TCOG T1219 trial: A Phase II Study of Nivolumab in Combination with Gemcitabine and TS-1 as the First-line Treatment in Patients with Advanced Biliary Tract Cancer

Nai-Jung Chiang[1,2], Li-Yuan Bai[3], Li-Tzong Chen[1,2,4], Chien-Jui Huang[2], San-Chi Chen[5], Yan-Shen Shan[2], Chin-Fu Hsaio[6], Yung-Yeh Su[1,2], Ming-Huang Chen[5]

on behalf of Taiwan Cooperative Oncology Group (TCOG)

[1]National Institute of Cancer Research, National Health Research Institutes, Tainan; [2]National Cheng Kung University Hospital & National Cheng Kung University, Tainan; [3]China Medical University Hospital, Taichung; [4]Kaohsiung Medical University Hospital & Kaohsiung Medical University, Kaohsiung; [5]Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei; [6]Institute of Population Health Sciences, NHRI, Miaoli, Taiwan.

Background

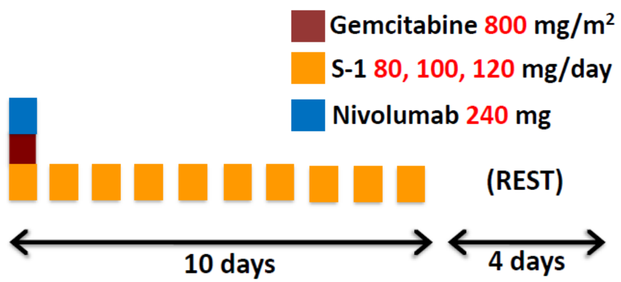
- Chemotherapy with gemcitabine and cisplatin (GC) is the standard therapy for advanced biliary tract cancer. *(N Engl J Med. 2010;362:1273-1281.)*
- Gemcitabine and S-1 (modified GS, mGS) showed that moderate efficacy with 21.6% of objective response rate (ORR) and a favorable safety profile with all grade 3/4 adverse events (AEs) <6% in our previous phase II trial, indicating that mGS regimen is an ideal backbone chemotherapy for combination therapy. *(Liver Int. 2020; 40(10):2535-2543)*
- Herein, we report the results of a single arm phase II of nivolumab plus mGS as the first-line treatment in patients with advanced biliary tract cancer. (ClinicalTrials.gov NCT04172402)

Patients

Inclusion criteria:

1. cyto-/histologically confirmed, **advanced or metastatic BTC with measurable lesions (including intrahepatic bile duct, extrahepatic bile duct, gallbladder, and ampulla of vater).**
2. no history of prior chemotherapy, except adjuvant setting that completed at least 6 months before documentation of recurrence.
3. Age: ≥ 20 y/o with ECOG ≤ 1
4. Hgb ≥ 9 mg/dl; absolute neutrophil count ≥ 1,500/ul; platelet count ≥ 100,000/ul.
5. serum alanine (ALT) ≤ 3 UNL & ≤ 5 times of UNL if liver metastasis; serum total bilirubin level ≤ 1.5 ULN & < 2.0 mg/dL, and CCr ≥ 50 mL/min

Study design



BSA	Dose of S-1
< 1.25 m²	80 mg/day
≥ 1.25, <1.5 m²	100 mg/day
≥ 1.5 m²	120 mg/day

- **The primary endpoint: ORR** (complete or partial response [CR/PR]), confirmed by two consecutive image examinations.
- The secondary endpoints: disease control rate (DCR), PFS, overall survival (OS) and safety profile.
- Tumor response was assessed by CT/MRI every 6 weeks according to RECIST v1.1.
- Simon's two-stage optimal design: p0=0.15, p1=0.35) for ORR, with given error probabilities (alpha=0.05, beta=0.1), the null hypothesis (p0) would be rejected if 10 or more patients had CR/PR among 44 evaluable cases. Considering 10% drop-out rate, 48 patients will be enrolled.

Results

Table 1. Baseline characteristics

Characteristics	N=48
Median Age (range), yrs	66 (30-80)
male/female (%)	22/26 (46/54%)
ECOG PS, 0/1 (%)	38/10 (79/21%)
LA/Metastasis (%)	7/41 (15/85%)
Tumor location IHCC (%) EHCC (%) GBC (%) AVC (%)	 29 (60.4%) 12 (25%) 5 (10.4%) 2 (4.2%)
Previous surgery, yes/no (%)	16/32 (33/67%)
Stage II IIIA IIIB IVA IVB	 1 (2.1%) 2 (4.2%) 5 (10.4%) 8 (16.7%) 32 (67.7%)

- enrolled period: 2019/12-2020/12
- currently ongoing: 13 patients

Table 3. Treatment-related AEs

All Tx-related AEs	N=48	
	All grade n (%)	Grade 3 n (%)
Neutropenia	8 (16.7%)	3 (6.3%)
Thrombocytopenia	12 (25%)	4 (8.3%)
Anemia	13 (27.1%)	3 (6.3%)
Oral mucositis	10 (20.8%)	3 (6.3%)
Diarrhea	9 (18.8%)	2 (4.2%)
Nausea	3 (6.3%)	0 (0%)
Vomiting	5 (10.4%)	0 (0%)
Fatigue	13 (27.1%)	7 (14.6%)
ALT increase	1 (2.1%)	0 (0%)
Anorexia	7 (14.6%)	0 (0%)
Bilirubin increase	2 (4.2%)	1 (2.1%)
Skin rash	10 (20.8%)	5 (10.4%)

- no grade 4 AE was reported.

Table 2. Therapeutic efficacy

Best tumor response	N=48
Complete response (CR)	1 (2.1%)
Partial response (PR)	20 (41.7%)
Stable disease (SD)	21 (43.8%)
PD + unevaluable	5 + 1 (12.5%)
Disease control rate*	38 (79.2%)

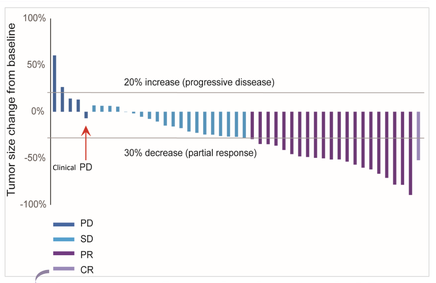
ORR: 43.8%

*Disease control rate = ORR + SD ≥ 12 weeks

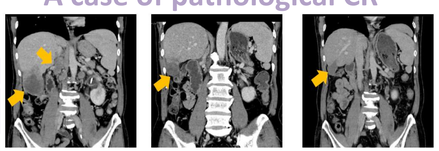
Table 4. Immune-related AEs

irAEs	N=48	
	All grade, n (%)	Grade 3 n (%)
Hypothyroidisim	4 (8.3%)	0 (0%)
Pneumonitis	3 (6.3%)	4 (8.3%)
Skin rash	10 (20.8%)	5 (10.4%)
Hypophysitis	4 (8.3%)	0 (0%)
Arthritis	1 (2.1%)	0 (0%)
Lipase increase	1 (2.1%)	1 (2.1%)

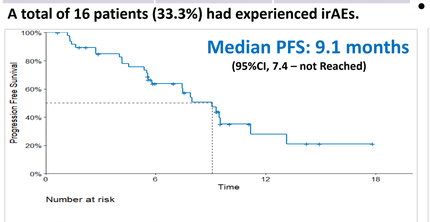
A total of 16 patients (33.3%) had experienced irAEs.

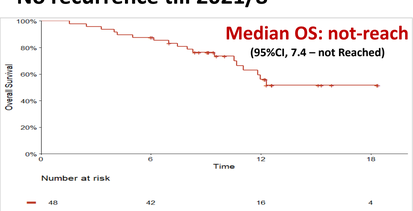


A case of pathological CR



- After Tx for 8 months of nivo + mGS, salvage operation in 2020/10 showed no residual tumor over liver with negative portal vein LN.
- No recurrence till 2021/8





Conclusions

- By the observation of 21 patients with CR/PR, the null hypothesis was rejected, indicating a positive result.
- Nivolumab in combination with modified GS is a promising regimen with good ORR and favorable safety profiles, which deserves further investigation in ABTC patients.
- Further post-hoc analysis is ongoing regarding the impact of PDL1 expression, genetic profiling and stool microbiota on treatment efficacies.

Acknowledgement

We would like to thank all the patients who participated in this study, clinicians from medical centers, statisticians and clinical research associates. We also thank the Clinical Trial Information Management System (CTIMeS) at NHRI for the data collection, and administrative staff who have contributed to the study. Free drug sponsors for this study: Opdivo® (Nivolumab) from Ono Pharmaceutical Co., Ltd.; Funding supports for this study: TCOG, NHRI, Taiwan & CA-110-PP-22, and CA-110-PP-20.