Anti-CEACAM and ROR ADCs

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Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

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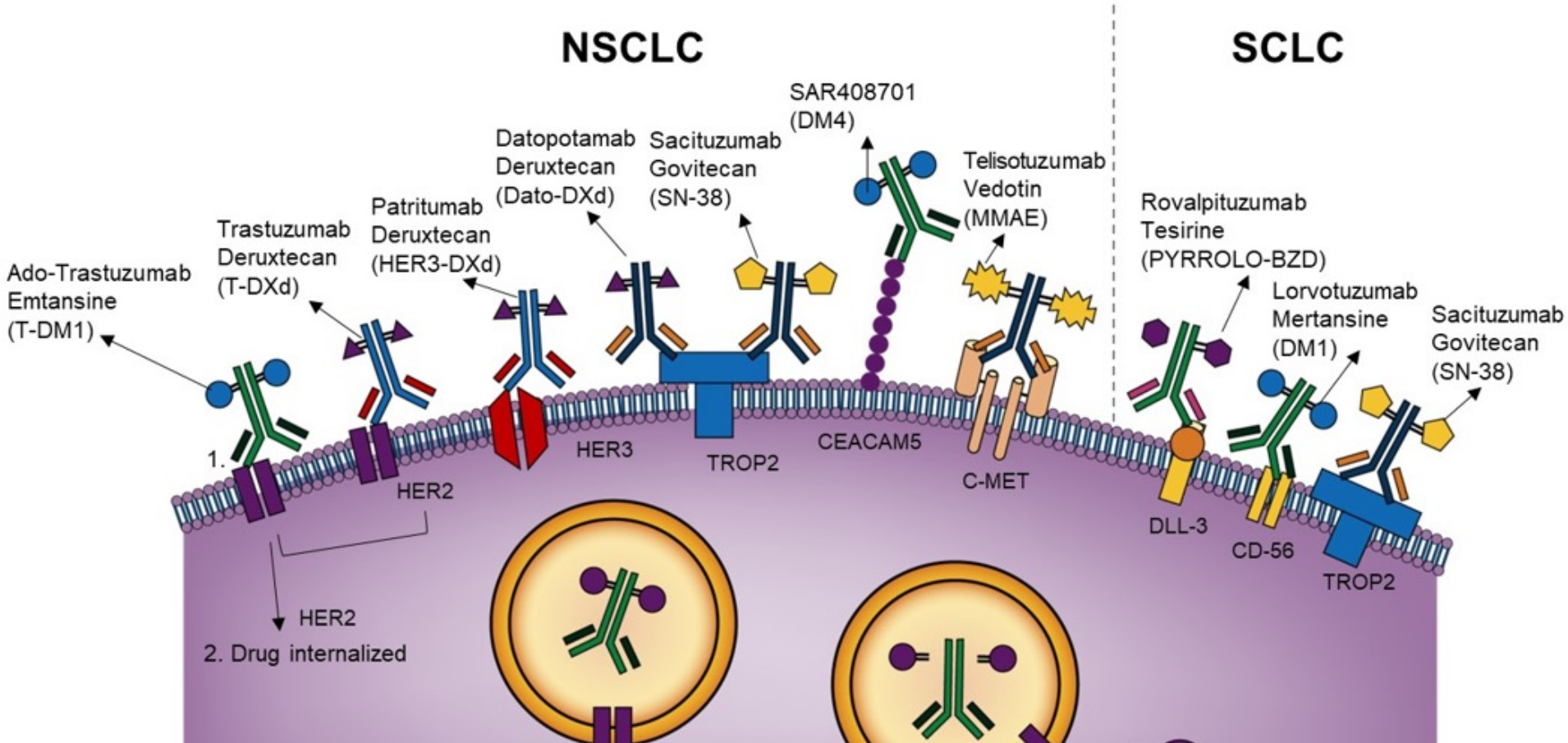
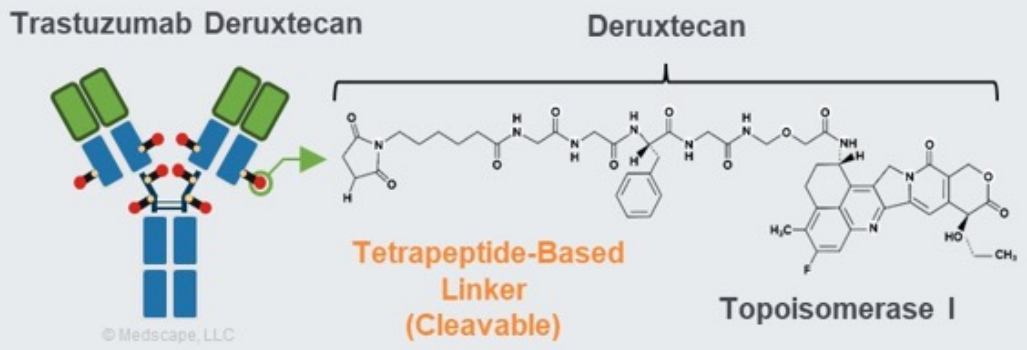
The Antigen: Ideal Characteristics for ADCs



The Linker: Cleavable vs Nonclevable

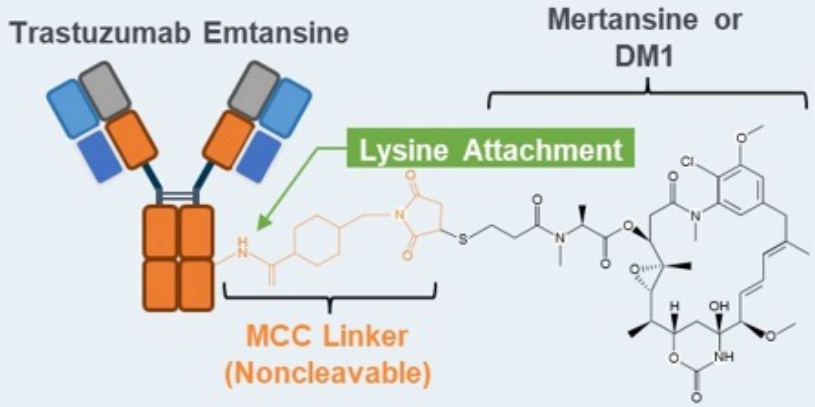
Cleavable Linkers

- Break down and release of the payload in response to tumor-associated factors
- Acidic/Reducing/proteolytic conditions
- May be more labile in plasma but have a higher therapeutic index



Noncleavable Linkers

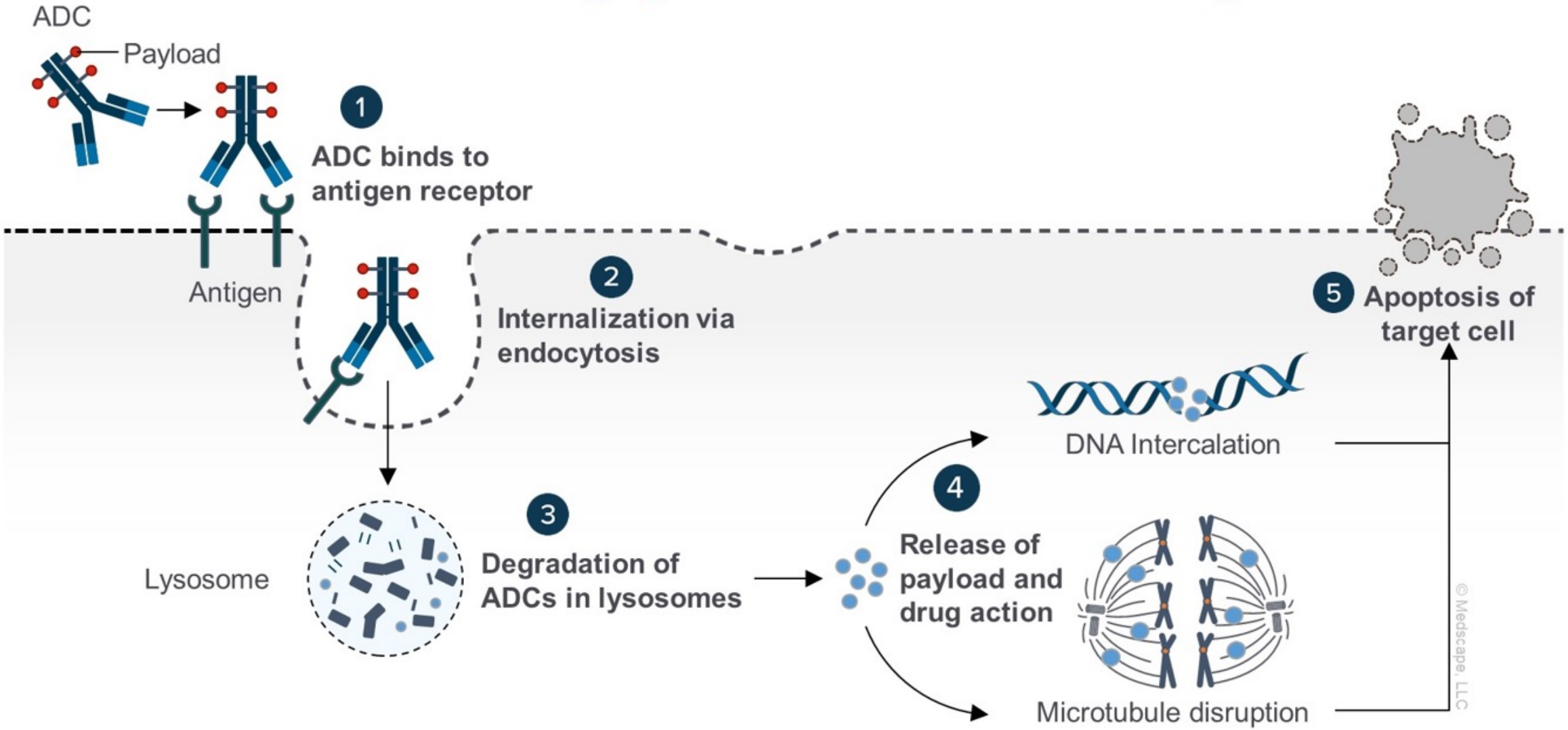
- Contingent specifically on lysosomal degradation of the entire antibody-linker complex which
- Require efficient internalization process and optimally traffic to lysosomes
- Potentially more stable in plasma



The WARHEAD

Warhead class	Mechanism	Payload	Drug
Auristatins	Microtubule Destablizers	MMAE MMAF	Telisotuzumab vedotin
Calicheamicins	Double stranded DNA breaks	Ozogamicin	Gemtuzumab ozogamicin
Maytansinoids	Microtubule Destablizers	DM1	Ado Trastuzumab Emstasine
Campothecins	Topoisomerase Inhibitors	Deruxtecan (TDXd)	Ttrastuzumab deruxetecan

Antibody-Drug Conjugates
Mechanism 1: mAB engagement of cell surface antigen



What's next for ADCs

First generation ADCs

e.g. T-DM1

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

Next-generation ADCs

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

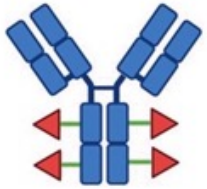
e.g. T-DXd

Future Perspectives

1) Bispecific ADCs

2) Dual-payload ADCs

3) ADCs with immune-stimulating payloads
(e.g. TLR8 agonist)



4) Radionuclide ADCs

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.

CEACAM5 Correlation in NSCLC

- In patients with NSCLC, no correlations have been found between CEACAM5 expression and patient gender, age, smoking history, or histology
- However, CEACAM5 expression has been correlated with:
  - T stage
  - Lymph invasion
  - Histological grade

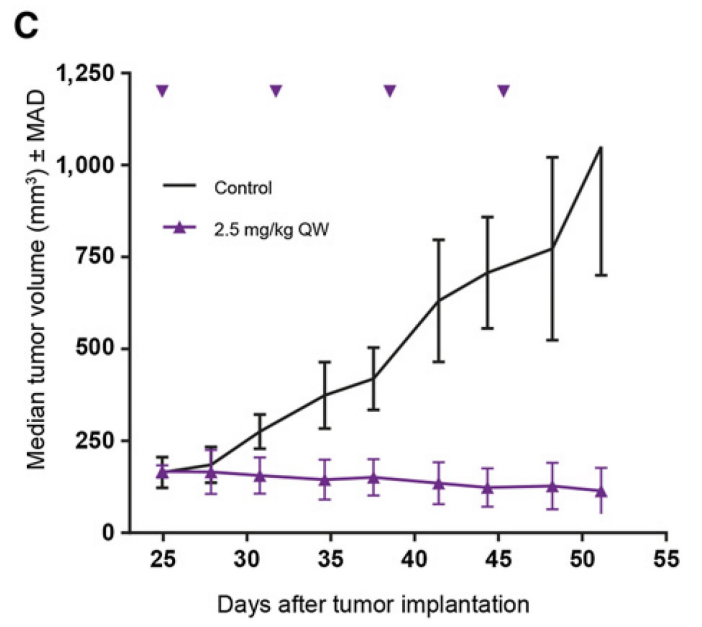
		CEACAM5 Expression		P value
		Low	High	
Gender	Female (n=34) Male (n=53)	13 18	21 35	0.685
Age	<60 years (n=35) ≥60 years (n=52)	15 16	20 36	0.248
Smoking history	Non-smoker (n=28) Smoker (n=59)	13 18	15 41	0.147
T stage	T1/2 (n=48) T3/4 (n=39)	12 19	36 20	**0.022**
Lymph invasion	N0 (n=45) N1 or N2 (n=42)	9 22	36 20	**0.002**
Histology	Squamous (n=32) Adenocarcinoma (n=27) Other (n=28)	9 11 11	23 16 17	0.534
Histological grade	Well (n=15) Moderate (n=41) Poor (n=31)	11 14 6	4 27 25	**0.002**

Zhang X, et al. *J Int Med Res.* 2020;48(9):0300060520959478.

SAR408701: Preclinical Activity

- SAR408701 is an anti-CEACAM5-DM4 (maytansinoid) antibody-drug conjugate (ADC)
- In vivo efficacy was demonstrated in a PDX model of lung cancer (see figure)

In vivo efficacy of SAR408701 in a PDX mouse model of lung cancer



Decary S, et al. *Clin Cancer Res.* 2020;26(24):6589-6599.

SAR408701: Expansion Study in 92 Patients With Nonsquamous NSCLC

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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%

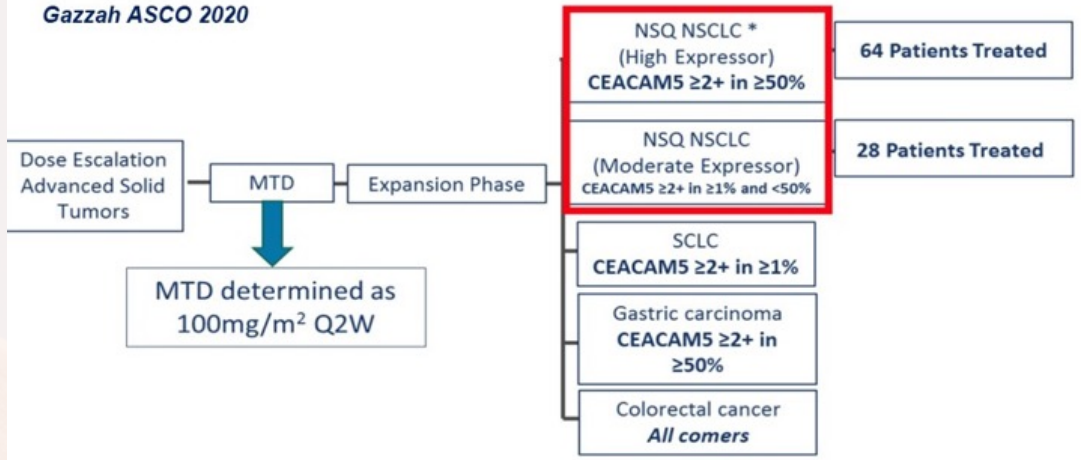
Hematologic Toxicity

	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.

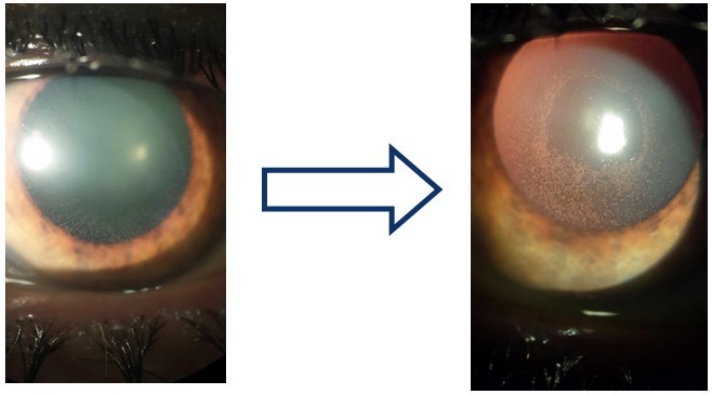
*Standardized MedDRA Queries (SMQ): "peripheral neuropathy" (broad + narrow)

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%)

Dose Modification and Ocular Events – Pooled Data of NSCLC Cohorts

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%)

DM4-induced microcystic corneal dystrophy



Images courtesy of Dr. Hierro and Dr. Tabernero, Vall d'Hebron Institute of Oncology

A total of 25 patients (27.2%) had corneal TEAEs leading to dose modification

- All 25 patients had at least one dose delay
- Ten patients had at least one dose reduction (10.9%)
- One patient permanently discontinued treatment (1.1%)

Ocular Events:

- Specific ADC-DM4 related events are reversible non-inflammatory deposits starting at the periphery of cornea
- First occurrence within the first 4 cycles of treatment for 28 patients (80%)
- Manageable with dose delay and/or dose reduction
- Median time to recovery was 18.5 (2-82) days
- Primary prophylaxis* is not effective; treatment of an event with topical ophthalmologic corticosteroid when it occurs is recommended

***Primary prophylaxis**: Unilaterally administered vasoconstrictive drops before SAR408701 administration, corticosteroid gel for 2 days starting on infusion, and cold compress during infusion

Conclusions

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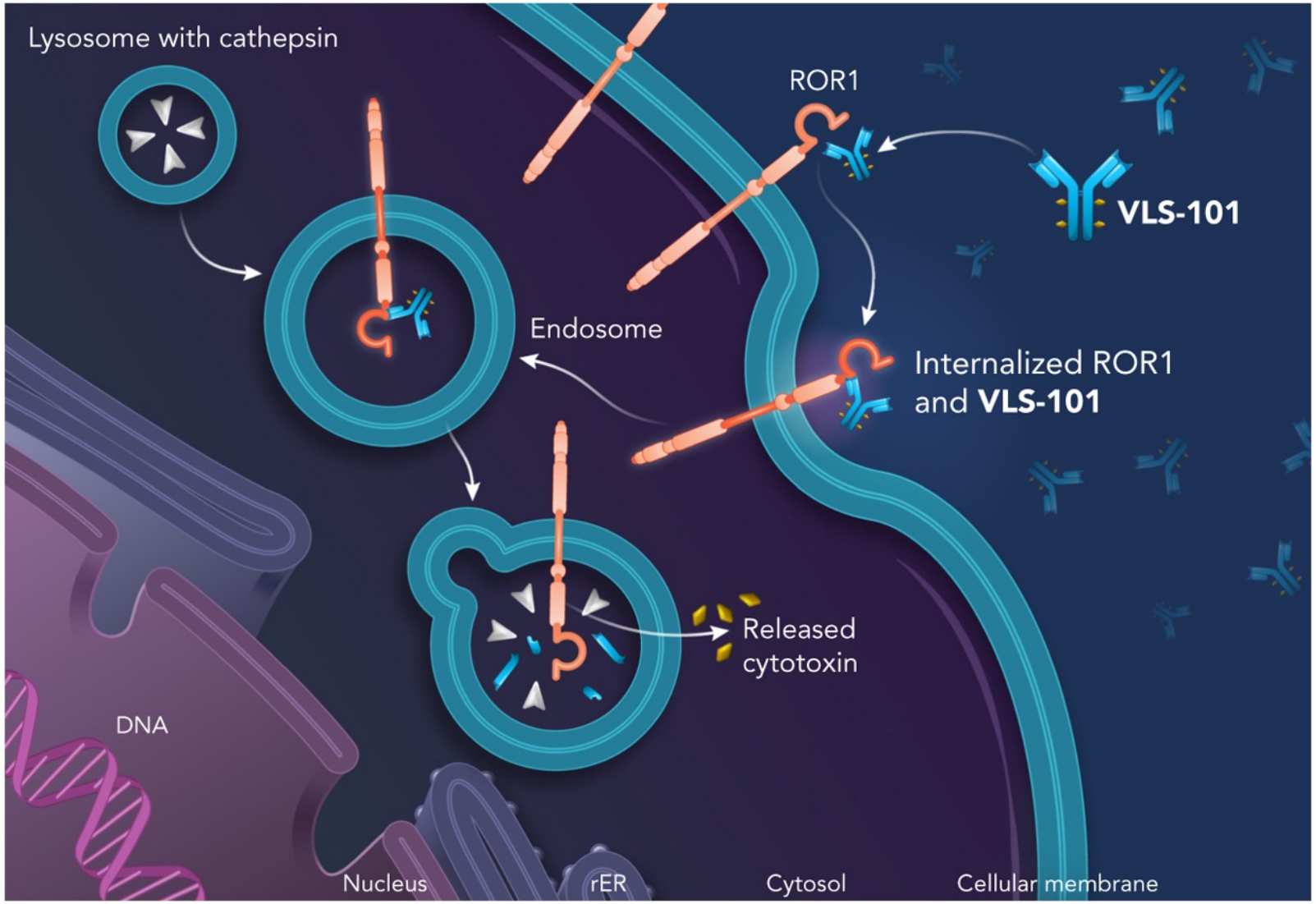
- SAR408701 showed promising antitumor activity in heavily pretreated advanced NSQ NSCLC patients with CEACAM5 expression in ≥ 50% of tumor cells
  - ORR of 20.3% (95% CI, 12.27-31.71) was observed in the high expressor cohort (DCR of 64.1% with SD of 43.8%; median DOR, 5.6 months)
- SAR408701 was well tolerated in this patient population
  - Minimal hematological toxicity
  - Reversible microcystic keratopathy was manageable with dose modification
- A phase 3 trial is underway evaluating the activity of CEACAM5-DM4 ADC monotherapy in comparison with docetaxel after failure of standard first-line chemotherapy and anti-PD1/PD-L1 in NSQ NSCLC patients with CEACAM5 expression in ≥ 50% of tumor cells

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


Lysosome with cathepsin
ROR1
VLS-101
Endosome
Internalized ROR1
and VLS-101
Released
cytotoxin
DNA
Nucleus
rER
Cytosol
Cellular membrane

ROR ADCs

Name	Indications	Status
Zilovertamab vedotin (MK2104, VLS-101)	B-cell lymphoma, DLBCL, breast cancer, Chronic Lymphocytic Leukemia, Mantle Cell Lymphoma, Follicular Lymphoma,NSCLC, etc	Phase II/III
NBE-002	Advanced Solid Tumor,Triple Negative Breast Cancer	Phase II
LCB-71 (CS5001)	Advanced Solid Tumor, Advanced Lymphoma	Phase I
huXBR1-402-G5-PNU	Leukemia	Preclinical
huXBR1-402-G5-PNU	Acute lymphoblastic leukemia, chronic lymphocytic leukemia, mantle cell lymphoma	Preclinical
cirmtuzumab-ADC-7	Tumor	Preclinical
ELN-11	Tumor	Preclinical

ROR ADCs

A setting of the sun? Clinical-stage Ror1 inhibitors		
Project	**Mechanism**	**Status**
Zilovertamab (formerly cirmtuzumab)	MAb	Ph3 Imbruvica study in mantle cell lymphoma being closed
Zilovertamab vedotin	ADC	Ph2/3 in B-cell lymphoma
NBE-002	ADC	Ph1/2 in solid tumours
ONCT-808	Car-T therapy	Ph1/2 in B-cell malignancies
LCB71/ CS5001	ADC	Ph1 in solid tumours
LYL797	Car-T therapy	Ph1 in solid tumours (2nd-gen LYL119 is preclinical)
NVG-111	T-cell engager	Ph1/2 in haematological cancers
PRGN-3007	Car-T therapy	Ph1 academic trial
Source: Evaluate Pharma & clinicaltrials.gov.		