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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 September 2017 (14.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/153932 A1

(51) International Patent Classification:
G01N 33/574 (2006.01) *A61P 35/00* (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:
PCT/IB2017/051360

(22) International Filing Date:
8 March 2017 (08.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2016/076046 10 March 2016 (10.03.2016) CN

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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, DJ, 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, 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, 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:

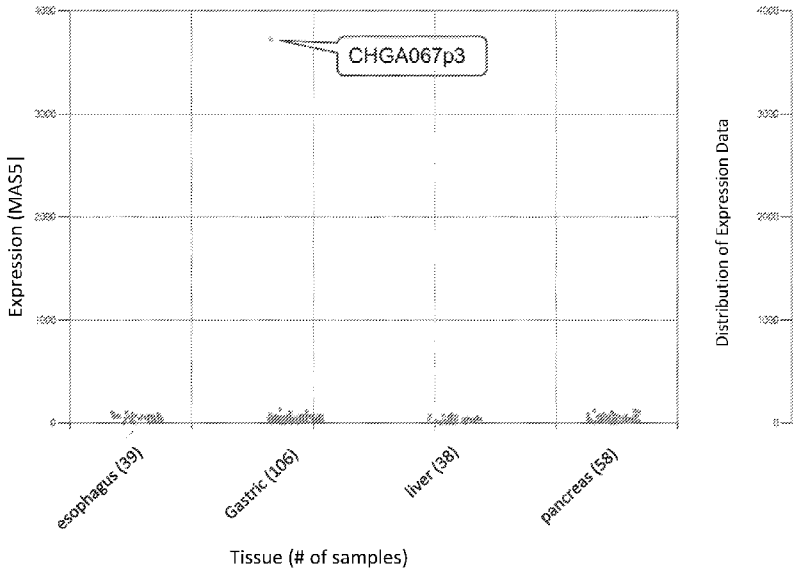
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) Title: STRN-ALK FUSION AS A THERAPEUTIC TARGET IN GASTRIC CANCER

Figure 1



(57) Abstract: The present disclosure relates to an ALK inhibitor for use in treating a mammalian cancer, particularly gastric cancer in human; use of an ALK inhibitor for the preparation of a medicament for the treatment of gastric cancer; methods of selectively treating a patient having gastric cancer with an ALK inhibitor or a drug other than ALK inhibitor; a method of or a kit for use in predicting the likelihood that a patient having a gastric cancer will respond to treatment with an ALK inhibitor; a kit for use in treating a patient having gastric cancer and other closely related methods and kits.

WO 2017/153932 A1

Published:

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

STRN-ALK FUSION AS A THERAPEUTIC TARGET IN GASTRIC CANCER

FIELD OF THE DISCLOSURE

The present disclosure relates to an ALK inhibitor for use in treating a mammalian cancer, particularly gastric cancer in human; use of an ALK inhibitor for the preparation of a medicament for the treatment of gastric cancer; methods of selectively treating a patient having gastric cancer with an ALK inhibitor or a drug other than ALK inhibitor; a method of or a kit for use in predicting the likelihood that a patient having a gastric cancer will respond to treatment with an ALK inhibitor; a kit for use in treating a patient having gastric cancer and other closely related methods and kits.

BACKGROUND OF THE DISCLOSURE

Epidemiological data from the WHO suggest that gastric cancer is the fifth most-common malignancy in the world, after cancers of the lung, breast, colorectum and prostate (Ferlay, J. et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer (2015), 136, E359–E386). Although, early detection rates have improved, most patients present at advanced stages and are subsequently treated by palliative chemotherapy, with median survival times of about 10–12 months (Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97).

Because traditional cytotoxic chemotherapies have generated only small improvements in survival outcomes for patients with advanced gastric cancer and in addition because of their toxicity, more specific therapeutic regimens such as targeted agents have been sought to improve the outcomes and quality of life of patients. Several candidate receptor tyrosine kinases (MET receptor, EGFR, HER2, and FGFR) have been discovered for targeted therapies for patients with gastric cancer (Deng N, Goh LK, Wang H, et al. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. Gut. 2012;61:673–84). Although many clinical trials are ongoing, only a small number of patients with gastric cancer are suited for molecular targeted therapies. Hence, more active searching of novel targets in gastric cancer is essential.

There is a continuing need in the art for uncovering so far unrecognized subsets of gastric cancer that may harbor genetic alterations which would help us to predict response to targeted therapies.

SUMMARY OF THE DISCLOSURE

It is an object of the present disclosure to provide a novel STRN-ALK gene fusion as a targetable genomic alteration in gastric cancer, and to provide an ALK inhibitor for

use in treating gastric cancer characterized by the presence a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

In accordance with the present disclosure a novel STRN-ALK gene fusion was surprisingly identified as a targetable genomic alteration by comprehensive analysis of patient derived gastric-tumor xenograft model. The therapeutic efficacy of ALK targeted tyrosine kinase inhibitor ceritinib was subsequently tested in the xenograft model carrying STRN-ALK gene fusion, and it has been demonstrated that the model was highly responsive to the treatment. Knowledge of the fact that the STRN-ALK fusion can drive the proliferation of gastric cancer and that the cancer can respond to an ALK inhibitor can be applied, among others, when characterizing a sample of gastric cancer, or for providing means to detect said alteration in gastric cancer, such as for example a method for detecting the STRN-ALK gene fusion or a STRN-ALK fusion polypeptide in a biological sample or a kit comprising a probe that is capable of detecting the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

In one aspect, the present disclosure relates to an ALK inhibitor for use in treating gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

In another aspect, the disclosure provides the use of an ALK inhibitor for the preparation of a medicament for the treatment of gastric cancer, wherein the gastric cancer is characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

In another aspect, the present disclosure relates to a method of selectively treating a patient having gastric cancer with an ALK inhibitor, wherein the method comprises the steps of:

(a) selecting the patient for the treatment with an ALK inhibitor on the basis of the patient having the gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and

(b) thereafter, administering a therapeutically effective amount of an ALK inhibitor to the patient.

In yet another aspect, the present disclosure relates to a method of selectively treating a patient having gastric cancer, comprising either:

(a) selectively administering a therapeutically effective amount of an ALK inhibitor to the patient on the basis of the patient having the gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; or

(b) selectively administering a therapeutically effective amount of a drug other than an ALK inhibitor to the patient on the basis of the patient not having the gastric cancer

characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

In a further aspect, the present disclosure relates to a method of selectively treating a patient having gastric cancer with an ALK inhibitor, comprising:

(a) assaying a biological sample obtained from the patient for a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide;

(b) thereafter, selecting the patient for the treatment with an ALK inhibitor on the basis of the patient having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and

(c) thereafter, administering a therapeutically effective amount of an ALK inhibitor to the patient.

In yet a further aspect, the present disclosure relates to a method of selectively treating a patient having gastric cancer, comprising:

(a) assaying a biological sample obtained from the patient for STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and

(b) thereafter, selectively administering to the patient either:

(i) a therapeutically effective amount of an ALK inhibitor on the basis of the biological sample obtained from the patient having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; or

(ii)a therapeutically effective amount of a drug other than an ALK inhibitor on the basis of the biological sample obtained from the patient not having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

In another aspect, the present disclosure relates to a method of predicting the likelihood that a patient having a gastric cancer will respond to treatment with an ALK inhibitor, comprising assaying a biological sample obtained from the patient for the presence or absence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide, wherein:

(a) the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor; and

(b) the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

In another aspect, the present disclosure relates to a method of characterizing a human gastric cancer, comprising

(a) obtaining a biological sample from said human gastric cancer; and

(b) detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide in said sample, thereby characterizing said gastric cancer based on the presence or absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

In yet another aspect, the present disclosure relates to a method for detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide in a biological sample from a human gastric cancer, comprising detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide in said sample, thereby detecting whether the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is present in said biological sample.

In a further aspect, the present disclosure relates to a kit for detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide in a biological sample from a human gastric cancer, comprising at least one probe capable of detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide and instructions for using the probe to assay the biological sample for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

In a further aspect, the present disclosure relates to a kit for use in predicting the likelihood that a patient having gastric cancer will respond to the treatment with an ALK inhibitor comprising:

(a) at least one probe capable of detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and

(b) instructions for using the probe to assay a biological sample from the gastric cancer patient for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor and the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

In yet a further aspect, the present disclosure relates to a kit for use in treating a patient having gastric cancer comprising:

(a) a therapeutically effective amount of an ALK inhibitor;

(b) at least one probe capable of detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide;

(c) instructions for using the probe to assay a biological sample obtained from the patient for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide,

(d) instructions for administering the ALK inhibitor to the patient if the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is present in the biological sample obtained from the patient ; and

(e) optionally, means for administering the ALK inhibitor to the patient.

Specifically, the present disclosure provides the following aspects, advantageous features and specific embodiments, respectively alone or in combination, as listed in the claims below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 ALK Over-expression in CHGA067p3. Gene expression data of primary xenograft tissues were characterized by Affymetrix GeneChip Human Genome U133 Plus 2.0 Array. Probe sets from the Affymetrix gene expression datasets were normalized using MAS5 with a trimmed-mean target of 500. The probe set 208212_s_at was used to represent the expression levels of *ALK*. Samples were grouped according to their cancer indications, and the number of samples in each group was indicated in parentheses.

FIG. 2 Tumor volumes in CHGA067 gastric tumor xenograft model after administration of vehicle control or different doses of ceritinib (LDK378). Treatments started on day 55 post implantation. LDK378 was administered po, at 25 mg/kg, 50mg/kg and 100mg/kg qd, 7 times a week for 22 days. Vehicle control for LDK378 (0.5% Methylcellulose, 0.5% Tween 80) was administered po, qd, for 22 days. Initial group size: 8 animals. All final data were recorded on day 76 post implantation.

FIG. 3 Change in body weight (CHGA067 gastric tumor xenograft model) after administration of vehicle control or different doses of ceritinib (LDK378). Treatments started on day 55 post implantation. LDK378 was administered po, at 25 mg/kg, 50mg/kg and 100mg/kg qd, 7 times a week for 22 days. Vehicle control for LDK378 (0.5% Methylcellulose, 0.5% Tween 80) was administered po, qd, for 22 days. Initial group size: 8 animals. Body weight was recorded twice a week during 22 day treatment. All final data were recorded on day 76 post implantation.

FIG. 4 Tumor volumes in CHGA067 gastric tumor xenograft model on Day 22 post treatment with either vehicle control or different doses of ceritinib (LDK378). Treatments started on day 55 post implantation. LDK378 was administered po, at 25 mg/kg, 50mg/kg and 100mg/kg qd, 7 times a week for 22 days. Vehicle control for LDK378 (0.5% Methylcellulose, 0.5% Tween 80) was administered po, qd, for 22 days. Initial group size: 8 animals. Distribution of individual tumor volume in each treatment group on final day of treatment (day 22 post treatment, day 76 post implantation) was plotted.

DETAILED DESCRIPTION OF THE DISCLOSURE

Use of specific therapeutic regimens is more beneficial for a patient, as it is proven to be less toxic and more effective. Previous studies uncovered only limited subset of gastric cancer characterized by specific genetic signatures, which allow predicting response to targeted therapies. The inventors have now identified a transforming STRN-ALK fusion as a therapeutic target in gastric cancer, and illustrated the potential for personalized molecular based therapy for the treatment of advanced malignancies. The disclosure is based on the identification of a novel transforming ALK fusion event involving STRN gene in gastric cancer xenograft model. Advantageously, the disclosure can be used for predicting the likelihood that a patient having a gastric cancer will respond to treatment with an ALK inhibitor based on the presence or absence of STRN-ALK gene fusion or STRN-ALK fusion polypeptide, and thus specifically select patients having gastric cancer who will benefit from treatment with an ALK inhibitor.

In one aspect, the present disclosure relates to an ALK inhibitor for use in treating gastric cancer characterized by the presence a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

The terms "a" and "an" and "the" and similar references in the context of describing the disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Where the plural form is used for compounds, patients, cancers and the like, this is taken to mean also a single compound, patient, or the like.

The term "ALK", as used herein, refers to anaplastic lymphoma kinase, also known as ALK tyrosine kinase receptor or CD246 (cluster of differentiation 246). The Entrez Gene ID is 238.

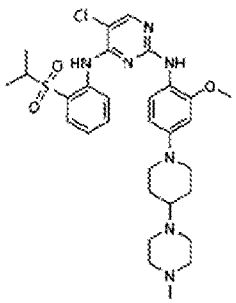
The term "STRN", as used herein, refers to striatin (calmodulin binding protein). The Entrez Gene ID is 6801. STRN encodes a calcium-dependent calmodulin-binding protein.

The term "STRN-ALK gene fusion", as used herein, refers to abnormal DNA rearrangement, where the STRN gene is fused to the ALK gene. This abnormal gene fusion leads to the production of a fusion protein (STRN-ALK), referred herein as "STRN-ALK fusion polypeptide". For example, as disclosed herein, an STRN-ALK gene fusion may involve the intrachromosomal translocation of exons 1-3 of STRN to exons 20-29 of ALK (E3:E20).

In the present disclosure, an ALK inhibitor can be a compound that inhibits ALK with the IC50 of less than 100 μM, preferably less than 10 μM, more preferably less than 1μM, measured by a Caliper mobility shift assay. The Caliper mobility shift technology is based on the separation of particles of different charges and sizes in an electrical field, similar to capillary electrophoresis. The Caliper kinase assays utilize fluorescently labeled peptides as kinase substrates. The phosphorylation of the peptide in the course of the

reaction introduces additional negative charges via the phosphate and hence permits its separation from the phosphorylated peptide. Both, the separation and the detection of the labeled peptides take place in the microfluidic system of the Caliper Lab Chip. The LabChips have 12 "sippers" enabling the parallel analysis of 12 samples at the same time. The fact that both, unphosphorylated peptide (substrate) and phosphorylated peptide (product) are measured and that the separation makes the readout relatively insensitive to interference by fluorescent compounds results in the excellent data quality of this assay. General assay procedure can be performed at 30°C for 60 min in a total volume of 9 µL including 0.050 µL of compound dilution or pure DMSO, respectively. The reaction can be terminated by the addition of 16 µL of stop solution (100 mM Hepes, 5 % (v/v) DMSO, 0.1 % (v/v) Coating reagent, 10 mM EDTA, 0.015 % (v/v) Brij 35). After termination of the reactions, the plates are transferred into the Caliper LabChip 3000 workstation for analysis. The effect of a compound on the enzymatic activity is obtained from the linear progress curves in the absence and presence of the compound and routinely determined from one reading (end point measurement).

According to the present disclosure, the ALK inhibitor can be for example a compound selected from the group consisting of



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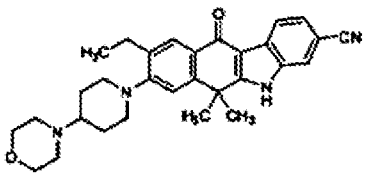
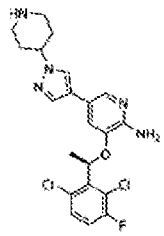
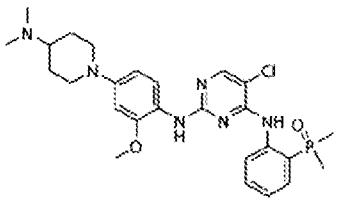


Alectinib



Crizotinib



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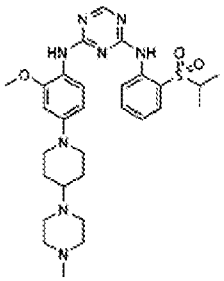

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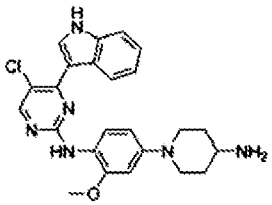


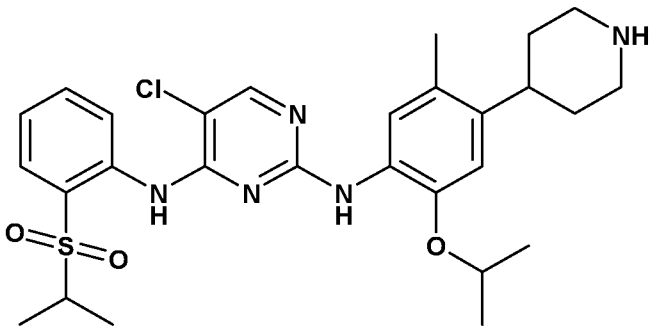
AZD3463

and 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compound when used according to this disclosure and, which typically are not biologically or otherwise undesirable. Pharmaceutically

acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide / hydrobromide, bicarbonate / carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate, trifluoroacetate salt or the like. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

In a preferred embodiment, the present disclosure relates to the ALK inhibitor 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof. The compound 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, also known under name ceritinib, is a compound of formula I, and is described in Example 7 (Compound 66) of WO2008/073687.



(I).

The term "gastric cancer", as used herein, also known as stomach cancer, is cancer developing from the lining of the stomach. Almost all gastric cancers are adenocarcinomas. Other types of gastric cancer are gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, and lymphomas. Gastric cancer is often diagnosed at an advanced stage because there are no early signs or symptoms. In one embodiment, the present disclosure relates to metastatic gastric cancer.

The term "treatment" as used herein comprises a treatment relieving, reducing or alleviating at least one symptom in a subject, increasing progression-free survival, overall survival, extending duration of response or delaying progression of a disease. For example, treatment can be the diminishment of one or several symptoms of a disorder or complete eradication of a disorder, such as cancer. Within the meaning of the present disclosure, the term "treatment" also denotes to arrest, delay the onset (i.e., the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease in a patient, e.g., a mammal, particularly the patient is a human. The term "treatment" as used herein comprises an inhibition of the growth of a tumor

incorporating a direct inhibition of a primary tumor growth and / or the systemic inhibition of metastatic cancer cells.

An ALK inhibitor can be used in treating gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide has been detected in a biological sample from the cancer obtained from a patient having said cancer.

The term “biological sample”, as used herein, refers to a biological specimen taken by sampling so as to be representative of any other specimen taken from the source of the specimen. In one embodiment, a biological sample is cells or tissue from the cancer obtained from a patient having said cancer.

A "subject," "individual" or "patient" is used interchangeably herein, which refers to a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, mice, simians, humans, farm animals, sport animals, and pets.

Before treatment, a patient population can be stratified according to the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide. For example, a patient having gastric cancer can be first selected for the treatment with an ALK inhibitor on the basis of the patient having STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and thereafter, a therapeutically effective amount of an ALK inhibitor is administered to the patient. Patient can be selected based on the presence of the fusion. Depending on the outcome of the selection step, or the characterization of the gastric cancer that a patient has, the patient can be administered an ALK inhibitor. For example, a patient can be administered a therapeutically effective dose of the ALK inhibitor once it has been determined that the fusion is present in the cancer. In alternative, if it turns out that the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide are not present in the patient sample or a cancer sample , the patient can be administered some other drug which may be better suited to treat the special cancer subtype.

The presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide can also be used as an indicator of an increased likelihood that the patient will respond to treatment with an ALK inhibitor. Therefore, the result of detection step can tell a physician or an informed person whether a patient is likely going to respond to the treatment with an ALK inhibitor. Generally, the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide can be indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor; and the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide can be indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

As used herein, “selecting” and “selected” in reference to a patient is used to mean that a particular patient is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria. Similarly, “selectively

treating" refers to providing treatment to a patient having a particular disease, where that patient is specifically chosen from a larger group of patients on the basis of the particular patient having predetermined criteria. Similarly, "selectively administering" refers to administering a drug to a patient that is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having predetermined criteria. By selecting, selectively treating and selectively administering, it is meant that a patient is delivered a personalized therapy based on the patient's particular biology, rather than being delivered a standard treatment regimen based solely on the patient having a particular disease. Selecting, in reference to a method of treatment as used herein, does not refer to fortuitous treatment of a patient that has the biomarker, but rather refers to the deliberate choice to administer treatment to a patient based on the patient having the biomarker. Thus, selective treatment differs from standard treatment, which delivers a particular drug to all patients, regardless of their biomarker.

The term "a therapeutically effective amount" of a compound of the present disclosure refers to an amount of the compound of the present disclosure that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc.

A therapeutically effective amount of an ALK inhibitor in vivo may range depending on the route of administration, between about 0.05 to about 50 mg per kg body weight per day, preferably about 0.1-25 mg/kg/day, more preferably from about 0.5-10 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to a preferable dosage range of about 35-700 mg per day. Daily dose of ceritinib can be for example 750 mg. The recommended dose and schedule for crizotinib is 250 mg orally, twice daily, with or without food. Alectinib can be for example used by administering 300 mg twice daily.

The patient having gastric cancer can be selected for the treatment with an ALK inhibitor based on assaying a biological sample obtained from the patient for STRN-ALK gene fusion or the STRN-ALK fusion polypeptide. An ALK inhibitor can be then used in treating a patient having gastric cancer characterized in that:

(a) a biological sample obtained from the patient is assayed for STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and

(b) a therapeutically effective amount of an ALK inhibitor is selectively administered to the patient on the basis of the biological sample from the patient having STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

The term "assaying" is used to refer to the act of identifying, screening, probing or determining, which act may be performed by any conventional means. For example, a sample may be assayed for the presence of a particular marker by using an ELISA assay, a Northern blot, imaging, etc. to detect whether that marker is present in the sample. The

terms "assaying" and "determining" contemplate a transformation of matter, e.g., a transformation of a biological sample, e.g., a blood sample or other tissue sample, from one state to another by means of subjecting that sample to physical testing. Further, as used herein, the terms "assaying" and "determining" are used to mean testing and/or measuring. The phrase "assaying a biological sample from the patient for..." and the like is used to mean that a sample may be tested (either directly or indirectly) for either the presence or absence of a given factor or for the level of a particular factor. It will be understood that, in a situation where the presence of a substance denotes one probability and the absence of a substance denotes a different probability, then either the presence or the absence of such substance may be used to guide a therapeutic decision.

The assaying or detection for STRN-ALK gene fusion or the STRN-ALK fusion polypeptide can comprise a technique selected from the group consisting of Next Generation Sequencing (NGS), Northern blot analysis, polymerase chain reaction (PCR), reverse transcription-polymerase chain reaction (RT-PCR), TaqMan-based assays, direct sequencing, dynamic allele-specific hybridization, high-density oligonucleotide SNP arrays, restriction fragment length polymorphism (RFLP) assays, primer extension assays, oligonucleotide ligase assays, Southern Blot, immunoassays, immunohistochemistry, ELISA, fluorescence in situ hybridization analysis (FISH), kinase activity assays, flow cytometry, Western blot, HPLC, immunohistochemistry (IHC) and mass spectrometry. In a preferred embodiment, the step of assaying or detection for STRN-ALK gene fusion comprises PCR, RT-PCR or fluorescence in situ hybridization analysis (FISH). In another preferred embodiment, the step of assaying or detection for the STRN-ALK fusion polypeptide comprises immunohistochemistry. Techniques are generally known to a person skilled in biochemistry, microbiology and diagnostic tests. In addition, the techniques can be applied according to explanation and instruction found in further references such as for example WO2008/127248, WO2012162373 or references cited therein.

An ALK inhibitor can be administered for at least 6 months. In a preferred embodiment, a therapeutically effective amount of the ALK inhibitor is administered for at least 6 months. In a further embodiment, the ALK inhibitor leads to a progression free survival of at least 6 months.

The ALK inhibitor can be administered as a first line or as a second line treatment. Generally, until further clinical data is generated, the ALK inhibitor is administered after a patient has been given a standard of care, but has relapsed or has become intolerant to the standard of care, or the cancer has become resistant to the first line medicaments. However, it is expected that targeted therapy may provide clinical benefit over the standard of care and thus it can be valuable to administer the ALK inhibitor as a first line treatment. Therefore, the present disclosure also relates to the administration of the ALK inhibitor as a first line treatment.

An ALK inhibitor can also be used for the preparation of a medicament for the treatment of gastric cancer, wherein the gastric cancer is characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

As used herein, "predicting" indicates that the methods described herein provide information to enable a health care provider to determine the likelihood that an individual having the disorder will respond to or will respond more favorably to treatment. It does not refer to the ability to predict response with 100% accuracy. Instead, the skilled artisan will understand that it refers to an increased probability.

As used herein, "likelihood" and "likely" is a measurement of how probable an event is to occur. It may be used interchangeably with "probability". Likelihood refers to a probability that is more than speculation, but less than certainty. Thus, an event is likely if a reasonable person using common sense, training or experience concludes that, given the circumstances, an event is probable. In some embodiments, once likelihood has been ascertained, the patient may be treated (or treatment continued, or treatment proceed with a dosage increase) with the test compound. In one embodiment, the "likelihood" and "likely" denote a chance in percent of how probable an event is to occur.

The phrase "increased likelihood" refers to an increase in the probability that an event will occur. For example, some methods herein allow prediction of whether a patient will display an increased likelihood of responding to treatment with the test molecule or an increased likelihood of responding better to treatment with the test molecule. In one embodiment the increased likelihood means that there is more than 50% chance, more than 60 % chance, more than 70 % or more than 80 % chance that an event will occur. Equally, a decreased likelihood means, that the chance is lower than 50%, lower than 60 %, lower than 70 % or lover than 80 %, respectively, that an event will occur.

The diagnosis or the determination of whether a patient with a gastric cancer can be done by using a kit for use in predicting the likelihood that a patient having gastric cancer will respond to the treatment with an ALK inhibitor comprising:

(a) at least one probe capable of detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and

(b) instructions for using the probe to assay a biological sample from the gastric cancer patient for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor and the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

In one embodiment, the probe is an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the STRN-ALK gene fusion, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic

marker of the STRN-ALK gene fusion, or the probe is an antibody that binds to the STRN-ALK fusion polypeptide. Further details on how to prepare for example an antibody that binds to a specific region of a polypeptide can be found in literature such as in WO2008/127248, WO2012162373 or references cited therein. Generally, well known techniques can be used in preparing, testing and validating a suitable probe that binds to a STRN-ALK gene fusion. Similarly, a process of preparing and selecting, testing and validating an antibody that binds to a specific target is also well known in the art. In the same manner the antibody can be prepared that binds to the STRN-ALK fusion polypeptide

The probe can be an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the STRN-ALK gene fusion, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic marker of the STRN-ALK gene fusion, or the probe is an antibody that binds to the STRN-ALK fusion polypeptide.

The following Examples illustrates the disclosure described above, but is not, however, intended to limit the scope of the disclosure in any way. Other test models known as such to the person skilled in the pertinent art can also determine the beneficial effects of the claimed disclosure.

Examples

Example 1:

SUMMARY:

A novel STRN-ALK gene fusion was identified as a targetable genomic alteration by comprehensive analysis of a gastric model CHGA067 from NIBR Shanghai Primary Xenograft Collection. The therapeutic efficacy of ALK targeted tyrosine kinase inhibitor ceritinib was subsequently tested in the xenograft model carrying STRN-ALK gene fusion, and it has been demonstrated that the model was highly responsive to the treatment.

METHODS:

Gene expression data of primary xenograft tissues were characterized by Affymetrix GeneChip Human Genome U133 Plus 2.0 Array. Probe sets from the Affymetrix gene expression datasets were normalized using MAS5 with a trimmed-mean target of 500. The probe set 208212_s_at was used to represent the expression levels of ALK.

One microgram of high-quality total RNA with an RNA integrity number (RIN) score ≥ 7 was also processed using the Illumina TruSeq RNA Sample Prep Kit according to the manufacturer's instructions. The libraries were sequenced on an Illumina HiSeq 2500

using a 100 nucleotide paired-end indexed run and the standard Illumina primers. Junction reads that were partially aligned to ALK open reading frame were identified using Bowtie. These reads were then assembled to identify ALK fusion genes.

RESULTS

STRN-ALK translocation in CHGA067 human gastric cancer xenograft model

Comprehensive analysis of a gastric model CHGA067 from Shanghai Primary Xenigraft Collection revealed ALK overexpression (Fig. 1), however no ALK activation mutations were found in CHGA067. Assembly of the RNA-Seq reads mapped to ALK Exon 20 sequence have revealed STRN-ALK Translocation in CHGA067. STRN is located on chromosome 2 between EML4 and ALK. It has been found that CHGA067 contains fusion of STRN exon 3 and ALK exon 20 (E3:E20), resulting into the following nucleotide sequence, where underlined sequence corresponds to STRN, and non-underlined sequence corresponds to ALK:

CAGGAAAGAGCCAAATACCACAAGTTGAAATACGGGACAGAATTGAATCAGGGAGATATGAAGCCTCCAAGC
TATGATTCTGTGTACCGCCGGAAGCACCAGGAGCTGCAAGCCATGCAGATGGAGCTGCAGAGCCCTGAGTAC
AAGCTGAGCAAGCTCCGCA

The corresponding amino acid sequence at the break point, where underlined sequence corresponds to STRN, non-underlined sequence corresponds to ALK and the amino acid residue V in bold font was resulted from the fusion, is:

QERAKYHKLKYGTELNQGDMKPPSYDS**V**YRRKHQELQAMQMELQSPEYKLSKLR

Response to ceritinib (LDK378) treatment

Based on the STRN-ALK fusion, the mice of CHGA067 gastric tumor xenograft model were injected with either vehicle control or different doses of ceritinib (LDK378). Tumor volumes (Fig. 2) and body weight (Fig. 3) were measured after administration of vehicle control or different doses of ceritinib (LDK378). LDK378 induced tumor regression in CHGA067 (Fig. 2-4). Furthermore, it has been demonstrated that tumor response was dose dependent: dose of 25 mg/kg (QD) induced ~20% tumor regression after 22 days of treatment, dose of 50&100 mg/kg induced nearly complete regression (~90%) (Fig. 4).

CONCLUSIONS:

A novel STRN–ALK gene fusion was identified in gastric cancer. The CHGA067 gastric tumor xenograft model had a dramatic response to the tyrosine kinase ALK inhibitor ceritinib, leading to nearly complete tumor regression at the dose of 50 mg/kg or at the dose of 100 mg/kg of ceritinib (LDK378). This is the first report of a transforming ALK fusion as a therapeutic target in gastric cancer and illustrates the potential for personalized molecular based therapy for the treatment of advanced malignancies.

CLAIMS

1. An ALK inhibitor for use in treating gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

2. The ALK inhibitor for use in treating gastric cancer according to claim 1, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide has been detected in a biological sample from the gastric cancer obtained from a patient having said cancer.

3. The ALK inhibitor for use in treating a patient having gastric cancer according to claim 2 characterized in that:
   (a) the patient is selected for the treatment with an ALK inhibitor on the basis of the patient having STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and
   (b) thereafter, a therapeutically effective amount of an ALK inhibitor is administered to the patient.

4. The ALK inhibitor for use in treating a patient having gastric cancer according to claim 2 or claim 3, characterized in that:
   (a) a biological sample obtained from the patient is assayed for STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and
   (b) a therapeutically effective amount of an ALK inhibitor is selectively administered to the patient on the basis of the biological sample from the patient having STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

5. Use of an ALK inhibitor for the preparation of a medicament for the treatment of gastric cancer, wherein the gastric cancer is characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

6. A method of selectively treating a patient having gastric cancer with an ALK inhibitor, wherein the method comprises the steps of:
   (a) selecting the patient for the treatment with an ALK inhibitor on the basis of the patient having the gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and
   (b) thereafter, administering a therapeutically effective amount of an ALK inhibitor to the patient.

7. A method of selectively treating a patient having gastric cancer, comprising either:
   (a) selectively administering a therapeutically effective amount of an ALK inhibitor to the patient on the basis of the patient having the gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; or

(b) selectively administering a therapeutically effective amount of a drug other than an ALK inhibitor to the patient on the basis of the patient not having the gastric cancer characterized by the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide.

8. A method of selectively treating a patient having gastric cancer with an ALK inhibitor, comprising:
   (a) assaying a biological sample obtained from the patient for a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide;
   (b) thereafter, selecting the patient for the treatment with an ALK inhibitor on the basis of the patient having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; and
   (c) thereafter, administering a therapeutically effective amount of an ALK inhibitor to the patient.

9. A method of selectively treating a patient having gastric cancer, comprising:
   (a) assaying a biological sample obtained from the patient for STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and
   (b) thereafter, selectively administering to the patient either:
      (i) a therapeutically effective amount of an ALK inhibitor on the basis of the biological sample obtained from the patient having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide; or
      (ii) a therapeutically effective amount of a drug other than an ALK inhibitor on the basis of the biological sample obtained from the patient not having the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

10. A method of predicting the likelihood that a patient having a gastric cancer will respond to treatment with an ALK inhibitor, comprising assaying a biological sample obtained from the patient for the presence or absence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide, wherein:
   (a) the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor; and
   (b) the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

11. A method of characterizing a human gastric cancer, comprising
   (c) obtaining a biological sample from said human gastric cancer; and
   (d) detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide in said sample, thereby characterizing said gastric cancer based on the presence or absence of the STRN-ALK gene fusion or the STRN-ALK

fusion polypeptide.

12. A method for detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide in a biological sample from a human gastric cancer, comprising detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide in said sample, thereby detecting whether the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is present in said biological sample.

13. The method of characterizing a human gastric cancer according to claim 11 or method for detecting according to claim 12, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is detected in the sample obtained from a patient having said gastric cancer.

14. A kit for detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide in a biological sample from a human gastric cancer, comprising at least one probe capable of detecting the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide and instructions for using the probe to assay the biological sample for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide.

15. A kit for use in predicting the likelihood that a patient having gastric cancer will respond to the treatment with an ALK inhibitor comprising:
(a) at least one probe capable of detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide; and
(b) instructions for using the probe to assay a biological sample from the gastric cancer patient for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide, wherein the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of an increased likelihood that the patient will respond to treatment with an ALK inhibitor and the absence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is indicative of a decreased likelihood that the patient will respond to treatment with an ALK inhibitor.

16. A kit for use in treating a patient having gastric cancer comprising:
(a) a therapeutically effective amount of an ALK inhibitor;
(b) at least one probe capable of detecting the presence of a STRN-ALK gene fusion or a STRN-ALK fusion polypeptide;
(c) instructions for using the probe to assay a biological sample obtained from the patient for the presence of the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide,
(d) instructions for administering the ALK inhibitor to the patient if the STRN-ALK gene fusion or the STRN-ALK fusion polypeptide is present in the biological sample obtained from the patient ; and

(e) optionally, means for administering the ALK inhibitor to the patient.

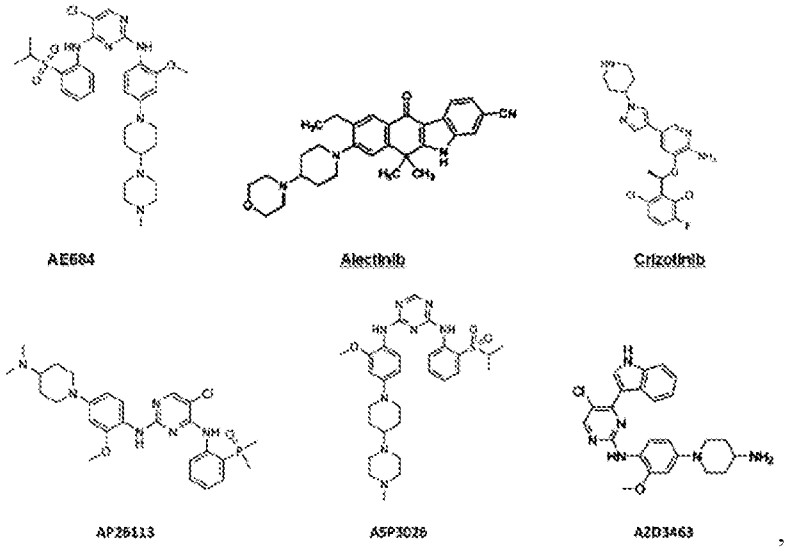
17. The kit according to any one of claims 14 to 16, wherein the probe is an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the STRN-ALK gene fusion, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic marker of the STRN-ALK gene fusion, or the probe is an antibody that binds to the STRN-ALK fusion polypeptide.

18. The ALK inhibitor for use according to any one of claims 1 to 4 or the method according to any one of claims 6 to 10, the method of characterizing a human gastric cancer according to claim 11 or claim 13, the method for detecting according to claim 12 or claim 13, or a kit according to anyone of claims 14 to 17, wherein the assaying or detecting for STRN-ALK gene fusion or the STRN-ALK fusion polypeptide comprises a technique selected from the group consisting of Next Generation Sequencing (NGS), Northern blot analysis, polymerase chain reaction (PCR), reverse transcription-polymerase chain reaction (RT-PCR), TaqMan-based assays, direct sequencing, dynamic allele-specific hybridization, high-density oligonucleotide SNP arrays, restriction fragment length polymorphism (RFLP) assays, primer extension assays, oligonucleotide ligase assays, Southern Blot, immunoassays, immunohistochemistry, ELISA, fluorescence in situ hybridization analysis (FISH), kinase activity assays, flow cytometry, Western blot, HPLC, immunohistochemistry (IHC) and mass spectrometry.

19. The ALK inhibitor for use according to any one of claims 1 to 4 or the method according to any one of claims 6 to 13, or a kit according to anyone of claims 14 to 17, wherein the step of assaying or detecting for STRN-ALK gene fusion comprises PCR, RT-PCR or fluorescence in situ hybridization analysis (FISH).

20. The ALK inhibitor for use according to any one of claims 1 to 4 or the method according to any one of claims 6 to 13, or a kit according to anyone of claims 14 to 17, wherein the step of assaying or detecting for the STRN-ALK fusion polypeptide comprises immunohistochemistry.

21. The ALK inhibitor for use according to any one of claims 1-4, 18 to 20, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 5 to 10, or 18 to 20, or a kit according to anyone of claims 15 to 20, wherein said inhibitor is selected from the group consisting of



and 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

22. The ALK inhibitor for use according to any one of claims 1-4, 18 to 21, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 5 to 10, or 18 to 21, or a kit according to anyone of claims 15 to 21, wherein said inhibitor is 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

23. The ALK inhibitor for use according to any one of claims 1-4, 18 to 22, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 6 to 13, or 18 to 22, or a kit according to anyone of claims 14 to 22, wherein said gastric cancer is metastatic.

24. The ALK inhibitor for use according to any one of claims 1-4, 18 to 23, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 6 to 13, or 18 to 23, or a kit according to anyone of claims 14 to 23, wherein the ALK inhibitor is administered for at least 6 months.

25. The ALK inhibitor for use according to any one of claims 1-4, 18 to 23, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 6 to 13, or 18 to 24, or a kit according to anyone of claims 14 to 23, wherein the ALK inhibitor leads to a progression free survival of at least 6 months.

26. The ALK inhibitor for use according to any one of claims 1-4, 18 to 25, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 6 to 13, or 18 to 25, or a kit according to anyone of claims 14 to 25, where the ALK inhibitor is administered as a second line treatment.

27. The ALK inhibitor for use according to any one of claims 1-4, 14 to 21, or the use of the ALK inhibitor according to claim 5, or the method according to any one of claims 6 to 13, or 18 to 25, or a kit according to anyone of claims 14 to 25, where the ALK inhibitor is administered as a first line treatment.

Figure 1

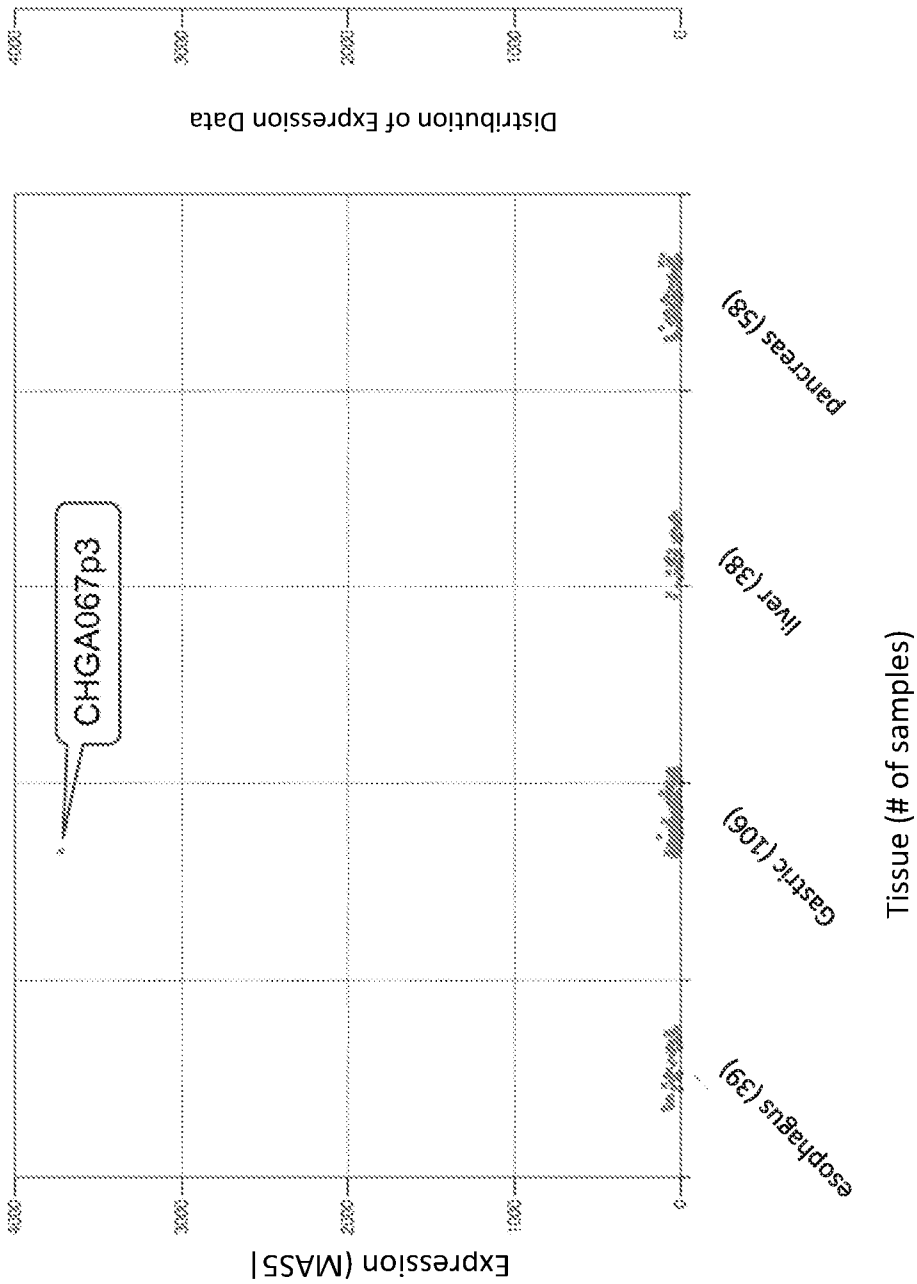

Distribution of Expression Data
0
1000
2000
3000
4000
CHGA067p3
esophagus (39)
Gastric (106)
liver (38)
pancreas (58)
Tissue (# of samples)
Expression (MAS5)

Figure 2

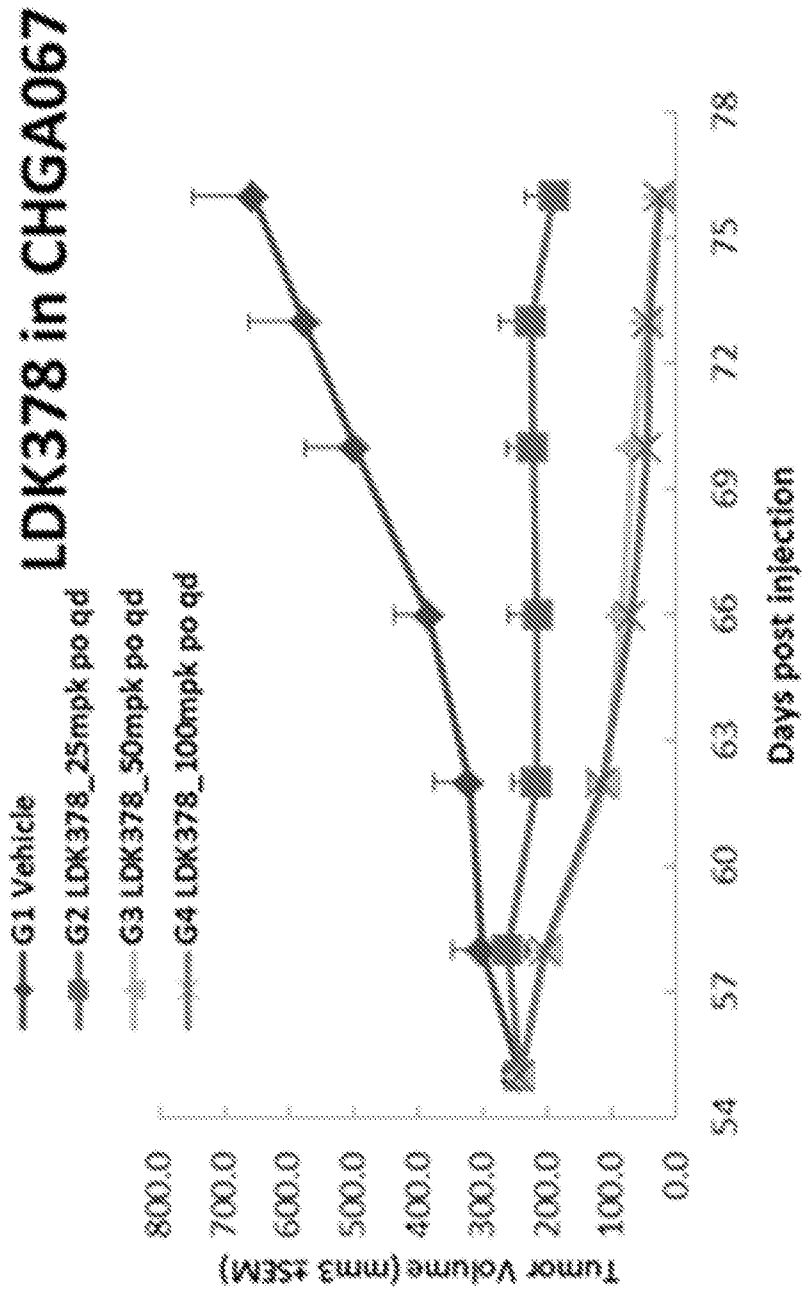

LDK378 in CHGA067
G1 Vehicle
G2 LDK378_25mpk po qd
G3 LDK378_50mpk po qd
G4 LDK378_100mpk po qd
Tumor Volume (mm3 ±SEM)
800,0
700,0
600,0
500,0
400,0
300,0
200,0
100,0
0,0
54
57
60
63
66
69
72
75
78
Days post injection

Figure 3

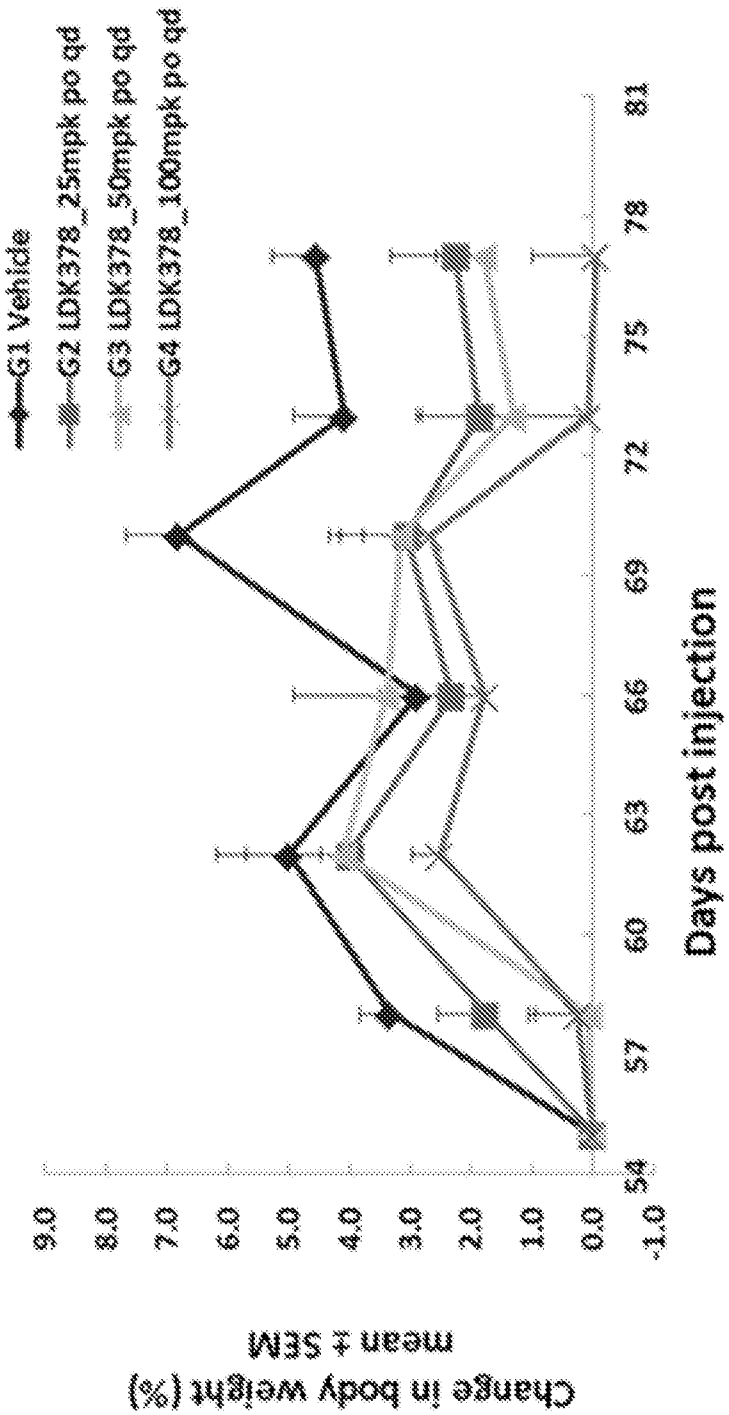
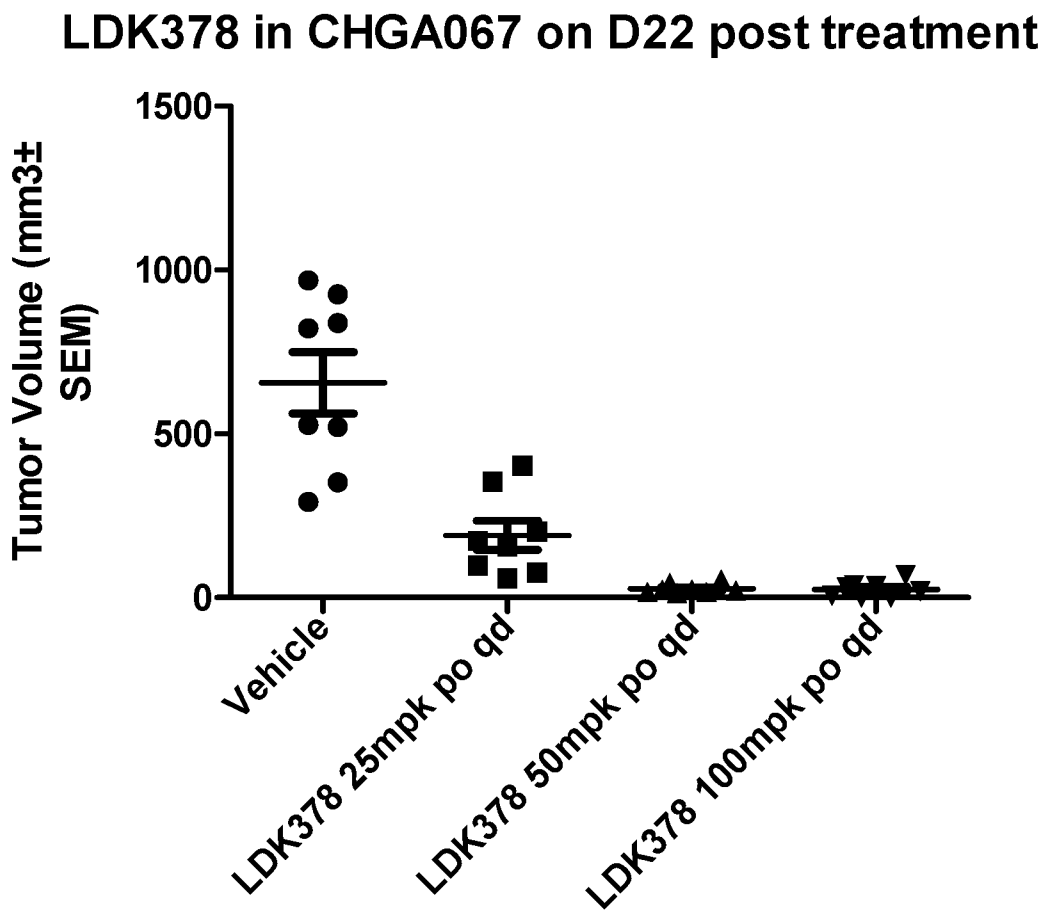

G1 Vehicle
G2 LDK378_25mpk po qd
G3 LDK378_50mpk po qd
G4 LDK378_100mpk po qd
Change in body weight (%)
mean ± SEM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
54
57
60
63
66
69
72
75
78
81
Days post injection

Figure 4


LDK378 in CHGA067 on D22 post treatment
Tumor Volume (mm3± SEM)
1500
1000
500
0
Vehicle
LDK378 25mpk po qd
LDK378 50mpk po qd
LDK378 100mpk po qd

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/051360

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/574 A61K31/506 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K G01N 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, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAKIREVICH EVGENY ET AL: "Oncogenic ALK Fusion in Rare and Aggressive Subtype of Colorectal Adenocarcinoma as a Potential Therapeutic Target", CLINICAL CANCER RESEARCH, vol. 22, no. 15, 1 March 2016 (2016-03-01) , pages 3831-3840, XP55373466, cited in the application	14-27
A	Abstract, "Fluorescence in situe hybridization (FISH)"; page 3833, column 2	1-13

-/--

[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
29 May 2017	21/06/2017

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	Langer, Astrid

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/051360

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	James G. Christensen: "Abstract SY33-01: The development of crizotinib in molecularly targeted patient populations", , 2012, XP002770571, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/72/8_Supplement/SY33-01 [retrieved on 2017-05-29] the whole document	1-27
A	YANG YANG ET AL: "MET overexpression and amplification define a distinct molecular subgroup for targeted therapies in gastric cancer", GASTRIC CANCER, SPRINGER JAPAN, TOKYO, vol. 19, no. 3, 24 September 2015 (2015-09-24), pages 778-788, XP036062680, ISSN: 1436-3291, DOI: 10.1007/S10120-015-0545-5 [retrieved on 2015-09-24] Abstract; page 779, column 1, paragraph 1; tables	1-27
A	WO 2015/116868 A2 (CARIS MPI INC [US]) 6 August 2015 (2015-08-06) claims	1-27
A	WO 2014/193229 A2 (STICHTING HET NL KANKER INST ANTONI VAN LEEUWENHOEK ZIEKENHUIS [NL]; A) 4 December 2014 (2014-12-04) claims	1-27
A	WO 2012/103025 A2 (EPIC SCIENCES INC [US]; YANG XING [US]; NELSON DAVID M [US]; KUHN PETE) 2 August 2012 (2012-08-02) claims	1-27
A	DENG NIANTAO ET AL: "A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets", GUT, vol. 61, no. 5, May 2012 (2012-05), pages 673-684, XP55373473, cited in the application the whole document	1-27

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/051360

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TOGASHI Y ET AL: "KLC1-ALK: a novel fusion in lung cancer identified using a formalin-fixed paraffin-embedded tissue only", PLOS ONE, PUBLIC LIBRARY OF SCIENCE, US, vol. 7, no. 2, 1 February 2012 (2012-02-01), pages e31323-1, XP002752563, ISSN: 1932-6203, DOI: 10.1371/JOURNAL.PONE.0031323 [retrieved on 2012-02-08] abstract; table 1	1-27

T	PANARESE ET AL.: "Predictive biomarkers along gastric cancer pathogenetic pathways", EXPERT REVIEW OF ANTICANCER THERAPY, vol. 17, no. 5, 4 May 2017 (2017-05-04), pages 417-425, XP9194478, the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/051360

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015116868 A2	06-08-2015	AU 2015210886 A1	01-09-2016
		WO 2015116868 A2	06-08-2015
WO 2014193229 A2	04-12-2014	EP 3004380 A2	13-04-2016
		US 2016186269 A1	30-06-2016
		WO 2014193229 A2	04-12-2014
WO 2012103025 A2	02-08-2012	AU 2012209329 A1	12-09-2013
		AU 2016228165 A1	29-09-2016
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