# LOXO-783: A potent, highly mutant selective and brain-penetrant allosteric PI3Kα H1047R inhibitor in combination with standard of care (SOC) treatments in preclinical PI3Kα H1047R-mutant breast cancer models

**Presented at:** San Antonio Breast Cancer Symposium
**Presented on:** December 8, 2022

P4-08-02

# LOXO-783: A potent, highly mutant selective and brain-penetrant allosteric PI3Kα H1047R inhibitor in combination with standard of care (SOC) treatments in preclinical PI3Kα H1047R-mutant breast cancer models

Loredana Puca, Michele Dowless, Carmen Perez, Maria Jesus Ortiz-Ruiz, Gregory Donoho, Andrew Capen, Lysiane Huber, Sarah Bogner, Dongling Fei, Jason R. Manro, Chun Ping Yu, Wei Guo Xu, Rui Wang, Shuang Chen, Mark Hicks, Parisa Zolfaghari, Andrew Faber, Raymond Gilmour, Monica Ramstetter, Matt Chang, Maria Jose Lallena, Xuequian Gong, David M. Hyman, Lillian M. Smyth, Barbara J. Brandhuber, Barry S. Taylor, Anke Klippel

Loxo@Lilly, Stamford, Connecticut

## Background

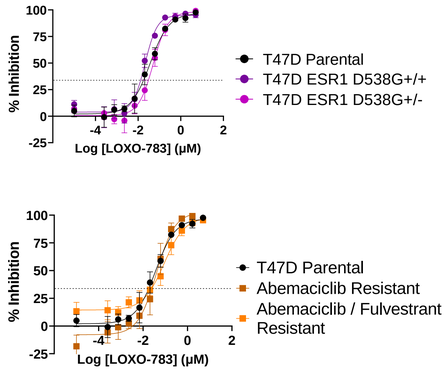
- Phosphoinositide 3-kinase alpha (PI3Kα) H1047R mutations are activating oncogenic events that occur in ~15% of breast cancers[1]
- Early generation PI3Kα inhibitors target both wild-type (WT) and mutant PI3Kα and, as a result, their efficacy may be limited by on-target WT PI3Kα-mediated toxicities, including hyperglycemia, skin rash, and diarrhea[2-3]
- LOXO-783 is an oral, potent and highly mutant-selective, brain-penetrant allosteric PI3Kα H1047R inhibitor that is currently in Phase 1 testing. Preclinically, LOXO-783 as a single agent is highly selective for PI3Kα H1047R over WT PI3Kα and other PI3K isoforms, and induces single-agent tumor regressions in ER+, HER2- PI3Kα H1047R-mutant breast cancer models without causing hyperglycemia or increases in plasma insulin / C-peptide[4]
- Here we report the efficacy of LOXO-783 with standard of care (SOC) treatments in preclinical breast cancer models as implemented in the ongoing PIKASSO-01 trial (NCT05307705)

## Methods

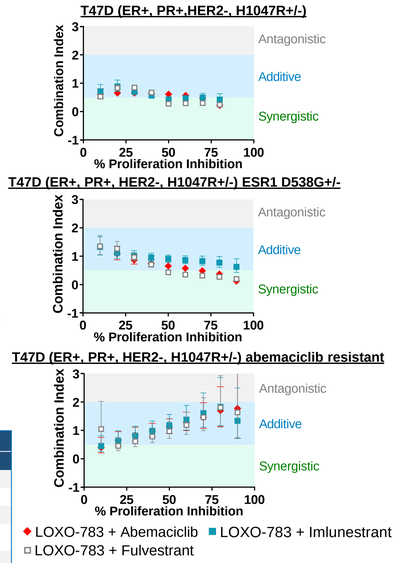
- Single agent treatment - Cells were treated with LOXO-783, abemaciclib, or fulvestrant at a dilution of 1:3 for two doubling times. Cell proliferation was assessed by imaging on a Cell Insight CX7
- Combination treatment - Cells were treated for two doubling times with LOXO-783 in combination with abemaciclib, imlunestrant, fulvestrant at a fixed ratio of 10μM : 1μM dose response or paclitaxel at a fixed ratio of 10μM : 0.1μM dose response. For each combination *in vitro*, a curve shift analysis following Loewe Additivity model was performed to identify synergistic or antagonistic interactions between two drugs. Combination Index (CI) was calculated for each percentage proliferation inhibition by comparing activity of the drug combination with the respective single agent. CI >2 demonstrated antagonism, >0.5 to <2 CI additivity, and CI<0.5 synergy
- *In vivo* studies were performed in various PI3Ka H1047R mutant HR+, HER2-, and triple negative breast cancer (TNBC) models. A Bliss Independence Method was used to evaluate the statistical significance of the combination effects

## Fig 1. LOXO-783 has additive effect in SOC combinations *in vitro*

**LOXO-783 as single agent is efficacious in ESR1-mutant and SOC-resistant breast cancer cells**




**LOXO-783 is additive in combination with a SERD or abemaciclib**



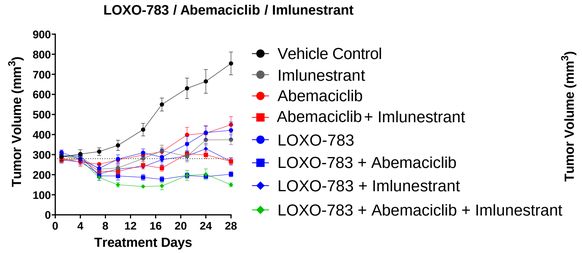

| Absolute $IC_{50}$ values (nM) | | | | |
|---|---|---|---|---|
| Cell Line | LOXO-783 | Abemaciclib | Fulvestrant | Imlunestrant |
| T47D Parental | 1.68 | 7.2 | 0.02 | 0.16 |
| T47D ESR1 D538G +/+ | 0.7 | 6.8 | 0.08 | 0.46 |
| T47D ESR1 D538G +/- | 1.96 | 8.8 | 0.03 | 0.4 |
| Abemaciclib Resistant | 1.89 | >2000 | 19.44 | 31.02 |
| Abemaciclib/ Fulvestrant Resistant | 3.12 | >2000 | 32.07 | 31.24 |

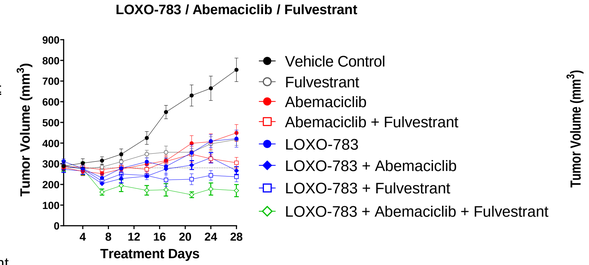
Values are FBS adjusted. LOXO-783 Fraction Unbound (FU): 0.035, Abemaciclib FU: 0.40, Fulvestrant FU: 0.01, Imlunestrant FU: 0.02

Combination Index (CI) >2 demonstrated antagonism, >0.5 to <2 CI additivity, and <0.5 CI synergy. CI was calculated for each percentage activity and plotted for each combination. n=4

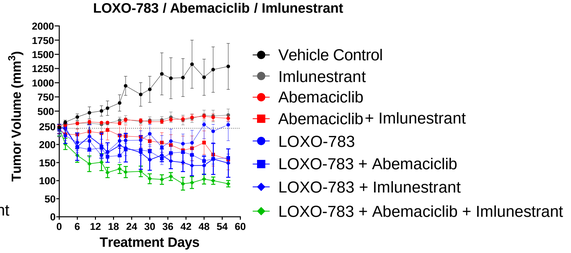
## Fig 2. LOXO-783 enhances efficacy of SOC agents in double or triple combinations *in vivo*

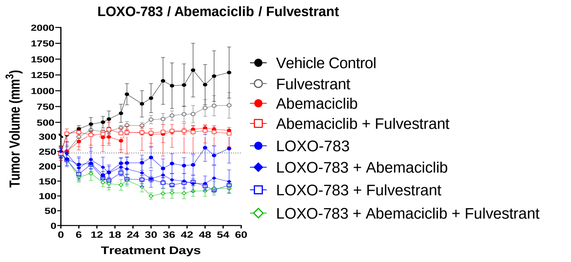
**T47D xenograft (H1047R+/-, ER+, PR+, HER2-)**




**PDX (H1047R/D350G+/-, ESR1 D538G+/-, ER+, PR+, HER2-)**



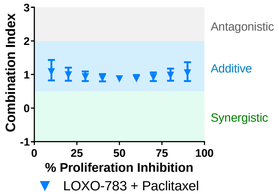

T47D cells and CTG-1260 PDX tumor fragments were implanted in NOD/SCID/gamma and athymic nude mice, respectively. Estrogen pellets were added to T47D model. CTG-1260 PDX was derived from a patient who had progressed on letrozole and taselisib. All treatments were tolerated by mice. Data are mean ± SEM. p<0.01 compared to vehicle control or single agent treatment. Dosing – Imlunestrant 5 mg/kg QD, Abemaciclib 50 mg/kg QD, Fulvestrant 5 mg/animal Q7D, LOXO-783 37.5 mg/kg BID in T47D xenografts, 75 mg/kg BID in PDX

## Fig. 3. LOXO-783 boosts paclitaxel efficacy in TNBC xenograft

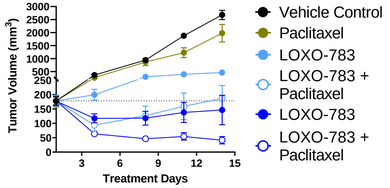
**CAL-148 (H1047R/D350N+/-, TNBC) with LOXO-783 + Paclitaxel**

| Absolute $IC_{50}$ values (nM) | | |
|---|---|---|
| Cell Line | LOXO-783 | Paclitaxel |
| CAL-148 | 27.1 | 1.97 |

Values are FBS adjusted. LOXO-783 Fraction Unbound (FU): 0.035, Paclitaxel FU: 0.68




**CAL-148 (H1047R/D350N+/-, TNBC)**




CAL-148 cells were implanted in NOD SCID mice and treated with compounds at indicated doses. All treatments were tolerated by mice. Data are mean ± SEM. p<0.01 compared to vehicle control or single agent treatment. For *in vitro* studies, CI was calculated for each percentage activity and plotted for each combination. n=4. Dosing – Paclitaxel 10 mg/kg IV QW , LOXO-783 75 mg/kg BID (●/○) or 125 mg/kg BID (●/○)

## Conclusions

- LOXO-783 shows promising additive effects for anti-tumor efficacy when combined with SOC treatments in breast cancers harboring the PI3Kα H1047R mutation (as single or double mutations) in both HR+ and triple negative settings
- LOXO-783 is efficacious in ESR1-mutant as well as in abemaciclib and abemaciclib / fulvestrant double-resistant models
- PIKASSO-01 is an ongoing Phase 1 trial of LOXO-783 alone or in combination with anticancer therapies (NCT05307705). See poster P-OT3-08-01

**References**
1. Meyer DS. *et al* 2011 *Cancer Res* 71: 4344-4351
2. Castel P. *et al* 2021 *Nat Cancer* 2: 587-597
3. Nunnery SE, Mayer IA. 2019 *Ann Oncol* 30(Suppl_10): x21-x26
4. Klippel A. *et al.* 2021 Mol *Cancer Ther* 20 (12_Supplement): P142