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Navigating the clinical impact of TROP2-targeting in NSCLC

Practice aid for advanced/metastatic NSCLC

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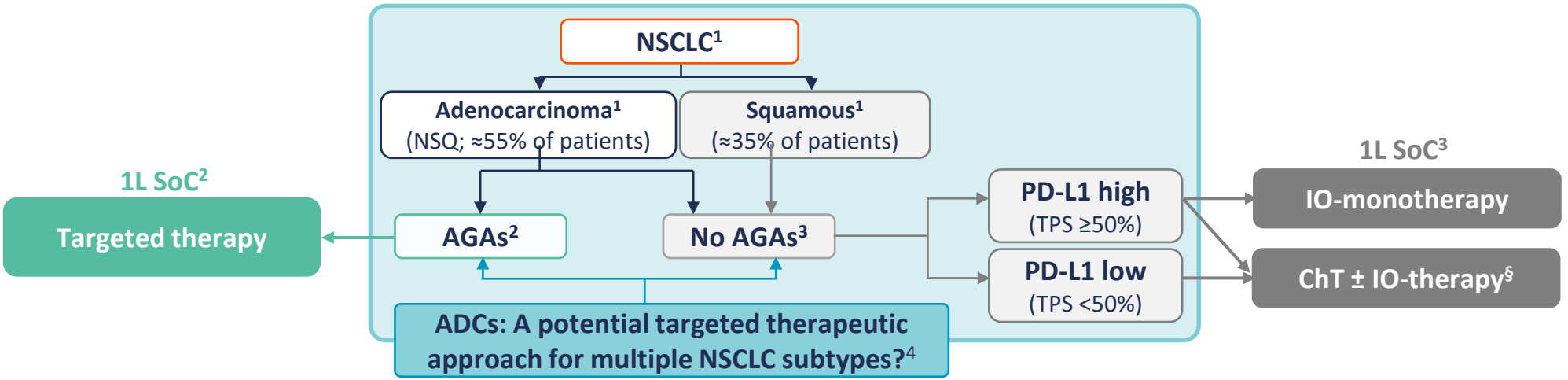
TROP2 ADCs: Insights from clinical trials about their role in the NSCLC therapeutic landscape



	SG	Dato-DXd	Sac-TMT
Line ≥2	**EVOKE-01, phase III:** SG vs docetaxel; ± AGAs[5] • OS: primary endpoint not met in ITT • OS: numerical benefit in ITT, NSQ and SQ	**TROPION-Lung01, phase III:** Dato-DXd vs docetaxel; ± AGAs[6] • mPFS: improved in ITT (p=0.004); OS, numerical benefit in ITT • OS: numerical benefit with Dato-DXd for NSQ not SQ • ORR and DCR: benefit for *EGFR*m (pooled with **TROPION-Lung05**[7])	**NCT04152499, phase II:** Sac-TMT monotherapy; + AGAs[8] • ORR, mPFS and OS: benefits in patients with pretreated, advanced NSCLC, including those with *EGFR*m
Line 1	**EVOKE-02, phase II:** SG + pembro + Pt-ChT; no AGAs any PD-L1 TPS[9] • ORR and mPFS: efficacy across NSQ and SQ histologies and PD-L1 status	**TROPION-Lung02, phase I:** Dato-DXd + pembro ± Pt-ChT; NSQ no AGAs[10] • ORR and mPFS: efficacy regardless of PD-L1 expression (preliminary)	

Prognostic role for TROP2 in NSCLC

TROP2 is expressed in 23–64% of adenocarcinoma[11–13, 17] and high TROP2 expression generally linked with worse prognosis:[11–16]

- Shorter OS
- Higher tumour grade
- Higher tumour stage
- TP53 mutation
- Larger tumour size
- Lymph node metastasis

A few studies show no link or a positive prognostic association with high TROP2[12,13]

Little evidence to support a prognostic role for TROP2 in SQ cell carcinoma[11,12]

In patients with **a/mNSCLC:**

High TROP2 mRNA → High **intracellular** TROP2

Worse outcomes (PFS and OS) with atezolizumab[18]

TROP2 as a patient selective biomarker

IHC H-score[19]

ICARUS-Lung01 study for a/mNSCLC

TROP2 **baseline** tumour **IHC**

Three H-score thresholds (<100, 100–200, ≥200)

TROP2 H-score ≥100 → **Longer PFS with Dato-DXd**

QCS-NMR[20]

Digital pathology: automated image analysis of TROP2 tumour IHC

Calculates **membrane/cytoplasm** ratio (NMR) in **every tumour cell**

Lower NMR = more TROP2 in **cytoplasm**

QCS-NMR status determination

- \+ **≥75%** tumour cells TROP2 NMR **≤0.56**
- \- **<75%** tumour cells TROP2 NMR **≤0.56***

Status by histology[20]

TROPION-Lung01 QCS-NMR positive status

Highest frequency

- **NSQ + AGA**
- **NSQ + non-AGA**
- **SQ NSCLC**

Lowest frequency

Outcomes[20]

TROPION-Lung01 study for a/mNSCLC

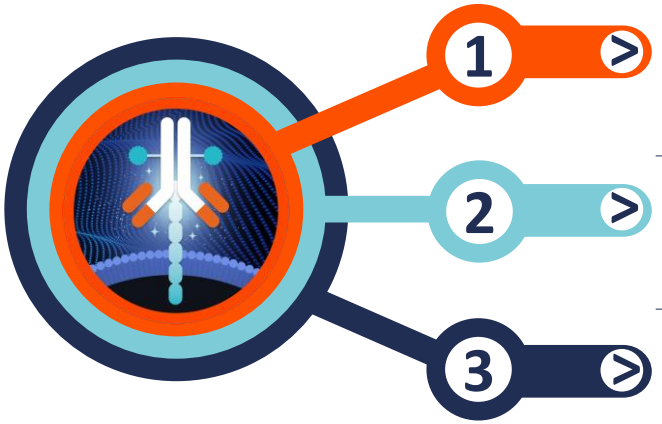
Outcomes in **whole** biomarker-evaluable population and **NSQ/non-AGA:**

QCS-NMR positive → **Longer PFS and higher ORR with Dato-DXd**

Using TROP2 as a biomarker to select patients for TROP2 ADC therapy may improve outcomes

*Or >25% of cells with NMR >0.56.

Mechanisms leading to toxicities with ADCS[21]



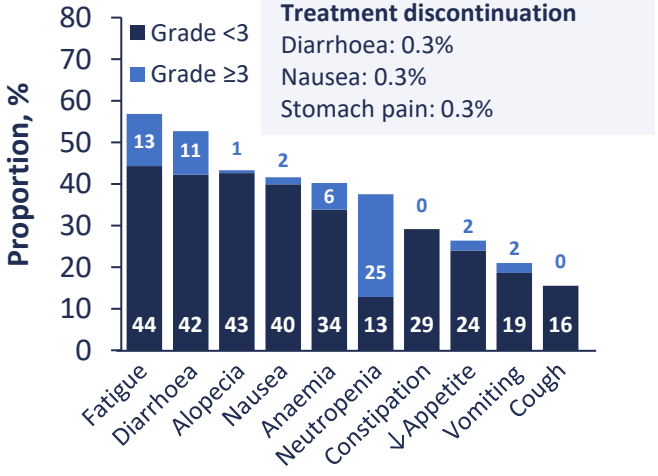
Payload release
Off-site, off-target delivery of the cytotoxic payload, the critical driver for ADC-tolerability

Payload linker
Balances drug stability and payload release to maximize efficacy, while minimizing off-target toxicity

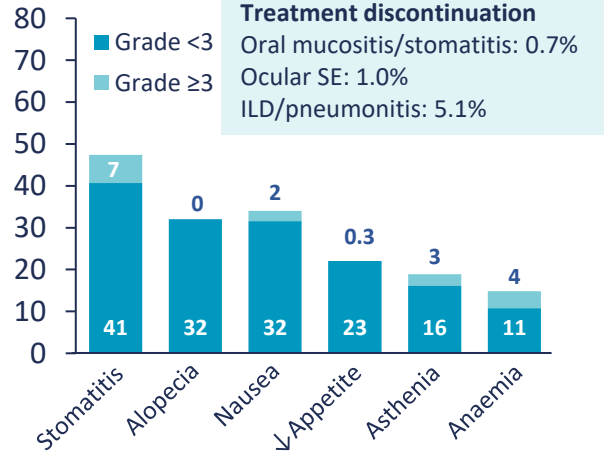
ADC internalization
Off-site, on-target binding to target antigens expressed in healthy tissues

Safety data from clinical trials with TROP2 ADCS

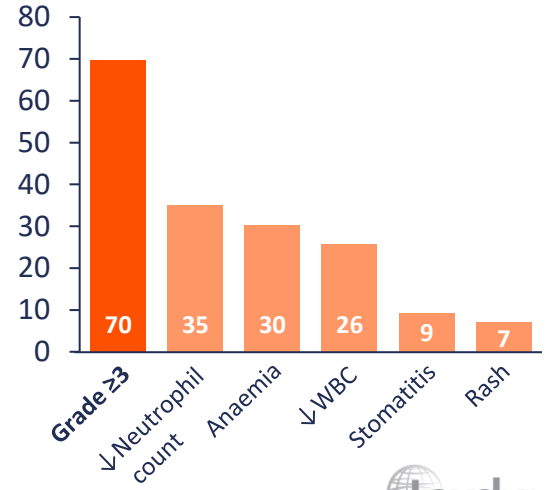
SG[5]
AEs observed in ≥15% (n=296)



Dato-DXd[6]
AEs observed in ≥15% (n=297)



Sac-TMT[8]
Most common grade ≥3 AEs (n=43)



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Summary of strategies for managing key TROP2 ADC-related AEs

SG[22,23]

- Monitor CBCs during treatment
  - Do not administer if absolute neutrophil count <1,500/mm^3 on day 1 or absolute neutrophil count <1,000/mm^3 on day 8 of any cycle
- Consider primary prophylaxis with G-CSF for patients at increased risk of febrile neutropenia
- Closely monitor patients with known reduced UGT1A1 activity*
- Avoid use of concomitant UGT1A1 inhibitors or inducers†
- Monitor patients for diarrhoea; give fluid and electrolytes as needed
  - Evaluate for infectious causes and, if negative, promptly give loperamide
- Use prophylactic antiemetics
  - Withhold for patients with grade 3 nausea or grade 3 or 4 vomiting at the time of scheduled treatment
- Consider premedication for infusion reaction

Dato-DXd‡[24]

- Monitor for new or worsening signs and symptoms of ILD/pneumonitis
  - If ILD/pneumonitis is suspected, withhold treatment and initiate corticosteroids
  - Permanently discontinue in patients with confirmed grade ≥2 ILD/pneumonitis
- Monitor patients for ocular AEs
  - Advise patients to use preservative-free eye drops and avoid using contact lenses during treatment
  - Based on ocular AE severity, withhold, reduce or permanently discontinue treatment
- To minimize the risk of stomatitis, advise patients to use a steroid-containing mouthwash when starting treatment and hold ice chips/ice water in the mouth during infusion
  - Based on stomatitis severity, withhold, reduce or permanently discontinue treatment

Sac-TMT

- Further research/guidance needed
- No drug-related ILD/pneumonitis reported[8]

*When unknown, no testing of UGT1A1 status is required, as the management of adverse reactions, including the recommended dose modifications, will be the same for all patients.[23] †Or use with caution. ‡The Committee for Medicinal Products for Human Use (CHMP) recommending the granting of a marketing authorisation for Dato-DXd for the treatment of breast cancer, on 30 January 2025.[25]

Abbreviations and references

Abbreviations

1L, first line; a/mNSCLC, advanced/metastatic NSCLC; ADC, antibody–drug conjugate; AE, adverse event; AGA, actionable genomic alteration; CBC, complete blood count; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; EGFRm, epidermal growth factor receptor mutant; G-CSF, granulocyte colony-stimulating factor; IHC, immunohistochemistry; ILD, interstitial lung disease; IO, immuno-oncology; ITT, intention-to-treat; m, median; NMR, normalized membrane ratio; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; Ph, phase; Pt-ChT, platinum-based-ChT; QCS, quantitative continuous scoring; Sac-TMT, sacituzumab tirumotecan; SE, surface event; SG, sacituzumab govitecan; SoC, standard of care; SQ, squamous; TP53, tumour protein 53; TPS, tumour proportion score; TROP2, trophoblast cell surface antigen-2; WBC, white blood cell count.

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