Multicenter Phase 1/2a trial of CLN-081 (TAS6417) in NSCLC Patients with EGFR Exon 20 Insertion Mutations

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Introduction

- Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) mutations have been developed and approved as anticancer agents, but are largely ineffective against EGFR exon 20 insertion (Ex20ins) mutations.
  - Median overall survival for Ex20ins mutation patients is ~9 months in contrast to >40 months for patients with sensitive mutations (e.g., Ex19del, L858R)
- There is a clinical need to develop novel EGFR TKIs targeting Ex20ins mutations while sparing wild type (WT) EGFR to simultaneously maximize efficacy and enhance the therapeutic window via reduction in WT EGFR driven toxicities.

CLN-081 Preclinical Data

- CLN-081 (formerly known as TAS6417) is a novel, orally available, broad spectrum EGFR inhibitor with activity against Ex20ins mutations.
  - Also active against exon19del, L858R, and T790M, as well as less common G719X, L861Q and S768I mutations.
- For Ex20ins mutations, selectivity indexes (WT EGFR/mutant EGFR ratio of inhibition) favored CLN-081 over poziotinib & osimertinib, suggestive of a wider therapeutic window.

Figure 1: Selectivity indexes - mutation selectivity calculated as ratios of IC_{50} values of WT NHEK-Neo to those of each cell line.

Figure 2: Selectivity indexes - Calculated as ratios of IC_{50} values of Ba/F3 expressing WT EGFR to those of Ba/F3 cells expressing each mutant EGFR.

Note: Data in Figures 1, 2, and 4 were generated by Drs. Hibiki Udagawa, Yumi Hakozaki, and Susumu Kobayashi.

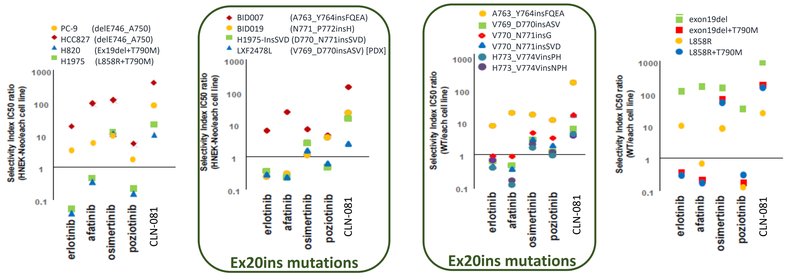


Figure 3: CLN-081 is WT EGFR sparing. Inhibition of EGFR phosphorylation from H1975-InsSVD (D770_N771insSVD) xenograft model in tumors (A) and in skin tissues (B).

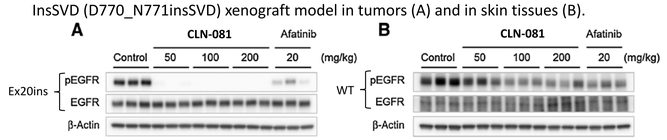
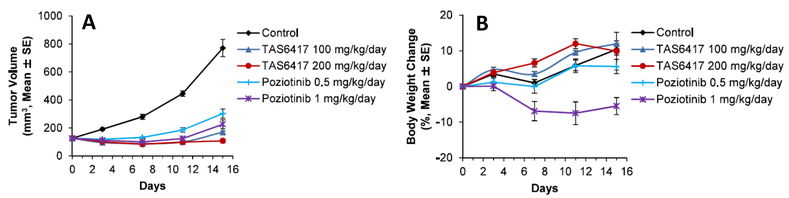


Figure 4: CLN-081 vs poziotinib anti-tumor activity (A) and toxicity (B) in H1975-insSVD xenografts



Rationale

- While several novel agents targeting EGFR Ex20ins are in development, preliminary reports suggest that WT EGFR-related adverse events are common and may limit efficacy and durability of responses.
- CLN-081 is a potent inhibitor of Ex20ins mutations with a broad spectrum of EGFR-mutant activity but also shows selectivity over WT EGFR suggesting a potentially wider clinical therapeutic window than most approved/in-development EGFR TKIs.

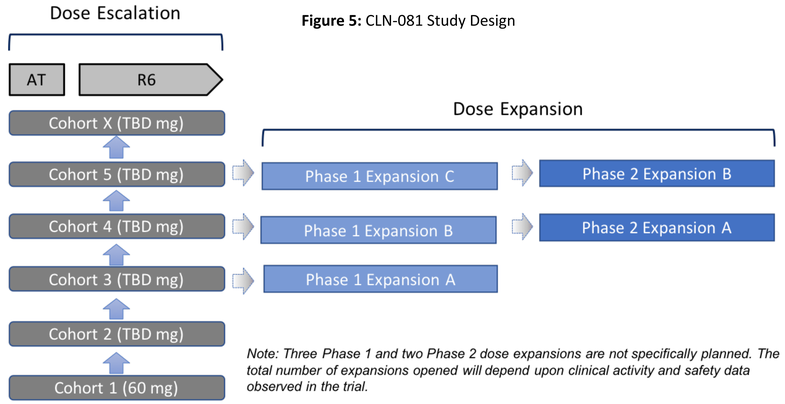
Study Objectives

	Phase 1	Phase 2a
Primary	• Assess the safety and tolerability of orally administered CLN-081 monotherapy. • Define the maximum tolerated dose (MTD).	• Evaluate the overall response rate (ORR). • Define the Recommended Phase 2 dose (RP2D).
Secondary	• To assess anti-tumor activity.	• Evaluate duration of response (DOR), disease control rate (DCR), progression free survival (PFS), survival rate, and OS. • Confirm safety and tolerability. • To compare the safety, tolerability and efficacy of twice daily (BID) dosing with the same total dose administered once daily (QD).
	• To characterize select pharmacokinetics (PK) parameters.	
	• To assess activity in patients with known central nervous system (CNS) disease.	
Exploratory	• To explore both blood and intra-tumoral pharmacodynamics (PD) markers.	

Study Design

- This is an adaptive Ph1/2a trial evaluating CLN-081 in advanced NSCLC harboring Ex20ins mutations.
- The trial consists of three parts: Ph1 Dose Escalation (Esc), Ph1 Dose Expansion (Exp), and Ph2a Dose Exp.
  - Dose esc will be explored utilizing Accelerated Titration[3] (AT) and Rolling Six[4] (R6) designs.
- Approximately 90 patients are planned. CLN-081 will be dosed continuously in 21-day cycles.
- QD and BID dosing schedules will be explored.

Figure 5: CLN-081 Study Design

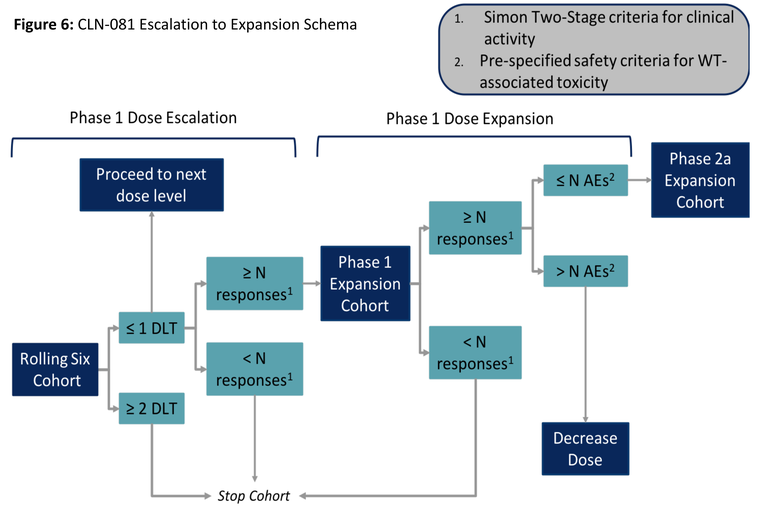


Note: Three Phase 1 and two Phase 2 dose expansions are not specifically planned. The total number of expansions opened will depend upon clinical activity and safety data observed in the trial.

Study Schema

- Dose esc will proceed initially according to AT design. The starting dose is 60 mg.
- Conversion to R6 design is based upon pre-specified safety criteria.
- Transition from each part of the trial, Ph 1 dose escalation to dose expansion to Ph 2a, is based upon a Simon-Two Stage design.
- Cohort expansion can occur at one or more doses:
  - Ph 1 exp based upon responses observed in Rolling Six cohorts.
  - Ph 2 exp based upon pre-specified response and safety criteria observed in Ph 1 dose exp.

Figure 6: CLN-081 Escalation to Expansion Schema



Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Histologically or cytologically confirmed recurrent, metastatic NSCLC with documented EGFR exon 20 insertion mutation as demonstrated by: • An FDA-approved device, or • A device or test validated and accepted by regulatory health authorities for patients enrolled in the trial outside of the United States	<u>For AT Cohorts</u> • No limit on prior EGFR TKIs, including prior EGFR exon 20 inhibitors such as poziotinib, TAK-788, etc <u>For All Other Cohorts</u> • Limited prior exposure to EGFR TKIs (< 6 mo of clinical benefit), including EGFR exon 20 inhibitors (< 3 cycles with no progression)
At least one prior treatment with platinum-based chemotherapy.	• Systemic anticancer treatment ≤ 14 days prior to C1D1 • Limited-field radiotherapy ≤ 7 days or extended-field thoracic radiotherapy ≤ 4 weeks • Major surgery ≤ 4 weeks
Age ≥ 18 and ECOG of 0 or 1	
Measurable disease and lab parameters within normal limits	
Brain metastases that are asymptomatic, treated, and stable x 4 weeks	Mean resting QTc > 470

References

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