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Research Article

Safety and Efficacy of Toripalimab in Patients with Cholangiocarcinoma: An Open-Label, Phase 1 Study

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ABSTRACT

Introduction: This was the first phase 1 study conducted in the United States. It consisted of dose-escalation (part A) and multiple indication-specific cohort expansion (part B), investigating the safety and preliminary efficacy of toripalimab (anti–programmed cell death-1 inhibitor) in patients with advanced malignancies. **Methods:** Patients with advanced malignancies that progressed after treatment with at least one prior line of standard systemic therapy, including the patients with advanced/recurrent cholangiocarcinoma (CCA), received toripalimab 240 mg every 3 weeks in part B. The primary endpoint was safety assessment. Efficacy endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) as assessed by the investigators according to Response Evaluation Criteria in Solid Tumors (version 1.1) and overall survival (OS). **Results:** In part B, 166 patients, including the 42 patients with CCA, were enrolled and received toripalimab. Among the 166 patients, treatment-emergent adverse events (TEAEs) of any grade occurred in 158 (95.2%) patients, and 97 (58.4%) patients experienced TEAEs of Grade 3 or greater. The most common TEAE was fatigue (42.2%). Seven (4.2%) patients experienced TEAEs with a fatal outcome, none of which were identified by investigators as related to toripalimab. Investigator-assessed immune-related adverse events (irAE) of Grade 3 or higher occurred in 7 (4.2%) patients. In the CCA cohort, with the median follow-up of 4.4 months, the ORR and DCR were 4.8% (95% CI: 0.58, 16.16) and 40.5% (95% CI: 25.63, 56.72), respectively; median DoR was 7.8 (range 4.4+ to 7.8) months; median PFS was 2.1 (95% CI: 1.91, 3.88) months; median OS was not estimable. **Conclusions:** Toripalimab had manageable side effects in patients with refractory cholangiocarcinoma and exhibited preliminary evidence of anti-tumor activity. However, further information regarding biomarkers is needed. **ClinicalTrials.gov ID: NCT03474640**

Keywords: immune checkpoint inhibitor, programmed cell death (PD-1), refractory cholangiocarcinoma, safety, anti-tumor activity

INTRODUCTION

Cholangiocarcinoma (CCA) encompasses malignancies arising from different locations within the biliary tree and is the second most common primary hepatic malignancy.[1,2] The incidence of CCA is less than 1% of all human cancers, and CCA exhibits geographical variation with higher incidence rates in the Eastern world compared with the West.[3,4] CCA is rarely diagnosed at an early stage because of the lack of biomarkers, silent clinical course, and anatomical location. Therefore, only one-third of the cases can be completely resected by surgery, resulting in a high mortality.[5,6] Among patients with advanced CCA, the 5-year overall survival (OS) rate is 5–10% and the median survival is less than 12 months.[6,7]

According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, the preferred initial systemic treatment during this trial for unresectable and metastatic disease was gemcitabine plus cisplatin. Treatment with gemcitabine and cisplatin resulted in a median OS of 11.7 months.[8,9] This regimen has been supplanted by the US Food and Drug Administration (FDA) approval of durvalumab, in combination with gemcitabine plus cisplatin, based on the results of the results of the TOPAZ-1 trial, which demonstrated modest but statistically significant improvements in OS and progression-free survival (PFS).[10] Second-line treatment with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) is recommended for patients who have progressed on gemcitabine and cisplatin, with a median OS of 6.2 months.[11] However, only 15–25% of patients can receive second-line therapy owing to the rapid decline in performance status following progression on first-line chemotherapy.[10–13] Since the initiation of this trial, targeted therapy has demonstrated statistically significant improvements in PFS in patients with previously treated isocitrate dehydrogenase 1 (*IDH1*)-mutant CCA and for fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangements; however, effects on survival could not be assessed or may have been obscured by postprogression-targeted therapy in the control arm.[14] Additionally, based on high overall response rates and durability of these responses, a number of drugs are now recommended by the NCCN practice guidelines for the initial or second-line treatment of metastatic CCA in patients with neurotrophic-tropomyosin receptor kinase (NTRK),[15–17] *IDH1* mutation[14], mismatch repair deficiencies (dMMR)[18] or microsatellite instability-high (MSI-H) tumors[19], high-mutation burden tumors (TMB-H),[20] or RET fusion tumors.[21] Targeted therapy is now also recommended for the second-line treatment of patients with *BRAF V600E*[22] or *HER2*-positive CCA.[23] During the clinical development of immunotherapy, treatment with immune checkpoint inhibitors (ICIs) in patients with CCA has been investigated and showed encouraging antitumor activity in early phase studies.[24] There is a need to further investigate the optimal sequence and combinations of drugs in patients with actionable target mutations and to further investigate more effective treatment alternatives for patients with advanced CCA without actionable driver mutations.

Toripalimab (also known as TAB001 or JS001) is a humanized IgG4κ monoclonal antibody that is specific for the programmed cell death-1 (PD-1) receptor, which the FDA approved for the first-line treatment of nasopharyngeal cancer in conjunction with standard chemotherapy based on demonstration of PFS and OS benefits.[25] In addition, multiple phase 3 studies conducted in China have demonstrated the efficacy of toripalimab for the perioperative, resectable non–small cell lung cancer (NSCLC),[26] first-line treatment of squamous NSCLC,[27] and squamous cell esophageal cancer.[28] Study TAB001-01 was conducted to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of toripalimab in patients among eight different tumor types of previously treated, advanced solid tumors in the US, including a cohort of patients with previously treated CCA. In this article, we report the safety and efficacy results of toripalimab in patients with CCA. This was the first clinical study of toripalimab conducted in the US and supported extrapolation of results from trials conducted in the Asia-Pacific region to Western populations. Furthermore, the clinical data of toripalimab in patients with CCA has first been reported in the present work.

METHODS

Study Design

This multicenter, open-label, phase 1 study (ClinicalTrials.gov Identifier: NCT03474640) was conducted at 14 study sites in the US from February 21, 2018 (first patient signed the informed consent form) to June 7, 2022 (study completion date). The institutional review board at each study site approved the protocol and all amendments, and informed consent was obtained from all patients. The study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice (ICH-E6), and applicable laws and regulations. An Electronic Data Capture System (EDC) was used for clinical site data collection.

This study consisted of the following two components: a dose-escalation (part A) component with toripalimab monotherapy, using a standard 3 + 3 design and three dose (80, 240, and 480 mg) levels, and a multiple disease-specific cohort expansion (part B) component, enrolling up to 40 patients per cohort. Based on the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data from part A, as well as external safety, PK, and PD data obtained in clinical studies in China, the dose selected for evaluation of the antitumor activity of toripalimab in part B was 240 mg on days 1 and 22 of each 42-day cycle (every 3 weeks [Q3W]) until

disease progression, intolerable toxicity, or a maximum of 24 months.[29–32]

Patient Eligibility

The eligibility criteria in part B were aged 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior anti–PD-1, anti–programmed death ligand 1 (PD-L1), or anti–PD-L2 antibody treatment. Patients were required to have a histologically or cytologically documented diagnosis of one of the following tumor types: gastric cancer, esophageal cancer, CCA, neuroendocrine tumor (NET) arising in any primary site except lung, nasopharyngeal carcinoma (NPC), hepatocellular carcinoma (HCC), sarcoma, or any tumor with evidence of DNA repair deficiency (MSI-H or dMMR. For all tumor types, the disease must have progressed after treatment with at least one line of standard systemic therapy for the respective tumor type in the metastatic setting or after the standard treatment for the locally advanced disease that was not amenable to definitive local therapy with curative intent. Patients with unresolved toxicities from prior anticancer therapy, active or prior documented autoimmune disease within the past 2 years, or a history of primary immunodeficiency were excluded for safety concerns. The full eligibility criteria are provided in the full protocol (see Supplemental Materials, available online).

Assessments and Endpoints

All adverse events (AEs), including serious AEs (SAEs), were captured from the first dose through 90 days after the last dose of toripalimab or until initiation of alternative anticancer therapy, whichever was earlier. AEs of special interest (AESI) captured in this study were hepatic function abnormalities meeting the definition of Hy's law and Grade 3 or greater endocrinopathy, dermatologic AEs, pneumonitis, enterocolitis, or serum sickness. The severity of AEs, laboratory abnormalities, or other abnormal clinical assessments were graded per the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03.

The investigator evaluated tumor status according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In Part B, radiological tumor assessment was performed approximately every 9 weeks (± 10 days) for the first 12 months and approximately every 18 weeks (± 10 days) thereafter; unscheduled tumor assessments between these intervals were performed at the investigator's discretion to evaluate possible disease progression.

Fresh tumor tissue (where feasible) or archival tumor samples for biomarker (PD-L1) analysis were obtained before treatment initiation. PD-L1 status (PD-L1–positive status defined as percentage of tumor cell [TC] and immune cell [IC] staining of $\geq$ 1% and PD-L1–negative status defined as percentage of TC and IC staining $<$ 1%) was determined by a validated IHC test (JS311) in a central lab (Q2 laboratory). Results of prior testing for genomic aberrations were collected.

The primary endpoint was safety assessment, including determining the maximum tolerated or maximum feasible dose, the incidence of AEs, SAEs, AESIs, and AEs leading to treatment interruption and discontinuation, and the incidence of anti-drug antibodies (ADA). The endpoints for antitumor activity assessment included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, and OS.

Statistical Analysis

The sample size in part A was based on the number of dose levels and a planned 3 + 3 design, with a planned enrollment of up to 18 patients and optional expansion to 10 patients at the cohorts closest to the planned recommended phase 2 dose (maximum 26 patients). The sample size in part B was to include up to 40 patients per disease-specific cohort across 7 disease-specific expansion cohorts (gastric cancer, esophageal cancer, CCA, NET, NPC, HCC, or MSI-H and dMMR cancers) and up to 80 patients in a sarcoma cohort (minimum of 40 patients with either angiosarcoma, undifferentiated pleomorphic sarcoma or alveolar soft part sarcoma). Three of the disease-specific cohorts (NPC, HCC, or MSI-H and dMMR cancers) were closed early because of poor accrual, with only three patients enrolled across these cohorts. Thus, the sample size in part B was driven primarily by the remaining five disease-specific cohorts with a planned enrollment of up to 240 patients.

Safety and efficacy were assessed in the safety analysis set (SS), which is defined as all patients who received at least one dose of toripalimab. AEs were coded using MedDRA version 25. The ORR and DCR were calculated in the SS and the Kaplan-Meier method was used to estimate the OS and PFS with associated 95% CI. Subgroup analyses were performed to determine the best overall response by PD-L1 status. All statistical analyses were performed using SAS Version 9.3 for Windows (SAS Institute Inc; Cary, NC, USA). Detailed information on statistical analyses is provided in the statistical analysis plan (see Supplemental Materials).

This article focused on the overall safety of toripalimab among enrolled patients in part B and the preliminary efficacy outcomes among patients with CCA.

RESULTS

Patients

In part B, 218 patients were screened for eligibility, of whom 166 patients were enrolled and received at least one dose of toripalimab. Among the 166 patients, 42 had CCA. The sponsor terminated the study early due to slow accrual in several of the disease-specific cohorts. See Figure 1 for details of patient enrollment and disposition in part B.

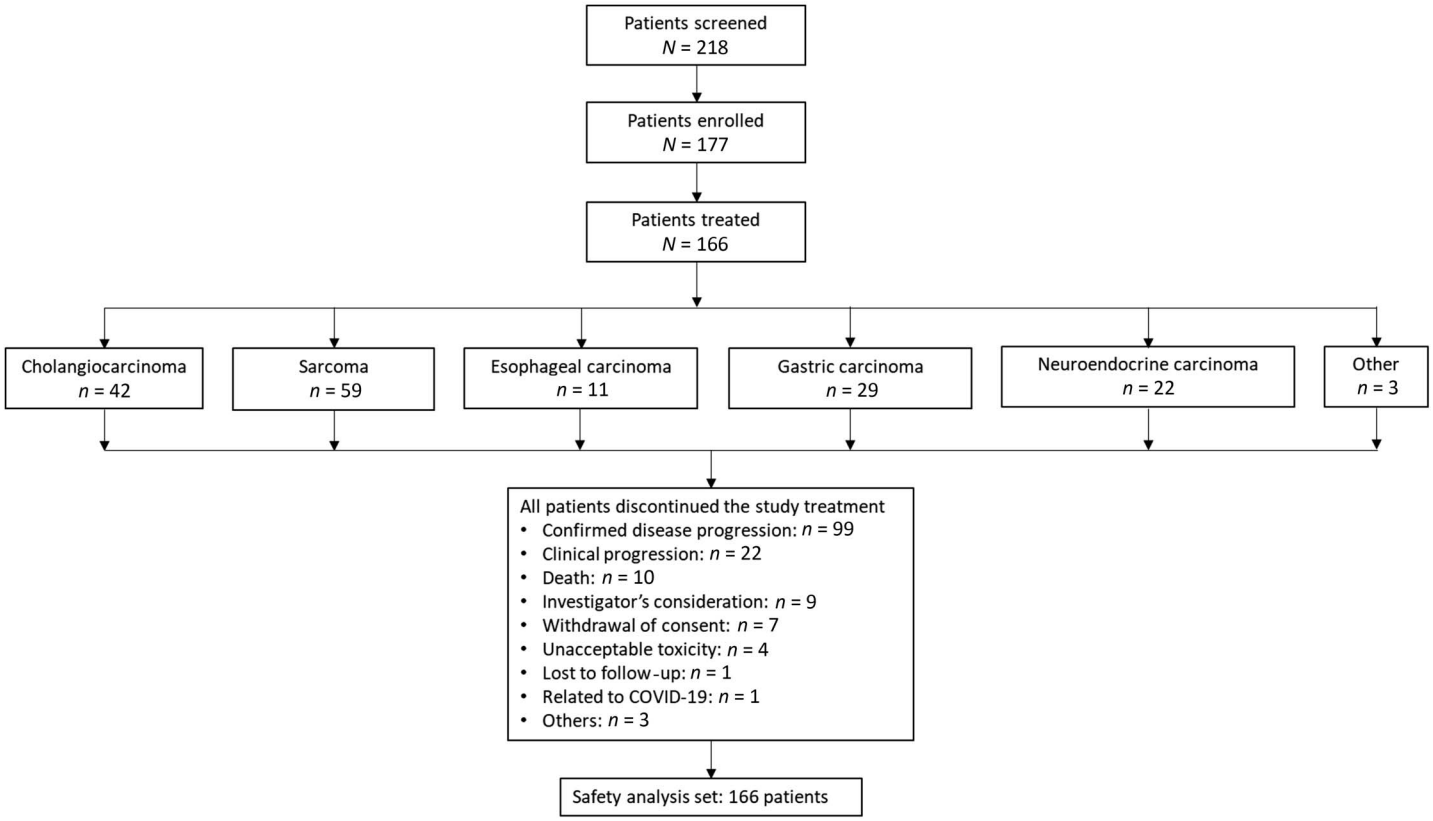

Figure 1. Study schema and patient disposition.

Of the 166 patients in part B, the median age was 63.0 (range 21–85). The majority were male (58.4%) and White (82.5%). Additionally, 24.1% and 75.9% of the patients had an ECOG performance status of 0 and 1. Of the 42 patients with CCA, the demographic characteristics were similar to those of the overall population, with the exception that the majority in the CCA cohort were female (66.7%). See Table 1 for demographics and baseline characteristics of patients with CCA.

Safety

Safety evaluation was based on the SS comprising 166 patients enrolled in any disease-specific cohort in part B, including the 42 patients with CCA. The median number of toripalimab infusions was 3.0 and the median duration of toripalimab administration was 6.43 weeks. A summary of AEs for the 166 patients in part B and the subgroup of 42 patients with CCA is provided in Table 2.

Of 166 patients, 95.2% (158/166) developed at least one TEAE. The most common (incidence $\geq$ 10%) TEAEs are listed in Table 3. As judged by the investigator, toripalimab-related TEAEs (TRAEs) occurred in 59.0% of the patients. Grade 3 or greater TEAEs occurred in 58.4% of the patients. There were 67 patients (40.4%) who experienced SAEs. AEs with a fatal outcome were observed in seven patients (4.2%), including respiratory failure (1.8%), esophageal fistula (0.6%), biliary tract infection (0.6%), cerebrovascular accident (0.6%), and renal injury (0.8%). Four patients (2.4%) experienced five AESIs, including a Grade 2 blood bilirubin increase, Grade 3 transaminase increase, serum sickness (Grade 3 hypersensitivity), pneumonitis (Grade 3 immune-mediated lung disease), and dermatologic toxicity (Grade 3 rash). Nine (5.4%) and 32 patients (19.3%) experienced TEAEs leading to study drug discontinuation and dose interruption, respectively. Investigator-assessed Grade 3 or greater irAEs occurred in seven patients (4.2%); the most common Grade 3 or greater irAE were lipase increased, transaminases increased, hyperthyroidism, hepatic and hepatobiliary disorders, hypersensitivity, arthritis, musculoskeletal pain, and rash (one patient each). One patient experienced a Grade 4 irAE; there were no Grade 5 irAEs. Most of the immune-related AEs of hypothyroidism were Grade 1 to 2 and managed with thyroid replacement. There were no patients who discontinued toripalimab due to hypothyroidism. A total of three patients (1.8%) developed infusion-related reactions, all of whom were negative for the presence of ADA.

Among the 42 patients with CCA, the incidence of TEAEs was similar to the overall population. TEAEs of any grade occurred in 97.6% of the patients and 69.0% developed TEAEs of Grade 3 or greater. The most common (incidence $\geq$ 20%) TEAEs in the CCA cohort included fatigue (47.6%), abdominal pain (40.5%), decreased appetite (33.3%), constipation (31.0%), transaminases increased (31.0%), nausea (23.8%), and blood

Table 1. Demographic and baseline characteristics (screened population)

	Cholangiocarcinoma Cohort (*N* = 42)	**Part B Cohort (*N* = 166)**
Age, y, median (range)	60.5 (35–85)	63.0 (21–85)
Age category, *n* (%)		
≥ 65 y	17 (40.5)	76 (45.8)
< 65 y	25 (59.5)	90 (54.2)
Sex, *n* (%)		
Male	14 (33.3)	97 (58.4)
Female	28 (66.7)	69 (41.6)
Race[a], *n* (%)		
American Indian or Alaskan Native	0	1 (0.6)
Asian	1 (2.4)	7 (4.2)
Black or African American	1 (2.4)	12 (7.2)
Native Hawaiian/Other Pacific Islander	0	1 (0.6)
White	38 (90.5)	137 (82.5)
Unknown/not available	2 (4.8)	8 (4.8)
Baseline ECOG performance status[b], *n* (%)		
0	10 (23.8)	40 (24.1)
1	32 (76.2)	126 (75.9)
Weight, kg		
Mean (SD)	75.3 (21.2)	79.0 (19.6)
Median (range)	71.8 (46–164)	76.7 (40–164)
BMI (kg/m^2)		
n	37	154
Mean (SD)	25.8 (5.9)	26.6 (5.6)
Median (range)	24.4 (17–45)	25.7 (17–45)
Tumor burden (sum of target lesion), mm, mean (SD)	77.5 (45.8)	90.0 (69.2)
Cholangiocarcinoma subtype, *n* (%)		
Intrahepatic	29 (69.0)	—
Extrahepatic[c]	13 (31.0)	—
Prior lines of therapy, *n* (%)		
0	0	3 (1.8)
1	0	14 (8.4)
2–4	22 (52.4)	73 (44.0)
5–10	17 (40.5)	65 (40.4)
≥ 10	3 (7.1)	9 (5.4)
Type of prior treatment, *n* (%)		
Chemotherapy	42 (100)	151 (91.0)
Small molecule targeted therapy	9 (21.4)	38 (22.9)
Monoclonal antibody	3 (7.1)	33 (19.9)
Hormonal	0	12 (7.2)
Other	9 (21.4)	29 (17.5)
Sites of metastases, *n* (%)		
Liver	32 (76.2)	81 (48.8)
Lung	18 (42.9)	64 (38.6)
Bone	0	13 (7.8)
Other	23 (54.8)	126 (75.9)
None	0	6 (3.6)
PD-L1 tumor status[d], *n* (%)		
Positive	19 (45.2)	74 (44.6)
Negative	12 (28.6)	52 (31.3)
Missing	11 (26.2)	40 (24.1)

Note: Baseline was defined as the screening or last available observation prior to the first administration of the study drug.
[a]A patient may be counted in more than one category.
[b]ECOG Performance Status: 0 = Fully active; 1 = Restricted in activity.
[c]Includes one patient with an ampulla of Vater primary and three patients with gallbladder primary sites.
[d]PD-L1 positive defined as tumor cell (TC) and/or immune cell (IC) ≥ 1% and PD-L1-negative status defined as TC and IC < 1%.

bilirubin increased (21.4%). Twenty-three (54.8%) patients experienced SAEs and three patients developed Grade 5 AEs (respiratory failure, biliary tract infection, and cerebrovascular accident). TEAEs leading to discontinuation or interruption of toripalimab occurred in two (4.8%) and six (14.3%) patients, respectively. Two patients (4.8%) developed investigator-assessed Grade 3 or greater irAEs, which were lipase increased and hepatic and hepatobiliary disorders in one patient each. No AESIs and infusion-related reactions occurred in patients with CCA.

Table 2. Summary of treatment-emergent adverse events (TEAEs) (safety population)

	Cholangiocarcinoma Cohort (*N* = 42)	**Pooled Population (*N* = 166)**
Patients with at least one TEAE	41 (97.6)	158 (95.2)
Grade ≥ 3 TEAE	29 (69.0)	97 (58.4)
Treatment-related adverse events (TRAEs)	27 (64.3)	98 (59.0)
Grade ≥ 3 TRAE	9 (21.4)	27 (16.3)
Serious adverse events (AEs)	23 (54.8)	67 (40.4)
AE leading to treatment discontinuation	2 (4.8)	9 (5.4)
AE leading to dose interruption of toripalimab	6 (14.3)	32 (19.3)
AE leading to death	3 (7.1)	7 (4.2)
Investigator-adjudicated immune-related AE (irAE)	5 (11.9)	24 (14.5)
Grade ≥ 3 irAE	2 (4.8)	7 (4.2)
TEAE with an incidence ≥10% in pooled population		
Fatigue	20 (47.6)	70 (42.2)
Abdominal pain	17 (40.5)	41 (24.7)
Musculoskeletal pain	8 (19.0)	40 (24.1)
Nausea	10 (23.8)	39 (23.5)
Transaminases increased	13 (31.0)	38 (22.9)
Decreased appetite	14 (33.3)	36 (21.7)
Constipation	13 (31.0)	33 (19.9)
Anemia	6 (14.3)	31 (18.7)
Dyspnea	8 (19.0)	30 (18.1)
Arthritis	8 (19.0)	27 (16.3)
Diarrhea	5 (11.9)	26 (15.7)
Cough	4 (9.5)	24 (14.5)
Insomnia	4 (9.5)	24 (14.5)
Edema	7 (16.7)	23 (13.9)
Vomiting	7 (16.7)	22 (13.3)
Dehydration	3 (7.1)	21 (12.7)
Rash	4 (9.5)	21 (12.7)
Blood alkaline phosphatase increased	8 (19.0)	20 (12.0)
Blood bilirubin increased	9 (21.4)	20 (12.0)
Pyrexia	4 (9.5)	19 (11.4)
Arrhythmia	3 (7.1)	19 (11.4)
Upper respiratory tract infection	2 (4.8)	18 (10.8)
Hypothyroidism	0	18 (10.8)
Hyponatremia	5 (11.9)	17 (10.2)
Abdominal distension	4 (9.5)	17 (10.2)
TEAEs of special interest (AESI)	0	4 (2.4)
Blood bilirubin increased	0	1 (0.6)
Hypersensitivity	0	1 (0.6)
Immune-mediated lung disease	0	1 (0.6)
Rash	0	1 (0.6)
Transaminases increased	0	1 (0.6)
TEAEs with a fatal outcome	3 (7.1)	7 (4.2)
Respiratory failure	1 (2.4)	3 (1.8)
Esophageal fistula	0	1 (0.6)
Biliary tract infection	1 (2.4)	1 (0.6)
Cerebrovascular accident	1 (2.4)	1 (0.6)
Renal injury	0	1 (0.6)
Grade ≥ 3 irAEs	2 (4.8)	7 (4.2)
Lipase increased	1 (2.4)	1 (0.6)
Transaminases increased	0	1 (0.6)
Hyperthyroidism	0	1 (0.6)
Hepatic and hepatobiliary disorders	1 (2.4)	1 (0.6)
Hypersensitivity	0	1 (0.6)
Arthritis	0	1 (0.6)
Musculoskeletal pain	0	1 (0.6)
Rash	0	1 (0.6)
Myocarditis	0	1 (0.6)

Data are presented as *n* (%).

Table 3. Overall summary of efficacy in patients with cholangiocarcinoma

	Cholangiocarcinoma Cohort (*N* = 42)
Confirmed BOR Per RECIST v1.1,[a] *n* (%)	
CR	1 (2.4)
PR	1 (2.4)
SD	15 (35.7)
PD	19 (45.2)
NE	0
No post-baseline response data	6 (14.3)
ORR Per RECIST v1.1,[b,c] *n* (%)	2 (4.8)
95% CI	(0.58, 16.16)
Disease control rate per RECIST v1.1,[b,d] *n* (%)	17 (40.5)
95% CI	(25.63, 56.72)
Median duration of response, mo[b]	7.8
95% CI	(NE, NE)
Range of duration of response, mo	4.4+, 7.8
Median follow-up time, mo (95% CI)	4.4 (3.5, 4.9)
Number of patients who died, *n* (%)	12 (28.6)
Number of patients who did not die (censored), *n* (%)	30 (71.4)
Median OS, mo	NE
95% CI	(3.91, –)
12-mo OS rate (95% CI)	NE (NE, NE)
PFS events, *n* (%)	38 (90.5)
Progression (PD)	33 (78.6)
Death without PD	5 (11.9)
PFS censored, *n* (%)	4 (9.5)
Censored because of alternative anti-cancer therapy	1 (2.4)
Censored because of other causes of study discontinuation	2 (4.8)
Censored without postbaseline radiological assessment	1 (2.4)
Median PFS, mo[a]	2.1
95% CI	1.9, 3.9
6-mo PFS rate (95% CI)	10.9 (3.5, 23.1)
12-mo PFS rate (95% CI)	0.0 (NE, NE)
Baseline PD-L1 status: positive ($n = 19$), *n* (%)	
CR	0
PR	1 (5.3)
SD	6 (31.6)
PD	11 (57.9)
NE/no postbaseline response assessment	1 (5.3)
Baseline PD-L1 status: negative ($n = 12$), *n* (%)	
CR	0
PR	0
SD	2 (16.7)
PD	5 (41.7)
NE/no postbaseline response assessment	5 (41.7)
Baseline PD-L1 status: missing ($n = 11$), *n* (%)	
CR	1 (9.1)
PR	0
SD	7 (63.6)
PD	3 (27.3)
NE	0

Overall responses are determined by the investigator at each postbaseline imaging visit using RECIST v1.1.
[a]BOR defined as best overall response across from the start of the study treatment until the end of treatment per RECIST v1.1.
[b]Patients without postbaseline response assessment were treated as nonresponders.
[c]Overall response rate was calculated as the percentage of patients in the analysis population with a BOR of CR or PR. Two-sided exact CI was based on the binomial distribution.
[d]Disease control rate was calculated as the percentage of patients in the analysis population with a BOR of CR, PR, or SD.
[e]PD-L1 positive defined as positive PD-L1 staining of tumor cell (TC) and/or immune cell (IC) $\geq$ 1% and PD-L1-negative status defined as TC and IC $<$ 1%.
Two-sided exact CIs are based on the binomial distribution.
BOR: Best overall response; CR: complete response; NE: not evaluable; ORR: objective response rate; OS: overall survival; PD-L1: programmed-death ligand 1; PD: progressive disease; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

An immunogenicity assessment was performed using 515 samples from 183 patients. There were 28 patients who were ADA-positive, including the 10 patients who were ADA positive at baseline. The treatment-emergent ADA-positive rate was 10.4% (18/173).

Efficacy

A summary of efficacy in patients with CCA is provided in Table 3. At study completion, the median follow-up time was 4.4 months. Among the 42 patients with CCA, one patient achieved a complete response (CR), one achieved a partial response (PR), and 15 patients achieved stable disease (SD) per RECIST v1.1, resulting in an ORR of 4.8% (95% CI: 0.58, 16.16), and a DCR of 40.5% (95% CI: 25.63, 56.72). The median DoR was 7.8 months (range 4.4+, 7.8). Figure 2A is a waterfall plot presenting the best response based on the change in the sum of diameters of target lesions from baseline for 36 patients with both a baseline and postbaseline tumor assessment. There were 38 patients who experienced a PFS event in this cohort; the median PFS was 2.1 months (95% CI: 1.91, 3.88), and the 6-month PFS rate was 10.9% (Fig. 2B). Twelve patients died during the study; the median OS could not be estimated due to the low number of OS events and short follow-up time.

Biomarker

In the CCA cohort, the ORR was 5.3%, and the DCR was 36.8% among the 19 patients with PD-L1–positive CCA, while no responses were observed and the DCR was 16.7% among 12 patients with PD-L1–negative CCA. Among 11 patients for whom PD-L1 tumor status was unknown, the ORR was 9.1%, and the DCR was 72.7%. While the number of patients in each subgroup are small, there is no strong correlation between PD-L1 status and likelihood of response. The CR occurred in an African American woman who received three prior lines of chemotherapy and whose PD-L1 tumor status was unknown but was reported to have an *IDH1* and AT-rich interactive domain-containing protein 1A mutation-positive tumor. The PR occurred in a patient who received four prior lines of therapy, including trastuzumab, and whose tumor was PD-L1 positive and reported to be *HER2* amplified, *p53*-mutation positive, with a TMB of 4 mut/Mb. Of note, no patient who was enrolled in the study was reported to have a TMB-H or MSI-H tumor.

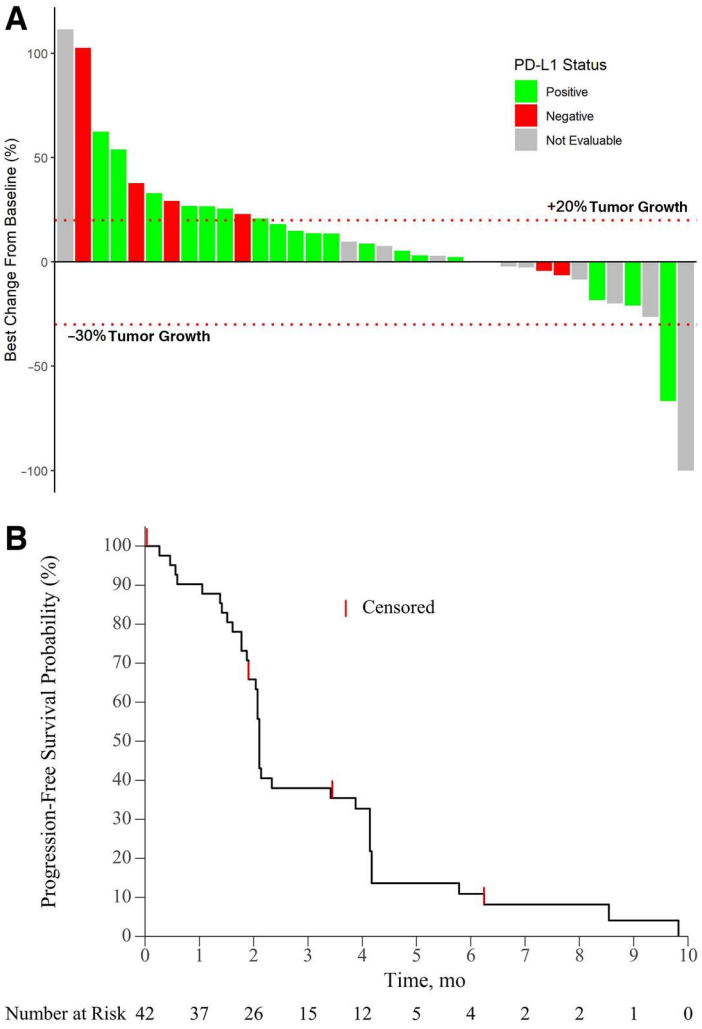

Figure 2. (A) Best change in sum of target lesion diameters from baseline and programmed-death ligand 1 (PD-L1) tumor expression status across 36 subjects in the cholangiocarcinoma cohort with postbaseline assessments. (B) Progression-free survival in the cholangiocarcinoma cohort.

DISCUSSION

CCA has a poor prognosis and, except for patients with druggable target mutations, limited treatment options exist after progression on standard therapies.[33,34] This study enrolled 42 patients with CCA in a disease-specific expansion cohort, demonstrating antitumor activity with an ORR of 4.8% and DCR of 40.5%. There were two responders, including one CR and one PR per RECIST v1.1, as assessed by the investigator; the response durations were 4.4+ and 7.8 months, respectively. In addition, stable disease was observed in 15 patients. The preliminary antitumor efficacy with toripalimab in the CCA cohort is similar to that observed in KEYNOTE-158 (ORR 5.8% and median PFS 2.0 months) and KEYNOTE-028 (ORR 13.0% and median PFS 1.8 months) in patients with histologically/cytologically confirmed incurable biliary tract cancers that had progressed after standard treatment.[24] The DCR in the CCA cohort was numerically lower than in the KEYNOTE-158 and KEYNOTE-028 studies but similar to that reported in a phase 2 study of nivolumab monotherapy in patients with advanced CCA of 59.0%.[34] The clinical activity of toripalimab was similar to that observed in the KEYNOTE-158 and KEYNOTE-028 studies despite substantially more lines of prior therapy (≥ 5 lines of treatment: 47.6% vs. 19% and 0), fewer patients with PD-L1–positive CCA (45.2% vs. 58.7% and 100%), and a higher proportion

of patients with ECOG PS 1 (76.2% vs. 59.6% and 62.5%), in the TAB001-01 CCA cohort compared with the KEYNOTE-158 and KEYNOTE-028 studies. Specific information on tumor location was not captured for the KEYNOTE-158 and KEYNOTE-028 studies; other differences include fewer Asian patients (2.4% vs. 35.6% and 50%) and female predominance (66.7% vs. 51% and 42%) in the TAB001-01 CCA cohort compared with KEYNOTE-158 and KEYNOTE-028. No patient in the CCA cohort of TAB001-01, KEYNOTE-158, or KEYNOTE-028 received prior ICI therapy.

Among patients with CCA, the median PFS was 2.1 months, suggesting rapid progression, consistent with the known natural history of CCA, an extremely aggressive cancer. Studies of other PD-L1–blocking antibodies showed similar results for median PFS, which was 2.0 months in Study KEYNOTE-158 and 1.8 months in Study KEYNOTE-028.[24] At study completion, 30 of 42 patients were alive in the CCA cohort. The median OS was not estimable due to the small number of deaths and short follow-up time of less than 1 year. While treatment of patients with CCA with toripalimab 240 mg Q3W produced similar DCR and median PFS compared with other ICIs, given the small numbers of patients, variation in extent, and type of prior treatment, comparative data should be interpreted carefully.

The preliminary evidence of antitumor activity of toripalimab in CCA is further supported by additional studies evaluating the antitumor activity of toripalimab with antiangiogenic agents in the second (or greater)-line treatment of biliary tract cancers (BTC) or intrahepatic cholangiocarcinoma (ICC) and in combination with chemotherapy and antiangiogenic therapy in the first-line treatment of ICC. Antitumor activity with toripalimab in combination with antiangiogenic agents was observed. In 15 patients with progression after or intolerance to first-line therapy for BTC, toripalimab plus anlotinib resulted in an ORR of 26.7%, DCR of 86.7%, a median PFS of 8.6 months, and a median OS of 14.5 months and one patient was downstaged sufficiently to undergo surgical resection.[35] In a retrospective study of patients with disease progression after first-line therapy for BTC, propensity matching was conducted to identify 40 patients who received toripalimab and lenvantinib alone ($n = 20$) or toripalimab and lenvantinib with radiotherapy to liver and soft tissues or lymph nodes.[36] In this study, the ORR was 20%, DCR was 75%, PFS was 4.8 months and median OS was 9.2 months in the toripalimab/lenvantinib group. These results compare favorably to recent studies of lenvatinib as a single agent for second-or-greater-line treatment of patients with disease progression after first-line therapy for BTC, suggesting at least additive activity with the combination of a lenvatinib and toripalimab. A study of 26 patients in Japan yielded an ORR of 11.5%, DCR of 84.6%, and median PFS of 3.2 months[37] for patients receiving single-agent lenvatinib and among 41 patients receiving second-or-greater-line therapy for BTC, the ORR was 12%, DCR was 78%, and median PFS was 3.8 months.[38]

In the first-line setting, among 31 patients with ICC, toripalimab plus lenvatinib resulted in an ORR of 32.3% (95% CI: 16.7, 51.4), DCR of 74.2%, and 6-month OS rate of 87.1% with two patients downstaged sufficiently to undergo surgical resection.[39] In light of the tolerability of this regimen, the combination of toripalimab and lenvatinib administered in combination with gemcitabine and oxaliplatin (GEMOX) was investigated in 30 patients receiving first-line treatment of advanced ICC.[40] In this trial, the ORR was 80%, with one CR and 23 PRs, the median duration of response was 11 months, the DCR was 90%, the median PFs was 10.2 months, and the median OS was 22.5 months. These promising results will be further evaluated in an ongoing three-arm, phase 3 trial.[41]

Among 166 patients who received toripalimab 240 mg intravenously Q3W, this regimen is reasonably safe, tolerable, and consistent with the safety profile of toripalimab administered as monotherapy conducted in China.[30–32,42–48] The majority of patients (95.2%) experienced at least one TEAE of any grade, and 64.3% of the patients experienced AEs related to toripalimab (TRAEs), which is consistent with the approved labeling for toripalimab in China based on the previous studies of toripalimab monotherapy (approximately 90% for TEAEs and 70%–80% for TRAEs). The most common TEAEs (incidence $\geq$ 20%) were abdominal pain, nausea, fatigue, decreased appetite and increased transaminases, and musculoskeletal pain. Of note, the incidence of Grade 3 or greater TEAEs was higher in this study compared with a pooled analysis of toripalimab monotherapy in 1133 patients across 14 clinical trials (58.4% vs. 40.7%) (unpublished data on file). Despite this, toripalimab had manageable side effects, with only 5.4% (9/166) patients requiring treatment discontinuation and 19.3% (32/166) requiring treatment interruption for AEs. The rate of infusion-related reactions (1.8%) was low and the incidence of ADA positivity was 10.4% among the 183 patients evaluated. There were insufficient numbers of patients with ADA to assess its effects on safety.

The safety profile of the 42 patients with CCA is similar to that of the overall population in part B (166 patients), with the exception that no AESIs or infusion-related reactions were observed in the CCA cohort. The common TEAEs in the CCA cohort were fatigue, abdominal pain, decreased appetite, constipation, increased transaminases, nausea, and increased blood bilirubin.Overall, the safety profile of toripalimab observed in this study was similar to other ICIs, and no unexpected AEs were found Toripalimab 240 mg Q3W was well tolerated in patients with advanced malignances. In addition, the incidence and patterns of AEs of toripalimab in patients with CCA were similar to the overall population.

Limitations

Limitations of this study include the heterogeneity of the patients with CCA regarding the type and extent of

prior therapy, leading to challenges in definitive conclusions regarding antitumor activity, and the fact that this was not a controlled study with direct comparisons to other treatment options. Therefore, a larger clinical study with a control group needs to be conducted to further validate the safety and relative antitumor activities of toripalimab in advanced CCA.

CONCLUSIONS

In summary, toripalimab monotherapy had manageable side effects in patients with refractory CCA and exhibited preliminary evidence of antitumor activity. Further information on the role, if any, of PD-L1 tumor expression and CCA-specific biomarkers, in patient selection is needed. The combination of toripalimab, lenvatinib, and gemcitabine and oxaliplatin (GEMOX) is currently being evaluated in a three-arm phase 3 study as a first-line treatment for advanced ICC.

DATA AVAILABLILTIY STATEMENT

This trial was registered at www.clinicaltrials.gov (NCT03474640). The summary results and clinical protocol, including analysis plan, will be made available at this website. Individual de-identified participant data obtained in this study will not be made available after publication.

Supplemental Material

Supplemental materials are available online with the article.

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