CLAIMS

Claim 1. An *in vitro* method for the prognosis of response to treatment for a patient suffering from hepatocellular carcinoma, the method comprising:

measuring expression of at least one immune marker comprising co-expression of CD8 and PD-1; or co-expression of CD8 and CCR5; or co-expression of CD8 and Tim-3; or expression of CD8 and CXCR6, or co-expression of CD8 and Tim-3 with CCR5, or co-expression of CD8 and Tim-3, with CXCR6 in a leukocyte sample taken from the patient with hepatocellular carcinoma;

classifying the patient sample into (i) sustained responder (SR) to selective internal radiation therapy (SIRT) or (ii) transient/non-responders (TR/NR) to (SIRT) based on the expression of the at least one immune marker in relation to a predetermined value.

Claim 2. The method of claim 1, wherein prior to measuring expression of the at least one immune marker a prediction model is created comprising:

Measuring expression of a plurality of immune markers in a sample taken from a plurality of patients with hepatocellular carcinoma;

Evaluating a clinical response of the patients with hepatocellular carcinoma to treatment with (SIRT) at 3 and/or 6 months after treatment wherein the clinical response is selected from (SR), and (TR/NR);

Determining if there is a correlation between each immune marker and either the clinical response (SR), or the clinical response (TR/NR);

Determining the probability of each immune marker one by one to positively affect the accuracy of the clinical response;

allocating a probability score to each sample based on the number of immune markers that positively affects the accuracy of the clinical response; and

allocating the same probability score for each immune marker in a leukocyte sample taken from a new patient with hepatocellular carcinoma to classify the new patient into predicted SR or predicted TR/NR.

Claim 3. The method of claim 2, further comprising comparing the predicted SR or predicted TR/NR with the classification of the patient samples based on the expression of the at least one immune marker in relation to the predetermined value to predict whether the patient will respond to treatment with (SIRT).

Claim 4. The method of claim 2 or 3, wherein the plurality of immune markers include additional immune markers selected from the group comprising co-expression of CD14 and HLRDR+; co-expression of PD-1 and CD4 with CD45RO; co-expression of CD4 and TNF-α; TNF-α, co-expression of CD4 and CD45RO with CXCR3; or co-expression of Granzyme B and CD56;.

Claim 5. The method of any one of claim 2 to 4, wherein the immune marker allocated with a higher probability score comprises the at least one immune marker.

Claim 6. The method of any one of claims 1 to 5, wherein the leukocyte sample comprises a tumour infiltrating leukocyte sample.

Claim 7. The method of any one of claims 1 to 5, wherein the leukocyte sample comprises a peripheral blood mononuclear cell (PBMC) sample.

Claim 8. The method of any one of claim 1 to 7, wherein the sample is analysed using mass spectrometry by time of flight (CyTOF).

Claim 9. The method of any one of claims 1 to 8, wherein the leukocyte sample comprises a T-cell expressing CD 8.

Claim 10. The method of any one of claims 1 to 9, wherein the leukocyte sample taken from patient with hepatocellular carcinoma classified as (ii) SR is identified as requiring treatment with SIRT or a combination of SIRT and an immunotherapy.

Claim 11. The method of claim 10, wherein the SIRT is Y90-RE.

Claim 12. The use of a composition comprising therapeutic agents associated with a selective internal radiation therapy (SIRT) and an immunotherapy comprising checkpoint inhibitor against the PD-1/PD-L1 or Tim-3 pathways in the manufacture of a medicament for use in the treatment of hepatocellular carcinoma in a patient

prognosticated as a sustained responder (SR) to SIRT according to the method of any one of claims 1 to 9.

Claim 13. The use of claim 12, wherein the therapeutic agents associated with SIRT is Y90-RE.

Claim 14. A composition comprising therapeutic agents associated with a selective internal radiation therapy (SIRT) and an immunotherapy comprising checkpoint inhibitor against the PD-1/PD-L1 or Tim-3 pathways for use in the treatment of hepatocellular carcinoma in a patient prognosticated as a sustained responder (SR) to SIRT according to the method of any one of claims 1 to 9.