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ESMO Gastrointestinal Cancers Congress 2025
2nd-5th July 2025. Barcelona, Spain

336P

The use of regorafenib in cholangiocarcinoma. A real-world data (RWD) review

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INTRODUCTION

There is an unmet clinical need for biliary tract cancer (BTC) patients after progression to first line treatment, particularly if an absence of targetable molecular alterations is found. Regorafenib (an oral tyrosine kinase inhibitor) can be offered via an early access medicines scheme after the results from phase II REACHIN trial[1,2].

METHODS

We included retrospective data from patients receiving regorafenib for advanced BTC treatment as part of an early access medicines scheme in UCLH between May 2021 and March 2024. Following the retrospective, observational nature of the study, individual informed consent was not requested.

RESULTS

We included a total of 53 patients treated at UCLH. First line was most commonly based on cisplatin and gemcitabine chemotherapy doublet and access to immunotherapy combination varied depending on availability at the time.

47% of patients who started regorafenib accessed it in second line and 53% in third or later lines. 15 patients never started treatment due to clinical deterioration. Mean age of patients on cycle 1 regorafenib was 62 (range 36-82). A dose escalation regimen was utilised for 23 patients, as shown in the ReDos trial[3].

Most frequent side effects were palmar-plantar erythrodysesthesia (PPE), fatigue, rash, mucositis and hypertension. Any grade toxicity was reported in 63% of patients. CTCAE grade >3 toxicity being reported in 24% of patients. Dose reductions occurred in 29% of patients. Treatment was discontinued in 87% of patients, most frequently due to disease progression or clinical deterioration and death. Ten patients older than 70 years old were included and half of them experienced G3/4 toxicities, which in 2 cases led to regorafenib discontinuation due to unacceptable PPE and mucositis.

Average duration of treatment was 3.6 cycles (range 0-23 cycles). Two patients have been particularly long responders and are still receiving treatment after more than 16 cycles.

Median progression free survival in the treated population was 3 months and median overall survival was 5 months.

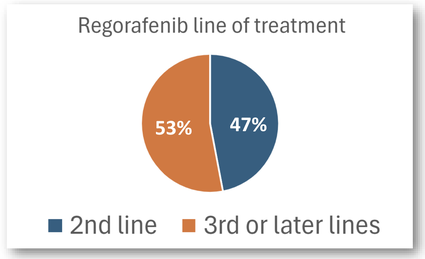


Figure 1. Regorafenib use according to systemic anticancer treatment line. Almost half of patients could access it on a second line after failure to cisplatin and gemcitabine-based treatment.

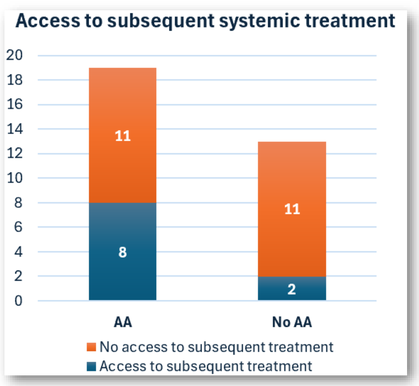


Figure 2. This figure represents the number of patients who received subsequent systemic anticancer treatment following progression or unacceptable toxicity on regorafenib. Patients harbouring actionable alterations accessed treatment more frequently after regorafenib.
AA (actionable molecular alteration present), no AA (no targetable molecular alteration present on profiling).

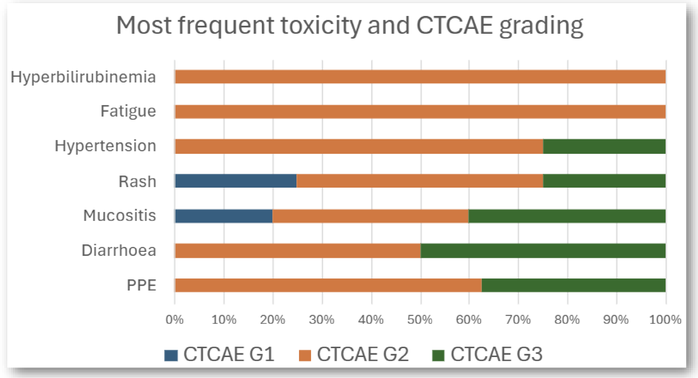
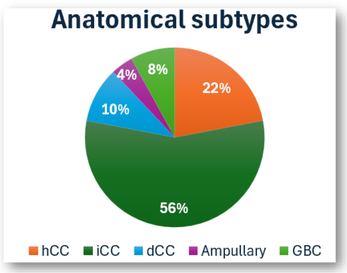


Figure 3. Most common toxicity and CTCAE version 5 grading.

Figure 4. Anatomical origin of the included cancers. *hCC (hilar cholangiocarcinoma), iCC (intrahepatic cholangiocarcinoma), dCC (distal cholangiocarcinoma), ampullary adenocarcinoma and GBC (gallbladder carcinoma).*



Molecular profiling was obtained on tissue profiling or liquid biopsy depending on availability. Some patients accessed profiling in the setting of clinical trial screening.

Longer responders	Cycles	Toxicity	BOR	Genomics
Patient 1	6	G3 diarrhoea	PR	No AA
Patient 2	7	G3 mucositis	SD	KRAS G12D
Patient 3	9	G2 PPE	SD	IDH1
Patient 4	16	G2 PPE	PR	FGFR2 fus.
Patient 5	23	G2 PPE	PR	IDH1

Table 1. Evolution, toxicity and molecular profile of longer responders (≥6 cycles received with disease control). Cycles received (only listed if more than 6 cycles). BOR (*best overall response*), PR (*partial response*), SD (*stable disease*), AA (*actionable alterations*).

Type of subsequent systemic treatment	NP
Targeted to genomic alteration	2
FGFR2 fusion received pemigatinib	1
HER2 IHC+ received zanidatamab	2
Not directed to genomic alteration	6

Table 3. Type of subsequent systemic treatment in the subgroup harbouring molecular alterations. 2 patients accessed targeted treatment after regorafenib failure. NP (*number of patients*).

Molecular alteration	NP	Molecular alteration	NP
IDH1 R132C	6	FGFR2 rearrangement	1
IDH1 R172L	1	FGFR2::FAM124B fus.	1
FGFR2 C382R	1	MDM2 amplification	2
FGFR2 L376_Y381 del	1	KRAS G12D	1
FGFR2::TACC2 fusion	1	KRAS G12V	1
FGFR2::AFF4 fusion	1	HER2 3+ IHC	1
BRCA2 mutations	2	ERBB2 mutation	1

Table 2. Molecular profiling. Out of 53 patients, 23 patients had different genomic alterations on profiling. The table shows potentially actionable findings and number of patients (NP) harbouring the alteration of interest.

Reason for treatment discontinuation	NP
Unacceptable toxicity	6
Disease progression	16
Patient death (incl response not assessed)	10
Other	1

Table 4. Reasons for treatment discontinuation in the whole cohort. Patient death includes clinical deterioration and decision for best supportive care if response to treatment was not assessed. NP (*number of patients*)

CONCLUSION

Patients with advanced biliary tract cancer represent a particularly challenging cohort, who often lack effective second line treatment options. It was seen that the tolerability of regorafenib was overall acceptable with monitoring and dose adjustments for optimal patient adherence and continuation. Regorafenib remains a viable treatment option for the older population of patients despite facing a slightly increased risk of severe toxicities.

Regorafenib demonstrates a promising role in cholangiocarcinoma but more studies are needed to evaluate its place within the current treatment conundrum. Many longer-term responders harboured potentially actionable alterations on molecular profiling.

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There are no known conflicts of interest regarding this project.

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