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LBA26

A phase I/II trial of LY4064809 (STX-478), a pan-mutant-selective PI3Kα inhibitor: Updated PIKALO-1 results

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Background

PI3Kα inhibitors (PI3Kαi) show benefit in the ⊠40% of HR+, HER2- ABC with (w/) *PIK3CA* mutations (*PIK3CAm*) but are limited by wild-type PI3Kα–mediated toxicities (tox) and (&) often restricted to patients (pts) without (w/o) diabetes (DM) or prediabetes (pDM). LY4064809 (LY) is an oral, allosteric, CNS-penetrant, pan-mutant-selective PI3Kαi w/ favorable safety, PK, & efficacy in pts w/ *PIK3CA*m tumors.

Methods

In PIKALO-1, pts w/ *PIK3CA*m advanced solid tumors received LY alone (≥1 prior therapies, txs); pts w/ HR+, HER2- *PIK3CA*m ABC (≤2 prior txs) received LY + fulvestrant (fulv; 1-2 prior txs) or LY + fulv + CDK4/6i. Pts w/ pDM/DM were eligible; pts w/ uncontrolled DM (HbA1c ≥8% / FPG ≥140mg/dL / on insulin) were excluded.

Results

As of 7 Jul 2025, 204 pts were treated: 132 (49 ABC, 83 other solid tumors) w/ LY (20-160 mg QD), 34 w/ LY (60-100 mg QD) + fulv, & 38 w/ LY (20-100 mg QD) + fulv + CDK4/6i (ribociclib, 9; palbociclib, 29). Median age was 62 (27-84) yrs, 53% had pDM/DM. Median prior txs for ABC was 2 (0-7) including prior: CDK4/6i (93%), SERD (51%), & PI3Kα/AKT/mTORi (8%). TEAEs (any G/G≥3) ≥20% in all pts were fatigue (32%/5%), hyperglycemia (31%/1% overall, 39%/2% & 21%/0% in pts w/ & w/o pDM/DM), nausea (30%/1%), diarrhea (25%/1%), decreased appetite (24%/1%) & ALT increase (20%/7%). Other common class-tox (rash [5%/0%] & stomatitis [7%/<1%]) were low. TEAEs led to dose reduction/discontinuation in 9%/3%. LY exposures achieved target coverage for *in vitro* pAKT IC_{80} (from 20 mg) & *in vivo* efficacy (from 40 mg). No significant drug-drug interactions were noted. *PIK3CA*m ctDNA was reduced at all dose levels/txs. Table shows efficacy.Table: LBA26

	LY + fulv (N=25)	LY + fulv + CDK4/6i (N=17)
ORR (cPR+uPR)	28% (7/25)[a]	24% (4/17)[b]
DCR (cPR+uPR+SD)	88% (22/25)[a]	82% (14/17)[b]

Efficacy evaluable pts had measurable disease and ≥1 post baseline response assessment or discontinued prior to the first post baseline response assessment.[a]Includes 2 uPR (ongoing, pending confirmation). [b]Includes 4 uPR (ongoing, pending confirmation).

Conclusions

LY alone or in combination was well-tolerated, w/ notably lower incidence of PI3Ki-class tox and no G≥3 hyperglycemia in pts with normal

baseline glycemic control. Robust target coverage & promising antitumor activity were observed in heavily pre-treated pts w/ *PIK3CA*m tumors, demonstrating LY's potential as a best-in-class mutant selective PI3Kαi.

Clinical trial identification

NCT05768139.

Legal entity responsible for the study

Eli Lilly and Company.

Funding

Eli Lilly and Company.

Disclosure

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