# OKI-219 enhances activity of SOC therapies and drives combination responses in pre-clinical models of PI3Kα$^{H1047R}$ breast cancer

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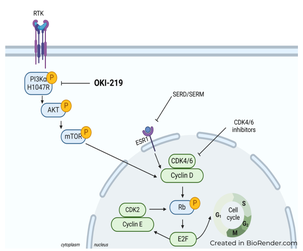
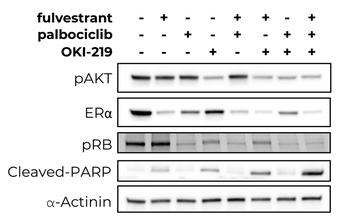
## OKI-219 is a potent & highly selective inhibitor of PI3Kα$^{H1047R}$

- PIK3CA is the most frequently mutated oncogene in cancer - found in approximately 13% of human cancers[1]
- OKI-219 is a PI3Kα$^{H1047R}$-selective inhibitor with greater than 100-fold selectivity for PI3Kα$^{H1047R}$ over PI3Kα$^{WT}$[2]
  - Directly targeting the PI3Kα$^{H1047R}$ mutation has potential to achieve greater target coverage while sparing inhibition of WT-PI3K, thus improving efficacy without on-target toxicity
- OKI-219 is active as a single agent in breast tumor models that have the PI3Kα$^{H1047R}$ mutation[2]
  - Active at low doses in xenograft models (<25 mg/kg per day)
  - Active in tumors heterozygous for PI3Kα$^{H1047R}$[2]
  - High selectivity *in vivo*: No on-target toxicity at doses >15-fold above those that drive tumor regressions
  - OKI-219 has superior preclinical activity compared to alpelisib at well-tolerated and clinically-achievable doses
  - OKI-219 shows high safety margins that support development in populations excluded by prior PI3Ki
- OKI-219 is brain penetrant and active in pre-clinical models of CNS disease[3]

## The triplet combination of OKI-219 + SERD + CDK4/6i drives enhanced anti-tumor activity



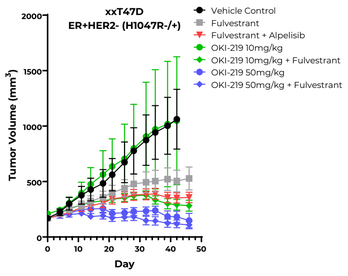



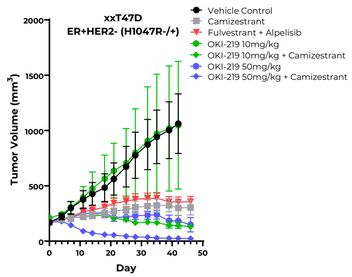

Inhibiting PI3K signaling, ER signaling and CDK4/6 signaling blocks three key signaling nodes which drive cell cycle progression (left) which leads to increases in cell death markers such as cleaved PARP (right).

[1] Millis SZ et al. JAMA Oncol 2016;2(12):1565-73. [2]Taylor MA. SABCS. 2023. [3]Strait AA. AACR. 2024.


## OKI-219 shows strong combination activity in doublet with SERDs and in triplet with SERD + CDK4/6 inhibitors

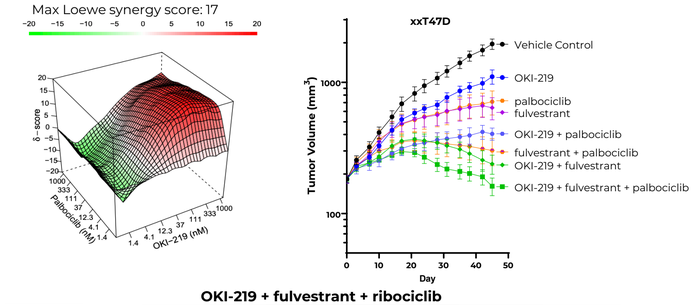
- ***In vivo* OKI-219 shows anti-tumor activity with fulvestrant or camizestrant**



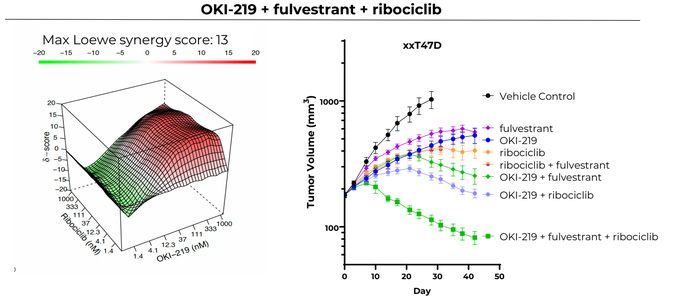




- ***In vitro* OKI-219 shows synergy with fulvestrant + CDK4/6**
- ***In vivo* OKI-219 shows anti-tumor activity with fulvestrant + CDK4/6**

**OKI-219 + fulvestrant + palbociclib**




**OKI-219 + fulvestrant + ribociclib**

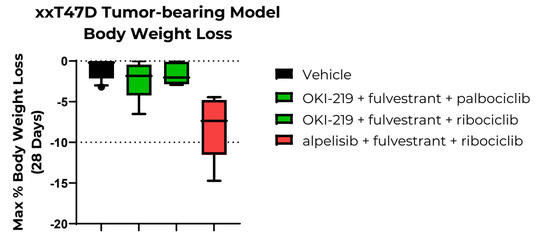



- **Investigation of OKI-219 with additional SERDs, CDKi, HER2i & other novel agents is ongoing**

*Top - In vivo* tumor volume after treatment with OKI-219 dosed PO QD as indicated as monotherapy or in combination with fulvestrant (5mg/dose SC QW) or camizestrant (10mg/kg PO QD) compared to fulvestrant + alpelisib (20mg/kg PO QD). Bottom - *In vitro* 7-day proliferation assay (left). T47D cells were dosed with combination of OKI-219 + fulvestrant + palbociclib, or ribociclib. Fulvestrant was dosed at 10nM, while concentrations of OKI-219 or the CDK4/6 inhibitors (palbociclib or ribociclib) were dosed in 3-fold dilutions. Loewe synergy scores were generated using Synergy Finder. *In vivo*, xxT47D (T47D cells passaged 2x through Balb/c mice) tumor volume (right) after OKI-219 + fulvestrant + CDK4/6 (palbociclib or ribociclib) treatment as indicated. Dosing – OKI-219 25mg/kg PO QD, fulvestrant 5mg/mouse SC QW, palbociclib 10mg/kg PO BID, ribociclib 75mg/kg PO QD alone or in combination, n=6/group, error bars indicate -/+ SEM.

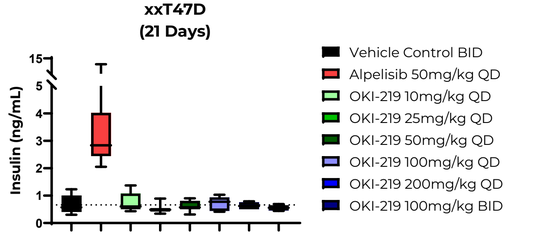
## OKI-219 is well-tolerated and does not induce metabolic changes

**OKI-219 is well-tolerated in triplet combinations**




- **OKI-219 shows no body weight loss compared to vehicle**
- **Alpelisib is not well tolerated in combination**

**OKI-219 does not affect markers of hyperglycemia**



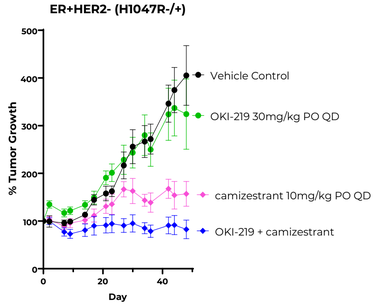

- **OKI-219 does not show any changes in insulin at 200mg/kg/day, a dose that is 8X higher than doses that induce strong activity in combinations**

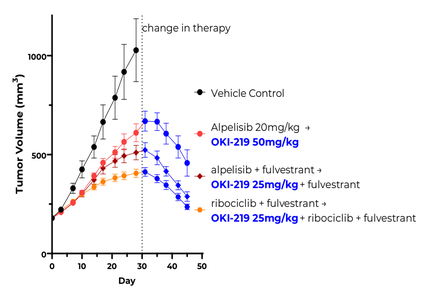
Maximum body weight loss measurements from xxT47D tumor-bearing animals over a 28-day dosing period with triplet combinations. Dosing: OKI-219 25mg/kg, alpelisib 20mg/kg PO QD, fulvestrant 5mg/mouse SC QW, palbociclib 10mg/kg PO BID, ribociclib 75mg/kg PO QD alone or in combination, n=6/group, error bars indicate -/+ SEM (left). Insulin measured at 1 hr post dose after 21 days of dosing in Balb/c nude xxT47D tumor-bearing mice, error bars indicate -/+ SEM (right).

## OKI-219 combinations are active in breast cancer models that have progressed on other therapies

**CTG-1260 PDX**

- PI3Kα double-mutated: H1047R, D350G
- Additional mutations of interest:
  - ESR1mut, PTEN LoF
- Patient responded then progressed on:
  - AI (anastrozole, letrozole)
  - SERD (fulvestrant)
  - PI3Ki+AI (taselisib + letrozole)
  - Chemo (capecitabine)




CTG-1260 PDX model taken from a patient with an ER+HER2- tumor that contained additional mutations of interest (PIK3CA D350G, ESR1, and one copy of PTEN LoF). The patient had responded, then progressed on AI (anastrozole, letrozole), SERD (fulvestrant), PI3Ki+AI (taselisib + letrozole), and chemo (capecitabine). n=6 animals/group (left). xxT47D tumors were treated for 30 days as indicated, then alpelisib was replaced with OKI-219 or OKI-219 was added to ribiociclib + fulvestrant. (right). Error bars indicate -/+ SEM.

## Summary

- OKI-219 shows synergy, inducing regressions in combination with SERD + CDK4/6 inhibitors
  - Informs the potential for exploring triplet combinations in the clinic in earlier lines of therapy
- High selectivity drives safety: No on-target toxicity at doses well above those needed for tumor regressions
- OKI-219 restores combination antitumor activity in models that progress on prior PI3Ki
  - Drives regressions in models that are progressing on or were previously treated with PI3Kα inhibitors
- OKI-219 is the only PI3Kα$^{H1047R}$-selective molecule in the clinic
- PIKture-01 Phase 1 clinical trial of OKI-219 is ongoing (NCT06239467). See Poster P3-08-19.