Lung Cancer ADCs: High Expectations, Limited Integration

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Disclosures (Dr. Leal)

Consultant/Advisor/Speaker: Jazz, Genentech, BI, AstraZeneca, Novocure, Catalyst, OncoC4, J&J

Disclosures – 24 months (Dr. Carlisle)

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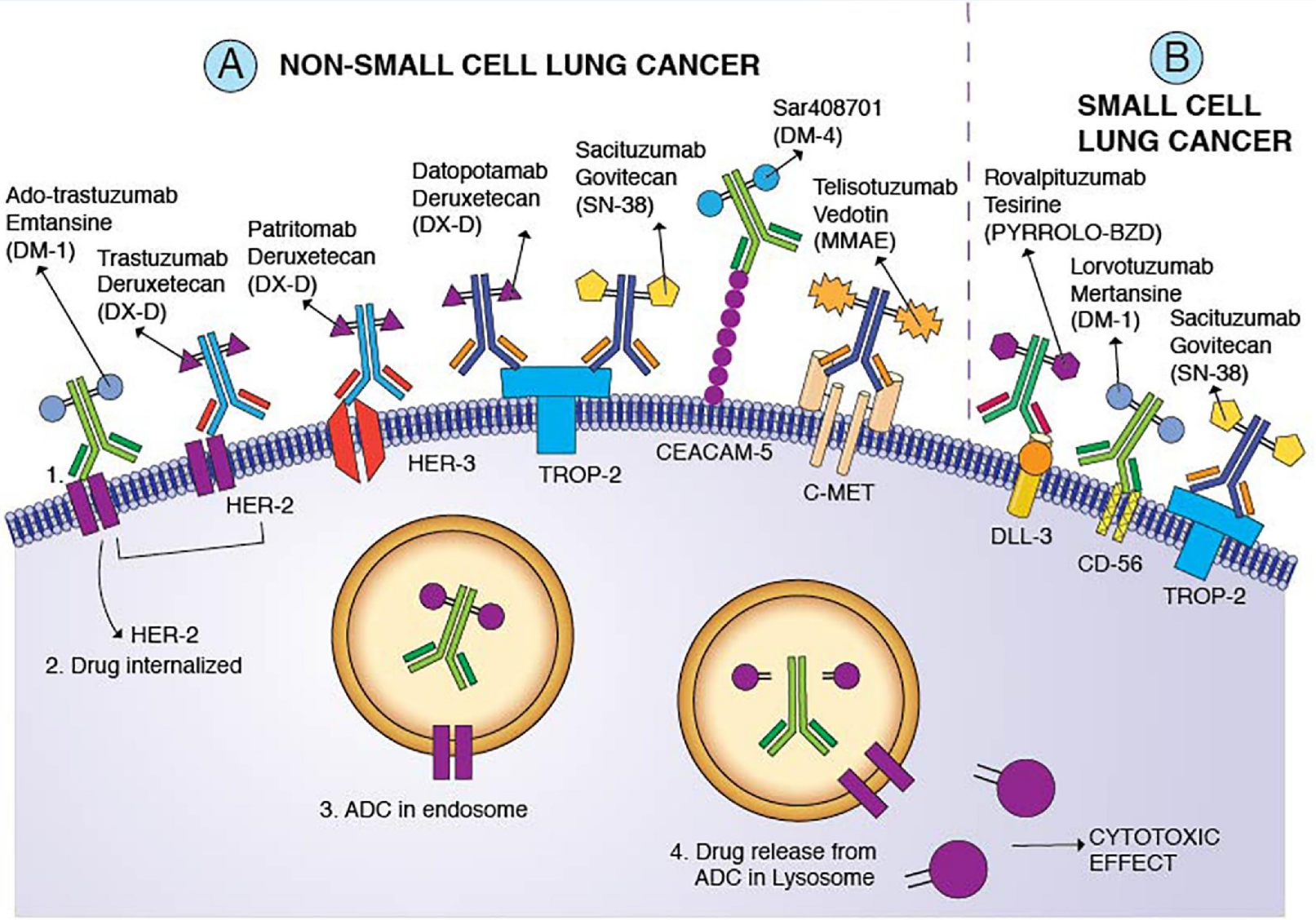
When you find out last minute you have to debate the interim associate division director of medical oncology…

You take it to the boardroom of the G8



FDA approved ADCs in lung cancer:

1. **Trastuzumab deruxtecan**
   HER2 mutation
2. **Telisotuzumab vedotin**
   MET overexpression (>50%)
3. **Datopotamab deruxtecan**
   EGFR post chemotherapy

Desai et al., Lung Cancer, 2022

Why ADCs Fall Short in Lung Cancer

- ❑ Lack Of Established Biomarkers
- ❑ Bystander Effect Can Be a Double-Edged Sword
- ❑ Payload Limitations impacting durability and sequencing
- ❑ PFS Has Not Translated To OS

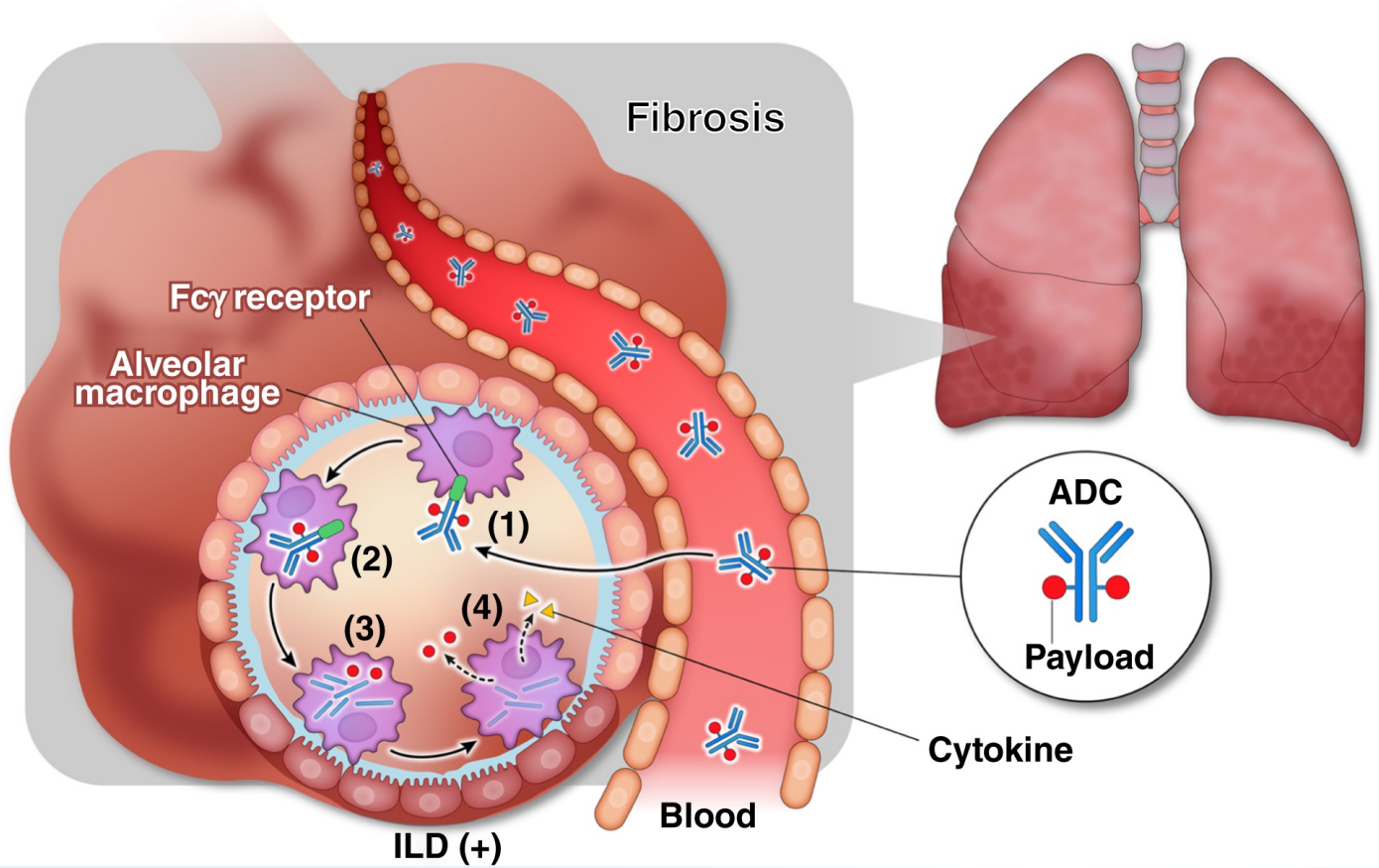
Lack Of Established Biomarker

1. No established correlation between cell surface protein and patient survival.

1. Efforts are underway to develop an AI-based assay that incorporates both intracellular and cell-surface expression of to overall survival.

1. The quantitative continuous scoring (QCS) in phase III TROPION-Lung01: Positive correlation between expression and survival but underpowered and limited to non-Sqcc NSCLC

Bystander Effect Can Be a Double-Edged Sword



Pro:

-Kills Neighboring Cancer Cells

-Overcomes Heterogeneity

Con

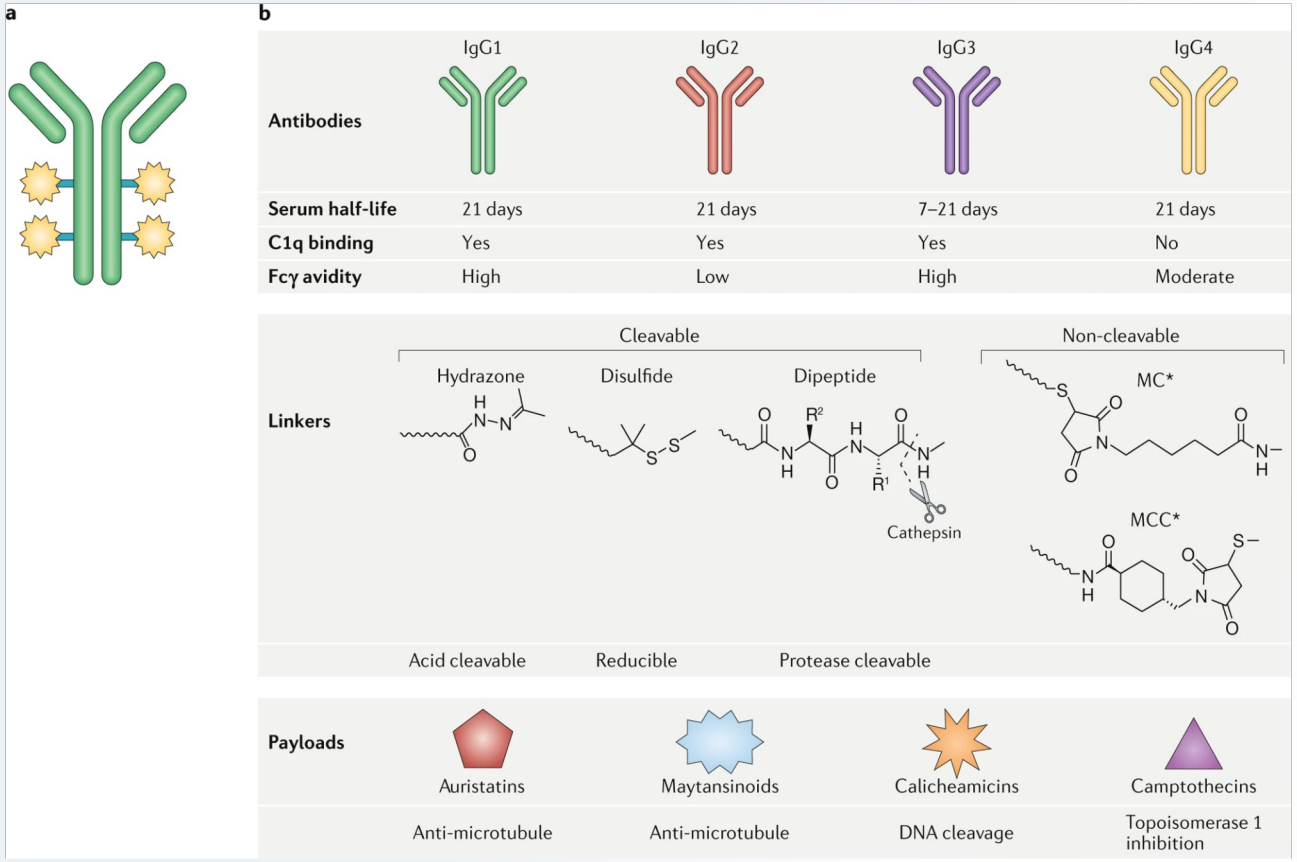
-Unintended Toxicity to Healthy Cells; Off target effect

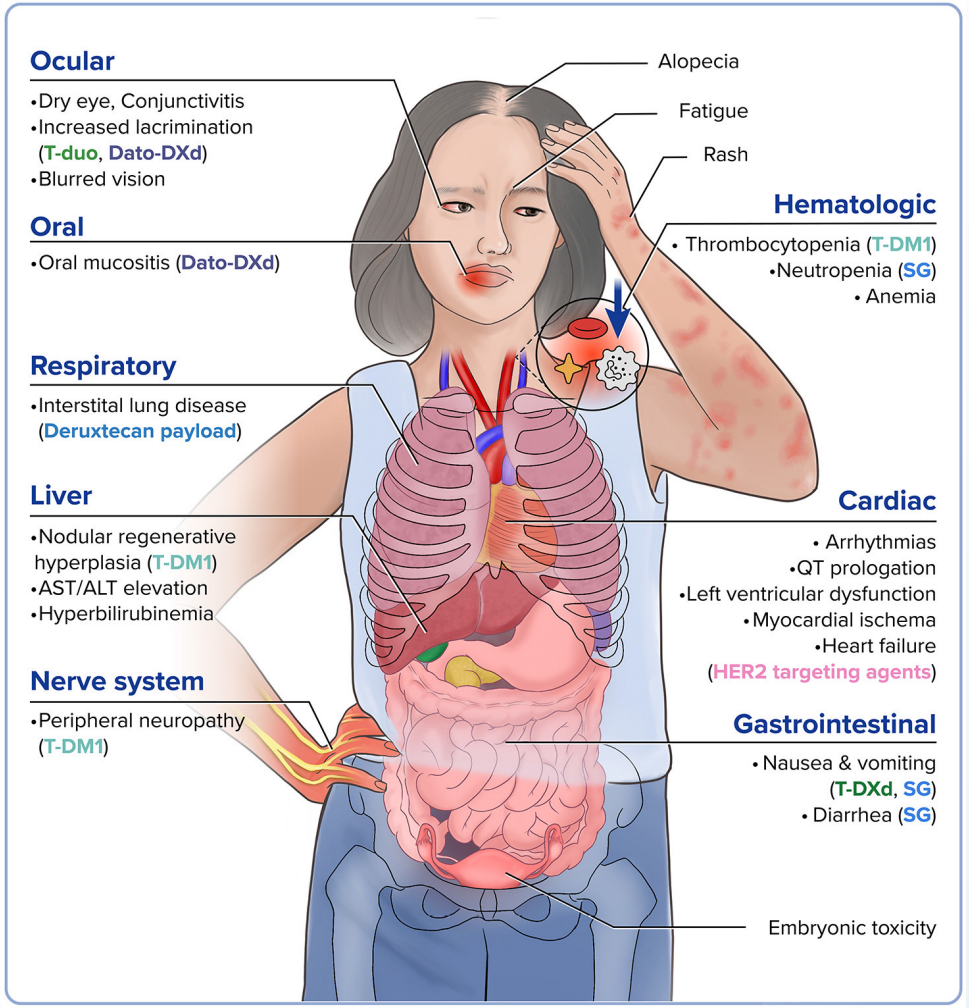
-Resistance Mechanisms Triggered by the Bystander Effect

-Non-Tumor Cell Damage and Inflammatory Response

Payload Limitations

❑ Topoisomerase inhibitors or tubulin disruptors: not a novel mechanism



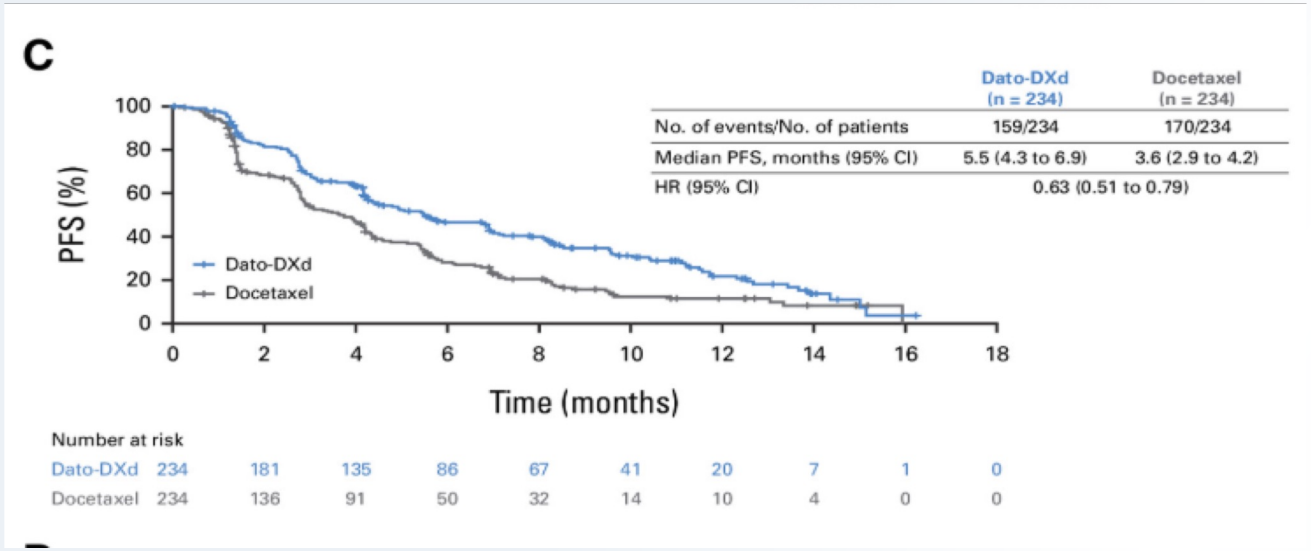


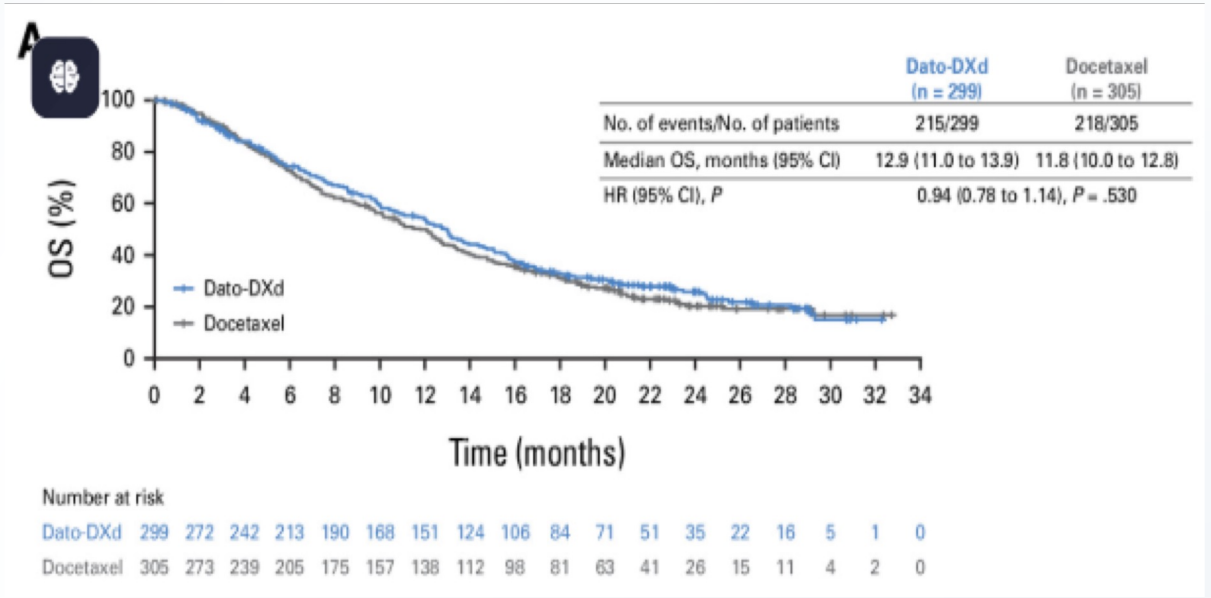
Dominant et al, Nature Review Drug Discovery, 2023

Kang and Kim, 2025
https://doi.org/10.1177/17588359251324889

PFS Has Not Translated To OS

TROPION-Lung01 Study





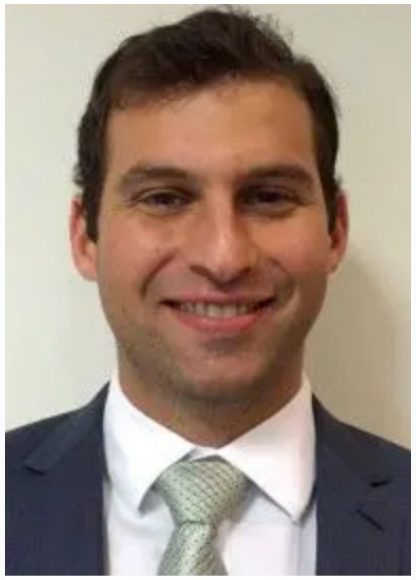
PFS: 5.5m vs. 3.6m
p=0 .004

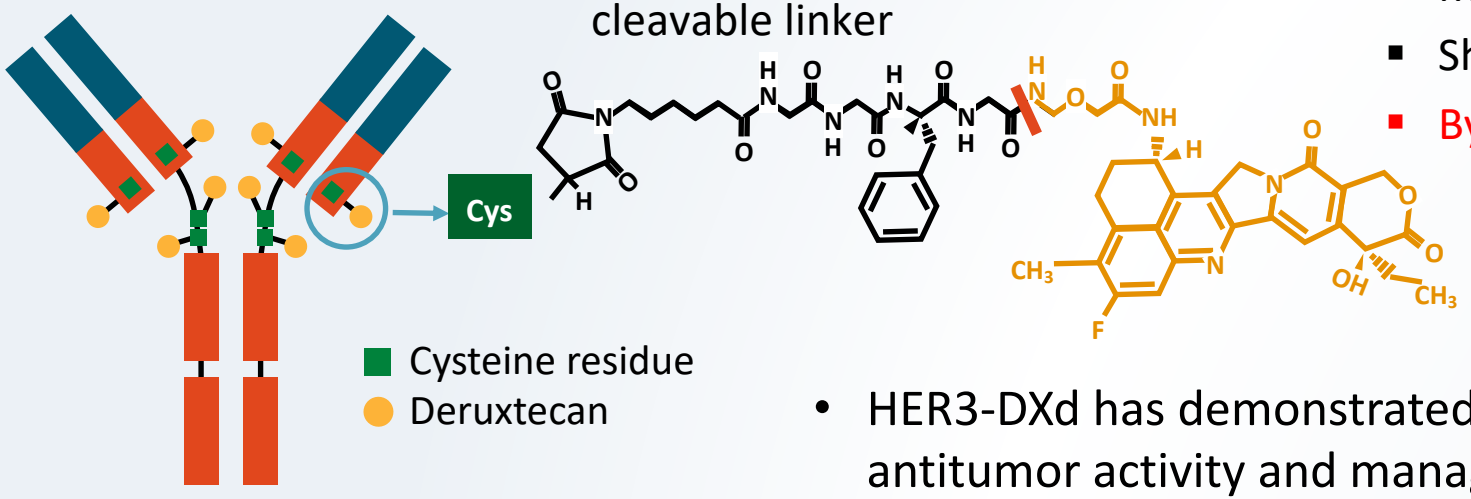
OS: 12.9m vs. 11.8m
p=0.53

Myung-Ju Ahn, MD, PhD et al., JCO 2024.

@Ardeshirfatemeh

The Patritumab Deruxtecan story





Anti-HER3 mAb
- Human IgG1

Tetrapeptide-Based Linker
- DAR ~8:1
- Tumor-selectable cleavable linker

DXd Payload
- Exatecan derivative
- Topoisomerase I inhibitor
- Membrane permeable
- Short systemic half-life
- Bystander killing effect

- HER3-DXd has demonstrated encouraging antitumor activity and manageable AEs in previously treated advanced *EGFR*-mutant NSCLC across multiple EGFR TKI resistance mechanisms in the HERTHENA-Lung01 phase II trial

Yu. WCLC 2020. Abstr OA03.04. Hashimoto. Clin Cancer Res. 2019;25:7151. Yu. JCO. 2023;41:5363.

Patritumab Deruxtecan (HER3-DXd; MK-1022) in Non–Small Cell Lung Cancer After Platinum-Based Chemotherapy and Immunotherapy

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DOI https://doi.org/10.1200/JCO-24-02744

ABSTRACT

PURPOSE Patritumab deruxtecan (HER3-DXd; MK-1022) is an investigational HER3-directed antibody-drug conjugate composed of a human immunoglobulin G1 monoclonal antibody to HER3 (patritumab) covalently linked via a stable tetrapeptide-based cleavable linker to a topoisomerase I inhibitor payload that has shown durable antitumor activity in previously treated patients with *EGFR*-mutated advanced non–small cell lung cancer (NSCLC). We extend these observations to patients with advanced NSCLC with other/no identified driver genomic alterations.

METHODS Patients with advanced squamous or nonsquamous NSCLC without a common *EGFR*-activating mutation whose disease had progressed on previous therapies including platinum-based chemotherapy, immune checkpoint inhibitors, and targeted therapy (for patients with known actionable genomic alterations) received HER3-DXd 5.6 mg/kg intravenously once every 3 weeks. The primary end point was confirmed objective response rate (cORR).

RESULTS Forty-seven patients were treated with HER3-DXd (median treatment duration, 4.2 [range, 0.7-19.8] months). The cORR was 27.7% (95% CI, 15.6% to 42.6%), and the median duration of response was 8.1 (95% CI, 4.2 to not evaluable) months. The median progression-free survival was 5.5 (95% CI, 4.0 to 11.2) months, and the median overall survival was 15.2 (95% CI, 10.8 to 17.7) months. Similar efficacy was observed in patients with NSCLC harboring identified driver genomic alterations and in those without such genomic features. The rate of study drug discontinuation associated with treatment-emergent adverse events (TEAEs) was 12.8%. Study drug–related grade ≥3 TEAEs occurred in 51.1% of patients and were serious in 12.8% (none were associated with death). Adjudicated treatment-related interstitial lung disease occurred in five patients (10.6%; all grade 1 or 2).

CONCLUSION The previously reported efficacy and safety of HER3-DXd in heavily pretreated patients with *EGFR*-mutated NSCLC are also observed in those with other NSCLC subtypes and warrant further clinical evaluation.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

Accepted May 2, 2025
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J Clin Oncol 00:1-11

View Online Article

HERTHENA-Lung02: Phase 3 Study (NCT05338970)

This is a randomized, open-label, phase 3 study of patritumab deruxtecan (HER3-DXd) vs platinum-based chemotherapy in metastatic or locally advanced *EGFR*m NSCLC after failure of EGFR TKI therapy

Select Eligibility Criteria

- **Locally advanced/metastatic NSCLC with an *EGFR*-activating mutation** (exon 19 deletion or L858R)
- **1 or 2 prior line(s) of an approved EGFR TKI (must include a third-generation EGFR TKI)**
- **Disease progression while receiving or after a third-generation EGFR TKI**
- **Pretreatment tumor biopsy or archived tumor tissue since progression is required**

200 Global Sites

N = 586

R 1:1

Arm 1
Patritumab Deruxtecan
5.6 mg/kg IV Q3W

Arm 2
Cisplatin (75 mg/m^2) or Carboplatin (AUC5) Q3W × 4 cycles + Pemetrexed (500 mg/m^2)[a] Q3W

No crossover

Treatment until PD, TEAE, death

Follow-up

End of Study

Drug (HERTHENA-Lung02)	ORR (%)	PFS (m)	PFS at 12 m	PFS (HR)	Gr≥3 ILD
Patritumab deruxtecan	35.2%	5.8 m	18%	0.77 (95% CI 0.63-0.94, p=0.011)	5%
Platinum-based chemotherapy	25.3%	5.4 m	5%		

Mok et al. Abstr #8506. Lung Cancer Oral session. June 1st 10:00 – 10:12 am; Arie Crown Theater

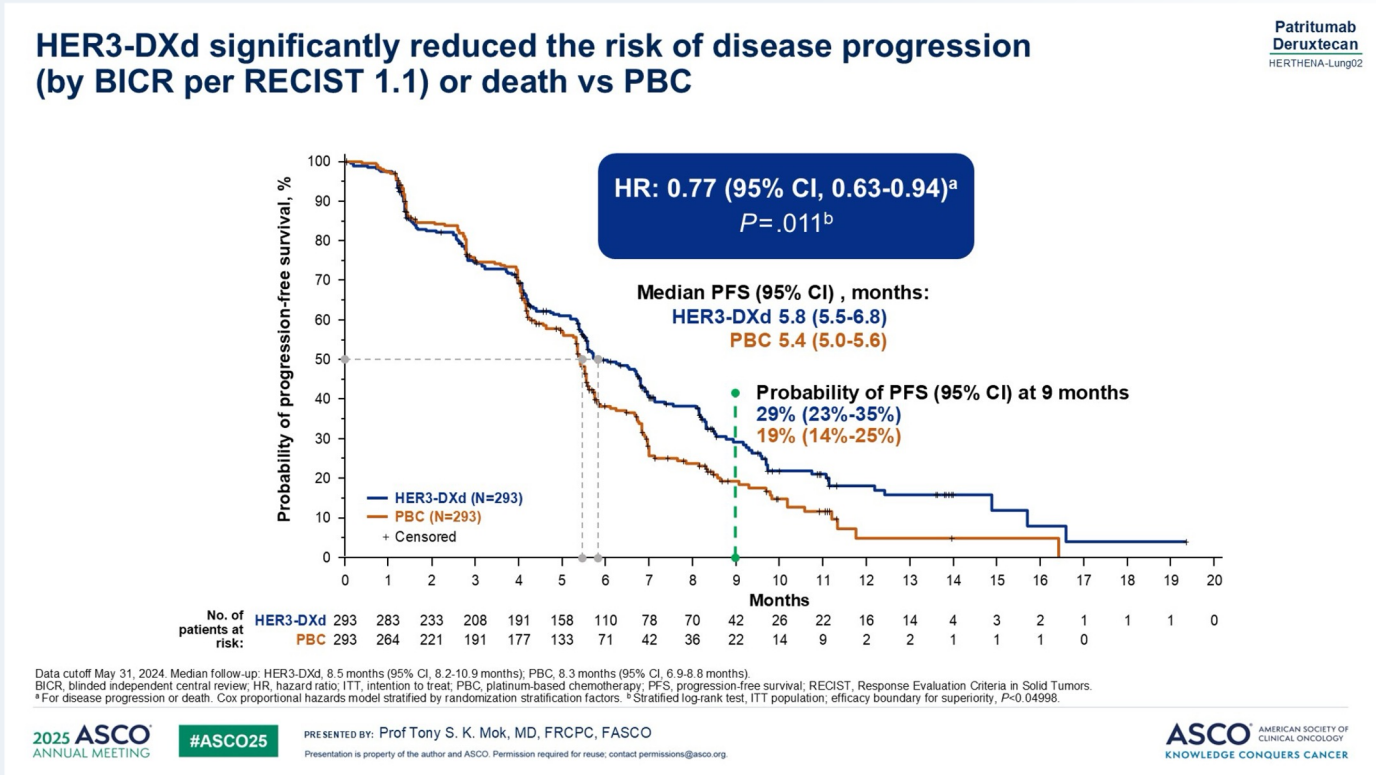
HERTHENA-Lung02: Phase 3 Study (NCT05338970)

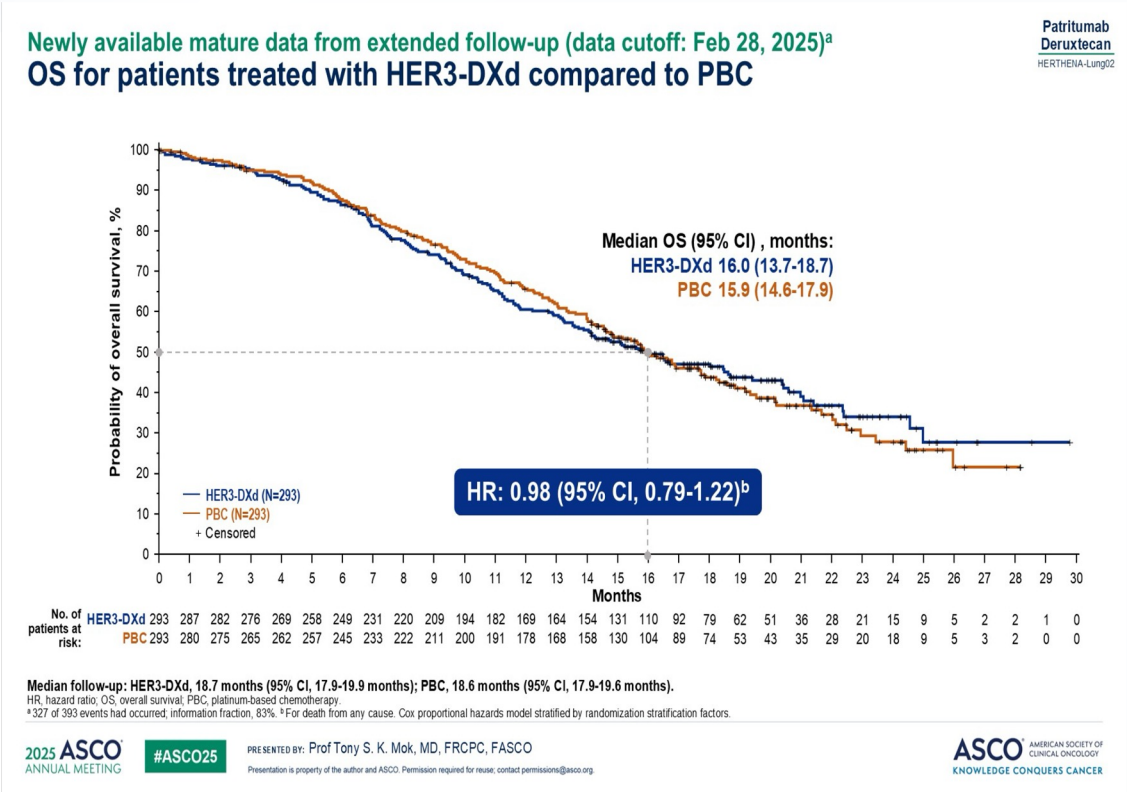
Press Release May 29, 2025:

The decision to withdraw the Biologics Licence Application is based on topline overall survival (OS) results from the confirmatory HERTHENA-Lung02 phase 3 trial where OS did not meet statistical significance as well as discussions with the U.S. Food and Drug Administration.

PFS Has Not Translated To OS

HERTHENA-Lung02: Patritumab deruxtecan (HER3-DXd) in resistant *EGFR*-mutated



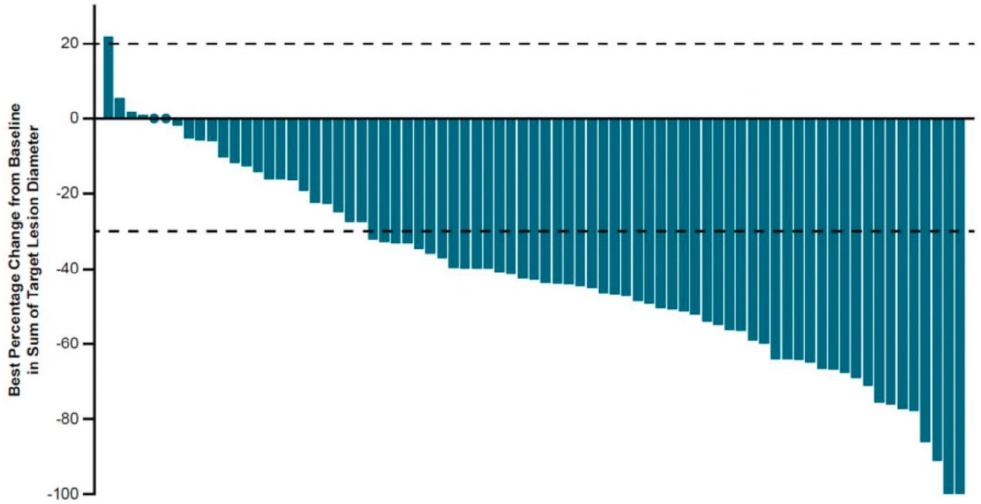


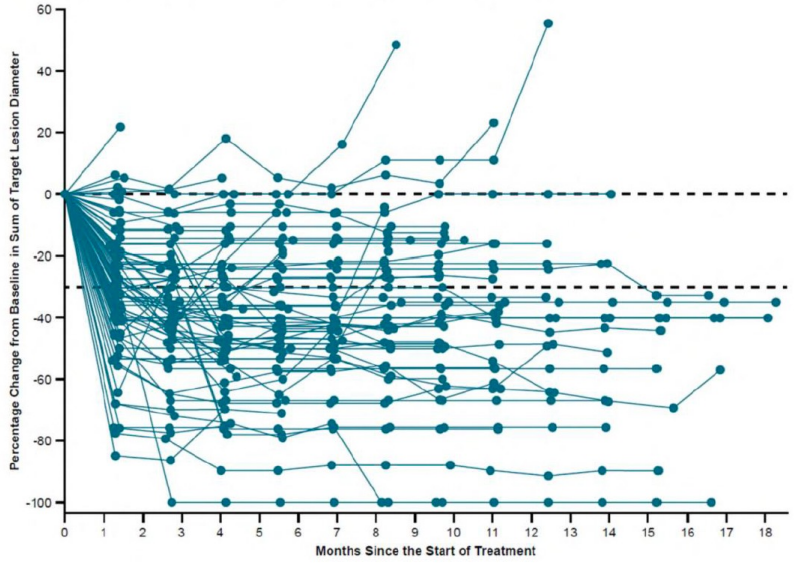
- PFS benefit in EGFR mutant lung cancer (HR:0.77), No OS benefit
- ≥3 TEAEs occurred in 73%
- ILD: 14 pts (5.2%): 11 G1/2, 1 G3, 2 G5 in the HER3-DXd arm

Slide curtesy of Fatemeh Ardeshir

Better options on the horizon?

Beamion LUNG-1 (Cohort 1, 120mg QD): Best Percent Change from Baseline





	ORR	DOR
HER-2 mut		
Zongertinib	**71%**	**14.1m**
fam-trastuzumab deruxtecan	**57.7%**	**9.3m**

Heymach JV et al. *NEJM*. 2025;392:2321-33.

ADCs have their place, but its not going to be first place

- ❑ Lack Of Established Biomarkers
- ❑ Bystander Effect Can Be a Double-Edged Sword
- ❑ Payload Limitations; limited duration of response
- ❑ PFS Has Not Translated To OS