gastrointestinal tumours, non-colorectal

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PHASE II A 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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Aim: ASLAN001 is a potent, specific inhibitor of the tyrosine kinase domains of human epidermal growth factor receptor (HER)-1, HER-2 and HER-4 (IC50 7, 2 & 0.195 nM). Approximately 30% of advanced gastric cancers (GCs) are known to co-express HER-1 and HER-2.

Methods: This study was designed to evaluate the biological activity of ASLAN001 (formerly called ARRY-334543) in tumour biopsies from patients with relapsed or metastatic GC where there was either co-expression of HER-1 and HER-2, or amplification of HER-2. Pretreated patients 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 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 (86%) 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 phosphorylated AKT, and 5 patients showed an increase in TUNEL staining. The study demonstrated that ASLAN001 was biologically active in HER-1/2 co-expressing GC, 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 GC.

Disclosure: M. Foster: not an employee of ASLAN, but an independent consultant histopathologist; M. McHale: co-founders and part owners of ASLAN Pharmaceuticals; A. Barge: co-founders and part owners of ASLAN Pharmaceuticals. All other authors have declared no conflicts of interest.