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CLINICAL TRIAL REPORT

Regorafenib-Avelumab combination in patients with biliary tract cancer (REGOMUNE) : a single arm, open-label, phase II trial

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ABSTRACT

Background: Regorafenib has shown substantial clinical activity in patients with advanced biliary tract cancers (BTC). Pre-clinical data suggested that this drug modulate anti-tumor immunity and is synergistic with immune-checkpoint inhibition.

Patients and Methods: This is a single-arm, multicentric phase II trial. Regorafenib was given 3 weeks/4, 160mg QD; Avelumab 10 mg/kg IV was given every 2 weeks, beginning at C1D15 until progression or unacceptable toxicity. The primary endpoint was the confirmed objective response rate under treatment, as per RECIST 1.1. The secondary endpoints included: 1-year non-progression rate, progression-free survival and overall survival, safety and biomarkers studies performed on sequential tumor samples obtained at baseline and at cycle 2 Day 1. **Results:** 34 patients were enrolled in 4 centers. 29 were assessable for efficacy after central radiological review. Best response was partial response for 4 patients (13.8%), stable disease for 11 patients (37.9%) and progressive disease for 14 patients (48.3%). The median progression-free survival (PFS) and overall survival were 2.5 months (95%CI [1.9 – 5.5]) and 11.9 months (95%CI [6.2 – NA]) respectively. The most common grade 3 or 4 clinical adverse events related to treatment were : Hypertension (17.6%), Fatigue (14.7%), and maculo-papular rash (11.8%). High baseline level of PD-L1 and of indoleamine 2, 3-dioxygenase expression were associated with improved outcome.

Conclusions: Regorafenib combined with avelumab has anti-tumor activity in a subset of heavily pre-treated biliary tract cancer population. Further investigations are needed in patients selected based on tumor microenvironment features.

Clinical Trial registration: NCT03475953

KEYWORDS: regorafenib, avelumab, biliary tract cancer, immunotherapy, cholangiocarcinoma

Introduction

Biliary tract cancers (BTCs) represent a group of aggressive malignancies classified based on their site of origin across the biliary tree as intrahepatic (iCCA), extrahepatic (eCCA), and gallbladder cancer.

Patients diagnosed with BTC have a poor prognosis because the majority of these patients are not eligible for curative surgery.^[1] In the advanced disease setting, systemic therapy combining cisplatin with gemcitabine represents the current standard of care.^[2]

After the failure of first-line therapy, therapeutic options are limited.^[2] Given the importance of angiogenesis in BTC tumorigenesis, several anti-angiogenic agents have been investigated in this setting.^[3] Regorafenib, a small molecule that targets several protein kinases including PDGFR, VEGFR, FGFR, Flt-3, RET, and c-Kit is the sole anti-angiogenic agent that has shown significantly improved clinical benefit compared to placebo in the context of a randomized study.^[4] Indeed, regorafenib significantly improved PFS and tumor control in comparison to placebo in a randomized phase II study including patients with previously treated metastatic/unresectable biliary tract cancer in the second- or third-line setting.^[4]

Inflammation and immune modulation have also been shown to play a crucial role in BTCs.^[5-6] Clinical trials investigating immune checkpoint inhibitors in patients with BTC have reported only modest results,^[7] underscoring the need for novel approaches including combination therapies and the identification of efficacy biomarkers.

There are several lines of evidence indicating that targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR) may be synergistic with immune checkpoint inhibition in human tumors.^[8,9] Therefore, we hypothesized that combining an anti-angiogenic agent with anti-programmed cell death 1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1) antibodies may be associated with significant clinical benefit in patients with advanced BTC that has not responded to previous standard chemotherapy regimens.

Here, we report the clinical and biomarker results of a phase II study investigating the combination of regorafenib plus the anti-PD-L1 antibody, avelumab, in patients with advanced BTC.

METHODS

Study design and participants

REGOMUNE is a single-arm, multicenter phase II basket study for which patients were recruited from four French sites. In the BTC cohort, patients were eligible if they were at least 18 years old and had histologically proven advanced or metastatic BTC, an Eastern Cooperative Oncology Group performance status of 0–1; measurable disease according to RECIST 1.1;^[10] at least one previous line of systemic treatment; and adequate hematological, renal, metabolic, and hepatic functions (see study protocol for a full list of eligibility criteria). Blood tests included the assessment of blood cell count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, bilirubin, lipase, creatinine phosphokinase, coagulation test, creatinine, and urea nitrogen. The main exclusion criteria included previous treatment with avelumab or regorafenib, previous treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, and are detailed in the protocol. As required by French regulations, the protocol was approved by a central institutional review board (Comité de Protection des Personnes Sud-Est II, Lyon, France), which reviewed the appropriateness of the clinical trial protocol and the risks and benefits to study participants. All patients provided written informed consent.

Procedures

After assessing eligibility, the patients received regorafenib, 160 mg per day on a 3 week on/1 week off schedule, in cycles of 28 days. Avelumab treatment began on Cycle 1 Day 15, by intravenous infusion once every 2 weeks at a dose of 10 mg/kg. Treatment was continued until disease progression, unacceptable toxicity, the investigator's decision to discontinue, or withdrawal of patient consent. Participants were monitored for adverse events at every follow-up assessment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Laboratory assessments were conducted at baseline, and every 2 weeks thereafter until treatment discontinuation. Regorafenib dose modifications to manage adverse events were allowed (see study protocol). The regorafenib dose could be reduced to 120 mg and then to 80 mg. Dose interruptions were allowed based on the clinical situation. Patients requiring a delay

of > 4 weeks since the last dose of regorafenib had to permanently discontinue regorafenib but could continue avelumab if it was deemed appropriate. No dose reduction of avelumab was allowed. Dose interruptions were allowed based on the severity of immune-related adverse events. Patients requiring two or more consecutive cancellations of avelumab injection had to permanently discontinue avelumab but were allowed to continue regorafenib. Tumor lesions were assessed according to RECIST version 1.1 at baseline (within 4 weeks prior to Cycle 1 Day 1) and every 8 weeks until disease progression or the start of another treatment. Tumor samples were collected at baseline and on Cycle 2 Day 1 for all consenting patients to assess the impact of treatment on the tumor microenvironment and to identify potential biomarkers associated with outcomes.

Outcomes

The primary endpoint was the objective response rate defined as the proportion of patients with objective response (confirmed or unconfirmed) under treatment based on adapted RECIST 1.1 after centralized radiological review.

Secondary objectives included best overall response, 1-year progression-free survival (PFS), 1-year overall survival (OS), and safety. Best overall response was defined as the best response across all time points. Durable clinical benefit was defined as the proportion of patients with objective response and/or stable disease lasting more than 6 months. PFS was defined as the time from study treatment initiation to death from any cause or the first occurrence of disease progression based on RECIST 1.1 after centralized radiological review. OS was defined as the time from study treatment initiation to death from any cause. Safety was graded as per the common toxicity criteria stated in NCI CTC-AE v5.0.

Statistical analysis

This study was based on a Bayesian adaptive phase 2 design approach and followed an adaptive trial design. The primary endpoint was the objective response rate under treatment. The probability of success was estimated from a beta-binomial model. The maximum response probability threshold and minimum response probability threshold were defined as 40% and 20%, respectively.^[11] The maximum sample size was set at 50 patients. The analysis of the primary endpoint was carried out

sequentially, with interim analyses planned after a 16-week follow-up for the first ten patients and then every five patients.

At each interim analysis, stopping rules recommended that the trial be stopped due to inefficacy (if there was a high predictive probability [$\geq 80\%$] that the objective response rate was less than or equal to 20%, the minimum response probability threshold) or efficacy (if there was a high predictive probability [$\geq 80\%$] that the objective response rate was greater than or equal to 40%, the maximum response probability threshold).

The efficacy population included all participants who met the eligibility criteria and who received at least one complete or two incomplete treatment cycles. All enrolled patients who initiated the study treatment were included in the safety analysis.

The median follow-up was calculated using the reverse Kaplan–Meier method, and survival endpoints were described using the Kaplan–Meier method. Data for patients who were alive and event-free were censored at the date of the last follow-up. Quantitative variables were described using the median and range. Qualitative variables were described using frequency, rates, and the 95% confidence interval (95%CI) (binomial law). Estimated parameters are reported with two-sided 95% CIs. P values less than 0.05 (typically ≤ 0.05) were considered to be statistically significant. The statistical analyses were performed using SAS software (version 9.4). This study is registered with ClinicalTrials.gov, number NCT03475953.

Tissue sample analysis

Tumor biopsies were collected at baseline and on Cycle 2 Day 1. These samples were analyzed to characterize the impact of regorafenib combined with avelumab on the tumor microenvironment and to identify potential predictive biomarkers of clinical benefit. Immunohistofluorescence analysis was performed on the automated Ventana Discovery XT staining platform (Ventana Medical Systems). Slides of tumor tissue were deparaffinized by heating to 69°C combined with the application of Discovery Wash solution during 8 minutes. This operation was repeated 3 times. The slides were incubated with the following primary antibodies: anti-CD8 (clone C8/144B, Dako), anti-CD163 (clone 10D6, Leica), anti-PD-L1 (clone QR1, Diagomics), and anti-cytokeratine 19 (clone A53-B/A2.26, Ventana). Bound primary

antibodies were detected using either OmniMap anti-Ms or Rb-HRP with the Opal detection kit (Akoya). The slides were counterstained with spectral DAPI (Akoya) and cover-slipped. The stained slides were imaged on a multispectral imaging system (Vectra Polans, Akoya) and analyzed using Inform image analysis software (Akoya, version 2.4.1) to segment the tissue into tumor and stroma and to phenotype the cells.

Role of the funding source

The study was sponsored by the Institut Bergonié, Comprehensive Cancer Center (Bordeaux, France). The data were collected with the sponsor data management system and were analyzed and interpreted by representatives of the sponsor in collaboration with the investigators. SC, CC, CB, and AI had access to the raw data. The funders of the study (Bayer and Merck) had no role in the study design, data collection, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had the final responsibility for deciding to submit the manuscript for publication.

RESULTS

A total of 34 patients were recruited for the study between November 21, 2018 and November 13, 2019. According to the Bayesian adaptive design, inclusion was stopped prematurely, as there was a high predictive probability (98.6%) that the objective response rate was less than or equal to 20%. Twenty-nine patients were eligible and included in the efficacy endpoint. Five patients were excluded from efficacy analysis for reasons prespecified in the protocol: one due to protocol deviation regarding the inclusion criteria and four because of early discontinuation without any tumor assessment (Figure 1). The patient characteristics are summarized in Table 1. The median age was 63 years (range 36–80), and 47.1% of the patients were women. All of the patients had already received systemic treatment for advanced disease, with a median of two (range 1–4) previous lines of treatment.

Out of the 29 patients included in the efficacy assessment, four patients (13.8%) achieved a partial response; as such, the primary efficacy criterion was not reached. Regarding the best overall response according to RECIST, 11 (37.9%) patients demonstrated stable disease, including 10 patients (34.5%) with tumor shrinkage

(range from -1.2% to -85.6%) (Figure 2). Fourteen patients (48.3%) had progressive disease. Among 15 patients with objective response or stable disease at 6 months, 14 had an iCCA intra-hepatic cholangiocarcinoma. The median duration of response was 10.4 months.

The median follow-up was 9.8 months (95%CI 6.6–12.4). The median PFS was 2.5 months (95%CI 1.9–5.5). The 6- and 12-month PFS were 27.6% (95%CI 13.1–44.3) and 6.9% (95%CI 0.6–24.3), respectively.

At the time of analysis, 24 patients discontinued treatment. Reasons for treatment discontinuation were disease progression for 23 patients (95.8%) and alteration of general status for 1 patient (4.2%). Seventeen patients (58.6%) patients were still alive, with 5 (17.2%) still under treatment. The median OS was 11.9 months (95%CI 6.2–NA) (Figure 3). The 6- and 12-month OS rates were 75.7% (95%CI 53.5–88.3) and 44.4% (95%CI 19.0–67.3), respectively.

Thirty-four patients received at least one dose of regorafenib and/or avelumab and were therefore evaluated for safety. The treatment was generally well-tolerated. Treatment-related adverse events and laboratory abnormalities that were reported in more than 5% of patients for grades 1–2 and any for grades 3 and 4 are shown in Table 2. The most common clinical treatment-related adverse events were fatigue, infusion-related reaction, palmo-plantar erythrodysesthesia, diarrhea, dysphonia, and mucositis. The most common treatment-related lab abnormalities were transaminitis and thyroid-stimulating hormone (TSH) increase. At least one serious adverse event was reported in 21 patients (62%). Twenty-six (76.5%) and 19 (55.9%) patients experienced treatment modifications with regorafenib (19 patients with temporary discontinuation, 12 patients with dose reduction, and 3 patients with permanent discontinuation) and avelumab (12 patients with perfusion interruption, 10 patients with administration cancellation but not permanent discontinuation), respectively. No patient died from drug-related toxicity.

Analysis of the tumor biopsies revealed that high expression by tumor cells of PD-L1 and indoleamine 2,3-dioxygenase 1 (IDO1) were associated with a better durable clinical benefit rate and improved PFS (46.15% for high PD-L1 expression versus 7.14% for low PD-L1 expression, 85.7% for high IDO1 expression versus 7.14% for low IDO1 expression; 5.45 (1.68–NA) months for high PD-L1 expression versus 2.28 (1.87–5.78) months for low PD-L1 expression, 5.78 (2.00–

NA) months for high IDO1 expression versus 1.91 (1.84–5.45) months for low IDO1 expression) (Figure 4). A comparison of the tumor microenvironment between iCCA and eCCA revealed a higher infiltration of eCCA by tumor-associated macrophages (TAMs) ($p=0.052$) (Supplementary Figure 1).

DISCUSSION

Biliary tract cancers are a heterogeneous group of adenocarcinomas for which next-generation sequencing has revealed several targetable alterations including fibroblast growth factor receptor (FGFR) fusion, isocitrate dehydrogenase (IDH) mutations, the human epidermal growth factor receptor (HER) family, DNA damage repair (DDR) pathways, and BRAF mutations with promising clinical results.^[12]

Although the first objective of our study was not reached, nearly 50% of patients experienced clinical benefit resulting in objective response (13.8%) or stable disease with tumor shrinkage (34.5%).

Several studies have shown that molecules such as VEGF and fibroblast growth factor that play a crucial role in tumor angiogenesis are upregulated in BTC.^[3,13] Interestingly, preclinical experiments investigating anti-angiogenic drugs such as bevacizumab,^[14] sorafenib,^[15] vandatenib,^[16] and axitinib^[17] have shown that such agents can reduce both tumor growth and neo-angiogenesis in xenograft models of BTC.

Regorafenib is the most-investigated antiangiogenic drug in patients with advanced BTC who have had progression despite standard therapy.^[4,18–19] Demols et al. reported the first double-blind, placebo-controlled clinical trial investigating regorafenib in this setting. A total of 66 patients with refractory BTC were randomized to receive regorafenib or a placebo.^[4] The study met its endpoint by showing an improvement from 1.5 to 3 months (HR, 0.49; 95%CI, 0.29–0.81; $p=0.005$). Despite demonstrating some level of regorafenib activity in patients with refractory BTC, these studies showed that such patients have a very poor outcome, with a median PFS and OS ranging from 3–3.9 months and 5.3–7.9 months, respectively.^[4,18–19]

Monoclonal antibodies targeting PD-1 and PD-L1 represent one of the most important breakthroughs in cancer treatment for several tumor types. Studies that

have evaluated these agents in patients with BTC report activity in a subset of patients, with response rates ranging from 3–11%, median PFS of 1.4–3.7 months, and median OS of 5.2–14.2 months. Interestingly, when responses occurred, they were durable—all lasting more than 6 months.^[7, 20]

Anti-angiogenic agents can reduce immunosuppression. Conversely, immunotherapies can impact the vasculature and have antivascular effects; thus, immunotherapy and anti-angiogenic drugs have the potential to create a virtuous cycle of immunostimulation and vascular remodeling within tumors.^[8-9] This potential synergy has been shown in several preclinical models and in the clinical setting, as illustrated by the recent approval of axitinib plus avelumab or pembrolizumab as a first-line treatment for advanced or metastatic renal cell carcinoma.^[21]

Little is known about the tumor microenvironment of BTC. Recent data have shown that the immunological profile of BTC is not dependent on the IDH1/2 mutational status ^[22]. In iCCA, two subgroups have been defined based on transcriptomic analysis; one of which includes up to 40% of cases and is characterized by an immunological signature resulting from strong T lymphocyte infiltration and the activation of immune checkpoints.^[5] Integrative molecular characterization of eCCA has also revealed that only a minority of BTCs (11%) are characterized by an inflammation signature.^[6] Interestingly, in our study, all but one patient with clinical benefit (objective response or stable disease) had an iCCA. Moreover, we found that eCCA had higher levels of TAM infiltration. Several lines of evidence suggest the important role of TAMs in cholangiocarcinoma progression, and their presence has been associated with poor outcomes.^[23]

In our cohort, patients with high PD-L1 expression were more likely to benefit from the treatment. These results agree with those of previous studies showing that high PD-L1 expression was associated with improved outcomes in patients with BTC treated with immune checkpoint inhibitors ^[24]. We also observed that high IDO1 expression was significantly associated with improved outcomes. IDO1 is a rate-limiting enzyme involved in the metabolism of the essential amino acid tryptophan and plays a crucial role in modulating the tumor microenvironment ^[25]. Our results are also in line with those of previous studies revealing that certain subsets of patients with solid tumors exhibiting IDO1 overexpression had favorable outcomes on anti-

PD-1 therapy. A possible explanation is that IDO1 overexpression is, in this context, a surrogate of the presence of tumor-reactive T cells within the tumor microenvironment. For instance, Hamid, et al. found that high IDO1 expression correlated with an improved efficacy of ipilimumab in patients with metastatic melanoma.^[26] Analyses of other patient cohorts, including patients with non-small cell lung cancer, have shown similar results.^[27]

Most of the patients required dose reductions of regorafenib due to adverse events. A recent open-label trial that included 116 evaluable patients with metastatic colorectal cancer showed that a regorafenib dose-escalation strategy (starting dose of 80 mg/day with weekly escalation in 40 mg increments to 160 mg/day if no significant drug-related adverse events occurred) may represent an alternative approach for optimizing regorafenib dosing with comparable activity and a lower incidence of adverse events compared with a standard dose strategy (160 mg/day for 21 days of a 28-day cycle).^[28] Such a strategy may be worth investigating when combining regorafenib with immune-oncology agents.

Although one limitation of our study is the limited sample size in relation to the heterogeneity of BTC, our results demonstrated clinical activity of the combined regorafenib and avelumab therapy in a subset of patients with advanced BTC. Further studies should investigate such a regimen in a population selected based on a favorable tumor microenvironment signature (high PD-L1 and/or high IDO1 expression).

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TABLES

Tables 1. Patients characteristics	
	Eligible patients for safety N=34
Median age (years, range)	63.1 (36 – 80)
Gender	
Female	16 (47.1%)
Male	18 (52.9%)
Performans status ECOG	
0	16 (47.1%)
1	17 (50.0%)
Unknown	1 (2.9%)
Tumor location	
Intra-hepatic	26 (76.5%)
Extra-hepatic	7 (20.6%)
Gallbladder	1 (2.9%)
Number of metastatic sites	
Single	6 (17.6%)
Multiple	28 (82.4%)
Metastatic sites	
Liver	27 (79.4%)
Lung	20 (58.8%)
Peritoneum	14 (41.2%)
Node	18 (52.9%)
Other	11 (32.4%)
Previous chemotherapy treatment	
Platinum-based	34 (100%)
Gemcitabine-based	34 (100%)
Topoisomerase I or II inhibitor	13 (38.2%)
Taxanes	3 (8.8%)
Previous lines of treatment for advanced disease	
1	14 (41.2%)
2	12 (35.3%)
>2	8 (23.5%)

Table 2. Treatment-related adverse events during the treatment period in > 5% of patients (N=34)			
Adverse event	Grade 1-2	Grade 3	Grade 4
Fatigue	22 (65%)	5 (15%)	
Infusion related reaction	16 (47%)	1 (2.9%)	
Palmo-plantar erythrodysesthesia	14 (41%)	3 (9%)	
Diarrhea	13 (38%)	2 (6%)	
Dysphonia	12 (35%)		
Oral mucositis	11 (32%)		
Anorexia	10 (29%)	2 (6%)	
AST and/or ALT increased	8 (24%)	4 (9%)	
Muscle cramp	8 (24%)		
Nausea	8 (24%)	1 (3%)	
Fever	8 (24%)		
Alkaline phosphatase and/or GGT increased	7 (21%)	3 (9%)	
Thrombopenia	7 (21%)	3 (9%)	
TSH increased	7 (21%)		
Vomiting	6 (18%)	1 (3%)	
Pruritus	6 (18%)		
Hypertension	5 (15%)	6 (18%)	
Maculo-papular rash	5 (15%)	4 (12%)	
Dry skin	5 (15%)		
Alopecia	5 (15%)		
Hypophosphatemia	5 (15%)		
Anemia	4 (12%)	1 (3%)	
Hypothyroidism	4 (12%)		
Abdominal pain	4 (12%)		
Headache	4 (12%)		
Dry mouth	4 (12%)		
Erythema multiforme	3 (9%)	2 (6%)	

Table 2. Treatment-related adverse events during the treatment period in > 5% of patients (N=34)			
Adverse event	Grade 1-2	Grade 3	Grade 4
Constipation	3 (9%)		
Lipase increased	3 (9%)		
Myalgia	3 (9%)		
Peripheral sensory neuropathy	3 (9%)		
Epistaxis	3 (9%)		
Dysphagia	3 (9%)		
Chills	3 (9%)		
Lymphocyte count decreased	2 (6%)	1 (3%)	
Blood bilirubin increased	2 (6%)	2 (6%)	
Gastrointestinal pain	2 (6%)		
Hemorrhoids	2 (6%)		
Periodontal disease	2 (6%)		
Blood lactate dehydrogenase increased	2 (6%)		
CPK increased	2 (6%)		
Arthralgia	2 (6%)		
Back pain	2 (6%)		
Proteinuria	2 (6%)		
Dyspnea	2 (6%)		
Hoarseness	2 (6%)		
Hyperkeratosis	2 (6%)		
Rash acneiform	2 (6%)		
Hyponatremia	1 (6%)	2 (6%)	
Neutrophil count decreased		2 (6%)	
Left ventricular systolic dysfunction		1 (3%)	

Table 2. Treatment-related adverse events during the treatment period in > 5% of patients (N=34)			
Adverse event	Grade 1-2	Grade 3	Grade 4
Esophageal ulcer		1 (3%)	
Biliary tract infection		1 (3%)	
Hyperglycemia		1 (3%)	

FIGURES

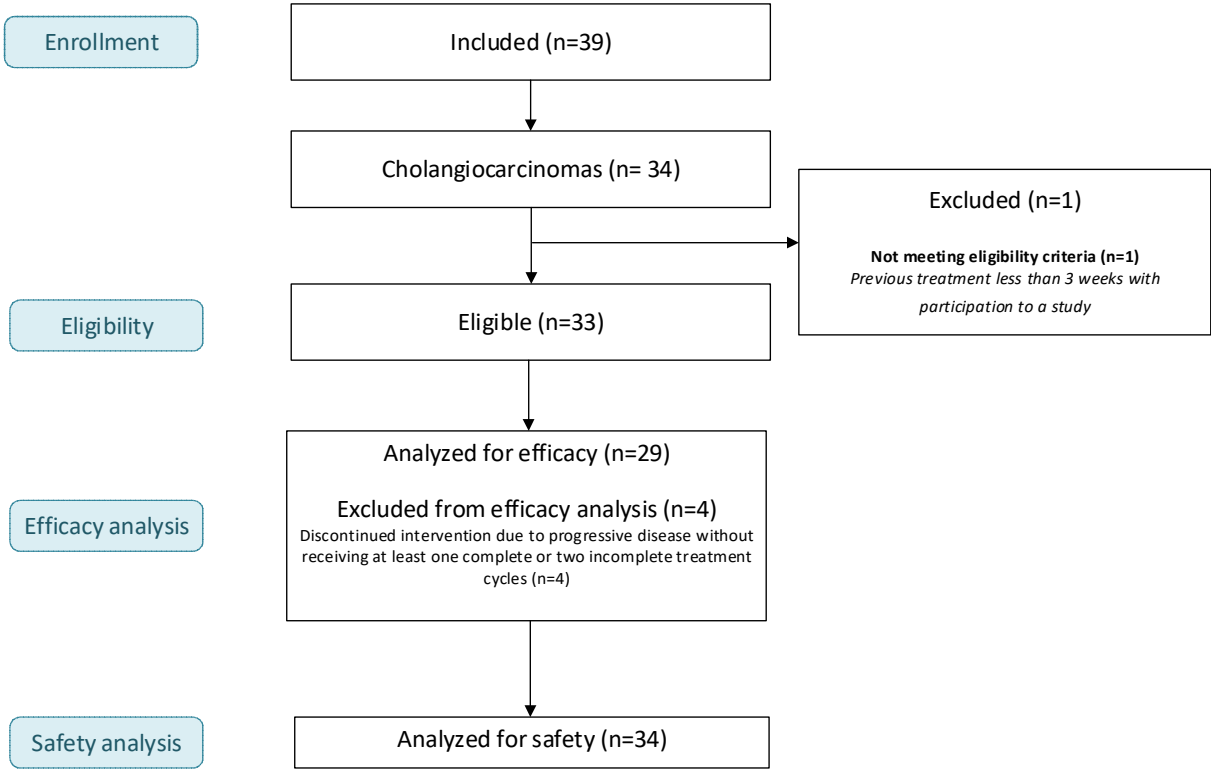


Figure 1. Flow chart of patients included in the REGOMUNE STUDY

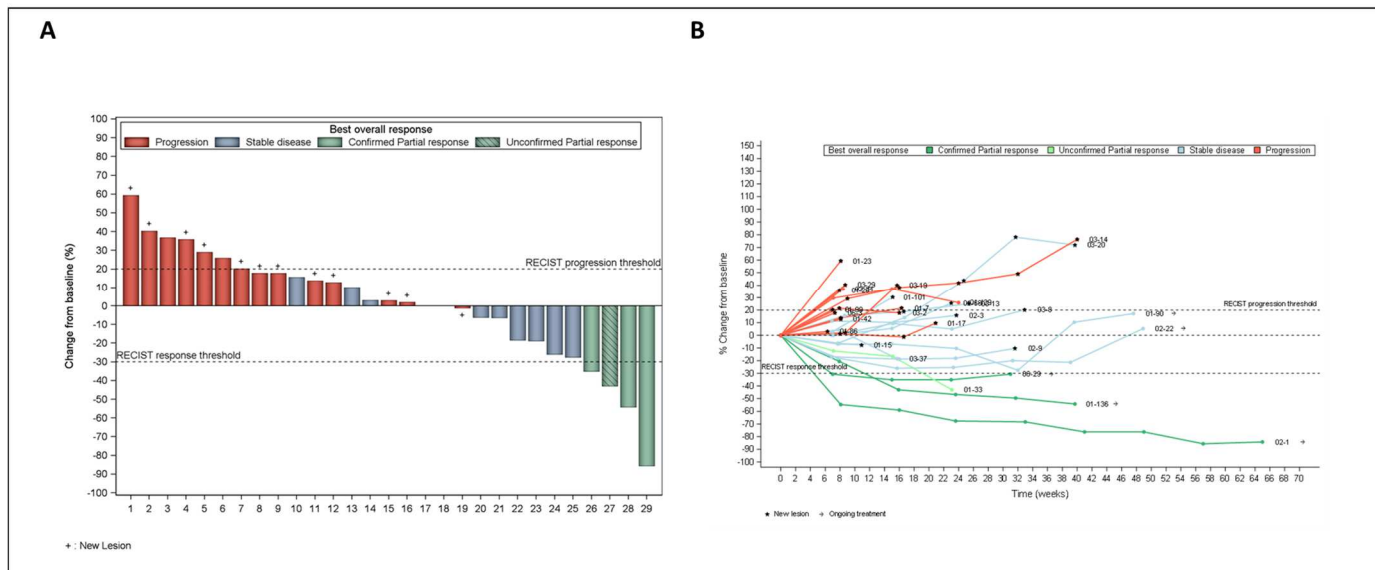


Figure 2. Waterfall plot (A) and spider plot (B) of best overall response in biliary tract cancer patients treated with regorafenib plus avelumab (n=29, Response based on central review assessment according to RECIST 1.1)

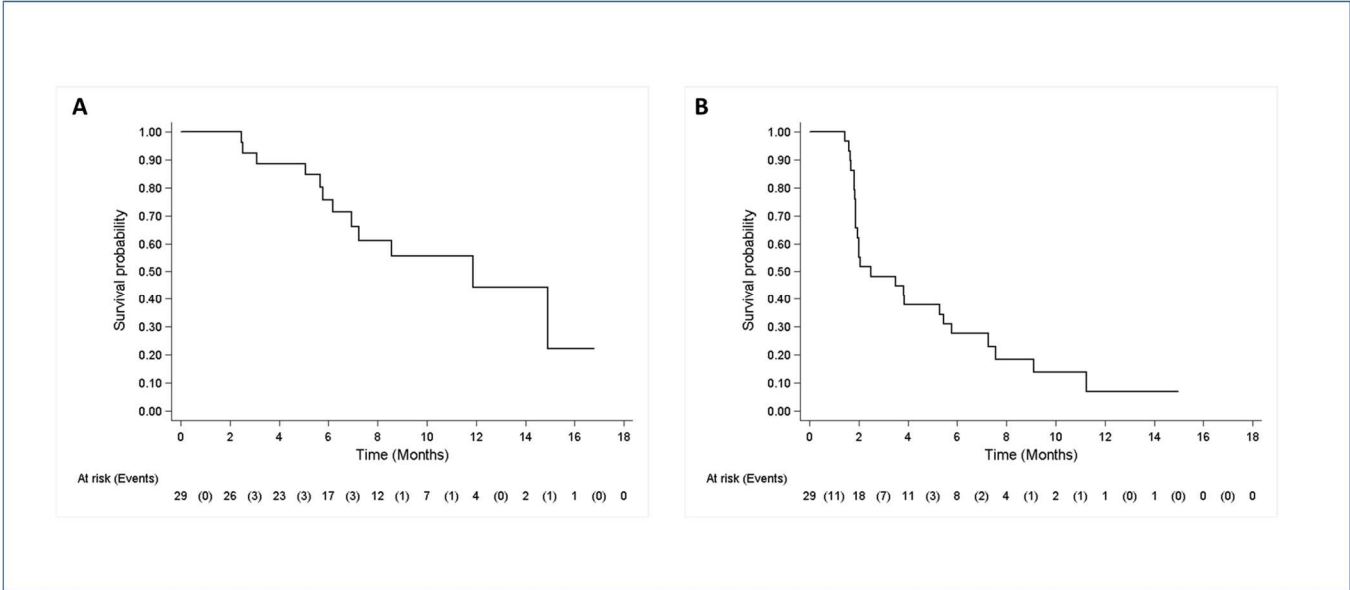


Figure 3. Kaplan-Meier curves of progression-free survival following central review (A) and overall survival (B) in biliary tract cancer patients treated with regorafenib and avelumab (29 patients eligible for efficacy analysis)

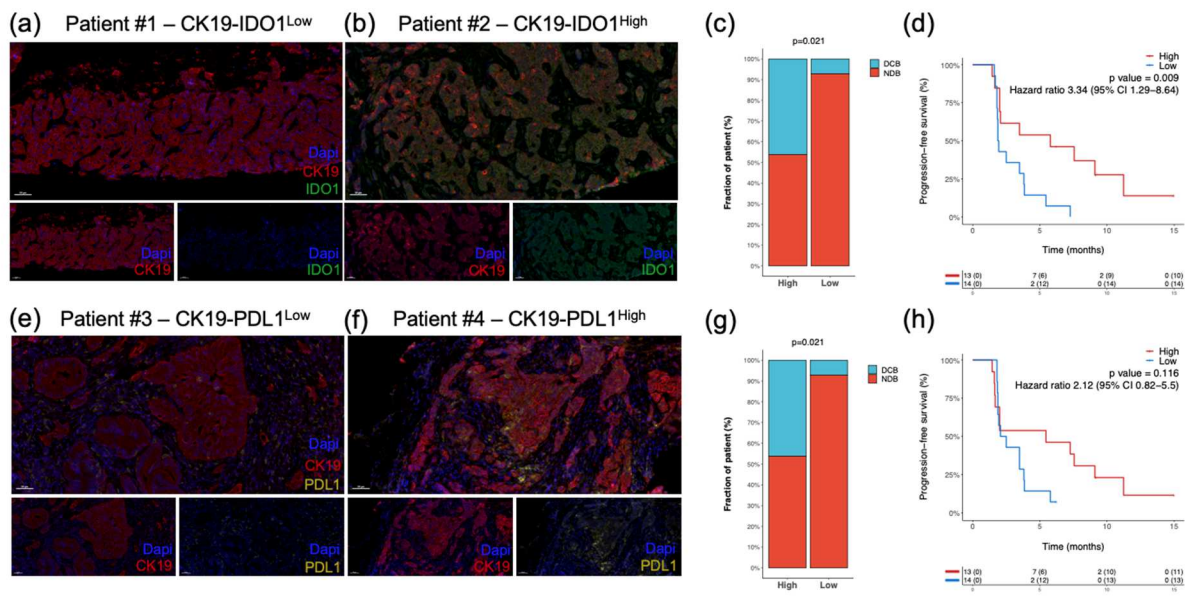


Figure 4. IDO1 and PDL1 expressing tumors are associated with a favorable clinical outcome in patients with BTC treated with regorafenib combined with velumab. Illustration of IDO1 and Cytokeratin 19 (CK19) stainings in tumor samples - collected before treatment onset - from **a)** Patient #1 with negative/low IDO1 expression and a poor clinical outcome (PFS: 1,8 mo) and **b)** Patient#2 with high IDO1 expression and a favorable clinical outcome (PFS: 7,5 mo). **c)** Rates of durable clinical benefit according to the expression level of IDO1 within CK19 positive tumor cells. **d)** Kaplan-Meier curves of progression-free survival according to the expression level of IDO1 in CK19 positive cells; blue curve: low IDO1 expression and red curve: high IDO1 expression. Illustration of PDL1 and Cytokeratin 19 (CK19) stainings in tumor samples - collected before treatment onset - from **e)** Patient #3 with low tumor expression of PDL1 and a poor clinical outcome (PFS: 3,8 months) and **f)** Patient#4 with high PDL1 expression by tumor cells and a favorable clinical outcome (PFS: 14,9 months). **g)** Rate of clinical benefit according to the expression level of PDL1 within tumor cells. **h)** Kaplan-Meier curves of progression-free survival according to the expression level of PDL1 in tumor cells; blue curve: low PDL1 expression and red curve: high PDL1 expression.