Evaluating second-line treatment approaches in advanced NSCLC: The role of ADCs

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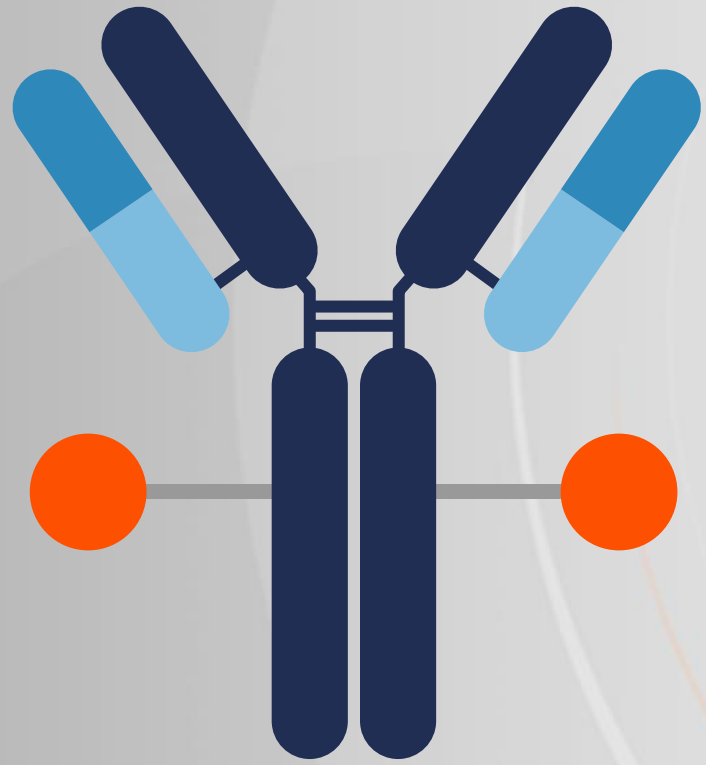
ADCs in NSCLC:
Linking structure with mechanism of action

Key components of ADCs



Antibody
Helps to deliver the conjugated payload to a specific disease site by targeting a tumour-associated antigen

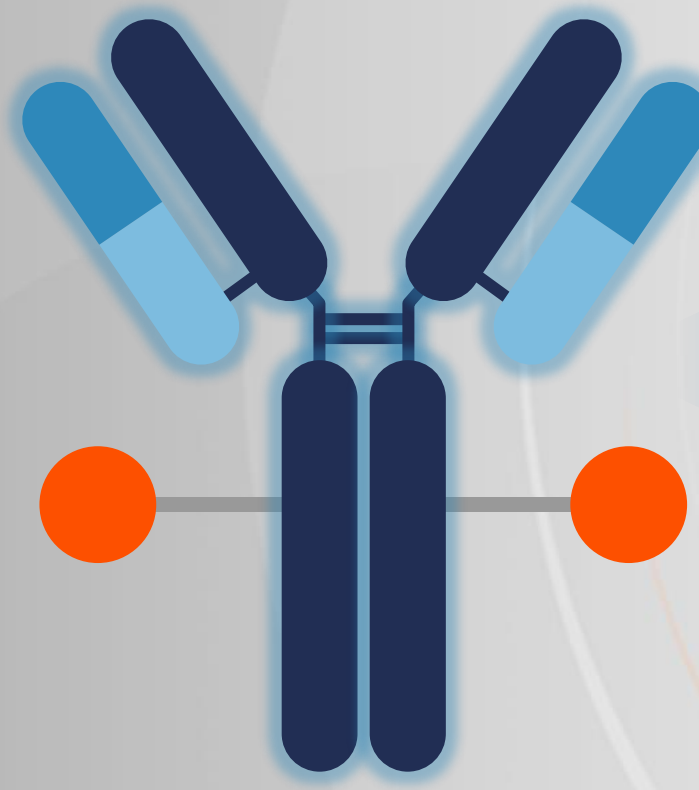
Linker
Bridge between the antibody and payload and controls release of the payload inside the cancer cells

Cytotoxic payload
Warhead for destroying cancer cells

ADC, antibody–drug conjugate.
Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Antibody selection

Characteristics of the ideal antibody for an ADC

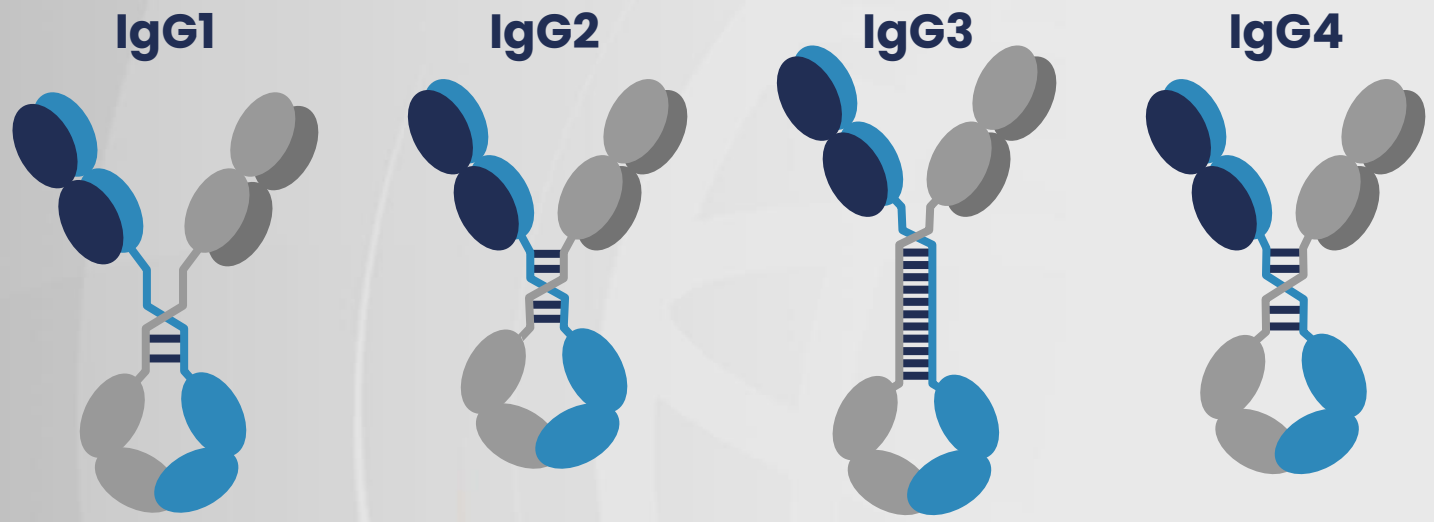


- High binding affinity to the target antigen
- Low immunogenicity
- Fast internalization
- Low molecular weight

ADC, antibody–drug conjugate.
Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Antibody selection

Classes of antibody



	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7 days	21 days
CDC	++	+	+++	–
Fcγ avidity	+++	+	++++	++

CDC, complement-dependent cytotoxicity; IgG, immunoglobulin G.
Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

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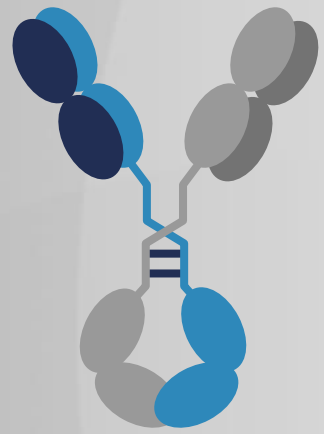
Antibody selection

Classes of antibody

IgG1



Serum half-life	**21 days**
CDC	**++**
Fcγ avidity	**+++**

IgG1 is the most used antibody in ADC development due to its solubility, long serum half-life and binding affinity for Fcγ receptors[1]

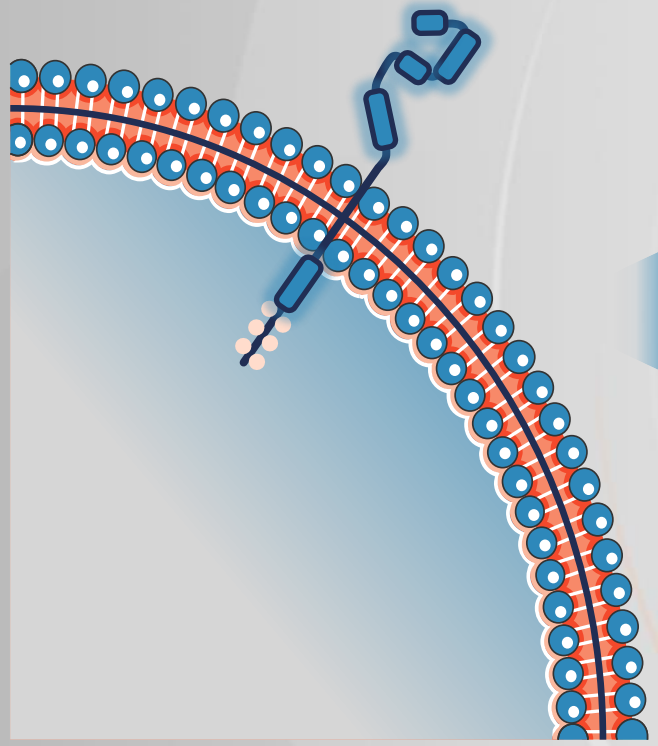
The primary ADCs in development for the treatment of patients with advanced NSCLC are **based on the IgG1 architecture**[1–3]

ADC, antibody–drug conjugate; CDC, complement-dependent cytotoxicity; IgG, immunoglobulin G; NSCLC, non-small cell lung cancer.

1. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5; 2. Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408; 3. Desai A, et al. *Lung Cancer.* 2022;163:96–106.

Antigen target selection

Characteristics of the ideal antigen target for an ADC



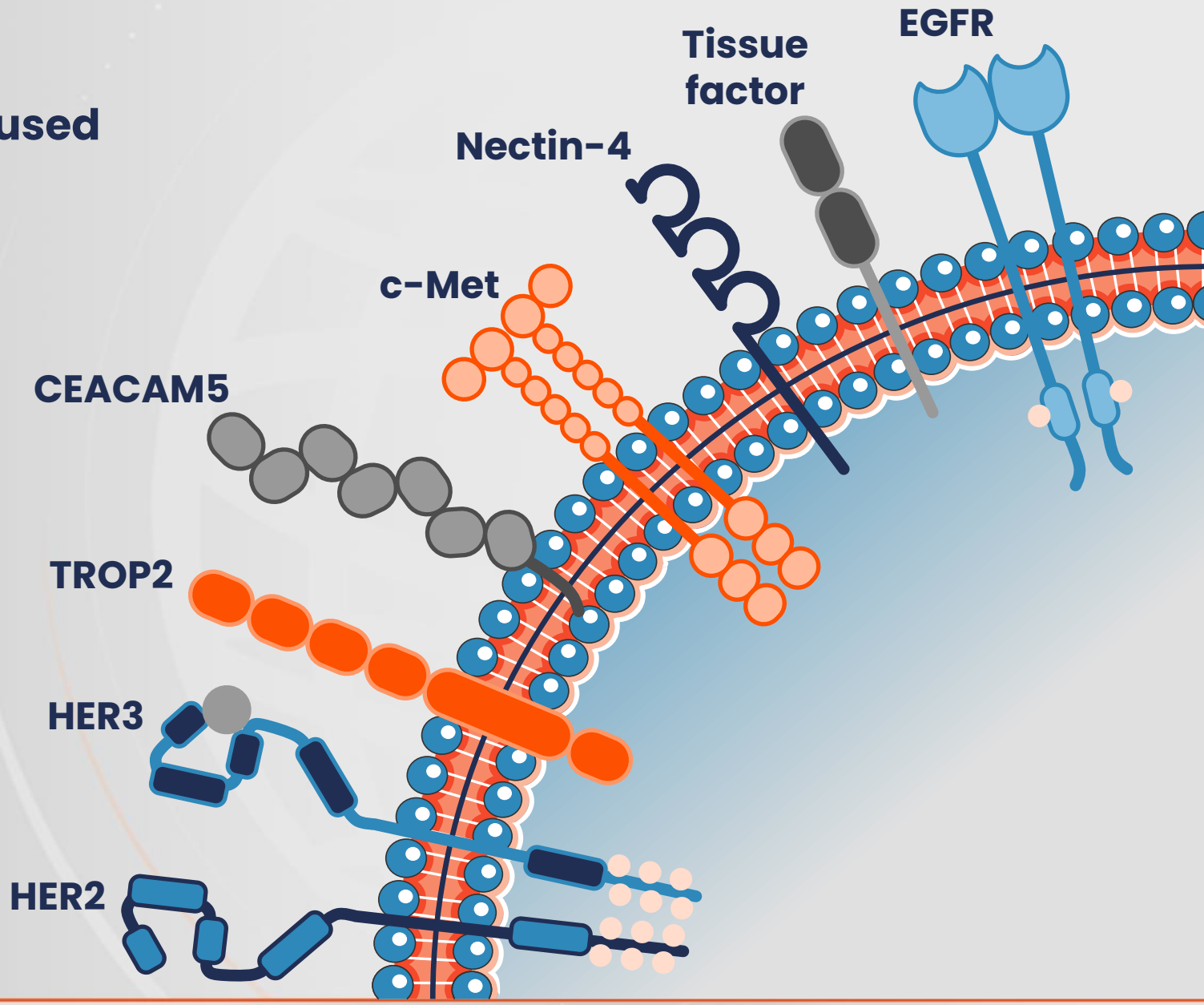
- Overexpressed on cancer cell surface compared with healthy cells
- External-facing binding site
- Absent from systemic circulation
- Potency to internalize bound ADC

ADC, antibody–drug conjugate.

Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Antigen target selection

Current antigenic targets for ADCs used in patients with NSCLC[1–3]



ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal epithelial transition factor; EGFR, epidermal growth factor receptor; HER2/3, human epidermal growth factor receptor 2/3; NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen 2.

1. Desai A, et al. *Lung Cancer.* 2022;163:96–106; 2. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5; 3. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393.

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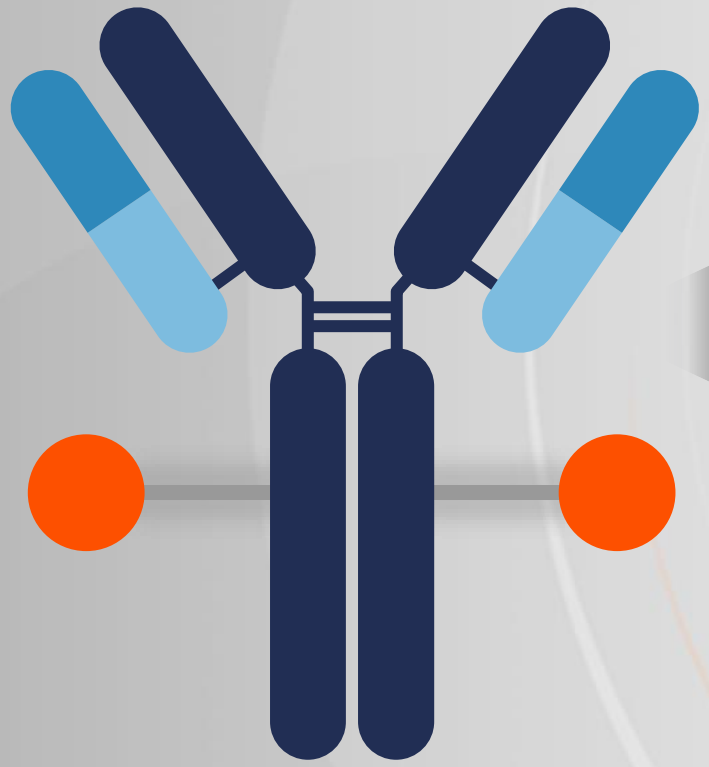
Linker molecules

Characteristics of the ideal linker for an ADC

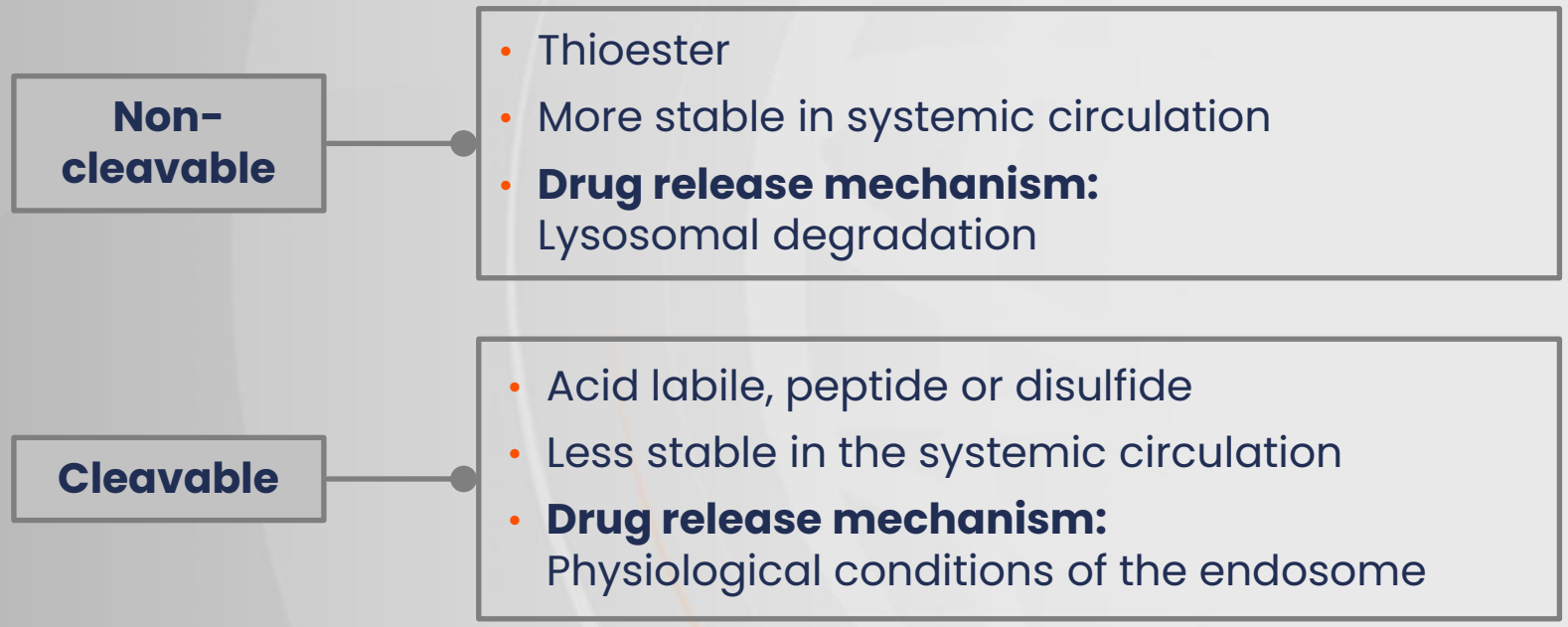


- Prevents aggregation of ADCs
- Prevents premature release of payload in the systemic circulation

ADC, antibody–drug conjugate.
Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Linker molecules

Key differences in linker cleavage

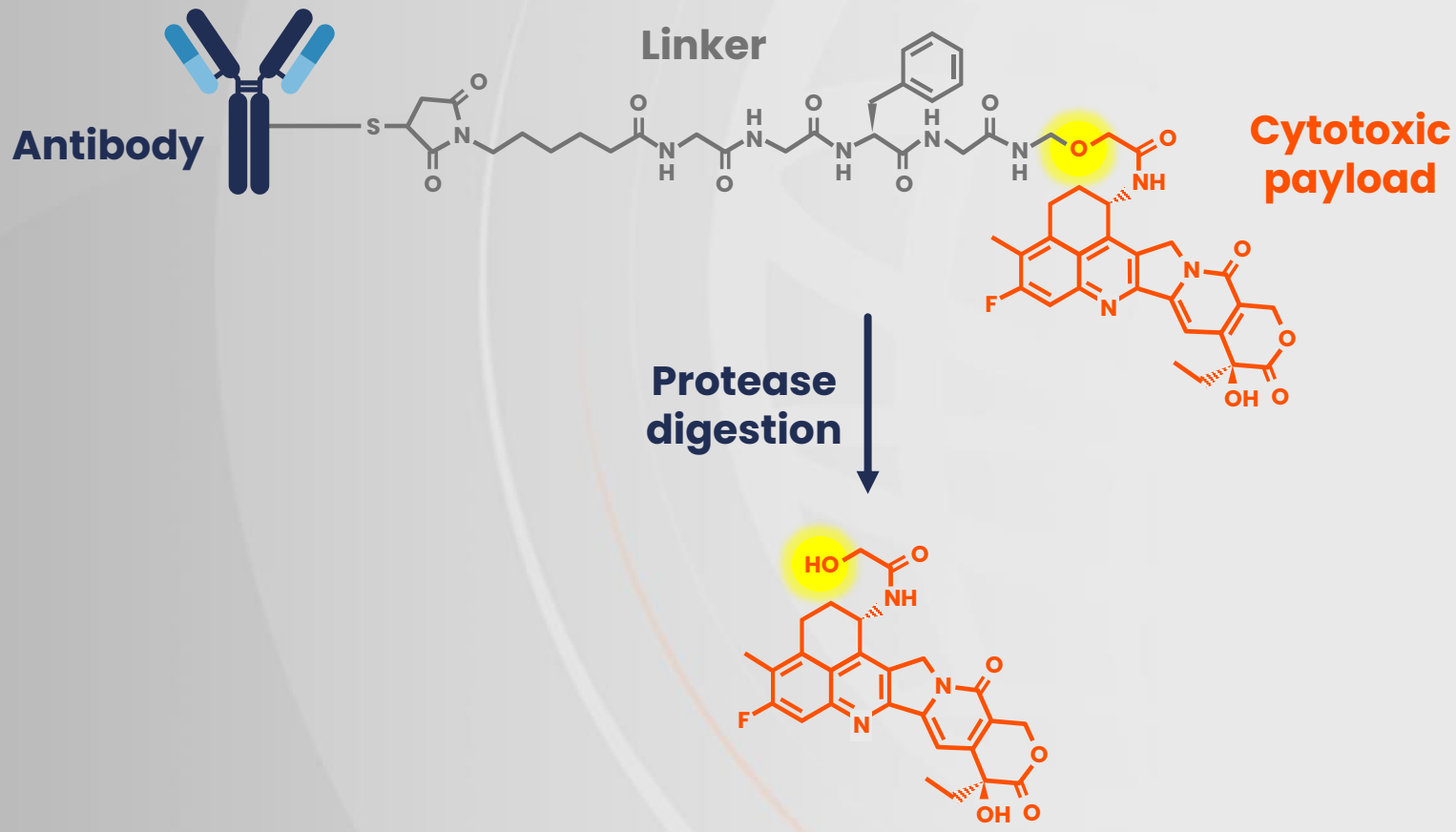


Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393.

Linker molecules

Trastuzumab deruxtecan:

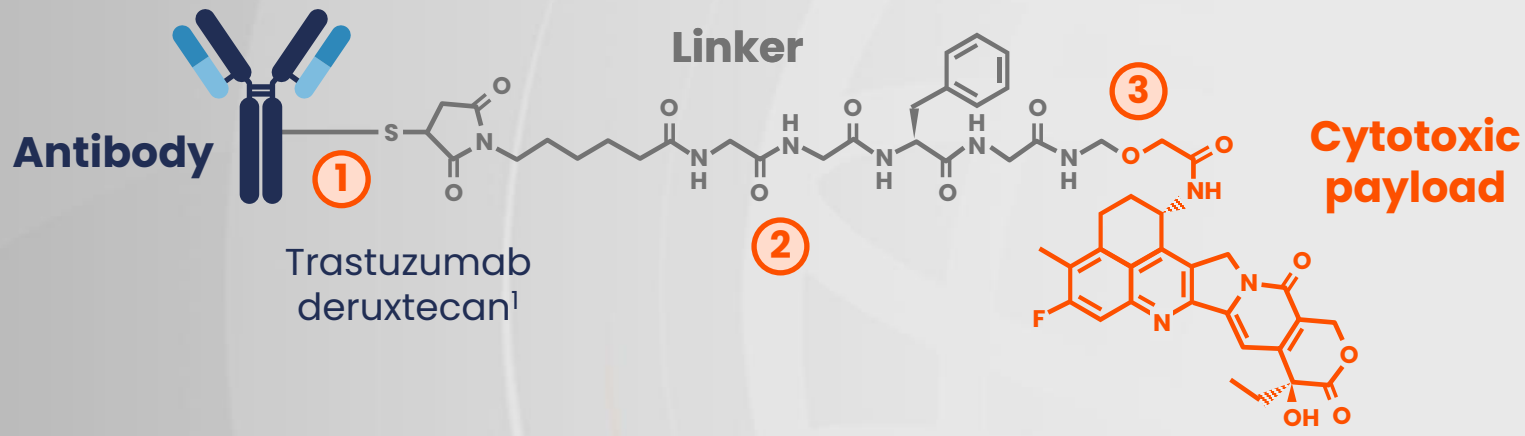
An example of a cleavable peptide linker



Ogitani Y, et al. *Clin Cancer Res.* 206;22:5097–108.

Linker molecules

Major factors affecting the stability of payload release

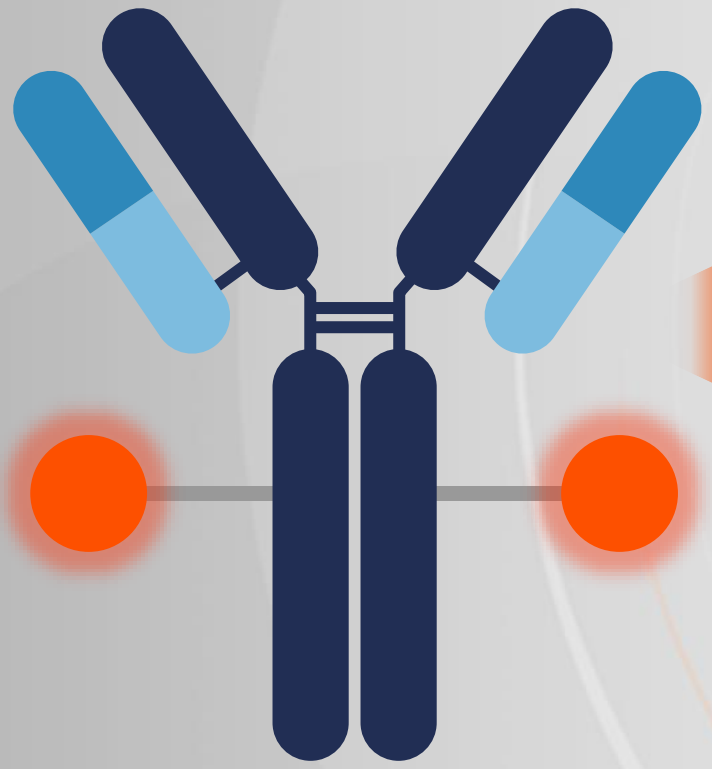


1. **Conjugation site chemistry**[2]
2. **Linker length**[2]
3. **Steric hinderance at the cleavage site**[2]

ADC, antibody–drug conjugate.
1. Ogitani Y, et al. *Clin Cancer Res.* 206;22:5097–108; 2. Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Cytotoxic payload

Characteristics of the ideal payload for an ADC



- Potent[1]
- Stable in the systemic circulation[1]
- High solubility[1]
- Low immunogenicity[2]
- Small molecular weight[2]
- Functional group for conjugation and membrane permeability[1]

ADC, antibody–drug conjugate.

1. Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408; 2. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393.

Cytotoxic payload

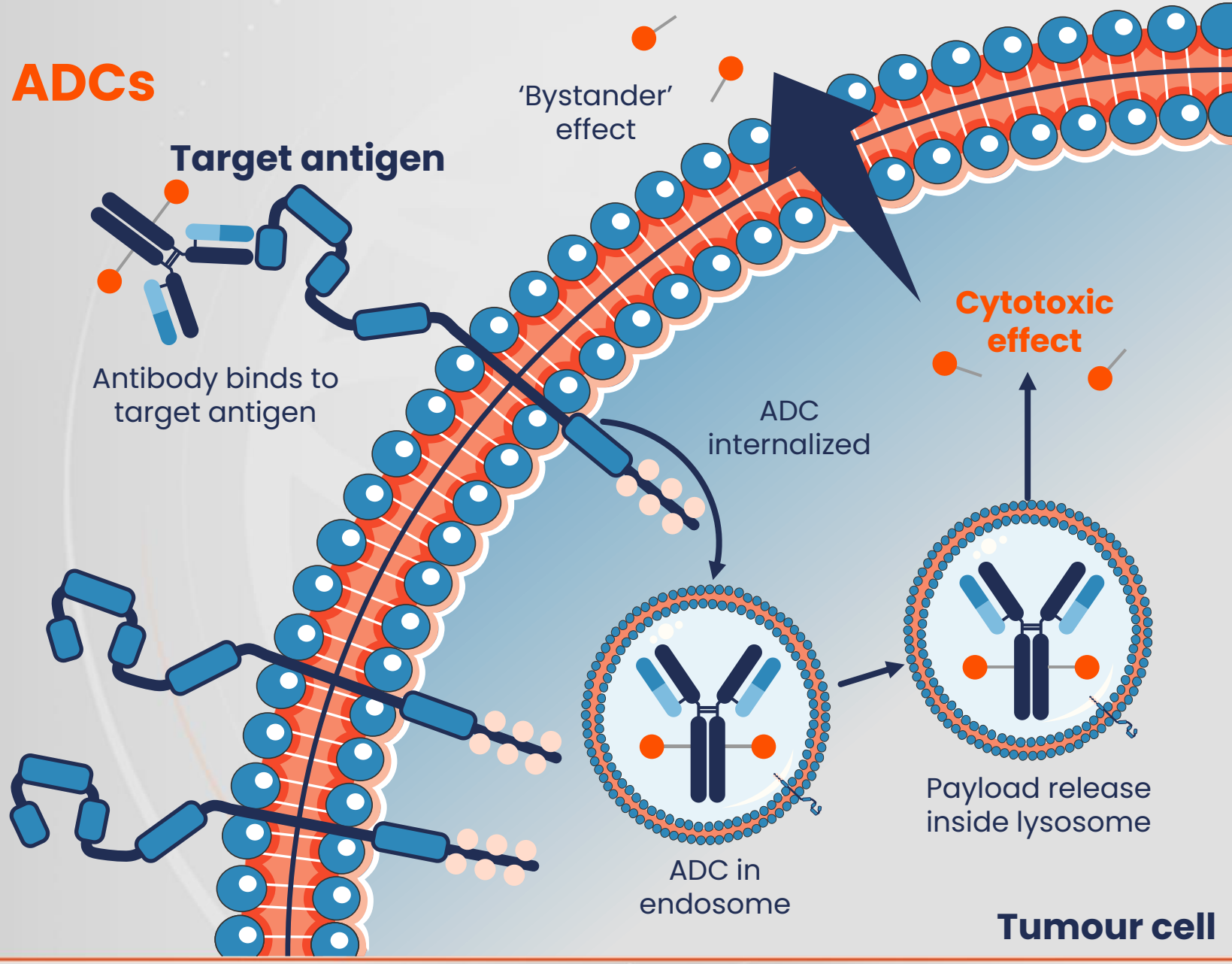
Current cytotoxic payloads used in ADCs for NSCLC

Emtansine	Microtubule inhibitor, DM1[1]
Ravtansine	Microtubule inhibitor, DM4[2]
Vedotin	Microtubule inhibitor, MMAE[1]
Deruxtecan	Topoisomerase I inhibitor[1]
Govitecan	Topoisomerase I inhibitor, SN-38[1]

ADC, antibody–drug conjugate; DM1, N_2'-deacetyl-N_2'-(3-mercapto-1-oxopropyl)-maytansine; DM4, N_2'-deacetyl-N_2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; MMAE, monomethyl auristatin E; NSCLC, non-small cell lung cancer; SN-38, (4*S*)-4,11-diethyl-4,9-dihydroxy-1,4-dihydro-3*H*,14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14-dione.

1. Desai A, et al. *Lung Cancer.* 2022;163:96–106; 2. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393.

Mechanism of action of ADCs



ADC, antibody–drug conjugate.
Desai A, et al. *Lung Cancer.* 2022;163:96–106.

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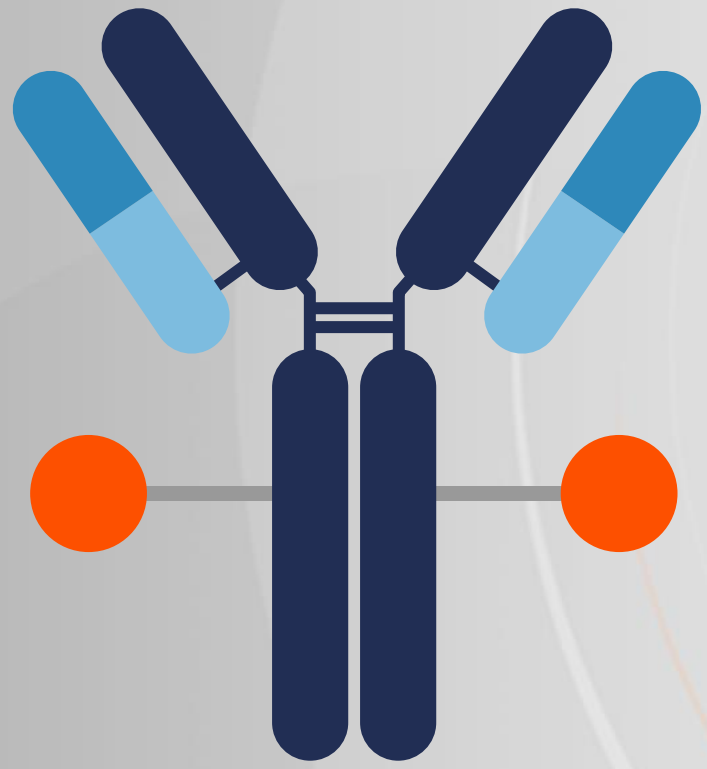
Linking ADC structure with efficacy and toxicity

Factors associated with the antibody, cytotoxic payload and linker components



Efficacy considerations

- Can possess direct and indirect anti-tumour activity[1]
- Drug–antibody ratio[1]
- Bystander effect[1,2]

Safety considerations

- Drug–antibody ratio[1]
- Bystander effect[1,2]
- Premature payload release in the systemic circulation[3]
- Inadequate linker stability[3]

ADC, antibody–drug conjugate.

1. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393; 2. Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713; 3. Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408.

Rationale for ADC use in patients with advanced NSCLC

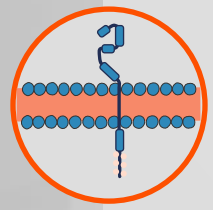
Systemic therapies	ADCs
Benefits of ChT are limited to a narrow therapeutic index[1]	Antigen-independent uptake of cytotoxic payload in antigen-negative cells is limited, contributing to a **wider therapeutic index**[2]
ChT is non-selective, which can lead to systemic toxicity[1]	ADCs combine the specificity of monoclonal antibodies with the cytotoxicity of ChT to **deliver payloads directly to cancer cells**[1]
The blood–brain barrier can limit intracranial drug delivery[3]	The 'bystander' effect seen with some ADCs **may facilitate antiproliferative activity 'behind' the blood–brain barrier**[3]
ChT, targeted therapies and immunotherapy linked to acquired resistance[1]	ADCs may **offer therapeutic benefit to patients with acquired resistance** to first-line therapy[1]

ADC, antibody–drug conjugate; ChT, chemotherapy; NSCLC, non-small cell lung cancer.

1. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393; 2. Fu Z, et al. *Signal Transduct Target Ther.* 2022;7:93; 3. Mair M, et al. *Nat Rev Clin Oncol.* 2023;20:372–89.

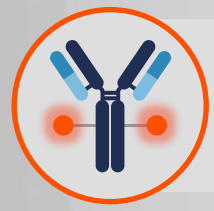
Mechanisms of resistance to ADCs

A variety of mechanisms have been described



Antigen related[1]

- Reduced antigen expression
- Truncated forms of the antigen ectodomain
- Tumour heterogeneity

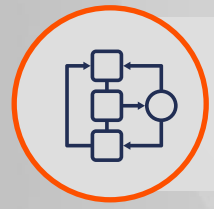


Payload related

- Increased expression of drug efflux pumps[1]
- Mutation in the payload target[1,2]

Mechanism of action related[1]

- Impaired ADC internalization
- Impaired lysosomal function



Activation of signalling pathways[1]

- PI3K/Akt/mTOR activation
- Wnt/β-catenin activation

ADC, antibody–drug conjugate; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase.

1. Khoury R, et al. *Int J Mol Sci.* 2023;24:9674; 2. Abelman RO, et al. *Cancers (Basel).* 2023:15; 1278.

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Current status of ADCs in advanced NSCLC[1]

ADC	Target antigen	Antibody	Linker	Payload	DAR
Ado-trastuzumab emtansine	HER2	Trastuzumab	Non-cleavable	Emtansine	3.5
Trastuzumab deruxtecan*			Cleavable	Deruxtecan	8
Patritumab deruxtecan	HER3	Patritumab		Deruxtecan	8
Sacituzumab govitecan	TROP2	Sacituzumab		SN-38	7.6
Datopotamab deruxtecan		Datopotamab		Deruxtecan	4
Telisotuzumab vedotin	c-Met	ABT-700		MMAE	3.1
Tusamitamab ravtansine	CEACAM5	Anti-CEACAM5	-	DM4	-

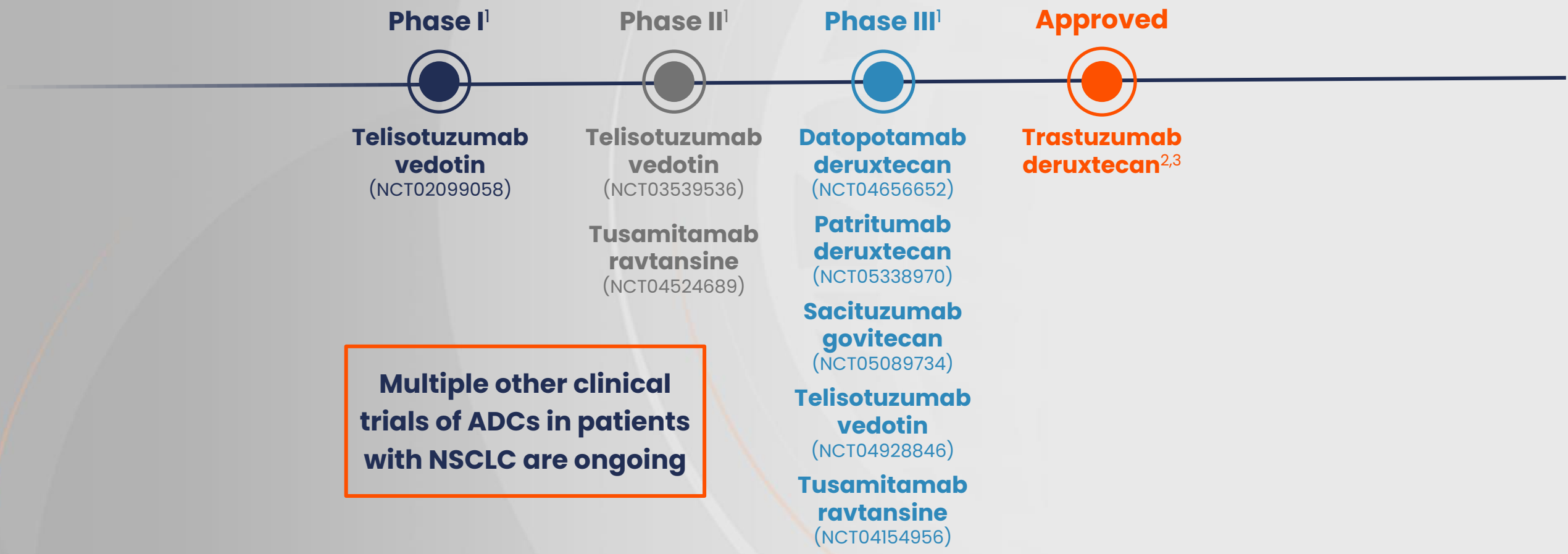
*FDA approved in August 2022 for the treatment of adult patients with unresectable or metastatic NSCLC whose tumours have activating *HER2* mutations and who have had received a prior systemic therapy.[2,3] EMA approved in October 2023 for the treatment of adult patients with advanced NSCLC whose tumours have an activating *HER2* mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.[4,5]

ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal epithelial transition factor; DAR, drug–antibody ratio; DM4, N_2'-deacetyl-N_2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER2/3, human epidermal growth factor receptor 2/3; MMAE, monomethyl auristatin E; NSCLC, non-small cell lung cancer; SN-38, (4*S*)-4,11-diethyl-4,9-dihydroxy-1,4-dihydro-3*H*,14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14-dione; TROP2, trophoblast cell surface antigen 2.

1. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393; 2. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3sRTJht (accessed 10 November 2023); 3. FDA. 2022. Available at: https://bit.ly/3uBQ08d (accessed 29 November 2023); 4. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/46C9J4Q (accessed 30 November 2023); 5. EMA. 2023. Available at: https://bit.ly/3sNPvHH (accessed 30 November 2023).

Pipeline for ADCs in advanced NSCLC

Ongoing trials in participants progressing on/after prior systemic treatment



Multiple other clinical trials of ADCs in patients with NSCLC are ongoing

ADC, antibody–drug conjugate; NSCLC, non-small cell lung cancer.

1. ClinicalTrials.gov. Available at: Available at: https://beta.clinicaltrials.gov/; all clinical trials searchable by NCT number (accessed 7 December 2023). 2. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3sRTJht (accessed 10 November 2023); 2. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/46C9J4Q (accessed 30 November 2023).

Summary

**ADCs comprise three key components:
An antibody, a cytotoxic payload and a linker molecule**[1]

ADCs target antigens expressed on cancer cells compared with healthy cells[1]

Each component of an ADC can be modified to optimize therapeutic benefit[1]

One ADC, trastuzumab deruxtecan, has been approved for use in patients with pretreated NSCLC with *HER2* mutations[2,3] **and many more are in clinical development**[4]

1. Samantasinghar A, et al. *Biomed Pharmacother.* 2023;161:114408; 2. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3sRTJht (accessed 10 November 2023);
3. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/46C9J4Q (accessed 30 November 2023); 4. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5.

ADCs in the second-line setting: Exploring the latest clinical trials data

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Latest data for trastuzumab deruxtecan

DESTINY-Lung01

Phase II

N=91

- Adults with relapsed or refractory unresectable or metastatic non-squamous NSCLC
- HER2-overexpressing or *HER2*-mutant NSCLC
- Patients with asymptomatic brain metastases eligible
- ECOG PS: 0 or 1

IV trastuzumab deruxtecan 6.4 mg/kg every 3 weeks

Primary endpoint: Confirmed ORR
55% (95% CI 44–65%)

Most common any-grade drug-related AEs
Nausea (73%), fatigue (53%), alopecia (46%)

Drug-related ILD
26%

AE, adverse event; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate.

Li BT, et al. *N Engl J Med.* 2022;386:241–51.

Latest data for trastuzumab deruxtecan

DESTINY-Lung02

Phase II

N=152

- Adults with *HER2*-mutant, unresectable, metastatic NSCLC
- Received ≥1 previous Pt-ChT
- Patients with stable, asymptomatic brain metastases eligible
- ECOG PS: 0 or 1

IV trastuzumab deruxtecan 5.4 mg/kg (n=102) or 6.4 mg/kg (n=50) every 3 weeks

Primary endpoint: Confirmed ORR
5.4 mg/kg: 49% (95% CI 39–59%)
6.4 mg/kg: 56% (95% CI 41–70%)

Grade ≥3 TEAEs
5.4 mg/kg: **39%** 6.4 mg/kg: **58%**

Drug-related ILD
5.4 mg/kg: **13%** 6.4 mg/kg: **28%**

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; Pt-ChT, platinum-based chemotherapy; TEAE, treatment-emergent adverse event.

Goto K, et al. *J Clin Oncol.* 2023;41:4852–63.

Latest data for trastuzumab deruxtecan

DESTINY-Lung01 and DESTINY-Lung02 pooled analysis: Intracranial activity

- Post hoc analysis of pooled data from DESTINY-Lung01 and DESTINY-Lung02 population
- Patients with vs without BM

DESTINY-Lung02 (5.4 mg/kg)	DESTINY-Lung01 / DESTINY-Lung02 pooled (6.4 mg/kg)
With BM: n=32 Without BM: n=70	With BM: n=54 Without BM: n=87

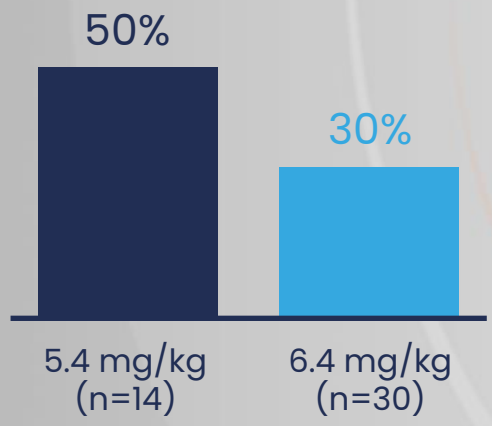
BM, brain metastases; HER2, human epidermal growth factor receptor 2.

Li BT, et al. *Ann Oncol.* 2023;34(Suppl. 2):S762–3.

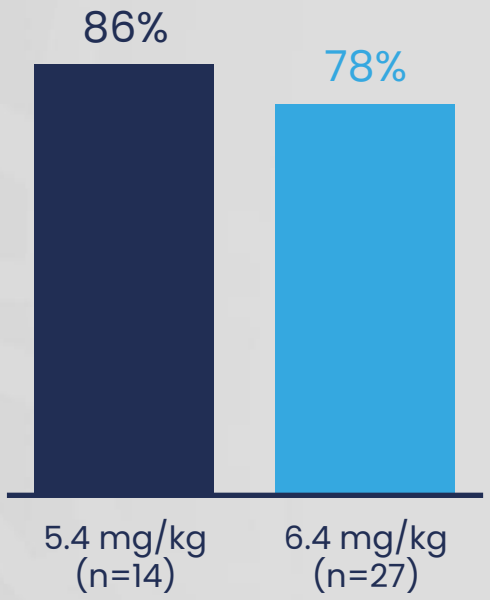
Latest data for trastuzumab deruxtecan

DESTINY-Lung01 and DESTINY-Lung02 pooled analysis: Patients with measurable BM at baseline

Intracranial ORR



Reduction in brain lesion size from baseline



BM, brain metastases; HER2, human epidermal growth factor receptor 2; ORR, objective response rate.
Li BT, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation 1321 MO.

Latest data for datopotamab deruxtecan

TROPION-PanTumor01: Dose escalation and expansion

Phase I

N=180

- Adults with relapsed/progressed, unresectable, advanced/metastatic NSCLC with standard treatment
- No minimum TROP2 expression level required
- Patients with clinically inactive brain metastases eligible*
- ECOG PS: 0 or 1

IV datopotamab deruxtecan 4 mg/kg (n=50), 6 mg/kg (n=50) or 8 mg/kg (n=80) every 3 weeks

Primary endpoint: Safety and tolerability, determination of maximum tolerated dose, recommended dose for expansion, TEAEs

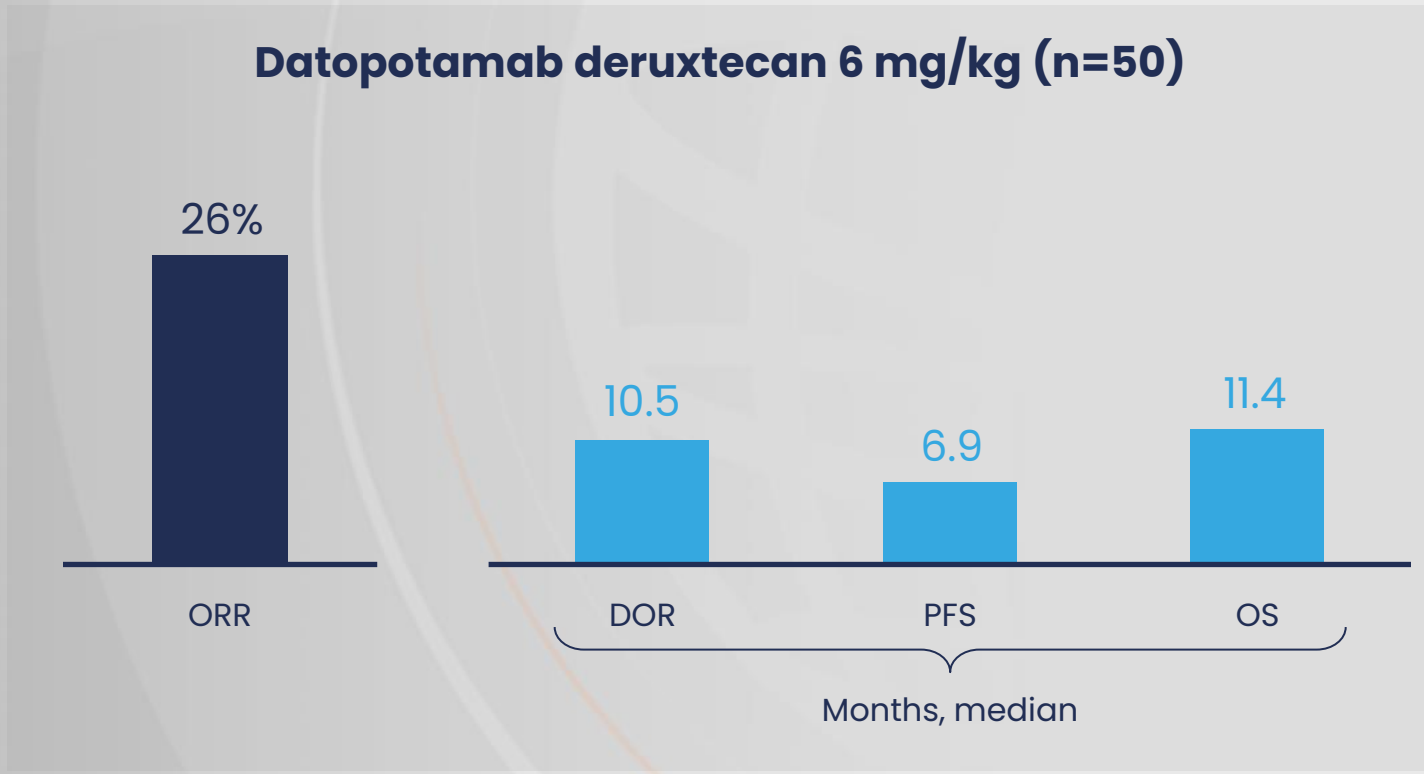
- Maximum tolerated dose 8 mg/kg every 3 weeks
- **6 mg/kg** dose selected for development

*If ≥2 weeks past whole-brain radiotherapy at the time of enrolment.
ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TROP2, trophoblast cell surface antigen 2.
Shimizu T, et al. *J Clin Oncol.* 2023;41:4678–87.

Latest data for datopotamab deruxtecan

TROPION-PanTumor01: Dose escalation and expansion

Phase I



DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TROP2, trophoblast cell surface antigen 2.

Shimizu T, et al. *J Clin Oncol.* 2023;41:4678–87.

Latest data for datopotamab deruxtecan

TROPION-Lung05

Phase II

57% had *EGFR* mutations

N=137

- Adults with advanced/metastatic NSCLC
- Progression on or after ≥1 kinase inhibitor and ≥1 line of Pt-ChT
- Actionable genomic alterations
- ECOG PS: 0 or 1

IV datopotamab deruxtecan 6 mg/kg every 21 days

Primary endpoint: Confirmed ORR
36% (95% CI 28–44%)
Confirmed ORR in patients with *EGFR* mutation
44%

Most common grade ≥3 TEAEs
Stomatitis (10%), anaemia (6%), ↑ amylase (6%)
Drug-related ILD
Grade 1 or 2: **3%** Grade ≥3: **1%**

↑, increased; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; Pt-ChT, platinum-based chemotherapy; TEAE, treatment-emergent adverse event; TROP2, trophoblast cell surface antigen 2.

Paz-Ares L, et al. *Ann Oncol.* 2023;34(Suppl. 2):S755–6.

Latest data for datopotamab deruxtecan

TROPION-Lung01

Phase III

N=590

- Adults with locally advanced/metastatic (stage IIIB, IIIC or IV) NSCLC[1,2]
- Without actionable genomic alterations: 1 or 2 prior lines including Pt-ChT and PD-(L)1[1,2]
- With actionable genomic alterations: 1 or 2 prior targeted therapies + Pt-ChT and ≤1 PD-(L)1 inhibitor[2]
- ECOG PS: 0 or 1[2]
- Patients with asymptomatic and stable/treated brain metastases eligible[1]

Randomized 1:1[1]

IV **datopotamab deruxtecan** 6 mg/kg every 3 weeks (n=299)[1,2]

IV **docetaxel** 75 mg/m^2 every 3 weeks (n=305)[1,2]

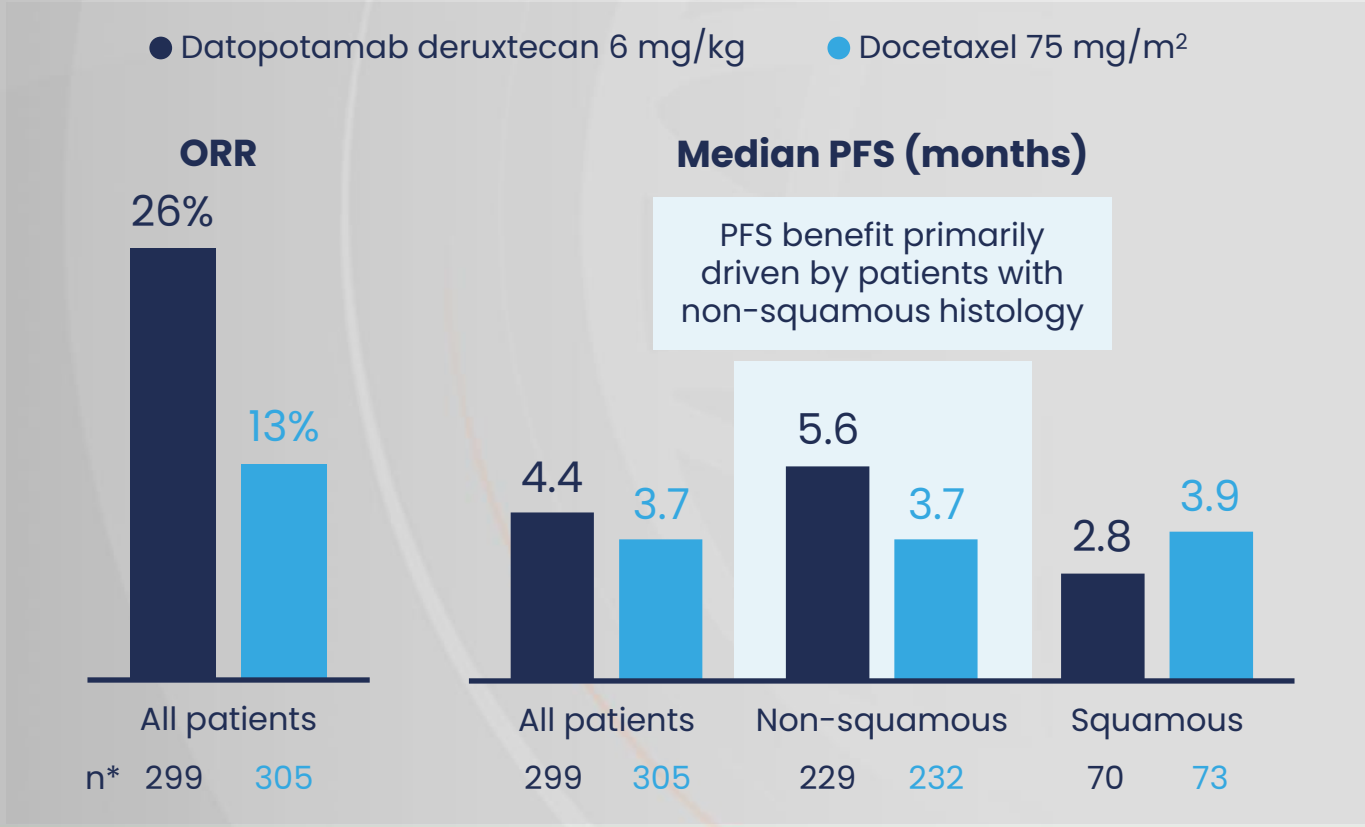
ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death (ligand) 1; Pt-ChT, platinum-based chemotherapy; TROP2, trophoblast cell surface antigen 2.

1. Yoh K, et al. *J Clin Oncol.* 2021;39(Suppl. 15):TPS9127; 2. Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Latest data for datopotamab deruxtecan

TROPION-Lung01: Efficacy data

Phase III

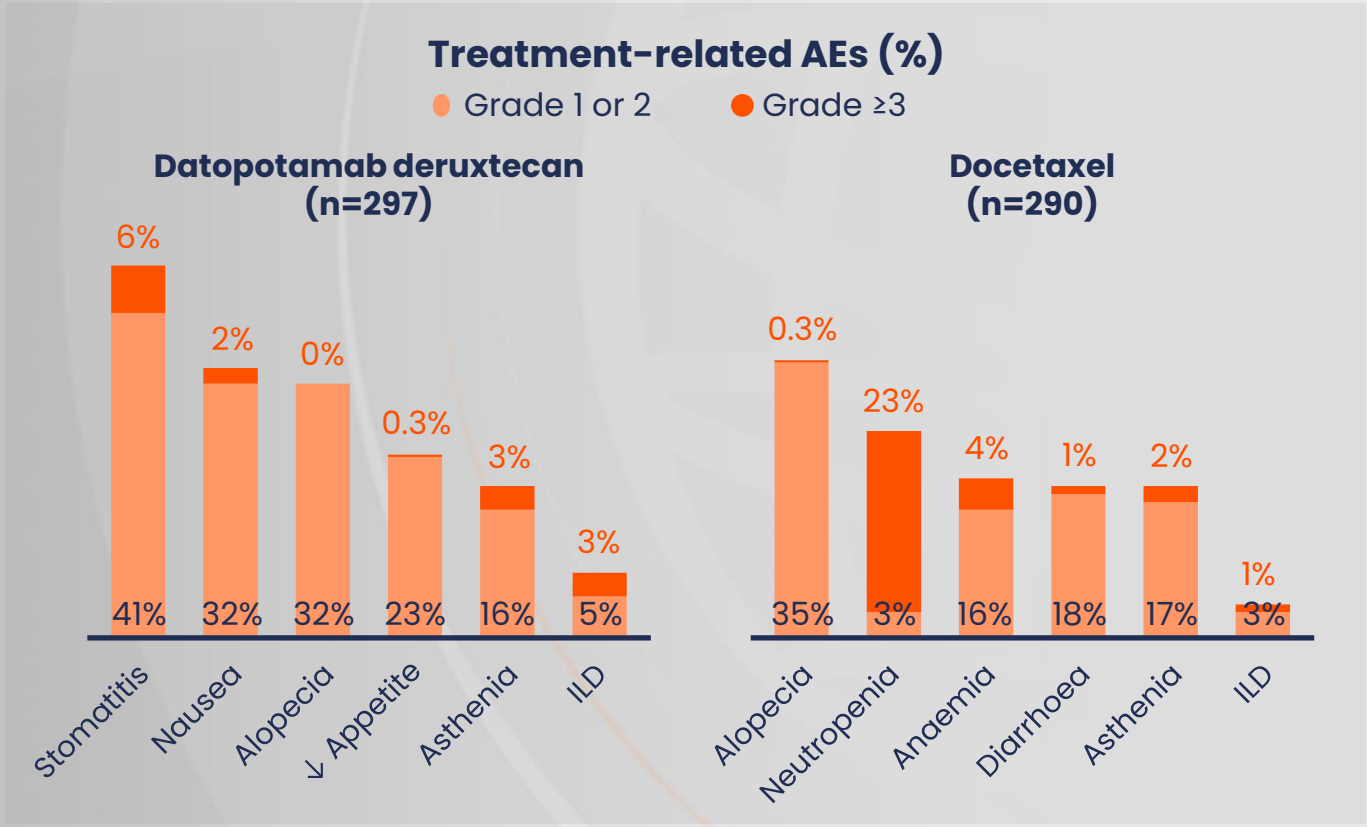


*Data represent total number of patients in each cohort.
ORR, objective response rate; PFS, progression-free survival; TROP2, trophoblast cell surface antigen 2.
Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Latest data for datopotamab deruxtecan

TROPION-Lung01: Safety data

Phase III



↓, decreased; AE, adverse event; ILD, interstitial lung disease; TROP2, trophoblast cell surface antigen 2.

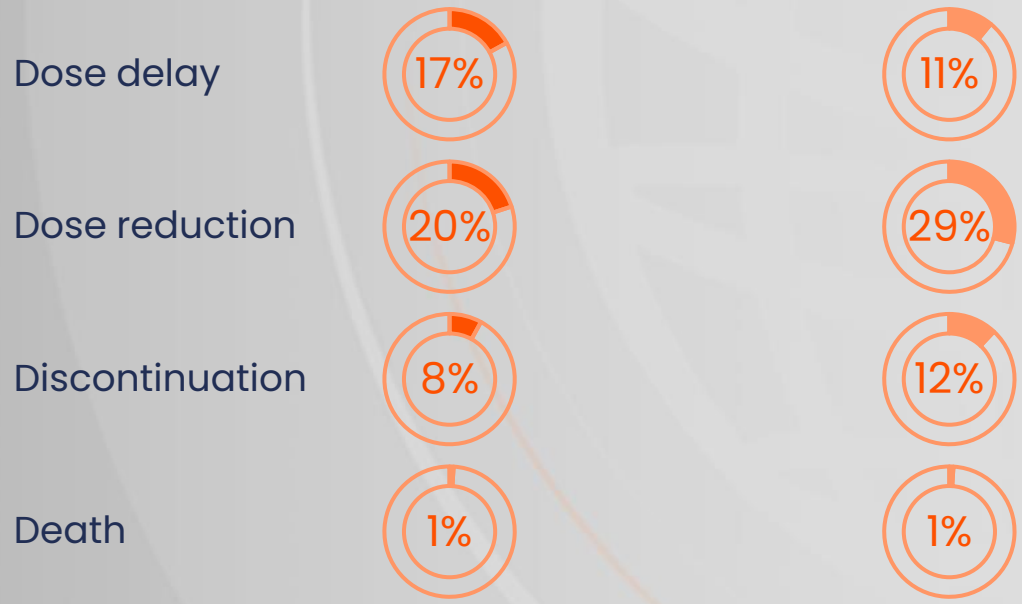
Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Latest data for datopotamab deruxtecan

TROPION-Lung01: Safety data

Phase III

Treatment-related AEs associated with:



AE, adverse event; TROP2, trophoblast cell surface antigen 2.

Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Early data for sacituzumab govitecan

IMMU-132-01: Single-arm expansion of the initial basket trial

Phase I/II

N=54

- Adults with metastatic squamous or non-squamous NSCLC
- ≥1 line of therapy for stage IV disease
- No preselection on the basis of TROP2 expression
- ECOG PS: 0 or 1

IV sacituzumab govitecan 8 mg/kg (n=8) or 10 mg/kg (n=46) on days 1 and 8 of 21-day cycles

Primary endpoint: Confirmed ORR

17%

Most common any grade AEs regardless of causality (all patients)

Nausea (80%), diarrhoea (61%), fatigue (46%)

Most common grade ≥3 events regardless of causality occurring in ≥5% of patients

Neutropenia (28%), leukopenia (9%), pneumonia (9%)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell surface antigen 2.

Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7.

Latest data for patritumab deruxtecan

HERTHENA-Lung01

Phase II

N=277

- Adults with locally advanced/metastatic NSCLC
- *EGFR*-activating mutations (ex19del or L858R)
- ≥1 EGFR TKI (osimertinib) and ≥1 line of Pt-ChT in any sequence
- Patients with asymptomatic, clinically inactive or treated brain metastases were eligible
- ECOG PS: 0 or 1

Randomized

IV **patritumab deruxtecan 5.6 mg/kg** every 3 weeks (n=226)

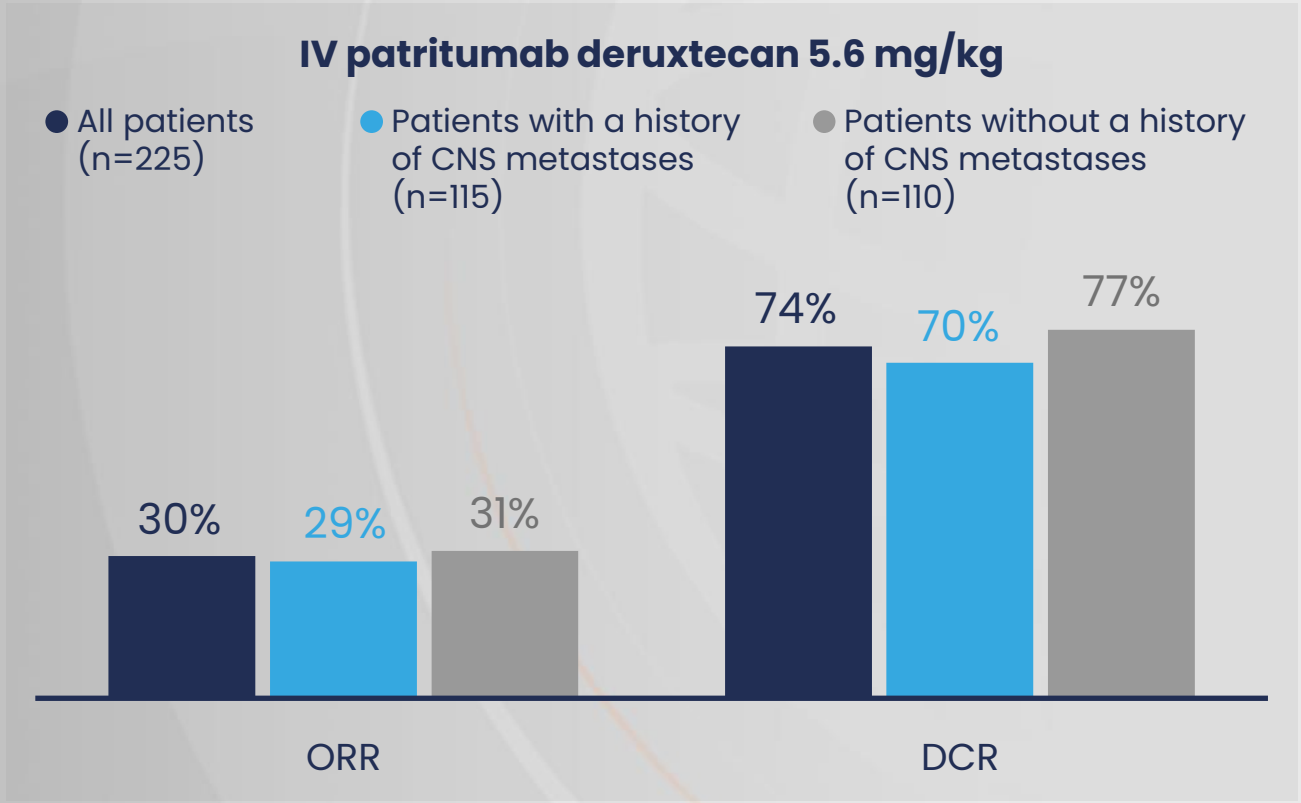
Uptitration regimen:* IV patritumab deruxtecan Cycle 1: **3.2 mg/kg** Cycle 2: **4.8 mg/kg** Cycle 3+: **6.4 mg/kg** (n=51)

*Enrolment into the uptitration arm closed early on the basis of a prespecified benefit-risk assessment of data from the phase I U31402-A-U102 trial.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; HER3, human epidermal growth factor receptor 3; IV, intravenous; NSCLC, non-small cell lung cancer; Pt-ChT, platinum-based chemotherapy; TKI, tyrosine kinase inhibitor.
Yu HA, et al. *J Clin Oncol.* 2023;41:5363–75.

Latest data for patritumab deruxtecan

HERTHENA-Lung01: Efficacy data

Phase II



CNS, central nervous system; DCR, disease control rate; HER3, human epidermal growth factor receptor 3; IV, intravenous; ORR, objective response rate.

Yu HA, et al. *J Clin Oncol.* 2023;41:5363–75.

Latest data for patritumab deruxtecan

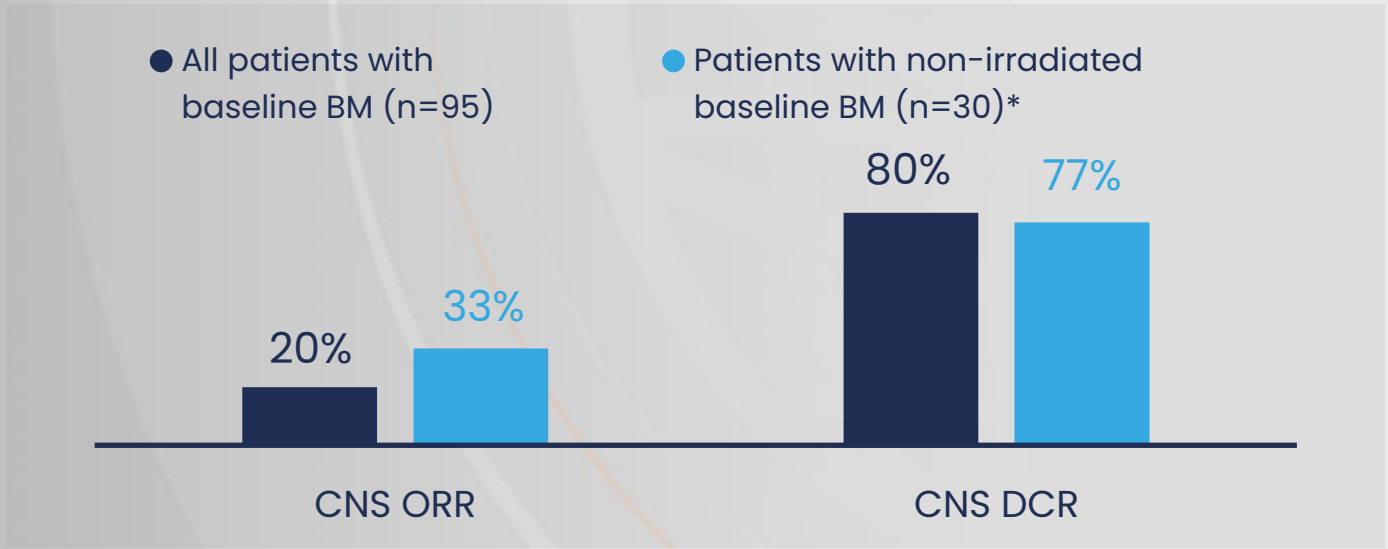
HERTHENA-Lung01: Intracranial responses

Phase II

IV patritumab deruxtecan 5.6 mg/kg every 3 weeks (n=226)

→ Patients with BM at baseline (n=95)

→ Patients whose BM had not been irradiated (n=30)*



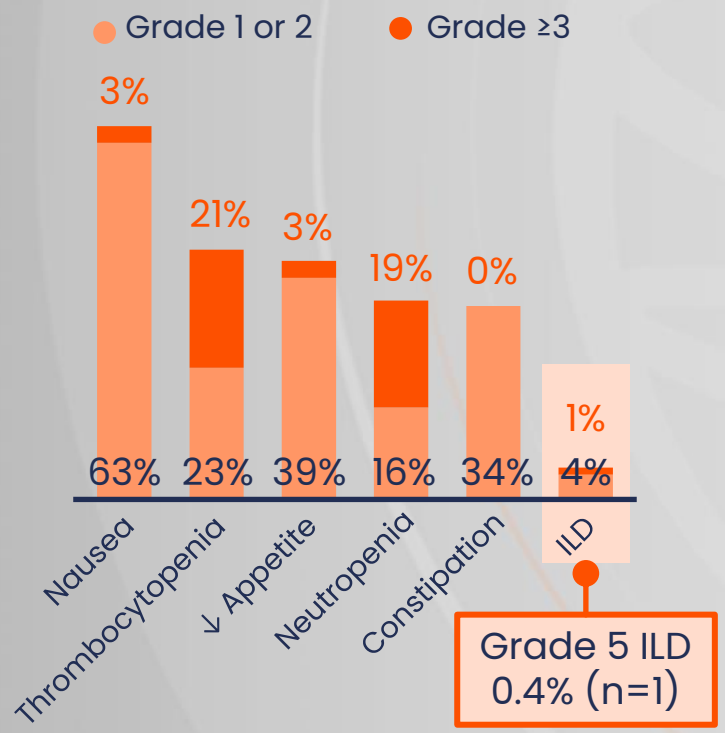
*n=7 with measurable target lesions; n=23 only non-target lesions.
BM, brain metastases; CNS, central nervous system; DCR, disease control rate; HER3, human epidermal growth factor receptor 3; IV, intravenous; ORR, objective response rate.
Johnson ML, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation 1319MO.

Latest data for patritumab deruxtecan

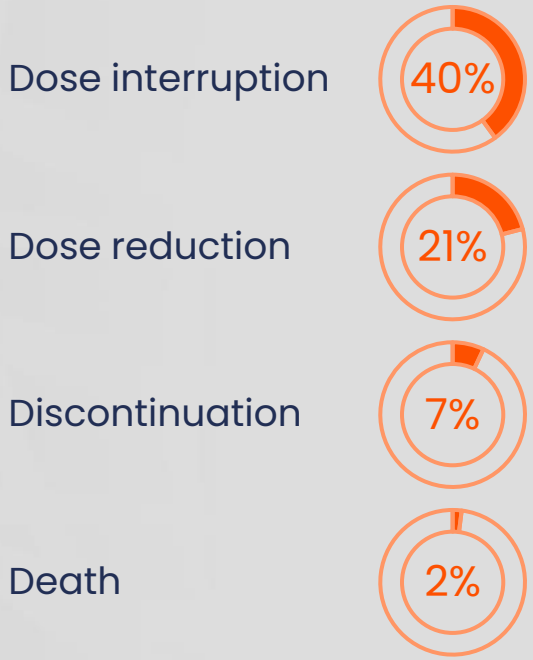
HERTHENA-Lung01: Safety data (whole population)

Phase II

Treatment-related AEs (n=225)



Treatment-related AEs associated with (n=225):

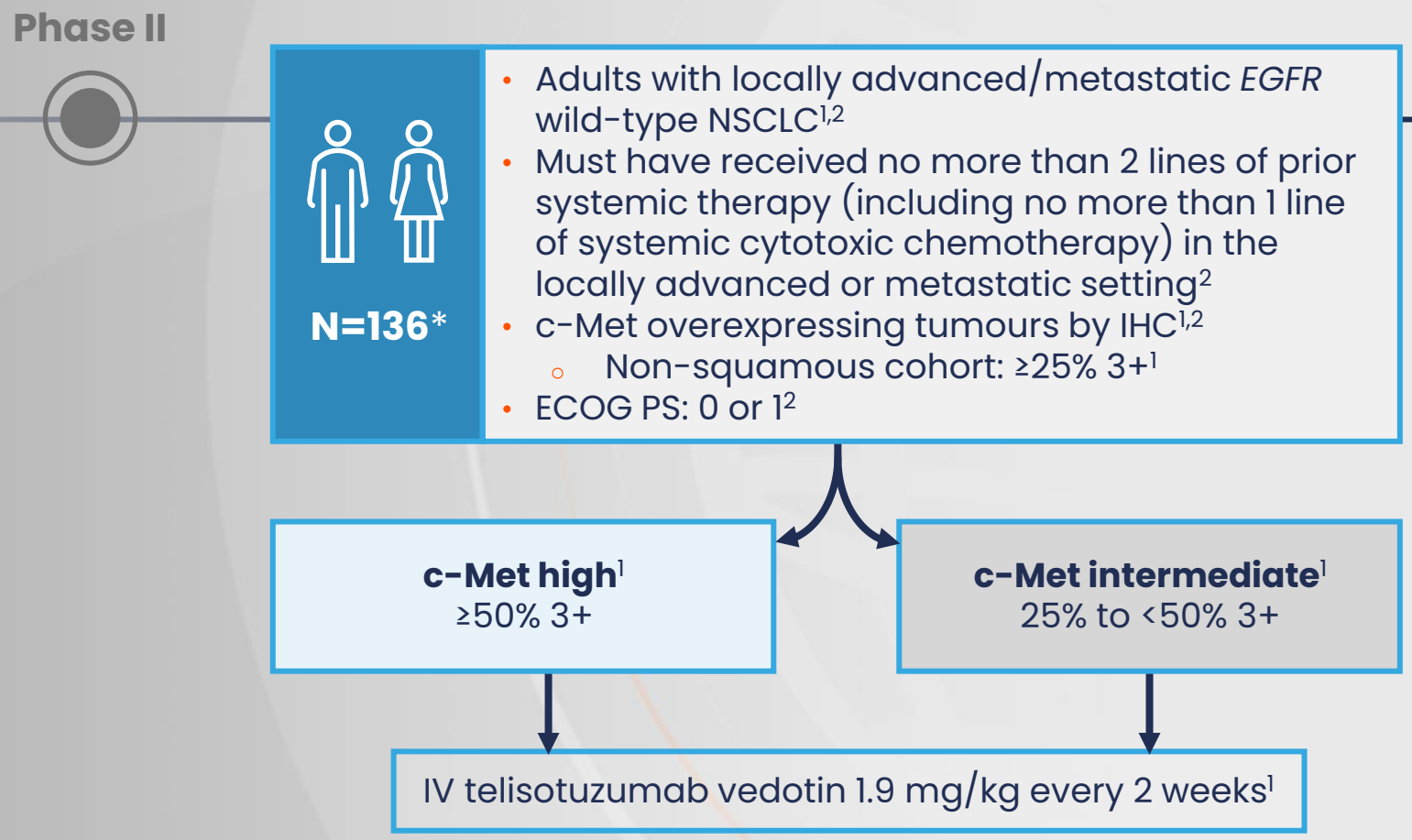


AE, adverse event; HER3, human epidermal growth factor receptor 3; ILD, interstitial lung disease.

Yu HA, et al. *J Clin Oncol.* 2023;41:5363–75.

Latest data for telisotuzumab vedotin

LUMINOSITY



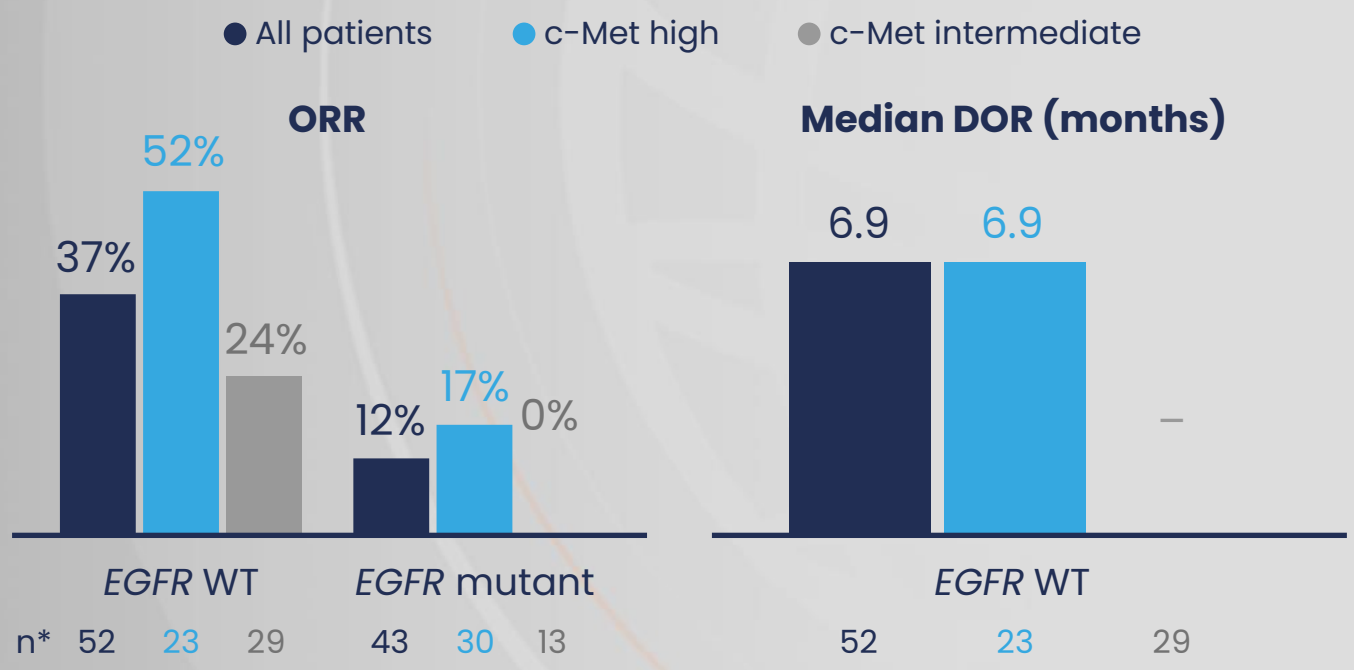
*N-136 treated with telisotuzumab vedotin, n=122 evaluable for ORR.
c-Met, mesenchymal epithelial transition factor; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer.
1. Camidge DR, et al. *J Clin Oncol*. 2022;40(Suppl. 16):9016; 2. ClinicalTrials.gov. NCT03539536. Available at: https://beta.clinicaltrials.gov/study/NCT03539536 (accessed 8 December 2023).

Latest data for telisotuzumab vedotin

LUMINOSITY: Efficacy data

Phase II

Telisotuzumab vedotin 1.9 mg/kg in patients with c-Met overexpressing non-squamous NSCLC



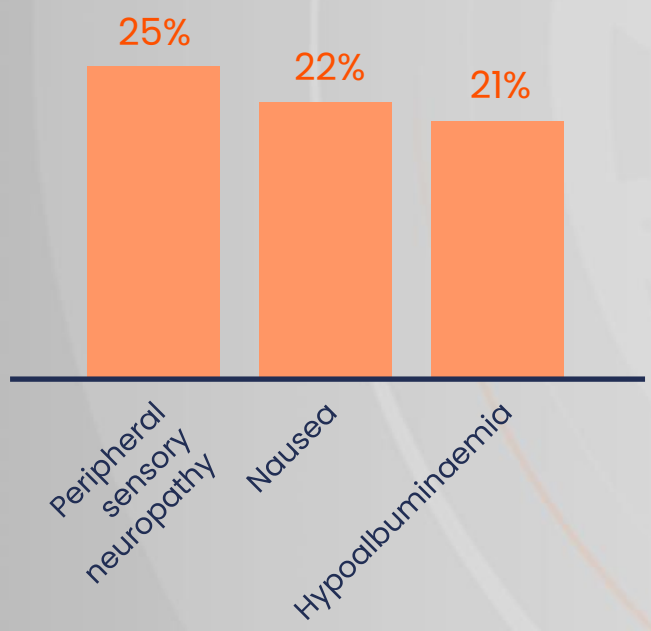
*Data represent total number of patients in each cohort.
c-Met, mesenchymal epithelial transition factor; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; WT, wild type.
Camidge DR, et al. *J Clin Oncol*. 2022;40(Suppl. 16):9016.

Latest data for telisotuzumab vedotin

LUMINOSITY: Safety data (whole population)

Phase II

Most common any-grade AEs (n=122)



Grade 5 AEs possibly related to telisotuzumab vedotin

- Sudden death (n=1)
- Pneumonitis (n=1)

Both grade 5 events were in the squamous NSCLC population

AE, adverse event; c-Met, mesenchymal epithelial transition factor; NSCLC, non-small cell lung cancer.

Camidge DR, et al. *J Clin Oncol*. 2022;40(Suppl. 16):9016.

Latest data for tusamitamab ravtansine

Overview of early the phase clinical trials

Phase I/II

N=92

- Adults with heavily pretreated non-squamous NSCLC[1]
- High or moderate CEACAM5 expression (by IHC)[1,2]

IV tusamitamab ravtansine 100 mg/m^2 every 2 weeks[1,2]

Primary endpoint: ORR[2]
Moderate expressors: **7%**
High expressors: **20%**

Most common TEAE in patients treated for ≥12 months (n=19)[1]
Corneal events (73%)

36% of corneal events were grade ≥3

CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; TEAE, treatment-emergent adverse event.

1. Ricordel C, et al. *J Clin Oncol.* 2022;40:9039; 2. Gazzah A, et al. *J Clin Oncol.* 2020;38:9505.

Ongoing clinical trials for ADCs in NSCLC

Second-line approaches

Trial / Phase	Treatment arms	Patient population	Primary endpoint
HERTHENA-Lung02 Phase III[1]	Patritumab deruxtecan vs Pt-ChT	Locally advanced or metastatic *EGFR*+ NSCLC after progression on EGFR TKI	**PFS**
DESTINY-Lung05 Phase II[2]	Trastuzumab deruxtecan	Metastatic non-squamous NSCLC with *HER2* mutation, relapsed or refractory to ≥1 treatment	**Confirmed ORR**
CARMEN-LC06 Phase II[3]	Tusamitamab ravtansine	Non-squamous NSCLC with negative or moderate CEACAM5-expressing tumours and high circulating CEA levels, and progression after Pt-ChT and ICI	**ORR**
EVOKE-01 Phase III[4]	Sacituzumab govitecan vs docetaxel	Advanced or metastatic NSCLC with progression on or after Pt-ChT and PD-(L)1 inhibitor in combination or sequentially	**OS**
TeliMET NSCLC-01 Phase III[5]	Telisotuzumab vedotin vs docetaxel	Locally advanced or metastatic c-Met overexpressing non-squamous NSCLC with *EGFR* wild type and progression on ≥1 line of prior treatment (≤1 line of ChT)	**PFS, OS**

ADC, antibody–drug conjugate; CEA, carcinoembryonic antigen; CEACAM5, CEA-related cell adhesion molecule 5; c-Met, mesenchymal epithelial transition factor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Pt-ChT, platinum-based chemotherapy; TKI, tyrosine kinase inhibitor.

1. ClinicalTrials.gov. NCT05338970; 2. ClinicalTrials.gov. NCT05246514; 3. ClinicalTrials.gov. NCT05245071; 4. ClinicalTrials.gov. NCT05089734; 5. ClinicalTrials.gov NCT04928846. All clinical trials searchable by NCT number. Available at: https://beta.clinicaltrials.gov/ (accessed 1 December 2023).

Implications of the data

More research is required to:

- Optimize patient selection
- Determine the optimal sequence for ADCs
- Develop strategies for patients with acquired resistance
- Confirm efficacy in patients with brain metastases

ADC, antibody–drug conjugate.

ADCs in clinical practice: Optimizing treatment for patients with advanced/metastatic NSCLC

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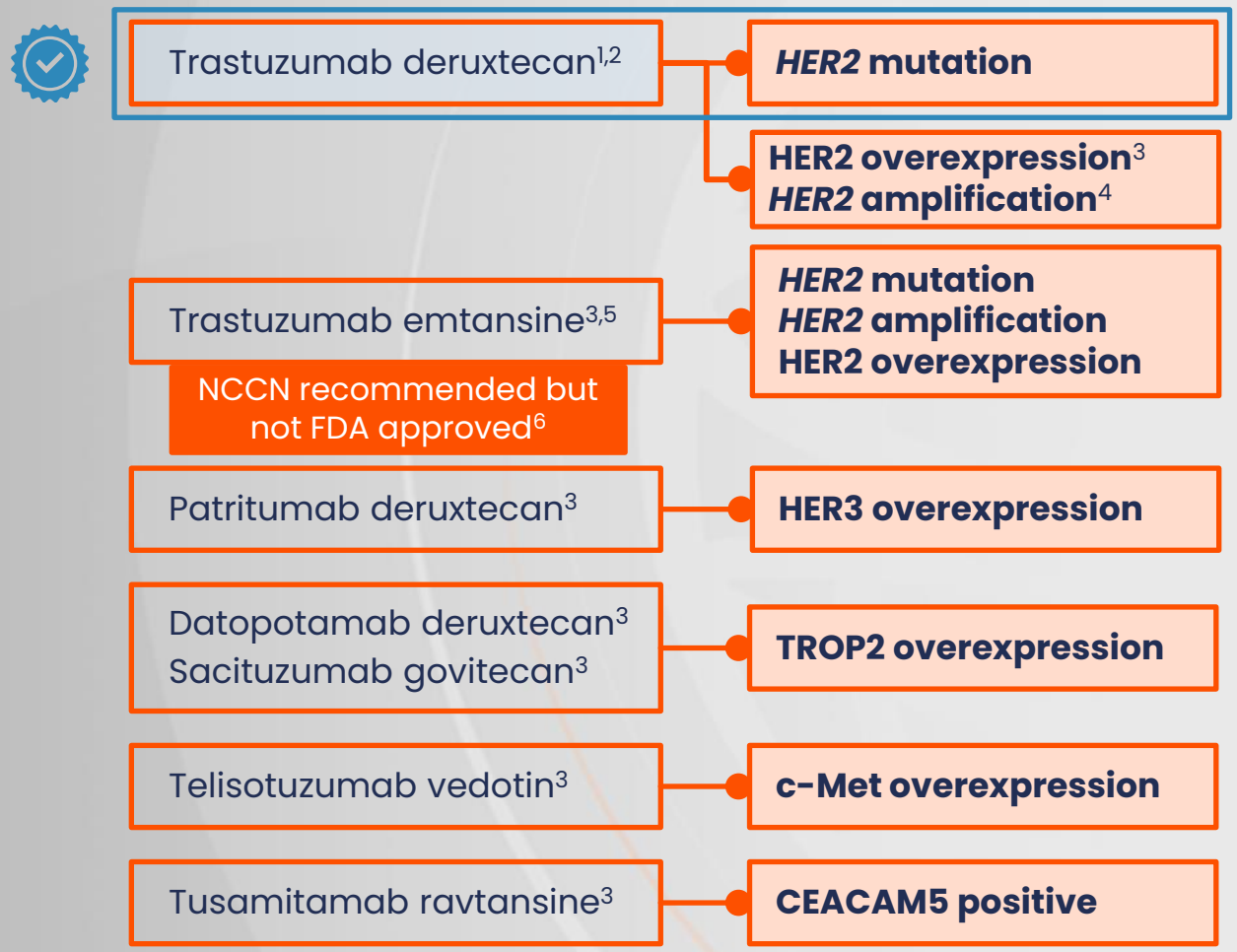
Antigen targets for current ADCs in NSCLC



ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal-epithelial transition factor; FDA, US Food and Drug Administration; HER2/3, human epidermal growth factor receptor 2/3; NCCN, National Comprehensive Cancer Network®; NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen.

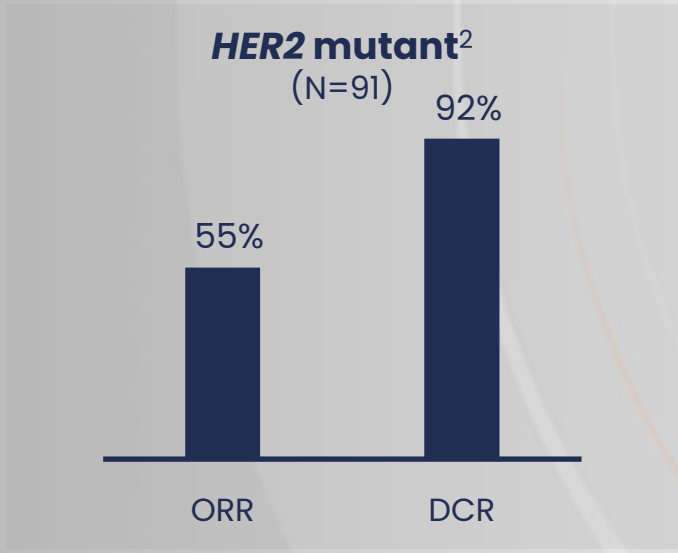
1. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3ONmHYa (accessed 27 November 2023); 2. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/3MMPBVK (accessed 27 November 2023); 3. Abuhelwa Z, et al. *Cancer Treat Rev.* 2022;106:102393; 4. Yun KM, Bazhenova L. *BMJ Case Rep.* 2023;16:e253260; 5. Peters S, et al. *Clin Cancer Res.* 2019;25:64–72; 6. NCCN. Non-small cell lung cancer. V5.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 28 November 2023).

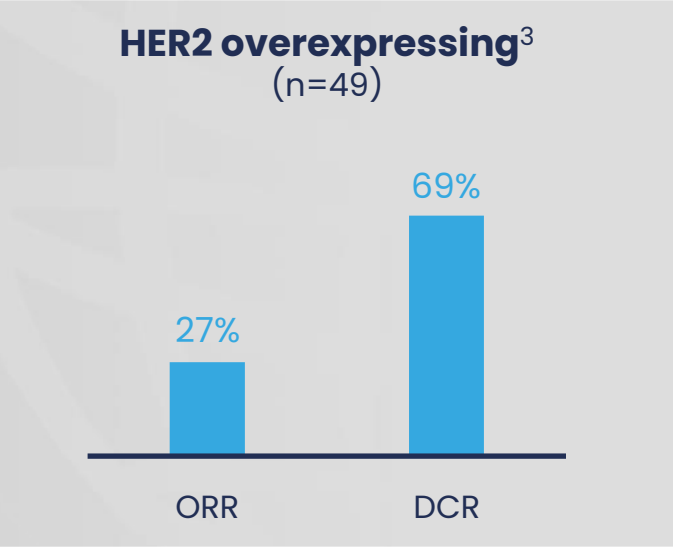
Refining patient selection for ADCs

Trastuzumab deruxtecan: A biomarker-guided approach

***HER2* mutation**[1]	**1–4%** of patients with NSCLC
HER2 overexpression[1]	**2–30%** of patients with NSCLC

DESTINY-Lung01 included two patient cohorts:*
***HER2*-mutant** metastatic NSCLC[2] and **HER2-overexpressing** metastatic NSCLC†[3]





Trastuzumab deruxtecan approved dose: 5.4 mg/kg[4,5] (ORR: 49.0%[6])

Direct comparisons between trials should not be made due to differences in trial design.
*All patients received intravenous trastuzumab deruxtecan 6.4 mg/kg every 3 weeks. †HER2 overexpression defined as HER2 immunohistochemistry 3+ or 2+.
ADC, antibody–drug conjugate; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate.
1. Riudavets M, et al. *ESMO Open*. 2021;6:100260; 2. Li BT, et al. *N Engl J Med*. 2022;386:241–51; 3. Smit, EF, et al. Presented at: ESMO Congress 2022, Paris, France. 9–13 September 2022. Poster 975P; 4. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3ONmHYa (accessed 27 November 2023); 5. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/3MMPBVK (accessed 27 November 2023); 6. Goto K, et al. *J Clin Oncol*. 2023;41:4852–63.

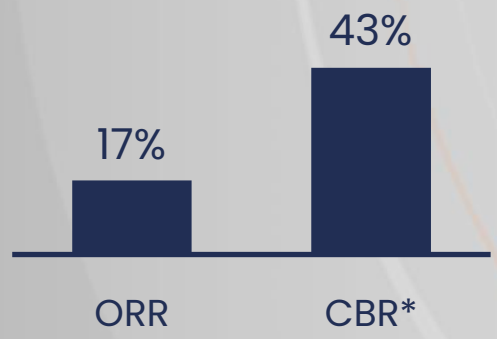
Refining patient selection for ADCs

Sacituzumab govitecan: A biomarker-agnostic approach

High TROP2 expression[1]

- **NSCLC adenocarcinoma: 64%**
- **NSCLC squamous cell carcinoma: 75%**

IMMU-132-01 trial: No preselection for TROP2 expression[2]
(N=54)



No correlation between patient outcomes and TROP2 expression[2]

Utility of TROP2 as a biomarker for sacituzumab govitecan treatment patient selection doubtful due to the **high expression of TROP2 in most epithelial cancers**[2]

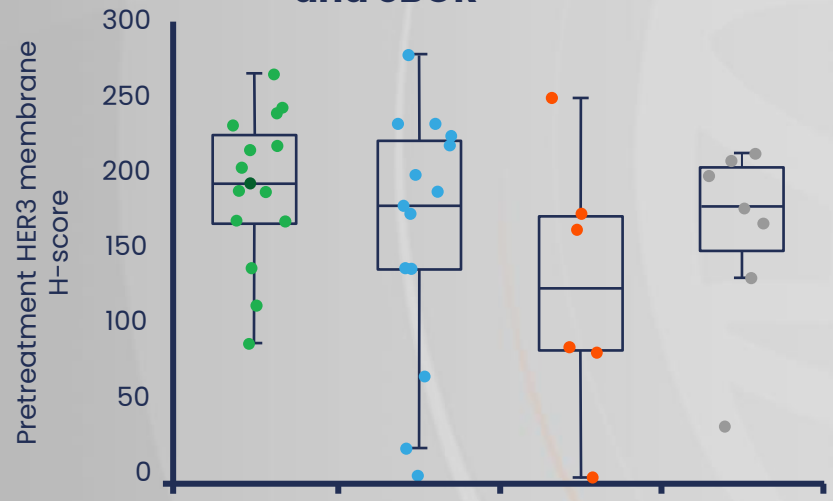
*CBR is defined as partial response plus stable disease ≥4 months.
ADC, antibody–drug conjugate; CBR, clinical benefit rate; NSCLC, non-small cell carcinoma; ORR, objective response rate; TROP2, trophoblast cell surface antigen.
1. Parisi C, et al. *Cancer Treat Rev*. 2023;118:102572; 2. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–97.

Refining patient selection for ADCs

Patritumab deruxtecan: A biomarker-agnostic approach

U31402-A-U102, a phase I dose escalation and dose expansion study[1]

Pretreatment HER3 membrane H-score* and cBOR[1]



	CR/PR	SD	PD	NE
Biomarker-evaluable patients, n	15	15	6	7
H-score, median (range)	195 (92–268)	180 (4–280)	126.5 (2–251)	180 (36–215)

- All tumour samples demonstrated HER3 expression[1]
- Confirmed responses seen across a wide range of baseline tumour HER3 membrane H-scores[1]

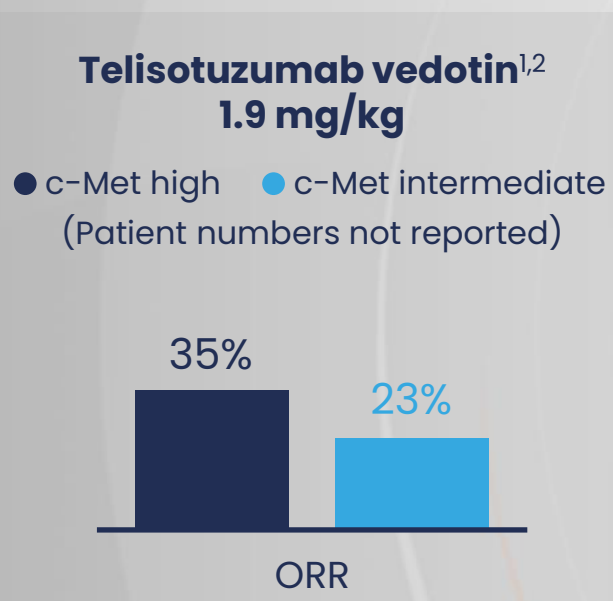
- Phase II data showed efficacy independent of HER3 expression and across diverse mechanisms of EGFR TKI resistance[2]

Figure reproduced with permission from Jänne PA, et al. *Cancer Discov.* 2022;12:1598.
*HER3 membrane expression was assessed by immunohistochemistry in pretreatment tumour samples.[1]
ADC, antibody–drug conjugate; BICR, blinded independent central review; cBOR, confirmed best overall response; CR, complete response; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
1. Jänne PA, et al. *Cancer Discov*. 2022;12:1598; 2. Yu HA, et al. *Future Oncol.* 2023;19:1319–29.

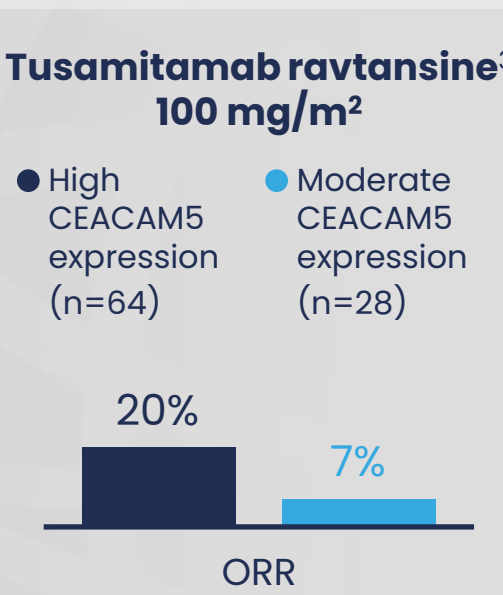
Refining patient selection for ADCs

Other targeted ADCs: Evidence for a biomarker approach

Telisotuzumab vedotin[1,2] 1.9 mg/kg



Tusamitamab ravtansine[3] 100 mg/m²

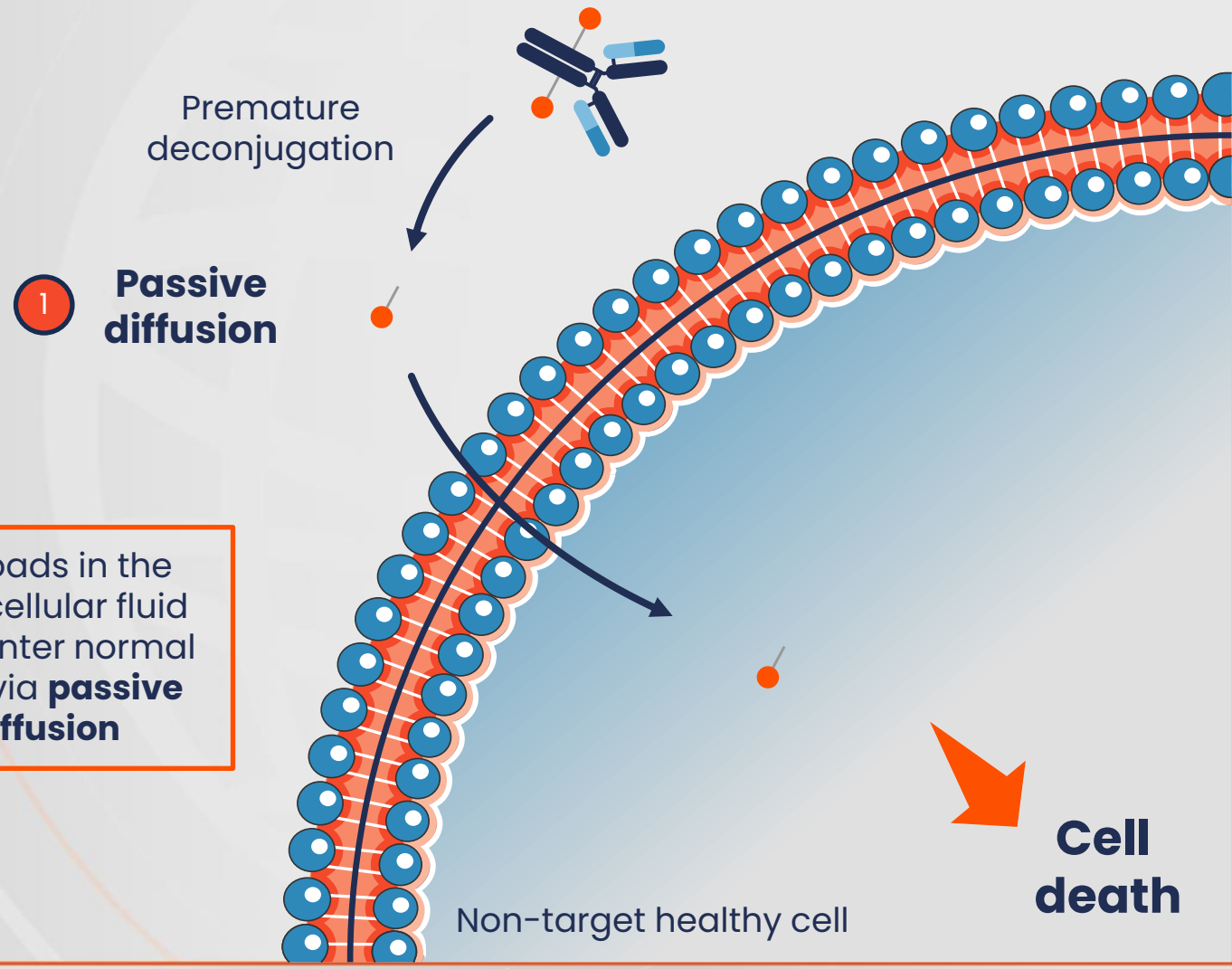


Evidence shows a greater clinical benefit with telisotuzumab vedotin and tusamitamab ravtansine in patients with high c-Met and CEACAM5 expression, respectively, than those with moderate expression,[1–3] indicating patient selection through a biomarker approach

c-Met and CEACAM5 expression assessed by immunohistochemistry.[2,3]
ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal-epithelial transition factor; ORR, objective response rate.
1. Data on file. November 2023. Available at: https://bit.ly/3RILwWo (accessed 8 December 2023); 2. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl. 16):9016;
3. Gazzah A, et al. *J Clin Oncol.* 2020;38:9505.

Mechanisms of ADC toxicity

Payload-mediated off-target mechanisms drive the majority of ADC toxicities



ADC, antibody–drug conjugate.

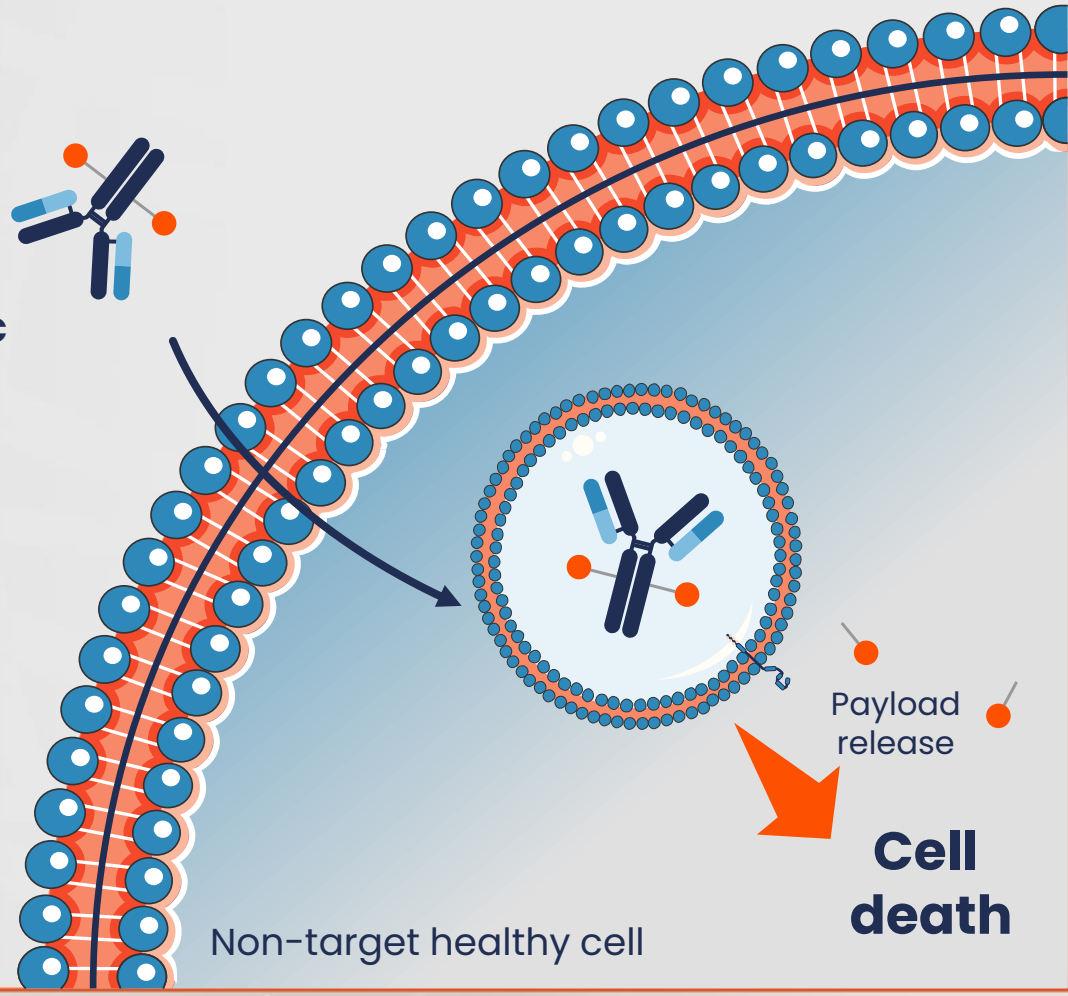
Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

Mechanisms of ADC toxicity

Payload-mediated off-target mechanisms drive the majority of ADC toxicities

2 **Non-specific endocytosis**

Non-specific endocytosis of intact ADC may also contribute to **off-site delivery** of payload



ADC, antibody–drug conjugate.

Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

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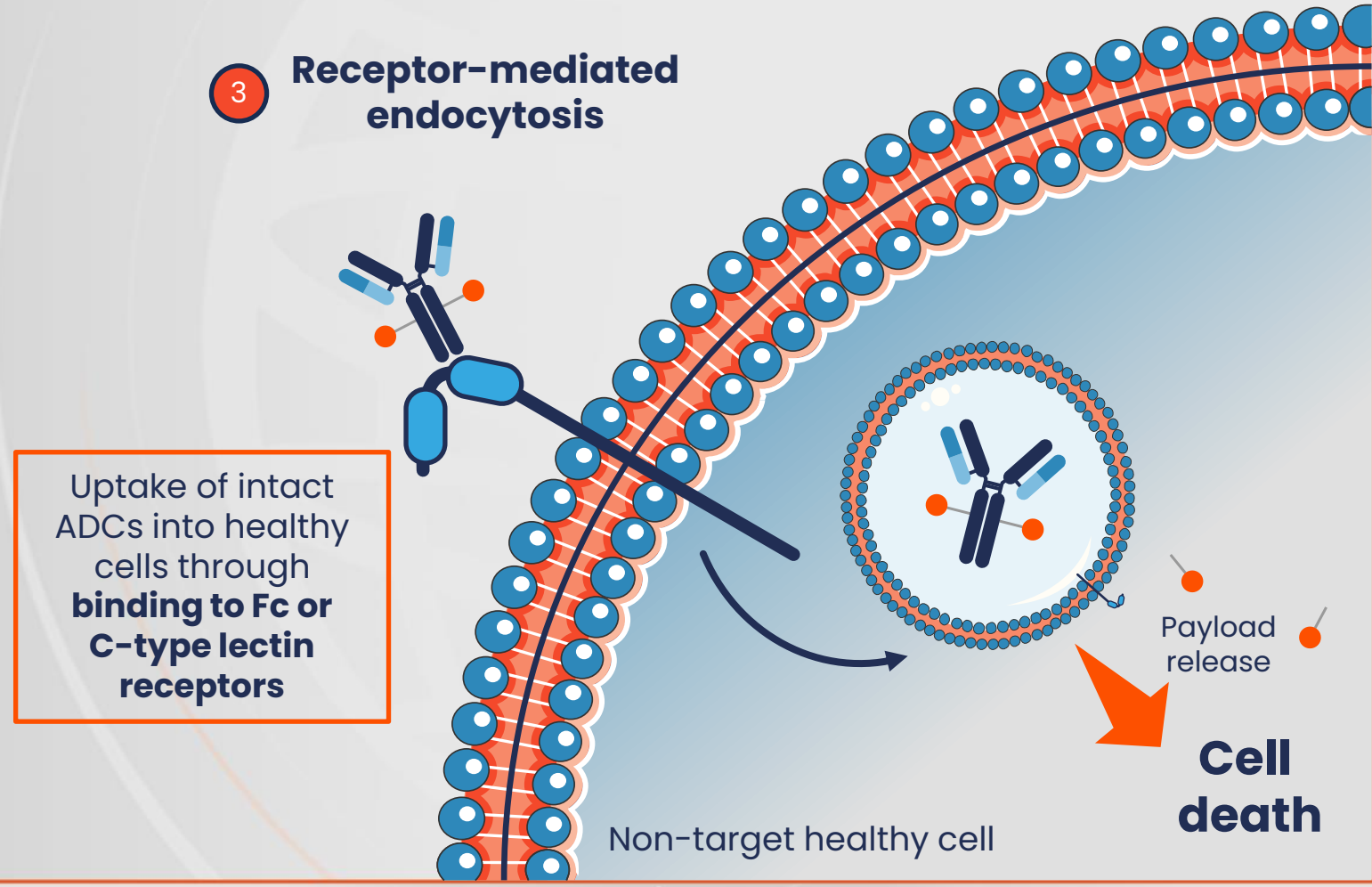
Mechanisms of ADC toxicity

Payload-mediated off-target mechanisms drive the majority of ADC toxicities



ADC, antibody–drug conjugate.

Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

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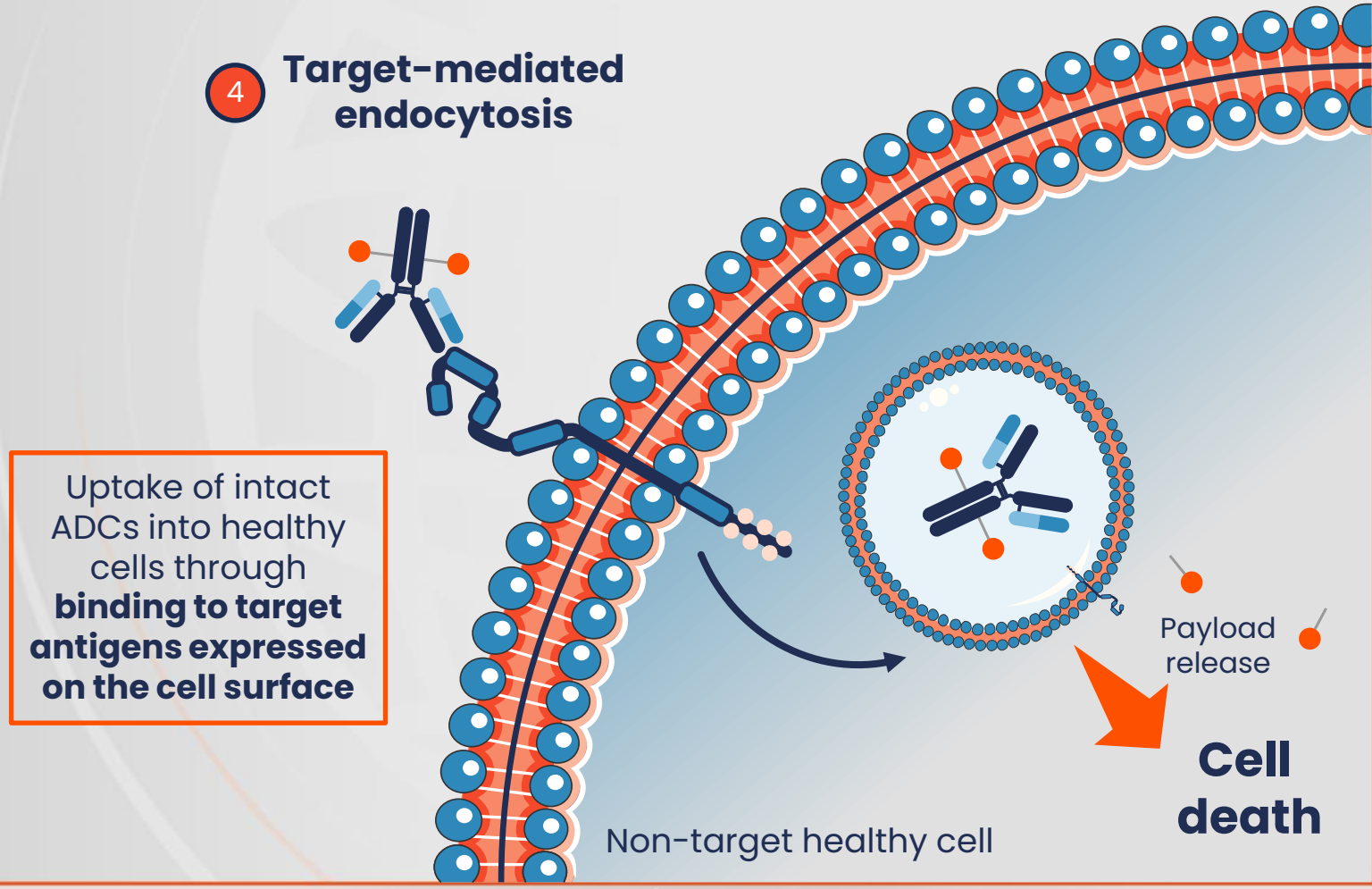
Mechanisms of ADC toxicity

Binding of ADCs to target antigens expressed in healthy tissues could also lead to significant toxicities



ADC, antibody–drug conjugate.

Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

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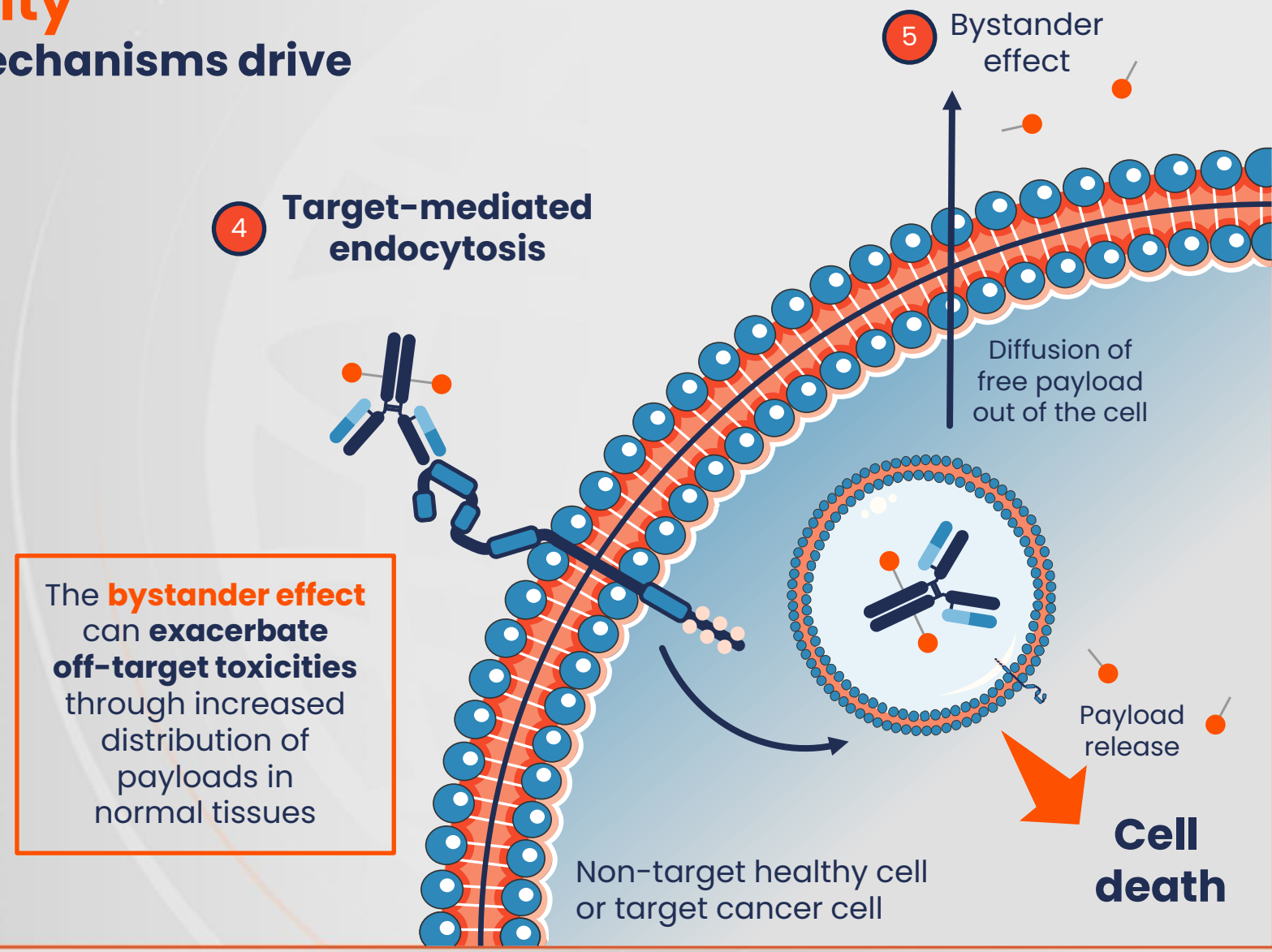
Mechanisms of ADC toxicity

Payload-mediated off-target mechanisms drive the majority of ADC toxicities



The **bystander effect** can **exacerbate off-target toxicities** through increased distribution of payloads in normal tissues

ADC, antibody–drug conjugate.

Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

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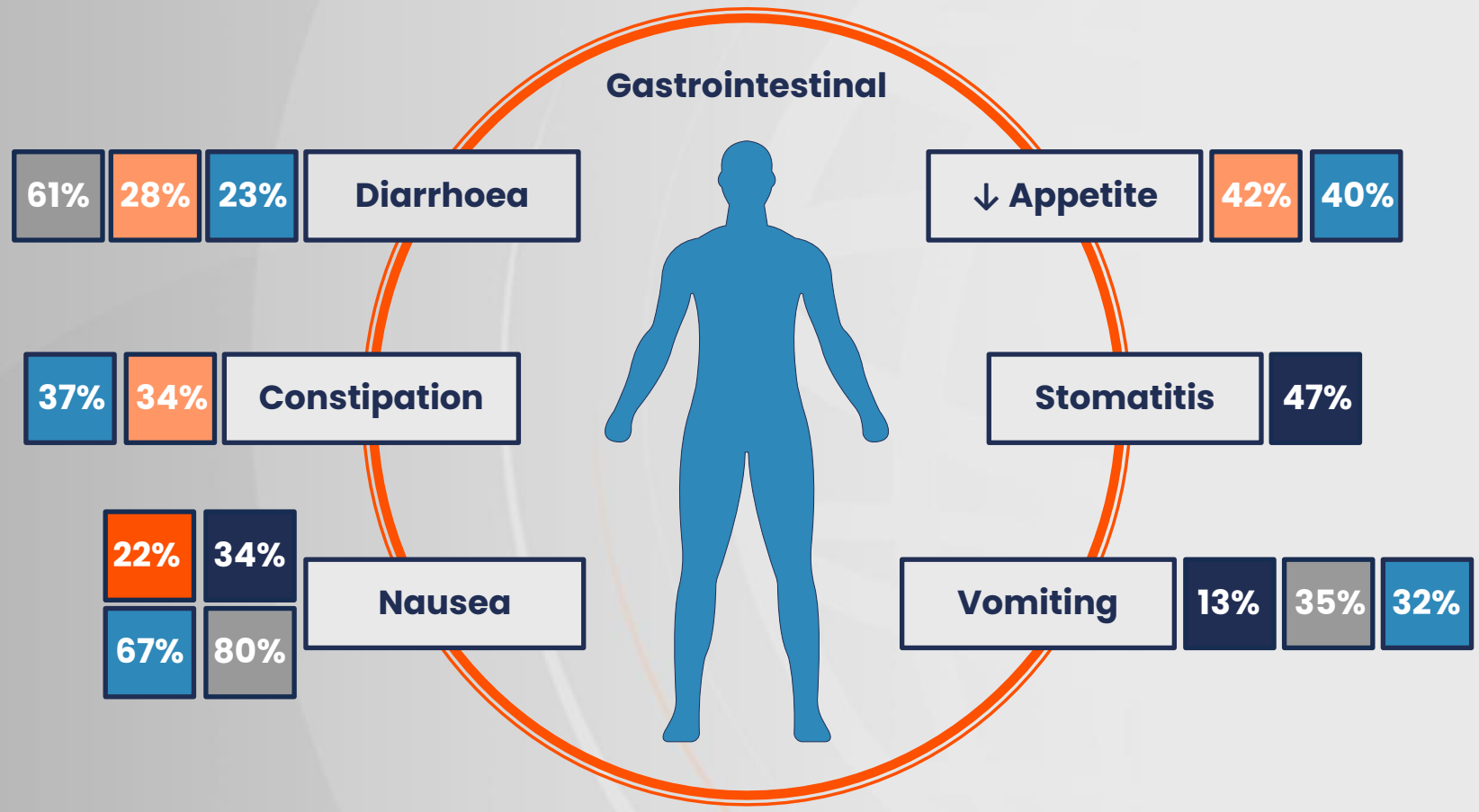
Common adverse events reported with ADCs

Most common any-grade AEs



Direct comparisons between trials should not be made due to differences in trial design.

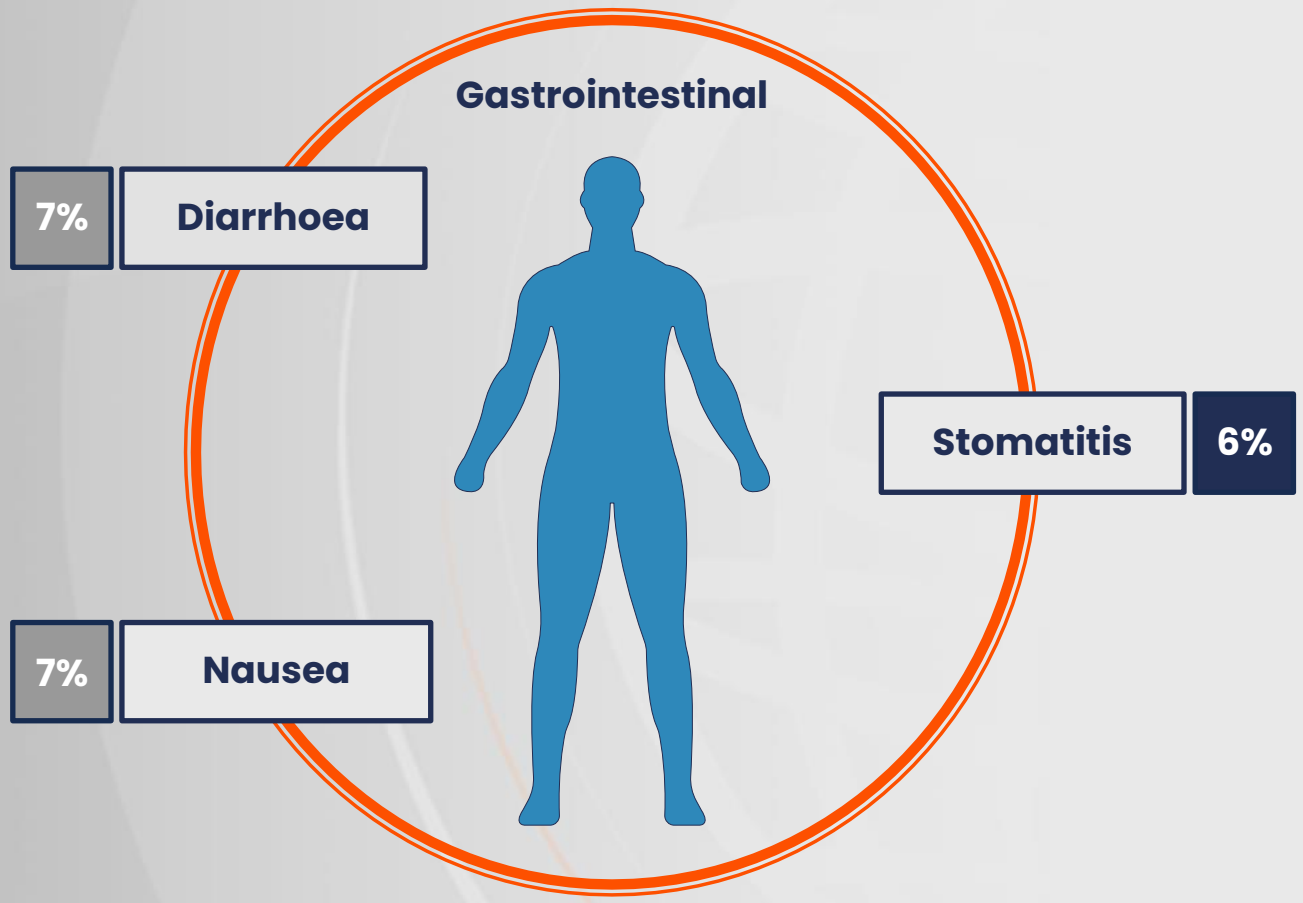
*AEs regardless of causality. †Adverse events for trastuzumab deruxtecan are for 5.4 mg/kg once every 3 weeks dose. ‡Treatment-emergent AEs. §Drug-related AEs.

ADC, antibody–drug conjugate; AE, adverse event.

1. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7; 2. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl. 16):9016; 3. Goto K, et al. *J Clin Oncol.* 2023;41:4852–63; 4. Yu HA, et al. *J Clin Oncol.* 2023;JCO2301476; 5. Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Common adverse events reported with ADCs

Grade ≥3 AEs with >5% incidence



Sacituzumab govitecan*	Telisotuzumab vedotin	Trastuzumab deruxtecan†‡	Patritumab deruxtecan‡	Datopotamab deruxtecan§
(N=54)[1]	(N=122)[2]	(n=101)[3]	(n=225)[4]	(n=297)[5]

Direct comparisons between trials should not be made due to differences in trial design.

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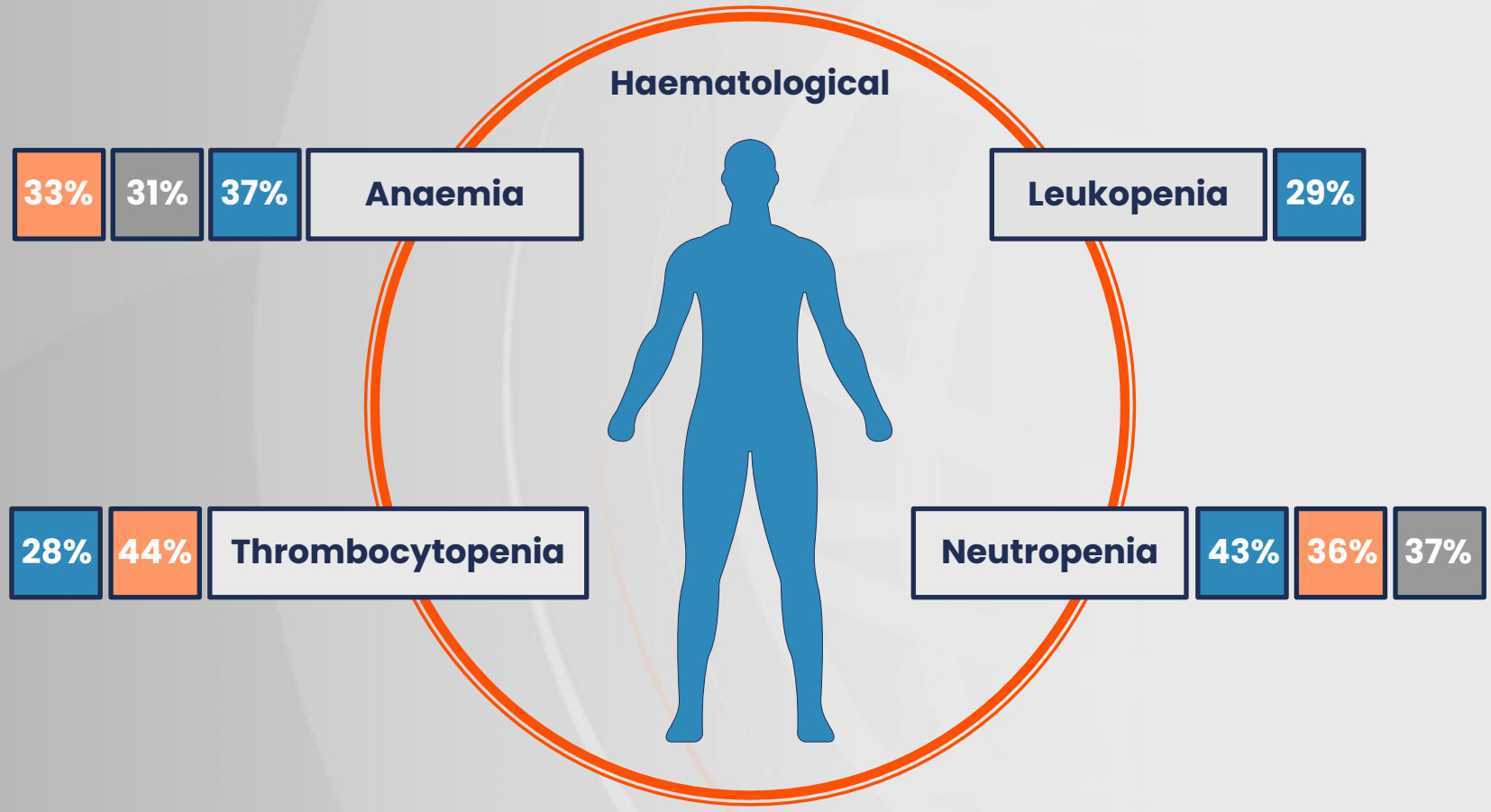
ADC, antibody–drug conjugate; AE, adverse event.

1. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7; 2. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl. 16):9016; 3. Goto K, et al. *J Clin Oncol.* 2023;41:4852–63; 4. Yu HA, et al. *J Clin Oncol.* 2023;JCO2301476; 5. Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12.

Common adverse events reported with ADCs

Most common any-grade AEs



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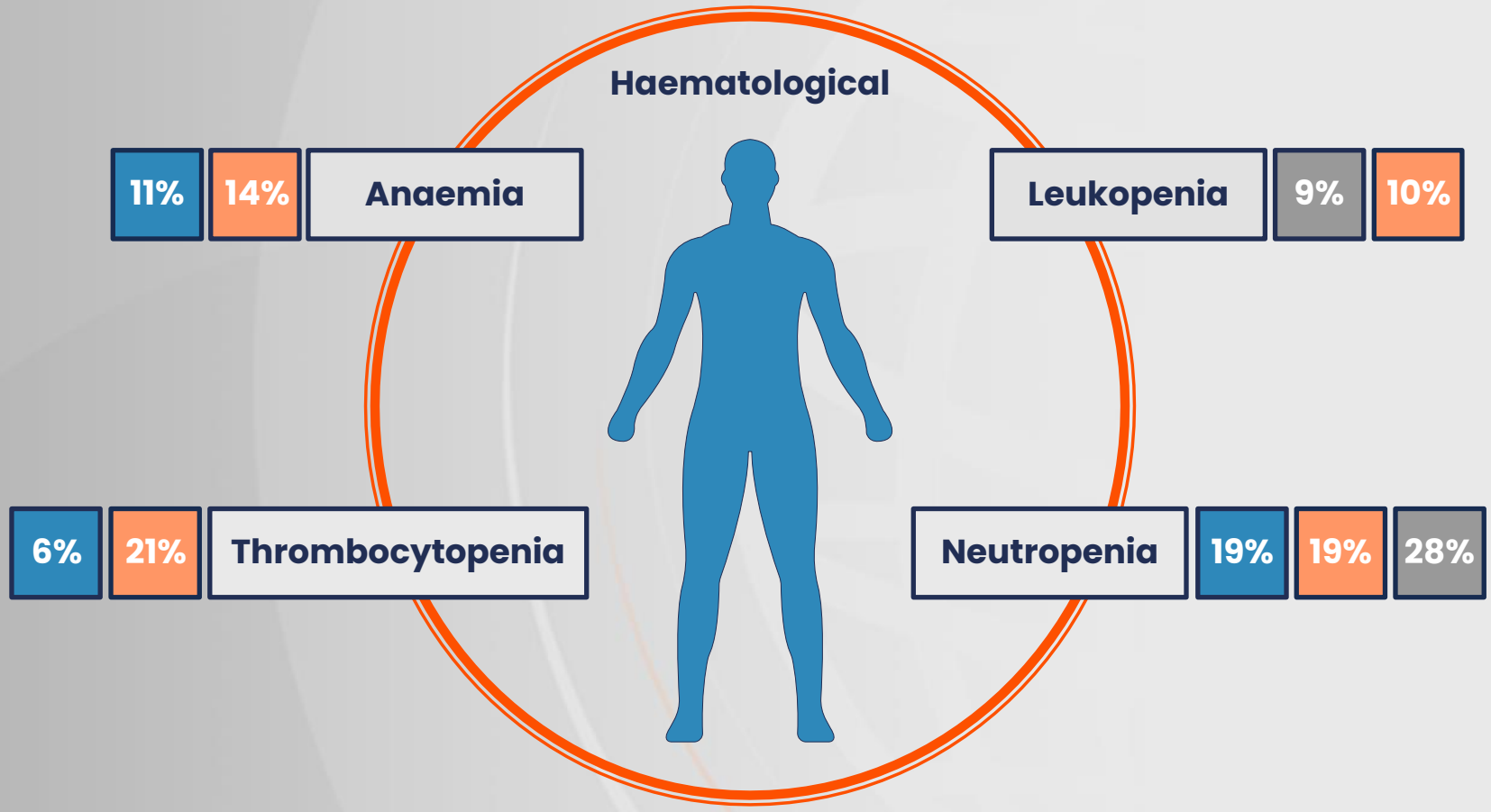

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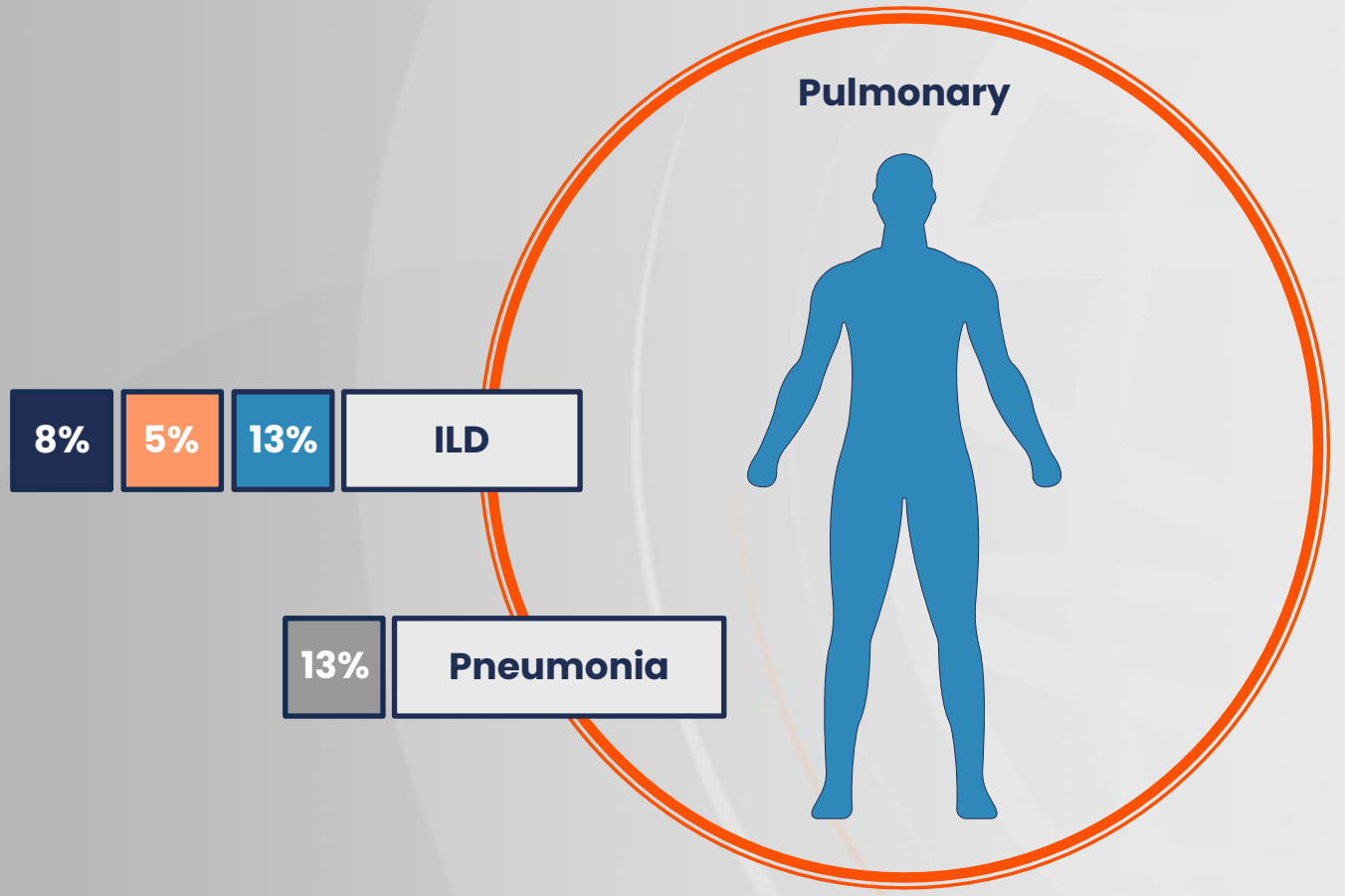

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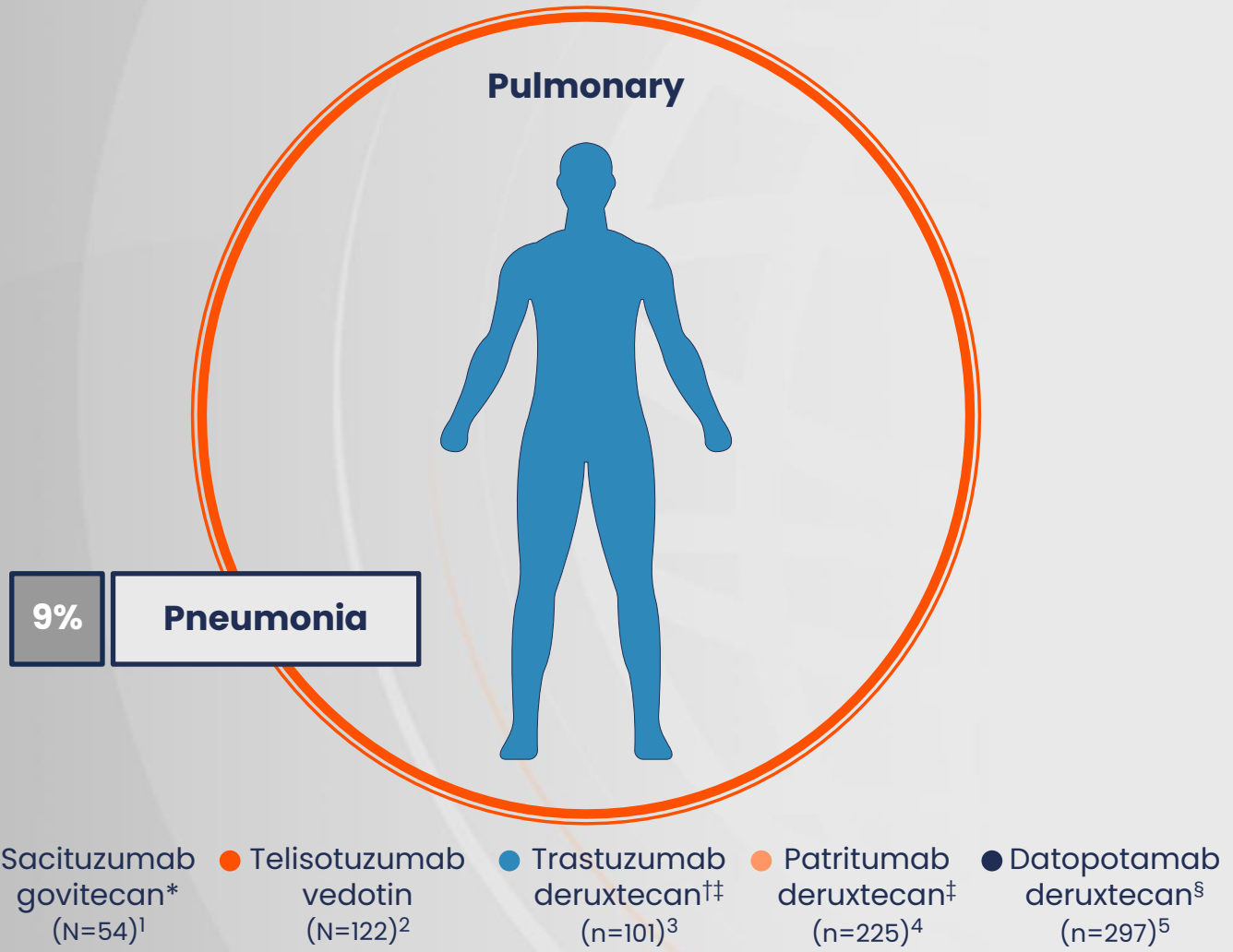

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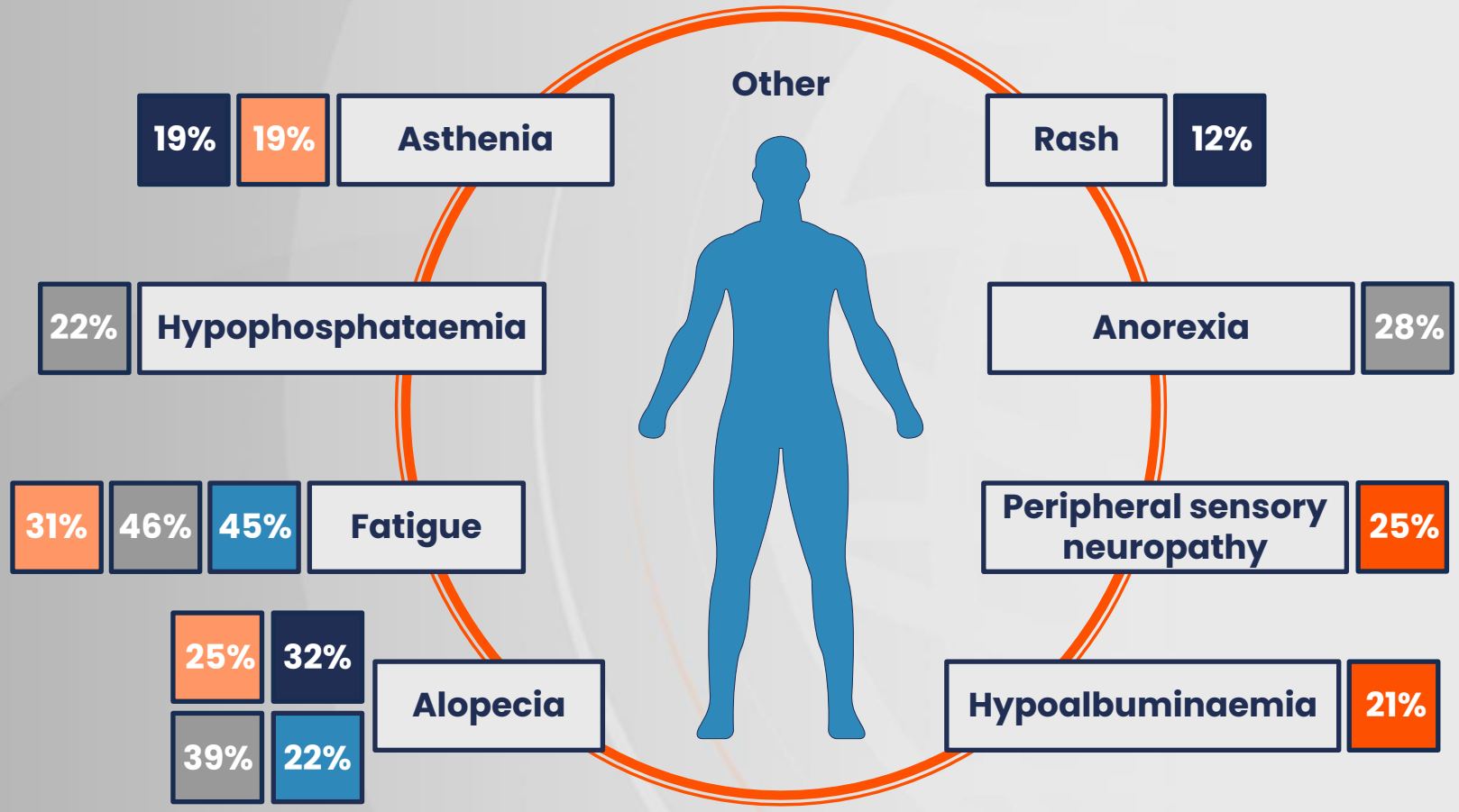

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Common adverse events reported with ADCs

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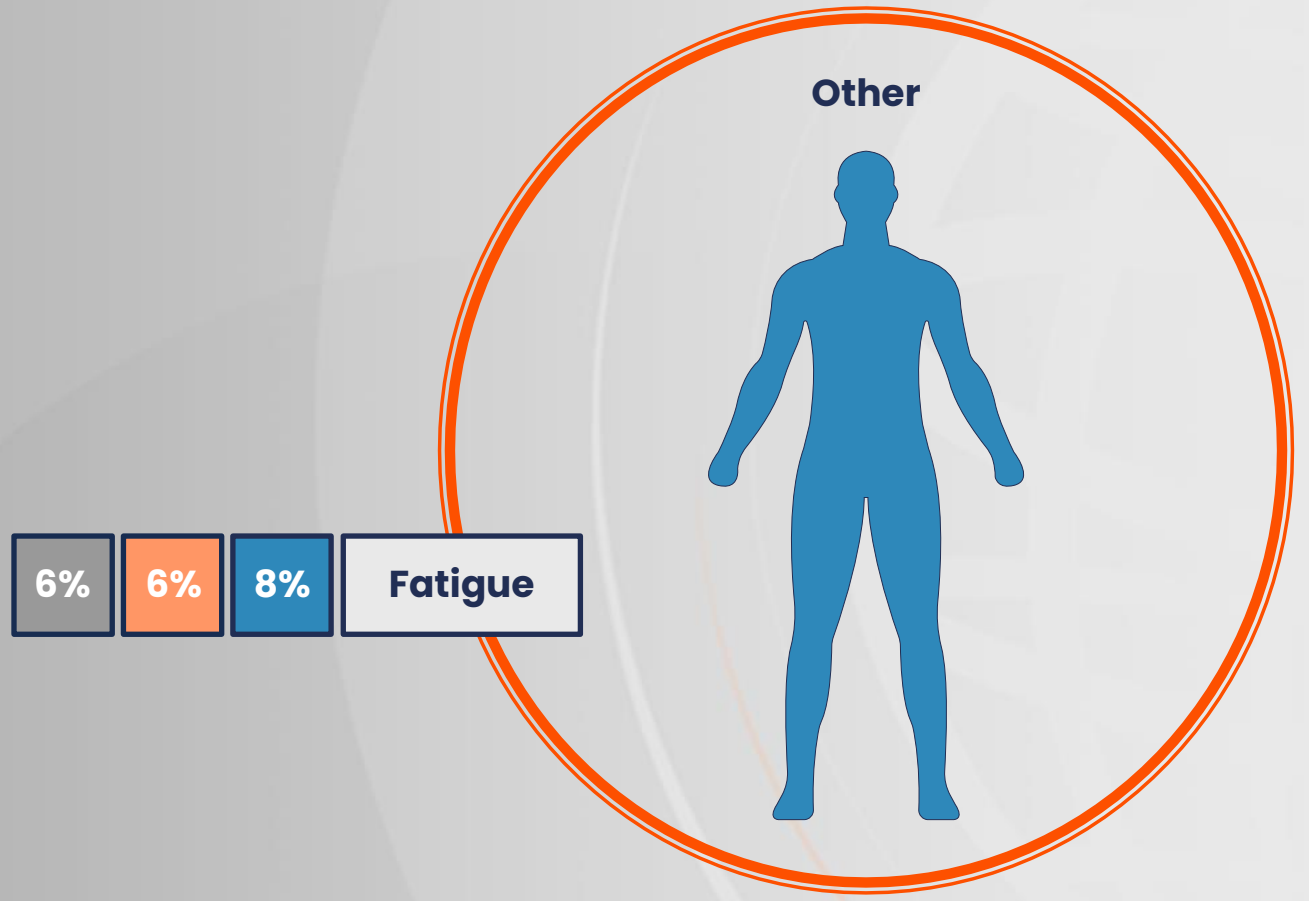

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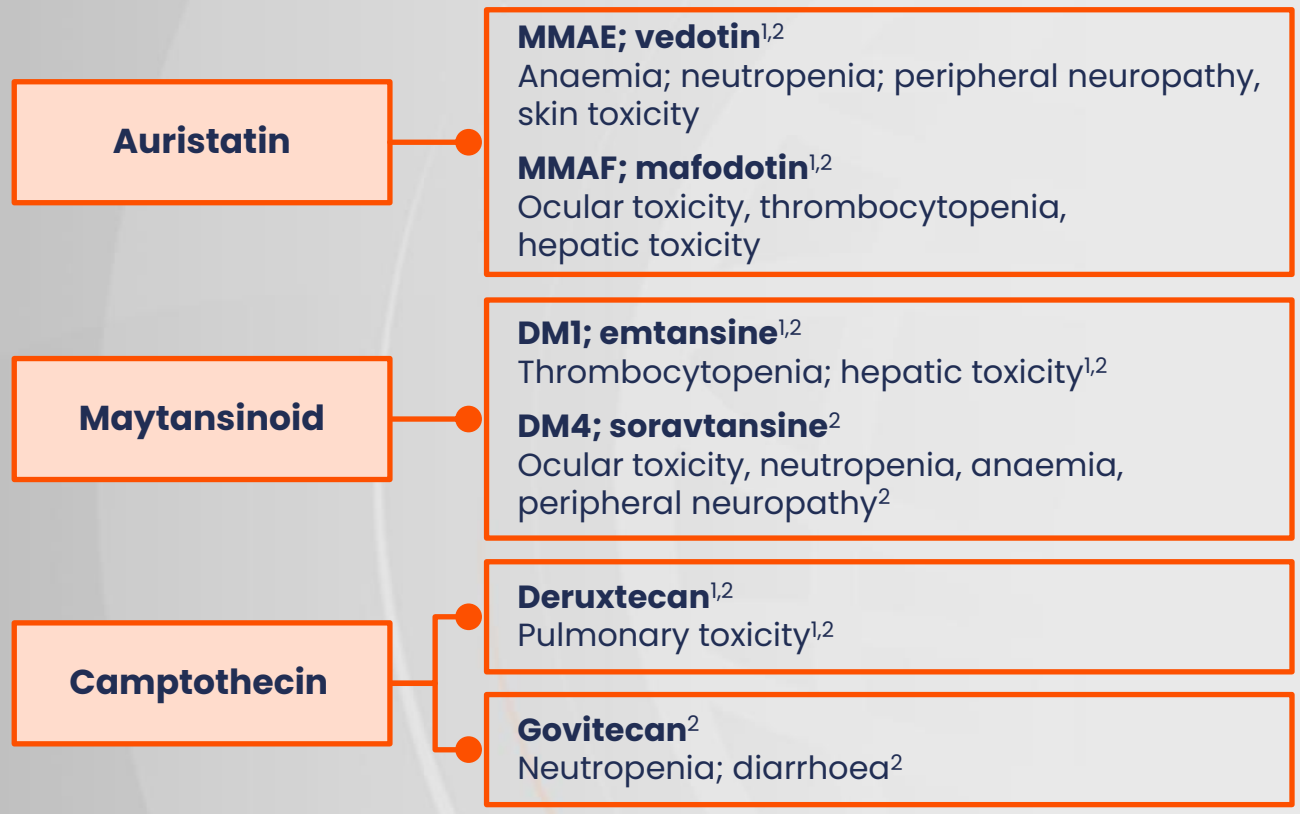
Potential class effects irrespective of antigen target



Toxicities are not always predictable

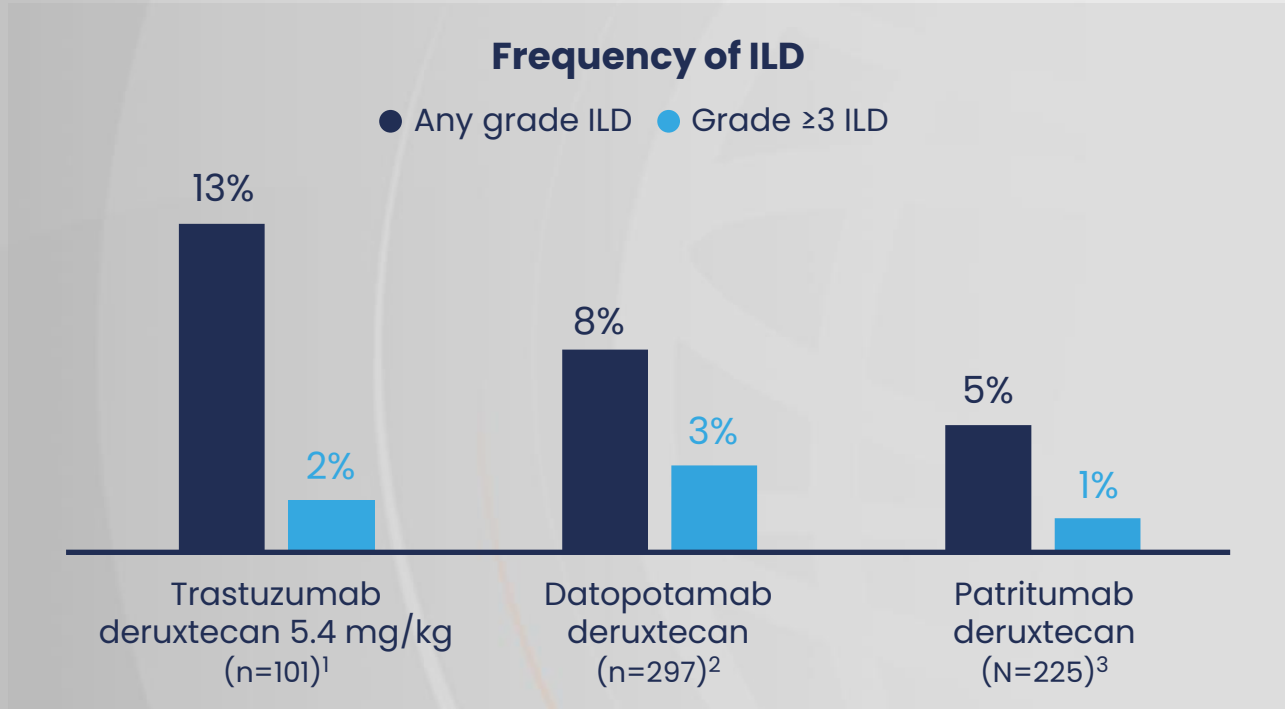
Two ADCs with the same payload, linker and similar DARs can have different toxicity profiles, and two ADCs with different payloads can cause the same toxicity[1]

ADC, antibody–drug conjugate; DAR, drug-to-antibody ratio; DM1, mertansine; DM4, ravtansine; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

1. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5; 2. Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713.

ADC-associated ILD

Reported events from phase II / III trials



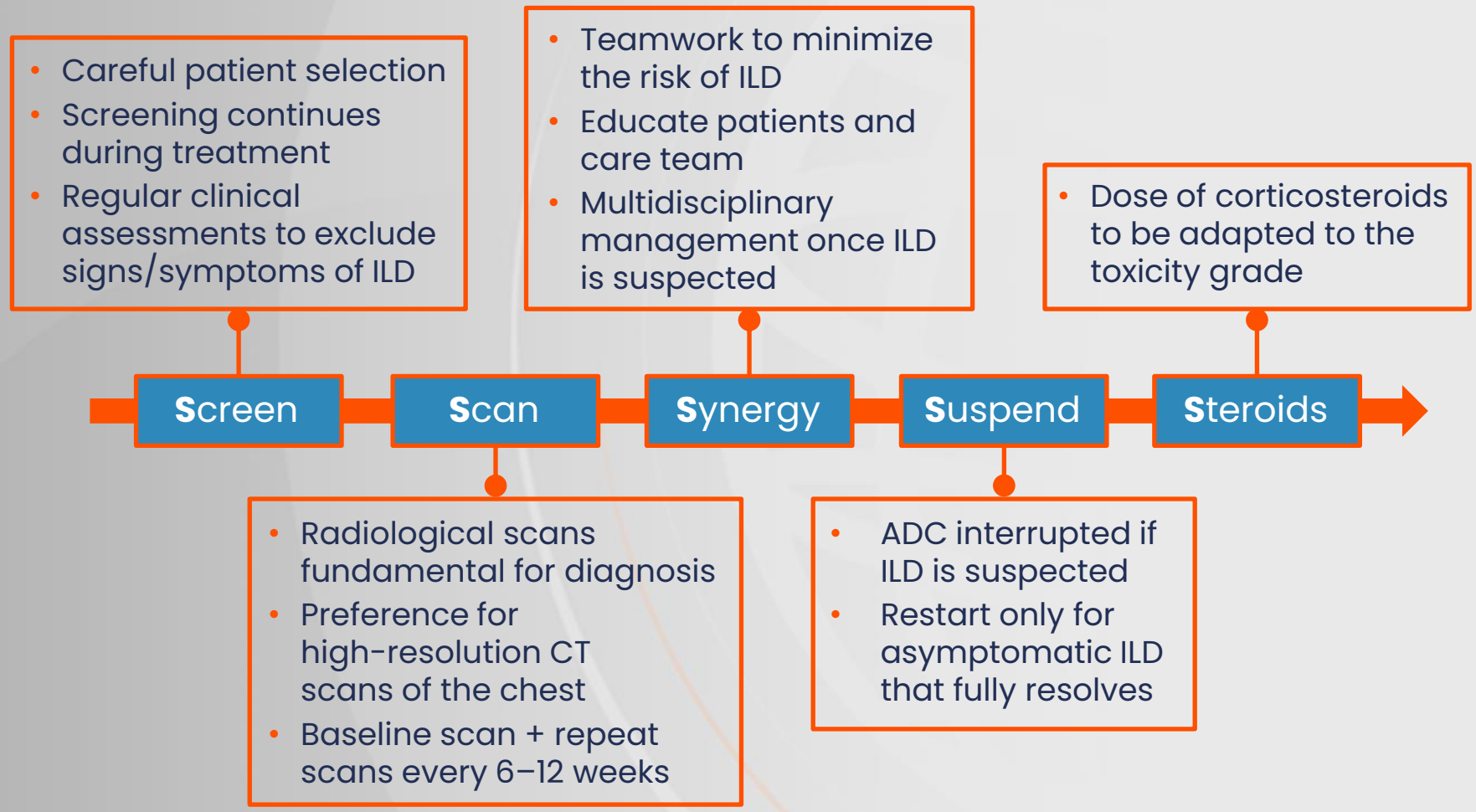
Consideration of toxicity profiles of ADCs is required, along with the use of strategies to minimize risk and impact of ILD[4]

Direct comparisons between trials should not be made due to differences in trial design.

ADC, antibody–drug conjugate; ILD, interstitial lung disease.

1. Goto K, et al. *J Clin Oncol.* 2023;41:4852–63; 2. Ahn MJ, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Presentation LBA12; 3. Yu HA, et al. *J Clin Oncol.* 2023;JCO2301476; 4. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5.

Steps to minimize risk and impact of ILD



ADC, antibody–drug conjugate; CT, computed tomography; ILD, interstitial lung disease.
Tarantino P, Tolaney SM. *JCO Oncol Pract.* 2023;19:526–7.

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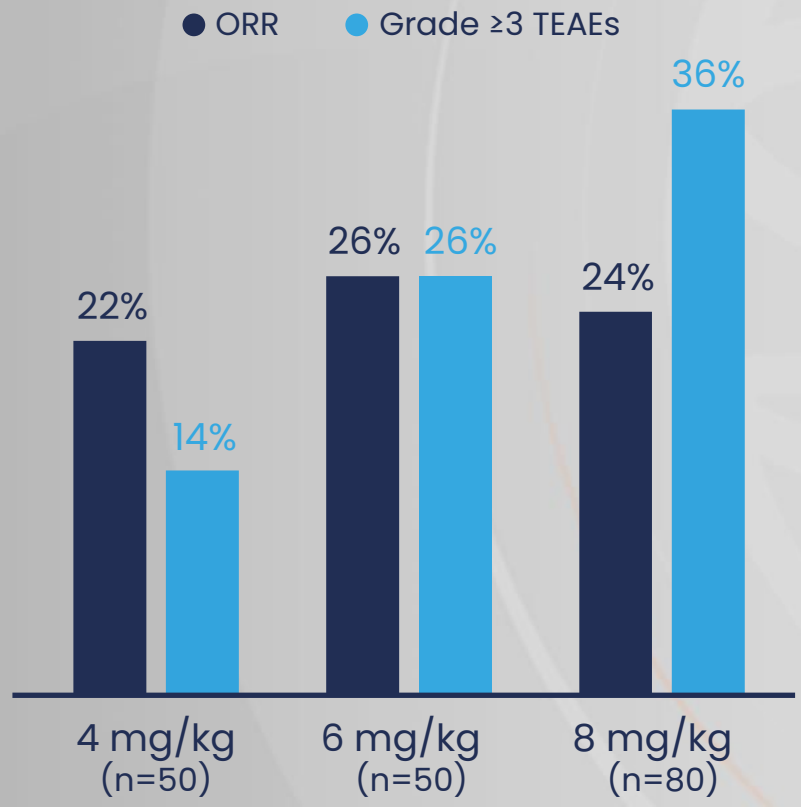
Dose-optimization strategies

Balancing efficacy with safety and quality of life

Response rates vs incidence of TEAEs at varying doses of trastuzumab deruxtecan (TROPION-PanTumour01)



- **TEAEs associated with discontinuation:**
  4 mg/kg = 16%
  6 mg/kg = 14%
  8 mg/kg = 24%
- **TEAEs associated with dose reduction:**
  4 mg/kg = 2%
  6 mg/kg = 10%
  8 mg/kg = 28%

6 mg/kg determined to have the optimal benefit–risk ratio

ORR, objective response rate; TEAE, treatment-emergent adverse event.
Shimizu T, et al. *J Clin Oncol.* 2023;41:4678–87.

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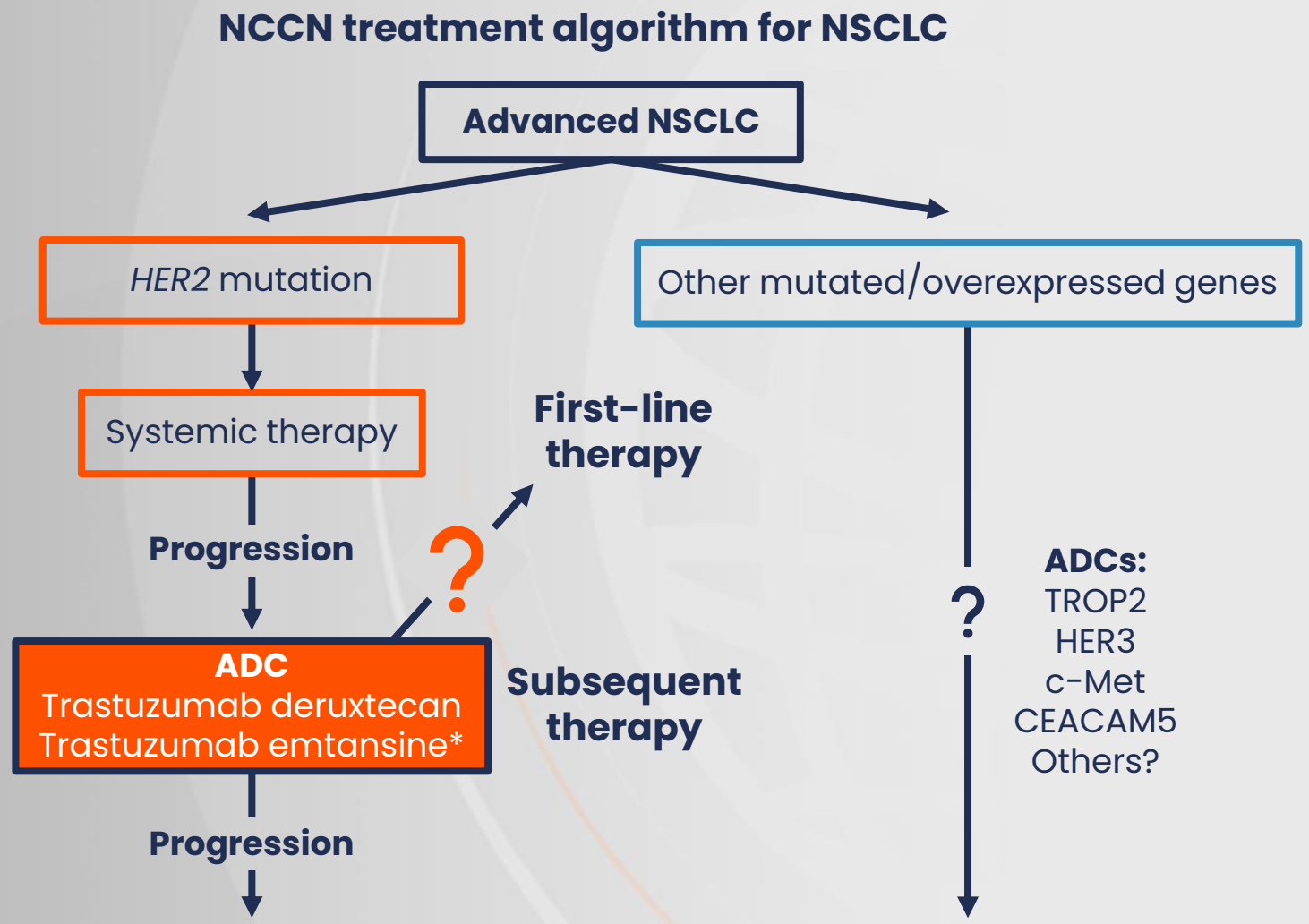
Future considerations for ADCs in NSCLC



*NCCN recommended but not FDA approved.
ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal epithelial transition factor; FDA, US Food and Drug Administration; HER2/3, human epidermal growth factor receptor 2/3; NCCN, National Comprehensive Cancer Network®; NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen.

NCCN. Non-small cell lung cancer. V5.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 28 November 2023).

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Future considerations for ADCs in NSCLC

First-line approaches

Trial / Phase	Treatment arms	Patient population	Primary endpoint
TROPION-Lung04 NCT04612751 Phase I[1]	Datopotomab deruxtecan + immunotherapy ± carboplatin	Advanced/metastatic NSCLC	**DLT**
EVOKE-02 NCT05186974 Phase II[2]	Sacituzumab govitecan + pembrolizumab ± Pt-ChT	Advanced/metastatic NSCLC	**ORR, DLT**
EVOKE-03 NCT05609968 Phase III[3]	Sacituzumab govitecan + pembrolizumab vs pembrolizumab	Metastatic NSCLC with PD-L1 TPS ≥50%	**PFS, OS**
DESTINY-Lung04 NCT05048797 Phase III[4]	Trastuzumab deruxtecan vs SoC (Pt-ChT + pembrolizumab + pemetrexed)	Locally advanced/metastatic non-squamous NSCLC with *HER2* mutation in exons 19 or 20	**PFS**

Multiple other clinical trials of ADCs in the first-line setting are ongoing

ADC, antibody–drug conjugate; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pt-ChT, platinum-based chemotherapy; SoC, standard of care; TPS, tumour proportion score.

1. ClinicalTrials.gov. NCT04612751; 2. ClinicalTrials.gov. NCT05186974; 3. ClinicalTrials.gov. NCT05609968; 4. ClinicalTrials.gov. NCT05048797.
All clinical trials searchable by NCT number. Available at: https://beta.clinicaltrials.gov/ (accessed 28 November 2023).

Summary

ADCs can be selected for using both biomarker-guided[1,2] and a biomarker-agnostic approaches,[3,4] depending on the ADC

There are multiple mechanisms of off-target ADC uptake that are thought to drive the majority of ADC toxicities[5]

Toxicities are not always predictable – similar ADCs can have different toxicity profiles[6]

The *5 S's* can help to minimize the risk and impact of ILD[7]

The role of ADCs is rapidly evolving in the second-line setting and are in trial in the first-line setting[8–11]

ADC, antibody–drug conjugate; ILD, interstitial lung disease.

1. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3ONmHYa (accessed 27 November 2023); 2. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/3MMPBVK (accessed 27 November 2023); 3. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–97; 4. Jänne PA, et al. *Cancer Discov*. 2022;12:1598; 5. Nguyen TD, et al. *Cancers (Basel)*. 2023;15:713; 6. Coleman N, et al. *NPJ Precis Oncol.* 2023;7:5; 7. Tarantino P, Tolaney SM. *JCO Oncol Pract.* 2023;19:526–7; 8. ClinicalTrials.gov. NCT04612751; 9. ClinicalTrials.gov. NCT05186974; 10. ClinicalTrials.gov. NCT05609968; 11. ClinicalTrials.gov. NCT05048797. All clinical trials searchable by NCT number. Available at: https://beta.clinicaltrials.gov/ (accessed 28 November 2023).