Composition comprising aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI)

The present invention relates to combinations of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinotecan which are therapeutically useful in the treatment of Colorectal Cancer (CRC) and in particular metastatic Colorectal Cancer (CRC).

Colorectal cancers are among the most frequent tumor types in the western countries, second to breast in women and third to lung and prostate in males. The end prognosis is dependent upon the extent of the disease. The five year survival rate in early localized stage of about 90%, decreased to approximately 60-65% after spread to adjacent organ(s) or lymph nodes and is of less than 10% after spread to distant sites.

When diagnosed before nodal involvement treatment is usually limited to surgical resection (and radiotherapy for patients with rectal cancer) and potential participation to clinical trials for adjuvant therapy. Patients with nodal involvement are candidates for adjuvant chemotherapy following initial surgery in the attempt to prevent metastatic recurrence of the disease. Once spread to distant sites treatment essentially consists of palliative chemotherapy.

About 75 to 80% of all the patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically removed. However, almost half of these patients will ultimately die from metastatic disease. Furthermore 20 to 25 % of the patients present with metastatic disease at diagnosis. Once metastases are present median overall survival with available combination therapy is around 20 months.

Over the past decades 5-Fluorouracil (5-FU) has remained the mainstay of the chemotherapy in colorectal cancer. During years the major determinant in the treatment of colorectal cancer patients has been the improvement in the schedules of 5-FU administration.

Among these, the bimonthly regimen (LV5FU2) of 5-FU given as bolus/infusion over 2 days has been shown to be superior to the monthly 5 day bolus regimen (Mayo regimen) in terms of response rate (RR) (32.6% *vs* 14.4%), in terms of progression free survival (PFS) (27.6 *vs* 22.0 weeks), and safety (de Gramont et al, Journal of Clinical Oncology 1997;15(2):808-815).

However, no statistically significant improvement in the overall survival (OS) was seen until development, starting in the beginning of nineties, of two novel cytotoxic agents, oxaliplatin, a DACH platinum, and the topoisomerase I inhibitor, irinotecan. With each of these two new agents median overall survival in the first line metastatic setting reached 15 to 19 months in multiple Phase III trials.

In a study, published in 2004 by Tournigand et al. (Journal of Clinical Oncology 2004;22(2):229-237), where these two drugs were administered in sequence in the same protocol, as first then second line treatment in metastatic colorectal cancer patients, the threshold of 20 months median overall survival was crossed whatever was the order of the treatment sequence.

Aflibercept is synthesized as a fusion protein comprising the signal sequence of VEGFR1 fused to the D2 Ig domain of the VEGFR1 receptor, itself fused to the D3 Ig domain of the VEGFR2 receptor, in turn fused to the Fc domain of IgGlAflibercept is also referred to as as VEGFR1 R2-Fc.DELTA.C1 or Flt1D2.F1k1D3.Fc.DELTA.C1.

The amino acid sequence (SEQ ID N°1) of Aflibercept is illustrated in Figure 1 and is also shown inter alia in FIG. 24) of patent application WO 00/75319.

5-fluorouracil (5-FU or f5U) is a drug that is a pyrimidine analog which is used in the treatment of cancer. It is a suicide inhibitor and works through irreversible inhibition of thymidylate synthase. It belongs to the family of drugs called antimetabolites.

Folinic acid or leucovorin is an adjuvant to cancer chemotherapy used in combination with 5-fluorouracil.

Irinotecan is a drug used for the treatment of cancer. Irinotecan is a topoisomerase 1 inhibitor, which prevents DNA from unwinding.

FOLFIRI is the combination of folinic acid, 5-fluorouracil (5-FU) and irinotecan and will be used throughout the document.

In a phase I study (TCD6118) aflibercept was administered IV in combination with irinotecan (180 mg/m^2 on day 1), leucovorin (200 mg/m^2 on day 1 and day 2), and 5-FU (bolus/infusional 400/600 mg/m^2 on day 1 and day 2), every 2 weeks in patients

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

CLAIMS

1. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC wherein the composition is for simultaneous administration.

2. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinotecan for treating patients with CRC wherein the composition is for sequential administration.

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

4. 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.

5. 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.