# ANTIBODY DRUG CONJUGATES IN NSCLC

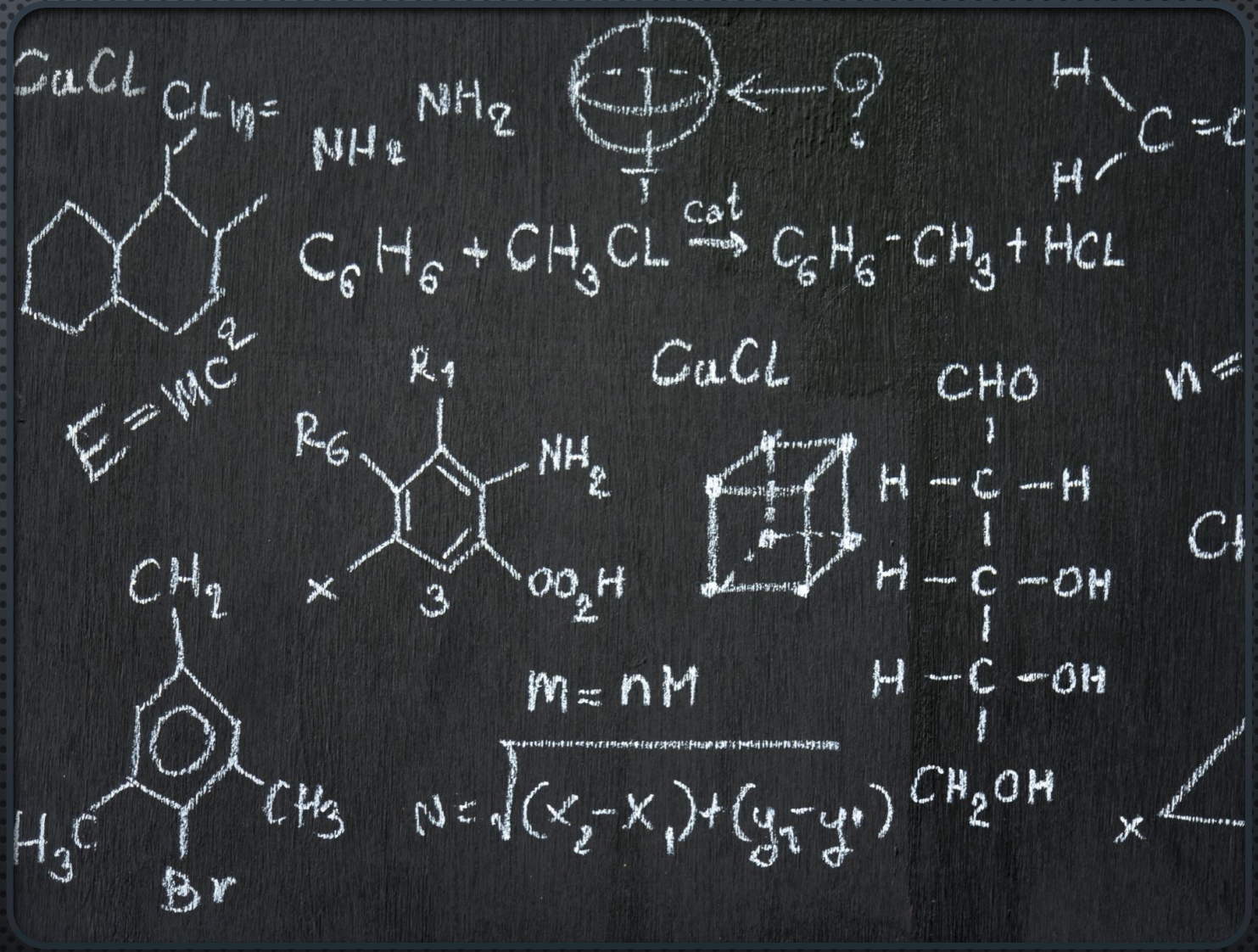
Jason Porter, MD

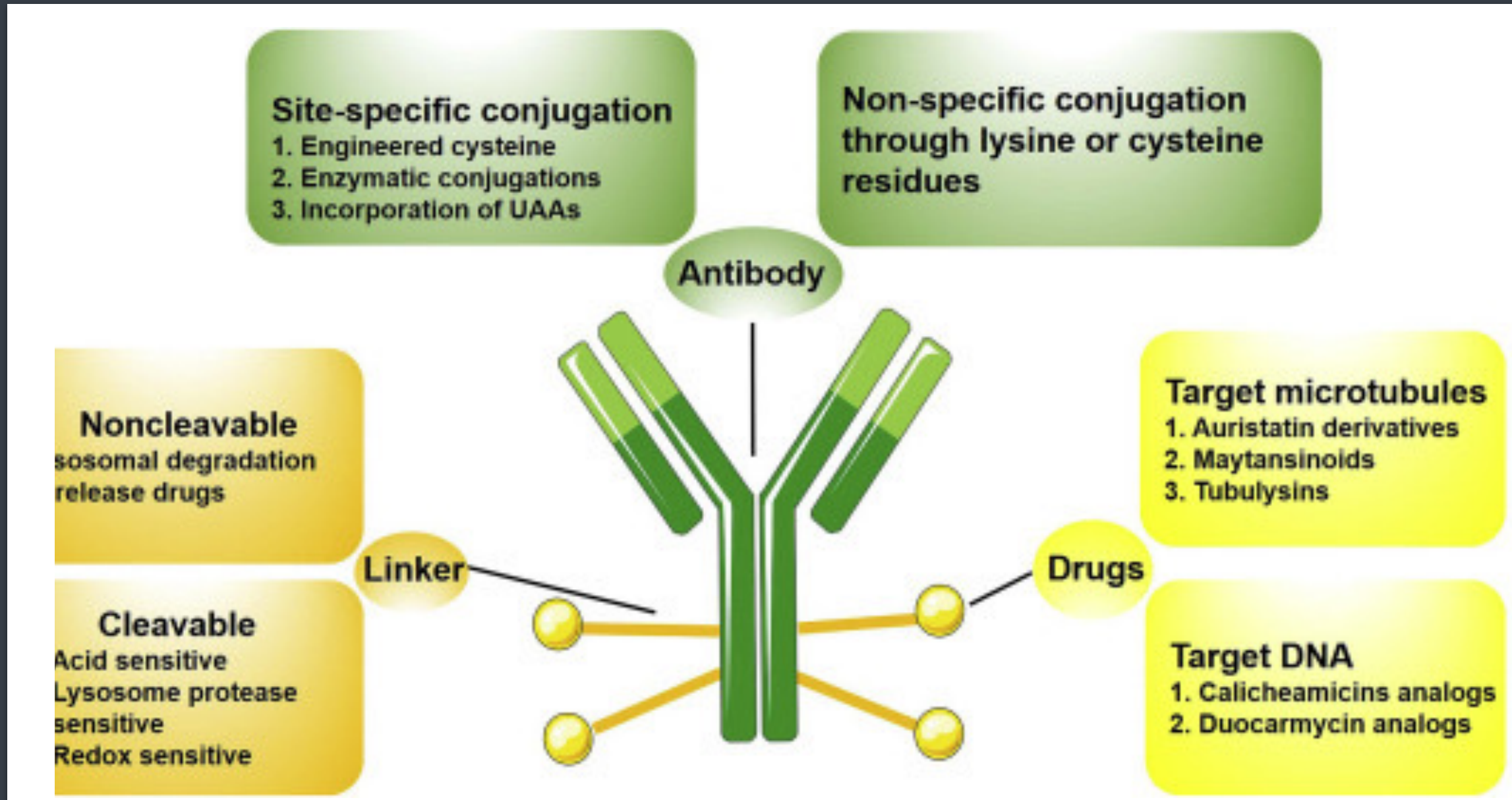
Thoracic Oncologist

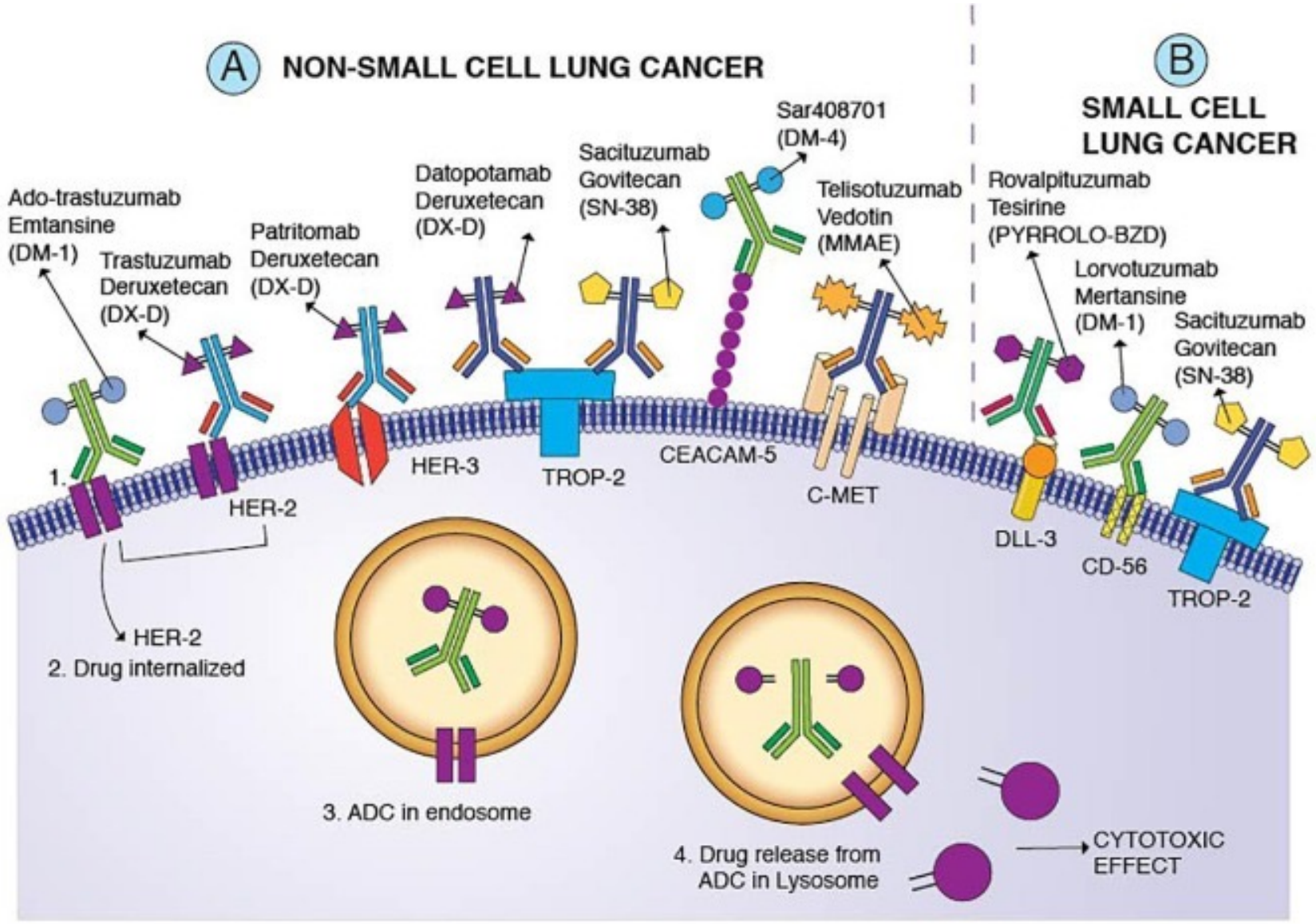
West Cancer Center and Research Institute

# OUTLINE

- ADC Basics
- ADC Targets
- Trop-2 ADC
  - Datopotamab Deruxtecan
  - Sacituzumab Govitecan
- HER-2 ADC
  - Trastuzumab Deruxtecan
- CEACAM-5
- MET
- Conclusions

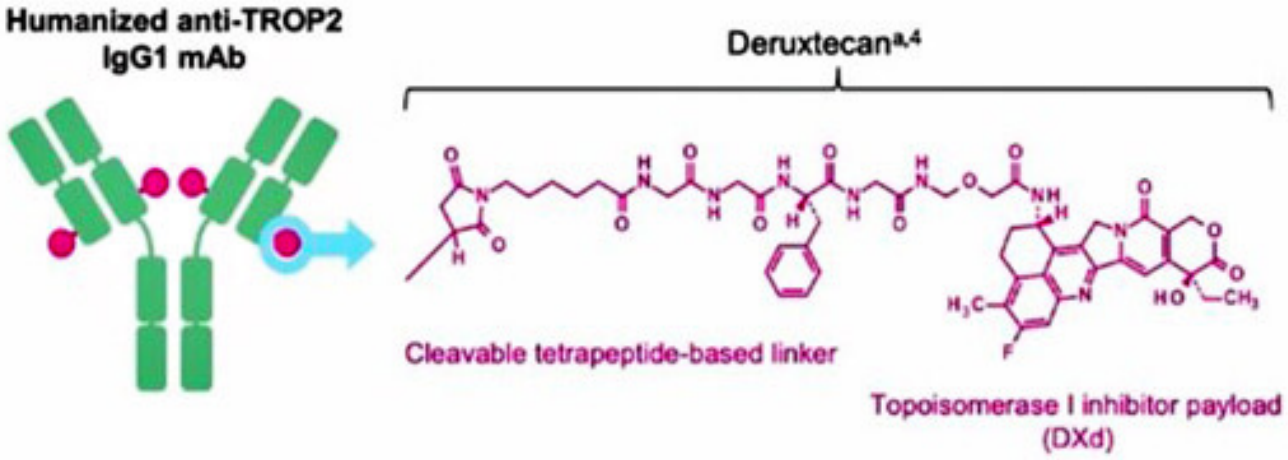



Site-specific conjugation
1. Engineered cysteine
2. Enzymatic conjugations
3. Incorporation of UAAs
Non-specific conjugation through lysine or cysteine residues
Antibody
Noncleavable
sosomal degradation
release drugs
Linker
Cleavable
Acid sensitive
Lysosome protease sensitive
Redox sensitive
Drugs
Target microtubules
1. Auristatin derivatives
2. Maytansinoids
3. Tubulysins
Target DNA
1. Calicheamicins analogs
2. Duocarmycin analogs


A
NON-SMALL CELL LUNG CANCER
B
SMALL CELL LUNG CANCER
Ado-trastuzumab Emtansine (DM-1)
Trastuzumab Deruxetecan (DX-D)
Patritomab Deruxetecan (DX-D)
Datopotamab Deruxetecan (DX-D)
Sacituzumab Govitecan (SN-38)
Sar408701 (DM-4)
Telisotuzumab Vedotin (MMAE)
Rovalpituzumab Tesirine (PYRROLO-BZD)
Lorvotuzumab Mertansine (DM-1)
Sacituzumab Govitecan (SN-38)
1.
HER-2
HER-3
TROP-2
CEACAM-5
C-MET
DLL-3
CD-56
TROP-2
HER-2
2. Drug internalized
3. ADC in endosome
4. Drug release from ADC in Lysosome
CYTOTOXIC EFFECT

## Dato-DXd is an ADC with 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker




| |
|---|
| Payload mechanism of action: topoisomerase I inhibitor[b,1] |
| High potency of payload[b,2] |
| Optimized drug to antibody ratio ≈4[b,c,1] |
| Payload with short systemic half-life[b,c,2] |
| Stable linker-payload[b,2] |
| Tumor-selective cleavable linker[b,2] |
| Bystander antitumor effect[b,2,5] |

# DATOPOTAMAB DERUXTECAN

# TROPION-Lung01 Study Design

## Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

### Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

**Without actionable genomic alterations[a]**

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

**With actionable genomic alterations**

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

**Dato-DXd**
**6 mg/kg Q3W**
**(N=299)**

**Docetaxel**
**75 mg/m$^2$ Q3W**
**(N=305)**

### Dual Primary Endpoints

- PFS by BICR
- OS

### Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

**Stratified by:** histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.

BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

# Demographics and Baseline Characteristics

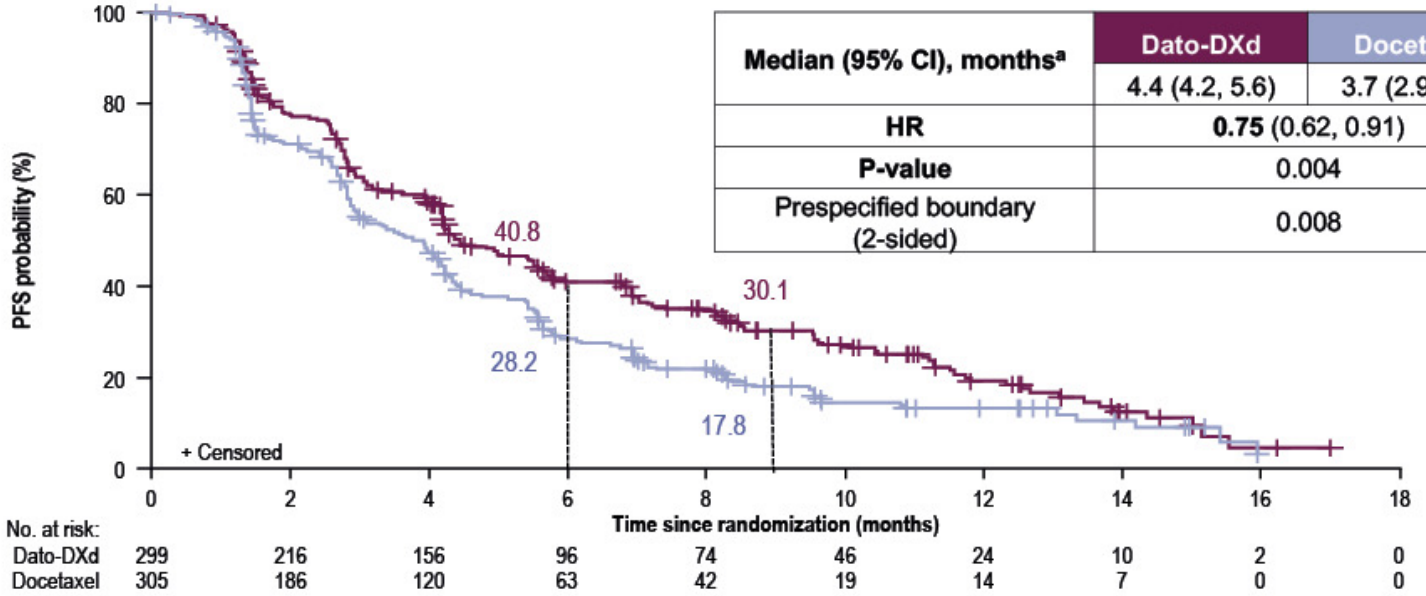
| Characteristic | | Dato-DXd N=299 | Docetaxel N=305 |
|---|---|---|---|
| **Age, median (range), years** | | 63 (26-84) | 64 (24-88) |
| **Male, n (%)** | | 183 (61) | 210 (69) |
| **Race, n (%)** | Asian | 119 (40) | 120 (39) |
| | White | 123 (41) | 126 (41) |
| | Black or African American | 6 (2) | 4 (1) |
| | Other[a] | 51 (17) | 55 (18) |
| **ECOG PS, n (%)** | 0 | 89 (30) | 94 (31) |
| | 1 | 210 (70) | 211 (69) |
| **Histology, n (%)** | Non-squamous | 234 (78) | 234 (77) |
| | Squamous | 65 (22) | 71 (23) |

| Characteristic | | Dato-DXd N=299 | Docetaxel N=305 |
|---|---|---|---|
| **Current or former smoker, n (%)** | | 238 (80) | 251 (82) |
| **Actionable genomic alterations, n (%)** | Present | 50 (17) | 51 (17) |
| | *EGFR* mutation | 39 (13) | 45 (15) |
| **Brain metastasis at baseline, n (%)[b]** | | 50 (17) | 47 (15) |
| **Prior lines of therapy, n (%)** | 1 | 167 (56) | 174 (57) |
| | 2 | 108 (36) | 102 (33) |
| | ≥3 | 22 (7) | 28 (9) |
| **Previous systemic therapy, n (%)[c]** | Platinum containing | 297 (99) | 305 (100) |
| | Anti–PD-(L)1 | 263 (88) | 268 (88) |
| | Targeted | 46 (15) | 50 (16) |

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death 1 (ligand 1).
[a]Race data missing for 8 patients in each arm. [b]Patients who are no longer symptomatic and who require no treatment with corticosteroids and anticonvulsants and have recovered from acute toxic effects of radiation are eligible.
[c]In the Dato-DXd arm, 2 patients did not receive prior treatment with a platinum-containing therapy and 1 patient with actionable genomic alterations did not receive previous targeted therapy, deviating from the protocol.

Data cutoff: 29 March 2023.

# Progression-Free Survival - ITT




| Median (95% CI), months[a] | Dato-DXd | Docetaxel |
|---|---|---|
| | 4.4 (4.2, 5.6) | 3.7 (2.9, 4.2) |
| **HR** | **0.75** (0.62, 0.91) | |
| **P-value** | 0.004 | |
| Prespecified boundary (2-sided) | 0.008 | |

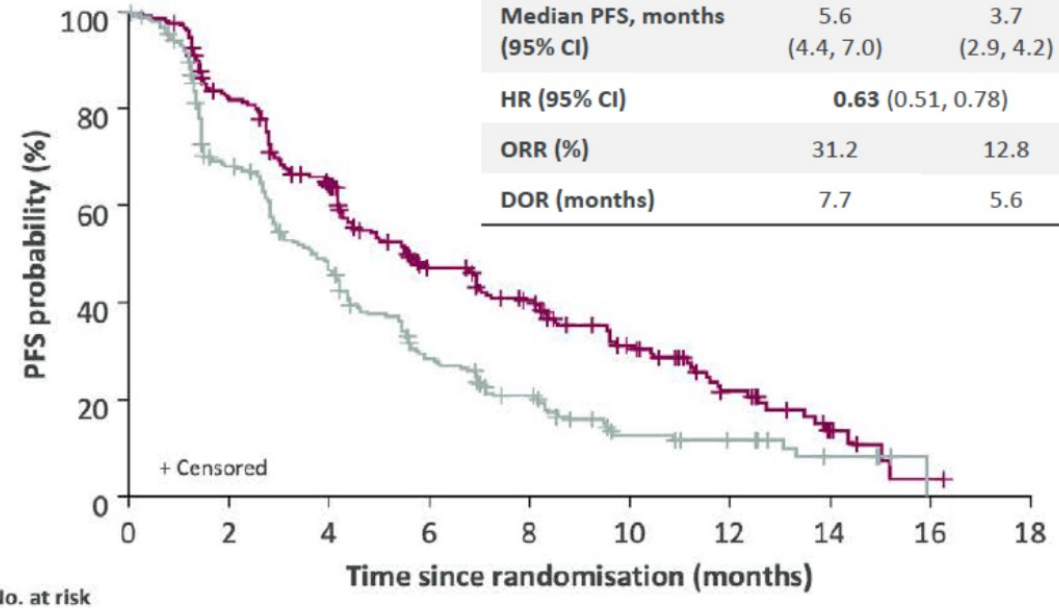
| | Dato-DXd | Docetaxel |
|---|---|---|
| **ORR**, % (95% CI)[b] | 26.4 (21.5, 31.8) | 12.8 (9.3, 17.1) |
| **DOR**, mo. (95% CI) | 7.1 (5.6, 10.9) | 5.6 (5.4, 8.1) |

CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ITT, intention-to-treat; mo., months; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

[a]Median PFS follow-up time was 10.9 months (95% CI: 9.8, 12.5) and 9.6 months (95% CI: 8.2, 11.9) for Dato-DXd and docetaxel, respectively. [b]Included four CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

## Non-squamous
(with and without AGA)

| | Dato-DXd | Docetaxel |
|---|---|---|
| Median PFS, months (95% CI) | 5.6 (4.4, 7.0) | 3.7 (2.9, 4.2) |
| HR (95% CI) | **0.63** (0.51, 0.78) | |
| ORR (%) | 31.2 | 12.8 |
| DOR (months) | 7.7 | 5.6 |



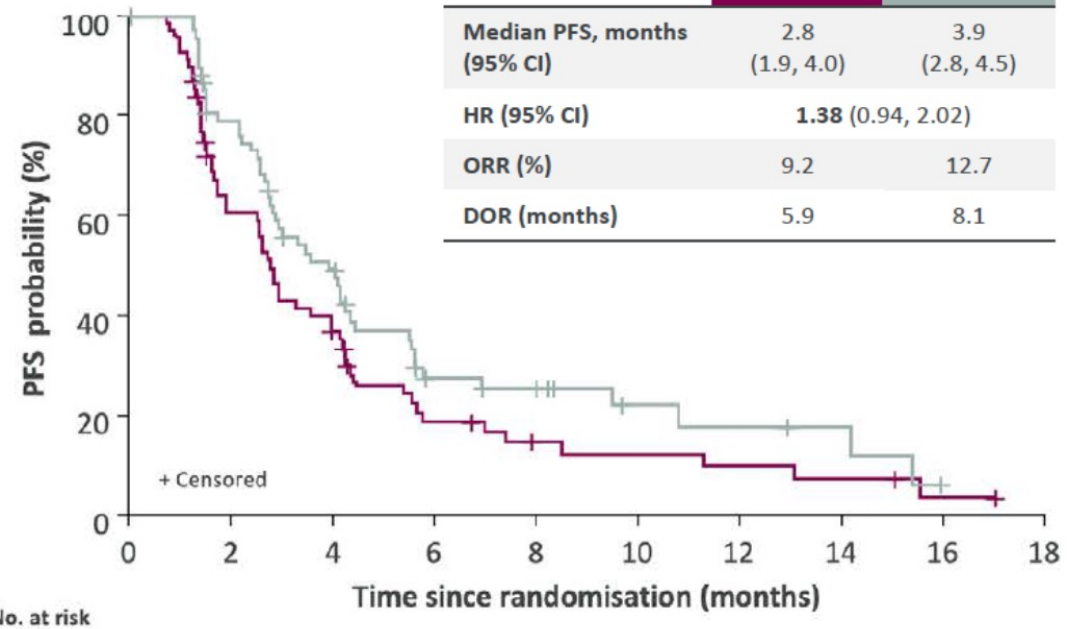

No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 229 | 178 | 134 | 86 | 68 | 41 | 20 | 7 | 1 | 0 |
| Docetaxel | 232 | 135 | 90 | 50 | 32 | 14 | 10 | 4 | 0 | 0 |

**PFS HR for non-squamous without AGA: 0.71 (0.56, 0.91)**

## Squamous
(with and without AGA)

| | Dato-DXd | Docetaxel |
|---|---|---|
| Median PFS, months (95% CI) | 2.8 (1.9, 4.0) | 3.9 (2.8, 4.5) |
| HR (95% CI) | **1.38** (0.94, 2.02) | |
| ORR (%) | 9.2 | 12.7 |
| DOR (months) | 5.9 | 8.1 |




No. at risk

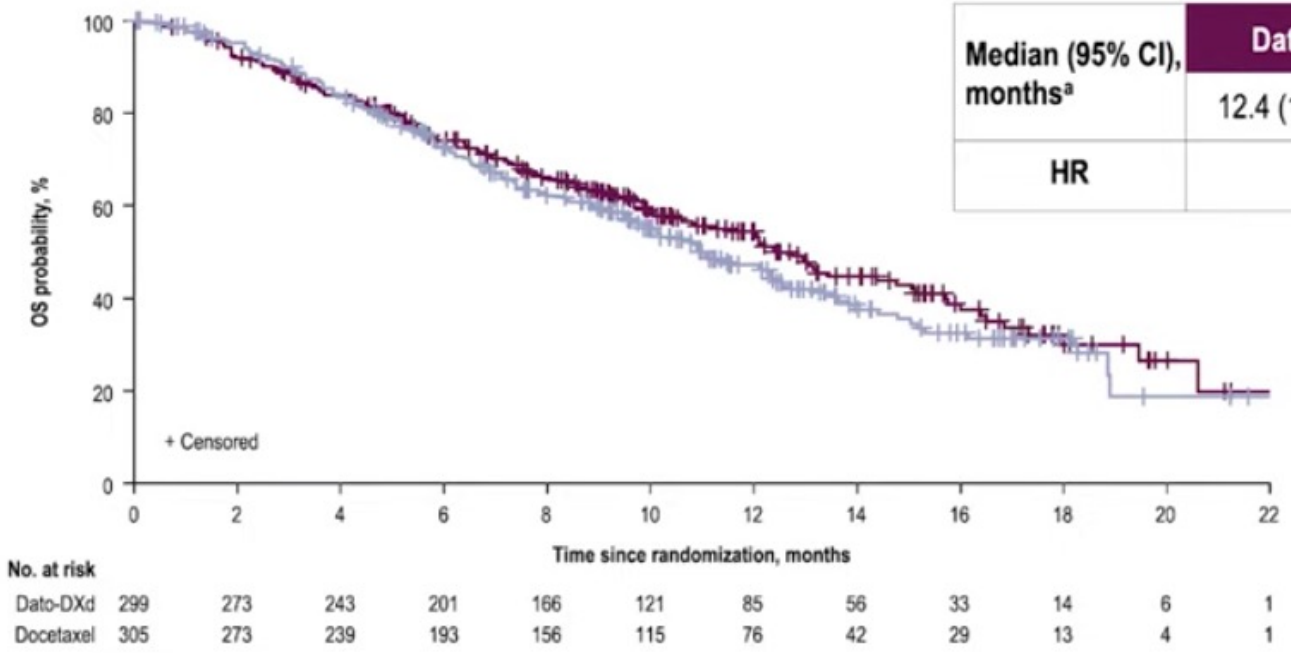
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 70 | 38 | 22 | 10 | 6 | 5 | 4 | 3 | 1 | 0 |
| Docetaxel | 73 | 51 | 30 | 13 | 10 | 5 | 4 | 3 | 0 | 0 |

MADRID 2023 ESMO congress

# The TROPION-Lung01 study

## Datopotamab deruxtecan *vs* docetaxel in previously treated advanced/metastatic non-small cell lung cancer

**Interim overall survival (ITT)**




| Median (95% CI), months[a] | Dato-DXd | Docetaxel |
|---|---|---|
| | 12.4 (10.8-14.8) | 11.0 (9.8-12.5) |
| HR | **0.90** (0.72-1.13) | |

Information fraction at interim analysis (events/total events required): **74%.**

**Non-squamous HR** (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Trial is continuing to final OS analysis

MADRID 2023 ESMO congress

# The TROPION-Lung01 study

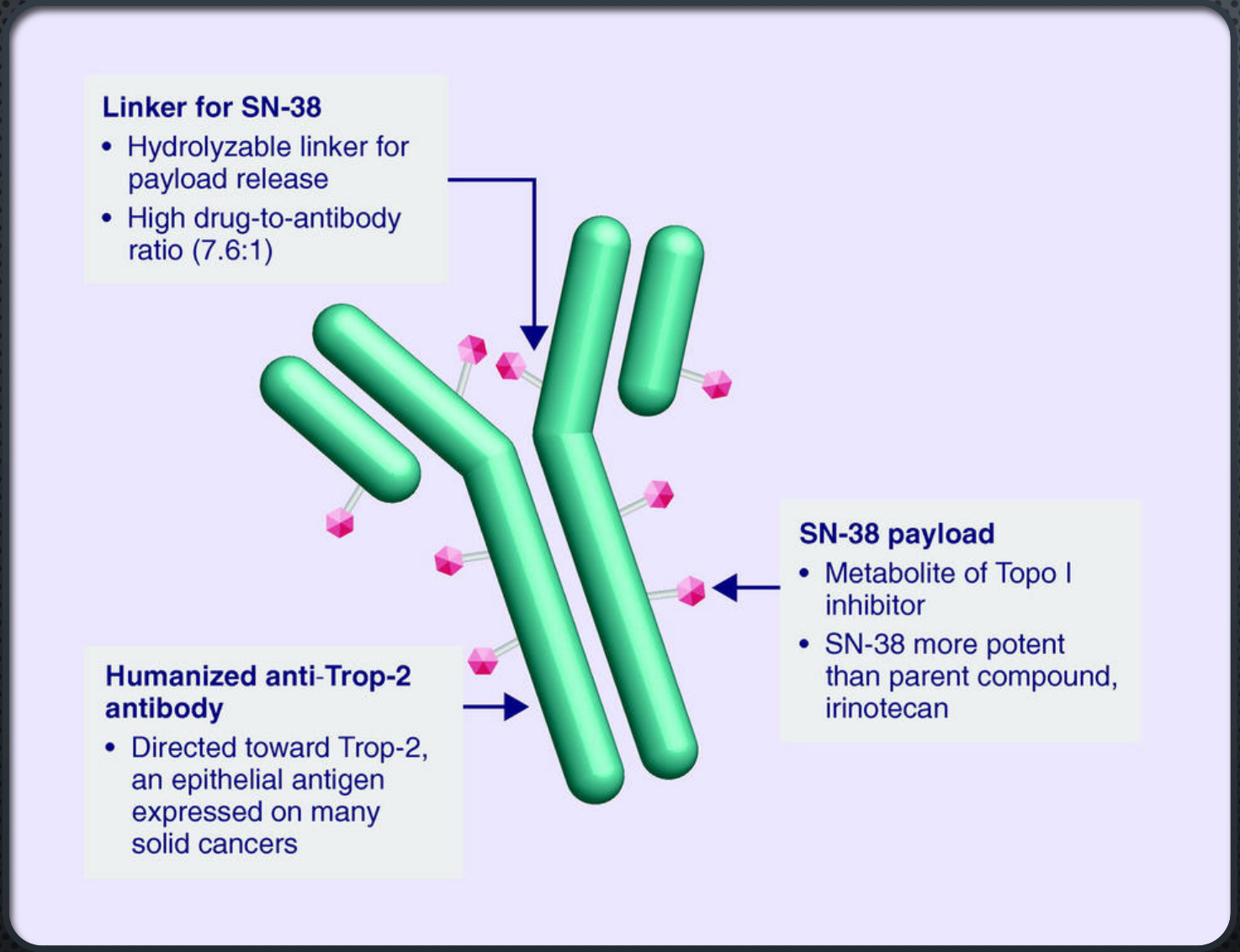
## Datopotamab deruxtecan *vs* docetaxel in previously treated advanced/metastatic non-small cell lung cancer

### Adverse events of special interest

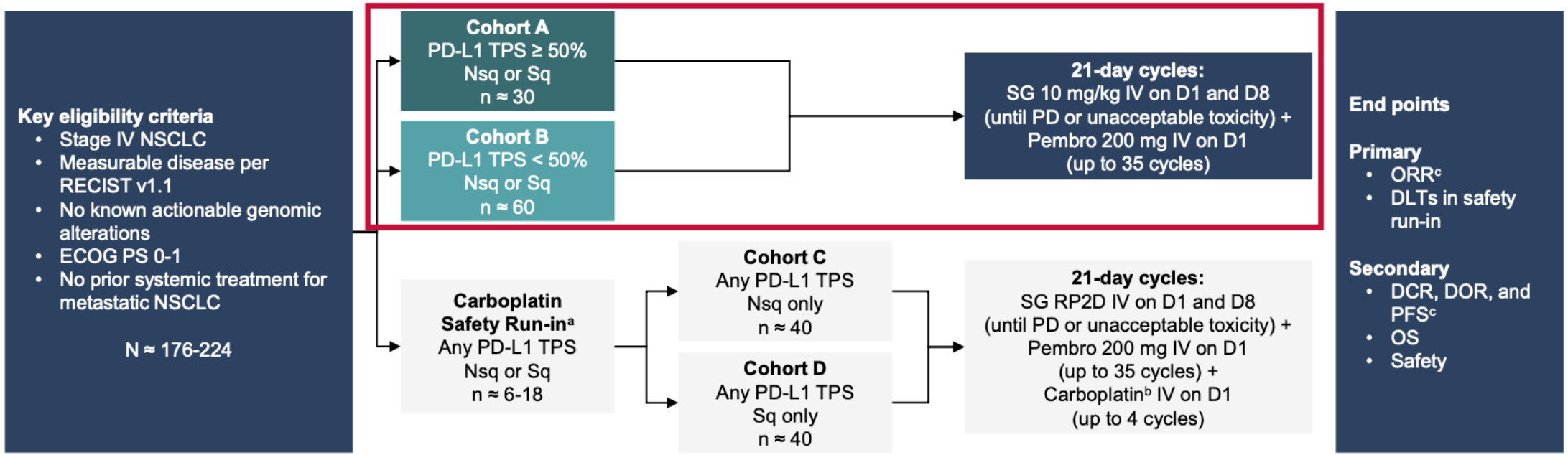
| AESI, n (%) | Dato-DXd N=297 | Docetaxel N=290 |
|---|---|---|
| **Stomatitis/oral mucositis[a]** | | |
| All grades | 160 (54) | 59 (20) |
| Grade ≥3 | 19 (6) | 4 (1) |
| **Ocular events[b]** | | |
| All grades | 57 (19) | 27 (9) |
| Grade ≥3 | 5 (2)[c] | 0 |
| **Adjudicated drug-related ILD[d]** | | |
| All grades | 25 (8) | 12 (4) |

- Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)
- Dato-DXd ocular events were primarily grade ≤2 dry eye (6.1%) and increased lacrimation (5.4%)
- Seven adjudicated drug-related grade 5 ILD events
  - Primary cause of death in 4 out of 7 was attributed to disease progression by investigator
  - Non-squamous: 4 of 232 patients (1.7%); Squamous: 3 of 65 patients (4.6%)[e]
- IRRs were observed in 24 patients (8%) with either

# SACITUZUMAB GOVITECAN



# EVOKE-02: An Open-Label, Multicohort Phase 2 Study

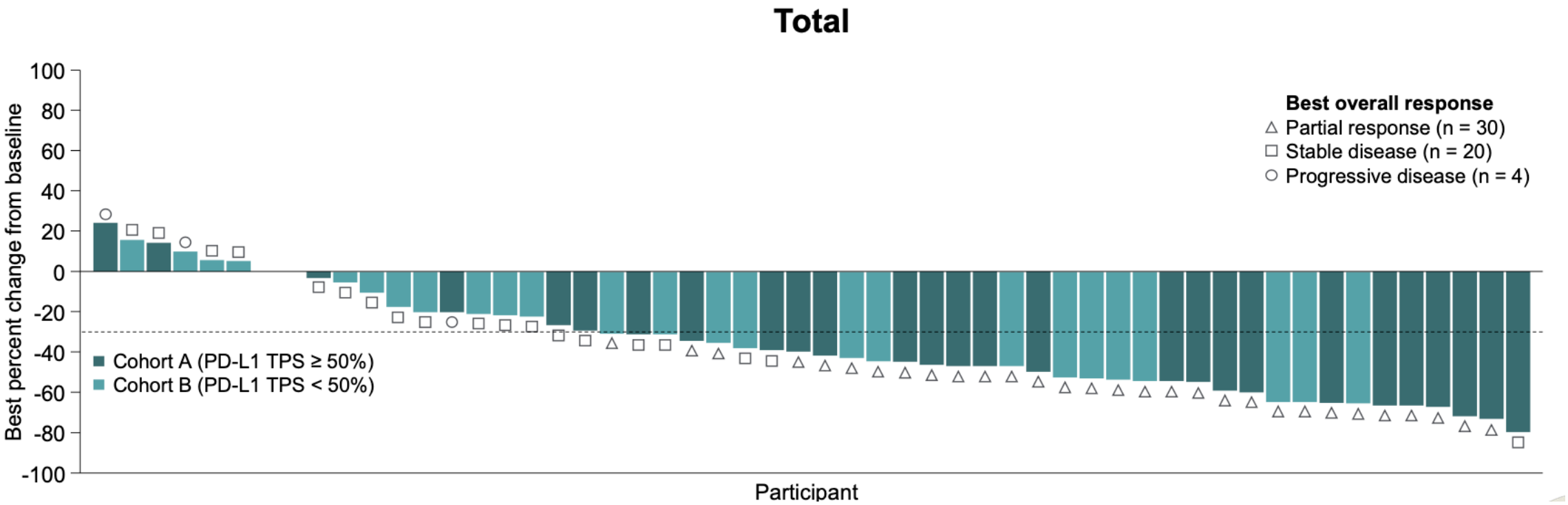


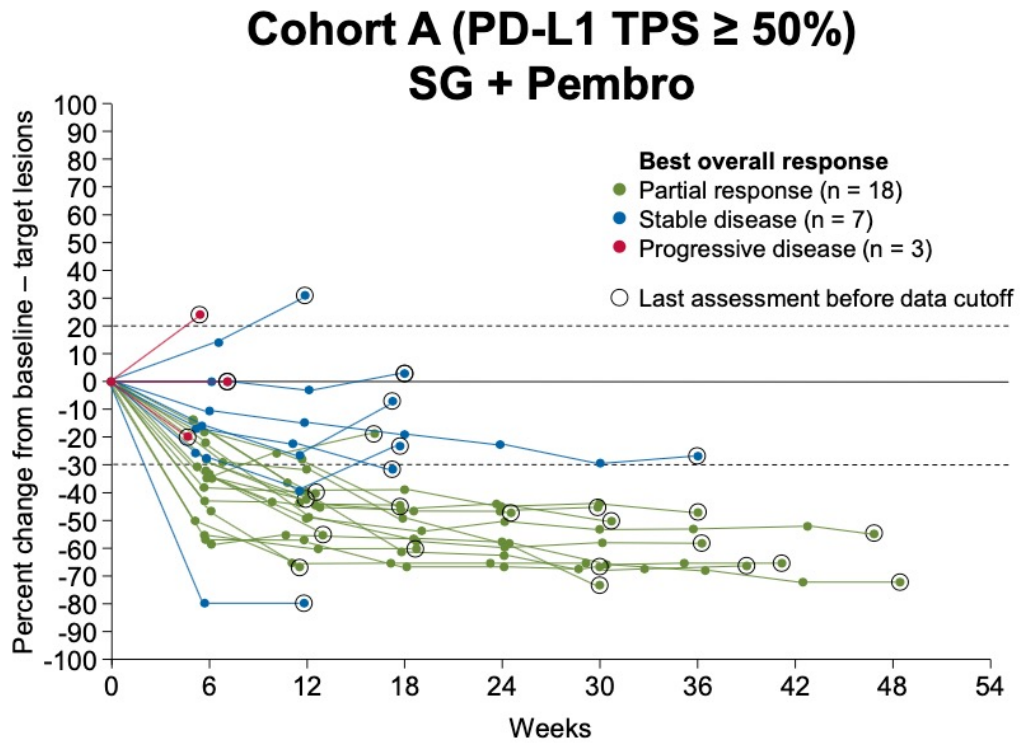

- At data cutoff (16 June 2023), median (range) follow-up for Cohorts A and B was 5.0 (1.7-12.0) and 5.8 (1.0-12.2) months, respectively
  - The preliminary efficacy data reported in this presentation are results by investigator assessment

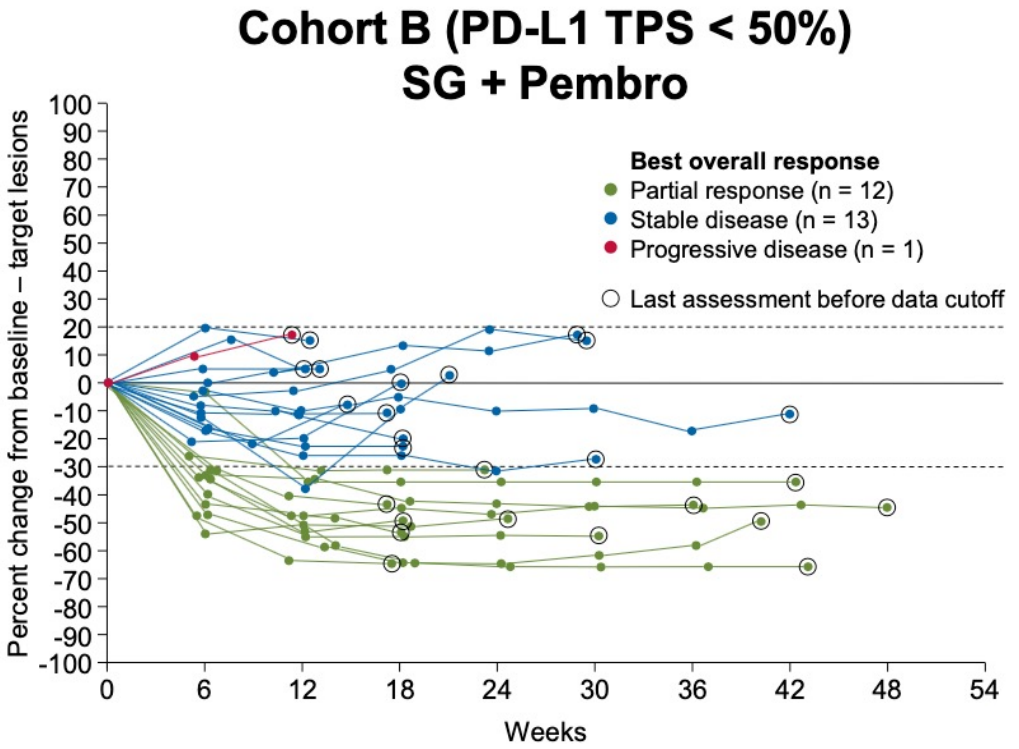
| Characteristic | Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 30 | Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 33 |
|---|---|---|
| **Median age (range), years** | 67 (47-77) | 68 (47-80) |
| **Male, %** | 80 | 79 |
| **Race, %** | | |
| Asian | 20 | 15 |
| Black | 7 | 3 |
| White | 73 | 82 |
| **ECOG PS 1, %** | 80 | 76 |
| **Histology, %** | | |
| Nonsquamous | 60 | 61 |
| Squamous | 40 | 39 |
| **Stage IV disease at diagnosis,[a] %** | 80 | 85 |
| **PD-L1 TPS,[b] %** | | |
| ≥ 50% | 100 | 0 |
| 1-49% | 0 | 48 |
| < 1% | 0 | 52 |

| Patient exposure and disposition | Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 30 | Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 33 |
|---|---|---|
| **Median duration of treatment (range), months** | | |
| SG | 4.1 (0-11.2+) | 4.1 (0-11.9+) |
| Pembro | 3.6 (0-11.2+) | 3.8 (0-11.7+) |
| **Median number of cycles received (range), cycles** | | |
| SG | 6 (1-17+) | 6 (1-17+) |
| Pembro | 6 (1-17+) | 6 (1-17+) |
| **Continuing treatment with SG, %** | 63 | 39 |
| **Continuing treatment with Pembro, %** | 63 | 42 |
| **Discontinued all study treatment, %** | 37 | 58 |

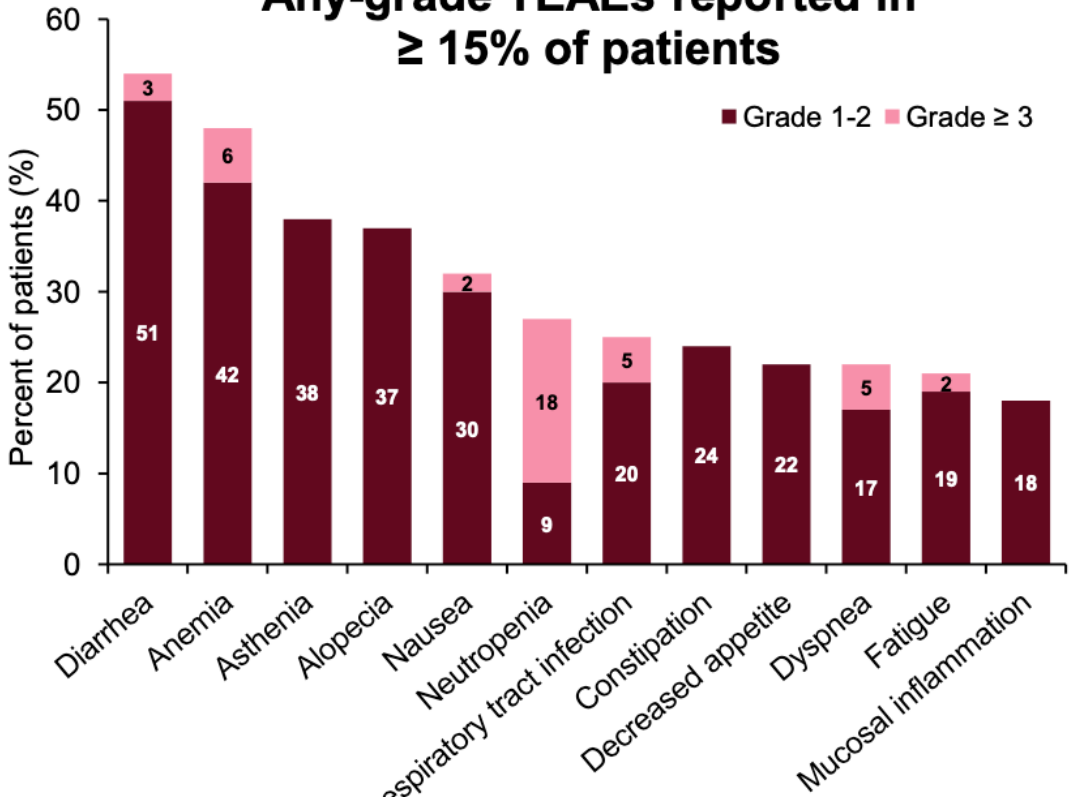
# Waterfall Plot for Change in Target Lesions



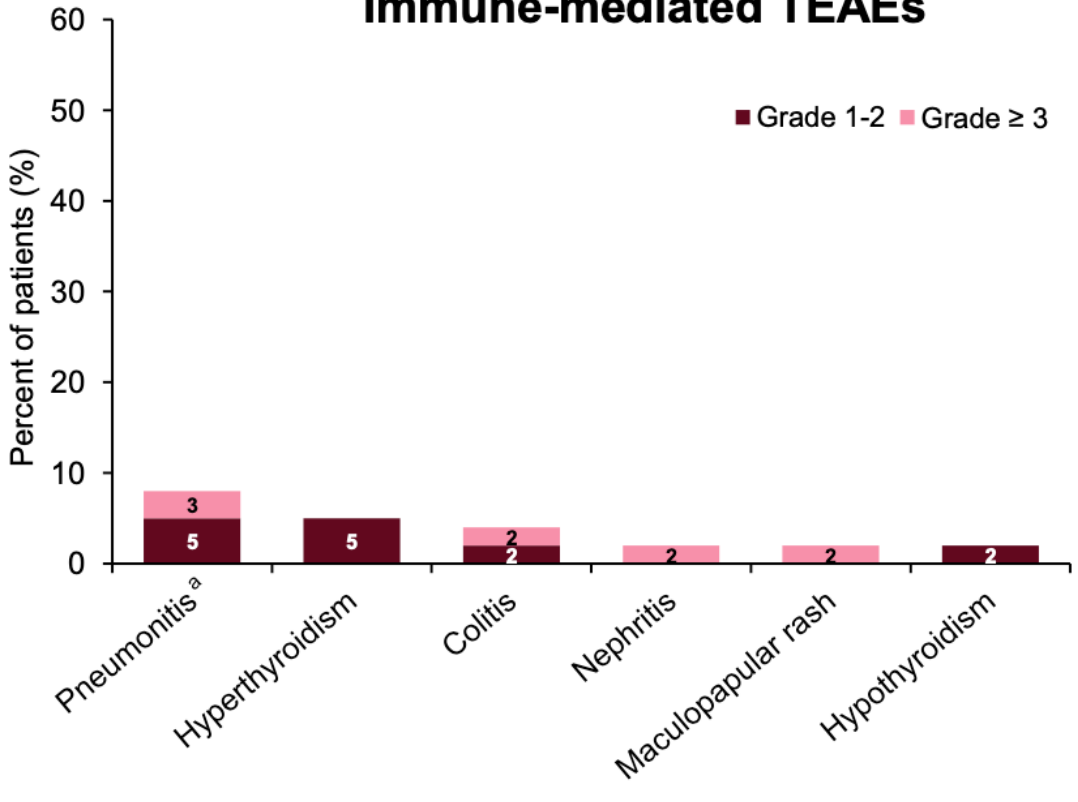

Cohort A (PD-L1 TPS ≥ 50%)
SG + Pembro
Best overall response
Partial response (n = 18)
Stable disease (n = 7)
Progressive disease (n = 3)
Last assessment before data cutoff
Percent change from baseline – target lesions
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
6
12
18
24
30
36
42
48
54
Weeks

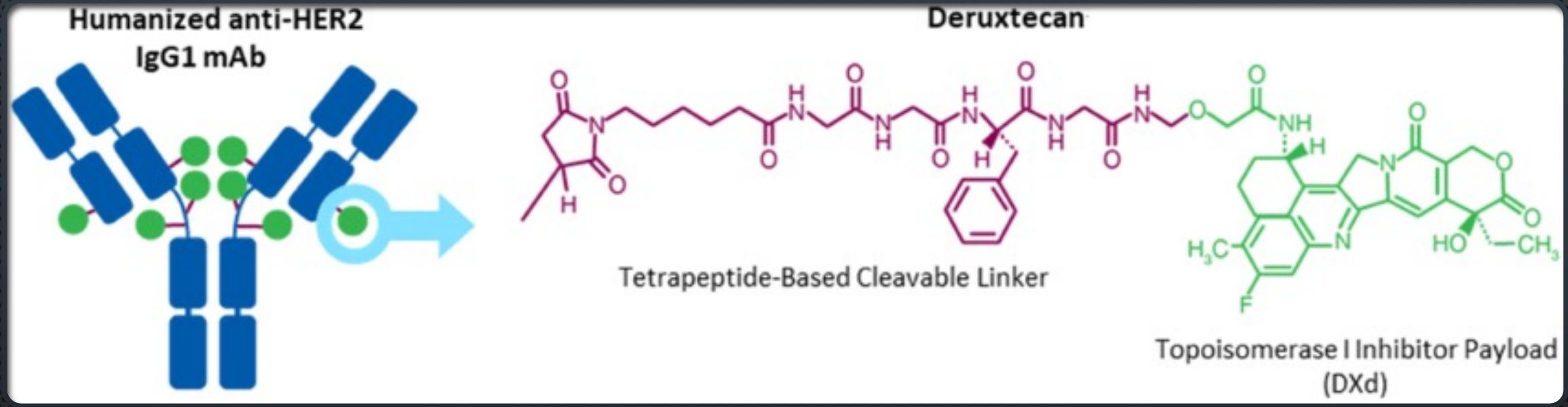

Cohort B (PD-L1 TPS < 50%)
SG + Pembro
Best overall response
Partial response (n = 12)
Stable disease (n = 13)
Progressive disease (n = 1)
Last assessment before data cutoff
Percent change from baseline – target lesions
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
6
12
18
24
30
36
42
48
54
Weeks

## Any-grade TEAEs reported in ≥ 15% of patients



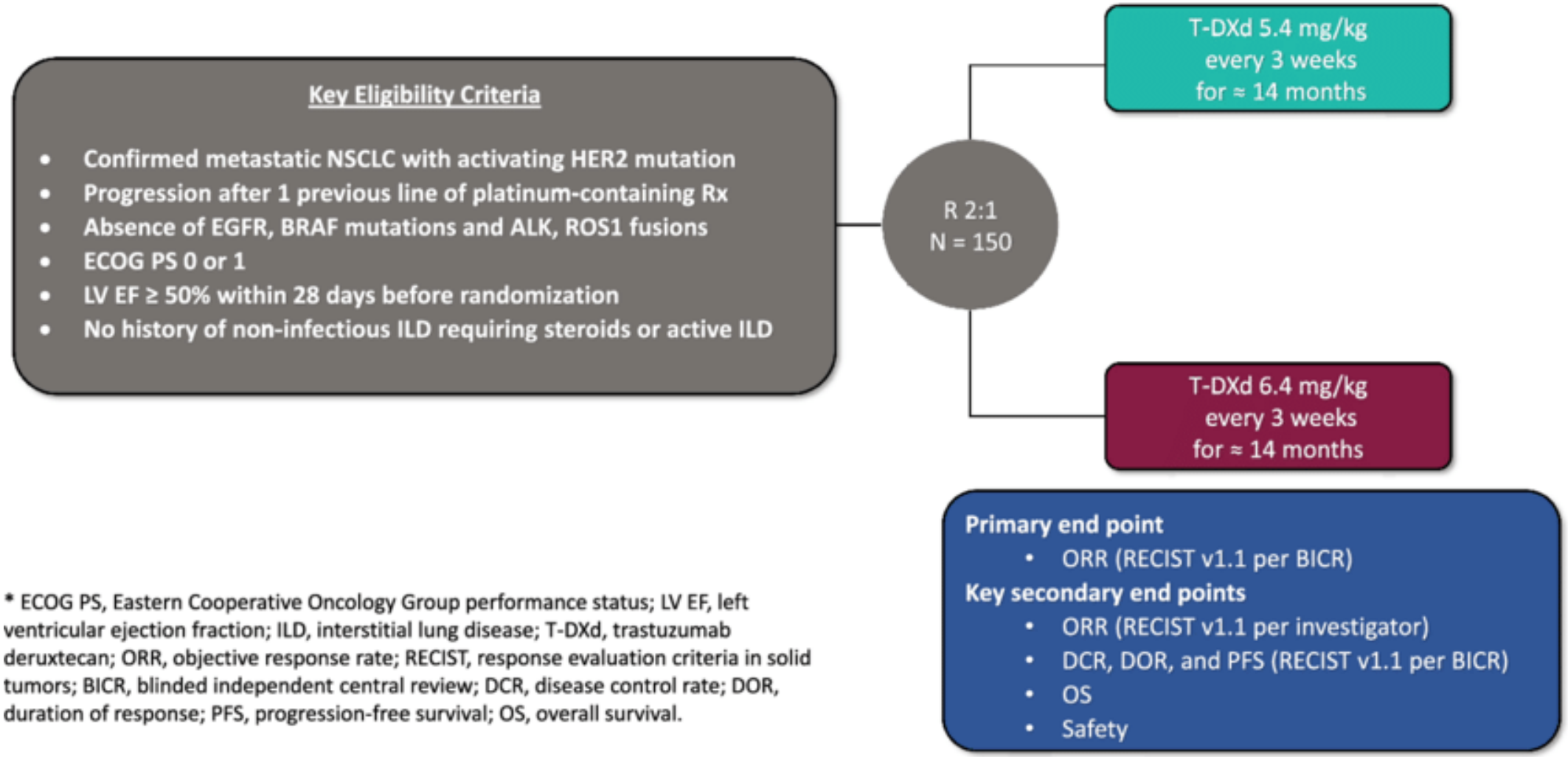

## Immune-mediated TEAEs





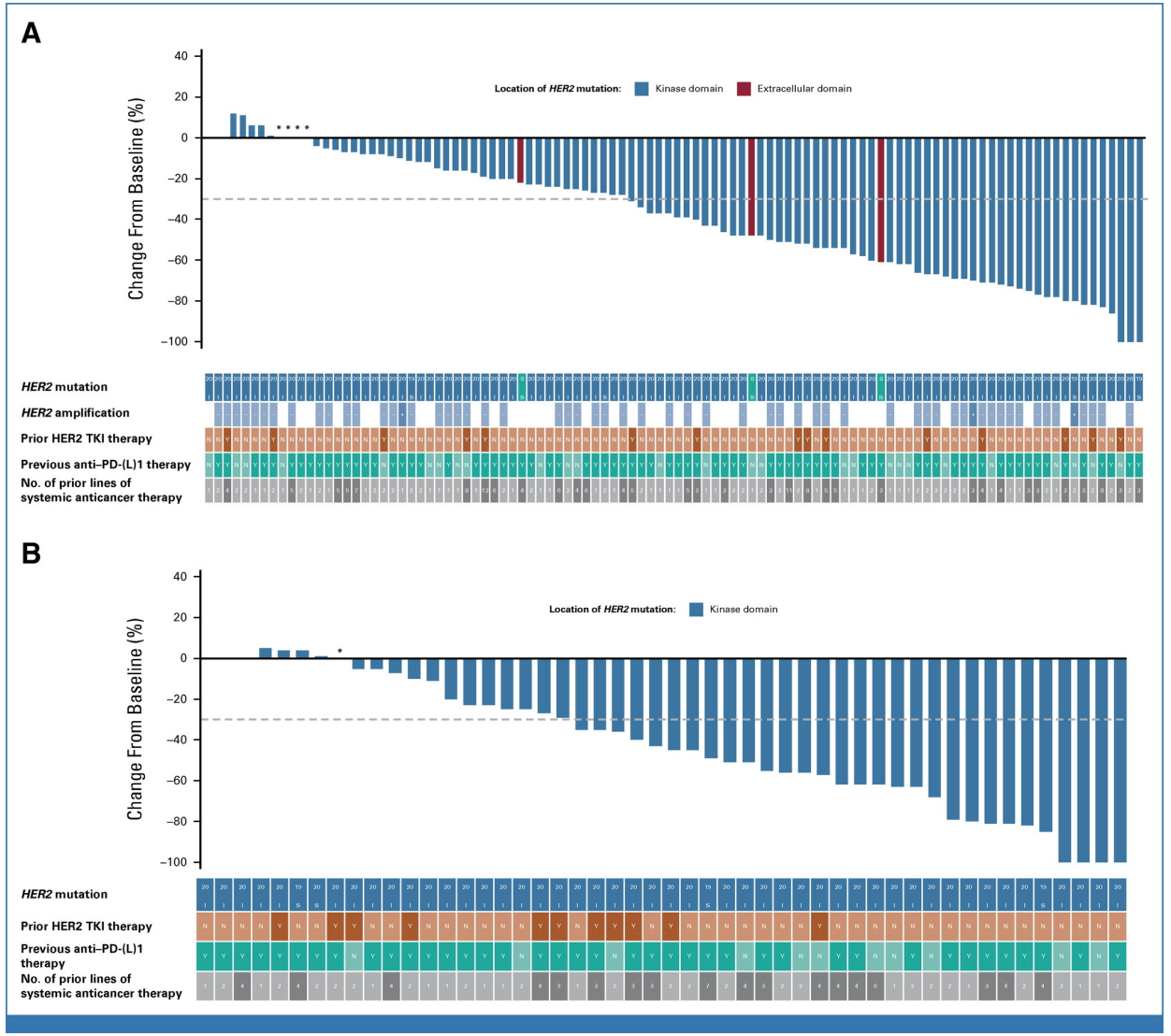

# TRASTUZUMAB DERUXTECAN

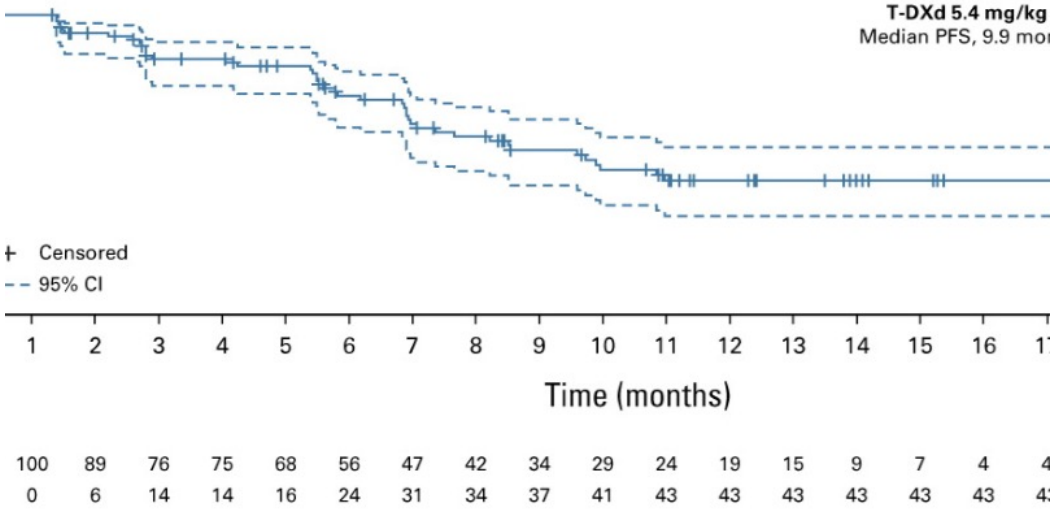
# DESTINY-Lung02

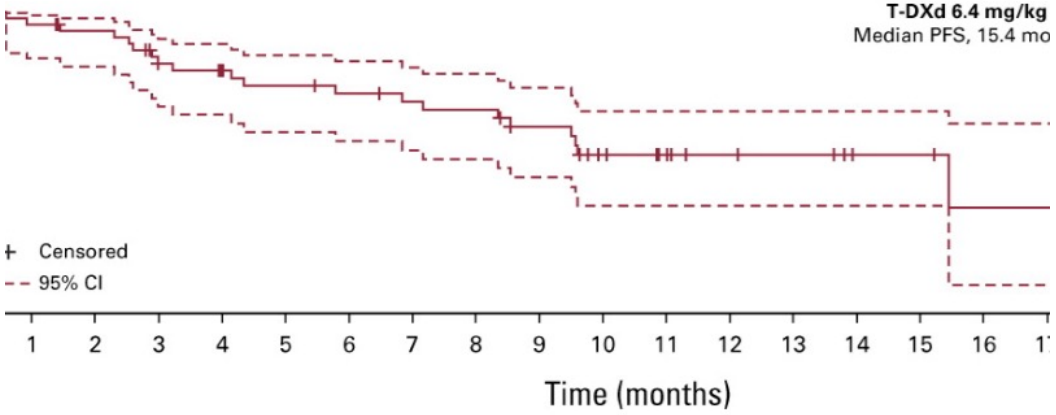


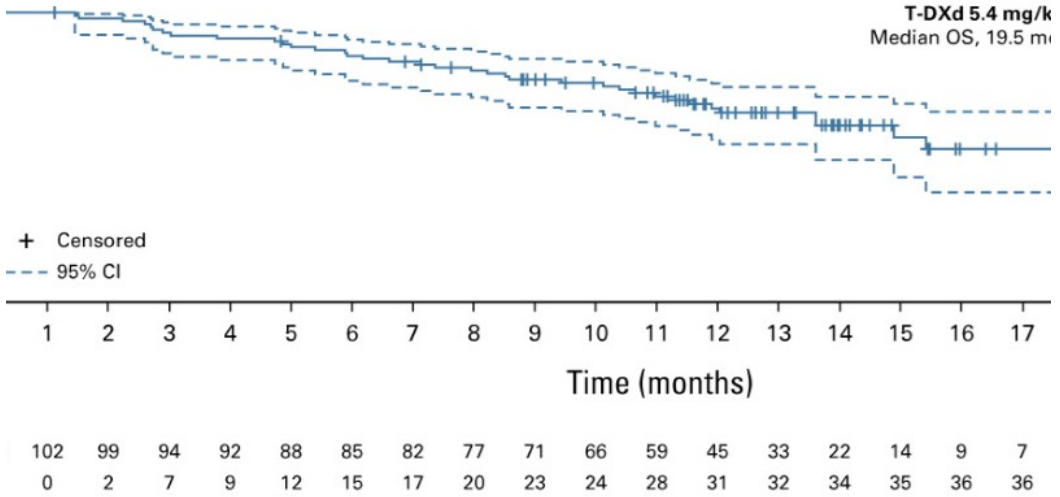

* ECOG PS, Eastern Cooperative Oncology Group performance status; LV EF, left ventricular ejection fraction; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival.

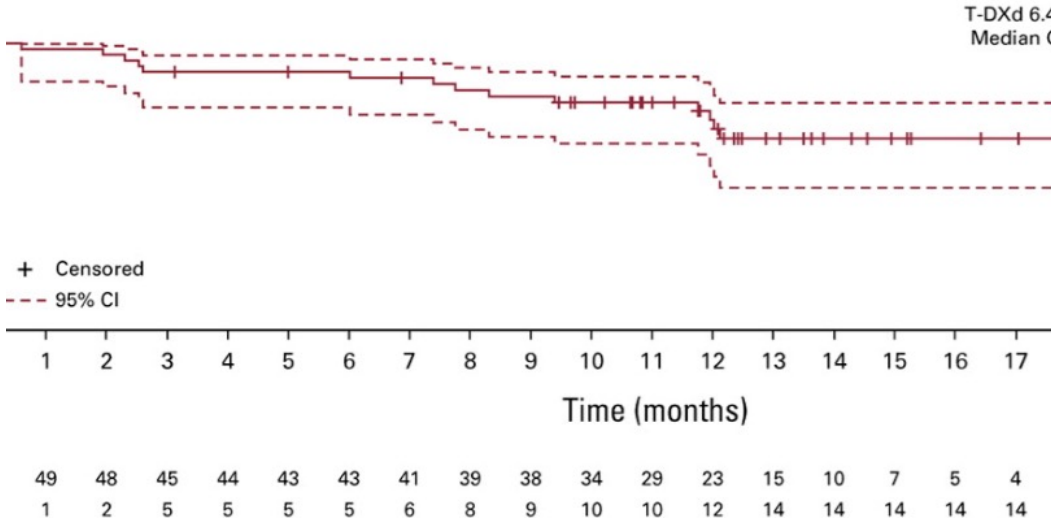
https://ascopubs.org/doi/figure/10.1200/JCO.23.01361




T-DXd 5.4 mg/kg
Median PFS, 9.9 mo
Censored
95% CI
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (months)
100 89 76 75 68 56 47 42 34 29 24 19 15 9 7 4
0 6 14 14 16 24 31 34 37 41 43 43 43 43 43 43


T-DXd 6.4 mg/kg
Median PFS, 15.4 mo
Censored
95% CI
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (months)


T-DXd 5.4 mg/k
Median OS, 19.5 m
Censored
95% CI
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time (months)
102 99 94 92 88 85 82 77 71 66 59 45 33 22 14 9 7
0 2 7 9 12 15 17 20 23 24 28 31 32 34 35 36 36


T-DXd 6.4
Median
Censored
95% CI
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time (months)
49 48 45 44 43 43 41 39 38 34 29 23 15 10 7 5 4
1 2 5 5 5 5 6 8 9 10 10 12 14 14 14 14 14

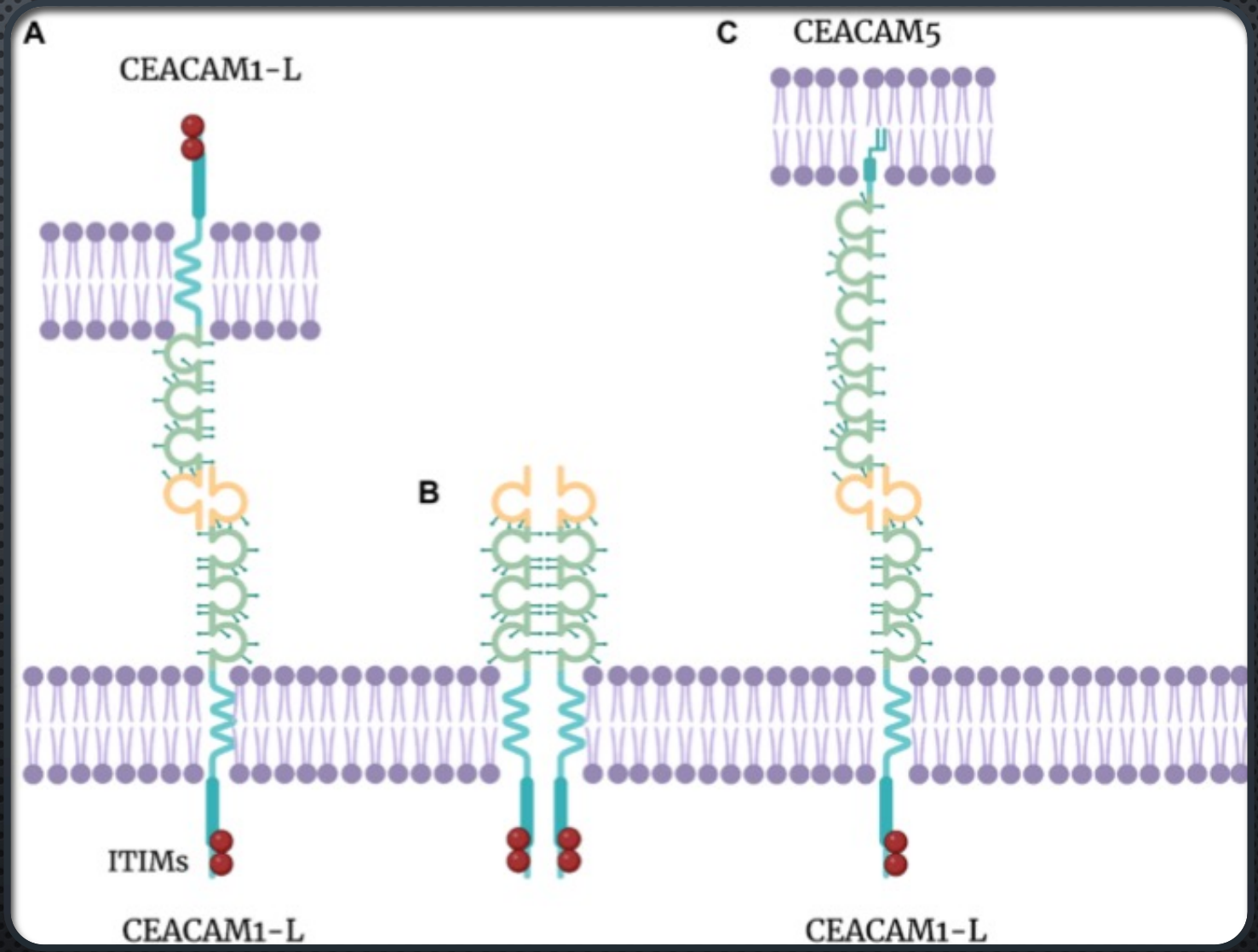
| Adjudicated Drug-Related ILD in Patients With Prior Anti–PD-(L)1 Therapy | T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 74), No. (%) | T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 39), No. (%) |
|---|---|---|
| Grade 1 | 4 (5.4) | 2 (5.1) |
| Grade 2 | 5 (6.8) | 9 (23.1) |
| Grade 3 | 1 (1.4) | 0 |
| Grade 4 | 0 | 0 |
| Grade 5 | 1 (1.4) | 0 |
| Total | 11 (14.9) | 11 (28.2) |

| Adjudicated Drug-Related ILD in Patients Without Prior Anti–PD-(L)1 Therapy | T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 27), No. (%) | T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 11), No. (%) |
|---|---|---|
| Grade 1 | 0 | 2 (18.2) |
| Grade 2 | 2 (7.4) | 0 |
| Grade 3 | 0 | 0 |
| Grade 4 | 0 | 0 |
| Grade 5 | 0 | 1 (9.1) |
| Total | 2 (7.4) | 3 (27.3) |

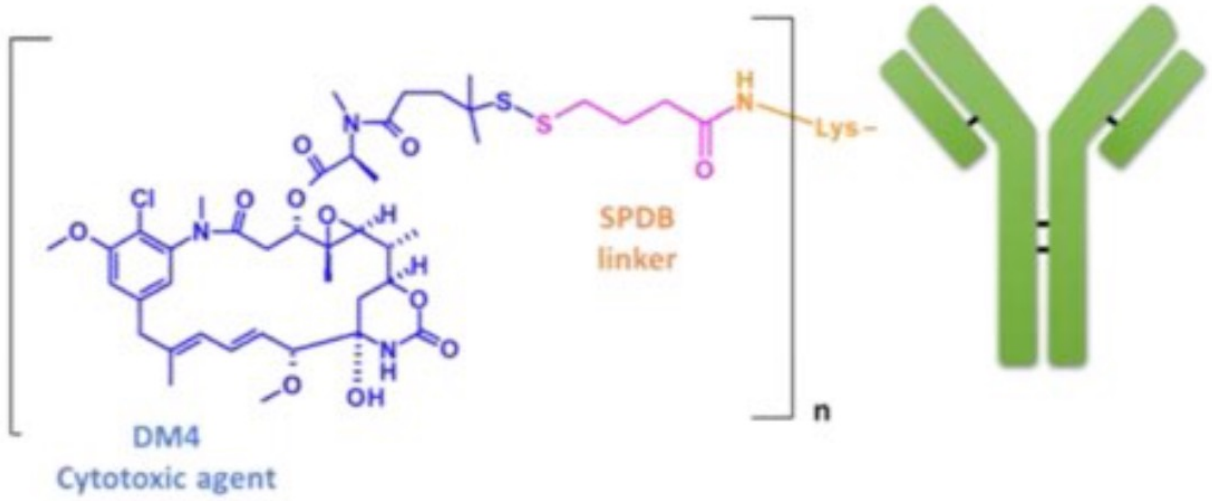
Abbreviations: AE, adverse event; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.
[b]TEAEs associated with death were malignant lung neoplasm in two patients, malignant neoplasm progression in two patients, cerebrovascular incident in one patient, and pneumonitis in one patient.
[c]TEAEs associated with death were abnormal general physical condition in one patient and ILD in one patient.

# CEACAM5

- GLYCOSYLPHOSPHATIDYLINOSITOL (GPI) LINKER PROVIDES MEMBRANE ANCHORING
- HAS ROLES IN REGULATING DIFFERENTIATION, IMMUNE MODULATION, AND INHIBITING ANOIKIS



# Structure of SAR408701




**Humanized antibody:** Specific for **CEACAM5**

**Cytotoxic agent:** Maytansinoid **DM4** (inhibits tubulin polymerization)

**SPDB linker:** Cleavable inside cells

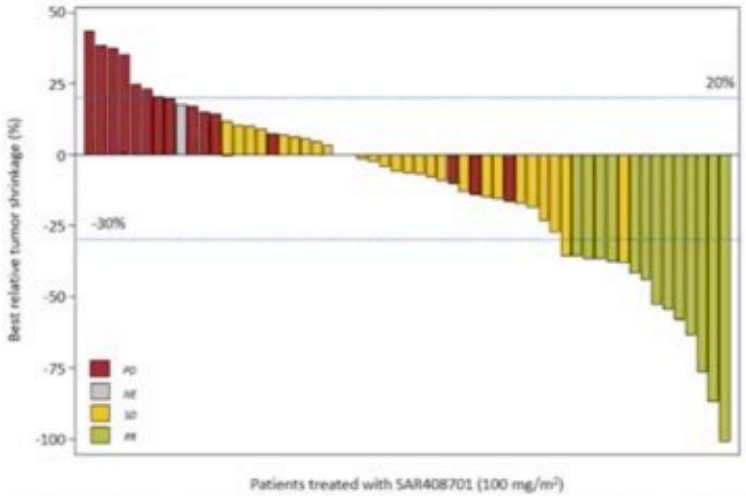
# Best Overall Response

## Overall Population

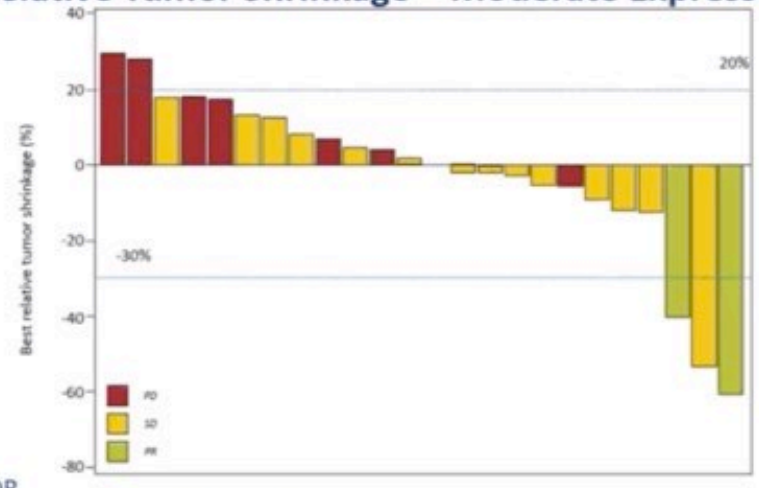
| Response, n (%) | High expressors (n = 64) | Moderate expressors (n = 28) |
|---|---|---|
| ORR [95% CI] | 13 (20.3%) [12.27-31.71] | 2 (7.1%) [1.98-22.65] |
| Confirmed PR | 13 (20.3%) | 2 (7.1%) |
| SD | 28 (43.8%) | 15 (53.6%) |
| DCR | 41 (64.1%) | 17 (60.7%) |
| PD | 21 (32.8%) | 10 (35.7%) |
| NE | 2 (3.1%) | 1 (3.6%) |

**Best relative tumor shrinkage:** Patients who had unconfirmed PR (≥30% decrease) were counted as SD for BOR

### Best Relative Tumor Shrinkage – High Expressor Cohort

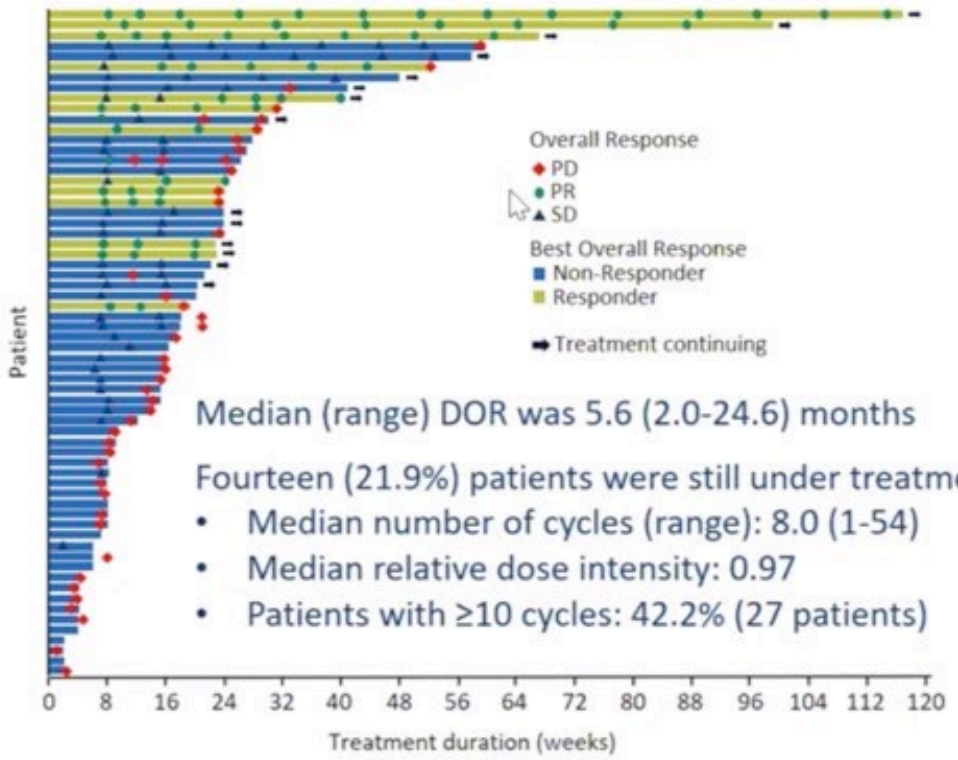



### Best Relative Tumor Shrinkage – Moderate Expressor Cohort



# Dose Intensity and Duration of Treatment

## High expressors

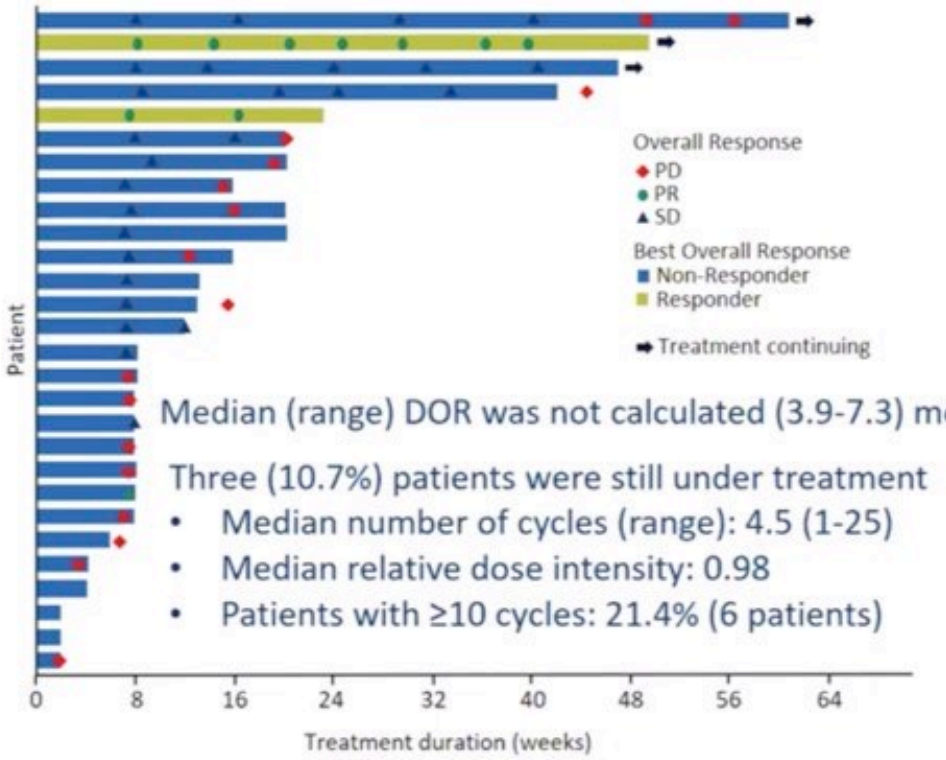



Median (range) DOR was 5.6 (2.0-24.6) months

Fourteen (21.9%) patients were still under treatment

- Median number of cycles (range): 8.0 (1-54)
- Median relative dose intensity: 0.97
- Patients with ≥10 cycles: 42.2% (27 patients)

## Moderate expressors




Median (range) DOR was not calculated (3.9-7.3) months

Three (10.7%) patients were still under treatment

- Median number of cycles (range): 4.5 (1-25)
- Median relative dose intensity: 0.98
- Patients with ≥10 cycles: 21.4% (6 patients)

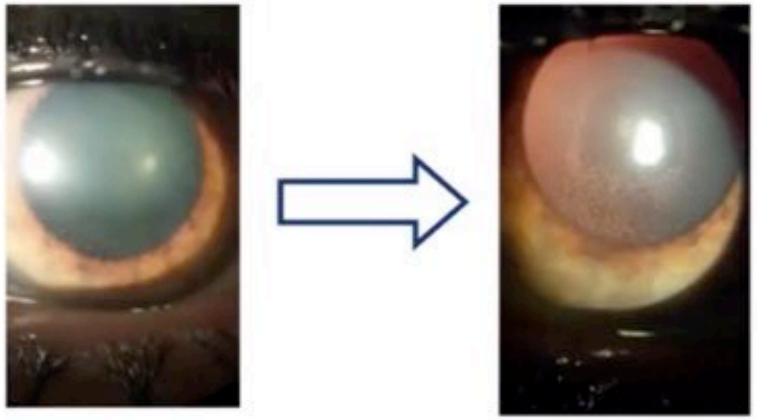
# Dose Modification and Ocular Events – Pooled Data of NSCLC Cohorts

| Ocular Events | SAR408701 100 mg/m² Q2W (n=92) | |
|---|---|---|
| | Grades 1-2, n (%) | Grade 3, n (%) |
| **Corneal AE** | 25 (27.2%) | 10 (10.9%) |
| **Dose modification** | | |
| Keratitis | 12 (13.0%) | 7 (7.6%) |
| Keratopathy | 8 (8.7%) | 1 (1.1%) |

A total of 25 patients (27.2%) had corneal TEAEs leading to dose modification

- All 25 patients had at least one dose delay
- Ten patients had at least one dose reduction (10.9%)
- One patient permanently discontinued treatment (1.1%)

DM4-induced microcystic corneal dystrophy



Images courtesy of Dr. Hierro and Dr. Tabernero.

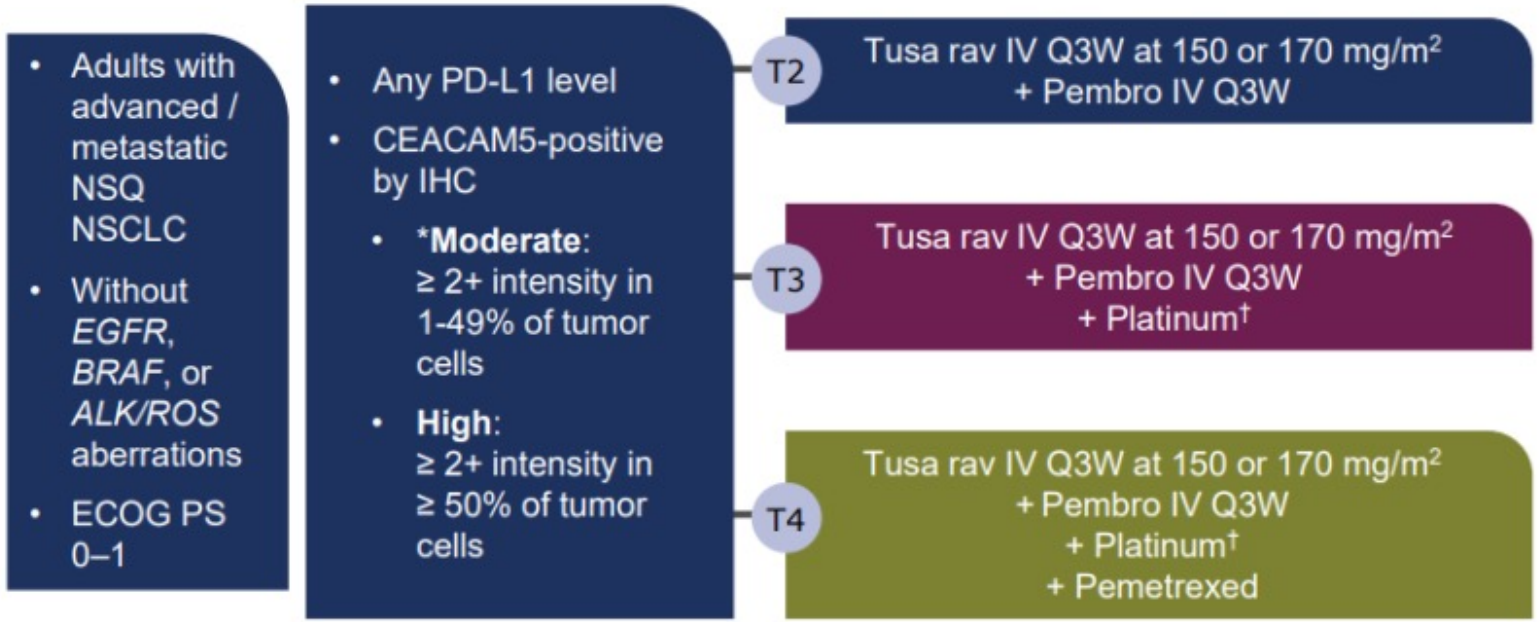
**Ocular Events:**

- Specific ADC-DM4 related events are reversible non-inflammatory deposits starting at the periphery of cornea
- First occurrence within the first 4 cycles of treatment for 28 patients (80%)
- Manageable with dose delay and/or dose reduction
- Median time to recovery was 18.5 (2-82) days
- Primary prophylaxis* is not effective; treatment of an event with topical ophthalmologic corticosteroid when it occurs is recommended

***Primary prophylaxis**: Unilaterally administered vasosonstrictive drops before SAR408701

# STUDY DESIGN

## CARMEN-LC05 (NCT04524689): Phase 2, open-label study assessing efficacy and safety of tusa rav in combination with pembro ± platinum† with or without pemetrexed




**Primary Endpoint:**
- DLT

**Secondary Endpoints:**
- TEAEs, SAEs, ORR

*Until a recent protocol amendment, enrollment of CEACAM5 moderate expressors was restricted to T4. †Cisplatin or carboplatin.
CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DLT, dose-limiting toxicity; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; Q3W, every 3 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; tusa rav, tusamitamab ravtansine.

# PATIENT DEMOGRAPHIC AND DISEASE CHARACTERISTICS

| Regimen | T2 | | T3 | | T4 | | All (n = 25) |
|---|---|---|---|---|---|---|---|
| Tusa rav dose ($mg/m^2$) | 150 (n = 3) | 170 (n = 2) | 150 (n = 4) | 170 (n = 1) | 150 (n = 12) | 170 (n = 3) | |
| **Age**, median (range), y | 63.0 (48-81) | 68.5 (68-69) | 66.5 (55-83) | 67.0 | 64.5 (38-74) | 51.0 (42-74) | 65.0 (38-83) |
| **Female**, n (%) | 3 (100) | 1 (50) | 1 (25) | 0 | 6 (50) | 1 (33.3) | 12 (48) |
| **ECOG PS**, n (%) | | | | | | | |
| 0 | 3 (100) | 1 (50) | 1 (25) | 1 (100) | 5 (41.7) | 3 (100) | 14 (56) |
| 1 | 0 | 1 (50) | 3 (75) | 0 | 7 (58.3) | 0 | 11 (44) |
| **CEACAM5 expression**, n (%) | | | | | | | |
| *Moderate (1-49%) | 0 | 0 | 0 | 0 | 6 (50) | 3 (100) | 9 (36) |
| High (≥50%) | 3 (100) | 2 (100) | 4 (100) | 1 (100) | 6 (50) | 0 | 16 (64) |
| **PD-L1 expression**, n (%) | | | | | | | |
| <1% | 0 | 0 | 0 | 0 | 2 (16.7) | 1 (33.3) | 3 (12) |
| 1-49% | 2 (66.7) | 0 | 4 (100) | 0 | 9 (75) | 1 (33.3) | 16 (64) |
| ≥50% | 1 (33.3) | 2 (100) | 0 | 1 (100) | 1 (8.3) | 1 (33.3) | 6 (24) |

*Until a recent protocol amendment, enrollment of CEACAM5 moderate expressors was restricted to T4. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; tusa rav, tusamitamab ravtansine.

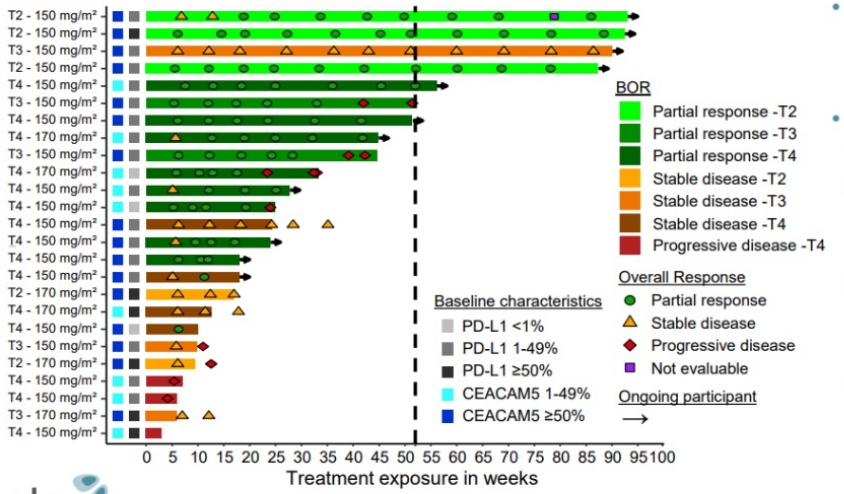
# SUMMARY OF BEST OVERALL RESPONSE

As 1L therapy, at the time of data cutoff, **confirmed ORR was 52%** (95% CI: 31.3–72.2), and **DCR was 88%** (95% CI: 68.8–97.5) across all treatment regimens and dose levels

| Regimen | T2 | | T3 | | T4 | | |
|---|---|---|---|---|---|---|---|
| Tusa rav dose (mg/m$^2$) | 150 (n = 3) | 170 (n = 2) | 150 (n = 4) | 170 (n = 1) | 150 (n = 12) | 170 (n = 3) | All (n = 25) |
| **Best Overall Response,* n (%)** | | | | | | | |
| PR (confirmed) | 3 (100) | 0 | 2 (50) | 0 | 6 (50) | 2 (66.7) | 13 (52) |
| SD[a] | 0 | 2 (100) | 2 (50) | 1 (100) | 3 (25) | 1 (33.3) | 9 (36) |
| PD | 0 | 0 | 0 | 0 | 3 (25) | 0 | 3 (12) |
| **ORR[b], n (%)** | **3 (100)** | **0** | **2 (50)** | **0** | **6 (50)** | **2 (66.7)** | **13 (52)** |
| **DCR[c], n (%)** | **3 (100)** | **2 (100)** | **4 (100)** | **1 (100)** | **9 (75)** | **3 (100)** | **22 (88)** |
| **Median treatment duration**, weeks | 92.4 | 13.2 | 48.2 | 6 | 21 | 33.3 | 24.3 |

* No complete responses occurred.
[a] Including participants with unconfirmed CR or PR.
[b] Confirmation of response (CR/PR) is required: the subsequent tumor assessment was done ≥28 days after the initial assessment. A response can be confirmed if there is a single non-evaluable tumor assessment performed in-between the two tumor assessments showing a response.
[c] Confirmed CR or PR, or SD.
1L, first-line; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; tusa rav, tusamitamab ravtansine.

## PATIENT-LEVEL TREATMENT EXPOSURE

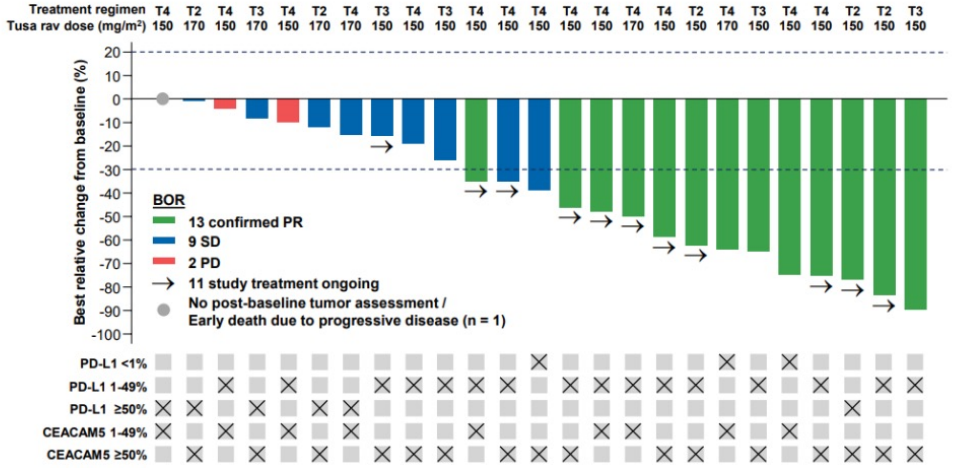



- Treatment duration is driven by the recruitment start time of each cohort
- As of January 10, 2023 data cut-off:
  - 25 patients were treated for a median of 24 weeks (range 3–93)
  - 7 patients had treatment durations of 12 months or longer
  - Study treatment was ongoing in 11 (44%) patients




BOR, best overall response; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; PD-L1, programmed cell death ligand 1.

## PATIENT-LEVEL ANTITUMOR ACTIVITY






BOR, best overall response; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease.



# EXPOSURE AND RESPONSE

# SAFETY

| Regimen | T2 | | T3 | | T4 | | |
|---|---|---|---|---|---|---|---|
| Tusa rav dose ($mg/m^2$) | 150 (n = 3) | 170 (n = 2) | 150 (n = 4) | 170 (n = 1) | 150 (n = 12) | 170 (n = 3) | All (n = 25) |
| Any TEAE, n (%) | 3 (100) | 2 (100) | 4 (100) | 1 (100) | 12 (100) | 3 (100) | 25 (100) |
| Grade ≥3 TEAE, n (%) | 2 (66.7) | 2 (100) | 2 (50.0) | 1 (100) | 8 (66.7) | 2 (66.7) | 17 (68.0) |
| Any treatment-emergent SAE | 1 (33.3) | 0 | 1 (25.0) | 1 (100) | 6 (50.0) | 2 (66.7) | 11 (44.0) |
| Grade 5 TEAE, n (%) | 0 | 0 | 0 | 0 | 4 (33.3) | 0 | 4 (16.0) |
| TEAE leading to permanent discontinuation (all treatments), n (%) | 0 | 0 | 0 | 1 (100) | 3 (25.0) | 1 (33.3) | 5 (20.0) |
| Corneal TEAE, n (%) | 2 (66.7) | 1 (50.0) | 0 | 1 (100) | 1 (8.3) | 1 (33.3) | 6 (24.0) |

**During the safety run-in period:**

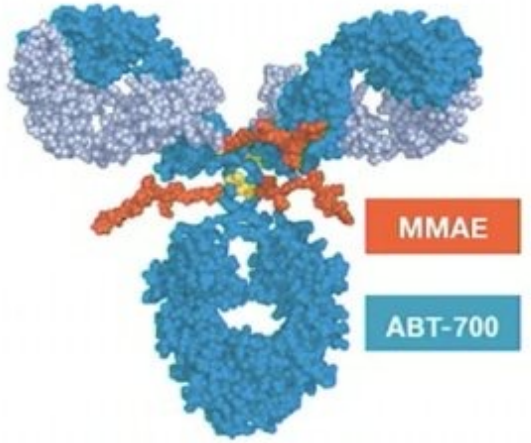
- Dose-limiting toxicity of increased aspartate aminotransferase occurred in 1 patient in the T4 tusa rav 170 $mg/m^2$ group

**Overall safety:**

- The most frequent TEAEs were nausea (44%), diarrhea (36%), and asthenia (32%)
- Grade ≥3 events occurred in 68% and Grade 5 events in 16% of patients in the treatment period (all unrelated to tusa rav)
- Corneal TEAEs of any grade occurred in 24% of patients and were manageable with dose modification
  - Only 1 was Grade 3 (keratitis) and occurred in the T2 tusa rav 170 $mg/m^2$ group; and no Grade 4 corneal events occurred
- Pneumonitis/interstitial lung disease and peripheral neuropathy occurred in 16% (4% Grade 3) and 28% (all Grade 1-2) of all patients, respectively

# Telisotuzumab Vedotin (Teliso-V) in Previously Treated c-Met–Overexpressing NSCLC

- c-MET is overexpressed in 40-60% of NSCLC, depending on the cutoff for overexpression. [1-2]
- Monoclonal antibodies targeting the extracellular domain of c-Met (onartuzumab) have had limited success in clinical trials in c-MET overexpressing NSCLC.[3-5]
  - Inconsistent correlation between protein overexpression and c-MET activation
- Teliso-V is an antibody-drug conjugate joining anti-c-Met humanized mAb (ABT-700) to cytotoxic microtubule inhibitor (MMAE) payload via a cleavable valine–citrulline linker




[1]Ma Cancer Research 2005, [2]Guo J Thoracic Oncology 2019, [3]Wakelee Clin Lung Cancer 2017, [4]Hirsch Clin Lung Cancer 2017, [5]Spigel J Clin Oncology 2017

# Teliso-V in c-Met–overexpressing NSCLC: LUMINOSITY 4th Interim Analysis

| TEAEs, n (%) | Total N=136 | |
|---|---|---|
| | Any Grade | Grade ≥3 |
| Any TEAE | 131 (96) | 65 (48) |
| Most common any-grade TEAEs (≥10%) | | |
| *Peripheral sensory neuropathy* | 34 (25) | 6 (4) |
| *Nausea* | 30 (22) | 1 (1) |
| *Hypoalbuminemia* | 28 (21) | 1 (1) |
| *Peripheral edema* | 25 (18) | 0 |
| *Blurred vision* | 25 (18) | 1 (1) |
| *Decreased appetite* | 24 (18) | 0 |
| *Fatigue* | 22 (16) | 5 (4) |
| *Anemia* | 19 (14) | 3 (2) |
| *Dyspnea* | 19 (14) | 4 (3) |
| *Asthenia* | 18 (13) | 3 (2) |
| *Increased gamma-glutamyl transferase* | 18 (13) | 3 (2) |
| *Keratitis* | 18 (13) | 0 |
| *Constipation* | 16 (12) | 1 (1) |
| *Cough* | 14 (10) | 0 |
| *Diarrhea* | 14 (10) | 0 |
| *Dizziness* | 14 (10) | 0 |
| *Malignant neoplasm progression* | 14 (10) | 11 (8) |
| *Vomiting* | 14 (10) | 1 (1) |

| | |
|---|---|
| Any TEAE related to Teliso-V* | 104 (76) |
| Any serious TEAE | 41 (30) |
| Any TEAE leading to Teliso-V discontinuation | 45 (33) |
| Any TEAE leading to Teliso-V discontinuation possibly related to Teliso-V* | 18 (13) |
| Any TEAE leading to death possibly related to Teliso-V* | 2 (1) |

n=1 sudden death,
n=1 pneumonitis

*Per investigator assessment.
TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

Pneumonitis reported in 9 (6.6%) patients, 3 of whom had grade ≥3 (2.2%) pneumonitis

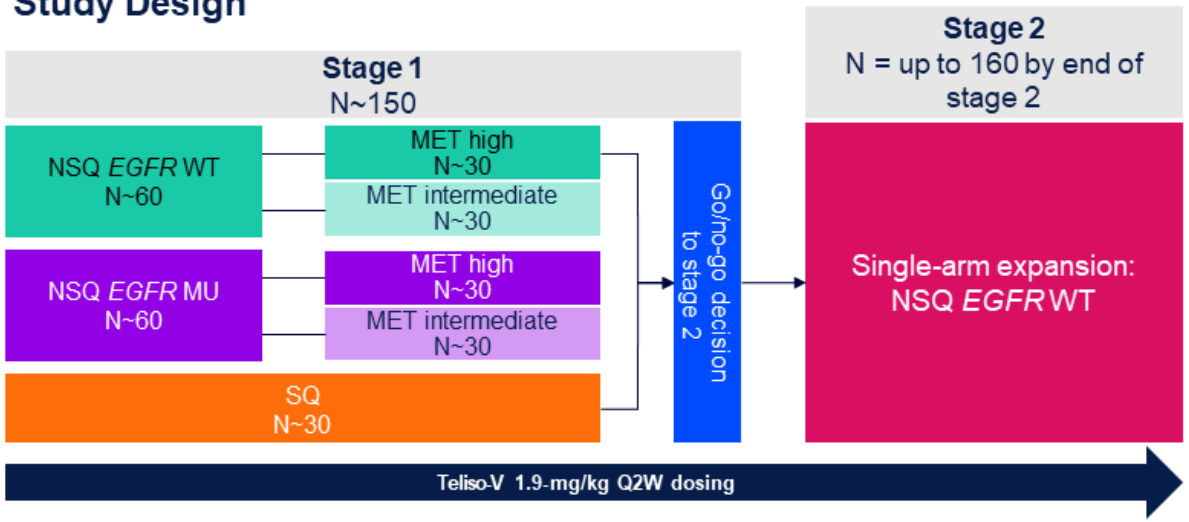


PRESENTED BY:
Ibiayi Dagogo-Jack, mD

# Phase 2 LUMINOSITY trial: Study design

**Primary endpoint:** ORR per independent central review according to RECIST v1.1

## Study Design




## Assessments

- *Efficacy:* ORR, DOR, disease control rate, PFS, overall survival
- *Safety:* AEs and changes in laboratory data and vital signs

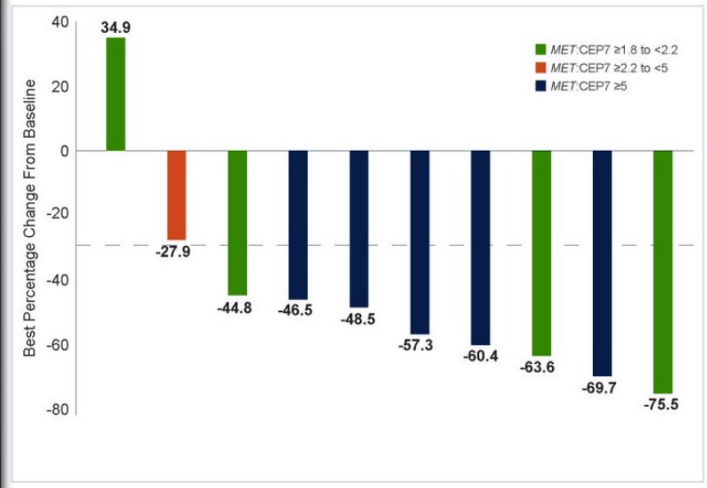
## Inclusion criteria

- Adult (≥18 years)
- Locally advanced/metastatic NSCLC
- c-Met–overexpressing* tumors (by central immunohistochemistry)
- ECOG performance status of 0 or 1
- ≤2 prior lines of systemic therapy, including ≤1 line of chemotherapy
- Adequate bone marrow, renal, and hepatic function

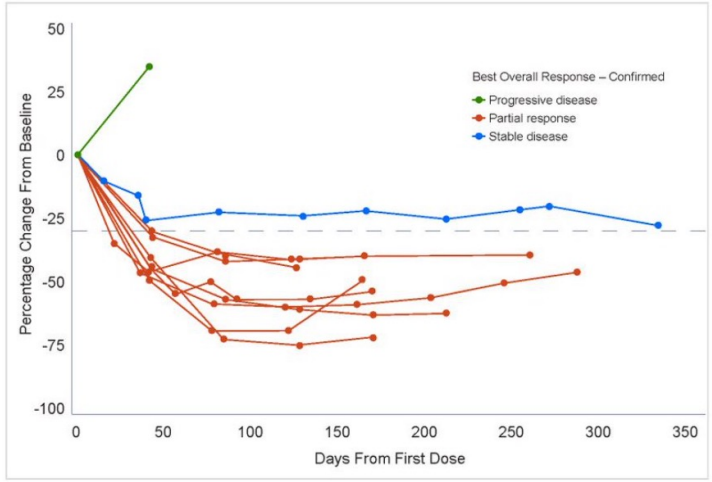
*Defined as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to <50% 3+) for the NSQ cohort, and as ≥75% of tumor cells at 1+ intensity for the SQ cohort.

AE, adverse event; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MU, mutant; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, overall response rate; PFS, progression-free survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wild-type.

## Best Percentage Change From Baseline in Target Lesions




## Percentage Reduction in Target Lesions




Percentage change in target lesions was determined by central review.

*Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 2–6, 2023, Chicago, IL, USA, and online*

ORR per ICR
- 35 % in c-Met High
- 23 % in c-Met Intermediate

mDOR per ICR
- 9 mos in c-Met High
- 7.2 mos in c-Met Intermediate

mOS
- 14.6 in c-Met High
- 14.2 in c-Met Intermediate

- In an ongoing phase 2 trial, LUMINOSITY (NCT03539536), Teliso-V monotherapy in previously treated patients with c-Met OE, epidermal growth factor receptor (*EGFR*) wild type (wt) NSQ NSCLC showed encouraging efficacy and acceptable safety with an ORR of 36.5%[6]
- A retrospective analysis[7] of the *EGFR*wt cohort in the LUMINOSITY trial identified 10 patients with *MET* amplification, defined as ≥1.8 *MET* gene to centromere of chromosome 7 (CEP7) copy number by fluorescence in situ hybridization (FISH)
  - ORR was 80% (8/10) with responses occurring across most levels of *MET* amplification
  - The median duration of response (DOR) was 6.9 months, and the median progression-free survival (PFS) was 8.0 months; 5 of 8 responders were event free at time of analysis
  - The safety dataset in the *MET* amplified patients was similar to the LUMINOSITY safety dataset

# STUDY DESIGN

- TeliMET NSCLC-02 (NCT05513703) is a global, phase 2, single-arm, open-label study, open to enrollment as of November 2022


*MET* Amp, *MET* amplified; NSCLC, non-small cell lung cancer; NSQ, non-squamous; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin.

# TAKE AWAYS AND CONCLUSIONS

ADCs are a rapidly growing class of agents that allow delivery of dose-intense cytotoxic therapy for aggressive malignancies

Targeting cellular surface as well as intracellular proteins/organelles allows more "targeted" delivery of payloads/chemo

Differential expression of cell surface targets may cause histology-related variability in response and outcomes

# TAKE AWAYS AND CONCLUSIONS

01

Commonly observed toxicities of interest include those typically noted with chemotherapy such nausea, vomiting, diarrhea and neuropathy, as well as myelosuppression

02

Interstitial lung disease is potentially problematic, is an adverse effect of interest for many of the ADCs

03

Payload for each ADC may predict which adverse event profile most likely to be observed

# THANK YOU FOR YOUR ATTENTION