Antibody Drug Conjugates in Cancer

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Woo U, 2022

Conflicts:

- **Research Support (Clinical Trials):**

  – Millennium, Merck/Celgene, BMS/Lilly

- **Advisory Board/Consultant:**

  – BMS, Lilly, Genentech, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTEO, Jazz, Janssen, Da Volterra, Kriya

- **Scientific Advisory Board:**

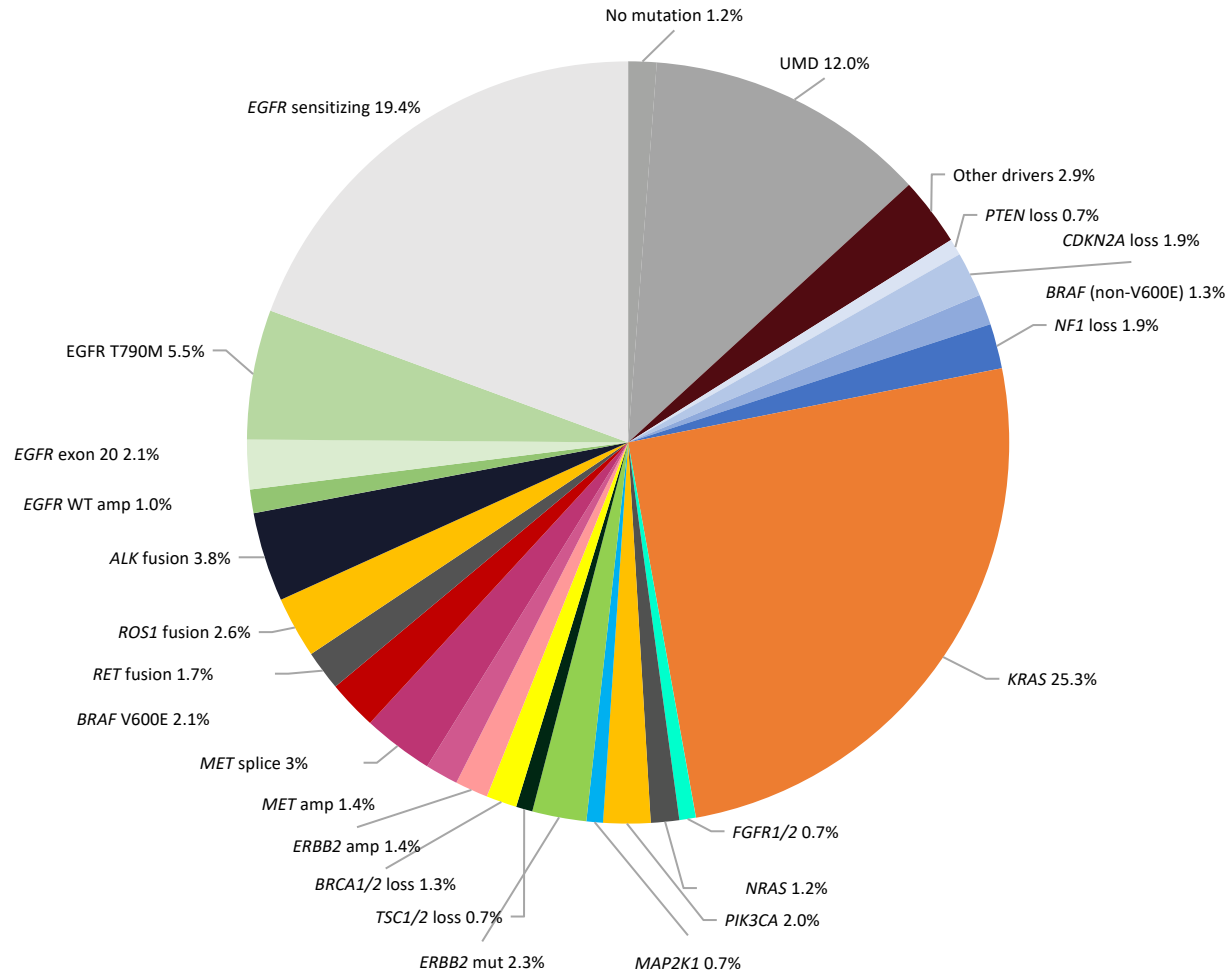 – Sonnetbio (Stock Options), Rgenix (Stock Options), Nucleai (Stock options)

- **Data and Safety Monitoring Board:**

  – University of Pennsylvania, CAR T Program, Takeda, Incyte

- **Employment:**
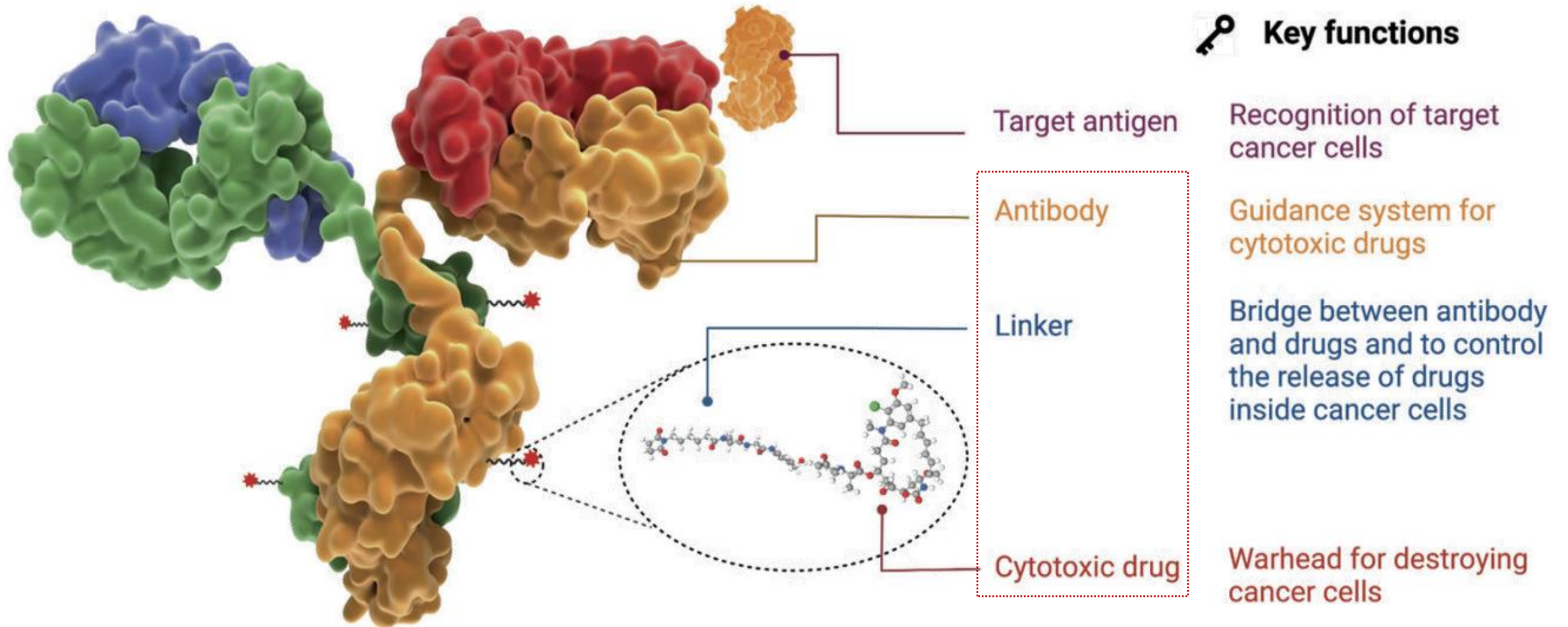
  – Fox Chase Cancer Center

Biomarker Testing Demands and Targeted Therapy Options for Lung Adenocarcinoma Continue to Expand
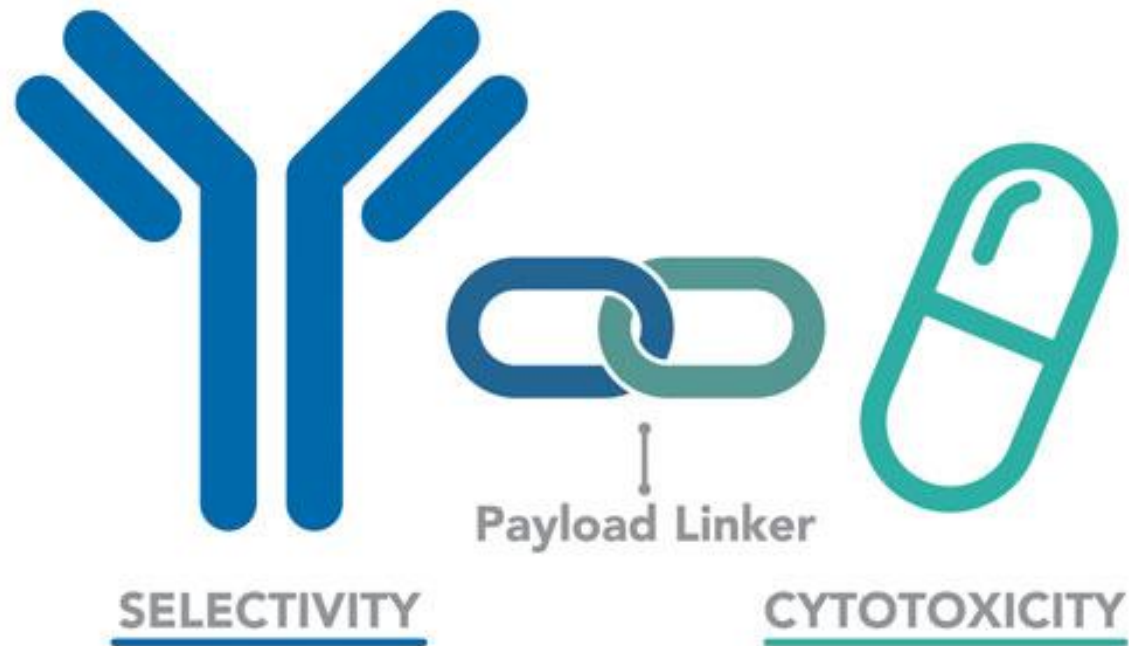

Jordan et al. *Cancer Discov*. 2017;7:596-609.
Slide: PeerView.com

Target	Approved Drugs
EGFR (common mutations)	Gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, erlotinib/ramucirumab
EGFR (exon 20)	Amivantamab, mobocertinib
ALK	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
ROS1	Crizotinib, entrectinib
RET	Selpercatinib, pralsetinib
NTRK1/2/3	Larotrectinib, entrectinib
BRAF V600E	Dabrafenib + trametinib
MET exon 14	Capmatinib, tepotinib
KRAS G12C	Sotorasib

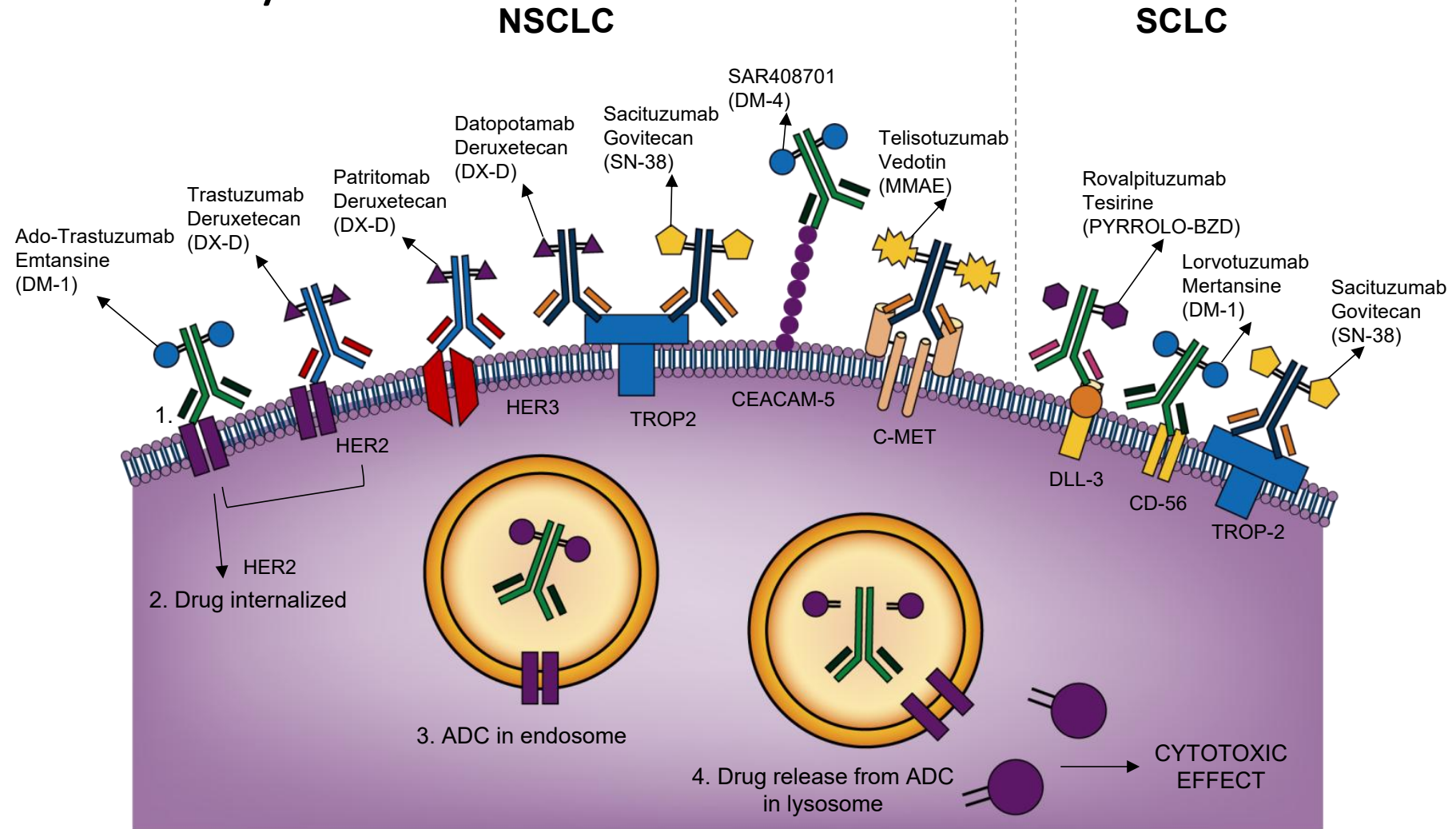# Antibody–Drug Conjugates (ADCs): What Are They?[1]

- Unlike conventional chemotherapy treatments, which can damage healthy cells, ADCs are targeted medicines that deliver chemotherapy agents to cancer cells

Key functions

Target antigen	Recognition of target cancer cells
Antibody	Guidance system for cytotoxic drugs
Linker	Bridge between antibody and drugs and to control the release of drugs inside cancer cells
Cytotoxic drug	Warhead for destroying cancer cells

1. Fu Z et al. *Signal Transduct Target Ther*. 2022;7:93.

What is an ADC?

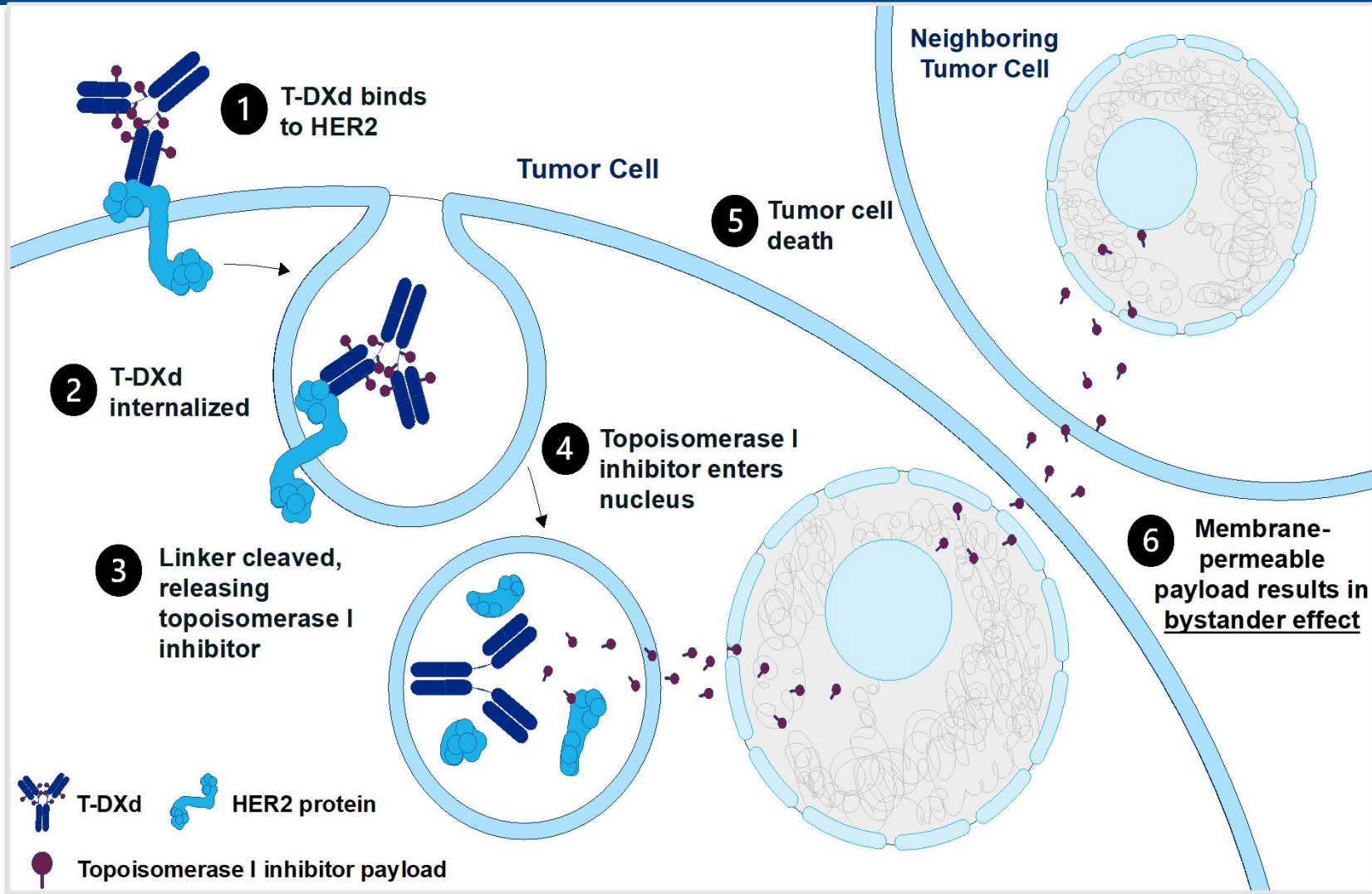SELECTIVITY

Payload Linker

CYTOTOXICITY

Landscape of Antibody–Drug Conjugates Under Study in Lung Cancer[1]

1. Desai A et al. *Lung Cancer*. 2022;163:96-106.
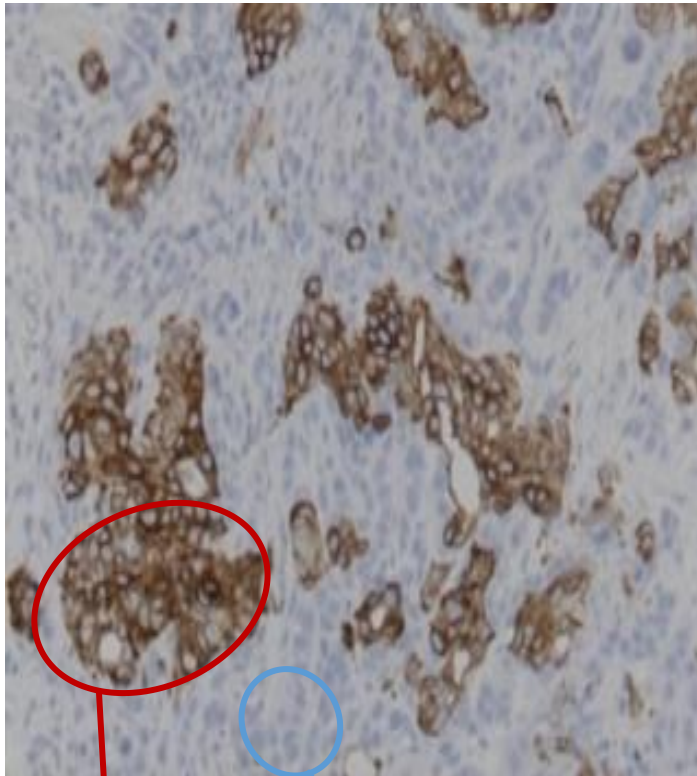
T-DXd MOA and Bystander Effect[1-3]

1. Modi S et al. *J Clin Oncol.* 2020;38:1887-1896. 2. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185.
3. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108.

Slide by PeerView

Bystander Effect of T-DXd Versus T-DM1[1]

Control

Co-culture of HER2+ and HER2- tumors in vivo

T-DM1, 10 mg/kg

HER2- cells still persist

T-DXd, 3.0 mg/kg

Both HER2+ and HER2- are impacted

HER2+ cells NCI-N87

HER2- cells MDA-MB-468
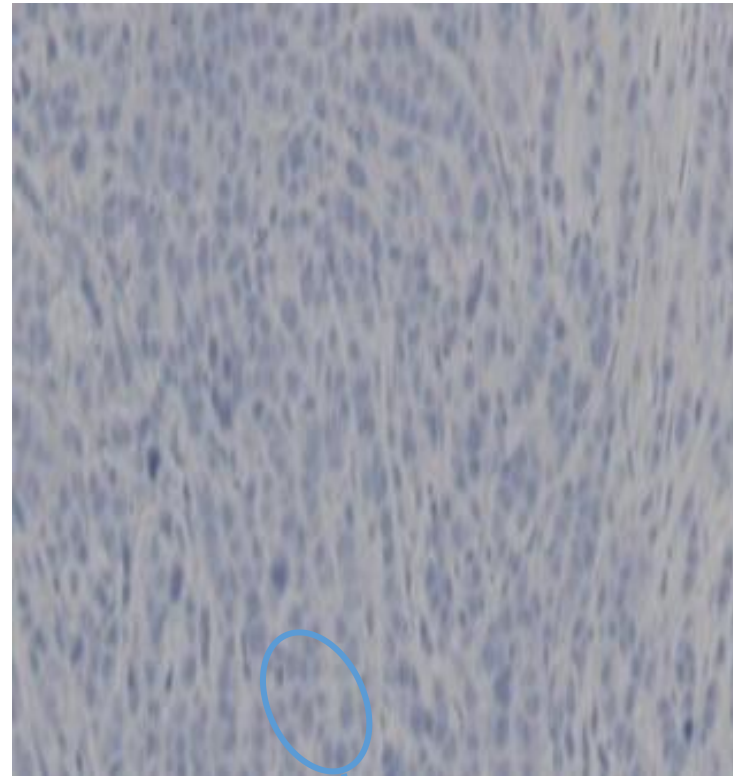
HER2- cells MDA-MB-468

Tumor regression

1. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-1046.

Slide by PeerView
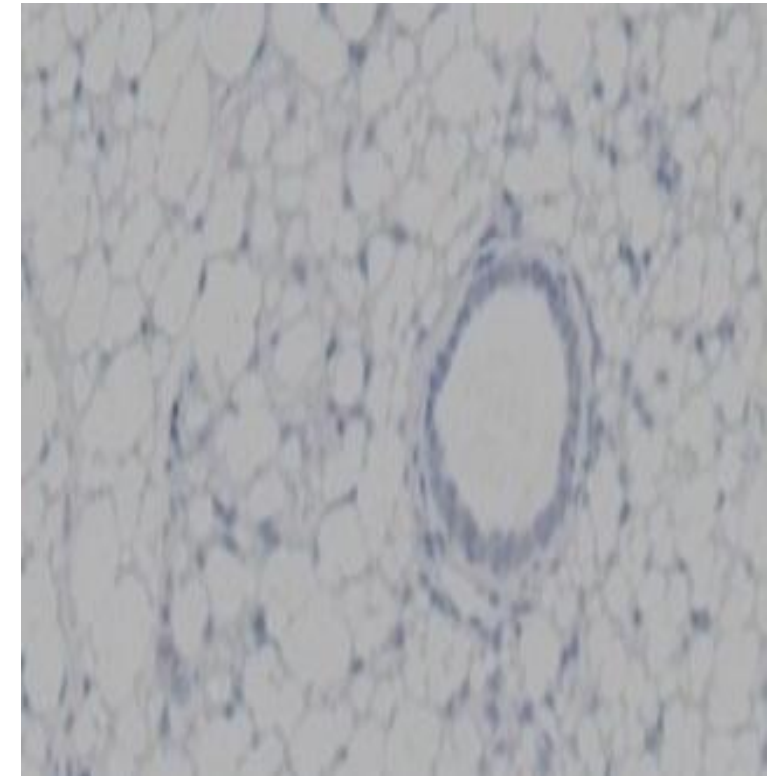
Components of an ADC
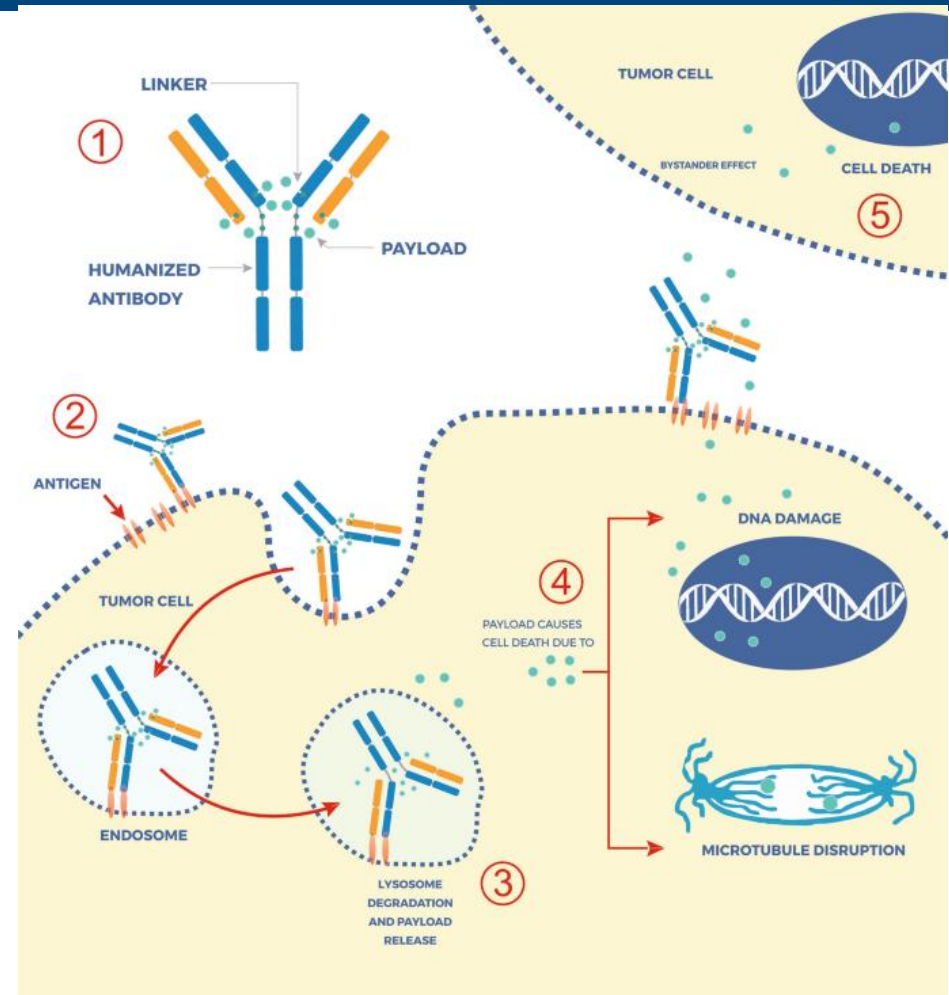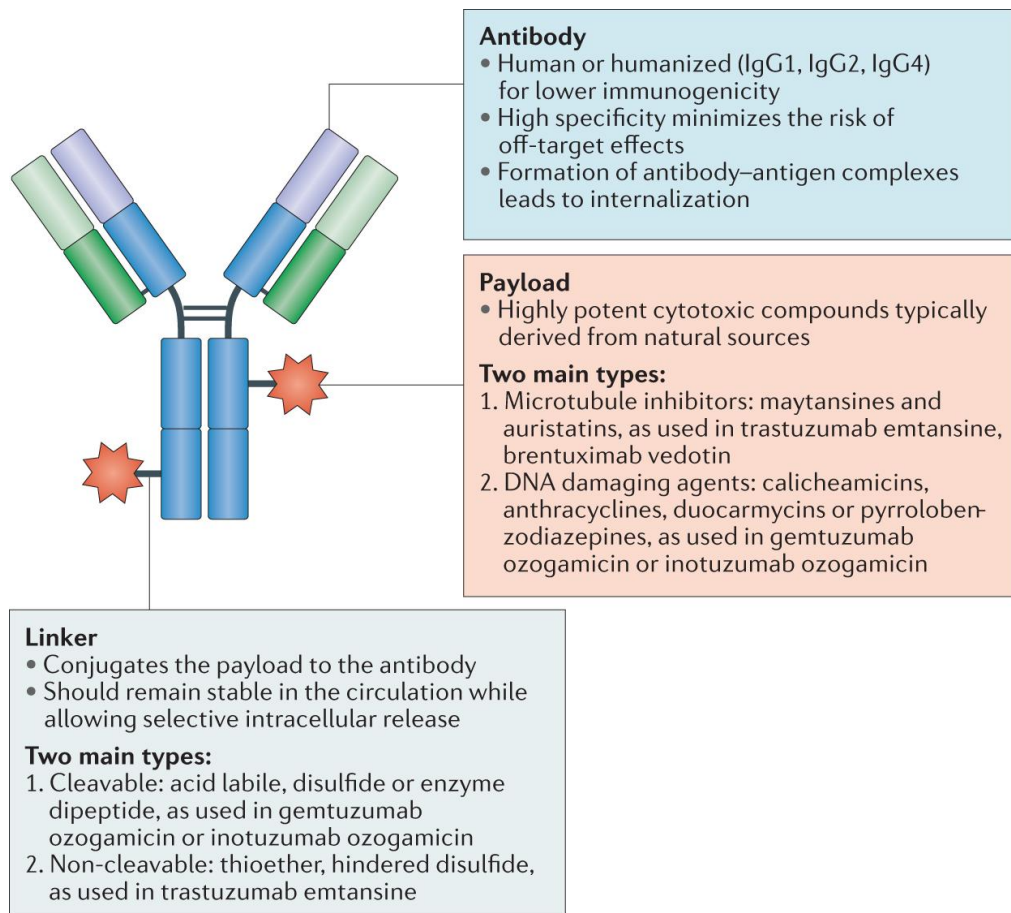
Evolution of ADCs
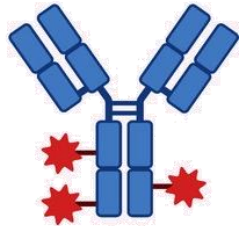
ADCs- FDA Approvals

Datopotamab-DXd demonstrates relevant activity in NSCLC and mTNBC

ASCO 2018
Two novel ADCs (T-DXd, T-DCZ) demonstrate relevant activity in HER2+ and HER2-low ABC

ASCO 2020
T-DXd demonstrates relevant activity in multiple HER2-driven cancers (GC, CRC, NSCLC)

T-DCZ improves PFS compared with chemo in HER2+ BC

First clinical reports of the use of ADCs to treat solid tumors

EMILIA trial establishes trastuzumab emtansine as standard 2nd line for HER2+ ABC

T-DXd outperforms T-DM1 in HER2+ ABC

| 1990 | 2000 | 2013 | 2018 | 2019 | 2020 | 2021 |

First ADC approved for an hematological malignancy
Gemtuzumab ozogamicin is approved for R/R AML

First ADC approved for the treatment of a solid tumor
Trastuzumab emtansine is approved for HER2+ ABC

Trastuzumab deruxtecan is approved for HER2+ ABC

Enfortumab Vedotin is approved for mUC

Trastuzumab emtansine approval expanded to HER2+ EBC

Sacituzumab govitecan is approved for pretreated mTNBC

Trastuzumab deruxtecan a approved for mGC

Sacituzumab govitecan approved for mUC
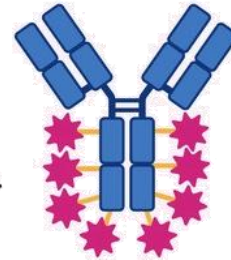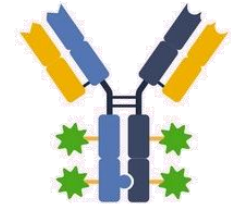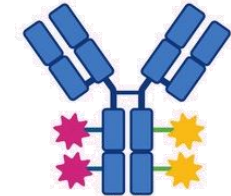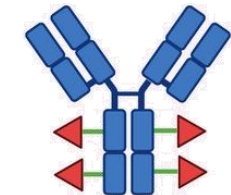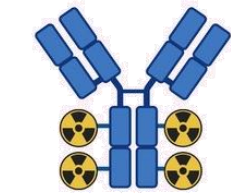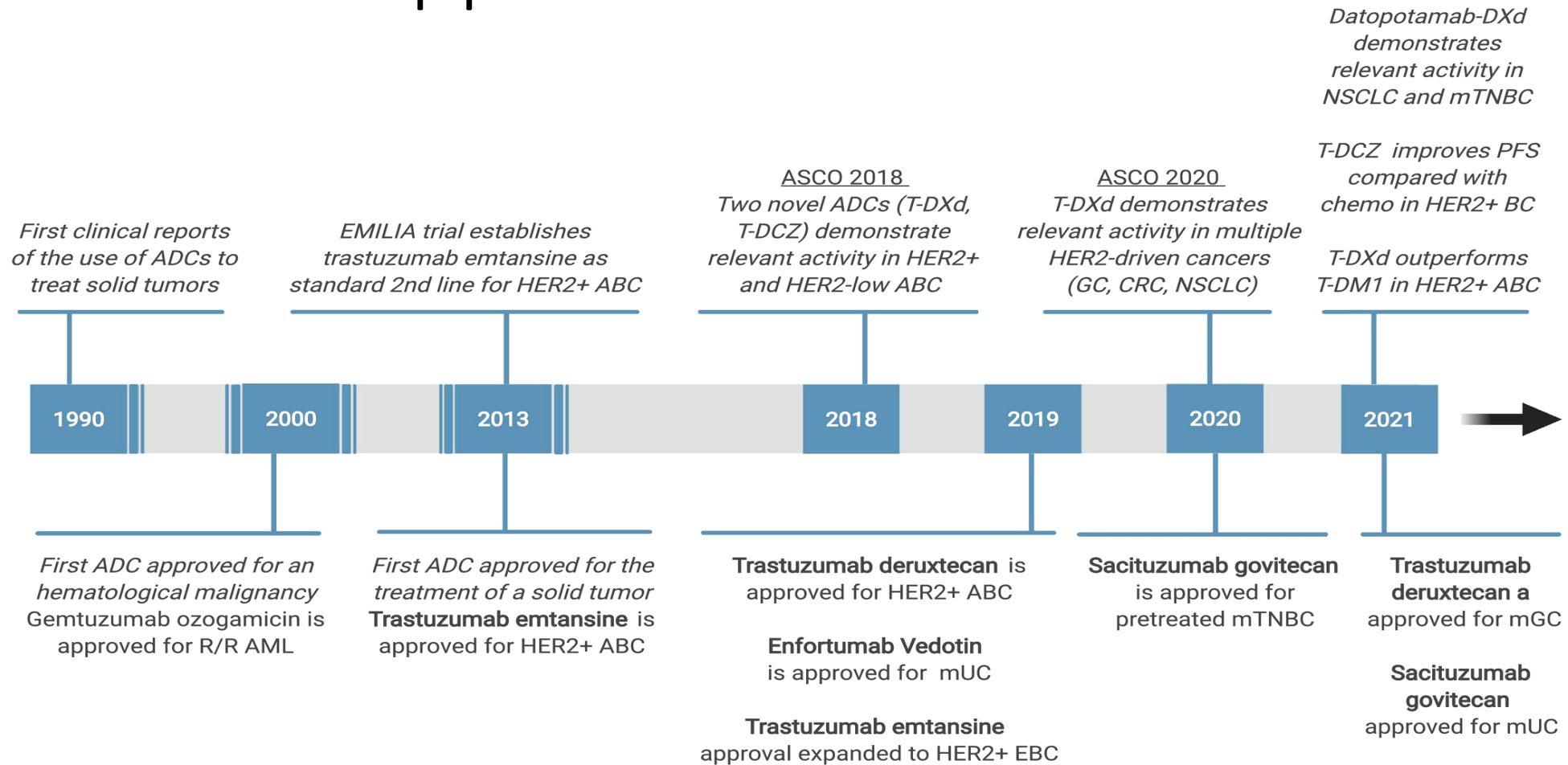
FDA APPROVALS

ADC Targets of Interest in NSCLC and other Malignancies

HER2
- Human epidermal growth factor receptor 2
- Activating mutations occur in 2-3% of NSCLCs

HER3
- Human epidermal growth factor receptor 3
- Overexpression shown in many cancer types

TROP2
- Transmembrane glycoprotein located on chromosome 1
- Overexpressed in multiple human epithelial cancers

CEACAM5
- Carcinoembryonic antigen-related cell adhesion molecule 5, aka cancer carcinoembryonic antigen

c-MET
- Tyrosine kinase receptor
- Signaling stimulates oncologic processes like cell motility, invasion, and metastasis

Components of Select ADCs - What's the Difference?

Target	ADC	mAb	Linker	Payload	DAR
HER2	Trastuzumab deruxtecan	Trastuzumab	Cleavable	Deruxtecan	8
TROP2	Datopotamab deruxtecan	Datopotamab	Cleavable	Deruxtecan	4
	Sacituzumab govitecan	Sacituzumab	Cleavable	SN-38	7.6
HER3	Patritumab deruxtecan	Patritumab	Cleavable	Deruxtecan	8
CEACAM5	Tusamitamab ravtansine	Tusamitamab	Cleavable inside cells	Maytansinoid DM4	3.8
c-MET	Telisotuzumab vedotin	Telisotuzumab	Cleavable	Monomethyl auristatin E	3.1

Abuhelwa Z et al. Cancer Treatment Reviews 106 (2022) 102393.

Toxicities Associated with ADCs

Hematologic: Thrombocytopenia, Anemia

GI: Nausea, vomiting, diarrhea

Constitutional: fevers, fatigue

LFTs

Ocular: Keratopathy

Pneumonitis

Alopecia

Peripheral neuropathy
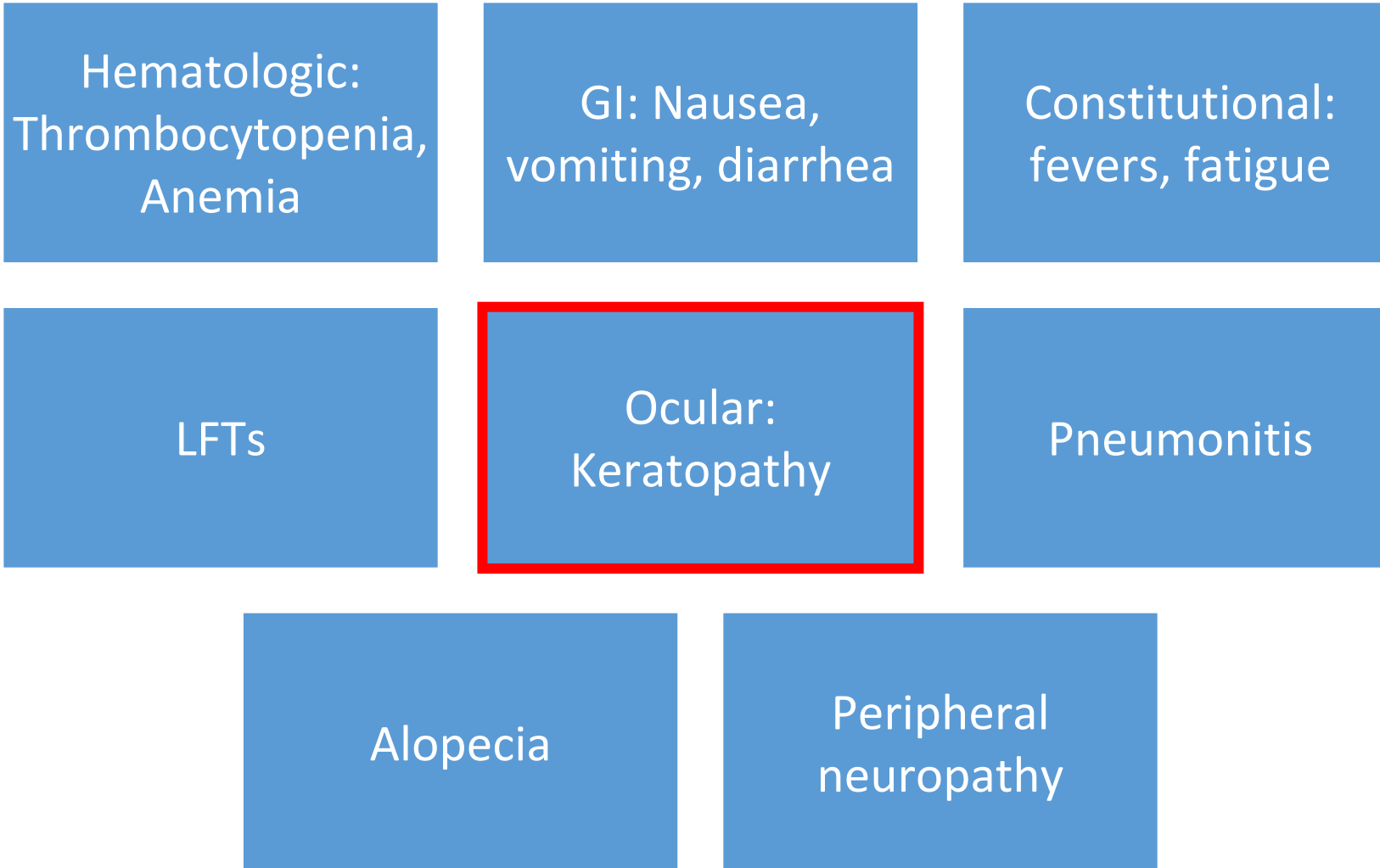
Mechanism of Action of HER2-Targeting Therapies: Focus on ADCs[1]

1. Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17:33-48.
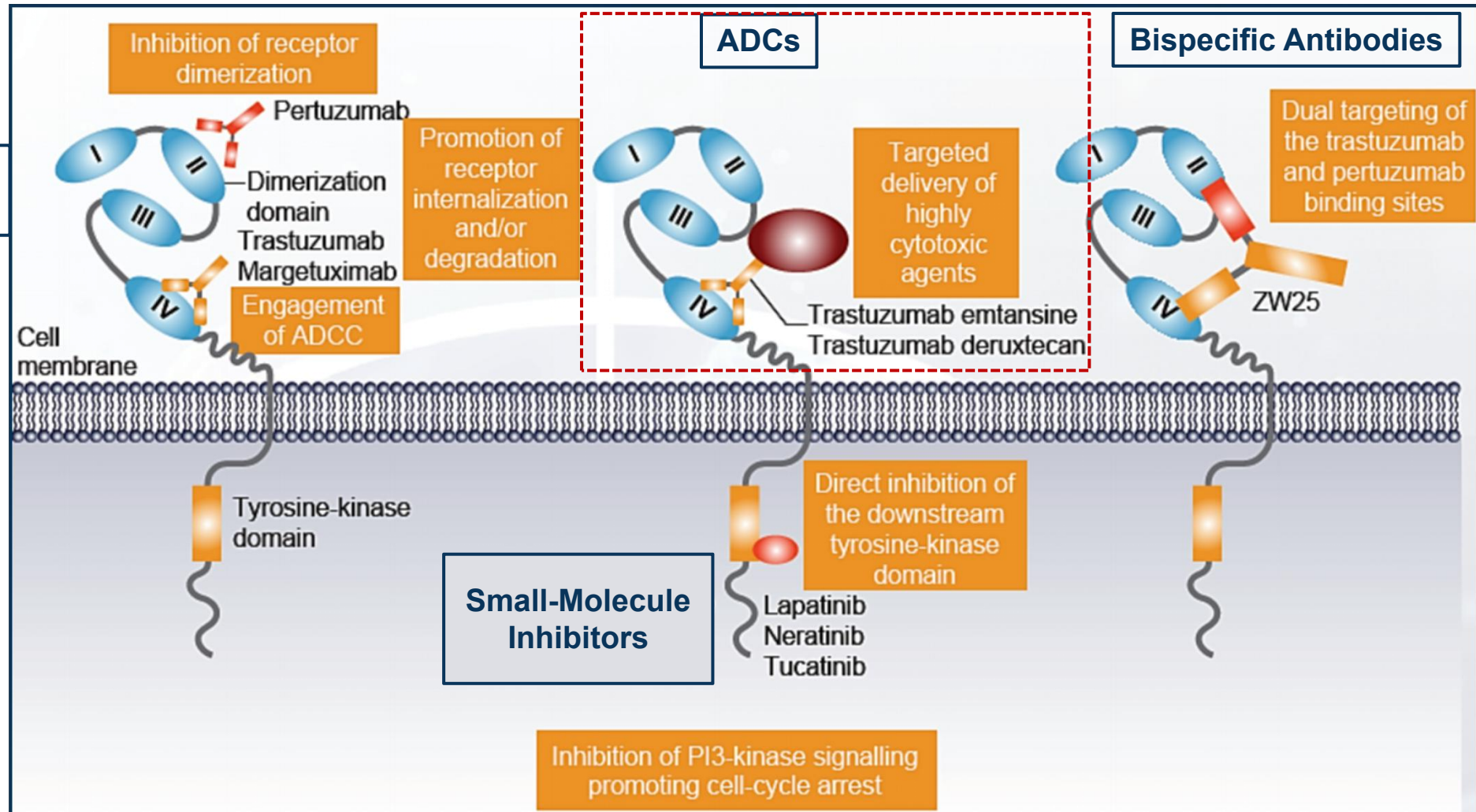
Ado-Trastuzumab Emtansine (T-DM1) in *HER2*-Mutated NSCLC[1,2]

Advanced solid tumor cancers
- *HER2* amplification (fold change ≥2) on MSK-IMPACT or another NGS platform at CLIA laboratory, or FISH (HER2/CEP17 ratio ≥2.0), *or*
- Lung cancer with *HER2* mutation (cohort 1 only)

HER2 **mutant**

HER2 **amplified**

Cohort 1: lung cancer

Cohort 2: lung cancer

Cohort 3: bladder and urinary tract cancer

Cohort 4: other solid tumors

Ado-trastuzumab emtansine at 3.6 mg/kg IV day 1 every 21 days until disease progression by RECIST v1.1 or unacceptable toxicity

For each cohort, enroll 7 patients in stage 1
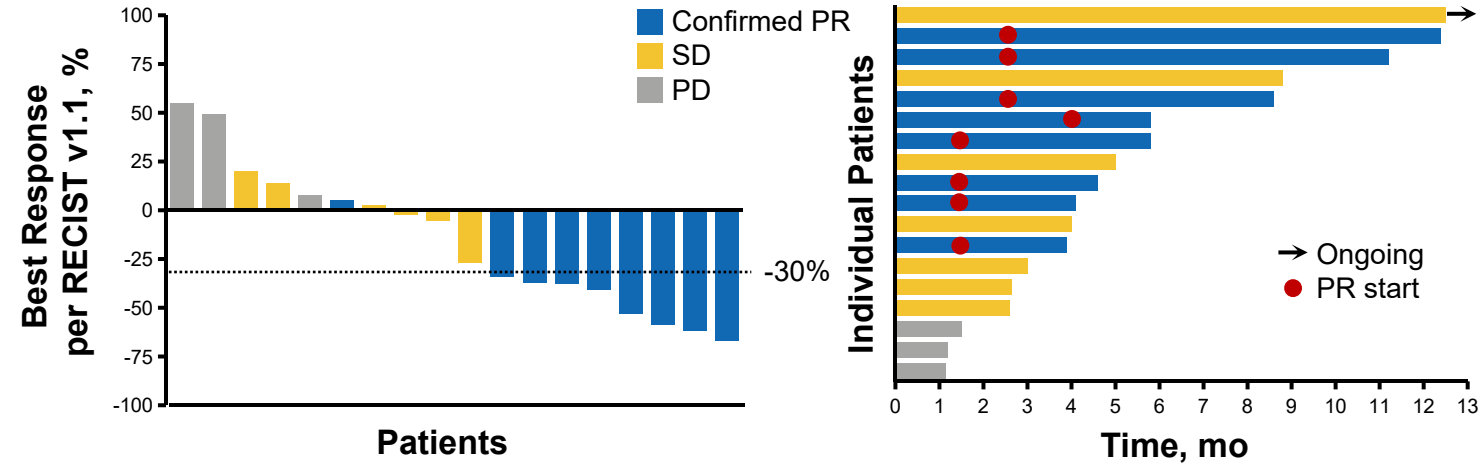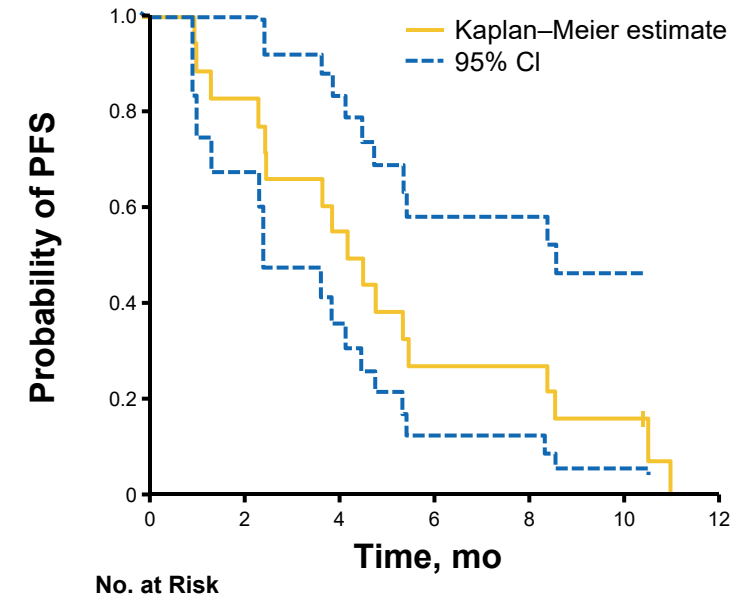
1. Li BT et al. *J Clin Oncol*. 2018;36:2532-2537.
2. Liu S et al. International Association for the Study of Lung Cancer 2021 Targeted Therapies of Lung Cancer Meeting (TTLC 2021). February 18, 2021.

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Novel Anti-HER2 ADC:
Trastuzumab Deruxtecan (T-DXd; DS-8201a)
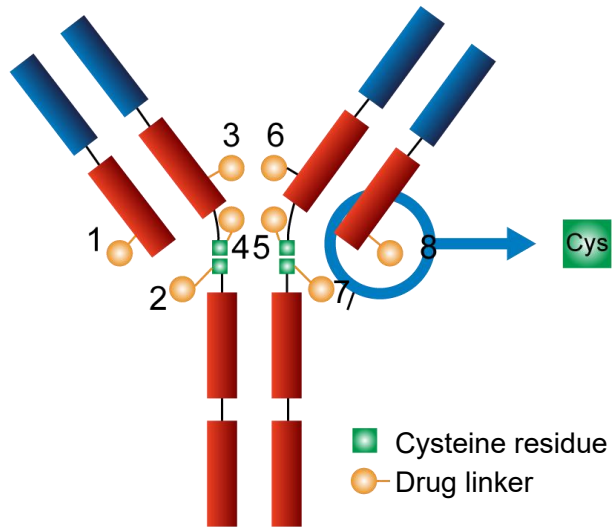
Conjugation Chemistry
The linker is connected to cysteine residue of the antibody

■ Cysteine residue
● Drug linker

Proprietary drug linker

Payload (DXd)
Exatecan derivative
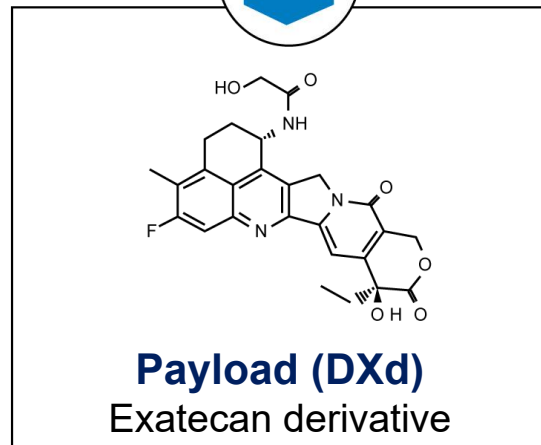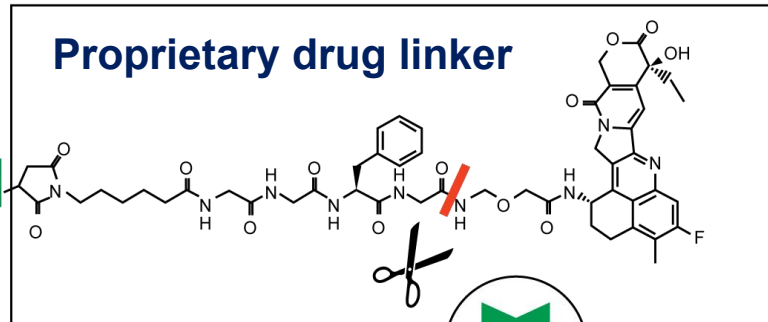
- ADC composed of three components
  - Humanized HER2-targeted mAb
  - Topoisomerase I inhibitor "payload"
  - Tetrapeptide-based cleavable linker

- High drug-to-antibody ratio (≈8:1)

- High potency payload that is membrane-permeable → nearby cells in tumor targeted regardless of HER2 expression ("bystander antitumor effect")

Characteristic Differences Between T-DXd and T-DM1[1-5]

HER2-Targeting ADCs With a Similar mAB Backbone

Trastuzumab deruxtecan (T-DXd)

Trastuzumab emtansine (T-DM1)

T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander antitumor effect?**	No
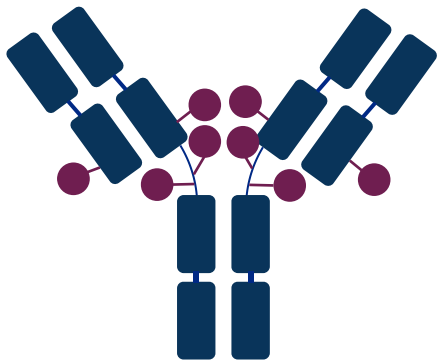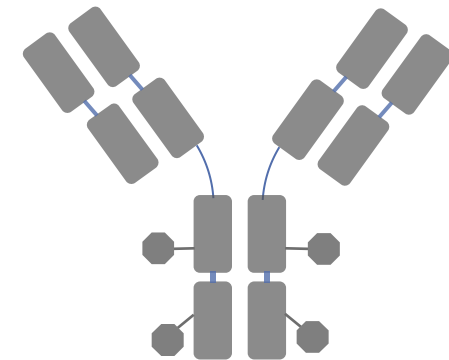
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108.
3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47.

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Response by BICR – 90-Day Follow Up (June 22, 2022 DCO for T-DXd 5.4 mg/kg arm)

Response Assessment by BICR	Prespecified early cohort T-DXd 5.4 mg/kg n = 52	
	DCO: March 24, 2022	DCO: June 22, 2022
Confirmed ORR,[a] % (95% CI)	53.8 (39.5, 67.8)	57.7 (43.2, 71.3)
Complete response, %	1.9	1.9
Partial response, %	51.9	55.8
Median DoR,[b] months (95% CI)	NE (4.2, NE)	8.7 (7.1, NE)

- As the median DoR for the T-DXd 5.4 mg/kg dose arm was not reached at the March 24, 2022 cutoff, an additional 90-day follow-up response analysis was conducted

  - Median DoR was reached with the additional follow-up response analysis

  - Confirmed ORR by BICR continued to demonstrate strong and clinically meaningful antitumor activity

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[a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. ORR 95% CI was calculated using the Clopper-Pearson method.
[b]Median DoR was based on Kaplan-Meier estimate. 95% CI was calculated using the Brookmeyer-Crowley method.

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Best Percent Change in Tumor Size by BICR

T-DXd 5.4 mg/kg (n = 52)

Legend:
- Both prior platinum therapy and PD-(L)1 therapy (n = 37)
- Prior platinum therapy but no PD-(L)1 therapy (n = 15)
- ✳ Patient with best percent change of zero

Best (minimum) change	T-DXd 5.4 mg/kg
n	49
Mean, %	**-38.6**
SD (range), %	26.9 (-100, 6.0)

T-DXd 6.4 mg/kg (n = 28)

Legend:
- Both prior platinum therapy and PD-(L)1 therapy (n = 22)
- Prior platinum therapy but no PD-(L)1 therapy (n = 6)
- ✳ Patient with best percent change of zero

Best (minimum) change	T-DXd 6.4 mg/kg
n	26
Mean, %	**-34.6**
SD (range), %	25.8 (-100, 7.0)

Data cutoff: Mar 24, 2022.
The red line at 20% indicates progressive disease, and the green line at −30% indicates a partial response.

Overall Safety Summary

Safety analysis set[a]

Drug-related TEAE, %

	T-DXd 5.4 mg/kg n = 101[c]	T-DXd 6.4 mg/kg n = 50
Any grade	92.1	100
Grade ≥3	31.7	58.0
Associated with drug discontinuation	7.9	16.0
Associated with dose reduction	9.9	26.0
Associated with drug interruption	13.9	30.0
Associated with death[b]	1.0	2.0

	T-DXd 5.4 mg/kg n = 101[c]	T-DXd 6.4 mg/kg n = 50
Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

Data cutoff: Mar 24, 2022.
[a]The safety analysis set included all randomized patients who received ≥1 dose of study drug. [b]In the safety analysis set, 6 patients overall had a TEAE associated with an o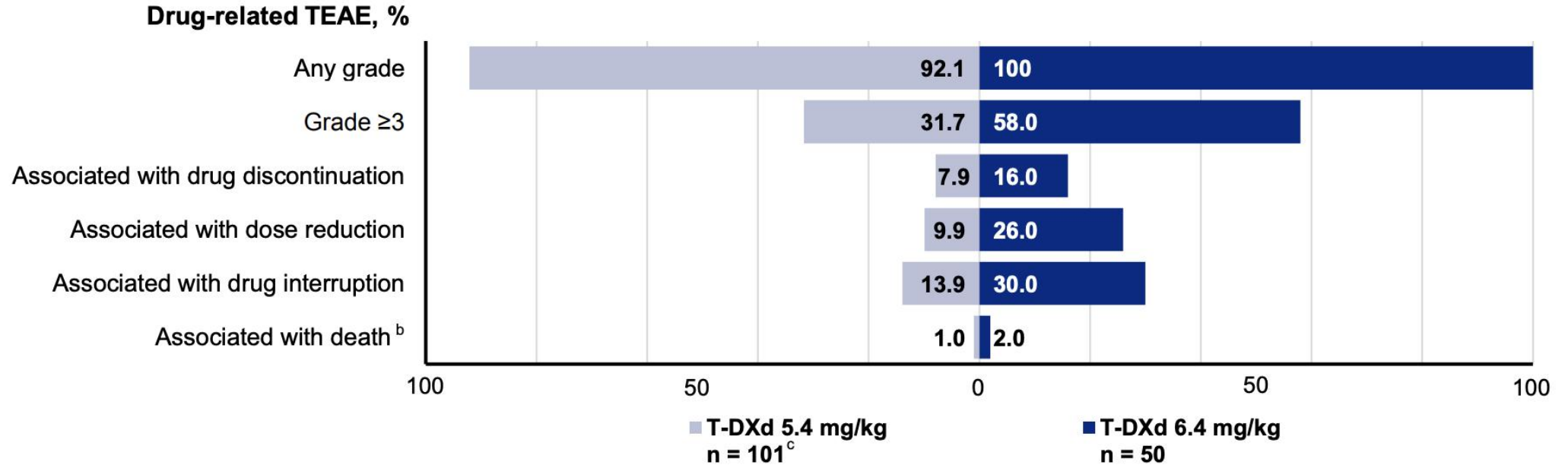utcome of death (2 drug-related deaths); 4 of the patients received T-DXd 5.4 mg/kg of whom 2 had malignant neoplasm progression, 1 had malignant lung neoplasm, and 1 had pneumonitis which was subsequently adjudicated by the adjudication ILD committee as not ILD; of the 2 patients who received T-DXd 6.4 mg/kg, 1 had a generally abnormal physical condition and 1 had ILD which was later confirmed by the ILD adjudication committee. [c]1 patient in the 5.4 mg/kg arm was randomized but did not receive treatment before discontinuing from the study.
TEAE, treatment-emergent adverse event.

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD[a]	Safety analysis set[b]	
	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**
Grade 1	3 (3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)

- The rate of adjudicated drug-related ILD was lower in the T-DXd 5.4 mg/kg arm compared with the 6.4 mg/kg arm
- Most cases of adjudicated drug-related ILD were low grade (grade 1/2)

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New and First FDA Approval for *HER2*-mutant NSCLC

On August 11, 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for *HER2*-mutant NSCLC.

FDA also approved the Oncomine™ Dx Target Test (tissue) and the Guardant360® CDx (plasma) as companion diagnostics for trastuzumab deruxtecan. If no mutation is detected in a plasma specimen, the tumor tissue should be tested.

Patritumab Deruxtecan (HER3-DXd; U3-1402): Novel Anti-HER3 ADC[1]

Patritumab (Anti-HER3 Antibody)

Proprietary drug linker
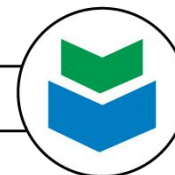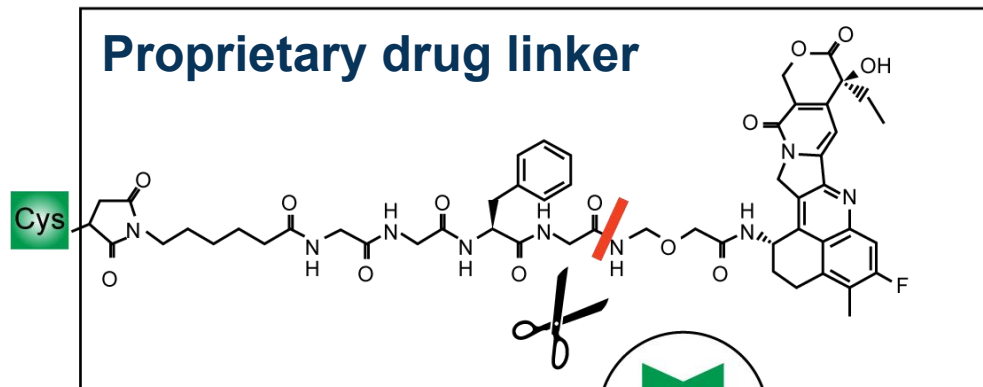
Cys

Cysteine residue

Drug linker

Conjugation chemistry
The linker is connected to cysteine residue of the antibody

Payload (DXd)
Exatecan derivative

1. Yonemori K et al. *Ann Oncol*. 2019;30(suppl 3):iii47-iii64.

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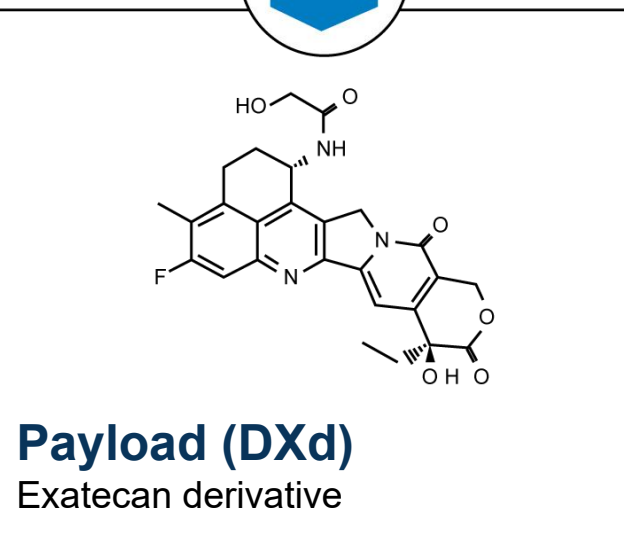
HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance[1,2]

Confirmed ORR **39%** Median DOR **6.9 mo** Median PFS **8.2 mo**
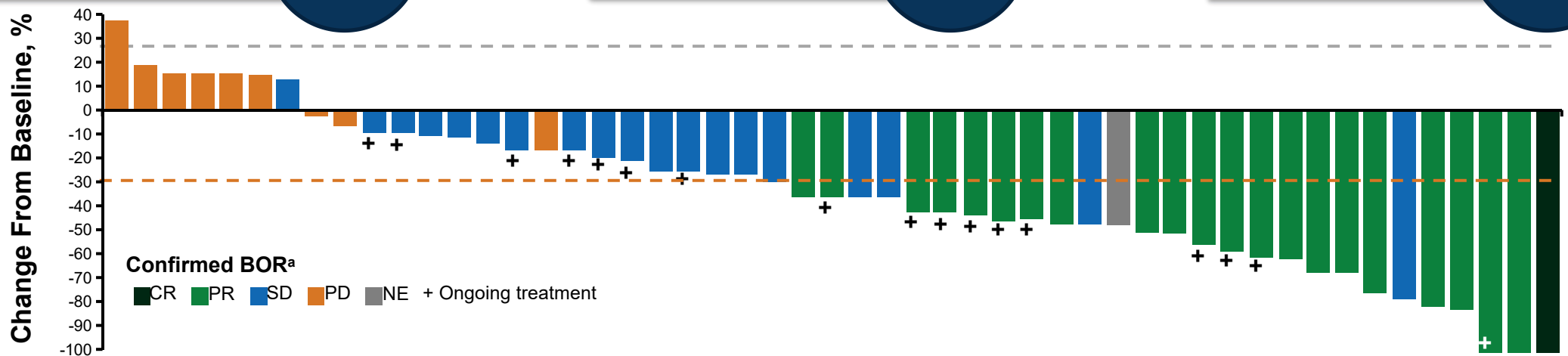
Confirmed BOR[a]: CR | PR | SD | PD | NE | + Ongoing treatment

[a] Six patients had BORs of NE due to no adequate postbaseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (<5 weeks) and is shown in gray.
[b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood; collected prior to treatment with HER3-DXd.
[c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*. Data cutoff: September 24, 2020.
1. Janne P et al. ASCO 2021. Abstract 9007. 2. Janne P et al. Cancer Discov. 2022;12:74-89.

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HER3-DXd Was Associated With a Manageable Safety Profile and a Low Rate of Discontinuation Due to AEs[1,2]

TEAEs, n (%) Median Treatment Duration: 5.7 (Range, 0.7-28.3), mo	5.6 mg/kg (n = 57)	All Doses (N = 81)
Any TEAE, n (%)	57 (100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE, n (%)	42 (74)	52 (64)
Treatment-related TEAE, n (%)	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
ILD[c]	4 (7)	4 (5)
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0

TEAEs Grade ≥3 in ≥5% of Patients (n = 81)
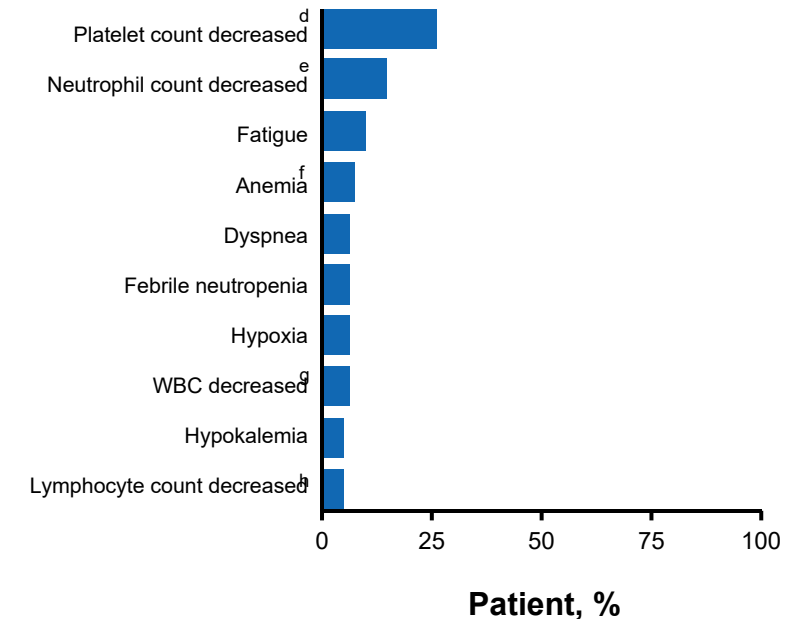
- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5

- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

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TROP2

- TROP2, a transmembrane glycoprotein, is highly expressed in NSCLC and other solid tumors[1-5]
  - High TROP2 expression is associated with poor prognosis, making it a promising therapeutic target[6]

B **Adenocarcinoma**

No/low TROP2 expression (n=98)

High TROP2 expression (n=172)

Log-rank: $P = 0.023$

Lenart et al, Cancers 2020
Inamura et al. Oncotarget 2018
Jiang et al. Oncol Lett 2013
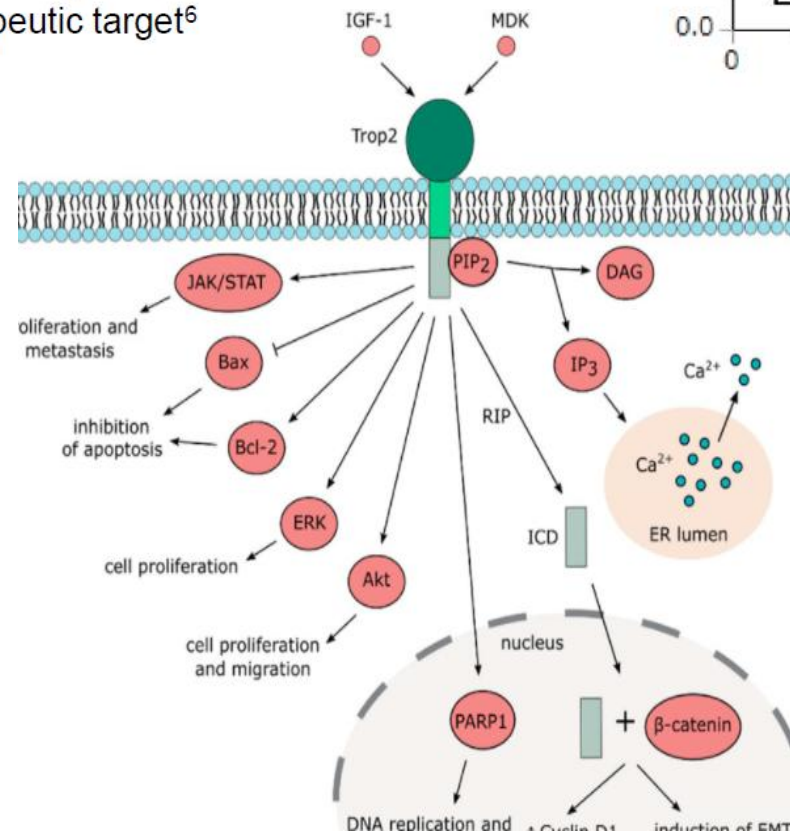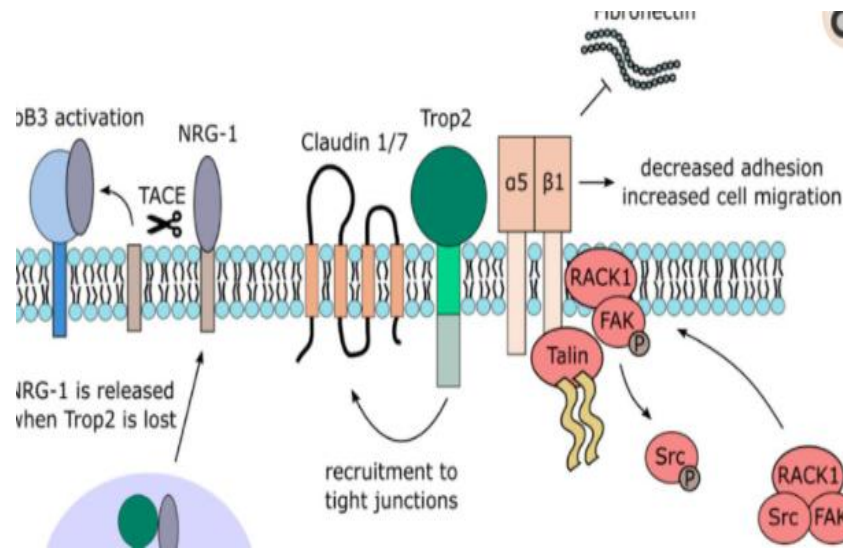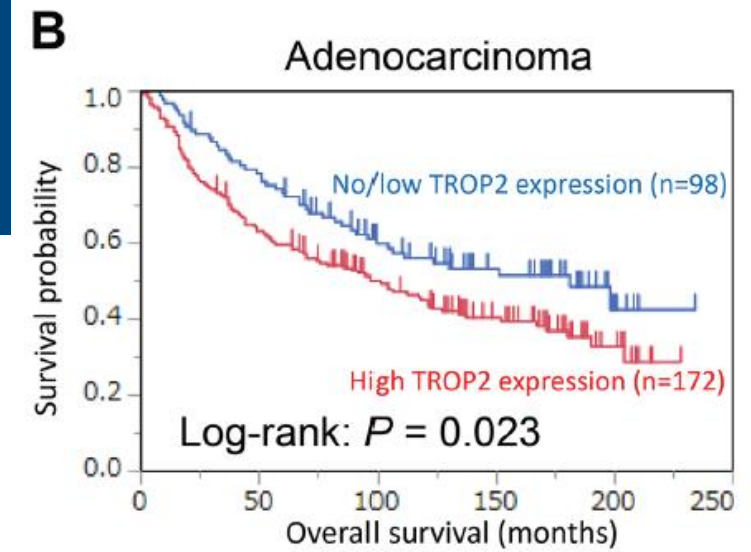
Sacituzumab govitecan
Results from IMMU-132-01
Single-arm expansion in 2L+ NSCLC

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)
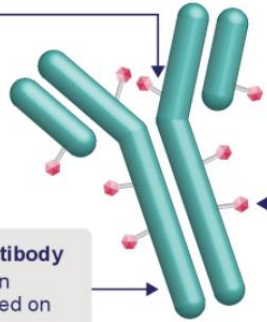
SN-38 payload
- Metabolite of topisomerase I inhibitor
- SN-38 more potent than parent compound, irinotecan

Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers
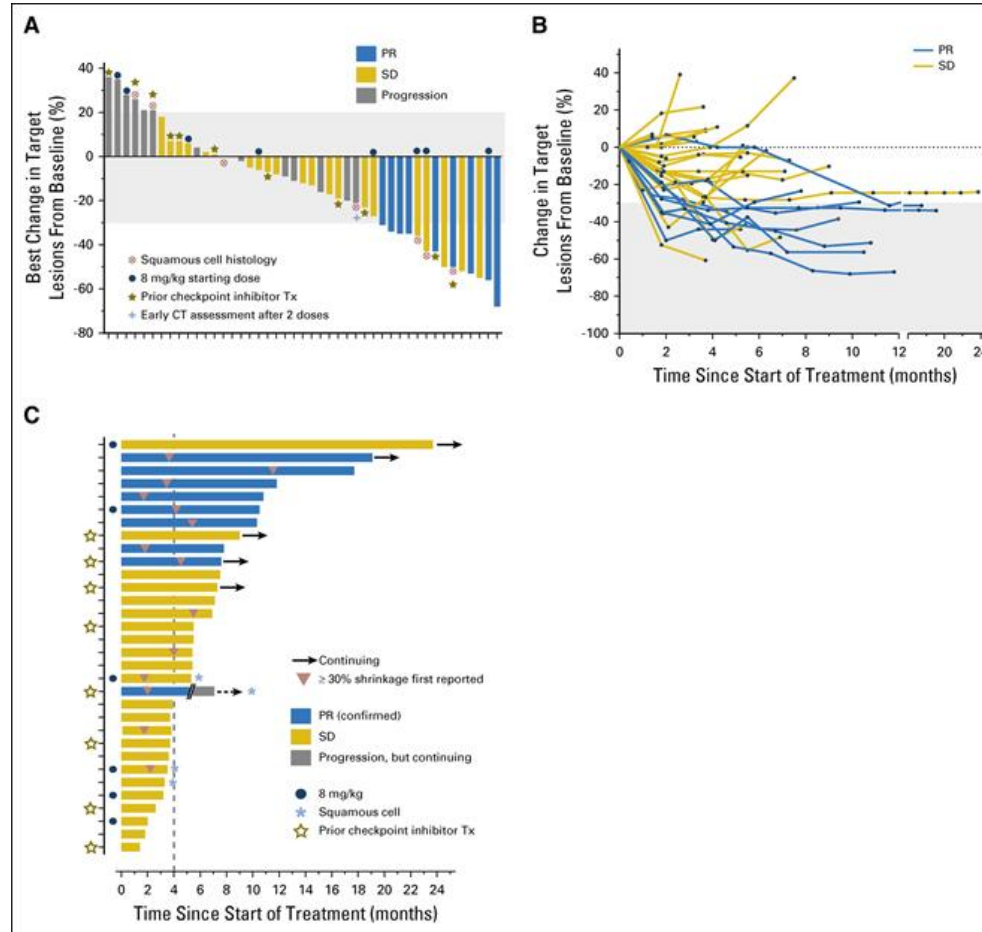
	NSCLC
Total, *n*	54
Dose (mg/kg)	8, 10, 12[b]
ORR, % (95% CI)	16.7 (7.9-29.3)
CR, *n* (%)	0
PR, *n* (%)	9 (16.7)
SD, *n* (%)	22 (40.7)
Median DOR, months, (95% CI)	6.0 (2.5-21.0)
Median OS, months, (95% CI)	7.3 (5.6-14.6)
Median PFS, months (95% CI)	4.4 (2.5-5.4)
CBR, *n* (%) [95% CI]	13 (24.1) [13.5-37.6]

Heist et al, JCO 2017
Goldenberg, Stein & Sharkey, Oncotarget 2018
Saxena et al, ASCO 2020

Datopotamab Deruxtecan (Dato-DXd; DS-1062)

Humanized anti-TROP2 IgG1 mAb

Deruxtecan[b,11]

Cleavable Tetrapeptide-Based Linker

Topoisomerase I Inhibitor Payload (DXd)
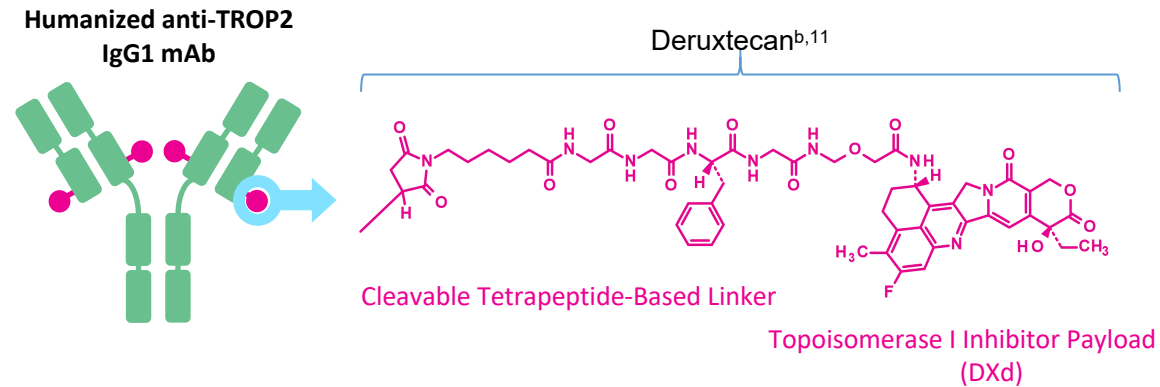
Designed With 7 Key Attributes:

- Payload mechanism of action: topoisomerase I inhibitor [a,7]
- High potency of payload [a,8]
- Optimized drug to antibody ratio ≈4 [a,c,7]
- Payload with short systemic half-life [a,c,8]
- Stable linker-payload [a,8]
- Tumor-selective cleavable linker [a,8]
- Bystander antitumor effect [a,8,12]

Figure 2. Study Design

Key inclusion criteria

- Relapsed/refractory advanced/metastatic NSCLC
- Unselected for TROP2 expression[a]
- Aged ≥18 (US) or ≥20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST version 1.1
- Stable, treated brain metastases allowed

Dose escalation[13]

Dato-DXd 0.27 mg/kg to 10 mg/kg Q3W[b]

MTD established: 8 mg/kg Q3W

Dose expansion[c]

50 patients at 4 mg/kg

50 patients at 6 mg/kg

80 patients at 8 mg/kg

Primary objectives
- Establish MTD, safety, tolerability

Secondary objectives[d]
- Efficacy,[e] PK

Data cutoff, January 8, 2021

Meric-Bernstam. pASCO. Abstract 9058

TROPION PanTumor01
NSCLC Cohort

Table 4. 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 (%)	12 (24)	13 (26)	19 (24)
CR/PR	10 (20)	11 (22)	19 (24)
CR/PR (too early to be confirmed)	2 (4)	2 (4)	0
DCR, n (%)	38 (76)	35 (70)	64 (80)
PD, n (%)	7 (14)	10 (20)	7 (9)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (4.1-NE)	9.0 (5.8-NE)
PFS, median (95% CI), mo[b]	4.3 (3.5-8.4)	6.9 (2.7-8.8)	5.2 (4.1-7.1)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] Median PFS was limited by immature duration of follow-up in the 4- and 6-mg/kg dosing cohorts.

Figure 4. Best Change in Sum of Diameters (BICR)
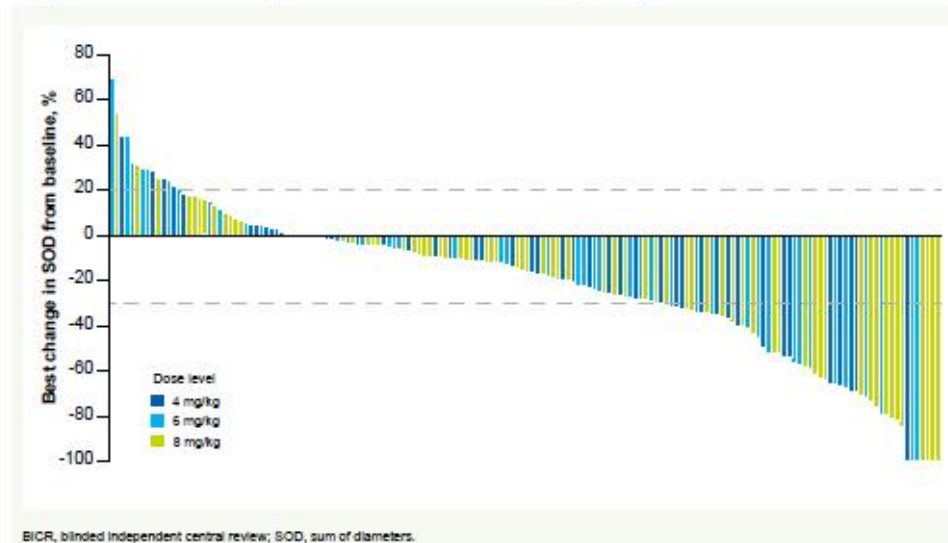
BICR, blinded independent central review; SOD, sum of diameters.

Figure 5. Change in Sum of Diameters for Target Lesion (BICR) Over Time
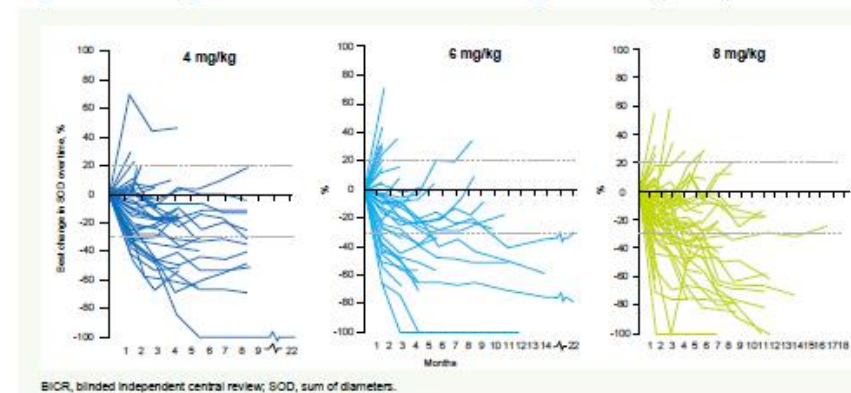
BICR, blinded independent central review; SOD, sum of diameters.

Meric-Bernstam et al. ASCO 2021, Abstract 9058

- Overall, manageable safety profile and no new safety signals observed
- Some AEs (eg, GI toxicity and anemia) may be reversible; clinical course of AEs will be further analyzed

Overall Safety Summary

Patients, n (%)	Dato-DXd Dose		
	4 mg/kg (n = 50)	6 mg/kg (n = 50)	8 mg/kg (n = 80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grade 3/4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)

TEAEs in ≥15% of Patients[b]

[a] Cases of ILD adjudicated as drug related comprised 5 patients in the 4 mg/kg cohort (1 grade 1, 3 grade , grade 4), and 11 patients
in the 8 mg/kg cohort (2 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). [b] Of 180 patients (4 mg/kg [n = 50]; 6 mg/kg [n = 50]; 8 mg/kg [n = 80]). Data cutoff: April 6, 2021.
1. Garon EB et al. WCLC 2021. Abstract MA03.02.
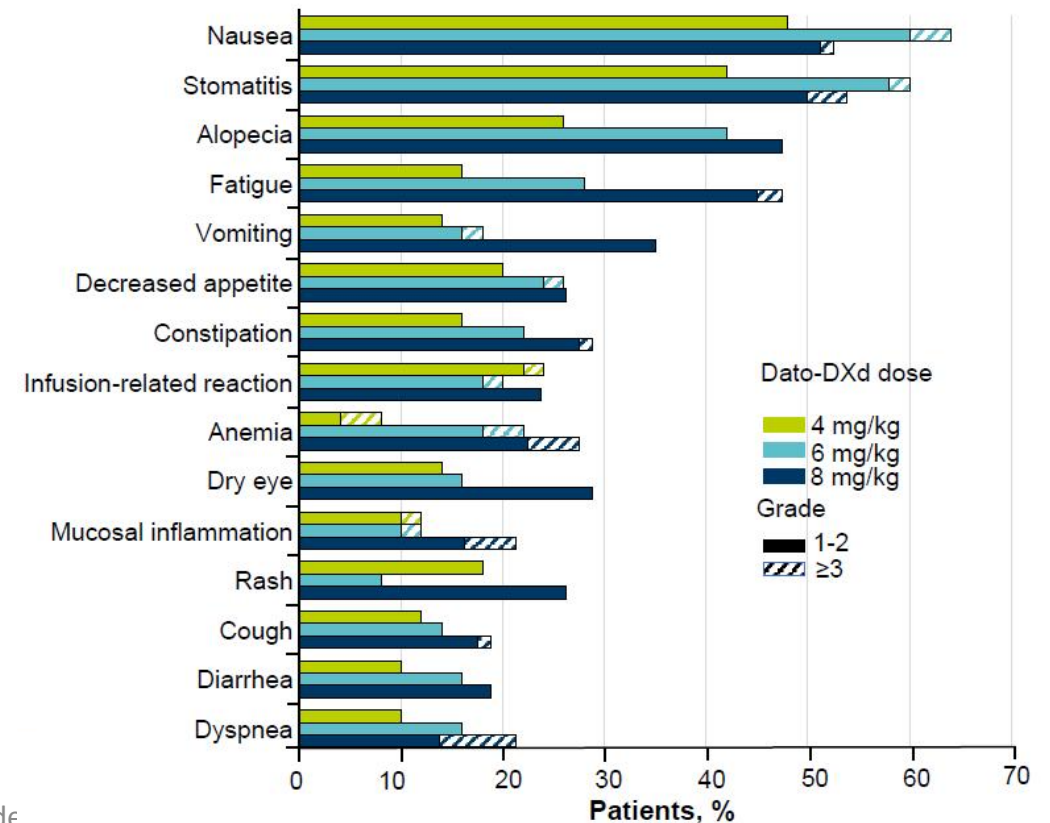
TROPION-Lung02

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]

	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20)[d]:	4 mg/kg	+	200 mg			"Doublet"
Cohort 2 (n=20)[d]:	6 mg/kg	+	200 mg			
Cohort 3 (n=17)[d]:	4 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 4 (n=20)[d]:	6 mg/kg	+	200 mg	+	carboplatin AUC 5	"Triplet"
Cohort 5 (n=7)[d]:	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	
Cohort 6 (n=4)[d]:	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	

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

In the overall population:
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

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%

Percent Change in Sum of Diameters[a]

Levy et al, WCLC 2022
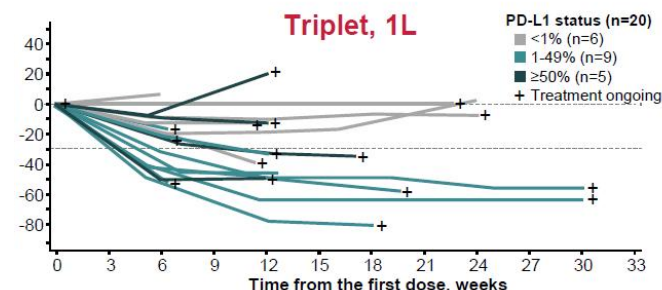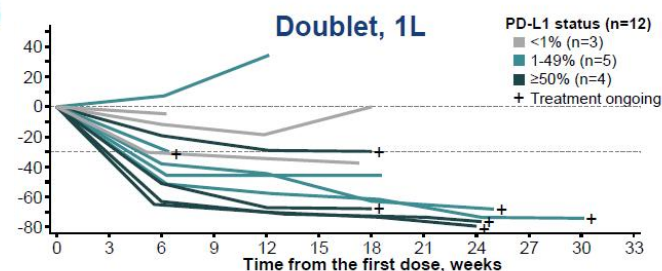
Targeting CEACAM5: ADC SAR408701 (Tusamitamab ravtansine)

- CEACAM5 (carcinoembryonic antigen-related adhesion molecule 5) overexpressed in multiple malignancies, including nonsquamous NSCLC[1,2]

SAR408701 Structure[1]
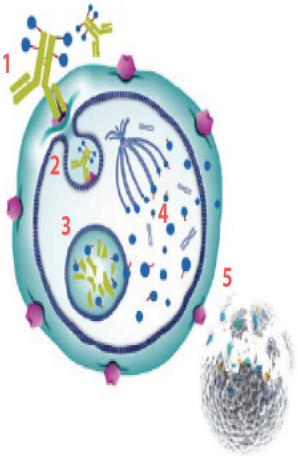
① Antibody portion of tusamitamab ravtansine binds to extracellular domain of CEACAM5

② Internalization of tusamitamab ravtansine

③ Release of DM4 into the tumor cell

④ Inhibition of microtubule assembly

⑤ Cell cycle arrest and apoptosis

SPDB Linker
Cleavable once inside cells

Humanized Ab
Targets CEACAM5

DM4 (Cytotoxic Agent)
maytansinoid derivative ravtansine

inhibiting tubulin polymerization

Average Drug Antibody Ratio (DAR) of 3.8

1. Johnson. ASCO 2020. Abstr TPS9625. 2. Gazzah. ASCO 2020. Abstr 9505.

Tusamitamab ravtansine is being developed for antitubulin-sensitive tumors with high CEACAM5 expression

Cancer type	Population with high CEACAM5 expression*	1L metastatic incidence (thousands, US)	Antitubulin sensitive
Gastric adenocarcinoma	25-30%	12	Yes
NSCLC adenocarcinoma	20-30%	74	Yes
Pancreatic adenocarcinoma	10-20%	27	Yes
Metastatic breast cancer	5-15%	39	Yes
Colorectal adenocarcinoma	80-90%	44	No
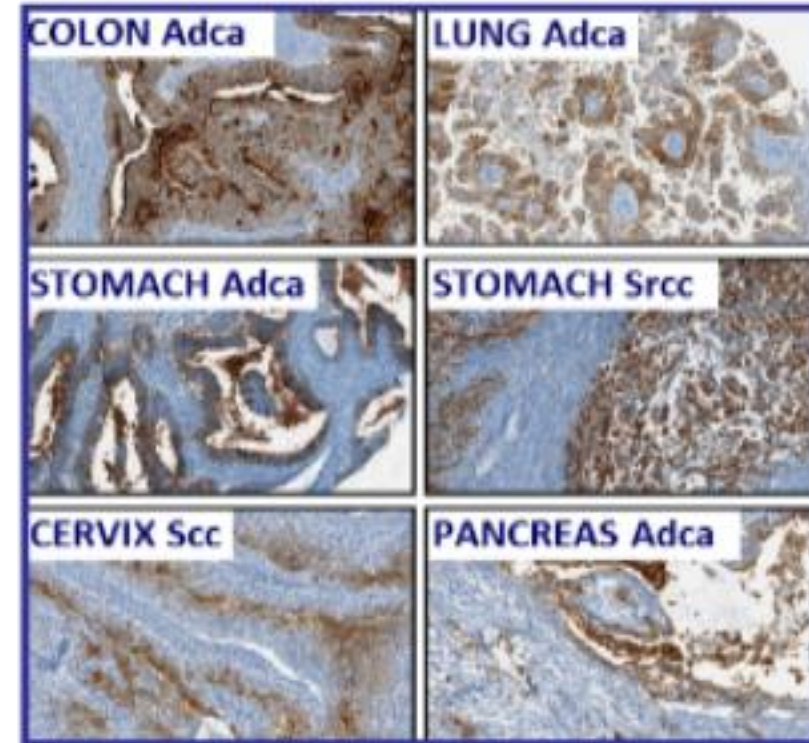
CEACAM5 is expressed with significant frequency and intensity in several cancer types

ASCO 2020 – Abstract 950 - Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) – Gazzah et al

Expansion Phase of tusamitamab ravtansine (MTD 100mg/m² Q2W) in NSCLC

A first-in-human study for the evaluation of the safety, PK and antitumor activity of SAR408701 in patients with advanced solid tumors (NCT02187848)
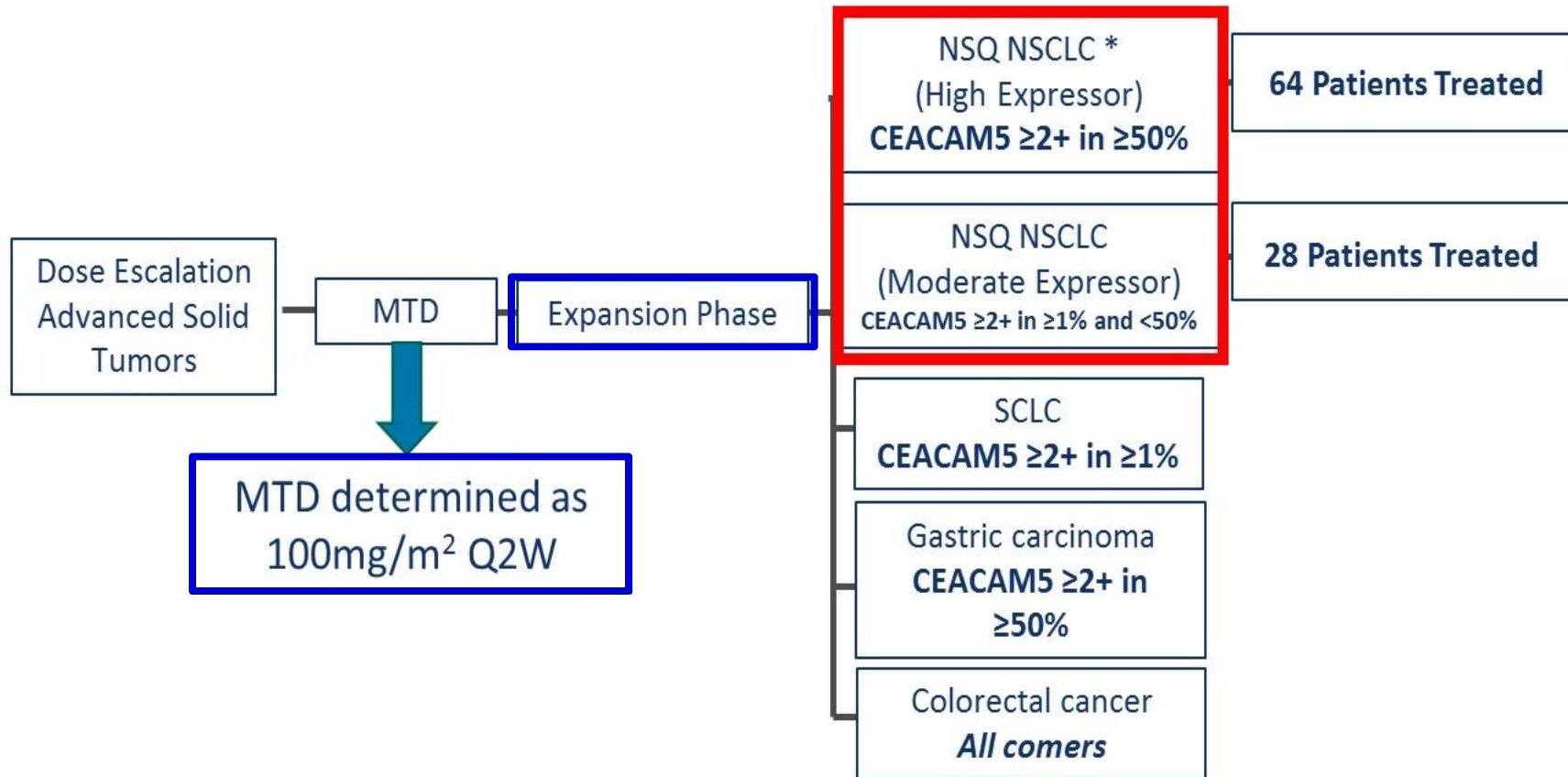
Expansion Phase in NSCLC

Inclusion restricted with CEACAM5 expression, via IHC testing in most recent archival tissue sample

- **High expressor cohort: CEACAM5 at ≥50% at ≥2+ intensity**
  - **20% of NSQ NSCLC**
- **Moderate expressor cohort: CEACAM5 between ≥1% and <50% at ≥2+ intensity**
  - **24% of NSQ NSCLC**

- Tumor assessments - every 4 cycles (8 weeks)

Primary endpoints: DLT (escalation phase), overall response rate (ORR; expansion phase)
Secondary endpoints: Safety, recommended Phase 2 dose identification, duration of response (DOR)
*High Expressor NSCLC – 2 interim analyses (at first 15 treated patients and at first 30 treated patients)

A.Gazzah et al, ASCO 2020

Patient characteristics

Characteristic	High expressors (n = 64)	Moderate expressors (n = 28)	Total (n = 92)
Age, years			
Median (range)	61.5 (41-91)	64.5 (31-73)	62.5 (31-91)
Race, n (%)			
White	52 (81.3%)	25 (89.3%)	77 (83.7%)
Asian	12 (18.8%)	3 (10.7%)	15 (16.3%)
Sex, n (%)			
Male	37 (57.8%)	10 (35.7%)	47 (51.1%)
Female	27 (42.2%)	18 (64.3%)	45 (48.9%)
ECOG PS, n (%)*			
0	19 (29.7%)	7 (25.0%)	26 (28.3%)
1	45 (70.3%)	20 (71.4%)	65 (70.7%)
Number of organs involved, n (%)			
≥3	38 (59.4%)	14 (50%)	52 (56.5%)
Number of prior regimens for advanced disease			
Median (range)	3.0 (1-10)	3.0 (1-7)	3.0 (1-10)
Prior treatment, n (%)			
Anti-tubulin	39 (60.9%)	17 (60.7%)	56 (60.9%)
Anti-PD-1/PD-L1	45 (70.3%)	24 (85.7%)	69 (75.0%)

A total of 91 patients had adenocarcinoma; *One patient in the moderate expressor cohort had an ECOG PS of 3.

A.Gazzah et al, ASCO 2020

Best overall response

Overall Population

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%)

Best relative tumor shrinkage: Patients who had unconfirmed PR (>30% decrease) were counted as SD for BOR

DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Best Relative Tumor Shrinkage – High Expressor Cohort

20.3%
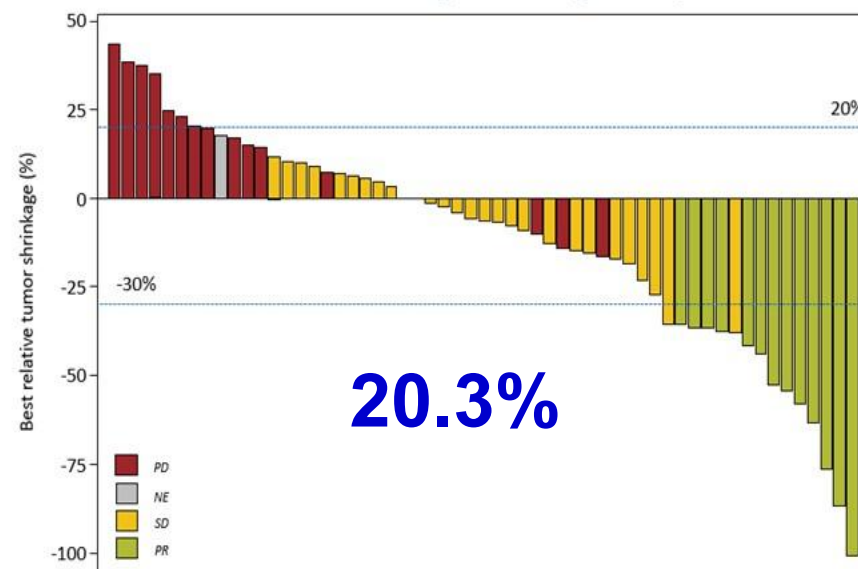
Patients treated with SAR408701 (100 mg/m²)

Best Relative Tumor Shrinkage – Moderate Expressor Cohort

7.1%

Patients treated with SAR408701 (100 mg/m²)

A.Gazzah et al, ASCO 2020

Dose intensity and duration of treatment

A.Gazzah et al, ASCO 2020
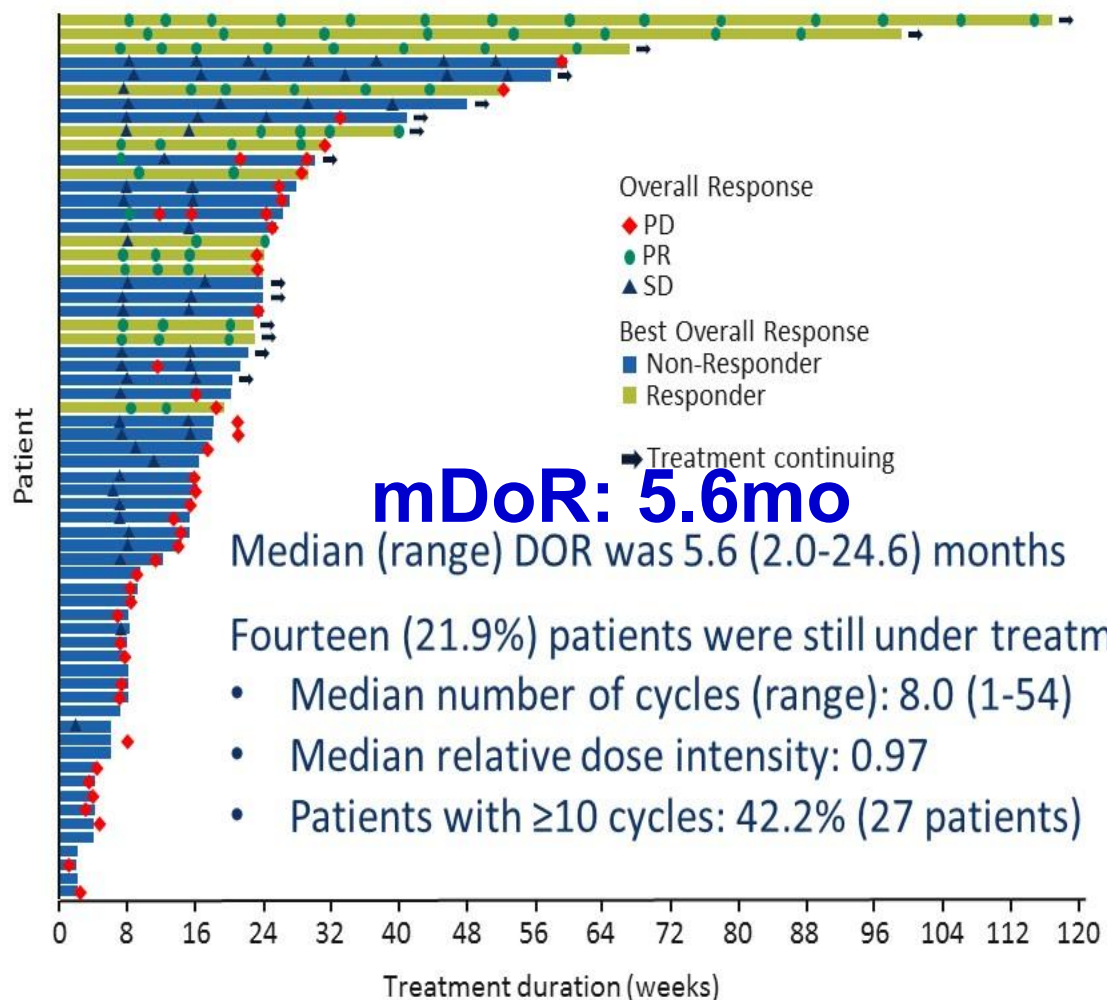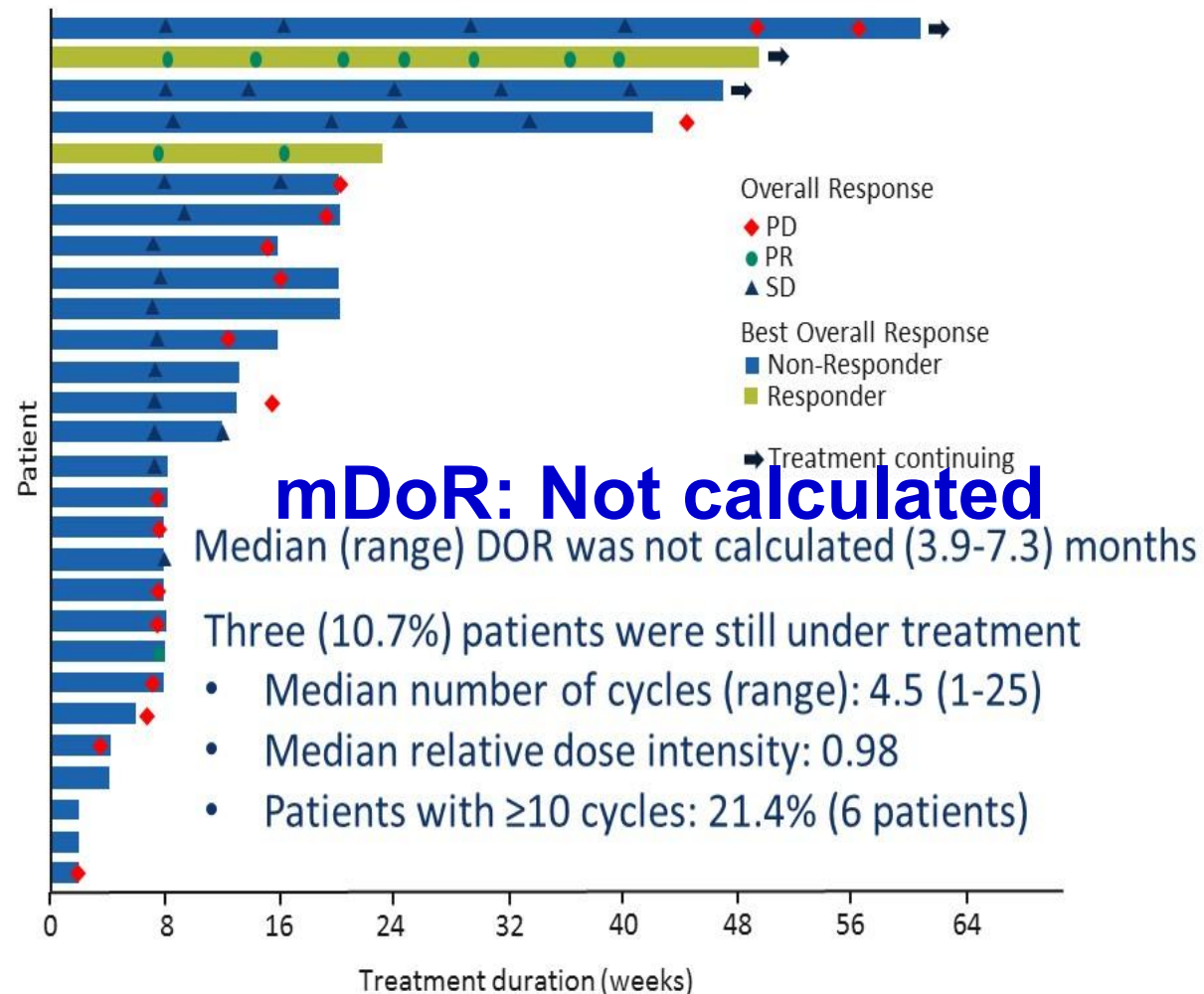
Treatment-emergent adverse events (TEAEs)
Pooled data of NSCLC cohorts

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)	**38%** 35 (38.0%)	**10.9%** 10 (10.9%)
Asthenia	34 (37.0%)	4 (4.3%)
Peripheral neuropathy (SMQ*)	**27%** 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)

Dose modification and ocular events

Ocular Events	SAR408701 100 mg/m² Q2W (n=92)	
	Grades 1-2, n (%)	Grade 3, n (%)
Corneal AE	25 (27.2%) **27%**	10 (10.9%) **11%**
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 25pts (27%) 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%)
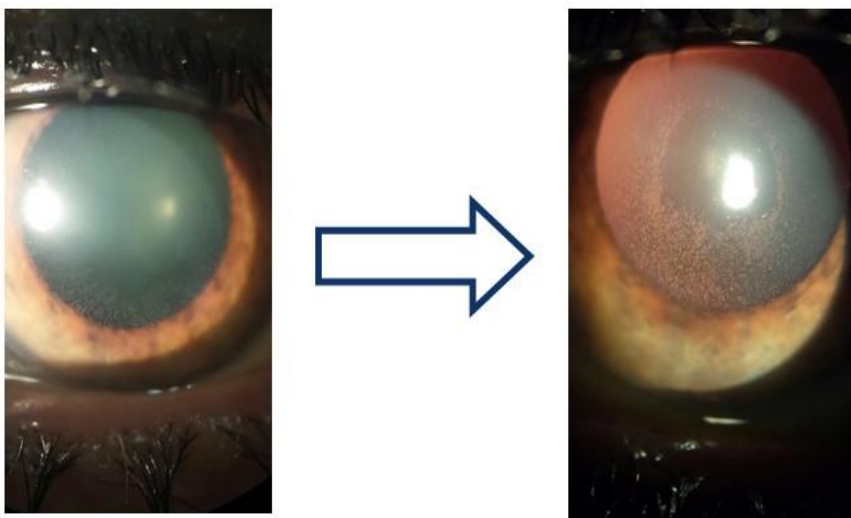
Ocular Events:

- 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

A.Gazzah et al, ASCO 2020

Tusamitamab ravtansine (SAR408701) in pts with advanced solid tumors: first-in-human dose-escalation study

Dose-escalation schematic
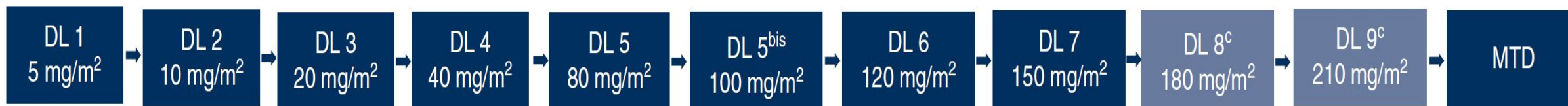
Baseline characteristics by dose level

Characteristic	Dose of tusamitamab ravtansine (mg/m²) administered Q2W								All patients (N = 31)
	5 (n = 2)	10 (n = 4[b])	20 (n = 1)	40 (n = 3)	80 (n = 3)	100 (n = 6)	120 (n = 9)	150 (n = 3)	
Age, years	64 (61, 67)	56.5 (52, 64)	53	52 (49, 74)	57 (44, 60)	61.5 (43, 74)	63 (48, 71)	54 (52, 60)	59 (43, 74)
Male sex, n (%)	2	4	0	0	1	6	5	1	19 (61.3)
ECOG PS score, n (%)									
0	0	2	1	0	2	3	5	1	14 (45.2)
1	2	2	0	3	1	3	4	2	17 (54.8)
Body surface area, m²	2.1 (2.1, 2.2)	1.9 (1.8, 2.1)	1.7	1.4 (1.3, 1.6)	1.6 (1.5, 2.1)	1.8 (1.5, 2.0)	1.9 (1.7, 2.6)	1.7 (1.7, 1.8)	1.8 (1.3, 2.6)
Primary tumor location, n (%)									
Colorectal	1	2	1	1	1	3	7	2	18 (58.1)
Stomach	0	0	0	2	2	2	0	1	7 (22.6)
Gastroesophageal junction	1	2	0	0	0	0	0	0	3 (9.7)
Pancreas	0	0	0	0	0	1	0	0	1 (3.2)
Breast	0	0	0	0	0	0	1	0	1 (3.2)
Esophageal	0	0	0	0	0	0	1	0	1 (3.2)
Measurable disease, n (%)	2	3	1	3	2	5	9	2	27 (87.1)
Number of prior regimens, n	2.5 (1, 4)	3 (2, 3)	3	4 (3, 4)	3 (2, 6)	3.5 (2, 5)	3 (2, 9)	4 (2, 4)	3 (1, 9)
Prior anti-tubulin exposure, n (%)	0	1	0	2	1	2	2	1	9 (29.0)
CEACAM5 expression[a], n (%)									
<50%	1	1	0	2	2	1	3	2	12 (38.7)
50%-79%	1	2	0	1	0	1	1	1	7 (22.6)
≥80%	0	1	1	0	1	4	5	0	12 (38.7)
Circulating CEA level, n (%)									
<5 µg/l	0	0	0	2	1	3	3	1	10 (33.3)
>5 µg/l	2	4	1	1	2	3	5	2	20 (66.7)

38%
22%
38%

66%

Pts with at least one DLT event (DLT-assessable population)

MTD 100mg/m² Q2W

Tusamitamab ravtansine dose level (mg/m²)	Patients treated, n	Patients with DLT/patients assessable for DLT, n/n	DLT event in C1−C2, grade, cycle of occurrence (total cycles)	Event meeting DLT definition occurring after C1−C2, grade, cycle of occurrence (total cycles)	Outcome
5	2	0/1			
10	4	0/3			
20	1	0/1			
40	3	0/3			
80	3	0/3			
100	6	0/6		Keratopathy, G3, C12 (16)	Recovered/resolved
120	9	3/8 **3/8pts**	**Keratopathy**, G3, C2 (10) **Keratopathy**, G3, C2 (11) **Keratopathy**, G3, C2 (4)	Punctate keratitis G3, C6 (10) Hemorrhagic erosive colitis, G4, C5 (5) Neutropenia, G4, C5, (5)	Recovered/resolved Recovered/resolved Recovered/resolved Recovered/resolved Recovered/resolved
150	3	2/3 **2/3pts**	**Keratopathy**, G3, C2 (2) **Keratopathy**, G3, C2 (4)		Recovered/resolved Recovered/resolved

The DLT determined to be reversible and manageable dose-related keratopathy
The MTD determined to be 100 mg/m2

Treatment-emergent adverse events occurring in ≥10% of pts by dose level (safety population)

Event	Dose of tusamitamab ravtansine (mg/m^2) administered Q2W					MTD 100mg/m^2 Q2W			All patients (N = 31)
	5 (n = 2)	10 (n = 4)	20 (n = 1)	40 (n = 3)	80 (n = 3)	100 (n = 6)	120 (n = 9)	150 (n = 3)	
Asthenia	0	1	1	0	0	2	3	1	8 (25.8%)
Decreased appetite	1	0	0	2	0	2	2	1	8 (25.8%)
Keratopathy	0	0	0	0	0	1	5	2	8 (25.8%)
Nausea	1	0	0	2	0	1	3	1	8 (25.8%)
Diarrhea	0	0	1	1	0	2	3	0	7 (22.6%)
Constipation	0	0	0	2	0	1	3	1	7 (22.6%)
Fatigue	0	0	0	1	1	1	2	1	6 (19.4%)
Abdominal pain	0	0	0	1	0	2	2	0	5 (16.1%)
Paresthesia	0	0	0	1	0	2	0	1	4 (12.9%)
Dry eye	0	0	0	1	0	1	1	1	4 (12.9%)
Vision blurred	0	0	0	1	0	1	1	1	4 (12.9%)
Cough	0	0	0	0	1	1	1	1	4 (12.9%)

Gazzah et al, Annals of onco 2021

Best overall response according to dose level

-3 pts (9.7%) had confirmed PRs with durations of 2.6, 6.1, and 4.0 mo
-11 pts (35.5%) SD, and 13 pts (41.9%) PD

-ORR achieved in 2 of 6 pts (33.3%) at 100 mg/m2, and in 1 of 9 pts (11.1%) at 120 mg/m2
-2 of the 3 pts with a PR experienced grade 3 keratopathy

Dose level (mg/m²): 5, 10, 20, 40, 80, 100, 120, 150

• indicates 0% tumor shrinkage

Tumor	GEJ	CRC	CRC	S	S	GEJ	CRC	CRC	P	S	CRC	GEJ	CRC	O	CRC	O	CRC	CRC	CRC	CRC	CRC	CRC	S	CRC	CRC	CRC
B/L CEA, ng/ml	57	64	25	6	3	25	162	2247	290	3	23	6	16	2	521	242	164	274	3	1375		178	1	2	98	5
CEACAM5 2+/3+	100	100	20	0	2	50	50	70	100	0	80	20	80	100	0	50	30	60	20	90	10	60	0	100	80	100
DOR, months																							2.6	6.1		4.0
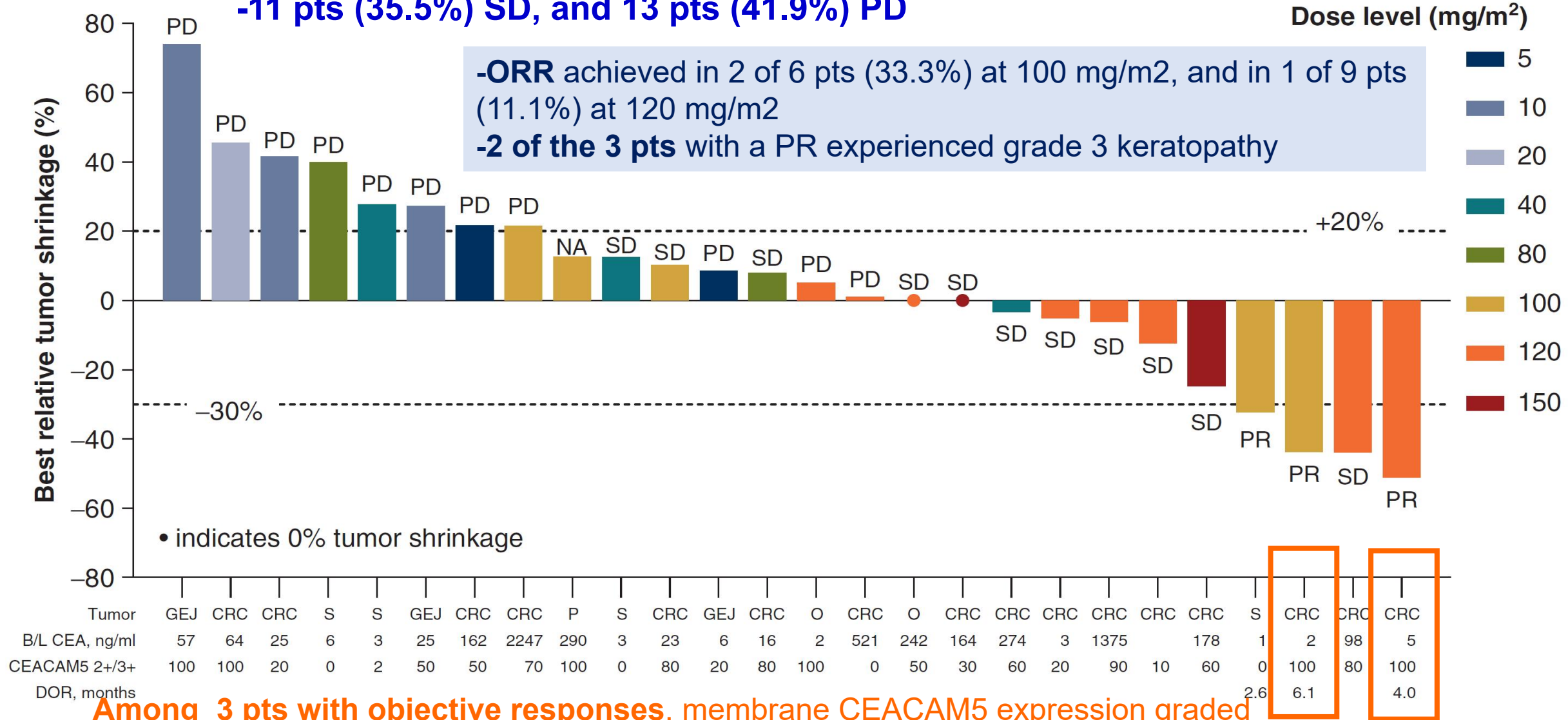
Among 3 pts with objective responses, membrane CEACAM5 expression graded as ≥2+ in 100% of the tumor cells in 2 pts, both of whom had colorectal cancer

Gazzah et al, Annals of onco 2021

Dose-escalation study of two different alternative dosing schedules of tusamitamab ravtansine (SAR408701)
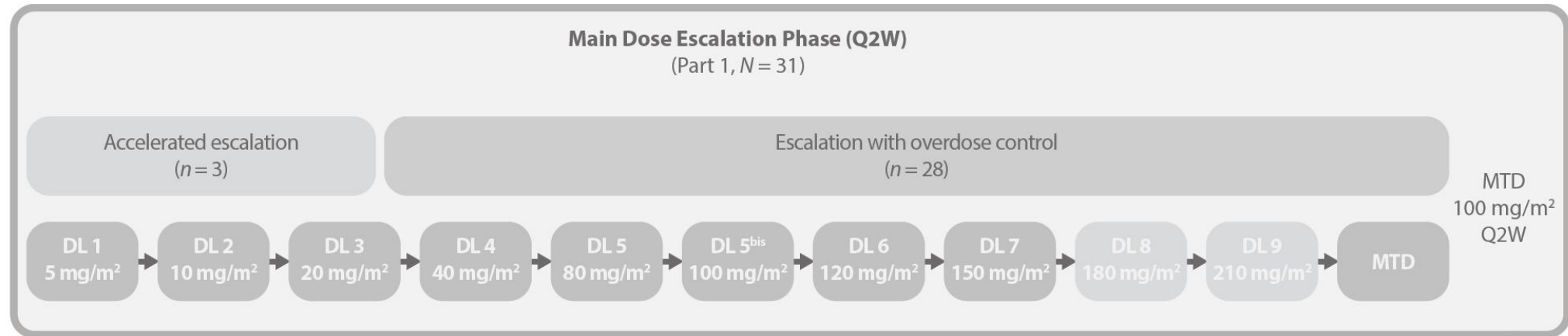
Part 2: escalating loading doses of tusamitamab ravtansine on Day 1, C1, followed by the MTD (100 mg/m^2) administered Q2W

Part 3: escalating doses of tusamitamab ravtansine administered Q3W
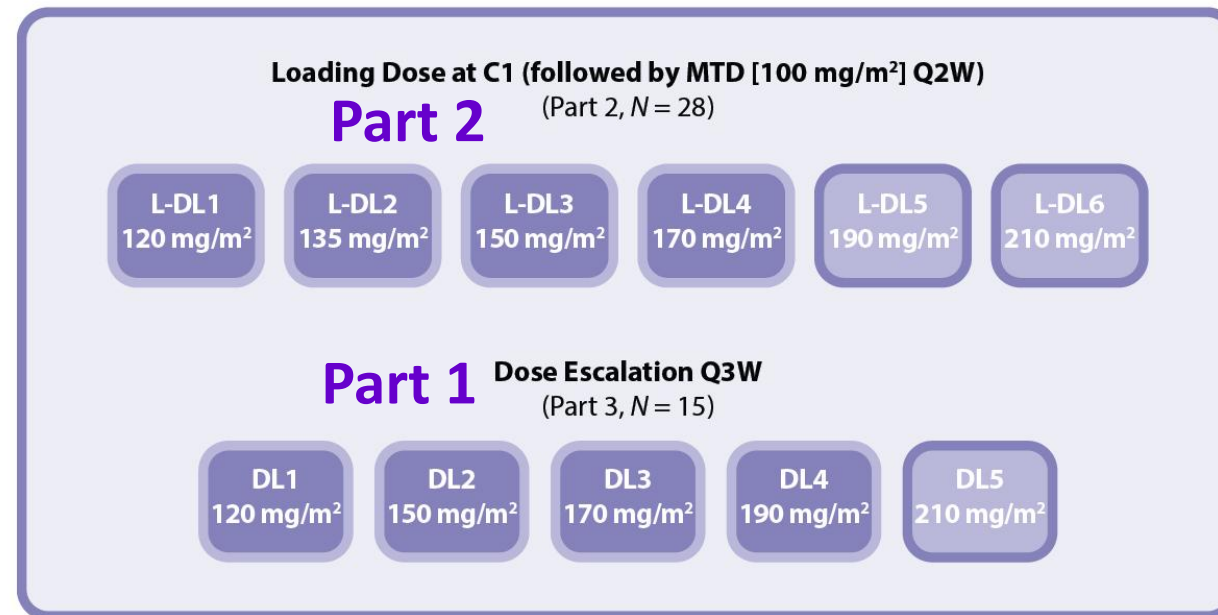
DL, dose level; L-DL, loading dose level; MTD, maximum tolerated dose; Q2W, every two weeks; Q3W, every three weeks.

Treatment-related TAEs in the loading dose part

2 of 9 DLT-evaluable pts experienced a DLT at the 170 mg/m² loading dose level
– 1 pt Grade 2 keratitis during C2 and withdrew from therapy
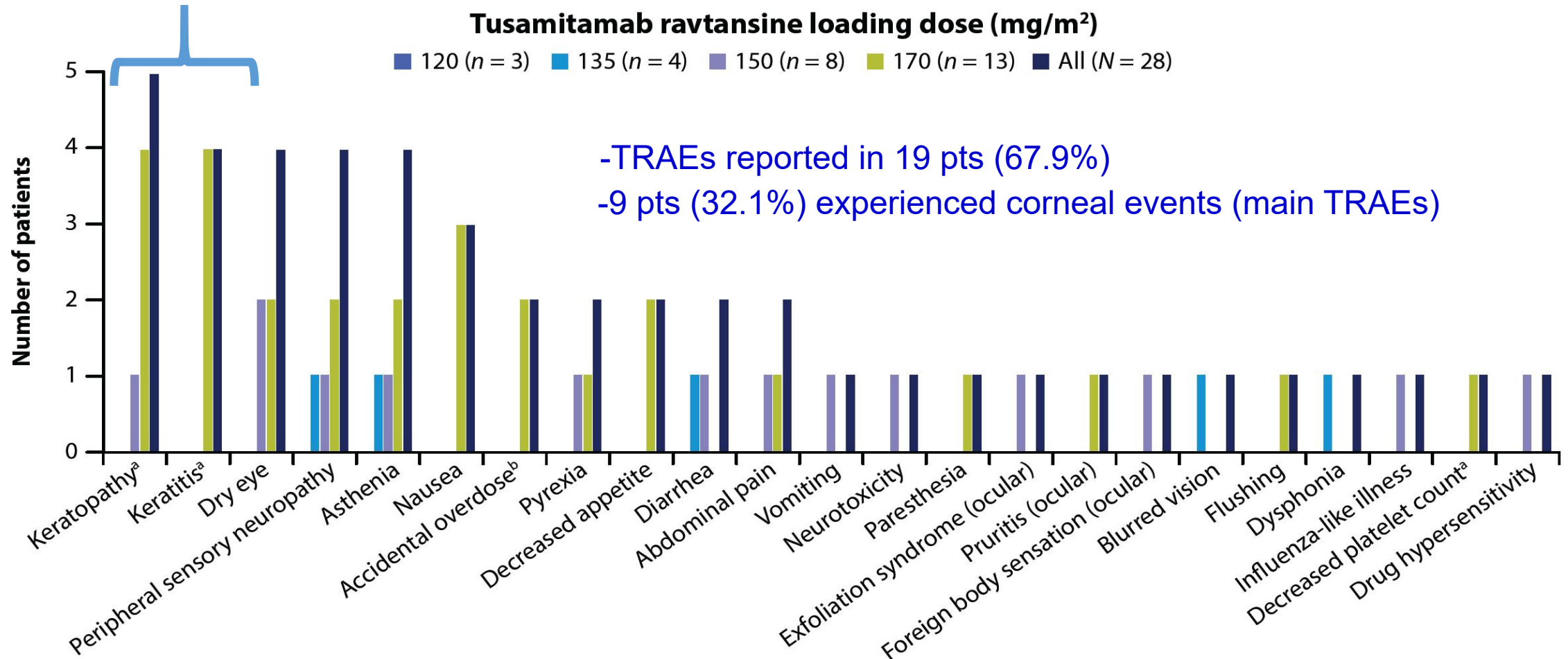– 1 pt Grade 2 keratopathy during C2, treatment delay, and then resumed trt at a reduced dose

Tusamitamab ravtansine loading dose (mg/m²)

■ 120 (n = 3) ■ 135 (n = 4) ■ 150 (n = 8) ■ 170 (n = 13) ■ All (N = 28)

-TRAEs reported in 19 pts (67.9%)
-9 pts (32.1%) experienced corneal events (main TRAEs)

Number of patients (y-axis)

Keratopathy[a], Keratitis[a], Dry eye, Peripheral sensory neuropathy, Asthenia, Nausea, Accidental overdose[b], Pyrexia, Decreased appetite, Diarrhea, Abdominal pain, Vomiting, Neurotoxicity, Paresthesia, Exfoliation syndrome (ocular), Pruritis (ocular), Foreign body sensation (ocular), Blurred vision, Flushing, Dysphonia, Influenza-like illness, Decreased platelet count[a], Drug hypersensitivity

TRAEs in pts in the Q3W part

- **2 of 3 DLT-evaluable pts experienced a DLT at the 190 mg/m² dose level**
- 1 pt Grade 3 increased transaminase levels during C1 and recovered after the drug withdrawn
- 1 pt Grade 2 keratopathy during C1 and recovered after a treatment delay and dose reduction

Tusamitamab ravtansine dose Q3W (mg/m²)

Legend: 120 (n = 3) | 150 (n = 3) | 170 (n = 6) | 190 (n = 3) | All (N = 15)

TRAEs reported in 13 pts
Corneal events reported by 6 pts, 1 of whom experienced Grade 3 keratopathy

Categories: Asthenia, Keratopathy[a], Keratitis, Peripheral sensory neuropathy, Fatigue, Nausea, Abdominal pain, Decreased appetite, Paresthesia, Diarrhea, Myalgia, Increased transaminases[a], Infusion-related reaction

Maria Vieito et al, ESMO 2021

Conclusions

- ADCs are clinically useful drugs for the treatment of most cancers
- In solid tumors multiple new ADCs are under investigation
- Toxicities of these agents seem to be related to the toxic payload and perhaps the antibody targeting the antigen of interest
- Combination studies are underway now to move some of these drugs to an earlier stage of treatment and not just in the treatment refractory setting