

THERAPEUTIC, DIAGNOSTIC, AND PROGNOSTIC METHODS FOR CANCER OF THE BLADDER

FIELD OF THE INVENTION

5 The present invention is directed to methods for treating, diagnosing, and providing prognoses for cancer, e.g., bladder cancer.

BACKGROUND

10 Cancer remains one of the most deadly threats to human health. In the United States, cancer affects nearly 1.3 million new patients each year, and is the second leading cause of death after heart disease, accounting for approximately 1 in 4 deaths. Solid tumors are responsible for most of those deaths. Malignant tumors metastasize and grow rapidly in an uncontrolled manner, making timely detection and treatment extremely difficult.

15 Bladder cancer is the fifth-most common malignancy worldwide, with close to 400,000 newly diagnosed cases and approximately 150,000 associated deaths reported per year. Approximately 75-80% of bladder cancer patients present with non-muscle-invasive bladder cancer (NMIBC) at the time of initial diagnosis. Although confined to the lamina propria and typically not life-threatening, approximately 50-80% of NMIBCs recur, often requiring costly clinical intervention. NMIBCs can progress in about 20-30% of instances to the more serious muscle-invasive bladder cancer (MIBC). MIBCs (T2 and T3)
20 constitute only ~10-15% of new cases, but they confer a higher risk for developing metastatic bladder cancer (pT4). Metastatic bladder cancer is associated with a dismal 5-year survival likelihood and represents a major unmet medical need with few effective therapies to date.

 Therefore, there remains a need for effective means for treating, diagnosing, and providing prognoses for cancer, for example, bladder cancer.

SUMMARY

25 The present disclosure is directed to methods for treating, diagnosing, and providing prognoses for cancer, e.g., bladder cancer.

30 Disclosed is a method of treating a patient suffering from a bladder cancer, the method comprising administering to the patient a therapeutically effective amount of an anti-cancer therapy, wherein the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample obtained from the patient has been determined to be increased relative to a reference level of the at least one gene. In one aspect, there is provided a use of an anti-cancer therapy in the manufacture of a medicament for treating a patient suffering from a bladder cancer, wherein the expression level of at least
35 one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of the at least one gene.

 In another aspect, there is provided a method for diagnosing a bladder cancer in a patient, the method comprising the steps of: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b)
40 comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient having a bladder cancer. In some embodiments, the method further comprises (c) informing the patient that they have a bladder cancer. In some embodiments, the method further comprises (d) selecting an anti-cancer therapy for treatment of said patient when an increase in
45 the level

of expression of the at least one gene in the patient sample relative to the reference level is detected. In some embodiments, the method further comprises (e) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

In another aspect, there is provided a method for the prognosis of a patient suffering from bladder cancer, the method comprising: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; (b) comparing the expression level of the at least one gene to a reference level of the at least one gene; and (c) determining a prognosis for the patient, wherein a poor prognosis is indicated by an expression level of the at least one gene in the patient sample that is increased relative to the reference level. In some embodiments, the prognosis is a prognosis of survival. In some embodiments, the method is carried out prior to administering an anti-cancer therapy to the patient. In some embodiments, the method further comprises (d) identifying the patient as likely to benefit from administration of an anti-cancer therapy when the patient is determined to have a poor prognosis of survival. In some embodiments, the method further comprises (e) administering a therapeutically effective amount of an anti-cancer therapy to the patient, if the patient is determined to have a poor prognosis of survival. In some embodiments, the survival is disease-free survival or overall survival.

In another aspect, there is provided a method of determining whether a patient having a bladder cancer is likely to respond to treatment with an anti-cancer therapy, the method comprising: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy. In some embodiments, the method further comprises (c) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

In another aspect, there is provided a method of optimizing therapeutic efficacy of an anti-cancer therapy for a patient having a bladder cancer, the method comprising: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy. In some embodiments, the method further comprises (c) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

Disclosed is a method of treating a patient suffering from a bladder cancer, the method comprising administering to the patient a therapeutically effective amount of an anti-cancer therapy other than Bacillus Calmette-Guérin (BCG) vaccine, wherein the expression level of *TP53* in a sample obtained from the patient has been determined to be increased relative to a reference level of *TP53*. In another aspect, there is provided use of an anti-cancer therapy other than Bacillus Calmette-Guérin (BCG) vaccine in the manufacture of a medicament for treating a patient suffering from a bladder cancer, wherein the expression level of *TP53* in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of *TP53*.

In some embodiments of any one of the above aspects, the anti-cancer therapy comprises an *FGFR3* antagonist, a *TP53* antagonist, and/or an *EGFR* antagonist. In some embodiments, the anti-cancer therapy comprises an *FGFR3* antagonist and an *EGFR* antagonist. In some embodiments, the

CLAIMS

What is claimed is:

1. Use of an anti-cancer therapy in the manufacture of a medicament for treating a patient suffering from a bladder cancer, wherein the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of the at least one gene.
2. A method for diagnosing a bladder cancer in a patient, the method comprising the steps of:
 - (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and
 - (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient having a bladder cancer.
3. The method of claim 2, further comprising (c) informing the patient that they have a bladder cancer.
4. The method of claim 2 or 3, further comprising (d) selecting an anti-cancer therapy for treatment of said patient when an increase in the level of expression of the at least one gene in the patient sample relative to the reference level is detected.
5. The method of any one of claims 2-4, wherein a therapeutically effective amount of an anti-cancer therapy is to be administered to the patient.
6. A method for the prognosis of a patient suffering from bladder cancer, the method comprising:
 - (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient;
 - (b) comparing the expression level of the at least one gene to a reference level of the at least one gene; and
 - (c) determining a prognosis for the patient, wherein a poor prognosis is indicated by an expression level of the at least one gene in the patient sample that is increased relative to the reference level.
7. The method of claim 6, wherein the prognosis is a prognosis of survival.
8. The method of claim 6 or 7, wherein the method is carried out prior to administration of an anti-cancer therapy to the patient.

9. The method any one of claims 6-8, further comprising (d) identifying the patient as likely to benefit from administration of an anti-cancer therapy when the patient is determined to have a poor prognosis of survival.

10. The method of any one of claims 6-9, wherein if the patient is determined to have a poor prognosis of survival, the patient is to be administered an anti-cancer therapy.

11. The method of any one of claims 6-10, wherein the survival is disease-free survival or overall survival.

12. A method of determining whether a patient having a bladder cancer is likely to respond to treatment with an anti-cancer therapy, the method comprising:

(a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and

(b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy.

13. A method of optimizing therapeutic efficacy of an anti-cancer therapy for a patient having a bladder cancer, the method comprising:

(a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and

(b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy.

14. The method of claim 12 or 13, wherein a therapeutically effective amount of an anti-cancer therapy is to be administered to the patient.

15. The method of any one of claims 1, 4, 5, or 8-14, wherein the anti-cancer therapy comprises an *FGFR3* antagonist, a *TP53* antagonist, and/or an *EGFR* antagonist.

16. The method of claim 15, wherein the anti-cancer therapy comprises an *FGFR3* antagonist and an *EGFR* antagonist.

17. The method of claim 15 or 16, wherein the *FGFR3* antagonist, *EGFR* antagonist, or *TP53* antagonist is an antibody or a functional fragment thereof.

18. The method of claim 17, wherein the FGFR3 antagonist is an anti-FGFR3 antibody, or a functional fragment thereof.
- 5 19. The method of claim 17, wherein the EGFR antagonist is an anti-EGFR antibody, or a functional fragment thereof.
20. The method of claim 17, wherein the TP53 antagonist is an anti-TP53 antibody, or a functional fragment thereof.
- 10 21. The method of claim 15 or 16 wherein the FGFR3 antagonist, TP53 antagonist, or EGFR antagonist is a small molecule antagonist.
22. The method of claim 21, wherein the FGFR3 antagonist or EGFR antagonist is a tyrosine kinase inhibitor.
- 15 23. The method of claim 22, wherein the EGFR antagonist is erlotinib (TARCEVA™).
24. The method of any one of claims 15-23, wherein the anti-cancer therapy further comprises (i) an agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth-inhibitory agent, and a cytotoxic agent, (ii) radiotherapy, or (iii) a combination thereof.
- 20 25. The method of any one of claims 1-24, wherein the expression level of the at least one gene in the sample that has been obtained from the patient is determined by measuring mRNA.
- 25 26. The method of claim 25, wherein the expression level of the at least one gene in the sample that has been obtained from the patient is determined by a polymerase chain reaction (PCR) assay.
- 30 27. The method of claim 26, wherein the PCR assay is a quantitative PCR assay.
28. The method any one of claims 1-24, wherein the expression level of the at least one gene in the sample that has been obtained from the patient is determined by measuring protein.
- 35 29. The method of claim 28, wherein the expression level of the at least one gene in the sample that has been obtained from the patient is determined by an immunohistochemical (IHC) method.

30. The method of any one of claims 1-29, wherein the sample that has been obtained from the patient is a tumor sample.

31. The method of claim 30, wherein the tumor sample is a formalin-fixed paraffin-embedded (FFPE) tumor sample.

32. The method of any one of claims 1-31, further comprising determining the expression level of at least two of the genes.

33. The method of claim 32, further comprising determining the expression level of all three of the genes.

34. The method of any one of claims 1-33, wherein the expression level of *FGFR3* has been determined to be increased at least 2-fold relative to a reference level.

35. The method of claim 34, wherein the expression level of *FGFR3* has been determined to be increased at least 4-fold relative to a reference level.

36. The method of any one of claims 1-35, wherein the expression level of *EGFR* has been determined to be increased at least 4-fold relative to a reference level.

37. The method of claim 36, wherein the expression level of *EGFR* has been determined to be increased at least 8-fold relative to a reference level.

38. The method of any one of claims 1-37, further comprising determining the expression level of at least one additional gene selected from the group consisting of: *DUSB3*, *FRS2*, *TSC1*, *ERBB3*, *CDKN1A*, *CCND1*, *TP63*, *MMP2*, *ZEB2*, *PIK3CB*, *PIK3R1*, *MDM2*, *SNAI2*, *AXL*, *ZEB1*, *BCL2B*, *TSC2*, *RB1*, *FGFR32*, *PIK3IP1*, *MTOR*, *PIK3CA*, *PTEN*, *AKT1*, *BCL2A*, *FRS3*, *ERBB2*, *FGFR31*, *FGF1*, *SNAI1*, *FGFR34*, *FGF9*, and *FGF2*, in a sample that has been obtained from the patient, wherein the expression level of the at least one additional gene is changed relative to a reference level of the at least one additional gene.

39. The method of any one of claims 1-38, wherein the bladder cancer is non-muscle-invasive bladder cancer, muscle-invasive bladder cancer, or metastatic bladder cancer.

40. The method of claim 39, wherein the non-muscle-invasive bladder cancer is a recurrent non-muscle-invasive bladder cancer.

41. Use of an anti-cancer therapy other than Bacillus Calmette-Guérin (BCG) vaccine in the manufacture of a medicament for treating a patient suffering from a bladder cancer, wherein the

expression level of *TP53* in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of *TP53*.

42. The use of claim 41, wherein the anti-cancer therapy comprises an FGFR3 antagonist, an EGFR antagonist, and/or a TP53 antagonist.

43. The use of claim 42, wherein the anti-cancer therapy comprises an FGFR3 antagonist and an EGFR antagonist.

44. The use of claim 42 or 43, wherein the FGFR3 antagonist, EGFR antagonist, or TP53 antagonist is an antibody, or a functional fragment thereof.

45. The use of claim 44, wherein the FGFR3 antagonist is an anti-FGFR3 antibody, or a functional fragment thereof.

46. The use of claim 44, wherein the EGFR antagonist is an anti-EGFR antibody, or a functional fragment thereof.

47. The use of claim 44, wherein the TP53 antagonist is an anti-TP53 antibody, or a functional fragment thereof.

48. The use of claim 42 or 43, wherein the FGFR3 antagonist, TP53 antagonist, or EGFR antagonist is a small molecule antagonist.

49. The use of claim 48, wherein the small molecule antagonist is a tyrosine kinase inhibitor.

50. The use of claim 49, wherein the EGFR antagonist is erlotinib (TARCEVA™).

51. The use of any one of claims 41-50, wherein the anti-cancer therapy further comprises (i) an agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth-inhibitory agent, and a cytotoxic agent, (ii) radiotherapy, or (iii) a combination thereof.

52. The use of any one of claims 41-51, wherein the expression level of *TP53* in the sample that has been obtained from the patient is determined by measuring mRNA.

53. The use of any one of claims 41-51, wherein the expression level of *TP53* in the sample that has been obtained from the patient is determined by measuring protein.