OnKure® THERAPEUTICS

San Antionio Breast Cancer Symposium Investor Call

December 10, 2024

Legends

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties of OnKure Therapeutics, Inc. ("OnKure" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations and plans regarding OnKure's product candidates and programs, including OKI-219; OnKure's ability to advance additional programs; and the expected milestones and timing of such milestones, including for OKI-219 and its discovery programs. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," "may," "plan," "potentially" "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: OnKure's limited operating history; the significant net losses incurred since inception; the ability to raise additional capital to finance operations; the ability to advance product candidates through preclinical and clinical development; the ability to obtain regulatory approval for, and ultimately commercialize, OnKure's product candidates; the outcome of preclinical testing and early clinical trials for OnKure's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements and the potential that the outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials; OnKure's limited resources; the risk of adverse events, toxicities or other undesirable side effects; potential delays or difficulties in the enrollment or maintenance of patients in clinical trials; the decision to develop or seek strategic collaborations to develop OnKure's current or future product candidates in combination with other therapies and the cost of combination therapies; OnKure's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition OnKure faces in discovering, developing, or commercializing products; the ability to attract, hire, and retain highly skilled executive officers and employees; the ability of OnKure to protect its intellectual property and proprietary technologies; the scope of any patent protection OnKure obtains or the loss of any of OnKure's patent protection; developments relating to OnKure's competitors and its industry, including competing product candidates and therapies; reliance on third parties, contract manufacturers, and contract research organizations; legislative, regulatory, political and economic developments and general market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in documents that OnKure files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

OKI-219 Clinical Update – PIKture-01

- Preliminary safety, tolerability, and pharmacokinetic data from the FIH Trial of OKI-219
  - OKI-219 was well tolerated across all doses with no hyperglycemia and only Grade 1 TRAEs reported
  - No dose interruptions, delays, reductions, or discontinuations were reported
  - Initial patient data show exposures of OKI-219 exceeding exposures associated with robust antitumor activity in preclinical models
- Data support the initiation of Part 1b to evaluate OKI-219 in combination with fulvestrant; first patient dosed
- Mature single agent and initial fulvestrant combination data expected in 2H-2025

Pipeline Updates

The aim of OnKure's discovery engine is to deliver highly selective drug candidates that preserve wild-type PI3Kα while effectively targeting the majority of PI3Kα-mutated cancers

- **Pan-Mutant Program**
  - Broadened expectations of the next-generation program beyond PI3Kα^{H1047} to target all the most common PI3Kα mutations (H1047R, E545K and E542K)
  - Pan-mutant candidate expected to be nominated in 1H 2025
- **Helical Domain / E-mutant Program**
  - Mutant-specific approach targeting the E545K and E542K mutations
  - Development candidate expected to be announced in 2026

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

Alexander Spira[1], Andreas Varkaris[2], Seock-Ah Im[3], Peter Kabos[4], Ramon Yarza[5], Yeon Hee Park[6], Kevin Litwiler[7], Guy Gammon[7], Amy Heim[7], Jud Williams[7], Brian Tunquist[7], Sayali Upasham Lewis[7], Molly A. Taylor[7], Sascha Strait[7], Robbie Alton[7], Duncan Walker[7], Samuel Agresta[7]

[1]Next Oncology, Fairfax, VA; [2]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [3]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [4]University of Colorado Medical Center, Denver, CO; [5]START Madrid, Madrid, Spain; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [7]OnKure Inc., Boulder

San Antonio Breast Cancer Symposium® | December 10-13, 2024

PI3Kα and OKI-219

- PI3Kα is one of the most commonly mutated oncogenes, found in approximately 13% of human cancers and 29% of breast cancer

- Currently approved PI3Kα inhibitors target both wild-type and mutant forms, leading to significant on-target toxicities, including hyperglycemia, rash, fatigue and diarrhea

- **OKI-219, is a potent, brain-penetrant, oral, highly mutant-selective PI3Kα^{H1047R} inhibitor**

PIKture-01 Study Design

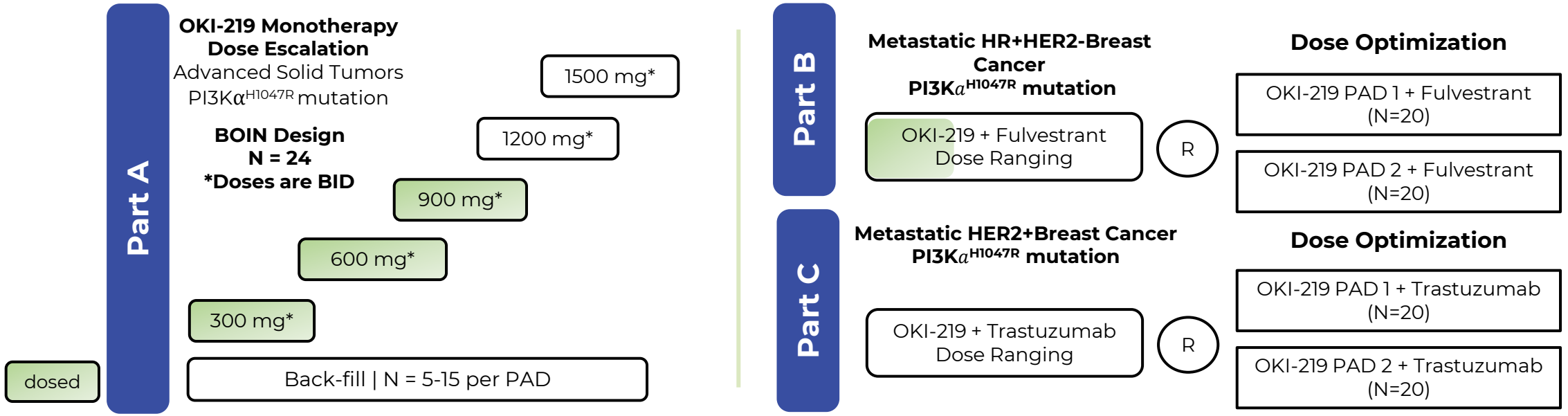
- PIKture-01 (OKI-219-101): Phase 1a/b, open-label, multicenter, dose-escalation and expansion study

- 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 28, 2024, 17 patients were treated across three dose levels in monotherapy as part of a BOIN design or back-fill**

PIKture-01 Study Design

As of October 28, 2024



Key Eligibility Criteria:

- PI3Kα^{H1047R} 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[1]
- 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; PFS: Progression Free Survival; PAD: Pharmacologically Active Dose; PD: Pharmacodynamics, PK: Pharmacokinetics; R: Randomization; RP2D: Recommended Phase 2 Dose; SOC: Standard of Care. NCT:06239467

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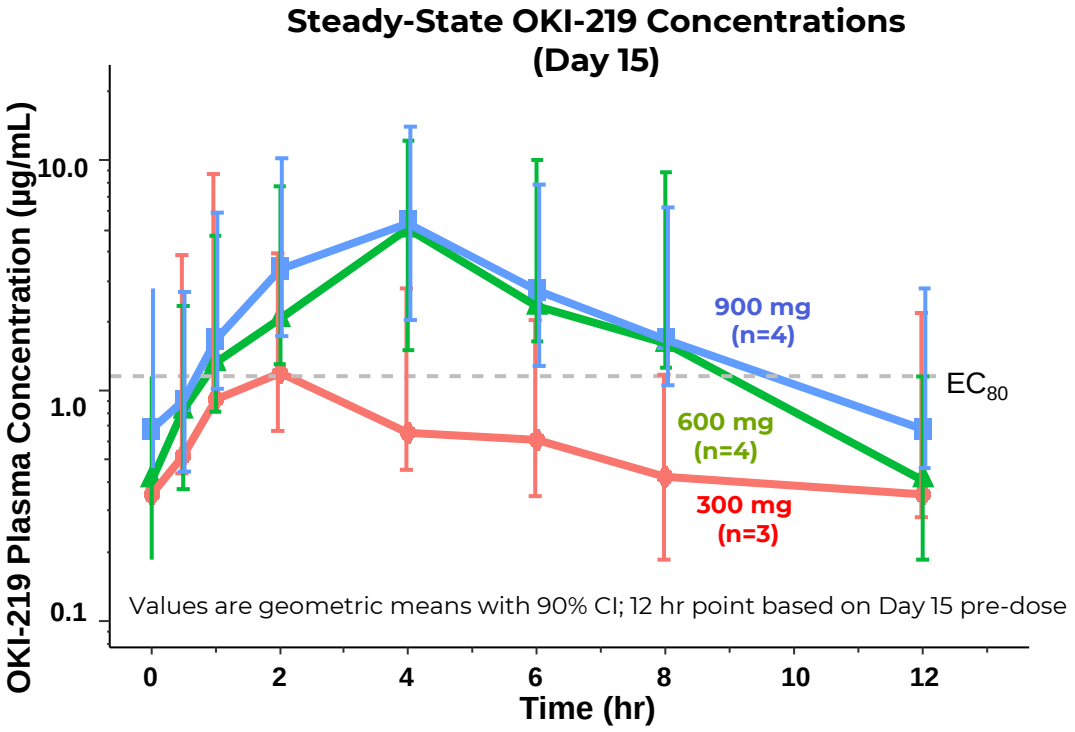
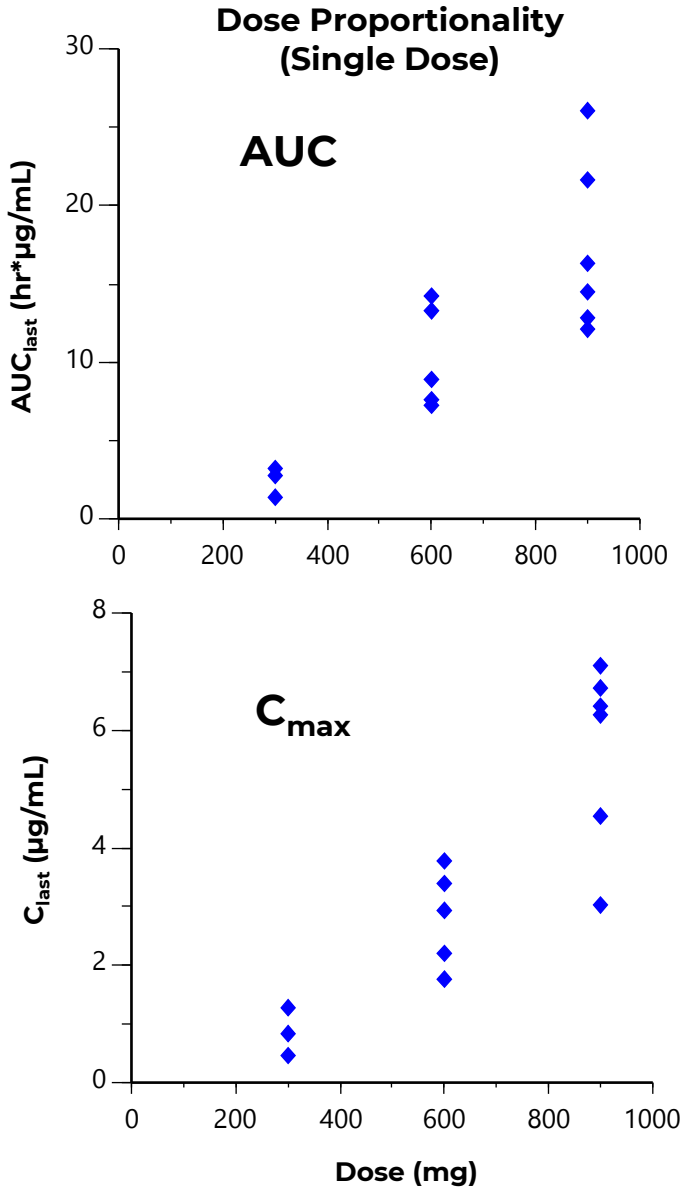
1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases

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: Highly Developable Candidate Profile





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

CI: Confidence Interval

- Steady-state exposures (900 mg BID) show near-continuous coverage
- Single dose, dose proportional exposure (C_{max}, AUC)
- OKI-219 is rapidly absorbed with modest accumulation

Only Grade 1 TRAEs Observed Across All Dose Levels

No Hyperglycemia, Stomatitis, or Rash Observed at Any Dose

	300 mg BID n = 3	600 mg BID n = 8	900 mg BID n = 6	ALL Pts n=17
Preferred Term	**Grade 1**	**Grade 1**	**Grade 1**	**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%)

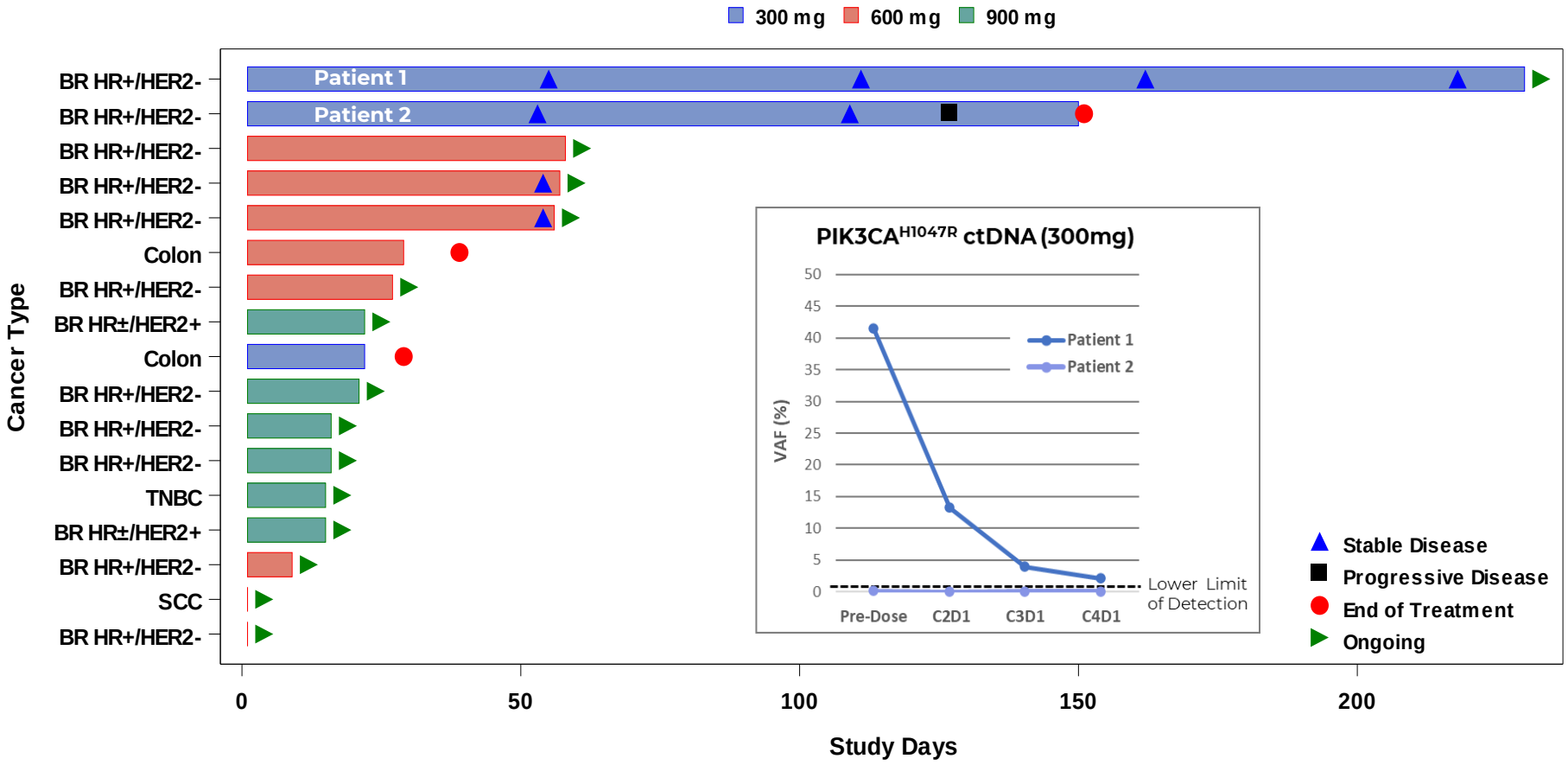
Data cut-off - October 28, 2024

- OKI-219 is well tolerated across all doses
- Adverse events were mild and infrequent
- No DLTs observed
- No dose interruptions, delays, reductions, or discontinuations for any AEs

TRAEs: Treatment Related Adverse Events; DLT: Dose Limiting Toxicities; AEs: Adverse Events

Time on Treatment

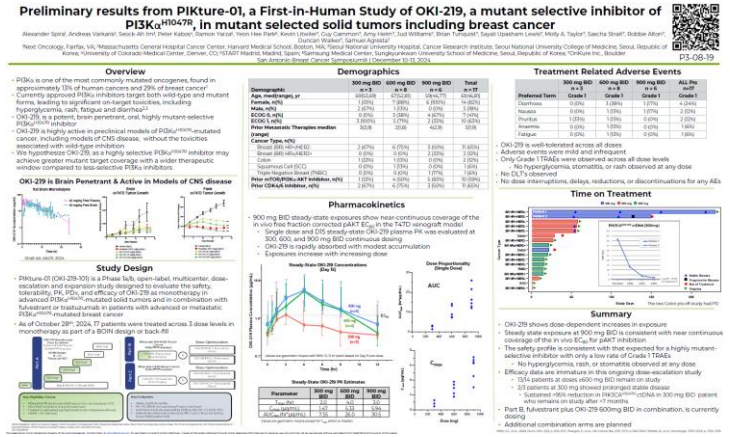
As of October 28, 2024

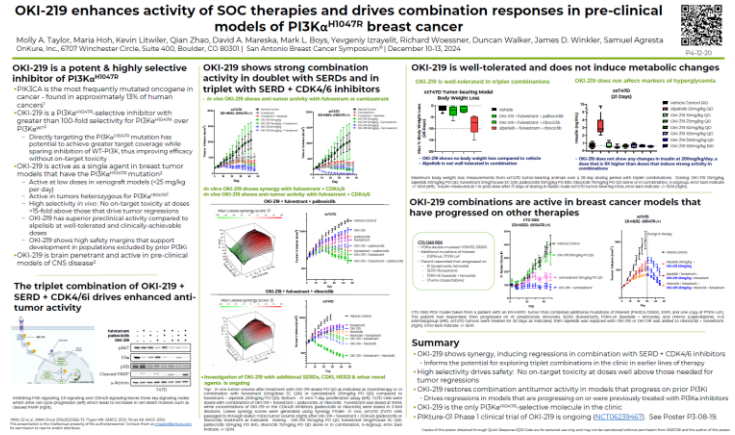


- 13/14 patients at doses ≥600 mg BID remain on study
- 2/3 patients at 300 mg showed prolonged stable disease
- Sustained >95% reduction in PIK3CA^{H1047R} ctDNA in 300 mg BID patient who remains on study after >7 months

Summary

- Data to date supports the continued development of OKI-219
- The fulvestrant combination arm has been initiated (OKI-219 | 600 mg BID)
- Mature single agent and initial fulvestrant data expected in 2H-2025





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