The budget impact of monoclonal antibodies used to treat metastatic colorectal cancer in Minas Gerais, Brazil.

The budget impact of MABs for mCRC in Brazil

Wânia Cristina da Silva(0000-0002-5108-5724)[1], Brian Godman(0000-0001-6539-6972)[2,3,4,5], Francisco de Assis Acúrcio(0000-0002-5880-5261)[1,6], Mariângela Leal Cherchiglia(0000-0001-5622-567X)[1,6], Antony Martin(0000-0003-4383-6038)[4], Konrad Maruszczyk[7], Jans Bastos Izidoro[8], Marcos André Portela[9], Agner Pereira Lana[6], Orozimbo Henriques Campos Neto(0000-0001-6415-3709)[10], Eli Iola Gurgel Andrade(0000-0002-0206-2462)[1,6].

[1]Postgraduate Program in Medicines and Pharmaceutical Services, School of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil. E-mail: wania_logistica@hotmail.com , fracurcio@gmail.com, mcherchiglia@gmail.com, eliola51@gmail.com

[2]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. E-mail: Brian.Godman@strath.ac.uk

[3]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden. Email: Brian.Godman@ki.se

[4]Health Economics Centre, University of Liverpool Management School, Liverpool, UK. E-mail: apmartin@liverpool.ac.uk

[5]Division of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa

[6]Postgraduate Program in Public Health, School of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. E-mail: fracurcio@gmail.com, mcherchiglia@gmail.com, iola@medicina.ufmg.br

[7]Health Economics Services, Warsaw, Poland. E-mail: maruszczyk@gmail.com

[8] Divisão de Medicamentos Essenciais, Departamento de Assistência Farmacêutica, Secretaria de Estado de Saúde de Minas Gerais. E-mail: jans.izidoro@saude.mg.gov.br

[9]Mario Penna Institute of Oncology – Minas Gerais, Belo Horizonte, Brazil. E-mail: marcosaportella@yahoo.com.br

[10]Associate Professor of Undergraduate Pharmacy. Faculdade Ciências da Vida (FCV) / Sete Lagoas, Brazil. E-mail: orozimbo1984@gmail.com

Corresponding author: Wânia Cristina da Silva - wania_logistica@hotmail.com or wania.silva2014@gmail.com

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Abstract

Introduction: Biological medicines have increased the cost of cancer treatment and has raised sustainability concerns. In Brazil, three monoclonal antibodies (MABs): bevacizumab (BEVA), cetuximab (CETUX) and panitumumab (PANIT), are indicated for the treatment of metastatic colorectal cancer (mCRC) but currently not currently funded by the Unified Health System (SUS). However, they have been funded following successful

litigation cases. **Objective:** Evaluate the budget impact of BEVA, CETUX and PANIT MABs if they became part of standard chemotherapy to treat mCRC within the SUS of Minas Gerais (MG), in Brazil. **Method**: Budget impact analysis incorporating MABs as first-line treatment of mCRC in MG/Brazil was explored. The Brazilian health system – SUS perspective was adopted and a 5-year time horizon was applied. Data from the lawsuits from January 2009 to December 2016 were collected and the model was populated based national databases and published sources. Costs are expressed in USD. **Results:** 351 court lawsuits were granted for first-line MAB treatment for mCRC. In three alternative scenarios analyzed there was an increase in costs, which ranged from 348 to 395% compared to the reference scenario. PANIT presented a $103,360,980 budget impact compared to the reference scenario over a 5-year time horizon. BEVA and CETUX presented a $111,334,890 and $113,772,870 budget impact, respectively. Considering the restrictions on the use of MABs Anti EGFR (CETUX and PANIT) in patients with about 41% KRAS mutations, the best cost alternative adopted for incorporation should be the combination of the PANIT and BEVA antibodies, which demonstrated a cost of approximately $106 million. **Conclusion:** These results highlight the appreciable costs for incorporating BEVA, CETUX and PANIT into the SUS. It is likely appreciable discounts will be needed to permit incorporation.
Keywords: Litigation, Monoclonal Antibodies, Metastatic colorectal cancer, budget impact, right to Health, Pharmaceutical Care, Brazil.

Key points for decision makers

-Monoclonal antibodies (MABs), bevacizumab, cetuximab and panitumumab are used to treat metastatic colorectal cancer (mCRC), only after a successful lawsuit because these are currently not financed by the Brazilian Unified Health System (SUS);

-The budgetary impact for SUS showed appreciable costs for incorporating BEVA, CETUX and PANIT into the SUS. It is likely that either appreciable price reductions or discounts will be necessary to expand the use of MABs for mCRC in Brazil in the future.

Ethical Standards

Author contributions

WCS, BG, MLC, FAA and EIGA conceived of and designed the paper and collected the data. AM, KM, BG were involved in writing or critical review of the paper, with important intellectual contributions and collection of some information. All authors analyzed, interpreted the data with substantial contribution and approved the final version of the article for submission. WCS acts as guarantor that all aspects that make up the manuscript have been reviewed, discussed, and agreed among the authors in order to be exposed with maximum precision and integrity.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data Availability

The major SUS Information Systems: Outpatient (SIA), Hospital (SIH) and Mortality (SIM), which contain approximately 3.5 million patients in cancer treatment, are not available not publicly. Their access is restricted and only allowed through a data usage agreement that has a non-disclosure provision.

1. Introduction

Colorectal cancer (CRC) poses a significant economic and humanistic burden on patients and society. According to data from the Global Health Observatory (GLOBOCAN) of the World Health Organization (WHO), CRC is the third most diagnosed cancer with nearly 1.1 million of new cases each year and the fourth leading cause of cancer deaths worldwide, totaling 881,000 deaths in 2018 (1).

In Brazil in 2018, the National Cancer Institute (INCA) estimated 600,000 new cases of cancer. With respect to CRC, Brazil had an incidence of 36,360 new cases of colorectal cancer being 17,380 and 18,980 cases among men and women, respectively, with an increasing incidence in those under 50 years of age (2). This increasing incidence is associated with a growing elderly population and increased mortality associated with CRC when combined with inactivity (3, 4). In Brazil, CRC is the third highest cause of cancer-related deaths in women and the fourth in men (4, 5). The projected CRC incidence in the state of Minas Gerais (MG) in 2018 was 1,510 new cases for men and 1,650 for women, totaling 3,160 new cases, considering all cancer stages (6). It is important to highlight that between 17% and 26% of patients with CRC were diagnosed in stage IV, with the presence of metastases distant from the original tumor (7, 8). The delay in diagnosis compromises the effectiveness of potential treatments and may increase overall costs, which presents a particular concern for developing countries (9-13).

Cancer treatment is one of the fastest-growing areas of health spending which is heightened by growing prevalence rates and the rising costs of medicines to treat patients with cancer (1, 14-17). This is a concern for the sustainability of healthcare among countries providing universal healthcare as the costs of medicines for cancer treatment in high income countries now dominate pharmaceutical expenditure (1, 15, 18). In Europe, the cost of cancer care now accounts for up to 30% of total hospital expenditure and is growing (19). Consequently, there is an increasing need for countries to evaluate and re-evaluate the cost and value of treatments and services provided for patients with cancer including palliative care to improve allocative efficiency (20-24).

Currently in Brazil, monoclonal antibodies (MABs), bevacizumab (BEVA), cetuximab (CETUX) and panitumumab (PANIT) are typically only used to treat metastatic colorectal cancer (mCRC) following a successful judicial demand as they are currently not funded by the Unified Health System (SUS) with the Pharmaceutical Assistance (PA) component. As a result, there is 100% co-payment unless funding via other means such as following a successful judicial ruling. In recent years, there has been pressure from pharmaceutical companies to incorporate new technologies into the SUS following the economic growth seen in Brazil. However, adoption of new treatments may be slow where there are concerns surrounding their value and budget impact compared with existing treatments (25-27). In view of this, many patients in Brazil go to court to obtain access to

medicines which are not funded by the SUS and where co-payment presents an issue (28-30). However, there are inconsistencies in the judicial rulings (31). In the State of Minas Gerais (MG) from 2009 to 2016, there was a significant increase in the number of lawsuits received by the Department of Health (SES-MG) requesting the acquisition of three MABs, to treat stage IV CRC, as these medicines were not included in the SUS at the time (32). This was perhaps not surprising with the prescribing of MABs for chemotherapy-refractory mCRC patients resulting in incremental cost-effectiveness ratios (ICERs) of US$58,240 for CETUX and US$52,772 for PANIT per life-year gained, exceeding pre-specified thresholds for cost-effectiveness in Brazil. The acquisition costs of the MABs was the principal driver of increased costs (33). A similar situation was seen with BEVA (34). It was observed that the number of court requests increased over 3,000% (from 4 cases in 2009 to 213 cases in 2014) during this five year period, representing more than 1,000% increase in treatment costs for SUS (32).

The efficacy and safety of MABs have been shown in a number of clinical trials (32, 35-37). However, the health outcomes associated with the use of BEVA and CETUX, or BEVA and PANIT when combined with traditional chemotherapy (CT) treatment, have been found to be similar (32, 38), although there can be differences in side-effects between the different MABs (39-41). A recent meta-analysis of observational studies analyzing the effectiveness and safety of MABs found though statistically significant differences in their respective safety (32), with Hecht et al. (2009) also raising concerns related to increased toxicity with MABs without any survival benefits (42). A study by Silva et al. (2018) which examined the effectiveness of bevacizumab and cetuximab had similar findings in terms of efficacy for mCRC, except for tumors on the colon right side where CETUX was associated with inferior health outcomes (37).

Whilst available evidence on the comparative effectiveness from observational studies is limited, and possible gains are modest, randomized studies have demonstrated gains in median survival of approximately three months, with equivalent benefits between the MABs (43-45). Evidence from randomized controlled trials (RCTs) also showed similar benefits in both meta-analysis (46, 47), with Venook et al. (2017) demonstrating the same median overall survival (OS) of 30 months with different MABs; however, this study included individuals with non-mutated KRAS (39).

In Brazil, Health Technology Assessments (HTA) are largely performed by Health Technology Assessment Centers (NATS) coordinated by the National Commission for the Incorporation of Technologies (CONITEC). NATS is part of the process for incorporating new therapies into SUS, subsidizing the incorporation and investment in new technologies, as well as disinvestment from potential technologies through considering the best scientific evidence available for comparative efficacy, effectiveness and safety (48-50). During the evaluation process, a Budget Impact Analysis (BIA) is performed to help inform decision-making (23, 51). A BIA is an operational forecast of likely increases in expenditures following the incorporation of new technologies into health systems especially where there are pressures on budgets (52-54). However, there have been concerns about the robustness of some BIAs performed, which may potentially impact on their usefulness in practice (52).

There have been a number of studies that have published on the costs of different aspects of cancer care in Brazil (20, 21, 23). This includes CT for people with mCRC in Brazil (24) and the cost effectiveness of different MABs for mCRC alongside CT (33, 34). In a number of cases, this information is obtained through cost-effectiveness analysis, which includes an analysis of costs and the effects of a health intervention. However to date, we are unaware of any studies assessing the potential budget impact of MABs to treat CRC in Brazil. This is important when CONITEC seeks to review potential listing of MABs for CRC in Brazil in the context of an

increasing number of judicial requests coupled with other requests on available funds since, as mentioned, SUS does not currently cover the costs of treating mCRC with MABs associated with chemotherapy regimens. Consequently, the objective of this study is to evaluate the budget impact for SUS arising from the inclusion of BEVA, CETUX and PANIT MABs alongside standard CT regimens into the treatment regimen for patients with mCRC in Brazil. These findings may be used to guide future decision-making in Brazil.

2. Methods

Three alternative scenarios were considered in the analysis: Reference scenario: Chemotherapy (CT) only; Alternative scenario A: BEVA + CT; Alternative scenario B: CETUX + CT; Alternative scenario C: PANIT + CT.

The procedures for preparing the Budget Impact Analysis document were described in the Manual for the Brazilian Health System. These were created to meet a demand from ANVISA, from the Ministry of Health. It was validated by REBRATS - BRAZILIAN TECHNOLOGY ASSESSMENT NETWORK of the Brazilian Ministry of Health, and follows the standards of the International Society for Pharmacoeconomics and Outcomes Research - ISPOR, which are summarized below: definition of the analytical structure and the assumptions of analysis.

- perspective and time horizon of the analysis;
- details of the health system, including possible restrictions on access to the new technology;
- degree of use (including size of the target population) and costs of the technology (s) in effect for the target condition;
- expected speed of incorporation of the new technology, and size of the target user population at the end of the analysis period;
- understanding of whether the new technology is a substitute for technologies in current use, or additive;
- other possible cost impacts (such as, for example, reducing hospitalizations due to the disease for better control of the disease);
- procedures for analyzing uncertainties;
- type of model to be used.

2.1 Study design and data source

A BIA was developed to consider hypothetical alternative scenarios with the incorporation of MABs for the treatment of mCRC added to CT regimens containing fluoropyrimidines (5-FU) associated with irinotecan (IRI) or oxaliplatin (OX) from the perspective of the SUS in MG and also considering judicial data collected from 2009 to 2016 and analyzed for 2018. The data were extracted from the National Database of Health, a data set and linked to integrate data from the major SUS Information Systems: Outpatient (SIA), Hospital (SIH) and Mortality (SIM), which contained approximately 3.5 million patients in cancer treatment. Judicial data was collected only from MG as this was the most comprehensive source available to us.

Before commencement of this research, this study was approved by the UFMG Research Ethics Committee CAAE:44121315.2.0000.5149(ANNEX A). Data were collected from the Brazilian Institute of Geography and

Statistics - IBGE, Department of Informatics of SUS - DATASUS, Management System of Procedures, Medicines and OPM (Orthesis, prosthesis and medical materials) of SUS Procedure Table Management System (SIGTAP), National Commission of Incorporation of Technologies (CONITEC), and the Brazilian Health Technology Assessment Network (REBRATS) as well as Regional Information - MG State Purchasing Portal, Integrated Pharmaceutical Assistance Management System (SIGAF) and Integrated Direct Administration System (SIAD). The study was part of a doctoral project undertaken by the lead author (WC da S)

Scientific literature was obtained from an electronic search through the Scientific Electronic Library Online (SciELO), PubMed, Embase, Cochrane, Google Scholar, and NATS websites. The search terms used included monoclonal antibody; colorectal neoplasia, inequality of access; Health technology assessment; Judicial demand; budget impact and Brazil.

Data were extracted for the judicial processes of the Center for Assistance to the Judicialization of Health (NAJS) of MG registered between January 2009 and December 2016. Data collection was performed at SES-MG by researchers from the Health Economics Research Group (GPES) at the Federal University of Minas Gerais (UFMG). In addition, sociodemographic and clinical data, as well as information on MABs registered in Brazil for the treatment of mCRC: BEVA, CETUX and PANIT, was collected.

The total population of MG estimated for 2018 was 21,235,870 inhabitants, and the number of new cases for the CRC estimated by INCA was 3,610 diagnosed at any stage of the disease. According to published data, 17% of individuals with CRC progress to the metastatic stage (IV) per year, which represents 635 individuals per year potentially eligible for treatment with MABs (7, 55-57) (Figure 1) (58, 59).

Figure 1 - Flowchart to describe the population included in this study

Data on overall survival (OS) of the general population were obtained from the scientific literature (43, 45, 60). The information was stored in a database and analyzed using MS Office (version 2010).

2.2 Methodological Procedures for Budget Impact Analysis

To examine the budget impact of alternative scenarios, we applied the analytical structure of a predefined framework from the Brazilian Ministry of Health in their manual of methodological guidelines on BIA (61). The analysis adopted the perspective of SUS, focusing on the population of patients with mCRC residing in the state of MG and considering a five-year time horizon (58).

The reference scenario was defined based on current chemotherapy regimens available and funded by SUS (62, 63). Alternative scenarios involved the inclusion of each of the three MABs (BEVA, CETUX or PANIT) with CT based on 5-FU, associated with IRI and/or OX, which are already standard chemotherapy regimens for the treatment of patients with mCRC across countries. The model assumed that one of the MABs would be used as a first-line therapy for eligible patients.

For mCRC, the primary outcome of treatments is OS in which an improved survival outcome may be realized with the prescribing of MABs (43, 45, 60, 64, 65). Table 1 presents the general parameters included in the BIA using the methodology documented in the Brazilian guidelines (58).

Table 1 - General parameters included in the BIA of MABs for mCRC in SUS (2009 to 2016)

Specific parameters and relevant evidence sources are described in Table 2.

Table 2 - Specific parameters used for BIA

An equivalent proxy was adopted in proportion with the legal demands for each of the MABs according to anticipated market shares for each MAB. Among the 351 successful court cases which resulted in funding treatment with MABs, the following proportions were observed: 49% BEVA; 43% CETUX and 8% PANIT. These percentages were subsequently applied to the number of individuals potentially eligible for treatment, i.e. 635 patients who were in the same clinical stage of mCRC.

For the reference scenario, CT was provided as CT alone as this is currently offered by the SUS and is provided to 100% of patients. Judicial authorizations were granted in approximately 10% of patients who received MABs (BEVA [5%], CETUX [4%] and PANIT [1%]). The reference scenario was based on the population estimated by IBGE for 2018 (56) comparing the population incidence of 635cases with the number of judicial authorizations to access MABs, i.e. the 44 lawsuits (approximately 10% of cases per year).

For the composition of alternative scenarios A, B and C, the MABs were considered as therapeutically equivalent in accordance with earlier findings (32, 54). The therapeutic coverage rate adopted was 59% for each MAB analyzed in each scenario alternative, according to data from the proportion of judicial requests. This assumes that even though 41% of cases had a therapeutic restriction on the use of anti-EGFR, all of them will receive approval for funding for the use of these MABs due to the mandatory legal actions. It was observed that in scenarios where the emphasis was on the anti-EGFR combination (PANIT and CETUX), the proportion of coverage always presented a lower percentage due to the application of restrictions related to the mutation of the *KRAS* gene mutations (in approximately 42% of situations) of the population affected by CRC which interferes with the anti-EGFR treatment (66, 67). BEVA has no use restrictions dependent on the *KRAS* gene mutation. Similarly, for all alternative scenarios, CT was kept at 5% to cover cases where no MABs could be provided.

The technology diffusion rate started at 40%, which was considered as a medium to high diffusion rate, followed by the addition of 20% for year 2 and 20% for 3. An increase of 10% for years 4 and 5 was also projected. The diffusion rate of 40% in the first year reflects the belief that MABs will have rapid dissemination within SUS once approved in view of the current high number of court demands between 2009 and 2016, with this analysis performed for each MAB from epidemiological estimates (68-70). These estimates for market shares are based on judicialization profiles given the lack of other usage data within the country.

With respect to diffusion rates, BEVA had with the greatest number of judicial requests and was perceived to have the highest uptake. Highest diffusion was anticipated for BEVA as it has been registered in Brazil since 2006 and has been widely prescribed for other therapeutic indications including breast cancer, lung cancer, macular degeneration, and ovarian cancer (61, 70).

The BIA model was also adapted to account for an average 4% increase in prevalence rates per year (71, 72). Mortality data were obtained from the scientific literature and a standardized mortality ratio of nine deaths per 100,000 population was applied (1). Since all considered treatments have a direct influence on OS, and are linked to health-related outcomes, the same scenarios were considered for all MABs, differing only in the reference scenario without MABs (43, 57, 60, 64).

Prices for medicines modelled were defined and readjusted by the Medicines Market Regulation Chamber (CMED) of the National Health Surveillance Agency (ANVISA). An average annual inflation adjustment of 7% for the period from 2005 to 2016 was subsequently applied. This procedure was applied as annual price readjustments are granted by the government, which may have an appreciable influence on the budget impact of medicines over a five-year time horizon (73).

Drug cost data were obtained through Public Acta of the MG Purchasing Portal Price Record, which were formalized in 2017 and 2018 by the public administration. Doses for dispensing and units of vials for each CT cycle were considered in whole units for each individual, according to medical prescription and pharmaceutical dispensation form attached to the lawsuits. The monthly pack quantities and concentrations for each medicine were: BEVA, ten vials (25 mg /mL solution for injection IV vial with 4 ml); CETUX, 20 vials (5 mg/mL solution for injection IV vial with 20 mL); and PANIT, ten vials (20 mg/mL solution for injection vial with 5 mL). The cost estimates of the oncological treatment with CT in the cases of procedures available in SUS were obtained through the reimbursement value records attributed to the High Complexity Procedure Authorizations (APAC) defined in the Management System Table of the Procedures - *Sistema de Gerenciamento da Tabela de Procedimentos* (SIGTAP) table.

2.3 Evaluation of model uncertainties

As recommended by the Brazilian BIA guidelines, the evaluation of the robustness of the results were explored with sensitivity analyses of the alternative scenarios. For this, the spreadsheets were recalculated with changes of the following variables: diffusion rate of BEVA, size of the CRC population and changes in unit price of the various medicines in 2018 (61, 70, 74) (Table 2).

The analysis also included the direct impact on OS and avoidable costs. The main event expected to be avoided with treatment was death.

Sensitivity analysis was performed to assess the influence of population size of interest due to the *KRAS* mutation (40%), which influences the response rate of anti-EGFR antibody treatments (CETUX and PANIT). Results of restrictions were used in sensitivity analysis to explore the cost impact and use of other treatments (58, 61, 74).

2.3 Budget Impact Analysis

The BIA compared the results of the reference scenario associated with the hypothetical incorporation of the MABs demanded by the court in clinical practice. It is important to note that the BEVA, CETUX and PANIT medicines for mCRC are not off-label for use in the SUS; however, currently only funded following a successful judicial review. Indirect costs were not considered for BIA calculations as these cost components are currently outside of the scope of SUS perspective of this analysis. In addition, no treatment substitutions were considered as the MABs were considered to be provided in addition to CT (52).

2.4 Costing, efficacy and avoided cost data

Costs were initially calculated in Brazilian Reals but subsequently converted into US$ to facilitate international comparison. We conducted the conversion through the Organization for Economic Cooperation and Development (OECD) website. We used the value corresponding to the dollar quotation of 12/28/2018, equal to R$3.87.

For the analysis of the costs involved with the treatments, the direct unit cost of each vial was obtained multiplied by the quantity used per patient in one month (Table 6). The average unit cost for BEVA was R$ 1,555 (US$402) for a monthly average of ten units per patient. The average unit cost of CETUX was R$732.20 (US$189.20), considering a monthly average of 20 units per patient. PANIT's average unit cost was R$1,194 (US$308 for a monthly average of ten units per patient. In the case of CT schemes, the unit identified in the APACs is related to the 5-FU-based treatment schemes associated with OX or IRI, whose financing is incorporated within the SUS with the monthly amount of R$2,224 (US$574) per procedure.

The efficacy data were extracted from the ARIES, CRYSTAL and PRIME studies and we calculated these as follows:

To consider the number of events (deaths) prevented from each study (ARIES, CRYSTAL, PRIME) per year, according to the use of the corresponding treatment for each of the alternatives represented in the studies (BEVA, CETUX and PANIT), as shown in the Table 7.

Calculations performed (study ARIES, CRYSTAL, PRIME):

a) Avoided deaths:

- Number of patients for reference: 1000 participants:
- Time horizon analyzed: 1 year (12 months)
- Follow-up period: 1 year; minimum period for calculating budgetary impact
- Number of events in the intervention group: ARIES: 103; CRYSTAL: 187; PRIME: 171
-Total number of participants in the intervention group: ARIES: 402; CRYSTAL: 599; PRIME: 259
* Mortality rate presented in each study (Number of events for every 100 patients in the intervention group): ARIES: 25.7; CRYSTAL: 30.6; PRIME: 25.7
- Number of events in the control group: ARIES: 150; CRYSTAL: 183; PRIME: 188
-Total number of participants in the control group: ARIES: 420; CRYSTAL: 599; PRIME: 253
* Mortality rate presented in each study (Number of events for every 100 patients in the control group): ARIES: 36.6; CRYSTAL: 31.2; PRIME: 34.0

Formula: (Number of reference patients for analysis / (time horizon period / ((Number of outcomes in the Control Group / Number of participants in the Control Group) - (Number of outcomes in the Intervention Group / Number of participants in the Intervention group))))) / follow-up period

b) Avoided costs

-Annual average number of events (deaths) avoided by MAB analyzed: BEVA ; CETUX; PANIT
- Average cost of each event (death) avoided (per patient): BEVA; CETUX; PANIT

Formula: (Number of annual events avoided) x Average cost of each event)

3. Results

3.1 Study population characteristics

Of the 1,024 lawsuits collected at the NAJS of SES-MG involving BEVA, CETUX and PANIT for mCRC, 351 were successful. The average age of the plaintiffs was 55.73 ± 13.57 years. Most were male and married, 29.3% were active workers, 36% retired, 41.9% had private health insurance, 34.8% came from private

clinics and 59.5% were treated in *Centro de Assistência de Alta Complexidade em Oncologia* (CACON) or *Unidades de Assistência de Alta Complexidade* (UNACON) from SUS. The median cost of lawsuits for MAB treatments between three and 12 months was R$60,000 (US$ 15,504), with a minimum variation of R$600 (US$155) and a maximum of R$1,200,000 (US$310,078). The judicial ratio for successful cases was 49% for BEVA, 43% for CETUX and 8% for PANIT (Table 3).

Table 3 - Profile of cases of judicialization of MABs for CRC in Minas Gerais from 2009 to 2016

3.2 Scenarios for Incorporation - Incremental Budget Impact

Considering the total period analyzed, all three alternative scenarios (scenario A = BEVA+CT or scenario B = CETUX+CT or scenario C = PANIT+CT) increased costs, which ranged from 348% to 395% over the reference scenario (CT only). As mentioned, estimates were made according to the methodology recommended in the Brazilian BIA Guideline framework (61) and based on data available for hypothetical incorporation of MABs for mCRC (2018).

According to the calculations, the third alternative scenario, consisting of PANIT + CT, would generate a smaller increase in costs compared to the reference scenario. Moreover, it could increase spending by more than R$ 400 million (US$ 103 million) as reported in Table 4 and figure 2.

3.3 Analysis of costs associated with treatments

When the cost base was established in 2018 with the prices collected in the Health Price Bank (BPS), the cost of BEVA was R$1,555 (US$401, whereas in the CMED price register of ANVISA, the price unit was R$1,600 (US$413) with an ICMS tax rate of 18%, corresponding to the state of MG. This indicates that there was a difference of R$45 (US$12) in each purchased unit between CMED price and BPS (Banco de Preço em Saúde). The price of CETUX in BPS was R$732 (US$189), while in CMED the value was R$879 (US$227), showing a difference of R$ 147 (US$38) in each purchased unit. The price of PANIT in BPS was R$1,194 (US$309), and in CMED it was R$1,274 (US$329), totaling a difference of R$20 (US$9) in each purchased unit. As for CT, the price remained the same as that of Authorization for High Complexity Procedures (APAC) and did not adjust.

For the real cost involved in the treatment, the monthly cost of each new therapy was calculated adding R$2,224.00 (US$574.68) from the CT schemes already incorporated in the APAC. This resulted in the respective total monthly value of each therapy of R$18,224 (US$4,709) for BEVA, R$19,804 (US$5,117) for CETUX and R$14,962 (US$3,866) for PANIT.

Table 4 - Incremental Budget Impact with the incorporation of MABs into the SUS, by comparison of scenarios

3.4 Comparison between the alternative scenarios

The comparison between alternative scenarios did not show great differences. It was observed that in the comparison between Scenario B vs Scenario A at the end of five years the difference was 2%, and for

Scenario C vs Scenario A, the difference was 6%. Finally, when comparing Scenario 3 vs Scenario 2 the difference was 7%.

3.5 Sensitivity analysis for population and technology diffusion rates

To perform the sensitivity analysis, the speed of diffusion of the MABs for incorporation and the factors that may interfere with the population size, such as mutation of the *KRAS* gene and the impact of the restrictions related to the technology cost, were examined (Table 2).

A sensitivity analysis was performed to assess the annual rate of diffusion, considering percentages of low, medium and high diffusion rates. When the rate applied was low diffusion, the results were: R$416,891,739 (US$107,723,964) for BEVA, R$435,493,090 (US$112,530,514) for CETUX and R$390,992,472 (US$101,031,647) for PANIT. When the diffusion rate was increased, the following results were observed: R$429,513,227 (US$110,985,330) for BEVA; R$439,835,551 (US$113,652,597) for CETUX and R$399,133,974 (US$103,135,394) for PANIT (Table 2; Table 5).

Alternatively, the total population served would be 635 patients per year. However, adopting the most advantageous scenario, with the choice of PANIT, the calculation should include the restriction of 40% of patients with a *KRAS* gene mutation. That is, only 381 patients would benefit from treatment with antiEGFR-class MABs (CETUX and PANIT). Consequently, by recalculating the expenses and adding 40% of the BEVA alternative in all groups with restriction, the total expenditure for SUS in the period analyzed would be approximately US$106 million for PANIT+BEVA, US$112 million for CETUX+BEVA and US$111 million for BEVA alone, as shown in Table 5.

Table 5 - Values for dissemination and restriction of spending by scenarios

When an incremental sensitivity analysis based on price changes was performed, the following five-year costs were obtained: R$483,152,318 (US$124,845,560) for BEVA, R$504,485,997 (US$130,358,139) for CETUX and R$407,304,665 (US$105,246,683) for PANIT.

When the three MABs were analyzed, considering the restriction by mutation of the KRAS gene, the following values were observed: US$44,248,269 for BEVA, US$68,116,279 for CETUX and US$61,740,155 for PANIT.

When considering only the number of patients in the lawsuit, the amounts were as follows for 5 years: US$7,665,054 for BEVA, US$7,866,447 for CETUX and US$7,130,097 for PANIT.

When comparing the prices of the Price Bank and CMED, it presented the following differences in favor of the Price Bank: US$14,224,806 for BEVA, US$16,831,008 and US$2,346,512.

Table 6 - Analysis of costs associated with treatment US$)

Table 6 shows the costs related to prices and unit quantities of the drug units involved with the treatments. It obtained the direct unit cost of each bottle and its quantities used per patient in one month.

The average unit cost of each MAB and the cost of the chemotherapy scheme incorporated (approved) in SUS. The unit values of each bottle and the cost of each treatment considering the two sources of official price registration in the country (CMED and Price Bank)

3.6 Events prevented and costs avoided with the incorporation of the MABs into SUS

When we applied the formula documented in the Methodology (Section 2.4) we asceruained that the number of events (deaths) prevented for every thousand patients treated for a year was 109 with BEVA equating to R$11,599,699 (US$2,997,391); 83 with PANIT equating to R$7,042,977 (US$1,819,941) and seven deaths avoided with CETUX equating to R$675,686 (US$174,678) (Table 7).

Ass mentioned in Section 2.4, the calculations performed for avoided deaths considered the efficacy data from the ARIES, CRYSTAL, PRIME studies.

Table 7 - Costs avoided (US$) or number of events prevented with the incorporation of MABs

In the hypothetical calculation, treatment with BEVA showed the highest number of avoided events (109 events/deaths) at a total cost of US$2,997,391. While PANIT had a total cost of R$1,819,941 for 83 avoided events and CETUX had a total cost of R$174,678 for 7 avoided events. Consequently, the individual cost of each event for each treatment is: U$27,499 for BEVA; U$21,927 for PANIT and U$24,954 for CETUX (Table 7).

4. ***Discussion***

To the best of our knowledge, this is the first study published in Brazil that assesses the budget impact of MABs for mCRC based on court cases using SUS costing data, in this case data were collected for MG to compare probable scenarios for the treatment for SUS patients over a five year horizon.

According to the evaluated scenarios, the combined incorporation of BEVA and PANIT (US$106 million) should be the most economical option. BEVA alone (US$ US$125million over 5 years) could be the second option when comparing the lowest investment value with the incremental budget impact for first-line treatment of mCRC considering patients with mutations in the KRAS gene. However, it is important to note that with any chosen alternative, the budget impact will be an increase since MABs are not a substitution for CT but an addition to already existing regimens. In addition, the budget impact will be greater if judicial considerations are relaxed with expenditures following a favourable judicial ruling currently only representing approximately 7 to 10% of the costs when compared to the possible full incorporation of MABs into SUS with no such restrictions. However, this is unlikely unless there is an appreciable price reduction or discount, or companies seek to manufacture the MABs internally at lower costs. Another alternative would be a form of risk sharing arrangement potentially including an outcome guarantee scheme as we know that the Ministry of Health in Brazil has very recently started considering such agreements for high-price medicines (75-77)

In clinical practice, it is important to note that the outcomes may favor BEVA compared to PANIT or CETUX as seen in a recent systematic review and meta-analysis (32). Of the three scenarios compared, the findings were that considering cost of the treatment for a thousand patients with MABs, BEVA had the highest

cost but had the highest number of deaths avoided. In the other words, an increase in costs associated with reducing deaths compared with the other scenarios. However, other studies have shown limited differences in effectiveness between the different MABs but there can, as mentioned, be differences in side-effects that can also equally affect treatment choices (39-41, 65, 78).

The findings from the sensitivity analysis, which included variations in dissemination and diffusion rates, restrictions of the population of interest due to genetic mutations and drug values, were consistent. However, despite large variations in the total cost impact of each option, we observed that the most advantageous alternative scenario would be the combined composition of BEVA+PANIT.

In view of the scarcity of resources in Brazil, it is important to also address concerns regarding early detection and diagnosis of CRC when the disease is curable versus delayed treatment with more expensive treatments under opportunity cost scenarios (79, 80). It is necessary to think about any public policy in such a way that the policy will result in a financially sustainable implementation of adequate diagnostic and treatment approaches including precision medicine programs to maximize health gain from available resources given current controversies surrounding the value of cancer medicines (81-84). Consequently, we believe it is important to demonstrate the real need for and value of potential treatments in view of the costs of their incorporation into SUS compared with other potential scenarios, i.e. their opportunity costs (79, 80). Such discussions and information needs will grow as more new cancer therapies become available alongside concerns surrounding their costs and value (15, 18, 83). This is important as these MABs are currently intended only for one stage of the tumor that is Stage IV mCRC. The costs involve are similar to those involved in constructing a 150 to 200 bedded hospital each year, including an s Intensive Care Unit, medical clinic, oncology and emergency rooms (85-87). Furthermore, the use of these MABs, concomitant with CT as a complementary treatment in stages IV, are still being analyzed in studies of effectiveness and safety, which may represent an even greater economic impact in the future due to the uncertainties surrounding such associations.

Limitations

There are always concerns in BIA studies with available data for different types of calculation for the population of interest. Estimates of market shares was based on the proxy of the profile of MABs authorized under the judiciary system.

Overall, important limitations of this analysis include uncertainty in the size of the market share of BEVA (41%) and the anti-EGFR-CETUX / PANIT (59%) presented in table 5, and uncertainty that therapeutic incorporation will occur in system and the speed of this incorporation. Overall, structural uncertainty of the assumptions adopted in the BIA were not analyzed, and we accept this as a limitation.

Information about price negotiations is confidential and is not provided by pharmaceutical manufacturers, including discount information. Few details are found in the literature about negotiations and prices, which can be considered a limitation due to high prices charged for new drugs launched on the market, together with the growing demand for resources.

We are also aware that in the case of MABs belonging to the antiEGFR group (CETUX and PANIT), one needs to be careful about the evaluation of the relationship with mutations in the *KRAS* gene. In the case of incorporation of the anti-EGFRs group (PANIT or CETUX). We believe BEVA should be incorporated to serve the population corresponding to approximately 40% of the cases that have mutations in the *KRAS* gene.

Conclusion

With the euphoria that surrounds the arrival of new cancer medicines, the judiciary system in Brazil creates a channel for access often without scientific evidence of improved safety, effectiveness and cost-effectiveness versus current approaches. This is especially important in the cancer area given increasing requested prices for new cancer medicines fueled by the emotive nature of the disease area and potentially generating inequalities in access to new medicines in Brazil.

The expectation in Brazil is to increase spending on MABs for the more advanced stages of mCRC building on successful cases in the judicial system in Brazil. In Minas Gerais for instance, public spending on bevacizumab (BEVA), cetuximab (CETUX) and panitumumab (PANIT) as a result of a successful litigation was approximately US$20 million between 2009 and 2016. This would appreciably increase if relaxations were allowed, which would be unsustainable given current pressure on budgets, the growing needs of the population and the MABs only targeted for Stage IV disease. It is likely that either appreciable price reductions or discounts under risk sharing arrangements will be necessary to expand the use of MABs for mCRC in Brazil in the future.

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Figures

Figure 1 - Flowchart to describe the population included in this study

Source: Prepared by the authors.
Caption: CRC = colorectal cancer; IBGE = Brazilian Institute of Geography and Statistics; INCA = National Cancer Institute; SIGAF = Integrated Pharmaceutical Care Management System.

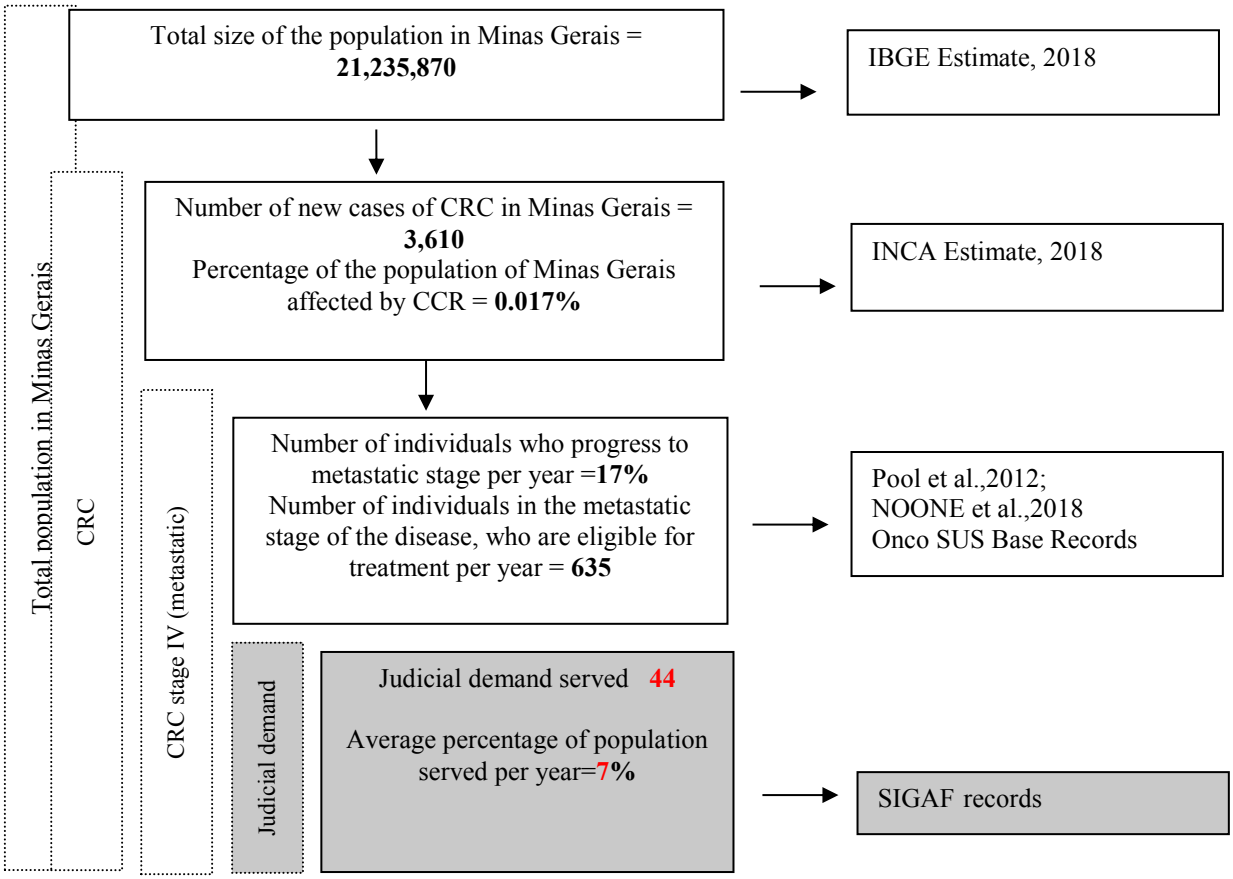
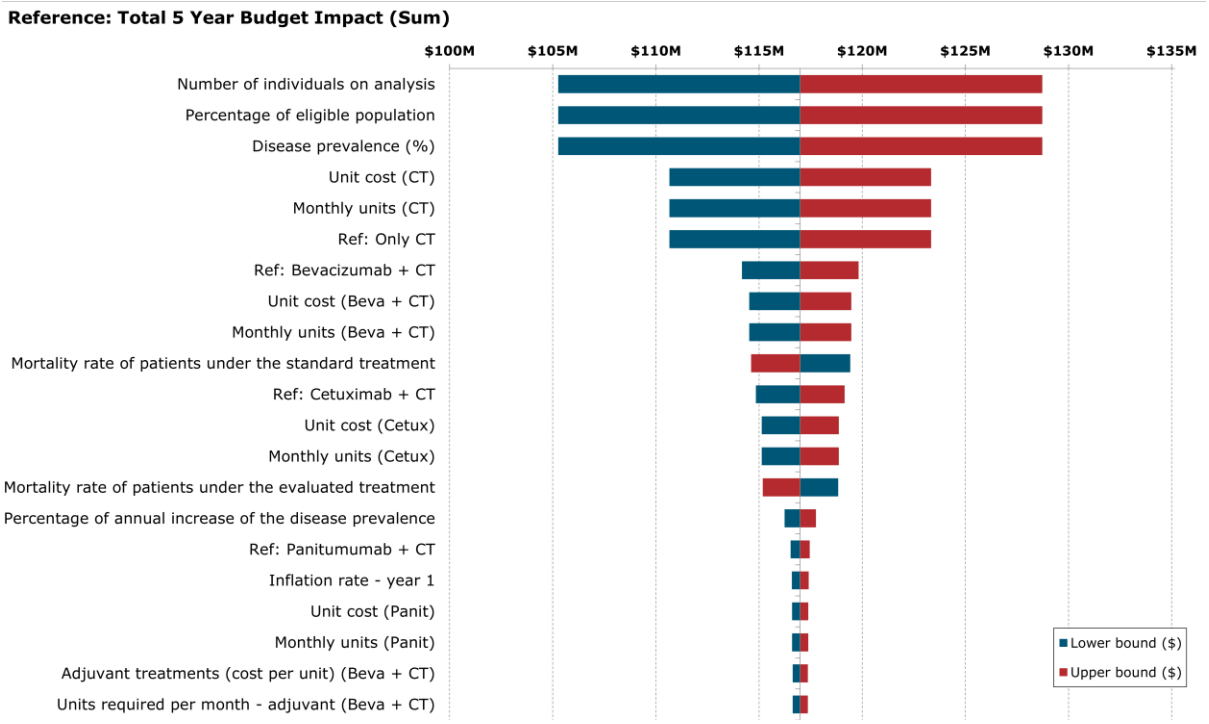


Figure 2 – OWSA

Reference: Total 5 Year Budget Impact (Sum)



Tables

Table 1 - General parameters included in the BIA of MABs for mCRC in SUS (2009 to 2016)

Budget Impact Study	
Pharmacological treatment of chronic disease	
Type of disease	Malignant neoplasm
Type of intervention	Adjuvant pharmacological
Effect of the intervention on the disease	Prolongs life expectancy
Criteria	
Characterization of the disease and the intervention under analysis	
Disease name	Metastatic colorectal cancer
Name of the drug	BEVA, CETUX, PANIT
Classification - ICD10	**C18= Malignant neoplasm of colon** **C19= Malignant neoplasm of the sigmoid rectus junction** **C20= Malignant neoplasm of rectum**
Perspective and Time Horizon	
Analysis perspective	SUS - Minas Gerais
The time frame of analysis	5 years
Identification of modeled scenarios	
Reference scenario (CT)	(CT) - Scenario according to PCDT 2012 and 2014
Alternative scenario A	A (BEVA+CT)
Alternative scenario B	B (CT+CETUX)
Alternative scenario C	C (CT+PANIT)
Complement - Characteristics of cancer treatment-SUS	
The SUS is structured to provide integral and integrated care to patients who need treatment for malignant neoplasia. The high complexity in the Oncology Care Network includes hospitals qualified as UNACON or CACON, as well as non-hospital health facilities authorized as Isolated Radiotherapy and Chemotherapy Services (66). Financing is through financial resources of the three federated entities (Union, States and Municipalities) from social contributions and taxes. Treatments of noncommunicable chronic diseases are established through specific PCDT for each disease (67). In the case of cancer, the patient receives treatment at CACON / UNACON from his regional health center through chemotherapy at regular intervals, at the discretion of the oncologist. It is noteworthy that CONITEC was created, established by Law 12,401, of April 28, 2011, which performs cost-effectiveness assessments, including antineoplastics (66).	

Source: Prepared by the authors.

Caption: BIA = Budget Impact Analysis; BEVA = bevacizumab; CACON = Center of High Complexity in Oncology; CETUX = cetuximab; ICD10 = International Classification of Diseases; CONITEC = National Commission for the Incorporation of Technologies in SUS; PANIT = panitumumab; PCDT = Clinical Protocol and Therapeutic Guideline; CT = chemotherapy; UNACON = High Complexity Unit in Oncology; SUS = Unified Health System

Table 2 - Specific parameters used for BIA

Scenarios (including references)	Variable (%)			
Composition of the scenarios understudy (31, 58, 88)	**BEVA**	**CETUX**	**PANIT**	**CT**
(CT)	5%	4%	1%	90%
A (BEVA+CT+CETUX+PANIT)	59%	29%	6%	5%
B (BEVA+CT+CETUX+PANIT)	29%	59%	7%	5%
C (BEVA+CT+CETUX+PANIT)	29%	7%	59%	5%
Annual diffusion /uptake fee - BEVA (68-70)	**Model (%)**	**Sensitivity Analysis**		
		LOW(%)	**MEDIUM(%)**	**HIGH(%)**
Year 1	40%	10%	30%	50%
Year 2	60%	25%	50%	60%
Year 3	80%	55%	70%	70%
Year 4	90%	80%	90%	80%
Year 5	100%	100%	100%	100%
Population of interest				
Definition of the population of interest (43)	**BEVA**	**CETUX**	**PANIT**	**CT**
Method	**Epidemiological**			
Unrestricted individuals	635	635	635	635
Individuals with restrictions (based on *KRAS* Mutation)	0	267	267	0
Quantitative data for sensitivity analysis based on *KRAS* mutations				
Largest population (without restrictions)	635	635	635	635
Smallest population (with all restrictions)	635	368	368	635
Restrictions and demands				
Restrictions on the use of the new treatment (42, 43, 89)	**BEVA**	**CETUX**	**PANIT**	**CT**
Restriction types	Without restriction	*KRAS* mutation = 42% for EGFR therapy CETUX and PAINT		Without restriction
Factors that can increase the demand for the new treatment (58, 88)	**BEVA**	**CETUX**	**PANIT**	**CT**
Induced demand (%)	No records			Incorporated
Forced demand - constraint failure (%)	No records			Incorporated
Potential lawsuit demand (%)	0.90%			Incorporated
Dynamics of the disease				
Treatment arms	BEVA vs IFL [ARIES study - (43)]	CETUX vs FOLFIRI [CRISTAL study (90)]	PANIT vs FOLFOX [PRIME study- (60)]	CT
Factors that can change the size of the population of interest (57, 71, 72)				
% annual increase in disease prevalence	4.0%	4.0%	4.0%	4.0%
Standard treatment mortality rate(%)	36.6%	31.2%	34.0%	N/A
New treatment mortality rate (%)	25.7%	30.6%	25.7%	N/A

Source: Prepared by the authors adapted from Brazilian spreadsheets with budget impact .

Caption: BEVA = bevacizumab; CETUX = cetuximab; PANIT = panitumumab; CT = chemotherapy; N/A = not available.

* The reference numbers mentioned in the tables refer to the studies that explain each parameter (31,41,43,57,58,60,67,68,70,71,72,73,74).

Table 3 - Profile of cases of judicialization of MABs for CRC in Minas Gerais from 2009 to 2016

Characteristics	Patients (N=351)	
	N or Mean ± DPM	Proportion (%) or median (range)
Sociodemographic characteristics		
Gender (Frequency%)		
Male	178	50,7
Female	173	49,3
Age	55.73 (13.57)	56 (20-85)
Marital status (Frequency%)		
Single	60	17.1
Married	179	51
Divorced	35	10
Widower	26	7.4
Not available	51	14.5
Occupation (Frequency%)		
Unemployed	32	9.1
Employee	103	29.3
Student	1	0.3
Retired	127	36.1
Not identified	88	25.1
SUS User	188	53.6
Has Private assistance	147	41.9
Not identified	16	4.6
Type of Cancer Care Assistance (Frequency%)		
CACON/UNACON	209	59.5
Private Clinic	122	34.8
Not identified	20	5.7
Cost of the lawsuit	351	US$15,504 (US$155 to US$331,693)
Clinical characteristics		
Type of cancer (Frequency%)		
Colon malignant neoplasm	258	73.5
Malignant neoplasm of rectum	93	26.5
Clinical stage (Frequency%)		
I	0	0
II	4	1.1
III	26	7.4
IV	317	90.3
Not identified	4	1.1
***Status KRAS* (Frequency %)**		
Wild	200	57
Mutated	59	16.8
Not identified	92	26.2
Monoclonal antibodies (Frequency %)		
Bevacizumab	171	49
Cetuximab	150	43
Panitumumab	28	8

Source: Prepared by the authors.

Caption: CACON = Center of High Complexity in Oncology; DPM = standard deviation of the mean; N = number of patients; UNACON = High Complexity Care Unit in Oncology

Table 4 - Incremental Budget Impact with the incorporation of MABs into the SUS, by comparison of scenarios

Analysis perspective: Unified Health System - SUS / MG		Comparison scenarios	
		Reference scenario	**CT only**
Time horizon: 5 years	**5 years**	**Alternative scenario A**	BEVA + CT
		Alternative scenario B	CETUX + CT
Population size:	635	**Alternative scenario C**	PANIT + CT
Adjustment for inflation?	**Yes**	**Average inflation for the period**	7,00%
Adjust for a discount?	**No**	**Discount rate amount**	Not applicable
Consider the avoided costs?	**No**		

Incremental Budget Impact: no avoided costs

Scenario A vs Reference scenario (US $)		**Difference%**
Year 1	21,131,270	319
Year 2	21,820,930	339
Year 3	22,494,830	361
Year 4	22,797,420	377
Year 5	23,090,440	393
In 5 years	**111,334,890**	**357**

Scenario B *vs* Scenario A (US$)		**Difference %**
Year 1	1,302,840	5
Year 2	817,830	3
Year 3	340,570	1
Year 4	104,650	0
Year 5	- 127	0
In 5 years	**2,437,980**	**2**

Scenario B vs Reference scenario (US$)		**Difference %**
Year 1	22,434,110	339
Year 2	22,638,760	352
Year 3	22,835.400	366
Year 4	22,901,810	378
Year 5	22,962,790	391
In 5 years	**113,772,870**	**364**

Scenario C *vs* Scenario A (US$)		**Difference %**
Year 1	-1,184,750	-4
Year 2	-1,431,520	-5
Year 3	-1,674,160	-6
Year 4	-1,786,560	-6
Year 5	-1,896,900	-7
In 5 years	**-30,859,000**	**-6**

Scenario C vs Reference scenario (US$)		**Difference %**
Year 1	19,946,510	301
Year 2	20,389,410	317
Year 3	20,820,410	334
Year 4	21,010,850	347
Year 5	21,193,540	361
In 5 years	**103,360,980**	**331**

Scenario C *vs* Scenario B (US$)		**Difference %**
Year 1	-2,487,600	-9
Year 2	-2,249,350	-8
Year 3	-2,014,730	-7
Year 4	-1,891,210	-7
Year 5	-1,769,510	-6
In 5 years	**-10,411,890**	**-7**

Source: Prepared by the authors.

Table 5 - Values for diffusion and restriction of spending by scenarios

Rate	Scenarios (with inflation adjustment)

Dissemination / Restriction	Population (variation)	Reference (CT)	BEVA	CETUX	PANIT
Dissemination%	**n**	**US$ (millions)**	**US$ (millions)**	**US$ (millions)**	**US$ (millions)**
Low difusion	635	31,220,930	107,724,222	112,530,491	101,031,525
Media difusion	635	31,220,930	110,250,388	113,399,742	102,661,240
High difusion	635	31,220,930	110,985,271	113,652,713	103,135,401
Model Difusion	635	31,220,930	110,620,672	113,527,132	102,900,258
Restriction	**n**	**US$ (millions)**	**US$ (millions)**	**US$ (millions)**	**US$ (millions)**
KRAS mutation (41%)	381	31,220,930	44,248,269	68,116,279	61,740,155
Judicial demand (7%)	44	31,220,930	7,665,054	7,866,447	7,130,097
Prices		**US$ (millions)**	**US$ (millions)**	**US$ (millions)**	**US$ (millions)**
BPS Prices	BP	31,220,930	110,620,672	113,527,132	102.900.258
CMED prices	CMED	31,220,930	124,587,080	130,358,140	105,246,770
Diference		0	14,224,806	16,831,008	2,346,512

Source: Prepared by the authors.

Caption: BEVA = bevacizumab; BPS = Health Price Bank; CETUX = cetuximab; CMED = Medicines Market Regulation Chamber; PANIT = panitumumab; CT = chemotherapy.

Table 6 - Analysis of costs associated with treatment US$)

Direct costs	BEVA 25 MG/ML(4ml)	CETUX 5 MG/ML (20ml)	PANIT 20 MG/ML(5ml)	CT
Unit cost of medication (US$)	401.92	189.20	308.70	574.68
Monthly quantity (units)	10	20	10	1
Costs associated with BP price (month)	**BEVA**	**CETUX**	**PANIT**	**CT**
MAB (month)	4,019.17	3,782.95	3,086.28	574.68
MAB (year)	48,230.40	45,395.40	37,035.36	6,896.16
CT (month)	574.68	574.68	574.68	574.68
Total (MAB + CT) (month)	4,593.85	4,357.62	3,660.96	574.68
Values for sensitivity analysis	**BEVA**	**CETUX**	**PANIT**	**CT (APAC)**
BPS Price (2018)	401.92	189.20	308.63	574.68
Price CMED 2018 PF (ICMS 18% MG)	413.54	227.13	329.17	574.68
difference (-)/ (+)	- 11.62	-37.93	-20.54	0.00
Associated costs CMED price (month)	**BEVA**	**CETUX**	**PANIT**	**CT (APAC)**
MAB	4,134.37	4,542.64	3,291.68	574.68
CT	574.68	574.68	574.68	574.68
Total (MAB + CT)	4,709.05	5,117.31	3,866.36	0.00

Source: Prepared by the authors.
Legend: APAC = Authorization for High Complexity Procedures; BEVA = bevacizumab; BPS = Health Price Bank; CETUX = cetuximab; CMED = Drug Price Regulation Chamber; ICMS = Tax on Transactions related to the Circulation of Goods and Provision of Interstate and Intermunicipal Transport and Communication Services; MAB = monoclonal antibody; PANIT = panitumumab; CT = chemotherapy (costs in US$= dollar)

Table 7 - Costs avoided (US$) or number of events prevented with the incorporation of MABs

Costs avoided with the new therapy (12 months)	ARIES STUDY BEVA + CT (43)	CRYSTAL STUDY CETUX+ CT (72)	PRIME STUDY PANIT+ CT (60)
Name of the prevented event (1 year)	**Deaths**	**Deaths**	**Deaths**
Number of outcomes in the intervention group	103	187	171
Total number in the intervention group	402	599	259
Mortality rate of patients who underwent the evaluated treatment	25,7	30,6	25,7
Number of outcomes in the control group	150	183	188
Total number in the control group	411	599	253
Mortality rate of patients who underwent the standard treatment	36,6	31,2	34,0
Individual cost of each event (median per patient) (US$)	27,499	24,954	21,927
Follow-up time in the study (in years)	1	1	1
Number of prevented events for every thousand patients treated with the new intervention for one year	109	7	83
Cost (US$) avoided per thousand patients treated with the new intervention	2,997,391	174,678	1,819,941

Source: Prepared by the authors adapted from Brazilian spreadsheets with budget impact. Caption: BEVA = bevacizumab; CETUX = cetuximab; PANIT = panitumumab; CT = chemotherapy

PRIME STUDY: *Panitumumab* Randomized *Trial* In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy
ARIES STUDY: *Avastin*(®) Registry - Investigation of Effectiveness and Safety
CRYSTAL=**C**etuximab combined with i**R**inotecan in first-line therap**Y** for meta**ST**atic colorect**AL** cancer