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Advances in Cancer Immunotherapy™

Antibody Drug Conjugates in Practice: Emerging Toxicities and Management Strategies in Breast Cancer

Aditya Bardia, MD, MPH
Director, Breast Cancer Research Program,
Associate Professor, Harvard Medical School,
Massachusetts General Hospital, Boston, MA

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Disclosures

- Consulting Fees: Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics/Gilead, Sanofi, Daiichi Pharma/Astra Zeneca, Phillips, Eli Lilly, Foundation Medicine
- Contracted Research: Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics/Gilead, Daiichi Pharma/Astra Zeneca, Eli Lilly.

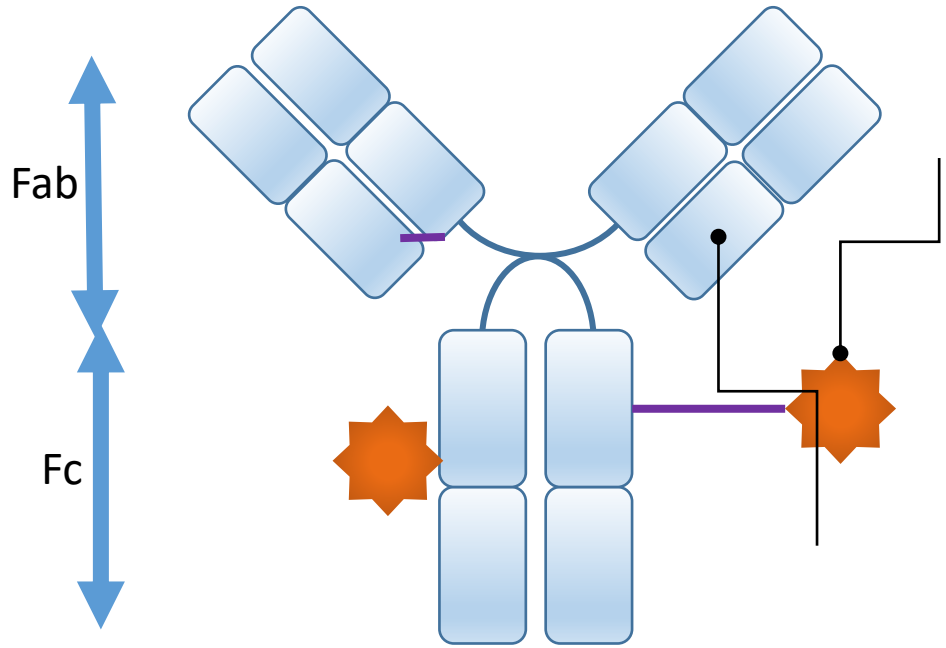
- I will be discussing non-FDA approved indications during my presentation.

Targets

- Understand the concept of novel antibody drug conjugates (ADCs) and relevant mechanism of action
- Review the common toxicities with ADCs and management strategies
- Evaluate the upcoming ADC therapies and expected toxicities

Components of ADC

Antibody
- High affinity and specificity to tumor antigen
- Efficient internalization
- Reduced immunogenicity
- ADCC/CDC



Payload
- Highly potent
- Microtubule inhibitors
  - Auristatins
  - Maytansines
- DNA damaging agents
  - Calicheamicin
  - Duocarmycins
  - SN-38

Linker
- Stable in the blood stream
- Capable of releasing payload once internalized

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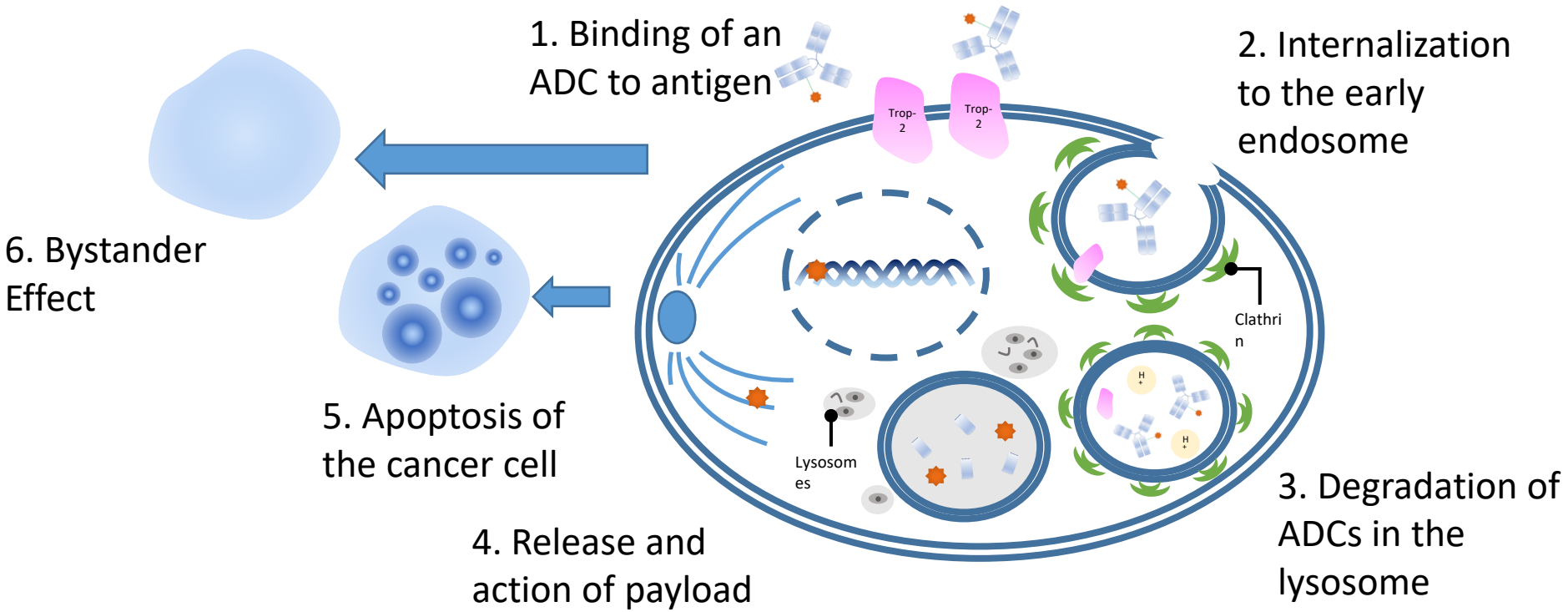
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Targeted payload delivery

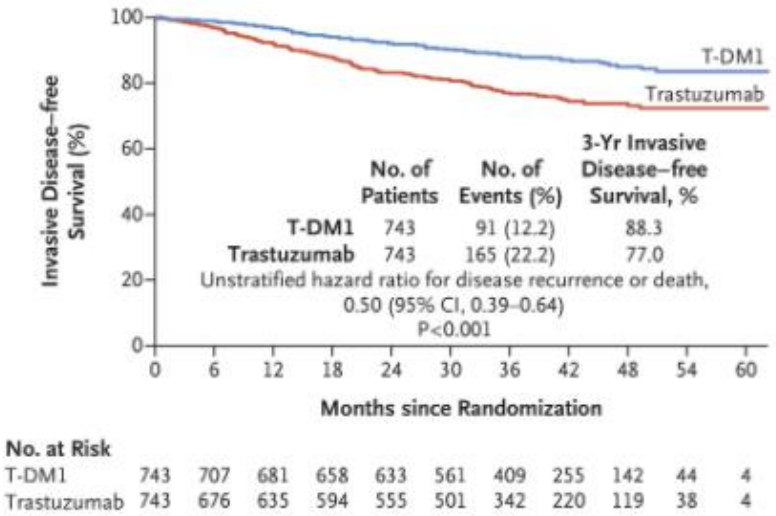


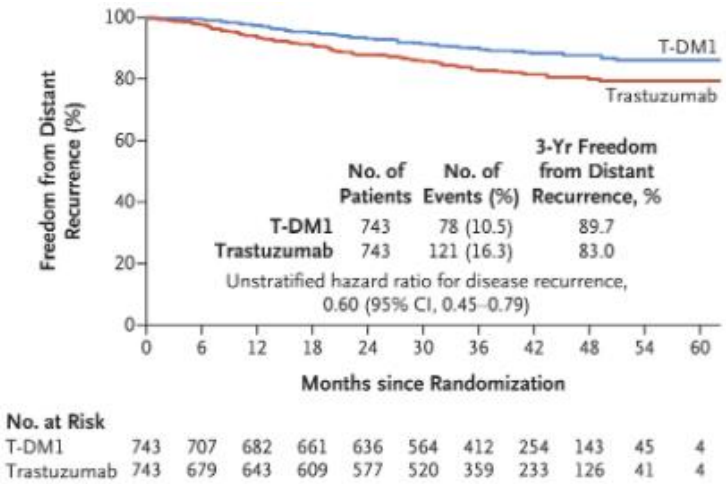
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

ADCs Approved in Breast Cancer

- Ado-trastuzumab emtansine (T-DM1)
- Fam-trastuzumab deruxtecan (DS-8201)
- Sacituzumab govitecan (IMMU-132)

T-DM1 Approval in HER2+ Breast Cancer





First ADC Approved for Early Breast Cancer

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Von Minckwitz G et al. NEJM. 2019.

T-DM1: Toxicity

Adverse Effect	Any Grade	Grade 3/4
Nausea	41.6%	0.5%
Thrombocytopenia	28.5%	3.6%
AST/ALT increase	23.1%	0.4%
Peripheral Neuropathy	18.6%	1.4%
Pneumonitis	2.6%	NR

Von Minckwitz G et al. NEJM. 2019.

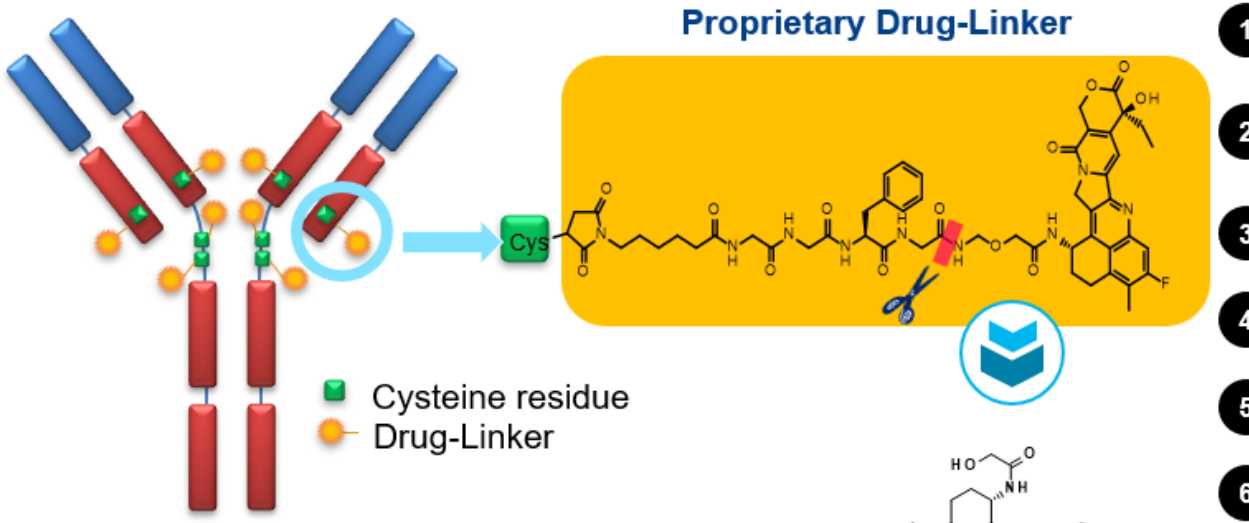
T-DM1: Management

Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	Grade 1 or 2 (≥75 x 10^9/L)	No dose adjustment required.
	Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Restart T-DM1 at the same dose level.
	Grade 4 (<25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Restart T-DM1 at the next lower dose level.

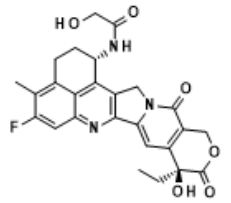
***Similarly for AST/ALT elevation**

Trastuzumab Deruxtecan (T-DXd): HER2 ADC with bystander effect

Trastuzumab Deruxtecan is a HER2 targeted ADC with 7 key attributes



Conjugation chemistry
The tetrapeptide-based cleavable linker is connected to cysteine residues on the humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab antibody

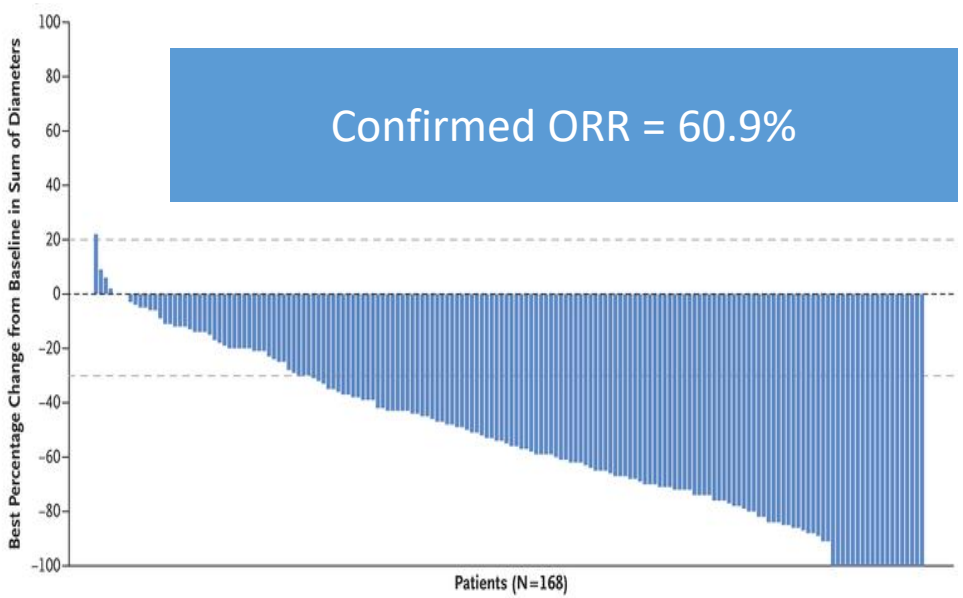


Proprietary Payload (DXd)
Exatecan derivative

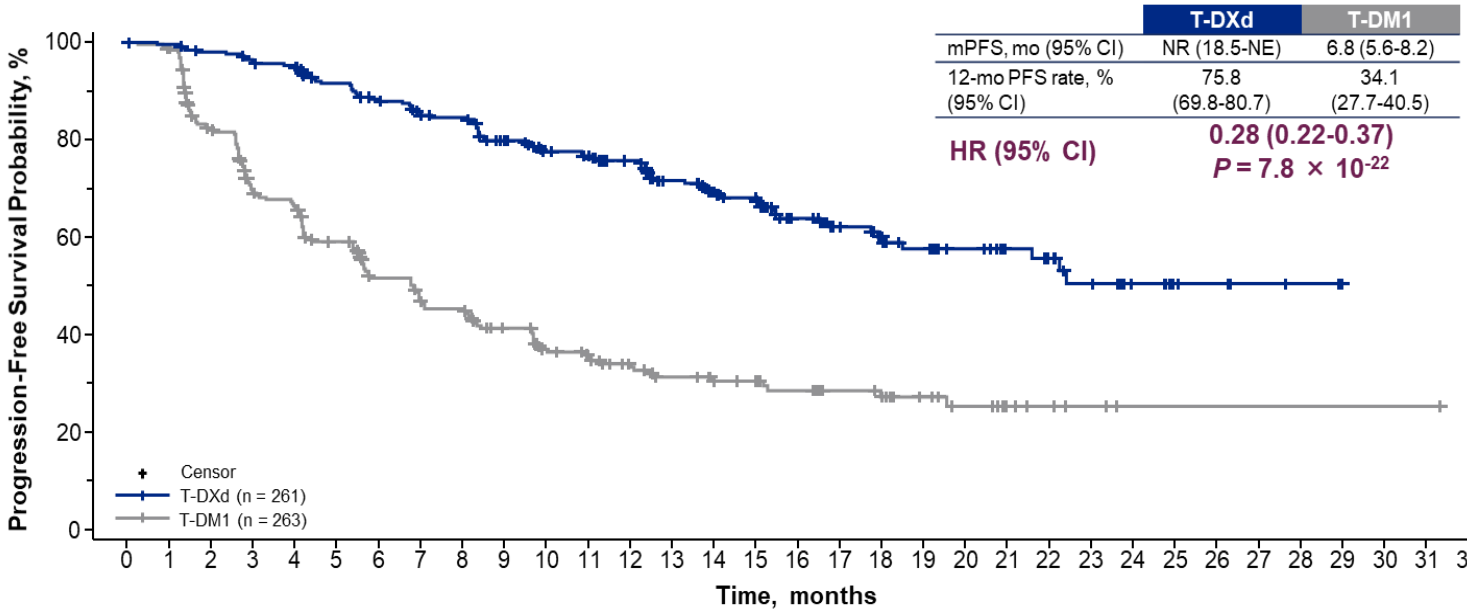
1. Topoisomerase I inhibitor payload
2. High potency of payload based on a cell-free assay topoisomerase I-mediated DNA relaxation assay
3. Payload with a short systemic half-life
4. Highly membrane permeable, which may enable a bystander effect
5. Stable in plasma
6. Designed to be cleaved by lysosomal enzymes overexpressed in tumor cells
7. Drug-to-antibody ratio of 7-8

ADC=antibody-drug conjugate; HER2=human epidermal growth factor receptor 2

Trastuzumab Deruxtecan (T-DXd): HER2+ MBC (Destiny-01 and 03)



Confirmed ORR = 60.9%



FDA Approval based on single arm phase 2 trial

Superior activity compared to T-DM1

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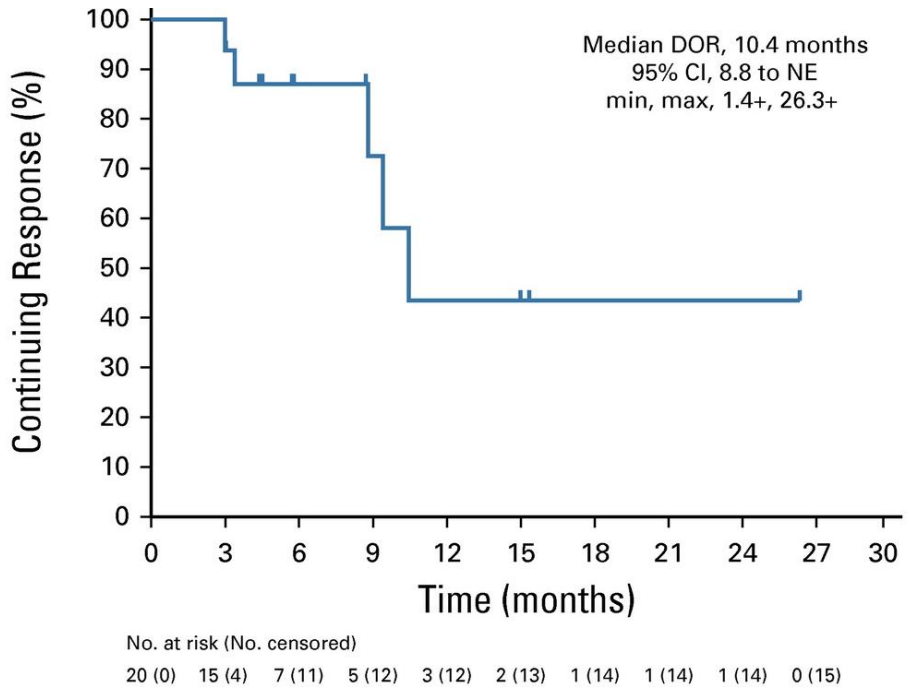
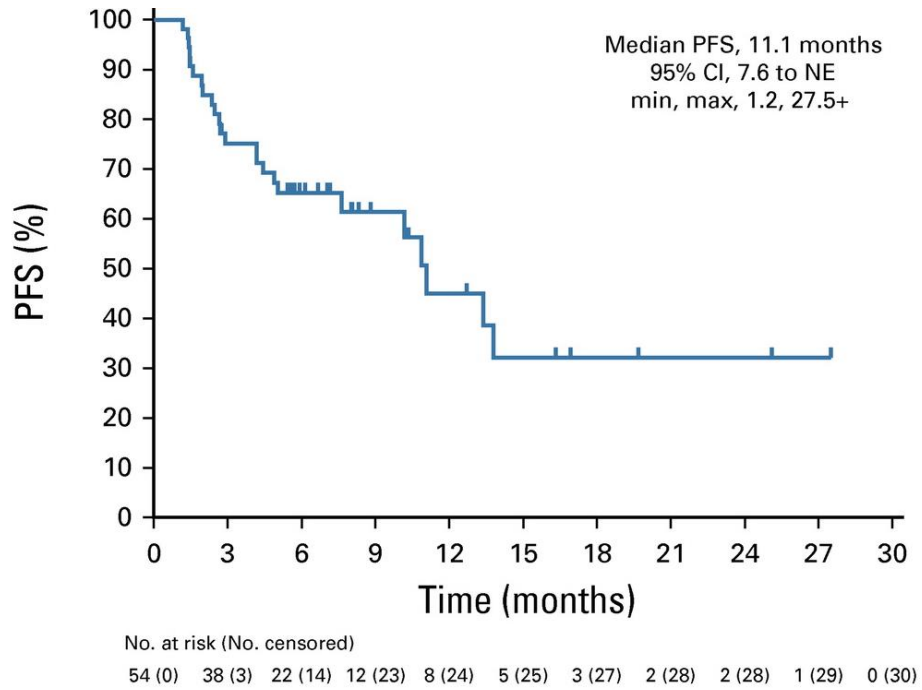
Modi S et al. NEJM 2020; Cortes J et al. ESMO 2021

Trastuzumab Deruxtecan (T-DXd): HER2 Low Tumors

Confirmed ORR = 44.4%





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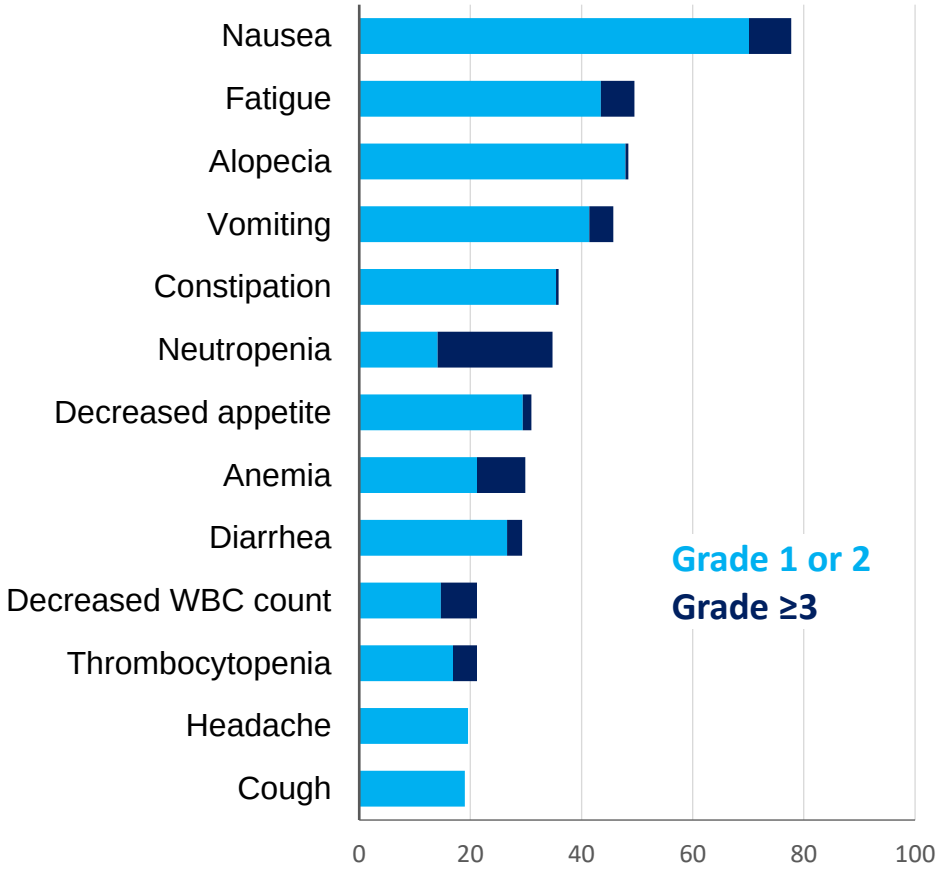
Modi S et al. J Clin Oncol. 2020.

Treatment Related Adverse Effects: Trastuzumab Deruxtecan



Different AE profile than T-DM1

Modi S et al. NEJM 2020

Adverse Effects: Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortes J et al. ESMO 2021

Pneumonitis Management: Initial work-up

Early recognition and treatment are critical to improving outcomes:

- Condition may be asymptomatic (Gr1) which only changes on radiographic imaging or is accompanied by symptoms including cough, shortness of breath, fever
- Evaluate for alternative etiology (infection, disease progression, other medications)
- In the absence of clear alternative etiology, all events should be considered to be related to T-DXd
- Management of all toxicities should be per toxicity related guidelines until toxicity resolves, unless or until proved to be due to alternate etiology
- Consider High-resolution CT scan of chest, and pulmonology or infectious disease consultation

Pneumonitis

Grade 1 (asymptomatic: clinical or diagnostic observations only)

- Monitor closely (weekly if indicated)
- Consider starting systemic steroids
- If no improvement or there is evidence of worsening radiologic, oximetric or PFT markers consider treating as G2 event
- If event resolves, re-start T-DXd

Grade 2 (Symptomatic; medical intervention indicated; limiting instrumental ADL)

- Monitor symptoms closely
- Promptly start systemic steroids (≥ 1 mg/kg/day of prednisone or equivalent) for ≥ 14 days or until complete resolution of clinical and Chest CT findings, followed by gradual taper over at least 4 weeks
- If no clinical improvement within 5 days of initial steroid therapy, re-evaluate for other causes, and/or switch to IV steroids such as methylprednisolone 2mg/kg/day
- **DISCONTINUE T-DXd**

Grade 3 or 4 (Severe symptoms, O2 indicated, life-threatening respiratory compromise

- Hospitalization required
- Promptly start methylprednisolone pulse therapy (500 – 1000mg/day) x 3 days followed by 1mg/kg/day of prednisone (or equivalent) for ≥ 14 days or until clinical resolution of clinical and Chest CT findings, followed by gradual taper over at least 4 weeks
- If no improvement within 3-5 days, re-evaluate with additional work-up for alternative causes. Consider other immunosuppressants
- **DISCONTINUE T-DXd**

Slide Courtesy: Sponsor

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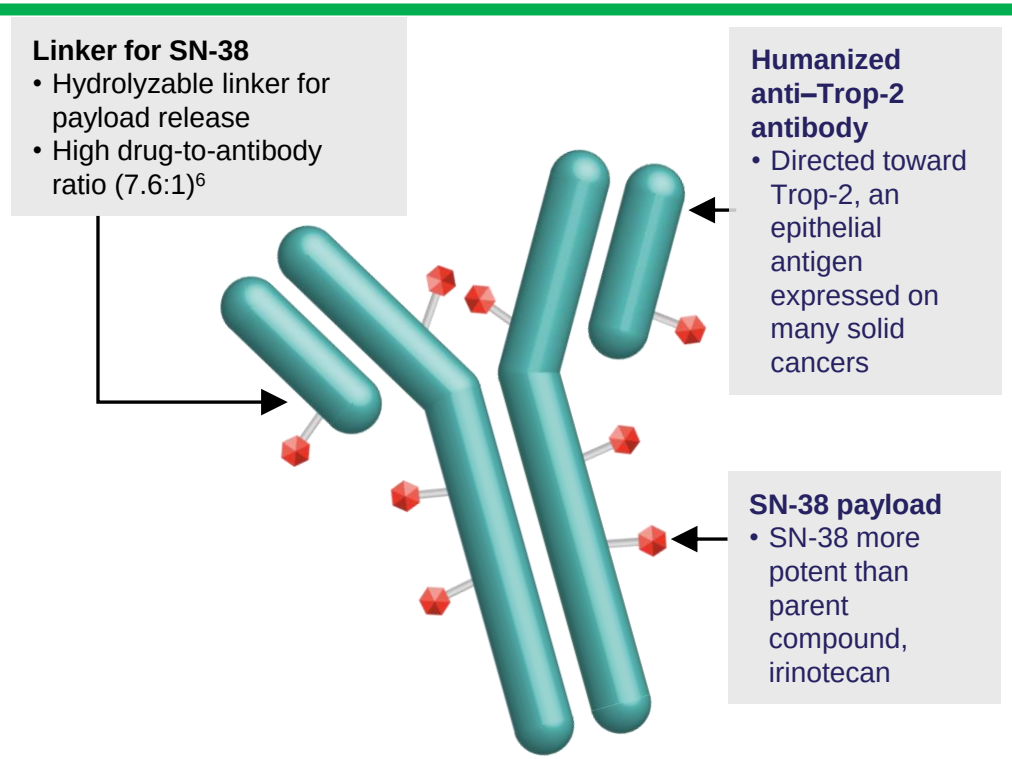
Sacituzumab Govitecan (IMMU132): ADC Targeting *trop-2* in TNBC

Sacituzumab Govitecan: First-in-class trop2 ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



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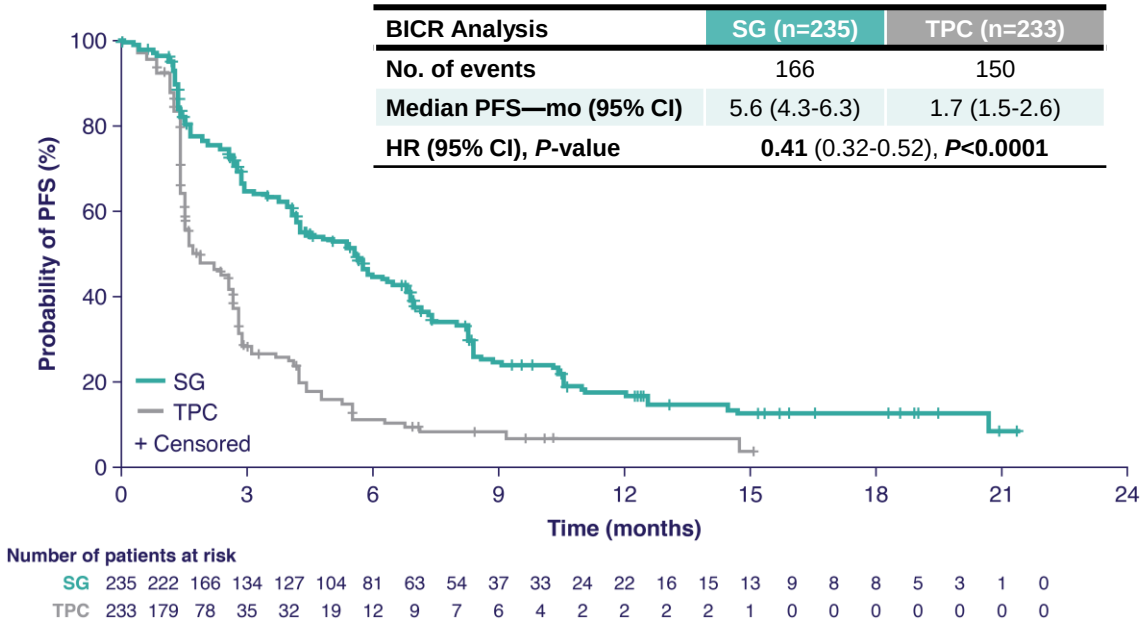
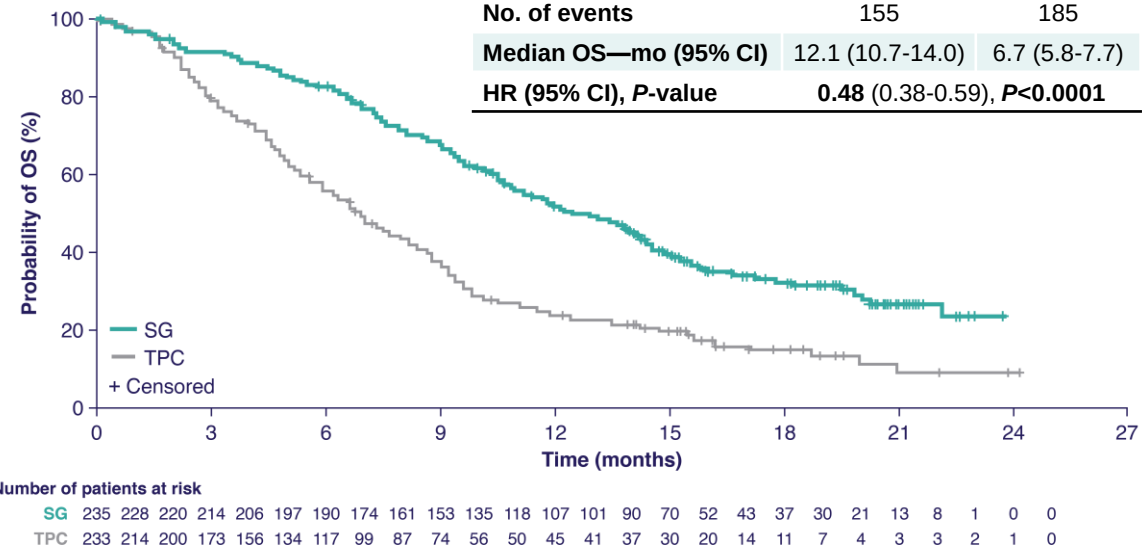
Bardia A et al. *ESMO.* 2020.

Sacituzumab Govitecan vs TPC



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Progression-Free Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Overall Survival

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Bardia A et al. *NEJM.* 2021.

Treatment Related Adverse Effects: Sacituzumab Govitecan (vs TPC)

		SG (n=258)			TPC (n=224)		
TRAE*		All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia**[†]	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia[‡]	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia[§]	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG

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Bardia A et al. *NEJM.* 2021.

Toxicity Management: Sacituzumab Govitecan

Adverse Event	Suggested Intervention

Neutropenia (Absolute neutrophil count below 1500/mm^3 on Day 1 or below 1000/mm^3 on Day 8 of any cycle)	- Initiate anti-infective treatment in patients with febrile neutropenia
	- Withhold treatment until resolved to Grade 1 and reduce subsequent doses
	  - First occurrence: 25% dose reduction and administer G-CSF
	  - Second occurrence: 50% dose reduction
	  - Third occurrence: Discontinue treatment

Diarrhea	- Give fluids and electrolytes as needed
	- Administer Atropine, if not contraindicated, for early diarrhea of any severity
	- At onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide
	- If severe diarrhea occurs, withhold treatment until resolved to Grade 1 and reduce subsequent doses
	  - First occurrence: 25% dose reduction
	  - Second occurrence: 50% dose reduction
	  - Third occurrence: Discontinue treatment

Other Adverse Events Grade ≥ 3	- Discontinue until resolved to Grade 1 and reduce subsequent doses:
	  - First occurrence: 25% dose
	  - Second occurrence: 50% dose reduction
	  - Third occurrence: Discontinue treatment

TRODELVY® (sacituzumab govitecan) [prescribing information]. 04/2021.

Drug Metabolism and toxicity: Sacituzumab Govitecan

UGT1A1 polymorphisms may modulate Incidence of Adverse Events

		SG (n=250)†					
		*1/*1 Wild-Type (n=113)		*1/*28 Heterozygous (n=96)		*28/*28 Homozygous (n=34)	
	TRAE‡	All grade, %	Grade ≥3, %	All grade, %	Grade ≥3, %	All grade, %	Grade ≥3, %
Hematologic	**Neutropenia§**	**76 (67)**	**60 (53)**	**55 (57)**	**45 (47)**	**24 (71)**	**20 (59)**
	Anemia‖	37 (33)	5 (4)	29 (30)	6 (6)	16 (47)	5 (15)
	Leukopenia**	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
	Lymphopenia¶	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
	Febrile neutropenia	**3 (3)**	**3 (3)**	**5 (5)**	**5 (5)**	**6 (18)**	**6 (18)**
	Thrombocytopenia≡	3 (3)	0	6 (6)	0	4 (12)	4 (12)
Gastrointestinal	**Diarrhea**	**65 (58)**	**11 (10)**	**57 (59)**	**9 (9)**	**21 (62)**	**5 (15)**

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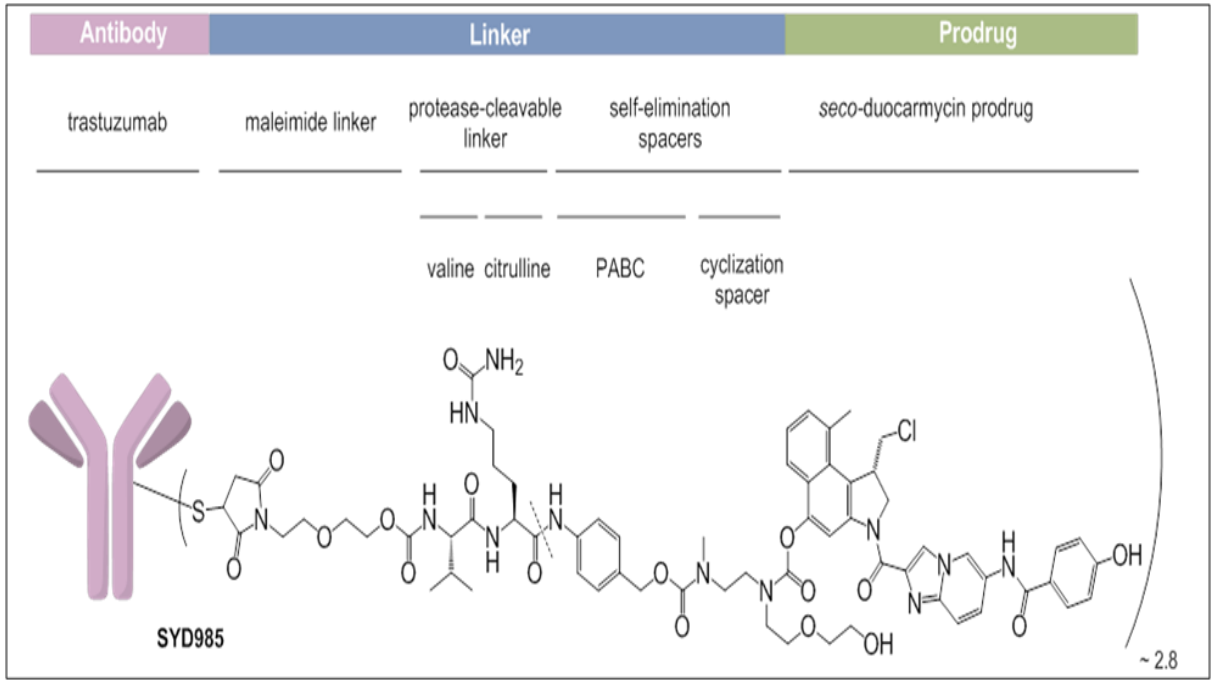
Rugo H et al. SABCS. 2020.

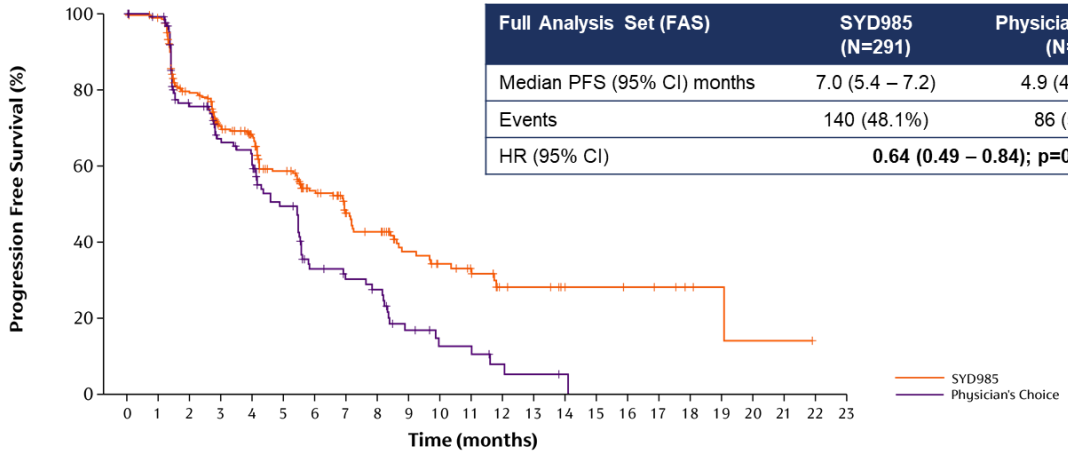
Adverse Effects: Summary

Drug	Toxicity
Ado-trastuzumab emtansine (T-DM1)	Thrombocytopenia, Peripheral Neuropathy
Trastuzumab deruxtecan (DS-8201a)	GI toxicity, Pneumonitis
Sacituzumab govitecan (IMMU-132)	Myelosuppression, GI toxicity

How about other Drugs?

Trastuzumab-Duocarmazine: HER2 ADC





Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

No. Patients at Risk																							
SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

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Dokter W et al. *Mol Cancer Ther.* 2014; Saura C, et al ESMO 2021.

Adverse Events and Management: Trastuzumab-Duocarmazine

Eye toxicity: Reported for 78.1% SYD985 patients, physician's choice 29.2%

- Grade ≥ 3 for 21.2% SYD985 patients
- Discontinuation of treatment due to eye toxicity in 20.8% of SYD985 patients
- Dose modifications due to eye toxicity in 22.9% of SYD985 patients

Risk mitigation strategy in trial: Patients with prior keratitis excluded, prophylactic lubricating eye drops, regular eye exams by ophthalmologist, Grade 3 or higher keratitis stop treatment, grade 3 conjunctivitis delay treatment until reduced to grade 2

ILD/pneumonitis: Reported for 7.6% (N=22/288) SYD985 patients, not reported for physician's choice

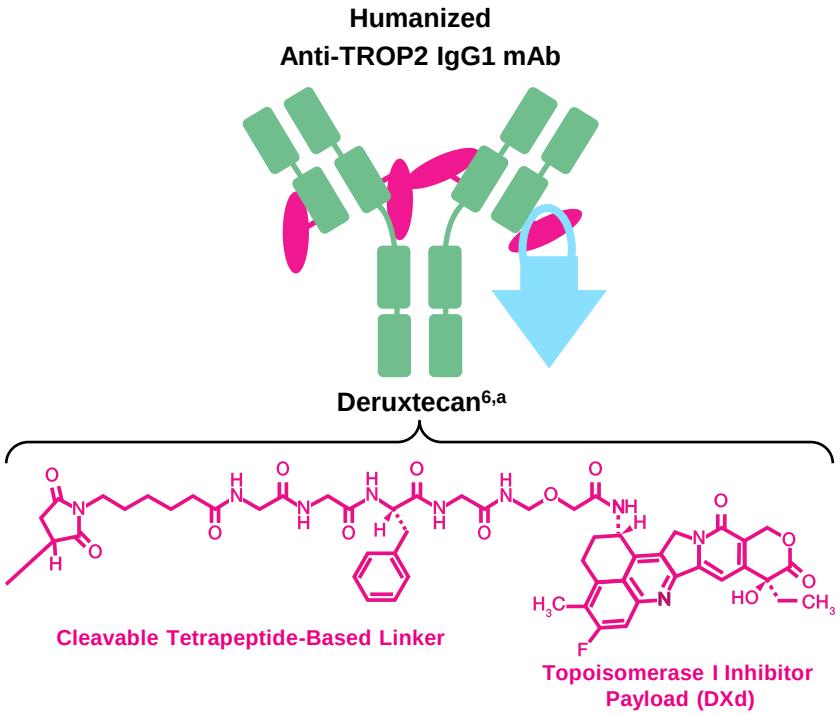
- Grade ≥ 3 for 2.4% SYD985 patients
- Discontinuation of treatment due to ILD/Pneumonitis in 15 (5.2%) of SYD985 patients
- Dose modifications due to ILD/Pneumonitis in 6 (2.1%) of SYD985 patients

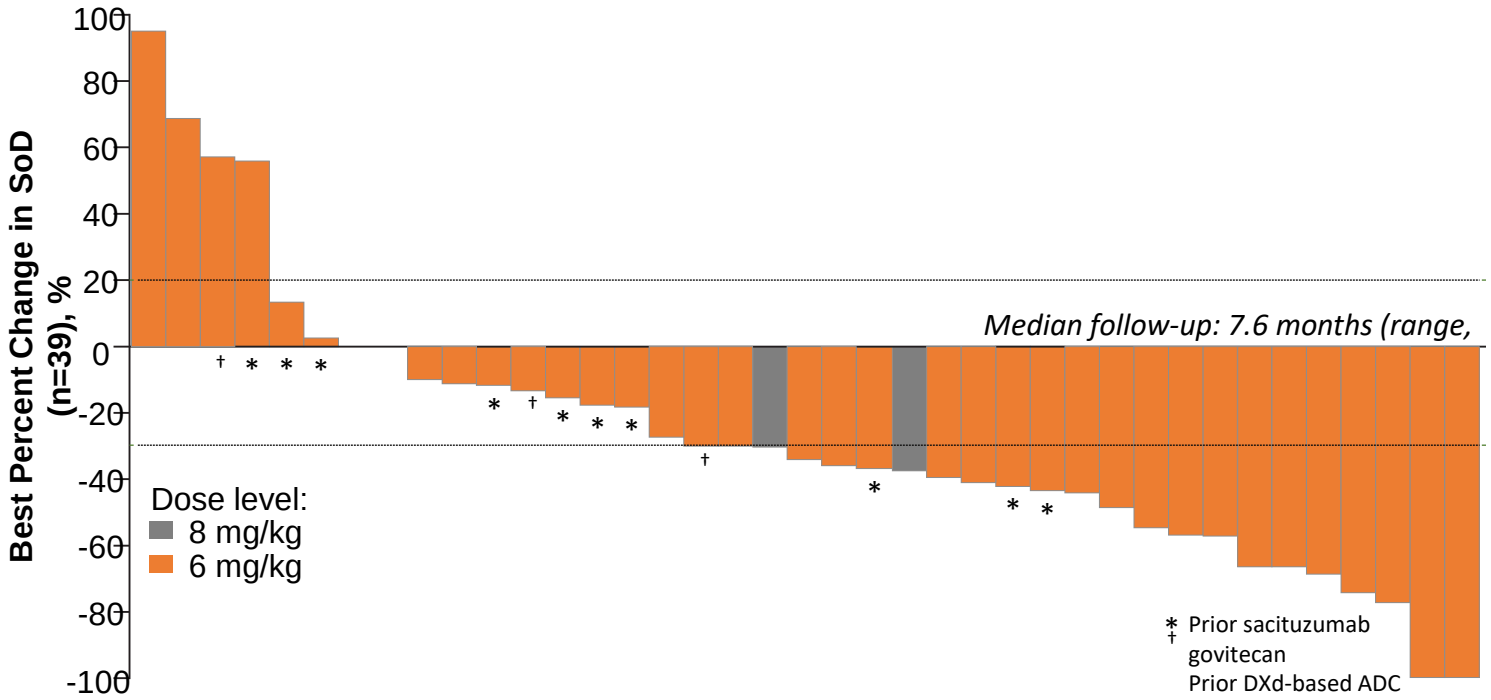
Risk mitigation strategy in trial: Patients with prior pneumonitis excluded, evaluate tumor CT scans for lung changes, do a full diagnostic work-up for new or worsening respiratory symptoms, grade 2 or higher pneumonitis stop treatment, grade 1 pneumonitis delay treatment until resolution

Slide Courtesy: J Cortes

Saura C, et al ESMO 2021.

Datopotamab Deruxtecan: Trop2 ADC





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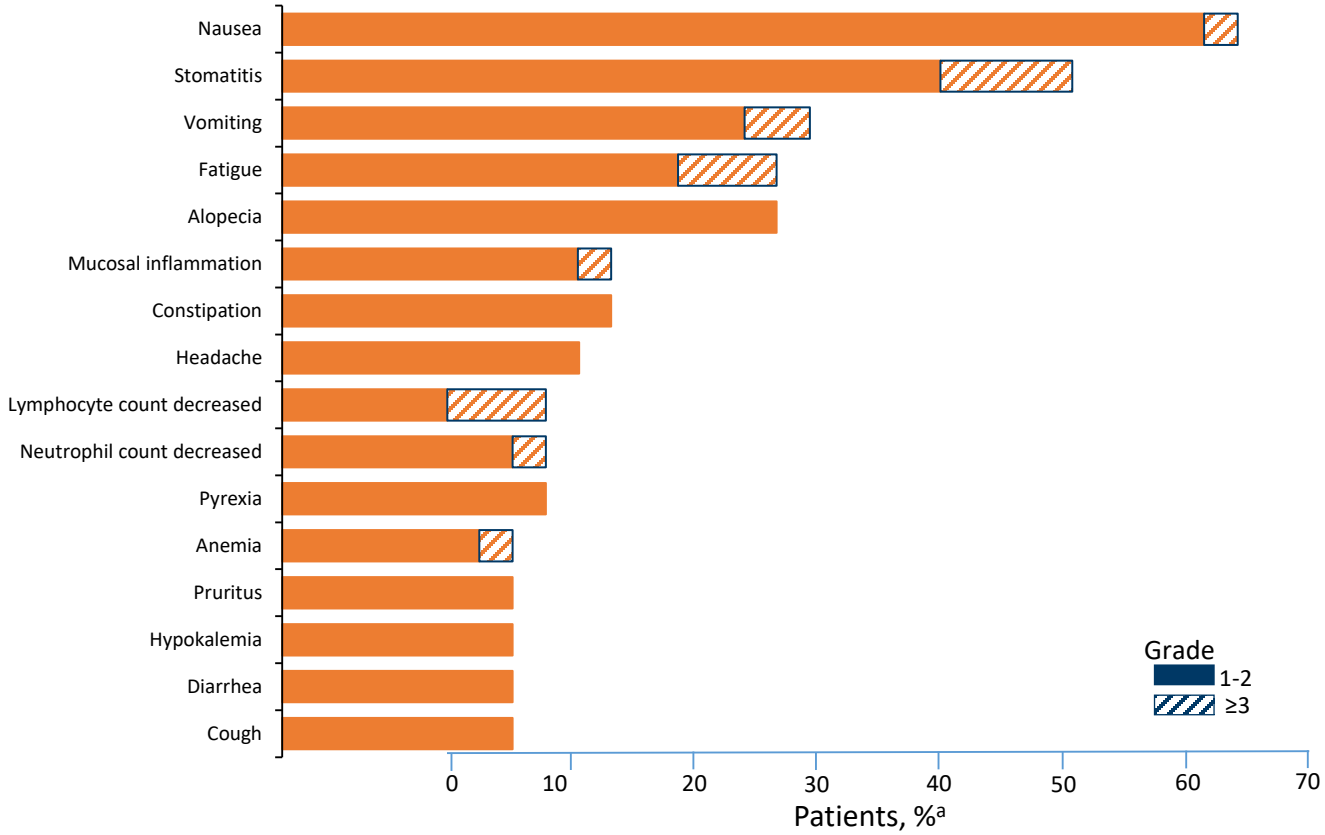
Krop I, et al SABCS 2021.

Treatment-Emergent Adverse Events: Datopotamab Deruxtecan



- Most common adverse events observed were nausea and stomatitis (predominantly grade 1-2)
- Low frequency of hematologic toxicity and diarrhea
- No cases of ILD

- Different from Sacituzumab Govitecan and Trastuzumab Deruxetcan!

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Krop I, et al SABCS 2021.

ADCs to target MBC: Multiple Agents in Development

Target	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
SAR408701	CEA-CAM5	Microtubule inhibitor
Praluzatamab ravtansine	CD166	Microtubule inhibitor

Conclusion

- While the toxic payload is a major determinant of toxicity, the composition of ADC including internalization efficiency, by-stander effect, and payload metabolism, all are important consideration that could impact toxicities associated with ADC.
- Early recognition and management critical for management of toxicities, particularly serious AEs such as pneumonitis.
- Toxicity can usually be managed with supportive therapy and dose-reductions.
- Different ADCs with different combinations of antibodies and payloads will shed additional light into mechanisms governing toxicities with ADCs.

Thank you for your attention