human patients has been reported that supports the contention that HCC patients having high levels of AFP respond to treatment with OSI-906.

Ramucirumab (also "IMC-1121B"), CAS registry number 947687-13-0, is a fully human monoclonal antibody directed against the vascular endothelial growth factor receptor 2 (VEGFR2 or VEGF receptor-2).

Ramucirumab and methods of making and using this compound, including for the treatment of neoplastic diseases such as solid and non-solid tumors, are disclosed in WO2003/075840 and all patents granted therefrom. Furthermore, clinical activity for ramucirumab has been reported in a Phase II study of patients with advanced hepatocellular cancer. (Zhu, et al., Clin. Cancer Res; 19(23):6614-6623 (2013).) AFP was not used as a predictive marker in this Phase II study.

There remains a need for treatments for advanced HCC and methods of predicting patient response to treatment for advanced HCC.

The present invention is derived from a Phase 3 clinical trial of the anti-VEGFR2 antibody, ramucirumab ("A Multicenter, Randomized, Double-Blind, Phase 3 Study of Ramucirumab (IMC-1121B) Drug Product and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients with Hepatocellular Carcinoma Following First-Line Therapy With Sorafenib") (the "Study").

It has surprisingly been found that HCC patients with AFP serum levels greater than or equal to 1.5 times the upper limit of normal (ULN) received an unexpected survival benefit of three months from treatment with ramucirumab as compared to treatment with placebo.

The method of treatment of the ~~invention~~ present disclosure unexpectedly provides a method for using AFP serum levels as a predictive selection marker for the treatment of patients with advanced HCC with ramucirumab.

It has surprisingly been found that HCC patients with AFP serum levels greater than or equal to 1.5 x ULN respond to treatment with ramucirumab, whereas patients with AFP serum levels less than 1.5 x ULN do not respond to treatment with ramucirumab.

Neither the patent disclosure of WO2003/075840 nor the clinical trial Study design provide any suggestion of the role of targeting patients who have high AFP serum levels for the treatment with ramucirumab.

In one aspect of the present disclosure, there is provided a use of ramucirumab in the manufacture of a medicament for the treatment of a patient with a hepatocellular tumor, wherein the patient has an alpha-fetoprotein level of 10 ng/mL or greater.

In another aspect of the present disclosure, there is provided an *in vitro* method of selecting a patient having a hepatocellular tumor for treatment with a therapeutically effective amount of ramucirumab, comprising assaying for the presence of alpha-fetoprotein in a sample taken from the patient, wherein the patient is selected for treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 10 ng/mL or greater.

In a further aspect of the present disclosure, there is provided a method of identifying a hepatocellular tumor patient eligible for treatment with ramucirumab, comprising assaying for the presence of alpha-fetoprotein in a sample taken from the patient prior to the administration of a therapeutically effective amount of ramucirumab, wherein the patient is eligible for treatment with ramucirumab if the alpha-fetoprotein level is 10 ng/mL or greater.

~~According to the first aspect of t~~The present disclosure also provides ~~invention there is~~ ramucirumab for use in the treatment of a hepatocellular tumor, wherein the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure also provides ~~invention is~~ ramucirumab for use in treating a hepatocellular tumor, comprising the steps of: (1) assaying a sample from a patient for alpha-fetoprotein, (2) determining the level of alpha-fetoprotein in the sample, and (3) administering ramucirumab to the patient if alpha-fetoprotein is present at a level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure further provides ~~invention is~~ the use of ramucirumab in the manufacture of a medicament for the treatment of a patient with a hepatocellular tumor, wherein the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The disclosure also provides ~~invention is~~ an *in vitro* method of selecting a patient having a hepatocellular tumor for treatment with a therapeutically effective amount of ramucirumab, comprising assaying for the presence of alpha-fetoprotein in a sample taken from the patient, wherein the patient is selected for

treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure further provides ~~invention is~~ a method of identifying a hepatocellular tumor patient eligible for treatment with ramucirumab, comprising assaying for the presence of alpha-fetoprotein in a sample taken from the patient prior to the administration of a therapeutically effective amount of ramucirumab, wherein the patient is eligible for treatment with ramucirumab if the alpha-fetoprotein level is 1.5 times the upper limit of normal or greater.

In an embodiment ~~another preferred aspect~~ of the present disclosure~~invention~~, the sample is plasma or serum.

~~Another aspect of t~~The present disclosure also provides ~~invention is~~ a therapeutic regimen for treating a patient with a hepatocellular tumor, comprising: (1) assaying for the presence of alpha-fetoprotein in a sample taken from a patient, (2) selecting the patient for treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 1.5 times the upper limit of normal or greater, and (3) administering ramucirumab to the patient.

~~Another aspect of t~~The present disclosure further provides ~~invention is~~ a therapeutic regimen for treating a hepatocellular tumor, comprising: (1) assaying for the presence of alpha-fetoprotein in a sample taken from a patient, (2) selecting a patient for treatment with ramucirumab if

alpha-fetoprotein is present in the sample at a level of 1.5 times the upper limit of normal or greater, and (3) administering ramucirumab to the selected patient.

~~Another aspect of t~~The present disclosure also provides ~~invention is~~ a pharmaceutical composition comprising ramucirumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, for use in the treatment of a patient having a hepatocellular tumor with ramucirumab, wherein the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure further provides ~~invention, there is~~ a method of treating a hepatocellular tumor in a patient, comprising administering a therapeutically effective amount of ramucirumab to the patient in need thereof, provided that the patient is selected for treatment on the basis of a sample taken from the patient that has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure also provides ~~invention is~~ a method of predicting the response of a hepatocellular tumor patient to treatment with ramucirumab, comprising assaying a sample taken from the patient to determine the presence of alpha-fetoprotein in the sample, wherein the presence of an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater is predictive of the patient's effective response to treatment with ramucirumab.

~~Another aspect of t~~The present disclosure further provides ~~invention is~~ a method of treating a hepatocellular tumor in a patient, comprising administering a therapeutically effective amount of ramucirumab to the patient in need thereof, provided that a sample taken from the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure also provides ~~invention is~~ a method of treating a hepatocellular tumor in a patient, comprising assaying a sample taken from the patient for alpha-fetoprotein prior to administering ramucirumab, and administering to the patient a therapeutically effective amount of ramucirumab if the sample has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.

~~Another aspect of t~~The present disclosure further provides ~~invention is~~ an improved method of treating a patient having a hepatocellular tumor with ramucirumab, the method comprising determining the presence of alpha-fetoprotein in a sample taken from the patient, and wherein the level of alpha-fetoprotein is determined prior to administration of a therapeutically effective amount of ramucirumab, and wherein the patient is selected for treatment with

ramucirumab if the alpha-fetoprotein level is 1.5 times the upper limit of normal or greater.

In an embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 10 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 15 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 20 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 30 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 40 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 50 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 60 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 70 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 80 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 90 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 100 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 110 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 120 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 130 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 140 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 150 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 160 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 170 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 180 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 190 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 200 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 210 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 220 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 230 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 240 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 250 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 260 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 270 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 280 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 290 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 300 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 310 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 320 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 330 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 340 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 350 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 360 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 370 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 380 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 390 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the alpha-fetoprotein level is 400 ng/mL or greater.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the sample is plasma or serum.

In another embodiment of the present disclosure~~another preferred aspect of the invention~~, the ramucirumab is administered at a dose of about 8 mg/kg.

As used herein, the term "ramucirumab," also known as IMC-1121B, refers to an anti-VEGFR2 antibody comprising: two heavy chains, each with the amino acid sequence of SEQ ID NO:1, and two light chains, each with the amino acid sequence of SEQ ID NO: 2.

As used herein, the term "antibody" includes immunoglobulin molecules comprising four polypeptide chains: two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Individual chains can fold into domains having similar sizes (110-125 amino acids) and structures, but different functions.

WE CLAIM:

~~1. Ramucirumab for use in the treatment of a hepatocellular tumor, wherein the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.~~

~~2. Ramucirumab for use in the treatment of a hepatocellular tumor, comprising the steps of: (1) assaying a sample from a patient for alpha-fetoprotein, (2) determining the level of alpha-fetoprotein in the sample, and (3) administering ramucirumab to the patient if alpha-fetoprotein is present at a level of 1.5 times the upper limit of normal or greater.~~

~~3. Ramucirumab for use according to claim 2, wherein the sample is plasma or serum.~~

~~4. Ramucirumab for use according to any one of claims 1-3, wherein the alpha-fetoprotein level is 10 ng/mL or greater.~~

~~5. Ramucirumab for use according to any one of claims 1-3, wherein the alpha-fetoprotein level is 15 ng/mL or greater.~~

~~6. Ramucirumab for use according to any one of claims 1-3, wherein the alpha-fetoprotein level is 400 ng/mL or greater.~~

~~7. Ramucirumab for use according to any one of claims 1 to 6, wherein ramucirumab is administered at a dose of about 8 mg/kg.~~

~~8~~1. Use of ramucirumab in the manufacture of a medicament for the treatment of a patient with a hepatocellular tumor, wherein the patient has an alpha-fetoprotein level of ~~1.5 times the upper limit of normal or greater.~~

~~9. The use according to claim 8 or 9, wherein the alpha-fetoprotein level is~~ 10 ng/mL or greater.

~~10~~2. The use according to claim ~~1, 8 or 9~~, wherein the alpha-fetoprotein level is 15 ng/mL or greater.

~~11~~3. The use according to claim ~~1, 8 or 9~~, wherein the alpha-fetoprotein level is 400 ng/mL or greater.

~~12~~4. The use according to any one of claims ~~1-3, 8-11~~, wherein ramucirumab is administered at a dose of about 8 mg/kg.

~~13~~5. An *in vitro* method of selecting a patient having a hepatocellular tumor for treatment with a therapeutically effective amount of ramucirumab, comprising

assaying for the presence of alpha-fetoprotein in a sample taken from the patient, wherein the patient is selected for treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 10 ng/mL ~~1.5 times the upper limit of normal~~ or greater.

~~14~~6. A method of identifying a hepatocellular tumor patient eligible for treatment with ramucirumab, comprising assaying for the presence of alpha-fetoprotein in a sample taken from the patient prior to the administration of a therapeutically effective amount of ramucirumab, wherein the patient is eligible for treatment with ramucirumab if the alpha-fetoprotein level is 10 ng/mL~~1.5 times the upper limit of normal~~ or greater.

~~15~~7. The method according to claim 6~~13 or 14~~, wherein the sample is plasma or serum.

16. ~~The method according to any one of claims 13-15, wherein the alpha-fetoprotein level is 10 ng/mL or greater.~~

~~17~~8. The method according to any one of claims 6-7~~13-15~~, wherein the alpha-fetoprotein level is 15 ng/mL or greater.

~~18~~9. The method according to any one of claims 6-8~~13-15~~, wherein the alpha-fetoprotein level is 400 ng/mL or greater.

~~19. A therapeutic regimen for treating a patient with a hepatocellular tumor, comprising: (1) assaying for the presence of alpha-fetoprotein in a sample taken from a patient (2) selecting the patient for treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 1.5 times the upper limit of normal or greater, and (3) administering ramucirumab to the patient.~~

~~20. A therapeutic regimen for treating a hepatocellular tumor, comprising: (1) assaying for the presence of alpha-fetoprotein in a serum sample taken from a patient (2) selecting a patient for treatment with ramucirumab if alpha-fetoprotein is present in the sample at a level of 1.5 times the upper limit of normal or greater, and (3) administering ramucirumab to the selected patient.~~

~~21. A pharmaceutical composition comprising ramucirumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, for use in the treatment of a patient having a hepatocellular tumor with ramucirumab, wherein the patient has an alpha-fetoprotein level of 1.5 times the upper limit of normal or greater.~~

22. The composition according to claim 21, wherein the alpha-fetoprotein level is 10 ng/mL or greater.

23. The composition according to claim 21, wherein the alpha-fetoprotein level is 15 ng/mL or greater.

24. The composition according to claim 21, wherein the alpha-fetoprotein level is 400 ng/mL or greater.