

CLAIMS

1. An *in vitro* method for identifying a cancer likely to respond to compound A comprising
(a) determining the levels of expression of FGFR1, FGFR2 and FGFR3 in a tumor or liquid biopsy from a subject suffering from a cancer, and

5 (b) if the determined level of expression of at least one of FGFR1, FGFR2 and FGFR3 exceeds a pre-established threshold level, the subject has a cancer likely to respond to an effective amount of Compound A,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salts; and

10 wherein levels of expression of FGFR1, FGFR2 and FGFR3 are measured at the messenger RNA level, and wherein the pre-established threshold level of expression of at least one FGFR corresponds to any level from the 44% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the
15 nCounter Gene Expression Assay from 0.104 to 0.641 for FGFR1, from 0.257 to 1.094 for FGFR2, and from 0.128 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

2. The *in vitro* method of claim 1, wherein the pre-established threshold level of the at least
20 one FGFR corresponds to:

(a) any level from the 60% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.301 to 0.641 for FGFR1, from 0.669 to 1.094 for FGFR2, and from 0.289 to 0.815 for
25 FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

(b) any level from the 65% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression
30 of a set of 16 reference genes measured by the nCounter Gene Expression Assay from

0.484 to 0.641 for FGFR1, from 0.884 to 1.094 for FGFR2, and from 0.490 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

- 5 (c) any level from the 70% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.558 to 0.641 for FGFR1, from 0.984 to 1.094 for FGFR2, and from 0.671 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0,
10 SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

3. The *in vitro* method of claim 1 or 2, wherein the cancer is gastric cancer and the pre-established threshold level of expression of FGFR2 corresponds to:

- 15 (a) any level from the 44% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.257 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

- 20 (b) any level from the 60% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.669 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7
25 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

- (c) any level from the 70% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.984 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19,
30 RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

(d) any level from the 80% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 1.460 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

4. The *in vitro* method of claim 1 or 2, wherein the cancer is esophageal squamous-cell carcinoma and the pre-established threshold level of expression of FGFR1 corresponds to:

10 (a) any level from the 44% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.104 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

(b) any level from the 60% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.301 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

25 (c) any level from the 70% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.558 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

30 (d) any level from the 80% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.759 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19,

RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

5. An *in vitro* method of selecting a subject suffering from a cancer likely to respond to a therapeutic regimen that comprises a pharmaceutical composition comprising an effective
5 amount of Compound A, the method comprising

(a) determining the levels of expression of FGFR1, FGFR2 and FGFR3 in a tumor or liquid biopsy from the subject suffering from a cancer, and

(b) if the determined level of expression of at least one of FGFR1, FGFR2 and FGFR3 exceeds a pre-established threshold level, considering the subject eligible for the
10 therapeutic regimen,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salts; and

wherein levels of expression of FGFR1, FGFR2 and FGFR3 are measured at the messenger RNA level, and wherein the pre-established threshold level of at least one
15 FGFR corresponds to any level from the 44% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.104 to 0.641 for FGFR1, from 0.257 to 1.094 for FGFR2, and from 0.128 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC,
20 MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

6. The *in vitro* method of claim 5, wherein the pre-established threshold level of the at least one FGFR corresponds to:

(a) any level from the 60% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression
25 of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.301 to 0.641 for FGFR1, from 0.669 to 1.094 for FGFR2, and from 0.289 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5,
30 EMC7 exon 3, GPI exon 4 and GPI exon 6;

(b) any level from the 65% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.484 to 0.641 for FGFR1, from 0.884 to 1.094 for FGFR2, and from 0.490 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

(c) any level from the 70% to the 73% cutoff level of expression for the at least one FGFR, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.558 to 0.641 for FGFR1, from 0.984 to 1.094 for FGFR2, and from 0.671 to 0.815 for FGFR3, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

7. The *in vitro* method of claim 5 or 6, wherein the cancer is gastric cancer and the pre-established threshold level of expression of FGFR2 corresponds to:

(a) any level from the 44% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.257 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

(b) any level from the 60% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.669 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

(c) any level from the 70% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.984 to 1.610

for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

5 (d) any level from the 80% to the 83% cutoff level of expression for FGFR2, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 1.460 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

10 8. The *in vitro* method of claim 5 or 6, wherein the cancer is esophageal squamous-cell carcinoma and the pre-established threshold level of expression of FGFR1 corresponds to:

15 (a) any level from the 44% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.104 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

20 (b) any level from the 60% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.301 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6;

25 (c) any level from the 70% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.558 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7
30 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6; or

(d) any level from the 80% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.759 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

9. Use of compound A in the preparation of a medicament for the treatment of a cancer identified as likely to respond to compound A according to any one of claims 1 to 4, or for a subject selected to be suffering from a cancer likely to respond to compound A according to any one of claims 5 to 8,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salts.

10. Use of compound A in the preparation of a medicament for the treatment of gastric cancer identified as likely to respond to compound A according to claim 3 or for a subject selected to be suffering from gastric cancer likely to respond to compound A according to claim 7,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salt.

11. Use of compound A in the preparation of a medicament for the treatment of esophageal squamous-cell carcinoma identified as likely to respond to compound A according to claim 4 or for a subject selected to be suffering from esophageal squamous-cell carcinoma likely to respond to compound A according to claim 8,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salt.

12. An *in vitro* method of selecting a subject suffering from a gastric cancer likely to respond to Compound A, the method comprising determining the level of expression FGFR2 in a tumor or liquid biopsy from the subject and if the determined level of expression of FGFR2 exceeds a pre-established threshold level, considering the subject eligible for treatment, wherein the pre-established threshold level of expression of FGFR2 corresponds to any level from the 44% to the 83% cutoff level of expression for FGFR2,

corresponding to expression levels relative to the median of levels of mRNA expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.257 to 1.610 for FGFR2, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3,
5 EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salts.

13. An *in vitro* method of selecting a subject suffering from an esophageal squamous-cell carcinoma likely to respond to Compound A, the method comprising determining the level
10 of expression FGFR1 in a tumor or liquid biopsy from the subject and if the determined level of expression of FGFR1 exceeds a pre-established threshold level, considering the subject eligible for treatment, wherein the pre-established threshold level of expression of FGFR1 corresponds to any level from the 44% to the 84% cutoff level of expression for FGFR1, corresponding to expression levels relative to the median of levels of mRNA
15 expression of a set of 16 reference genes measured by the nCounter Gene Expression Assay from 0.104 to 1.362 for FGFR1, the 16 reference genes being ACTB, ALAS1, CLTC, MRPL19, RPL19, RPLP0, SF3A1, TBP, TUBB, c1orf43 exon 1, c1orf43 exon 2, CHMP2A exon 3, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6,

wherein compound A is 5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone and its pharmaceutically acceptable salts.
20