elcc European Lung Cancer Congress 2025

Osimertinib + datopotamab deruxtecan in patients with *EGFR*-mutated advanced NSCLC whose disease progressed on first-line osimertinib: ORCHARD

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Final Publication Number: 1O

Organisers: ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE; IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Partners: ESTRO; ETOP·IBCSG PARTNERS FOUNDATION

Declaration of interests

Xiuning Le

Research funding: ArriVent, Bayer AG, Boehringer Ingelheim, Dizal, Eli Lilly, EMD Serono, Janssen (J&J), Regeneron, Takeda, Teligene and ThermoFisher

Consultant, advisor: AbbVie, Abion, Allist, ArriVent, AstraZeneca, Aviston, Bayer AG, BlossomHill, Blueprint Medicines, Boehringer Ingelheim, BioNTech, Bristol Myers Squibb, Daiichi-Sankyo, Dizal, Eli Lilly, EMD Serono (Merck KGaA), GuardantHealth, Hengrui Therapeutics, InnvoVent, Janssen (J&J), Novartis, Pfizer, Regeneron, Roche/Genentech, Sensei Biotherapeutics, SystImmune, Teligene, and Taiho

Travel support : Allist, EMD Serono and Janssen

Introduction

- The third-generation, irreversible EGFR-TKI osimertinib is a preferred 1L treatment for *EGFR*m advanced NSCLC[1–3]
- Subsequent treatment options following disease progression on osimertinib are limited, with a range of novel agents under investigation[2–4]
- Dato-DXd is a TROP2-directed antibody-drug conjugate that has demonstrated promising efficacy as monotherapy in pretreated *EGFR*m advanced NSCLC[5–8]
  - Based on findings from the TROPION-Lung05 (TL05) and TROPION-Lung01 (TL01) studies, Dato-DXd recently received Breakthrough Therapy Designation and Priority Review from the US FDA[6–10]
- The global, Phase 2 ORCHARD study was designed to assess novel post-progression combination therapies in patients who progressed on 1L osimertinib[11]

Here, we report results from module 10 of the ORCHARD platform study, which assessed a combination of osimertinib with Dato-DXd (4 mg/kg or 6 mg/kg)

1. Soria J-C, et al. N Engl J Med 2018;378:113–125; 2. Hendriks LE, et al. Ann Oncol 2023;34:339–357; 3. Bazhenova L, et al. J Clin Oncol 2024;42:e72–e86; 4. Lee, et al. Ther Adv Med Oncol 2022;14:17588359221144099; 5. Okajima D, et al. Mol Cancer Ther 2021;20:2329–2340; 6. Ahn M-J, et al. J Clin Oncol 2024;43:260–272; 7. Sands J, et al. J Clin Oncol 2025;Online ahead of print; 8. Ahn M-J, et al. Ann Oncol 2024;35(suppl 4):S1630–S1631; 9. AstraZeneca; available from: https://www.astrazeneca.com/media-centre/press-releases/2024/datopotamab-deruxtecan-granted-breakthrough-therapy-designation-us-patients-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html;
10. AstraZeneca; available from: https://www.astrazeneca.com/media-centre/press-releases/2025/datopotamab-deruxtecan-granted-priority-review-in-the-us-for-patients-with-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html; 11. Yu, et al. Clin Lung Cancer 2021;22:601–606. 1L, first-line; Dato-DXd, datopotamab deruxtecan; *EGFR*(m), epidermal growth factor receptor(-mutated); NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell-surface antigen 2

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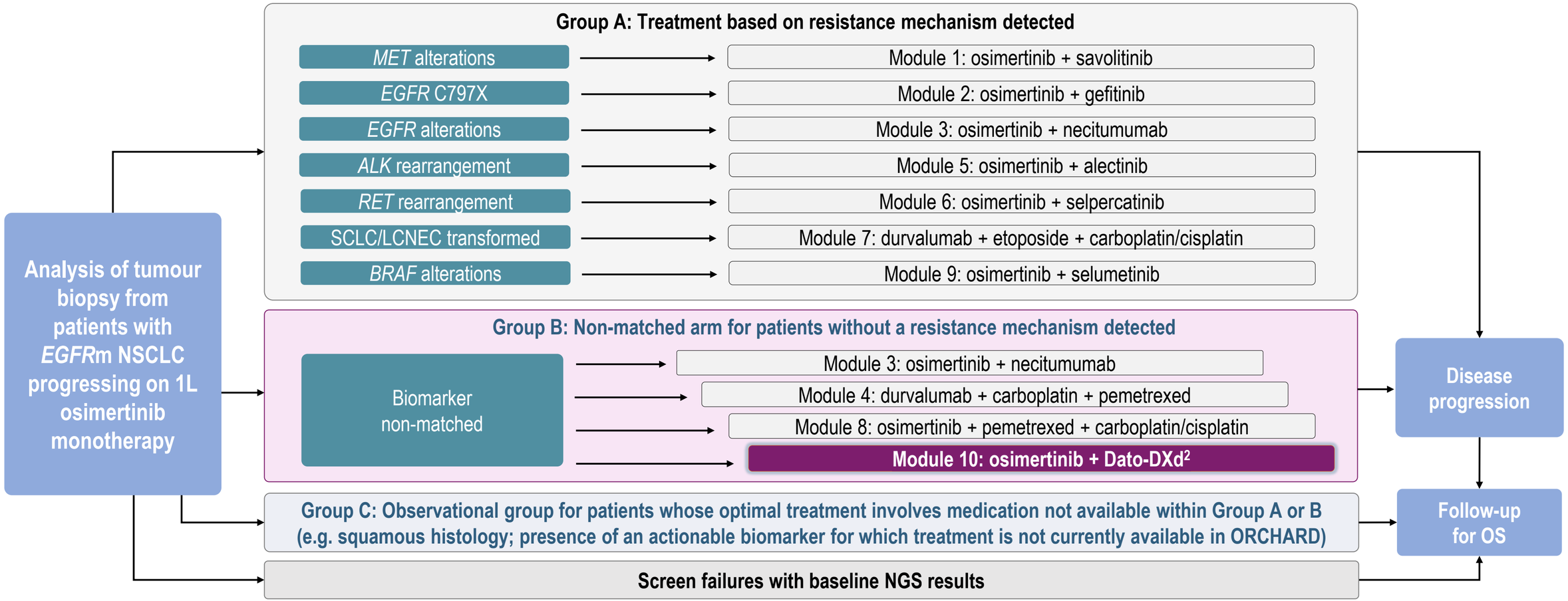
ORCHARD: biomarker-directed platform study

- **NCT03944772:** a global, Phase 2, open-label, multicentre, biomarker-directed platform study in patients with *EGFR*m advanced NSCLC whose disease progressed on 1L osimertinib[1]



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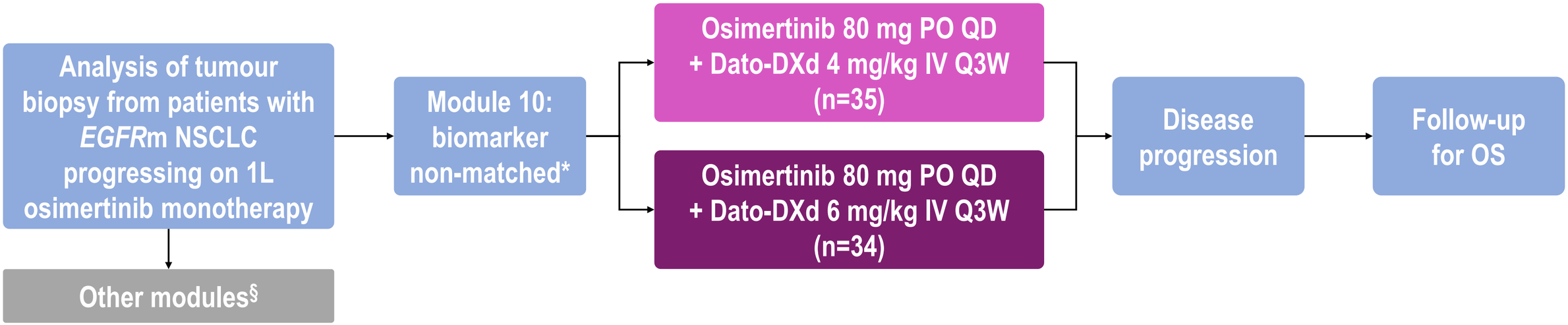
1. Yu HA, et al. Clin Lung Cancer 2021;22:601–606; 2. De Langen J, et al. Ann Oncol 2022;33(suppl 7):S1091–S1092. 1L, first-line; *ALK*, anaplastic lymphoma kinase; Dato-DXd, datopotamab deruxtecan; *EGFR*m, epidermal growth factor receptor-mutated; LCNEC, large-cell neuroendocrine carcinoma; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OS, overall survival; SCLC, small-cell lung cancer

ORCHARD module 10 study design



- **Primary endpoint:** ORR based on RECIST v1.1 by investigator assessment
- **Key secondary endpoints:** PFS‡, DoR‡, OS, AEs, SAEs

We present the first disclosure of safety and efficacy data from ORCHARD module 10 (data cut-off: 12 October 2024)¶

*Includes 17 safety run-in patients followed by 52 patients enrolled to either cohort. §Modules 2, 5, 6, 7, 8 and 9 were open for enrolment at the same time as module 10; modules 1, 3 and 4 were closed. ‡Based on RECIST v1.1 by investigator assessment. ¶The data are not yet locked, although efforts have been made to clean. Inconsistencies in the data may remain and the data are subject to change

1L, first-line; AE, adverse event; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; *EGFR*m, epidermal growth factor receptor-mutated IV, intravenous; PFS, progression-free survival; PO, orally; NSCLC, non-small cell lung cancer; ORR, objective response rate OS, overall survival; Q3W, every 3 weeks; QD, daily; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event

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Baseline characteristics

Characteristics, %	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=34)
Age		
Median (range), years	62 (37, 76)	64 (42, 78)
≥65 years, n (%)	13 (37)	16 (47)
Female sex, n (%)	24 (69)	22 (65)
Race, n (%)		
Asian	12 (34)	10 (29)
White	21 (60)	22 (65)
Other or missing	2 (6)	2 (6)
Time to PD on 1L osimertinib, n (%)		
<12 months	18 (51)	3 (9)
≥12 to ≤18 months	2 (6)	12 (35)
>18 months	14 (40)	19 (56)
Missing	1 (3)	0
WHO PS, n (%)		
(0) Normal	18 (51)	15 (44)
(1) Restricted activity	17 (49)	19 (56)
CNS metastases at baseline, n (%)	16 (46)	11 (32)
Liver metastases at baseline, n (%)	13 (37)	4 (12)

Safety analysis set.

1L, first-line; CNS, central nervous system; Dato-DXd, datopotamab deruxtecan; PD, progressive disease; WHO PS, World Health Organization performance status

Efficacy summary

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
PFS		
mPFS, months (95% CI)	**9.5 (7.2, 9.8)**	**11.7 (8.3, NC)**
6-month rate, % (95% CI)	74 (56, 85)	80 (61, 91)
9-month rate, % (95% CI)	50 (33, 65)	70 (49, 83)
12-month rate, % (95% CI)	21 (9, 35)	39 (21, 57)
ORR, % (80% CI)	**43 (31, 55)**	**36 (25, 49)**
DoR		
mDoR, months (95% CI)*	**6.3 (3.8, 8.2)**	**20.5 (6.2, NC)**
6-month rate, % (95% CI)	60 (32, 80)	92 (54, 99)
9-month rate, % (95% CI)	15 (2, 38)	64 (30, 85)
Median time to onset of response, months (Q1, Q3)	**2.7 (1.5, 4.1)**	**1.4 (1.2, 2.1)**
Median duration of follow-up, months	13.4	13.8
OS events, n (%)	16 (46)	9 (27)

*mDoR not yet mature for 6 mg/kg cohort. Data cut-off: 12 October 2024. Evaluable for efficacy set.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; (m)DoR, (median) duration of response; mPFS, median progression-free survival; NC, not calculable; ORR, objective response rate; OS, overall survival; Q, quartile

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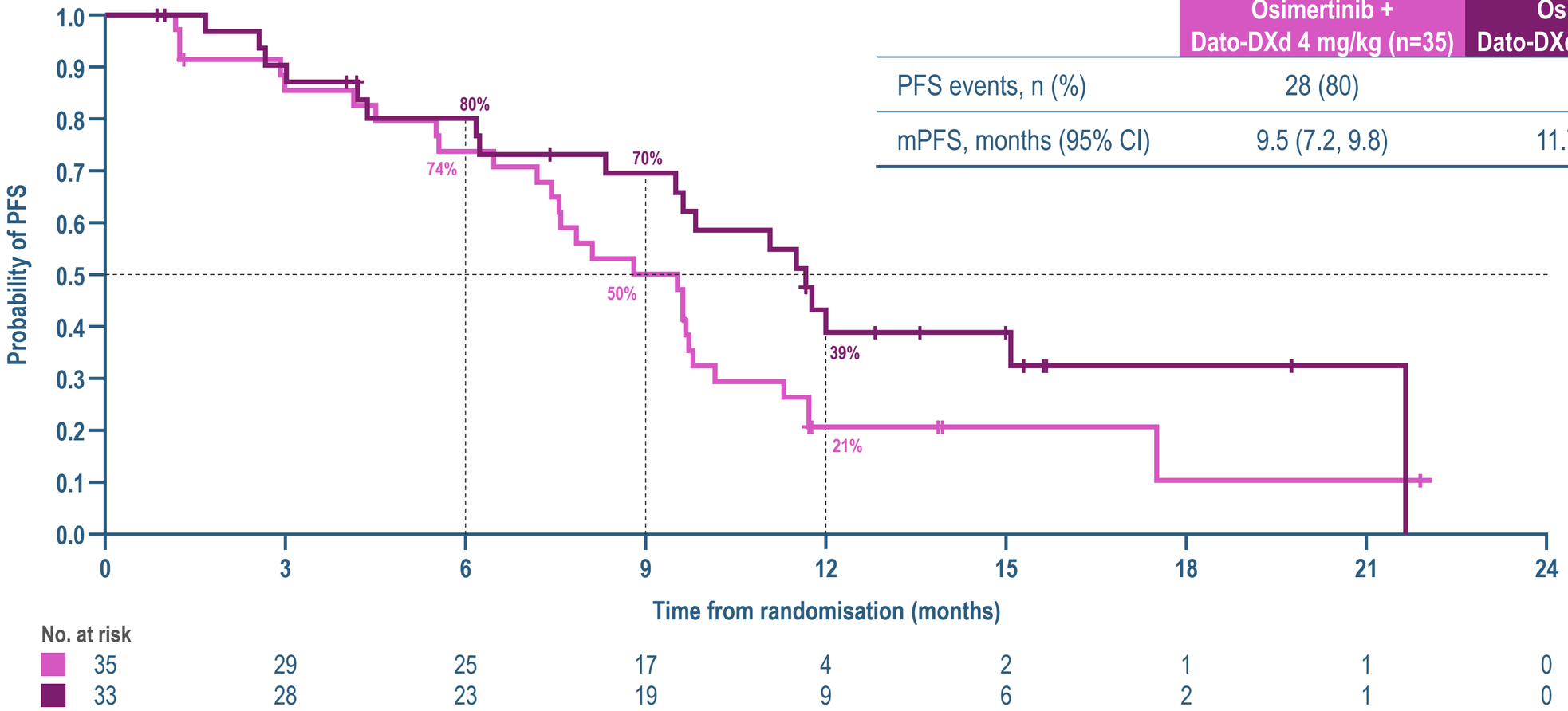
PFS favoured the 6 mg/kg cohort

- mPFS: 11.7 months with osimertinib + Dato-DXd 6 mg/kg

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
PFS events, n (%)	28 (80)	19 (58)
mPFS, months (95% CI)	9.5 (7.2, 9.8)	11.7 (8.3, NC)



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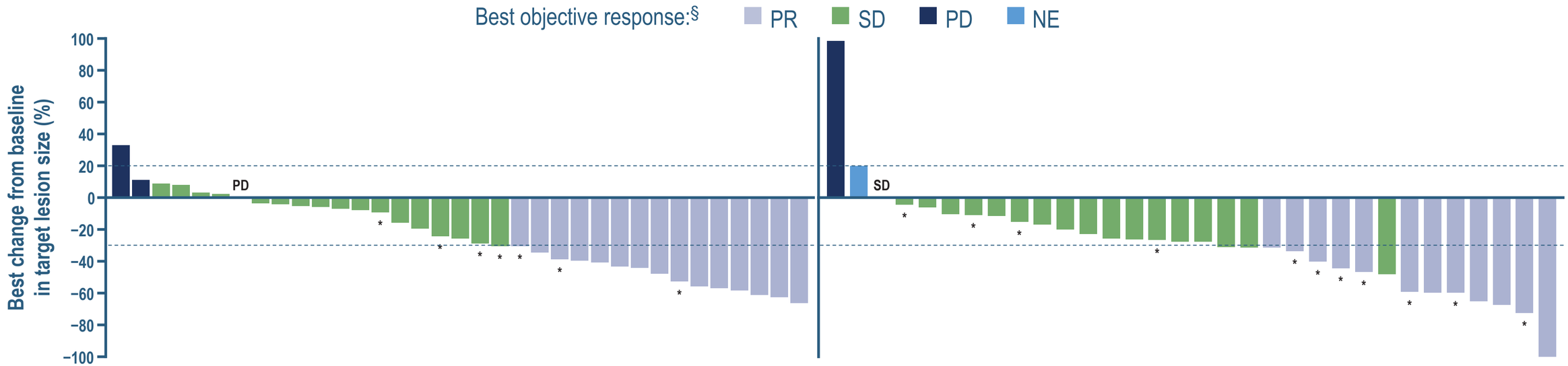
Data cut-off: 12 October 2024. Evaluable for efficacy set.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; NC, not calculable; mPFS, median progression-free survival

ORR was similar between the two cohorts

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
ORR, % (80% CI)	43 (31, 55)	36 (25, 49)
Median time to onset of response, months (Q1, Q3)	2.7 (1.5, 4.1)	1.4 (1.2, 2.1)



- Faster time to response and greater target lesion shrinkage in the 6 mg/kg cohort

*Patients ongoing study treatment at data cut-off. §There were no complete responses.
Data cut-off: 12 October 2024. Evaluable for efficacy set.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease

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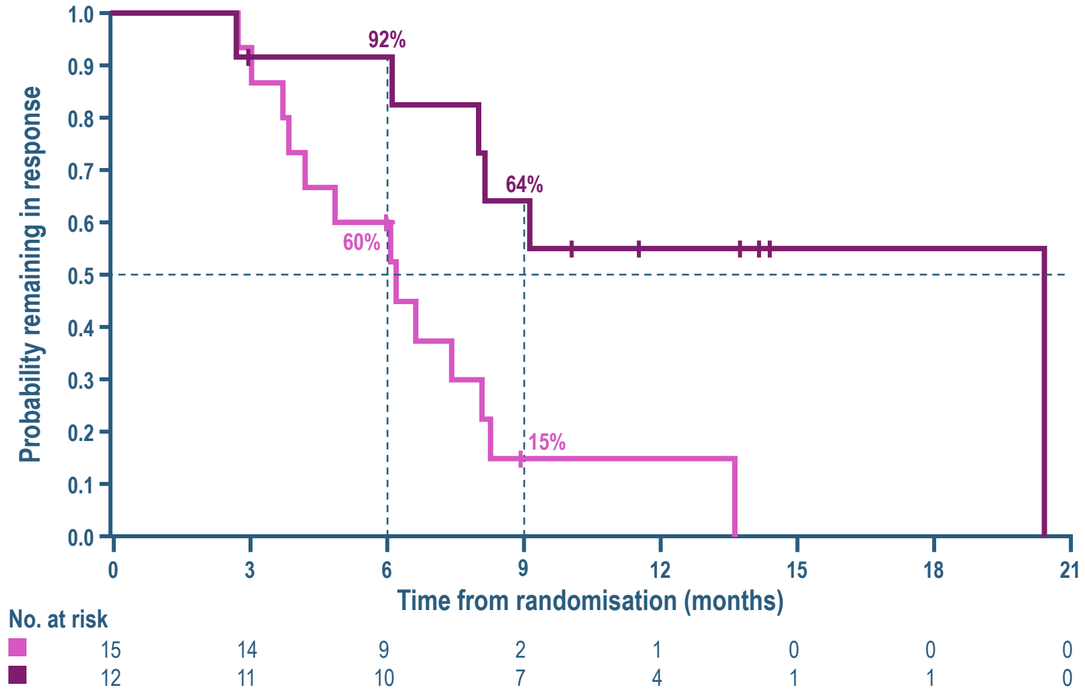
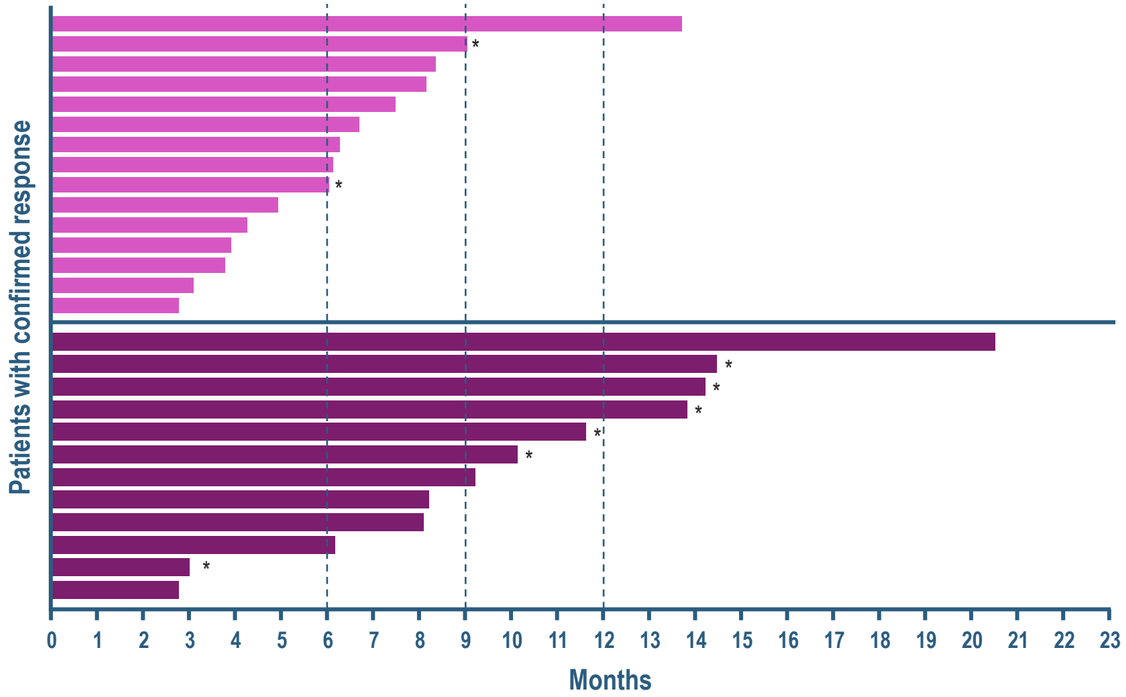
DoR favoured the 6 mg/kg cohort

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
Responders, n	15	12
Responders who died or progressed, n	13	6
mDoR, months (95% CI)§	6.3 (3.8, 8.2)	20.5 (6.2, NC)





*Patients censored at data cut-off. §mDoR not yet mature for 6 mg/kg cohort.
Data cut-off: 12 October 2024. Evaluable for efficacy set.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; (m)DoR, (median) duration of response; NC, not calculable

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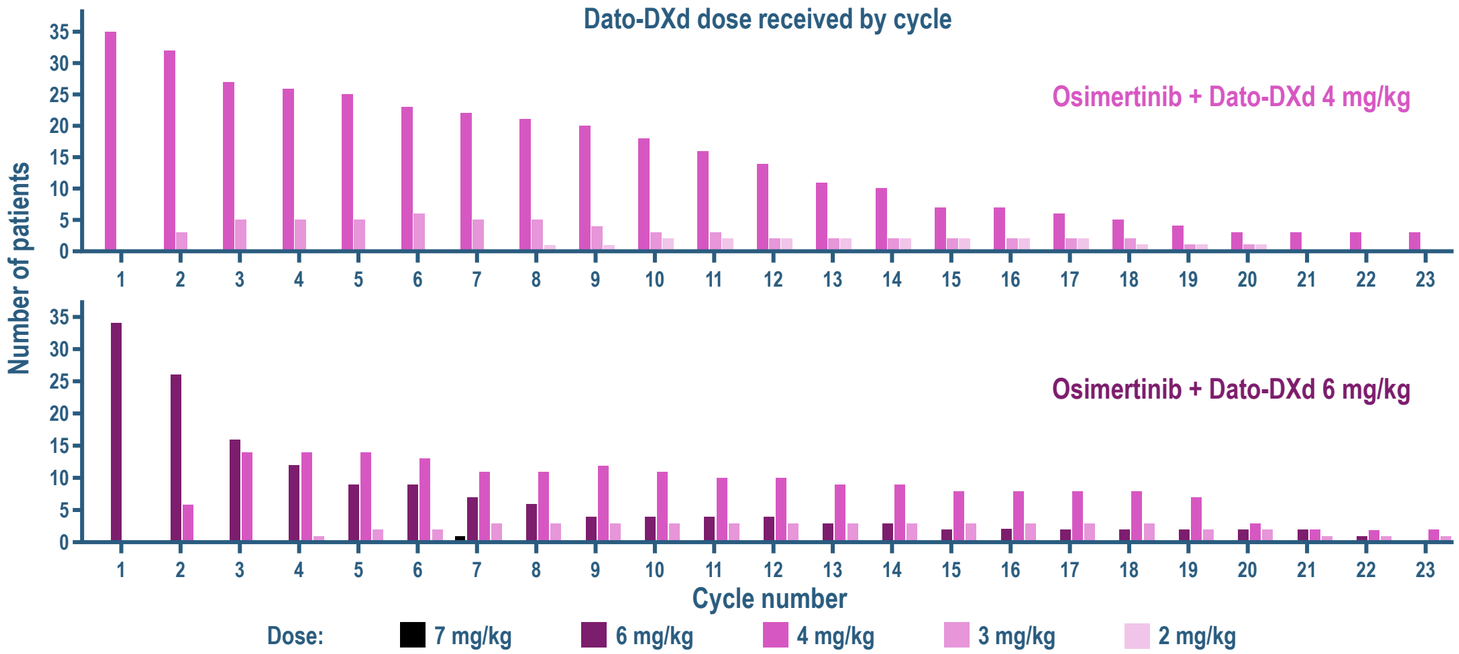
Treatment exposure

	Osimertinib + Dato-DXd 4 mg/kg (n=35)		Osimertinib + Dato-DXd 6 mg/kg (n=34)	
	Osimertinib	Dato-DXd 4 mg/kg	Osimertinib	Dato-DXd 6 mg/kg
Median treatment duration, months	9.0		9.8	
Osimertinib/Dato-DXd dose reduction, n (%)	6 (17)	8 (23)	0	21 (62)
Osimertinib/Dato-DXd dose interruption, n (%)	14 (40)	10 (29)	12 (35)	11 (32)
Osimertinib/Dato-DXd discontinuation, n (%)	28 (80)	28 (80)	23 (68)	23 (68)

- The duration of treatment was similar between the 4 and 6 mg/kg cohorts
- There were no osimertinib dose reductions in the 6 mg/kg cohort
- From Cycle 4 onwards, more than half of patients in the 6 mg/kg cohort reduced their Dato-DXd dose to 4 mg/kg
- Similar proportions of patients in each cohort had osimertinib and Dato-DXd dose interruptions



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Data cut-off: 12 October 2024. Safety analysis set.

Dato-DXd, datopotamab deruxtecan

Safety summary

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=34)
Treatment-related AE, n (%)	34 (97)	33 (97)
Grade ≥3	12 (34)	19 (56)
Grade ≥3 possibly related to osimertinib only	2 (6)	0
Grade ≥3 possibly related to Dato-DXd only	5 (14)	12 (35)
Any Grade ≥3 AE, n (%)	17 (49)	25 (74)
SAE, n (%)*	11 (31)	14 (41)
AE with outcome of death, n (%)	1 (3)	0
Dose reduction, n (%)		
AE leading to osimertinib dose reduction	6 (17)	0
AE leading to Dato-DXd dose reduction	8 (23)	20 (59)
Dose interruption, n (%)		
AE leading to osimertinib dose interruption	15 (43)	12 (35)
AE leading to Dato-DXd dose interruption	16 (46)	22 (65)
Discontinuation, n (%)		
AE leading to osimertinib discontinuation	6 (17)	8 (24)
AE leading to Dato-DXd discontinuation	6 (17)	9 (26)

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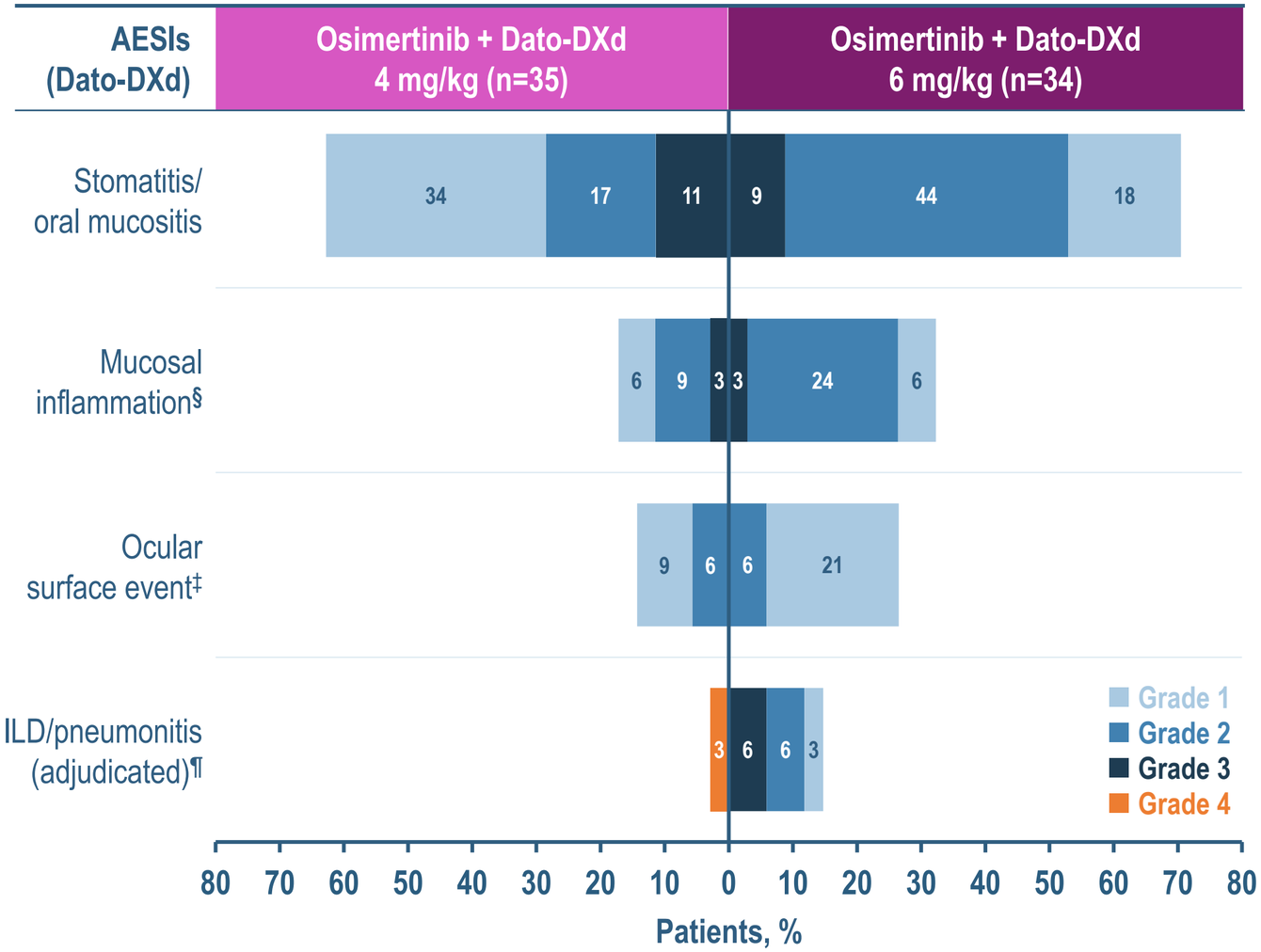
*Including AE with outcome of death. Data cut-off: 12 October 2024. Safety analysis set.

AE, adverse event; Dato-DXd, datopotamab deruxtecan; SAE, serious adverse event

Safety summary (cont'd)

Most common AEs by PT*, n (%)	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=34)
Nausea	20 (57)	25 (74)
Alopecia	18 (51)	23 (68)
Stomatitis	18 (51)	19 (56)
Constipation	16 (46)	14 (41)
Cough	9 (26)	18 (53)
Diarrhoea	16 (46)	11 (32)
Decreased appetite	12 (34)	14 (41)
Vomiting	6 (17)	17 (50)
Fatigue	10 (29)	12 (35)
Paronychia	11 (31)	10 (29)
Asthenia	4 (11)	10 (29)



*AEs occurring in ≥20% of patients overall. AEs are shown in descending order of frequency in the overall study population. §Other than stomatitis/oral mucositis. ‡The majority of ocular surface events were lacrimation increased. ¶One case of ILD in the 6 mg/kg cohort is awaiting adjudication (Grade 2 per investigator); currently assumed to be ILD. Data cut-off: 12 October 2024. Safety analysis set.

AE, adverse event; AESI, adverse event of special interest; Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease; PT, preferred term

Conclusions

- In the ORCHARD study, which enrolled patients with *EGFR*m advanced NSCLC whose disease had progressed after 1L osimertinib, osimertinib in combination with Dato-DXd demonstrated promising efficacy
- In the cohort receiving **Dato-DXd 6 mg/kg with osimertinib 80 mg, mPFS was 11.7 months and ORR was 36%**; follow-up data for OS are awaited
- No new safety signals were identified in either cohort
- Considering the overall benefit/risk profile, 6 mg/kg is the preferred Dato-DXd starting dose for combination with osimertinib 80 mg
- The recently initiated Phase 3 TROPION-Lung14[1] and TROPION-Lung15[2] studies are assessing Dato-DXd with or without osimertinib for patients with *EGFR*m advanced NSCLC

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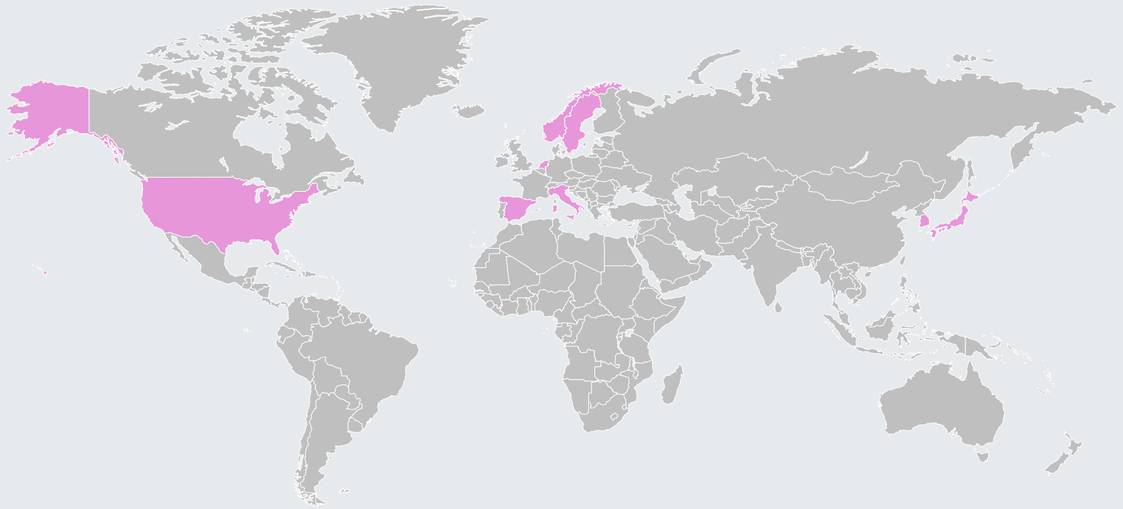
1. Clinicaltrials.gov NCT06350097; available at: https://clinicaltrials.gov/study/NCT06350097;
2. Clinicaltrials.gov NCT06417814; available at: https://clinicaltrials.gov/study/NCT06417814. 1L, first-line; Dato-DXd, datopotamab deruxtecan; *EGFR*m, epidermal growth factor receptor-mutated; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival

Acknowledgements

- **We thank all patients and their families, as well as staff and investigators at each study site**
- The ORCHARD study (NCT03944772) is funded by AstraZeneca, Cambridge, UK
- In July 2020, AstraZeneca entered into a global development and commercialisation collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan

69 patients from 8 countries enrolled in module 10 of the ORCHARD study



- We would like to acknowledge Marine Pillet, of Fortrea Development Limited, for her contribution to the statistical analyses for this study
- We would like to acknowledge Emeka Uhiara, MPharm, PhD, of Ashfield MedComms, an Inizio Company, for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice (GPP) guidelines (https://www.ismpp.org/gpp-2022)

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Plain language summary

Encouraging outcomes were observed with osimertinib plus Dato-DXd in patients with *EGFR*-mutated advanced NSCLC whose cancer had progressed on first treatment with osimertinib, warranting further investigation of this combination in Phase 3 studies

Why did we perform this research?

- The epidermal growth factor receptor (EGFR) is a protein that controls cell growth and division; changes (mutations) in the *EGFR* gene can cause tumour growth
- Osimertinib is a treatment that blocks the effect of mutated EGFR on cancer cells, reducing their growth and spread. Osimertinib is a preferred first treatment for patients with advanced non-small cell lung cancer (NSCLC) that has a mutation in the *EGFR* gene, known as *EGFR*-mutated NSCLC. While osimertinib can be beneficial, the cancer can worsen over time or spread to other areas of the body (known as disease progression)
- Dato-DXd is a treatment that has shown encouraging results in *EGFR*-mutated NSCLC
- ORCHARD was a platform study designed to evaluate new treatment combinations in patients with *EGFR*-mutated advanced NSCLC whose cancer had progressed on osimertinib; one part of the ORCHARD study, known as module 10, assessed the combination of osimertinib with Dato-DXd

How did we perform this research?

- A total of 69 patients were enrolled and received osimertinib plus Dato-DXd at a dose of either 4 mg/kg (35 patients) or 6 mg/kg (34 patients); patients were followed closely to monitor disease progression
- Treatment continued until the cancer progressed, or until the patient and their doctor decided to stop treatment for other reasons, such as side effects

What were the findings and implications of this research?

- Osimertinib plus Dato-DXd showed promising efficacy, and side effects were manageable
- The time at which half of the patients' cancer had grown or spread, or patients had died (median progression-free survival) was longer with the Dato-DXd 6 mg/kg dose (11.7 months) than with the 4 mg/kg dose (9.5 months)
- This Phase 2 study had a small number of patients; therefore, randomised Phase 3 studies are underway to further evaluate this combination

Where can I access more information?

- More information on the ORCHARD study can be found at ClinicalTrials.gov (NCT03944772): https://clinicaltrials.gov/ct2/show/NCT03944772

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This study was funded by AstraZeneca. Presented at the European Lung Cancer Congress 2025 by Xiuning Le