

Ramucirumab – A new hope for colorectal cancer patient

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Abstract

Metastatic colorectal cancer remains one of the deadliest types of cancer having significant presence globally. Exhaustive research throughout the scientific fraternities worldwide is now getting focused on selectively targeting the cancer cells. One such achievement has been the recent approval of ramucirumab by USFDA which has added to the existing armamentarium of angiogenesis inhibitors. Ramucirumab is a fully humanized monoclonal antibody directed against the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR-2) which selectively inhibits the human VEGFR-2 with a much greater affinity than its natural ligands and can be used in the second-line treatment of metastatic colorectal cancer. The current review focuses on the details regarding ramucirumab, its journey from preclinical trial to clinical trial and the way forward.

Keywords: Colorectal Cancer, Monoclonal antibody, Vascular endothelial growth factor receptor 2, Ramucirumab.

Introduction

Colorectal cancer is a cancer that starts in the colon or the rectum. Most colorectal cancers begin as a growth on the inner lining of the colon or rectum called a polyp. Some types of polyps can change into cancer over the course of several years, but not all polyps become cancer. Colorectal cancer is one of the most deadly cancer types having equal presence in men and women. It is the second most common cancer in women and the third most common cancer in men. Colorectal cancer is the third most frequent cancer worldwide and was responsible for nearly 700,000 deaths worldwide in 2012.⁽¹⁾ Approximately 25% of patients are diagnosed with metastatic disease and 50% will develop metastasis.⁽²⁾ Patients with metastatic disease have a poor prognosis with a 5-year survival rate of only 13.1%.⁽³⁾ Colorectal cancer (CRC) remains a major public health problem in the United States, with an estimated 1,33,000 new cases in 2015.⁽⁴⁾ In about 20% of patients, newly diagnosed CRC is metastatic at the time of initial presentation and more than 50% of patients with early-stage CRC at initial diagnosis eventually develop metastatic disease. Despite significant progress in the treatment of metastatic CRC (m CRC) during the past 2 decades, the prognosis of patients with m CRC remains disappointing. Systemic chemotherapy continues to be the main treatment modality for patients with m CRC.⁽⁵⁾ Angiogenesis, the formation of new blood vessels, plays

a critical role in the tumor growth, invasion and metastasis and thus the tumor vasculature is a good target for cancer therapy.⁽⁶⁻⁹⁾ Exhaustive research in scientific fraternity worldwide has given rise to newer drugs with extended therapeutic effect and advanced safety and quality.

One of the drugs of interest is Ramucirumab which has recently been approved by United States Food and Drug Administration (USFDA) for its use in metastatic colorectal cancer in the second-line setting in combination with 5-fluorouracil, Leucovorin and Irinotecan (FOLFIRI).⁽¹⁰⁾ Basically it is a monoclonal antibody active against the extracellular domain of vascular endothelial growth-factor receptor-2 (VEGFR-2). The RAISE (A randomized, double blind, multicenter phase III study of Irinotecan, folinic acid and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo in patients with metastatic colorectal carcinoma progressive) trial, a randomized phase III trial, confirmed the benefit from ramucirumab in colorectal cancer after progression on bevacizumab, oxaliplatin, and a fluoropyrimidine.⁽¹¹⁾ A total of 1,072 patients with metastatic colorectal cancer who had progressed on FOLFOX plus bevacizumab were randomized to receive FOLFIRI plus ramucirumab or FOLFIRI plus placebo. The trial demonstrated a median overall survival (OS) benefit of 1.6 months (hazard ratio [HR]: 0.84) with the use of ramucirumab.^(12,13)

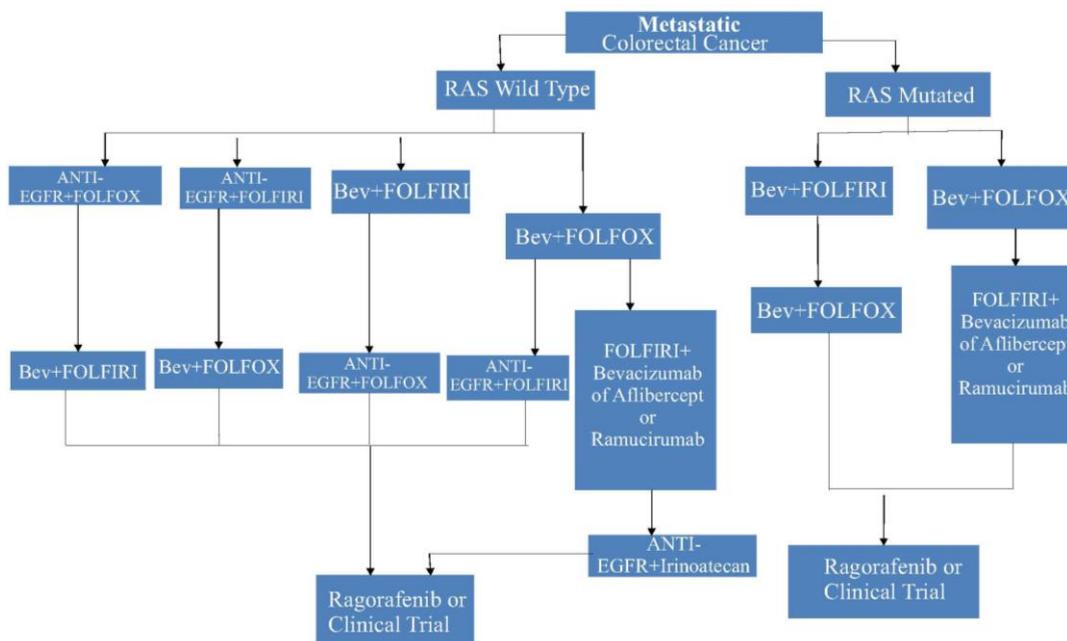


Fig. 1: Scheme for Contemporary therapy of Unresectable Metastatic Colorectal Cancer⁽¹⁴⁾

Ramucirumab: Drug profile

Approval Date: April 24, 2015

Description:

- Protein Chemical formula: $C_{6374}H_{9864}N_{1692}O_{1996}S_{46}$
- Molar Mass: 143.6 kg/mol
- Protein average weight: 143600.0 Da
- Protein Structure:

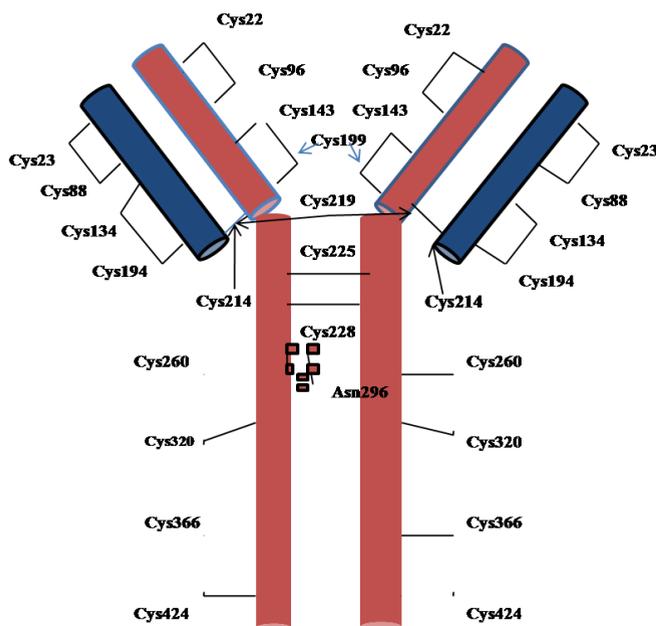


Fig. 2: Protein Structure of Ramucirumab⁽¹⁵⁾

Ramucirumab drug substance (DS) is a clear to slightly opalescent and colourless to slightly yellow liquid with pH 5.7 - 6.3. Ramucirumab is typical IgG1 molecule consisting of two κ -light chains (LC) and two

γ 1-heavy chains (HC). Each HC and LC contains 446 and 214 amino acids, respectively. The molecule has 16 disulfide bonds and two N-linked glycosylation sites at Asn296 of HC, no O-linked glycosylation has been

observed. The molecular weight of glycosylated ramucirumab is 146756 Da.⁽¹⁵⁾

Indications and usage, dosage

- **Indication:** Ramucirumab in combination with FOLFIRI (irinotecan, folinic acid and 5-fluorouracil) is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and fluoropyrimidine.
- **Dosage and Administration:** Ramucirumab should not be administered as an intravenous push or bolus.

The recommended dose of Ramucirumab is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration. Continue Ramucirumab until disease progression or unacceptable toxicity.

Other uses of ramucirumab

- Gastrointestinal cancers
- Lung cancer
- Metastatic breast cancer

Table 1: Comparison of Ramucirumab with other drugs available in the market

Sr. No.	Drug name	Trade name/ Company	Mechanism of action	Pharmacokinetic
1.	Ramucirumab	Cyramza/Eli Lilly and Company	Ramucirumab is a vascular endothelial growth factor receptor 2 antagonist that specifically binds VEGF receptor-2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells.	The mean (% coefficient of variation [CV%]) clearance for Ramucirumab is 0.015 L/hour (30%) and the mean terminal half-life is 14 days.
2.	Irinotecan	Camptosar/ Pfizer	Irinotecan functions as a potent inhibitor of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription.	Protein binding - <60% Metabolism- Hepatic glucuronidation Biological Half life- 6-12 hours Excretion- Biliary and renal
3.	Capecitabine	Xeloda/ Hikma Pharmaceuticals	In vivo capecitabine gets converted to 5-fluorouracil (5-FU). Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) which are mainly responsible for their anticancer effects.	Bioavailability- Extensive Protein binding-<60% Metabolism- Hepatic to 5'-DFCR, 5'-DFUR(Inactive), Neoplastic tissue, 5'-DFUR to active fluorouracil Biological Half-life- 38-45 minutes Excretion- Renal (95.5%), Faecal (2.6%)
4.	Cetuximab	Erbitux/ Eli Lilly	Cetuximab binds to the extracellular domain of the EGFR(Epidermal growth factor receptor) preventing its binding	Biological Half-life 114 hrs

			with its endogenous ligand, blocking the receptor-dependent transduction pathway and providing many antitumor effects, involving cell-cycle arrest, induction of apoptosis, and inhibition of angiogenesis, inhibition of metastasis, internalization and down regulation of the EGFR.	The volume of the distribution for cetuximab is independent of dose and is approximated at 2–3 L/m ² .
5.	Oxaliplatin	Eloxatin/ Sanofi	Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoquo and diaquo DACH platinum, which covalently bind with macromolecules causing crosslinks and inhibiting DNA replication and transcription.	Bioavailability- Complete Biological Half-life- 10-25 min Excretion- Renal
6.	5-FU (Fluorouracil Injection)	Adrucil (Euphoria Healthcare Pharmacy)	5-Flouro Uracil causes irreversible inhibition of thymidylate synthase	Bioavailability- 28 to100% Protein binding- 8 to12% Metabolism- Intracellular and hepatic (CYP-mediated) Biological Half-life- 16 min Excretion- Renal
7.	Folinic acid	<ul style="list-style-type: none"> Leucovorin/ Bedford Laboratories 	<p>Folinic acid is a 5-formyl derivative of tetrahydrofolic acid. It is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate), thus has vitamin activity equivalent to that of folic acid. Since it does not require the action of dihydrofolate reductase for its conversion, its function as a vitamin is unaffected by inhibition of this enzyme by drugs such as methotrexate. This is the classical view of folinic acid rescue therapy</p> <p>Folinic acid allows for some purine/pyrimidine synthesis to occur in the presence of dihydrofolate</p>	Bioavailability- Dose dependent Protein binding- 15% Biological Half-life- 6.2 hours Excretion- Urinary

			reductase inhibition, so some normal DNA replication processes can proceed.	
8.	Panitumumab	Vectibix/ Amgen	Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR. Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR.	Pharmacokinetic data Biological Half-life- 9.4 days The pharmacokinetics (PK) of panitumumab shows the so-called target-mediated disposition behavior. However, the PK is approximately linear at clinical doses, and the terminal half-life for a typical male patient of 80 kg and 60 years of age with colorectal cancer is about 9.4 days.
9.	Regorafenib	Stivarga/ Bayer	Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically.	Pharmacokinetic data Bioavailability- 69-83% Protein binding- 99.5% Metabolism- Hepatic Biological Half-life-20-30 hours Excretion- Faces(71%), Urine(19%)

10.	Aflibercept	Zaltrap/ Sanofi	Aflibercept is a recombinant fusion protein that acts as a decoy receptor for the ligands, vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF). It prevents these ligands to binding to endothelial receptors, VEGFR-1 and VEGFR-2, to suppress neovascularization and decrease vascular permeability.	Cmax of free aflibercept in the plasma is 0.02 mcg/mL attained in 1 to 3 days. Volume of distribution of free aflibercept 6L. Half-life (t1/2)- 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.
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Mechanism of action: Ramucirumab is a vascular endothelial growth factor receptor 2 (VEGFR2) antagonists that specifically binds VEGF Receptor 2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C and VEGF-D. As a result, ramucirumab inhibits ligand - stimulated activation of VEGF Receptor 2, thereby inhibiting ligand - induced proliferation, and migration of human endothelial cells. Ramucirumab binds specifically to the extracellular domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2) inhibiting VEGF-stimulated activation of VEGFR-2 and p44/p42 mitogen-activated protein kinases and neutralizing VEGF-induced mitogenesis of human endothelial cells. Ramucirumab does not involve Fc-region effector functions as a part of its mode of action.⁽¹⁶⁾

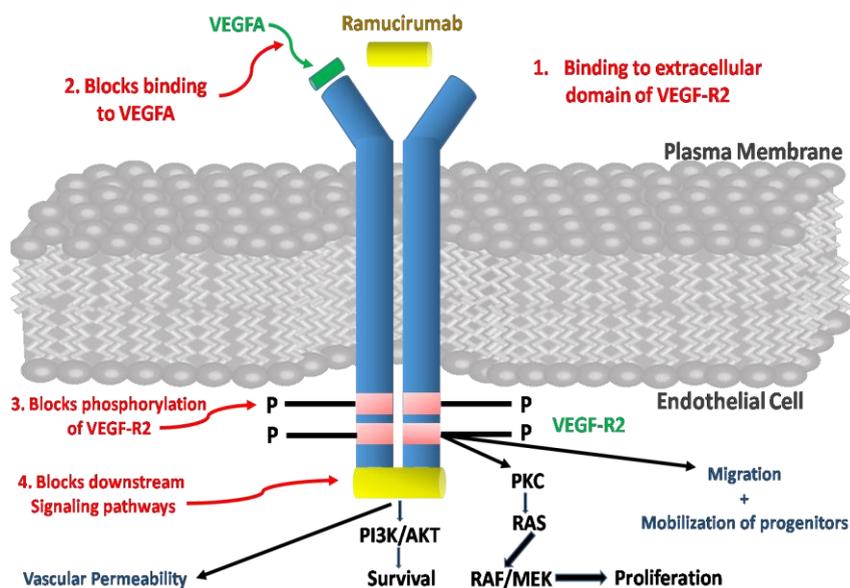


Fig. 3 Mechanism of action of Ramucirumab⁽¹⁷⁾

- Ramucirumab binds specifically to VEGFR-2 (part 1)
- blocks VEGF/VEGFR-2 interaction (part 2)
- (part 3) inhibits VEGF-stimulated receptor phosphorylation in endothelial cell resulting in disruption of downstream signalling
- (part 4) AKT, protein kinase B; MEK, mitogen-activated protein kinase kinase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma.

Pharmacokinetics: Ramucirumab follows nonlinear pharmacokinetics. The clearance decreases disproportionately with increasing dose and number of infusion.⁽¹⁸⁾ After single infusion of 8 mg/kg dose and 10 mg/kg dose, the elimination T_{1/2} is approximately 123 h and 110 h respectively. The target trough level of ramucirumab has been found to be approximately 20 µg/ml and the approximate doses of ramucirumab that can maintain these trough are 6 mg/kg every week, 8 mg/kg every two weeks, and 10 mg/kg administered

every three weeks.⁽¹⁹⁾ The pharmacokinetic (PK) characteristics of ramucirumab are similar for patients with gastric cancer, NSCLC, and mCRC based on a population PK analysis. The mean (% coefficient of variation [CV%]) clearance for ramucirumab is 0.015 L/hour (30%) and the mean terminal half-life is 14 days (20%). Age, sex, and race had no clinically meaningful effect on the PK of ramucirumab based on a population PK analysis.

Renal Impairment: Based on a population PK analysis, no clinically meaningful differences in the average concentration of ramucirumab at steady state (C_{ss}) has been observed in patients with mild (calculated creatinine clearance [CL_{cr}] 60-89 mL/min, n=687), moderate (CL_{cr} 30-59 mL/min, n=244) or severe (CL_{cr} 15-29 mL/min, n=6) renal impairment compared to patients with normal renal function (CL_{cr} ≥90 mL/min, n=697).

Hepatic impairment: No formal studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ramucirumab. Based on PopPK, ramucirumab exposure in patients with mild hepatic impairment (total bilirubin >1.0-1.5 upper limit of normal (ULN) and any AST or total bilirubin ≤1.0 ULN and AST >ULN) or moderate hepatic impairment (total bilirubin > 1.5-3.0 ULN and any AST) was similar to patients with normal hepatic function (total and AST ≤ ULN). Ramucirumab has not been studied in patients with severe hepatic impairment (total bilirubin >3.0 ULN and any AST).

Pre Clinical Study: As ramucirumab does not cross-react with the murine homolog of human VEGFR-2, certain *in vivo* evaluations were done using a surrogate of ramucirumab, DC101, a rat antimouse VEGFR-2 specific monoclonal antibody.⁽²⁰⁾ DC101 got binded with high affinity to the extracellular domain of mouse VEGFR-2 and inhibited VEGF-mediated signalling *via* VEGFR-2. DC101 exhibited antitumour activity in several mouse xenograft models as well.⁽²¹⁾ *In vivo* experiments were conducted using DC101 in a murine model of colon carcinoma liver metastases, to investigate the hypothesis that blockade of the VEGF function may lead to both inhibition of angiogenesis and decreased endothelial cell survival. Human colon carcinoma cells were injected into the spleen of a nude mice to produce liver metastases. After 7 days of tumour growth, mice received either DC101 or vehicle. Blocking VEGFR-2 activation with the DC101 antibody caused decreased vessel counts in liver metastases from

human colon carcinoma cells. An increase in tumour cell death in DC101-treated mice was also seen. Furthermore, those studies demonstrated that blockade of VEGFR-2 led to endothelial cell apoptosis.⁽²²⁾ When combined with various other agents in mouse models, DC101 exhibited an enhanced reduction in tumour growth rate.^(23,24,25) In one study, DC101 combined with IFL inhibited growth of the colorectal carcinoma cell line HT-29. This cell line is resistant to oxaliplatin and S12, a murine antibody that blocks circulating VEGF in a similar way to bevacizumab. By contrast, inhibition of tumour growth was not seen in animals treated with IFL plus S12, oxaliplatin plus S12, or control. These results suggest that inhibition of VEGFR-2 could inhibit growth in colorectal tumours resistant to other antiangiogenic.^(22,26)

Clinical Study: A case study of RCB and FOLFIRI versus placebo plus FOLFIRI, in patients with mCRC clearly indicates a greater overall survival of patients who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. A total of 1072 patients were randomized (1:1) to receive either RCB (n=536) at 8 mg/kg as an intravenous infusion or placebo (n=536), in combination with FOLFIRI: irinotecan 180 mg/m² administered intravenously over 90 minutes and folinic acid 400 mg/m² administered intravenously simultaneously over 120 minutes; followed by 5-fluorouracil 400 mg/m² intravenous bolus over 2 to 4 minutes; followed by 5-fluorouracil 2400 mg/m² administered intravenously by continuous infusion over 46 to 48 hours. Treatment cycles on both arms were repeated every 2 weeks. Patients who discontinued one or more components of treatment because of an adverse event were permitted to continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival and the supportive efficacy outcome measure was progression free survival. Demographic and baseline characteristics were similar between treatment arms. Median age was 62 years; 57% of patients were men; 76% were White and 20% Asian; 49% had ECOG PS 0; 49% of patients had KRAS mutant tumors; and 24% of patients had <6 months from time to disease progression after beginning first-line treatment. Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive RCB plus FOLFIRI compared to patients randomized to receive placebo plus FOLFIRI. The treatment effect was consistent across the pre-specified stratification factors.

Randomized Trial of RCB plus FOLFIRI versus Placebo plus FOLFIRI in mCRC

	RCB + FOLFIRI N=536	Placebo + FOLFIRI N=536
Overall Survival		
Number of deaths (%)	372 (69%)	397 (74%)
Median – months (95% CI)	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)
Hazard Ratio (95% CI)	0.85 (0.73, 0.98)	
Stratified Log-rank p-value	0.023	
Progression-free Survival		
Number of events (%)	476 (89%)	494 (92%)
Median – months (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
Hazard Ratio (95% CI)	0.79 (0.70, 0.90)	
Stratified Log-rank p-value	<0.001	

Abbreviations: CI = confidence interval.

Adverse Drug Reaction (ADRs)

Adverse Drug Reactions (ADRs) which were reported in patients with mCRC is listed below:

Table ADRs reported in $\geq 5\%$ of Ramucirumab treated patients in RAISE (full form)

System organ class	Frequency	ADR	Cyranza plus FOLFIRI (N=529)		Placebo plus FOLFIRI (N=528)	
			All grades toxicity (%)	Grade ≥ 3 toxicity (%)	All grades toxicity (%)	Grade ≥ 3 toxicity (%)
Blood and lymphatic system disorders	Very Common	Neutropenia	58.8	38.4	45.6	23.3
	Very Common	Thrombocytopenia	28.4	3.0	13.6	0.8
Metabolism and nutrition disorders	Common	Hypoalbuminaemia	5.9	1.1	1.9	0.0
Vascular disorder	Very Common	Hypertension	26.1	11.2	8.5	2.8
Respiratory, thoracic, and mediastinal disorders	Very Common	Epistaxis	33.5	0.0	15.0	0.0
Gastrointestinal disorders	Very Common	Gastrointestinal haemorrhage events	12.3	1.9	6.8	1.1
	Very common	Stomatitis	30.8	3.8	20.8	2.3
Renal and urinary disorders	Very Common	Proteinuria*	17.0	3.0	4.5	0.2
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysesthesia syndrome	12.9	1.1	5.5	0.4
General disorders and administration site disorders	Very Common	Peripheral oedema	20.4	0.2	9.1	0.0

* Includes cases of nephrotic syndrome.

In the RAISE study, in mCRC patients treated with ramucirumab plus FOLFIRI, the most frequent ($\geq 1\%$) ADR that led to the discontinuation of ramucirumab was proteinuria (1.5%). The most frequent ($\geq 1\%$) ADRs leading to discontinuation of one or more components of FOLFIRI were: neutropenia (12.5%), thrombocytopenia (4.2%), diarrhoea (2.3%) and stomatitis (2.3%). The most frequent component of FOLFIRI to be discontinued was the 5-FU bolus.⁽¹⁶⁾

More common adverse effect of Ramucirumab are

- Diarrhea
- High blood pressure
- Headache

Future Directions and Conclusion

Ramucirumab alone or in combination with chemotherapy has demonstrated significant improvement in patient with advanced colorectal cancer. Ramucirumab is a landmark treatment for colorectal cancer but the early disease progression in most patients suggests that the benefit to select patients who could benefit from this drug is an important issue to consider for the future development and use of ramucirumab in this disease. An important issue in favor of ramucirumab is its potential use in all-comers without histotype selection, because patients with squamous cell carcinoma seemed to have similar benefit from ramucirumab compared with the non-squamous group. For this reason, ramucirumab could be a good option for pretreated patients with squamous cell carcinoma, potentially being the only anti-angiogenic agent for this histotype, as bevacizumab is registered for non-squamous cell carcinoma. Nevertheless, in the era of targeted agents, a biomarker-selected population should be considered the standard approach. But as regards ramucirumab, we can only remain hopeful that the identification of a specific biomarker might help select patients who will respond. Clearly, an adequate selection would be paramount for achieving better results and containing the expenses for this drug, which has a prohibitive cost (\$7,140 per infusion).⁽²⁷⁾

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