Combined Treatment of Durvalumab, Bevacizumab and Tremelimumab in Subjects with Biliary Tract Carcinoma (BTC).

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Background

Our group conducts clinical trials evaluating different immunotherapy regimen in CCA.

We were the first to test anti-CTLA4 and anti-CTLA4 + anti-PDL1 in BTC.

Dual blockade of VEGF and PD-1/PD-L1 has demonstrated synergistic clinical efficacy and survival benefits in cancers such as HCC, RCC, and NSCLC, through favorable modulation of the tumor microenvironment.

Addition of CTLA-4 inhibitors to PD-1/PD-L1 therapy offers a complementary mechanism to further amplify T-cell–mediated responses, supporting the rationale for multi-pathway immunomodulation.

Preclinical studies in murine BTC models and early clinical observations suggest that triplet blockade of VEGF, PD-L1, and CTLA-4 may be a promising novel strategy in BTC, warranting further investigation.

Here we present data from a clinical trial testing the combination of anti-vegf/anti-CTLA4 + anti-PD-L1 in BTC.

Methods

This was an open label Phase II trial conducted to evaluate efficacy of durvalumab, bevacizumab and tremelimumab in advanced HCC BCLC stage C or BTC. Here we report results in BTC.

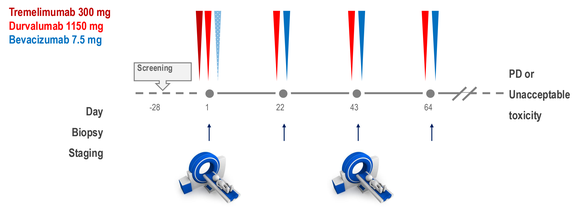
Participants received a single IV infusion of durvalumab (1,150 mg) and tremelimumab (300 mg) on Day 1 of Cycle 1. Starting on Day 1 of Cycle 2, bevacizumab (7.5 mg/kg) and durvalumab (1,150 mg) were administered every 3 weeks by IV infusion. Treatment with the durvalumab and bevacizumab combination continued in 3-week cycles until disease progression or unacceptable toxicity.

Primary endpoint was 6-month progression-free survival (PFS) and secondary endpoints were safety, overall survival (OS) and best overall response (BOR).

Key eligibility criteria
Histopathological confirmation of BTC
ECOG 0-1

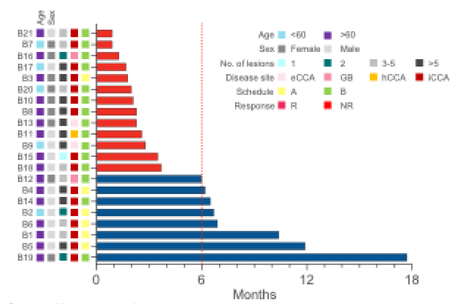
Primary Endpoint
6-month PFS

Secondary Endpoint
Safety
Overall Survival
Best overall response

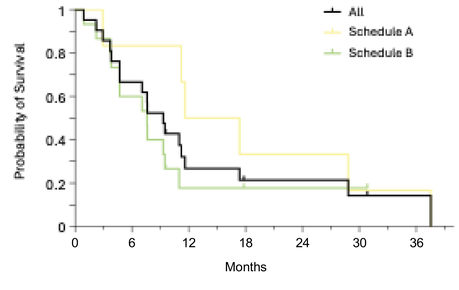


Figures

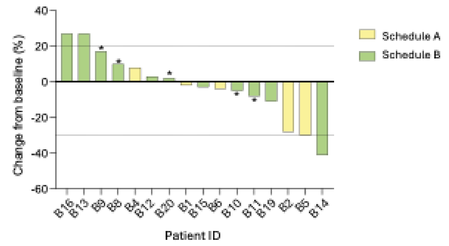
Baseline criteria and Progression free survival



Overall survival



Tumor responses



Adverse Event Term (CTCAE v 5.0)*	1	2	3	4
Alanine aminotransferase increased		2		
Aspartate aminotransferase increased	1	2		
Colitis			1	1
Colonic perforation				1
Diarrhea	5	1	2	
Dyspepsia	1			
Immune-related hepatotoxicity			1	
Lipase increased		1	1	
Serum amylase increased		2		
Cardiac toxicity**		3	2	
Rash	6	2		
Endocrine thyroid toxicity**	3	4	2	
Anemia	2		2	
Lymphocyte count decreased	2	9	3	
Neutrophil count decreased		1		
Platelet count decreased	8	2		
White blood cell decreased	4	3		
Blood bicarbonate decreased	1			
Hypercalcemia	1			
Immune mediated Diabetes			1	
Myositis			1	
Polymyalgia rheumatica exacerbation		1		
Dry mouth	1			
Generalized muscle weakness			1	
Hoarseness	2			

Results

Study population
21 patients with advanced BTC were enrolled between March 2021 and August 2024.

Median age: 65 years (range 44-80 years).

Intrahepatic BTC (16 / 21, 76%)
Presence of extrahepatic disease (19 / 21, 90%).

13 / 21 (62%) patients had received at least two lines of prior treatment.

Safety
Immune related Grade 3 and 4 adverse events: colitis, colonic perforation, endocrine toxicity and laboratory abnormalities.

Unexpected high rate of uncommon irAEs in the first six patients treated with the combination of bevacizumab + STRIDE: Myositis, cardiac toxicity, and hepatotoxicity.

Some irAEs were not only unexpected but also occurred early upon treatment start (within 60 days of treatment initiation).

This led us to modify the treatment schedule: The first bevacizumab dose (C1D1) was dropped, and the first dose of bevacizumab was given on day 29 (C2D1) instead.

This revised treatment schedule (**schedule B**) led to a lower frequency and severity of irAE (15 events of Grade 2 or higher across 15 patients, 1 colonic perforation (grade 4), and 1 generalized muscle weakness (grade 3)).

3/6 patients in schedule A had to discontinue treatment due to an irAE versus only 1 / 15 in schedule B.

Clinical outcomes
Median follow-up time: 31 months

Median PFS: 2.8 months for all patients (6.8 months for schedule A, 2.3 months for schedule B). 8 / 21 patients had met the primary endpoint of 6-month PFS, 5 of whom received schedule A.

Median OS: 9.3 months in all patients (14.5 months for schedule A, and 7.6 months for schedule B). Patients in schedule A showed a trend towards better overall survival.

16 patients were evaluable for response assessment (4 in schedule A and 11 in schedule B).

DCR was 56 % for all patients (9 / 16 evaluable patients), 100% for schedule A (5 / 5 evaluable patients), and 36 % for schedule B (4 / 11 evaluable patients). 2 showed a partial response (1 in schedule A and 1 in schedule B).

In summary, patients receiving schedule A showed a trend towards better clinical outcomes, which was accompanied by more frequent and severe irAEs.

My group conducts clinical trials testing immunotherapy.

What was this study about?
This study looked at a new **combination of 3 cancer drugs** to treat **biliary tract cancer (BTC)**, which affects the bile ducts.
The three medicines were: **Durvalumab**, **Tremelimumab** and **Bevacizumab.**
These drugs help the immune system fight cancer in different ways.

Why try this treatment?
We believe that **combining these drugs might work better together** than using them alone.
The goal was to:
Help the immune system attack cancer more strongly.
Slow down or stop cancer growth.

Who was in the study?
21 patients with advanced bile duct cancer.
Most had already tried other treatments before.

How was the treatment given?
Patients received the drugs through an IV (in a vein)
Treatment was given every **3 weeks**
Doctors later adjusted the schedule to make it safer.

⚠ **Side effects (safety)**
Some patients had **serious side effects**, including:
Inflammation of the colon (colitis) ,muscle problems , heart or liver issues.
👉 Early in the study, side effects were **more severe and happened quickly.**
👉 After changing the treatment schedule, **side effects became less frequent and less severe.**

What were the results?
About **half of the patients** had their cancer **controlled** (did not grow for a time).
A small number had **tumor shrinkage**
On average:
Cancer stayed stable for about **2–3 months**
Patients lived about **9 months on average**
👉 One treatment schedule worked **better**, but also caused **more side effects.**

What does this mean?
This 3-drug combination **may help some patients.**
But it can also cause **serious side effects.**
More research is needed to find the **best balance between benefit and safety.**

Key takeaway

This study shows a **promising but challenging treatment option**:
It may improve cancer control in some patients
But doctors must carefully manage side effects.

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