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Phase I study of LY3866288, a potent, highly isoform-selective FGFR3 inhibitor in FGFR3-altered advanced solid tumors (FORAGER-1): Dose optimization

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Background

Activating alterations in *FGFR3* are present in 15-20% of advanced or metastatic urothelial cancer (mUC). LY3866288 (LY) is an oral, potent and highly isoform-selective FGFR3 inhibitor (FGFR3i) with favorable safety and antitumor activity in patients (pts) with *FGFR3*-altered mUC. Preclinically, LY increases nectin 4 cell surface expression and enhances the antitumor activity of enfortumab vedotin (EV) in *FGFR3*-altered mUC *in vivo* models.

Methods

Adults with advanced or metastatic solid tumors with an *FGFR3* alteration (tumor or blood) were eligible in dose escalation (A1). Dose optimization (A2) randomized *FGFR3*-altered mUC into 3 DLs (200, 300, and 400 mg BID), stratified by prior FGFRi treatment. LY plus EV and pembrolizumab (EVP) is being studied in 1L mUC (B5). Data are pooled results from A1 + A2.

Results

As of 27 Mar 2025, 176 pts (A1, n=113; A2, n=63) were treated at 10 DLs of LY (6 mg QD–400 mg BID). Median age was 67, 69% had ECOG PS 1 and 75% had mUC. Median prior lines of therapy was 3 (range, 1-9; 22% prior FGFRi). Exposures increased with DLs up to 200 mg BID which achieved sustained IC_{90}. 139 pts received ≥200 mg BID and most common (≥20%) TEAEs were diarrhea (71%), hyperphosphatemia (38%), increased AST/ALT (25%/26%), stomatitis (26%) and fatigue (22%), all predominately grade (gr) 1-2. In 42 pts treated at 200 mg BID, most common TEAEs were diarrhea (67%), AST/ALT (21%/24%) and fatigue (24%). Hyperphosphatemia (26%) was transient and predominately gr1. Gr3 anemia (10%; all unrelated) was the only severe TEAE reported in ≥5% of pts. TEAEs associated with poor tolerance and compliance to erdafitinib were uncommon (PPE 7%, onycholysis 0%, retinopathy 0%). Few related AEs led to dose reduction (10%) or discontinuation (2%). In pts treated with ≥200 mg BID, the ORR was 38% (31/82; 24 cPR [confirmed PR], 7 uPR [pending/ongoing]) and the ORR at 200 mg BID was 43% (12/28; 11 cPR, 1 uPR) including 43% (3/7 cPR) in FGFRi pretreated pts. Cohort B5 opened at 200 mg BID and updated data will be presented.

Conclusions

LY3866288 at 200 mg BID was well-tolerated and demonstrated promising antitumor activity in FGFRi pretreated and naive pts with *FGFR3*-altered mUC, warranting further study as monotherapy and combined with EVP.

Clinical trial identification

NCT05614739.

Legal entity responsible for the study

Eli Lilly and Company.

Funding

Eli Lilly and Company.

Disclosure

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