ANTIBODY DRUG CONJUGATES + IO COMBINATIONS IN NSCLC

Alissa Cooper, MD

Memorial Sloan Kettering Cancer Center

@alissajcooper

April 19, 2024

Endorsed by

IASLC International Association for the Study of Lung Cancer
Conquering Thoracic Cancers Worldwide

Accredited by

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

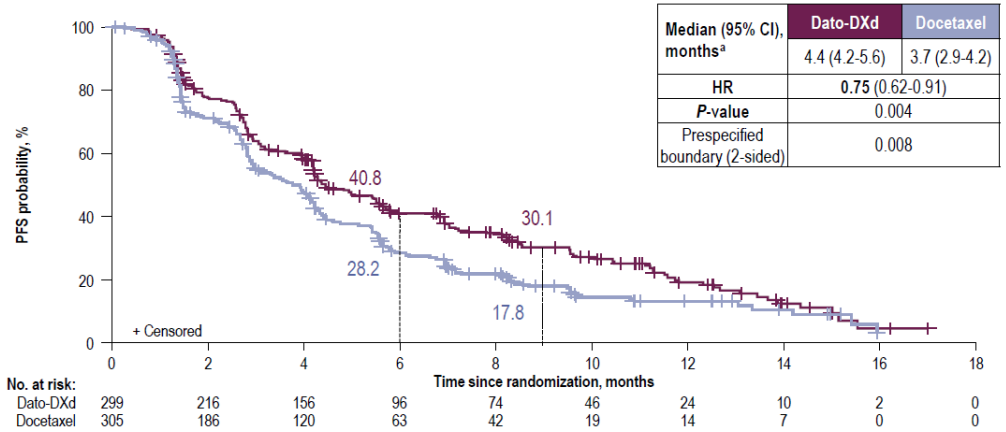
Presented by

IDEOlogy Health
Creating Aha! Moments In Healthcare

The limitations of single agent ADCs

Dato-DXd vs docetaxel in NSCLC – ESMO 2023

Progression-Free Survival: ITT



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

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

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

MADRID 2023 ESMO congress

Aaron Lisberg

Lisberg et al, presented at ESMO 2023

Sanofi press release 12/21/23

Press Release

sanofi

Sanofi announces end of program evaluating tusamitamab ravtansine after a 2L NSCLC Phase 3 trial did not meet a primary endpoint

- CARMEN-LC03 trial did not meet dual primary endpoint of improving progression-free survival; tusamitamab ravtansine clinical development program will be discontinued
- Sanofi reinforces commitment to broader oncology development program including CEACAM5-directed antibody drug conjugates (ADC) with additional anticipated trials

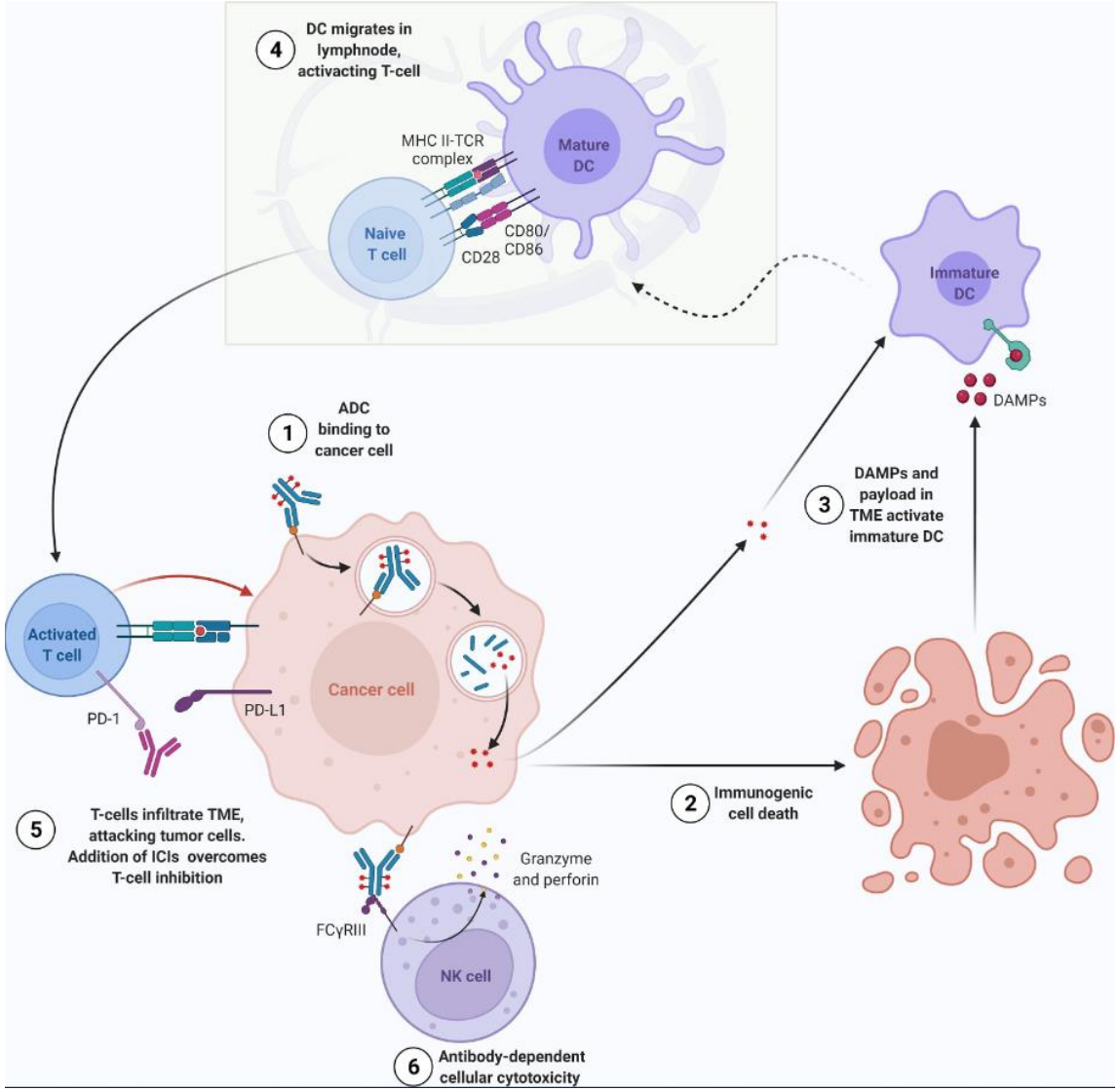
Gilead press release 1/22/24

January 22, 2024

Gilead Provides Update on Phase 3 EVOKE-01 Study

FOSTER CITY, Calif.--(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the Phase 3 EVOKE-01 study did not meet its primary endpoint of overall survival (OS) in previously treated metastatic non-small cell lung cancer (NSCLC). EVOKE-01 is evaluating Trodelvy® (sacituzumab govitecan-hziy; SG) vs. docetaxel in patients with metastatic or advanced NSCLC that had progressed on or after platinum-based chemotherapy and checkpoint inhibitor therapy.

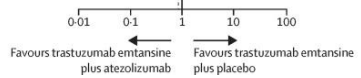
ADCs interact with immunotherapy in myriad ways



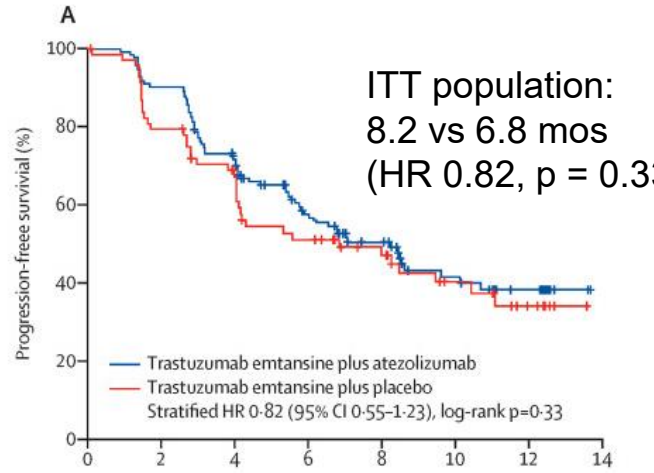
Nicolo et al, Cancer Treatment Reviews 2022

Clinical experience of ADCs + IO: TDM-1 + atezolizumab in breast cancer

	Trastuzumab emtansine plus placebo		Trastuzumab emtansine plus atezolizumab		HR (95% CI)
	n/N	Median (95% CI) progression-free survival, months	n/N	Median (95% CI) progression-free survival, months	
Age, years					
<65	32/58	8·0 (4·0–NE)	63/118	7·1 (5·8–10·1)	0·89 (0·58–1·3
≥65	7/11	4·3 (4·0–NE)	5/15	NE (3·1–NE)	0·57 (0·18–1·8
Race					
Asian	17/23	3·0 (1·6–9·5)	26/49	8·4 (4·4–NE)	0·53 (0·29–0·9
White	21/44	8·5 (4·2–NE)	37/72	8·2 (5·6–10·7)	1·19 (0·69–2·0
Other	1/2	NE (4·0–NE)	5/12	NE (5·5–NE)	0·75 (0·08–6·7
World region					
Rest of world	21/32	5·3 (2·7–10·4)	33/62	8·2 (5·6–NE)	0·63 (0·36–1·0
USA	7/11	4·0 (1·7–NE)	8/21	NE (4·0–NE)	0·52 (0·19–1·4
Western Europe	11/26	NE (8·0–NE)	27/50	8·5 (4·7–10·7)	1·55 (0·76–3·1
Liver metastases					
No	24/47	4·3 (4·0–NE)	40/89	8·5 (5·9–NE)	0·73 (0·44–1·2
Yes	15/22	8·0 (4·0–11·1)	28/44	6·2 (4·0–8·6)	1·13 (0·60–2·1
ECOG performance status					
0	19/40	11·1 (4·2–NE)	52/93	7·0 (5·7–9·6)	1·34 (0·79–2·2
1	20/28	4·0 (2·6–6·8)	16/39	NE (4·1–NE)	0·44 (0·23–0·8
Visceral disease					
Absent	8/21	NE (4·0–NE)	15/30	NE (6·8–NE)	0·95 (0·40–2·2
Present	31/48	4·3 (4·0–9·5)	53/95	6·8 (5·4–8·5)	0·82 (0·53–1·2
Lines of previous treatment for metastatic breast cancer					
0	4/6	2·0 (1·3–NE)	3/15	NE (NE–NE)	0·17 (0·04–0·7
1	22/40	8·0 (4·1–NE)	36/68	6·8 (4·7–10·7)	1·09 (0·64–1·8
2	6/9	8·2 (3·0–10·4)	13/23	8·5 (4·1–NE)	0·77 (0·29–2·0
≥3	7/14	NE (2·7–NE)	16/27	5·6 (4·0–NE)	1·12 (0·46–2·7
Hormone receptor status					
Negative	17/29	4·1 (2·8–NE)	23/48	8·4 (6·0–NE)	0·58 (0·31–1·10)
Positive	21/38	8·5 (4·2–11·1)	42/79	6·8 (5·4–10·1)	1·08 (0·64–1·82)
PD-L1 IHC status					
IC 0	21/42	8·2 (4·2–NE)	1/76	6·8 (5·4–NE)	1·06 (0·63–1·80)
IC 1/2/3	18/27	4·1 (2·7–11·1)	27/57	8·5 (5·7–NE)	0·62 (0·34–1·13)
PD-L1* gene expression					
≤−0·307	12/25	9·5 (3·8–NE)	27/48	5·8 (4·1–10·1)	1·25 (0·63–2·48)
>−0·307	16/23	4·0 (2·7–8·5)	22/49	8·6 (5·6–NE)	0·46 (0·24–0·89)
CD8* gene expression					
≤2·008	16/26	6·8 (2·8–11·1)	26/47	6·8 (4·0–NE)	0·84 (0·45–1·57)
>2·008	12/22	4·3 (2·8–NE)	23/50	7·1 (5·6–NE)	0·71 (0·35–1·44)
CD8 IHC invasive margin*					
≤1·005	14/26	6·8 (3·8–NE)	30/57	8·2 (5·4–NE)	0·96 (0·51–1·82)
>1·005	19/26	4·1 (2·8–8·2)	24/55	8·6 (6·8–NE)	0·47 (0·25–0·85)
TILs					
≥5%	26/40	5·3 (4·0–9·5)	36/80	8·5 (6·2–NE)	0·62 (0·37–1·03)
<5%	11/25	NE (4·0–NE)	29/45	5·5 (3·9–9·6)	1·52 (0·76–3·04)
T_{eff} gene signature*					
≤0·0047	13/26	9·5 (2·8–NE)	24/47	8·2 (5·4–NE)	0·95 (0·48–1·87)
>0·0047	15/22	4·0 (2·8–11·1)	25/50	6·8 (4·4–NE)	0·60 (0·31–1·14)
Tumour mutational burden*†					
≤4·39	17/28	4·1 (3·0–NE)	34/63	8·2 (5·4–10·1)	0·83 (0·46–1·50)
>4·39	12/24	8·5 (4·0–NE)	26/46	5·9 (4·4–10·7)	1·16 (0·58–2·30)

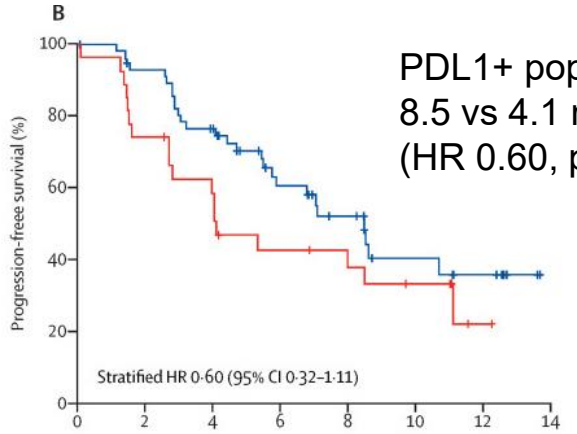


Emens et al, Lancet Oncology 2020



ITT population:
8.2 vs 6.8 mos
(HR 0.82, p = 0.33)

Number at risk (number censored)								
Trastuzumab emtansine plus atezolizumab	133 (0)	118 (2)	90 (6)	59 (21)	42 (31)	25 (42)	15 (50)	0 (65)
Trastuzumab emtansine plus placebo	69 (0)	54 (1)	42 (5)	31 (6)	23 (12)	15 (17)	7 (23)	0 (30)



PDL1+ population:
8.5 vs 4.1 mos
(HR 0.60, p = 0.099)

Number at risk (number censored)								
Trastuzumab emtansine plus atezolizumab	57 (0)	51 (2)	40 (4)	24 (13)	16 (18)	9 (22)	6 (24)	0 (30)
Trastuzumab emtansine plus placebo	27 (0)	20 (0)	15 (1)	10 (2)	8 (3)	6 (4)	4 (8)	0 (9)

TDM-1 + atezolizumab in breast cancer

	TDM-1 + atezolizumab (n=132)	TDM-1 + placebo (n=68)
Serious AEs (treatment related)	25 (19%)	2 (3%)
Pyrexia leading to hospitalization	7 (5.3%)	0
AE leading to treatment discontinuation	34 (26%)	10 (15%)
Death (disease related)	12 (9%)	8 (12%)
Death (treatment related)	1 – HLH	0

Emens et al, Lancet Oncology 2020

Clinical experience of ADCs + IO: EV + pembrolizumab in urothelial cancer

EV-302/KEYNOTE-A39 (NCT04223856)

Patient population
- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

N=886, R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Dual primary endpoints:
- PFS by BICR
- OS

Select secondary endpoints:
- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

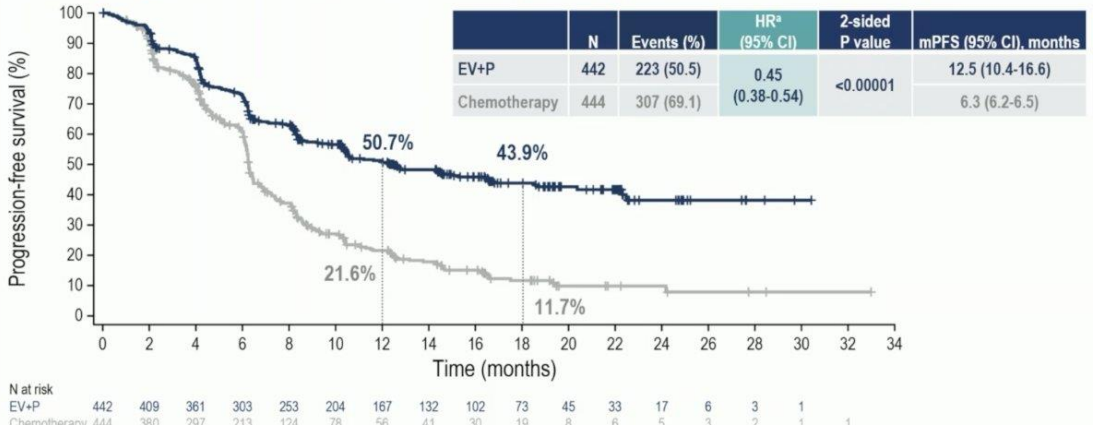
Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P



	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)

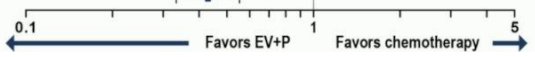
N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1

Subgroup Analysis of PFS per BICR

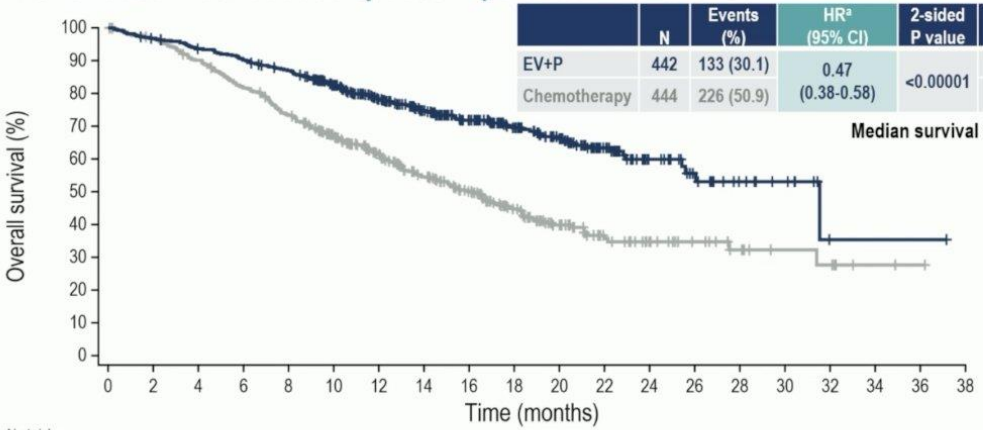
PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



Overall Survival

Risk of death was reduced by 53% in patients who received EV+P



	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months

N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Powles et al, Presented at ESMO 2023

EV + pembrolizumab in urothelial cancer

	EV+P (N=77)	EV Mono (N=74)
Patients on treatment, n (%)	25 (32.5)	8 (10.8)
Patients off treatment, n (%)	51 (66.2)	65 (87.8)
Reason for treatment discontinuation, n (%)		
Progressive disease	33 (42.9)	40 (54.1)
Adverse event	12 (15.6)	18 (24.3)
Patient decision	4 (5.2)	3 (4.1)
Physician decision	1 (1.3)	3 (4.1)
Other	1 (1.3)	1 (1.4)
Patients off study, n (%)	23 (29.9)	28 (37.8)
Reason for study discontinuation, n (%)		
Patient withdrawal of consent	2 (2.6)	1 (1.4)
Death	20 (26.0)	26 (35.1)
Other	1 (1.3)	1 (1.4)

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

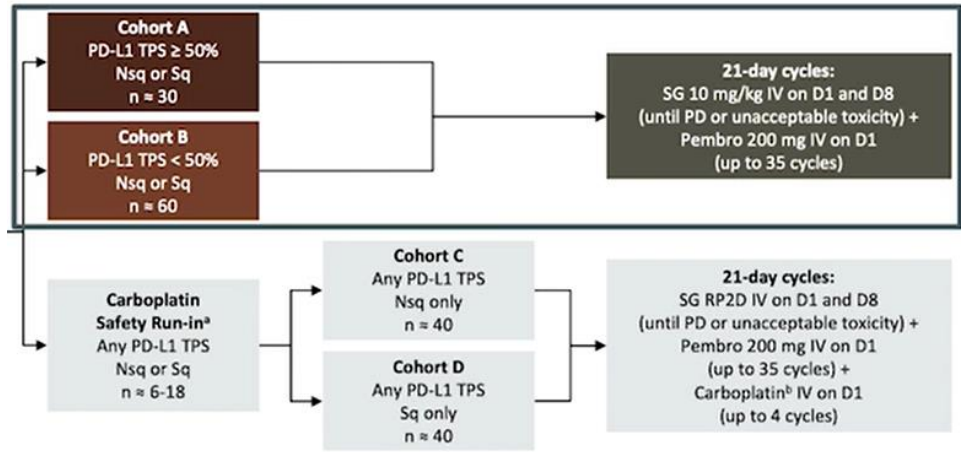
Serious TRAEs
- 18 (23.7%) EV+P
- 11 (15.1%) EV Mono

TRAEs leading to death (per investigator)
- 3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)
- 2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)

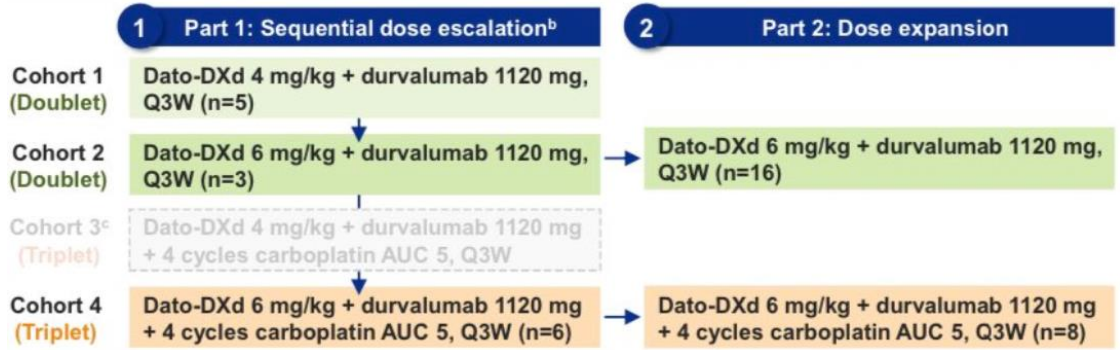
Rosenberg et al, presented at ESMO 2022

Clinical experience with ADC + IO in non-small cell lung cancer

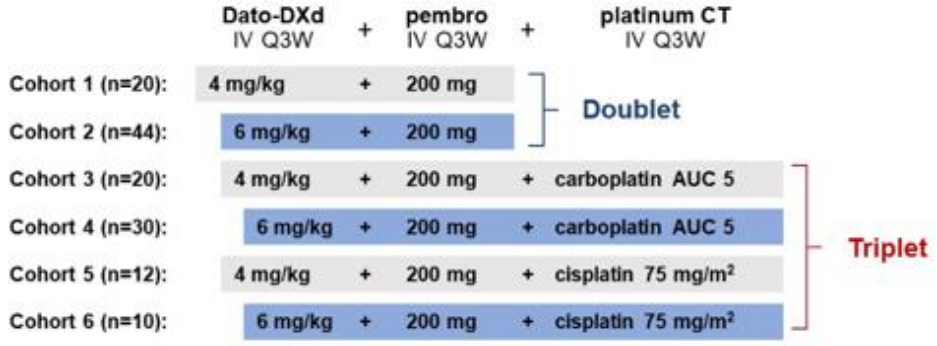
EVOKE-02: Sacituzumab govitecan + pembroliuzmab



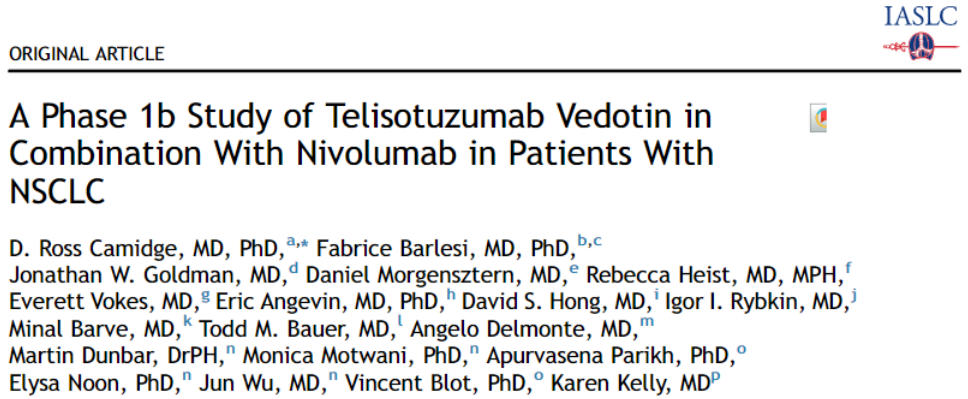
TROPION-Lung04: Dato-DXd + durvalumab +/- chemo



TROPION-Lung02: Dato-DXd + pembrolizumab +/- chemo



Telisotuzumab vedotin + nivolumab



ORIGINAL ARTICLE

IASLC

A Phase 1b Study of Telisotuzumab Vedotin in Combination With Nivolumab in Patients With NSCLC

D. Ross Camidge, MD, PhD,[a,*] Fabrice Barlesi, MD, PhD,[b,c] Jonathan W. Goldman, MD,[d] Daniel Morgensztern, MD,[e] Rebecca Heist, MD, MPH,[f] Everett Vokes, MD,[g] Eric Angevin, MD, PhD,[h] David S. Hong, MD,[i] Igor I. Rybkin, MD,[j] Minal Barve, MD,[k] Todd M. Bauer, MD,[l] Angelo Delmonte, MD,[m] Martin Dunbar, DrPH,[n] Monica Motwani, PhD,[n] Apurvasena Parikh, PhD,[o] Elysa Noon, PhD,[n] Jun Wu, MD,[n] Vincent Blot, PhD,[o] Karen Kelly, MD[p]

Cho et al, presented at WCLC 2023 abst OA05.04, Papadopoulos et al, presented at WCLC 2023, abst OA05.06, Goto et al, presented at ASCO 2023, Camidge et al, JTO CRR 2022

EVOKE-02: Sacituzumab govitecan + pembrolizumab in 1L

Efficacy by Investigator	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 (95% CI), %	**69 (49-85)**	**44 (26-62)**	**56 (42-69)**
PR, n (%) – conf + unconf Confirmed PR, n (%)	20 (69) 18 (62)	14 (44) 12 (38)	34 (56) 30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR (95% CI), months DOR rate at 6 months (95% CI), %	NR (5.6-NR) 88 (39-98)	NR (3.5-NR) 88 (39-98)	NR (7.9-NR) 87 (58-97)

Safety-evaluable patients, n (%)	Total SG + Pembro n = 63
Any-grade TEAEs / Related to study treatment	63 (100) / 57 (90)
Grade ≥ 3 TEAEs / Related to study treatment	44 (70) / 24 (38)
Serious TEAEs / Related to study treatment	34 (54) / 9 (14)
TEAEs leading to treatment discontinuation / SG dc / pembro dc	11 (18) / 9 (14) / 8 (13)
TEAEs leading to SG dose reduction	11 (18)
TEAEs leading to death / Related to study treatment	4 (6) / 1 (2)

Top toxicities: diarrhea, cytopenias

Cho et al, presented at WCLC 2023

TROPION-Lung04: Dato-DXd + durvalumab +/- chemotherapy

Antitumor Activity

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]

Safety Summary

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)	
Grade 2		1 (5.3)	1 (7.1)
Grade ≥3		1 (5.3)[b]	

Top toxicities: stomatitis, anemia

Papadopoulos et al, presented at WCLC 2023

TROPION-Lung01: Dato-DXd + pembrolizumab +/- chemotherapy

Antitumor Activity

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]	23 (38)	35 (49)	17 (50)	30 (57)
[95% CI]	[26-51]	[37-61]	[32-68]	[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	NE	NE	NE	NE
[95% CI]	[8.8-NE]	[5.8-NE]	[5.5-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]

Safety Summary

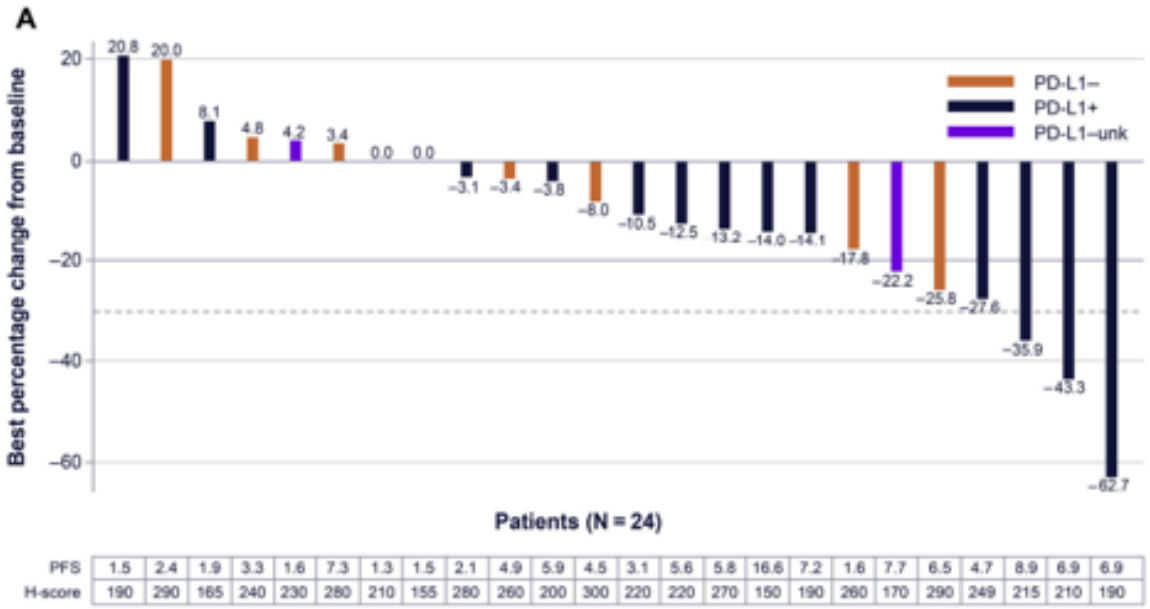
Event, n (%)	Doublet (n=64)	Triplet (n=72)
TEAEs[a]	62 (97)	72 (100)
Study treatment related[b]	58 (91)	72 (100)
Grade ≥3 TEAEs	34 (53)	55 (76)
Study treatment related[b]	20 (31)	42 (58)
Serious TEAEs	20 (31)	29 (40)
Study treatment related	6 (9)	16 (22)
TEAEs associated with:		
Death[f]	3 (5)	5 (7)
Dose reduction of any drug	14 (22)	14 (19)
Dose reduction of Dato-DXd	14 (22)	11 (15)
Discontinuation of any drug	18 (28)	27 (38)
Discontinuation of Dato-DXd[g]	15 (23)	20 (28)

Top toxicities: stomatitis, anemia, nausea, fatigue

Goto et al, presented at ASCO 2023

Telisotuzumab vedotin + nivolumab

Response	N = 27*
PR	2 (7.4%) (1 PD-L1+, 1 PD-L1-)
SD	19 (70.4%) (10 PD-L1+, 7 PD-L1-, 2 PD-L1 unk)
PD	4 (14.8%) (3 PD-L1+, 1 PD-L1 unk)



Camidge et al, JTO CRR 2022

Table 2. Treatment-Emergent Adverse Events by Preferred Term Occurring in Greater Than or Equal to 15% (Any Grade), Greater Than or Equal to 5% (Grade ≥3), or One or More Patients (Serious) Treated With Teliso-V

	Teliso-V ≥1.6 mg/kg Plus Nivolumab Q2W (N = 37)					
	Regardless of Relationship to Teliso-V			Reasonable Possibility of Relationship to Teliso-V		
Adverse Event, n (%)	Any Grade	Grade ≥3	Serious	Any Grade	Grade ≥3	Serious
Any adverse event	36 (97)	23 (62)	15 (41)	29 (78)	12 (32)	6 (16)
Fatigue	17 (46)	2 (5)	0	10 (27)	2 (5)	0
Decreased appetite	11 (30)	1 (3)	0	6 (16)	0	0
Cough	10 (27)	0	0	0	0	0
Hypoalbuminemia	10 (27)	1 (3)	0	6 (16)	0	0
Nausea	8 (22)	0	0	5 (14)	0	0
Peripheral edema	8 (22)	0	0	5 (14)	0	0
Peripheral sensory neuropathy	8 (22)	0	0	7 (19)	0	0
Decreased weight	8 (22)	0	0	2 (5)	0	0
Constipation	6 (16)	0	0	0	0	0
Diarrhea	6 (16)	1 (3)	1 (3)	2 (5)	1 (3)	1 (3)
Dyspnea	6 (16)	0	0	1 (3)	0	0
Hypotension	6 (16)	1 (3)	1 (3)	3 (8)	1 (3)	1 (3)
Hypertension	4 (11)	2 (5)	0	0	0	0
Peripheral neuropathy	4 (11)	2 (5)	1 (3)	4 (11)	2 (5)	1 (3)
Malignant neoplasm progression	3 (8)	3 (8)	3 (8)	0	0	0
Peripheral sensorimotor neuropathy	3 (8)	2 (5)	1 (3)	3 (8)	2 (5)	1 (3)
Pulmonary embolism	3 (8)	3 (8)	2 (5)	0	0	0
Colitis	2 (5)	2 (5)	2 (5)	0	0	0
Immune-related adverse events						
Rash	5 (14)	0	0	1 (3)	0	0
Upper respiratory tract infection	3 (8)	0	0	0	0	0
Pruritus	2 (5)	0	0	2 (5)	0	0
Urinary tract infection	2 (5)	0	0	0	0	0
Bronchitis	1 (3)	1 (3)	1 (3)	0	0	0
Genital herpes simplex	1 (3)	0	0	1 (3)	0	0
Herpes simplex	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)
Hypothyroidism	1 (3)	0	0	0	0	0
Pneumonia	1 (3)	1 (3)	1 (3)	0	0	0
Rash maculopapular	1 (3)	0	0	0	0	0
Sepsis	1 (3)	1 (3)	1 (3)	0	0	0
Staphylococcal infection	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)
Staphylococcal skin infection	1 (3)	0	0	0	0	0
Viral infection	1 (3)	0	0	0	0	0

Notable toxicities: hypoalbuminemia, peripheral edema, neuropathy

*missing pts did not have post tumor baseline assessments

Overall efficacy summary of ADC + IO

Combination	n	% non-squam	Line	ORR (95% CI)	DCR (95% CI)
SG + pembro, PD-L1 ≥ 50%[a]	29	60	1	69% (51 – 83)	86% (68 – 96)
SG + pembro, PD-L1 < 50%[a]	32	61	1	44% (28 – 61)	78% (60 – 91)
SG + pembro, all PD-L1[a]	61	-	1	56% (43 – 68)	82% (70 – 91)
Dato-DXd + durva[b]	14	-	1	50% (27 – 73)	93% (66 – 99.8)
	19	73.7	All	47.4% (27 – 68)	-
Dato-DXd + durva + platinum CT[b]	13	-	1	76.9% (50 – 92)	92% (64 – 99.8)
	14	71.4	All	71.4% (45 – 88)	-
Dato-DXd + pembro[c]	34	-	1	50% (32 – 68)	91% (77 – 97)
	61	70	All	38% (26 – 51)	84% (72 – 91)
Dato-DXd + pembro + platinum CT[c]	53	-	1	57% (42 – 70)	91% (80 – 96)
	71	68	All	49% (37 – 61)	87% (78 – 93)
Teliso-V + nivolumab[d]	27	89	All	7.4% (1.3 – 23)	78% (59 – 89)
Platinum CT + pem + pembro (KN189)[e]	410	100	1	47.6% (43 – 53)	84.6% (81 – 88)
Pembro, PD-L1 ≥ 50% (KN024)[f]	154	81.2	1	44.8% (37 – 53)	-

a. Cho et al, presented at WCLC 2023 abst OA05.04. b. Papadopoulos et al, presented at WCLC 2023, abst OA05.06 c. Goto et al, presented at ASCO 2023, d. Camidge et al, JTO CRR 2022, e. Gandi et al NEJM 2018, f. Reck et al, NEJM 2016

Overall toxicity summary of ADC + IO

Combination	n	Line	Grade ≥ 3 TRAE	RED	DC	Tox Profile
SG + pembro[a]	61	1	38%	SG: 18%	Any: 18%	Diarrhea, counts
Dato-DXd + durva[b]	19	All	31.6%	-	Any: 21.1%	Stomatitis, counts, GI
Dato-DXd + durva + platinum CT[b]	14	All	57.1%	-	Any: 21.4%	Stomatitis, counts, GI
Dato-DXd + pembro[c]	64	All	31%	Any: 22%	Any: 28%	Stomatitis, counts, GI
Dato-DXd + pembro + platinum CT[c]	72	All	58%	Any: 19%	Any: 38%	Stomatitis, counts, GI
Teliso-V + nivolumab[d]	27	All	32%	-	TV: 33%	Fatigue, edema, neuropathy
Platinum CT + pem + pembro (KN189)[e]	410	1	TEAE: 67.2%	-	Any: 27.7%	GI, counts, fatigue
Pembro, PD-L1 ≥ 50% (KN024)[f]	154	1	26.6% 9.7% iRAE	-	7.1%	Diarrhea, fatigue, pyrexia

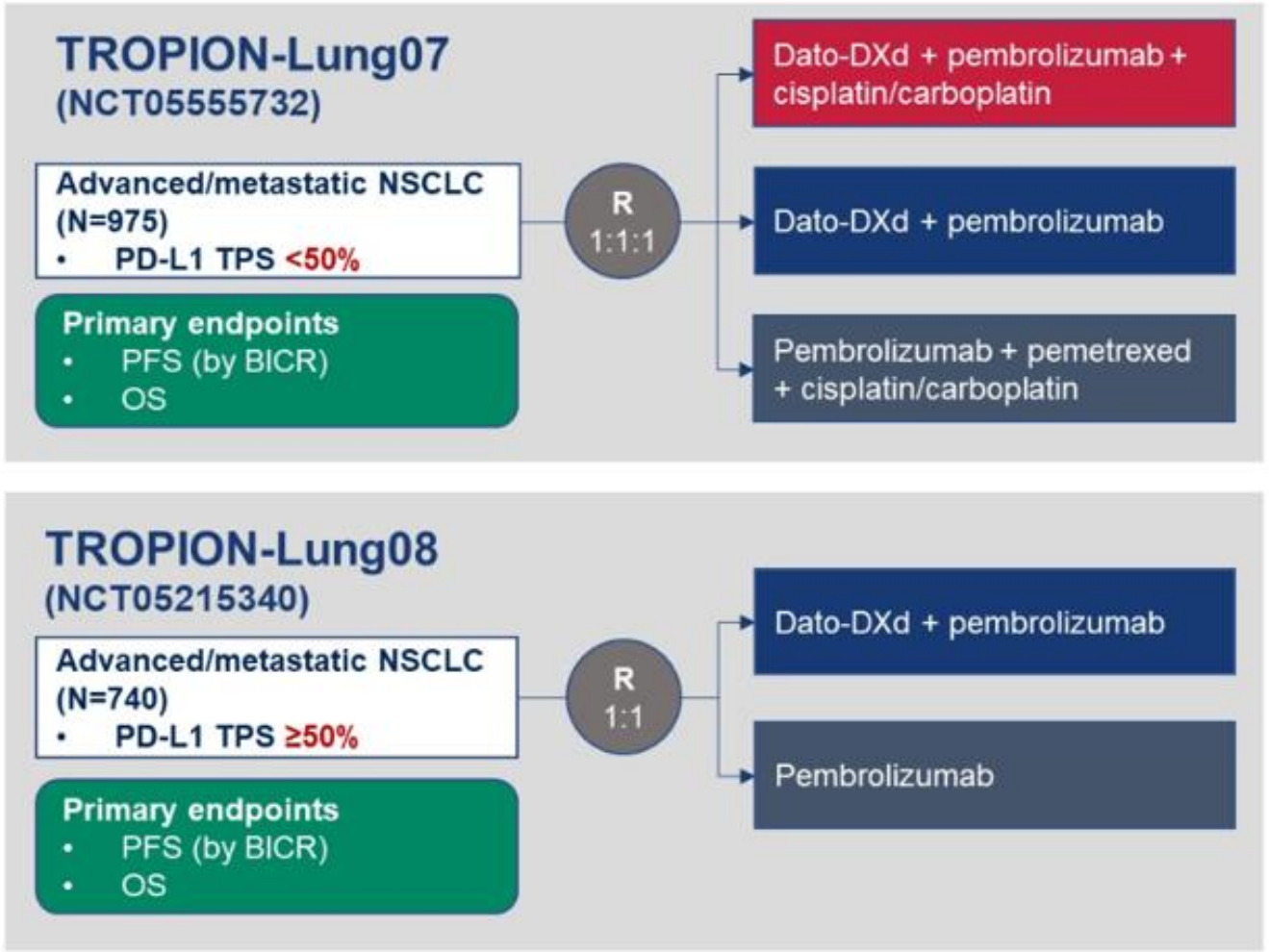
a. Cho et al, presented at WCLC 2023 abst OA05.04. b. Papadopoulos et al, presented at WCLC 2023, abst OA05.06 c. Goto et al, presented at ASCO 2023, d. Camidge et al, JTO CRR 2022, e. Gandi et al NEJM 2018, f. Reck et al, NEJM 2016

Selected ongoing clinical trials of ADC + IO in NSCLC

Agents	n	Phase	Indication	Endpoints	NCT #
Dato-DXd + pembro + CT vs Dato-DXd + pembro vs CT + pembro	975	III	1L adv NSCLC PD-L1 < 50%	PFS, OS	NCT05555732
Dato-DXd + pembro vs pembro	740	III	1L adv NSCLC PD-L1 ≥ 50%	PFS, OS	NCT05215340
SG + pembro vs pembro	614	III	1L adv NSCLC PD-L1 ≥ 50%	PFS, OS	NCT05609968
T-DXd + durva + CT; T-DXd + MEDI5752 (bispecific ab targeting PD-1 and CTLA-4) +/- CT	168	Ib	1L or pretreated adv non-sq NSCLC, HER2 over-expressed (not mut)	Safety	NCT04686305
T-DXd + durva	531	II	Pretreated adv NSCLC	ORR	NCT03334617
T-DXd + pembro	115	Ib	PD1 naïve HER2 over-expressed or mut NSCLC	Safety, ORR	NCT04042701

ADC + IO: Takeaway points

- **Integration into vs replacement of SOC**



Goto et al, presented at ASCO 2023

ADC + IO: Takeaway points

- **Tolerability**

Dato-DXd and pembro +/- chemotherapy

AESI, n (%)[a,b]	Doublet (n=64)		Triplet (n=72)	
	All grades	Grade ≥3	All grades	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

Goto et al, presented at ASCO 2023

ADC + IO: Takeaway points

- **Special populations – brain metastases**

T-DXd in pts with NSCLC and brain mets

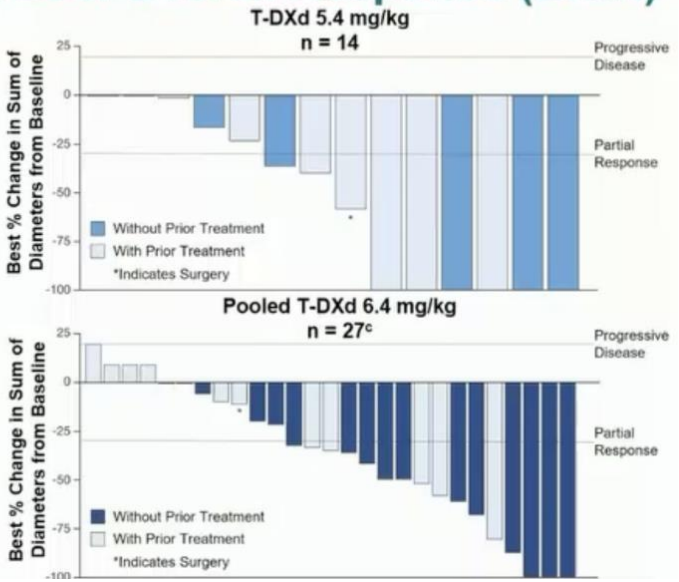
DESTINY-Lung01 and -02

IC Objective Response Rates & Best Overall Response (BICR)

Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



Phase II Atezo-Brain trial

TABLE 2. Efficacy Results

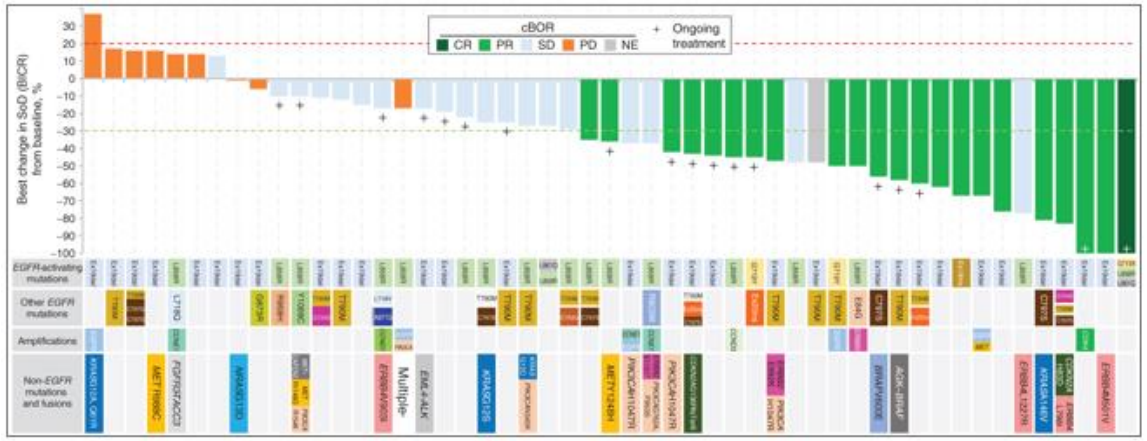
Result (N = 40)	Intracranial	Systemic
Best overall response, No. (%)		
CR	5 (12.5)	1 (2.5)
PR	12 (30.0)	17 (42.5)
SD	17 (42.5)	16 (40.0)
PD	5 (13.0)	4 (10.0)
NE	1 (2.5)	2 (5.0)
ORR, % (95% CrI)	42.7 (28.1 to 57.9)	45.0 (28.1 to 57.9)
Median DOR, months (95% CI)	14 (10 to NR)	11.9 (8.9 to NR)
12-week PFS rate, % (95% CrI)	62.2 (47.1 to 76.2)	
Median PFS, months (95% CI)	6.9 (4.7 to 11.9)	8.9 (6.7 to 13.8)

Planchard et al, presented at ESMO 2023; Nadal et al, JCO 2023

ADC + IO: Takeaway points

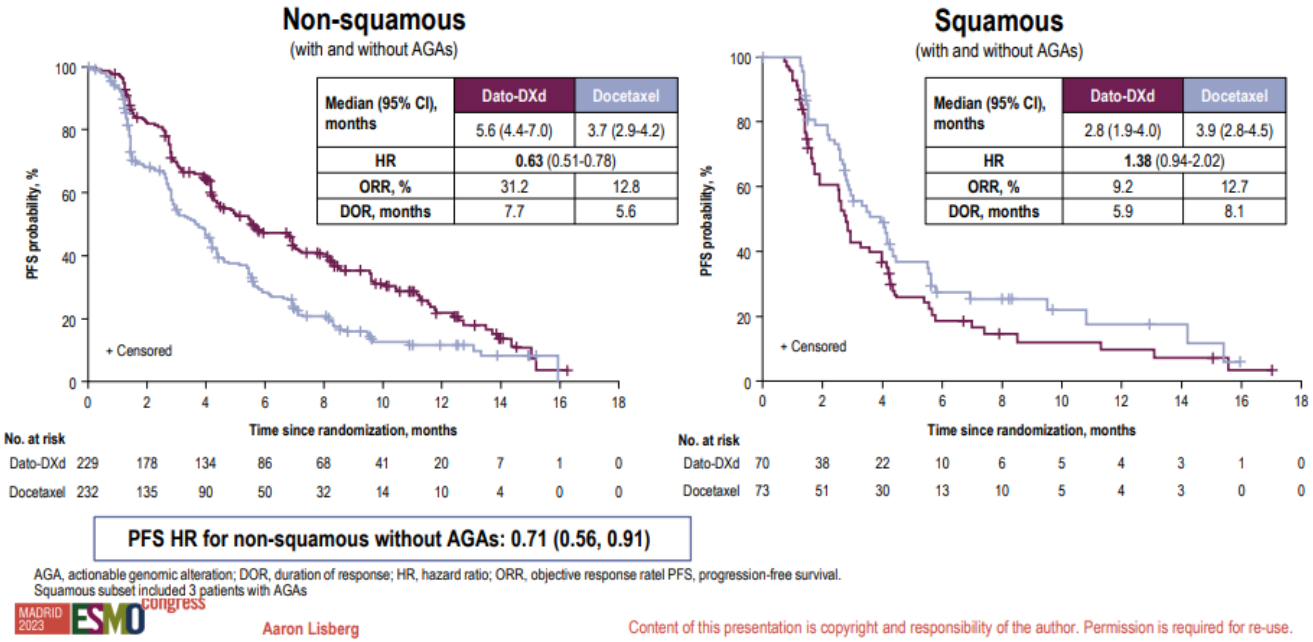
- **Patient selection**
  - Oncogene driven cancers
  - Identification of biomarkers

HER3-DXd in *EGFR*-mut NSCLC



TROPION-Lung01: Dato-DXd vs docetaxel

PFS by Histology



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

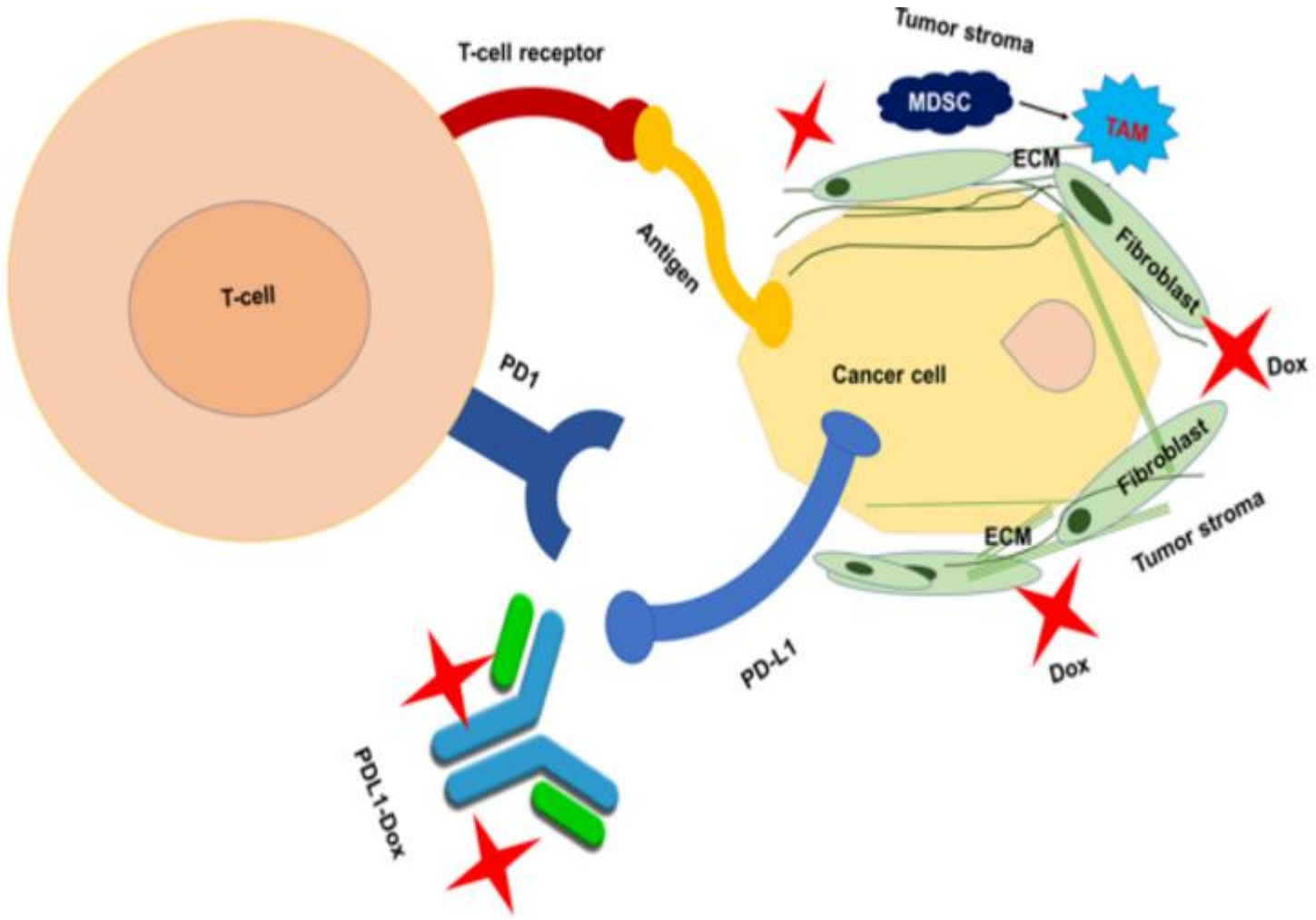
AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

MADRID 2023 ESMO congress

Aaron Lisberg

Janne et al, Cancer Discov 2022; Lisberg et al, presented at ESMO 2023

The next frontier of combination: PD-L1 targeting ADCs



Sau et al, Cancers 2019

Many agents in preclinical development; clinical trials underway

First Subject Dosed for Phase 1 Clinical Trial of Henlius' ADC Candidate HLX43

2023-11-24

Shanghai, China, November 24, 2023 – Shanghai Henlius Biotech, Inc. (2696.HK) announced that the first subject was dosed for a phase 1 clinical trial of HLX43, a novel PD-L1-targeting antibody-drug conjugate (ADC), for the treatment of advanced/metastatic solid tumours. HLX43 was developed by the company based on the collaboration with MediLink Therapeutics and is the first PD-L1-targeting ADC in China to enter a clinical trial.

Phase 1 study of SGN-PDL1V, a novel, investigational vedotin antibody–drug conjugate directed to PD-L1, in patients with advanced solid tumors (SGNPDL1V-001, trial in progress).

Authors: Amita Patnaik, Justin A Call, Anna Spreafico, Lisle Nabell, Mingjin Yan, Andres Forero-Torres, and Maura L. Gillison

PD-L1 targeting ADCs in clinical trials

	HLX43	SGN-PDL1V
Payload	Topoisomerase I inhibitor	MMAE
DAR	8	-
Schedule	Q3W	-
Recruiting	China	US, Belgium, Canada, France, Germany, Italy, Spain, UK
Disease	Solid tumors after standard treatment	Initial: NSCLC, HNSCC, Esophageal SCC, TNBC after standard treatment

Future directions and outstanding questions

- Is there any role for combination ADC + IO in the first- or later-line for NSCLC?
- Might PD-L1 targeting ADCs represent the best of all worlds for cancer treatment?
- How can we continue to refine our biomarkers to determine which patients can benefit from novel therapies without undue toxicity?