Phase IIA study to evaluate the biological activity of ASLAN001 in HER-1/2 co-expressing or HER-2 amplified advanced gastric cancer

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Abstract

Background: ASLAN001 (formerly called ARRAY-334543) is a potent, specific inhibitor of the tyrosine kinase domains of human epidermal growth factor receptor (HER)-1, HER-2 and HER-4 (IC_{50} 7, 2 & 0.195 nM). Approximately 30% of advanced gastric cancers are known to co-express HER-1 and HER-2.

Methods: This study was designed to evaluate the biological activity of ASLAN001 in tumour biopsies from patients with relapsed or metastatic gastric cancer where there was either co-expression of HER-1 and HER-2, or amplification of HER-2. Patients who failed previous 2nd line palliative therapies and had gastric tumors with immunohistochemical evidence of HER-1 expression (at level from 1+ to 3+) and HER-2 expression (at level from 1+ to 3+) using standard criteria or with HER-2 gene-amplification by standard HER2 FISH were enrolled. Patients underwent endoscopic biopsy for screening on Day 0. Patients received ASLAN001 500 mg bid orally for 28 days. Post-treatment endoscopic repeated biopsy was performed on D28. Activation of the downstream molecules involving signal transduction pathways was evaluated using antibodies to the total and phosphorylated forms of mitogen activated protein kinase (MAPK) and AKT using immunohistochemistry. Proliferation in the tumour was evaluated using Ki-67 and apoptosis by Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay.

Results: Nineteen patients (12 HER-1/2 co-expressing and 7 HER-2 amplified) were enrolled between July 2012 and June 2013. Seven patients (58.3%) had activation of MAPK at the baseline in the HER1/2 co-expressing group. Of these, 6 (85.7%) had significant reduction in MAPK activity on D28. All of these patients also showed a marked reduction in Ki-67 staining. Two of these patients also showed reduction in pAKT, and 5 patients showed an increase in TUNEL staining. The study demonstrated that ASLAN001 was biologically active in HER-1/2 co-expressing gastric cancer, and has the potential for future trial in this population

Conclusions: The pan-HER tyrosine kinase inhibitor ASLAN001 is a potent inhibitor of signal transduction in HER-1 and HER-2 co-expressing gastric cancer.

Background

Gastric cancer is the fifth most common malignancy in the world (incidence rate 6.8% in 2012) and the third leading cause of cancer-related deaths in both sexes worldwide (mortality rate 8.8% in 2012). Approximately 95% of all malignant gastric neoplasms are adenocarcinomas. The treatment for these advanced and unresectable diseases has remained essentially unchanged for the past 2 decades. The molecular biology responsible for carcinogenesis, tumour biology, and response to therapy in gastric cancer are active areas of investigation. Amplification and/or over-expression of 1 of the receptor tyrosine kinases – human epidermal growth factor receptor-2 (HER-2) – has been shown to promote tumourigenesis and to be involved in the pathogenesis of gastric cancer. In an earlier study, HER-2 has been shown to be an important target in the treatment of patients with unresectable gastric cancer. A systematic analysis of earlier studies also demonstrates potential role for HER-2 as a negative prognostic factor in gastric cancer. Epidemiological studies of archived gastric tumour samples suggest that approximately 40% of intestinal, and 30% of diffuse subsets co-express two or more members of the HER-family of receptors

ASLAN001 is an orally active, potent small molecule tyrosine kinase inhibitor targeting both EGFR and ErbB2. The compound is a reversible, ATP-competitive inhibitor with nanomolar potency in both in vitro and in cell- based assays showing strong activity against EGFR, ErbB2 and ErbB-4. It shows good activity in pre-clinical xenograft models of HER-familiy expressing human tumours, including breast and gastric cancer. It has been studied in 202 patients with advanced malignancy, and shows good bioavailability, reproducible PK and generally good tolerability. The MTD as monotherapy was 500mg bid in Phase 1

Objectives of study

Primary Objective

•To determine the effect of ASLAN001 (ARRY-334543) on activation of HER-1 and HER-2 receptors and their associated signal transduction pathways in patients with recurrent/metastatic gastric cancer whose tumours co-express HER-1 and HER-2 or whose tumours are HER-2 gene-amplified

Secondary Objectives

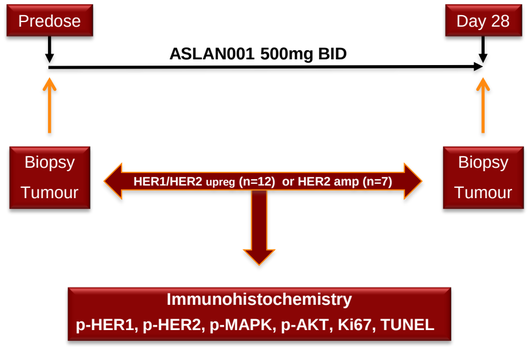
•To determine the RECIST Objective Response Rate (ORR)

•To determine the tolerability of ASLAN001 (ARRY-334543) in patients with recurrent/metastatic gastric cancers

Exploratory Objective

•To determine the effect of ASLAN001 (ARRY-334543) on activation of other HER-family receptors, and their associated signal transduction pathways

Design of study



Demographics and Baseline Characteristics

	Overall (n=22)
Gender (Male:Female)	16:6
Age*	64 (48-76)
Number of prior therapies*	3 (1-6)

* Median (range)

- All patients were ECOG Status 0 or 1
- Sites of metastases: Bone (n=1), Lung (n=4), Liver (n=10), Lymphatic (n=16), Other (n=10)

Analysis Populations and PK findings

Analysis Set	HER1/HER2	HER-2 Amplified	All patients
Treated patient (safety)	14	8	22
ITT PK	14	8	22
Evaluable PK[1]	6	2	8
ITT PD	11	7	18
Evaluable PD[2]	7	2	9

1. A subset of the ITT PK set, containing patients with paired Day 1 and Day 29 PK samples, and excluding any patients whose Day 29 PK was believed to be affected by the consumption of proton-pump inhibitors [PPIs] or high-dose H2-antagonists, or by poor treatment compliance
2. A subset of the ITT PD set, excluding any patients who were excluded form the Evaluable PK set due to poor compliance or PK affecting concommitant medications.

The evaluable PD set was defined as the primary analysis set for addressing the study objectives. The solubility of ASLAN001 is critically pH dependent. Above pH4.0, the solubility falls by approximately 100 fold in-vitro. Pharmacokinetic analysis revealed that 7 patients in the HER-1/2 co-expressing, and 2 in the HER-2 amplified populations had high exposures – these patients were not receiving acid-modifying medications (proton-pump inhibitors (PPIs)
Patients receiving full dose PPIs achieved very low exposures. Patients on maintenance doses of PPIs achieved intermediate levels of exposure.

Immunohistochemistry Results

Inhibition of Phospho-MAPK

	Evaluable PD Set	ITT PD Set
HER1/HER2	86% (6 of 7)	64% (7 of 11)
HER2 amplified	50% (1 of 2)	43% (3 of 7)
TOTAL	**78% (7 of 9)**	**56% (10 of 18)**

Down-regulation of Ki-67

	Evaluable PD Set	ITT PD Set
HER1/HER2	71% (5 of 7)	50% (5 of 10)
HER2 amplified	50% (1 of 2)	43% (3 of 7)
TOTAL	**66% (6 of 9)**	**47% (8 of 17)**

Up-regulation of TUNEL

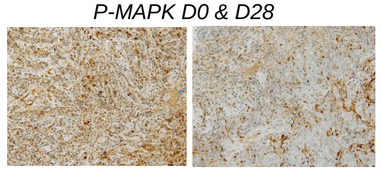
	Evaluable PD Set	ITT PD Set
HER1/HER2	60% (3 of 5)	50% (4 of 8)
HER2 amplified	100% (2 of 2)	71% (5 of 7)
TOTAL	**71% (5 of 7)**	**60% (9 of 15)**

Inhibition of Phospho-AKT

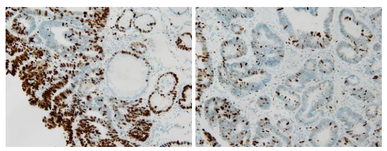
	Evaluable PD Set	ITT PD Set
HER1/HER2	29% (2 of 7)	36% (4 of 11)
HER2 amplified	0% (0 of 2)	29% (2 of 7)
TOTAL	**22% (2 of 9)**	**33% (6 of 18)**

Reduction in pMAPK & Ki-67

P-MAPK D0 & D28



Ki-67 D0 & D28



Summary

- ASLAN001 inhibited signaling through both proliferation and survival pathways in patients with HER-1/2 co-expressing gastric cancer
- Clear signs of *proliferation*- pathway modulation (the objective of the study) in the patients with sufficient drug exposure
- Clear evidence of a reduction of cell proliferation in the patients with sufficient drug exposure
- Clear evidence of induction of apoptosis as measured by (TUNEL)
- Exposure is significantly influenced by gastric acidity/PPI exposure
- ASLAN001 is being re-formulated to address this
- ASLAN001 is about to enter randomised Phase 2B studies in *combination with chemotherapy* in patients with HER-1/HER-2 co-expressing gastric cancer and HER-2-amplified metastatic breast cancer