

Enozertinib (ORIC-114), a Brain-Penetrant, Highly Selective EGFR Inhibitor, in Treatment-Naïve Advanced NSCLC with EGFR Atypical Mutations

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BACKGROUND

- Epidermal growth factor receptor (EGFR) mutations occur in approximately 10%–15% of patients with non–small cell lung cancer (NSCLC) in Western populations and up to 50% in Asian populations^{1–3}
 - Atypical and exon 20 insertion mutations in EGFR comprise 10%–30% of EGFR mutations in NSCLC and are molecularly heterogeneous^{4–6}
- Approximately 35% of patients with metastatic EGFR-mutated NSCLC present with de novo central nervous system (CNS) metastases, and approximately 50% develop CNS metastases during their disease course⁷
- Enozertinib is an oral, highly brain-penetrant, selective, irreversible inhibitor⁸ designed for potent activity against EGFR atypical and exon 20 insertion mutations being evaluated in an ongoing, first-in-human, open-label, multi-center Phase 1b study (NCT05315700)

METHODS

- A total of 26 patients treated with enozertinib 80 mg orally once daily are presented here with data cutoff date of September 4, 2026 (Figure 1, Table 1)

Figure 1. Summary of Key Eligibility Criteria and Endpoints

Key Eligibility Criteria	Key Endpoints
- Treatment-naïve, locally advanced or metastatic NSCLC with EGFR atypical mutations - PACC or classical-like - Singleton or compound mutations - Measurable disease per RECIST 1.1 - ECOG PS 0 or 1 - Treated, or untreated and asymptomatic CNS metastases permitted	- Antitumor activity per RECIST 1.1 – ORR / DOR / PFS - Intracranial response per modified RECIST 1.1 (INV) and RANO-BM (BICR) - ctDNA molecular response - Safety

BASELINE CHARACTERISTICS

- Seventeen of 26 patients (65%) had brain metastases at baseline, including 12 patients (46%) with untreated brain metastases (Table 1)

Table 1. Baseline Characteristics

Characteristic	Patients (N=26)
Age, years, median (range)	66 (26–79)
Female, n (%)	10 (38)
Asian / White / Other, n (%)	20 (77) / 6 (23) / 0
Never smoker, n (%)	9 (35)
ECOG PS 0 / 1, n (%)	7 (27) / 19 (73)
Brain metastases at baseline ¹ , n (%)	17 (65)
Previously untreated brain metastases	12 (46)
Atypical mutation type, n (%)	
PACC	23 (88)
L861Q ²	3 (12)
Compound mutations ³ , n (%)	18 (69)

¹As determined by investigator. ²Without PACC mutations. ³Includes tumors harboring more than one EGFR mutation.

SAFETY

- Enozertinib demonstrated a manageable safety profile, consistent with known toxicities associated with wild-type EGFR inhibition (Table 2, Table 3)

Table 2. Summary of Treatment-Related Adverse Events in All Patients

TRAEs, n (%)	N=26
Grade 3	6 (23)
Serious adverse events	1 (4)
Dose interruptions	9 (35)
Dose reductions	10 (39)
Treatment discontinuations	0

Data cutoff: September 4, 2026.

- TRAEs predominantly Grades 1-2
- All Grade 3 TRAEs resolved with dose modifications
- No Grade 4 or Grade 5 TRAEs
- No significant off-target toxicities (e.g., cardiac, hematologic, hepatic)
- No discontinuations due to TRAEs

Table 3. Treatment-Related Adverse Events (TRAEs) Occurring in ≥20% of Patients

TRAEs, n (%)	N=26	
Preferred term, n (%)	Grade 1–2	Grade 3
Diarrhea	15 (58)	2 (8)
Paronychia	15 (58)	1 (4)
Dermatitis acneiform	12 (46)	2 (8)
Rash	14 (54)	0
Stomatitis	12 (46)	0
Pruritus	7 (27)	0
Decreased appetite	6 (23)	0
Dry skin	6 (23)	0
Nausea	6 (23)	0

SYSTEMIC EFFICACY

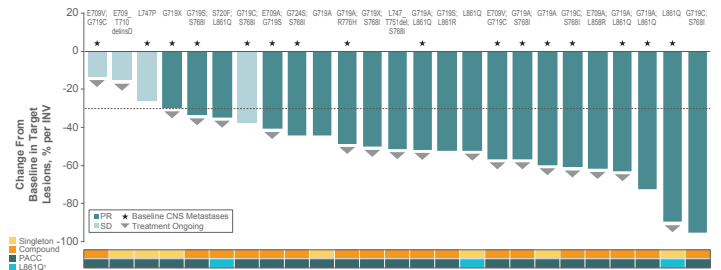
Table 4. Investigator and BICR-Assessed Response Rates

Systemic Objective Response Rate	Response-Evaluable ¹ (n=25)
Investigator-assessed	
Best ORR, % (95% CI)	88 (69, 98)
Confirmed ORR, % (95% CI)	84 (63, 96)
Partial response, n (%)	21 (84)
Stable disease, n (%)	4 (16)
DCR, n (%)	25 (100)
BICR-assessed	
Confirmed ORR, % (95% CI)	80 (59, 93)

¹Includes all patients with opportunity for two post-baseline systemic tumor assessments.

Data cutoff: September 4, 2026.

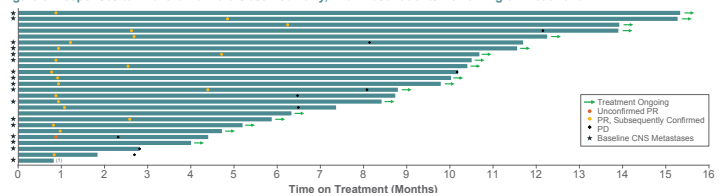
Figure 2. Tumor Reduction Observed in All Efficacy-Evaluable Patients, Including Patients with CNS Disease at Baseline



¹Without PACC mutations.

Includes all patients with opportunity for two post-baseline systemic tumor assessments.

Figure 3. Responses to Enozertinib Were Observed Early, With Most Patients Remaining on Treatment



¹Patient discontinued due to unrelated adverse event.

- At a median follow-up of 10.5 mo (95% CI: 8.4, 13.9), median time on treatment has not been reached. 69% (18/26) of patients remained on study treatment
- At a landmark of 6 months, 88% of patients remain progression-free

Figure 4. EGFR-Mutant ctDNA Clearance Observed in 82% of Patients by Cycle 3 Day 1



¹Without PACC mutations.

- ctDNA data analysis as of September 15, 2026. Includes all patients with EGFR mutation detected in plasma at baseline and opportunity for two post-baseline systemic tumor assessments. ctDNA assessed with Guardant Infinity Liquid assay. Clearance is defined as change from detected to undetectable mutant EGFR in plasma after up to two treatment cycles and is shown as %100 on waterfall plot.
- All 22 ctDNA-evaluable patients had a ≥90% reduction in EGFR-mutant ctDNA clearance by Cycle 3 Day 1, with ctDNA clearance achieved in 18 patients (82%)

INTRACRANIAL EFFICACY

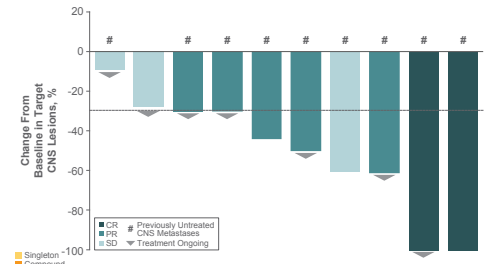
Table 5. Investigator-Assessed Intracranial Response Rates

Response Rate per modified RECIST 1.1	Response-Evaluable ¹ (n=10)
Best ORR, % (95% CI)	80 (44, 98)
Confirmed ORR, % (95% CI)	70 (35, 93)
Complete response, n (%)	2 (20)
Partial response, n (%)	5 (50)
Stable disease, n (%)	3 (30)
DCR, n (%)	10 (100)

¹Includes all patients with measurable target CNS lesions per investigator assessment.

Data cutoff: September 4, 2026.

Figure 5. In the Context of 90% of Response-Evaluable Patients Having No Prior Treatment for their CNS Metastases, All Patients Achieved CNS Tumor Reductions



¹Without PACC mutations.

- No new CNS lesions in patients with or without baseline CNS metastases

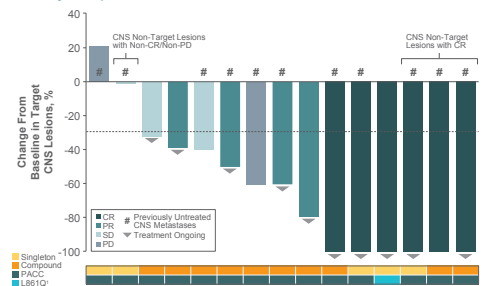
Table 6. BICR-Assessed Intracranial Response Rates

Response Rate per RANO-BM	Response-Evaluable ² (n=15)
Confirmed ORR, % (95% CI)	67 (38, 88)
Complete response, n (%)	6 (40)
Partial response, n (%)	4 (27)
Stable disease ¹ , n (%)	3 (20)
Progressive disease, n (%)	2 (13)
DCR, n (%)	13 (87)

¹Includes one patient with non-target lesions with non-CR/non-PD. ²Per BICR assessment, 16 patients presented with baseline CNS metastases; of these, one patient was deemed not evaluable for RANO assessment.

Data cutoff: September 4, 2026.

Figure 6. Intracranial Tumor Reduction Observed in Nearly All Efficacy-Evaluable Patients by BICR per RANO-BM

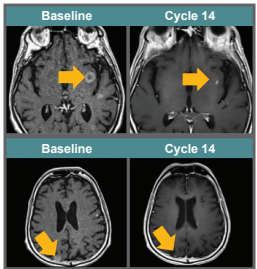


¹Without PACC mutations.

- Six complete responses, including in three patients with non-measurable CNS disease

Complete Intracranial Response in Patient with Treatment-Naïve EGFR Atypical Mutation and Previously Untreated CNS Metastases

- 59yo M with G719C-S768I mutation
- Baseline CNS Metastases:** 3 target lesions and 2 non-target lesions, all previously untreated
- Systemic Response:** Confirmed PR (~81%) after Cycle 4
- CNS Response:** PR after Cycle 3 and CR after Cycle 14
- TRAEs:** G2 dermatitis acneiform (resolved), G1 diarrhea (resolved), G1 dry skin
- Duration of Treatment:** Cycle 18 (ongoing)



CONCLUSIONS

- Enozertinib 80 mg once daily demonstrated clinically meaningful antitumor activity in a population of patients with treatment-naïve advanced NSCLC harboring EGFR atypical mutations and an exceptionally high rate of CNS metastases
 - Meaningful clinical responses:** confirmed INV-ORR 84%, BICR-ORR 80%; 88% remain progression free at 6 months
 - Compelling intracranial responses:** confirmed INV-ORR 70%, BICR-RANO-BM ORR 67%; multiple complete responses
 - Molecular responses:** 82% of evaluable patients achieved full clearance of EGFR-mutant ctDNA
- Enozertinib demonstrated a manageable safety profile, with no significant off-target toxicity and no TRAE-related discontinuations
- These data support continued investigation of enozertinib as frontline therapy for patients with NSCLC harboring EGFR atypical mutations

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DISCLOSURES

MA reports personal financial interests in the form of consulting fees from Alkermes, Amgen, AstraZeneca, BionTech, Boehringer Ingelheim, Daiichi Sankyo, Genexis, Gilead, GSK, Merck, MSD, ONO, Pfizer, Roche, Takeda, Voronoi, and Yuhari; and honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Merck, MSD, ONO, Roche, Takeda, and Yuhari.

ABBREVIATIONS

BICR, blinded independent central review; ctDNA, circulating tumor DNA; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; INV, investigator-assessed; ORR, objective response rate; PACC, P-loop and cC-helix compressing; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; TRAE, treatment-related adverse event.

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Enozertinib Is a Promising Candidate for NSCLC Patients with EGFR Atypical Mutations, Including Those with CNS Metastases

Enozertinib Target Candidate Profile



Robust Potency

- Robust in vitro potency & in vivo efficacy against a breadth of EGFR mutations



Exquisite Selectivity

- Exquisite selectivity that limits potential for off-target toxicity



Highly Brain Penetrant

- High brain exposure and intracranial tumor regression in preclinical studies

Enozertinib Preclinical Profile Validated with Clinical Data

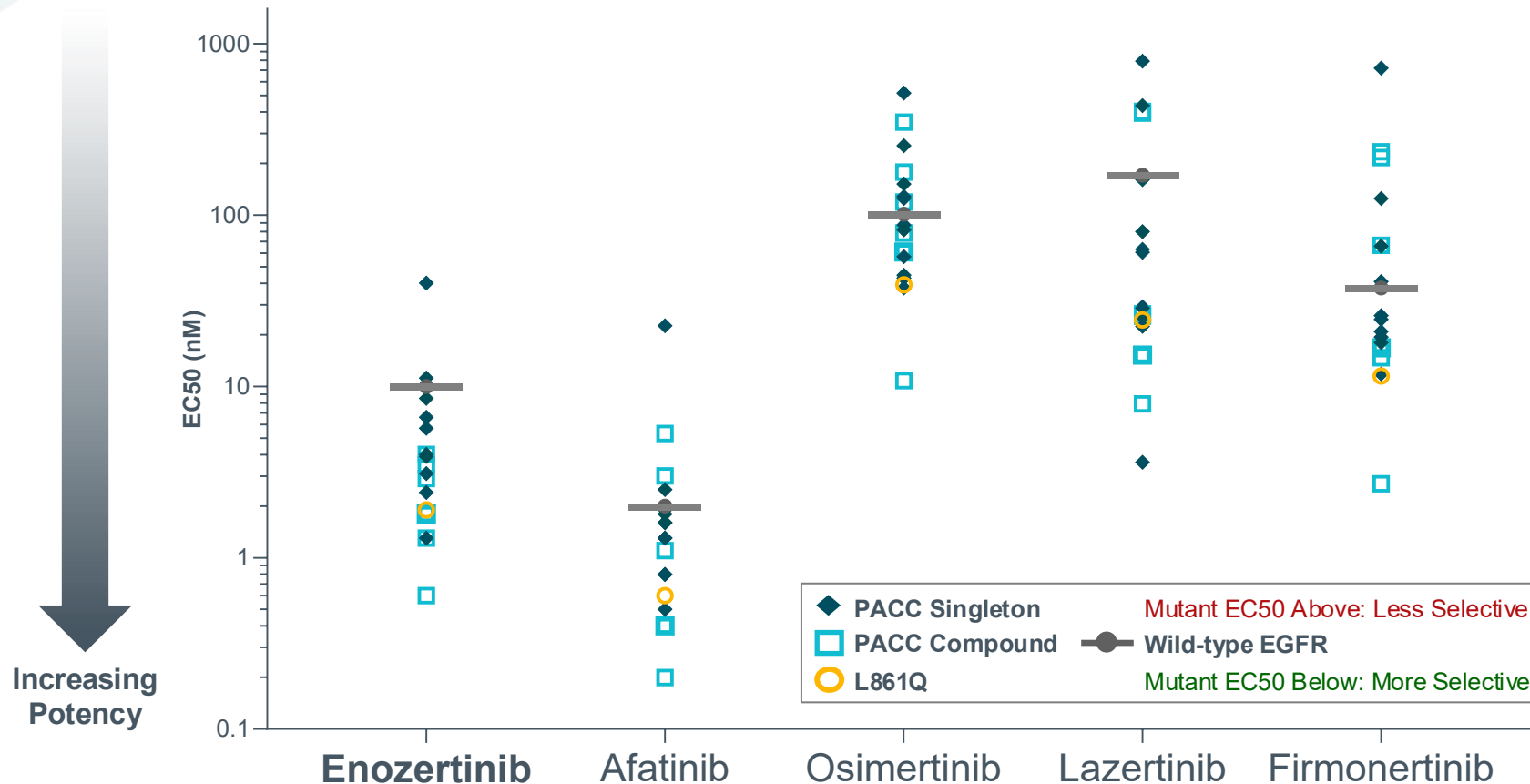


- ✓ **Potency:** meaningful systemic ORR
- ✓ **Selectivity:** no significant off-target toxicity
- ✓ **CNS-penetrance:** compelling CNS ORR

Enozertinib is a potential best-in-class inhibitor of EGFR atypical mutations, with superior potency and selectivity, and excellent brain-penetrance driving intracranial responses

Enozertinib Demonstrates Superior Relative Potency for EGFR Atypical Mutations Versus Competitors

Comparison of Cell Potency and EGFR Wild-Type Selectivity



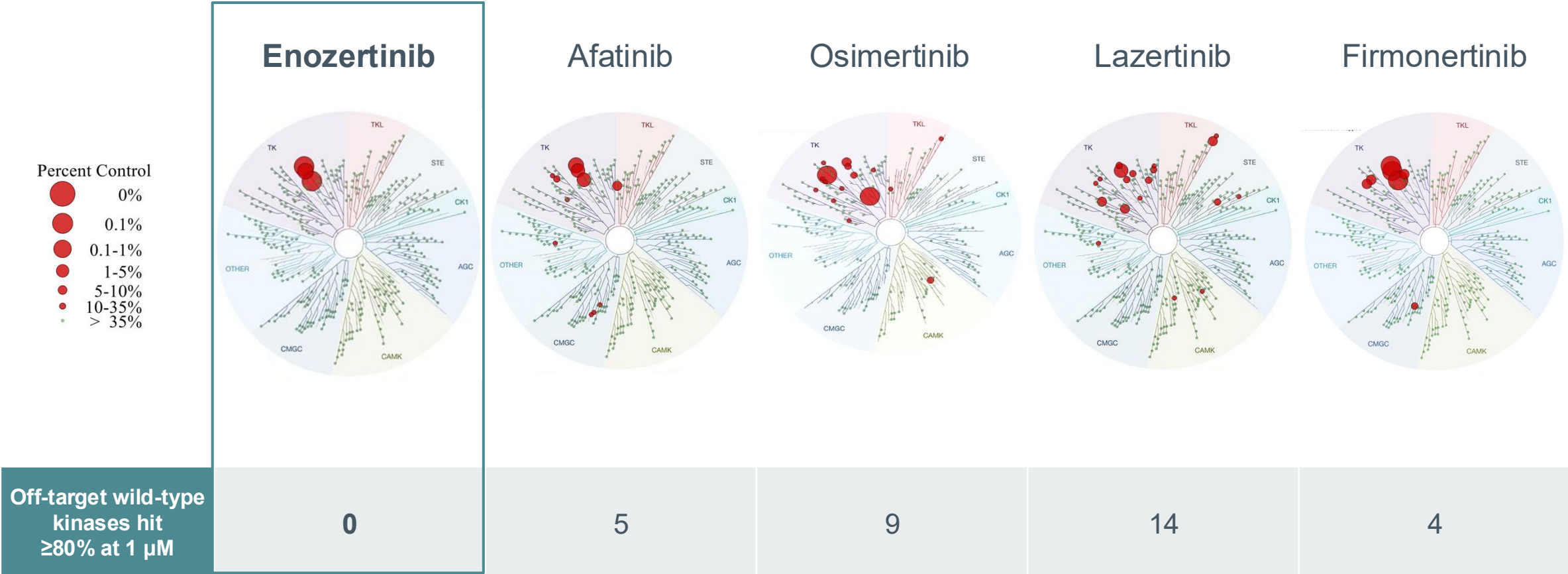
Enozertinib demonstrates:

- ✓ Strong potency across a broad range of EGFR atypical mutations
- ✓ More consistent selectivity for mutant versus wild-type EGFR than comparators

Enozertinib demonstrates more favorable EGFR mutant potency and selectivity versus competitors, leading to the potential for a superior therapeutic index in patients

Enozertinib Was Designed to Selectively Target EGFR with No Off-Target Hits

Kinome Selectivity Comparison

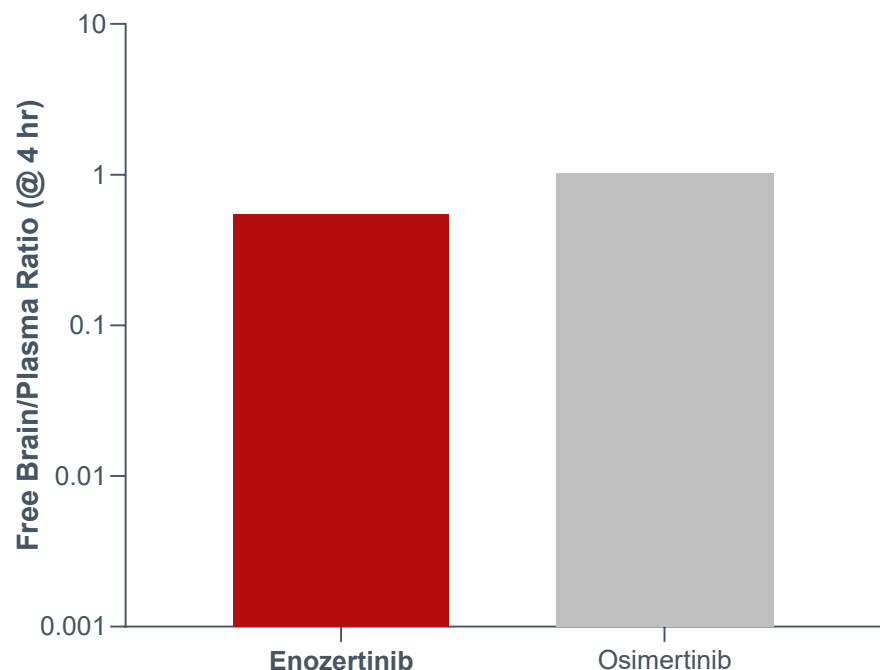


Enozertinib has demonstrated an exquisitely clean kinome panel, mitigating the potential for off-target toxicities

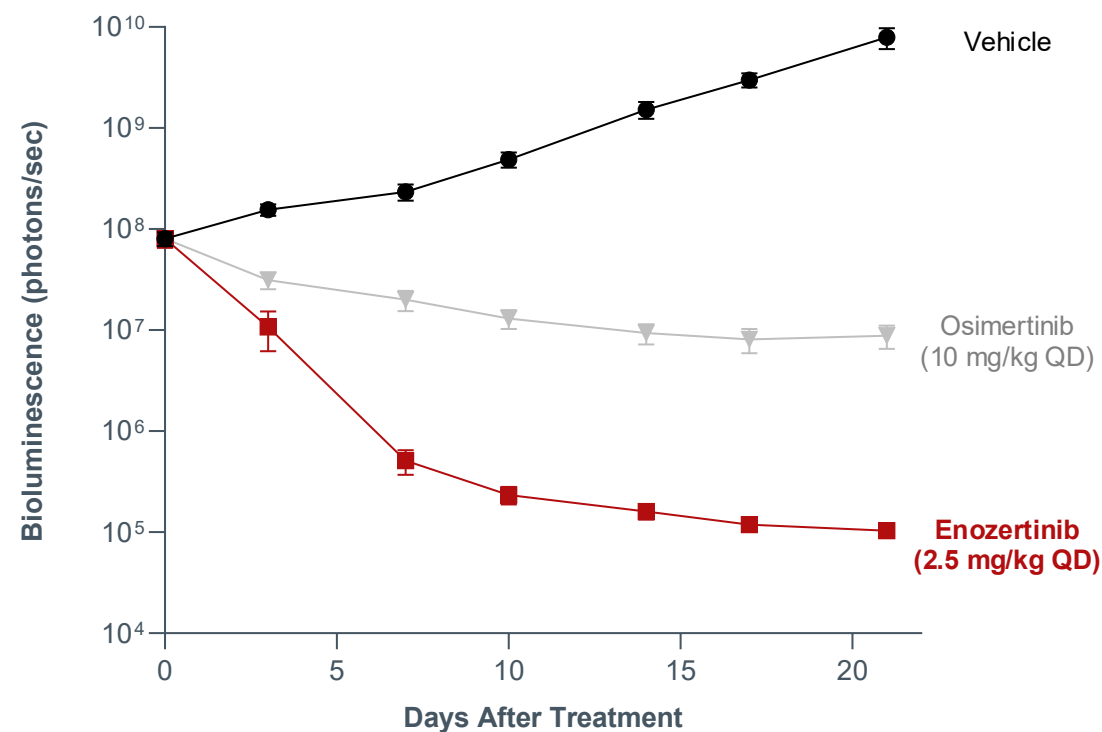
Brain Penetration of Enozertinib Leads to Intracranial Tumor Regressions In Vivo

Preclinical CNS Exposure and Intracranial Efficacy

Enozertinib Exhibits High Ratio of Free (Unbound) Brain/Plasma Exposure in Mice



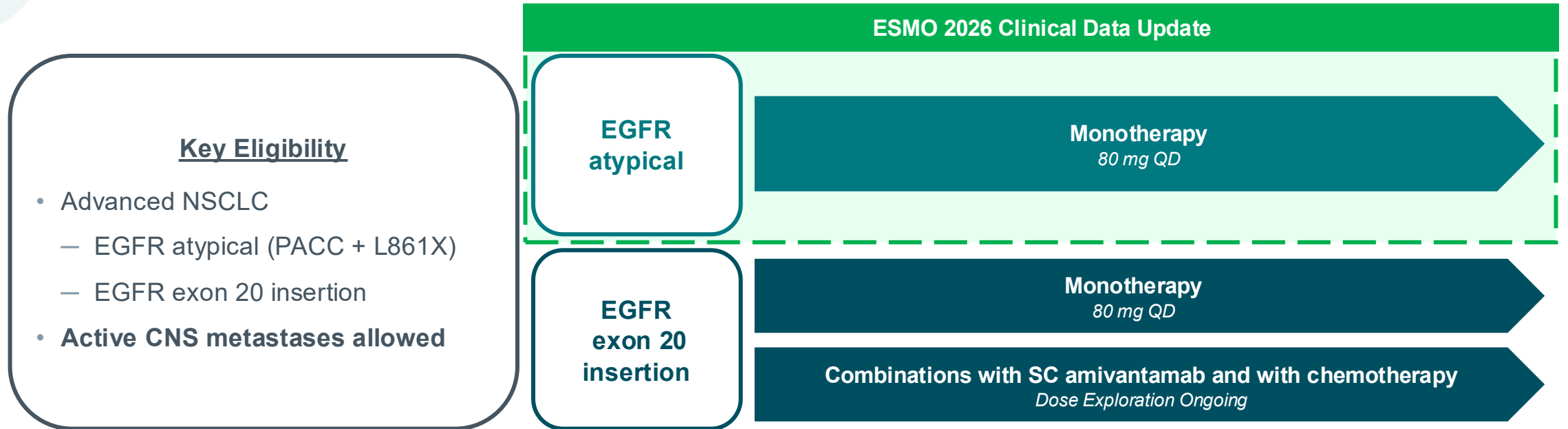
Enozertinib CNS Efficacy vs Osimertinib in Intracranial NSCLC EGFR Classical Mutant In Vivo Model



Enozertinib demonstrates excellent CNS exposure and strong tumor regressions in an intracranial NSCLC model

Enozertinib Phase 1b Trial Enrolled NSCLC Patients with EGFR Atypical and Exon 20 Mutations

Phase 1b, Multicenter, Open-Label Trial



Primary endpoints: Safety, selection of recommended phase 2 dose (RP2D), and PK

Key secondary endpoints: ORR/PFS (per RECIST v1.1), DOR, and intracranial ORR/PFS (per modified RECIST v1.1 and RANO-BM)

Enozertinib previously demonstrated strong clinical activity in 1L NSCLC patients with EGFR atypical or exon 20 mutations; ESMO 2026 data further reinforce potential best-in-class profile in 1L EGFR atypical NSCLC

Enozertinib Achieved Deep ctDNA Molecular Responses in 1L EGFR Atypical NSCLC Patients with All Reductions Observed Early in Treatment

ctDNA Molecular Response Data



- Deep EGFR-mutant ctDNA reductions achieved in all evaluable patients (n=22) across diverse mutations
 - 100% of patients achieved MR90 ⁽¹⁾
 - 82% of patients achieved full clearance
- Phase 3 NSCLC trials have shown that EGFR-mutant ctDNA clearance associates with improved long-term survival outcomes ⁽²⁾

All patients had ≥90% reduction by C3D1, with ctDNA clearance observed in 82% of patients

Patient Vignette 2: Complete Intracranial Response in Patient with Treatment-Naïve EGFR Atypical Mutation and Previously Untreated CNS Metastases

- **Patient:** 67-year-old male with G719A mutation
- **Baseline CNS Metastases:** 1 target lesion, previously untreated
- **Enozertinib Dose:** 80 mg oral, once-daily
- **Systemic Response:** Partial response (-60%) after Cycle 1
- **CNS Response:** Partial response after Cycle 1; complete response after Cycle 4
- **Treatment-Related Adverse Events:** Grade 1 acneiform rash
- **Duration of Treatment:** Cycle 18 (ongoing)

