

OFF-LABEL USE OF BEVACIZUMAB IN ONCOLOGY PATIENTS. INFLUENCE ON EFFECTIVENESS, SECURITY AND COSTS

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Abstract

We evaluated the prevalence of data on the off-label use (OFLU) of bevacizumab for oncology patients and we analysed the influence on health outcomes and economic costs in the context of general clinical practice. We collected data on the oncology prescriptions of patients in a regional hospital of southern Spain (years 2006 - 2012). We collected progression free survival (PFS), overall survival (OS), duration of treatment and costs as outcome variables. The analysis comprised 240 prescriptions, 57.1% were on-label use (ONLU) versus 42.9% OFLU. The median of the treatment duration, PFS and OS at ONLU/OFLU was 6.1/5.4 months, 7.2/6.5 months and 12.9/12.6 months, respectively. The sensitivity analysis showed a statistically significant difference for PFS and OS in favour of ONLU prescriptions. Patients with ONLU prescriptions had a frequency of adverse effects of 71.5% while patients with OFLU prescriptions 60.2%. The cost of bevacizumab for the ONLU treatments was 2,850,370.42 € and 3,586,419.60 € for the OFLU treatments. The results of efficacy and safety do not vary significantly between ONLU and OFLU prescriptions, but do vary in the sensitivity analysis. The consumption of bevacizumab increases significantly with bevacizumab OFLU.

Rezumat

Am evaluat prevalența datelor privind utilizarea *off-label* (OFLU) a bevacizumabului pentru pacienții oncologici și am analizat eficiența farmacoterapeutică, precum și costul economic în contextul practicii clinice generale. Am colectat date privind prescripțiile oncologice ale pacienților dintr-un spital regional din sudul Spaniei (2006 - 2012) și am evaluat supraviețuirea fără progresia bolii (PFS), supraviețuirea globală (OS), durata tratamentului și costurile. Analiza a cuprins 240 de prescripții, dintre care 57,1% au respectat indicațiile (ONLU) față de 42,9% care au fost OFLU. Mediana duratei tratamentului, PFS și OS în cazul ONLU/OFLU, a fost 6,1/5,4 luni, 7,2/6,5 luni și, respectiv 12,9/12,6 luni. Analiza sensibilității a arătat o diferență statistic semnificativă pentru PFS și OS în favoarea prescripțiilor ONLU. Pacienții cu prescripții ONLU au avut o frecvență a efectelor adverse de 71,5%, în timp ce la pacienții cu prescripții OFLU frecvența a fost de 60,2%. Costul bevacizumabului pentru tratamentele ONLU a fost de 2.850.370,42 € și, respectiv 3.586.419,60 € pentru tratamentele OFLU. Rezultatele eficacității și siguranței nu variază semnificativ între prescrierile ONLU și OFLU. Consumul de bevacizumab a crescut semnificativ cu prescrierea acestuia *off-label*.

Keywords: bevacizumab, off-label prescribing, oncology, outcome research

Introduction

The use of a marketed drug in other conditions than those authorized including changes in the therapeutic indication, dose of the drug and association with other drugs, use in different populations such as the paediatric [1], lines of treatment, and change in the route of administration is commonly named of off-label use (OFLU). In the oncology area off-label use of drugs is a widespread practice due to the rapid evolution of biomedical research, the great diversity of therapeutic options and large interindividual variability of patients.

A study conducted in USA in 1991 by the US Government Accountability Office estimated the OFLU in 33% of all prescriptions for a selected

group of chemotherapy agents. The same study found that up to 56% of the patients had an OFLU prescription at some point in their treatment with at least one drug [2].

With new anticancer drugs from the monoclonal antibodies group, a study conducted in 2012 in France detected 1,499 OFLU situations involving 3,267 patients. The OFLU of anticancer drugs affected 53% of the patients. The molecule mostly involved in these situations was bevacizumab, in 34% of patients [3]. A study conducted in Switzerland in 2012 found a total of 473 administrations OFLU (27.2%) for a total of 1,737 drugs that affected 32.4% of the patients enrolled in the study. The OFLU frequency for bevacizumab was 29.6% [4].

In several research studies conducted in Spain, the average of OFLU for cetuximab, trastuzumab and rituximab were 70.3%, 37.7% and 37.1% respectively [5-7].

A systematic review [8] of OFLU in the clinical practice detected a frequency of bevacizumab in oncology of 54% and 62.2% in other two studies [9, 10].

This work analysed the influence of bevacizumab off-label use on health benefits routine clinical practice in terms of effectiveness, safety and costs with respect to the criteria of technical label (TL), on-label use (ONLU) [11].

Materials and Methods

Study design. An observational study regarding the post-marketing use of drugs and evaluation of health outcomes, was conducted in the area served by a regional hospital that covers a population of 665,000 patients in the Southern Spain. The results shown in this work are part of a larger observational study MAR-BEV-2013-01, carried out on the same population [12]. The protocol was approved by the institutional review board of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Population. All patients of the hospital receiving bevacizumab-containing therapy between 2006 and 2012 were included. Patients treated within other clinical trial protocol were excluded. The selection of patients for this study was conducted using the records of the pharmacy oncology service.

Case Definition. Prescription of bevacizumab: covering the treatment in patients from the beginning until the withdrawal of bevacizumab for any reason.

Data Collection. The variables used for the study were collected from the records of the hospital. The collected variables for each case were related to the terms and conditions of use of bevacizumab during treatment, which includes diagnosis, line of treatment, dosage, drugs administered with bevacizumab and treatment duration (TD). It was determined if the use of bevacizumab met the criteria of ONLU or OFLU according to TL at the time of the closure of the recruitment of cases (Table I). The variables related to health outcomes were progression-free survival (PFS), overall survival (OS), incidence of adverse effects and the number of hospital admissions. The economic variable collected was the cost of the chemotherapy used throughout the treatment of the patients included in the study.

Table I
Indications of technical label (TL) for Bevacizumab in 2012

Diagnosis	Line (&)	Associated drugs	Dose/Pattern	EMA Approval Date
Metastatic Colorectal Cancer	1 st	Fluoropyrimidine derivatives and/or irinotecan	5 mg/kg bw/14 days	20/10/2004
Metastatic breast cancer	1 st	Paclitaxel	10 mg/kg bw/14 days	27/03/2007
Non small-cell lung unresectable metastatic or recurrent cancer	1 st	Chemotherapy based-platinum	15 mg/kg bw/21 days	21/08/2007
Metastatic renal cancer cells	1 st	Interferon alfa 2a	15 mg/kg bw/21 days	14/12/2007
Metastatic Colorectal Cancer (Extension of indication)	1 st and 2 nd	Oxaliplatin fluoropyrimidine	5 - 10 mg/kg bw/15 days or 7.5 - 15 mg/kg bw/21 days	25/01/2008
Metastatic breast cancer (Extension of indication)	1 st	Docetaxel	15 mg/kg bw/21 days	23/07/2009 (\$)
Metastatic breast cancer (Extension of indication)	1 st	Capecitabine	15 mg/kg bw/21 days	29/06/2011
Advanced Ovarian Cancer	1 st	Carboplatin + Paclitaxel	15 mg/kg bw/21 days	19/12/2011
Advanced Ovarian Cancer (Extension of indication)	2 nd	Carboplatin + Gemcitabine	15 mg/kg bw/21 days	24/10/2012
(\$) This decision was subsequently revoked in 28/02/2011 by benefit/risk balance negative. This study considered all treatments with docetaxel ONLU.				
(&) For the purposes of adequacy to technical label, non-first-line treatment was considered second line.				

Statistical analysis. The mean, median and measures of dispersion were used for the descriptive analysis of bevacizumab use. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was used to compare the survival curves of TD, PFS and OS for ONLU and OFLU. Statistical analyses were performed using *G-Stat 2.0*; *Dep. Biometría GSK. Madrid*.

Sensitivity analysis. For the primary analysis we considered ONLU all prescriptions in 2nd line or later in metastatic colorectal cancer (mCRC). There will be a new analysis considering OFLU the prescriptions of bevacizumab for mCRC in 3rd line or later on the basis of the studies E3200 and ML18147 that led to the approval of this indication.

Results and Discussion

The total number of prescriptions/cases with bevacizumab included was 240, which corresponded to 226 patients. A total of 137 prescriptions (57.1%) were ONLU *versus* 103 prescriptions OFLU (42.9%). The result obtained in this study was slightly lower than other studies concerning this drug 54% [9] and

62.2% [10]. The frequency of off-label use in oncology varies among studies because of the methodological differences. Thus, this makes difficult to compare and extrapolate results [13].

The complete results of ONLU and OFLU classified by reason of inadequacy are shown in Figure 1 and Table II.

Table II

Prescriptions of bevacizumab ONLU/OFLU by diagnosis, line (II-A) and drug/associated scheme (II-B)

Table II-A			Table II-B			
Line	No. Prescriptions (%)	ONLU/OFLU (n)	Associated Drug	No. Prescriptions (%)	ONLU/OFLU (n)	
Global: 240 (100%)						
1 st line	80 (33.3 %)					
2 nd or later	160 (66.7 %)					
mCRC: 107 (44.6%)						
1 st line	35 (14.6 %)	35/0	Irinotecan+fluoropyrimidine	48 (20 %)	96/0	
2 nd line	26 (10.8 %)	61/11	Oxaliplatin+fluoropyrimidine	30 (12.5 %)		
3 rd line	25 (10.4 %)		Fluoropyrimidine	18 (7.5 %)		
4 th or later	21 (8.8 %)		Monotherapy	11 (4.6 %)	0/11	
mBC: 47 (19.6%)						
1 st line	16 (6.2 %)	16/0	Paclitaxel or docetaxel	36 (15 %)	16/20	
2 nd line	10 (4.2 %)	0/31	Capecitabine	4 (1.7 %)	0/4	
3 rd line	9 (3.7 %)		Vinorelbine	3 (1.2 %)	0/3	
4 th or later	12 (5 %)		Monotherapy	3 (1.2 %)	0/3	
			Paclitaxel+Gemcitabine	1 (0.4 %)	0/1	
NSCLC: 34 (14.2%)						
1 st line	29 (12.1 %)	29/0	Paclitaxel +Carboplatin	21 (8.8 %)	21/0	
2 nd line	2 (0.8 %)	0/5	Cisplatin+Gemcitabine	9 (3.7 %)	8/1	
3 rd or later	3 (1.2 %)		Pemetrexed	2 (0.8 %)	0/2	
			Monotherapy	2 (0.8 %)	0/2	
OC: 16 (6.7%)						
3 rd line	4 (1.7 %)	16/0	Topotecan	6 (2.5 %)	0/16	
4 th or later	12 (5 %)		Monotherapy	5 (2.1 %)		
			Pegylated liposomal doxorubicin	4 (1.7 %)		
			Oxaliplatin	1 (0.4 %)		
GLB: 24 (10%)						
2 nd line	24 (10 %)	0/24	Irinotecan	21 (8.8 %)		
			Monotherapy	3 (1.2 %)		
Other (&): 12 (5%)						
(&): 4 patients soft tissue sarcoma, 2 endometrial cancer, 1 prescription for kidney, gastric, adrenal, pancreas cancer, mesothelioma, and melanoma (ONLU/OFLU: 1/11) mCRC – metastatic colorectal cancer, mBC – metastatic breast cancer, NSCLC – non small cell lung cancer, OC – ovarian cancer, GLB – glioblastoma.						

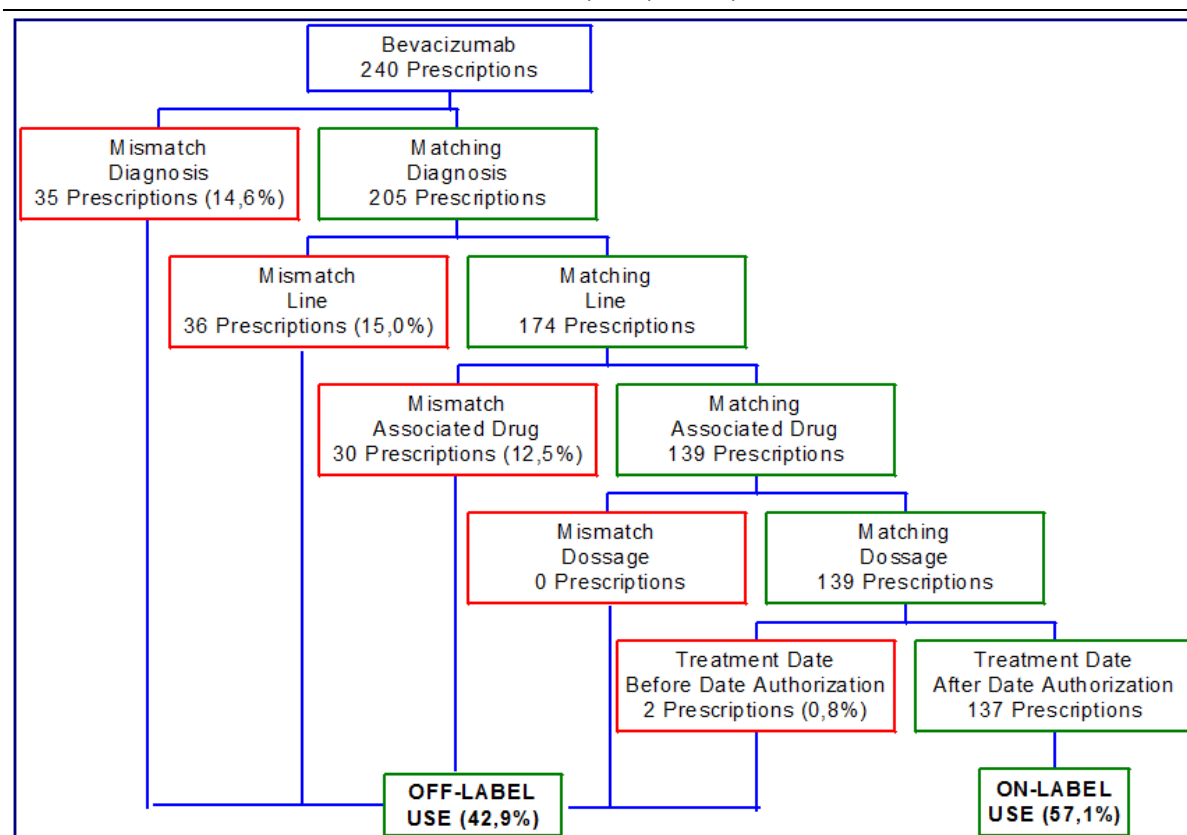


Figure 1.

Flowchart for classification of prescription in off-label use (OFLU) and on-label use (ONLU)

The profile of OFLU in this study was composed by patients in 2nd or subsequent line of therapy for metastatic breast cancer (mBC) (n = 31), glioblastoma (GLB) (n = 24) and non-small-cell lung cancer (NSCLC) (n = 5), mCRC patients treated with monotherapy (n = 11) and ovarian cancer (OC) patients treated with combinations not approved by the TL (n = 16). There is also an important group of patients (n = 11) with diagnosis of very diverse sarcoma, endometrium, gastric, adrenal cancers not approved at the closing date of this study. Bevacizumab monotherapy is approved by U.S FDA (Food and Drug Administration), not by the EMA (European Medicines Agency), in relapse after treatment with temozolomide for GLB [14], the patients of this study were treated mostly with bevacizumab in combination with irinotecan [15]. Bevacizumab has received authorization by EMA [16], after the closing date of the study, in OC patients resistant to platinum, which have not received more than two previous lines, associated with paclitaxel, topotecan or liposomal pegylated doxorubicin. This indication is based on the study AURELIA [17].

In the descriptive analysis, the mean duration of all treatments with bevacizumab was 8.4 months [95% CI: 7.19 - 9.61]. The mean duration of treatment ONLU was 8.3 months [95% CI: 6.8 - 9.8] and for

treatments with prescription OFLU was 8.6 months [95% CI: 6.6 - 10.6].

Health outcomes in this study for the ONLU and OFLU groups did not differ statistically for the median values obtained in the survival analysis. The median for the TD, PFS and OS according to the Kaplan-Meier for primary analysis, depending on whether the prescription of bevacizumab was ONLU or OFLU the hazard ratio were 1.01 [95% CI: 0.78 - 1.32]; 0.94 [95% CI: 0.71 - 1.25]; 1.00 [95% CI: 0.77 - 1.32], respectively (Table III). The lack of statistically significant difference was observed for these variables between the two groups. We can see there is a large variability in the diagnosis and lines of each group as well as in the number of cases within each type of patient.

The results obtained in the sensitivity analysis did not find statistically significant differences for TD between ONLU and OFLU prescriptions. However, the median of PFS was significantly higher, 7.5 months and 6.3 months (p = 0.0319), for ONLU than OFLU prescriptions. Equally, the median of OS was significantly higher, 14.2 months and 11.7 months (p = 0.0210) for ONLU than OFLU prescriptions (Table III).

The survival curves for PFS and OS for sensitivity analysis are shown in Figures 2a, 2b.

Table III

Results of bevacizumab effectiveness, ONLU and OFLU prescriptions

Primary analysis			
	Median (months)	hr [95% CI]	log-rank p
Duration of treatment			
ONLU	6.1	1.01 [0.78 -1.32]	0.8986
OFLU	5.4		
Progression Free Survival (PFS)			
ONLU	7.2	0.94 [0.71 -1.25]	0.6778
OFLU	6.5		
Overall Survival (OS)			
ONLU	12.9	1.00 [0.77 – 1.32]	0.9748
OFLU	12.6		
Sensitivity analysis			
	Median (months)	hr [95% CI]	log-rank p
Duration of treatment			
ONLU	6.3	0.87 [0.67-1.13]	0.2959
OFLU	5.4		
Progression Free Survival (PFS)			
ONLU	7.5	0.72 [0.54-0.97]	0.0319
OFLU	6.3		
Overall Survival (OS)			
ONLU	14.2	0.72 [0.55-0.95]	0.0210
OFLU	11.7		

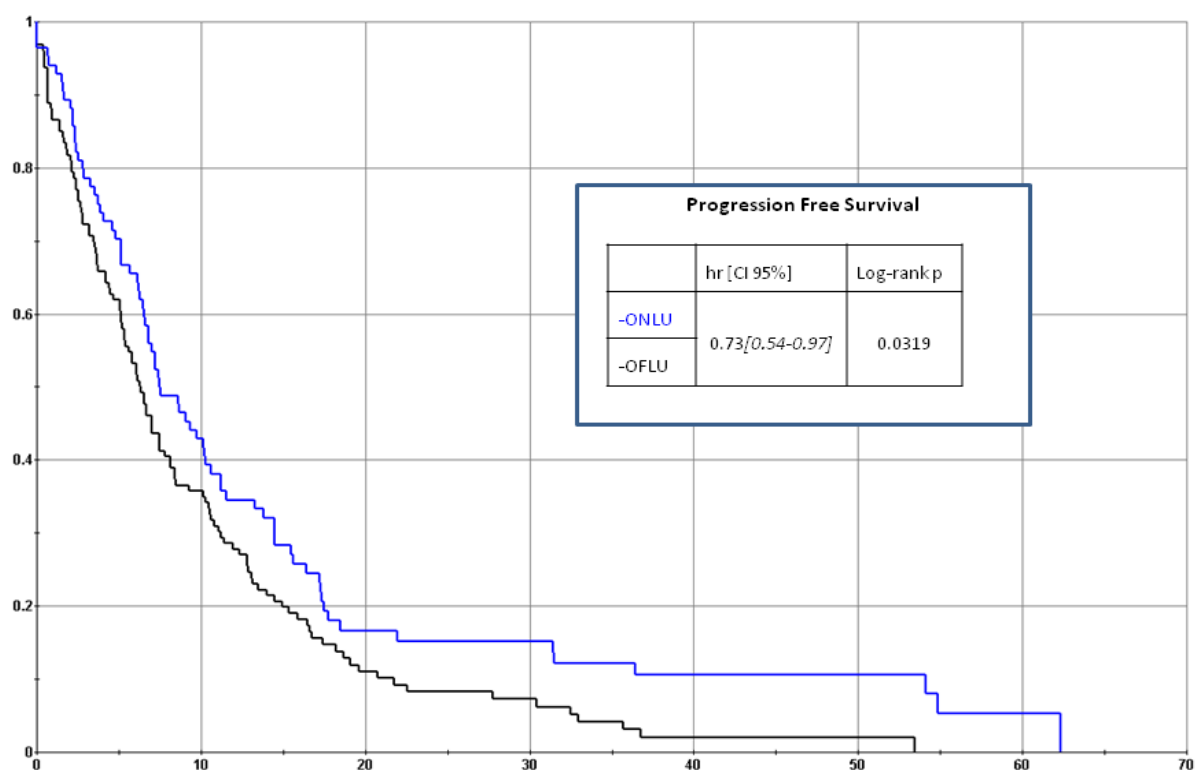


Figure 2a.
Survival curves for PFS, sensitivity analysis

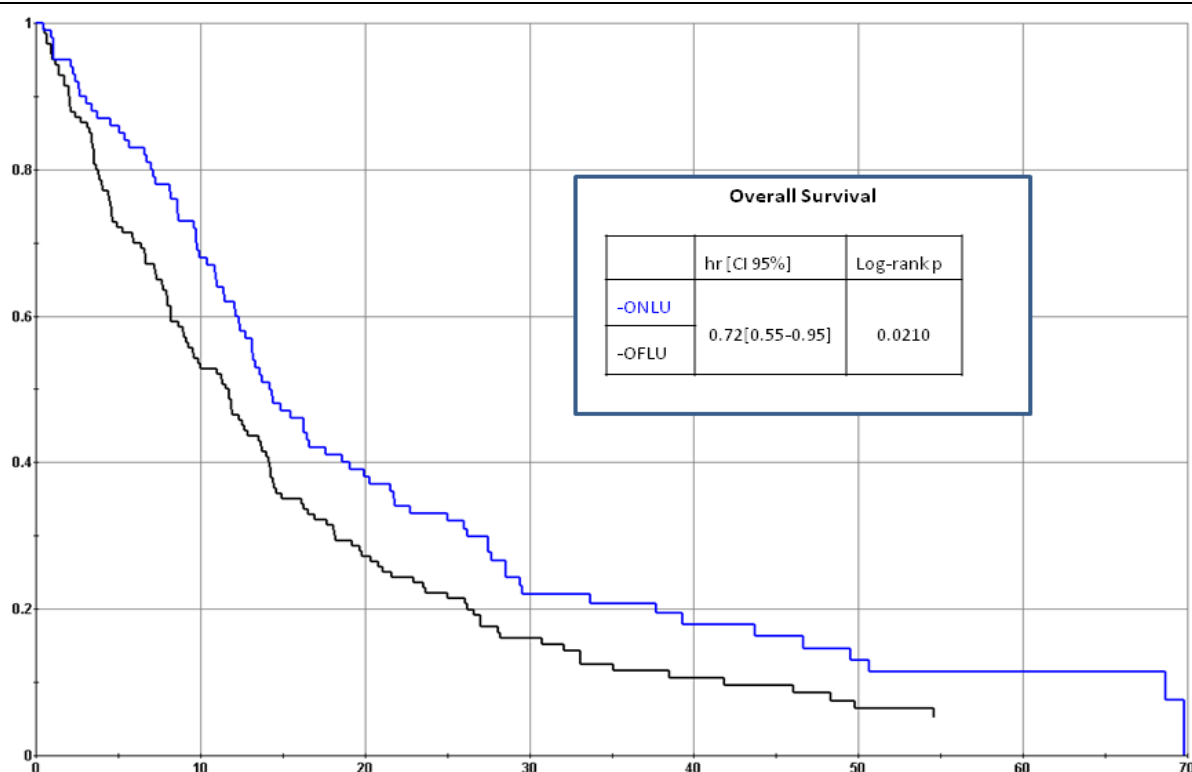


Figure 2b.
Survival curves for OS, sensitivity analysis

The sensitivity analysis showed that the TD remains without a significant difference between ONLU and OFLU prescriptions, no matter if there is a statistically significant difference for the results of PFS and OS. This result would indicate that to find a significant difference in survival curves for PFS and OS treatments with bevacizumab in 3rd or later mCCR line are less effective than in 2nd line. In addition the results of TD do not vary and the high cost of bevacizumab should reconsider the use of bevacizumab in these lines of treatment in terms of efficiency.

21.9% of the patients treated with ONLU prescription had some hospital admissions during their treatment compared to 24.3% of patients with OFLU prescription, $p = 0.6649$. Whereas 71.5% of the patients treated

with ONLU prescription had adverse effects during their treatment with bevacizumab compared to 60.2% of patients with OFLU prescription, $p = 0.0651$. No difference in terms of the incidence of adverse effects was observed in the frequency of patients requiring hospital admission among patients with ONLU and OFLU treatments. However, there is a trend towards a lower frequency of adverse effects in the OFLU group, which could be due to a slight difference in the frequency of adverse effects of bevacizumab related to the pathology [18].

The overall treatment cost of intravenous chemotherapy for patients included in this study was 9,552,405 €, distributed in 4,694,070 € (50.9%) for ONLU prescriptions and 4,858,335€ (49.1%) for OFLU prescriptions (Table IV).

Table IV
Consumption and cost for ONLU and OFLU prescription

	Consumption (€)		
	Total prescriptions	OFLU prescriptions	ONLU prescriptions
Total Chemotherapy (%)	9,552,404 €	4,858,334 €	4,694,070 €
Bevacizumab (%)	6,436,790 €	3,586,419 €	2,850,370 €
Cost Chemotherapy/patient	39,802 €	47,168 €	34,263 €
Cost Bevacizumab/patient	26,820 €	34,820 €	20,806 €
Median OS (m) (Primary analysis/ Sensitivity analysis)		12.6/11.7	12.9/14.2
Cost/month OS/patient (Primary analysis - Sensitivity analysis)		2,763 € - 2,976 €	1,613 € - 1,465 €

The cost for the consumption of bevacizumab was 67.4% of the total cost of intravenous chemotherapy, distributed in 29.9% for ONLU treatment and 37.5% for OFLU treatments. The distribution of consumption of bevacizumab was 55.7% for OFLU group and 44.3% for ONLU group; this percentage is similar at 62% of consumption in OFLU treatments for bevacizumab in oncologic patients during 2010 in USA [13].

The percentage of the cost of bevacizumab with regard to the total cost of chemotherapy of each type of prescription was 60.7% [95% IC: 55.3 - 66.1] in ONLU prescriptions and 73.8% [95% IC: 67.4 - 80.2] in OFLU prescriptions. In the ONLU group there is a high percentage of patients with mCRC whose prescribed dose was 2.5 mg/kg bw/week whereas in the OFLU group, all the prescribed doses were adjusted to 5 mg/kg bw/week, resulting in an increased consumption of bevacizumab for OFLU group related to the total cost of chemotherapy.

The cost for ONLU treatment of bevacizumab was 20,806 € [95% IC: 17,305 - 24,235] and 34,820 € [95% IC: 26,457 - 43,275] for OFLU treatment with a much higher cost for each month OS/patient obtained.

Conclusions

The OFLU frequency of bevacizumab in our hospital area is similar to that of other studies, taking into account the intrinsic variability of the date it was done and the methodology followed in each study. It is important to mention that there have been found no differences in regard to results of effectiveness and safety between the ONLU and OFLU treatments with the profile that presents the group of patients from this study. However, the high cost added by bevacizumab makes it necessary to establish a control and a rigorous selection of OFLU treatments, based on the best evidence for the specific conditions of each patient, as is evident from the sensitivity analysis.

Financing and conflict of interest

This work has been carried out with their own means from researchers, without external sponsor.

The authors declare they do not have conflict of interest in the conduct of this study.

References

1. Man S.C., Primejdie D.P., Sarkozi I.K., Popa A., Off-label and unlicensed prescribing in hospitalized children: prevalence and reasons. *Farmacia*, 2017; 65(3): 460-466.
2. Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies. United States General Accounting Office: Off-Label Drugs, 1991. www.archive.gao.gov.
3. Kabiche S., Monzat D., Le Jouan M., Farinotti R., Montagnier-Petrissans C., Le Gonidec P., Off-label use of "High-cost" drugs in Paris area hospitals. *Int. J. Clin. Pharm.*, 2013; 35: 1251-1351.
4. Joerger M., Schaer-Thuer C., Koeberle D., Matter-Walstra K., Gibbons-Marsico J., Diem S., Thuerlimann B., Cerny T., Off-label use of anticancer drugs in eastern Switzerland: a population-based prospective cohort study. *Eur. J. Clin. Pharmacol.*, 2014; 70(6): 719-725.
5. Marín Pozo J.F., Oya Alvarez de Morales B., Caba Porras I., Aranda García J., Study into the use of cetuximab in metastatic colorectal cancer in a third level hospital. *Farm. Hosp.*, 2009; 33(2): 72-79.
6. Vargas Rivas J., Montes Casas M., Cancel Diez B., Martínez Martínez F., Sabater Hernández D., Calleja Hernández M., Estudio de adecuación a la ficha técnica de las prescripciones de trastuzumab en un hospital de tercer nivel. *Farmacia Hospitalaria*, 2012, 36(3): 135-140.
7. Conde García M.C., Fernández Feijoo M.A., Calleja Hernández M.A., Estudio de adecuación a la ficha técnica, efectividad, seguridad y coste del rituximab en un hospital de tercer nivel. *Farm. Hosp.*, 2009; 33(6): 305-311.
8. Zarkali A., Karageorgopoulos D.E., Rafailidis P.I., Falagas M.E., Frequency of the off-label use of monoclonal antibodies in clinical practice: a systematic review of the literature. *Curr. Med. Res. Opin.*, 2014; 30(3): 471-480.
9. Freeman C.P., Leonard C.E., de Nava K.L., Molina T., MaCurdy T., Utilization of anticancer biologic products among medicare beneficiaries, By Diagnostic Cancer Subchapter, 2006–2009: Data Points #7. In: Data Points Publication Series. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011. www.ncbi.nlm.nih.gov.
10. Bonifazi M., Rossi M., Moja L., Scigliano V.D., Franchi M., La Vecchia C., Zocchetti C. Negri E., Bevacizumab in clinical practice: Prescribing appropriateness relative to national indications and safety. *Oncologist*, 2012; 17(1): 117-124.
11. European Medicines Agency. Londres. Comité for Medicinal Products for Human Use. Avastin, INN-bevacizumab. Anexo I: Ficha Técnica o resumen de las características de producto. 2013. www.ema.europa.eu.
12. Marín-Pozo J.F., Duarte-Pérez J.M., Sánchez-Rovira P., Safety, effectiveness, and costs of bevacizumab-based therapy in southern Spain: a real world experience. *Medicine (Baltimore)*, 2016; 95(19): 1-7.
13. Conti R.M., Bernstein A.C., Villaflor V.M., Schilsky R.L., Rosenthal M.B., Bach P.B., Prevalence of off-label use and spending in 2010 among patent-protected chemotherapies in a population-based cohort of medical oncologists. *J. Clin. Oncol.*, 2013; 31(9): 1134-1139.
14. Food and Drug Administration. Silver Spring. Center for Drug Evaluation and Research (CDER). Avastin Label. Highlights of Prescribing Information. 2013. www.accessdata.fda.gov.
15. Friedman H.S., Prados M.D., Wen P.Y., Mikkelsen T., Schiff D., Abrey L.E., Yung W.K., Paleologos N., Nicholas M.K., Jensen R., Vredenburg J., Huang J., Zheng M., Cloughesy T., Bevacizumab alone and in

- combination with irinotecan in recurrent glioblastoma. *J. Clin. Oncol.*, 2009; 27(28): 4733-4740.
16. European Medicines Agency. Londres. Comité for Medicinal Products for Human Use. Avastin, INN-bevacizumab. Anexo I: Ficha Técnica o resumen de las características de producto. 2015. www.ema.europa.eu.
17. Pujade-Lauraine E., Hilpert F., Weber B., Reuss A., Poveda A., Kristensen G., Sorio R., Vergote I., Witteveen P., Bamias A., Pereira D., Wimberger P., Oaknin A., Mirza M.R., Follana P., Bollag D., Ray-Coquard I., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized Phase III trial. *J. Clin. Oncol.*, 2014; 32(13): 1302-1308.
18. Amit L., Ben-Aharon I., Vidal L., Leibovici L., Stemmer S., The Impact of bevacizumab (Avastin) on survival in metastatic solid tumors - a meta-analysis and systematic review. *PLoS One*, 2013; 8(1): 1-10.