Background The PD-1/PD-L1 molecular pathway is one of the primary mechanisms of immune evasion deployed by cancer cells and several anti-PD-L1 monoclonal antibodies (mAbs) have been approved for the treatment of multiple cancers, including cancers of the GI tract and liver. In such cancers, one of the issues observed is broad-spectrum autoimmune toxicities, including pneumonitis, and others, primarily owing to their long systemic half-life. Therefore, small molecule inhibitors of PD-L1 with gut restricted exposure should potentially be able overcome these toxicities. JBI-1527 is a small molecule PD-L1 inhibitor with similar binding and mechanism of action as anti-PD-L1 antibodies that shows much higher exposure in gastrointestinal tract and liver as compared to plasma. It shows comparable efficacy as approved mAbs in preclinical studies.

Methods Structure based drug design was used to design PD-L1 inhibitors; potency of these inhibitors was assessed in an in-vitro TR-FRET assay. Reporter assays and ex-vivo co-culture assays were used to assess T-cell proliferation and function. Pharmacokinetics studies were performed in multiple pre-clinical species to assess tissue distribution. In vivo efficacy was assessed in partially humanized mice efficacy models.

Results JBI-1527 showed strong in vitro IC$_{50}$ of 2.9 nM in TR-FRET assay that measures interaction between PD-1 and PD-L1 and led to stabilization of PD-L1 protein as measured by thermal shift assay. This molecule also augmented T-cell co-inhibitory signalling as observed by Jurkat cell/SHP-1 assay. Competition study between anti-PD-L1 blocking antibody suggested that JBI-1527 finger-printing on PD-L1 is similar to mAbs. X-ray crystal structure studies clearly demonstrated that JBI-1527 caused dimerization of PD-L1. More importantly, JBI-1527 showed favourable gastrointestine localised pharmacokinetic profile with high exposure in colon, jejunum, duodenum, ileum (11 to >280 fold vs. plasma) as compared to plasma in preclinical species when dosed orally. JBI-1527 showed comparable efficacy to the anti-PD-L1 antibody Atezolizumab in hPD-L1/MC38 syngeneic and orthotopic models by oral administration and is well tolerated at efficacious doses.

Conclusions Gastrointestine localised pharmacokinetic profile of JBI-1527 provides an attractive option to be used in the treatment of colon cancer, HCC and other GI-related cancers with minimal systemic toxicity as compared to mAbs.