Safety and Efficacy of CoFactor®/5-Fluorouracil/Bevacizumab Versus Leucovorin/5-Fluoro-uracil/ Bevacizumab as Initial Treatment for Metastatic Colorectal Carcinoma Clinical Colorectal Cancer, Vol. 6, No. 3, 229-234, 2006], and in another phase I/II clinical trial it was demonstrated that CoFactor® combined with 5-FU showed clinical benefit in pancreas cancer, defined as stable disease or tumor response, in 40% of patients [Saif, M.W., Makrilia N., Syrigos K., 2010. CoFactor: Folate Requirement for Optimization of 5-Fluouracil Activity in Anticancer Chemotherapy. Journal of Oncology Vol. 1-5]. However, apart from presenting an unnecessary hepatic detoxification burden, the unnatural (6S)-isomer is a partial competitive inhibitor of the natural [6R]-isomer regarding its effect as co-substrate for TS [Leary, R.P., Gaumont, Y., Kisliuk, R.L., 1974. Effects of the diastereoisomers of methylenetetrahydrofolate on the reaction catalyzed by thymidylate synthetase. Biochem. Biophys. Res. Commun. 56, 484–488]. Furthermore, in a Phase IIb study CoFactor® in colorectal cancer was not demonstrated to be more efficacious than leucovorin as no significant differences between the study arms with regard to either efficacy or safety could be found, and a planned Phase III study colorectal cancer was discontinued before completion [Press release: ADVENTRX Provides Update on Cofactor Program. Nov 2, 2007]. Consequently, there remains a need for an improved folate-enhanced 5-FU treatment protocol.

SUMMARY

[0009a] In one aspect, the present disclosure refers to a use of a pharmaceutical composition comprising 6R]-5,10-methylene tetrahydrofolate (6R-MTHF)~~bevacizumab~~ in the manufacture of a medicament for treatment~~ing~~ of a patient diagnosed with colorectal cancer or metastatic colorectal cancer, wherein the treatment comprises the following steps:

a. a~~said~~ pharmaceutical composition comprising bevacizumab is to be administered at a dose of 5 mg/kg bevacizumab by intravenous infusion;

and wherein

b. a pharmaceutical composition comprising oxaliplatin is to be further administered at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion following step (a);

c. a pharmaceutical composition comprising 5-fluorouracil (5-FU) is to be further administered at a dose of 400 mg/m^2 5-FU by intravenous bolus following step (b);

d. said pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus following step (c);

e. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours following step (d); and

f. said pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.

[0009b] In another aspect, the present disclosure refers to a use of a pharmaceutical composition comprising ~~bevacizumab~~ 6R-MTHF in the manufacture of a medicament for treatment~~ing~~ of a patient diagnosed with at least one solid tumor of colorectal cancer or metastatic colorectal cancer, wherein the treatment comprises the following steps:

a. a~~said~~ pharmaceutical composition comprising bevacizumab is to be administered at a dose of 5 mg/kg bevacizumab by intravenous infusion;

and wherein

b. a pharmaceutical composition comprising oxaliplatin is to be further administered at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion following step (a);

c. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 400 mg/m^2 5-FU by intravenous bolus following step (b);

d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus following step (c);

e. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours following step (d); and

f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus,

wherein the progression of said at least one solid tumor is reduced.

~~**[0009c]** In yet another aspect, the present disclosure refers to a use of a pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), in the manufacture of a medicament for treating a patient diagnosed with cancer, wherein:~~

~~a. said pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) is to be administered at a dose of 5 mg/kg by intravenous infusion;~~

~~and wherein~~

~~b. a pharmaceutical composition comprising an alkylating antineoplastic agent containing a platinum (II) center is to be further administered at a dose of 85 mg/m^2 by intravenous infusion;~~

~~c. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 400 mg/m^2 by intravenous bolus;~~

~~d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus;~~

~~e. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 2,400 mg/m^2 by intravenous infusion over 46 hours; and~~

~~f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.~~

[0009d] In a further aspect, the present disclosure refers to a use of a pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), in the manufacture of a medicament for retarding growth of a solid tumor in a patient diagnosed with cancer, wherein:

a. said pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) is to be administered at a dose of 5 mg/kg by intravenous infusion;

and wherein

b. a pharmaceutical composition comprising an alkylating antineoplastic agent containing a platinum (II) center is to be further administered at a dose of 85 mg/m^2 by intravenous infusion;

c. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 400 mg/m^2 by intravenous bolus;

d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus;

e. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 2,400 mg/m^2 by intravenous infusion over 46 hours; and

f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus,

wherein the progression of said at least one solid tumor is reduced.

[0010] The inventors have discovered methods of treating patients diagnosed with colorectal cancer or metastatic colorectal cancers comprising the administration of [6R]-5,10-methylene tetrahydrofolate (6R-MTHF), 5-fluorouracil (5-FU), bevacizumab, and oxaliplatin. These methods surprisingly reduce disease progression, maintain stable disease and provide

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition comprising [6R]-5,10-methylene tetrahydrofolate (6R-MTHF)~~bevacizumab~~ in the manufacture of a medicament for ~~treating~~ treatment of a patient diagnosed with colorectal cancer or metastatic colorectal cancer, wherein the treatment comprises the following steps:

    a. ~~said~~ a pharmaceutical composition comprising bevacizumab is to be administered at a dose of 5 mg/kg bevacizumab by intravenous infusion;

    and wherein

    b. a pharmaceutical composition comprising oxaliplatin is to be further administered at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion following step (a);

    c. a pharmaceutical composition comprising 5-fluorouracil (5-FU) is to be further administered at a dose of 400 mg/m^2 5-FU by intravenous bolus following step (b);

    d. ~~a~~ said pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus following step (c);

    e. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours following step (d); and

    f. ~~a~~ said pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.

2. The use of claim 1, wherein the intravenous bolus administration of step (d) follows completion of the intravenous bolus administration of step (c) by up to 120 minutes.

3. The use of claim 2, wherein the intravenous bolus administration of step (d) follows completion of the intravenous bolus administration of step (c) by up to 30 minutes.

4. The use of claim 1, wherein the intravenous bolus administration of step (f) follows initiation of the intravenous infusion of step (e) by up to 120 minutes.

5. The use of claim 4, wherein the intravenous bolus administration of step (f) follows initiation of the intravenous infusion of (e) by up to 30 minutes.

6. The use of claim 1, wherein the intravenous infusion of step (e) is paused during the intravenous bolus administration of step (f).

7. The use of claim 1, wherein the intravenous bolus administration of step (f) is completed within 60 minutes of the initiation of step (d).

8. The use of claim 1, wherein the intravenous bolus administration of step (f) is completed within 30 minutes of the initiation of step (d).

9. The use of claim 1, wherein the intravenous bolus administration of step (f) follows initiation of step (c) by up to 180 minutes.

10. The use of claim 1, wherein the intravenous bolus administration of step (f) follows initiation of step (c) by up to 60 minutes.

11. The use of claim 1, wherein the intravenous bolus administration of step (f) follows initiation of step (c) by up to 30 minutes.

12. The use of claim 1, wherein the intravenous bolus administration of step (d) and step (f) are completed within 10 minutes.

13. The use of claim 12, wherein the intravenous bolus administration of step (d) and step (f) are completed within 5 minutes.

14. The use of claim 13, wherein the intravenous bolus administration of step (d) and step (f) are completed within 3 minutes.

15. The use of claim 1, wherein steps (a) to (f) are repeated about every 2 weeks.

16. The use of claim 1, wherein steps (a) to (f) are repeated every 2 weeks.

17. The use of claim 1, wherein the 6R-MTHF is provided as a pharmaceutically acceptable salt.

18. The use of claim 17, wherein the pharmaceutically acceptable salt is provided as a lyophilisate.

19. The use of claim 18, wherein the lyophilisate is prepared from 6R-MTHF hemisulfate salt.

20. The use of claim 19, wherein the lyophilisate is prepared from 6R-MTHF hemisulfate salt and trisodium citrate dihydrate.

21. The use of claim 18, wherein the lyophilisate is reconstituted in aqueous media.

22. The use of claim 18, wherein the lyophilisate comprises 100 mg of 6-MTHF.

23. The use of claim 21, wherein the aqueous media is water or saline.

24. The use of claim 23, wherein the lyophilisate is reconstituted in water.

25. The use of claim 22, wherein the lyophilisate is reconstituted in 10 mL water.

26. The use of claim 24, wherein the lyophilisate is reconstituted in 10 mL water.

27. The use of claim 24, wherein the reconstituted pharmaceutically acceptable salt of 6R-MTHF forms a solution of a concentration of between 5 and 20 mg/mL.

28. The use of claim 27, wherein the reconstituted pharmaceutically acceptable salt of 6R-MTHF forms a solution of a concentration of 10 mg/mL.

29. The use of claim 24, wherein the reconstituted lyophilisate is isotonic.

30. The use of claim 24, wherein the lyophilisate has a pH of between 7.0 and 9.0.

31. The use of claim 30, wherein the lyophilisate has a pH of between 8.0 and 9.0.

32. The use of claim 1, wherein the 6R-MTHF has a diastereomeric purity of at least 98% d.e.

33. The use of claim 32, wherein the 6R-MTHF has a diastereomeric purity of at least 99% d.e.

34. The use of claim 33, wherein the 6R-MTHF has a diastereomeric purity of at least 99.8% d.e.

35. The use of claim 34, wherein the 6R-MTHF has a diastereomeric purity of at least 99.9% d.e.

36. The use of claim 1, wherein said patient has at least one solid tumor.

37. The use of claim 36, wherein the colorectal cancer is colorectal adenocarcinoma.

38. The use of claim 36, wherein the colorectal cancer or metastatic colorectal cancer is verified by biopsy.

39. The use of claim 36, wherein the solid tumor has a reduced size after treatment compared to the solid tumor before treatment.

40. The use of claim 36, wherein the solid tumor has a reduced size after treatment compared to baseline size of said solid tumor.

41. The use of claim 39, wherein size of the solid tumor is evaluated by computerized axial tomography (CAT or CT) or magnetic resonance imaging (MRI).

42. The use of claim 41, wherein the size of the solid tumor is evaluated by CT or MRI at 8, 16, and 24 weeks.

43. The use of claim 39, wherein the solid tumor has a reduced size after 2, 4, 8, 16 or 24 weeks of treatment compared to the solid tumor before treatment.

44. The use of claim 36, wherein steps (a) to (f) are repeated every 2 weeks.

45. The use of claim 44, wherein there is no progression of said solid tumors after 2, 4, 8, 16, or 24 weeks of treatment.

46. The use of claim 36, wherein the solid tumor has a reduced size compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and folinic acid (LV) are to be administered to said patient.

47. The use of claim 46, wherein ~~the administering of~~ at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient,~~comprises~~ comprising the steps of:

a. ~~administering to said patient~~ a pharmaceutical composition comprising bevacizumab is to be administered to said patient at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by ~~administering to said patient~~ a pharmaceutical composition comprising oxaliplatin, which is to be administered to said patient at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion;

c. followed by ~~administering to said patient~~ a pharmaceutical composition comprising a pharmaceutically acceptable salt of ~~folinic acid (~~LV, which is to be administered to said patient~~)~~ at a dose of 400 mg/m^2 ~~folinic acid~~LV by intravenous infusion;

d. followed by ~~administering to said patient~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 5-FU by intravenous bolus; and

e. followed by ~~administering~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~, which is to be administered to said patient at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours.

48. The use of claim 36, wherein the progression of said solid tumors is reduced compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient.

49. The use of claim 48, wherein ~~the administering of~~ at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient, ~~comprises~~ comprising the steps of:

a. ~~administering to said patient~~ a pharmaceutical composition comprising bevacizumab is to be administered to said patient at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by ~~administering to said patient~~ a pharmaceutical composition comprising oxaliplatin, which is to be administered to said patient at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion;

c. followed by ~~administering to said patient~~ a pharmaceutical composition comprising a pharmaceutically acceptable salt of ~~folinic acid (~~LV~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 folinic acid by intravenous infusion;

d. followed by ~~administering to said patient~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 5-FU by intravenous bolus; and

e. followed by ~~administering~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours.

50. The use of claim 1, wherein the treatment is a first-, second-, third-, fourth- or fifth-line treatment.

51. The use of claim 44, wherein the use has an overall response rate (ORR) of at least 40, 50, 60, 70 or 75% after 8 weeks.

52. The use of claim 44, wherein the use has an overall response rate (ORR) of at least 40, 50, 60, 70 or 75% after 16 weeks.

53. The use of claim 44, wherein stable disease is maintained between 8 and 16 weeks.

54. The use of claim 44, wherein the use has an ORR of at least 10, 15, 20, 25, or 30% greater than treating patients diagnosed with colorectal cancer or metastatic colorectal cancer for 8 or 16 weeks comprising the steps of:

a. ~~administering to said patient~~ a pharmaceutical composition comprising bevacizumab is to be administered to said patient at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by ~~administering to said patient~~ a pharmaceutical composition comprising oxaliplatin, which is to be administered to said patient at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion;

c. followed by ~~administering to said patient~~ a pharmaceutical composition comprising a pharmaceutically acceptable salt of ~~folinic acid (~~LV~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 folinic acid by intravenous infusion;

d. followed by ~~administering to said patient~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 5-FU by intravenous bolus; and

e. followed by ~~administering~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours.

55. The use of claim 44, wherein the patient has not received any prior cancer treatment.

56. The use of claim 55, wherein the use produces a partial response after 8 or 16 weeks of treatment.

57. The use of claim 55, wherein the use produces stable disease after 8 or 16 weeks of treatment.

58. The use of claim 55, wherein the use has an overall response rate (ORR) of at least 50% after 8 weeks.

59. The use of claim 55, wherein the use has an overall response rate (ORR) of at least 60% after 8 weeks.

60. The use of claim 55, wherein the use has an overall response rate (ORR) of at least 70% after 8 weeks.

61. The use of claim 54, wherein the patient has not received any prior cancer treatment.

62. The use of claim 61, wherein the use has an ORR of at least 20% greater.

63. The use of claim 61, wherein the use has an ORR of at least 25% greater.

64. The use of claim 61, wherein the use has an ORR of at least 30% greater.

65. The use of claim 61, wherein the use has an ORR of at least 35% greater.

66. The use of claim 1, wherein the patient is diagnosed with metastatic colorectal cancer.

67. The use of claim 18, wherein the lyophilisate is prepared from 6R-MTHF sulfate salt.

68. Use of a pharmaceutical composition comprising ~~bevacizumab~~ 6R-MTHF in the manufacture of a medicament for ~~treating~~ treatment of a patient diagnosed with at least one solid tumor of colorectal cancer or metastatic colorectal cancer, wherein the treatment comprises the following steps:

    a. ~~said~~ a pharmaceutical composition comprising bevacizumab is to be administered at a dose of 5 mg/kg bevacizumab by intravenous infusion;

    and wherein

    b. a pharmaceutical composition comprising oxaliplatin is to be further administered at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion following step (a);

    c. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 400 mg/m^2 5-FU by intravenous bolus following step (b);

    d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus following step (c);

e. a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ is to be further administered at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours following step (d); and

f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus,

wherein the progression of said at least one solid tumor is reduced.

69. The use of claim 68, wherein progression-free survival is increased compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient.

70. The use of claim 69, wherein ~~the administering of~~ at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient, comprising~~es~~ the steps of:

a. ~~administering to said patient~~ a pharmaceutical composition comprising bevacizumab is to be administered to said patient at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by ~~administering to said patient~~ a pharmaceutical composition comprising oxaliplatin, which is to be administered to said patient at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion;

c. followed by ~~administering to said patient~~ a pharmaceutical composition comprising a pharmaceutically acceptable salt of ~~folinic acid (~~LV~~)~~, which is to be administered to said patient at a dose of 400 mg/m^2 ~~folinic acid~~LV by intravenous infusion;

d. followed by ~~administering to said patient~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~ , which is to be administered to said patient at a dose of 400 mg/m^2 5-FU by intravenous bolus; and

e. followed by ~~administering~~ a pharmaceutical composition comprising ~~5-fluorouracil (~~5-FU~~)~~, which is to be administered to said patient at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours; and

f. ~~administering to said patient~~ a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF, which is to be administered to said at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.

71. The use of claim 69, wherein progression-free survival is increased compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient after 1, 2, 3, 4 or 5 years.

72. The use of claim 70, wherein progression-free survival is increased compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer treated by administering at least bevacizumab, oxaliplatin, 5-FU and LV after 1, 2, 3, 4 or 5 years.

73. The use of claim 69, wherein overall survival is increased compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient after 3 or 5 years.

74. The use of claim 70, wherein overall survival is increased compared to treatment of solid tumors in a patient diagnosed with colorectal cancer or metastatic colorectal cancer ~~treated by administering~~wherein at least bevacizumab, oxaliplatin, 5-FU and LV are to be administered to said patient after 3 or 5 years.

~~75. Use of a pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), in the manufacture of a medicament for treating a patient diagnosed with cancer, wherein:~~

~~a. said pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) is to be administered at a dose of 5 mg/kg by intravenous infusion;~~

~~and wherein~~

~~b. a pharmaceutical composition comprising an alkylating antineoplastic agent containing a platinum (II) center is to be further administered at a dose of 85 mg/m^2 by intravenous infusion;~~

c. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 400 mg/m^2 by intravenous bolus;

d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus;

e. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 2,400 mg/m^2 by intravenous infusion over 46 hours; and

f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.

76. The use of claim 75, wherein the recombinant humanized monoclonal antibody directed against VEGF is selected from the group consisting of anti-VEGF humanized monoclonal antibody, anti-VEGF monoclonal antibody, anti-VEGF rhuMAb, bevacizumab biosimilar BAT1706, bevacizumab biosimilar BEVZ92, bevacizumab biosimilar BI 695502, bevacizumab biosimilar CBT-124, bevacizumab biosimilar FKB238, bevacizumab, biosimilar HD204, bevacizumab biosimilar HLX04, bevacizumab biosimilar MB02, bevacizumab biosimilar MIL60, bevacizumab biosimilar PF-06439535, bevacizumab biosimilar QL-1101, immunoglobulin G1 (human-mouse monoclonal rhuMab-VEGF gamma-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMab-VEGF light chain, and dimer recombinant humanized anti-VEGF monoclonal antibody.

77. The use of claim 75, wherein the alkylating antineoplastic agent containing a platinum (II) center is cisplatin, carboplatin or oxaliplatin.

78. The use of claim 75, wherein the fluorinated pyrimidine base is 5-FU, 2'-deoxy-5-fluorouridine, or 5'-deoxy-5-fluorouridine.

79. The use of claim 75, wherein the cancer is colorectal cancer or metastatic colorectal cancer.

80. Use of a pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), in the manufacture of a medicament for retarding growth of a solid tumor in a patient diagnosed with cancer, wherein:

a. said pharmaceutical composition comprising a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) is to be administered at a dose of 5 mg/kg by intravenous infusion;

and wherein

b. a pharmaceutical composition comprising an alkylating antineoplastic agent containing a platinum (II) center is to be further administered at a dose of 85 mg/m^2 by intravenous infusion;

c. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 400 mg/m^2 by intravenous bolus;

d. a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus;

e. a pharmaceutical composition comprising a fluorinated pyrimidine base is to be further administered at a dose of 2,400 mg/m^2 by intravenous infusion over 46 hours; and

f. a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF is to be further administered at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus,

wherein the progression of said at least one solid tumor is reduced.

81. The use of claim 80, wherein the recombinant humanized monoclonal antibody directed against VEGF is selected from the group consisting of anti-VEGF humanized monoclonal antibody, anti-VEGF monoclonal antibody, anti-VEGF rhuMAb,

~~bevacizumab biosimilar BAT1706, bevacizumab biosimilar BEVZ92, bevacizumab biosimilar BI 695502, bevacizumab biosimilar CBT 124, bevacizumab biosimilar FKB238, bevacizumab, biosimilar HD204, bevacizumab biosimilar HLX04, bevacizumab biosimilar MB02, bevacizumab biosimilar MIL60, bevacizumab biosimilar PF-06439535, bevacizumab biosimilar QL 1101, immunoglobulin G1 (human-mouse monoclonal rhuMab-VEGF gamma-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMab-VEGF light chain, and dimer recombinant humanized anti-VEGF monoclonal antibody.~~

~~82. The use of claim 80, wherein the alkylating antineoplastic agent containing a platinum (II) center is cisplatin, carboplatin or oxaliplatin.~~

~~83. The use of claim 80, wherein the fluorinated pyrimidine base is 5-FU, 2'-deoxy-5 fluorouridine, or 5'-deoxy-5-fluorouridine.~~

~~84. The use of claim 80, wherein the cancer is colorectal cancer or metastatic colorectal cancer.~~