Abstract 9077: Safety and activity of CLN-081 (TAS6417) in NSCLC with EGFR Exon 20 insertion mutations (Ins20)

Authors: Zofia Piotrowska[1], Helena Alexandra Yu[2], James Chih-Hsin Yang[3], Marianna Koczywas[4], Egbert F. Smit[5], Daniel Shao-Weng Tan[6], Victor Ho-Fun Lee[7], Ross A. Soo[8], John M. Wrangle[9], Alexander I. Spira[10], Vamsidhar Velcheti[11], Mark A. Socinski[12], Asher Page[13], David Witter[13], Leigh Zawel[13], Jon M Wigginton[13], Myles Steven Clancy[13], Danny Nguyen[14]

[1]Massachusetts General Hospital, Boston, MA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]National Taiwan University Cancer Center and National Taiwan University Cancer Center, Taipei, Taiwan; [4]City of Hope National Medical Center, Duarte, CA; [5]Netherlands Cancer Institute, Amsterdam, Netherlands; [6]National Cancer Centre Singapore, Singapore, Singapore; [7]Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong; [8]National University Hospital, Singapore, Singapore; [9]Medical University of South Carolina, Charleston, SC; [10]Virginia Cancer Specialists, Fairfax, VA; [11]NYU Langone, Perlmutter Cancer Center, New York, NY; [12]Advent Health Cancer Center, Orlando, FL; [13]Cullinan-Pearl, Cambridge, MA; [14]Pacific Shores Medical Group, Long Beach, CA

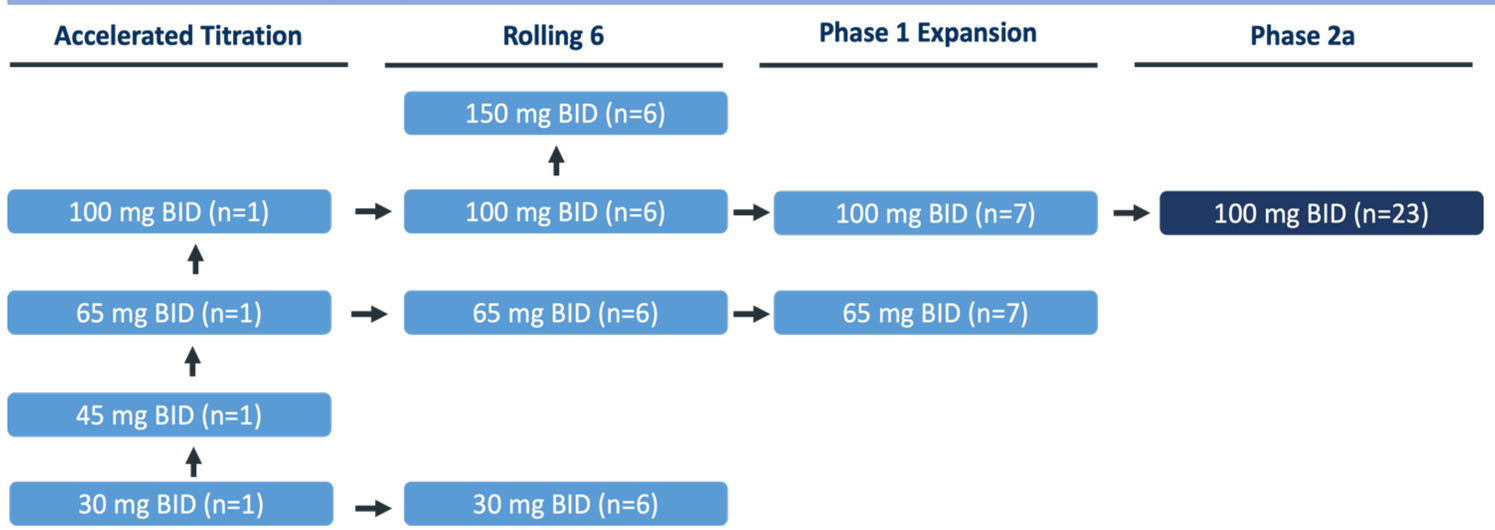
Background

- Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) mutations have been approved for the treatment of patients with NSCLC, but have modest efficacy in patients whose tumors harbor EGFR exon 20 insertion mutations (Ins20)
- Toxicities related to inhibition of wild-type EGFR, including rash and diarrhea, can limit the effectiveness of EGFR Ins20 inhibitors currently in development
- CLN-081 (also known as TAS6417) is a novel, oral EGFR inhibitor with a unique pyrrolopyrimidine scaffold, and potent, broad spectrum activity against EGFR mutations, including EGFR Ins20[1,2]
- CLN-081 demonstrates improved selectivity for inhibition of EGFR Ins20 mutant versus wild-type (WT) EGFR, suggesting that CLN-081 should have meaningful efficacy with an improved safety and overall risk-benefit profile compared to other EGFR TKIs in patients with NSCLC
- CLN-081 has limited activity against WT and Exon 20 mutant HER2
- We present interim results of the ongoing first-in-human, Phase 1/2a trial of CLN-081 (NCT04036682)

Methods

- Patients (pts) with EGFR Ins20 (identified by local, CLIA [or equivalent]-certified testing) previously treated with platinum-based therapy were eligible
- CLN-081 was dosed twice daily (BID) in 21-day cycles
- Dose levels including 30, 45, 65, 100, and 150 mg BID were explored during escalation
- Efficacy expansions were initiated at 30, 65 and 100 mg BID
- Ph2a expansion was initiated at 100 mg BID after meeting protocol-specified safety and efficacy criteria
- Tumor assessments were performed at baseline, after 6 weeks of CLN-081 administration, and every 9 weeks thereafter

Figure 1: CLN-081-001 Study Design



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Results – Patient Summary

- At the data cut (01 Apr 2021), 45 pts received at least 1 dose of CLN-081
- 42 of 45 pts were response evaluable; 1 pt discontinued treatment before their 1st post-baseline response assessment and 2 pts had not been restaged at the time of the data cut, but remain on treatment
- All pts received ≥ 1 prior systemic platinum chemotherapy regimen
- 32/44 (73%) pts received ≥ 2 prior therapies before study entry
- 25/44 (56 %) pts received prior immunotherapy
- 18/44 (40%) pts received a prior EGFR TKI

Table 1: Patient Demographics

Characteristic	N=44*
Median Age, years (Range)	64 (44-82)
Male / Female / Not Reported, n (%)	20 (47) / 22 (51) / 1 (2)
Race, n (%)	
Asian	15 (35)
Black	2 (5)
White	24 (56)
Other or Not Reported	2 (5)
ECOG 0 / 1, n (%)	15 (34) / 29 (66)
Stable, asymptomatic brain mets at BL, n (%)	12 (27)

**Sex and Race data not captured on one patient*

Table 2: Prior Therapies

Characteristic	N=44*
Number of Prior Systemic Therapies, Median (range)	2 (1-9)
1, n (%)	12 (27)
2, n (%)	17 (39)
≥ 3, n (%)	15 (34)
Prior afatinib or gefitinib, n (%)	8 (18)
Prior osimertinib, n (%)	9 (20)
Prior pozitinib and/or mobocertinib, n (%)	4 (9)
Prior immunotherapy, n (%)	25 (56)

** Prior therapy data not reported on one patient*

Results – Safety Summary

- 44/45 (98 %) pts experienced an adverse event (AE), irrespective of grade or attribution, including 20/45 (44%) pts with Grade (Gr) ≥ 3 events
- The most common AEs, irrespective of attribution or grade, have been rash, anemia, and diarrhea
- 44/45 (98 %) pts experienced a treatment related adverse event (TRAE), irrespective of grade, including 8/45 (18%) pts with Gr ≥ 3 events
- 1 pt experienced a DLT; Gr 3 diarrhea at 150 mg BID
- Dose reductions were required in 5 (11%) pts
- Treatment-related discontinuations were required in 4 (9%) pts

<u>Wild-Type EGFR Associated TRAEs</u>

- No pts experienced Gr ≥ 3 treatment-related rash
- Only 1 pt experienced treatment-related Gr 3 diarrhea (at 150 mg BID)
- 1 pt discontinued CLN-081 due to treatment-related Gr 2 pneumonitis; this pt also experienced pneumonitis while receiving prior osimertinib

Table 3: TRAEs in ≥ 15 % of Patients (N=45)

Preferred Term	n (%)
Rash*	34 (76)
Diarrhea	10 (22)
Paronychia	10 (22)
Stomatitis	8 (18)
Nausea	8 (18)
Anemia	8 (18)
Increased AST	7 (16)
Dry Skin	7 (16)

Table 4: Grade ≥ 3 TRAEs in All Patients (N=45)

Preferred Term	n (%)
Anemia	4 (9)
Increased AST	2 (4)
Increased ALT	2 (4)
Diarrhea	1 (2)
Increased Amylase	1 (2)
Neutropenia	1 (2)
Stomatitis	1 (2)

** Includes rash, rash maculo-papular, rash macular, pruritus, dermatitis acneiform, dermatitis, and urticaria*

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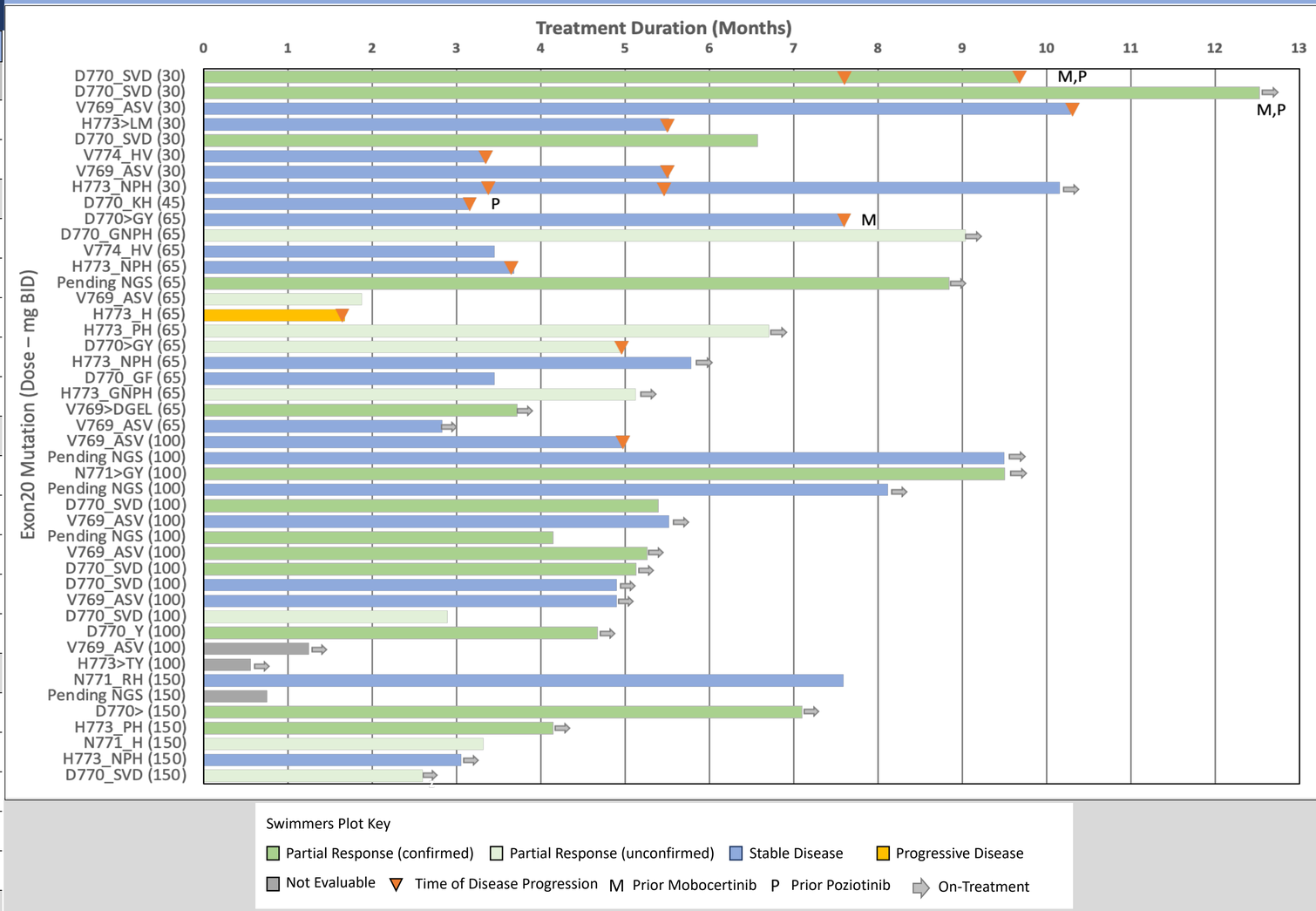
Results – Safety Summary

Table 5: TRAEs of Interest by Dose and Grade

Dose (BID)	30 mg	45 mg	65 mg	100 mg	150 mg
Safety Population, n	8	1	14	15	7
DLTs, n	--	--	--	--	1
Grade 1 TRAEs					
Rash, n	6	--	7	5	4
Diarrhea, n	2	--	1	3	1
Elevated ALT, n	--	--	1	1	1
Elevated AST, n	1	--	1	1	1
Anemia, n	--	--	1	2	--
Grade 2 TRAEs					
Rash, n	--	--	6	5	1
Diarrhea, n	--	--	--	1	1
Elevated ALT, n	--	--	--	--	--
Elevated AST, n	--	--	--	1	--
Anemia, n	--	--	--	1	--
Grade 3 TRAEs					
Rash, n	--	--	--	--	--
Diarrhea, n	--	--	--	--	1
Elevated ALT, n	--	--	1	1	--
Elevated AST, n	--	--	1	--	1
Anemia, n	1	--	2	--	1
Grade 4 TRAEs					
Rash, n	--	--	--	--	--
Diarrhea, n	--	--	--	--	--
Elevated ALT, n	--	--	--	--	1
Elevated AST, n	--	--	--	--	--
Anemia, n	--	--	--	--	--

Figure 2: Duration of Treatment with CLN-081



Results – Efficacy Summary

- CLN-081 is active across all dose levels and across a spectrum of EGFR Ins20
- 22/42 (52%) response-evaluable pts across all dose levels remained on treatment at the time of the data cutoff
- Responses observed in prior EGFR TKIs 8/18 (44%), including pts with prior mobocertinib and/or poziotinib

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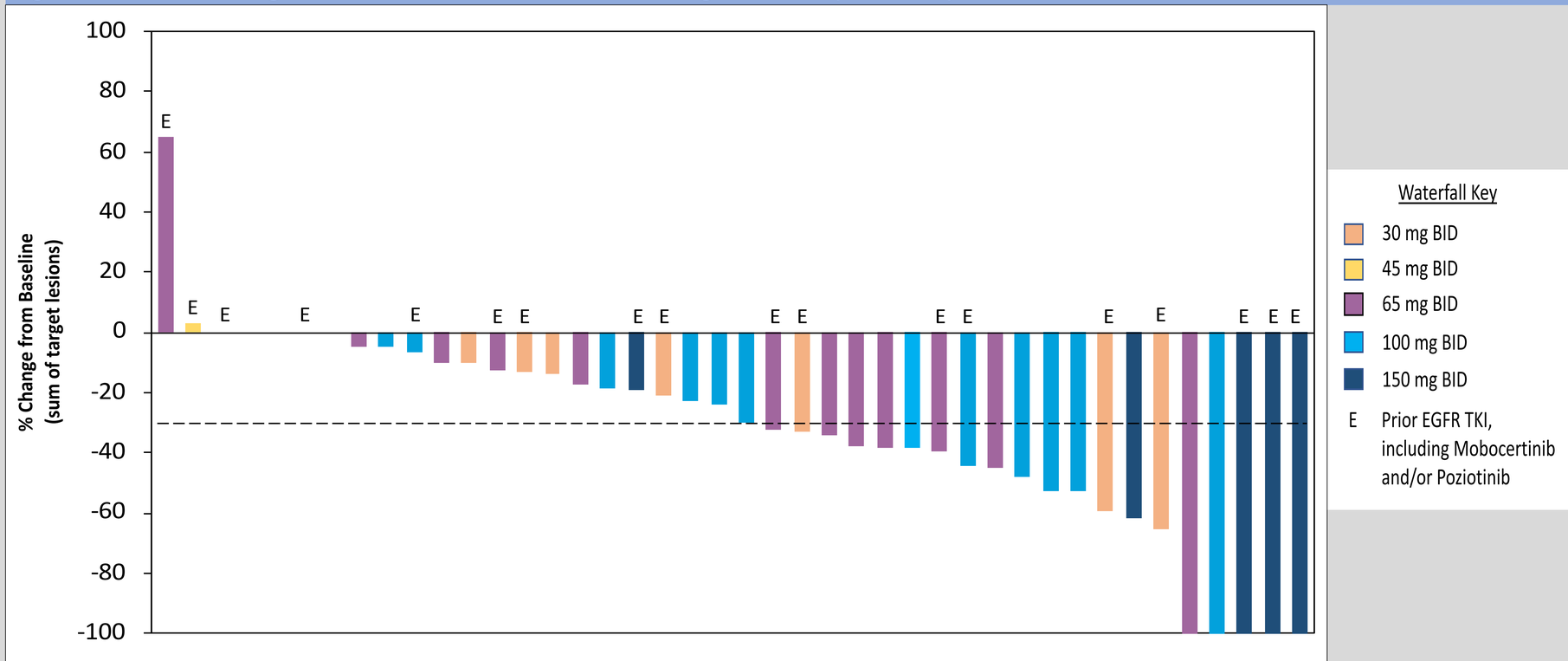
Results – Efficacy Summary

- Objective responses (all partial responses [PR]) were observed in 21/42 (50 %) response evaluable patients treated across <u>all</u> dose levels
- Of the 21, 13 pts (31%) achieved a confirmed objective response; objective responses were unconfirmed in 8 patients, including 5 pts who were pending a confirmatory scan at the data cutoff
- At 100 mg BID, 7/13 (54%) patients achieved a PR, including 6/13 (46%) pts with a confirmed PR and 1 pt was unconfirmed
- 41/42 (98 %) response evaluable patients have achieved stable disease (SD) or PR as best response
- Disease control (PR or SD $\geq$ 6 months) was achieved in 27/42 (64%) pts across all dose levels

Table 6: Response Characteristics by Dose

Best Response n, (%)	30 mg BID (n=8)	45 mg BID (n=1)	65 mg BID (n=14)	100 mg BID (n=13)	150 mg BID (n=6)	**Total (n=42)**
PR	3 (38)	0	7 (50)	7 (54)	4 (67)	**21 (50)**
SD	5 (62)	1 (100)	6 (43)	6 (46)	2 (33)	**20 (48)**
PD	0	0	1 (7)	0	0	**1 (2)**
Confirmed Response	3 (38)	0	2 (14)	6 (46)	2 (33)	**13 (31)**
Unconfirmed Response	0	0	2 (14)	1 (8)	0	**3 (7)**
Pending Confirmation	0	0	3 (21)	0	2 (33)	**5 (12)**
Disease Control Rate (PR + SD ≥ 6 mo)	5 (62)	0	8 (57)	9 (69)	5 (83)	**27 (64)**

Figure 3: Percent Change From Baseline in Dimensions of Target Lesions (Waterfall)



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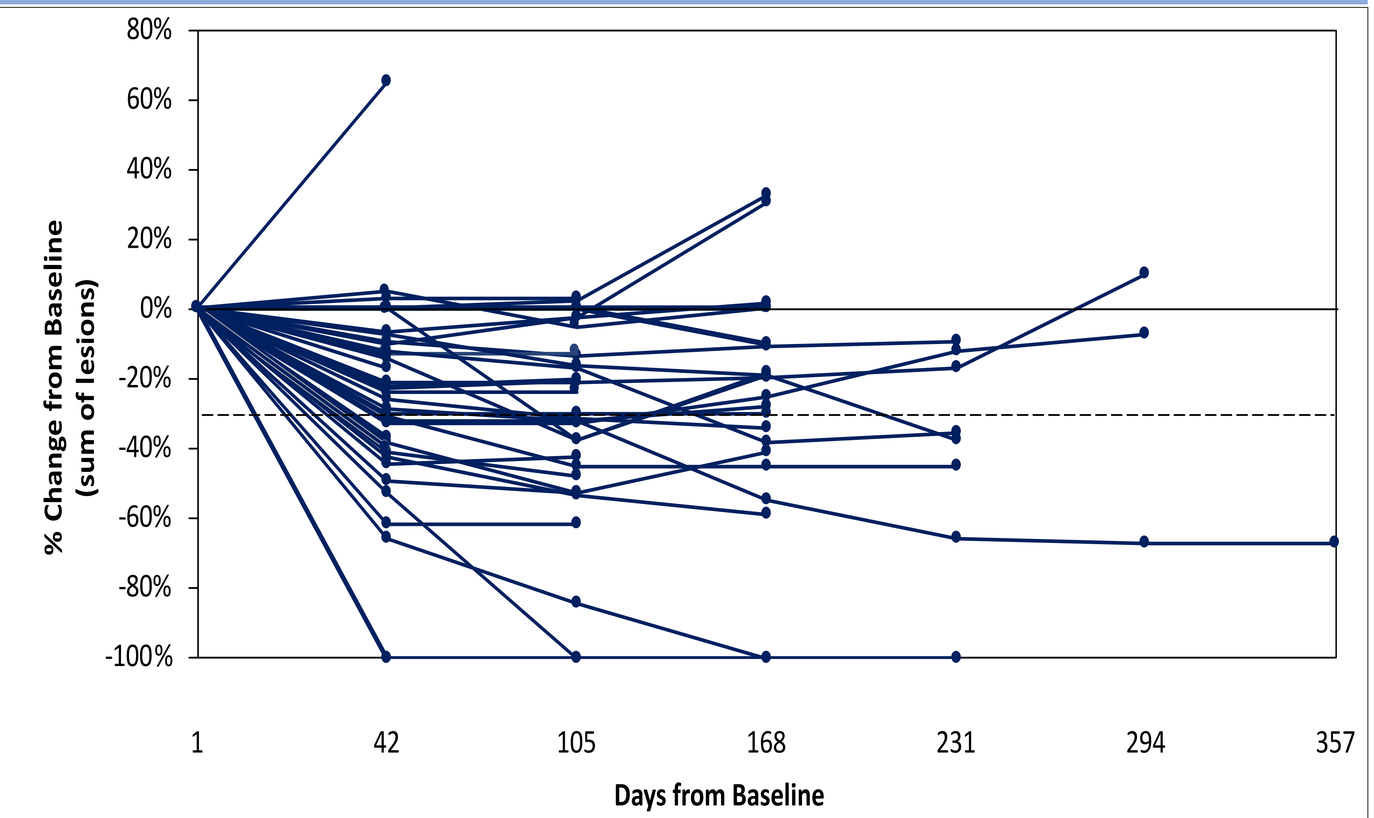
Results – Efficacy Summary

Figure 4: % Change in Sum of Target Lesions from Baseline



- CLN-081 acts rapidly, with 32/42 (76%) pts experiencing some degree of tumor regression at their first post-baseline response assessment
- Anecdotal examples of patients reporting rapid symptom improvement (dyspnea, shortness of breath, cough)

Conclusions

- CLN-081 has an acceptable safety profile, including reduced frequency and severity of diarrhea compared to historical experience with other EGFR inhibitors.
- AEs to date have been manageable and reversible with no requirement for prophylaxis of GI or skin-related toxicity
- CLN-081 demonstrated dose proportional increases in C_{max} and AUC, and no evidence of meaningful drug accumulation across the dose range tested
- CLN-081 has encouraging preliminary antitumor activity in heavily-pretreated patients, including:
  - Across the range of dose levels tested to date
  - Across a spectrum of EGFR Ins20 variants
  - After progression on prior EGFR TKIs, including mobocertinib and/or poziotinib
  - After progression on prior checkpoint inhibitors
  - High rates of response with encouraging disease control in a maturing data set
- Phase 2 expansion cohort currently enrolling at 100 mg BID

References

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Correspondence to: Myles Clancy (mclancy@cullinanoncology.com)