2022 ASCO® ANNUAL MEETING

Phase1/2a Study of CLN-081 in NSCLC Patients with EGFR Exon 20 Insertion (ex20ins) Mutations

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EGFR exon 20 insertion (ex20ins) mutations in NSCLC

~2-3% of all non-small cell lung cancer (NSCLC) cases harbor EGFR ex20ins mutations[1]

- This frequency is higher than RET, ROS1, and NTRK fusions are observed in NSCLC

Patients with ex20ins have poorer outcomes than those with more common EGFR mutations[2]

- Survival for ex20ins patients is inferior to patients with sensitive mutations

Agents targeting EGFR ex20ins mutations have been recently approved for the treatment of patients with NSCLC

- Currently approved agents demonstrate significant toxicity

Toxicities related to inhibition of wild-type EGFR, including rash and diarrhea, may limit the tolerability of some ex20ins inhibitors

- Therapeutic window between wild-type EGFR and EGFR ex20ins is narrow

1. Burnett H, et al. PLOS ONE. 2021;16(3).

2. Leal JL, et al. Clin Lung Cancer. 2021;22(6).

Safer and more effective novel therapies to treat ex20ins NSCLC remain an unmet medical need

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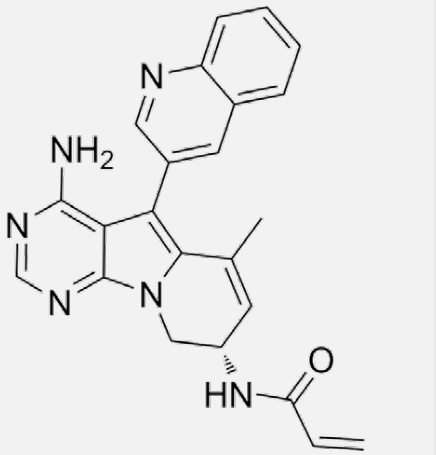
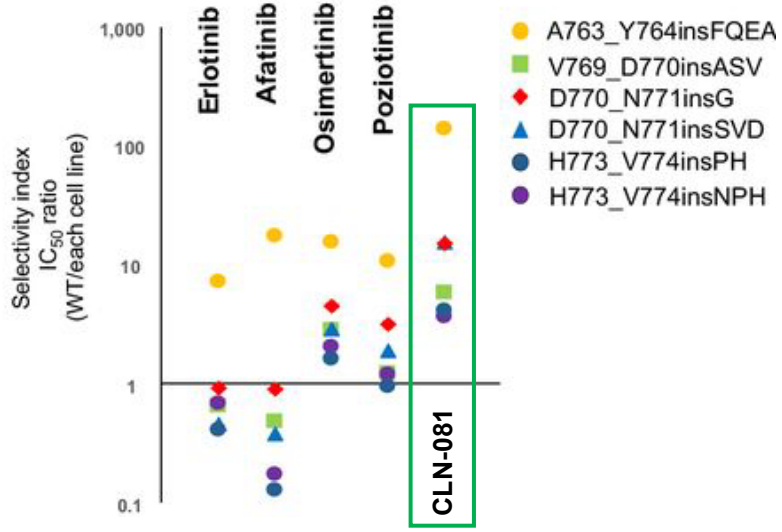
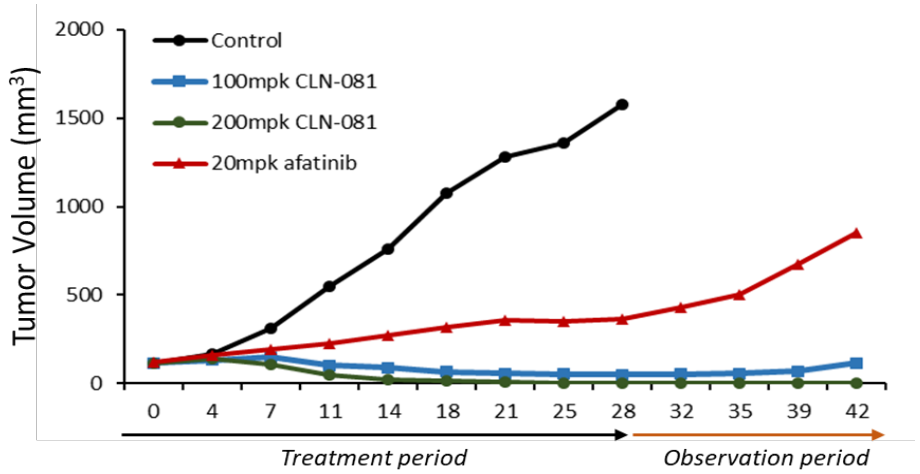
CLN-081: A selective EGFR inhibitor for NSCLC patients with exon 20 insertion mutations



CLN-081

Select CLN-081 pre-clinical data





LXF2478 PDX model for lung cancer harboring EGFR V769_D770INSASV

- CLN-081 (TAS6417) is a novel, irreversible, oral EGFR inhibitor with a unique pyrrolopyrimidine scaffold, and potent, broad-spectrum activity against EGFR mutations, including EGFR ex20ins[1,2]
- Demonstrates selectivity for inhibition of EGFR ex20ins mutant vs wild-type EGFR

[1]Hasako S, et al. *Mol Cancer Ther* 2018; [2]Udagawa H, et al. *Mol Cancer Res* 2019

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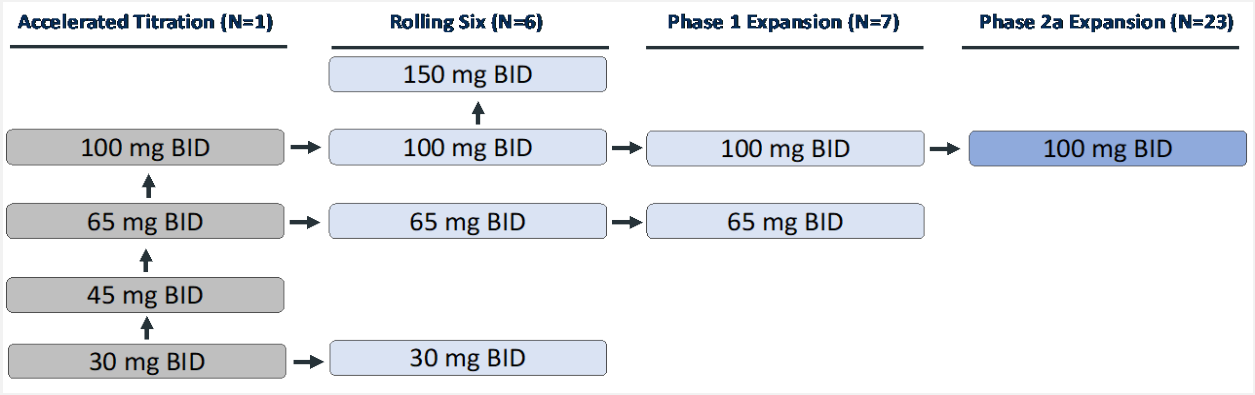
CLN-081-001: Phase 1/2a Study Design (NCT04036682)

STUDY SCHEMA



- Dose escalation used both an accelerated titration and rolling-six design
- Phase 1 and Phase 2a dose expansion cohorts enrolled additional patients at dose levels meeting pre-defined thresholds for efficacy and tolerability

KEY ELIGIBILITY

- Confirmed recurrent or metastatic NSCLC with documented EGFR ex20ins mutation demonstrated by local laboratory
- Prior treatment in the recurrent/metastatic setting including a platinum-based chemotherapy regimen unless declined
- Prior treatment with an EGFR exon20in-targeting drug was allowed only in dose-escalation cohorts
- Patients with CNS metastases stable for ≥4 weeks prior to C1D1 were eligible

TREATMENT PLAN

- Patients receive CLN-081 twice daily and may continue to receive treatment until disease progression, unacceptable toxicity or withdrawal of consent
- Tumor response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) at 6 weeks and every 9 weeks thereafter

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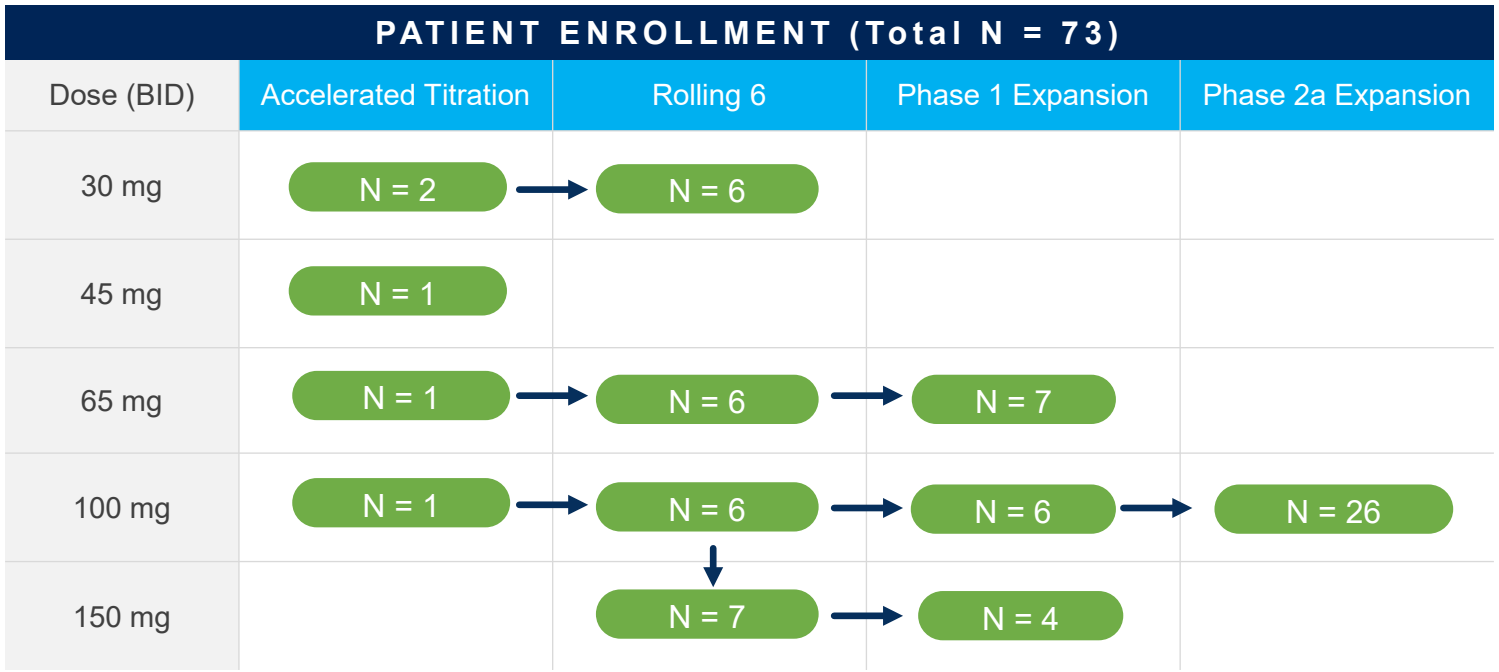
CLN-081-001: Patient Disposition



GEOGRAPHIC FOOTPRINT					
Location	US	Netherlands	Singapore	Hong Kong	Taiwan
# of Sites	9	1	2	1	1

- **Data cut-off 9 May 2022**
- 73 patients enrolled across doses ranging from 30 to 150 mg BID
- Enrollment at 150 mg BID stopped after 11 patients based on toxicity

N (%)	N = 73
Treatment Ongoing	24 (33%)
Discontinued	49 (67%)
Progressive Disease	30 (61%)
Adverse Event	12 (25%)
Withdrawal of Consent	3 (6%)
Other	4 (8%)

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Baseline characteristics of enrolled patients

CHARACTERISTIC	ALL PATIENTS (N=73)
Median age (range)	64 (36-82)
Female	41 (56%)
ECOG PS (0, 1)	22 (30%), 51(70%)
Number of prior systemic anticancer regimens[1]	
1 (%)	22 (30%)
2 (%)	**32 (44%)**
≥3 (%)	**16 (22%)**
Median (range)	2 (1-9)
Prior EGFR TKI (non-Ex20)	**26 (36%)**
Prior afatinib or gefitinib	13 (18%)
Prior osimertinib	13 (18%)
Prior poziotinib and/or mobocertinib (%)	**3 (4%)**
Prior immunotherapy (%)	40 (55%)
History of CNS involvement (%)	**28 (38%)**

[1]Three patients with no prior therapy (declined chemotherapy)

- Heavily pre-treated patients
- 66% of patients with ≥2 prior lines of treatment
- Prior EGFR TKI treatment in 36% of patients, including 3 patients who had received prior poziotinib and/or mobocertinib
- 55% of patients received prior immunotherapy
- 38% had history of CNS metastases at baseline

Treatment-Related Adverse Events Occurring in ≥10% of Patients

Dose BID	≤65 mg (N = 23)		100 mg (N = 39)		150 mg (N = 11)		Overall (N = 73)	
AE Term, n (%)	**All grade[1]**	**Grade ≥ 3**	**All grade**	**Grade ≥ 3**	**All grade**	**Grade ≥ 3**	**All grade**	**Grade ≥3**
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17)	5 (13)	1 (3)	2 (18)	2 (18)	14 (19)	7 (10)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4)	3 (8)	1 (3)	2 (18)	1 (9)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0
Dose Interruptions	5 (22)		13 (33)		6 (55)		24 (33)	
Dose Reductions	2 (9)		5 (13)		3 (27)		10 (14)	
Dose Discontinuations	2 (9)		2 (5)		2 (18)		6 (8)	

- Most AEs Grade 1/2
- Dose reductions and discontinuations were uncommon at doses below 150 mg
- No Grade ≥3 rash or diarrhea observed at doses <150 mg
- Treatment-related pneumonitis was observed in 4 patients (1 at 65, 2 at 100, and 1 at 150 mg), but cases were asymptomatic (1) or confounded by comorbid medical illness (3)[2]

[1]CTCAE v5.0; [2]100 mg patient with Gr3 pneumonitis confounded by recent treatment with CPI and concurrent hydropneumothorax in contralateral lung; 150 mg patient with Gr3 pneumonitis confounded by concurrent pneumocystis infection, had stopped CLN-081 3 weeks prior to event; 100 mg patient with grade 1 pneumonitis treated with steroids with resolution and continued therapy; 65 mg patient with Gr 2 pneumonitis previously had pneumonitis on osimertinib.

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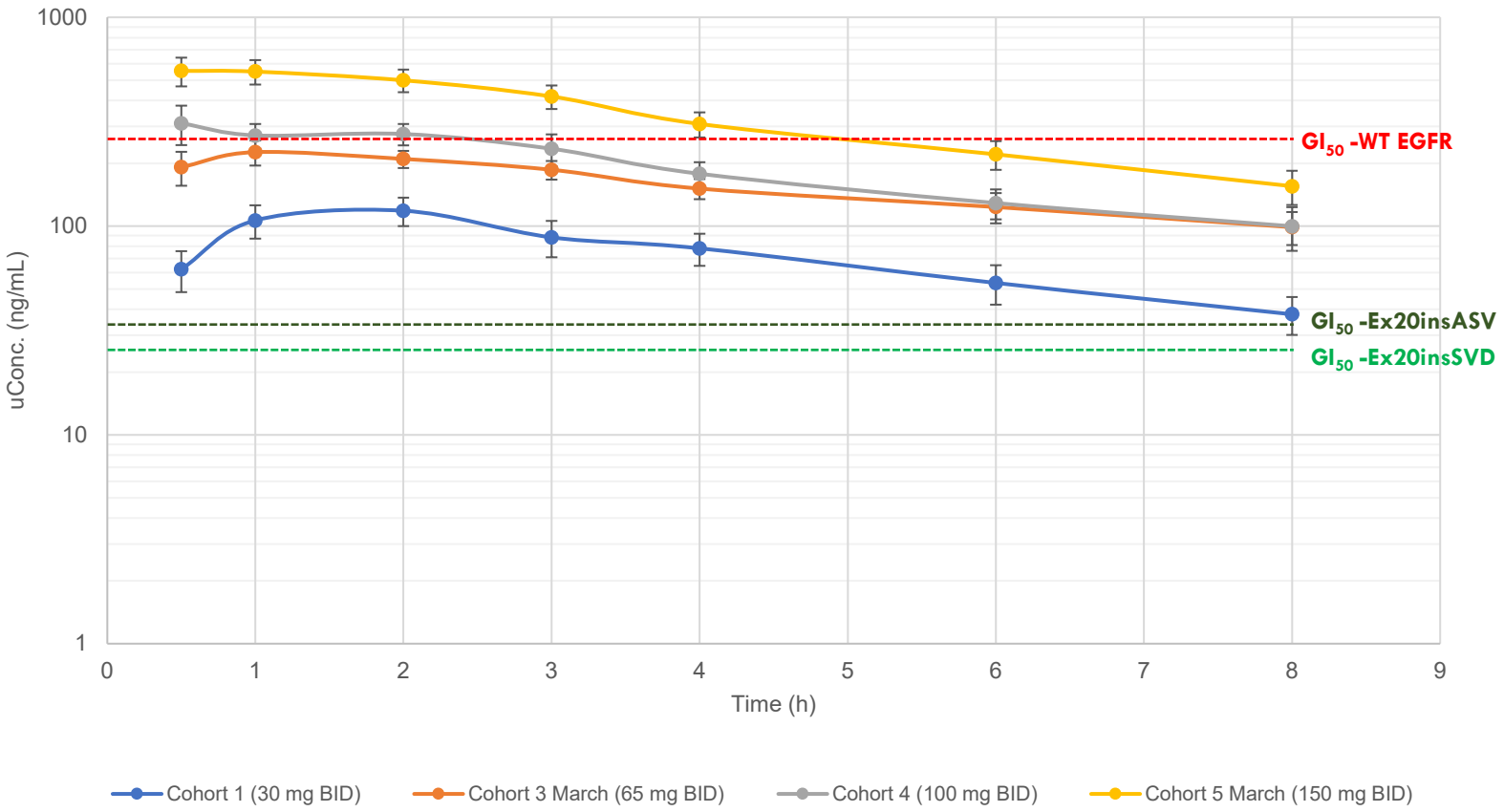
Pharmacokinetic (PK) profile consistent with clinical observations

AVERAGE UNBOUND PLASMA CONCENTRATION OVER TIME*



*Data from Phase 1 patients. Uses standard error of the mean.

- Sustained PK exposure over GI_{50} for ex20ins EGFR for 8h post dose
- Limited time of exposure over GI_{50} for WT EGFR at doses < 150 mg BID
- Consistent with clinical safety profile at 100 mg vs 150 mg BID dose levels

GI50 – 50% Growth inhibition
WT – Wild type
Ex20insASV – Exon 20 insertion V769_D770
Ex20insSVD - Exon 20 insertion D770_N771insSVD

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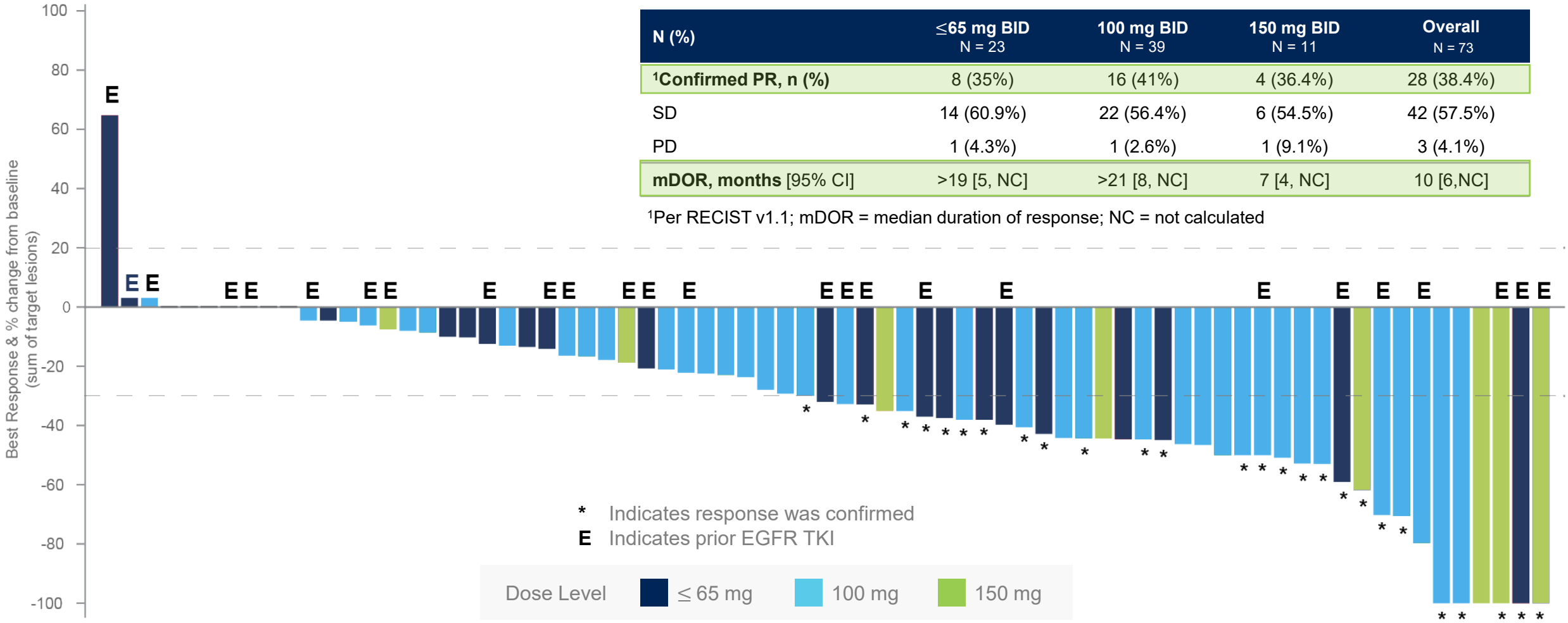
CLN-081-001: Best percentage change from baseline in target lesion dimensions and confirmed response by dose level

N (%)	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
[1]**Confirmed PR, n (%)**	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDOR, months [95% CI]	>19 [5, NC]	>21 [8, NC]	7 [4, NC]	10 [6,NC]

[1]Per RECIST v1.1; mDOR = median duration of response; NC = not calculated



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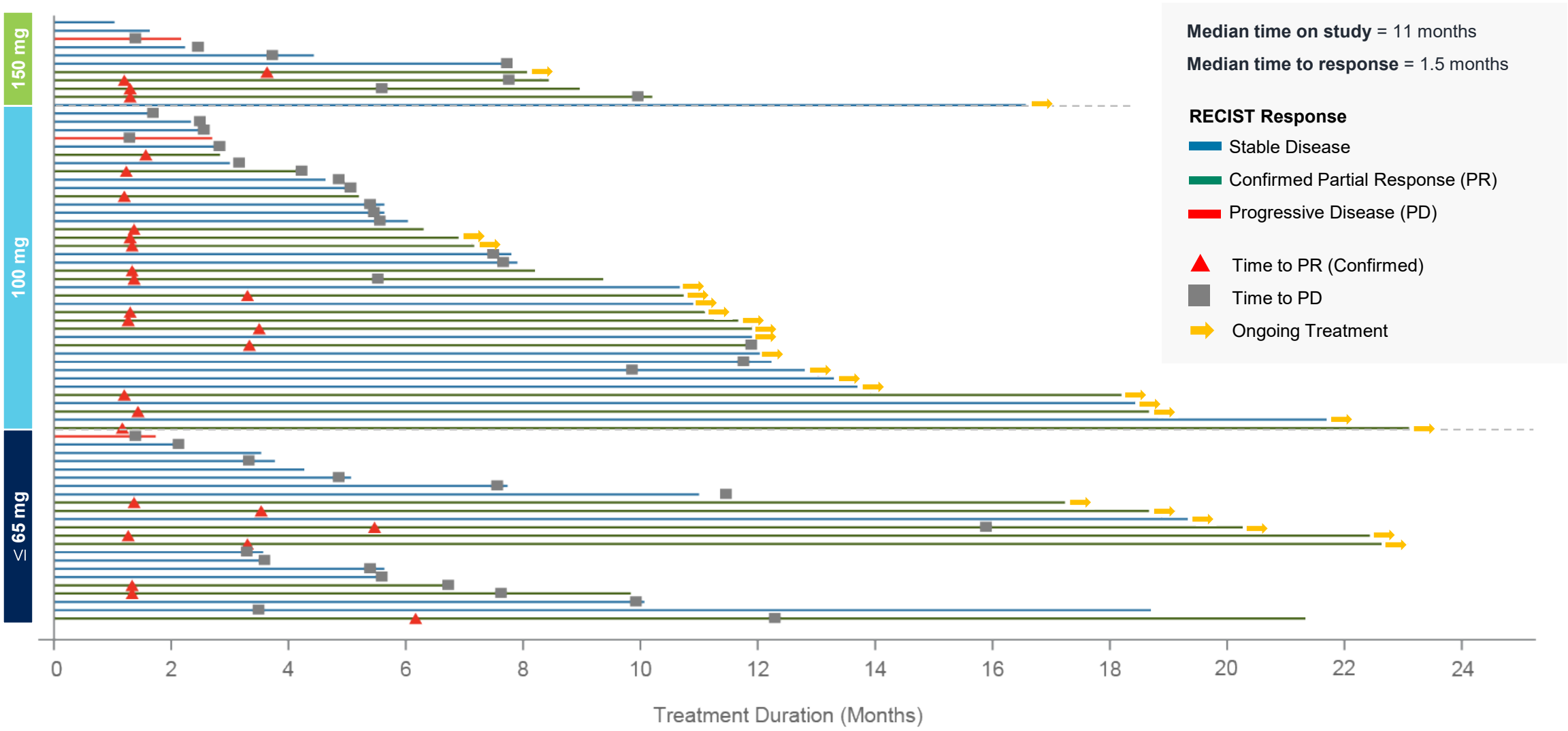
CLN-081-001: Time on treatment and activity, all patients by dose level



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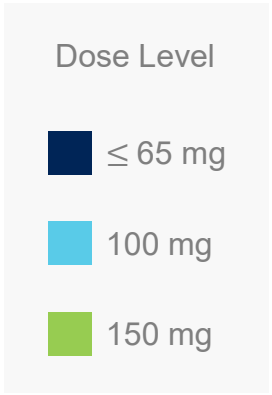
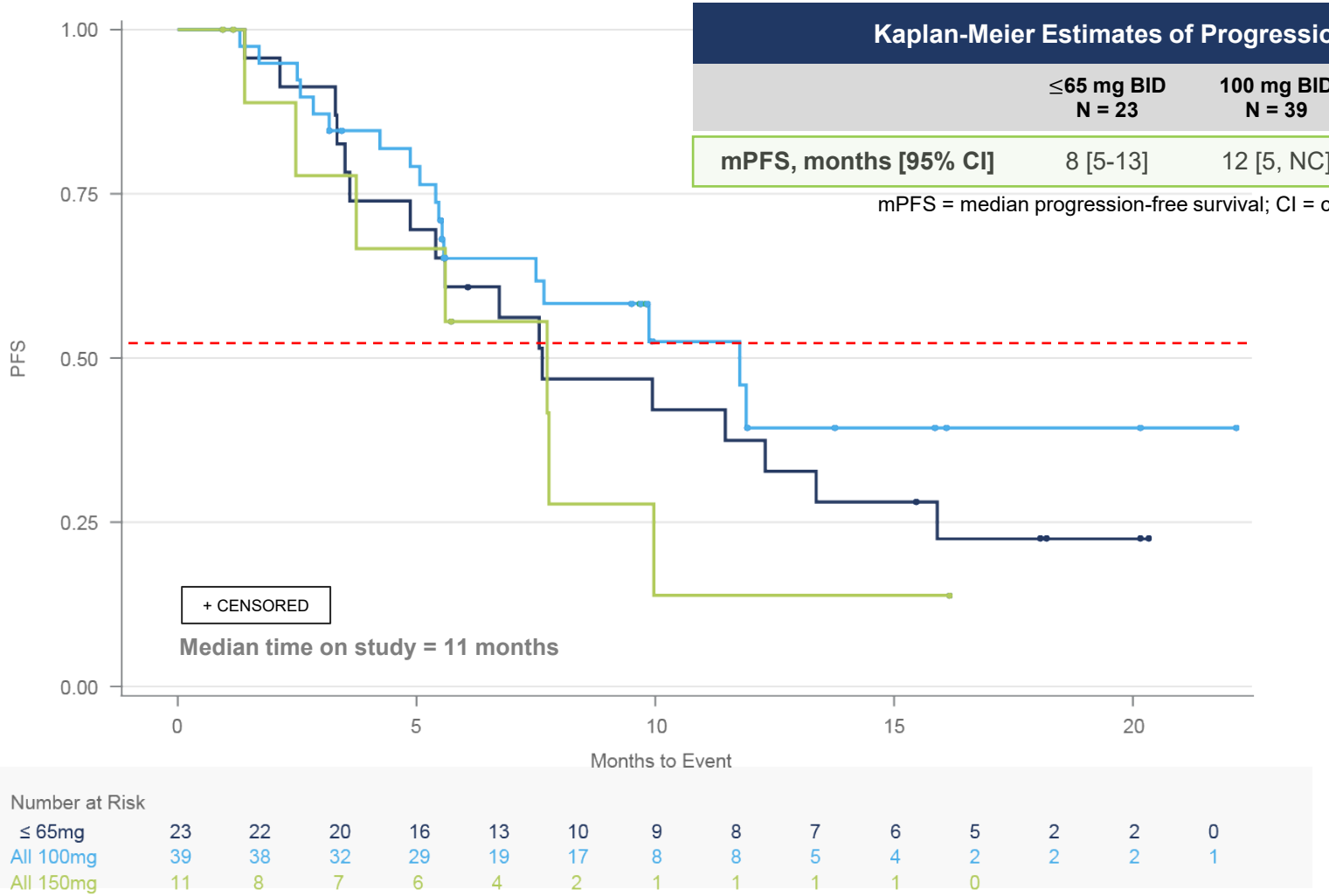
CLN-081-001: Progression-Free Survival (PFS) by dose level





Kaplan-Meier Estimates of Progression-Free Survival

	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
mPFS, months [95% CI]	8 [5-13]	12 [5, NC]	8 [1,10]	10 [6,12]

mPFS = median progression-free survival; CI = confidence interval; NC = not calculated

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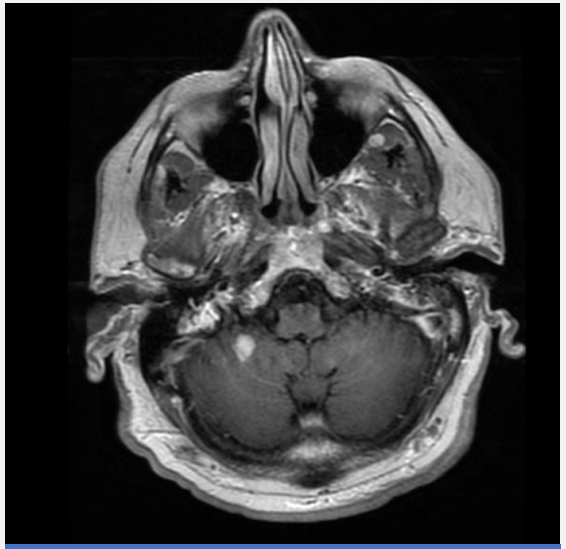
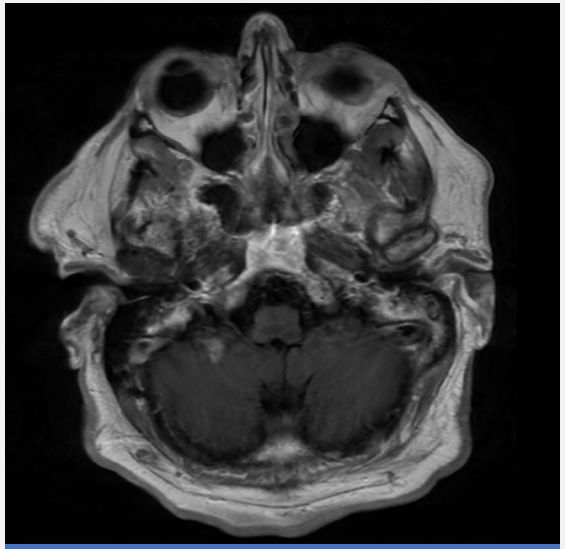
Intracranial response observed in a patient with CNS target lesion at baseline



Baseline 19 mm



Cycle 6 10 mm

69M underwent surgical resection and adjuvant chemotherapy with cisplatin and pemetrexed. A right frontal lobe brain mass was resected and irradiated approximately 1 year later. A separate asymptomatic cerebellar lesion was identified prior to study entry.

- 3 patients entered the study with CNS target lesions at baseline:[1]
  - **Patient #1 achieved both an intracranial and systemic response at cycle 6 and remains in PR at cycle 16** (images at left)
  - Patient #2 continues on treatment after 1 year with stable disease both intracranially and systemically
  - Patient #3 progressed in the brain at cycle 3
- A dedicated study in patients with CNS metastases is planned

[1]Brain MRIs were required only for patients with a history of known CNS metastases or with signs or symptoms suggestive of CNS disease

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Conclusions

Safety

Safety profile amenable for long-term treatment at doses <150 mg BID

- Most adverse events Grade 1/2
- **No Grade ≥3 rash or diarrhea at doses <150 mg BID**

Efficacy

Objective responses observed in heavily pre-treated patients, including patients who progressed on treatment with other EGFR TKIs

- **At 100 mg BID: ORR 41%, mDOR >21 mos, mPFS 12 mos**

Summary

Enrollment to the phase 2b portion of the study is planned for 2H 2022

- Studies in patients with active CNS metastases and those who have relapsed after prior ex20ins therapies are planned

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Acknowledgements

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- This trial was sponsored by Cullinan Pearl Corporation, a Cullinan Oncology portfolio company
- CLN-081/TAS56417 was discovered by Taiho Pharmaceuticals

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