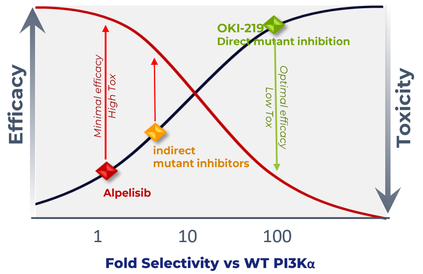
PO3-25-09

OKI-219, a PI3Kα H1047R mutant-selective inhibitor demonstrates efficacy as a single agent and drives combination responses in pre-clinical PI3Kα H1047R mutant breast models

Molly A. Taylor, Qian Zhao, David A. Mareska, Maria Hoh, Yevgeniy Izrayelit, Kevin Litwiler, Mark L. Boys, Rich Woessner, Duncan Walker, James D. Winkler, Jennifer Diamond
OnKure, Inc., 6707 Winchester Circle, Suite 400, Boulder, CO 80301.
San Antonio Breast Cancer Symposium®- December 5-9, 2023

Mutant selective inhibition of PI3Kα H1047R provides greater target coverage without on-target toxicity



- PIK3CA is the most frequently mutated oncogene in cancer - found in approximately 13% of human cancers[1]
- There are 3 hotspot mutations in PI3Kα, with the H1047R mutation in the catalytic domain being the most common, representing approximately one-third of all PI3Kα mutations[2]
  - On-target toxicity associated with inhibition of PI3Kα^{WT} significantly limits efficacy
  - 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 a potent and highly selective inhibitor of PI3Kα H1047R with strong anti-tumor activity *in vivo*

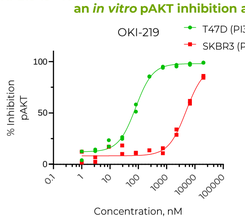
OKI-219 is highly selective for PI3Kα^{H1047R} over for PI3Kα^{WT}

A

Assay	OKI-219	Alpelisib
pAKT Selectivity (H1047R/WT)	106X	1X
T47D pAKT IC50 (nM)	81	111
Proliferation Selectivity (H1047R/WT)	159X	1X
T47D Proliferation IC50 (nM)	97	551

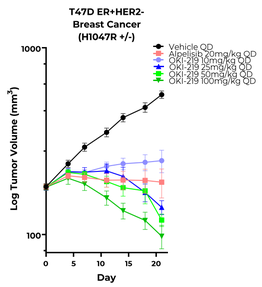
OKI-219 is >100X Selective for PI3Kα^{H1047R} over for PI3Kα^{WT} in an *in vitro* pAKT inhibition assay

B



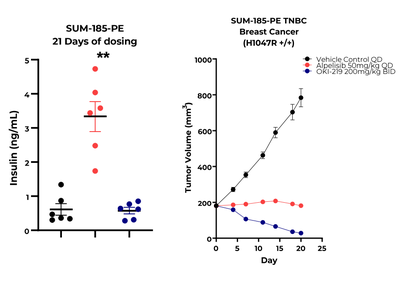
OKI-219 induces tumor regressions at doses as low as 25mg/kg

C



OKI-219 does not induce any increase in insulin, even at doses >15X those that drive *in vivo* activity

D

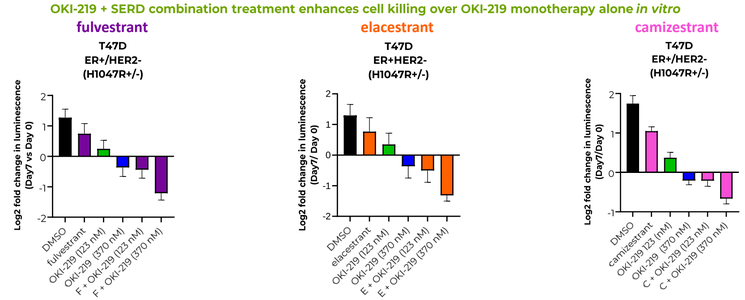


(A) OKI-219 is highly selective (>100X) for PI3Kα^{H1047R} over PI3Kα^{WT} in both pAKT (HTRF) and proliferation (Cell Titer Glo) assays. **(B)** OKI-219 shows selectivity for pAKT inhibition in PI3Kα^{H1047R} expressing T47D cells over PI3Kα^{WT} expressing SKBR3 cells. **(C)** Dose dependent anti-tumor responses in T47D tumors after treatment with OKI-219 compared to alpelisib dosed at the clinically relevant dose, n=9/group. **(D)** Plasma insulin levels in samples taken from SUM-185-PE tumor-bearing mice on day 21 of treatment, 2 hours post dose ** p<0.01 by ANOVA (left). Tumor regressions in SUM-185-PE tumors after treatment with indicated doses of OKI-219 compared to alpelisib dosed at ~2X the clinically relevant dose n=6/group (right). Error bars indicate -/+ SEM.

OKI-219 overcomes PI3Kα mediated resistance to SERDs

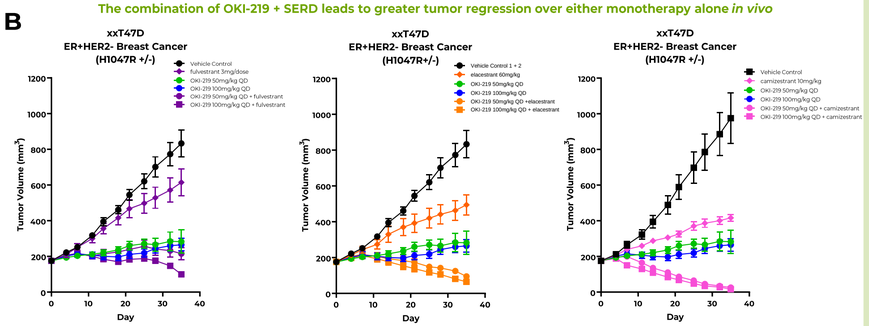
A

OKI-219 + SERD combination treatment enhances cell killing over OKI-219 monotherapy alone *in vitro*



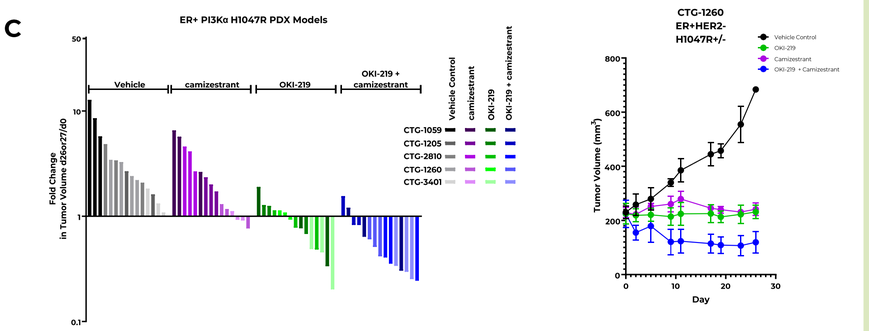
B

The combination of OKI-219 + SERD leads to greater tumor regression over either monotherapy alone *in vivo*



The combination of OKI-219 + the SERD camizestrant leads to greater tumor regression over either monotherapy alone in a panel of ER+ PDX models

C

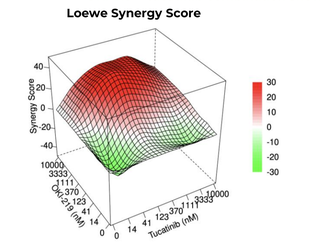


(A) *In vitro* 7-day proliferation assay with combination of OKI-219 and a SERD, fulvestrant (F) 14nM, Elacestrant (E) 123nM, or Camizestran (C) n=6/group. **(B)** *In vivo*, xxT47D (T47D cells passaged through 2x through Balb/c mice) tumor volume after OKI-219 + SERD treatment. **(C)** *In vivo* PDX data across multiple ER+ PI3Kα^{H1047R} PDX models for OKI-219 + Camizestrant, n=3 per treatment group in each model(*left*) and representative ER+ PDX model data from CTG-1260 PDX model, n=3 per treatment group (*right*). Error bars indicate -/+ SEM.

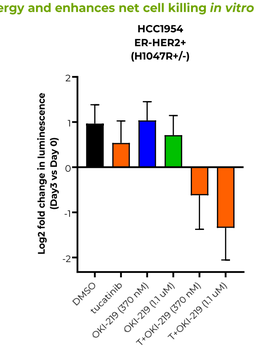
OKI-219 overcomes PI3Kα-mediated resistance to HER2 inhibition

OKI-219 + tucatinib combination shows synergy and enhances net cell killing *in vitro*

A

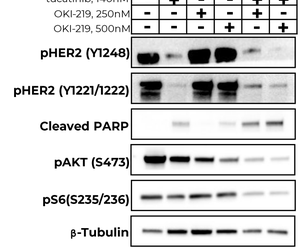


Combination	Synergy Score
tucatinib (123 nM) + OKI-219 (370 nM)	29
tucatinib (123 nM) + OKI-219 (1111 nM)	38



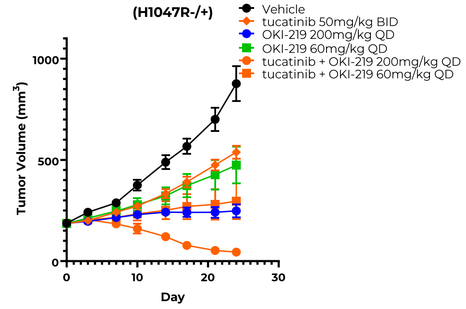
OKI-219 + tucatinib combination enhances inhibition of the PI3K signaling pathway and enhances cell death over either monotherapy alone

B



OKI-219 + tucatinib combination leads to enhanced tumor regression

C



(A) *In vitro* 7-day proliferation assay with combination of OKI-219 and tucatinib (T) 123nM. Loewe synergy score (*left*) and net cell death (*right*). **(B)** Western blot of HCC1954 cells for pHER2, pAKT, pS6 (HER2/PI3K signaling) and cleaved PARP (apoptosis) after 72 hours of OKI-219 + tucatinib. **(C)** *In vivo*, HCC1954 tumor volumes after indicated treatments, n=8/group. Error bars indicate -/+ SEM.

Summary

- OKI-219 is greater than 100-fold selective for PI3Kα^{H1047R} over PI3Kα^{WT}
- OKI-219 is active as a single agent in breast tumor models that have the PI3Kα^{H1047R} mutation
  - Active at low doses in xenograft models (<25 mg/kg per day)
  - Active in tumors heterozygous for PI3Kα^{H1047R}
- High selectivity *in vivo*: No on-target toxicity at doses >15X above those that drive tumor regressions
- OKI-219 shows enhanced activity with SERDs in models of ER+ breast cancer
- OKI-219 shows enhanced activity with HER2 inhibitors in a model of HER2+ breast cancer
- Multi-arm Phase 1 for OKI-219 starting in early 2024

[1] Millis SZ et al. JAMA Oncol 2016;2(12):1565-73 . [2]Tate JG et al. Nucleic Acids Res 2018;47(D1):D941-D947.