with advanced solid malignancies. The aflibercept 4 mg/kg dose every 2 weeks was considered to be the optimum dose.

In a phase II trial (NC17498) aflibercept was administered in previously treated patients with metastatic colorectal cancer. This trial showed that aflibercept is well tolerated in pre-treated patients with MCRC. The conclusions are that based on the study results, studies of aflibercept as single agent or in combination should be explored (Tang et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 4027).

But the results provided in these two studies provided no insight as to efficacy.

Furthermore a phase III trial of aflibercept in metastatic pancreatic cancer was discontinued in 2009 and in 2011 the data of a phase III trial evaluating aflibercept for the second-line treatment of non-small cell lung cancer (NSCLC) showed that adding aflibercept to the chemotherapy drug docetaxel did not meet the pre-specified criteria for the primary endpoint of improvement in overall survival compared with a regimen of docetaxel plus placebo.

It has now been found, and this is an object of the present invention, that the effectiveness of aflibercept on Overal Survival (OS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is another object of the present invention, that the effectiveness of aflibercept on Progression Free Survival (PFS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is yet another object of the present invention, that the effectiveness of aflibercept on Overal Response Rate (ORR) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

The invention relates to methods, compositions and articles as disclosed herein.

In one aspect the invention provides for a method of treating Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom in a patient in need thereof, said method

comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI. This method is safe and effective.

In a second aspect the invention provides for a method of increasing Overall Survival (OS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a third aspect the invention provides a method of increasing Overall Response Rate (ORR) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a fourth aspect the invention provides a method of increasing Progression Free Survival (PFS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a first feature the invention provides a method according to any one of the first to fourth aspects wherein said patient has already been treated for the CRC or CRC symptom (second-line treatment).

In a specific embodiment CRC is a Metastatic Colorectal Cancer.

In a second feature the invention provides for a method according to any one of the first to fourth aspects or the first feature wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery. In an embodiment said patient has failed chemotherapy, radiotherapy or surgery.

In a third feature the invention provides a method according to any one of the first to fourth aspects or the first feature wherein said patient has previously been treated with therapy based on oxaliplatin or on bevacizumab.

In an embodiment said patient has failed therapy based on oxaliplatin or on bevacizumab.

In a fourth feature the invention provides a method wherein folinic acid at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU) at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2, irinotecan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and aflibercept at

a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

In the present application the dosage of folinic acid indicated should be understood as the dosage of the racemate of folinic acid, i.e. comprising the D and L forms. Should only the L form be used the dosage should be half of the dosage indicated for the racemate.

In other words a dosage of folinic acid of about 200 mg/m^2 as indicated in the present application corresponds to about 200 mg/m^2 of racemate and about 100 mg/m^2 of L form.

In a fifth feature the invention provides a method wherein folinic acid at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinotecan at a dosage of about 180 mg/m^2 and aflibercept at a dosage of about 4 mg/kg are administered to patient.

In a sixth feature the invention provides a method wherein said patient receives intravenous folinic acid at a dosage comprised of about 400 mg/m^2, intravenous 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, intravenous irinotecan at a dosage comprised of about 180 mg/m^2 and intravenous aflibercept at a dosage of about 4 mg/kg every two weeks.

In a seventh feature the invention provides a method wherein said patient receives intravenous folinic acid, intravenous 5-fluorouracil (5-FU), intravenous irinotecan and intravenous aflibercept every two weeks for a period comprised between about 9 and about 18 weeks.

In another feature the invention provides a method wherein said patient receives intravenous folinic acid immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives intravenous irinotecan immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives intravenous irinotecan immediately after aflibercept administration over almost 90 minutes.

In another feature the invention provides a method wherein said patient receives intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives a first quantity of intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration and a second quantity in continous infusion.

In another feature the invention provides a method wherein said patient receives about 400 mg/m^2 of intravenous 5-fluorouracil (5-FU) over about 2 to 4 minutes after aflibercept administration and 2400 mg/m^2 over about 46 hours after aflibercept administration in continuous infusion.

In a fifth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for simultaneous administration.

In a sixth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for sequential administration.

In a seventh aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for administration that is spaced out over a period of time so as to obtain the maximum efficacy of the combination.

In a eighth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan and comprising a pharmaceutically acceptable carrier for treating patients with CRC.

In another feature of any of these aspects the patient has liver metastases.

In an ninth aspect the invention features an article of manufacture comprising:

a) a packaging material

b) aflibercept, and

c) a label or package insert contained within said packaging material indicating that aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan is effective for the treatment of CRC

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Survival (OS).

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Progression Free Survival (PFS).

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Response Rate (ORR).

In a tenth aspect the invention features a kit for treating patients with CRC comprising:

a) at least one compound chosen from the list consisting of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinotecan; and

b) a label or package insert contained within said kit indicating that aflibercept is to be used in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) or folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) is to be used in combination with Aflibercept

In an eleventh aspect the invention features a kit comprising in separate containers pharmaceutical compositions for combined use in treating CRC in a patient which comprises (1) a pharmaceutical composition comprising aflibercept, (2) a pharmaceutical composition comprising folinic acid, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinotecan.

The aflibercept can be formulated as described in W02006/104852. The man skilled in the art may refer in particular to W02006/104852 or to WO 00/75319 to carry out the present invention.

Figures

Figure 1 : Aflibercept amino acid sequence (SEQ ID NO:1)

Figure 2 : Overall survival (months) — Kaplan-Meier curves by treatment group— ITT population

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It has now been found, and this is an object of the present invention, that the effectiveness of aflibercept on Overall Survival (OS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is another object of the present invention, that the effectiveness of aflibercept on Progression Free Survival (PFS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is yet another object of the present invention, that the effectiveness of aflibercept on Overal Response Rate (ORR) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

The invention relates to methods, compositions and articles as disclosed herein.

Summary

In one embodiment, there is provided a method of treating Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom in a patient in need thereof, said method

comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI. This method is safe and effective.

In a second embodiment, there is provided a method of increasing Overall Survival (OS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a third embodiment, there is provided a method of increasing Overall Response Rate (ORR) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a fourth embodiment, there is provided a method of increasing Progression Free Survival (PFS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a first feature, there is provided a method according to any one of the first to fourth embodiments wherein said patient has already been treated for the CRC or CRC symptom (second-line treatment).

In a specific embodiment CRC is a Metastatic Colorectal Cancer.

In a second feature, there is provided a method according to any one of the first to fourth embodiments or the first feature wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery. In an embodiment said patient has failed chemotherapy, radiotherapy or surgery.

In a third feature, there is provided a method according to any one of the first to fourth embodiments or the first feature wherein said patient has previously been treated with therapy based on oxaliplatin or on bevacizumab.

In an embodiment said patient has failed therapy based on oxaliplatin or on bevacizumab.

In a fourth feature, there is provided a method wherein folinic acid at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU) at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2, irinotecan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and aflibercept at

a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

In the present application the dosage of folinic acid indicated should be understood as the dosage of the racemate of folinic acid, i.e. comprising the D and L forms. Should only the L form be used the dosage should be half of the dosage indicated for the racemate.

In other words a dosage of folinic acid of about 200 mg/m^2 as indicated in the present application corresponds to about 200 mg/m^2 of racemate and about 100 mg/m^2 of L form.

In a fifth feature, there is provided a method wherein folinic acid at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinotecan at a dosage of about 180 mg/m^2 and aflibercept at a dosage of about 4 mg/kg are administered to patient.

In a sixth feature, there is provided a method wherein said patient receives intravenous folinic acid at a dosage comprised of about 400 mg/m^2, intravenous 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, intravenous irinotecan at a dosage comprised of about 180 mg/m^2 and intravenous aflibercept at a dosage of about 4 mg/kg every two weeks.

In a seventh feature, there is provided a method wherein said patient receives intravenous folinic acid, intravenous 5-fluorouracil (5-FU), intravenous irinotecan and intravenous aflibercept every two weeks for a period comprised between about 9 and about 18 weeks.

In another feature, there is provided a method wherein said patient receives intravenous folinic acid immediately after aflibercept administration.

In another feature, there is provided a method wherein said patient receives intravenous irinotecan immediately after aflibercept administration.

In another feature, there is provided a method wherein said patient receives intravenous irinotecan immediately after aflibercept administration over almost 90 minutes.

In another feature, there is provided a method wherein said patient receives intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration.

In another feature, there is provided a method wherein said patient receives a first quantity of intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration and a second quantity in continuous infusion.

In another feature, there is provided a method wherein said patient receives about 400 mg/m^2 of intravenous 5-fluorouracil (5-FU) over about 2 to 4 minutes after aflibercept administration and 2400 mg/m^2 over about 46 hours after aflibercept administration in continuous infusion.

In a fifth embodiment, there is provided a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for simultaneous administration.

In a sixth embodiment, there is provided a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for sequential administration.

In a seventh embodiment, there is provided a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC for administration that is spaced out over a period of time so as to obtain the maximum efficacy of the combination.

In an eighth embodiment, there is provided a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan and comprising a pharmaceutically acceptable carrier for treating patients with CRC.

In another feature of any of these embodiments the patient has liver metastases.

In a ninth embodiment, there is provided an article of manufacture comprising:

a) a packaging material

b) aflibercept, and

c) a label or package insert contained within said packaging material indicating that aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan is effective for the treatment of CRC.

In one feature of the ninth embodiment the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Survival (OS).

In one feature of the ninth embodiment the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Progression Free Survival (PFS).

In one feature of the ninth embodiment the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Response Rate (ORR).

In a tenth embodiment, there is provided a kit for treating patients with CRC comprising:

a) at least one compound chosen from the list consisting of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinotecan; and

b) a label or package insert contained within said kit indicating that aflibercept is to be used in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) or folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) is to be used in combination with Aflibercept.

In an eleventh embodiment, there is provided a kit comprising in separate containers pharmaceutical compositions for combined use in treating CRC in a patient which comprises (1) a pharmaceutical composition comprising aflibercept, (2) a pharmaceutical composition comprising folinic acid, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinotecan.

In one aspect, there is provided use of a composition comprising aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan in the manufacture of a medicament for treating CRC in a patient, wherein the composition is for simultaneous administration.

In another aspect, there is provided use of a composition comprising aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan in the manufacture of a medicament for treating CRC in a patient, wherein the composition is for sequential administration.

In another aspect, there is provided use of a composition comprising aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan in the manufacture of a medicament for treating CRC in a patient, wherein the composition is for administration spaced out over a period of time so as to obtain the maximum efficacy of the combination.

The aflibercept can be formulated as described in W02006/104852. The man skilled in the art may refer in particular to W02006/104852 or to WO 00/75319 to carry out the present invention.

Figures

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