New Agents after Immunotherapy Resistance

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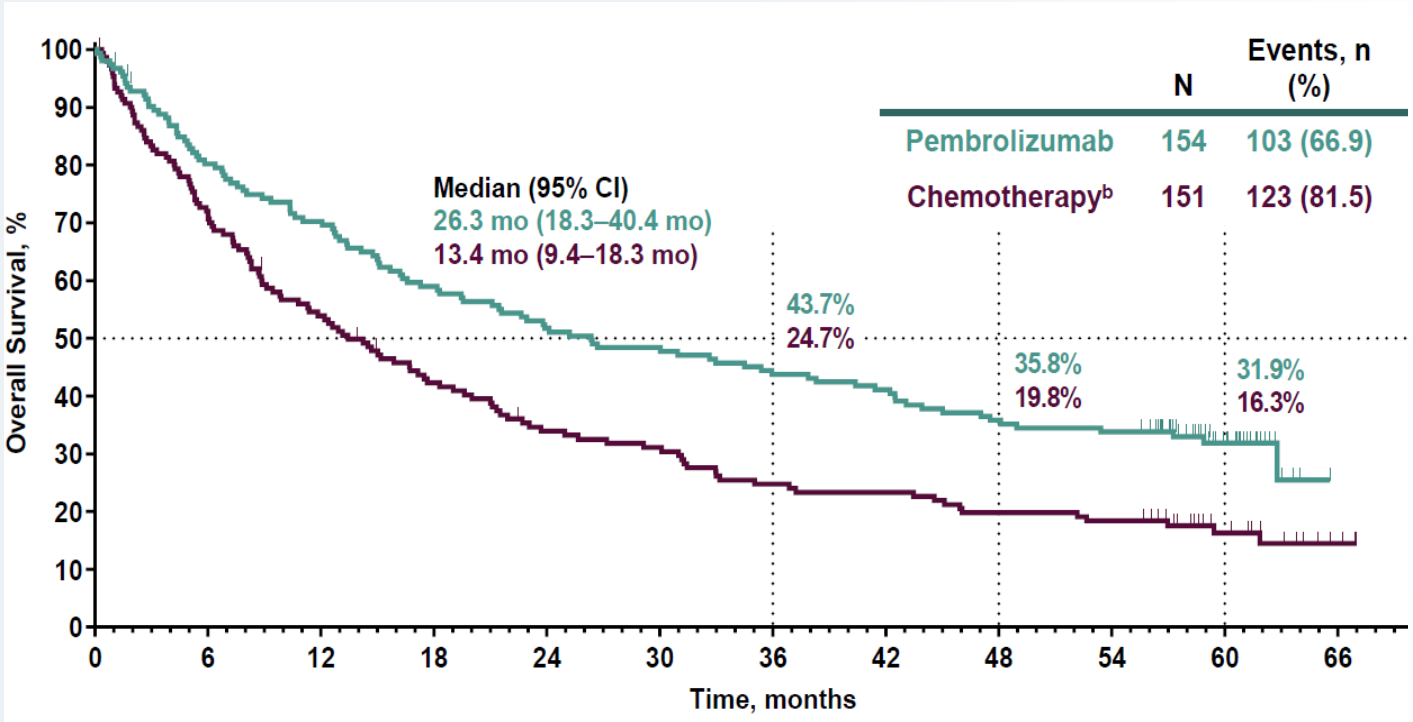
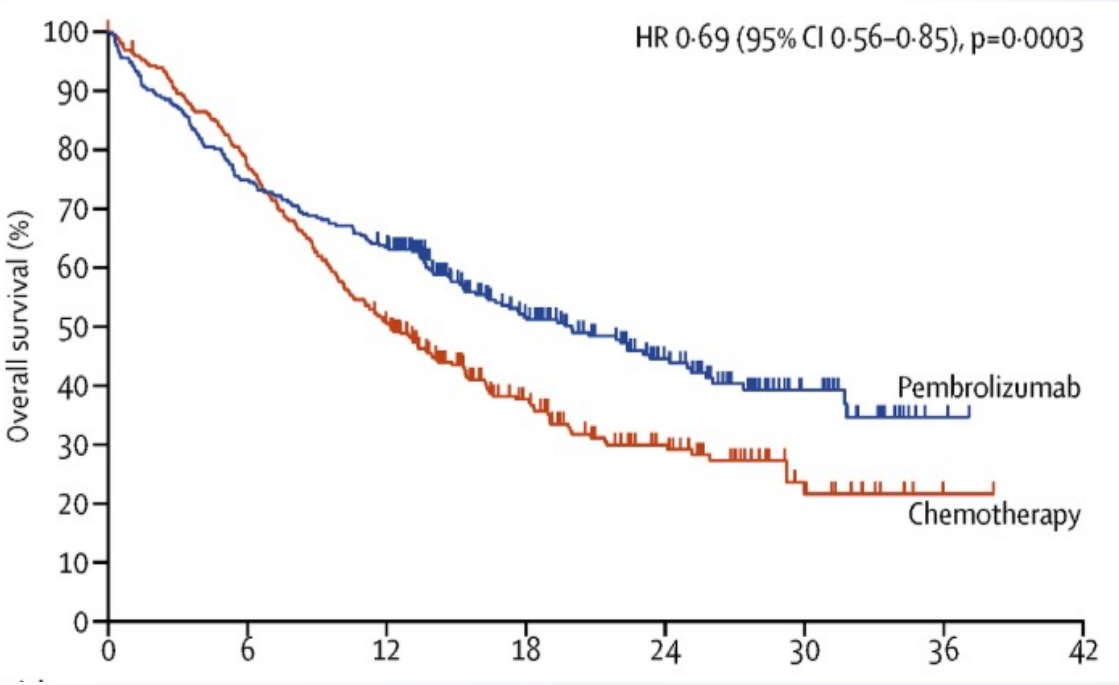
KEYNOTE-024, 042 and 189 (TPS>49): 5-Year OS Update

KN 024

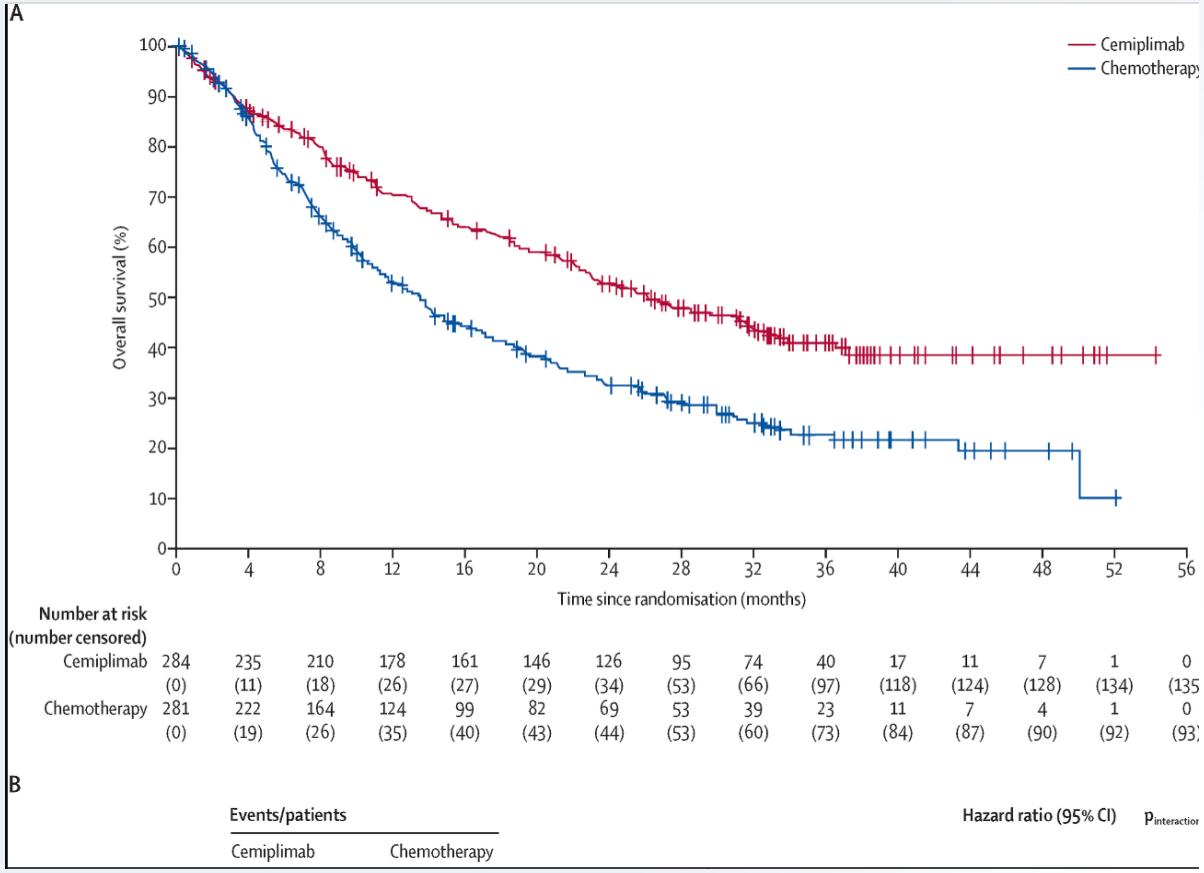


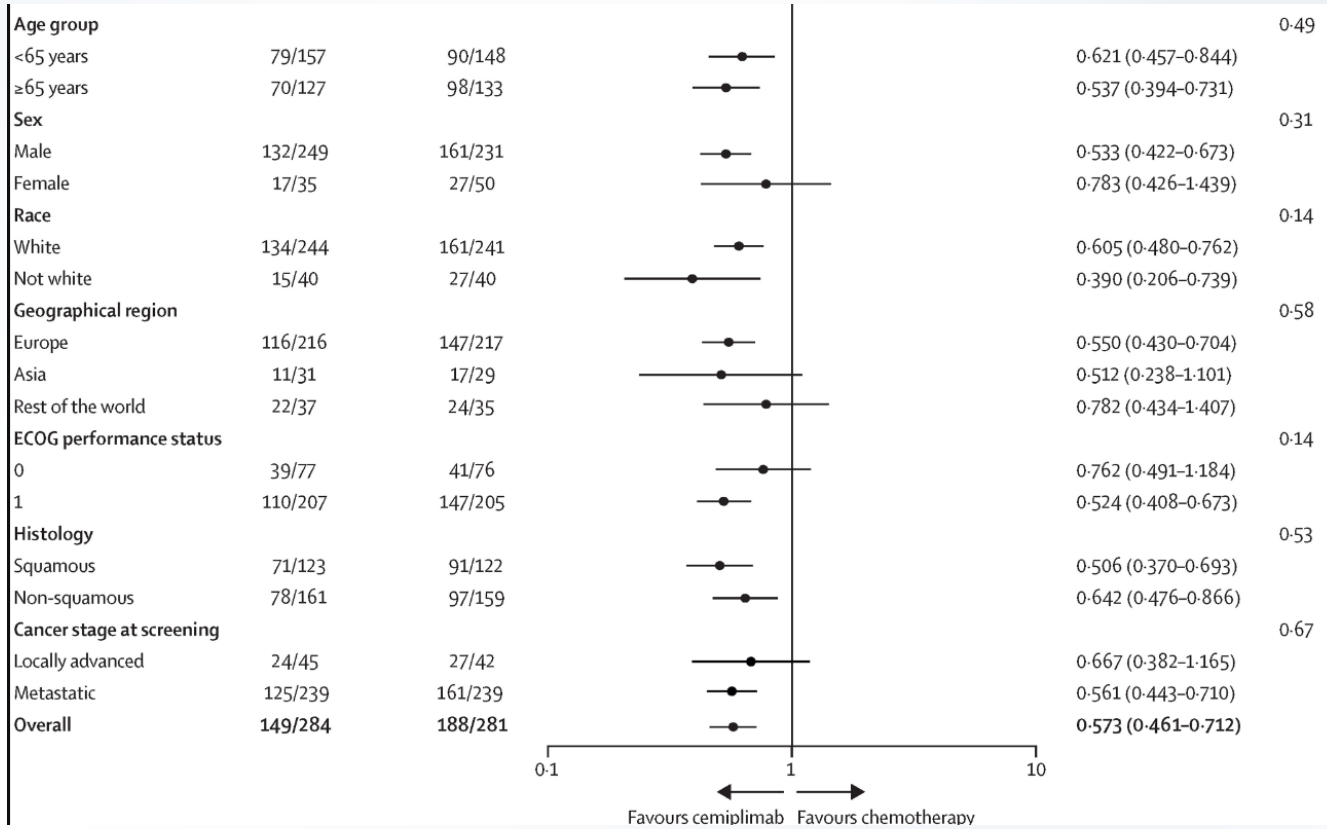
KN 042



Conclusion: Checkpoint inhibitors alone or with chemotherapy produce 5 year survival rates of about 30% in stage 4 adenoca of lung with TPS>49

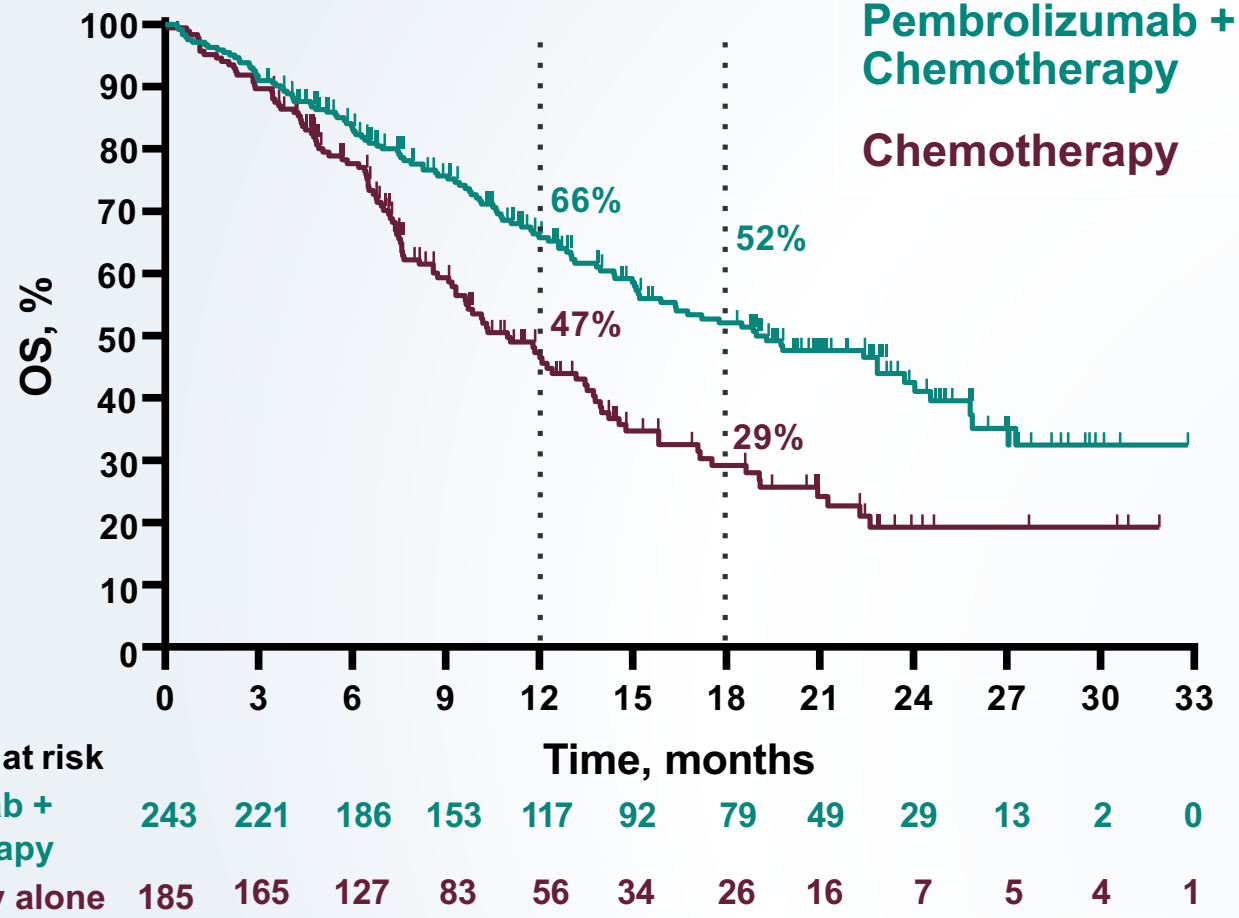
Cemiplimab EMPOWER –Lung 1:(TPS>49): 5-Year OS Update





For patients with high PDL1, multiple PD1 and PDL1 inhibitors produce 30% long term survival rates but 70% will relapse and require alternative systemic therapy. For patients receiving single agent IO, platininum doublet therapy would be standard at progression.

KN 189: Overall Survival
Patients Without Tumor PD-L1 Expression (TPS <1%)



	Events, n	HR (95% CI)
Pembrolizumab + Chemotherapy	112	0.56 (0.43–0.73)
Chemotherapy	110	

Median (95% CI) OS

19.0 (15.2–24.0) mo

11.0 (9.2–13.5) mo

Patients with low PDL1 may also experience long term survival with platinum doublet CT + IO but would not receive platinum doublet CT at PD unless late PD.

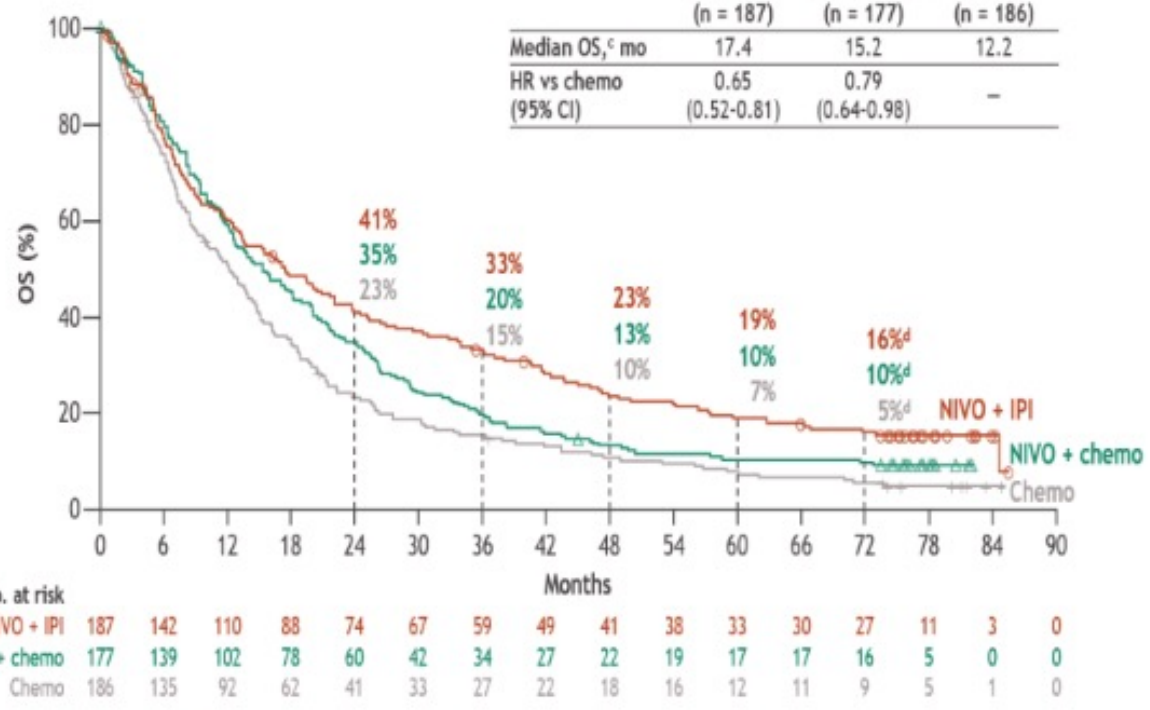
Borghaei, WCLC 2019

Do individual patients benefit selectively from distinct immunotherapies? Which patients need CTLA-4 blockade?

CM227, PD-L1 ≤ 1%

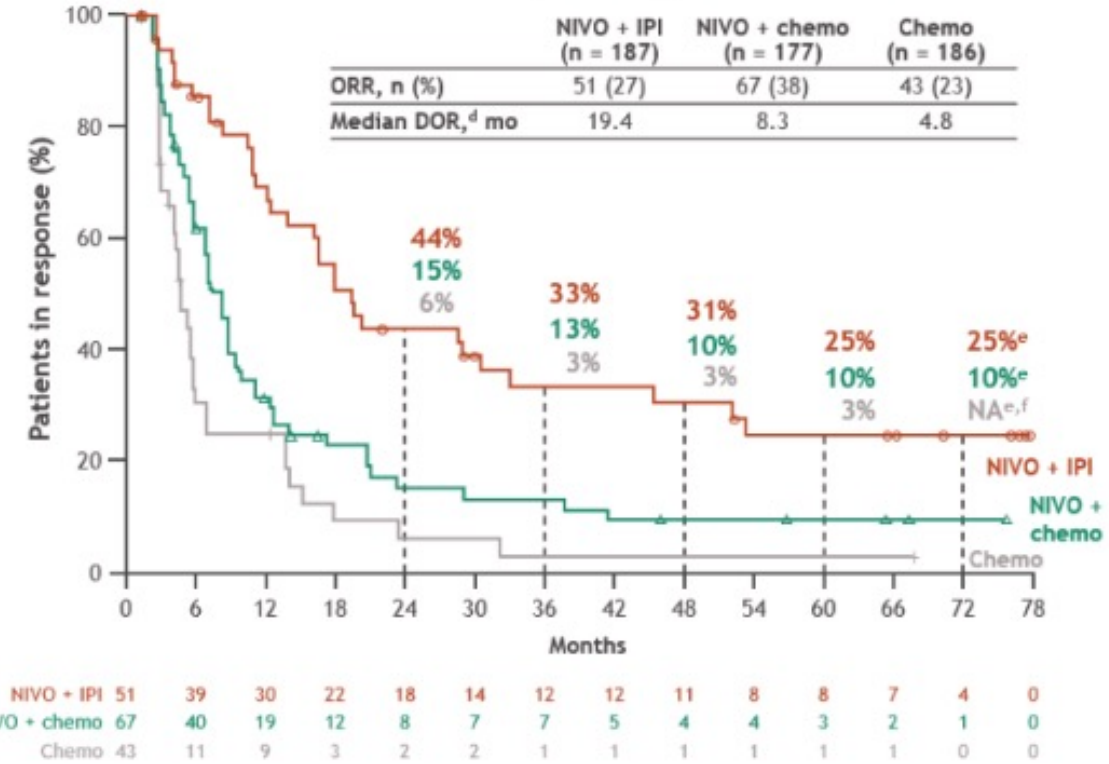
OS

	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52-0.81)	0.79 (0.64-0.98)	–



DoR

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
ORR, n (%)	51 (27)	67 (38)	43 (23)
Median DOR,[d] mo	19.4	8.3	4.8

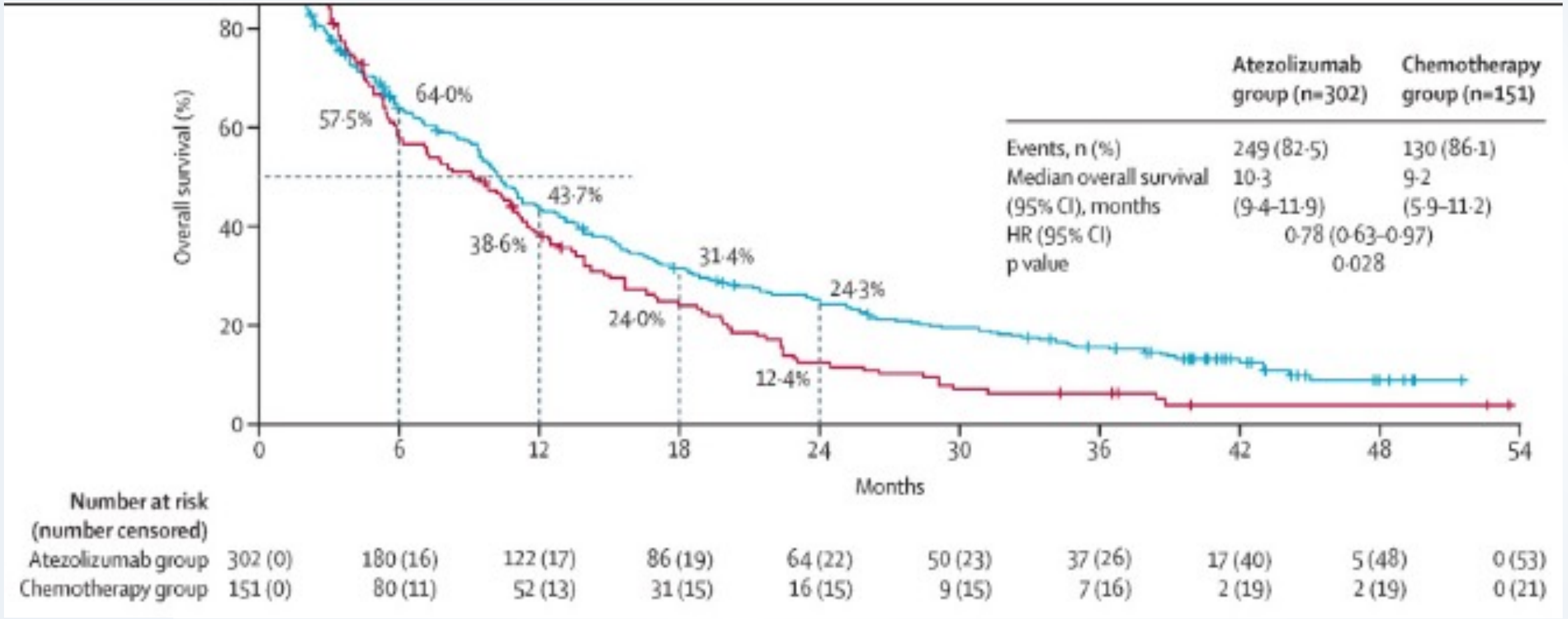


- In patients with SQ NSCLC and PD-L1 < 1% the 6 year OS rate with ipi/nivo vs chemo was 18% vs 4%

Platinum doublet CT may be given at PD in those treated with ipi/nivo

Ramalingam SS….Peters S et al, WCLC 2023

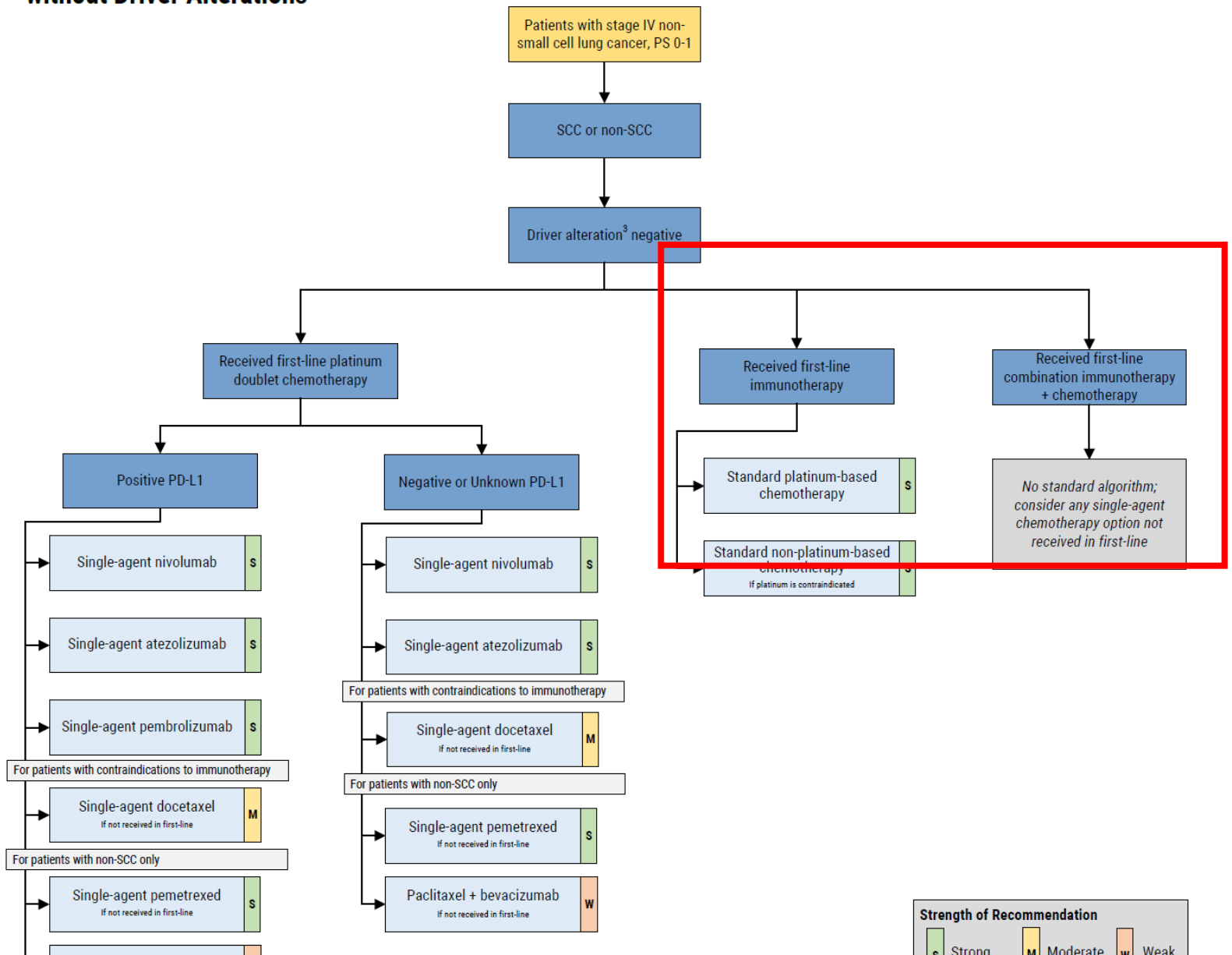
First-line atezolizumab versus single-agent CT in patients with NSCLC ineligible for treatment with a platinum regimen (IPSOS): a phase 3, randomised study



Lee sm et al: Lancet 402:451-463,2023

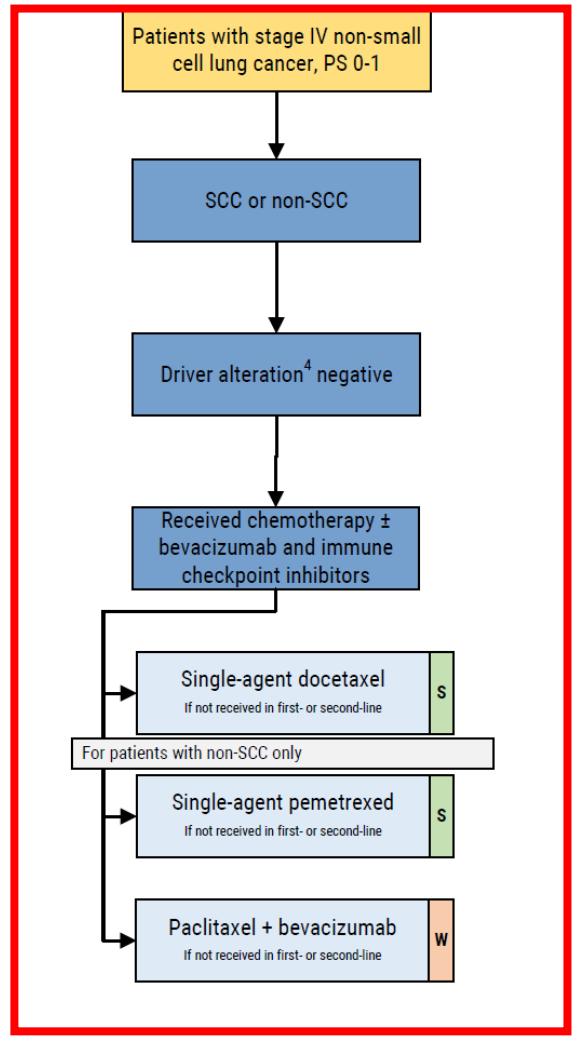
ASCO® Guidelines

Second-Line Treatment Options for Patients with Stage IV Non-Small Cell Lung Cancer without Driver Alterations



ASCO® Guidelines Third-Line

Third-Line Treatment Options for Patients with Stage IV Non-Small Cell Lung Cancer without Driver Alterations



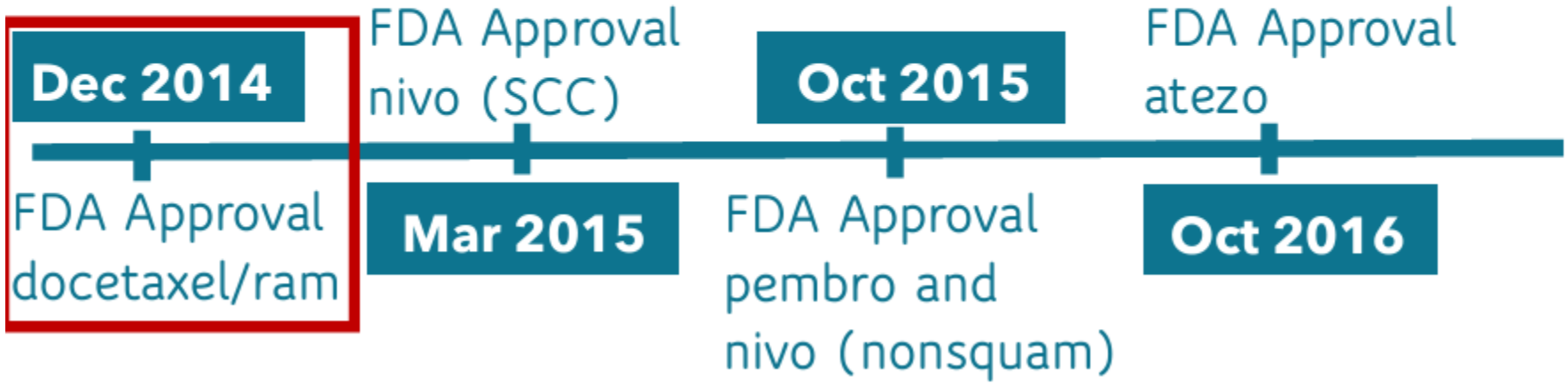
Strength of Recommendation

S Strong M Moderate W Weak

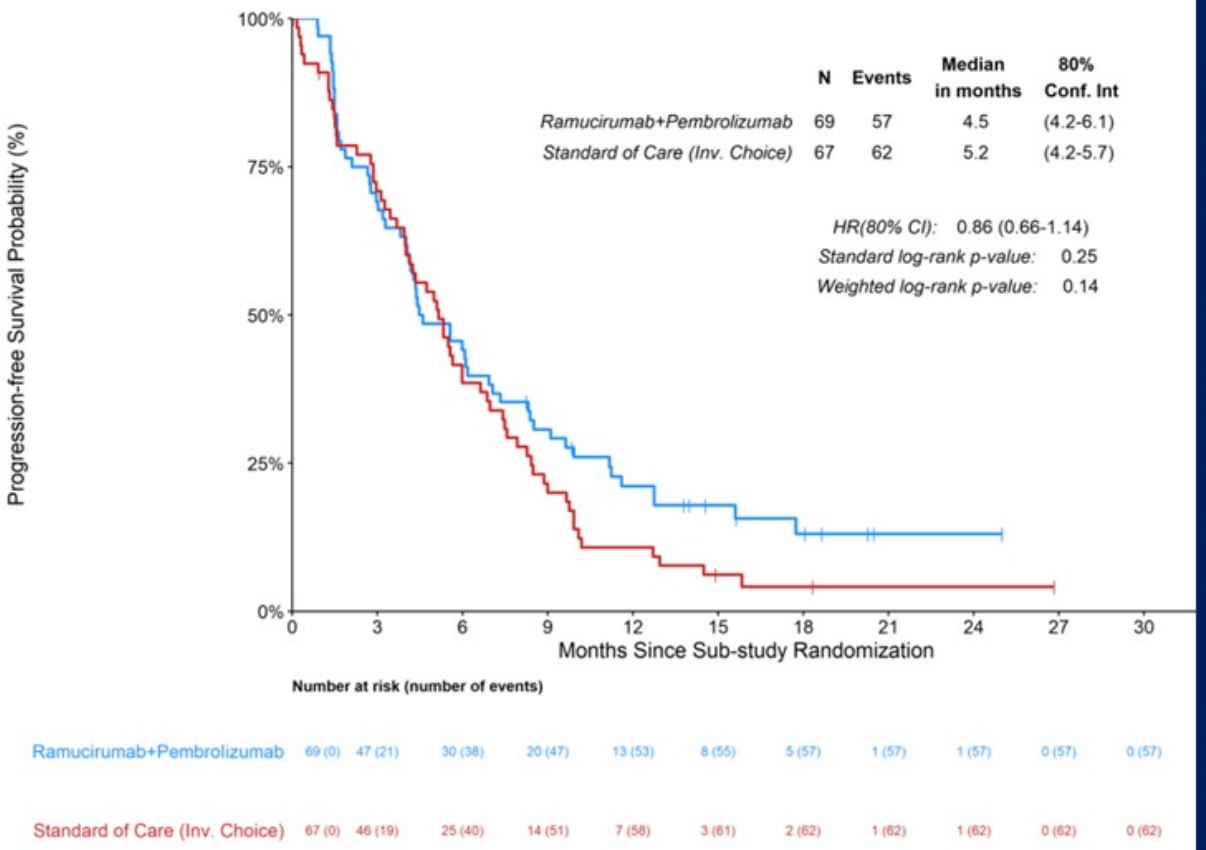
Notes. [4] Driver alterations including *EGFR*, *ALK*, *ROS-1*, *BRAF* V600E, *MET* exon 14, *NTRK*, *KRAS*, and *RET*

Abbreviations. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; PS, performance status

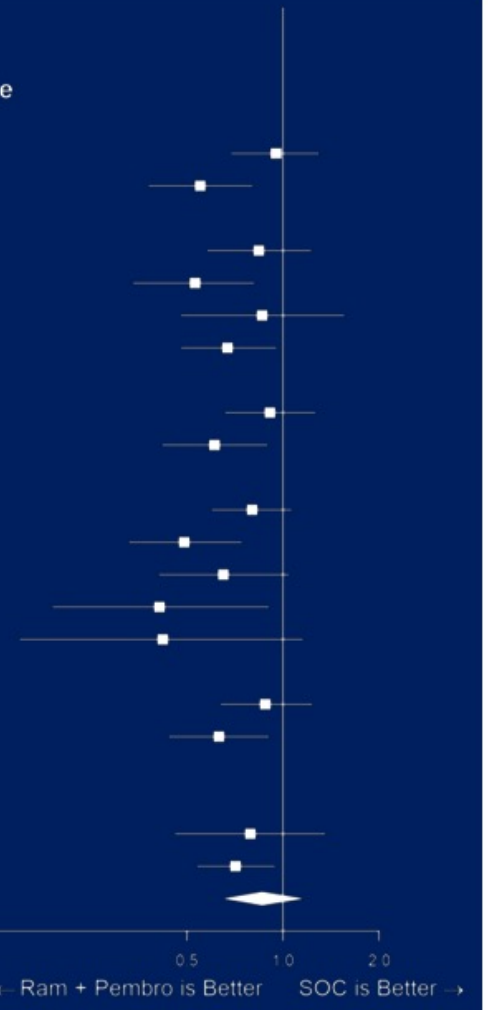
Second-line therapy for advanced NSCLC



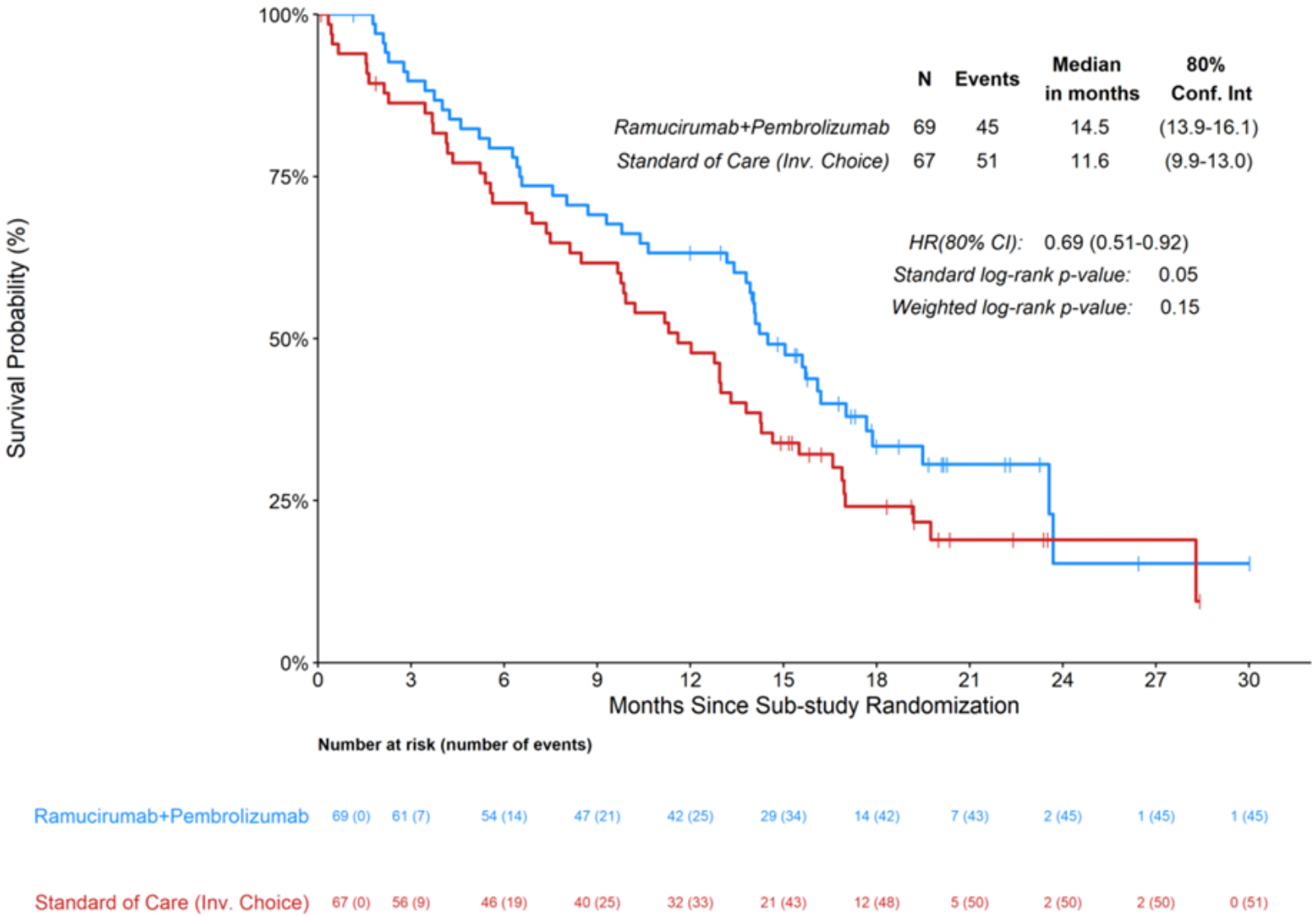
Progression free survival with subgroup analysis



	Ram+ Pembro Events/N	SOC Events/N	HR (80% CI)	P-value
HISTOLOGY				
Non-Squamous	34/40	34/39	0.95 (0.69,1.29)	0.41
Squamous/Mixed	23/29	28/28	0.55 (0.38,0.80)	0.02
PD-L1				
PD-L1 0	27/29	25/26	0.84 (0.58,1.22)	0.28
PD-L1 1-49	16/21	22/22	0.53 (0.34,0.81)	0.03
PD-L1 50+	8/12	12/16	0.86 (0.48,1.55)	0.37
PD-L1 1+	24/33	34/38	0.67 (0.48,0.95)	0.07
TMB				
TMB <10	29/32	36/38	0.91 (0.66,1.26)	0.36
TMB 10+	24/33	23/25	0.61 (0.42,0.89)	0.05
BIOMARKER				
TP53	39/48	43/48	0.80 (0.60,1.06)	0.16
CDKN2A	22/27	24/24	0.49 (0.33,0.74)	0.01
KRAS	16/21	15/16	0.65 (0.41,1.04)	0.12
STK11	5/7	10/10	0.41 (0.19,0.90)	0.07
KEAP1	2/3	10/10	0.42 (0.15,1.15)	0.14
PRIOR TREATMENT				
IO+CHEMO COMBO	26/32	40/42	0.88 (0.64,1.23)	0.31
CHEMO->IO	31/36	21/23	0.63 (0.44,0.90)	0.05
PERFORMANCE STATUS				
PS 0	21/23	8/9	0.79 (0.46,1.35)	0.28
PS 1	36/46	54/58	0.71 (0.54,0.94)	0.06
OVERALL	**57/69**	**62/67**	**0.86 (0.66,1.14)**	**0.25**



S1800A—Overall survival



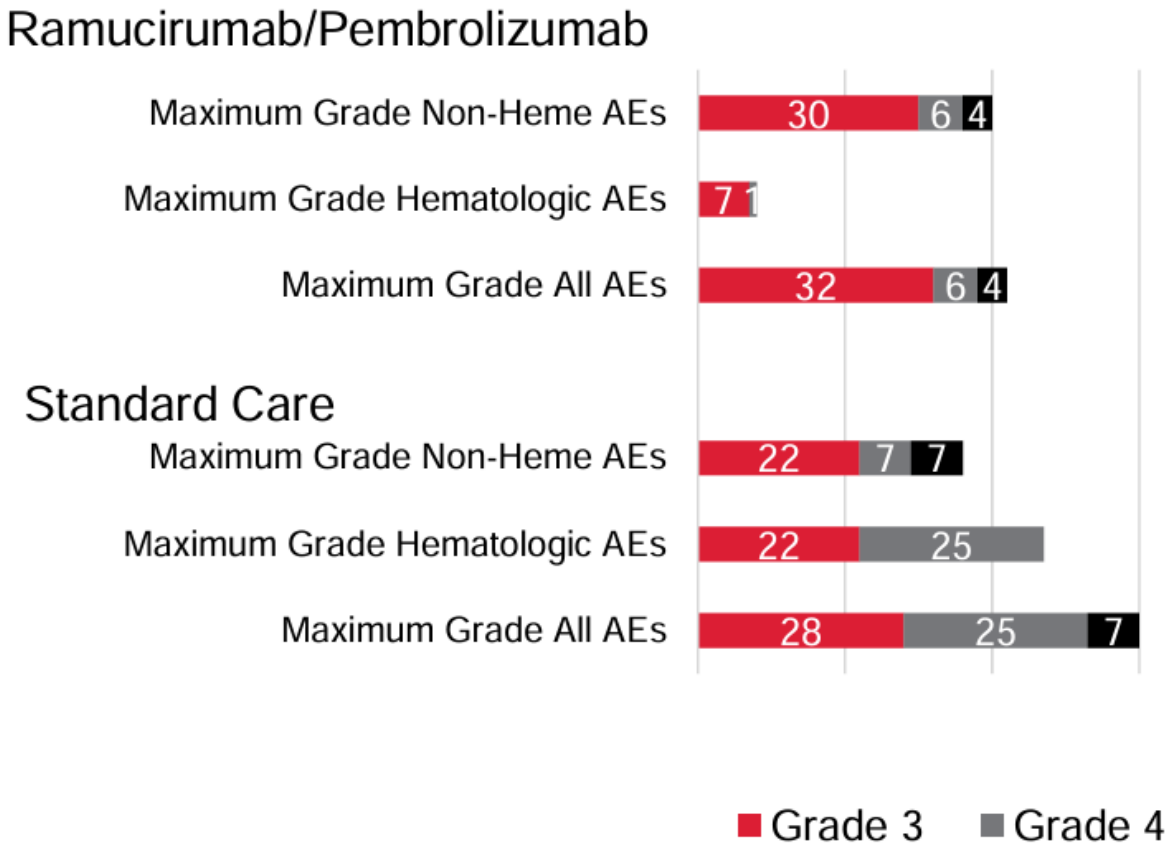
Median OS for RP 14.5 months v. SOC 11.6 months

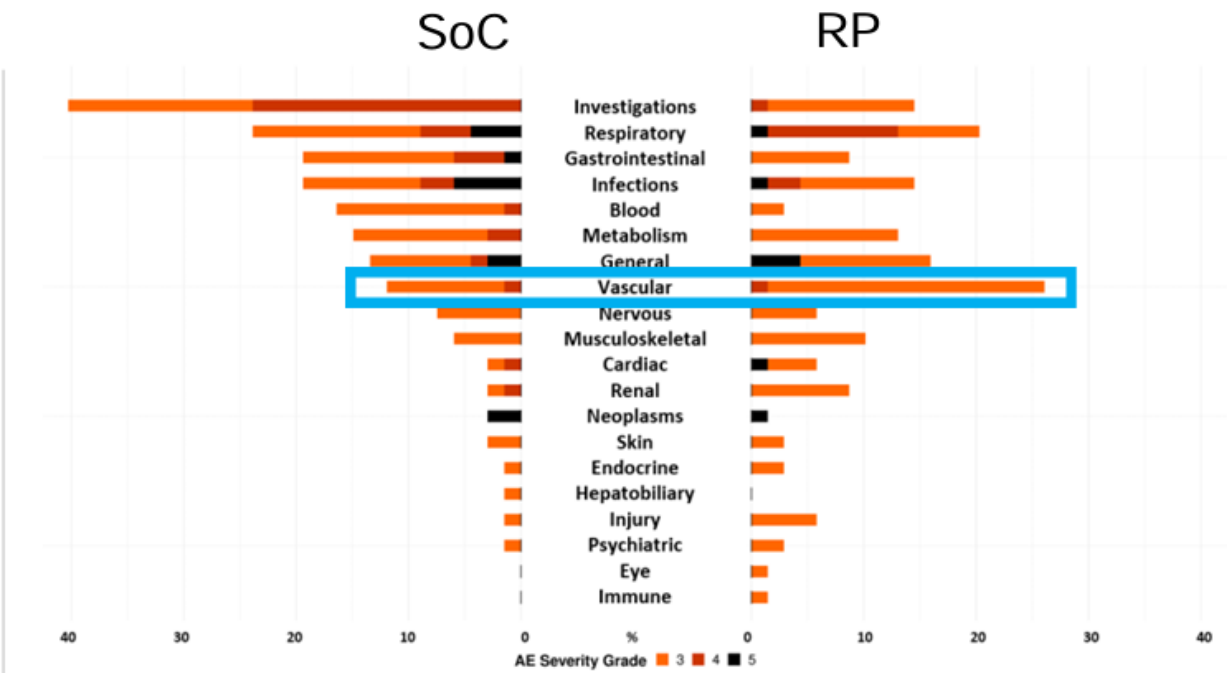
HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

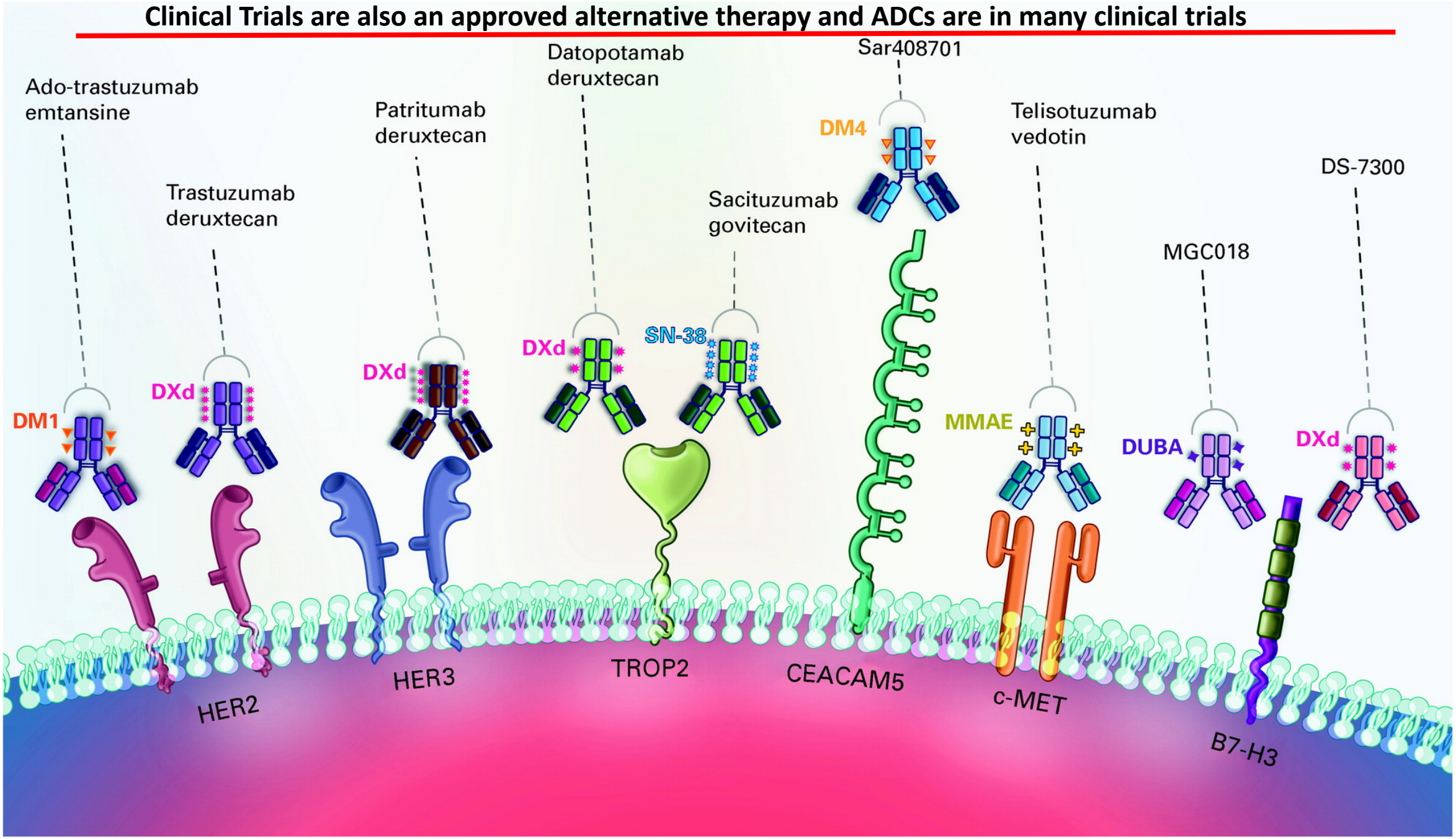
S1800A Safety summary—Percentage of patients with Grade 3-5 AEs





- Grade ≥3 TRAEs: 42% on RP; 60% on SOC
- Nine (31%) Grade 3–5 irAEs on RP

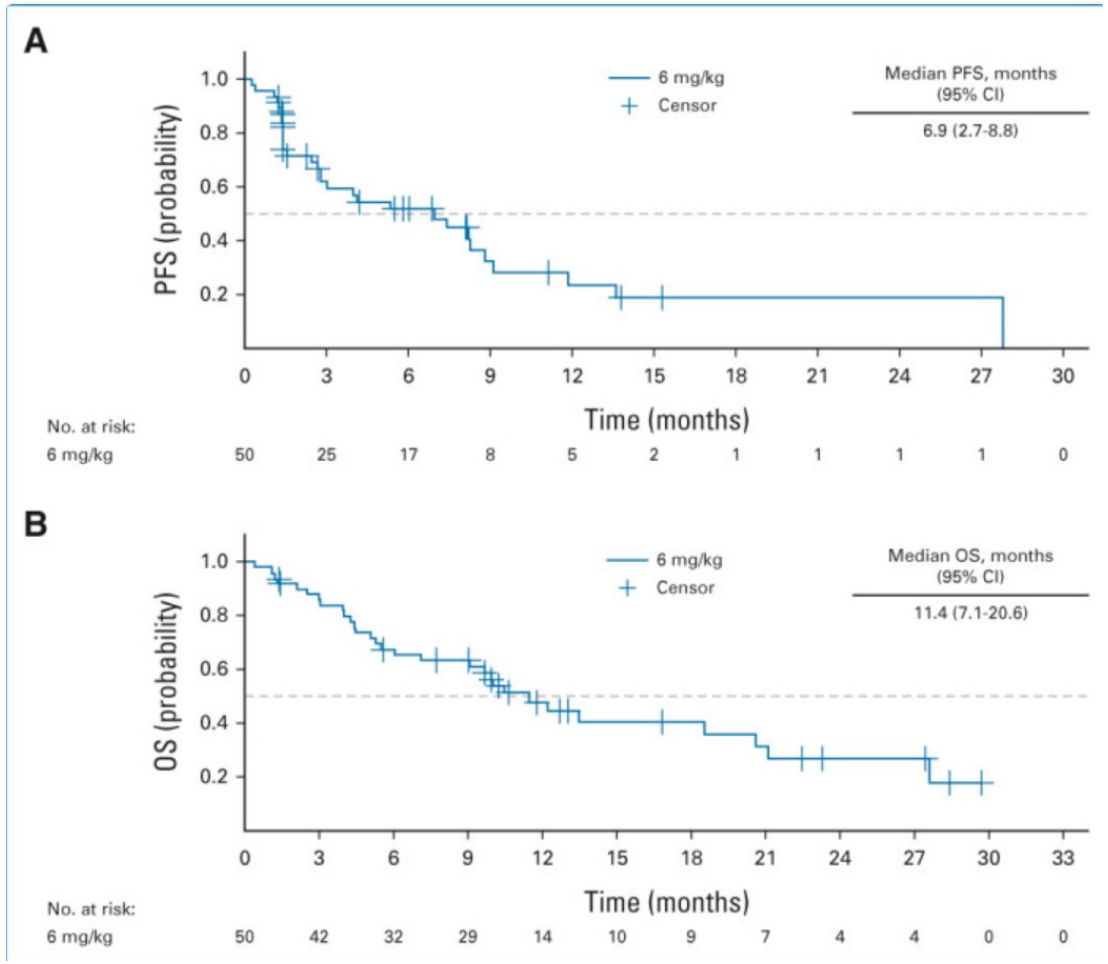
Clinical Trials are also an approved alternative therapy and ADCs are in many clinical trials



TROPION –pan Tumor 01

TABLE 2. Efficacy in the NSCLC Cohort

Response	Dato-DXd Dose 4 mg/kg (n = 50)	6 mg/kg (n = 50)	8 mg/kg (n = 80)
Confirmed ORR, No. (%)	11 (22)	13 (26)	19 (23.8)
95% CI	11.5 to 36.0	14.6 to 40.3	14.9 to 34.6
CR	0	0	1 (1.3)
PR	11 (22)	13 (26)	18 (22.5)
ORR confirmed and pending confirmation, No. (%)	15 (30)	16 (32)	25 (31.3)
PR pending confirmation	4 (8)	3 (6)	6 (7.5)
DCR, No. (%)	38 (76)	35 (70)	63 (78.8)
95% CI	61.8 to 86.9	55.4 to 82.1	68.2 to 87.1
SD, No. (%)	26 (52)	20 (40)	42 (52.5)
Non-CR/PD, No. (%)	1 (2)	2 (4)	2 (2.5)
PD, No. (%)	7 (14)	10 (20)	8 (10)
NE, No. (%)	5 (10)	5 (10)	9 (11.3)
TTR, months, median (range)	1.4 (1.2-8.2)	1.4 (1.2 to 5.7)	1.4 (1.2 to 13.7)
DOR, months, median (95% CI)	12.7 (2.8 to NE)	10.5 (5.6 to 26.5)	9.6 (5.8 to NE)
PFS, months, median (95% CI)	4.3 (2.9 to 6.9)	6.9 (2.7 to 8.8)	5.2 (4.1 to 7.1)
OS, months, median (95% CI)	12.9 (9.4 to NE)	11.4 (7.1 to 20.6)	10.5 (8.0 to 12.0)



Shimizu T et al JCO 41:4678-4687,2023

TROPION-Lung01 Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m^2 Q3W
(N=305)

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

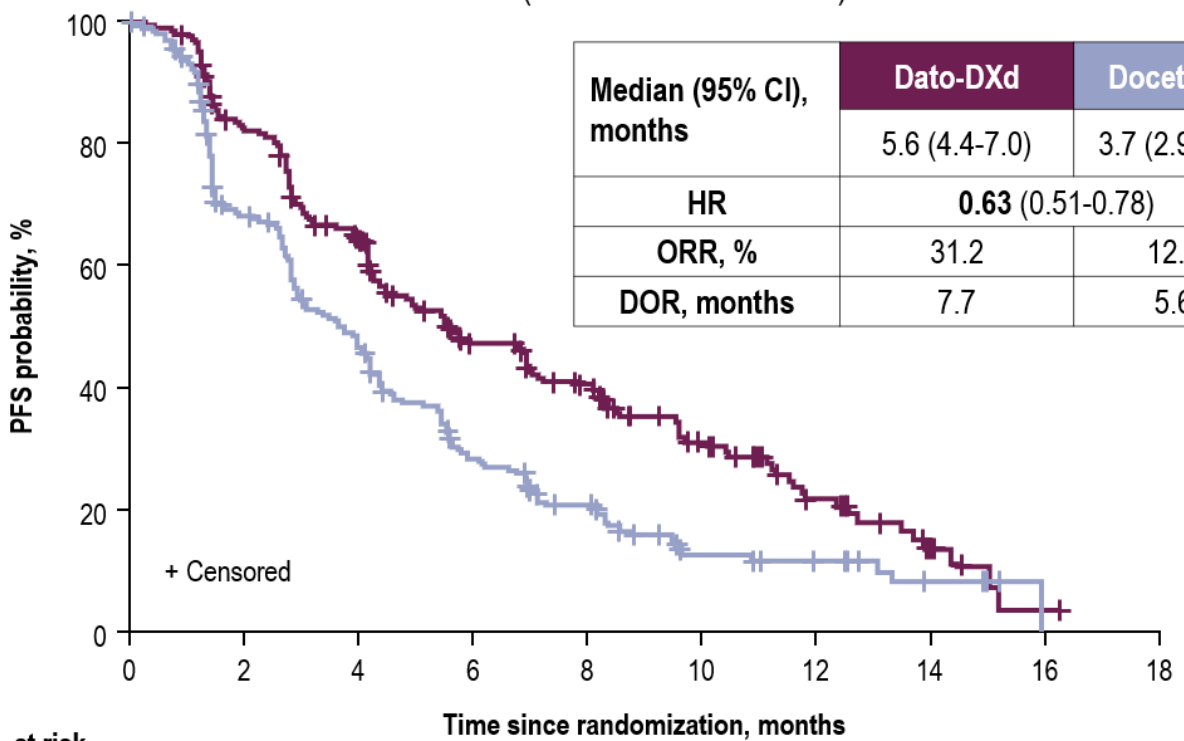
Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

PFS by Histology

Non-squamous

(with and without AGAs)

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

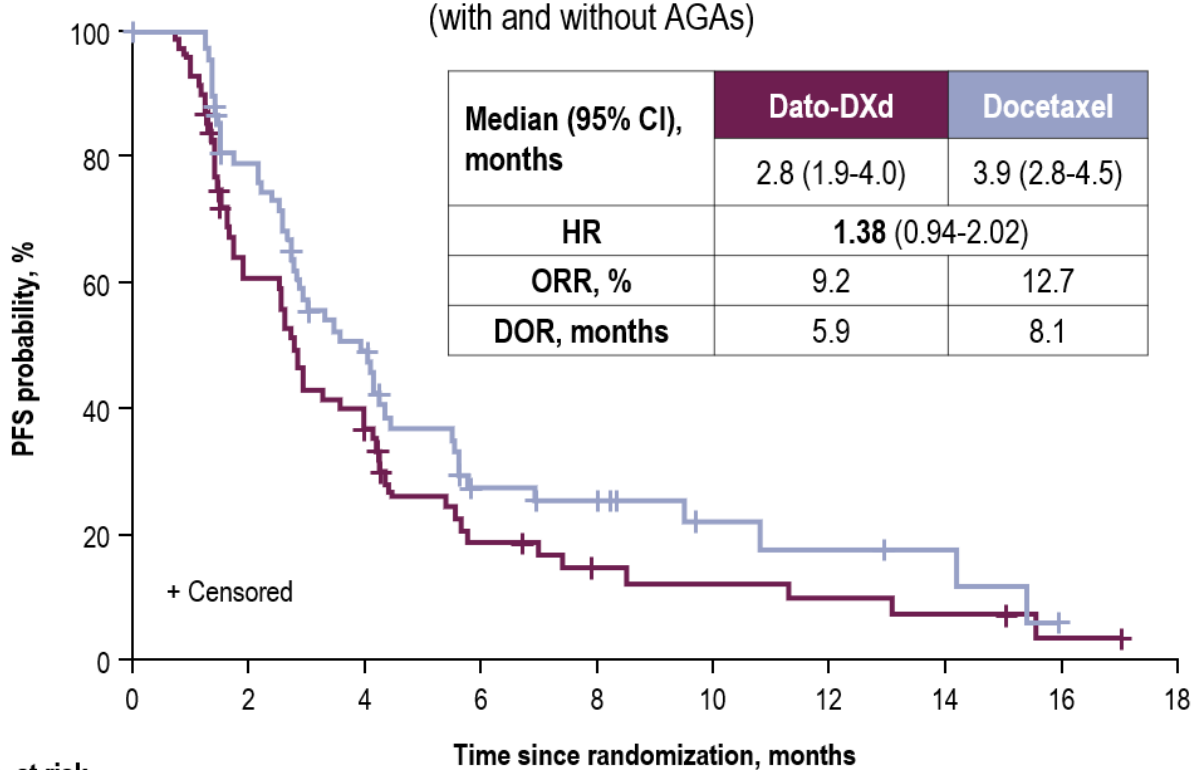


No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous

(with and without AGAs)

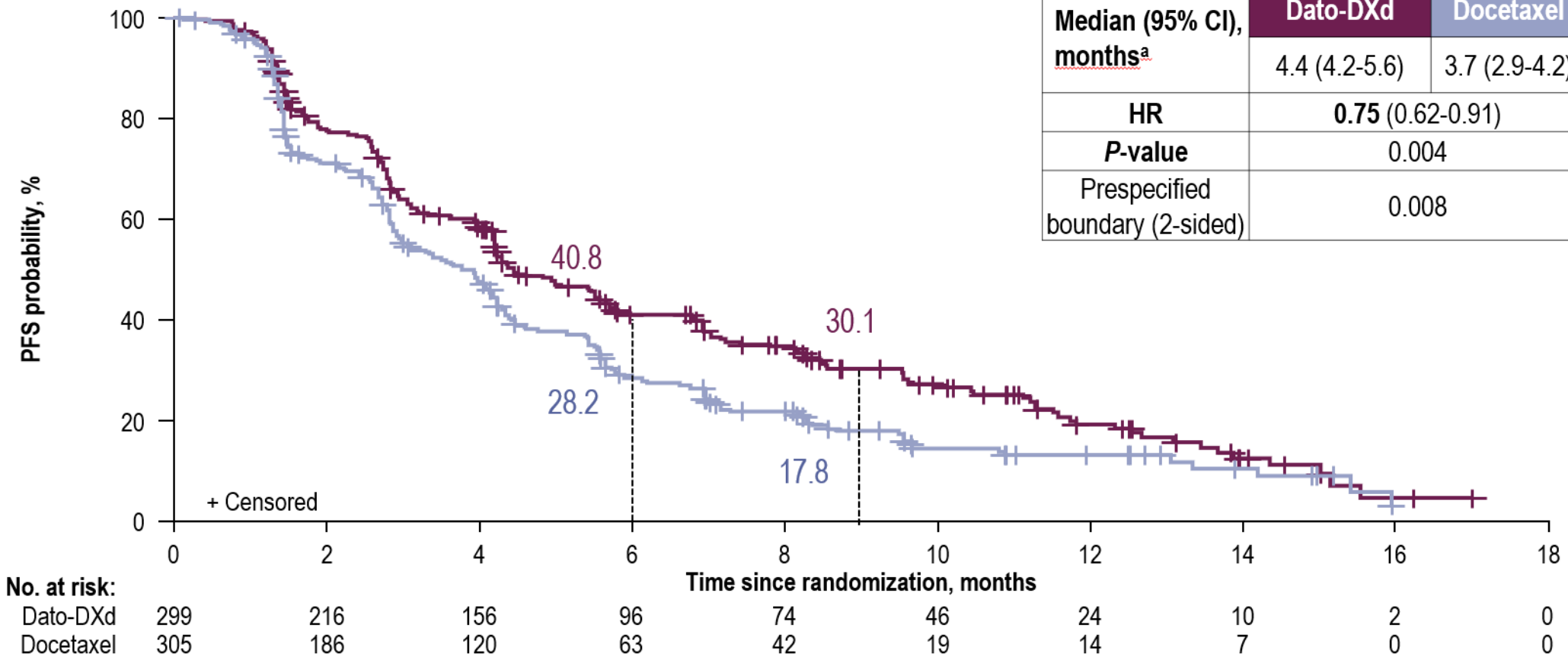
Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1



No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

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

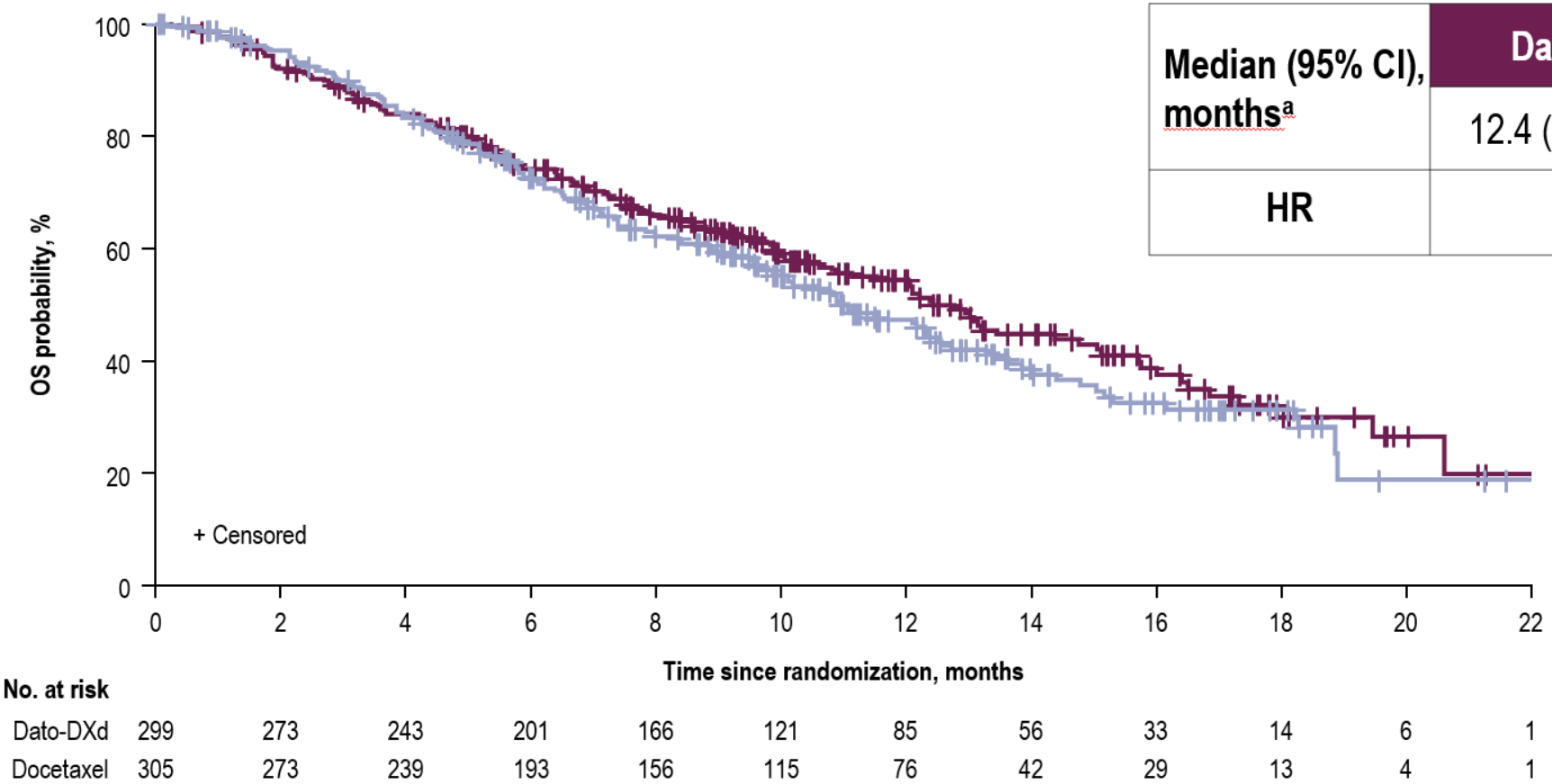
Progression-Free Survival: ITT



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)

Interim Overall Survival: ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

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

Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

TROPION-Lung04 Study Design

Phase 1b, multicenter, open-label, dose escalation/confirmation and expansion study

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)

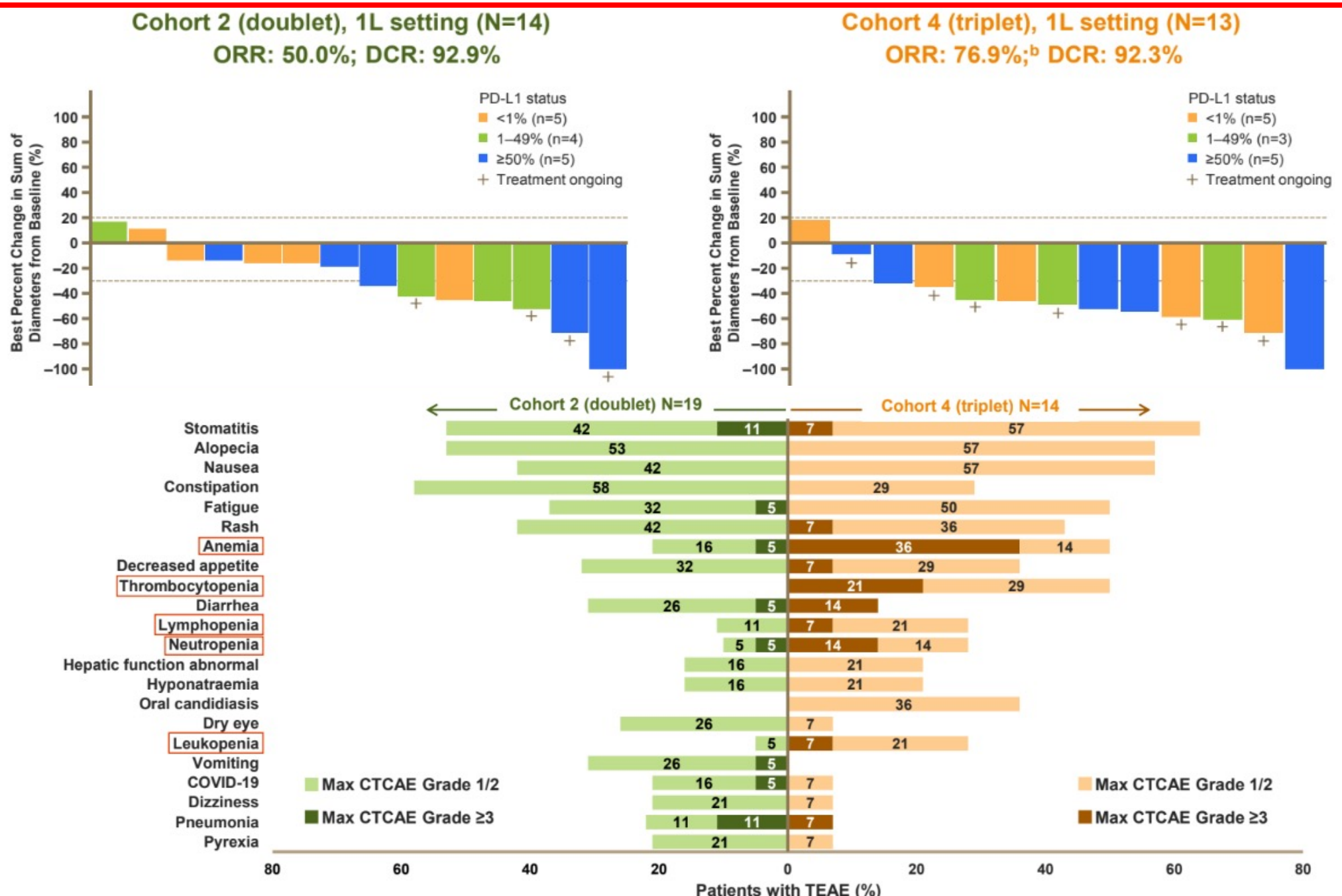
- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

Data cut-off: March 6 2023.

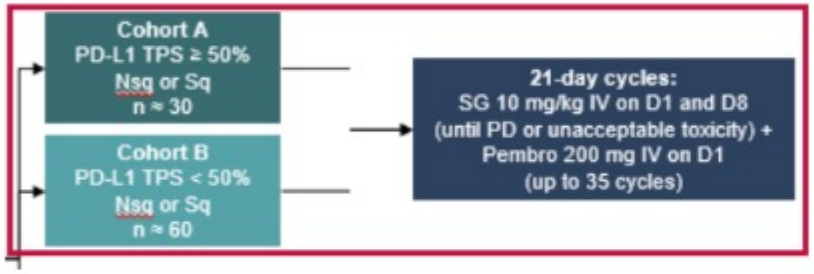
[a] Patients in Cohort 1 and one patient in Cohort 2 had received ≥1 platinum-based chemotherapy regimen and anti-PD-1/PD-L1 therapy as per an earlier version of the clinical study protocol. Subsequent patients were treatment-naïve or had ≤1 prior line of systemic chemotherapy without concomitant immune checkpoint inhibitors. [b] Dose escalation was guided by a mTPI-2 design and conducted sequentially from Cohort 1 to 2 (Dato-DXd 4 mg/kg to 6 mg/kg) and Cohort 2 to 4 (doublet to triplet combination). [c] Cohort 3 was skipped as there were sufficient data available from the Dato-DXd development program to conclude that 4 mg/kg Dato-DXd in combination with immunotherapy and carboplatin has an acceptable safety profile.

AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; mTPI-2, modified toxicity probability interval-2; Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Dato-Dxd in 1L NSCLC



EVOKE-02: An Open-Label, Multicohort Phase 2 Study, 1st Line

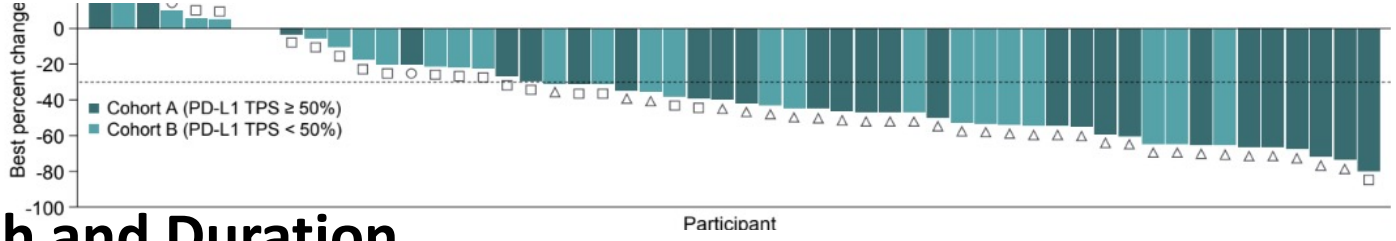


Efficacy by Investigator Assessment

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)

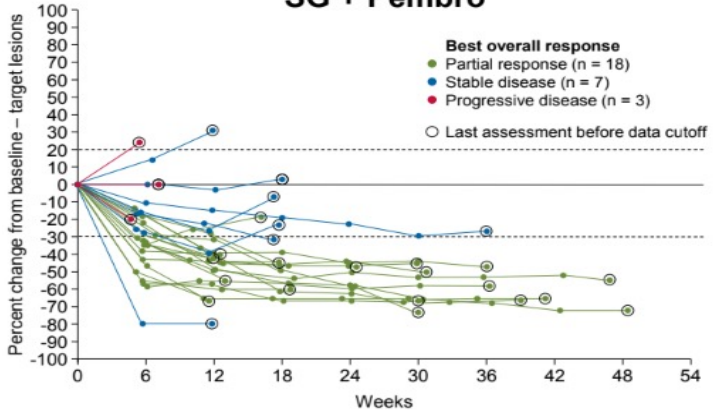
KEYNOTE 189: ORR: 62.1% (TPS≥50%), 50% (TPS 1-49%), 48.3% all comers

Waterfall Plot of Response

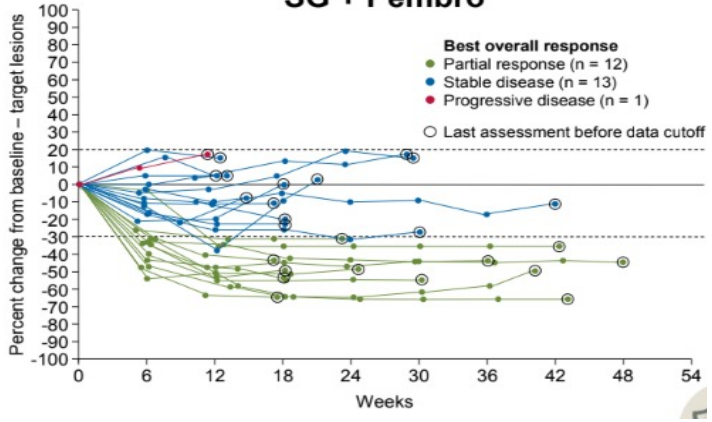


Depth and Duration

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



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



- SG + Pembro demonstrated encouraging antitumor activity in patients with 1L mNSCLC across PD-L
  - ORR was 69% and DCR was 86% in Cohort A
  - ORR was 44% and DCR was 78% in Cohort B
  - Median DOR was not reached, and DOR rate at 6 months was 88% in both cohorts
- The safety profile of SG + Pembro was manageable and consistent with the known safety of each ag
  - The most common any-grade TEAEs were diarrhea, anemia, and asthenia
  - TEAEs leading to treatment discontinuation were low (18%)

Prevalence of CEACAM5

CEACAM5 is expressed in 38% of lung adenocarcinoma and 20% of lung squamous cell carcinoma but not in healthy lung tissue.

			Prevalence IHC (% of total cases)			
Tissue type	**N**	**Membrane-positive cases, n (%)**	**Weak**	**Moderate**	**Strong**	**Very strong**
Lung adenocarcinoma	58	22 (38%)	10	21	7	0
Lung squamous cell carcinoma	143	28 (20%)	7	12	1	0
Normal lung tissue	75	0	0	0	0	0

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) stimulates NSCLC progression through the promotion of cell proliferation and migration[1]. In vitro, ablation of CEACAM5 blocks NSCLC cell proliferation and migration[1]. CEACAM5 is an attractive target for antibody-based therapies designed to selectively deliver cytotoxic drugs to some epithelial tumors[2]

1. Decary S, et al. *Clin Cancer Res.* 2020;26(24):6589-6599. **2.** Zhang X, et al. *J Int Med Res.* 2020;48(9):0300060520959478.

SAR408701: Expansion Study in 92 Patients With Nonsquamous NSCLC

Efficacy

	Moderate expressors (n=28)	High expressors (n=64)
ORR, % PR, n (%)	7.1% 2 (7.1%)	20.3% (95% CI 12.27-31.71) 13 (20.3%)
SD, n (%)	NR	27 (42.2%)
ORR in prior anti-PD1/PDL1, %	NR	17.8%

- Dose modifications due to TEAEs: 31 patients (33.7%)
  - Dose reduction for keratopathy/keratitis: 10 patients (10.9%)
- Grade ≥3 TEAEs occurred in 47.8% of patients
  - Assessed as drug-related: 15.2%

Most Common TEAEs (All Grades)

	All patients (n=92)
Asthenia	38.0%
Keratopathy/keratitis	38.0%
Peripheral neuropathy	26.1%
Dyspnea	23.9%
Diarrhea	22.8%

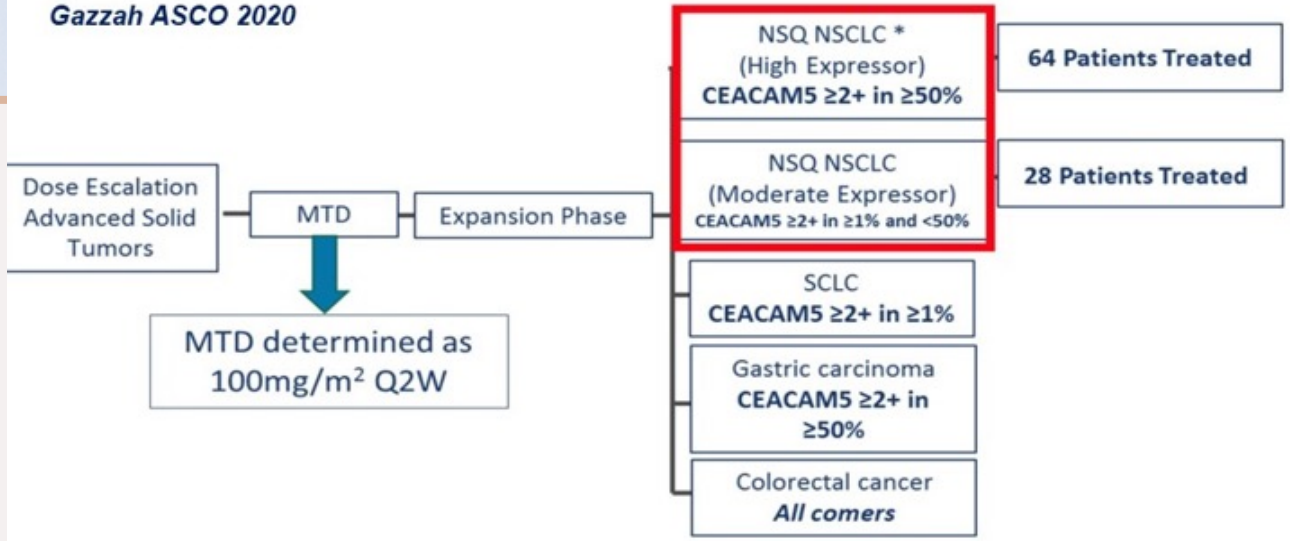
Hematologic Toxicity

	All patients (n=92)
Leukopenia	14.4%
Neutropenia	4.4%
Thrombocytopenia	13.3%

Gazzah A, et al. J Clin Oncol. 2020;38(15_suppl):9505.

Efficacy and safety of SAR408701 in patients with non-squamous NSCLC expressing CEACAM5

Gazzah ASCO 2020



Best overall response

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%)

Treatment-Emergent Adverse Events (TEAEs) – Pooled Data of NSCLC Cohorts

Preferred Term	SAR408701 100 mg/m² Q2W (n=92)	
	All Grades, n (%)	Grade ≥3, n (%)
Any class, TEAEs ≥ 10%	92 (100%)	47 (51.1%)
Corneal AE (Keratopathy/Keratitis)	35 (38.0%)	10 (10.9%)
Asthenia	34 (37.0%)	4 (4.3%)
Peripheral neuropathy (SMQ*)	25 (27.2%)	1 (1.1%)
Diarrhea	21 (22.8%)	1 (1.1%)
Dyspnea	20 (21.7%)	10 (10.9%)
Decreased appetite	19 (20.7%)	0
Cough	14 (15.2%)	0
Nausea	12 (13.0%)	1 (1.1%)
Arthralgia	10 (10.9%)	0
Constipation	10 (10.9%)	0

Laboratory Abnormalities	SAR408701 100 mg/m² Q2W (n=92)	
	All Grades, n (%)	Grade ≥3, n (%)
Hematological toxicity		
Neutropenia	4 (4.4%)	0
Anemia	69 (75.8%)	2 (2.2%)
Thrombocytopenia	11 (12.2%)	0

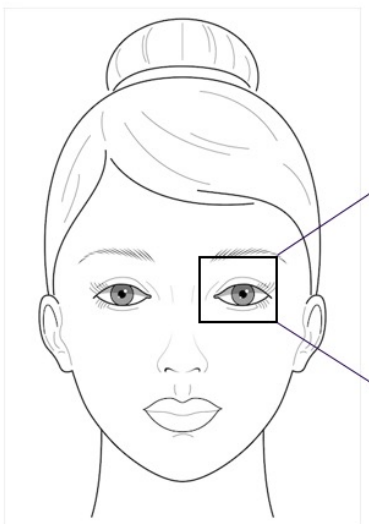
Dyspnea was the most frequent serious TEAE, reported in 5 (5.4%) patients, all as a symptom of progressive disease.

*Standardized MedDRA Queries (SMQ): "peripheral neuropathy" (broad + narrow)

Ocular Events	SAR408701 100 mg/m² Q2W (n=92)	
	Grades 1-2, n (%)	Grade 3, n (%)
Corneal AE	25 (27.2%)	10 (10.9%)
Dose modification		
Keratitis	12 (13.0%)	7 (7.6%)
Keratopathy	8 (8.7%)	1 (1.1%)

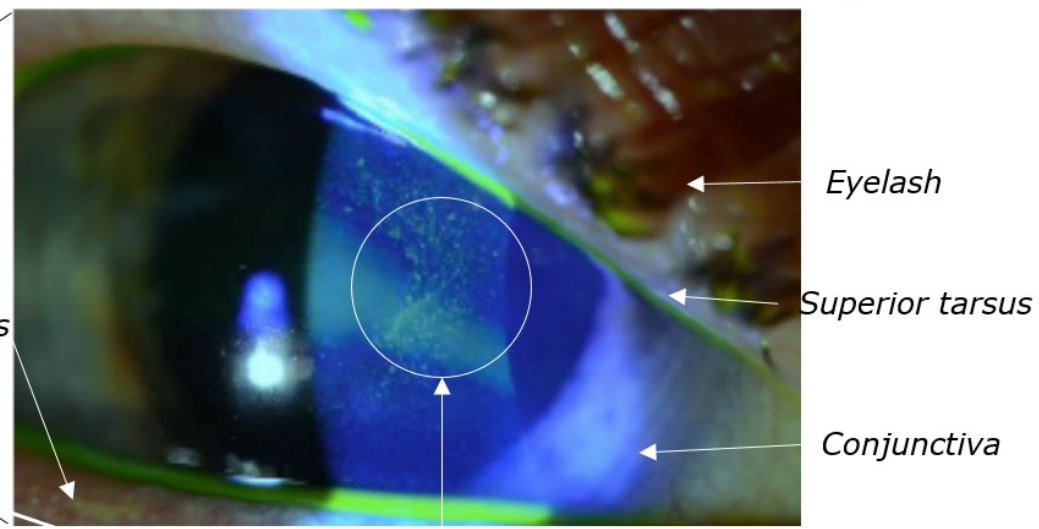
Keratopathy: Clinical Presentation

- Keratopathy presents as deposits of microcysts, initially at the periphery of the cornea[1]
- As it progresses, the deposits typically migrate towards the center of the cornea[2]
- Symptomatic keratopathy may manifest as dry eye, blurred vision, decrease in visual acuity, eye irritation, or punctate keratitis[2]
- In asymptomatic keratopathy, microcysts are present on routine ocular examination but the patient is asymptomatic, including no changes in vision[3]



For illustrative purposes only.

Microcysts visualized by fluorescein staining[2]



Microcystic deposits on the cornea of a patient with lung cancer treated with an ADC

ADC, Antibody-drug conjugate

1. Eaton JS, et al. *J Ocul Pharmacol Ther*. 2015;31(10):589-604. 2. Gazzah A, et al. *Ann Oncol*. 2022;33(4):416-425. 3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Published June 14, 2010.

Selected ongoing trials with tusamitamab ravtansine, (anti-CEACAM5) ADC in NSCLC

ClinicaTrial.gov ID	Phase	Setting	N	Treatment arms	1 endpoint
CARMEN-LC03 NCT04154956	**3**	**Previously treated, CEACAM5 positive metastatic non-squamous NSCLC patients**	**450**	**Tusamitamab ravtansine *vs* docetaxel**	**PFS, OS**
CARMEN-LC05 NCT04524689	2	Patients with no prior systemic CT CEACAM5 positive expression advanced/metastatic non-squamous NSCLC	120	Tusamitamab ravtansine combined with pembrolizumab Tusamitamab ravtansine combined with pembrolizumab and platinum-based CT with or without pemetrexed	Incidence of drug-related dose-limiting toxicity
CARMEN-LC06 NCT05245071	2	Non-squamous NSCLC patients with progression after platinum-based CT and immune checkpoint inhibitor with negative or moderate CEACAM5 expression tumors and high circulating CEA	38	Tusamitamab ravtansine	ORR
CARMEN-LC04 NCT04394624	2	Metastatic, non-squamous, NSCLC patients with CEACAM5-positive tumors, previously treated with platinum-based CT and an immune checkpoint Inhibitor	43	Tusamitamab ravtansine + pembrolizumab Tusamitamab ravtansine and ramucirumab and pembrolizumab	Incidence of drug-related dose-limiting toxicity

TABLE 1. Clinical Data With ADCs in Lung Cancer (excluding HER2-directed ADCs)

Target	Agent	Study	Sample Size—Patients (No.)	Treatment (RP2D or RDE)	ORR, No. (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Safety and Toxicities (%)	References
TROP-2	Dato-DXd	Phase I, dose-escalation and expansion study	180	6 mg/kg every 3 weeks	25	6 (NE)	NE	Grade 3 stomatitis (2%), nausea (1%), neutropenia (1%). ILD by independent adjudication any grade: 4 mg/kg 10% (one grade 1, three grade 2, one grade 3), 6 mg/kg 4% (two grade 2), and 8 mg/kg 15% (three grade 1, five grade 2, one grade 3, three grade 5	Meric-Bernstam et al,[42] Spira et al,[43] Garon et al[44]
	SG	Phase I/II basket trial	54	10 mg/kg D1 D8 every 3 weeks	16.7	4.4 (3.6 to 9.7)	16.8 (9.0 to 21.9)	Grade 3 nausea (3.6%), diarrhea (7.9%), vomiting (2.8%) grade 3 anemia (10.3%) Neutropenia: grade 3 28.9%, grade 4 13.5% Febrile neutropenia: grade 3 4.2%, grade 4 1.0%	Bardia et al[23]
HER3	HER3-DXd	Phase I dose-escalation/ expansion study	57 (EGFRm) 47 (EGFRwt)	5.6 mg/kg every 3 weeks	39 (EGFRm) 28 (EGFRwt)	EGFRm 8.2 (4.4 to 8.3) EGFRwt 5.4 (3. 9 to 12.7)	NE	Grade 3 thrombocytopenia 30%, anemia 9%, neutropenia 19%, Adjudicated treatment-related ILD 7% (two grade 1, one grade 2, one grade 3)	Janne et al[45] Steuer et al[46]
MET	Teliso-V	Phase I dose-escalation/ expansion study	16 c-MET+ by IHC	2.7 mg/kg every 3 weeks	18.8	5.7 (1.2 to 15.4)	NE	Grade 3 fatigue (14.3%), grade 3 anemia (7.1%), grade 3 neutropenia (7.1%) grade 3 hypoalbuminemia (4%), grade 3 peripheral edema (2.1%), grade 3 hypophosphatemia (2.1%)	Strickler et al[47]
		Phase II	136 c-MET+ by IHC: OE ≥25% 3+	1.9 mg/kg every 2 weeks	36.5	NE	NE	Any grade AEs: peripheral sensory neuropathy (25%), nausea (22.1%), hypoalbuminemia (20.6%)	Camidge et al[48]
CEACAM-5	TUSA	Phase I dose-expansion study	92 CEACAM+ by IHC: 64 high 28 moderate	100 mg/kg every 2 weeks	20.1 (high) 7.1 (moderate)	NE	NE	Grade 3 keratopathy (10.9%), dyspnea (11%), asthenia (4.3%)	Gazzah et al[49]
B7-H3	I-DXd	Phase I dose escalation/ expansion study. SCLC cohort	19	12 mg/kg every 3 weeks	58	NE	NE	Grade 3 anemia (19%), neutropenia (7%), nausea (3%), pneumonia (3%). Any grade IRR 32%, one grade 3, one case of grade 5 ILD	Doi et al[50]

Abbreviations: ADCs, antibody-drug conjugates; AEs, adverse events; Dato-DXd, datopotamab deruxtecan; HER3-DXd, patritumab deruxtecan; I-DXd, ifinitamab deruxecan; IHC, immunohistochemistry; ILD, interstitial lung disease; IRR, infusion-related reaction; m, mutant; NE, not evaluated; OE, overexpression; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RDE, recommended dose for expansion; RP2D, recommended phase II dose; SCLC, small-cell lung cancer; SG, sacituzumab govitecan; Teliso-V, telisotuzumab vedotin; TUSA, tusamitamab ravtansine; wt, wild-type.

Ongoing Phase III 2nd line trials vs docetaxel

Datopotamab-DXd	TROP2					
		NCT03401385 [TROPION-PanTumor01]	I	NSCLC (multiple cohorts) Pretreated SCLC	Dato-DXd	DLTs AEs
		NCT05460273 (TROPION-PanTumor02)	I/II	Pretreated (≥2L) NSCLC without AGA in Chinese patients	Dato-DXd	ORR
		NCT04612751 (TROPION-Lung04)	I	First-line and pretreated NSCLC without AGA	Dato-DXd plus ICI (different agents) ± carboplatin	DLTs
		NCT04656652 (TROPION-Lung01)	III	Pretreated NSCLC with or without AGA	Dato-DXd *v* docetaxel	PFS OS
		NCT04484142 (TROPION-Lung05)	II	Pretreated NSCLC with AGA	Dato-DXd	ORR
		NCT04940325 (ICARUS-Lung01)	II	Pretreated NSCLC with or without AGA	Dato-DXd	ORR
		NCT04526691 (TROPION-Lung02)	I	NSCLC without AGA (≤two prior lines)	Dato-DXd plus pembrolizumab ± platinum chemotherapy	DLTs
		NCT05215340 (TROPION-Lung08)	III	First-line NSCLC with PD-L1 ≥50% (no AGA)	Dato-DXd plus pembrolizumab *v* pembrolizumab monotherapy	PFS OS
		NCT05555732 (TROPION-Lung07)	III	First-line NSCLC with PD-L1 <50% (no AGA)	Dato-DXd plus pembrolizumab +/- platinum-doublet *v* platinum-doublet plus pembrolizumab	PFS OS
Sacituzumab govitecan (SG)	TROP2	NCT03337698 (Morpheus-Lung)	Ib/II	(Multiarm) NSCLC Pretreated cohort	Atezolizumab plus SG	ORR
		NCT05633667 (VELOCITY-Lung)	II	NSCLC without AGA	1L: Zimberelimab (ZIM) + SG + domvanalimab (DOM) Previous CTx and ICI: SG + ZIM + etrumadenant	ORR
		NCT05609968 (EVOKE-03)	III	First-line NSCLC with PD-L1 ≥50% (no AGA)	Pembrolizumab *v* pembrolizumab + SG	PFS OS
		NCT05186974 (EVOKE-02)	II	First-line NSCLC without AGA	SG plus pembrolizumab or SG plus pembrolizumab plus platinum	ORR DLTs
		NCT05089734 (EVOKE-01)	III	Pretreated NSCLC with/without AGA (previous CTx and ICI)	SG *v* docetaxel	OS
		NCT04826341	I/II	Pretreated SCLC cohort	SG + berzosertib (PARPinh)	MTD ORR
Tusamitamab ravtansine (TUSA)	CEACAM5	NCT04154956 (CARMEN-LC03)	III	Pretreated nonsq NSCLC CEACAM5+ (previous CTx and ICI)	TUSA *v* docetaxel	PFS OS
		NCT04524689 (CARMEN-LC05)	II	First-line and pretreated nonsq NSCLC nonsq without AGA, CEACAM5+	TUSA plus pembrolizumab or TUSA plus pembrolizumab plus platinum ± pemetrexed	DLTs
		NCT05245071 (CARMEN-LC06)	II	Pretreated NSCLC nonsq CEACAM5 0-2+ High circulating CEA levels (previous CTx and ICI)	TUSA	ORR
		NCT04394624 (CARMEN-LC04)	II	Pretreated NSCLC nonsq CEACAM5 ≥2+ (previous CTx and ICI)	TUSA plus ramucirumab	DLTs ORR
Telisotuzumab vedotin (Teliso-V)	c-MET	NCT03539536	II	NSCLC c-MET+ (IHC) ≤two prior lines	Teliso-V	ORR AEs
		NCT05513703	II	First-line NSCLC c-MET amplified	Teliso-V	ORR
		NCT04928846	III	Pretreated NSCLC c-MET+ (IHC)	Teliso-V *v* docetaxel	PFS OS
Ifinatamab Deruxtecan (I-DXd)	B7-H3	NCT05280470	II	Pretreated ES-SCLC	I-DXd 8 or 12 mg/kg	ORR
Vobramitamab duocarmazine (MGC018)	B7-H3	NCT03729596	I/II	NSCLC cohort	MGC018	AEs DLTs
Mecbotamab vedotin (BA3011)	AXL	NCT04681131	II	NSCLC	BA3011 monotherapy or plus anti–PD-1	ORR AEs
Cofetuzumab pelidotin	PK7	NCT04189614	I	Pretreated NSCLC PK7+ (IHC)	Cofetuzumab pelidotin	ORR
Enfortumab vedotin	PRVL4	NCT04225117	II	Pretreated NSCLC cohorts	Enfortumab vedotin	ORR
Tisotumab vedotin	TF	NCT03485209	II	Pretreated sq NSCLC	Tisotumab vedotin	ORR
MRG003	EGFR	NCT04838548	II	Pretreated EGFR-mutant NSCLC	MRG003	ORR
Ozuriftamab vedotin (BA3021)	ROR2	NCT03504488	II	Pretreated NSCLC (failed all available SoC therapy)	CAB-ROR2-ADC plus anti–PD-1	ORR
Upifitamab rilsodotin	NaPi2b	NCT03319628	I/II	Pretreated nonsq NSCLC	Upifitamab rilsodotin	MTD ORR