CLAIMS

1. Use of lenvatinib or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for treatment of renal cell carcinoma, the treatment comprising a first dosage regimen to be administered to a human subject that has a renal cell carcinoma, the first dosage regimen comprising (i) lenvatinib or a pharmaceutically acceptable salt thereof at a dose of 18 mg/day and (ii) everolimus at a dose of 5 mg/day,

wherein the human subject develops an occurrence of a first persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality during treatment with the first dosage regimen, and the treatment further comprises:

(a) terminating administration of the first dosage regimen after the occurrence of the first persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality and a second dose regimen to be administered to the human subject, the second dosage regimen comprising lenvatinib or a pharmaceutically acceptable salt thereof at a dose of 14 mg/day, wherein the human subject develops an occurrence of a second persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality during treatment with the second dosage regimen;

(b) terminating administration of the second dosage regimen after the occurrence of the second persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality and a third dosage regimen to be administered to the human subject, the third dosage regimen comprising lenvatinib or a pharmaceutically acceptable salt thereof at a dose of 10 mg/day, wherein the human subject develops an occurrence of a third persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality during treatment with the third dosage regimen; and

(c) terminating administration of the third dosage regimen after the occurrence of the third persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality and a fourth dosage regimen to be administered to the human subject, the fourth dosage regimen comprising lenvatinib or a pharmaceutically acceptable salt thereof at a dose of 8 mg/day.

2. The use of claim 1, wherein:

the second dosage regimen is not initiated until the first persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality is resolved to Grade 0-1 or baseline;

the third dosage regimen is not initiated until the second persistent and

intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality is resolved to Grade 0-1 or baseline; and

the fourth dosage regimen is not initiated until the third persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality is resolved to Grade 0-1 or baseline.

3. The use of claim 1, wherein medical management of each of the first, second, and third persistent and intolerable Grade 2 or Grade 3 adverse reactions or Grade 4 laboratory abnormalities is to be initiated prior to terminating administration of the dosage regimen administered at the time of onset of the adverse reaction or laboratory abnormality.

4. The use of claim 2, wherein medical management of each of the first, second, and third persistent and intolerable Grade 2 or Grade 3 adverse reactions or Grade 4 laboratory abnormalities is to be initiated prior to initiating administration of the dosage regimen that occurs after resolution of the adverse reaction or laboratory abnormality to Grade 0-1 or baseline.

5. The use of any one of claims 1 to 4, wherein the first persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality is the same as the second and/or third persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality.

6. The use of any one of claims 1 to 4, wherein the first persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality is different from the second and/or third persistent and intolerable Grade 2 or Grade 3 adverse reaction or Grade 4 laboratory abnormality.

7. The use of any one of claims 1 to 6, wherein the Grade 2 or Grade 3 adverse reaction is selected from the group consisting of Grade 3 hypertension, Grade 2 hypertension, Grade 3 cardiac dysfunction, Grade 2 cardiac dysfunction, Grade 3 arterial thromboembolic event, Grade 2 arterial thromboembolic event, Grade 3 proteinuria, Grade 2 proteinuria, Grade 3 renal failure or impairment, Grade 2 renal failure or impairment, Grade 3 diarrhea, Grade 2 diarrhea, Grade 3 gastrointestinal perforation or fistula, Grade 2 gastrointestinal perforation or fistula, Grade 3 vomiting, Grade 2 vomiting, Grade 3 decreased appetite, Grade 2 decreased appetite, Grade 3 fatigue, Grade 2 fatigue, Grade 3 nausea, Grade 2 nausea, Grade 3 cough, Grade 2 cough, Grade 3 decreased weight, Grade 2

decreased weight, Grade 3 dehydration, Grade 2 dehydration, Grade 3 thrombocytopenia, Grade 2 thrombocytopenia, Grade 3 anemia, Grade 2 anemia, Grade 3 acute renal failure, Grade 2 acute renal failure, Grade 3 QT/QTc interval prolongation, Grade 2 QT/QTc interval prolongation, Grade 3 reversible posterior leukoencephalopathy syndrome (RPLS), Grade 2 RPLS, Grade 3 hemorrhagic events, Grade 2 hemorrhagic events, Grade 3 hyperthyroidism, and Grade 2 hyperthyroidism.

8. The use of claim 7, wherein the Grade 2 or Grade 3 adverse reaction is selected from the group consisting of Grade 3 diarrhea, Grade 2 diarrhea, Grade 3 vomiting, Grade 2 vomiting, Grade 3 nausea, Grade 2 nausea, Grade 3 proteinuria, and Grade 2 proteinuria.

9. The use of any one of claims 1 to 8, wherein the Grade 4 laboratory abnormality is selected from the group consisting of Grade 4 increase in aspartate aminotransferase, Grade 4 increase in alanine aminotransferase, Grade 4 increase in alkaline phosphatase, Grade 4 hyperkalemia, Grade 4 hypokalemia, Grade 4 hyponatremia, Grade 4 hypocalcemia, Grade 4 hypophosphatemia, Grade 4 hyperglycemia, Grade 4 hypertriglyceridemia, Grade 4 increase in cholesterol, Grade 4 increase in lipase, Grade 4 decrease in hemoglobin, Grade 4 decrease in platelet count, and Grade 4 decrease in lymphocyte count.

10. The use of any one of claims 1 to 9, wherein each of the second dosage regimen, the third dosage regimen, and the fourth dosage regimen is not initiated until resolution of an adverse reaction or toxicity associated with administration of everolimus.

11. The use of any one of claims 1 to 10, wherein each of the second dosage regimen, the third dosage regimen, and the fourth dosage regimen comprises everolimus at a dose of 5 mg/day.

12. The use of any one of claims 1 to 10, wherein each of the second dosage regimen, the third dosage regimen, and the fourth dosage regimen comprises everolimus at a dose of 5 mg every other day.

13. The use of any one of claims 1 to 12, wherein lenvatinib or the pharmaceutically acceptable salt thereof is formulated as a capsule.

14. The use of any one of claims 1 to 13, wherein everolimus is formulated as a tablet.

15. The use of any one of claims 1 to 14, wherein lenvatinib or the pharmaceutically acceptable salt thereof and everolimus are to be administered to the human subject orally.

16. The use of any one of claims 1 to 15, wherein the human subject has received a prior vascular endothelial growth factor (VEGF)-targeted therapy.

17. The use of any one of claims 1 to 16, wherein lenvatinib or the pharmaceutically acceptable salt thereof and everolimus are to be administered once daily.

18. The use of any one of claims 1 to 16, wherein lenvatinib or the pharmaceutically acceptable salt thereof and everolimus are to be administered once daily for at least 28 weeks, at least 56 weeks, at least 84 weeks, at least 112 weeks, at least 140 weeks, or at least 168 weeks.

19. The use of any one of claims 1 to 18, wherein the renal cell carcinoma is an unresectable advanced renal cell carcinoma.

20. The use of any one of claims 1 to 18, wherein the renal cell carcinoma is a metastatic renal cell carcinoma.

21. The use of any one of claims 1 to 18, wherein the renal cell carcinoma is an advanced renal cell carcinoma.

22. The use of any one of claims 1 to 21, wherein lenvatinib or a pharmaceutically acceptable salt thereof is lenvatinib mesylate.