19th Annual

ATLANTA
LUNG CANCER SYMPOSIUM

Will ADCs Be Incorporated in 1L NSCLC Without Driver Mutations?

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No!

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Disclosures

Consultant/ Advisory Board Involvement/ Speakers Bureau	**Advisory board/Consultant:** (Personal fees) AstraZeneca, Abbvie, Boehringer Ingelheim, EMD Serono, Genentech, Janssen, Jazz, Loxo Lilly, Mirati/BMS, Pfizer, Regeneron, Revolution Medicines, Sanofi Genzyme, Takeda **Research support:** (Institutional) Janssen, Loxo Lilly, Boehringer Ingelheim, Mirati/BMS, Regeneron
Stock or Shareholder	None

Presentation may include discussion of therapies which are not yet approved for use.

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Stock or Shareholder	None

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To date, there are no FDA approved ADCs in the Driver Mutation Negative 1L NSCLC

Disclosures

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Maybe...

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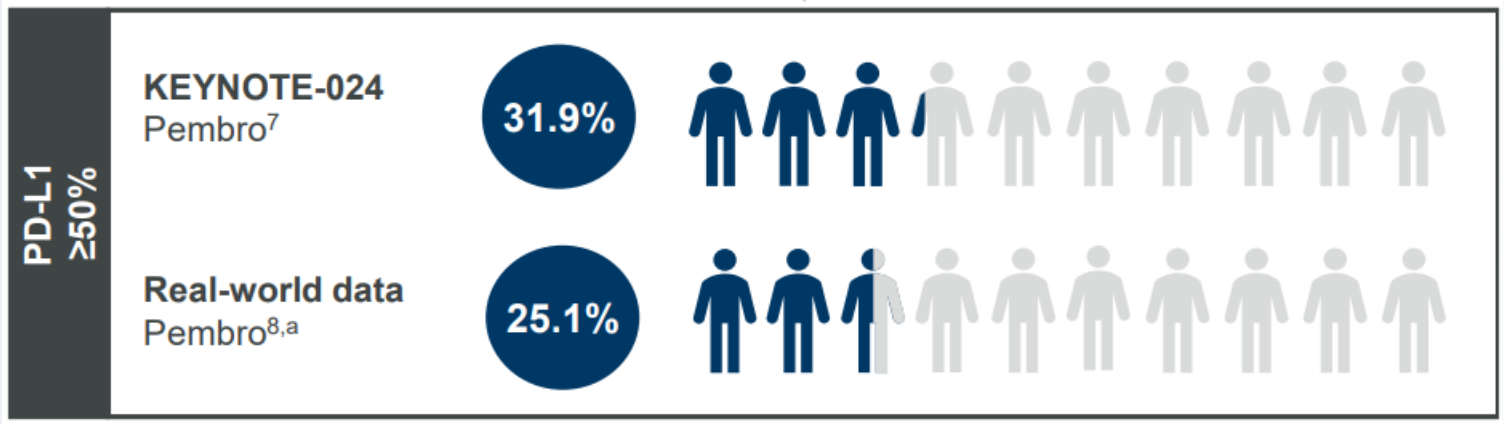
5 Year Overall Survival Driver Mutation Negative NSCLC



1. Mok T, et al. Lancet. 2019;393:1819–1830; 2. Paz-Ares L, et al. J Thorac Oncol. 2020;15:P1657–P1669; 3. Garassino MC, et al. J Clin Oncol. 2023;41:1992–1998; 4. Cortellini A, et al. Eur J Cancer. 2021;148:P24–P35; 5. Socinski MA, et al. N Engl J Med. 2018;378:2288-2301. 6. Peters S, et al. Presented at ESMO IO 2022; December 7-9, 2022; Geneva, Switzerland; 7. Reck M, et al. J Clin Oncol. 2021;39:2339-2349; 8. Velcheti V, et al. Clin Lung Cancer. 2025;8:e2514527; 9. Garassino MC, et al. J Clin Oncol. 2023;41:1992-1998

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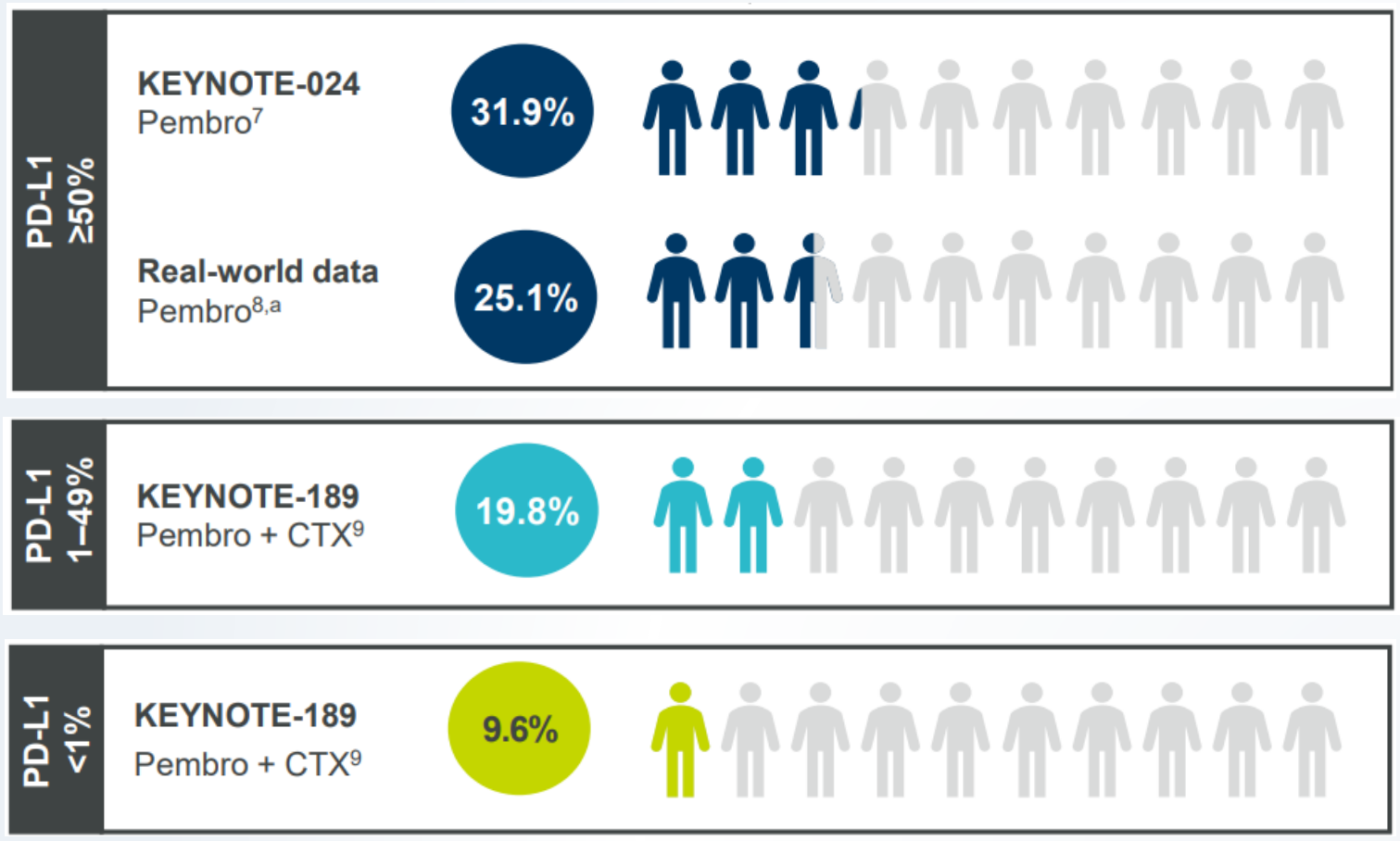

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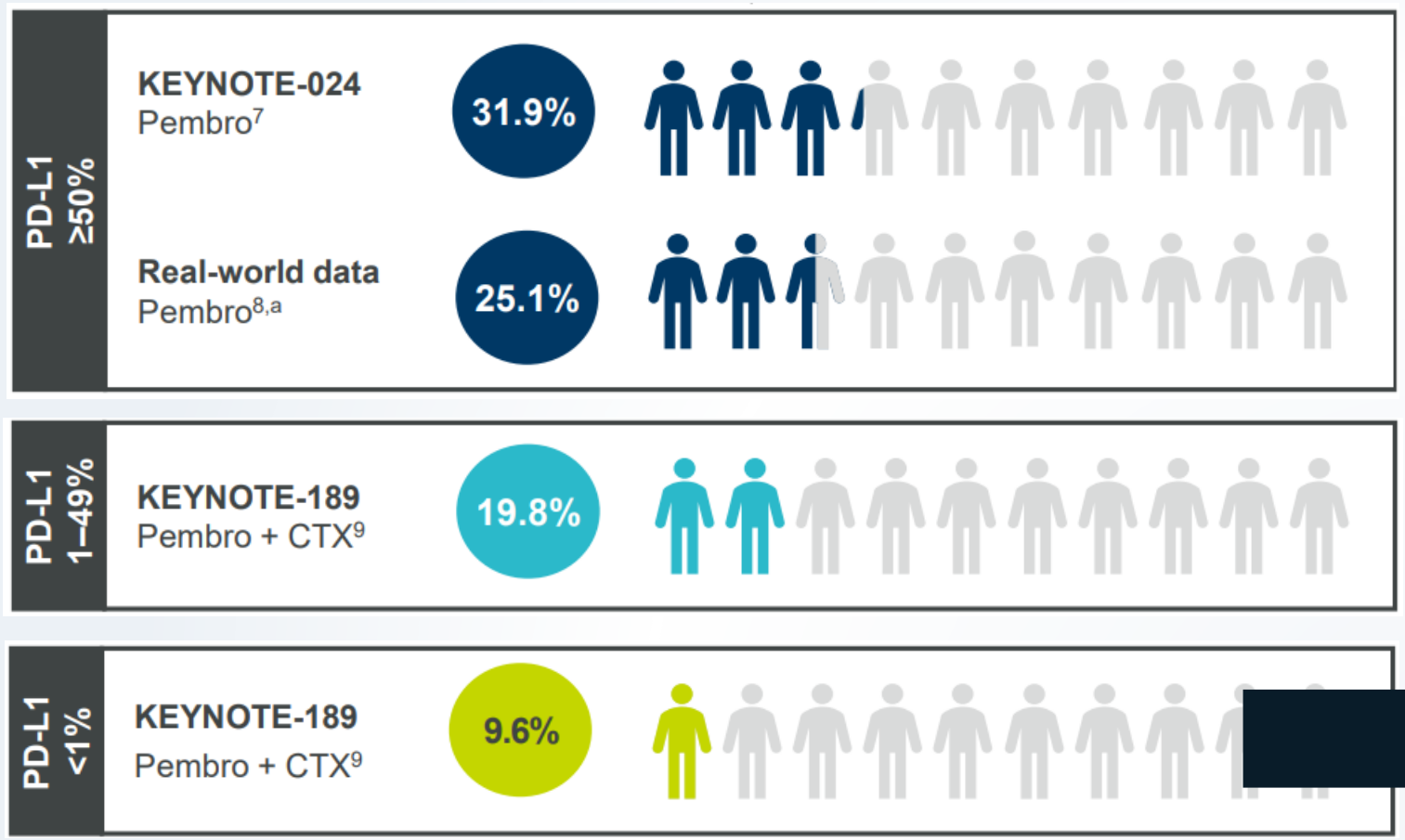

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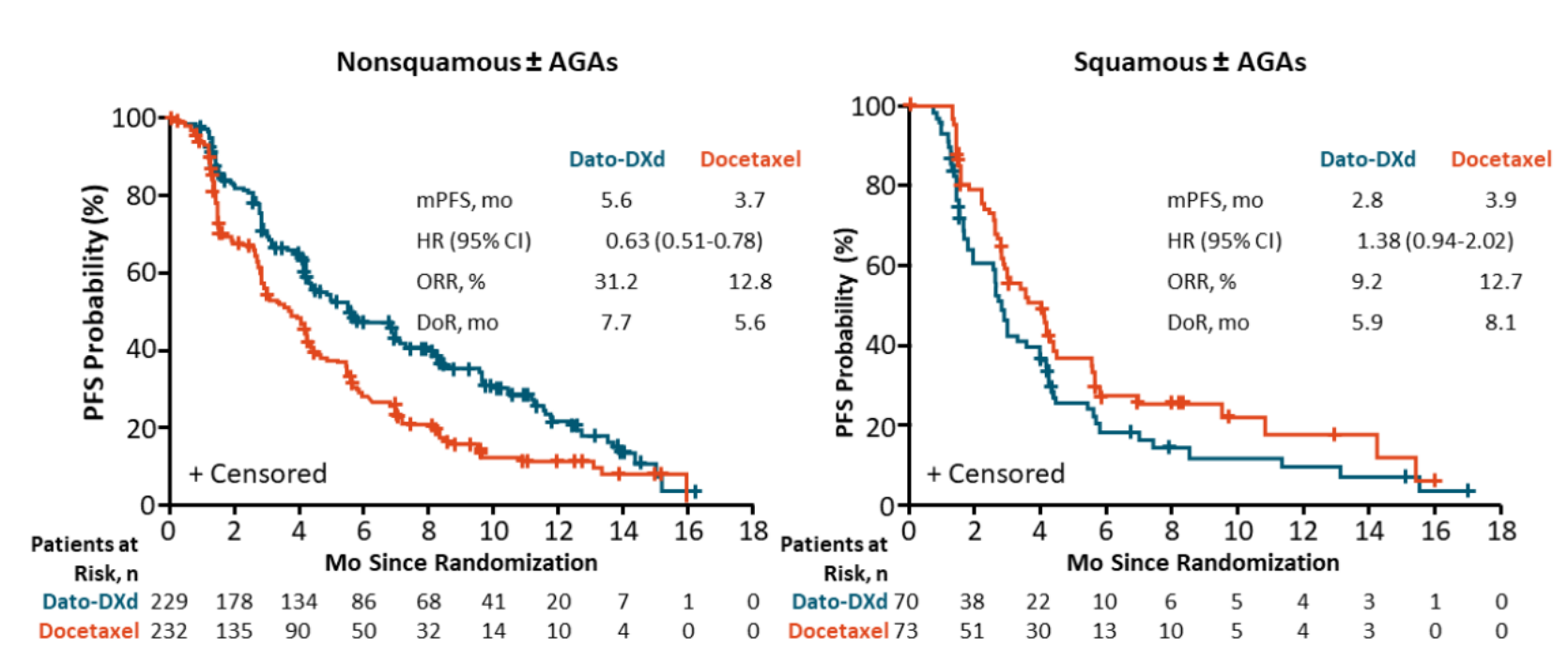
Squamous cell histology?
Tropion Lung 01: Subset Analysis by Histology

Lisberg A et al ESMO 2023 LBA12

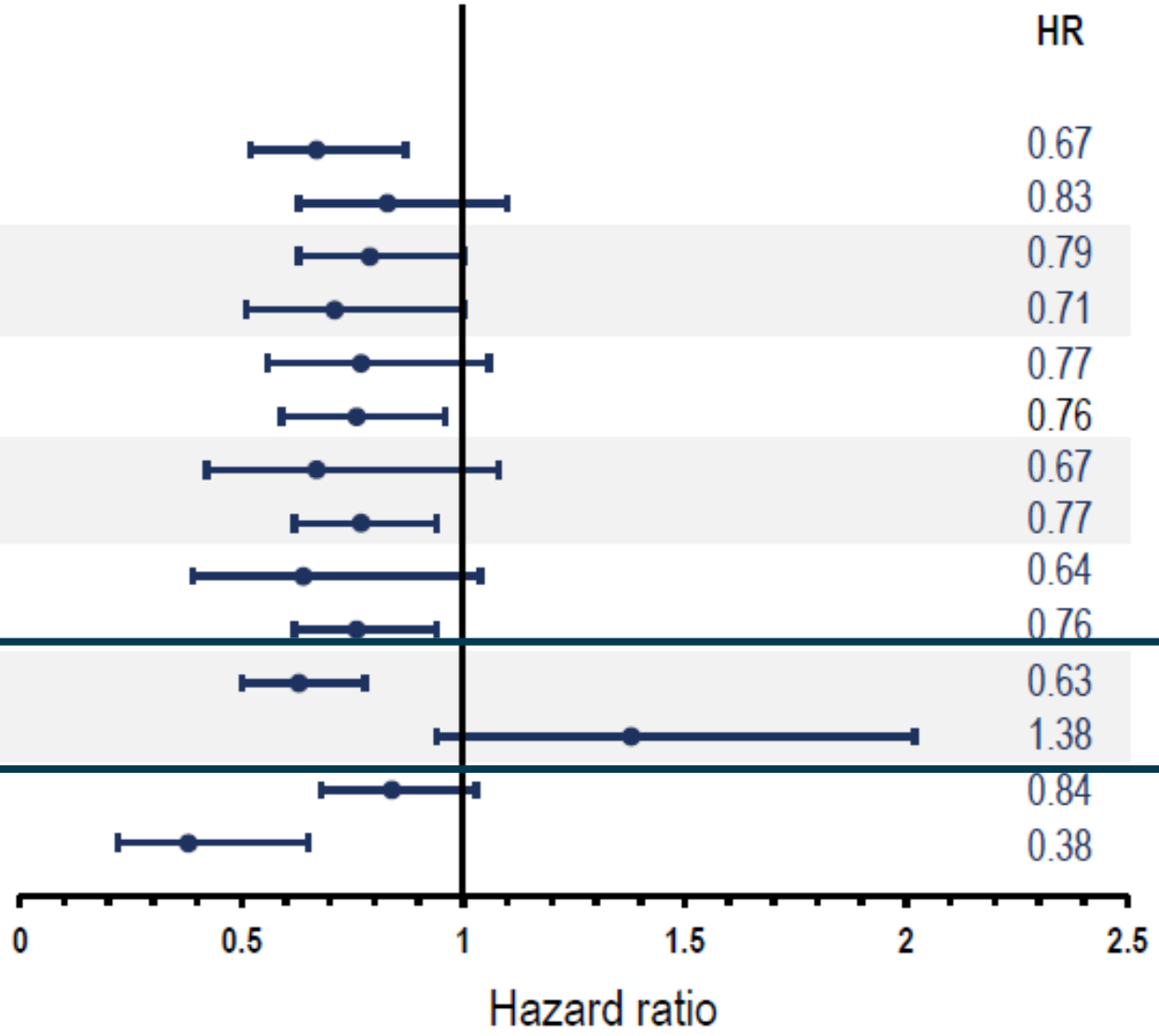
Squamous cell histology?
Tropion Lung 01: Subset Analysis by Histology



Lisberg A et al ESMO 2023 LBA12

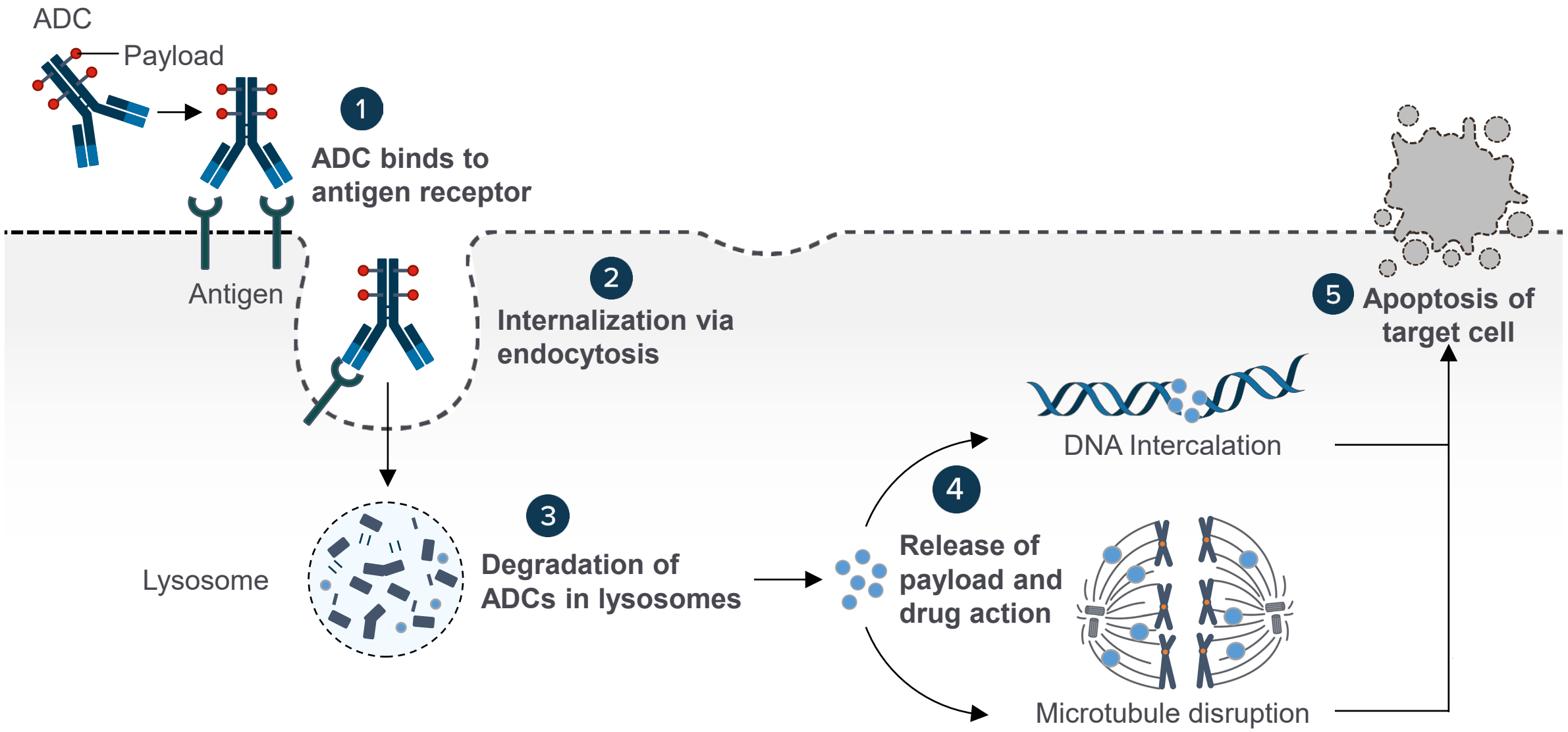
TROPION Lung 01 Subset Analysis

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38



Lisberg A et al ESMO 2023 LBA12

Mechanism 1: The ADC is Internalized and Degraded

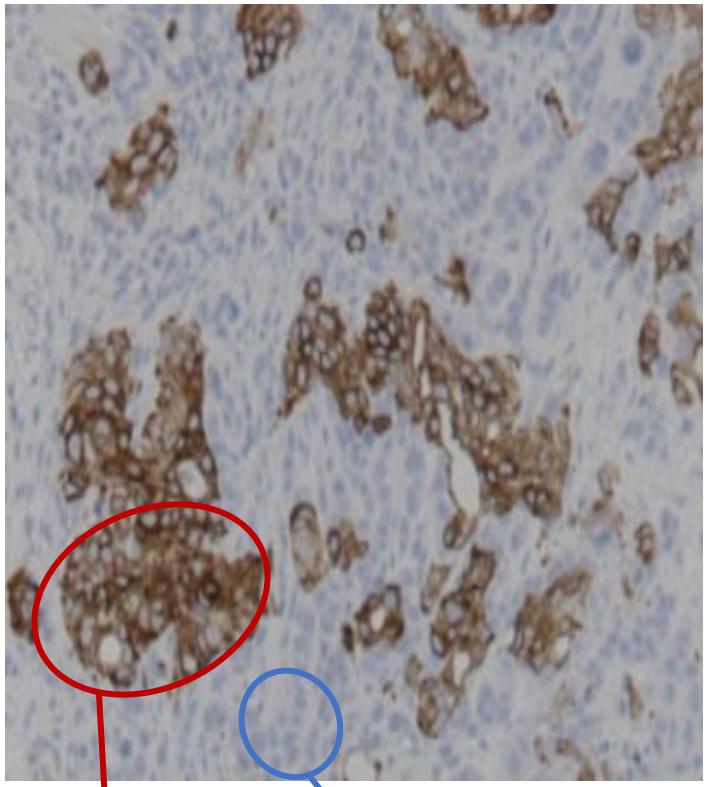


Slide Courtesy: Dr. Ben Levy; Chau CH, et al. Lancet. 2019

Mechanism 2: Bystander Effect

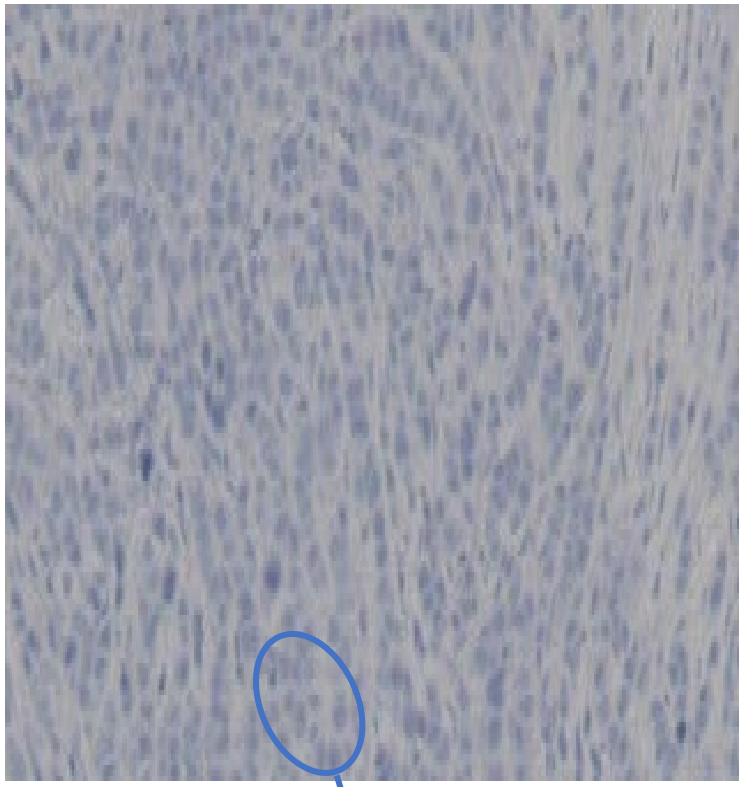
Control

Co-culture of HER2+ and HER2- tumors in vivo



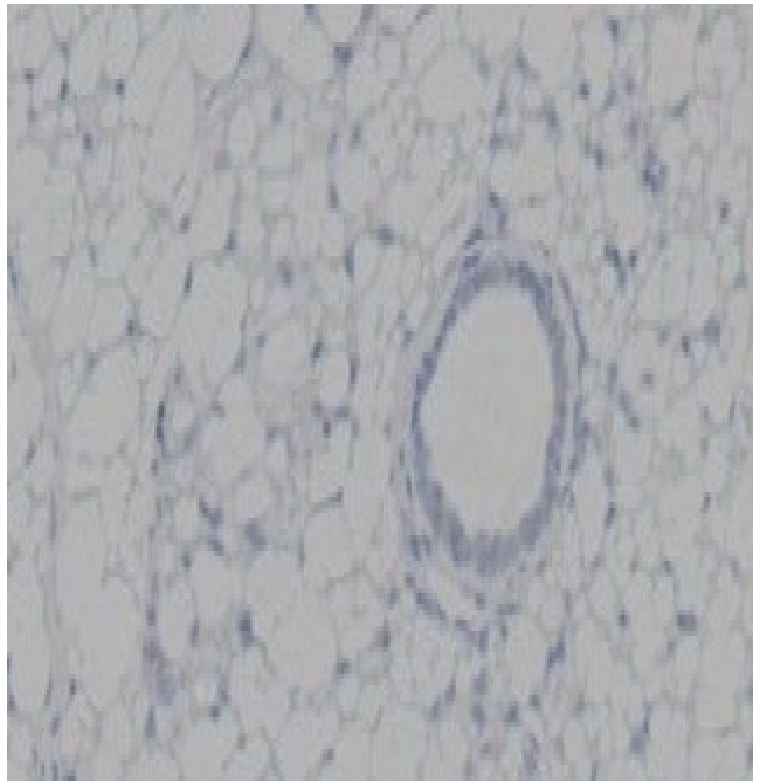
T-DM1, 10 mg/kg

HER2- cells still persist



T-DXd, 3.0 mg/kg

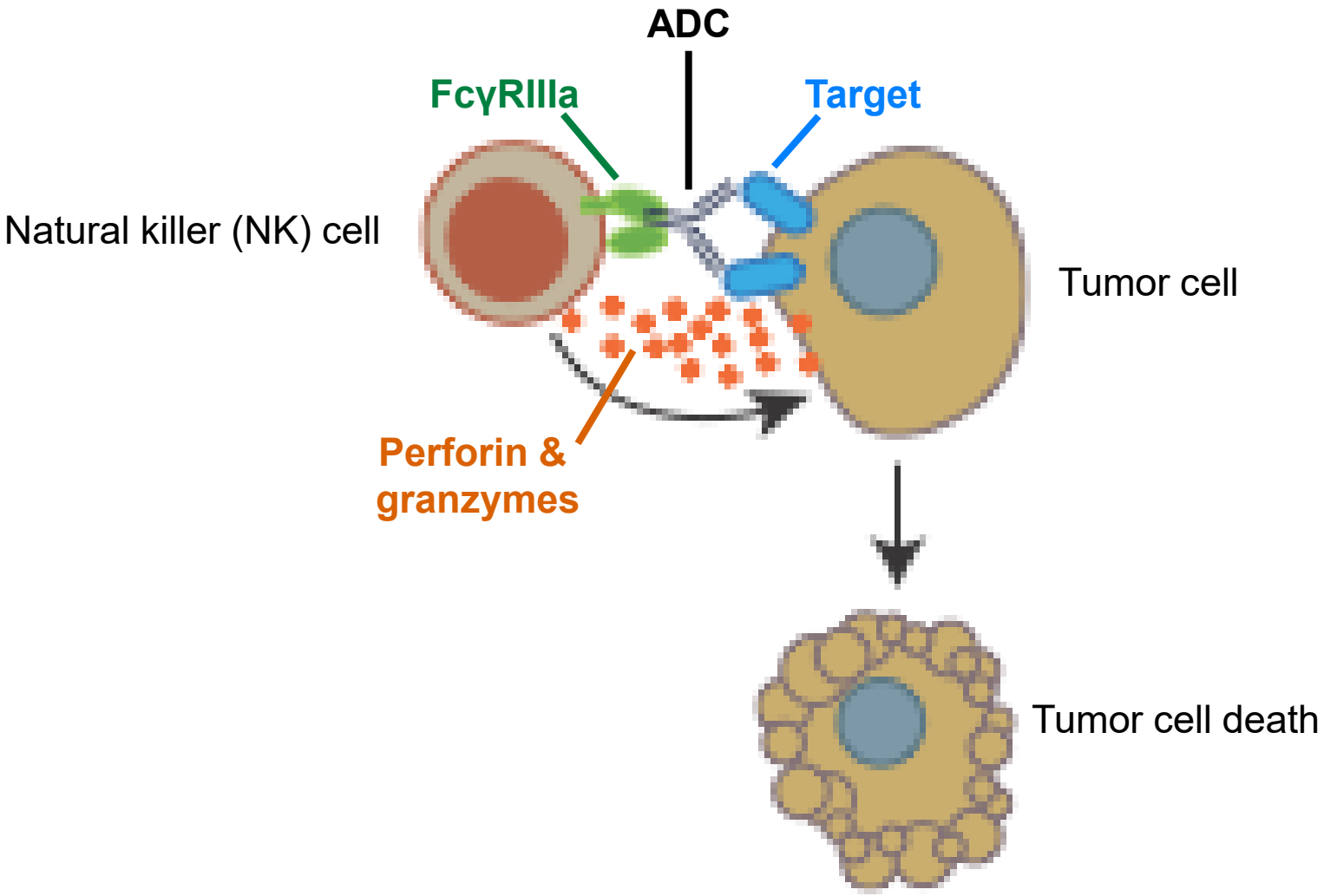
Both HER2+ and HER2- are impacted



Tumor regression

Slide Courtesy: Dr. Ben Levy; Ogitani Y et al. Cancer Sci. 2016

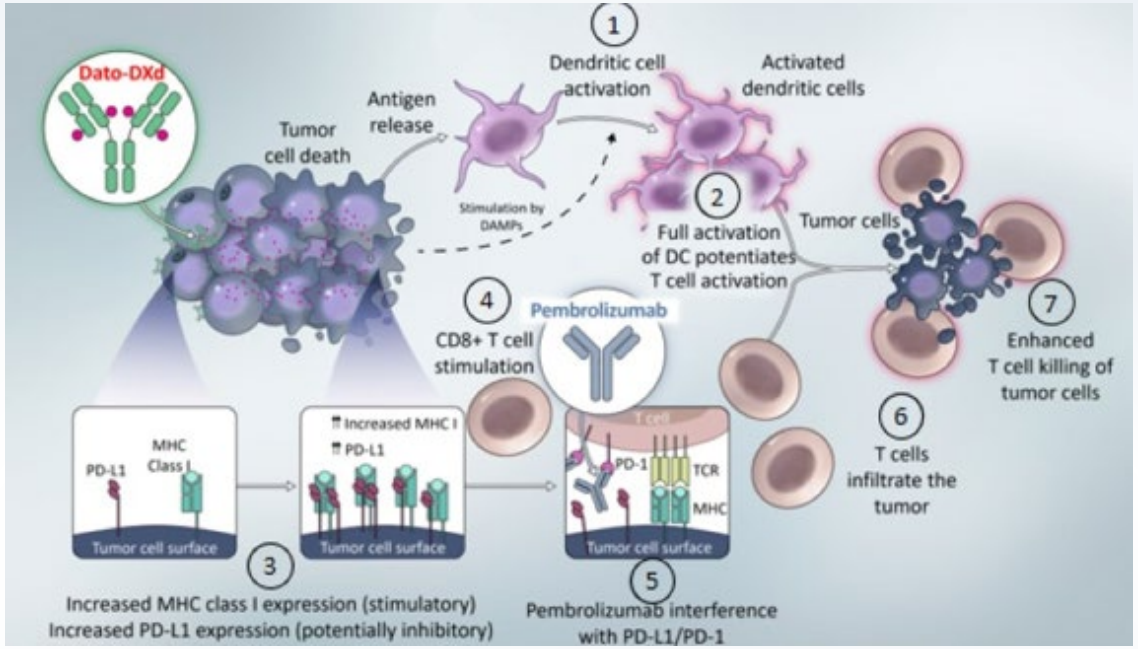
Mechanism 3: Antibody-Dependent Cellular Cytotoxicity



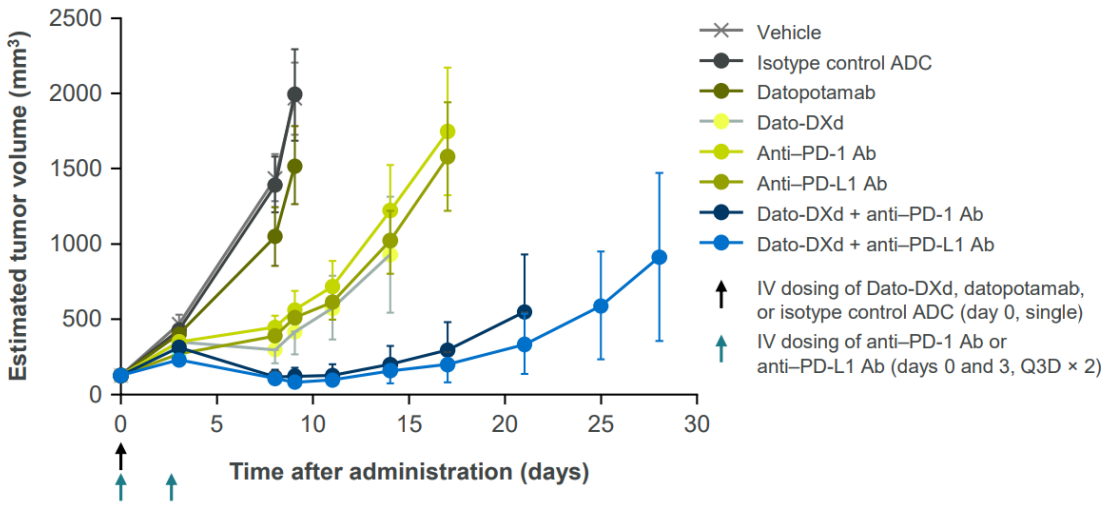
Slide Courtesy: Joseph Murray, MD, Phd

Rationale for combining ADCs with Immunotherapy

- Dato-DXd increased antitumor activity in immunocompetent mouse models expressing TROP2 compared to mice without TROP2 expression
- Combination of Dato-DXd + PD1/PDL1 blockade enhanced antitumor activity over monotherapy in tumors expressing TROP2
    - Increase in tumor infiltrating CD8+ T cells
- Dato-DXd activity was attenuated by depletion of CD8+ T cells



hTROP2-MC38 tumor volume in C57BL/6 mice[1]



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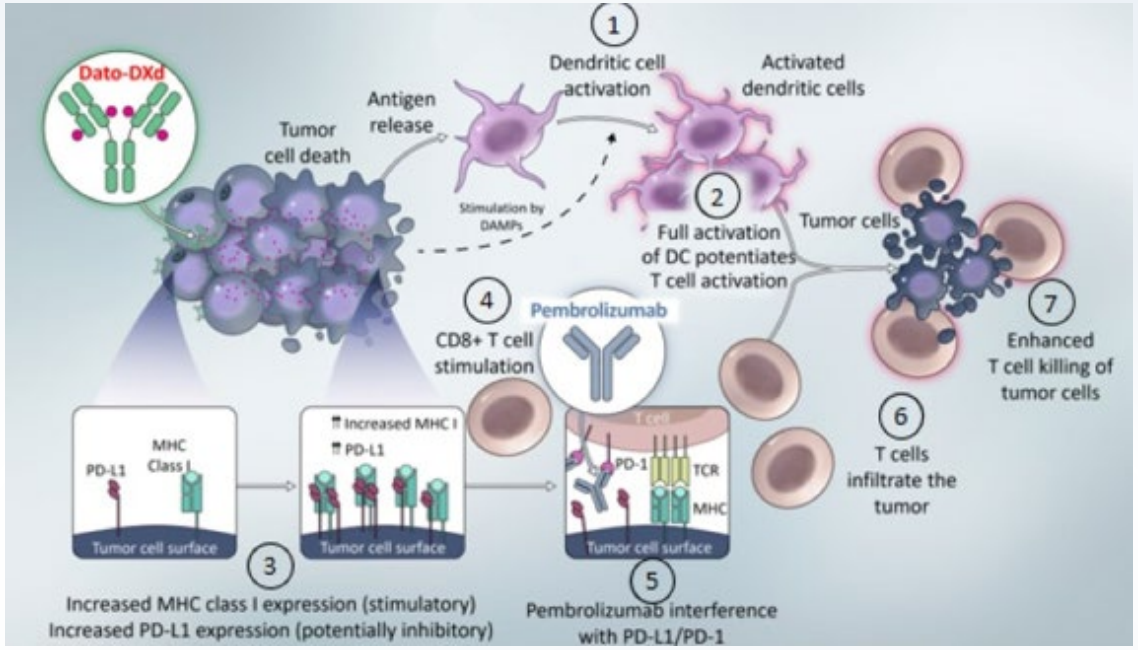
  - Increase in tumor infiltrating CD8+ T cells
- Dato-DXd activity was attenuated by depletion of CD8+ T cells
- **Is this significantly different from conventional chemotherapy?**



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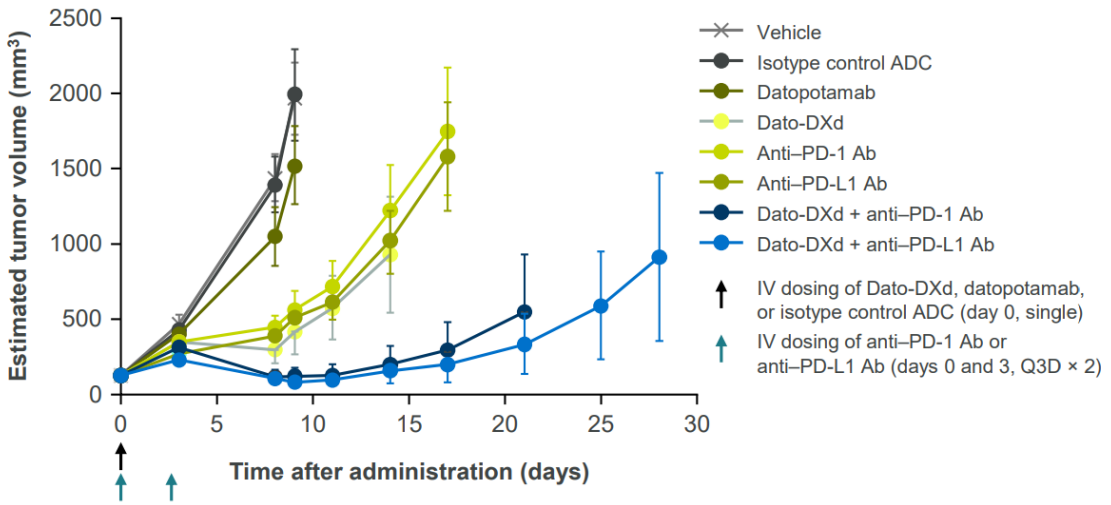

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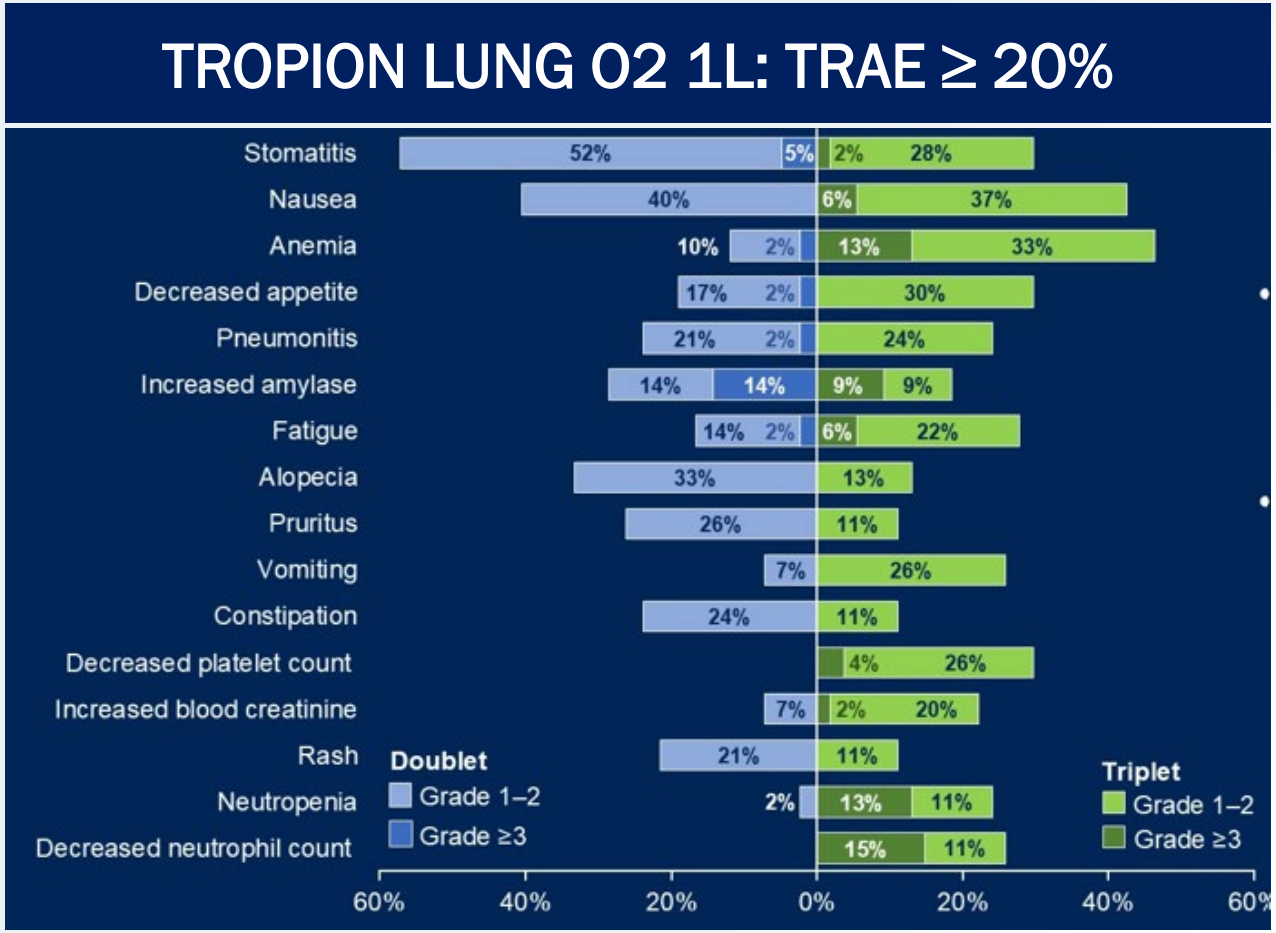
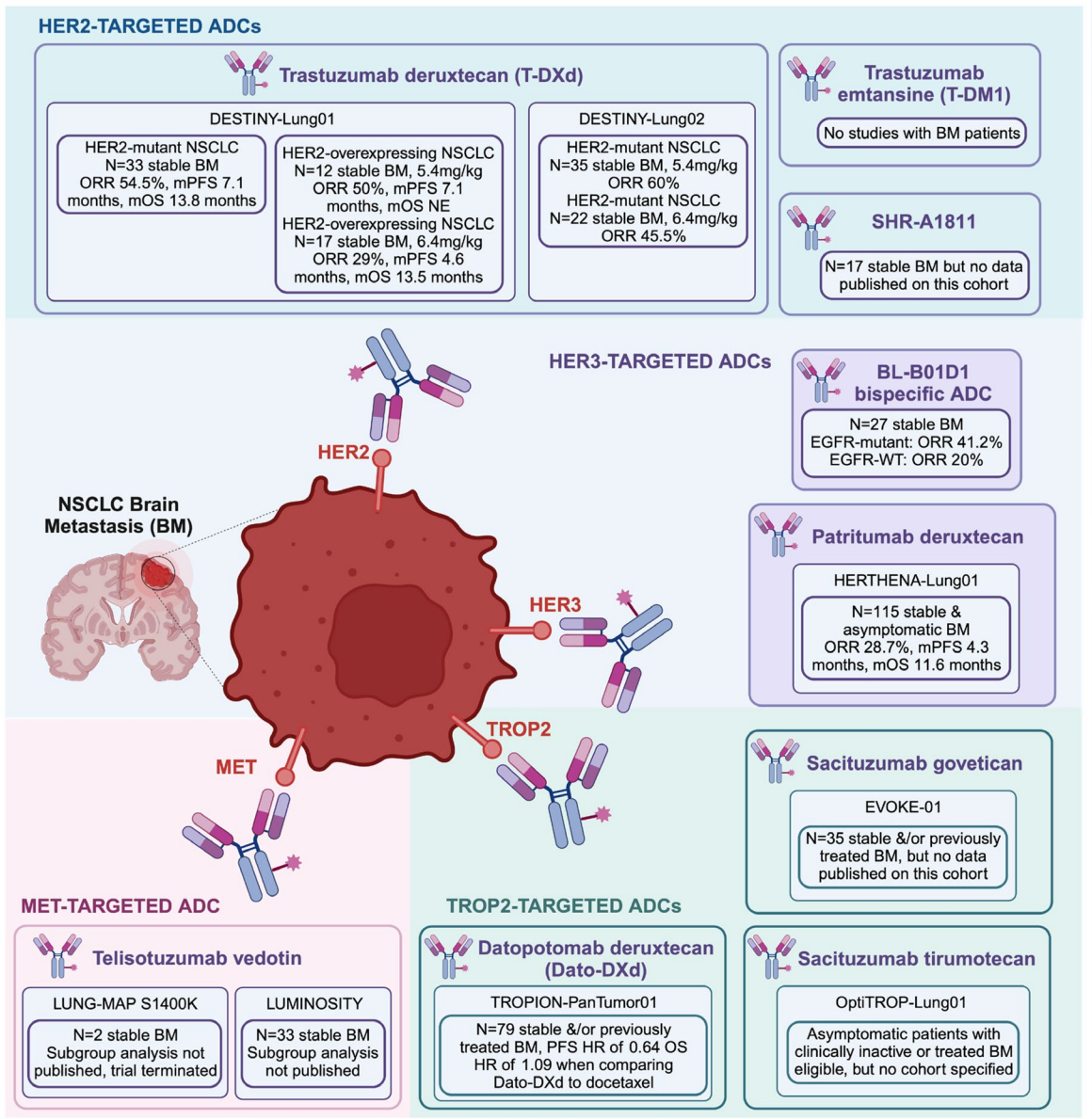
Barriers to ADCs in the 1L Setting



- Toxicity / Quality of life
  - Stomatitis, nausea, fatigue, diarrhea, ILD
  - Subspecialty care: Ophtho, Pulm, Derm
- Dose reduction / Discontinuation of SOC / Efficacy
- Lack of Biomarker Selection
- Payload Resistance
- CNS Activity
- Financial burden:
  - Cost of therapy, supportive meds, chair time

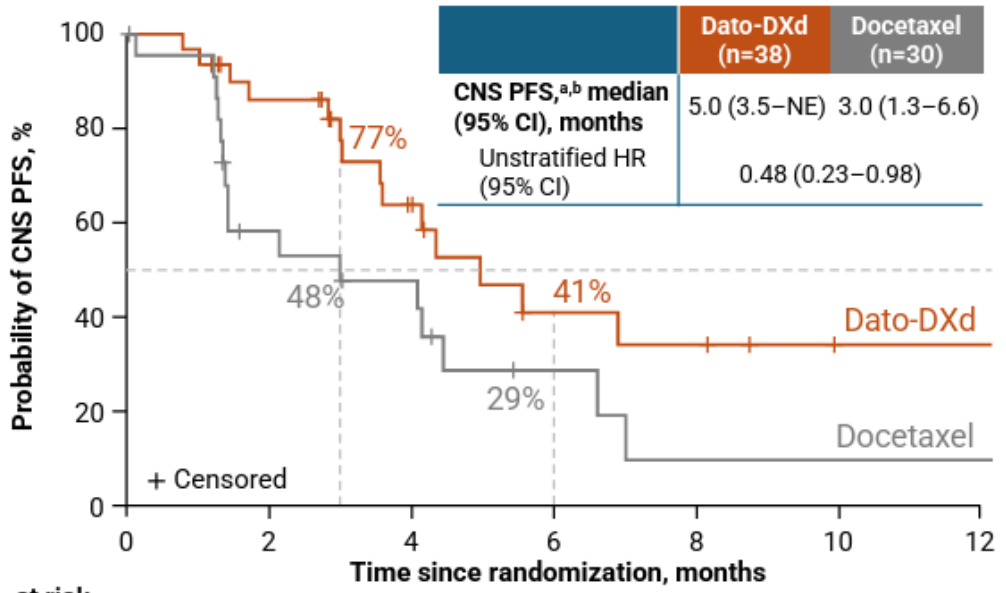
Levy B et al ASCO 2025 Tropion Lung 02

CNS Activity of ADCs



	Dato-DXd (n=16)	Docetaxel (n=11)
CNS confirmed ORR,[a] % (95% CI)	38 (15–65)	0 (0–29)
CNS confirmed BOR,[a] n (%)		
CR	1 (6)	0
PR	5 (31)	0
SD	8 (50)	4 (36)
PD	0	2 (18)
NE	2 (13)	5 (46)
CNS confirmed DCR,[a] % (95% CI)	88 (62–98)	36 (11–69)

All Patients With Untreated BM or Progression After RT



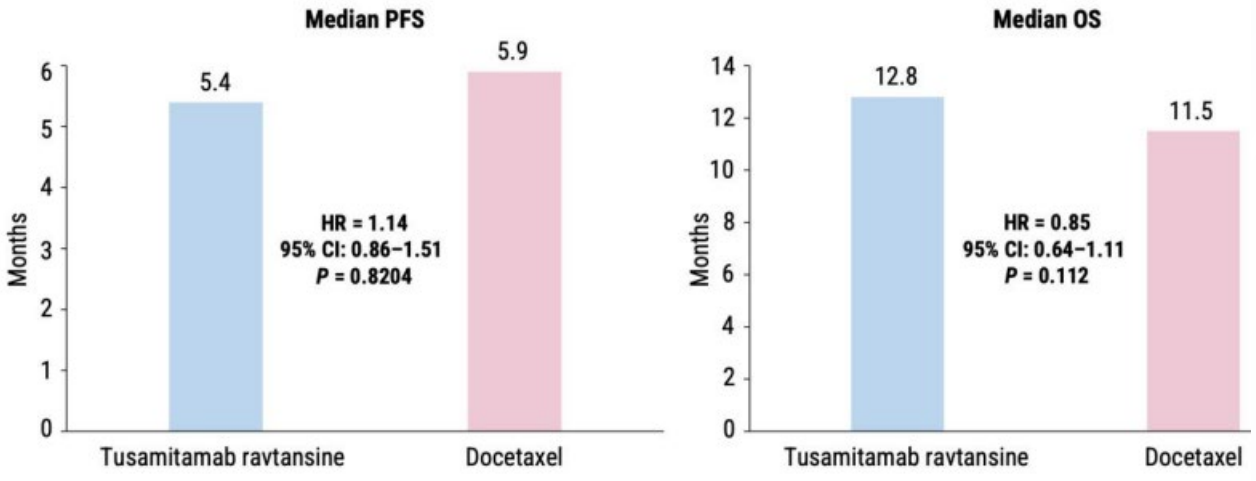
	Dato-DXd (n=38)	Docetaxel (n=30)
CNS PFS,[a,b] median (95% CI), months	5.0 (3.5–NE)	3.0 (1.3–6.6)
Unstratified HR (95% CI)	0.48 (0.23–0.98)	

Pons-Tostivint E. et al WCLC 2025 Post Hoc Analysis Tropion Lung 01

Driver Mutation Negative NSCLC, Second Line Setting
To date (10/25/25), No ADCs have shown OS improvement over SOC

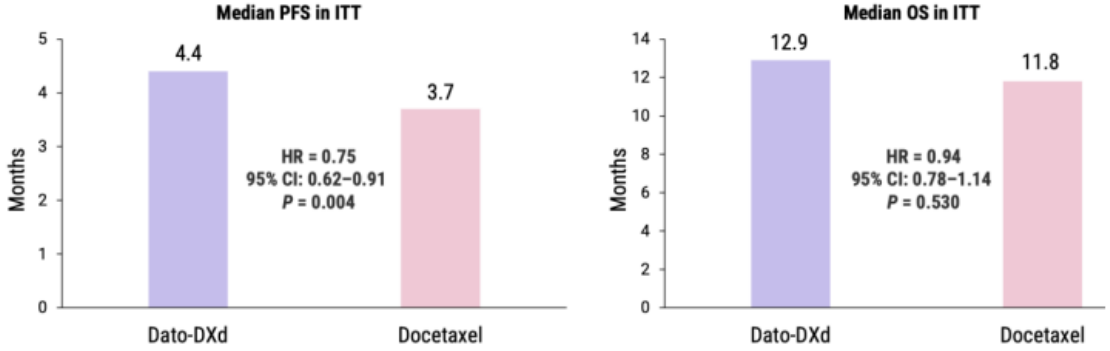
CARMEN-LC03: Results[1,2]

Phase 3, randomised, open-label, study examining tusamitamab ravtansine vs docetaxel in patients with pretreated, advanced, non-squamous CEACAM5-positive NSCLC



TROPION-Lung01: Results

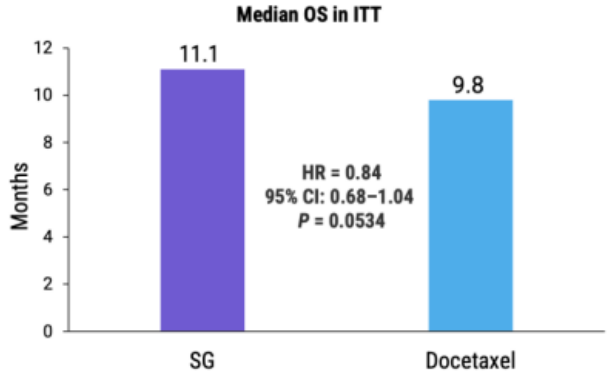
Phase 3 study examining datopotamab deruxtecan vs docetaxel in pre-treated patients with advanced/metastatic NSCLC with or without actionable genomic alterations



EVOKE-01: Efficacy

Phase 3 study examining sacituzumab govitecan vs docetaxel in patients with mNSCLC progressing on or after PBC and anti-PD-(L)1 treatment

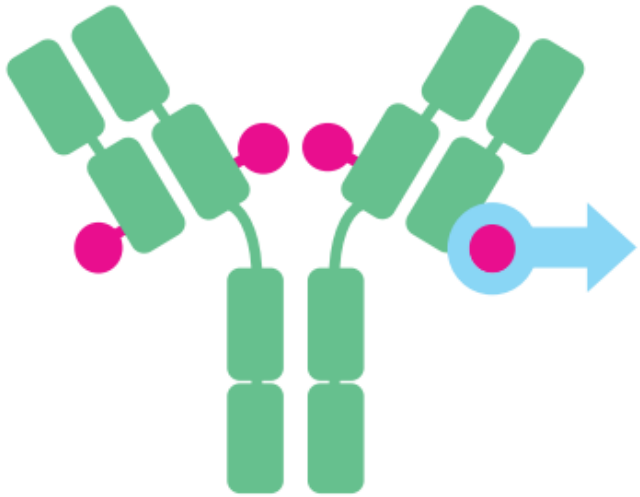
- Patients were randomised to receive either 10 mg/kg sacituzumab govitecan on Day 1 and 8 or 75 mg/m^2 docetaxel on Day 1 of each 21-day cycle



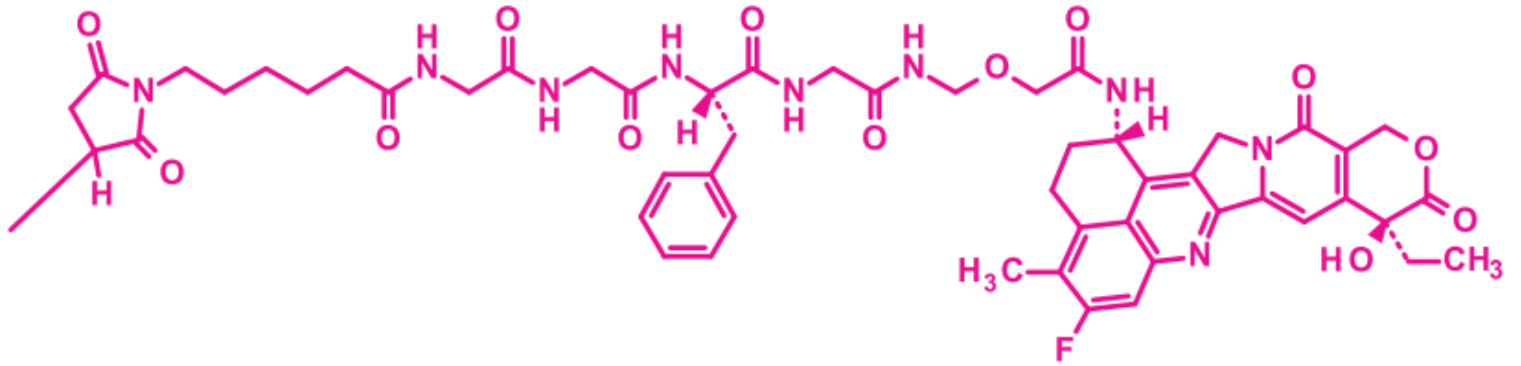
Ahn MJ, et al. JCO 2025; Paz-Ares L, et al. JCO 2024; The ASCO post Aug 2025

Dato DXd

Humanized anti-TROP2 IgG1 mAb[6]



Deruxtecan[6]



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

Front line studies of Dato DXd

TROPION-Lung02 (NCT04526691) Phase 1b DatoDXd + Pembrolizumab +/- Chemotherapy

TROPION-Lung04 (NCT04612751) Phase 1b DatoDXd + IO [Durvalumab, AZD2936, MEDI5752] +/- Chemo

TROPION-Lung07 (NCT05555732) Phase 3 DatoDXd + Pembrolizumab +/- Chemotherapy vs KN189 in 1L

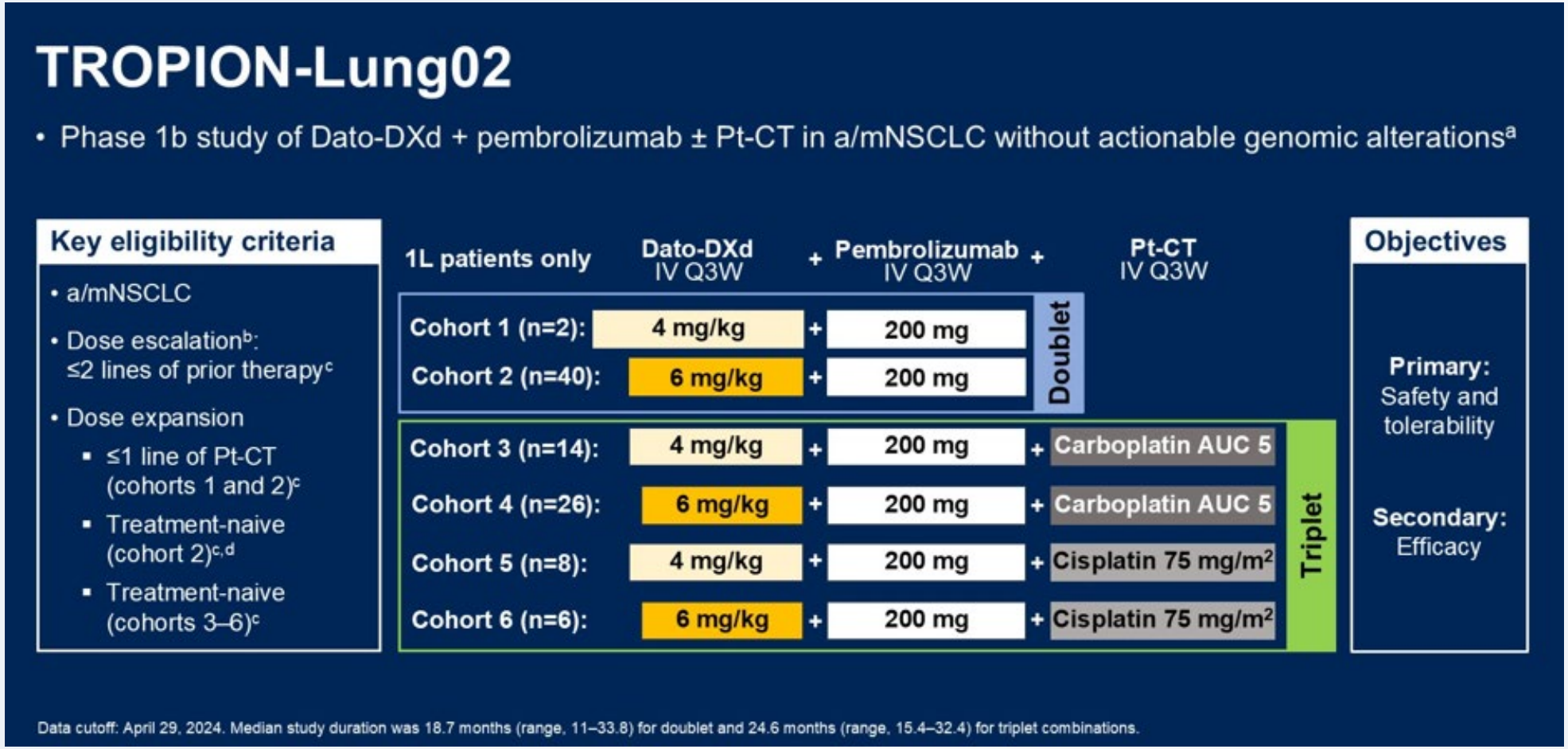
TROPION-Lung08 (NCT05215340) Phase 3 DatoDXd + Pembrolizumab vs Pembrolizumab in 1L

AVENZAR (NCT05687266) Phase 3 DatoDXd + Durvalumab + Chemotherapy vs Chemotherapy + Pembrolizumab in 1L

TROPION-Lung10 (NCT06357533) Phase 3 DatoDXd + Rivegostomig vs Pembrolizumab in 1L PDL1 >50%

NCT05555732; NCT04612751; NCT0555732; NCT05215430: NCT05687266; NCT06357533

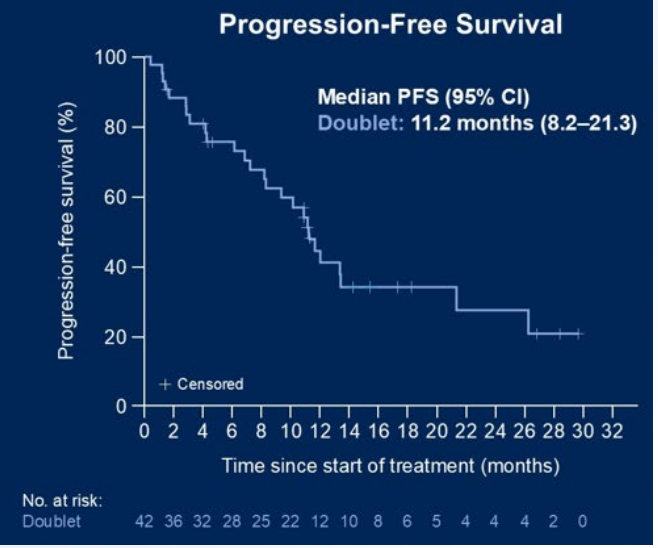
TROPION Lung 02 Schema:
Doublet: Dato DXd + Pembrolizumab
Triplet: Dato DXd + Pembrolizumab + Platinum Chemotherapy



Efficacy of Dato DXd 1L Doublet

Efficacy, 1L Doublet

	Doublet (n=42)
Confirmed ORR*, n (%)	**23 (54.8)**
95% CI	38.7–70.2
Median DOR, months	**20.1**
95% CI	9.7–NE
DCR, n (%)	**37 (88.1)**
95% CI	74.4–96.0
Median TTR, months	**1.4**
Range	1.2–7.0
Median PFS, months	**11.2**
95% CI	8.2–21.3
Median OS, months	**NE**
95% CI	19.2–NE



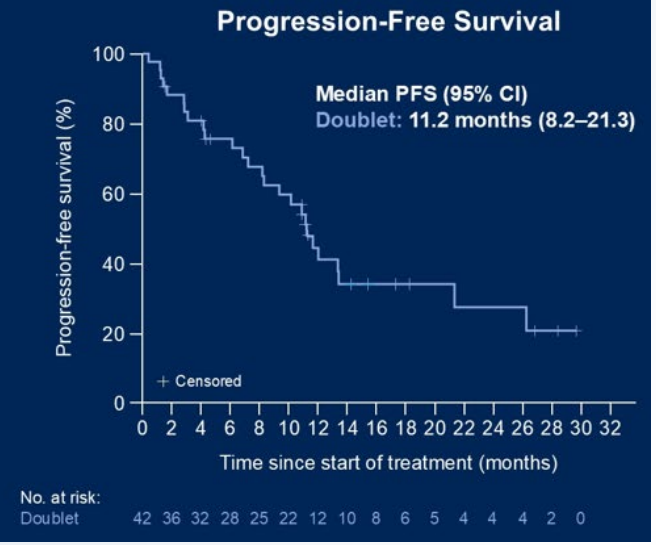
DOUBLET: ORR 54.8%; mPFS 11.2 months

Levy B et al ASCO 2025 Tropion Lung)2

Efficacy of Dato DXd 1L Doublet and 1L Triplet

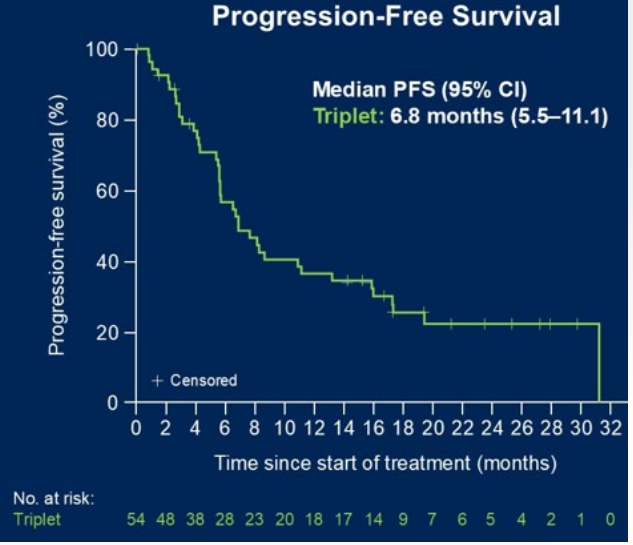
Efficacy, 1L Doublet

	Doublet (n=42)
Confirmed ORR*, n (%)	23 (54.8)
95% CI	38.7–70.2
Median DOR, months	20.1
95% CI	9.7–NE
DCR, n (%)	37 (88.1)
95% CI	74.4–96.0
Median TTR, months	1.4
Range	1.2–7.0
Median PFS, months	11.2
95% CI	8.2–21.3
Median OS, months	NE
95% CI	19.2–NE



Efficacy, 1L Triplet

	Triplet (n=54)
Confirmed ORR*, n (%)	30 (55.6)
95% CI	41.4–69.1
Median DOR, months	13.7
95% CI	5.7–NE
DCR, n (%)	48 (88.9)
95% CI	77.4–95.8
Median TTR, months	1.4
Range	1.2–9.6
Median PFS, months	6.8
95% CI	5.5–11.1
Median OS, months	17.4
95% CI	9.1–NE



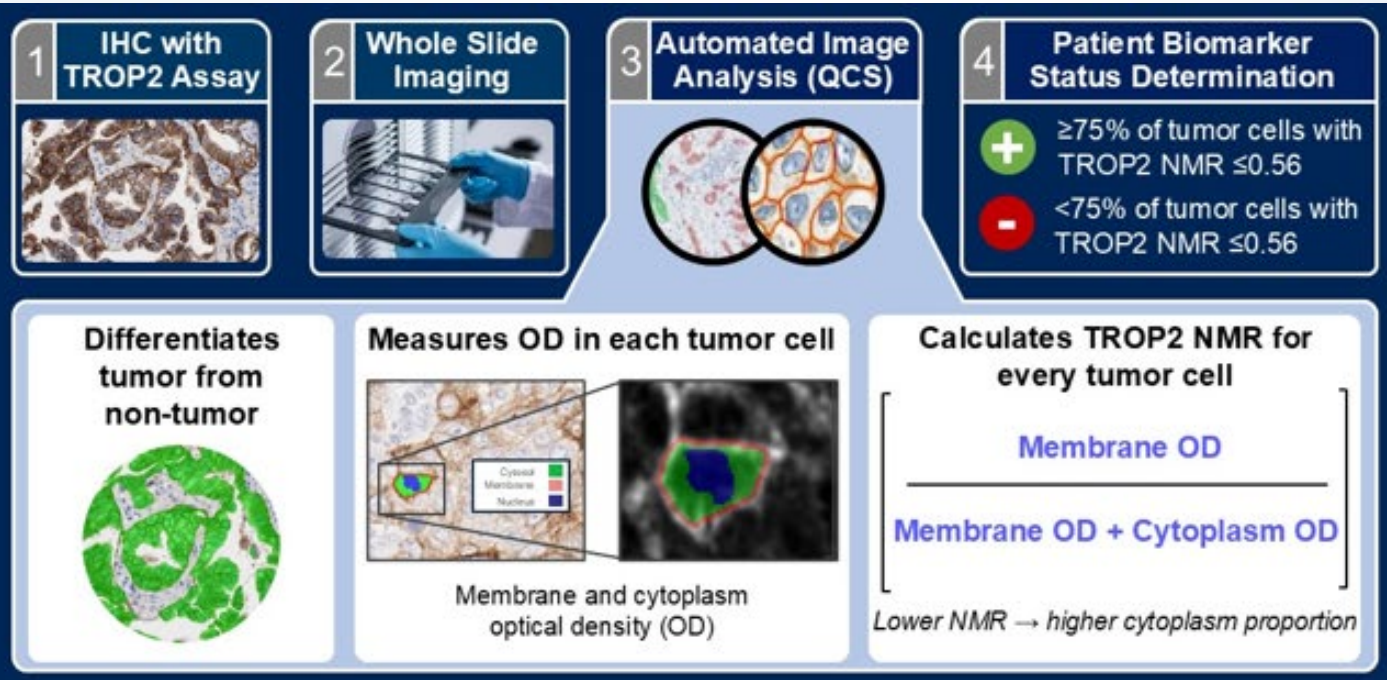
DOUBLET: ORR 54.8%; mPFS 11.2 months

TRIPLET: ORR 55.6%; mPFS 6.8 months

Levy B et al ASCO 2025 Tropion Lung)2

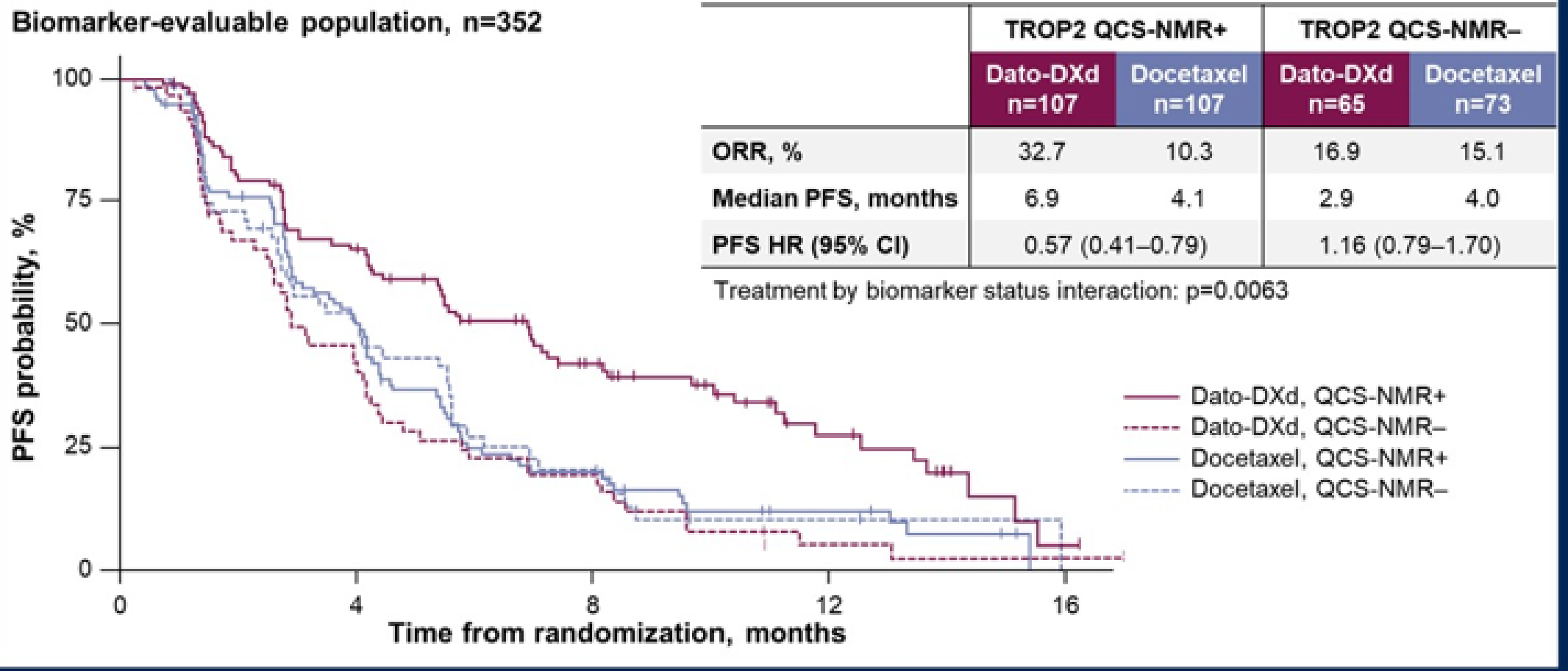
TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

- TROP2 tumor membrane expression using conventional IHC and pathology visual scoring does not enrich for response
- TROP2 NMR as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm)



Levy B et al ASCO 2025 Tropion Lung02

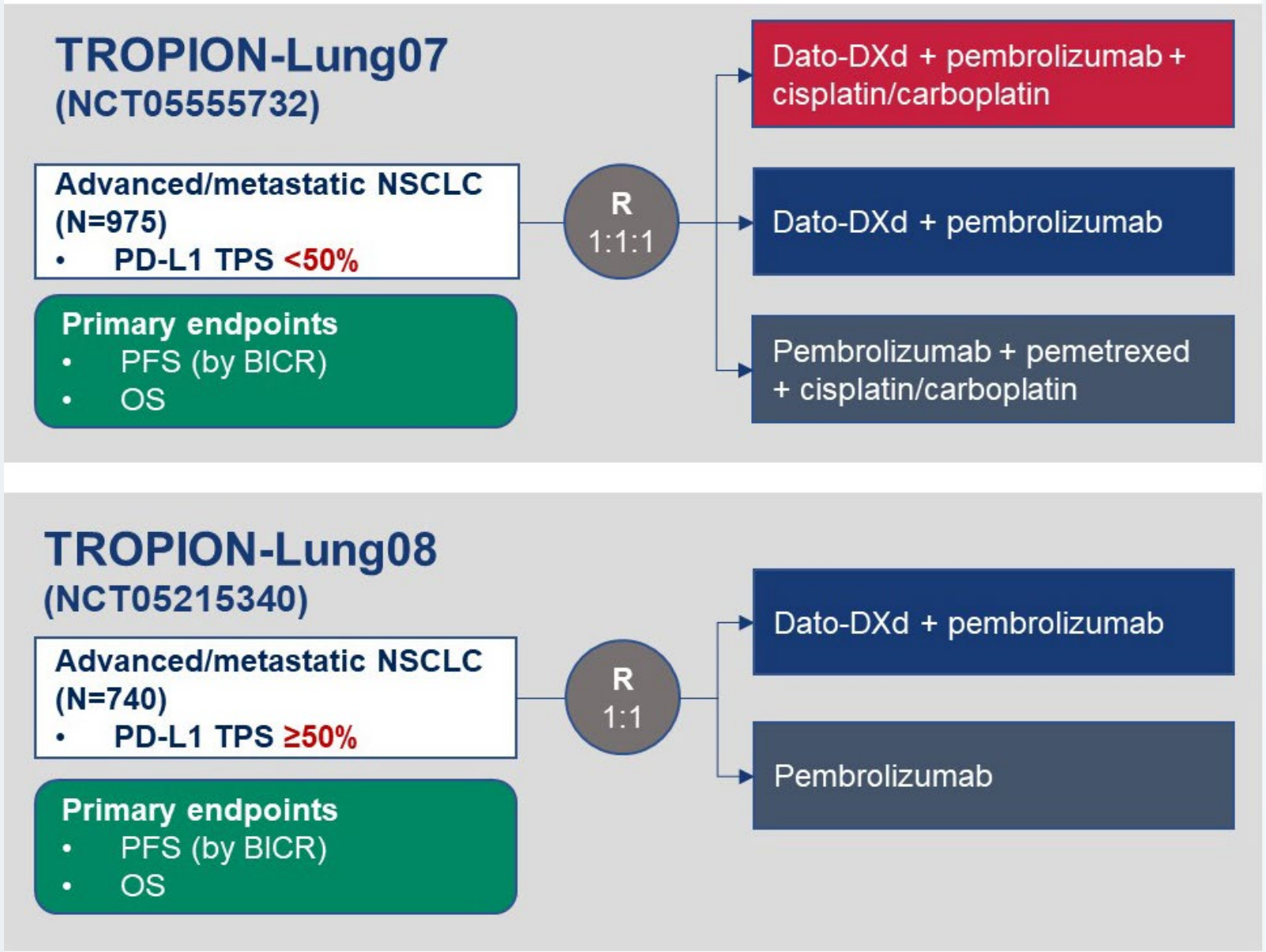
TROP2 NMR Positivity was Predictive for Longer PFS with Dato-DXd in TROPION Lung 01



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Garrasino MC et al J Thorac Oncol 2024



NCT0555732; NCT052115340

AVANZAR: Phase III Dato DXd + Durvalumab + Carboplatin vs Keynote189

Study Design

Patients with advanced/metastatic NSCLC (N=1280)

- Stage IIIB, IIIC, or IV NSCLC
- Squamous and nonsquamous histology
- No prior first-line chemotherapy or other systemic therapy for advanced/metastatic NSCLC
- No actionable genomic alterations
- ECOG PS 0 or 1
- Measurable disease per RECIST[2]
- Mandatory tumor sample required

Locations: North America, South America, Asia, Europe
ClinicalTrials.gov Identifier: NCT05687266

Randomization (1:1)

Dato-DXd 6 mg/kg + **durvalumab** 1120 mg + **carboplatin** AUC 5 IV Q3W for four cycles

→ **Maintenance**[2]
Dato-DXd 6 mg/kg + **durvalumab** 1120 mg IV Q3W

Histology-specific therapy with **pembrolizumab + platinum-based CT**

Stratification Factors

- PD-L1 expression (<1%, 1–49%, ≥50%)
- Histology (squamous vs nonsquamous)
- Smoking status (never vs ever)

Primary Endpoints

- PFS in TROP2 biomarker positive[b,f,g]
- OS in TROP2 biomarker positive[f,g]
- PFS in the NSQ population
- OS in the NSQ population

Secondary Endpoints

ITT and TROP2[g] defined populations

- PFS[b]
- OS

In ITT, NSQ and TROP2 defined populations

- ORR (CR + PR)[c,d]
- DOR[c,d]
- PFS[d,e]
- PFS2[2]
- PRO[2]
- ADA, PK

Safety Endpoints

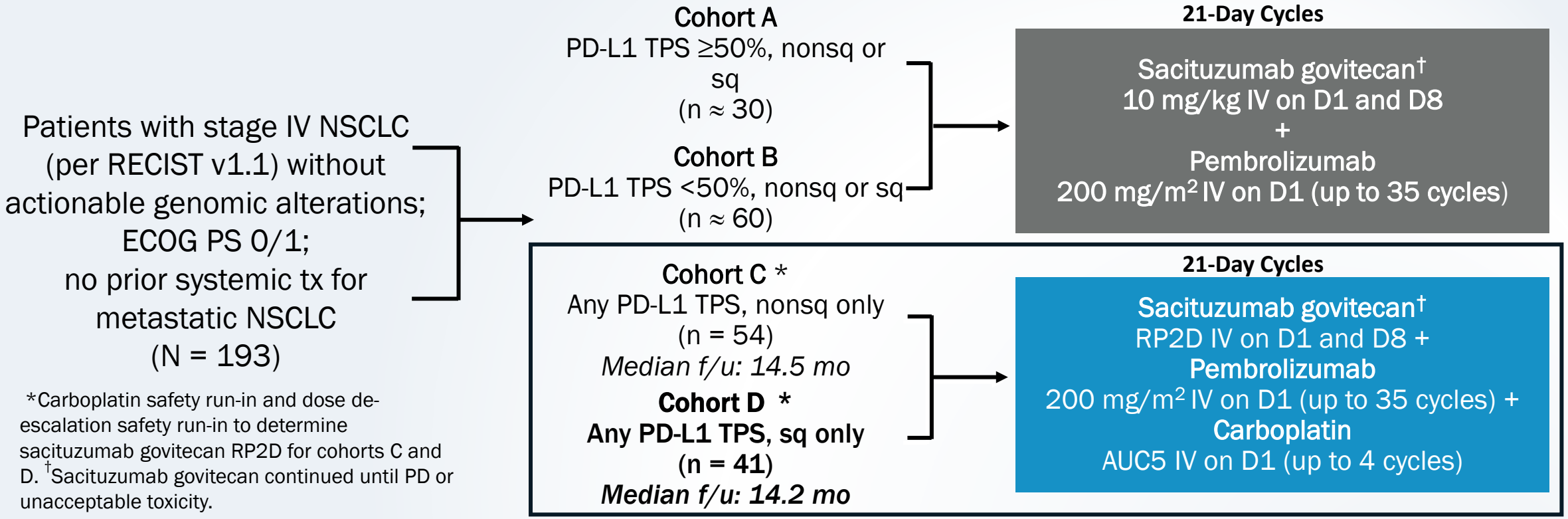
- Safety and tolerability

Sacituzumab Govitecan 1L
TROP2 ADC SN38 Payload

EVOKE 02 (NCT05186974) Phase 2 Sacituzumab Govitecan + Pembrolizumab +/- Chemotherapy in 1L

EVOKE 03 (NCT05609968) Phase 3 Sacituzumab Govitecan + Pembrolizumab vs Pembrolizumab in PDL1 high 1L

EVOKE-02 (Cohorts C & D): Sacituzumab Govitecan + Carboplatin/Pembrolizumab in 1L Untreated NSCLC

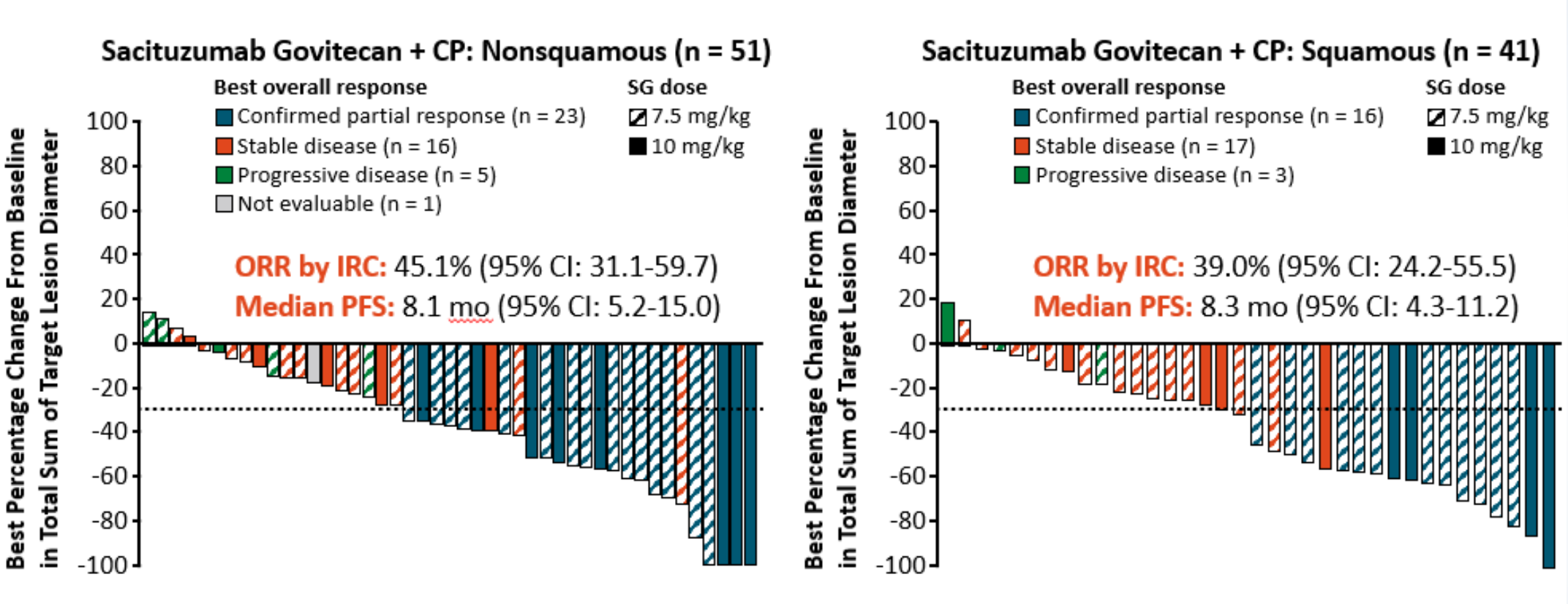


*Carboplatin safety run-in and dose de-escalation safety run-in to determine sacituzumab govitecan RP2D for cohorts C and D. †Sacituzumab govitecan continued until PD or unacceptable toxicity.

- **Primary endpoints:** ORR per RECIST v1.1, dose-limiting toxicity in safety run-in
- **Secondary endpoints:** DCR, DoR, and PFS per RECIST v1.1; OS; safety

Gray. WCLC 2024. Abstr OA08.07. NCT05186974

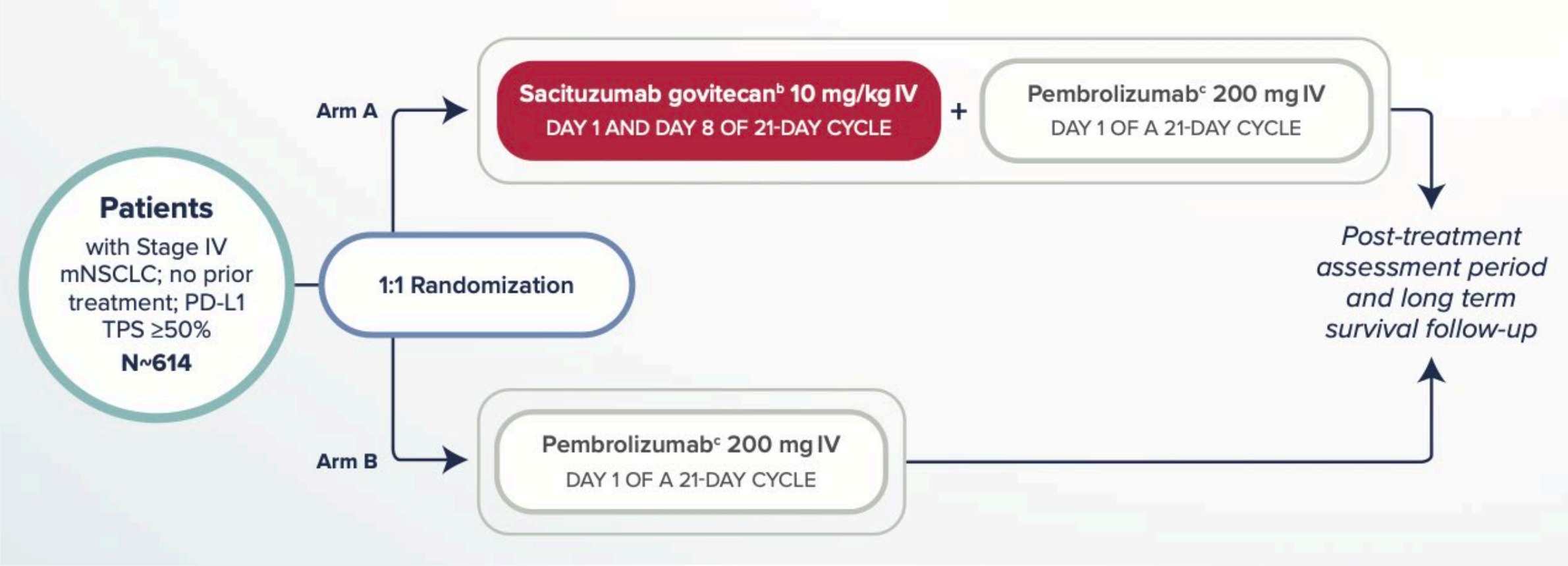
EVOKE 02: Sacituzumab Govitecan Antitumor Activity (Cohort C & D)



Outcome	PD-L1 TPS <1% (n = 44)	PD-L1 TPS 1%-49% (n = 36)	PD-L1 TPS ≥50% (n = 16)
ORR, % (95% CI)	43.2 (28.3-59.0)	33.3 (18.6-51.0)	66.7 (34.9-90.1)
Median PFS, mo (95% CI)	8.3 (5.2-15.0)	6.8 (4.0-10.7)	NR (1.9-NR)

Gray. WCLC 2024. Abstr OA08.07. NCT05186974

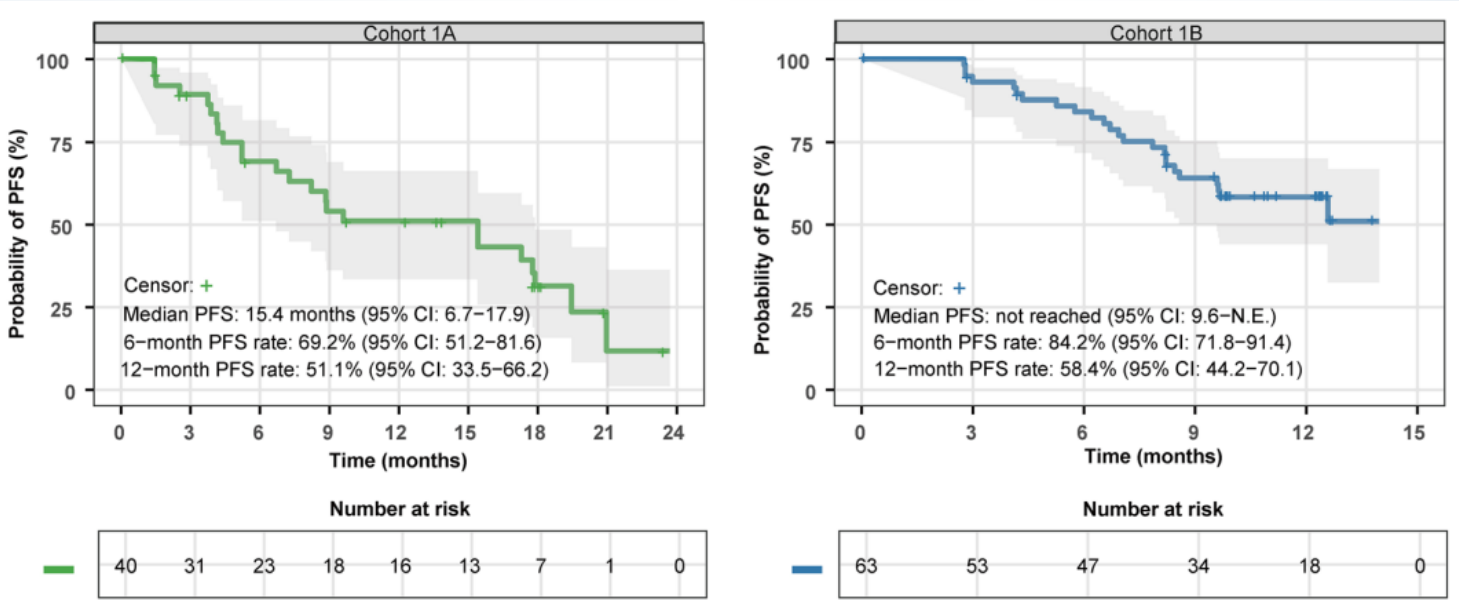
EVOKE 3: 1L Sacituzumab Govitecan + Pembrolizumab vs Pembrolizumab in PD-L1 TPS ≥50% mNSCLC Patients



NCT05609968

First-line sacituzumab tirumotecan with tagitanlimab in advanced non-small-cell lung cancer: a phase 2 trial

	Cohort 1ASac-TMT (5 mg kg^{-1} Q3W) + tagitanlimab (1,200 mg Q3W) *n*=40	Cohort 1BSac-TMT (5 mg kg^{-1} Q2W) + tagitanlimab (900 mg Q2W) *n*=63
Median follow-up[a] (95% CI), months	19.3 (18.6–21.9)	13.0 (11.3–13.3)
Median treatment duration for sac-TMT (range), months	8.1 (0–23.9)	9.9 (0–14.7)
Median treatment duration for tagitanlimab (range), months	6.7 (0–21.6)	9.7 (0–14.7)
BOR, *n* (%)		
PR	18 (45.0)	45 (71.4)
Confirmed PR	16 (40.0)	42 (66.7)
SD	16 (40.0)	13 (20.6)
PD	3 (7.5)	0
Not evaluable[b]	3 (7.5)	5 (7.9)
ORR[c], *n* (%)	18 (45.0)	45 (71.4)
(95% CI)	(29.3–61.5)	(58.7–82.1)
Confirmed ORR, *n* (%)	16 (40.0)	42 (66.7)
(95% CI)	(24.9–56.7)	(53.7–78.0)
DCR[d], *n* (%)	34 (85.0)	58 (92.1)
(95% CI)	(70.2–94.3)	(82.4–97.4)
Median DOR (95% CI), months	16.6 (8.3–N.E.)	NR (11.2–N.E.)
Median PFS (95% CI), months	15.4 (6.7–17.9)	NR (9.6–N.E.)



OPTITROP Lung 01 Hong S et al Nature Medicine 2024

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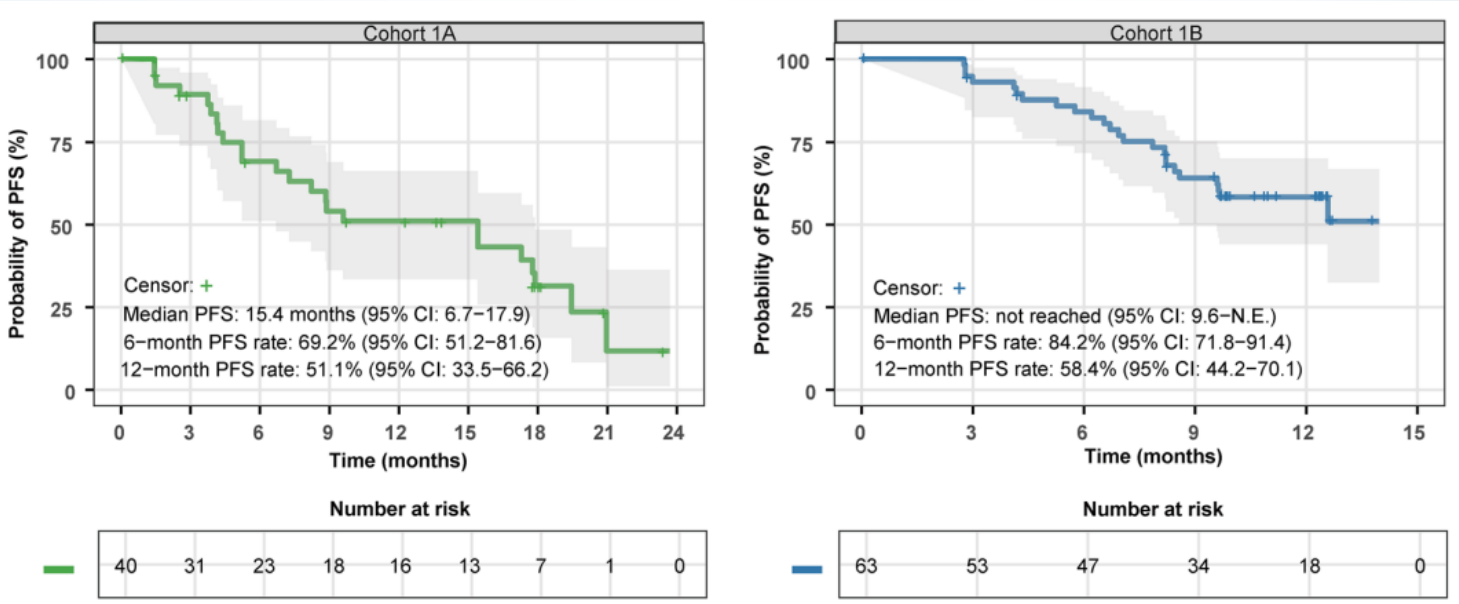

Our study indicated that sac-TMT plus tagitanlimab is active in squamous NSCLC, a subtype with a high unmet medical need[30]. Specifically, patients with squamous carcinoma demonstrated an ORR of 36.4% in cohort 1A and 69.0% in cohort 1B. These results are comparable with those observed in patients with nonsquamous lung cancer, who demonstrated ORR of 44.4% in cohort 1A and 64.7% in cohort 1B.

OPTITROP Lung 01 Hong S et al Nature Medicine 2024

Other ADCs in development...

Conclusions

- ADCs represents a novel therapeutic modality combining targeted antibody delivery with cytotoxic payloads

- Clear role for ADCs in the Driver Mutation population
  - Dato DXd approved in EGFRm NSCLC post 3G TKI and Chemo;
  - Trastuzumab Deruxtecan HER2 mutation and HER2 3+ IHC
  - Teliso V MET high 3+ IHC;

Conclusions

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  - Dato DXd approved in EGFRm NSCLC post 3G TKI and Chemo;
  - Trastuzumab Deruxtecan HER2 mutation and HER2 3+ IHC
  - Teliso V MET high 3+ IHC;

- In first-line metastatic driver negative NSCLC, role for ADC remain **investigational.**
  - Need biomarkers to select correct population
  - Combination strategies / balancing toxicity and efficacy
  - CNS activity remains limited
  - OS benefit has not yet been seen
  - Need further data on squamous histology

- ADCs will not replace immunotherapy, may replace chemo in combination strategies in the front-line setting

- KRAS G12C and other RAS mutations with competing strategies in the front line