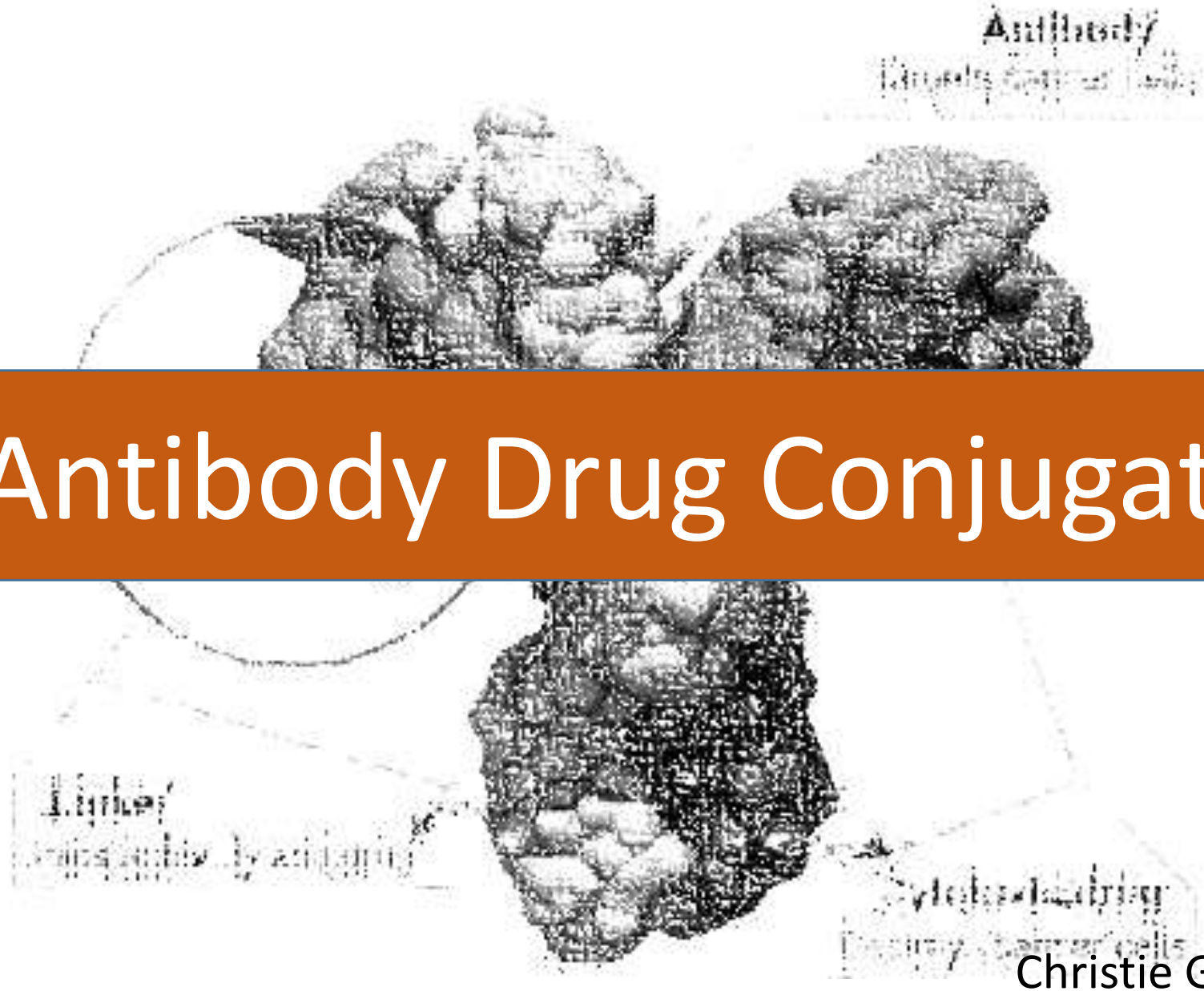
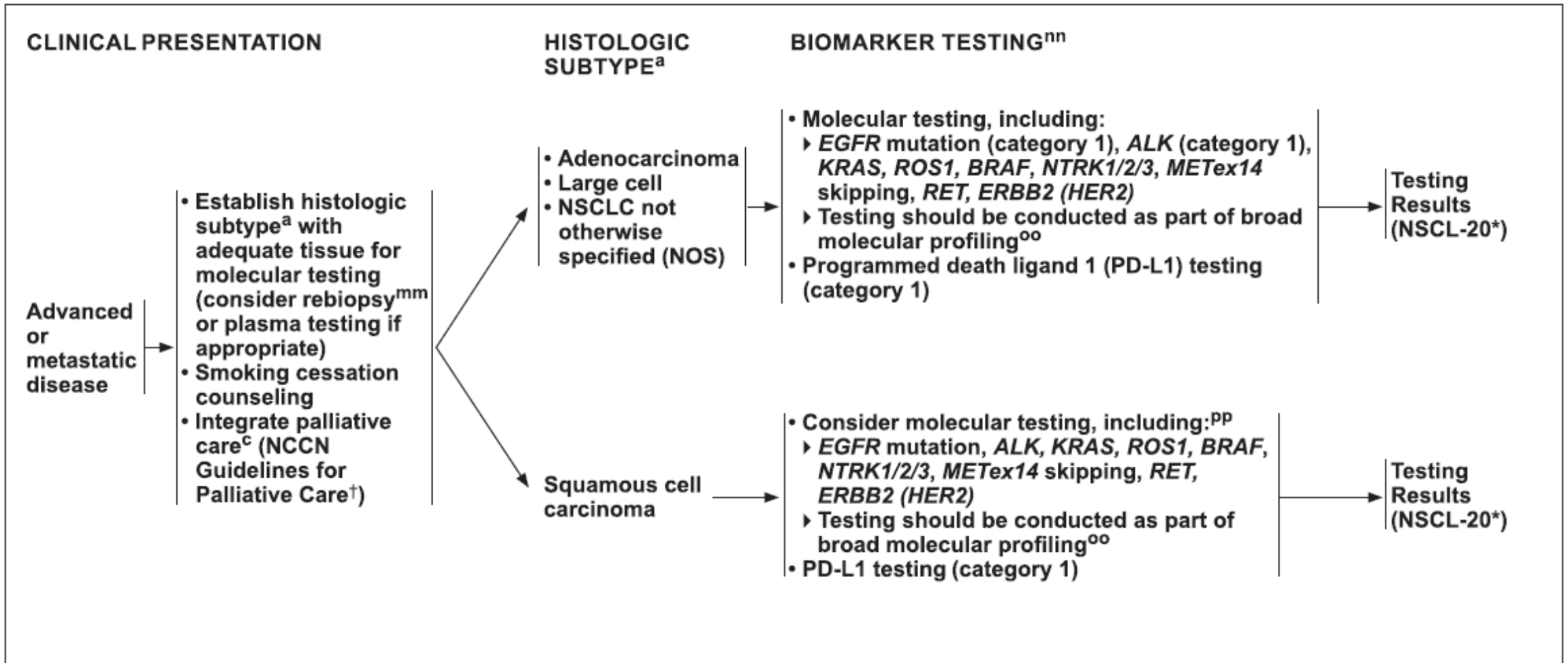
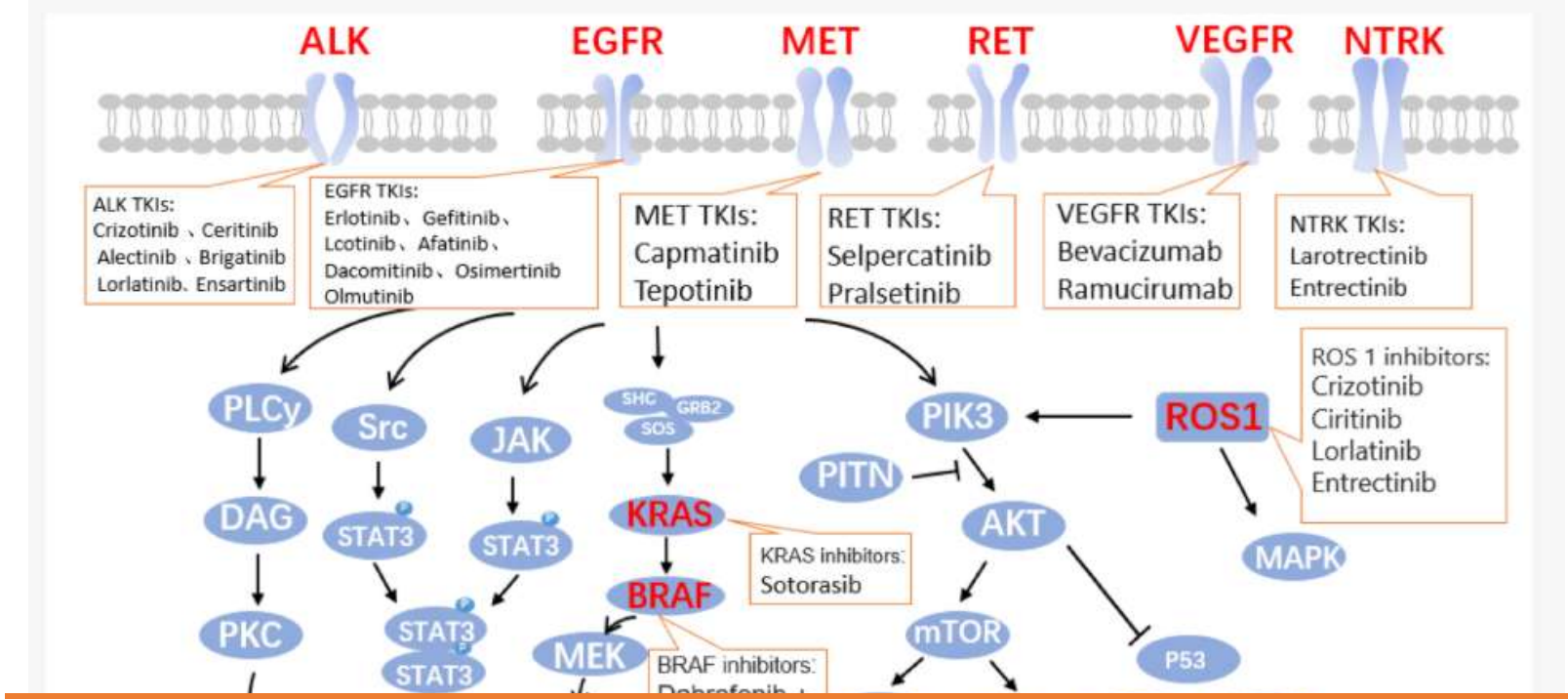


Antibody Drug Conjugates

Christie George Joseph


CLINICAL PRESENTATION
HISTOLOGIC SUBTYPE[a]
BIOMARKER TESTING[nn]
Advanced or metastatic disease
• Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[mm] or plasma testing if appropriate)
• Smoking cessation counseling
• Integrate palliative care[c] (NCCN Guidelines for Palliative Care[†])
• Adenocarcinoma
• Large cell
• NSCLC not otherwise specified (NOS)
• Molecular testing, including:
▸ *EGFR* mutation (category 1), *ALK* (category 1), *KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET, ERBB2 (HER2)*
▸ Testing should be conducted as part of broad molecular profiling[oo]
• Programmed death ligand 1 (PD-L1) testing (category 1)
Testing Results (NSCL-20*)
Squamous cell carcinoma
• Consider molecular testing, including:[pp]
▸ *EGFR* mutation, *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET, ERBB2 (HER2)*
▸ Testing should be conducted as part of broad molecular profiling[oo]
• PD-L1 testing (category 1)
Testing Results (NSCL-20*)



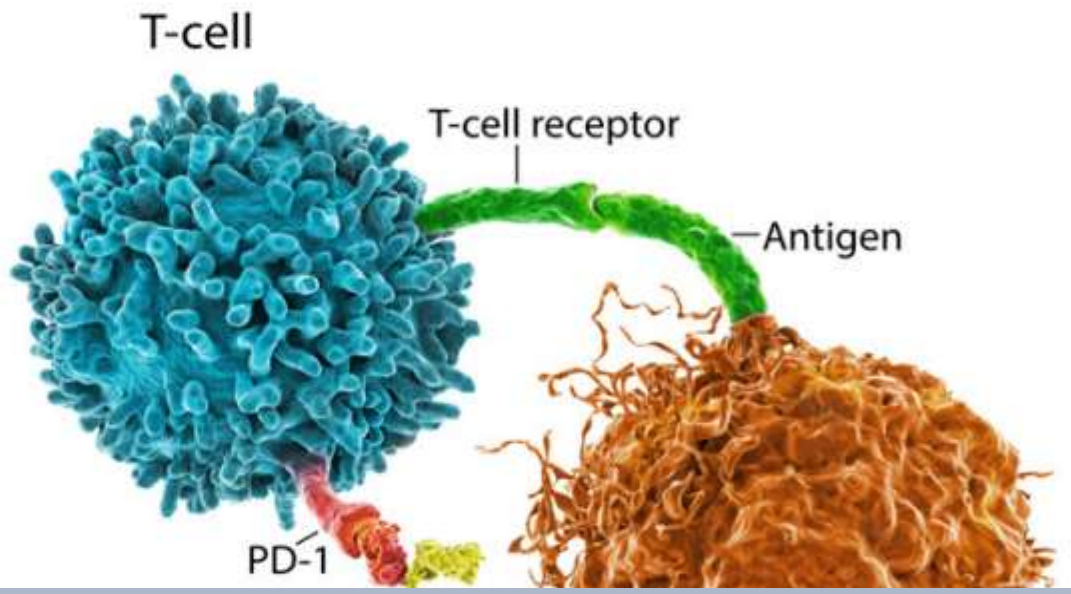
Approximately one third of patients with NSCLC harbor EGFR mutations, whereas 5% harbor ALK rearrangements.

For patients harboring EGFR mutations, osimertinib is the preferred first-line treatment

However, resistance invariably occurs and disease progression is observed after a median of 19 months.

Immunotherapy

Some lung cancers consist of cells that have PD-L1 on their surface. PD-L1 can attach to PD-1 on T cells and stop T cells from killing cancer cells. Immunotherapy stops PD-L1 from attaching. As

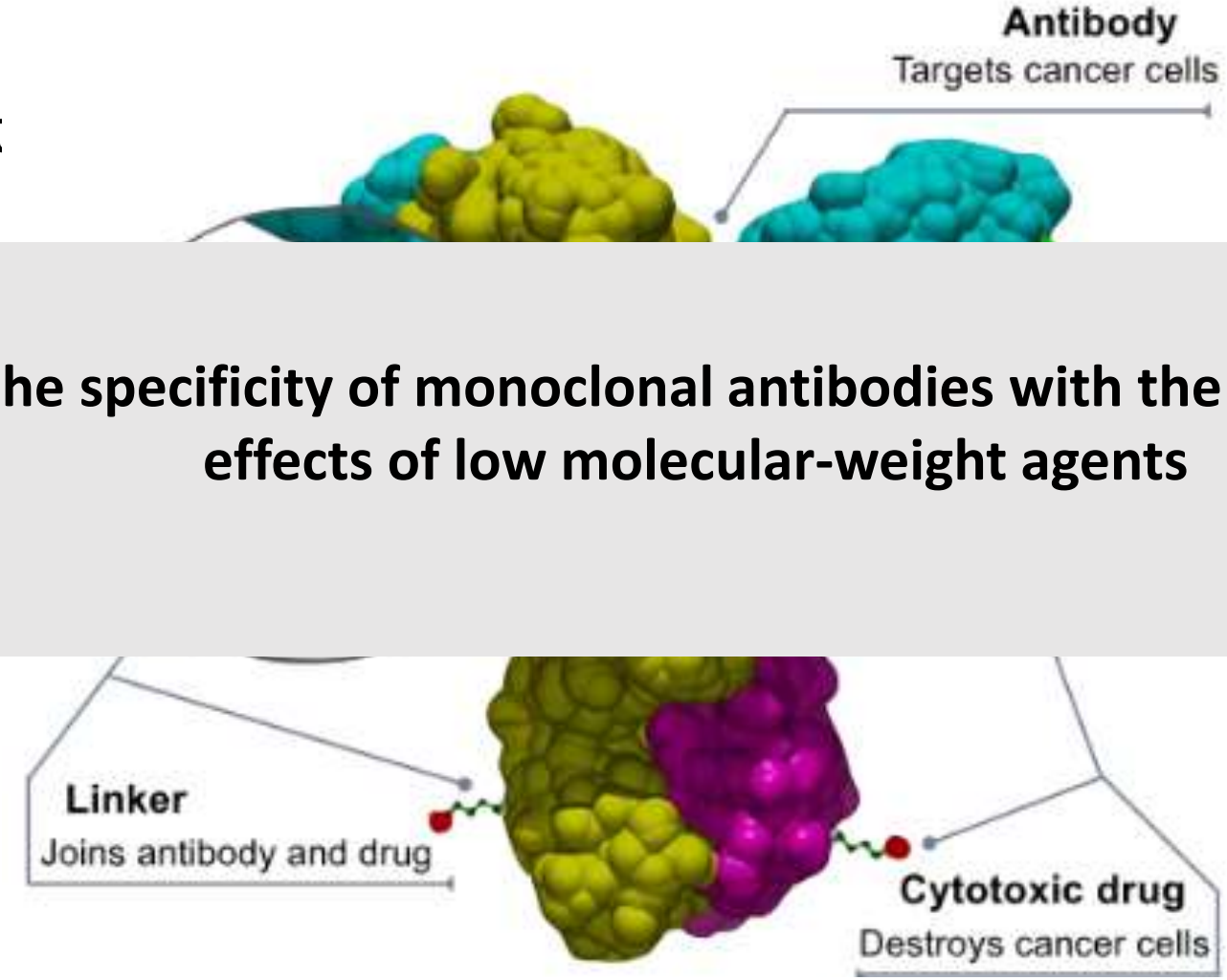


In the first-line setting, only about 30% to 60% of patients achieve objective response to immune therapy alone or combined with chemotherapy

Antibody-drug conjugates

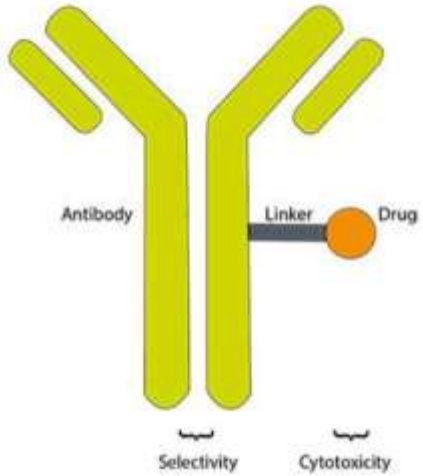
- ADCs are immuno-conjugates
- combine the tumour targeting ability of monoclonal antibodies with cytotoxic agents
- “magic bullet”: drugs that go straight to their intended cell-structural targets

Three essent



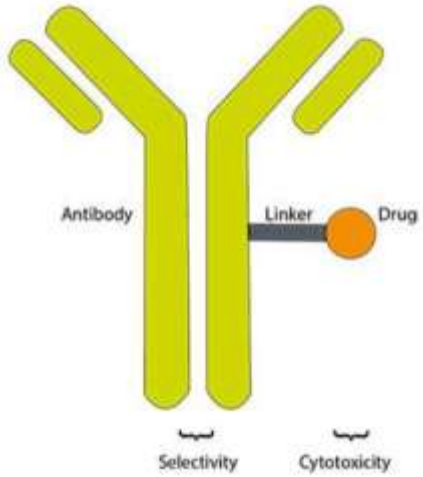
Combine the specificity of monoclonal antibodies with the potent cytotoxic effects of low molecular-weight agents

(i) The antibody



- Recognises and binds to specific antigens on the surface of cancer cells (eg: HER2, TROP2)
- Highly specific – recognise tumour specific antigens that are over-expressed in cancer cells.
- Most ADCs use IgG (especially IgG1 and IgG4)
- excellent solubility and higher affinity for Fcγ receptors
  - helps pH-dependent cycling,
  - avoiding degradation ----> longer plasma half-life

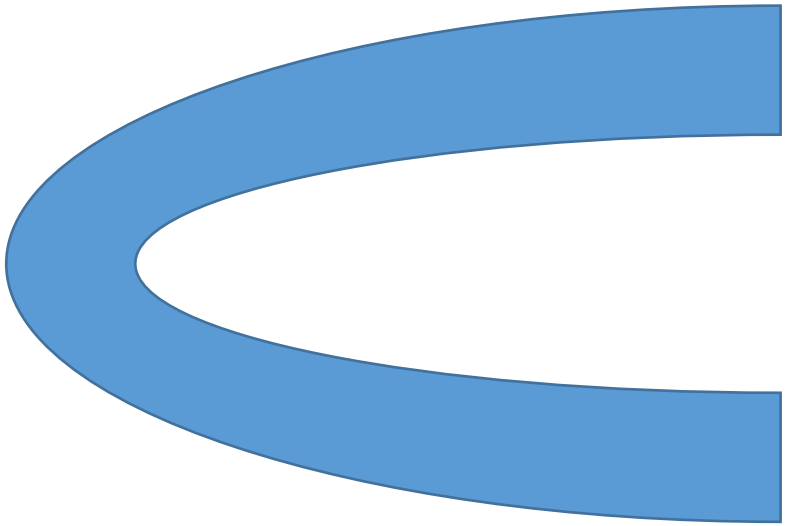
(ii) The linker



- Bridge the antibody and the cytotoxic drug.
- ADCs stability and payload release determinant

➢In plasma – highly stable : prevents non specific release

➢On internalisation – release of cytotoxic drug

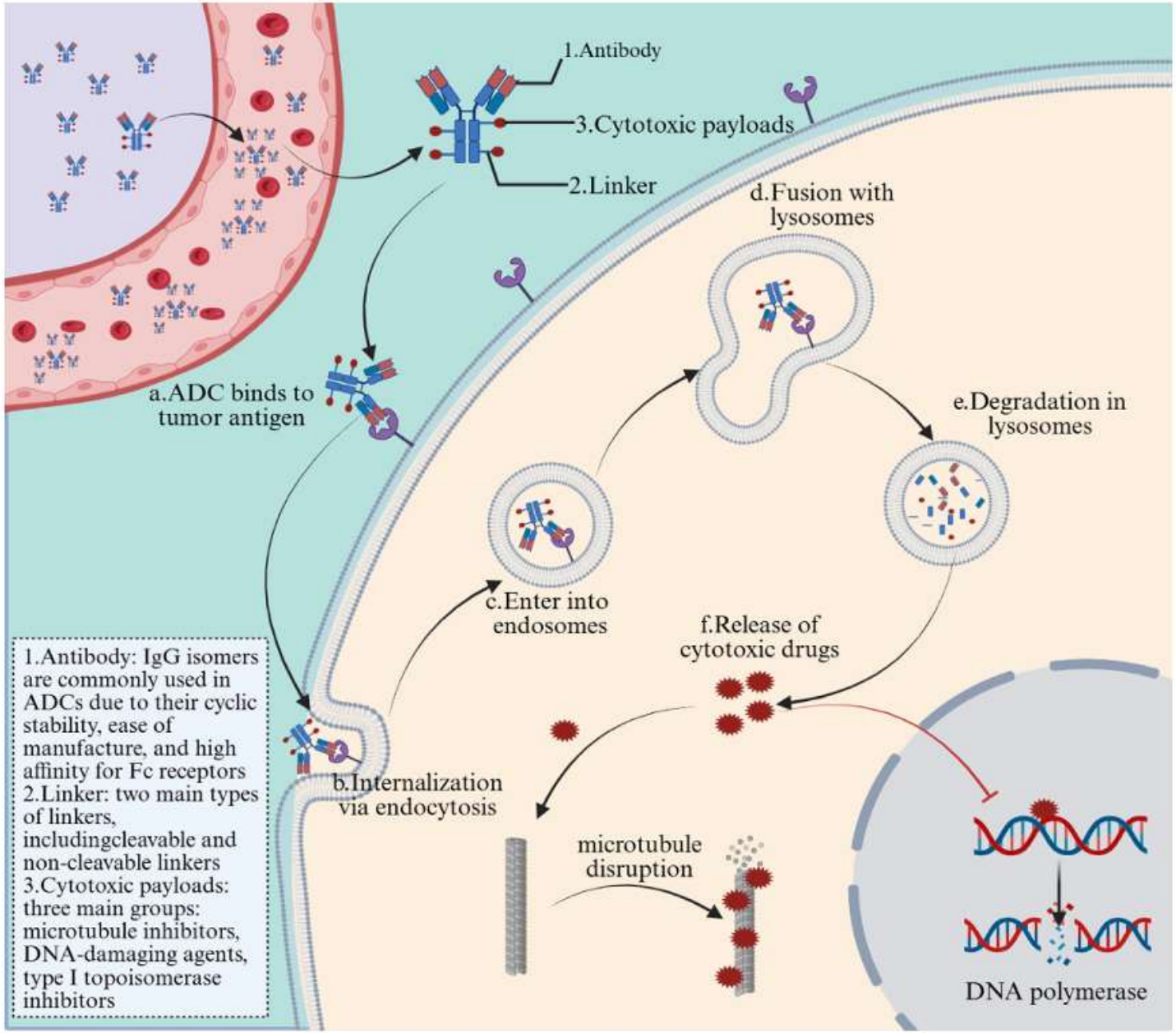


<u>Non-cleavable linkers:</u>

- stability in systemic circulation,
- minimal cleavage in plasma.
- Broader safety margin

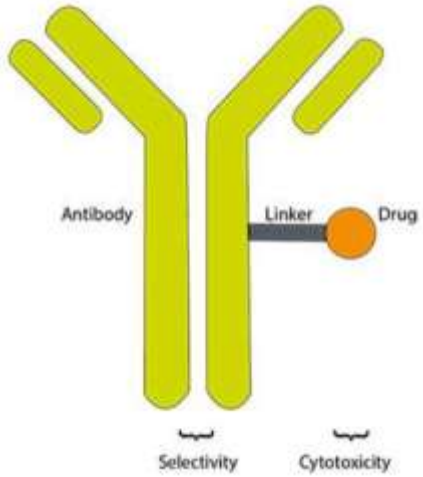
<u>Cleavable linkers:</u>

- degrade in the tumour micro-environment or in response to specific enzymes or reducing agents within cells
- ? potential increased toxicity.



Chemical cleable linkers	Enzymatic cleable linkers
Eg: Hydrazone and disulfide bonds	Eg: glucuronic acid bonds and peptide bonds
Hydrazone cleaved by lysosome pH 4.8 and endosome pH 5.5–6.2 conditions	- amino acids bonds released through the enzymatic hydrolysis by proteases
Disulphide sensitive to the concentration of reducing glutathione (GSH	

(iii) The cytotoxic payload



- The principal therapeutic effector for inducing tumour cell death, often too toxic to be administered in systemic form

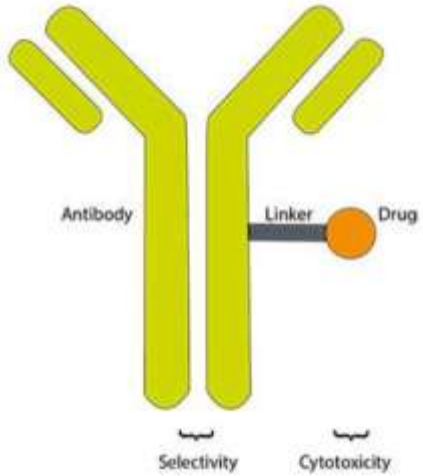
❖ microtubule inhibitors

❖ DNA-damaging compounds : calicheamicin and duocarmycin analogues

❖ Type I topoisomerase inhibitors

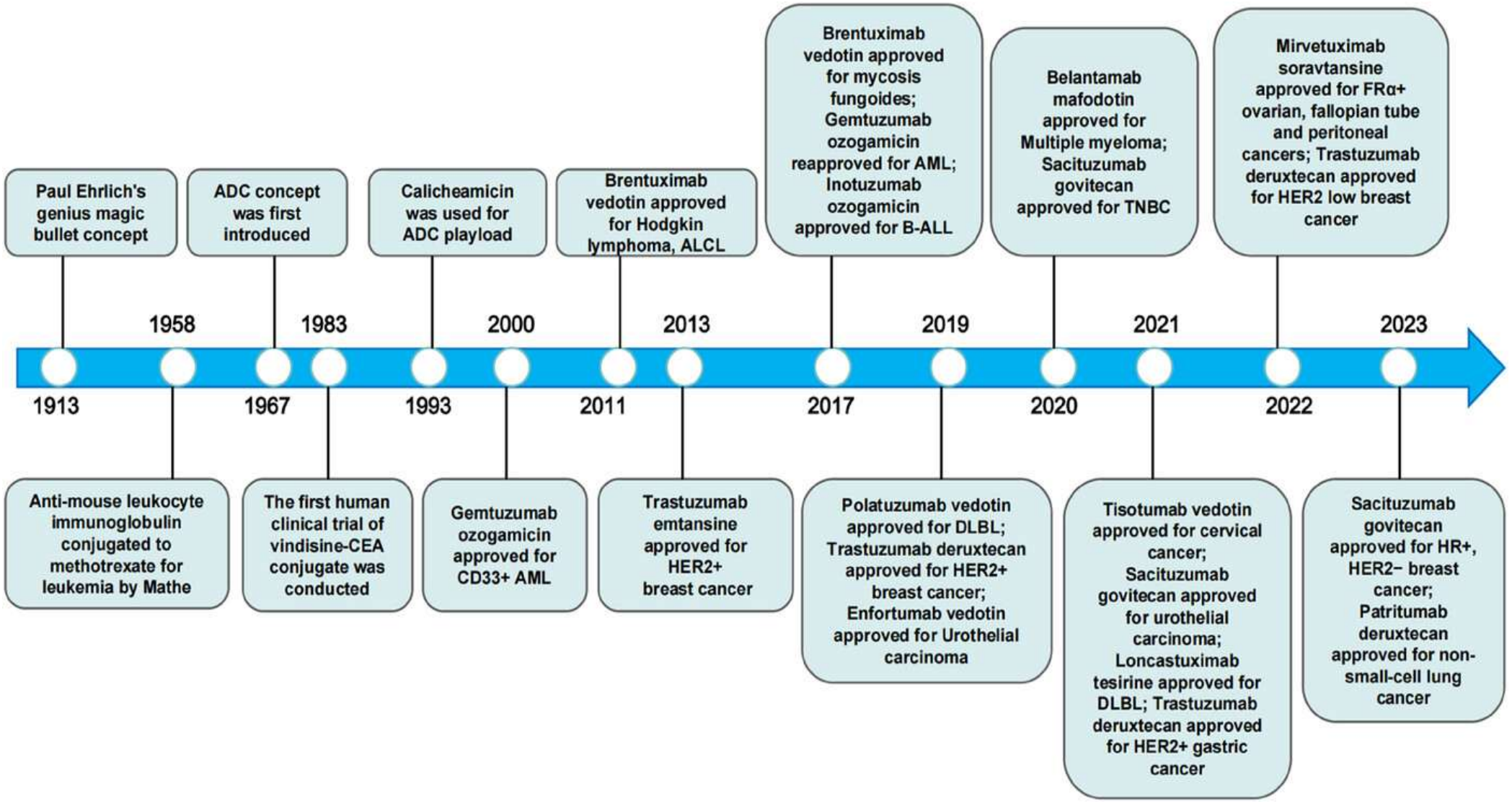
❖ Immune-modulating agents and protease-targeting payloads (in pipeline)

(iii) The cytotoxic payload - DAR



Benefit of cytotoxic payload: potent drugs can be precisely delivered – even small amounts can kill targeted cancer cells

- Drug Antibody Ratio: the average number of drug molecules linked to each antibody
- Higher DAR values - enhances the cytotoxicity of each ADC molecule
- Excessively high DAR - uncontrolled release of drug loads - nonspecific toxicity to normal cells
- Typical DAR value - 3 to 6



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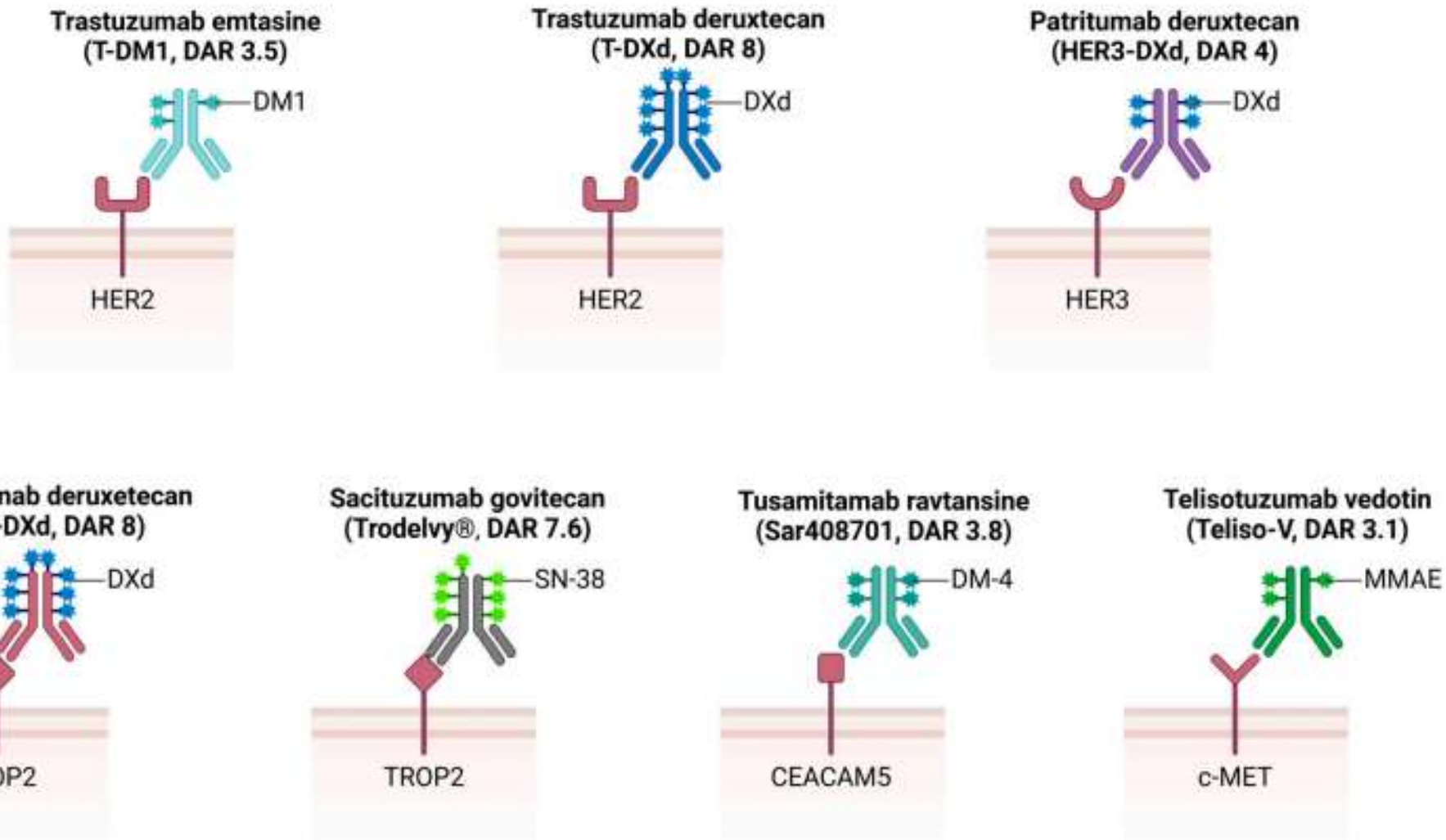
Antibody drug conjugates in lung cancer:



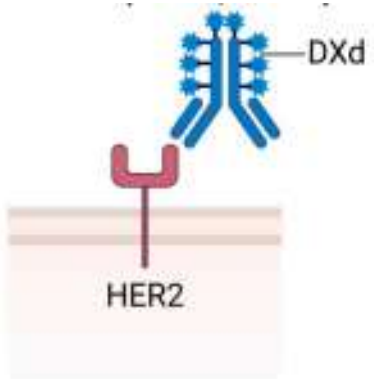
(I) Human epidermal growth factor receptor 2, (HER-2)

- EGFR tyrosine kinase family - facilitates tumour cell proliferation, cellular survival, metastasis, and invasion in lung cancer
- In NSCLC, the incidences of HER2 overexpression : 7.7%-23%,
  HER2 amplification : 2%-22%
  HER2 mutation : 1%-6.7%
- exon-20 insertions account for 90% of HER2 mutations
- associated with female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and higher incidence of brain metastases

- Current first-line treatment options for patients with *HER2*-mutant (*HER2*m) NSCLC - chemotherapy and/or immunotherapy

  - limited efficacy in the second-line setting.

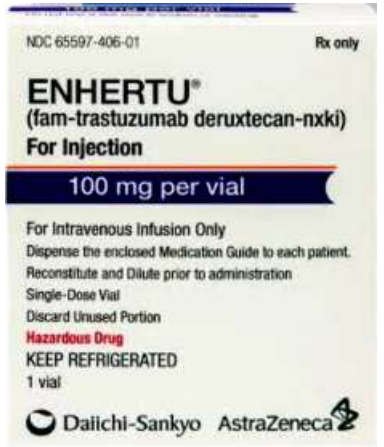
(Ia) Transtuzumab deruxtecan



- The first ADC authorized for clinical application in NSCLC (2022)

DESTINY-Lung01	T-DXd 6.4 mg/kg in patients with *HER2*m mNSCLC : cORR, 54.9% [50/91])
	Rate of adjudicated drug-related interstitial lung disease (ILD) - 26.4% (24/91)
DESTINY-Lung02	Efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg - assessed in patients with previously treated *HER2*m mNSCLC

Rs 1,40,000/ 100 mg



Destiny-Lung 02	Randomized, multi-center, dose- blinded, two-cohort, phase 2 study (March 19, 2021, and March 24, 2022)
ELIGIBILITY	• Pathologically documented mNSCLC with a known activating HER2 mutation documented from an archival or fresh biopsy tumor tissue sample by certified local laboratory assessment • Received at least one prior anticancer (including platinum-based chemotherapy • Had at least one measurable lesion by BICR per RECIST v.1.1. • Patients with stable brain metastases (asymptomatic and not requiring corticosteroids or anticonvulsants) were eligible.
EXCLUSION	• A known driver mutation in the EGFR, BRAF, or MET exon 14 gene or a known ALK, ROS1, RET, or NTRK fusion; • Clinically active brain metastases (untreated, symptomatic, or requiring corticosteroids or anticonvulsants) • history of non-infectious ILD requiring steroids or current or suspected ILD
Intervention	152 patients, randomly assigned 2:1 to receive T-DXd 5.4 mg/kg or 6.4 mg/kg, administered intravenously once every 3 weeks. Two dose reductions were permitted in each arm; thereafter, patients were withdrawn from the study if further toxicity occurred that met the requirement for dose reduction
End-points	The primary efficacy end point was cORR, (sum of complete response (CR) and partial response (PR) rates, assessed by BICR) Secondary efficacy end points - cORR based on investigator assessment, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)

Patient Characteristic	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
Age, median (Q1-Q3), y	59.4 (51.1-69.2)	61.3 (51.8-67.2)
Female, n (%)	65 (63.7)	34 (68.0)
Region, n (%)		
Asia	63 (61.8)	30 (60.0)
Europe	33 (32.4)	17 (34.0)
North America	4 (3.9)	2 (4.0)
Australia	2 (2.0)	1 (2.0)
ECOG performance status, n (%)		
0	29 (28.4)	19 (38.0)
1	73 (71.6)	31 (62.0)
Histology, n (%)		
Adenocarcinoma	100 (98.0)	50 (100)
Squamous	1 (1.0)	0
Other	1 (1.0)	0
HER2 mutation, n (%)		
Kinase domain	99 (97.1)	50 (100)
Extracellular domain	3 (2.9)	0
Central nervous system metastases at baseline, n (%)	35 (34.3)	22 (44.0)
Tobacco users, n (%)		
Never	55 (53.9)	29 (58.0)
Former	47 (46.1)	21 (42.0)
Renal function at baseline,[a] n (%)		
Normal	38 (37.3)	16 (32.0)
Mild impairment	41 (40.2)	29 (58.0)
Moderate impairment	23 (22.5)	5 (10.0)
History of prior lung resection, n (%)	22 (21.6)	12 (24.0)
History of any prior systemic cancer therapy, n (%)	102 (100)	50 (100)
Lines of prior systemic therapy for advanced/metastatic disease, n (%)		
<2 lines	69 (67.6)	31 (62.0)
>2 lines	33 (32.4)	19 (38.0)
Median (Q1-Q3)	2.0 (1.0-3.0)	1.7 (2.0-3.0)
Prior treatment, n (%)		
Platinum-based	102 (100)	50 (100)
Anti-PD-(L)1	75 (73.5)	39 (78.0)
Platinum and anti-PD-(L)1 (in combination)	51 (50.0)	29 (58.0)
Platinum and anti-PD-(L)1 (not in combination)	24 (23.5)	10 (20.0)
Docetaxel	30 (29.4)	17 (34.0)
HER2-targeted therapy	15 (14.7)	11 (22.0)
Prior radiation therapy, n (%)		
Yes	58 (56.9)	25 (50.0)
No	44 (43.1)	25 (50.0)
Time since radiotherapy (Q1-Q3), mo	6.5 (2.1-11.2)	5.3 (1.3-16.7)
Prior cancer surgery, n (%)		
Yes	25 (24.5)	13 (26.0)
No	77 (75.5)	37 (74.0)
Anti-PD-(L)1 therapy as prior immediate treatment, n (%)		
Yes	29 (28.4)	15 (30.0)
No	46 (45.1)	24 (48.0)
Missing	27 (26.5)	11 (22.0)
Time from IO therapies (Q1-Q3), mo	4.2 (1.9-13.0)	7.1 (2.0-10.7)

Jänne PA, Goto Y, Kubo T, et al. Final analysis results and patient-reported outcomes from DESTINY-Lung02—a dose- blinded, randomized, phase 2 study of trastuzumab deruxtecan in patients with HER2-mutant metastatic NSCLC. J Thorac Oncol

Table 2. Efficacy Summary by BICR

Efficacy Measure	T-DXd 5.4 mg/kg (n = 102)	T-DXd 6.4 mg/kg (n = 50)
Confirmed objective response rate,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
Best overall response, n (%)		
Complete response[c]	3 (2.9)	4 (8.0)
Partial response	48 (47.1)	24 (48.0)
Stable disease	44 (43.1)	18 (36.0)
Progressive disease	4 (3.9)	2 (4.0)
Non-evaluable	3 (2.9)	2 (4.0)
Median disease control rate,[d] n (% [95% CI])	95 (93.1 [86.4-97.2])	46 (92.0 [80.8-97.8])
Duration of response,[b] median (95% CI), mo	12.6 (6.4-NE)	12.2 (7.0-NE)
Progression-free survival,[b] median (95% CI), mo	10.0 (7.7-15.2)	12.9 (7.2-16.7)
Time to initial response,[b] median (Q1-Q3), mo	1.8 (1.4-3.0)	1.6 (1.4-3.5)

[a]Proportion of patients with confirmed complete response or partial response.
[b]Assessed by BICR per RECIST v.1.1.
[c]Two additional complete responses were reported in each arm since the prior data cutoff. In the 5.4-mg/kg arm, one patient improved from partial response to complete response at week 78. Another patient was reassessed from partial to complete response starting from week 6 onward; the remaining lymph node initially assessed as partial response was later confirmed as com
had a partial response at the time of the primary analysis and w
at week 60 and week 42, respectively.
[d]Proportion of patients with confirmed complete response, par
BICR, blinded independent central review; NE, not estimable;
deruxtecan.

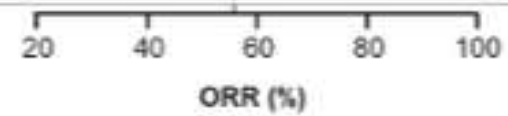
Benchmark ORR : 266.4% - the upper limit of the 95% CI (ORR, 22.9%; 95% CI, 19.7 to 26.4%) in the ramucirumab plus docetaxel arm of the REVEL trial, - second-line treatment for patients with advanced NSCLC after platinum-based therapy

Jänne PA, Goto Y, Kubo T, et al. Final analysis results and patient-reported outcomes from DESTINY-Lung02—a dose- blinded, randomized, phase 2 study of trastuzumab deruxtecan in patients with HER2-mutant metastatic NSCLC. J Thorac Oncol

A)

	No. CR or PR/ total no. of patients	ORR (95% CI)
All patients (T-DXd 5.4 mg/kg)	50/102	49.0 (39.0 to 59.1)
***HER2* mutation domain**		
Kinase domain	48/99	48.5 (38.3 to 58.7)
Prior anti–PD-(L)1 treatment		
Yes	36/75	48.0 (36.3 to 59.8)
No	14/27	51.9 (31.9 to 71.3)
CNS metastasis		
Yes		
No		

	No. CR or PR/ total no. of patients	ORR (95% CI)
All patients (T-DXd 6.4 mg/kg)	28/50	56.0 (41.3 to 70.0)
***HER2* mutation domain**		
Kinase domain	28/50	56.0 (41.3 to 70.0)
Prior anti–PD-(L)1 treatment		
Yes	19/39	48.7 (32.4 to 65.2)
No	9/11	81.8 (48.2 to 97.7)
CNS metastasis		
Yes	10/22	45.5 (24.4 to 67.8)
No	18/28	64.3 (44.1 to 81.4)



Supplemental Table 4. Most common treatment-emergent adverse events in ≥20% of patients by preferred/grouped term and worst CTCAE grade

n (%)	T-DXd 5.4 mg/kg n = 101[a]					T-DXd 6.4 mg/kg n = 50[a]				
Preferred/Grouped Term	Any grade	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Nausea	68 (67.3)	64 (63.4)	4 (4.0)	0	0	41 (82.0)	38 (76.0)	3 (6.0)	0	0
Fatigue[b]										
Neutropenia[b]										
Decreased appetite										
Anemia[b]										
Constipation										
Vomiting										
Thrombocytopenia[b]										
Leukopenia[b]										
Diarrhea										
Transaminases increased[b]										
Alopecia										
Blood bilirubin increased[b]										

CTCAE, Common Terminology Criteria for A
[a]Randomly assigned patients who received ≥1
[b]Grouped terms include fatigue (fatigue, asth
decreased), thrombocytopenia (platelet count
aminotransferase increased, alanine aminotra
hypertransaminasaemia), and blood bilirubin

Supplemental Table 5. Treatment-emergent adverse events associated with study drug discontinuation by preferred/grouped term

n (%)	T-DXd 5.4 mg/kg n = 101[a]	T-DXd 6.4 mg/kg n = 50[a]
Any treatment-emergent adverse event	17 (16.8)	16 (32.0)
Interstitial lung disease[b]	6 (5.9)	5 (10.0)
Pneumonitis[b]	5 (5.0)	4 (8.0)
Pneumonia	1 (1.0)	2 (4.0)
Blood bilirubin increased[c]	1 (1.0)	1 (2.0)
Hypokalaemia[c]	1 (1.0)	0
Metastases to meninges	1 (1.0)	0
Myocarditis	1 (1.0)	0
Pulmonary toxicity	1 (1.0)	0
Acute kidney injury	0	1 (2.0)
Anxiety	0	1 (2.0)
Lymphangiosis carcinomatosis[a]	0	1 (2.0)
Neutropenia[c]	0	1 (2.0)

T-DXd, trastuzumab deruxtecan.
[a]Randomly assigned patients who received ≥1 T-DXd dose.
[b]As reported by investigator.
[c]Grouped terms are neutropenia (neutrophil count decreased, neutropenia), hypokalemia (hypokalemia, blood potassium decreased), and blood bilirubin increased (blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, blood bilirubin unconjugated increased).

Table 3. Adjudicated Drug-Related ILD[a]

Adjudicated Drug-Related ILD Variable	T-DXd 5.4 mg/kg n = 101[b]	T-DXd 6.4 mg/kg n = 50[b]
Any grade, n (%)	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)[c]	1 (2.0)[c]
Grade ≥3	2 (2.0)	2 (4.0)
Outcome of ILD events,[d,e] n/N (%)		
Fatal	1/15 (6.7)	1/16 (6.3)
Not recovered/not resolved	3/15 (20.0)	6/16 (37.5)
Recovering/resolving	1/15 (6.7)	0
Recovered/resolved with sequelae	0	1/16 (6.3)
Recovered/resolved	10/15 (66.7)	8/16 (50.0)
Treatment of ILD,[e,f] n/N (%)		
Steroids[g]	12/15 (80.0)	13/16 (81.3)
Antibiotics	7/15 (46.7)	5/16 (31.8)
Steroids and antibiotics	6/15 (40.0)	4/16 (25.0)
Anti-PD-(L)1 as prior immediate treatment, n/N (%)		
Yes	6/15 (40.0)	5/16 (31.3)
No	5/15 (33.3)	8/16 (50.0)
Missing	4/15 (26.7)	3/16 (18.8)
Time since the completion of prior anti-PD-(L)1 therapy,[h] n/N (%)		
>3 mo	5/44 (11.4)	10/28 (35.7)
≤3 mo	6/30 (20.0)	3/11 (27.3)
No prior therapy	4/27 (14.8)	3/11 (27.3)
Prior IO therapy,[i] n/N (%)		
Yes	10/15 (66.7)	12/16 (75.0)
No	5/15 (33.3)	4/16 (25.0)
Time from IO therapies, n/N (%)		
<3 mo	6/15 (40.0)	3/16 (18.8)
≥3 to ≤6 mo	0	3/16 (18.8)
>6 mo	4/15 (26.7)	6/16 (37.5)
Tobacco users, n/N (%)		
Never	7/15 (46.7)	9/16 (56.3)
Former	8/15 (53.3)	7/16 (43.8)

[a]At data cutoff (August 25, 2023), all potential cases of ILD were adjudicated by the adjudication committee, with no pending cases.
[b]Randomly assigned patients who received ≥1 T-DXd dose.
[c]At the 5.4-mg/kg dose, the fatal case involved a 73-year-old (age at screening) female patient who had received two earlier anticancer regimens, including carboplatin, pemetrexed, anti-PD-(L)1 therapy, and an EGFR TKI; her most recent anti-PD-(L)1 treatment occurred 2 years before study enrollment. At the 6.4-mg/kg dose, the fatal case involved an 85-year-old female patient with no history of prior IO therapy. She had received two prior systemic anticancer treatments, which included carboplatin, pemetrexed, and a taxane. Both patients developed respiratory symptoms after several treatment cycles. Initial management did not include corticosteroids for the patient in the T-DXd 6.4-mg/kg arm, but the patient in the T-DXd 5.4-mg/kg arm received IV methylprednisolone 1000 mg once daily starting on 8 March 2022, following the onset of grade 3 respiratory failure (later determined to be pneumonitis). Pneumonitis was not suspected until later stages and progressed quickly, resulting in death.
[d]The outcome of the worst ILD event denominator is based on the adjudicated drug-related ILD.
[e]Percentages are calculated using the total number of patients with adjudicated drug-related ILD as the denominator.
[f]Treatment of ILD includes the antibiotics and/or steroids used and reported by investigators for patients with adjudicated drug-related ILD.

Adv:

- The primary end point of confirmed ORR by BICR was met and exceeded the statistical hypothesis
- Responses were consistent regardless of HER2 mutation type and amplification status and presence or absence of baseline CNS metastases and prior treatment.
- More favorable benefit/risk profile observed with T-DXd 5.4 mg/kg
- FDA approved T-DXd 5.4mg/kg for previously treatedHER2m mNSCLC.
- Lack of a comparator arm?

DESTINY-Lung03 (DL03): Phase Ib Study of the Safety of T-DXd and Immunotherapy Agents With and Without Chemotherapy in Advanced or Metastatic HER2+, Non-squamous NSCLC

Last Update
September 9, 2025

Status

Phase
I

Enrollment Goal
244

Age
≥18

Study drugs
pemetrexed, rilvegostomig (AZD2936), cisplatin, trastuzumab deruxtecan, durvalumab, volrustomig, carboplatin

Modalities
Chemotherapy, Immunotherapy, Monoclonal Antibody

Contact Us

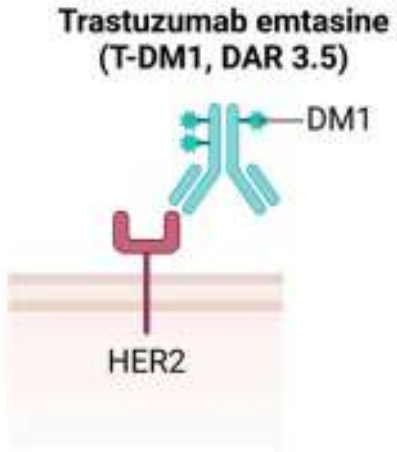
or

1-844-432-3892

Our clinical Trial Navigators can help you connect with a site, find a match, or join our registry to receive updates.

Monday - Friday
9:00 am - 6:00 pm ET
Se habla Español.

(Ib) Trastuzumab Emtansine, T-DM1



- First ADC to be used in the treatment of solid tumors.
- Robust efficacy with mild toxicity for HER2-overexpressing amplified breast cancer -approved for its treatment
- Currently ”under investigation” for non-small cell lung cancer (NSCLC

ELIGIBILITY	• Histologically or cytologically confirmed adenocarcinoma of the lung at stage III or IV or postoperative recurrence that tested positive for HER2 exon-20 insertion mutations; • history of treatment with one or two chemotherapeutic lines, *with the exception of monotherapy with an immune checkpoint inhibitor*; • ECOG status of 0-2 • Adequate organ function including a left ventricular ejection fraction of 50%. • A lesion that was measurable as per Response Evaluation Criteria in Solid Tumours (version 1.1) was required for evaluation of response.
EXCLUSION	History of treatment with HER2 inhibitors including trastuzumab, pertuzumab, afatinib or dacomitinib, and evidence of other driver oncogenic alterations in EGFR, ALK, ROS1, BRAF, RET, MET or NTRK genes
Intervention	22 patients, T-DM1 (3.6 mg/kg) was administered by intravenous infusion every 21 days until disease progression, unacceptable toxicity or withdrawal of consent.
End-points	Primary end-point - investigator- assessed ORR, defined as the proportion of per-protocol patients for whom the best response was a complete or partial response. Secondary end-points were PFS, overall survival (OS), duration of response and safety

Iwama E, Zenke Y, Sugawara S, Daga H, et al Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. Eur J Cancer. 2022 Feb;162:99-106.

Characteristics of the study patients (n = 22).

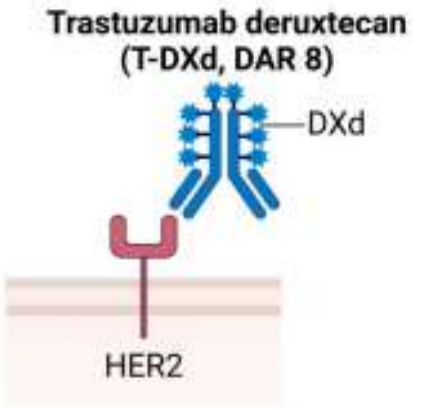
Characteristics	No.	%
[Median age (range), years	61.5 (35–80)]	
Sex		
Male	12	54.5
Female	10	45.5
Smoking status		
Never smoker	11	50.0
Former smoker	9	40.9
Current smoker	2	9.1
ECOG performance status		
0	10	45.5
1	10	45.5
2	2	9.1
Histology, adenocarcinoma	22	100
Clinical stage at screening		
IV	16	72.7
Postoperative recurrence	6	27.3
Baseline CNS metastasis		
Positive	9	40.9
Negative	13	59.1
No. of lines of prior systemic therapy		
1	14	63.6
2	8	36.4
Type of *HER2* exon-20insertion mutation		
A775_G776insYVMA	19	86.4
Other	3	13.6
Confirmation of *HER2* exon-20 insertion mutation		
NGS platform	21	95.5
Multiplex real-time PCR	1	4.5

ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; *HER2, human epidermal growth factor receptor 2;* NGS, next-generation sequencing; PCR, polymerase chain reaction.

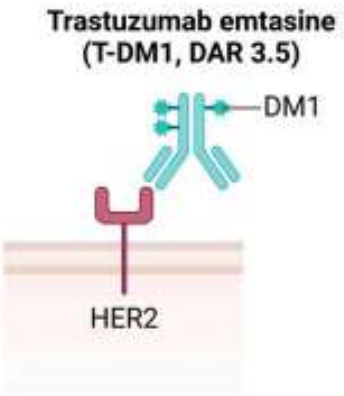
All patients included in the efficacy analysis (n = 21) had discontinued the protocol treatment as a result of progressive disease (n = 19) or unacceptable toxicity (n = 2) by the date for data cut-off (26th February 2021)

Median follow-up time	**8.0 months (range : 0.3 - 24.7 months**
Median number of cycles of T-DM1	2.5 (range: 1 to 15 cycles).
Reduction in tumor size from baseline	11 patients (PR in 8 and SD in 3)
ORR	38.1% (90% CI, 23.0- 55.9%, P 0.2091)
Disease control rate	52.4% (90% CI, 35.2- 69.0%)
Median duration of response	3.5 months (95% CI, 2.7-6.5 months)
Median PFS	2.8 months (95% CI, 1.4-4.4 months)
Median OS	8.1 months (95% CI, 3.5-13.2 months)

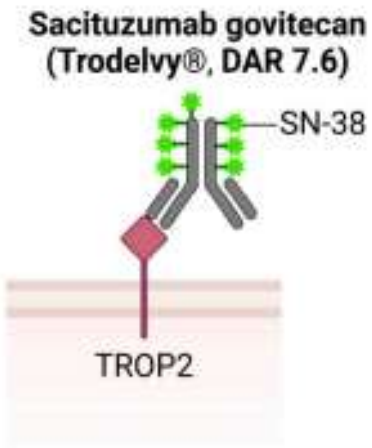
Iwama E, Zenke Y, Sugawara S, Daga H, et al Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. Eur J Cancer. 2022 Feb;162:99-106.



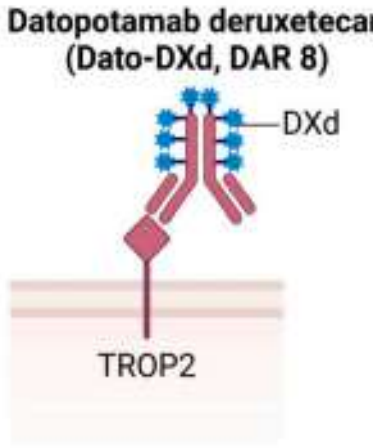
T-deruxtecan vs T- emtasine



Both bind to HER2 on the surface of malignant tumour cells expressing the receptor and are internalised into early endosomes and then transferred to lysosomes.	
T-DXd payload is liberated by lysosomal enzymes such as cathepsins that are upregulated in the tumour microenvironment	T-DM1 releases its cytotoxic payload after its degradation in lysosomes
DAR : 8	3.5
T-DXd payload capable of permeating membranes- cytotoxic effect to neighbouring tumour cells	
ORR: 50 (95% CI: 39.0 to 59.1)	38.1% (90% CI, 23.0- 55.9%)
PFS: 10 months	2.8 months



(II) Trophoblast surface antigen 2 TROP-2



- Transmembrane glycoprotein initially identified in trophoblast cells.
- Highly expressed in epithelial cancers such as lung adenocarcinoma, is associated with an aggressive oncogenic phenotype.
- Sacituzumab govitecan : selectively delivers topoisomerase I inhibitor SN-38, an active metabolite of irinotecan, to cancer cells and the surrounding tumor microenvironment

EVOKE-01 trial	a global, randomized, open-label, phase III study of SG versus docetaxel in advanced or metastatic NSCLC
ELIGIBILITY	• Age 18 years and older with pathologically documented NSCLC and measurable stage IV disease that progressed after platinum-based chemotherapy in combination or sequential with an anti–PD-(L)1–containing regimen. • Must have received treatment with ≥ one appropriate tyrosine kinase inhibitor (TKI), reflecting standard clinical practice. *EGFR*, *ALK*, and PD-L1 status were required before enrollment. • Patients with stable, previously treated brain metastases (prednisone ≤10 mg maximum per day or equivalent and neurologic symptoms returned to baseline for ≥4 weeks) were also eligible.
Intervention	From December 2013 to March 2016, 603 patients Randomly assigned (1:1) with stratification receive one 10 mg/kg intravenous infusion of SG (n=299) on days 1 and 8 or one 75 mg/m^2 intravenous infusion of docetaxel (n=304) on day 1 of every 21-day cycle.
End-points	The primary end point was overall survival (OS). Secondary efficacy end points were investigator-assessed progression-free survival (PFS), ORR (percentage of patients with confirmed CR or PR), DoR, disease control rate

Paz-Ares LG, Juan-Vidal O, Mountzios GS, et al. Sacituzumab Govitecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III EVOKE-01 Study. J Clin Oncol. 2024 Aug 20

TABLE 1. Patient Baseline Characteristics and Demographics

Characteristic	SG (n = 299)	Docetaxel (n = 304)
Age, years, median (range)	66 (31-84)	64 (32-83)
<65, No. (%)	136 (45.5)	161 (53.0)
≥65, No. (%)	163 (54.5)	143 (47.0)
Sex, No. (%)		
Male	194 (64.9)	216 (71.1)
Female	105 (35.1)	88 (28.9)
Race or ethnic group, No. (%)		
White	229 (76.6)	216 (71.1)
Black	6 (2.0)	7 (2.3)
Asian	17 (5.7)	26 (8.6)
Other/not specified[a]	47 (15.7)	55 (18.1)
ECOG PS,[b] No. (%)		
0	101 (33.8)	89 (29.3)
1	198 (66.2)	212 (69.7)
2[c]	0	1 (0.3)
Histology, No. (%)		
Nonsquamous[d]	215 (71.9)	224 (73.7)
Squamous	84 (28.1)	80 (26.3)
Disease stage at diagnosis,[e] No. (%)		
Stage I-III	76 (25.4)	102 (33.6)
Stage IV	219 (73.2)	202 (66.4)
Patients with brain metastasis, No. (%)	35 (11.7)	39 (12.8)
Previous lines of therapy, No. (%)		
1	167 (55.9)	167 (54.9)
2	103 (34.4)	101 (33.2)
≥3	29 (9.7)	36 (11.8)
Best response to last anti–PD-(L)1–containing regimen,[f] No. (%)		
Responder (CR/PR)	106 (35.5)	113 (37.2)
Nonresponder (SD/PD)	192 (64.2)	191 (62.8)
Not available	1 (0.3)	0
Previous therapy for AGA, No. (%)		
Yes	19 (6.4)	25 (8.2)
EGFR alteration[g]	6 (2.0)	13 (4.3)
ALK alteration[g]	1 (0.3)	1 (0.3)
No	280 (93.6)	279 (91.8)

Variable	SG (n = 299)	Docetaxel (n = 304)
OS, months, median (95% CI)	11.1 (9.4 to 12.3)	9.8 (8.1 to 10.6)
HR for death (95% CI), one-sided P[a]	0.84 (0.68 to 1.04), .0534	
OS in patients nonresponsive (SD/PD) to last anti–PD-(L)1 regimen, months, median (95% CI)	11.8 (9.6 to 12.5)	8.3 (7.0 to 10.6)
HR for death (95% CI)	0.75 (0.58 to 0.97)	
OS in patients responsive (CR/PR) to last anti–PD-(L)1 regimen, months, median (95% CI)	9.6 (8.1 to 14.4)	10.6 (8.9 to 12.8)
HR for death (95% CI)	1.09 (0.76 to 1.56)	
PFS (95% CI), months, median (95% CI)	4.1 (3.0 to 4.4)	3.9 (3.1 to 4.2)
HR for disease progression[b] or death (95% CI)	0.92 (0.77 to 1.11)	
ORR,[b,c] No. (%)	41 (13.7)	55 (18.1)
CR	0	3 (1.0)
PR	41 (13.7)	52 (17.1)
SD	161 (53.8)	149 (49.0)
PD	66 (22.1)	64 (21.1)
Not evaluable/not assessed	31 (10.4)	36 (11.8)
DCR,[d] No. (%)	202 (67.6)	204 (67.1)
DoR,[e] months, median (95% CI)	6.7 (4.4 to 9.8)	5.8 (4.1 to 8.3)
DoR rate at 6 months[e,f]	52.5 (35.6 to 66.9)	46.5 (31.9 to 59.8)

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; v1.1, version 1.1.

[a]On the basis of stratified log-rank test (two-sided $P = .1068$).

[b]Investigator-assessed per RECIST v1.1.

[c]Patients without tumor assessment (SG, n = 28; docetaxel, n =
tested.

[d]Disease control defined best overall response of confirmed C

[e]Evaluated in patients with confirmed CR or PR.

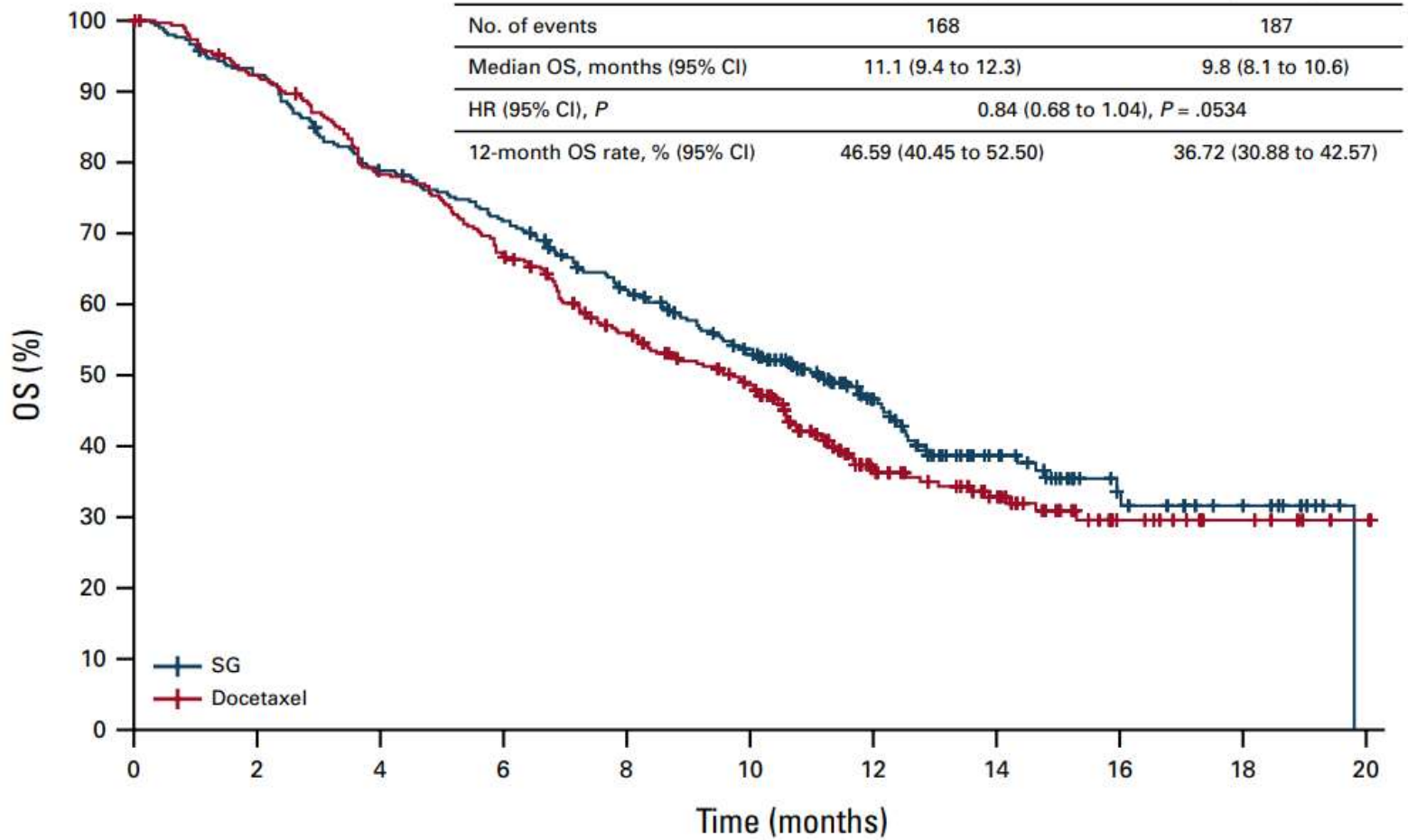
[f]On the basis of Kaplan-Meier estimates.

Comparator Standard of Care:
REVEL study, OS for docetaxel (median, 9.1 months; HR, 0.86 [95% CI, 0.75 to 0.98]

At the protocol-specified primary analysis, the study did not meet statistical significance for the primary end point of OS.
(powered to detect a hazard ratio (HR) of 0.7 for SG versus docetaxel at the one-sided alpha of .025)

A

	SG (n = 299)	Docetaxel (n = 304)
No. of events	168	187
Median OS, months (95% CI)	11.1 (9.4 to 12.3)	9.8 (8.1 to 10.6)
HR (95% CI), *P*	0.84 (0.68 to 1.04), *P* = .0534	
12-month OS rate, % (95% CI)	46.59 (40.45 to 52.50)	36.72 (30.88 to 42.57)



No. at risk:

SG	299	275	234	212	175	140	76	40	17	10	0
Docetaxel	304	277	234	201	158	128	64	41	15	7	2

B

Subgroup	OS Median, Months (95% CI) SG	Docetaxel	HR (95% CI)
Overall (N = 603)	11.1 (9.4 to 12.3)	9.8 (8.1 to 10.6)	0.84 (0.68 to 1.04)
Histology[a]			
Squamous (n = 164)	10.2 (8.1 to 12.7)	9.2 (6.9 to 11.0)	0.83 (0.56 to 1.22)
Nonsquamous (n = 439)	11.3 (9.4 to 12.6)	9.9 (7.8 to 10.8)	0.87 (0.68 to 1.11)
Response to last anti–PD-(L)1–containing regimen[a]			
Nonresponder (PD/SD) (n = 383)	11.8 (9.6 to 12.5)	8.3 (7.0 to 10.6)	0.75 (0.58 to 0.97)
Responder (CR/PR) (n = 219)	9.6 (8.1 to 14.4)	10.6 (8.9 to 12.8)	1.09 (0.76 to 1.56)
Received previous therapy for actionable genomic alteration[a]			
No (n = 559)	11.0 (9.2 to 12.3)	9.9 (8.1 to 10.7)	0.89 (0.72 to 1.11)
Yes (n = 44)	NR (7.2 to NR)	7.0 (5.2 to 11.6)	0.52 (0.22 to 1.23)
Geographic region			
United States (n = 60)	12.2 (7.9 to NR)	7.4 (5.1 to 14.2)	0.68 (0.36 to 1.27)
Canada/western EU/Australia (n = 455)	10.8 (8.9 to 12.3)	9.8 (7.9 to 10.6)	0.87 (0.69 to 1.10)
Rest of the world (n = 88)	10.2 (7.8 to NR)	12.8 (6.4 to NR)	0.98 (0.53 to 1.83)
Age group, years			
<65 (n = 297)	12.1 (9.7 to 14.7)	10.1 (7.3 to 10.8)	0.80 (0.59 to 1.08)
≥65 (n = 306)	9.9 (8.4 to 12.2)	9.6 (7.6 to 11.2)	0.90 (0.68 to 1.20)
Race			
White (n = 445)	10.7 (8.9 to 12.2)	8.9 (7.3 to 10.6)	0.87 (0.68 to 1.10)
Non-White (n = 65)	12.9 (12.9 to NR)	11.2 (9.3 to 15.3)	0.41 (0.15 to 1.13)
Baseline ECOG status			
0 (n = 190)	12.9 (10.0 to NR)	13.6 (10.4 to NR)	1.06 (0.70 to 1.60)
1 (n = 410)	9.6 (8.1 to 11.9)	7.6 (6.8 to 9.8)	0.81 (0.64 to 1.04)
Sex			
Male (n = 410)	9.5 (8.1 to 12.3)	8.5 (7.3 to 10.2)	0.89 (0.70 to 1.14)
Female (n = 193)	12.1 (10.6 to 16.0)	10.6 (8.2 to 13.9)	0.85 (0.58 to 1.26)

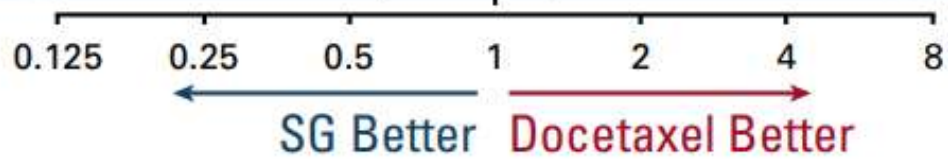


TABLE 3. Summary of Treatment-Emergent Adverse Events in All Treated Patients

	SG (n = 296), No. (%)		Docetaxel (n = 288), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAEs[a,b]	295 (99.7)	197 (66.6)	282 (97.9)	218 (75.7)
TEAEs reported in ≥10% in either group[c]				
Fatigue	168 (56.8)	37 (12.5)	161 (55.9)	28 (9.7)
Diarrhea	156 (52.7)	31 (10.5)	97 (33.7)	11 (3.8)
Alopecia	128 (43.2)	2 (0.7)	86 (29.9)	2 (0.7)
Nausea	123 (41.6)	5 (1.7)	75 (26.0)	3 (1.0)
Anemia	119 (40.2)	19 (6.4)	89 (30.9)	17 (5.9)
Neutropenia	111 (37.5)	73 (24.7)	123 (42.7)	106 (36.8)
Constipation	86 (29.1)	0	49 (17.0)	1 (0.3)
Decreased appetite	78 (26.4)	7 (2.4)	69 (24.0)	6 (2.1)
Vomiting	62 (20.9)	7 (2.4)	43 (14.9)	6 (2.1)
Cough	46 (15.5)	0	45 (15.6)	1 (0.3)
Dyspnea	42 (14.2)	4 (1.4)	51 (17.7)	13 (4.5)
Stomatitis	39 (13.2)	3 (1.0)	58 (20.1)	7 (2.4)
Leukopenia	38 (12.8)	15 (5.1)	63 (21.9)	50 (17.4)
Pruritus	37 (12.5)	1 (0.3)	11 (3.8)	0
Pyrexia	37 (12.5)	2 (0.7)	34 (11.8)	2 (0.7)
Back pain	33 (11.1)	2 (0.7)	19 (6.6)	2 (0.7)
Abdominal pain	31 (10.5)	3 (1.0)	14 (4.9)	0
Arthralgia	30 (10.1)	2 (0.7)	29 (10.1)	1 (0.3)
Rash	30 (10.1)	0	19 (6.6)	0
Febrile neutropenia	23 (7.8)	23 (7.8)	29 (10.1)	27 (9.4)
Lymphopenia	23 (7.8)	9 (3.0)	31 (10.8)	12 (4.2)
Peripheral edema	16 (5.4)	0	35 (12.2)	4 (1.4)
Dysgeusia	14 (4.7)	0	30 (10.4)	0
Peripheral neuropathy	11 (3.7)	0	38 (13.2)	2 (0.7)
Treatment-related[c]	279 (94.3)	156 (52.7)	262 (91.0)	173 (60.1)
TEAEs leading to discontinuation	29 (9.8)		48 (16.7)	
Treatment-related[c]	20 (6.8)		41 (14.2)	
TEAEs leading to death	10 (3.4)		13 (4.5)	
Treatment-related[d]	4 (1.4)		3 (1.0)	
TEAEs leading to dose reduction	87 (29.4)		112 (38.9)	
TEAEs leading to treatment interruption	171 (57.8)		81 (28.1)	

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

[a]TEAE is any AE with an onset date on or after the study drug start date and no later than 30 days after last dose of study drug.

[b]Coded according to MedDRA version 26.1 and AE severity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Multiple AEs were counted only once per participant for the highest severity grade for each preferred term.

[c]Determined by investigator.

[d]Treatment-related TEAEs that led to death, investigator-assessed, included cardiac failure, cerebrovascular accident, death, febrile neutropenia, hematemesis, ischemic stroke, myocardial ischemia, neutropenic colitis, sepsis, and septic shock (one each) in the SG group and death (n = 4), pneumonia (n = 3), cardiac failure, acute respiratory failure, cardiorespiratory arrest, intestinal obstruction, pneumonitis, and respiratory failure (one each) in the docetaxel group.

SG vs Docetaxel

- Trend towards benefit with SG :

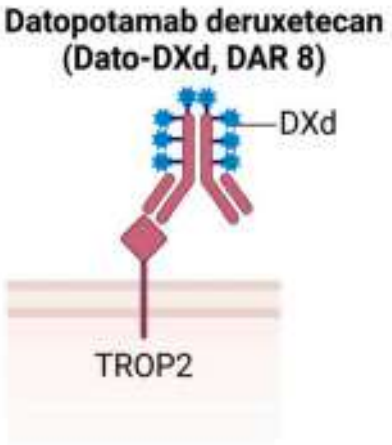
  (i) At 12 months, the OS rate for patients with SG was approximately 10% higher than with docetaxel,

  (ii) incidence of high-grade TEAEs and TEAEs leading to dis continuation were lower with SG than docetaxel

- Benefit seen in both squamous and non-squamous histologies
- Among those previously treated with anti–PD-(L) 1 :

3.5-month OS improvement was observed favoring SG over docetaxel, with 25% reduction in risk of death in patients who were nonresponsive to their last anti–PD-(L) 1–containing regimen.

(IIb) Datopotamab deruxtecan



- Consists of a TROP2-targeting antibody – datopotamab – conjugated to deruxtecan, an exatecan derivative topoisomerase I inhibitor, via a stable tetrapeptide-based cleavable linker

Study Name	Phase	Study Population	Treatment Arms	Primary Endpoint	Secondary Endpoint	ORR, confirmed	Median DOR	PFS	OS	Findings
TROPION-PanTumor01	I	Advanced/Metastatic NSCLC	Dato-DXd 4 mg/kg ($n = 40$), 6 mg/kg ($n = 50$), 8 mg/kg ($n = 80$)	Safety/tolerability	ORR, survival, pharmaco-kinetics	26% (95% CI 14.6–40.3) (6 mg/kg)	10.5 (95% CI 5.6–26.5) (6 mg/kg)	6.9 (95% CI 2.7–8.8) (6 mg/kg)	11.4 (95% CI 7.1–20.6) (6 mg/kg)	Recommended dose of 6 mg/kg
TROPION-Lung05	II	Advanced/Metastatic NSCLC with AGA	Dato-DXd (6 mg/kg)	ORR	DOR, safety/tolerability, survival	35.8% (95% CI 27.8–44.4)	7.0 (95% CI 4.2–9.8)	5.4 (95% CI 4.7–7.0)	13.6 (95% CI 9.9-NE[non evaluable])	Promising response in metastatic pretreated AGA population
TROPION-Lung01	III	Pretreated Advanced/Metastatic NSCLC, with and without AGA, squamous and nonsquamous	Dato-DXd (6 mg/kg) vs Docetaxel (75 mg/m^2), subcategories of squamous vs nonsquamous for each	PFS, OS	ORR, DOR, safety	Dato-DXd: 26.4 (95% CI 21.5–31.8), Docetaxel: 12.8 (95% CI 9.3–17.1)	Dato-DXd: 7.1 (95% CI 5.6–10.9), Docetaxel: 5.6 (95% CI 5.4–8.1)	Dato-DXd: 4.4 (95% CI 4.2–5.6), Docetaxel: 3.7 (95% CI 2.9–4.2)	Dato-DXd: 12.9 (95% CI 11.0-13.9), Docetaxel: 11.8 (95% CI 10.1–12.8)	Significantly improved PFS and a non statistically significant increase in OS for nonsquamous histology

TROPION-Lung01	randomized, open-label, global phase III study for Dato-DXd versus docetaxel in patients with advanced/ metastatic NSCLC
ELIGIBILITY	• Age 18 years and older with stage IIIB/C or IV NSCLC. • Patients without actionable genomic alterations must have only received platinum-based chemotherapy and anti–PD-1/PD-L1 immunotherapy. • Patients with protocol-specified actionable genomic alterations (EGFR, ALK, ROS1, NTRK, BRAF, MET exon14skipping,orRET) must have received one to two lines of targeted therapy and platinum-based chemotherapy, with or without anti–PD-1/PD-L1. • Patients with inactive or treated asymptomatic brain metastases.
Exclusion	• Current or suspected diagnosis or history of interstitial lung disease (ILD) requiring steroids.
Intervention	February 17, 2021, and November 7, 2022 Patients were randomly assigned 1:1 (stratified by histology, actionable genomic alteration status, geographic region, and immediate previous therapy with anti–PD-1/PD-L1) to receive Dato-DXd 6 mg/kg (**299 patients**) or docetaxel 75 mg/m2 (**305 patients**) intravenously once every 3 weeks until disease progression,
End-points	The dual primary end points were progression-free survival (PFS) and overall survival (OS). Objective response rate (ORR), duration of response (DOR), and safety were secondary end points.

Ahn MJ, Tanaka K, Paz-Ares L, Cornelissen R, et al TROPION-Lung01 Trial Investigators. Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study. J Clin Oncol. 2025 Jan 20;43(3):260-272.

Characteristic	Dato-DXd (n = 299)	Docetaxel (n = 305)
Age, years, median (range)	63.0 (26.0-84.0)	64.0 (24.0-88.0)
Sex, male, No. (%)	183 (61.2)	210 (68.9)
Race, No. (%)		
White	123 (41.1)	126 (41.3)
Asian	119 (39.8)	120 (39.3)
Black or African American	6 (2.0)	4 (1.3)
American Indian or Alaska Native	1 (0.3)	0
Other/missing	50 (16.7)	55 (18.0)
Ethnic group, No. (%)		
Hispanic or Latino	10 (3.3)	8 (2.6)
Not Hispanic or Latino	251 (83.9)	253 (83.0)
Unknown/missing	38 (12.7)	44 (14.4)
Geographic region, No. (%)		
Europe	137 (45.8)	152 (49.8)
Asia	113 (37.8)	118 (38.7)
North America	39 (13.0)	26 (8.5)
Australia	7 (2.3)	8 (2.6)
South America	3 (1.0)	1 (0.3)
Smoking status, No. (%)		
Current	39 (13.0)	42 (13.8)
Former	199 (66.6)	209 (68.5)
Never	61 (20.4)	52 (17.0)
Missing	0	2 (0.7)
ECOG performance status score, No. (%)[a]		
0	89 (29.8)	94 (30.8)
1	210 (70.2)	211 (69.2)
Histology, No. (%)		
Adenocarcinoma	222 (74.2)	223 (73.1)
Large cell	2 (0.7)	1 (0.3)
Squamous	65 (21.7)	71 (23.3)
Other	10 (3.3)	10 (3.3)
Actionable genomic alterations, No. (%)		
Absent	249 (83.3)	254 (83.3)
Present	50 (16.7)	51 (16.7)
PD-L1 expression, No. (%)		
<1%	104 (34.8)	116 (38.0)
≥1%	158 (52.8)	147 (48.2)
Unknown/missing	11 (3.7)	9 (3.0)
Not done	26 (8.7)	33 (10.8)
Brain metastases at baseline, No. (%)	79 (26.4)	91 (29.8)
Previous cancer therapy, No. (%)		
Platinum chemotherapy	297 (99.3)	305 (100)
Nonplatinum chemotherapy	298 (99.7)	304 (99.7)
Anti–PD-L1 therapy	263 (88.0)	268 (87.9)
Targeted therapy	46 (15.4)	50 (16.4)
Other	60 (20.1)	64 (21.0)
Previous lines of systemic therapy for metastatic disease, No. (%)[b]		
1	167 (55.9)	174 (57.0)
2	108 (36.1)	102 (33.4)
3	17 (5.7)	23 (7.5)
≥4	5 (1.7)	5 (1.6)

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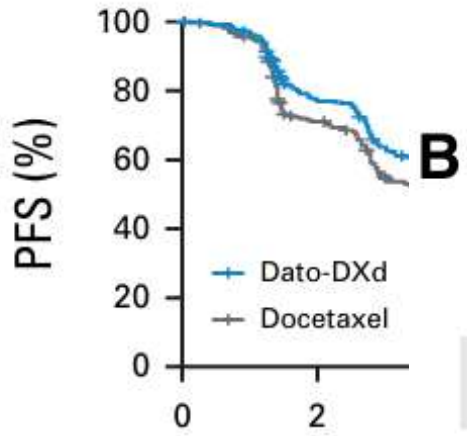
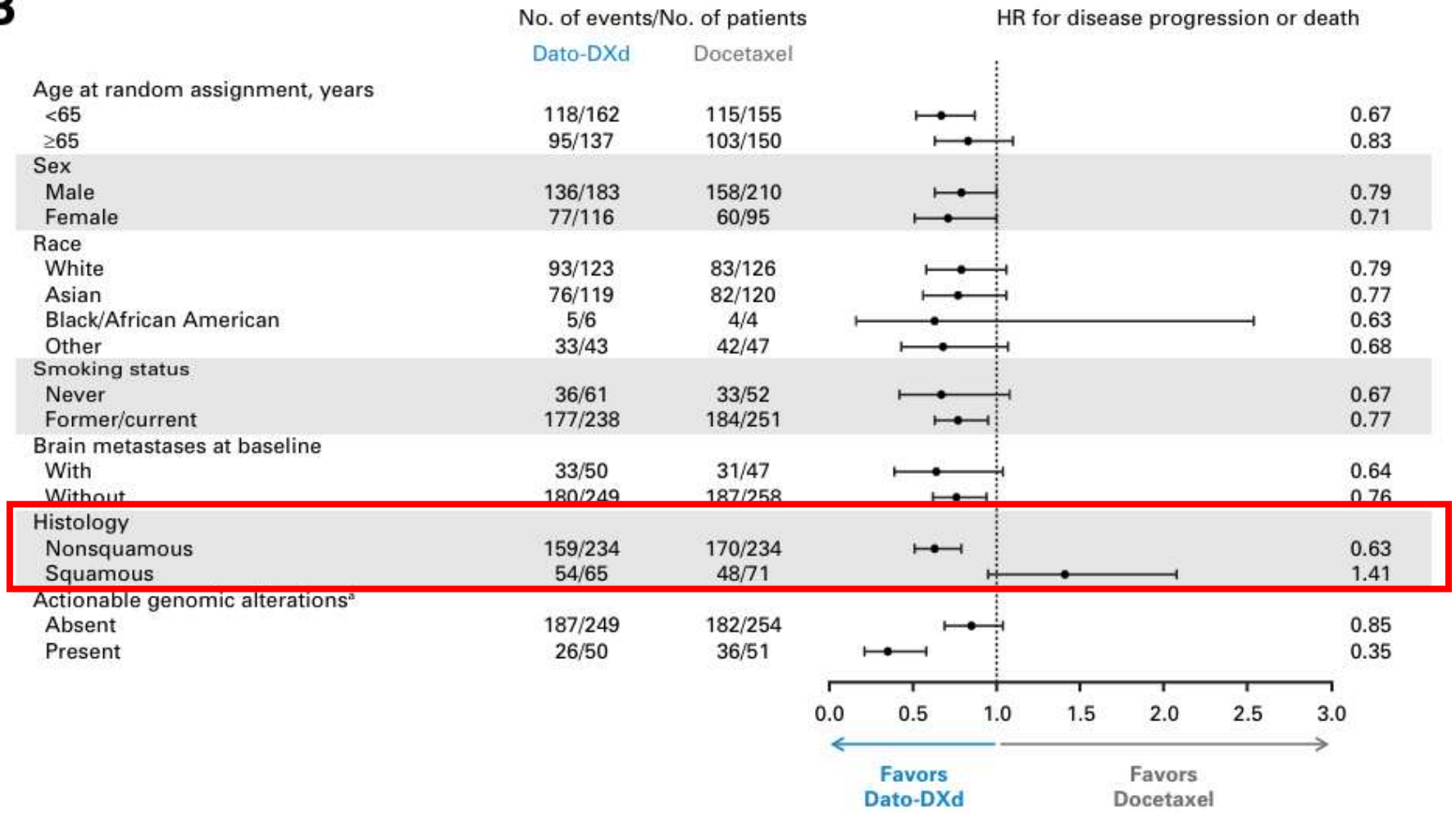


Number at risk

Dato-DXd	299	216
Docetaxel	305	186

B

	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)



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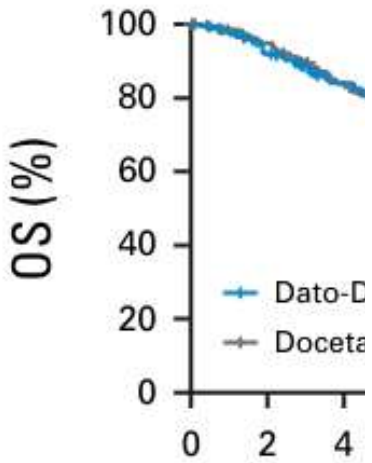
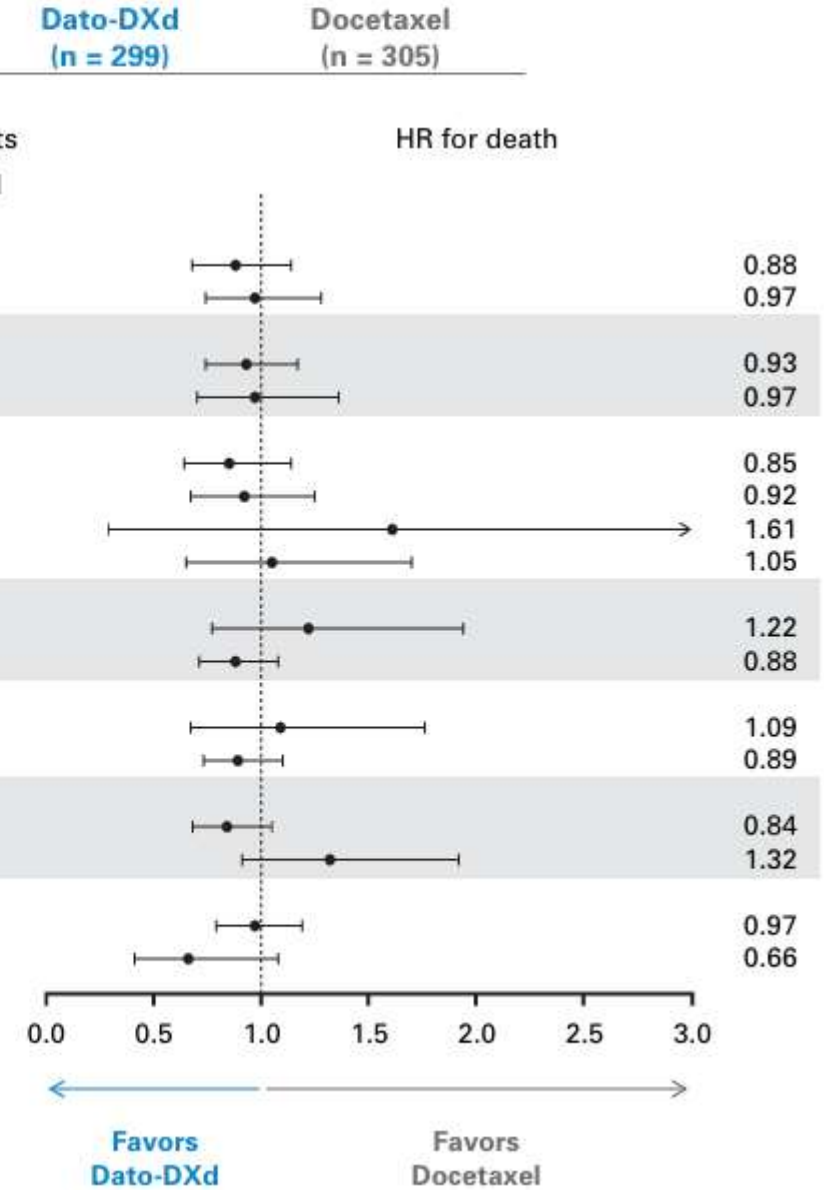


Number at risk

Dato-DXd	299	272	242
Docetaxel	305	273	239

B

	No. of events/No. of patients	
	Dato-DXd	Docetaxel
Age at random assignment, years		
<65	117/162	112/155
≥65	98/137	106/150
Sex		
Male	136/183	156/210
Female	79/116	62/95
Race		
White	90/123	95/126
Asian	83/121	79/120
Black/African American	4/6	2/4
Other	33/43	35/47
Smoking status		
Never	43/60	31/52
Former/current	172/239	186/251
Brain metastases at baseline		
With	37/50	31/47
Without	178/249	187/258
Histology		
Nonsquamous	160/234	163/234
Squamous	55/65	55/71
Actionable genomic alterations[a]		
Absent	182/249	185/254
Present	33/50	33/51



Variable	All Patients	
	Dato-DXd (n = 299)	Docetaxel (n = 305)
PFS, months, median (95% CI)[a,b]	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)
HR for disease progression or death (95% CI)	0.75 (0.62 to 0.91)	
P	.004	
OS, months, median (95% CI)[c,d]	12.9 (11.0 to 13.9)	11.8 (10.1 to 12.8)
HR for death (95% CI)	0.94 (0.78 to 1.14)	
P	.530	
Confirmed ORR, No.[a,e]	79	39
Percent (95% CI)	26.4 (21.5 to 31.8)	12.8 (9.3 to 17.1)
Best overall response, No. (%)[a]		
CR	4 (1.3)	0
PR	75 (25.1)	39 (12.8)
SD	149 (49.8)	153 (50.2)
Non-CR/non-PD	3 (1.0)	6 (2.0)
PD	46 (15.4)	64 (21.0)
NE	22 (7.4)	43 (14.1)
DCR, No.[a,f]	231	198
Percent (95% CI)	77.3 (72.1 to 81.9)	64.9 (59.3 to 70.3)
DOR, months, median (95% CI)[a,g]	7.1 (5.6 to 10.9)	5.6 (5.4 to 8.1)
TTR, months, median[a]	1.6	2.6

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TABLE 4. TRAEs Observed in ≥15% of Patients and Adjudicated Drug-Related ILD or Pneumonitis

	Dato-DXd (n = 297), No. (%)		Docetaxel (n = 290), No. (%)	
Patients With Events	Any Grade	Grade ≥3	Any Grade	Grade ≥3
GI disorders[a]				
Stomatitis	141 (47.5)	20 (6.7)	45 (15.5)	3 (1.0)
Nausea	101 (34.0)	7 (2.4)	48 (16.6)	3 (1.0)
Diarrhea	30 (10.1)	1 (0.3)	55 (19.0)	4 (1.4)
Hematologic disorders[a]				
Anemia[b]	44 (14.8)	12 (4.0)	60 (20.7)	12 (4.1)
Neutropenia[c]	14 (4.7)	2 (0.7)	76 (26.2)	68 (23.4)
Leukopenia[d]	9 (3.0)	0	45 (15.5)	38 (13.1)
Skin and subcutaneous tissue disorders[a]				
Alopecia	95 (32.0)	0	101 (34.8)	1 (0.3)
Metabolism and nutrition disorders[a]				
Decreased appetite	68 (22.9)	1 (0.3)	46 (15.9)	1 (0.3)
General disorders and administration site conditions[a]				
Asthenia	56 (18.9)	8 (2.7)	56 (19.3)	5 (1.7)
Adjudicated drug-related ILD or pneumonitis[e]	26 (8.8)	11 (3.7)	12 (4.1)	4 (1.4)

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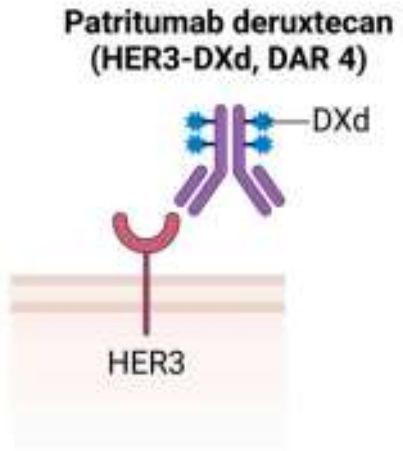
TROPION-Lung01

- PFS showed a statistically significant improvement for Dato-DXd over docetaxel in patients with pre-treated advanced/metastatic NSCLC.
- In patients with non-squamous histology, PFS with Dato-DXd was superior to what was seen with docetaxel.
- OS, did not reach statistical significance in the full analysis set.
- In non-squamous NSCLC, patients with and without actionable genomic alterations had better PFS, OS with Dato-DXd.

Patritumab Deruxtecan Biologics License Application for Patients With Previously Treated Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer Voluntarily Withdrawn

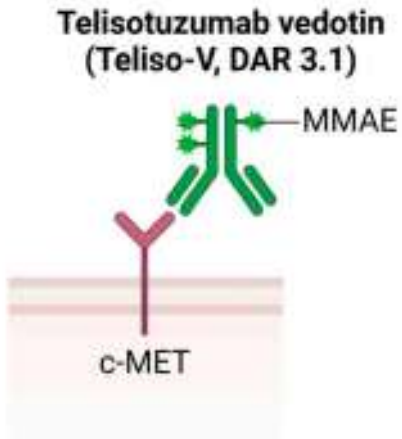


May 29, 2(

BASKING RIDGE, N.J. & RAHWAY, N.J., May 29, 2025 – The Biologics License Application (BLA) seeking accelerated approval in the U.S. for Daiichi Sankyo (TSE: 4568) and Merck's (NYSE: MRK), known as MSD outside of the United States and Canada, patritumab deruxtecan (HER3-DXd), based on the HERTHENA-Lung01 Phase 2 trial for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies, has been voluntarily withdrawn.

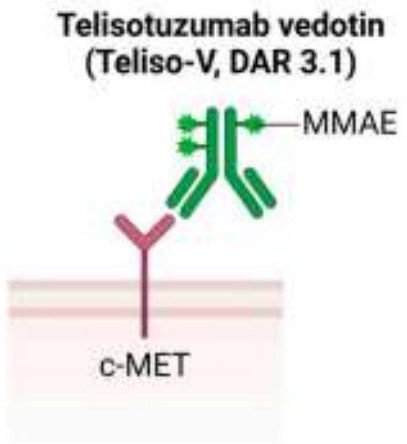
The decision to withdraw the BLA is based on topline overall survival (OS) results from the confirmatory HERTHENA-Lung02 Phase 3 trial where OS did not meet statistical significance, as well as discussions with the U.S. Food and Drug Administration. The decision is unrelated to the Complete Response Letter that was received in June 2024 and outlined findings pertaining to an inspection of a third-party manufacturing facility.

(IV) Telisotuzumab vedotin



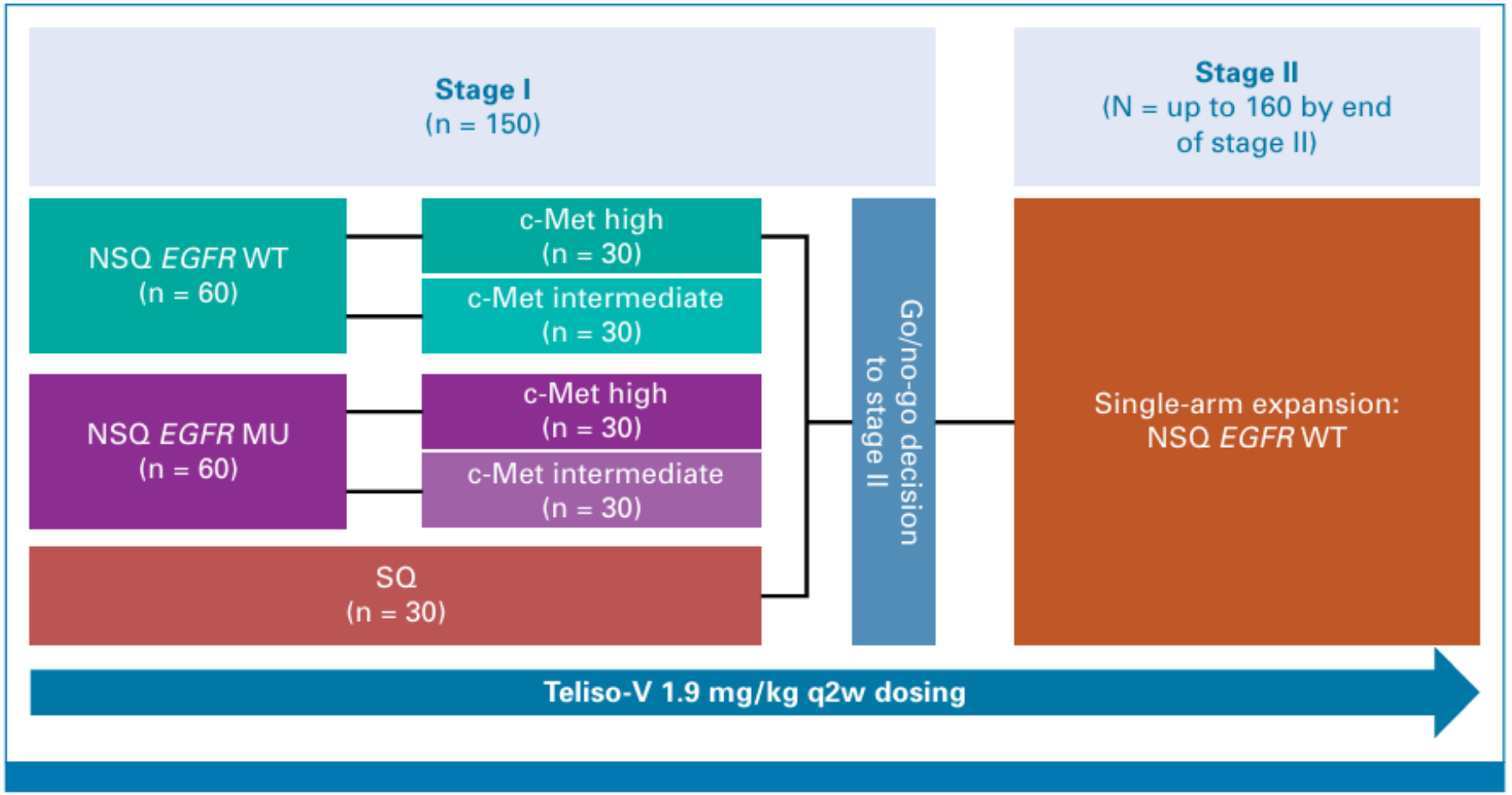
- MET proto-oncogene encodes the c-Met protein (also known as MET protein and proliferation, survival, and angiogenesis
- C-MET protein overexpression: 25%-39% of patients with NSCLC

- Telisotuzumab vedotin: the monoclonal antibody telisotuzumab conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE) via a cleavable di-peptide linker



On 14 May 2025, telisotuzumab vedotin received accelerated approval in the USA for the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC with high c-Met protein overexpression [≥ 50% of tumour cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy

LUMINOSITY	A phase II, multicenter, nonrandomized, two-stage study Stage I enrolled patients into three cohorts defined by histology and *EGFR* mutation status: (1) c-Met protein-overexpressing, nonsquamous *EGFR*-wildtype NSCLC, (2) c-Met protein-overexpressing, nonsquamous *EGFR*-mutant NSCLC, and (3) c-Met protein-overexpressing squamous NSCLC. Patients with c-Met protein-overexpressing, nonsquamous *EGFR*-wildtype were enrolled in stage II.
ELIGIBILITY	• Adults (age ≥18 years) with locally advanced/metastatic, c-Met protein–overexpressing, nonsquamous NSCLC with known EGFR status or squamous cell NSCLC were enrolled. • c-Met protein–overexpressing, nonsquamous EGFR wildtype NSCLC was required for stage II. • ECOG status 0-1, measurable disease per RECIST v1.1, and ≤2 lines of previous systemic therapy in the locally advanced/metastatic setting, including cytotoxic chemo therapy (maximum one line), immunotherapy, and therapy targeting driver gene alterations (if eligible).
EXCLUSION	History of interstitial lung disease (ILD) or pneumonitis that required systemic steroid treatment
Intervention	Teliso-V dosed at 1.9 mg/kg IV once every 2 weeks in stages I and II.
End-points	The primary end point was overall response rate (ORR) Sec ondary end points were duration of response (DOR), disease control rate (DCR; per RECIST v1.1), progression-free sur vival (PFS), and overall survival (OS).



Camidge DR, Bar J, Horinouchi H, et alTelisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011..

- The aim was to identify the population best suited for Teliso-V in the second or third line (stage I) and to further assess the efficacy and safety in the selected population (stage II).

- The c-Met protein–overexpressing, nonsquamous EGFR-wildtype NSCLC population was selected for further evaluation in stage II.

(overexpression : ≥ 25 % of tumor cells with membrane staining at 3+ intensity)

Camidge DR, Bar J, Horinouchi H, et alTelisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011..

- The non-squamous EGFR-wildtype NSCLC cohort met protocol-specified criteria for expansion at Interim Analysis 3 .
- The squamous and nonsquamous EGFR-mutant cohorts met protocol-specified criteria for futility at Interim Analyses 3 and 4,respectively.

TABLE 1. Baseline Demographics and Disease Characteristics of Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Characteristic	c-Met High (n = 78)	c-Met Intermediate (n = 83)	c-Met OE Total (N = 161)[a]
Age, years, median (range)	64.0 (38-83)	66.0 (38-82)	64.0 (33-83)
Sex, No. (%)			
Male	58 (74.4)	53 (63.9)	111 (68.9)
Female	20 (25.6)	30 (36.1)	50 (31.1)
Race, No. (%)			
White	51 (65.4)	59 (71.1)	110 (68.3)
Black or African American	1 (1.3)	2 (2.4)	3 (1.9)
Asian	26 (33.3)	22 (26.5)	48 (29.8)
Region, No. (%)			
North America	9 (11.5)	19 (22.9)	28 (17.4)
Asia	25 (32.1)	19 (22.9)	44 (27.3)
Europe	29 (37.2)	22 (26.5)	51 (31.7)
Rest of world	15 (19.2)	23 (27.7)	38 (23.6)
Tobacco use, No. (%)			
Current	10 (12.8)	15 (18.1)	25 (15.5)
Former	54 (69.2)	47 (56.6)	101 (62.7)
Never	14 (17.9)	21 (25.3)	35 (21.7)
Stage IV at study entry, No. (%)	77 (98.7)	81 (97.6)	158 (98.1)
Brain metastasis, No. (%)	14 (17.9)	19 (22.9)	33 (20.5)
ECOG performance status, No. (%)			
0	20 (25.6)	27 (32.5)	47 (29.2)
1	57 (73.1)	56 (67.5)	113 (70.2)
2	1 (1.3)	0	1 (0.6)
No. of previous systemic cancer therapies, median (range)	1 (1-3)	1 (1-3)	1 (1-3)
Type of previous systemic cancer therapies, n (%)			
Platinum-based	75 (96.2)	82 (98.9)	157 (97.5)
Immune checkpoint inhibitor–based	66 (84.6)	66 (79.5)	132 (82.0)
Targeted therapy[b,c]	4 (5.1)	8 (9.6)	12 (7.5)

TABLE 2. Efficacy Summary in Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Outcome	c-Met High (n = 78)	c-Met Intermediate (n = 83)	c-Met OE Total (N = 161)
ORR,[a] % (95% CI)	34.6 (24.2 to 46.2)	22.9 (14.4 to 33.4)	28.6 (21.7 to 36.2)
DCR,[a] % (95% CI)	60.3 (48.5 to 71.2)	57.8 (46.5 to 68.6)	59.0 (51.0 to 66.7)
DOR,[a] months, median (95% CI)	9.0 (4.2 to 13.0)	7.2 (5.3 to 11.5)	8.3 (5.6 to 11.3)
DOR ≥6 months,[a] n/no. of responders (%)	17/27 (63.0)	9/19 (47.4)	26/46 (56.5)
PFS,[a] median, months (95% CI)	5.5 (4.1 to 8.3)	6.0 (4.5 to 8.1)	5.7 (4.6 to 6.9)
6-month PFS,[a,b] % (95% CI)	45.8 (33.8 to 57.1)	50.1 (37.9 to 61.1)	48.0 (39.5 to 56.1)
OS, months, median (95% CI)	14.6 (9.2 to 25.6)	14.2 (9.6 to 16.6)	14.5 (9.9 to 16.6)
12-month OS,[b] % (95% CI)	57.0 (45.0 to 67.4)	55.0 (43.5 to 65.2)	56.0 (47.7 to 63.4)

Abbreviations: DCR, disease control rate; DOR, duration of response; *EGFR*, epidermal growth factor receptor; NE, not estimable; NSCLC, non–small cell lung cancer; OE, overexpressing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]Per independent central review.

[b]Estimated using the Kaplan-Meier method.

Camidge DR, Bar J, Horinouchi H, et alTelisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011..

- Highest ORR - patients with c-Met protein–overexpressing, non-squamous EGFR-wild type NSCLC.
- Contrasts with studies evaluating ADCs targeting trophoblast antigen 2 (TROP2) in NSCLC, where TROP2 expression was not predictive of response
- DCR, PFS, and OS were comparable between c-Met high, c-Met interme diate, and c-Met total overexpression - Teliso-V efficacious in patients with c-Met protein–overexpressing tumors regardless of the level of expression.

Camidge DR, Bar J, Horinouchi H, et alTelisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. J Clin Oncol. 2024 Sep 1;42(25):3000-3011..

TABLE A4. Investigator-Assessed Overall Response Rates of Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Response Rate	c-Met High (n = 78)	c-Met Intermediate (n = 83)	NSQ *EGFR* WT NSCLC Total (N = 161)
ORR (CR + PR) [95% CI]	29 (37.2) [26.5 to 48.9]	18 (21.7) [13.4 to 32.1]	47 (29.2) [22.3 to 36.9]

Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; ORR, overall response rate; PR, partial response; WT, wildtype.

Study	Setting	Result
LUME-Lung 1	Docetaxel with or without nintedanib in patients whose NSCLC progressed after first-line chemotherapy	ORR per ICR was 4.7 % for docetaxel plus nintedanib and 3.6% for docetaxel plus placebo
REVEL trial	Docetaxel with or without Ramucirumab	ORR 21.9% (95%CI,18.3 to 26.0) for docetaxel plus ramucirumab and 14.5% (95%CI,11.4 to 18.2) for docetaxel plus placebo
CheckMate 057	NSCLC that had progressed during or after platinum-based doublet chemotherapy : nivolumab vs docetaxel	OS at 18 months was 39% (95% CI, 34 to 45) with nivolumab versus 23% (95% CI, 19 to 28) with docetaxel.

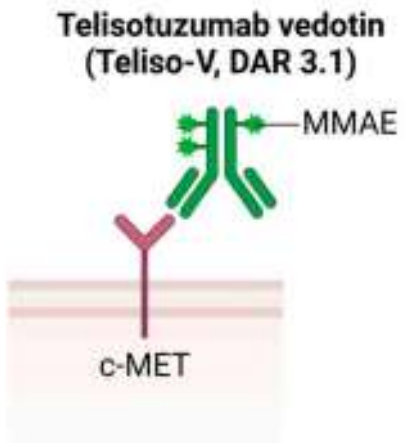
TABLE 3. The Most Common Any-Grade and Grade ≥3 TRAEs Experienced by Patients in the c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC Cohort

	c-Met High (n = 84), No. (%)		c-Met Intermediate (n = 84), No. (%)		c-Met OE Total (N = 172), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAE	83 (98.8)	50 (59.5)	80 (95.2)	45 (53.6)	167 (97.1)	97 (56.4)
TRAE	68 (81.0)	25 (29.8)	69 (82.1)	23 (27.4)	140 (81.4)	48 (27.9)
TRAEs occurring in >5% of patients in the NSQ *EGFR* WT NSCLC population						
Peripheral sensory neuropathy	24 (28.6)	5 (6.0)	27 (32.1)	7 (8.3)	52 (30.2)	12 (7.0)
Peripheral edema	17 (20.2)	2 (2.4)	11 (13.1)	1 (1.2)	28 (16.3)	3 (1.7)
Fatigue	11 (13.1)	3 (3.6)	12 (14.3)	1 (1.2)	24 (14.0)	4 (2.3)
Decreased appetite	7 (8.3)	0	13 (15.5)	1 (1.2)	20 (11.6)	1 (0.6)
Increased alanine aminotransferase	8 (9.5)	2 (2.4)	11 (13.1)	4 (4.8)	19 (11.0)	6 (3.5)
Pneumonitis[a]	11 (13.1)	3 (3.6)	7 (8.3)	2 (2.4)	18 (10.5)	5 (2.9)
Hypoalbuminemia	10 (11.9)	0	8 (9.5)	0	18 (10.5)	0
Nausea	6 (7.1)	0	11 (13.1)	0	17 (9.9)	0
Vision blurred	11 (13.1)	1 (1.2)	5 (6.0)	1 (1.2)	16 (9.3)	2 (1.2)
Increased aspartate aminotransferase	7 (8.3)	0	9 (10.7)	0	16 (9.3)	0
Asthenia	4 (4.8)	1 (1.2)	9 (10.7)	0	13 (7.6)	1 (0.6)
Anemia	7 (8.3)	1 (1.2)	2 (2.4)	0	10 (5.8)	1 (0.6)
Increased gamma-glutamyltransferase	5 (6.0)	1 (1.2)	5 (6.0)	0	10 (5.8)	1 (0.6)
Keratitis	5 (6.0)	0	5 (6.0)	0	10 (5.8)	0
Peripheral neuropathy	6 (7.1)	1 (1.2)	3 (3.6)	0	9 (5.2)	1 (0.6)
Decreased weight	4 (4.8)	0	4 (4.8)	0	9 (5.2)	0

NOTE. Considered possibly related to study drug by the investigator. TRAEs are shown by the MedDRA Preferred Term according to investigative site reporting.

Abbreviations: *EGFR*, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OE, overexpressing; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WT, wildtype.

[a]Pneumonitis events shown are those with a MedDRA preferred term of pneumonitis according to the investigative site reporting. In addition, TRAEs with a preferred term of ILD according to investigative site reporting were noted in 4 (2.3%) patients with c-Met OE total (c-Met high, n = 2 [2.4%]; c-Met intermediate, n = 2 [2.4%]). Investigative site-reported events of potential ILD, including the terms of pneumonitis and ILD, were also adjudicated as ILD or not ILD by an independent committee. Adjudicated events of ILD occurred in 17 patients (9.9%); nine had events adjudicated as grade ≥3 (5.2%), of which three were grade 5.



On 14 May 2025, telisotuzumab vedotin received accelerated approval in the USA for the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC with high c-Met protein overexpression [≥ 50% of tumour cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy

Results from a phase Ib study of telisotuzumab vedotin in combination with osimertinib in patients with c-Met protein-overexpressing, *EGFR*-mutated locally advanced/metastatic non-small-cell lung cancer (NSCLC) after progression on prior osimertinib

A total of 38 patients received Teliso-V (1.6 mg/kg, *n* = 20; 1.9 mg/kg, *n* = 18) plus osimertinib and were included in this analysis. No dose-limiting toxicities were observed. Most frequent any-grade treatment-emergent adverse events (TEAEs) were peripheral sensory neuropathy (50%), peripheral edema (32%), and nausea (24%). Most common grade 3/4 TEAEs were anemia (11%) and pulmonary embolism (8%). Five TEAEs led to death; none were reported as being related to Teliso-V or osimertinib. The pharmacokinetic profile of Teliso-V plus osimertinib was similar to Teliso-V monotherapy. After a median follow-up of 7.4 months, the ORR was 50.0% per independent central review (ICR) (DOR not reached), and median PFS per ICR was 7.4 months (95% confidence interval 5.4 months-not reached).

Horinouchi H, Cho BC, Camidge DR, et al Results from a phase Ib study of telisotuzumab vedotin in combination with osimertinib in patients with c-Met protein-overexpressing, EGFR-mutated locally advanced/metastatic non-small-cell lung cancer (NSCLC) after progression on prior osimertinib. Ann Oncol. 2025 May;36(5):583-591

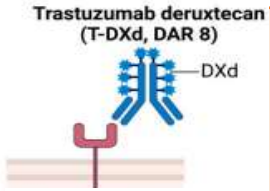
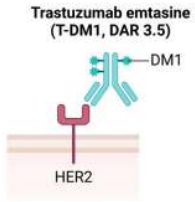
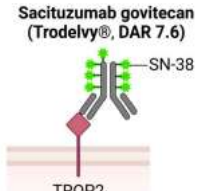
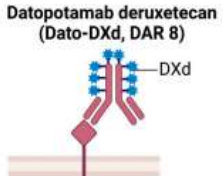
Future directives: Combined ADC and ICI

Rationale: When combined with ADCs, immune checkpoint inhibitors can activate previously suppressed T cells, further improving the immune system's ability to clear tumors.

Ongoing studies:

ADC	Immunotherapy
Trastuzumab Deruxtecan (T-DXd)	Nivolumab (PD-1 inhibitor)
Datopotamab Deruxtecan (Dato-DXd)	Pembrolizumab (PD-1 inhibitor) +/- Chemo
Sacituzumab Govitecan (SG)	Pembrolizumab (PD-1 inhibitor)
Patritumab Deruxtecan (HER3-DXd)	Osimertinib (EGFR-TKI)
Telisotuzumab vedotin	Osimertinib

Summary

Target		ADCs	Indications	Key clinical research results
HER2		Trastuzumab Deruxtecan (T-DXd)	Advanced NSCLC with HER2 mutation (second-line treatment)	**DESTINY-Lung02:** Confirmed ORR by BICR 50%, PFS 10 months, ILD 5.9% in 5.4 mg/kg
HER2		Trastuzumab Emtansine (T-DM1)	HER2 exon 20 insertion mutation NSCLC (second-line)	**Phase II:** ORR 38.1%, mPFS 2.8 mo, mOS 8.1 mo; Grade ≥ 3 TEAEs 14.3%.
TROP2		Sacituzumab Govitecan (SG)	Advanced NSCLC (late-line treatment)	**EVOKE-1:** OS 11.1 mo, HR 0.84 vs Docetaxel, trend to resp in previosly treated PD-L1. Grade ≥ 3 neutropenia 25%.
TROP2		Datopotamab deruxtecan	Advanced NSCLC	**Tropion-Lung 01:** PFS 4.4 mo, OS 12.9 mo, vs Docetaxel. Grade ≥ 3 TEAEs Stomatitis 6%, ILD 3.7%
c-MET		Telisotuzumab Vedotin (Teliso-V)	c-MET overexpression NSCLC	**LUMINOSITY:** ORR 35% (high-expression group), PFS 5.7 mo; Peripheral neuropathy 30%.

Thank you