High lights from ESMO 2023 Updates in NSCLC management

DR .Tariq Alhamdi
Medical Oncologist
Syrian medical oncology association meeting
Aleppo 14-15-16 December 2023

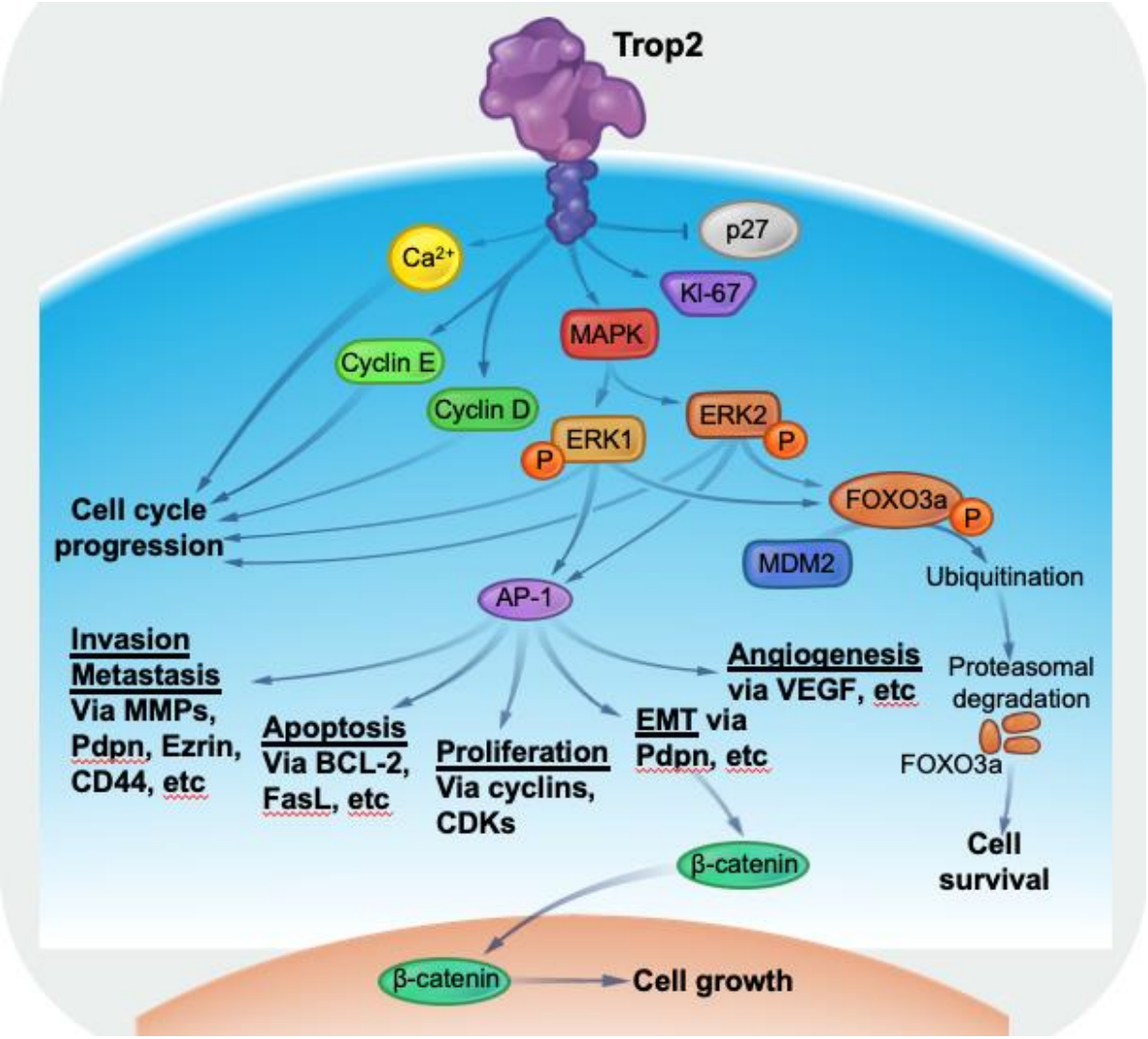
Questions need to answers

- Is it Time for antibody–drug conjugate (ADC) in NSCLC?
- Does Immunotherapy still the legend?
- Between Neoadjuvant and metastatic cases , do we need more of view points ?

Trophoblast Antigen 2

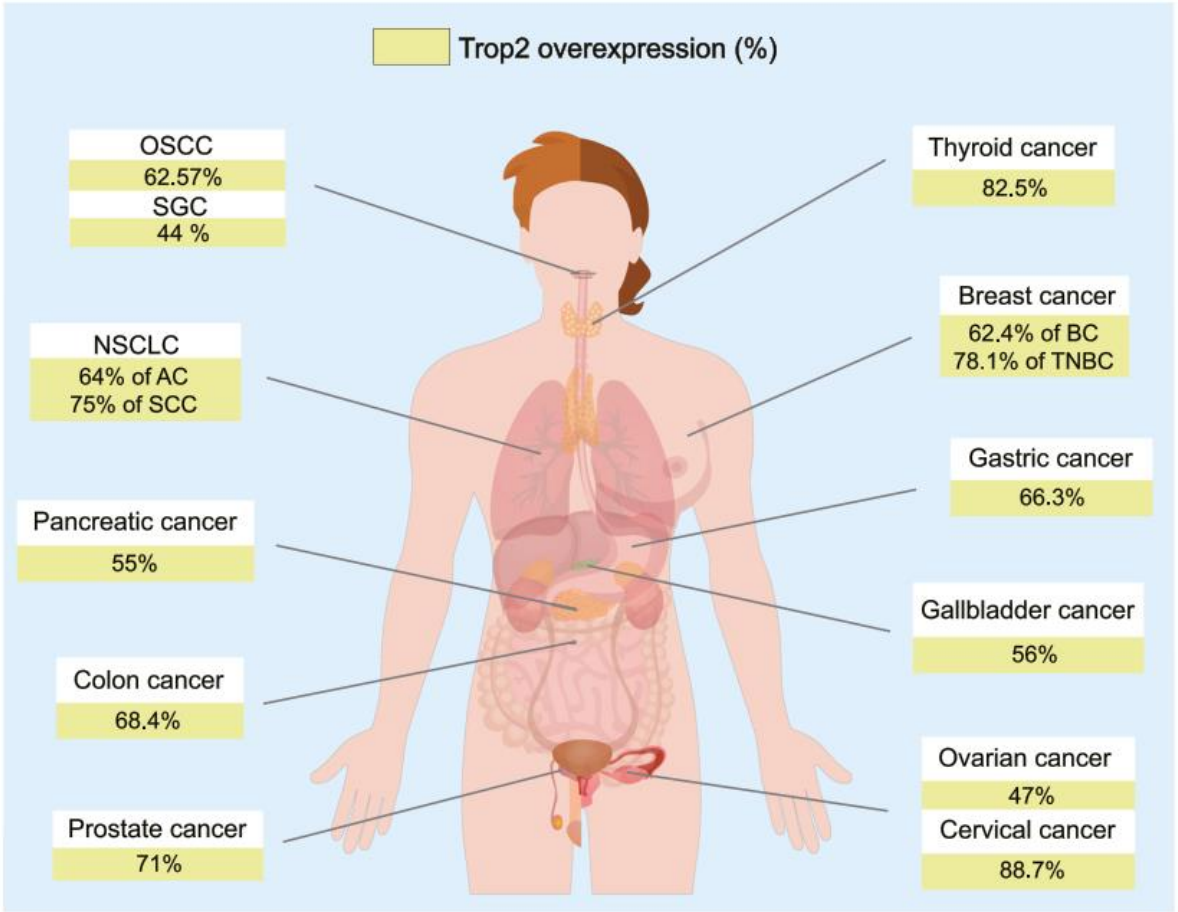
- TROP2 is a transmembrane glycoprotein overexpressed in many solid tumors[1]
  - TNBC and NSCLC are associated with TROP2 overexpression[2,3]
- TROP2 is an epithelial adhesion molecule and stem cell marker associated with cell regeneration[1]

TROP2: Cell Signaling



Slide credit: clinicaloptions.com

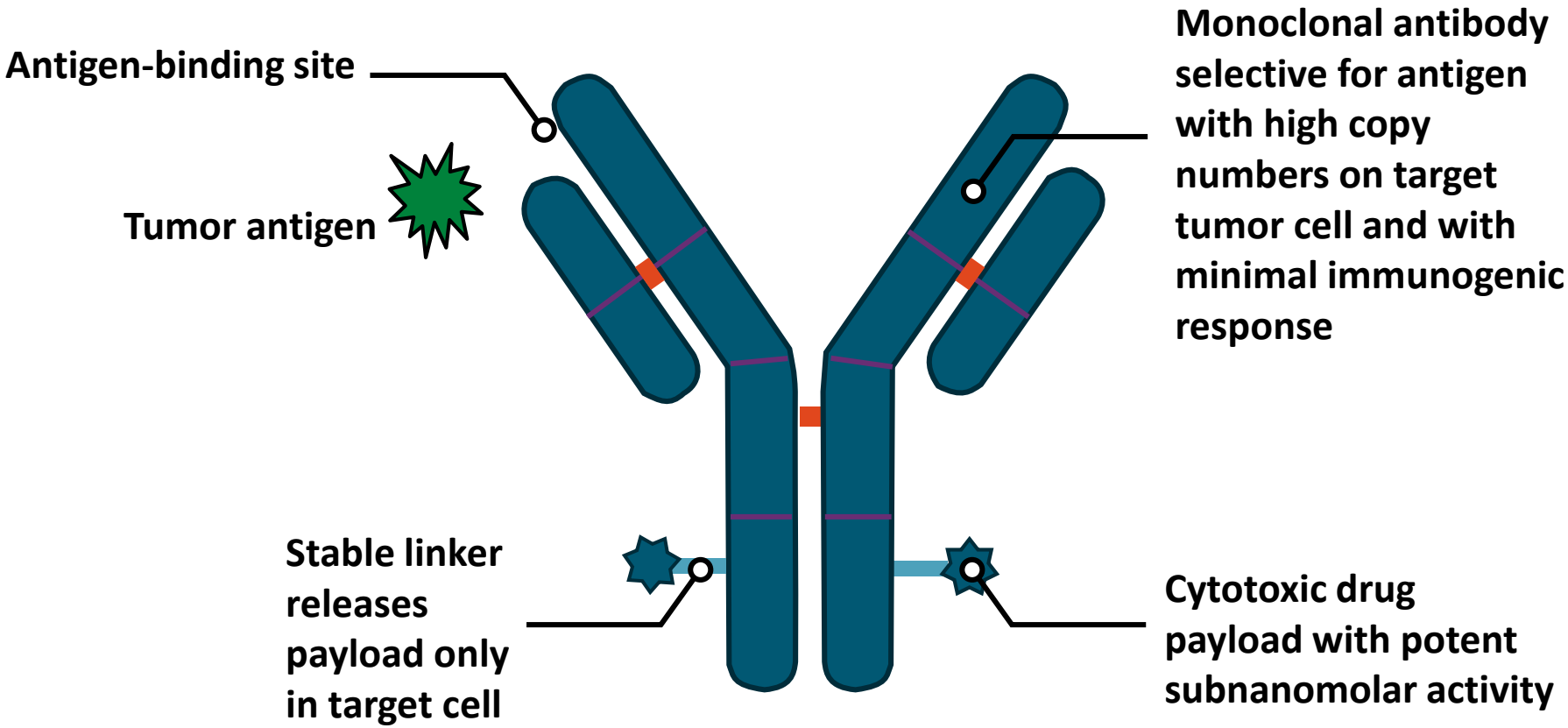
TROP-2 Overexpression in NSCLC and Other Cancers



Slide credit: clinicaloptions.com

What Are Antibody–Drug Conjugates?

- Monoclonal antibody linked to a cytotoxic drug designed to widen the therapeutic window by focusing delivery to specific cells



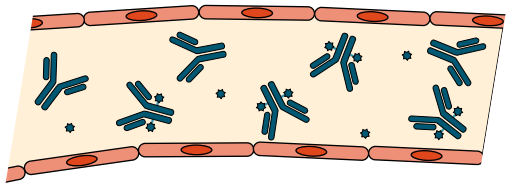
Drago. Nat Rev Clin Oncol. 2021;18:327.

Slide credit: clinicaloptions.com

Antibody–Drug Conjugates: Mechanism of Action

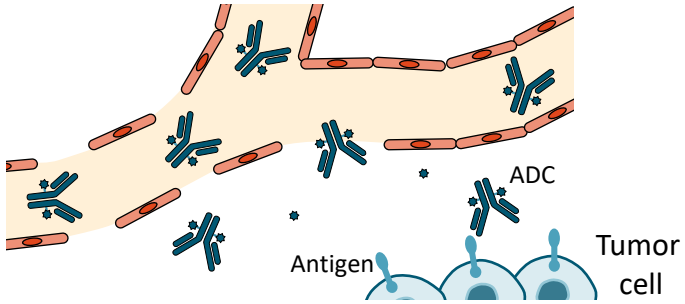
- Antibody binds target antigen→ internalized → payload release + bystander effect

ADCs may circulate as dynamic mixture of intact conjugate, naked antibodies, and free payload

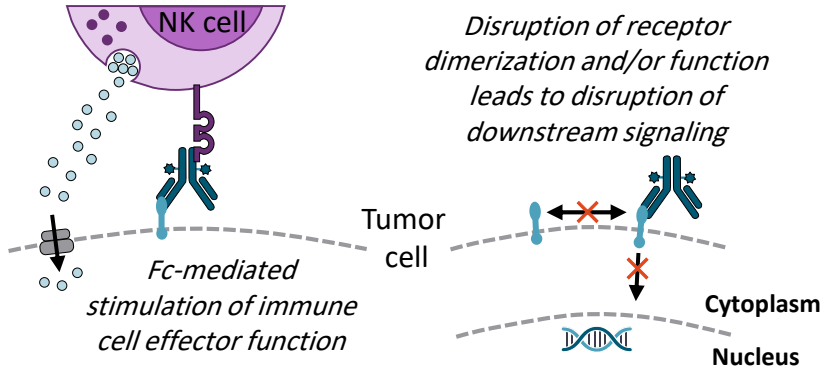


For stable ADCs, intact conjugate is predominant circulating form

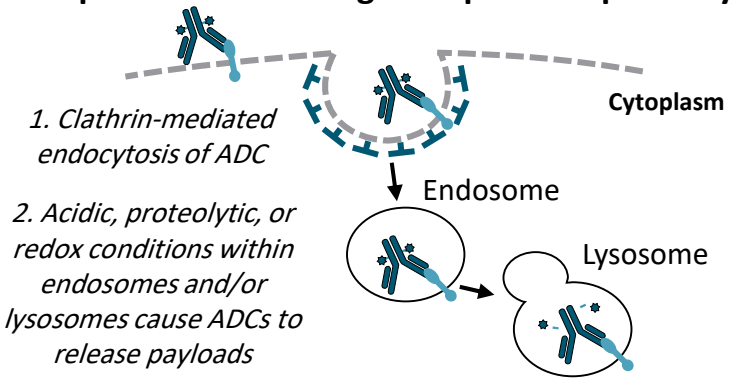
ADCs reach tumors via capillaries, releasing some payload into tumor microenvironment as diffuse toward target



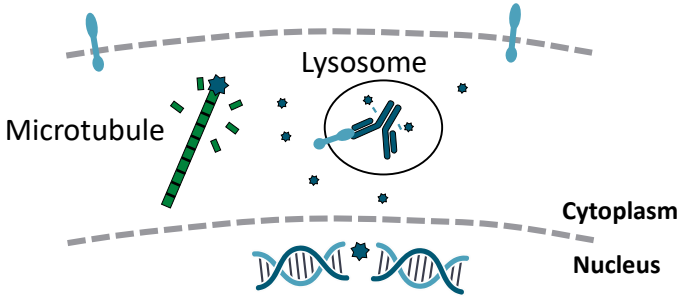
Antibody engagement → payload-independent antitumor activity



Most ADC–antigen complexes internalized, processed via antigen-dependent pathways

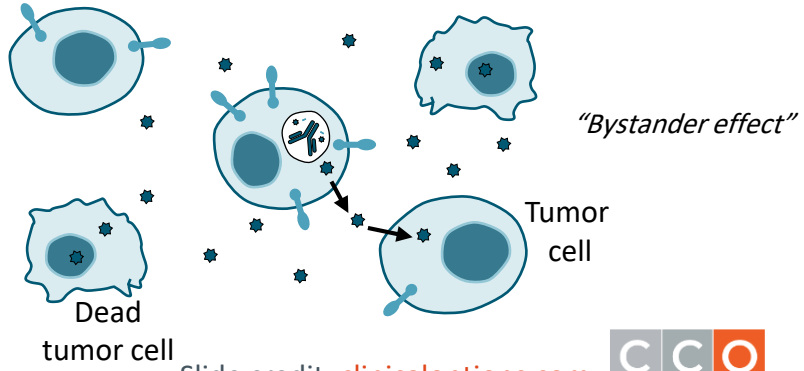


Payload released from endosomes and lysosomes (sometimes extracellularly) → apoptosis



Payload acts on target substrates

Membrane-permeable payloads affect nearby cells regardless of target antigen expression

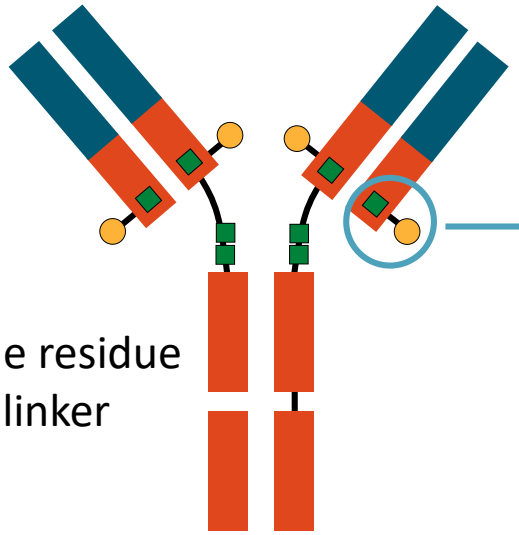


Drago. Nat Rev Clin Oncol. 2021;18:327.

Slide credit: clinicaloptions.com

Datopotamab Deruxtecan: TROP2-Targeted ADC

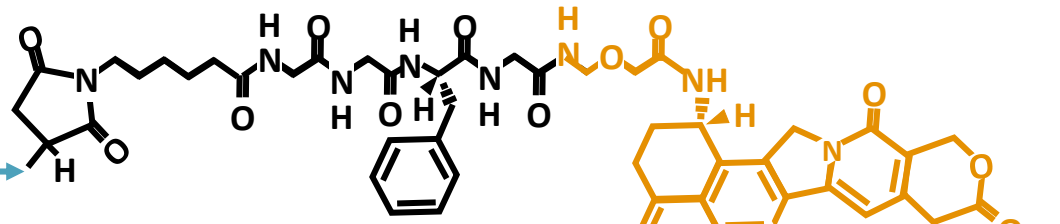
Datopotamab
Humanized
anti-TROP2 mAb



Cysteine residue
Drug + linker

Conjugation Chemistry
Drug + linker conjugated to
cysteine residues of mAb

Tetrapeptide-Based Cleavable Linker



Topoisomerase I Inhibitor Payload (DXd)
Exatecan derivative

- High-potency, membrane-permeable payload with short systemic half-life
- Optimized DAR: ~4:1
- Stable linker–payload
- cleavable linkTumor-selectableer
- Bystander killing effect

Okajima. Mol Cancer Ther. 2021;20:2329. Shastry. Breast. 2022;66:169.
Bardia. SABCS 2022. Abstr P6-10-03. Yasuda. AACR 2023. Abstr 4893.

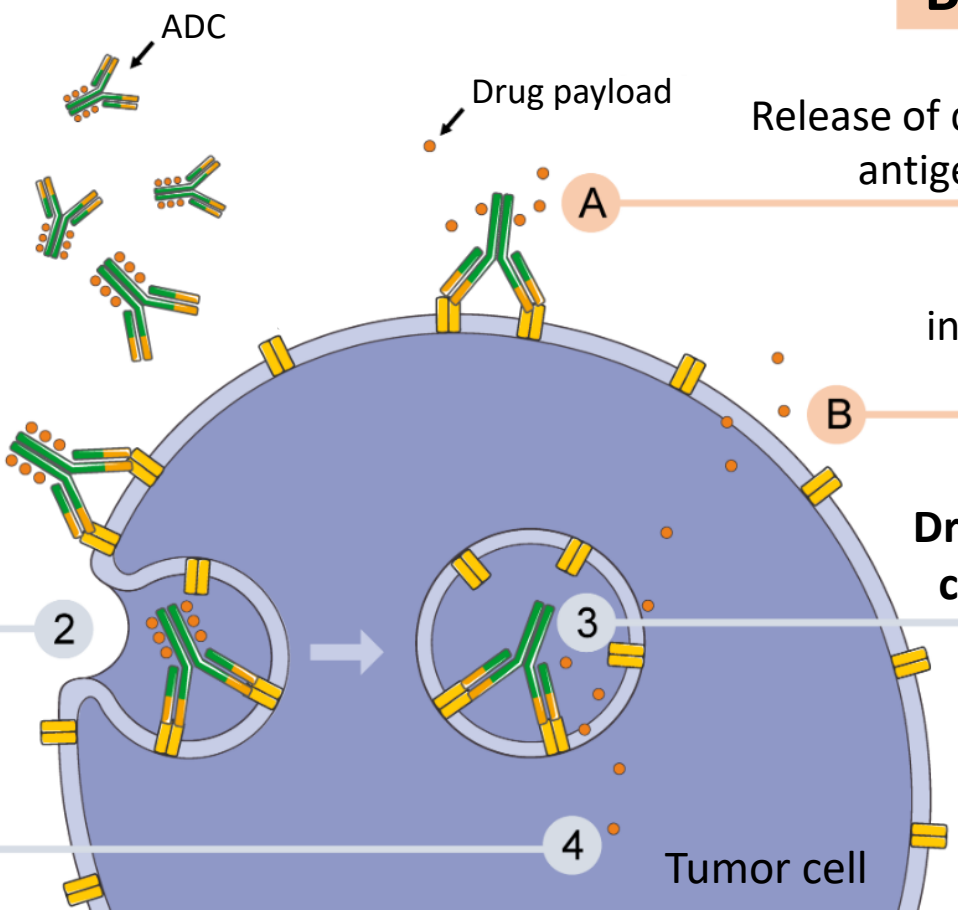
Mechanism of Action of ADCs

Classical ADC Mode of Action

ADC binding to receptor (1)

Internalization by endocytosis (2)

Cytotoxic effect induced by drug payload (4)



Bystander Killing Effect

Release of drug payload from antibody after antigen binding, before internalization (A)

Release of drug payload into intercellular space because of high drug membrane permeability (B)

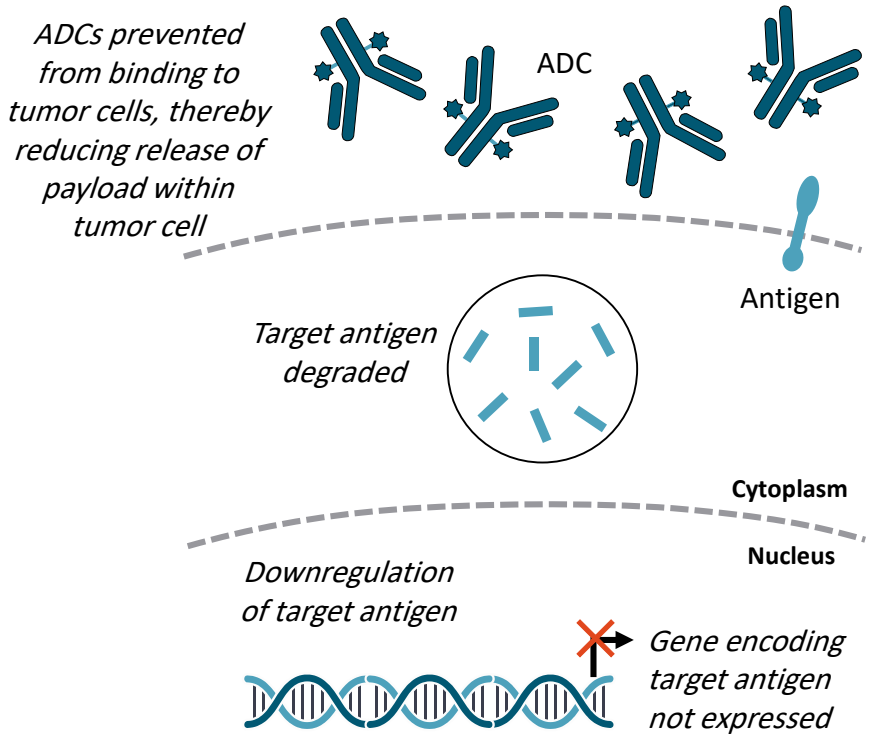
Drug payload release after linker cleavage by lysosomal enzymes (3)

A high drug-to-antibody ratio increases antitumoral efficacy despite low antigen density on tumor cells

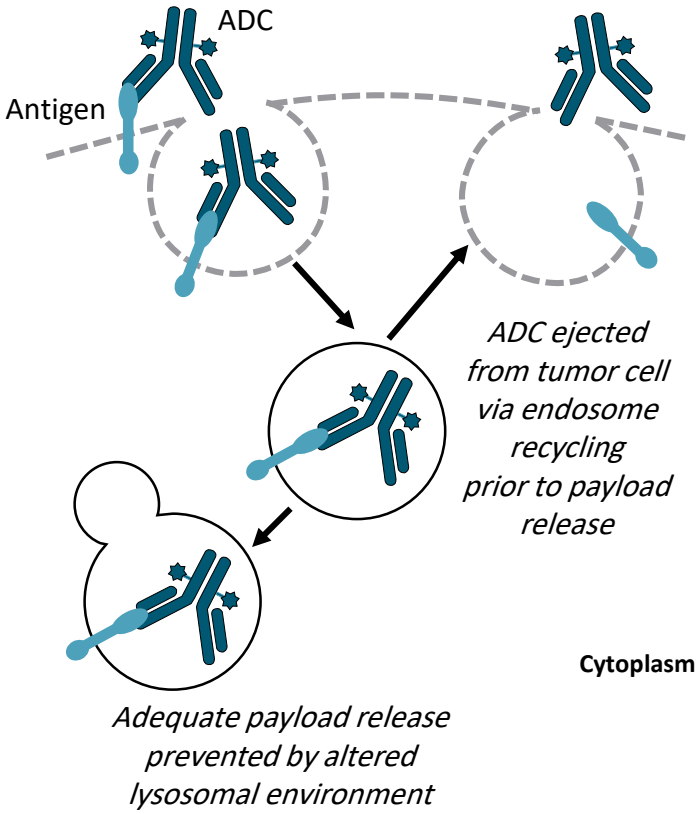
- Some ADCs require internalization for payload cleavage, but others can be hydrolyzed extracellularly

Acquired Resistance to TROP-2–Directed ADCs: 3 Main Mechanisms

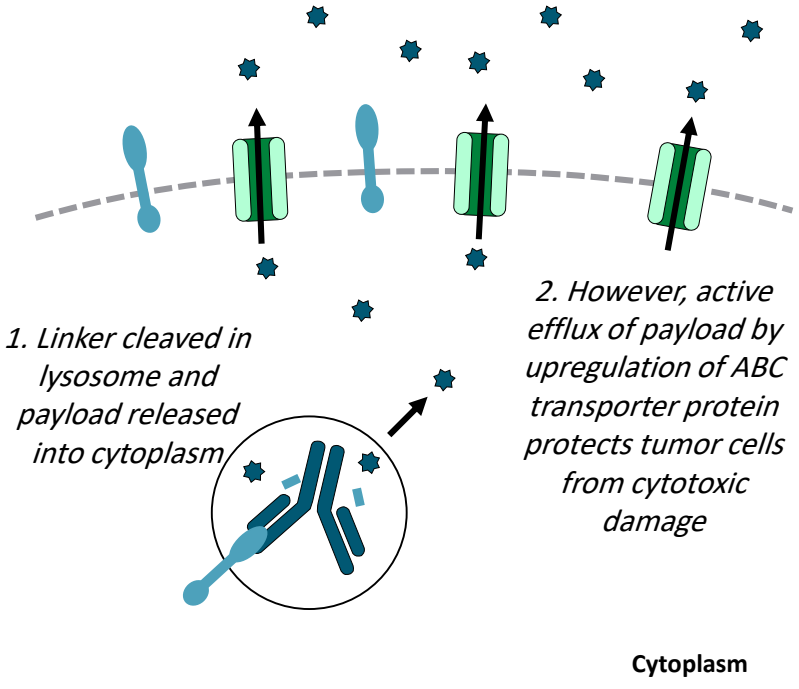
Downregulation of Antigen Expression by Tumor Cells



Altered Intracellular Trafficking Pathways or Drug Breakdown In Lysosomes



Payload Resistance by Upregulation of Drug Efflux Pumps



Drago. Nat Rev Clin Oncol. 2021;18:327.

Slide credit: clinicaloptions.com

MADRID 2023 ESMO congress

Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase 3 study TROPION-Lung01

Myung-Ju Ahn,[1,a] Aaron Lisberg,[2,a,b] Luis Paz-Ares,[3] Robin Cornelissen,[4] Nicolas Girard,[5] Elvire Pons-Tostivint,[6] David Vicente Baz,[7] Shunichi Sugawara,[8] Manuel Angel Cobo,[9] Maurice Pérol,[10] Céline Mascaux,[11] Elena Poddubskaya,[12] Satoru Kitazono,[13] Hidetoshi Hayashi,[14] Jacob Sands,[15] Richard Hall,[16] Yong Zhang,[17] Hong Zebger-Gong,[18] Deise Uema,[17] Isamu Okamoto[19]

[a]Equal contribution as first author. [b]Indicates presenting author.

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [5]Institut Curie, Paris, France; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]Hospital Universitario Virgen Macarena, Seville, Spain; [8]Sendai Kousei Hospital, Sendai, Japan; [9]FEA Oncología Médica, Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [10]Centre Léon Bérard, Lyon, France; [11]Hôpitaux Universitaires de Strasbourg (CHRU), Strasbourg, France; [12]Vitamed LLC, Moscow, Russia; [13]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [14]Kindai University, Osaka, Japan; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]University of Virginia Health System, Charlottesville, VA, USA; [17]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [18]Daiichi Sankyo Europe GmbH, Munich, Germany; [19]Kyushu University Hospital, Fukuoka, Japan

Background

- Standard-of-care, **second-line chemotherapy** for metastatic NSCLC is associated with a **modest benefit and substantial toxicity**
- **Dato-DXd** is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload directly into tumor cells[1]
- **Promising antitumor activity** was seen with Dato-DXd in patients with adv/met NSCLC in the phase 1 TROPION-PanTumor01 trial (26% ORR)[1]

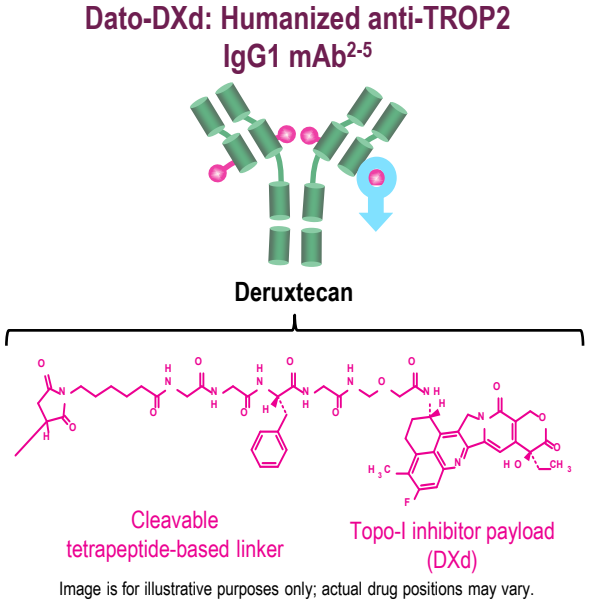


Image is for illustrative purposes only; actual drug positions may vary.

ADC, antibody-drug conjugate; adv/met, advanced/metastatic; Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell-surface antigen 2.

1. Shimizu T, et al. *J Clin Oncol.* 2023;41:4678-4687. 2. Okajima D, et al. *Mol Cancer Ther.* 2021;20:2329-2340. 3. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185. 4. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-5108. 5. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-1046.

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.

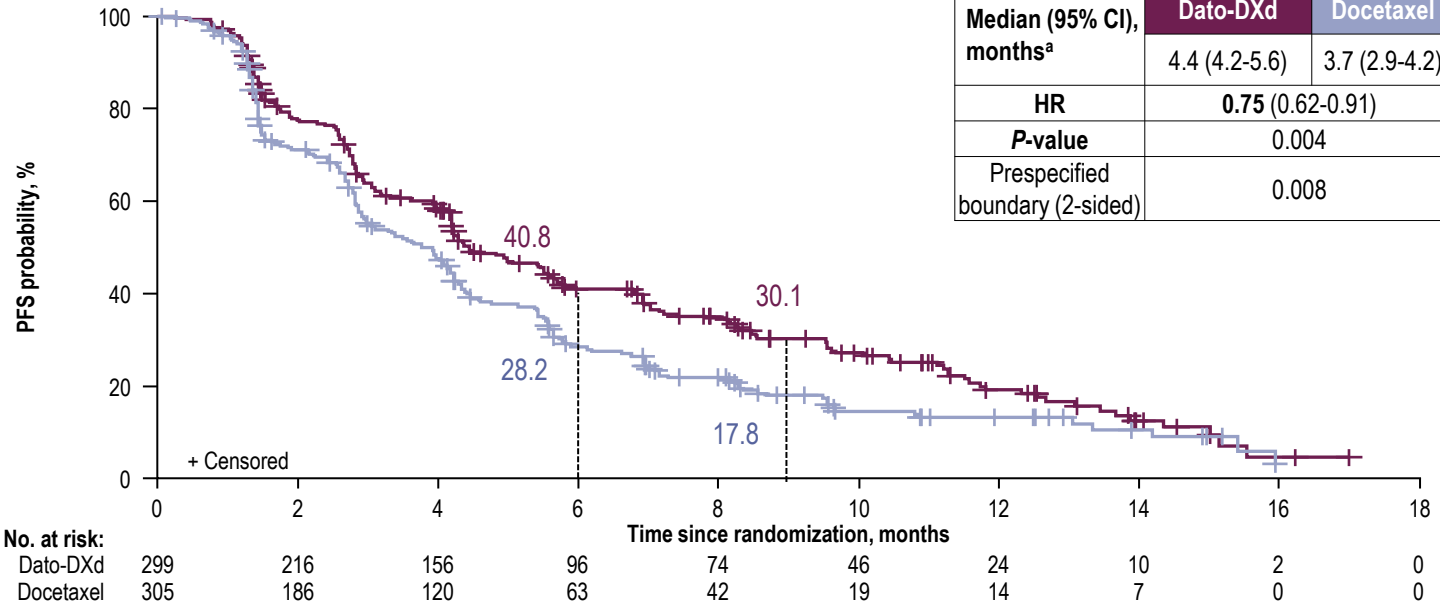
Data cutoff: 29 March 2023.

Patient Disposition

Disposition, n (%)	Dato-DXd N=297	Docetaxel N=290
Treatment status		
Ongoing on study treatment	52 (18)	17 (6)
Discontinued from study treatment	245 (83)	273 (94)
Treatment duration		
0-3 months	118 (40)	168 (58)
>3 to ≤6 months	73 (25)	66 (23)
>6 to ≤9 months	47 (16)	34 (12)
>9 months	59 (20)	22 (8)
Primary reason for treatment discontinuation		
Adverse event	39 (13)	46 (16)
Progressive disease	173 (58)	180 (62)
Clinical progression	9 (3)	11 (4)
Withdrawal/physician decision	12 (4)	23 (8)
Death	10 (3)	10 (3)
Other	2 (1)	3 (1)

Median study follow-up: Dato-DXd – **13.1** months; docetaxel – **13.0** months

Progression-Free Survival: ITT



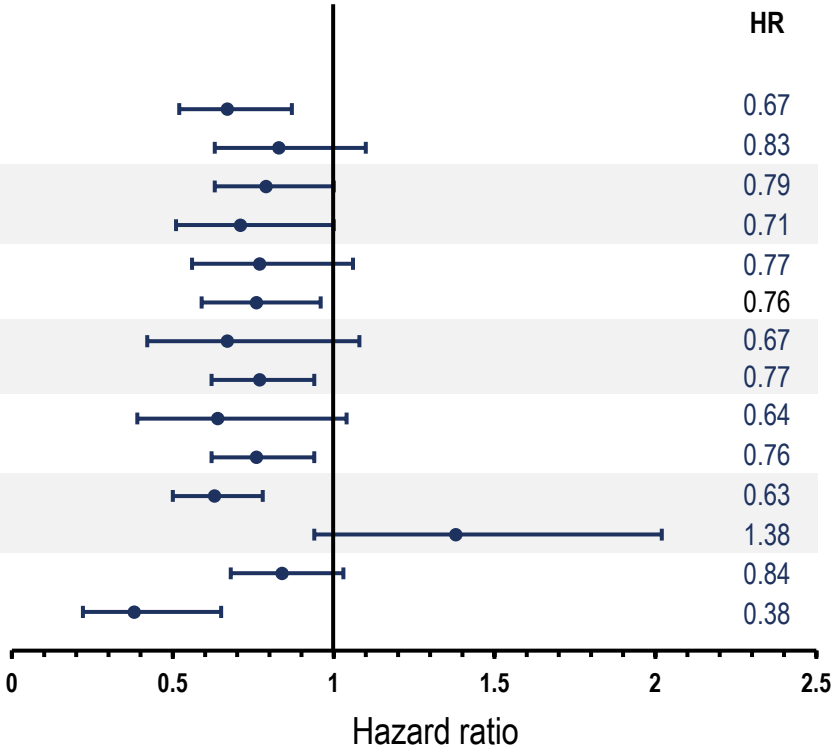
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
***P*-value**	0.004	
Prespecified boundary (2-sided)	0.008	

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

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

PFS in Key Subgroups

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

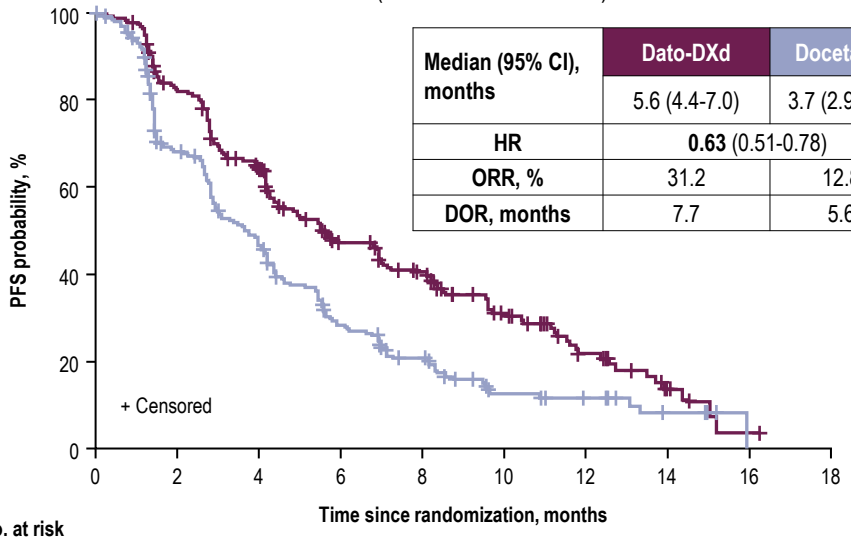


[a]Regardless of histology.

PFS by Histology

Non-squamous

(with and without AGAs)

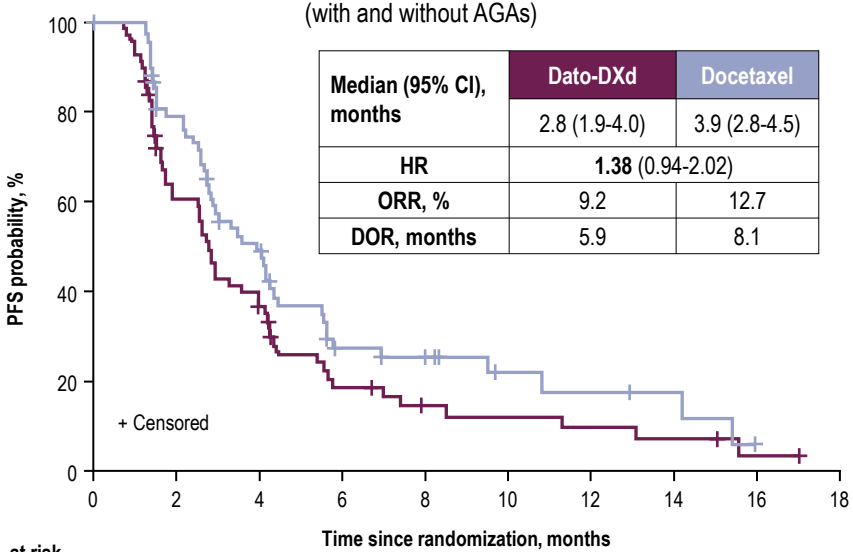


Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

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

Squamous

(with and without AGAs)



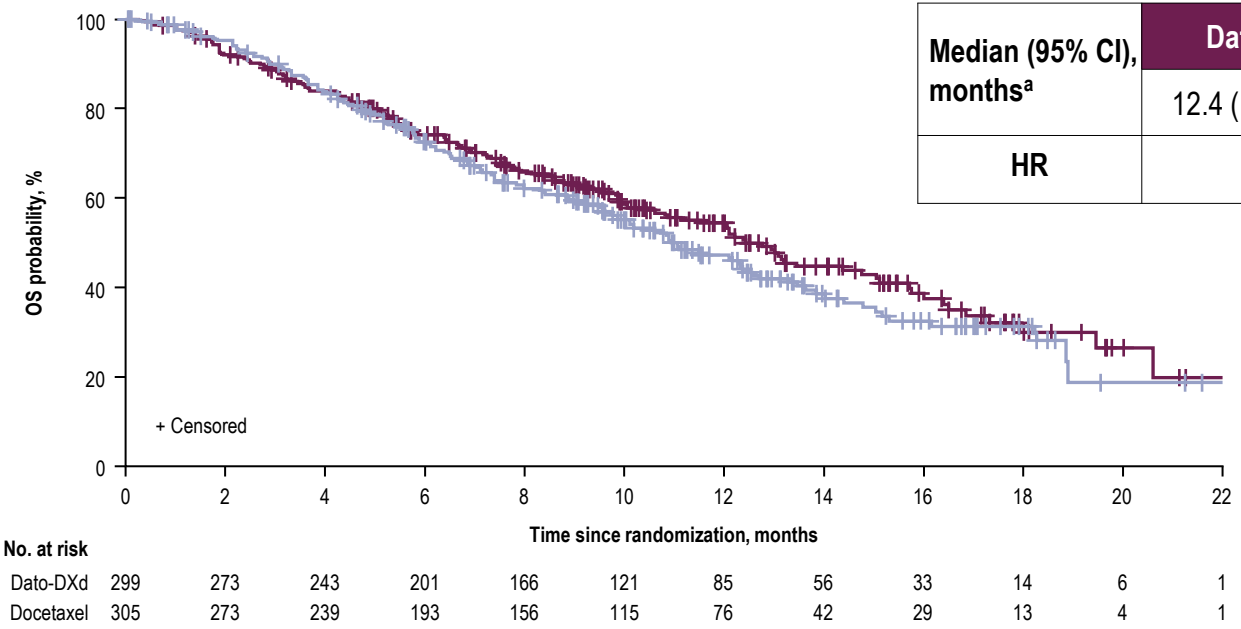
Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

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

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

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

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

HR, hazard ratio; ITT, intention to treat; OS, overall survival.

[a]Median OS follow-up was 11.8 (95% CI, 11.3-12.7) and 11.7 (95% CI, 10.9-12.9) months for Dato-DXd and docetaxel, respectively.

Overall Safety Summary

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[a]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

- The median treatment durations for Dato-DXd and docetaxel were **4.2** and **2.8** months, respectively
- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

ILD, interstitial lung disease; TRAE, treatment-related adverse event.
[a]Investigator assessed. Dato-DXd: 2 cases of ILD/pneumonitis and 1 case of sepsis; docetaxel: 1 case of ILD/pneumonitis and 1 case of septic shock.
The safety analysis set included all randomized patients who received ≥1 dose of the study drug.

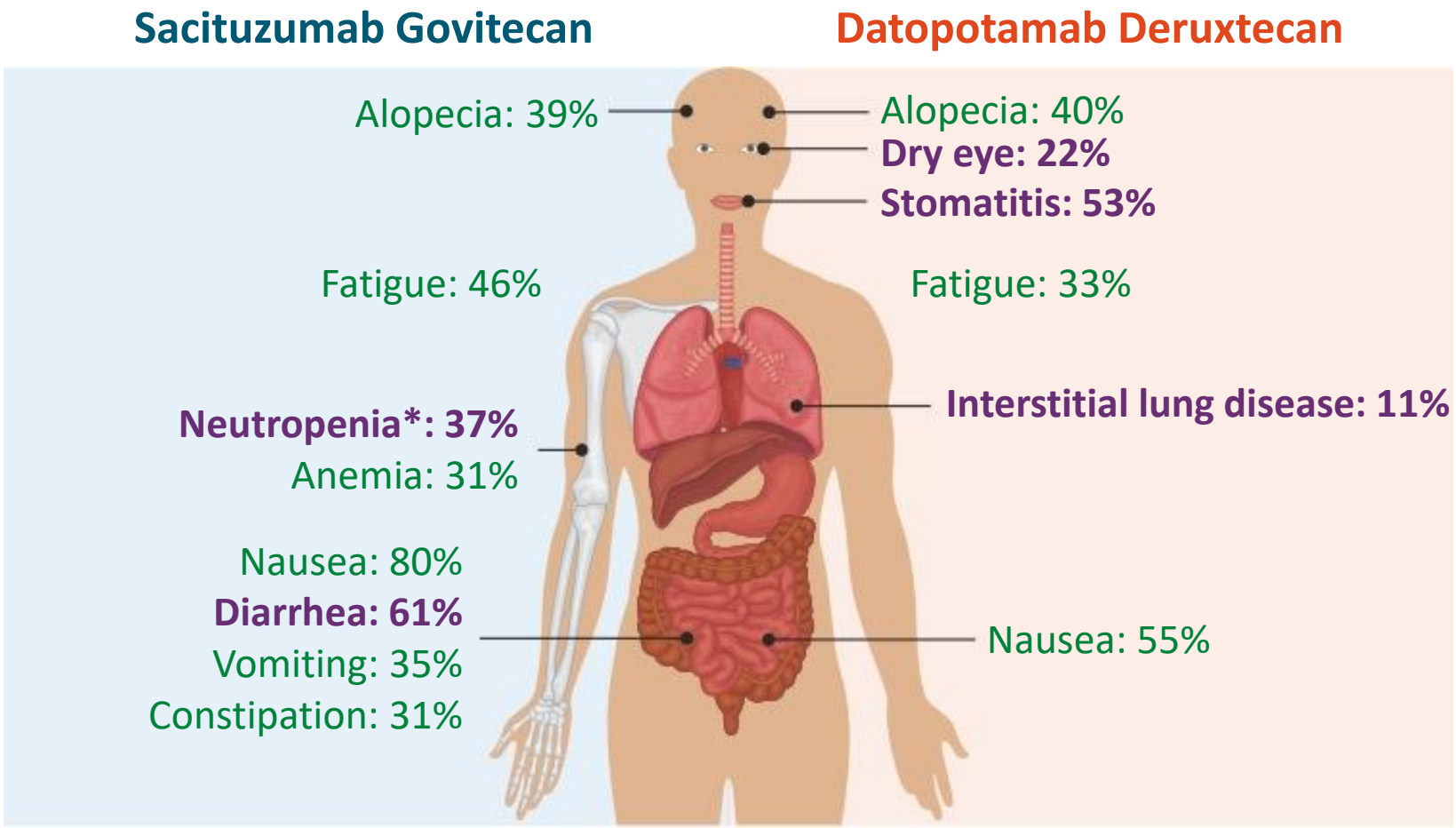
TRAEs Occurring in ≥10% of Patients

System organ class Preferred term, n (%)	Dato-DXd N=297		Docetaxel N=290	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system				
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia[a]	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
Nausea	100 (34)	7 (2)	48 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
General				
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and subcutaneous				
Alopecia	95 (32)	0	101 (35)	1 (0.3)[b]
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

- Stomatitis and nausea were the most frequent TRAEs seen with Dato-DXd and were predominantly grade 1 or 2
- Hematologic toxicities, including neutropenia and febrile neutropenia[c], were more common with docetaxel
- No new safety signals were observed with Dato-DXd

TRAE, treatment-related adverse event.
[a]This category includes the preferred terms "neutropenia" and "neutrophil count decreased". [b]Includes an event incorrectly reported as grade 3. [c]7% vs 0.3% for Docetaxel and Dato-DXd, respectively

Common and Notable Toxicities Associated With TROP-2–Directed ADCs



*Most common severe AE.

Heist. JCO. 2017;35:2790. Shimizu. JCO. 2023;[Epub].

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)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

- Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)
- Dry eye was the most common ocular event seen with Dato-DXd (6.1%; primarily grade ≤2), followed by 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 8% of patients in each arm, all were grade ≤2 with the exception of 1 grade 3 event with Dato-DXd

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class. AESIs listed in this slide are treatment emergent and include all PTs that define the medical concept.

[a]Events included the selected PTs oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. [b]Ocular events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. [c]Included 4 cases of keratitis and 1 case of ulcerative keratitis. [d]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [e]Among treated patients, histology information per the case report form.

Conclusions

- Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in patients with previously treated, locally advanced or metastatic NSCLC
- PFS benefit was primarily driven by patients with non-squamous histology
- Fewer grade ≥3 TRAEs and no new safety signals were observed with Dato-DXd
- Grade ≥3 ILD was seen, highlighting the need for careful monitoring and adherence to ILD management guidelines
- The interim OS findings favor Dato-DXd, and the trial is continuing to final analysis

Dato-DXd is a potential new meaningful therapy for patients with previously treated non-squamous NSCLC

ADC, antibody-drug conjugate; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

Additional Clinical Trials With Datopotamab Deruxtecan in Advanced or Metastatic NSCLC

TROPION-Lung02 (NCT04526691)[1]	TROPION-Lung04 (NCT04612751)[2]	TROPION-Lung05 (NCT04484142)[3]
Global, multicenter, 2-part, dose-escalation and dose-expansion, phase Ib trial	Global, multicenter, 2-part, dose-escalation and dose-expansion, phase Ib trial	Global, multicenter, phase II trial
Dato-DXd + pembrolizumab ± 4 cycles platinum-based CT in patients with previously treated or treatment-naive advanced or metastatic NSCLC with no actionable genomic alterations	Dato-DXd + durvalumab ± 4 cycles platinum-based CT in patients with previously treated or treatment-naive advanced or metastatic NSCLC with no actionable genomic alterations	Dato-DXd 6 mg/kg Q3W in patients with advanced or metastatic NSCLC with known actionable genomic alterations after PD with platinum-based CT and ≥1 line of targeted therapy for known genomic alterations
Primary objective: tolerability and safety	Primary objective: tolerability and safety	Primary objective: efficacy of Dato-DXd

1. Levy. WCLC 2021. Abstr P47.04. 2. Borghaei. WCLC 2021. Abstr P47.06. 3. Johnson. WCLC 2021. Abstr P47.05.

Slide credit: clinicaloptions.com

- Thank you for listening
- Have a nice day