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# Trials in Progress: Phase 1a/b study of ELVN-002 in solid tumors with HER2 mutations, amplification, or overexpression

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## KEY POINTS

- ELVN-002 is a potent, selective, irreversible, and CNS-penetrant inhibitor of HER2, including mutated HER2, with >100-fold selectivity over EGFR
- ELVN-002 is designed to provide a meaningful therapeutic option to patients with HER2-altered solid tumors
- ELVN-002 may address unmet needs for patients with *HER2*-mutant NSCLC and HER2-overexpressed MBC, including those with brain metastases, alone or in combination with HER2-targeted ADCs
- ELVN-002-001 is a first-in-human, phase 1, open-label, multicenter, dose escalation and expansion study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of ELVN-002 monotherapy and in combination with T-DXd or T-DM1 in patients with solid tumors with HER2 alterations, including *HER2*-mutant NSCLC and HER2-overexpressed MBC

## BACKGROUND

- Up to 27% of non-small cell lung cancers (NSCLCs) are associated with activating HER2 alterations, including gene mutations, gene amplifications, and protein overexpression[1,2]
- Up to 20% of patients with NSCLC have brain metastases at diagnosis, which can negatively impact longevity and quality of life[3]
- There are no approved tyrosine kinase inhibitors (TKIs) that target *HER2*-mutant NSCLC, and many investigational agents have been limited by EGFR-driven toxicity[4]

### ELVN-002

- Potent, selective, irreversible, and central nervous system (CNS)-penetrant HER2 TKI designed to inhibit HER2 and multiple HER2 mutants, including $HER2^{YVMA}$ and $HER2^{L755S/P}$ (**Figure 1**)
- >100-fold selectivity over EGFR to potentially decrease EGFR-related toxicities (**Table 1**)
- Demonstrated antitumor activity in *in vitro* and *in vivo* mouse tumor xenograft models, including a $HER2^{YVMA}$-mutant and a HER2-overexpressing model (NCI-N87)[5] (**Table 1**, **Figure 2**)
  - Elicited tumor regression at exposures predicted to be clinically achievable in all models
  - Yielded tumor regressions in the NCI-N87 intracranial model
  - Showed additive antitumor activity in combination with trastuzumab deruxtecan (T-DXd)

### ELVN-002-001 (NCT05650879) Is a First-in-Human Study With 2 Objectives

- Evaluate the safety, tolerability, and pharmacokinetics (PK) of monotherapy ELVN-002 in patients with solid tumors with HER2 alterations (ie, HER2 mutations, amplifications, or overexpression), and evaluate the preliminary efficacy in *HER2*-mutant NSCLC
- Evaluate the safety of ELVN-002 with T-DXd in *HER2*-mutant NSCLC, and with trastuzumab emtansine (T-DM1) in HER2-overexpressed metastatic breast cancer (MBC)

## STUDY DESIGN

- ELVN-002-001 is a phase 1, open-label, multicenter, dose escalation and expansion study (**Figure 3**)

### Phase 1a Monotherapy Dose Escalation

- Successive cohorts of patients with HER2-altered advanced solid tumors will receive escalating doses of monotherapy ELVN-002

### Phase 1a Combination Dose Escalation

- Successive cohorts of patients with *HER2*-mutant NSCLC will receive escalating doses of ELVN-002 in combination with a fixed dose of T-DXd
- Successive cohorts of patients with HER2-overexpressed breast cancer will receive escalating doses of ELVN-002 in combination with a fixed dose of T-DM1

### Phase 1b Monotherapy Dose Expansion

- Patients with *HER2*-mutant NSCLC will be randomized between 2 dose levels of n=20 patients each

## OBJECTIVES AND ENDPOINTS

### Phase 1a Monotherapy and Combination Dose Escalation

**Primary Objectives**
- Determine the recommended dose of ELVN-002 alone and in combination with T-DXd or T-DM1
- Evaluate the safety and tolerability of treatment with ELVN-002 alone and in combination with T-DXd or T-DM1

**Secondary Objectives**
- Assess the PK profile of ELVN-002
- Assess preliminary antitumor activity of ELVN-002 in HER2-altered solid tumors
- Assess preliminary antitumor activity of ELVN-002 in combination with T-DXd in *HER2*-mutant NSCLC or T-DM1 in HER2-overexpressed breast cancer

**Primary Endpoints**
- Dose-limiting toxicities
- Incidence of adverse events (AE), laboratory abnormalities, and electrocardiogram (ECG) abnormalities

**Secondary Endpoints**
- PK parameters
- Confirmed overall response rate (ORR) as assessed by investigators per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

### Phase 1b Monotherapy Dose Expansion

**Primary Objective**
- Evaluate the safety and tolerability of ELVN-002 in *HER2*-mutant NSCLC

**Secondary Objective**
- Evaluate the clinical benefits and PK of ELVN-002 in *HER2*-mutant NSCLC

**Primary Endpoint**
- Incidence of AEs, laboratory abnormalities, and ECG abnormalities

**Secondary Endpoints**
- Confirmed ORR per RECIST v1.1
- Duration of response
- Brain metastases response in patients with measurable brain metastases at baseline
- Plasma concentrations of ELVN-002

## INCLUSION/EXCLUSION CRITERIA

### Phase 1a Monotherapy Dose Escalation and Dose Exploration

- Patients with HER2-altered advanced solid tumors based on local testing
- For patients with NSCLC, no known *EGFR*, *ROS1*, *ALK*, or $BRAF^{V600E}$ mutations
- Patients with brain metastases (treated or untreated) are not excluded unless requiring immediate local therapy
- Progressed following all standard treatments or not appropriate for standard treatment. No limit on prior number of therapies
- Eastern Cooperative Oncology Group performance status 0-1

### Phase 1a Dose Escalation Combination With T-DXd in *HER2*-Mutant NSCLC

- *HER2*-mutant, advanced-stage NSCLC progressed after ≥1 prior therapy
- No known *EGFR*, *ROS1*, *ALK*, or $BRAF^{V600E}$ mutations
- No prior T-DXd

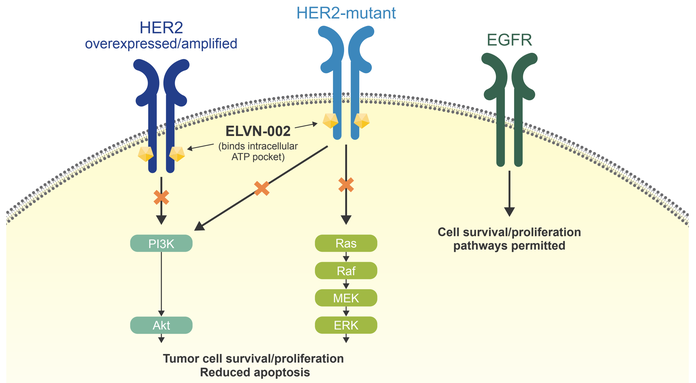
### Phase 1a Dose Escalation Combination With T-DM1 in HER2-Overexpressed MBC

- Patients with HER2-overexpressed (IHC3+ or IHC2+/ISH+) breast cancer, and have previously received trastuzumab, taxane, and T-DXd (if available and appropriate) in the metastatic setting
- No prior T-DM1

### Phase 1b *HER2*-Mutant NSCLC

- Nonsquamous NSCLC with measurable disease
- *HER2* mutation identified by tissue (fresh or archival) or circulating tumor DNA
- No known *EGFR*, *ROS1*, *ALK*, or $BRAF^{V600E}$ mutations
- Progressed after receiving ≥1 prior systemic therapy including a platinum-based chemotherapy ± anti–PD-(L)1
  - Prior antibody-drug conjugate (ADC) or antibody (eg, T-DXd, T-DM1, or trastuzumab) is allowed

### Figure 1: ELVN-002 Mechanism of Action (MOA)




**Targeted MOA**
- Small molecule covalent inhibitor of HER2 targeting the ATP binding pocket of the kinase domain
- Irreversibly inhibits wild-type (WT) HER2 including in the overexpressed setting with broad activity against multiple clinically relevant *HER2* mutations

**Kinase specificity**
- Selective inhibition of HER2 while sparing WT EGFR to minimize/prevent EGFR-related toxicity
- Broadly selective across a panel of >370 protein kinases

**Preclinical antitumor activity**
- Pharmacodynamic and anti-tumor activity in HER2-overexpressed and *HER2*-mutant models, including against $HER2^{YVMA}$ and $HER2^{L755S/P}$ mutants
- Demonstrated robust antitumor activity in an intracranial mouse model
- Well tolerated in all preclinical studies alone and in combination with ADCs

### Table 1: ELVN-002 Selectively and Potently Inhibits HER2 and HER2 Mutants While Sparing EGFR

| | Poziotinib | Pyrotinib | Tucatinib | ELVN-002 | |
|---|---|---|---|---|---|
| BT474 $HER2^{WT}$ pHER2 $IC_{50}$ | 3.5 | 13 | 12 | 13 | |
| Beas2b $HER2^{S310F}$ pHER2 $IC_{50}$ | 1.9 | 2 | 16 | 2.8 | |
| **Beas2b $HER2^{L755S}$ pHER2 $IC_{50}$** | **4** | **3.5** | **99** | **4.7** | In contrast to tucatinib, potent pharmacodynamic activity for $HER2^{YVMA}$ (71% of E20IM NSCLC) & $HER2^{L755S/P}$ (22% $HER2^{mut}$ BC) |
| **Beas2b $HER2^{YVMA}$ pHER2 $IC_{50}$** | **2.1** | **5** | **127** | **4.2** | |
| Beas2b $HER2^{YVMA}$ pHER2 $IC_{50}$ in 100% human serum (fold shift) | 69 (33×) | 324 (65×) | >1000 (~10×) | 33 (8×) | |
| BT474 ($HER2^{WT}$) cytotox $IC_{50}$ | 0.9 | 2.3 | 22 | 3.9 | |
| NCI-N87 ($HER2^{WT}$) cytotox $IC_{50}$ | 0.4 | 2.6 | 44 | 3.3 | |
| Ba/F3 $HER2^{YVMA}$ cytotox $IC_{50}$ | 1.5 | 3.2 | 119 | 5.1 | |
| H2073 ($EGFR^{WT}$) pEGFR $IC_{50}$ | 1.4 | 6.4 | >10000 | 2160 | In contrast to dual inhibitors, ELVN-002 spares EGFR with >100-fold selectivity for HER2 over EGFR |
| A431 ($EGFR^{WT}$) pEGFR $IC_{50}$ | 1.3 | 10 | >10000 | 2290 | |
| A431 ($EGFR^{WT}$) cytotox $IC_{50}$ | 0.6 | 75 | >10000 | 3530 | |
| Human hepatocyte stability, extraction ratio | 68 | 74 | 76 | **22** | Improved *in vitro* ADME properties over tucatinib and dual inhibitors, poziotinib, and pyrotinib |
| GSH in human liver cytosol, (% remaining at 1h) | 80% | 34% | - | 70% | |
| Kinetic solubility pH 7.4 (μM) | 5.6 | < 0.1 | 9.3 | **260** | |

**Table 1**. Beas2b cells derived from normal bronchial epithelium were engineered to express $HER2^{YVMA}$, $HER2^{S310F}$, or $HER2^{YVMA}$. Phosphorylated HER2 (pHER2) signal was measured in Beas2b $HER2^{YVMA}$ cells in the presence of 100% human serum to model the attenuating effect of human plasma protein binding on compound potency to provide a more clinically relevant context. Phosphorylated EGFR (pEGFR) and pHER2 $IC_{50}$ values were determined by AlphaLISA® colorimetric ELISA or in cell western. Cytotoxicity $IC_{50}$ values were determined via CellTiter-Glo® after compound treatment for 3-5 days. All $IC_{50}$ values are [nM] and represent average values from multiple experiments. Hepatocyte stability, glutathione (GSH) reactivity, and kinetic solubility assays represent a subset of our absorption, disposition, metabolism, and excretion (ADME) screening assays.
BC, breast cancer; E20IM, exon 20 insertion mutation.

### Figure 2: ELVN-002 Demonstrated Antitumor Activity, Including in an Intracranial Model, and Additive Activity in Combination With T-DXd at Well-Tolerated Doses

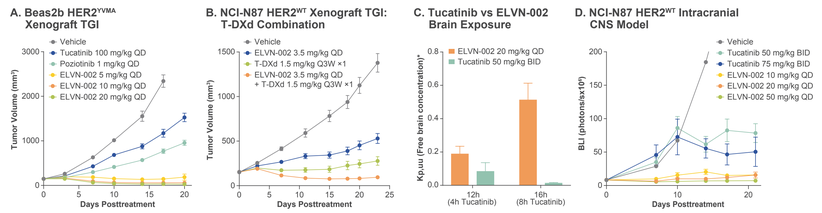



**Figure 2. (A) Beas2b $HER2^{YVMA}$ xenograft model.** Beas2b cells derived from normal bronchial epithelium were engineered to express $HER2^{YVMA}$. Tucatinib, poziotinib, and ELVN-002 were dosed daily, PO for 21 days. N=8 NOD-SCID mice per group. **(B) ELVN-002 and T-DXd combination.** ELVN-002 was dosed daily, PO for 21 days. T-DXd was dosed once intravenously. N=8 BALB/c nude mice per group. **(C) Mouse Brain Exposure.** Steady state $K_{p,uu}$ for ELVN-002 and tucatinib in non–tumor-bearing BALB/c nude mice (N=3). Measurements were taken after 5 days of dosing at timepoints corresponding to estimated clinically relevant plasma concentrations. Tucatinib was dosed BID and measurements were made at 12h and 16h; however, $K_{p,uu}$ levels were even lower than at 4h and 8h, respectively. $K_{p,uu}$ is the unbound brain to plasma partition coefficient, which is used to define the unbound drug concentration in the brain relative to blood with a reference. $K_{p,uu}$ × Free brain concentration (total brain concentration adjusted for brain tissue binding)/ Free plasma concentration (total plasma concentration adjusted for protein binding). **(D) Intracranial efficacy.** Mice were injected with luciferase-expressing NCI-N87 cells into the right forebrain, and tumor growth was measured by bioluminescent signal obtained from imaging (IVIS® Lumina III). Tucatinib and ELVN-002 were dosed daily, PO for 21 days. N=10 BALB/c nude mice per group. BID, twice daily; BLI, bioluminescence imaging; CNS, central nervous system; PO, by mouth; QD, once daily; Q3W, every 3 weeks; TGI, tumor growth inhibition; WT, wild-type.

### Figure 3: ELVN-002-001 Study Design

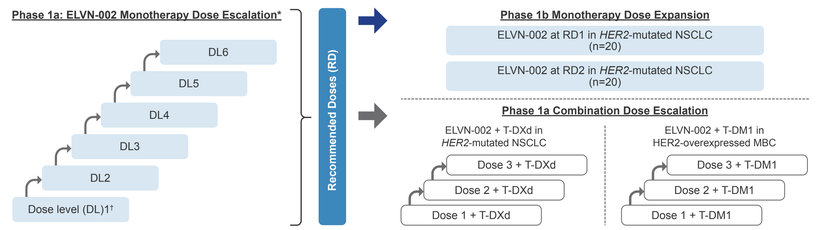



**Figure 3. Study schema.**
*Successive cohorts will receive escalating doses of once-daily (QD) ELVN-002. Dose escalation decisions will follow a Bayesian Design. Dosing will be continuous in 21-day cycles until disease progression or unacceptable toxicity. Dose escalation may continue until the maximum tolerated dose is identified. Two recommended doses (RDs) for Phase 1b monotherapy expansion will be chosen. Evaluation of twice daily (BID) regimen and intermediate dose levels may occur upon approval of the Safety Review Committee. Dose exploration may consist of up to 30 patients who may be enrolled at ≥1 dose level to further evaluate the safety, tolerability, PK, and clinical activity. A maximum of 10 patients may be enrolled at any given dose level. †Single patient cohort.

### Figure 4: Clinical Trial Sites

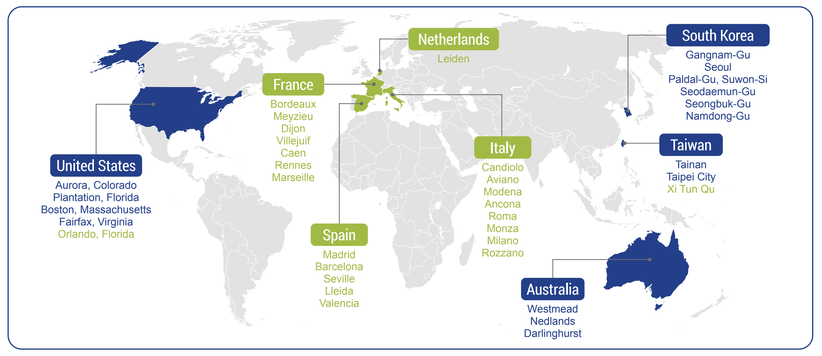



**Figure 4**. ELVN-002-001 (NCT05650087) opened for enrollment in February 2023. Locations currently enrolling patients (blue) or where enrollment is anticipated to open (green) are highlighted.

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