**Toripalimab in advanced biliary tract cancer**

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**GRAPHICAL ABSTRACT**

**PUBLIC SUMMARY**

- Toripalimab plus GS for aBTC
- mPFS and mOS: 7.0 and 15.0 months
- Acceptable tolerability
Toripalimab in advanced biliary tract cancer

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INTRODUCTION

Biliary tract cancers (BTCs) are a group of malignant tumors derived from the bile duct and gallbladder that are prone to progress with poor prognosis. Most patients, at the time of diagnosis, have already developed advanced-stage cancers and therefore have missed the opportunity for curative surgical resection.1,2

Germicetabine combined with platinum/fluouracil drugs is the standard first-line treatment for advanced biliary tract cancers (BTCs). We explored the safety and efficacy of toripalimab plus gemcitabine and S-1 (GS) as the first-line treatment for advanced BTCs. At a one-sided significance level of 0.025, a total of 50 patients could provide 80% power to show the efficacy at targeted progression-free survival (PFS) rate at 6 months of 70% versus 40% for the combined treatment. This single-arm, phase II study enrolled 50 patients with advanced BTCs who previously received no systemic treatment.1

The regimen was as follows: toripalimab (240 mg, i.v., d1), gemcitabine (1,000 mg/m², i.v., d1 and d8), and S-1 (40–60 mg bid p.o., d1–14, Q21d). The primary endpoint was progression-free survival. The secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR), and safety. The associations between response with PD-L1 expression, tumor mutational burden (TMB), and genetic variations were explored. Patients were enrolled from January 2019 to August 2020, with a median follow-up time of 24.0 months (IQR: 4.3–31.0 months). The 6-month PFS rate was 62%. The median PFS was 7.0 months (95% CI: 5.0–9.8 months), and median OS was 15.0 months (95% CI: 11.6–18.4 months). Forty-nine patients completed the evaluation for tumor response. The ORR was 30.6% (95% CI: 17.2%–44.0%), and the disease control rate was 87.8% (95% CI: 78.2%–97.3%). The most common treatment-related adverse events (TRAEs) were leukopenia (98.0%), neutropenia (92%), and anemia (86.0%).

Grade III/IV TRAEs included leukopenia (38.0%), neutropenia (32%), skin rash (6%), anemia (2.0%), mucositis (2%), and immune-related colitis (2%).

Among them, the grade III/IV immune-related adverse events (irAEs) were skin rash and colitis. In addition, biomarker analysis showed that negative PD-L1 expression and SMARCA4 mutation were significantly associated with worse survival outcomes, while no significant associations were observed for TP53, KRAS, or CDKN2A mutation as well as TMB. In conclusion, our data suggest that a regimen of toripalimab plus GS could improve PFS and OS with a good safety profile as a first-line treatment option for advanced BTC and warrants further verification.

MATERIALS AND METHODS

Study design and population

This was an open-label, single-arm, single-center, prospective, phase II clinical study (ClinicalTrials.gov identifier NCT03796429) designed to evaluate the efficacy and safety of toripalimab combined with GS chemotherapy for patients with advanced BTCs. Patients were enrolled at Shanghai Zhongshan Hospital between January 2019 and August 2020. This study was approved by the ethics committee of Zhongshan Hospital, Fudan University (B2018-294), and conducted in accordance with the Declaration of Helsinki and the international standards of good clinical practice. All patients provided written informed consent prior to enrollment. Inclusion criteria were as follows: (1) newly diagnosed advanced BTC pathologically determined to be adenocarcinoma, including intrahepatic cholangiocarcinoma, gallbladder carcinoma, and extrahepatic cholangiocarcinoma; (2) age 18–75 years; (3) Karnovsky performance score (KPS) ≥ 80 points within 7 days before enrollment; (4) at least one measurable lesion on abdominal computed tomography (CT)/magnetic resonance imaging (MRI) according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1, and (5) adequate functions of major organs: neutrophil count ≥ 1.5 × 10⁹/L, platelet count ≥ 100 × 10⁹/L, and creatinine clearance ≥ 60 mL/min.

Procedures

Patients were treated as below after enrollment: the PD-1 antibody toripalimab (240 mg, intravenous [i.v.]) on day 1 and gemcitabine (1,000 mg/m²) infusion on days 1 and 8 every 3 weeks. S-1 was administered orally twice a day (40 mg for body surface area [BSA] < 1.25 m², 50 mg for BSA between 1.25 and 1.50 m², and 60 mg for BSA > 1.50 m²) on days 1–14. This regimen was repeated every 3 weeks. Once 9 cycles of chemotherapy were completed or any chemotherapy intolerance occurred, the PD-1 antibody toripalimab (240 mg, i.v.) was applied until occurrence of disease progression, intolerable adverse effects, withdrawal of consent, or completion of 24 months of study. Histological samples of each patient were collected for examination of PD-L1 expression and next-generation sequencing (NGS) before the first cycle of treatment.

Assessment and study endpoints

Adverse events (AEs) were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All AEs from the time of treatment allocation till 90 days after cessation of treatment were reported. CT scanning or MRI examinations were performed every 9 weeks (a 7-day window was allowed), and the tumor response of each patient was evaluated by the same investigator according to the Response Evaluation Criteria in Solid Tumors version 1.1.
The primary endpoint of the study was progression-free survival (PFS), defined as the time from enrollment to the last day of either disease progression or death. After pseudo-progression, continued medication was allowed, but the time of disease progression was modified according to the time of the first imaging evaluation. The secondary endpoints included OS, objective response rate (ORR), duration of response (DOR), AEs, and treatment-related AEs (TRAEs). OS was defined as the time from enrollment to death or censorship (by September 20, 2021) for any reason. Patients were followed up every 2 months for the assessment of survival outcomes. ORR was defined as the proportion of patients whose best response during treatment was complete response (CR) or partial response (PR). DOR was defined as the time from first RECIST response to progression in patients who achieved PR or CR.

The baseline biopsy specimens and blood samples were obtained from patients for assessing the exploratory biomarkers, including PD-L1 expression, tumor mutational burden (TMB), and genetic variations identified by NGS. PD-L1 expression was detected by the Dako 22c3 antibody, and PD-L1-positive status was defined as combined positive score (CPS) ≥ 1. Genomic DNA from tumor tissues was extracted for NGS and TMB analysis. TMB was estimated per the methods of Chalmers et al.12

### Table 1. Demographic and baseline disease characteristics of the intention-to-treat population

| Variable                          | Patients (n = 50) |
|----------------------------------|------------------|
| **Age, y, median (range)**       | 62 (32–75)       |
| **Sex, n (%)**                   |                  |
| Male                             | 28 (56)          |
| Female                           | 22 (44)          |
| **ECOG performance status, n (%)**|                  |
| 0                                | 2 (4)            |
| 1                                | 48 (96)          |
| **Status of disease, n (%)**     |                  |
| Metastatic                       | 47 (94)          |
| Locally advanced                 | 3 (6)            |
| **Tumor type, n (%)**            |                  |
| IHCC                             | 20 (40)          |
| GBC                              | 20 (40)          |
| EHCC                             | 10 (20)          |
| **Biliary drainage, n (%)**      |                  |
| Yes                              | 10 (20)          |
| No                               | 40 (80)          |
| **PD-L1 expression, n (%)**      |                  |
| CPS ≥ 1                          | 16 (32)          |
| CPS < 1                          | 16 (32)          |
| Unknown                          | 18 (36)          |
| **TMB, n (%)**                   |                  |
| TMB-H                            | 20 (40)          |
| TMB-L                            | 28 (56)          |
| Unknown                          | 2 (4)            |

ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma.

### RESULTS

#### Patients

From January 3, 2019, to August 4, 2020, fifty-three patients with advanced BTCs were identified and screened for eligibility. Of these patients, 3 were deemed ineligible because they did not meet the inclusion criteria. A total of 50 patients were enrolled in the primary analysis and constituted the intention-to-treat population. Twenty-eight of the enrolled patients (56.0%) were men, with a median age of 62 years (32–75 years). Baseline information is presented in Table 1.

The median duration of follow-up was 24.0 months (interquartile range [IQR]: 4.3–31.0 months). Treatment for two patients (4%) was suspended because of biliary tract infection. Forty-four patients (88%) discontinued their treatment because of disease progression. Among these patients, 33 patients were dead, and the remaining 11 patients were still under follow-up. One patient was suspended because CR was achieved. Three participants were still receiving the treatment (Figure 1).

#### Efficacy

One patient discontinued treatment because of infection prior to first radiographic assessment. Among the 49 patients who completed the evaluation for tumor response with radiologic imaging, one had achieved CR, 14 patients had achieved PR, 28 patients had achieved stable disease (SD), and 6 patients had suffered progressive disease (PD). The waterfall plots demonstrating the best changes in comparison with the baseline tumor size are presented in Figure 2. Thus, an ORR of 30.6% (95% CI: 17.2%–44.0%) and a disease control rate of 87.8% (95% CI: 78.2%–97.3%) were achieved. In addition, DOR of the 15 CR/PR patients was 16.1 months (1.9–16.1 months).

Among the enrolled patients (n = 50), the median PFS was 7.0 months (95% CI: 5.0–8.9 months); median OS was 15.0 months (95% CI: 11.6–18.4 months). The 6-month PFS rate was 62% (Figure 3). The subgroup analyses (Table S1) showed that there was no significant difference in mPFS between different primary sites (6.0 months for intrahepatic cholangiocarcinoma, 7.6 months for gallbladder cancer, and 7.5 months for extrahepatic cholangiocarcinoma).

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**Figure 1. Flow of participants in the study**

- Assessed for eligibility (N=53)
- 3 Excluded
  - 2 abnormal liver function
  - 1 without target lesion
- 50 patients enrolled
- 50 patients received a 1 cycle treatment
- 47 discontinued
  - 44 had progressive disease
  - 1 complete remission
  - 2 infection
  - 3 treatment ongoing

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**Figure 2. Waterfall plots demonstrating the best changes in comparison with the baseline tumor size**

**Figure 3. Kaplan-Meier survival curves**

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**Table S1. Subgroup analyses of the intention-to-treat population**

| Primary site                  | Median PFS (months) | 6-month PFS (%) |
|-------------------------------|---------------------|-----------------|
| Intrahepatic cholangiocarcinoma| 6.0                 | 62              |
| Gallbladder cancer            | 7.6                 |                 |
| Extrahepatic cholangiocarcinoma| 7.5                 |                 |

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**Note:** The Innovation 3(4): 100255, July 12, 2022 www.cell.com/the-innovation
The TRAEs reported during the trial are summarized in Table 2. The most common TRAEs were leukocytopenia (98% [49 of 50]), neutropenia (92% [46 of 50]), and anemia (86% [43 of 50]). The grade 3 or worse TRAEs were leukocytopenia (38% [19 of 50]), neutropenia (32% [16 of 50]), rash (6% [3 of 50]), mucositis (2% [1 of 50]), anemia (2% [1 of 50]), and colitis (2% [1 of 50]). Among them, the immune-related adverse events (irAEs) were rash, hypothyroidism, pneumonia, and colitis. Two patients discontinued toripalimab (one for immune-related colitis, another for skin reaction).

Biomarker analysis

Thirty-two of the 50 patients were examined for PD-L1 expression (Dako 22c3). Compared with patients with negative PD-L1 expression, those positive for PD-L1 had statistically prolonged PFS (14.5 versus 4.85 months, \( p = 0.019 \)) (Figure 4A), while no significant difference was observed with regard to OS (16.1 versus 12.0 months, \( p = 0.09 \)) (Figure 4B). TMB was examined in 48 cases, with a median value of 4.3 mutations/Mb (0.5–34.8 mutations/Mb). We thus considered 4.5 mutations/Mb (TMB top 20) as the cut-off point to evaluate the correlation between TMB and survival outcomes. The results showed that the survival differences were not statistically significant (Figure S1).

In the enrolled patients, the genes with the highest mutation frequency were TP53, KRAS, and CDKN2A. Distribution of genetic variations associated with the response to toripalimab is depicted in Figure 4. The \( p \) values for the association between gene alteration and PFS and OS showed that SMARCA4 mutation was significantly associated with worse survival outcomes (PFS: 4.2 versus 7.9 months \( p = 0.0029 \); OS: 10.0 versus 16 months \( p = 0.069 \); Figure S2).

DISCUSSION

To our best knowledge, this is the first study to report the efficacy and safety of toripalimab combined with chemotherapy in advanced BTC patients. The results suggested that toripalimab plus GS could achieve desirable efficacy with a manageable safety profile among patients with newly diagnosed advanced BTC.

With the consensus of the poor prognosis in patients diagnosed with advanced BTC, only a limited number of available strategies are recommended, although various treatment regimens have been examined globally. The survival time of patients with BTC treated by GP regimen is slightly different across studies, ranging from 4.6 to 11.7 months, and the response rate ranges from 17.1% to 36.6%.

In Asia, the JCOG1113 study confirmed that the GS regimen was not inferior to the GP regimen, with an average 6.8 month mPFS. Although cross-trial comparisons should be made cautiously, it is worth noting that the proportion of patients with distant metastasis was higher in our study (94%), and 20% of our patients had biliary drainage due to jaundice, suggesting that the patients in our study might have been in a relatively more advanced stage of cancer and/or had heavier tumor load. However, our study showed 7 month PFS (95% CI: 5.0–8.9 months) and 15-month OS (95% CI: 11.6–18.4 months) for advanced BTC patients, suggesting the potential possibility of first-line treatment with immunotherapy combined with chemotherapy for advanced BTCs.

In recent years, several studies have explored the clinical benefit of immune check-point inhibitors in BTCs. However, not all patients can benefit from immunotherapy. In the KEYNOTE-158 biliary cohort (n = 104), the ORR to immunotherapy alone (5.8%) was generally low, even when only those patients with...
positive PD-L1 expression were considered, the effective rate was still unsatisfactory (6.6%). To cope with this situation, the synergistic anti-tumor effect of immune check-point inhibitor combined with chemotherapy has been discussed and confirmed in a series of exploratory studies in different tumor types. 

Recently, a phase II RCT to examine the efficacy and safety of camrelizumab plus gemcitabine and oxaliplatin reported median PFS of 6.1 months (95% CI: 5.1–6.8 months) and median OS of 11.8 months (95% CI: 8.3–15.4 months). Although the results of these studies were comparable with those of our analysis, which supported the potential efficacy of the combined therapy of PD-1 and chemotherapy in patients with advanced BTC, the differences in the characteristics and sample size between studies should still be noted for further investigation.

In terms of the safety profile, toripalimab plus GS was relatively safe and tolerable. The most frequent grade 3 or worse TRAEs were leukocytopenia (38%) and neutropenia (32%), which were also commonly reported with a similar incidence in previous gemcitabine involved studies. Compared with chemotherapy alone, chemotherapy combined with immunotherapy did not increase the incidence of hematological toxicity. Of note, potential immune-related AEs were rash (52%), hypothyroidism (28%), colonitis (2%), and pneumonia (2%). There were no life-threatening irAEs. Compared with similar studies in this area, the incidence of immune-related rash in this study is relative higher, which may be related to the skin toxicity of both gemcitabine and S-1 in the combination therapy. However, all these immune-related adverse reactions were well controlled and alleviated after treatment, suggesting an acceptable safety level for the combination therapy.

Table 2. Adverse events in all treated patients

| TRAEs               | All TRAEs | Grade ≥ 3 TRAEs |
|---------------------|-----------|-----------------|
| Leukocytopenia      | 49 (98%)  | 19 (38%)        |
| Neutropenia         | 46 (92%)  | 16 (32%)        |
| Thrombocytopenia    | 34 (68%)  | 0               |
| Anemia              | 43 (86%)  | 1 (2%)          |
| Nausea/Vomiting     | 12 (24%)  | 0               |
| Rash*               | 26 (52%)  | 3 (6%)          |
| Transferease increased | 20 (40%) | 0               |
| Hypothyroidism*     | 14 (28%)  | 0               |
| Mucositis*          | 4 (8%)    | 1 (2%)          |
| Pneumonia*          | 1 (2%)    | 0               |
| Colonitis*          | 1 (2%)    | 1 (2%)          |

*aImmune related adverse events.

Figure 3. Survival outcomes (A) Progression-free survival curve. (B) Overall survival curve. (C) Progression-free survival for patients with BTCs by PD-L1 expression. (D) Overall survival for patients with BTCs by PD-L1 expression.
SMARCA4 mutation and survival outcomes in BTC, while the association between SMARCA4 mutation with benefit of immunotherapy was still unclear.

This study was not a randomized controlled trial and had a relatively small sample size. As an exploratory study, the rate of PFS at 6 months was 62%, which did not reach the preset goal (70%). However, compared with other studies enrolling only Chinese BTC patients, the results showed promising PFS and OS. This single-arm noncomparative study is the first to investigate the efficacy and safety of toripalimab in advanced BTC patients. A well-designed and sophisticated two-armed study with a sufficient sample size is needed for improvement in the clinical outcomes for patients with BTC.

In summary, the present phase II clinical trial demonstrated promising efficacy and safety of toripalimab combined with GS as the first-line treatment in patients with advanced BTCs. The prognostic findings between PD-L1 expression and clinical response needs to be further investigated in large comparative studies.

REFERENCES

1. Hezel, A.F., Deshpande, V., and Zhu, A.X. (2010). Genetics of biliary tract cancers and emerging targeted therapies. J. Clin. Oncol. 28, 3531–3540.
2. Valle, J., Wasan, H., Palmer, D.H., et al. (2010). Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N. Engl. J. Med. 362, 1273–1281.
3. Valle, J.W., Furuse, J., Jitlal, M., et al. (2014). Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann. Oncol. 25, 391–398.
4. Okusaka, T., Nakachi, K., Fukutomii, A., et al. (2010). Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br. J. Cancer 103, 469–474.
5. Morizane, C., Okusaka, T., Mizusawa, J., et al. (2019). Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann. Oncol. 30, 1950–1958.
6. Heymach, J., Klitso, L., Alberg, A., et al. (2018). Clinical cancer advances 2018 annual report on progress against cancer from the American society of clinical oncology. J. Clin. Oncol. 36, 1020–1044.
7. Tang, B., Yan, X., Sheng, X., et al. (2019). Safety and clinical activity with an anti-PD-1 antibody JS01 in advanced melanoma or urologic cancer patients. J. Hematol. Oncol. 12, 7.
8. Zheng, Y., Liu, X.B., Sun, H.B., et al. (2021). A phase III study on neoadjuvant chemotherapy versus neoadjuvant toripalimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: heran Cancer Hospital Thoracic Oncology Group 1909 (HCTYPEQ909). Ann. Transl. Med. 9, 73.
9. Wang, F.H., Wei, X.L., Peng, J., et al. (2021). Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02). J. Clin. Oncol. 39, 704–712.
10. Wang, F., Wei, X.L., Wang, F.H., et al. (2019). Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripa- limab, a PD-1 antibody in phase IIb clinical trial NCT02915432. Ann. Oncol. 30, 1479–1486.
11. Eisenhauer, E.A., Therasse, P., Bogaerts, J., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 45, 228–247.
12. Chalmers, Z.R., Connelly, C.F., Fabrizio, D., et al. (2017). Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 9, 34.
13. Park, J.O., Oh, D.Y., Hsu, C., et al. (2015). Gemcitabine plus cisplatin for advanced biliary tract cancer: an uncontrolled phase II trial. J. Hematol. Oncol. 8, 90.
14. Piha-Paul, S.A., Oh, D.Y., Leen, M., et al. (2020). Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. Int. J. Cancer 147, 2190–2198.
15. Chen, X., Wu, X., Wu, H., et al. (2020). Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. J. Immunother. Cancer 8, e001240.
16. Bang, Y.J., Leen, M., Malka, D., et al. (2019). Pembrolizumab (pembro) for advanced biliary adenocarcinoma: results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basis- ket studies. J. Clin Oncol 37, 6579.
17. Marabelle, A., Fakih, M., Lopez, J., et al. (2020). Association of tumour mutational burden with response to immune checkpoint inhibitors in advanced solid tumours. J. Clin Oncol 38, 2198–2208.
18. Ueno, M., Ikeda, M., Morizane, C., et al. (2019). Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase I study. Lancet Gastroenterol. Hepatol. 4, 611–621.
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AUTHOR CONTRIBUTIONS
Conceptualization, Methodology, Writing – Review & Editing, T.L. and H.L.; Writing – Original Draft, Investigation, and Formal Analysis, W.L. and Yueqi Wang; Investigation and Resources, Y.Y., Q.L., Yan Wang, C.Z., X.X., X.G., and Y.C.; Data Curation and Visualization, Y.D., Q.H., and L.H.

DECLARATION OF INTERESTS
The authors declare no competing interests.

SUPPLEMENTAL INFORMATION
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