Lung Cancer UPDATES
IASLC HIGHLIGHTS
09-12 SEPTIEMBRE 2023
Singapore

Iniciativa científica de:
GECP
lung cancer research

Anticuerpos conjugados

Juan Coves Sarto

H. Universitario Son Llàtzer

Antibody-Drug Conjugates (ADCs): *a rapidly evolving scene…*


Paul Ehrlich (1854- 1915)

1910

1913
Paul Ehrlich described the concept of a **'magic bullet'** and drug targeting

1950

1958
MTX linked to an antibody targeting leukaemia cells

1960

1967
ADCs proposed; immune-radioactive agent

1970

1975
Hybridoma technology

1975
Covalent linked ADCs tested in animal models

1980

1988
Humanised mAbs reported

2000

2000
First FDA-approved ADC – Gemtuzumab ozogamicin

2010

2011
Brentuximab vedotin approved

2013
T-DM1 approved

2017
Inotuzumab ozogamicin approved

2020

2018
>100 ADCs in clinical development, 14 FDA approved in oncology

2021-22-23

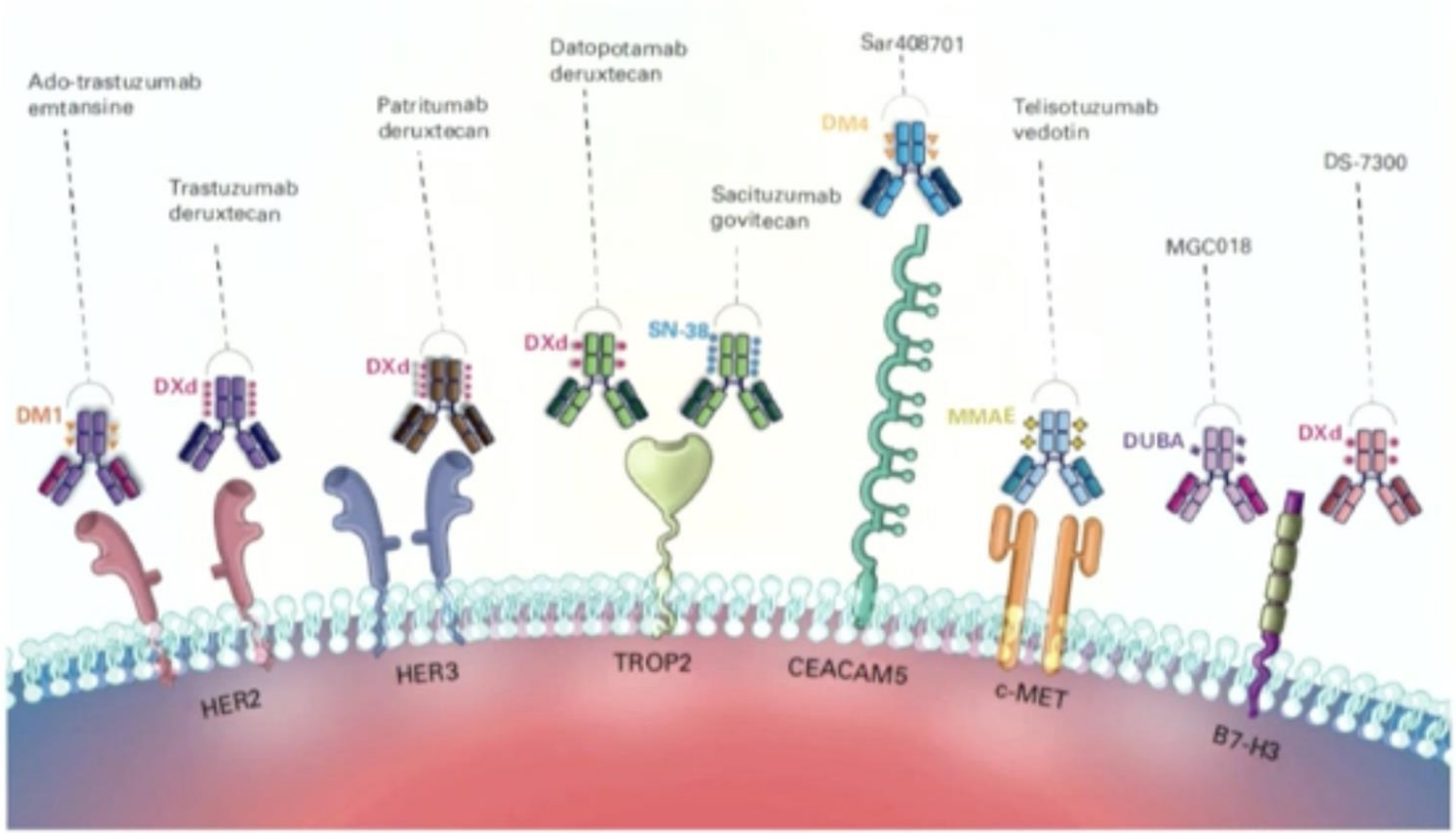
2021
Trastuzumab deruxtecan approved for NSCLC

2021-22
FDA Breakthrough Therapy Designation for NSCLC: Patritumab deruxtecan, Telisotuzumab vedotin

2022-23
T-DXd and Sacituzumab govitecan approved for Breast Ca, Enfortumab vedotin for Urothelial Ca

Adapted from Fu, Z et al. Sig Transduct Target Ther 7, 93 (2022)

Targets and ADCs in advanced clinical development in lung cancer



Passaro et al. J Clin Oncol 2023; 41:3747-3761

- **HER-2**
- **HER-3**
- **TROP-2**
- **C-MET**
- **CEACAM-5**
- **B7-H3**

- CD56, AXL, PK7, ROR2, TF, EGFR, PVRL4, NaPi2b

Presented studies

HER3 targeting:

- ❑ OA05.03. **Patritumab Deruxtecan (HER3-DXd)** in EGFR-Mutated NSCLC Following EGFR TKI and Platinum-Based Chemotherapy: **HERTHENA-Lung01**. *Yu et al.*

Trop-2 targeting, combinations:

- ❑ OA05.04. **Sacituzumab Govitecan + Pembrolizumab** in 1L Metastatic Non-Small Cell Lung Cancer: Preliminary Results of the **EVOKE-02** Study. *Cho et al.*
- ❑ OA05.06. **Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin** in Advanced/mNSCLC: Initial Results from Phase 1b **TROPION-Lung04**. *Papadopoulos et al.*

ADC in SCLC:

- ❑ OA05.05. **Ifinatamab Deruxtecan (I-DXd**; DS-7300) in Patients with Refractory SCLC: A Subgroup Analysis of a Phase 1/2 Study. *Johnson et al.*

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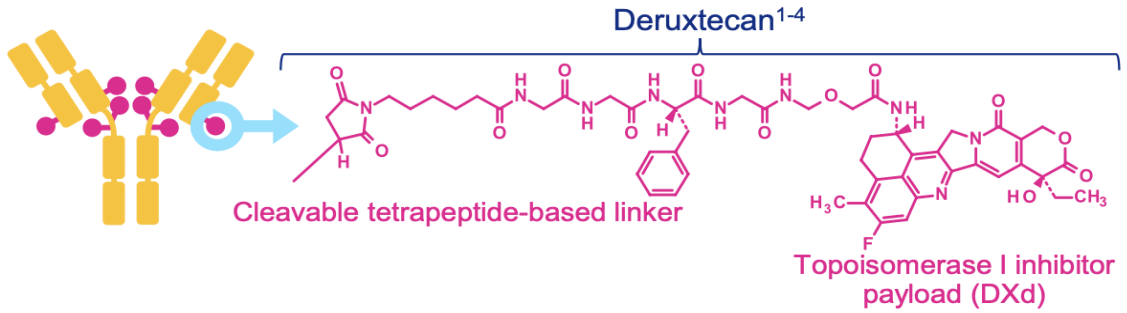
Patritumab Deruxtecan (HER3-DXd) in *EGFR*-Mutated NSCLC Following EGFR TKI and Platinum-Based Chemotherapy: HERTHENA-Lung01

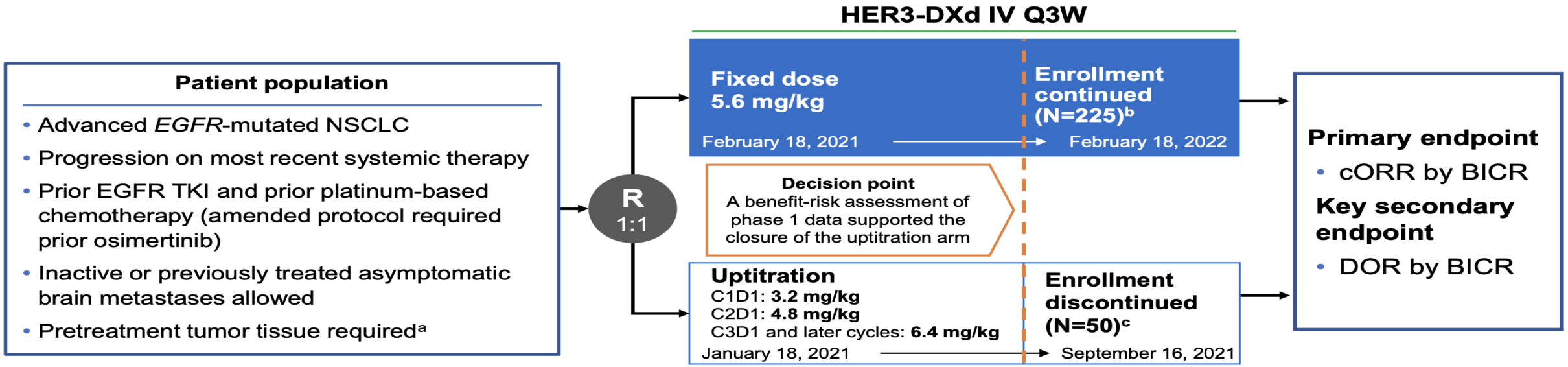
Helena A. Yu,[1] Yasushi Goto,[2] Hidetoshi Hayashi,[3] Enriqueta Felip,[4] James Chih-Hsin Yang,[5] Martin Reck,[6] Kiyotaka Yoh,[7] Se-Hoon Lee,[8] Luis Paz-Ares,[9] Benjamin Besse,[10] Paolo Bironzo,[11] Dong-Wan Kim,[12] Melissa L. Johnson,[13] Yi-Long Wu,[14] Qian Dong,[15] Pang-Dian Fan,[15] Pomy Shrestha,[15] David W. Sternberg,[15] Dalila Sellami,[15] Pasi A. Jänne[16]

HER3-DXd is an ADC composed of 3 parts[1-4]:

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



HERTHENA-Lung01 Study Design[1]



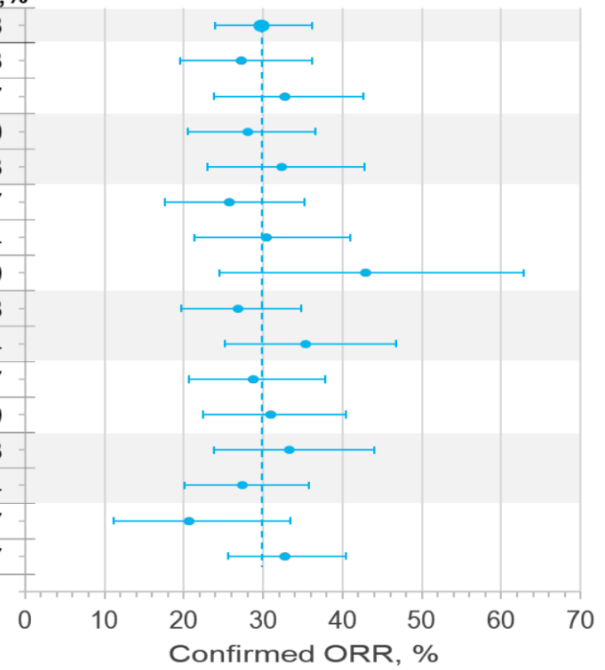
Baseline characteristics		HER3-DXd 5.6 mg/kg (N=225)
Age, median (range), years		64 (37-82)
Female, n (%)		132 (59)
Asian, n (%)		105 (47)
Time since initial NSCLC diagnosis, median (range), months		41.0 (9.1-224.7)
ECOG performance status, n (%)	0/1	73 (32)/149 (66)
	2[a]	3 (1)
Sum of target lesion diameters at baseline (BICR), median (range), mm		68 (11-248)
History of CNS metastasis, n (%)		115 (51)
Brain metastasis at baseline (BICR), n (%)		72 (32)
Liver metastasis at baseline (BICR), n (%)		75 (33)
EGFR-activating mutations, n (%)[b]	Ex19del	142 (63)
	L858R	82 (36)
No. of prior lines of systemic therapy (locally advanced/metastatic)	Median (range)	3 (1-11)[c]
	2 prior lines, n (%)	58 (26)
	>2 prior lines, n (%)	165 (73)
Prior cancer regimens, n (%)	Prior EGFR TKI therapy	225 (100)
	Prior third-generation EGFR TKI	209 (93)
	Prior platinum-based chemotherapy	225 (100)
	Prior immunotherapy	90 (40)

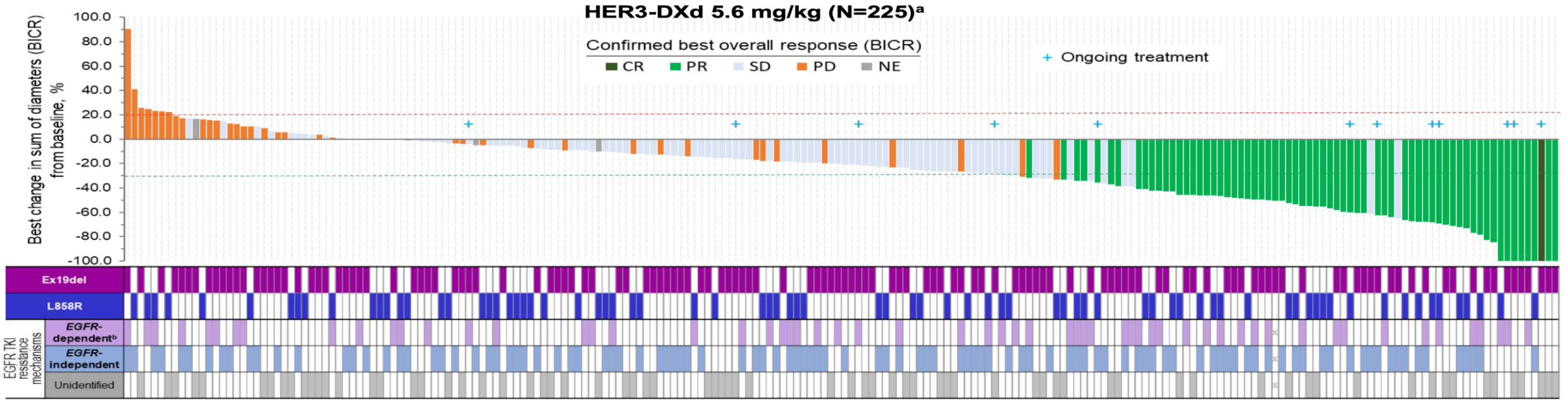
Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

cORR by Patient and Disease Characteristics at Study Entry

		N	cORR,%
Overall		225	29.8
Age	<65 y	121	27.3
	≥65 y	104	32.7
Sex	Female	132	28.0
	Male	93	32.3
Race	Asian	105	25.7
	White	92	30.4
	Other	28	42.9
EGFR-activating mutation	Ex19del	142	26.8
	L858R	82	35.4
History of brain metastasis	Yes	115	28.7
	No	110	30.9
Prior immunotherapy	Yes	90	33.3
	No	135	27.4
No. of prior regimens for advanced disease	2	58	20.7
	>2	165	32.7



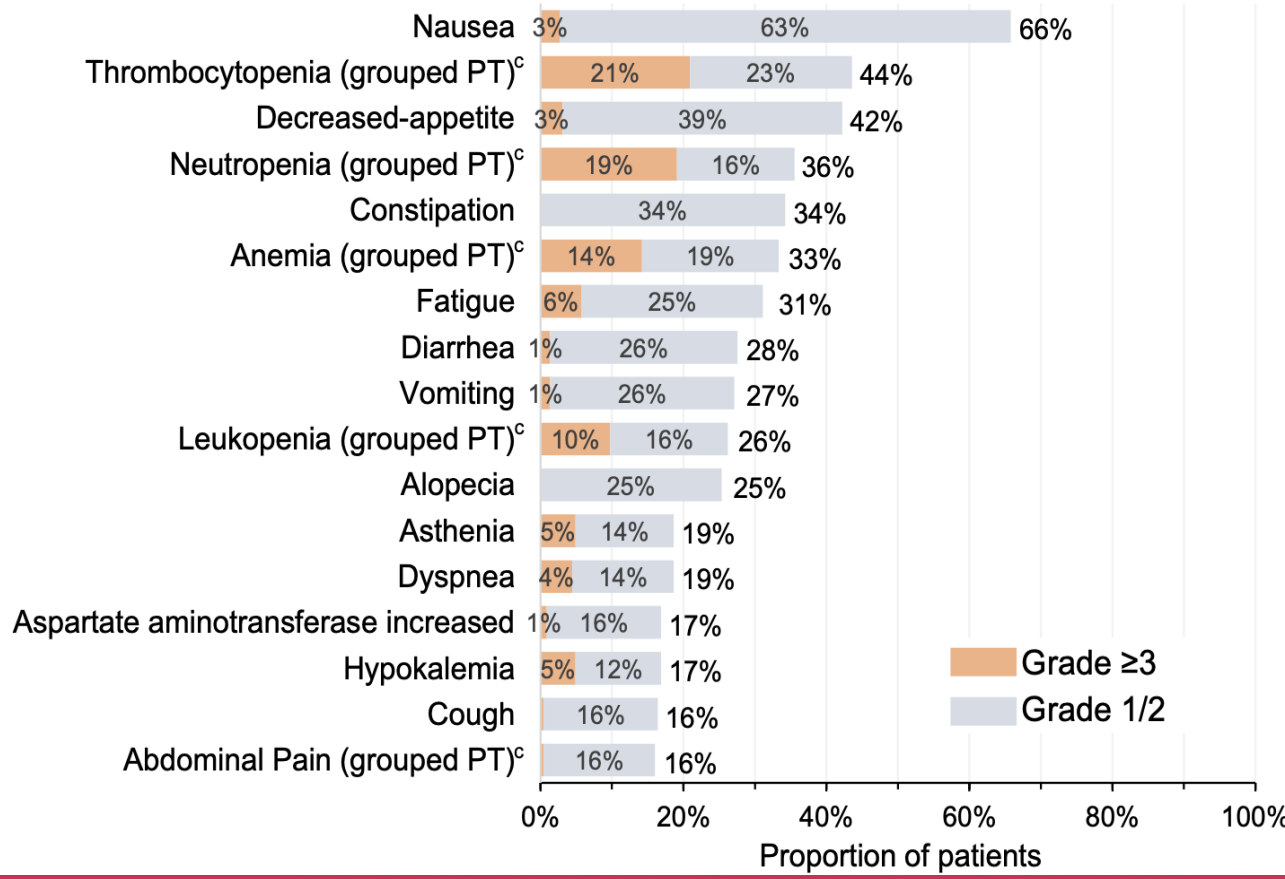


	Type of EGFR TKI resistance mechanism			
	EGFR-dependent, only (n=34)	*EGFR*-independent, only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

Primary data cutoff, 21 Nov 2022.
Median treatment duration: 5.5 (range, 0.7-18.2) months.

Most Common TEAEs Occurring in ≥15% of Patients (N=225)



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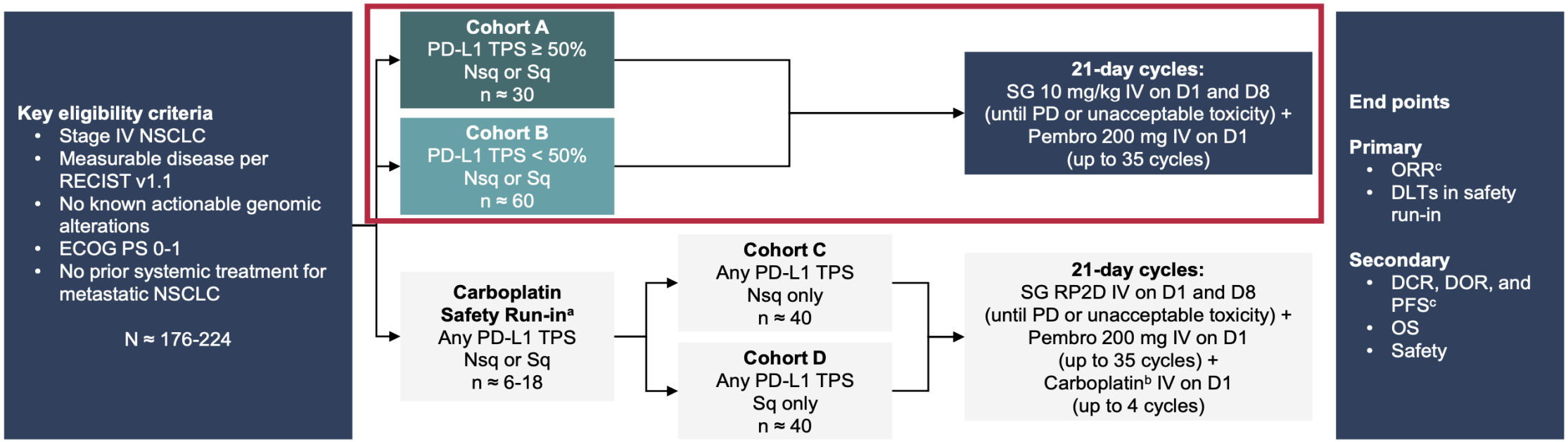
Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non-Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study

Byoung Chul Cho,[1] Manuel Cobo Dols,[2] Roxana Reyes Cabanillas,[3] David Vicente,[4] Jose Fuentes Pradera,[5] Salvatore Grisanti,[6] Afshin Eli Gabayan,[7] Ki Hyeong Lee,[8] Eun Kyung Cho,[9] Sabeen Mekan,[10] Farnoush Safavi,[10] Nelumka Fernando,[10] Michael J. Chisamore,[11] Martin Reck[12]

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



Patient Baseline Characteristics, Exposure, and Disposition

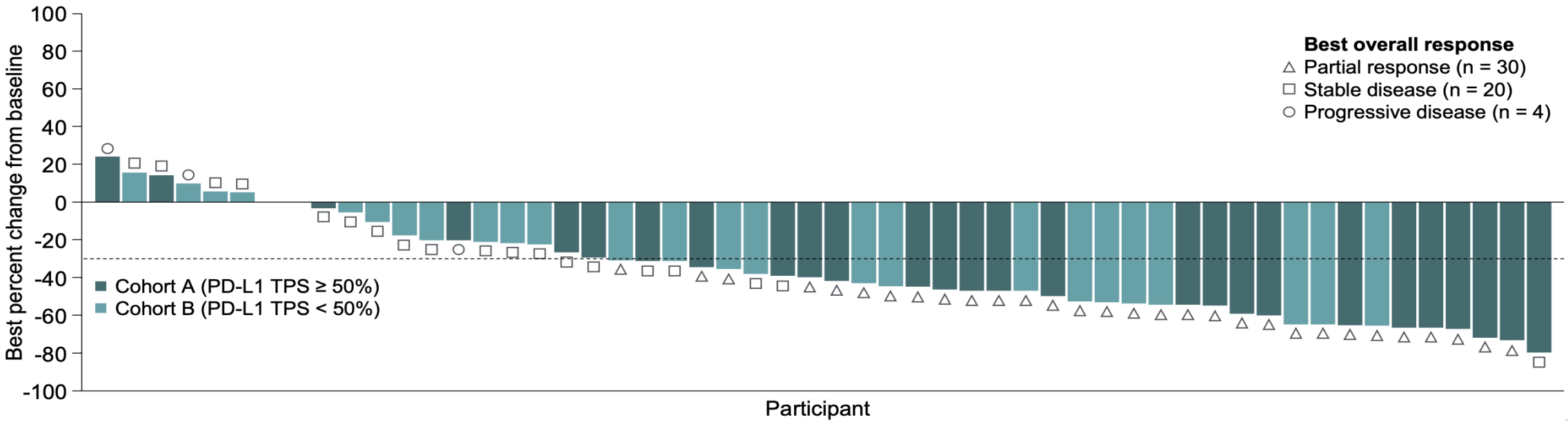
Characteristic	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 30	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 33
Median age (range), years	67 (47-77)	68 (47-80)
Male, %	80	79
Race, %		
Asian	20	15
Black	7	3
White	73	82
ECOG PS 1, %	80	76
Histology, %		
Nonsquamous	60	61
Squamous	40	39
Stage IV disease at diagnosis,[a]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

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

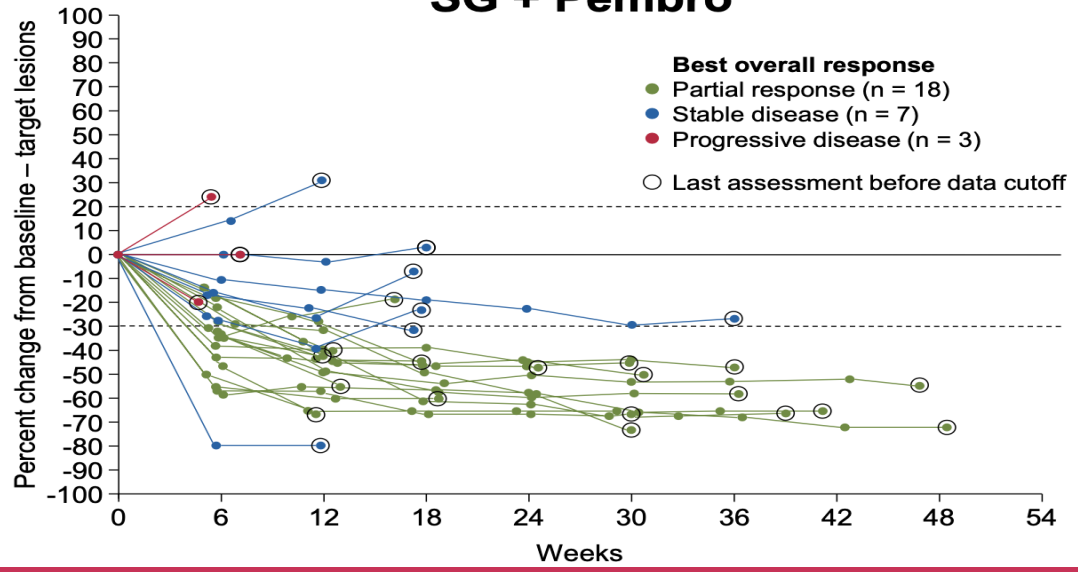
- Across both cohorts, the most common reason for discontinuation of sacituzumab govitecan was progressive disease

Efficacy by INV[a]	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 29	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 32	Total SG + Pembro n = 61
ORR[b] (95% CI), %	**69 (49-85)**	**44 (26-62)**	**56 (42-69)**
PR, n (%) – confirmed and unconfirmed	20 (69)	14 (44)	34 (56)
Confirmed PR, n (%)	18 (62)	12 (38)	30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR[c] (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR[d,e] (95% CI), months	NR (5.6-NR)	NR (3.5-NR)	NR (7.9-NR)
DOR rate at 6 months[d,e] (95% CI), %	88 (39-98)	88 (39-98)	87 (58-97)

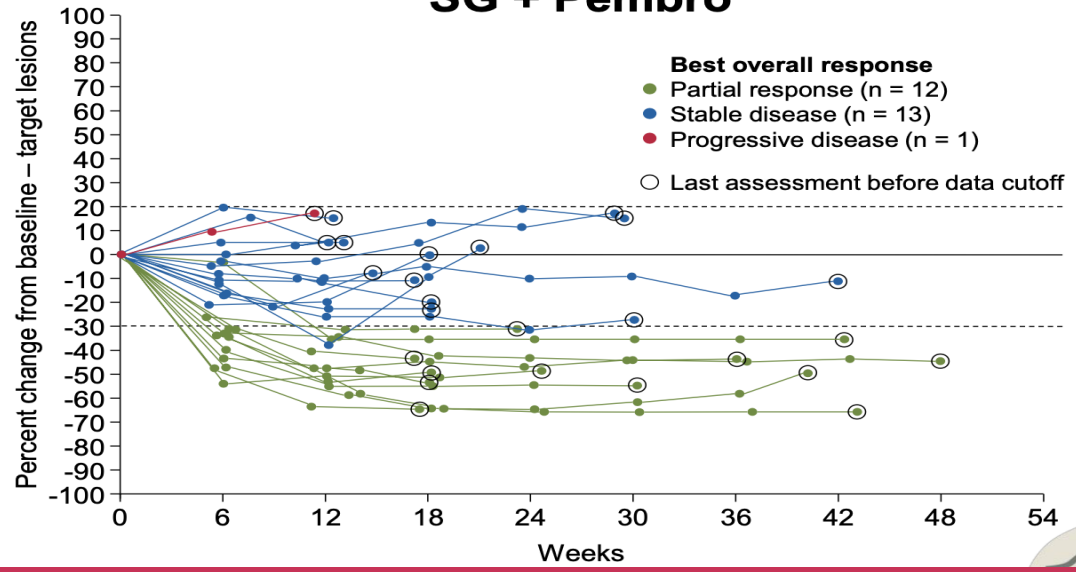
Total

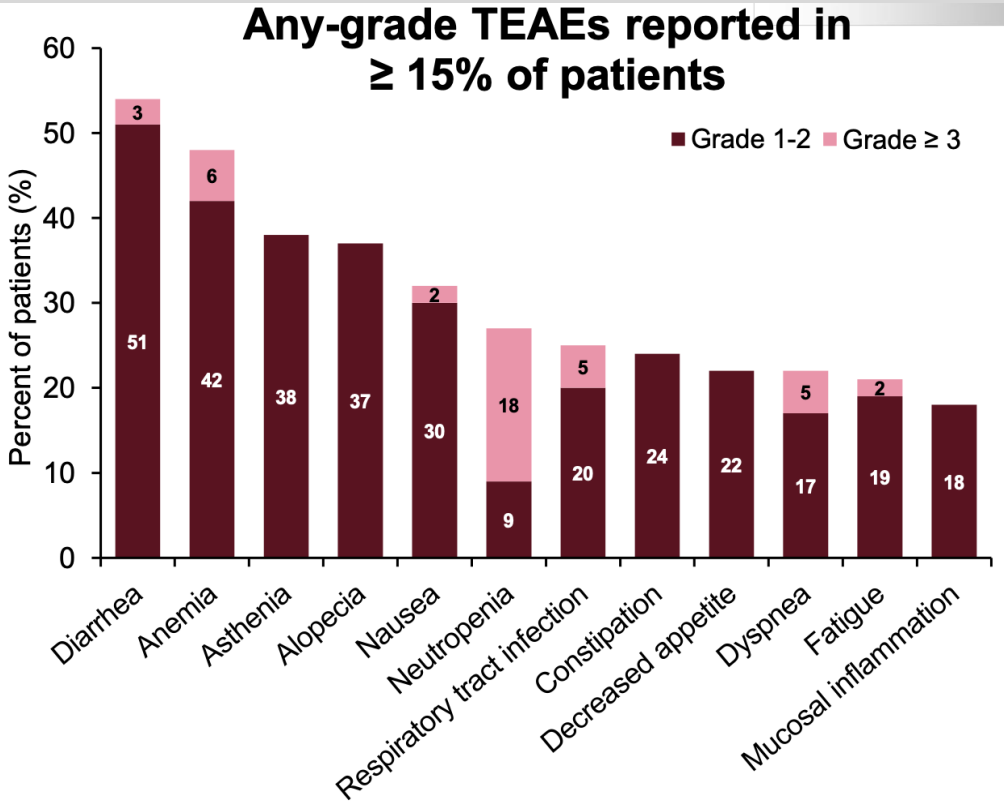


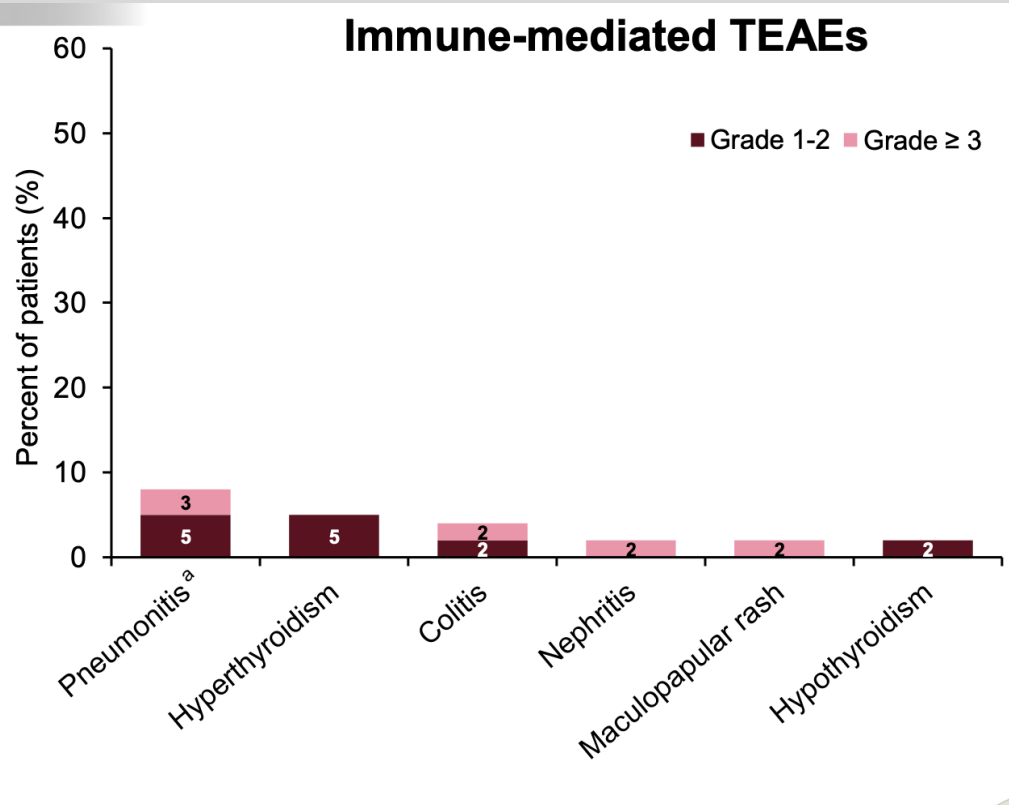
Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro



Cohort B (PD-L1 TPS < 50%) SG + Pembro







- The most common any-grade TEAEs were diarrhea (54%),

- Immune-mediated TEAEs were consistent with the known

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Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin in Advanced/Metastatic NSCLC: Initial Results from the Phase 1b TROPION-Lung04 Study

Kyriakos P. Papadopoulos,[1] Debora S. Bruno,[2] Satoru Kitazono,[3] Shuji Murakami,[4] Martin Gutierrez,[5] Kazushige Wakuda,[6] Alexander Spira,[7] Kristof Cuppens,[8,9] Susan Lovick,[10] Adriana Hepner,[11] Gabriel Mak,[11] Saiama N. Waqar[12]

TROPION-Lung04 is investigating Dato-DXd in combination with different immunotherapy agents ± carboplatin across 11 cohorts. This interim analysis reports the first data from Cohorts 2 and 4

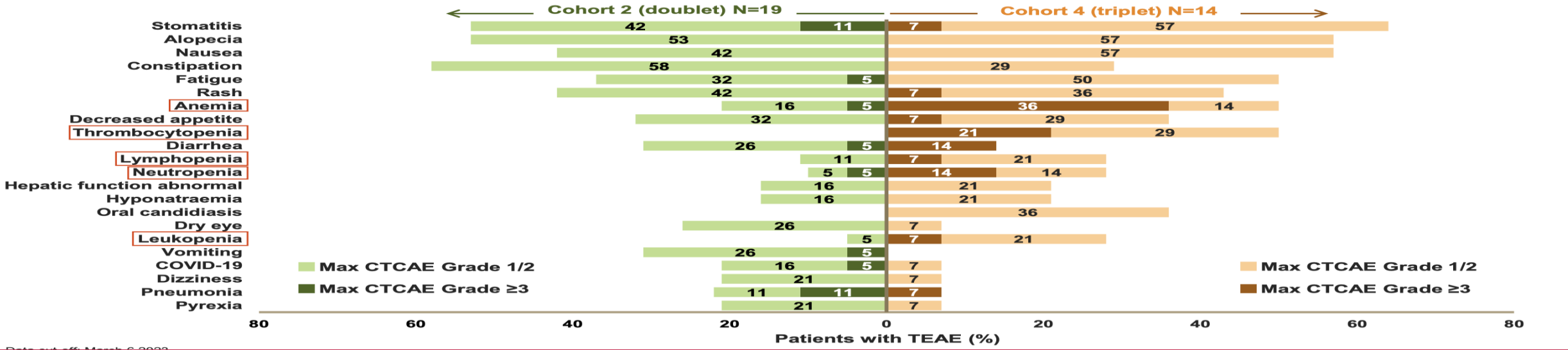
Key eligibility
- Adults (≥18 years) with previously treated or treatment-naïve advanced or metastatic NSCLC[a]
- No actionable genomic alterations
- ECOG PS 0–1

	1 Part 1: Sequential dose escalation[b]	2 Part 2: Dose expansion
Cohort 1 (Doublet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg, Q3W (n=5)	
Cohort 2 (Doublet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=16)
Cohort 3[c] (Triplet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W	
Cohort 4 (Triplet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=8)

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

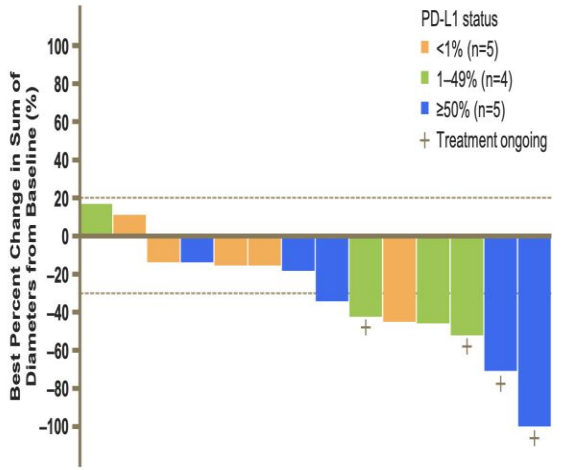
Characteristic, n (%)		Cohort 2 (doublet) N=19[a]	Cohort 4 (triplet) N=14[a]
Age, median (range), years		63 (49–75)	67 (55–72)
Male		14 (73.7)	9 (64.3)
Dato-DXd combination line of therapy	1L	14 (73.7)	13 (92.9)
	2L+	5 (26.3)[b]	1 (7.1)[b]
Histology	Squamous	5 (26.3)	4 (28.6)
	Non-squamous	14 (73.7)	10 (71.4)
History of brain metastases		4 (21.1)	3 (21.4)
PD-L1 expression	<1%	6 (31.6)	6 (42.9)
	1–49%	6 (31.6)	3 (21.4)
	≥50%	7 (36.8)	5 (35.7)
Tumor stage at study entry	IIIA, IIIB or IIIC	0	2 (14.3)
	IV, IVA or IVB	19 (100)	12 (85.7)

Events, n (%)		Cohort 2 (doublet) N=19	Cohort 4 (triplet) N=14
TEAEs		**19 (100)**	**14 (100)**
Study treatment-related[a]		19 (100)	14 (100)
Grade ≥3 TEAEs		**8 (42.1)**	**10 (71.4)**
Study treatment-related[a]		6 (31.6)	8 (57.1)
SAEs		**7 (36.8)**	**5 (35.7)**
Study treatment-related[a]		6 (31.6)	5 (35.7)
TEAEs associated with	Death	0	0
	Discontinuation of any drug	4 (21.1)	3 (21.4)
	Discontinuation of Dato-DXd	4 (21.1)	2 (14.3)
ILD adjudicated as drug-related		**3 (15.8)**	**1 (7.1)**
Grade 1		1 (5.3)	0
Grade 2		1 (5.3)	1 (7.1)
Grade ≥3		1 (5.3)[b]	0

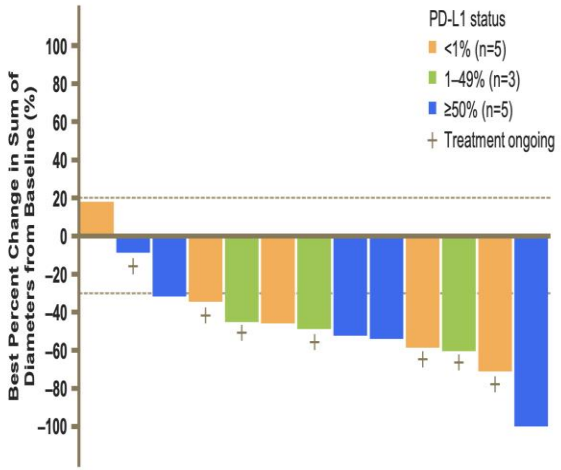


Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		**7 (50.0)**	**10 (76.9)[b]**
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		**13 (92.9)**	**12 (92.3)**
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

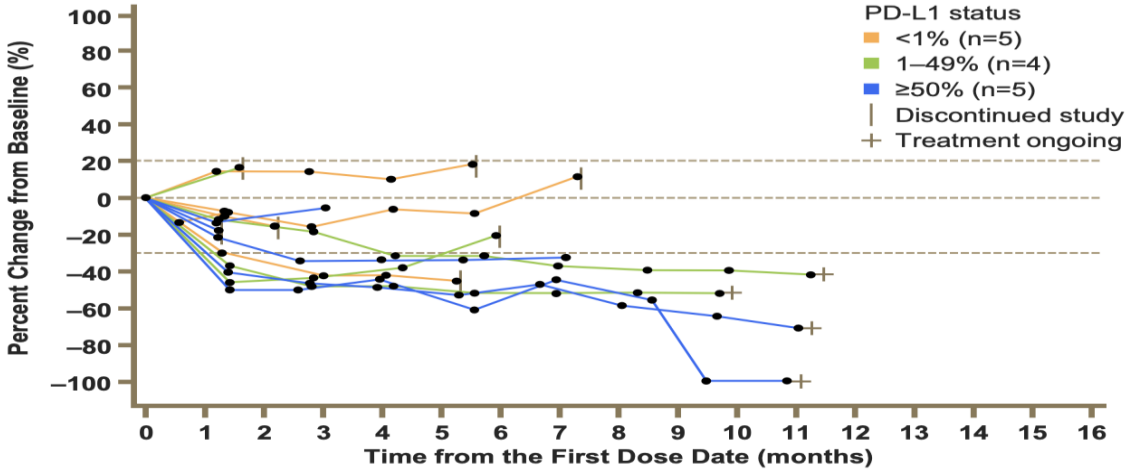
Cohort 2 (doublet), 1L setting (N=14)
ORR: 50.0%; DCR: 92.9%



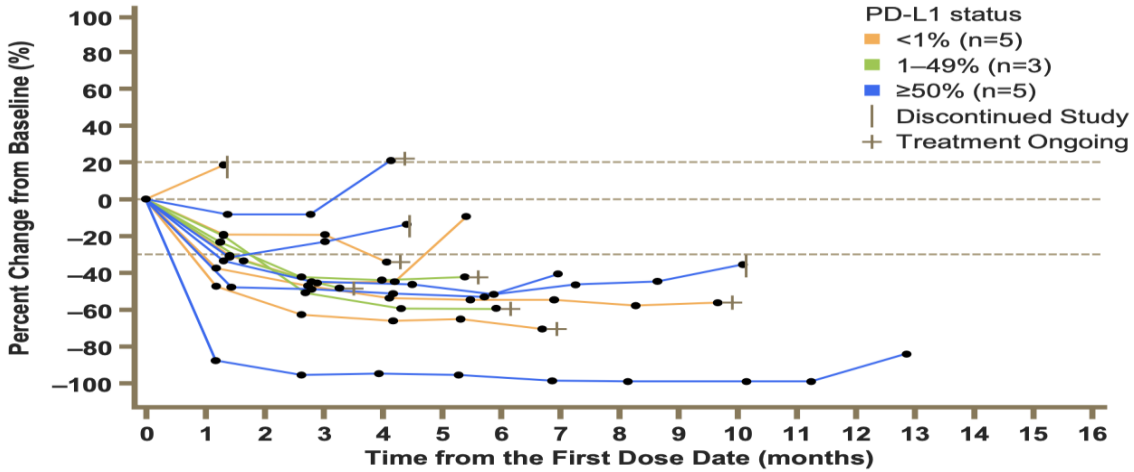
Cohort 4 (triplet), 1L setting (N=13)
ORR: 76.9%;[b] DCR: 92.3%



Cohort 2 (doublet), 1L setting (N=14)



Cohort 4 (triplet), 1L setting (N=13)



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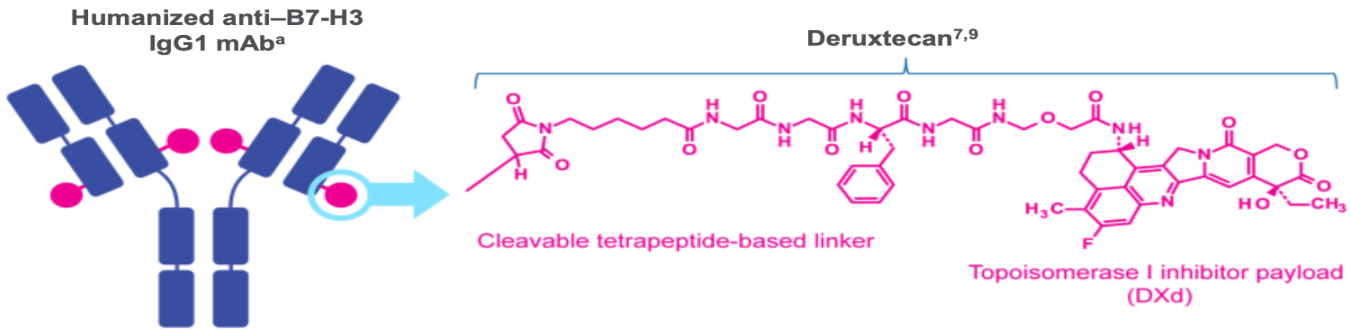
Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study

Melissa Johnson,[1] Mark Awad,[2] Takafumi Koyama,[3] Martin Gutierrez,[4] Gerald S Falchook,[5] Sarina A Piha-Paul,[6] Toshihiko Doi,[7] Taroh Satoh,[8] Naoko Okamoto,[9] Jasmeet Singh,[9] Naoto Yoshizuka,[9] Meng Qian,[9] Xiaozhong Qian,[9] Brittany P Tran,[9] Ololade Dosunmu,[1] Rakesh Mucha,[1] Hillarie Windish,[1] Manish R Patel[1,10]

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)

Patients with advanced/unresectable or metastatic solid tumors (unselected for B7-H3 expression)
N ≈ 205

Part 1: dose escalation
- I-DXd IV Q3W monotherapy for advanced solid tumors[b]

16.0 mg/kg (n = 2)
12.0 mg/kg (n = 8)
8.0 mg/kg (n = 10)
6.4 mg/kg (n = 1)
Minimum effective dose → 4.8 mg/kg (n = 0)
3.2 mg/kg (n = 1)
1.6 mg/kg (n = 0)
0.8 mg/kg (n = 0)

RDE

Part 2: dose expansion (12.0 mg/kg)
- I-DXd IV Q3W monotherapy for selected advanced solid tumors

Cohort 1: ESCC (n = 25)

Cohort 2: mCRPC (n = 40)

Cohort 3: sqNSCLC (n = 20)

Key primary endpoints

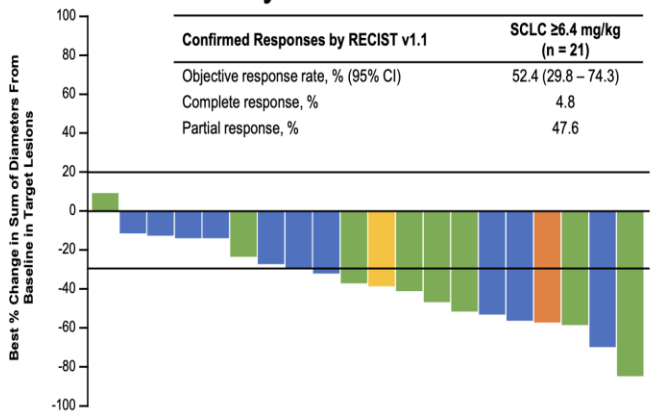
- *Dose escalation*: DLTs, SAEs, TEAEs, AESI
- *Dose expansion*: ORR, DOR, DCR, PFS, OS

Key secondary endpoints

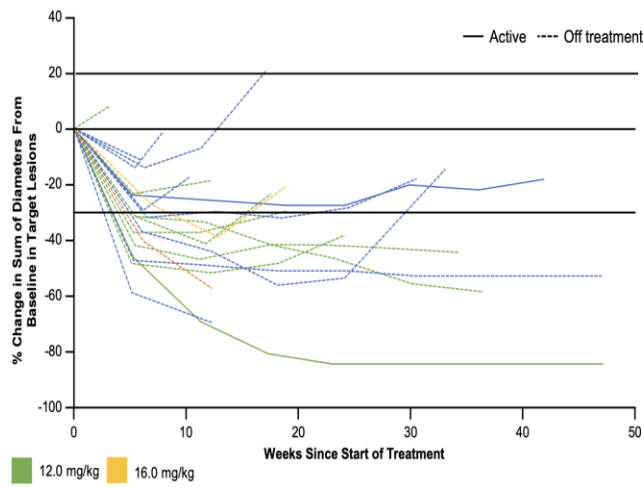
- PK
- Immunogenicity

Patient or Disease Characteristic	SCLC (N = 22)
Age, median (range)	61 (40 – 84)
Male, n (%)	14 (63.6)
ECOG PS, n (%)	
0	7 (31.8)
1	15 (68.2)
Brain metastasis at baseline, n (%)	2 (9.1)
Number of prior systemic regimens, median (range)	2 (1 – 7)
Prior anticancer therapy received, n (%)	
Platinum-based chemotherapy	22 (100)
Immuno-oncology	18 (81.8)
Taxane	5 (22.7)
Irinotecan or topotecan	5 (22.7)[a]
Region of enrollment, n (%)	
United States	17 (77.3)
Japan	5 (22.7)

Antitumor Activity[a]

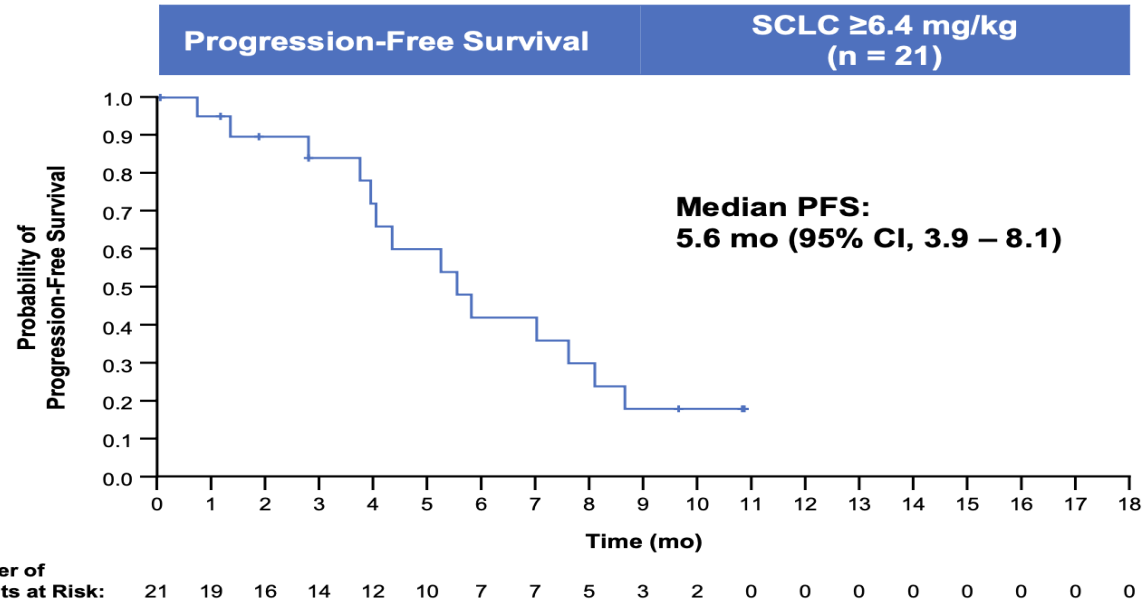


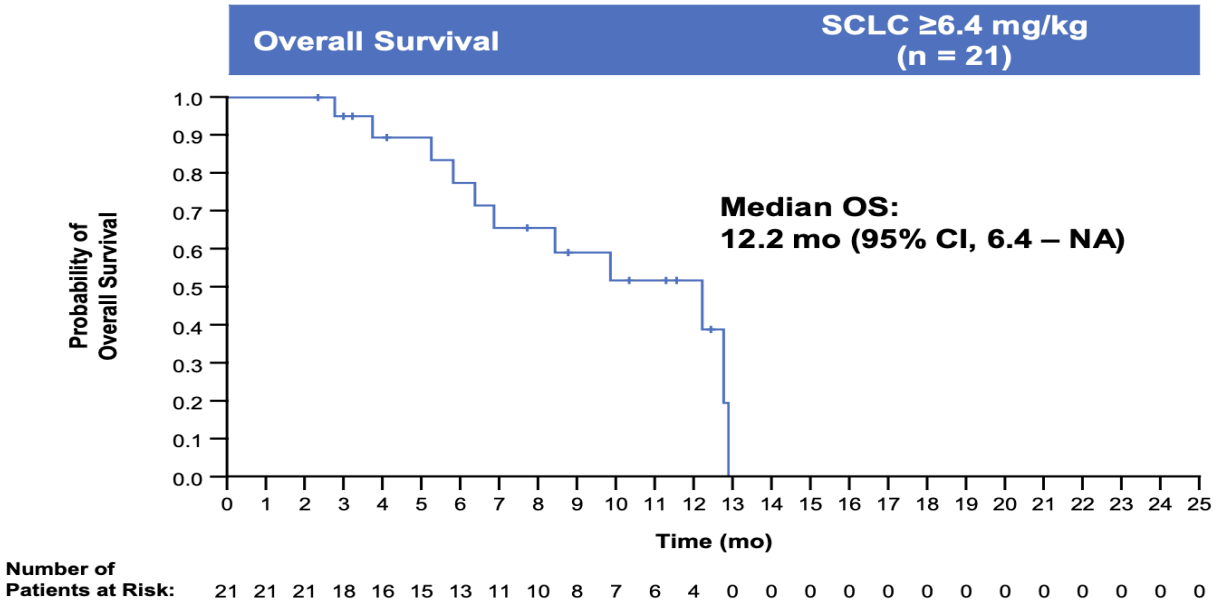
Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6



- Nearly all patients with post-baseline scans had a reduction in target lesions
- Median time to response was 1.2 months (95% CI, 1.2 – 1.4)
- Median duration of response was 5.9 months (95% CI, 2.8 – 7.5); two patients remain on treatment
- Median follow-up was 11.7 months (95% CI, 4.63 – 12.88)

Progression-Free and Overall Survival





Most Common (≥10%) All-Grade TEAEs Regardless of Causality

System Organ Class Preferred Term, n (%)	SCLC (N = 22)	
	Any Grade	Grade ≥3
Nausea	13 (59.1)	1 (4.5)
Fatigue	11 (50.0)	0 (0.0)
Anemia	6 (27.3)	1 (4.5)
Vomiting	6 (27.3)	0 (0.0)
Decreased appetite	5 (22.7)	1 (4.5)
Pyrexia	4 (18.2)	0 (0.0)
Constipation	4 (18.2)	1 (4.5)
IRR	3 (13.6)	0 (0.0)
Diarrhea	3 (13.6)	0 (0.0)
Dehydration	3 (13.6)	0 (0.0)
Dyspnea	3 (13.6)	0 (0.0)
Platelet count decreased	3 (13.6)	0 (0.0)
Arthralgia	3 (13.6)	0 (0.0)
Hyponatremia	3 (13.6)	0 (0.0)

- A total of three patients (13.6%) experienced an ILD or pneumonitis event (two Gr 1, one Gr 2)
  - All events were adjudicated by the ILD adjudication committee, of which one was adjudicated as drug-related ILD (Gr 2, 8.0 mg/kg) and discontinued treatment per protocol[a]
- Prophylactic premedication for nausea, vomiting, and IRR were not permitted for primary prophylaxis during cycle 1 of dose escalation

Conclusiones

- **Los anticuerpos conjugados se están desarrollando de forma rápida en cáncer de pulmón**
- **Patritumumab-deruxtecan parece un tratamiento eficaz en pacientes con CPNM EGFR mutado resistentes a TKI independiente de su mecanismo de resistencia.**
- **Las combinaciones de IO con Anticuerpos conjugados frente a TROP 2 parece un tratamiento altamente eficaz que puede alcanzar similares datos que las actuales combinaciones de QT**
- **Ifinatamab deruxtecan muestra datos de eficacia y seguridad interesantes en CPCP previamente tratados con un buen perfil de seguridad y con datos de OS en torno a 12 meses**