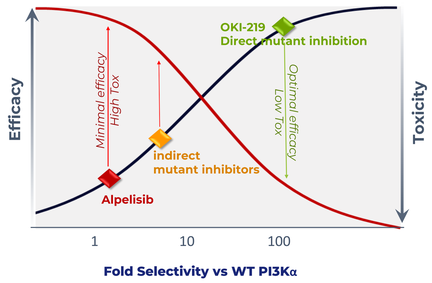
OKI-219 is a brain-penetrant PI3Kα^{H1047R} inhibitor that has increased activity in combination with SERDs

Alexander A. Strait, Molly A. Taylor, Kevin S. Litwiler, Qian Zhao, David A. Mareska, Mark L. Boys, Yevgeniy Izrayelit, Richard Woessner, James D. Winkler. OnKure, Inc., 6707 Winchester Circle, Suite 400, Boulder, CO 80301.

Abstract LB174

Targeting mutant PI3Kα isoforms avoids on-target toxicity of nonselective inhibitors



Assay	OKI-219	Alpelisib
pAKT Selectivity (H1047R/WT)	106X	1X
T47D pAKT IC_{50} (nM)	81	111
Proliferation Selectivity (H1047R/WT)	159X	1X
T47D Proliferation IC_{50} (nM)	97	551

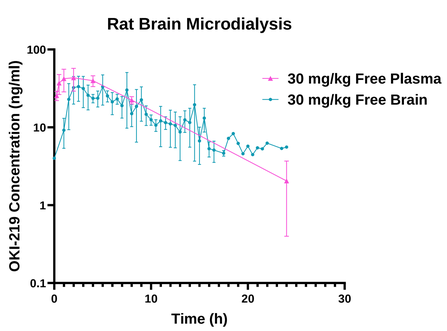
- PIK3CA is mutated in 13% of human cancers, and the H1047R mutation is the most prevalent.[1]
  - PIK3CA H1047R is present in 19% of ER+, 14% of HER2+, and 7% of triple-negative breast cancers.[2]
  - 31% of HER2+ and 15% of ER+/HER2- breast cancer patients develop brain metastases.[3]
- Alpelisib is the only FDA-approved PI3K inhibitor, but it is nonselective and lacks brain penetrance.
  - Dosing is often interrupted or stopped due to toxicity associated with wild-type PI3K inhibition.
  - Clinical trials with alpelisib in combination with selective estrogen receptor degraders (SERDs) suggest that have a synergistic antitumor effect.[4]
- **OKI-219** is a brain penetrant, orally available PI3K inhibitor with greater than 100-fold selectivity for the H1047R mutation over wild-type PI3Kα.

OKI-219 demonstrates brain penetrance across multiple species

A

Species	Tissue	$K_{p,uu}$
Rat	CSF	0.42
Dog	CSF	0.60
Monkey	CSF	0.59

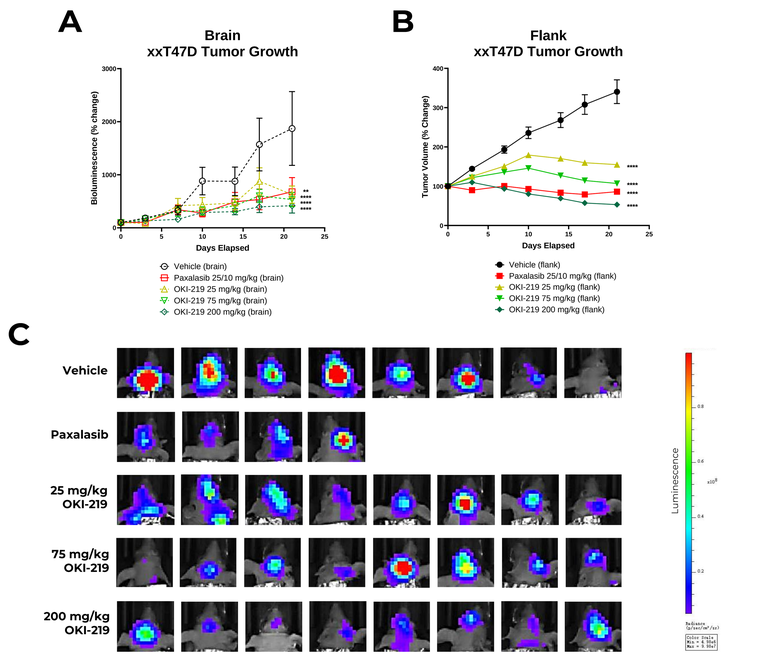
B

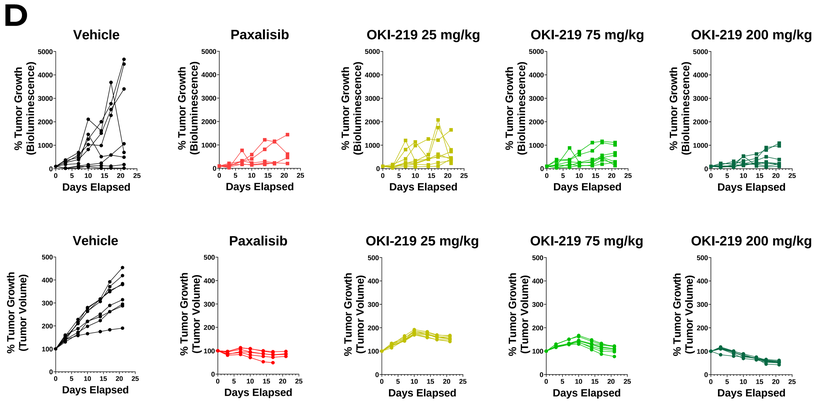


A) Animals (n=3) were dosed once with 10 mg/kg OKI-219 PO, and 2h post-dose drug concentrations were measured and corrected for tissue binding. $K_{p,uu}$ is the ratio between unbound drug in tissue to unbound drug in plasma.

B) Male SD rats (n=3) were fitted with a microdialysis probe in the striatum brain region and dosed once with 30 mg/kg OKI-219 PO. Free brain levels of drug were measured over 24h, and plasma drug levels were measured separately and corrected for plasma protein binding. Relative recovery was determined using an internal standard.[5] Following the absorption phase, the free brain and plasma concentrations were nearly identical, with a $K_{p,uu}$ of 0.68 by AUC ratio.

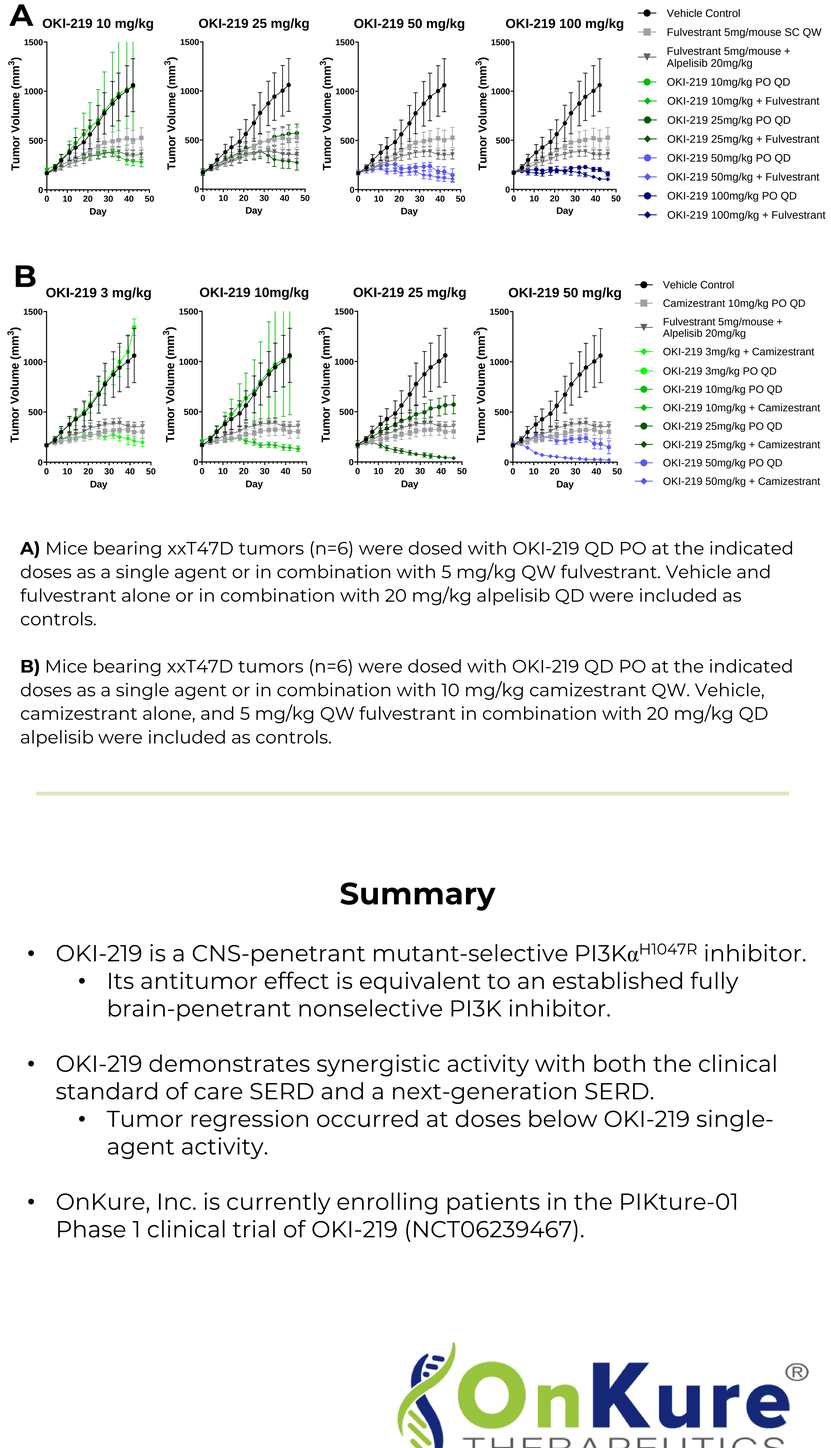
OKI-219 demonstrates intracranial activity in a mouse model of PI3Kα^{H1047R} breast cancer





Mice bearing luciferase-tagged xxT47D-luc tumors both intracranially in the left striatum and subcutaneously on the flank were dosed for 21 days QD PO with vehicle, OKI-219, and paxalasib, a brain-penetrant non-selective PI3K inhibitor (paxalasib dose was reduced from 25 to 10 mg/kg after 3 days of dosing).
A) Mean tumor growth of intracranial tumors at the indicated doses, shown as percent change from start of dosing.
B) Mean tumor growth of subcutaneous tumors at the indicated doses, shown as percent change from start of dosing.
C) Representative luminescence images of intracranial tumors after 21 days of treatment at the indicated doses. Luminescence (color scale) is overlaid against infrared images of the head (grayscale).
D) Individual tumor tracks of intracranial (top) and flank (bottom) tumors.

OKI-219 shows improved activity in combination with multiple SERDs over its use as single agent



A) Mice bearing xxT47D tumors (n=6) were dosed with OKI-219 QD PO at the indicated doses as a single agent or in combination with 5 mg/kg QW fulvestrant. Vehicle and fulvestrant alone or in combination with 20 mg/kg alpelisib QD were included as controls.

B) Mice bearing xxT47D tumors (n=6) were dosed with OKI-219 QD PO at the indicated doses as a single agent or in combination with 10 mg/kg camizestrant QW. Vehicle, camizestrant alone, and 5 mg/kg QW fulvestrant in combination with 20 mg/kg QD alpelisib were included as controls.

Summary

- OKI-219 is a CNS-penetrant mutant-selective PI3Kα^{H1047R} inhibitor.
  - Its antitumor effect is equivalent to an established fully brain-penetrant nonselective PI3K inhibitor.
- OKI-219 demonstrates synergistic activity with both the clinical standard of care SERD and a next-generation SERD.
  - Tumor regression occurred at doses below OKI-219 single-agent activity.
- OnKure, Inc. is currently enrolling patients in the PIKture-01 Phase 1 clinical trial of OKI-219 (NCT06239467).

[1] cBioportal. [2] cBioportal, METABRIC (2021). [3] Kuksis et al., *Neuro. Oncol.* (2021) 23(6):894-904. [4] Andre et al., *Ann. Oncol.* (2021) 32(2):208-217. [5] Chefer et al., *Curr. Protoc. Neurosci.* (2009) Unit 7.1.

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