Harnessing the Power of **Antibody-Drug Conjugates** for the **Treatment of Hematologic and Solid Cancers**

MOA of ADCs and Their Rationale for Use in Patients with Cancer

Originally Aired: Monday, March 7, 2022

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Introductions

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This activity is supported by independent educational grants from

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ADC Therapeutics,
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Disclosures

Sara Hurvitz, MD FACP

Nothing to disclose.

Giuseppe Curigliano, MD PhD

Consultant: Astra Zeneca, Celcuity, Daichii Sankyo, Exact Sciences, Gilead, Lily, MS, Novartis, Pfizer, Roche, Seagen
Speaker Bureau: Astra Zeneca, Daichii Sankyo, Exact Sciences, Lily, Novartis, Pfizer, Roche, Seagen
Institutional Funding: Merk

Sven de Vos, MD PhD

Advisory Board: Beigene

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP
Bio Ascend: Patti Bunyasaranand, MS; Tisheeka Graham-Steed; Lacey Schmeidler, Kraig Steubing

Learning Objectives

- Describe the mechanism of action of ADCs and their rationale for use in patients with cancer
- Evaluate the safety and efficacy of current and emerging ADCs for patients with solid tumors
- Assess clinical trial results of approved and investigational ADCs that are being examined in patients with hematologic malignancies
- Review adverse events associated with the use of ADCs in patients with cancer and strategies to mitigate these adverse events

Reminders

Visit bioascend.com/antibody-drug-conjugates to register for upcoming webinars

Harnessing the Power of **Antibody-Drug Conjugates** for the **Treatment of Hematologic and Solid Cancers**

Antibody drug conjugates in Hematologic Malignancies

Sven de Vos, MD PhD

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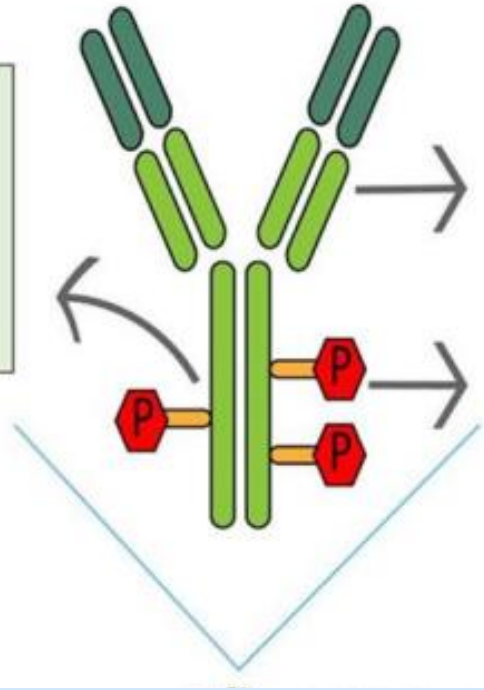
Disclosures

- Advisory Board meeting: BeiGene

Antibody–drug conjugates (ADCs): three main components

Linker:
- Determines solubility, stability in systemic circulation and overall antitumor activity
- Considered optimal when off-target interaction is minimized
- Generally categorized into cleavable and non-cleavable designs



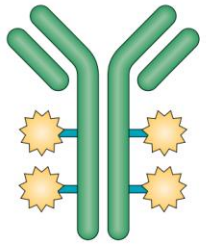
Antibody:
- Serve a dual purpose as they act both as transporters and as targeting agents
- High specificity and affinity for the target antigen
- Favorable pharmacokinetic properties
- Minimal immunogenicity

Payload:
- Ultimate effector component
- Potent in subnanomolar concentrations
- Generally categorized into:
1) DNA-damaging agents
2) Microtubule disrupting agents

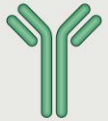
- The clinical properties of ADCs depend on the characteristics of all three components
- Primary goal is to improve therapeutic index of antineoplastic drugs by restricting systemic delivery to cells that express the target antigen of interest

(Theocharopoulos C, et al. Therapeutic Advances in Medical Oncology 2020;12:1-20)

Antibody–drug conjugates (ADCs): modular design



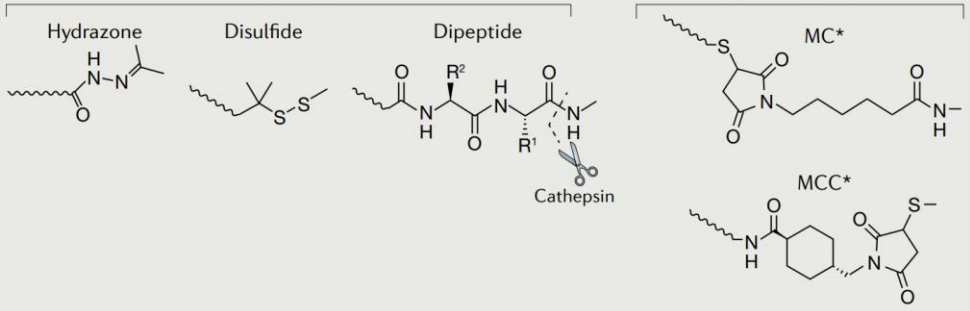
The selection of all 3 components for ADCs is important and has a significant impact on efficacy, pharmacokinetic/pharmacodynamic profiles and therapeutic index.

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

Linkers

Cleavable: Hydrazone, Disulfide, Dipeptide (Cathepsin)

Non-cleavable: MC*, MCC*

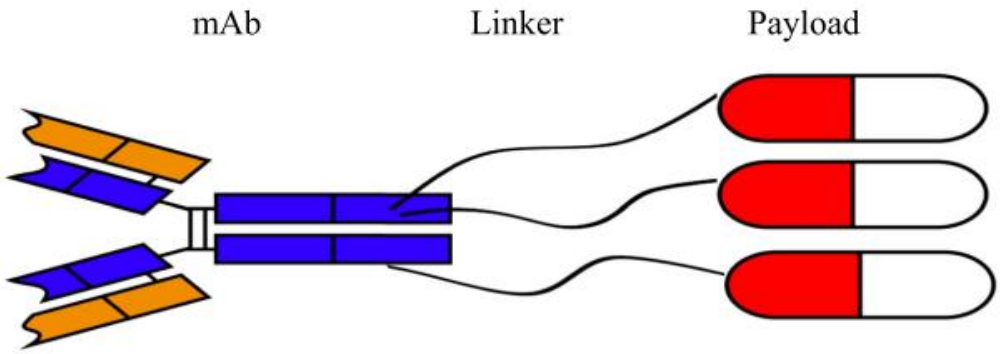


	Acid cleavable	Reducible	Protease cleavable

Payloads	Auristatins	Maytansinoids	Calicheamicins	Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

(Drago JZ, et al. Nature Reviews/Clinical Oncology 2021;18:327-344)

Antibody–drug conjugates (ADCs): modular design



Antigens	Linkers	Payloads
CD30	Acid-labile linker (Hydrazone)	DM1
CD22		DM4
CD79b	Protease-cleavable linker(Val-Cit, Val-Ala)	MMAE
CD19		MMAF
CD25	Disulfide linker (SPDB)	Calicheamicin
CD37		PBD dimer
CD70	Non-cleavable linker(SMCC, MC)	Doxorubicin
CD56		PE38
CD74		Duocarmycin derivative
CD138		
CD269		

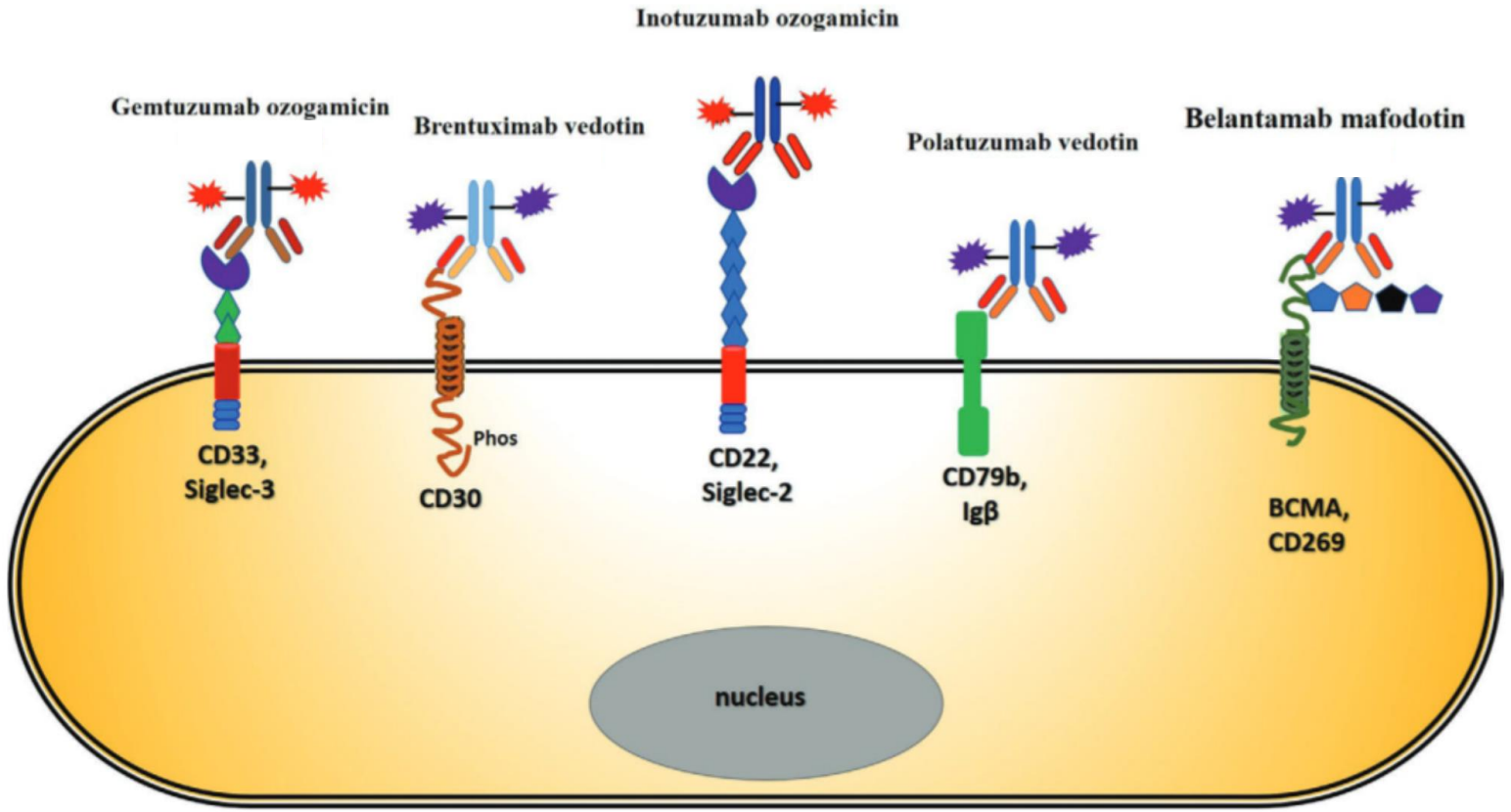
(Yu B, et al. Journal of Hematology & Oncology 2019.12:94)

Target expression in hematologic malignancies

Target	HL	B-NHL	T-NHL	MM	CLL	Myeloid leukemia
CD3						
CD19						
CD22						
CD30						
CD33						
CD56						
CD74						
CD138						

(Leslie LA, and Younes A. 2013 ASCO educational book; asco.org/edbook)

ADCs FDA approved for treatment of hematologic malignancies



(Firer MA, et al. Adv. Funct. Mater. 2021;31:2100032)

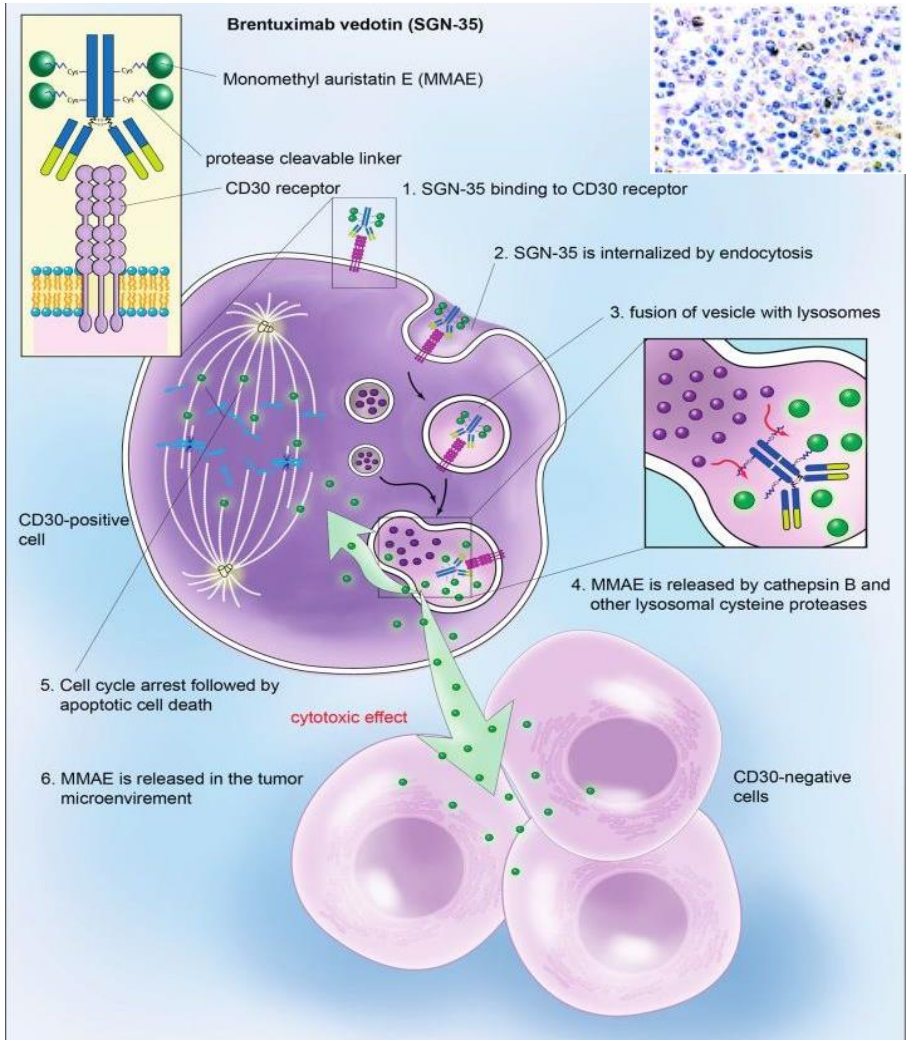
ADCs - FDA approved for treatment of hematological malignancies

Name/Sponsor	Target Antigen	mAb isotype	Linker	Drug (MOA)	DAR	FDA approved indications	Year approved	Clinical efficacy	Recommended dose	Main AEs
Gemtuzumab ozogamicin Wyeth, Pfizer	CD33	IgG4	Acid-labile hydrazine linker	Calicheamicin (DNA cleavage)	2-3	Newly Dx CD33+ **AML** R/R CD33+ AML - lower dose - different schedule	2000 2017	GO vs. GO + chemo: mEFS 17.3 mo vs. 9.5 mo GO vs. best supp. Care: mOS 4.9 mo vs. 3.6 mo	3-6mg/m2	Infusion reactions Cytopenias Liver toxicity Vaso-occlusive disease (VOD)
Brentuximab Vedotin Seattle Genetics	CD30	IgG1	Cathepsin B-cleavable peptide	Monomethyl auristatin E (MMAE)	4	R/R **sALCL** or **cHL** R/R **pcALCL** or **CD30+ MF** **cHL, sALCL** or **CD30+ PTCL**	2011 2017 2018		1.2 – 1.8 mg/kg	Neutropenia GI symptoms Fatigue Peripheral neuropathy
Polatuzumab vedotin-piiq Genentech	CD79b	IgG1	Dipeptide cleavable	Monomethyl auristatin E (MMAE)	3.5 (mean)	R/R **DLBCL**	2019		1.8 mg/kg	Infusion reactions neuropathy myelosuppression hepatotoxicity
Loncastuximab tesirine-lpyl ADC Therapeutics	CD19	IgG1	valine-alanine linker cleavable	SG3199 pyrrolobenzodiazepine (PBD) dimer (alkylater)	2.3 (mean)	R/R **DLBCL** incl. transformed DLBCL and high-grade B-cell lymphoma	2021	ORR 48.3% CR 24.1 %	0.15 mg/kg 0.075 mg/kg	edema and effusions myelosuppression infections cutaneous reactions

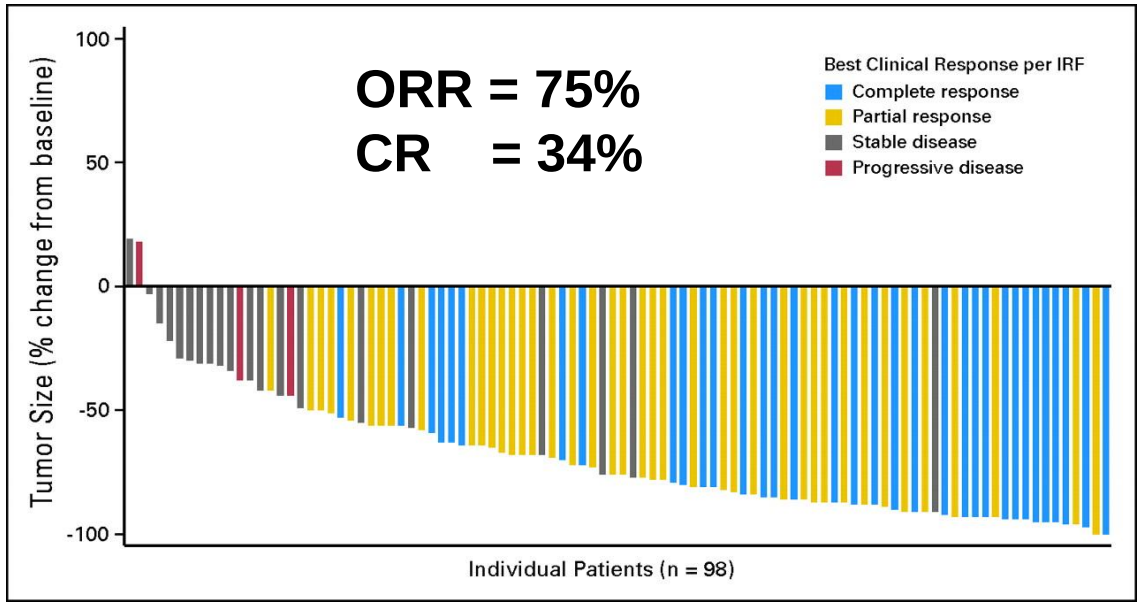
ADCs - FDA approved for treatment of hematological malignancies

Name/Sponsor	Target Antigen	mAb isotype	Linker	Drug (MOA)	DAR	FDA approved indications	Year approved	Clinical efficacy	Recommended dose	Main AEs
Inotuzumab ozogamicin Wyeth/Pfizer	CD22	IgG4	Acid-labile hydrazine linker	Calicheamicin (DNA cleavage)	4	R/R **B-cell ALL**	2017	2 yr OS 22%	0.5-0.8 mg/m2	Infusion reactions cytopenias Vaso-occlusive disease (VOD)
Moxetumomab pasudotox-tdfk AstraZeneca	CD22	Ig variable domains	Disulfide linker	Pseudomonas exotoxin A, PE38		R/R **hairy cell leukemia** (HCL), third line or beyond	2018	ORR 75%, CR 41%, durable CR 30%	0.04 mg/kg	Capillary leak syndrome hemolytic uremic syndrome (HUS)
Belantamab mafodotin GlaxoSmithKline	CD69 (BCMA)	IgG1	Tetrapeptide cleavable	Monomethyl auristatin F (MMAF)	4	R/R **multiple myeloma** fifth-line setting or beyond	2020		2.5mg/kg	Ocular effects anemia, neutropenia infusion reactions

Brentuximab vedotin



BV approved for rel/refr HL after ASCT or following 2 prior lines of therapy

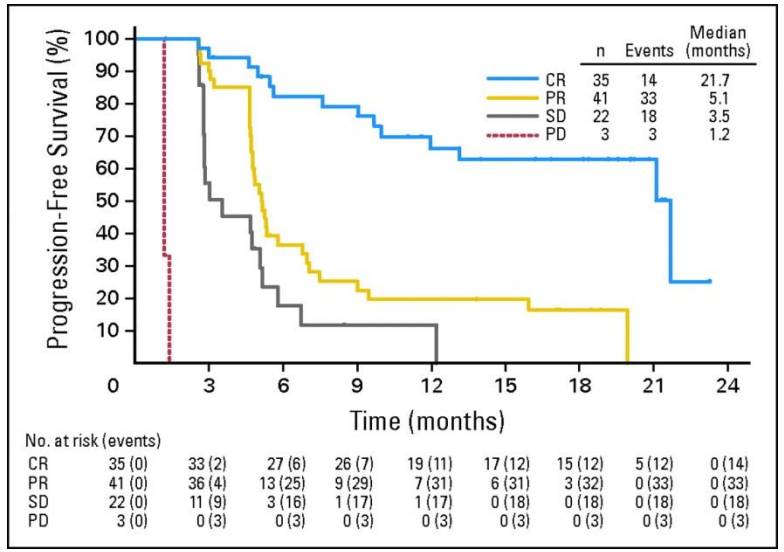


Vaklavas et al. Ther Adv Hem. 2012;3(4):209-225 Brown et al. Immunotherapy. 2014 Apr;6(4):371-5.

(Younes A, et al. J Clin Oncol. 2012;30:2183-2189)

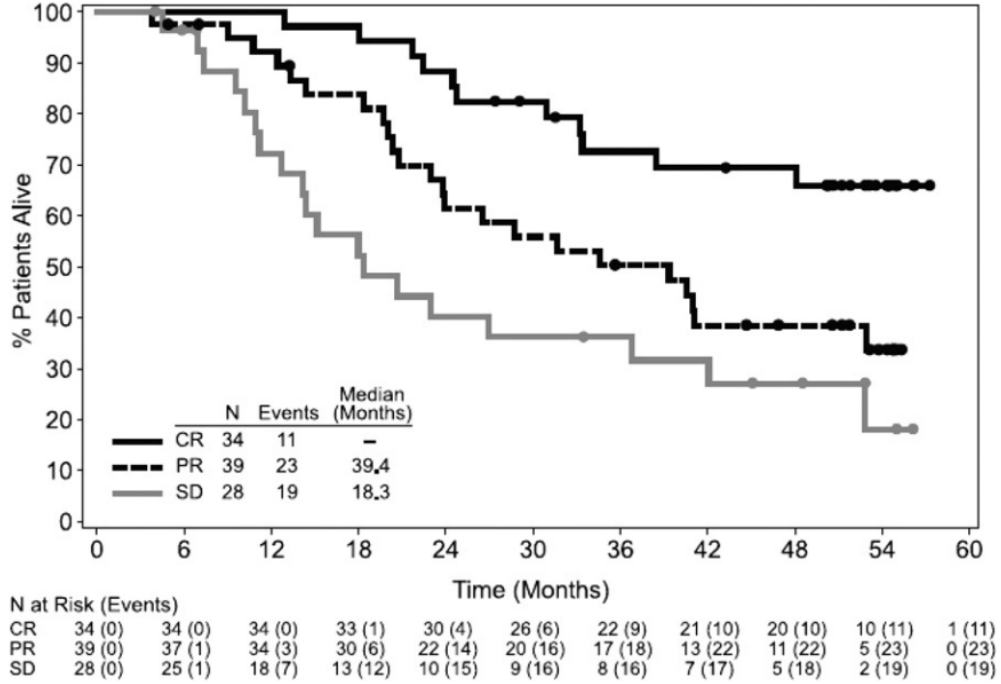
PFS of patients treated with brentuximab vedotin according to best response

Pivotal trial



(Younes A, et al. J Clin Oncol. 2012;30:2183-2189)

Longer F/U

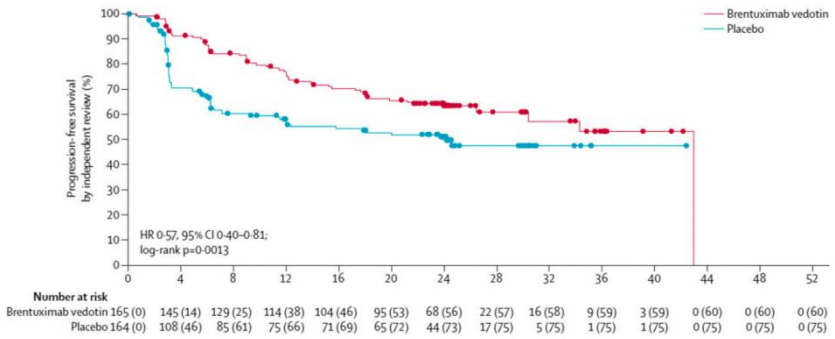


(Gopal AK, Blood, 2015;125(8):1236-1243)

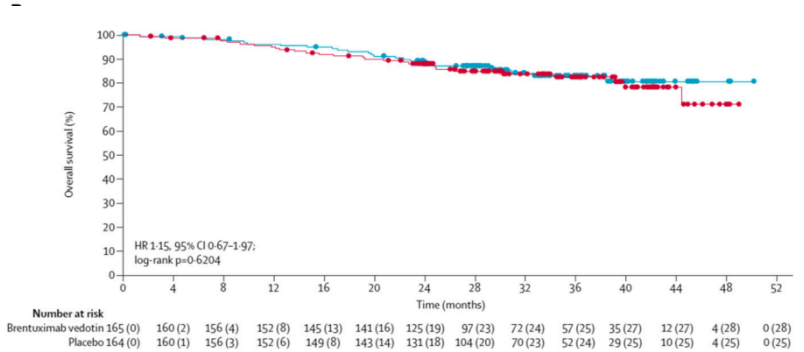
47% of patients in CR remained in remission at a median follow-up of 53 months

BV approved as adjuvant therapy following ASCT in high-risk patients (AETHERA trial)

PFS



OS



High risk definition:

- No CR with initial chemotherapy
- Progressed within 1 year following initial treatment
- Extranodal involvement at relapse

But:

- No survival benefit
- + Neurotoxicity
- Overtreatment?
- Similar outcomes if patients were treated with BV at time of relapse?

(Younes A, Lancet. 2015;385(9980):1853-1862)

Phase 3 trial of brentuximab vedotin in comb. with AVD vs. ABVD as frontline therapy for advanced Hodgkin lymphoma

Unblinded, open-label, multicenter, phase III trial

Hodgkin Lymphoma

Stage IIA bulky disease
Stage IIB-IV disease

→ **Randomization 1:1**

A: ABVD

B: AVD + **Brentuximab Vedotin (SGN-35)**

Arm A: - Standard doses of ABVD Q 14 days

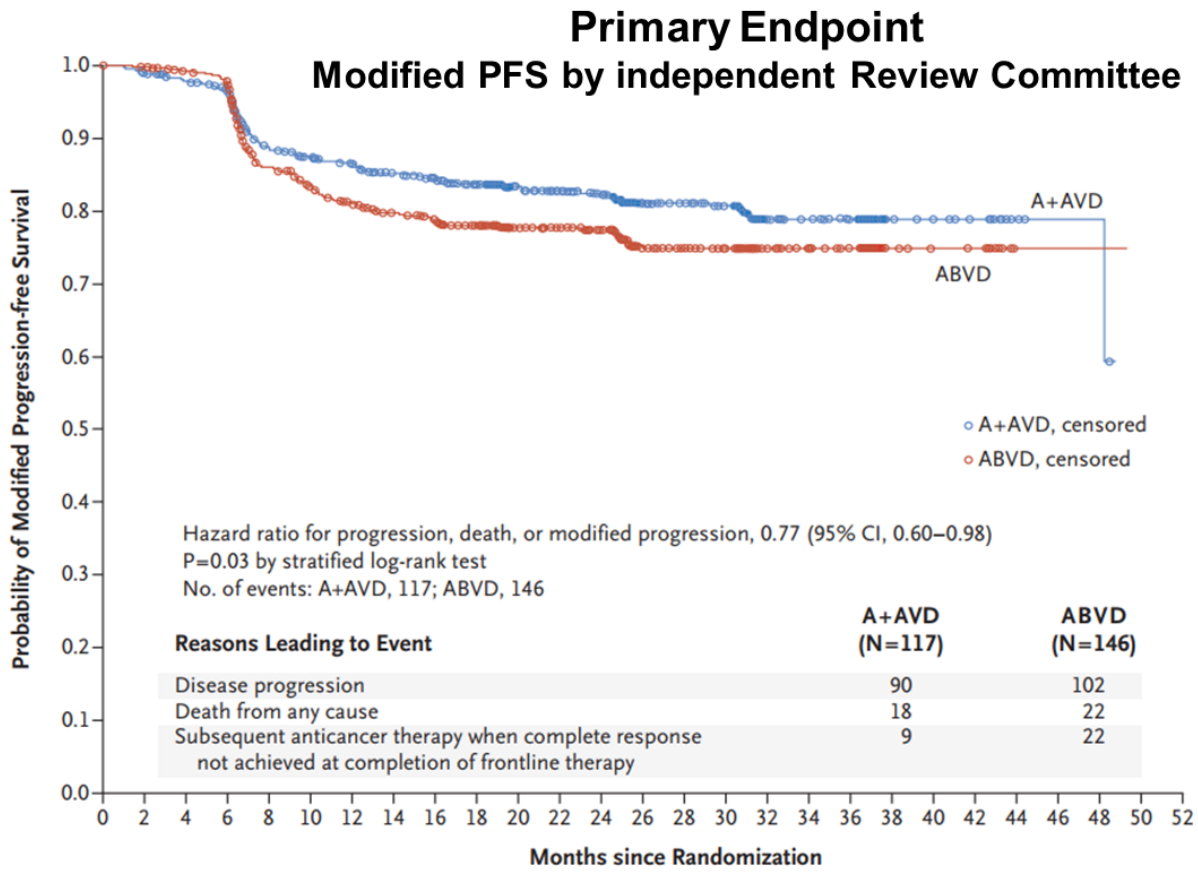
Arm B: - Standard doses of AVD Q 14 days
- Brentuximab vedotin 1 hour after completion of AVD therapy.

Primary endpoint: modified PFS

New frontline Hodgkin lymphoma regimen

Less toxic + more efficacious?

Phase 3 trial of brentuximab vedotin in comb. with AVD vs. ABVD as frontline therapy for advanced Hodgkin lymphoma



Reasons Leading to Event	A+AVD (N=117)	ABVD (N=146)
Disease progression	90	102
Death from any cause	18	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	9	22

(Connors JM, et al. N Engl J Med. 2017 Dec 10 [Epub ahead of print])

Phase 3 trial of brentuximab vedotin in comb. with AVD vs. ABVD as frontline therapy for advanced Hodgkin lymphoma

Efficacy	A+AVD	ABVD	
2 yr mod PFS	82.1 %	77.2 %	P= 0.03
2 yr OS	96.6 %	94.9 %	P= 0.19

Safety	A+AVD	ABVD	comments
Neutropenia	58 %	45 %	Use of G-CSF
Neuropathy	67 %	43 %	2/3 improve or resolve
Pulm tox grade >3	< 1 %	3 %	Use of B in ABVD
Deaths	7/9 Neutropenia	11/13 Pulm tox	

(Connors JM, et al. N Engl J Med. 2017 Dec 10 [Epub ahead of print])

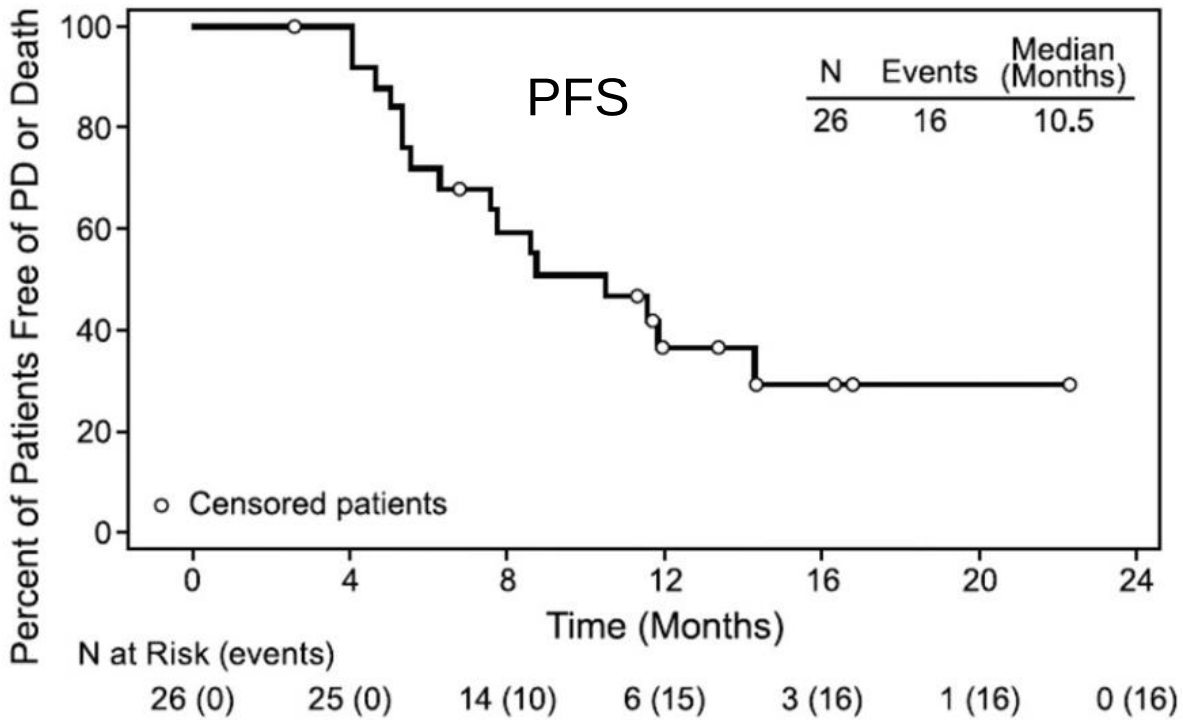
Phase 3 trial of brentuximab vedotin in comb. with AVD vs. ABVD as frontline therapy for advanced Hodgkin lymphoma

- Oct 2017: U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation to BV in combination with chemotherapy for the frontline treatment of patients with advanced classical Hodgkin lymphoma.

- "The study results represent the first successful effort in more than 30 years to improve outcomes of first-line treatment in patients with advanced HL without escalating the toxicity of the chemotherapy to unacceptable levels." (Joseph M. Connors)

- However…
  - RATHL trial (Response-Adapted Therapy for Advanced Hodgkin Lymphoma): Bleomycin was withheld from ABVD after a negative interim PET scan. Retain clinical benefits with reduced toxicity.
  - No overall survival benefit
  - Costs of supportive thx

Single-agent brentuximab vedotin as front-line therapy for newly diagnosed HL patients aged 60 or older



- **High Relapse Rate**
- ORR 92%, CR 73%
- Median DOR 1.8 months for those achieving CR
- Toxicity more severe: 78% peripheral sensory neuropathy, 30% grade 3

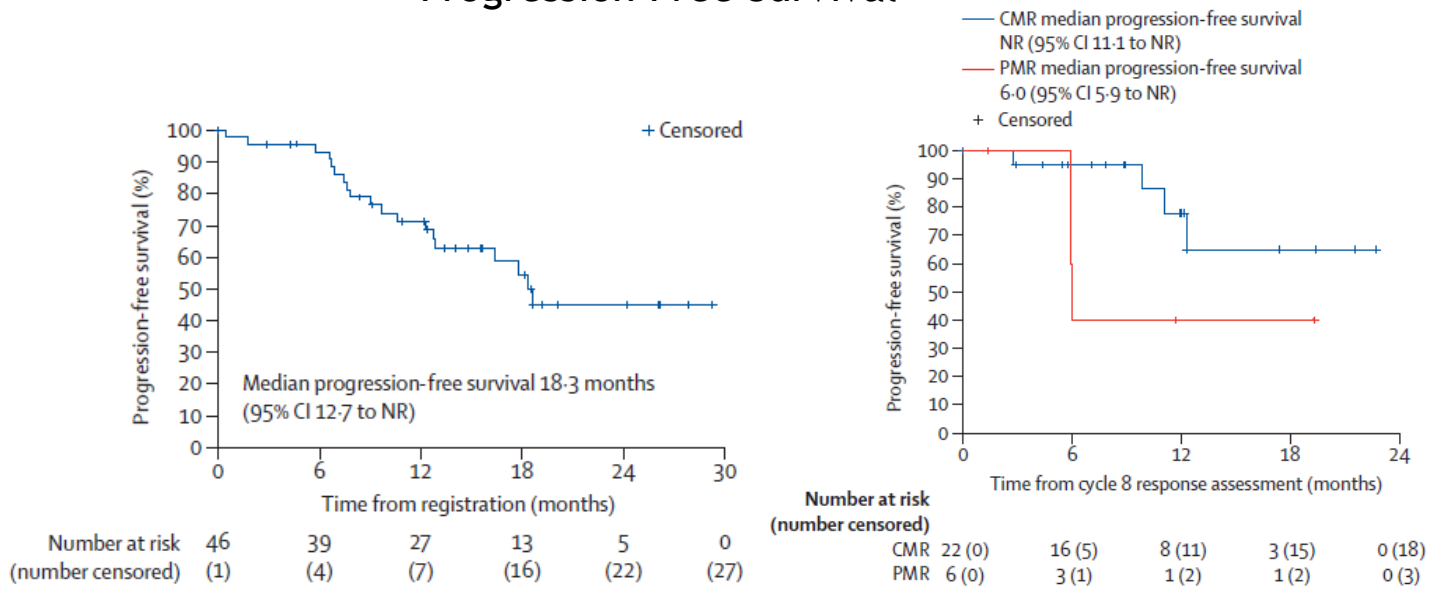
(Forero-Torres A, Blood. 2015;126(26):2798-2804)

Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma

- brentuximab vedotin 1·8 mg/kg
  + nivolumab at 3 mg/kg
  every 21 days for 8 cycles
- N = 46 patients, median age 71.5 years

Best overall response rate (all cycles)	91% (79–98)
Complete metabolic response	30 (65%)
Partial metabolic response	12 (26%)
No metabolic response	1 (2%)
Progressive metabolic disease	1 (2%)
Not evaluated	2 (4%)
Median duration of response	NR (11·1–NR)
Median overall survival	NR (NR–NR)
Median progression-free survival (months)	18·3 (12·7 to NR)

Progression Free Survival



- Trial closed to accrual on Oct 14, 2019, after the interim analysis failed to meet the predefined criteria
- Well tolerated in the majority of patients in this older population

(Cheson BD; Lancet/Haematology 2020, 7, E808-E815)

The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma

Brentuximab Vedotin in PTCL (FDA approval 2018)

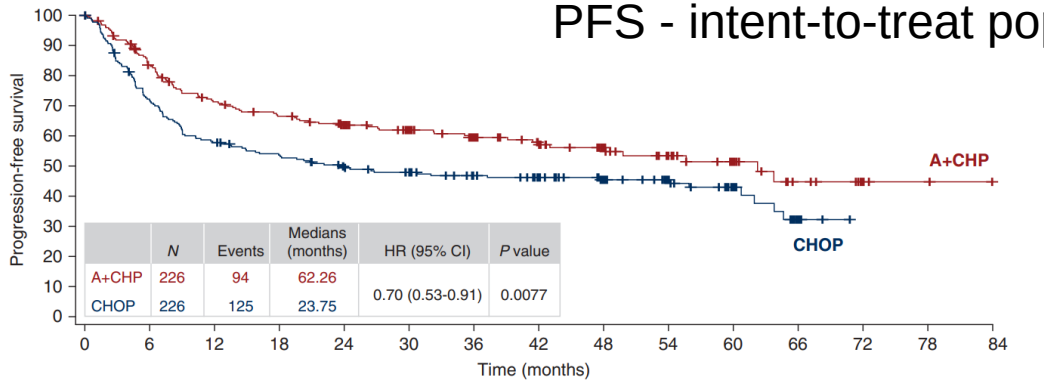
ECHELON-2:

- Double-blind, randomized, placebo-controlled, phase III study
- Randomized (1:1) to 6-8 cycles of A+CHP (N = 226) or CHOP (N = 226)
- Median F/U of 47.6 months
- 5-year PFS rates: 51.4% vs. 43.0% (hazard ratio 0.70)
- 5-year OS rates: 70.1% vs. 61.0% (hazard ratio 0.72)
- PFS and OS consistent across key subgroups
- Peripheral neuropathy: resolved or improved in 72% (84/117) of patients in the A+CHP arm and 78% (97/124) in the CHOP arm

(Horwitz S, et al. Annals of Oncology 2021;33:288-298)

The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma

PFS - intent-to-treat population

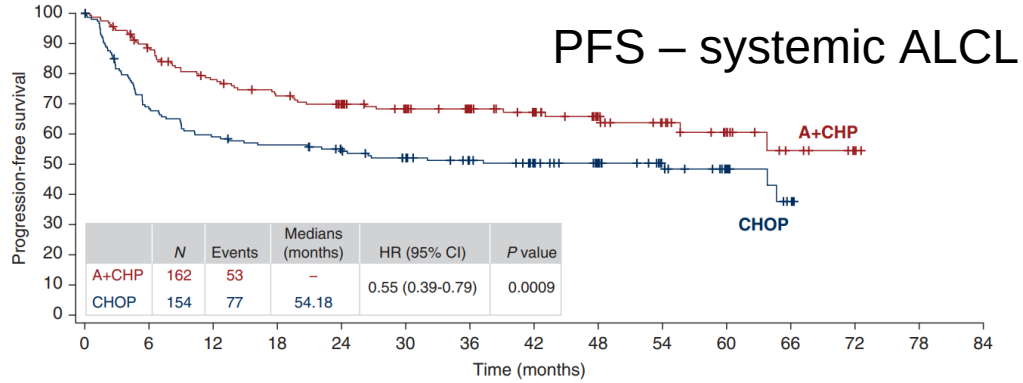


	N	Events	Medians (months)	HR (95% CI)	P value
A+CHP	226	94	62.26	0.70 (0.53-0.91)	0.0077
CHOP	226	125	23.75		

N at risk (events)

A+CHP	226 (0)	179 (36)	150 (62)	138 (72)	123 (78)	104 (81)	85 (85)	67 (88)	44 (89)	31 (91)	21 (92)	10 (94)	4 (94)	2 (94)	0 (94)
CHOP	226 (0)	159 (63)	128 (94)	116 (103)	101 (112)	94 (115)	79 (117)	70 (118)	55 (119)	39 (119)	24 (121)	6 (125)	0 (125)	0 (125)	0 (125)

PFS – systemic ALCL



	N	Events	Medians (months)	HR (95% CI)	P value
A+CHP	162	53	–	0.55 (0.39-0.79)	0.0009
CHOP	154	77	54.18		

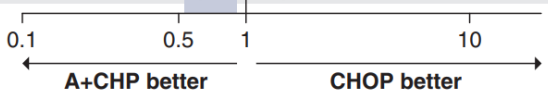
N at risk (events)

A+CHP	162 (0)	136 (18)	117 (34)	107 (42)	95 (46)	81 (48)	67 (48)	55 (49)	33 (50)	23 (51)	15 (52)	7 (53)	2 (53)	0 (53)	0 (53)
CHOP	154 (0)	103 (48)	89 (62)	84 (66)	75 (69)	68 (72)	57 (73)	48 (74)	38 (74)	26 (74)	16 (75)	4 (77)	0 (77)	0 (77)	0 (77)

(Horwitz S, et al. Annals of Oncology 2021;33:288-298)

The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma

ITT subgroups	Event/*N* A+CHP	Event/*N* CHOP	Hazard ratio (95% CI)
PFS per investigator	94/226	125/226	0.70 (0.53-0.91)
IPI score			
0-1	14/52	27/48	0.42 (0.22-0.81)
2-3	59/141	79/145	0.72 (0.51-1.01)
4-5	21/33	19/33	1.14 (0.61-2.15)
Age, years			
<65	51/157	74/156	0.64 (0.45-0.92)
≥65	43/69	51/70	0.68 (0.45-1.04)
Sex			
Male	60/133	79/151	0.84 (0.60-1.17)
Female	34/93	46/75	0.44 (0.28-0.69)
Baseline ECOG status			
0	36/84	56/93	0.63 (0.41-0.96)
1	38/90	50/86	0.61 (0.40-0.93)
2	20/51	19/47	0.99 (0.52-1.88)
Disease stage			
I	3/12	2/9	2.15 (0.22-20.88)
II	12/30	18/37	0.93 (0.43-1.99)
III	26/57	36/67	0.63 (0.37-1.05)
IV	53/127	69/113	0.66 (0.46-0.95)
Disease indication			
ALK-positive sALCL	7/49	16/49	0.40 (0.17-0.98)
ALK-negative sALCL	46/113	61/105	0.58 (0.40-0.86)
ATLL	2/4	2/3	0.69 (0.10-4.94)
AITL	19/30	12/24	1.41 (0.64-3.11)
EATL	1/1	2/2	Not estimable
PTCL-NOS	19/29	32/43	0.79 (0.43-1.43)
sALCL	53/162	77/154	0.55 (0.39-0.79)
Non-sALCL	41/64	48/72	0.96 (0.63-1.47)



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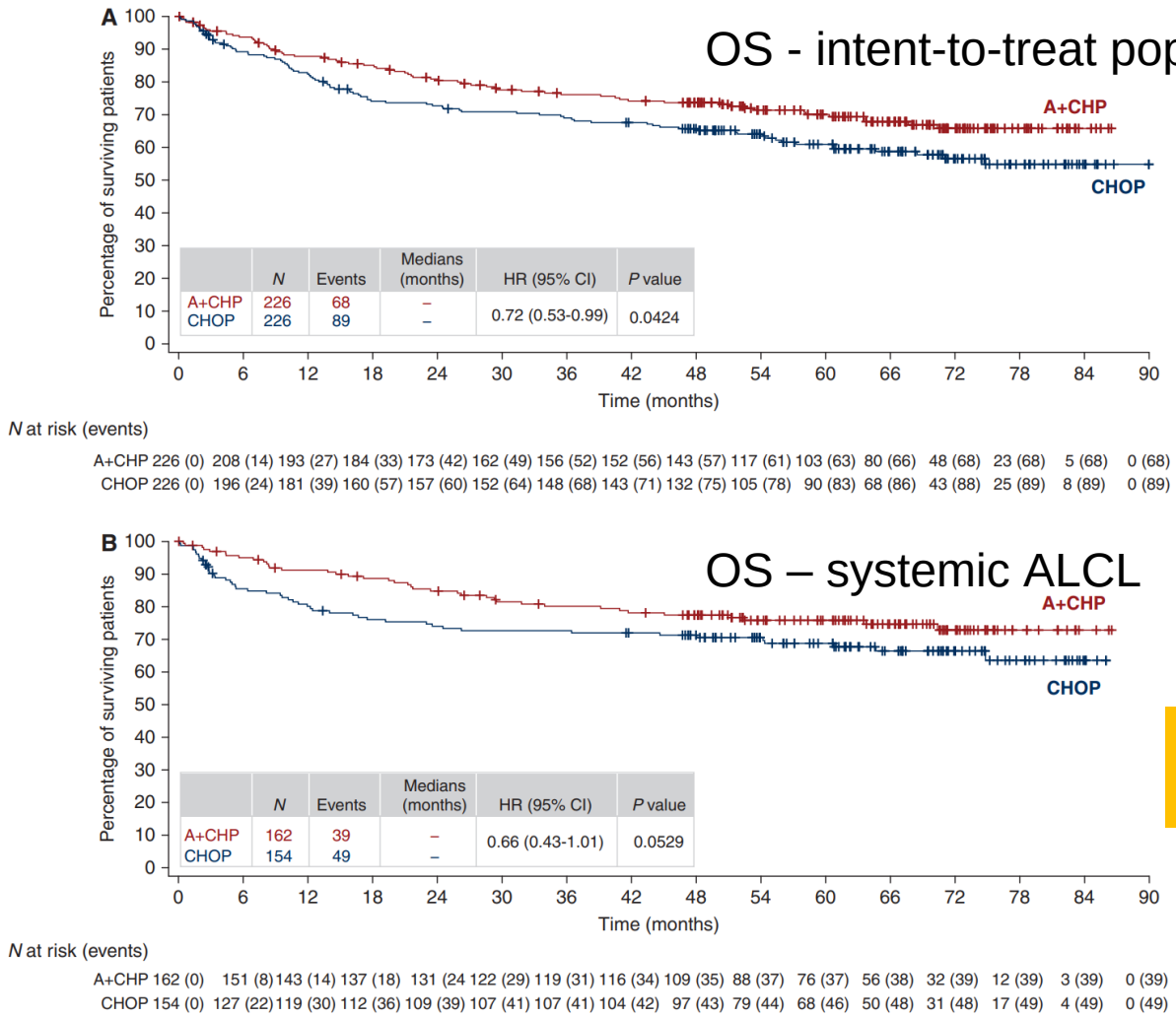
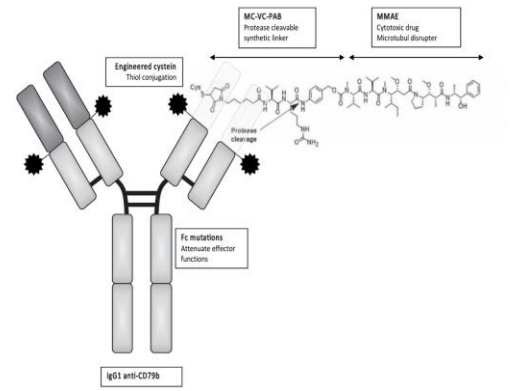
The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma



Ongoing remission in >60% of patients with sALCL at 5 years

(Horwitz S, et al. Annals of Oncology 2021;33:288-298)

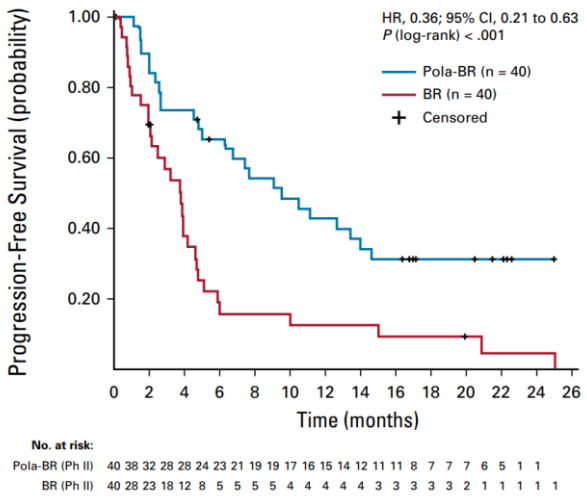
Polatuzumab vedotin – R/R DLBCL (FDA approved)

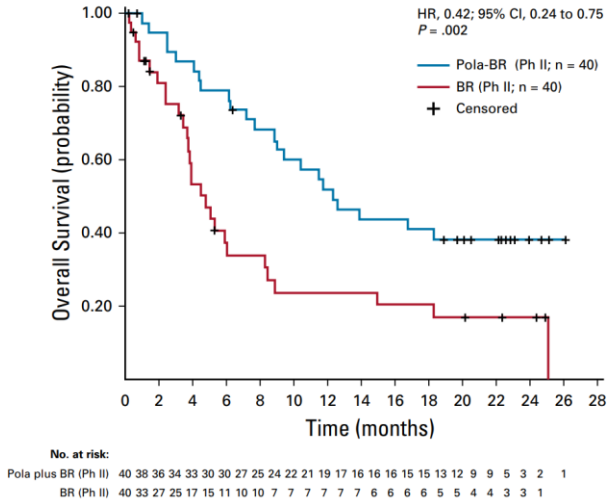


Phase II randomization: pola-BR *v* BR

R/R DLBCL → 1:1 randomization
Stratification: DOR ≤ 12 mo, > 12 mo

- Pola-BR (n = 40)
- BR (n = 40)





Results:

- CR rate (40.0% v 17.5%)
- PFS (median, 9.5 v 3.7 months)
- OS (median, 12.4 v 4.7 months)
- median follow up 22.3 months

Pola-BG and pola-BR had a tolerable safety profile:

- grade 3-4 neutropenia (46.2% v 33.3%)

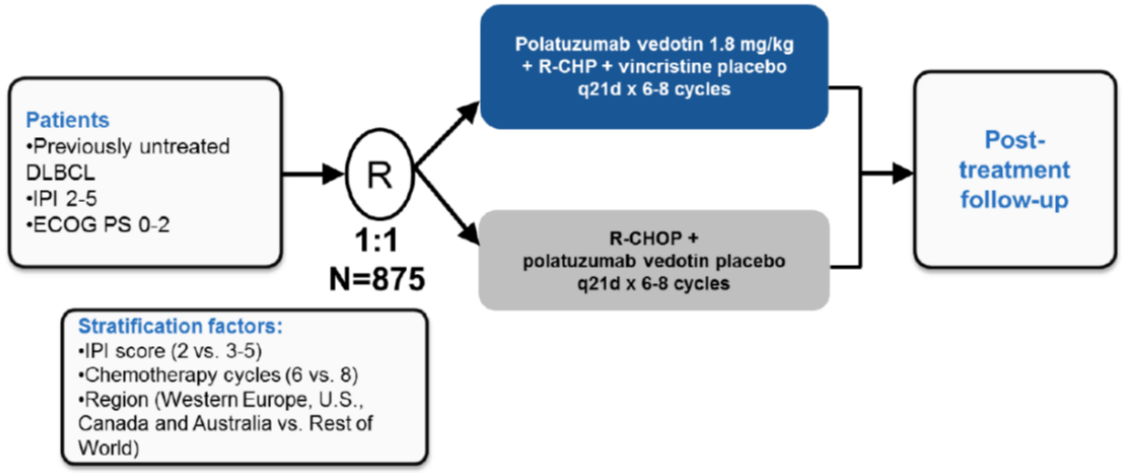
  similar grade 3-4 infections (23.1% v 20.5%)
- Peripheral neuropathy associated with polatuzumab vedotin (43.6% of patients) was grade 1-2 and resolved in most patients.

Polatuzumab vedotin combined with BR resulted in a significantly higher CR rate and reduced the risk of death by 58% compared with BR in patients with transplantation-ineligible R/R DLBCL.

(Sehn LH, et al. J Clin Oncol 2019;38:155-165)

Polatuzumab vedotin – in 1st line DLBCL (POLARIX)

Randomized and double-blind international phase 3 trial



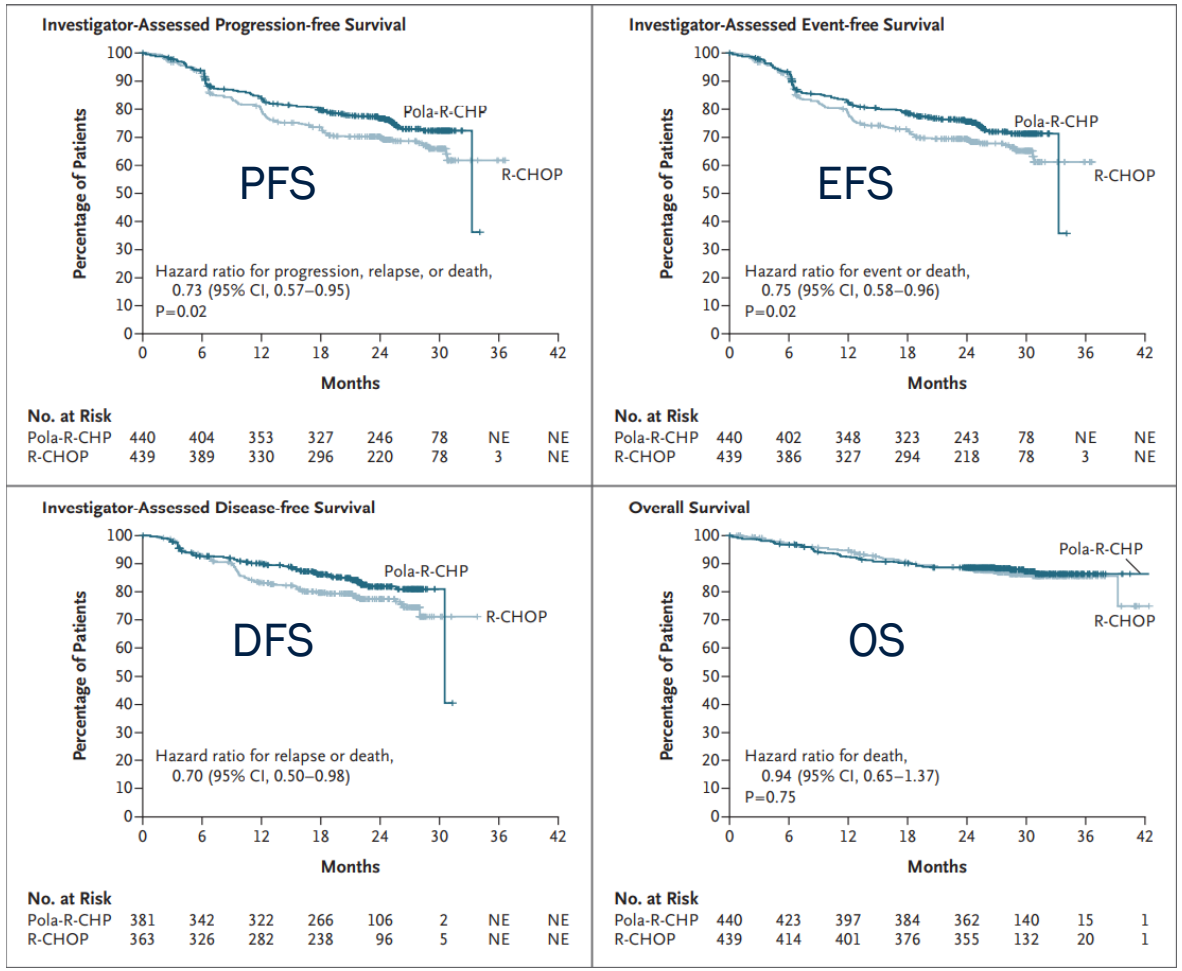
- N = 879 (440/439)
- Well balanced
- Med FU = 28.2 mo
- **Primary endpoint:** Investigator-assessed PFS
- 76.7% vs. 70.2% at 2 years
  - Stratified hazard ratio for progression, relapse, or death, 0.73 by Cox regression; P=0.02
- Overall survival at 2 years: 88.7% vs 88.6%
- The safety profile was similar in the two groups

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)

In previously untreated intermediate-risk or high-risk DLBCL, the risk of disease progression, relapse, or death was lower among those who received pola-R-CHP than among those who received R-CHOP.

(Tilly, F et al. N Engl J Med. 2022;386:351-63)

Polatuzumab vedotin – in 1st line DLBCL (POLARIX)



- More FU needed to see if the PFS benefit translates into an improved overall survival
- Not included in this trial:
  - Transformed DLBCL
  - Primary mediastinal lymphoma
  - Patients older than 80 years
- A phase 3 trial investigating an age-adapted combination of pola-R-CHP with dose-attenuated chemotherapy in the older patient population is ongoing (ClinicalTrials.gov number, NCT04332822)

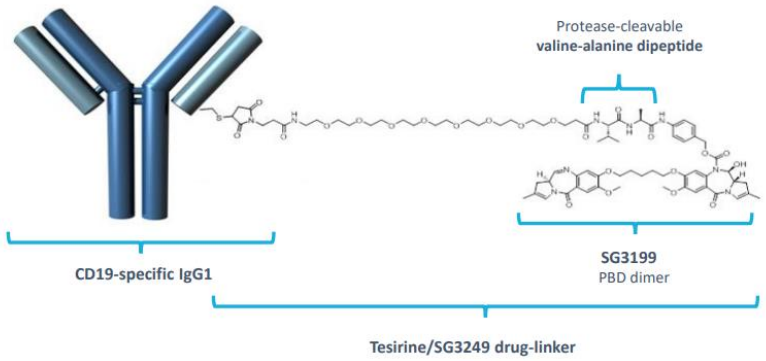
(Tilly, F et al. N Engl J Med. 2022;386:351-63)

Randomized clinical trials incorporating targeted agents in newly diagnosed DLBCL

Study	COO enrolled	Tretament	N	Results	
ECOG 1412 Phase 2	GCB and non-GCB	R-CHOP vs R-CHOP + Lenalidomide	N/A	2 yr PFS 70% vs 76% CR rate 67% vs 72% - Trend but not stat significant	-
ROBUST Phase 3	ABC	R-CHOP vs R-CHOP + Lenalidomide	N/A	2 yr PFS 64% vs 67% CR rate 65% vs 69%	-
PRELUDE	GCB and non-GCB	R-CHOP vs R-CHOP + Enzastaurine	758	4 yr DFS 71% vs 70%	-
PYRAMID	Non-GCB	R-CHOP vs R-CHOP + Bortezomib	206	CR rate 49% vs 58% 2 yr PFS 78% vs 82%	-
REMoDLB	GCB and non-GCB	R-CHOP vs R-CHOP + Bortezomib	1,076	30 mo PFS 70.1% vs 74.3%	-
LYM2034	Non-GCB	R-CHOP vs R-CAP + Bortezomib	164	CR 66.2% vs 64.4% 2 ys PFS 77.1% vs 76.2%	-
PHOENIX	Non-GCB	R-CHOP vs R-CHOP + Ibrutinib	838	CR 68% vs 67.3% No diff in EFS in ITT or ABC - Not stat significant EFS and OS benefit in patients <65yrs	-
Polatuzumab Vedotin	All subtypes	R-CHOP vs R-CHP + Polatuzumab Vedotin	879	PFS 76.7% vs. 70.2%; P=0.02 OS 88.7% vs 88.6%	+

Loncastuximab tesirine-lpyl – R/R DLBCL (FDA approved)

Loncastuximab tesirine in relapsed or refractory DLBCL (LOTIS-2): a multicenter, open-label, single-arm, phase 2 trial



- Rel/refr DLBCL after ≥ 2 multiagent systemic treatments
- **loncastuximab tesirine** iv on day 1 of each 21-day cycle
  - 150 µg/kg for two cycles
  - then 75 µg/kg thereafter, for up to 1 year

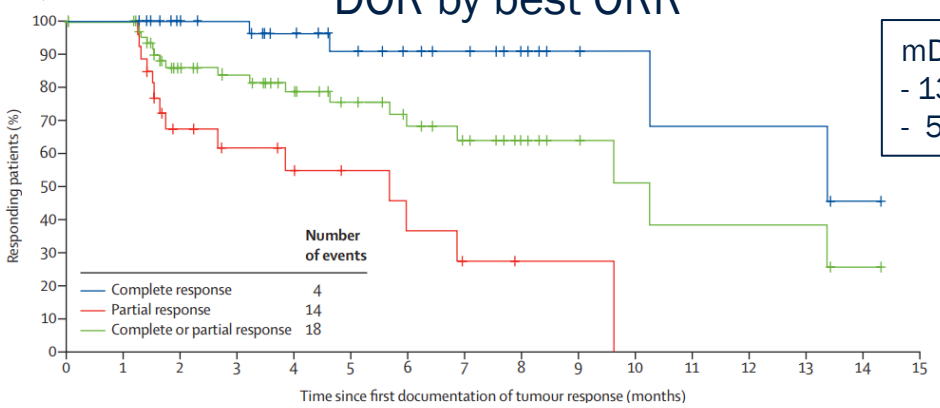
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-emergent adverse event	38 (26%)	61 (42%)	36 (25%)	8 (6%)
Haematological treatment-emergent adverse events				
Anaemia	23 (16%)	15 (10%)	0	0
Thrombocytopenia	22 (15%)	18 (12%)	8 (6%)	0
Neutropenia	20 (14%)	14 (10%)	23 (16%)	0
Leukopenia	8 (6%)	9 (6%)	4 (3%)	0
Lymphopenia	3 (2%)	3 (2%)	5 (3%)	0
Febrile neutropenia	0	5 (3%)	0	0

	Participants (n=145)
Sex	
Female	60 (41%)
Male	85 (59%)
Age, years	
Median (IQR)	66 (56–71)
<65	65 (45%)
≥65 to <75	59 (41%)
≥75	21 (14%)
Histology	
DLBCL, not otherwise specified	127 (88%)
HGBCL	11 (8%)
PMBCL	7 (5%)
GCB or ABC DLBCL*	
GCB	48 (33%)
ABC	23 (16%)
Unknown	74 (51%)
Double-hit or triple-hit DLBCL†	15 (10%)
Double-expressor or triple-expressor DLBCL	20 (14%)
Bulky disease	
Yes	8 (6%)
No	137 (94%)
Transformed DLBCL	29 (20%)
Refractory to all previous therapies¶	
Yes	25 (17%)
No	115 (79%)
Other‖	5 (3%)
Relapse within 3 months of first-line therapy††	
Yes	35 (24%)
No	110 (76%)
Relapse within 6 months of first-line therapy††	
Yes	57 (39%)
No	88 (61%)
Previous HSCT	
Allogeneic	2 (1%)
Autologous	21 (14%)
Both	1 (1%)
Previous CAR T-cell therapy	
Yes	13 (9%)
No	132 (91%)

(Caimi PF, et al. Lancet Oncol. 2021;22:790-800)

Loncastuximab tesirine in relapsed or refractory DLBCL (LOTIS-2): a multicenter, open-label, single-arm, phase 2 trial

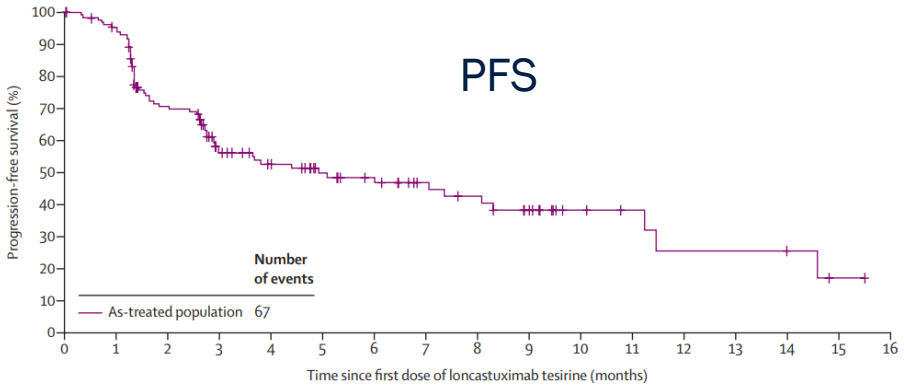
DOR by best ORR



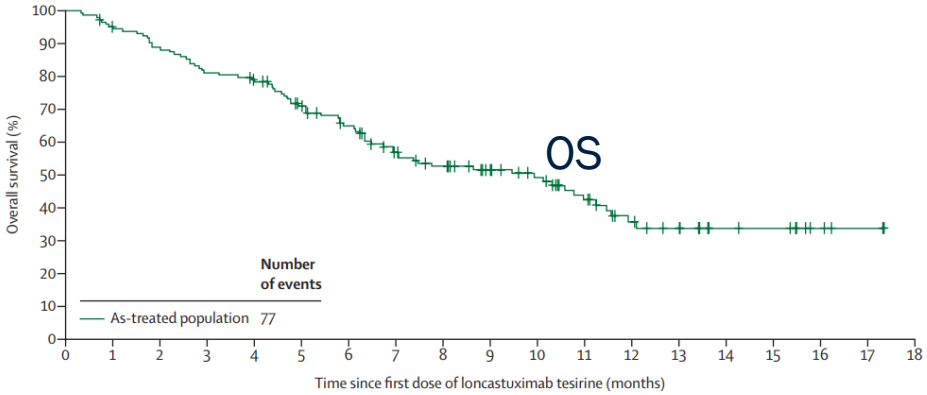
mDOR 10.3 mo
- 13.4 mo (CR)
- 5.7 mo (PR)

	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)
Stable disease	22 (15%)
Progressive disease	30 (21%)
Not evaluable*	23 (16%)

PFS



OS



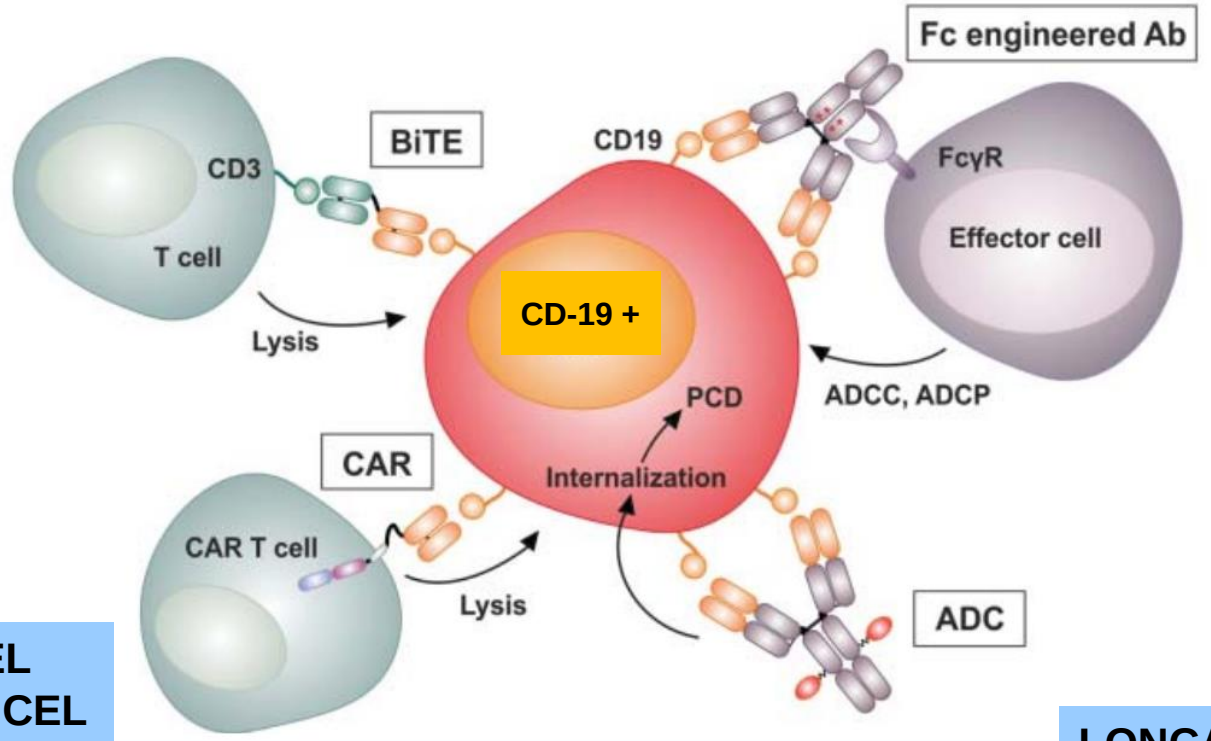
- Loncastuximab tesirine has substantial single-agent antitumor activity with an acceptable safety profile, offering a new therapeutic option for heavily pretreated patients with rel/ref DLBCL.
- FDA approval 2021

(Caimi PF, et al. Lancet Oncol. 2021;22:790-800)

Target CD19
- many different FDA approved targeting therapies -

BLINATUMOMAB

TAFASITAMAB

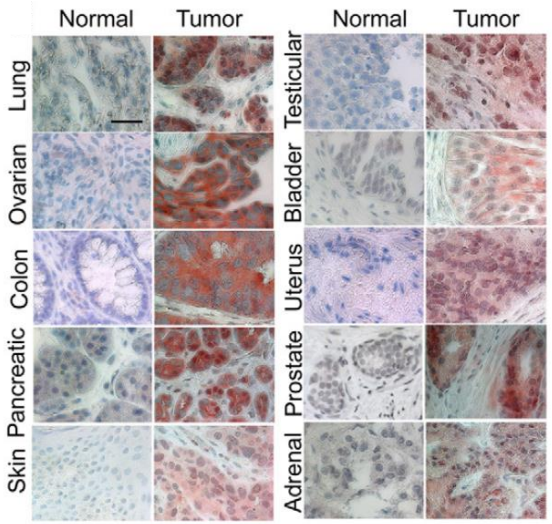


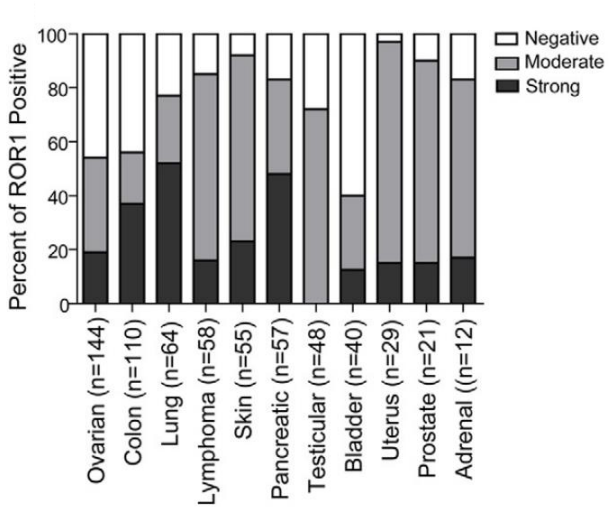
- **AXICABTAGENE CILOLEUCEL**
- **LISOCABTAGENE MARALEUCEL**
- **TISAGENLECLEUCEL**

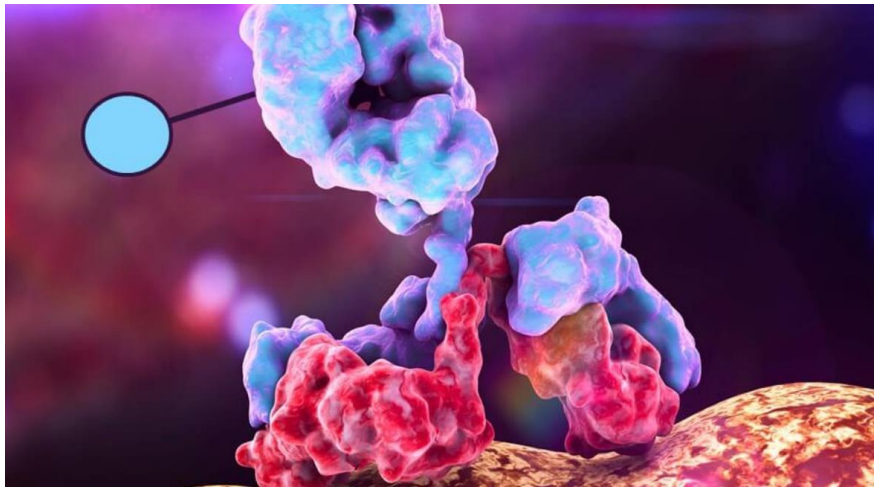
LONCASTUXIMAB TESIRINE-LPYL

(Schmitz et al.,https://www.researchgate.net/publication/323651667)

New target ROR-1







Receptor tyrosine kinase-like orphan receptor 1 (ROR1)

- Orphan-receptor tyrosine-kinase-like surface antigen
- Oncofetal protein
- Expressed by many tissues during embryogenesis, some B-cell malignancies, and various cancer cell lines
- Not expressed by virtually all normal adult tissues
- Large proportions of many different human cancers also express ROR1, particularly high-grade histologies

(Zhang S, et al. American Journal of Pathology, Vol. 181, 2012;181:1903-1910)

Zilovertamab Vedotin (VLS-101)

- Novel ADC targeting ROR1
- Humanized IgG monoclonal antibody
- Anti-microtubule toxin, MMAE
- Cleavable linker

(Wang, M, et al. NEJM Evid 2022; 1:1-11)

Zilovertamab vedotin (ZV) Targeting of ROR1 as therapy for lymphoid cancers

Phase 1, first-in-human, dose-escalation study

- R/R NHL
- N = 32 patients, 15 MCL, 7 CLL, 5 DLBCL, 3 Follicular lymphoma, 1 Richter's, 1 MZL.
- Median of 4 prior thx
- ZV q3 weeks until PD or unacceptable toxicity
- Starting dose levels 0.5 (n=1), 1.0 (n=3), 1.5 (n=3), 2.25 (n=11), 2.5 (n=14) mg/kg
- PK and PD data documented systemic ZV exposure and exposure-dependent ZV targeting of ROR1 on circulating tumor cells.

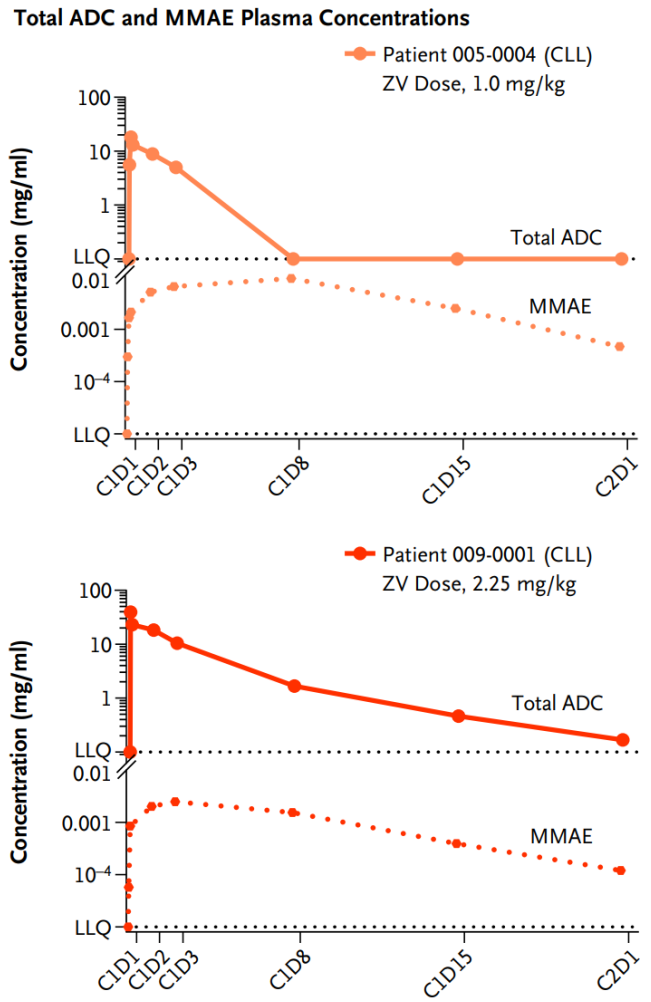
Adverse events:

- acute neutropenia
- cumulative neuropathy

Recommended ZV dosing regimen of 2.5 mg/kg every 3 wks

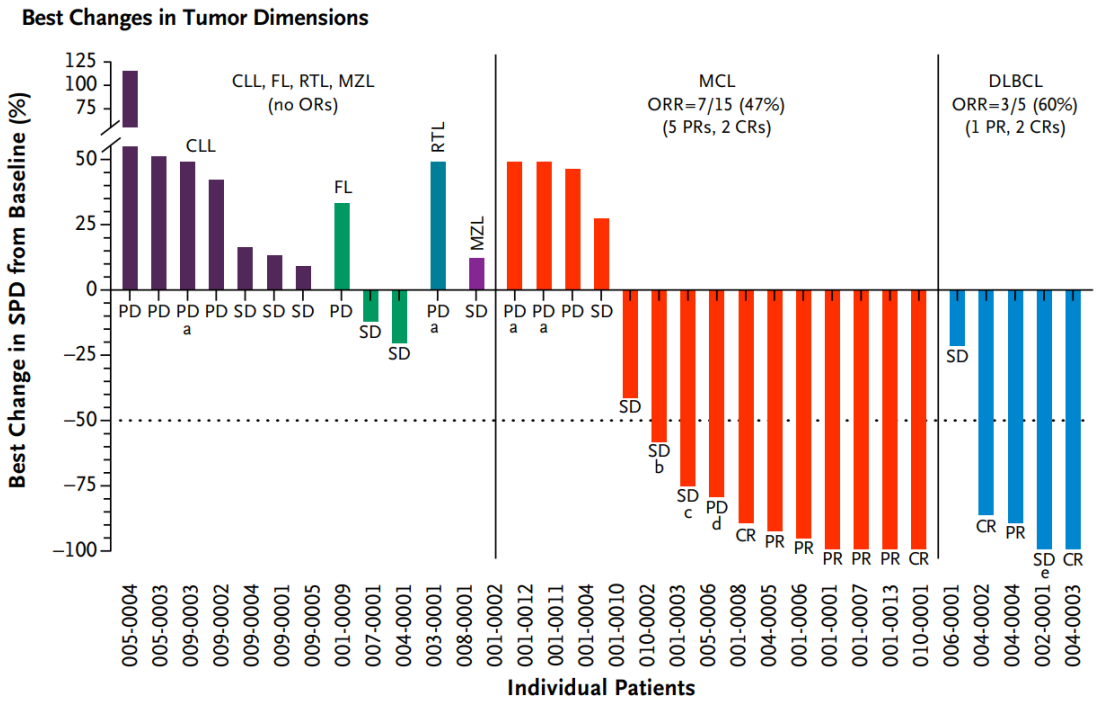
Responses:

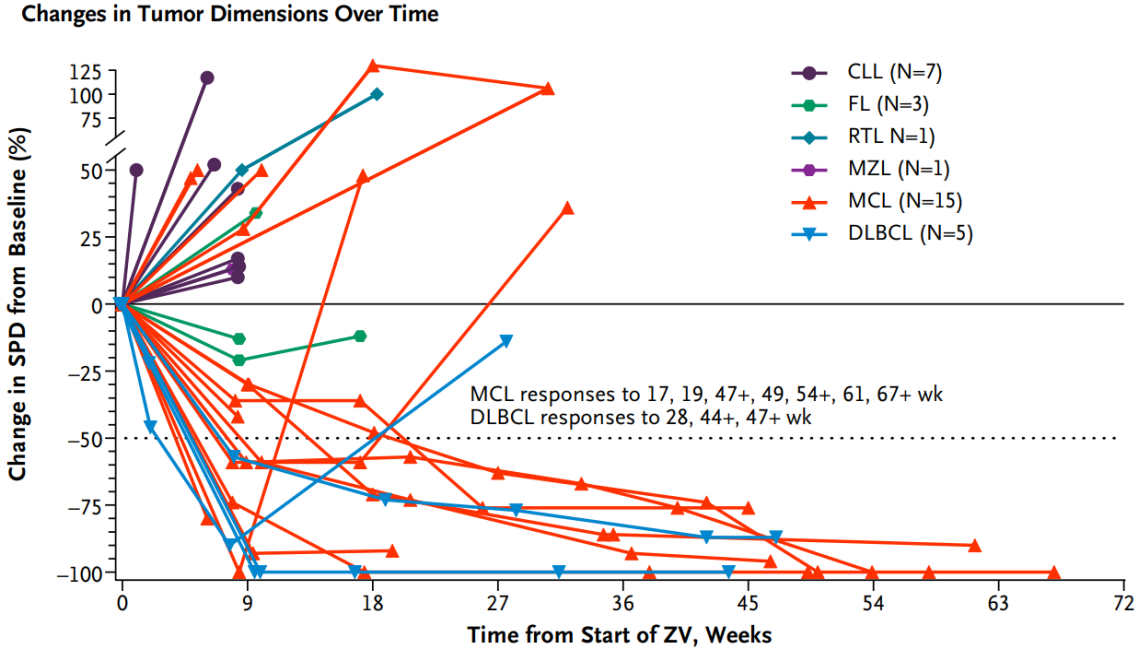
- 7 of 15 patients with MCL (47%; 4 PR and 3 CR)
- 3 of 5 patients with DLBCL (60%; 1 PR and 2 CR)
- No responses seen in other tumor types



(Wang, M, et al. NEJM Evid 2022; 1:1-11)

Zilovertamab vedotin (ZV) targeting of ROR1 as therapy for lymphoid Cancers





In heavily pretreated patients, ZV demonstrated no unexpected toxicities and showed evidence of antitumor activity, providing clinical proof of concept for selective targeting of ROR1 as a potential new approach to cancer therapy.

(Wang, M, et al. NEJM Evid 2022; 1:1-11)

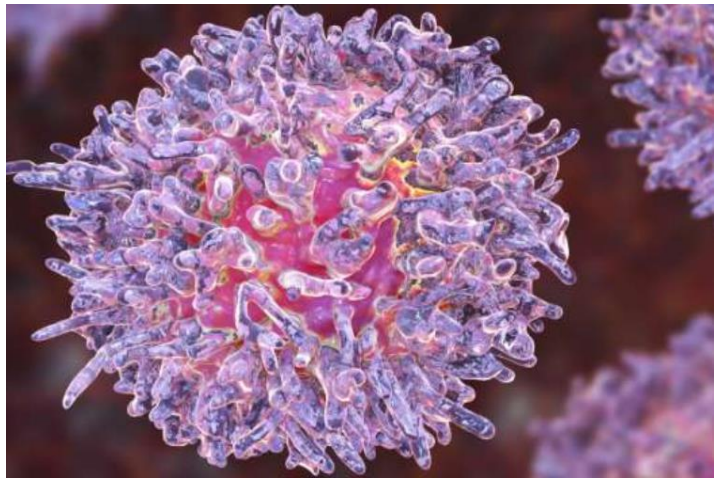
Active clinical trials of ADC in development for lymphoma (selected)

ADC Name (sponsor)	Target	Additional Agents	Phase	NCT Number	Eligible Histologies	Start Date	Completion Date
Loncastuximab tesirine (Lonca, ADCT-402; ADC Therapeutics)	CD19	None	2	NCT03589469	R/R DLBCL	August 2018	March 2021
		Durvalumab	1	NCT03685344	R/R DLBCL, MCL, FL	December 2018	January 2021
		Ibrutinib	1/2	NCT03684694	R/R DLBCL, MCL	December 2018	April 2023
		Rituximab, gemcitabine, oxaliplatin	3	NCT04384484	R/R DLBCL	September 2020	December 2024
MT-3724 (Molecular Templates)	CD20	None	1/2	NCT02361346	R/R B-cell NHL, CLL	February 2015	September 2021
		Gemcitabine, oxaliplatin	2	NCT03488251	R/R B-cell NHL	August 2018	February 2023
		Lenalidomide	2	NCT03645395	R/R B-cell NHL	April 2019	July 2022
TRPH-222 (Triphase)	CD22	None	1	NCT03682796	R/R DLBCL, MCL, FL, MZL	October 2018	August 2022
Camidanlumab tesirine (Cami, ADCT-301; ADC Therapeutics)	CD25	None	2	NCT04052997	R/R HL	September 2019	May 2024
Naratuximab emtansine (Debio1562, IMGN592; Debiopharm)	CD37	Rituximab	2	NCT02564744	R/R DLBCL, MCL, FL, MZL	June 2016	January 2021
STRO-001 (Sutro Biopharma)	CD74	None	1	NCT03424603	R/R B-cell NHL, MM	February 2018	November 2023
VLS-101 (VelosBio)	ROR1	None	1	NCT03833180	R/R B cell NHL, CLL, Richter transformation, T-cell NHL, ALL, AML, Waldenström macroglobulinemia	February 2019	June 2021

(Russler-Germain DA, et al. ONCOLOGY 2020, Vol 34 Issue 12)

Moxetumomab pasudotox-tdfk: first-in-class treatment approved for hairy cell leukemia

Moxetumomab pasudotox-tdfk



- CD22-directed cytotoxin
- Resulting in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis and apoptotic cell death

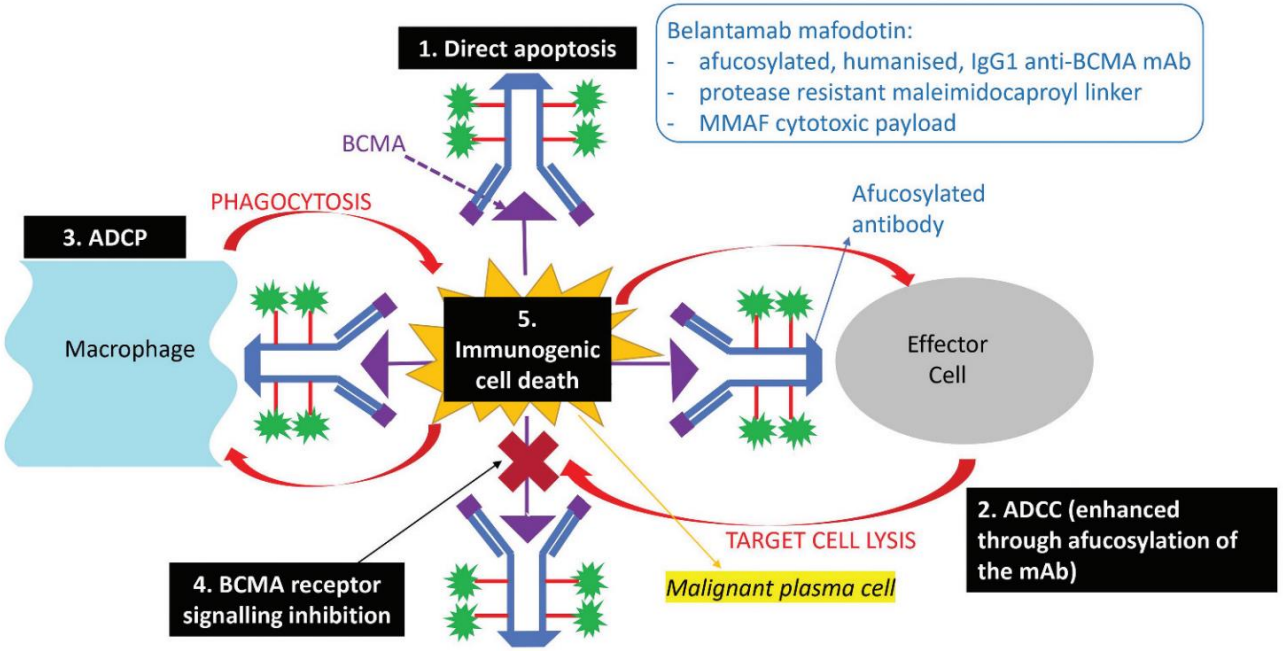
- FDA approved for the treatment of adult patients with rel/ref hairy cell leukemia (HCL), who received ≥2 prior systemic therapies, including treatment with a purine nucleoside analog

- Phase 3 single-arm, open-label trial (N=80)
- Lumoxiti 0.04mg/kg as an intravenous infusion over 30 minutes on Days 1, 3, and 5 of each 28-day cycle for a maximum of 6 cycles
- Durable CR rate = **30%** (24/80 patients); ORR = **75%**. Median time to hematologic remission **1.1 mo**

- Boxed Warning: capillary leak syndrome and hemolytic uremic syndrome

(Kreitman RJ,, et al. Leukemia 2018;32(8):1768–77)

Recent approval (2020): Belantamab mafodotin for rel/refr multiple myeloma



- **FDA approved**
  - 4 prior lines of therapy, including an anti-CD38 mAb, a proteasome inhibitor, and an immunomodulatory agent
- **DREAMM-2**
  - ORR **31%**
- **Adverse Events: Corneal epithelium**
  - REMS

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Keratopathy or changes to corneal epithelium*	41 (43%)	26 (27%)	0	0	53 (54%)	20 (20%)	1 (1%)	0

(McMillan A, et al. Expert Opinion on Biological Therapy 2021, 21: 889–901

(Lonial S, et al. Lancet Oncology 2020, 21: 207-221)

Safety of ADCs in cancer

- ADCs exhibit both on-target and off-target toxicities
- Most toxicities seem to be related to the nature of the payload
- Off-target toxicities can be attributable to payload release in the circulation, in non-tumor tissues or in the tumor microenvironment
- Moderate to high levels of neutropenia, alopecia, and gastrointestinal side effects have been observed in clinical trials of many novel ADCs

Conclusions and future perspectives

- ADCs have had a significant impact on treating hematological malignances, being part of front line regimen for AML, Hodgkin lymphoma, PTCL and sALCL.
- New ADC targets (such as ROR-1) have been identified and potentially practice-changing innovations in ADC design, biomarker development and combination therapies are ongoing in preclinical and clinical studies.
- An improved understanding of the interactions between ADCs, tumors, and the tumor microenvironment is essential to realize the true potential of this class of drugs in the treatment of cancer.
- There are more than 80 ADCs under clinical development worldwide in approximately 150 active clinical trials. *(Dean AQ et al. mAbs. 2021; 13(1): 1951427)*

University of California, Los Angeles

David Geffen School of Medicine

Antibody drug conjugates in solid tumors: old and new targets

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DI MILANO

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Istituto Europeo
di Oncologia

Disclosures

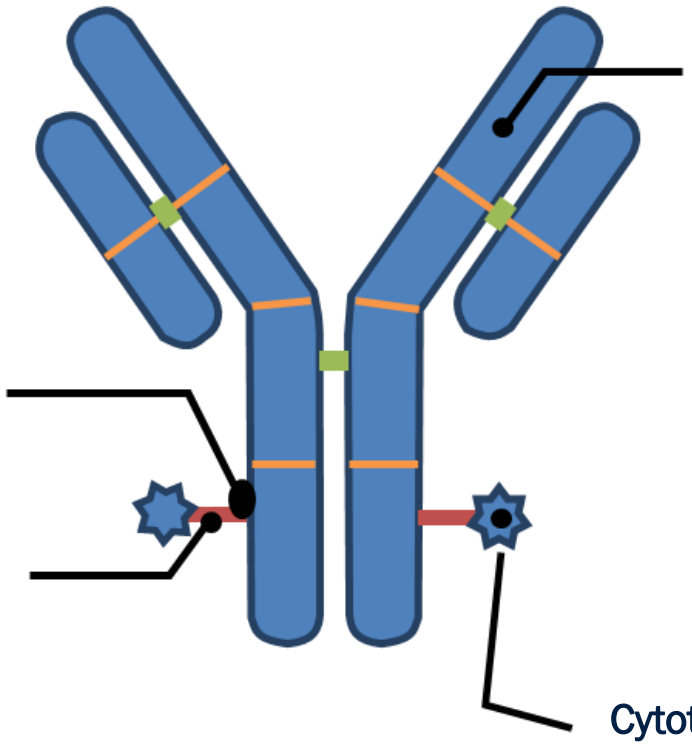
- Board Member: Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my Institute : MSD, Astra Zeneca
- Speakers bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None

ADCs consist of numerous elements, including the monoclonal antibody, conjugated drug, and stable linker

Monoclonal antibody
- Selective for an antigen with high copy numbers on the target tumour cell
- Internalises in target cell
- Minimal immunogenic response

Conjugation chemistry
- Lys or Cys residue of the mAb; controls drug distribution and DAR

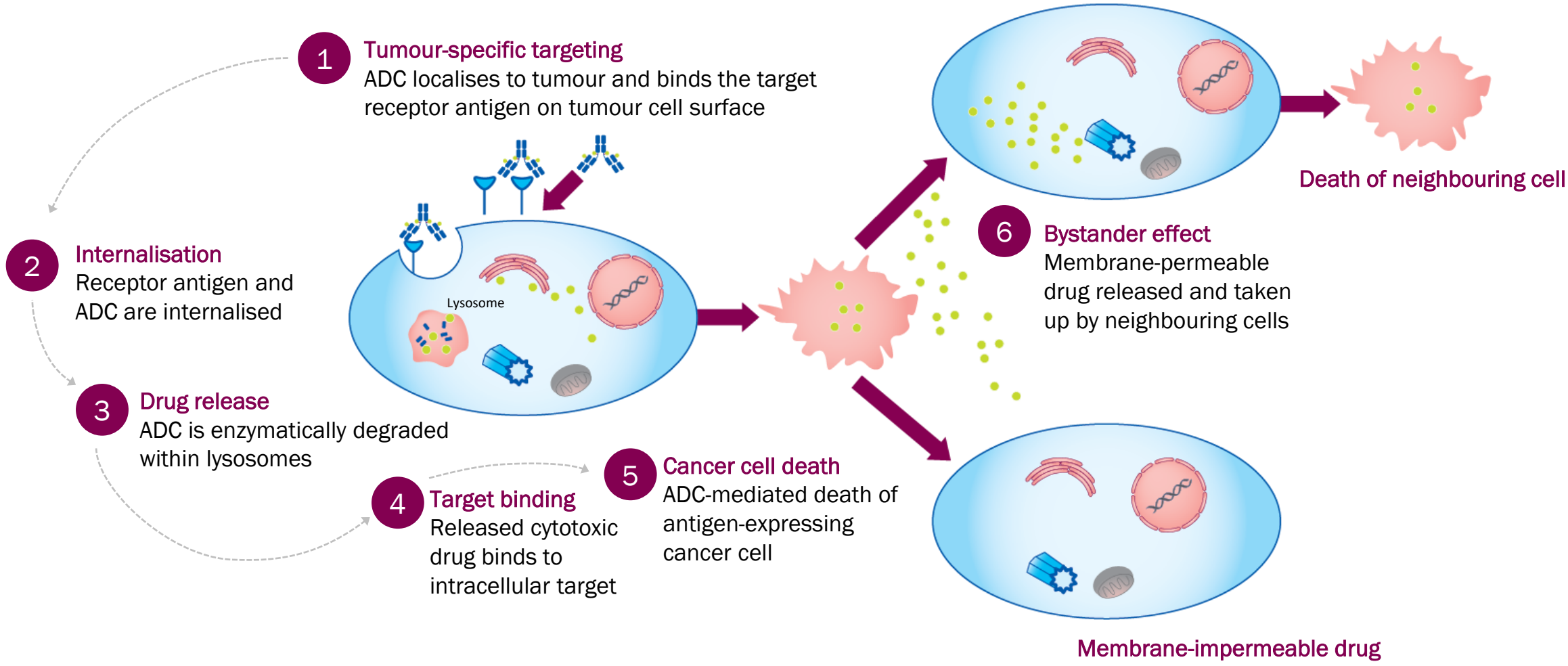
Stable linker
- Selectively releases drug in target cell
- Long term stability

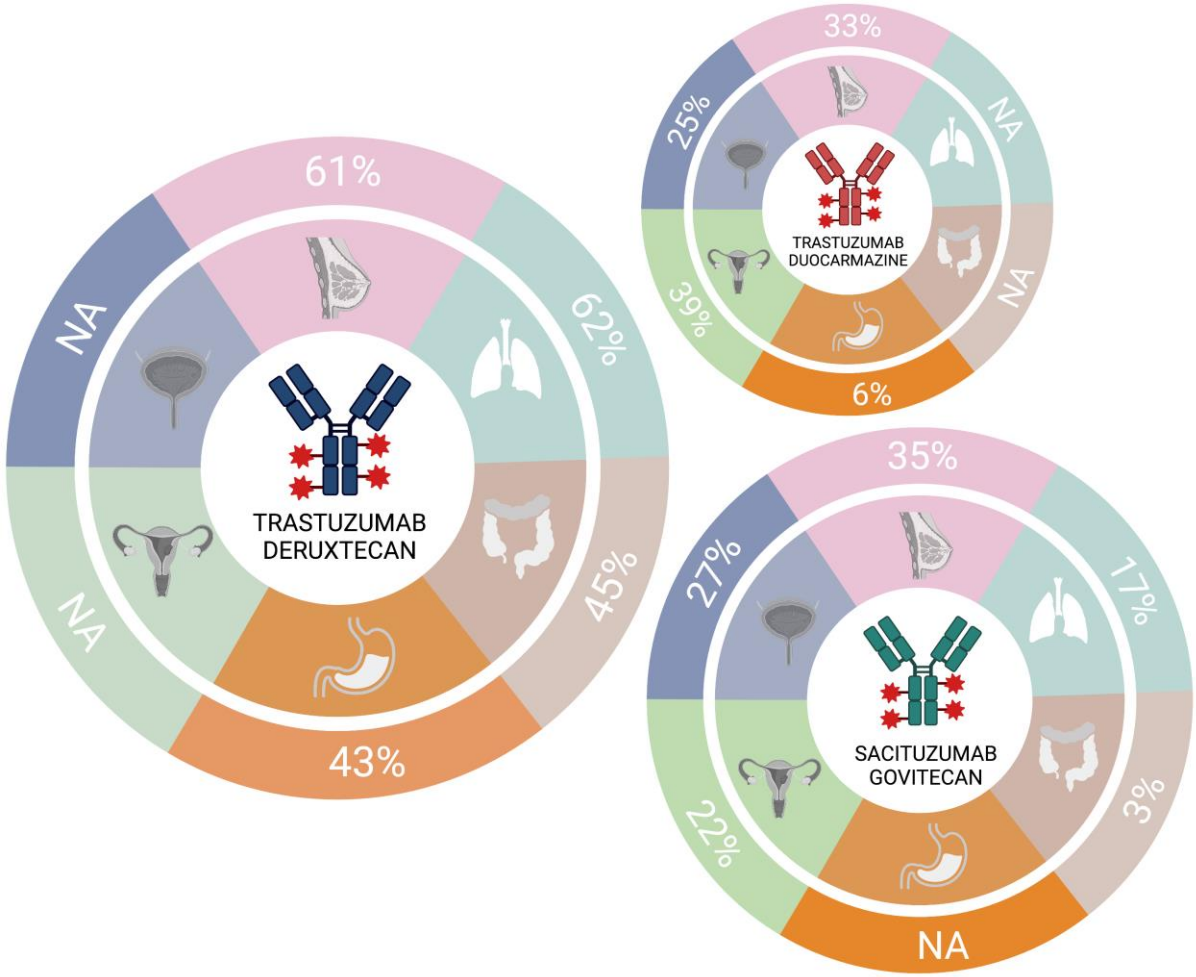


Linker Payload Disulphide bonds

Cytotoxic drug
- Highly potent subnanomolar activity
- Functional groups for linking
- Lower hydrophobicity

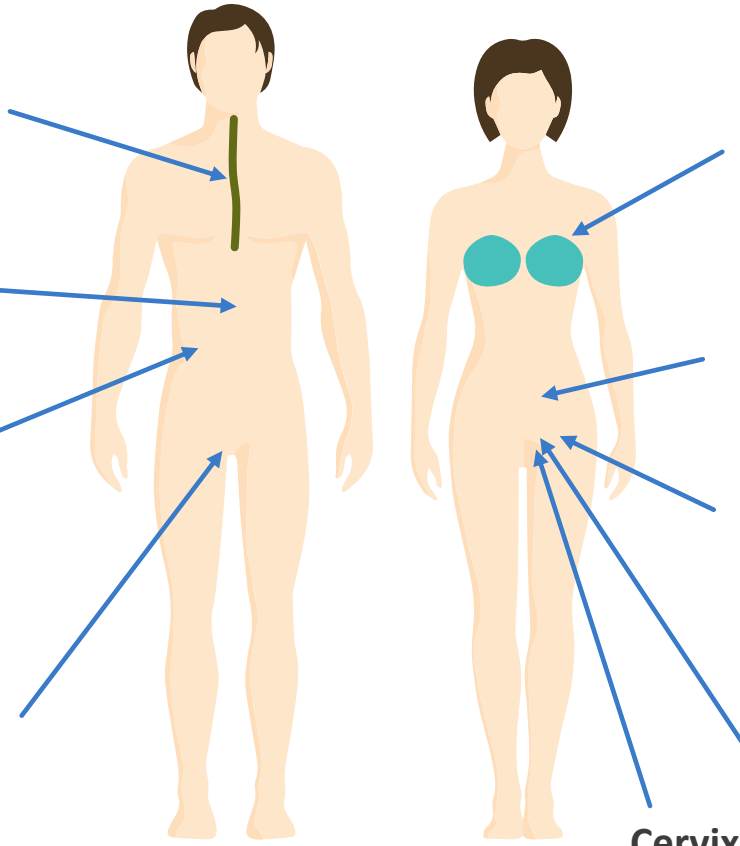
ADC technology enables tumour-specific targeting





Tarantino et al. *CA Journal 2022*

Selecting target antigens in solid tumours



Oesophageal/GEJ:
HER2 11–14%

Gastric:
HER2 5–34%
HER3 34–59%
TROP2 66%

Pancreas:
HER2 0.7%
HER3 41%
TROP2 55%

Colorectal:
HER2 2–5%
HER3 17–70%
TROP2 35%

Melanoma:
LIV-1 82%
HER3 65%

Breast:
LIV-1 93%
HER2 11–25%
HER3 18–43%

Bladder:
HER2 8–70%
Nectin 4 60%

Ovary:
LIV-1 48%
HER2 2%
HER3 53%
TROP2 16%

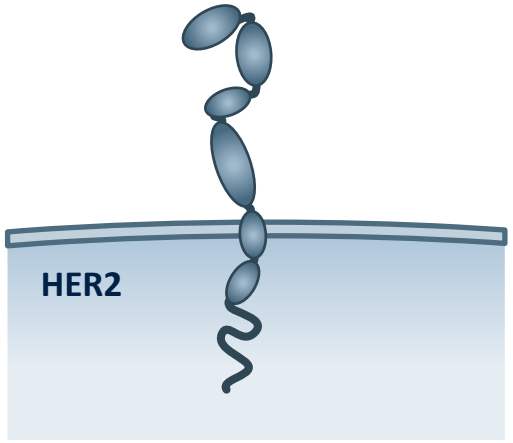
Uterus:
LIV-1 30%

Cervix:
HER2 4%
HER3 56%
TROP2 89%

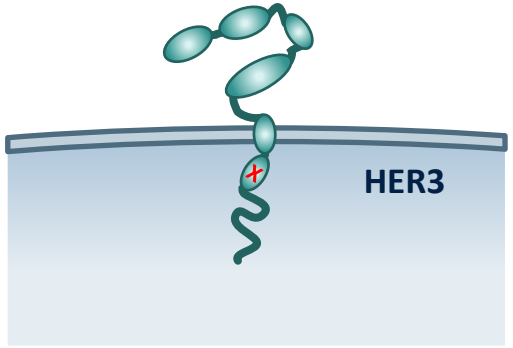
- Several studies noted expression of LIV-1[1], HER2[2], HER3[3] and TROP2[4]
- High expression of HER3 correlated with poor prognosis:[2]
  - in patients with breast cancer and gastric cancer
  - in patients with HER2 overexpressing tumours
- High expression of TROP2 correlated with poor prognosis in female genital systems neoplasms and gastrointestinal neoplasms[3]

Promising targets for antibody–drug conjugates

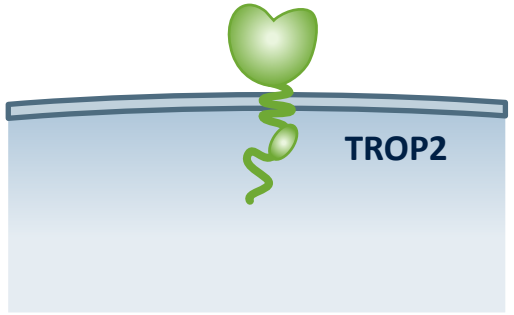
T-DXd,
SYD985



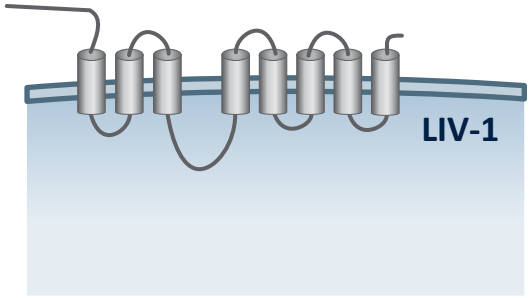
HER3-DXd,
EV20-MMAF,
EV20-Sap

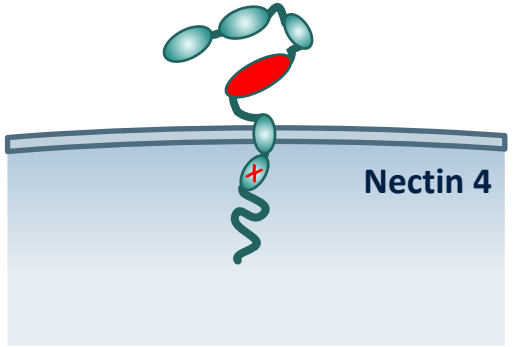


Dato-DXd,
IMMU-132



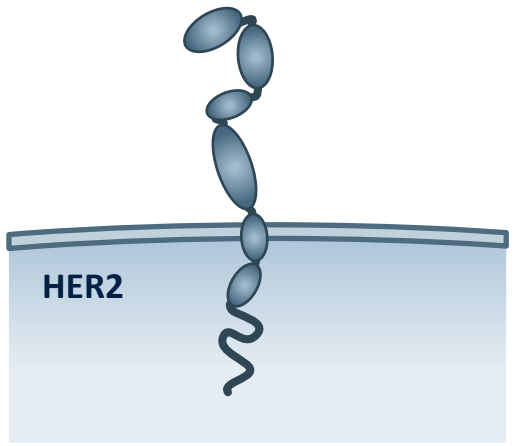
Ladiratuzumab
vedotin

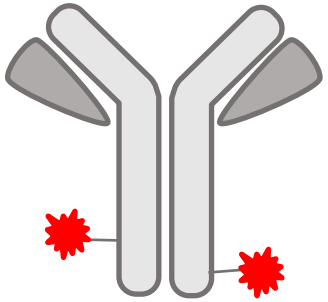




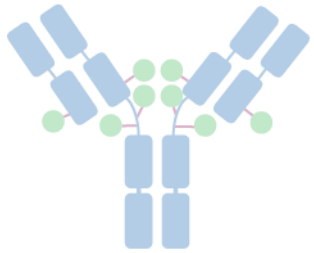
Enfortumab
vedotin

Antibody–drug conjugates targeting HER2



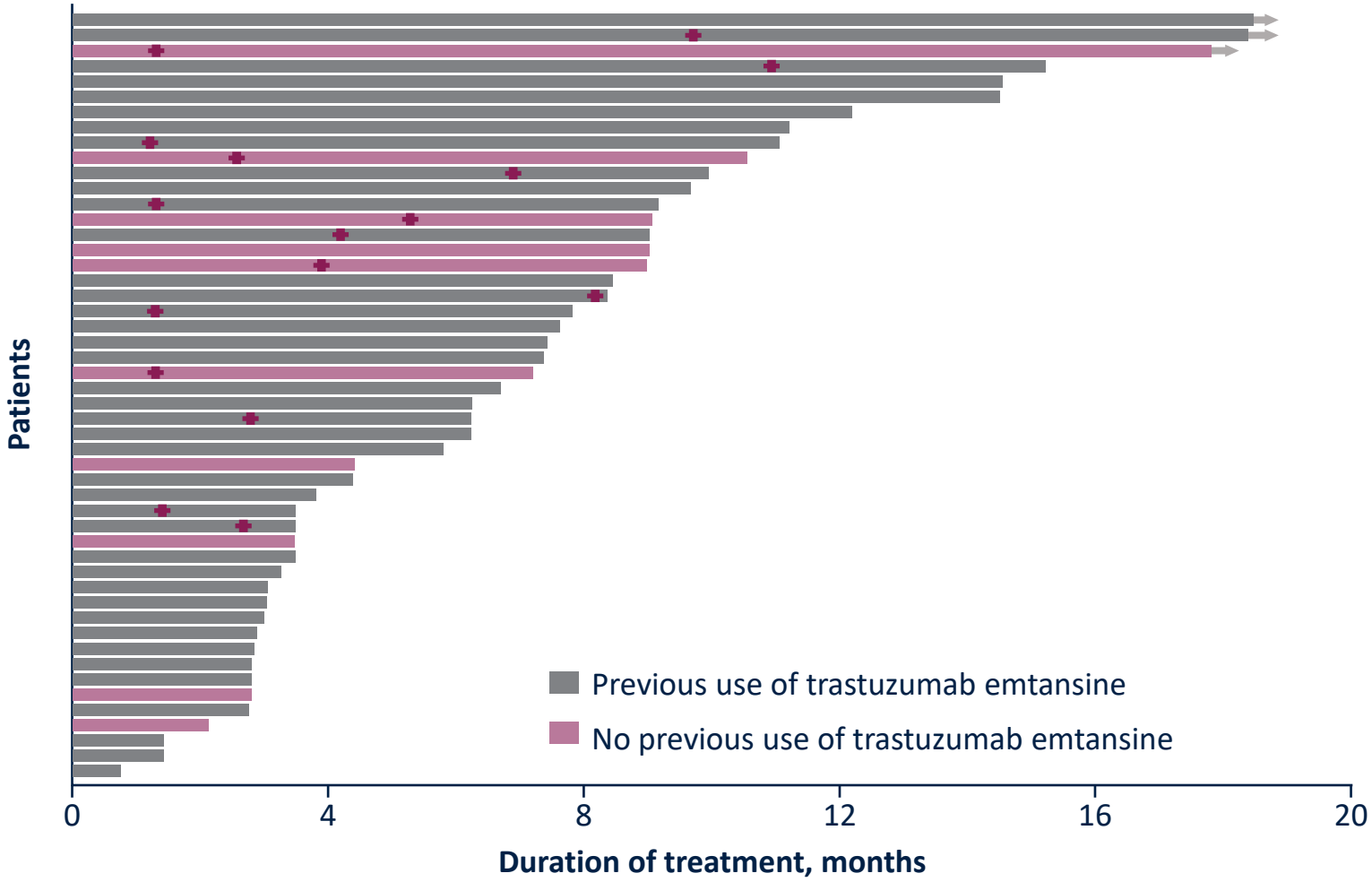


- Trastuzumab duocarmazine (SYD985)



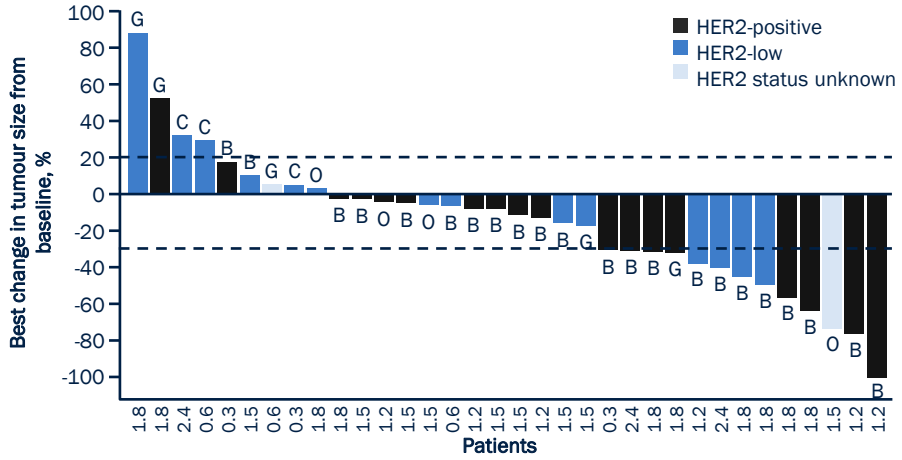
- Trastuzumab deruxtecan (T-DXd)

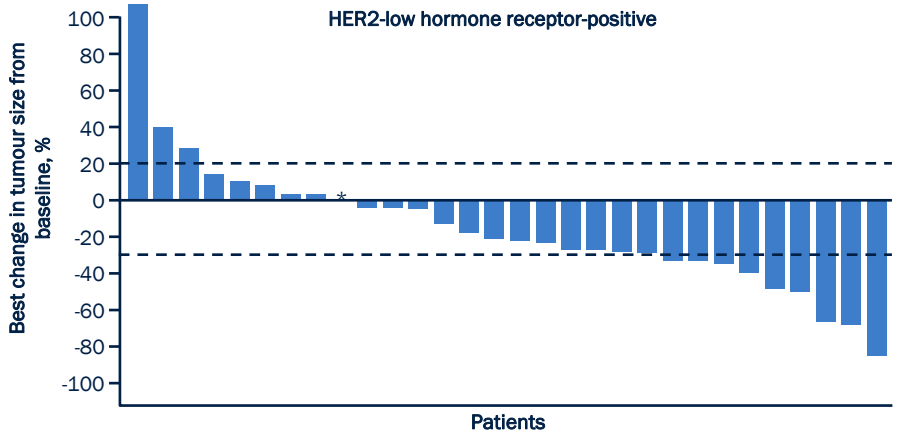
SYD985 Phase 1: Duration of treatment for HER2-positive breast cancer expansion cohort

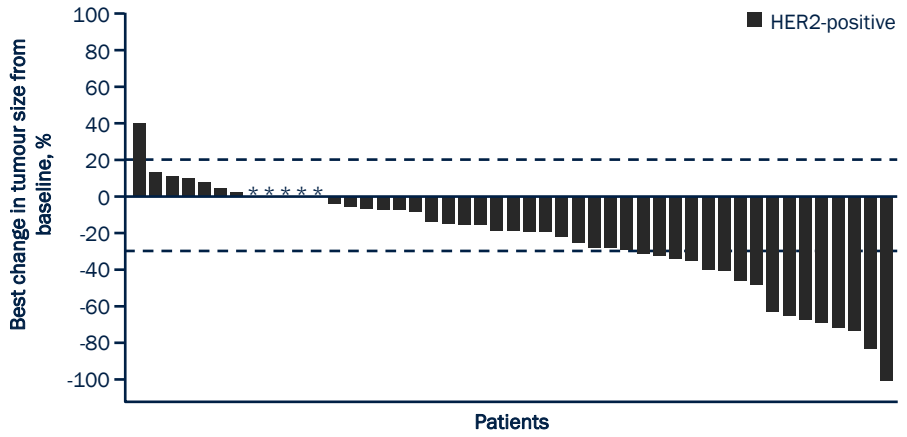


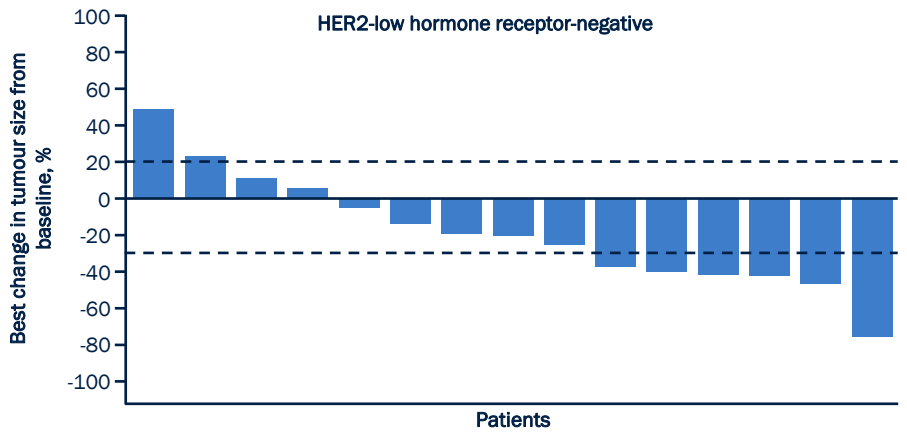
HER2, human epidermal growth factor receptor 2.
Banerji U, et al. Lancet Oncol. 2019;20:1124–1135.

SYD985 Phase 1: Best percentage change in tumour size from baseline in target lesions for accessible patients







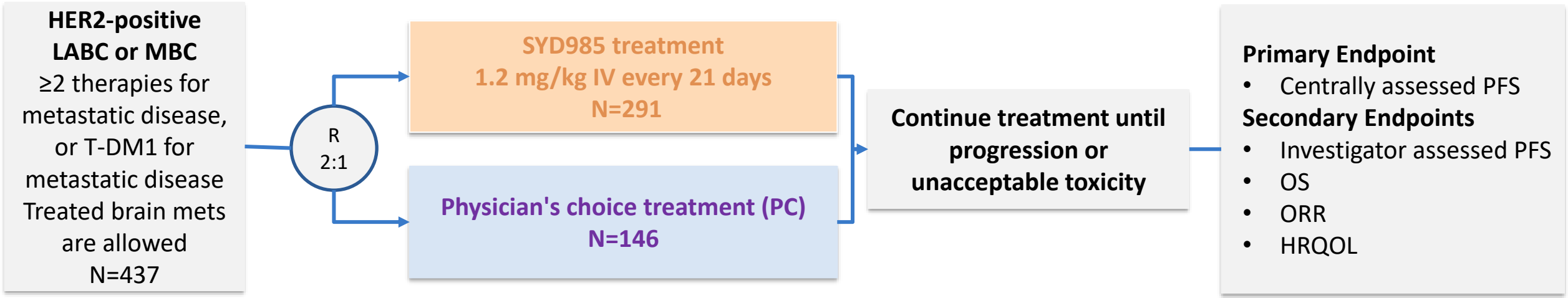


HER2, human epidermal growth factor receptor 2.

Banerji U, et al. Lancet Oncol. 2019;20:1124–1135.

Reduction in target lesions in 70.5% of patients with breast cancer • Confirmed ORR in these patients was 24.2%

TULIP - Phase III Trial Design



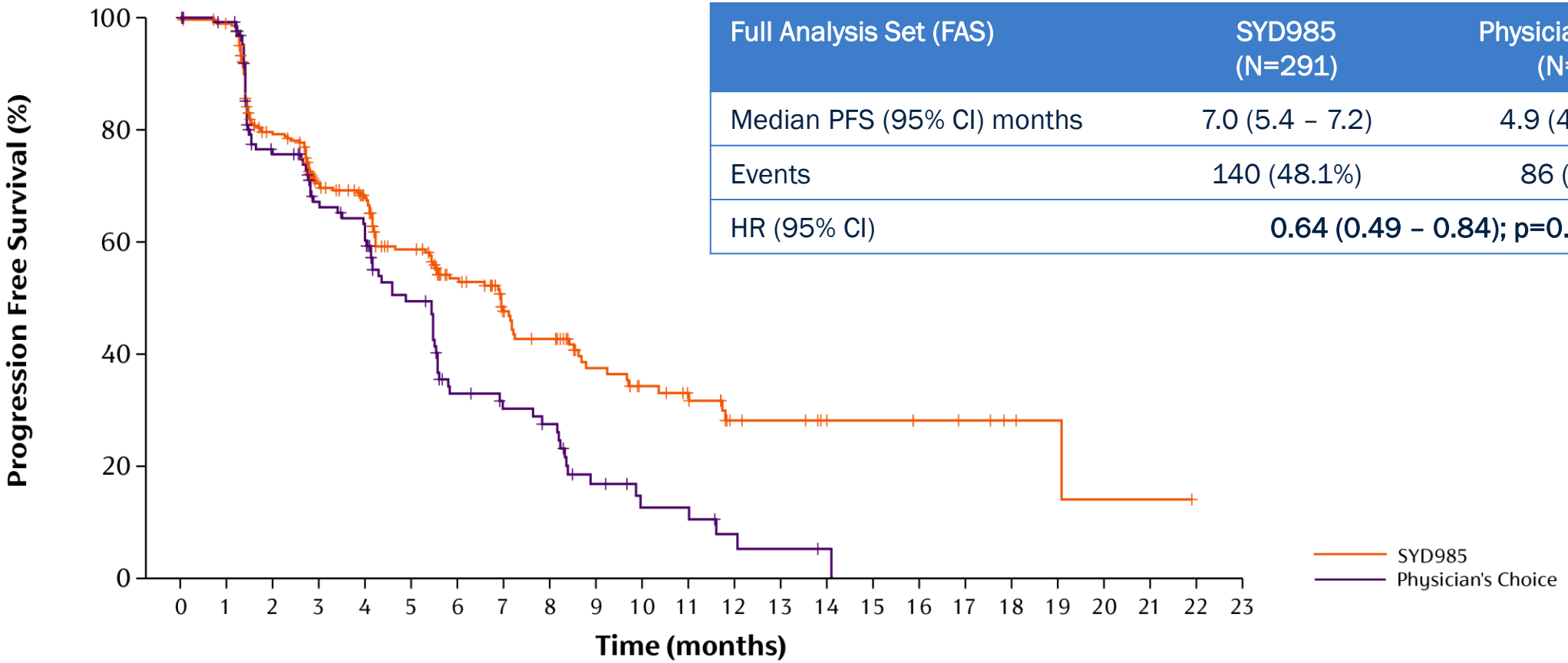
Stratification - Treatment - Participating Countries

- **Stratification factors**
  - Region (EU+Singapore vs North America)
  - Number of prior treatment lines for LMBC/MBC (1-2 vs >2)
  - Prior treatment with pertuzumab (yes vs no)
- **Physician's choice**
  - Lapatinib + Capecitabine
  - Trastuzumab + Capecitabine
  - Trastuzumab + Vinorelbine
  - Trastuzumab + Eribulin
- **NCT03262935**
- **83 sites**
  - USA, Canada, Belgium, Denmark, France, Italy, Netherlands, Spain, Sweden, UK, Singapore

Saura et al, ESMO 2021

TULIP – Centrally Reviewed PFS

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							

Saura et al, ESMO 2021

TULIP – Safety – AEs of Special Interest

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

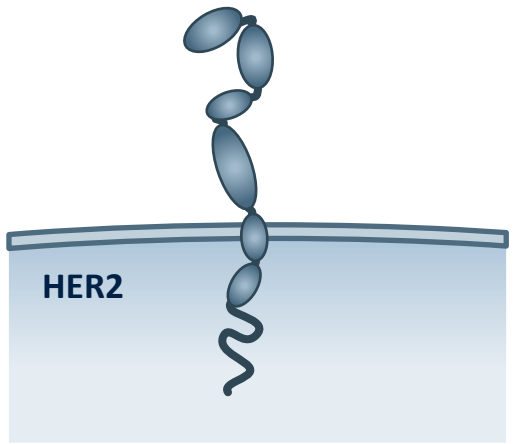
Risk mitigation strategy in trial: Patients with prior pneumonitis excluded, evaluate tumor CT scans for lung changes, do a full diagnostic work-up for new or worsening respiratory symptoms, grade 2 or higher pneumonitis stop treatment, grade 1 pneumonitis delay treatment until resolution

Fatal cases: Reported for 2.1% (N=6) SYD985 patients, not reported for physician's choice

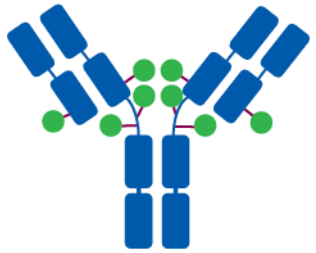
- Related: Respiratory failure (0.3%, N=1), Pneumonia (0.3%, N=1), Pneumonitis (0.7%, N=2)
- Not related: Acute respiratory failure (0.3%, N=1), COVID-19 Pneumonia (0.3%, N=1)

Saura et al, ESMO 2021

Antibody–drug conjugates targeting HER2

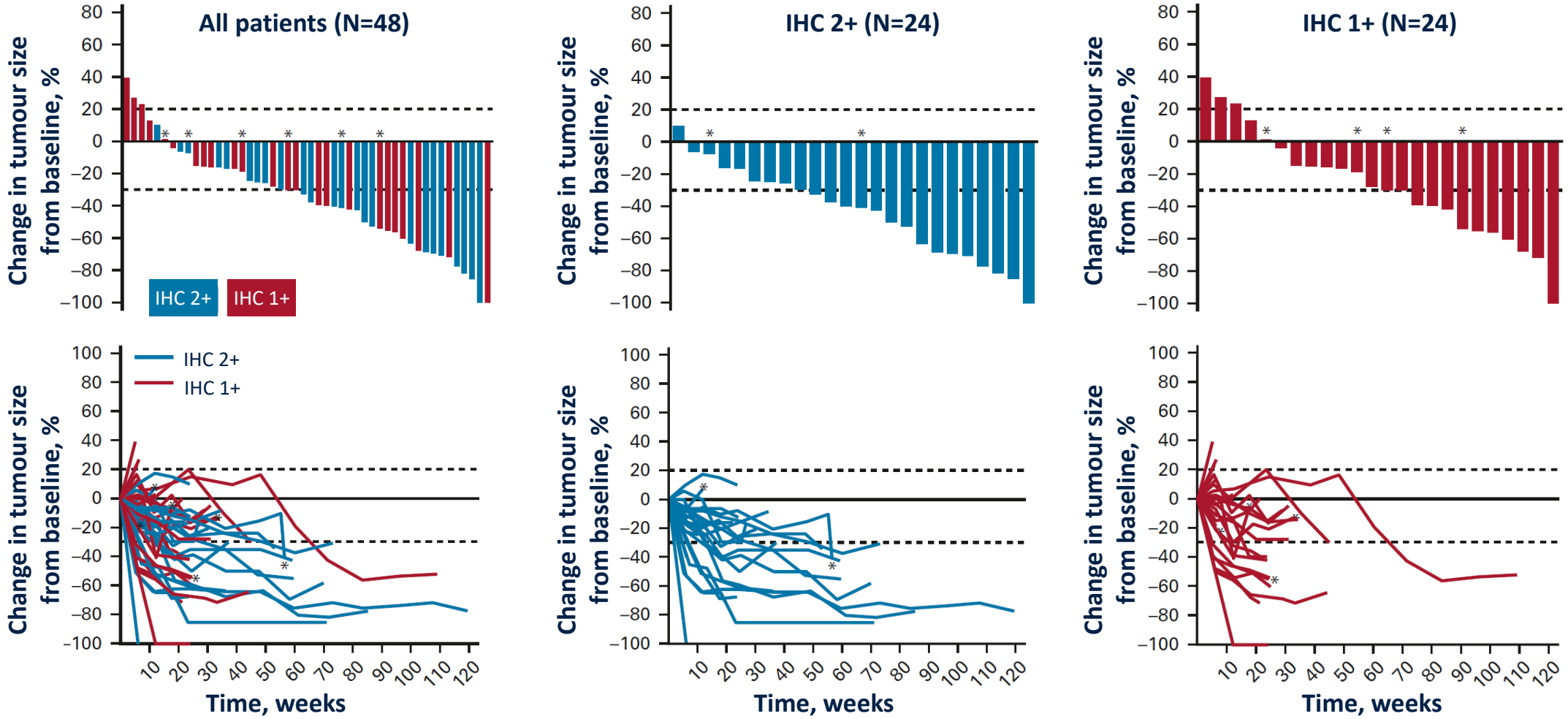


- Trastuzumab duocarmazine (SYD985)



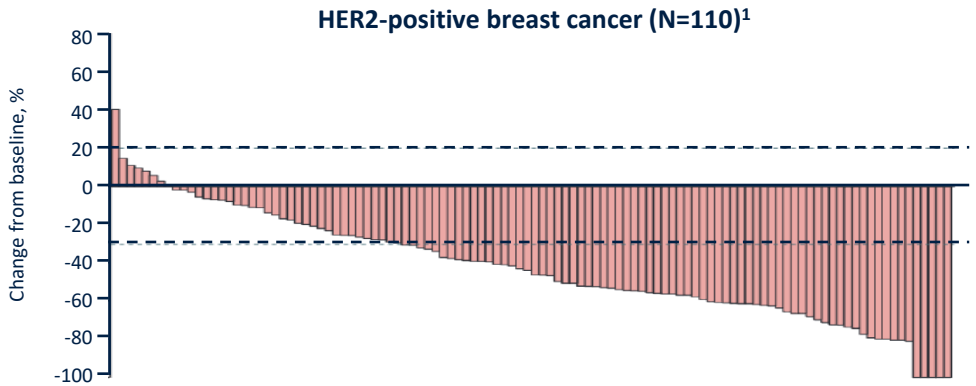
- Trastuzumab deruxtecan (T-DXd)

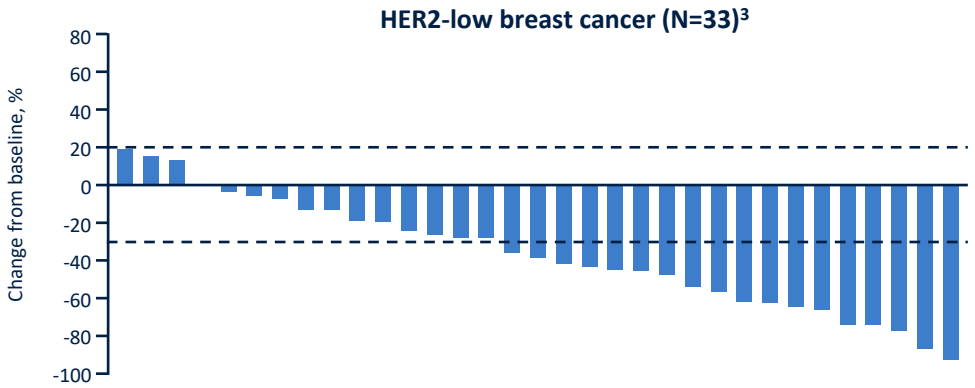
T-DXd: Activity in patients with HER2-low advanced BC

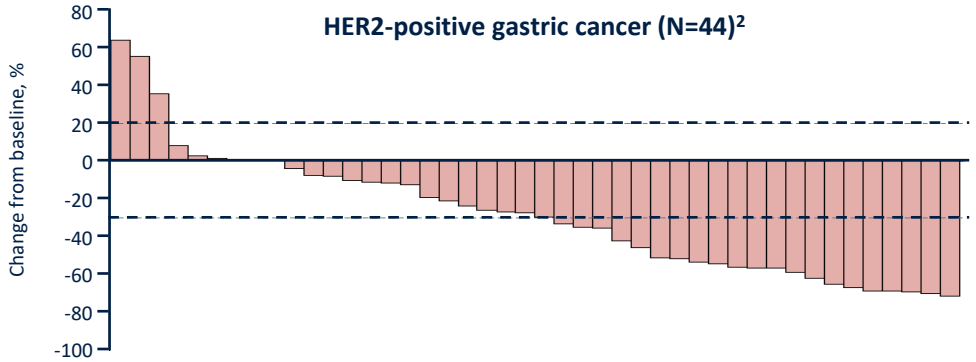


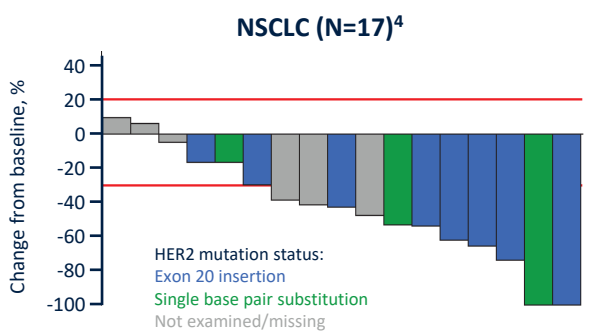
BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DXd, trastuzumab deruxtecan.
Modi S, et al. J Clin Oncol. 2020;38:1887–96.

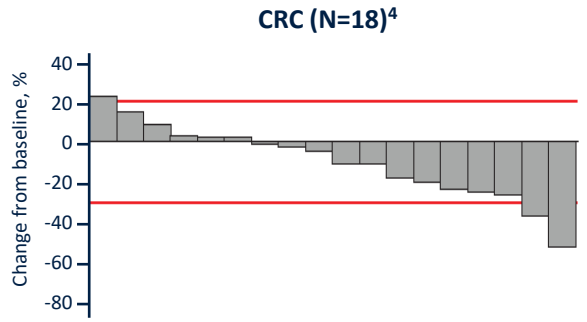
T-DXd Phase 1: Consistent response across tumour types











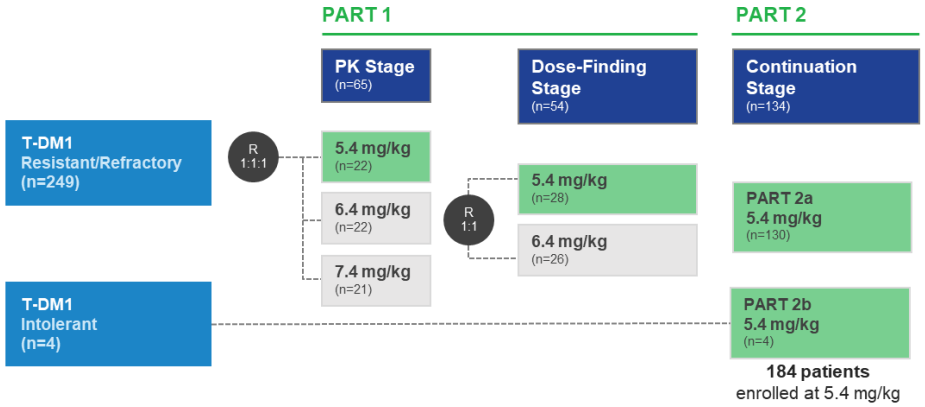
Reduction in target lesions was observed across patient populations

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer; ORR, overall response rate; T-DXd, trastuzumab deruxtecan. 1. Tamura K, et al. Lancet Oncol. 2019;20:816–26; 2. Shitara K, et al. Lancet Oncol. 2019;20:827–36; 3. Iwata H, et al. J Clin Oncol. 2018;36 (suppl; abstr 2501); 4. Tsuritani J, et al. Cancer Discov. 2020;10:688–701.

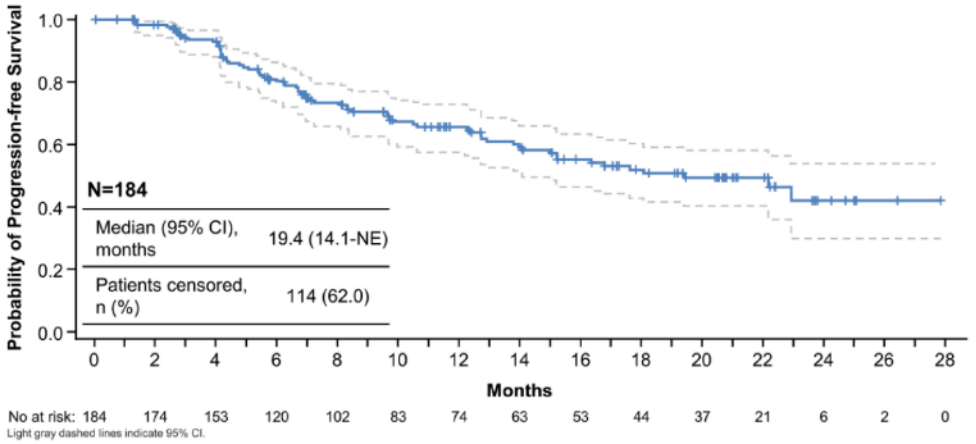
DESTINY-Breast01: Phase 2 study of T-DXd in advanced/metastatic breast cancer

DESTINY-Breast01 Study Design

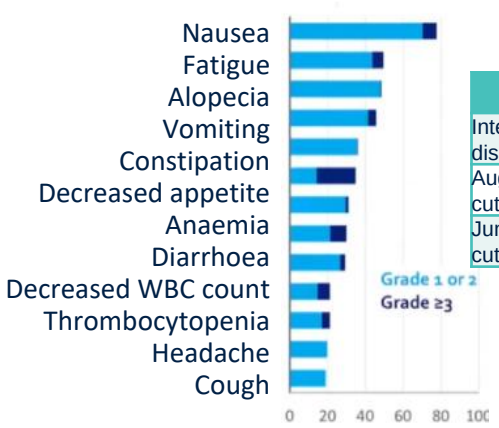
Population
- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



Progression-free survival



Safety Results

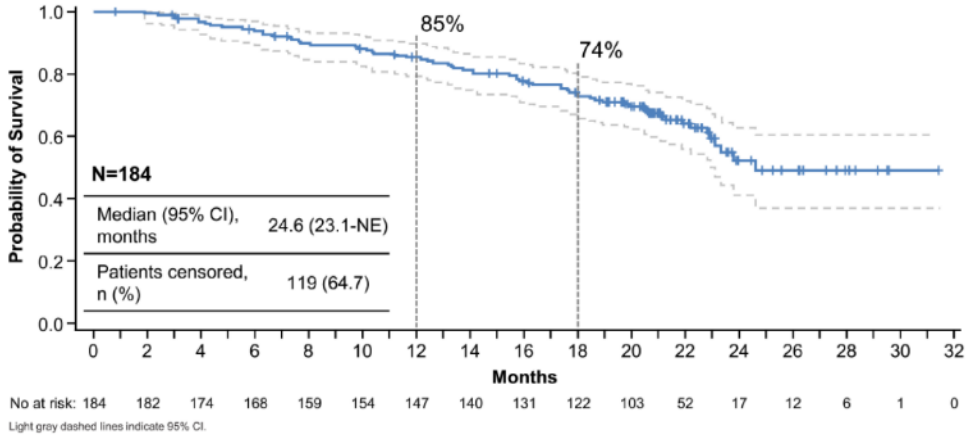


ILD requires awareness via monitoring, dose interruption and modification, and adherence to the management guidelines

	Patients who received T-DXd 5.4 mg/kg (N=184)					
Interstitial lung disease, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
August 2019 data cut-off	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
June 2020 data cut-off	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)

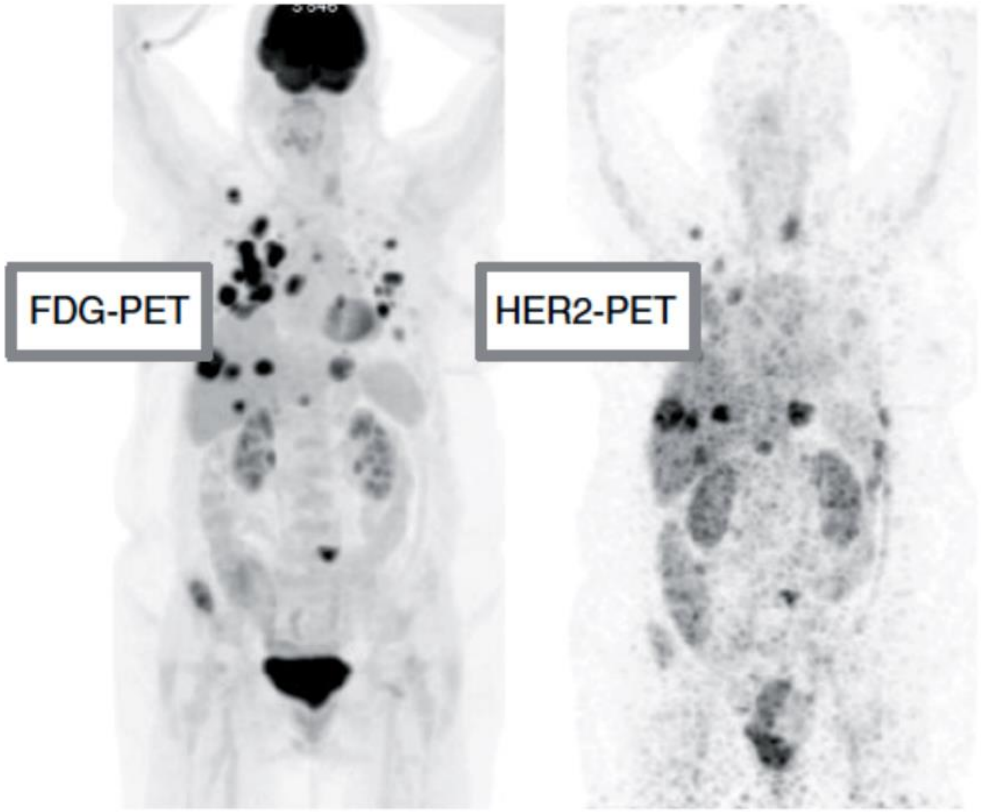
Median time to onset of ILD was 27.6 weeks (range, 6–76 weeks)
Rate of discontinuation due to ILD did not increase over time

Overall survival



BC, breast cancer; CI, confidence interval; ILD, interstitial lung disease; NE, not estimable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.Modi S, et al. PD3-06, Poster presented at SABCS 2020.

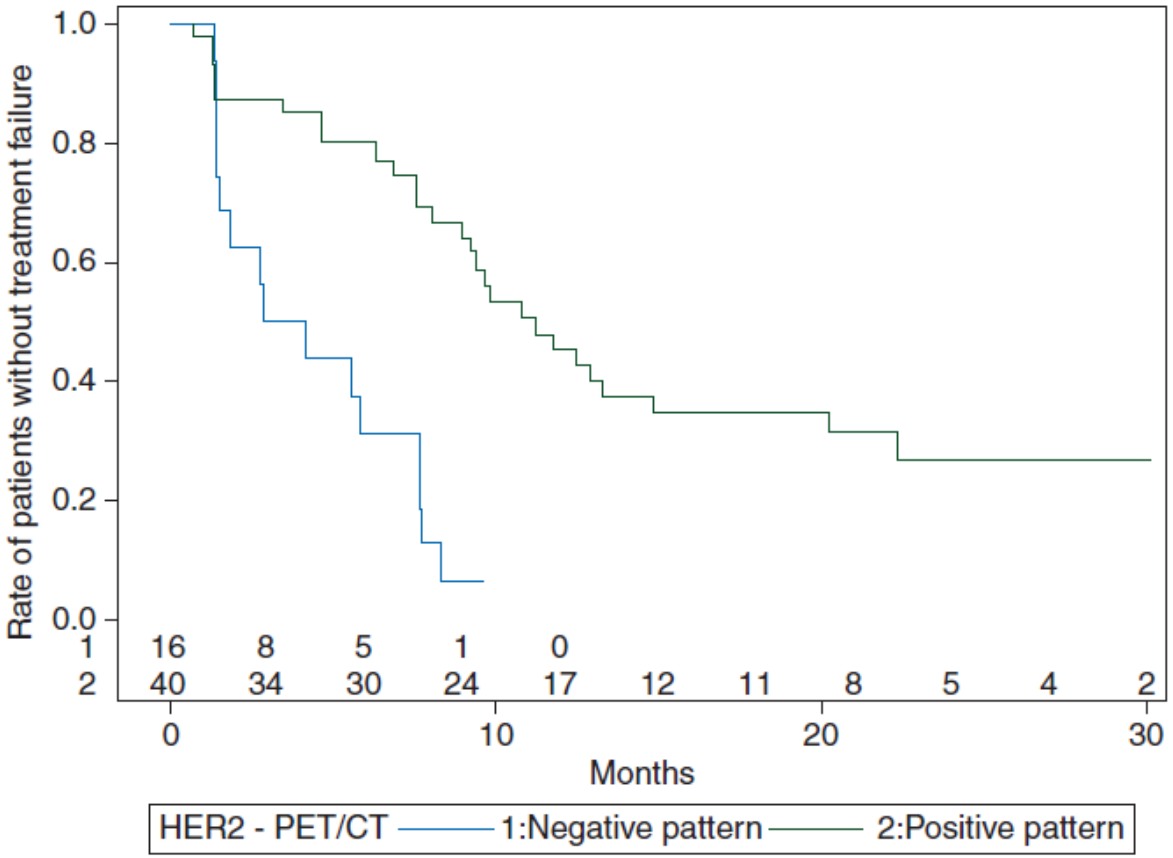
Macro-Heterogeneity of Disease



Lung, liver + bone involvement seen on FDG-PET:
not all lung lesions are seen on HER2-PET

Gebhart et al; Annals of Oncology v27 p619–624 (2016)

Efficacy of T-DM1 varies according to inter-metastases heterogeneity



Pretreatment imaging of HER2 targeting, combined with early metabolic response assessment holds great promise for improving the understanding of tumor heterogeneity in mBC and for selecting patients who will/will not benefit from T-DM1

Gebhart et al; Annals of Oncology v27 p619–624 (2016)

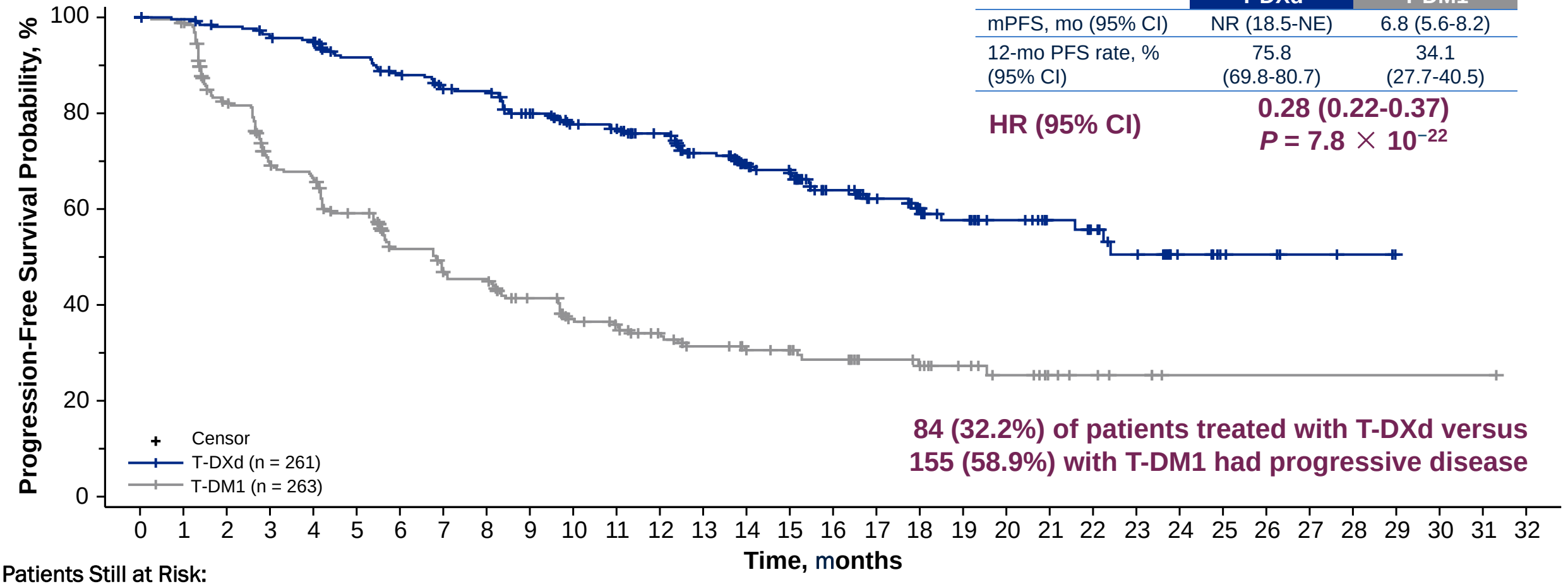
Baseline Characteristics and Prior Therapies

	T-DXd n = 261	T-DM1 n = 263
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, n (%)	260 (99.6)	262 (99.6)
Region, n (%)		
Europe	54 (20.7)	50 (19.0)
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Rest of world	41 (15.7)	36 (13.7)
HER2 status (IHC[a]), n (%)		
3+	234 (89.7)	232 (88.2)
2+ (ISH amplified)	25 (9.6)	30 (11.4)
1+ | Not evaluable	1 (0.4) | 1 (0.4)	0 | 1 (0.4)
ECOG PS, n (%)		
0 | 1	154 (59.0) | 106 (40.6)	175 (66.5) | 87 (33.1)
Hormone receptor, n (%)		
Positive | Negative	131 (50.2) | 130 (49.8)	134 (51.0) | 129 (49.0)
History of BM, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
BM at baseline,[b] n (%)		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)
Visceral disease, n (%)		
Yes | No	184 (70.5) | 77 (29.5)	185 (70.3) | 78 (29.7)
Prior treatment for mBC, n (%)	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting,[c] n (%)		
0-1 | ≥2	132 (50.6) | 129 (49.4)	126 (47.9) | 137 (52.1)
Prior cancer therapy,[d] n (%)		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)

BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; BC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2-status as evaluated by central laboratory. [b]Patients with BM at baseline compose the patient population described in all subsequent slides. [c]includes patients with rapid progression as 1 line of treatment. Rapid progression defined as progression within 6 months of (neo)adjuvant therapy or 12 months if regimen contained pertuzumab. Line of therapy does not include endocrine therapy. [d]All patients received at least 1 prior cancer therapy. One patient who underwent prior T-DM1 treatment was enrolled in error in the T-DXd arm.

Primary End Point: PFS by BICR

	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	



84 (32.2%) of patients treated with T-DXd versus 155 (58.9%) with T-DM1 had progressive disease

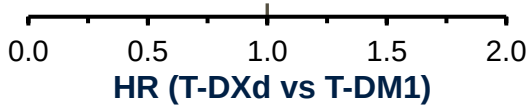
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.
Cortés et al. *Ann Oncol*. 2021; 32(suppl_5):S1283-S1346. 10.1016/annonc/annonc741

PFS in Key Subgroups

		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone receptor status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior pertuzumab treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior lines of therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Patients with BM	Yes (n = 82)	22/43	27/39	15.0 (12.5-22.2)	3.0 (2.8-5.8)	0.2465 (0.1341-0.4529)
	No (n = 442)	65/218	131/224	NE (22.4-NE)	7.1 (5.6-9.7)	0.2971 (0.2199-0.4014)



BM, brain metastasis; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Confirmed ORR Across Patient Subgroups

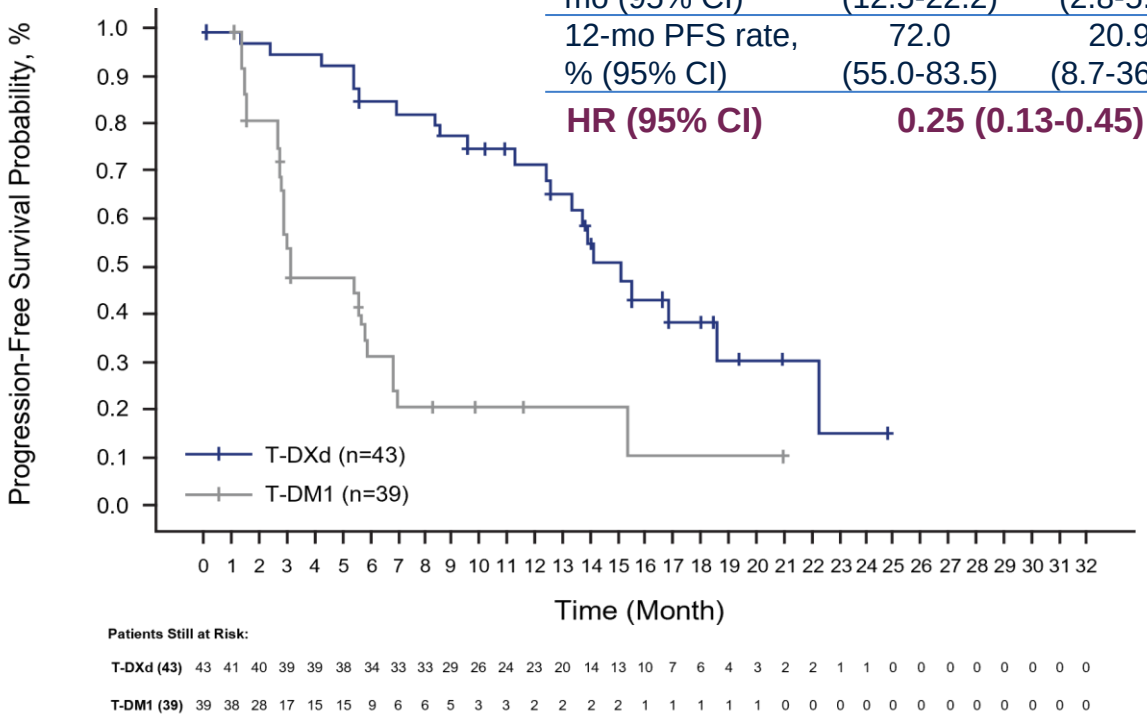
		T-DXd (n = 261)	T-DM1 (n = 263)		
		No. of Patients With Confirmed CR/PR	No. of Patients With Confirmed CR/PR	ORR, % (95% CI)	Difference of T-DXd vs T-DM1, % (95% CI)
All patients		208/261	90/263	79.7 34.2	45.5 (37.6-53.4)
Hormone receptor status	Positive (n = 272)	104/133	43/139	78.2 30.9	47.3 (36.1-58.4)
	Negative (n = 248)	103/126	47/122	81.7 38.5	43.2 (31.5-55.0)
Prior pertuzumab treatment	Yes (n = 320)	129/162	52/158	79.6 32.9	46.7 (36.5-56.9)
	No (n = 204)	79/99	38/105	79.8 36.2	43.6 (30.5-56.7)
Visceral disease	Yes (n = 384)	151/195	55/189	77.4 29.1	48.3 (39.1-57.6)
	No (n = 140)	57/66	35/74	86.4 47.3	39.1 (23.6-54.6)
Prior lines of therapy[a]	0-1 (n = 258)	99/132	45/126	75.0 35.7	39.3 (27.3-51.2)
	≥2 (n = 266)	109/129	45/137	84.5 32.8	51.6 (40.9-62.4)
Patients with BM	Yes (n = 82)	29/43	8/39	67.4 20.5	46.9 (25.6-68.3)
	No (n = 442)	179/218	82/224	82.1 36.6	45.5 (36.9-54.1)

BM, brain metastasis; CR, complete response; ORR, objective response rate; PR, partial response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

PFS KM Curves for Patients With and Without BM

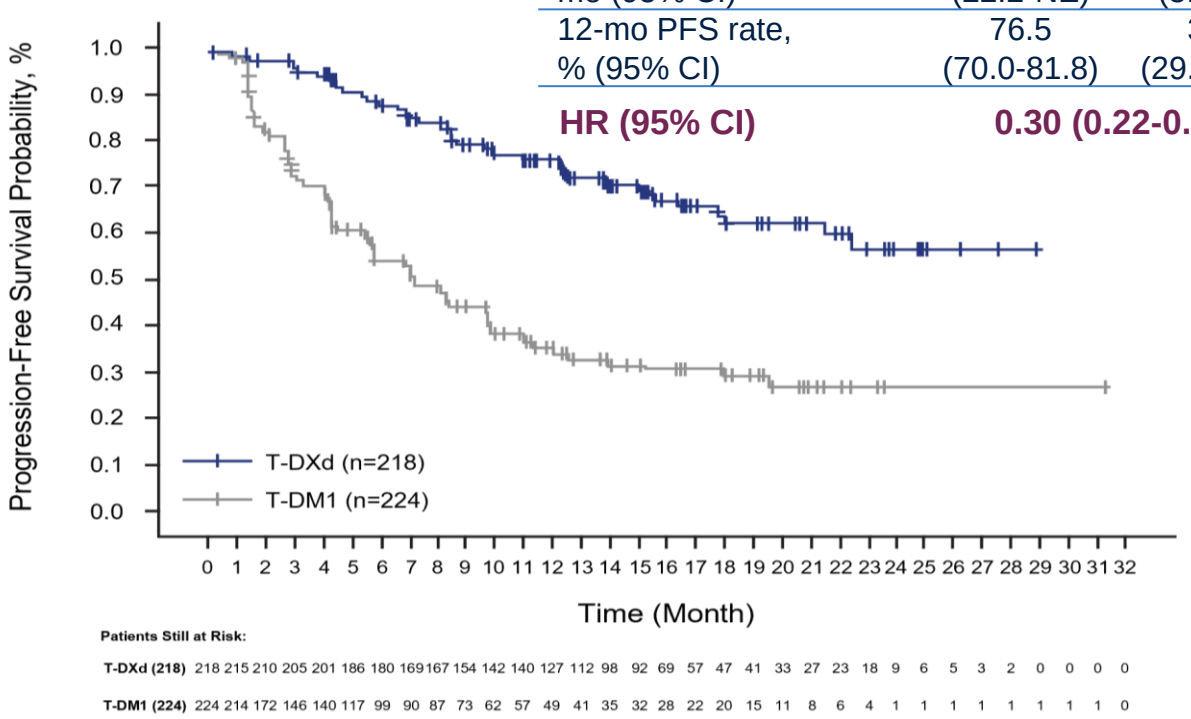
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	**0.25 (0.13-0.45)**	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	**0.30 (0.22-0.40)**	



In patients with BM at baseline, PD was observed:

- In 48.8% (21/43) treated with T-DXd versus 69.2% (27/39) with T-DM1
- In the brain in 42.9% (9/21) treated with T-DXd versus 40.7% (11/27) with T-DM1

In patients without BM at baseline, PD was observed:

- In 28.9% (63/218) treated with T-DXd versus 57.1% (128/224) with T-DM1
- In the brain in 6.3% (4/63) treated with T-DXd versus 0.8% (1/128) with T-DM1

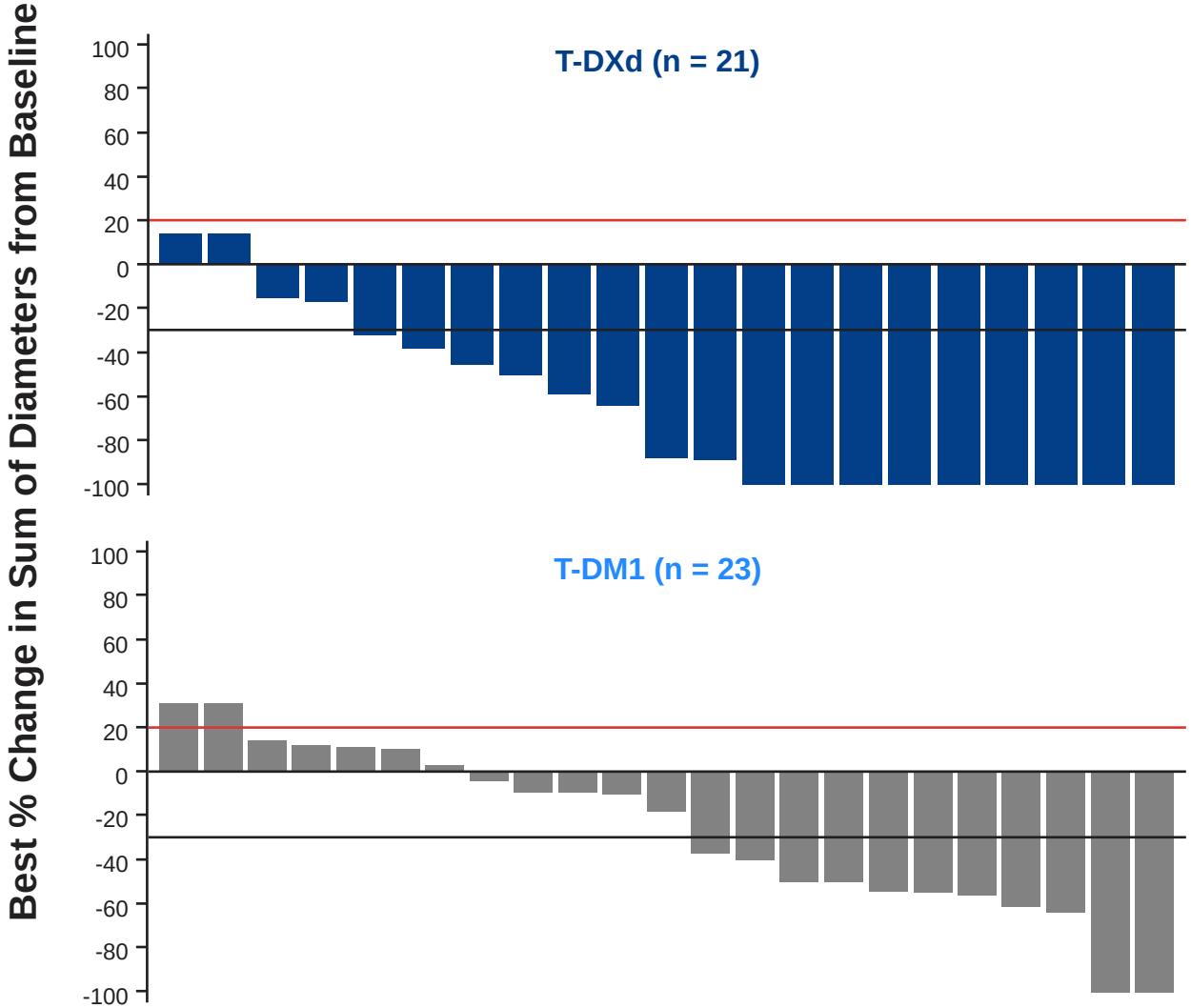
mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Confirmed ORR and Best Overall Response

	T-DXd			T-DM1		
	Overall Population (n = 261)[a]	Patients with BMs (n = 43)	Patients without BMs (n = 218)	Overall Population (n = 263)[a]	Patients with BMs (n = 39)	Patients without BMs (n = 224)
Confirmed ORR						
n (%)[b]	208 **(79.7)**	29 (67.4)	179 (82.1)	90 **(34.2)**	8 (20.5)	82 (36.6)
[95% CI]	[74.3-84.4]	[51.5-80.9]	[76.4-87.0]	[28.5-40.3]	[9.3-36.5]	[30.3-43.3]
CR	42 **(16.1)**	2 (4.7)	40 (18.3)	23 **(8.7)**	0	23 (10.3)
PR	166 **(63.6)**	27 (62.8)	139 (63.8)	67 **(25.5)**	8 (20.5)	59 (26.3)
SD	44 (16.9)	11 (25.6)	33 (15.1)	112 (42.6)	22 (56.4)	90 (40.2)
PD	3 (1.1)	1 (2.3)	2 (0.9)	46 (17.5)	7 (17.9)	39 (17.4)
Not evaluable	6 (2.3)	2 (4.7)	4 (1.8)	15 (5.7)	2 (5.1)	13 (5.8)
CR + PR + SD (DCR)	252 (96.6)	40 (93.0)	212 (97.2)	202 (76.8)	30 (76.9)	172 (76.8)
mDOR, mo	NE	12.9	NE	NE	7.2	NE
[95% CI]	[20.3-NE]	[8.5-NE]	[20.3-NE]	[12.6-NE]	[2.8-NE]	[12.6-NE]

BM, brain metastasis; CR, complete response; DCR, disease control rate; mDOR, median duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.

Intracranial Response per BICR using RECIST 1.1



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

TEAEs in ≥20% of Patients

System Organ Class Preferred Term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	31 (11.9)	8 (3.1)
Anemia[b]	84 (32.7)	15 (5.8)	45 (17.2)	11 (4.2)
Leukopenia[c]	78 (30.4)	17 (6.6)	22 (8.4)	1 (0.4)
Thrombocytopenia[d]	66 (25.7)	18 (7.0)	139 (53.3)	65 (24.9)
Gastrointestinal disorders				
Nausea	195 (75.9)	17 (6.6)	79 (30.3)	1 (0.4)
Vomiting	126 (49.0)	4 (1.6)	26 (10.0)	1 (0.4)
Diarrhea	75 (29.2)	1 (0.4)	18 (6.9)	1 (0.4)
Constipation	88 (34.2)	0	51 (19.5)	0
General disorders				
Fatigue[e]	126 (49.0)	13 (5.1)	90 (34.5)	2 (0.8)
Headache	56 (21.8)	0	42 (16.1)	0
Investigations				
AST increased	66 (25.7)	2 (0.8)	105 (40.2)	13 (5.0)
ALT increased	56 (21.8)	4 (1.6)	77 (29.5)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	75 (29.2)	3 (1.2)	44 (16.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	95 (37.0)	1 (0.4)[f]	8 (3.1)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Adverse events were managed according to the protocol.
[a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise. [f]Cases of alopecia reported during the study were graded based on the clinical judgement of the investigator. One case of alopecia was categorized as grade 3 by investigator despite grade 3 alopecia not being recognized by the NCI Common Terminology criteria. The events outcome is reported as recovered by investigator.

Interstitial Lung Disease/Pneumonitis in Different Regions

Adjudicated as Drug-Related ILD/Pneumonitis,[a] n (%)							
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Overall	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)
Asia subgroup	T-DXd (n = 147)	5 (3.4)	10 (6.8)	1 (0.7)	0	0	16 (10.9)
	T-DM1 (n = 159)	3 (1.9)	1 (0.6)	0	0	0	4 (2.5)
Non-Asia subgroup	T-DXd (n = 110)	2 (1.8)	8 (7.3)	1 (0.9)	0	0	11 (10.0)
	T-DM1 (n = 102)	1 (1.0)	0	0	0	0	1 (1.0)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd
- ILD/pneumonitis rates were similar between the overall population and the Asia subgroup and between the Asia and the non-Asia subgroups

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Asia subgroup defined as patients enrolled in China, Hong Kong, Japan, Republic of Korea, and Taiwan.
[a]Patients with history of ILD/pneumonitis necessitating steroids were excluded.

Conclusions

T-DXd demonstrated consistent efficacy benefit (PFS and ORR) over T-DM1 across patient subgroups

- PFS by BICR HR of 0.28 ($P = 7.8 \times 10^{-22}$) overall
- Confirmed ORR for T-DXd of 79.7% versus 34.2% for T-DM1 (CR, 16.1% vs 8.7%)

In patients with and without BMs, T-DXd resulted in greater disease control compared to T-DM1

- Patients with BMs: mPFS of 15.0 mo with T-DXd versus 3.0 mo with T-DM1; confirmed ORR of 67.4% for T-DXd versus 20.5% for T-DM1

The strong systemic disease control observed with T-DXd resulted in slower disease progression including in patients with BM

- Lower rates of PD with T-DXd (32.2%) versus T-DM1 (58.9%); for patients with BMs, 48.8% with T-DXd versus 69.2% with T-DM1

T-DXd treatment resulted in robust reduction of CNS lesions

- 27.8% intracranial CR for T-DXd versus 2.8% for T-DM1
- 2.8% intracranial PD for T-DXd versus 22.2% for T-DM1

T-DXd demonstrated a tolerable and comparable safety profile to T-DM1, with lower exposure-adjusted rates of TEAEs

- No difference between Asia (10.9%) and non-Asia (10.0%) regions in ILD/pneumonitis rates, with no grade 4 or 5 ILD/pneumonitis events

These data support T-DXd becoming the standard of care for second-line HER2+ mBC

BICR, blinded independent central review; BM, brain metastasis; CR, complete response; HR, hazard ratio; ILD, interstitial lung disease; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

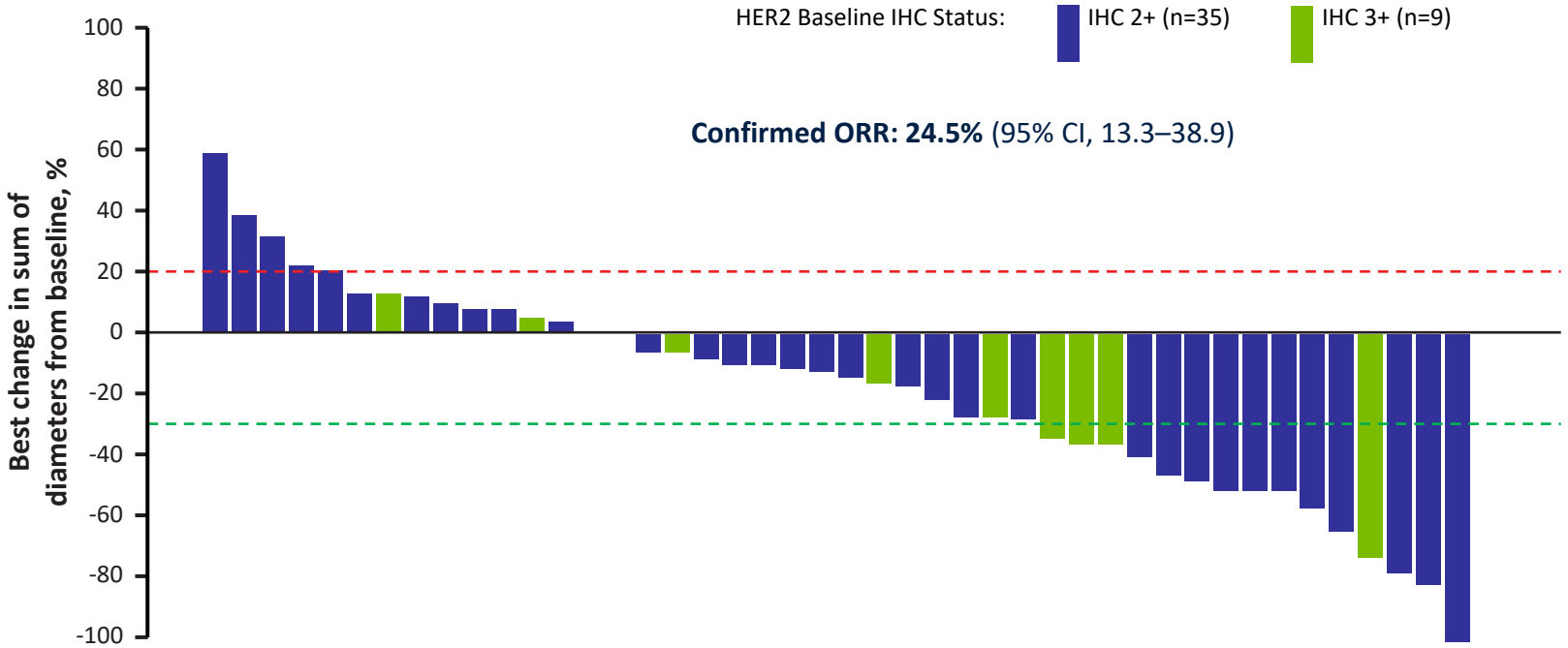
DESTINY-Lung01: Phase 2 study of T-DXd in HER2-overexpressing NSCLC

Response assessment by ICR	IHC 3+ (n=10)	IHC 2+ (n=39)	Overall (N=49)
Confirmed ORR, % **n (95% CI)**	20.0 2 (2.5–55.6)	25.6 10 (13.0–42.1)	24.5 12 (13.3–38.9)
CR, n (%)	0	1 (2.6)	1 (2.0)
PR, n (%)	2 (20.0)	9 (23.1)	11 (22.4)
SD, n (%)	6 (60.0)	16 (41.0)	22 (44.9)
PD, n (%)	1 (10.0)	10 (25.6)	11 (22.4)
Not evaluable, n (%)	1 (10.0)	3 (7.7)	4 (8.2)
DCR, % **n (95% CI)**	80.0 8 (44.4–97.5)	66.7 26 (49.8–80.9)	69.4 34 (54.6–81.8)
Median DoR, months (95% CI)	6.0 (NE–NE)	5.8 (3.2–NE)	6.0 (3.2–NE)

CR, complete response; DCR, disease control rate; DoR, duration of response; ICR, independent central review; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.
Nakagawa et al. Presented at World Conference on Lung Cancer Annual Meeting; January 28-31, 2021.

DESTINY-Lung01: Phase 2 study of T-DXd in HER2-overexpressing NSCLC

Best Change in Tumour Size[a]

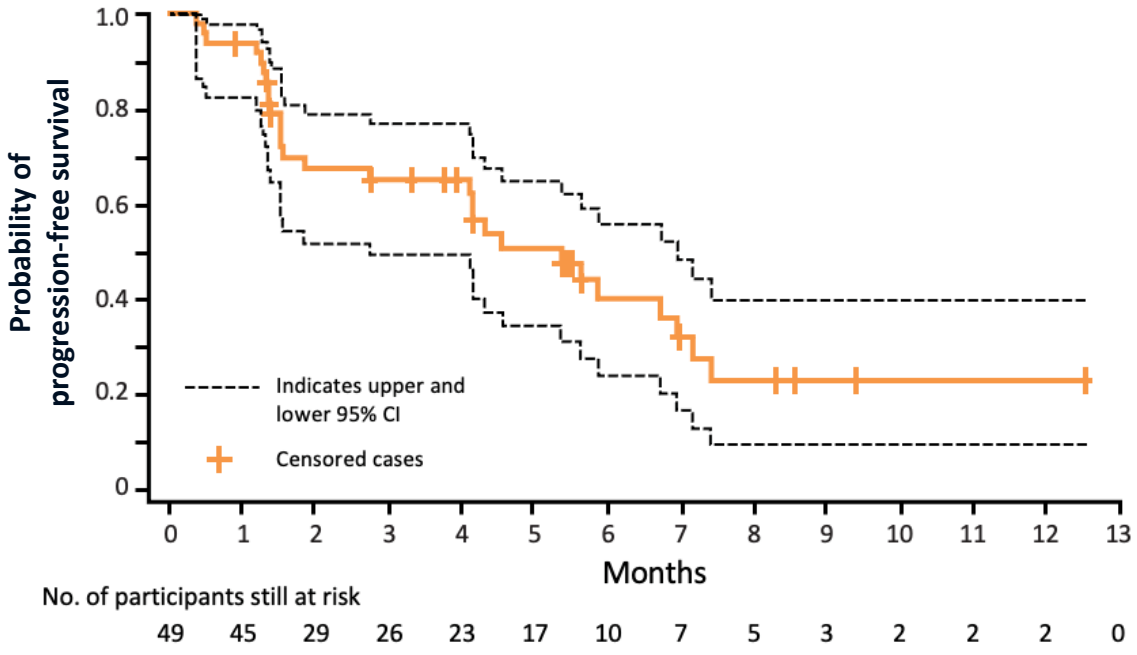


[a]Best (minimum) percentage change from baseline in the sum of diameters for all target lesions, based on ICR. Baseline was last measurement taken before enrollment. Red line at 20% indicates PD, and green line at −30% indicates PR (when considering only target lesions). Full analysis set data are shown.

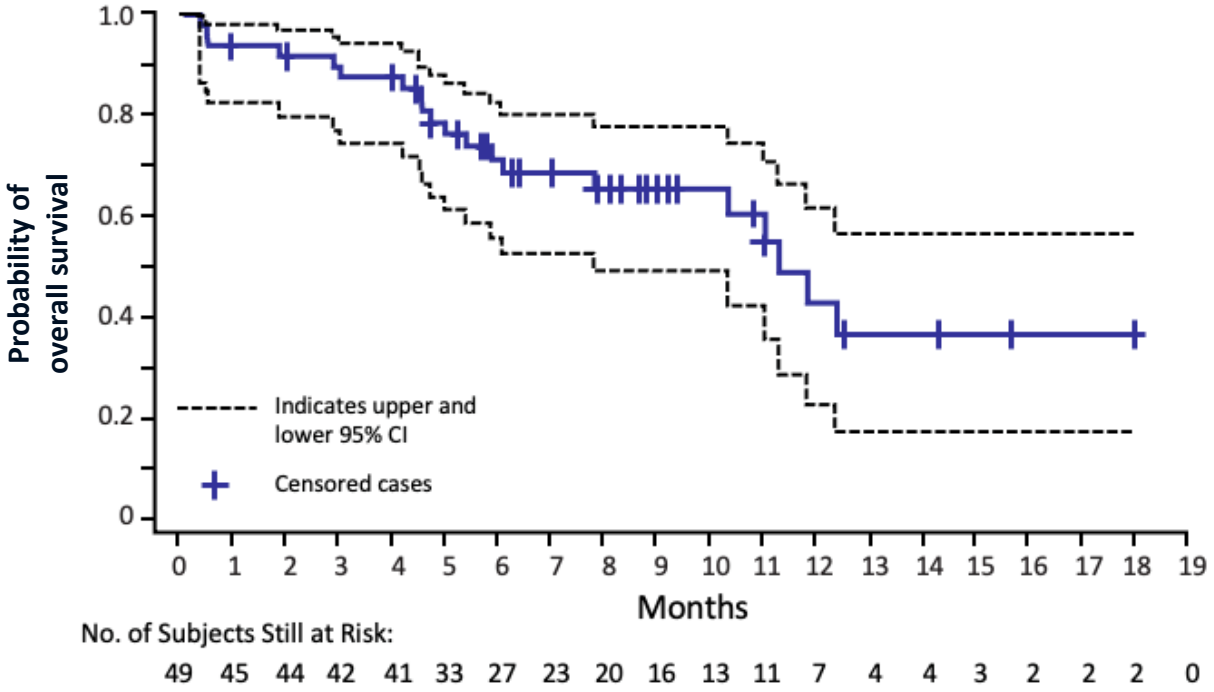
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ORR, overall response rate; T-DXd, trastuzumab deruxtecan.
Nakagawa et al. Presented at World Conference on Lung Cancer Annual Meeting; January 28-31, 2021.

DESTINY-Lung01: Phase 2 study of T-DXd in HER2-overexpressing NSCLC

Progression-free survival (N=49)
Median: 5.4 months (95% CI, 2.8–7.0)



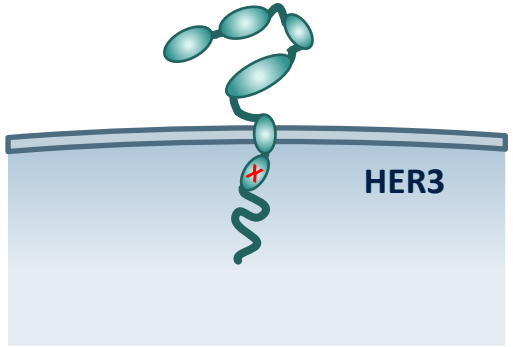
Overall survival (N=49)
Median: 11.3 months (95% CI, 7.8–NE)

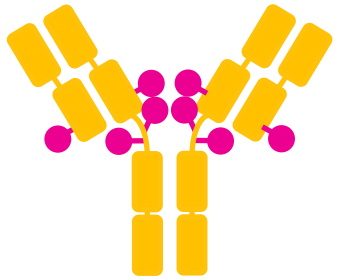


Progressive disease was assessed by ICR using RECIST v1.1. The median was based on Kaplan-Meier estimate, 95% CI for median was computed using the Brookmeyer-Crowley method. Median follow-up was 6.1 months (range, 0.4-18.0 months). Full analysis set data are shown.

CI, confidence interval; HER2, human epidermal growth factor receptor 2; ICR, independent central review; NE, not estimable; NSCLC, non-small-cell lung cancer; T-DXd, trastuzumab deruxtecan.
Nakagawa et al. Presented at World Conference on Lung Cancer Annual Meeting; January 28-31, 2021.

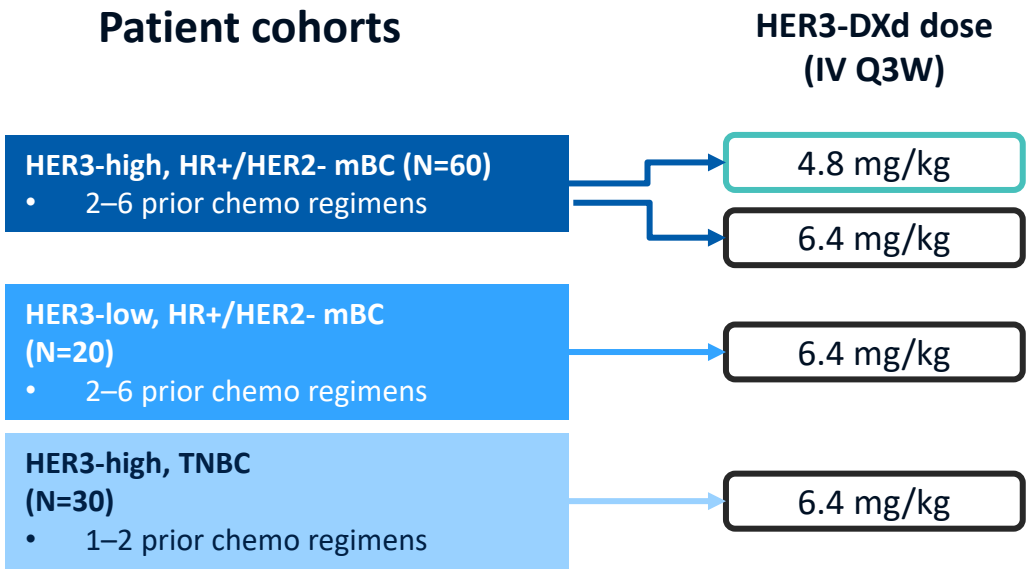
Antibody–drug conjugates targeting HER3





- Patritumab deruxtecan (HER3-DXd)

ADC targeting HER3, patritumab deruxtecan, in advanced breast cancer



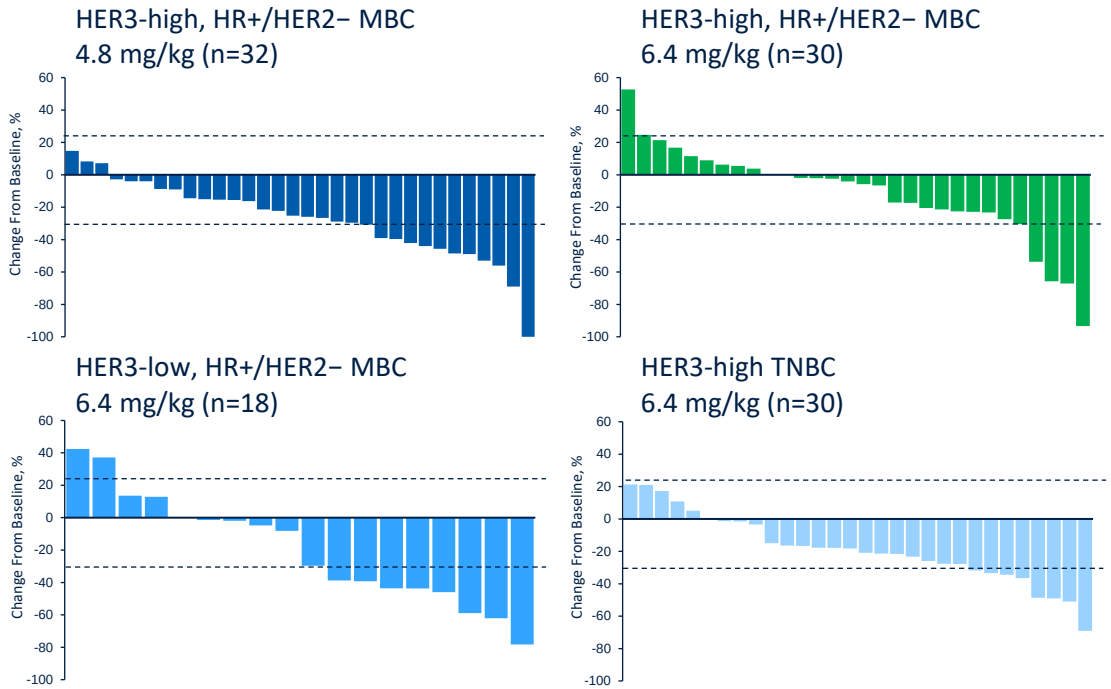
IV, intravenously. [a]HER3-DXd at doses of 1.6, 3.2, 4.8, 6.4, and 8.0 mg/kg Q3W was evaluated in the dose escalation and dose finding parts of the study. [b]≥2 lines in the locally advanced/metastatic setting. [c] In the locally advanced/metastatic setting.

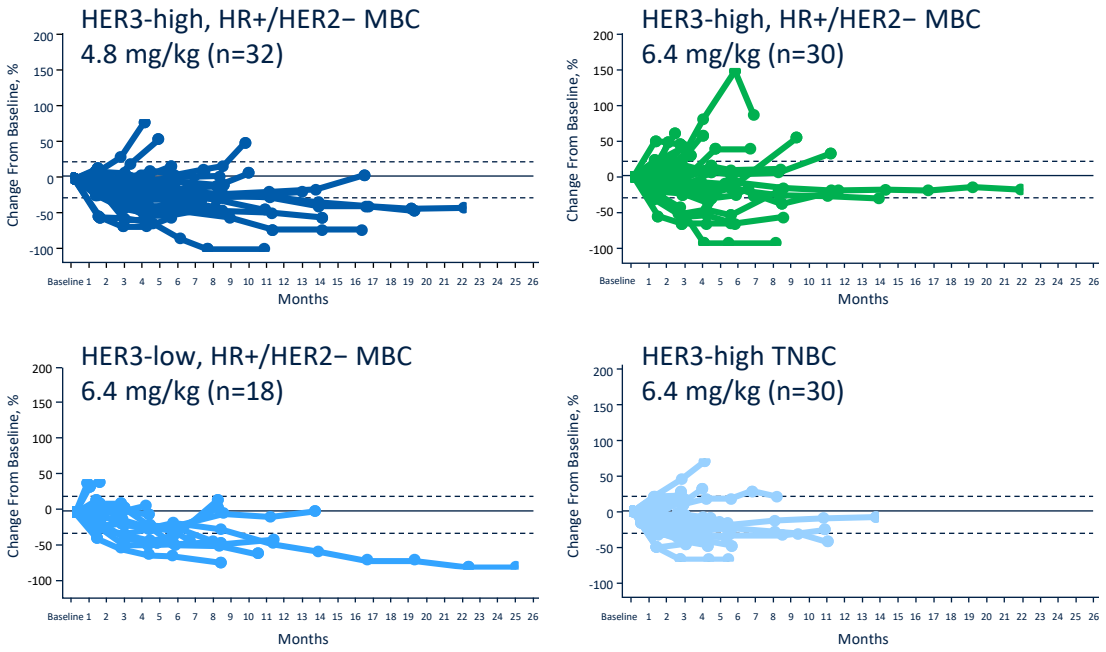
Preferred term, n (%)[a]	HER3-DXd (N=116)	
	Any grade	Grade ≥3
Any TEAE	115 (99.1)	83 (71.6)
Nausea	89 (76.7)	5 (4.3)
Platelet count decreased[b]	70 (60.3)	38 (32.8)
Neutrophil count decreased[b]	67 (57.8)	49 (42.2)
Decreased appetite	59 (50.9)	6 (5.2)
Vomiting	51 (44.0)	3 (2.6)
Diarrhea	48 (41.4)	3 (2.6)
Anemia[b]	47 (40.5)	21 (18.1)
White blood cell count decreased[b]	43 (37.1)	19 (16.4)
Alanine aminotransferase increased	38 (32.8)	5 (4.3)
Aspartate aminotransferase increased	37 (31.9)	5 (4.3)
Fatigue	37 (31.9)	3 (2.6)
Stomatitis[b]	32 (27.6)	1 (0.9)
Constipation	30 (25.9)	0
Alopecia	29 (25.0)	0

[a] TEAEs occurring in ≥25% of patients, all causality as determined by the treating investigator.

ADC, antibody–drug conjugate; HER2/3, human epidermal growth factor receptor 2/3; HER3-DXd, patritumab deruxtecan; IV, intravenous; mBC, metastatic breast cancer; Q3W, every 3 weeks; TNBC, triple negative breast cancer.
Krop I, et al. PD1-09, Presented at SABCS 2020.

ADC targeting HER3, patritumab deruxtecan, in advanced breast cancer





ADC, antibody–drug conjugate; HER2/3, human epidermal growth factor receptor 2/3; HER3-DXd, patritumab deruxtecan; IV, intravenous; mBC, metastatic breast cancer; Q3W, every 3 weeks; TNBC, triple negative breast cancer.

Krop I, et al. PD1-09, Presented at SABCS 2020.

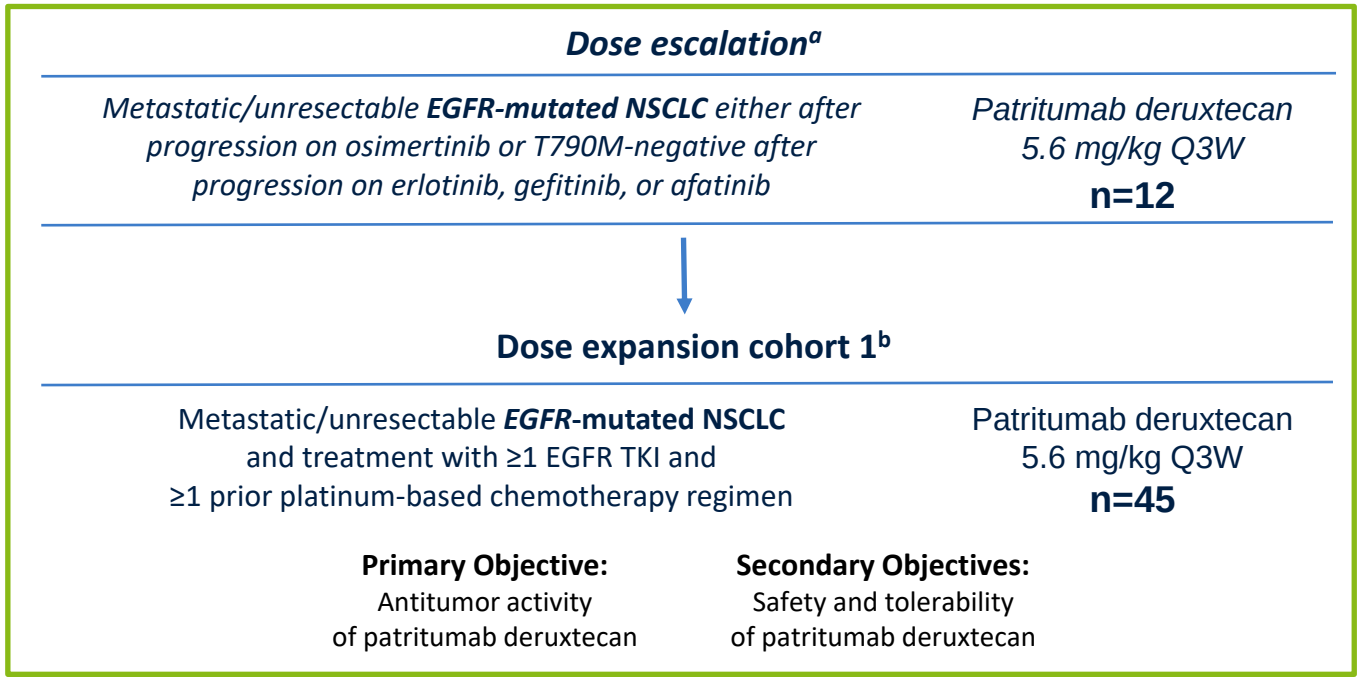
ADC targeting HER3, patritumab deruxtecan, in advanced breast cancer

	HER3-high, HR+/HER2– mBC		HER3 low, HR+/HER2– mBC 6.4 mg/kg (n=21)	HER3-high TNBC 6.4 mg/kg (n=31)
	4.8 mg/kg (n=33)	6.4 mg/kg (n=31)		
Follow-up, median (range), months	16.8 (8.4–23.5)	20.4 (8.1–26.5)	18.7 (11.0–25.7)	7.4 (3.2–14.5)
Confirmed ORR (95% CI)	30.3% (15.6–48.7)	12.9% (3.6–29.8)	33.3% (14.6–57.0)	16.1% (5.5–33.7)
PR	30.3%	12.9%	33.3%	16.1%
SD	60.6%	61.3%	33.3%	67.7%
PD	6.1%	22.6%	14.3%	9.7%
Not evaluable	3.0%	3.2%	19.0%	6.5%
DCR (95% CI)	90.9% (75.7–98.1)	74.2% (55.4–88.1)	66.7% (43.0–85.4)	83.9% (66.3–94.5)
CBR (95% CI)	48.5% (30.8–66.5)	22.6% (9.6–41.1)	38.1% (18.1–61.6)	19.4% (7.5–37.5)
Median DoR (95% CI), months	5.0 (2.8–NE)	7.2 (5.5–7.2)	5.3 (3.0–NE)	Not reached (4.2–NE)
Median PFS (95% CI), months	8.4 (5.6–9.9)	2.8 (1.9–8.2)	5.8 (1.4–11.0)	5.5 (3.9–NE)
Median OS (95% CI), months	14.3 (10.9–NE)	9.7 (6.6–19.5)	9.2 (4.7–21.9)	Not reached (6.4–NE)

ADC, antibody–drug conjugate; HER2/3, human epidermal growth factor receptor 2/3; HER3-DXd, patritumab deruxtecan; IV, intravenous; mBC, metastatic breast cancer; Q3W, every 3 weeks; TNBC, triple negative breast cancer.

Krop I, et al. PD1-09, Presented at SABCS 2020.

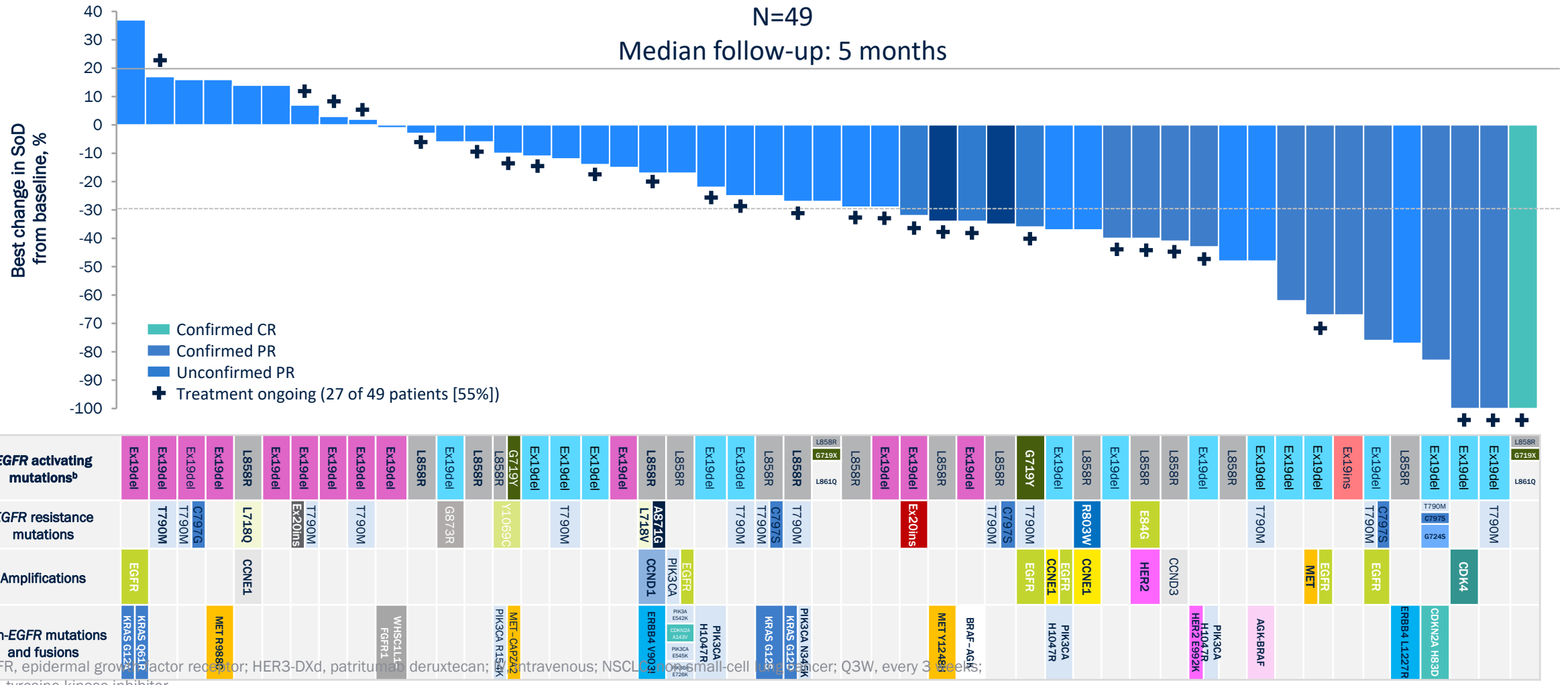
Phase 1 study of patritumab deruxtecan (HER3-DXd) in EGFR-mutated NSCLC



[a]Patients in dose escalation had NSCLC (adenocarcinoma) and received 3.2 mg/kg-6.4 mg/kg of patritumab deruxtecan, which was guided by mCRM following EWOC principle.
[b]Patients in dose expansion were enrolled into 3 cohorts; **data for patients with NSCLC (adenocarcinoma) enrolled in Cohort 1 are included in this analysis**. Patients with squamous or nonsquamous NSCLC without *EGFR* activating

EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.
Yu HA, et al. Presented at ESMO 2020.

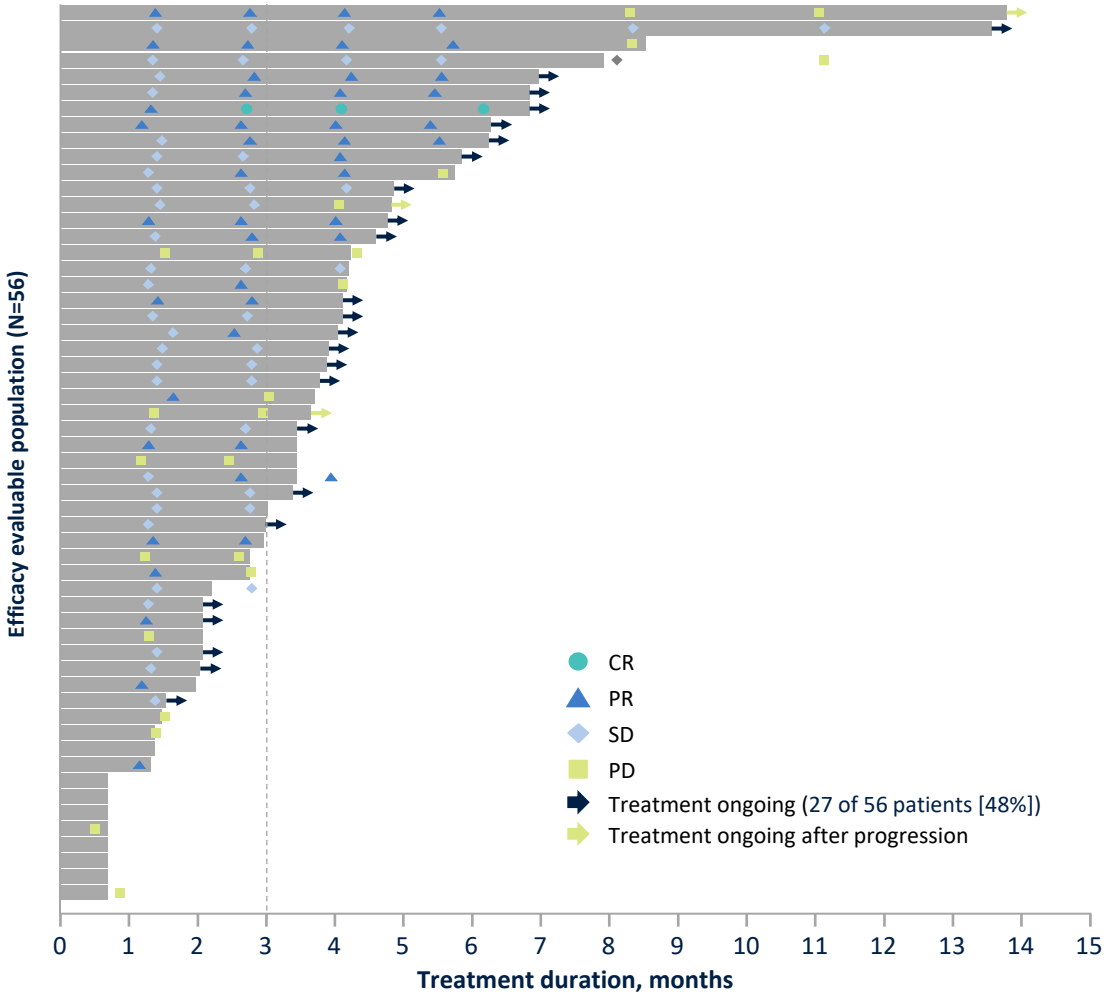
Activity of HER3-DXd in EGFR-mutated NSCLC with diverse TKI resistance mechanisms



EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.

Yu HA, et al. Presented at ESMO 2020.

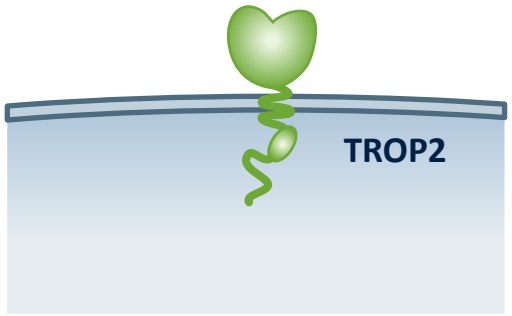
Phase 1 study of patritumab deruxtecan (HER3-DXd) in EGFR-mutated NSCLC: Tumour response

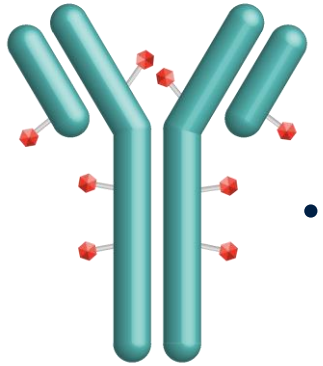


Activity according to BICR evaluation (efficacy-evaluable population) N = 56	
Confirmed best overall response, n/N (%)	
CR	1/56 (2%)
PR	13/56 (23%)
SD	25/56 (45%)
PD	9/56 (16%)
Not evaluable	8/56 (14%)
Confirmed ORR, % (n/N; 95% CI)	25% (14/56; 14.4-38.4)
DCR, % (n/N; 95% CI)	70% (39/56; 55.9-81.2)
Median TTR, months (range)	2.0 (1.2-2.8)
Median DoR, months (range)	6.9 (3.0-7.0)

EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.
Yu HA, et al. Presented at ESMO 2020.

Antibody–drug conjugates targeting TROP2





- Sacituzumab govitecan (IMMU-132)

- Datopotamab deruxtecan (Dato-DXd)

Sacituzumab govitecan in metastatic TNBC

Metastatic TNBC
(per ASCO/CAP)

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]

N=529

NCT02574455

R
1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

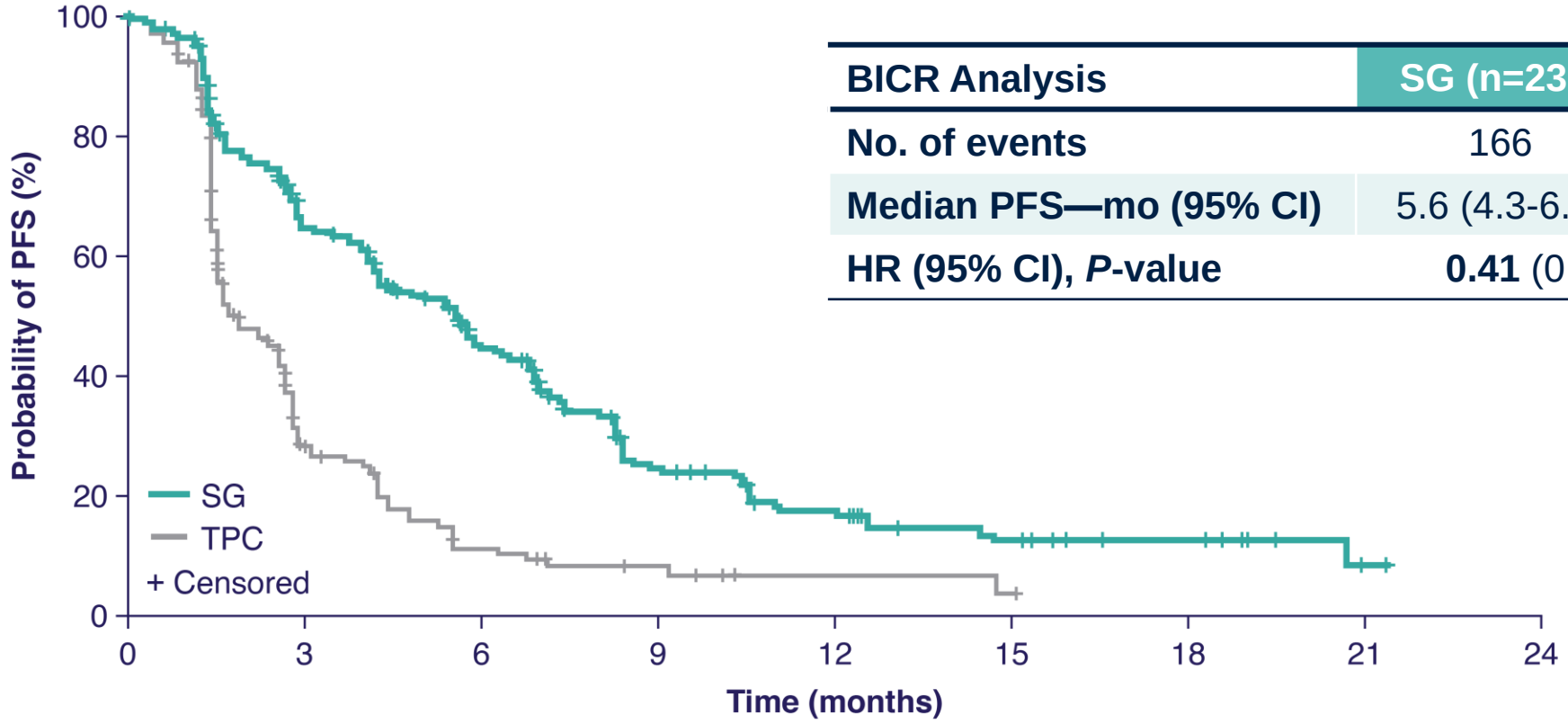
Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

- *TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
- ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia A, et al. LBA17, Presented at ESMO 2020.

Sacituzumab govitecan in metastatic TNBC



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**	

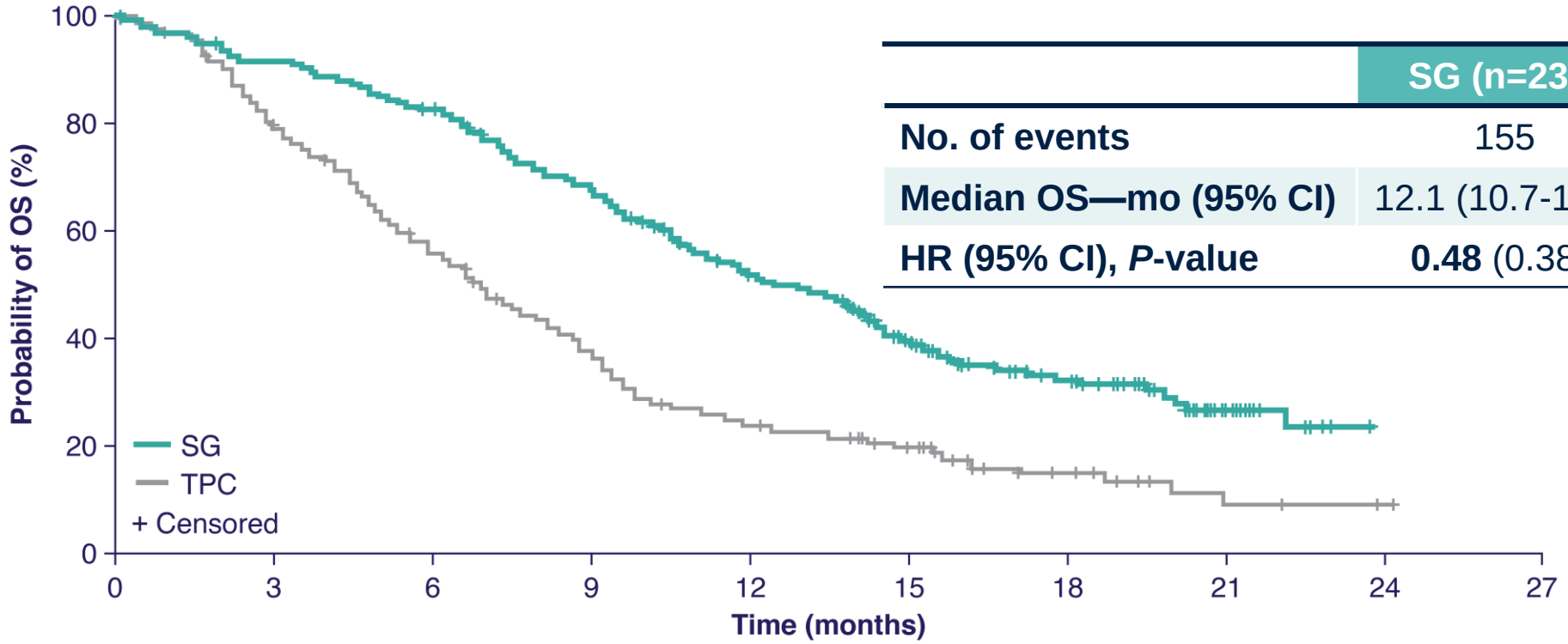
Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia A, et al. LBA17, Presented at ESMO 2020.

Sacituzumab govitecan in metastatic TNBC



	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**	

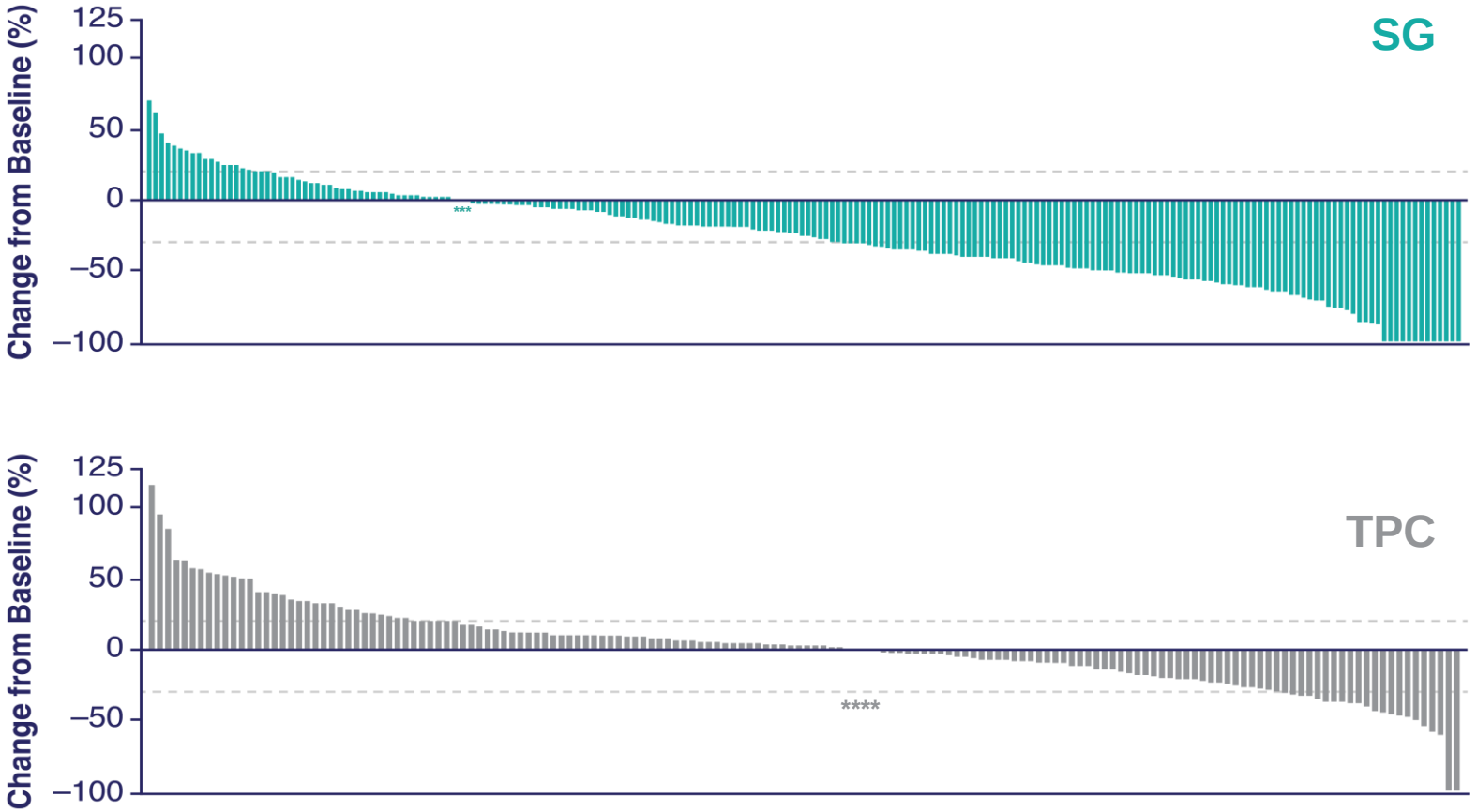
Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.

Bardia A, et al. LBA17, Presented at ESMO 2020.

Sacituzumab govitecan in metastatic TNBC

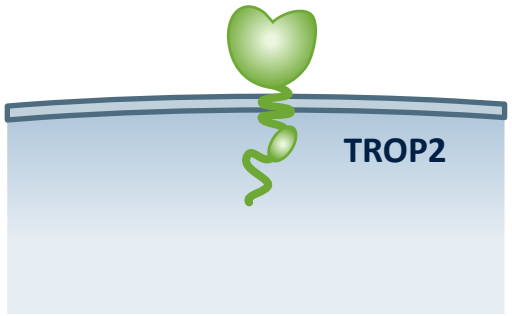


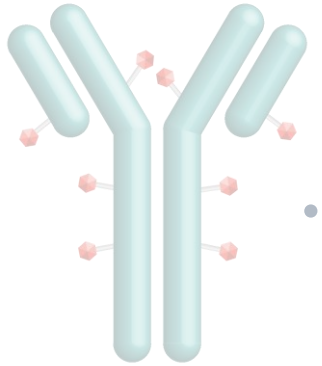
	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
***P*-value**	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
***P*-value**	**<0.0001**	
Median DOR —mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
***P*-value**	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

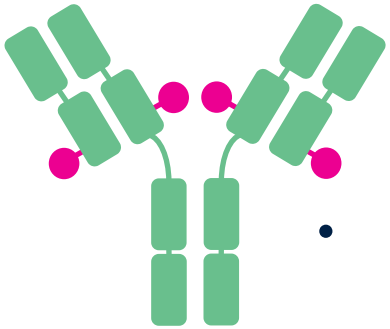
Bardia A, et al. LBA17, Presented at ESMO 2020.

Antibody–drug conjugates targeting TROP2





- Sacituzumab govitecan (IMMU-132)



- Datopotamab deruxtecan (Dato-DXd)

TROPION-PanTumor01 (NCT03401385) Phase 1 study of datopotamab deruxtecan in NSCLC

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

Dose escalation[1]

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

MTD established: 8 mg/kg Q3W

Dose expansion

- 50 patients at 4 mg/kg[c]
- 50 patients at 6 mg/kg[c,d]
- 80 patients at 8 mg/kg[c]

Primary objectives

- Establish MTD, Safety, Tolerability

Secondary objectives

- Efficacy, PK

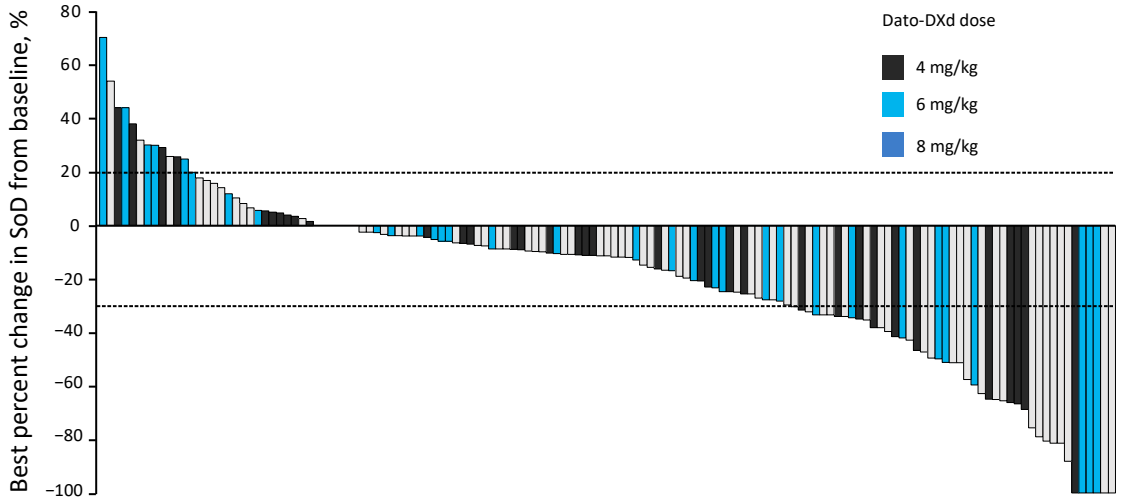
- NSCLC enrollment complete[d]
- TNBC cohort 6 mg/kg Q3W is enrolling; cohorts in other tumor types may be added
- Here we report updated results for the NSCLC dose expansion cohort (175 patients treated at 4, 6, or 8 mg/kg of Dato-DXd)

Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TROP2, trophoblast cell surface antigen 2.

Spira A, et al. Presented at WCLC 2021. IASLC 2020 World Conference on Lung Cancer Singapore; 28-31 January 2021

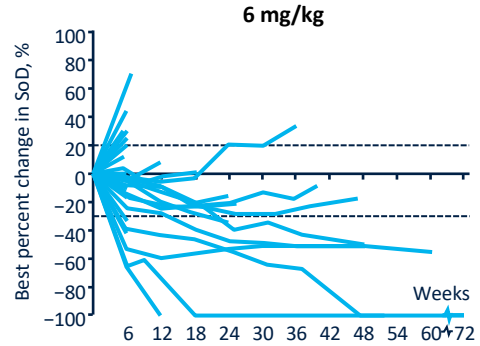
Antitumour activity of Dato-DXd in NSCLC

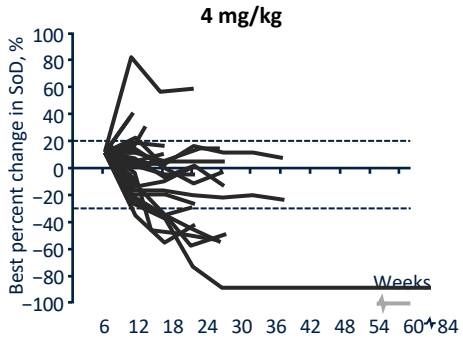
Best change in sum of diameters and overall response (BICR)

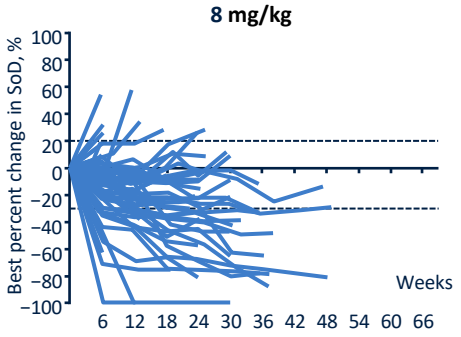


Dato-DXd dose	Response-evaluable patients,[a] n	Confirmed CR/PR,[b] n	CR/PR (too early to be confirmed),[b] n	ORR,[b] % (n)	DCR, % (n)	PD, % (n)
4 mg/kg	40	7	2	23 (9)	73 (29)	15 (6)
6 mg/kg	39	6	2	21 (8)	67 (26)	21 (8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)

Change in sum of diameters for target lesions (BICR)







Preliminary Progression-free Survival (BICR)

- 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)

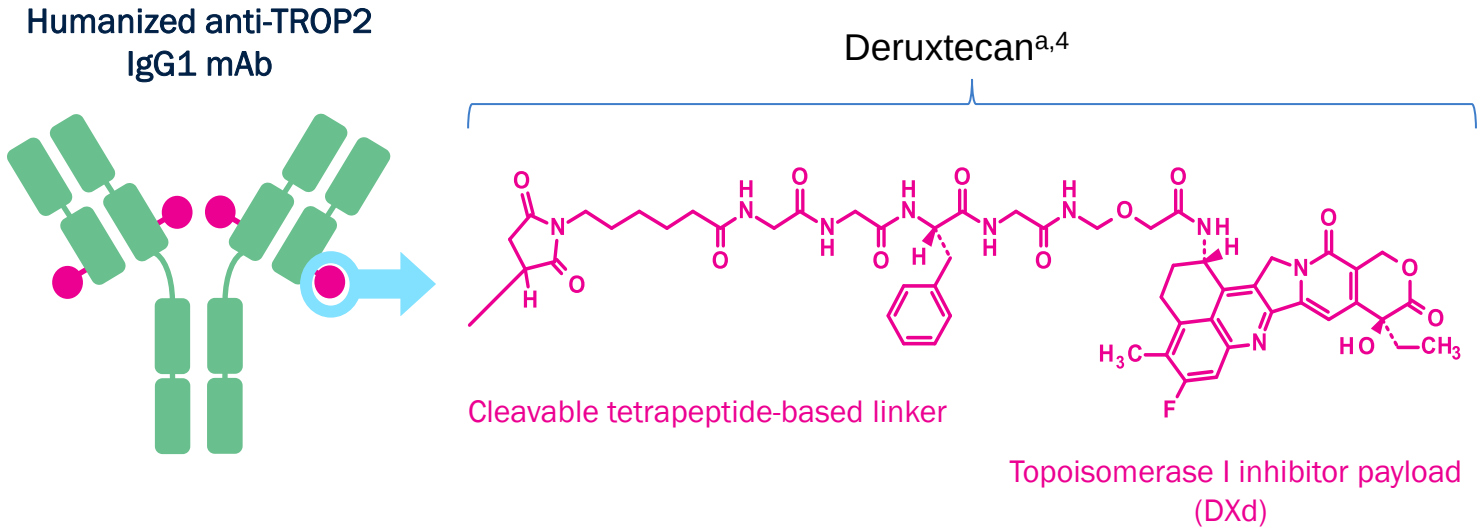
Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TROP2, trophoblast cell surface antigen 2.

Spira A, et al. Presented at WCLC 2021. IASLC 2020 World Conference on Lung Cancer Singapore; 28-31 January 2021

Datopotamab Deruxtecan (Dato-DXd) Was Designed With 7 Key Attributes

Dato-DXd is an ADC with 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



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

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

1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 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. SABCS 2019; [abstract GS1-03]; 5. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

TROPION-PanTumor01 (NCT03401385)

Phase 1 Study in Relapsed/Refractory Metastatic Solid Tumors

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

→ NSCLC[b] (0.27 to 10 mg/kg IV Q3W)

→ TNBC[c] 8 mg/kg (n=2); 6 mg/kg (n=42)

→ HR+/HER2− breast cancer[d]

→ Other tumor types (including SCLC, bladder, gastric, esophageal)

Primary objectives

- Safety
- Tolerability

Secondary objectives[e]

- Efficacy[f]
- Pharmacokinetics
- Antidrug antibodies

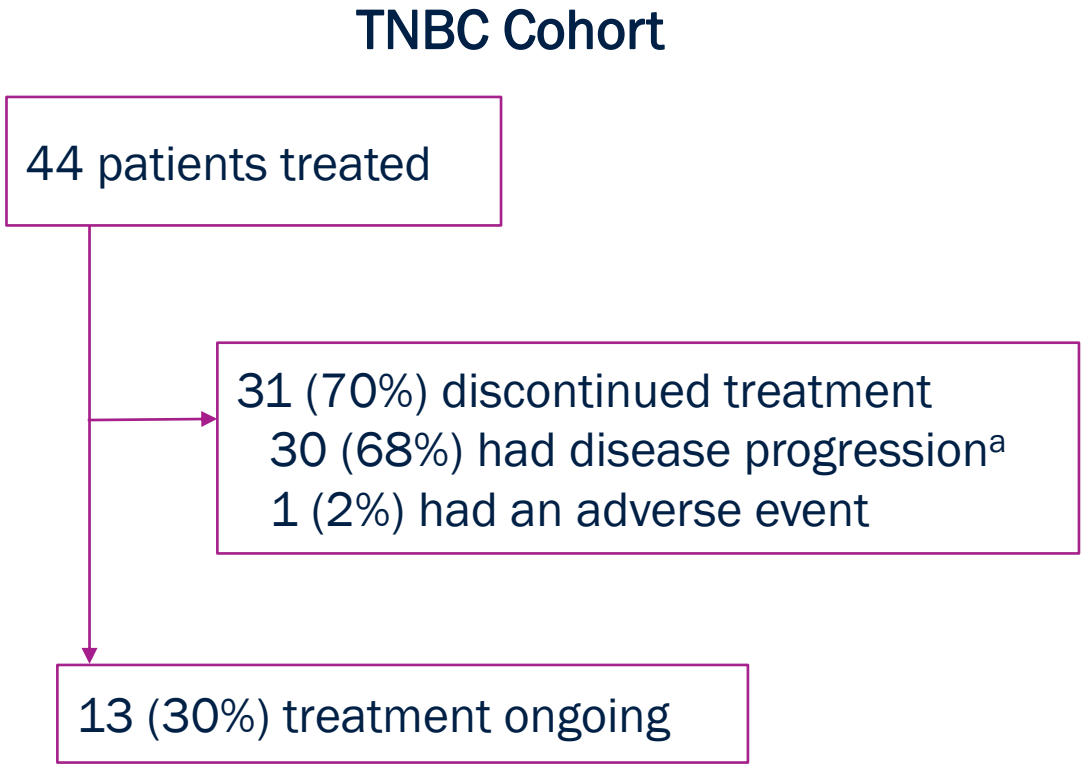
Data cutoff: July 30, 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Results from the NSCLC cohort have been previously reported.[1,2] [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Enrollment in the HR+/HER2− cohort is now complete and data will be forthcoming. [e] Exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST 1.1.

1. Garon E, et al. WCLC 2021. Abstract 156; 2. Meric-Bernstam F, et al. ASCO 2021.

Patient Disposition



Last patient enrolled April 2021; median follow-up: 7.6 months (range, 4-13 months)

[a] **Progression includes progressive disease per RECIST 1.1 and clinical progression.**

Data cutoff: July 30, 2021

Baseline Characteristics

Patient characteristics	TNBC n=44
Age, median (range), years	53 (32-82)
Country, n (%)	
US	31 (70)
Japan	13 (30)
ECOG PS, n (%)	
0	18 (41)
1	26 (59)
De novo metastatic disease, n (%)	
Yes	14 (32)
No	30 (68)

Patient characteristics	TNBC n=44
Brain metastases, n (%)	5 (11)
Prior therapies in metastatic setting, median (range), n	3 (1-10)
≥2 prior lines of therapy, n (%)[a]	30 (68)
Previous systemic treatment, n (%)	
Taxanes	40 (91)
Platinum-based chemotherapy	23 (52)
Immunotherapy	19 (43)
PARPi	7 (16)
Topo I inhibitor-based ADC[b]	13 (30)

PARPi, poly(ADP-ribose) polymerase inhibitor; Topo I, topoisomerase I.

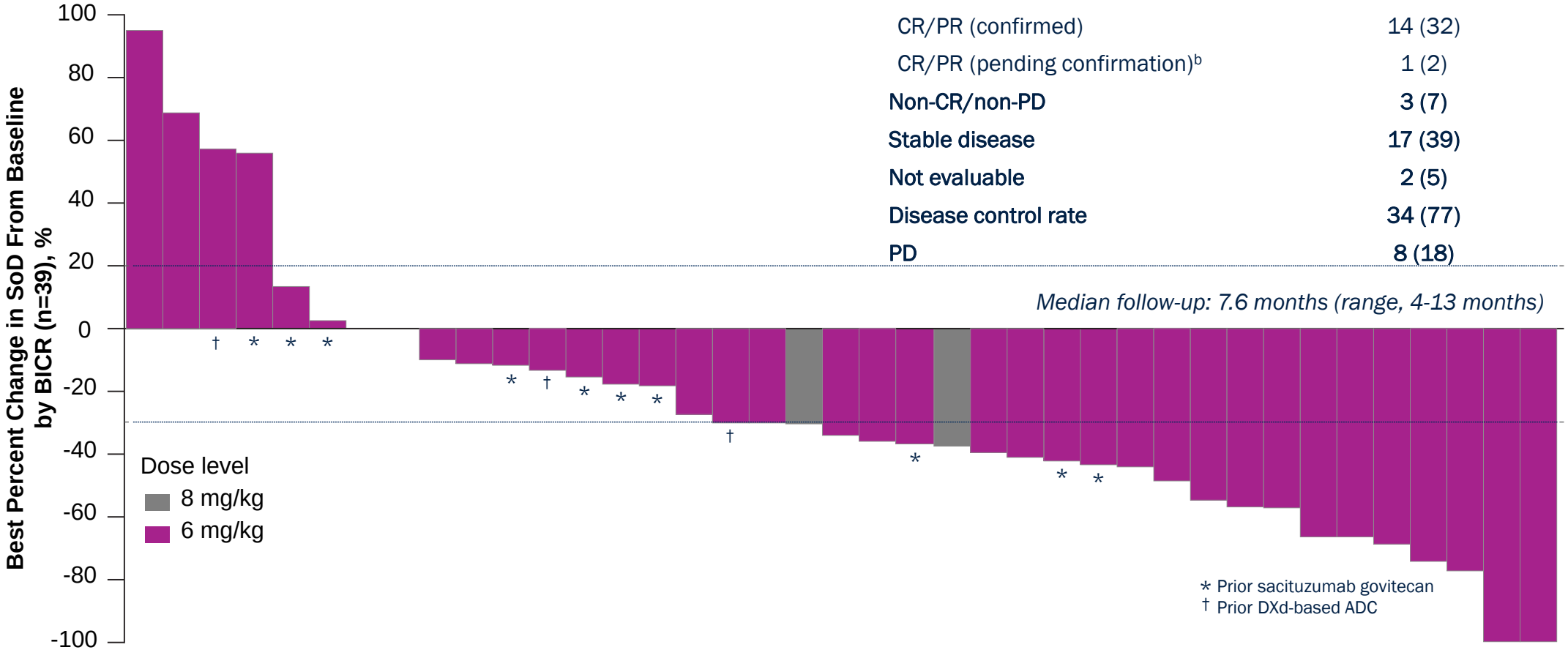
[a] Includes prior lines of therapy in the metastatic setting. [b] Sacituzumab govitecan, n=10; trastuzumab deruxtecan, n=2; patritumab deruxtecan, n=1.

Data cutoff: July 30, 2021

Antitumor Responses by BICR

All patients with TNBC

Patients, n (%)[a]	All Patients (n=44)
ORR	15 (34)
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	3 (7)
Stable disease	17 (39)
Not evaluable	2 (5)
Disease control rate	34 (77)
PD	8 (18)



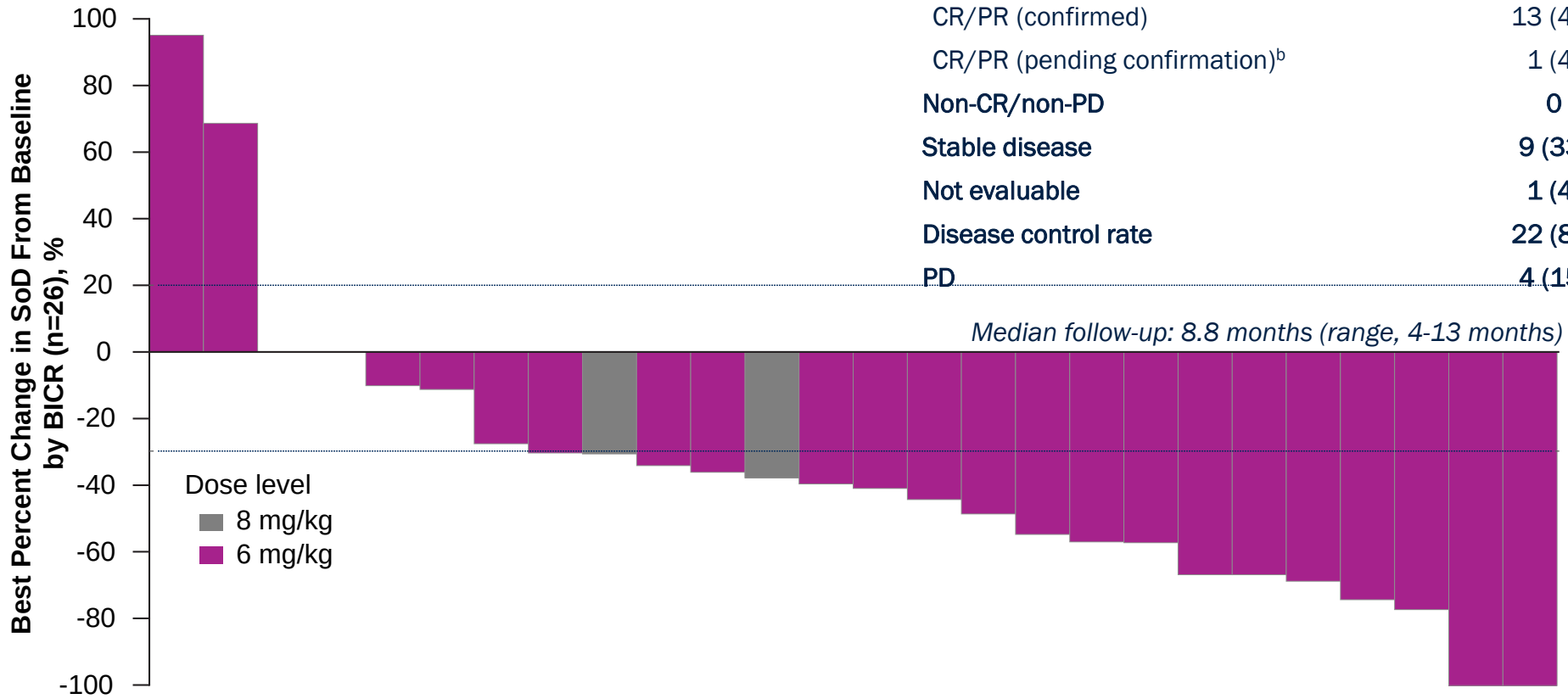
BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SoD, sum of diameters.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at the data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.
[b] Includes patients with an unconfirmed response but are ongoing treatment.

Data cutoff: July 30, 2021

Antitumor Responses by BICR

Patients with TNBC without prior Topo I inhibitor-based ADC

Patients, n (%)[a]	SG/DXd Naïve Patients with Measurable Disease at BL (n=27)
ORR	14 (52)
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[b]	1 (4)
Non-CR/non-PD	0
Stable disease	9 (33)
Not evaluable	1 (4)
Disease control rate	22 (81)
PD	4 (15)



Median follow-up: 8.8 months (range, 4-13 months)

BL, baseline; SG; sacituzumab govitecan..

[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 1 patient at the data cutoff. [b] Includes patients with an unconfirmed response but are ongoing treatment.

Data cutoff: July 30, 2021

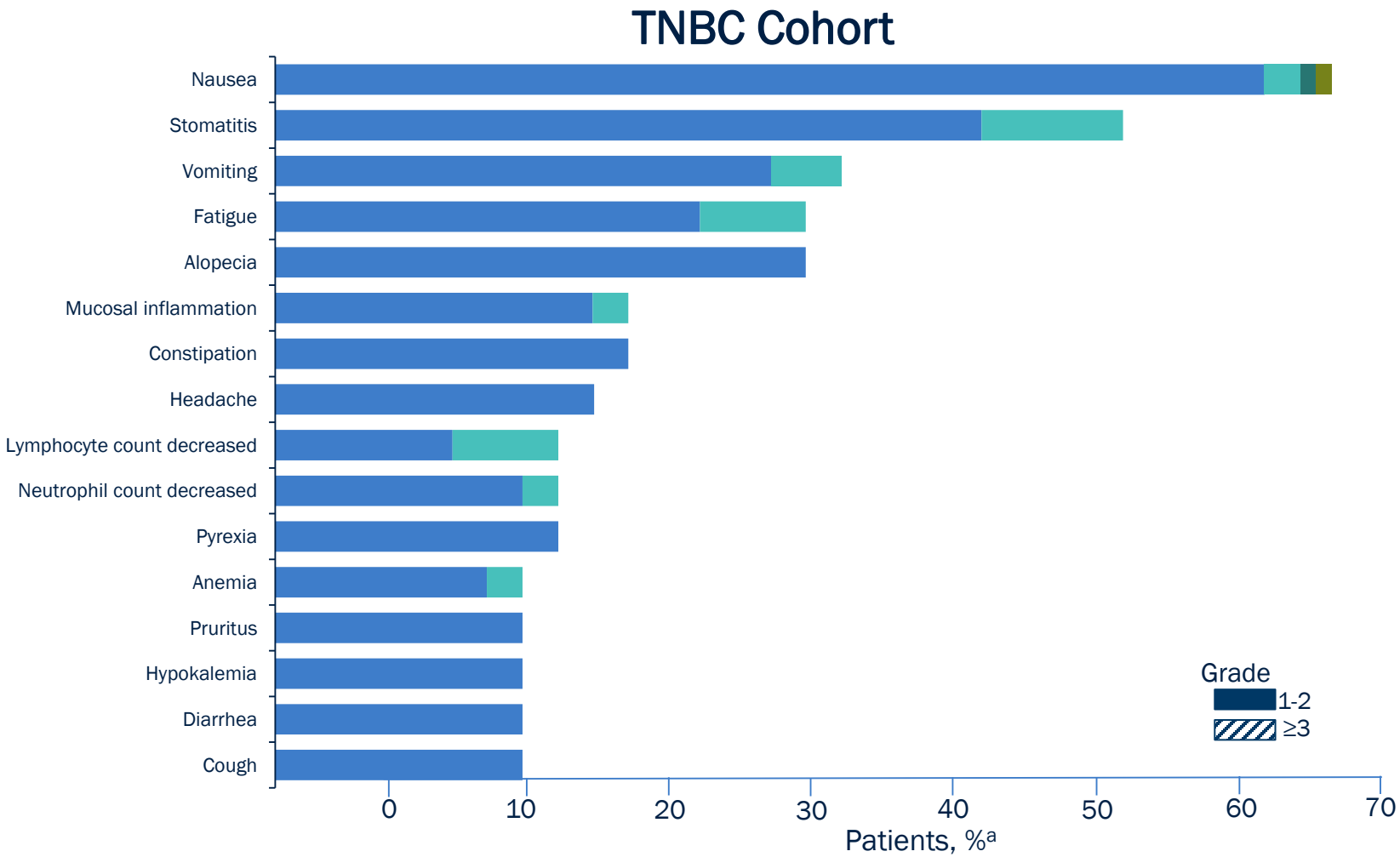
Overall Safety Summary

Patients, n (%)	TNBC n=44
All-grade TEAEs	43 (98)
Grade ≥3	20 (45)
All-grade treatment-related TEAEs	43 (98)
Grade ≥3	10 (23)
Dose adjustments	
Dose reduction due to AEs	8 (18)
Treatment interruption due to AEs	6 (14)
Treatment discontinuation due to AEs	1 (2)
Serious TEAEs	8 (18)
Treatment related	2 (5)
Fatal TEAEs	0
Treatment related	0

Data cutoff: July 30, 2021

AE, adverse event; TEAE, treatment-emergent adverse event.

Treatment-Emergent Adverse Events in ≥ 15% of Patients



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

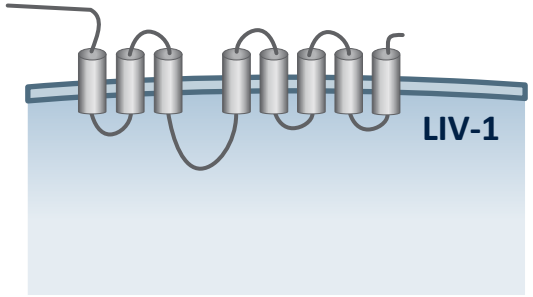
ILD, interstitial lung disease.
[a] n=44 patients.

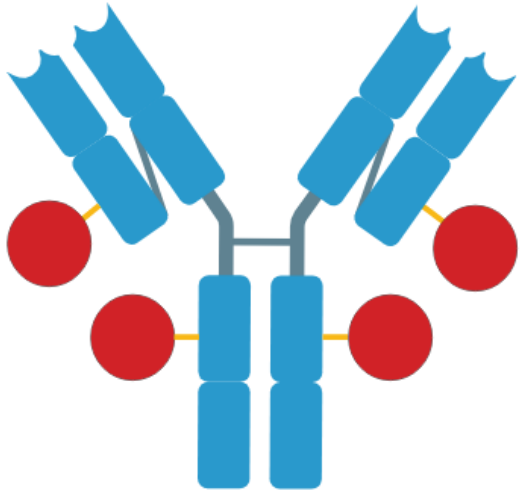
Data cutoff: July 30, 2021

Conclusions

- In heavily pretreated patients with TNBC, Dato-DXd showed highly encouraging and durable efficacy
  - ORR by BICR was 34% in all patients with TNBC
  - ORR by BICR was 52% in patients with measurable disease at baseline who are treatment naïve to Topo I inhibitor-based ADC therapies
- Dato-DXd demonstrated a manageable safety profile with no new safety signals
  - Low grade nausea and stomatitis were most frequent
  - Neutropenia and diarrhea were uncommon
- The HR+/HER2- cohort is now fully enrolled and data are forthcoming
- Further studies of Dato-DXd in breast cancer are warranted
  - BEGONIA is an ongoing trial in TNBC to evaluate efficacy and safety of Dato-DXd plus durvalumab
  - TROPION-Breast01, a phase 3 trial in HR+/HER2- BC, has been initiated (NCT05104866)
  - Phase 3 trial in TNBC is planned

Antibody–drug conjugates targeting LIV-1

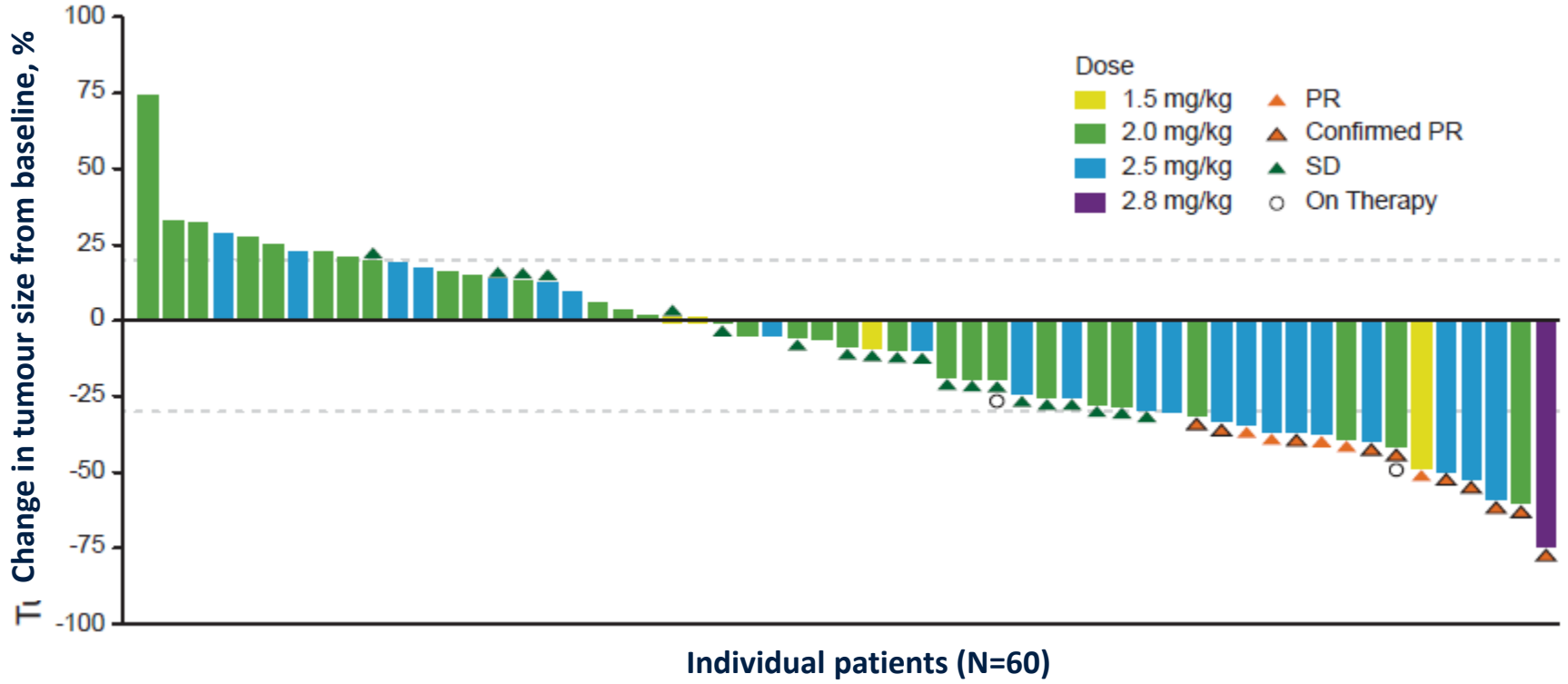




- Ladiratuzumab vedotin

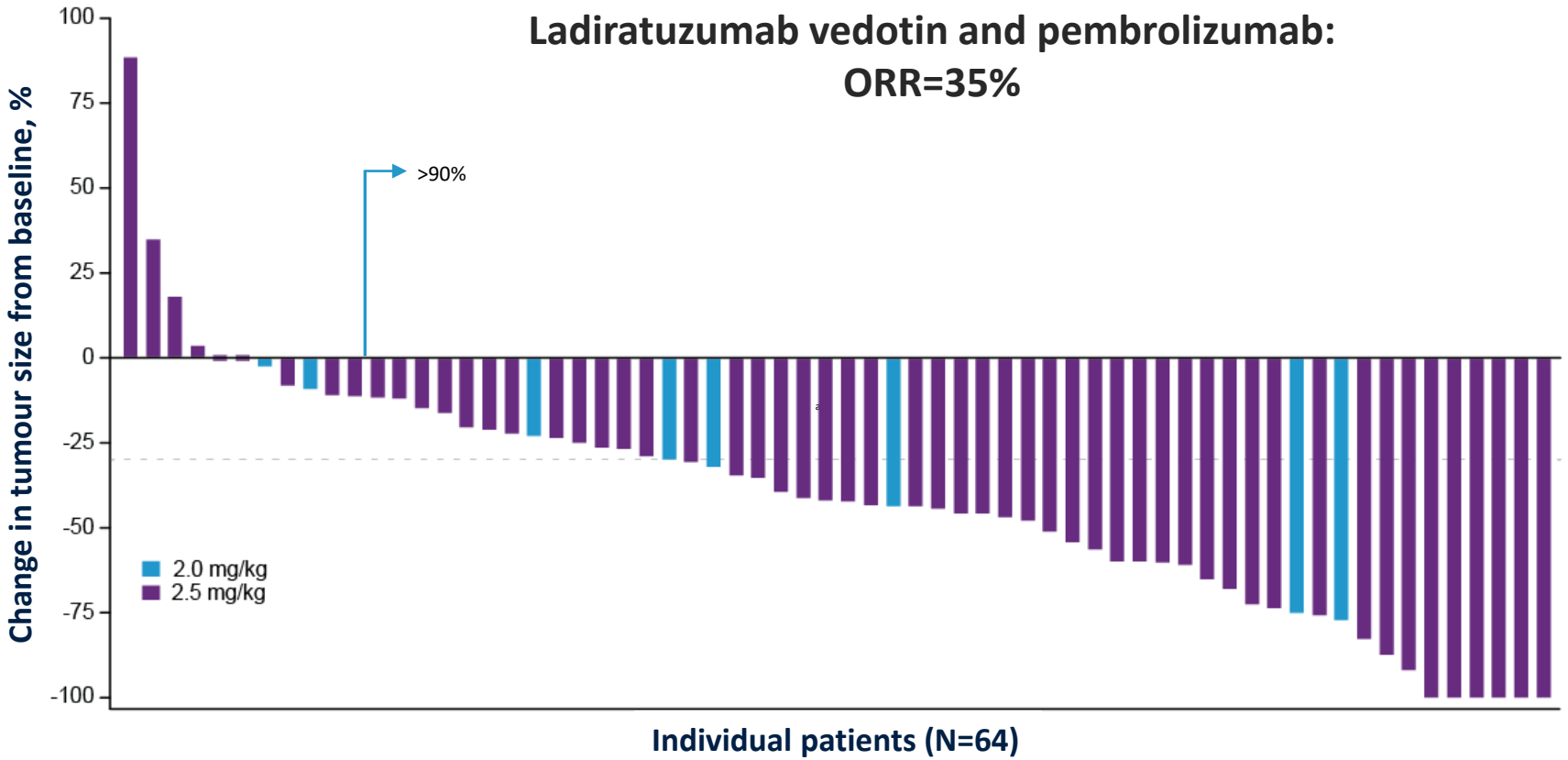
Ladiratuzumab vedotin: Activity in triple negative breast cancer

Confirmed ORR=25% (15/60)



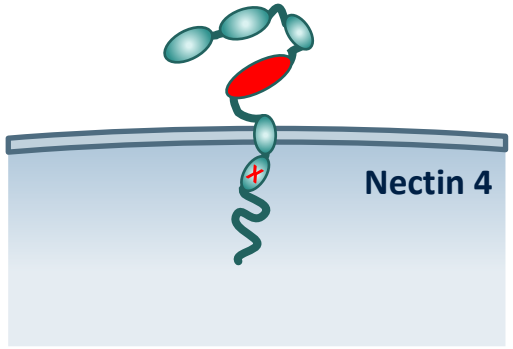
ORR, overall response rate; PR, partial response; SD, stable disease.
Modi S, et al. Presented at SABCS 2017.

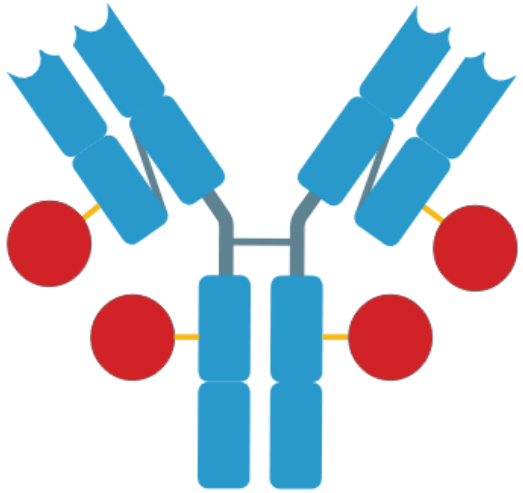
Triple negative breast cancer: Combining ADC and IO



ADC, antibody–drug conjugate; IO, immunooncology; ORR, overall response rate.
Han H, et al. Presented at SABCS 2019.

Antibody–drug conjugates targeting Nectin-4





- Enfortumab vedotin

Enfortumab vedotin in bladder cancer

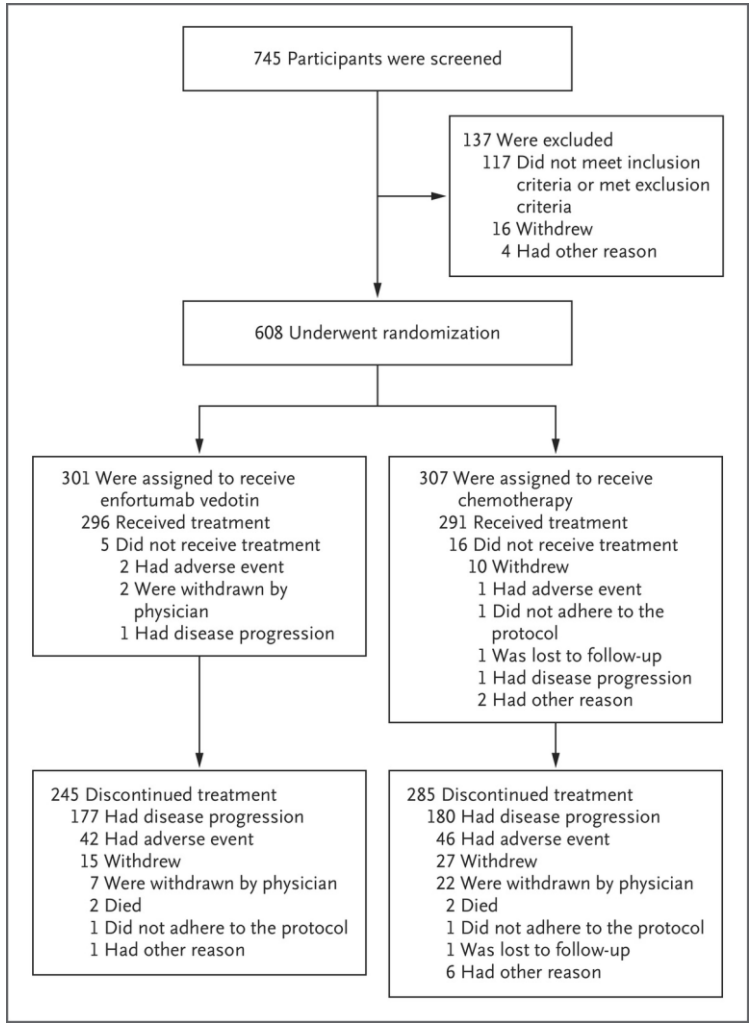


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Enfortumab Vedotin (N=301)	Chemotherapy (N=307)
Median age (range) — yr	68.0 (34.0–85.0)	68.0 (30.0–88.0)
Age ≥75 yr — no. (%)	52 (17.3)	68 (22.1)
Sex — no. (%)		
Male	238 (79.1)	232 (75.6)
Female	63 (20.9)	75 (24.4)
Geographic region — no. (%)		
Western Europe	126 (41.9)	129 (42.0)
United States	43 (14.3)	44 (14.3)
Rest of the world	132 (43.9)	134 (43.6)
Tobacco use — no. (%)		
Former user	167 (55.5)	164 (53.4)
Current user	29 (9.6)	31 (10.1)
Never used	91 (30.2)	102 (33.2)
Not reported or unknown	14 (4.7)	10 (3.3)
History of diabetes or hyperglycemia — no. (%)	56 (18.6)	58 (18.9)
ECOG performance-status score — no. (%)†		
0	120 (39.9)	124 (40.4)
1	181 (60.1)	183 (59.6)
Bellmunt risk score — no. (%)‡		
0–1	201 (66.8)	208 (67.8)
≥2	90 (29.9)	96 (31.3)
Not reported	10 (3.3)	3 (1.0)
Origin site of primary disease — no. (%)		
Upper urinary tract	98 (32.6)	107 (34.9)
Bladder or other site	203 (67.4)	200 (65.1)
Histologic type at initial diagnosis — no./total no. (%)		
Urothelial or transitional-cell carcinoma	229/301 (76.1)	230/305 (75.4)
Urothelial carcinoma, mixed types	45/301 (15.0)	42/305 (13.8)
Other§	27/301 (9.0)	33/305 (10.8)
Sites of metastasis — no./total no. (%)		
Lymph node only	34/301 (11.3)	28/306 (9.2)
Visceral site	234/301 (77.7)	250/306 (81.7)
Liver	93/301 (30.9)	95/307 (30.9)
Previous systemic therapies — no. (%)		
1–2	262 (87.0)	270 (87.9)
≥3	39 (13.0)	37 (12.1)
Best response among patients who previously received checkpoint inhibitor treatment — no. (%)¶		
Response	61 (20.3)	50 (16.3)
No response	207 (68.8)	215 (70.0)
Median time since diagnosis of metastatic or locally advanced disease (range) — mo	14.8 (0.2–114.1)	13.2 (0.3–118.4)

* Percentages may not total 100 because of rounding.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 4, with higher scores indicating greater disability.
‡ Bellmunt risk scores range from 0 to 3 according to the presence of the following risk factors: a hemoglobin level of less than 10 g per deciliter, an ECOG performance-status score of greater than 0, and liver metastasis.
§ Other histologic types include adenocarcinoma, squamous-cell carcinoma, and pseudosarcomatic differentiation.
¶ The best response among patients who had a response was defined as a confirmed complete or partial response; among patients who did not have a response, the best response was defined as stable disease or progressive disease.

T Powles et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2035807

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Parameter/Variable	Enfortumab Vedotin Group (N=288)	Chemotherapy Group (N=296)
Overall response		
Patients, n (%)	117 (40.6)	53 (17.9)
95% CI, %	34.90, 46.54	13.71, 22.76
Stratified 1-sided P-value	<0.001	
Disease control rate*		
Patients, n (%)	207 (71.9)	158 (53.4)
95% CI, %	66.30, 76.99	47.52, 59.17
Stratified 1-sided P-value	<0.001	
Time to response, months		
Median	1.87	1.91
Range	1.1, 5.7	1.2, 8.6
Duration of response†		
Events, n/N (%)	63/117 (53.8)	29/53 (54.7)
Median, months	7.39	8.11
95% CI, months	5.59, 9.46	5.65, 9.56
At 6 months, %	53.8	56.0
At 12 months, %	27.7	19.8
Best overall response, n (%)‡		
Complete response	14 (4.9)	8 (2.7)
Partial response	103 (35.8)	45 (15.2)
Stable disease	90 (31.3)	105 (35.5)
Progressive disease	44 (15.3)	83 (28.0)
Not evaluable	37 (12.8)	55 (18.6)

*Disease control rate is defined as the proportion of patients who had a best overall response of confirmed complete response, confirmed partial response, or stable disease (at least 7 weeks).
†In all patients with confirmed complete or partial response.
‡The definition of best overall response was according to RECIST v1.1. Complete or partial response was confirmed by two scans at least 4 weeks apart. The minimum duration for stable disease was 7 weeks.
CI denotes confidence interval, and RECIST Response Evaluation Criteria in Solid Tumors.

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Table 2. Treatment-Related Adverse Events (Safety Population).*

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

* The safety population included all patients who received any amount of trial drug. Included are treatment-related adverse events that occurred in at least 20% of patients in either treatment group or treatment-related adverse events of grade 3 or higher that occurred in at least 5% of patients in either treatment group. Treatment-related adverse events are those for which there is a reasonable possibility that they were caused by the trial treatment, as assessed by the investigator. If data regarding the relationship to treatment were missing, the event was considered to be related to treatment.

† A total of 113 patients (55 in the enfortumab vedotin group and 58 in the chemotherapy group) had preexisting peripheral neuropathy.

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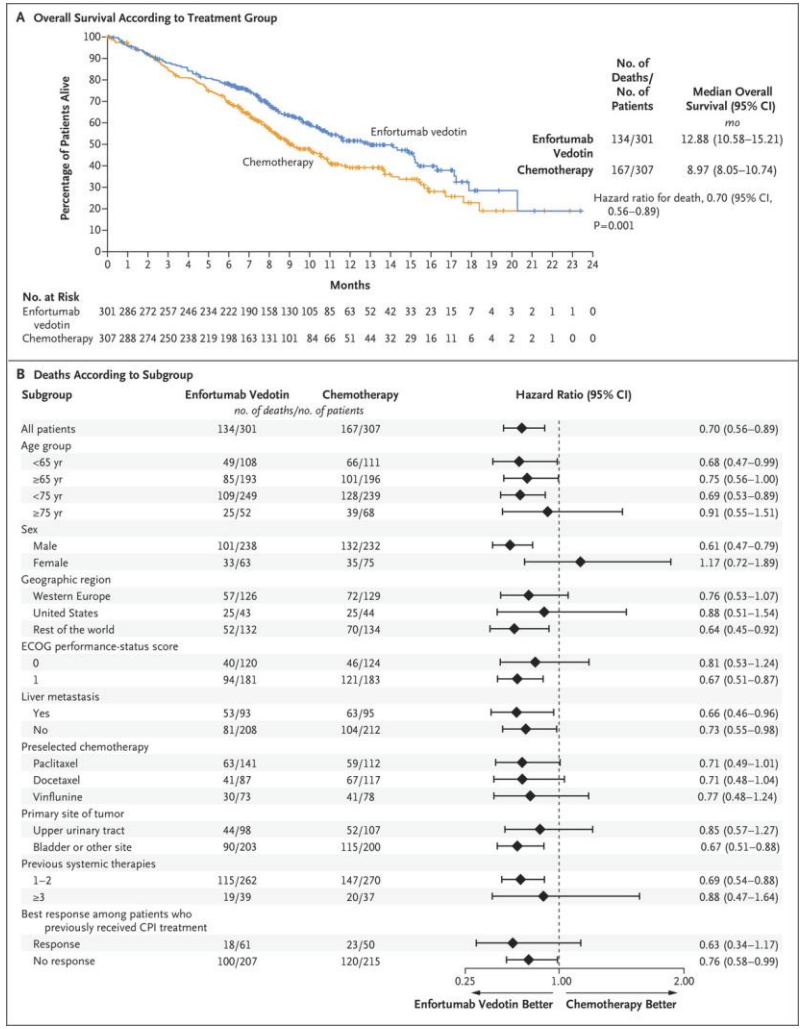

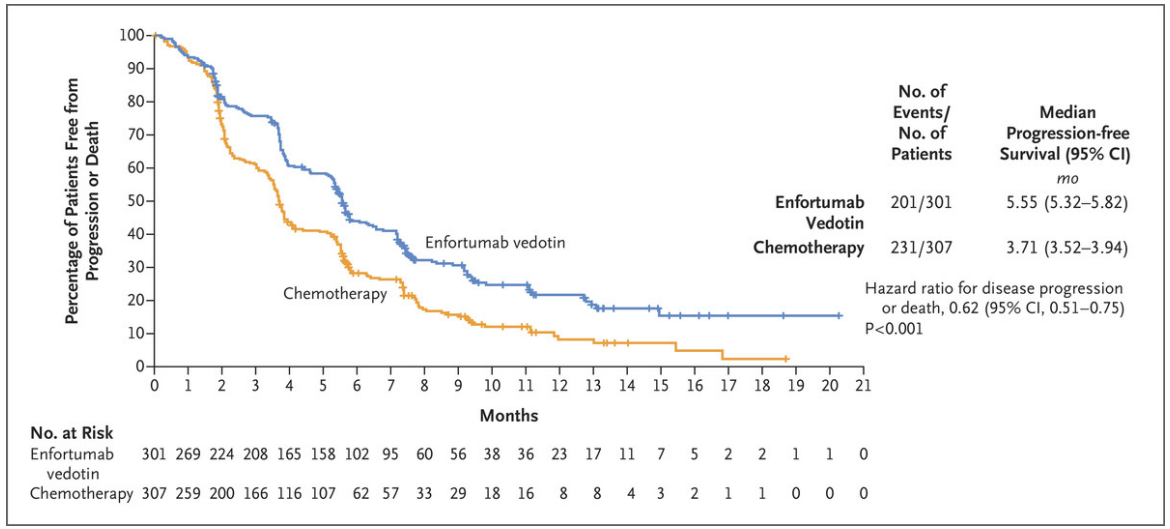

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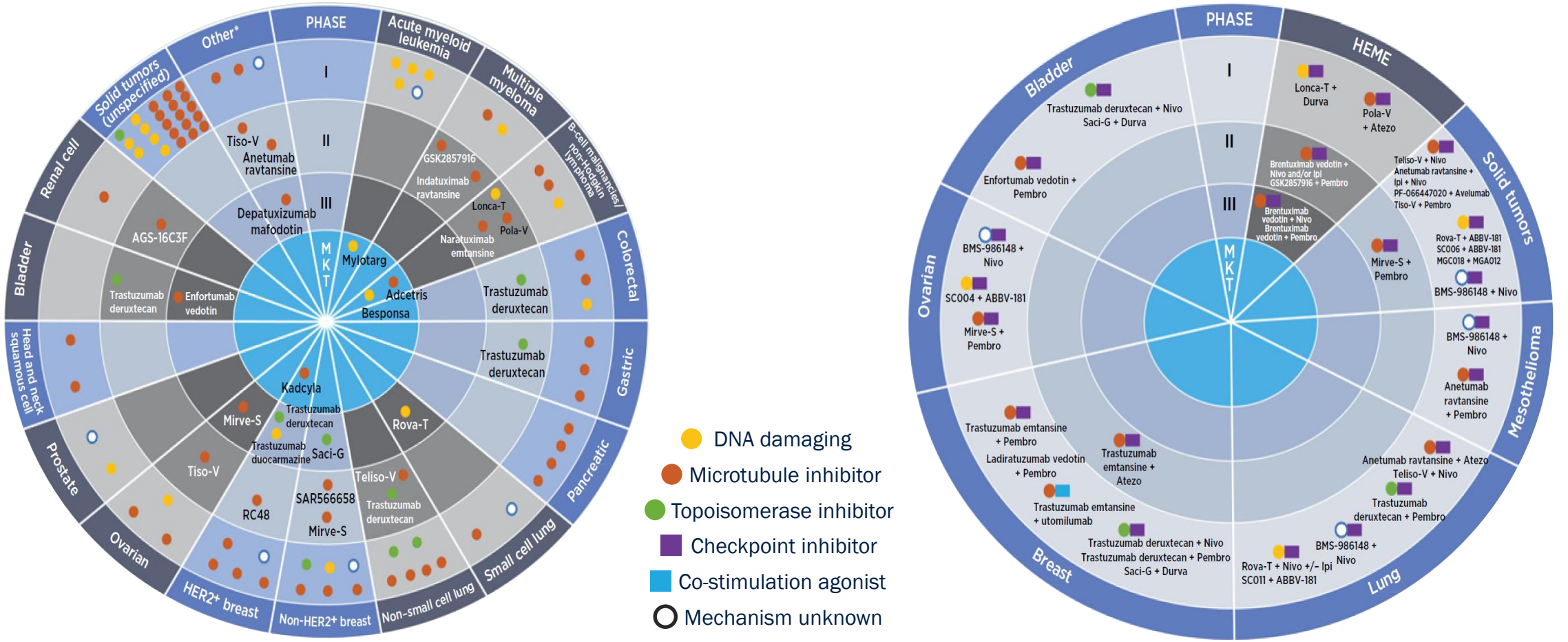
2021 – ADCs in clinical development



ADC, antibody–drug conjugate.
Coats S, et al. Clin Cancer Res. 2019;25:5441–5448.

ADCs: The New Wave

- ADCs are an exciting and effective new therapy for mBC with evolving studies
- Established role in TNBC, HER2+ disease
  - SG is a new standard of care for mTNBC
    - Ongoing TROPiCS-02 trial in HR+ MBC
    - Post-neoadjuvant SASCIA trial
  - Dato-DXd is a new anti-TROP2 ADC
    - Phase III studies in HR+ and TNBC
  - T-DXd is a new standard of care for mHER2+ BC
    - Ongoing Destiny Breast-04 in HER2 low disease
    - Multiple trials in mHER2+ disease, CNS mets, post-neoadjuvant in HER2+
  - New data with SYD985 for mHER2+ BC
- Studies are ongoing or are planned in combination with immunotherapy and in early-stage disease

Conclusions

- Current medical needs in cancer therapy include overcoming treatment resistance and improving response to multiple lines of treatment
- ADC technology has several important benefits:
  - Combination of antigen targeting with potent cytotoxic agents
  - Broad applicability across different tumour types
  - Possibility to develop and expanded platform against new antigens
- Recent clinical studies show improved patient outcomes with ADCs and provide insights into safety and toxicity profiles of next-generation ADCs

Thank You

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