

CLAIMS

1. A method of predicting responsiveness of an individual having non-small cell lung cancer (NSCLC) to treatment with a DNA-damaging therapeutic agent comprising:
 - a. measuring expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;
 - b. deriving a test score that captures the expression levels;
 - c. providing a threshold score comprising information correlating the test score and responsiveness;
 - d. and comparing the test score to the threshold score; wherein responsiveness is predicted when the test score exceeds the threshold score and/or wherein a lack of responsiveness is predicted when the test score does not exceed the threshold score.
2. The method of claim 1, wherein the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3 and/or the group consisting of CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR211P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.
3. The method of claim 2, comprising measuring the expression level of all of the biomarkers.
4. The method of claim 1, comprising measuring the expression level of:
 - a. at least 10 of the biomarkers from Table 1A in the test sample; and/or
 - b. at least one or more up to all of CD2, FYB, ITGAL and RAC2
5. The method of claim 4, comprising measuring the expression level of all 58 different biomarkers listed in Table 1A.
6. The method of any of claims 1 to 5 where expression levels are measured using primers or probes which bind to at least one of the target sequences set forth as SEQ ID NO: 1-80 (Table 1A), 81-260 (Table 3A), 261-313 (Table 3B), 314-337 (Table 1B), 338-363 (Table 1C) or comprise at least 15 contiguous nucleotides of any one of SEQ ID NOs 364-455 (Table 3C).
7. The method of any one of claims 1 to 6, wherein the NSCLC is early stage, late stage or metastatic disease.
8. The method of any one of claims 1 to 7, wherein the NSCLC is selected from one or more of adenocarcinoma, large-cell lung carcinoma and squamous cell carcinoma.
9. The method of any one of claims 1 to 8, wherein the DNA-damaging therapeutic agent comprises one or more substances selected from the group consisting of: a DNA damaging

agent, a DNA repair targeted therapy, an inhibitor of DNA damage signalling, an inhibitor of DNA damage induced cell cycle arrest, a histone deacetylase inhibitor, a heat shock protein inhibitor and an inhibitor of DNA synthesis.

10. The method of claim 9, wherein the DNA-damaging therapeutic agent comprises one or more of a platinum-containing agent, a nucleoside analogue such as gemcitabine or 5-fluorouracil or a prodrug thereof such as capecitabine, an anthracycline such as epirubicin or doxorubicin, an alkylating agent such as cyclophosphamide, an ionising radiation or a combination of radiation and chemotherapy (chemoradiation).

11. The method of any one of claims 1 to 10, wherein the DNA-damaging therapeutic agent comprises a platinum-containing agent.

12. The method of claim 11, wherein the platinum based agent is selected from cisplatin, carboplatin and oxaliplatin.

13. The method of any one of claims 1 to 12, which predicts responsiveness to treatment with the DNA-damaging therapeutic agent together with a further therapy.

14. The method of claim 13 wherein the further therapy is (treatment with) a mitotic inhibitor.

15. The method of claim 14, wherein the mitotic inhibitor is a vinca alkaloid.

16. The method of claim 15, wherein the vinca alkaloid is vinorelbine.

17. The method of any one of claims 1 to 13 which predicts responsiveness to a combination therapy comprising a DNA-damaging therapeutic agent, wherein the combination therapy is selected from:

- a. cisplatin/carboplatin and 5-fluorouracil
- b. cisplatin/carboplatin and capecitabine
- c. epirubicin/doxorubicin, cisplatin/carboplatin and fluorouracil
- d. epirubicin/doxorubicin, oxaliplatin and capecitabine
- e. cisplatin/carboplatin and etoposide
- f. gemcitabine and cisplatin/carboplatin
- g. cyclophosphamide, epirubicin/doxorubicin and vincristine
- h. cyclophosphamide, epirubicin/doxorubicin, vincristine and etoposide
- i. epirubicin/doxorubicin, cyclophosphamide and etoposide

18. The method of any one of claims 1 to 17 wherein the treatment is adjuvant treatment and/or neoadjuvant treatment.

19. The method of any one of claims 1 to 18 wherein if responsiveness is predicted, the individual is treated with the DNA-damaging therapeutic agent.
20. The method of any one of claims 1 to 18 wherein if a lack of responsiveness is predicted, the individual is not treated with the DNA-damaging therapeutic agent.
21. The method of any one of claims 1 to 20 wherein the treatment is adjuvant cisplatin/vinorelbine treatment.
22. The method of claim 20 wherein if a lack of responsiveness is predicted, the individual is treated with a mitotic inhibitor.
23. The method of any one of claims 1 to 22 wherein responsiveness comprises or is increased overall survival, progression free survival and/or disease free survival.
24. (a) A method of treating NSCLC comprising administering a DNA-damaging therapeutic agent to a subject, wherein the subject is predicted to be responsive to the DNA-damaging therapeutic agent on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C; or
(b) A DNA-damaging therapeutic agent for use in a method of treating NSCLC, wherein the subject is predicted to be responsive to the DNA-damaging therapeutic agent on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C.
25. (a) A method of treating NSCLC comprising administering a mitotic inhibitor to a subject, wherein the subject is predicted to be non-responsive to a DNA-damaging therapeutic agent on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C; or
(b) A mitotic inhibitor for use in a method of treating NSCLC, wherein the subject is predicted to be non-responsive to a DNA-damaging therapeutic agent on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, wherein the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C.
26. The method or use of claim 24 or 25 wherein the test score has been derived according to a method as claimed in any one of claims 1 to 23.
27. A kit for predicting responsiveness of an individual having non-small cell lung cancer (NSCLC) to treatment with a DNA-damaging therapeutic agent comprising primers or probes which hybridize

to at least one of the target sequences set forth as SEQ ID NO: 1-80 (Table 1A), 81-260 (Table 3A), 261-313 (Table 3B), 314-337 (Table 1B), 338-363 (Table 1C) or comprise at least 15 contiguous nucleotides of any one of SEQ ID NOs 364-455 (Table 3C).

- 5 28. The kit of claim 27 wherein the primers or probes hybridize to at least 10 of the target sequences.
29. The kit of claim 27 or 28 further comprising a DNA-damaging therapeutic agent.
- 10 30. The kit of claim 29 wherein the DNA-damaging therapeutic agent is provided in a dosage form specifically for treatment of NSCLC.
31. The kit of claim 30 wherein the treatment is neo-adjuvant or adjuvant treatment.
- 15 32. The kit of any one of claims 27 to 31 wherein the DNA-damaging therapeutic agent comprises a platinum-based agent.

CLAIMS

1. A method of predicting responsiveness of an individual having non-small cell lung cancer (NSCLC) to treatment with a cancer therapeutic agent comprising:

(a) measuring expression levels of one or more biomarkers in a test sample obtained from the individual, in which one or more of the biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;

(b) deriving a test score that captures the expression levels;

(c) providing a threshold score comprising information correlating the test score and responsiveness; and

(d) comparing the test score to the threshold score; in which responsiveness is predicted when the test score exceeds the threshold score and/or in which a lack of responsiveness is predicted when the test score does not exceed the threshold score.

2. A method of detecting a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response in an individual comprising:

(a) measuring expression levels of one or more biomarkers in a test sample obtained from the individual, in which the one or more of the biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;

(b) deriving a test score that captures the expression levels;

(c) providing a threshold score comprising information correlating the test score and responsiveness; and

(d) comparing the test score to the threshold score; in which the NSCLC with DNA damage repair deficiency and/or elevated immune response is detected when the test score exceeds the threshold score.

3. A method of selecting an appropriate therapy to treat a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response in an individual comprising:

(a) measuring expression levels of one or more of the biomarkers in a test sample obtained from the individual, in which the one or more biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;

- (b) deriving a test score that captures the expression levels;
- (c) providing a threshold score comprising information correlating the test score and responsiveness; and
- (d) comparing the test score to the threshold score; in which a therapeutic agent appropriate for treatment of the individual is selected when the test score exceeds the threshold score.

4. A method of selecting an appropriate therapy to treat a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response in an individual comprising:

- (a) measuring expression levels of one or more biomarkers in a test sample obtained from the individual, in which the one or more of the biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;

- (b) deriving a test score that captures the expression levels;

- (c) providing a threshold score comprising information correlating the test score and responsiveness; and

- (d) comparing the test score to the threshold score; in which a therapeutic agent that targets tumors with abnormal DNA repair is selected when the test score exceeds the threshold score.

5. A method of selecting an appropriate therapy to treat a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response in an individual comprising:

- (a) measuring expression levels of one or more biomarkers in a test sample obtained from the individual, in which the one or more of the biomarkers are selected from Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C;

- (b) deriving a test score that captures the expression levels;

- (c) providing a threshold score comprising information correlating the test score and responsiveness; and

(d) comparing the test score to the threshold score; in which a therapeutic agent that inhibits expression of at least one of the biomarkers is selected when the test score exceeds the threshold score.

6. (a) A method of treating a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response comprising administering a therapeutic agent to a subject, in which the subject is predicted to be responsive to the therapeutic agent, or the therapy is selected, on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the subject, in which one or more of the biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C; or

(b) A therapeutic agent for use in a method of treating a non-small cell lung cancer (NSCLC) with DNA damage repair deficiency and/or elevated immune response, in which the subject is predicted to be responsive to the therapeutic agent, or the therapy is selected, on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, in which one or more of the biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C.

7. (a) A method of treating a non-small cell lung cancer (NSCLC) without DNA damage repair deficiency and/or elevated immune response comprising administering a mitotic inhibitor to a subject, in which the subject is predicted to be non-responsive to a DNA damaging therapeutic agent, or the therapy is selected, on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the subject, in which one or more of the biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C; or

(b) A therapeutic agent for use in a method of treating a non-small cell lung cancer (NSCLC) without DNA damage repair deficiency and/or elevated immune response, in which the subject is predicted to be non-responsive to a DNA damaging therapeutic agent, or the therapy is selected, on the basis of a test score derived from expression levels of one or more biomarkers in a test sample obtained from the individual, in which one or more of the biomarkers are selected from those listed in Table 2B, 1A, 1B, 1C, 2A, 3A, 3B and/or 3C.

8. A method according to any preceding claim, in which the one or more biomarkers are selected from the group consisting of CXCL10, MX1, IDO1, IF144L, CD2, GBP5, PRAME, ITGAL, LRP4, and APOL3 and/or the group consisting of CDR1, FYB, TSPAN7, RAC2, KLHDC7B, GRB14, AC138128.1, KIF26A, CD274, CD109, ETV7, MFAP5, OLFM4, PI15, FOSB, FAM19A5, NLRC5, PRICKLE1, EGR1, CLDN10, ADAMTS4, SP140L, ANXA1, RSAD2, ESR1, IKZF3, OR211P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.
9. A method according to Claim 8, comprising measuring the expression level of all of the biomarkers.
10. A method according to any of Claims 1 to 7, comprising measuring the expression level of:
 - (a) at least 10 of the biomarkers from Table 1A in the test sample; and/or
 - (b) at least one or more up to all of CD2, FYB, ITGAL and RAC2
11. A method according to Claim 10, comprising measuring the expression level of all different biomarkers listed in Table 1A.
12. A method according to any of Claims 1 to 11 where expression levels are measured using primers or probes which bind to at least one of the target sequences set forth as SEQ ID NO: 1-80 (Table 1A), 81-260 (Table 3A), 261-313 (Table 3B), 314-337 (Table 1B), 338-363 (Table 1C) or comprise at least 15 contiguous nucleotides of any one of SEQ ID NOs 364-455 (Table 3C).
13. A method according to any of Claims 1 to 12, in which the NSCLC is early stage, late stage or metastatic disease.
14. A method according to any of Claims 1 to 13, in which the NSCLC is selected from one or more of adenocarcinoma, large-cell lung carcinoma and squamous cell carcinoma.
15. A method according to any of Claims 1 and 3 to 6 in which the therapy comprises a DNA-damaging therapeutic agent, optionally together with a further therapy.
16. A method according to Claim 15, in which the DNA-damaging therapeutic agent comprises one or more substances selected from the group consisting of: a DNA damaging agent, a DNA repair targeted therapy, an inhibitor of DNA damage signalling, an inhibitor of

DNA damage induced cell cycle arrest, a histone deacetylase inhibitor, a heat shock protein inhibitor and an inhibitor of DNA synthesis.

17. A method according to Claim 15 or 16, in which the DNA-damaging therapeutic agent comprises one or more of a platinum-containing agent, a nucleoside analogue such as
 - 5 gemcitabine or 5-fluorouracil or a prodrug thereof such as capecitabine, an anthracycline such as epirubicin or doxorubicin, an alkylating agent such as cyclophosphamide, an ionising radiation or a combination of radiation and chemotherapy (chemoradiation).
18. A method according to Claim 15, in which the DNA-damaging therapeutic agent comprises a platinum-containing agent.
- 10 19. A method according to Claim 18, in which the platinum based agent is selected from cisplatin, carboplatin and oxaliplatin.
20. A method according to any of Claims 15 to 19 in which the further therapy is (treatment with) a mitotic inhibitor.
21. A method according to Claim 20, in which the mitotic inhibitor is a vinca alkaloid.
- 15 22. A method according to Claim 21, in which the vinca alkaloid is vinorelbine.
23. A method according to any of Claims 1 and 3 to 6 in which the therapy is a combination therapy comprising a DNA-damaging therapeutic agent, in which the combination therapy is selected from:
 - (a) cisplatin/carboplatin and 5-fluorouracil
 - 20 (b) cisplatin/carboplatin and capecitabine
 - (c) epirubicin/doxorubicin, cisplatin/carboplatin and fluorouracil
 - (d) epirubicin/doxorubicin, oxaliplatin and capecitabine
 - (e) cisplatin/carboplatin and etoposide
 - (f) gemcitabine and cisplatin/carboplatin
 - 25 (g) cyclophosphamide, epirubicin/doxorubicin and vincristine
 - (h) cyclophosphamide, epirubicin/doxorubicin, vincristine and etoposide
 - (i) epirubicin/doxorubicin, cyclophosphamide and etoposide

24. A method according to any of Claims 1 and 3 to 23 in which the therapy is adjuvant treatment and/or neoadjuvant treatment.
25. A kit for predicting responsiveness of an individual having non-small cell lung cancer (NSCLC) to treatment with a DNA-damaging therapeutic agent comprising primers or probes
5 which hybridize to at least one of the target sequences set forth as SEQ ID NO: 1-80 (Table 1A), 81-260 (Table 3A), 261-313 (Table 3B), 314-337 (Table 1B), 338-363 (Table 1C) or comprise at least 15 contiguous nucleotides of any one of SEQ ID NOs 364-455 (Table 3C).
26. A kit according to Claim 27 in which the primers or probes hybridize to at least 10 of the target sequences.
- 10 27. A kit according to Claim 25 or 26 further comprising a DNA-damaging therapeutic agent.
28. A kit according to Claim 27 in which the DNA-damaging therapeutic agent is provided in a dosage form specifically for treatment of NSCLC.
29. A kit according to Claim 28 in which the treatment is neo-adjuvant or adjuvant
15 treatment.
30. A kit according to any of Claims 24 to 28 in which the DNA-damaging therapeutic agent comprises a platinum-based agent.