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ORIGINAL ARTICLE

Sequential biological therapies in metastatic colorectal cancer (mCRC): a cost comparison analysis for wild-type RAS mCRC patients in Brazil

Sequenciamento de biológicos em câncer colorretal metastático (CCRm): uma análise de comparação de custos para pacientes CCRm RAS selvagens no Brasil

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Keywords:
metastatic colorectal cancer, bevacizumab, cetuximab, panitumumab, multiple lines, TML

ABSTRACT

Objective: To compare the treatment costs of different sequences of regimens including monoclonal antibodies in metastatic colorectal cancer (CRCm) treatment for the Brazilian Supplementary Healthcare System. **Methods:** Sixteen scenarios were analyzed, each one comparing a sequence of bevacizumab TML plus an anti-EGFR therapy in the third–line with another sequence without bevacizumab TML (non-Bev TML) in patients with CRCm wild-type RAS. The anti-EGFRs cetuximab and panitumumab were included. The monthly and total costs of the therapeutic sequences were compared per patient. **Results:** The sequences with Bev TML were cost-saving in 50% of all scenarios, and especially observed over regimens starting with cetuximab in the first-line treatment. Regarding scenarios which the non-Bev TML sequences were less costly, they all started with bevacizumab followed by an anti-EGFR biologic drug. **Conclusion:** The Bev TML regimens were cost-saving compared to scenarios of non-Bev TML which started with cetuximab, and sequential use of bevacizumab beyond progression and the addition of an anti-EGFR biologic drug in the third-line for mCRC treatment. Considering the remaining scenarios in which Bev-TML was not cost-saving, those starting with Bev presented lower costs in total. Therefore, starting a treatment with bevacizumab seems to enable a more rational management of resource usage, as well as, to allow physicians to add a biologic drug in the third-line, potentially enhancing the long term management of wild-type RAS mCRC.

Palavras-chave:
câncer colorretal metastático, bevacizumabe, cetuximabe, panitumumabe, múltiplas linhas, TML

RESUMO

Objetivo: Comparar o custo de tratamento de diferentes sequências de regimes incluindo anticorpos monoclonais no tratamento de câncer colorretal metastático (CCRm) no Sistema de Saúde Suplementar Brasileiro. **Métodos:** Dezesseis cenários foram analisados, cada um comparando uma sequência de bevacizumabe TML (Bev TML) mais um anti-EGFR em terceira linha, com outra sequência sem bevacizumabe TML (não-Bev TML). Os anti-EGFRs cetuximabe e panitumumabe forma incluídos. Os custos mensais e totais do sequenciamento terapêutico foram comparados por pacientes. **Resultados:** As sequências com Bev TML trouxeram economia de recursos em 50% de todos os cenários, e especialmente comparado aos regimes iniciando com cetuximabe em primeira linha de tratamento. Considerando os cenários em que os regimes não-Bev TML apresentaram menos custo, todos iniciaram o sequenciamento com bevacizumabe seguido de um medicamento biológico anti-EGFR. **Conclusões:** Os regimes Bev TML apresentaram economia de recursos comparado aos cenários com não-Bev TML que iniciaram com cetuximabe, apesar do uso de bevacizumabe em múltiplas linhas e da adição de medicamento biológico anti-EGFR em terceira linha no tratamen-

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to de CCRm. Considerando os demais cenários em que os regimes Bev-TML não apresentaram economia de recursos, os regimes iniciando com Bev apresentaram menor custo total. Desta maneira, iniciar o tratamento com bevacizumabe proporciona um gerenciamento mais racional de uso de recursos, assim como, permite aos médicos adicionar um medicamento biológico em terceira linha, potencialmente melhorando o manejo a longo prazo do CCRm com RAS selvagem.

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide, with about 1,361,000 new cases and 614,000 deaths in 2012 (GLOBOCAN, 2012). In Brazil, the CRC is the third most common incident of tumors in the population, excluding non-melanoma skin. It is the third most frequent incident in men and second in women. In 2014, it was estimated at around 33 thousand new cases of this disease in the country (INCA, 2014).

In Brazil, the proportion of cases between men and women is 46.2% and 53.8% (INCA, 2014). Approximately 25% of patients present metastatic disease at diagnosis and about 50% of patients will develop metastatic disease (GLOBOCAN, 2012; Van Cutsem & Oliveira, 2009).

Over the past 10 years, various combinations of chemotherapy were investigated for the treatment of metastatic CRC (mCRC) (Jackson et al., 2009). Chemotherapy combinations recommended usually contain fluorouracil (5-FU) or capecitabine, associated with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) (Colucci et al., 2005; Schmoll et al., 2007; Fuchs et al., 2007; Van Cutsem et al., 2001; de Gramont et al., 2000; Douillard et al., 2000; Saltz et al., 2000).

Recently, molecular targeted therapies have had special attention from the medical community worldwide. Especially in the treatment of mCRC, bevacizumab (Bev), a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF), has shown favorable results when combined with chemotherapy regimens in phase III studies (Hurwitz et al., 2004; Welch et al., 2010; Guan et al., 2011; Hurwitz et al., 2005). Cetuximab (Cet) and panitumumab (Pan), monoclonal antibodies that target the epidermal growth factor receptor (EGFR), also demonstrated favorable results in combination with chemotherapy in the treatment of mCRC, but their benefits are restricted to patients with wild-type RAS (wtRAS) (Bokemeyer et al., 2012; Sobrero et al., 2008; Peeters et al., 2010), while Bev can be included as a treatment option for mCRC patients regardless of their RAS status (Fuchs et al., 2007; Hurwitz et al., 2004; Saltz et al., 2008). Therapy combining these agents is the most commonly used regimen for mCRC in Brazil.

The best sequence of use of these therapies, particularly regarding biological or molecular targeted therapies in mCRC, is still undefined (Bennouna et al., 2013). In 2012, ML18147 trial (Bennouna et al., 2013) – a randomized, open, multicenter study – was published. This study assessed the continuous use of Bev associated with chemotherapy (FOLFOX, FOLFIRI) in second-line (2L) treatment in patients who were refractory to chemotherapy with Bev in first-line (1L) therapy. The study showed higher overall survival rates in patients treated with Bev associated with chemotherapy through multiple lines (TML) in mCRC.

With a similar approach, in 2014, Rautenberg et al. evaluated clinical and economic outcomes of sequences with Bev in 1L and 2L, followed by an anti-EGFR in the third-line (3L). The authors concluded that Bev TML followed by 3L anti-EGFR could potentially yield better health outcomes, associated with saving costs when compared to 1L anti-EGFR regimens.

The aim of this study was to compare treatments of different sequences of therapy that include Bev, Cet or Pan for the treatment of mCRC from a payer perspective in the Brazilian Supplementary Healthcare System. None other biologic drug is available in Brazil for mCRC treatment.

Methods

The treatment sequences described in the ML18147 trial (Bennouna et al., 2013) were compared to commonly used regimens to treat mCRC, according to main Phase III randomized clinical trials summarized in Table 1 and the local products labels.

In order to compare the economic outcomes, the monthly cost and the total cost of the sequence per patient, according to the 1L, 2L and 3L combinations, calculations were made using a tool developed in Microsoft Excel® (Microsoft, Redmond, WA), which allowed estimating the costs associated with the treatment of mCRC.

The focus of the analysis was the direct costs of treatment, including drug acquisition, intravenous (IV) administration fees and supportive care in the private healthcare system. Neither indirect costs, nor the costs of managing adverse events were included in the calculations.

Scenarios

To estimate the treatment costs of the use of Bev or Cet/Pan sequences, 16 different comparison scenarios were developed (Table 2). These drug regimens are the most widely used treatment for mCRC in 1L and 2L in Brazil, and they are described in most treatment guidelines for metastatic disease (Van Cutsem & Oliveira, 2009; Sobrero et al., 2008; Peeters et al., 2010; Rautenberg et al., 2014; Van Cutsem et al., 2007; Chari et al., 2006; Glimelius & Oliveira, 2008; Glimelius & Oliveira, 2009; Nordlinger et al., 2009; Nordlinger et al., 2007; Papamichael et al., 2009; Van Cutsem & Oliveira, 2008).

Table 1. Studies referenced for bevacizumab and cetuximab

Study name	Study reference	Regimen	Outcomes
Bevacizumab			
NO16966	Saltz et al., 2008	Bev 5 mg/kg + FOLFOX4 vs. FOLFOX4	Primary Endpoint: mPFS – 9.4 mo vs. 8.0 mo (HR, 0.83; 97.5% CI, 0.72 to 0.95; p=0.0023) Secondary Endpoint: mOS - 21.3 mo vs. 19.9 mo (HR, 0.89; 97.5% CI, 0.76 to 1.03; p=0.077)
ML18147	Bennouna et al., 2013	Bev 5 mg/kg + simplified FOLFIRI/ Bev 5 mg/kg + FOLFOX 6 vs. simplified FOLFIRI/ FOLFOX	Primary Endpoint: mOS – 11.2 mo vs. 9.8 mo (hazard ratio 0.81, 95% CI 0.69–0.94; unstratified log-rank test p=0.0062) Secondary Endpoint: mPFS – 5.7 mo vs. 4.1 mo (HR 0.68, 95% CI 0.59–0.78; unstratified log-rank p<0.0001)
E3200	Giantonio et al., 2007	Bev 10 mg/kg + FOLFOX4 vs. FOLFOX4	Primary Endpoint: mOS – 12.9 mo vs. 10.8 mo (HR=0.75; p= 0.0011) Secondary Endpoint: mPFS – 7.3 mo vs. 4.7 mo (HR=0.61; p < 0.0001)
BICC-C	Fuchs et al., 2007	Bev 5 mg/kg + FOLFIRI vs. Bev 7.5 mg/kg + mIFL	Primary Endpoint: mPFS – 11.2 mo vs. 8.3 mo (p=0.28) Secondary Endpoint: mOS – 28.0 mo vs. 19.2 mo (HR for death =1.79; 95% CI, 1.12 - 2.88; p=0.037)
CALGB80405	Venook et al., 2014	Bev 5 mg/kg + mFOLFOX6/ Bev 5 mg/kg + FOLFIRI vs. Cet 400 mg/m^2 1st cycle , then 250 mg/m^2 weekly + mFOLFOX6/ Cet 400 mg/m^2 1st cycle, then 250 mg/m^2 weekly + FOLFIRI	Primary Endpoint: mOS – 29.04 mo vs. 29.93 mo (HR=0.92, 95% CI 0.78, 1.09; p=0.34) Secondary Endpoint: mPFS – 10.84 mo vs. 10.45 mo (statistical analysis not published)
Cetuximab and BSC			
CRYSTAL	Van Cutsem et al., 2009	Cet 400 mg/m^2 1st cycle , then 250 mg/m^2 weekly + FOLFIRI vs. FOLFIRI	Primary Endpoint: mPFS – 8.9 mo vs. 8.0 mo (HR=0.85; 95% CI, 0.72 to 0.99; p=0.048) Secondary Endpoint: mOS – 19.9 mo vs. 18.6 mo (HR=0.93; 95% CI, 0.81 to 1.07; p=0.31)
EPIC	Sobrero et al., 2008	Cet 400 mg/m^2 1st cycle , then 250 mg/m^2 weekly + IRI vs. IRI	Primary Endpoint: mOS – 10.7 mo vs. 10.0 mo (HR=0.975; 95% CI, 0.854 to 1.114; p=0.71) Secondary Endpoint: mPFS – 4.0 mo vs. 2.6 mo (HR=0.692; 95% CI, 0.617 to 0.776; p<0.0001)
CO.17	Karapetis et al., 2008	Cet 400 mg/m^2 1st cycle , then 250 mg/m^2 weekly + BSC vs. BSC	Primary Endpoint: mOS – 9.5 mo vs. 4.8 mo (HR=0.55; 95% CI, 0.41 to 0.74; p<0.001) Secondary Endpoint: mPFS – 3.7 mo vs. 1.9 mo (HR=0.40; 95% CI, 0.30 to 0.54; p<0.001)
Panitumumab			
Peeters	Peeters et al., 2010	Pan 6 mg/kg + FOLFIRI vs. FOLFIRI	Coprimary Endpoints: mPFS – 5.9 mo vs. 3.9 mo (HR=0.73; 95% CI, 0.59 to 0.90; p=0.004); mOS – 14.5 mo vs. 12.5 mo (HR=0.85, 95% CI, 0.70 to 1.04; p=0.12)
Van Cutsem	Van Cutsem et al., 2007	Pan 6 mg/kg + BSC vs. BSC	Primary Endpoint: mPFS – 8.0 weeks vs. 7.3 weeks (HR=0.54; 95% CI, 0.44 to 0.66, p<0.0001) Secondary Endpoint: mOS –HR=1.00; 95% CI, 0.82 to 1.22

*Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care; mPFS: median progression free survival; mOS: median overall survival; HR: hazard ratio

Treatment duration

Two different approaches were used to estimate the treatment duration. Each scenario was evaluated based on median progression-free survival (PFS) data from randomized clinical trials and also on the estimated average treatment duration for each line from Rautenberg et al (2014). Data on treatment duration are described in Table 3.

Costs

The acquisition costs for each biological and chemotherapeutic drug included in the analysis were obtained from local official databases. Acquisition costs per milligram of each drug are shown in Table 4.

Supportive care and intravenous administration costs were obtained from Brazilian Hierarchical Classification of

Table 2. Treatment regimens compared in the cost analysis

	Bevacizumab Multiple Line	Non-Bevacizumab Multiple Lines	
Scenario 1	1L	Bev + FOLFOX4 (NO16966)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + simplified FOLFIRI (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 2	1L	Bev + FOLFIRI (BICC-C)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + FOLFOX6 (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 3	1L	Bev + mFOLFOX6 (CALGB)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + simplified FOLFIRI (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 4	1L	Bev + FOLFIRI (CALGB)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + FOLFOX6 (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 5	1L	Bev+ FOLFOX4 (NO16966)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + simplified FOLFIRI (ML18147)	Pan + FOLFIRI (Peeters)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 6	1L	Bev + FOLFIRI (BICC-C)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + FOLFOX6 (ML18147)	Pan + FOLFIRI (Peeters)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 7	1L	Bev + FOLFOX4 (NO16966)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + simplified FOLFIRI (ML18147)	Pan + FOLFIRI (Peeters)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 8	1L	Bev+ FOLFIRI (BICC-C)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + FOLFOX6 (ML18147)	Pan + FOLFIRI (Peeters)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 9	1L	Bev + FOLFOX4 (NO16966)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + simplified FOLFIRI (ML18147)	Cet + IRI (EPIC)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 10	1L	Bev + FOLFIRI (BICC-C)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + FOLFOX6 (ML18147)	Cet + IRI (EPIC)
	3L	Cet + BSC (CO.17)	BSC (CO.17)
Scenario 11	1L	Bev + FOLFOX4 (NO16966)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + simplified FOLFIRI (ML18147)	Cet + IRI (EPIC)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 12	1L	Bev + FOLFIRI (BICC-C)	Bev + FOLFOX 4 (NO16966)
	2L	Bev + FOLFOX6 (ML18147)	Cet + IRI (EPIC)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 13	1L	Bev + FOLFOX4 (NO16966)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + simplified FOLFIRI (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 14	1L	Bev + FOLFIRI (BICC-C)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + FOLFOX6 (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 15	1L	Bev + mFOLFOX6 (CALGB)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + simplified FOLFIRI (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)
Scenario 16	1L	Bev + FOLFIRI (CALGB)	Cet + FOLFIRI (CRYSTAL)
	2L	Bev + FOLFOX6 (ML18147)	Bev + FOLFOX4 (E3200)
	3L	Pan + BSC (Van Cutsem)	BSC (CO.17)

*FOLFOX: bolus and infusion fluorouracil/ leucovorin + oxaliplatin; FOLFIRI: bolus and infusion fluorouracil/ leucovorin + irinotecan; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab

Table 3. Estimated treatment time based on standard treatment time and PFS reported on clinical trials

Treatment Line	Study Name	Regimen	PFS (months)	Average treatment duration*
1L	NO16966	Bev 5 mg/kg+FOLFOX4	9.4	6.1
1L	BICC-C	Bev 5 mg/kg+FOLFIRI	11.2	6.1
1L	CALGB80405	Bev 5 mg/kg+mFOLFOX6	10.8	6.1
1L	CALGB80405	Bev 5 mg/kg+FOLFIRI	10.8	6.1
1L	CRYSTAL	Cet 250 mg/m^2+FOLFIRI	9.9	6.1
1L	CALGB80405	Cet 250 mg/m^2+FOLFIRI	10.4	6.1
2L	E3200	Bev 10 mg/kg+FOLFOX4	7.3	4.0
2L	ML18147	Bev 5 mg/kg+ simplified FOLFIRI	5.7	4.0
2L	ML18147	Bev 5 mg/kg+FOLFOX6	5.7	4.0
2L	EPIC	Cet 250 mg/m^2 + IRI	4.0	4.0
2L	Peeters	Pan 6 mg/kg+ FOLFIRI	5.9	4.0
3L	CO.17	Cet 250 mg/m^2+ BSC	3.7	2.7
3L	CO.17	BSC	1.9	2.7
3L	Van Cutsem	Pan 6 mg/kg+BSC	1.9	2.7

*Rautenberg et al. †FOLFOX: bolus and infusion fluorouracil/ leucovorin + oxaliplatin; FOLFIRI: bolus and infusion fluorouracil/ leucovorin + irinotecan; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab

Table 4. Description of costs per mg concerning biological and chemotherapeutic treatments evaluated in the study

Biological treatment	Cost per mg (R$)*
Bevacizumab	13.59
Cetuximab	7.71
Panitumumab	12.86
Chemotherapeutic treatment	**Cost per mg (R$)***
5-Fluorouracil (5-FU)	0.04
Oxaliplatin	38.26
Irinotecan	16.57
Folinic acid	1.01

*Source: CMED (April 2015) – Ex-Factory price, ICMS 18%

Medical Procedures (CBHPM) table from the Brazilian Medical Association and are described in Tables 5 and 6.

In the case of individual drugs with the same duration of the cycle, it was considered that they are administered sequentially with the cost of a single administration.

Results

The results presented in Tables 7-24 refer to the average cost for treatment of a single patient, considering the amounts described in the "Costs" section that comprises each treatment regimen.

To confirm the robustness of the data, a one-way sensitivity analysis was performed to measure the impact of each parameter and assess the uncertainty of the results. The parameters described as shown in Table 25 varied in a 10% range (up and down). A sensitivity analysis within the same conditions was conducted for all scenarios.

A one-way analysis was performed and revealed that, in all scenarios, the maximum variation was 6% and occurred varying the biologic drug cost acquisition, weight and 1L treatment (months). All simulations showed that Bev TML sequences were more influenced by the patients' body surface area (BSA) and weight, Bev acquisition price and months of treatment (1L and 2L treatments). For Non-TML regimens, it was observed that besides those parameters, the total cost treatment was influenced by cetuximab and panitumumab acquisition prices.

Discussion

According to the results of the ML18147 trial (Bennouna et al., 2013), Bev resistance seems to occur at different times and with different mechanisms than chemotherapy resis-

Table 5. Supportive care and intravenous administration

Procedure	Cost (R$)	Period
Best supportive care*	255.74	Monthly
Administration of intravenous therapy	184.38	Per adm
Administration of infusion therapy	251.49	Infusion (≥22h)

*see Table 6 for further information

Table 6. Supportive care costs (per month)

Procedure	Quantity	Cost per unit (R$)*	Cost per month (R$)
Paliative Radiotherapy	0.17	82.11	13.69
Physical examination and history (medical consultation)	0.33	65.45	21.82
Morphine 10 mg (tablet)	90.00	0.47	42.21
Osteolysis inhibitor	1.00	1'089.30	108.93
Radiograph (bone metastasis control)	0.25	308.94	7.72
Radiograph (lung metastasis control)	0.25	35.13	1.32
Abdominal computarized tomography	0.17	620.38	31.02
Complete blood count (CBC)	0.33	12.34	4.11
Glucose dosage	0.33	5.56	1.85
Urea dosage	0.33	5.56	1.85
Creatinine dosage	0.33	5.56	1.85
Alkaline phosphatase dosage	0.33	10.24	3.41
GT gamma	0.33	10.24	3.41
Glutamic oxalacetic transminase dosage	0.33	10.24	3.41
Glutamic pyruvate transminase dosage	0.33	10.69	3.56
Sodium dosage	0.33	5.56	1.85
Potassium dosage	0.33	5.56	1.85
Calcium dosage	0.33	5.56	1.85
TOTAL (R$)	**255. 74**		

*Brazilian Hierarchical Classification of Medical Procedures (CBHPM), 2014

tance, suggesting that Bev remains effective after the development of resistance to chemotherapy. Therefore, the factors that could help define the best sequence of treatment – such as the expression of wtRAS; regimens with higher response rates to turn initially unresectable lesions into resectable lesions; performance status; and acceptable toxicities of patients – should be considered (Cartwright, 2012). Also, based on the ML18147 trial, it is possible to assume that the use of Bev beyond progression can also be studied in other tumors in other parts of the body such as the lung and breast.

Two randomized phase III clinical trials aimed to compare the efficacy of Bev or Cet in first-line treatment of mCRC, FIRE-3 (Heinemann et al., 2014) and CALGB 80405 (Venook et al., 2014). In FIRE-3, patients were randomized to receive FOLFIRI plus Cet or FOLFIRI plus Bev with a primary endpoint of response rate according to RECIST. In the intent-to-treat (ITT) population (KRAS exon 2 wild type), there was no significant difference in the primary endpoint between treatment arms (odds ratio 1·18; p=0·18). Progression-free survival (PFS) was also similar between both groups (hazard ratio [HR] 1·06; p=0·55), however, overall survival (OS), a secondary endpoint, was better in the Cet arm (hazard ratio [HR], 0.77; p=0.017). This finding is still to be explained, although the Bev group in this study seems to have an outlier result of OS survival when compared to other studies (CALGB 80405 (Venook et al., 2014), TRIBE (Cremolini et al., 2015); hypothesizing that this arm could have received less efficacy treatments in subsequent lines.

The results from the CALGB 80405 study (Venook et al., 2014) were presented as well in 2014, demonstrating similar efficacy outcomes (overall survival and progression-free survival) of Bev and Cet combined with chemotherapy (mFOLFOX6 or FOLFIRI) in the first-line treatment of mCRC in patients with wild-type KRAS. The quality of life was assessed at baseli-

Table 7. Total costs for each treatment regimen – Scenario 1

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			423'828.06		287'683.40
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CRYSTAL)	9.9	291'047.28	6.1	180'104.87
2L	Bev 10 mg + FOLFOX (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			539'479.55		316'804.34

* ???

Table 8. Total costs for each treatment regimen – Scenario 2

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (BICC-C)	11.2	270'272.94	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			485'846.29		300'700.65
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CRYSTAL)	9.9	291'047.28	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			539'479.55		316'804.34

*Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; BSC: best supportive care

Table 9. Total costs for each treatment regimen – Scenario 3

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + mFOLFOX6 (CALGB/SWOG 80405)	10.8	271'592.65	6.1	153'399.55
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			469'008.78		294'156.06
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CALGB/SWOG 80405)	10.4	305'644.96	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			554'347.24		316'804.34

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; BSC: best supportive care

Table 10. Total costs for each treatment regimen – Scenario 4

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (CALGB/SWOG 80405)	10.8	260'620.33	6.1	147'202.22
2L	Bev + FOLFOX6 (ML18147)	5.7	155.706.86	4.0	109'267.97
3L	Cet + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			476'193.69		300'700.65
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CALGB/SWOG 80405)	10.4	305'644.96	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			554'347.24		316'804.34

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; BSC: best supportive care

Table 11. Total costs for each treatment regimen – Scenario 5

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	Cet + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			423'781.87		287'632.40
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966, Saltz, 2008)	10.4	226'411.94	6.1	146'926.89
2L	Pan + FOLFIRI (Peeters, 2010)	5.9	14'797.16	4.0	98'845.53
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			372'695.00		246'462.92

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 12. Total costs for each treatment regimen – Scenario 6

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (BICC-C)	9.9	270'272.94	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			485'846.29		300'700.65
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Pan + FOLFIRI (Peeters, 2010)	5.9	14'797.16	4.0	98'845.53
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			372'695.00		246'462.92

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 13. Total costs for each treatment regimen – Scenario 7

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'642.69	2.7	31'176.46
Total			386'604.25		275'629.40
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Pan + FOLFIRI (Peeters, 2010)	5.9	14'797.16	4.0	98'845.53
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			372'695.00		246'462.92

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 14. Total costs for each treatment regimen – Scenario 8

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev 5 mg + FOLFIRI (BICC-C)	11.2	270'272.94	6.1	147'202.22
2L	Bev 5 mg + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	Pan 6 mg + BSC (Van Cutsem, 2007)	1.9	22'642.69	2.7	31'176.46
Total			448'622.48		288'646.65
Non-bevacizumab TML					
1L	Bev 5 mg + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Pan 6 mg + FOLFIRI (Peeters, 2010)	5.9	14'797.16	4.0	98'845.53
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			372'695.00		246'462.92

* Standard treatment duration ; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 15. Total costs for each treatment regimen – Scenario 9

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			423'828.06		287'683.40
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Cet + IRI (EPIC)	4.0	122'012.96	4.0	122'012.96
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			348'910.80		269'630.35

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 16. Total costs for each treatment regimen – Scenario 10

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (BICC-C)	11.2	270'272.94	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	CET + BSC - wild-type KRAS (CO.17)	3.7	59'866.50	2.7	44'230.45
Total			485'846.29		300'700.65
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Cet + IRI (EPIC)	4.0	122'012.96	4.0	122'012.96
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			348'910.80		269'630.35

* Standard treatment duration ; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; BSC: best supportive care

Table 17. Total costs for each treatment regimen – Scenario 11

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total			386'604.25		275'629.40
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Cet + IRI (EPIC)	4.0	122'012.96	4.0	122'012.96
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			348'910.80		269'630.35

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 18. Total costs for each treatment regimen – Scenario 12

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (BICC-C)	11.2	270'272.94	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total			448'622.48		288'646.65
Non-bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Cet + IRI (EPIC)	4.0	122'012.96	4.0	122'012.96
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			348'910.80		269'630.35

* Standard treatment duration ; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 19. Total costs for each treatment regimen – Scenario 13

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFOX4 (NO16966)	9.4	226'411.94	6.1	146'926.89
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total	386'604.25		275'629.40		
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CRYSTAL)	9.9	291'047.28	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			539'749.55		316'804.34

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 20. Total costs for each treatment regimen – Scenario 14

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (BICC-C)	11.2	270'272.94	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155'706.86	4.0	109'267.97
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total			448'622.48		288'646.65
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CRYSTAL)	9.9	291'047.28	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			539'749.55		316'804.34

* Standard treatment duration ; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 21. Total costs for each treatment regimen – Scenario 15

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + mFOLFOX6 (CALGB/SWOG 80405)	10.8	271'592.65	6.1	153'399.55
2L	Bev + simplified FOLFIRI (ML18147)	5.7	137'549.62	4.0	96'526.05
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total			431'784.97		282'102.06
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CALGB/SWOG 80405)	10.4	305'644.96	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			554'347.24		316'804.34

* Standard treatment duration; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 22. Total costs for each treatment regimen – Scenario 16

	Treatment Regimen	Treatment months (PFS)	Total Cost (R$)	Treatment months*	Total Cost (R$)
Bevacizumab TML					
1L	Bev + FOLFIRI (CALGB/SWOG 80405)	10.8	260'620.33	6.1	147'202.22
2L	Bev + FOLFOX (ML18147)	5.7	155.706.86	4.0	109'267.97
3L	Pan + BSC (Van Cutsem, 2007)	1.9	22'624.69	2.7	32'176.46
Total			438'969.88		288'646.65
Non-bevacizumab TML					
1L	Cet + FOLFIRI (CALGB/SWOG 80405)	10.4	305'644.96	6.1	180'104.87
2L	Bev + FOLFOX 4 (E3200)	7.3	248'216.37	4.0	136'008.97
3L	BSC - wild-type KRAS (CO.17)	1.9	485.90	2.7	690.49
Total			554'347.24		316'804.34

* Standard treatment duration ; PFS: progression-free survival; TML: through multiple lines; Bev: bevacizumab; Cet: cetuximab; Pan: panitumumab; BSC: best supportive care

Table 23. Total treatment cost per month based on PFS approach

	Months of treatment	Total treatment cost (R$)	Treatment cost/ month (R$)	Months of treatment	Total treatment cost (R$)	Treatment cost/ month (R$)
		Bev TML			Non-Bev TML	
Scenario 1	18.8	423'828.06	22'544.05	19.1	539'749.55	28'259.14
Scenario 2	20.6	485'846.29	23'584.77	19.1	539'749.55	28'259.14
Scenario 3	20.2	469'008.77	23'218.26	19.6	554'347.23	28'283.02
Scenario 4	20.2	476'193.69	23'573.94	19.6	554'347.23	28'283.02
Scenario 5	18.8	423'828.06	22'544.05	17.2	372'695.00	21'668.31
Scenario 6	20.6	485'846.29	23'584.77	17.2	372'695.00	21'668.31
Scenario 7	17.0	386'604.25	22'741.43	17.2	372'695.00	21'668.31
Scenario 8	18.8	448'622.48	23'862.90	17.2	372'695.00	21'668.31
Scenario 9	18.8	423'828.06	22'544.05	15.3	348'910.80	22'804.63
Scenario 10	20.6	485'846.29	23'584.77	15.3	348'910.80	22'804.63
Scenario 11	17.0	386'604.25	22'741.43	15.3	348'910.80	22'804.63
Scenario 12	18.8	448'622.48	23'862.90	15.3	348'910.80	22'804.63
Scenario 13	17.0	386'604.25	22'741.43	19.1	539'749.55	28'259.14
Scenario 14	18.8	448'622.48	23'862.90	19.1	539'749.55	28'259.14
Scenario 15	18.4	431'784.96	23'466.57	19.6	554'347.23	28'283.02
Scenario 16	18.4	438'969.88	23'857.06	19.6	554'347.23	28'283.02

Table 24. Total treatment cost per month based on average duration approach

	Months of treatment	Total treatment cost (R$)	Treatment cost/ month (R$)	Months of treatment	Total treatment cost (R$)	Treatment cost/ month (R$)
		Bev TML			Non-Bev TML	
Scenario 1	12.8	287'683.40	22'475.27	12.8	316'804.34	24'750.34
Scenario 2	12.8	300'700.65	23'492.24	12.8	316'804.34	24'750.34
Scenario 3	12.8	286'950.29	22'417.99	12.8	316'804.34	24'750.34
Scenario 4	12.8	293'690.27	22'944.55	12.8	316'804.34	24'750.34
Scenario 5	12.8	287'683.40	22'475.27	12.8	246'462.92	19'254.92
Scenario 6	12.8	300'700.65	23'492.24	12.8	246'462.92	19'254.92
Scenario 7	12.8	275'629.40	21'533.55	12.8	246'462.92	19'254.92
Scenario 8	12.8	288'646.65	22'550.52	12.8	246'462.92	19'254.92
Scenario 9	12.8	287'683.40	22'475.27	12.8	269'630.35	21'064.87
Scenario 10	12.8	300'700.65	23'492.24	12.8	269'630.35	21'064.87
Scenario 11	12.8	275'629.40	21'533.55	12.8	269'630.35	21'064.87
Scenario 12	12.8	288'646.65	22'550.52	12.8	269'630.35	21'064.87
Scenario 13	12.8	275'629.40	21'533.55	12.8	316'804.34	24'750.34
Scenario 14	12.8	288'646.65	22'550.52	12.8	316'804.34	24'750.34
Scenario 15	12.8	274'896.30	21'476.27	12.8	316'804.34	24'750.34
Scenario 16	12.8	281'636.27	22'002.83	12.8	316'804.34	24'750.34

Table 25. Parameters that were varied at the one-way sensitivity analysis

Parameter	Minimum value	Maximum value
Weight	60.5 kg	73.9 kg
BSA	1.57 m^2	1.91 m^2
FOLFOX cost (5FU, leucovorin, oxaliplatin cost per mg)	R$/mg 0.04, 0.91, 34.43	R$/mg 0.05, 1.11, 42.08
FOLFIRI cost (5FU, leucovorin, irinotecan cost per mg)	R$/mg 0.04, 0.91, 14.91	R$/mg 0.05, 1.11, 18.23
Bevacizumab cost per mg	R$ 12.23/mg	R$ 14.94/mg
Cetuximab cost per mg	R$ 6.94/mg	R$ 8.48/mg
Panitumumab cost per mg		
BSC cost	R$ 230.61	R$ 281.31
Intravenous administration fee	R$ 165.94	R$ 202.82
Infusion (>22h) fee	R$ 226.34	R$ 276.64
Average treatment duration	11.5 months	14.1 months
1L	5.5 months	6.7 months
2L	3.6 months	4.4 months
3L	2.4 months	3.0 months

*FOLFOX: bolus and infusion fluorouracil/ leucovorin + oxaliplatin; FOLFIRI: bolus and infusion fluorouracil/leucovorin + irinotecan; BSC: best supportive care

ne, at 6 weeks, and at 3, 6 and 9 months after the randomization, using EORTC QLQ-30 and Dermatology-Specific Quality of Life (DSQL) Scale. There were no differences in global health functioning (p=0.164) or other EORTC items/subscales at 3 months by treatment arm. However, significant differences were found across the arms in skin symptoms (p<.0001), limitations in social activities due to a skin condition (p=0.008), and concerns about appearance (p<.0001), as measured by DSQL. Patients randomized to receive Bev reported fewer skin symptoms, social limitations and appearance concerns than patients receiving Cet (alone or in combination with Bev) (Naughton et al., 2013). Based on this data, it is widely accepted that either Bev or Cet might be part of the 1L therapy for patients with wtRAS mCRC and it seems reasonable to have a cost-minimization approach to compare at least the costs for 1L and 2L of treatment. Therefore, comparing the total and monthly treatment costs of Bev and Cet in 1L treatment in mCRC, the regimens starting with bevacizumab beyond first-progression (Bev TML) were cost-saving in 50% of all scenarios and in 100% of scenarios with non-Bev TML regimens starting with Cet (Non-Bev TML). Despite the switch of Cet to Pan in 3L biologic drug in Bev TML regimens.

There were no scenarios starting with Pan, since both pivotal trials for Pan in 1L and Bev in 2L were in combination with FOLFOX, which would not allow simulating the backbone chemotherapy switch after first progression.

Regarding the 3L treatment options, it might be possible to add irinotecan to Cet in metastatic colorectal cancer patients who were refractory to treatment to irinotecan in prior lines of therapy. Those findings were demonstrated in a phase II trial, BOND (Cunningham et al., 2004). According to the authors, Cet in combination with irinotecan had significant clinical activity in patients who had been previously treated with this drug. Despite its clinical relevance, this scenario with irinotecan in combination with Cet was not included in the analysis due to the study methodology, which included only phase III trials. As irinotecan cost is not a parameter with high influence in the model according to the sensitive analysis, the addition of irinotecan in 3L treatment is expected to not have a significant impact on the final results.

The remaining scenarios which Non-Bev TML regimens were cost-saving all started with Bev, followed by an anti-EGFR (Cet or Pan). However, one of the main reasons for this result is the impossibility of adding a biologic drug in 3L to these non-Bev TML regimens.

It is relevant to highlight that diverse chemotherapy regimens in combination with monoclonal antibodies resulted in different outcomes for patients, as specified in Table 1. Thus, it is important to consider this information when selecting the most suitable sequence of treatment both from clinical and pharmacoeconomical perspectives.

The use of molecular therapies in mCRC features a breakthrough in the treatment of many tumors, especially in mCRC. The maintenance of Bev with other lines of chemotherapy can spare or delay the use of other molecular therapy in the 2L treatment of mCRC, without causing any harm to the patient. Besides that, the possibility of using Bev in sequential lines allows the potential of adding more treatment line options, using biologic drugs, optimizing health and survival outcomes.

Conclusion

Even though the sequential use of Bev beyond the progression for mCRC might be expected to be more costly than Non-TML regimens because of the addition of an anti-EGFR biologic drug in 3L treatment, the Bev TML regimens were cost-saving in 50% of the scenarios of Non-Bev TML, especially over those which had started with Cet in 1L treatment. Despite the possibility of adding either Cet or Pan as a 3L treatment for mCRC, the Bev TML regimens allowed not only the optimization of subsequent treatment lines for mCRC patients, but also the enhancement of the long term disease management, as well as, potentially saving resources in the wt RAS mCRC settings in Brazil. In scenarios favoring non-Bev TML, all of them started with Bev.

All sixteen scenarios showed that starting mCRC treatment in wtRAS patients with Bev seems to be a suitable choice, balancing economic and clinical benefits.

This study is the first economic assessment evaluating biological sequences in mCRC under Brazilian Supplementary Healthcare system perspective. With new therapeutic options available and better knowledge regarding biomarkers and targeted therapies in oncology, economic studies become more valuable for decision making and should also be expanded to evaluate not only direct treatment costs, but also the quality of life and indirect costs.

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