Preliminary Safety and Activity of CLN-081 in NSCLC with EGFR Exon 20 Insertion Mutations (Ins20)

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Background

- 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 (mOS) for Ex20ins mutation patients is ~9 months in contrast to >40 months for patients with sensitive mutations (e.g., Ex19del, L858R)[1]
- There is a clinical need to develop novel EGFR TKIs targeting Ex20ins mutations while sparing wild type (WT) EGFR to maximize efficacy and enhance the therapeutic window via reduction in WT driven toxicities
- CLN-081 (also known as TAS6417) is a novel, orally administered, EGFR inhibitor with activity against Ex20ins mutations[1,2]
- CLN-081 is a potent inhibitor of Ex20ins mutations with selectivity over WT EGFR, suggesting a potentially wider clinical therapeutic window than most approved/in-development EGFR TKIs
- We present the interim results of the ongoing first-in-human, Phase 1/2a trial of CLN-081 (NCT04036682).

Methods

- CLN-081 is dosed in 21-day cycles
- Five dose levels have been explored at 30, 45, 65, 100, and 150 mg (all BID), utilizing Accelerated Titration (AT) and Rolling Six (R6) designs[3,4]
- All enrolled patients had adenocarcinoma of the lung with documented EGFR ex20ins mutations
- Patients treated with prior ins20 targeting drugs are allowed in AT cohorts only. Patients treated in R6 and in the expansions are excluded if previously treated with ins20 targeting drugs. All patients received ≥ 1 dose of CLN-081 are part of the safety population
- Transition from Dose escalation to Ph 1 exp then to Ph 2a based upon a Simon-Two stage design

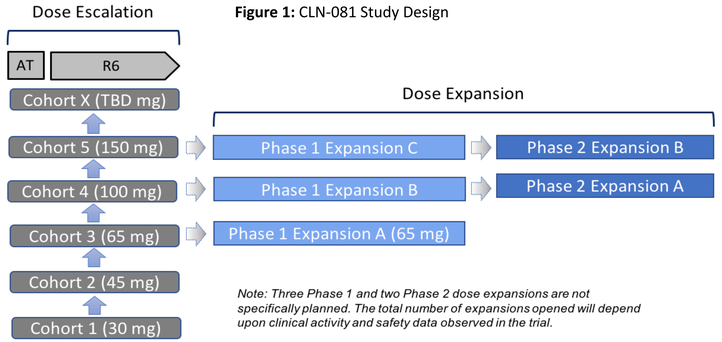


Figure 1: CLN-081 Study Design

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.

Key Eligibility Criteria
NSCLC with documented EGFR ex20ins mutation
≥ 1 prior platinum-based chemotherapy.
Measurable disease and lab parameters within normal limits
Brain metastases (mets)that are stable x 4 weeks

Key Study Objectives
Define the Maximum Tolerated Dose
Evaluate response rate and duration of response
Define the Recommended Phase 2 Dose

Results

Patients Summary

- At the time of the data cut (01 Sep 2020), 22 patients across five dose escalation cohorts received at least 1 dose of CLN-081
- 17 of 22 patients were response evaluable; 5 patients had not been restaged at the time of the data cut but remain on treatment
- All received ≥ 1 platinum containing regimen
- > 80 % (18/22) of patients received ≥2 prior therapies before study entry

Table 1: Demographics and Baseline Characteristics of Patients Treated with CLN-081

Characteristic	N=22
Median Age, years (Range)	65 (54-83)
Male / Female, n (%)	11 (50) / 11 (50)
Race, n (%)	
Asian	8 (36)
Black	1 (5)
White	13 (59)
ECOG 0 / 1, n (%)	6 (27) / 16 (73)
Brain mets at BL, n (%)	2 (9)

Characteristic	N=22
Number of Prior Systemic Therapies, Median (range)	3 (1-9)
1, n (%)	4 (18)
2, n (%)	7 (32)
≥ 3, n (%)	11 (50)
Prior TKI, inc. pozio / TAK-788, n (%)	12 (55)
Prior pozio or TAK-788, n (%)	4 (18)
Prior immunotherapy, n (%)	11 (50)

Safety Summary

- 20 of 22 (91 %) patients experienced ≥ 1 adverse event (AE), irrespective of attribution; AEs have been manageable and reversible
- The most common treatment emergent AEs, irrespective of attribution, have been rash, cough, and anemia
- There have been no DLTs, CLN-081 related SAEs, or CLN-081 related Grade (Gr) ≥ 3 AEs
- CLN-081 related AEs leading to dose interruption or reduction were all due to Gr 2 rash
- Dose interruptions were required for 3 patients (at 100 mg and 65 mg)
- Dose reductions were required for 2 patients (at 100 mg and 65 mg); both patients continued to derive clinical benefit (SD) or achieved an objective response (PR) after dose reduction
- WT EGFR Associated AEs
  - No Gr ≥ 3 rash or Gr ≥ 2 diarrhea
  - 1 patient has experienced CLN-081 related Gr 1 diarrhea

Table 2: Related Adverse Events Summary in Patients Treated with CLN-081 (N=22)

All AEs ≥ 10 % (Preferred Term)	All Grades, n (%)	Gr 2, n (%)	Gr ≥ 3, n (%)
Rash[a]	13 (60)	6 (27)	0 (0)
Stomatitis	3 (13)	2 (9)	0 (0)
Dry Skin	3 (13)	0 (0)	0 (0)

[a] Include rash, rash maculo-papular, rash macular, pruritus, dermatitis acneiform, dermatitis, and urticaria

AE Characteristics	n (%)
Serious AEs	0 (0)
Grade ≥ 3 AEs	0 (0)
AEs leading discontinuation	0 (0)
AEs leading to dose interruption	3 (13)
AEs leading to dose reduction	2 (9)

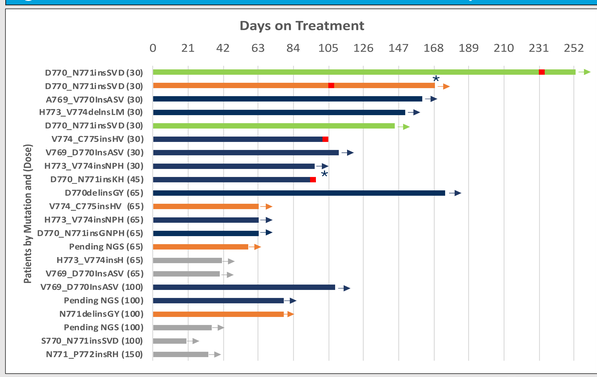
Pharmacokinetics Summary

- C_{max} and AUC values from time 0 to 8 h values increase with increasing dose from 30 to 100 mg
- Minimal to no increase in exposure levels from C1D1 to C1D15
- CLN-081 has typically been rapidly absorbed with T_{max} values ranging from 0.5 to 2 h with a mean average terminal phase elimination half-life of approximately 4 h

Efficacy Summary

- All 17 (100 %) response evaluable patients have achieved SD or PR as best response
- Objective responses (all PRs) were observed in 6 of 17 (35 %) response evaluable patients. Two PRs have been confirmed. After the data cut, one additional patient achieved a PR on their first post-baseline scan
- Of the 4 patients that received prior poziotinib, TAK-788, or both, 2 achieved a PR (1 confirmed, 1 unconfirmed) with median time on treatment of 5 months (range: 3-8 months)

Figure 2 and Table 3: Duration of Treatment and Best Response



Response Characteristics	N=17
Best response:	
Progressive Disease (PD), n (%)	0 (0 %)
Stable Disease (SD), n (%)	11 (65 %)
Partial Response (PR), n(%)	6* (35 %)
Complete Response (CR), n (%)	0 (0 %)
Confirmed response, n	2
Unconfirmed response, n	1
Pending confirmation, n	3*

** one additional PR achieved after 01 Sep data cut.*

Figure 3: Maximal Change in Sum of Target Lesions (TLs)

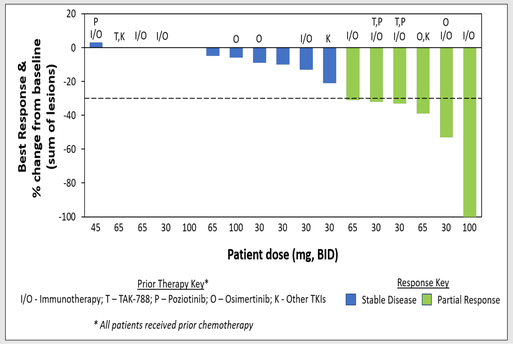
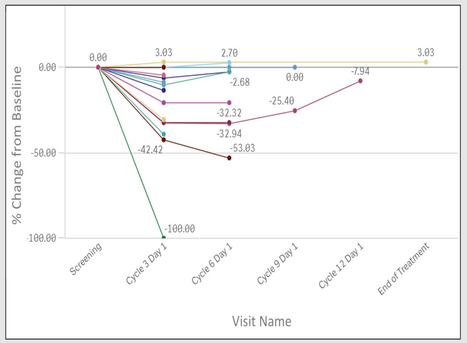


Figure 4: % Change in Sum of TLs from Baseline



Conclusions

- CLN-081 is a potent, selective, orally administered inhibitor of Exon-20 mutant EGFR
- In a group of heavily-pretreated patients with NSCLC, CLN-081 demonstrated encouraging initial antitumor activity across a broad range of dose levels tested, including at the starting dose of 30 mg po bid
- Objective responses observed in major exon20 variants and in patients post-poziotinib and/or TAK-788
- Initial safety profile of CLN-081 in patients treated to date is encouraging with Gr 1/Gr 2 rash, single case of Gr 1 drug-related diarrhea, and no Gr 3 or greater drug-related AE
- Dose escalation is ongoing and Phase 1 expansions have been initiated

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