Poster 449P

Identification of DXd sensitivity biomarkers and osimertinib-enhanced datopotamab deruxtecan (Dato-DXd) internalization as potential mechanisms for enhanced activity of Dato-DXd in preclinical models of EGFR-mutant non-small cell lung cancer

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Objective

- To evaluate (i) preclinical activity of Dato-DXd across NSCLC models stratified by histology and EGFRm status, (ii) candidate biomarkers associated with DXd/Dato-DXd sensitivity or resistance, and (iii) whether osimertinib pre-treatment alters TROP2 expression/localization and Dato-DXd internalization in EGFRm NSCLC models.

Conclusions

- These preclinical data demonstrate that Dato-DXd has robust activity across EGFRm NSCLC models and that TROP2 gene expression alone does not sufficiently explain response heterogeneity.
- NRF2 signature correlates with reduced DXd and Dato-DXd sensitivity in NSCLC models and appears to be less prevalent in EGFRm NSCLC models. NRF2 signature contains ABCC1 (a known DXd efflux pump) and shows similar findings. These data support a potential mechanistic rationale for the broad Dato-DXd activity in EGFRm models.
- Additionally, osimertinib treatment can enhance Dato-DXd internalization in EGFRm models, suggesting that EGFR TKI exposure may dynamically influence ADC uptake biology. Clinical validation in appropriately annotated cohorts is warranted.

Plain language summary

Why did we perform this research?

Dato-DXd is a targeted therapy that delivers chemotherapy inside TROP2-expressing cancer. Patients with EGFRm NSCLC can respond well to Dato-DXd, and we wanted to understand biological reasons that might explain this.

How did we perform this research?

We tested Dato-DXd in lung cancer cells and in patient-derived tumor models grown in mice. We also studied genes and pathways that might be linked to sensitivity or resistance, and we tested whether treatment with osimertinib changes how Dato-DXd enters EGFRm NSCLC cells.

What were the findings of this research?

Dato-DXd showed broad activity in NSCLC models, including those with EGFRm. Markers linked to reduced DXd sensitivity (including a NRF2-related signature and ABCC1) were less prevalent in EGFRm models. Osimertinib treatment may increase Dato-DXd internalization in some EGFRm models.

What are the implications of this research?

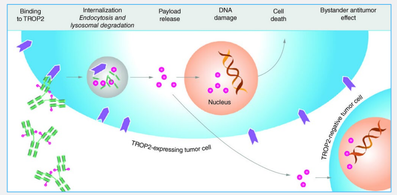
Multiple biological factors, including payload resistance pathways and treatment-induced changes in ADC internalization may contribute to Dato-DXd activity in EGFRm lung cancer.

This study was sponsored by AstraZeneca and Daiichi Sankyo. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration agreement with AstraZeneca for datopotamab deruxtecan (Dato-DXd).
Poster presented at 2026 European Lung Cancer Conference by Matthew Sung. Corresponding author email address: matthew.sung@astrazeneca.com.

Introduction

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed antibody–drug conjugate (ADC) delivering a topoisomerase I inhibitor payload (DXd) to TROP2-expressing cancer cells (Figure 1) and has demonstrated clinical activity in patients with NSCLC including those harboring EGFR mutations (EGFRm)[1].
- The biological basis for the enhanced activity of Dato-DXd in patients with EGFRm NSCLC remains incompletely defined.
- We investigated determinants of Dato-DXd and DXd payload sensitivity across preclinical models of NSCLC and assessed whether EGFR TKI (e.g. osimertinib) exposure can modulate TROP2 biology and Dato-DXd internalization, providing mechanistic rationale relevant to post-TKI EGFRm NSCLC.

Figure 1. Dato-DXd Mechanism of Action.



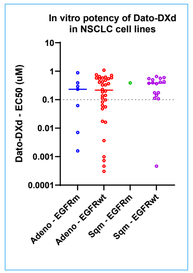
[2]Dent et al. Future Onc. 2023

Methods

- In vitro viability profiling: Dato-DXd activity was evaluated using cell viability assays across non-squamous (NSQ) and squamous (SQ) NSCLC cell lines (n=59 total, including 8 EGFRm). Response was summarized using an EC50-based responder definition (e.g. for Dato-DXd, cell lines with EC50 < 0.1 uM were defined as Responders)
- Biomarker analyses: Associations between response and TROP2 gene expression as well as candidate DXd resistance pathways were assessed. A NRF2 pathway signature[3] and ABCC1 expression were evaluated as putative markers of reduced DXd/Dato-DXd sensitivity.
- Internalization assays: Live-cell imaging was used to quantify Dato-DXd internalization in EGFRm NSCLC cell lines following osimertinib pre-treatment, and to assess whether changes were attributable to altered binding versus altered internalization dynamics.
- In vivo efficacy: Single-dose Dato-DXd (10 mg/kg) activity was assessed in NSCLC patient-derived xenograft (PDX) models (n=38, including 15 EGFRm). Best overall response was calculated as the minimum % change from baseline for each tumor model within 21 days after administration of Dato-DXd. PDX models showing <-30% change from baseline were identified as Responders.

Results

Figure 2. Dato-DXd shows differential activity across relevant subtypes of NSCLC cell lines

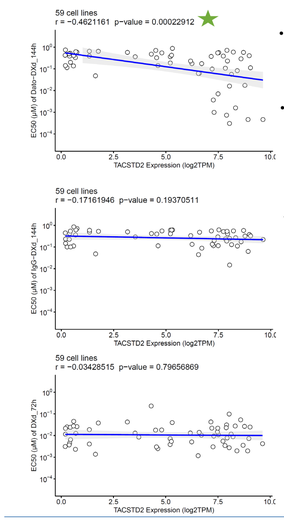


Histology	EGFR Status	# of cell lines
NSCLC NSQ	EGFRm	8
	EGFRwt	34
NSCLC Sqm	EGRm	1
	EGFRwt	16

Group	Res*/Total (%)
Adeno_EGFRm	3/8 (**38%**)
Adeno_EGFRwt	12/34 (**36%**)
Sqm_EGFRm	0/1 (**0%**)
Sqm_EGFRwt	1/15 (**7%**)

Note: arbitrary cut-off for Responders of Dato-DXd defined as EC50 <0.1 uM

Figure 3. TROP2 gene (TACSTD2) expression is required, but not sufficient, for Dato-DXd activity across panel of NSCLC cell lines



- Most cell lines sensitive to Dato-DXd (EC50 <0.1 uM) express TROP2
- Not all TROP2-high cell lines are sensitive to Dato-DXd
- No strong correlation between TROP2 gene expression and un-targeted control ADC activity
- No strong correlation between TROP2 gene expression and free DXd activity

Figure 4. TROP2 gene expression appears enriched in EGFRm NSCLC cell lines but does not correlate with Dato-DXd activity in EGFRm NSCLC cell lines

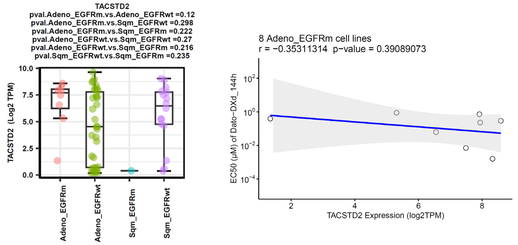


Figure 5. NRF2 signature enrichment correlates with reduced sensitivity to Dato-DXd and DXd; EGFRm cell lines trend toward having lower NRF2 signature

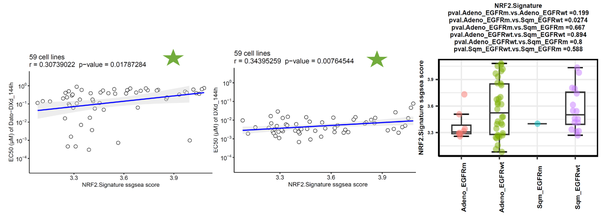
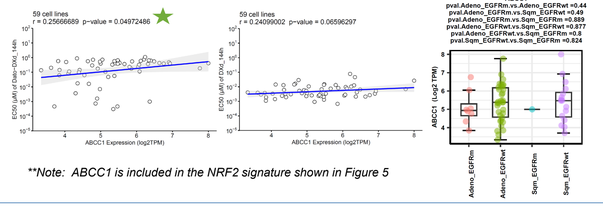
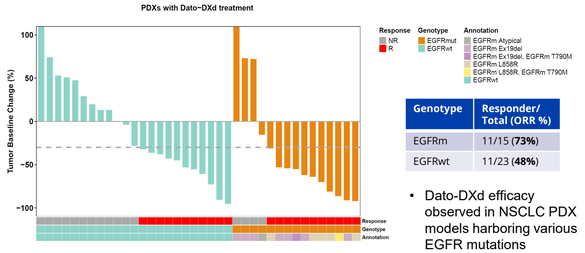


Figure 6. ABCC1, a drug pump for DXd and whose expression is regulated by NRF2**, correlates with reduced sensitivity to Dato-DXd and DXd; EGFRm cell lines trend toward lower expression of ABCC1



**Note: ABCC1 is included in the NRF2 signature shown in Figure 5

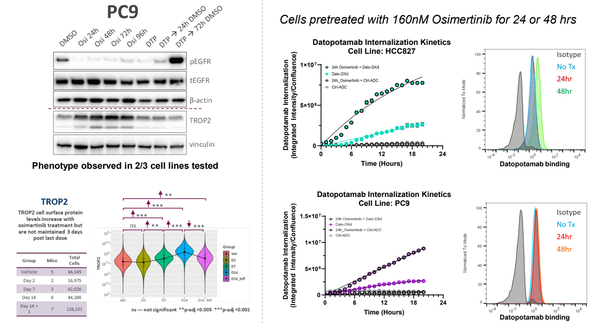
Figure 7. Dato-DXd displays inherent broad activity across EGFRm PDX models



Genotype	Responder/ Total (ORR %)
EGFRm	11/15 (**73%**)
EGFRwt	11/23 (**48%**)

- Dato-DXd efficacy observed in NSCLC PDX models harboring various EGFR mutations

Figure 8. Osimertinib treatment of EGFRm cell lines can induce TROP2 expression and enhance Dato-DXd internalization, a key step in the mechanism of action of Dato-DXd



- Treatment of EGFRm cells (HCC827, PC9) with Osimertinib enhances Dato-DXd internalization (even w/o significantly enhanced binding)

Key Take-Aways:

- **Differential activity of Dato-DXd across NSCLC subtype preclinical models is associated with broad efficacy within EGFRm.**
- **NRF2 signature and ABCC1 (a known DXd efflux pump and a component of the NRF2 signature) may represent tumor cell-intrinsic mechanisms of insensitivity to Dato-DXd and DXd.**
- **Lower prevalence of NRF2 signature in EGFRm models is a potential indicator of differential payload sensitivity across NSCLC subtypes**
- **Osimertinib may enhance Dato-DXd internalization in preclinical models of NSCLC which may also contribute to the potential added benefit for the combination which being evaluated in the ongoing Phase 3 TROPION-Lung14 and TROPION-Lung15 studies.**

Abbreviations

ABCC1: ATP-binding cassette subfamily C member 1; ADC: antibody–drug conjugate; BOR: best overall response; Dato-DXd: datopotamab deruxtecan; DXd: topoisomerase I inhibitor; EGFRm: EGFR-mutant; EGFRwt: EGFR-wild-type; NSCLC: non-small cell lung cancer; NSQ: non-squamous; PDX: patient-derived xenograft; SQ: squamous; TACSTD2: tumor associated calcium signal transducer 2; TROP2: trophoblast cell surface antigen 2.

Acknowledgments

We would like to thank all the Dato-DXd researchers across Daiichi-Sankyo and Astrazeneca Alliance for their support.

Disclosures

All authors are employees of either Astrazeneca PLC or Daiichi-Sankyo, Inc.

References

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2. Dent et al. Future Oncology. 2023.
3. Romero et al. Nat Med. 2017.
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