

Claims:

What is claimed is:

1. A method for prognosis of a cancerous solid tumour in a patient, comprising providing a sample of tumour core tissue obtained from the patient, determining the following biomarker in said sample:
 - (i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, providing a prognosis for the patient based on said biomarker, wherein a shorter duration of patient survival, recurrence free survival (RFS), progression free survival (PFS) or time to progression (TTP) is indicated by a greater ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.
2. A method according to claim 1, comprising determining the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, and comparing said ratio against a reference value, wherein a ratio higher than the reference value indicates a prognosis of shorter duration of survival, RFS, PFS or TTP.
3. A method according to claim 2, wherein the tumour is hepatocellular carcinoma and the reference value is a ratio of 0.1 ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.
4. A method according to any of claims 1 to 3, comprising determining from said biomarker that the patient has a prognosis of shorter duration of survival, RFS, PFS or TTP.
5. A method according to claim 4, comprising determining the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, and comparing said ratio against a reference value, wherein a ratio higher than the reference value indicates a prognosis of shorter duration of survival, RFS, PFS or TTP, determining that said ratio is higher than the reference value, and

providing a prognosis of shorter duration of survival, RFS, PFS or TTP.

6. A method according to any of claims 1 to 3, comprising determining from said biomarker that the patient has a prognosis of longer duration of survival, RFS, PFS or TTP.

7. A method according to claim 6, comprising determining the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, and
 comparing said ratio against a reference value, wherein a ratio higher than the reference value indicates a prognosis of shorter duration of survival, RFS, PFS or TTP,
 determining that said ratio is lower than the reference value, and
 providing a prognosis of longer duration of survival, RFS, PFS or TTP.

8. Use of a biomarker for prognosis of a cancerous solid tumour in a patient, wherein the biomarker is the following as determined in tumour core tissue from the patient:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

9. A method of determining likelihood of a cancerous solid tumour in a patient to respond to an anti-ICOS and/or anti-TReg immunotherapeutic agent, comprising
 providing a sample of tumour core tissue obtained from the patient, and
 determining the following biomarker in said sample:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, wherein

a greater likelihood of the patient to respond to the immunotherapeutic agent is indicated by

a greater ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

10. A method according to claim 9, comprising determining the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, and

comparing said number against a reference value, wherein
a ratio higher than the reference value indicates an increased likelihood of responding to the immunotherapeutic agent.

11. A method according to claim 10, wherein the tumour is hepatocellular carcinoma and the reference value is a ratio of 0.1 ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

12. A method according to any of claims 9 to 11, comprising identifying the patient as having an increased likelihood of responding to the immunotherapeutic agent and optionally thereby selecting an anti-ICOS and/or anti-TReg immunotherapeutic agent for treatment of said patient.

13. A method according to claim 12, comprising determining the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells,

comparing said ratio against a reference value, wherein a ratio higher than the reference value indicates an increased likelihood of responding to the immunotherapeutic agent,

determining that said ratio is higher than the reference value, and thereby identifying the patient as having an increased likelihood of responding to the immunotherapeutic agent.

14. Use of a biomarker for determining likelihood of a cancerous tumour in a patient to respond to an anti-ICOS and/or anti-TReg immunotherapeutic agent, wherein the biomarker is the following as determined in tumour core tissue from the patient:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

15. A method of monitoring a patient's response to an anti-ICOS and/or anti-TReg immunotherapeutic agent for a cancerous solid tumour, comprising

providing a sample of tumour core tissue obtained from a patient who has received an anti-ICOS and/or anti-TReg immunotherapeutic agent,

determining the following biomarker in said sample:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells,

comparing said biomarker in said sample against the same biomarker in a sample of tumour core tissue obtained from the patient prior to administration of said immunotherapeutic agent, and

determining whether a change has occurred in said biomarker and thereby assessing whether the patient is responding to the immunotherapeutic agent, wherein response is indicated by the following change from the sample prior to administration of said immunotherapeutic agent:

a reduction in the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

16. A method according to claim 15, comprising
measuring a reduction in the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells compared with prior to therapy, and
prescribing continued treatment with the anti-ICOS and/or anti-TReg immunotherapeutic agent for the patient.

17. Use of a biomarker for monitoring a patient's response to an anti-ICOS and/or anti-TReg immunotherapeutic agent for a cancerous solid tumour, wherein the biomarker is the following as determined in tumour core tissue from the patient:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells, wherein response to the immunotherapeutic agent is indicated by the following change as compared with a sample of tumour core tissue obtained prior to administration of the immunotherapeutic agent:

a reduction in the ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells.

18. A method of identifying a reference value for classifying patients with cancerous solid tumours according to their predicted prognosis or predicted response to an anti-ICOS and/or anti-TReg immunotherapeutic agent, comprising

providing samples of tumour core tissue obtained from each of a population of patients with cancerous solid tumours of the same type for whom disease outcome is known or response to the anti-ICOS and/or anti-TReg immunotherapeutic agent is known,

determining the following biomarker in each of said samples:

(i) ratio of the number of ICOS FOXP3 double positive cells within a defined radius of influence around ICOS single positive cells to the total number of ICOS single positive cells,

pairing data of said biomarker with data for disease outcome or response to the anti-ICOS and/or anti-TReg immunotherapeutic agent in each patient, and

grouping data of said biomarker to identify a numerical cut-off which defines two groups of statistically significant data for disease outcome or response to the anti-ICOS and/or anti-TReg immunotherapeutic agent,

wherein said cut-off represents a reference value for classifying patients with the same type of cancerous solid tumours according to their predicted prognosis or predicted response to the anti-ICOS and/or anti-TReg immunotherapeutic agent.

19. A method according to claim 18, wherein the samples are obtained from a population of patients with liver cancer, renal cell cancer, head and neck cancer, melanoma, non-small cell lung cancer, bladder cancer, ovarian cancer, cervical cancer, gastric cancer, pancreatic cancer, breast cancer (including triple negative breast cancer), carcinoma, leiomyosarcoma, anal cancer, squamous cell cancer and oesophageal cancer.

20. A method according to claim 19, wherein the samples are obtained from a population of patients with hepatocellular carcinoma.

21. A method, use or immunotherapeutic agent for use according to any one of claims 9 to 20, wherein the immunotherapeutic agent is an anti-ICOS antibody comprises an ICOS binding site comprising the CDRs of KY1044, wherein

HCDR1 is SEQ ID NO: 1

HCDR2 is SEQ ID NO: 2

HCDR3 is SEQ ID NO: 3

LCDR1 is SEQ ID NO: 8

LCDR2 is SEQ ID NO: 9 and

LCDR3 is SEQ ID NO: 10.

22. A method, use or immunotherapeutic agent for use according to claim 21, wherein the antibody comprises a VH domain amino acid sequence at least 90 % identical to the KY1044 VH domain SEQ ID NO: 5 and a VL domain amino acid sequence at least 90 % identical to the KY1044 VL domain SEQ ID NO: 12.

23. A method, use or immunotherapeutic agent for use according to claim 22, wherein the antibody comprises the KY1044 VH domain SEQ ID NO: 5 and the KY1044 VL domain SEQ ID NO: 12.

24. A method, use or immunotherapeutic agent for use according to claim 23, wherein the antibody is a human IgG1 κ comprising the KY1044 heavy chain SEQ ID NO: 7 and the KY1044 light chain SEQ ID NO: 14.