SYMPOSIUM

Navigating the clinical impact of TROP2-targeting in NSCLC

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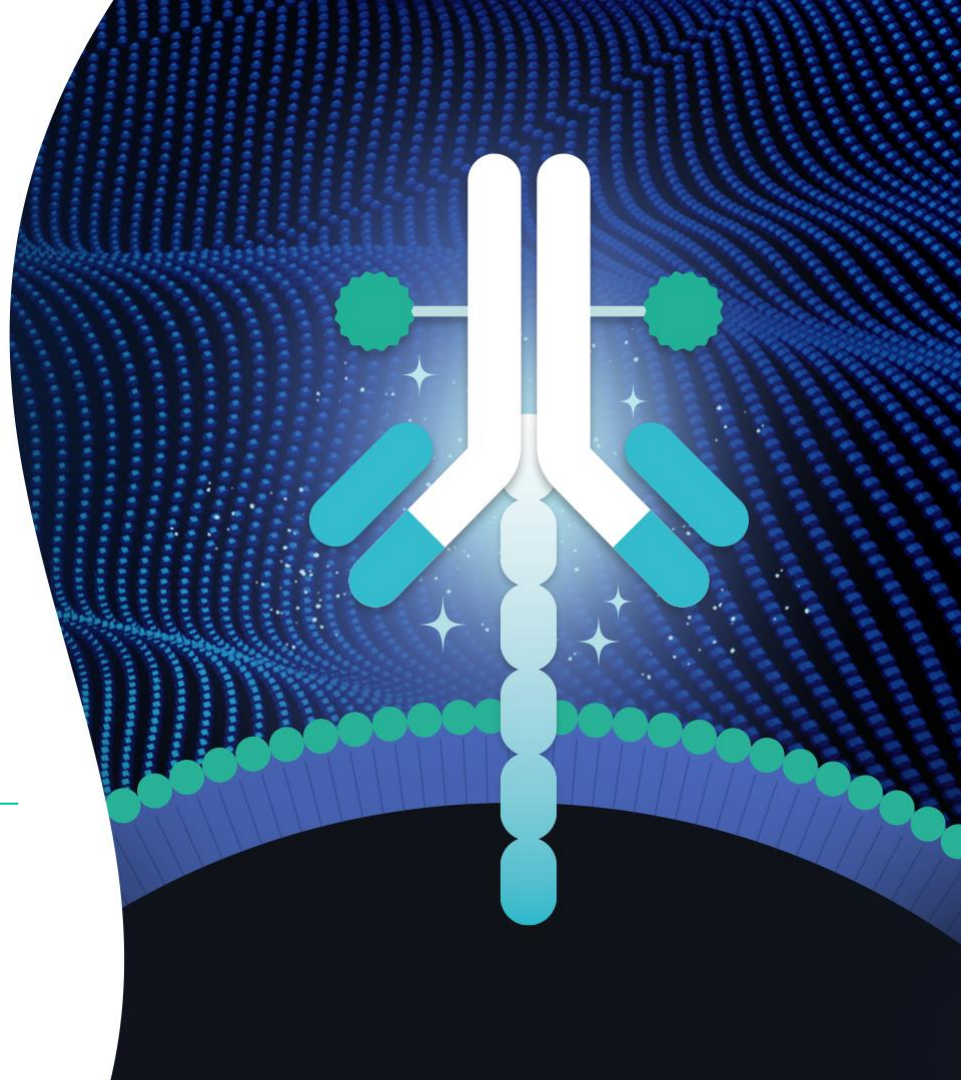

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Expert panel

Prof. Marina Garassino (Chair)
University of Chicago
Chicago, IL, USA

Prof. Jarushka Naidoo
Beaumont RCSI Cancer Centre,
Dublin, Ireland

Prof. David Planchard
Institut Gustave Roussy,
Villejuif, France

Agenda

- **Welcome and introduction**
  Prof. Marina Garassino
- **The emergence of TROP2 in NSCLC** (5 minutes)
  Prof. Marina Garassino
- **Clinical impact of targeting TROP2 in NSCLC** (15 minutes)
  Prof. Jarushka Naidoo
- **Clinical utility of TROP2 expression in NSCLC** (15 minutes)
  Prof. David Planchard
- **Panel discussion – Managing ADC toxicities in NSCLC clinical practice** (20 minutes)
  All faculty
- **Summary and close**
  Prof. Marina Garassino

Sessions will include interactive audience polling and audience Q&As

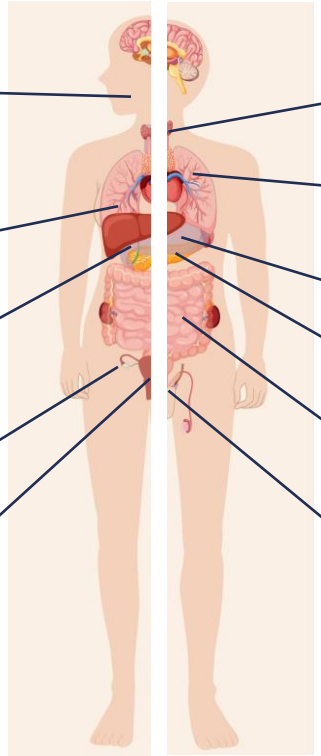
Learning objectives

1. Assess the efficacy and safety profiles of TROP2 ADCs compared with standard treatments in NSCLC
2. Evaluate the utility of measuring TROP2 expression levels in NSCLC and the specific patient populations included in clinical trials to determine eligibility for TROP2-targeted therapies
3. Develop evidence-based management approaches for specific TROP2-targeted ADC toxicities in NSCLC

Introduction and welcome

Prof. Marina Garassino (Chair)
University of Chicago
Chicago, IL, USA

TROP2: An ADC target overexpressed in multiple solid tumours



Oropharyngeal cancer
63% of OSCC
44% of SGC

Breast cancer
62%
78% of TNBC

Gallbladder cancer
56%

Ovarian cancer
47%

Cervical cancer
89%

Thyroid cancer
83%

Lung cancer (NSCLC)
64% of AC
75% of SCC

Gastric cancer
66%

Pancreatic cancer
55%

Colon cancer
68%

Prostate cancer
71%

Figure adapted from Liu X, et al. *Pharmacol Ther.* 2022:239:108296. Human anatomy image by brgfx on www.freepik.com.
AC, adenocarcinoma; ADC, antibody–drug conjugate; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; SCC, squamous cell carcinoma; SGC, salivary gland carcinoma; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen-2.

TROP2 ADCs: Current status in NSCLC

3

TROP2 ADCs in **late-stage clinical development** for NSCLC

6

Ongoing* phase II/III trials in NSCLC **2L+** setting[1]

10

Ongoing* phase II/III trials in **locally advanced /metastatic 1L setting** in combination[2]

5

Ongoing* phase II/III trials in **resectable NSCLC**[3]

*Status as of 11 February 2025, based on searches of https://clinicaltrials.gov. Includes investigational trials with status 'recruiting' or 'active, not recruiting' where primary data have not yet been published and where sponsor or collaborator is listed as the entity developing/co-developing the ADC.
1L, first line; 2L+, second or later line; ADC, antibody–drug conjugate; NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen-2.
1. ClinicalTrials.gov. NCT05633667, NCT03944772, NCT06417814, NCT06312137, NCT06305754, NCT06074588;
2. ClinicalTrials.gov. NCT05633667, NCT05609968, NCT05186974, NCT06357533, NCT06350097, NCT05555732, NCT05215340, NCT05687266, NCT06422143, NCT06170788;
3. ClinicalTrials.gov. NCT05061550, NCT06564844, NCT05633667, NCT06788912, NCT06312137.
All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

TROP2 ADCs: Current status in NSCLC

Datopotamab deruxtecan

Multiple phase II/III studies ongoing in NSCLC.[2] **FDA breakthrough therapy designation and priority review** for patients with **advanced/metastatic *EGFR*m** NSCLC and **prior systemic therapies including an EGFR-directed therapy[3]**

Sacituzumab govitecan

Several phase II/III studies ongoing in NSCLC 1L setting in combination[1]

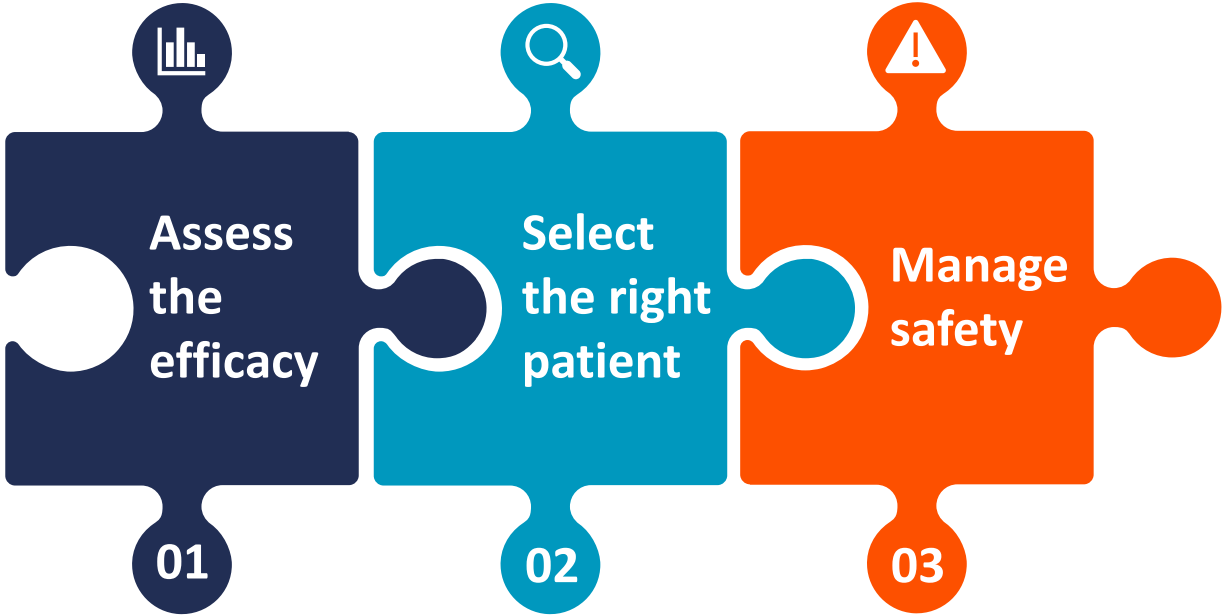
Sacituzumab tirumotecan

Multiple phase II/III studies ongoing in NSCLC[4]
Approved in China and has **FDA breakthrough therapy designation** for patients with **advanced/metastatic *EGFR*m** NSCLC and **prior TKI and platinum-based chemotherapy[5,6]**

1L, first line; ADC, antibody–drug conjugate; EGFRm; epidermal growth factor receptor mutant; FDA, US Food and Drug Administration; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell surface antigen-2.

1. ClinicalTrials.gov. NCT05633667, NCT05609968, NCT05186974; 2. NCT06357533, NCT06350097, NCT05555732, NCT05215340, NCT05061550, NCT03944772, NCT06417814, NCT06564844, NCT05687266; 3. CancerNetwork. 2025. Available at: https://bit.ly/4axhcpD (accessed 27 March 2025); 4. NCT06422143, NCT06170788, NCT06788912, NCT06312137, NCT06305754, NCT06074588. All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ (accessed 27 March 2025); 5. CancerNetwork.com. Available at: https://bit.ly/3Qo8bpp (accessed 27 March 2025); 6. PR Newswire.com. Available at: https://bit.ly/4ivzOcy (accessed 27 March 2025).

Key questions for NSCLC clinical practice

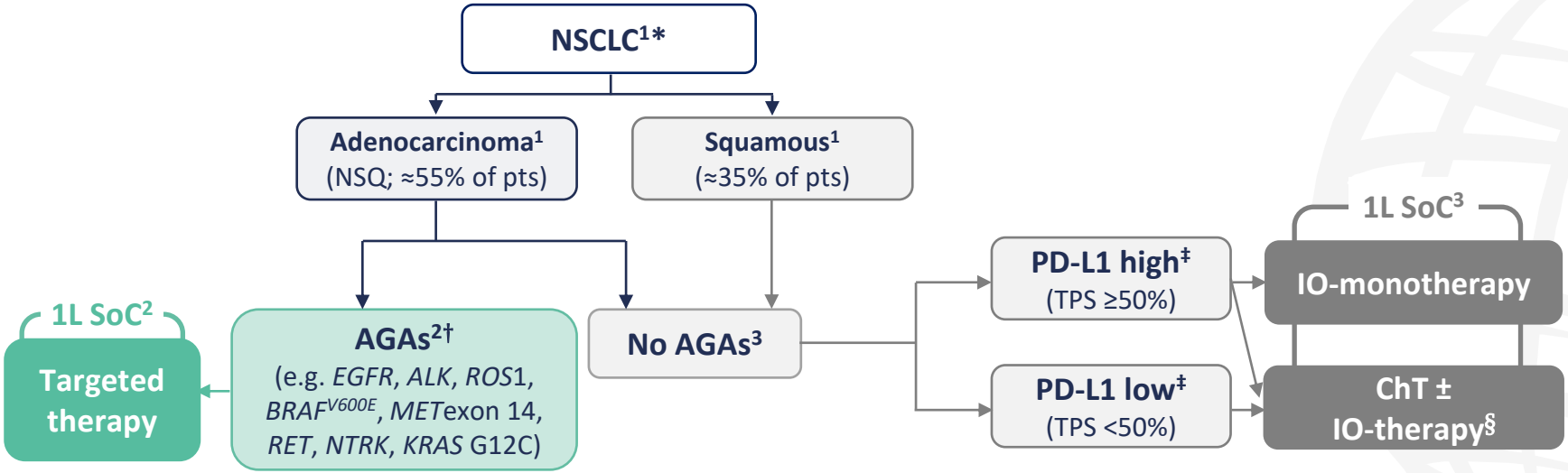


NSCLC, non-small cell lung cancer.

Clinical impact of targeting TROP2 in NSCLC

Prof. Jarushka Naidoo
Beaumont RCSI Cancer Centre,
Dublin, Ireland

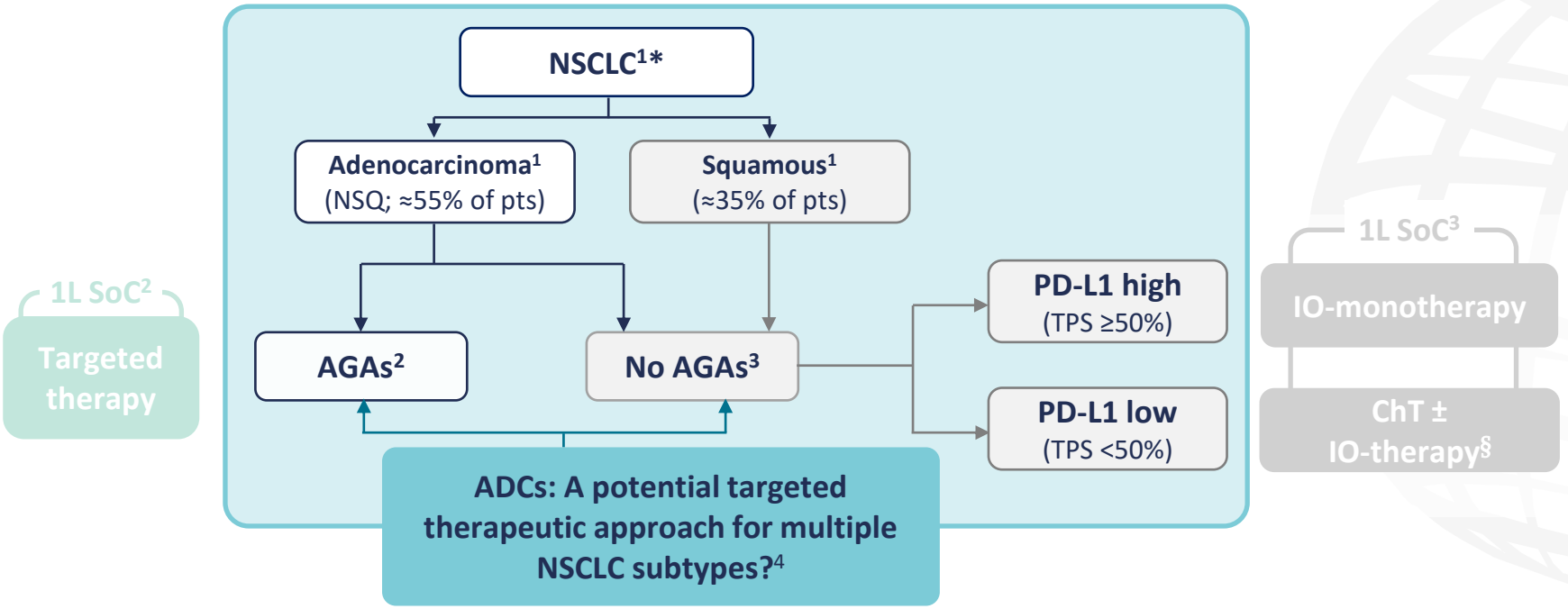
NSCLC: Matching histology and genomic profiling with optimal treatment approaches



- The emergence of tailored approaches to the management of NSCLC has improved survival outcomes[1]

*Approximately 10% of cases are non-specified subtypes of NSCLC.[1] †Molecular testing is used to identify patients with oncogenic disease drivers and guide treatment selection.[2]
‡Established using immunohistochemistry testing.[3] §Therapy selection is also influenced by ECOG PS and any contradictions to IO therapy.[3]
1L, first line; AGA, actionable genetic alterations; ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immuno-oncology; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; PD-L1, programmed death-ligand 1; pts, patients; SoC, standard of care; TPS, tumour proportion score.
1. Rolfo C, et al. *J Am Board Fam Med*. 2015;28:124–33; 2. Hendricks LE, et al. *Ann Oncol*. 2023;34:339–57; 3. Hendricks LE, et al. *Ann Oncol*. 2023;34:358–76.

NSCLC and ADCs: Expanding therapeutic potential across the treatment continuum



*Approximately 10% of cases are non-specified subtypes of NSCLC.[1]
1L, first line; ADC, antibody–drug conjugate; AGA, actionable genetic alterations; ChT, chemotherapy; IO, immuno-oncology; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; PD-L1, programmed death-ligand 1; pts, patients; SoC, standard of care; TPS, tumour proportion score.
1. Rolfo C, et al. *J Am Board Fam Med*. 2015;28:124–33; 2. Hendricks LE, et al. *Ann Oncol*. 2023;34:339–57; 3. Hendricks LE, et al. *Ann Oncol*. 2023;34:358–76; 4. Coleman N, et al. *NPJ Precis Oncol*. 2023;7:5.

TROP2-targeted ADCs: Phase III clinical trials in pre-treated a/mNSCLC

Sacituzumab govitecan[1,2]

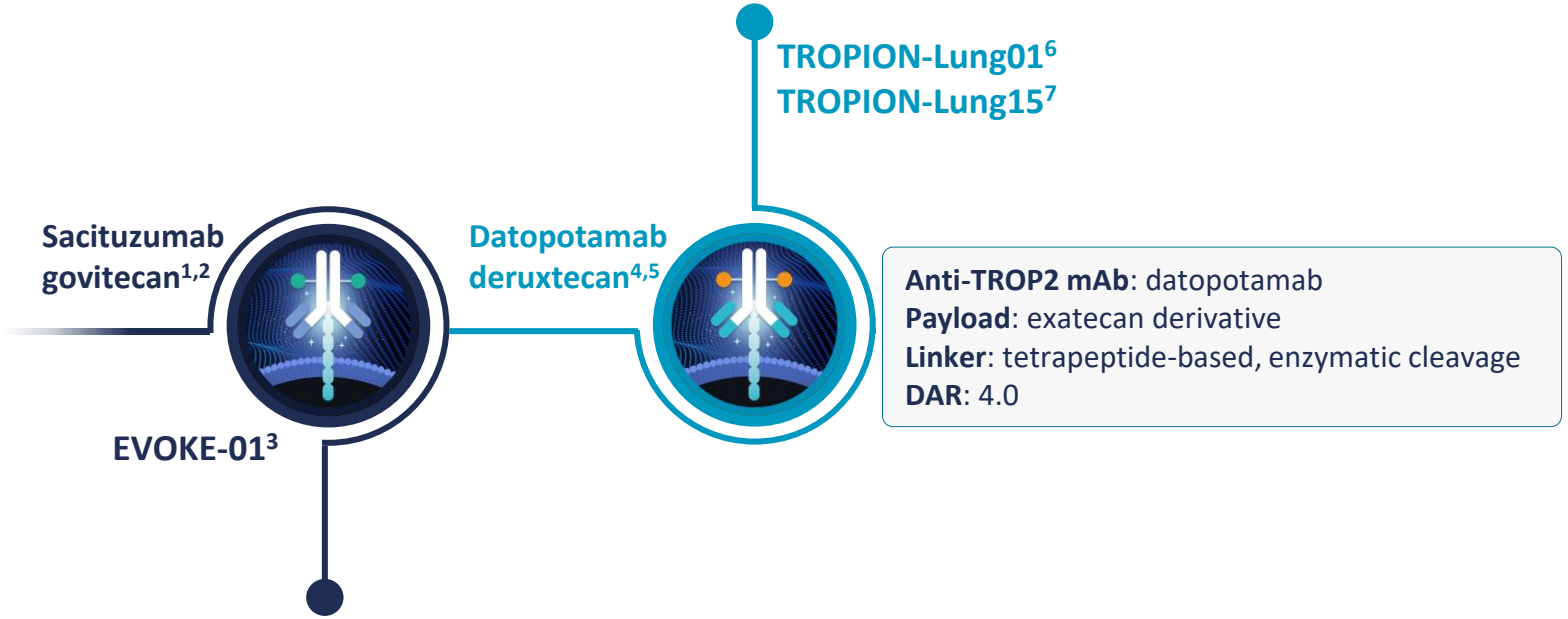
EVOKE-01[3]

Anti-TROP2 mAb: sacituzumab
Payload: SN-38
Linker: CL2A-based, hydrolytic cleavage
DAR: 7.6

a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody–drug conjugate; DAR, drug-to-antibody ratio; mAb, monoclonal antibody; TROP2, trophoblastic cell surface antigen-2.

1. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496–512; 2. Kopp A, et al. *Mol Cancer Ther*. 2022;22:102–11; 3. ClinicalTrials.gov. NCT05089734.
All clinical trials are available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

TROP2-targeted ADCs: Phase III clinical trials in pre-treated a/mNSCLC



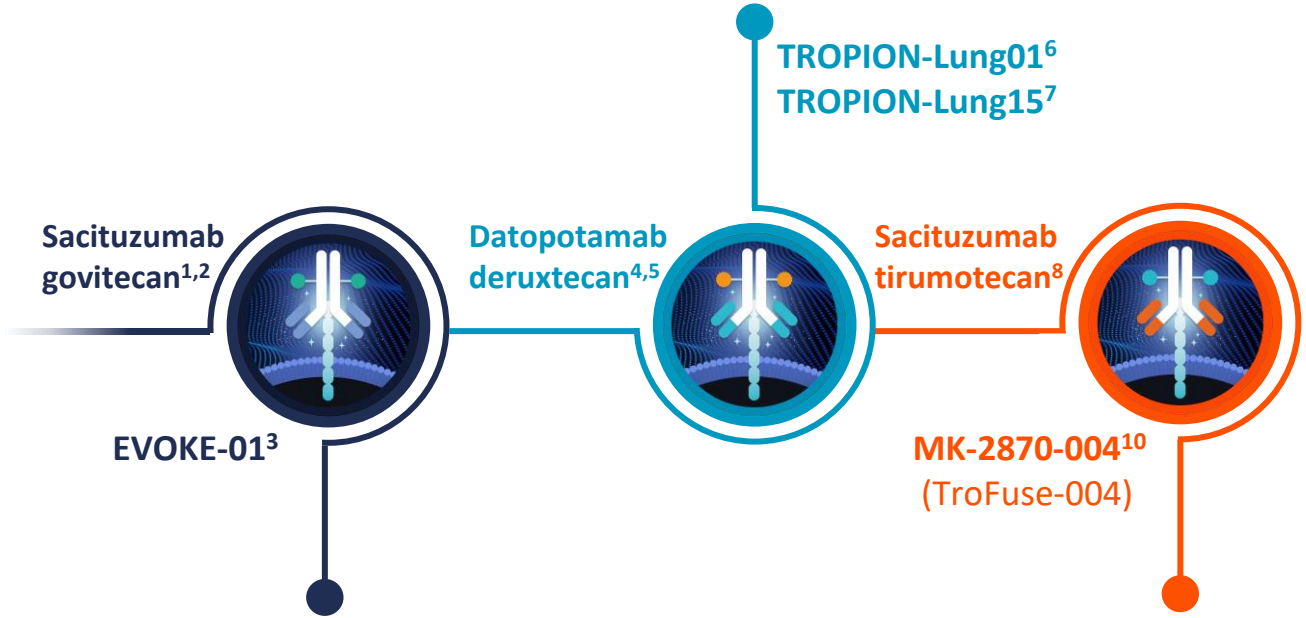
Anti-TROP2 mAb: datopotamab
Payload: exatecan derivative
Linker: tetrapeptide-based, enzymatic cleavage
DAR: 4.0

a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody–drug conjugate; DAR, drug-to-antibody ratio; mAb, monoclonal antibody; TROP2, trophoblastic cell surface antigen-2.

1. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496–512; 2. Kopp A, et al. *Mol Cancer Ther*. 2022;22:102–11; 3. ClinicalTrials.gov. NCT05089734; 4. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–40; 5. Heist, RS et al. *Cancer Treat Rev*. 2024;125:102720; 6. ClinicalTrials.gov. NCT04656652; 7. ClinicalTrials.gov. NCT06417814.

All clinical trials are available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

TROP2-targeted ADCs: Phase III clinical trials in pre-treated a/mNSCLC



Anti-TROP2 mAb: sacituzumab
Payload: belotecan-derivative
Linker: sulfonyl pyrimidine-CL2A-carbonate, both **extracellular** pH-sensitive and **intracellular** enzymatic cleavage[9]
DAR: 7.4

a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody–drug conjugate; DAR, drug-to-antibody ratio; mAb, monoclonal antibody; TROP2, trophoblastic cell surface antigen-2.

1. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496–512; 2. Kopp A, et al. *Mol Cancer Ther*. 2022;22:102–11; 3. ClinicalTrials.gov. NCT05089734; 4. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–40; 5. Heist, RS et al. *Cancer Treat Rev*. 2024;125:102720; 6. ClinicalTrials.gov. NCT04656652; 7. ClinicalTrials.gov. NCT06417814; 8. Fang W, et al. *J Clin Oncol*. 2024;42(Suppl. 16):8502; 9. Fang W, et al. *Cancer Res*. 2024;84(Suppl. 7):CT247; 10. ClinicalTrials.gov. NCT06074588.
All clinical trials are available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

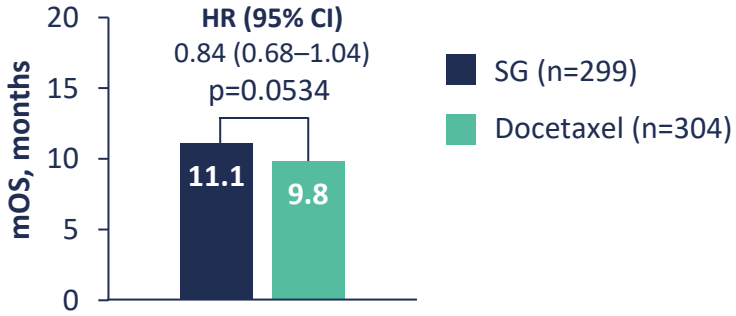
Efficacy of SG vs SoC in pre-treated a/mNSCLC

EVOKE-01 (phase III, NCT05089734)
Median follow-up: 12.7 months

N=603

Patients: a/mNSCLC ± AGAs
Nonsquamous histology: ≈73%
Prior 1L therapy: 55%

Primary endpoint (ITT population)



Secondary endpoints and safety

	SG	Docetaxel
mPFS, months	4.1	3.9
ORR, %	13.7	18.1

TRAEs*
Grade ≥3: **SG** 67%; **docetaxel** 76%
Discontinuations: **SG** 7%; **docetaxel** 14%

- A clinically meaningful improvement in OS was observed in patients nonresponsive to their last anti-PD-(L)1–containing regimen (mOS: 12 months with SG vs 8 months with docetaxel)
- The **primary endpoint was not met** and the clinical trial programme to treat a/mNSCLC in ≥2L was discontinued

*Safety analysis cohort: SG, n=296; docetaxel, n=288.
1L, first line; 2L, second line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-(L)1, programmed death-(ligand) 1; SG, sacituzumab govitecan; SoC, standard of care; TRAE, treatment-related adverse event.
Paz-Ares LG, et al. *J Clin Oncol*. 2024;42:2860–72.

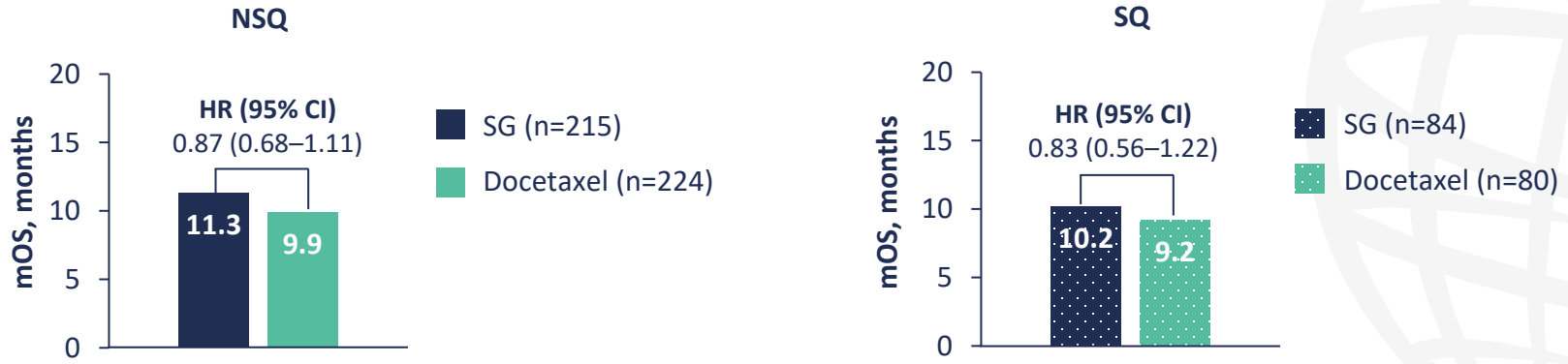
Efficacy of SG vs SoC: Impact of histology

EVOKE-01 (phase III, NCT05089734)
Median follow-up: 12.7 months

N=603

Patients: a/mNSCLC ± AGAs
Nonsquamous histology: ≈73%
Prior 1L therapy: 55%

mOS according to histology[1]



- A numerical improvement reported in OS for SG vs docetaxel in both NSQ and SQ histologies
- Plan to initiate a phase III clinical trial of SG for extensive SCLC, following promising phase II data[2,3]

1L, first line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; CI, confidence interval; HR, hazard ratio; m, median; NSQ, nonsquamous; OS, overall survival; SCLC, small cell lung cancer; SG, sacituzumab govitecan; SoC, standard of care; SQ, squamous.

1. Paz-Ares LG, et al. *J Clin Oncol*. 2024;42:2860–72; 2. Dowlati A, et al. *J Thoracic Oncol*. 2024;19:S16; 3. Respiratory therapy. Available at: https://bit.ly/4aqyuV4 (accessed 27 March 2025).

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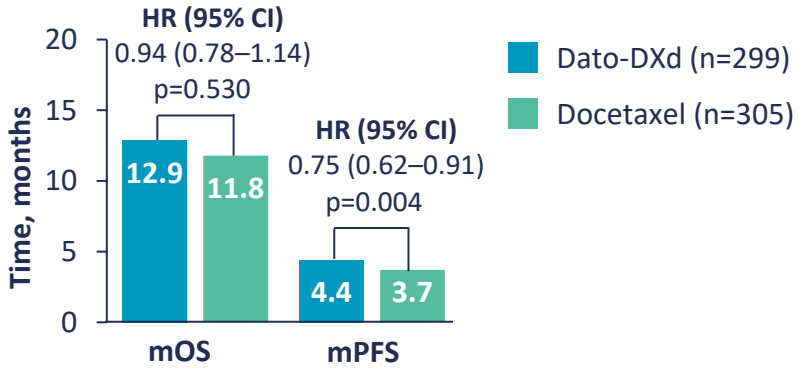
Efficacy of Dato-DXd vs SoC in pre-treated a/mNSCLC

TROPION-Lung01 (phase III, NCT04656652)[1]
Median follow-up: 23.1 months (OS)
≈10 months (PFS)

N=605

Patients: a/mNSCLC ± AGAs
Nonsquamous histology: ≈74%
Prior 1L therapy: ≈56%

Dual primary endpoints (ITT population)



Secondary endpoint and safety

	Dato-DXd	Docetaxel
ORR, %	26.4	12.8

TRAEs*
Grade ≥3: **Dato-DXd** 26%; **docetaxel** 42%
Discontinuations: **Dato-DXd** 8%; **docetaxel** 12%

- Dato-DXd significantly improved PFS vs docetaxel; OS showed a numerical benefit **but did not reach statistical significance**
- A previously submitted BLA for NSQ a/mNSCLC was voluntarily withdrawn in November 2024[2]

*Safety analysis set: Dato-DXd, n=297; docetaxel, n=290.
1L, first line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; BLA, Biologics License Application; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ITT, intent-to-treat; m, median; NSQ, nonsquamous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SoC, standard of care; TRAE, treatment-related adverse event.

1. Ahn M-J, et al. *J Clin Oncol*. 2025;43:260–72; 2. CancerNetwork. 2025. Available at: https://bit.ly/4axhcpD (accessed 27 March 2025).

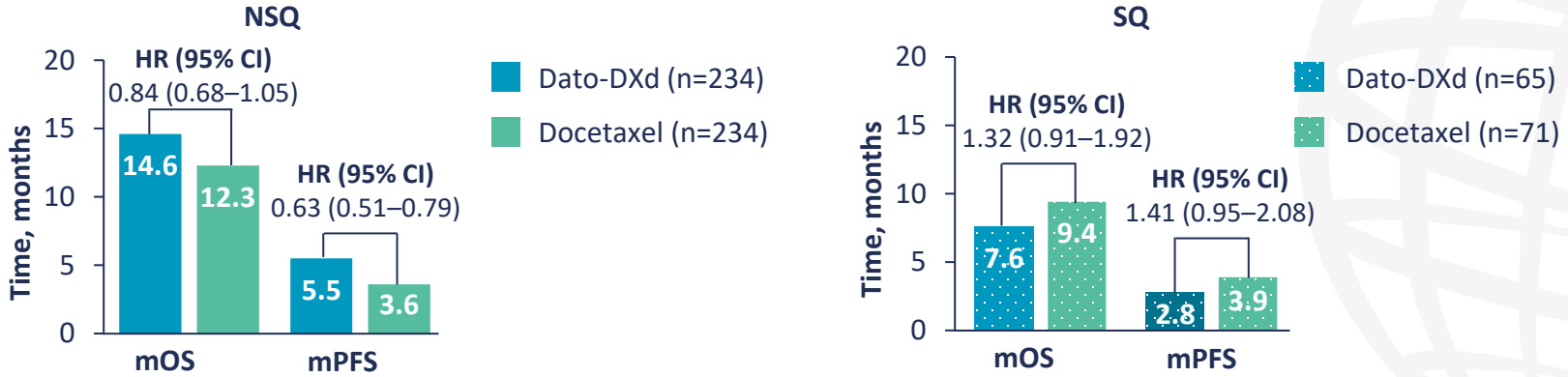
Efficacy of Dato-DXd vs SoC: Impact of histology

TROPION-Lung01 (phase III, NCT04656652)[1]
Median follow-up: 23.1 months (OS)
≈10 months (PFS)

N=605

Patients: a/mNSCLC ± AGAs
Nonsquamous histology: ≈74%
Prior 1L therapy: ≈56%

mOS and mPFS according to histology



- Clinical activity of Dato-DXd monotherapy is distinctly different in histologic subgroups of a/mNSCLC
- Results have been independently supported by findings from the ICARUS-Lung01[2] and TROPION-PanTumor02[3]

a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; m, median; NSQ, nonsquamous; OS, overall survival; PFS, progression-free survival; SoC, standard of care; SQ, squamous.

1. Ahn M-J, et al. *J Clin Oncol*. 2025;43:260–72; 2. Planchard D, et al. *J Clin Oncol*. 2024(Suppl. 16);42:8501; 3. Sun Y, et al. *J Clin Oncol.* 2024;42(Suppl. 16):8548.

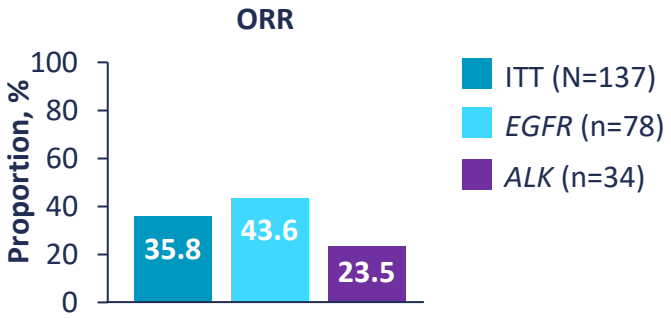
Efficacy of Dato-DXd in patients with AGAs

TROPION-Lung05 (phase II, NCT04484142)[1]
Follow-up: ≥9 months or up to treatment discontinuation, whichever occurred first

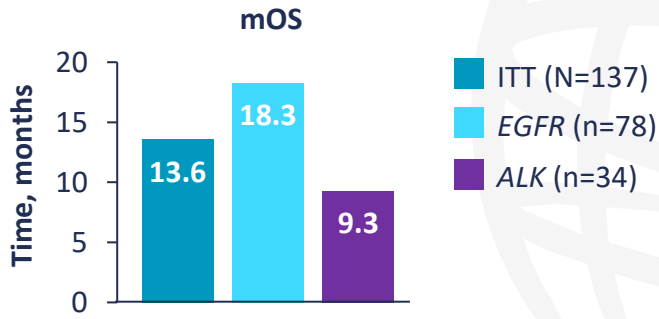
N=137

Patients: a/mNSCLC with AGAs (***EGFR*m:*** 57%; ***ALK***: 25%)
≥3L therapy: 72%

Primary endpoint



Secondary endpoint



- Pooled data from TROPION-Lung05 and TROPION-Lung01 showed an ORR of 43% and a DCR 86% in previously treated *EGFR*m a/mNSCLC;[2] TROPION PanTumor01 (median 3L) showed an ORR without AGAs 28% and with AGAs 44%[3]
- Based on TROPION-Lung01 and -Lung05, **Dato-DXd was granted a BTD for *EGFR*m a/mNSCLC** (December 2024)[4]

*49.6% of these patients had exon 19 deletions, L858R mutations and/or T790M mutations.
3L, third line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; ALK, anaplastic lymphoma kinase; BTD, Breakthrough Therapy Designation; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; EGFRm, epidermal growth factor receptor mutant; ITT, intent-to-treat; mOS, median overall survival; ORR, objective response rate.

1. Sands J, et al. *J Clin Oncol.* 2025:JCO2401349; 2. Ahn M-J, et al. *Ann Oncol*. 2024;35(Suppl. 4):S1630–31; 2. Shimizu T, et al. *J Clin Oncol*. 2023;41:4678–87; 4. CancerNetwork.com. Available at: https://bit.ly/41wuXRl (accessed 27 March 2025).

ELCC 2025, #10: Osimertinib + Dato-DXd in aNSCLC

ORCHARD (phase II, NCT03944772)
Median follow-up: ≈14 months

N=69

Patients: aNSCLC + *EGFR*m following 1L osi
Osi + Dato-DXd, 4 mg/kg: n=35
Osi + Dato-DXd, 6 mg/kg: n=33

Primary endpoint: ORR

Osi + 4 mg Dato-DXd

43%

Osi + 6 mg Dato-DXd

36%

Grade ≥3 TRAEs

4 mg Dato-DXd, 34%
6 mg Dato-DXd, 56%

- Osi + Dato-DXd showed promising efficacy and no new safety signals in patients with *EGFR*m aNSCLC who progressed on 1L osi; longer term follow-up data are awaited
- More patients remained in response at 9 months in the group treated with 6 mg/kg Dato-DXd (**64%** vs **15%**)

1L, first line; aNSCLC, advanced non-small cell lung cancer; Dato-DXd, datopotamab deruxtecan; EGFRm, epidermal growth factor receptor mutant; ORR, objective response rate; osi, osimertinib; TRAE, treatment-related adverse event.
Le X, et al. To be presented at: ELCC, Paris, France. 26 March 2025.

Efficacy of Sac-TMT for a/mNSCLC ± *EGFRm*

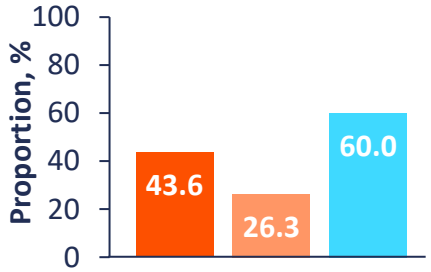
Phase II, NCT04152499[1]
Median follow-up: 17.2 months

N=43

Patients: a/mNSCLC with AGAs
***EGFR*wt:** median 3L, including anti-PD-(L)1
***EGFR*m:** progressed on/after TKI therapy

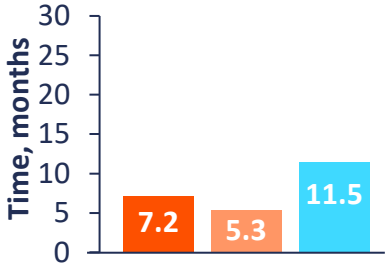
Primary endpoint

ORR

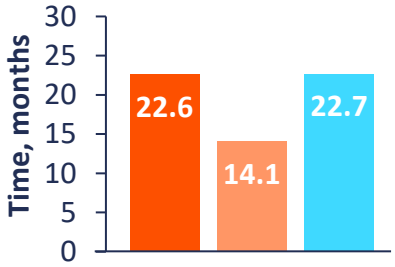


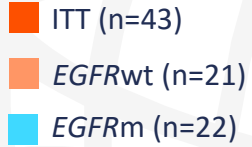
Secondary endpoints

mPFS



mOS

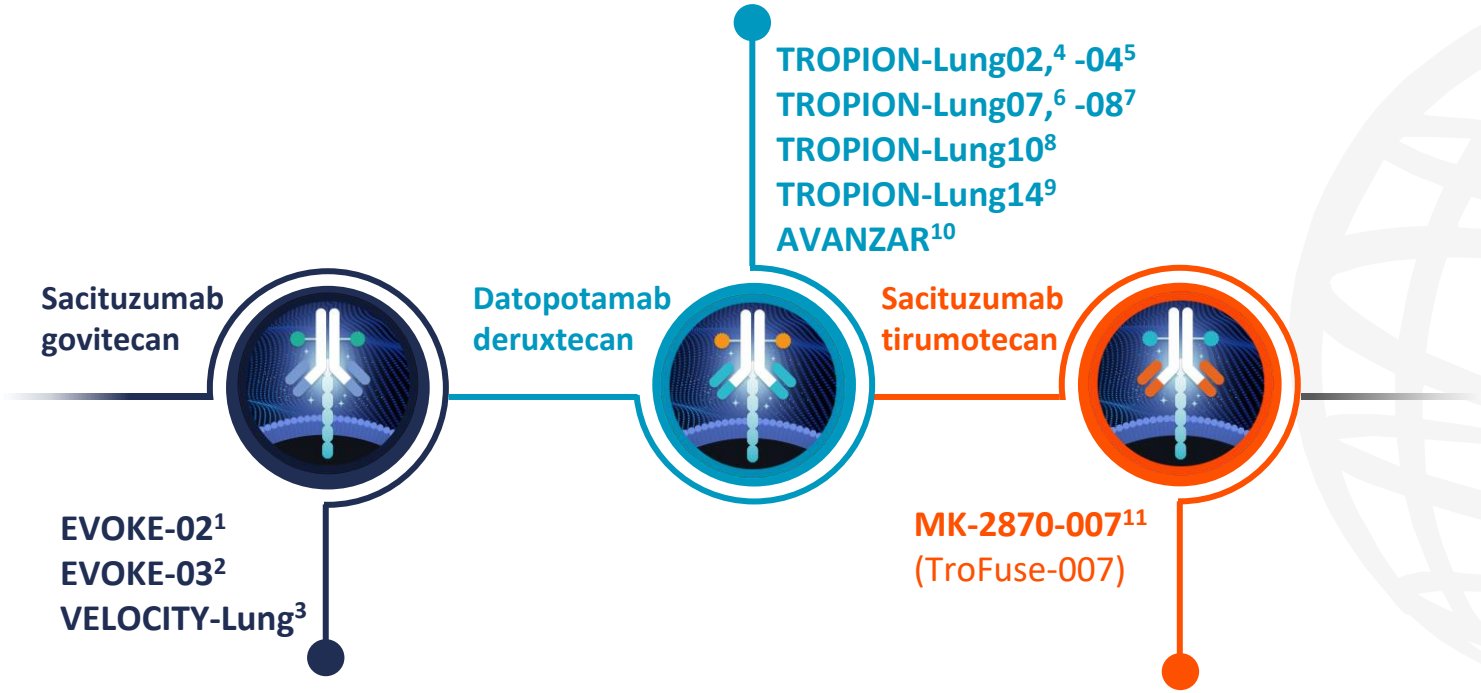




- Grade ≥3 TRAEs: 70%; no discontinuations or deaths
- The FDA granted Sac-TMT a BTD (3 December 2024);[2] approved in China for later-stage *EGFR*m[3]
- Ongoing phase III trials: **Global** (*EGFR*m or other AGAs in 2L or 3L, NCT06074588)[4]; **China** (*EGFR*m in 2L, NCT05870319)[5]

2L, second line; 3L, third line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; BTD, breakthrough therapy designation; EGFRm, epidermal growth factor receptor mutant; EGFRwt, EGFR wild-type; FDA, US Food and Drug Administration; ITT, intention-to-treat; m, median; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; Sac-TMT, sacituzumab tirumotecan; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.
1. Fang W, et al. *Cancer Res.* 2024;84(Suppl. 7):CT247; 2. CancerNetwork.com. Available at: https://bit.ly/3Qo8bpp (accessed 27 March 2025); 3. PR Newswire.com. Available at: https://bit.ly/4ivzOcy (accessed 27 March 2025); 4. ClinicalTrials.gov. NCT06074588; 5. ClinicalTrials.gov. NCT05870319.
All clinical trials are available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

TROP2-targeted ADCs: Clinical trials in 1L a/mNSCLC



1L, first line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody drug conjugate; TROP2, trophoblastic cell surface antigen-2.

1. ClinicalTrials.gov. NCT05186974; 2. ClinicalTrials.gov. NCT05609968; 3. ClinicalTrials.gov. NCT05633667; 4. ClinicalTrials.gov. NCT04526691; 5. ClinicalTrials.gov. NCT04612751; 6. ClinicalTrials.gov. NCT05555732; 7. ClinicalTrials.gov. NCT05215340; 8. ClinicalTrials.gov. NCT06357533; 9. ClinicalTrials.gov. NCT06350097; 10. ClinicalTrials.gov. NCT05687266; 11. ClinicalTrials.gov. NCT06170788. All clinical trials are available at: https://clinicaltrials.gov/ (accessed 27 March 2025).

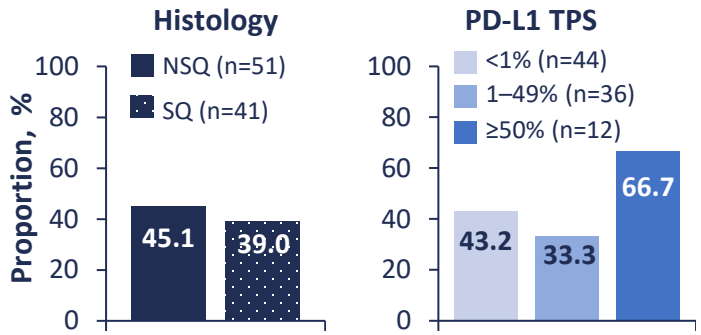
Efficacy of SG for a/mNSCLC in the first line

EVOKE-02 (phase II, NCT05186974)
Therapy: SG (10 or 7.5 mg/kg) + pembro + Pt-ChT
Median follow-up: ≈14.4 months

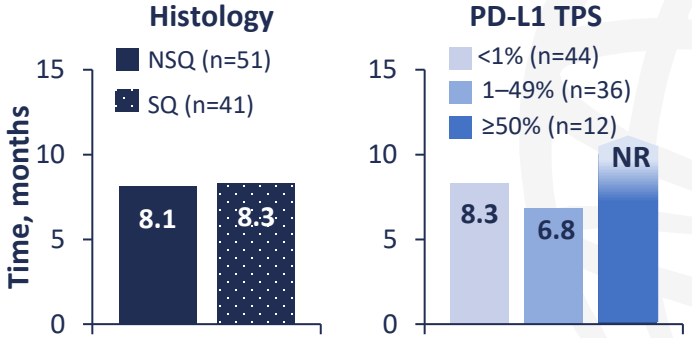
N=92

Patients: a/mNSCLC without AGAs; any PD-L1 TPS
Cohort: C (NSQ); D (SQ)

ORR



mPFS



Incidence of grade ≥3 TRAEs was lower for SG 7.5 vs 10.0 mg/kg **(86.4% vs 93.1%)**
TRAEs leading to discontinuation were also lower for SG 7.5 vs 10.0 mg/kg **(13.6% vs 31.0%)**

- Efficacy seen across NSQ and SQ histology and PD-L1 status
- SG continues to be studied in various combinations in first-line mNSCLC with a recommended dose of 7.5 mg/kg

a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; mPFS, median progression-free survival; NR, not reached; NSQ, nonsquamous; ORR, objective response rate; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; Pt-ChT, platinum-based chemotherapy; SG, sacituzumab govitecan; SQ, squamous; TPS, tumour proportion score; TRAE, treatment-related adverse event.

Gray JE, et al. *J Thorac Oncol.* 2024;19(Suppl.):S27.

Efficacy of Dato-DXd for a/mNSCLC in the first line

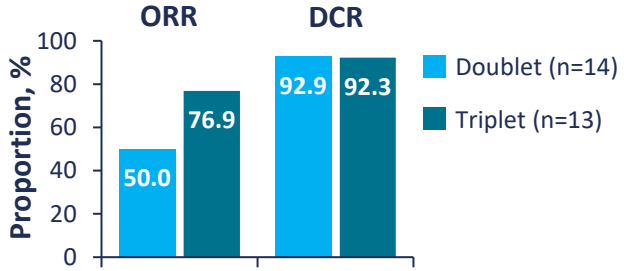
TROPION-Lung02 (phase I, NCT04526691)[1,2]
Therapy: Dato-DXd + **pembrolizumab** ± Pt-ChT
Patients: a/mNSCLC, NSQ without AGAs
Median treatment duration: ≈6 months
Primary endpoint: Safety and tolerability

Grade ≥3 TRAEs: Doublet 57% vs Triplet 76%
Discontinuations: Doublet 29% vs Triplet 39%

Therapy (n)	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	Doublet (37)	Triplet (39)	Doublet (5)	Triplet (15)
ORR, %	46	56	100	53
mPFS, months	9.3	6.8	NE	6.8

TROPION-Lung04 (phase Ib, NCT04612751)[3,4]
Therapy: Dato-DXd + **durvalumab** ± Pt-ChT
Patients: a/mNSCLC, without AGAs
Median treatment duration: ≈6 months
Primary endpoint: Safety and tolerability

Grade ≥3 TRAEs: Doublet 32% vs Triplet 57%
Discontinuations (Dato-DXd): Doublet 21% vs Triplet 14%



- Efficacy was observed **regardless of PD-L1 expression** with manageable safety
- TROPION-LUNG02 is the largest dataset to date to assess any ADC + anti-PD-(L)1 combination for a/mNSCLC in 1L

1L, first line; a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody–drug conjugate; AGA, actionable genomic alteration; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; mPFS, median progression-free survival; NE, not evaluable; NSQ, nonsquamous; ORR, objective response rate; PD-(L)1, programmed death-(ligand) 1; Pt-ChT, platinum-based chemotherapy; TPS, tumour proportion score; TRAE, treatment-related adverse event.

1. ClinicalTrials.gov. NCT04526691. Available at: https://bit.ly/3DSTJCX (accessed 27 March 2025); 2. Levy P, et al. *J Clin Oncol.* 2024;42(Suppl. 16);8617; 3. ClinicalTrials.gov. NCT04612751. Available at: https://bit.ly/40rCy49 (accessed 27 March 2025); 4. Papadopoulos KP, et al. *J Thorac Oncol.* 2023;18(Suppl.):S55.

TROP2-targeted ADCs: Where are we now?

Efficacy was demonstrated with TROP2-ADCs in previously treated patients with a/mNSCLC

Do some patients benefit more than others?

Patients enrolled in the clinical trials were unselected for TROP2 expression

Will a biomarker-guided approach help to select patients?

There are promising early data in the first line for TROP2-ADCs as a combination therapy

Will we see greater benefit in the first line vs the second line?

a/mNSCLC, advanced/metastatic non-small cell lung cancer; ADC, antibody–drug conjugate; TROP2, trophoblastic cell surface antigen-2.

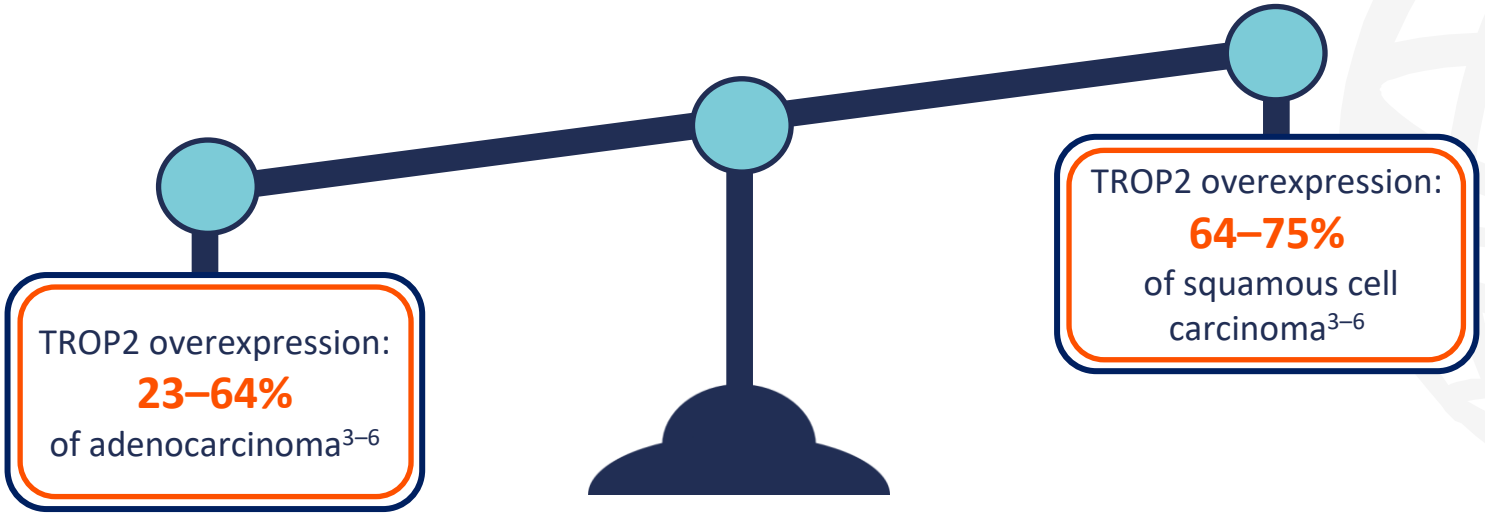
Clinical utility of TROP2 expression in NSCLC

Prof. David Planchard
Institut Gustave Roussy,
Villejuif, France

TROP2 overexpression in NSCLC

TROP2 overexpressed in NSCLC relative to normal lung tissue[1–3]

Overexpression more common in squamous cell carcinoma compared with adenocarcinoma[3–5]

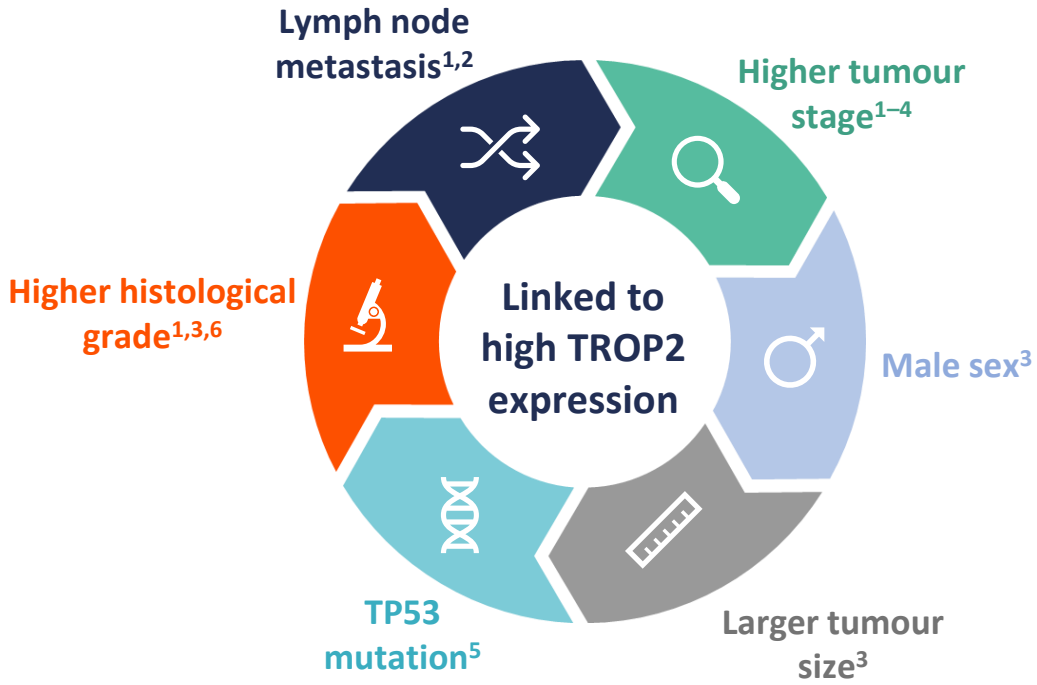


NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen-2.

1. Guo X, et al. *Tumour Biol.* 2017;39:1010428317694324; 2. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197–204; 3. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 4. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 5. Pak MG, et al. *World J Surg Oncol.* 2012;10:53; 6. Parisi C, et al. *Cancer Treat Rev.* 2023;118:102572.

TROP2 in adenocarcinoma

Expression linked to clinical and pathological tumour features



TP53, tumour protein 53; TROP2, trophoblast cell surface antigen-2.

1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197–204; 3. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 4. Guo X, et al. *Tumour Biol.* 2017;39:1010428317694324. 5. Mito R, et al. *Pathol Int.* 2020;70:287–94; 6. Pak MG, et al. *World J Surg Oncol.* 2012;10:53.

TROP2 as a negative prognostic biomarker in adenocarcinoma

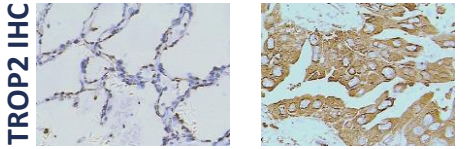
Prognostic

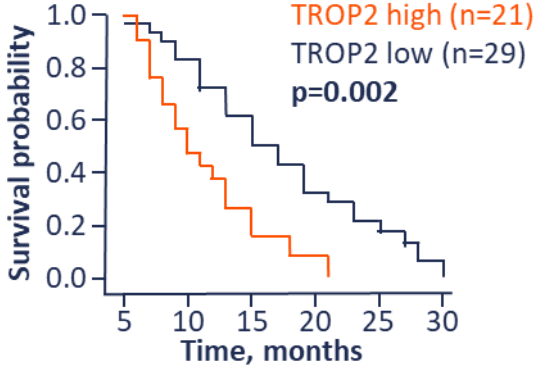
- Higher TROP2 expression associated with **shorter OS**[1–4]
- Multivariate analysis: TROP2 expression an **independent prognostic** biomarker[1,3,5]

Median OS shorter in TROP2 high* patients with a/mNSCLC[1†]

TROP2 high 11.5 months

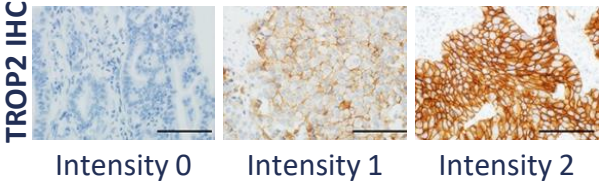
TROP2 low 17.3 months

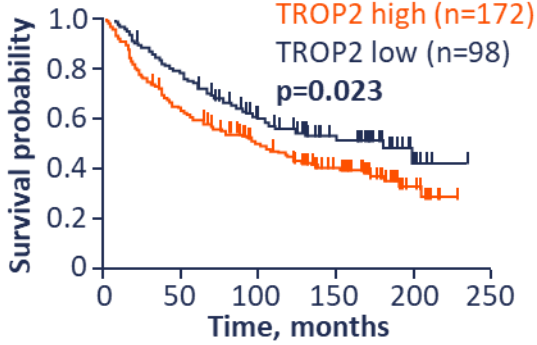




High‡ TROP2 associated with shorter OS (stage I–IV NSCLC)[2]

HR 1.49 (95% CI 1.06–2.13)





Figures reproduced from Jiang A, et al. 2013 (censoring marks not shown) and Inamura K, et al. 2017. *Defined by authors as TROP2+/-; †Stage IIIb/IV; ‡Defined by authors as TROP2 high or low/negative. a/mNSCLC, advanced/metastatic non-small cell lung cancer; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; OS, overall survival; TROP2, trophoblast cell surface antigen-2.

1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 3. Mito R, et al. *Pathol Int.* 2020;70:287–94; 4. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197–204; 5. Kobayashi H, et al. *Virchows Arch*. 2010;457:69–76.

TROP2 as a prognostic biomarker in adenocarcinoma

Some data do not support a negative prognostic role

Prognostic

- Higher TROP2 expression associated with **shorter OS**[1–4]
- Multivariate analysis: TROP2 expression an **independent prognostic** biomarker[1,3,5]

Role unclear

- Higher TROP2 expression associated with **longer OS**[6]
- TROP2 expression only prognostic in **certain subgroups**, such as those with more advanced disease or specific *EGFR* status[3,6]

TROP2 overexpression* associated with longer OS in patients with stage I–III NSCLC[6]

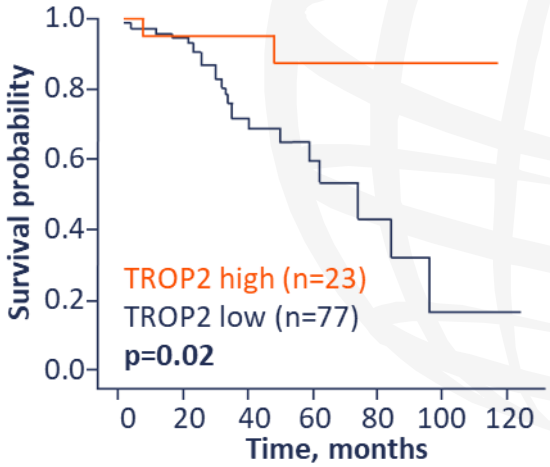
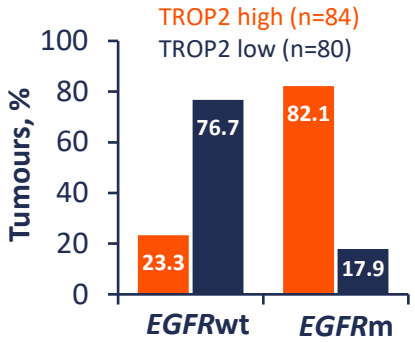
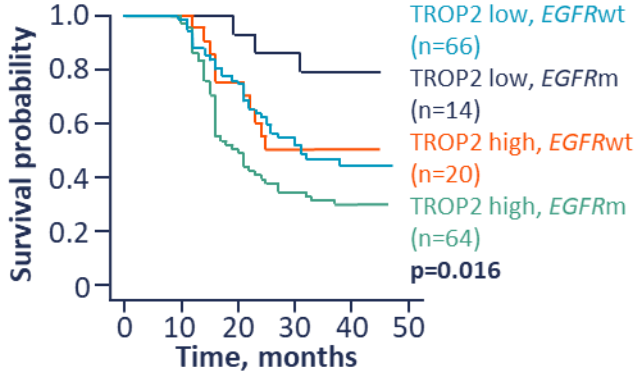


Figure reproduced from Pak MG, et al. 2012; censoring marks not shown. *Groups defined by authors as overexpression/no overexpression.
EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; TROP2, trophoblast cell surface antigen-2.
1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 3. Mito R, et al. *Pathol Int.* 2020;70:287–94;
4. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197–204; 5. Kobayashi H, et al. *Virchows Arch*. 2010;457:69–76; 6. Pak MG, et al. *World J Surg Oncol.* 2012;10:53.

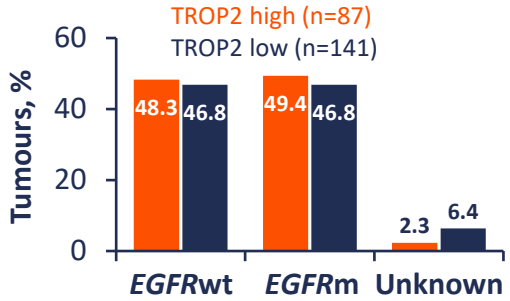
Link between TROP2 expression, *EGFR* status and OS unclear

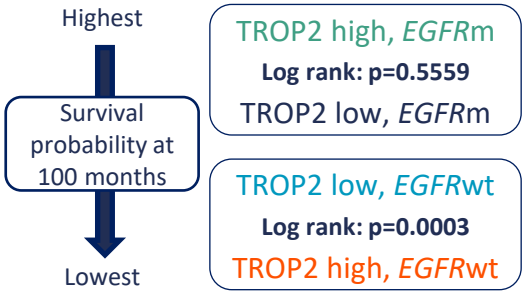
TROP2 over-expression **more common in *EGFR*m** tumours, and **shorter OS** in **TROP2 high/*EGFR*m** patients with stage I–IV NSCLC[1]





In a different study, no link between TROP2 expression and *EGFR* status, but **shorter OS** in **TROP2 high/*EGFR*wt** patients with stage I–IV NSCLC[2]





OS figure reproduced from Sun X, et al. 2021 (censoring marks not shown).
EGFR, epidermal growth factor receptor; m, mutant; NSCLC, non-small cell lung cancer; OS, overall survival; TROP2, trophoblast cell surface antigen-2; wt, wild-type.
1. Sun X et al. *J Cancer*. 2021;12:5310–19; 2. Mito R, et al. *Pathol Int.* 2020;70:287–94.

TROP2 as a prognostic biomarker in adenocarcinoma

Some data do not support a negative prognostic role

Prognostic

- Higher TROP2 expression associated with **shorter OS**[1–4]
- Multivariate analysis: TROP2 expression an **independent prognostic** biomarker[1,3,5]

Role unclear

- Higher TROP2 expression associated with **longer OS**[6]
- TROP2 expression only prognostic in **certain subgroups** such as those with more advanced disease or specific *EGFR* status[3,6]

Not prognostic

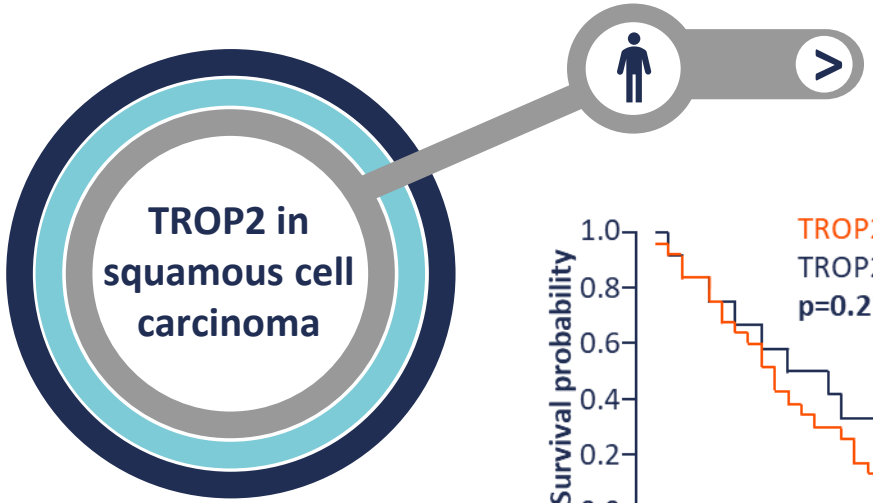
- Multivariate analysis: TROP2 expression **not associated** with prognosis[2,6]

EGFR, epidermal growth factor receptor; OS, overall survival; TROP2, trophoblast cell surface antigen-2.

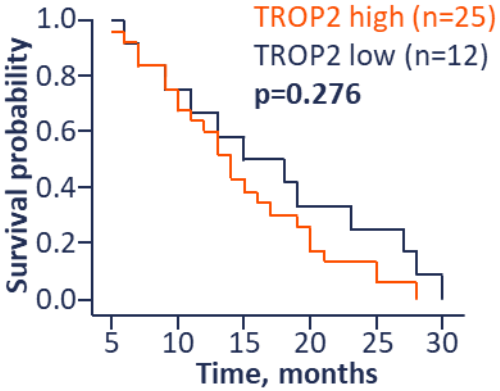
1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 3. Mito R, et al. *Pathol Int.* 2020;70:287–94;
4. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197–204; 5. Kobayashi H, et al. *Virchows Arch*. 2010;457:69–76; 6. Pak MG, et al. *World J Surg Oncol.* 2012;10:53.

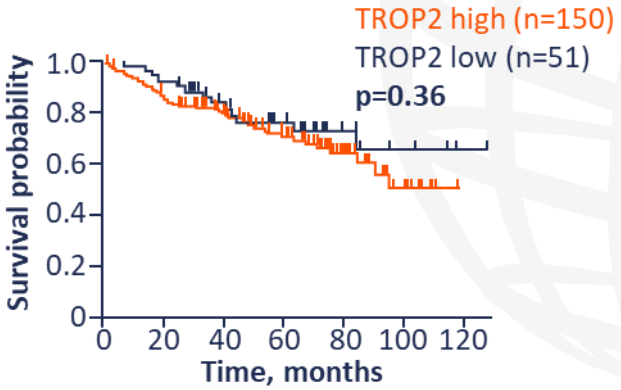
TROP2 in squamous cell carcinoma

Less evidence to support a prognostic role



No link between TROP2 expression* and **OS** in patients with stage I–IV NSCLC[1,2]

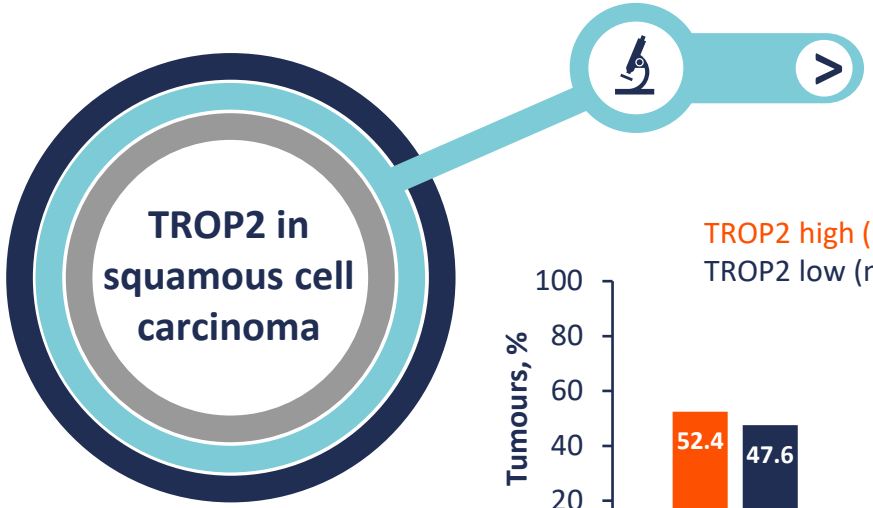




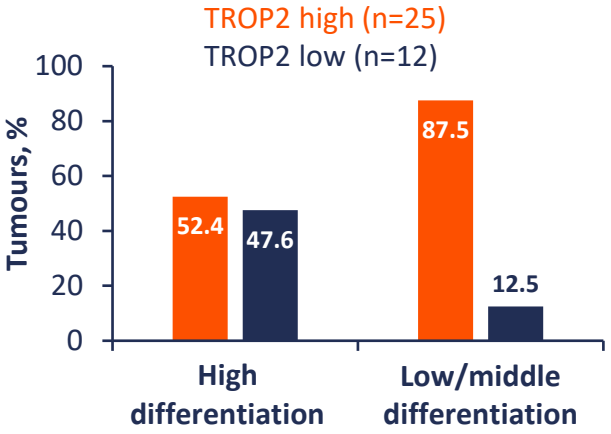
Figures reproduced from Jiang A, et al. 2013 (censoring marks not shown) and Inamura K, et al. 2017.
*Defined by Jiang et al. as TROP2+/- and by Inamura et al. as TROP2 high or low/negative.
NSCLC, non-small cell lung cancer; OS, overall survival; TROP2, trophoblast cell surface antigen-2.
1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Inamura K, et al. *Oncotarget.* 2017;8:28725–35.

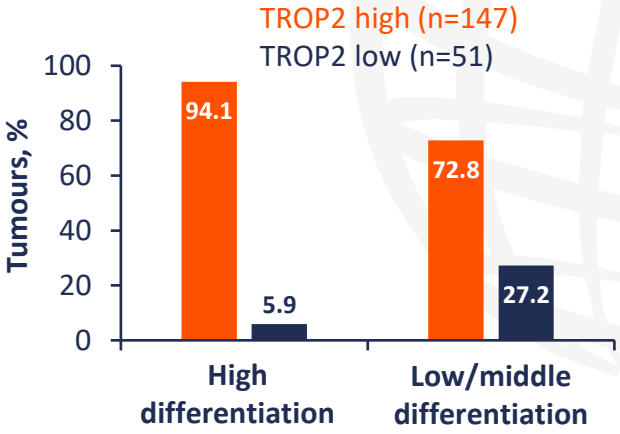
TROP2 in squamous cell carcinoma

Less evidence to support a prognostic role



TROP2 expression* associated with **tumour grade** in patients with stage I–IV NSCLC[1,2]

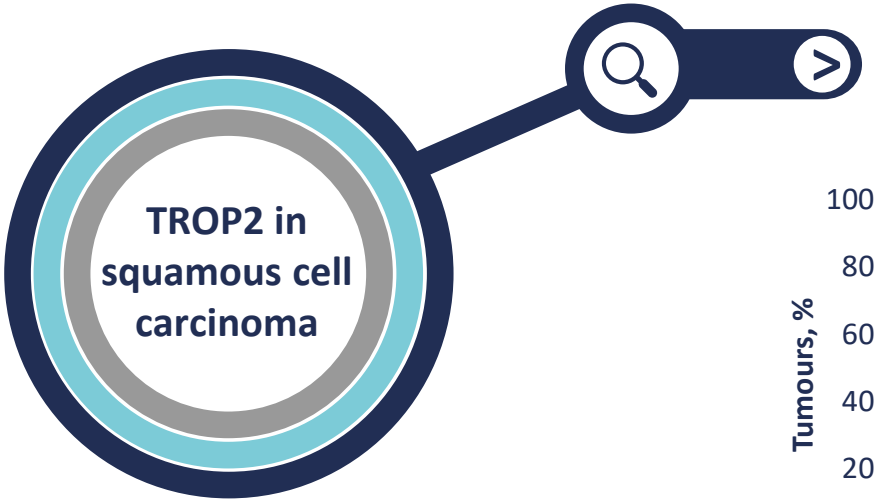




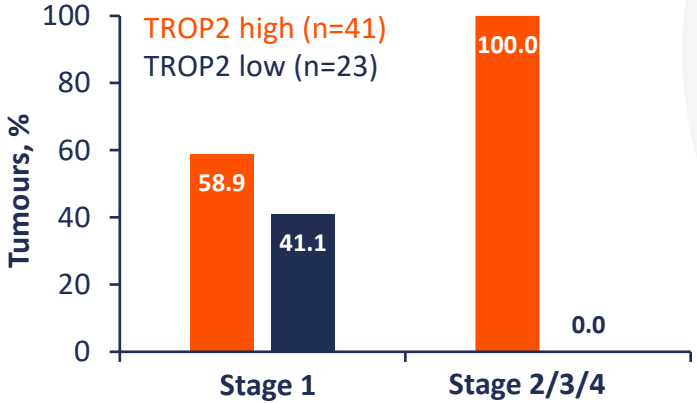
*Defined by Jiang et al. as TROP2+/- and by Inamura et al. as TROP2 high or low/negative.
NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen-2.
1. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 2. Inamura K, et al. *Oncotarget*. 2017;8:28725–35.

TROP2 in squamous cell carcinoma

Less evidence to support a prognostic role



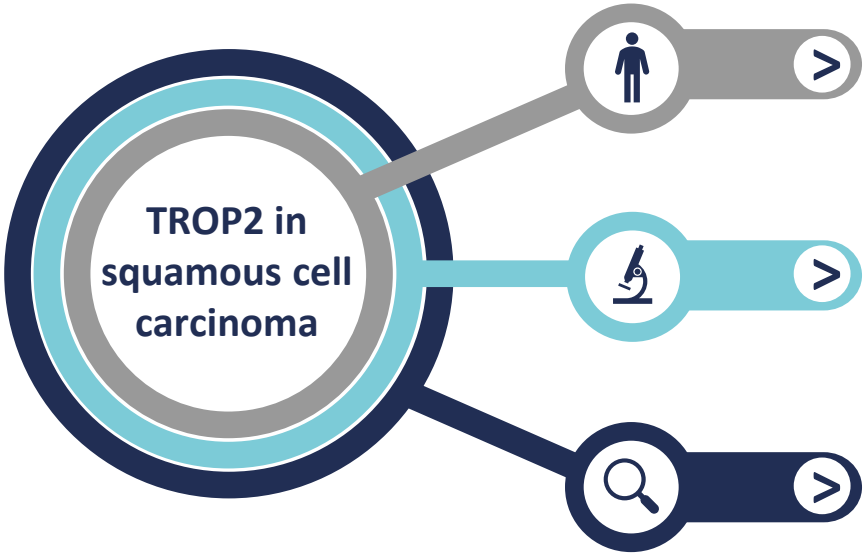
High TROP2 expression associated with **higher tumour stage** in patients with stage I–III NSCLC



NSCLC, non-small cell lung cancer; TROP2, trophoblast cell surface antigen-2.
Pak MG, et al. *World J Surg Oncol.* 2012;10:53.

TROP2 in squamous cell carcinoma

Less evidence to support a prognostic role



No link between TROP2 expression* and **OS** in patients with stage I–IV NSCLC[1,2]

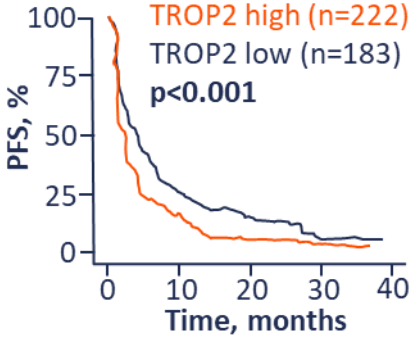
TROP2 expression* associated with **tumour grade** in patients with stage I–IV NSCLC[1,2]

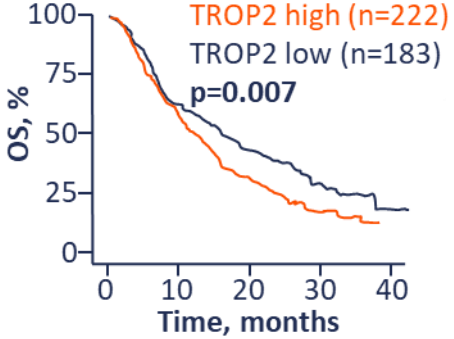
High TROP2 expression associated with **higher tumour stage** in patients with stage I–III NSCLC[3]

*Defined by Jiang et al. as TROP2+/- and by Inamura et al. as TROP2 high or low/negative.
NSCLC, non-small cell lung cancer; OS, overall survival; TROP2, trophoblast cell surface antigen-2.
1. Inamura K, et al. *Oncotarget.* 2017;8:28725–35; 2. Jiang A, et al. *Oncol Lett*. 2013;6:375–80; 3. Pak MG, et al. *World J Surg Oncol.* 2012;10:53.

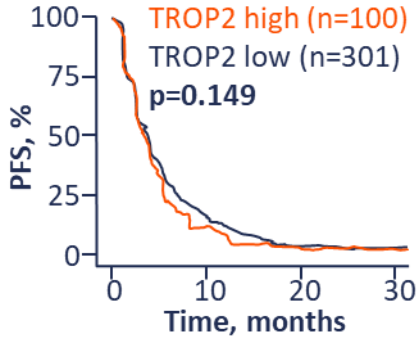
TROP2 as a biomarker of primary immunotherapy resistance

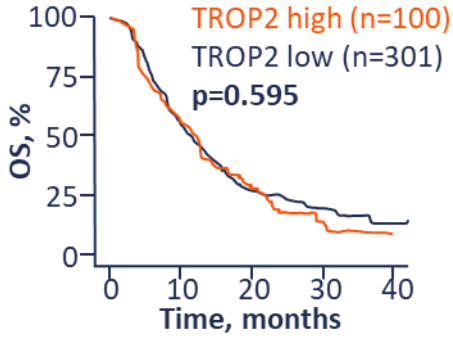
High TROP2 mRNA associated with **worse PFS and OS** in patients with a/mNSCLC* receiving **atezolizumab**





No link between TROP2 mRNA expression and PFS or OS in patients with a/mNSCLC* receiving **docetaxel**



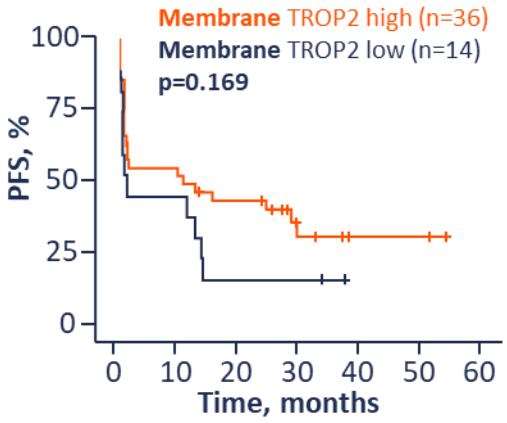


Figures reproduced from Bessede A, et al. 2024; censoring marks not shown. *Stage IIIb/IV.
a/mNSCLC, advanced/metastatic non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TROP2, trophoblast cell surface antigen-2.
Bessede A, et al. *Clin Cancer Res.* 2024;30:779–85.

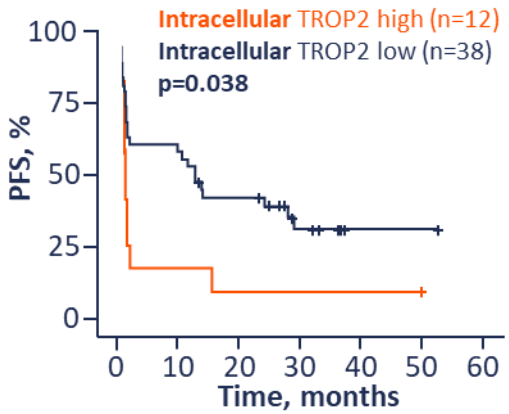
Intracellular TROP2 association with immunotherapy resistance

High **intracellular** TROP2 expression, indicating nuclear activity, associated with **poor response** to atezolizumab in patients with a/mNSCLC*

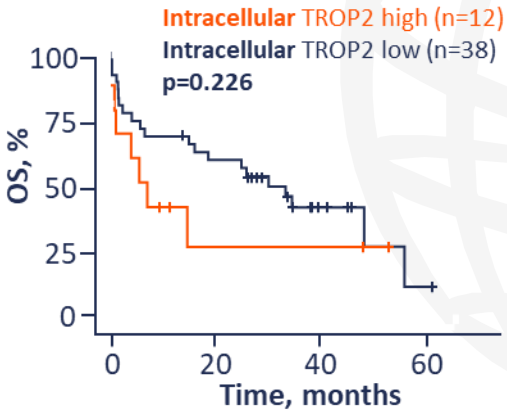
PFS by membrane TROP2



PFS by intracellular TROP2



OS by intracellular TROP2



Figures reproduced from Bessede A, et al. 2024. *Stage IIIb/IV.
a/mNSCLC, advanced/metastatic non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TROP2, trophoblast cell surface antigen-2.
Bessede A, et al. *Clin Cancer Res.* 2024;30:779–85.

TROP2 as a selective biomarker in NSCLC

TROP2-targeted ADC data currently derived from an unselected population

Potential for patient selection on the basis of TROP2 expression?

TROP2 as a selective biomarker: Data from patients receiving Dato-DXd

ICARUS-Lung01:
TROP2 membrane IHC analysis, link to PFS[1]

TROPION-Lung01:
TROP2 QCS-NMR computational pathology approach, link to ORR and PFS[2]

ADC, antibody–drug conjugate; Dato-DXd, datopotomab deruxtecan; IHC, immunohistochemistry; NMR, normalized membrane ratio; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen-2.

1. Planchard D, et al. *J Clin Oncol.* 2024;42(Suppl. 16):8501; 2. Garassino MC, et al. *J Thorac Oncol.* 2024;19:S2–3.

ICARUS-Lung01: Biomarker analysis

TROP2 expression by IHC n=78

TROP2 spatial distribution
Machine learning analysis

Gene expression modulation, n=71
Bulk RNAseq

Modulation of immune cells
Imaging mass cytometry

Genomic alterations associated with treatment response/resistance n=71
Whole exome sequencing

Blood samples n=36

CTC, ctDNA
(Baseline, C1D3 or C2D3, C2D1, EOT)

Tumour samples n=81

Modulation of immune cells
Imaging mass cytometry

Gene expression modulation, n=66
Bulk RNAseq

TROP2 expression by IHC

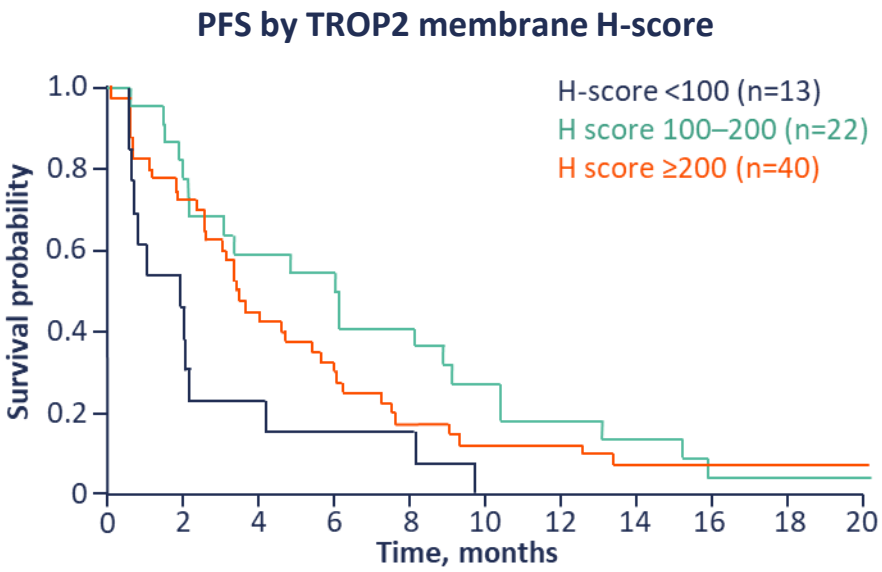
Tumour samples n=15

Genomic alterations associated with treatment response/resistance n=5
Whole exome sequencing

Figure reproduced from Planchard D, et al. 2024.
C, cycle; CTC, circulating tumour cells; ctDNA, circulating tumour DNA; D, day; EOT, end of treatment; IHC, immunohistochemistry; RNAseq, RNA sequencing; TROP2, trophoblast cell surface antigen-2.
Planchard D, et al. Presented at: ASCO annual meeting, Chicago, USA. 31 May–4 June 2024; presentation 8501. Available at: https://bit.ly/4gZzam5 (accessed 27 March 2025).

ICARUS-Lung01: Baseline tumour sample IHC

PFS with Dato-DXd by TROP2 membrane expression



Baseline TROP2 H-score (n)	<100 (13)	100–200 (22)	≥200 (40)
Median PFS, months (95% CI)	**2.0** (0.7–2.2)	**6.1** (2.1–9.2)	**3.5** (2.6–5.5)
PFS HR (95% CI)*	-	**0.37** (0.18–0.75)	**0.50** (0.26–0.94)

- Patients with a/mNSCLC[†] and **TROP2 H-score ≥100** seem to derive greatest clinical benefit from Dato-DXd

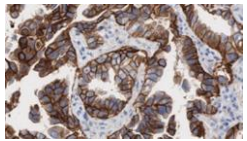
Figure reproduced from Planchard D, et al. 2024. *p=0.02 [†]Stage IIIb, IIIc or IV. a/mNSCLC, advanced/metastatic non-small cell lung cancer; CI, confidence interval; Dato-DXd, datopotomab deruxtecan; HR, hazard ratio; IHC, immunohistochemistry; PFS, progression-free survival; TROP2, trophoblast cell surface antigen-2.
Planchard D, et al. Presented at: ASCO annual meeting, Chicago, USA. 31 May–4 June 2024; presentation 8501. Available at: https://bit.ly/4gZzam5 (accessed 27 March 2025).

TROPION-Lung01: TROP2 biomarker (QCS-NMR) analysis

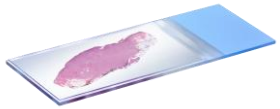
Potential for patient selection on the basis of TROP2 expression?

→ Computational pathology approach: Quantitative continuous scoring

1 TROP2 IHC



2 Whole slide imaging



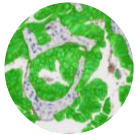
3 Automated imaging analysis (QCS)

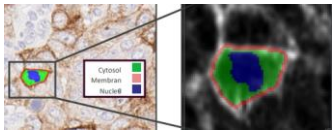
4 QCS-NMR status determination

\+ **≥75%** of tumour cells with TROP2 NMR ≤0.56

\- **<75%** of tumour cells with TROP2 NMR ≤0.56*

Differentiates tumour from non-tumour → Measures membrane and cytoplasm OD in each cell → Calculates TROP2 NMR for every tumour cell





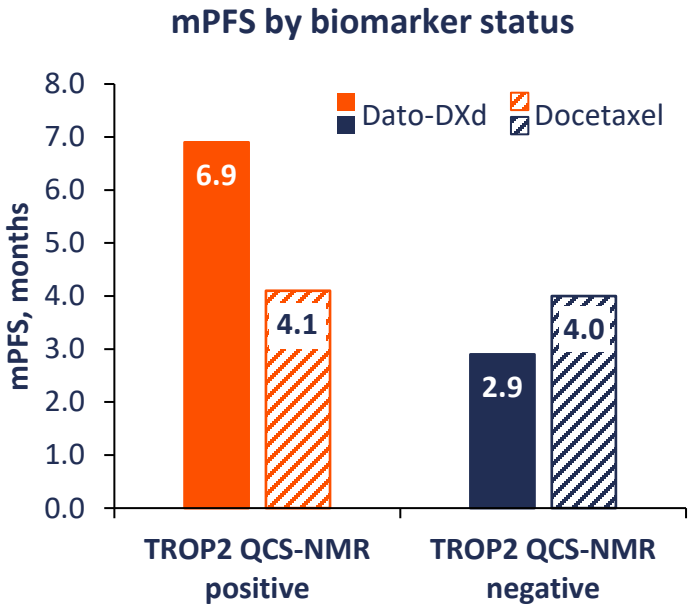
$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

Lower NMR = higher cytoplasm proportion

Figure reproduced from Garassino MC, et al. WCLC 2024. *Or >25% of cells with NMR >0.56.
IHC, immunohistochemistry; NMR, normalized membrane ratio; OD, optical density; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen-2.
Garassino MC, et al. Presented at: WCLC, San Diego, USA. 7–10 September 2024; presentation PL02-11. Available at: https://bit.ly/4kgFokv (accessed 27 March 2025).

TROPION-Lung01: Efficacy by TROP2 QCS-NMR status

Overall biomarker-evaluable population, a/mNSCLC*



Biomarker status	TROP2 QCS-NMR positive		TROP2 QCS-NMR negative	
Treatment group (n)	**Dato-DXd** (107)	**Docetaxel** (107)	**Dato-DXd** (65)	**Docetaxel** (73)
ORR, %	32.7	10.3	16.9	15.1
PFS HR (95% CI)	**0.57** (0.41–0.79)		**1.16** (0.79–1.70)	

In patients treated with Dato-DXd

TROP2 QCS-NMR positivity associated with greater ORR and mPFS

Compared with TROP2 QCS-NMR negative

Compared with docetaxel

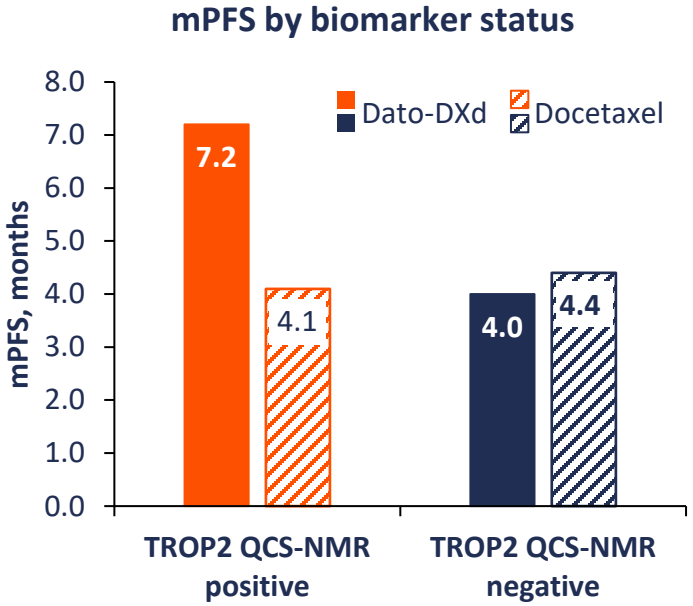
*Stage IIIb, IIIc or IV.

a/mNSCLC, advanced/metastatic non-small cell lung cancer; CI, confidence interval; Dato-DXd, datopotomab deruxtecan; HR, hazard ratio; m, median; NMR, normalized membrane ratio; ORR, overall response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen-2.

Garassino MC, et al. Presented at: WCLC, San Diego, USA. 7–10 September 2024; presentation PL02-11. Available at: https://bit.ly/4kgFokv (accessed 27 March 2025).

TROPION-Lung01: Efficacy by TROP2 QCS-NMR status

Nonsquamous, non-AGA biomarker-evaluable population, a/mNSCLC*



Biomarker status	TROP2 QCS-NMR positive		TROP2 QCS-NMR negative	
Treatment group (n)	**Dato-DXd** (68)	**Docetaxel** (72)	**Dato-DXd** (40)	**Docetaxel** (n=41)
ORR, %	36.8	15.3	22.5	12.2
PFS HR (95% CI)	**0.52** (0.35–0.78)		**1.22** (0.74–2.00)	

TROP2 QCS-NMR positivity more frequent in patients with nonsquamous histology

- Nonsquamous + AGA — **76%** biomarker positive
- Nonsquamous + non-AGA — **63%** biomarker positive
- Squamous — **44%** biomarker positive

*Stage IIIb, IIIc or IV.

a/mNSCLC, advanced/metastatic non-small cell lung cancer; AGA, actionable genomic alteration; CI, confidence interval; Dato-DXd, datopotomab deruxtecan; HR, hazard ratio; m, median; NMR, normalized membrane ratio; ORR, overall response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen-2.

Garassino MC, et al. Presented at: WCLC, San Diego, USA. 7–10 September 2024; presentation PL02-11. Available at: https://bit.ly/4kgFokv (accessed 27 March 2025).

Conclusions

Data support a prognostic role for TROP2 in adenocarcinoma, though evidence is contradictory
Will further evidence support a prognostic role for TROP2 in NSCLC?

TROP2 expression varies according to *EGFR* status
Could TROP2 be a predictive biomarker for *EGFR*-targeted therapies?

High intracellular TROP2 expression is linked to poor response to immunotherapy
Is TROP2 intracellular trafficking more predictive of outcomes than total TROP2?

TROP2 biomarker-positive patients responded better to Dato-DXd than biomarker-negative
How will the QCS-NMR approach impact patient selection and outcomes?

Dato-DXd, datopotomab deruxtecan; EGFR, epidermal growth factor receptor; NMR, normalized membrane ratio; NSCLC, non-small cell lung cancer; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen-2.

touchIME

Managing ADC toxicities in NSCLC clinical practice

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Summary

TROP2 ADCs are emerging as a novel class of drugs with a distinct mechanism of action, offering potential benefits for certain patients with a/mNSCLC

TROP2 ADCS are associated with distinct adverse event profiles; additional research is required to establish optimal usage strategies to enhance patient outcomes

Digital biomarkers mark the beginning of a new era in biomarker technology; they are easy to use and highly reproducible

ADC, antibody–drug conjugate; a/mNSCLC, advanced/metastatic non-small cell lung cancer; TROP2, trophoblastic cell surface antigen-2.