

# 500: Isocitrate Dehydrogenase 1 Mutations In Biliary Tract Cancer Patients In Spanish RETUD Registry

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## Background

Biliary tract cancer (BTC) is a heterogeneous group of tumors, including cholangiocarcinoma (intra and extrahepatic) and gallbladder carcinoma.<sup>1</sup> Isocitrate dehydrogenase 1 (IDH1) mutations define a distinct molecular subtype of biliary tract cancer<sup>2,3</sup>. In this study, we characterized the epidemiological characteristics, treatment patterns and efficacy outcomes of a cohort of BTC patients harboring pathogenic IDH1 mutations.

## Methods

BTC diagnosis occurred between January 1st, 2017, and May 30th, 2025. IDH1 status was assessed by next-generation sequencing (NGS), polymerase chain reaction (PCR), immunohistochemistry (IHC), or pyrosequencing (PSQ). Analysis comprised demographic and clinical data, tumor molecular profile, therapeutic procedures and efficacy outcomes (objective response rate [ORR], overall survival [OS] and progression-free survival [PFS]). PFS and OS were estimated using the Kaplan-Meier method. P-value < 0.05 was considered statistically significant. All analysis were done using statistical software R version 4.5.1.

## Results

IDH1 status was determined in 445 BTC patients from 31 centers. Among them, 77 (17.3%) presented IDH1 mutations, **73 (16.4%)** patients presented **confirmed pathogenic mutations**, and 4 patients presented variants of unknown significance (VUS). Most frequent IDH1 pathogenic mutations were **R132C** (39 patients, 53.4%), R132L (12 patients, 16.4%) and R132G (9 patients, 12.3%). Main baseline and clinic characteristics for IDH1 mutated (IDH1mut) and IDH1 wild type (IDH1wt) patients are shown in **table 1** and **table 2**.

**Table 1.** Demographic and clinic characteristics by IDH1 status

Variable	IDH1mut (n=73)	IDH1wt (n=372)	p-value
Median age at diagnosis (Q1, Q3)	67.0 (59.0, 72.0)	66.0 (59.0, 73.0)	0.709
Sex (female)	48 (65.8)	154 (41.4)	<b>&lt; 0.001</b>
Median follow-up time (Q1, Q3)	18.2 (12.4, 28.7)	16.3 (9.6, 25.9)	0.074
Resectable disease	17 (23.3)	135 (36.3)	<b>0.032</b>
Advanced disease	73 (100.0)	347 (93.3)	<b>0.022</b>
ECOG			0.260
0	18 (31.6)	84 (29.1)	
1	34 (59.7)	145 (50.2)	
2	1 (1.8)	27 (9.3)	
3	0 (0.0)	3 (1.0)	
Unknown	4 (7.0)	30 (10.4)	
Missing	16	83	

This analysis provides insights into the **characterization** of real-world **IDH1 BTC** patients. Patients receiving **anti-IDH1** therapies showed a trend towards **improved survival**.

**Table 2.** IDH1 status by tumor location

Variable	Ampulla of Vater	Extrahepatic distal	Extrahepatic hilar	Gallbladder carcinoma	Intra-extrahepatic	Intrahepatic	Unknown	p-value
IDH1 status								<b>&lt; 0.001</b>
IDH1mut	0 (0.0)	1 (1.7)	3 (7.5)	1 (1.9)	0 (0.0)	68 (24.2)	0 (0.0)	
IDH1wt	10 (100.0)	59 (98.3)	37 (92.5)	51 (98.1)	1 (100.0)	213 (75.8)	1 (100.0)	

Treatments received by IDH1mut and IDH1wt populations are shown in **table 3**. Most frequent schemes for first and second line in IDH1mut patients were CISGEM (53 patients, 71.6%) and FOLFOX (21 patients, 41.2%), respectively. A total of 20 IDH1mut patients (**27.4%**) **received anti-IDH1 therapy**: Ivosidenib in 13 patients (65.0%), Ranosidenib in 4 patients (20.0%) and Crelosidenib in 3 patients (15.0%).

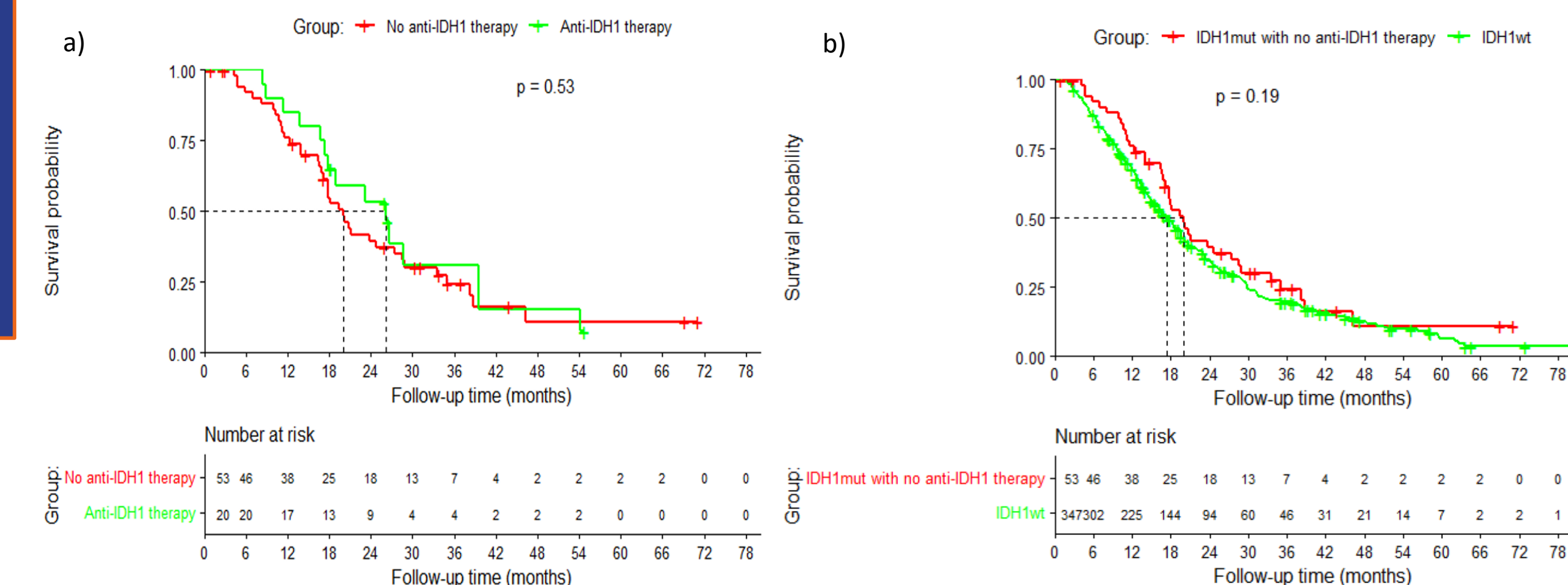
**Table 3.** Treatments received by IDH1 status

Variable	IDH1mut (n=73)	IDH1wt (n=372)	p-value
Surgery	17 (23.3)	130 (35.0)	0.053
Other locoregional procedure	7 (9.6)	43 (11.6)	0.626
Neoadjuvant treatment	0 (0.0)	12 (3.3)	0.231
Adjuvant treatment	10 (13.7)	79 (21.6)	0.126
First line	72 (98.6)	343 (93.7)	0.153
Second line	51 (69.9)	188 (51.4)	<b>0.004</b>
Third line	22 (30.1)	71 (19.4)	<b>0.040</b>

Median OS (mOS) in IDH1mut was 20.2 months (95% CI 17.8-28.6) versus 18.4 months (95% CI 16.5-20.4) for IDH1 wt (p=0.270). First line median PFS (**mPFS**) was **8.3** months (95% CI 7.7-9.5) in IDH1mut vs **6.1** months (95% CI 5.4-7.3) in IDH1wt (**p=0.029**). No significant differences were found in first line ORR between groups.

mOS in IDH1mut patients treated with **anti-IDH1 therapies** was **26.1** months (95% CI 17.8-54.1); mOS for IDH1mut patients with **other treatments** was **20.0** months (95% CI 17.1-28.6) (p=0.530) (**Figure 1a**) versus mOS in IDH1wt patients of **17.3** months (95% CI 15.6-19.6) (p=0.190) (**Figure 1b**).

**Figure 1.** Overall survival. **a)** IDH1mut patients receiving anti-IDH1 therapy vs IDH1mut patients without anti-IDH1 therapy. **b)** IDH1mut patients without anti-IDH1 therapy vs IDH1wt patients



A total of 49 (67.1%) IDH1mut patients presented co-expression with other biomarkers, 8 of them ESCAT-I. The most frequent co-mutations were CDKN2A (20.4%), CDKN2B (16.3%) and ARID1A (16.3%). Mutations of genes involved in RAS/MAPK signaling pathway like KRAS, BRAF and ERBB2 were less frequent in IDH1mut patients than in IDH1wt patients (10.2% vs 23.8%, 6.1% vs 6.7% and 4.1% vs 9.2% respectively). Regarding TP53/RB pathway, frequency was lower in IDH1mut patients for TP53 (10.2% vs 36.5%) and MDM2 amplification (4.1% vs 4.4%) but not for CDKN2A/B (36.7% vs 34.2%).

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