

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 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
10 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 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,
15 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 one FGFR corresponds to:

(a) any level from the 60% to the 73% cutoff level of expression for the at least one FGFR,
20 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 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,
25 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
30 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.

10 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:

(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

(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.

5 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:

(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
10 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
15 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;

(c) any level from the 70% to the 84% cutoff level of expression for FGFR1, corresponding
20 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
25 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,
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.

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 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 therapeutic regimen,

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 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, 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 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, 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

(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.

5 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:

(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
10 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
15 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;

(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
20 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
25 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
30 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 comprising levels of expression of FGFR1, FGFR2 and FGFR3 in a tumor or liquid biopsy of the cancer exceeding a pre-established threshold level, considering the subject eligible for treatment 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 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.

10. Use of compound A in the preparation of a medicament for the treatment of gastric cancer comprising levels of expression of FGFR2 exceeding a pre-established threshold level in a tumor or liquid biopsy of the gastric cancer 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, EMC7 exon 5, EMC7 exon 3, GPI exon 4 and GPI exon 6.

11. Use of compound A in the preparation of a medicament for the treatment of esophageal squamous-cell carcinoma comprising levels of expression of FGFR1 exceeding a pre-established threshold level in a tumor or liquid biopsy of the esophageal squamous-cell carcinoma 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 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.

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
5 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,
10 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.

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 of expression FGFR1 in a tumor or liquid biopsy from the subject and if the determined
15 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 expression of a set of 16 reference genes measured by the nCounter Gene Expression
20 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.