



# Fenotipo triple negativo: nuevas alternativas. ¿Tenemos un estándar más allá de la primera línea?

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# Disclosures

- Employment: Servicio Navarro de Salud.
- Advisory role: Alianza AstraZeneca-Daichi Sankyo, Seagen, Adamed, Lilly, Novartis, Pfizer.
- Travel grant: Novartis, Pfizer.

# Introduction

Triple negative breast cancer (TNBC) definition:

- Lack of expression of estrogen receptor and progesterone receptor
- HER2 not overexpressed/amplified

High cell proliferation, poor cellular differentiation, many recurrent copy number imbalances, and TP53 mutations

Heterogeneity

- TNBC includes rare histologies: metaplastic, medullary, adenoid cystic carcinoma, secretory
- Molecular heterogeneity

Usually high chemosensitivity

~30% de novo MBC<sup>1</sup>

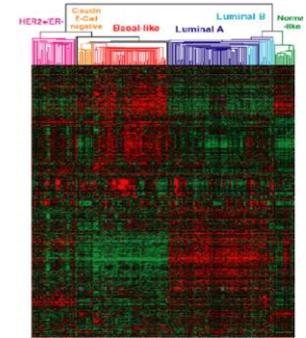
Chemotherapy has been the standard for decades

Most patients received A-T as adjuvant/neoadjuvant treatment

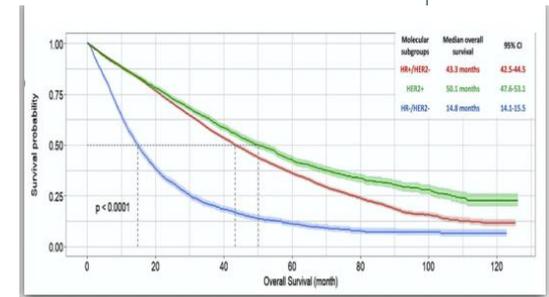
Frequent visceral metastases, poor survival from the onset of MBC

High attrition rate from first to subsequent lines<sup>2</sup>: a long-term treatment sequence is not possible

Best option first, enrolment in clinical trials



Perou, Nature 2000



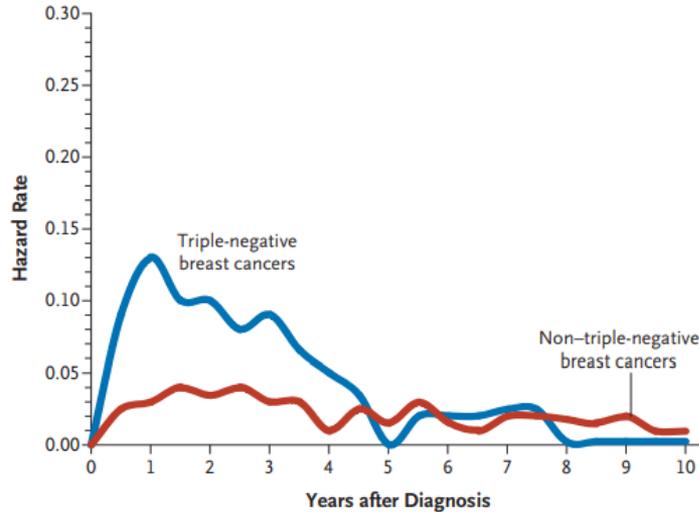
<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf>

Caswell-Jin et al ASCO 2022

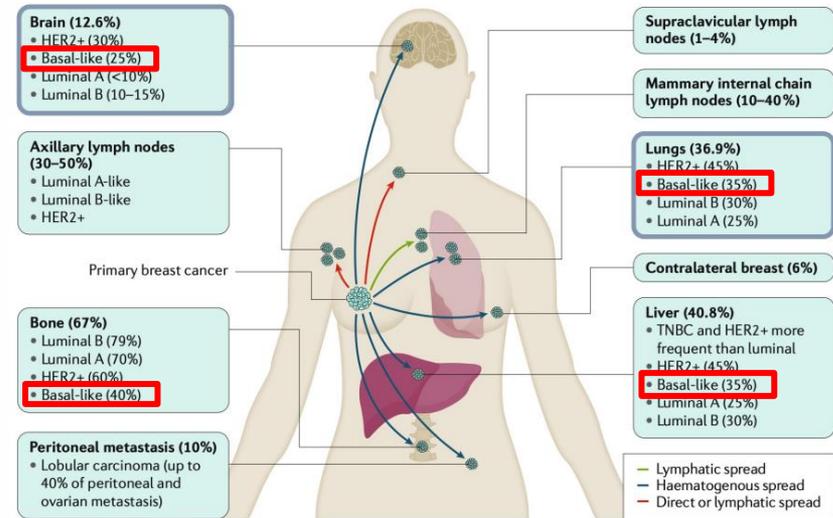
1. Grinda T, et al, ESMO Open 2021; 2. Seah DSE, et al. J Natl Compr Canc Netw 2014;12:71–80.

# TNBC is a highly invasive subtype associated with high rates of relapse and metastasis

HAZARDS RATIO OF RELAPSES/METASTASIS AT 10 YEARS<sup>1</sup>



MOST FREQUENT METASTASIS SITES ACCORDING TO THE MOLECULAR SUBTYPE OF CM<sup>2</sup>



- Different chemo sensitivity.
- Different relapse pattern.
- Different prognostic.

ORIGINAL RESEARCH

# Evolution of overall survival and receipt of new therapies by subtype among 20446 metastatic breast cancer patients in the 2008-2017 ESME cohort

T. Grinda<sup>1</sup>, A. Antoine<sup>2</sup>, W. Jacot<sup>3</sup>, C. Blaye<sup>4</sup>, P.-H. Cottu<sup>5</sup>, V. Diéras<sup>6</sup>, F. Dalenc<sup>7</sup>, A. Gonçalves<sup>8</sup>, M. Debled<sup>9</sup>, A. Patsouris<sup>10</sup>, M.-A. Mouret-Reynier<sup>11</sup>, A. Mailliez<sup>12</sup>, F. Clatot<sup>13</sup>, C. Levy<sup>14</sup>, J.-M. Ferrero<sup>15</sup>, I. Desmoulin<sup>16</sup>, L. Uwer<sup>17</sup>, T. Petit<sup>17</sup>, C. Jouannaud<sup>18</sup>, M. Lacroix-Triki<sup>19</sup>, E. Deluche<sup>20</sup>, M. Robain<sup>21</sup>, C. Courtinard<sup>22</sup>, T. Bachelot<sup>24</sup>, E. Brain<sup>25</sup>, D. Pérol<sup>26</sup> & S. Delaloge<sup>27</sup>

**Background:** Treatment strategies for metastatic breast cancer (MBC) have made great strides over the past 10 years. Real-world data allow us to evaluate the actual benefit of new treatments. ESME (Epidemiology-Strategy-Medico-Economical)-MBC, a nationwide observational cohort (NCT03275311), gathers data of all consecutive MBC patients who initiated their treatment in 18 French Cancer Centres since 2008.

**Patients and methods:** We evaluated overall survival (OS) in the whole cohort (N = 20 446) and among subtypes: hormone receptor positive, human epidermal growth factor 2 negative (HR+/HER2-, N = 13 590), HER2+ (N = 3919), and triple-negative breast cancer (TNBC; N = 2937). We performed multivariable analyses including year of MBC diagnosis as one of the covariates, to assess the potential OS improvement over time, and we described exposure to newly released drugs at any time during MBC history by year of diagnosis (YOD).

**Results:** The median follow-up of the whole cohort was 65.5 months (95% CI 64.6-66.7). Year of metastatic diagnosis appears as a strong independent prognostic factor for OS [Year 2016 HR 0.89 (95% CI 0.82-0.97); P = 0.009, using 2008 as reference]. This effect is driven by the HER2+ subcohort, where it is dramatic [Year 2016 HR 0.52 (95% CI 0.42-0.66); P < 0.001, using 2008 as reference]. YOD had, however, no sustained impact on OS among patients with TNBC [Year 2016 HR 1.02 (95% CI 0.91-1.13); P = 0.41, using 2008 as reference] nor among those with HR+/HER2- MBC [Year 2016 HR 1.02 (95% CI 0.91-1.13); P = 0.41, using 2008 as reference]. While exposure to newly released anti-HER2 therapies appeared very high (e.g. >70% of patients received pertuzumab from 2016 onwards), use of everolimus or eribulin was recorded in less than one-third of HR+/HER2- and TNBC cohorts, respectively, whatever YOD.

**Conclusion:** OS has dramatically improved among HER2+ MBC patients, probably in association with the release of several major HER2-directed therapies, whose penetrance was high. This trend was not observed in the other subtypes, but the impact of CDK4/6 inhibitors cannot yet be assessed.

**Key words:** metastatic breast cancer, real-life, overall survival, HER2, new drugs

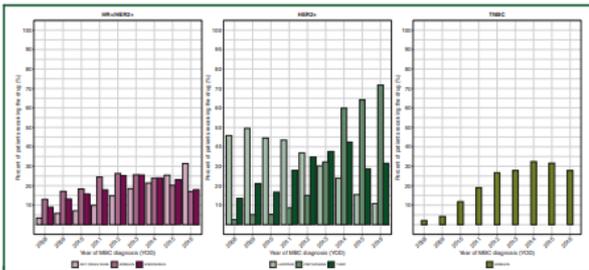
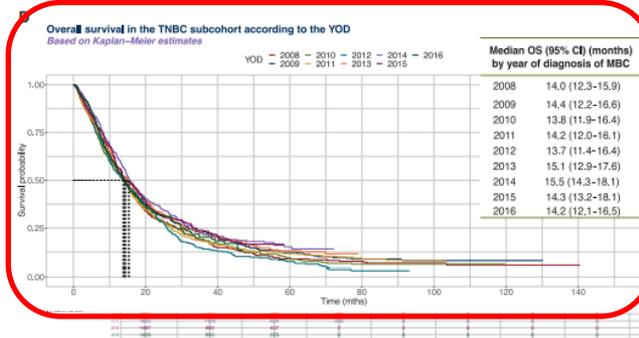
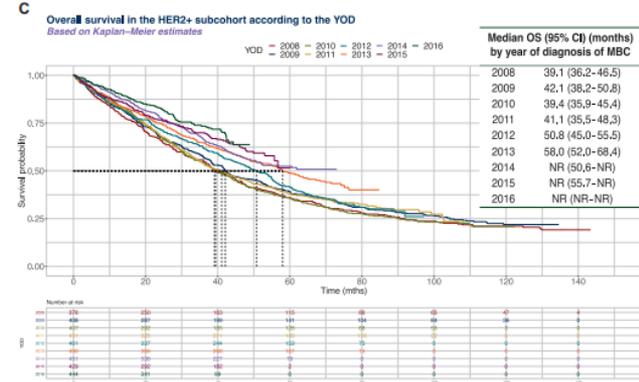
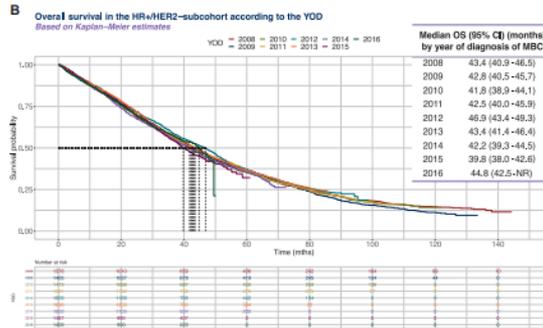
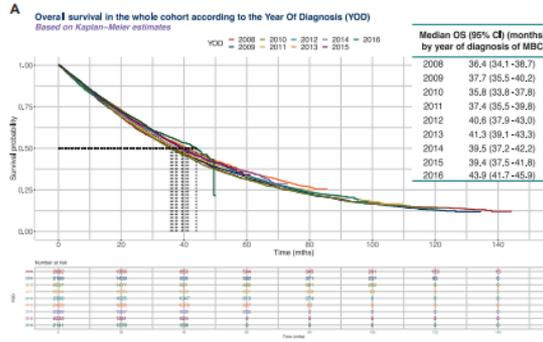
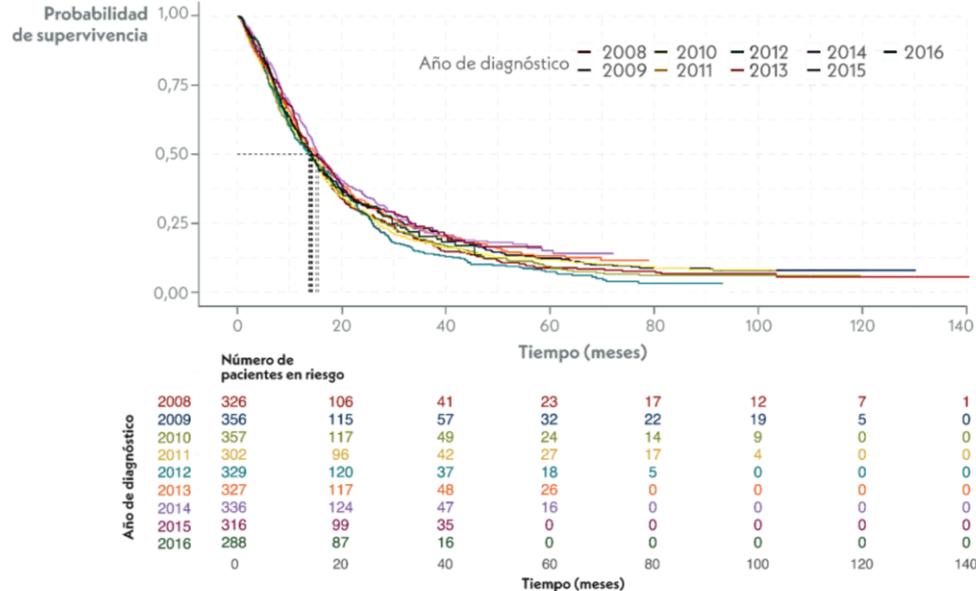


Figure 3. Receipt of newly released treatments per subtype and year of diagnosis.



# Treatment options for mTNBC are limited, with the median OS “staggered” with conventional chemotherapy <sup>1,2</sup>

## OS IN METASTATIC TNBC, DIAGNOSED IN 2008-2016<sup>2</sup>



### Median OS (IC 95%) (months)

2008	<b>14,0</b> (12,3-15,9)
2009	<b>14,4</b> (12,2-16,6)
2010	<b>13,8</b> (11,9-16,4)
2011	<b>14,2</b> (12,0-16,1)
2012	<b>13,7</b> (11,4-16,4)
2013	<b>15,1</b> (12,9-17,6)
2014	<b>15,5</b> (14,3-18,1)
2015	<b>14,3</b> (13,2-18,1)
2016	<b>14,2</b> (12,1-16,5)

CMTNm: cáncer de mama triple negativo metastásico; IC: intervalo de confianza; SG: supervivencia global.

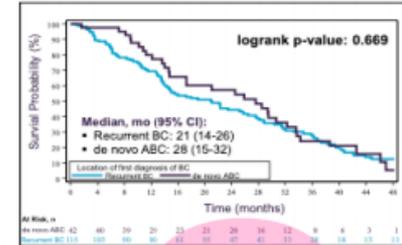
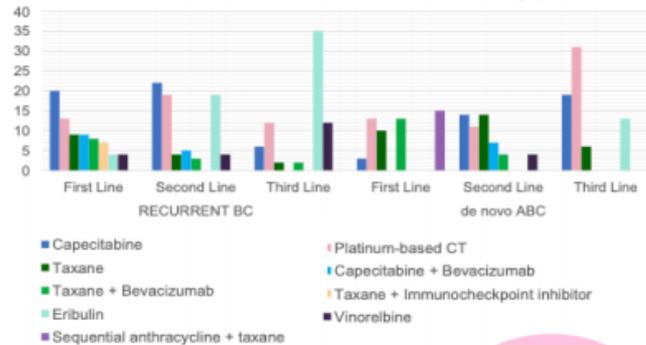
1. Mina LA, *et al.* Immunotherapy for the Treatment of Breast Cancer: Emerging New Data. *Breast Cancer* (Dove Med Press). 2019;11:321–328. 2. Grinda T, *et al.* Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open*. 2021;6(3):100114.

# RegistEM GEICAM mTNBC

## RegistEM\_GEICAM/2014-03 (2016-19)

	Recurrent BC N=115 (73%)	de novo ABC N=42 (27%)	Total N=157
MBC	104 (90)	41 (98)	145 (92)
ULABC	11 (10)	1 (2)	12 (8)
<b>Age (years) at diagnosis of ABC</b>			
Median (Min;Max)	58 (31;84)	55 (30;87)	57 (30;88)
<b>TNM stage at EBC diagnosis, n (%)</b>			
I	19 (17)		19 (17)
II	57 (50)	NA	57 (50)
III	34 (29)		34 (29)
UK	5 (4)		5 (4)
<b>Time to recurrence, n (%)</b>			
0-12 mo	10 (9)		10 (9)
12-24 mo	45 (39)	NA	45 (39)
24-36 mo	15 (13)		15 (13)
> 36 mo	45 (39)		45 (39)
<b>Time to ABC, mo</b>			
Median (interquartile range)	25 (16;52)	NA	25 (16;52)
<b>Menopausal Status, n (%)</b>			
Postmenopausal	79 (69)	27 (64)	106 (68)
Premenopausal	36 (31)	15 (36)	51 (32)
<b>Family History of BC and/or Ovarian cancer, n (%)</b>			
No	63 (55)	28 (67)	91 (58)
Yes	47 (41)	11 (26)	58 (37)
Unknown	5 (4)	3 (7)	8 (5)
<b>Patients with any Hereditary-risk Genetic test, n (%)</b>			
No	84 (73)	32 (76)	116 (74)
Yes	31 (27)	10 (24)	41 (26)
<b>Most Frequently Mutated Genes only in pts with any genetic test*, n (%)</b>			
BRCA1/2	5/21 (24)	1/7 (14)	6/28 (21)
TP53	6/12 (50)	2/5 (40)	8/17 (47)
<b>Metastatic Lesions**, n (%)</b>			
Bone	37 (32)	12 (29)	49 (31)
Liver	25 (22)	12 (29)	37 (24)
Lung	48 (42)	21 (50)	69 (44)
Lymph nodes	48 (42)	34 (81)	82 (52)
Soft Tissue	16 (14)	3 (7)	19 (12)
CNS	18 (16)	0	18 (16)
<b>N° of different metastatic locations, n (%)</b>			
One	50 (44)	1 (2)	51 (33)
Multiple (2 or 3)	54 (47)	32 (76)	86 (55)
Multiple (>3 to 6)	11 (10)	9 (22)	20 (13)

• 10% TNBC of 1559 pts in database @Apr 2022



	Recurrent BC n=115 (73%)			de novo ABC n=42 (27%)		
Line	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>
n	106	73	52	40	28	16
<b>Pts who reach next line, n (%)</b>	73 (69)	52 (71)	31 (60)	28 (70)	16 (57)	7 (44)
<b>Lost of follow up, n (%)</b>	0	0	0	1 (2)	0	0
<b>Patients ongoing, n (%)</b>	9 (8)	1 (1)	0	4 (10)	3 (11)	0
<b>Deaths, n (%)</b>	24 (23)	20 (28)	21 (40)	7 (8)	9 (32)	9 (56)
<b>Median treatment duration, mo</b>	4	3	2	5	3	3
<b>TTP (mo), median (range)</b>	5 (0-42)	3 (0-23)	3 (0-35)	8 (1-31)	3 (0-22)	4 (0-10)
<b>Median PFS, mo (95% CI)</b>	5 (4-7)	3 (3-4)	3 (2-4)	8 (7-9)	4 (2-5)	4 (1-6)
<b>Median Follow Up, mo (range)</b>		18 (1-61)			19 (2-56)	
<b>Median Survival from ABC, mo (95% CI)</b>		21(14-26)			28(15-32)	



First line in mTNBC: IO

# First line mTNBC: Chemo + IO

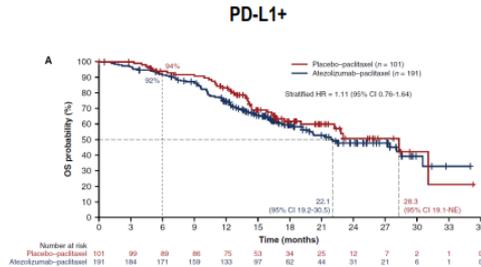
## ATEZOLIZUMAB + NABPACLITAXEL AS 1L: IMPASSION 130

- Metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC
  - Prior (neo)adjuvant chemo allowed if TFI  $\geq 12$  months
- ECOG PS 0-1

### Stratification factors

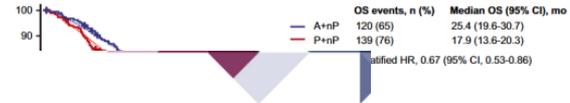
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive  $\geq 1\%$  vs negative  $< 1\%$ )

Co-PFS OS



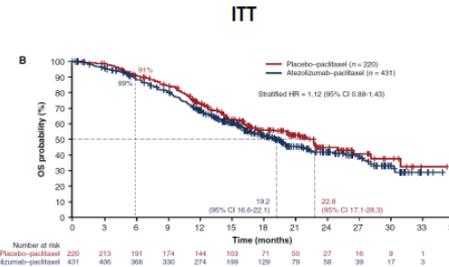
Paclitaxel/placebo: 28.3 months  
Paclitaxel/Atezolizumab: 22.1 months

## IMPASSION130: OS IN PDL1+ (MFU~19 MONTHS; EVENTS~74%)

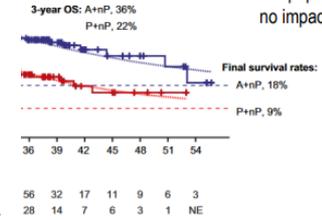


$\Delta$  mOS = 7.5m

ITT population: 18.7 vs 21.0m;  
no impact in PD-L1



Paclitaxel/placebo: 22.8 months  
Paclitaxel/Atezolizumab: 19.2 months



# First line mTNBC: Chemo + IO

## PEMBROLIZUMAB + CT FOR 1L: KEYNOTE 355

### Key Eligibility Criteria

- Age ≥ 18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥ 6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥ 12 weeks from randomization
- Adequate organ function
  - No systemic steroids
  - No active CNS metastases
  - No active autoimmune disease

R  
2:1

Pembrolizumab<sup>a</sup> + Chemotherapy<sup>b</sup>

Placebo<sup>c</sup> + Chemotherapy<sup>b</sup>

Progressive disease<sup>d</sup>/cessation of study therapy

### Stratification Factors:

- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥ 1 vs CPS < 1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

### Primary endpoints:

PFS and OS to be tested according to hierarchical statistical design (CPS ≥ 10 → CPS ≥ 1 → ITT)

<sup>a</sup>Pembrolizumab 200 mg IV q3w;

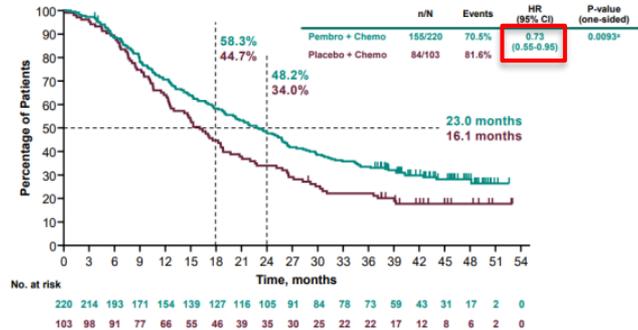
<sup>b</sup>chemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m<sup>2</sup> IV on Days 1, 8, and 15 every 28 days; paclitaxel 90 mg/m<sup>2</sup> IV on Days 1, 8, and 15 every 28 days; gemcitabine 1000 mg/m<sup>2</sup>/carboplatin AUC 2 on Days 1 and 8 every 21 days;

<sup>c</sup>normal saline;

<sup>d</sup>treatment may be continued until confirmation of progressive disease.

Cortes J. et al. Lancet 2020;396(10265):1817-28.

## OVERALL SURVIVAL: PD-L1 CPS ≥ 10



No significant difference in CPS ≥ 1 and ITT

\*Prespecified P value boundary of 0.0113 met.  
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

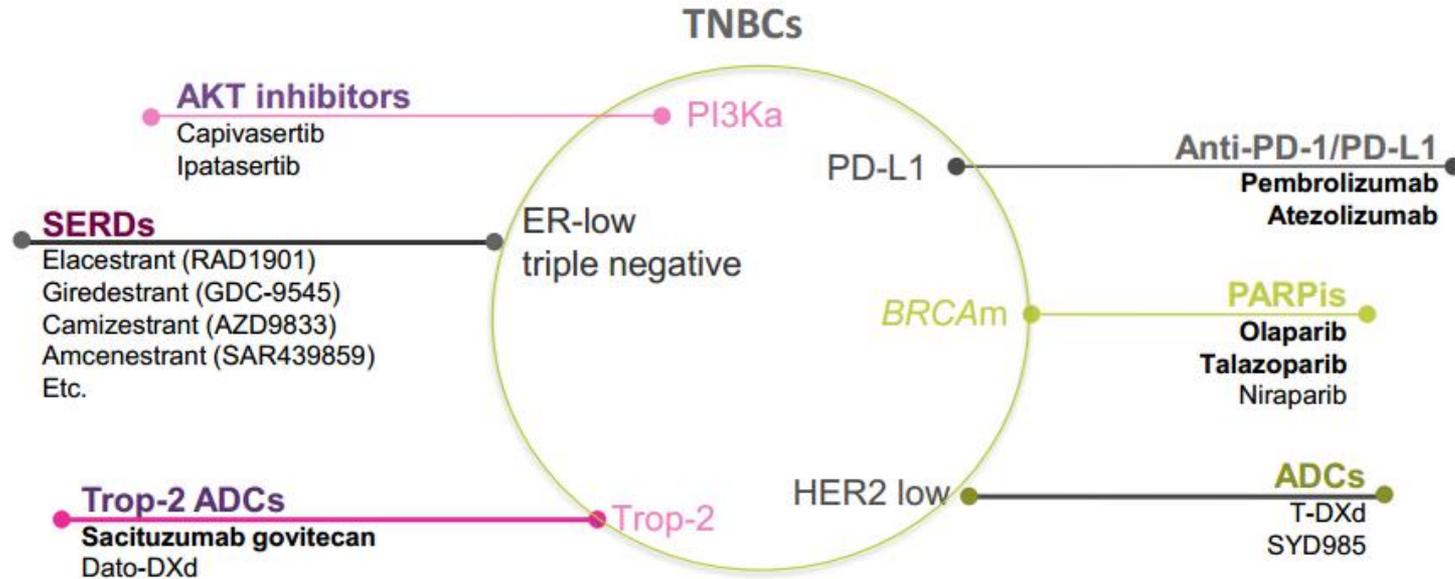
Rugo H. ESMO 2021. By permission of Prof Hope S. Rugo.

“Standar” for 30-40% mTNBC



Do we have a standard after the first line?

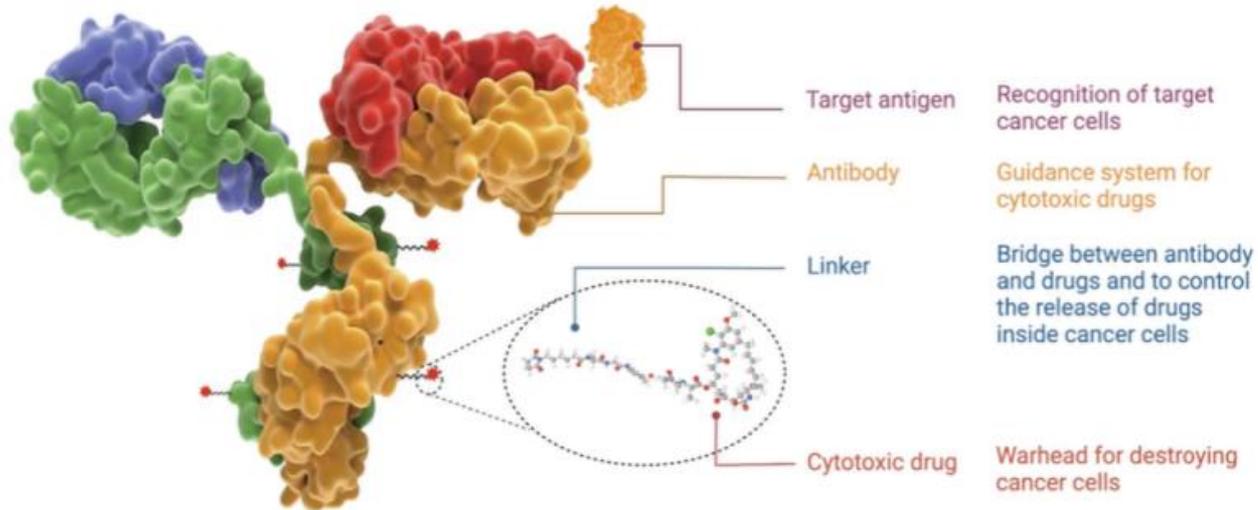
# New drugs in mTNBC



Therapies in bold have been approved for the treatment of TNBC.

ADC=antibody-drug conjugate; AKT= protein kinase B; BRCAm=breast cancer mutation; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; PARPi=poly (ADP-ribose) polymerase inhibitor; PD-L1=programmed death ligand 1; PI3Ka=phosphatidylinositol-4,5-bisphosphate 3-kinase; SERD=selective estrogen receptor degrader; TNBC=triple-negative breast cancer; Trop2=trophoblastic cell surface antigen 2.

## ADCs- Key Components

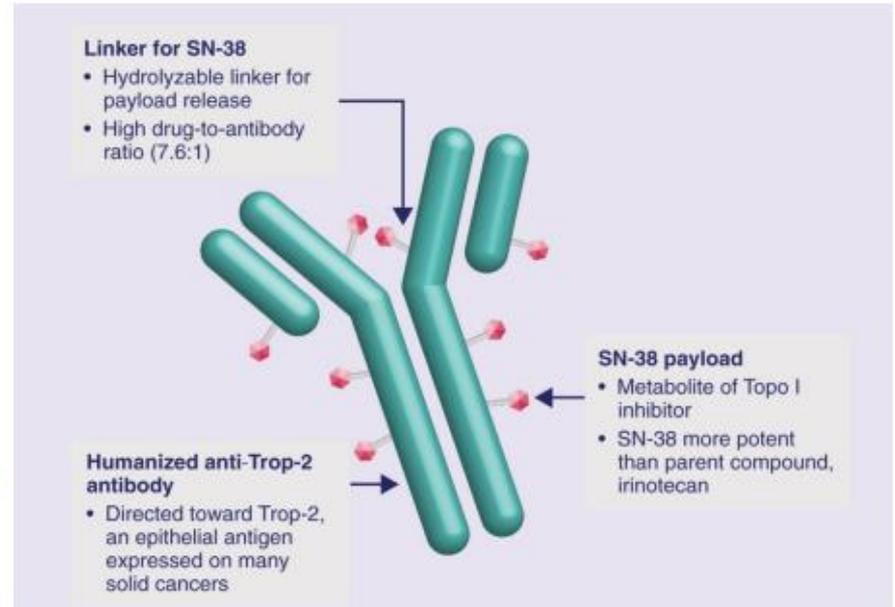


Chau et al. *Lancet* 2019; 394(10200) Fu et al.

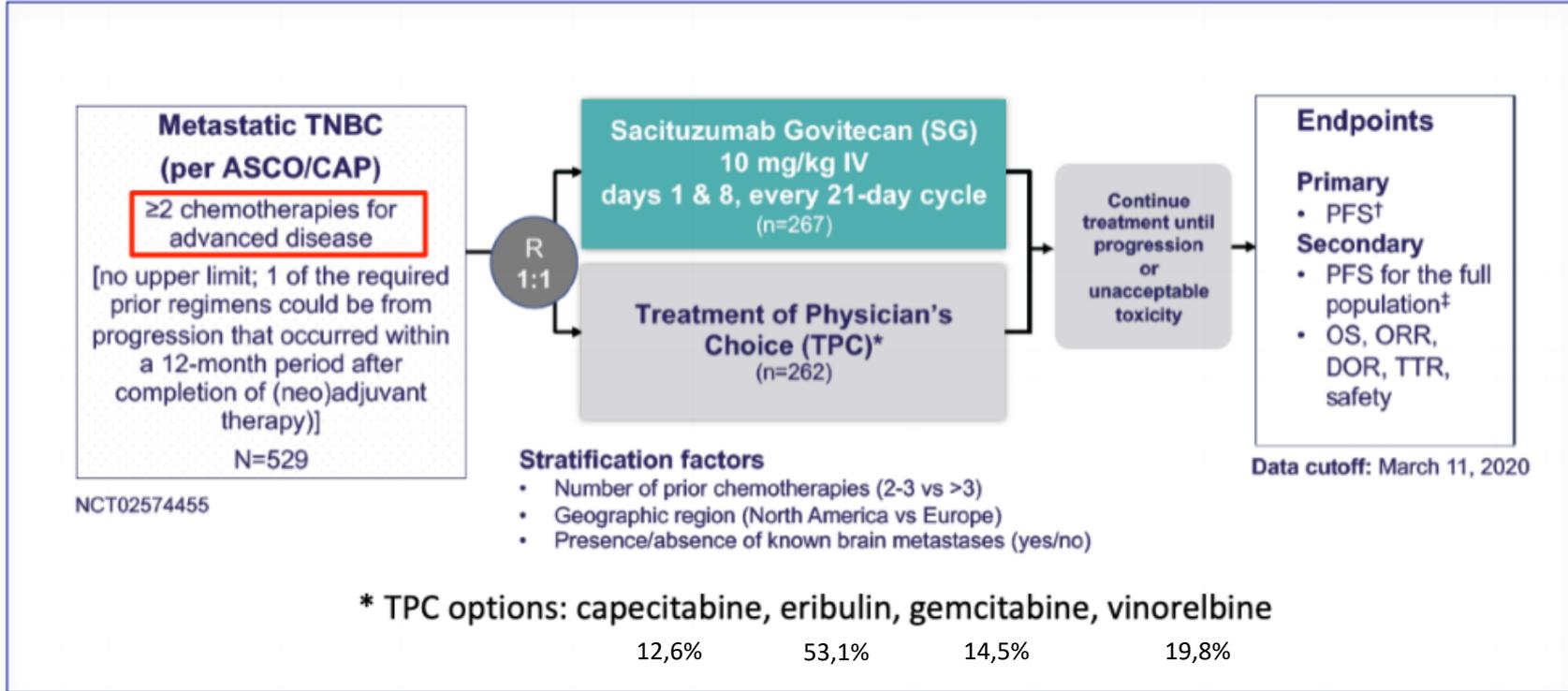
*Signal Transduction and Targeted Therapy* 2022; 7(93)

# SACITUZUMAB GOVITECAN

- Humanised **anti-TROP2** antibody
- TROP2: epithelial antigen highly expressed on most epithelial cancers, including TNBC; minimal expression in normal tissues
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.6:1)
  
- Payload: SN-38, topoisomerase I inhibitor (active metabolite of irinotecan; 100–1000-fold more potent)
- Sacituzumab govitecan delivers SN-38 to tumour cells at a much higher level than irinotecan



## Phase 3 ASCENT Trial: Sacituzumab Govitecan vs TPC in mTNBC



# LOS PACIENTES DEL ESTUDIO ASCENT ERAN COMPARABLES A LOS OBSERVADOS EN LA PRÁCTICA CLÍNICA HABITUAL<sup>1</sup>

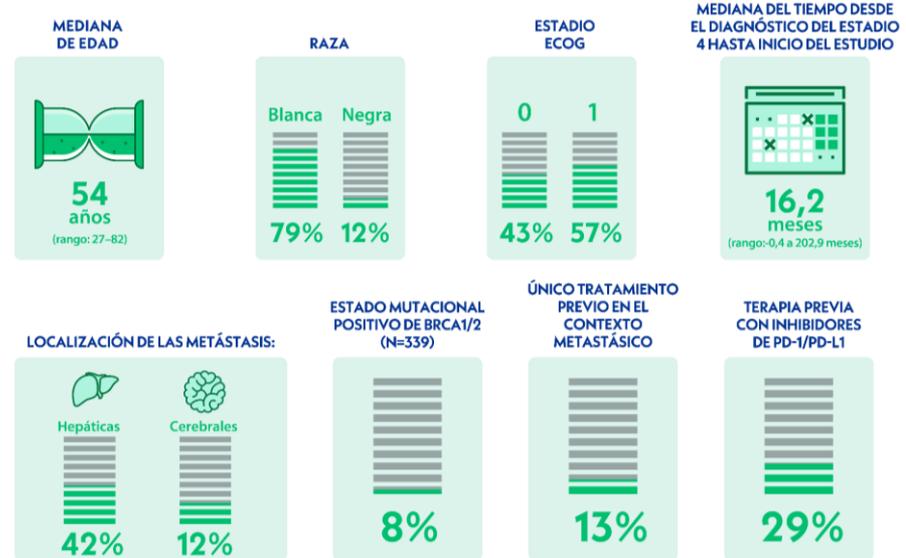
## Características de la población general (n=529)<sup>2</sup>

Characteristic	Sacituzumab Govitecan (N=235)	Chemotherapy (N=233) <sup>†</sup>
Sex — no. (%)		
Female	233 (99)	233 (100)
Male	2 (1)	0
Median age (range) — yr	54 (29–82)	53 (27–81)
Race or ethnic group — no. (%) <sup>‡</sup>		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG performance-status score at screening — no. (%) <sup>§</sup>		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
Germline BRCA1 or BRCA2 mutation status — no. (%) <sup>¶</sup>		
Negative	133 (57)	125 (54)
Positive <sup>  </sup>	16 (7)	18 (8)
Triple-negative breast cancer at initial diagnosis — no. (%)		
Yes	165 (70)	157 (67)
No <sup>**</sup>	70 (30)	76 (33)
Median time from diagnosis of metastatic disease to enrollment (range) — mo <sup>††</sup>	15.8 (0–202.9)	15.2 (0–140.1)
Major tumor locations — no. (%) <sup>‡‡</sup>		
Lung	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Axillary lymph nodes	57 (24)	73 (31)
Bone <sup>§§</sup>	48 (20)	55 (24)
Median no. of previous anticancer regimens (range) <sup>¶¶</sup>	3 (1–16)	3 (1–12)
Previous chemotherapy regimens — no. (%)		
2 or 3	166 (71)	164 (70)
>3	69 (29)	69 (30)
Previous chemotherapy drugs — no. (%) <sup>   </sup>		
Taxanes	235 (100)	233 (100)
Anthracyclines	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous use of PARP inhibitors — no. (%)	17 (7)	18 (8)
Previous use of PD-1 or PD-L1 inhibitors — no. (%)	67 (29)	60 (26)

<sup>a</sup> PARP denotes poly(adenosine diphosphate-ribose) polymerase, PD-1 programmed death 1, and PD-L1 programmed death ligand 1.

<sup>†</sup> The chemotherapy group included patients randomly assigned to receive eribulin (126 patients), vinorelbine (47), capecitabine (31), and gemcitabine (29).

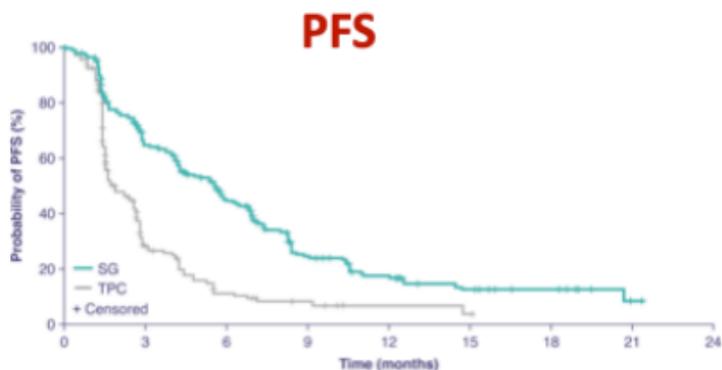
<sup>‡</sup> Race was reported by the patients.



BRCA: gen del cáncer de mama; ECOG: Eastern Cooperative Oncology Group.

1. CADTH. CADTH Reimbursement Review of Sacituzumab Govitecan (Trodelvy). Disponible en: <https://www.canjhealthtechnol.ca/index.php/cjht/article/view/pc0254r/619>. Último acceso: mayo 2023. 2. Ficha técnica de TRODELVY. Febrero 2023. Disponible en: [https://fjileadspain.com/files/Repositorio/57/FT\\_Trodelvy\\_publicidad.pdf](https://fjileadspain.com/files/Repositorio/57/FT_Trodelvy_publicidad.pdf).

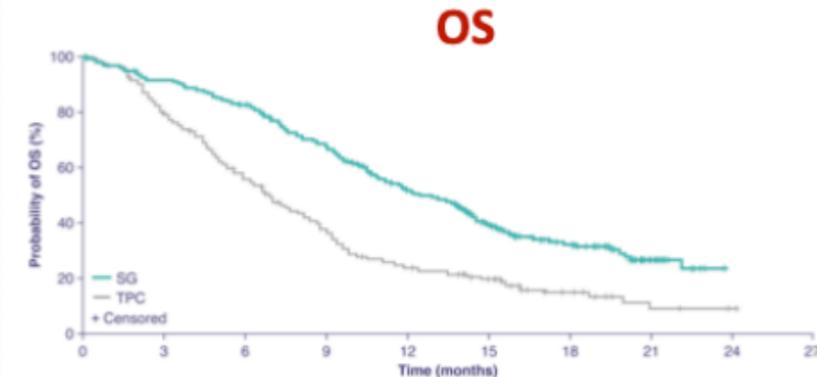
## Sacituzumab Govitecan (SG): PFS and OS



Number of patients at risk

Time (months)	0	3	6	9	12	15	18	21	24															
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	0

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

Time (months)	0	3	6	9	12	15	18	21	24	27																
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

	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	

Sacituzumab approved for metastatic TNBC with at least one line of prior Tx

## ASCENT STUDY: SAFETY

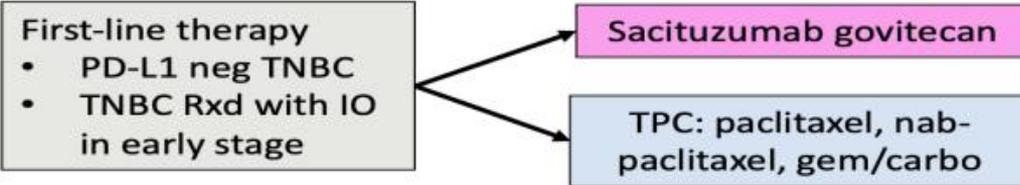
Summary of treatment-related adverse events in the safety population

	Sacituzumab-govitecan			Chemotherapy		
	Any G	G3	G4	Any G	G3	G4
Neutropenia	63%	34%	17%	43%	20%	13%
Anemia	34%	8%	0	24%	5%	0
Leukopenia	16%	9%	1%	11%	4%	1%
Thrombocytopenia	5%	1%	1%	11%	1%	0
Febrile neutropenia	6%	5%	1%	2%	2%	<1%
Diarrhea	59%	10%	0	12%	<1%	0
Nausea	57%	2%	<1%	26%	<1%	0
Vomiting	29%	1%	<1%	10%	<1%	0
Fatigue	45%	3%	0	30%	5%	0
Alopecia	46%	0	0	16%	0	0

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

## ASCENT-03 (NCT05382299): PD-L1 negative

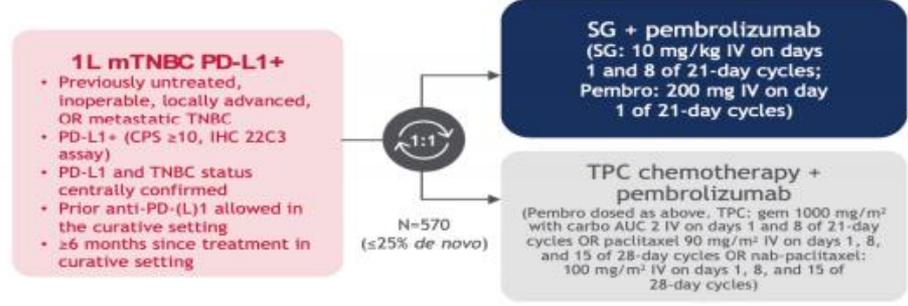
N=540



1<sup>st</sup>L

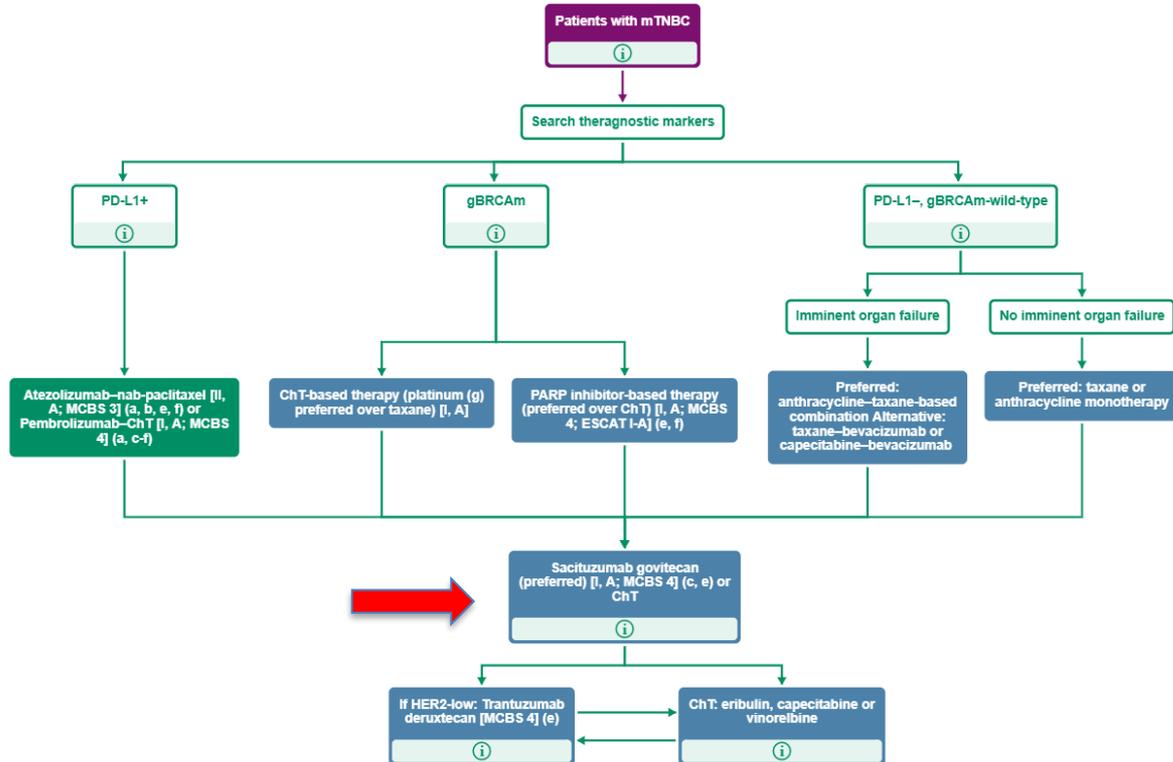
## ASCENT-04 (NCT05382286): PD-L1 positive

N=570



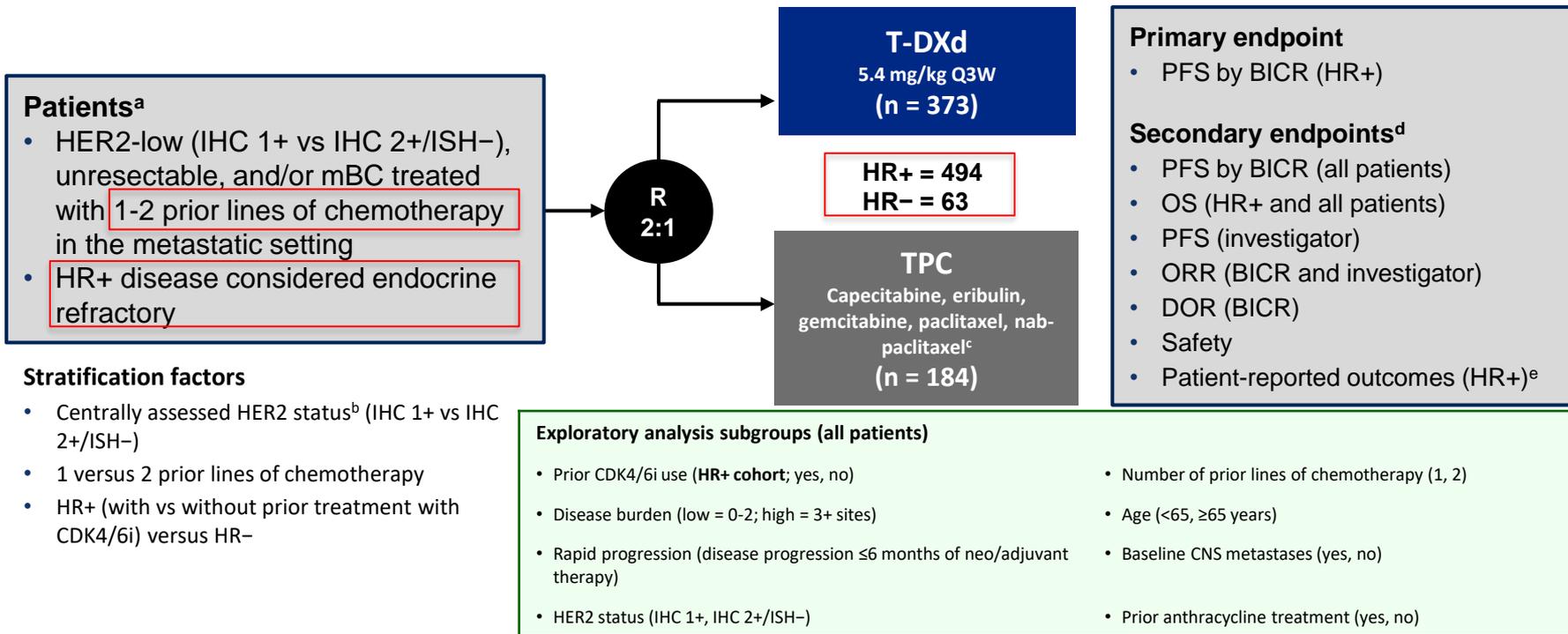
# ESMO guidelines

v1.1 - May 2023



# DESTINY-Breast04

An open-label, multicenter, phase 3 study (NCT03734029)<sup>1-3</sup>

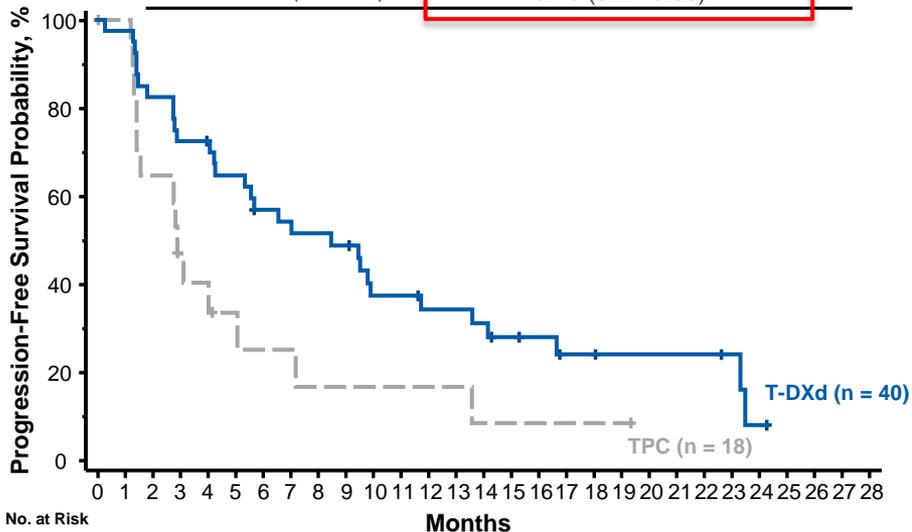


<sup>a</sup>If patients had HR+ mBC, prior endocrine therapy was required. <sup>b</sup>Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. <sup>c</sup>TPC was administered according to the label. <sup>d</sup>Efficacy in the HR- cohort was an exploratory endpoint. <sup>e</sup>The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

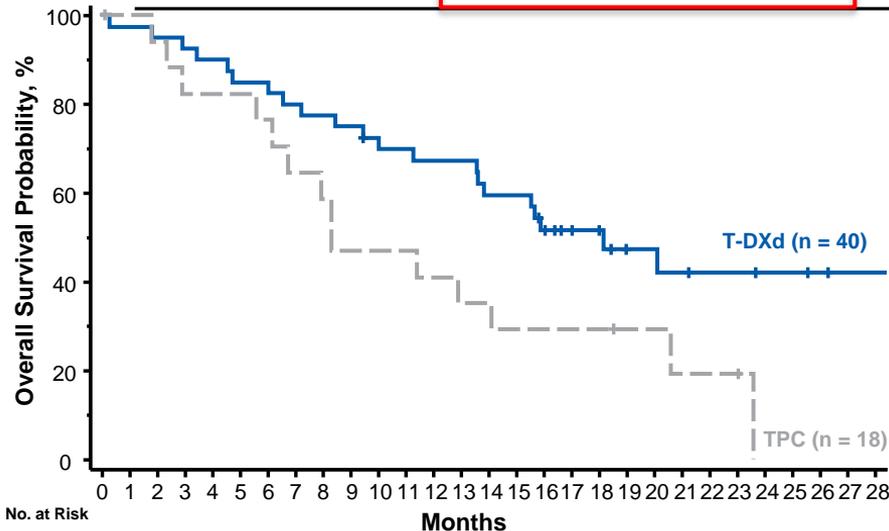
1. Modi S et al. *N Engl J Med.* 2022;387(1):9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

# Exploratory endpoints: PFS and OS in HR-

	PFS in hormone receptor-negative	
	T-DXd (n = 40)	TPC (n = 18)
mPFS (95% CI), mo	8.5 (4.3-11.7)	2.9 (1.4-5.1)
Hazard ratio (95% CI)	0.46 (0.24-0.89)	

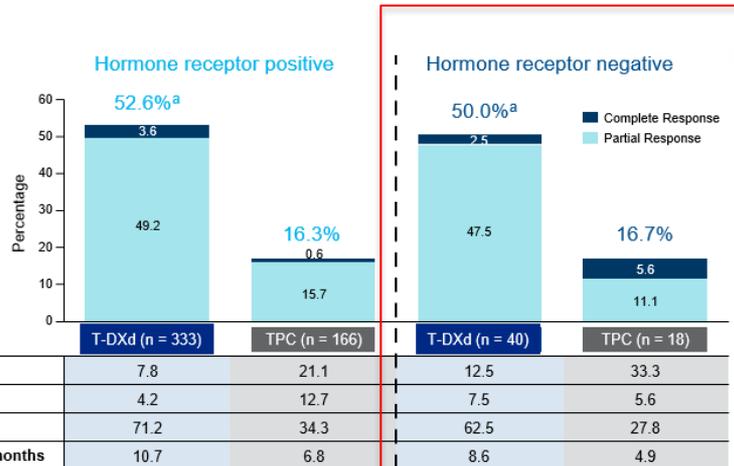
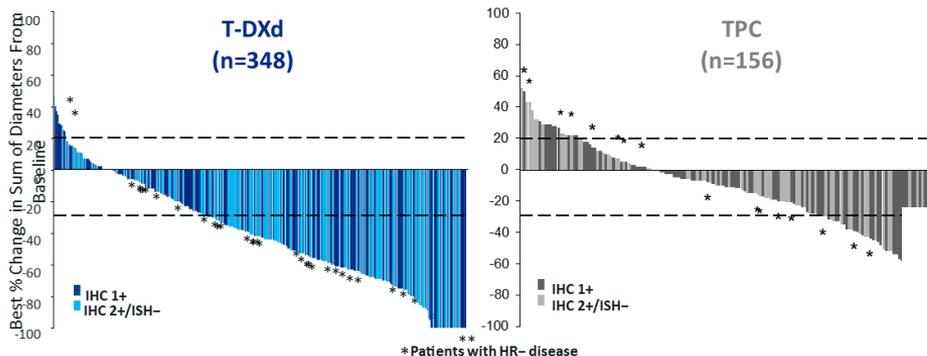


	OS in hormone receptor-negative	
	T-DXd (n = 40)	TPC (n = 18)
mOS (95% CI), mo	18.2 (13.6-NE)	8.3 (5.6-20.6)
Hazard ratio (95% CI)	0.48 (0.24-0.95)	



For efficacy in the hormone receptor negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.  
 Modi S et al. *N Engl J Med.* 2022;387(1):9-20. Supplement.

# Confirmed ORR and best overall response



Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
<b>Clinical benefit rate,<sup>b</sup> %</b>	<b>71.2</b>	<b>34.3</b>	<b>62.5</b>	<b>27.8</b>
<b>Duration of response, months</b>	<b>10.7</b>	<b>6.8</b>	<b>8.6</b>	<b>4.9</b>

<sup>a</sup>Hormone receptor status is based on data from the electronic data capture corrected for misstratification. <sup>b</sup>Analyses of the HR+ cohort and all patients were secondary endpoints; analyses of the HR- cohort were exploratory endpoints. <sup>c</sup>The clinical benefit rate is defined as the sum of complete response, partial response, and more than 6 months' stable disease, based on blinded independent central review.

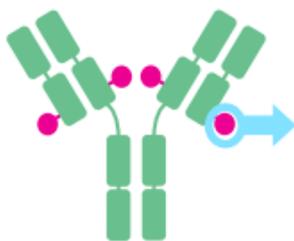
Modi S et al. *N Engl J Med.* 2022;387(1):9-20. [Click here to view CORR from Modi S et al. Presented at American Society of Clinical Oncology \(ASCO\) 2022, June 2022, LBA3](#)

# Datopotamab Deruxtecan (Dato-DXd)

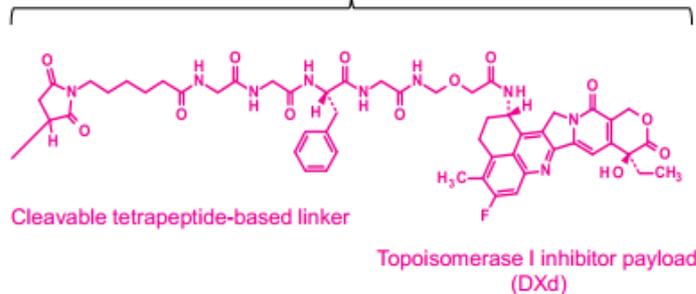
## Dato-DXd is an ADC with 3 components<sup>1,2</sup>:

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

Humanized anti-TROP2  
IgG1 mAb



Deruxtecan<sup>a,4</sup>



Payload mechanism of action:  
topoisomerase I inhibitor<sup>b,1</sup>

High potency of payload<sup>b,2</sup>

Optimized drug to antibody ratio  $\approx 4$ <sup>b,c,1</sup>

Payload with short systemic half-life<sup>b,c,2</sup>

Stable linker-payload<sup>b,2</sup>

Tumor-selective cleavable linker<sup>b,2</sup>

Bystander antitumor effect<sup>b,2,5</sup>

<sup>a</sup> Image is for illustrative purposes only; actual drug positions may vary. <sup>b</sup> The clinical relevance of these features is under investigation. <sup>c</sup> 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](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.

# Dato-DXd: TROPION-PanTumor01 TNBC Cohort<sup>1</sup>

- Advanced/metastatic HR-/HER2-negative breast cancer (TNBC)<sup>a</sup>
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression<sup>b</sup>
- Measurable disease (per RECIST version 1.1)

Dato-DXd  
6mg/kg IV Q3W

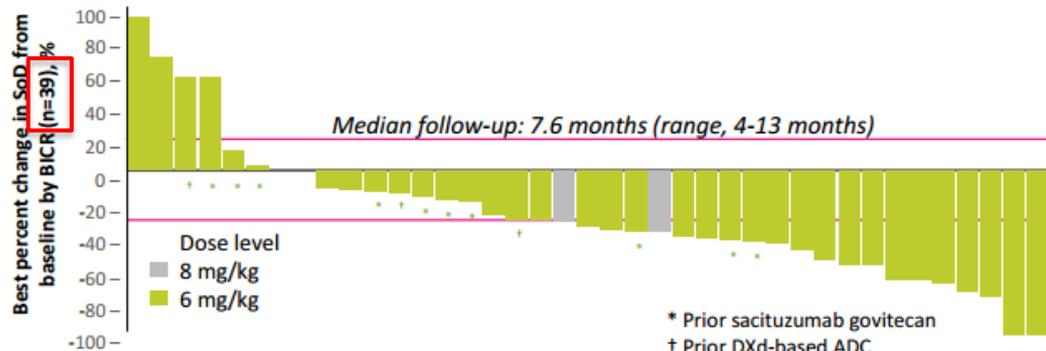
2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

Primary objectives include:

- Safety, Tolerability

Secondary objectives include:

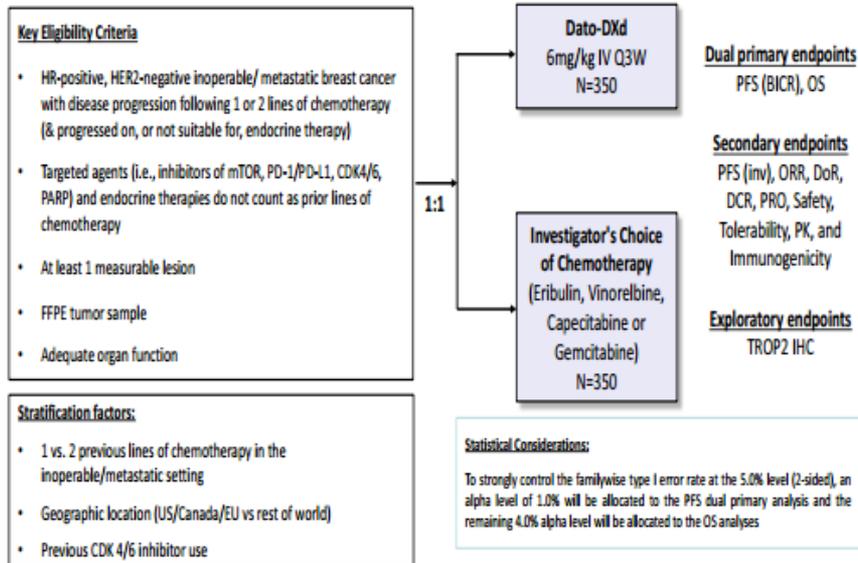
- Efficacy, Pharmacokinetics



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

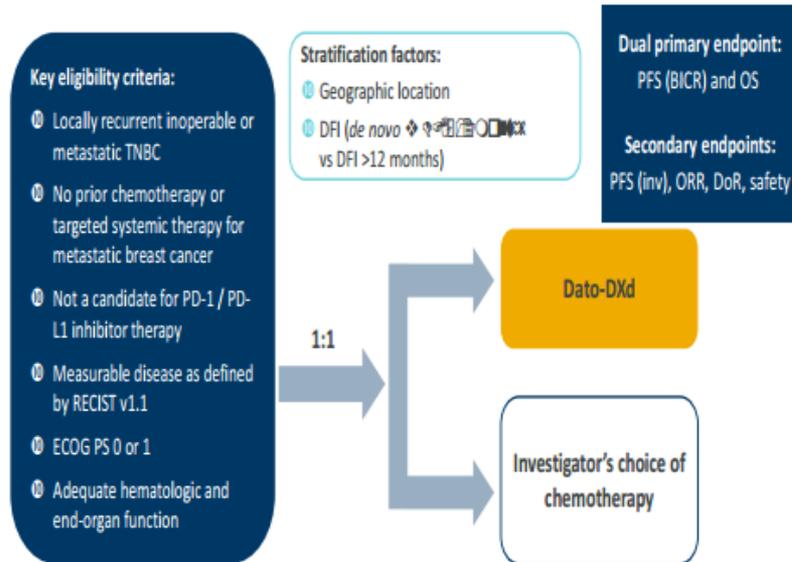
# TROPION-Breast01

## NCT05104866



# TROPION-Breast02

## NCT05374512



Response assessment: Scan Q6W for 48 weeks, then Q9W until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per imaging schedule.

- 2<sup>nd</sup>-3<sup>rd</sup> line therapy for HR+/HER2- mBC
- Completed accrual

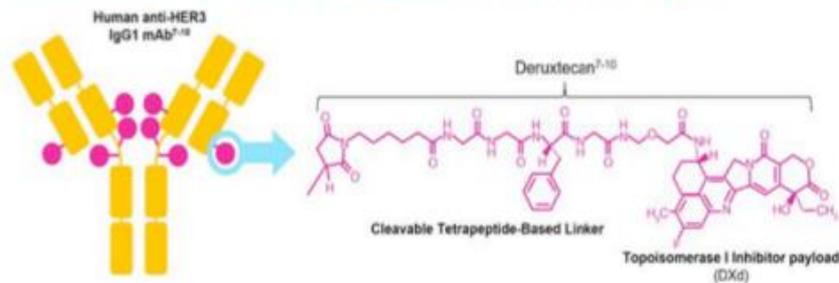
- 1st line therapy for TNBC
- PD-L1 negative

## Patritumab Deruxtecan(U3-1402): a HER3-directed ADC

High HER3 expression measured by immunohistochemistry has been observed in several studies:

Tumor type	% high HER3 expression by IHC
Pancreatic	41
Breast	43, 18
Colorectal	17, 70, 21
Gastric	59, 34
Melanoma	65
Ovary	53
Head and neck	9
Cervix	56

### Structure of HER3-DXd (Antibody-Drug Conjugate)



- humanized anti-HER3 mAB
- topoisomerase 1 inhibitor, exatecan derivative
- tetrapeptide-based cleavable linker

# Clinical activity of her3-DXc across BC subtypes



Outcomes (BICR per RECIST 1.1)	HR+/HER2- (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI) <sup>a</sup>	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, % <sup>b</sup>			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
PFS, median (95% CI), mo	7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)	38.2 (24.2-52.0)	51.6 (22.1-74.8)
OS, median (95% CI), mo	14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

## HER3-DXd demonstrated durable antitumor activity across BC subtypes

- Confirmed ORR for all patients (N=182), 28.6% (95% CI, 22.1%-35.7%); median DOR, 7.0 mo (95% CI, 5.5-8.5 months)

CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

<sup>a</sup>95% exact binomial confidence interval (by Clopper-Pearson method).

<sup>b</sup>No patients had a CR.

7

ORR and CBR were not higher for patients with HER3 expression  $\geq 75\%$  compared with patients with HER3 expression 25% to 74%.

### Response Summary Irrespective of HER3 Membrane Expression

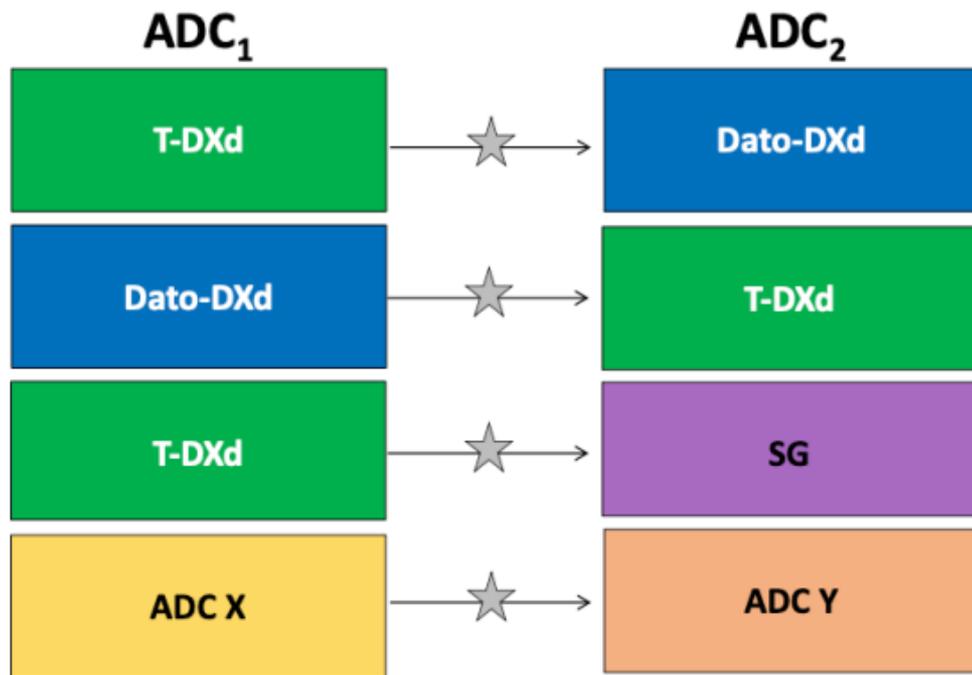
	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	12 (41.4)	4 (21.1)
95% CI	(23.5, 61.1)	(6.1, 45.6)

Krop et al, ASCO 2022

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ORR, overall response rate.

Data cutoff: September 6, 2022

# Will Need to Understand Sequencing of ADCs



Need comparison and sequencing studies

# Sequential Use of Antibody-Drug Conjugate after Antibody-Drug Conjugate for Patients with Metastatic Breast Cancer: ADC after ADC (A3) study

Rachel O. Abelman<sup>1</sup>, Laura M. Spring<sup>1</sup>, Geoffrey Feil<sup>1</sup>, Phoebe K Ryan<sup>1</sup>, Neelima Vidula<sup>1</sup>, Seth Wander<sup>1</sup>, Arielle J. Medford<sup>1</sup>, Jennifer Shin<sup>1</sup>, Elizabeth Abraham<sup>1</sup>, Steven J. Isakoff<sup>1</sup>, Beverly Moy<sup>1</sup>, Leif W. Ellisen<sup>1</sup>, Aditya Bardia<sup>1</sup>  
<sup>1</sup>Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; <sup>2</sup>Dana Farber Cancer Institute, Harvard Medical School, Boston, MA



## BACKGROUND

- Antibody-drug conjugates (ADCs) allow antibody-directed delivery of chemotherapy, improving efficacy and toxicity compared to standard chemotherapy.
- The recent approvals of sacituzumab govitecan (SG) for HR+/HER2- and triple negative metastatic breast cancer (MBC) and trastuzumab deruxtecan (T-DXd) for HER2-low MBC make many patients candidates for more than one ADC.
- Optimal sequencing is uncertain given potential for cross-resistance based on antibody target or payload (Coates et al., Cancer Discov. 2021).
- This study evaluated the efficacy and safety of patients with HER2-negative MBC who received ADC after ADC.

## METHODS

- All patients were treated with 2+ ADCs for MBC at a single academic institution (HR+/HER2-, TNBC). HER2+ (amplified) MBC was not included. T-DM1 was not counted as an ADC.
- "Cross-resistance" was defined as progressive disease at/before first restaging on second ADC.
- PFS estimation was done using the Kaplan-Meier estimator.
- Pairwise comparisons were performed using a Wilcoxon Rank Sum test.
- Significance was declared as a type I error less than 0.05.

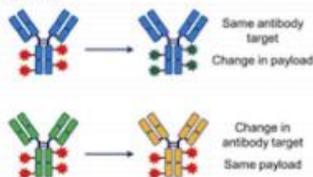
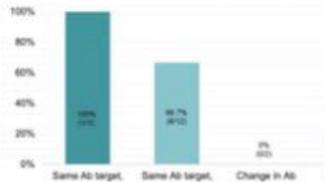


Table 1: Demographics

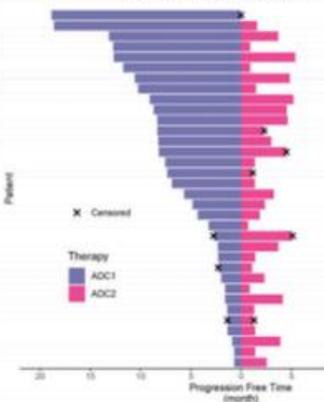
MBC patients treated with ADCs	193
Multiple ADCs	35
Breast cancer subtype	
HR+/HER2-	15 (42.9%)
TNBC	20 (57.1%)
HER2-low	24 (68.6%)
Median age at second ADC	56 years
Median prior lines of treatment	
HR+/HER2-	7
TNBC	3
Antibody target of ADC1	
HER2	8 (22.9%)
Trop2	26 (74.3%)
Other	1 (2.9%)
Antibody target of ADC2	
HER2	14 (40.0%)
Trop2	19 (54.3%)
Other	2 (5.7%)
Payload of ADC1	
Topoisomerase-I inhibitor	35 (100%)
Microtubule inhibitor	0
Other	0
Payload of ADC2	
Topoisomerase-I inhibitor	31 (88.6%)
Microtubule inhibitor	2 (5.7%)
Other	2 (5.7%)

## RESULTS

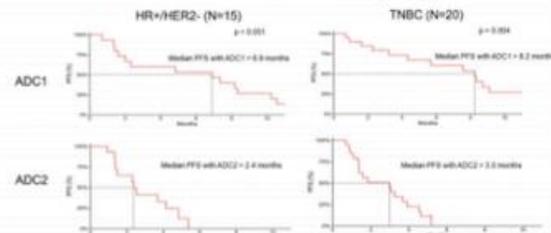
Cross-Resistance with ADC1 vs. ADC2



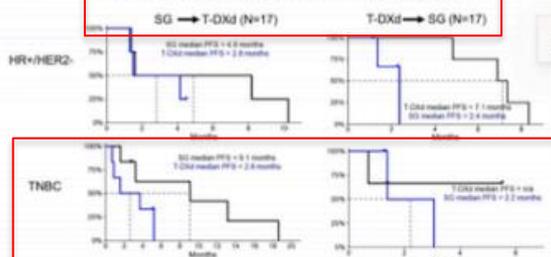
PFS with ADC1 vs. ADC2



PFS with ADC1 vs. ADC2, by Subtype



PFS with T-DXd after SG (and vice-versa), by Subtype

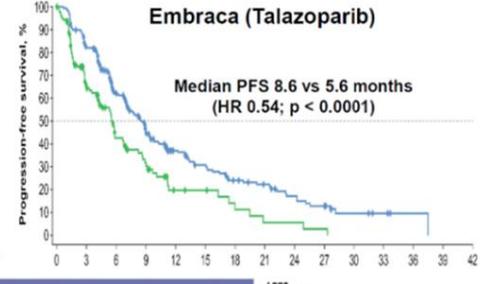
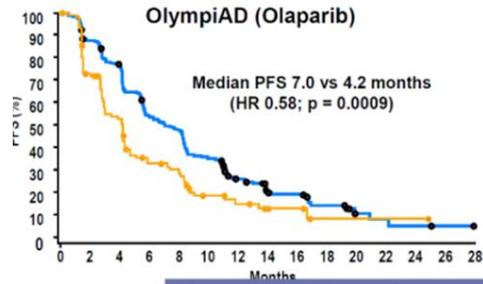
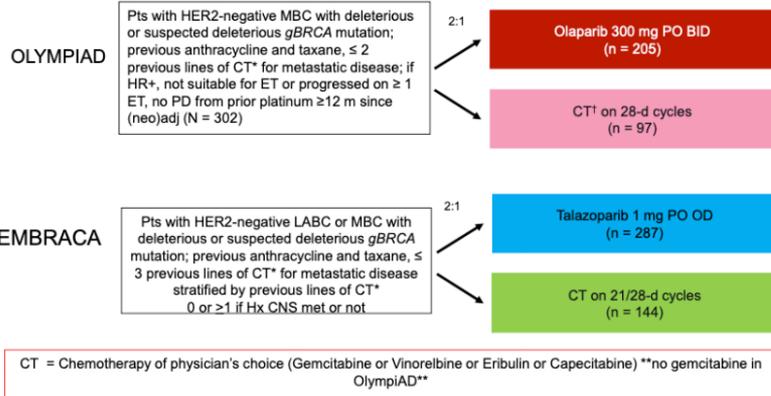


## CONCLUSIONS AND FUTURE DIRECTIONS

- Optimal sequencing of ADCs is an unmet clinical need that is growing in importance as more therapies are approved for a wider population.
- A subset of patients had cross-resistance at first restaging. Others had durable responses, particularly if a different tumor-associated antigen was targeted.
- Further research is needed to validate these findings and determine mechanisms of resistance to guide optimal ADC sequencing.

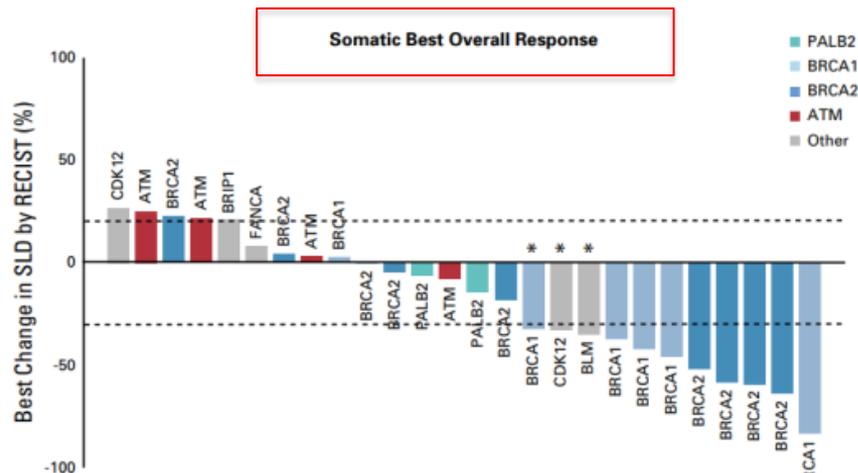
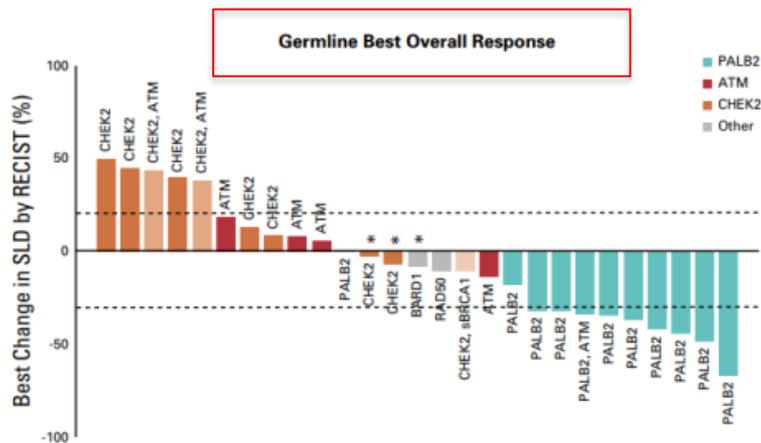
# PARP inhibitors

## PARP inhibitors in aTNBC



Response rates	Olympia	Embraca
PARPi	60%	62.6%
Chemo	29%	27.2%

# Efficacy of PARP inhibitors in patients with somatic BRCA1/2 alterations or PALB2 mutations



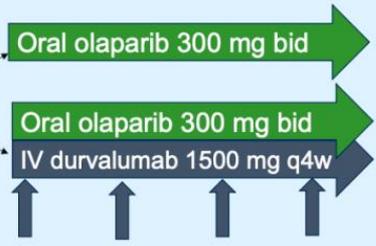
# DORA maintenance trial design



- Inoperable locally advanced or metastatic TNBC<sup>a</sup>
- Investigator-assessed clinical benefit after 1st- or 2nd-line platinum-based therapy<sup>b</sup>
- No prior PARPi or anti-PD-(L)1 therapy
- No known active CNS metastasis

Mandatory blood and tissue banking (archival or fresh biopsy)

R  
A  
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Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal

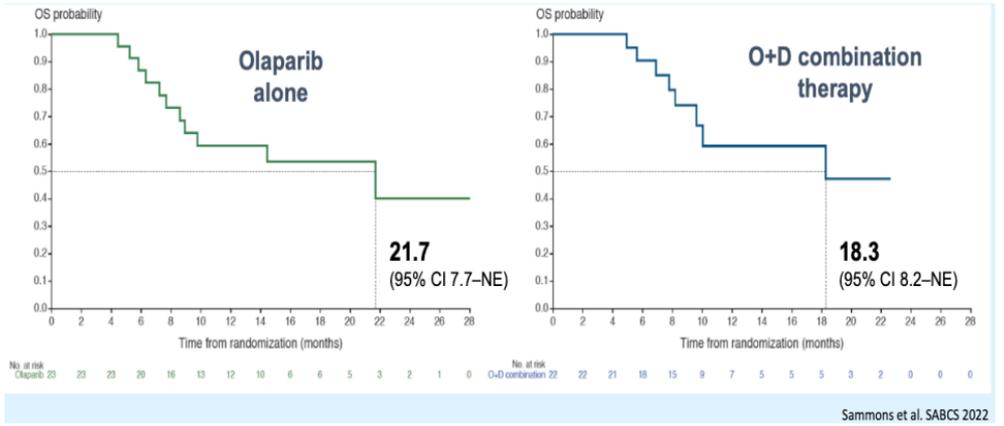
Optional progression biopsy tissue banking

- Stratification factors:
- Line of chemotherapy
  - Study site

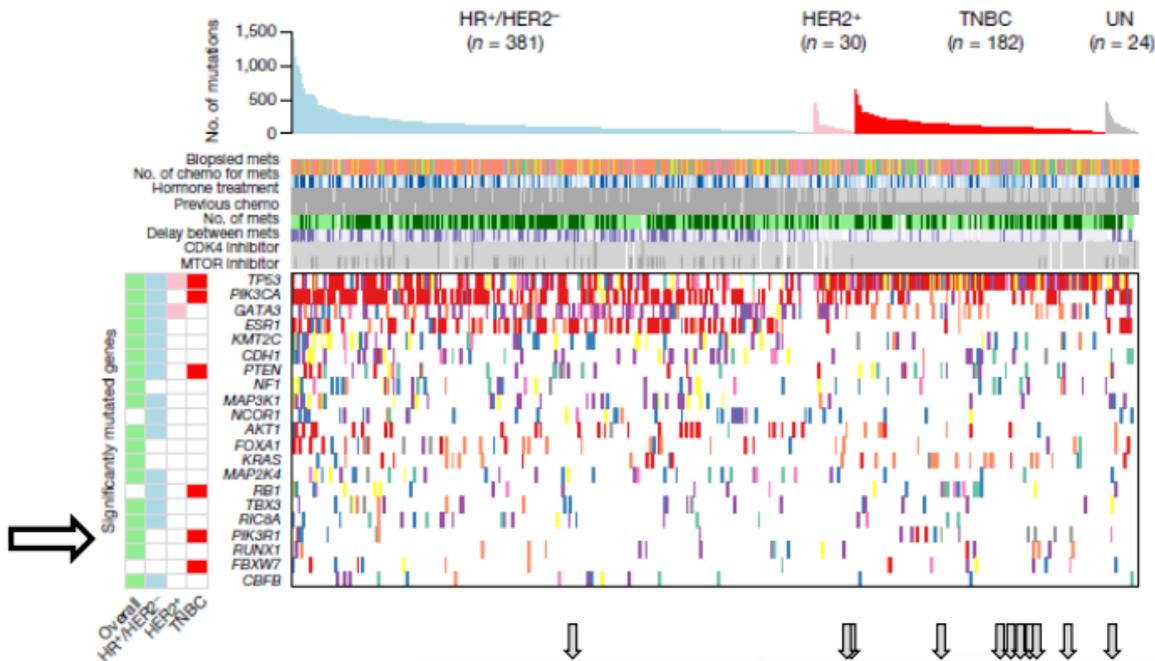
<sup>a</sup>bid = twice daily; <sup>b</sup>IV = intravenous; <sup>c</sup>q4w = every 4 weeks.  
<sup>a</sup>Enrollment of known gBRCA carriers was limited to 10 patients. <sup>b</sup>At least three 3-weekly cycles or at least six weekly cycles.

## EC-DORA: Overall survival

Sammons et al. SABCs 2022



# Mutations in the regulatory subunit of PI3K (PIK3R1)



Bertucci, Nature, 2019

**PIK3R1 mutation in TNBC samples**  
**82% cases = the alteration affects PIK3CA interaction**



# AKT inhibitors in patients with TNBC

Trial (NCT identifier)	Phase	Disease setting	Breast cancer subtype	Line of therapy	Patients with TNBC (n)	Treatment	Results in patients with TNBC	Refs
<i>AKT inhibitors</i>								
PAKT (NCT02423603)	II	Metastatic	TNBC	First	140	Paclitaxel plus either capivasertib or placebo	PFS in ITT: HR 0.74, 95% CI 0.50–1.08 (one-sided $P=0.06$ ); PFS in patients with <i>PIK3CA/AKT1/PTEN</i> alterations: HR 0.30, 95% CI 0.11–0.79 ( $P=0.01$ ); mPFS in ITT: 5.9 mo vs 4.2 mo; mPFS in patients with <i>PIK3CA/AKT1/PTEN</i> alterations: 9.2 mo vs 3.7 mo	<sup>110</sup>
LOTUS (NCT02162719)	II	Metastatic	TNBC	First	166	Paclitaxel plus either ipatasertib or placebo	PFS in ITT: HR 0.60, 95% CI 0.37–0.98 ( $P=0.04$ ); PFS in patients with <i>PTEN</i> <sup>low</sup> tumours: HR 0.59, 95% CI 0.26–1.32 ( $P=0.18$ ); mPFS in ITT: 6.2 mo vs 4.9 mo; mPFS in patients with <i>PTEN</i> <sup>low</sup> tumours: 6.2 mo vs 3.7 mo	<sup>109</sup>
IPATunity130 (NCT03337724)	III	Metastatic	TNBC (with <i>PIK3CA/AKT1/PTEN</i> alterations)	First	255	Paclitaxel plus either ipatasertib or placebo	PFS: HR 1.02, 95% CI 0.71–1.45 ( $P=0.92$ ); mPFS: 7.4 mo vs 6.1 mo ORR: 39% vs 35%	<sup>105</sup>
FAIRLANE (NCT02301988)	II	Early stage (I–II)	TNBC	Neoadjuvant	151	Paclitaxel plus either ipatasertib or placebo	pCR rate in ITT: 17% vs 13%; pCR rate in patients with <i>PTEN</i> <sup>low</sup> tumours: 16% vs 13%; pCR rate in patients with <i>PIK3CA/AKT1/PTEN</i> alterations: 18% vs 12%	<sup>111</sup>

**No validation of the efficacy in phase III trial so far**

# ¿Tenemos un estándar más allá de la primera línea en cáncer de mama metastásico TN?



- Sacituzumab Govitecan es el fármaco que ha demostrado una evidencia más robusta con beneficio en PFS y OS en pacientes pretratadas con CMM TN (ASCENT).
- T-DXd ha demostrado actividad en pacientes HER2 low con RH negativos (DestinyB-04).
- Otros ADCs (anti-TROP2, antiHER3) presentan una actividad prometedora:
  - Datopotamab-deruxtecan (TROPION).
  - Patritumab-deruxtecan.
- Necesidad de estudiar las secuencias.
- Alt en PIK3CA/AKT muy frecuentes en TNBC → Estudios FIII con inh AKT: negativos (capivasertib, ipatasertib).
- iPARP: actividad en mutaciones somáticas BRCA 1/2 y gPALB2.
- Quimioterapia: Platinos, Eribulina, +Bevacizumab.....

Muchas gracias 

[sdelacrs@navarra.es](mailto:sdelacrs@navarra.es)