A phase 1/2 study of AVZO-1418, a bispecific antibody-drug conjugate (ADC), as a single agent and in combination therapy in patients with locally advanced or metastatic solid tumors

Anthony Tolcher,[1] Stephen V. Liu,[2] Alex Spira,[1] Sarah W. Gordon,[3] Reva Schneider,[4] Mohammad Hirmand,[5] Sanjay Thamake,[5] Minal Mehta,[5] Pasi A. Jänne[6]

[1]NEXT Oncology, San Antonio, TX, USA; [2]Georgetown University, Washington, DC, USA; [3]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; [4]Sarah Cannon Research Institute (SCRI) at Mary Crowley Cancer Research, Dallas, TX, USA; [5]Avenzo Therapeutics, Inc., San Diego, CA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA.

FOR ADDITIONAL INFORMATION

NCT07038343

LB-B014

BACKGROUND[1-11]

Aberrant ErbB Signaling Drives Oncogenesis

- Epidermal growth factors drive epithelial proliferation and migration via transmembrane receptor tyrosine kinases (TKs) in the ErbB family, including **EGFR and HER3**[1,2]
- Genetic alterations in these TKs or their overexpression can lead to tumorigenesis, progression, and metastasis[1,2]

Dual Targeting of EGFR-HER3 Is a Promising Therapeutic Strategy

- EGFR and HER3 are commonly mono- and co-expressed across solid tumor types, including non-small cell lung cancer (NSCLC)[3,4]
- EGFR inhibition can increase HER3 membrane expression, suggesting that **dual EGFR-HER3 targeting** may enhance tumor selectivity and **improve therapeutic efficacy** in EGFR TK inhibitor (TKI)-resistant tumors[4-6]
- Clinical trials evaluating EGFR and HER3 therapeutics have validated these targets in several tumor types[1]

AVZO-1418 Is Designed to Overcome EGFR-TKI Resistance While Maintaining Tolerability

- AVZO-1418 is a **novel bispecific antibody-drug conjugate** (ADC) composed of the topoisomerase (TOPO) I inhibitor (**P1021 payload**) and a monovalent anti-EGFR IgG-like antibody fused to an anti-HER3 single-chain fragment variable (scFv) (Figure 1)[6]
- The P1021 linker payload used in AVZO-1418 has been evaluated in other investigational studies in solid tumors and demonstrated a **manageable safety profile**[7-9]

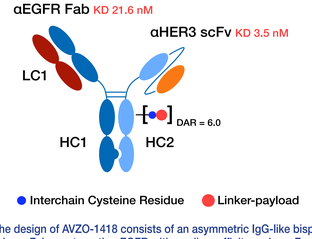


Figure 1. The design of AVZO-1418 consists of an asymmetric IgG-like bispecific ADC, featuring a Fab arm targeting EGFR with medium affinity and a scFv arm targeting HER3 with high affinity. The antibody is connected via a KIH Fc domain and conjugated through a tetrapeptide-based cleavable linker with a TOPO I inhibitor (P1021) payload at DAR of 6.0.[a]

AVZO-1418 Demonstrates High Dual EGFR-HER3 Cellular Binding Affinity and Robust Tumor Growth Inhibition in Nonclinical Studies

- AVZO-1418 has demonstrated dual EGFR-HER3 binding affinity with high internalization compared with parental bivalent monoclonal antibodies in co-expressing cell lines[6]
- **Robust tumor growth inhibition** has been observed in xenograft models, including those derived from osimertinib-resistant NSCLC human cancer cell lines (Figure 2)[6]

AVZO-1418 showed superior antitumor activity in HNSCC, CRC, and EGFR TKI-resistant NSCLC CDX or PDX models

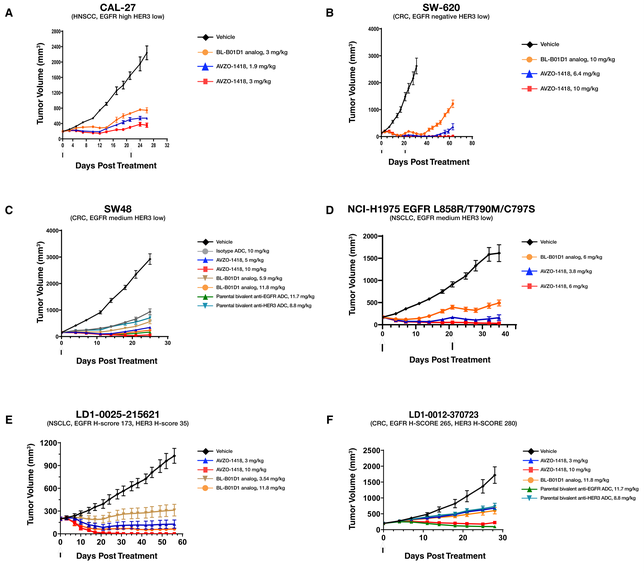


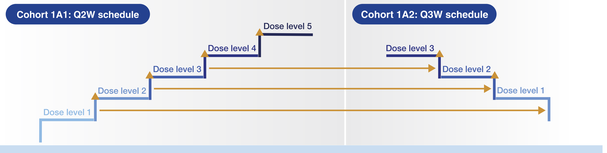
Figure 2. AVZO-1418 inhibits tumor growth in vivo in adult immune-deficient mice inoculated with CAL-27 HNSCC (A), SW-620 colon cancer cells (B), SW-48 colon cancer cells (C), NCI-H1975 NSCLC cells harboring engineered osimertinib-resistant mutation C797S (D), LD1-0025-215621 non-small cell lung adenocarcinoma patient–derived tumor xenograft (E), or LD1-0012-370723 colon cancer patient–derived tumor xenograft (F). The doses were based either on equal ADC molar or mass concentration, or equal payload molar concentration. Each value represents the mean and SEM (N=5 or 6).[c]

AVZO-1418-1001 TRIAL DESIGN[10,11]

Phase 1 of **AVZO-1418-1001:** evaluating the tolerability, safety, and pharmacokinetics (PK) of AVZO-1418 as monotherapy and in combinations with standard of care (SOC) in patients with locally advanced or metastatic epithelial solid tumors

Phase 1 Part A: Dose Escalation in Monotherapy Arm (n=60 dose escalation & 40 backfill)

- Patients with the following tumor types will be included in Part A: *EGFR*m NSCLC, NSCLC without AGA, SCLC, SCCHN, NPC, TNBC, or UC



Phase 1 Part B: Dose Escalation in Combination Arm (n=30 dose escalation & 20 backfill)

- Combination schedules to be determined by Part A outcomes

Figure 3. Study Design of AVZO-1418-1001.

Abbreviations: AGA, actionable genetic alterations; *EGFR*m, epidermal growth factor receptor mutation; NPC, nasopharyngeal carcinoma; NSCLC, non–small cell lung cancer; Q2W, every 2 weeks; Q3W, every 3 weeks; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; UC, urothelial cancer.

Study Design and Objectives

- Phase 1 of AVZO-1418-1001 includes dose-escalation **monotherapy** (Part A) and **combination arms** (Part B) in patients with locally advanced or metastatic solid tumors
- The objective of Phase 1 is to determine safety and preliminary recommended Phase 2 dose (**RP2D**) and/or the maximum tolerated dose (**MTD**) using a BOIN design, and to evaluate efficacy and pharmacokinetics of AVZO-1418

Dose Schedules

- Part A includes **2 escalating schedules** of AVZO-1418 monotherapy at every 2 weeks (Q2W) and every 3 weeks (Q3W)[a]
- Each dose level will enroll 3 to 12 dose-limiting toxicity (DLT)-evaluable patients
- Combination schedules and the combination RP2D and/or MTD for Part B will be determined based on preliminary data from dose escalation in monotherapy Part A

Sample Size

- Part A plans to enroll up to 100 patients (~60 patients in dose escalation and ~40 patients with NSCLC as backfill[b])
- Part B plans to enroll up to 50 patients (~30 patients in dose escalation and ~20 patients as backfill)

[a]Dosing will initially occur in a 28-day cycle schedule; based on evolving safety data, safety review committee (SRC) will confirm an appropriate dose level to run dose escalation in a 21-day cycle schedule.
[b]Backfill will include patients with NSCLC without actionable genetic alterations (AGA) or TKI-progressed *EGFR*m NSCLC.

KEY ELIGIBILITY CRITERIA[10,11]

Key Inclusion Criteria

- Age 18-75 years
- Histologically or cytologically confirmed locally advanced or metastatic epithelial solid tumors[c] for whom SOC is no longer effective, appropriate, safe, or refused by patients
- Measurable disease as assessed by investigator using RECIST v1.1
- ECOG performance status ≤1
- Life expectancy of >3 months
- Adequate organ function, including renal, liver, and bone marrow function
- ≤3 prior systemic lines of cytotoxic chemotherapy (including ADCs) in the metastatic setting[d,e]
- Backfill enrollment includes patients with NSCLC without AGA who have received prior immunotherapy and platinum-based chemotherapy, either sequentially or in combination, and patients with TKI-progressed *EGFR*m NSCLC[f]; all must have received ≤2 prior lines of systemic therapy for metastatic disease

Exclusion Criteria

- Patients who previously received a prior ADC with a TOPO 1 inhibitor payload (with exception to TNBC patients who can receive no more than 1 prior ADC with TOPO 1 inhibitor payload)
- Active CNS metastases[g]
- Other active malignancy within 3 years prior to the first dose[h]
- History of or ongoing drug-induced interstitial lung disease
- Radiation pneumonitis requiring ongoing steroid treatment
- Any other clinically significant medical disease or other condition that may interfere with protocol adherence or substantially increase the risk of AEs

[c] Patients with select advanced solid tumors (Figure 3) will be enrolled; other solid tumors expressing EGFR and HER3 may be enrolled with prior approval [d] Other therapies are permitted. [e] Patients with NSCLC without AGA, SCCHN, or NPC should have received platinum-based chemotherapy and anti–PD(L)-1 therapy. [f] Patients with *EGFR*m NSCLC should have progressed on 1 prior TKI therapy. [g] Patients with asymptomatic and treated brain metastases may participate if they are radiologically stable for ≥4 weeks prior to the first dose and do not require steroid treatment; patients with suspected or confirmed leptomeningeal disease are not eligible, even if treated. [h] Except for adequately treated basal cell carcinoma or squamous cell skin cancer, carcinoma in situ, colorectal adenomatous polyps, or other malignancy for which the patient is not on active anticancer therapy.

TRIAL ENDPOINTS[10,11]

Primary Endpoints

- **MTD** (based on **the number of patients** with DLT during the first cycle and/or preliminary RP2D of AVZO-1418 as monotherapy and in combination therapy
- **Treatment-emergent Adverse Events (TEAEs):** Incidence and severity of **TEAEs** and serious adverse events (**SAEs**)
- **Safety and Tolerability:** Changes in clinical laboratory values including **hematology** and **chemistry** values, vital signs, electrocardiograms, dose interruptions, reductions, and dose intensity

Secondary Endpoints

- **Antitumor Activity:** Preliminary antitumor activity, including **ORR, DOR, DCR, PFS, OS** of AVZO-1418 as monotherapy and in combination therapy, using RECIST v1.1 as assessed by the Investigator
- **Pharmacokinetics (PK):** PK of AVZO-1418, total **antibody**, and **free payload** (P1021)
- **Immunogenicity:** Immunogenicity of AVZO-1418

This study is expected to enroll at ~50 locations across North America, Europe, and APAC.
The latest information on this study can be found at **ClinicalTrials.gov**, identifier **NCT07038343.**[10]

REFERENCES

1. Wee P, Wang Z. *Cancers (Basel)*. 2017;9(5):52. doi:10.3390/cancers9050052 **2.** Pines G, Köstler WJ, Yarden Y. *FEBS Lett*. 2010;584(12):2699-2706. doi:10.1016/j.febslet.2010.04.019 **3.** Wood M, et al. Patterns of EGFR and HER3 co-expression in solid tumors. Presented at: American Association for Cancer Research Annual Meeting; April 5-10, 2024; San Diego, CA. **4.** Haikala HM, et al. *Cancer Res*. 2022;82(1):130-141. doi:10.1158/0008-5472.CAN-21-2426 **5.** Chen Q, et al. *Front Immunol*. 2024;14:1332057. doi:10.3389/fimmu.2023.1332057 **6.** Zhou Y, et al. DB-1418 (AVZO-1418), a bispecific antibody-drug conjugate targeting EGFR and HER3, demonstrates superior and broad antitumor efficacy and favorable safety in preclinical studies. Presented at: American Association for Cancer Research Annual Meeting; April 25-30, 2025; Chicago, IL. **7.** Lisberg A, et al. *J Clin Oncol*. 2025;43(16 suppl):3000. doi:10.1200/JCO.2025.43.16_suppl.3000 **8.** Parsonson AO, et al. *J Clin Oncol*. 2025;43 (16 suppl):5015. doi:10.1200/JCO.2025.43.16_suppl.5015 **9.** Marathe O, et al. *Ann Oncol*. 2023;34(suppl 2):S480. **10.** Study of AVZO-1418 as a Single Agent and in Combination Therapy in Patients With Locally Advanced or Metastatic Solid Tumors (AVZO-1418-1001). ClinicalTrials.gov Identifier: NCT07038343. Accessed August 5, 2025. https://clinicaltrials.gov/study/NCT07038343 **11.** Avenzo Therapeutics. Data on file. 2025.

ACKNOWLEDGMENTS

The authors thank participants and their caregivers, the investigators, and all the site staff who have participated and who are participating in this study. This study is sponsored by Avenzo Therapeutics. Medical writing assistance was provided by Bluprint Oncology and was funded by Avenzo Therapeutics.

CONTACT

Please contact the presenting author atolcher@nextoncology.com for questions or comments.