SINGAPORE 2025 ESMO ASIA

Enozertinib (ORIC-114), a Highly Selective, Brain Penetrant EGFR and HER2 Inhibitor in EGFR Exon 20 Mutant NSCLC

Thomas John[1], Nisha Mohindra[2], Min Hee Hong[3], Ki Hyeong Lee[4], Natasha Leighl[5], Julia Rotow[6], Laura Alder[7], Rafald Dziadziuszko[8], Matthew Krebs[9], Joshua Sabari[10], Alex Spira[11], Chul Kim[12], Michael Cheng[13], Art Weber[14], Karen Velastegui[14], Anneleen Daemen[15], Jian Wang[14], Edna Chow Maneval[14], Pratik S. Multani[14], Myung-Ju Ahn[16]

[1]Peter MacCallum Cancer Center, Melbourne, VIC, Australia; [2]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [3 1]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Chungbuk National University Hospital, Cheongju, Republic of Korea; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Duke Cancer Center, Durham, NC, USA; [8]Medical University of Gdansk, Gdansk, Poland; [9]The Christie NHS Foundation Trust, Manchester, UK; [10]New York University Langone Health, New York, NY, USA; [11]NEXT Oncology, Fairfax, VA, USA; [12]Georgetown University Hospital, Washington DC, USA; [13]University of California, San Francisco, San Francisco, CA, USA; [14]ORIC Pharmaceuticals, Inc. San Diego, CA, USA; [15]ORIC Pharmaceuticals, Inc., South San Francisco, CA, USA; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Thomas John, MBBS, PhD, FRACP
Peter MacCallum Cancer Centre, VIC, Australia

06 December 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

DECLARATION OF INTERESTS

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Honoraria/Advisory:

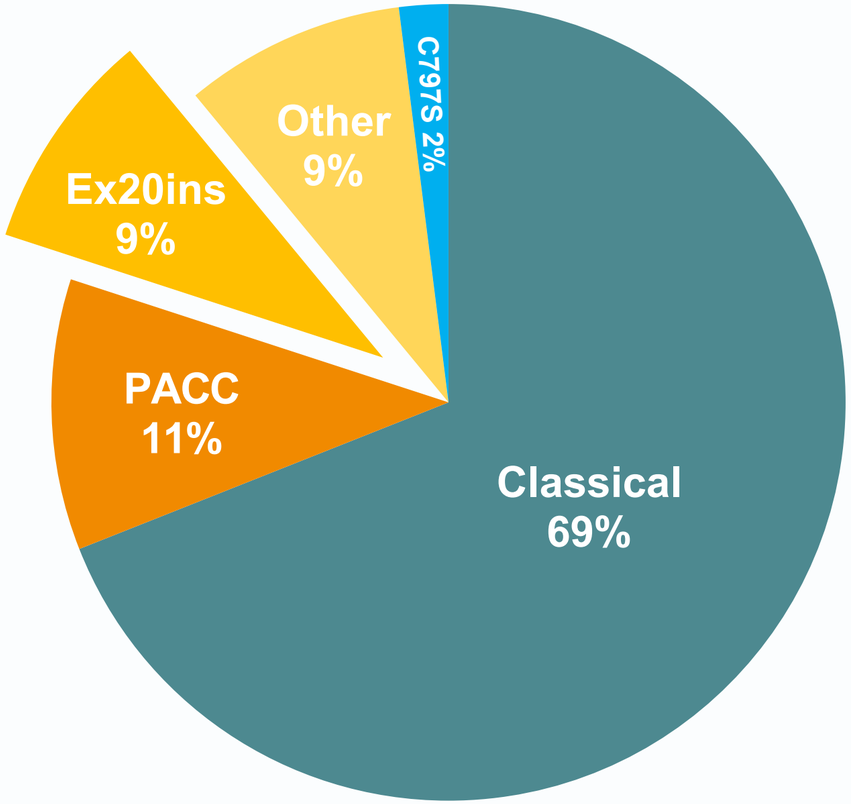
- BMS, AstraZeneca, Amgen, Arrivent, Roche, Pfizer, Takeda, Boehringer Ingelheim, MSD, Merck, Puma, Specialised Therapeutics, Gilead, Seagen, Johnson and Johnson, Bayer, Beigene

Travel/speaker fees

- AstraZeneca, Beigene, Dizal

Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertion Mutations in Non-Small Cell Lung Cancer (NSCLC)

- EGFR exon 20 insertion mutations (ex20ins) occur in 2.1% of NSCLC[1] and account for 9% of all EGFR mutations[2]
- ~30% of patients with EGFR-mutant NSCLC present with de novo CNS disease highlighting a propensity for CNS spread independent of therapeutic resistance[3]
- ~50% of patients with EGFR-mutant NSCLC develop brain metastases over the course of their disease, which contribute to a worse prognosis and for which effective treatment options are limited[4]



There are no approved brain-penetrant therapies for the treatment of NSCLC with EGFR ex20ins mutations

Pie chart: n=3,092 EGFR-mutant NSCLC. Classical = L858R and del19. Other = Non-PACC atypical mutations located in exons 18-21. T790M complexes are distributed over other categories.[2]

[1]Heymach JV et al, IASLC 19th World Conference on Lung Cancer, 2018, Toronto, Canada; [2]AACR Project GENIE Consortium, *Cancer Disc.* 2017, 7(8):813-31; [3]Patil T, et al. *Clin Lung Cancer;2021;21:e191–204*; [4]Wilcox JA, et al. *Ann Oncol.;*36(10):1142-53.

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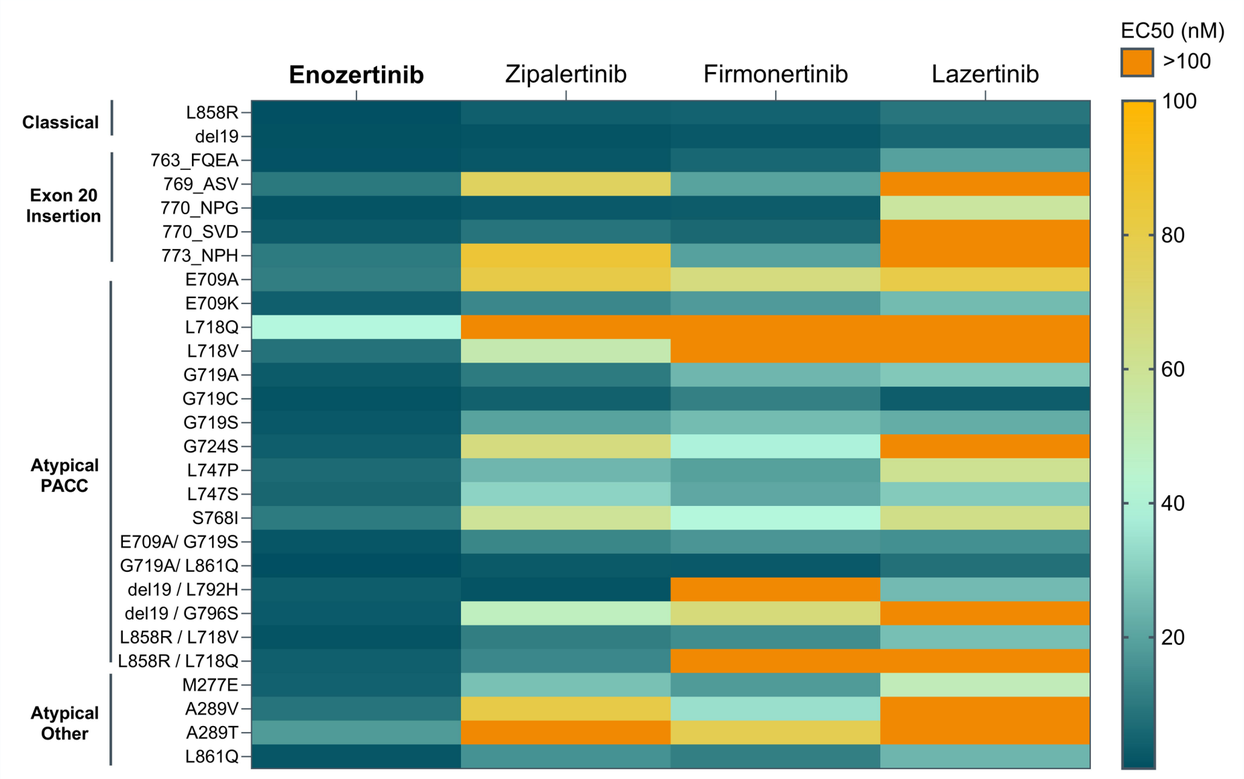
Enozertinib Was Designed with Best-in-Class Drug Properties Including Brain Penetration

- Enozertinib is a selective, orally bioavailable, highly CNS-penetrant, irreversible small molecule inhibitor of mutant EGFR and HER2
  - Exquisite kinome selectivity with no off-target inhibition
  - Strong potency across EGFR ex20ins mutations
  - Regressions in EGFR ex20ins NSCLC patient-derived xenograft models at well-tolerated doses
  - Superior unbound brain to plasma exposure ratio *in vivo* relative to other EGFR exon 20-targeted agents
  - Regressions in intracranial EGFR mutant lung tumor model
- Enozertinib at 80 mg and 120 mg once daily (QD) were selected as provisional RP2Ds for dose optimization based on Phase 1 dose escalation safety, efficacy, PK and PD results

Enozertinib Demonstrates Superior *in vitro* Potency Across EGFR Mutants Compared with other EGFR Inhibitors[1]



Enozertinib is a selective, CNS-penetrant EGFR inhibitor with best-in-class potency against EGFR ex20ins mutations

HER2, human epidermal growth factor receptor 2; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase 2 dose.

[1]Junttila et al. Cancer Research 2025, in press.

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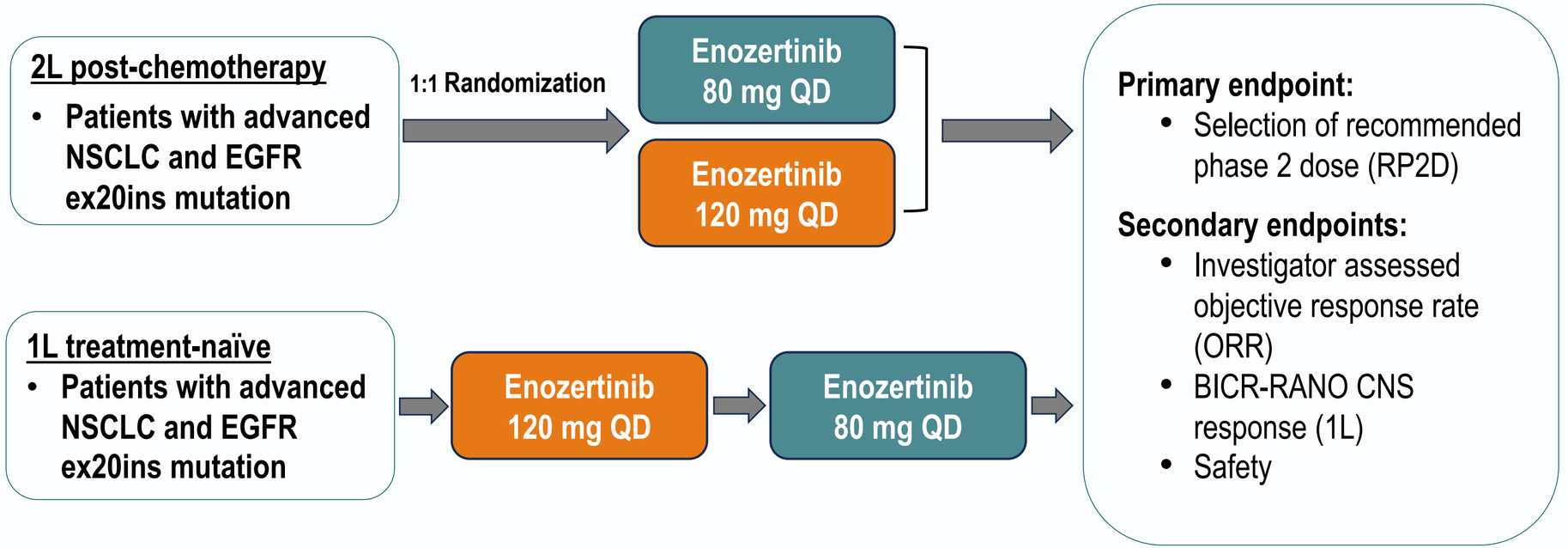
Enozertinib in Advanced NSCLC with or without CNS Involvement

Phase 1/2 Study Design (NCT05315700)

- First-in-human, global study evaluating the safety and preliminary efficacy of enozertinib in patients with advanced NSCLC harboring EGFR or HER2 alterations

Key Eligibility Criteria:

- Locally advanced or metastatic NSCLC with EGFR ex20ins mutation
- Untreated, stable, asymptomatic brain metastases allowed
- Treatment-naïve or received 1L platinum-based chemotherapy



Study enrolled 1L and 2L NSCLC patients with EGFR ex20ins mutations, including those with active brain metastases

1L, first-line; 2L, second-line; BICR, blinded independent central review; QD, once daily
Tumor restaging, including with brain MRI, performed at 4 weeks and every 8 weeks thereafter

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Patient Demographics and Baseline Characteristics

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations

Patient Characteristic	80 mg (n=24)	120 mg (n=21)
Age, years, median (range)	63 (44-75)	70 (28-86)
Female, n (%)	17 (71)	16 (76)
Non-smoker, n (%)	22 (92)	21 (100)
Race: Asian / White / Other, %	42 / 50 / 8	57 / 43 / 0
ECOG performance status: 0 / 1, %	29 / 71	19 / 81
Brain metastases at baseline,* n (%)	10 (42)	7 (33)
Prior chemotherapy, n (%)	24 (100)	21 (100)
Prior EGFR targeted therapies, n (%)	0	2 (10)†

Data cutoff: August 29, 2025

*Patients with brain metastases at study entry, including active brain metastases

†One patient each received prior erlotinib or afatinib

38% of 2L patients had brain metastases at study entry, including those with active CNS disease

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Treatment-Related Adverse Events (TRAEs) in ≥20% of Patients

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations

Event, n (%)	80 mg (n=24)	120 mg (n=21)
TRAEs Grade ≥3	10 (42)	7 (33)
Dose reduction due to TRAE	8 (33)	12 (57)
Discontinued due to TRAE	3 (13)	0

- Well tolerated safety profile with TRAEs predominantly Grades 1–2
- One Grade 4 TRAE (pneumonitis at 120 mg); no Grade 5 TRAEs
- No significant off-target toxicities (e.g., myelosuppression, QTc prolongation, hepatoxicity)
- Low rate of discontinuations due to TRAEs

Event	80 mg (n=24)		120 mg (n=21)	
Preferred term, n (%)	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Diarrhea	19 (79)	2 (8)	12 (57)	5 (24)
Paronychia	20 (83)	0	14 (67)	0
Stomatitis	10 (42)	0	12 (57)	1 (5)
Dermatitis acneiform	9 (38)	1 (4)	4 (19)	0
Rash	9 (38)	1 (4)	12 (57)	1 (5)
Nausea	8 (33)	0	9 (43)	0
Decreased appetite	6 (25)	0	6 (29)	0
Mucosal inflammation	6 (25)	0	3 (14)	0
Alopecia	6 (25)	0	5 (24)	0
Dysgeusia	8 (33)	0	2 (10)	0

Enozertinib was generally well tolerated with mainly Grade 1 or 2 adverse events and no significant off-target toxicities; 80 mg cohort experienced lower rate of dose reductions compared to 120 mg cohort

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Objective Response Rate (ORR)

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations

Evaluable Population*	80 mg (n=20)	120 mg (n=15)
Best ORR,† % [95% CI]	**45** [23, 69]	**20** [4, 48]
Confirmed ORR, % [95% CI]	**45** [23, 69]	**13** [2, 41]
Partial response, n (%)	9 (45)	2 (13)
Stable disease, n (%)	11 (55)	13 (87)
Progressive disease, n (%)	0	0
Disease control rate (CR + PR + SD), % [95% CI]	**100** [83, 100]	**100** [78, 100]
With CNS disease at baseline,‡ % (n)	**40** (8)	**33** (5)
Best ORR,† % [95% CI]	**38** [9, 76]	**40** [5, 85]
Confirmed ORR, % [95% CI]	**38** [9, 76]	**40** [5, 85]
Partial response, n (%)	3 (38)	2 (40)
Stable disease, n (%)	5 (63)	3 (60)
Progressive disease, n (%)	0	0
Disease control rate (CR + PR + SD), % [95% CI]	**100** [63, 100]	**100** [48, 100]

CR, complete response; PR, partial response; SD, stable disease
Data cutoff: August 29, 2025. Percentages in the table may not total 100% due to rounding
*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
‡CNS disease at baseline includes patients with brain metastases at study entry, including active brain metastases

Enozertinib demonstrated strong systemic and CNS antitumor activity in 2L NSCLC patients with EGFR ex20ins mutations

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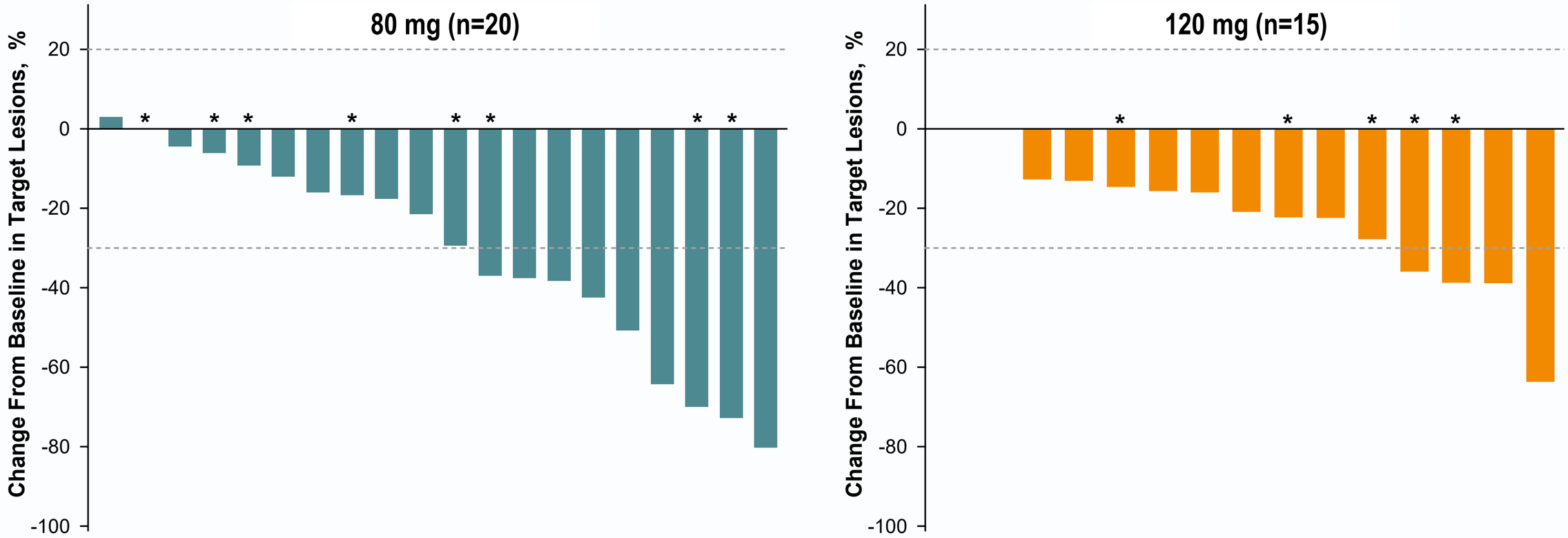
Best Tumor Reduction

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations



*Patients with brain metastases at study entry, including active brain metastases

- Higher efficacy seen at 80 mg dose; efficacy at 120 mg limited by higher rate of adverse events leading to frequent dose interruptions

Enozertinib 80 mg once daily achieves a balance between acceptable tolerability with strong clinical activity

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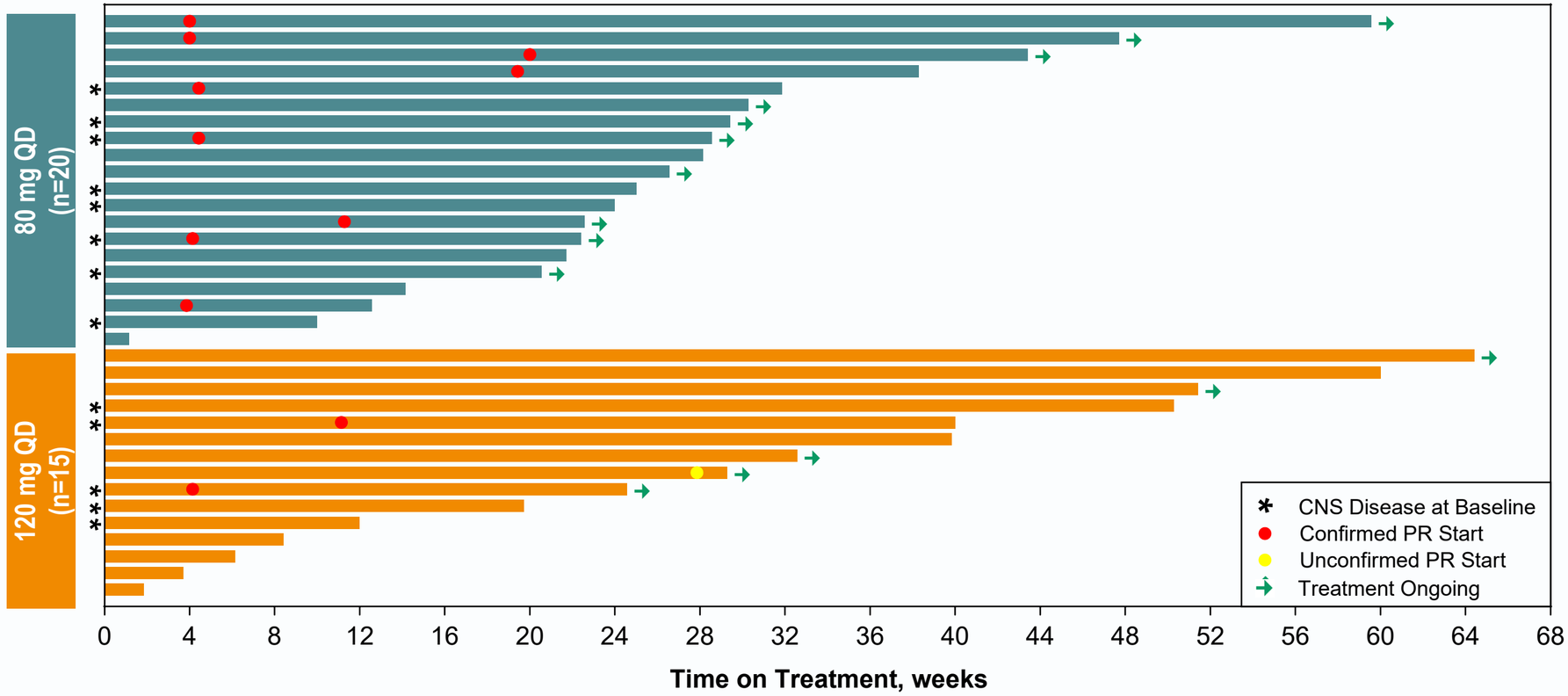
Treatment Duration and Time of Responses

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations



- Responses generally occur by 4 weeks, but tumor regression continues over time, with late responses seen after 4+ months on treatment
- Median follow-up of 43.4 weeks; 67% (8/12) of responders remain on treatment

Progression-free survival and duration of response are immature; 67% of responders are still on treatment

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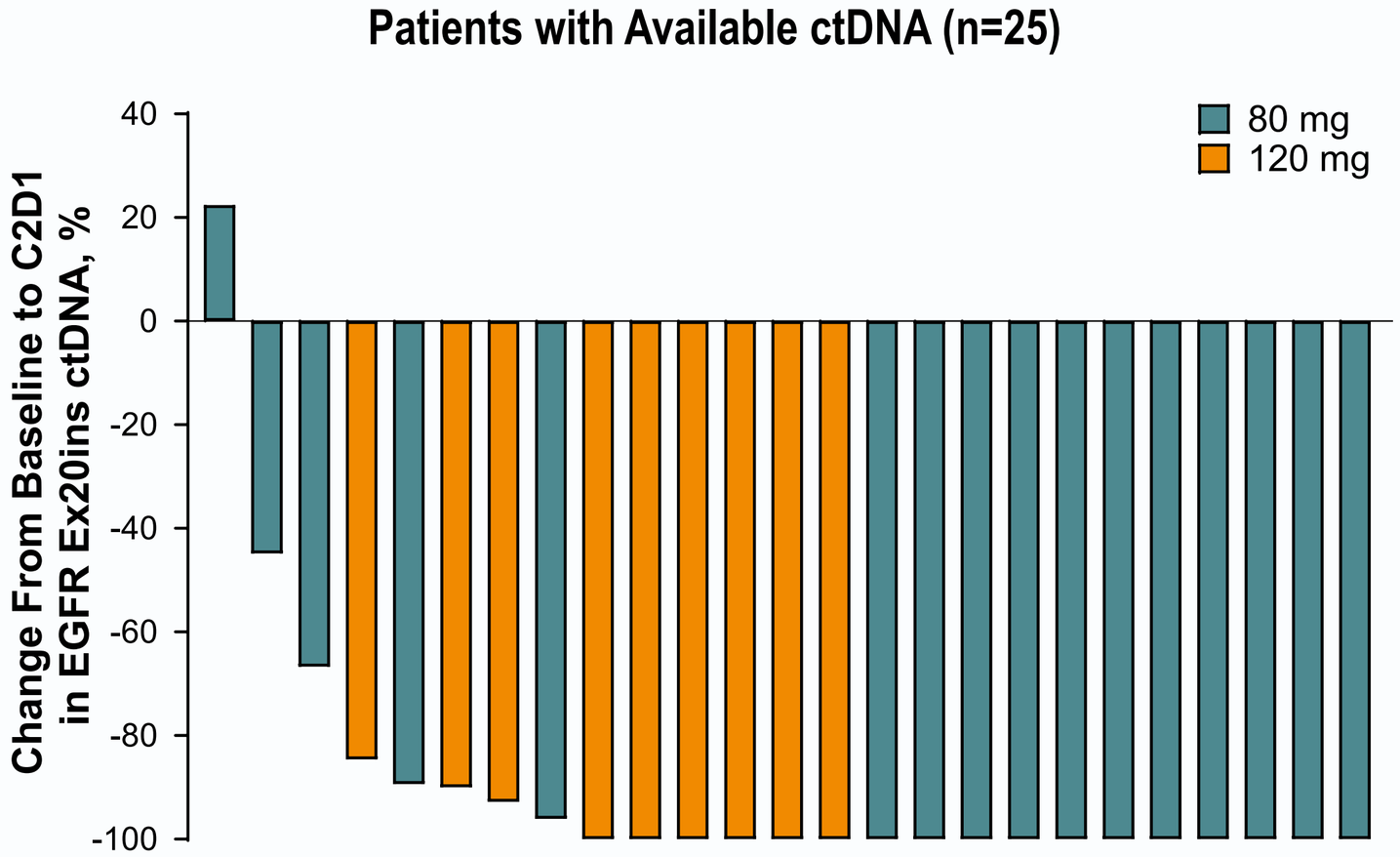
Circulating Tumor DNA (ctDNA) Levels

2L post-chemotherapy, advanced NSCLC with EGFR ex20ins mutations



- ctDNA clearance rate of 69% (11/16) at 80 mg and 67% (6/9) at 120 mg

Enozertinib achieved robust ctDNA responses across doses in 2L NSCLC patients with EGFR ex20ins mutations

ctDNA assessed with Guardant360 Liquid assay; C2D1 = cycle 2 day 1, day 29; Clearance is defined as change from detected to undetected EGFR ex20ins in plasma after one treatment cycle and is shown as -100% on waterfall plot

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Patient Demographics and Baseline Characteristics

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations

Patient Characteristic	80 mg (n=18)	120 mg (n=15)
Age, years, median (range)	72 (43-95)	66 (48-82)
Female, n (%)	13 (72)	11 (73)
Non-smoker, n (%)	18 (100)	15 (100)
Race: Asian / White / Other, %	17 / 78 / 6	20 / 73 / 7
ECOG performance status: 0 / 1, %	39 / 61	40 / 60
Brain metastases at baseline,* n (%)	5 (28)	8 (53)
Prior chemotherapy	0	0
Prior EGFR targeted therapies	0	0

Data cutoff: August 29, 2025. Percentages in the table may not total 100% due to rounding
*Patients with brain metastases at study entry, including active brain metastases

39% of 1L patients had brain metastases at study entry, including those with active CNS disease

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Treatment-Related Adverse Events (TRAEs) in ≥20% of Patients

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations

Event, n (%)	80 mg (n=18)	120 mg (n=15)
TRAEs Grade ≥3	4 (22)	9 (60)
Dose reduction due to TRAE	3 (17)	12 (80)
Discontinued due to TRAE	2 (11)	0

- Well tolerated safety profile with TRAEs predominantly Grades 1–2
- No significant off-target toxicities (e.g., myelosuppression, QTc prolongation, hepatotoxicity)
- Low rate of discontinuations due to TRAEs
- Higher rate of dose reductions at 120 mg (80%) vs 80 mg (17%)
  - 58% of reductions at 120 mg dose occurred by ~8 weeks (2 cycles)

Event	80 mg (n=18)		120 mg (n=15)	
Preferred term, n (%)	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Diarrhea	15 (83)	2 (11)	9 (60)	1 (7)
Paronychia	8 (44)	0	11 (73)	1 (7)
Stomatitis	7 (39)	1 (6)	4 (27)	0
Dermatitis acneiform	5 (28)	0	4 (27)	6 (40)
Rash	4 (22)	1 (6)	2 (13)	1 (7)
Nausea	6 (33)	0	3 (20)	0
Pruritis	4 (22)	0	3 (20)	0
Mucosal inflammation	4 (22)	0	5 (33)	1 (7)
Dry skin	1 (6)	0	6 (40)	0
Alopecia	1 (6)	0	8 (53)	0
Rash maculo-papular	5 (28)	0	2 (13)	0

High rate of dose reductions in 120 mg cohort led to subsequent cohort of patients being dosed at 80 mg QD

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Objective Response Rate (ORR) and Best Tumor Reduction

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations

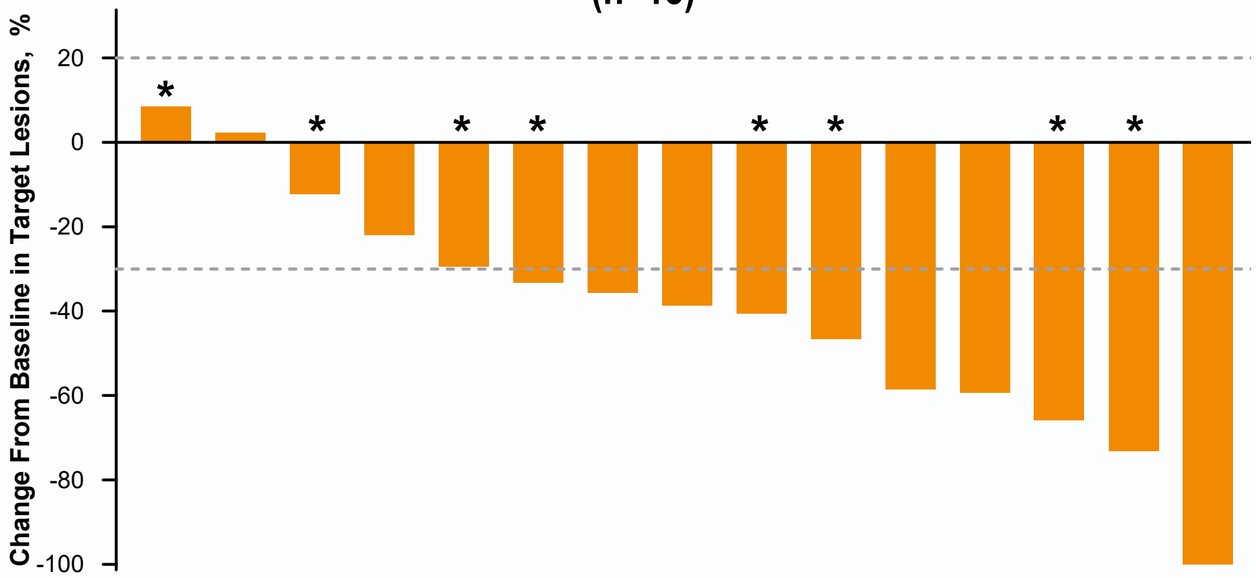
- Initial cohort of efficacy evaluable patients were treated at 120 mg; given 80% dose reduction rate, most patients effectively received 80 mg
- Subsequent cohort of patients was treated at 80 mg; follow-up is still in progress

Systemic Objective Response Rate

Evaluable Population*	120 mg (n=15)
Best ORR,† % [95% CI]	**67** [38, 88]
Confirmed ORR, % [95% CI]	**60** [32, 84]
Partial response, n (%)	9 (60)
Stable disease, n (%)	5 (33)
Progressive disease, n (%)	1 (7)
Disease control rate (CR + PR + SD), % [95% CI]	**93** [68, 100]

CR, complete response; PR, partial response; SD, stable disease
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

Best % Change in Lesions in Patients Receiving 120 mg Dose (n=15)



*Patients with brain metastases at study entry, including active brain metastases

Enozertinib demonstrated encouraging ORR and disease control in 1L NSCLC patients with EGFR ex20ins mutations

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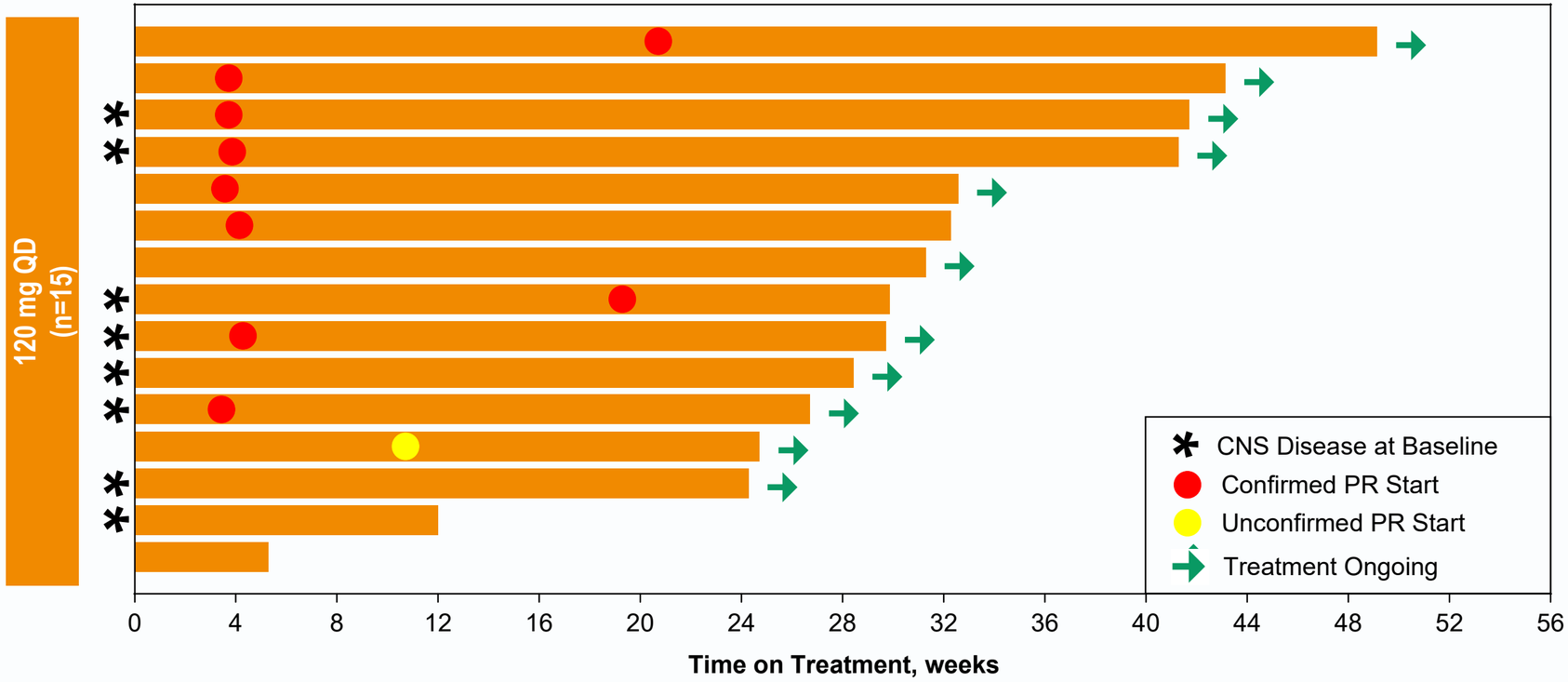
Treatment Duration and Time of Responses

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations



- Initial cohort of efficacy evaluable patients were treated at 120 mg; given 80% dose reduction rate, most patients effectively received 80 mg
- Responses generally occur by 4 weeks, but tumor regression continues over time, with late responses seen after 4+ months on treatment
- Median follow-up of 32.6 weeks; 80% (8 of 10) of responders are still on treatment

Good response durability supports enozertinib 80 mg QD as go-forward dose

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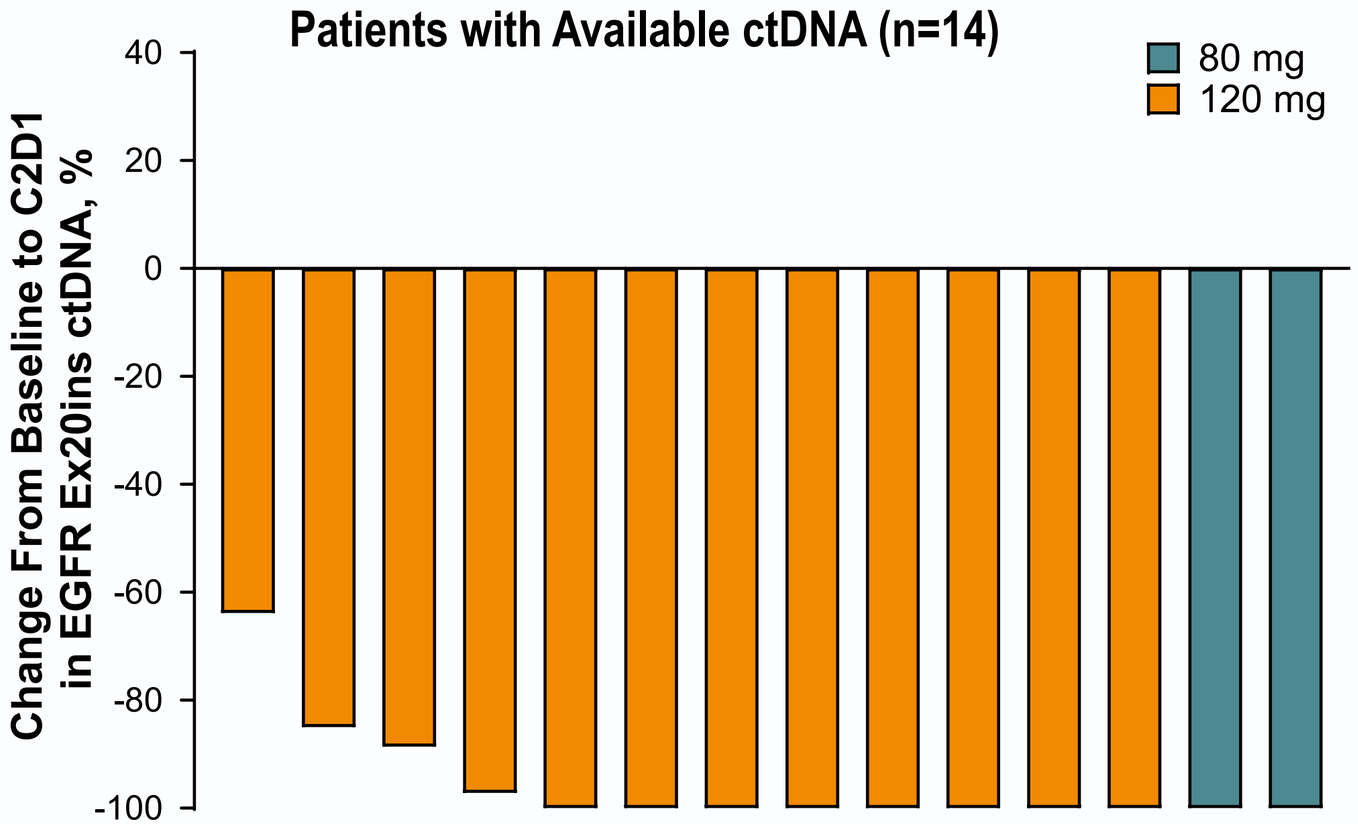
Circulating Tumor DNA (ctDNA) Levels

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations



- ctDNA clearance rate of 71% (10/14)

Enozertinib achieved robust ctDNA responses in 1L NSCLC patients with EGFR ex20ins mutations

ctDNA assessed with Guardant360 Liquid assay; C2D1 = cycle 2 day 1, day 29; Clearance is defined as change from detected to undetected EGFR ex20ins in plasma after one treatment cycle and is shown as -100% on waterfall plot

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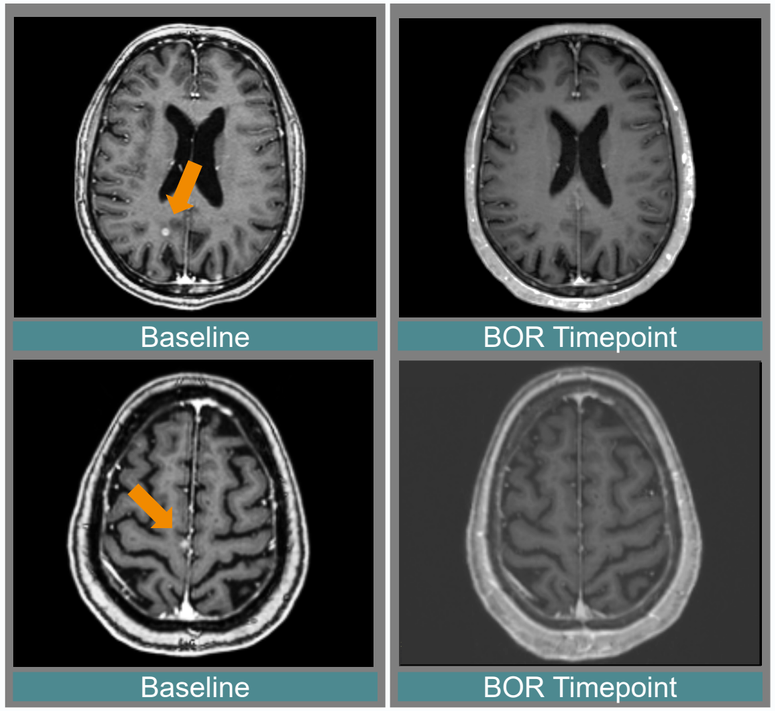
CNS Objective Response Rate (ORR) by BICR-RANO

1L treatment-naïve, advanced NSCLC with EGFR ex20ins mutations

CNS Response†	120 mg (n=7)*
Best ORR,‡ % [95% CI]	**71** [29, 96]
Confirmed ORR, % [95% CI]	**71** [29, 96]
Complete response, n (%)	2 (29)
Partial response, n (%)	3 (43)
Stable disease, n (%)	0
Progressive disease, n (%)	2 (29)
Disease control rate (CR + PR + SD), % [95% CI]	**71** [29, 96]

BICR, blinded independent central review; CR, complete response; PR, partial response; SD, stable disease
Data cutoff: August 29, 2025. Percentages in the table may not total 100% due to rounding
*One patient was deemed not evaluable by BICR
†Per RANO by BICR
‡Best objective response rate includes both confirmed and unconfirmed responses

Complete Intracranial Responses in 1L Patient with Active Brain Metastases



- 60-year-old female, no prior therapy
- Brain metastases at baseline: 5 non-target lesions; no prior radiation therapy (active disease)
- Enozertinib dose: 120 mg
- Achieved systemic PR and CNS CR at Cycle 2
- TRAEs: Grade 1 paronychia, Grade 2 mucositis, dose reduced for Grade 3 palmar erythrodysesthesia
- On treatment in Cycle 6 at data cut-off in response

Strong CNS ORR by BICR-RANO, including in patients with active brain metastases, highlights enozertinib's CNS activity and positions it favorably for future clinical development in 1L NSCLC patients with EGFR ex20ins mutations

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Conclusions

- Enozertinib was generally well tolerated with mainly Grade 1 or 2 adverse events and no significant off-target toxicities; 80 mg cohort experienced lower rate of dose reductions compared to 120 mg cohort
- Enozertinib demonstrated strong systemic and CNS antitumor activity in 1L and 2L NSCLC patients with EGFR ex20ins mutations
    - 71% CNS ORR by BICR-RANO, including in patients with active brain metastases, highlights enozertinib's CNS activity and positions it favorably for future clinical development in the front-line setting
- Enozertinib 80 mg once daily achieves a balance between acceptable tolerability with encouraging clinical activity and is the selected go-forward dose

Tom John, MBBS, PhD, FRACP

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Acknowledgements

- We thank the patients, families, caregivers, and investigators who participated in this study
- This study was sponsored by ORIC Pharmaceuticals, Inc.
- Editorial assistance was provided by ICON plc (Blue Bell, PA), and was funded by ORIC Pharmaceuticals, Inc.

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

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