AVZO-021-1001: A First-in-Human Open-Label, Multicenter Phase 1/2 Dose-Escalation and Expansion Study Evaluating AVZO-021 in Advanced Solid Tumors

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FOR ADDITIONAL INFORMATION

NCT05867251

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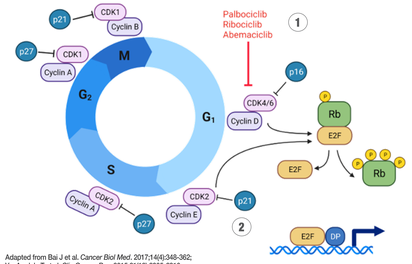
BACKGROUND

- Amplification or overexpression of cyclin E1 (*CCNE1*) in human cancers is associated with resistance to targeted therapies and chemotherapies and poor prognosis.[1] The presence of elevated CDK2 in these tumors, including epithelial ovarian cancer, suggest that CDK2 may be an ideal target[2]
- AVZO-021 is an investigational, reversible, orally available CDK2 inhibitor with nanomolar potency and high selectivity that has shown promising preclinical activity as monotherapy in *CCNE1*-amplified xenograft models and in combination with CDK4/6i in HR+/HER2- breast cancer models[3,4] (Figure 1)
- AVZO-021 is being developed as:
  - Monotherapy to treat patients with *CCNE1*-amplified, solid tumor malignancies
  - Combination therapy in the post-CDK4/6i setting to treat patients with HR+/HER2- mBC and as combination therapy to treat *CCNE1*-amplified EOC

AVZO-021 MECHANISM OF ACTION

Figure 1: Role for CDK2 Inhibition in Abnormal Cell Cycle Progression



Adapted from Bai J et al. *Cancer Biol Med*. 2017;14(4):348-362; VanArsdale T et al. *Clin Cancer Res*. 2015;21(13):2905-2910.

1 The cyclin D1-CDK4/6-pRB axis acts as a checkpoint during the cell cycle transition from cell growth (G1) to DNA synthesis (S). Its deregulation or overexpression induces abnormal cell proliferation[5,6]

2 CDK2 inhibition:

- In combination with a CDK4/6i may lead to more durable responses and disease control in HR+/HER2- breast cancer; may overcome primary and acquired resistance to CDK4/6i[7,8]
- 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]

PRECLINICAL RATIONALE

- In NanoBRET and enzymatic assays, AVZO-021 showed highly selective and potent activity against CDK2 (Table 1)

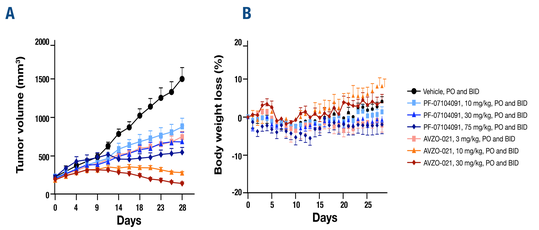
Table 1: AVZO-021 Is a Potent and Selective CDK2 Inhibitor That Spares Activity of Other CDKs

	COMPOUND	CDK2	CDK1	CDK4	CDK6	CDK7	CDK9
NanoBRET ACTIVITY IC_{50} (nM)	AVZO-021	0.2*	107	789	412	5073	>10,000
	PF-07104091	2.0	129	7274	>10,000	8181	>10,000
ENZYMATIC ACTIVITY IC_{50} (nM)	AVZO-021	1.4	942	477	1237	2834	7440
	PF-07104091	5.0	1139	3077	3689	>10,000	>10,000

Top row: 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. **Bottom row:** 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, cyclin H/MAT1, and cyclin T1, respectively.
*Below low limit of quantification (<0.5 nM).

- Treatment of *CCNE1*-amplified ovarian human cancer cells with AVZO-021 inhibited tumor growth with no overt changes in body weight (Figure 2)

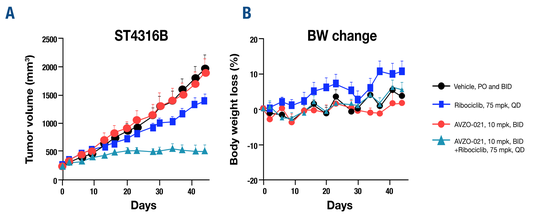
Figure 2: AVZO-021 Exhibited Antitumor Activity in a *CCNE1*-amplified Ovarian Cancer Xenograft Model



(A) Antitumor activity of AVZO-021 and PF-07104091 in OVCAR3 PDX xenograft model. **(B)** Body weight changes in OVCAR3 PDX xenograft mice treated with AVZO-021 or PF-07104091.

- AVZO-021 enhanced the antitumor activity of ribociclib with no overt change in body weight in a CDK4/6i-resistant HR+/HER2- breast cancer PDX model[9]

Figure 3: AVZO-021 and Ribociclib Activity in a CDK4/6i-resistant HR+/HER2- Breast Cancer PDX Model[9,*]

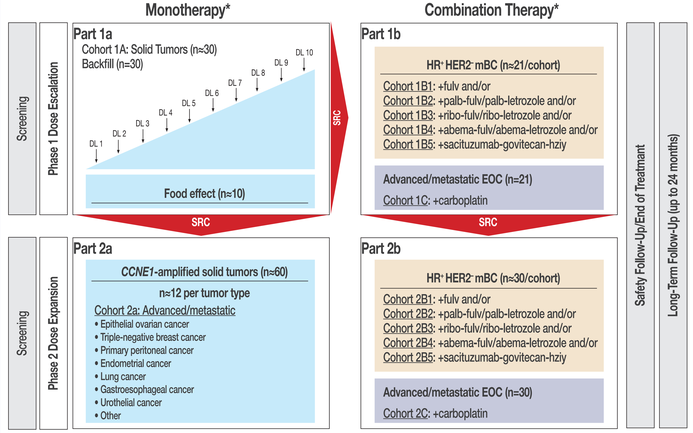


(A) Antitumor activity of AVZO-021 and ribociclib in ST4316B PDX model. **(B)** Body weight changes associated with AVZO-021 and ribociclib treatment in the ST4316B PDX model.
*ST4316B was derived from a patient that progressed on 1L palbociclib + fulvestrant and 2L abemaciclib + fulvestrant.

AVZO-021-1001 STUDY DESIGN

- AVZO-021-1001 (NCT05867251) is an open-label, multicenter, Phase 1/2 study of AVZO-021 as a single agent and in combination therapy in patients with relapsed/ refractory, unresectable, locally advanced, or metastatic solid tumors (Figure 4)
- The Phase 1 dose escalation study includes 2 parts and uses a Bayesian Optimal Interval (BOIN) design to characterize the safety, tolerability, and the MTD/ RP2D of AVZO-021
- The Phase 2 dose expansion study will assess the antitumor activity of AVZO-021 in select cohort of patients as assessed by blinded independent central review (BICR) using Response Criteria for Evaluation of Solid Tumors, version 1.1 (RECIST v1.1)

Figure 4: AVZO-021-1001 Study Design



*A treatment cycle is defined as 28 days. The starting dose of AVZO-021 is 20 mg and it is administered orally QD without interruption until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

AVZO-021-1001 METHODS & OBJECTIVES

AVZO-021-1001 is ongoing and conducted in 2 Phases, each of which includes multiple parts and cohorts wherein AVZO-021 is administered until disease progression or unacceptable/intolerable toxicity:

- **Phase 1 Part 1a – Monotherapy in Solid Tumors:** Oral AVZO-021 is administered to determine the MTD/RP2D. Up to 10 DLs are planned
- **Phase 1 Part 1b Cohorts 1B1 to 1B5 – Combination Therapy With Endocrine Therapy or CDK4/6i and Endocrine Therapy or With Sacituzumab-govitecan-hziy in Patients With LA or Metastatic HR+/ HER2- BC:** Patients are dosed until the MTD/RP2D of the combination therapy is reached. The starting dose of AVZO-021 is at least 1 DL below the monotherapy dose that is concurrently being enrolled and evaluated for dose-limiting toxicities (DLTs) in Part 1a, or at least 1 DL below the MTD (if already determined)
- **Phase 1 Part 1b Cohort 1C – Combination Therapy With Carboplatin in Patients With LA or Metastatic EOC:** Oral AVZO-021 at least 1 DL below the monotherapy dose that is concurrently being enrolled and evaluated for DLTs in Part 1a, or at least 1 DL below the MTD (if already determined)
- **Phase 2 Part 2a – Monotherapy in Patients With *CCNE1*-amplified LA or Metastatic Solid Tumors:** AVZO-021 is administered at the RP2D determined in Part 1a
- **Phase 2 Part 2b Cohorts 2B1 to 2B5 – Combination Therapy With Endocrine Therapy or CDK4/6i and Endocrine Therapy or With Sacituzumab-govitecan-hziy in Patients With LA or Metastatic HR+/ HER2- BC:** AVZO-021 is administered at the RP2D determined in Part 1b
- **Phase 2 Part 2b Cohort 2C – Combination Therapy With Carboplatin in Patients With LA or Metastatic EOC:** AVZO-021 is administered at the RP2D determined in Part 1c in combination with carboplatin

Objectives and endpoints for AVZO-021-1001 are shown in Table 2

Table 2: AVZO-021-1001 Endpoints and Objectives

	Objectives	Endpoints
Phase 1: Dose Escalation	**Primary**	
	• Characterize safety and tolerability of AVZO-021	• First cycle DLT
	• Determine the MTD/RP2D of AVZO-021	• AEs, SAEs, clinical laboratory values, vital signs, ECG, dose interruptions, reductions, and dose intensity
		• MTD and RP2D
	Secondary	
	• Assess preliminary antitumor activity, as assessed by investigator using RECIST v1.1	• ORR, DOR, PFS, OS
	• Characterize plasma PK properties of AVZO-021	• PK: C_{max}, AUC_{0-last}, AUC_{0-tau}, T_{max}, $C_{min, ss}$, R_{ac}, $t_{1/2}$, CL/F, V_z/F
	• Evaluate the effect of a high-fat meal on the PK of AVZO-021	
Phase 2: Dose Expansion	**Objectives**	**Endpoints**
	Primary	
	• Assess the antitumor activity of AVZO-021 as assessed by BICR using RECIST v1.1	• ORR, DOR, PFS, OS
	Secondary	
	• Characterize safety and tolerability of AVZO-021	• ORR, DOR, PFS, OS
	• Characterize plasma PK properties of AVZO-021	• AEs, SAEs, clinical laboratory values, vital signs, ECG, dose interruptions, reductions, and dose intensity
		• PK: C_{max}, AUC_{0-last}, AUC_{0-tau}, T_{max}, $C_{min, ss}$, R_{ac}, $t_{1/2}$, CL/F, V_z/F

KEY ELIGIBILITY CRITERIA

- Key inclusion and exclusion criteria are shown in Table 3. For more information, please see ClinicalTrials.gov

Table 3: AVZO-021-1001 Key Eligibility Criteria

Key Inclusion Criteria

- Aged ≥18 years old; ECOG PS: 0-1; adequate organ function as demonstrated on screening labs
- LA or metastatic solid tumor, for which standard therapies are no longer effective, appropriate, or safe in the opinion of the investigator
  - Patients should have no more than 2 prior cytotoxic chemotherapy regimens for LA/metastatic disease (prior chemotherapy in the adjuvant or neoadjuvant setting allowed if >12 months prior to starting AVZO-021 treatment and is not considered a prior line) with the exception of ovarian cancer patients who should be platinum refractory and progressed beyond standard of care
  - Patients should have measurable disease as determined by RECIST version 1.1. In Phase 2, measurable disease as determined by BICR using RECIST v1.1
- Phase 1
  - Part 1a: LA or metastatic solid tumor associated with dependency on CDK2 (eg, HR+/HER2- breast cancer, *CCNE1* amplified solid tumors, FBXW7 loss of function mutation/deletion and retinoblastoma protein [Rb]1 loss of function mutation/deletion) for which standard therapies are no longer effective, appropriate, or safe in the opinion of the investigator
  - Part 1b Cohorts 1B1-1B5: Histologically or cytologically confirmed diagnosis of locally advanced or metastatic HR+ HER2- BC who have been previously treated with no more than 1 prior CDK4/6 inhibitor and endocrine therapy
  - Part 1b Cohort 1C: Histologically or cytologically confirmed diagnosis of *CCNE1*-amplified, locally advanced or metastatic, platinum-refractory or platinum-resistant EOC
- Phase 2
  - Part 2a: Histologically or cytologically confirmed diagnosis of LA or metastatic *CCNE1*-amplified solid tumors
  - Part 2b Cohorts 2B1-2B5: Histologically or cytologically confirmed diagnosis of LA or metastatic HR+ HER2- BC who have been previously treated with no more than 1 prior CDK4/6 inhibitor and endocrine therapy
  - Part 2b Cohort 2C: Histologically or cytologically confirmed diagnosis of *CCNE1*-amplified locally advanced or metastatic, platinum-refractory or platinum-resistant EOC

Key Exclusion Criteria

- Have received an investigational agent or anticancer therapy within 2 weeks or 5 half-lives of the drug, whichever is shorter, prior to planned start of AVZO-021
- Have received any CDK2 inhibitor, protein kinase membrane associated tyrosine/threonine 1 (PKMYT1) inhibitor, or WEE1 inhibitor anticancer therapy; for patients enrolled in cohort B5, prior therapy with topoisomerase inhibitors is not permitted
- Have undergone major surgery within 4 weeks prior to planned start of AVZO-021
- Have received RT with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving WBRT, which must be completed at least 4 weeks prior to the first dose of study treatment
- Active CNS metastases, leptomeningeal disease, or asymptomatic and treated brain metastases that have been stable <4 weeks

AVZO-021 STUDY ENROLLMENT & LOCATIONS

The Phase 1 Part 1a monotherapy dose escalation study is ongoing at 6 sites in the US

- Case Western Reserve University, Cleveland, OH 44106
- Florida Cancer Specialists, Sarasota, FL 34232
- Stephenson Cancer Center, Oklahoma City, OK 73104
- Yale Cancer Center, New Haven, CT 06510
- Sidney Kimmel Cancer Center, Philadelphia, PA 19107
- Virginia Cancer Specialists, Fairfax, VA 22031

There are ~50 planned global sites for Phase 1 and Phase 2 participation from the US, EU, and/or Asia-Pacific

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ABBREVIATIONS

abema; abemaciclib; AE; adverse event; ATP, adenosine triphosphate; AUC, area under the concentration-time curve; BC, breast cancer; BICR, blinded independent central review; BID, twice daily; BOIN, Bayesian Optimal Interval; BW, body weight; CCNE1, cyclin E1; CDK, cyclin-dependent kinase; CDKi, cyclin-dependent kinase inhibitor; CDK2, cyclin dependent kinase 2; CDK4/6, cyclin-dependent kinase 4/6; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; C_{max}, maximum concentration; $C_{min, ss}$, minimum observed plasma concentration at steady state; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CL/F, apparent clearance; CNS, central nervous system; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; EOC, epithelial ovarian cancer; FBXW7, F-box/WD repeat-containing protein 7; fulv, fulvestrant; G1, cell growth; GI, gastrointestinal; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor positive; IC_{50}, half-maximal inhibitory concentration; IV, intravenous; LA, locally advanced; mBC, metastatic breast cancer; MTD, maximum tolerated dose; ND, not determined; ORR, objective response rate; OS, overall survival; palb, palbociclib; PDX, patient derived xenograft; PFS, progression-free survival; PK, pharmacokinetics; PO, by mouth; Q4W, every 4 weeks; QD, once daily; QW, once weekly; R_{ac}, accumulation ratio; ribo, ribociclib; RECIST v1.1, Response Criteria for Evaluation of Solid Tumors, version 1.1; RP2D, recommended Phase 2 dose; RT, radiotherapy; S, DNA synthesis; SAE, serious adverse event; SRC, Safety Review Committee; $t_{1/2}$, elimination half-life; T_{max}, time to maximum observed plasma concentration; V_z/F, apparent volume of distribution during terminal phase; WBRT, whole brain radiotherapy.

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DISCLOSURES

Afshin Dowlati has participated in advisory boards for Jazz Pharmaceuticals, AstraZeneca, Puma Biotechnology, Prelude Therapeutics, Amgen, and AbbVie. Dr Dowlati can be reached at afshin.dowlati@uhhospitals.org.