

20th ANNUAL

ATLANTA

LUNG CANCER SYMPOSIUM

Are ADCs Truly Transformational in NSCLC?

Joshua Sabari, MD

November 7, 2026

Partners for Advancing Clinical Education

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20th ANNUAL ATLANTA LUNG CANCER SYMPOSIUM

YES!

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Disclosures

Consultant/ Advisory Board Involvement	Advisory board/Consultant: (Personal) AstraZeneca, Abbvie, Boehringer Ingelheim, EMD Serono, Genentech, Janssen J&J, Jazz, Loxo Lilly, Mirati/BMS, Pfizer, Regeneron, Revolution Medicines, Sanofi Genzyme, Takeda Research support: (Institutional) Johnson and Johsnon Janssen, Boehringer Ingelheim, Loxo Eli Lilly, Mirati / Bristol Myers Squibb, Regeneron
Stock or Shareholder	None

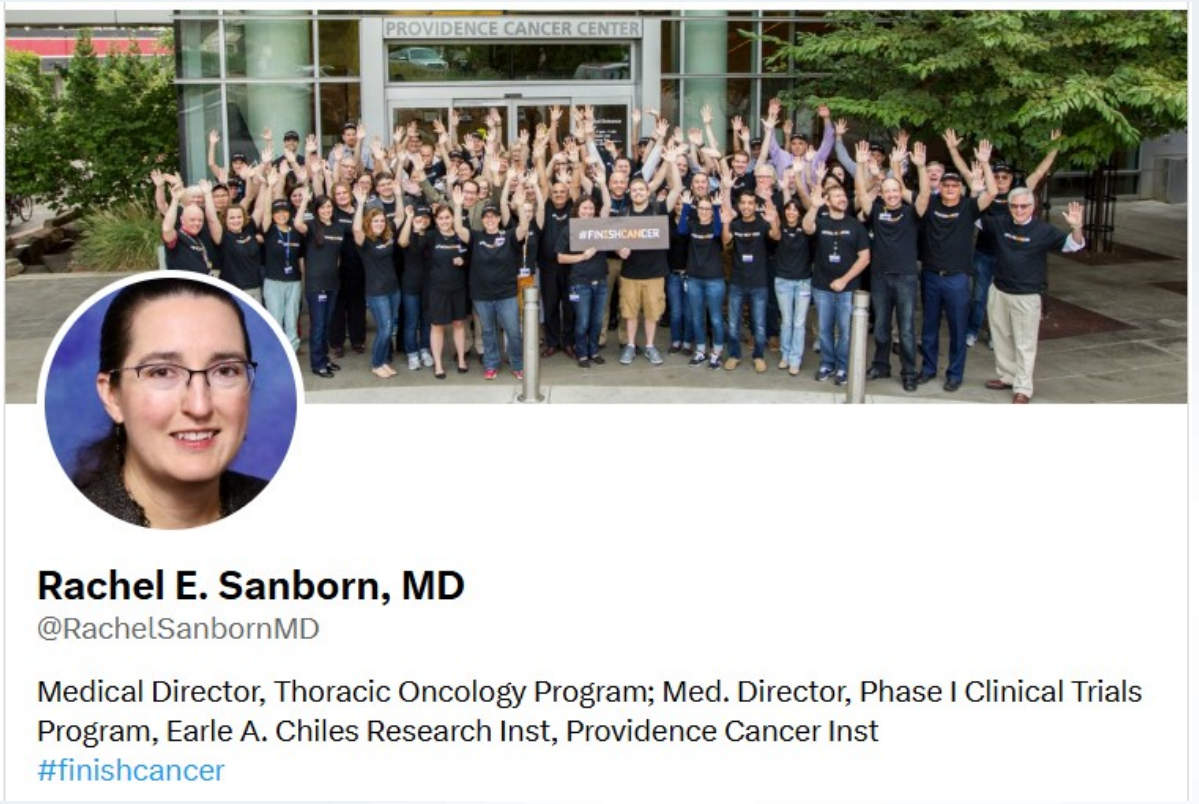
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To date, there are no FDA approved ADCs in the 1L NSCLC Setting

Rachel Sanborn, MD

1. Medical Director Thoracic Medical Oncc
2. Medical Director Phase I Clinical Trials
3. Extensive publication record
4. Great clinician
5. Nice person



Portland OR

1. Vibrant food culture: pods/trucks, breweries,
2. Expansive green spaces; Urban Forest
3. Progressive
4. Crafts
5. Quirky culture



FDA Approved ADCs in NSCLC

- Clear role for ADCs in the Driver Mutation / Biomarker Selected Population
  - Dato DXd approved in EGFRm NSCLC post 3G TKI and Chemotherapy
    - Tropion Lung 14 and 15 ongoing
  - Trastuzumab Deruxtecan HER2 mutation and HER2 3+ IHC
    - Recent DESTINY-Lung 04
  - Teliso V MET high 3+ IHC
    - Teliso A (Temab-A, ABBV400) ongoing





WARNING

ADC Failures in NSCLC

- Datopotomab Deruxtecan (TROP2) 2L NSCLC - Tropion Lung 01
- Sacituzumab Govitecan (TROP2) 2L NSCLC - EVOKE-01
- Sigvotatug Vedotin (IB6) 2L NSCLC - SigVie-002
- Tusamitamab Ravtansine (CEACAM5) 2L NSCLC - CARMEN-LCO3
- Patritumab Deruxtecan (HER3) 2L EGFRm - HERTHENA-lung02

- Sacituzumab Govitecan (TROP2) 1L NSCLC – EVOKE-03
- Tusamitamab Ravtanise (CEACAM5) 1L NSCLC – CARMEN-LCO5
- [illegible]



What is transformational?

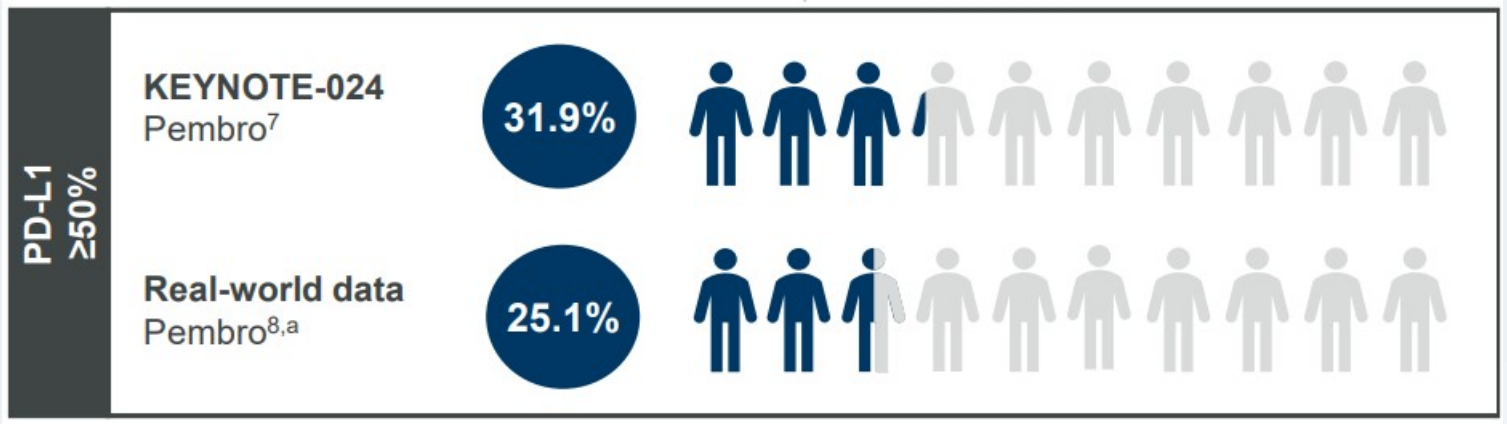
A drug therapy is considered **transformational** (often referred to in medicine as a "transformative drug" or "breakthrough therapy") when it fundamentally alters the natural history of a disease, replaces a highly toxic or inadequate standard of care, or provides a dramatic, survival-extending benefit where no viable options existed before. National Institutes of Heal...

What is transformational?

A drug therapy is considered **transformational** (often referred to in medicine as a "transformative drug" or "breakthrough therapy") **when it fundamentally alters the natural history of a disease, replaces a highly toxic or inadequate standard of care, or provides a dramatic, survival-extending benefit where no viable options existed before**. National Institutes of Heal...

Unlike *incremental* drugs—which offer minor, iterative improvements over existing options (such as slightly better dosing convenience or mild side-effect reductions)—transformational therapies create an immediate shift in clinical paradigms. Regulatory bodies like the U.S. Food and Drug Administration (FDA) formalize this concept through specialized pathways like the **Breakthrough Therapy designation**, which requires preliminary clinical evidence demonstrating a *substantial improvement* over available therapies on clinically significant endpoints. U.S. Food and Drug Ad... +1

5 Year Overall Survival Driver Mutation Negative NSCLC



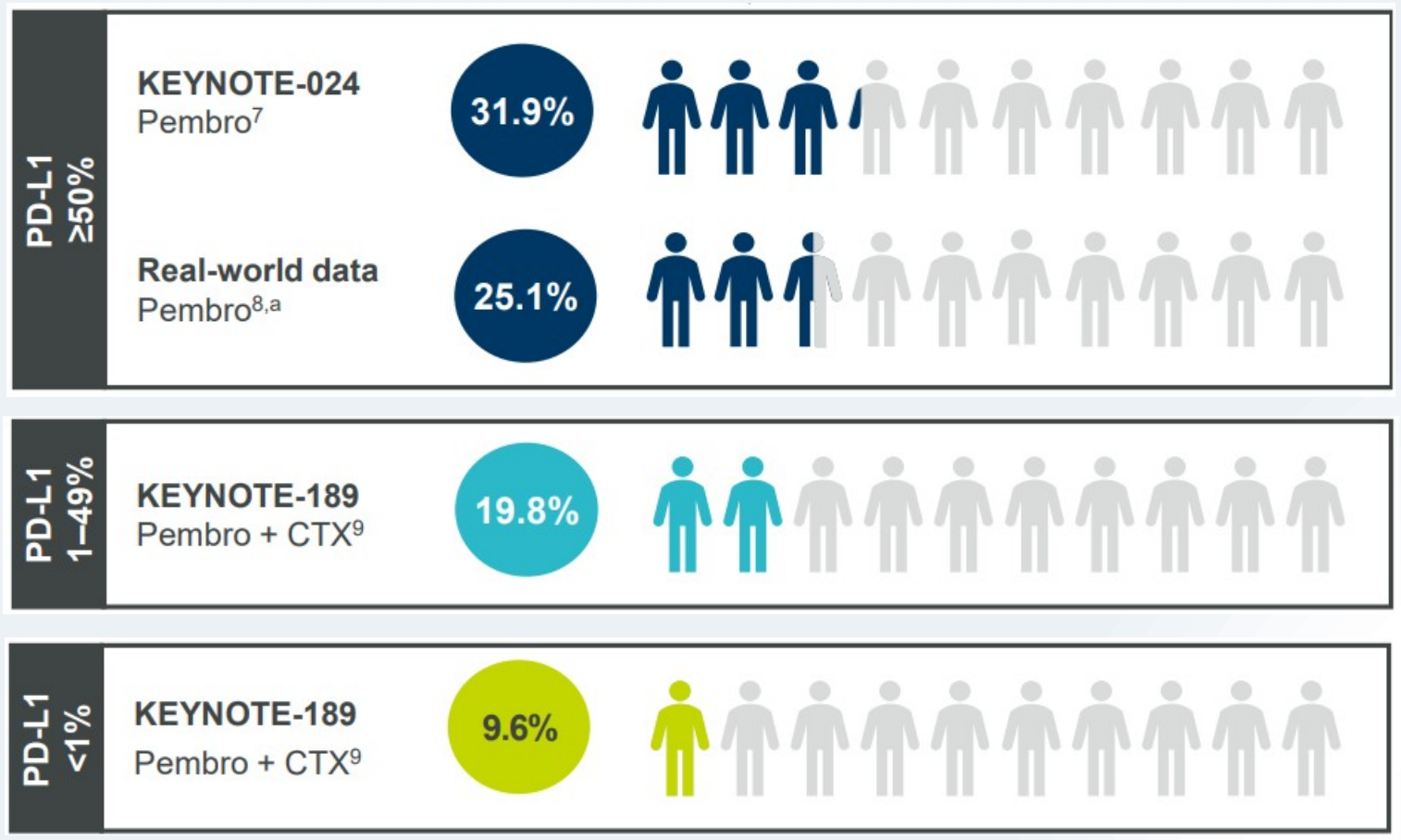
1. Mok T, et al. Lancet. 2019;393:1819–1830; 2. Paz-Ares L, et al. J Thorac Oncol. 2020;15:P1657–P1669; 3. Garassino MC, et al. J Clin Oncol. 2023;41:1992–1998; 4. Cortellini A, et al. Eur J Cancer. 2021;148:P24–P35; 5. Socinski MA, et al. N Engl J Med. 2018;378:2288-2301. 6. Peters S, et al. Presented 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

5 Year Overall Survival Driver Mutation Negative NSCLC



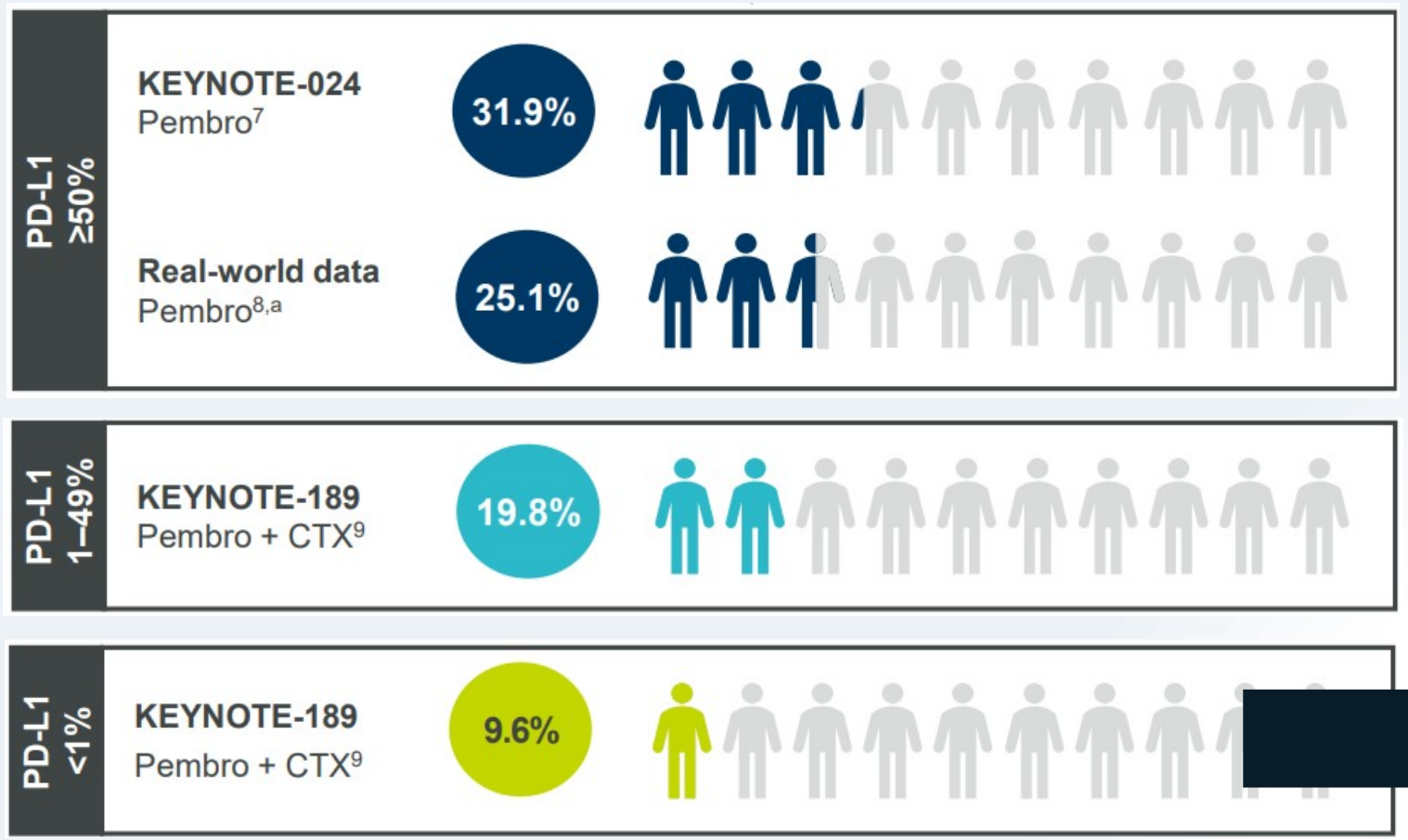
1. Mok T, et al. Lancet. 2019;393:1819–1830; 2. Paz-Ares L, et al. J Thorac Oncol. 2020;15:P1657–P1669; 3. Garassino MC, et al. J Clin Oncol. 2023;41:1992–1998; 4. Cortellini A, et al. Eur J Cancer. 2021;148:P24–P35; 5. Socinski MA, et al. N Engl J Med. 2018;378:2288-2301. 6. Peters S, et al. Presented 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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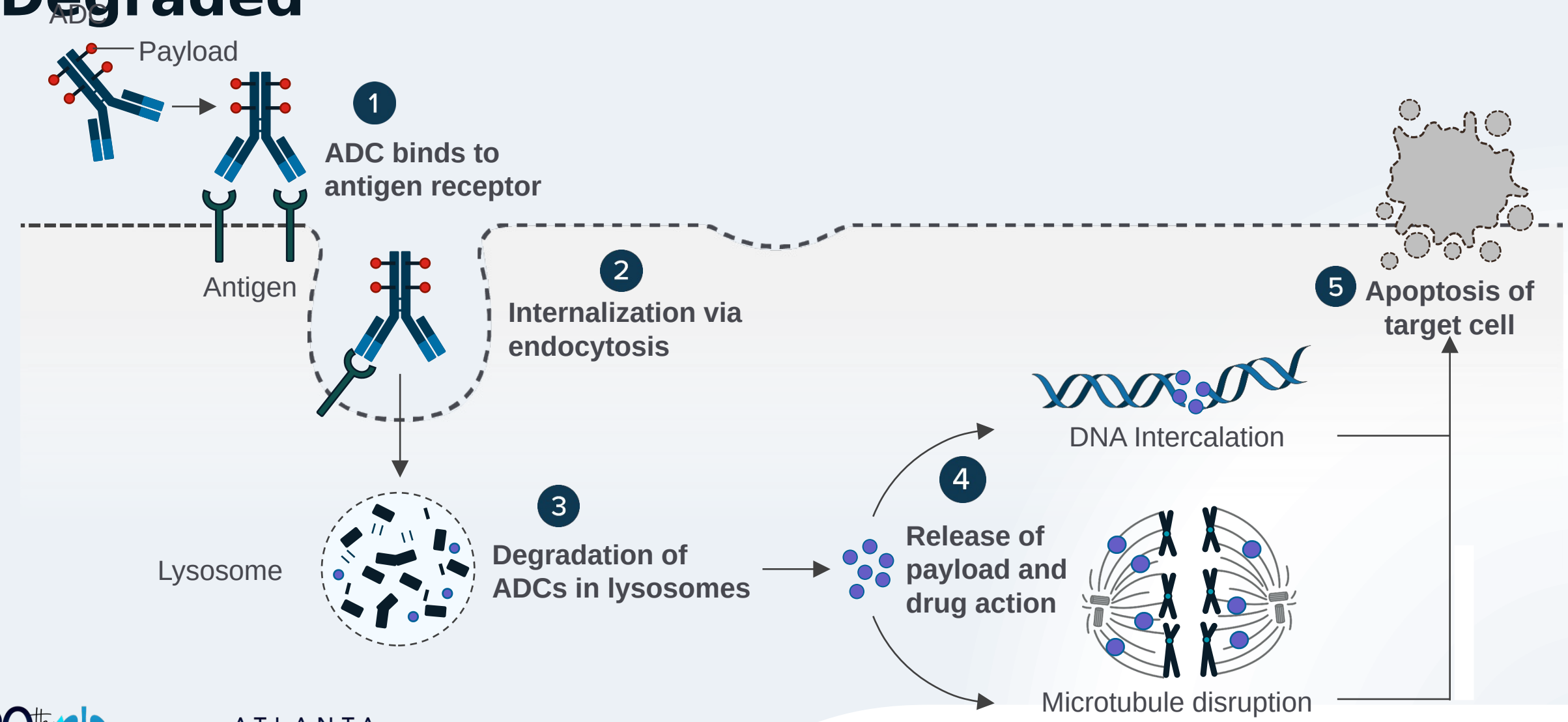
5 Year Overall Survival Driver Mutation Negative NSCLC



STK11
KEAP1
PTEN
TP53
SMARCA 4

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

Mechanism 1: The ADC is Internalized and Degraded



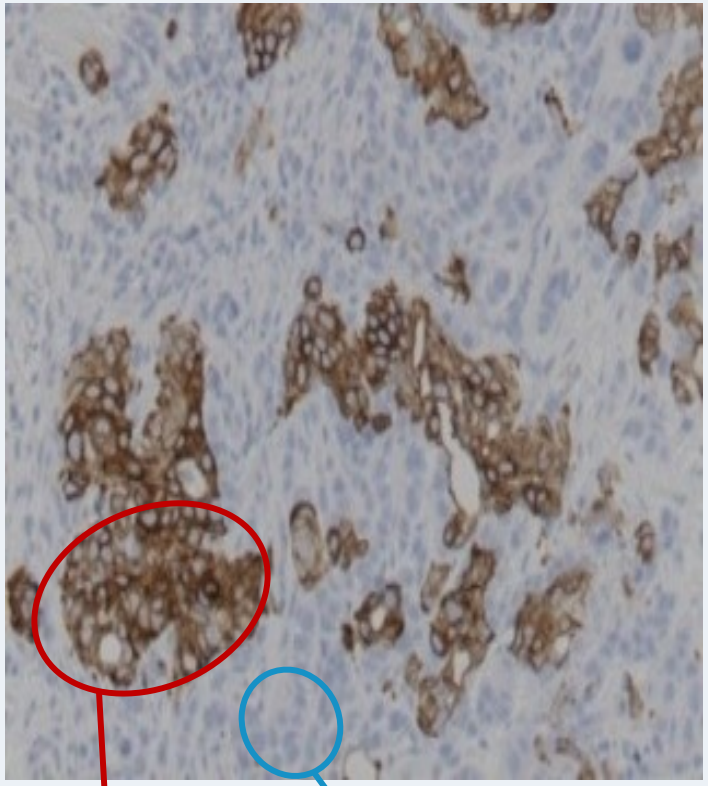
Slide Courtesy: Dr. Ben Levy; Chau CH, et al. Lancet. 2019

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Mechanism 2: Bystander Effect

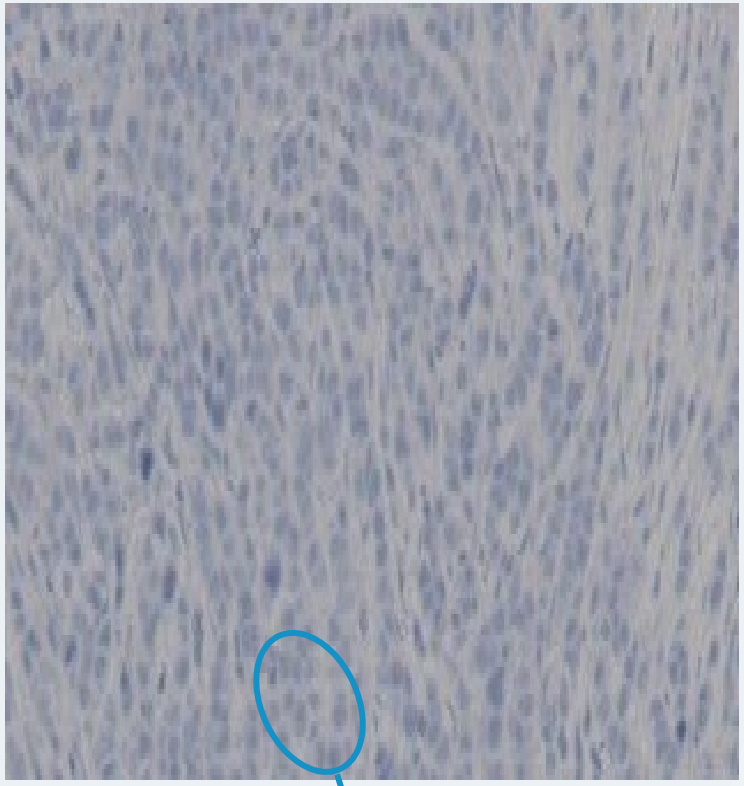
Control

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



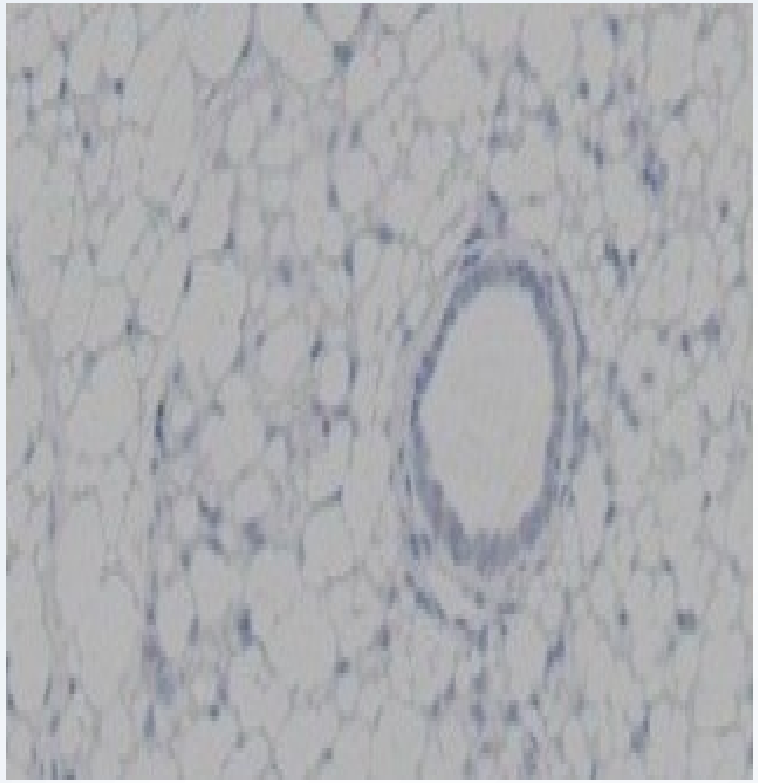
T-DM1, 10 mg/kg

HER2- cells still persist



T-DXd, 3.0 mg/kg

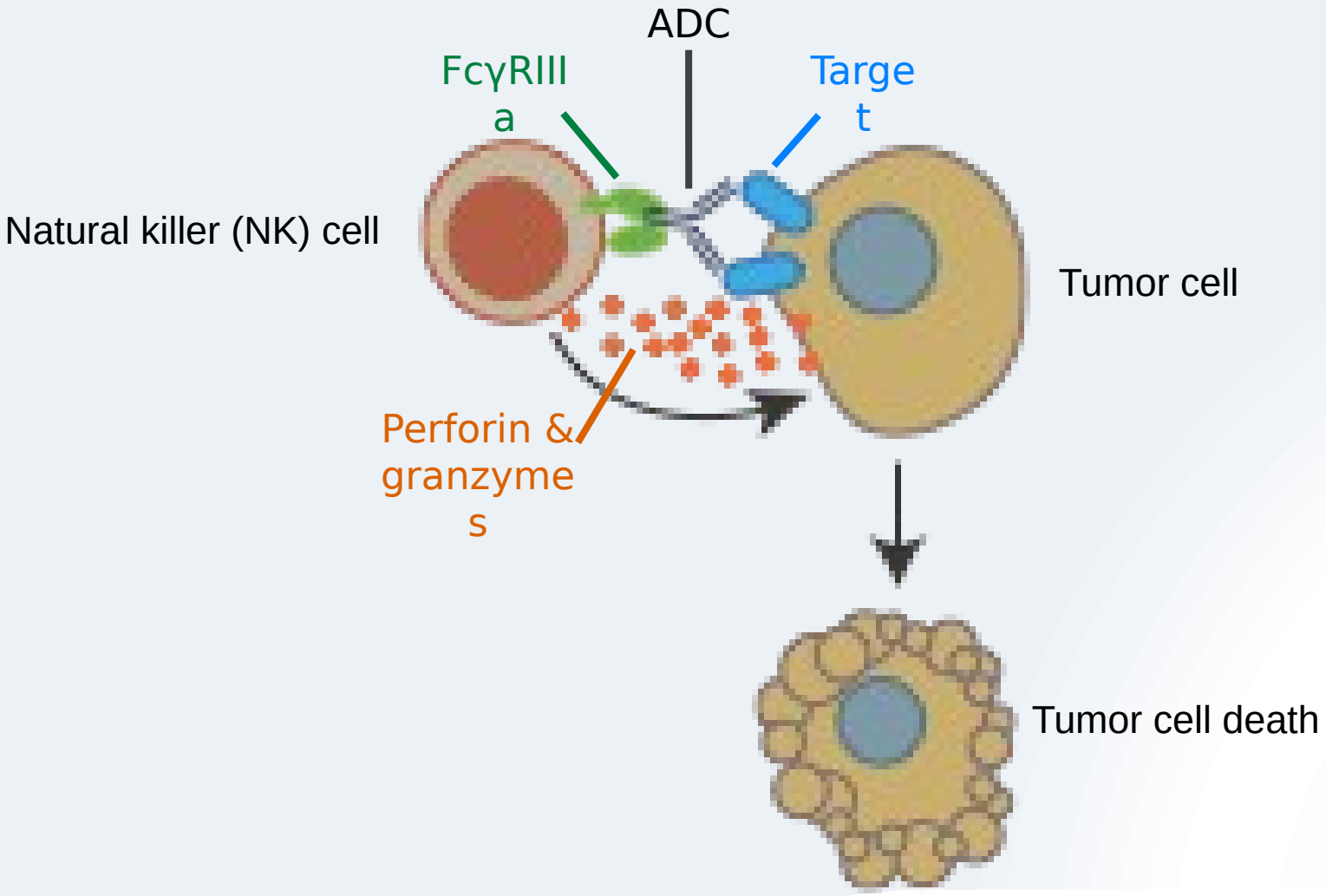
Both HER2+ and HER2- are impacted



Tumor regression

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

Mechanism 3: Antibody-Dependent Cellular Cytotoxicity

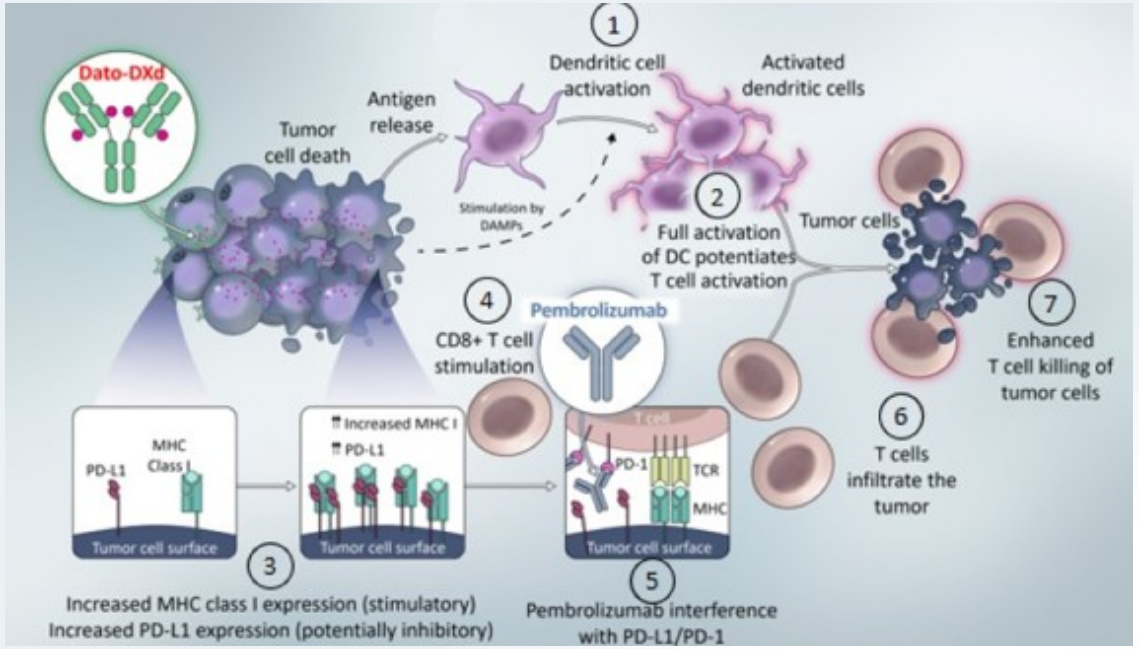


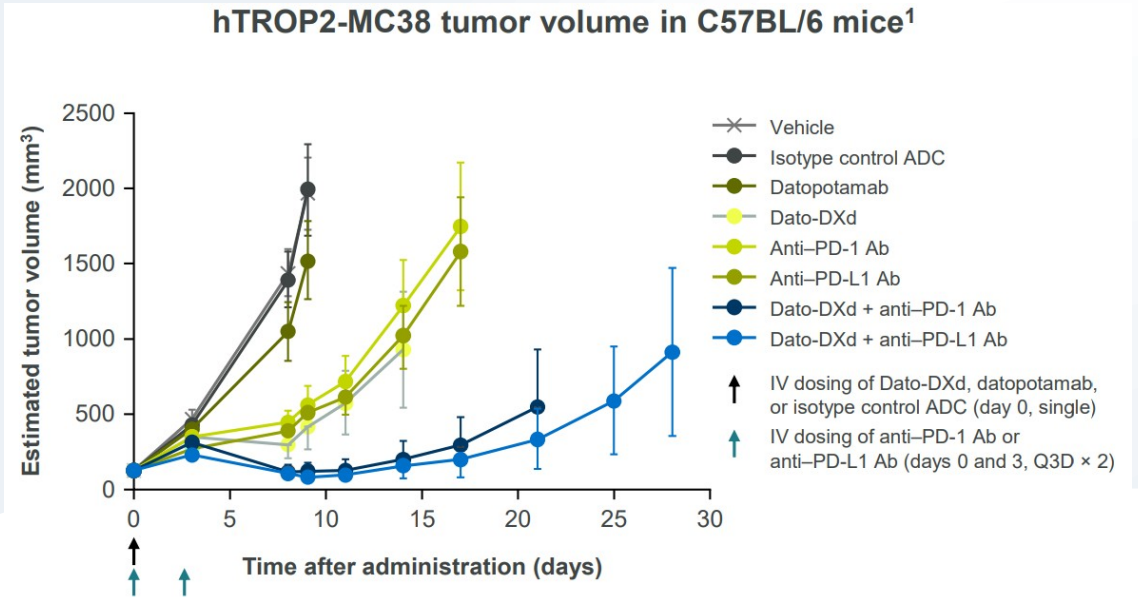
Slide Courtesy: Joseph Murray, MD, Phd

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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

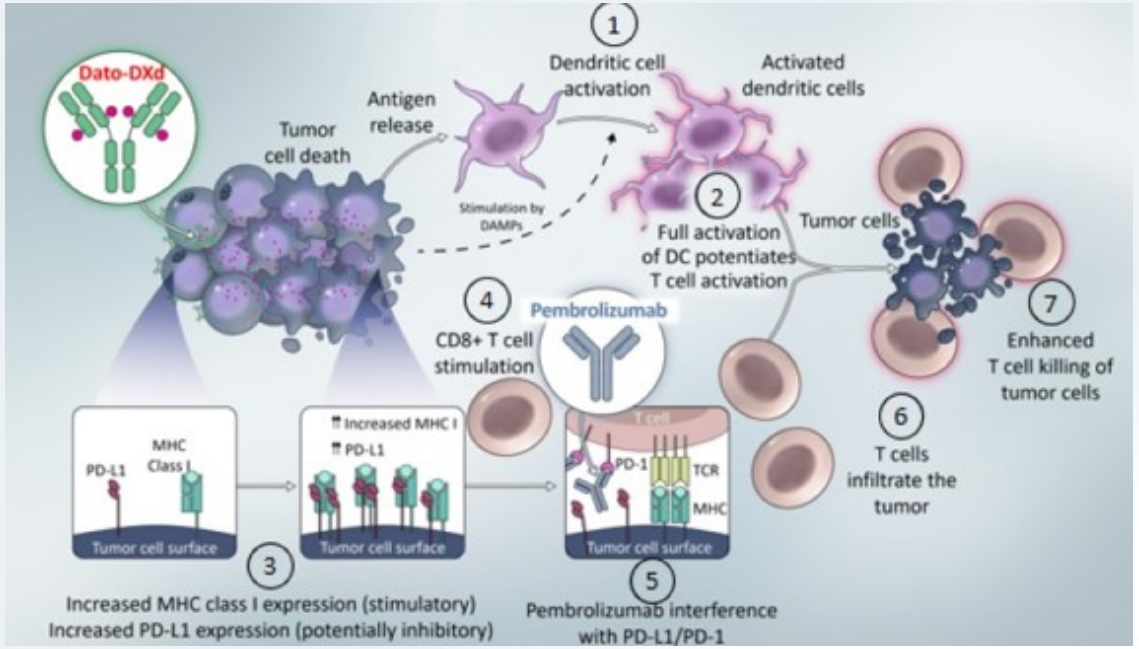


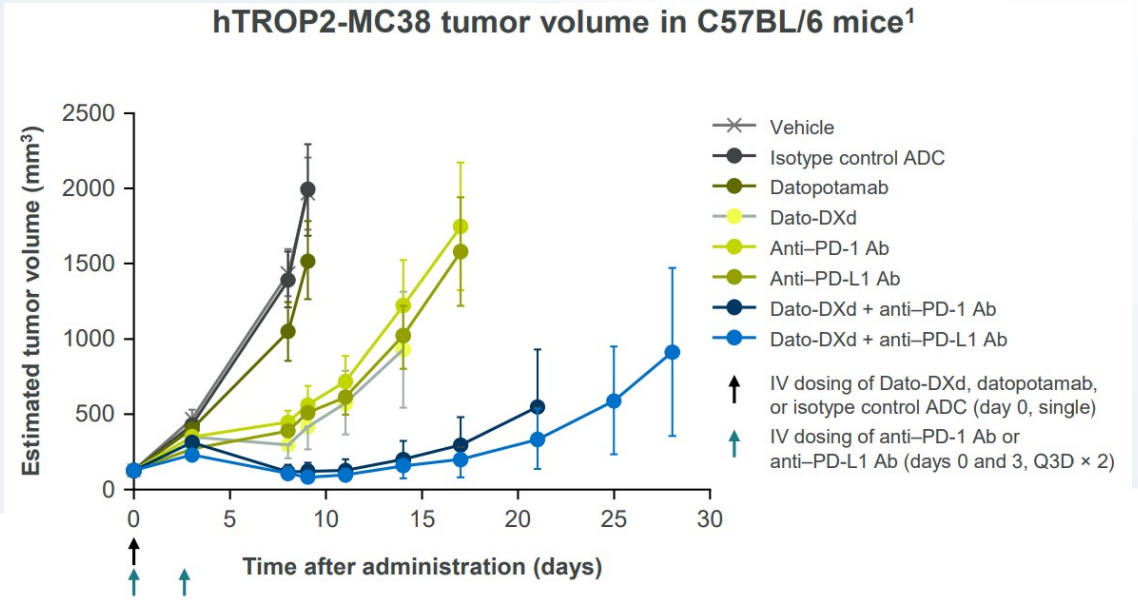


1. Okajima D, et al. Presented at the AACR Annual Meeting 2023, April 14–19, 2023, Orlando, FL, USA. Abstract 2932; 2. Forveille S, et al. Cell Stress. 2025;9:194-200 4. Schmid P et al Cancer Res 2023

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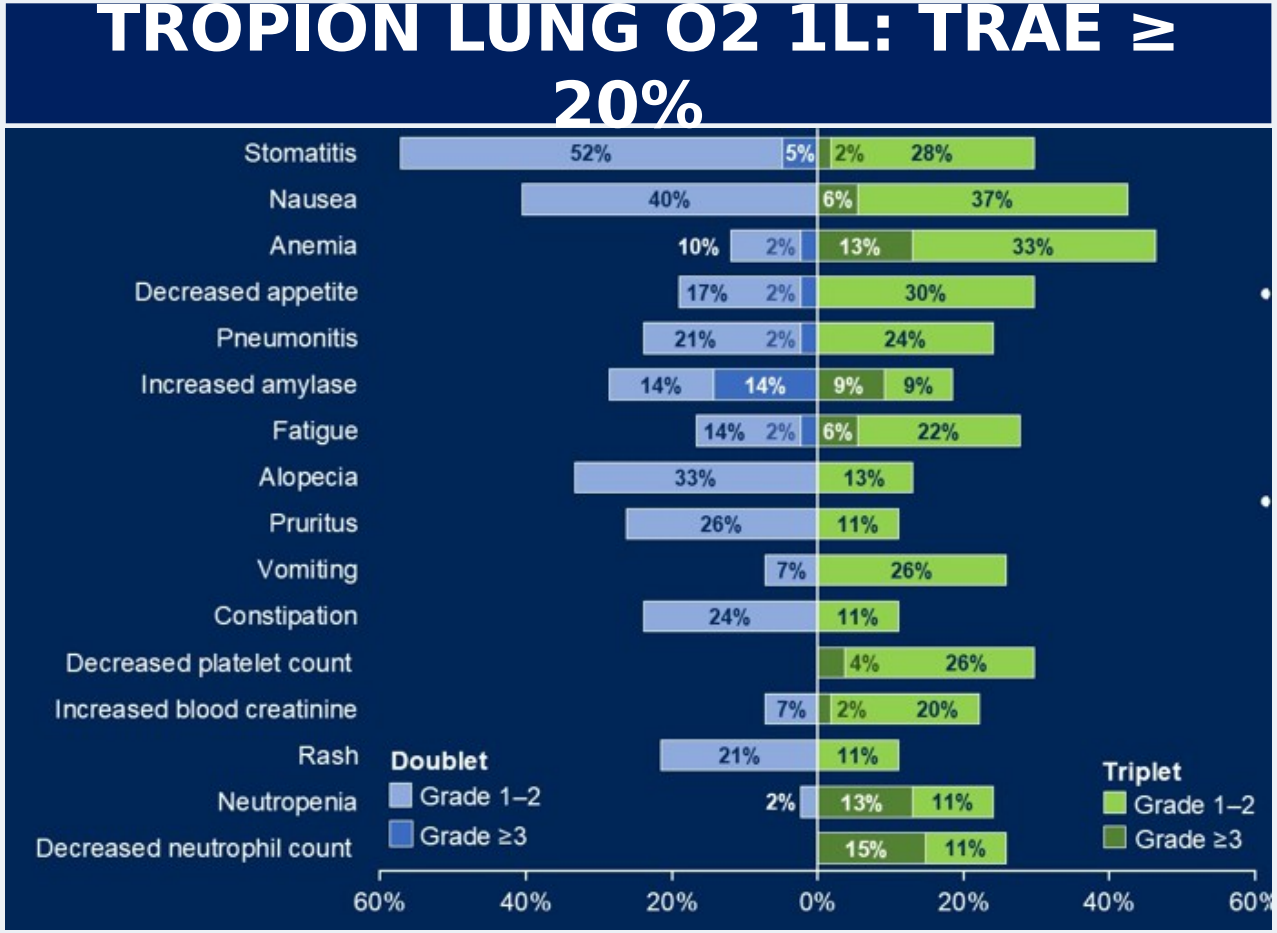
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- Dato-DXd activity was attenuated by depletion of CD8+ T cells
- **Is this significantly different from conventional chemotherapy?**





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Barriers to ADCs in the 1L Setting

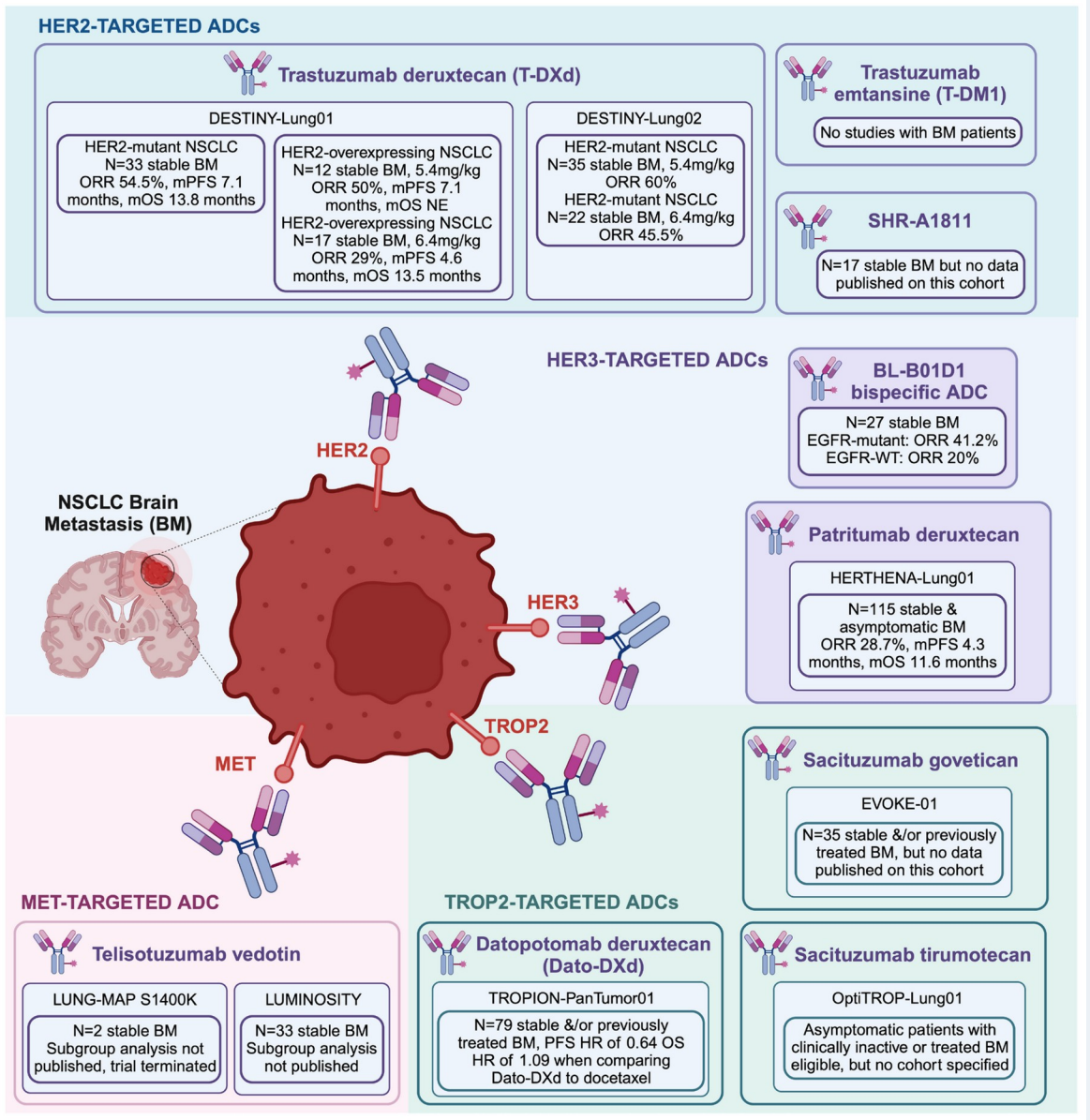


- Toxicity / Quality of life
  - Stomatitis, nausea, fatigue, diarrhea, ILD
  - Subspecialty care: Ophtho, Pulm, Derm
- Dose reduction / Discontinuation of SOC / Efficacy
- Lack of Biomarker Selection
- Payload Resistance
- CNS Activity
- Financial burden:
  - Cost of therapy, supportive meds, chair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

Levy B et al ASCO 2025 Tropion Lung 02

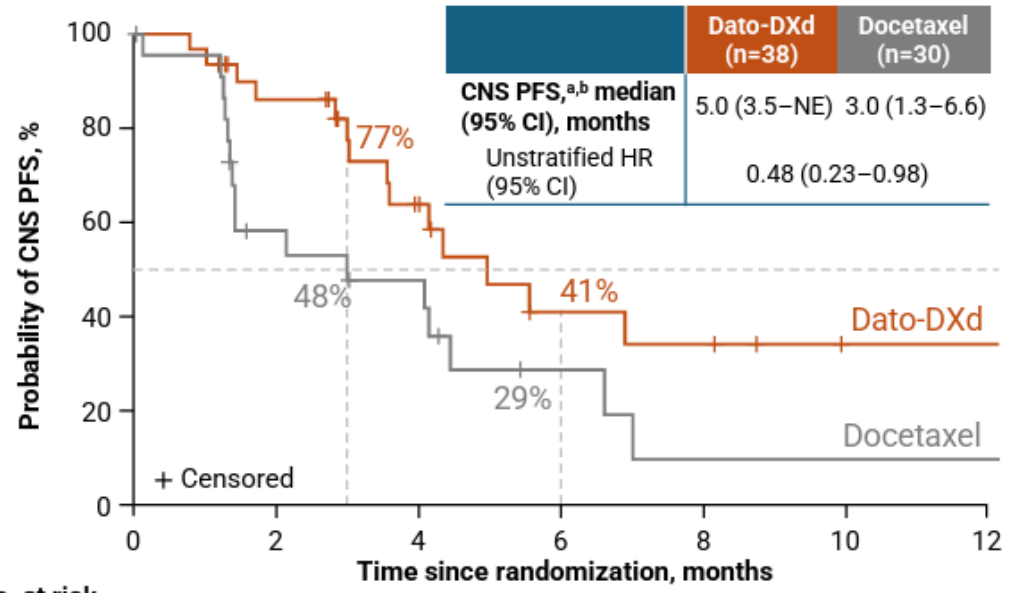
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CNS Activity of ADCs



	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

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

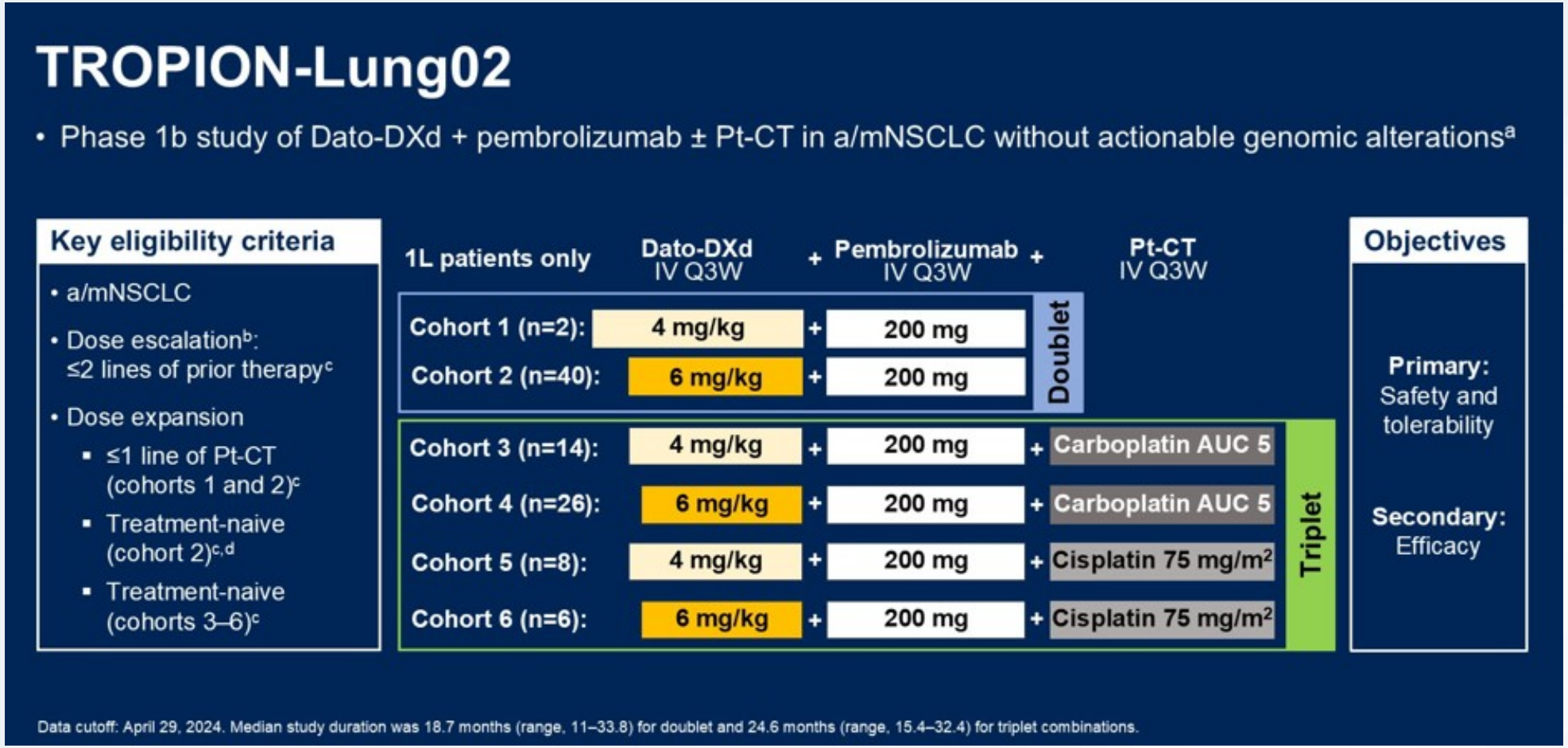
TROPION-Lung08 (NCT05215340) Phase 3 DatoDXd + Pembrolizumab vs Pembrolizumab in 1L

AVANZAR (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

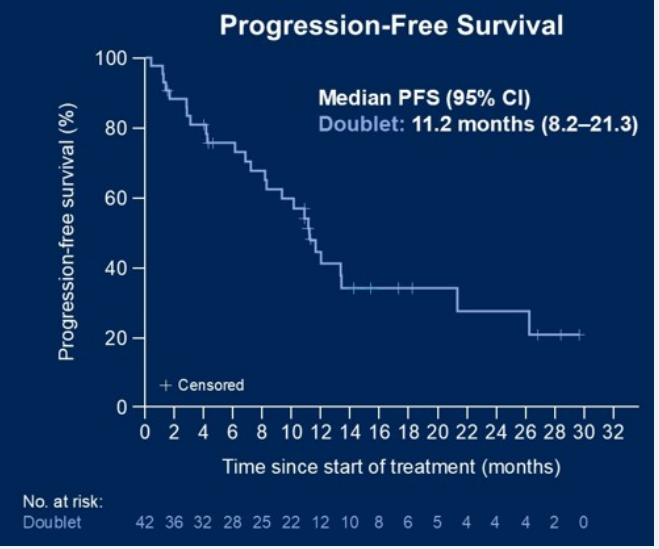
TROPION-Lung02 Schema:
Doublet: Dato DXd + Pembrolizumab
Triplet: Dato DXd + Pembrolizumab + Platinum Chemotherapy



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

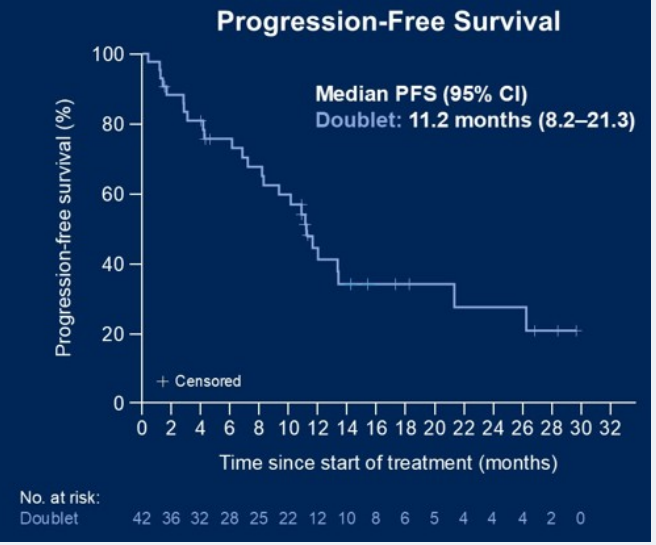


DOUBLET: ORR 54.8%; mPFS 11.2 months

Efficacy of Dato DXd 1L Doublet and 1L Triplet

Efficacy, 1L Doublet

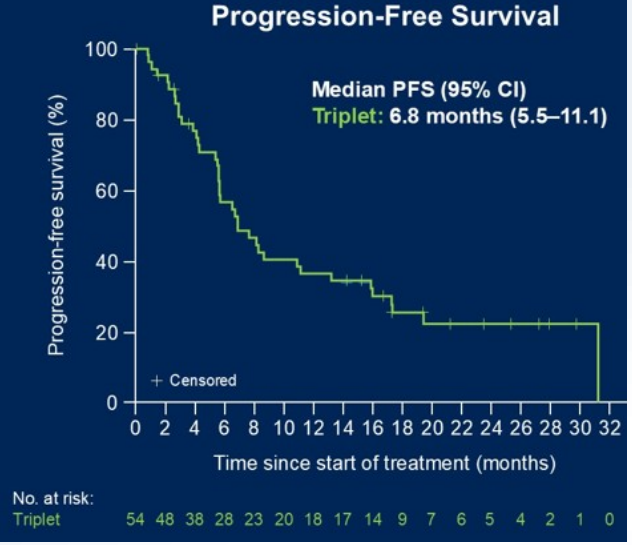
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Median TTR, months	1.4
Range	1.2–7.0
Median PFS, months	11.2
95% CI	8.2–21.3
Median OS, months	NE
95% CI	19.2–NE



DOUBLET: ORR 54.8%; mPFS 11.2 months

Efficacy, 1L Triplet

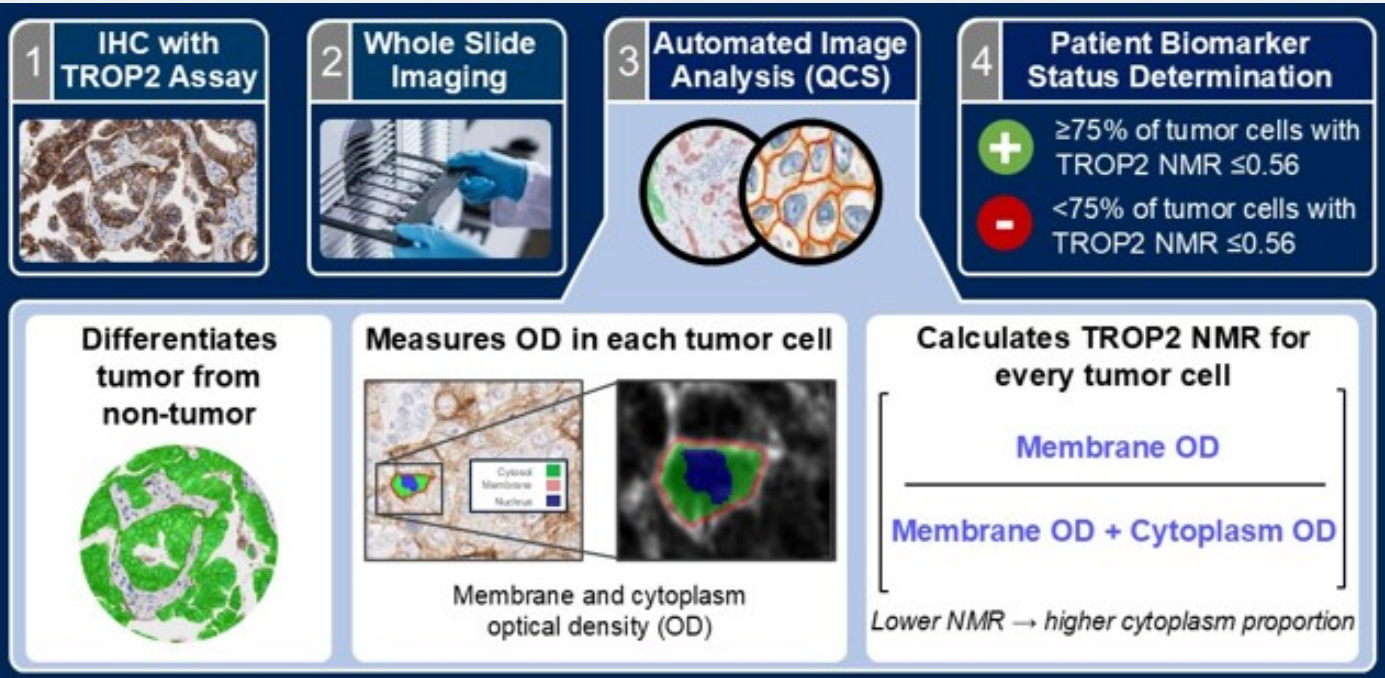
	Triplet (n=54)
Confirmed ORR*, n (%)	30 (55.6)
95% CI	41.4–69.1
Median DOR, months	13.7
95% CI	5.7–NE
DCR, n (%)	48 (88.9)
95% CI	77.4–95.8
Median TTR, months	1.4
Range	1.2–9.6
Median PFS, months	6.8
95% CI	5.5–11.1
Median OS, months	17.4
95% CI	9.1–NE



TRIPLET: ORR 55.6%; mPFS 6.8 months

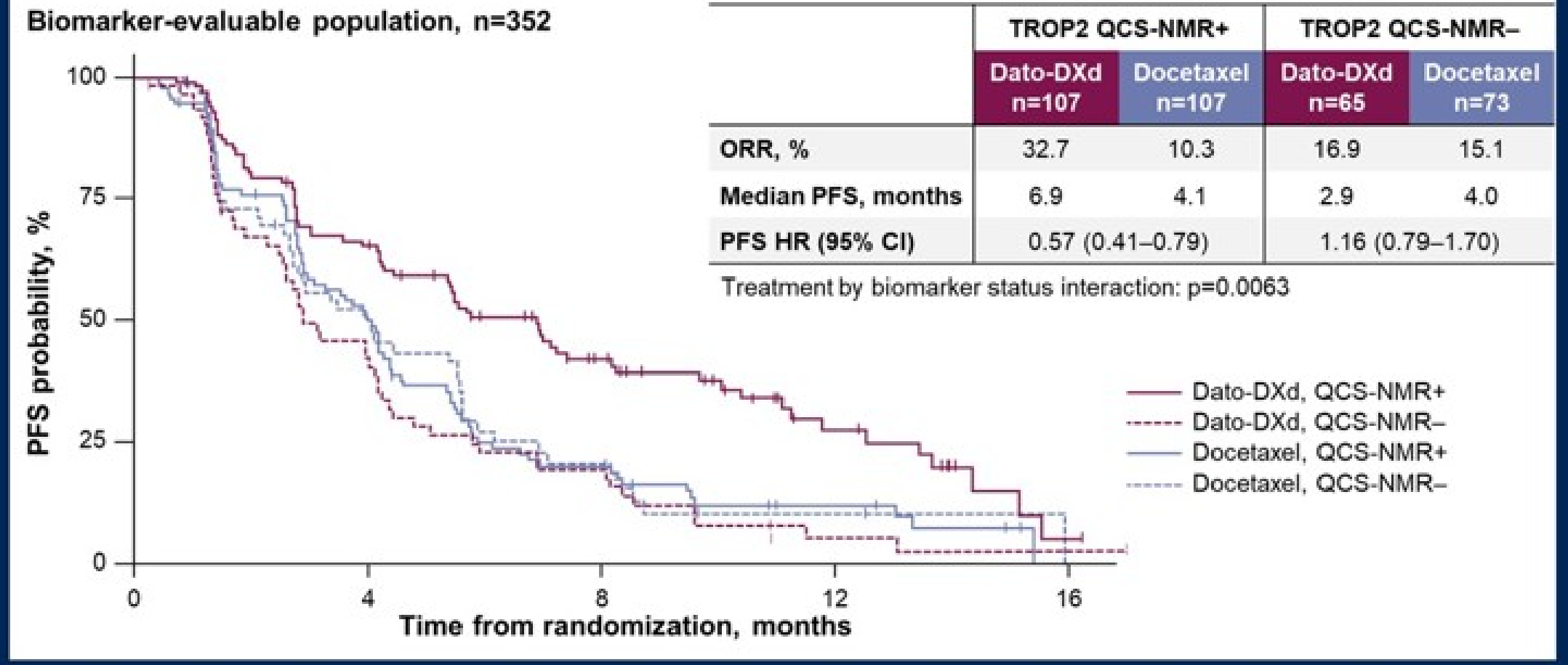
TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

- 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)



Garrasino MC et al J Thorac Oncol 2024

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

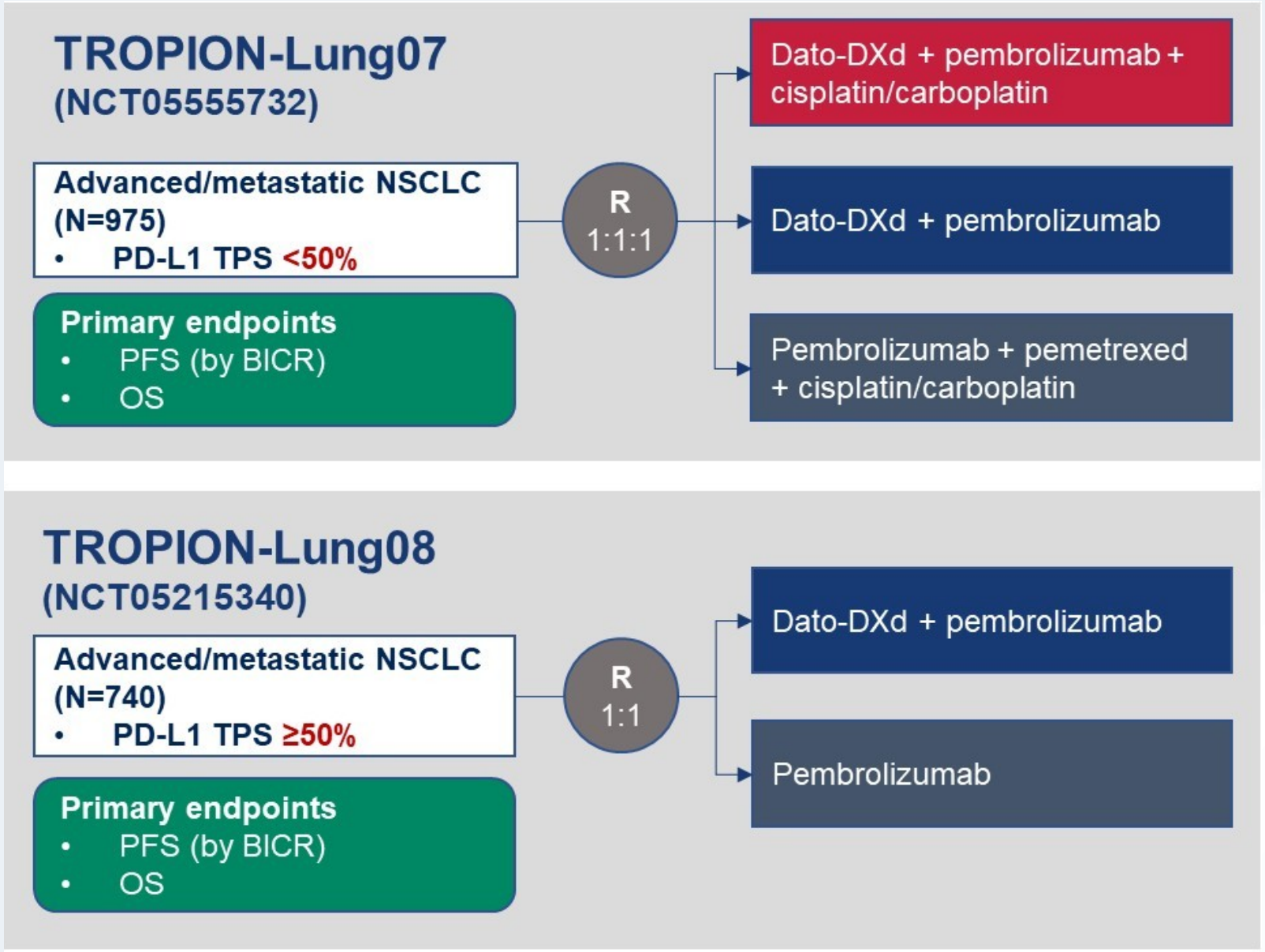


	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Garrasino MC et al J Thorac Oncol 2024

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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

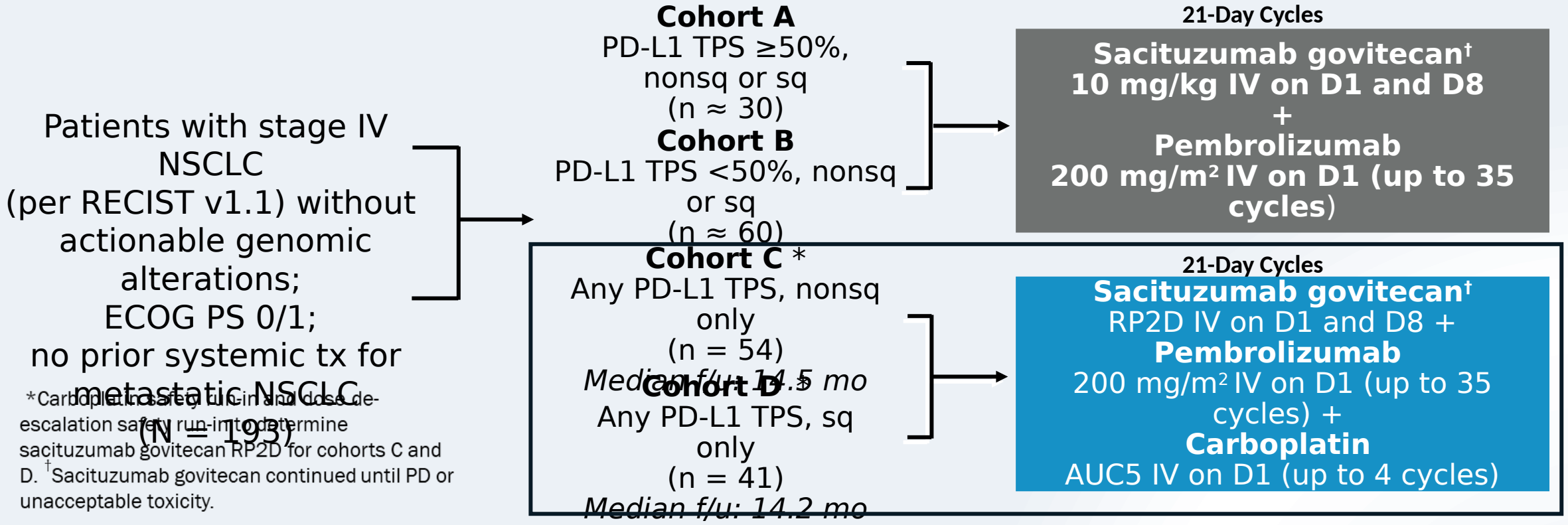
- Safety and tolerability

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



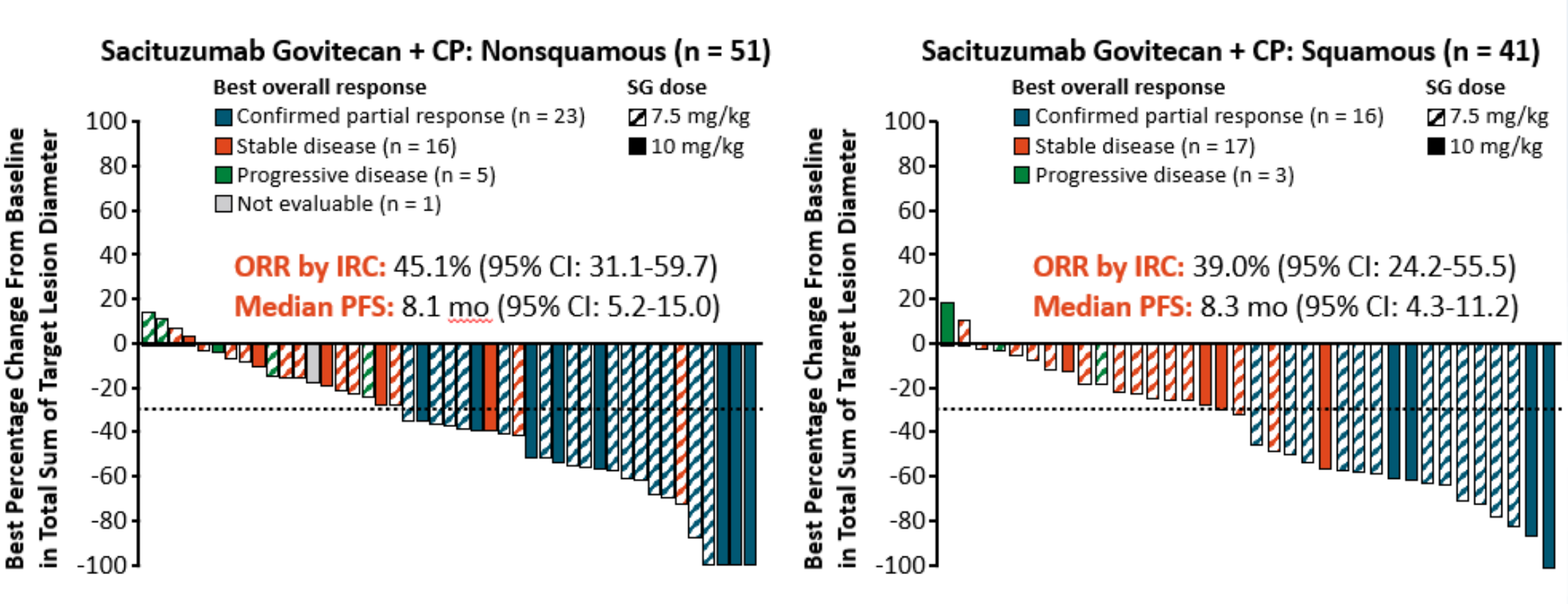
*Carboplatin safety run-in and dose de-escalation safety run-in to determine sacituzumab govitecan RP2D for cohorts C and D. †Sacituzumab govitecan continued until PD or unacceptable toxicity.

- **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

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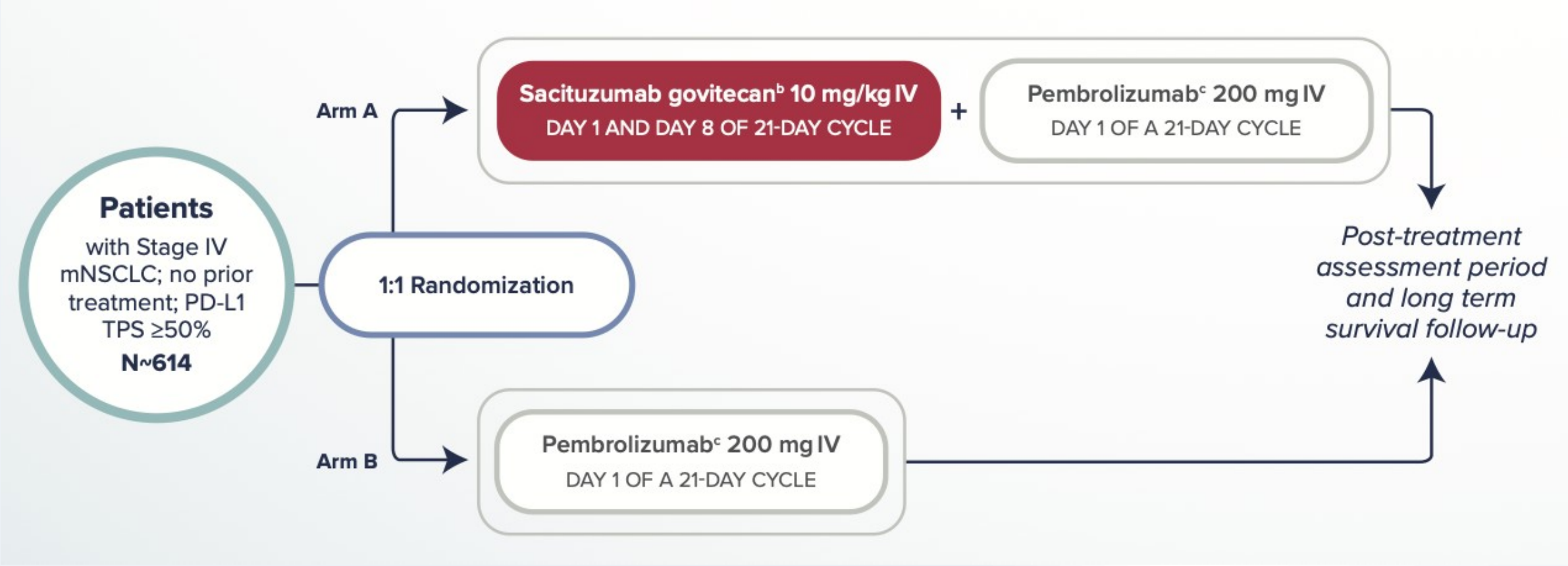
EVOKE 02: Sacituzumab Govitecan Antitumor Activity (Cohort C & D)



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-03 Keynote-D46: 1L Sacituzumab Govitecan + Pembrolizumab vs Pembrolizumab in PD-L1 TPS ≥50% mNSCLC Patients

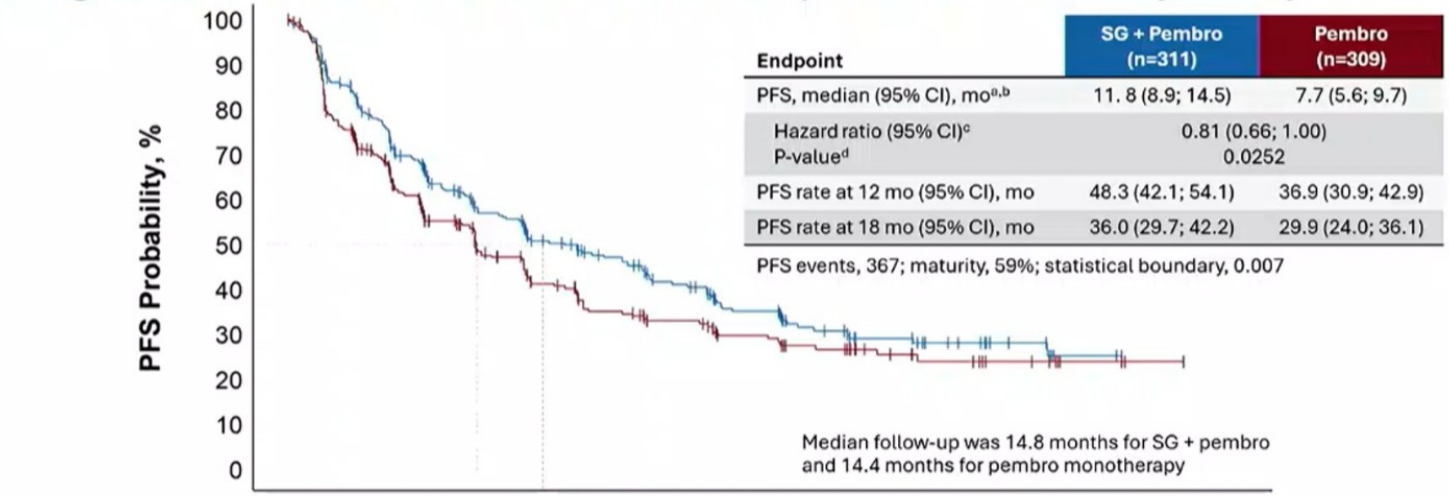


NCT05609968

EVOKE 03

Endpoint	SG + Pembro (n=311)	Pembro (n=309)
Confirmed ORR, % (95% CI)[a]	55.6 (49.9; 61.2)	43.7 (38.1; 49.4)
Best overall response, %[b,c]		
CR	7.7	3.9
PR	47.9	39.8
SD	27.7	29.4
PD	7.1	16.5
Not evaluable	1.3	2.3
Disease control, % (95% CI)[a]	83.3 (78.7; 87.3)	73.1 (67.8; 78.0)
DOR, median (95% CI), mo[a,d]	21.4 (14.9–NE)	21.3 (15.7–NE)

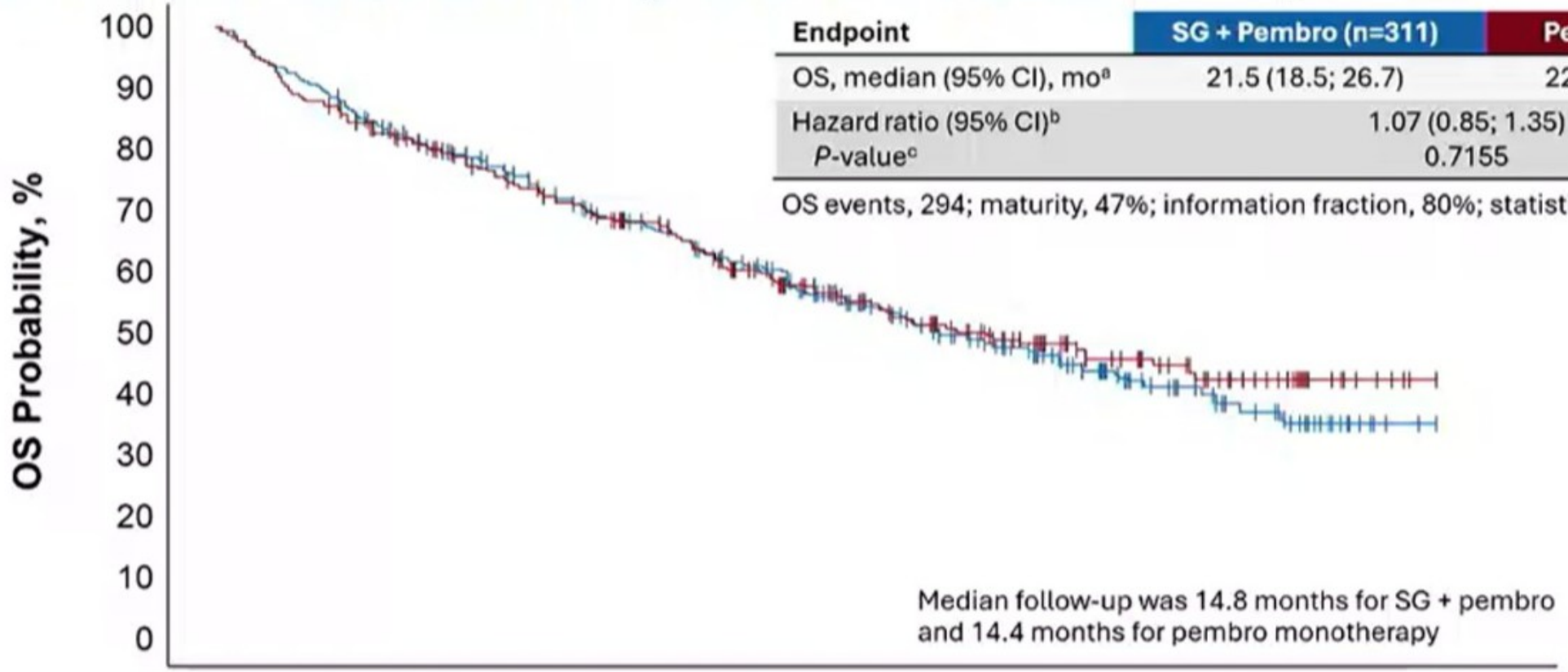
Progression-Free Survival in the ITT Population – Primary Analysis



Endpoint	SG + Pembro (n=311)	Pembro (n=309)
PFS, median (95% CI), mo[a,b]	11. 8 (8.9; 14.5)	7.7 (5.6; 9.7)
Hazard ratio (95% CI)[c]	0.81 (0.66; 1.00)	
P-value[d]	0.0252	
PFS rate at 12 mo (95% CI), mo	48.3 (42.1; 54.1)	36.9 (30.9; 42.9)
PFS rate at 18 mo (95% CI), mo	36.0 (29.7; 42.2)	29.9 (24.0; 36.1)

PFS events, 367; maturity, 59%; statistical boundary, 0.007

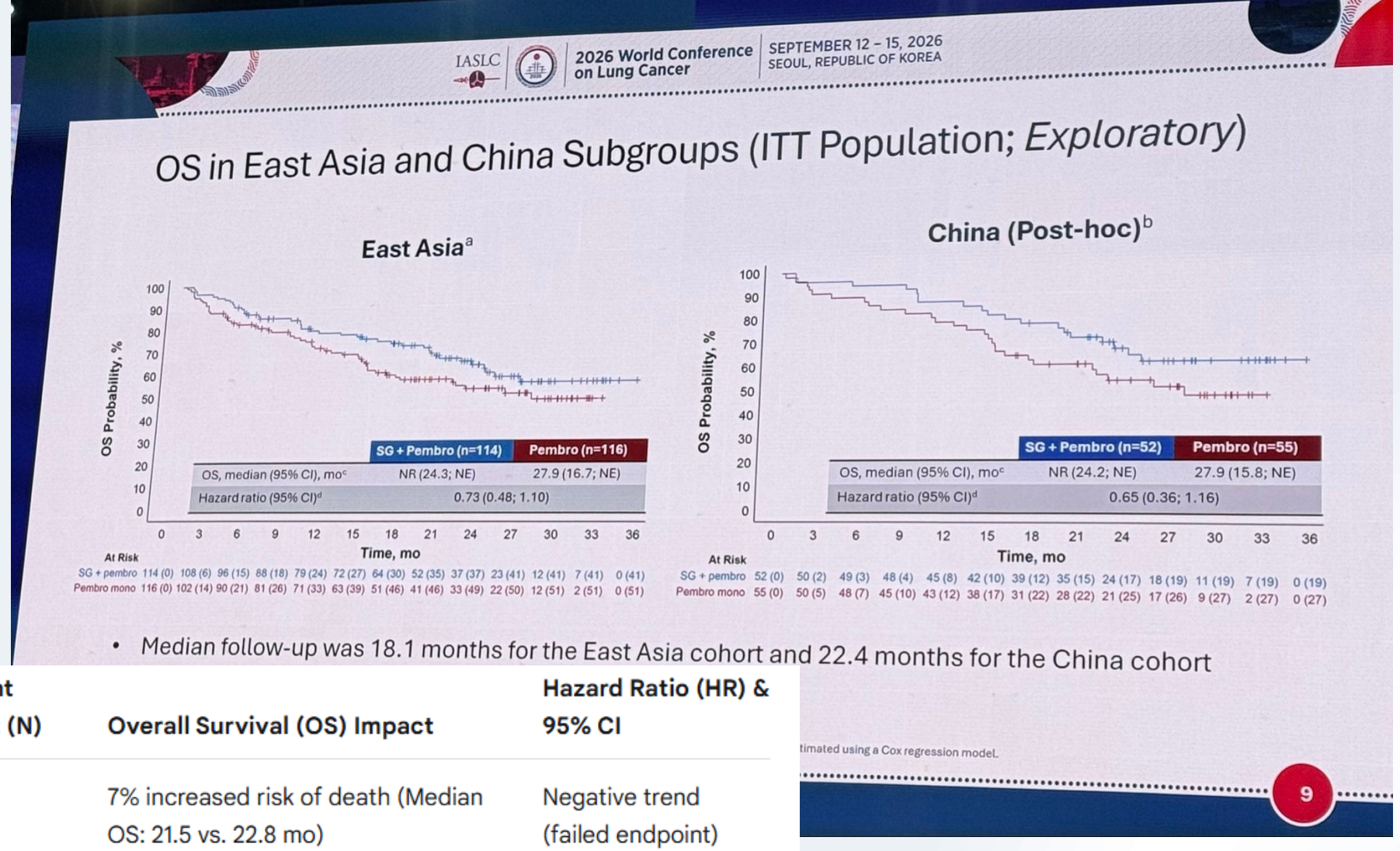
Overall Survival in the ITT Population – Interim Analysis



Endpoint	SG + Pembro (n=311)	Pembro (n=309)
OS, median (95% CI), mo[a]	21.5 (18.5; 26.7)	22.8 (18.7; 29.0)
Hazard ratio (95% CI)[b]	1.07 (0.85; 1.35)	
P-value[c]	0.7155	

OS events, 294; maturity, 47%; information fraction, 80%; statistical boundary, 0.008

At Risk														
SG + pembro	311	282	243	214	180	153	123	95	71	46	27	14	1	0
Pembro mono	309	272	237	205	178	148	120	91	69	47	29	11	1	0



Population Cohort	Patient Count (N)	Overall Survival (OS) Impact	Hazard Ratio (HR) & 95% CI
Global ITT Population	620	7% increased risk of death (Median OS: 21.5 vs. 22.8 mo)	Negative trend (failed endpoint)
East Asian Subgroup	230	27% improvement in OS (Median OS not reached vs. 27.9 mo)	HR 0.73 (95% CI: 0.48–1.10)
Chinese Subgroup	107	35% improvement in OS (Median OS not reached vs. 27.9 mo)	HR 0.65 (95% CI: 0.36–1.16)

Mountzios G, et al. WCLC 2026 PL02-06

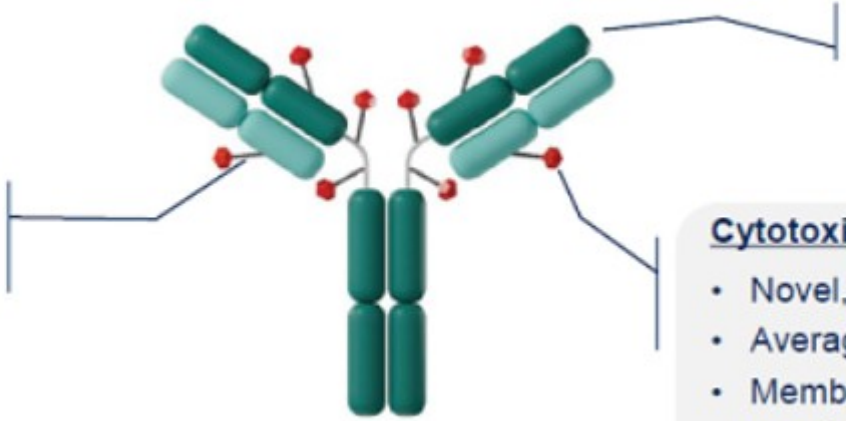
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Sacituzumab Tirumotecan

Sac-TMT (TROP2 ADC) design

Unique, bifunctional linker

- Maximizes payload delivery to tumor cells
- Irreversible connection with the antibody ensures minimal payload loss in the circulation
- pH-sensitive cleavage from the payload in the lysosome ensures payload release in the tumor cell



Monoclonal antibody

- Sacituzumab, a humanized anti-TROP2 antibody with high affinity for TROP2

Cytotoxic payload

- Novel, **belotecan-derived** topoisomerase I inhibitor
- Average DAR of 7.4 (range, 7–8)
- Membrane permeability elicits a bystander effect in nearby tumor cells

OptiTROP-Lung06 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT06711900)

Key eligibility criteria

- Locally advanced (stage IIIB/IIIC) or metastatic (stage IV) nsq-NSCLC
- No prior systemic therapy for advanced disease
- No sensitizing *EGFR* or *ALK* alteration
- PD-L1 TPS< 1% (IHC 22C3, central lab)
- ECOG PS score 0 or 1

R 1:1

n = 455

- Sac-TMT 4 mg/kg Q2W + Pembro 400 mg Q6W[a] (n = 229)
- Pemetrexed 500 mg/m² + Carboplatin AUC 5 or Cisplatin 75 mg/m² Q3W[b] + Pembro 400 mg Q6W[a] (n = 226)

Endpoints [c]

Primary

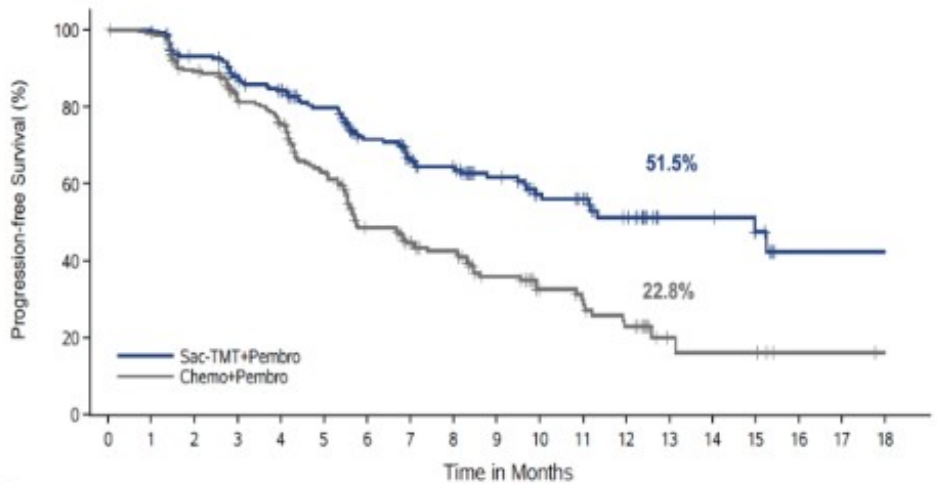
- PFS assessed by BICR

Secondary endpoints included

- OS
- PFS assessed by investigator
- ORR, DCR, DOR
- Safety

PFS by BICR

Sac-TMT + pembro significantly improved PFS vs. Chemo + pembro, with a 51% reduction in risk of disease progression or death



At Risk

Sac-TMT+Pembro	229	224	197	173	162	141	107	88	77	60	45	41	28	15	15	12	2	2	2
Chemo+Pembro	226	221	192	157	141	109	77	64	56	38	25	22	16	5	4	4	1	1	0

	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
PFS events, n (%)	79 (34.5)	126 (55.8)
Median, mo (95%CI)	15.0 (9.9, NE)	5.7 (5.5, 7.4)

HR 0.49 (95%CI: 0.36, 0.65)
p < 0.0001[a]

Zhou F et al ESMO 2026 LBA66; NEJM 2026

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Endpoints [c]

Primary

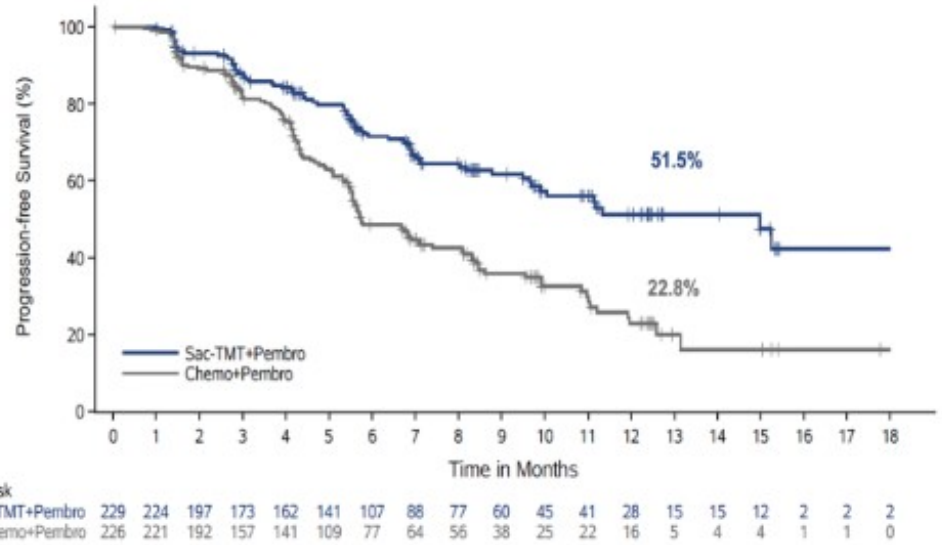
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PFS by BICR

Sac-TMT + pembro significantly improved PFS vs. Chemo + pembro, with a 51% reduction in risk of disease progression or death



Trial	Patient Population	Experimental Arm	Control Arm	Primary Efficacy Outcome (BICR)
OptiTROP-Lung04	EGFR-mutant NSCLC post-TKI failure	Sac-TMT monotherapy	Platinum chemotherapy	**Median OS:** 25.9 mo vs. 17.4 mo (HR 0.69)
OptiTROP-Lung05	1L PD-L1 Positive (TPS ≥1%) advanced NSCLC	Sac-TMT + pembrolizumab	Pembrolizumab monotherapy	**Median PFS:** Not Reached vs. 5.7 mo (HR 0.35)
OptiTROP-Lung06	1L PD-L1 Negative (TPS <1%) non-squamous NSCLC	Sac-TMT + pembrolizumab	Chemotherapy + pembrolizumab	**Median PFS:** 15.0 mo vs. 5.7 mo (HR 0.49)

Zhou F et al ESMO 2026 LBA66; NEJM 2026

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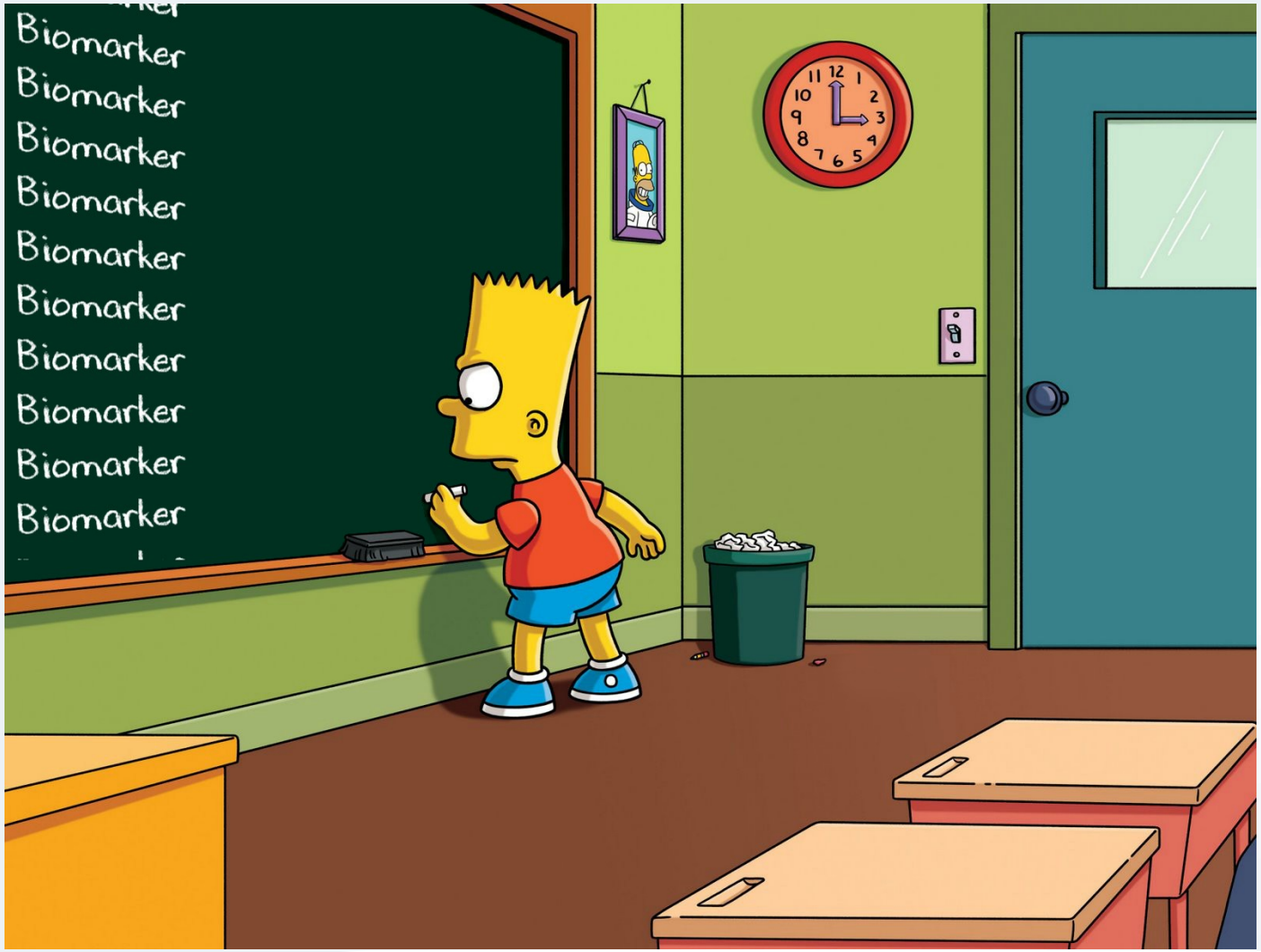
What we need to do as a community?

- Rationally design combination studies
  - Biomarker selection
  - Focus on cost/benefit, toxicity
  - CNS penetration

- Bi and tri-paratopic ADCs
  - Driving Internalization via Receptor Clustering

- Bi and tri-specific ADCs
  - Overcoming Heterogeneity and "Antigen Escape"

- Understand resistance mechanisms



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 an
  - Trastuzumab Deruxtecan HER2 mutation and HER2 3
  - Teliso V MET high 3+ IHC;



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;

- 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

- 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

Rachel E. Sanborn, MD, discusses the novel IB6-directed ADC sigvotatug vedotin for the treatment of patients with NSCLC.



Rachel E. Sanborn, MD

The novel integrin beta-6 (IB6)–directed antibody-drug conjugate (ADC) sigvotatug vedotin (formerly SGN-B6A) demonstrated early efficacy data alone and in combination with pembrolizumab (Keytruda) in patients with non–small cell lung cancer (NSCLC), warranting further study, according to Rachel E. Sanborn, MD.

It's really hoped that ADCs are going to offer greater efficacy than chemotherapy in the treatment of [patients with] lung cancer. So far, the effects have been muted compared with the hopes. However, the science is continuing to evolve, and we're continuing to try to optimize these agents to make them better. ADCs on their own at this point don't accomplish what our overall goal is, which is to cure [patients] with no or minimal toxicity. That's what we all want. ADCs don't offer that, [although] that's a tall order for any treatment. [Nevertheless], ADCs are going to have roles to play, especially in combination with other treatments to enhance efficacy over broad-based chemotherapy alone as we continue to learn more. Josh, clearly wins the debate!