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Efficacy and safety of *varlitinib*, a reversible pan-HER tyrosine kinase inhibitor, in combination with platinum-based regimens in biliary tract cancers: A pooled analysis from three phase 1 studies

Aaron C. Tan[1], Do-Youn Oh[2], Yee Chao[3], Chih-Yi Hsieh[4], Wei-Ling Chang[4], Fenny Isanto[4], Ying-Chen Chen[4], Mark McHale[4], Bertil Lindmark[4], Matthew C.H. Ng[1]

[1]National Cancer Centre Singapore, Singapore; [2]Seoul National University Hospital, Seoul, Korea, Republic of (South); [3]Taipei - Veterans General Hospital, Taipei, Taiwan; [4]ASLAN Pharmaceuticals, Singapore

Background

- Advanced biliary tract cancer (ABTC) encompasses cholangiocarcinoma (CCA), gallbladder cancer (GBC) and cancers of the ampulla of Vater. These tumours have a highly aggressive disease course and a poor prognosis. Molecular heterogeneity exists between tumour and geographical origin.[1]
- The doublet chemotherapy of gemcitabine with cisplatin or S-1 are standard first line regimens for ABTC.[2,3] The triplet combining all 3 agents recently showed improved response rates and survival over gem-cisplatin in Japanese patients. There is no standard of care second-line systemic treatment option.
- 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 family has been reported in a significant proportion of patients with BTC in several studies. The overexpression of EGFR, HER2, HER3, and HER4 vary from 23-57%, 4-13%, 12-23% and 59-60% of BTCs, respectively.[4-9]
- *Varlitinib*, a reversible pan-HER oral RTK inhibitor targets EGFR, HER2, and HER4, and has potent activity as monotherapy in preclinical BTC models and clinical activity in combination with capecitabine in BTC patients in phase 1 trials.

Study objectives and methods

- To conduct a pooled analysis of ABTC patients from three phase 1 studies (ASLAN001-002, ASLAN001-002SG, and ASLAN001-007), assessing the safety and efficacy of *varlitinib* in combination with platinum-based chemotherapy.
- The depth of tumour response, investigator-assessed objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events were analysed.

Results

- As of 26 Nov 2018, 43 patients with ABTC had been enrolled across the three phase 1 studies.

Phase 1 clinical trials included in the analysis

Trial	No. of pts	Chemo-regimen#	*Varlitinib* doses (mg, BID)*
ASLAN001-002	12 (27.9%)	Cisplatin/5-FU/leucovorin	**300**, 400
		Cisplatin/capecitabine	**300**, 400, 500
ASLAN001-002SG	10 (23.3%)	Oxaliplatin/capecitabine	300, **400**
		Oxaliplatin/5-FU/leucovorin	200, 300, **400**
ASLAN001-007 (first line)	21 (48.8%)	Cisplatin/gemcitabine	200, 300

#In the absence of unmanageable toxicities or disease progression, chemotherapy given for 6-9 cycles, before patients continued on varlitinib monotherapy. More cycles were allowed in ASLAN001-007 at the discretion of the investigator.
*In bold: maximum tolerated dose (MTD)

Patient characteristics

	n (%)
Gender	
Male	20 (46.5)
Female	23 (53.5)
Age (years)	
Median (range)	62 (42 – 82)
Primary tumour site	
Cholangiocarcinoma	31 (72.1)
Gallbladder	8 (18.6)
Ampulla of Vater	4 (9.3)
Prior lines of palliative treatment	
0	29 (67.4)
1	7 (16.3)
2	3 (7.0)
≥3	4 (9.3)
ECOG	
0	21 (48.8)
1	22 (51.2)

Efficacy

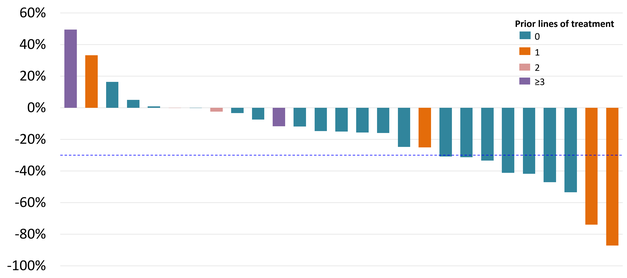
- Measurable population: 39 patients with measurable disease at baseline.
- Evaluable population for efficacy analysis: 27 treated patients that completed the first cycle of chemotherapy with at least 1 post-treatment scan.

Response rate

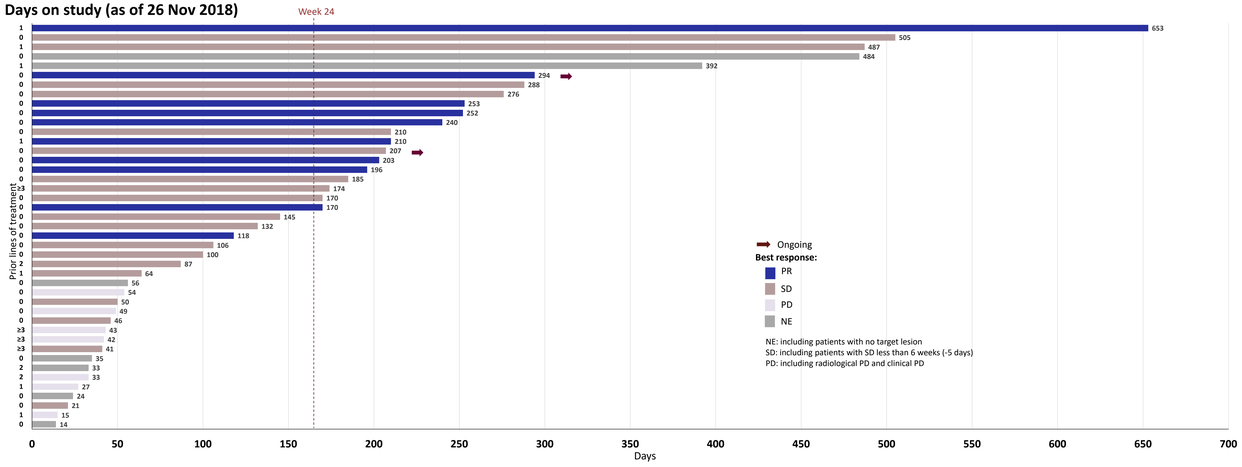
Population	Measurable	Efficacy evaluable
No. of pts dosed	39	27
Response		
CR	0	0
PR (overall)	10 (25.6%)	9 (33.3%)
PR (1st line, n=29)	8 (20.5%)	7 (25.9%)
PR (≥2nd line, n=14)	2 (5.1%)	2 (7.4%)
SD	19 (48.7%)	14 (51.9%)
PD	5 (12.8 %)	4 (14.8%)
Efficacy assessment		
ORR	10 (25.6%)	9 (33.3%)
DCR (≥ 6 weeks)[1]	26 (66.7%)	22 (81.5%)

[1] DCR is defined as the % of patients with at least one visit response of CR, PR, or SD ≥6 weeks (+/-5 days) from starting treatment

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



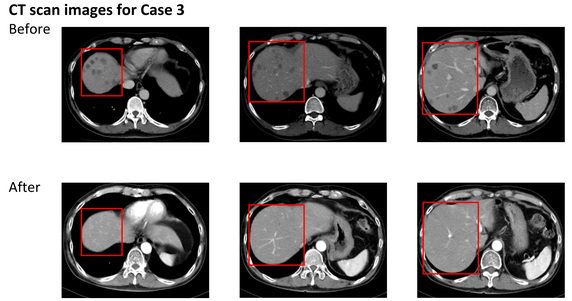
Days on study (as of 26 Nov 2018)



Patient case studies

	Case 1 Long-term survivor	Case 2 Long-term survivor	Case 3 Significant tumour shrinkage
Demographics	51 years, female	66 years, male	58 years, male
Diagnosis	Cholangiocarcinoma	Gallbladder	Cholangiocarcinoma
Treatment regimen	*Varlitinib* 400 mg BID + oxaliplatin/5-FU/ leucovorin	*Varlitinib* 300 mg BID + oxaliplatin/5-FU/ leucovorin	*Varlitinib* 400 mg BID + cisplatin/capecitabine
Prior treatments	• Resection of locally advanced disease • Adjuvant cisplatin + gemcitabine 6 cycles • Palliative cisplatin + gemcitabine 2 cycles	• Resection of stage III disease • Palliative cisplatin + gemcitabine 8 cycles with early relapse	• Modified Whipple's operation • Palliative gemcitabine 4 cycles with early relapse
Best response	PR	SD	PR
Last cycle	C27 D1	C21 D1	C10 D20
Days on study	653	487	210
Max % tumour change	-73.9%	-25.0%	-87.1%

CT scan images for Case 3



Safety and tolerability profile

Most common treatment-related adverse events (>10%)

Preferred term	Any grade	
	n	(%)
Any AE	41	95%
Fatigue	17	40%
Nausea	15	35%
Decreased appetite	15	35%
Diarrhoea	12	28%
Vomiting	10	23%
Stomatitis	10	23%
Blood bilirubin increased	10	23%
Anemia	7	16%
Platelet count decreased	7	16%
Neutrophil count decreased	6	14%
Aspartate aminotransferase increased	6	14%
Blood creatinine increased	6	14%

Conclusion

- *Varlitinib* in combination with platinum-based doublet chemotherapy has demonstrated promising efficacy in ABTC. Of 27 patients evaluable for efficacy assessment, 9 patients showed PR and 13 had SD for more than 6 weeks. ORR and DCR were 33.3% and 81.5% respectively. Overall, 20 patients have remained in the studies for more than 24 weeks.
- *Varlitinib* was tolerable in combination with platinum-based chemotherapy in ABTC.
- A pivotal, randomised study of *varlitinib* and capecitabine in second-line BTC patients and a phase 1b/2 study of *varlitinib* with platinum-based chemotherapy in first-line BTC are ongoing. (NCT03093870 and NCT02992340)

Other information

- Clinical trial identification: ClinicalTrials.gov NCT02648425, NCT02435927, and NCT02992340
- Contact information:
  aaron.tan@singhealth.com.sg; matthew.ng.c.h@singhealth.com.sg;
  mark.mchale@aslanpharma.com

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References

1. Jusakul A, et al. Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma. Cancer Discov. 2017;7(10):1116-1135
2. Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010, 362:1273-1281.
3. Okusaka T. et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010, 103:469-474..
4. Zhang H, et al. ErbB receptors: from oncogenes to targeted cancer therapies. *J Clin Invest* 2007, 117:2051-2058.
5. Mitsunaga S, et al. Membranous expressions of ErbB family in biliary tract cancer [Abstract]. The 76th Annual Meeting of the Japanese Cancer Association, Japan
6. Yang X, et al. Characterization of EGFR family gene aberrations in cholangiocarcinoma. Oncol Rep. 2014;32(2):700-8
7. Pignochino Y, et al. Targeting EGFR/HER2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC Cancer 2010, 10:631.
8. Yoshikawa D, et al. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer 2008, 98(2):418-25
9. Galdy S, et al. HER2/HER3 pathway in biliary tract malignancies; systematic review and meta-analysis: a potential therapeutic target? Cancer Metastasis Rev 2017, 36(1):141-157.