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Efficacy and safety of datopotamab deruxtecan in patients with previously treated *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): pooled analysis of TROPION-Lung01 and TROPION-Lung05

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DECLARATION OF INTERESTS

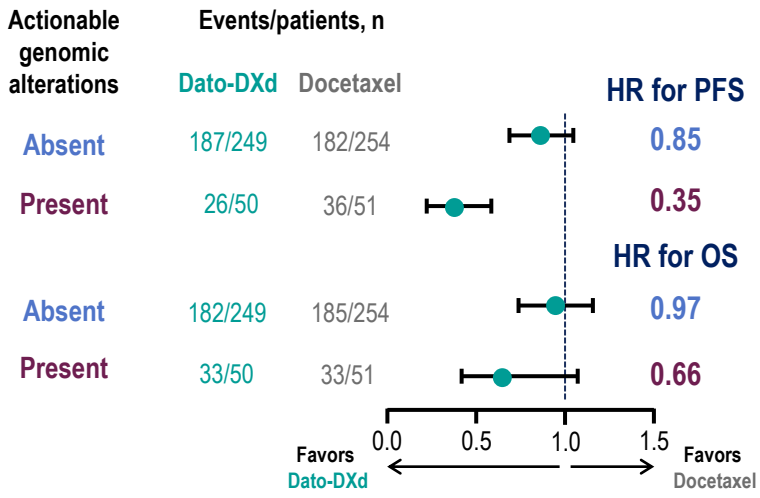
Dr. Myung-Ju Ahn

- **Honoraria:** Daiichi Sankyo, AstraZeneca, Lilly, MSD, TAKEDA, Amgen, Merck Serono, YUHAN
- **Consulting or Advisory Role:** Daiichi Sankyo, AstraZeneca, Lilly, MSD, TAKEDA, Alpha Pharmaceutical, Amgen, Merck Serono, Pfizer, YUHAN, Arcus Ventures
- **Research Funding:** YUHAN

Background

- Treatment options for patients with **metastatic *EGFR*m NSCLC** following failure on EGFR TKI therapy and Pt-CT confer limited clinical benefit[1]
- Datopotamab deruxtecan **(Dato-DXd)** is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload to the site of tumors[2]
- Dato-DXd has demonstrated **meaningful clinical activity and manageable safety** in patients with metastatic NSCLC and **actionable genomic alterations** across multiple studies[3–5]

Hazard Ratios for Progression-Free and Overall Survival, TROPION-Lung01[3]



We report here a pooled analysis of patients with *EGFR*m NSCLC from TROPION-Lung01 and TROPION-Lung05 treated with Dato-DXd who had received prior targeted therapies and chemotherapy

ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; *EGFR*m, *EGFR* mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; Pt-CT, platinum-based chemotherapy; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell surface antigen 2. 1. Patel J et al. *Adv Ther*. 2024;41(8):3299-3315; 2. Okajima D et al. *Mol Cancer Ther*. 2021;20(12):2329-2340; 3. Ahn MJ et al. *J Clin Oncol*. 2024 Sep 9:JCO2401544; 4. Paz-Ares L et al. *Ann Oncol*. 2023;34(S2):S755-S851; 5. Shimizu T et al. *J Clin Oncol*. 2023;41(29):4678-4687.

Pooled Analysis from TROPION-Lung05[1] and TROPION-Lung01[2]

Patients with *EGFR*m NSCLC who received Dato-DXd 6 mg/kg Q3W were included in the pool

TROPION-Lung05 (Phase II study)

- **Presence of ≥1 actionable genomic alteration** (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
  - ≥1 line of targeted therapy
  - 1–2 prior cytotoxic agent–containing therapies including Pt-CT in the metastatic setting
  - Radiographic disease progression after most recent therapy

TROPION-Lung01 (Phase III study)

- **In those with actionable genomic alterations** (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
  - 1–2 prior approved targeted therapies + Pt-CT, and ≤1 anti–PD-(L)1 mAb
  - No prior docetaxel

R 1:1

Dato-DXd
6 mg/kg Q3W[a]
(N=137)

Dato-DXd
6 mg/kg Q3W[b]
(N=299)

Docetaxel
75 mg/m^2 Q3W[b]
(N=305)

***EGFR*m Pool: N=117**

TROPION-Lung05 (n=78)

TROPION-Lung01 (n=39)

Endpoints:

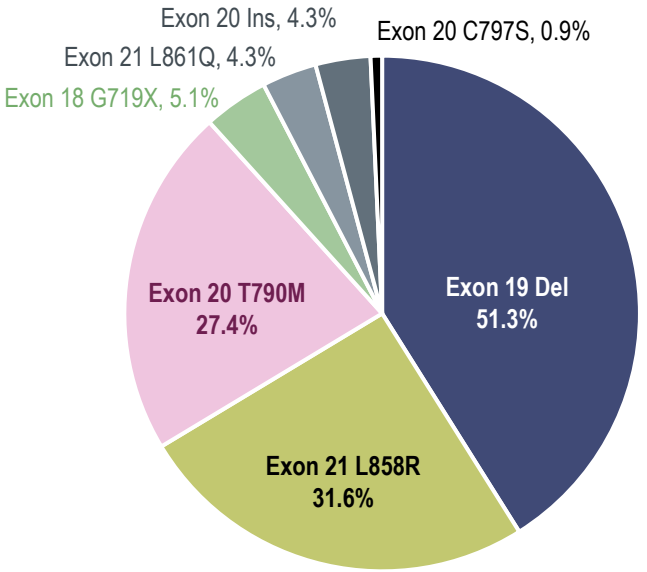
- ORR per BICR
- BOR per BICR
- DCR per BICR
- DOR per BICR
- PFS per BICR
- OS
- Safety

[a]Data cut off: December 14, 2022; [b]Data cut off: March 1, 2024 (OS and safety) or March 29, 2023 (all other efficacy endpoints). BICR, blinded independent central review; BOR, best overall response; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; mAb, monoclonal antibody; *EGFR*m, *EGFR* mutated; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Pt-CT, platinum-based chemotherapy; Q3W, once every 3 weeks; R, randomized. 1. Paz-Ares L et al. *Ann Oncol*. 2023;34(S2):S755-S851; 2. Ahn MJ et al. *J Clin Oncol*. 2024 Sep 9:JCO2401544.

Demographics and Baseline Characteristics

Characteristic	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female, n (%)	73 (62.4)	52 (66.7)	21 (53.8)
Race, n (%)			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (0.9)	0	1 (2.6)
Other/missing	8 (6.8)	3 (3.8)	5 (12.8)
ECOG PS, n (%)			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a], n (%)	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b], n (%)	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry, n (%)	36 (30.8)	21 (26.9)	15 (38.5)
Median lines systemic therapy (range)[c]	3 (1–5)	3 (1–5)	2 (1–5)
Prior osimertinib[d], n (%)	96 (82.1)	61 (78.2)	35 (89.7)
First line	47 (40.2)	27 (34.6)	20 (51.3)
Second line	34 (29.1)	20 (25.6)	14 (35.9)

EGFR Mutational Profile (N=117)[e]



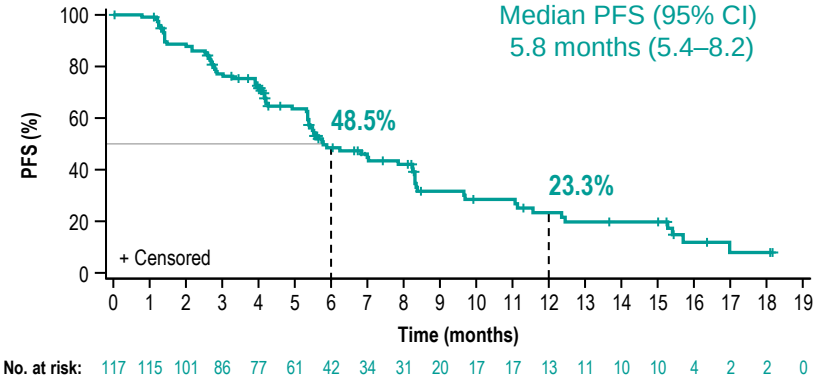
[a]Current/former; [b]Adenocarcinoma and other nonsquamous types; [c]Prior lines in the locally advanced/metastatic setting; [d]Additional patients may have received osimertinib as third line or later therapy; [e]Analyses based on local testing reported by investigators in the electronic case report form. Patients may have ≥1 *EGFR* mutation with or without a non-*EGFR* mutation. Other mutation types identified alongside *EGFR* were *ALK* rearrangement, n=2; *ROS1* rearrangement, n=2; *NTRK* fusion, n=1; *MET* amplification, n=5; *MET* Exon 14 skipping, n=1. Del, deletion; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Ins, insertion.

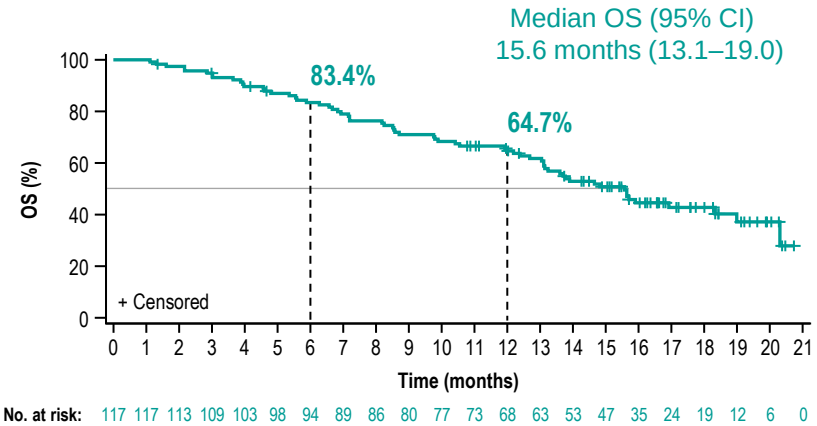
Efficacy

Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%) [95% CI]	50 (**42.7**) [33.6–52.2]	43 (**44.8**) [34.6–55.3]
BOR, n (%)		
CR	5 (**4.3**)	4 (**4.2**)
PR	45 (**38.5**)	39 (**40.6**)
SD	48 (41.0)	37 (38.5)
Non-CR/Non-PD	3 (2.6)	2 (2.1)
PD	12 (10.3)	10 (10.4)
NE	4 (3.4)	4 (4.2)
Median DOR, months (95% CI)	**7.0** (4.2–9.8)	**6.9** (4.2–9.8)
DCR,[b] n (%) [95% CI]	101 (**86.3**) [78.7–92.0]	82 (**85.4**) [76.7–91.8]
Median PFS, months (95% CI)	**5.8** (5.4–8.2)	**5.7** (5.4–7.9)
Median OS, months (95% CI)	**15.6** (13.1–19.0)	**14.7** (13.0–18.3)

[a]CR+PR; [b]CR+PR+SD or non-CR/non-PD. BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; *EGFR*m, *EGFR* mutated; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

PFS and OS in the *EGFR*m Pool (N=117)

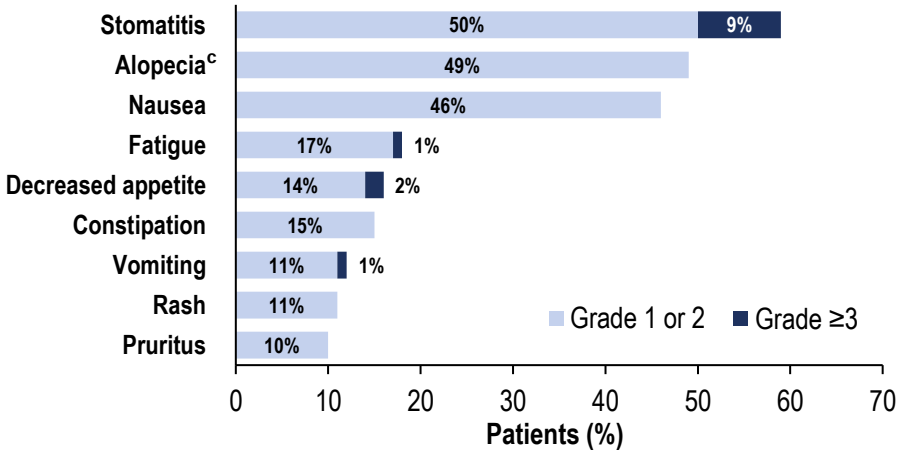




Safety Summary

	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs[a], n (%)	
Stomatitis/oral mucositis	81 (69)
Grade 3[b]	11 (9)
Ocular surface events	38 (32)
Grade 3[b]	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3[b]	1 (1)

TRAEs Occurring in ≥10% of *EGFR*m Pool (N=117)



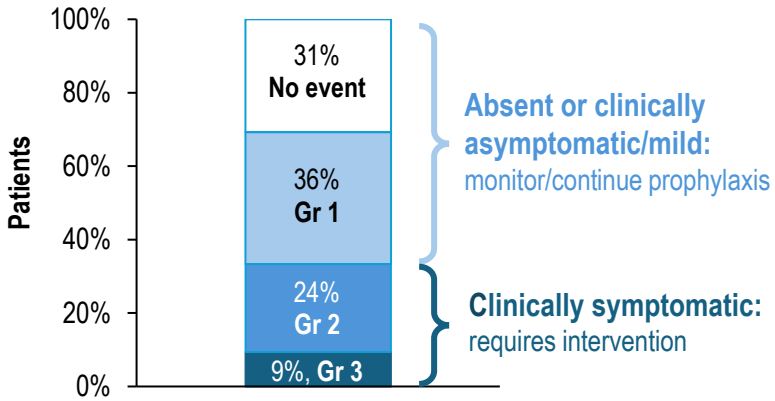
- Median Dato-DXd treatment duration: **6.1 months**

- Overall safety profile consistent with TROPION-Lung01 and 05
- No grade 4 or 5 adjudicated drug-related ILD
- Ocular surface events[a] were primarily dry eye (12%), vision blurred and keratitis (each 7%)
- No TRAEs associated with death

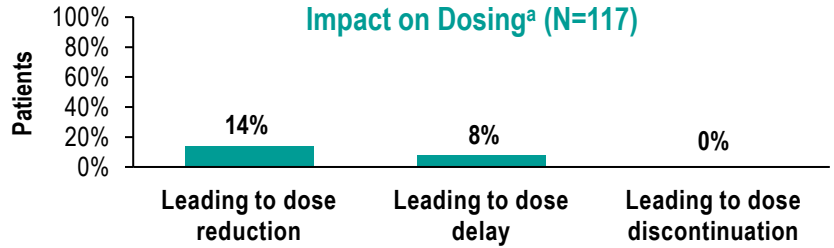
[a]AESIs listed are treatment emergent and include all preferred terms that define the medical concept. Some patients may have had >1 event. [b]No grade 4 or 5 events occurred. [c]Includes an event incorrectly reported as grade 3 per CTCAE grades.
AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; *EGFR*m, *EGFR* mutated; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Stomatitis/Oral Mucositis

Patients with Treatment-Emergent Stomatitis/Oral Mucositis (N=117)



Impact on Dosing[a] (N=117)



- Median time to onset[b]: **29 days**
- Median time to asymptomatic resolution[c]: **50 days**
- Cases that resolved[c]: **82%**[d]

Toxicity management recommendations[1]

- **Daily use of prophylactic steroid-containing mouthwash highly recommended** (4 times daily, swish for 1–2 minutes)
  - If steroid-containing mouthwash is not available, substitute with non-alcoholic and/or bicarbonate-containing mouthwash (4 to 6 times per day)
- **Good oral hygiene and education** (gentle teeth brushing after meals/bedtime with bland, fluoride toothpaste; daily flossing; hygiene/hydration education)
- **Cryotherapy** (iced chips or iced water held in mouth throughout infusion)

[a]For Gr 2 events, dose reductions or delays considered if clinically indicated. [b]Of Gr ≥2 events. [c]Of first Gr ≥2 stomatitis event from clinically symptomatic to asymptomatic (Gr 1 or resolved). [d]32 of 39 events. Gr, grade.

1. Heist RS et al. *Cancer Treat Rev*. 2024:125:102720.

Conclusions

Previously treated patients with **NSCLC harboring a range of *EGFR* mutations** who received Dato-DXd 6 mg/kg Q3W across the **TROPION-Lung05** and **TROPION-Lung01** clinical trials experienced:

- **Robust clinical activity**
  - ORR: 42.7% (95% CI: 33.6–52.2); median DOR: 7.0 months (range: 4.2–9.8); median PFS: 5.8 months; median OS: 15.6 months
  - Outcomes for patients with prior osimertinib treatment were similar to the overall pooled population
- **A manageable safety profile with no new safety signals**
  - Low rates of serious TRAEs or TRAEs leading to treatment discontinuations
  - Grade ≥2 stomatitis/oral mucositis seen in ~1/3 patients was effectively managed with dose reductions/delays, and no treatment discontinuations due to stomatitis occurred
  - The most common ocular surface event was dry eye (grade 1 or 2)
  - No grade 4 or fatal ILD events

These findings suggest that Dato-DXd is a potential treatment option for patients with *EGFR*m disease in the second-line and later settings

Dato-DXd, datopotamab deruxtecan; DOR, duration of response; *EGFR*, epidermal growth factor receptor; *EGFR*m, *EGFR* mutated; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; TRAE, treatment-related adverse event.

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bit.ly/DS24ESMOASIA

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