

SUMMARY

[0005a] In one aspect, the present disclosure refers to a method of predicting susceptibility of a subject suffering from cancer to a treatment with an anti-cancer drug, wherein the method comprises detecting the presence or absence of a genetic alteration in a long non-coding RNA (lncRNA) that resides in an antisense strand of an oncogene; wherein the oncogene is EGFR, and the genetic alteration is a homozygous G>A mutation at Q787Q position in exon 20 of EGFR; wherein in case the homozygous genetic alteration is present, the subject is predicted to show improved susceptibility to the treatment with the anti-cancer drug compared to a subject not carrying the genetic alteration; and wherein the anti-cancer drug is an EGFR tyrosine kinase inhibitor. In another aspect, the present disclosure refers to method of predicting the susceptibility of a subject suffering from cancer related to EGFR to a treatment with an EGFR tyrosine kinase inhibitor, the method comprising determining whether either one or both of the following is given: i) the subject has a homozygous silent G>A genetic mutation at Q787Q position in exon 20 of EGFR; ii) the subject has lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to subject that does not respond to treatment with an EGFR inhibitor; wherein in case one or both of i) to ii) is given, the subject is predicted to show improved susceptibility to a treatment with an EGFR inhibitor compared to a subject not showing any of i) to ii). In yet another aspect, the present disclosure refers to the use of an anti-cancer drug in the manufacturing of a medicament for treating cancer in a subject, wherein the subject has been determined to have one or both of: i) a homozygous silent G>A mutation at Q787Q position in exon 20 of EGFR; and ii) lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to subject that does not respond to treatment with a tyrosine kinase inhibitor; and wherein the anti-cancer drug is an EGFR tyrosine kinase inhibitor. In still another aspect, the present disclosure refers to the use of a therapeutic agent suppressing EGFR-AS1 lncRNA or EGFR-AS1 expression in the manufacture of a medicament for treating EGFR related cancer, wherein the medicament is to be administered in combination with an EGFR tyrosine kinase inhibitor.

[0006] In one example, the present disclosure refers to a method of predicting susceptibility of a subject suffering from cancer to a treatment with an anti-cancer drug, wherein the method comprises detecting the presence or absence of a genetic alteration in long non-coding RNA (lncRNA) that resides in an antisense strand of an oncogene, wherein the genetic alteration alters or disrupts expression of the oncogene; wherein in case the

genetic alteration is present, the subject is predicted to show improved susceptibility to the treatment with the anti-cancer drug compared to a subject not carrying the mutation.

[0007] In another example, the present disclosure refers to a method of predicting the susceptibility of a subject suffering from cancer related to EGFR to a treatment with an EGFR inhibitor, the method comprising determining whether either one or two or all of the following is given: i) the subject has a silent G>A mutation (genetic alteration) at Q787Q position in exon 20 of EGFR (nucleotide 2361; as shown in NCBI sequence ID: NM_005228.4 and SEQ ID NO: 27); ii) the subject has lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to subject that does not respond to treatment with an EGFR inhibitor; iii) the subject has higher EGFR isoform D/isoform A ratio compared to subject that does not respond to treatment with an EGFR inhibitor; wherein in case one or two or all of i) to iii) is given the subject is predicted to show improved susceptibility to a treatment with an EGFR inhibitor compared to a subject not showing any of i) to iii).

[0008] In yet another example, the present disclosure refers to a method of treating cancer in a subject suffering from said cancer, wherein the method comprises detecting the presence or absence of a mutation in a long non-coding RNA on an antisense strand of an oncogene related to the cancer, wherein the genetic alteration alters or disrupts expression of the oncogene; administering an anti-cancer drug for the cancer type the subject suffers from in case the presence of the genetic alteration is confirmed.

[0009] In a further example, the present disclosure refers to a method of treating a subject suffering from cancer, comprising administering to the subject an effective amount of a therapeutic agent affecting expression of a non-coding RNA an oncogene, wherein the genetic alteration alters or disrupts expression of the oncogene; and administering to the subject an effective amount of an anti-cancer drug specific for the cancer related to the oncogene.

[0010] In one example, the present disclosure refers to a method of treating a subject suffering from an EGFR-related cancer, comprising administering to the subject an effective amount of a therapeutic agent affecting EGFR-AS1 lncRNA expression, or affecting EGFR-AS1 expression, or increasing the amount of EGFR isoform D and/or decreasing EGFR isoform A or a combination thereof; and administering to the subject an effective amount of a tyrosine kinase inhibitor used to treat the EGFR-related cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

5 [0012] **FIG. 1** is a collection of **FIG. 1A – FIG. 1E** showing the correlation of a point mutation in a lncRNA of EGFR, referred to herein as Q787Q, with sensitivity of primary HNSCC cell lines to EGFR tyrosine kinase inhibitors. **FIG. 1A** is a set of line graphs showing the result of a cell proliferation assays and the effect of a treatment with gefitinib, erlotinib or afatinib on the inhibition of cell proliferation. Error bars indicate one standard deviation. **FIG. 1B** is a set of DNA sequence trace chromatograms of Sanger sequencing, showing the disclosed AA genotype in cell lines with increased sensitivity to EGFR tyrosine kinase inhibitors (NCC-HN19 and NCC-HN64). **FIG. 1C** is a set of images of western blot results showing EGFR pathway activation with and without tyrosine kinase inhibitors treatment in HNSCC cell lines with the indicated Q787Q genotype. Each cell line is compared in terms of rate of phosphorylation and also in terms of the effect of a treatment of gefitinib on the rate of phosphorylation, that is the presence of the p-version of the protein, versus the unphosphorylated version of the protein. For example, the first two rows compare the level of phosphorylation between EGFR and p-EGFR (that is the phosphorylated version of EGFR). As gefitinib is a known tyrosine kinase inhibitor, it is expected that the rate of phosphorylation is anti-proportional to the amount of gefitinib administered. That is to say the rate of phosphorylation will decrease with an increase in the amount of gefitinib administered. GAPDH acts as a loading control. **FIG. 1D** is a graph of IC₅₀ values showing sensitivity to gefitinib in correctly targeted G/A^{AAV} clones (CL16, CL19 and CL63) compared to G/G^{AAV} negative controls (clones CL12, CL76 and CL77). This shows that the presence of the G/A mutation results in a stark difference in IC₅₀ values for gefitinib. In terms

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Claims

1. A method of predicting susceptibility of a subject suffering from cancer to a treatment with an anti-cancer drug, wherein the method comprises detecting the presence or absence of a genetic alteration in a long non-coding RNA (lncRNA) that resides in an antisense strand of an oncogene; wherein the oncogene is EGFR, and the genetic alteration is a homozygous G>A mutation at Q787Q position in exon 20 of EGFR; wherein in case the homozygous genetic alteration is present, the subject is predicted to show improved susceptibility to the treatment with the anti-cancer drug compared to a subject not carrying the genetic alteration; and wherein the anti-cancer drug is an EGFR tyrosine kinase inhibitor.
2. The method of claim 1, wherein the cancer is head and neck cancer.
3. The method of claim 2, wherein the head and neck cancer is head and neck squamous cell carcinoma (HNSCC) or oral squamous cell carcinoma (OSCC).
4. The method of any one of claims 1 to 3, further comprising measuring of either one or both of the following for predicting the susceptibility: i) whether the subject has lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to a subject that does not respond to treatment with the anti-cancer drug; ii) whether the subject has higher EGFR isoform D/isoform A ratio compared to a subject that does not respond to treatment with the EGFR tyrosine kinase inhibitor.
5. The method of any one of claims 1 to 4, wherein the EGFR tyrosine kinase inhibitor is selected from the group consisting of gefitinib, erlotinib and afatinib.
6. A method of predicting the susceptibility of a subject suffering from cancer related to EGFR to a treatment with an EGFR tyrosine kinase inhibitor, the method comprising determining whether either one or both of the following is given:
 - i) the subject has a homozygous silent G>A genetic mutation at Q787Q position in exon 20 of EGFR;
 - ii) the subject has lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to subject that does not respond to treatment with an EGFR inhibitor;

wherein in case one or both of i) to ii) is given, the subject is predicted to show improved susceptibility to a treatment with an EGFR inhibitor compared to a subject not showing any of i) to ii).

- 5 7. Use of an anti-cancer drug in the manufacturing of a medicament for treating cancer in a subject, wherein the subject has been determined to have one or both of: i) a homozygous silent G>A mutation at Q787Q position in exon 20 of EGFR; and ii) lower EGFR-AS1 or EGFR-AS1 lncRNA expression level compared to subject that does not respond to treatment with a tyrosine kinase inhibitor; and wherein the anti-cancer drug is an EGFR tyrosine kinase inhibitor.
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8. The method of claim 6 or the use of claim 7, wherein the cancer is head and neck cancer.
- 15 9. The method or use of claim 8, wherein the head and neck cancer is head and neck squamous cell carcinoma (HNSCC) or oral squamous cell carcinoma (OSCC).
10. The method of claim 6, the use of claim 7, or the method or use according to any of claims 8-9, wherein the EGFR tyrosine kinase inhibitor is selected from the group
20 consisting of gefitinib, erlotinib and afatinib.
11. The method or use according to claim 10, wherein the EGFR tyrosine kinase inhibitor is gefitinib.
- 25 12. Use of a therapeutic agent suppressing EGFR-AS1 lncRNA or EGFR-AS1 expression, in the manufacture of a medicament for treating EGFR related cancer, wherein the medicament is to be administered in combination with an EGFR tyrosine kinase inhibitor.
- 30 13. The use according to claim 12, wherein the medicament and the tyrosine kinase inhibitor are to be administered simultaneously, or the EGFR tyrosine kinase inhibitor is to be administered after the medicament.

14. The use according to claim 13, wherein when the tyrosine kinase inhibitor is to be administered after the medicament, the time interval between the administration of the medicament and the EGFR tyrosine kinase inhibitor is at least 1 to 24 hours, or at least 1 or 2 or 3 or 4 or 5 or 6 or 7 days, or at least one week.
15. The use according to any one of claims 12 to 14, wherein the therapeutic agent affecting EGFR-AS1 or EGFR-AS1 lncRNA expression comprises miRNA, shRNA, LNAs, siRNA or combinations thereof.
16. The use according to any one of claims 12 to 14, wherein the therapeutic agent suppressing EGFR-AS1 or EGFR-AS1 lncRNA expression comprises EGFR-AS1 targeting LNA.
17. The use according to any one of claims 12 to 16, wherein the EGFR tyrosine kinase inhibitor is selected from the group consisting of gefitinib, erlotinib, erlotinib HCl, lapatinib, dacomitinib, TAE684, afatinib, dasatinib, saracatinib, veratinib, AEE788, WZ4002, icotinib, osimertinib, BI1482694, ASP8273, EGF816, AZD3759, cetuximab, necitumumab, panitumumab, nimotuzumab and combinations thereof.
18. The use according to claim 17, wherein the EGFR tyrosine kinase inhibitor is selected from the group consisting of gefitinib, erlotinib and lapatinib.