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A phase 1/2 trial of LY4064809 (STX-478), a pan-mutant-selective PI3Kα inhibitor in HR+, HER2- advanced breast cancer (ABC): Updated results from PIKALO-1

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OBJECTIVES

- Determine the safety, tolerability, PK, and antitumor activity of LY4064809 as monotherapy and in combination in patients with *PIK3CA*m HR+, HER2- advanced BC (ABC)

CONCLUSIONS

- LY4064809, either alone or in combination with fulvestrant +/- CDK4/6 inhibitors, was well-tolerated, with notably low incidence of PI3K inhibitor (PI3Ki)-class toxicities
- Robust target coverage and promising antitumor activity were observed in heavily pre-treated patients with *PIK3CA*m HR+, HER2- ABC, highlighting LY4064809's potential as a best-in-class mutant selective PI3Kα inhibitor, although doublet and triplet therapy require additional time to mature
- PIKALO-2, a phase 3 global registrational trial investigating LY4064809 in combination with endocrine therapy and CDK4/6 inhibitors is actively enrolling a dose optimization lead-in (NCT07174336)

Study is sponsored by Eli Lilly and Company

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BACKGROUND

- PI3Kα inhibitors (PI3Kαi) have demonstrated clinical benefit in the approximately 40% of HR+, HER2- ABC with *PIK3CA* mutations (*PIK3CA*m).[1] However, broad use is often constrained by: 1) toxicities mediated through wild-type PI3Kα inhibition and 2) the exclusion of patients with diabetes or prediabetes
- LY4064809 is an oral, allosteric, CNS-penetrant, pan-mutant-selective PI3Kαi with favorable safety, PK, and efficacy in patients with *PIK3CA*m HR+, HER2- ABC[2]
- Here we present updated data from PIKALO-1, a global, first-in-human phase 1/2 trial of LY4064809 (NCT05768139)

STUDY DESIGN & METHODS

HR+, HER2- *PIK3CA*-mutant[a] ABC

- FBG <140 mg/dL, HbA1c <8%, controlled T2DM permitted
- Prior PI3K/AKT/mTOR inhibitor permitted if stopped due to intolerance
- Measurable / evaluable disease per RECIST v1.1

LY4064809[b] Monotherapy

- **Prior standard therapy required**

LY4064809[c] + Fulvestrant

- **1-2 prior therapies**
  - ≥1 CDK4/6i + ET
  - ≤1 prior chemotherapy

LY4064809[c] + ET[d] + CDK4/6i[e]

- **≤2 prior therapies**
  - CDK4/6i-naive/ongoing[f]/pretreated
  - ≤1 prior chemotherapy

Objectives

- Safety
- Pharmacokinetics
- Dose determination
- ORR and DCR per RECIST v1.1

- Biomarker analysis: Serial plasma samples were collected for ctDNA analysis (InVisionSeq or Foundation One Liquid assay was used)
- Data cutoff date was 7 Oct 2025

[a]Presence of an activating *PIK3CA* mutation detected in tumor or blood samples; [b]Dose escalation and expansion; [c]Dose expansion and optimization; [d]Physician's choice ET (endocrine therapy) includes fulvestrant or an aromatase inhibitor; [e]CDK4/6i (cyclin-dependent kinase 4/6 inhibitor) includes palbociclib, ribociclib, or abemaciclib. [f]≤6 months

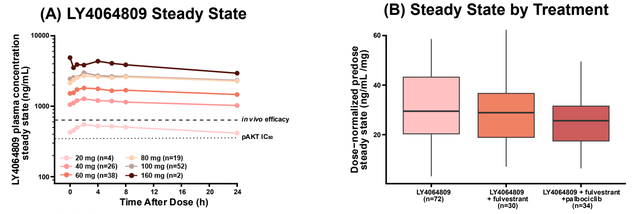
RESULTS

Table 1. Patient and Disease Characteristics

Characteristics	HR+, HER2- ABC			
	Total (N=154)	LY4064809 (n=50)	LY4064809 + Fulv (n=41)	LY4064809 + Fulv + CDK4/6i[a] (n=63)
Median age, years (range)	61 (27-84)	64 (37-84)	61 (36-81)	59 (27-81)
Female, n (%)	152 (99)	49 (98)	40 (98)	63 (100)
Median BMI[b], (kg/m^2) (range)	26 (18-50)	25 (18-39)	25 (19-50)	29 (19-47)
Pre-diabetic[c] / T2DM[d], n (%)	52 (34) / 26 (17)	18 (36) / 9 (18)	10 (24) / 6 (15)	24 (38) / 11 (18)
ECOG PS, 0 / 1, n (%)	89 (58) / 65 (42)	21 (42) / 29 (58)	25 (61) / 16 (39)	43 (68) / 20 (32)
PIK3CA-mutation, n (%)				
Kinase domain / Helical domain / Double	84 (55) / 73 (47) / 12 (8)	36 (72) / 20 (40) / 6 (12)	24 (59) / 18 (44) / 1 (2)	24 (38) / 35 (56) / 5 (8)
Median number of prior lines for advanced disease (range)	2 (0-7)	3 (1-7)	1 (0-5)	1 (0-6)
Prior therapy for ABC, (%)				
CDK4/6 inhibitor	83%	96%	85%	70%
Palbo / Ribo / Abema	38% / 30% / 27%	58% / 30% / 24%	34% / 37% / 32%	24% / 25% / 27%
SERD	50%	72%	39%	40%
Fulv / Other SERDs	49% / 3%	68% / 6%	39% / -	40% / 2%
PI3K/AKT/mTOR inhibitor	7%	18%	-	2%
Chemotherapy / ADC	28% / 9%	62% / 24%	12% / 5%	11% / -

[a]Palbociclib (49/63; 78%), Ribociclib (13/63; 21%), Abemaciclib (1/63; 2%). [b]Patients with missing BMI data - LY4064809 (1), LY+ Fulv (1), and LY + Fulv + CDK4/6i (3). [c]Baseline HbA1c ≥5.7 to <6.5, fasting glucose ≥100 to <126, or medical history of pre-diabetes mellitus. [d]Baseline HbA1c ≥6.5, fasting glucose ≥126, medical history of DM, or patient received anti-hyperglycemic treatment at baseline. 4/36 pts with T2DM had history of prior insulin requirement, 2 were on insulin at study entry and continued insulin on study; In protocol amendment 7.2., eligibility criteria were modified to include patients with HbA1c <8% and/or FBG <140 mg/dL [7.7 mmol/L] except in those who required insulin. Abema, abemaciclib; ADC, antibody-drug conjugate; Fulv, fulvestrant; Palbo, palbociclib; Ribo, ribociclib

Fig 1. Pharmacokinetics



CDK4/6i DDI analyses confined to palbociclib; limited ribociclib PK data available at data cutoff date

- Approximate dose proportional increases in steady state exposure
- No significant drug-drug interaction between LY4064809 and fulvestrant or palbociclib
- Steady state LY4064809 exposures maintained target coverage for *in vitro* pAKT IC_{80} from 20 mg and for *in vivo* efficacy from 40 mg

RESULTS

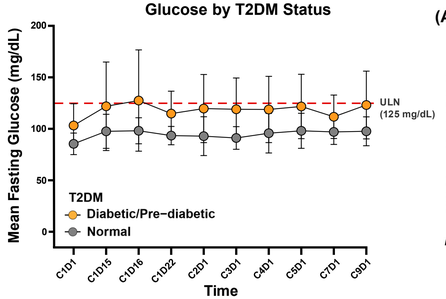
Table 2. Safety and Tolerability

Adverse Event, n (%)	Treatment-Emergent AEs (≥15%), HR+, HER2- ABC							
	Total (N=154)[a]		LY4064809 (n=50)		LY4064809 + Fulv (n=41)		LY4064809 + Fulv + CDK4/6i (n=63)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	57 (37)	7 (5)	20 (40)	4 (8)	12 (29)	1 (2)	25 (40)	2 (3)
Neutropenia[b]	52 (34)	34 (22)	1 (2)	-	6 (15)	-	45 (71)	34 (54)
Nausea	50 (33)	1 (<1)	19 (38)	-	13 (32)	1 (2)	18 (29)	-
Diarrhea	42 (27)	1 (<1)	11 (22)	-	13 (32)	1 (2)	18 (29)	-
Hyperglycemia	38 (25)	1 (<1)	19 (38)	-	13 (32)	1 (2)	6 (10)	-
Pts with baseline pre-DM/DM	28/78[c] (36)	1/78[c] (<1)	13/27[c] (48)	-	9/16[c] (56)	1/16[c] (6)	6/35[c] (17)	-
Pts without baseline pre-DM/DM	10/76[c] (13)	-	6/23[c] (26)	-	4/25[c] (16)	-	-	-
ALT/AST increased[b]	33 (21)	13 (8)	13 (26)	7 (14)	16 (39)	5 (12)	4 (6)	1 (2)
Decreased appetite	23 (15)	1 (<1)	12 24)	-	6 (15)	1 (2)	5 (8)	-
Other class effect AEs								
Stomatitis	15 (10)	1 (<1)	5 (10)	-	1 (2)	-	9 (14)	1 (2)
Rash[b]	6 (4)	-	3 (6)	-	-	-	3 (5)	-
Dose reductions due to TEAEs[c]	21 (14)		14 (28)		6 (15)		1 (2)	
Discontinuations due to TEAEs[c]	2 (1)		1 (2)		1 (2)		-	

[a]LY4064809 (20 - 160 mg QD) doses were evaluated. [b]Consolidated terms: ALT/AST increased includes both alanine aminotransferase increased and aspartate aminotransferase increased; neutropenia includes neutropenia and neutrophil count decreased; rash includes rash and rash maculo-papular. [c]Dose reductions/discontinuations of LY4064809 only

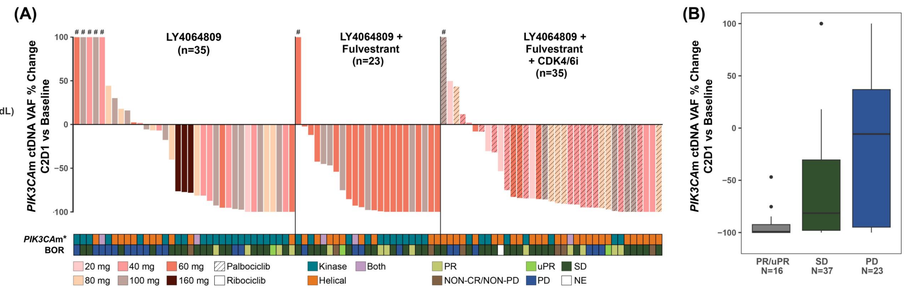
- Most common LY4064809 related AEs (TRAEs) were fatigue (27%), nausea (23%), hyperglycemia (23%; 33%/12% in pts with/without pre-DM/DM), and diarrhea (21%)
- Grade ≥3 TRAEs occurred in 20% of patients, most commonly ALT/AST increased (7%), fatigue (4%), and neutropenia (4%)
- 1 patient discontinued due to a TRAE (AST increased in 100 mg LY4064809 + fulvestrant)

Fig 2. Impact on Glucose Metabolism



- Overall minimal impact on the glucose metabolism with a marginal impact in patients with pre-DM/DM
- Effectively managed following supportive care interventions, which may have included adjustments to antihyperglycemic medications/regimens and dose modifications of study drug

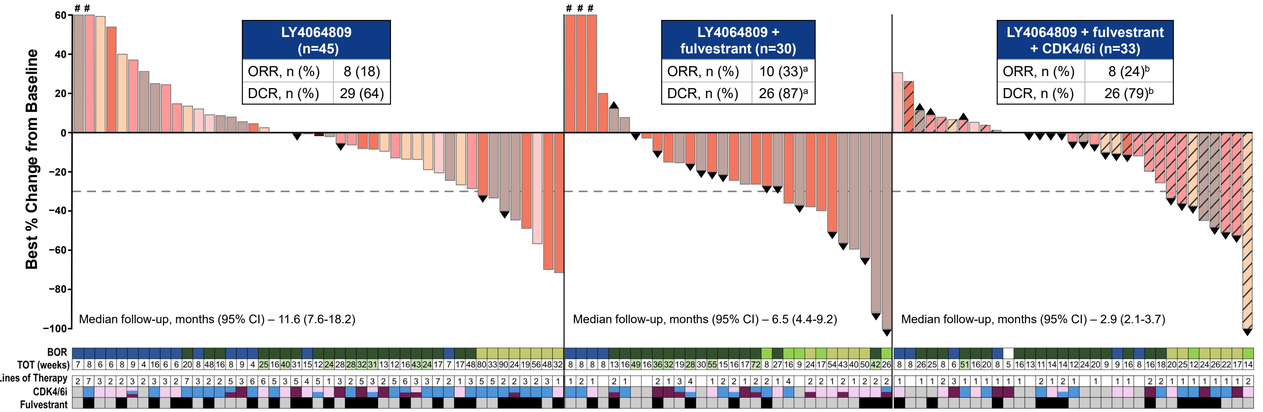
Fig 3. *PIK3CA*m ctDNA VAF Dynamics



(A, B) Breast cancer patients with *InVisionSeq- or Foundation Medicine One Liquid-detected baseline enrollment-eligible *PIK3CA* mutations (*PIK3CA*m) with variant allele frequency (VAF) ≥0.4%. Percent changes calculated using only enrollment-eligible *PIK3CA*m. **(B)** Objective response limited to patients with measurable disease. [a]Patients with >100% *PIK3CA*m VAF % change from baseline

- Consistent with LY4064809 target engagement, kinase and helical domain *PIK3CA*m VAF decreases at C2D1 were observed
- Greater declines in *PIK3CA*m VAF correlated positively with objective responses

Fig 4. Tumor Response in ABC Patients with Measurable Disease



Efficacy evaluable patients are those who had measurable disease and ≥1 post-baseline tumor assessment or discontinued prior. ORR = PR and uPR; DCR = PR, uPR, and SD. Includes [a]1 and [b]2 unconfirmed PRs, ongoing and pending confirmation. [a]Patients with a best % change from baseline >60%. TOT, time on treatment

Majority of patients in the combination cohorts are ongoing

References [1]MyCancerGenome.org 08/2024
[2]Juric D et al. LBA 26 Presented at ESMO, Oct 17-21, 2025