11	11,46	11,86	12,88	15,97	19,87		21,16	33,47		
Compd. A1 , 200 mg/kg QD + Docetaxel, 15/10 mg/kg QW	12,07	12,71	11,78	15,15	13,90	18,40		17,03	19,67		

Table 4

Dose-dependent efficacy of Compound A1 in combination with docetaxel in the xenogeneic A549 human NSCLC mouse model. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Area[a]	Max. Body Weight Loss[b]	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle 1 + Vehicle 2	Equal volumes QD, p.o. + Q7D i.v.	1.00	1.00	2%	0/12	0%	0	0	0	12
Vehicle 1 + Docetaxel	QD, p.o. 15 mg, Q7D i.v.	n.d.	0.28*	1%	0/12	0%	0	0	6	6
Compound A1 +Vehicle 2	200, QD p.o. Q7D i.v.	0.36*	0.45*	6%	0/12	8%	0	1	0	11
Compound A1 +Vehicle 2	100, QD p.o. Q7D i.v.	0.43*	0.53*	5%	1/12	0%	0	0	0	12
Compound A1 + Docetaxel	12.5, QD p.o. 15, Q7D i.v.	n.d.	0.30*	3%	2/12	17%	0	2	4	6
Compound A1 + Docetaxel	25, QD p.o. 15, Q7D i.v.	n.d.	0.24*	7%	0/12	8%	0	1	11	0
Compound A1 + Docetaxel	50, QD p.o. 15, Q7D i.v.	n.d.	0.23*	4%	2/12	17%	0	2	9	1
Compound A1 + Docetaxel	100, QD p.o. 15, Q7D i.v.	n.d.	0.24*	7%	4/12	17%	0	2	8	2
Compound A1 + Docetaxel	200, QD p.o. 15, Q7D i.v.	n.d.	0.22*	11%	1/12	25%	0	3	4	5

*statistically significant *vs.* vehicle control ($p < 0.05$)
n.d.= not determined (groups were terminated on a different day than the vehicle group)
a) T/C = Treatment/Control ratio, calculated from mean tumor areas on day 39 or final tumor weights at sacrifice.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response: PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Table 5

Efficacy of Compound A1 and docetaxel in Lu7166 human NSCLC patient-derived xenograft model in mice. Measured data; tumor volume +/-SD (referring to Figure 3).

Group A=vehicle control; Group B=Compound A1, Group C=Docetaxel, Group D=Compound A1+Docetaxel

	Meas.		1	2	3	4	5	6	7	8
	Date:		9.1.14	13.1.14	16.1.14	20.1.14	23.1.14	27.1.14	30.1.14	4.2.14
Group	Day:		15	19	22	26	29	33	36	41
A	(n)		10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,091	0,225	0,308	0,475	0,583	0,807	0,924	1,216
		Mean	0,092	0,212	0,288	0,471	0,602	0,869	1,038	1,287
		[S.D.]	0,0221	0,0740	0,0990	0,1792	0,2377	0,4423	0,5871	0,8239
	RTV	Median	1,0000	2,4	3,1	4,7	6,5	9,2	10,7	12,6
		Mean	1,0000	2,3	3,1	5,0	6,5	9,4	11,2	13,8
	Meas.		Gr. B M1	Gr. B M2	Gr. B M3	Gr. B M4	Gr. B M5	Gr. B M6	Gr. B M7	Gr. B M8
B	(n)		10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,093	0,123	0,186	0,234	0,366	0,489	0,624	0,577
		Mean	0,092	0,159	0,242	0,324	0,426	0,533	0,691	0,705
		[S.D.]	0,0223	0,0872	0,1509	0,1861	0,2276	0,2862	0,4015	0,3909
	RTV	Median	1,0000	1,6	2,5	3,0	4,4	5,9	7,4	7,9
		Mean	1,0000	1,7	2,6	3,5	4,6	5,8	7,5	7,8
	T/C [%]		99,9	75,3	84,1	68,8	70,8	61,3	66,6	54,8
	Meas.		Gr. C M1	Gr. C M2	Gr. C M3	Gr. C M4	Gr. C M5	Gr. C M6	Gr. C M7	Gr. C M8
C	(n)		10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,089	0,138	0,201	0,265	0,365	0,391	0,470	0,582
		Mean	0,093	0,141	0,185	0,237	0,285	0,347	0,435	0,566
		[S.D.]	0,0217	0,0624	0,0856	0,1116	0,1548	0,2016	0,2610	0,3586
	RTV	Median	1,0000	1,6	2,1	2,3	3,2	3,5	4,5	5,3
		Mean	1,0000	1,6	2,0	2,6	3,0	3,7	4,6	6,1
	T/C [%]		101,6	66,7	64,2	50,3	47,4	39,9	41,9	44,0
	Meas.		Gr. D M1	Gr. D M2	Gr. D M3	Gr. D M4	Gr. D M5	Gr. D M6	Gr. D M7	Gr. D M8
D	(n)		10	10	10	10	10	10	10	10
	Tumor Volume	Median	0,088	0,142	0,163	0,164	0,169	0,196	0,301	0,349
	[cm³]	Mean	0,094	0,140	0,151	0,155	0,154	0,203	0,263	0,340
		[S.D.]	0,0215	0,0457	0,0483	0,0488	0,0638	0,1253	0,1626	0,2065
	RTV	Median	1,0000	1,5	1,7	1,8	1,9	2,0	3,1	3,7
		Mean	1,0000	1,5	1,6	1,7	1,7	2,3	2,9	3,8
	T/C [%]		102,5	66,3	52,4	32,9	25,6	23,4	25,4	26,5

Table 6

Efficacy of Compound A1 and docetaxel in Lu7166 human NSCLC patient-derived xenograft model in mice. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Vol[a]	Max. Body Weight Loss[b] (%)	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle	Equal volume QD, p.o.	1.00	1.00	1	0/10	0%	0	0	0	10
Compound A1	200 QD, p.o.	0.47	0.55*	9	0/10	0%	0	0	0	10
Docetaxel	12.5 Q7Dx4, i.v.	0.46	0.44*	6	0/10	10%	0	1	0	9
Compound A1 + docetaxel	200 QD, p.o. + 12.5 Q7Dx4, i.v.	0.25	0.26*	18	0/10	0%	0	0	2	8

*statistically significant *vs.* vehicle control ($p < 0.05$)
a) T/C = Treatment/Control ratio, calculated from mean tumor volumes or tumor weights at study end.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response: PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Table 7

Efficacy of Compound A1 and docetaxel in Lu7187 human NSCLC patient-derived xenograft model in mice. Measured data; tumor volume +/- SD (referring to Figure 4).

Group A=vehicle control; Group B=Compound A1, Group C=Docetaxel, Group D=Compound A1+Docetaxel

	Meas.		1	2	3	4	5	6	7	8	9	10
	Date:		4.2.14	6.2.14	10.2.14	13.2.14	17.2.14	19.2.14	21.2.14	24.2.14	27.2.14	3.3.14
Group	Day:		20	22	26	29	33	35	37	40	43	47
A	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,155	0,176	0,309	0,335	0,401	0,411	0,615	0,609	0,733	0,844
		Mean	0,122	0,156	0,301	0,359	0,466	0,541	0,587	0,676	0,802	0,966
		[S.D.]	0,0627	0,0904	0,2063	0,2658	0,3397	0,4100	0,3872	0,4995	0,5989	0,7178
	RTV	Median	1,0	1,2	2,0	2,4	2,9	3,3	4,1	3,9	5,0	6,4
		Mean	1,0	1,3	2,2	2,6	3,4	4,0	4,4	4,9	5,8	7,0
	Meas.		Gr. B M1	Gr. B M2	Gr. B M3	Gr. B M4	Gr. B M5	Gr. B M6	Gr. B M7	Gr. B M8	Gr. B M9	Gr. B M10
B	(n)		10	10	10	10	10	10	10	10	9	9
	Tumor Volume [cm³]	Median	0,095	0,170	0,308	0,346	0,501	0,576	0,767	0,876	0,738	0,816
		Mean	0,130	0,209	0,278	0,334	0,429	0,508	0,661	0,762	0,748	0,820
		[S.D.]	0,0952	0,1427	0,2029	0,2550	0,3124	0,3778	0,4664	0,5408	0,6245	0,6396
	RTV	Median	1,0	1,6	1,9	2,4	3,2	3,8	4,8	5,5	6,3	6,6
		Mean	1,0	1,8	2,2	2,6	3,5	4,1	5,5	6,5	6,7	7,6
	T/C [%]		106,3	134,2	92,5	93,2	92,0	94,0	112,6	112,6	93,3	84,9
	Meas.		Gr. C M1	Gr. C M2	Gr. C M3	Gr. C M4	Gr. C M5	Gr. C M6	Gr. C M7	Gr. C M8	Gr. C M9	Gr. C M10
C	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,138	0,163	0,244	0,268	0,295	0,313	0,327	0,260	0,237	0,233
		Mean	0,136	0,173	0,280	0,341	0,328	0,359	0,348	0,325	0,323	0,246
		[S.D.]	0,0442	0,1238	0,2169	0,2930	0,2527	0,2959	0,2529	0,2770	0,3156	0,1867
	RTV	Median	1,0	1,4	2,1	2,6	2,6	2,6	2,7	2,1	1,7	1,9
		Mean	1,0	1,2	2,0	2,4	2,4	2,7	2,6	2,4	2,4	1,9
	T/C [%]		110,7	111,2	93,1	95,1	70,4	66,3	59,3	48,0	40,3	25,4
	Meas.		Gr. D M1	Gr. D M2	Gr. D M3	Gr. D M4	Gr. D M5	Gr. D M6	Gr. D M7	Gr. D M8	Gr. D M9	Gr. D M10
D	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume	Median	0,097	0,117	0,153	0,147	0,162	0,137	0,134	0,107	0,095	0,093
	[cm³]	Mean	0,122	0,170	0,242	0,240	0,233	0,255	0,266	0,237	0,178	0,167
		[S.D.]	0,0907	0,1430	0,2564	0,2630	0,2433	0,2829	0,3053	0,2762	0,2045	0,1875
	RTV	Median	1,0	1,5	1,7	1,5	1,6	1,6	1,7	1,7	1,0	1,0
		Mean	1,0	1,4	1,6	1,5	1,6	1,7	1,7	1,6	1,2	1,1
	T/C [%]		99,4	108,8	80,4	67,0	50,0	47,1	45,4	35,0	22,2	17,2

	Meas.		11	12	13	14	15	16
	Date:		6.3.14	10.3.14	13.3.14	17.3.14	20.3.14	24.3.14
Group	Day:		50	54	57	61	64	68
A	(n)		10	10				
	Tumor Volume [cm³]	Median	0,947	1,108				
		Mean	1,066	1,230				
		[S.D.]	0,8256	0,9195				
	RTV	Median	7,4	8,8				
		Mean	7,6	9,0				
	Meas.		Gr. B M11	Gr. B M12	Gr. B M13	Gr. B M14	Gr. B M15	Gr. B M16
B	(n)		9	9				
	Tumor Volume [cm³]	Median	0,877	0,813				
		Mean	0,942	0,898				
		[S.D.]	0,7495	0,7113				
	RTV	Median	8,1	6,7				
		Mean	8,7	8,8				
	T/C [%]		88,4	73,0				
	Meas.		Gr. C M11	Gr. C M12	Gr. C M13	Gr. C M14	Gr. C M15	Gr. C M16
C	(n)		10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,219	0,244	0,304	0,447	0,498	0,614
		Mean	0,255	0,302	0,380	0,546	0,562	0,713
		[S.D.]	0,2438	0,3043	0,3953	0,5658	0,5348	0,6594
	RTV	Median	1,8	2,0	2,5	3,3	4,0	5,2
		Mean	2,0	2,3	2,9	4,1	4,3	5,4
	T/C [%]		23,9	24,5				
	Meas.		Gr. D M11	Gr. D M12	Gr. D M13	Gr. D M14	Gr. D M15	Gr. D M16
D	(n)		10	10	10	10	10	10
	Tumor Volume	Median	0,075	0,077	0,053	0,053	0,049	0,056
	[cm³]	Mean	0,134	0,123	0,133	0,203	0,255	0,361
		[S.D.]	0,1396	0,1310	0,1866	0,3126	0,4030	0,5856
	RTV	Median	1,1	0,8	0,7	0,6	0,7	1,2
		Mean	1,0	1,0	1,0	1,5	1,9	2,6
	T/C [%]		12,6	10,0				

Table 8

Efficacy of Compound A1 and docetaxel in Lu7187 human NSCLC patient-derived xenograft model in mice. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Vol[a]	Max. Body Weight Loss[b] (%)	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle	Equal volume QD, p.o.	1.00	1.00	1%	0/10	0%	0	0	0	10
Compound A1	200 QD, p.o.	0.79	0.73	14%	1/10	10%	0	1	0	9
Docetaxel	12.5 Q7Dx4, i.v.	n.d.	0.25	11%	1/10	20% 20%	1 1	1 1	2 0	6 8
Compound A1 + Docetaxel	200 QD p.o. 12.5 Q7Dx4, i.v.	n.d.	0.10	20%	0/10	50% 40%	0 0	5 4	2 1	3 5

* n.d.= not determined (groups were terminated on a different day than the vehicle group)
a) T/C = Treatment/Control ratio, calculated from mean tumor volumes on day 54 or final tumor weights at sacrifice.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response as measured on day 54 (upper row) and 68 (lower row): PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Table 9

Efficacy of Compound A1 and docetaxel in Lu7558 human NSCLC patient-derived xenograft model in mice. Measured data; tumor volume +/-SD (referring to Figure 5).

Group A=vehicle control; Group B=Compound A1, Group C=Docetaxel, Group D=Compound A1+Docetaxel

	Meas.		1	2	3	4	5	6	7	8	9	10
	Date:		20.1.14	23.1.14	27.1.14	30.1.14	4.2.14	6.2.14	10.2.14	13.2.14	17.2.14	20.2.14
Group	Day:		5	8	12	15	20	22	26	29	33	36
A	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,107	0,120	0,098	0,085	0,062	0,073	0,095	0,082	0,077	0,100
		Mean	0,110	0,115	0,097	0,091	0,070	0,078	0,118	0,114	0,111	0,132
		[S.D.]	0,0236	0,0356	0,0284	0,0330	0,0209	0,0432	0,0909	0,0893	0,1089	0,1290
	RTV	Median	1,0	1,0	0,9	0,8	0,6	0,7	0,9	1,0	0,7	0,9
		Mean	1,0	1,0	0,9	0,8	0,7	0,7	1,1	1,1	1,1	1,3
	Meas.		Gr. B M1	Gr. B M2	Gr. B M3	Gr. B M4	Gr. B M5	Gr. B M6	Gr. B M7	Gr. B M8	Gr. B M9	Gr. B M10
B	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,121	0,098	0,070	0,063	0,069	0,066	0,072	0,078	0,106	0,130
		Mean	0,111	0,101	0,073	0,071	0,062	0,068	0,082	0,087	0,108	0,128
		[S.D.]	0,0196	0,0234	0,0220	0,0191	0,0219	0,0251	0,0305	0,0401	0,0520	0,0591
	RTV	Median	1,0	0,9	0,7	0,6	0,6	0,6	0,7	0,7	1,0	1,2
		Mean	1,0	0,9	0,7	0,7	0,6	0,6	0,8	0,8	1,0	1,2
	T/C [%]		101,4	88,0	75,4	78,4	88,3	88,0	69,9	76,9	97,0	96,8
	Meas.		Gr. C M1	Gr. C M2	Gr. C M3	Gr. C M4	Gr. C M5	Gr. C M6	Gr. C M7	Gr. C M8	Gr. C M9	Gr. C M10
C	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,107	0,118	0,085	0,091	0,061	0,058	0,066	0,050	0,084	0,070
		Mean	0,112	0,118	0,085	0,089	0,060	0,062	0,069	0,052	0,082	0,076
		[S.D.]	0,0207	0,0208	0,0225	0,0266	0,0194	0,0138	0,0189	0,0318	0,0391	0,0279
	RTV	Median	1,0	1,0	0,9	0,9	0,6	0,6	0,6	0,5	0,7	0,6
		Mean	1,0	1,1	0,8	0,8	0,5	0,6	0,6	0,5	0,8	0,7
	T/C [%]		102,1	102,2	87,4	97,8	85,3	79,5	58,7	45,8	74,1	57,5
	Meas.		Gr. D M1	Gr. D M2	Gr. D M3	Gr. D M4	Gr. D M5	Gr. D M6	Gr. D M7	Gr. D M8	Gr. D M9	Gr. D M10
D	(n)		10	10	9	9	9	9	9	9	9	9
	Tumor Volume	Median	0,109	0,081	0,053	0,056	0,044	0,056	0,056	0,042	0,042	0,032
	[cm³]	Mean	0,112	0,085	0,063	0,062	0,049	0,052	0,063	0,047	0,042	0,035
		[S.D.]	0,0202	0,0203	0,0220	0,0213	0,0179	0,0096	0,0243	0,0209	0,0147	0,0162
	RTV	Median	1,0	0,8	0,5	0,5	0,4	0,5	0,5	0,3	0,4	0,3
		Mean	1,0	0,8	0,6	0,6	0,4	0,5	0,6	0,4	0,4	0,3
	T/C [%]		102,3	74,2	64,6	68,8	69,1	67,6	53,6	41,5	38,2	26,6

	Meas.		11	12	13	14	15	16	17	18	19	20
	Date:		24.2.14	27.2.14	3.3.14	6.3.14	10.3.14	13.3.14	17.3.14	20.3.14	24.3.14	27.3.14
Group	Day:		40	43	47	50	54	57	61	64	68	71
A	(n)		10	10	10	10	10	10	10	10	10	
	Tumor Volume [cm³]	Median	0,102	0,118	0,151	0,181	0,198	0,224	0,285	0,373	0,402	
		Mean	0,145	0,168	0,196	0,203	0,250	0,268	0,351	0,429	0,464	
		[S.D.]	0,1362	0,1743	0,1962	0,1556	0,2232	0,2186	0,2864	0,3004	0,3257	
	RTV	Median	0,9	1,0	1,3	1,7	1,8	1,9	2,6	3,5	3,4	
		Mean	1,4	1,6	1,8	1,9	2,3	2,5	3,4	4,0	4,3	
	Meas.		Gr. B M11	Gr. B M12	Gr. B M13	Gr. B M14	Gr. B M15	Gr. B M16	Gr. B M17	Gr. B M18	Gr. B M19	Gr. B M20
B	(n)		9	9	9	9	9	9	9	9	9	
	Tumor Volume [cm³]	Median	0,138	0,140	0,214	0,271	0,330	0,304	0,424	0,557	0,663	
		Mean	0,139	0,148	0,205	0,221	0,266	0,304	0,392	0,516	0,594	
		[S.D.]	0,0847	0,0826	0,1134	0,1361	0,1613	0,1736	0,2300	0,2519	0,3509	
	RTV	Median	1,1	1,3	1,9	2,3	2,7	2,9	3,6	5,2	5,4	
		Mean	1,3	1,4	1,9	2,1	2,5	2,9	3,7	5,0	5,6	
	T/C [%]		96,0	88,1	104,6	108,9	106,4	113,4	111,7	120,1	128,1	
	Meas.		Gr. C M11	Gr. C M12	Gr. C M13	Gr. C M14	Gr. C M15	Gr. C M16	Gr. C M17	Gr. C M18	Gr. C M19	Gr. C M20
C	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,060	0,051	0,085	0,086	0,114	0,128	0,186	0,208	0,243	0,254
		Mean	0,065	0,062	0,089	0,089	0,123	0,149	0,193	0,221	0,236	0,263
		[S.D.]	0,0370	0,0381	0,0549	0,0581	0,0825	0,0896	0,1336	0,1386	0,1549	0,1749
	RTV	Median	0,6	0,6	0,8	0,8	1,1	1,2	1,7	2,0	2,0	2,1
		Mean	0,6	0,6	0,9	0,8	1,1	1,4	1,9	2,1	2,3	2,5
	T/C [%]		45,0	36,7	45,5	43,7	49,2	55,5	55,1	51,4	50,9	
	Meas.		Gr. D M11	Gr. D M12	Gr. D M13	Gr. D M14	Gr. D M15	Gr. D M16	Gr. D M17	Gr. D M18	Gr. D M19	Gr. D M20
D	(n)		9	9	9	8	8	8	8	8	8	8
	Tumor Volume	Median	0,032	0,025	0,036	0,011	0,033	0,039	0,048	0,075	0,086	0,068
	[cm³]	Mean	0,035	0,029	0,037	0,018	0,033	0,040	0,051	0,071	0,075	0,073
		[S.D.]	0,0186	0,0205	0,0302	0,0175	0,0295	0,0328	0,0457	0,0545	0,0544	0,0623
	RTV	Median	0,3	0,3	0,4	0,1	0,4	0,4	0,5	0,7	0,7	0,7
		Mean	0,3	0,3	0,3	0,2	0,3	0,4	0,5	0,7	0,7	0,7
	T/C [%]		23,9	17,2	19,0	8,7	13,1	14,8	14,6	16,6	16,2	

	Meas.		21	22	23	24	25	26	27	28	29	30
	Date:		31.3.14	3.4.14	7.4.14	11.4.14	14.4.14	17.4.14	22.4.14	25.4.14	28.4.14	30.4.14
Group	Day:		75	78	82	86	89	92	97	100	103	105
A	(n)											
	Tumor Volume [cm³]	Median										
		Mean										
		[S.D.]										
	RTV	Median										
		Mean										
	Meas.		Gr. B M21	Gr. B M22	Gr. B M23	Gr. B M24	Gr. B M25	Gr. B M26	Gr. B M27	Gr. B M28	Gr. B M29	Gr. B M30
B	(n)											
	Tumor Volume [cm³]	Median										
		Mean										
		[S.D.]										
	RTV	Median										
		Mean										
	T/C [%]											
	Meas.		Gr. C M21	Gr. C M22	Gr. C M23	Gr. C M24	Gr. C M25	Gr. C M26	Gr. C M27	Gr. C M28	Gr. C M29	Gr. C M30
C	(n)		10	10	10	10	10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,286	0,267	0,344	0,405	0,407	0,468	0,431	0,442	0,378	0,345
		Mean	0,266	0,263	0,347	0,373	0,385	0,444	0,444	0,421	0,352	0,374
		[S.D.]	0,1602	0,1760	0,2323	0,2449	0,2590	0,2748	0,3027	0,2580	0,2227	0,2770
	RTV	Median	2,5	2,4	2,9	3,6	3,2	4,3	4,0	4,1	3,0	2,7
		Mean	2,5	2,5	3,3	3,5	3,7	4,2	4,2	4,0	3,4	3,6
	T/C [%]											
D	Meas.		Gr. D M21	Gr. D M22	Gr. D M23	Gr. D M24	Gr. D M25	Gr. D M26	Gr. D M27	Gr. D M28	Gr. D M29	Gr. D M30
	(n)		8	8	8	8	8	8	8	8	8	8
	Tumor Volume	Median	0,091	0,071	0,085	0,095	0,107	0,101	0,106	0,104	0,082	0,049
	[cm³]	Mean	0,083	0,070	0,087	0,088	0,104	0,100	0,110	0,106	0,100	0,094
		[S.D.]	0,0692	0,0592	0,0731	0,0653	0,0852	0,0775	0,0879	0,0815	0,0867	0,1044
	RTV	Median	0,7	0,6	0,6	0,8	0,9	0,9	0,9	1,1	0,7	0,4
		Mean	0,8	0,6	0,8	0,9	1,0	1,0	1,0	1,2	1,0	1,0
	T/C [%]											

	Meas.		31	32	33	34	35	36
	Date:		5.5.14	8.5.14	15.5.14	22.5.14	29.5.14	4.6.14
Group	Day:		110	113	120	127	134	140
A	(n)							
	Tumor Volume [cm³]	Median						
		Mean						
		[S.D.]						
	RTV	Median						
		Mean						
	Meas.		Gr. B M31	Gr. B M32	Gr. B M33	Gr. B M34	Gr. B M35	Gr. B M36
B	(n)							
	Tumor Volume [cm³]	Median						
		Mean						
		[S.D.]						
	RTV	Median						
		Mean						
	T/C [%]							
	Meas.		Gr. C M31	Gr. C M32	Gr. C M33	Gr. C M34	Gr. C M35	Gr. C M36
C	(n)		10	10	10	10	10	10
	Tumor Volume [cm³]	Median	0,307	0,347	0,374	0,428	0,518	0,561
		Mean	0,342	0,391	0,470	0,487	0,604	0,646
		[S.D.]	0,2534	0,2805	0,3680	0,3275	0,4229	0,4572
	RTV	Median	2,7	2,9	3,5	3,5	4,7	5,0
		Mean	3,3	3,8	4,5	4,7	5,8	6,3
	T/C [%]							
	Meas.		Gr. D M31	Gr. D M32	Gr. D M33	Gr. D M34	Gr. D M35	Gr. D M36
D	(n)		8	8	8	8	8	8
	Tumor Volume	Median	0,051	0,062	0,059	0,059	0,066	0,066
	[cm³]	Mean	0,080	0,084	0,089	0,093	0,113	0,140
		[S.D.]	0,0857	0,0866	0,1006	0,1020	0,1262	0,1754
	RTV	Median	0,6	0,5	0,5	0,6	0,7	0,6
		Mean	0,7	0,8	0,8	0,9	1,0	1,3
	T/C [%]							

Table 10

Efficacy of Compound A1 and docetaxel in Lu7558 human NSCLC patient-derived xenograft model in mice. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Vol[a]	Max. Body Weight Loss[b] (%)	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle	Equal volume QD, p.o.	1.00	1.00	0%	0/10	0%	0	0	1	9
Compound A1	200 QD, p.o.	1.38	1.28	8%	1/10	10%	0	1	0	9
Docetaxel	12.5 Q7Dx4, i.v.	n.d.	0.51	0%	0/10	20% 0%	0 0	2 0	1 1	7 9
Compound A1 + Docetaxel	200 QD, p.o. 12.5 Q7Dx4, i.v.	n.d.	0.16	20%	2/10	40% 40%	1 1	3 3	2 2	4 4

n.d.= not determined (groups were on a different day than the vehicle group)
a) T/C = Treatment/Control ratio, calculated from mean tumor volumes on day 68 or final tumor weights at sacrifice.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response as measured on day 68 (upper row) and 140 (lower row):
PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Table 11

Efficacy of Compound A1 and docetaxel in Lu7700 human NSCLC patient-derived xenograft model in mice. Measured data; tumor volume +/-SD (referring to Figure 6).

Group A=vehicle control; Group B=Compound A1, Group C=Docetaxel, Group D=Compound A1+Docetaxel

	Meas.		1	2	3	4	5
	Date:		2.1.14	6.1.14	9.1.14	13.1.14	16.1.14
Group	Day:		8	12	15	19	22
A	(n)		10	10	10	10	10
	Tumor Volume [cm³]	Median	0,109	0,257	0,512	0,670	0,857
		Mean	0,115	0,239	0,469	0,667	0,853
		[S.D.]	0,0257	0,0962	0,2093	0,3542	0,5094
	RTV	Median	1,0000	2,1	4,2	5,7	7,3
		Mean	1,0000	2,0	4,0	5,7	7,3
	Meas.		Gr. B M1	Gr. B M2	Gr. B M3	Gr. B M4	Gr. B M5
B	(n)		10	10	9	8	8
	Tumor Volume [cm³]	Median	0,114	0,164	0,181	0,260	0,340
		Mean	0,112	0,191	0,285	0,428	0,536
		[S.D.]	0,0287	0,1084	0,2163	0,3707	0,4438
	RTV	Median	1,0000	1,5	2,1	2,9	4,1
		Mean	1,0000	1,7	2,4	3,6	4,6
	T/C [%]		97,4	79,8	60,7	64,1	62,8
	Meas.		Gr. C M1	Gr. C M2	Gr. C M3	Gr. C M4	Gr. C M5
C	(n)		10	10	10	10	10
	Tumor Volume [cm³]	Median	0,118	0,158	0,103	0,072	0,089
		Mean	0,114	0,159	0,126	0,086	0,100
		[S.D.]	0,0218	0,0399	0,0581	0,0428	0,0625
	RTV	Median	1,0000	1,4	1,0	0,9	0,8
		Mean	1,0000	1,4	1,1	0,7	0,9
	T/C [%]		99,6	66,6	26,8	12,9	11,7
	Meas.		Gr. D M1	Gr. D M2	Gr. D M3	Gr. D M4	Gr. D M5
D	(n)		10	10	10	10	10
	Tumor Volume	Median	0,108	0,156	0,190	0,169	0,174
	[cm³]	Mean	0,111	0,167	0,224	0,226	0,226
		[S.D.]	0,0363	0,0767	0,1456	0,1735	0,2006
	RTV	Median	1,0000	1,8	1,9	1,6	1,6
		Mean	1,0000	1,5	2,1	2,1	2,1
	T/C [%]		96,3	70,0	47,7	33,8	26,5

Table 12

Efficacy of Compound A1 and docetaxel in Lu7700 human NSCLC patient-derived xenograft model in mice. Data summary of in vivo study.

Compound	Dose [mg/kg] Schedule	T/C Weight[a]	T/C Vol[a]	Max. Body Weight Loss[b] (%)	Fatal Tox[c]	Response Rate[d]	CR	PR	SD	PD
Vehicle	Equal volume QD, p.o.	1.00	1.00	0%	0/10	0%	0	0	0	10
Compound A1	200 QD, p.o.	0.71	0.63*	9%	2/10	0%	0	0	1	9
Docetaxel	12.5 Q7Dx4, i.v.	0.07	0.12*	0%	0/10	30%	0	3	4	2
Compound A1 + Docetaxel	200 QD, p.o. + 12.5 Q7Dx4, i.v.	0.17	0.26*	9%	0/10	10%	0	1	3	6

*statistically significant *vs.* vehicle control ($p < 0.05$)
a) T/C = Treatment/Control ratio, calculated from mean tumor volumes or final tumor weights at study end.
b) Body Weight Loss: The maximum mean body weight loss expressed as a percentage of the animal weight at the start of the study. Weight loss greater than 20% is considered toxic.
c) Tox: Death or sacrifice due to reaching sacrificing criteria.
d) Response: PD = progressive disease, the number of tumors exhibiting >20% tumor growth;
SD = stable disease, the number of tumors exhibiting <30% tumor shrinkage and <20% tumor growth;
PR = partial response, the number of tumors exhibiting >30% tumor shrinkage;
CR = complete response, the number of non-measureable tumors.

Conclusions:

To evaluate the potential of Compound A1 for combination with chemotherapy we initiated preclinical testing together with docetaxel, one of the mainstays of cancer therapies. Compound A1 has shown additive effects in combination with docetaxel, in several cell-line derived as well as patient-derived NSCLC xenograft in vivo models leading to partial response or stable disease, and significant delay in tumor progression during re-growth phase.

In more detail, there was a varied response to docetaxel and Compound A1 combination in patient-derived NSCLC xenograft (PDX) models resulting in either partial response (model Lu7558), stable disease (Lu7187 and Lu7166) and significant delay in tumor progression during re-growth phase (Lu7558 xenograft model). In some PDX models, it is possible that the docetaxel-mediated tumor growth inhibition was already maximal and any significantly improved therapeutic effects with Compound A1 were therefore not likely to be achieved (see figure 1, figure 3 and figure 6).

Surprisingly, in models where docetaxel monotherapy provided partial and/or incomplete anti-tumor response, the combination Compound A1 with docetaxel provided improved therapeutic efficacy (e.g. increased tumor growth inhibition over the respective monotherapies) and/or delayed/stopped tumor regrowth/progression, particularly since the tumor did not respond to Compound A1 monotherapy at the maximum tolerated dose (MTD) (see figure 4).

Surprisingly, in models where docetaxel could not stop and/or delay tumor progression/regrowth due to (acquired or intrinsic) resistance of the tumor to docetaxel, the combination Compound A1 with docetaxel provided improved therapeutic efficacy (e.g. increased tumor growth inhibition over the respective monotherapies) and/or delayed/stopped tumor regrowth/progression, particularly since the tumor did not respond to Compound A1 monotherapy at MTD (see figure 5).

In addition, therapeutic combination potential of compound A1 with Pemetrexed, another standard of care chemotherapeutic agent approved for NSCLC treatment, was evaluated. Monotherapy as well as combination treatment of Compound A1 and Pemetrexed were tested in the patient-derived NSCLC xenograft (PDX) model Lu7462 (see figure 7). This tumor model shows moderate response to Compound A1 or Pemetrexed monotherapy treatment respectively.

In contrast, combination therapy of Compound A1 and pemetrexed resulted in a significantly improved therapeutic benefit and clear tumor regrowth delay as compared to the respective monotherapies.

Taken together the substantial effects observed in the *in vivo* PDX and tumor xenograft models support Compound A1 as a strong candidate for combination therapy with taxanes, particularly with docetaxel, or with pemetrexed, which may potentiate anti-tumor efficacy and/or overcome chemotherapy resistance.

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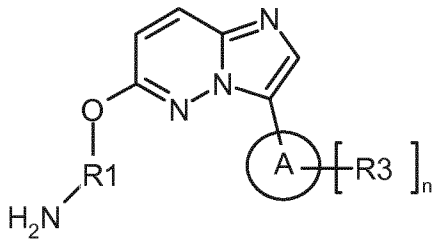
CLAIMS

1. Combination of at least two components, component A and component B, comprising a component A being an inhibitor of MKNK1 of general formula (I),



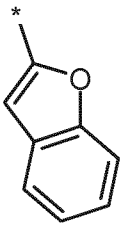
(I)

in which :

R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-linear C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl-, aryl which is optionally substituted one or more times independently from each other with R, heteroaryl-, heteroaryl- which is optionally substituted one or more times independently from each other with R, -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'' group ;

A represents a :


group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy- group ;

R represents a substituent selected from :
a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same, and component B being an anti-hyperproliferative, cytotoxic and/or cytostatic agent selected from:

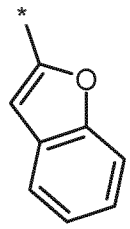
- a taxane, such as docetaxel or paclitaxel, or combinations thereof, and
- pemetrexed.

2. The combination according to claim 1, wherein component A is an inhibitor of MKNK1 of general formula (I), in which:

R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-C_1-C_6-alkyl- group which is optionally substituted, one or more times, independently from each other, with a substituent selected from :

an $-NH_2$, C_1-C_6-alkyl-, a C_2-C_6-alkenyl-, a C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl- group, aryl which is optionally substituted one or more times independently from each other with R, a heteroaryl-, or a heteroaryl- which is optionally substituted one or more times independently from each other with R ;

A represents a :



group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy- group ;

R represents a substituent selected from :
a halogen atom, a -CN, C_1-C_6-alkyl-, C_1-C_6-haloalkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, C_3-C_{10}-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R', -C(=O)NH_2, -C(=O)N(H)R',-C(=O)N(R')R'', -C(=O)OR', -NH_2, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH_2, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH_2, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -NO_2, -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)$_2$R', -N(R')S(=O)$_2$R', -N=S(=O)(R')R'', -OH, C_1-C_6-alkoxy-, C_1-C_6-haloalkoxy-, -OC(=O)R', -OC(=O)NH_2, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C_1-C_6-alkyl-S-, -S(=O)R', -S(=O)$_2$R', -S(=O)$_2$$NH_2$, -S(=O)$_2$NHR', -S(=O)$_2$N(R')R'', - S(=O)(=NR')R''group ;

R' and R'' represent, independently from each other, a substituent selected from :

C_1-C_6-alkyl-, C_1-C_6-haloalkyl- ;

n represents an integer of 0, 1, 2, 3, 4 or 5 ;

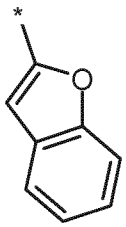
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

3. The combination according to claim 1 or 2, wherein component A is an inhibitor of MKNK1 of general formula (I), in which :
R1 represents a linear C_2-C_5-alkyl-, a linear C_1-C_5-alkyl-O-linear C_1-C_5-alkyl-, a branched C_3-C_5-alkyl-, a C_4-C_6-cycloalkyl, a linear C_1-C_6-alkyl-C_4-C_6-cycloalkyl- or a C_4-C_6-cycloalkyl-C_1-C_6-alkyl- group which is optionally

substituted, one or more times, independently from each other, with a substituent selected from :

an $-NH_2$, C_2-C_6-alkenyl-, a C_3-C_{10}-cycloalkyl- which is optionally connected as spiro, a 3- to 10-membered heterocycloalkyl which is optionally connected as spiro, aryl, aryl which is optionally substituted one or more times independently from each other with R, a heteroaryl- group, or a heteroaryl- which is optionally substituted one or more times independently from each other with R ;


represents a :


group ;

wherein * indicates the point of attachment of said group with the rest of the molecule ; and

R3 represents a substituent selected from :

a halogen atom, C_1-C_6-alkoxy- group, C_1-C_6-alkyl- group ;

R represents a substituent selected from :

a halogen atom, a C_1-C_6-haloalkyl-, C_1-C_6-alkoxy- ;

n represents an integer of 0 or 1 ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

4. The combination according to any of claims 1 to 3, wherein the component A is a compound selected from the group consisting of :

4-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}butan-1-amine ;

trans-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine ;

cis-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine ;

3-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

2-{[3-(4-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

2-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

(2*S*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine ;

4-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}butan-1-amine ;

3-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-methylbutan-1-amine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

(2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

4-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylbutan-2-amine ;

(2*R*)-2-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

(2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-phenylethan-amine ;

(1*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethan-amine ;

(1*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethan-amine ;

(1*S*)-2-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethanamine ;

1-(*trans*-3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutyl)-methanamine ;

2-(2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethoxy)ethan-amine ;

trans-3-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclo-butanamine ;

(1*R*,2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclohexan-amine;

(1*S*,2*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclopentan-amine;

(1*S*,2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclopentan-amine salt with formic acid

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-phenylpropan-1-amine salt with formic acid

1-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclobutan-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}hex-5-en-1-amine;

1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylpropan-2-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-cyclopropylethan-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(morpholin-4-yl)-propan-1-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-(tetrahydro-2*H*-pyran-4-yl)ethanamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-4-methylpentan-1-amine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propane-1,3-diamine;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-(tetrahydrofuran-3-yl)ethanamine;

trans-3-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

trans-3-{[3-(5-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}cyclobutanamine;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-methylpropan-1-amine;

1-Cyclopropyl-2-{[3-(4-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine;

(2*R*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

(2*R*)-1-{[3-(5-Chloro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

1-[3-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)oxetan-3-yl]methanamine;

(2*S*)-1-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-2-amine;

(1*S*)-2-{[3-(4-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-1-phenylethanamine;

(2*S*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*R*)-2-{[3-(7-Fluoro-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*R*)-2-{[3-(5-Methyl-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine;

(2*S*)-1-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-phenylpropan-2-amine;

1-({[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}methyl)cyclopropanamine ;

3-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-2-phenylpropan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(4-fluorophenyl)-propan-1-amine ;

2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-3-(pyridin-4-yl)propan-1-amine ;

(2R)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(pyridin-3-yl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(4-fluorophenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(pyridin-2-yl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(3-isopropoxyphenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-[3-(trifluoromethyl)phenyl]ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-(2,4-difluorophenyl)ethanamine ;

(1S)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(4-fluorophenyl)ethanamine ;

(1S)-2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(4-chlorophenyl)ethanamine ;

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(pyridin-3-yl)ethanamine ; and

2-{[3-(1-benzofuran-2-yl)imidazo[1,2-b]pyridazin-6-yl]oxy}-1-(pyridin-3-yl)ethanamine,
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

5. The combination according to any of claims 1 to 4, wherein the component A is (2*R*)-2-{[3-(1-Benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a pharmaceutically acceptable salt, or a mixture of same.

6. The combination according to any of claims 1 to 5, wherein component B is docetaxel.

7. The combination according to any of claims 1 to 5, wherein component B is paclitaxel.

8. The combination according to any of claims 1 to 5, wherein component B is pemetrexed.

9. The combination according to any of claims 1 to 8, for use in the treatment or prophylaxis of a cancer and/or metastases thereof.

10. The combination according to any of claims 1 to 9, for use in the treatment or prophylaxis of NSCLC and/or metastases thereof.

11. Use of a combination according to any of claims 1 to 8 for the preparation of a medicament for the treatment or prophylaxis of a cancer, such as NSCLC and/or metastases thereof.

12. A method of treatment or prophylaxis of a cancer, such as NSCLC, and/or metastases thereof, in a subject, comprising administering to said subject a therapeutically effective amount of a combination according to any of claims 1 to 8.

13. A kit comprising a combination according to any of claims 1 to 8, and, optionally, one or more further pharmaceutical agents C; in which optionally both or either of said compound of general formula (I) and anti-hyperproliferative, cytotoxic and/or cytostatic agent are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

14. A composition containing a combination according to any of claims 1 to 8 together with pharmaceutically acceptable ingredients.

15. The combination according to any of claims 1 to 8, for use in the treatment or prophylaxis of a cancer and/or metastases thereof, wherein said cancer is resistant and/or insensitive to treatment with standard of care drugs selected from:

- a taxane, such as docetaxel or paclitaxel; or combinations thereof, and
- pemetrexed.

16. The combination according to claim 15, wherein the cancer is NSCLC and/or metastases thereof.

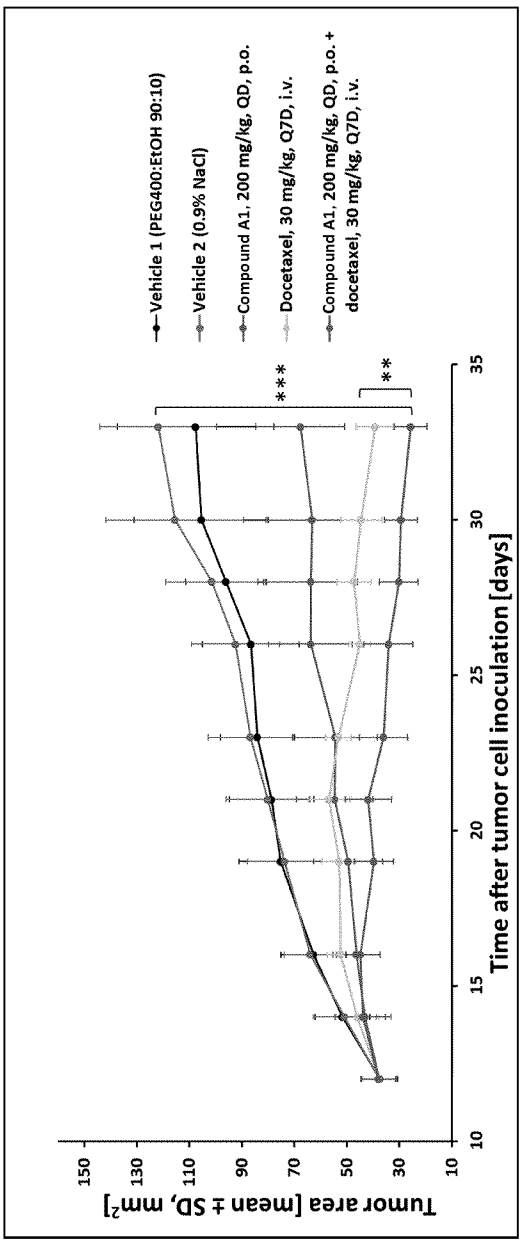

Vehicle 1 (PEG400:EtOH 90:10)
Vehicle 2 (0.9% NaCl)
Compound A1, 200 mg/kg, QD, p.o.
Docetaxel, 30 mg/kg, Q7D, i.v.
Compound A1, 200 mg/kg, QD, p.o. + docetaxel, 30 mg/kg, Q7D, i.v.
***
**
Tumor area [mean ± SD, mm²]
Time after tumor cell inoculation [days]
10
30
50
70
90
110
130
150
10
15
20
25
30
35

Figure 1

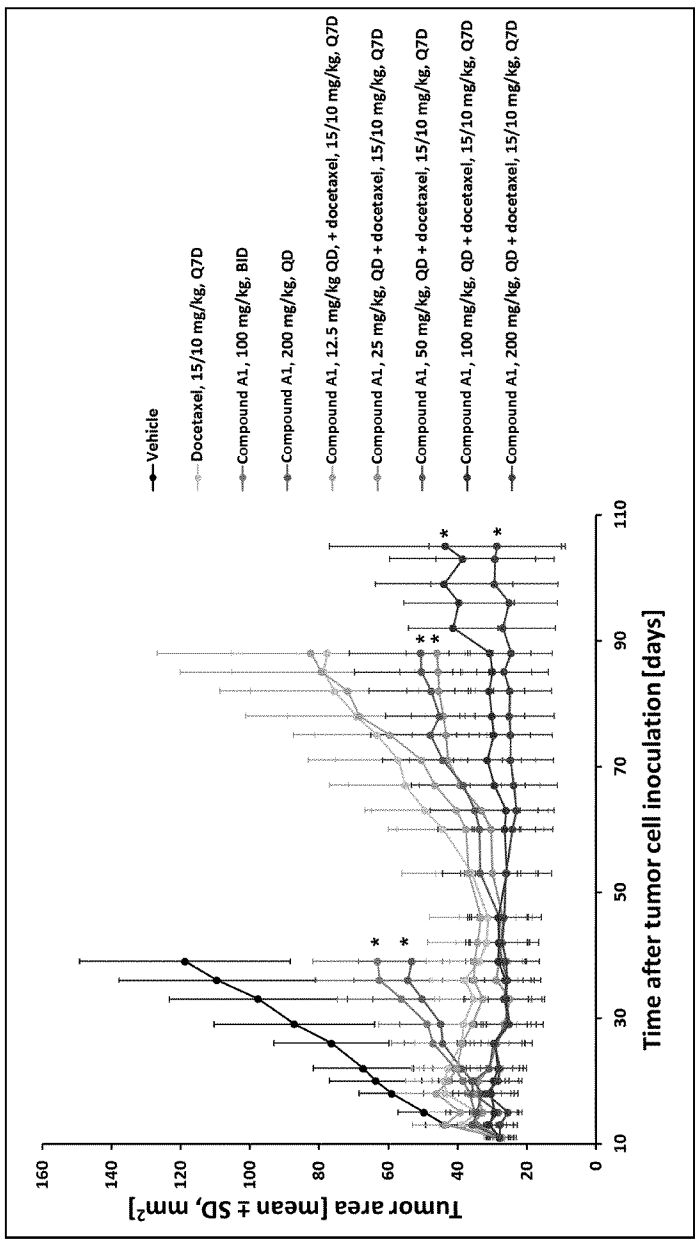

Vehicle
Docetaxel, 15/10 mg/kg, Q7D
Compound A1, 100 mg/kg, BID
Compound A1, 200 mg/kg, QD
Compound A1, 12.5 mg/kg QD, + docetaxel, 15/10 mg/kg, Q7D
Compound A1, 25 mg/kg, QD + docetaxel, 15/10 mg/kg, Q7D
Compound A1, 50 mg/kg, QD + docetaxel, 15/10 mg/kg, Q7D
Compound A1, 100 mg/kg, QD + docetaxel, 15/10 mg/kg, Q7D
Compound A1, 200 mg/kg, QD + docetaxel, 15/10 mg/kg, Q7D
Tumor area [mean ± SD, mm²]
Time after tumor cell inoculation [days]
0
20
40
60
80
100
120
140
160
10
30
50
70
90
110
*

Figure 2

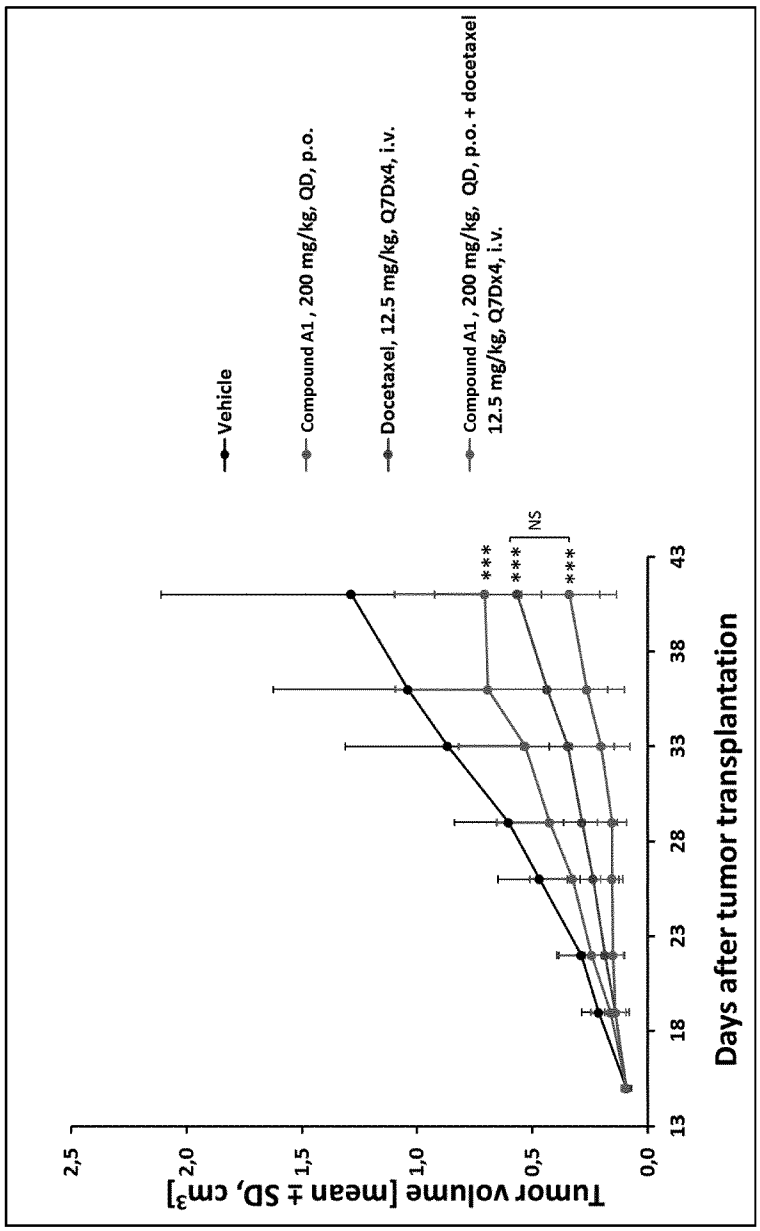

Vehicle
Compound A1 , 200 mg/kg, QD, p.o.
Docetaxel, 12.5 mg/kg, Q7Dx4, i.v.
Compound A1 , 200 mg/kg, QD, p.o. + docetaxel 12.5 mg/kg, Q7Dx4, i.v.
***
***
***
NS
Tumor volume [mean + SD, cm³]
2,5
2,0
1,5
1,0
0,5
0,0
13
18
23
28
33
38
43
Days after tumor transplantation

Figure 3

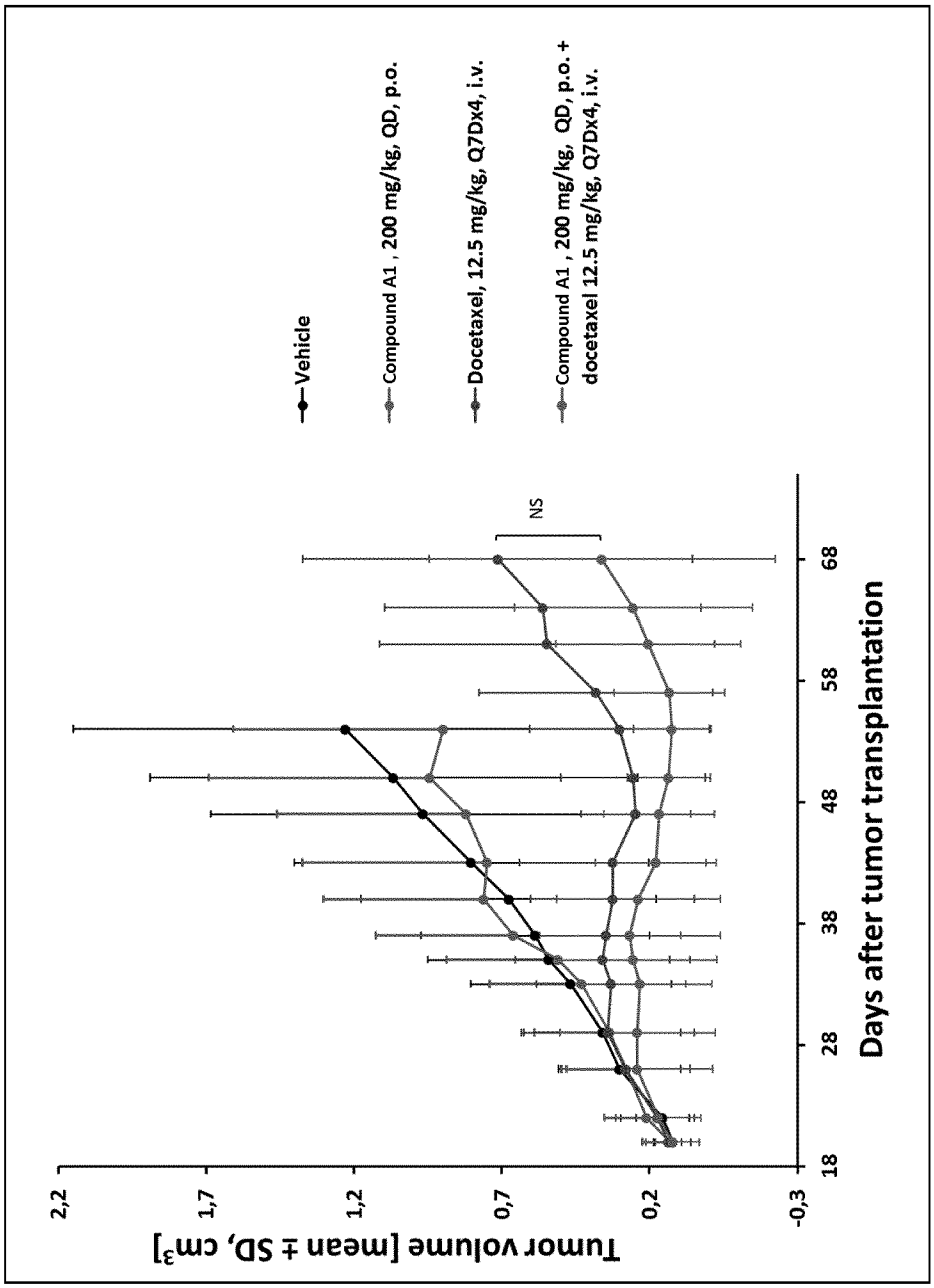

Tumor volume [mean ± SD, cm³]
2,2
1,7
1,2
0,7
0,2
-0,3
18
28
38
48
58
68
Days after tumor transplantation
NS
Vehicle
Compound A1 , 200 mg/kg, QD, p.o.
Docetaxel, 12.5 mg/kg, Q7Dx4, i.v.
Compound A1 , 200 mg/kg, QD, p.o. + docetaxel 12.5 mg/kg, Q7Dx4, i.v.

Figure 4

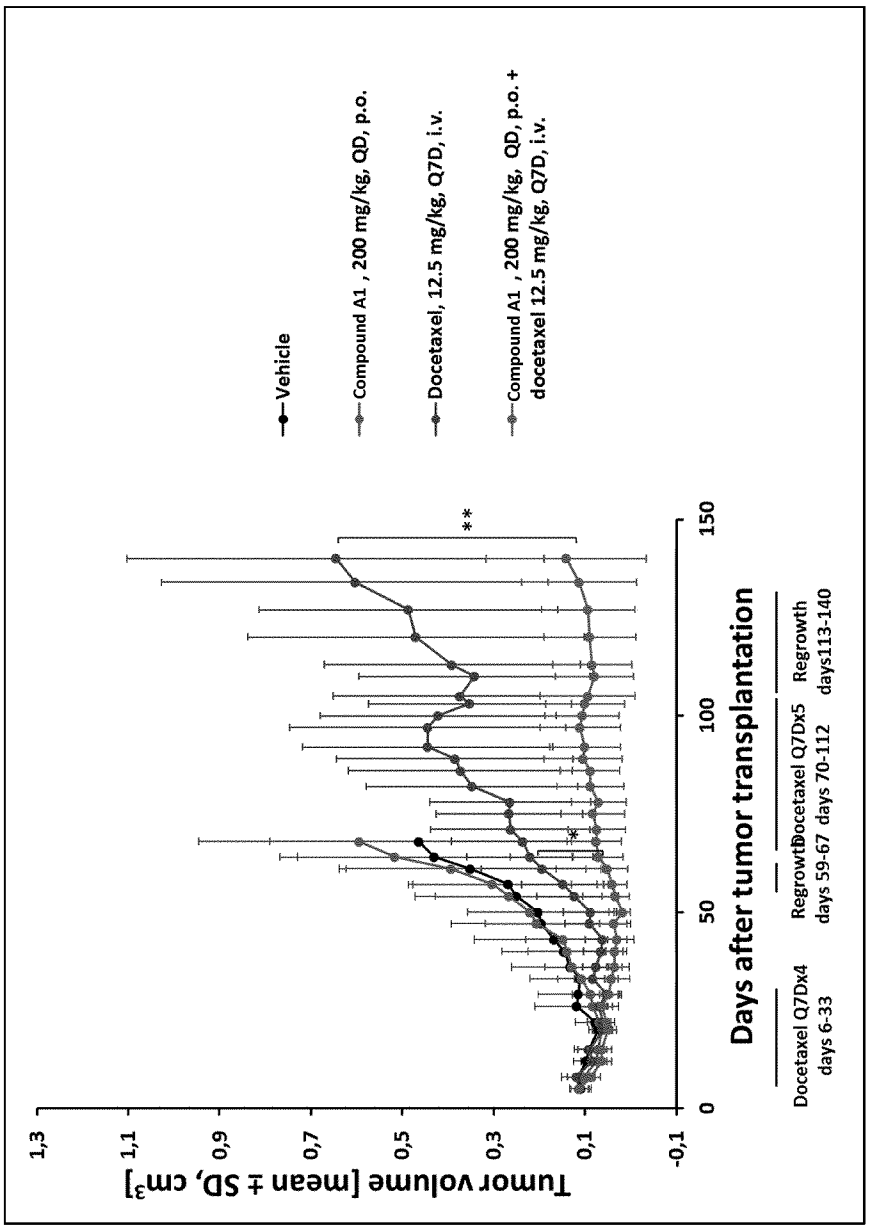

Tumor volume [mean ± SD, cm³]
1,3
1,1
0,9
0,7
0,5
0,3
0,1
-0,1
0
50
100
150
Days after tumor transplantation
Vehicle
Compound A1 , 200 mg/kg, QD, p.o.
Docetaxel, 12.5 mg/kg, Q7D, i.v.
Compound A1 , 200 mg/kg, QD, p.o. + docetaxel 12.5 mg/kg, Q7D, i.v.
**
*
Docetaxel Q7Dx4 days 6-33
Regrowth days 59-67
Docetaxel Q7Dx5 days 70-112
Regrowth days113-140

Figure 5

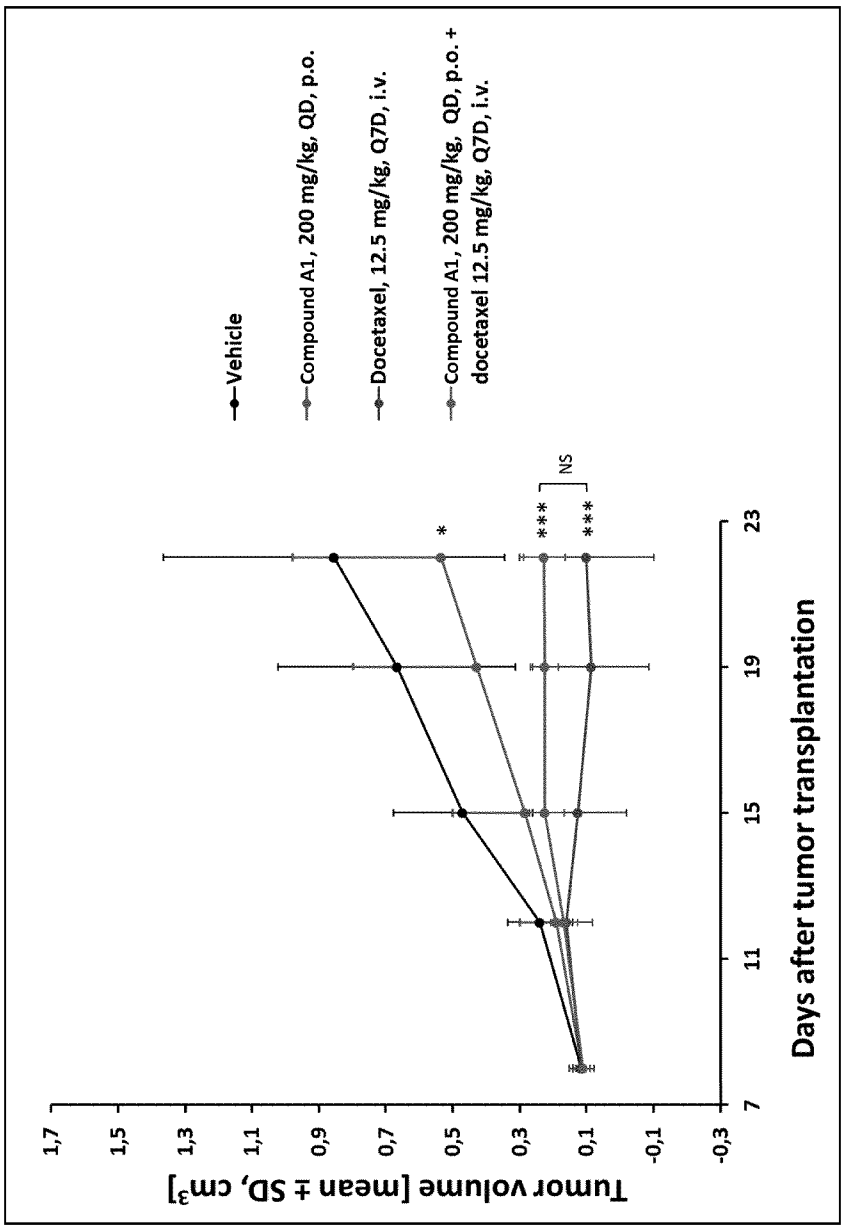

Tumor volume [mean ± SD, cm³]
1,7
1,5
1,3
1,1
0,9
0,7
0,5
0,3
0,1
-0,1
-0,3
7
11
15
19
23
Days after tumor transplantation
Vehicle
Compound A1, 200 mg/kg, QD, p.o.
Docetaxel, 12.5 mg/kg, Q7D, i.v.
Compound A1, 200 mg/kg, QD, p.o. + docetaxel 12.5 mg/kg, Q7D, i.v.
*
***
***
NS

Figure 6

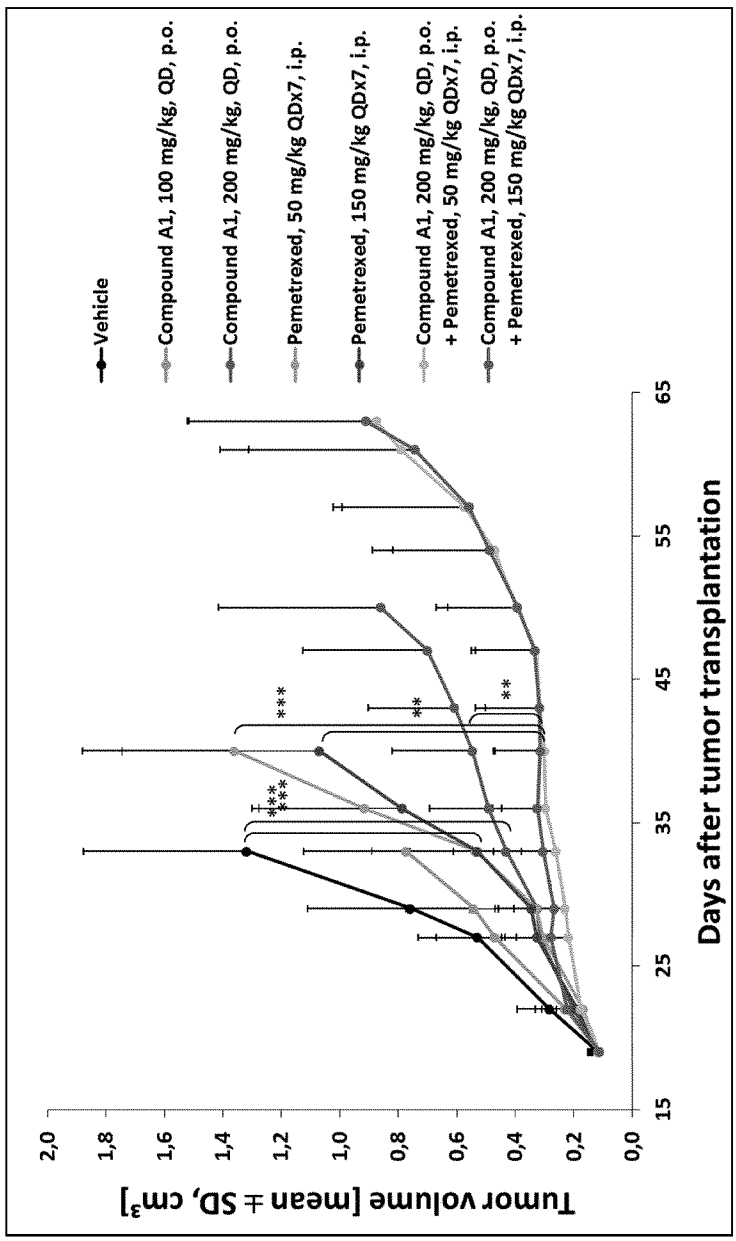

Vehicle
Compound A1, 100 mg/kg, QD, p.o.
Compound A1, 200 mg/kg, QD, p.o.
Pemetrexed, 50 mg/kg QDx7, i.p.
Pemetrexed, 150 mg/kg QDx7, i.p.
Compound A1, 200 mg/kg, QD, p.o. + Pemetrexed, 50 mg/kg QDx7, i.p.
Compound A1, 200 mg/kg, QD, p.o. + Pemetrexed, 150 mg/kg QDx7, i.p.
Tumor volume [mean + SD, cm³]
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
15
25
35
45
55
65
Days after tumor transplantation
***
***
***
**
**

Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/055499

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/5025 A61K31/337 A61K35/00
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, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/034570 A1 (BAYER IP GMBH [DE]; EIS KNUT [DE]; PUEHLER FLORIAN [DE]; ZORN LUDWIG []) 14 March 2013 (2013-03-14) cited in the application	1-7,9-16
Y	claims 1,2,5,6 example 13 page 155, line 19 - line 27	1-7,9-16
	----- -/--	

[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)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 2016	03/05/2016

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	Loher, Florian

1

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.
Y	SU X -Y ET AL: "Low concentration of MNK1 inhibitor CGP57380 inhibits the proliferation of human lung adenocarcinoma A549 cells and induces their apoptosis", TUMOR 20131025 SHANGHAI JIAO TONG UNIVERSITY CHN, vol. 33, no. 10, 25 October 2013 (2013-10-25), pages 873-878, XP009185799, ISSN: 1000-7431 abstract	1-7,9-16
Y	MANEGOLD C: "[Docetaxel (Taxotere) as first-line therapy of advanced non-small cell lung cancer (NSCLC)].", ONKOLOGIE DEC 2003, vol. 26 Suppl 7, December 2003 (2003-12), pages 26-32, XP009185797, ISSN: 0378-584X the whole document	1-7,9-16
Y	WO 2010/055072 A2 (NOVARTIS FORSCHUNGSSTIFTUNG [CH]; UNIV HOSPITAL BASEL [CH]; HEMMINGS B) 20 May 2010 (2010-05-20) figure 5 page 3, last paragraph - page 4, line 11	15,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/055499

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013034570 A1	14-03-2013	AU 2012306422 A1	27-03-2014
		CA 2847514 A1	14-03-2013
		CL 2014000543 A1	26-09-2014
		CN 103958515 A	30-07-2014
		CO 6900146 A2	20-03-2014
		CR 20140113 A	02-05-2014
		DO P2014000051 A	01-06-2014
		EA 201400311 A1	30-09-2014
		EC SP14013231 A	30-04-2014
		EP 2758401 A1	30-07-2014
		GT 201400043 A	06-04-2015
		HK 1199732 A1	17-07-2015
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