Preliminary results from PIKture-01, a First-in-Human Study of OKI-219, a mutant selective inhibitor of PI3Kα^{H1047R}, in mutant selected solid tumors including breast cancer

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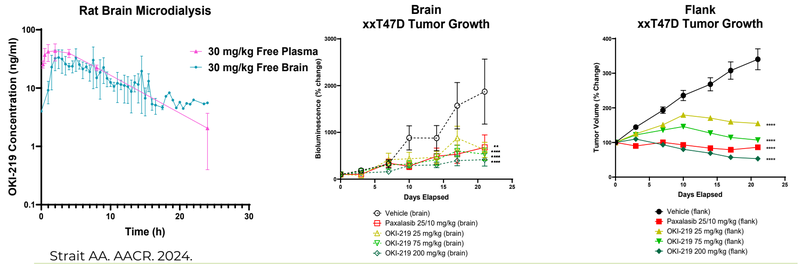
Overview

- PI3Kα is one of the most commonly mutated oncogenes, found in approximately 13% of human cancers and 29% of breast cancer[1]
- Currently approved PI3Kα inhibitors target both wild-type and mutant forms, leading to significant on-target toxicities, including hyperglycemia, rash, fatigue and diarrhea[2,3]
- OKI-219, is a potent, brain penetrant, oral, highly mutant-selective PI3Kα^{H1047R} inhibitor
- OKI-219 is highly active in preclinical models of PI3Kα^{H1047R}-mutated cancer, including models of CNS disease, without the toxicities associated with wild-type inhibition
- We hypothesize OKI-219, as a highly selective PI3Kα^{H1047R} inhibitor may achieve greater mutant target coverage with a wider therapeutic window compared to less-selective PI3Kα inhibitors

OKI-219 is Brain Penetrant & Active in Models of CNS disease



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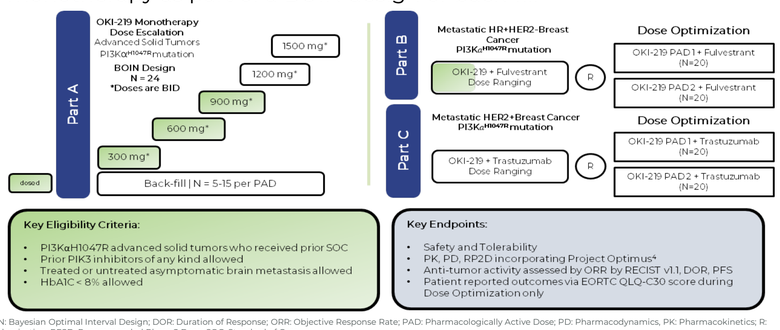
Study Design

- PIKture-01 (OKI-219-101) is a Phase 1a/b, open-label, multicenter, dose-escalation and expansion study designed to evaluate the safety, tolerability, PK, PDx, and efficacy of OKI-219 as monotherapy in advanced PI3Kα^{H1047R}-mutated solid tumors and in combination with fulvestrant or trastuzumab in patients with advanced or metastatic PI3Kα^{H1047R}-mutated breast cancer
- As of October 28th, 2024, 17 patients were treated across 3 dose levels in monotherapy as part of a BOIN design or back-fill



Key Eligibility Criteria:

- PI3KαH1047R advanced solid tumors who received prior SOC
- Prior PIK3 inhibitors of any kind allowed
- Treated or untreated asymptomatic brain metastasis allowed
- HbA1C < 8% allowed

Key Endpoints:

- Safety and Tolerability
- PK, PD, RP2D incorporating Project Optimus*
- Anti-tumor activity assessed by ORR by RECIST v1.1, DOR, PFS
- Patient reported outcomes via EORTC QLQ-C30 score during Dose Optimization only

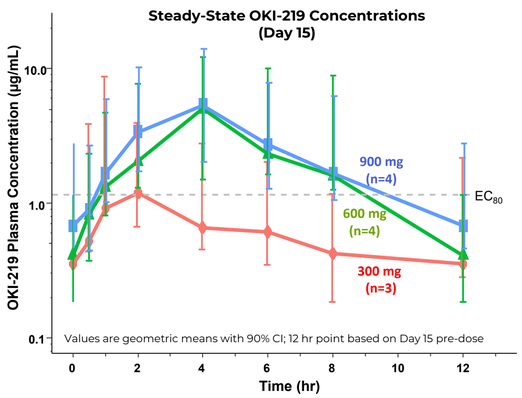
BOIN: Bayesian Optimal Interval Design; DOR: Duration of Response; ORR: Objective Response Rate; PAD: Pharmacologically Active Dose; PD: Pharmacodynamics, PK: Pharmacokinetics; R: Randomization; RP2D: Recommended Phase 2 Dose; SOC: Standard of Care.
NCT:06239467

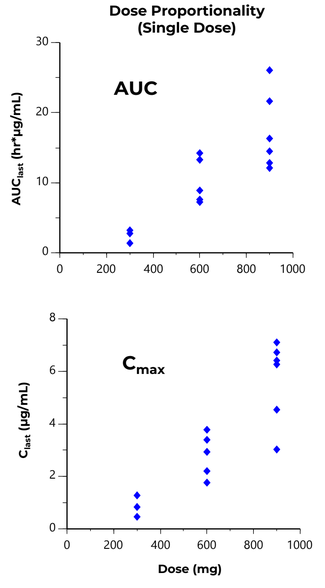
Demographics

Demographic	300 mg BID n = 3	600 mg BID n = 8	900 mg BID n = 6	Total n = 17
Age, med(range), yr	69(53,69)	67(52,81)	59(46,77)	61(46,81)
Female, n(%)	1 (33%)	7 (88%)	6 (100%)	14 (82%)
Male, n(%)	2 (67%)	1 (13%)	0 (0%)	3 (18%)
ECOG 0, n(%)	0 (0%)	3 (38%)	4 (67%)	7 (41%)
ECOG 1, n(%)	3 (100%)	5 (71%)	2 (33%)	10 (63%)
Prior Metastatic Therapies median (range)	3(3,9)	2(1,8)	4(2,9)	3(1,9)
Cancer Type, n(%)				
Breast (BR) HR+/HER2-	2 (67%)	6 (75%)	3 (50%)	11 (65%)
Breast (BR) HR±/HER2+	0 (0%)	0 (0%)	2 (33%)	2 (12%)
Colon	1 (33%)	1 (13%)	0 (0%)	2 (12%)
Squamous Cell (SCC)	0 (0%)	1 (13%)	0 (0%)	1 (6%)
Triple Negative Breast (TNBC)	0 (0%)	0 (0%)	1 (17%)	1 (6%)
Prior mTOR/PI3Kα/AKT inhibitor, n(%)	1 (33%)	4 (50%)	5 (83%)	10 (59%)
Prior CDK4/6 inhibitor, n(%)	2 (67%)	6 (75%)	3 (50%)	11 (65%)

Pharmacokinetics

- 900 mg BID steady-state exposures show near-continuous coverage of the in vivo free fraction corrected pAKT EC_{80} in the T47D xenograft model
  - Single dose and D15 steady-state OKI-219 plasma PK was evaluated at 300, 600, and 900 mg BID continuous dosing
  - OKI-219 is rapidly absorbed with modest accumulation
  - Exposures increase with increasing dose





Steady-State OKI-219 PK Estimates

Parameter	300 mg BID	600 mg BID	900 mg BID
T_{max} (hr)	2.0	4.0	3.0
C_{max} (µg/mL)	1.47	5.33	5.94
AUC_{tau} (hr*µg/mL)	7.55	26.0	30.5

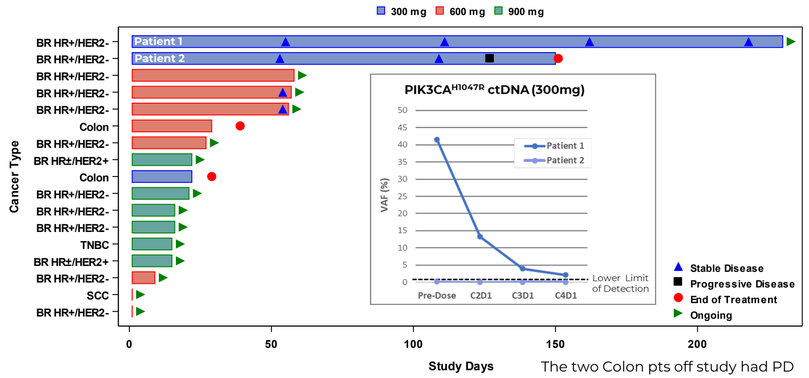
Values are geometric means except for T_{max} which is median

Treatment Related Adverse Events

Preferred Term	300 mg BID n = 3 Grade 1	600 mg BID n = 8 Grade 1	900 mg BID n = 6 Grade 1	ALL Pts n=17 Grade 1
Diarrhoea	0 (0%)	3 (38%)	1 (17%)	4 (24%)
Nausea	0 (0%)	1 (13%)	1 (17%)	2 (12%)
Pruritus	1 (33%)	1 (13%)	0 (0%)	2 (12%)
Anaemia	0 (0%)	1 (13%)	0 (0%)	1 (6%)
Fatigue	0 (0%)	1 (13%)	0 (0%)	1 (6%)

- OKI-219 is well-tolerated across all doses
- Adverse events were mild and infrequent
- Only Grade 1 TRAEs were observed across all dose levels
  - No hyperglycemia, stomatitis, or rash observed at any dose
- No DLT's observed
- No dose interruptions, delays, reductions, or discontinuations for any AEs

Time on Treatment



The two Colon pts off study had PD

Summary

- OKI-219 shows dose-dependent increases in exposure
- Steady state exposure at 900 mg BID is consistent with near continuous coverage of the in vivo EC_{80} for pAKT inhibition
- The safety profile is consistent with that expected for a highly mutant-selective inhibitor with only a low rate of Grade 1 TRAEs
  - No hyperglycemia, rash, or stomatitis observed at any dose
- Efficacy data are immature in this ongoing dose-escalation study
  - 13/14 patients at doses ≥600 mg BID remain on study
  - 2/3 patients at 300 mg showed prolonged stable disease
    - Sustained >95% reduction in PIK3CA^{H1047R} ctDNA in 300 mg BID patient who remains on study after >7 months
- Part B, fulvestrant plus OKI-219 600mg BID in combination, is currently dosing
- Additional combination arms are planned

[1]Millis, S.Z., et al., JAMA Oncol, 2016. 2(12): p. 1565-1573. [2]Narayan, P., et al., Clin Cancer Res, 2021. 27(7): p. 1842-1849. [3]Shields, M., et al. Oncotarget, 2020. 11(42): p. 3793-3799.