Safety and Efficacy of CoFactor®/5-Fluorouracil/Bevacizumab Versus Leucovorin/5-Fluorouracil/ 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 bevacizumab in the manufacture of a medicament for treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer, wherein:

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;

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;

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 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; 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.

[0009b] In another aspect, the present disclosure refers to a use of a pharmaceutical composition comprising bevacizumab in the manufacture of a medicament for treating a patient diagnosed with at least one solid tumor of colorectal cancer or metastatic colorectal cancer, wherein:

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;

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;

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 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; 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

improved overall response rates compared to standard treatments that utilize folates such as folinic acid.

[0011] In one example, the present disclosure provides methods for treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer comprising the steps of:

a) administering to said patient a pharmaceutical composition comprising bevacizumab at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b) followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m^2 oxaliplatin by intravenous infusion;

c) followed by administering to said patient a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 400 mg/m^2 5-FU by intravenous bolus;

d) followed by administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable salt of a folate, 6R-MTHF, at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus;

e) followed by administering a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours; and

f) administering a pharmaceutical composition comprising a pharmaceutically acceptable salt of 6R-MTHF at a dose of 60 mg/m^2 6R-MTHF by intravenous bolus.

[0012] The pharmaceutical compositions of 6R-MTHF, 5-FU, bevacizumab, and oxaliplatin are administered intravenously either as an intravenous infusion or as a bolus. As used herein, "intravenous bolus" means a method of intravenous administration wherein a single dose of a pharmaceutical composition is given all at once. In one example, administration by intravenous bolus is completed within 10 minutes. In a preferred example, administration by intravenous bolus is completed within 5 minutes. In a preferred example, administration by intravenous bolus is completed within 3 minutes. In a preferred example, administration by intravenous bolus is completed within 2 minutes. In a preferred example, administration by intravenous bolus of steps (c), (d) and (f) is completed within 10, 5, 3 or 2 minutes.

[0013] In one example, administration by intravenous bolus of 6R-MTHF of steps (d) and (f) are at a dose of 30, 60 or 120 mg/m^2. In a preferred example, the administration by intravenous bolus of 6R-MTHF of steps (d) and (f) is at a dose of 60 mg/m^2.

[0014] In contrast, as used herein, "intravenous infusion" refers to intravenous infusion of a single dose given over at constant concentration over a period of time. For example, administration by intravenous infusion is completed in at least 30 minutes, 60, 90, 120, or 180

minutes. In another example, administration by intravenous infusion of step (e) is conducted over a period 46 hours.

[0015] In certain examples, the intravenous bolus administration of step (d) follows completion of the intravenous bolus administration of step (c) by up to 30, 60, 90 or 120 minutes. In another example, the intravenous bolus administration of step (f) follows initiation of the intravenous infusion of step (e) by up to 30, 60, 90 or 120 minutes. In yet another example, the intravenous bolus administration of step (f) is completed within 30 or 60 minutes of the initiation of step (d). In another example, the intravenous bolus administration of step (f) follows initiation of step (c) by up to 30, 60, 90, 120 or 180 minutes.

[0016] In one example,the intravenous bolus administration of step (f) may be initiated before the initiation of the intravenous infusion of step (e). In another example, the intravenous infusion of step (e) is paused during the intravenous bolus administration of step (f).

[0017] The method of treating patients diagnosed with colorectal cancer and metastatic colorectal cancers comprising steps (a) to (f) may be repeated about every two weeks. As used herein, "about every two weeks" means between 10 and 18 days. In one example, the methods disclosed herein may be repeated every two weeks.

[0018] The pharmaceutical compositions of [6R]-5,10-methylene tetrahydrofolate (6R-MTHF) used in the methods disclosed herein, are provided as pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In one example, the pharmaceutically acceptable salt of 6R-MTHF is the sulfate salt. In one example, the pharmaceutically acceptable salt of 6R-MTHF is the hemisulfate salt. In certain examples, the pharmaceutically acceptable salts of 6R-MTHF used in the methods disclosed herein may be provided as a lyophilisate. In another example, the lyophilisates used in the methods disclosed herein are prepared from 6R-MTHF hemisulfate salt. In a preferred example, the lyophilisate used in the methods disclosed herein is prepared from a 6R-MTHF hemisulfate salt and further comprises other salts and excipients and in one exampletrisodium citrate dihydrate.

[0019] In certain examples, the lyophilisates used in the methods disclosed herein are reconstituted in aqueous media prior to use. In one example, the aqueous media is water or saline. In a preferred example, the aqueous media is water. In other examples, the lyophilisate comprises 100 mg of 6-MTHF. In a preferred example, the lyophilisate comprising 100 mg 6R-MTHF is reconstituted by the addition of 10 mL water. In yet another example, the lyophilisate comprising 100 mg of 6R-MTHF is provided in a container. In another exampleof the methods disclosed herein, the reconstituted lyophilisate forms a solution with a concentration of between 5 and 20 mg/mL 6R-MTHF. In a preferred example, the reconstituted lyophilisate forms a solution with a concentration of between 7 and 12 mg/mL 6R-MTHF. More preferably, the reconstituted lyophilisate forms a solution with a concentration of 10 mg/mL 6R-MTHF. In other examplesof the methods disclosed herein, the reconstituted lyophilisate is isotonic. In yet another example, the reconstituted lyophilisate has a pH of between 7.0 and 9.0, more preferably between pH 8.0 and 9.0, most preferably between 8.3 and 8.7 and even more preferably pH 8.5.

[0020] The 6R-MTHF or pharmaceutically acceptable salts thereof has a diastereomeric purity of at least 98% d.e., preferably 99% d.e., more preferably 99.8% d.e. and most preferably 99.9% d.e.

[0021] In one example, the methods of treating colorectal cancer and metastatic colorectal cancer is practiced on a patient diagnosed with colorectal cancer or metastatic colorectal cancer having at least one solid tumor. In another example, the colorectal cancer is colorectal adenocarcinoma and in yet another examplethe colorectal cancer or colorectal adenocarcinoma is verified by biopsy.

[0022] In one example, the methods of treating colorectal cancer and metastatic colorectal cancer reduces the size of one or more solid tumors compared to the one or more solid tumors before treatment or compared to “baseline size”, as that term is defined herein. In another example, the methods disclosed herein reduce the size of one or more solid tumors after 2, 4, 8, 16 or 24 weeks of treatment after repeating steps (a) to (f) about every two weeks. In another example, the size of the one or more solid tumors is evaluated by computerized axial tomography (CAT or CT) or magnetic resonance imaging (MRI) at 8, 16, or 24 weeks after repeating steps (a) to (f) about every two weeks.

[0023] In yet another example, the solid tumor has a greater reduction in size (relative to untreated tumor or "baseline size", as that term is defined herein) 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 folinic acid (LV). In another example, the administering of at least bevacizumab, oxaliplatin, 5-FU and LV comprises the steps of:

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

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours.

[0024] In one example, the methods of treating colorectal cancer and metastatic colorectal cancer, the methods produce no progression of said solid tumors after 2, 4, 8, 16, or 24 weeks of treatment after repeating steps (a) to (f) about every two weeks. In another example, the methods of treating colorectal cancer and metastatic colorectal cancer produce no statistically significant progression of said solid tumors after 2, 4, 8, 16, or 24 weeks of treatment after repeating steps (a) to (f) about every two weeks.

[0025] In yet another example, the methods of treating colorectal cancer and metastatic colorectal cancer, the methods produce no progression of said solid tumors after 2, 4, 8, 16, or

24 weeks of treatment after repeating steps (a) to (f) about every two weeks 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 folinic acid (LV). In another example, the administering of at least bevacizumab, oxaliplatin, 5-FU and LV comprises the steps of:

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

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) at a dose of 2,400 mg/m^2 5-FU by intravenous infusion over 46 hours.

[0026] In one example, the methods disclosed herein of treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer is a first-, second-, third-, fourth- or fifth-line treatment.

[0027] In one example, the methods disclosed herein of treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer has an overall response rate (ORR) of at least 40, 50, 60, 70 or 75% after 8 weeks. In another example, the method has an overall response rate (ORR) of at least 40, 50, 60, 70 or 75% after 16 weeks. In yet another example, the methods disclosed herein maintain stable disease between 8 and 16 weeks of treatment.

[0028] In another example, the methods disclosed herein of treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer has an overall response rate (ORR) of at least 10, 15, 20, 25, 30 or 35% greater than a method of 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m2 oxaliplatin by intravenous infusion;

c. followed by administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable salt of folinic acid (LV) at a dose of 400 mg/m2 folinic acid by intravenous infusion;

d. followed by administering to said patient a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 400 mg/m2 5-FU by intravenous bolus; and

e. followed by administering a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 2,400 mg/m2 5-FU by intravenous infusion over 46 hours.

[0029] In one example, the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, including but not limited to chemotherapy, radiotherapy, immunotherapy, or surgery. In another example, the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, except chemotherapy or radiotherapy for colorectal cancer shorter than 8 weeks duration, including but not limited to chemotherapy, radiotherapy, immunotherapy, or surgery less than 6 months before initiation of the treatment methods disclosed herein.

[0030] In one examplewhere the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein

produce a partial response after 8 or 16 weeks of treatment. In another examplewhere the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce stable disease after 8 or 16 weeks of treatment. In yet another example, where the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce an overall response rate (ORR) of at least 50% after 8 weeks. In a further examplewhere the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods of the present disclosure produces an ORR of at least 60% after 8 weeks. In a yet a further examplewhere the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods of the present disclosure produces an ORR of at least 70% after 8 weeks.

[0031] In one example, where the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce an ORR of at least 20% greater than a method of 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m2 oxaliplatin by intravenous infusion;

c. followed by administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable salt of folinic acid (LV) at a dose of 400 mg/m2 folinic acid by intravenous infusion;

d. followed by administering to said patient a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 400 mg/m2 5-FU by intravenous bolus; and

e. followed by administering a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 2,400 mg/m2 5-FU by intravenous infusion over 46 hours.

[0032] In another example, where the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce an ORR of at least 25% greater than a method of 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m2 oxaliplatin by intravenous infusion;

c. followed by administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable salt of folinic acid (LV) at a dose of 400 mg/m2 folinic acid by intravenous infusion;

d. followed by administering to said patient a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 400 mg/m2 5-FU by intravenous bolus; and

e. followed by administering a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 2,400 mg/m2 5-FU by intravenous infusion over 46 hours.

[0033] In yet another example, where the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce an ORR of at least 30% greater than a method of 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m2 oxaliplatin by intravenous infusion;

c. followed by administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable salt of folinic acid (LV) at a dose of 400 mg/m2 folinic acid by intravenous infusion;

d. followed by administering to said patient a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 400 mg/m2 5-FU by intravenous bolus; and

e. followed by administering a pharmaceutical composition comprising 5-fluorouracil (5-FU) at a dose of 2,400 mg/m2 5-FU by intravenous infusion over 46 hours.

[0034] In a further example, where the patient diagnosed with colorectal cancer or metastatic colorectal cancer has not received any prior cancer treatment, the methods disclosed herein produce an ORR of at least 35% greater than a method of 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin at a dose of 85 mg/m2 oxaliplatin by intravenous infusion;

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition comprising bevacizumab in the manufacture of a medicament for treating a patient diagnosed with colorectal cancer or metastatic colorectal cancer, wherein:

    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;

    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;

    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 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; 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.

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 at least bevacizumab, oxaliplatin, 5-FU and LV.

47. The use of claim 46, wherein the administering of at least bevacizumab, oxaliplatin, 5-FU and LV comprises the steps of:

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

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) 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 at least bevacizumab, oxaliplatin, 5-FU and LV.

49. The use of claim 48, wherein the administering of at least bevacizumab, oxaliplatin, 5-FU and LV comprises the steps of:

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

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) 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 at a dose of 5 mg/kg bevacizumab by intravenous infusion;

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) 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 in the manufacture of a medicament for treating a patient diagnosed with at least one solid tumor of colorectal cancer or metastatic colorectal cancer, wherein:

    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;

    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;

    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 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; 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 at least bevacizumab, oxaliplatin, 5-FU and LV.

70. The use of claim 69, wherein the administering of at least bevacizumab, oxaliplatin, 5-FU and LV comprises the steps of:

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

b. followed by administering to said patient a pharmaceutical composition comprising oxaliplatin 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) 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) 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) 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 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 at least bevacizumab, oxaliplatin, 5-FU and LV 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 at least bevacizumab, oxaliplatin, 5-FU and LV 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 at least bevacizumab, oxaliplatin, 5-FU and LV 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.