

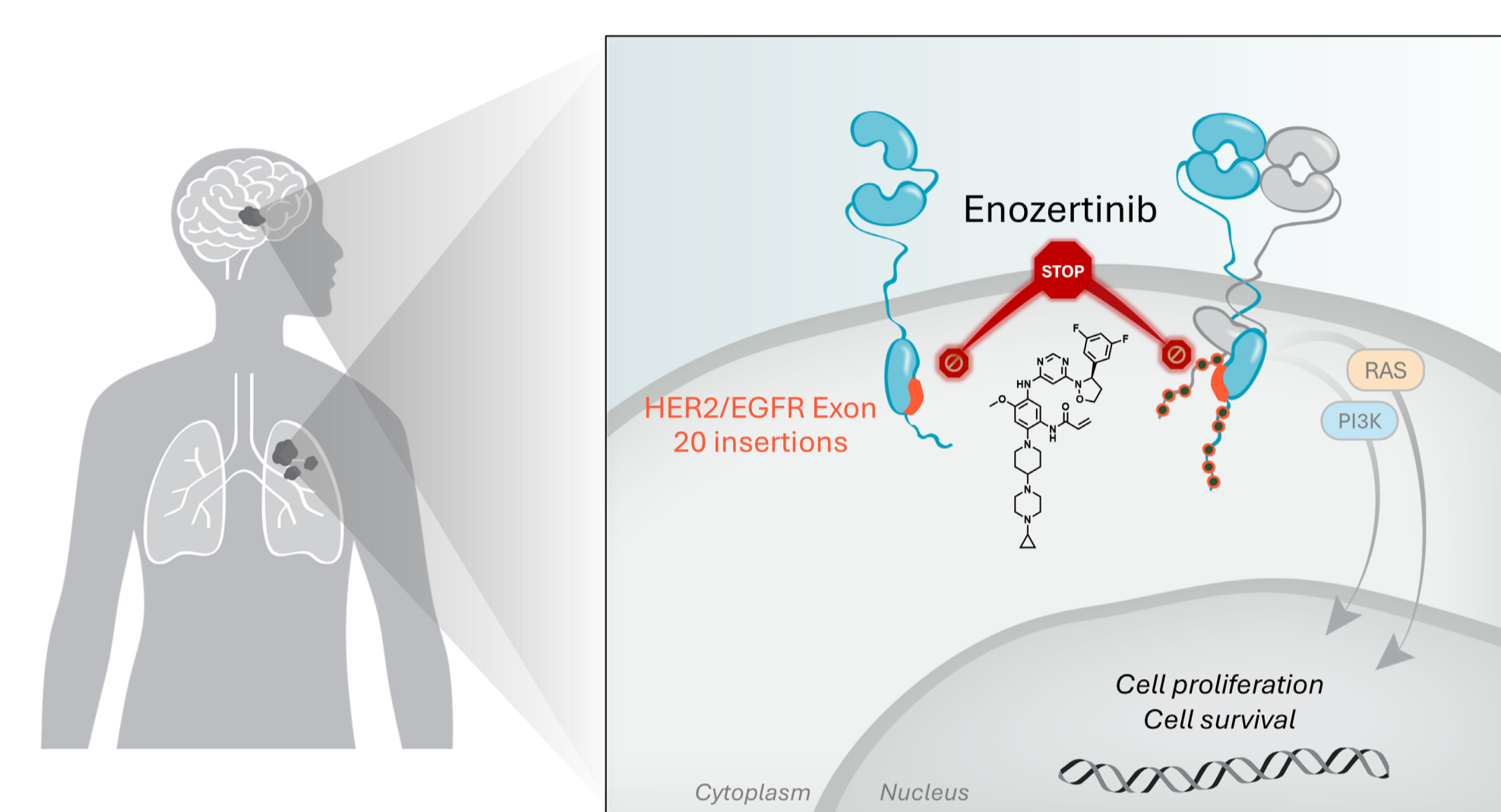
# Enozertinib (ORIC-114), a Highly Selective, Brain-Penetrant, EGFR and HER2 Inhibitor, in Patients with HER2 Exon 20 Mutant NSCLC: Randomized Dose Optimization

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## BACKGROUND

- Human epidermal growth factor receptor 2 (HER2) exon 20 insertion (ex20ins) mutations occur in 2.3% of non-small cell lung cancer (NSCLC) cases and account for ~90% of HER2 mutations in NSCLC<sup>2</sup>
- Central nervous system (CNS) metastases are a poor prognostic factor for NSCLC and develop in approximately 40%–70% of patients<sup>3</sup>
- NSCLC with HER2 mutations has been shown to be resistant to pan-HER2 tyrosine kinase inhibitors (TKIs), and the overall ability of HER2 TKIs to penetrate the CNS is limited, highlighting the need for selective brain-penetrant therapies that can target both systemic and CNS HER2-mutant NSCLC<sup>4</sup>



Enozertinib targets systemic and metastatic CNS disease in NSCLC driven by HER2 and EGFR mutations

- Enozertinib is a highly selective, orally bioavailable, CNS-penetrant, and irreversible small-molecule inhibitor of mutant epidermal growth factor receptor (EGFR) and HER2
- Phase 1 clinical data from a dose-escalation study demonstrated a favorable safety profile with a half-life supporting once daily dosing<sup>5</sup>
- Once daily doses of enozertinib 80 mg or 120 mg were selected as the provisional recommended phase 2 doses (RP2Ds) for dose optimization based on the safety, efficacy, pharmacokinetic, and pharmacodynamic results from the phase 1 dose-escalation study
- Here we report safety and efficacy of enozertinib 80 mg and 120 mg in a randomized dose-optimization cohort of previously treated patients with NSCLC harboring HER2 ex20ins

## STUDY DESIGN

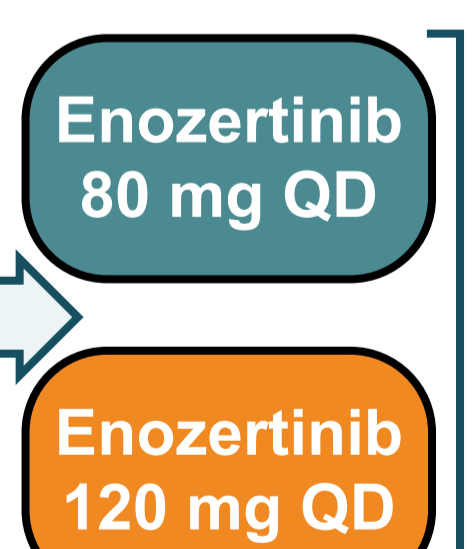
- First-in-human, global, open-label, single-arm, phase 1/2 trial evaluating the safety and antitumor activity of enozertinib in patients with advanced NSCLC harboring EGFR and HER2 alterations

Phase 1/2 Study Design (NCT05315700)

### Key Eligibility Criteria:

- Locally advanced or metastatic NSCLC with HER2 ex20ins mutation
- Untreated, stable, asymptomatic brain metastases allowed
- No prior HER2 ex20ins-targeted tyrosine kinase inhibitors

1:1 Randomization



### Primary endpoint:

- Selection of RP2D

### Secondary endpoints:

- Investigator-assessed ORR and CBR
- Safety

CBR, clinical benefit rate; ORR, objective response rate; QD, once daily  
Tumor restaging, including with brain MRI, performed at 4 weeks and every 8 weeks thereafter

## CONCLUSIONS

- Enozertinib demonstrated systemic and CNS antitumor activity in previously treated NSCLC patients with HER2 ex20ins mutations
- Enozertinib was generally well tolerated, with mainly Grade 1 or 2 TRAEs
- Patients receiving 80 mg enozertinib experienced a lower rate of dose reductions due to TRAEs compared with those receiving 120 mg, which may explain the deeper tumor regressions seen with the 80 mg dose level
- The safety and efficacy profile supports a once daily dose of 80 mg enozertinib as the RP2D

## RESULTS

### DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- 47% of previously treated patients had brain metastases at study entry (Table 1)

Table 1. Patient Characteristics; Safety Population

Characteristic	80 mg (n=26)	120 mg (n=23)
Age, years, median (range)	60 (35, 83)	61 (27, 75)
Female, n (%)	17 (65)	16 (70)
Never smoked, n (%)	19 (73)	19 (83)
Race: Asian / White / Other, %	54 / 46 / 0	44 / 48 / 9
ECOG PS: 0 / 1, %	31 / 69	35 / 65
Brain metastases at baseline,* n (%)	12 (46)	11 (48)
Prior therapies, median (range)	1 (0–4)	1 (0–4)
Prior cytotoxic chemotherapy, n (%)	21 (81)	18 (78)
Prior HER2-targeted therapies,† n (%)	9 (35)	8 (35)

Data cutoff: August 29, 2025

ECOG PS, Eastern Cooperative Oncology Group performance status

\*Patients with brain metastases at study entry, including active brain metastases, per Response Evaluation Criteria in Solid Tumors, v 1.1

†Includes trastuzumab deruxtecan and trastuzumab emtansine

### SAFETY

Table 2. Disposition of Patients

Event, n (%)	80 mg (n=26)	120 mg (n=23)
TRAEs Grade ≥3	9 (35)	7 (30)
Dose reduction due to TRAE	9 (35)	14 (61)
Discontinuation due to TRAE	1 (4)	1 (4)

TRAE, treatment-related adverse event

Table 3. TRAEs Occurring in ≥20% of Patients

Event, n (%)	80 mg (n=26)		120 mg (n=23)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Preferred term				
Paronychia	23 (89)	0	18 (78)	0
Diarrhea	20 (77)	0	15 (65)	2 (9)
Dermatitis acneiform	14 (54)	4 (15)	8 (35)	3 (13)
Stomatitis	10 (39)	1 (4)	10 (44)	1 (4)
Rash	7 (27)	3 (12)	9 (39)	0
Decreased appetite	7 (28)	0	5 (21)	0
Pruritus	11 (42)	0	4 (17)	0
Dry skin	5 (19)	0	7 (30)	0
Mucosal inflammation	5 (19)	0	4 (17)	1 (4)
Dry mouth	4 (15)	0	6 (26)	0

- Well-tolerated safety profile, with TRAEs predominantly Grades 1–2 (Table 3)
- No Grade 4 or 5 TRAEs
- No significant non-EGFR/HER2-related toxicities (e.g., myelosuppression, QTc prolongation, hepatotoxicity)

### EFFICACY

Table 4. Response Rates

Evaluable Population*	80 mg (n=23)	120 mg (n=22)
Best ORR† % [95% CI]	35 [16, 57]	32 [14, 55]
Confirmed ORR % [95% CI]	26 [10, 48]	27 [11, 50]
Partial response, n (%)	6 (26)	6 (27)
Stable disease, n (%)	17 (74)	12 (56)
Progressive disease, n (%)	0	4 (18)
CBR‡ % [95% CI]	50 [28, 72]	68 [45, 86]

Data cutoff: August 29, 2025

\*Reported in the evaluable population, which includes patients who have received ≥1 dose, have ≥1 measurable lesion at baseline, and have had the opportunity for ≥3 post-baseline scans

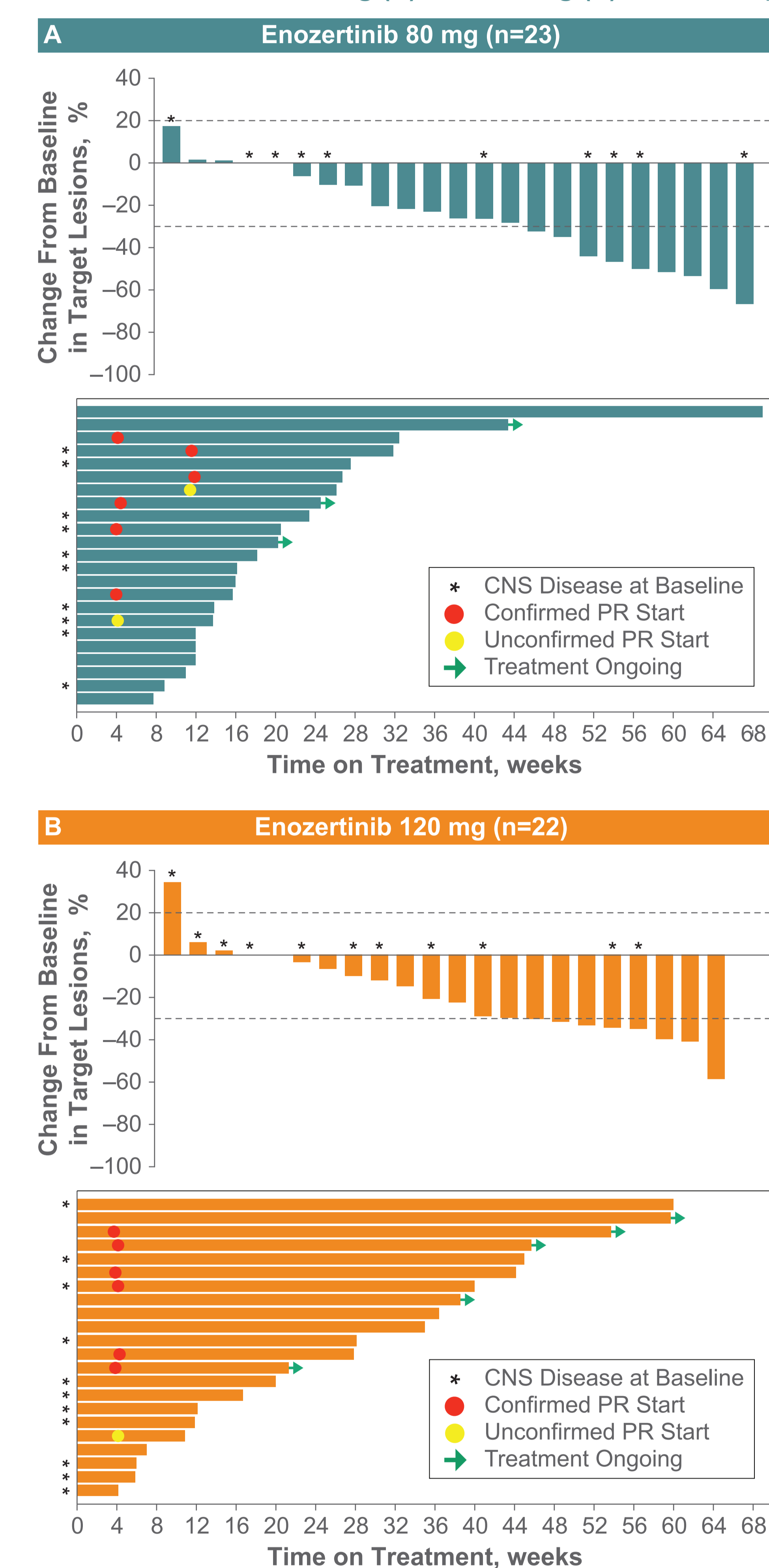
†Best objective response rate includes both confirmed and unconfirmed responses

‡CBR includes complete response, partial response, or stable disease for ≥6 months

- Tumor responses were observed for the 80 mg and 120 mg enozertinib doses, including in patients with baseline brain metastases
- Responses in CNS target lesions were also observed in multiple patients at both doses

- Tumor regressions were deeper at the 80 mg than the 120 mg dose level, potentially because of the lower rate of dose reduction (Figure 1)
- Responses generally occur by 4 weeks, but tumor regression continues over time, with late responses seen after 3+ months on treatment (Figure 1)
- At a median follow-up of 50 weeks, 32% of all patients remained on treatment

Figure 1. Change in Target Lesion from Baseline and Time on Treatment for the 80 mg (A) and 120 mg (B) Dose Groups



PR, partial response

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### DISCLOSURES

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