TRIAL IN PROGRESS: PHASE 1 FIRST-IN-HUMAN STUDY OF XL092 ADMINISTERED ALONE OR IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH INOPERABLE LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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Background XL092 is a novel oral multi-targeted inhibitor of receptor tyrosine kinases. In preclinical studies, oral dosing with XL092 resulted in pharmacodynamic inhibition of MET, TAM kinases (AXL, MER), and VEGFR2 phosphorylation and was associated with significant anti-tumor activity in xenograft tumor models. Drugs targeting TAM kinases may promote an immune-permissive environment, which may enhance response to immune checkpoint inhibitors (ICIs). The combination of XL092 and anti-PD-1 ICI exhibited greater anti-tumor activity in a syngeneic tumor model than either agent alone.[1] Preliminary XL092 pharmacokinetic data indicate a median terminal half-life of 21 hours, suitable for daily dosing.

Methods This multi-center, phase 1, open-label study aims to enroll approximately 800 patients total in dose-escalation and cohort-expansion stages (NCT03845166). The dose-escalation stage will enroll patients with inoperable locally advanced or metastatic solid tumors in a 3+3 design (monotherapy cohorts) or rolling 6 design (combination cohorts). Patients will receive escalating doses of XL092 alone or in combination with ICIs (atezolizumab 1200mg Q3W or avelumab 800mg Q2W). Following identification of the maximum tolerated dose (MTD) and/or recommended dose (RD) of XL092 monotherapy, the expansion stage will enroll XL092 monotherapy cohorts in 3 tumor-specific indications (renal cell carcinoma [RCC], metastatic castration-resistant prostate carcinoma [mCRPC], and hormone-receptor positive breast carcinoma [HR+ BC]) using a Simon's optimal 2-stage design. Once the MTDs/RDs are identified for XL092 in combination with each ICI, the expansion stage will also enroll patients in tumor-specific cohorts for XL092+atezolizumab (RCC, mCRPC, HR+ BC, and colorectal carcinoma) and XL092 +avelumab (urothelial carcinoma) using Simon's optimal 2-stage design or a Precision-Based design. A limited number of patients will be enrolled in dedicated biomarker cohorts, with tumor and blood samples collected, to evaluate the pharmacodynamic effects of XL092 alone and in combination with ICIs. Key eligibility criteria include unresectable or metastatic solid tumors; measurable disease per RECIST 1.1 (expansion cohorts only); available tumor tissue (archival or fresh biopsy); and ECOG 0-1. The primary objective of the dose-escalation stage is to determine MTDs/RDs of XL092 when administered alone or in combination with ICIs, and the primary objective of the expansion stage is to evaluate objective response rate and progression-free survival rate by investigator per RECIST 1.1 of XL092 as monotherapy or in combination with ICIs. Secondary objectives include evaluation of the safety of XL092 alone and in combination with ICIs and evaluation of plasma pharmacokinetics of XL092 and its potential metabolites. The study is open for enrollment.

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Trial Registration NCT03845166

REFERENCES

1. Hsu J, Chong C, Goon L, et al. XL092, a Multi-targeted Inhibitor of MET, VEGFR2, AXL and MER with an Optimized Pharmacokinetic Profile. *European Journal of Cancer [abstract 33]* 2020;**138** Suppl 2:S16.

Ethics Approval Study approved by institutional Review Boards at each investigational site.

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