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Are ADCs Truly Transformational in NSCLC?

Rachel E. Sanborn, M.D.
Medical Director of Clinical Research;
Medical Director, Thoracic Oncology Program;
Medical Director, Phase I Clinical Trials Program;
Earle A. Chiles Research Institute, Providence Cancer Institute

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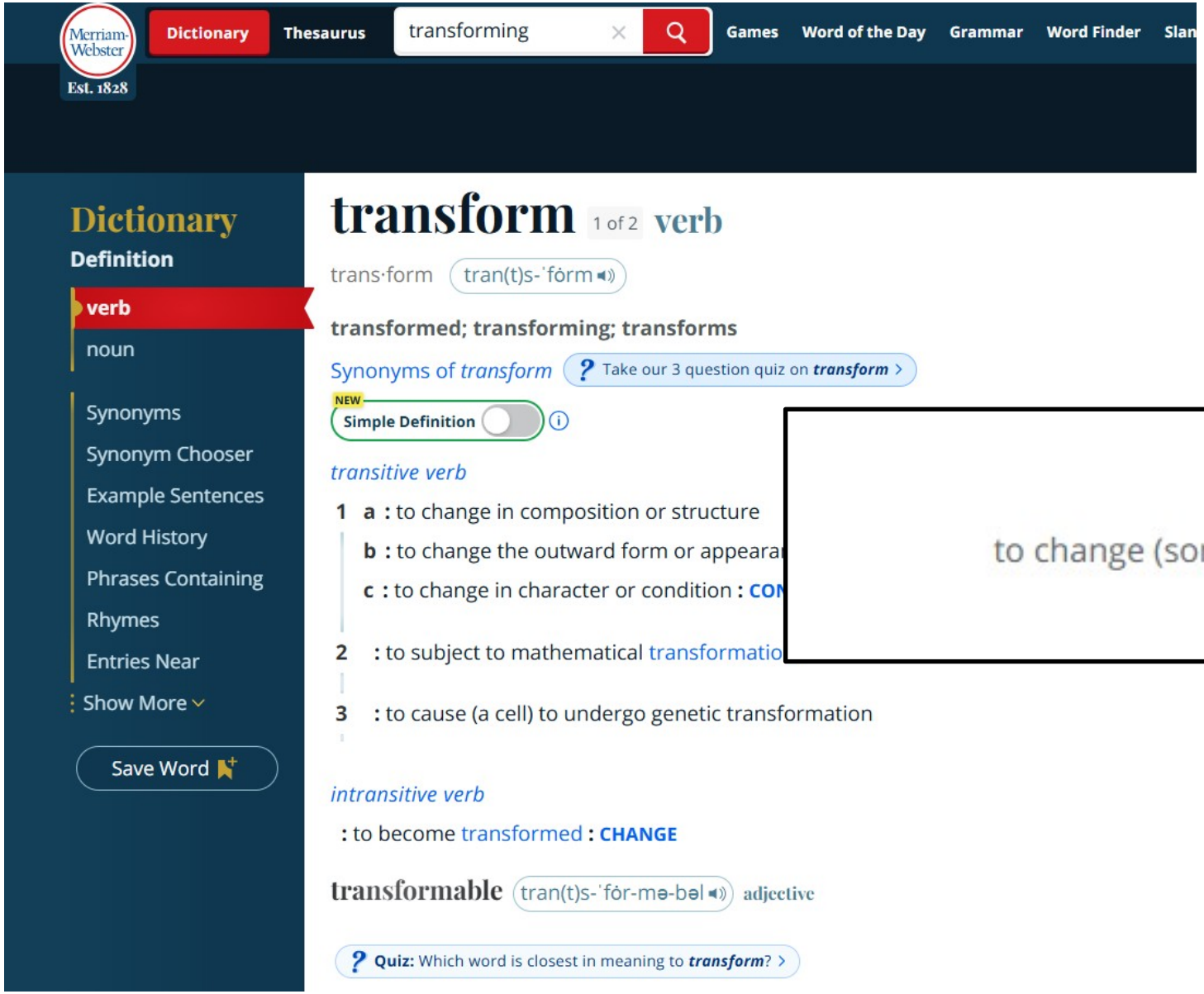
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Disclosures: 2 Years

- Advisory
  - Abbvie Oncology; Amgen; AstraZeneca; Boehringer Ingelheim; Curio Science; Daiichi Sankyo; Exelixis; Gilead; HotSpot Therapeutics; IDEOlogy Health; Janssen Oncology/Johnson & Johnson; Natera; Nuvation Bio; OncLive; Pfizer; Rigel Therapeutics; Summit Therapeutics; Targeted Oncology
- Data Safety Monitoring Board
  - OSE Immunotherapeutics
- Honoraria (Educational Presentations)
  - Binaytara Foundation; Bio Ascend; IDEOlogy Health; MECC Conferences; MJH Life Sciences; PRIME Education
- Travel
  - HotSpot Therapeutics, Macrogenics

Definition of Transform



transform

to change (something) completely and usually in a good way

Transformation in Ancient Science



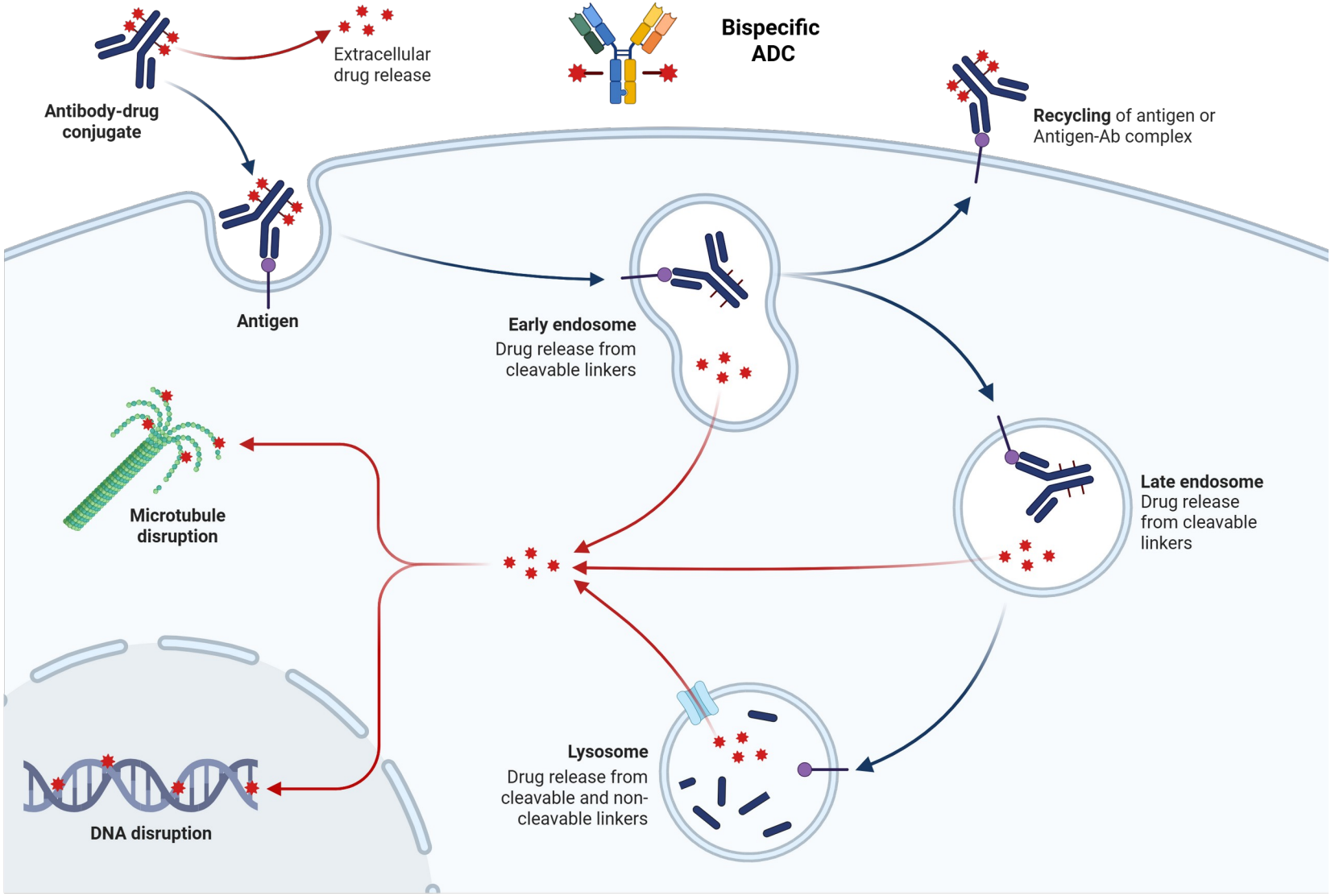
ADC Structure

- Different types of ADC
- Antibody to bind
- Linker
- Payloads: Primarily chemo

- Next gen bispecifics







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Transformation in Oncology

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

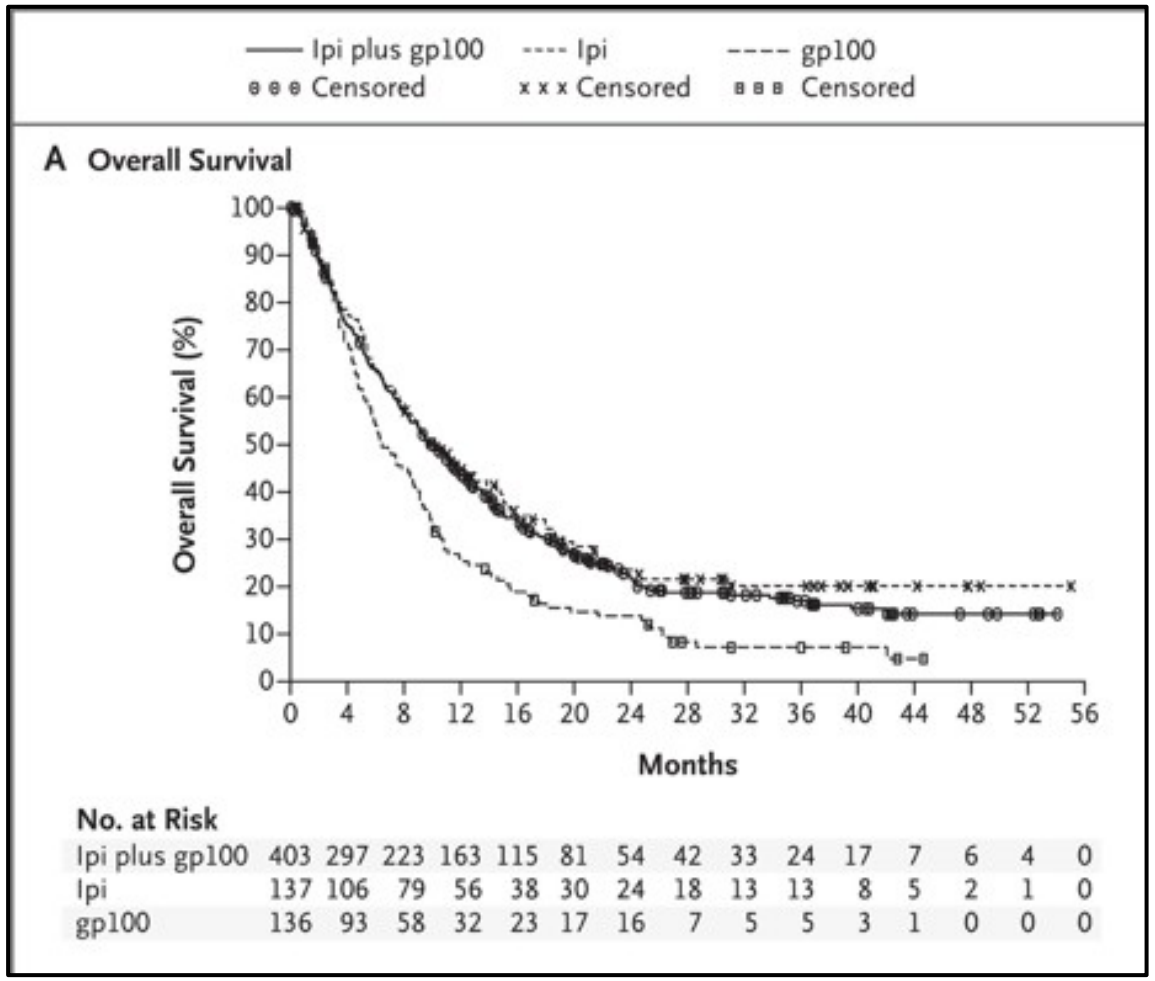
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

This article has been corrected. VIEW THE CORRECTION

Authors: F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., +21 , and Walter J. Urba, M.D., Ph.D. Author Info & Affiliations

Published August 19, 2010 | N Engl J Med 2010;363:711-723 | DOI: 10.1056/NEJMoa1003466 | VOL. 363 NO. 8

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Hodi, FS et al; NEJM 2010

Transformation in Oncology

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

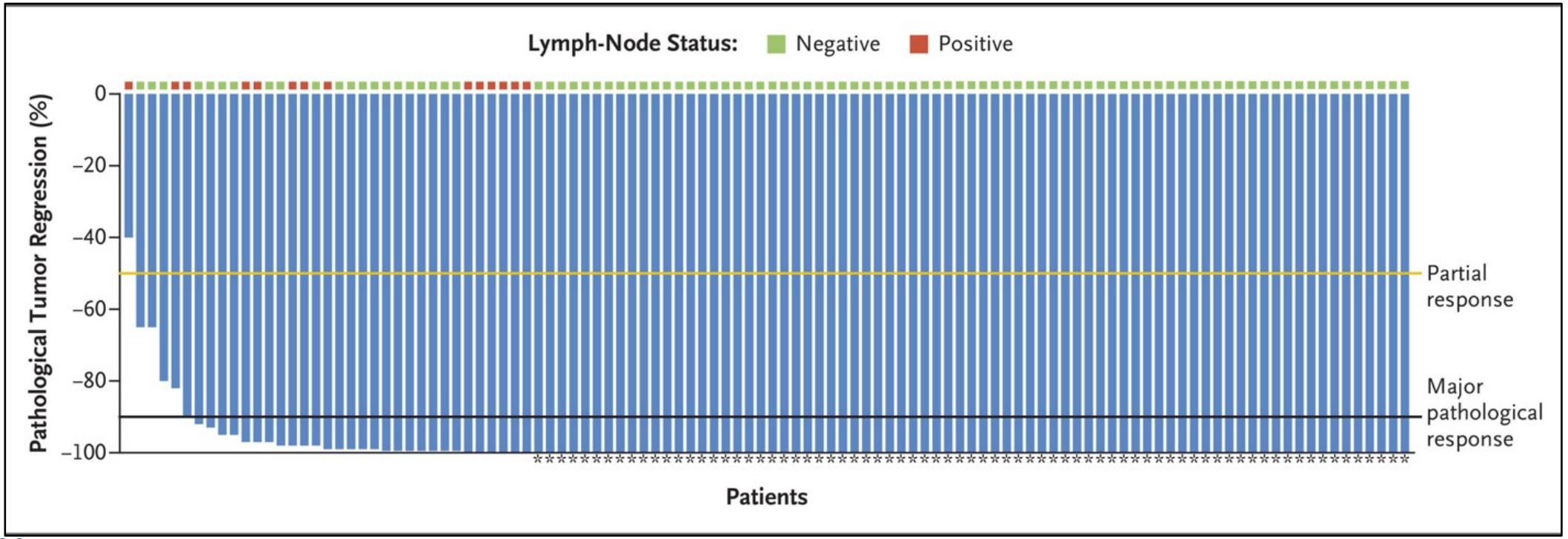
ORIGINAL ARTICLE

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Authors: Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., +16, and John B. Haanen, M.D., Ph.D. Author Info & Affiliations

Published June 5, 2024 | N Engl J Med 2024;390:1949-1958 | DOI: 10.1056/NEJMoa2400634 | VOL. 390 NO. 21

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Have ADCs Been Transformational?

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

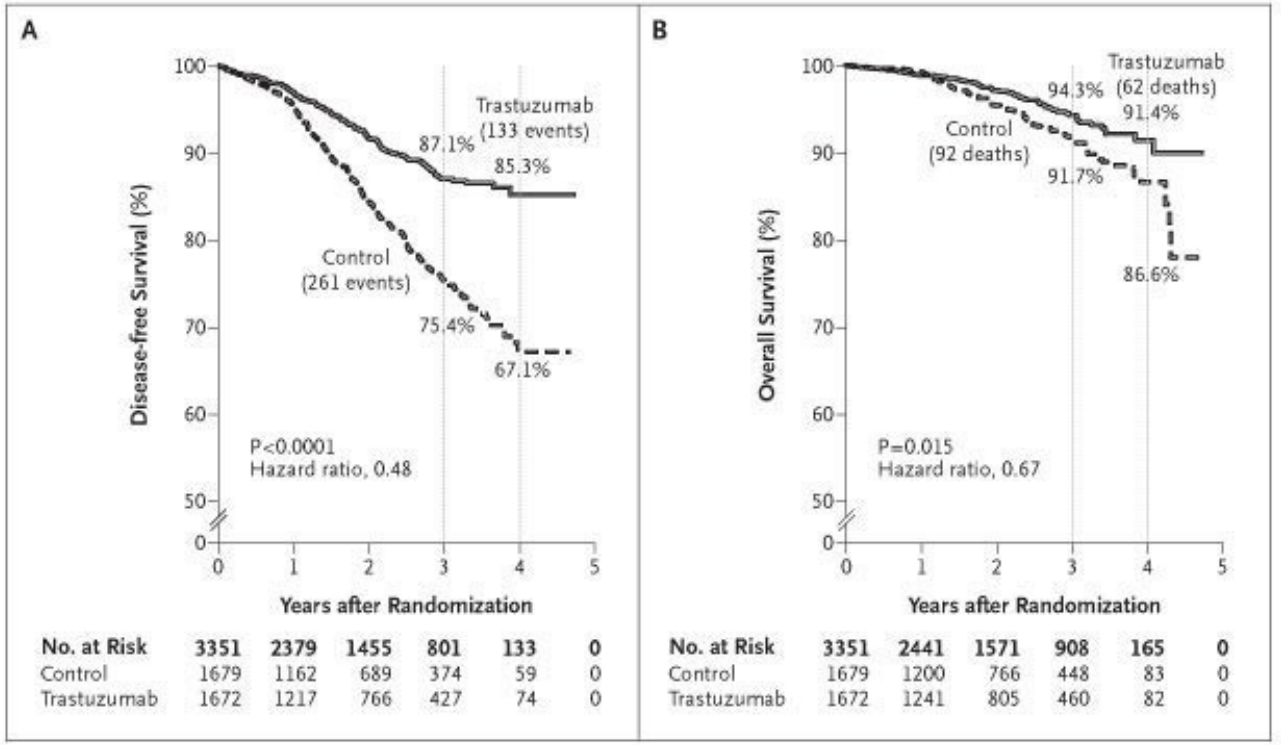
ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Authors: Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., +17 , and Norman Wolmark, M.D. Author Info & Affiliations

Published October 20, 2005 | N Engl J Med 2005;353:1673-1684 | DOI: 10.1056/NEJMoa052122

VOL. 353 NO. 16 | Copyright © 2005

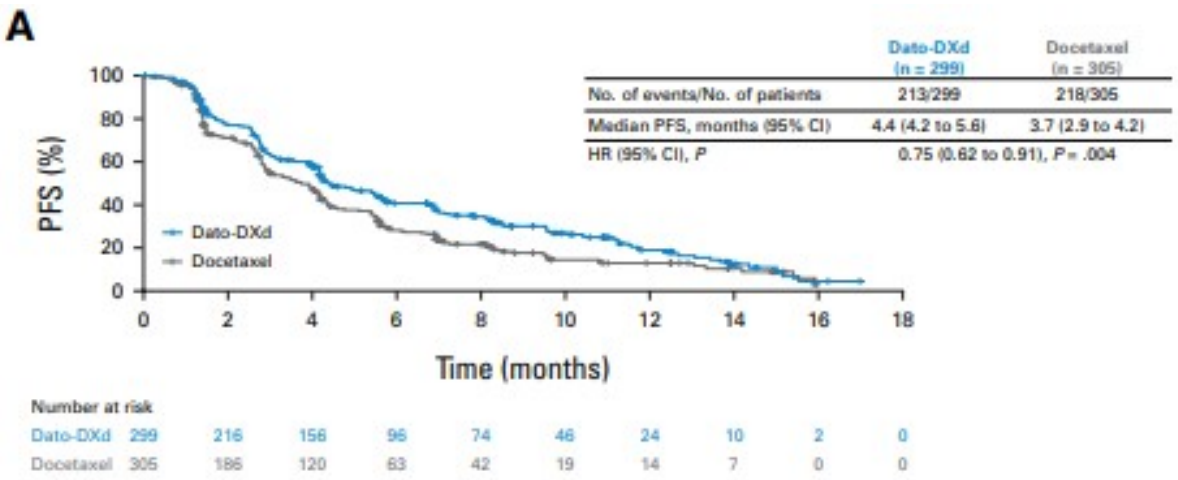


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ADCs in NSCLC

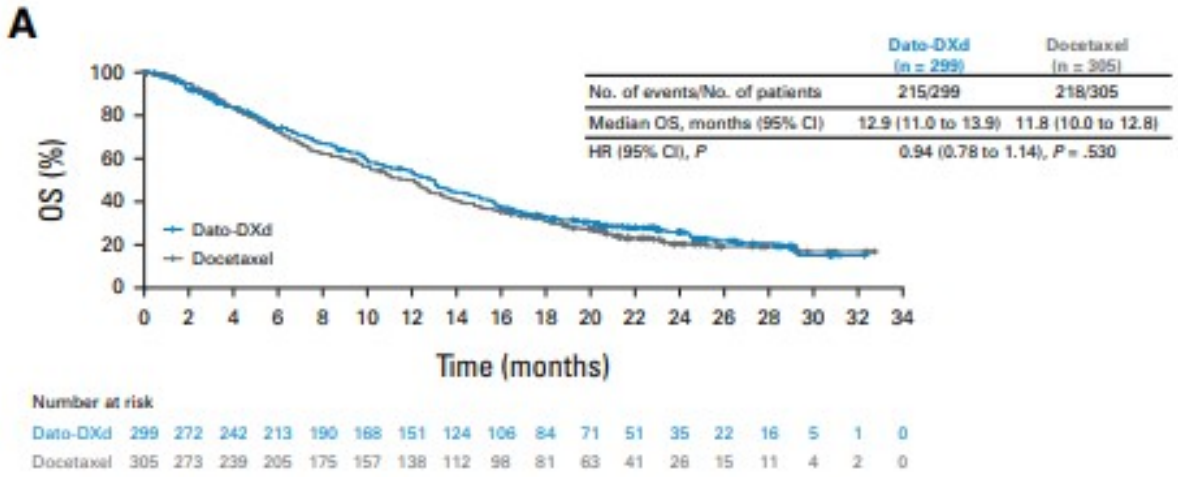
(TROP-2) Dato-DXd: TROPION-Lung01

Primary Endpoint PFS



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	213/299	218/305
Median PFS, months (95% CI)	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)
HR (95% CI), *P*	0.75 (0.62 to 0.91), *P* = .004	

Median Overall Survival



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	215/299	218/305
Median OS, months (95% CI)	12.9 (11.0 to 13.9)	11.8 (10.0 to 12.8)
HR (95% CI), *P*	0.94 (0.78 to 1.14), *P* = .530	

- Does a statistically significant PFS delta of 3 weeks create a CLINICALLY MEANINGFUL difference?
- Especially in the setting of NO DIFFERENCE in OS?

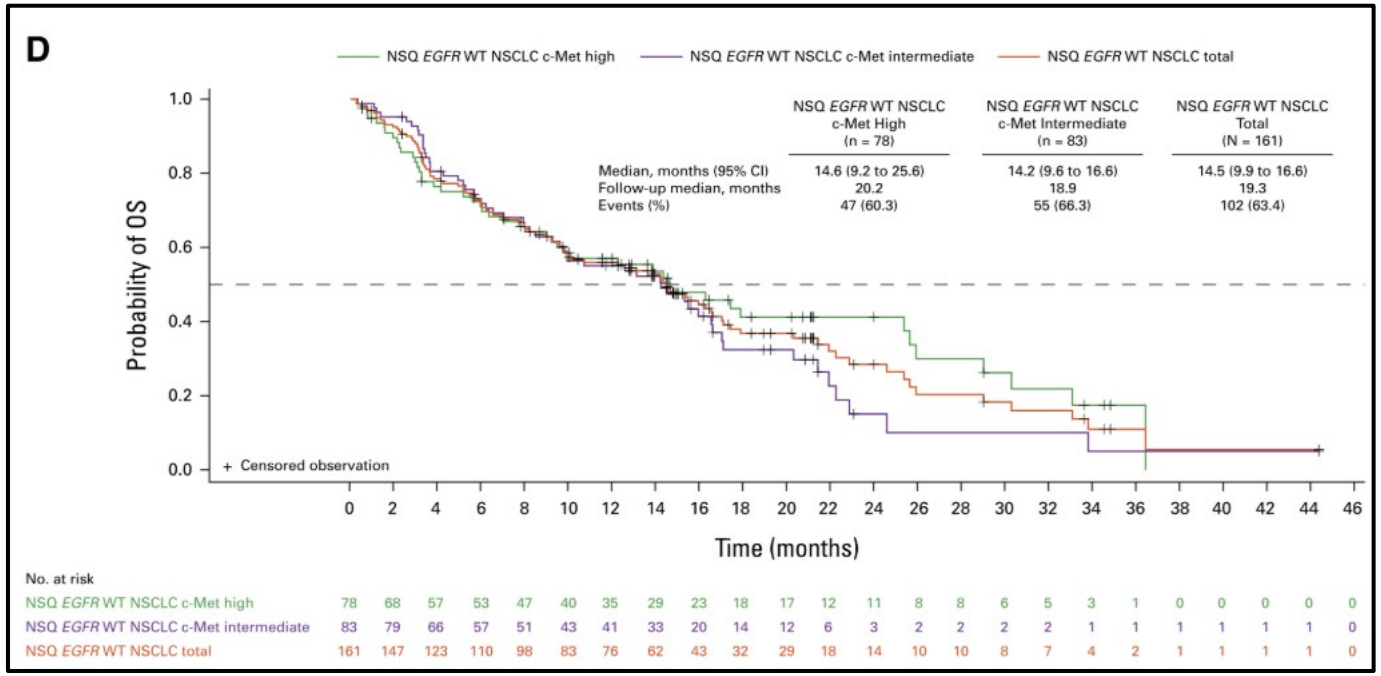
Ahn M-J et al, J Clin Oncol 2024

(c-MET) Telisotuzumab vedotin (Teliso-V)

- c-MET directed ADC
- Cleavable dipeptide linker
- Monomethyl auristatin E (MMAE) payload

- Phase 2 LUMINOSITY

- Previously-treated non-squam NSCLC
- c-MET High:
  - PFS 5.5 months
  - OS 14.3 months
- c-MET Intermediate:
  - PFS 5.9 months
  - OS 14.2 months
- FDA accelerated approval, c-MET high



Tail on the curve?

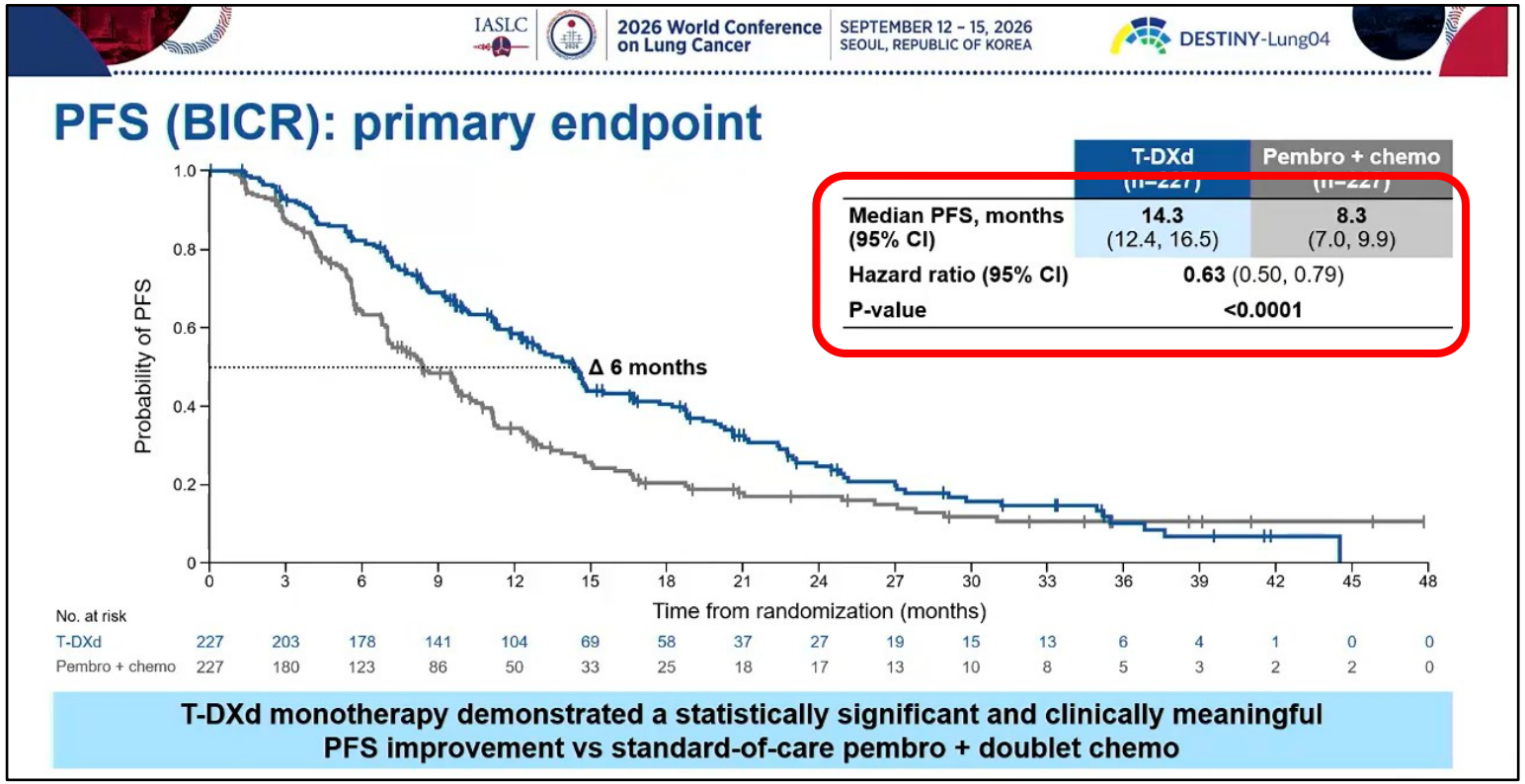
= 1 patient left

Camidge DR, et al, J Clin Oncol 2024; Girard N et al, JTO Clin Res Reports 2026

(HER2 Mutation) T-DXd: DESTINY-Lung04

- Randomized phase 3, HER2 exon 19 or 20 mutation
- T-DXd vs Platinum/pemetrexed/pembro

DESTINY-Lung04 Primary Endpoint

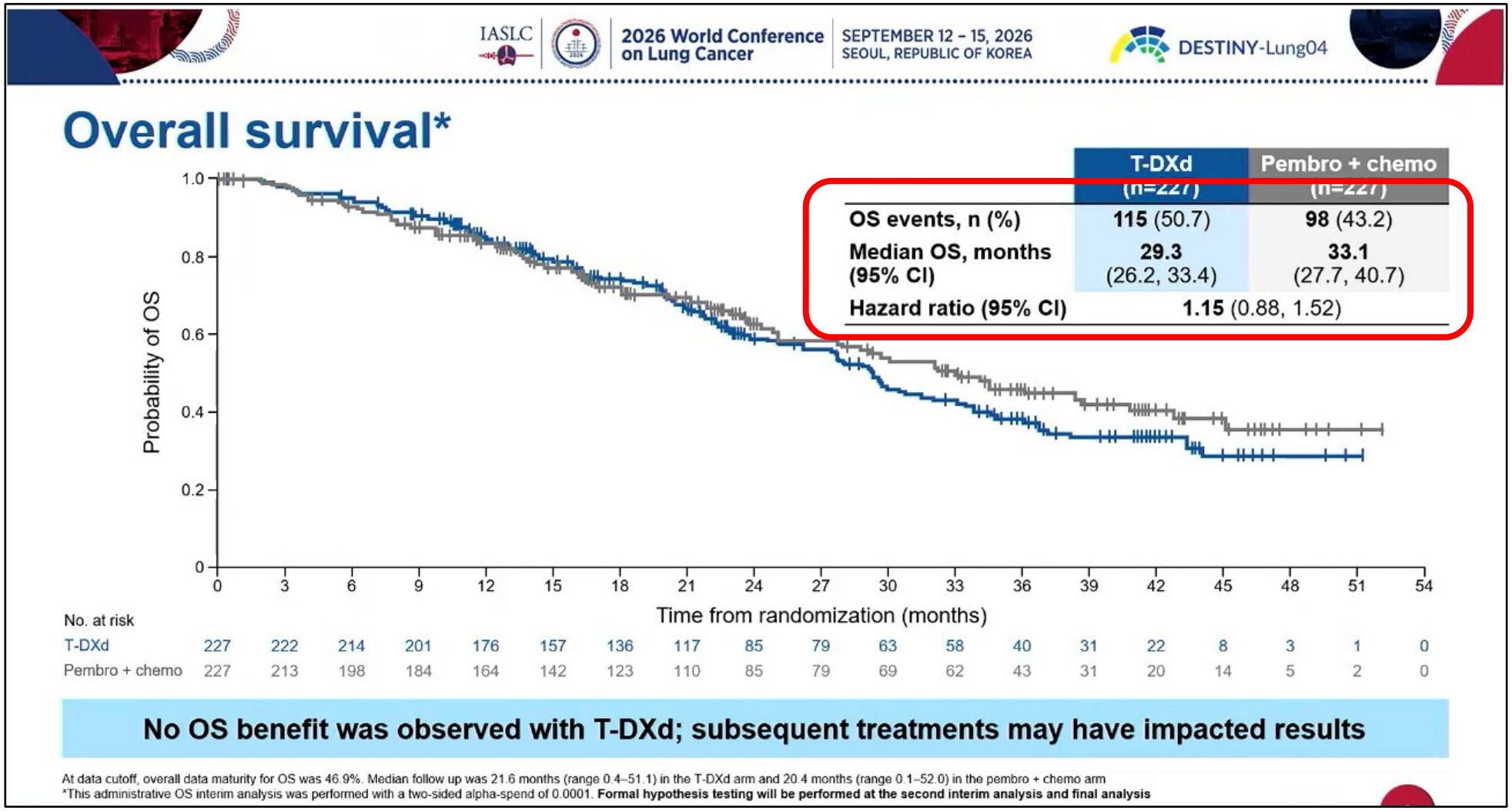


Rotow J et al, WCLC 2026

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DESTINY-Lung04: --INTERIM– Overall Survival

- Questions:
- How will this compare with TKIs?
- Zongertinib
- Sevabertinib
- Others?



Rotow J et al, WCLC 2026

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TROP-2 ADC: Sacituzumab Govitecan (Saci-G)

IASLC 2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

Primary Results From Phase 3 EVOKE-03/KEYNOTE D46: Sacituzumab Govitecan + Pembrolizumab in PD-L1 TPS ≥50% Metastatic NSCLC

Giannis Mountzios, MD, MSc, PhD

Henry Dunant Hospital Center, Athens, Greece

- Payload: Topo-1 (SN-38)

EVOKE-03/KEYNOTE D46 Study Design

Key eligibility criteria
- Stage IV NSCLC (AJCC 8th)
- No prior systemic treatment for mNSCLC
- ECOG PS 0 or 1
- PD-L1 TPS ≥50%
- No ILD
- No untreated or unstable brain metastases
- EGFR/ALK/ROS-1–negative disease

Stratification
- ECOG PS (0 or 1)
- Predominant tumor histology (squamous or non-squamous)
- Geographic region (East Asia vs Western Europe/North America/Australia vs Rest of World)

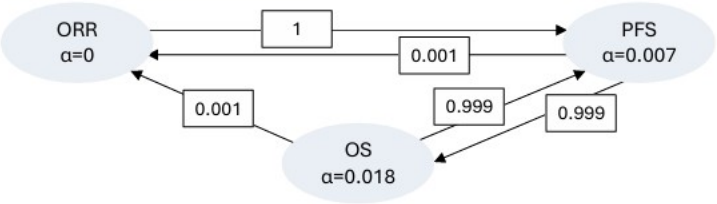
Randomized 1:1 N = 620

Sacituzumab govitecan 10 mg/kg D1, D8, Q3W + Pembrolizumab 200 mg IV D1 Q3W 35 cycles

Pembrolizumab 200 mg IV D1 Q3W 35 cycles

Primary endpoints
- PFS[a]
- OS

Secondary endpoints
- ORR[a]
- DOR[a]
- PROs
- Safety

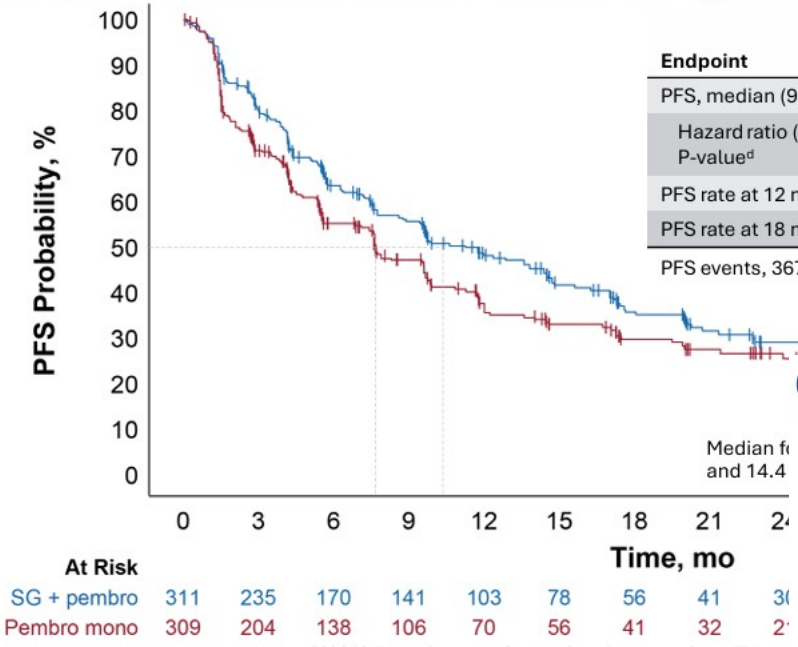


Mountzios G et al, IASLC WCLC 2026

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TROP-2 ADC: Sacituzumab Govitecan (Saci-G)

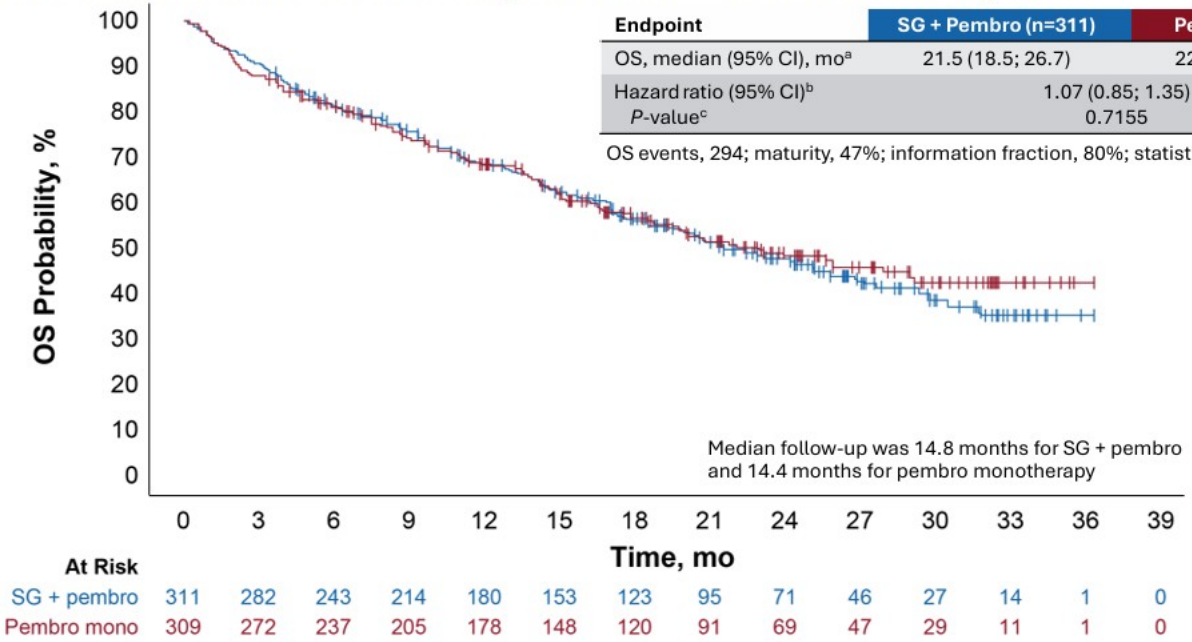
Progression-Free Survival in the ITT Population – Primary Analysis



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, 0.00

Mountzios G et al, IASLC WCLC 2026

Other Options for Transformation:

Toxicity

TROP-2 ADC: Sacituzumab Govitecan (Saci-G)

- Maybe it's not too toxic?
- Oh, wait…

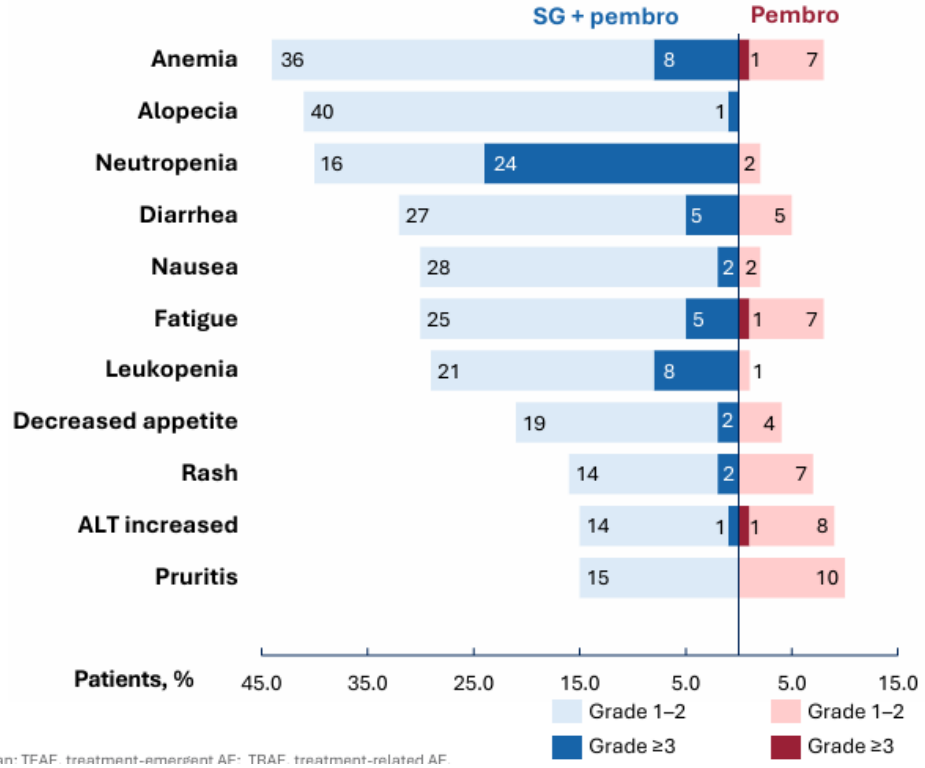
Safety Summary (Safety Population)

- Median duration of study drug exposure was 8.5 months for SG + pembro and 6.2 months for pembro monotherapy
- SG + pembro had a safety profile consistent with each agent, with no new or additional toxicities observed

Adverse Events, n (%)	SG + Pembro (n=307)	Pembro (n=309)
Any grade TEAEs	**302 (98.4)**	**294 (95.1)**
Grade ≥3	226 (73.6)	139 (45.0)
Serious TEAEs	**164 (53.4)**	**122 (39.5)**
Treatment-related	94 (30.6)	41 (3.3)
TEAEs leading to discontinuation of any drug	**95 (30.9)**	**62 (20.1)**
TEAEs leading to death	**35 (11.4)**	**30 (9.7)**
Treatment-related[b]	5 (1.6)	4 (1.3)

AESI, adverse event of special interest; ALT, alanine transaminase; pembro, pembrolizumab; SG, sacituzumab govitecan; TEAE, treatment-emergent AE; TRAE, treatment-related AE

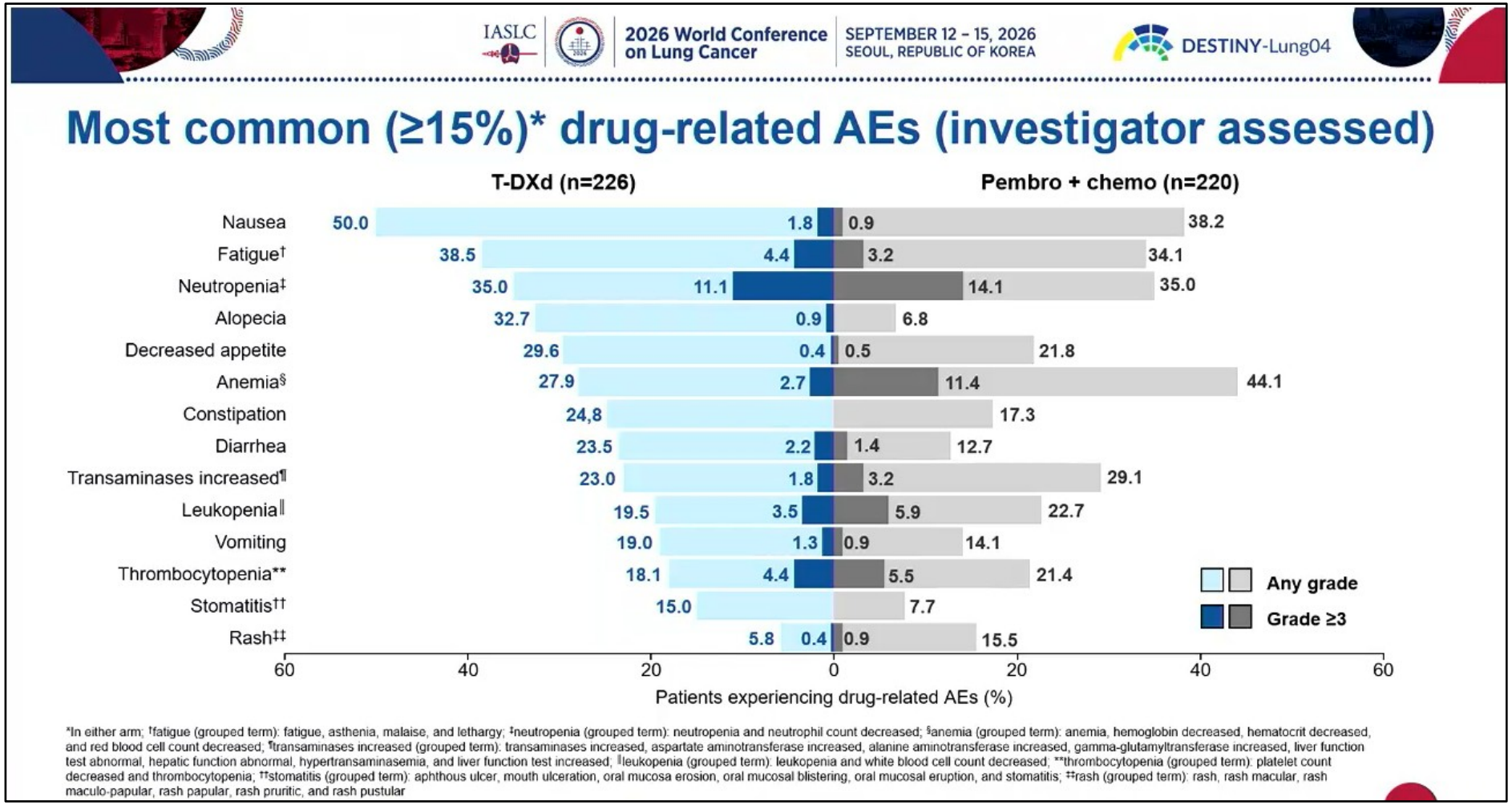
TRAEs Occurring >15% of Participants[a]



Mountzios G et al, IASLC WCLC 2026

Trastuzumab deruxtecan: Toxicities

- Interstitial Lung Disease: (21%)



Li BT et al, NEJM 2021; Rotow et al, WCLC 2026

Telisotuzumab vedotin (Teliso-V): Toxicities

- Peripheral neuropathy
- Peripheral edema
- Fatigue
- Anorexia
- Increased LFTs
- Ocular events: Blurred vision, keratitis, dry eye

- Pneumonitis/Interstitial lung disease (10%)

Camidge DR, et al, J Clin Oncol 2024; Girard N et al, JTO Clin Res Reports 2026

Signals of Promise:

TROP-2 ADC: Sacituzumab Govitecan (Saci-G)

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

Stratification factors
- Sex (male vs. female)
- ECOG PS score (0 vs. 1)
- Disease stage (IIIB/IIIC vs. IV)

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)

Treatment until disease progression or unacceptable toxicity

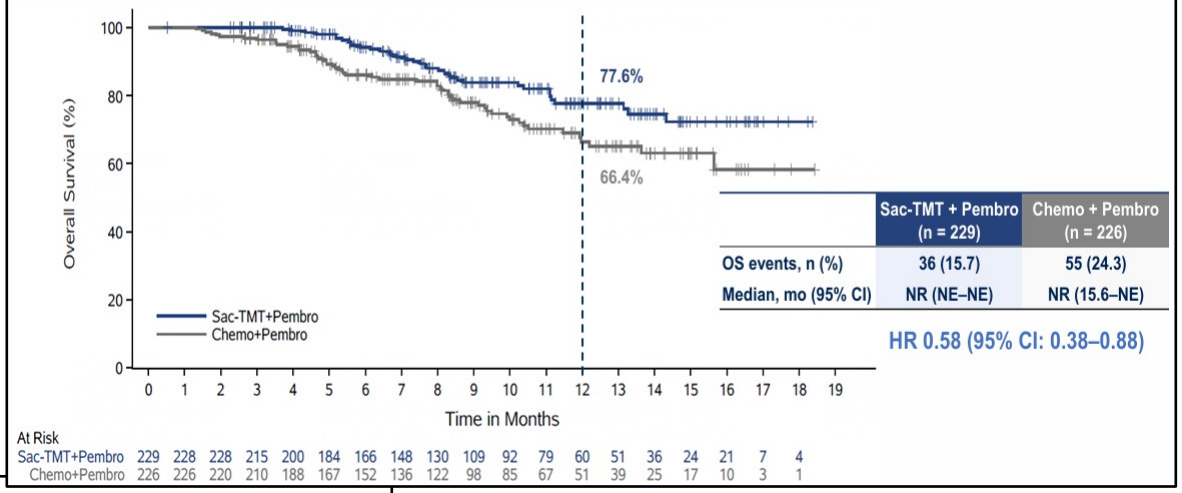
Endpoints [c]

Primary
- PFS assessed by BICR

Secondary endpoints included
- OS
- PFS assessed by investigator
- ORR, DCR, DOR
- Safety

Descriptive Overall Survival at PFS IA

A favorable trend in overall survival was observed with sac-TMT + pembro over chemo + pembro.

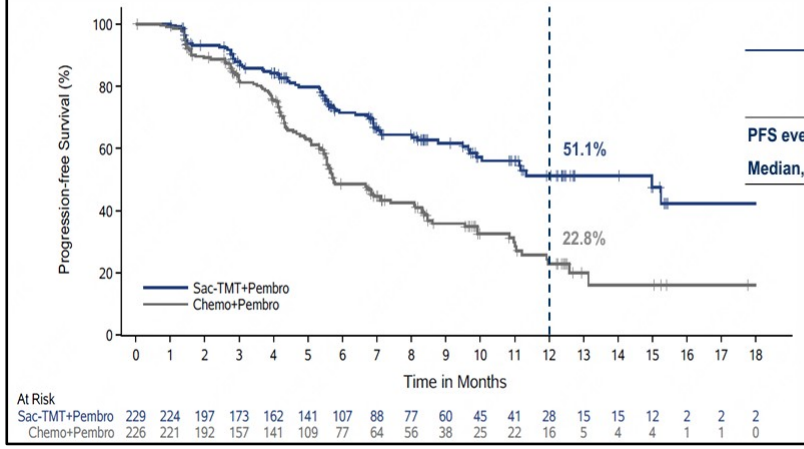


	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
OS events, n (%)	36 (15.7)	55 (24.3)
Median, mo (95% CI)	NR (NE–NE)	NR (15.6–NE)

HR 0.58 (95% CI: 0.38–0.88)

PFS by BICR

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



	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]

- Confirmation in global population pending

Zhou C et al, ESMO 2026

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Back to ADC Structure Issue

- Goal of the delivery platform as it currently stands:
  - Delivery of chemo

Patient Definition of Transformation

- Cure
- WITHOUT toxicity, Thank You

Physician Definition of Transformation

- Cure
- WITHOUT toxicity, Thank You

ADCs in NSCLC

- Will they provide a tool?
- Could they improve survival?
- Could they improve chance of cure IN COMBINATION with other modalities?

Will ADCs Provide Tranformational Care in NSCLC?

- No

- Will they have a role?
- Yes

- Will they replace (some) “traditional” chemotherap
- Hopefully

- Will they meet the definition of transfo
- No

