

First-in-Human Trial of BGB-58067, an MTA-Cooperative PRMT5 Inhibitor, in MTAP-Deficient Advanced Tumors

FPN: 1043P

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CONCLUSIONS

- BGB-58067, an MTA-cooperative PRMT5 inhibitor, demonstrated promising monotherapy activity in heavily pretreated patients with MTAP-deficient solid tumors, including NSCLC
- In patients with EGFR wild-type NSCLC, BGB-58067 demonstrated encouraging and durable clinical activity with an ORR of 38.5% and a median PFS of 8.1 months
- The low incidence of CNS progression in 2L+ NSCLC, together with an intracranial objective response rate of 30.8% observed in patients with brain metastases, shows clinically meaningful CNS activity of BGB-58067
- BGB-58067 demonstrated a well-tolerated and manageable safety profile
- BGB-58067 demonstrated a favorable PK profile across the evaluated dose ranges, and robust tumor cell target engagement as suggested by SDMA depletion observed in paired biopsy
- These data support ongoing exploration of combination cohorts in 1L NSCLC and PDAC with standard-of-care treatments, and with RAS inhibitors in PDAC

INTRODUCTION

- Protein arginine methyltransferase 5 (PRMT5) is a type II arginine methyltransferase that participates in the methylation of substrates involved in cellular activities, including transcription, RNA splicing, DNA damage repair, apoptosis, and cell-cycle regulation¹
- Homozygous loss of *methylthioadenosine phosphorylase (MTAP)* leads to the accumulation of methylthioadenosine (MTA), which partially inhibits PRMT5 and increases the susceptibility of tumor cell lines to additional PRMT5 inhibition^{2,4}
- BGB-58067 is an oral, potent, brain-penetrant, MTA-cooperative PRMT5 inhibitor that selectively binds to and stabilizes the catalytically inactive PRMT5/MTA complex and demonstrates antitumor activity in MTA phosphorylase (MTAP)-deficient tumor models⁵
- Here, we present the first results from the dose-escalation/safety expansion stage of the phase 1 trial of BGB-58067 in patients with advanced solid tumors with MTAP deficiency, with a focus on patients with non-small cell lung cancer (NSCLC) (NCT06589596)

METHODS

Trial Design

- This dose-escalation/safety expansion stage of the phase 1, open-label, global, multicenter trial was conducted across trial sites in Australia, China, Denmark, France, South Korea, Spain, and the United States (Figure 1)

Figure 1. Study Design

Key eligibility criteria

- Pathologically confirmed advanced, metastatic, or unresectable solid tumors
- ECOG PS of 0 or 1 or Karnofsky Performance Scale ≥ 70
- Evidence of homozygous deletion of *MTAP* gene, or lost MTAP expression in the tumor tissue
- Patients with prior treatment with any PRMT5 inhibitor or methionine adenosyltransferase 2a inhibitor were excluded
- Patients with untreated brain metastases were eligible if both of the following criteria were met:
 - Neurologically asymptomatic on stable doses of corticosteroids and/or anti-epileptic drugs ≥ 2 weeks prior to first dose of study treatment
 - Immediate local treatment for brain metastases is not indicated in the opinion of the investigator
- Patients with any malignancy ≤ 2 years before first dose of study drug except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively were excluded

Key endpoints

- Safety/tolerability and the RDE(s) of BGB-58067
- Preliminary antitumor activity (assessed by the investigator per RECIST v1.1 or RANO 2.0)
- PK/pharmacodynamic profile

Phase 1a Dose Escalation and Safety Expansion (N=182)

Part A: BGB-58067 Dose Escalation

800 mg QD, n=7

600 mg QD, n=34

450 mg QD, n=29

300 mg QD, n=42

200 mg QD, n=36

100 mg QD, n=23

50 mg QD, n=2

Supplemental enrollment at cleared DLs

Part B: BGB-58067 Safety Expansion and Food Effect

Cohort A and B: Previously Treated NSCLC and PDAC

Cohort C: Food Effect Cohort

Advanced solid tumors with MTAP deficiency were enrolled

Supplemental enrollment at 400 mg QD was retrospectively opened and nine patients were enrolled. **Abbreviations:** DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; MTAP, methylthioadenosine phosphorylase; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PRMT5, protein arginine methyltransferase 5; QD, once daily; RANO, Response Assessment in Neuro-Oncology; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors.

Analysis and Statistical Methods

- Dose escalation was guided using the modified toxicity probability interval-2 method⁶
- Efficacy endpoints such as ORR and disease control rate (DCR) were summarized by dose level along with their 95% CIs. The time-to-event endpoints were analyzed using the Kaplan–Meier method
- The safety analysis set included all patients who received ≥ 1 dose of study drug. The clinical activity evaluable analysis set included all patients who received ≥ 1 dose of study drug, had radiologically evaluable disease at baseline, and ≥ 1 evaluable postbaseline radiological tumor response assessment prior to discontinuation, subsequent anticancer therapies or death

RESULTS

Baseline Characteristics and Patient Disposition

- As of the data cutoff date of September 12, 2026, 182 patients were treated; 43 patients remain on treatment
- Median (range) study follow-up time was 5.1 (0.2-17.8) months for all treated patients and 7.1 (0.2-17.8) months for the NSCLC cohort
- Baseline characteristics for all treated patients, including those with glioma, are shown in **Table 1**
- Baseline characteristics for the NSCLC cohort included a median (range) age of 63 (35-81) years; 79.5% were Asian; median (range) number of prior treatment lines in the metastatic/advanced setting was 3 (1-10); 50.6%, 19.3%, and 37.3% had bone, liver, and brain metastases, respectively; and 66.3% were treated with prior immuno-oncological agents

Table 1. Baseline Characteristics (Safety Analysis Set)

	Total (N=182)
Median (range) age, years	63 (20-86)
Age group, n (%)	
<65 years ≥ 65 years	105 (57.7) 77 (42.3)
Sex, n (%)	
Male Female	97 (53.3) 85 (46.7)
Race, n (%)	
Asian White Other	106 (58.2) 57 (31.3) 19 (10.4)
ECOG PS, n (%)	
0 1 2	40 (22.0) 117 (64.3) 11 (0.5)
Median prior lines of therapy (range)	2 (0-10)
Prior treatment lines, n (%)	
0 1 2 ≥ 3	4 (2.2) 52 (28.6) 50 (27.5) 75 (41.2)
Type of cancer at initial diagnosis, n (%)	
NSCLC PDAC Glioma Other	83 (45.6) 41 (22.5) 24 (13.2) 34 (18.7)
Baseline MTAP status	
MTAP homozygous deletion via NGS MTAP expression loss via IHC	90 (49.5) 92 (50.5)

Baseline value is defined as the last non-missing result on or before the date of the first dose of study drug. **Abbreviations:** IHC, immunohistochemistry; MTAP, methylthioadenosine phosphorylase; NOS, next-generation sequencing; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

Safety and Tolerability

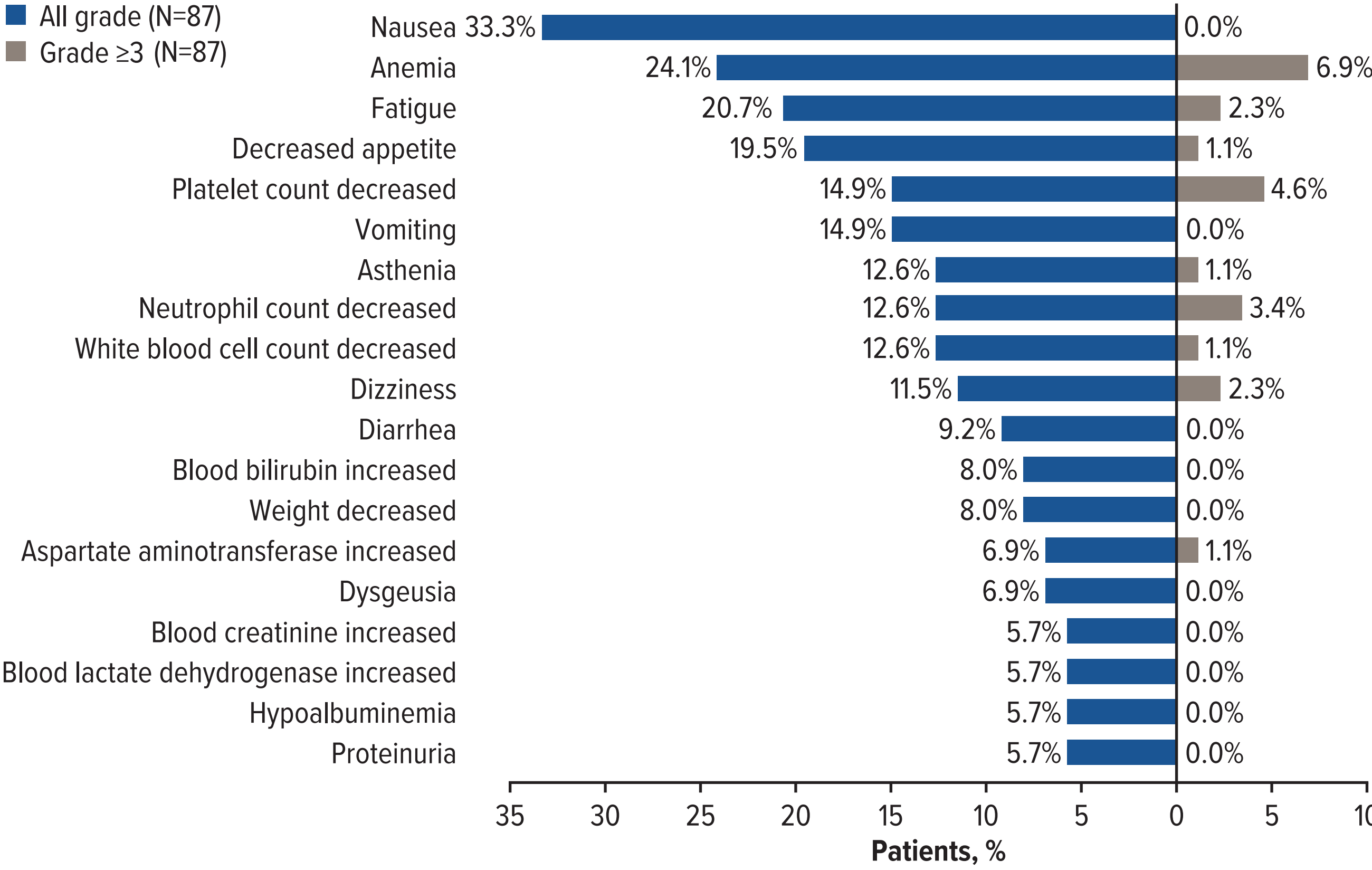
- BGB-58067 monotherapy had a well-tolerated safety profile (**Table 2**)
- The recommended doses for expansion and dose optimization were 200 mg once daily (QD), 300 mg QD, and 400 mg QD
 - The most common treatment-related TEAEs across BGB-58067 200-400 mg were nausea (33.3%), anemia (24.1%), and fatigue (20.7%) (**Figure 2**)
 - The most common treatment-related grade ≥ 3 TEAEs across BGB-58067 200-400 mg were anemia (6.9%), platelet count decreased (4.6%), and neutrophil count decreased (3.4%) (**Figure 2**)
- During dose escalation, only one patient had a dose-limiting toxicity (DLT) event (grade 4 platelet count decreased) which occurred after one cycle of BGB-58067 800 mg
- In the food effect cohort, one patient with dedifferentiated liposarcoma and substantial tumor burden at baseline had a treatment-related TEAE of grade 5 acute tumor lysis syndrome after a single dose of BGB-58067 200 mg

Table 2. Overall Safety Summary (Safety Analysis Set)

	Total (N=182)	BGB-58067 200-400 mg (n=87)
Any TEAE, n (%)	180 (98.9)	85 (97.7)
Grade ≥ 3	101 (55.5)	44 (50.6)
Serious	61 (33.5)	27 (31.0)
Leading to treatment discontinuation	17 (9.3)	6 (6.9)
Any treatment-related TEAE, n (%)	164 (90.1)	78 (89.7)
Grade ≥ 3	65 (35.7)	24 (27.6)
Serious	21 (11.5)	8 (9.2)
Leading to treatment discontinuation	11 (6.0)	5 (5.7)
Leading to death	1 (0.5)	1 (1.1)

Total includes BGB-58067 50-800 mg. AEs were graded for severity using CTCAE v5.0. A TEAE is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug through 30 days after the last dose (permanent discontinuation of study drug) or the initiation of new anti-cancer therapy, whichever is earlier. Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. **Abbreviations:** CTCAE, Common Terminology Criteria for AEs.

Figure 2. Treatment-Related TEAEs in $\geq 5\%$ of Patients for BGB-58067 200-400 mg (Safety Analysis Set)



Antitumor Activity

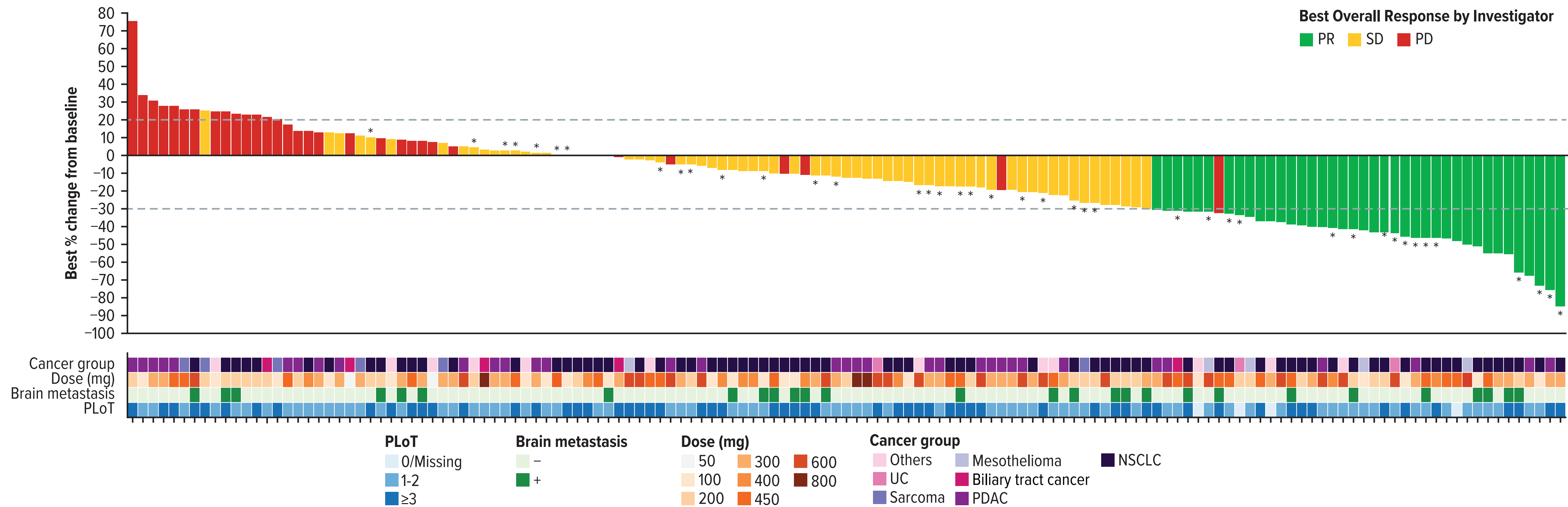
- In the overall cohort (excluding patients with glioma), confirmed ORR (95% CI) was 21.3% (14.8-29.0) (**Table 3**)
 - Of the 30 responders, 12 achieved partial response (PR) at their first tumor assessment and 16 remain on treatment. An additional nine PRs were unconfirmed
 - A total of 41 patients remain on treatment (**Figure 3**)
- In the NSCLC cohort, confirmed ORR (95% CI) was 25.3% (16.0-36.7) across all evaluated dose levels (**Table 4**/**Figure 4**); median duration of response was not mature
 - In patients with or without brain metastases (BM), respectively, 11.1% and 6.3% had central nervous system (CNS) progression, and 33.3% and 6.3% had new brain lesion or unequivocal progression of brain non-target lesion (**Table 5**)
 - Intracranial ORR (95% CI) in patients with BM in the NSCLC cohort was 30.8% (9.1-61.4) (**Table 5**)

Table 3. Antitumor Activity in the Overall Cohort (Excluding Glioma) (Clinical Activity Evaluable Analysis Set)

	Total (N=141)*
Best overall response, n (%)	
PR	30 (21.3)
SD	77 (54.6)
PD	34 (24.1)
ORR,* % (95% CI)	21.3 (14.8-29.0)
DCR,* % (95% CI)	75.9 (68.0-82.7)
Median TTR (range), months	2.6 (1.2-11.1)
6-month DoR rate (95% CI),[‡] %	61.4 (38.5-77.9)

TTR is defined as the time from start date to the date of earliest qualifying response. *The table excluded 24 patients with glioma and 17 patients with non-CNS tumors who did not have an evaluable post-baseline tumor assessment. [‡]95% CIs were estimated using the Clopper–Pearson method. **Abbreviations:** CNS, central nervous system; DCR, disease control rate; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Figure 3. Best Percent Change from Baseline in Target Lesion Sum of Diameters in the Overall Cohort (Excluding Glioma) (Clinical Activity Evaluable Analysis Set)



*Patient's status is treatment ongoing. **Abbreviations:** NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PLoT, prior line of treatment; UC, urothelial carcinoma.

Table 4. Antitumor Activity in the NSCLC Cohort (Clinical Activity Evaluable Analysis Set*)

	EGFR mutant (n=35)	EGFR wild-type (n=39)	Total (N=75)
Best overall response, n (%)			
PR	4 (11.4)	15 (38.5)	19 (25.3)
SD	20 (57.1)	17 (43.6)	38 (50.7)
PD	11 (31.4)	7 (17.9)	18 (24.0)
ORR (95% CI),* %	11.4 (3.2-26.7)	38.5 (23.4-55.4)	25.3 (16.0-36.7)
DCR (95% CI),* %	68.6 (50.7-83.1)	82.1 (66.5-92.5)	76.0 (64.7-85.1)
Median TTR (range), months	2.1 (1.4-3.0)	2.7 (1.2-11.1)	2.7 (1.2-11.1)
6-month DoR rate (95% CI),[‡] %	75.0 (12.8-96.1)	75.2 (40.7-91.4)	74.5 (45.0-89.7)
Median PFS (95% CI),[‡] months*	6.6 (1.5-8.4)	8.1 (4.2-11.3)	7.7 (4.5-8.4)

EGFR status was determined from investigator-reported historical testing and/or baseline plasma cDNA testing. EGFR-mutant status was defined by a positive result from either source. EGFR wild-type status was defined by negative results from both sources when available, or a wild-type result from the only available source. One patient with unknown EGFR status from both sources was excluded from the subgroup analysis. TTR is defined as the time from start date to the date of earliest qualifying response. *The clinical activity-evaluable analysis set excluded 8 patients who did not have evaluable post-baseline tumor assessment. [‡]95% CIs were estimated using the Clopper–Pearson method. [‡]DoR rates were estimated using the Kaplan–Meier method with 95% CIs estimated using the Greenwood formula. *Medians and other quartiles were estimated using the Kaplan–Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation. [‡]Median PFS is based on safety analysis set. **Abbreviations:** cDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TTR, time to response.

Figure 4. Percent Change From Baseline in Target Lesion Sum of Diameters in the NSCLC Cohort (Clinical Activity Evaluable Analysis Set)

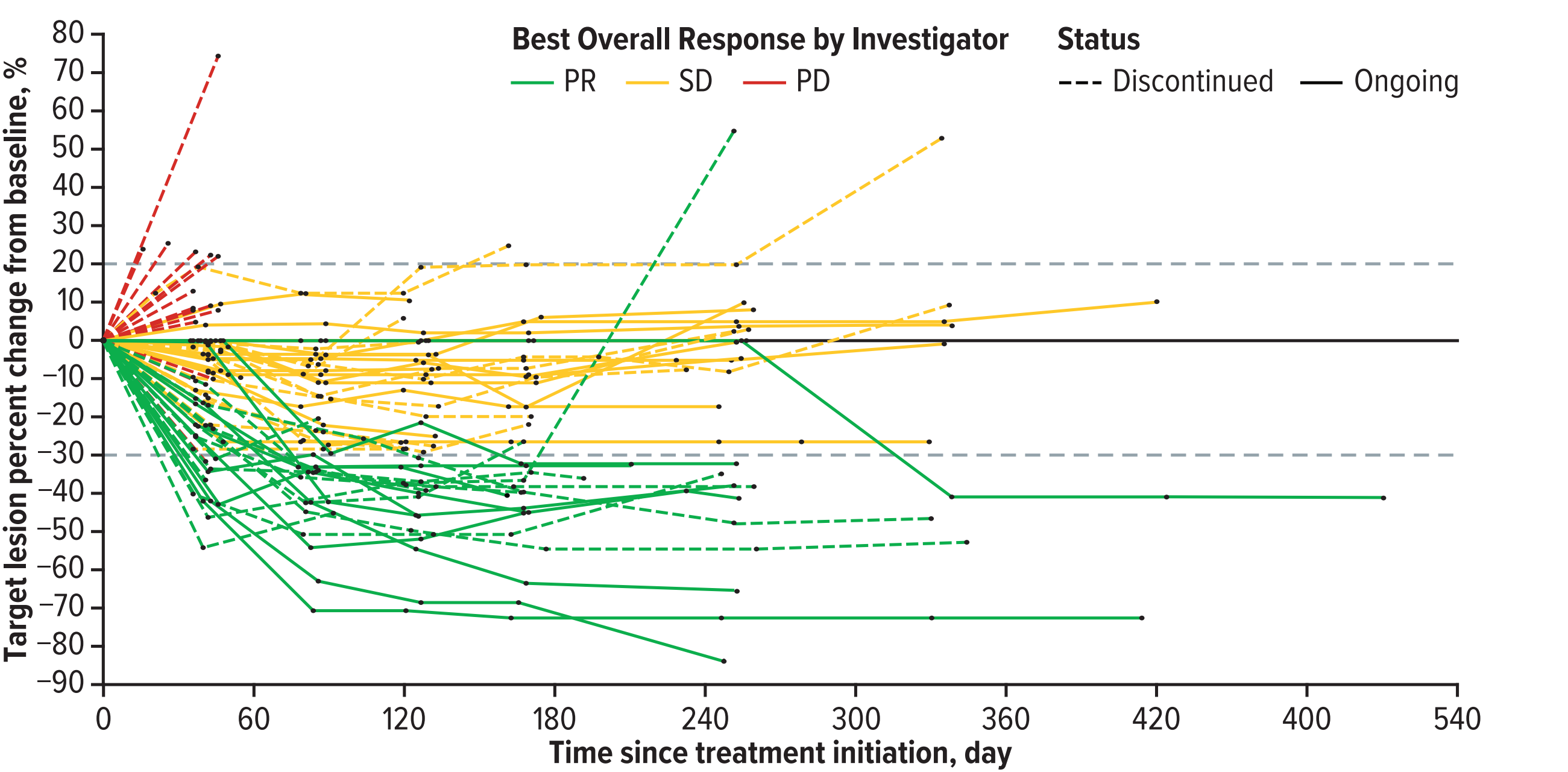
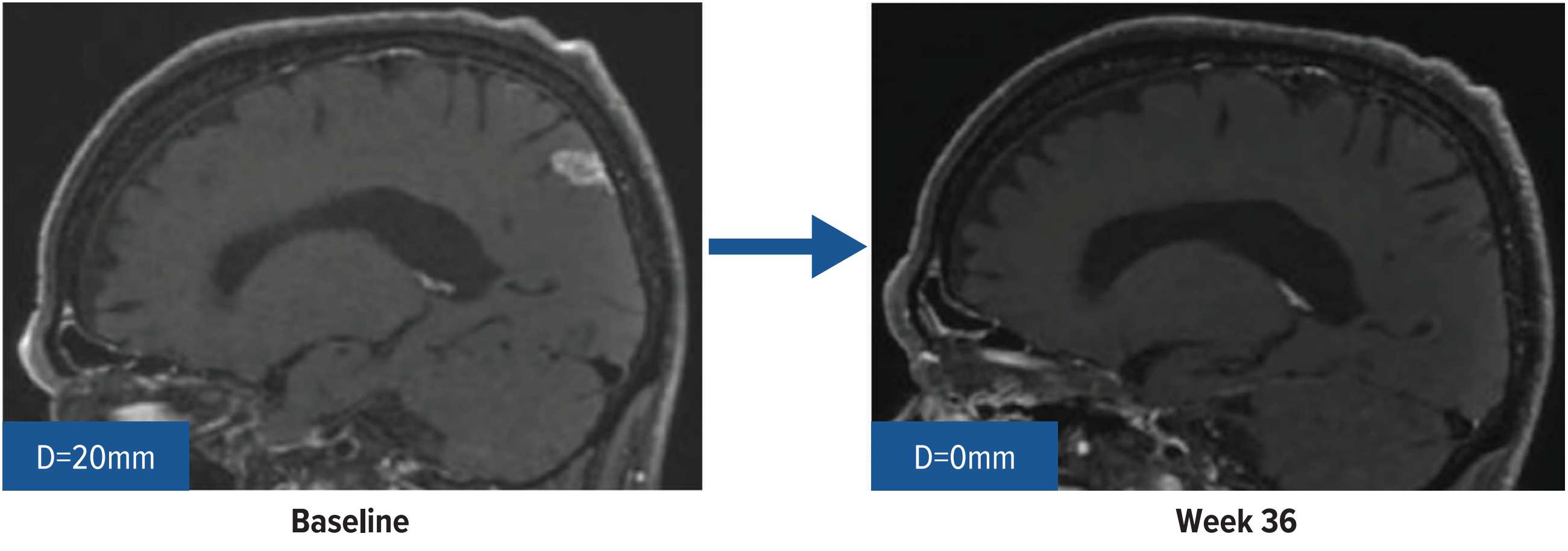


Table 5. Antitumor Activity in Patients With or Without Brain Metastases in the NSCLC Cohort (Clinical Activity Evaluable Analysis Set)

	Systemic Response per RECIST Without BM (n=48)	Systemic Response per RECIST With BM (n=27)	Intracranial Response per modified RECIST* With BM (n=13)
Best overall response, n (%)			
PR	13 (27.1)	6 (22.2)	4 (30.8)
SD	25 (52.1)	13 (48.1)	7 (53.8)
PD	10 (20.8)	8 (29.6)	2 (15.4)
ORR (95% CI),* %	27.1 (15.3-41.8)	22.2 (8.6-42.3)	30.8 (9.1-61.4)
DCR (95% CI),* %	79.2 (65.0-89.5)	70.4 (49.8-86.2)	84.6 (54.6-98.1)
CNS progression (new brain lesion), n (%)	3 (6.3)	3 (11.1)	-
CNS progression (new brain lesion or unequivocal progression of brain non-target lesion), n (%)	3 (6.3)	9 (33.3)	-

*95% CIs were estimated using the Clopper–Pearson method. ^{*}Intracranial evaluable for response analysis set. **Abbreviations:** BM, brain metastases; CNS, central nervous system; DCR, disease control rate; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 5. Intracranial Response in a Patient With SQ NSCLC With Untreated Brain Metastases

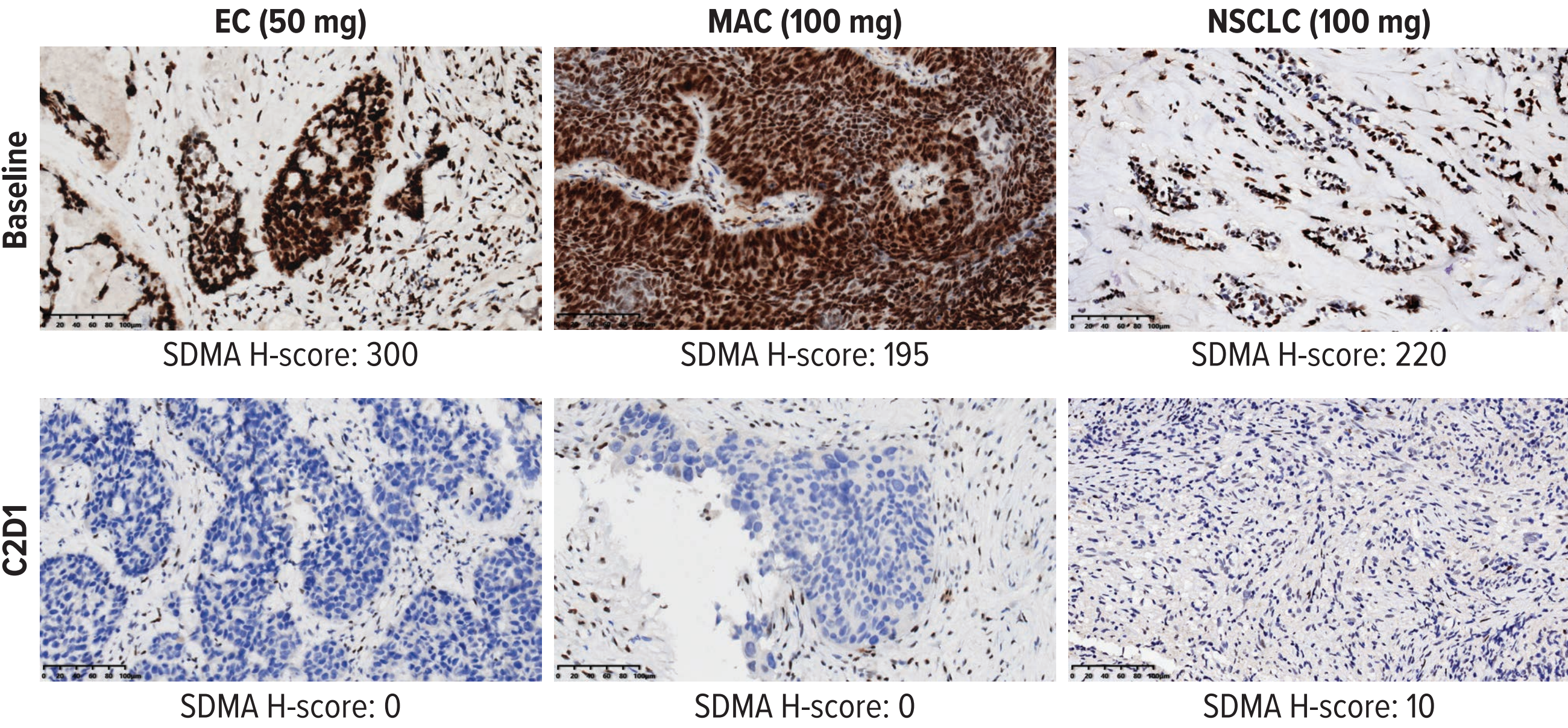


In a 72-year-old male with SQ NSCLC and untreated brain metastases, treatment with BGB-58067 200 mg resulted in a PR with 100% decrease in the diameter of brain target lesion. **Abbreviations:** D, lesion diameter; NSCLC, non-small cell lung cancer; SQ, squamous.

Biomarkers

- Target engagement was confirmed by symmetric dimethylarginine (SDMA) depletion in tumor tissue in several histologically diverse tumor types
 - SDMA levels in baseline and on-treatment tumor tissues were measured by immunohistochemistry. SDMA depletion in tumor cells was observed at C2D1 (**Figure 6**)

Figure 6. SDMA Level Change in Tumor Tissue by Immunohistochemistry

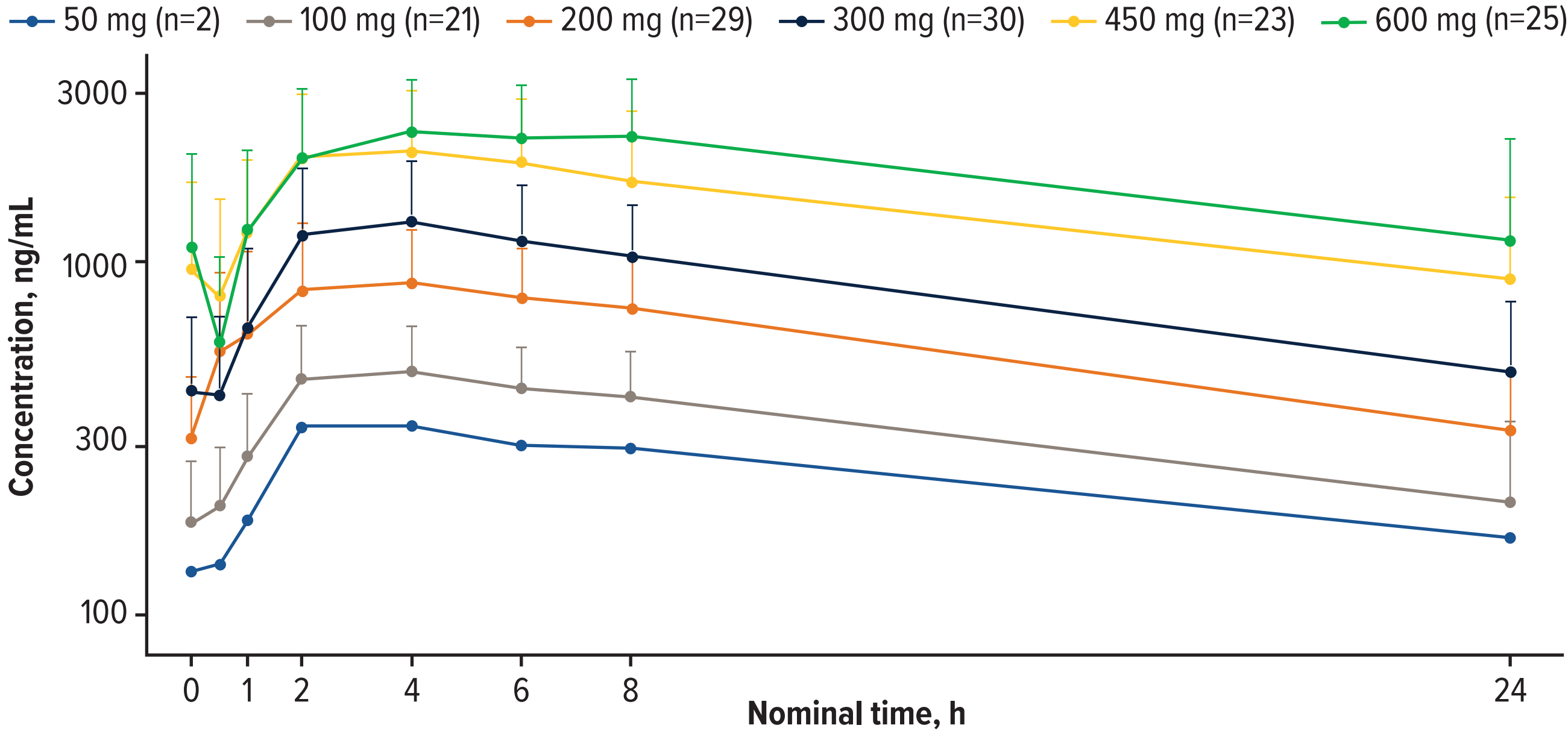


Abbreviations: C2D1, Cycle 2 Day 1; EC, esophageal cancer; MAC, maxillary ameloblastic carcinoma; NSCLC, non-small cell lung cancer; SDMA, symmetric dimethylarginine.

Pharmacokinetics

- Maximum plasma concentrations were reached at 2-4 hours post-dose (**Figure 7**)
- PK showed an approximately dose-proportional increase in steady-state exposure (C_{max} or AUC) from BGB-58067 50 mg to 600 mg

Figure 7. Mean (SD) Plasma Concentration–Time Profiles for BGB-58067



Abbreviations: h, hours; SD, standard deviation.

REFERENCES

- Stopa N, et al. *Cell Mol Life Sci*. 2015;72:2041-2059; 2. Kryukov GV, et al. *Science*. 2016;351:1214-1218; 3. Cottrell KM, et al. *J Med Chem*. 2024;67:6064-6080; 4. Engstrom LD, et al. *Cancer Discov*. 2023;13:2412-2431; 5. Jiang A, et al. *Cancer Res*. 2026;86(7_Suppl):3901; 6. Guo W, et al. *Contemp Clin Trials*. 2017;58:23-33

DISCLOSURES

JR: Consulting or advisory fees: Vall d'Hebron Institute of Oncology, Chinese University of Hong Kong, Boxer Capital, LLC, Tang Advisors, LLC, Guidepoint, and Axiom; Research funding: Blueprint Medicines, Merck Sharp & Dohme, Hummingbird, AstraZeneca, 280 Bio, Vall d'Hebron Institute of Oncology/Cancer Core Europe; Non-financial support and travel fees: European Society for Medical Oncology, American Society of Medical Oncology, National Taiwan University Cancer Center, 280-Biotech, Dava Oncology, STOP Cancer; Consulting and travel fees: Ellipses Pharma, IONCTURA, Sardana, Mekanistic, Amgen, Merus, MonteRosa, Aadi, and BridgeBio.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing was provided by Lee Blackburn, MSc of Amiculum, and supported by BeOne Medicines.