UCSF Helen Diller Family Comprehensive Cancer Center

Other Novel Treatment Options and Investigational Strategies for TNBC

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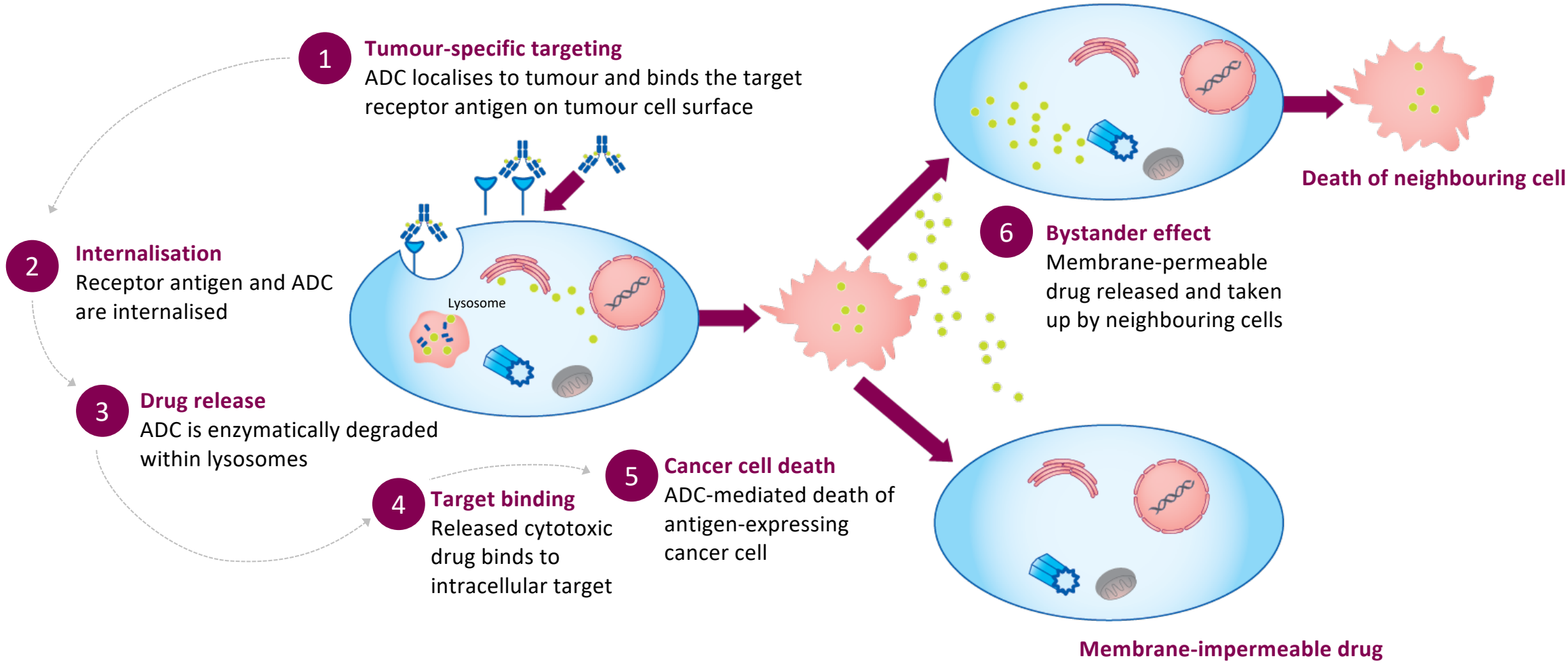
ADC technology enables tumour-specific targeting



ADC=antibody-drug conjugate

1. Adapted from: Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

Overview of ADCs in development for breast cancer

ADC	Target	Antibody	Payload	DAR	Clinical programme	Company
Trastuzumab emtansine (T-DM1, KADCYLA)	HER2	Trastuzumab	DM1	3.5	Approved in mBC with prior therapy, multiple trials in mBC	Roche Holding AG
Trastuzumab deruxtecan (T-DXd, DS-8201, ENHERTU)	HER2	Trastuzumab	DXd	8	Approved in mBC with two prior therapies, multiple trials in mBC	AstraZeneca and Daiichi Sankyo
(vic-)trastuzumab duocarmazine (SYD985)	HER2	Trastuzumab	Seco-DUBA	2.8	Phase 1 BC, Phase 3 mBC	Synthon Biopharmaceuticals BV
Sacituzumab govitecan (TRODELVY)	TROP2	RS7	SN-38	7.6	Approved in TNBC with two prior therapies, multiple trials in mTNBC, mBC	Gilead Sciences, Inc.
Datopotamab deruxtecan (Dato-DXd, DS-1062)	TROP2	Datopotamab	DXd	4	Phase 1 TNBC and HR+/HER2-	AstraZeneca and Daiichi Sankyo
Ladiratuzumab vedotin (SGN-LIV1A)	LIV1	hLIV22	Vc-MMAE	4	Phase 1 mBC, Phase 1/2 mTNBC	Seagen
RC48-ADC	HER2	Hertuzumab	MMAE	4	Phase 1 BC	RemeGen Co
Patritumab deruxtecan (U3-1402)	HER3	Patritumab	DXd	8	Phase 1/2 mBC	Daiichi Sankyo
A166	HER2	Trastuzumab	ND	ND	Phase 1/2 BC	Klus Pharma, Inc.
ALT-P7 (HM2-MMAE)						
ARX788						
DHES0815A (anti-HER2/PBC-MA)	HER2	ND	PBD-MA	ND	Phase 1 mBC	Genentech and Roche Holding AG
MEDI4276	HER2	Trastuzumab scFv	AZI13599185	4	Phase 1 BC	MedImmune, LLC
XMT-1522 (TAK-522)	HER2	HT-18	AF-HPA	12	Phase 1 BC	Mersana Therapeutics, Inc.
AVID100	EGFR	MAB100	DM1	ND	Phase 1/2 TNBC	Formation Biologics, Inc.
CAB-ROR2-ADC	Ror2	CAB	ND	ND	Phase 1/2 TNBC	BioAtla
Anti-CA6-DM4 immunoconjugate (SAR566658)	CA6	DS6	SPDB-DM4	1	Phase 2 TNBC	Sanofi

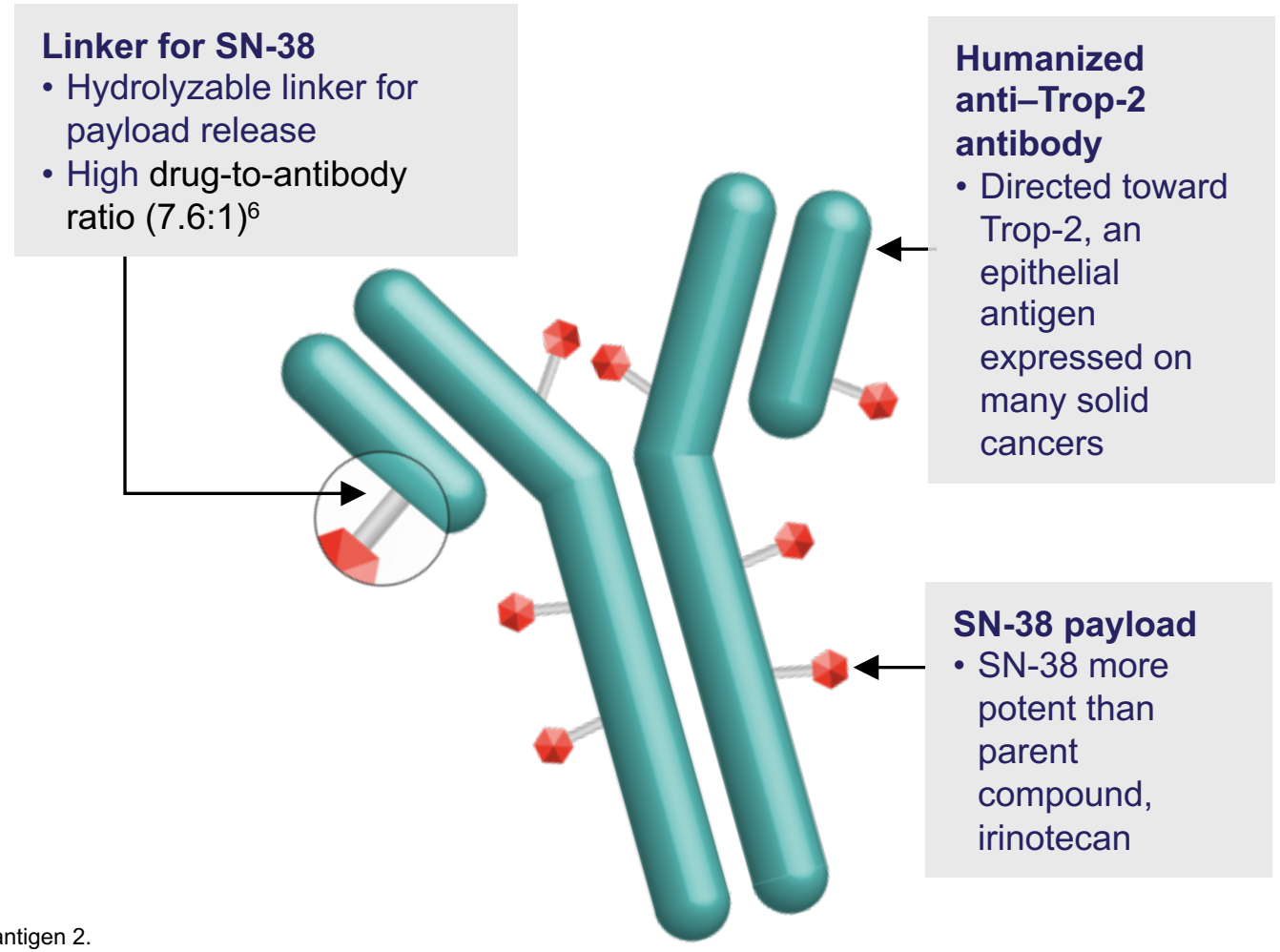
We will discuss these ADCs in more detail in this session

ADC=antibody-drug conjugate; AF-HPA=auristatin F-hydroxypropylamide; DM1=mertansine; DXd=trastuzumab deruxtecan; mBC=metastatic breast cancer; HER2/3=human epidermal growth factor receptor 2/3; MMAE=monomethyl auristatin E; ND=not defined; PBD-MA=pyrrolo benzodiazepine monoamide; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan; (m)TNBC=(metastatic) triple-negative breast cancer; TROP-2=trophoblast cell surface antigen 2.

1. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12175883592091598O; 2. Rinnerthaler G, et al. *Int J Mol Sci*. 2019;20:1115.

Sacituzumab Govitecan (SG): First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- Distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Accelerated FDA approval for metastatic TNBC in 2020 and fast-track designation in metastatic urothelial cancer[7]



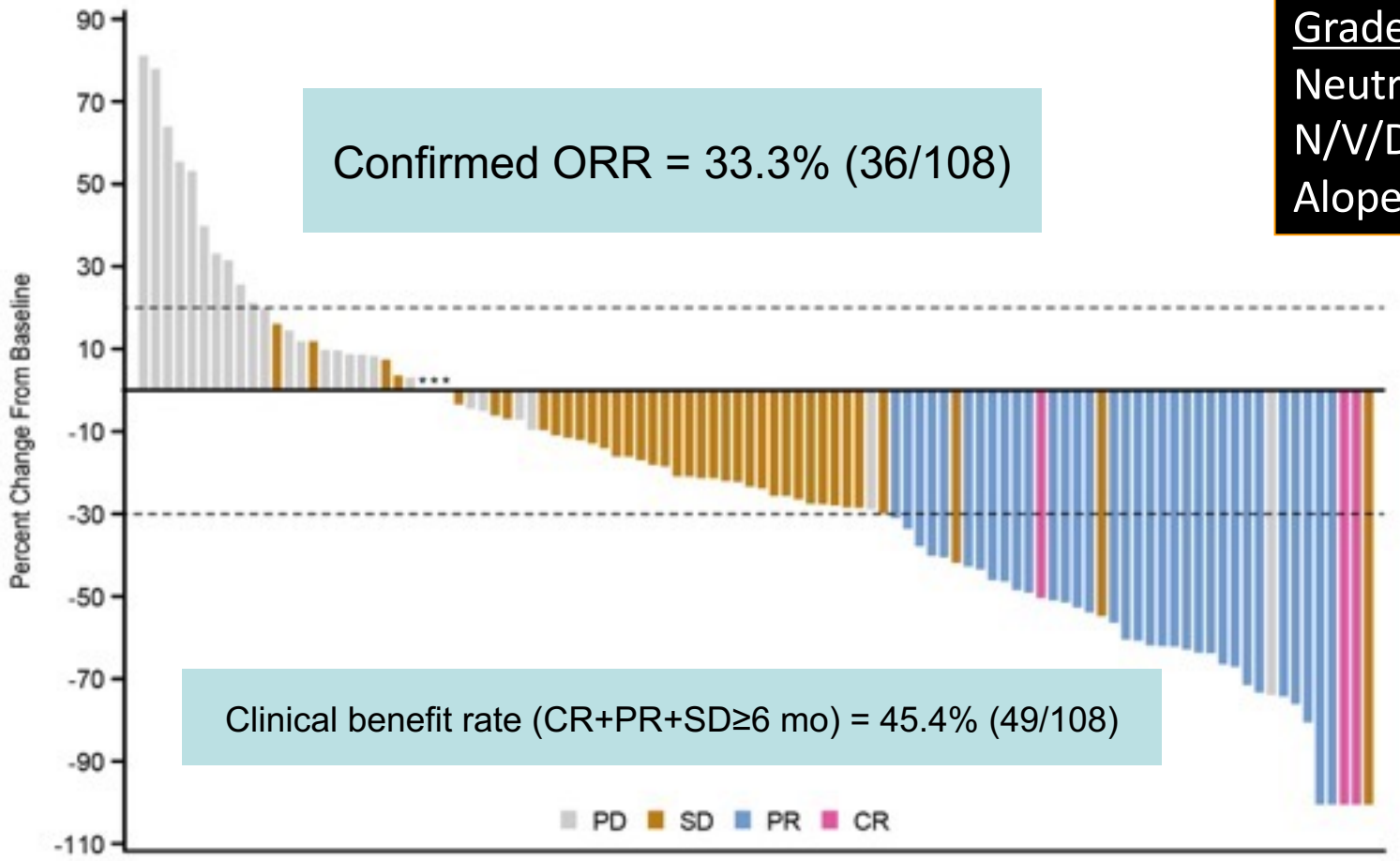
ADC, antibody−drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther.* 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget.* 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

Sacituzumab Govitecan: Phase I/II Trial in mTNBC

108 patients with refractory mTNBC

Median of 3 prior lines of therapy (range 2-10) in the advanced setting



Confirmed ORR = 33.3% (36/108)

Clinical benefit rate (CR+PR+SD≥6 mo) = 45.4% (49/108)

Grade 3/4 toxicity:

Neutropenia: 41%; FN 8%

N/V/D: 5/5/8%

Alopecia: 36%

Bardia et al. *NEJM*. 2019.

ASCENT: Phase III Confirmatory Trial of SG in Refractory Metastatic TNBC

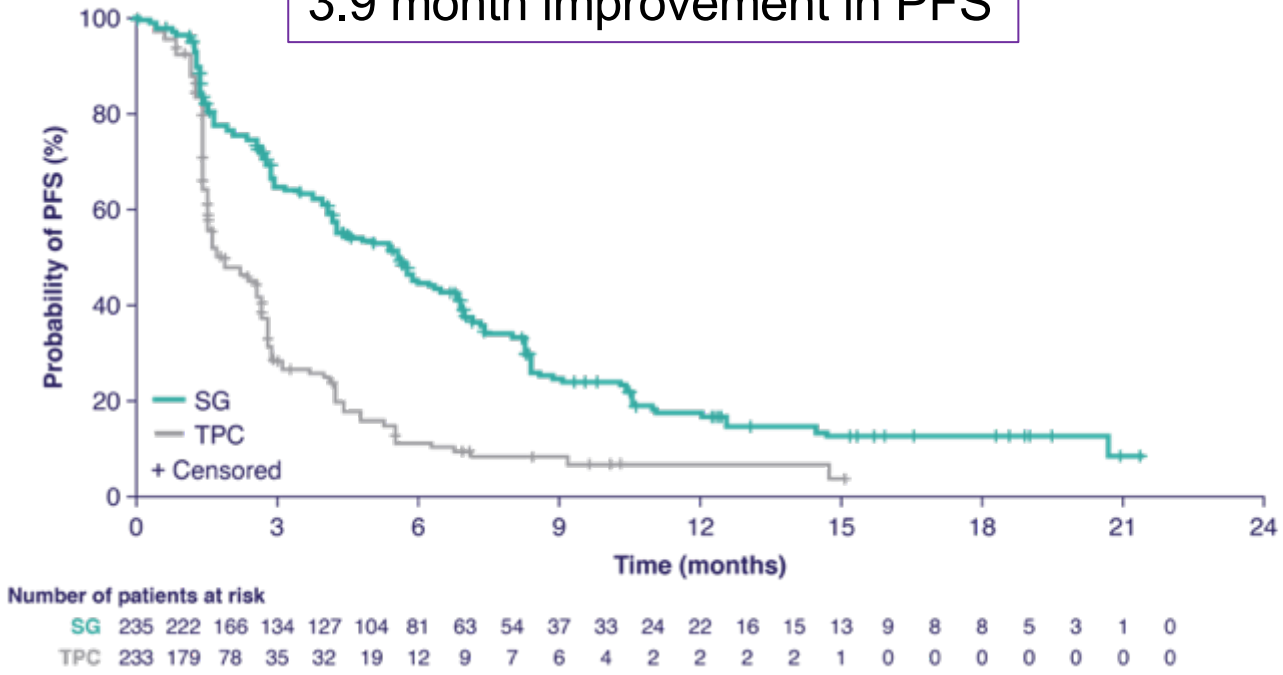
- 529 pts with mTNBC and ≥2 chemotherapies for advanced disease
- Randomized 1:1 to SG (10 mg/kg D1, 8 q 21d) vs TPC (eribulin, vinorelbine, gemcitabine, capecitabine)
- Primary endpoint: PFS in patients without brain metastases
  - Pre-defined maximum 15% cap for pts with brain mets
- Demographics
  - TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine
  - 70% TN at initial diagnosis
  - Median prior regimens 4 (2-17)
  - ~88% with visceral disease

ASCENT halted early due to compelling evidence of efficacy by unanimous DSMC recommendation

Bardia et al, NEJM 2021

Progression-Free Survival (BICR Analysis)

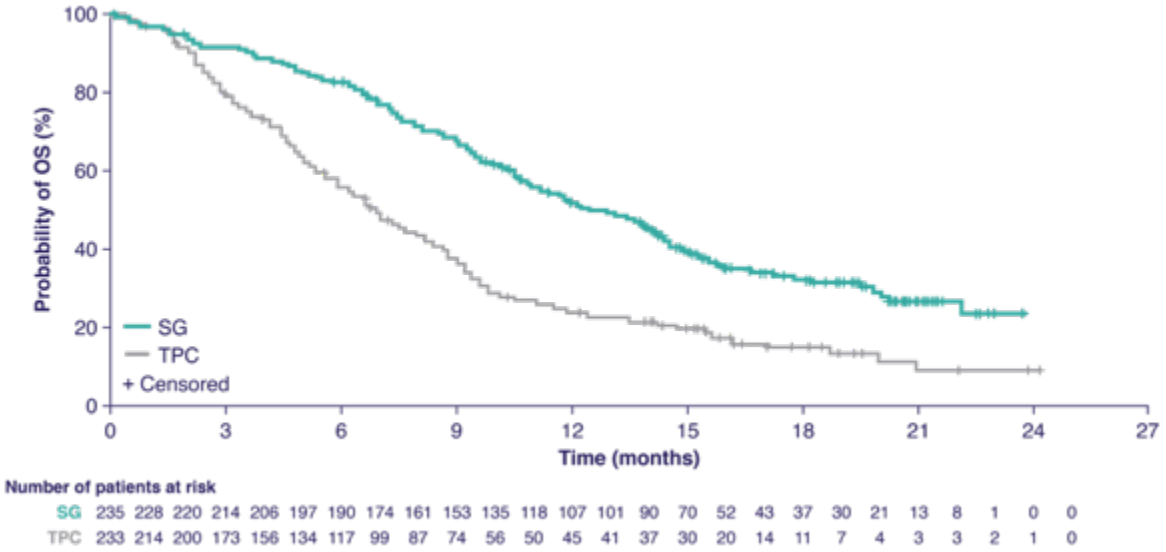
3.9 month improvement in PFS



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**	

Overall Survival

5.4 month improvement in OS

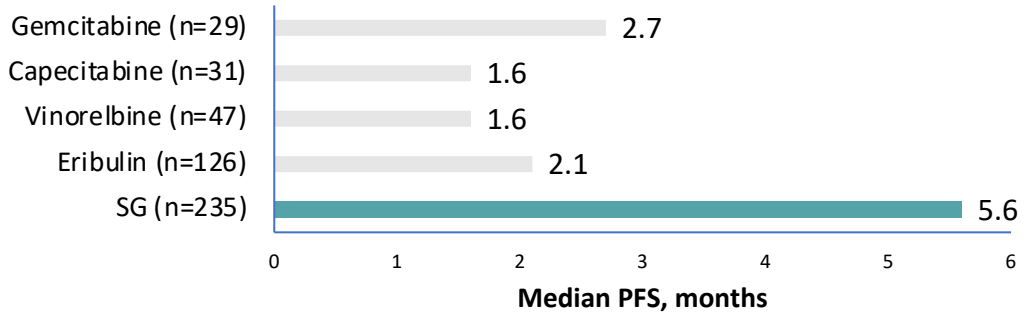


	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

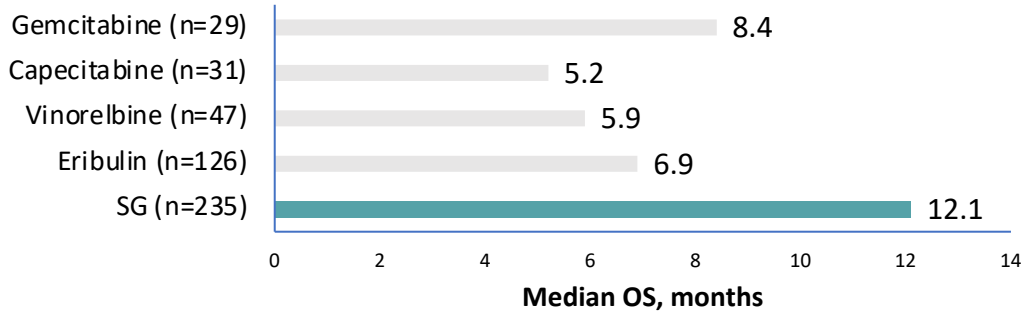
Bardia et al, NEJM 2021

ASCENT: Assessment of SG vs TPC, by Agent

PFS in ASCENT



OS in ASCENT



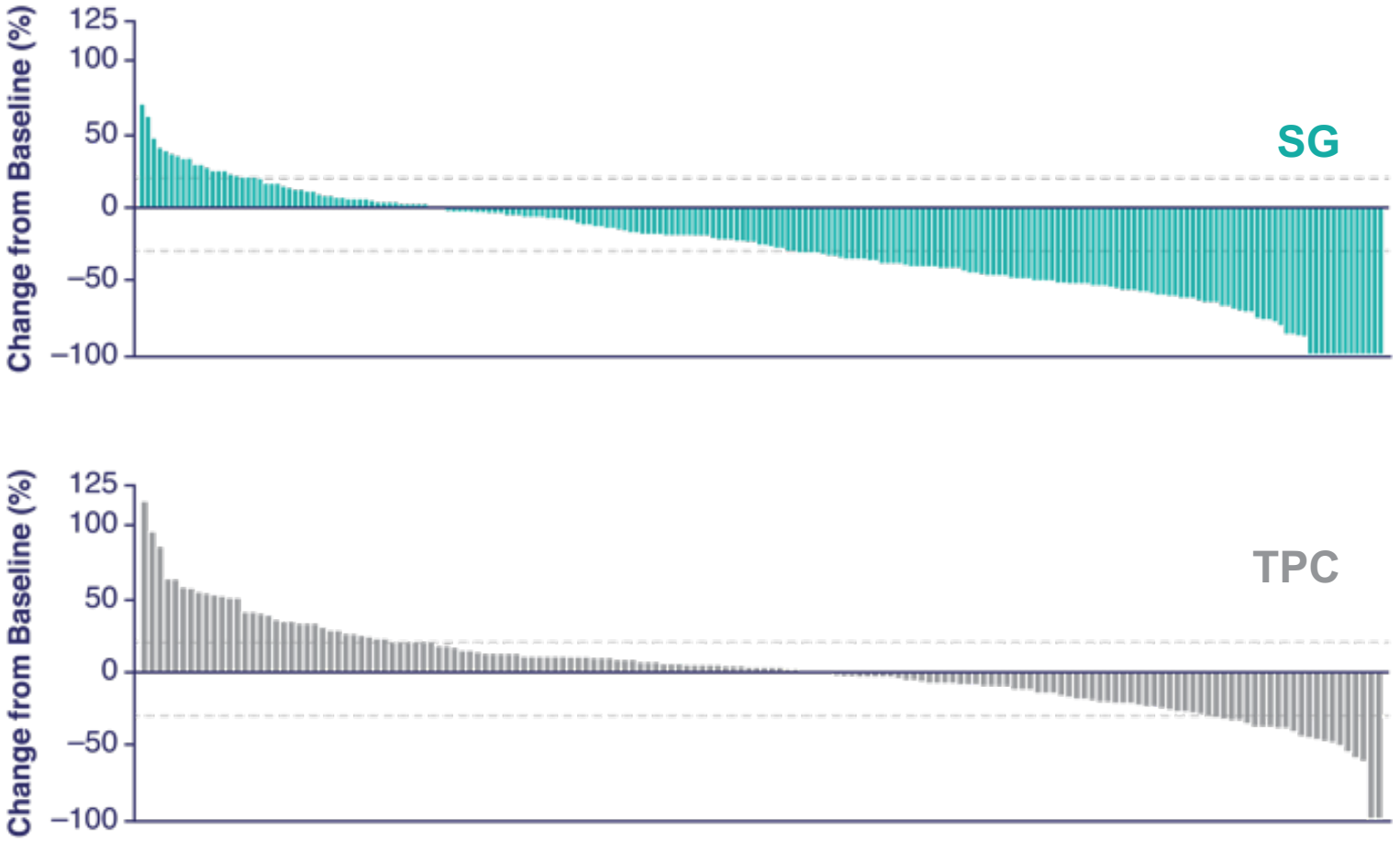
	Sacituzumab Govitecan (n=235)	TPC (n=233)			
		Eribulin (n=126)	Vinorelbine (n=47)	Gemcitabine (n=29)	Capecitabine (n=31)
ORR	**35%**	**5%**	**4%**	**3%**	**6%**
CBR	**45%**	**8%**	**6%**	**14%**	**10%**

The efficacy benefit observed with SG was retained when evaluating each TPC chemotherapy agent individually

CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

O'Shaughnessy J, et al. ASCO 2021 (Poster 1077).

Overall Response and Best Percent Change From Baseline in Tumour Size

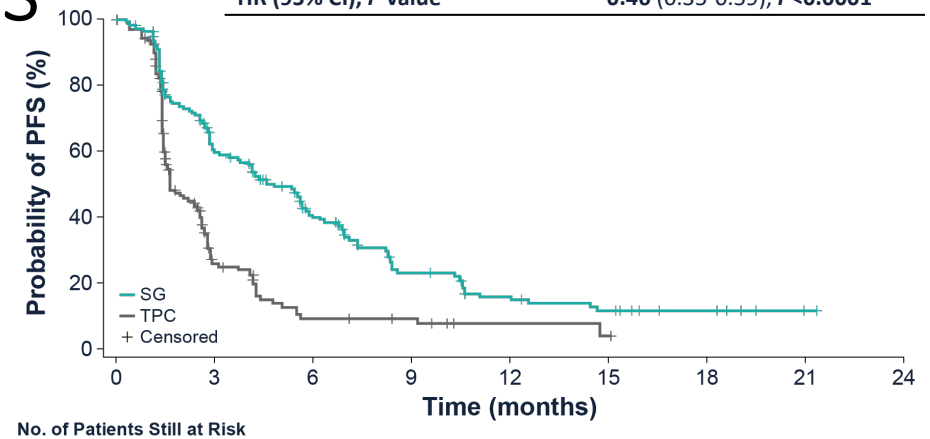


	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	
Median DOR —mo (95%CI)	6.3 (5.5–9.0)	3.6 (2.8–NE)
P-value	0.057	

Bardia et al, NEJM 2021

Comparable Benefit Across Age Groups

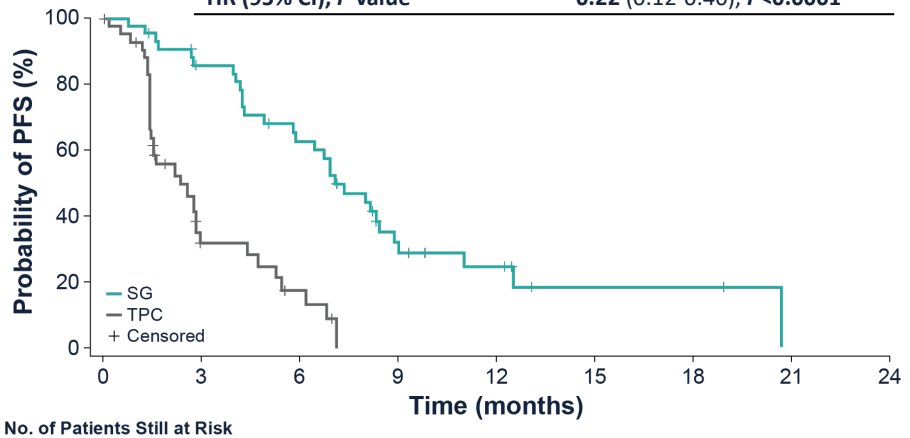
PFS BICR Analysis	<65 y SG (n=191)	<65 y TPC (n=187)
No. of events	136	117
Median PFS—mo (95% CI)	4.6 (3.7-5.7)	1.7 (1.5-2.5)
HR (95% CI), *P* value	**0.46** (0.35-0.59), ***P*<0.0001**	



No. of Patients Still at Risk

SG	191	179	128	100	94	77	57	43	37	27	26	17	16	13	13	11	7	6	6	4	2	1	0
TPC	187	140	59	26	23	12	8	8	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

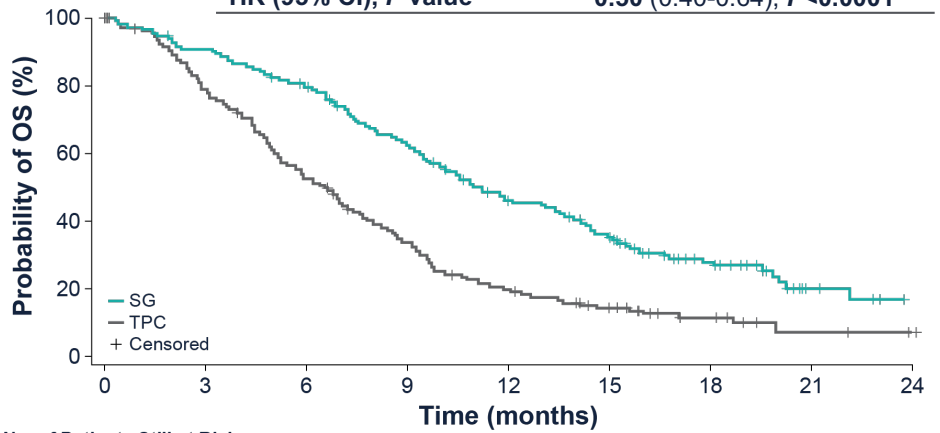
PFS BICR Analysis	≥65 y SG (n=44)	≥65 y TPC (n=46)
No. of events	30	33
Median PFS—mo (95% CI)	7.1 (5.8-8.9)	2.4 (1.4-2.9)
HR (95% CI), *P* value	**0.22** (0.12-0.40), ***P*<0.0001**	



No. of Patients Still at Risk

SG	44	43	38	34	33	27	24	20	17	10	7	7	6	3	2	2	2	2	2	1	1	0	
TPC	46	39	19	9	9	7	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

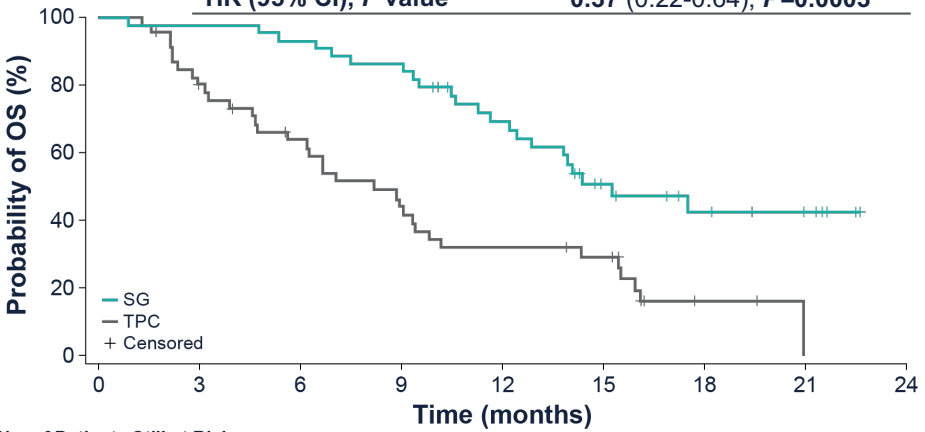
	<65 y SG (n=191)	<65 y TPC (n=187)
No. of events	133	150
Median OS—mo (95% CI)	11.2 (9.9-13.4)	6.6 (5.3-7.4)
HR (95% CI), *P* value	**0.50** (0.40-0.64), ***P*<0.0001**	



No. of Patients Still at Risk

SG	191	185	177	171	163	155	149	135	123	115	102	89	80	77	68	56	40	32	28	22	14	7	6	1	0
TPC	187	168	157	138	125	106	91	77	66	56	42	37	32	28	25	19	14	11	9	5	3	3	3	2	1

	≥65 y SG (n=44)	≥65 y TPC (n=46)
No. of events	22	35
Median OS—mo (95% CI)	15.3 (12.4-NE)	8.2 (5.6-9.8)
HR (95% CI), *P* value	**0.37** (0.22-0.64), ***P*=0.0003**	



No. of Patients Still at Risk

SG	44	43	43	43	43	42	41	39	38	38	33	29	27	24	22	14	12	11	9	8	7	6	2	0	
TPC	46	46	43	35	31	28	26	22	21	18	14	13	13	13	12	11	6	3	2	2	1	0	0	0	

Kalinsky et al, ASCO 2021

ASCENT: Exploratory analysis of TROP2 and gBRCA

- Trop-2 expression assessed by IHC
  - H-score <100 (including H-score 0): Trop-2 Low
  - H-score 100-200: Trop-2 Medium
  - H-score 200-300: Trop-2 High
- Clinical benefit with SG versus TPC in previously treated mTNBC is irrespective of level of Trop-2 expression

	SG (n=235)	TPC (n=233)
BRCA1/2 mutational status—no. (%)	149 (63)	143 (61)
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Trop-2 expression—no. (%)	151 (64)	139 (60)
(High) H-score 200-300	85 (56)	72 (52)
(Medium) H-score 100-200	39 (26)	35 (25)
(Low) H-score <100	27 (18)	32 (23)

	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median PFS – mo (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median OS – mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Hurvitz et al, SABCS 2020

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

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

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhoea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)z

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.

G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

1. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.
Bardia A, et al. ESMO 2020. Oral LBA17.

ASCENT: Exploratory Safety Analyses By UGT1A1 Allele Status

		SG (n=250)[a]					
		*1/*1 Wild-Type (n=113)		*1/*28 Heterozygous (n=96)		*28/*28 Homozygous (n=34)	
	TRAE[b]	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %
Haematologic	Neutropenia[c]	76 (67)	60 (53)	55 (57)	45 (47)	24 (71)	20 (59)
	Anemia[d]	**37 (33)**	**5 (4)**	**29 (30)**	**6 (6)**	**16 (47)**	**5 (15)**
	Leukopenia[e]	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
	Lymphopenia[f]	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
	Febrile neutropenia	**3 (3)**	**3 (3)**	**5 (5)**	**5 (5)**	**6 (18)**	**6 (18)**
	Thrombocytopenia[f]	3 (3)	0	6 (6)	0	4 (12)	4 (12)
Gastrointestinal	Diarrhoea	65 (58)	11 (10)	57 (59)	9 (9)	21 (62)	5 (15)

***UGT1A1* *28/*28 had higher rates of:**

Grade ≥3 treatment-related AESIs (*28/*28 vs *1/*1 vs *1/*28)
- Anemia: 15% vs 4% vs 6%
- Febrile neutropenia: 18% vs 3% vs 6%
- Diarrhoea: 15% vs 10% vs 9%

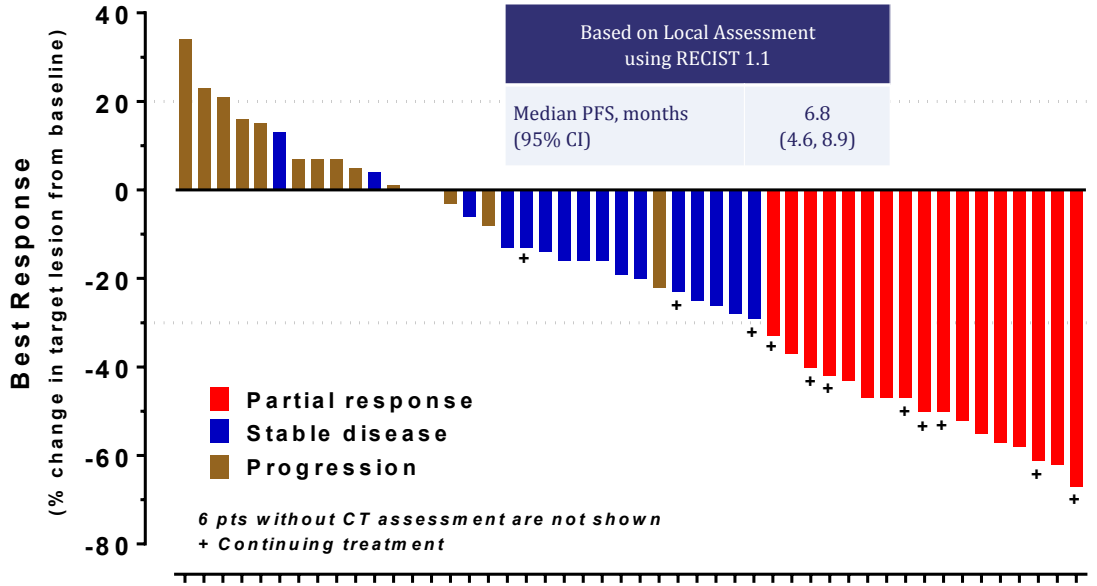
Treatment Discontinuations (*28/*28 vs *1/*1 vs *1/*28)
- 6% vs 2% vs 1%

Conclusions: Individuals with *UGT1A1* *28/*28 genotype were at modestly higher risk for anemia and febrile neutropenia with SG and should be monitored closely. These data suggest that *UGT1A1* status does not alter recommendations for treatment or management. Note: The frequency of *28/*28 mutation was low, so this limited the ability to discern additional differences.

Assessed in the safety population of patients with *UGT1A1* genotype. Shown are key TRAEs significantly impacted by the *UGT1A1* *28/*28 genotype. Other TRAEs like nausea, vomiting, constipation, fatigue, alopecia, and decrease appetite were not significantly impacted. [a]Seven patients had *UGT1A1* genotypes not listed in the table. [b]Patients may report more than 1 event per preferred term. Adverse events were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. [c]Combined preferred terms of "Neutropenia" and "Decreased neutrophil count." [d]Combined preferred terms of "Anemia" and "Decreased hemoglobin." [e]Combined preferred terms of "Leukopenia" and "Decreased white blood cell count." [f]Combined preferred terms of "Lymphopenia" and "Decreased lymphocyte count." [f]Combined preferred terms of "Thrombocytopenia" and "Decreased platelet count."
SG, sacituzumab govitecan; TRAE, treatment-related adverse event; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

1.Rugo H, et al. Poster. SABCS [virtual meeting]. 2020 (abstr PS11-09).

Sacituzumab in ER+ MBC
n=54



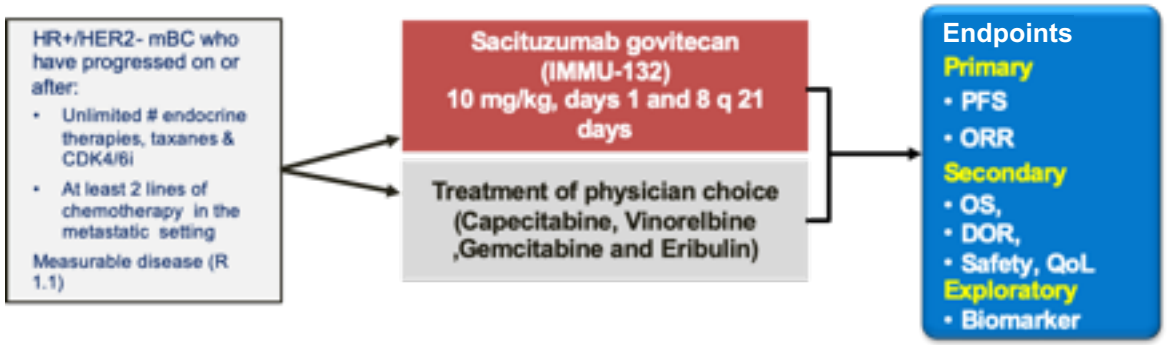
- Median number of metastatic chemo lines: 2
- Median number of prior metastatic lines: 5

Local Response Evaluation by RECIST1.1	
Objective response rate	31% (17/54)
CR	0
PR	17
Clinical benefit rate (CR+PR+SD ≥6 months)	48% (26/54)

Bardia et al, ASCO 2018

TROPiCS-02: Phase III Study mHER2-/HR+ mBC

At least two prior lines of chemotherapy
N=400; 1:1 randomization



Rugo, PI

SACI-IO TNBC: SG +/- pembrolizumab in 1st line PD-L1- TNBC

mTNBC:
No Prior Chemo
No Prior PD-1/L1

PD-L1 <1% by SP-142
ER ≤ 5%
PR ≤ 5%
HER2-

Stable brain mets
Strata: Neo/adjuvant progression <12m

Exclude prior: PD-1/L1, SG, Irinotecan

R 1:1

N=110 pts

sacituzumab govitecan 10mg/kg IV d1,8 q21 days + pembrolizumab 200mg/kg Q3wks

sacituzumab govitecan 10mg/kg d1,8 q21 days

Primary Endpoint
- PFS

Secondary Endpoints
- OS, ORR
- DOR, CBR

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

PI: Sara Tolaney/Ana Garrido-Castro

TBCRC 047: InCITe Trial Design

Metastatic TNBC
- Measurable disease
- No more than 2 prior metastatic lines of chemotherapy
- Known PD-L1 status
- Prior IO allowed

REGISTER

RANDOMIZE

Binimetinib → **Binimetinib + Avelumab + Liposomal doxorubicin**

Sacituzumab govitecan → **Sacituzumab govitecan + Avelumab**

Liposomal doxorubicin → **Avelumab + Liposomal doxorubicin**

*Novel agent 1: Binimetinib, a MEK inhibitor (oral)
#Novel agent 2: Sacituzumab govitecan
Avelumab: PD-L1 inhibitor, IV every 2 wks
Liposomal doxorubicin: IV every 4 wks

15 day lead-in

1 Cycle=4 weeks
Tumor assessments & PRO q 8 wks

Tumor biopsy
Blood collection

Tumor biopsy
Blood collection

Blood collection (at 8 weeks and at PD)

*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

PI: Hope S. Rugo

GBG: SASCIA Post-Neoadjuvant Trial

N=1200

HER2-negative early breast cancer

- **At least 16 weeks of taxane-based NACT**
- **No pCR:**
  - **TNBC**
  - **HR-positive and CPS-EG score ≥3 or 2 and ypN+**

R 1:1

Sacituzumab govitecan (8 cycles d1, 8 q3w)

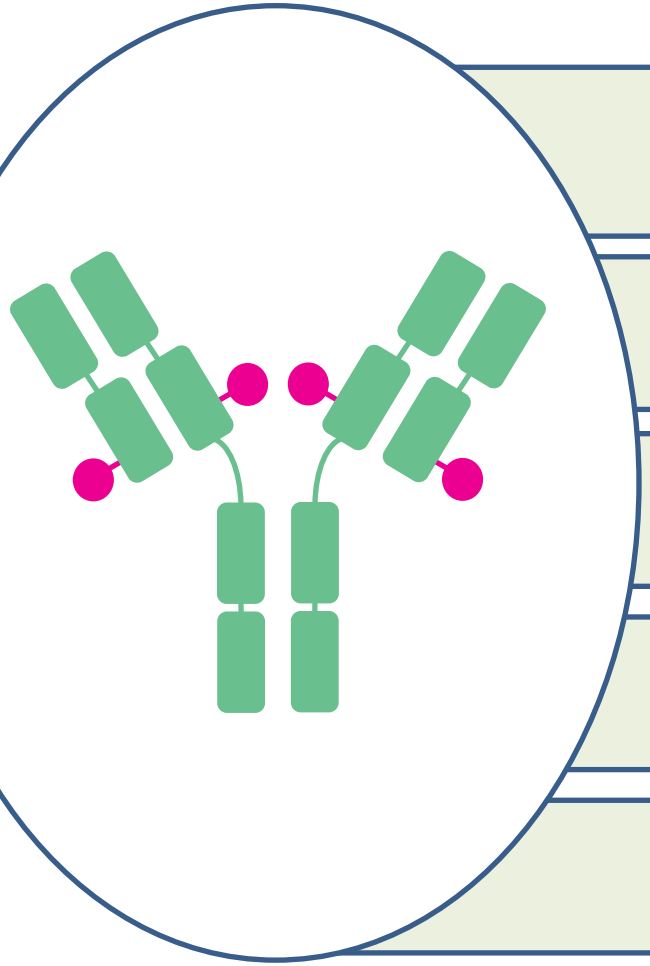
Treatment of physician´s choice*

Follow-up

Stratification factors:
- HR-positive vs HR-negative
- ypN+ vs ypN-0

*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Datopotamab Deruxtecan (Dato-DXd): TROP2 ADC IN DEVELOPMENT



- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release
- DS-1062 has a DAR of 4 for optimized therapeutic index[2]
- DS-1062 has a substantially **longer half-life** than SG (≈ 5 days vs 11-14 hours), enabling a more optimal dosing regimen
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation

Dato-DXd: TROPION-PanTumor01 (NCT03401385)—TNBC Cohort

- Advanced/metastatic TNBC
- Relapsed/progressed on standard Rx
- Unselected for TROP2 expression
- Measurable disease (per RECIST v1.1)
- Stable treated brain mets allowed

→ **Dato-DXd 6mg/kg IV Q3W**
N=44

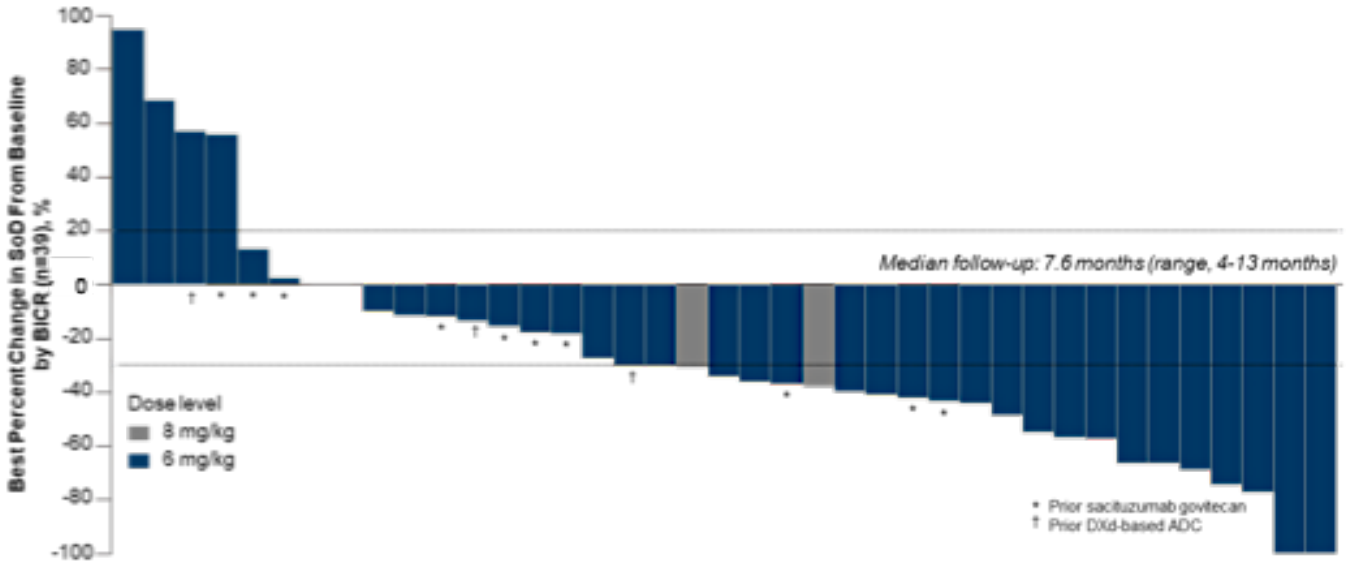
6-mg/kg dose (n=42)
8-mg/kg dose (n=2)

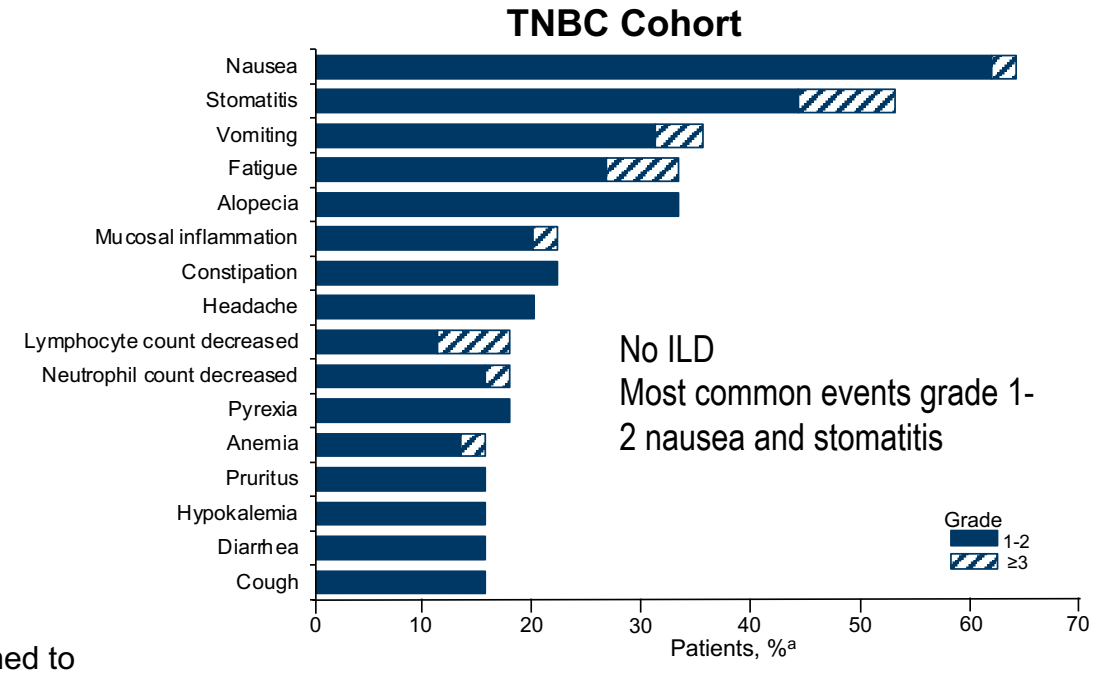
→ **Primary objectives include:**
- Safety, Tolerability

Secondary objectives include:
- Efficacy, Pharmacokinetics, Antidrug Antibodies

Patients, n (%)[a]	All Patients (n=44)
ORR	15 (34)
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)	1 (2)
SD	**17 (39)**
DCR	**34 (77)**
PD	**8 (18)**

Data cutoff: JUL 30, 2021. Treatment ongoing in 13 pts (30%); 31 pts (70%) discontinued treatment (30 due to PD, 1 due to AE)





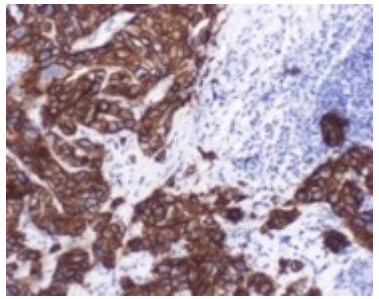
a. Postbaseline tumor assessments were not yet available for 2 pts at data cutoff. 3 pts not confirmed to have a target lesion per BICR; therefore, had best OR of non-CR/non-PD.

Krop I, et al. SABCS 2021. S1-05. Bardia A, et al. ESMO Breast Ca Virtual Congress 2021. LBA4.

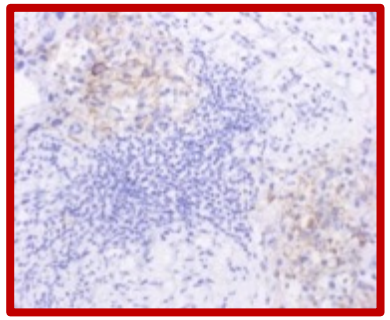
Prevalence of HER2 Low

HER2 IHC examples

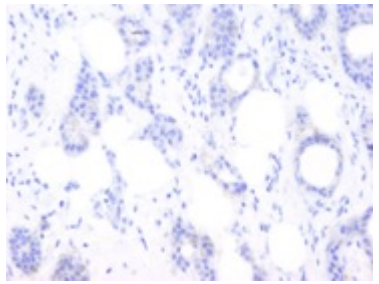
HER2+



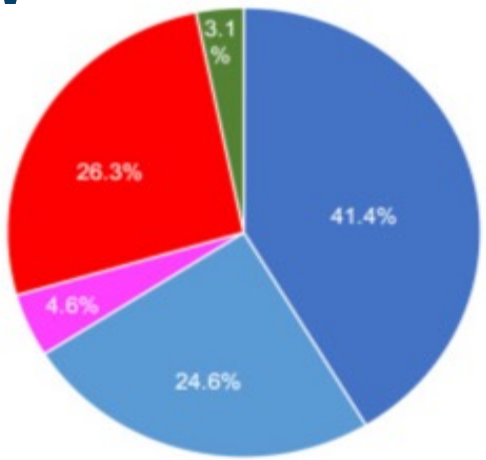
HER2-low



HER2-

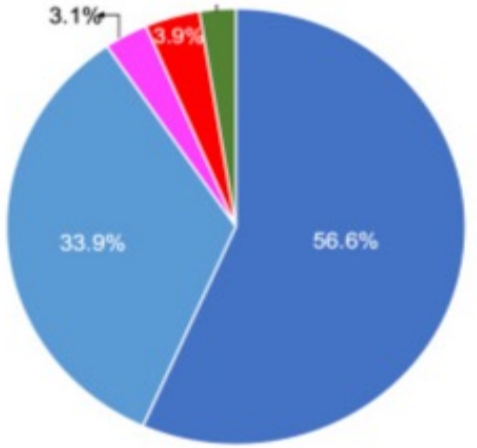


HER2 neg



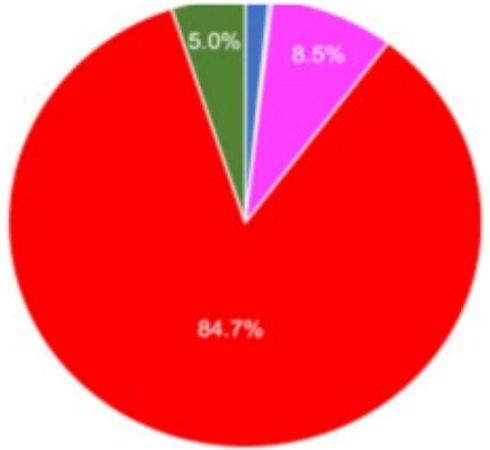
N=1576

HR pos



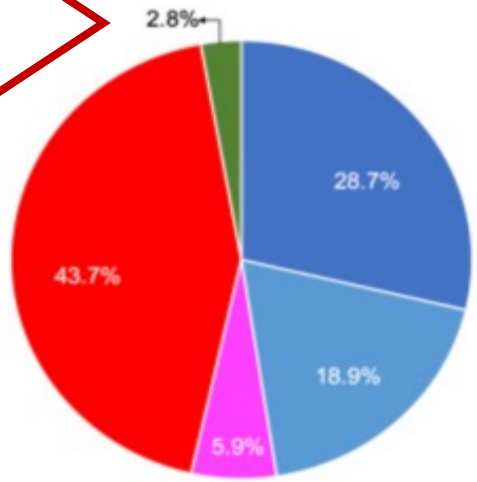
N=1137

Triple Negative



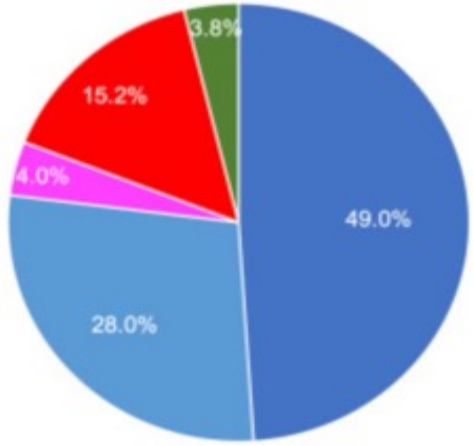
N=437

IHC 0



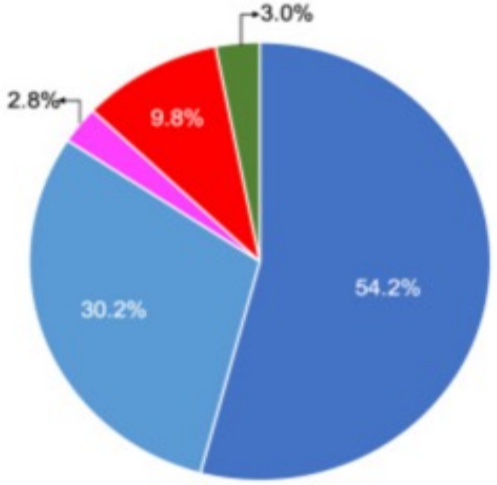
N=673

IHC 1+



N=701

IHC 2+not amplified

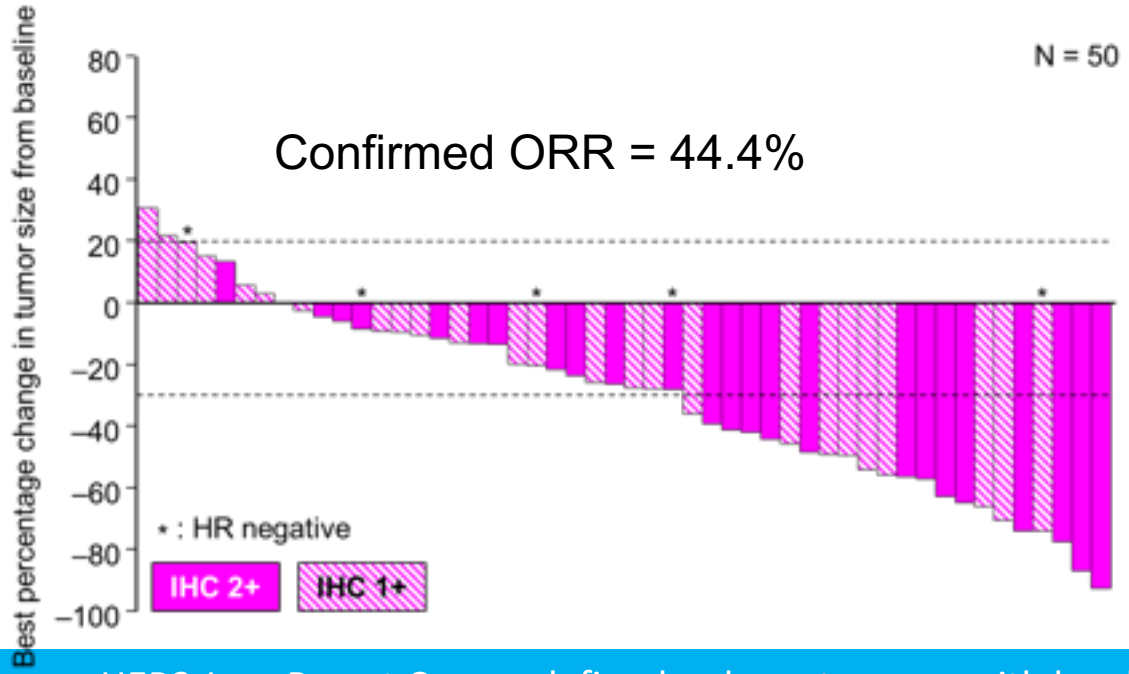


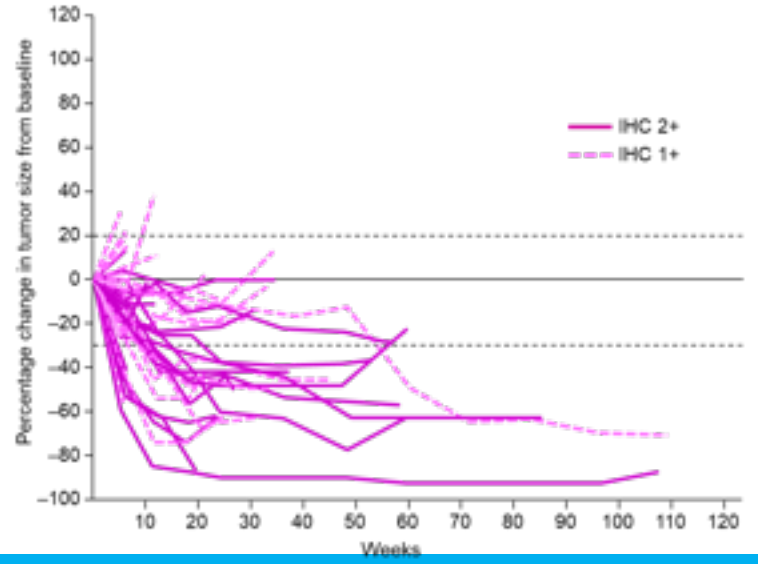
N=325

Luminal A Luminal B HER2-enriched Basal-like Normal-like

Schettini et al, NPJ Breast Cancer 2021

Trastuzumab Deruxtecan Has Clinical Activity in HER2-low MBC





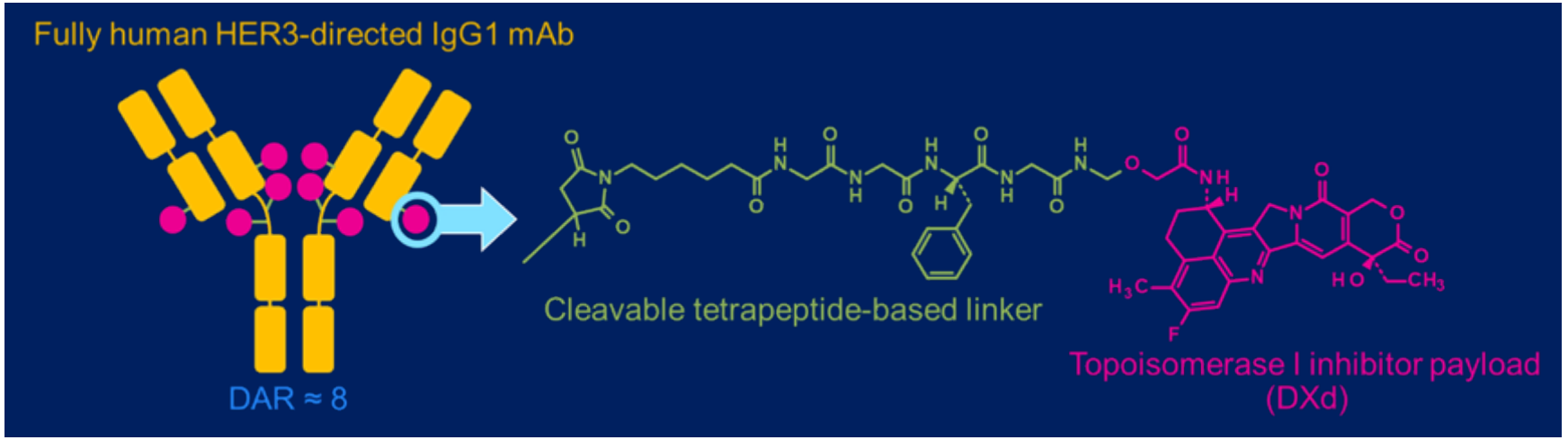
HER2-Low Breast Cancer defined as breast cancer with low levels of HER2 expression (ie, IHC 1+ or 2+/ISH-negative)

	Confirmed ORR	mDoR	mPFS
All (N = 51)	44.2% (N=43)	9.4m	7.6m

DESTINY-Breast04	**HER2-low**, unresectable and/or metatastic breast cancer **vs. physician's choice**	NCT03734029* 2018-003069-33	Completed Accrual

Modi S et al. J Clin Oncol. 2020.

New ADCs against HER3: Patritumab deruxtecan (U3-1402)



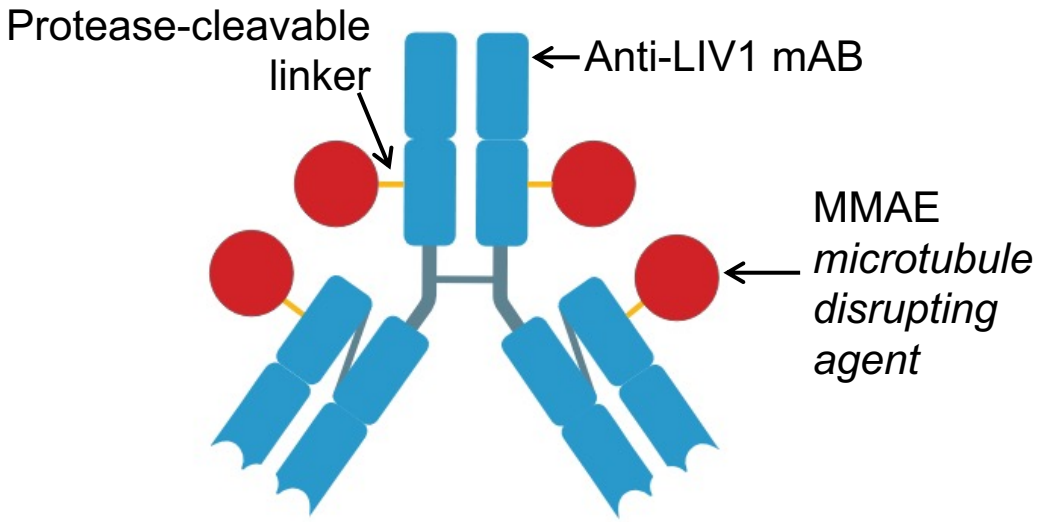
Study in progress: Phase I/II study of patritumab deruxtecan in HER3-positive BC (NCT02980341)

Patient population	HER3-DXd dose
HER3-high, HR+/HER2- mBC (n≈60)	4.8 mg/kg IV Q3W 6.4 mg/kg IV Q3W
HER3-low, HR+/HER2- mBC (n≈20)	6.4 mg/kg IV Q3W
HER3-high TNBC (n≈30)	6.4 mg/kg IV Q3W

	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)		
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)
mDOR (95% CI), mo	5.0 (2.8–NE)	7.2 (5.5–7.2)	5.3 (3.0–NE)	NR (4.2–NE)
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)
mPFS (95% CI), mo	8.4 (5.6–9.9)	2.8 (1.9–8.2)	5.8 (1.4–11.0)	5.5 (3.9–NE)
mOS (95% CI), mo	14.3 (10.9–NE)	9.7 (6.6–19.5)	9.2 (4.7–21.9)	NR (6.4–NE)

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

Ladiratuzumab Vedotin: ADC Targeting LIV1



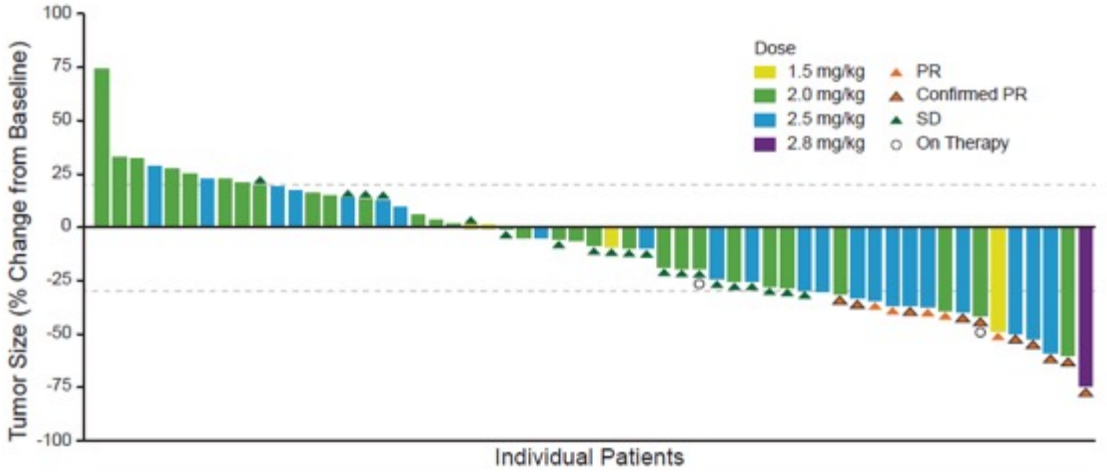
LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer

Mech. of Action:

1. Binds to antigen
2. Complex internalized and trafficked to lysosome
3. Release of MMAE payload
4. Microtubule disruption
5. Cell cycle arrest/disruption

Phase I Study of Ladiratuzumab Vedotin

Confirmed ORR = 25% (15/60)



Next steps:
Weekly therapy to reduce toxicity

Modi S, et al. SABCS. 2017.

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+
- Studies are ongoing or are planned in combination with immunotherapy and in early-stage disease
- New ADCs in clinical trials!

Thank you!