ADC in NSCLC: TROP2 and HER3

Hossein Borghaei, MS, DO

Professor and Chief, Thoracic Oncology

The Gloria and Edmund M. Dunn Chair in Thoracic Oncology

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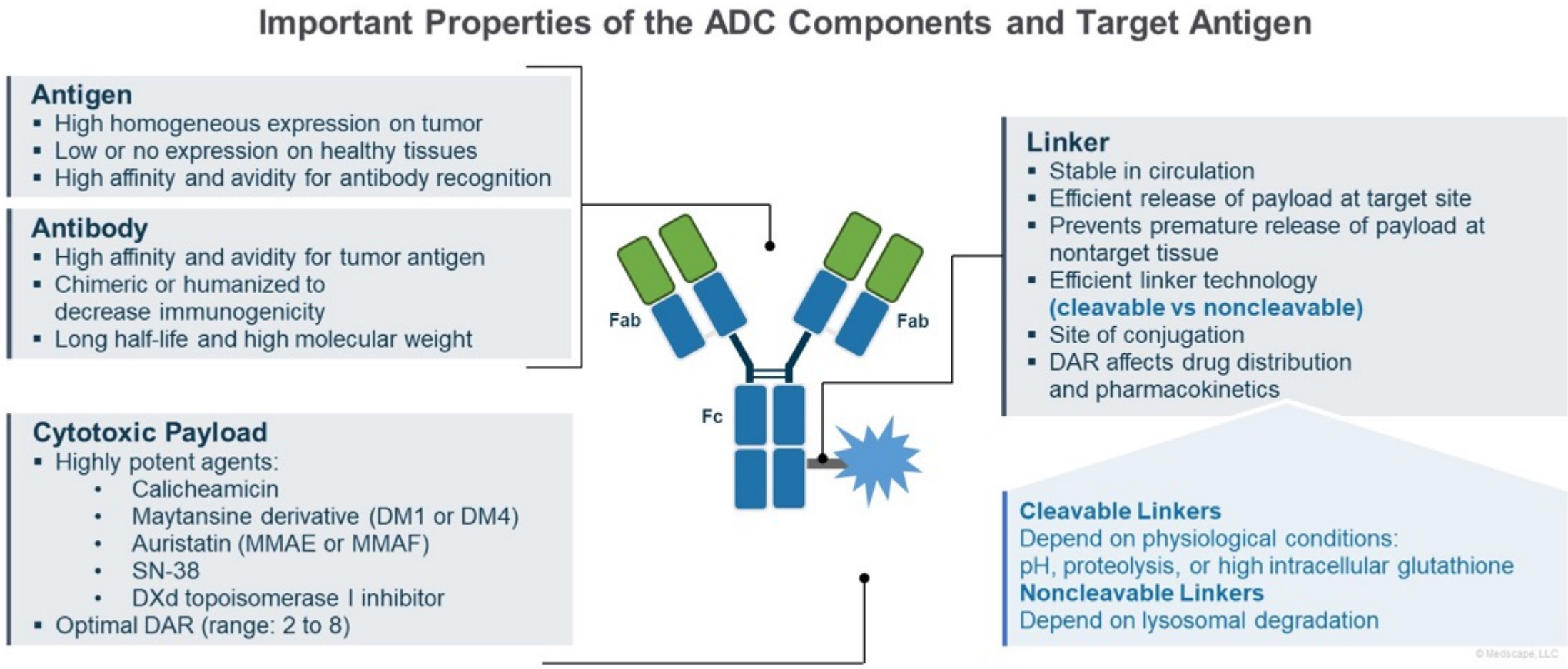
Antibody-Drug Conjugates



Chau CH, Lancet 2019;394

TROP2 ADCs

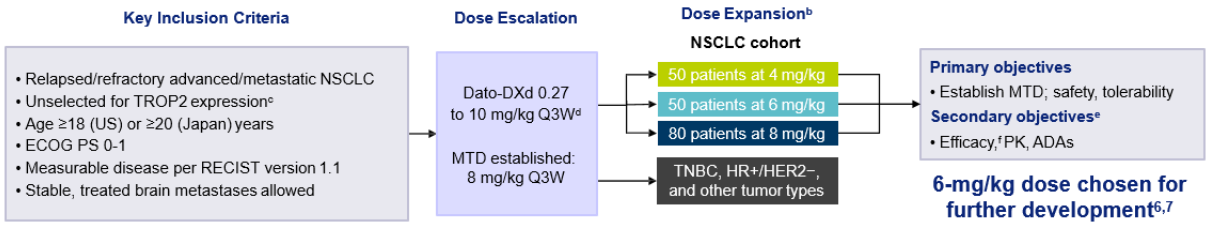
ADCs targeting TROP2 under development in NSCLC

	Antibody	Linker type	Payload	Action
Datopotamab deruxtecan	Humanized IgG1	Cleavable	Deruxtecan	Topoisomerase I inhibitor
Sacituzumab govitecan	Humanized IgG1	Cleavable	SN-38 (active metabolite of irinotecan	Topoisomerase I inhibitor

- In lung cancer, TROP2 overexpression in up to 64% of adenocarcinomas and up to 75% of SCC[1]
- TROP2 overexpression seems to be a negative prognostic factor in NSCLC[2]

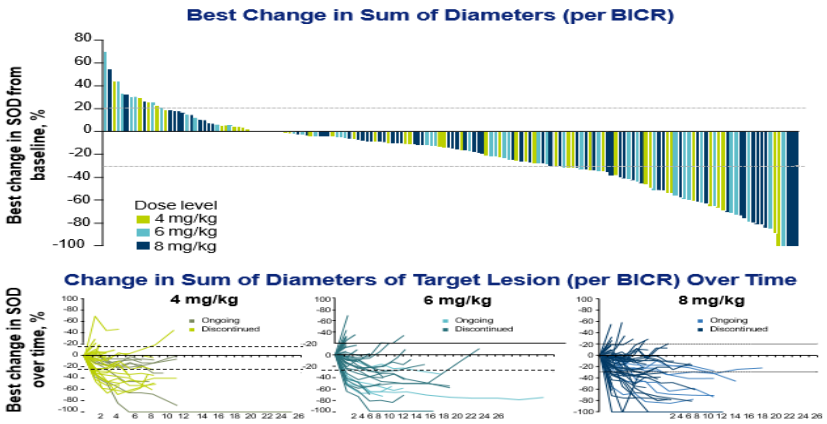
1 Inamura Oncotarget 2017, 2 Jiang Oncol Lett 2013

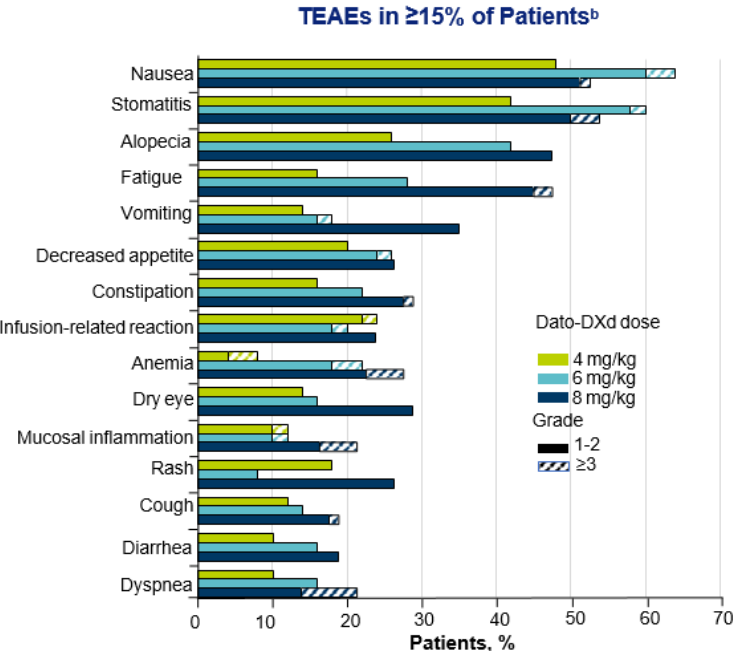
TROPION-PanTumor01 Study Design



Best Overall Response (BICR)

Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)



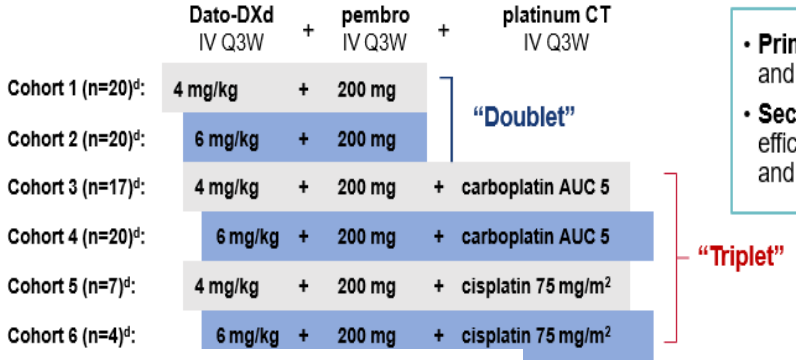


- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median duration of response of 10.5 months in the 6-mg/kg cohort

Garon, WCLC, 2021

TROPIAN-Lung02: Datopotamab Deruxtecan Plus Pembrolizumab and chemotherapy

Key eligibility
- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and anti-drug antibodies

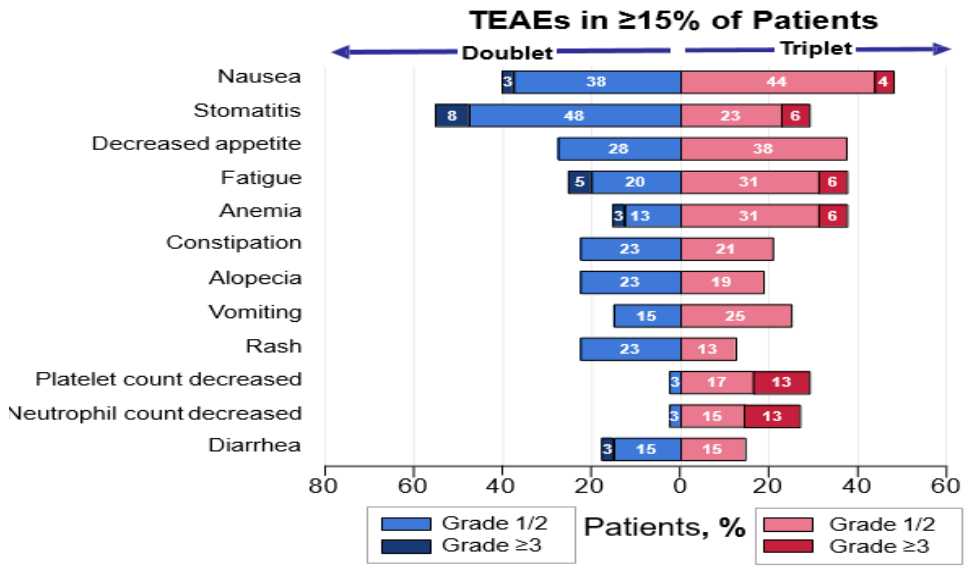
Safety

Events, n (%)	Doublet (n=40)	Triplet (n=48)
TEAEs	37 (93%)	47 (98%)
Study treatment-related[a]	33 (83%)	46 (96%)
Grade ≥3 TEAEs	16 (40%)	29 (60%)
Study treatment-related[a]	14 (35%)	26 (54%)
Serious TEAEs	9 (23%)	13 (27%)
Study treatment-related	4 (10%)	7 (15%)
TEAEs associated with		
Death[b]	2 (5%)	1 (2%)
Discontinuation due to any drug	9 (22%)	9 (19%)
Discontinuation due to Dato-DXd	6 (15%)	5 (10%)
ILD adjudicated as drug related[c]		
Grade 1/2	2 (5%)	0
Grade 3	1 (3%)	1 (2%)

BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%



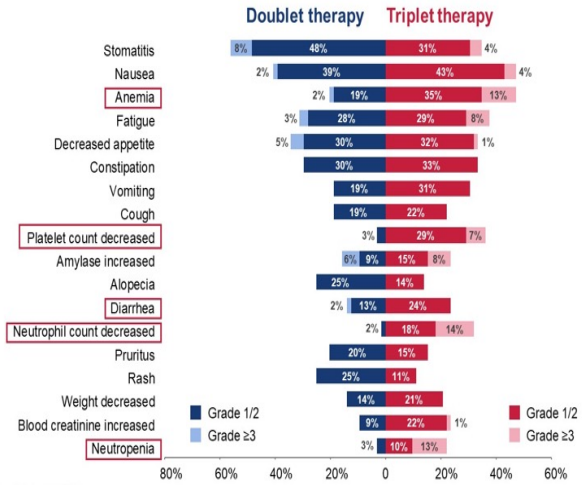
Levy, WCLC, 2022

TROPIAN-Lung02: ASCO 2023 Update

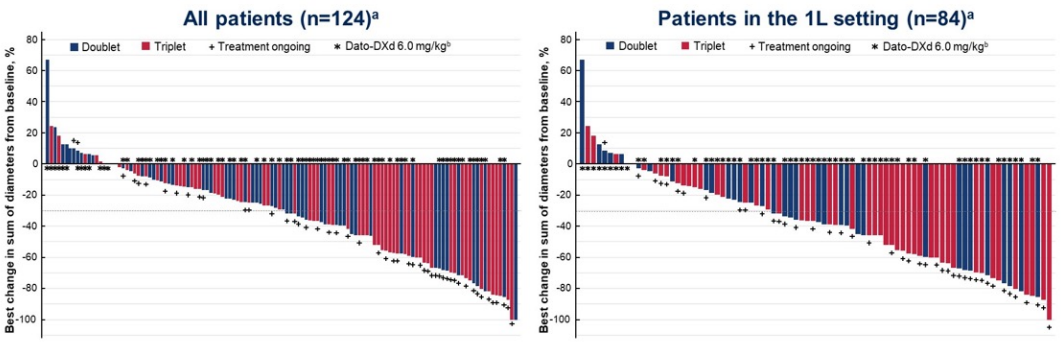
Response[a]	All patients: Doublet (n=61)[b]	All patients: Triplet (n=71)[b]	Patients in 1L: Doublet (n=34)[b]	Patients in 1L: Triplet (n=53)[b]
Confirmed + pending ORR, n (%)[c,d] [95% CI]	23 (38) [26-51]	35 (49) [37-61]	17 (50) [32-68]	30 (57) [42-70]
Confirmed + pending BOR, n (%)[d,e]				
Confirmed CR	0	1 (1)	0	1 (2)
Pending CR[d]	0	0	0	0
Confirmed PR	21 (34)	34 (48)	15 (44)	29 (55)
Pending PR[d]	2 (3)	0	2 (6)	0
SD, n (%)[f]	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)[g]	51 (84)	62 (87)	31 (91)	48 (91)
Median DOR, months [95% CI]	NE [8.8-NE]	NE [5.8-NE]	NE [5.5-NE]	NE [5.7-NE]

Preliminary PFS in all patients, median (95% CI), months: doublet, 8.3 (6.8-11.8); triplet 7.8 (5.6-11.1)[h]

- In the 1L setting, the ORR (confirmed and pending)[d] was 50% in patients receiving doublet therapy and 57% in those receiving triplet therapy
- Among all patients, the DCR was 84% (doublet) and 87% (triplet); in the 1L setting, the DCR was 91% in both therapy subgroups



- The most frequent TEAEs of any grade were stomatitis, nausea, anemia, and fatigue
- In general, hematologic TEAEs, particularly those of grade ≥3, were more frequently observed with triplet therapy than with doublet therapy



AESI, n (%)[a,b]	Doublet (n=64) All grades	Doublet (n=64) Grade ≥3	Triplet (n=72) All grades	Triplet (n=72) Grade ≥3
Oral mucositis/stomatitis	37 (58)	5 (8)	31 (43)	4 (6)
ILD/pneumonitis adjudicated as drug related[c]	11 (17)	2 (3)	16 (22)	2 (3)
Ocular surface toxicity[d]	10 (16)	1 (2)	17 (24)	2 (3)
IRR[e]	15 (23)	0	10 (14)	0

- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- No grade 5 AESIs have occurred
- There were no grade 4 or 5 adjudicated ILD/pneumonitis events[f]

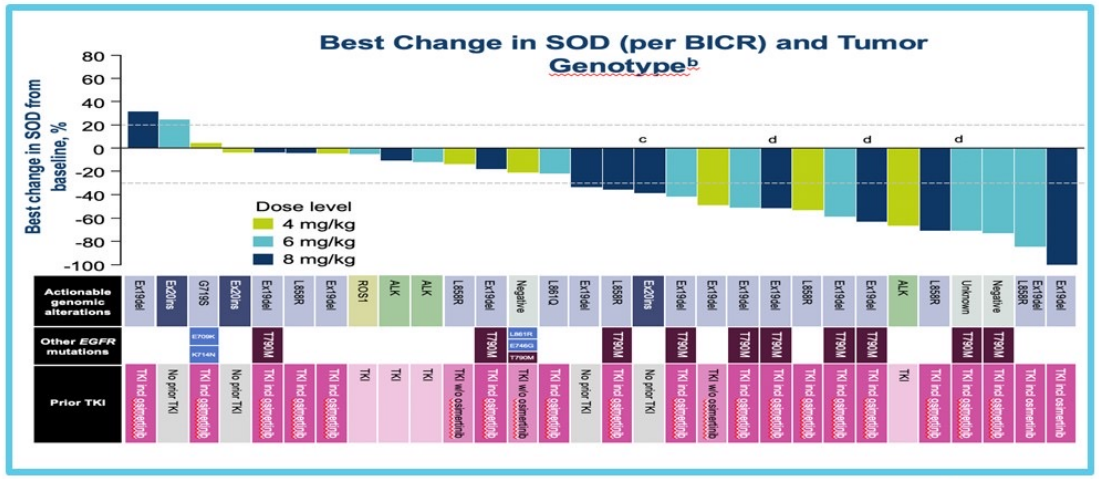
Goto, ASCO 2023

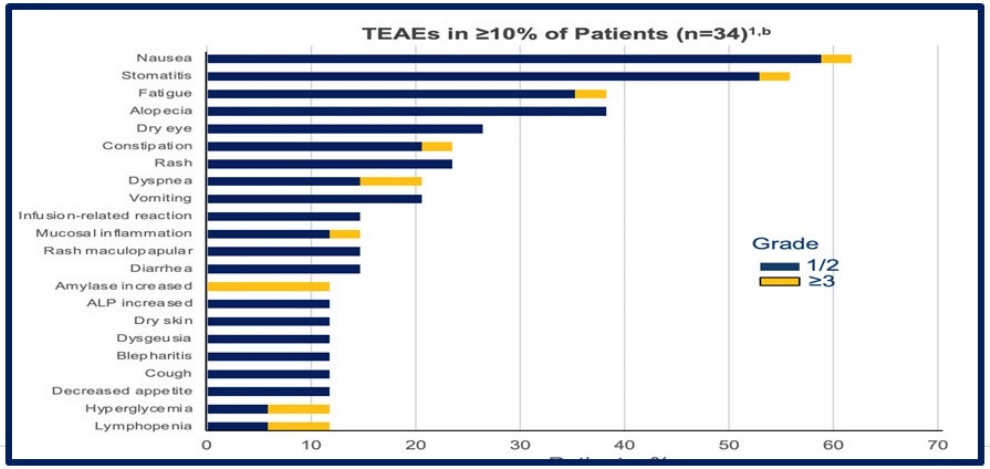
Datopotamab deruxtecan in actionable genomic alteration (AGA) NSCLC subset analysis (TROPION-PanTumor01 phase I, NSCLC cohort)

Garon ESMO 2021

Best Overall Response (per BICR)

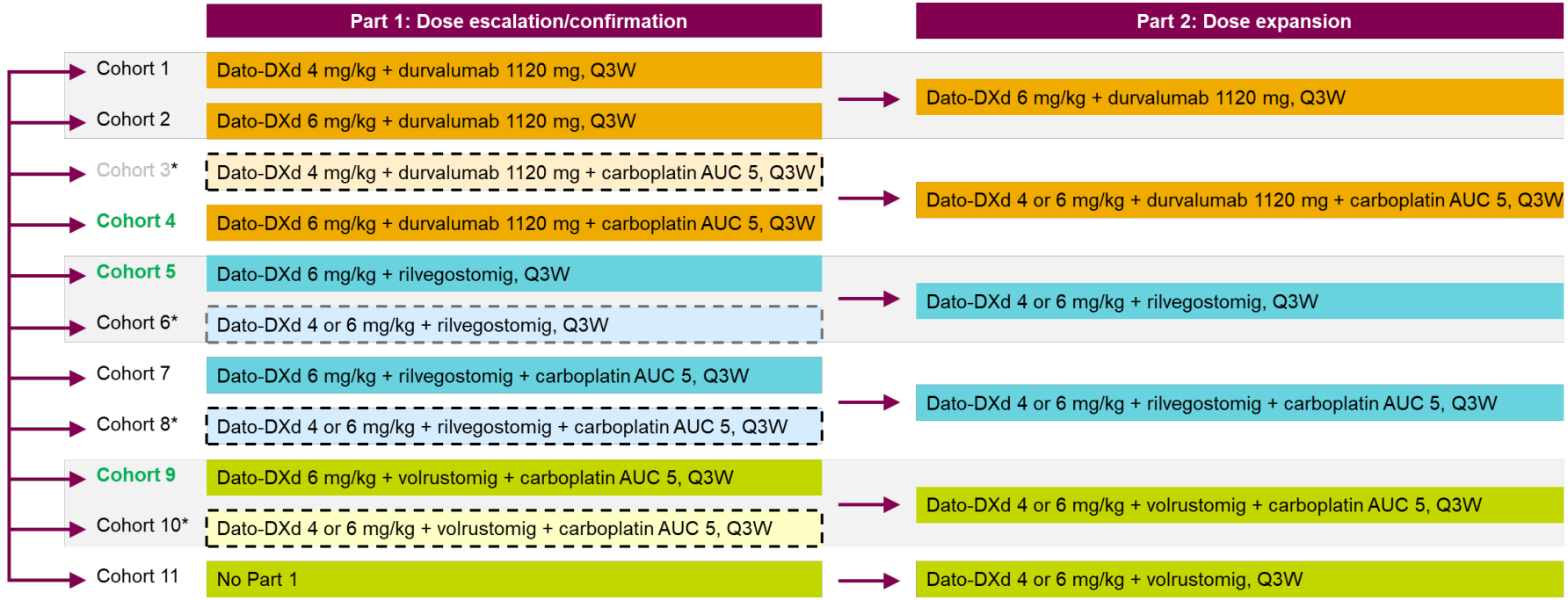
Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)





TROPION-Lung04: Phase 1b, multicenter study of datopotamab deruxtecan (Dato-DXd) in combination with immunotherapy ± carboplatin in advanced/metastatic non-small cell lung cancer (NSCLC)

- In Part 1 (dose escalation/confirmation), patients (N≈230) will be enrolled to 1 of 11 cohorts
  - Details of Cohorts 1–4 have been previously described[14]
- Dose confirmation in Cohorts 5–10 will be guided by an mTPI-2 design where a minimum of 6 and a maximum of 9 patients will be assessed for DLTs during Cycle 1; dependent on observed DLTs in Part 1, Part 2 dose expansions may be opened
- Cohort 11 may be opened at the dose of Dato-DXd and volrustomig deemed tolerated in combination with carboplatin (Cohorts 9 and 10)
- Cohorts below in **green** are currently open for recruitment (correct at the time of presentation)

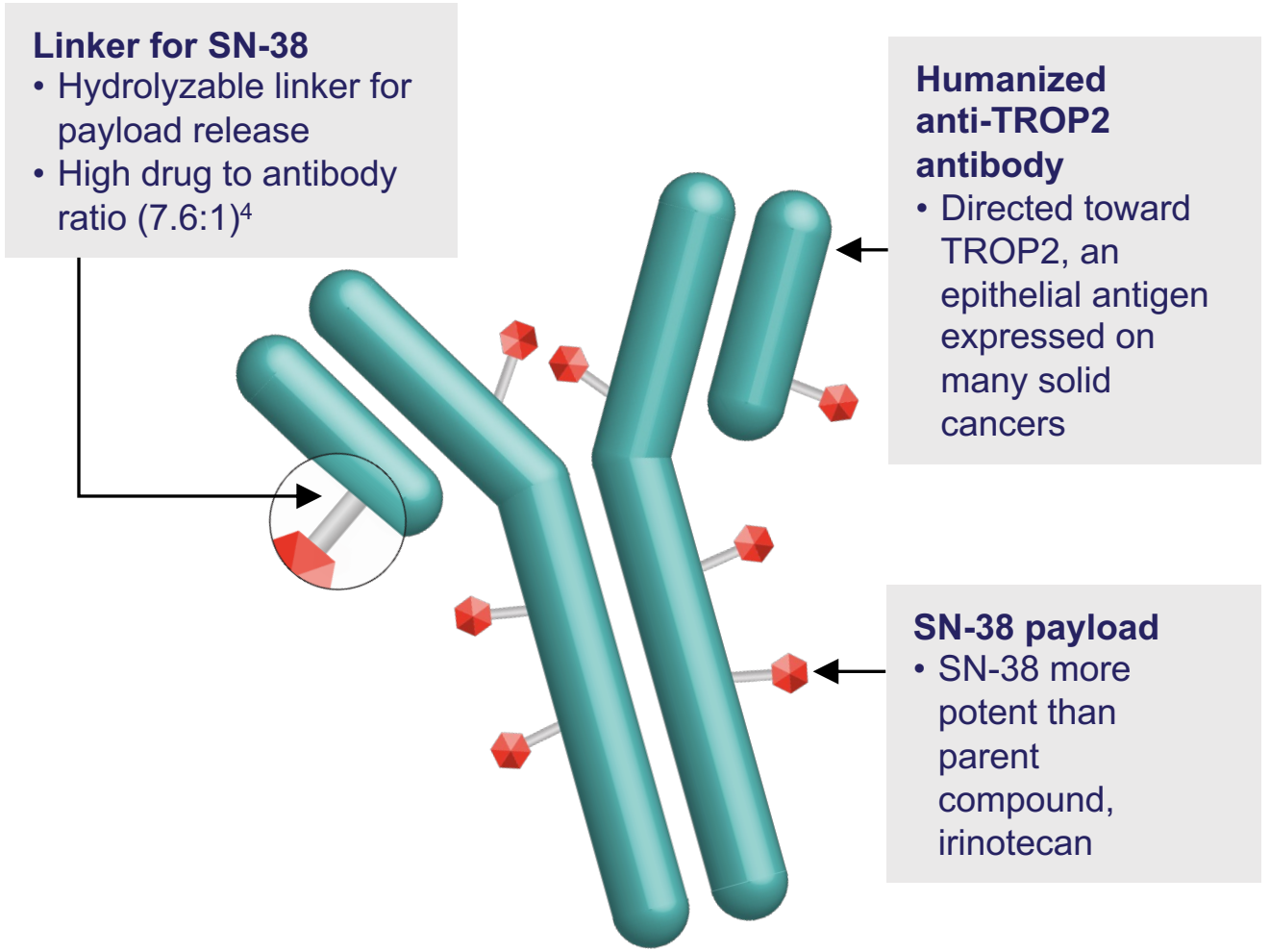


Borghaei, ASCO 2023

Poster 353b

Sacituzumab Govitecan (SG) Is a TROP2 Directed ADC

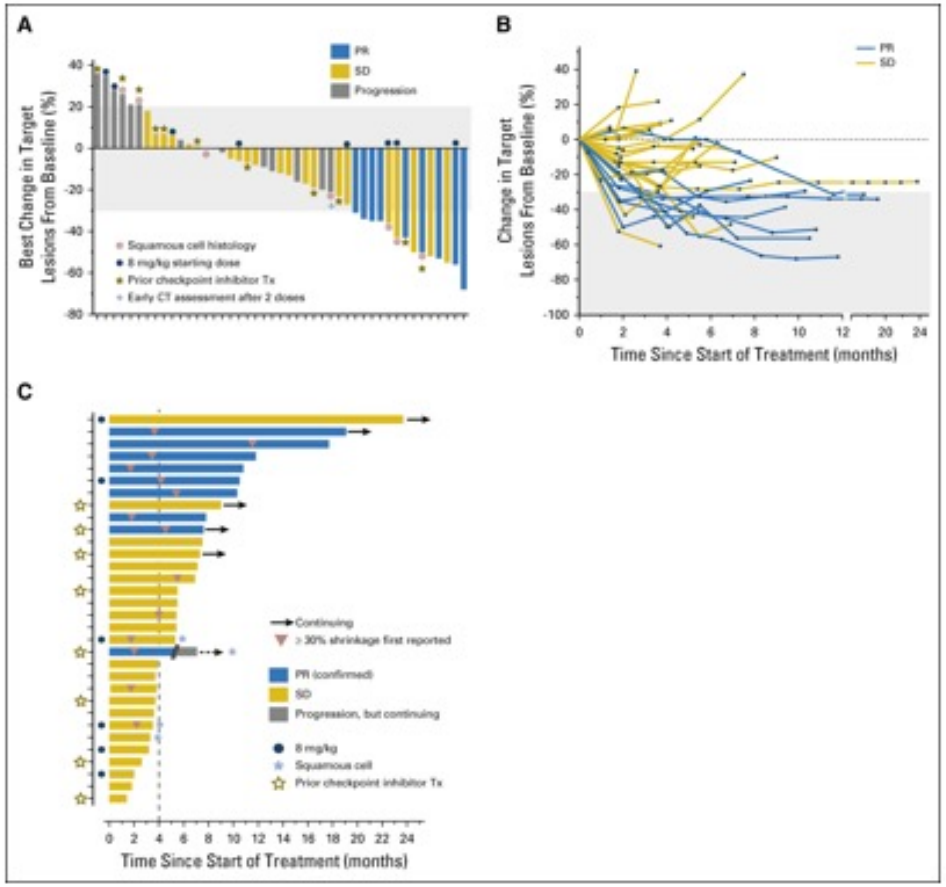
- SG is distinct from other ADCs[1-4]
  - Antibody highly specific for TROP2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Bardia A, et al. Presented at: ESMO Virtual Congress 2020. Abstract LBA4.

1. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-85. 2. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Cardillo TM, et al. *Bioconjugate Chem.* 2015;26:919-31. 4. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-512.

Sacituzumab Govitecan in NSCLC



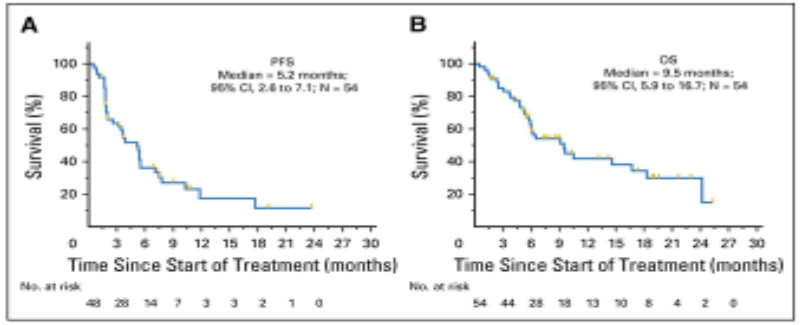


Fig 3. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) for all patients (N = 54). (A) For PFS, the initial number of patients at risk is 48 because six patients withdrew before their first computed tomography assessment and were censored at time 0. (B) For OS, 20 patients are currently alive, 31 died, and three were lost to follow-up after 1.7, 2.0, and 13.2 months.

Published in: Rebecca Suk Heist; Michael J. Guarino; Gregory Masters; W. Thomas Purcell; Alexander N. Starodub; Leora Horn; Ronald J. Scheff; Aditya Bardia; Wells A. Messersmith; Jordan Berlin; Allyson J. Ocean; Serengulam V. Govindan; Pius Maliakal; Boyd Mudenda; William A. Wegener; Robert M. Sharkey; David M. Goldenberg; D. Ross Camidge; *Journal of Clinical Oncology* 2017 352790-2797.
DOI: 10.1200/JCO.2016.72.1894

Nearly all tumor samples showed ≥50% positivity of viable tumor cells for TROP2 expression by IHC

Published in: Rebecca Suk Heist; Michael J. Guarino; Gregory Masters; W. Thomas Purcell; Alexander N. Starodub; Leora Horn; Ronald J. Scheff; Aditya Bardia; Wells A. Messersmith; Jordan Berlin; Allyson J. Ocean; Serengulam V. Govindan; Pius Maliakal; Boyd Mudenda; William A. Wegener; Robert M. Sharkey; David M. Goldenberg; D. Ross Camidge; *Journal of Clinical Oncology* 2017 352790-2797.
DOI: 10.1200/JCO.2016.72.1894
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Sacituzumab Govitecan in NSCLC

Table 3. Summary of Responses for Assessable Patients With an Intention-to-Treat Analysis for PFS and OS

Response	No. (%)
All patients	
Best overall response (n = 47)	
PR	9 (19)
SD	23 (49)
PD	15 (32)
Objective response duration, months	
Median (95% CI)	6.0 (4.8 to 8.3)
Clinical benefit (PR + SD ≥ 4 months)	20 (43)
PFS (n = 54), months	
Median (95% CI)	5.2 (3.2 to 7.1)
OS (n = 54), months	
Median (95% CI)	9.5 (5.9 to 16.7)
Patients with prior CPI therapy (n = 14)	
Best overall response	
PR	2 (14)
SD	7 (50)
PD	5 (36)
Clinical benefit (PR + SD ≥ 4 months)	5 (36)
PFS, months	
Median (95% CI)	5.2 (2.0 to 5.5)
OS, months	
Median (95% CI)	14.6 (5.9 to 14.6)

Table 2. Frequency of Adverse Events Regardless of Causality

	All Grades, No. (%)			Grade ≥ 3, No. (%)		
Adverse Event	All Patients	8 mg/kg Dose	10 mg/kg Dose	All Patients	8 mg/kg Dose	10 mg/kg Dose
No. of patients	54	8	46	54	8	46
Nausea	43 (80)	7 (88)	36 (78)	4 (7)	0 (0)	4 (9)
Diarrhea	33 (61)	5 (63)	28 (61)	4 (7)	1 (13)	3 (7)
Fatigue	25 (46)	3 (38)	22 (48)	3 (6)	0 (0)	3 (7)
Alopecia	21 (39)	3 (38)	18 (39)	NA	NA	NA
Neutropenia	20 (37)	2 (25)	18 (39)	15 (28)	1 (13)	14 (30)
Vomiting	19 (35)	4 (50)	15 (33)	2 (4)	1 (13)	1 (2)
Anemia	17 (31)	1 (13)	16 (35)	2 (4)	0 (0)	2 (4)
Constipation	17 (31)	3 (38)	14 (30)	0 (0)	0 (0)	0 (0)
Anorexia	13 (28)	0 (0)	13 (28)	1 (2)	0 (0)	1 (2)
Hypophosphatemia	12 (22)	1 (13)	11 (24)	1 (2)	0 (0)	1 (2)
Dehydration	10 (19)	0 (0)	10 (22)	2 (4)	0 (0)	2 (4)
Weight decrease	10 (19)	0 (0)	10 (22)	0 (0)	0 (0)	0 (0)
Leukopenia	10 (19)	2 (25)	8 (17)	5 (9)	1 (13)	4 (9)
Hypomagnesemia	9 (17)	0 (0)	9 (20)	0 (0)	0 (0)	0 (0)
Dyspnea	8 (15)	2 (25)	6 (13)	2 (4)	1 (13)	1 (2)
Pneumonia	7 (13)	1 (12)	6 (13)	5 (9)	0 (0)	5 (11)

Published in: Rebecca Suk Heist; Michael J. Guarino; Gregory Masters; W. Thomas Purcell; Alexander N. Starodub; Leora Horn; Ronald J. Scheff; Aditya Bardia; Wells A. Messersmith; Jordan Berlin; Allyson J. Ocean; Serengulam V. Govindan; Pius Maliakal; Boyd Mudenda; William A. Wegener; Robert M. Sharkey; David M. Goldenberg; D. Ross Camidge; *Journal of Clinical Oncology* 2017 352790-2797.
DOI: 10.1200/JCO.2016.72.1894

Sacituzumab govitecan for patients with refractory metastatic epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial

Bardia Ann Oncol 2021

	NSCLC cohort
Total, *n*	54
Dose, mg/kg	8, 10, 12
ORR, %	16.7
mDoR, months	6.0
mPFS, months	4.4
mOS, months	7.3

In the overall safety population (*n*=495)

- Most common treatment-related AEs: nausea (62.6%), neutropenia (57.8%), diarrhea (56.2%), fatigue (48.3%) and alopecia (40.4%)
- Neutropenia was numerically more frequent in *UGT1A1*28* homozygotes (60.9%) tan heterozygotes (38.3%) or *UGT1A1*1* wt (33.3%)
  - *Of those patients with available UGT1A1 status, 9.3% were homozygous*

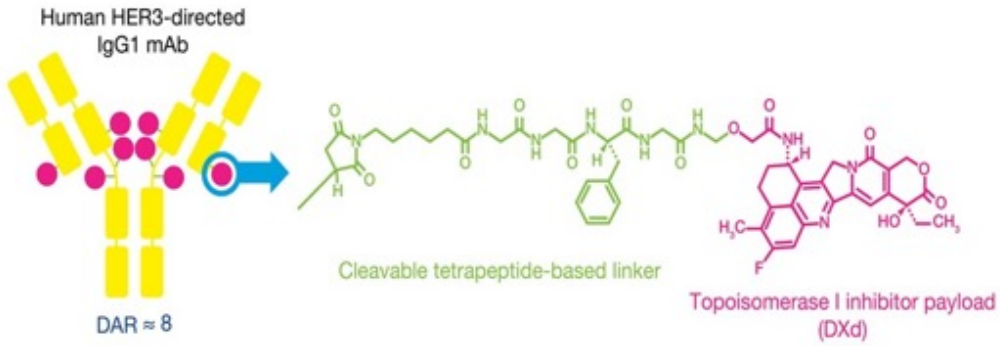
HER3 ADC

HER3 in NSCLC

- Member of the ERbB/HER family of receptor tyrosine kinases that has minimal kinase activity.
  - Rationale for antibody-based approaches over TKIs
- Expressed in approximately 80% of NSCLC.[1]
- High HER3 expression is associated with increased metastatic potential and poor prognosis.[2,3]
- Increased HER3 signaling implicated in resistance to EGFR, ALK, and MET TKIs.[4-6]

Patritumab Deruxtecan (HER3-DXd)

A HER3 directed antibody drug conjugate composed of the monoclonal antibody patritumab, a tetrapeptide-based linker, and a topoisomerase I inhibitor payload



[1] Scharpenseel Sci Rep 2019, [2]Li Oncotarget 2017, [3]Muller-Tidow Cancer Research 2005, [4]Yonesaka Clin Cancer Res 2022, [5]McCoach Clin Cancer Res 2018, [6]Recondo Clin Cancer Res 2020

Slide by: Dagogo-Jack, ASCO 2022

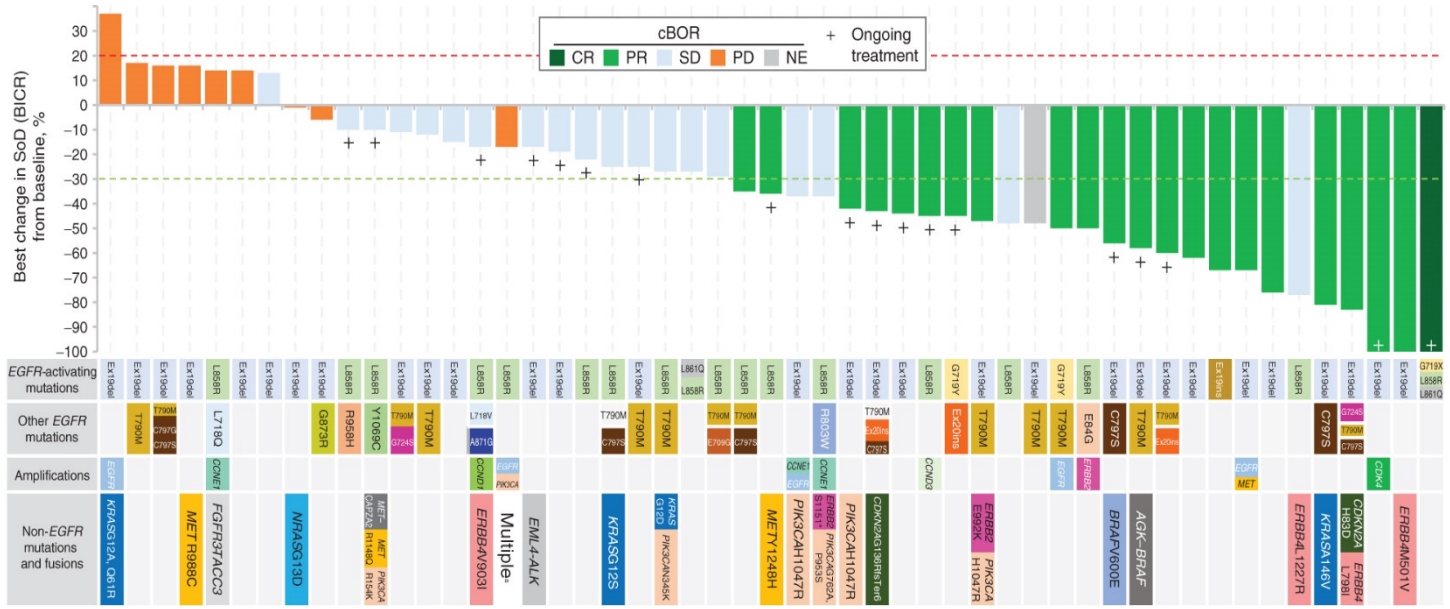
ADCs targeting HER3 under development in NSCLC

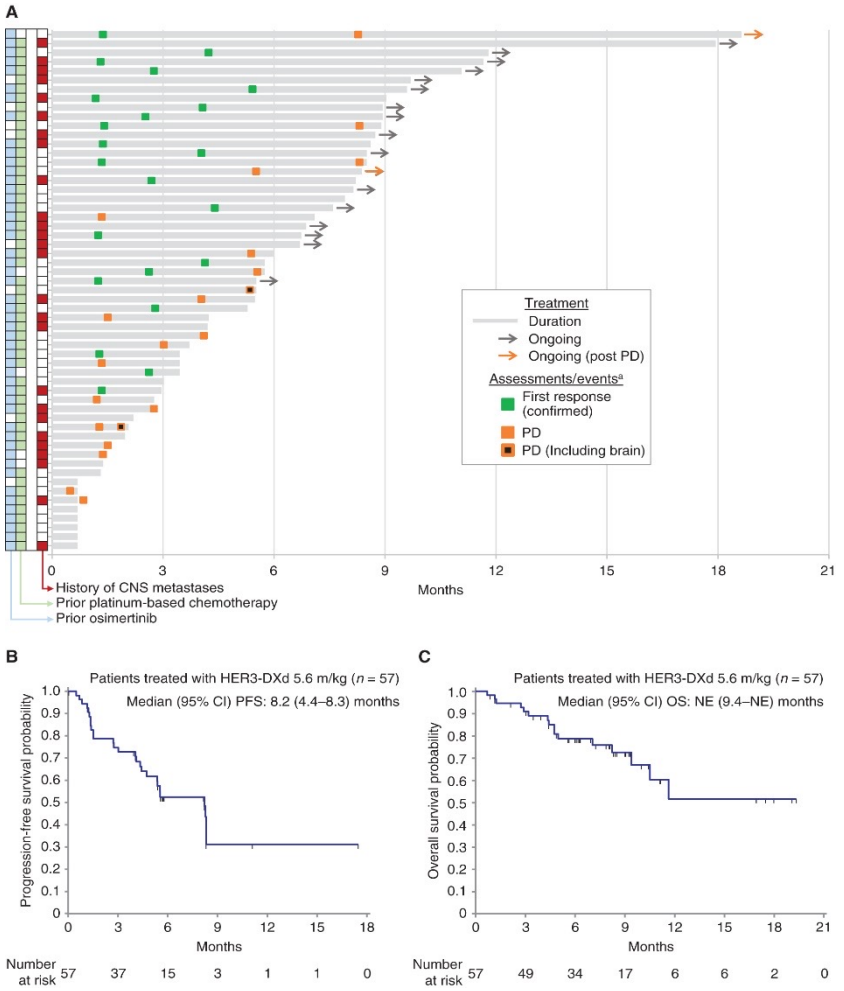
	Antibody	Linker type	Payload	Action
Patritumab deruxtecan	Humanized IgG1	Cleavable	Deruxtecan	Topoisomerase I inhibitor

- HER3 is overexpressed in 42-83% of NSCLC and associated with poor prognosis[1-3]
- HER3 expression can mediate resistance to targeted therapy via maintenance of HER3-mediated activation of PI3K/AKT signalling[4]

1 Manickavasagar Lung Cancer Mag 2021, 2 Sharpenseel Sci Rep 2019, 3 Yi Mod Pathol 97, 4 Lyu Acta Pharm Sin B 2018

Patritumab Deruxtican (HER3-DXd) in EGFR Mutated NSCLC

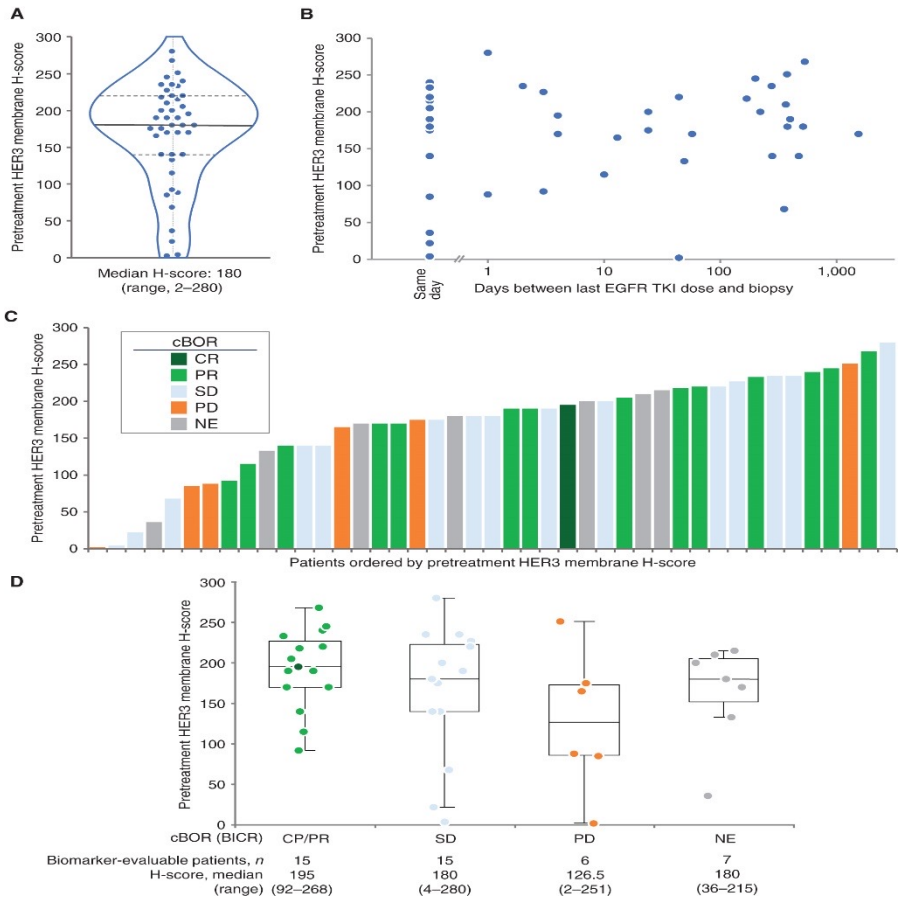




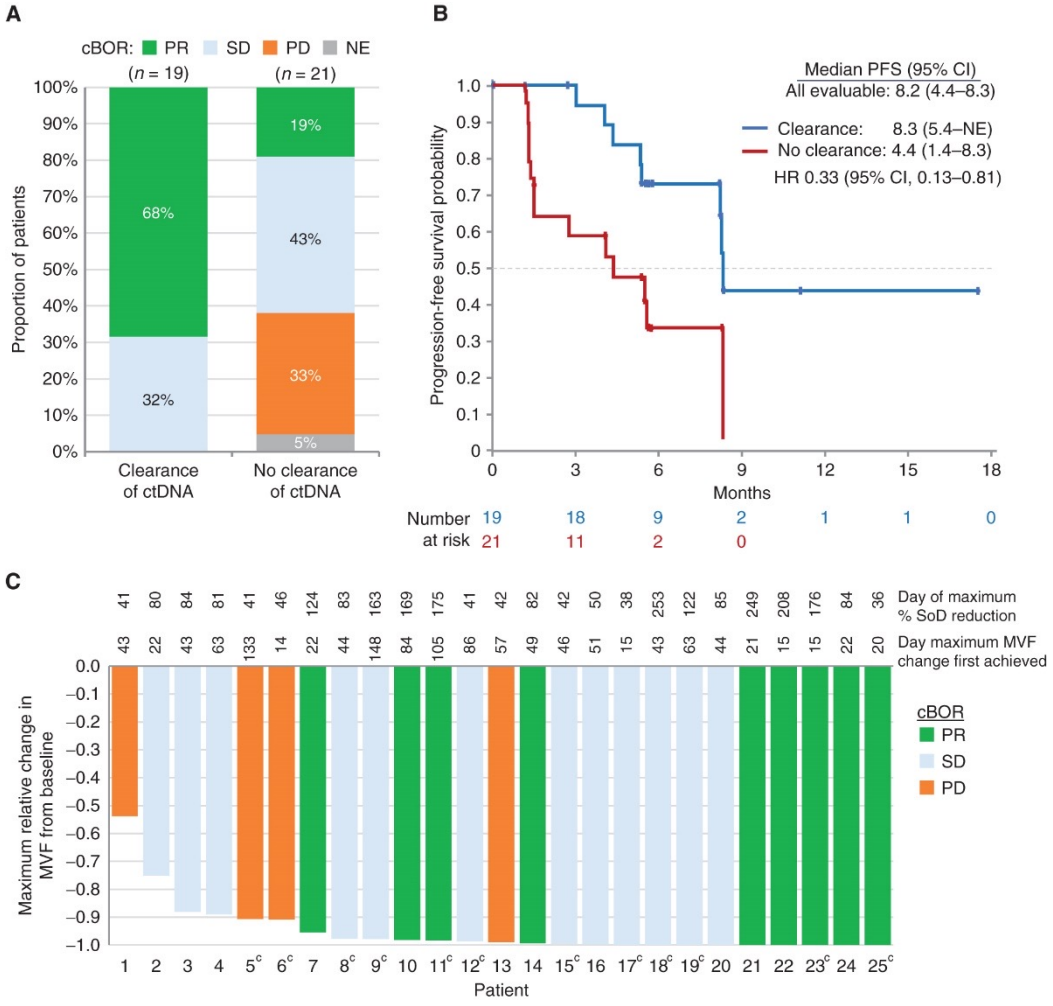
Janne et al; Cancer Discov. 2022;12(1):74-89. doi:10.1158/2159-8290.CD-21-0715

Patritumab Deruxtican (HER3-DXd) in EGFR Mutated NSCLC

HER3 Expression



ctDNA Clearance



Janne et al; Cancer Discov. 2022;12(1):74-89. doi:10.1158/2159-8290.CD-21-0715

Patritumab Deruxtican (HER3-DXd) in EGFR Mutated NSCLC

Table 3. Responses by BICR per RECIST 1.1

Characteristics	Pooled RDE (5.6 mg/kg) All pooled (*n* = 57)	Pooled RDE (5.6 mg/kg) Prior PBC and osimertinib (*n* = 44)
Confirmed ORR, % (*n*) [95% CI]	39 (22) [26.0-52.4]	39 (17) [24.4-54.5]
BOR, *n* (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD	19 (33)	13 (30)
PD	9 (16)	8 (18)
NE	7 (12)	6 (14)
DCR,[a] % (*n*) [95% CI]	72 (41) [58.5-83.0]	68 (30) [52.4-81.4]
TTR, median (range), months	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), months	6.9 (3.1-NE)	7.0 (3.1-NE)
Progression-free survival, median (95% CI), months	8.2 (4.4-8.3)	8.2 (4.0-NE)
Overall survival, median (95% CI), months	NE (9.4-NE)	NE (8.2-NE)

Abbreviation: PBC, platinum-based chemotherapy.

[a]DCR = rate of confirmed BOR of CR, PR, or SD.

Table 2. Adverse events summary

TEAEs	Pooled RDE 5.6 mg/kg (*n* = 57), *n* (%)	All patients 3.2/4.8/5.6/6.4 mg/kg (*n* = 81), *n* (%)
Any TEAE	57 (100)	81 (100)
Grade ≥3 TEAEs	42 (74)	52 (64)
Serious TEAEs	25 (44)	32 (40)
TEAEs associated with treatment discontinuation	6 (11)[a]	7 (9)[b]
TEAEs associated with dose reduction	12 (21)	18 (22)
TEAEs associated with dose interruption	21 (37)	30 (37)
TEAEs associated with death	4 (7)[c]	5 (6)[d]
Treatment-related TEAEs	55 (96)	78 (96)
Grade ≥3 treatment-related TEAEs	31 (54)	38 (47)
Treatment-related TEAEs associated with death	0	0
Serious treatment-related TEAEs	12 (21)	15 (19)
Grade ≥3 TEAEs occurring in ≥5% of patients		
Platelet count decrease/thrombocytopenia	17 (30)	21 (26)
Neutrophil count decrease/neutropenia	11 (19)	12 (15)
Fatigue	8 (14)	8 (10)
Anemia/hemoglobin decrease	5 (9)	6 (7)
Dyspnea	5 (9)	5 (6)
Febrile neutropenia	5 (9)	5 (6)
Hypoxia	4 (7)	5 (6)
White blood cell count decrease/leukopenia	4 (7)	5 (6)
Hypokalemia	3 (5)	4 (5)
Lymphocyte count decrease/lymphopenia	3 (5)	4 (5)
Adjudicated ILD	5 (9)[e]	5 (6)[e]
Adjudicated treatment-related ILD	4 (7)[f]	4 (5)[f]

[a]Fatigue (two patients); decreased appetite, interstitial lung disease (ILD), neutrophil count decrease, pneumonitis, and upper respiratory tract infection (one patient each).

[b]Fatigue (two patients); nausea, decreased appetite, ILD, neutrophil count decrease, pneumonitis, and upper respiratory tract infection (one patient each).

[c]TEAEs associated with death were respiratory failure (two patients) and disease progression and shock (one patient each).

[d]TEAEs associated with death were respiratory failure and disease progression (two patients each) and shock (one patient).

[e]Two grade 1, one grade 2, one grade 3, and one grade 5.

[f]Two grade 1, one grade 2, and one grade 3.

Janne et al; Cancer Discov. 2022;12(1):74-89. doi:10.1158/2159-8290.CD-21-0715

- **Study objective**
  - To evaluate the efficacy and safety of patritumab deruxtecan in patients with advanced or metastatic NSCLC without EGFR-activating mutations

Key patient inclusion criteria

- Advanced or metastatic NSCLC
- No EGFR-activating mutations
- Stable brain metastases permitted
- Prior platinum-based chemotherapy ± immunotherapy

(n=47)

Patritumab deruxtecan
5.6 mg IV q3w

Primary endpoint

- ORR (RECIST v1.1, BICR)

Secondary endpoints

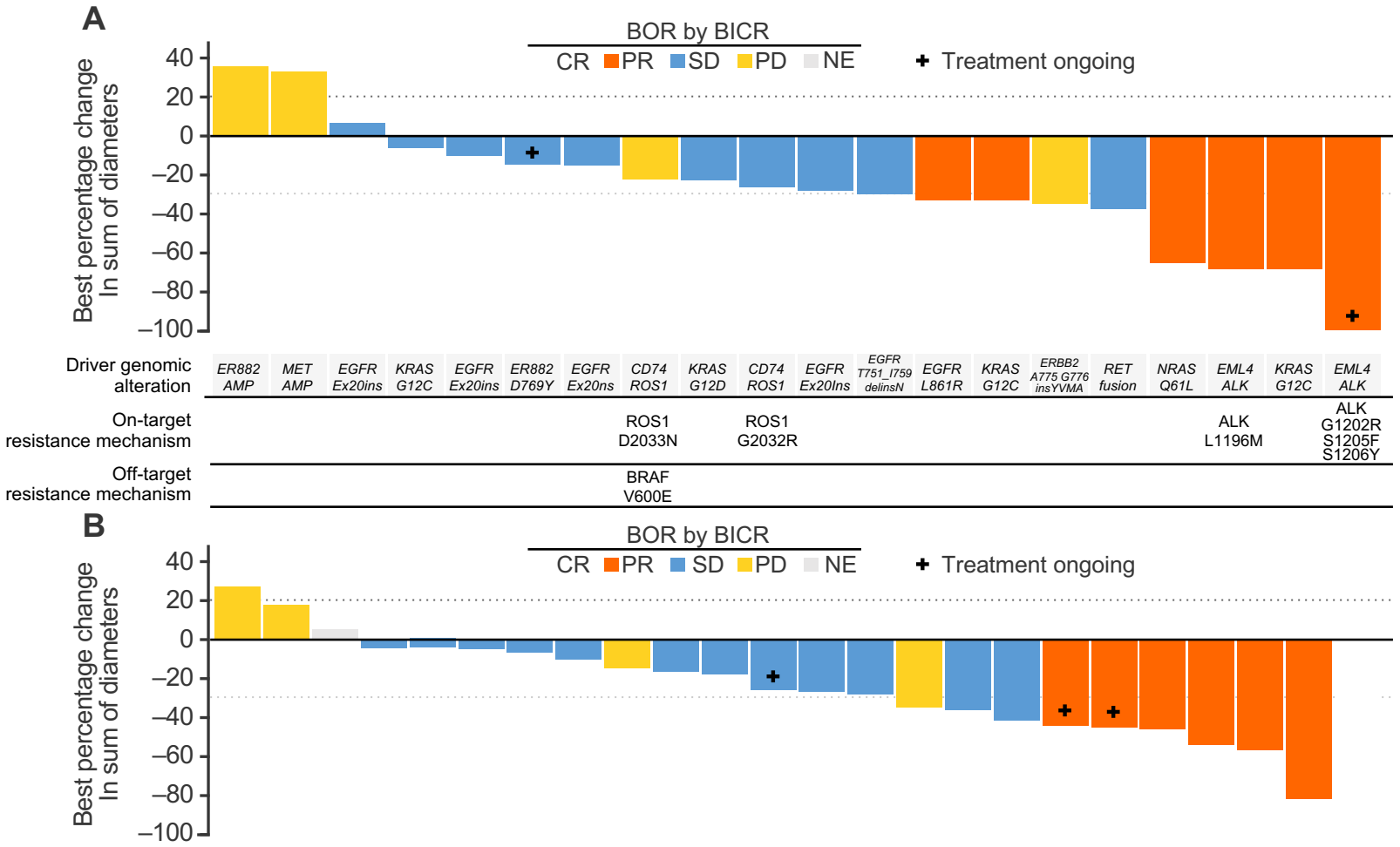
- DoR, PFS, safety

Steuer CE, et al. J Clin Oncol 2022;40(suppl):Abstr 9017

9017: Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without EGFR-activating mutations – Steuer CE, et al

- **Key results**

Antitumor activity in patients with (A) and without (B) identified genomic alterations



With Driver Mutations

Outcomes	n=21
ORR, % (95%CI)	28.6 (11.3, 52.2)
DCR, % (95%CI)	76.2 (52.8, 91.8)
mTTR, mo (95%CI)	2.8 (1.3, 4.6)
mDoR, mo (95%CI)	9.4 (4.2, NE)
mPFS, mo (95%CI)	10.8 (2.8, 16.0)

Without Driver Mutations

Outcomes	n=26
ORR, % (95%CI)	26.9 (11.6, 47.8)
DCR, % (95%CI)	73.1 (52.2, 88.4)
mTTR, mo (95%CI)	2.1 (1.2, 6.0)
mDoR, mo (95%CI)	9.6 (1.6, NE)
mPFS, mo (95%CI)	4.2 (2.5, 10.8)

Steuer CE, et al. J Clin Oncol 2022;40(suppl):Abstr 9017

9017: Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without EGFR-activating mutations – Steuer CE, et al

- **Key results (cont.)**

AEs, n (%)	n=54
TEAEs	47 (100)
Led to treatment discontinuation	5 (10.6)
Led to dose reduction	11 (23.4)
Led to dose interruption	24 (51.1)
Death	7 (14.9)
Grade ≥3	34 (72.3)
SAE	19 (40.4)
TRAEs	47 (100)
Death	0
Grade ≥3	24 (51.1)
SAE	6 (12.8)
Adjudicated treatment-related interstitial lung disease	5 (10.6)
Grade 1	1 (2.1)
Grade 2	4 (8.5)
Grade ≥3	0

- **Conclusions**
  - In patients with advanced or metastatic NSCLC without EGFR-activating mutations, patritumab deruxtecan demonstrated encouraging antitumor activity regardless of the presence of concomitant genomic alterations and had a manageable safety profile

Steuer CE, et al. J Clin Oncol 2022;40(suppl):Abstr 9017

Ongoing Trials with patritumab deruxtecan

ClinicaTrial.gov ID	Phase	Setting	N	Treatment arms	1 endpoint
HERTHENA-Lung02 NCT05338970	**3**	**Metastatic NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) after failure of third-generation EGFR TKI therapy**	**560**	**Patritumab deruxtecan *vs* platinum-based CT**	**PFS**
HERTHENA-Lung01 NCT04619004	2	Advanced EGFR-mutated NSCLC refractory to Osimertinib and platinum-based CT	420	5.6 mg/kg fixed dose regimen or an up-titration dose regimen of patritumab deruxtecan	ORR
NCT04676477	1	Osimertinib-refractory and treatment-naïve advanced EGFR-mutated NSCLC Dose-escalation and dose-expansion study	252	Patritumab deruxtecan plus osimertinib	Safety, ORR

Enriqueta Felip, MD, PhD, ASCO 2023

Final Thoughts

- ADCs with improved safety and toxicity profile are potentially useful treatment options for some patients
- Patient selection based on biomarkers have proven to be a bit more difficult
- Response rate in the disease refractory/relapsed setting is reasonable
- It remains to be proven that these agents can be moved to the front line treatment setting