CLAIMS

1. A method of predicting responsiveness of an individual having oesophageal adenocarcinoma (OAC) 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 those listed in Table 2B, 1A, 1B, 2A, 3 and/or 4;
   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, OR2I1P, 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 any of claims 1 to 3 where expression levels are measured using primers and/or probes which bind to at least one of the target sequences set forth in Tables 1A (SEQ ID NO: 1-24), 1B (SEQ ID NO: 25-50) and/or 3 (SEQ ID NO: 51-230).

5. The method of any one of claims 1 to 4, wherein the OAC is early stage, late stage or metastatic disease.

6. The method of any one of claims 1 to 5, 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.

7. The method of claim 6, 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).

8. The method of any one of claims 1 to 7, wherein the DNA-damaging therapeutic agent comprises a platinum-containing agent.

9. The method of claim 8, wherein the platinum based agent is selected from cisplatin, carboplatin and oxaliplatin.

10. The method of any one of claims 1 to 9, which predicts responsiveness to treatment with the DNA-damaging therapeutic agent together with a further therapy.

11. The method of claim 10 wherein the further therapy is a mitotic inhibitor.

12. The method of claim 11, wherein the mitotic inhibitor is a vinca alkaloid or a taxane.

13. The method of claim 12, wherein the vinca alkaloid is vinorelbine.

14. The method of claim 12, wherein the taxane is paclitaxel or docetaxel.

15. The method of any one of claims 1 to 9 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 paclitaxel
f. cisplatin/carboplatin and irinotecan
g. cisplatin/carboplatin and vinorelbine

16. The method of claim 15 wherein the combination therapy further comprises one or more of a taxane such as paclitaxel, a topoisomerase inhibitor such as iriniotecan, a vinca alkaloid such as vinorelbine or chemoradiation,

17. The method of any one of claims 1 to 16 wherein the treatment is neoadjuvant treatment and/or adjuvant treatment.

18. The method of any one of claims 1 to 17 wherein if responsiveness is predicted, the individual is treated with the DNA-damaging therapeutic agent.

19. The method of any one of claims 1 to 17 wherein if a lack of responsiveness is predicted, the individual is not treated with the DNA-damaging therapeutic agent.

20. The method of any one of claims 1 to 19 wherein the treatment is neoadjuvant platinum-based therapy treatment.

21. The method of claim 19 wherein if a lack of responsiveness is predicted, the individual is treated with a mitotic inhibitor.

22. The method of any one of claims 1 to 21 wherein responsiveness comprises or is increased overall survival, progression free survival and/or disease free survival.

23. (a) A method of treating oesophageal adenocarcinoma (OAC) 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, 2A, 3 and/or 4; or
(b) A DNA-damaging therapeutic agent for use in a method of treating oesophageal adenocarcinoma (OAC), 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, 2A, 3 and/or 4.

24. (a) A method of treating oesophageal adenocarcinoma (OAC) 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, 2A, 3 and/or 4; or
(b) A mitotic inhibitor for use in a method of treating oesophageal adenocarcinoma (OAC), 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, 2A, 3 and/or 4.

25. The method or use of claim 23 or 24 wherein the test score has been derived according to a method as claimed in any one of claims 1 to 22.

26. A kit for predicting responsiveness of an individual having oesophageal adenocarcinoma (OAC) to treatment with a DNA-damaging therapeutic agent comprising primers or probes which hybridize to at least one of the target sequences set forth in Table 3 (SEQ ID NO: 51-230).

27. The kit of claim 26 wherein the primers or probes hybridize to at least 10 of the target sequences set forth in Table 3.

28. The kit of claim 26 or 27 further comprising a DNA-damaging therapeutic agent.

29. The kit of claim 28 wherein the DNA-damaging therapeutic agent is provided in a dosage form specifically for treatment of OAC.

30. The kit of claim 29 wherein the treatment is neo-adjuvant or adjuvant treatment.

31. The kit of any one of claims 26 to 30 wherein the DNA-damaging therapeutic agent comprises a platinum-based agent.

CLAIMS

1. A method of predicting responsiveness of an individual, having an oesophageal adenocarcinoma (OAC) 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 those listed in Table 2B, 1A, 1B, 2A, 3 and/or 4;

(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 an oesophageal adenocarcinoma (OAC) with DNA damage repair deficiency in an individual 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, 2A, 3 and/or 4;

(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 OAC with DNA damage repair deficiency is detected when the test score exceeds the threshold score.

3. A method of selecting an appropriate therapy to treat an oesophageal adenocarcinoma (OAC) with DNA damage repair deficiency in an individual 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, 2A, 3 and/or 4;

(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 an oesophageal adenocarcinoma (OAC) with DNA damage repair deficiency in an individual 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, 2A, 3 and/or 4;

(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 an oesophageal adenocarcinoma (OAC) with DNA damage repair deficiency in an individual 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, 2A, 3 and/or 4;

(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 therapeutic agent for use in a method of treating an oesophageal adenocarcinoma (OAC) with DNA damage repair deficiency, 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 the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 2A, 3 and/or 4.

7. A mitotic inhibitor for use in a method of treating oesophageal adenocarcinoma (OAC), in which 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, in which the one or more biomarkers are selected from those listed in Table 2B, 1A, 1B, 2A, 3 and/or 4.

8. A method according to any of Claims 1 to 5, a therapeutic agent according to Claim 6 or a mitotic inhibitor according to Claim 7, 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, OR2l1P, EGFR, NAT1, LATS2, CYP2B6, PTPRC, PPP1R1A, and AL137218.1.

9. A method according to any of Claims 1 to 5 or 8, comprising measuring the expression level of all of the biomarkers or a therapeutic agent according to Claim 6 or 8 or mitotic inhibitor according to Claim 7 or 8, in which the test score is derived from expression levels of all of the biomarkers.

10. A method, therapeutic agent or mitotic inhibitor according to any preceding claim, in which expression levels are measured using primers and/or probes which bind to at least one of the target sequences set forth in Tables 1A (SEQ ID NO: 1-24), 1B (SEQ ID NO: 25-50) and/or 3 (SEQ ID NO: 51-230).

11. A method, therapeutic agent or mitotic inhibitor according to any preceding claim, in which the OAC is early stage, late stage or metastatic disease.

12. A method, therapeutic agent or mitotic inhibitor according to any preceding claim, in which the therapy or therapeutic agent comprises a DNA-damaging therapeutic agent, optionally together with a further therapy.

13. A method, therapeutic agent or mitotic inhibitor according to Claim 12, 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.

14. A method, therapeutic agent or mitotic inhibitor according to Claim 12 or 13, in which 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).

15. A mitotic inhibitor according to Claim 7 or a method according to any of Claims 12 to 14, in which the DNA-damaging therapeutic agent comprises a platinum-containing agent.

16. A mitotic inhibitor or method according to Claim 15, in which the platinum based agent is selected from cisplatin, carboplatin and oxaliplatin.

17. A method according to any of Claims 1 to 5 and 8 to 16, which predicts responsiveness to treatment with the DNA-damaging therapeutic agent together with a further therapy.

18. A method according to Claim 17 in which the further therapy is a mitotic inhibitor.

19. A method according to Claim 18, in which the mitotic inhibitor is a vinca alkaloid or a taxane.

20. A method according to Claim 19, in which the vinca alkaloid is vinorelbine.

21. A method according to Claim 19, in which the taxane is paclitaxel or docetaxel.

22. A method according to any one of Claims 1 to 5 or 8 to 12 which predicts responsiveness to a combination therapy comprising a DNA-damaging therapeutic agent, in which 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 paclitaxel

(f) cisplatin/carboplatin and irinotecan

(g) cisplatin/carboplatin and vinorelbine.

23. A method according to Claim 22 in which the combination therapy further comprises one or more of a taxane such as paclitaxel, a topoisomerase inhibitor such as iriniotecan, a vinca alkaloid such as vinorelbine or chemoradiation,

24. A method according to any of Claims 1 to 5 or 8 to 23 in which the treatment is neoadjuvant treatment and/or adjuvant treatment.

25. A method according to any of Claims 1 to 5 or 8 to 24 in which responsiveness comprises or is increased overall survival, progression free survival and/or disease free survival.

26. A kit for predicting responsiveness of an individual having oesophageal adenocarcinoma (OAC) to treatment with a DNA-damaging therapeutic agent comprising primers or probes which hybridize to at least one of the target sequences set forth in Table 3 (SEQ ID NO: 51-230).

27. A kit according to Claim 26 in which the primers or probes hybridize to at least 10 of the target sequences set forth in Table 3.

28. A kit according to Claim 26 or 27 further comprising a DNA-damaging therapeutic agent.

29. A kit according to Claim 28 in which the DNA-damaging therapeutic agent is provided in a dosage form specifically for treatment of OAC.

30. A kit according to Claim 29 in which the treatment is neo-adjuvant or adjuvant treatment.

31. A kit according to any of Claims 26 to 30 in which the DNA-damaging therapeutic agent comprises a platinum-based agent.