

12º SIMPÓSIO  
INTERNACIONAL DE

# CÂNCER DE PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

GERENCIAMENTO E PRODUÇÃO

**RV+**  
EVENTOS MÉDICOS



12º SIMPÓSIO  
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CÂNCER DE  
PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

# Novas terapias no câncer de pulmão: anticorpos droga-conjugados e bi-específicos, HER2, CEACAM5 e outros alvos

**Aknar Calabrich**

Oncologia AMO/DASA

GERENCIAMENTO E PRODUÇÃO



# Declaração de conflitos de interesse

De acordo com a resolução RDC 96/2008 da Agência de Vigilância Sanitária declaro que:

Palestras e atividades educacionais e treinamentos: *Astrazeneca, GSK, Lilly, Janssen, Pfizer, MSD, Roche*

*Advisory board ou Expert Input Forum: Pfizer, AstraZeneca, GSK, MSD, GSK, Lilly, Beigene, Adium*

Investigador principal de estudos de pesquisa clínica patrocinada: AstraZeneca, GSK, Janssen, AMGEN,  
Roche

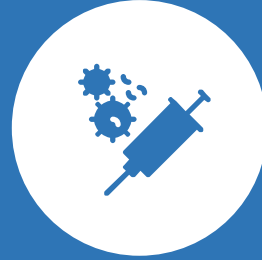
# ADC – NOVO PILAR DO TRATAMENTO SISTÊMICO DA ONCOLOGIA



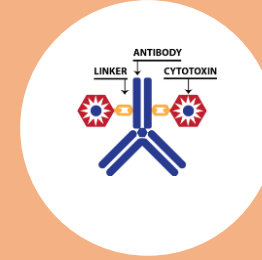
Quimioterapia



Terapia Alvo

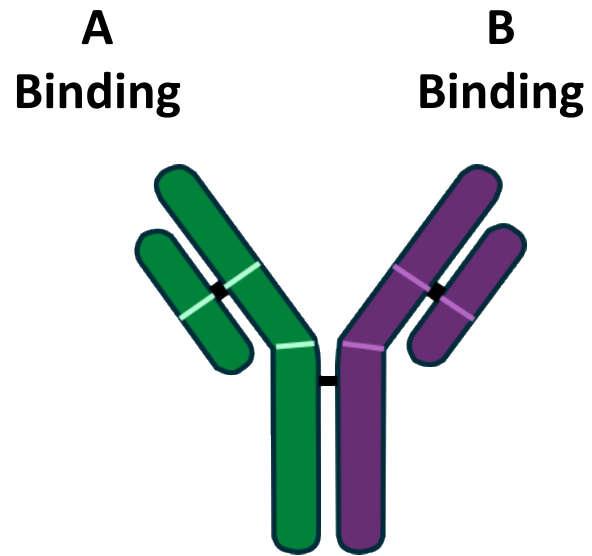


Imunoterapia

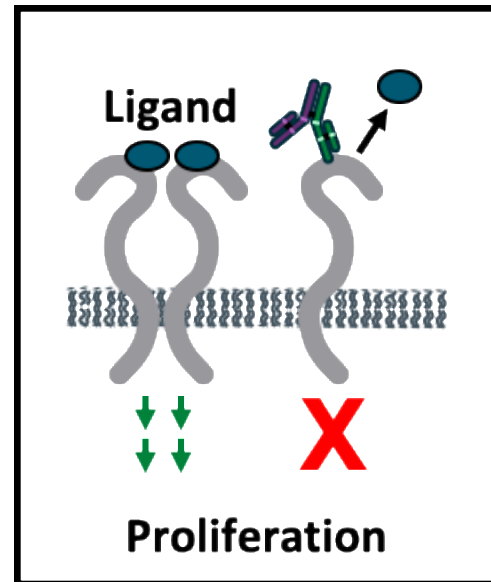


Anticorpo droga  
conjugada (ADC) +  
Anticorpos  
biespecíficos

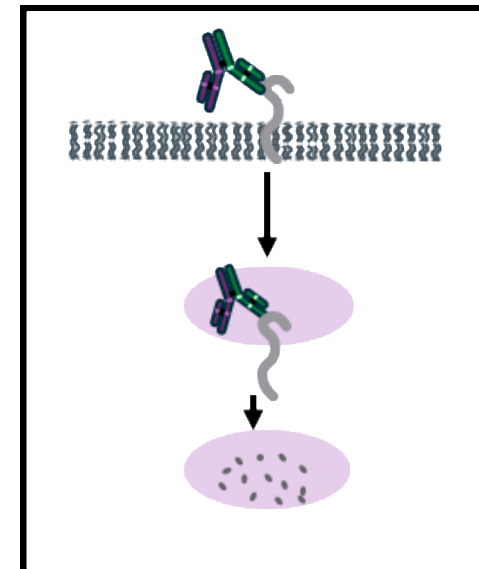
# Anticorpo biespecífico



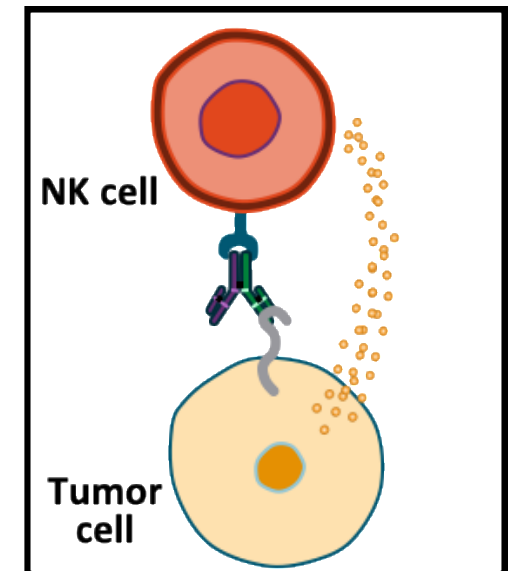
**Inhibition of  
Ligand Binding**



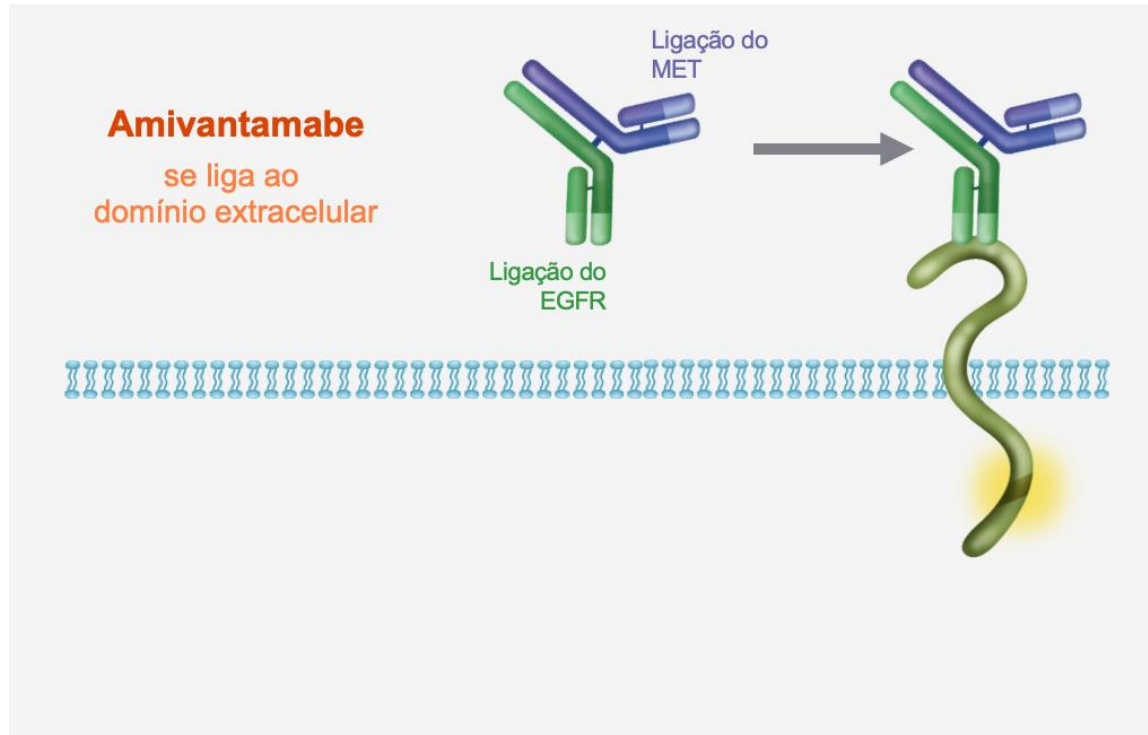
**Receptor  
Degradation**



**Immune Cell-  
Directing Activity**

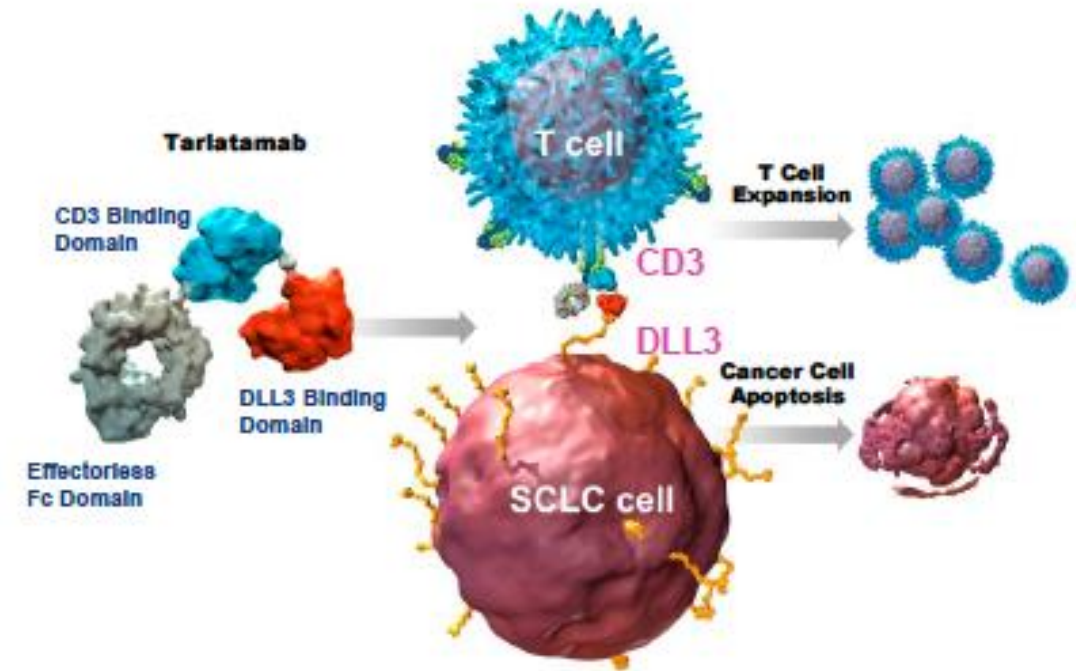


# Exemplos Anticorpos biespecíficos



**Amivantamab**  
**EGFR + MET**  
**Tumorais**

MARIPOSA  
MARIPOSA2  
PAPILLON



**Tarlatamab (BiTE) – biespecific T-cell engager**  
**DLL3 – tumor**  
**CD3 – Linfócito T**

# DeLLphi-301: phase 2 trial in previously treated SCLC



## Tarlatamab for patients with previously treated small cell lung cancer (SCLC): Primary analysis of the phase 2 DeLLphi-301 study

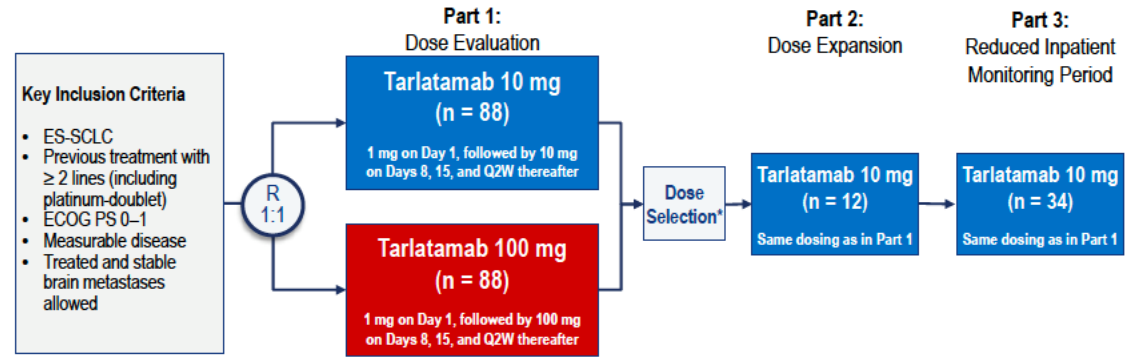
Luis Paz-Ares<sup>1</sup>, Myung-Ju Ahn<sup>2</sup>, Enriqueta Felip<sup>3</sup>, Sabin Handzhiev<sup>4</sup>, Ippokratis Korantzis<sup>5</sup>, Hiroki Izumi<sup>6</sup>, Kadoaki Ohashi<sup>7</sup>, Margarita Majem<sup>8</sup>, Jürgen Wolf<sup>9</sup>, Martin Reck<sup>10</sup>, Horst-Dieter Hummel<sup>11</sup>, Fiona Blackhall<sup>12</sup>, Anne-Marie C. Dingemans<sup>13</sup>, Taofeek K. Owonikoko<sup>14</sup>, Suresh S Ramalingam<sup>15</sup>, Jacob Sands<sup>16</sup>, Tony Jiang<sup>17</sup>, Sujoy Mukherjee<sup>17</sup>, Erik S. Anderson<sup>17</sup>, Byoung Chul Cho<sup>18</sup>

<sup>1</sup>Hospital Universitario 12 de Octubre, Universidad Complutense, CNIO-H12o Lung Cancer Unit and Ciberonc, Madrid, Spain; <sup>2</sup>Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; <sup>3</sup>Lung Cancer Unit, Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; <sup>4</sup>Klinische Abteilung für Pneumologie, Universitätsklinikum Krems, Krems, Austria; <sup>5</sup>Department of Medical Oncology, Saint Loukas Hospital, Thessaloniki, Greece; <sup>6</sup>Department of Thoracic Oncology, National Cancer Center Hospital East, Kashima, Japan; <sup>7</sup>Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan; <sup>8</sup>Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; <sup>9</sup>Department of Internal Medicine - Center for Integrated Oncology, Universitätsklinikum Köln (UKR), Cologne, Germany; <sup>10</sup>Lungen Clinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; <sup>11</sup>Translational Oncology/Early Clinical Trial Unit, Universitätsklinikum Würzburg, Comprehensive Cancer Center Mainfranken, Würzburg, Germany; <sup>12</sup>The Christie NHS Foundation Trust, Manchester, UK; <sup>13</sup>Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, Netherlands; <sup>14</sup>Division of Hematology-Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, USA; <sup>15</sup>Winship Cancer Institute of Emory University, Atlanta, GA, USA; <sup>16</sup>Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; <sup>17</sup>Amgen Inc., Thousand Oaks, CA, USA; <sup>18</sup>Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul, South Korea.



## DeLLphi-301 Study Design

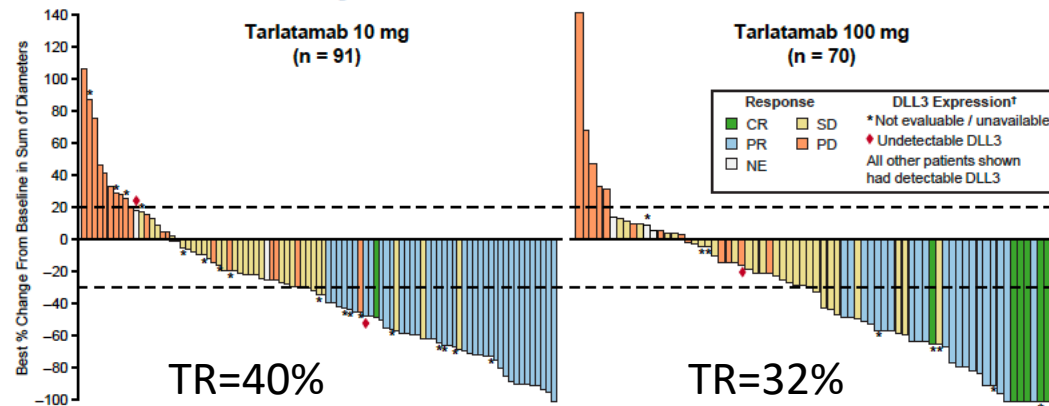
Phase 2, open-label study (NCT05060016)



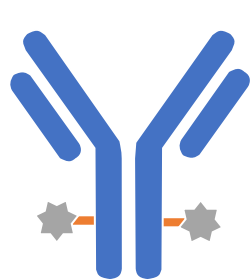
**Primary Endpoint:** ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations  
**Secondary Endpoints Included:** DOR, DCR, PFS per RECIST v1.1 by BICR, OS



\*Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or  $\geq 13$  weeks of follow-up, whichever occurred first. BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage-small cell lung cancer; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.



# Antibody–Drug Conjugates (ADC): Components



Antibodies	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7-21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

**ANTIBODY:** Chimeric/humanized monoclonal IgG antibody targeting a protein preferentially expressed on the tumor cell surface

Linkers	Cleavable		Noncleavable
	Hydrazone (acid cleavable)	Disulfide (reducible)	MC* MCC*
	<chem>O=C(N)N</chem>	<chem>S-S</chem>	<chem>O=C(N)N</chem>
		Dipeptide (protease cleavable)	
		<chem>O=C(N)R1-NH-C(=O)R2</chem>	
		Cathepsin	

**LINKER:** Ensures payload is attached to antibody in plasma but is efficiently released in tumor cells. Linkers can be cleavable (via tumor-associated factors) or noncleavable (lysosomal degradation)

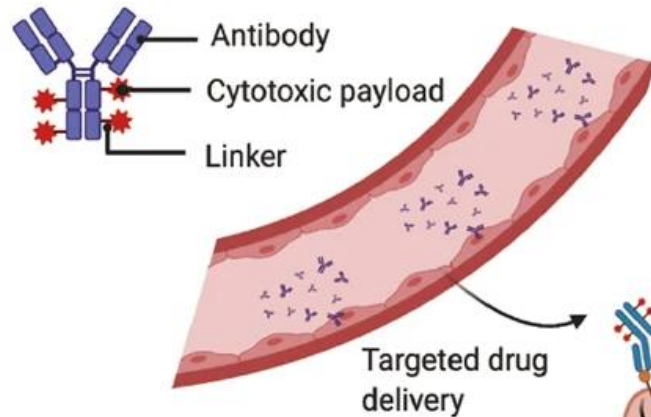
Payloads	Auristatins (MoA: antimicrotubule)	Maytansinoids (MoA: antimicrotubule)	Calicheamicins (MoA: DNA cleavage)	Camptothecins (MoA: Topoisomerase 1 inhibition)
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**PAYLOAD:** Enhances cytotoxicity, although variable drug:antibody ratio affects efficacy and clearance

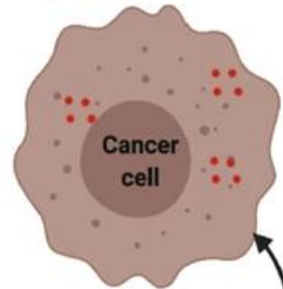


# ADC: mecanismo de ação

## Antibody-Drug Conjugate

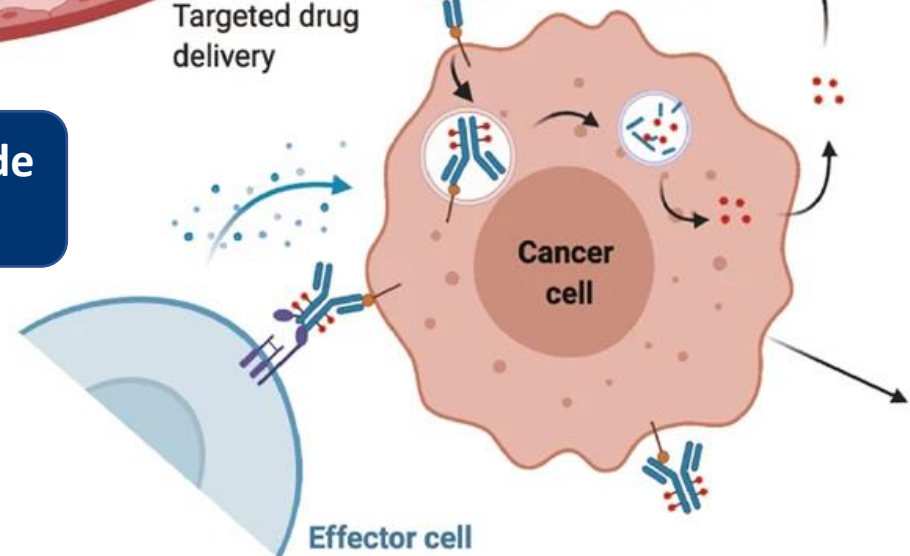


Bystander effects



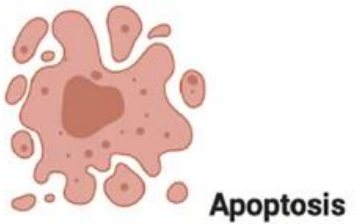
**Destruição de células tumorais vizinhas**

**Citotoxicidade celular depende de anticorpos (ADCC)**

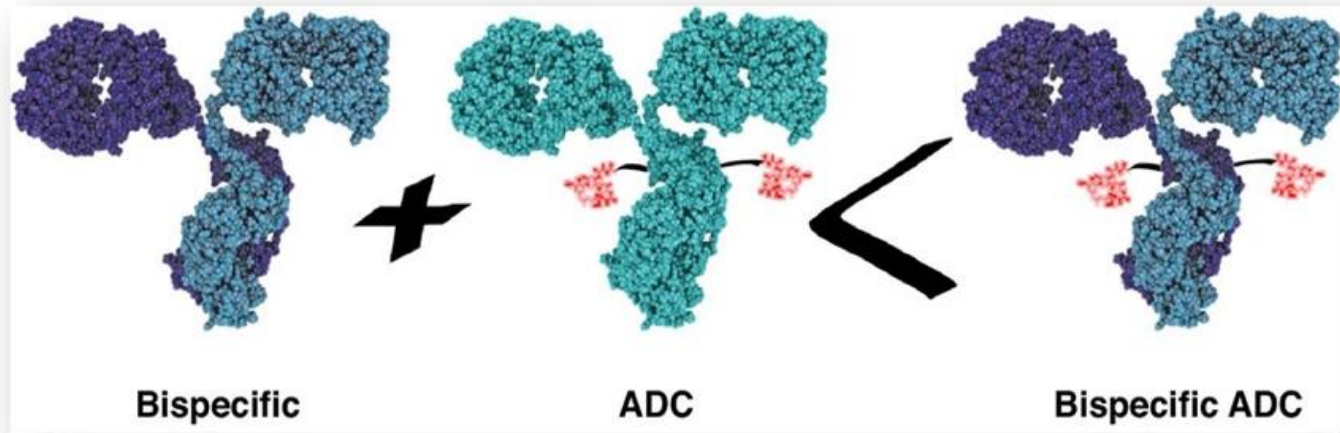


**Efeito citotóxico celular**

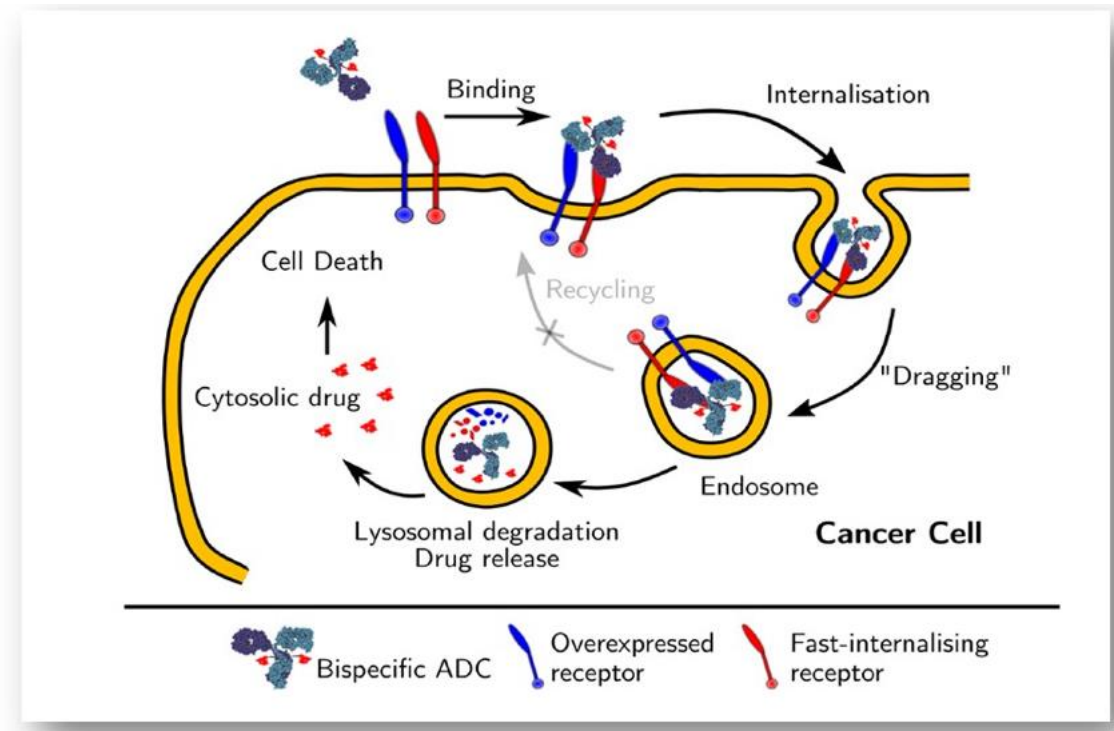
**Bloqueio do alvo/sinalização intracelular**



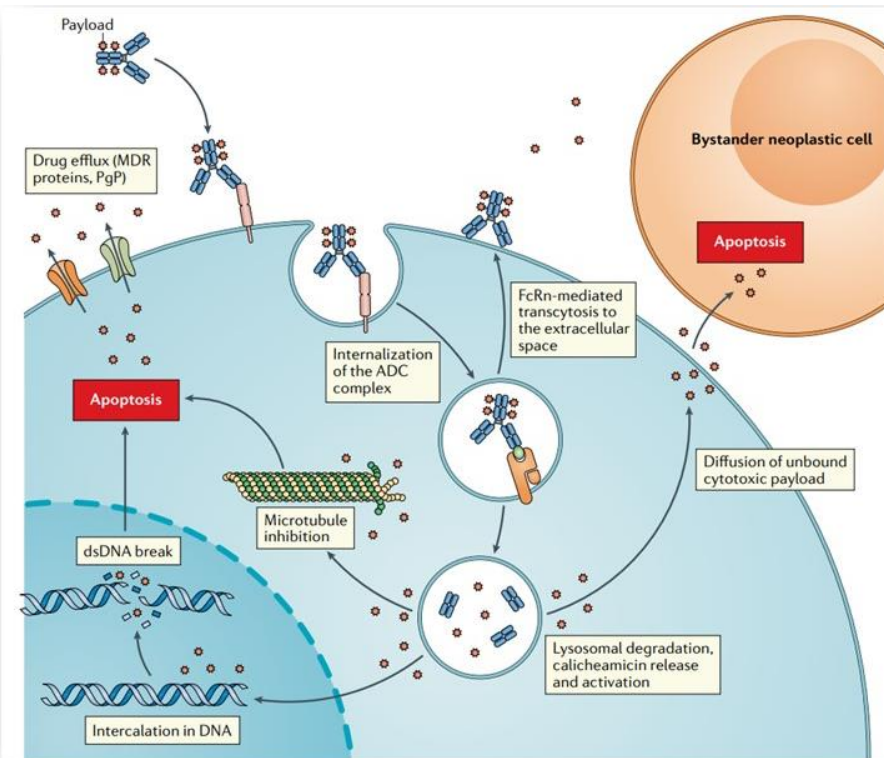
# ADC biespecífico



- Aumenta a especificidade tumoral
- Aumenta a internalização e efeito antitumoral
- Reverte a resistência de um alvo único



# ADCs atualmente aprovados na oncologia

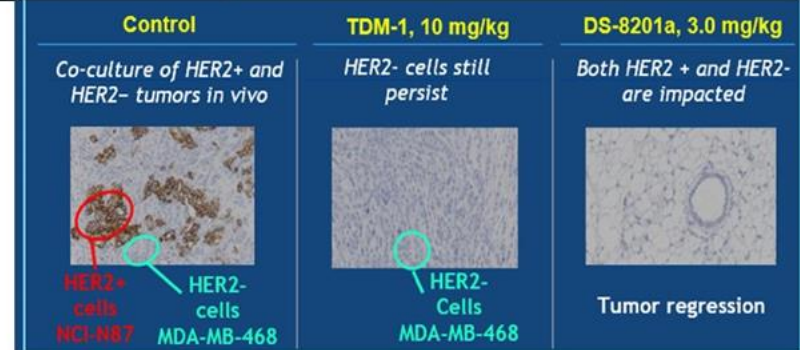
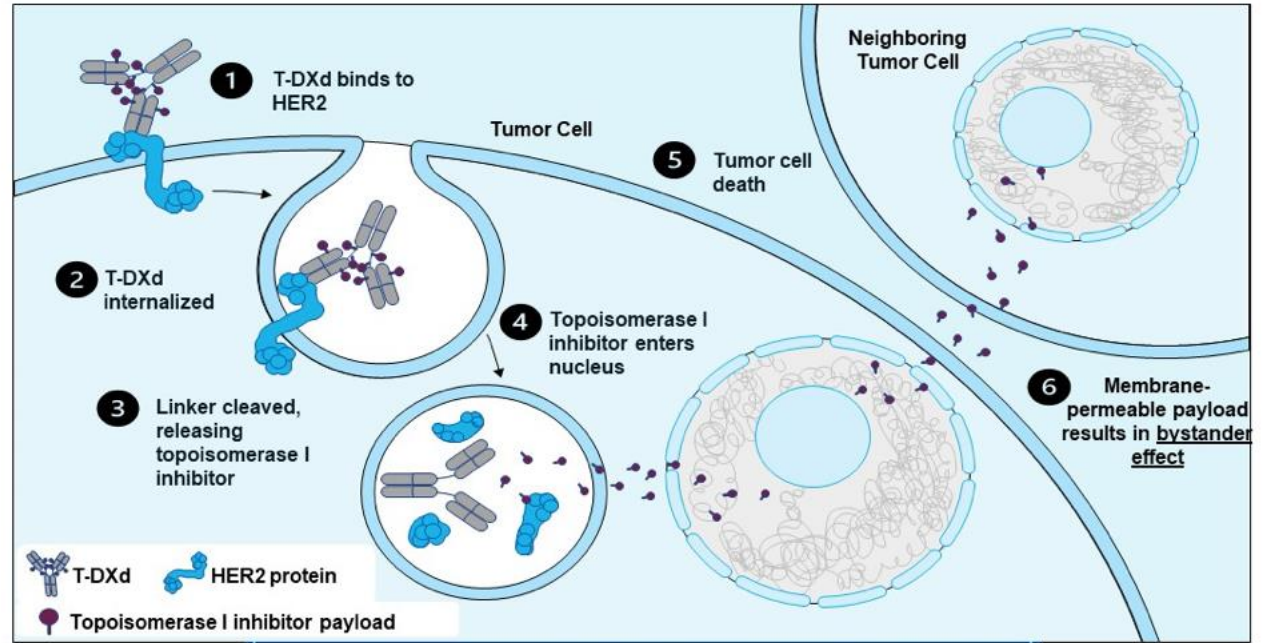
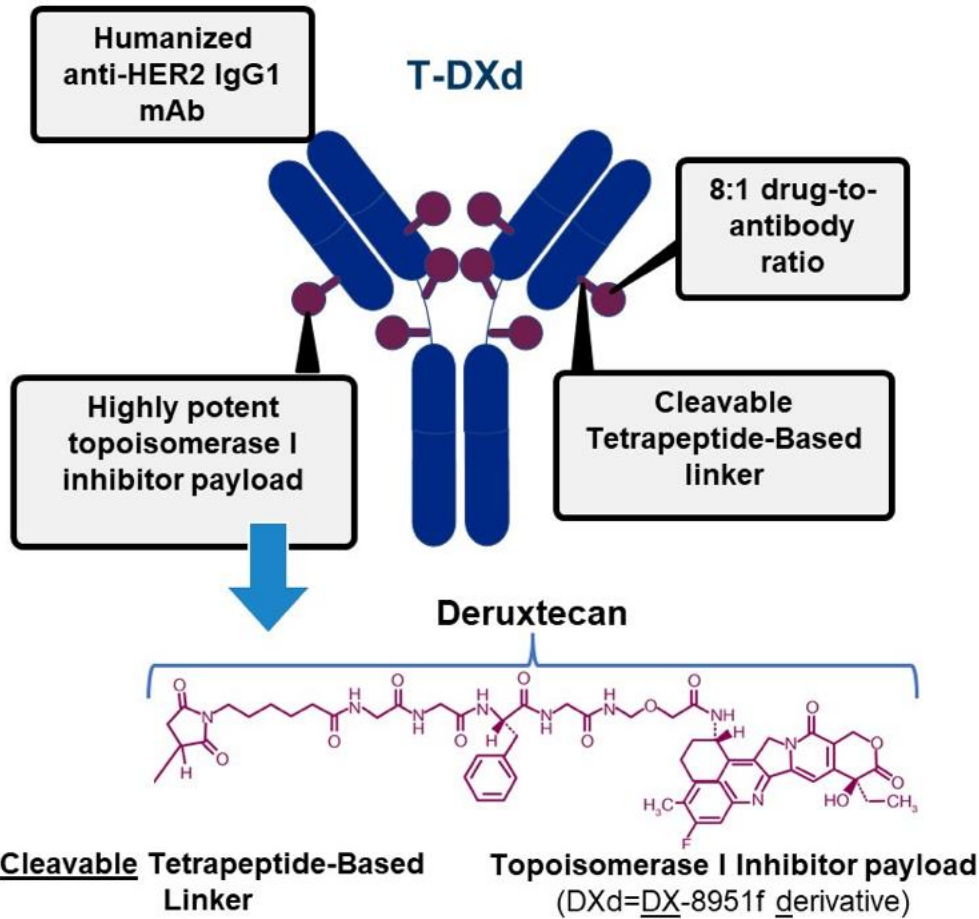


Agent for solid tumors	Target	Payload (site)	DAR	Linker	FDA approval	Indication
Trastuzumab emtansine	HER2	DM1 (tubulin)	3.5	SMCC (non-cleavable)	2013	Breast
Enfortumab vedotin	Nectin-4	MMAE (tubulin)	3.8	mc-VC-PABC (cleavable)	2019	Urothelial
Trastuzumab deruxtecan	HER2	DXd (DNA)	8	GGFG tetrapeptide (cleavable)	2019	Breast Gastric Lung
Sacituzumab govitecan	Trop-2	SN-38 (DNA)	7.6	CL2A (cleavable)	2020 2021	Breast Urothelial
Tisotumab vedotin	TF	MMAE (tubulin)	4	mc-VC-PABC (cleavable)	2021	Cervical
Mirvetuximab soravansine	FR $\alpha$	DM4 (tubulin)	3.5	sulfo-SPDB (cleavable)	2022	Ovarian

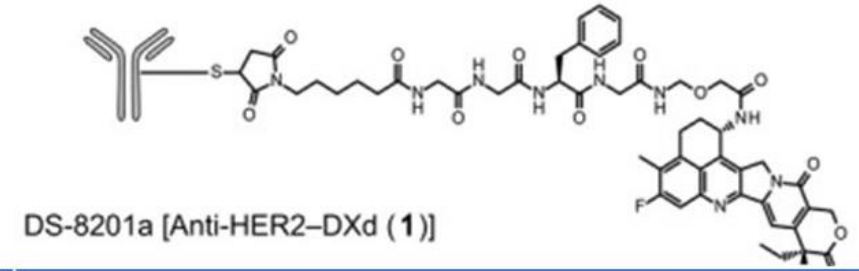
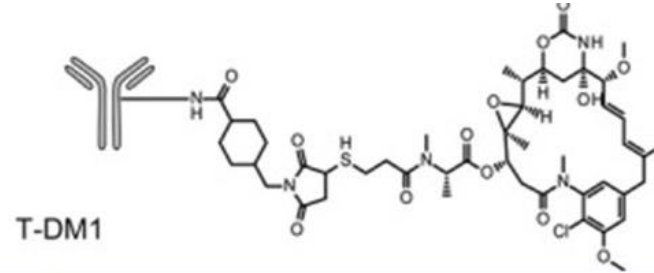
- Target-specific anti-cancer killing effect
- ↑ therapeutic index

- 6 agents for 5 targets in solid tumors

# Trastuzumabe deruxtecan (T-DXd)



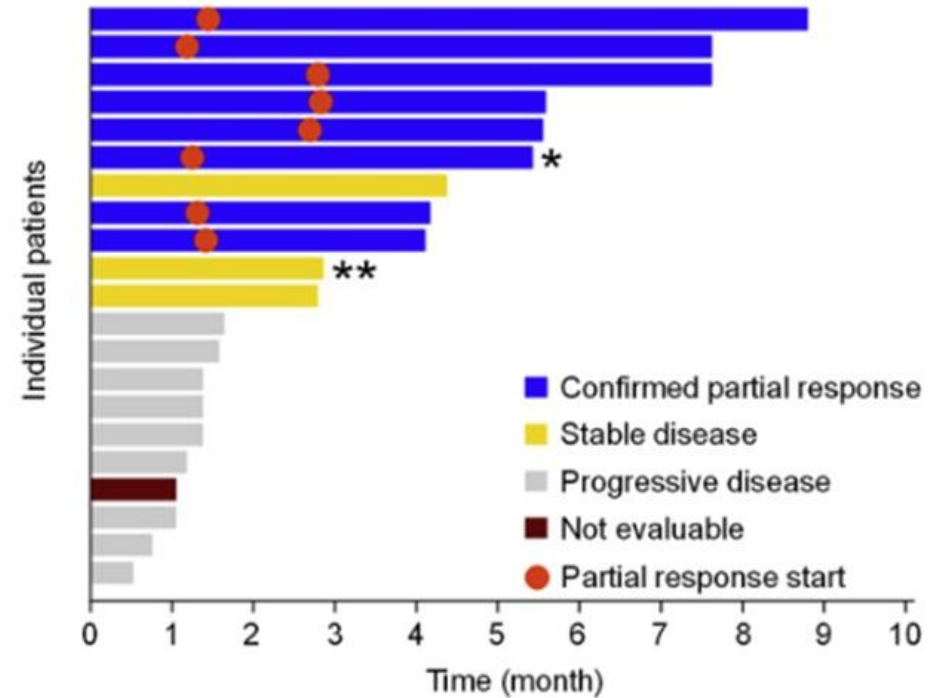
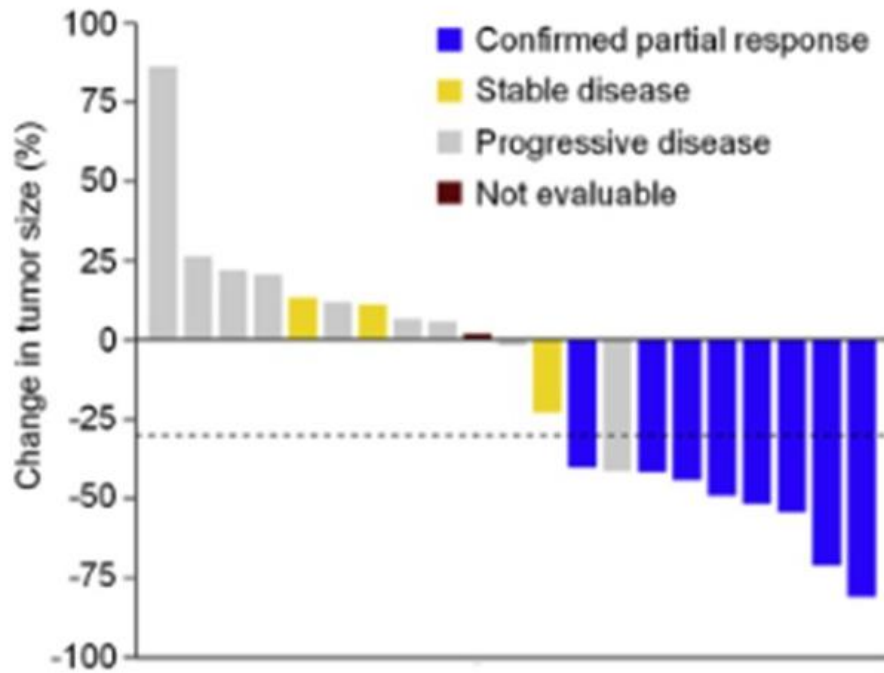
# Comparison of T-DM1 and T-DXd



	Trastuzumab Emtansine (TDM-1)	Trastuzumab Deruxtecan (T-DXd)
HER2 targeting Ab	Trastuzumab	Trastuzumab
Linker	Non-Cleavable	Cleavable (in tumor, stable in plasma)
Drug-Antibody Ratio (DAR)	3.5:1	8:1
Payload	Mytansine derivative	Extecan derivative
Mechanism of action	Antimicrotubule agent	Topoisomerase inhibitor
Bystander Effect	No	Yes

Ogitani Cancer Sci 2016; Eiger Cancer 2021

# Trastuzumab emtansine in HER2 exon 20 mutation positive NSCLC



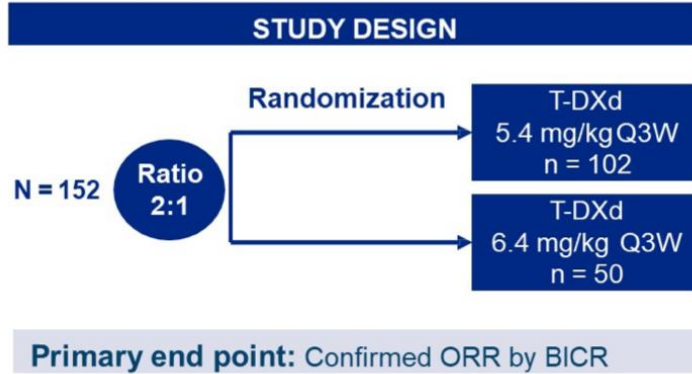
N=22

ORR:38.1%, median DOR 3.5 months

Median PFS 2.8 months



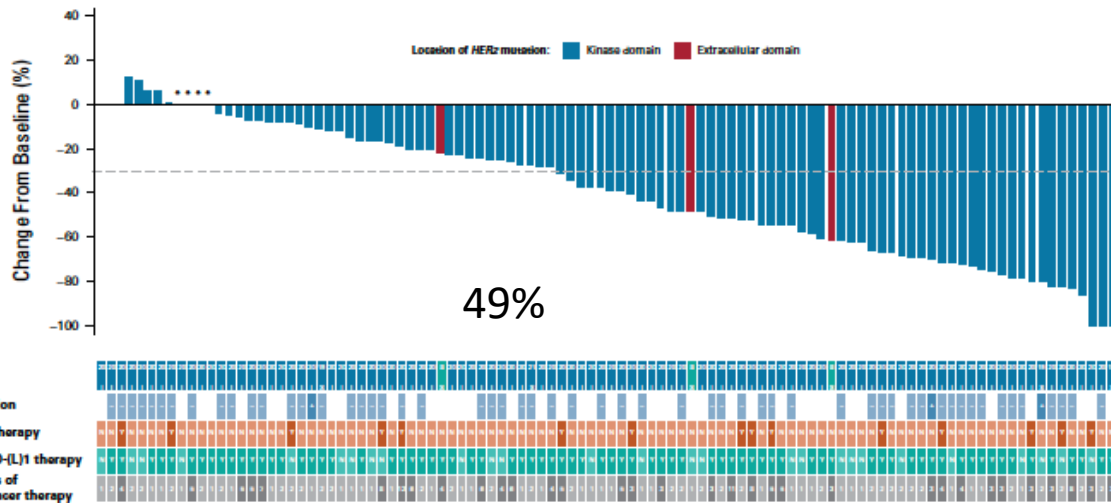
# Destiny Lung-02



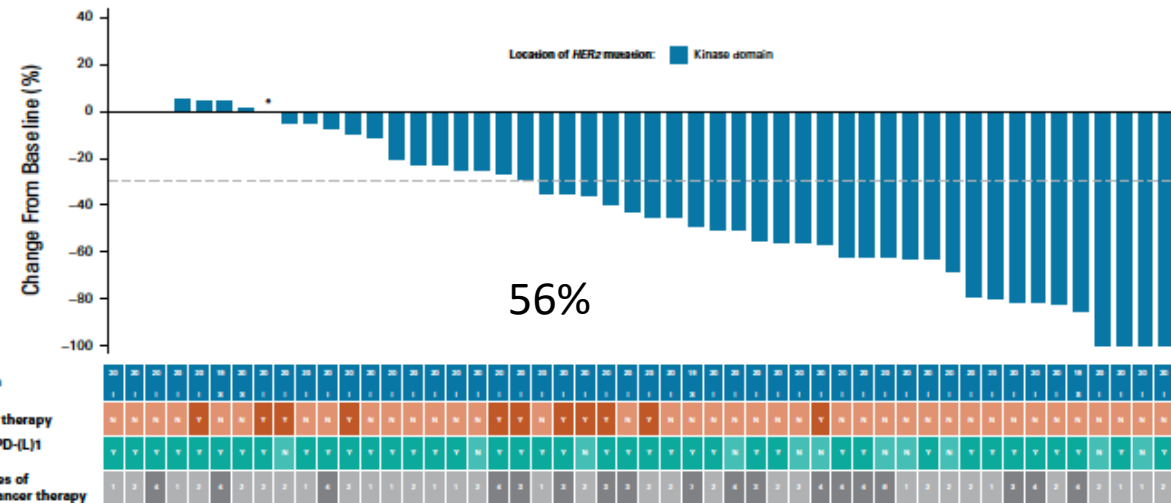
Non comparative design

DESTINY-Lung02 is a randomized, phase 2 trial assessing the efficacy and safety of 2 doses of T-DXd (5.4 and 6.4 mg/kg) in previously patients with metastatic *HER2m* NSCLC

A



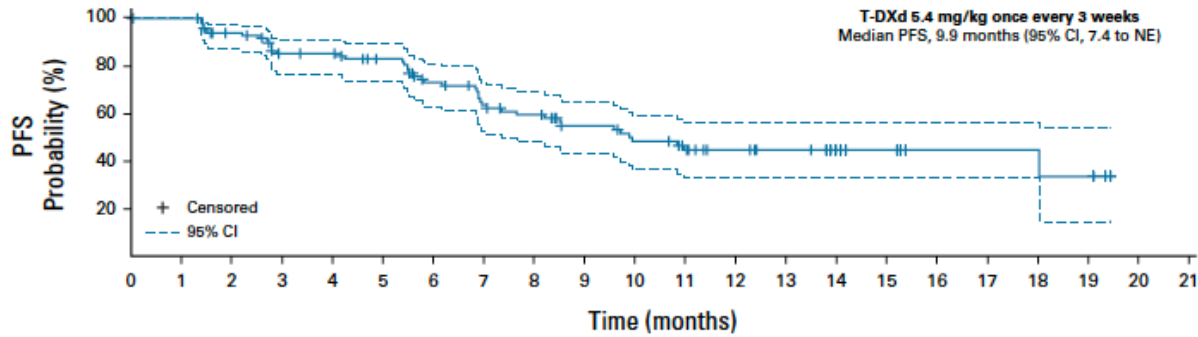
B



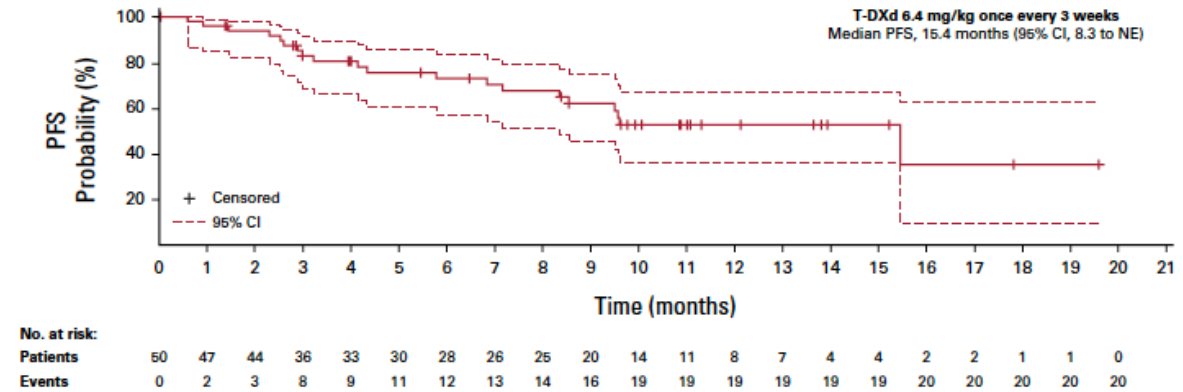


# Destiny Lung-02

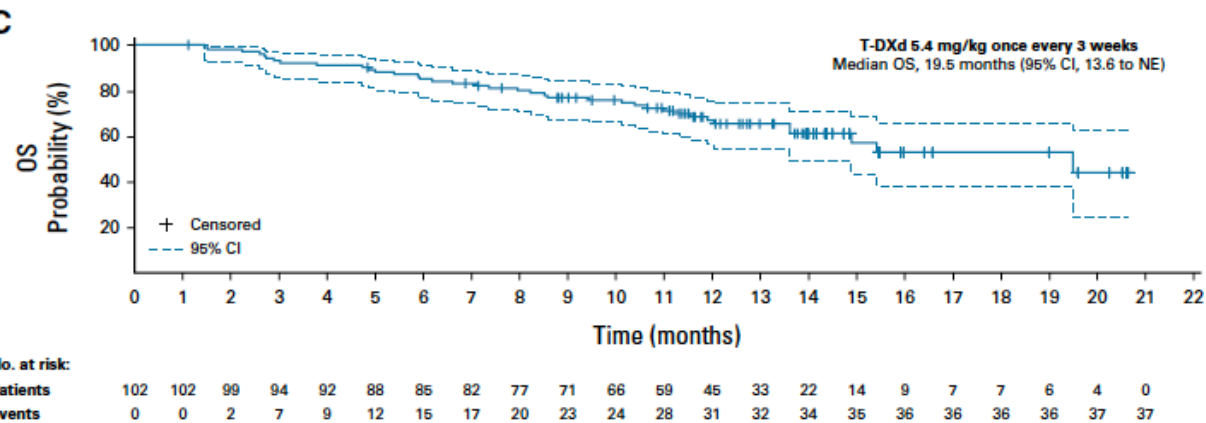
**A** PFS With T-DXd 5.4 mg/kg  
Median PFS: 9.9 mo (95% CI: 7.4-NE)



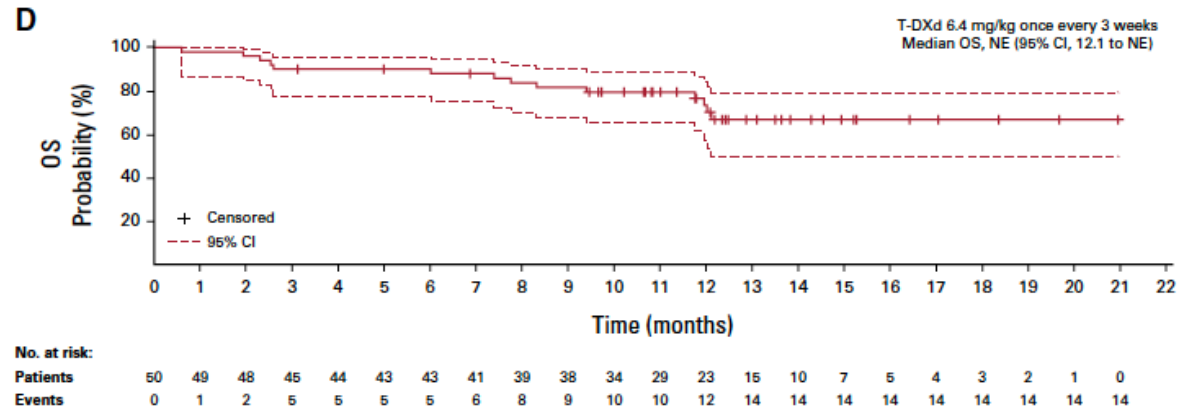
**B** PFS With T-DXd 6.4 mg/kg  
Median PFS: 15.4 mo (95% CI: 8.3-NE)



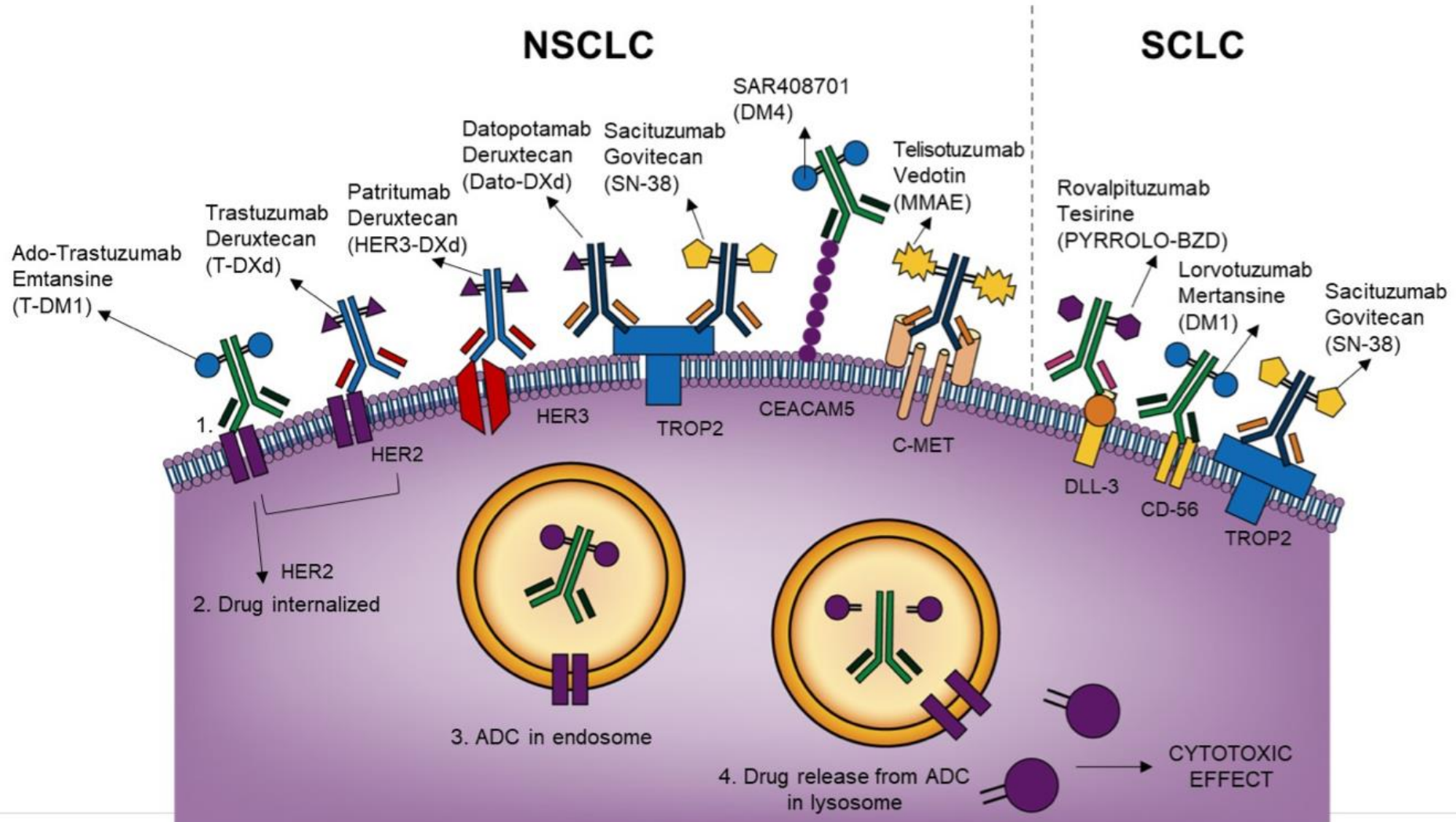
**C** OS With T-DXd 5.4 mg/kg  
Median OS: 19.5 mo (95% CI: 13.6-NE)



**D** OS With T-DXd 6.4 mg/kg  
Median OS: NE (95% CI: 12.1-NE)



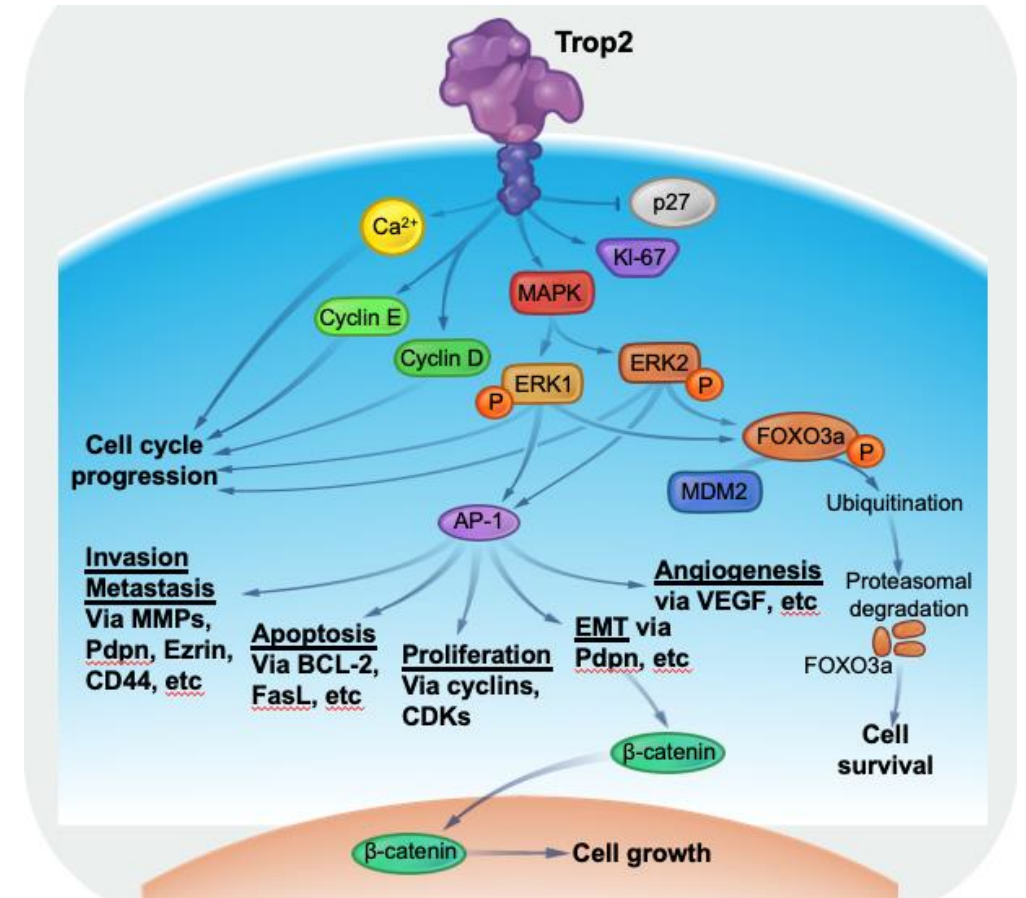
# Câncer de pulmão: antígenos/ADCs promissores



# TROP2 Is a Transmembrane Glycoprotein

- TROP2 is a transmembrane glycoprotein that is expressed in various epithelial tissues, including:
  - Lung, breast, stomach, bladder, uterine, head and neck, esophageal, skin, pancreatic, prostate, colorectal, and liver (bile duct)<sup>1-4</sup>
- While the physiological function of TROP2 is still under investigation, it appears that TROP2 plays a role in multiple intracellular signaling pathways<sup>3-7</sup>
  - Preclinical evidence suggests that TROP2 promotes cell proliferation, cell survival, invasion, and metastasis<sup>4-6</sup>

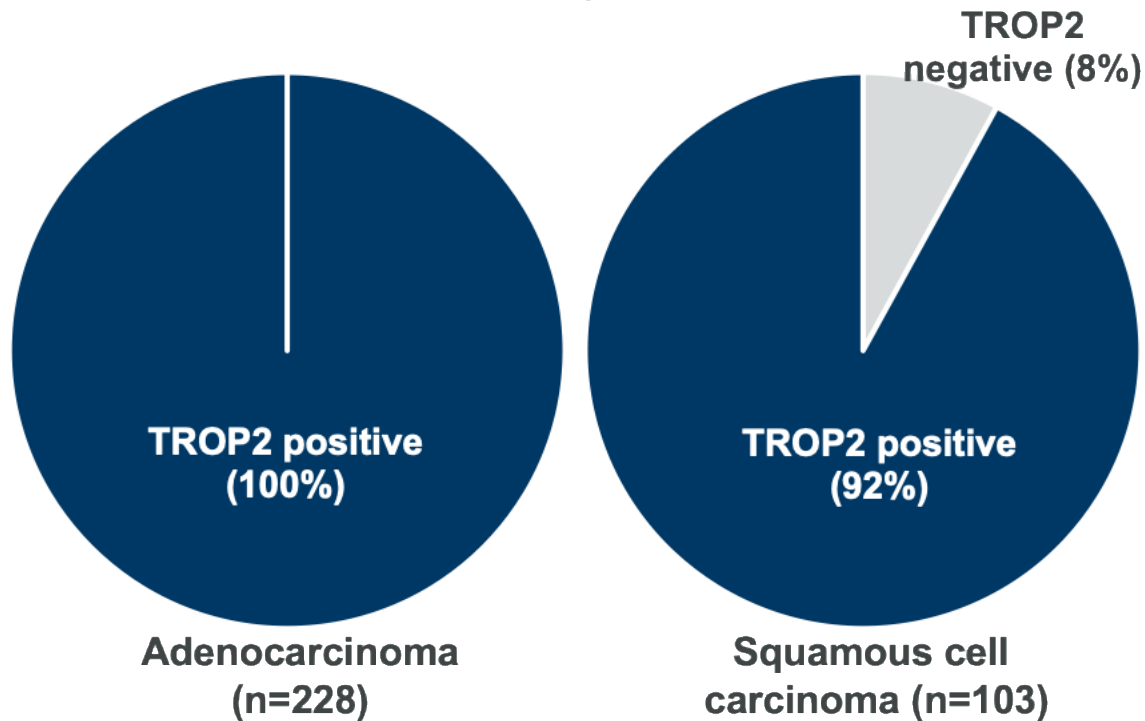
## Cell Signaling and Functions of TROP2<sup>4-7</sup>



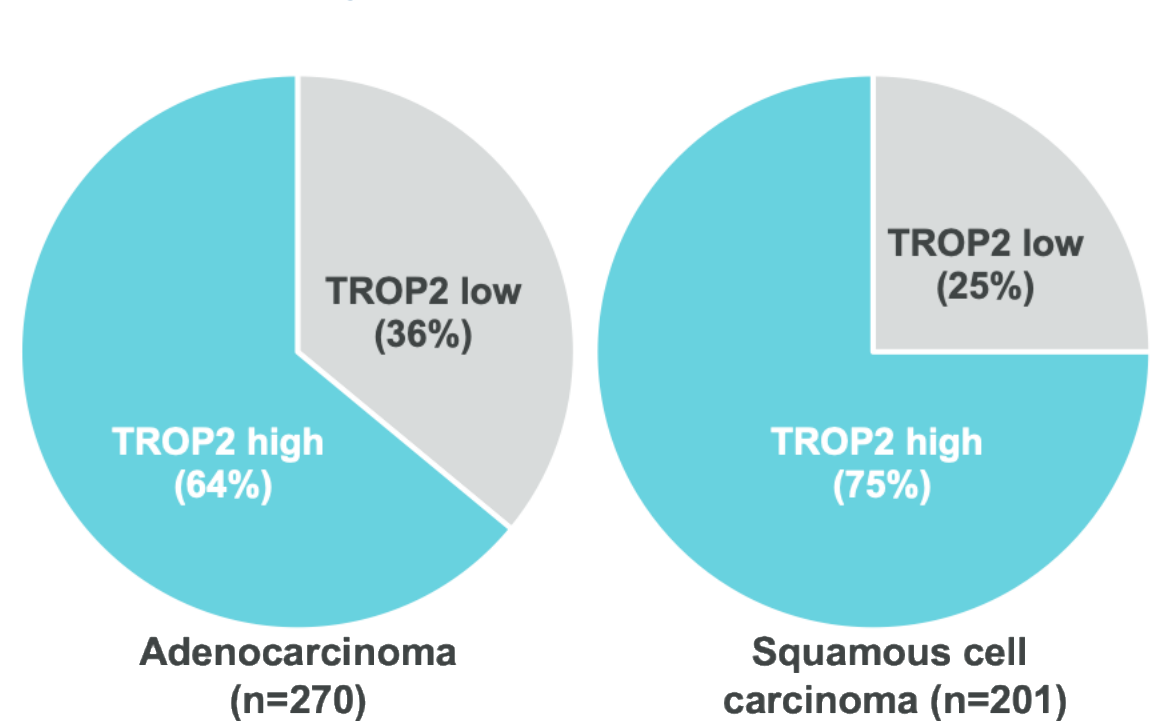
# TROP2 Has Been Found to Be Widely Expressed in NSCLC<sup>1,2</sup>

- TROP2 has been found to be highly expressed in NSCLC, determined by TROP2 immunostaining of paraffin-embedded sections of patient tumor samples in multiple studies<sup>1,2</sup>

**Proportion of Lung Cancers With TROP2 Positive/Negative Expression<sup>1,a</sup>**



**Proportion of Lung Cancers With High/Low TROP2 Expression<sup>2,a</sup>**



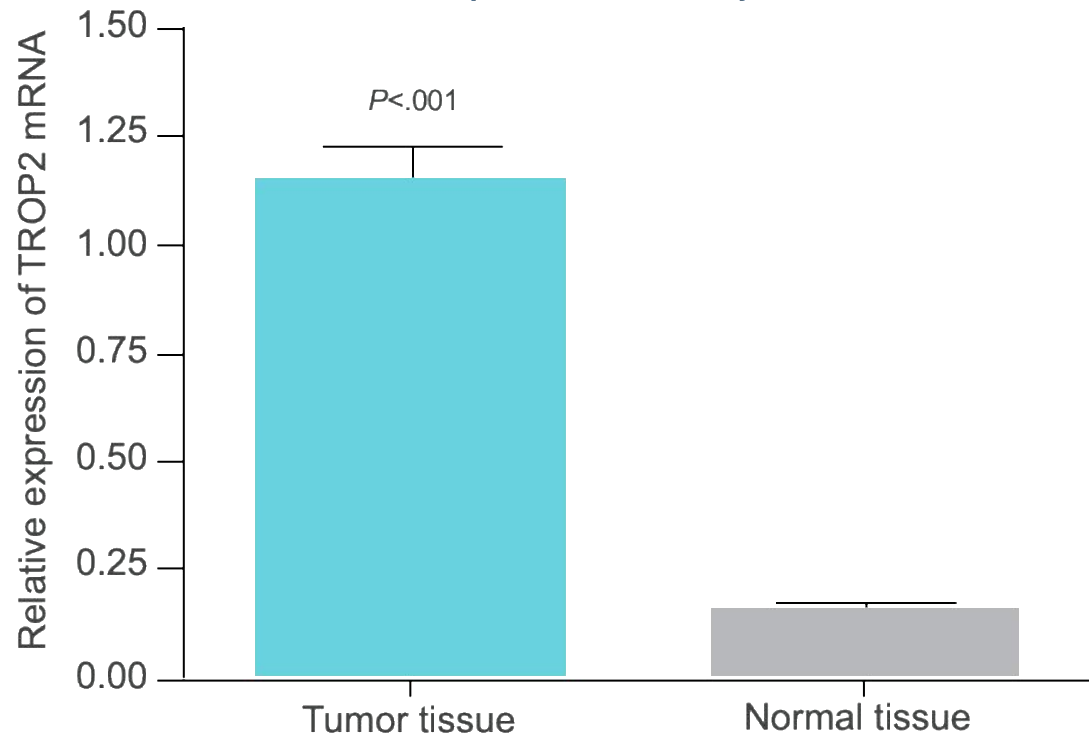
<sup>a</sup>TROP2 expression was measured by IHC and scored based on a combination of intensity and proportion of cells with that intensity. Please see slide notes for additional information on how TROP2 scores were defined.

1. Mito R, et al. *Pathol Int.* 2020;70:287-294. 2. Inamura K, et al. *Oncotarget.* 2017;8:28725-28735.

# TROP2 Expression Is Higher in NSCLC Tissue Than in Normal Adjacent Tissue<sup>1,2</sup>

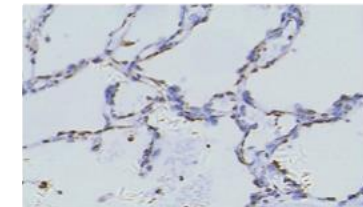
TROP2 protein expression has been found to be higher in tumor tissue than in normal tissue based on immunohistochemical staining of paraffin-embedded tissue samples<sup>1,2</sup>

## TROP2 Expression in NSCLC and Matched Normal Tissues (n=20; $P<.001$ )<sup>1</sup>

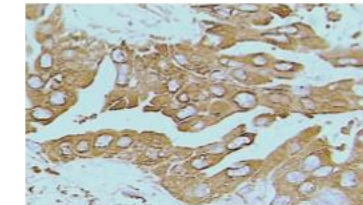


## IHC Staining of TROP2 Expression<sup>2</sup>

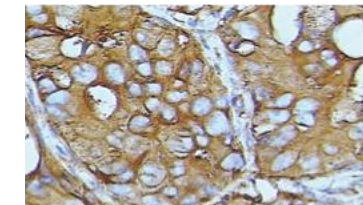
Normal tissue



Adenocarcinoma



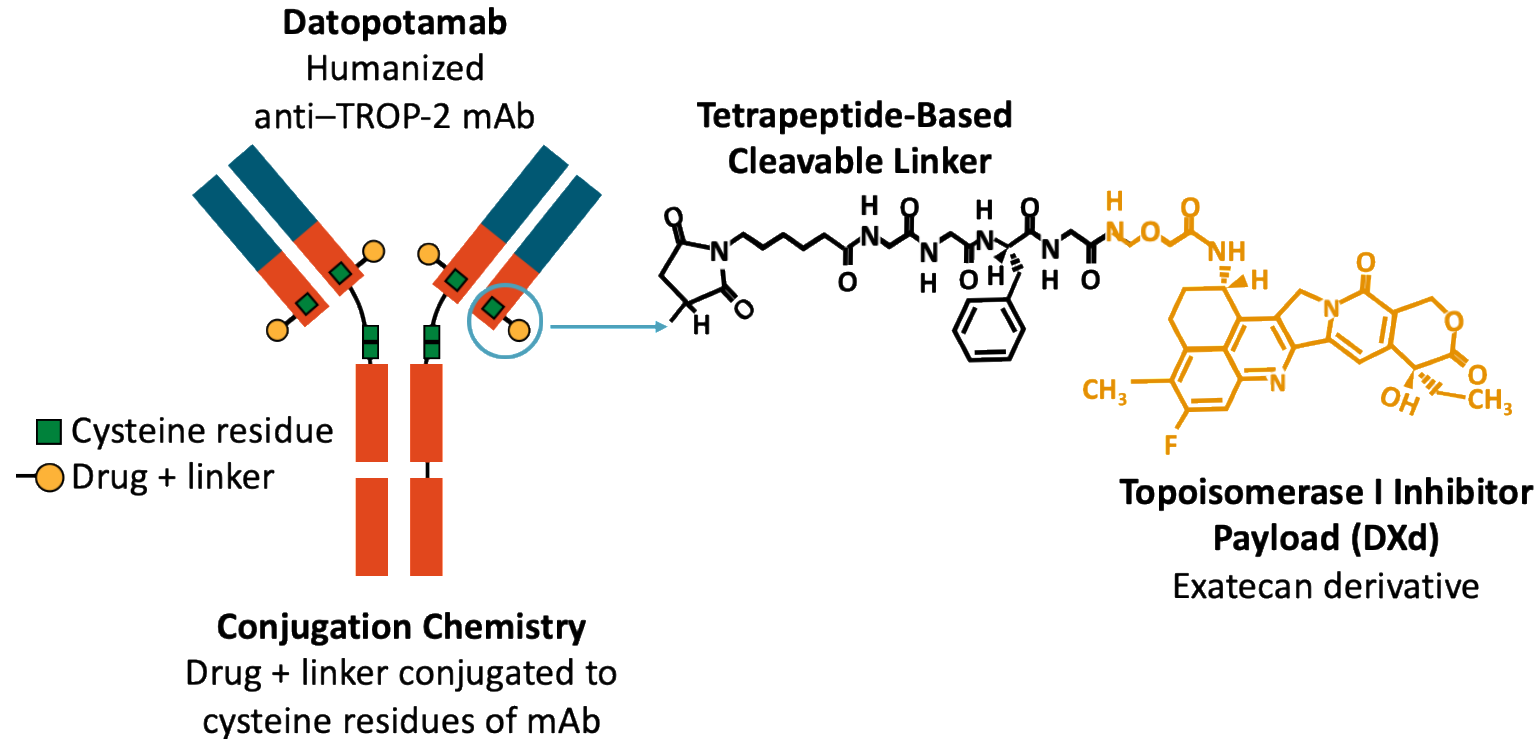
Squamous cell carcinoma



TROP2 expression was higher in advanced NSCLC tissues than in tumor-adjacent normal tissues ( $P=.000$ ; advanced NSCLC, n=87; tumor-adjacent normal tissues, n=17)

- 1. Li Z, et al. *Biochem Biophys Res Commun.* 2016;470:197-204. 2. Jiang A, et al. *Oncol Lett.* 2013;6:375-380.

# Datopotamab Deruxtecan: TROP2-Targeted ADC



- High-potency, membrane-permeable payload with short systemic half-life
- Optimized DAR: ~4:1
- Stable linker–payload
- Tumor-selectable cleavable linker
- Bystander killing effect
- Payload mechanism of action: topoisomerase I inhibitor<sup>1-3t</sup>

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

<sup>a</sup>Equal contribution as first author. <sup>b</sup>Indicates presenting author.

<sup>1</sup>Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; <sup>2</sup>David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; <sup>3</sup>Hospital Universitario 12 de Octubre, CNIO-H120 Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; <sup>4</sup>Erasmus MC Cancer Institute, Rotterdam, The Netherlands; <sup>5</sup>Institut Curie, Paris, France; <sup>6</sup>Centre Hospitalier Universitaire de Nantes, Nantes, France; <sup>7</sup>Hospital Universitario Virgen Macarena, Seville, Spain; <sup>8</sup>Sendai Kousei Hospital, Sendai, Japan; <sup>9</sup>FEA Oncología Médica, Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; <sup>10</sup>Centre Léon Bérard, Lyon, France; <sup>11</sup>Hôpitaux Universitaires de Strasbourg (CHRU), Strasbourg, France; <sup>12</sup>Vitamed LLC, Moscow, Russia; <sup>13</sup>The Cancer Institute Hospital of JFCR, Tokyo, Japan; <sup>14</sup>Kindai University, Osaka, Japan; <sup>15</sup>Dana-Farber Cancer Institute, Boston, MA, USA; <sup>16</sup>University of Virginia Health System, Charlottesville, VA, USA; <sup>17</sup>Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; <sup>18</sup>Daiichi Sankyo Europe GmbH, Munich, Germany; <sup>19</sup>Kyushu University Hospital, Fukuoka, Japan



# 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<sup>a</sup>**
- 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<sup>2</sup> Q3W  
(N=305)

## Dual Primary Endpoints

- PFS by BICR
- OS

## Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

**Stratified by:** histology,<sup>b</sup> actionable genomic alteration,<sup>c</sup> anti-PD-(L)1 mAb included in most recent prior therapy, geography<sup>d</sup>

Enrollment period: 19 February 2021 to 7 November 2022.

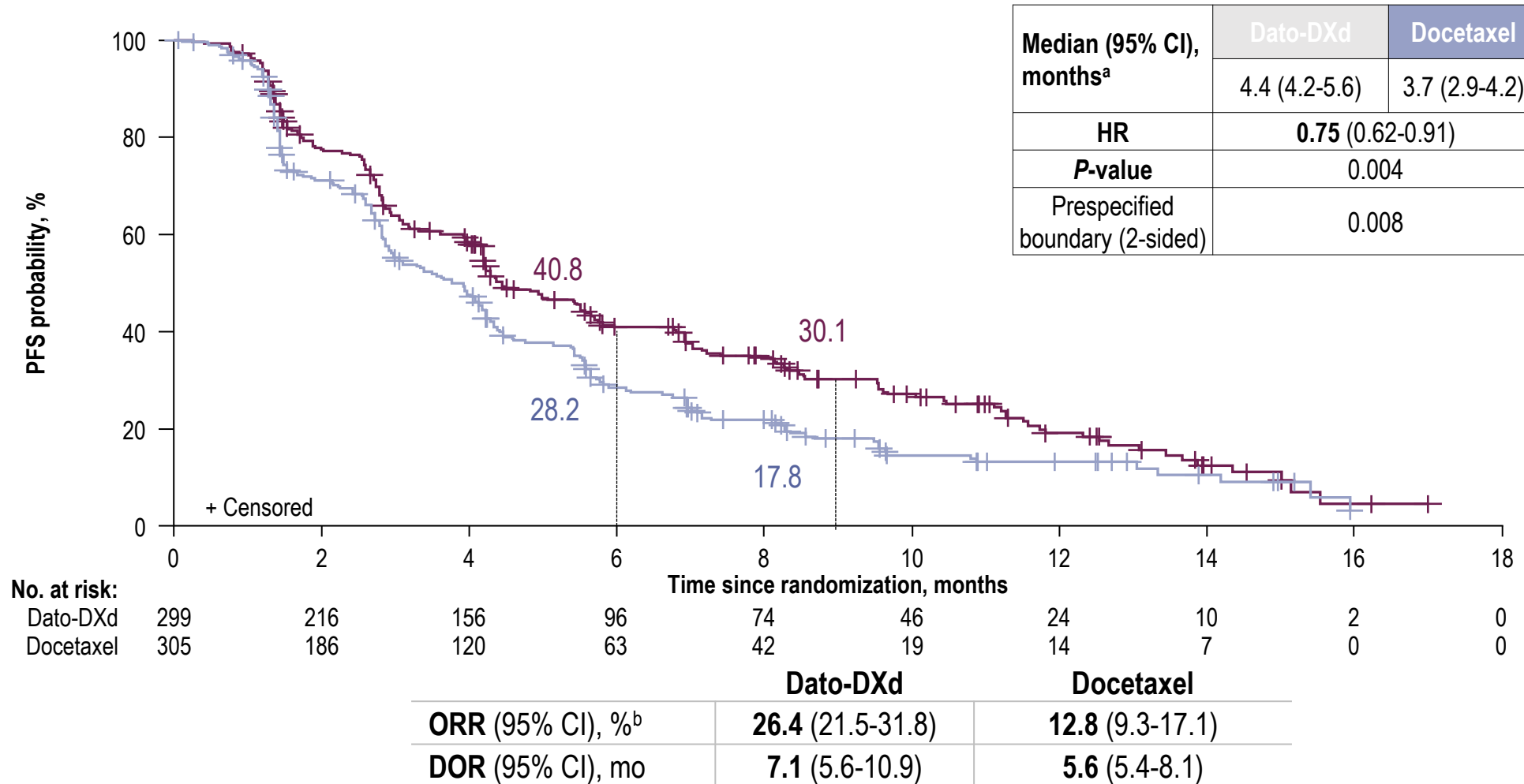
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand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

<sup>a</sup>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. <sup>b</sup>Squamous vs non-squamous.

<sup>c</sup>Presence vs absence. <sup>d</sup>United States/Japan/Western Europe vs rest of world.



# Progression-Free Survival: ITT



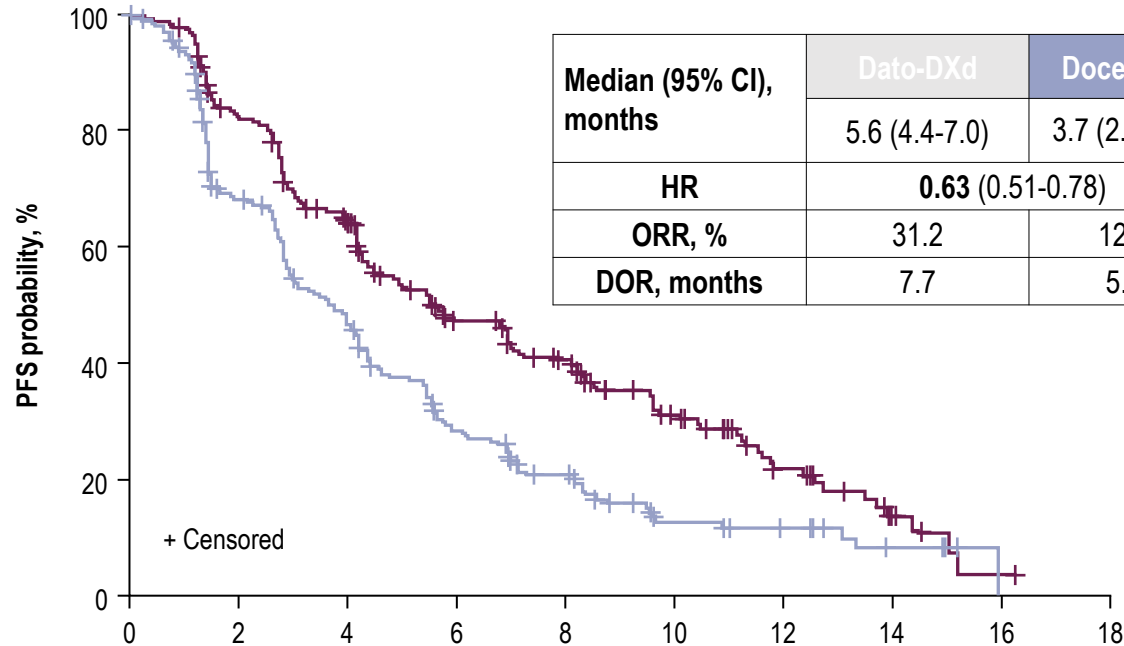
CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

<sup>a</sup>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. <sup>b</sup>Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

# PFS by Histology

## Non-squamous

(with and without AGAs)

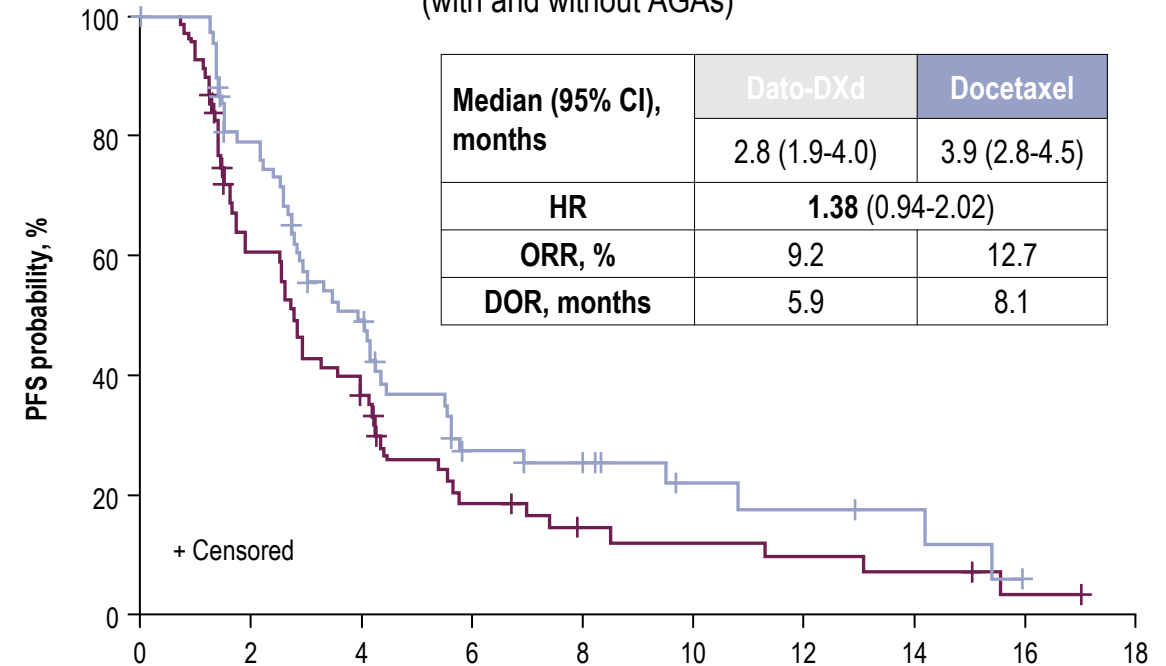


Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	<b>0.63 (0.51-0.78)</b>	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

No. at risk	Time since randomization, months									
	0	2	4	6	8	10	12	14	16	18
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	<b>1.38 (0.94-2.02)</b>	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

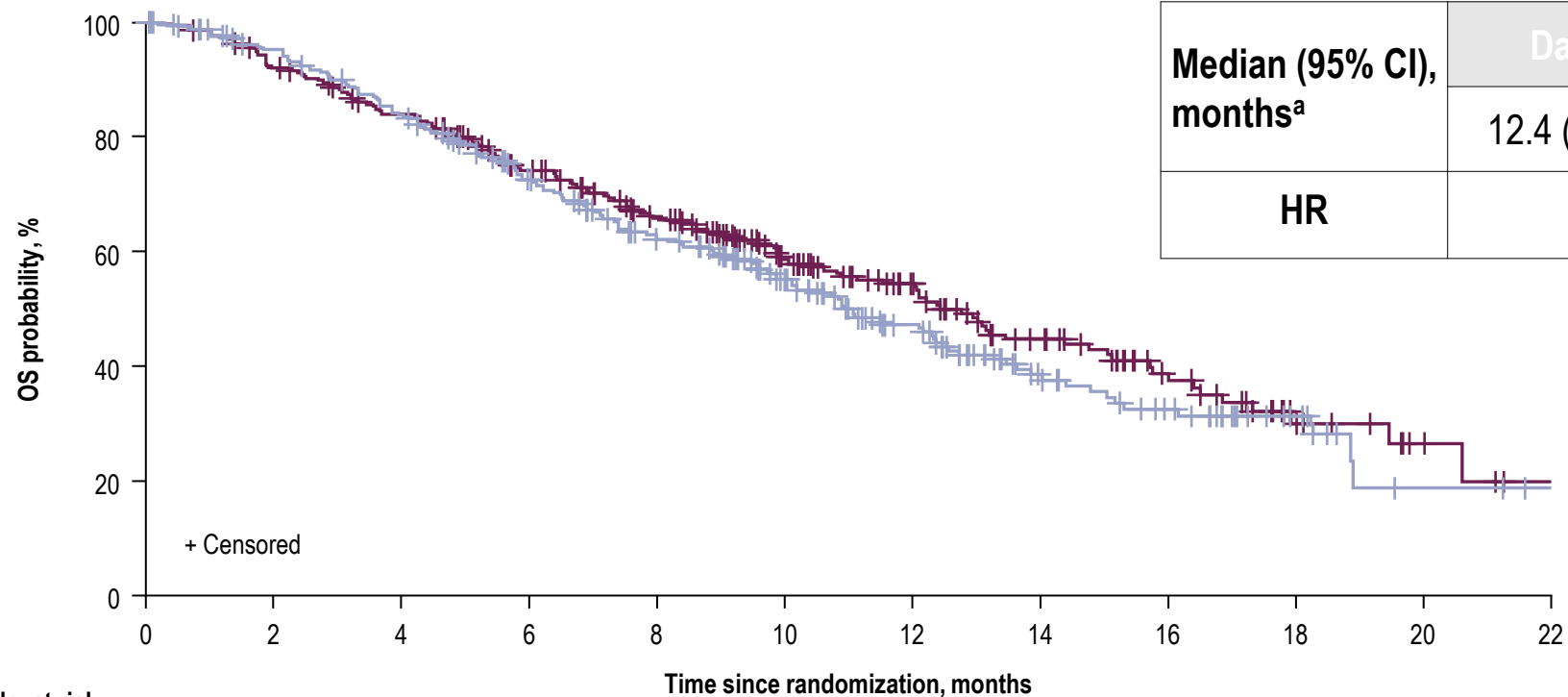
No. at risk	Time since randomization, months									
	0	2	4	6	8	10	12	14	16	18
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

**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 rate; PFS, progression-free survival.

Squamous subset included 3 patients with AGAs

# Interim Overall Survival: ITT



<b>Median (95% CI), months<sup>a</sup></b>	<b>Dato-DXd</b>	<b>Docetaxel</b>
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
<b>HR</b>	<b>0.90 (0.72-1.13)</b>	

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

No. at risk	Time since randomization, months											
	0	2	4	6	8	10	12	14	16	18	20	22
Dato-DXd	299	273	243	201	166	121	85	56	33	14	6	1
Docetaxel	305	273	239	193	156	115	76	42	29	13	4	1

**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.

<sup>a</sup>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.

# TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

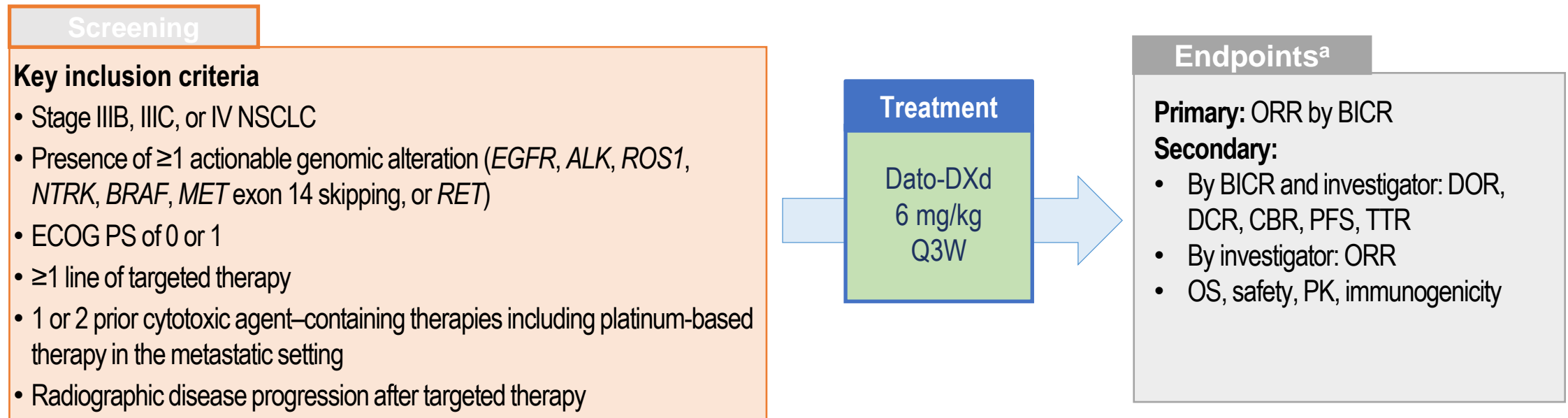
Luis Paz-Ares,<sup>1</sup> Myung-Ju Ahn,<sup>2</sup> Aaron Lisberg,<sup>3</sup> Satoru Kitazono,<sup>4</sup> Byoung Chul Cho,<sup>5</sup> George Blumenschein Jr,<sup>6</sup> Elaine Shum,<sup>7</sup> Elvire Pons Tostivint,<sup>8</sup> Yasushi Goto,<sup>9</sup> Kiyotaka Yoh,<sup>10</sup> Rebecca Heist,<sup>11</sup> Paul Baas,<sup>12</sup> David Planchard,<sup>13</sup> Maurice Pérol,<sup>14</sup> Enriqueta Felip,<sup>15</sup> Wu-Chou Su,<sup>16</sup> Hong Zebger-Gong,<sup>17</sup> Lan Lan,<sup>18</sup> Chelsea Liu,<sup>18</sup> Jacob Sands<sup>19</sup>

<sup>1</sup>Hospital Universitario 12 de Octubre, Madrid, Spain; <sup>2</sup>Samsung Medical Center, Seoul, South Korea; <sup>3</sup>David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; <sup>4</sup>The Cancer Institute Hospital of JFCR, Tokyo, Japan; <sup>5</sup>Severance Hospital, Seoul, South Korea; <sup>6</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>7</sup>NYU Langone Health Perlmutter Cancer Center, New York, NY, USA; <sup>8</sup>University Hospital of Nantes, Nantes, France; <sup>9</sup>National Cancer Center Hospital, Tokyo, Japan; <sup>10</sup>National Cancer Center Hospital East, Kashiwa, Japan; <sup>11</sup>Massachusetts General Hospital Cancer Center, Boston, MA, USA; <sup>12</sup>The Netherlands Cancer Institute, Amsterdam, the Netherlands; <sup>13</sup>Gustave Roussy, Villejuif, France; <sup>14</sup>Centre Léon Bérard, Lyon, France; <sup>15</sup>Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; <sup>16</sup>National Cheng Kung University Hospital, Tainan, Taiwan; <sup>17</sup>Daiichi Sankyo Europe GmbH, Munich, Germany; <sup>18</sup>Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; <sup>19</sup>Dana-Farber Cancer Institute, Boston, MA, USA



# Introduction and Study Design

- **Dato-DXd** is a TROP2-directed ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker<sup>1</sup>
- In the **phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations<sup>2</sup>
- **TROPION-Lung05** (NCT04484142) is a **phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy



ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2; TTR, time to response.

<sup>a</sup>The primary completion date will occur when all patients have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study.

1. Okajima D, et al. *Mol Cancer Ther.* 2021;20:2329-2340. 2. Shimizu T, et al. *J Clin Oncol.* Published online June 16, 2023.

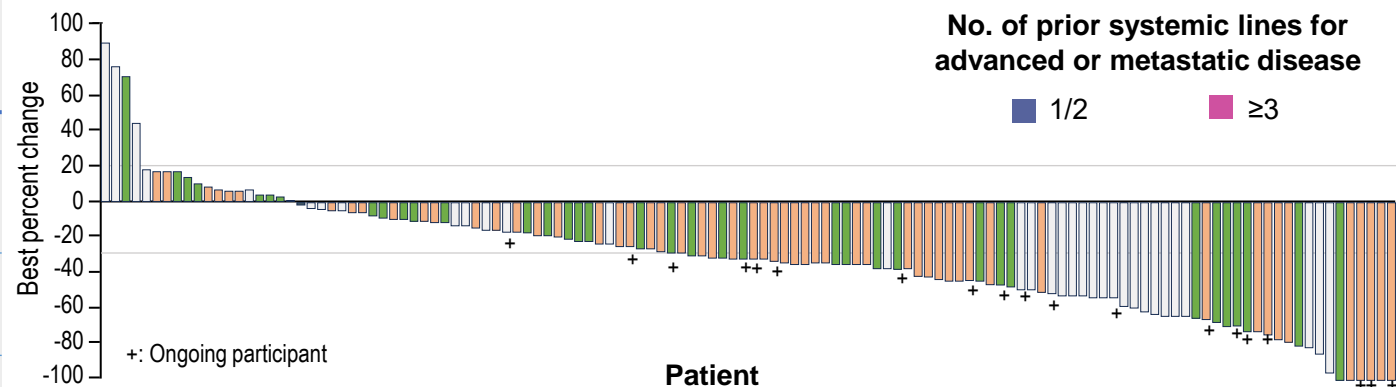
# Efficacy Summary

Response per BICR	All treated patients (N=137)	Patients with <i>EGFR</i> mutations (N=78)	Patients with <i>ALK</i> rearrangement (N=34)
<b>ORR confirmed, n (%)</b> [95% CI] <sup>a</sup>	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
<b>Median DOR (95% CI), months</b>	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
<b>DCR confirmed, n (%)</b> [95% CI] <sup>a</sup>	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
<b>Median PFS, (95% CI), months<sup>b</sup></b>	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

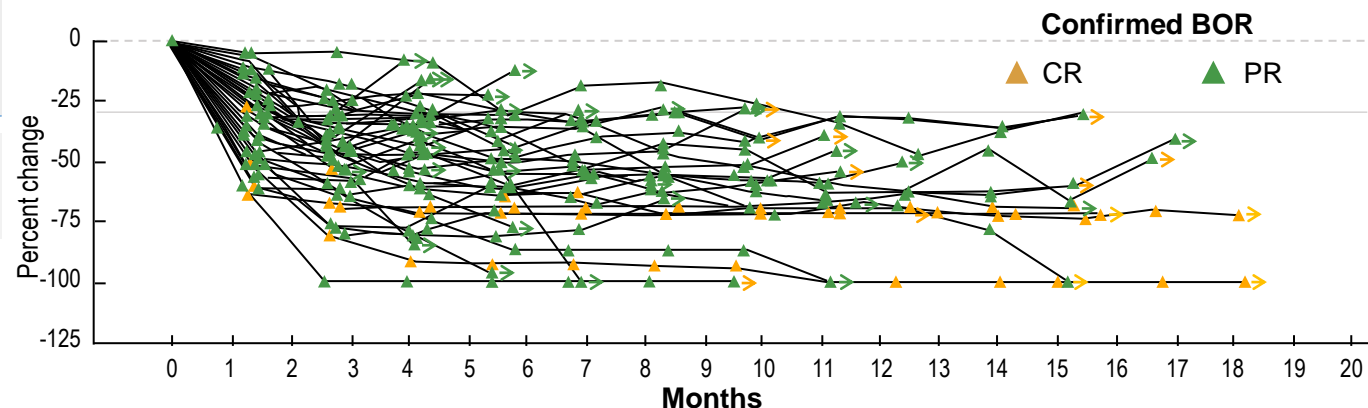
**BOR:** In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

**Best Percent Change From Baseline in Sum of Diameters of Target Lesions**



**Percent Change From Baseline in Sum of Diameters of Target Lesions in Patients With Confirmed CR/PR<sup>c</sup>**



BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

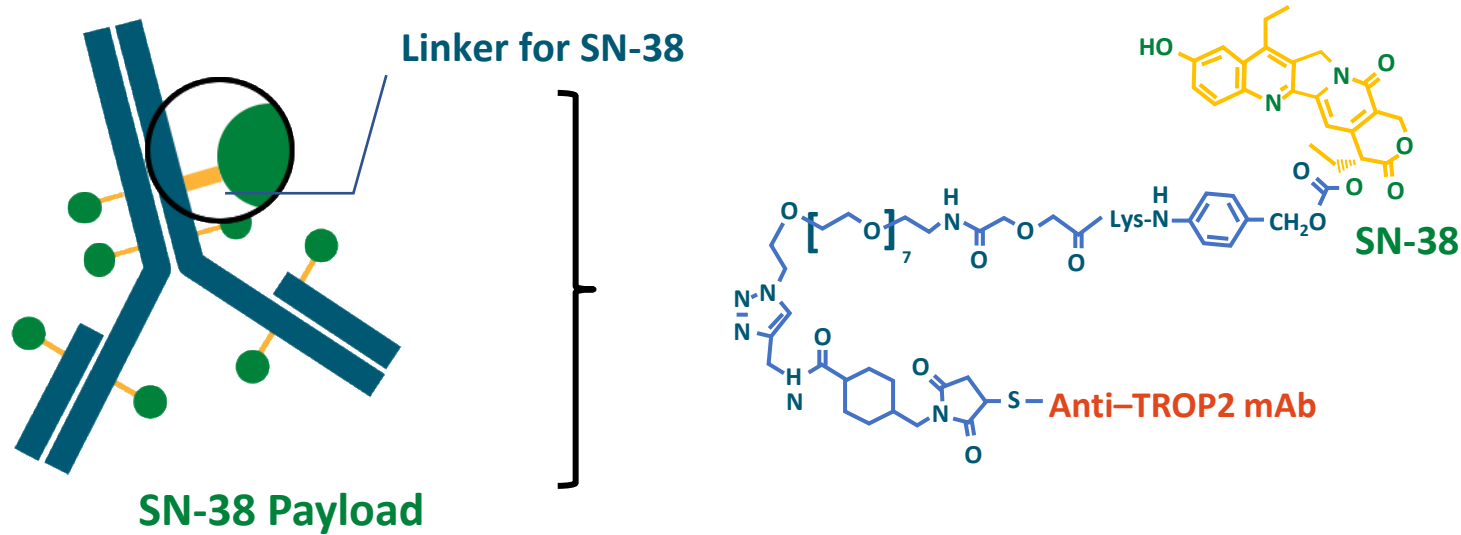
<sup>a</sup>The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method. <sup>b</sup>Median PFS and PFS probabilities are based on the Kaplan-Meier method. <sup>c</sup>Per BICR.

# Estudos com ADCs TROP2 em combinação na 1ª linha para CPNPC

TROPION-Lung02	IB	Dato-DXd + pembro + pembro + platinum	1L/2L	NCT04526691
TROPION-Lung04	IB	Dato-DXd + durva + durva + platinum	1L/2L	NCT04612751
TROPION-Lung07	III	Dato-DXd + pembro + platinum Dato-DXd + pembro Pembro + pemetrexed + platinum	1L PDL1 < 50%	NCT05555732
TROPION-Lung08	III	Dato-DXd + pembro Pembro	1L PDL1 ≥ 50%	NCT05215340
AVANZAR	III	Dato-DXd + durva + carboplatin Pembro + histology-specific platinum doublet	1L	NCT05687266
EVOKE-03	III	Sacituzumab + pembro Pembro	1L PDL1 ≥ 50%	NCT05609968
EVOKE-02	II	Sacituzumab + pembro Sacituzumab + pembro + platinum	1L	NCT05186974

# Sacituzumab Govitecan: TROP2-Targeted ADC

## Humanized RS7 Antibody

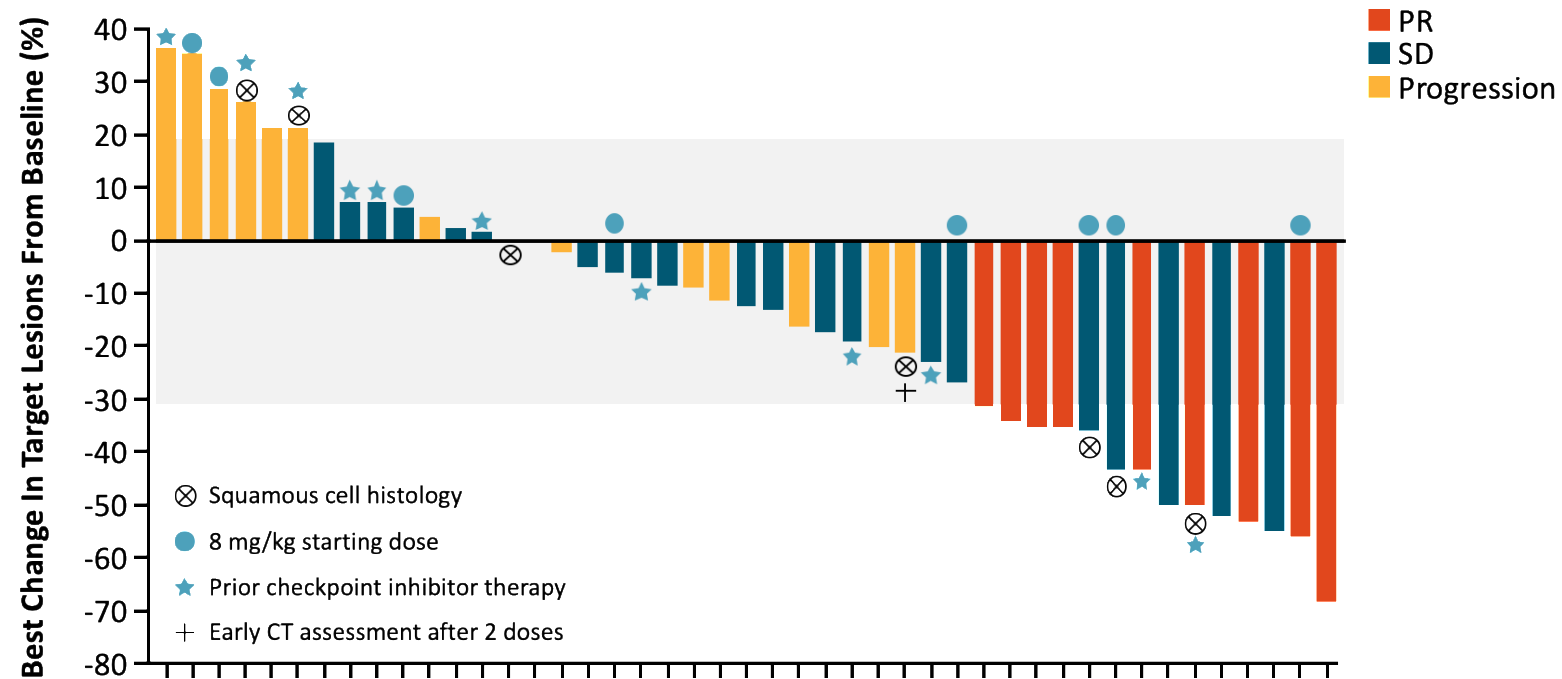


**Bystander effect:** In acidic tumor microenvironment, SN-38 is released from anti-TROP2 antibody, diffuses into neighboring TROP2-negative cells

- Targets TROP2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor
- Delivers 136-fold more than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



# ADCs targets in NSCLC: TROP2 - IMMU-132-01 Sacituzumab Govitecan



	NSCLC Cohort (n = 54)
ORR, % (95% CI)	16.7 (7.9-29.3)
PR, n (%)	9 (16.7)
SD, n (%)	22 (40.7)
Median DOR, mo (95% CI)	6.0 (2.5-21.0)
Median OS, mo (95% CI)	7.3 (5.6-14.6)
Median PFS, mo (95% CI)	4.4 (2.5-5.4)

Heist. JCO. 2017;35:2790.

Bardia A et al. Ann Oncol. 2021

# Sacituzumab govitecan as second-line treatment for extensive stage small cell lung cancer

Preliminary results from the phase 2 TROPiCS-03 basket trial

Afshin Dowlati,<sup>1</sup> Andres Cervantes,<sup>2</sup> Sunil Babu,<sup>3</sup> Erika Hamilton,<sup>4</sup> Shu Fen Wong,<sup>5</sup> Andrea Tazbirkova,<sup>6</sup> Ivana Gabriela Sullivan,<sup>7</sup> Cédric van Marcke,<sup>8</sup> Antoine Italiano,<sup>9</sup> Jilpa Patel,<sup>10</sup> Sabeen Mekan,<sup>10</sup> Tia Wu,<sup>10</sup> Anne C. Chiang<sup>11</sup>

<sup>1</sup>University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; <sup>2</sup>INCLIVA Instituto de Investigación Sanitaria, University of Valencia, Valencia, Spain; <sup>3</sup>Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; <sup>4</sup>Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; <sup>5</sup>Andrew Love Cancer Centre, Geelong, Australia; <sup>6</sup>Pindara Private Hospital, Benowa, Queensland, Australia; <sup>7</sup>Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; <sup>8</sup>Cliniques Universitaires Saint-Luc, Brussels, Belgium; <sup>9</sup>Institut Bergonié, Bordeaux, France; <sup>10</sup>Gilead Sciences, Inc., Foster City, CA, USA; <sup>11</sup>Yale School of Medicine, New Haven, CT, USA

**Presenter: Afshin Dowlati, MD**

Saturday, October 21, 2023, 14:55-15:00

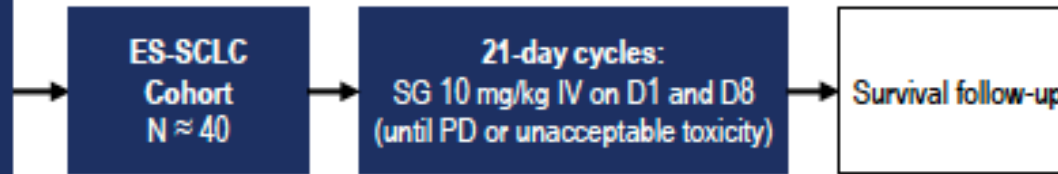
FPN: 1990MO



# Sacituzumab Govitecan in second line SCLC

## Key eligibility criteria

- Histologically confirmed ES-SCLC
- Disease progression after no more than 1 prior line of platinum-based chemo and anti-PD-(L)1 therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- No known active CNS metastases and/or carcinomatous meningitis<sup>a</sup>



## End points

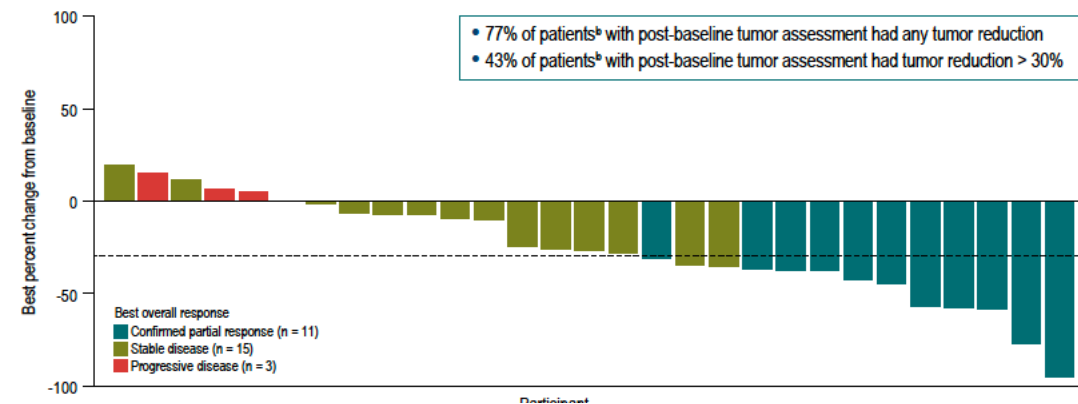
### Primary

- ORR by INV<sup>b</sup>

### Secondary

- DOR, CBR, PFS (all by INV<sup>b</sup>)
- ORR, DOR, CBR, PFS (all by BICR<sup>b</sup>)
- OS
- Safety

Efficacy by INV <sup>a</sup>	ES-SCLC N = 30 <sup>b</sup>
ORR [Confirmed CR + PR] (95% CI), %	37 (20-56)
<b>BOR, n (%)</b>	
Confirmed PR	11 (37)
SD	15 (50)
PD	3 (10)
DCR [Confirmed CR + PR + SD] (95% CI), %	87 (69-96)
CBR [Confirmed CR + PR + SD ≥ 6 months] (95% CI), %	40 (23-59)
Median DOR (95% CI), <sup>c,d</sup> months	6.3 (2.7-NR)
DOR rate at 6 months (95% CI), <sup>c,d</sup> %	63 (14-89)



**TR 37%**

# Phase I/II IMMU-132-01 Basket Trial of Sacituzumab Govitecan in Solid Tumors: Efficacy

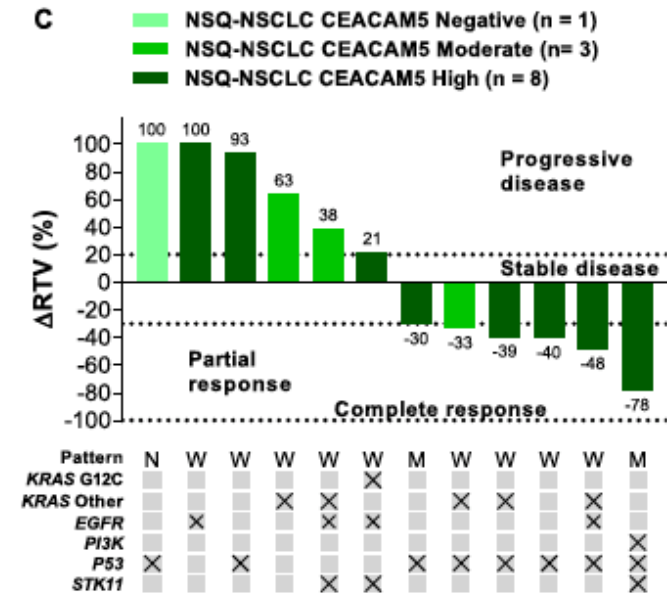
Cohort	n	ORR, %	Median DoR, Mo	Median PFS, Mo (95% CI)	Median OS, Mo (95% CI)
mTNBC	108	33	9.1	5.6 (4.8-6.6)	13.0 (11.2-14.0)
HR+/HER2- mBC	54	32	8.7	5.5 (3.6-7.6)	12.0 (9.0-18.2)
mUC	45	29	12.9	6.8 (3.6-9.7)	16.8 (9.0-21.9)
<b>NSCLC</b>	<b>54</b>	<b>17</b>	<b>6.0</b>	<b>4.4 (2.5-5.4)</b>	<b>7.3 (5.6-14.6)</b>
SCLC	62	18	5.7	3.7 (2.1-4.8)	7.1 (5.6-8.1)

CEACAM5 é uma proteína altamente glicosilada envolvida na migração, adesão e sinalização intercelular

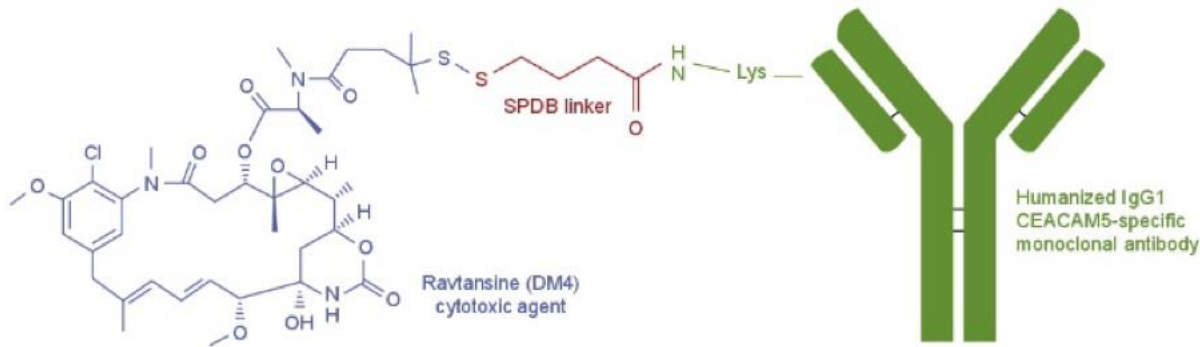
CEACAM5 é altamente expresso no tumor de pulmão



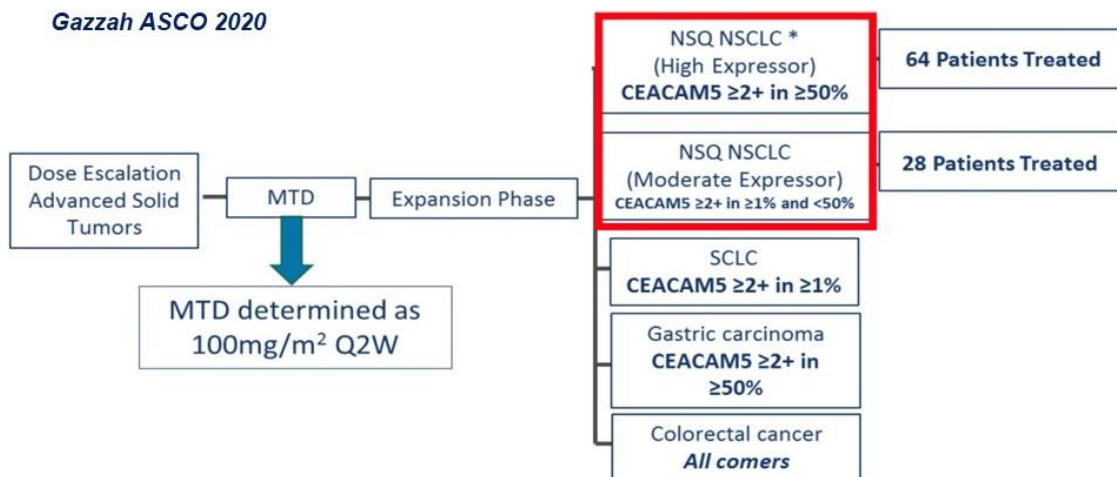
Estudo pre clínico



# Tusamitamab ravtansine: CEACAM5– targeted ADC



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%)



News |

## Sanofi to end tusamitamab ravtansine development after trial failure

Tusamitamab ravtansine did not meet the primary endpoint of progression-free survival versus docetaxel in the CARMEN-LC03 trial.

December 21, 2023

ClinicaTrial.g

CARMEN-LC  
NCT0415495

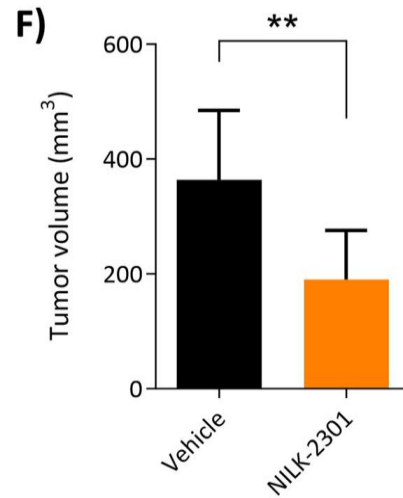
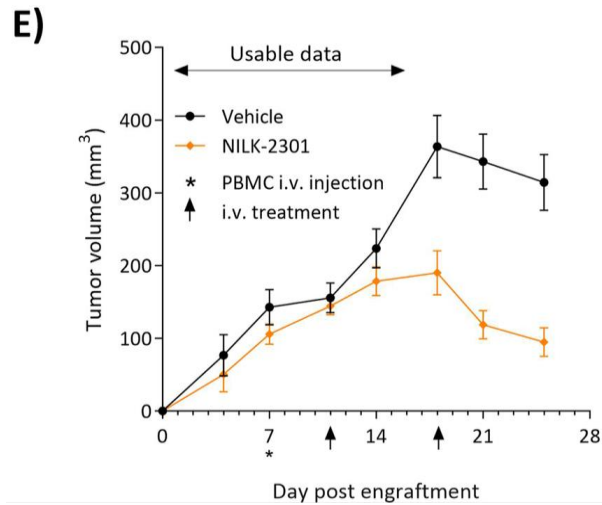
CARMEN-LC  
NCT0452468

t

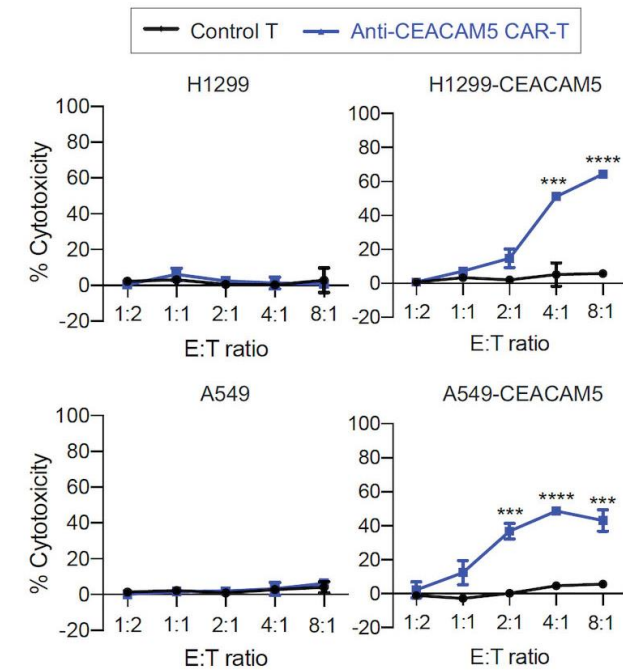
of drug-  
dose-  
toxicity

# ACD biespecífico e CAR-T cells targeting CEACAM5

## NILK-2301, a novel CEACAM5xCD3 κλ bispecific antibody



## Chimeric antigen receptor-T cells against CEACAM5

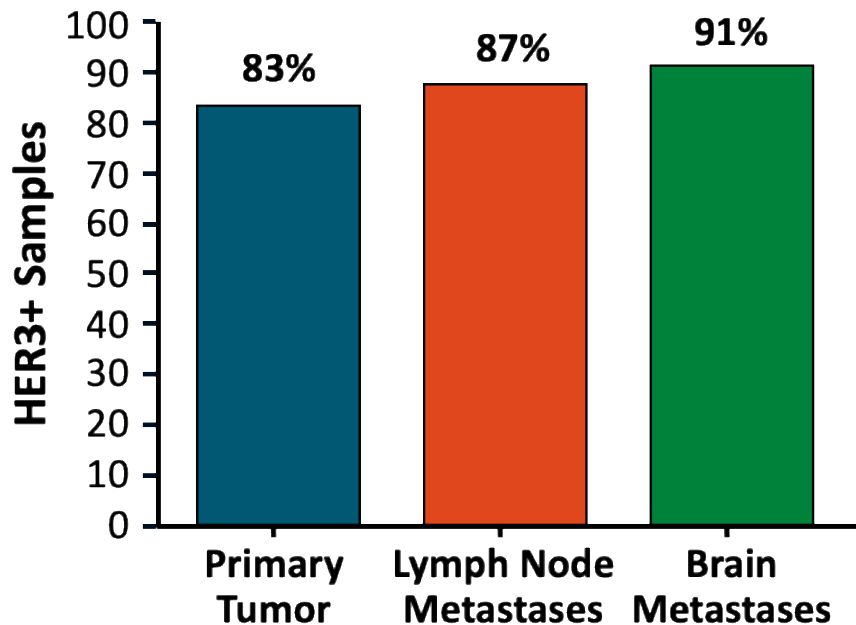




# HER3 ADCs in NSCLC

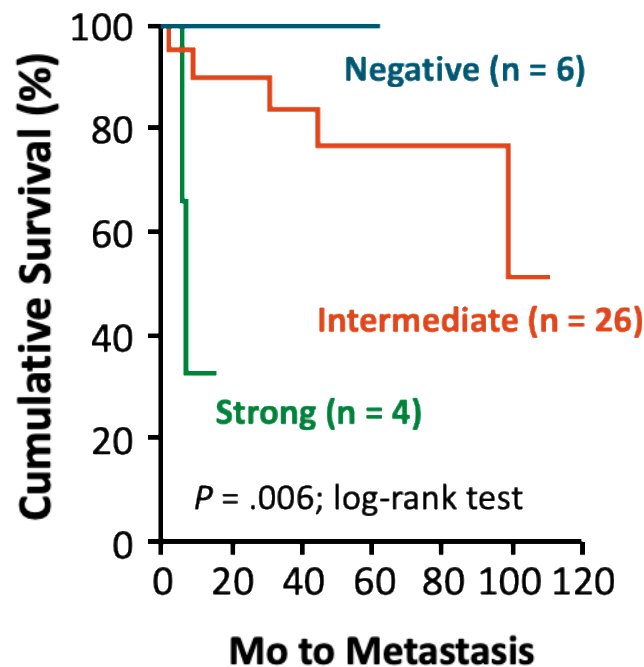
- HER3 is overexpressed in NSCLC primary tumors and metastases
- HER3 expression level is associated with poor prognosis and treatment resistance in NSCLC

## HER3 Expression in NSCLC Metastases

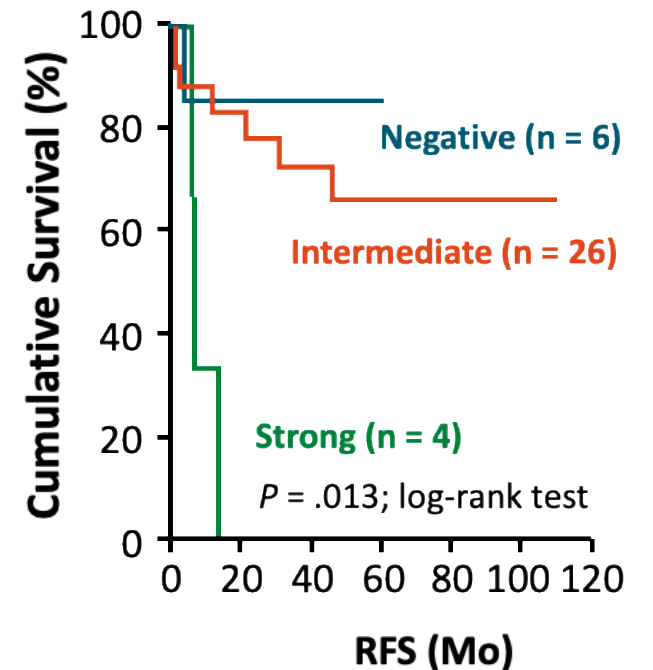


## HER3 Expression and Risk of Progression and Relapse

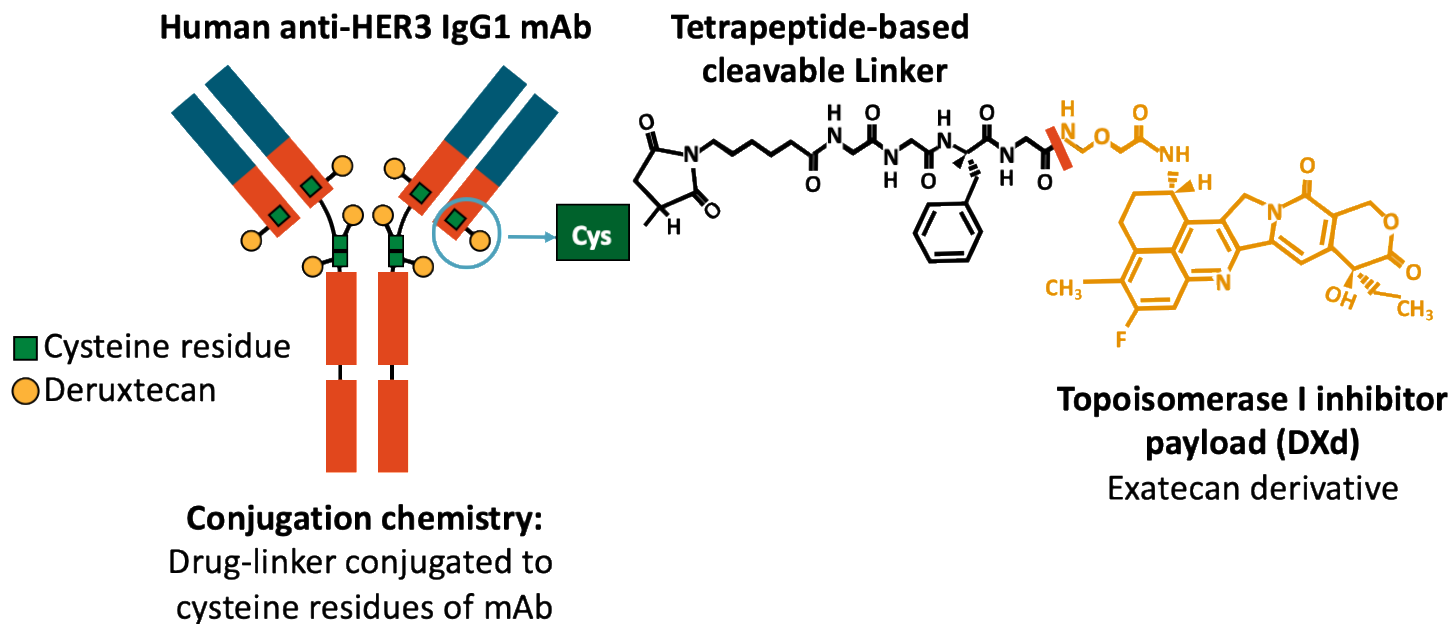
### Metastatic progression



### Relapse-free survival



# Patritumab Deruxtecan (HER-DXd): HER3-Targeted ADC



- High potency, membrane-permeable payload with short systemic half-life
- High drug:antibody ratio: ~8:1
- Stable linker-payload
- Tumor-selectable cleavable linker
- Bystander killing effect

Racional para uso em pacientes mutados pós falha TKI

- Principais parceiros dimerização HER3: EGFR e HER2
- Aumento progressivo de expressão HER3 em pacientes com EGFR em uso de TKI

Multicenter, randomized, open-label phase II trial

Patients with advanced  
*EGFR*-mutated NSCLC progressing on  
most recent systemic therapy;  
prior treatment with *EGFR* TKI\* and  
platinum-based chemotherapy;  
inactive or previously treated asymptomatic  
brain mets allowed; pretreatment tissue  
biopsy required but not selected for by  
HER3 expression  
(N = 277)

## Current Report

**HER3-DXd**  
5.6 mg/kg IV Q3W fixed dose  
(n = 226<sup>†</sup>)

**HER3-DXd**  
IV Q3W uptitration<sup>‡</sup>  
(n = 51<sup>§</sup>)

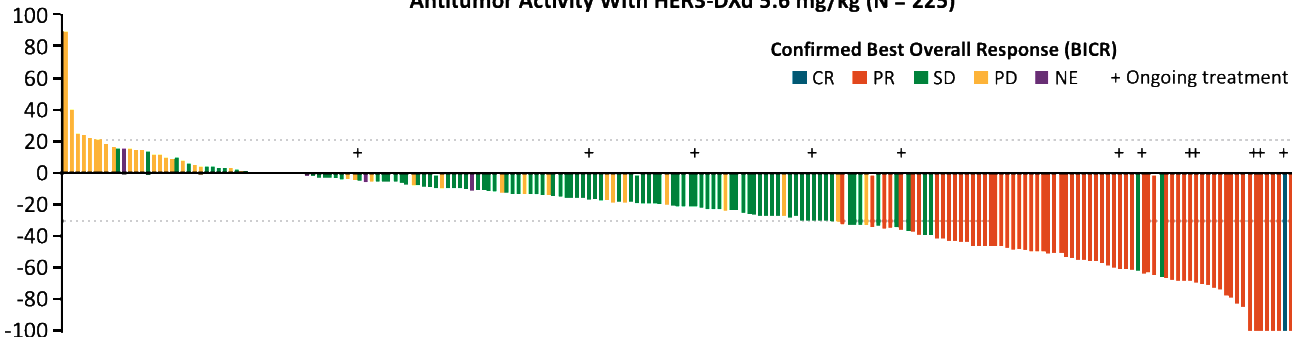
- **Median f/u for efficacy:**  
18.9 mo (range: 14.9-27.5)
- **Median tx duration for safety:**  
5.5 mo (range: 0.7-18.2)

\*Protocol amended to require prior osimertinib. <sup>†</sup>n = 226 enrolled; n = 225 received ≥1 dose. <sup>‡</sup>Dosing: 3.2 mg/kg C1D1, 4.8 mg/kg C2D1, 6.4 mg/kg C3D1+. <sup>§</sup>n = 51 enrolled; n = 50 received ≥1 dose. Enrollment discontinued after risk–benefit assessment.

- **Primary endpoint:** confirmed ORR by BICR
- **Key secondary endpoint:** DoR by BICR

# HERTHENA-Lung01: Efficacy Summary

Antitumor Activity With HER3-DXd 5.6 mg/kg (N = 225)



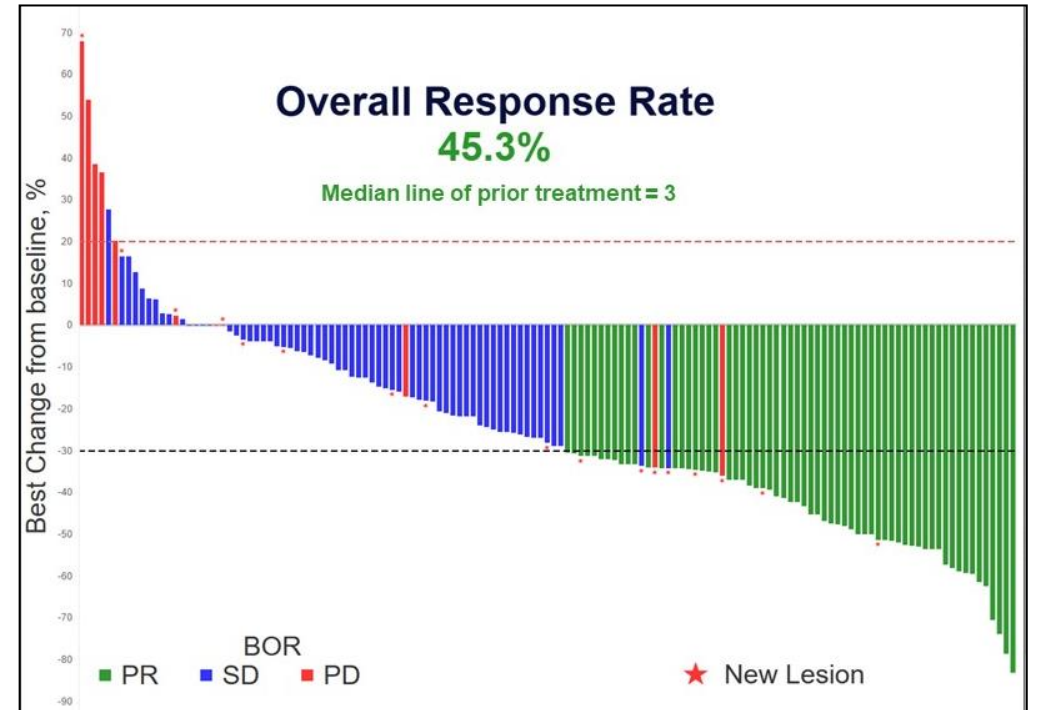
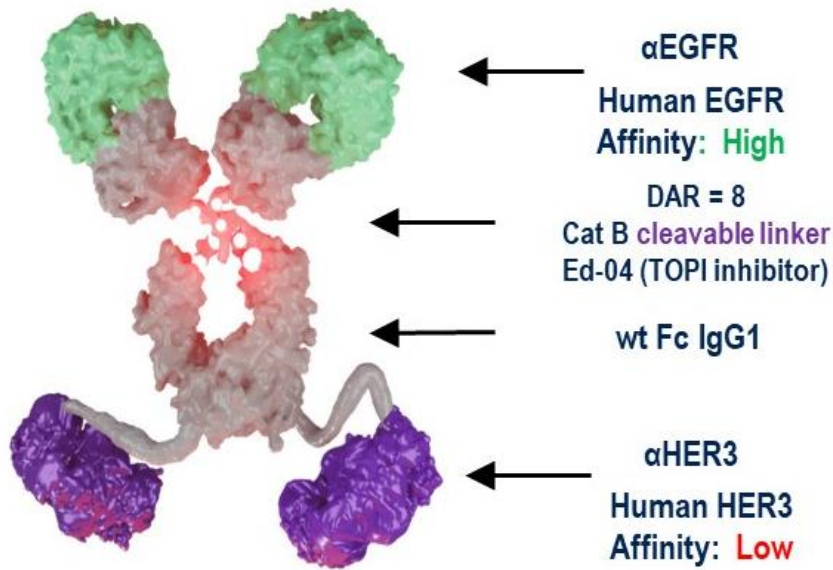
Type of EGFR TKI Resistance Mechanism

	EGFR Dependent Only (n = 34)	EGFR Independent Only (n = 81)	Both EGFR Dependent and Independent (n = 32)	None Identified (n = 77)
Confirmed ORR, % (95% CI)	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

Efficacy Outcome	HER3-DXd 5.6 mg/kg	
	All Patients (N = 225)	Patients Who Received 3G EGFR TKI (n = 209)
Confirmed ORR, % (95% CI)	29.8 (23.9-36.2)	29.2 (23.1-35.9)
Best overall response, n (%)		
▪ CR	1 (0.4)	1 (0.5)
▪ PR	66 (29.3)	60 (28.7)
▪ SD	99 (44.0)	91 (43.5)
▪ PD	43 (19.1)	41 (19.6)
▪ NE	16 (7.1)	16 (7.7)
DCR, % (95% CI)	73.8 (67.5-79.4)	72.7 (66.2-78.6)
Median DoR, mo (95% CI)	6.4 (4.9-7.8)	6.4 (5.2-7.8)
Median PFS, mo (95% CI)	5.5 (5.1-5.9)	5.5 (5.1-6.4)
Median OS, mo (95% CI)	11.9 (11.2-13.1)	11.9 (10.9-13.1)

# BL-B01D1 as a EGFRxHER3 bsADC

## BL-B01D1 (EGFRxHER3-ADC)



	EGFRmt NSCLC (n=38)	EGFRwt NSCLC (n=49)	NPC (n=28)	SCLC (n=7)	HNSCC (n=15)	Other (n=2)
PR	24	22	15	1	1	0
SD	10	23	13	5	11	2
PD	4	2	0	1	3	0
NE	0	2	0	0	0	0
ORR, %	<b>63.2%</b>	<b>44.9%</b>	<b>53.6%</b>	14.3%	6.7%	0
DCR, %	89.5%	91.8%	100%	85.7%	80%	100%

# Telisotuzumab vedotin: cMET targeted ADC

## Structure:

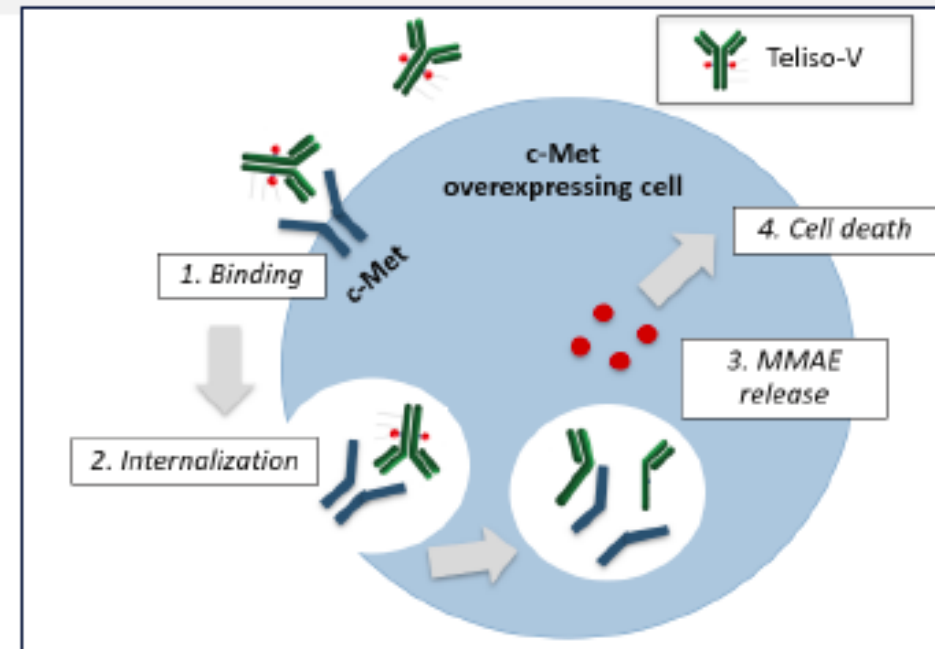
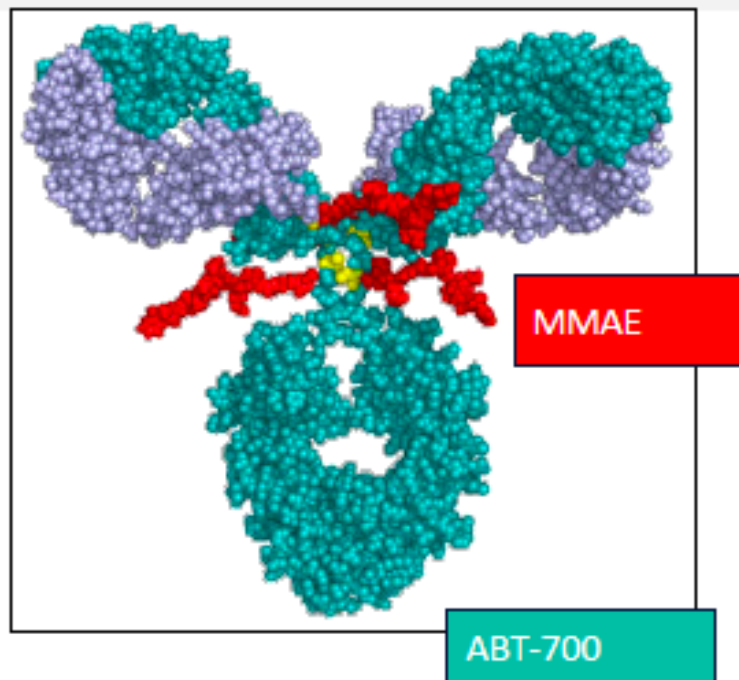
- ✓ Antagonist **anti-c-Met antibody** (ABT-700) linked to **cytotoxin** monomethyl auristatin E (MMAE) through a cleavable linker (VC)

## Target: c-Met

- ✓ Cell surface tyrosine kinase receptor that provides pro-survival and proliferation signaling
- ✓ Overexpressed in high proportion of select tumor types (NSCLC, H&N, gastric, esophageal)

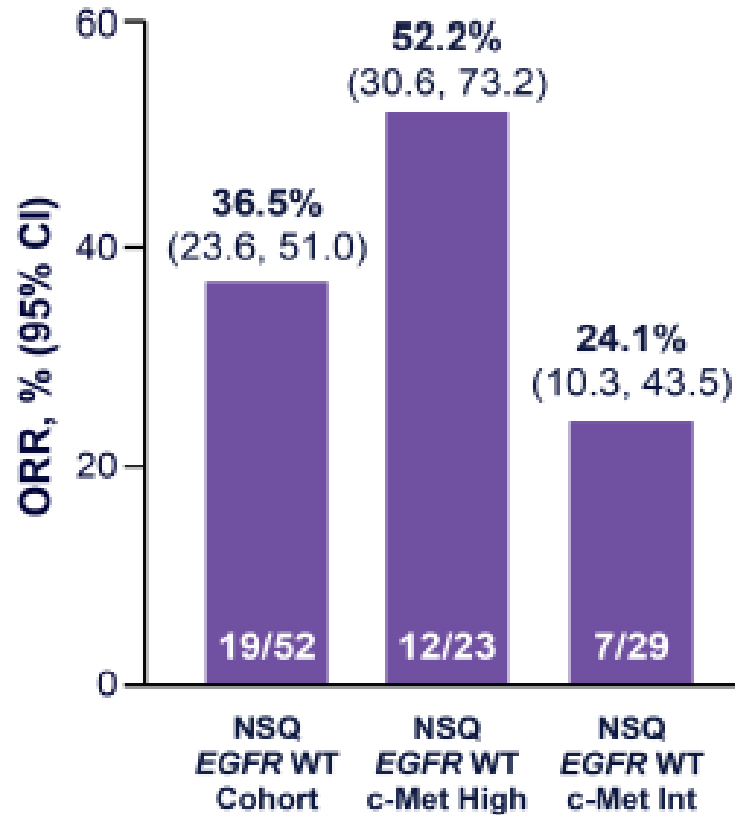
## Mechanism of Action:

- ✓ Targeted delivery of cytotoxin MMAE to tumor cells via c-Met binding



# LUMINOSITY: phase 2 trial of Teliso-V monotherapy in previously treated c-MET overexpressing NSCLC

## ORR per Central Review



- The NSQ *EGFR* WT NSCLC cohort met protocol-specified criteria for expansion in Stage 2
- DoR per central review:
  - NSQ *EGFR* WT Cohort: 6.9 months (95% CI, 4.1- NR)
  - NSQ *EGFR* WT c-Met High: 6.9 months (95% CI, 2.4 - NR)

*Teliso-V dosed at 1.9 mg/kg Q2W*

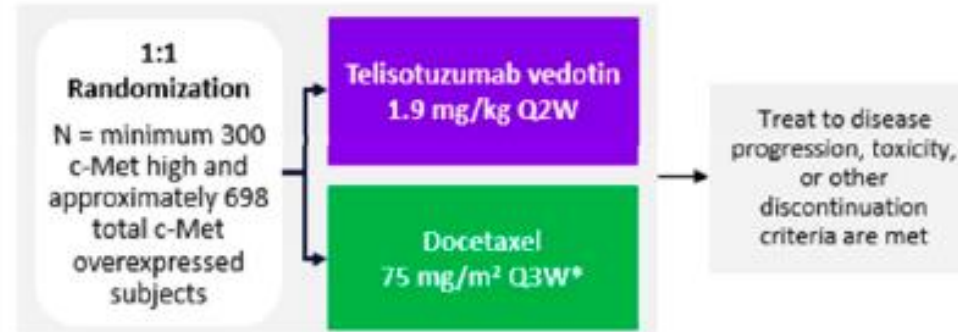
Camidge, D.R. et al. Presented at 2022 ASCO Annual Meeting, Chicago. Abstract 9016.

# TeliMET NSCLC-01 (M18-808): phase III trial

## Overall Study Design Schematic



Population
<ul style="list-style-type: none"> <li>Locally advanced/metastatic non-squamous NSCLC</li> <li>c-Met overexpressing per AbbVie designated laboratory</li> <li>No actionable EGFR activating mutations</li> <li>Progressed on at least 1 line of prior therapy for locally advanced/metastatic disease</li> <li>Previously progressed on (or ineligible for) targeted agent, chemotherapy, immune checkpoint inhibitor</li> </ul>
Stratification Factors
<ul style="list-style-type: none"> <li>c-Met high status (Positive vs Negative)</li> <li>Prior immune checkpoint inhibitor (Yes vs No)</li> <li>Region (US/Canada, Europe, Pan-Asia, Rest-of-World)</li> </ul>



**Co- Primary Endpoints:**  
PFS per independent central review  
Overall Survival  
*Evaluated in c-Met high population and c-Met overexpressed population*

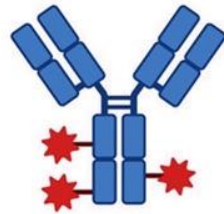
\*or at a dose in accordance with local Package Insert recommendations.



# O que esperar?

## First generation ADCs

e.g. T-DM1

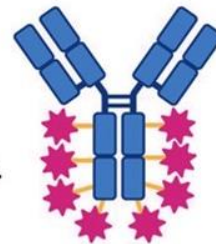


-New linker technologies (↑ DAR);  
-improved conjugation chemistry;  
-membrane-permeable payloads



## Next-generation ADCs

- ↑ therapeutic index  
- bystander effect;  
- ↑ tissue agnostic profile.



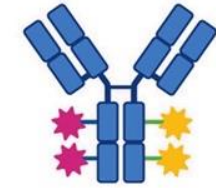
e.g. T-DXd

## Future Perspectives

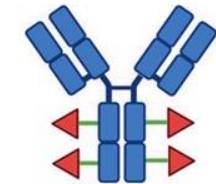
1) Bispecific  
ADCs



2) Dual-payload  
ADCs



3) ADCs with  
immune-  
stimulating  
payloads

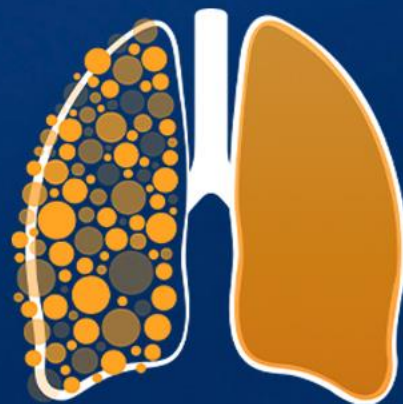


(e.g. TLR8 agonist)

4) Radionuclide  
ADCs



- ADCs é uma nova estratégia para o tratamento do câncer de pulmão
- TDXd já está aprovado no Brasil e indicado para pacientes portadores de mutação Her2 pós falha de primeira linha de tratamento
- Dato-DXd foi comparado docetaxel em segunda linha de tratamento dos pacientes com CPNPC com aumento modesto da SLP na histologia não escamosa. Ainda sem dados de SG
- Outros cenários como pós falha a TKI nos pacientes com mutações acionáveis ou combinações em primeira linha estão em andamento
- Novos alvos como cMET, HER3, CEACAM estão sendo avaliados
- Novas moléculas mais seletivas e potentes são esperadas nesse cenário



12º SIMPÓSIO  
INTERNACIONAL DE

# CÂNCER DE PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

GERENCIAMENTO E PRODUÇÃO

