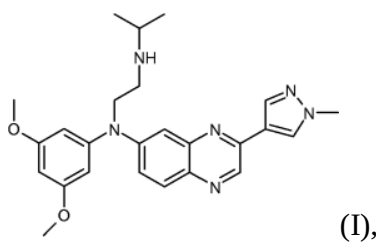


CLAIMS

1. A method of identifying a cancer patient that is responsive to treatment with a fibroblast growth factor receptor (FGFR) inhibitor, wherein the FGFR inhibitor comprises a compound having the structure of Formula (I),

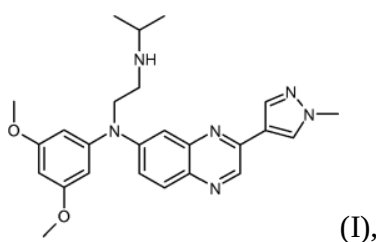


a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof, and wherein the method comprises

evaluating a biological sample from the patient for a FGFR mutant comprising a FGFR fusion gene comprising FGFR3:TACC3 v1 (FGFR3 exon 18-TACC3 exon 11 fusion), FGFR3:TACC3 v3 (FGFR3 exon 18-TACC3 exon 10 fusion), FGFR3:TACC3 Intron (FGFR3 exon 18-TACC3 exon 4 fusion), or a combination thereof, and wherein said evaluating comprises

amplifying cDNA with a pair of primers that amplify the FGFR mutant; and
determining whether the FGFR mutant is present in the sample, wherein the presence of the FGFR mutant indicates that the patient is responsive to treatment with the FGFR inhibitor.

2. A method of identifying a cancer patient that is responsive to treatment with a fibroblast growth factor receptor (FGFR) inhibitor, wherein the FGFR inhibitor comprises a compound having the structure of Formula (I),



a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof, and wherein the method comprises:

evaluating a biological sample from the patient for the presence of a FGFR mutant comprising a FGFR fusion gene comprising FGFR3:TACC3 v1 (FGFR3 exon 18-TACC3 exon 11 fusion), FGFR3:TACC3 v3 (FGFR3 exon 18-TACC3 exon 10 fusion), FGFR3:TACC3 Intron (FGFR3 exon 18-TACC3 exon 4 fusion), or a combination thereof, and wherein the presence of the one or more FGFR mutants indicates that the patient is responsive to treatment with the FGFR inhibitor.

3. The method of claim 1 or 2, wherein the FGFR mutant further comprises FGFR3:BAIAP2L1 (FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1 (FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3 (FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7 (FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6 (FGFR3 exon 19-TACC3 exon 2 fusion), or FGFR2:OFD1 (FGFR3 exon 19-TACC3 exon 3 fusion), or any combination thereof.
4. The method of claim 1 or 2, wherein the FGFR mutant further comprises a FGFR single nucleotide polymorphism comprising R248C, S249C, G370C, or Y373C, or any combination thereof.
5. The method of claim 1 or 2, wherein the cancer is bladder cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1 (FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1 (FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3 (FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7 (FGFR3 exon 19-TACC3 exon 4 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
6. The method of claim 1 or 2, wherein the cancer is metastatic bladder cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1 (FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1 (FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3 (FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7 (FGFR3 exon 19-TACC3 exon 4 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.

7. The method of claim 1 or 2, wherein the cancer is ovarian cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3(FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
8. The method of claim 1 or 2, wherein the cancer is esophageal cancer and the FGFR mutant further comprises FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
9. The method of claim 1 or 2, wherein the cancer is metastatic esophageal cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3(FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6(FGFR3 exon 19-TACC3 exon 2 fusion), or FGFR2:OFD1(FGFR3 exon 19-TACC3 exon 3 fusion), or any combination thereof.
10. The method of claim 1 or 2, wherein the cancer is non-small-cell lung adenocarcinoma and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:AFF3(FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
11. The method of claim 1 or 2, wherein the cancer is non-small cell lung squamous cell carcinoma and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3(FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6(FGFR3 exon 19-TACC3 exon 2 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
12. The method of claim 1 or 2, wherein the cancer is metastatic endometrial cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2

- fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6(FGFR3 exon 19-TACC3 exon 2 fusion), or FGFR2:OFD1(FGFR3 exon 19-TACC3 exon 3 fusion), or any combination thereof.
13. The method of claim 1 or 2, wherein the cancer is breast cancer and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3 (FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6(FGFR3 exon 19-TACC3 exon 2 fusion), or FGFR2:OFD1(FGFR3 exon 19-TACC3 exon 3 fusion), or any combination thereof.
 14. The method of claim 1 or 2, wherein the cancer is hepatocellular carcinoma and the FGFR mutant further comprises FGFR3:BAIAP2L1(FGFR3 exon 18-TACC3 exon 2 fusion), FGFR2:BICC1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR2:AFF3(FGFR3 exon 19-TACC3 exon 8 fusion), FGFR2:CASP7(FGFR3 exon 19-TACC3 exon 4 fusion), FGFR2:CCDC6(FGFR3 exon 19-TACC3 exon 2 fusion), FGFR2:OFD1(FGFR3 exon 19-TACC3 exon 3 fusion), FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.
 15. The method of any one of claims 3-14, wherein the evaluating comprises amplifying a cDNA with a pair of primers that amplify the FGFR mutant .
 16. The method of claim 15, wherein the cDNA is a pre-amplified cDNA.
 17. The method of any one of the previous claims, wherein the FGFR mutant and pair of primers are:
 - FGFR3:TACC3 v1 (FGFR3 exon 18-TACC3 exon 11 fusion) and primers having the sequences of SEQ ID NO:5 and SEQ ID NO:6;
 - FGFR3:TACC3 v3 (FGFR3 exon 18-TACC3 exon 10 fusion) and primers having the sequences of SEQ ID NO:7 and SEQ ID NO:8;
 - FGFR3:TACC3 Intron (FGFR3 exon 18-TACC3 exon 4 fusion) and primers having the sequences of SEQ ID NO:9 and SEQ ID NO: 10 , or a combination thereof, and optionally:

FGFR3 :BAIAP2L1 (FGFR3 exon 18-TACC3 exon 2 fusion) and primers having the sequences of SEQ ID NO: 11 and SEQ ID NO:12;

FGFR2:BICC1 (FGFR3 exon 19-TACC3 exon 3 fusion) and primers having the sequences of SEQ ID NO: 13 and SEQ ID NO:14;

FGFR2:AFF3 (FGFR3 exon 19-TACC3 exon 8 fusion) and primers having the sequences of SEQ ID NO: 15 and SEQ ID NO:16;

FGFR2:CASP7 (FGFR3 exon 19-TACC3 exon 4 fusion) and primers having the sequences of SEQ ID NO: 17 and SEQ ID NO:18;

FGFR2:CCDC6 (FGFR3 exon 19-TACC3 exon 2 fusion) and primers having the sequences of SEQ ID NO: 19 and SEQ ID NO:20;

FGFR2:OFD1 (FGFR3 exon 19-TACC3 exon 3 fusion) and primers having the sequences of SEQ ID NO:21 and SEQ ID NO:22;

R248C and primers having the sequences of SEQ ID NO:23 and SEQ ID NO:24 or SEQ ID NO:31 and SEQ ID NO:32;

S249C and primers having the sequences of SEQ ID NO:25 and SEQ ID NO:26 or SEQ ID NO:33 and SEQ ID NO:34;

G370C and primers having the sequences of SEQ ID NO:27 and SEQ ID NO:28 or SEQ ID NO:35 and SEQ ID NO:36;

Y373C and primers having the sequences of SEQ ID NO:29 and SEQ ID NO:30 or SEQ ID NO:37 and SEQ ID NO:38;

or any combination thereof.

18. The method of any one of the previous claims, wherein the evaluating comprises: isolating a RNA from the biological sample and synthesizing cDNA from the isolated RNA.
19. The method of claim 18, further comprising pre-amplifying the cDNA prior to the amplifying step.
20. The method of any one of claims 1, or 3-19, wherein the cDNA is preamplified.
21. The method of any one of claims 1, or 3-19, wherein the amplifying step comprises performing a real-time PCR.

22. The method of claim 21, wherein the real-time PCR is performed with one or more probes comprising SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:46, and optionally in combination with one or more probes comprising SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, and/or SEQ ID NO:55.
23. The method of claim 21 or 22, wherein the real-time PCR is performed with one or more 3' blocking oligonucleotides comprising SEQ ID NO:39, SEQ ID NO:41, and SEQ ID NO:42.
24. The method of any one of claims 1, or 3-19, wherein said determining step comprises sequencing the amplified cDNA.
25. A kit for performing the method of claim 1 or 2, comprising:
 - one or more pairs of primers having the sequences of SEQ ID NO:5 and SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO: 10, or a combination thereof and optionally in combination with one or more pairs of primers having the sequences of:
 - SEQ ID NO: 11 and SEQ ID NO:12, SEQ ID NO:13 and SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16, SEQ ID NO: 17 and SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO:20, SEQ ID NO:21 and SEQ ID NO:22, SEQ ID NO:23 and SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26, SEQ ID NO:27 and SEQ ID NO:28, SEQ ID NO:29 and SEQ ID NO:30, SEQ ID NO:31 and SEQ ID NO:32, SEQ ID NO:33 and SEQ ID NO:34, SEQ ID NO:35 and SEQ ID NO:36, SEQ ID NO:37 and SEQ ID NO:38, or any combination thereof; and
 - instructions for performing an assay to detect one or more FGFR mutant genes.
26. The kit of claim 25, further comprising one or more probes, one or more 3' blocking oligonucleotides, or both.
27. The kit of claim 26, wherein
 - a. the pair of primers have the sequences SEQ ID NO:5 and SEQ ID NO:6 and the or each probe has the sequence of SEQ ID NO:43;

- b. the pair of primers have the sequences SEQ ID NO:7 and SEQ ID NO:8 and the or each probe has the sequence of SEQ ID NO:44; or
- c. the pair of primers have the sequences SEQ ID NO:9 and SEQ ID NO: 10 and the or each probe has the sequence of SEQ ID NO:46, or a combination thereof, and optionally in combination with:
- d. the pair of primers have the sequences SEQ ID NO: 11 and SEQ ID NO: 12 and the or each probe has the sequence of SEQ ID NO:47;
- e. the pair of primers have the sequences SEQ ID NO: 13 and SEQ ID NO: 14 and the or each probe has the sequence of SEQ ID NO:45;
- f. the pair of primers have the sequences SEQ ID NO: 15 and SEQ ID NO: 16 and the or each probe has the sequence of SEQ ID NO:48;
- g. the pair of primers have the sequences SEQ ID NO: 17 and SEQ ID NO: 18 and the or each probe has the sequence of SEQ ID NO:49;
- h. the pair of primers have the sequences SEQ ID NO: 19 and SEQ ID NO:20 and the or each probe has the sequence of SEQ ID NO:50;
- i. the pair of primers have the sequences SEQ ID NO:21 and SEQ ID NO:22 and the or each probe has the sequence of SEQ ID NO:51;
- j. the pair of primers have the sequences SEQ ID NO:23 and SEQ ID NO:24 and the or each probe has the sequence of SEQ ID NO:52;
- k. the pair of primers have the sequences SEQ ID NO:25 and SEQ ID NO:26 and the or each probe has the sequence of SEQ ID NO:53;
- l. the pair of primers have the sequences SEQ ID NO:27 and SEQ ID NO:28 and the or each probe has the sequence of SEQ ID NO:54;
- m. the pair of primers have the sequences SEQ ID NO:29 and SEQ ID NO:30 and the or each probe has the sequence of SEQ ID NO:55;
- n. the pair of primers have the sequences SEQ ID NO:31 and SEQ ID NO:32, the or each probe has the sequence of SEQ ID NO:52, and the 3' blocking oligonucleotide has the sequence of SEQ ID NO:39;
- o. the pair of primers have the sequences SEQ ID NO:33 and SEQ ID NO:34, and the or each probe has the sequence of SEQ ID NO:53, ;

- p. the pair of primers have the sequences SEQ ID NO:35 and SEQ ID NO:36, the or each probe has the sequence of SEQ ID NO:54, and the 3' blocking oligonucleotide has the sequence of SEQ ID NO: 41;
- q. the pair of primers have the sequences SEQ ID NO:37 and SEQ ID NO:38, the or each probe has the sequence of SEQ ID NO:55, and the 3' blocking oligonucleotide has the sequence of SEQ ID NO:42; or
- r. any combination thereof.