Navigating the complexities of the NSCLC treatment pathway: A focus on antibody-drug conjugates

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Expert panel

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Agenda

ADCs: An emerging therapeutic class in advanced NSCLC

ADCs in advanced NSCLC: A look into their impact and efficacy

ADCs in advanced NSCLC: Considerations for safe and effective administration

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

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Antibody-drug conjugates: An emerging therapeutic class in advanced NSCLC

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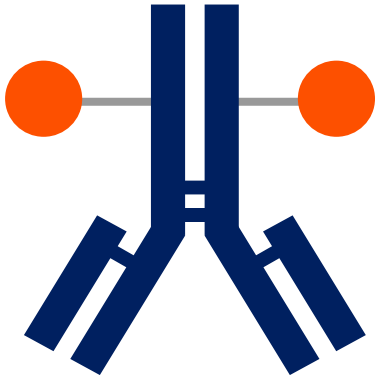
ADC structure



Key components:

- Antibody
- Linker
- Cytotoxic agent/payload

ADCs differ in:

- The antigen that they target
- The type of payload
- Drug–antibody ratio (DAR)
- The biochemistry/structure of the antibody and linker
- ADC–cell binding levels and internalization rates

ADC, antibody-drug conjugate.

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

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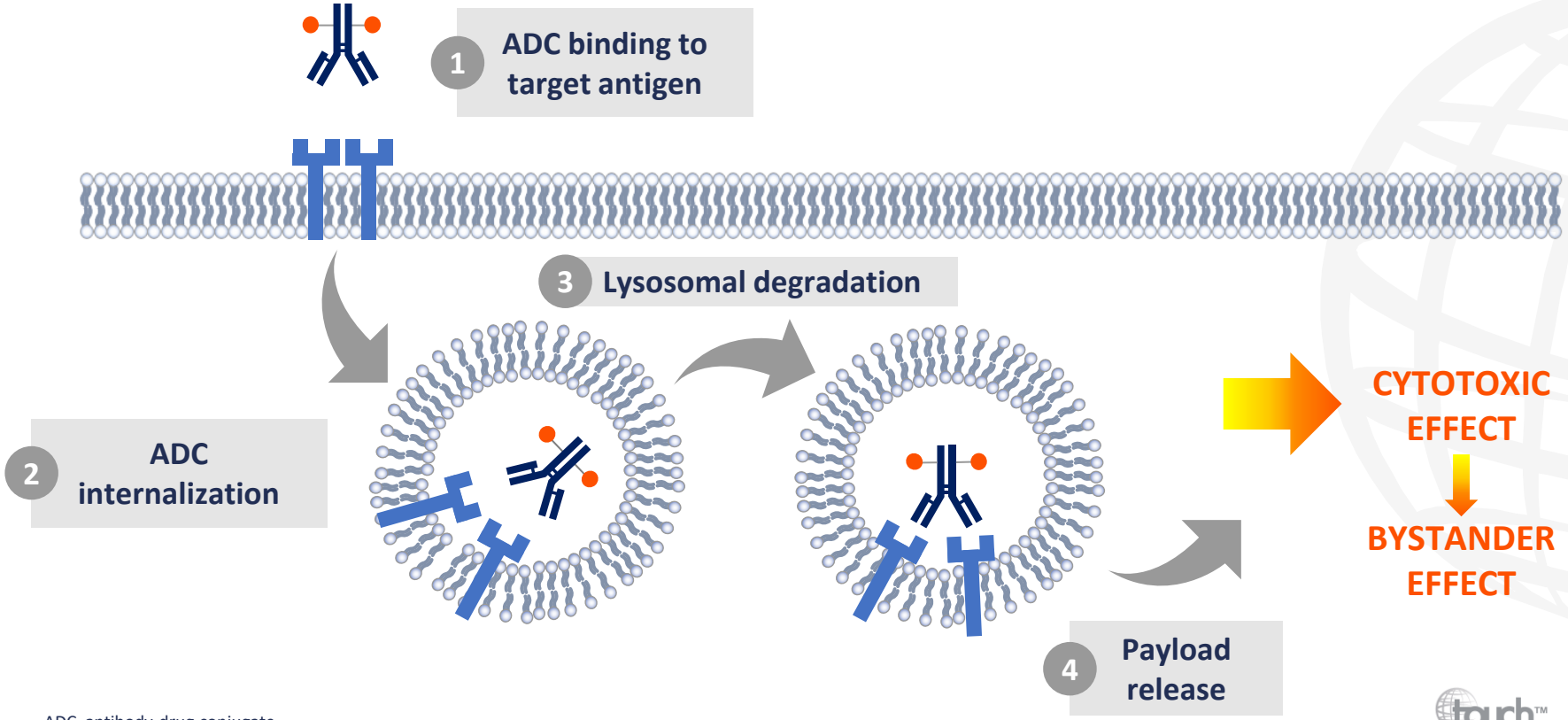
ADC mechanism of action



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

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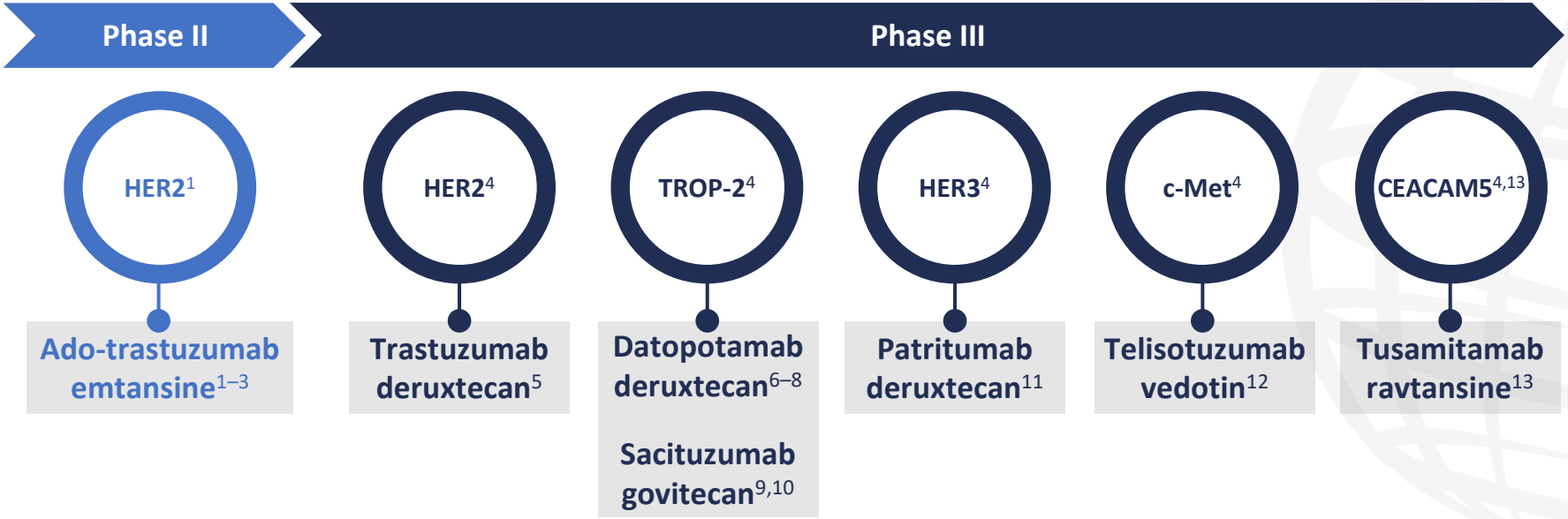
The ADCs in development target different antigens



ADC, antibody-drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, c-mesenchymal-epithelial transition factor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; TROP-2, trophoblast cell-surface antigen 2.

1. Hotta K, et al. *J Thorac Oncol.* 2018;13:273–9; 2. Peters S, et al. *Clin Cancer Res.* 2019;25:64–72; 3. Li BT, et al. *J Clin Oncol.* 2018;36:2532–7; 4. Desai A, et al. *Lung Cancer.* 2022;163:96–106; 5. ClinicalTrials.gov. NCT05048797; 6. ClinicalTrials.gov. NCT05215340; 7. ClinicalTrials.gov. NCT04656652; 8. ClinicalTrials.gov. NCT05555732; 9. ClinicalTrials.gov. NCT05609968; 10. ClinicalTrials.gov. NCT05089734; 11. ClinicalTrials.gov. NCT05338970; 12. ClinicalTrials.gov. NCT04928846; 13. ClinicalTrials.gov. NCT04154956. All clinical trials searchable by NCT number. Available at: https://beta.clinicaltrials.gov/ (accessed 14 December 2022).

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Use of biomarker testing to guide treatment decisions

Some ADCs require preselection through biomarker testing, while others can be used regardless of genetic mutation or protein expression pattern

HER2

Ado-trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan

Selection: Patients with *HER2* mutation-positive unresectable or metastatic NSCLC[1–4]

- *HER2* mutations present in ~**3%** of patients with metastatic or recurrent **lung adenocarcinomas**[1,5]
- In clinical trials, patients with *HER2*-mutant NSCLC have shown response rates of **50%** (ado-trastuzumab emtansine) and **62%** (trastuzumab deruxtecan)[6]

TROP-2

Sacituzumab govitecan

Selection: None recommended;[7] phase III EVOKE-01 trial will not select patients based on TROP-2[8]

- High TROP-2 expression in **75%** of patients with **squamous cell lung cancer** (not associated with mortality) and **64%** of patients with **lung adenocarcinoma** (associated with higher mortality)[9]
- Clinical trial data indicate efficacy **regardless** of preselecting patients for high TROP-2 expression[10,11]

ADC, antibody-drug conjugate; *HER2*, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TROP-2, trophoblast cell-surface antigen 2.
1. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 2. Li BT, et al. *J Clin Oncol.* 2018;36:2532–7; 3. National Comprehensive Cancer Network. 2022. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 21 December 2022); 4. FDA. Trastuzumab deruxtecan PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf (accessed 13 January 2023); 5. Pillai RN, et al. *Cancer.* 2017;123:4099–105; 6. Riudavets M, et al. *ESMO Open.* 2021;6:100260; 7. Bardia A, et al. *Ann Oncol.* 2021;32:746–56; 8. Garassino MC, et al. *J Clin Oncol.* 2022;40(Suppl.):TPS9149; 9. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 10. Starodub AN, et al. *Clin Cancer Res.* 2015;21:3870–8; 11. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7.

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ADCs in advanced NSCLC: A look into their impact and efficacy

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Response to ADCs in previously-treated patients

ADC	Trastuzumab deruxtecan[1]	Datopotamab deruxtecan[3]	Sacituzumab govitecan[5,6]	Patritumab deruxtecan[8]	Telisotuzumab vedotin[11]
Study	**DESTINY-Lung01** Phase II, NCT03505710	**TROPION-PanTumor01** Phase I, NCT03401385	**IMMU-132-01** Phase I/II, NCT01631552[5,6]	**U31402-A-U102** Phase I, NCT03260491	**LUMINOSITY** Phase II, NCT03539536
Patient population	Metastatic/unresectable *HER2*-mutant or HER2-overexpressing NSCLC (N=91*)	Metastatic, advanced or unresectable NSCLC unselected for TROP-2 expression (N=180)	Metastatic NSCLC unselected for TROP-2 expression (n=54†)[5,6]	Locally advanced or metastatic *EGFR*-activating mutant NSCLC (N=57)	Locally advanced or metastatic NSCLC overexpressing c-Met (N=136)
Key efficacy results	**ORR: 55%** (95% CI, 44–65) **mDOR: 9.3 months** (95% CI, 5.7–14.7) **mOS: 17.8 months** (95% CI, 13.8–22.1)	**ORR:** 4 mg/kg: 24% **6 mg/kg: 26%** 8 mg/kg: 24%	**ORR: 17%**[5] (95% CI, 7.9–29.3) **mDOR: 6.0 months**[5] (95% CI, 2.5–21.0) **mOS: 7.3 months**[5] (95% CI, 5.6–14.6)	**ORR: 39%** (95% CI, 26.0–52.4) **mDOR: 6.9 months** (95% CI, 3.1–NE) **mOS: NE** (95% CI, 9.4–NE)	**ORR: 36.5%** c-Met high: 52.2% c-Met intermediate: 24.1%
Ongoing trials	Phase III **DESTINY-Lung04** NCT05048797[2]	Dose-finding study: **6 mg/kg** dose for phase III **TROPION-Lung01**[3] NCT04656652[4]	Dose-finding study:[5] **10 mg/kg** dose for phase III **EVOKE-01** NCT05089734[7]	Phase II **HERTHENA-Lung01** NCT04619004[9] Phase III **HERTHENA-Lung02** NCT05338970[10]	Phase III NCT04928846[12]

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

*All 91 patients had a tumour with a locally reported *HER2* mutation.[1] †Patients with various tumour types included. Overall safety population N=495,[5] of whom 54 had NSCLC.[5,6]

ADC, antibody-drug conjugate; c-Met, c-mesenchymal-epithelial transition factor; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; mDOR, median duration of response; mOS, median overall survival; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP-2, trophoblast cell-surface antigen 2.

1. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 2. ClinicalTrials.gov. NCT05048797; 3. Garon EB, et al. *J Thorac Oncol.* 2021;16(Suppl.):S892–3; 4. ClinicalTrials.gov. NCT04656652; 5. Bardia A, et al. *Ann Oncol.* 2021;32:746–56; 6. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7; 7. Garassino MC, et al. *J Clin Oncol.* 2022;40(Suppl.):TPS9149; 8. Jänne PA, et al. *Cancer Discov.* 2022;12:74–89; 9. ClinicalTrials.gov. NCT04619004; 10. ClinicalTrials.gov. NCT05338970. 11. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl.):9016; 12. ClinicalTrials.gov. NCT04928846. All clinical trials searchable by NCT number. Available at: www.clinicaltrials.gov/ct2/home (4 January 2022).

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ADC combination therapy trials are ongoing

ADC	Trastuzumab deruxtecan[1]	Datopotamab deruxtecan[2,3]	Datopotamab deruxtecan[4]	Datopotamab deruxtecan[5]	Sacituzumab govitecan[6]	Patritumab deruxtecan[7]
Combined treatment	**+ durvalumab + ChT**	**+ pembrolizumab ± Pt ChT**	**+ pembrolizumab ± Pt ChT**	**+ pembrolizumab**	**+ pembrolizumab ± Pt ChT**	**+ osimertinib**
Study	**DESTINY-Lung03** Phase Ib NCT04686305	**TROPION-Lung02** Phase Ib NCT04526691	**TROPION-Lung07** Phase III NCT05555732	**TROPION-Lung08** Phase III NCT05215340	**EVOKE-02** Phase II NCT05186974	**NCT04676477** Phase I
Published results	N/A trial ongoing Expected completion: July 2025	**– ChT (n=38)**[2] • ORR: 37% • DCR: 84% **+ ChT (n=37)**[2] • ORR: 41% • DCR: 84%	N/A trial ongoing Expected primary completion date: August 2027	N/A trial ongoing Expected primary completion date: June 2026	N/A trial ongoing Expected primary completion date: May 2023	N/A trial ongoing Expected primary completion date: January 2024

ADC, antibody-drug conjugate; ChT, chemotherapy; DCR, disease control rate; N/A, not available; ORR, objective response rate; Pt, platinum-based.

ClinicalTrials.gov. NCT04686305; 2. Levy B, et al. Presented at: IASLC 2022 World Conference on Lung Cancer, Vienna, Austria. 6–9 August 2022. Abstr MA13.07; 3. ClinicalTrials.gov. NCT04526691; 4. ClinicalTrials.gov. NCT05555732; 5. ClinicalTrials.gov. NCT05215340; 6. ClinicalTrials.gov. NCT05186974; 7. ClinicalTrials.gov. NCT04676477. All clinical trials searchable by NCT number. Available at: www.clinicaltrials.gov/ct2/home (accessed 15 December 2022).

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ADCs in advanced NSCLC: Considerations for safe and effective administration

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Safety of ADCs in previously-treated patients

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Key safety results	≥1 drug-related TEAE: **97%** ≥1 drug-related grade ≥3 TEAE: **46%** Drug-related TEAE associated with discontinuation: **25%**	≥1 any-cause grade ≥3 TEAE: **47%** TEAE associated with discontinuation: **15%** Drug-related ILD: **11%**	**Most common any-grade events**[4] Nausea: 80% Diarrhoea: 61% Fatigue: 46% **Most common grade ≥3 events**[4] Neutropenia: 28% Leukopenia: 9% Pneumonia: 9%	≥1 drug-related TEAE: **96%** ≥1 drug-related grade ≥3 TEAE: **54%** Drug-related TEAE associated with discontinuation: **11%**	**Most common any-grade events** PSN: 25% Nausea: 22% Hypoalbuminemia: 21% Possible drug-related grade 5 AEs: Sudden death (n=1) Pneumonitis (n=1)

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

*All 91 patients had a tumour with a locally reported *HER2* mutation.[1] †Patients with various tumour types included. Overall safety population N=495,[3] of whom 54 had NSCLC.[3,4]

ADC, antibody-drug conjugate; AE, adverse event; c-Met, c-mesenchymal-epithelial transition factor; *EGFR*, epidermal growth factor receptor; HER2, human epidermal growth factor 2; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; PSN, peripheral sensory neuropathy; TEAE, treatment-emergent AE; TROP-2; trophoblast cell surface antigen 2.

1. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 2. Garon EB, et al. *J Thorac Oncol.* 2021;16(Suppl.):S892–3; 3. Bardia A, et al. *Ann Oncol.* 2021;32:746–56; 4. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7; 5. Jänne PA, et al. *Cancer Discov.* 2022;12:74–89; 6. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl.):9016.

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Study	DESTINY-Lung01	TROPION-PanTumor01	IMMU-132-01	U31402-A-U102	LUMINOSITY
Common AEs	**Any grade** Nausea: 73% Fatigue: 53% Alopecia: 46% **Grade 3** Neutropenia: 15% Anaemia: 10% Nausea: 9%	**Any grade** Nausea: 52% Stomatitis: 48% Alopecia: 39% **Grade ≥3** Stomatitis: 2% Nausea: 1% Neutropenia: 1%	**Any grade** Nausea: 80% Diarrhoea: 61% Fatigue: 46% **Grade ≥3** Neutropenia: 28% Leukopenia: 9% Pneumonia: 9%	**Any grade** Fatigue: 65% Nausea: 60% Thrombocytopenia: 53% **Grade ≥3** Thrombocytopenia: 30% Neutropenia: 19% Fatigue: 14%	**Any grade** PSN: 25% Nausea: 22% Hypoalbuminemia: 21% **Grade 5** Sudden death: n=1 Pneumonitis: n=1
ILD	**Drug-related: 26%** (n=24) Grade 1: n=3 Grade 2: n=15 Grade 3: n=4 Grade 5: n=2	**Drug-related: 11%** (n=19) Grade 1: n=4 Grade 2: n=10 Grade 3: n=2 Grade 5: n=3	Not reported	**Drug-related: 7%** (n=4) Grade 1: n=2 Grade 2: n=1 Grade 3: n=1	Not reported

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

*Data presented for population who received the recommended dose for expansion: 5.6 mg/kg once every 3 weeks (n=57).

ADC, antibody-drug conjugate; AE, adverse event; 2; ILD, interstitial lung disease; PSN, peripheral sensory neuropathy.

1. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 2. Garon EB, et al. *J Thorac Oncol.* 2021;16(Suppl.):S892–3; 3. Heist RS, et al. *J Clin Oncol.* 2017;35:2790–7;
4. Jänne PA, et al. *Cancer Discov.* 2022;12:74–89; 5. Camidge DR, et al. *J Clin Oncol.* 2022;40(Suppl.):9016.

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Conclusions

ADCs enable the targeted delivery of highly potent and broadly cytotoxic agents

Further research is needed to determine which approach to apply to each ADC: biomarker driven or biomarker agnostic

Promising efficacy data from ongoing trials of ADCs monotherapy and ADCs in combination with other agents

Payload class-effect and general toxicities have been reported

Goal is to balance efficacy with safety and QoL, helping patients live longer and live better

ADC, antibody-drug conjugate; QoL, quality of life.

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