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Phase I/II study of nivolumab plus lenvatinib for advanced biliary tract cancer (JCOG1808/NCCH1817, SNIPE)

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Background

- Although gemcitabine (GEM) combination chemotherapies have improved the survival of advanced biliary tract cancer (BTC) patients (pts), high unmet medical needs remain for the treatment of BTC.
- Lenvatinive monotherapy have shown modest efficacy in advanced BTC.
- Immune checkpoint inhibitors have shown limited efficacy in monotherapy for advanced BTC.
- Recently, combinations of them with other therapies have shown remarkable efficacy in multiple cancer types.
- This study aimed to assess the efficacy and safety of nivolumab plus lenvatinib in second-line treatment for advanced BTC.

Methods

- The study included pts receiving second-line treatment for advanced BTC, aged ≥ 20 years, ECOG Performance status (PS) 0-1, sufficient oral intake, with measurable lesion.
- Nivolumab (240 mg) was administered biweekly. Phase I was performed to determine the recommended phase II dose of lenvatinib (from 20 mg to 14 mg, daily). The primary endpoint in phase I is proportion of adverse events corresponding toxicity evaluation criteria.
- In phase II, the primary endpoint was the objective response rate (ORR). Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.
- The tumor response was evaluated in accordance with the RECIST1.1 by blinded independent central review.

Study design

Phase I (n=6)
Determine the recommended dose of lenvatinib
Lenvatinib initial dose: 20 mg or 14mg /daily
Nivolumab fixed dose: 240 mg/day every 2 weeks
Proportion of adverse events (AEs) corresponding toxicity evaluation criteria *
observed in 0-2 pts: move to Phase II
observed in 3-6 pts: add 6 pts to 1 level lower lenvatinib dose

Phase II (n=32)
Evaluation of efficacy and safety
Lenvatinib 20 mg/day, daily
Nivolumab 240 mg/day every 2 weeks
Planned sample size is 32 including 6 pts enrolled in phase I part.

Expansion cohort (n=15)
First-line treatment for BTC

CR or PR is observed in 7 pts and more with insititutional diagnosis

* Toxicity evaluation criteria:
✓ Hematological toxicities: febrile-neutropenia, Grade 4 neutropenia for 7 days, Grade 4 platelet count decreased, Grade 3 platelet count decreased for 7 days or with bleeding, Grade 4 anemia
✓ Non-hematological toxicities: Grade 4 AEs, Grade 3 gastrointestinal perforation, Thromboembolic event, Uveitis, Pneumonitis, Bronchospasm, Allergic reaction, Infusion related reaction, Wound dehiscence needed treatment, Grade 3 AEs for 3 days after proper treatment, Grade 2 Uveitis, eye pain, blurred vision treated locally and not improved to Grade 1 in re-administration period or needed systemically, Adverse reactions requiring lenvatinib discontinuation for more than 8 days every 2 weeks

- The planned sample size was 32 pts in phase I+II, which provided 80% power for the primary endpoint with a one-sided alpha error of 5%, threshold ORR of 10% and expected ORR of 30%.
- If efficacy was expected in phase II, we planned to initiate a first-line expansion cohort.

Results

- Between Aug and Oct 2019, 6 pts were enrolled in phase I part, and until Nov 2020, 32 patients were totally enrolled in phase I+II part, from 5 centers.
- The recommended dose of lenvatinib was determined to be 20 mg in the 6 pts in phase I with one AE corresponding toxicity evaluation criteria of myocarditis.
- The trial was completed without a first-line expansion cohort because the efficacy in the phase II part was limited.

Table 1. Patient characteristics (n=32)

		n (%)
Median age, years [range]		63 [44-78]
Sex	Male	23 (71.9)
	Female	9 (28.1)
ECOG PS	0	23 (71.9)
	1	9 (28.1)
Primary tumor site	Gallbladder	7 (21.9)
	Extrahepatic bile duct	5 (15.6)
	Intrahepatic bile duct	15 (46.9)
	Ampullary	5 (15.6)
Extent of disease	Unresectable	25 (78.1)
	Recurrent	7 (21.9)
Prior chemotherapy (First line)	GEM + CDDP	23 (71.9)
	GEM + CDDP + S-1	9 (28.1)
Microsatellite instability status (MSI status)	Stable	27 (84.4)
	High	0 (0.0)
	Unknown	5 (15.6)
Biliary drainage	Presence	14 (43.8)
	Absence	18 (56.3)
Usage of antibiotics**	Yes	9 (28.1)
	No	23 (71.9)

** within 1 month before starting protocol treatment

Table 2. Overall response (n=32)

RECIST 1.1	n (%)
Complete response	0 (0.0)
Partial response	3 (9.4)
Stable disease	14 (43.8)
Progressive disease	14 (43.8)
Not evaluated	1 (3.1)
ORR [90% CI]	**3 (9.4) [2.6-22.5]**
DCR [95% CI]	**17 (53.1) [34.7-70.9]**

CI: confidence interval

Figure 1. PFS and OS (n=32)

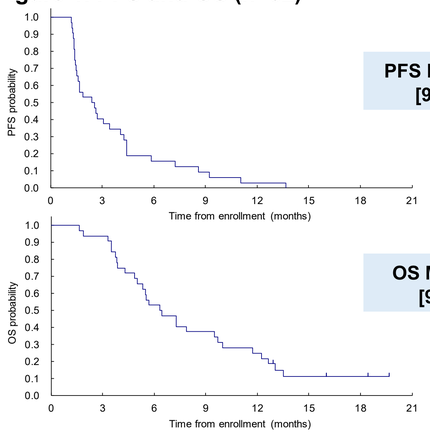

Table 4. Treatment-emergent adverse events (n=32)

CTCAE ver. 5.0	Any grade n (%)	Grade 3/4 n (%)
Hypertension	25 (78.1)	19 (59.4)
Proteinuria	20 (62.5)	2 (6.3)
Anorexia	17 (53.1)	2 (6.3)
Platelet count decreased	16 (50.0)	3 (9.4)
Hoarseness	14 (43.8)	0
Biliary tract infection	13 (40.6)	12 (37.5)
Malaise	13 (40.6)	1 (3.1)
Rash	12 (37.5)	2 (6.3)
Fever	11 (34.4)	1 (3.1)
Hypothyroidism	11 (34.4)	0
AST increased	9 (28.1)	0
Lymphocyte count decreased	9 (28.1)	3 (9.4)
Diarrhea	9 (28.1)	1 (3.1)
Nausea	9 (28.1)	0
Hypoalbuminemia	9 (28.1)	2 (6.3)
Weight loss	8 (25.0)	0
Palmar-plantar erythrodysesthesia syndrome	8 (25.0)	0
Vomiting	7 (21.9)	0
ALT increased	6 (18.8)	1 (3.1)
Fatigue	6 (18.8)	0
Neutrophil count decreased	5 (15.6)	4 (12.5)

Table 3. Overall response rate subgroup analysis (n=32)

Factor	Subgroup	ORR (%)	[95% CI]
MSI status	Stable	7.4	[0.9-24.3]
	Unknown	20.0	[0.5-71.6]
Primary tumor site	Gallbladder	28.6	[3.7-71.0]
	Extrahepatic bile duct	0.0	[0.0-52.2]
	Intrahepatic bile duct	0.0	[0.0-28.1]
	Ampullary	20.0	[0.5-71.6]
Biliary drainage	Presence	7.1	[0.2-33.9]
	Absence	11.1	[1.4-34.7]
Usage of antibiotics**	Yes	0.0	[0.0-33.6]
	No	13.0	[2.8-33.6]

Table 5. Immune-mediated adverse events (n=32)

CTCAE ver. 5.0	Any grade n (%)	Grade 3/4 n (%)
Rash	9 (28.1)	1 (3.1)
Hypothyroidism	7 (21.9)	0
Malaise	6 (18.8)	1 (3.1)
Fever	4 (12.5)	0
Anorexia	4 (12.5)	0
Diarrhea	3 (9.4)	1 (3.1)
Blood corticotrophin increased	3 (9.4)	0
Hyperthyroidism	2 (6.3)	0
ALT increased	2 (6.3)	0
Mucositis oral	2 (6.3)	1 (3.1)
Pneumonitis	2 (6.3)	0

Conclusions

- Nivolumab plus lenvatinib had a manageable safety profile in pts with advanced BTC.
- The efficacy in second-line treatment was limited.
- Biomarker studies will be analyzed in the future.

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