A phase 1/2, first-in-human study of AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), as 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: updated safety and efficacy results

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FOR ADDITIONAL INFORMATION

Poster# 208

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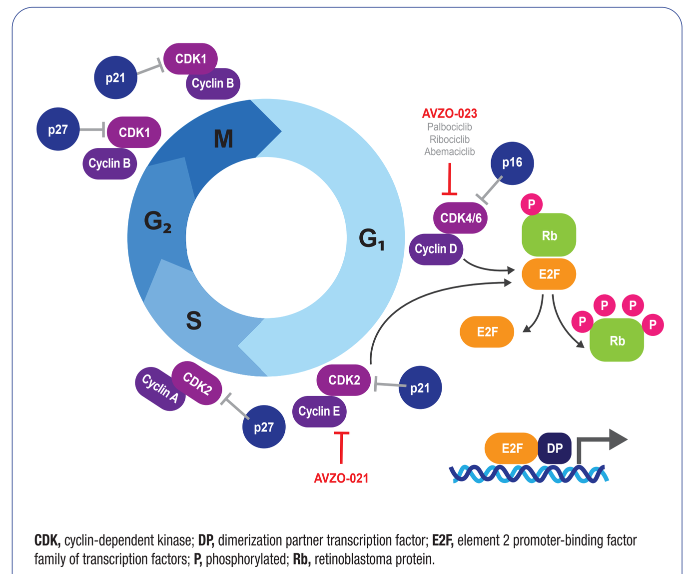
KEY TAKEAWAYS

- **AVZO-021 is a potential best-in-class, once-daily, oral selective CDK2 inhibitor**
- **Updated phase 1 data continue to show low incidence and severity of gastrointestinal and hematologic adverse events, both as monotherapy and in combination with fulvestrant**
- **Tumor reductions including multiple confirmed responses have been observed in heavily pre-treated patients with HR+/HER2- breast cancer treated as monotherapy or in combination with fulvestrant. Median PFS was 5.3 months (95% CI: 1.9, 7.2) for AVZO-021 monotherapy**
- **AVZO-021 is also being studied in patients with HR+/HER2- breast cancer in combination with AVZO-023, a selective oral CDK4 inhibitor, and fulvestrant in an ongoing Phase 1 / 2 study (ORION-1) (NCT06998407)**

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 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]

UNMET NEED

The combination of selective CDK2 and CDK4 inhibitors represents a promising strategy to overcome resistance. AVZO-021 is a more potent and selective CDK2i with a favorable tolerability profile that may enable the combination with a selective CDK4i (AVZO-023) to achieve a sustained and favorable benefit–risk profile for patients.[6]

TRIAL DESIGN

DESIGN

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

PRIMARY OBJECTIVES

- Evaluate safety/tolerability and determine RP2D/MTD

SECONDARY OBJECTIVES

- Assess preliminary anti-tumor activity
- Characterize PK parameters of AVZO-021

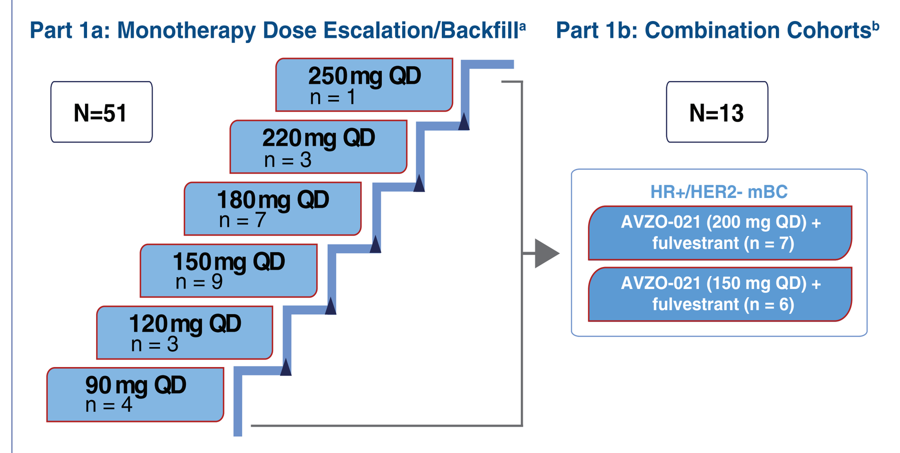


Figure 2. Part 1a and 1b study design[7]

[a]Includes accelerated titration 20-60 mg QD (n=4) and additional backfill patients treated at 100 (n=10) and 200 mg QD (n=10).
[b]Other combination cohorts not depicted in figure.

HER2, human epidermal growth factor receptor 2; **HR+**, hormone receptor-positive; **mBC**, metastatic breast cancer; **QD**, once a day.

Key Inclusion Criteria:

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

Key Exclusion Criteria:

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

[a]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.

RESULTS

Data are presented for patients in Part 1a dose escalation and Part 1b combination with fulvestrant as of data cut-off date of 30 March 2026[a]:

- Monotherapy: Patients with advanced solid tumors dosed with AVZO-021 at 20 to 250 mg QD (n=51)
- Fulvestrant combination: Patients with HR+/HER2- mBC (n=13) dosed with AVZO-021 at 150 mg QD (n=6) and 200 mg QD (n=7)
- Median follow-up time for all treated patients (N=64) is 5.91 months (range: 0.03+, 16.49+)

Efficacy-evaluable population:

- Monotherapy: Patients treated at ≥150 mg QD with HR+/HER2- breast cancer (n=20) or CCNE1-amplified solid tumors (n=6), with at least one evaluable post-baseline scan (n=26)
- Fulvestrant combination: Patients treated at ≥150 mg QD with at least one evaluable post-baseline scan (n=13)

These are updated results from the 49th Annual San Antonio Breast Cancer Symposium (SABCS), held December 8–11, 2026.
[a]Efficacy and disposition data updated as of 07 May 2026.

Table 1. Demographics and baseline characteristics

	Safety Population Monotherapy and Fulvestrant Combination Cohorts (N=64)	Efficacy Population (N=39)[a] HR+/HER2- Breast Cancer Monotherapy (n=20)	Efficacy Population (N=39)[a] CCNE1-Amplified Solid Tumors Monotherapy (n=6)	Efficacy Population (N=39)[a] Fulvestrant Combination (n=13)
Age, years				
Median (min, max)	63.0 (33, 83)	62.5 (37, 75)	67.0 (53, 73)	60.0 (49, 83)
Sex, n (%)				
Female	61 (95.3)	20 (100.0)	6 (100.0)	12 (92.3)
Baseline ECOG Score, n (%)				
0	30 (46.9)	11 (55.0)	2 (33.3)	6 (46.2)
1	34 (53.1)	9 (45.0)	4 (66.7)	7 (53.8)
Tumor Type, n (%)				
Breast	50 (78.1)	20 (100.0)	1 (16.7)	13 (100.0)
Ovarian/fallopian tube	6 (9.4)	0	4 (66.7)	0
Endometrial/uterine	3 (4.7)	0	1 (16.7)	0
Other[b]	5 (7.8)	0	0	0
Prior Systemic Therapy in Metastatic Setting				
No. of Prior Lines				
Median (min, max)	3.0 (0, 11)	2.0 (1, 8)	2.5 (1, 4)	3.0 (2, 8)
Type of Prior Therapy, n (%)				
Chemotherapy	44 (68.8)	8 (40.0)	5 (83.3)	10 (76.9)
Prior CDK4/6i	47 (73.4)	20 (100.0)	NA	13 (100.0)
>1 prior CDK4/6i	12 (18.8)	5 (25.0)	NA	3 (23.1)
Hormonal therapy	47 (73.4)	20 (100.0)	NA	13 (100.0)
Other therapy[c]	30 (46.9)	7 (35.0)	5 (83.3)	2 (15.4)

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

CCNE1, cyclin E1; **CDK**, cyclin-dependent kinase; **ECOG**, Eastern Cooperative Oncology Group; **HER2**, human epidermal growth factor receptor 2; **HR+**, hormone receptor-positive; **NA**, not applicable; **QD**, once a day.

Data cut-off date: 30 March 2026

Table 2. AVZO-021 safety and tolerability
TEAEs occurring in ≥10% patients by grade

	AVZO-021 Monotherapy and Fulvestrant Combination (N=64) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4[a] n (%)	All Grade n (%)
Any TEAE, n (%)	6 (9.4)	28 (43.8)	20 (31.2)	6 (9.4)	60 (93.8)
Nausea	23 (35.9)	9 (14.1)	1 (1.6)	0	33 (51.6)
Fatigue	21 (32.8)	10 (15.6)	0	0	31 (48.4)
Anemia	4 (6.3)	9 (14.1)	12 (18.8)	0	25 (39.1)
Vomiting	15 (23.4)	5 (7.8)	2 (3.1)	0	22 (34.4)
Diarrhea	10 (15.6)	2 (3.1)	1 (1.6)	0	13 (20.3)
Alopecia	12 (18.8)	0	0	0	12 (18.8)
Neutrophil count decreased	2 (3.1)	4 (6.3)	3 (4.7)	2 (3.1)	11 (17.2)
Edema peripheral	8 (12.5)	1 (1.6)	1 (1.6)	0	10 (15.6)
Platelet count decreased	6 (9.4)	1 (1.6)	2 (3.1)	1 (1.6)	10 (15.6)
Arthralgia	7 (10.9)	2 (3.1)	0	0	9 (14.1)
Constipation	7 (10.9)	2 (3.1)	0	0	9 (14.1)
Cough	7 (10.9)	2 (3.1)	0	0	9 (14.1)
Hypokalemia	2 (3.1)	5 (7.8)	2 (3.1)	0	9 (14.1)
Dizziness	7 (10.9)	1 (1.6)	0	0	8 (12.5)
Gastroesophageal reflux disease	3 (4.7)	4 (6.3)	0	0	7 (10.9)
Headache	7 (10.9)	0	0	0	7 (10.9)

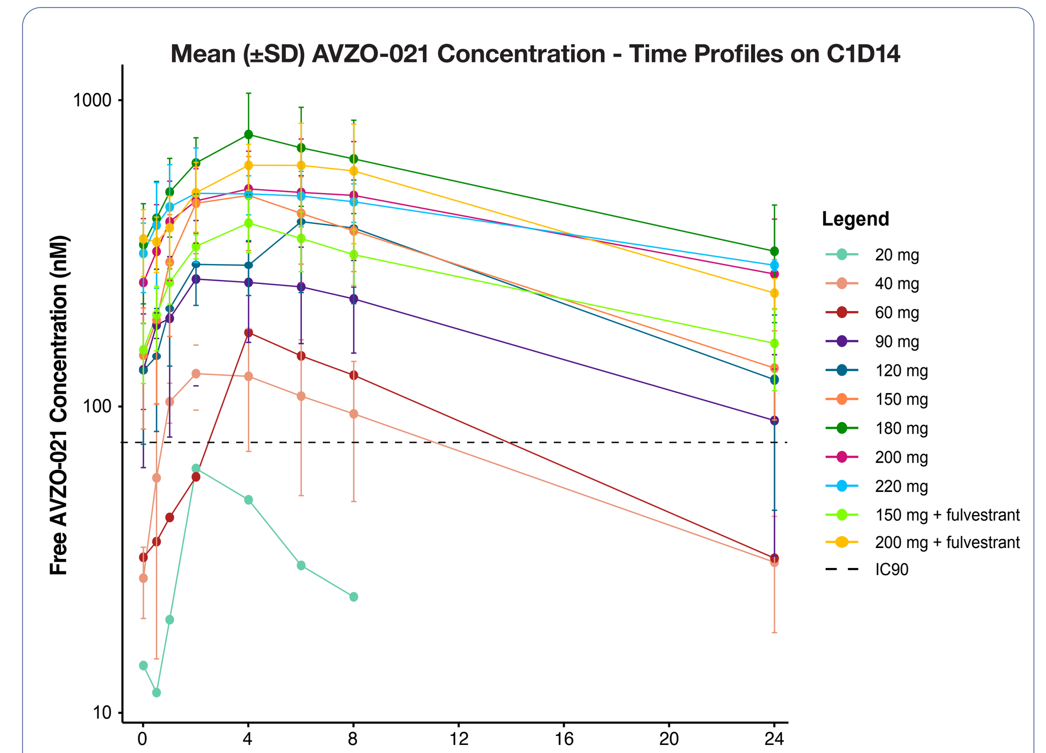
Note: TEAEs by preferred term and maximum grade. [a]Additional Grade 4 events: 1 patient at 120 mg QD with hypovolemic shock (not related), 1 patient at 200 mg QD with cholestatic jaundice (not related) and 1 patient at 200 mg QD with neutropenia (related). [b]One patient discontinued due to Grade 4 neutropenia (related); one patient discontinued due to Grade 4 cholestatic jaundice (unrelated).

No patient reported a Grade 5 TEAE.

QD, once a day; **TEAE,** treatment-emergent adverse event.

- Generally well tolerated
- Most TEAEs were Grade 1 or 2
- Two patients had TEAEs leading to treatment discontinuation[b]
- Most commonly reported TEAEs were nausea, fatigue, anemia, and vomiting
  - Anemia present at baseline in 10 of 12 patients with on-treatment Grade 3 anemia
- 14 patients with TEAEs leading to dose reduction
- Dose-limiting toxicities (DLTs):
  - Monotherapy: 1 DLT at 250 mg QD of Grade 3 syncope
  - Fulvestrant combination: 1 DLT at 200 mg QD of Grade 4 thrombocytopenia

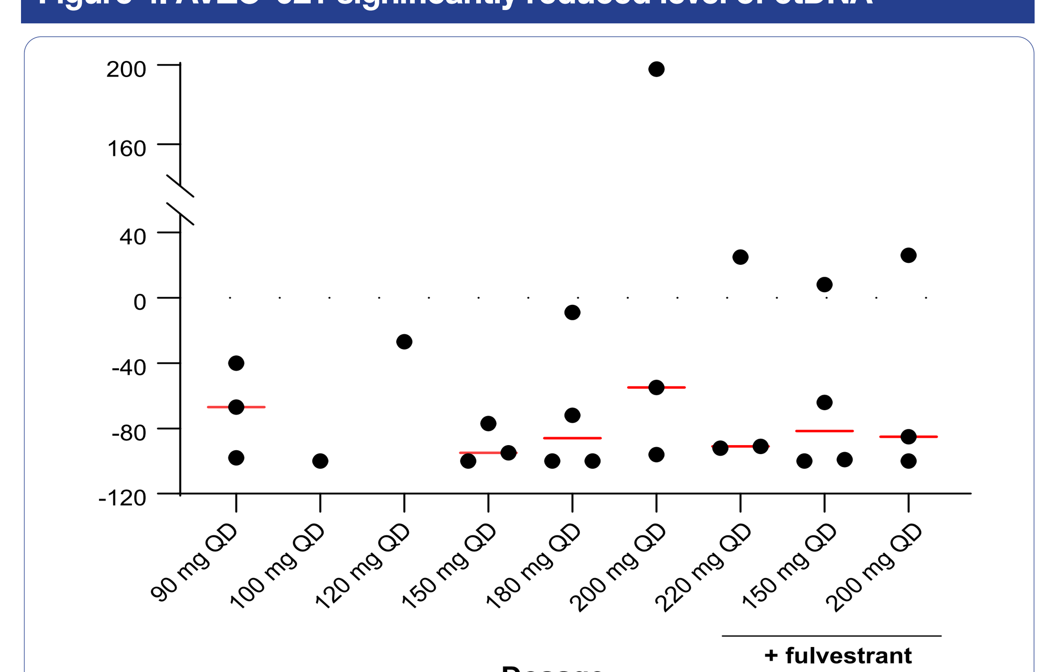
Figure 3. AVZO-021 PK profile



- 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 a 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 and 200 mg QD, indicating no drug-drug interaction
- No food effects were observed in the pilot food effect substudy (10 patients in 100 mg QD backfill cohort)

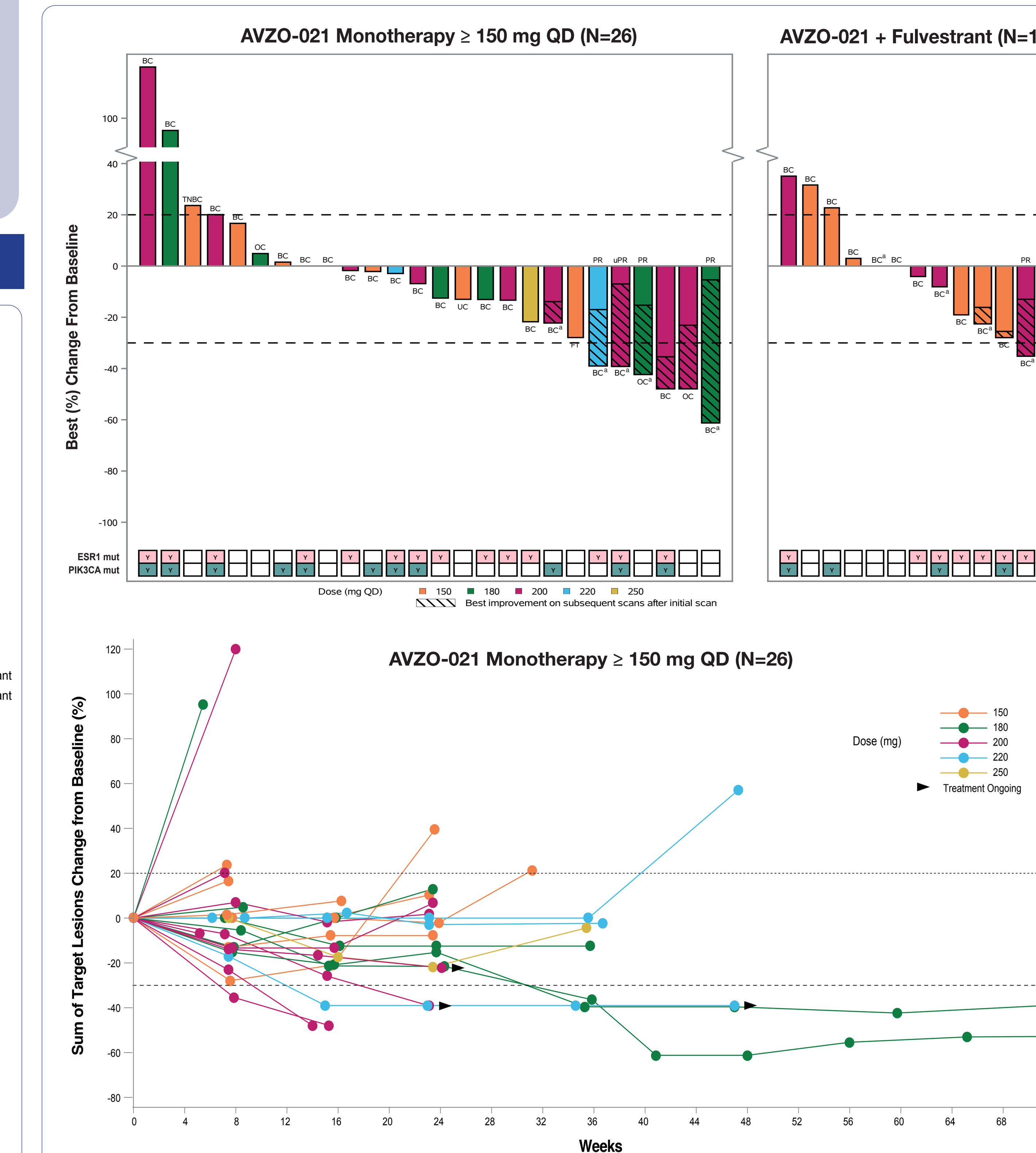
Concentration data for 250 mg QD was not available for C1D14.
CDK, cyclin-dependent kinase; C_{max}, maximum concentration; C_{min}, minimum concentration; **PK**, pharmacokinetics; **QD**, once a day.

Figure 4. 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 and 200 mg QD combination with fulvestrant

Figure 5. AVZO-021 showed encouraging efficacy in HR+/HER2- mBC and in CCNE1-amplified solid tumors



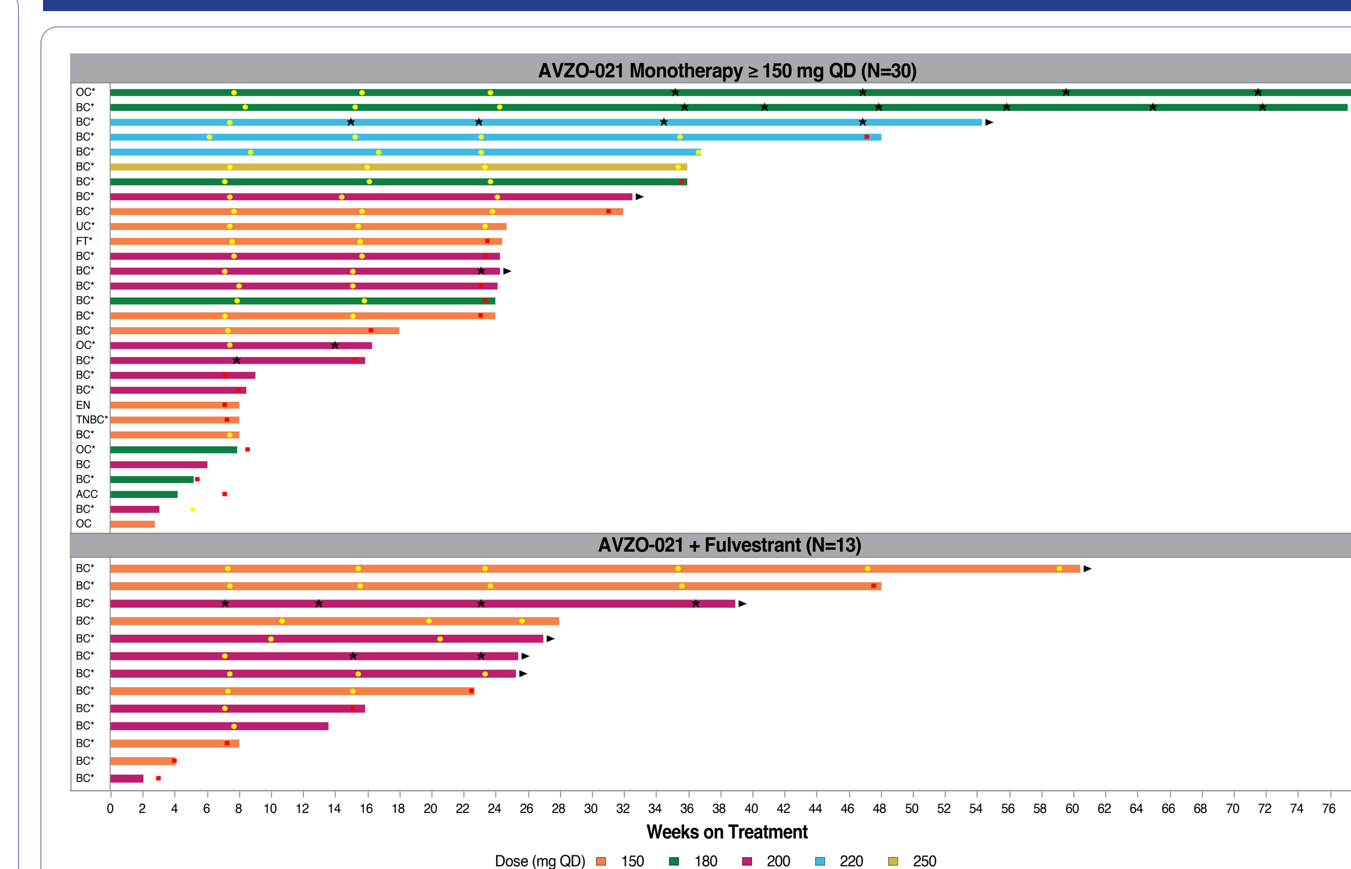
- Across all monotherapy doses, median PFS for all HR+/HER2- mBC patients (n=33) was 5.3 months (95% CI: 1.9, 7.2) with median follow-up time of 8.4 months (range 0.03 to 16.6+)
- The disease control rate[b] for HR+/HER2- mBC efficacy evaluable patients treated with ≥150 mg QD monotherapy (n=20) was 85% (95% CI: 62.1, 96.8)
- Multiple patients had improved tumor shrinkage over time
- All patients with response (PR and uPR) remain on treatment (range: 24.3 - 78.1 weeks)[c]

[a]Study treatment ongoing. [b]Disease control rate is the proportion of subjects with a confirmed best overall response of CR, PR, or SD. [c]An additional patient with HR+/HER2- mBC had uPR at 100 mg QD monotherapy and remains on treatment awaiting a confirmatory scan (not shown on waterfall plot due to dose less than 150 mg QD).

BC, HR+/HER2- breast cancer; **BOR,** best overall response; **CCNE1,** cyclin E1; **CR,** complete response; **ESR1,** estrogen receptor 1; **FT,** CCNE1-amplified fallopian tube cancer; **HER2,** human epidermal growth factor receptor 2; **HR+,** hormone receptor-positive; **mBC,** metastatic breast cancer; **mut,** mutated; **OC,** CCNE1-amplified ovarian cancer; **PD,** progressive disease; **PR,** partial response; **QD,** once a day; **SD,** stable disease; **TNBC,** CCNE1-amplified triple negative breast cancer; **UC,** CCNE1-amplified uterine cancer; **uPR,** unconfirmed partial response; **WT,** wild type.

Data cut-off date 07 May 2026.

Figure 6. Duration of treatment in safety population treated at ≥150 mg QD (N=43)



- All patients with responses (5 PR and 1 uPR awaiting confirmatory scan) remain on treatment, with 3 patients for ≥48 weeks
- Among 34 HR+/HER2- breast cancer patients treated at ≥150 mg QD:
  - 9 patients remain on treatment
  - 20 patients on treatment for ≥24 weeks
- Among 7 CCNE1-amplified solid tumor patients treated at ≥150 mg QD:
  - 1 patient remains on treatment
  - 3 patients on treatment for ≥24 weeks

* Efficacy evaluable. Note: Data cut-off date 07 May 2026. N=21 patients treated with <150 mg QD monotherapy not shown.

ACC: adrenal cortical carcinoma; **BC:** HR+/HER2- breast cancer; **EN:** endometrial cancer; **FT:** CCNE1-amplified fallopian tube cancer; **OC:** CCNE1-amplified ovarian cancer; **TNBC:** CCNE1-amplified triple negative breast cancer; **UC:** CCNE1-amplified uterine cancer

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DEFINITIONS

ADC, antibody-drug conjugate; **CCNE1,** cyclin E1; **CDK,** cyclin-dependent kinase; **CNS,** central nervous system; **ctDNA,** circulating tumor DNA; **ECOG,** Eastern Cooperative Oncology Group; **HER2,** human epidermal growth factor receptor 2; **HIV,** human immunodeficiency virus; **HR+,** hormone receptor-positive; **mBC,** metastatic breast cancer; **MTD,** maximum tolerated dose; **PK,** pharmacokinetics; **QD,** once a day; **RECIST,** Response Evaluation Criteria in Solid Tumors; **RP2D,** recommended phase 2 dose.

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