PHASE 2 STUDY ASSESSING TOLERABILITY, EFFICACY AND BIOMARKERS FOR DURVALUMAB ± TREMELIMUMAB AND GEMCITABINE/CISPLATIN IN CHEMO-NAÏVE ADVANCED BILIARY TRACT CANCER

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Introduction

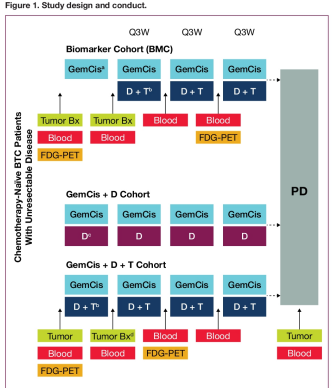
- Biliary tract cancer (BTC) includes extrahepatic and intrahepatic cholangiocarcinoma (ECC and ICC, respectively), gallbladder cancer (GBC), and ampulla of Vater cancer (AVC).[1]
- BTC is often diagnosed at an advanced stage as it is largely asymptomatic.
- The first-line standard-of-care treatment for advanced BTC (aBTC) is gemcitabine plus cisplatin (GemCis) though prognosis remains poor (median survival, 11.7 months), demonstrating a need for improved treatments.[2,3]
- Early studies of immunotherapies have shown promising efficacy in some patients with BTC, and there is rationale for combining immunotherapy with chemotherapy.[1,5]
- This study evaluated the tolerability and efficacy of GemCis plus durvalumab (D) with or without tremelimumab (T), as well as the role of programmed death ligand-1 (PD-L1) and circulating tumor DNA (ctDNA) (previously shown to be associated with survival in non-small cell lung cancer and urothelial cancer) as response biomarkers.

Methods

Study Design

- This Phase 2 study (NCT03046862) assessed the safety and efficacy of D, with or without T, and GemCis in treatment-naïve Korean patients with unresectable or recurrent BTC.
- Patients were enrolled in 3 cohorts (**Figure 1**).

Figure 1. Study design and conduct.



Bx, biopsy; FDG-PET, fluorodeoxyglucose-positron emission tomography; Q3W, every 3 weeks; PD, progressive disease.
[a]Gemcitabine 1000 mg/m² + cisplatin 25 mg/m² on Days 1 and 8.
[b]Durvalumab 1120 mg on Day 1 + tremelimumab 75 mg on Day 1 (for up to 4 cycles).
[c]Durvalumab 1120 mg on Day 1.
[d]Optional tumor biopsy after first cycle of therapy for GemCis + D and GemCis + D + T.

Outcome Measures

- The primary endpoint was response rate according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.
- Secondary endpoints included progression-free survival (PFS) and disease control rate, duration of response (DoR), and overall survival (OS).
  - PFS events were defined as either disease progression or death.

Biomarker Analyses in the BMC

- Whole exome sequencing (WES) was performed on pretreatment tumor and matched blood DNA for samples from the BMC.
- Early ctDNA changes upon D + T immunotherapy were evaluated using PredicineATLAS™ panel in plasma samples taken at baseline and cycle 3.
- Germline variants and synonymous mutations were removed prior to WES and ctDNA mutation analyses.
- Tumor mutation burden (TMB) was assessed based on pretreatment tumor nonsynonymous variants with allelic frequency 5% or higher. TMB-high was defined as TMB ≥median.
- PD-L1 expression was assessed in pre- and post-treatment biopsy samples using the VENTANA PD-L1 (SP263) Assay.

Results

- The study enrolled 121 patients with evaluable data (**Table 1**).
  - Median duration of follow-up (95% confidence interval [CI]) was 28.5 months (26.5–30.5) for the BMC, 11.3 (9.1–13.5) months for the GemCis + D cohort, and 11.9 (8.4–15.4) months for the GemCis + D + T cohort.

Table 1. Patient demographics and baseline characteristics.

Characteristics	BMC n=30	GemCis + D n=45	GemCis + D + T n=46
Age, median (range), years	64 (36–74)	61 (45–81)	66 (29–93)
Male, n (%)	17 (56.7)	19 (42.2)	25 (54.3)
ECOG performance status, n (%)			
0	30 (100.0)	17 (37.8)	23 (50.0)
1	0	28 (62.2)	23 (50.0)
Disease extent, n (%)			
Initially unresectable	14 (46.7)	25 (55.6)	27 (58.7)
Recurrent	16 (53.3)	20 (44.4)	19 (41.3)
Primary tumor site, n (%)			
ICC	17 (56.7)	27 (60.0)	20 (43.5)
ECC	2 (6.7)	9 (20.0)	3 (6.5)
GBC	7 (23.3)	7 (15.6)	15 (32.6)
AVC	4 (13.3)	2 (4.4)	8 (17.4)
Treatment history, n (%)[a]			
Surgery	16 (53.3)	26 (57.8)	28 (60.9)
Adjuvant therapy	11 (36.7)	14 (31.1)	13 (28.3)
Patients recurring after adjuvant therapy, n	11	14	13
During adjuvant therapy, n (%)	1 (3.3)	1 (2.2)	1 (2.2)
<6 months after completion, n (%)	6 (20.0)	8 (17.8)	8 (17.4)
≥6 months after completion, n (%)	4 (13.3)	5 (11.1)	4 (8.7)
Metastatic site, n (%)			
Liver	24 (80.0)	20 (44.5)	23 (50.0)
Lung	14 (46.7)	7 (15.6)	10 (21.7)
Bone	4 (13.3)	4 (8.9)	5 (10.9)
Peritoneum	3 (10.0)	10 (23.2)	11 (23.6)
Distant lymph nodes	21 (70.0)	18 (40.0)	27 (58.7)
Brain	0	1 (2.2)	0
HBV, n (%)[a]	3 (10.0)	2 (4.4)	2 (4.3)

ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis virus B.
[a]Treatment of a previous occurrence of BTC.
[b]There were no patients enrolled who had hepatitis virus C.

- Objective response rate (ORR) was 50% for the BMC and approximately 73% for both the GemCis + D and GemCis + D + T cohorts (**Table 2**, **Figure 2**).
- Overall, patients had a median 2.3 months (range, 1.1–9.0) to onset of treatment response.

Table 2. Treatment response (RECIST v1.1) and survival rates.

Treatment response	BMC n=30	GemCis + D n=45	GemCis + D + T n=46
Objective response rate, % (95% CI)	50.0 (32.1–67.9)	73.4 (60.5–86.3)	73.3 (60.4–86.2)
Complete response	6.7 (0–15.6)	6.7 (0–14.0)	2.2 (0–6.5)
Partial response	43.3 (25.6–61.0)	66.7 (52.9–80.5)	71.1 (58.5–84.9)
Stable disease	46.7 (28.8–64.6)	26.7 (13.8–39.6)	24.4 (11.9–36.9)
Disease progression	3.3 (0–9.7)	0	2.2 (0–6.5)
Disease control rate, % (95% CI)	96.7 (90.3–100.0)	100.0 (100.0–100.0)	97.8 (93.5–100.0)
Median DoR, months (95% CI)	11.0 (3.9–18.1)	9.8 (8.1–11.4)	9.1 (0.0–18.8)

Key conclusions

- These are the first clinical data of D ± T plus GemCis in chemotherapy-naïve aBTC patients.
- The addition of immunotherapy to chemotherapy was tolerable and showed very promising efficacy.
- We identified candidate biomarkers that may be indicative of response to these therapies; further analyses in the GemCis + D and GemCis + D + T cohorts are ongoing.
- The combination of D + GemCis versus GemCis is being investigated in the global Phase 3 TOPAZ-1 trial (NCT03875235); enrollment is ongoing.

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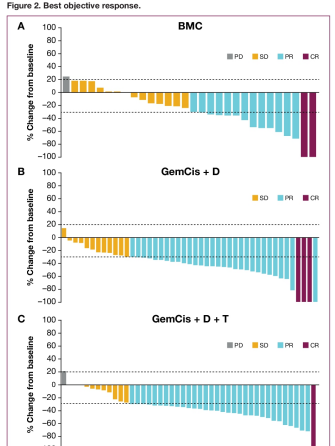
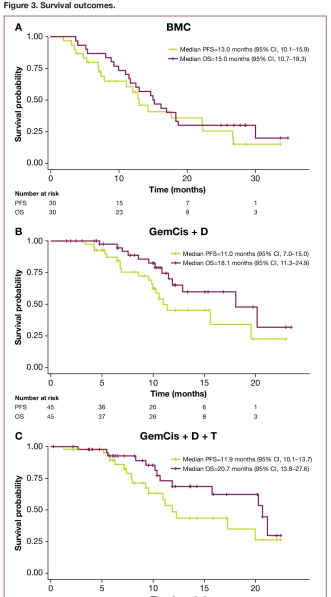
Figure 2. Best objective response.



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

- Median PFS was 13.0 months for the BMC and 11.0 and 11.9 months for the GemCis + D and GemCis + D + T cohorts, respectively (**Figure 3**).
- Median OS was 15.0 months for the BMC and 18.1 and 20.7 months for the GemCis + D and GemCis + D + T cohorts, respectively (**Figure 3**).
- Although this study was not designed to evaluate this combination regimen against a comparator arm, OS for the BMC was longer than historic OS for GemCis chemotherapy (11.7 months), and OS for the GemCis + D and GemCis + D + T cohorts was even longer than that of the BMC. However, this should be cautiously interpreted as the follow-up duration for the GemCis + D and GemCis + D + T cohorts is shorter than that of the BMC.

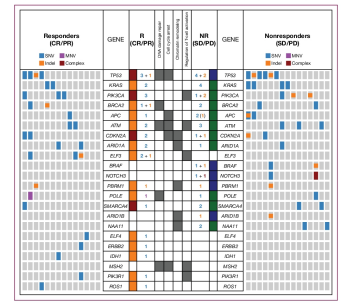
Figure 3. Survival outcomes.



Biomarker analysis data in the BMC

- Tumor WES analysis revealed frequent mutations of genes involved in DNA damage repair, cell cycle regulation, and genome instability in chemo-naïve BTC patients (**Figure 4**).
- Distinct sets of somatic variants were found in treatment responders versus nonresponders (**Figure 4**).
- Baseline tissue TMB did not correlate significantly with PFS and OS.

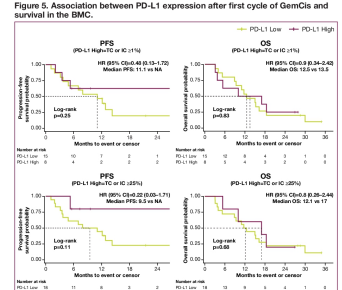
Figure 4. Somatic mutations in responders and nonresponders in the BMC.



MMV, multiple nucleotide variant; NR, nonresponders; R, responders; SNV, single-nucleotide variant.

- Tumor biopsies were assessed for PD-L1 expression pre- and post-treatment with GemCis in the BMC.
- Pretreatment PD-L1 expression was not associated with PFS or OS; however, a trend toward longer PFS was observed after 1 cycle of GemCis in patients with higher PD-L1 tumor expression versus patients with lower PD-L1 expression (**Figure 5**).

Figure 5. Association between PD-L1 expression after first cycle of GemCis and survival in the BMC.



HR, hazard ratio; IC, tumor-associated immune cells; NA, not applicable; TC, tumor cell.

- Deep reduction in ctDNA variant allele frequency (VAF) was more prominent among responders during early cycles of D + T treatment.
- ctDNA VAF at cycle 3 Day 1 was significantly correlated with ORR ($P<0.014$) (**Figure 6**).
- The most common adverse events (any grade) were nausea (59.5%), neutropenia (54.5%), and pruritus (55.4%) (**Table 3**).
  - The most common Grade 3/4 adverse events were neutropenia (50.4%), anemia (35.5%), and thrombocytopenia (16.5%). There were no Grade 5 events.
- Toxicity for the chemotherapy-immunotherapy combination was tolerable and liver toxicity did not appear to be a concern.

Figure 6. ctDNA VAF levels at baseline and cycle 3.

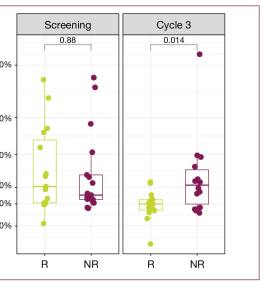


Table 3. Common adverse events (>10% in any cohort).

Adverse events, n (%)	BMC n=30	GemCis + D n=45	GemCis + D + T n=46
Any grade			
Neutropenia	18 (60.0)	25 (55.6)	23 (50.0)
Anemia	17 (56.7)	20 (44.4)	14 (30.4)
Thrombocytopenia	13 (43.3)	12 (26.7)	12 (26.1)
Nausea	21 (70.0)	29 (64.4)	22 (47.8)
Pruritus	22 (73.3)	24 (53.3)	21 (45.6)
Anorexia	24 (80.0)	17 (37.8)	19 (41.3)
Fatigue	21 (70.0)	14 (31.1)	18 (39.1)
Fever	13 (43.3)	14 (31.1)	20 (43.5)
Papulopustular rash	13 (43.3)	13 (28.9)	22 (47.9)
Constipation	6 (20.0)	19 (42.2)	16 (34.8)
Vomiting	10 (33.3)	17 (37.8)	13 (28.3)
Diarrhea	7 (23.3)	10 (22.2)	10 (21.7)
Peripheral sensory neuropathy	8 (26.7)	10 (22.2)	4 (8.7)
Weakness	9 (30.3)	3 (6.7)	8 (17.4)
AST/ALT elevated	1 (3.3)	6 (13.3)	4 (8.7)
Stomatitis	7 (23.3)	3 (6.7)	3 (6.5)
Bilirubin increased	1 (3.3)	4 (8.9)	5 (10.9)
Grade 3/4			
Neutropenia	16 (53.3)	24 (53.3)	21 (45.7)
Anemia	13 (43.3)	17 (37.8)	13 (28.3)
Thrombocytopenia	4 (13.3)	7 (15.6)	9 (19.6)

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