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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2022 (24.02.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/038038 A2

(51) International Patent Classification:
A61K 31/395 (2006.01) *A61K 31/517* (2006.01)
A61K 31/444 (2006.01) *A61K 45/06* (2006.01)
A61K 31/47 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2021/072486

(22) International Filing Date:
12 August 2021 (12.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10 2020 005 002.6
17 August 2020 (17.08.2020) DE

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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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title:** MEANS FOR THE THERAPY OF TUMOR DISEASES

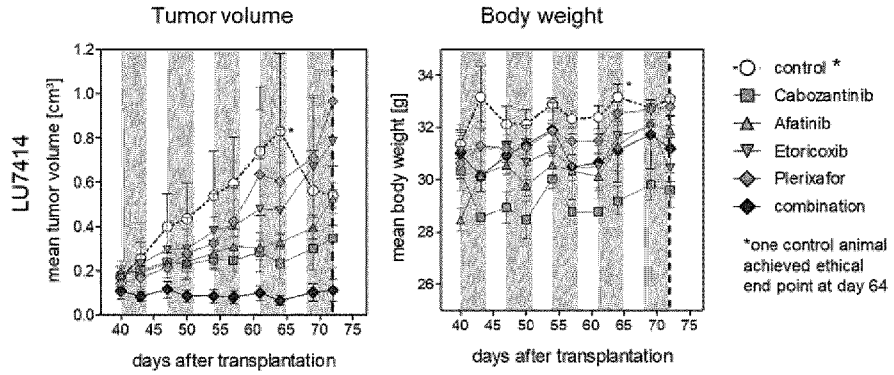

FIG. 2f)

(57) **Abstract:** The present invention relates to a pharmaceutical composition comprising a plurality of active agents respectively inhibiting VEGF's and/or VEGFR1-3; SDF1alpha and/or CXCR4; EGF and/or EGFR1-3; COX2 and/or PGE2 and/or EP; and HGF and/or HGFR (MET), in particular for use in the treatment or prophylaxis of tumor diseases, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC) with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF including a respective treatment method.

WO 2022/038038 A2

TITLE

MEANS FOR THE THERAPY OF TUMOR DISEASES

FIELD OF INVENTION

The present invention relates to a pharmaceutical composition comprising a plurality of active agents respectively inhibiting VEGF's and/or VEGFR1-3; SDF1alpha and/or CXCR4; EGF and/or EGFR1-3; COX2 and/or PGE2 and/or EP; and HGF and/or HGFR (MET), in particular for use in the treatment or prophylaxis of tumor diseases, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF, including a respective treatment method.

BACKGROUND

Drug-based tumor therapy has made immense progress in recent decades. A large number of very differentiated drugs are available for the therapy of tumor diseases.

As an example, Epidermal Growth Factor Receptor (EGFR) – Tyrokinase Inhibitors (TKIs), in particular EGFR1-3 can be used to target proliferation of malignant tumor cells, if present, to their driver mutations, such as EGFR-mutated tumors. Using EGFR1-3 tyrosine kinase inhibitors, such as afatinib, erlotinib, osimertinib, or gefitinib, for the first-line treatment of advanced NSCLC with activating EGFR

mutations is well established. However, treatment options after development of resistance for advanced squamous NSCLC, are limited, particularly in the second-line setting after progression. Vascular Endothelial Growth Factor (VEGF) inhibitors or Vascular Endothelial Growth Factor Receptors (VEGFR) inhibitors can be used to target tumor endothelial cells in order to decrease angiogenesis, tumor cell survival, and metastasis. Here also therapy resistances occur in view of VEGF / VEGFR inhibitors.

At the same time, the spectrum of side effects of therapy has expanded considerably. Overall, most antineoplastic substances belong to the drugs with the smallest therapeutic window.

Thus, there exists a need in providing a pharmaceutical composition effectively treating and/or preventing a tumor disease, wherein the therapy is safe, preferably provides a broader therapeutic window, results in less side effects and/or overcomes a therapeutic resistance to the therapy regime.

SUMMARY OF INVENTION

The aforementioned need is attended to at least in part by means of the claimed inventive subject matter. Advantages (preferred embodiments) are set out in the detailed description hereinafter and/or the accompanying figures as well as in the dependent claims.

Accordingly, a first aspect of this invention relates to a pharmaceutical composition comprising a plurality of active agents in a therapeutically effective amount and one or more pharmaceutical excipients, characterized in that

a. at least one active agent inhibits VEGF's and/or VEGFR1-3 signaling,

b. at least one active agent inhibits SDF1alpha and/or CXCR4 signaling,

c. at least one active agent inhibits EGF and/or EGFR in particular EGFR1-3 signaling,

d. at least one active agent inhibits COX2 and/or PGE2 and/or EP signaling, and

e. at least one active agent inhibits HGF and/or HGFR (MET) signaling.

A second aspect of this invention relates to a pharmaceutical composition according to the first inventive aspect for use in the treatment or prophylaxis of a tumor disease, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF.

A third aspect of the invention relates to a method of treatment or prophylaxis of a tumor disease, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF.

The inventive aspects of the present invention as disclosed hereinbefore can comprise – in case it is reasonable for a person skilled in the art – any possible combination of the preferred inventive embodiments as set out in the dependent claims or disclosed in the following detailed description including the experimental section.

BRIEF DESCRIPTION OF DRAWINGS

Further aspects, characteristics and advantages of the invention will ensue from the following description of the embodiments with reference to the accompanying drawings, wherein

Fig. 1 is a simplified model of the inventive combination therapy regimen overcoming drug resistances in the therapy of tumor diseases.

FIGS. 2 a) to f) are diagrams displaying tumor volume and bodyweight during therapy regimen in the respective in vivo models LU 7406 (FIG. 2a), LU7414 (Fig. 2b), LU7177 (Fig. 2c), LU7766 (Fig. 2d), LU7860 (Fig. 2e), and LU7414 (Fig. 2f).

DETAILLED DESCRIPTION OF EMBODIMENTS

As set out in more detail hereinafter, the inventors of the different aspects of this invention combine for the first time anti-tumor drugs from the group of VEGF and/or VEGFR inhibitors and EGF and/or EGFR, in particular EGFR1-3 inhibitors with active agents blocking the chemokine stromal-cell derived factor-1 (SDF-1alpha, also known as CXCL12) and C-X-C Motif Chemokine Receptor 4 (CXCR4) axis, and active agents inhibiting cyclooxygenase 2 (COX2) and/or prostaglandin E2 (PGE2) and/or E series of prostaglandin receptors (EP), as well as active agents inhibiting hepatocyte growth factor (HGF) and/or hepatocyte growth factor receptor (HGFR) (MET) in order to suppress a tumor disease already at lower concentrations compared to a respective monotherapy, in particular a tumor that is resistant to anti-tumor drugs from the group of VEGF and/or VEGFR inhibitors and EGF and/or EGFR, in particular EGFR1-3 inhibitors (see executive example below). In addition, the inventive combination regimen showed at the same time an excellent safety profile of the inventive pharmaceutical composition and might lead to less pronounced side effects in patients. Together with its excellent efficacy this inventive combination is deemed to be superior in comparison to a higher dose therapy regimen of a VEGFR inhibitor monotherapy, e.g. using cabozantinib (a multi-kinase inhibitor that targets MET, AXL, and VEGFR2), or a higher dose therapy regimen of a EGFR, in particular EGFR1-3 inhibitor monotherapy, e.g. using afatinib.

The fact, that the inventive pharmaceutical composition not only simultaneously inhibits VEGF / VEGFR, HGF / HGFR (MET) and EGF / EGFR in particular EGFR1-3 signaling pathways, but in addition simultaneously inhibits SDF-1 / CXCR4, and COX2 / PGE2 / EP signaling pathways seems to be necessary in order to suppress tumor growth by effectively target the paracrine signaling from

different cell types including immune cells, tumor endothelial cells, cancer associated fibroblasts and tumor cells forming a cellular tumorigenic network (see Fig. 1).

It is surprising, that the inventive combination of active agents overcomes tumor resistances, as it has previously been shown that a combination of cabozantinib and erlotinib, an EGFR inhibitor, did not appear to re-sensitize the resistant patients to erlotinib (Wakelee HA, et al., A phase Ib/II study of cabozantinib (XL184) with or without erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol. 2017 May;79(5):923-932. doi: 10.1007/s00280-017-3283-z.).

Previous studies furthermore showed that plerixafor as an inhibitor of the SDF-1 – CXCR4 axis was found to abolish cabozantinib induced tumor growth inhibition (Patnaik A, et al. Cabozantinib Eradicates Advanced Murine Prostate Cancer by Activating Antitumor Innate Immunity. Cancer Discov. 2017 Jul;7(7):750-765. doi: 10.1158/2159-8290.CD-16-0778. Epub 2017 Mar 8. PMID: 28274958; PMCID: PMC5501767.).

In the context of the present invention the expression "*pharmaceutical composition comprising a plurality of active agents in a therapeutically effective amount*" means that the combination of inhibitory active agents a) to e) and optionally f) are comprised in the pharmaceutical composition in such an amount, that therapeutically suppresses tumor growth, i.e. wherein the volume and/or the weight of tumor or metastatic lesions remain constant or preferably decrease (i.e. as measured in the clinic by the revised RECIST criteria) and/or wherein the events of metastasis are decreased. In view of the synergistic effects provided by the inventive pharmaceutical composition, the concentrations in particular of the respective active agents a), b) and/or c) can be the same or preferably reduced in comparison to the concentration used when applying the respective active agents in monotherapy.

In the context of the present invention the term "active agent" may synonymously be used to "therapeutic agents", "therapeutics", "drugs", "biologicals", "targeted drugs", "immunologicals", "antibodies", "small molecules" and the like.

The first aspect of the present invention thus relates to a pharmaceutical composition comprising a plurality of active agents in a therapeutically effective amount and one or more pharmaceutical excipients, characterized in that

a. at least one active agent inhibits VEGF's and/or VEGFR1-3 signaling,

b. at least one active agent inhibits SDF1alpha and/or CXCR4 signaling,

c. at least one active agent inhibits EGF and/or EGFR in particular EGFR1-3 signaling,

d. at least one active agent inhibits COX2 and/or PGE2 and/or EP signaling, and

e. at least one active agent inhibits HGF and/or HGFR (MET) signaling.

According to an alternative or additive preferred embodiment of the present invention

a. at least one VEGF's and/or VEGFR1-3 inhibitor is selected from the group consisting of cabozantinib, regorafinib, bevacizumab, ramucirumab, pazopanib, sunitinib, sorafinib, ponatinib, vandetanib, axitinib, lenvatinib, ziv-Aflibercept, tivozanib, golvatinib, and foretinib, preferably cabozantinib and regorafinib, and/or

b. at least one SDF1alpha and/or CXCR4 inhibitor is selected from the group consisting of plerixafor, motixafortide, LY2510924, and WZ811, preferably plerixafor, and/or

c. at least one EGF and/or EGFR in particular EGFR1-3 inhibitor is selected from the group consisting of afatinib, erlotinib, cetuximab, neratinib, necitumumab, gefitinib, lapatinib, osimertinib, canertinib, and saracatinib, preferably afatinib, cetuximab, neratinib, necitumumab, gefitinib, lapatinib, and osimertinib, more preferably afatinib, and/or

d. at least one COX2 and/or PGE2 and/or EP inhibitor is selected from the group consisting of etoricoxib, celecoxib, parecoxib, rofecoxib, and valdecoxib, preferably etoricoxib and celecoxib, and/or

e. at least one active agent inhibiting HGF and/or HGFR (MET) is selected from the group consisting of cabozantinib, tivantinib, crizotinib, capmatinib, tepotinib, savolitinib, golvatinib, and foretinib, preferably cabozantinib and tivantinib.

Excluded from the present invention is an embodiment, wherein the plurality of active agents in the pharmaceutical composition is limited to active agents inhibiting a) VEGF and/or VEGFR, in particular wherein the respective inhibitors consist of bevacizumab, sunitinib, and sorafinib; b) SDF1alpha and/or CXCR4, in particular wherein the respective inhibitors consist of plerixafor; c) EGF and/or EGFR, in particular wherein the respective inhibitors consist of afatinib, gefitinib, erlotinib, necitumumab, and osimertinib; and d) COX2 and/or PGE2 and/or EP, in particular wherein the respective inhibitors consist of celcoxib, and etoricoxib.

According to an alternative or additive preferred embodiment of the present invention Cabozantinib is selected in groups a) and e). In doing so, only four active agents can be selected in order to inhibit the five signaling pathways a) to e).

According to an alternative or additive preferred embodiment of the present invention the inventive composition comprises a combination of active agents selected from the group consisting of

i. cabozantinib, afatinib, plerixafor, and etoricoxib,

ii. cabozantinib, afatinib, plerixafor, and celecoxib,

iii. cabozantinib, osimertinib, plerixafor, and etoricoxib,

iv. cabozantinib, osimertinib, plerixafor, and celecoxib,

v. cabozantinib, necitumumab, plerixafor, and etoricoxib,

vi. cabozantinib, necitumumab, plerixafor, and celecoxib,

vii. cabozantinib, cetuximab, plerixafor, and etoricoxib,

viii. cabozantinib, cetuximab, plerixafor, and celecoxib,

ix. cabozantinib, neratinib, plerixafor, and etoricoxib,

x. cabozantinib, neratinib, plerixafor, and celecoxib,

xi. cabozantinib, lapatinib, plerixafor, and etoricoxib ,

xii. cabozantinib, lapatinib, plerixafor, and celecoxib,

xiii. cabozantinib, gefitinib, plerixafor, and etoricoxib,

xiv. cabozantinib, gefitinib, plerixafor, and celecoxib,

xv. regorafenib, necitumumab, plerixafor, etoricoxib and tivantinib,

xvi. regorafenib, necitumumab, plerixafor, celecoxib and tivantinib,

xvii. regorafenib, cetuximab, plerixafor, etoricoxib and tivantinib,

xviii. regorafenib, cetuximab, plerixafor, celecoxib and tivantinib,

xix. regorafenib, osimertinib, plerixafor, etoricoxib and tivantinib,

xx. regorafenib, osimertinib, plerixafor, celecoxib and tivantinib,

xxi. regorafenib, afatinib, plerixafor, etoricoxib and tivantinib,

xxii. regorafenib, afatinib, plerixafor, celecoxib and tivantinib,

xxiii. regorafenib, cetuximab, plerixafor, etoricoxib and cabozantinib,

xxiv. regorafenib, cetuximab, plerixafor, celecoxib and cabozantinib,

xxv. regorafenib, necitumumab, plerixafor, etoricoxib and crizotinib, and

xxvi. regorafenib, necitumumab, plerixafor, celecoxib and crizotinib.

Combinations i) to xiv) are specifically preferred, as they comprise only four active agents in order to inhibit the five signaling pathways. In doing so, the overall amount of active agents and, thus, the body burden can be reduced, which in turn increases the safety profile of the inventive pharmaceutical composition and may decrease the risk of showing drug related side effects.

According to an alternative or additive preferred embodiment of the present invention the inventive composition further comprises

f. at least one active agent inhibiting programmed death 1 receptor (PD-1) and/or programmed death ligand 1 (PD-L1), wherein the PD-1 and/or PD-L1 inhibitor is preferably selected from the group consisting of

pembrolizumab, nivolumab, durvalumab, and atezolizumab, preferably durvalumab.

The following table 1 summarizes the information on the selected active agents effectively inhibiting the respective signaling pathways including their presently approved indications including approved dosing as well as a potential dosing in the inventive pharmceutical combination:

Tab. 1 Active agents suitable to be used within the inventive pharmaceutical composition including approved indications and dosing and potential dosing in a combination regimen

Molecular paracrine signaling pathway	**Drug**	**Approved indications** (in subgroups thereof)	**Approved dosing**	**Potential dosing in combination regimen**
VEGFA-VEGFR2	cabozantinib	RCC, HCC	60mg/day	20-55mg/day
	regorafinib	CRC, HCC, GIST	160mg/day	50-150mg/day
	bevacizumab	CRC, breast cancer, NSCLC, RCC, ovarian cancer, peritoneal cancer cervical cancer, fallopian tube cancer	15mg/kg/ 3 weeks	5-15mg/kg/ 3weeks
	ramucirumab	GC, GEJ cancer, CRC, NSCLC	8mg/kg/2 weeks	4-7mg/kg/ 2 weeks
	pazopanib	RCC, Sarcoma	800mg/day	250-750mg/day
	sunitinib	GIST, NETs, RCC	50mg/day	20-45mg/day
	sorafinib	HCC, RCC, DTC, AML	800mg/day	250-750mg/day
	ponatinib	CML, ALL	45mg/day	15-40 mg/day
	vandetanib	Thyroid carcinoma	300mg/day	100-250mg/day
	axitinib	RCC	10mg/day	10mg/day
	lenvatinib	RCC, HCC, thyroid carcinoma	18-24mg/day	18-24mg/day
	ziv-aflibercept	CRC	4 mg per kg every two weeks	4 mg per kg every two weeks
	tivozanib	Not approved		
	golvatinib	Not approved		
	foretinib	Not approved		
EGF-EGFRwt	afatinib	NSCLC	40mg/day	10-35mg/day
	erlotinib	NSCLC, pancreatic cancer	150mg/day	50-145mg/day
	cetuximab	CRC, Head & Neck carcinoma	250mg/m^2/ week	125-240 mg/m^2/week

	neratinib	Breast cancer	240mg/day	150-230mg/day
	necitumumab	NSCLC	800mg/day 1 and 8 in 3 week cycles	300-750mg/day 1 and 8 in 3 week cycles
	gefitinib	NSCLC	250mg/day	75-245mg/day
	lapatinib	Breast cancer	1250mg/day	500-1200 mg/day
	osimertinib	NSCLC	80mg/day	20-75mg/day
	canertinib	Not approved		
	saracatinib	Not approved		
SDF1a-CXCR4	plerixafor	Stem cell mobilization prior transplantation	20mg/day/5 days	5-15 mg/day/5days
	motixafortide	Not approved		
	LY2510924	Not approved		
	WZ811	Not approved		
COX2-PGE2	etoricoxib	Arthrosis, rheumatoid arthritis, gout, morbus bechterew, tooth pain	60mg/day	10-55mg/day
	celecoxib	Arthrosis, rheumatoid arthritis, morbus bechterew	200mg/day	50-185mg/day
	parecoxib	Post-surgery pain	40mg/day	20-35mg/day
	rofecoxib	Not approved		
	valdecoxib	Not approved		
HFG-MET	cabozantinib	RCC, HCC	60mg/day	20-55mg/day
	crizotinib	NSCLC	500mg/day	100-450mg/kg
	tivantinib	NSCLC	450mg/day	100-445mg/kg
	capmatinib	Not approved		
	tepotinib	Not approved		
	savolitinib	Not approved		
	golvatinib	Not approved		
	foretinib	Not approved		

Generally, the present invention the inventive composition may contain one, two or more separate pharmaceutical dosage formulations, wherein each dosage formulation contains at least one active agent. The respective pharmaceutical dosage forms may comprise one or more dosage units. In case the pharmaceutical composition includes two or more separate pharmaceutical dosage formulations, the combination of dosage formulations may be commercialized in one kit /

package comprising the inventive pharmaceutical composition including the different dosage formulations. As an example, in case one dosage formulation may represent a solid composition, such as a tablet, and one dosage formulation may represent a liquid composition, such as an injection solution, the respective inventive pharmaceutical composition may comprise in the commercialized kit / package one or more units (single tablets) of the solid dosage formulation and one or more units (vials comprising the injection solution) of the liquid dosage formulation. Accordingly, the one, two or more pharmaceutical dosage formulations may independently of each other be the same or different, and may be selected from the group consisting of

i. solid dosage forms for oral or enteral application, wherein solid dosage forms are preferably include tablets, capsules, spheroids, mini-tablets, pellets, granules, and pills;

ii. semi-solid dosage forms for topical application to skin or mucous membranes, wherein semi-solid dosage forms are preferably include creams, gels, ointments, and suppositories; and

iii. liquid dosage forms for oral, external, or parenteral application, wherein liquid dosage forms preferably include mixtures, linctuses, elixirs, syrups, drops, lotions, liniments, collodions, nasal drops, nasal sprays, eye drops, inhalations, aerosols, and injections, e.g., *sub cutan* (s.c.) injections*, intra muscular* (i.m.) injections, *intra venous* (i.v.) injections, *intra peritoneal* (i.p.), *intra pleural* (i.pl.), *intra tumoral* (i.t.), *intra thecal* (i.th.), *intra cerebral / intra cranial* (i.c.) injections.

The one or more pharmaceutical excipients for the respective pharmaceutical formulations may readily be selected as necessary from suitable excipients classes including fillers, diluents, binders, disintegrants, antiadherent, lubricants, glidants, coatings, sorbents, preservatives, antioxidants, flavoring agents, sweeting agents, coloring agents, solvent & co-solvent, buffering agents, chelating agents, viscosity imparting agents, surface active agents, humectants and the like. The technical content regarding the aforementioned solid, semi-solid and liquid dosage forms as well as the aformentioned respective exemplary excipient classes and their respective constitents disclosed in Hand book of pharmaceutical excipients, Edition-Nine, Edited by-Raymond Crowe Paul J Sheskey and Marian E Quinn,

Publisher-Pharmaceutical Press; Aulton's Pharmaceutics The design and manufacture of medicines, Edition-Six, Edited by- Michael E.Aulton, Publisher-Elsevier; Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Edition- Twelve, Author Loyd Allen Jr, Timothy B. McPherson,Publisher- Lippincott Williams and Wilkins; Pharmazeutische Technologie: Mit Einführung in Biopharmazie und Biotechnologie, Authors Kurt-Heinz Bauer, Karl-Heinz Frömming and Claus Führer is incorporated herein by reference. As an example, a respectively suitable solid dosage form may be a tablet or a capsule composition and preferably may exhibit in addition to the one or more active agents pharmaceutically acceptable excipients selected from a diluent, a binder, a disintegrant, a lubricant, and optionally a coating. As a further example, a suitable liquid dosage form may be an injection solution, preferably a s.c. injection solution, which may comprise in addition to one or more active agents a suitable solvent, such as water for injections, and a suitable buffer agent / pH adjusting agent.

According to an alternative or additive preferred embodiment of the present invention, the inventive composition may comprise a first pharmaceutical dosage formulation that contains at least one active agent inhibiting b) SDF1alpha and CXCR4 signaling pathway, and at least a second pharmaceutical dosage formulation that contains two or more, preferably all of the at least one active agents respectively inhibiting a) VEGF's and/or VEGFR1-3, c) EGF and/or EGFR in particular EGFR1-3, d) COX2 and/or PGE2 and/or EP, e) HGF and/or HGFR (MET), and optionally f) PD-1 and/or PD-L1 signaling pathways. More preferably, the first pharmaceutical formulation may be a liquid dosage formulation, preferably an s.c. injection dosage form and in particular, and/or wherein the second pharmaceutical dosage form is a solid dosage form, preferably a tablet or capsule and may contain as an example one or more of the remaining active agents. As an example, the first pharmaceutical dosage formulation may be an s.c. injection solution comprising plerixafor in particular in an amount of 24 mg or less per dosage unit, the dosage unit may comprise 1.2 ml. The second pharmaceutical dosage formulation may be selected from a solid dosage formulation, preferably a tablet or a capsule comprising one or more of the remaining active agents, in particular cabozantinib, afatinib, and etoricoxib or celecoxib. In case one or more of the remaining active agents may physically or chemically interact with each other in the respective dosage formulation, e.g. solid dosage formulation, suitable

counter measures will be taken as available in the art, such as separating the respective active agents in different compartments of the dosage formulation, masking the respective active agents, etc. and/or separating the respective interacting active agents in separate pharmaceutical dosage formulations.

Regarding a suitable dosing regimen, the active agents of the inventive pharmaceutical composition containing one or more pharmaceutical dosage formulations may generally be administered daily, wherein preferably in this case at least active agents a), b) and/or c) may be administered in a concentration, which is lower than the concentration commonly used in their respective monotherapy in order to decrease side effects. In addition or alternatively, one or more of the active agents of the inventive pharmaceutical composition containing one or more pharmaceutical dosage formulations may be administered less than every day, which may also decrease the risk of side effects.

As shown in the example section, during the complete treatment duration, no tumor outgrowth was observed in either PDX model, indicating a strong therapy efficacy by preventing development of an adaptive resistance against this regimen. After treatment discontinuation growth suppression remained up to 18 days (LU7860) with only slight increase in tumor growth. This indicates a long-lasting and sustained effect of the combination therapy on the tumor biology. In other words, a preferred dose regimen includes the administration of the inventive pharmaceutical composition in intervals from e.g. weeks to months, such as administration of inventive pharmaceutical composition for one or more, preferably five or more days, followed by a one or more, preferably two or more days without administration of the inventive pharmaceutical composition (also called "*drug holiday*"). Such interval dose regimen may improve the patient compliance in particular due to a reduced risk of side effects.

According to an alternative or additive preferred embodiment of the present invention, the dose regimen may comprise or consist of

a. at least one active agent inhibiting VEGF's and/or VEGFR1-3 is administered once daily for one, two, three, four or five days followed by at least one, preferably two days without administration,

b. at least one active agent inhibiting SDF1alpha and/or CXCR4 is administered once daily for one, two, three, four or five days, preferably for

one day followed by at least one, preferably five days without administration,

c. at least one active agent inhibiting EGF and/or EGFR in particular EGFR1-3 is administered once daily for one, two, three, four or five days followed by at least one, preferably two days without administration,

d. at least one active agent inhibiting COX2 and/or PGE2 and/or EP is administered once daily for one, two, three, four or five days followed by at least one, preferably two days without administration,

e. at least one active agent inhibiting HGF and/or HGFR (MET) is administered once daily for one, two, three, four or five days followed by at least one, preferably two days without administration, and optionally

f. at least one active agent inhibiting PD-1 and/or PD-L1 that is administered once daily for one, two, three, four or five days followed by at least one, preferably two days without administration.

The aforementioned (preferred) embodiments of the first aspect of the present invention may be combined throughout. In particular, the different preferred embodiments of the first aspect of the present invention can alternatively or in addition be combined with each other.

All aforementioned embodiments including the combination of preferred embodiments in relation to the first aspect of the present invention can also be used for combination with (preferred) embodiments of the second and third aspect of the present invention.

The second aspect of the present invention relates to a pharmaceutical composition according to the first inventive aspect for use in the treatment or prophylaxis of a tumor, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic

cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF. Preferably, the tumor is a non-small cell lung cancer (NSCLC), more preferably without driver mutations.

According to a preferred embodiment the pharmaceutical composition, in particular comprising one or more pharmaceutical formulations is/are respectively provided facilitating enteral administration, preferably oral administration, and/or intranasal administration and/or sub-lingual administration and/or buccal administration. Such an embodiment is preferred, as it may facilitate treatment at home and would not require hospitalization and may improve patient compliance.

As shown in the example section, during the complete treatment duration, no tumor outgrowth was observed in either PDX model, indicating a strong therapy efficacy by preventing development of an adaptive resistance against this regimen. After treatment discontinuation growth suppression remained up to 18 days (LU7860) with only slight increase in tumor growth. This indicates a long-lasting and sustained effect of the combination therapy on the tumor biology. In other words, a preferred dose regimen includes the administration of the inventive pharmaceutical composition in intervals from e.g. weeks to months, such as administration of inventive pharmaceutical composition for one or more, preferably five or more days, followed by a one or more, preferably two or more days without administration of the inventive pharmaceutical composition (also called "*drug holiday*"). Such interval dose regimen may improve the patient compliance in particular due to a reduced risk of side effects.

The respective dosing regimens disclosed with respect to the first inventive aspect also apply with respect to the third inventive aspect. In particular, all aforementioned embodiments including a (sub)combination of preferred embodiments disclosed in relation to the first aspect of the present invention can also be used in combination with respect to the second aspect of the present invention.

The third aspect of the present invention relates to a method of treatment or prophylaxis of a tumor disease, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal

junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF. Preferably, the tumor is a non-small cell lung cancer (NSCLC), more preferably without driver mutations.

As already set out with respect to the second inventive aspect, a preferred embodiment of the inventive method of treatment requires the enteral administration, preferably oral administration, and/or intranasal administration and/or sub-lingual administration and/or buccal administration of an inventive pharmaceutical composition that comprises one or more pharmaceutical formulations. Such an embodiment is preferred, as it may facilitate treatment at home and would not require hospitalization and thereby may improve patient compliance.

Moreover, an interval administration of the inventive pharmaceutical composition may be preferred as set out with respect to the second inventive aspect, as the experimental data shows that the tumor growth suppression maintains constant within 18 days after administration of the last dose. Such an interval administration from weeks to months, in particular from one or more, preferably five or more days followed by an interval without administration of inventive pharmaceutical composition of one or more days, in particular two or more days is preferred.

The respective dosing regimens disclosed with respect to the first inventive aspect also apply with respect to the third inventive aspect. In particular, all aforementioned embodiments including a (sub)combination of preferred embodiments disclosed in relation to the first aspect of the present invention can also be used in combination with respect to the third aspect of the present invention.

The present invention is explained further with the aid of the following non-limiting examples, illustrating the parameters of and compositions employed within

the present invention. Unless stated otherwise, all data, in particular percentages, parts and ratios are by weight.

According to the present invention the individual features of the exemplary embodiments of the inventive pharmaceutical tablet as disclosed in the detailed description or claims of the present application can respectively be separately combined with features of the exemplary embodiments herein below.

EXECUTIVE EAMPLES

The following embodiments show the results of treatments of patient-derived NSCLC xenografts (PDX) treated with various anti-cancer monotherapies including chemotherapies, small molecules and monoclonal antibodies and the combination therapy listed within the scope of the present invention (Therapy). Efficacy was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) and according to the measured ratio of the treated tumor (T) versus a placebo control (C) with the largest difference that occurred (optimal).

PD: progressive disease; SD: stable disease; PR: partial response.

Methods

Patient-Derived Xenograft (PDX) lung cancer models

The establishment and characterization of PDX mouse models and lung PDX models in particular, was previously described (Tab. 2) (Fichtner at., 2008, Rolff et al., 2016). Generation of the PDX has been approved by the local ethics committee at Charite Berlin and patients have provided informed consent.

In brief, fresh tumor samples were cut into pieces of 3 x 3 mm and were subcutaneously transplanted to Rj:NMRI-Foxn1nu/nu nude recipient mice. Once subcutaneous (s.c.) tumors became palpable, tumor size was measured twice weekly with a digital caliper. Individual tumor volumes (TV) were calculated by the formula $V= (length \times width^2)/2$ and related to the values at the first day of treatment (relative tumor volume, RTV). In addition, therapeutic efficacy was assessed by applying Response Evaluation Criteria In Solid Tumors (RECIST) (Eisenhauer et al., 2009). According to these criteria a reduction in tumor volume of at least 30% was defined as partial response (PR), an increase in tumor volume of at least 20% was defined as progressive disease (PD). Stable disease (SD) was defined as neither sufficient reduction to qualify for PR nor sufficient increase to qualify for PD. The Objective Response Rate (ORR) includes all tumors with Complete Response (CR) and PR and the Clinical Benefit Rate includes all tumors with CR, PR and SD expressed in percentage. The body weight (BW) of mice was recorded regularly at least two times per week and the change in body weight was utilized as variable for tolerability.

Tab. 2. Characterization of selected NSCLC tumor models

		Tumor Models				
		LU7406	**LU7414**	**LU7177**	**LU7766**	**LU7860**
Characterization	**Histology**	Adeno Ca	SCC	SCC	SCC	SCC
	Gender	Female	Female	Male	Male	Male
	Age	53	64	42	71	71
	TNM Classification	ypT2 ypN2 cM0 G3 R0	pT2 pN0 cM0 G3 R0	pT2 pN2 M0 G3 R0	pT2 pN2 cM0 G3 R0	pT1 pN0 cM0 G3 R0
	Stage	IIIA	IIA	IIIA	IIIA	IA
	Best Response for all Therapies Tested (RECIST)	PD	PD	CR (gemcitabine)	PR (paclitaxel)	SD (paclitaxel)
	Identified Driver Mutation	none	none	none	none	none

Legend: Adeno CA: adenocarcinoma; SCC: squamous cell carcinoma; PD: progressive disease; CR: complete response; SD: stable disease; PR: partial response

After 25 to 40 days, the mean tumor volume reached the indicated starting volume (150-200 mm3). Mice were randomly assigned to control and treatment groups (1-4 mice per group) and treatment was started on the day of randomization.

The mice were treated using the following drug dosages and treatment schedules: cabozantinib 15 mg/kg, afatinib 15 mg/kg, etoricoxib 10 mg/kg orally and plerixafor 5 mg/kg intra-peritoneally for 5 days on treatment and 2 days off treatment for four cycles in total (Tab. 3a). Common dosing regimes in the

respective model for monotherapeutic applications require the once daily application throughout of all active ingredients optionally in a higher dose, such as of cabozantinib 30-60 mg/kg (Paratala et al., 2018; Scott et al., 2018), afatinib 20 mg/kg (Floc'h N et al., 2018), etoricoxib 10 mg/kg (Floc'h N et al., 2018) orally and plerixafor 5 mg/kg intra-peritoneally (Singla et al., 2015). Placebo control mice were treated with corresponding vehicles only (p.o. with 0.5% methyl cellulose and s.c. with aqua ad iniectabilia) or with respective monotherapy at the same dosages. At the end of the experiments, tumors were excised and one half snap frozen and stored at −80 °C for further analyses. The second half was fixed in formalin fixed and embedded in paraffin (FFPE).

All mice were handled in accordance with the Guidelines for the Welfare and Use of Animals in Cancer Research (Workman et al., 2010) and according to the German Animal Protection Law, approved by the responsible local authorities.

Tab. 3a. Characteristics of the Low Dose Combination Drug Regimen

Target	**Drug***	**Route of Administration**	**Dosing in Combination Therapy (Fig. 2a-e) and in Monotherapy Controls (Fig. 2f)**	
			Dosing	**Schedule**
VEGFR2 (KDR) / MET (HGFR)	**Cabozantinib**	oral	15mg/kg	5 days on / 2 days off for 4 cycles
CXCR4	**Plerixafor**	intra-peritoneal	5mg/kg	
EGFRwt	**Afatinib**	oral	15mg/kg	
COX2 (PTGS2)	**Etoricoxib**	oral	10mg/kg	

* In combination therapy cabozantinib, afatinib and etoricoxib were administered in a single combined gavage dose and plerixafor was administered separately intra-peritoneal

Table 3b. Characteristics of the Drug Regimen of Monotherapy according to state of the art

Target	Drug*	Route of Adminis-tration	Common Dosing *in vivo* Models (state of the art)	
			Dosing	Schedule
VEGFR2 (KDR) / MET (HGFR)	**Cabozantinib**	oral	30-60mg/kg (Paratala et al., 2018; Scott et al., 2018)	once daily
CXCR4	**Plerixafor**	intra-peritoneal	5mg/kg (Singla et al., 2015)	
EGFRwt	**Afatinib**	oral	20mg/kg (Floc'h N et al., 2018)	
COX2 (PTGS2)	**Etoricoxib**	oral	10mg/kg (Jayaraman et al., 2010)	

Drawings

Fig. 1 displays a simplified model of the inventive combination therapy regimen overcoming drug resistances by simultaneous targeting interdependent signaling in a cellular tumorigenic network of NSCLC tumors.

In Fig. 1 the following reference signs have the meaning:

(1) Immune cell;

(2) Tumor endothelial cell;

(3) Cancer associated fibroblast;

(4) Tumor cell;

(10) Evading immune destruction;

(20) angiogenesis, proliferation, migration, cell survival and vascular permeability;

(30) secretion of protumorigenic factors;

(40) proliferation, cell survival, metastasis and secretion of VEGF;

(11) active agents inihibiting PD-1-PD-L1 signalling

(21) active agents inihibiting VEGF-VEGFR signalling

(41) active agents inihibiting COX2-PGE2-EP signalling

(42) active agents inihibiting EGF-EGFR signalling

(43) active agents inihibiting SDF1alpha-CXCR4 signalling

(44) active agents inihibiting HGF-MET signalling

PGE2 prostaglandin E2

VEGFR vascular endothelial growth factor receptor;

EGFR epidermal growth factor receptor;

COX2 (PTGS2) cyclooxygenase 2

HGF hepatocyte growth factor.

Signaling axes of PD-1-PD-L1, VEGF-VEGFR, COX2-PGE2-EP, EGF-EGFR, SDF-1-CXCR4, and HGF-MET are exemplary shown for some of the known paracrine pathways binding the cellular tumorigenic network in NSCLC tumors using respective inhibiting active agents (11), (21), (41), (42), (43), and (44), which are inventively selected as follows:

(11) nivolumab, pembrolizumab, stezolizumab, durvalumab;

(21) cabozantinib, regorafinib, bevacizumab, ramucirumab, pazopanib, sunitinib, sorafinib, ponatinib, vandetanib, axitinib, lenvatinib, ziv-aflibercept, tivozanib, golvatinib, foretinib

(41) atoricoxib, celecoxib, parecoxib, rofecoxib, valdecoxib

(42) afatinib, erlotinib, cetuximab, neratinib, necitumumab, gefitinib, lapatinib, osimertinib, canertinib, saracatinib

(43) plerixafor, motixafortide, LY2510924 and WZ811

(44) cabozantinib, crizotinib, tivantinib, capmatinib, tepotinib, savolitinib, golvatinib, foretinib

Figs. 2a) to 2f) display *in vivo* efficacy testing of innovative combination treatment regime in selected NSCLC PDX mouse models *versus* monotherapy regiment of the state of the art. In all trials, treatment with the innovative combination was highly effective in preventing tumor propagation and tumor out-growth achieving stable disease and partial response as best response criteria in all experiments. Stable body weight throughout the complete trials indicate distinguished safety profile of the applied combination treatment.

Resistance profiles of all tumor models against carboplatin, paclitaxel, gemcitabine, etoposide, cetuximab, erlotinib and bevacizumab was evaluated in the initial characterization as follows: Fig. 2a. LU7406 and Fig. 2b. LU7414 showed progressive disease (PD) for all tested therapies. Fig. 2c. LU177 showed PD for all but one therapies tested. For gemcitabine complete response (CR) was determined. Fig. 2d. LU7766 showed for four out of the seven tested therapies PD. For carboplatin stable disease (SD), for paclitaxel partial response (PR) and for cetuximab SD was observed. Fig. 2e. LU7860 showed PD for all but one therapies tested. For paclitaxel SD was observed.

In the experiment LU7414 displayed in Fig. 2f. with compounds administered as monotherapies at the same drug dosages used for the innovative combination therapy *versus* control and the innovative combination groups reveal a superior effect of the innovative combination therapy.

Results

Complete suppression of tumor growth and absence of toxicity in all NSCLC PDX models treated with the combination therapy regimen

In total, 16 nude mice bearing one of the selected NSCLC PDX tumors were randomized for treatment with the innovative combination therapy regimen consisting of low dose cabozantinib, afatinib, plerixafor and etoricoxib for at least four cycles with 5 days on and 2 days off treatment controlled by a placebo (N=18) *versus* state of the art monotherapy treatment (N=12) group (Tab. 3a). The safety profile of this combination regimen was assessed by the continuous measurement of body weight (BW) of treated mice compared to the placebo group as an indicator for toxicity.

Throughout the experiments only in the LU7414 trial a BW reduction between 5-13% was detected for the innovative combination during the second treatment cycle after day 4 resulting in drug holiday from day 5-7 in this cycle. However, the cumulative dose of these mice was the same compared to all other animals treated with the combination since the first cycle was tested with 6 days on and 1 day off treatment. In none of the remaining mice at any time point a significant difference in BW between the verum and the placebo or the monotherapy group was observed. In general, all mice included in these experiments either gained weight during the course of treatment or remained at the baseline BW level with minimal variances. None of the mice had to be discontinued from treatment, died or had to be euthanized during the course of treatment. This observation reflects the beneficial safety profile of this inventive combination regimen and is in alignment with the low dose therapy compared to regular state of the art concentrations used of these drugs in in vivo experiments (Tab. 3a).

16 out of 16 NSCLC PDX tumors combined from all models showed a treatment response for the applied innovative combination regimen as evaluated per RECIST analysis (Figs. 2a) to 2f)). In 13 tumors a partial response (PR) and in 3 tumors a stable disease (SD) was induced. In contrast, in 29 out of 30 placebo or monotherapy treated tumors progressive disease (PD) was observed. Only for a single tumor of the cabozantinib monotherapy group a partial response was observed and transformed into progressive disease during the later course of treatment (Fig. 2f). Thus, the ORR is 81% and the CBR is 100% across all NSCLC PDX tumors treated with the combination regimen. In none of the mice treated with the innovative combination regime a tumor outgrowth was observed during the treatment period. In contrast, all tumors in the placebo- or monotherapy group showed a progressive disease at the last day of treatment.

In addition, the growth of all tumors in the innovative combination regimen group remained suppressed in the follow up period for up to 18 days (LU7860) (Fig. 2e).

Overall, these data indicate that innovative combined targeting of the paracrine cellular tumorigenic network elicits strong anti-tumoral effects in NSCLC PDX tumors which are characterized by profound resistances to standard therapies.

Discussion

Despite some recent progress in the treatment of NSCLC, no impactful advances have been in the state of the art when treating tumors without an actionable driver mutation and without the expression of PD-L1 >50% (Herbst et al., 2018).

For the first time, the present inventors showed that the inventive targeting of paracrine signaling from different cell types of the cellular tumorigenic network breaks the intercellular crosstalk and demonstrates a highly effective treatment of tumors that are resistant to monotherapies of chemotherapeutics and targeted drugs against EGFR1-3 and VEGFR. In all treated NSCLC tumors randomly selected from a panel of 38 NSCLC tumors, growth was completely suppressed by the applied low dose inventive combination regimen. Among them were two highly treatment resistant tumors that did not respond to any tested therapy previously (LU7406 and LU7414). During the complete treatment duration, no tumor outgrowth was observed in either PDX model, indicating a strong therapy efficacy by preventing development of an adaptive resistance against this regimen. After treatment discontinuation growth suppression remained up to 18 days (LU7860) with only slight increase in tumor growth. This indicates a long-lasting and sustained effect of the combination therapy on the tumor biology.

The inventive combination therapy regimen can be considered as a low dose treatment regimen. The two drugs with a more pronounced safety profile in this therapy regimen are cabozantinib and afatinib. Cabozantinib is approved for the treatment of renal cell carcinoma and hepatocellular carcinoma and is efficacious in different tumor models at dosages between 30-60mg/kg once a day (You et al., 2011; Paratala et al., 2018; Kato et al., 2018). Therefore, the inventive drug combination use in our study only includes 50% or less of typically used cabozantinib concentrations in recently published preclinical studies. Afatinib is approved for the treatment of NSCLC either with activating EGFR mutation or in squamous cell carcinoma under or after progression on platinum-based chemotherapy and is efficacious in tumor models at dosages from 20mg/kg or higher once a day (Floc'h N et al., 2018). In the inventive combination therapy regimen used in this preclinical study, both drugs were used significantly below these state of the art drug doses, each at 15mg/kg and in addition to that paused after every 5 days of treatment. Plerixafor, approved for stem cell mobilization, and

etoricoxib, approved for pain treatment and degenerative and auto-inflammatory diseases, were used at state of the art concentration levels in the respective *in vivo* models (Singla et al., 2015; Jayaraman et al., 2010). The usage of this inventive combination regimen showed an excellent safety profile of the inventive pharmaceutical composition and might lead to less pronounced side effects in patients. Together with its excellent efficacy this inventive combination would be superior to a higher prescribed medication of single cabozantinib or afatinib.

Treatment with the inventive combination therapy does not seem to change the histopathological composition of tumors when compared to placebo treatment regarding the extent of the tumor and the stroma compartment as well as the number of blood vessels. Since the studies have been performed in nude mice, it remains open whether this treatment regimen impacts the infiltration, composition and effector phenotype of T cells. However, our studies also revealed that the expression of PD-L1, whose therapeutic targeting has essentially improved the prognoses of even metastasized NSCLC patients, was not affected by the inventive combination therapy, offering the opportunity of innovative combination therapies including immune checkpoint inhibitors.

Taken together the inventive pharmaceutical composition including the combination of active agents simultaneously inhibiting pathways forming a cellular tumorigenic network in NSCLC tumors can overcome resistance mechanisms of targeted therapy drugs. All of the active agents used in this inventive combination regimen are approved for different indications, and therefore their clinical profiles such as pharmacokinetics, pharmacodynamics and toxicities are well known. They are readily available as study drugs for usage in a clinical trial. In order to identify NSCLC patient subgroups that may respond to this therapeutic concept, inclusion criteria should require the proof of expression of the respective target gene set. Collected tumor specimens can easily be used for mRNA expression analysis by RNA sequencing or by a customized gene expression array. The analysis of mRNA expression as a predictive biomarker is already in clinical development (Schuler et al., 2019).

FURTHER EMBODIMENTS OF THE PRESENT INVENTION

1. Agents for the therapy of tumor diseases, comprising the combination therapy for the simultaneous inhibition of the signaling pathways (a) VEGFs and VEGFR1-3, (b) SDF1alpha and CXCR4, (c) EGF and EGFR, (d) COX2, PGE2 and EP, and (e) HGF and HGFR (MET).

2. Agents according to embodiment 1, additionally comprising a further combination of (1) with a PD-L1 or PD-1 inhibitor.

3. Agents according to embodiment 1, comprising a specific combination therapy of cabozantinib (against VEGFR2 and HGFR), afatinib (against EGFR), plerixafor (against CXCR4), and etoricoxib (against COX2) at doses equal to or below the approved monotherapies for each drug.

4. Agents according to embodiment 3, comprising a further combination with pembrolizumab or nivolumab or durvalumab or another PD-1/PD-L1 inhibitor targeting PD-1 or PD-L1.

The indication(s) of the claimed agent(s) are for:

Non-small cell lung cancer (NSCLC) of any histology (adenocarcinoma or squamous cell carcinoma).

Non-small cell lung cancer (NSCLC) with or without driver mutations such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF.

Other lung tumor diseases including small cell lung cancer and large cell lung cancer with or without driver mutation.

Tumor diseases of any origin with or without driver mutation.

The further embodiments as mentioned above relate to a therapeutic anti-cancer regimen comprising small molecules, e.g., tyrosine kinase inhibitors, and/or antibodies that target the following signal transduction pathways in a simultaneous, combined therapeutic approach: (a) VEGFs and VEGFRs, (b) SDF1alpha and CXCR4, (c) EGF and EGFR, (d) COX2, PGE2 and EP, and (e) HGF and HGFR. An example of the present invention is the combination therapy of the FDA and EMA approved drugs of (a) cabozantinib (or bevacizumab or sunitinib or sorafinib) with (b) afatinib (or gefitinib or osimertinib or cetuximab or erlotinib) with (c)

plerixafor and with (d) etoricoxib (or celecoxib) for the treatment of patients with non-small cell lung cancer.

The applied therapeutic dose of each drug for this combination treatment is either equal to the dose for each approved indication of that drug or at a therapeutic dose below the approved drug doses.

Treatment of highly resistant patient-derived NSCLC tumors with combination therapy of cabozantinib, afatinib, plerixafor, and etoricoxib results in complete inhibition of tumor growth at low doses and throughout the duration of treatment.

CLAIMS:

1. A pharmaceutical composition comprising a plurality of active agents in a therapeutically effective amount and one or more pharmaceutical excipients, characterized in that

   a. at least one active agent inhibits VEGF's and/or VEGFR1-3 signaling,

   b. at least one active agent inhibits SDF1alpha and/or CXCR4 signaling,

   c. at least one active agent inhibits EGF and/or EGFR1-3 signaling,

   d. at least one active agent inhibits COX2 and/or PGE2 and/or EP signaling, and

   e. at least one active agent inhibits HGF and/or HGFR (MET) signaling.

2. The pharmaceutical composition according to claim 1, wherein the

   a. at least one VEGF's and/or VEGFR1-3 inhibitor is selected from the group consisting of cabozantinib, regorafinib, bevacizumab, ramucirumab, pazopanib, sunitinib, sorafinib, ponatinib, vandetanib, axitinib, lenvatinib, ziv-Aflibercept, tivozanib, golvatinib, and foretinib, preferably cabozantinib and regorafinib, and/or

   b. at least one SDF1alpha and/or CXCR4 inhibitor is selected from the group consisting of plerixafor, motixafortide, LY2510924, and WZ811, preferably plerixafor, and/or

   c. at least one EGF and/or EGFR1-3 inhibitor is selected from the group consisting of afatinib, erlotinib, cetuximab, neratinib, necitumumab, gefitinib, lapatinib, osimertinib, canertinib, and saracatinib, preferably afatinib, cetuximab, neratinib, necitumumab, gefitinib, lapatinib, and osimertinib, more preferably afatinib, and/or

   d. at least one COX2 and/or PGE2 and/or EP inhibitor is selected from the group consisting of etoricoxib, celecoxib, parecoxib, rofecoxib, and valdecoxib, preferably etoricoxib and celecoxib, and/or

   e. at least one active agent inhibiting HGF and/or HGFR (MET) is selected from the group consisting of cabozantinib, tivantinib, crizotinib, capmatinib,

tepotinib, savolitinib, golvatinib, and foretinib, preferably cabozantinib and tivantinib.

3. The pharmaceutical composition according to claim 1 or 2, wherein the composition comprises a combination of active agents selected from the group consisting of

i. cabozantinib, afatinib, plerixafor, and etoricoxib,

ii. cabozantinib, afatinib, plerixafor, and celecoxib,

iii. cabozantinib, osimertinib, plerixafor, and etoricoxib,

iv. cabozantinib, osimertinib, plerixafor, and celecoxib,

v. cabozantinib, necitumumab, plerixafor, and etoricoxib,

vi. cabozantinib, necitumumab, plerixafor, and celecoxib,

vii. cabozantinib, cetuximab, plerixafor, and etoricoxib,

viii. cabozantinib, cetuximab, plerixafor, and celecoxib,

ix. cabozantinib, neratinib, plerixafor, and etoricoxib,

x. cabozantinib, neratinib, plerixafor, and celecoxib,

xi. cabozantinib, lapatinib, plerixafor, and etoricoxib ,

xii. cabozantinib, lapatinib, plerixafor, and celecoxib,

xiii. cabozantinib, gefitinib, plerixafor, and etoricoxib,

xiv. cabozantinib, gefitinib, plerixafor, and celecoxib,

xv. regorafenib, necitumumab, plerixafor, etoricoxib and tivantinib,

xvi. regorafenib, necitumumab, plerixafor, celecoxib and tivantinib,

xvii. regorafenib, cetuximab, plerixafor, etoricoxib and tivantinib,

xviii. regorafenib, cetuximab, plerixafor, celecoxib and tivantinib,

xix. regorafenib, osimertinib, plerixafor, etoricoxib and tivantinib,

xx. regorafenib, osimertinib, plerixafor, celecoxib and tivantinib,

xxi. regorafenib, afatinib, plerixafor, etoricoxib and tivantinib,

xxii. regorafenib, afatinib, plerixafor, celecoxib and tivantinib,

xxiii. regorafenib, cetuximab, plerixafor, etoricoxib and cabozantinib,

xxiv. regorafenib, cetuximab, plerixafor, celecoxib and cabozantinib,

xxv. regorafenib, necitumumab, plerixafor, etoricoxib and crizotinib, and

xxvi. regorafenib, necitumumab, plerixafor, celecoxib and crizotinib.

4. The pharmaceutical composition according to any one of the preceding claims, wherein the composition further comprises

   g. at least one active agent inhibiting PD-1 and/or PD-L1, wherein the PD-1 and/or PD-L1 inhibitor is preferably selected from the group consisting of pembrolizumab, nivolumab, durvalumab, and atezolizumab, preferably durvalumab.

5. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition contains one, two or more separate pharmaceutical dosage formulations, wherein each dosage formulation contains at least one active agent.

6. The pharmaceutical composition according to claim 5, wherein the one, two or more pharmaceutical dosage formulations are independently of each other the same or different, selected from the group consisting of

   i. solid dosage forms for oral or enteral application, wherein solid dosage forms are preferably include tablets, capsules, spheroids, mini-tablets, pellets, granules, and pills;

   ii. semi-solid dosage forms for topical application to skin or mucous membranes, wherein semi-solid dosage forms are preferably include creams, gels, ointments, and suppositories; and

   iii. liquid dosage forms for oral, external, or parenteral application, wherein liquid dosage forms preferably include mixtures, linctuses, elixirs, syrups, drops, lotions, liniments, collodions, nasal drops, nasal sprays, eye drops, inhalations, aerosols, and injections.

7. The pharmaceutical composition according to claim 5 or 6, wherein a first pharmaceutical dosage formulation contains the at least one active agent inhibiting b) SDF1alpha and CXCR4 and at least a second pharmaceutical dosage formulation contains two or more of the at least one active agents respectively inhibiting a) VEGF's and/or VEGFR1-3, c) EGF and/or EGFR1-3, d) COX2 and/or PGE2 and/or EP, e) HGF and/or HGFR (MET), and optionally f) PD-1 and/or PD-L1.

8. The pharmaceutical composition according to claim 7, wherein the first pharmaceutical formulation is a liquid dosage form, preferably an injection dosage form, and/or wherein the second pharmaceutical dosage form is a solid dosage form, preferably a tablet or capsule.

9. The pharmaceutical composition according to any of the preceding claims, wherein the dose regimen may comprise or consist of

   a. At least one active agent inhibiting VEGF's and/or VEGFR1-3 is administered once daily for up to five days followed by at least one, preferably two days without administration,

   b. At least one active agent inhibiting SDF1alpha and/or CXCR4 is administered once daily for up to five days, preferably for one day followed by at least one, preferably five days without administration,

   c. At least one active agent inhibiting EGF and/or EGFR1-3 is administered once daily for up to five days followed by at least one, preferably two days without administration,

   d. At least one active agent inhibiting COX2 and/or PGE2 and/or EP is administered once daily for up to five days followed by at least one, preferably two days without administration,

   e. At least one active agent inhibiting HGF and/or HGFR (MET) is administered once daily for up to five days followed by at least one, preferably two days without administration, and optionally

   f. At least one active agent inhibiting PD-1 and/or PD-L1 that is administered once daily for up to five days followed by at least one, preferably two days without administration.

10. A pharmaceutical composition according to any one of the preceding claims for use in the treatment or prophylaxis of a tumor, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF.

11. A method of treatment or prophylaxis of a tumor disease, preferably selected from the group consisting of renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastrointestinal stroma tumor (GIST), colorectal cancer (CRC), gastric cancer (GC) gastro-esophageal junction cancer (GEJ), neuro-endocrine tumor (NET), non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML) acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), differentiated thyroid cancer (DTC), breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, sarcoma, pancreatic cancer, Head & Neck carcinoma, glioma, lymphoma, respectively with or without driver mutations, such as EGFRm, KRAS, FGFR, ALK, cKIT, BRAF, comprising administering to a patient in need a pharmaceutical composition in accordance with any one of claims 1 to 10.

12. The pharmaceutical composition according to claim 10, or the method of treatment or prophylaxis of a tumor disease according to claim 11, wherein the pharmaceutical composition is administered by one or more of the administration routes selected from enteral administration, preferably oral administration, and/or intranasal administration and/or sub-lingual administration and/or buccal administration of the inventive pharmaceutical composition that comprises one or more pharmaceutical formulations.

13. The pharmaceutical composition according to claim 10 or 12, or the method of treatment or prophylaxis of a tumor disease according to claim 11 or 12, wherein the inventive pharmaceutical composition is administered in an interval

without administration of the pharmaceutical composition, preferably in an interval comprising one or more, preferably five or more days of administration of the pharmaceutical composition followed by one or more days without administration of pharmaceutical composition.

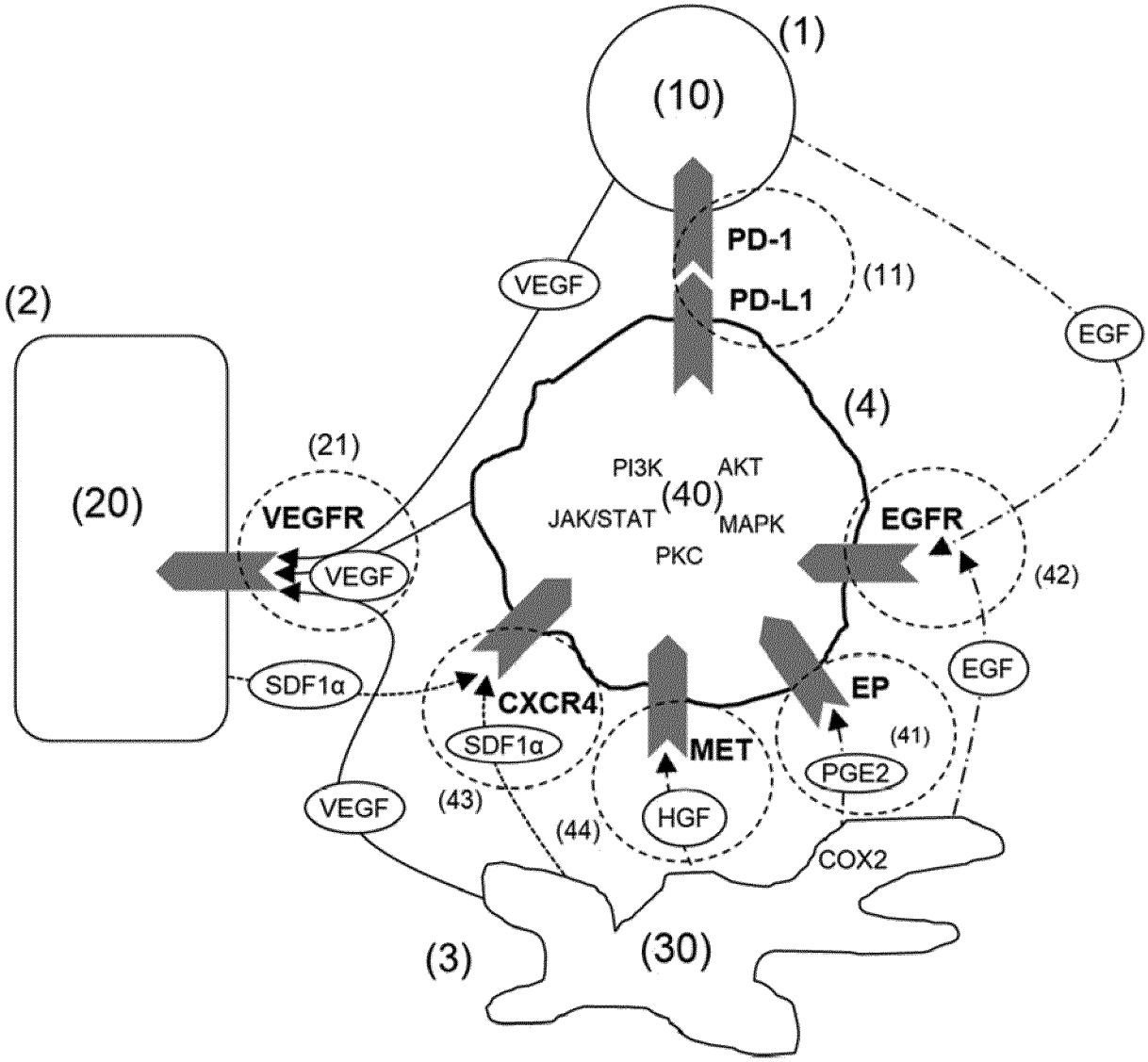
(1)
(10)
PD-1
PD-L1
(11)
VEGF
EGF
(2)
(20)
(21)
VEGFR
VEGF
(4)
PI3K
AKT
(40)
JAK/STAT
MAPK
PKC
EGFR
(42)
SDF1α
CXCR4
SDF1α
MET
HGF
EP
PGE2
(41)
EGF
VEGF
(43)
(44)
COX2
(3)
(30)

FIG. 1

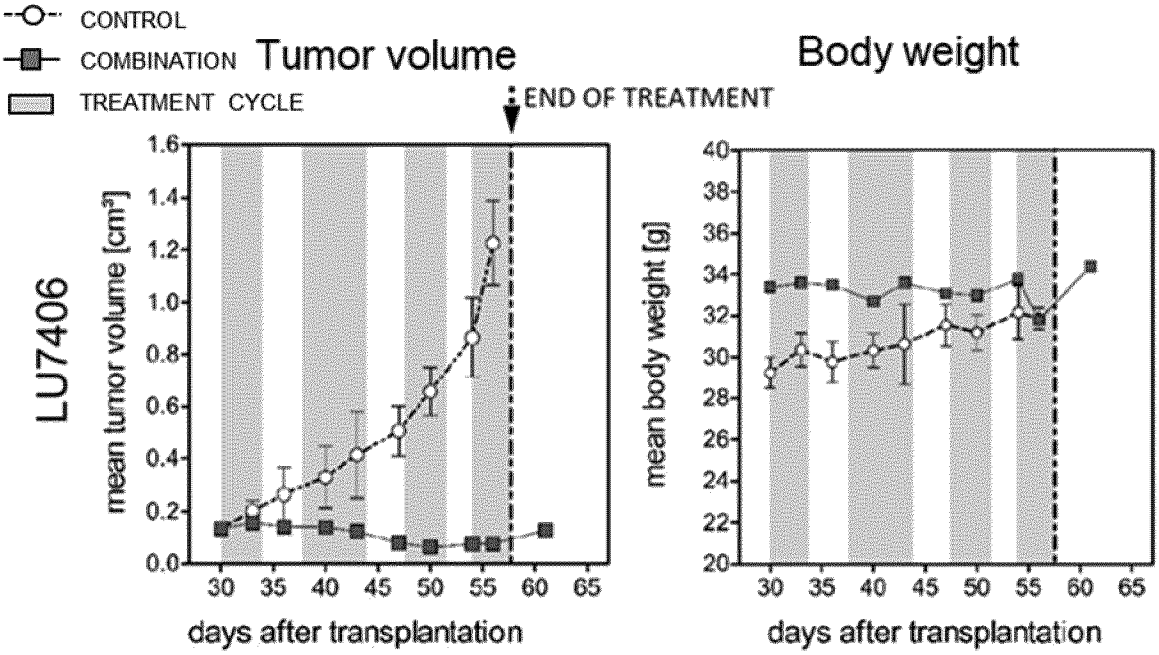
CONTROL
COMBINATION
TREATMENT CYCLE
Tumor volume
Body weight
END OF TREATMENT
LU7406
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation

FIG. 2a)

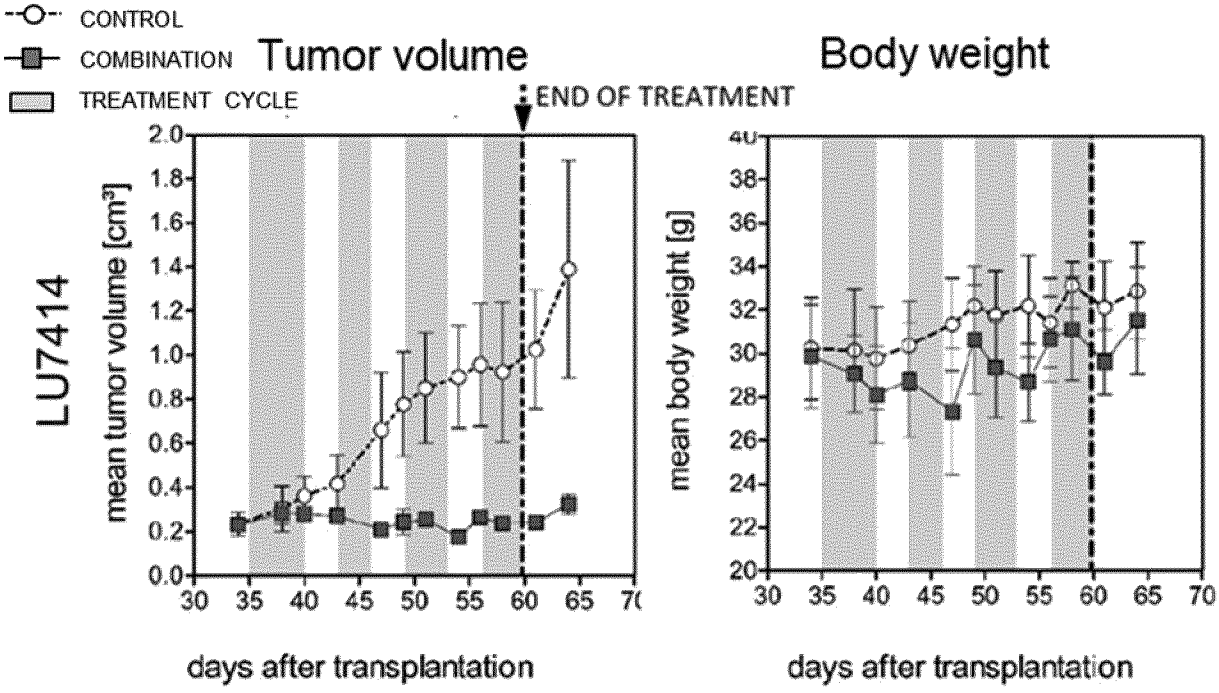
CONTROL
COMBINATION
TREATMENT CYCLE
Tumor volume
Body weight
END OF TREATMENT
LU7414
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation

FIG. 2b)

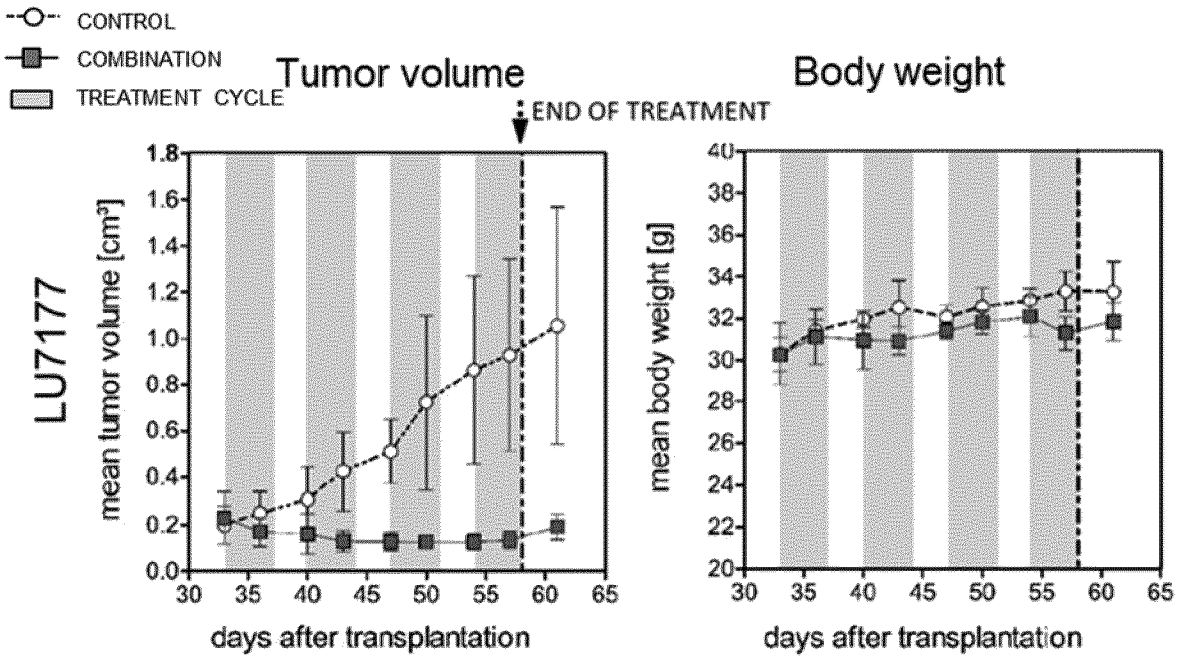
CONTROL
COMBINATION
TREATMENT CYCLE
Tumor volume
END OF TREATMENT
Body weight
LU7177
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation

FIG. 2c)

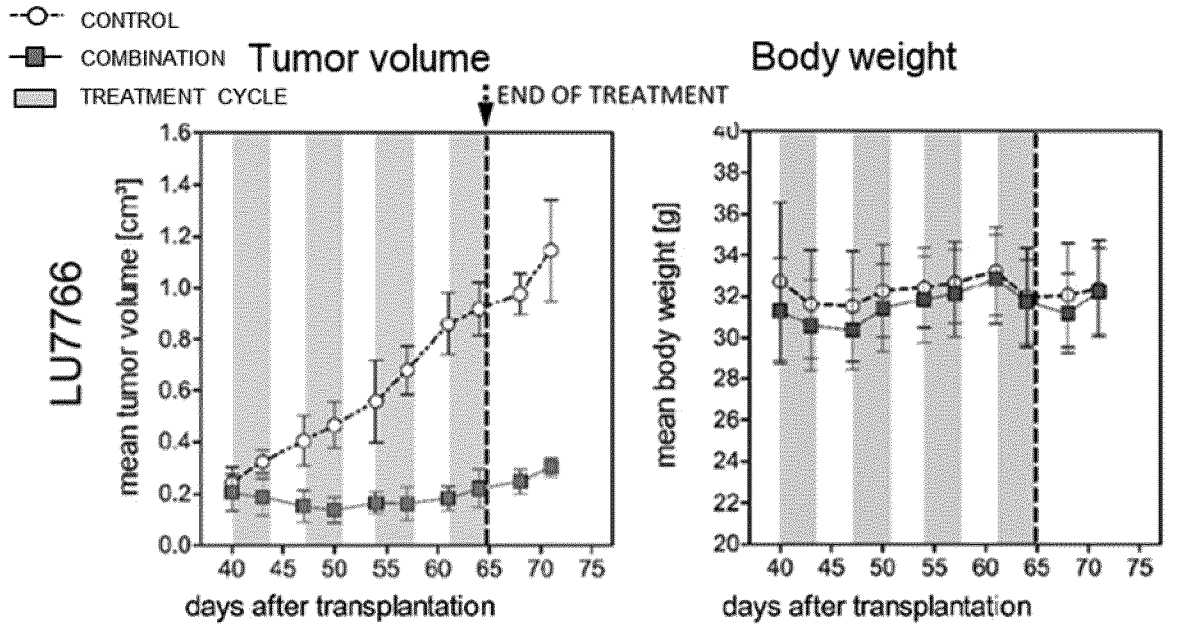
CONTROL
COMBINATION
TREATMENT CYCLE
Tumor volume
END OF TREATMENT
Body weight
LU7766
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation

FIG. 2d)

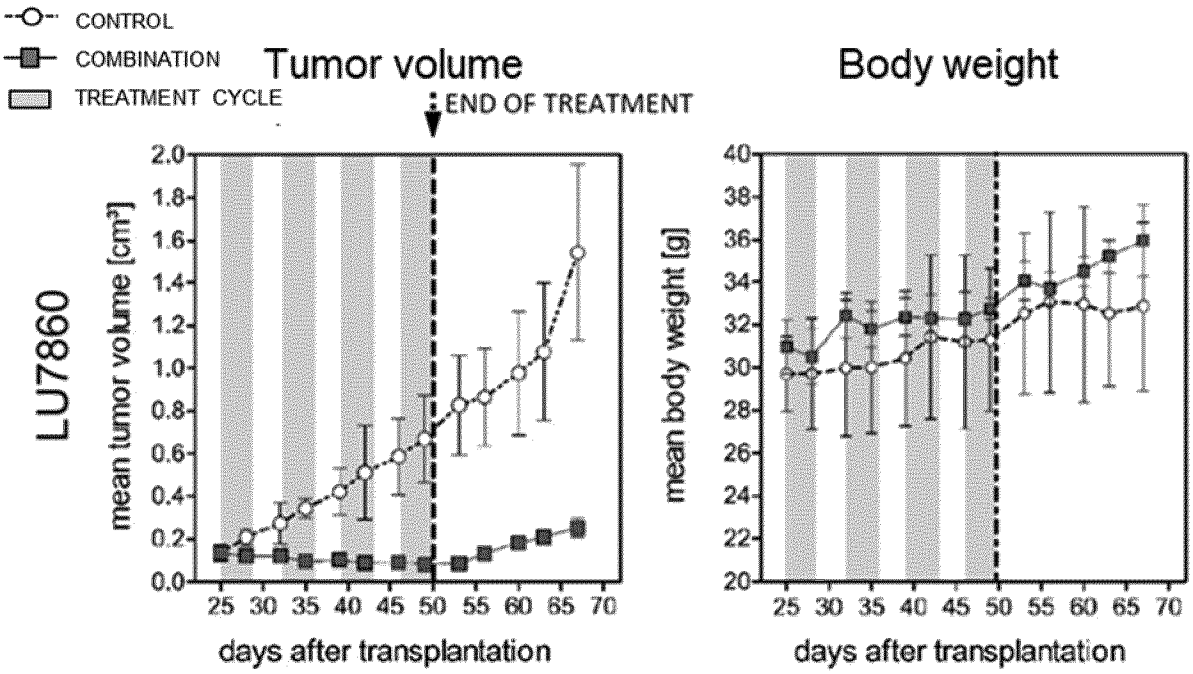
CONTROL
COMBINATION
TREATMENT CYCLE
Tumor volume
END OF TREATMENT
Body weight
LU7860
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation

FIG. 2e)

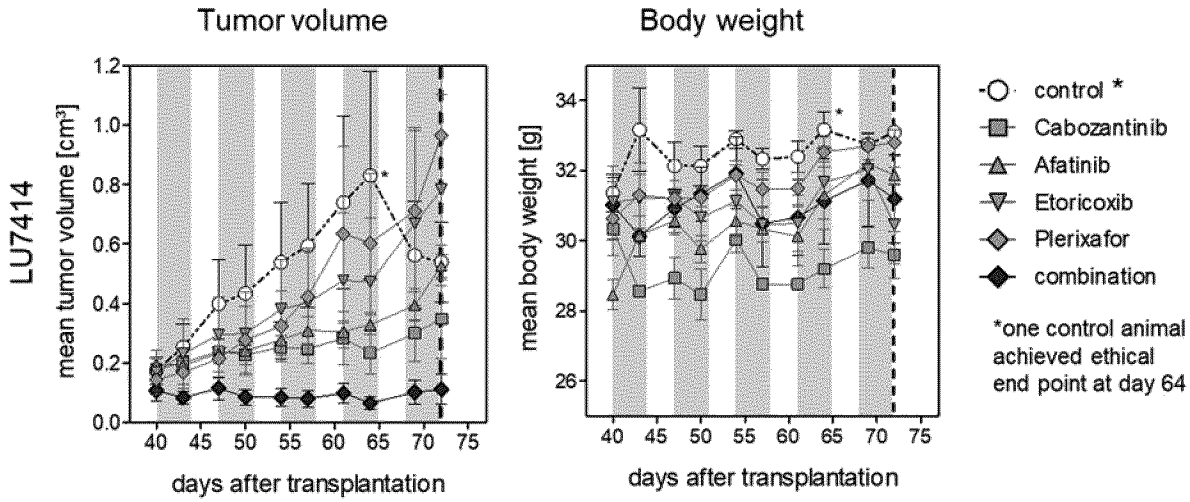
Tumor volume
Body weight
LU7414
mean tumor volume [cm³]
mean body weight [g]
days after transplantation
days after transplantation
control *
Cabozantinib
Afatinib
Etoricoxib
Plerixafor
combination
*one control animal achieved ethical end point at day 64

FIG. 2f)