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A multicentre, phase 1B/2 study of *varlitinib* in combination with gemcitabine and cisplatin as first-line treatment for advanced or metastatic biliary tract cancer

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Background

- Biliary tract cancer (BTC) is a rapidly progressing cancer with limited response to chemotherapy.
- The doublet combination of gemcitabine and cisplatin (gem/cis) is recommended as a standard first-line treatment regimen for patients with advanced/metastatic BTC based on the ABC-02 and BT-22 studies. The median overall survival (OS) is 11.7 months.
- The human epidermal growth factor receptor (HER) family is a group of receptor tyrosine kinases (RTK) consisting of four members: EGFR (HER1), HER2, HER3 and HER4. Aberrant expression and/or activation of the HER receptor family have been reported in many cancer types.
- Overexpression of HER receptor family in patients with BTC has been reported in several studies and may be involved in tumour proliferation and survival.
- *Varlitinib*, a reversible pan-HER inhibitor, which targets EGFR, HER2, and HER4, shows potent activity as monotherapy in preclinical BTC models and clinical activity in BTC patients in phase 1 trials.

Study objectives

This is a multicentre, phase 1B/2 study to assess *varlitinib* in combination with gem/cis in patients with advanced or metastatic BTC who have not received prior systemic therapy. The study is ongoing, and the results of the phase 1B part are presented here.

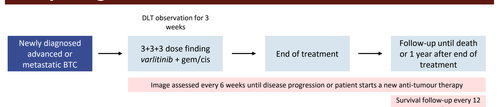
Primary objectives for phase 1B:

- To determine the maximum tolerated dose (MTD), as determined by dose-limiting toxicities (DLTs), and to characterise the safety profile of *varlitinib* in combination with gem/cis.

Secondary objectives for phase 1B:

- To evaluate the preliminary efficacy of *varlitinib* in combination with gem/cis, as measured by objective response rate (ORR), duration of response (DoR), progression free survival (PFS) and disease control rate (DCR).
- To evaluate the pharmacokinetics (PKs) of *varlitinib* and any relevant circulating metabolite when given in combination with gem/cis.

Study design



- A modified 3+3+3 study dose escalation design: starting dose of 200 mg twice daily (BID), followed by 300 mg BID.
- Patients received *varlitinib* BID daily in combination with gem/cis on Day 1 and Day 8 of a 21 day cycle.
- The study is being conducted in Korea, Taiwan, and Singapore.

Major inclusion criteria

- Have histologically or cytologically confirmed advanced (unresectable) or metastatic BTC, including intrahepatic or extrahepatic cholangiocarcinoma (CCA), gallbladder cancer, or carcinoma of the Ampulla of Vater, with no prior systemic therapy for advanced/metastatic disease. This includes clinical diagnosis of BTC with histological confirmation of adenocarcinoma.
- Without known brain metastases.
- With Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- With adequate organ and haematological function prior to first dose of study medication
- Measurable disease according to RECIST v1.1
- Be able to understand and willing to provide informed consent

Results

Patient characteristics

- As of 26 Nov 2018, 21 patients had been enrolled (11 in 200 mg cohort and 10 in 300 mg cohort).

	All	200 mg	300 mg
Gender, n (%)			
Male	11 (52.4)	10 (90.9)	1 (10.0)
Female	10 (47.6)	1 (9.1)	9 (90.0)
Age (year)			
Median (range)	65 (47 – 82)	63 (47 – 76)	66 (48 – 82)
ECOG at C1D1, n (%)			
0	8 (38.1)	5 (45.5)	3 (30.0)
1	13 (61.9)	6 (54.5)	7 (70.0)
Primary tumour site, n (%)			
Intrahepatic bile duct	10 (47.6)	6 (54.5)	4 (40.0)
Extrahepatic bile duct	4 (19.0)	2 (18.2)	2 (20.0)
Ampulla of Vater	3 (14.3)	1 (9.1)	2 (20.0)
Gallbladder	4 (19.0)	2 (18.2)	2 (20.0)

Study status

Status	Total (n=21)	200 mg (n=11)	300 mg (n=10)
Ongoing	2	0	2
Discontinued treatment	19	11	8
Reason for treatment discontinuation			
Disease progression	12	9	3
Consent withdrawal	4	0	4
Unacceptable toxicity	2	1	1
Other*	1	1	0

*Other: deemed by the investigator that it is not in the patient's interest to continue in the study

DLT events

- Evaluable for MTD: patients with *varlitinib* treatment compliance ≥80% and have received 2 doses of chemotherapy in Cycle 1, or patients who have experienced a DLT in Cycle 1 (regardless of their compliance).

Cohort	Evaluable for DLT	Number of Patients with DLT	DLT Details
200 mg	9	2	G3 unconjugated hyperbilirubinemia
			G3 ALT elevation & G4 AST elevation
300 mg	4	1	G4 thrombocytopenia, G3 febrile neutropenia, G3 AST elevation

ALT = alanine aminotransferase; AST = aspartate aminotransferase

References

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Efficacy

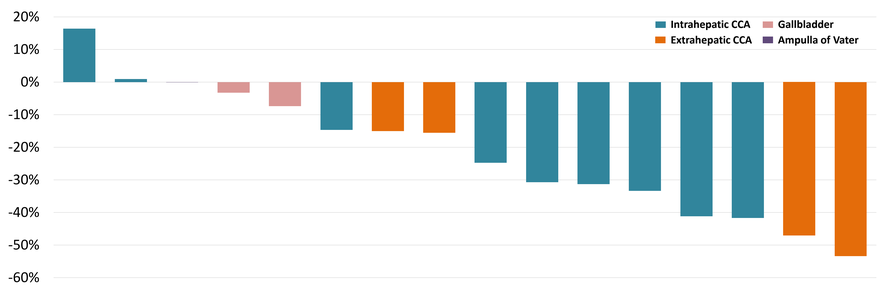
- Intention to treat (ITT) population: 21 treated patients with measurable disease at baseline.
- Efficacy evaluable population: 16 patients completed the first cycle of chemotherapy and had at least 1 post-treatment scan.

Response rate

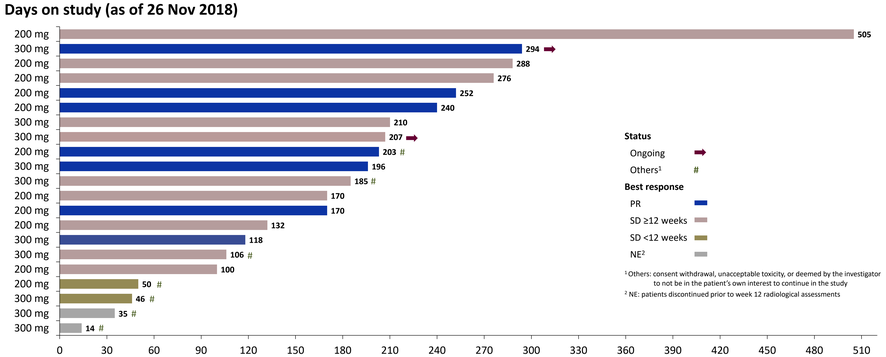
Population	ITT	Efficacy evaluable			ABC-02 gem/cis
		All	200 mg	300 mg	
No. of pts dosed	21	16	11	5	161
Response					
CR	0	0	0	0	1 (0.6%)
PR	7 (33.3%)	7 (43.8%)	4 (36.4%)	3 (60%)	41 (25.5%)
SD (≥12 weeks)	10 (47.6%)	8 (50.0%)	6 (54.5%)	2 (40%)	89 (55.3%)
SD (<12 weeks)	2 (9.5%)	1 (6.3%)	1 (9.1%)	0	0
PD	0	0	0	0	30 (18.6%)
NE[1]	2 (9.5%)	0	0	0	NA
Efficacy assessment					
ORR	7 (33.3%)	7 (43.8%)	4 (36.4%)	3 (60%)	42 (26.1%)
DCR[2]	17 (81.0%)	15 (93.8%)	10 (90.9%)	5 (100%)	131 (81.4%)

[1] Patients discontinued prior to week 12 radiological assessments
[2] DCR is defined as the % of patients with at least one visit response of CR, PR, or SD ≥12 weeks from starting treatment

Maximum change from baseline in target lesions in efficacy evaluable population (%)



Days on study (as of 26 Nov 2018)



[1] Others: consent withdrawal, unacceptable toxicity, or deemed by the investigator to not be in the patient's own interest to continue in the study
[2] NE: patients discontinued prior to week 12 radiological assessments

Safety and tolerability profile

Most common adverse events (AEs >25%, regardless of causality)

200 mg (n=11)				
Preferred term	Any grade		≥ Grade 3	
	n	(%)	n	(%)
Any AE	11	100	9	83
Platelet count decreased	8	73	5	45
Neutrophil count decreased	7	64	7	64
Anaemia	5	45	4	36
Diarrhoea	5	45	0	0
Nausea	5	45	0	0
Dyspepsia	4	36	0	0
Blood creatinine increased	4	36	0	0
Decreased appetite	4	36	0	0
Pyrexia	3	27	0	0
Aspartate aminotransferase increased	3	27	2	18
Blood bilirubin increased	3	27	1	9
Rash	3	27	0	0

300 mg (n=10)				
Preferred term	Any grade		≥ Grade 3	
	n	(%)	n	(%)
Any AE	10	100	8	80
Stomatitis	5	50	0	0
Anaemia	4	40	3	30
Vomiting	4	40	3	30
Fatigue	4	40	2	20
Platelet count decreased	4	40	2	20
Decreased appetite	4	40	2	20
Abdominal pain upper	3	30	0	0
Diarrhoea	3	30	1	10
Nausea	3	30	0	0
Acute kidney injury	3	30	0	0

Conclusion

- *Varlitinib* 300 mg BID in combination with gem/cis is well tolerated in BTC patients. The incidence and severity of AEs was comparable in 300 mg and 200 mg cohorts.
- Of 16 patients evaluable for efficacy, 7 patients showed PR and 8 had SD for more than 12 weeks, ORR and DCR are 43.8% and 93.8% respectively.
- In the higher *varlitinib* 300 mg dose cohort, 3 of 5 patients achieved PR and 2 had SD, ORR and DCR are 60% and 100% respectively.
- These results suggest that varlitinib in combination with gem/cis may result in increased efficacy compared to gem/cis alone for the treatment of first line advanced/metastatic BTC, where ORR and DCR rates of 26.1% and 81.4% have been reported (ABC-02).
- The study is on-going. MTD and RP2D have not been determined.

Other information

- Clinical trial identification: ClinicalTrials.gov NCT02992340
- Contact information: ohdoyoun@snu.ac.kr; mark.mchale@aslanpharma.com

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