Antibody Drug Conjugates

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NORTH CAROLINA Oncology Association

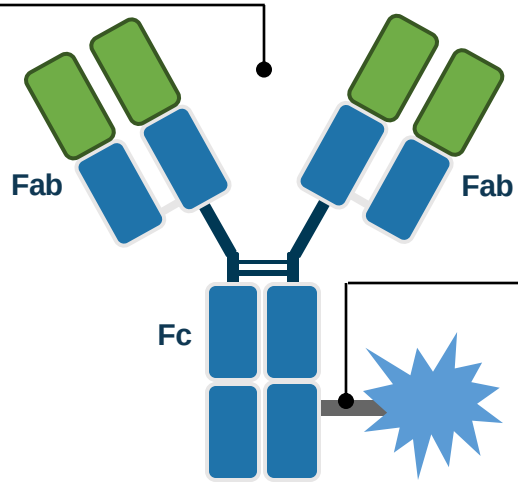
Antibody-Drug Conjugates: New kids on the block

Important Properties of the ADC Components and Target Antigen

Antigen
- High homogeneous expression on tumor
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumor antigen
- Chimeric or humanized to decrease immunogenicity
- Long half-life and high molecular weight

Cytotoxic Payload
- Highly potent agents:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (MMAE or MMAF)
  - SN-38
  - DXd topoisomerase I inhibitor
- Optimal DAR (range: 2 to 8)



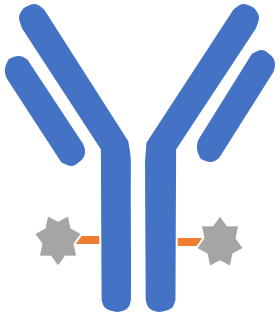
Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at nontarget tissue
- Efficient linker technology **(cleavable vs noncleavable)**
- Site of conjugation
- DAR affects drug distribution and pharmacokinetics

Cleavable Linkers
Depend on physiological conditions: pH, proteolysis, or high intracellular glutathione

Noncleavable Linkers
Depend on lysosomal degradation

Chau CH, et al. Lancet. 2019;394:793-804.

The Antibody



Antibodies	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7-21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

Chimeric/humanized monoclonal IgG antibody targeting a protein preferentially expressed on the tumor cell surface

Drago. Nat Rev Clin Oncol. 2021

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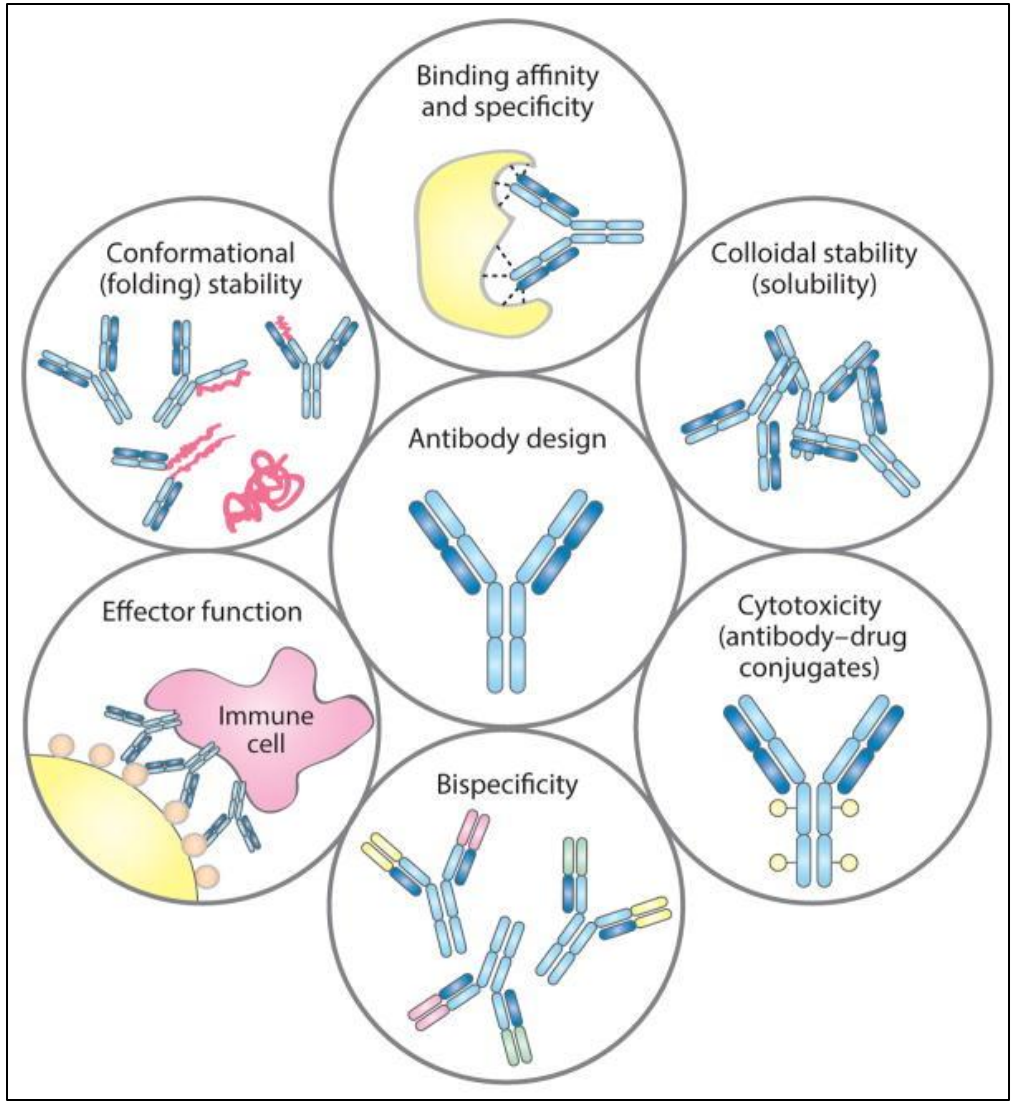
The Antibody: Consideration in design



Tiller KE, et al.. Annual Review of Biomedical Engineering. 2015

The Antigen: Ideal Characteristics for ADCs

High antigen density
in tumors, not normal tissue, to limit on-/off-target toxicity

Accessible to circulating antibody
by being present on the cell surface

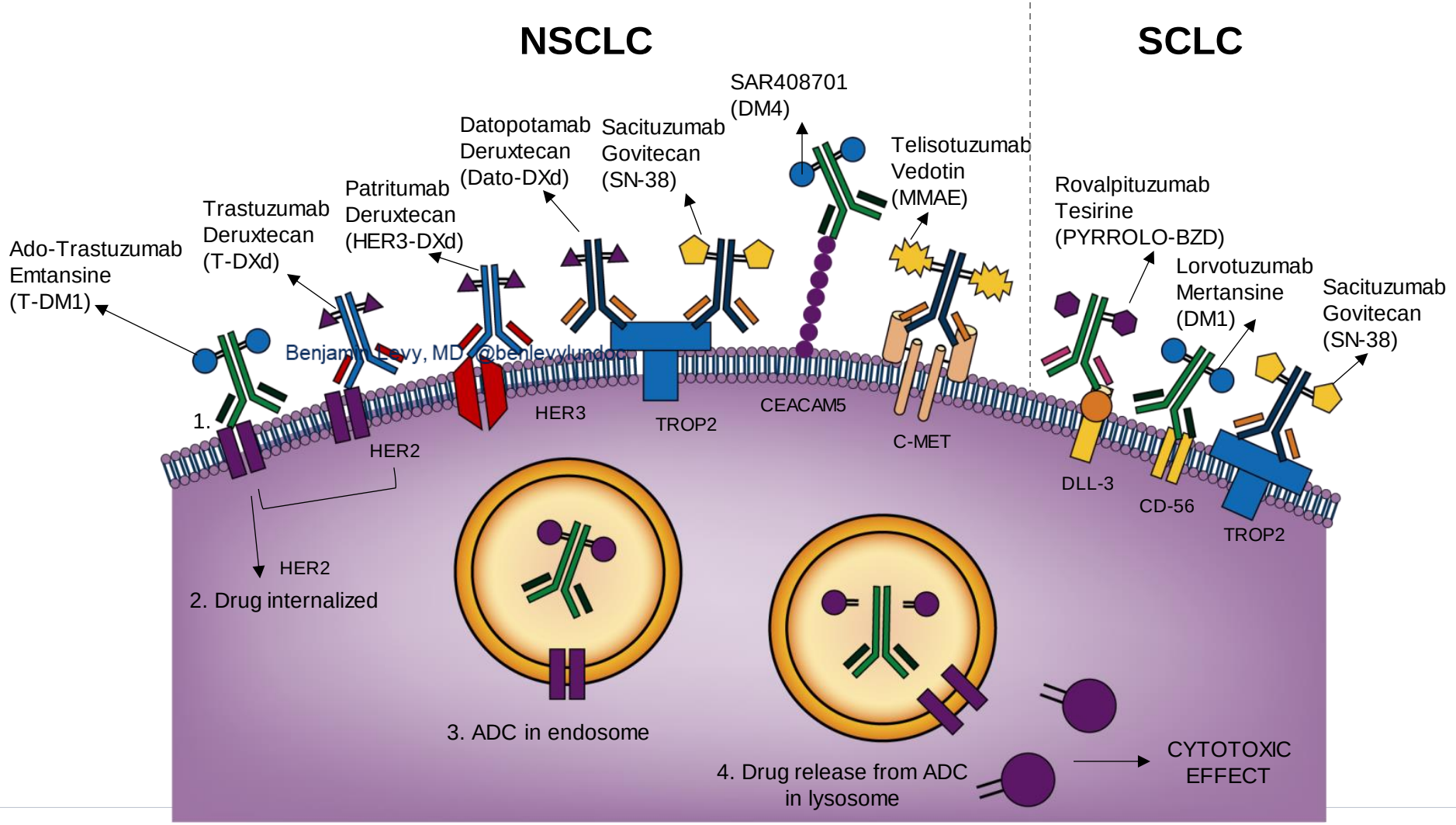
High internalization capacity
to facilitate rapidity of transmembrane trafficking enhancing intracellular ADC toxicity

Role in pathophysiology
including extracellular mechanisms of action such as ADCC or ADCP

Slide Courtesy of Medscape

Slide courtesy of Medscape

The Antigen: Ideal Characteristics for ADCs



Desai A et al. Lung Cancer. 2022

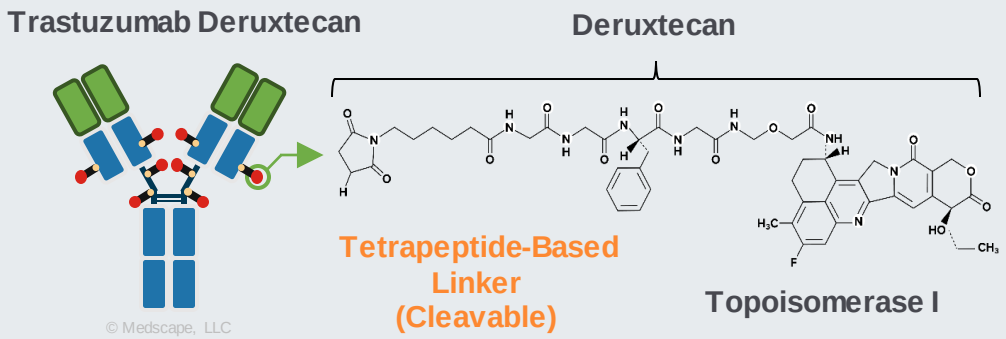
The Linker: Ideal Properties

- Cytotoxic payload remains firmly attached to the antibody moiety while the drug circulates in plasma
- Efficient release of payload once internalized
  - Non-cleavable (lysosomal degradation)
  - Cleavable (acid/redox/lysosomal sensitive)
- Minimal premature release of payload (in non-target tissue)
- Selective intracellular payload release

The Linker: Cleavable vs Nonclevable

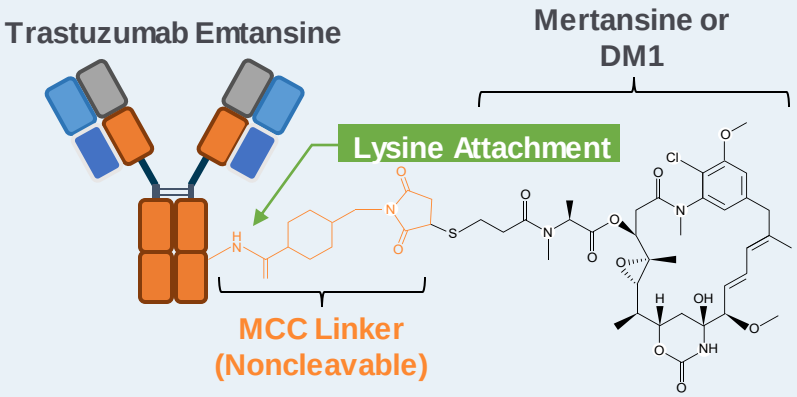
Cleavable Linkers

- Break down and release of the payload in response to tumor-associated factors (flexible)
- Acidic/Reducing conditions
- Abundance of proteolytic enzymes 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
- Require efficient internalization process and optimally traffic to lysosomes
- Potentially more stable in plasma



Slide Courtesy of Medscape

The Warhead or Payload

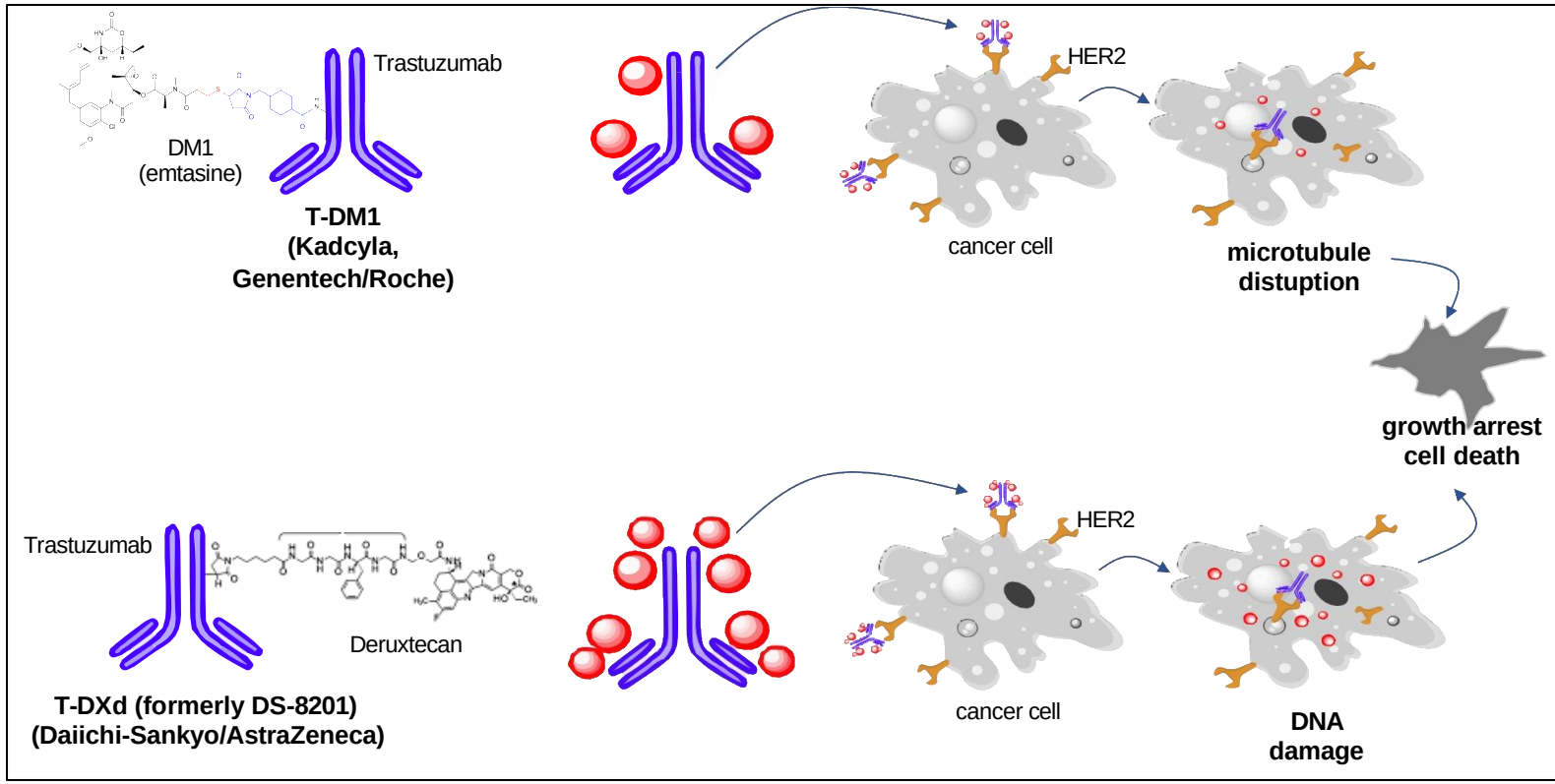
- Highly potent drugs
- Cytotoxic at sub-nanomolar concentrations
- Physiochemical properties are important
  - Amenable to conjugation
  - Water soluble
  - Prolonged stability in the blood

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

DAR: Drug to Antibody Ratio

- Average number of payload moieties attached to each mAB
- Range from 2-8
- Crucial in determining ADC potency and toxicity
- Higher DARs may increase activity but also may broaden off target effects
- Higher DARs might also enhance drug clearance by the liver



Slide Courtesy of Medscape

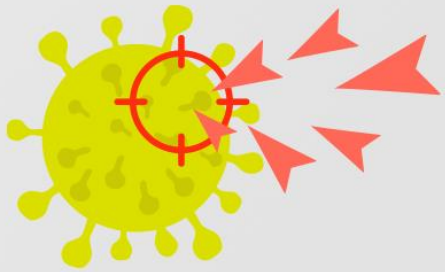
How do these drugs truly work?

Chemotherapy ?

Targets rapidly dividing cells (mostly cancer cells)

Hair loss, intestinal damage, nausea

Cancer cells develop resistance to chemotherapy, not specific



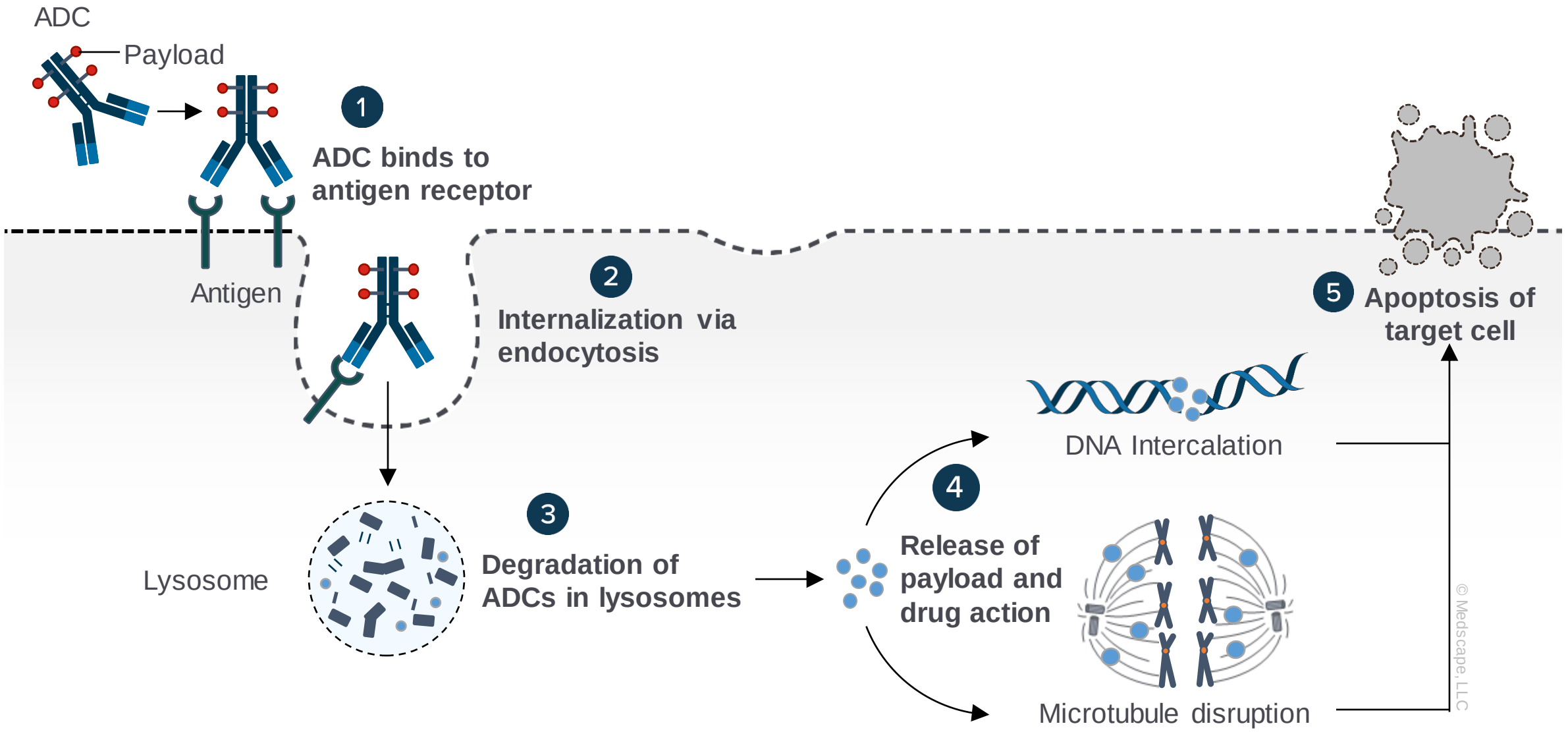
Targeted Therapy ?

Targets Proteins required for cancer growth

Liver problems, diarrhea, skin rash

Cancer cells develop resistance

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



Chau CH, et al. Lancet. 2019

DESTINY-Lung01: Interesting observation

- **Study objective**
  - To evaluate the efficacy and safety of trastuzumab deruxtecan in patients with HER2-mutated NSCLC in the DESTINY-Lung01 study

Key patient inclusion criteria

- Unresectable/metastatic non-squamous NSCLC
- Relapsed/refectory to standard treatment
- HER2 expressing or HER2-activating mutation
- No prior HER2-targeted therapy
- CNS metastasis allowed

Cohort 1:
HER2-expressing (IHC3+ or IHC2+)
trastuzumab deruxtecan 6.4 mg/kg q3w
(n=90)

RR: 24%

Cohort 2:
HER2-mutated
trastuzumab deruxtecan 6.4 mg/kg q3w
(n=91)

RR: 50%

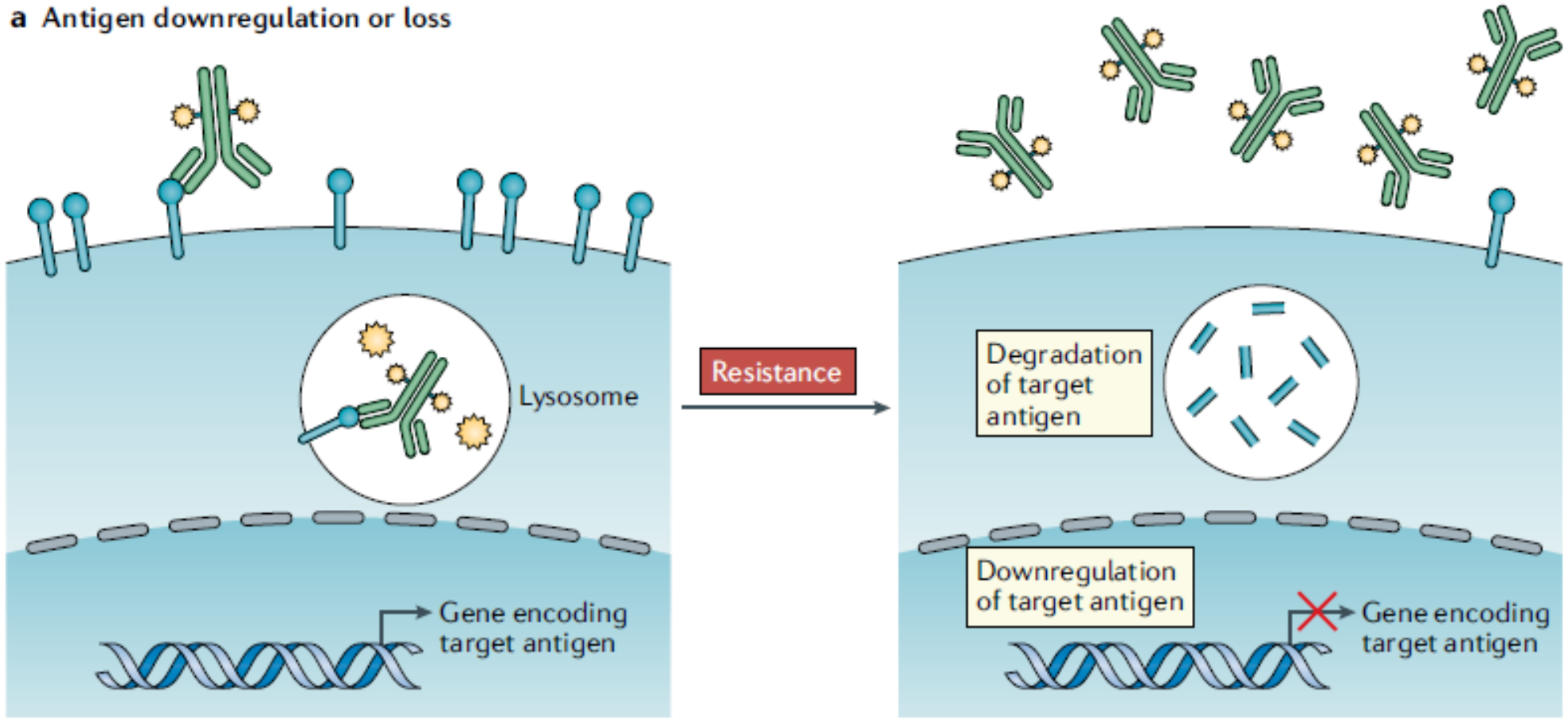
Primary endpoint

- ORR (ICR)

Secondary endpoints

- DCR, DoR, PFS, OS, safety

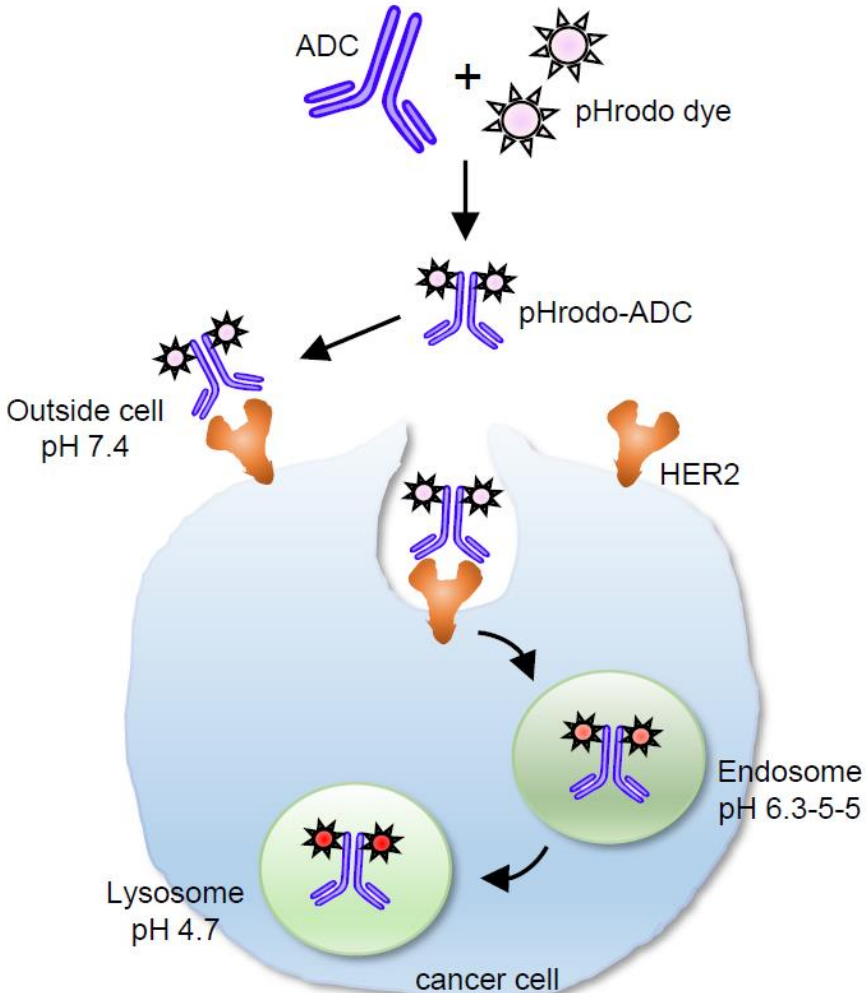
Antigen downregulation



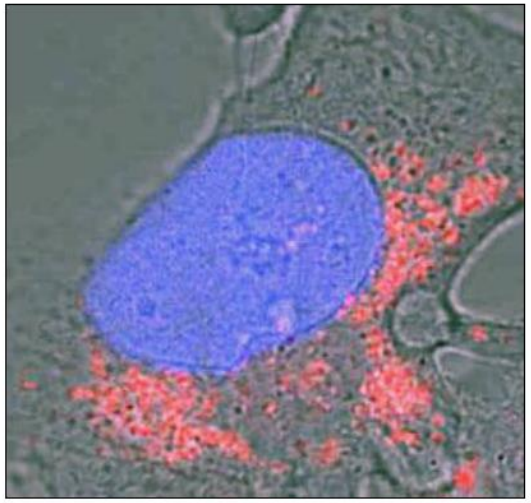
Drago. Nat Rev Clin Oncol. 2021

Dye-labeled HER-2 directed ADC

Methods: pHrodo-ADC internalization assay



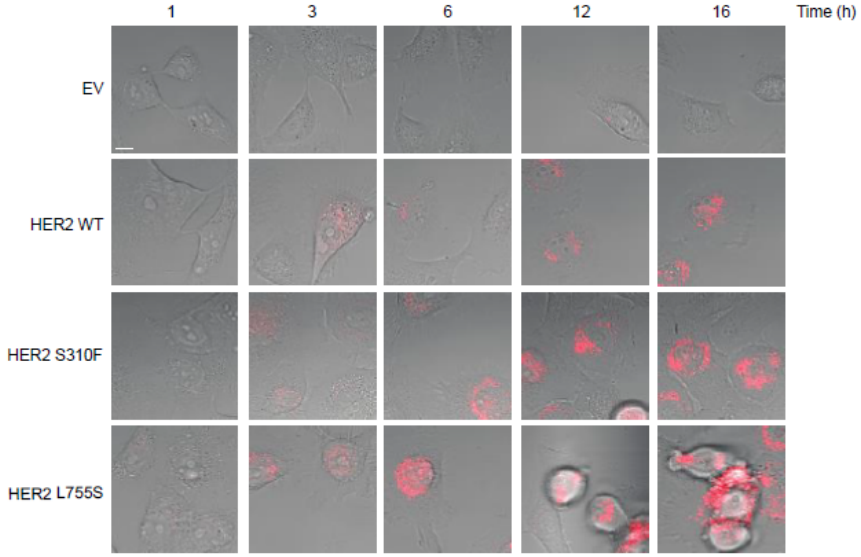
DAPI
pHrodo-ADC

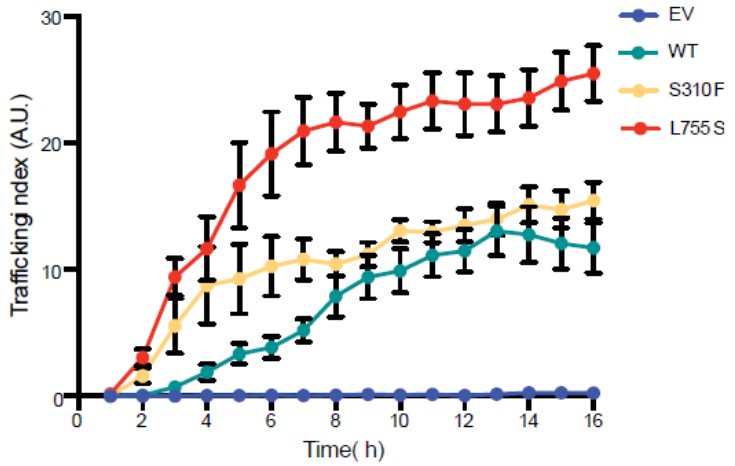


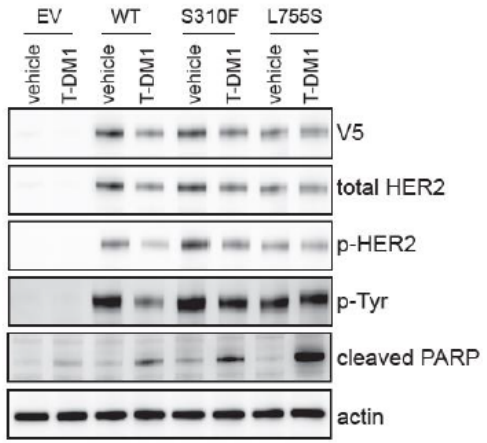
Li BT, et al. Ann Oncol 2021

Internalization and efficacy of T-DM1 depends on HER2 mutational status

Activity of these compounds is predicated not on expression but on the high-rate of receptor internalization and trafficking







MCF10A transduced with different HER2 mutants

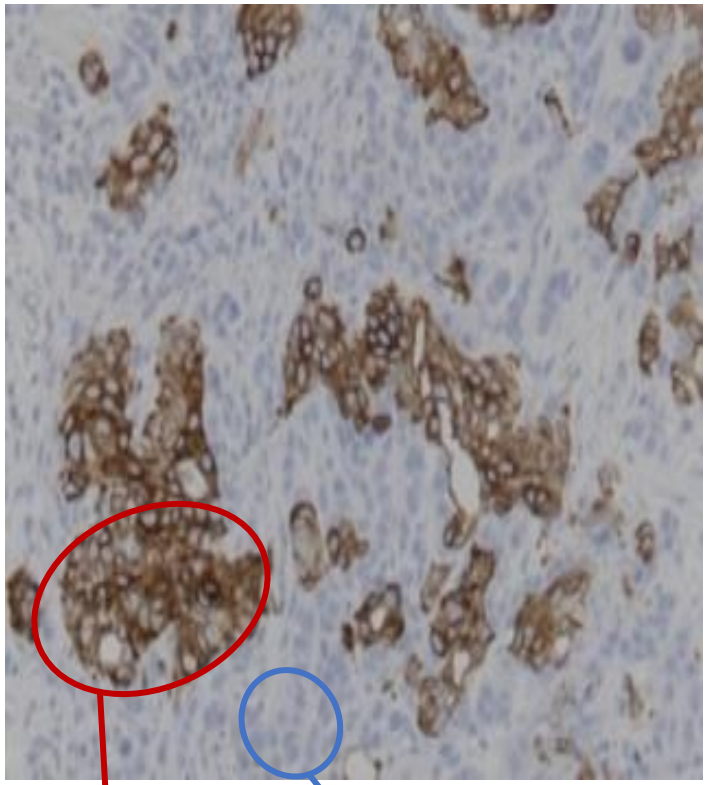
Li et al, Cancer Discovery 2020

Li BT, et al. Ann Oncol 2021

Antibody-Drug Conjugates
Mechanism 2: By-Stander Effect

Control

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

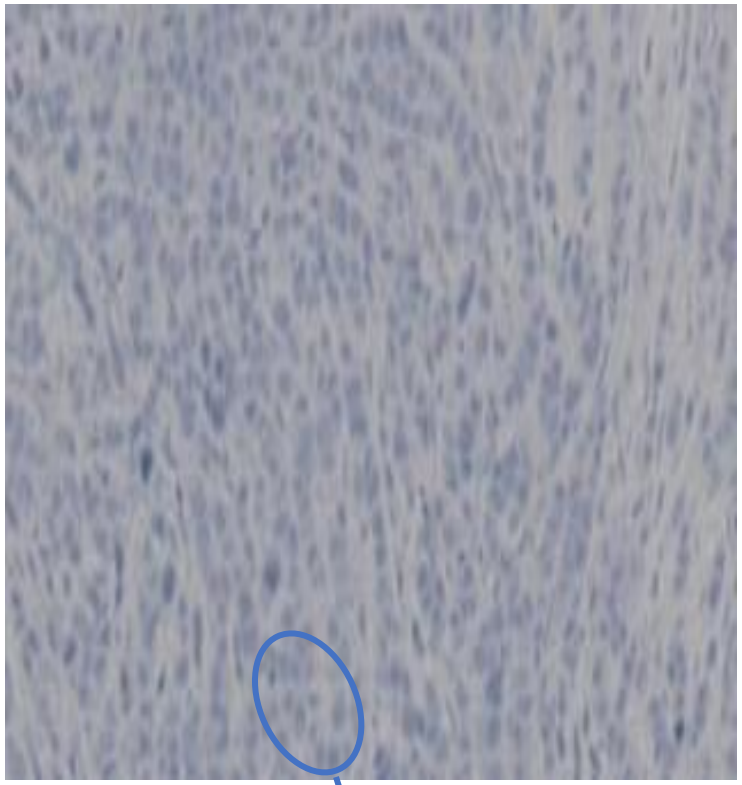


HER2+ cells NCI-N87

HER2- cells MDA-MB-468

T-DM1, 10 mg/kg

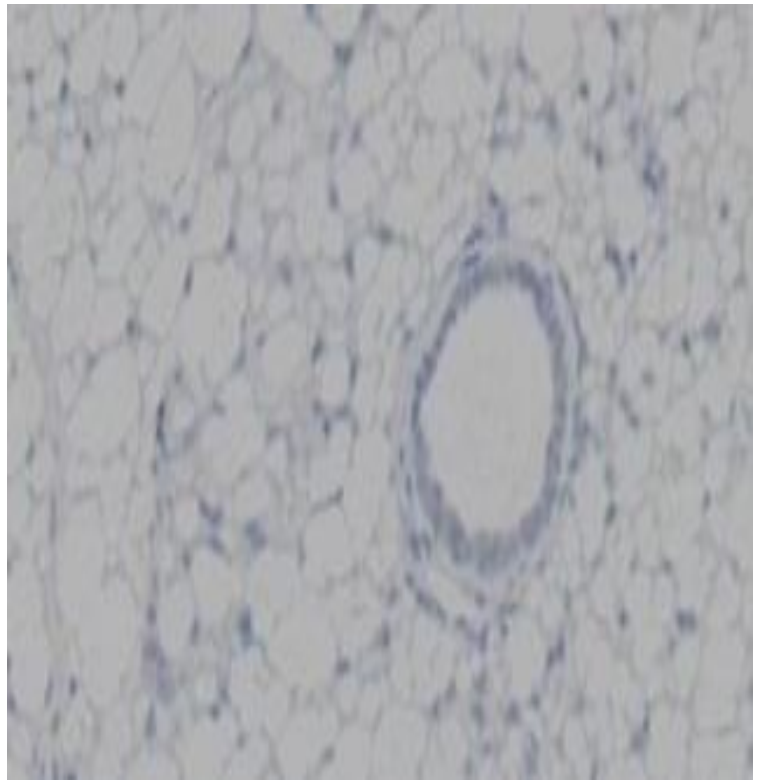
HER2- cells still persist



HER2- cells MDA-MB-468

T-DXd, 3.0 mg/kg

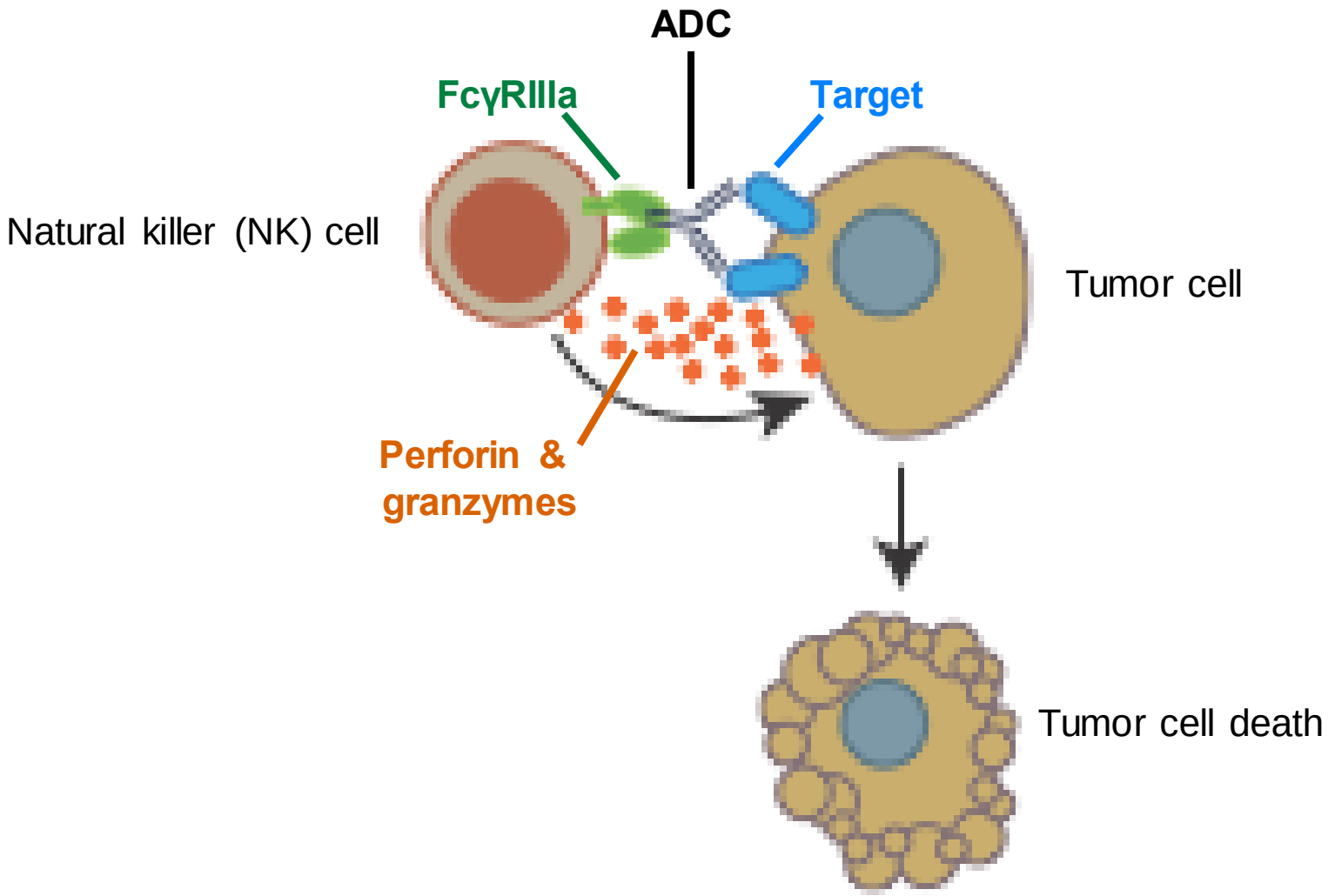
Both HER2+ and HER2- are impacted



Tumor regression

Ogitani Y et al. Cancer Sci. 2016

Antibody-Drug Conjugates
Mechanism 3:Antibody Dependent Cellular Cytotoxicity



Slide courtesy of Joseph Murray, MD, Phd

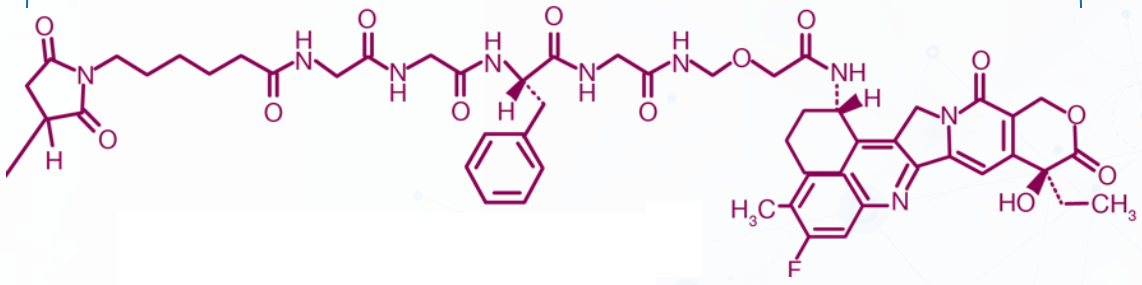
Trastuzumab Deruxtecan (T-DXd) Is an ADC Designed to Deliver an Optimal Antitumor Effect

T-DXd is an ADC with 3 components:

- **A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab**
- **A topoisomerase I inhibitor payload, an exatecan derivative**
- **A tetrapeptide-based cleavable linker**

Humanized anti-HER2 IgG1 mAb[1-3]

Deruxtecan[1,2]



Topoisomerase I inhibitor payload
(DXd=DX-8951f derivative)

[a]The clinical relevance of these features is under investigation.

- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug to antibody ratio ≈ 8 [a,1,2]
- Payload with short systemic half-life [a,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2]
- Bystander antitumor effect [a,1,4]

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142.
4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

DESTINY-Lung02: Study Design

International, randomized, multicenter, 2-arm, noncomparative phase II trial

Stratified by previous use of anti–PD-1/PD-L1 therapy

Prespecified interim analysis with 80 patients (early cohort: randomized ≥4.5 mo)

Patients with metastatic *HER2*-mutated NSCLC with activating *HER2* mutations; ≥1 previous anticancer therapy, including platinum-based CT; measurable disease by BICR; ECOG PS ≤1 (N = 152)

2:1

T-DXd 5.4 mg/kg Q3W (n = 102)	**T-DXd** 5.4 mg/kg Q3W (n = 52)
T-DXd 6.4 mg/kg Q3W (n = 50)	**T-DXd** 6.4 mg/kg Q3W (n = 28)

This analysis

- **Primary endpoint:** confirmed ORR by BICR
- **Secondary endpoints:** ORR by investigator, DoR,* DCR,* PFS,* OS,* PK, PROs, safety and tolerability

- Study not powered to compare 2 arms
- Data cutoff: March 24, 2022
- Median follow-up: 5.54 (range: 0.6-12.1 mo)

NCT04644237. Goto. ESMO 2022. Abstr LBA55.

DESTINY-Lung02: Response by BICR

Response	T-DXd 5.4 mg/kg (n = 52)	T-DXd 6.4 mg/kg (n = 28)
Confirmed ORR,* n (%; 95% CI)	28 (53.8; 39.5-67.8)	12 (42.9; 24.5-62.8)
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
NE†	3 (5.8)	1 (3.6)
DCR‡, n (%; 95% CI)	47 (90.4; 79.0-96.8)	26 (92.9; 76.5-99.1)
Median DoR, mo (95% CI)	NE (4.2-NE)	5.9 (2.8-NE)
Median TTIR, mo (range)	1.4 (1.2-5.8)	1.4 (1.2-3.0)
Median follow-up, mo (range)	5.6 (1.1-11.7)	5.4 (0.6-12.1)

*Proportion of patients with confirmed PR or CR assessed by BICR per RECIST v1.1. †3 patients were not evaluable at 5.4-mg/kg dose; 1 patient never received treatment due to COVID-19; 2 patients discontinued before first tumor assessment; 1 patient was not evaluable at 6.4-mg/kg dose due to discontinuation for adverse event before first tumor assessment. ‡Proportion of patients with confirmed CR, PR, or ST and assessed by BICR.

Key results (cont.)

TEAEs, n (%)	Trastuzumab deruxtecan (n=91)
Any	88 (96.7)
Grade ≥3	42 (46.2)
Serious	18 (19.8)
Led to discontinuation	23 (25.3)
Led to dose reduction	31 (34.1)
Led to death	2 (2.2)

TRAEs occurring in ≥20% of all patients, n (%)	Trastuzumab deruxtecan (n=91)	
	Any grade	Grade ≥3
Nausea	66 (72.5)	8 (8.8)
Fatigue	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia	32 (35.2)	17 (18.7)
Anaemia	30 (33.0)	9 (9.9)
Diarrhoea	29 (31.9)	3 (3.3)
Decreased appetite	27 (29.7)	0
Leukopenia	21 (23.1)	4 (4.4)
Constipation	20 (22.0)	0

- Any grade TEAE ILD/pneumonitis was reported in 26.4% of patients, 75% were grade 1/2 and 2.2% were grade 5
- TEAE ILD and pneumonitis led to discontinuation in 5.5% and 13.2% of patients, respectively

Conclusions

- In previously treated patients with HER2-mutated NSCLC, trastuzumab deruxtecan demonstrated encouraging activity and was generally well-tolerated

Li BT, et al. Ann Oncol 2021;32(suppl): Abstr LBA45

NCT04644237. Goto. ESMO 2022. Abstr LBA55.

DESTINY-Lung02: Adjudicated Drug-Related ILD in Safety Analysis Set

Adjudicated Drug-Related ILDs*	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)

*Cases of potential ILD or pneumonitis were evaluated via independent adjudication committee. Data reported are for cases that were deemed drug related by ILD adjudication committee. †In safety analysis set, 1 investigator reported grade 3 for 5.4-mg/kg dose, and 1 investigator reported grade 5 ILD with 6.4-mg/kg dose were pending adjudication at data cutoff and were later adjudicated as grade 2 and grade 5 ILD, respectively.

Rates of adjudicated drug-related ILD lower in T-DXd 5.4 mg/kg vs 6.4 mg/kg

Adjudicated ILD mostly of low grade (grade 1 or 2) Goto. ESMO 2022. Abstr LBA55.

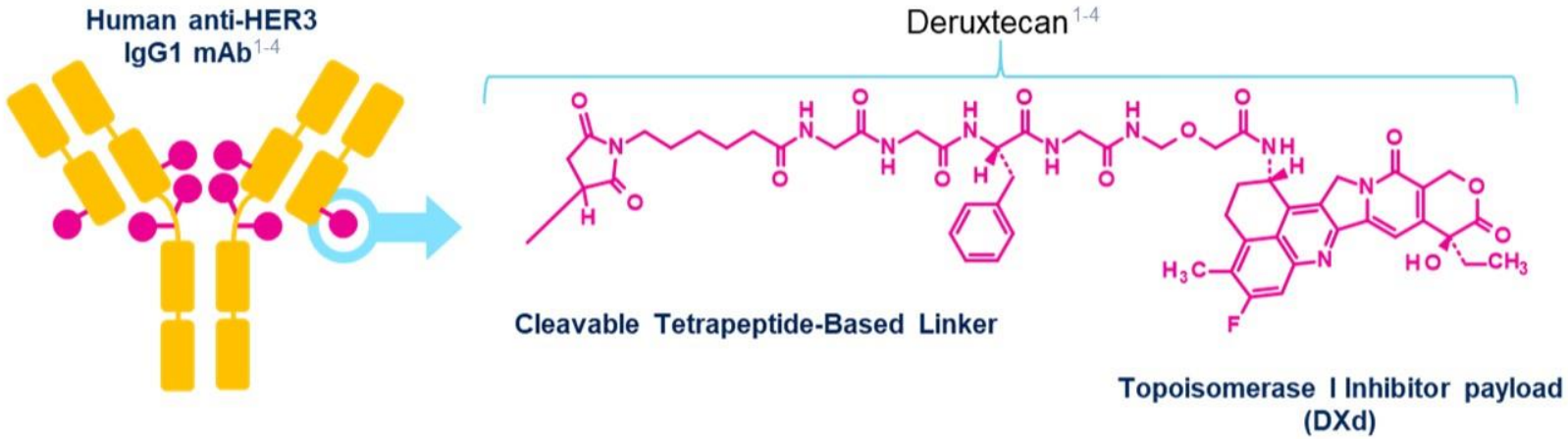
NCT04644237. Goto. ESMO 2022. Abstr LBA55.

Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

HER3 is expressed in 83% of NSCLC tumors[7,a]

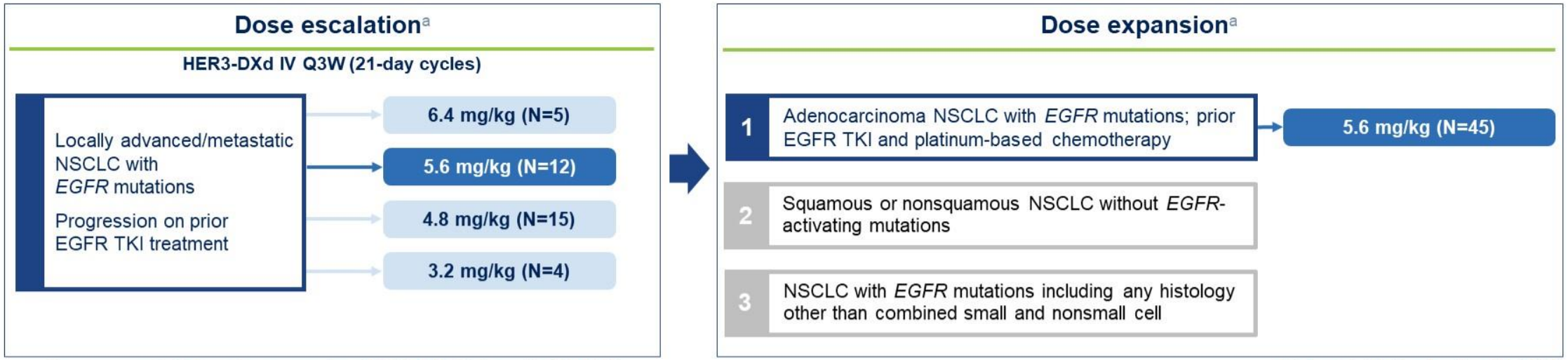
HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC



[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050.
5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 7. Scharpenseel H et al, *Sci Rep* 2019;9(1):7406.

U31402-A-U102 is a Phase 1 Dose Escalation and Dose Expansion Study in Patients With NSCLC



57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.
[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

Passe, J. ASCO 2021 Oral Presentation. Abstract 9001.

Patients with *EGFR*m NSCLC were Heavily Pre-treated with Majority Receiving Prior Platinum-based Chemotherapy

Patient Characteristics and Treatment History	HER3-DXd 5.6 mg/kg (N=57)	HER3-DXd All Doses (N=81)
Age, median (range), years	65 (40-80)	64 (40-80)
Female, n (%)	36 (63)	52 (64)
ECOG performance status 0/1, n (%)	23 (40) / 34 (60)	34 (42) / 47 (58)
Sum of diameters at baseline,[a] median (range), mm	54 (13-195)	51.5 (10-195)
History of CNS metastases, n (%)	27 (47)	43 (53)
Prior lines of systemic therapy, median (range)[b]	4 (1-9)	4 (1-9)
Prior cancer regimens		
Prior EGFR TKI therapy, n (%)	57 (100)	81 (100)
Prior osimertinib, n (%)	49 (86)	72 (89)
Prior platinum-based chemotherapy, n (%)	52 (91)	65 (80)
Prior immunotherapy, n (%)	23 (40)	28 (35)

Data cutoff: September 24, 2020.
[a] By blinded independent central review per RECIST 1.1. [b] In the locally advanced or metastatic setting

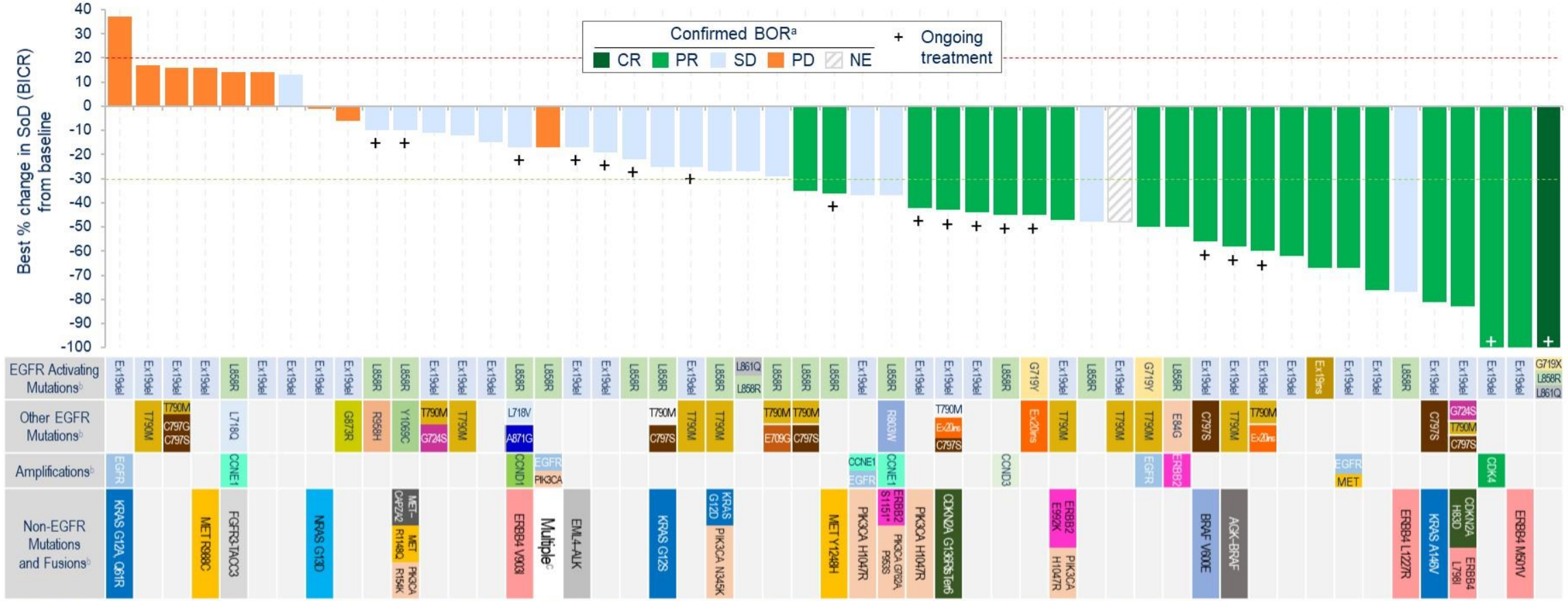
HER3-DXd Demonstrated Durable Antitumor Activity After Failure of EGFR TKI and Platinum-based Chemotherapy (PBC)

Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	 Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

The subgroup of patients treated with prior **osimertinib (OSI)** and **platinum-based chemotherapy** demonstrated similar efficacy to the overall efficacy population

BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.
[a] For patients treated with the recommended dose for expansion of HER3-DXd (N=57)

HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance

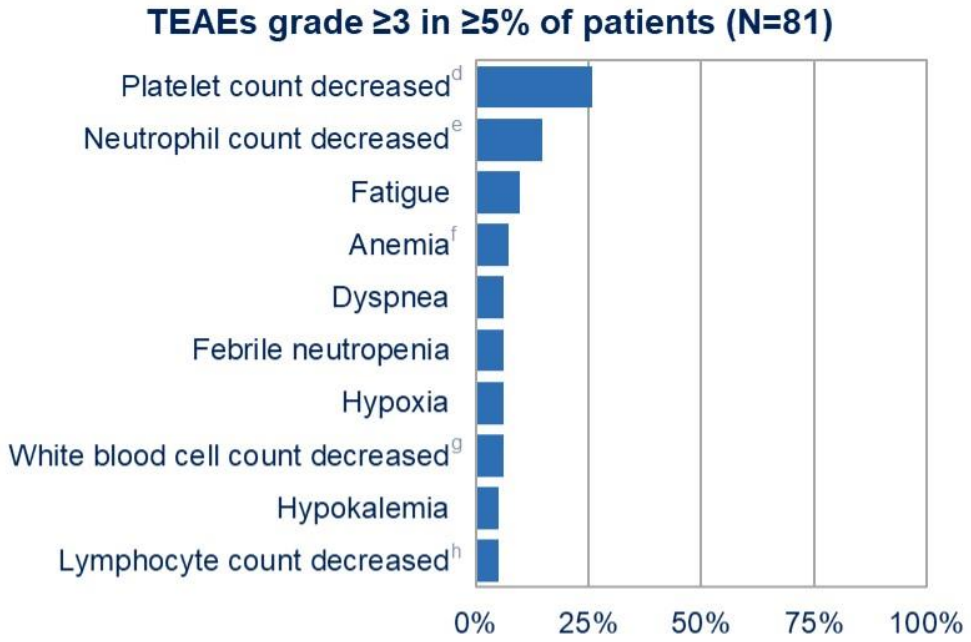


BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD stable disease; SoD, sum of diameters.
Data cutoff: September 24, 2020.
[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [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*.

Passe, J. ASCO 2021 Oral Presentation. Abstract 9001.

HER3-DXd Was Associated With a Manageable Safety Profile and a Low Rate of Discontinuations Due to Adverse Events

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	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	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[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



- 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

Data cutoff: September 24, 2020.

[a] TEAEs associated with treatment discontinuation were fatigue (2); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b] TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c] One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d] Includes thrombocytopenia. [e] Includes neutropenia. [f] Includes hemoglobin decreased. [g] Includes leukopenia. [h] Includes lymphopenia.

Phase 1 Study of Patritumab Deruxtecan in Combination With Osimertinib *EGFR*-Mutated NSCLC (NCT04676477)

Eligibility criteria

Dose escalation; dose expansion Arms 1 and 2 (second line)

- Metastatic/unresectable NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- Progression after treatment with osimertinib; no other prior systemic therapies in the locally advanced/metastatic setting

Dose expansion Cohort 3 (first line)[c]

- Metastatic/unresectable NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- No prior systemic treatment for locally advanced/metastatic disease
  - Patients may have received prior neoadjuvant or adjuvant therapy (except with osimertinib)

Dose escalation[a]

HER3-DXd (patritumab deruxtecan) IV Q3W + osimertinib PO QD

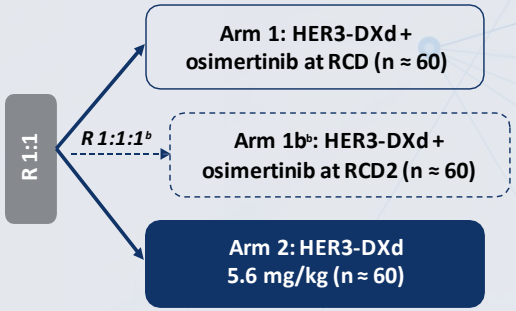
Planned cohort	Osimertinib dose, mg	HER3-DXd dose, mg/kg
1a	80	1.6
1b		3.2 *(starting dose)*
1c		4.8
1d		5.6
2a	40	1.6
2b		3.2
2c		4.8
2d		5.6

Guided by BLRM

Dose expansion

HER3-DXd (patritumab deruxtecan) IV Q3W + osimertinib PO QD

Second line:



Cohort 3 (first line)[c]:

HER3-DXd + osimertinib at RCD (n ≈ 30)

Primary objectives[d,e]

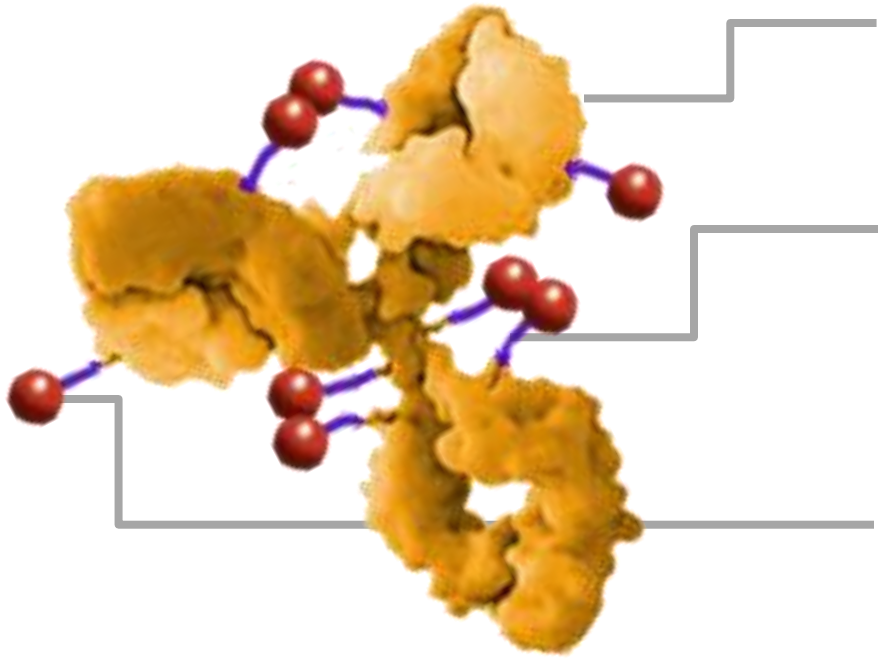
Dose escalation
- Determine RCD
- Safety and tolerability

Dose expansion Arms 1 and 2
- ORR by BICR

Dose expansion Cohort 3
- Safety and tolerability

Jänne PA, et al. Presented at: WCLC 2020; January 28-31, 2021; virtual meeting.

Sacituzumab Govitecan (SG) Is a Trop-2–Directed ADC



Monoclonal antibody (hRS7)

Binds to Trop-2, a cell surface antigen highly expressed by several cancers, including TNBC

Hydrolyzable linker (CL2A)

- Helps to ensure that an active concentration of SN-38 is maintained in the tumor
- Hydrolysis of the linker releases the cytotoxic intracellularly and in the tumor microenvironment to kill cells

Cytotoxic (SN-38)

The payload is SN-38, a topoisomerase I inhibitor that blocks DNA replication by stabilizing Top1-DNA complex during replication, leading to dsDNA breaks through multiple mechanisms.

SG binds to the antigen Trop-2 and concentrates the cytotoxic SN-38 in tumor tissue

SG linker lends itself to a Bystander Effect

Favorable Therapeutic Index

- SG has a high DAR (7–8 molecules of SN-38 per antibody) enhancing drug delivery to tumor
- Moderate drug potency mitigates toxicity, while increased intratumoral drug release enhances efficacy

Trop-2 trophoblast cell surface antigen 2; DAR, Drug Antibody Ratio;
Goldenberg DM, et al. *Oncotarget*. 2015;6(26):22496-512. Gray JE, et al. *Clin Cancer Res*. 2017;23:5711-5719. Takimoto CH, Arbuck SG. Camptothecins. In: Chabner BA, Long DL, editors. Cancer chemotherapy and biotherapy. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1966. p. 463–84.

IMMU-132-01 Study Design and Population[1,2]

IMMU-132-01 (NCT01631552) is a single-arm, open-label, multicenter Phase 1/2 dose-escalation and cohort-expansion study of sacituzumab govitecan (TROP2-directed antibody and topoisomerase inhibitor drug conjugate) in advanced/metastatic NSCLC and other epithelial cancers progressing after SoC

Patient population

- Relapsed/refractory advanced/metastatic NSCLC
- Unselected for TROP2 expression[a]
- Age ≥18 years
- ECOG PS 0 or 1
- Measurable disease per RECIST v1.1
- Progression after ≥1 line of therapy for Stage IV disease

Dose expansion

NSCLC cohort (N=54)

Sacituzumab govitecan 8 mg/kg IV (n=8) D1 and D8 of 21-day cycle

Sacituzumab govitecan 10 mg/kg IV (n=46) D1 and D8 of 21-day cycle

TNBC, mUC, HR+ mBC, SCLC, CRC, esophageal carcinoma, endometrial, pancreatic ductal adenocarcinoma, CRPC, EOC, gastric adenocarcinoma, GBM, SCCHN, hepatocellular, cervical, clear cell RCC

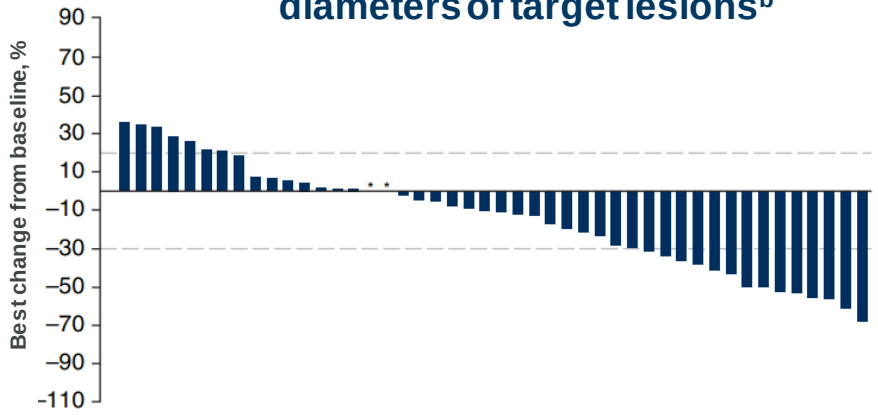
Primary endpoints

- Confirmed objective response[b]
- Safety
- PK

IMMU-132-01 Safety and Efficacy Outcomes

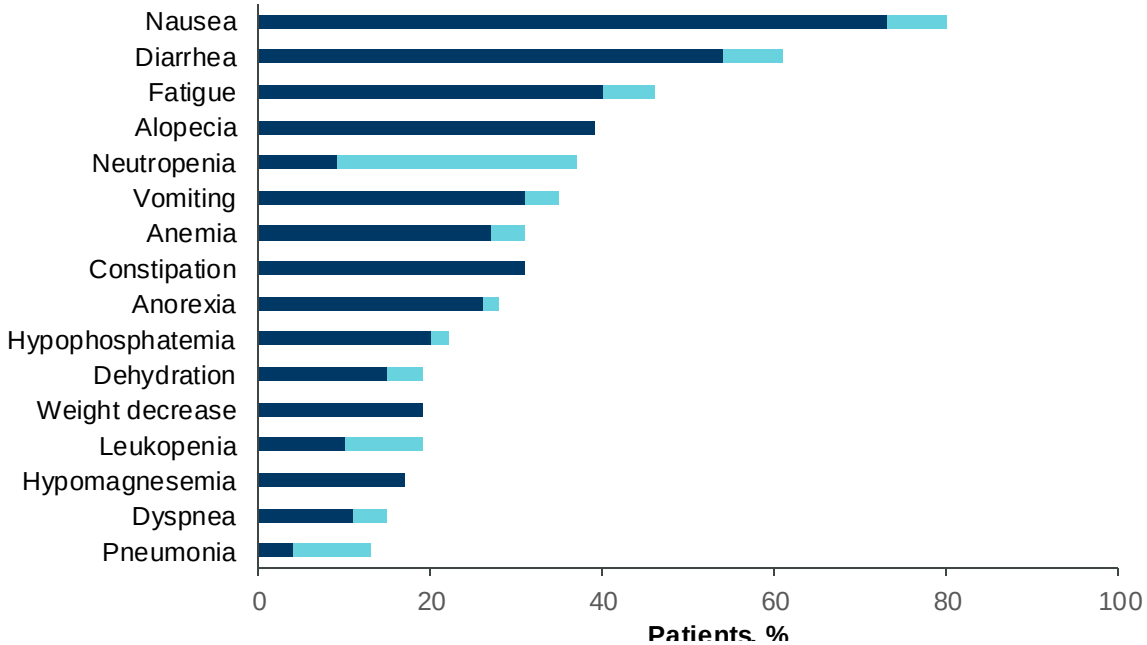
	NSCLC cohort (n=54)[a]
ORR, % (95% CI)	16.7 (7.9–29.3)
PR, n (%)	9 (16.7)
SD, n (%)	22 (40.7)
Median DOR, mo (95% CI)	6.0 (2.5–21.0)
Median OS, mo (95% CI)	7.3 (5.6–14.6)
Median PFS, mo (95% CI)	4.4 (2.5–5.4)

Best change from baseline in the sum of the diameters of target lesions[b]



n (%)	NSCLC cohort (n=54)
AEs leading to dose reductions[c]	23 (43)
AEs leading to discontinuation[d]	2 (4)

AEs regardless of causality



Santin A, et al. 2020 ASCO, abs 6081

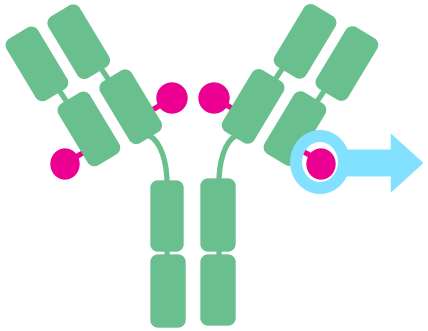
NORTH CAROLINA Oncology Association

Datopotamab deruxtecan (Dato-DXd; DS-1062) Was Designed With 7 Key Attributes

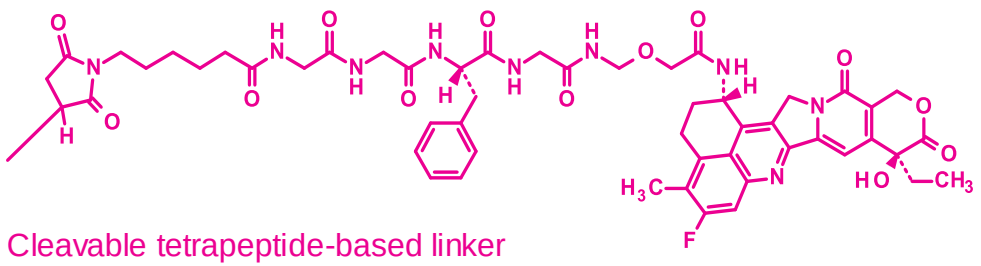
Dato-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

Humanized anti-TROP2 IgG1 mAb



Deruxtecan[b,4]



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

[a] The clinical relevance of these features is under investigation.
[b] Image is for illustrative purposes only; actual drug positions may vary.
[c] Based on animal data.

- Payload mechanism of action: topoisomerase I inhibitor [a,1]
- High potency of payload [a,2]
- Optimized drug to antibody ratio ≈4[a,c,1]
- Payload with short systemic half-life [a,c,2]
- Stable linker-payload [a,2]
- Tumor-selective cleavable linker [a,2]
- Bystander antitumor effect [a,2,5]

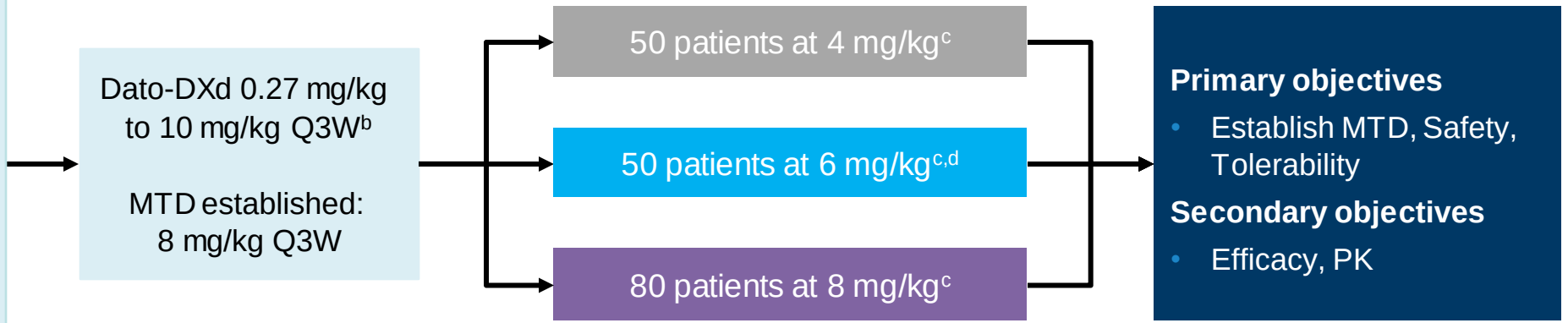
1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA [abstract C026].
2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185. (DS-8201 drug discovery MS)
3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf
4. Krop I, et al. Oral presentation at: SABCS Symposium; December 10-14, 2019; San Antonio, TX [abstract GS1-03].
5. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4946713/pdf/CAS-107-1039.pdf - DS-8201 preclin MS

TROPION-PanTumor01 (NCT03401385) Study Design

Phase 1 FIH Dose Escalation and Expansion Study

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 v1.1
- Stable, treated brain metastases allowed

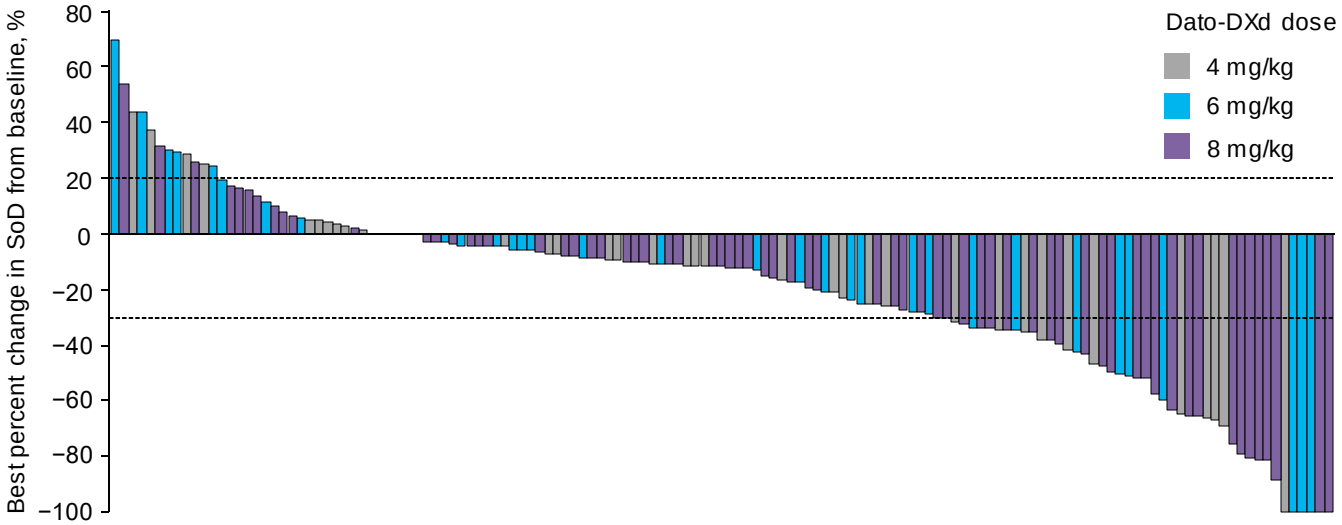


- NSCLC enrollment complete[d]
- TNBC cohort 6 mg/kg Q3W is enrolling; cohorts in other tumor types may be added
- Here we report updated results for the NSCLC dose expansion cohort (175 patients treated at 4, 6, or 8 mg/kg of Dato-DXd)

Lisberg AE, et al. Presented at: ASCO Annual Meeting; May 29-June 2, 2020; virtual meeting. Abstract 9619.

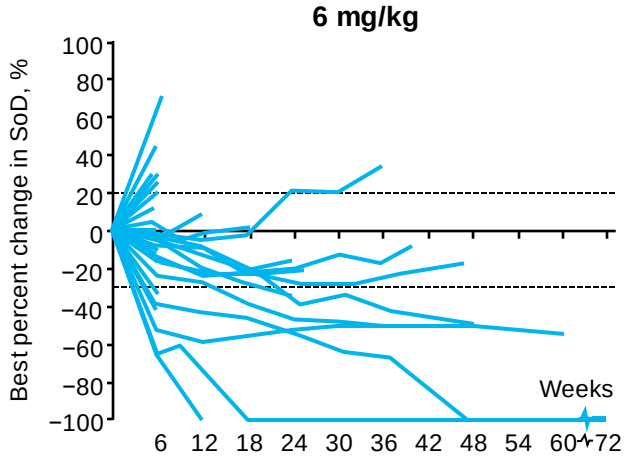
Antitumor Activity of Dato-DXd

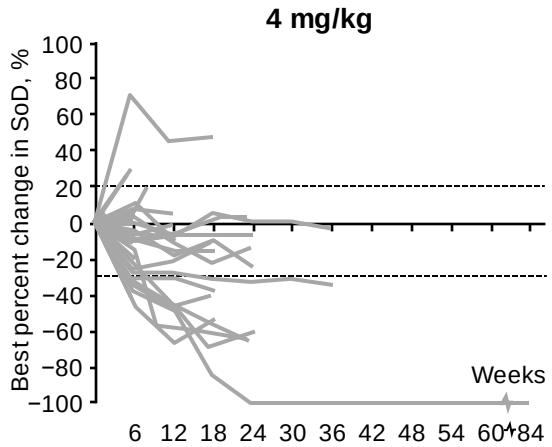
Best Change in Sum of Diameters and Overall Response (BICR)

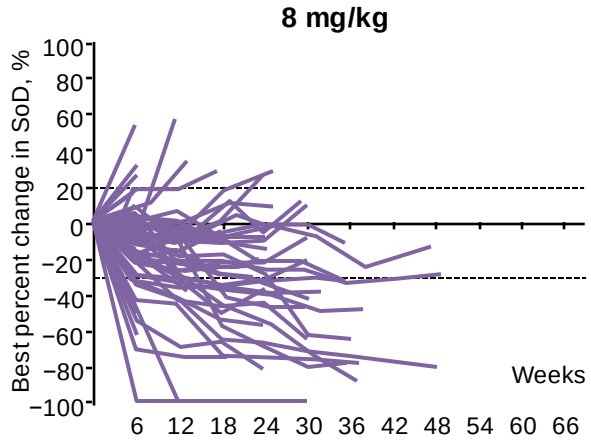


Dato-DXd dose	Response-evaluable patients,[a] n	Confirmed CR/PR,[b] n	CR/PR (too early to be confirmed),[b] n	ORR,[b] % (n)	DCR, % (n)	PD, % (n)
4 mg/kg	40	7	2	23 (9)	73 (29)	15 (6)
6 mg/kg	39	6	2	21 (8)	67 (26)	21 (8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)

Change in Sum of Diameters for Target Lesions (BICR)



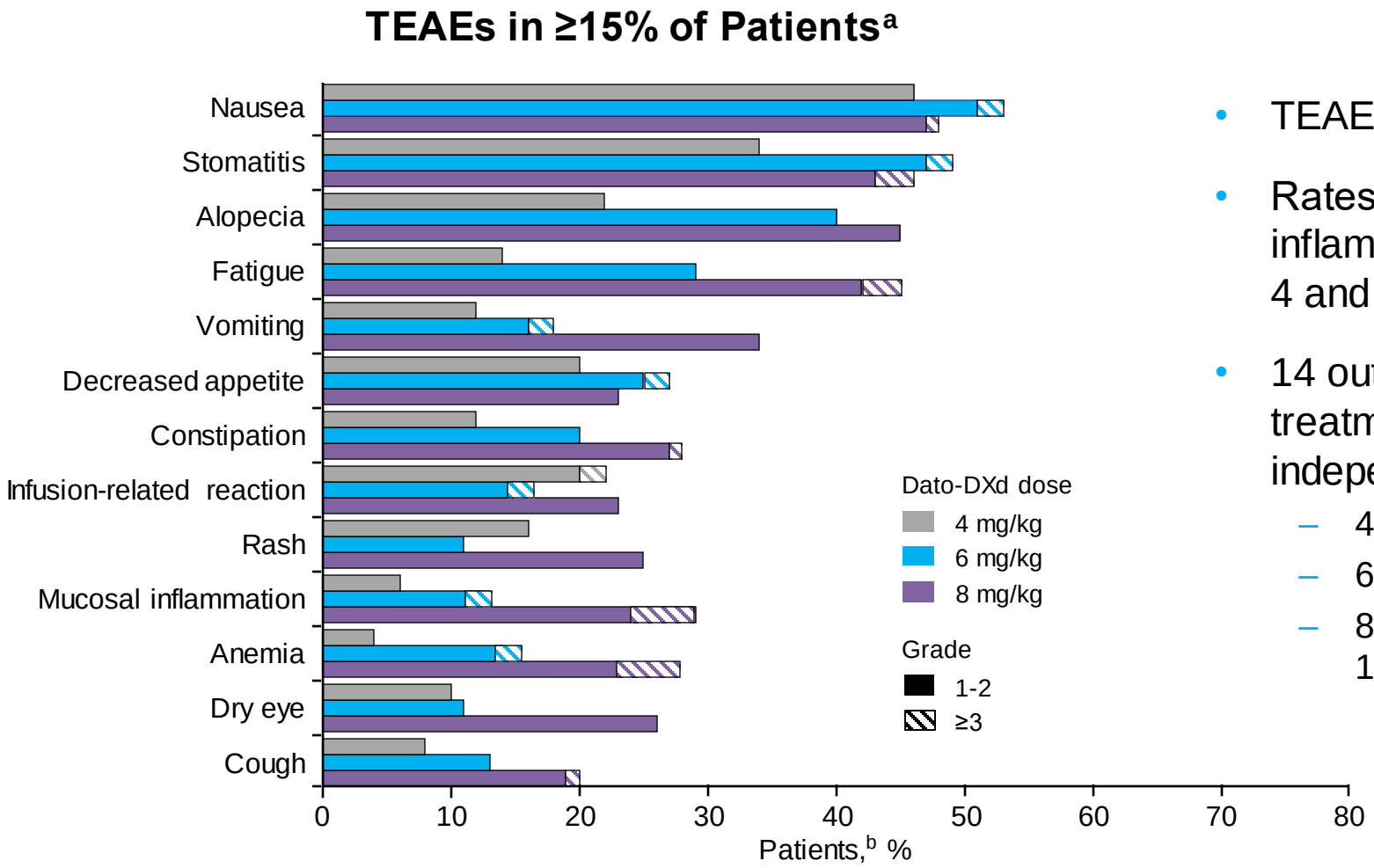




Preliminary Progression-free Survival (BICR)[c]

- Median PFS (95% CI)
  - 4 mg/kg: 4.3 months (2.0-NE), 6 mg/kg: 8.2 months (1.5-11.8), 8 mg/kg: 5.4 months (4.1-7.1)

Treatment-Emergent Adverse Events



- TEAEs were predominantly nonhematologic
- Rates of grade ≥3 stomatitis and mucosal inflammation were higher with 8 mg/kg vs 4 and 6 mg/kg[c]
- 14 out of 175 patients (8%) had treatment-related ILD as adjudicated by an independent committee[d]
  - 4 mg/kg: 1 patient (grade 3)
  - 6 mg/kg: 1 patient (grade 2)
  - 8 mg/kg: 12 patients (8 patients grade 1-2; 1 patient grade 3; 3 patients grade 5)

TROPION-PanTumor01: NSCLC With Actionable Genomic Mutations—Baseline Characteristics

Characteristics	Dato-DXd (n = 34)
Median age, yr (range)	62 (42-80)
Median weight, kg (range)	60 (38-107)
Female, %	56
Nonsquamous histology, %	97
≥3 prior lines of therapy, %	82
Previous systemic treatment, %	
▪ Immunotherapy	41
▪ Platinum-based chemotherapy	91
▪ Tyrosine kinase inhibitor	85
▪ Osimertinib	69*
Actionable genomic alterations, %	
▪ *EGFR* mutation†	85
▪ *ALK* fusion	9
▪ *ROS1* fusion	3
▪ *RET* fusion	3

Characteristics	Dato-DXd (n = 34)
Dato-DXd dose received, %	
▪ 4 mg/kg	24
▪ 6 mg/kg	29
▪ 8 mg/kg	47
Ongoing study treatment, %	12
Reason for discontinuation, %	
▪ Progression	65
▪ AE	15
▪ Death	3
▪ Other	6
Median treatment duration, mo (range)	13.4 (7-28)
Median exposure, mo (range)	5.8 (0.7-17.2)

*Among patients with *EGFR* mutations.
†*EGFR* exon 20 mutations present in 10%.

Garon. ESMO 2021. Abstr LBA49.

Slide credit: clinicaloptions.com

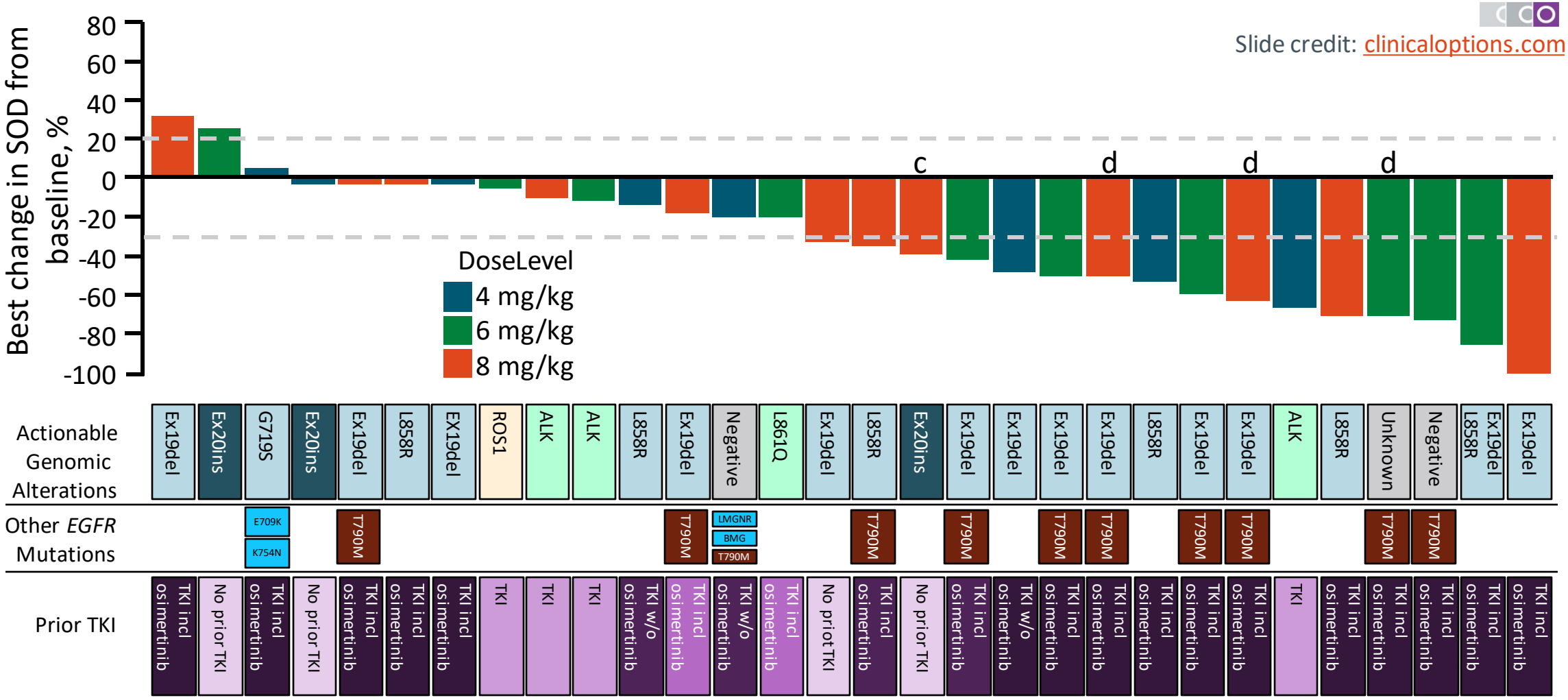
TROPION-PanTumor01: NSCLC With Actionable Genomic Mutations—Responses

Best Overall Response (BICR)	Dato-DXd (n = 34)
ORR, n (%) ▪ CR, n (%) ▪ PR, n (%)	12 (35) 0 12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
Median DoR, mo (95% CI)	9.5 (3.3-NE)

Slide credit: clinicaloptions.com

TROPION-PanTumor01: NSCLC With Actionable Genomic Mutations—Antitumor Activity

Slide credit: clinicaloptions.com

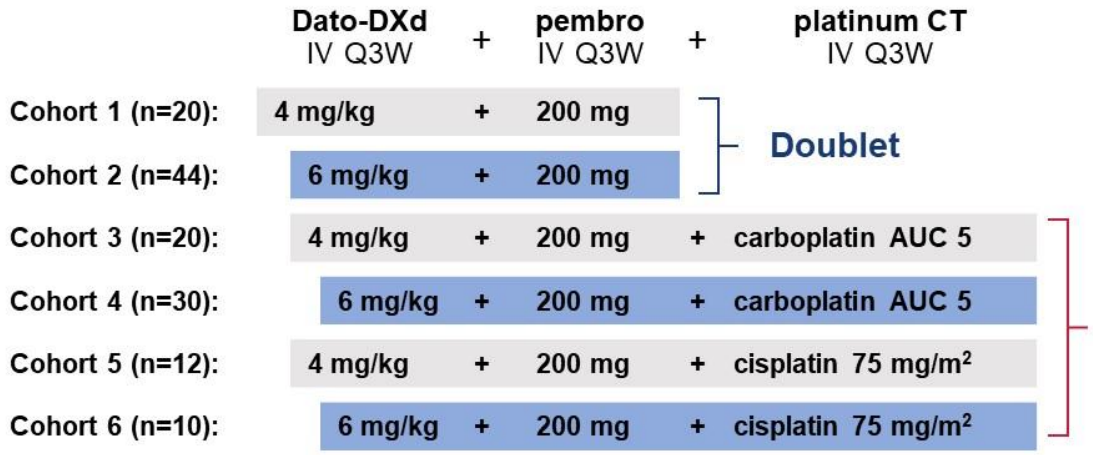


TROPION-Lung02: Phase 1b Study

- TROPION-Lung02 is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT[a] in advanced NSCLC without actionable genomic alterations[b] (NCT04526691)
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations

Key eligibility criteria

- **Advanced/metastatic NSCLC**
- **Dose escalation**[c]: ≤2 lines of prior therapy[d]
- **Dose expansion**
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[d]
  - Treatment naive (cohort 2; enrollment after Jun 30, 2022)[d]
  - Treatment naive (cohorts 3-6)[d]



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

Data cutoff: April 7, 2023.
AUC, area under the curve; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; Q3W, every 3 weeks.
[a] Administered sequentially at the same visit. [b] Patients with known actionable *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET* mutations or alterations in other actionable oncogenic driver kinases were not eligible for this study. Testing for *EGFR* and *ALK* alterations was not required for patients with squamous histology who were smokers or ≥40 years of age. [c] The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion (for which enrollment was ongoing at the time of data cutoff). [d] Prior therapy requirements are for treatment in the advanced/metastatic setting.

Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Patient Baseline Characteristics

Characteristic	Doublet (n=64)	Triplet (n=72)
Age, median (range), years	65 (44-83)	64 (33-84)
Male, n (%)	48 (75)	48 (67)
Histology, n (%)		
Adenocarcinoma	45 (70)	49 (68)
Squamous	16 (25)	15 (21)
History of brain metastases, n (%)	11 (17)	14 (19)
PD-L1 expression, n (%)[a]		
<1%	23 (36)	29 (40)
1%-49%	28 (44)	24 (33)
≥50%	13 (20)	18 (25)
Prior lines of therapy, median (range)[b]	0 (0-4)[c]	0 (0-3)[c]
Previous systemic treatment, n (%)		
Immunotherapy	12 (19)	18 (25)
Platinum chemotherapy	24 (38)	17 (24)
Dato-DXd combination line of therapy, n (%)[d]		
1L	37 (58)	54 (75)
2L+	27 (42)	18 (25)

- Of patients receiving doublet or triplet therapy, 58% and 75%, respectively, were treated in the 1L setting
- Immunotherapy was previously given in 19% of patients receiving doublet therapy and 25% of patients receiving triplet therapy

Data cutoff: April 7, 2023.
1L, first line; 2L+, second line and later; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.
[a] PD-L1 expression testing was not performed in 1 patient (1%) receiving triplet therapy. [b] Prior therapy for advanced/metastatic NSCLC. [c] Additional prior lines of therapy were permitted under earlier versions of the protocol.
[d] In the advanced/metastatic setting.

Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

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

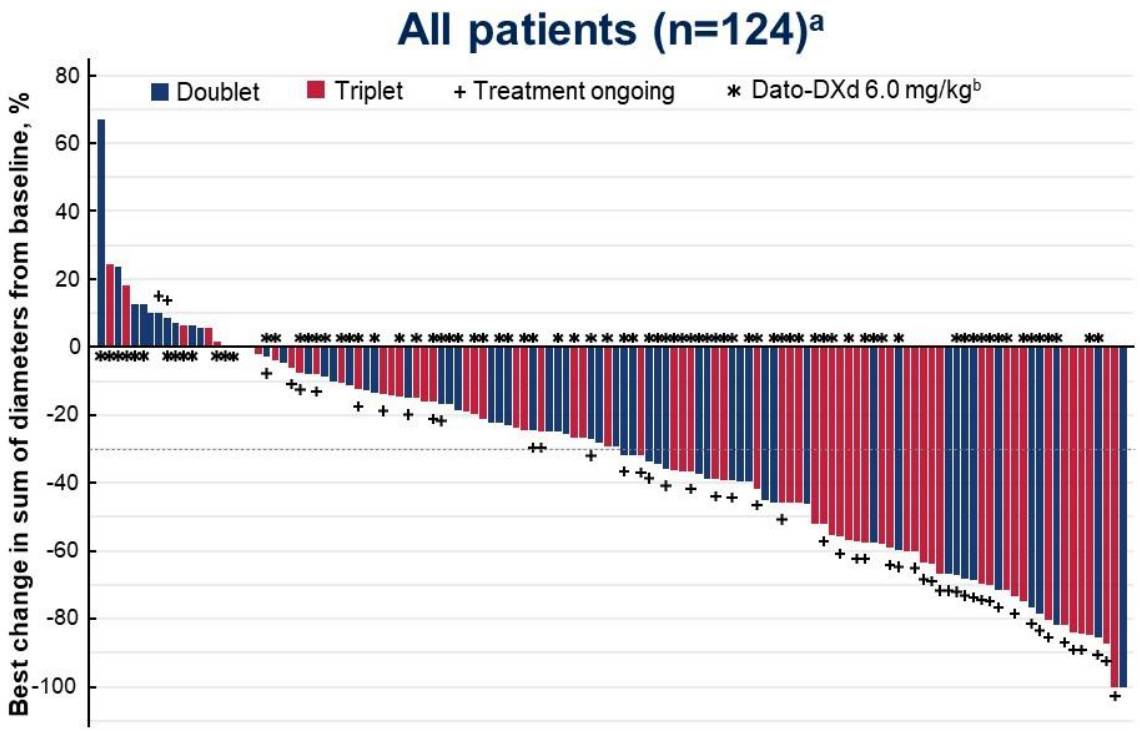
- In the 1L setting, the ORR (confirmed and pending)[d] was 50% in patients receiving doublet therapy and 57% in those receiving triplet therapy
- Among all patients, the DCR was 84% (doublet) and 87% (triplet); in the 1L setting, the DCR was 91% in both therapy subgroups

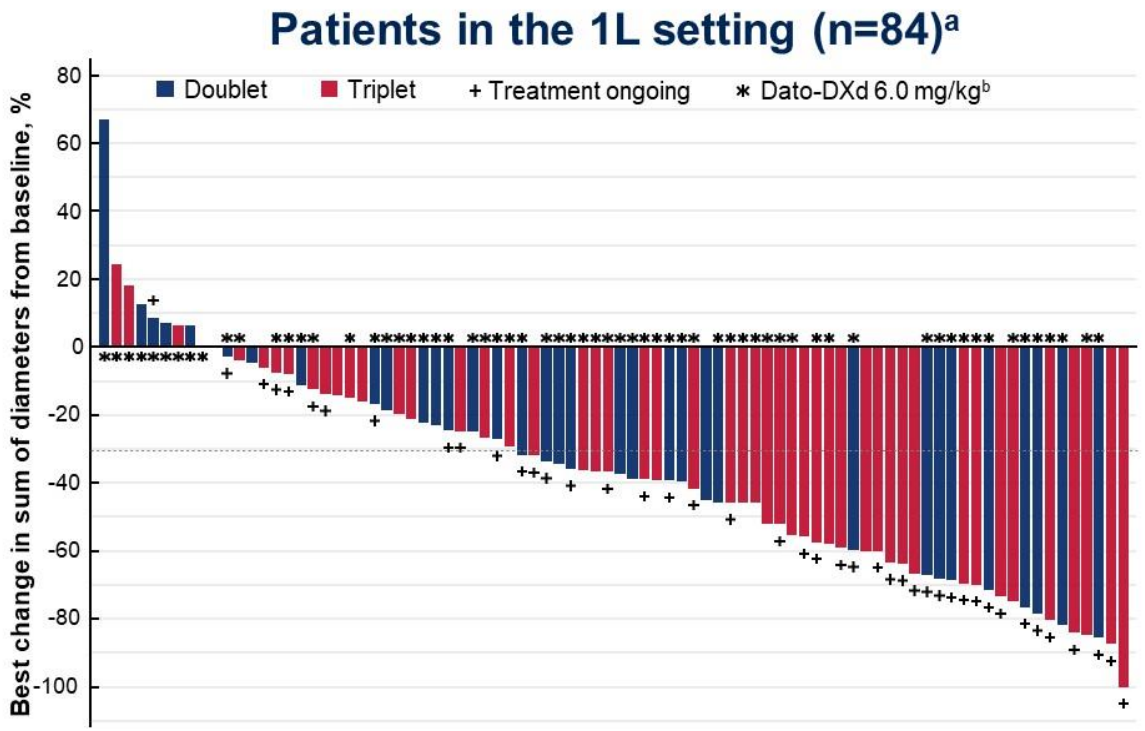
Preliminary PFS in all patients, median (95% CI), months: doublet, 8.3 (6.8-11.8); triplet 7.8 (5.6-11.1)[h]

Data cutoff: April 7, 2023.
1L, first line; 2L+, second line and later; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] By investigator. [b] Response-evaluable patients, which includes patients with ≥1 postbaseline overall response and those who discontinued without a postbaseline overall response. [c] ORR defined as BOR of CR + PR. [d] Responses pending confirmation. [e] BOR was determined using tumor assessments at different evaluation time points from the date of the first dose of study treatment until documented disease progression or the start of the next line of nonpalliative anticancer therapy (inclusive), whichever was earlier. [f] SD defined as ≥1 SD assessment (or better) ≥5 weeks after starting treatment and before progression without qualification for CR or PR (includes pending responses). [g] DCR defined as BOR of confirmed CR + confirmed PR + SD. [h] Preliminary PFS is limited by immature duration of follow-up.

Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Best Overall Tumor Change From Baseline



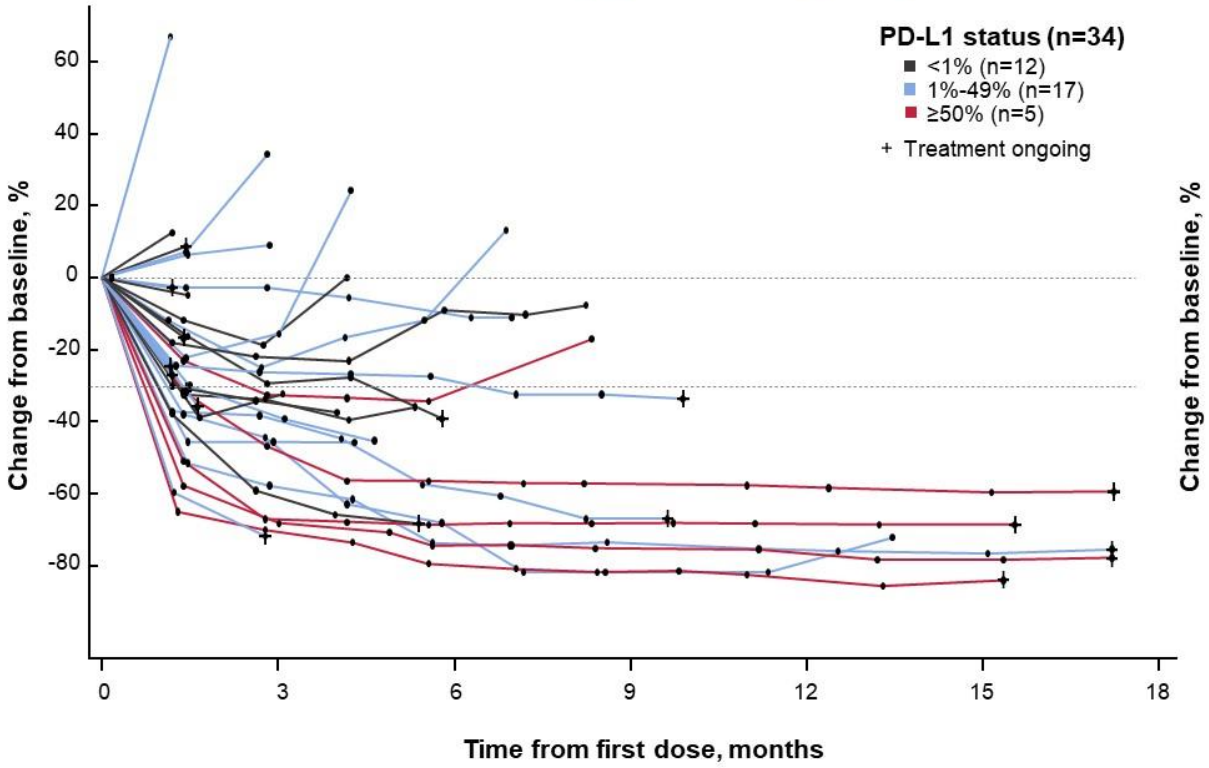


Data cutoff: April 7, 2023.
1L, first line.
[a] Patients with no baseline target lesions or no postbaseline tumor assessments were excluded from the waterfall plots. [b] Planned dose level.

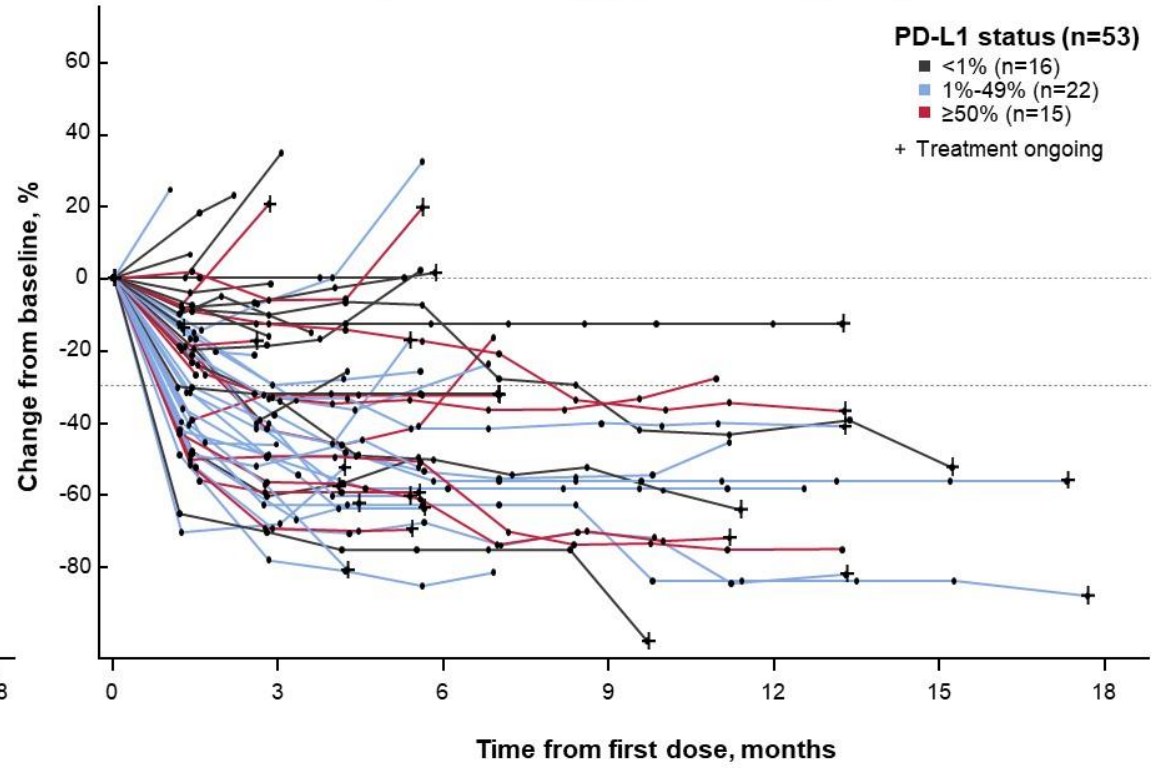
Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Depth and Duration of Response

Doublet therapy, 1L subgroup

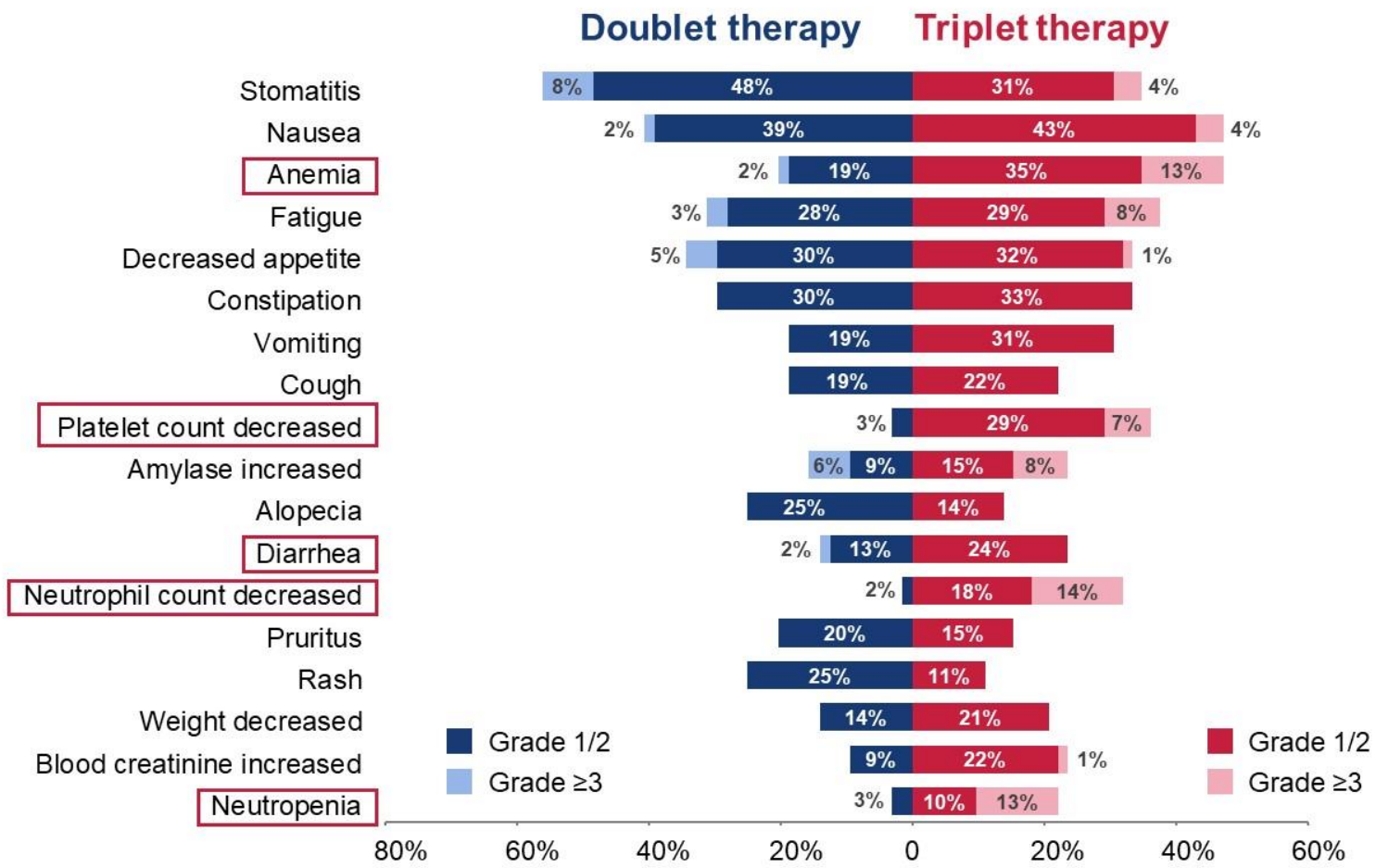


Triplet therapy, 1L subgroup



Data cutoff: April 7, 2023.
1L, first line; NE, not estimable; PD-L1, programmed death ligand 1.

TEAEs Occurring in ≥20% of Patients



Data cutoff: April 7, 2023.
TEAE, treatment-emergent adverse event.

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

Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Adverse Events of Special Interest

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

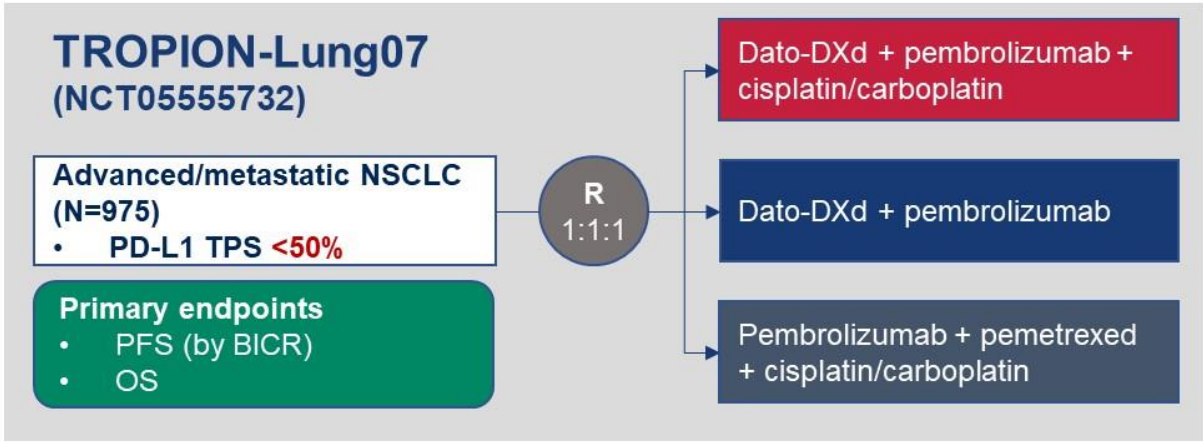
- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- No grade 5 AESIs have occurred
- There were no grade 4 or 5 adjudicated ILD/pneumonitis events[f]

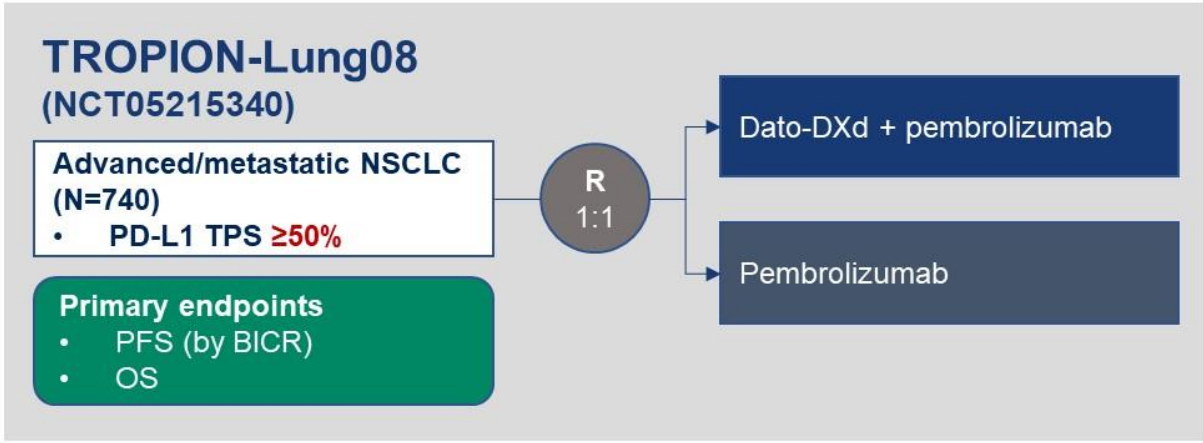
Data cutoff: April 7, 2023.
AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction.
[a] AESIs listed in this slide include all preferred terms that define the medical concept. [b] No cases of mucosal inflammation occurred in patients receiving doublet or triplet therapy. [c] Five ILD cases are pending adjudication. [d] The majority of these events were cases of dry eye (n=12 patients) and lacrimation increased (n=8 patients); grade ≥3 events were keratitis (n=2 patients) and dry eye (n=1 patient). [e] IRR refers to all IRR events that occurred in a patient who experienced any of the preselected preferred terms within the same day of Dato-DXd infusion. [f] There was 1 grade 5 event initially adjudicated as drug-related ILD in a patient receiving triplet therapy; this event was ultimately readjudicated to be grade 2.

Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Conclusions and Ongoing Studies With Pembrolizumab

- In this study, Dato-DXd + pembrolizumab ± platinum chemotherapy demonstrated encouraging antitumor activity in patients with NSCLC in the 1L and 2L+ settings
- No new safety signals were observed
  - The most frequent TEAEs of any grade were stomatitis, nausea, anemia, and fatigue
- Dato-DXd + pembrolizumab ± chemotherapy is being compared with SOC therapies in the 1L setting in the pivotal phase 3 TROPION-Lung07 and TROPION-Lung08 studies



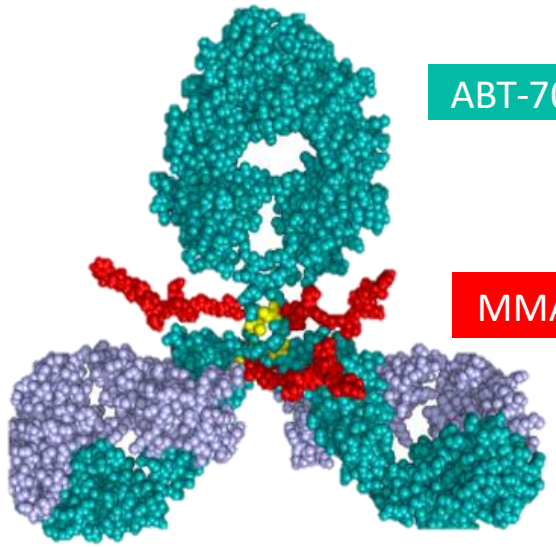


1L, first line; 2L+, second line and later; BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; R, randomized; SOC, standard of care; TEAE, treatment-emergent adverse event; TPS, tumor proportion score.

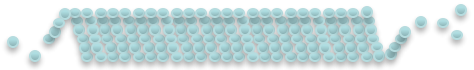
Goto, Y. ASCO 2023 Oral Presentation. Abstract 9005.

Telisotuzumab vedotin (ABBV-399) is a first-in-class anti-c-Met ADC delivering MMAE cytotoxin directly to tumor cells

Telisotuzumab vedotin: Anti-c-Met antibody (ABT-700) linked to cytotoxin (MMAE)



- Targets a unique epitope of c-Met receptor resulting in **blockade of both HGF-dependent and HGF-independent c-Met signaling**[1,2]
- MMAE is internalized, resulting in inhibition of microtubule polymerization[1,3]

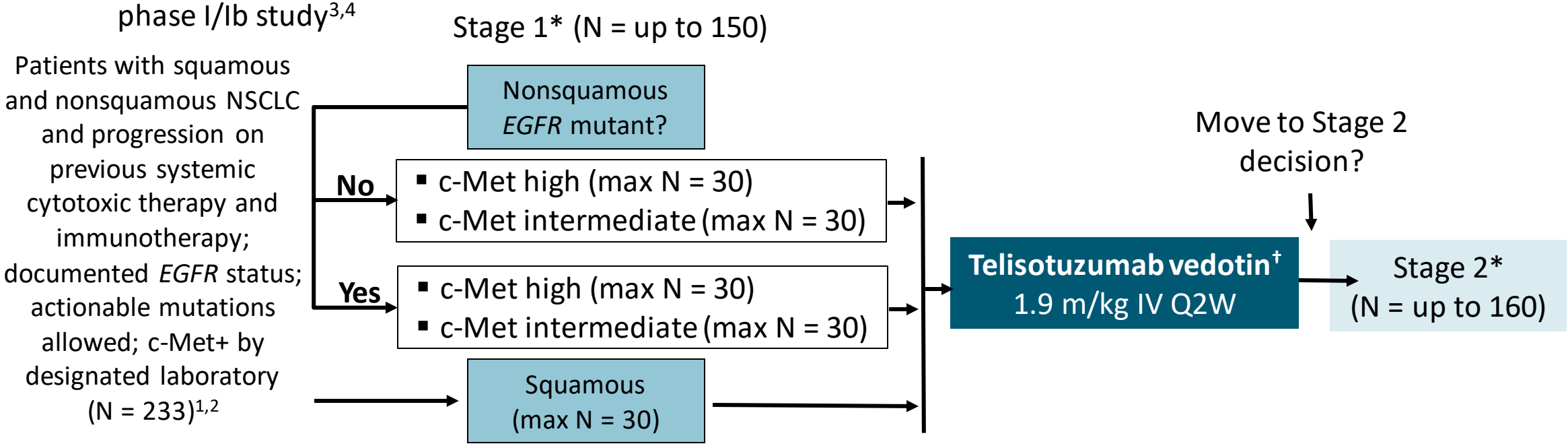


- Targeted delivery of cytotoxin MMAE to tumor via c-Met binding[1–3]
- Antitumor activity in both *MET* amplified and c-Met overexpressing tumor models[1]
- **MMAE acts via inhibition of microtubule polymerization rather than c-Met signaling inhibition seen with TKIs**[1,3]

1. Wang J, *et al. Clin Cancer Res* 2017; **23:**992–1000; 2. Gonzalez A, *et al. Int J Cancer* 2016; **139:**1851–1863; 3. Camidge R, *et al.* AACR 2021; Poster presentation CT179.

Phase II Study of Telisotuzumab Vedotin (ABBV-399) in c-Met–Positive NSCLC

- Open-label phase II study of safety and efficacy of telisotuzumab vedotin, an anti–c-Met ADC, in previously treated NSCLC[1,2]
  - Previously, telisotuzumab vedotin exhibited favorable safety and encouraging antitumor activity in a phase I/Ib study[3,4]

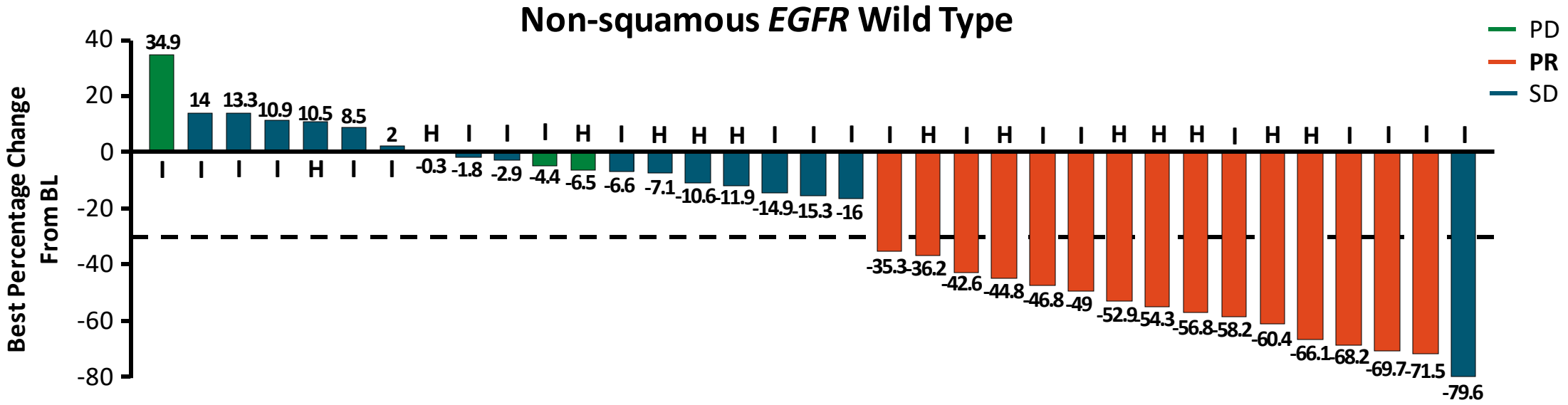


- **Primary endpoint:** ORR
- **Secondary endpoints:** DoR, DCR, PFS, and OS

1. NCT03539536. 2. Ocampo. WCLC 2019. Abstr P2.01-19.
3. Strickler. JCO. 2018;36:3298. 4. Camidge. ASCO 2018. Abstr 3011.

NORTH CAROLINA Oncology Association

Telisotuzumab Vedotin (ABBV-399) in c-Met–Positive NSCLC: Responses



NSCLC Group	ORR (CR+PR) by ICR, n/N (%) [95% CI]	ORR (CR+PR) by INV, n/N (%) [95% CI]	mDOR by ICR, mos [95% CI]	mDOR by INV, mos [95% CI]
Non-Sq *EGFR* WT	13/37 (35.1) [20.2, 52.5]	13/36 (36.1) [20.8, 53.8]	6.9 [3.8, -]	5.5 [4.2, 9.6]
c-Met high	7/13 (53.8) [25.1, 80.8]	6/12 (50.0) [21.1, 78.9]	----	----
c-Met int	6/24 (25.0) [9.8, 46.7]	7/24 (29.2) [12.6, 51.1]	----	----
Non-Sq *EGFR* MU	4/30 (13.3) [3.8, 30.7]	8/31 (25.8) [11.9, 44.6]	NA	5.9 [2.6, -]
c-Met high	4/22 (18.2) [5.2, 40.3]	8/22 (36.4) [17.2, 59.3]	----	----
c-Met int	0/8 (0) [-, -]	0/9 (0) [-, -]	----	----
Sq	3/21 (14.3) [3.0, 36.3]	1/22 (4.5) [0.1, 22.8]	4.4 [3.0, -]	4.4 [-, -]

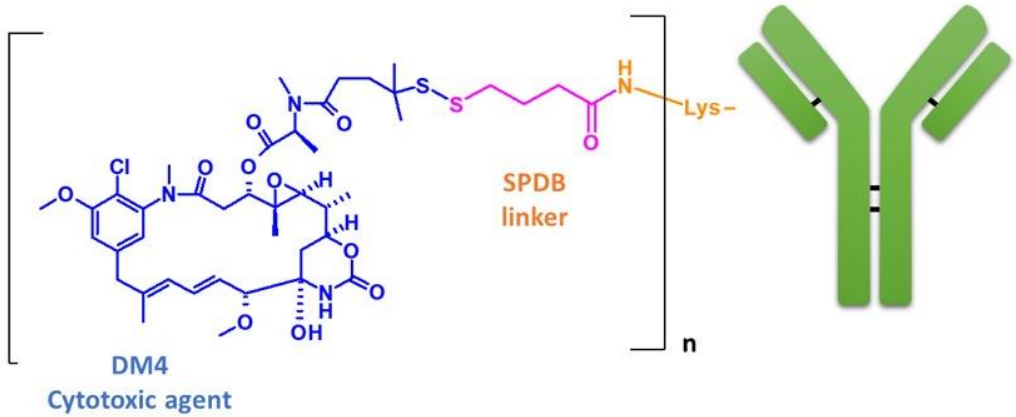
Camidge. AACR 2021. Abstr CT179

Slide credit: clinicaloptions.com

Tusamitamab ravtansine (SAR40871) a potent first-in-class ADC that selectively targets CEACAM5-expressing tumors

- CEACAM5 is overexpressed in several tumor types, including NSQ NSCLC[1]

Structure of SAR408701



Humanized antibody: Specific for **CEACAM5**

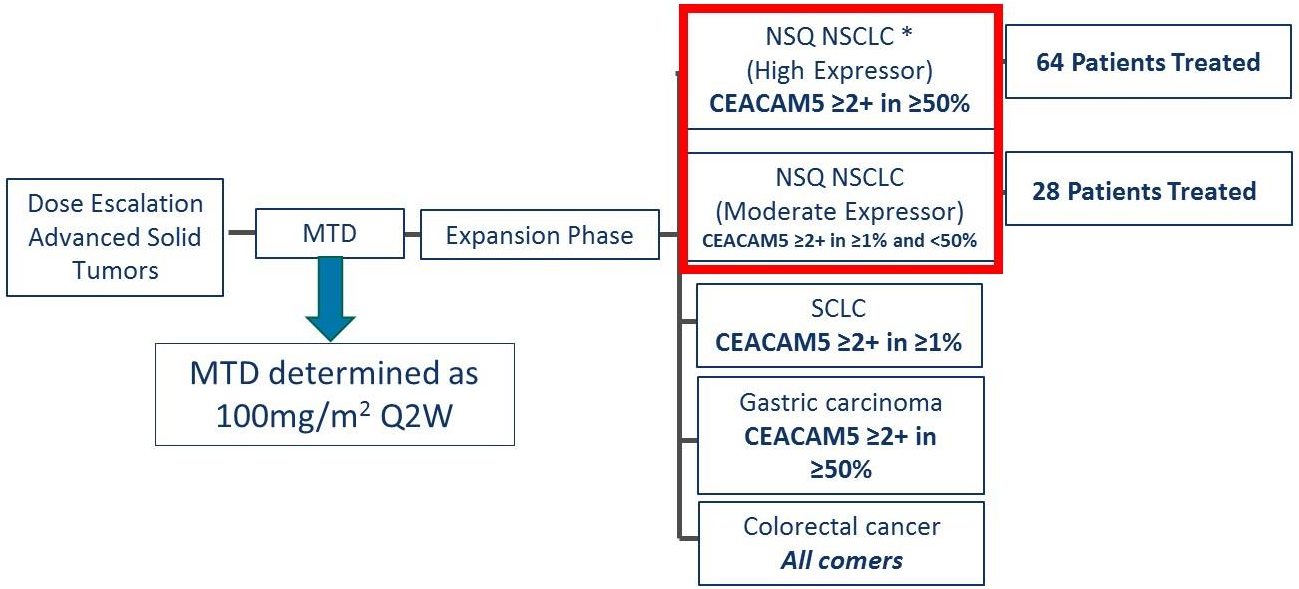
Cytotoxic agent: Maytansinoid **DM4** (inhibits tubulin polymerization)

SPDB linker: Cleavable inside cells

Gazzah A, Ann Oncol. 2022 Apr;33(4):416-425

Study Design

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)

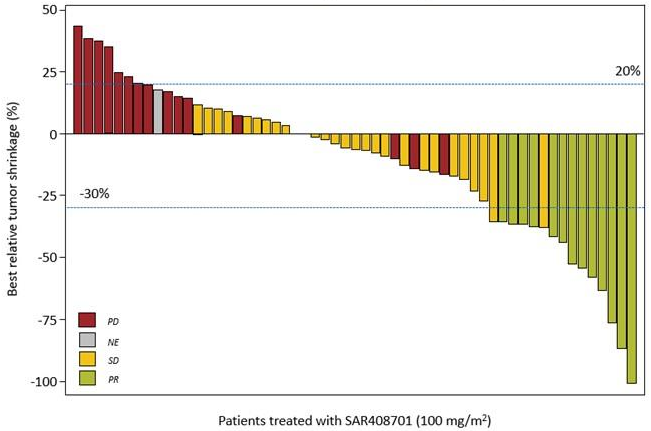
Gazzah A, Ann Oncol. 2022 Apr;33(4):416-425

Best Overall Response

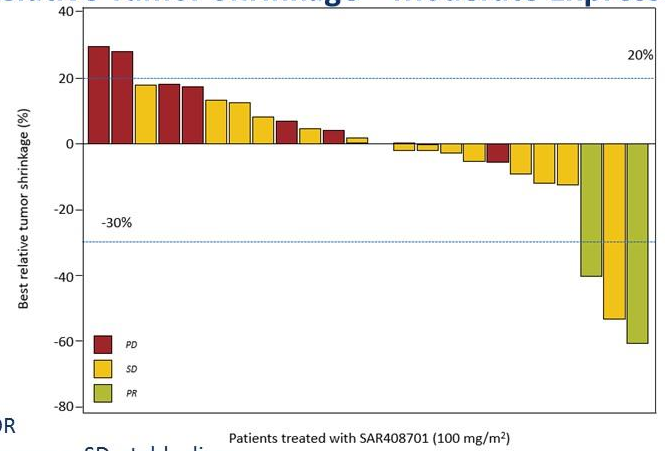
Overall Population

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 – High Expressor Cohort



Best Relative Tumor Shrinkage – Moderate Expressor Cohort



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.

Gazzah A, Ann Oncol. 2022 Apr;33(4):416-425

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)

Gazzah A, Ann Oncol. 2022 Apr;33(4):416-425

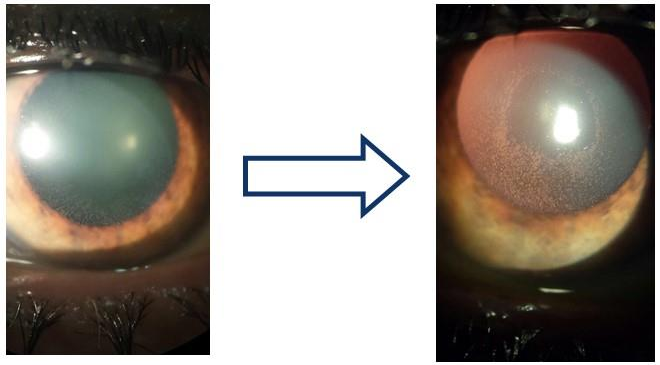
Dose Modification and Ocular Events – Pooled Data of NSCLC Cohorts

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%)

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%)

DM4-induced microcystic corneal dystrophy



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

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

Gazzah A, Ann Oncol. 2022 Apr;33(4):416-425

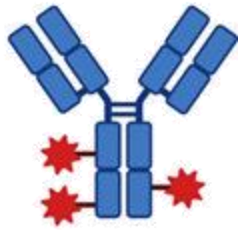
Select ADC Clinical Trials in Advanced/Metastatic NSCLC

Trial	Phase	Study population	ADC target	Treatment arm(s)	Estimated enrollment	Primary endpoint(s)
EVOKE-01	3	Advanced/metastatic NSCLC with progression on or after platinum-based CT and IO	TROP2	Sacituzumab govitecan vs docetaxel	520	OS
CARMEN-LC03	3	Previously treated, CEACAM5+ metastatic nonsquamous NSCLC	CEACAM5	Tusamitamab ravtansine vs docetaxel	554	PFS OS
TROPION LUNG 01	3	Advanced/metastatic NSCLC with progression on or after platinum-based CT and IO	TROP2	Datopotamab deruxtecan vs docetaxel	500	PFS OS
LUMINOSITY	2	Previously treated c-MET+ locally advanced or metastatic NSCLC	C-MET	Telisotuzumab vedotin	270	ORR
HERTHENA-Lung01	2	Previously treated metastatic or locally advanced EGFRm NSCLC	HER3	Patritumab deruxtecan	420	ORR
DESTINITY Lung04	3	Treatment Naive HER 2 mutation + adenocarcinoma	HER2	Trastuzumab deruxtecan	260	PFS

What's next for ADCs

First generation ADCs

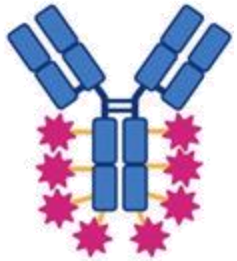
e.g. T-DM1



-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

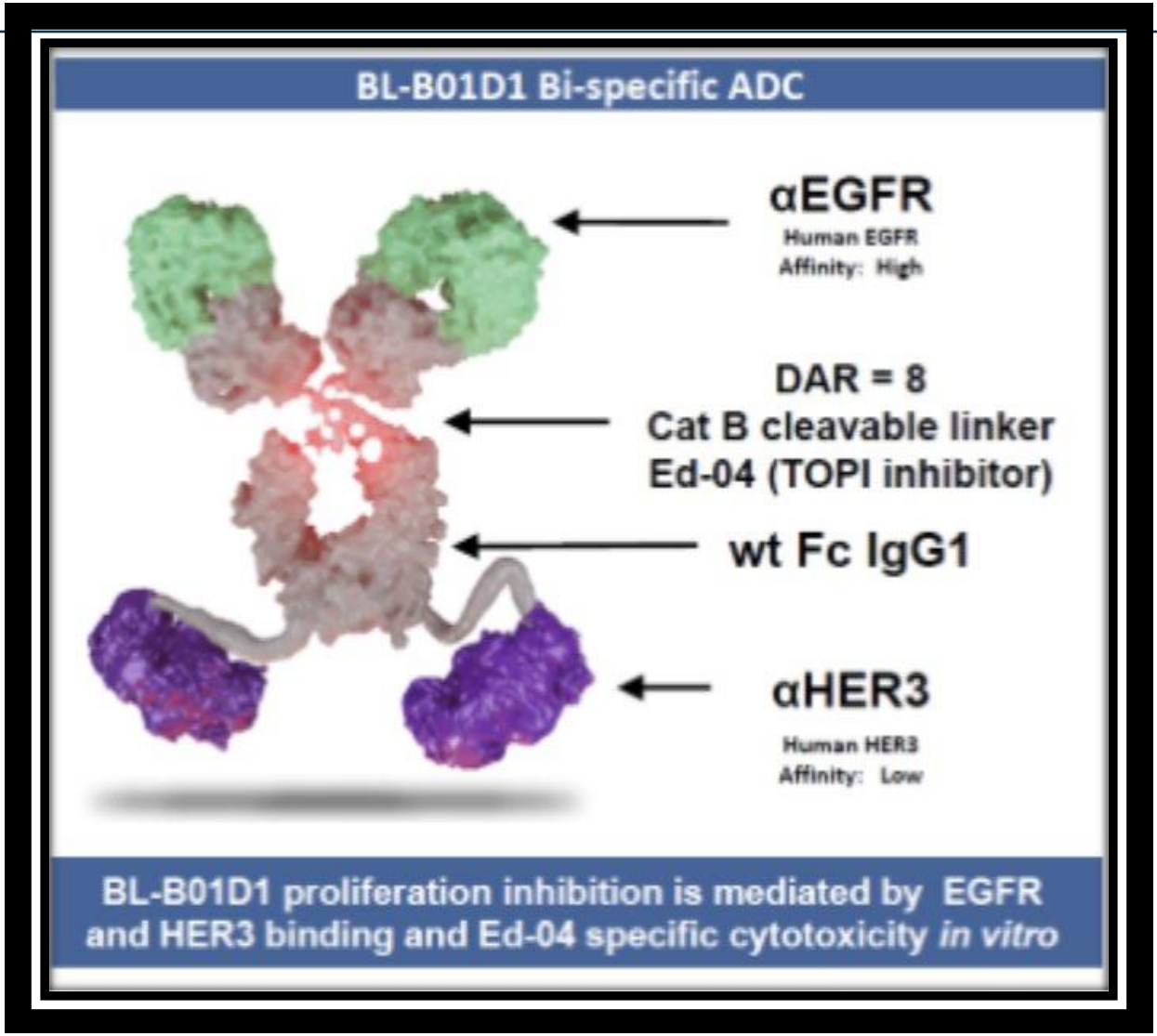
2) Dual-payload ADCs

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

4) Radionuclide ADCs

Tarantino et al. CA Cancer J Clin (2022)

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic solid tumor: Results from a first-in-human phase 1 study.



NSCLC (EGFRmut) (n=34)[1]	NSCLC (EGFRwt) (n=42)[2]	(SCLC) (n=7)	(NPC) (n=24)	HNSCC (n=13)	
Median prior treatment line (range)	4 (1-7)	2 (1-8)	2 (1-2)	3 (1-9)	3 (1-7)
Best overall response, n[3]					
cPR	15	7	1	3	/
PR[4]	6	10	0	8	1
SD (n with shrinkage)	10 (10)	23 (16)	5 (4)	13 (12)	9 (8)
PD	3	2	1	/	3
ORR[5], % (95% CI)	61.8 (43.6-77.8)	40.5 (25.6-56.7)	14.3 (0.4-57.9)	45.8 (25.6-67.2)	7.7 (0.2-36.0)
DCR, % (95% CI)	91.2 (76.3-98.1)	95.2 (83.8-99.4)	85.7% (42.1-99.6)	100% (85.8-100)	76.9% (46.2-95.0)

Conclusions

- Antibody drug conjugates (ADCs) represent a novel therapeutic for patients with NSCLC
- Key components include the antibody, linker and warhead
- Further work both preclinically and clinically needs to be done to better understand how these drugs work
- Outstanding questions
  - Biomarker selection
  - Toxicity mitigation
  - BBB activity?
  - Combination strategies