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ORIGINAL ARTICLE

MDM2 amplification in a real-world cohort of patients with biliary tract cancer from the Spanish RETUD gastrointestinal registry

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Background: Antagonist of mouse double minute 2 homolog (*MDM2*) represents a novel therapeutic strategy in biliary tract cancer (BTC). We aimed to characterize the epidemiology of *MDM2* amplifications in patients with BTC, associations of *MDM2* with other genetic alterations, and survival outcomes.

Materials and methods: A real-world cohort of patients diagnosed with BTC (1 January 2017 to 31 December 2022) was evaluated (RETUD NCT06711211). Next-generation sequencing (NGS) testing was carried out. Demographic and clinical characteristics, molecular profile, treatments, and effectiveness [overall response rate (ORR) and survival outcomes] were assessed. Progression-free survival (PFS), overall survival (OS), and ORR were estimated for patients receiving first-line therapy, using the Kaplan—Meier method. Descriptive analyses were used to assess demographic, clinical, and molecular features.

Results: A total of 301 patients were included. *MDM2* amplification was reported in 19 patients (6.3%); two of them (10.5%) had *TP53* mutations. Most patients (63.2%; 12/19) with *MDM2* amplification had intrahepatic tumors. However, *MDM2* amplification was more frequent in patients with gall-bladder carcinoma (12.9%; 4/31). Patients with/without *MDM2* amplification receiving first-line therapy [cisplatin and gemcitabine (CisGem)] showed a median OS [95% confidence interval (CI)] of 18.4 months (12.3-19.9 months) and 17.8 months (12.3-19.9 months, $P = 0.247$), a median PFS (95% CI) of 5.3 months (2.7-8.9 months) and 6.0 months (5.3-6.8 months, $P = 0.423$), and an ORR of 21.4% and 29.6% ($P = 0.762$), respectively.

Conclusions: Incidence of *MDM2* amplification was similar to that described in other BTC cohorts. Comparable results in demographic/clinical characteristics, molecular profile, and survival outcomes between patients with/without *MDM2* amplification was observed.

Key words: *MDM2* amplification, biliary tract cancer, RETUD registry, real-world data, Spain

INTRODUCTION

Biliary tract cancer (BTC) constitutes a heterogeneous group of aggressive epithelial tumors of the gall-bladder and biliary tract, further divided into gall-bladder carcinoma (GBC), ampullary cancer (AC) (also known as ampulla of Vater), intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA).[1-5] BTC is a rare cancer with a low incidence that accounts for <1% of all human cancers,[1,3] and comprises ~3% of all gastrointestinal tract neoplasms.[6] Moreover, iCCA is the second most common primary hepatobiliary malignancy behind hepatocellular carcinoma.[1,6] BTC is more common in Asian countries, and its etiology varies in different parts of the world, due to the genetic predisposition of some populations and prevailing risk factors in some areas (such as cholelithiasis in Latin America or parasitic infection by the liver fluke, *Opisthorchis viverrini*, and hepatitis B in Southeast Asia).[2,6,7]

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Although BTC is one of the most aggressive cancers, often its symptoms are nonspecific, causing a late diagnosis. Hence it is usually detected at an advanced and inoperable stage, when treatment options are limited, leading to a poor prognosis.[1,4,6,8] Moreover, BTC recurrence rate is high.[6] Therefore, optimal treatment of BTC is essential. The first-line standard of care for patients with recurrent, locally advanced, or metastatic BTC who are ineligible for resection is chemotherapy with cisplatin and gemcitabine (CisGem) with checkpoint inhibitors.[2,8-10] The second line is established without molecular selection based on the ABC-06 study with limited efficacy with expected survival of 7 months.[11] For patients with targetable alterations, target therapy is recommended in second line. Furthermore, due to BTC heterogeneity and targetable genetic alterations, a personalized approach is necessary to ensure quality care.[8,12]

According to the European Society for Medical Oncology (ESMO) Clinical Practice Guideline 2023,[10] it is important to confirm the location of BTC (iCCA, pCCA, dCCA, or GBC), since every subtype has specific clinical and molecular features, and it is recommended to perform next-generation sequencing (NGS) on all advanced cholangiocarcinoma.[13] A comprehensive molecular analysis encompassing testing at the DNA level [isocitrate dehydrogenase 1 (*IDH1*), human epidermal growth factor receptor 2 (*HER2*), *BRAF*, and fibroblast growth factor receptor 2 (*FGFR2*)], RNA level [*FGFR2* and neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions], and protein level (expression of the DNA mismatch repair proteins MLH1, MSH2, MSH6 and PMS2, and *HER-2*) is strongly recommended. For molecular diagnosis, parallel sequencing of multiple genes using NGS is preferred over single-gene testing.[14]

Antagonist of mouse double minute 2 homolog (*MDM2*) represents a novel therapeutic strategy in BTC.[2,3,15] *MDM2* is involved in regulating a protein called p53, which is responsible for stopping the growth of damaged cells, and, if the damage cannot be repaired, killing that cell before it turns into cancer.[3,15] It is estimated that *TP53*, the gene encoding p53, is inactivated (mutated or damaged) in ~50% of cancers.[15] The amplification of *MDM2* leads to overexpression of the MDM2 protein, which interferes with the cancer-preventive tumor suppressor role of functional *TP53*, inactivating p53 and potentially leading to tumorigenesis.[2,3] BTC is one of most frequent cancer types with increased levels of *MDM2*.[3] *MDM2* amplifications generally appear to be mutually exclusive with other alterations, such as *FGFR2* fusions, *HER2* amplifications, and *IDH1* mutations.[2]

A greater understanding of the molecular mechanisms involved in the genesis, progression, and dissemination of digestive tumors, such as BTC, is essential for the development of diagnostic methods that allow for earlier detection of the disease and for the design of more appropriate, individualized, and effective therapeutic strategies. Real-world studies allow us to understand how patients are treated outside of clinical trials, what their demographic and epidemiological characteristics are, and what their response to treatment is. The RETUD (Registro Español TUmores Digestivos)[16] is a multicenter Spanish registry for gastrointestinal malignances coordinated by the Cooperative Group for the Treatment of Digestive Tumors (Grupo de Tratamiento de los Tumores Digestivos; TTD group). Here, we evaluated a large real-world cohort of patients diagnosed with BTC from the RETUD registry to characterize the epidemiology of this population in comparison with that harboring *MDM2* amplifications, the potential associations of *MDM2* to other genetic alterations, and survival outcomes.

MATERIALS AND METHODS

Study population and design

This was a registry-based, noninterventional, and multicenter study from the Spanish RETUD registry (NCT06711211) in patients diagnosed with BTC from 1 January 2017 to 31 December 2022. A total of 24 centers contributed to the study. The main eligibility criteria were adult patients included in the RETUD registry diagnosed with BTC and who provided informed consent to participate and allow collection of biological samples.

An assessable patient was a patient who met the eligibility criteria, had a molecular study (NGS) available, and whose information has been completed in the database. Demographic and clinical characteristics, molecular profile, systemic oncologic treatment, and treatment effectiveness were collected for all assessable patients.

This study was conducted in accordance with the Helsinki Declaration, the guidelines for Good Clinical Practice and local laws and regulations. Protocol approval was received from the University Hospital Central de Asturias Ethics Committee on 6 June 2020, and informed consent was obtained from all patients before any study procedure.

Molecular profile

Every patient included had molecular testing carried out based on a sample of the tumor tissue used to diagnose the disease (primary tumor or metastasis).

Most common actionable genomic alterations including *MDM2* amplifications were sequenced using Foundation Medicine test (FoundationOne® DX, Cambridge, MA),[17] Panel NGS 300 of Vall d'Hebron Institute of Oncology (VHIO, Barcelona, Spain),[18] or Oncomine Comprehensive assay v3 (ThermoFisher, Waltham, MA).[19] The genes to be analyzed in this study were chosen for their fundamental role in the development and behavior of the tumor, providing important information about the disease.[1,3,14]

Study outcomes

Progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) were assessed. Analyses were carried out for the overall population and among patients with and without *MDM2* amplification. PFS and OS in patients exposed to CisGem as first-line treatment of BTC were also assessed.

PFS was defined as the time (months) from the start of first-line chemotherapy to disease progression or death from any cause, whichever occurred first, as assessed by the investigator. Patients without subsequent treatment or follow-up were censored at the last date available. OS was defined as the time (months) from diagnosis to death from any cause, with data censored at the last contact date for patients who were alive or lost to follow-up. Moreover, ORR was defined as the percentage of patients who had a partial or complete response to first-line treatment.

Statistical analysis

Since this was an epidemiological study, statistical results were mainly descriptive. Continuous variables were summarized using either the mean or median, along with measures of variability such as standard deviation or interquartile range (IQR). Categorical variables were shown as absolute counts and percentages. Descriptive statistics were used to analyze demographic data, tumor characterization, molecular analysis, and ORR. PFS and OS were estimated by the Kaplan—Meier method, with results reported as median survival times and 95% confidence intervals (CIs). The log-rank test was used to compare time-to-event distributions. *P* value <0.05 was considered statistically significant for all analyses.

All analyses were carried out with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

A total of 301 patients from the RETUD-BTC registry with molecular profiling carried out were included (Table 1). Patients were followed up for a median (IQR) of 14.7 months (8.3-22.3 months). Mean (IQR) follow-up for the *MDM2* amplification population was 17.9 months (11.9-22.0 months), whereas for the population without *MDM2* amplification mean (IQR) follow-up was 14.3 months (7.8-22.9 months).

Median age (IQR) for the entire population was 67.1 years (58.2-74.0 years), and 48.2% of patients were women. Regarding anatomical origin, iCCA was the most frequent (64.8% of patients). At primary diagnosis, half of patients (52.2%) had metastatic disease. Metastasis was in the liver in 68.2% of patients. Of the patients, 54.8% had Eastern Cooperative Oncology Group (ECOG) performance status 1 at metastasis diagnosis and 91.4% had received a first-line treatment, mainly with CisGem (64.9%). *TP53* mutations were reported in 27.6% of patients (Table 1).

MDM2 amplifications were observed in 19 (6.3%) patients, with a median (IQR) age of 67.6 years (65.3-74.3 years), mainly in men (57.1%). Similarly to the overall population, in the *MDM2* amplification population, the tumor was mostly iCCA (63.2% of patients). When considering the incidence of *MDM2* amplification according to the anatomic subtype, the most frequent was GBC (12.9% of patients; 4/31 patients). Metastatic disease at diagnosis was found in 52.6% of patients, with liver the most common location of metastasis (64.3% of patients). Most patients (89.5%) received first-line chemotherapy and the main first-line treatment was CisGem (47.4% of patients). Two patients (10.5%) had *TP53* mutations (Table 1).

Comparable results were observed in clinical characteristics (age, sex, stage, status, and metastatic tumor location) and in the remaining molecular profiling (*BRAF, HER2, IDH, FGFR2*) in patients with *MDM2* amplification compared with patients without *MDM2* amplification. Significant differences in tumor location ($P = 0.003$) and ECOG performance ($P = 0.046$) were observed between groups (Table 1).

Progression-free survival

The median PFS for the overall population in patients receiving first-line treatment was 5.8 months (95% CI 5.3-6.6 months). No significant differences in median PFS between patients with versus without *MDM2* amplification [5.3 months (95% CI 2.7-8.9 months) versus 6.0 months (95% CI 5.3-6.8 months), $P = 0.423$] were reported (Figure 1). Similarly, when comparing patients with versus without *MDM2* amplification receiving CisGem, no significant differences were observed [6.1 months (95% CI 0.9-11.3 months) versus 6.5 months (95% CI 5.5-7.1 months), respectively, $P = 0.707$] (Figure 2).

Overall survival

The median OS for the overall population of patients receiving first-line treatment was 17.8 months (95% CI 16.1-19.6 months). No significant differences between patients with versus without *MDM2* amplification were observed [18.4 months (95% CI 12.3-19.9 months) versus 17.8 months (95% CI 16.1-20.1 months), respectively, $P = 0.247$] (Figure 3), neither when comparing patients receiving CisGem with or without *MDM2* amplification [18.4 months (95% CI 7.9-20.0 months) versus 18.9 months (95% CI 16.1-21.0 months), respectively; $P = 0.416$] (Figure 4).

Overall response rate

The ORR in patients with first-line treatment was 21.4% in patients with *MDM2* amplification versus 29.6% in patients without *MDM2* amplification, without statistically significant differences ($P = 0.762$) (Table 2).

DISCUSSION

In a real-world setting, early diagnosis and tumor molecular profiling of BTC are essential for the design of individualized and optimal therapeutic strategies. Clinical practice information provides invaluable real-world data on the characteristics and health conditions of patients with BTC and on the use of the therapeutic resources. MDM2 is a potential therapeutic target for the treatment of specific molecular

Table 1. Demographic and clinical characteristics

	Overall population, $N = 301$	*MDM2* amplification population, $N = 19$ (6.3%)	No *MDM2* amplification population, $N = 282$ (93.7%)	*P* value
Age at diagnosis (years), median (IQR)	67.1 (58.2-74.0)	67.6 (65.3-74.3)	66.9 (58.0-74.0)	0.460
Female sex, *n* (%)	145 (48.2)	8 (42.1)	137 (48.6)	0.584
Location of primary tumor,[a] *n* (%)				
iCCA	195 (64.8)	12 (63.2)	183 (64.9)	0.003
pCCA	24 (8.0)	2 (10.5)	22 (7.8)	
dCCA	46 (15.3)	1 (5.3)	45 (16.0)	
GBC	31 (10.3)	4 (21.0)	27 (9.6)	
Other	5 (1.7)	0 (0.0)	5 (1.8)	
Disease status at diagnosis, *n* (%)				
Resectable	83 (27.6)	4 (21.0)	79 (28.0)	0.712
Locally advanced	61 (20.3)	5 (26.3)	56 (19.9)	
Metastatic	157 (52.2)	10 (52.6)	147 (52.1)	
ECOG at metastasis diagnosis, *n*/*N* (%)				
0	58/199 (29.1)	4/14 (28.6)	54/185 (29.2)	0.046
1	109/199 (54.8)	9/14 (64.3)	100/185 (54.0)	
2	28/199 (14.1)	1/14 (7.1)	27/185 (14.6)	
3	4/199 (2.0)	0/14 (0.0)	4/185 (2.2)	
Metastasis location, *n*/*N* (%)				
Liver	150/220 (68.2)	9/14 (64.3)	141/206 (68.4)	-
Bone	24/220 (10.9)	1/14 (7.1)	23/206 (11.2)	
Lungs	55/220 (25.0)	3/14 (21.4)	52/206 (25.2)	
Distant lymph nodes	57/220 (25.9)	4/14 (28.6)	53/206 (25.7)	
Peritoneum	64/220 (29.1)	5/14 (35.7)	59/206 (28.6)	
Pleura	2/220 (0.9)	1/14 (7.1)	1/206 (0.5)	
Systematic treatment lines, *n*/*N* (%)				
Adjuvant	59/278 (21.1)	3/19 (15.8)	56/259 (21.5)	-
First-line	255/278 (91.4)	17/19 (89.5)	238/259 (91.5)	
Second-line	136/278 (48.7)	9/19 (47.4)	127/259 (48.8)	
≥Third-line	50/278 (17.9)	3/19 (15.8)	47/259 (18.1)	
Chemotherapy regimens in first-line, *n*/*N* (%)				
CisGem	181/255 (64.9)	9/17 (47.4)	172/238 (66.2)	-
GEMOX	13/255 (4.7)	2/17 (10.5)	11/238 (4.2)	
Gemcitabine	37/255 (13.3)	2/17 (10.5)	35/238 (13.5)	
Clinical trial	25/255 (9.0)	3/17 (15.8)	22/238 (8.5)	
Molecular profile, *n*/*N* (%)				
BRAF mutation	13/244 (5.3)	1/18 (5.6)	12/226 (5.3)	1.000
IDH1 mutation	39/241 (16.2)	2/18 (11.1)	37/223 (16.6)	0.745
FGFR2 fusions	16/233 (6.9)	1/18 (5.6)	15/215 (7.0)	1.000
HER2 amplification	9/216 (4.2)	1/16 (6.3)	8/200 (4.0)	0.507
TP53 mutation	83/301 (27.6)	2/19 (10.5)	81/282 (28.7)	—

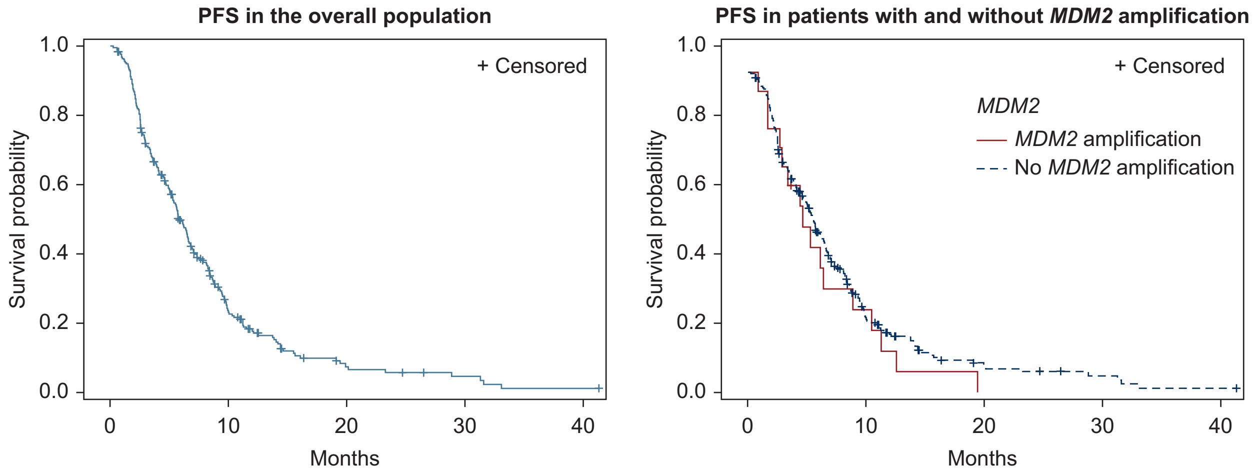
CisGem, cisplatin/gemcitabine; dCCA, distal cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; *FGFR2*, fibroblast growth factor receptor 2; GEMOX, gemcitabine/oxaliplatin; GBC, gall-bladder carcinoma; *HER2*, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; *IDH*, isocitrate dehydrogenase; IQR, interquartile range; *MDM2*, mouse double minute 2; *N*, total number of patients; *n*, number of patients with certain characteristics; pCCA, perihilar cholangiocarcinoma; *TP53*, tumor protein 53.

[a] In our sample, 6.2% (12/195) of patients with iCCA had *MDM2* amplification; 8.3% (2/24) of patients with pCCA had *MDM2* amplifications; 2.2% (1/46) of patients with dCCA had *MDM2* amplifications; and 12.9% (4/31) of patients with GBC had *MDM2* amplifications.

subtypes of BTC in order to offer personalized treatment approaches.[1]

The RETUD registry, which is representative of routine clinical practice in gastrointestinal cancers in Spain, provides a unique opportunity to characterize the epidemiology of total population versus that harboring *MDM2* amplification, the potential associations of *MDM2* to other genetic alterations, and the specific survival outcomes.

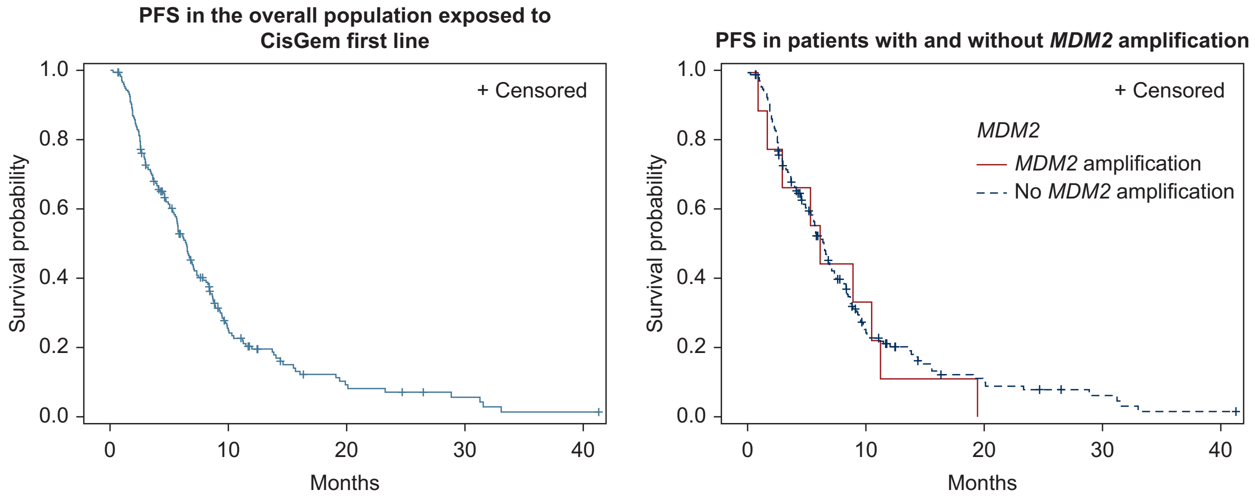
Diagnostic and therapeutic decisions require molecular information to benefit the care of the oncological patient. Among the molecular markers, *MDM2* amplification can inactivate p53, leading to tumorigenesis; little is known, however, about how patients with BTC and *MDM2* amplification respond to first- and second-line treatment or about their survival in real-world clinical practice. In our sample, 6.3% (19/301) of patients had *MDM2* amplification, in line with the percentage observed in other studies.[1,3,20] Regarding the anatomical location, a total of 12.9% (4/31) patients with GBC had *MDM2* amplifications, followed by 8.3% (2/24) of patients with pCCA, and 6.2% (12/195) of patients with iCCA, consistent with other publications.[1,3,20] In a systematic review of clinical trials regarding molecular testing and characterization of novel drug targets for the treatment of BTC,[3] it was concluded that *MDM2* amplifications were detected in ∼5%-8% of patients with BTC. Moreover, 16% of patients with AC had *MDM2* amplifications, followed by 13%-14% of patients with GBC and 2%-6% of patients with iCCA.[3] In another systematic review of publications containing data on BTC epidemiology and *MDM2* amplification,[1] 3.4%-10.0% of BTC samples exhibited *MDM2* amplifications and GBC had the highest proportion



	Overall population ***N* = 251**	***MDM2* amplification population** ***n* = 17**	**No *MDM2* amplification population** ***n* = 234**
Events	209	16	193
Censored	42	1	41
Median, months (95% CI)	5.8 (5.3-6.6)	5.3 (2.7-8.9)	6.0 (5.3-6.8)
P value	–	0.423	

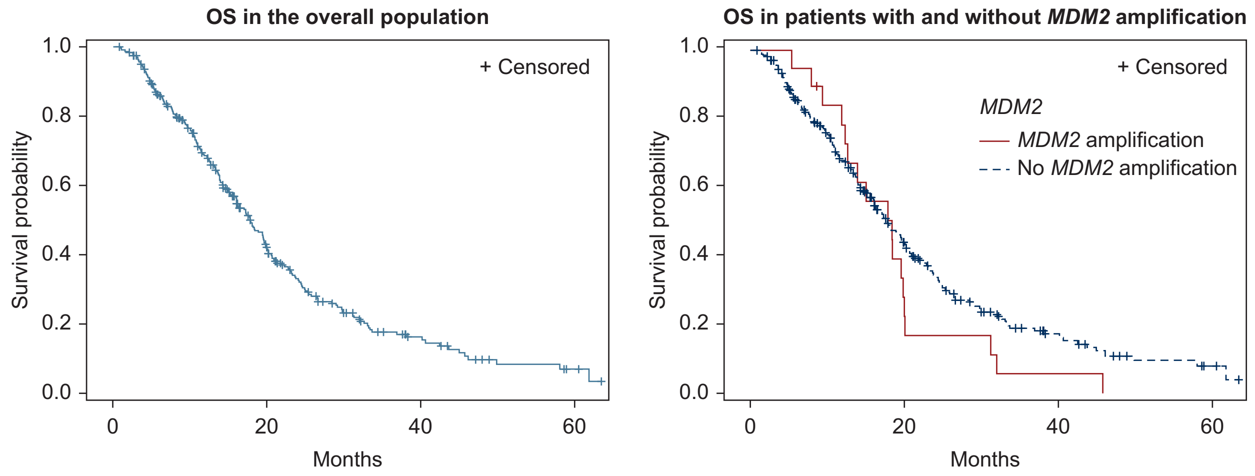
Figure 1. Progression-free survival (PFS) in the overall population and by groups according to *MDM2* amplification.
CI, confidence interval; *MDM2*, mouse double minute 2.

of samples with *MDM2* (10.9%-17.5% of samples). In an exploratory study of patients with diverse malignancies between 2012 and 2016 in the United States,[20] 11% (62/554) of patients with GBC presented with *MDM2* amplification. Similar to other studies,[2,3,20] our results showed that *MDM2* amplification appears to be mutually



	Overall population exposed to CisGem first line ***N* = 178**	***MDM2* amplification population** ***n* = 9**	**No *MDM2* amplification population** ***n* = 169**
Events	147	9	138
Censored	31	0	31
Median, months (95% CI)	6.5 (5.6-7.1)	6.1 (0.9-11.3)	6.5 (5.5-7.1)
P value	–	0.707	

Figure 2. Progression-free survival (PFS) in patients exposed to CisGem as first-line treatment.
CI, confidence interval; CisGem, cisplatin/gemcitabine; *MDM2*, mouse double minute 2.

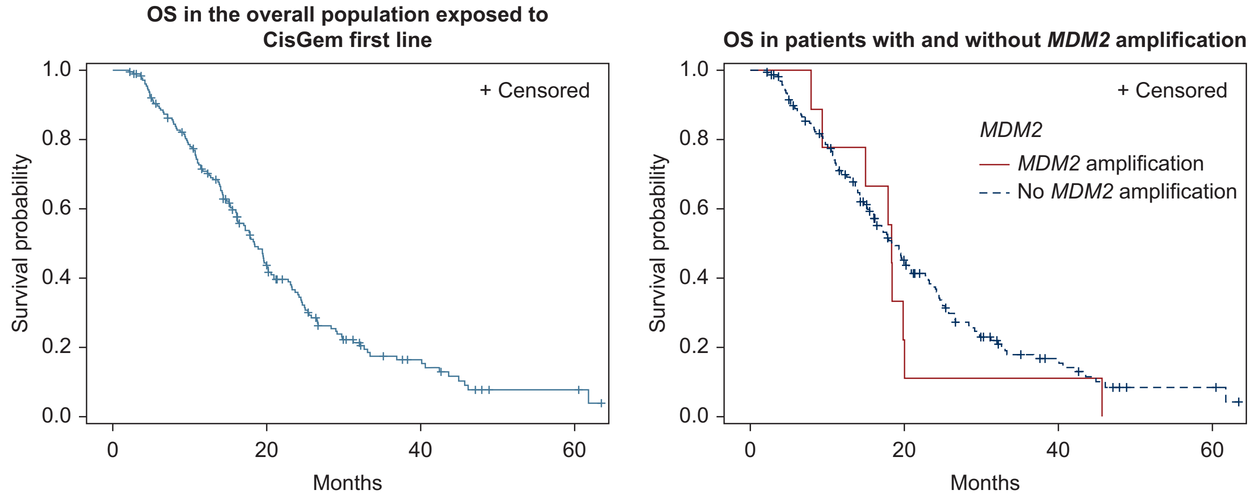


	Overall population *N* = 297	*MDM2* amplification population *n* = 19	No *MDM2* amplification population *n* = 278
Events	211	18	193
Censored	86	1	85
Median, months (95% CI)	17.8 (16.1-19.6)	18.4 (12.3-19.9)	17.8 (16.1-20.1)
P value	–	0.247	

Figure 3. Overall survival (OS) in the overall population and by groups according to *MDM2* amplification.
CI, confidence interval; *MDM2*, mouse double minute 2.

exclusive with other alterations, since few patients presented *IDH* mutation (11.1%; 2/18 patients) or *TP53* mutation (10.5%; 2/19 patients). However, among patients with BTC without *MDM2* amplifications, 28.7% (81/282) of patients presented with *TP53* mutation and 16.6% (37/223) of patients presented with *IDH* mutation.

Our overall population showed PFS, OS, and ORR values (5.8 months and 17.8 months, respectively, and 29.1%) in



	Overall population exposed to CisGem first line *N* = 178	*MDM2* amplification population *n* = 9	No *MDM2* amplification population *n* = 169
Events	135	9	126
Censored	43	0	43
Median, months (95% CI)	18.4 (16.1-20.2)	18.4 (7.9-20.0)	18.9 (16.1-21.0)
P value	–	0.416	

Figure 4. Overall survival (OS) in patients exposed to CisGem as first-line treatment.
CI, confidence interval; CisGem, cisplatin/gemcitabine; *MDM2*, mouse double minute 2.

Table 2. Objective response rate in the overall population and by groups according to *MDM2* amplification

	Overall population *N* (%)	*MDM2* amplification population, *n* (%)	No *MDM2* amplification population, *n* (%)
No	156 (70.9)	11 (78.6)	145 (70.4)
Yes	64 (29.1)	3 (21.4)	61 (29.6)
Total	220 (100.0)	14 (100.0)	206 (100.0)
P value 0.762			

MDM2, mouse double minute 2.

patients receiving first-line treatment of BTC comparable with those reported in previous studies. In particular, a study from the United States including 124 consecutive patients with BTC who progressed on standard therapies [21] showed an OS of 15.2 months from the date of diagnosis of advanced unresectable or metastatic disease, and 19.2 months from the date of diagnosis. In another study including 121 consecutive patients with recurrent or metastatic/unresectable BTC from the Republic of Korea,[22] the median PFS for first-line chemotherapy was 5.1 months, OS was 14.8 months, and ORR was 20.7%.

To our knowledge, this is the first study of patients with BTC comparing subgroups with and without *MDM2* amplification regarding PFS, OS, and ORR in a real-world setting. In our study, no significant differences in PFS, OS, and ORR between patients with and without *MDM2* amplification were observed, suggesting that *MDM2* amplification is not a clear prognostic nor predictive factor for any first-line chemotherapy regimen. Although BTC patients were not included, similar results were obtained in a retrospective study in the United States[23] that included patients with solid tumors (liposarcoma, and breast, bladder, liver, lung, salivary gland, and kidney tumors) with *MDM2* amplification ($n = 23$ patients) and without *MDM2* amplification ($n = 124$ patients) (median OS 13.6 months versus 10.6 months, respectively; $P = 0.12$).

Regarding the treatment, most of the patients received first-line chemotherapy (91.4%), with CisGem the most common (64.9%). In our RETUD series, patients received a similar rate of adjuvant treatment and first (91.4% of patients), second (48.7% of patients), and third (17.9% of patients) lines. When comparing patients with *MDM2* amplification who received CisGem as first line with those without *MDM2* amplification, no significant differences were observed, suggesting the same sensitivity to platinum in patients with *MDM2* amplification compared with the overall population.

Due to its observational nature, this study is not free of limitations, including the small sample size of patients with *MDM2* amplification, the inclusion of patients from clinical practice who were not monitored and who did not meet the profile of patients participating in clinical trials (without homogenous characteristics), and the presence of missing information. Despite these limitations, this study provides a large real-world cohort of patients with valuable evidence that can be used for future research in patients with BTC with or without *MDM2* amplification.

Conclusion

In clinical practice, diagnostic and therapeutic decisions require molecular information in order to offer personalized attention to patients with BTC, due to its heterogeneity. Our results suggest that the presence of *MDM2* amplification has a neutral impact on prognosis and a similar sensitivity to platinum-based chemotherapy compared with patients without *MDM2* amplification. To our knowledge, this is the first study in a real-world setting that assesses therapeutic response and survival between patients with BTC with and without *MDM2* amplification. Future studies are needed to support our results.

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DISCLOSURE

The authors have declared no conflicts of interest.

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