A phase 1/2, first-in-human study of AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), as a monotherapy and in combination for patients with advanced solid tumors, including hormone receptor–positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer and cyclin E1 (CCNE1)-amplified solid tumors: preliminary safety and efficacy results

Alberto J. Montero, MD, MBA[1]; Manish R. Patel, MD[2]; Alex Spira, MD, PhD[3]; Babar Bashir, MD, MS[4]; Debra L. Richardson, MD[5]; Sanjay Thamake, PhD, MBA[6]; Denise Trone, MS[6]; Bogdan Veresh, MD[6]; Patricia LoRusso, DO, PhD (hc)[7]

[1]University Hospitals/Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio, US; [2]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, Florida, US; [3]NEXT Oncology-Virginia, Fairfax, Virginia, US; [4]Sidney Kimmel Comprehensive Cancer Center at Thomas Jefferson University, Philadelphia, Pennsylvania, US/Sarah Cannon Research Institute, Nashville, Tennessee, US; [5]Stephenson Cancer Center/Sarah Cannon Research Institute, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, US; [6]Avenzo Therapeutics, San Diego, California, US; [7]Yale Medicine, New Haven, Connecticut, US

FOR ADDITIONAL INFORMATION

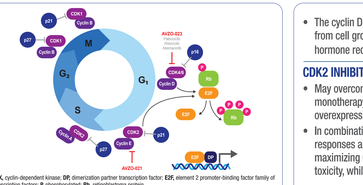
NCT05867251

Poster# 2206

KEY TAKEAWAYS

- **AVZO-021 is a potential best-in-class, once-daily, oral CDK2 inhibitor with high selectivity against CDK1**
- **Initial phase 1 data show an encouraging tolerability profile with low incidence and severity of gastrointestinal and hematologic adverse events as monotherapy and in combination with fulvestrant, allowing patients to continue therapy for a prolonged treatment period**
- **AVZO-021 monotherapy at doses ≥90 mg QD achieved continuous CDK2 target coverage and significantly reduced ctDNA. Tumor reductions were observed over time, including multiple confirmed responses in patients with HR+/HER2- breast cancer and CCNE1-amplified solid tumors. Tumor reductions were also observed in patients treated with fulvestrant combination, with 1 patient ongoing with confirmed partial response. All responding patients continue on treatment**
- **Enrollment in monotherapy backfill and combination cohorts is ongoing**
- **AVZO-021 is planned to be studied in combination with AVZO-023, a highly potent, selective oral CDK4 inhibitor, which is currently enrolling patients with HR+/HER2- mBC in combination with fulvestrant (NCT06998407)[a]**

BACKGROUND



CDK, cyclin-dependent kinase; DP, dimerization partner transcription factor; E2F, element 2 promoter-binding factor family of transcription factors; P, phosphorylated; Rb, retinoblastoma protein.

Figure 1. Role of CDK2 inhibition in abnormal cell cycle progression[1,2]

- The cyclin D1-CDK4/6-pRB pathway drives the cell cycle transition from cell growth (G1) to DNA synthesis (S) and is often deregulated in hormone receptor-positive (HR+) breast cancer[1,2]

CDK2 INHIBITION

- May overcome abnormal cell cycle regulation when used as monotherapy for tumors driven by CCNE1 amplification or cyclin E overexpression that promotes CDK2-cyclin activity[3]
- In combination with a selective CDK4i may lead to more durable responses and disease control in HR+/HER2- breast cancer by maximizing CDK4 target coverage and sparing CDK6-associated toxicity, while targeting a key mechanism of resistance[4,5]

AVZO-021 is highly potent and selective against CDK2

Table 1. AVZO-021 is a potent and selective CDK2 inhibitor that spares activity of other CDKs, specifically CDK1

	BIOCHEMICAL					NANOBRET				
	POTENCY (nM)	SELECTIVITY				POTENCY (nM)	SELECTIVITY			
CDK2i	CDK2(IC_{50})	CDK1	CDK4	CDK6	CDK9	CDK2(IC_{50})	CDK1	CDK4	CDK6	CDK9
AVZO-021	1.4	673x	341x	884x	5,314x	0.2[a]	535x	3,945x	2,060x	>50,000x
PF-07104091	5.0	228x	615x	738x	>2,000x	2.0	65x	3,637x	>5,000x	>5,000x

NanoBRET: HEK-293T cells were transfected with canonical CDK/cyclin pairs as in the enzyme assay and treated with compound and a tracer for 1 hour before measurements were collected.
Enzymatic: Enzymatic assays were conducted using the Caliper assay (ATP concentration, 1 mM). CDK1, CDK2, CDK4, CDK6, CDK7, and CDK9 were in complex with cyclin B1, cyclin E1, cyclin D1, cyclin D3, and cyclin T1, respectively.
[a]Below lower limit of quantification (<0.5 nM).

TRIAL DESIGN

DESIGN

- Single patient accelerated titration (20, 40, 60 mg) followed by Bayesian Optimal Interval (BOIN) of AVZO-021 administered orally once daily (QD) in 28-day cycles
- Response evaluation by RECIST v1.1

PRIMARY OBJECTIVES

- Evaluate safety/tolerability and determine RP2D/MTD

SECONDARY OBJECTIVES

- To assess preliminary anti-tumor activity
- To characterize PK parameters of AVZO-021

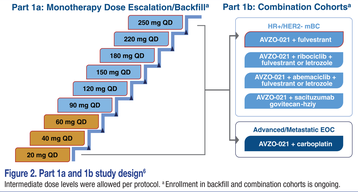


Figure 2. Part 1a and 1b study design[6]
Intermediate dose levels were allowed per protocol. [a]Enrollment in backfill and combination cohorts is ongoing.

Key Inclusion Criteria:

Age ≥18 years	Fulvestrant combination: HR+/HER2- mBC previously treated with at least 1 prior CDK4/6 inhibitor and endocrine therapy
ECOG 0-1	Measurable disease by RECIST v1.1
Histologically or cytologically confirmed locally advanced or metastatic solid tumors	Adequate hepatic, renal, and hematologic function
≤2 prior cytotoxic chemotherapy regimens for advanced/metastatic disease[b]	

Key Exclusion Criteria:

Prior CDK2 inhibitors	Radiation therapy within 7 days (whole brain radiotherapy within 4 weeks)
Investigational agents or anticancer therapy within 2 weeks or 5 half-lives	Active uncontrolled bacterial, viral, fungal, or parasitic infections, including untreated hepatitis B/C or HIV
Major surgery within 4 weeks	
Active CNS metastases	

RESULTS

Data presented here for patients in Part 1a dose escalation and Part 1b combination with fulvestrant as of data cut-off date of October 10, 2025:

- Monotherapy: Patients with advanced solid tumors dosed with AVZO-021 at 20 to 250 mg QD (n=35)
- Assessment of MTD/RP2D in monotherapy cohort is ongoing
- Fulvestrant combination: Patients with HR+/HER2- mBC (n=10) dosed with AVZO-021 at 150 mg QD (n=6) and 200 mg QD (n=4)
- Median (range) follow-up time for patients (N=45) is 5.39 months (0.03+ to 10.81+)

Efficacy-evaluable population:

- Monotherapy: Patients treated at ≥150 mg QD with HR+/HER2- breast cancer (n=14) or CCNE1-amplified solid tumors (n=5), with at least 1 post-baseline scan (n=19)
- Fulvestrant combination: Patients with at least 1 post-baseline scan (n=9)

Table 2. Demographics and baseline characteristics

	Safety Population Monotherapy and Fulvestrant Combination Cohorts (N=45)	Efficacy Population (N=28)[a]		
		HR+/HER2- Breast Cancer Monotherapy (n=14)	CCNE1-Amplified Solid Tumors Monotherapy (n=5)	Fulvestrant Combination (n=9)
Age, years				
Median (min, max)	63 (33, 79)	61 (40, 75)	65 (53, 73)	67 (54, 79)
Sex, n (%)				
Female	43 (95.6)	14 (100.0)	5 (100.0)	9 (100.0)
Baseline ECOG Score, n (%)				
0	19 (42.2)	7 (50.0)	1 (20.0)	3 (33.3)
1	26 (57.8)	7 (50.0)	4 (80.0)	6 (66.7)
Tumor Type, n (%)				
Breast	32 (71.1)	14 (100.0)	1 (20.0)	9 (100.0)
Ovarian/fallopian tube	5 (11.1)	0	3 (60.0)	0
Endometrial/uterine	3 (6.7)	0	1 (20.0)	0
Other[b]	5 (11.1)	0	0	0
Prior Systemic Therapy in Metastatic Setting				
No. of Prior Lines				
Median (min, max)	3.0 (0, 11)	2.5 (1, 5)	3.0 (1, 4)	4.0 (2, 8)
Type of Prior Therapy, n (%)				
Chemotherapy	28 (62.2)	5 (35.7)	4 (80.0)	7 (77.8)
Prior CDK4/6i	29 (64.4)	14 (100.0)	NA	9 (100.0)
>1 prior CDK4/6i	9 (20.0)	4 (28.6)	NA	3 (33.3)
Hormonal therapy	29 (64.4)	14 (100.0)	NA	9 (100.0)
Other therapy[c]	22 (48.9)	4 (28.6)	4 (80.0)	3 (33.3)

[a]Patients treated at ≥150 mg QD with HR+/HER2- breast cancer or CCNE1-amplified solid tumors, with ≥1 post-baseline scan. [b]Other tumor types include n=1 patient each of colorectal, esophageal, stomach, head and neck, and adrenal cortical cancers. [c]Including immunotherapy, monoclonal antibody, antibody-drug conjugates, and other agents.

Table 3. AVZO-021 safety and tolerability

TEAEs occurring in ≥10% patients by grade

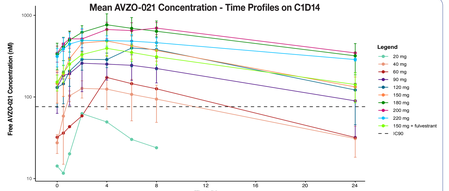
	AVZO-021 Monotherapy and Fulvestrant Combination (N=45)			
	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3[a] n (%)	All Grade n (%)
Any TEAE, n (%)	7 (15.6)	19 (42.2)	14 (31.1)	40 (88.9)
Nausea	13 (28.9)	6 (13.3)	1 (2.2)	20 (44.4)
Fatigue	10 (22.2)	7 (15.6)	0	17 (37.8)
Anemia	3 (6.7)	5 (11.1)	7 (15.6)	15 (33.3)
Vomiting	10 (22.2)	2 (4.4)	1 (2.2)	13 (28.9)
Alopecia	8 (17.8)	0	0	8 (17.8)
Platelet count decreased	4 (8.9)	1 (2.2)	3 (6.7)	8 (17.8)
Cough	4 (8.9)	2 (4.4)	0	6 (13.3)
Decreased appetite	3 (6.7)	3 (6.7)	0	6 (13.3)
Diarrhea	4 (8.9)	1 (2.2)	1 (2.2)	6 (13.3)
Edema peripheral	4 (8.9)	1 (2.2)	1 (2.2)	6 (13.3)
Arthralgia	5 (11.1)	0	0	5 (11.1)
Dizziness	4 (8.9)	1 (2.2)	0	5 (11.1)
Gastroesophageal reflux disease	2 (4.4)	3 (6.7)	0	5 (11.1)
Neutrophil count decreased	1 (2.2)	2 (4.4)	2 (4.4)	5 (11.1)
Urinary tract infection	0	4 (8.9)	1 (2.2)	5 (11.1)

- No patients had TEAEs leading to treatment discontinuation
- 7 patients reported 11 TEAEs leading to dose reduction:
  - Grade 2: fatigue (n=2), thrombocytopenia (n=1), neutrophil count decreased (n=1), vaginal infection (n=1), oral mucositis (n=1), diarrhea (n=1)
  - Grade 3: anemia (n=2), neutrophil count decreased (n=1), platelet count decreased (n=1)
- Anemia present at baseline in 5 of 7 patients with on-treatment Grade 3 anemia:
  - 3 patients had Grade 1 anemia, and 2 patients had Grade 2 anemia at baseline
- DLTs:
  - Monotherapy: 1 DLT at 250 mg QD: Grade 3 syncope secondary to Grade 2 anemia. Patient continues treatment at 200 mg QD without recurrence of event[b]
  - Fulvestrant combination: 1 DLT at 200 mg QD: Grade 4 thrombocytopenia leading to drug interruption in patient with bone metastasis; subsequent scan confirmed disease progression

[a]1 patient at 120 mg QD reported Grade 4 hypovolemic shock (not related) and 1 patient at 200 mg QD AVZO-021 + fulvestrant reported Grade 4 platelet count decrease (related). No patient reported a Grade 5 TEAE. [b]Dose reduction post data cut-off date.

Figure 3. AVZO-021 PK profile

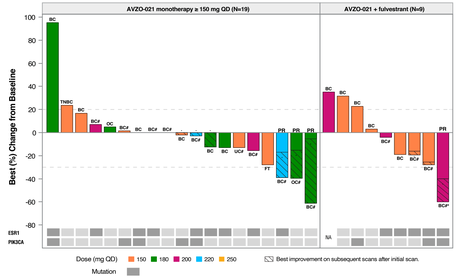
- Mean half-life was 14 hours. AVZO-021 plasma exposures increased with dose in an approximately dose-proportional manner
- Continuous CDK2 target coverage was achieved at doses ≥90 mg QD
- AVZO-021 had flat PK profile with low C_{max} to C_{min} ratio, minimizing toxicity potential
- Fulvestrant combination: Comparable exposures of AVZO-021 between monotherapy and combination treatment at 150 mg QD, indicating no drug-drug interaction



Concentration data for 250 mg QD dose level and 200 mg QD AVZO-021 + fulvestrant was not available for C1D14 at data cut-off date.

Figure 4. AVZO-021 showed encouraging efficacy in HR+/HER2- mBC and in CCNE1-amplified solid tumors

- At doses of ≥150 mg for AVZO-021 monotherapy (n=19), multiple confirmed responses (n=3)
  - In HR+/HER2- mBC, 2 responding patients: (1) ESR1wt and (1) ESR1m
  - In CCNE1-amplified ovarian cancer, 1 responding patient
- One confirmed response in HR+/HER2- mBC in combination with fulvestrant[a]
- Many patients showed improved tumor shrinkage over time
- All responding patients remain on treatment



[a]Response confirmed at week 12 after data cut-off date.
#, study treatment ongoing; **BC**, breast cancer (HER+/HER2-); **FT**, fallopian tube cancer (CCNE1-amplified); **NA**, not available; **OC**, ovarian cancer (CCNE1-amplified); **PR**, partial response; **TNBC**, triple negative breast cancer (CCNE1-amplified); **UC**, uterine cancer (CCNE1-amplified).
Three subjects (one each at 150 mg QD, 200 mg QD, and 250 mg QD) with unchanged tumor size post-baseline are indicated in the figure with 0% change.
Data cut-off date 10 October 2025

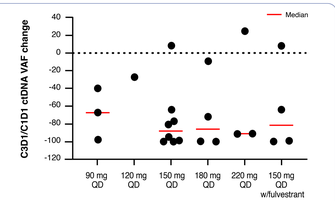
Figure 5. Duration of treatment (N=45)

- Of the 26 patients with HR+/HER2- breast cancer treated at ≥150mg QD:
  - 15 patients remain on treatment
  - 10 patients were on treatment for ≥24 weeks
  - 2 confirmed responses with onset at Weeks 15 and 36
  - 1 confirmed response with onset at Week 7 in fulvestrant combination cohort[a]
- Of the 6 patients with CCNE1-amplified solid tumors treated at ≥150mg QD:
  - 2 patients remain on treatment
  - 2 patients on treatment for ≥24 weeks
  - 1 confirmed response with onset at Week 35
- All responding patients remain on treatment, with 2 for ≥48 weeks

[a]Response confirmed at week 12 after data cut-off date. [b]Efficacy evaluable
ACC, adrenal cortical carcinoma; **BC**, breast cancer (HER+/HER2-); **CRC**, colorectal cancer; **EN**, endometrial cancer; **FT**, fallopian tube cancer (CCNE1-amplified); **HNC**, head and neck cancer; **OC**, ovarian cancer (1 pt at 90 mg QD not CCNE1 amplified); **SC**, stomach cancer; **TNBC**, triple negative breast cancer (CCNE1-amplified); **UC**, uterine cancer (CCNE1-amplified).
Data cut-off date 10 October 2025

Figure 6. AVZO-021 significantly reduced level of ctDNA

- Genomic alterations in circulating tumor DNA (ctDNA) were analyzed using the 74-gene Guardant360 assay with plasma samples at Cycle 1 Day 1 and Cycle 3 Day 1
- Mean variant allele frequency (VAF) of somatic single-nucleotide variants, indels, amplification and fusions was determined
- Significant decreases in ctDNA mean VAF at Cycle 3 Day 1 compared to Cycle 1 Day 1 were observed at ≥90 mg QD monotherapy and at 150 mg QD combination with fulvestrant



The ctDNA analysis for 200 mg AVZO-021+ fulvestrant was not available at data cut-off date.

AVZO-021 PATIENT VIGNETTES

Partial response in a patient with HR+/HER2- mBC

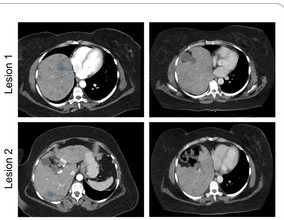
- 50-year-old female with HR+/HER2- metastatic breast cancer treated with 4 prior lines of therapy in the metastatic setting, including anastrozole + leuprolide, letrozole + palbociclib, everolimus + exemestane, leuprolide + fulvestrant
- Target and nontarget lesions in liver

Course of treatment

- Dosed with AVZO-021 180 mg QD
- No Grade ≥3 AEs
- Initial response at Cycle 9 (-36%), which was confirmed at Cycle 12 (-61%) with ongoing partial response
- Patient continues on treatment in Cycle 12

Biomarker response

- At Cycle 3 Day 1, ctDNA reduced by 100% from baseline



Partial response in a patient with CCNE1-amplified ovarian cancer

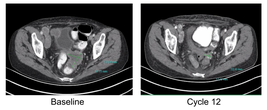
- 69-year-old female with CCNE1-amplified ovarian cancer treated with 3 prior lines of therapy in the metastatic setting, including olaparib, mirvetuximab, bevacizumab + topotecan
- Target lesions in pelvis and nontarget lesions in bone

Course of treatment

- Dosed with AVZO-021 at 180 mg QD reduced to 150 mg QD due to Grade 2 fatigue in Cycle 10
- No Grade ≥3 AEs
- Initial response at Cycle 9 (-40%), which was confirmed at Cycle 12 (-40%) with ongoing partial response
- Patient continues on treatment in Cycle 13

Biomarker response

- At Cycle 3 Day 1, ctDNA reduced by 100% from baseline
- At Cycle 7 Day 1, CA125 was 21 U/mL vs 115 U/mL at baseline



[a]Visit trial in progress poster: Yap T et al. A phase 1/2 study of AVZO-023, a next generation selective cyclin-dependent kinase 4 inhibitor (CDK4i), as a single agent and in combination with AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), and/or endocrine therapy in patients with breast cancer. Poster presented at: SABCS 2025; San Antonio, TX. Poster #2262 *Exceptions include prior ADC treatment, patients with platinum-resistant or refractory ovarian cancer with disease progression on any number of prior lines of treatment, and patients with prior chemotherapy in the adjuvant or neoadjuvant setting >12 months prior to starting AVZO-021 treatment.

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DEFINITIONS

ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; EOC, epithelial ovarian cancer; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; mBC, metastatic breast cancer; MTD, maximum tolerated dose; NA, not applicable; QD, once a day; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event.

PRESENTING AUTHOR CONTACT INFORMATION

Address: Case Western Reserve University; 11100 Euclid Avenue, Lakeside Suite 1200; Cleveland, OH 44106
Email: alberto.montero@uhhospitals.org
Phone: +1 (216) 844-3951

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