

NOVEL KIF5B-RET FUSION MOLECULES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/526,613, filed August 23, 2011; U.S. Provisional Application No. 61/537,024, filed September 20, 2011; U.S. Provisional Application No. 61/542,112, filed September 30, 2011; and U.S. Provisional Application No. 61/594,739, filed February 3, 2012. ~~The contents of all these prior applications are incorporated herein by reference in their entirety.~~

BACKGROUND

Cancer represents the phenotypic end-point of multiple genetic lesions that endow cells with a full range of biological properties required for tumorigenesis. Indeed, a hallmark genomic feature of many cancers, including, for example, B cell cancer, lung cancer, breast cancer, ovarian cancer, pancreatic cancer, and colon cancer, is the presence of numerous complex chromosome structural aberrations, including translocations, intra-chromosomal inversions, point mutations, deletions, gene copy number changes, gene expression level changes, and germline mutations, among others.

The need still exists for identifying novel genetic lesions associated with cancer. Such genetic lesions can be an effective approach to develop compositions, methods and assays for evaluating and treating cancer patients.

SUMMARY

The invention is based, at least in part, on the discovery of novel inversion events that include a fragment of a KIF5B gene (“Kinesin Family Member 5B- RET proto-oncogene”) and a fragment of a RET proto-oncogene in a cancer, *e.g.*, a lung cancer, referred to herein as “KIF5B-RET.” The term “KIF5B-RET” or “KIF5B-RET fusion” is used generically herein, and includes any fusion molecule (*e.g.*, gene, gene product (*e.g.*, cDNA, mRNA, or polypeptide), and variant thereof) that includes a fragment of KIF5B and a fragment of RET, including, *e.g.*, a 5’KIF5B-3’RET.

In one embodiment, a KIF5B-RET fusion includes an in-frame fusion of an exon of KIF5B (*e.g.*, one more exons encoding a kinesin motor domain or a fragment thereof)

and materials are described below. ~~All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.~~ In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and the example are illustrative only and not intended to be limiting.

5 The details of one or more embodiments featured in the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages featured in the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

10 FIG. 1 is a snapshot of the sequencing reads illustrating that there are RET read pairs that map on one end to 5'KIF5B and on the other end to 3'RET, and other RET read pairs that map on one end to 5'RET and on the other end to 3'KIFB.

FIGs. 2A and 2B are schematic diagrams illustrating the inversion event that brings together exon 15 of KIF5B and exon 12 of RET. FIGs 2A and 2B disclose SEQ
15 ID NOS 6 and 7, respectively.

FIGs. 3A to 3D are the predicted cDNA sequence (SEQ ID NO:1) and protein sequence of the KIF5B-RET fusion (SEQ ID NO:2). The KIF5B portion of the cDNA sequence is equivalent to nucleotides 471-2195 of RefSeq NM_004521.2, and the KIF5B portion of the protein sequence is equivalent to amino acids 1-575 of RefSeq NP_004512.
20 The KIF5B portions of the cDNA and protein sequences are underlined. The RET portion of the cDNA sequence is equivalent to nucleotides 2327-3535 of RefSeq NM_020975, and the RET portion of the protein sequence is equivalent to amino acids 713-1114 of RefSeq NP_066124.1. The intact tyrosine kinase domain of RET is represented by a gray box (see FIG. 3C).

25 FIGs. 4A to 4D are the predicted cDNA sequence (SEQ ID NO:3) and protein sequence of the RET-KIF5B fusion (SEQ ID NO:4). The cDNA sequence of the RET portion of the fusion transcript is equivalent to nucleotides 190-2326 of RefSeq NM_020975, and the protein sequence is equivalent to amino acids 1-712 of RefSeq NP_066124.1. The cDNA sequence of the KIF5B portion of the fusion transcript is
30 equivalent to nucleotides 2196-3362 of RefSeq NM_004521.2, and the protein portion is equivalent to amino acids 576-963 of RefSeq NP_004512. The KIF5B portions of the cDNA and protein sequences are underlined.

least 75%, at least 80%, at least 85%, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more.

"Likely to" or "increased likelihood," as used herein, refers to an increased probability that an item, object, thing or person will occur. Thus, in one example, a subject that is likely to respond to treatment with a kinase inhibitor, alone or in combination, has an increased probability of responding to treatment with the inhibitor alone or in combination, relative to a reference subject or group of subjects.

"Unlikely to" refers to a decreased probability that an event, item, object, thing or person will occur with respect to a reference. Thus, a subject that is unlikely to respond to treatment with a kinase inhibitor, alone or in combination, has a decreased probability of responding to treatment with a kinase inhibitor, alone or in combination, relative to a reference subject or group of subjects.

"Sequencing" a nucleic acid molecule requires determining the identity of at least 1 nucleotide in the molecule. In embodiments, the identity of less than all of the nucleotides in a molecule are determined. In other embodiments, the identity of a majority or all of the nucleotides in the molecule is determined.

"Next-generation sequencing or NGS or NG sequencing" as used herein, refers to any sequencing method that determines the nucleotide sequence of either individual nucleic acid molecules (*e.g.*, in single molecule sequencing) or clonally expanded proxies for individual nucleic acid molecules in a highly parallel fashion (*e.g.*, greater than 10^5 molecules are sequenced simultaneously). In one embodiment, the relative abundance of the nucleic acid species in the library can be estimated by counting the relative number of occurrences of their cognate sequences in the data generated by the sequencing experiment. Next generation sequencing methods are known in the art, and are described, *e.g.*, in Metzker, M. (2010) *Nature Biotechnology Reviews* 11:31-46; ~~incorporated herein by reference~~. Next generation sequencing can detect a variant present in less than 5% of the nucleic acids in a sample.

"Sample," "tissue sample," "patient sample," "patient cell or tissue sample" or "specimen" each refers to a collection of similar cells obtained from a tissue of a subject or patient. The source of the tissue sample can be solid tissue as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, or aspirate; blood or any blood constituents; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid or

ratio of hybridization of the nucleic acids is determined by the ratio of the two (first and second) labels binding to each fiber in the array. Where there are chromosomal deletions or multiplications, differences in the ratio of the signals from the two labels will be detected and the ratio will provide a measure of the copy number. Array-based CGH can also be performed with single-color labeling (as opposed to labeling the control and the possible tumor sample with two different dyes and mixing them prior to hybridization, which will yield a ratio due to competitive hybridization of probes on the arrays). In single color CGH, the control is labeled and hybridized to one array and absolute signals are read, and the possible tumor sample is labeled and hybridized to a second array (with identical content) and absolute signals are read. Copy number difference is calculated based on absolute signals from the two arrays.

Hybridization protocols suitable for use with the methods of the invention are described, *e.g.*, in Albertson (1984) *EMBO J.* 3: 1227-1234; Pinkel (1988) *Proc. Natl. Acad. Sci. USA* 85: 9138-9142; EPO Pub. No. 430,402; *Methods in Molecular Biology*, Vol. 33: *In situ* Hybridization Protocols, Choo, ed., Humana Press, Totowa, N.J. (1994), *etc.* In one embodiment, the hybridization protocol of Pinkel, *et al.* (1998) *Nature Genetics* 20: 207-211, or of Kallioniemi (1992) *Proc. Natl Acad Sci USA* 89:5321-5325 (1992) is used. Array-based CGH is described in U.S. Patent No. 6,455,258, the contents of each of which are incorporated herein by reference.

In still another embodiment, amplification-based assays can be used to measure presence/absence and copy number. In such amplification-based assays, the nucleic acid sequences act as a template in an amplification reaction (*e.g.*, Polymerase Chain Reaction (PCR)). In a quantitative amplification, the amount of amplification product will be proportional to the amount of template in the original sample. Comparison to appropriate controls, *e.g.*, healthy tissue, provides a measure of the copy number.

Methods of "quantitative" amplification are well known to those of skill in the art. For example, quantitative PCR involves simultaneously co-amplifying a known quantity of a control sequence using the same primers. This provides an internal standard that can be used to calibrate the PCR reaction. Detailed protocols for quantitative PCR are provided in Innis, *et al.* (1990) *PCR Protocols, A Guide to Methods and Applications*, Academic Press, Inc. N.Y.). Measurement of DNA copy

samples). Alternatives to DNA shearing methods can also be used to avoid a ligation step during library preparation.

The methods described herein can be performed using a small amount of nucleic acids, *e.g.*, when the amount of source DNA is limiting (*e.g.*, even after whole-genome amplification). In one embodiment, the nucleic acid comprises less than about 5 μg , 4 μg , 3 μg , 2 μg , 1 μg , 0.8 μg , 0.7 μg , 0.6 μg , 0.5 μg , or 400 ng, 300 ng, 200 ng, 100 ng, 50 ng, or 20 ng or less of nucleic acid sample. For example, to prepare 500 ng of hybridization-ready nucleic acids, one typically begins with 3 μg of genomic DNA. One can start with less, however, if one amplifies the genomic DNA (*e.g.*, using PCR) before the step of solution hybridization. Thus it is possible, but not essential, to amplify the genomic DNA before solution hybridization.

In some embodiments, a library is generated using DNA (*e.g.*, genomic DNA) from a sample tissue, and a corresponding library is generated with RNA (or cDNA) isolated from the same sample tissue.

Design of Baits

A bait can be a nucleic acid molecule, *e.g.*, a DNA or RNA molecule, which can hybridize to (*e.g.*, be complementary to), and thereby allow capture of a target nucleic acid. In one embodiment, a bait is an RNA molecule. In other embodiments, a bait includes a binding entity, *e.g.*, an affinity tag, that allows capture and separation, *e.g.*, by binding to a binding entity, of a hybrid formed by a bait and a nucleic acid hybridized to the bait. In one embodiment, a bait is suitable for solution phase hybridization.

Baits can be produced and used by methods and hybridization conditions as described in US 2010/0029498 and Gnirke, A. *et al.* (2009) *Nat Biotechnol.* 27(2):182-189, and USSN 61/428,568, filed December 30, 2010, incorporated herein by reference. For example, biotinylated RNA baits can be produced by obtaining a pool of synthetic long oligonucleotides, originally synthesized on a microarray, and amplifying the oligonucleotides to produce the bait sequences. In some embodiments, the baits are produced by adding an RNA polymerase promoter sequence at one end of the bait sequences, and synthesizing RNA sequences using RNA polymerase. In one embodiment, libraries of synthetic oligodeoxynucleotides can be obtained from

sequencing by mass spectrometry (see, for example, U.S. Patent Number 5,547,835 and international patent application Publication Number WO 94/16101, entitled *DNA Sequencing by Mass Spectrometry* by H. Köster; U.S. Patent Number 5,547,835 and international patent application Publication Number WO 94/21822 entitled *DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation* by H. Köster), and
5 U.S. Patent Number 5,605,798 and International Patent Application No. PCT/US96/03651 entitled *DNA Diagnostics Based on Mass Spectrometry* by H. Köster; Cohen *et al.* (1996) *Adv Chromatogr* 36:127-162; and Griffin *et al.* (1993) *Appl Biochem Biotechnol* 38:147-159).

10 Sequencing of nucleic acid molecules can also be carried out using next-generation sequencing (NGS). Next-generation sequencing includes any sequencing method that determines the nucleotide sequence of either individual nucleic acid molecules or clonally expanded proxies for individual nucleic acid molecules in a highly parallel fashion (*e.g.*, greater than 10^5 molecules are sequenced simultaneously). In one
15 embodiment, the relative abundance of the nucleic acid species in the library can be estimated by counting the relative number of occurrences of their cognate sequences in the data generated by the sequencing experiment. Next generation sequencing methods are known in the art, and are described, *e.g.*, in Metzker, M. (2010) *Nature Biotechnology Reviews* 11:31-46, incorporated herein by reference.

20 In one embodiment, the next-generation sequencing allows for the determination of the nucleotide sequence of an individual nucleic acid molecule (*e.g.*, Helicos BioSciences' HeliScope Gene Sequencing system, and Pacific Biosciences' PacBio RS system). In other embodiments, the sequencing method determines the nucleotide sequence of clonally expanded proxies for individual nucleic acid molecules (*e.g.*, the
25 Solexa sequencer, Illumina Inc., San Diego, Calif; 454 Life Sciences (Branford, Conn.), and Ion Torrent). *e.g.*, massively parallel short-read sequencing (*e.g.*, the Solexa sequencer, Illumina Inc., San Diego, Calif.), which generates more bases of sequence per sequencing unit than other sequencing methods that generate fewer but longer reads. Other methods or machines for next-generation sequencing include, but are not limited
30 to, the sequencers provided by 454 Life Sciences (Branford, Conn.), Applied Biosystems (Foster City, Calif.; SOLiD sequencer), and Helicos BioSciences Corporation (Cambridge, Mass.).

Data analysis

After NGS reads have been generated, they can be aligned to a known reference sequence or assembled *de novo*.

5 For example, identifying genetic variations such as single-nucleotide polymorphism and structural variants in a sample (*e.g.*, a tumor sample) can be accomplished by aligning NGS reads to a reference sequence (*e.g.*, a wild-type sequence). Methods of sequence alignment for NGS are described *e.g.*, in Trapnell C. and Salzberg S.L. *Nature Biotech.*, 2009, 27:455-457.

10 Examples of *de novo* assemblies are described, *e.g.*, in Warren R. *et al.*, *Bioinformatics*, 2007, 23:500-501; Butler J. *et al.*, *Genome Res.*, 2008, 18:810-820; and Zerbino D.R. and Birney E., *Genome Res.*, 2008, 18:821-829.

Sequence alignment or assembly can be performed using read data from one or more NGS platforms, *e.g.*, mixing Roche/454 and Illumina/Solexa read data.

15 Algorithms and methods for data analysis are described in USSN 61/428,568, filed December 30, 2010, incorporated herein by reference.

KIF5B-RET Fusion Expression Level

In certain embodiments, KIF5B-RET fusion expression level can also be
20 assayed. KIF5B-RET fusion expression can be assessed by any of a wide variety of methods for detecting expression of a transcribed molecule or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse
25 transcription methods, and nucleic acid amplification methods.

In certain embodiments, activity of a particular gene is characterized by a measure of gene transcript (*e.g.*, mRNA), by a measure of the quantity of translated protein, or by a measure of gene product activity. KIF5B-RET fusion expression can be monitored in a variety of ways, including by detecting mRNA levels, protein
30 levels, or protein activity, any of which can be measured using standard techniques. Detection can involve quantification of the level of gene expression (*e.g.*, genomic DNA, cDNA, mRNA, protein, or enzyme activity), or, alternatively, can be a

5 *Additional references:*

James *et al.*, *Nucl. Acids Res.* 16:1999-2014, 1988.

Levin *et al.*, *Genome Biol.* 10:R115, 2009.

Li and Durbin, *Bioinformatics* 26:589-95, 2010.

Li *et al.*, *Bioinformatics* 25:2078-9, 2009.

10 online at picard.sourceforge.net

McKenna *et al.*, *Genome Res.* 20:1297-303, 2010.

Forbes *et al.*, *Nucl. Acids Res.* 39 (suppl 1): D945-D950, 2011.

Smigielski *et al.*, *Nucl. Acids Res.* 28:352-355, 2000.

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~~Incorporation by Reference~~

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~~———— All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.~~

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~~———— Also incorporated by reference in their entirety are any polynucleotide and polypeptide sequences which reference an accession number correlating to an entry in a public database, such as those maintained by the COSMIC database, available on the worldwide web at sanger.ac.uk/genetics/CGP/cosmic/; and the Institute for Genomic Research (TIGR) on the world wide web at tigr.org and/or the National Center for Biotechnology Information (NCBI) on the world wide web at ncbi.nlm.nih.gov.~~

30 **Equivalents**

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

We Claim:

1. The use of an anti-cancer agent for the manufacture of a medicament for the treatment of a cancer in a subject, wherein knowledge of the presence of a RET fusion in said subject has been acquired, and wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

2. The use of claim 1, wherein said anti-cancer agent is a kinase inhibitor.

3. The use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a RET fusion, wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

4. The use of any of claims 1-3, wherein said RET fusion is a KIF5B-RET fusion.

5. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is a RET-specific inhibitor.

6. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is a multi-kinase inhibitor.

7. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is chosen from sorafenib (NEXAVAR®), sunitinib (SUTENT®, SU11248), vandetanib (CAPRELSA®, ZD6474), or NVP-AST487.

8. The use of any of claims 1-4, wherein the anti-cancer agent or the RET kinase inhibitor is chosen from:

(i) antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic acid encoding RET, or a transcription regulatory region that blocks or reduces mRNA expression of RET; or

~~(ii) an anti-cancer agent or RET kinase inhibitor that inhibits the expression of nucleic acid encoding RET.~~

9. The use of claim 8, wherein the nucleic acid encodes KIF5B-RET, and/or wherein the transcription regulatory region blocks or reduces mRNA expression of KIF5B-RET.

10. The use of any of claims 1-9, wherein the anti-cancer agent or the RET kinase inhibitor is to be administered responsive to the determination of the presence of a RET fusion in a tumor sample from said subject.

11. The use of any of claims 1-10, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the RET fusion in said subject.

12. The use of any of claims 1-11, wherein the medicament is to be administered responsive to acquiring knowledge or information of the presence of the RET fusion in said subject from another party.

13. The use of any of claims 1-12, wherein a communication of the presence of the RET fusion in the subject is received.

14. The use of any of claims 1-13, wherein the medicament is to be administered responsive to an identification of the presence of a KIF5B-RET fusion in the subject.

15. The use of any of claims 1-14, wherein the presence of the RET fusion is determined by sequencing.

16. The use of any of claims 1-15, wherein said cancer is lung cancer.

~~17. The use of claim 16, wherein said lung cancer is chosen from: small cell lung cancer (SCLC), adenocarcinoma of the lung, bronchogenic carcinoma, non-small cell lung cancer (NSCLC), squamous cell carcinoma (SCC), or a combination thereof.~~

18. The use of claim 17, wherein the lung cancer is non-small cell lung cancer (NSCLC).

19. The use of claim 17, wherein the lung cancer is squamous cell carcinoma (SCC).

20. The use of claim 7, wherein the anti-cancer agent is sorafenib (NEXAVAR®).

21. The use of claim 7, wherein the anti-cancer agent is sunitinib (SUTENT®, SU11248).

22. The use of claim 7, wherein the anti-cancer agent is vandetanib (CAPRELSA®, ZD6474).

23. The use of claim 7, wherein the anti-cancer agent is NVP-AST487.

24. The use of claim 2, wherein the kinase inhibitor inhibits the expression of nucleic acid encoding KIF5B-RET.

25. The use of claim 2, wherein the kinase inhibitor is selected from antisense molecules, ribozymes, RNAi, triple helix molecules that hybridize to a nucleic acid encoding KIF5B-RET, or a transcription regulatory region that blocks or reduces mRNA expression of KIF5B-RET.

26. The use of any of claims 1-25, wherein the anti-cancer agent or RET kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.

27. The use of a kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a RET fusion in a patient, wherein the patient is selected according to the method, comprising:

identifying, selecting, or obtaining information or knowledge that the patient has participated in a clinical trial or has been treated for cancer;

acquiring genotype information that identifies a RET fusion as being in the patient; and

identifying the patient as having an increased risk for, or having, a cancer associated with the RET fusion by detecting the presence of the RET fusion;

wherein the cancer is chosen from lung cancer, pancreatic cancer, melanoma, colorectal cancer, esophageal-gastric cancer, or adenocarcinoma.

28. The use of claim 27, further comprising providing a report to a party.

29. The use of claim 28, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company or government office.

30. The use of claim 28, wherein said report is in electronic, web-based, or paper form.

31. The use of claim 28, wherein said report identifies the presence or absence of an alteration in a RET nucleic acid sequence, and optionally includes an identifier for the patient from which the sequence was obtained.

32. The use of claim 28, wherein said report comprises;
information on the role of a RET fusion, or wild type sequence, in disease;
information on prognosis, resistance, or potential or suggested therapeutic options;
information on the likely effectiveness of a therapeutic option, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to a patient; or
information, or a recommendation on, the administration of a drug.

~~33. A method for generating a personalized cancer treatment report, by obtaining a sample from a subject, detecting a RET fusion in the sample, and selecting a treatment based on the presence or absence of the RET fusion and any other mutation identified.~~

34. The use of any of claims 27-32, or the method of claim 33, wherein the RET fusion is a KIF5B-RET fusion.

We Claim:

1. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a Kinesin Family Member 5B (KIF5B)-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, and wherein the cancer is chosen from a lung cancer, a pancreatic cancer, a melanoma, a colorectal cancer, an esophageal-gastric cancer, or an adenocarcinoma.

2. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer in a subject, wherein the RET kinase inhibitor is to be administered responsive to a determination of a presence of a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said cancer, and wherein the kinase inhibitor is chosen from cabozantinib, lenvatinib, vandetanib, sorafenib, sunitinib, NVP-AST487, regorafenib, motesanib, apatinib, or DCC-2157.

3. The use of claim 1 or 2, wherein the RET-kinase inhibitor is a RET-specific inhibitor.

4. The use of claim 1 or 2, wherein the RET kinase inhibitor is a multi-kinase inhibitor that inhibits the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide.

5. The use of any of claims 1 or 4, wherein the RET kinase inhibitor is chosen from cabozantinib, lenvatinib, vandetanib, sorafenib, sunitinib, NVP-AST487, regorafenib, motesanib, apatinib, or DCC-2157.

6. The use of any of claims 1, 3 or 4, wherein the RET kinase inhibitor is chosen from:
(i) an antisense molecule, a ribozyme, an RNAi molecule, or a triple helix molecules that hybridizes to the nucleic acid molecule encoding the KIF5B-RET polypeptide, or a transcription regulatory region that blocks or reduces mRNA expression of the nucleic acid molecule encoding the KIF5B-RET polypeptide; or

(ii) an RET kinase inhibitor that inhibits the expression of the nucleic acid encoding the KIF5B-RET polypeptide.

7. The use of any of claims 1-6, wherein the RET kinase inhibitor is to be administered responsive to the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from said subject.

8. The use of claim 7, wherein the tumor sample:

- (i) comprises fluid, cells, and/or a tissue;
- (ii) is a nucleic acid sample or a protein sample; and/or
- (iii) comprises a tumor biopsy or a circulating tumor cell or nucleic acid.

9. The use of any of claims 1-8, wherein:

(i) the level or activity of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is evaluated;

(ii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected prior to initiating, during, or after, the treatment in the subject;

(iii) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at the time of diagnosis of the subject with the cancer; and/or

(iv) the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is detected at a pre-determined interval.

10. The use of any of claims 1-9, wherein the determination of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises acquiring knowledge or information of the presence of the KIF5B-RET polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in said subject from another party.

11. The use of any of claims 1-10, wherein a communication of the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a subject is received.

12. The use of any of claims 1-11, wherein the presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide is determined by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCT-RFLP assay, real-time PCR, sequencing, a screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC, or mass-spectrometric genotyping.

13. The use of any of claims 1-12, wherein said cancer is a lung cancer.

14. The use of claim 13, wherein said lung cancer is chosen from: a small cell lung cancer (SCLC), an adenocarcinoma of the lung, a bronchogenic carcinoma, a non-small cell lung cancer (NSCLC), a squamous cell carcinoma (SCC), or a combination thereof.

15. The use of claim 13 or 14, wherein the lung cancer is a non-small cell lung cancer (NSCLC).

16. The use of claim 13 or 14, wherein the lung cancer is a squamous cell carcinoma (SCC).

17. The use of any of claims 1-12, wherein the cancer is a colon cancer.

18. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is cabozantinib.

19. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is lenvatinib.

20. The use of any of claims 1, 2 or 4-17, wherein the RET kinase inhibitor is vandetanib.

21. The use of any of claims 1-20, wherein the RET kinase inhibitor is administered in combination with a second therapeutic agent or a different therapeutic modality.

22. Use of a RET kinase inhibitor for the manufacture of a medicament for the treatment of a cancer associated with a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a patient, wherein the patient is selected according to a method, comprising:

identifying, selecting, or obtaining information or knowledge that the patient has participated in a clinical trial or has been treated for the cancer;

acquiring genotype information that identifies the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide as being in the patient,

identifying the patient as having an increased risk for, or having, the cancer associated with the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide by detecting a presence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide.

23. The use of claim 22, wherein the cancer is chosen from a lung cancer, a pancreatic cancer, a melanoma, a colorectal cancer, an esophageal-gastric cancer, a thyroid cancer, or an adenocarcinoma.

24. The use of claim 22 or 23, wherein the method further comprises providing a report to another party.

25. The use of claim 24, wherein the party is the patient, a caregiver, a physician, an oncologist, a hospital, a clinic, a third-party payor, an insurance company, or a government office.

26. The use of claim 24 or 25, wherein said report is in an electronic, web-based, or paper form.

27. The use of any of claims 24-26, wherein the report identifies the presence or absence of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the patient, and optionally includes an identifier for the patient.

28. The use of any of claims 24-27, wherein said report comprises;
information on the role of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide, or a wildtype sequence, in a disease;
information on prognosis, resistance, or potential or suggested therapeutic options;
information on the likely effectiveness of a therapeutic option, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to the patient; or
information, or a recommendation on, the administration of a drug.

29. A method for generating a personalized cancer treatment report, by detecting a KIF5B-RET fusion polypeptide or a nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in a tumor sample from a patient, and selecting a RET-kinase inhibitor for the patient based on an identification of the KIF5B-RET fusion polypeptide or the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide in the tumor sample.

30. The use of any of claims 1-28, or the method of claim 29, wherein the KIF5B-RET fusion polypeptide is an in-frame fusion polypeptide comprising at least the amino acid sequence encoded by exon 15 of KIF5B, and at least the amino acid sequence encoded by exon 12 of RET of SEQ ID NO: 1.

31. The use of any of claims 1-28 or 30, or the method of claim 29 or 30, wherein the nucleic acid molecule encoding the KIF5B-RET fusion polypeptide comprises nucleotides 1720-1731, 1717-1734, or 1714-1737 of SEQ ID NO: 1.

32. The use of any of claims 1-28, 30 or 31, or the method of any of claims 29-31, wherein the KIF5B-RET fusion polypeptide comprises a RET tyrosine kinase domain, and a KIF5B kinesin motor domain and coiled-coil domain, of SEQ ID NO: 2.

33. The use of any of claims 1-28 or 30-32, or the method of any of claim 29-32, wherein the KIF5B-RET fusion polypeptide comprises amino acids 1-575 of SEQ ID NO: 2 corresponding to KIF5B and amino acids 576-977 of SEQ ID NO: 2 corresponding to RET.