RAGMA 23

16ª Revisión Anual GEICAM de Avances en Cáncer de Mama

Realidades y esperanzas

Enfermedad triple negativa metastásica

Cristina Reboredo Rendo

Complexo Hospitalario Universitario A Coruña

Organizado por:

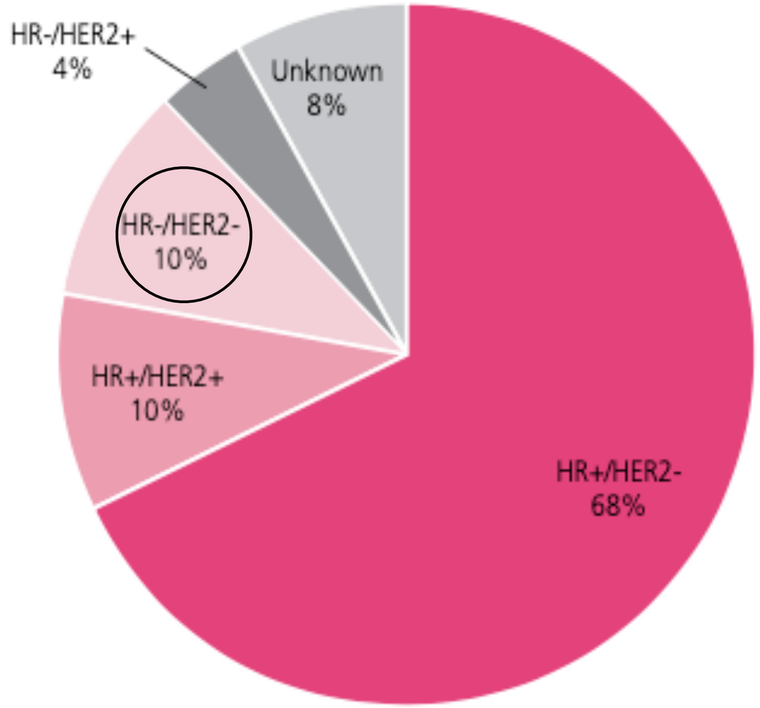
GEICAM investigación en cáncer de mama

Summary

Introduction

Epidemiology

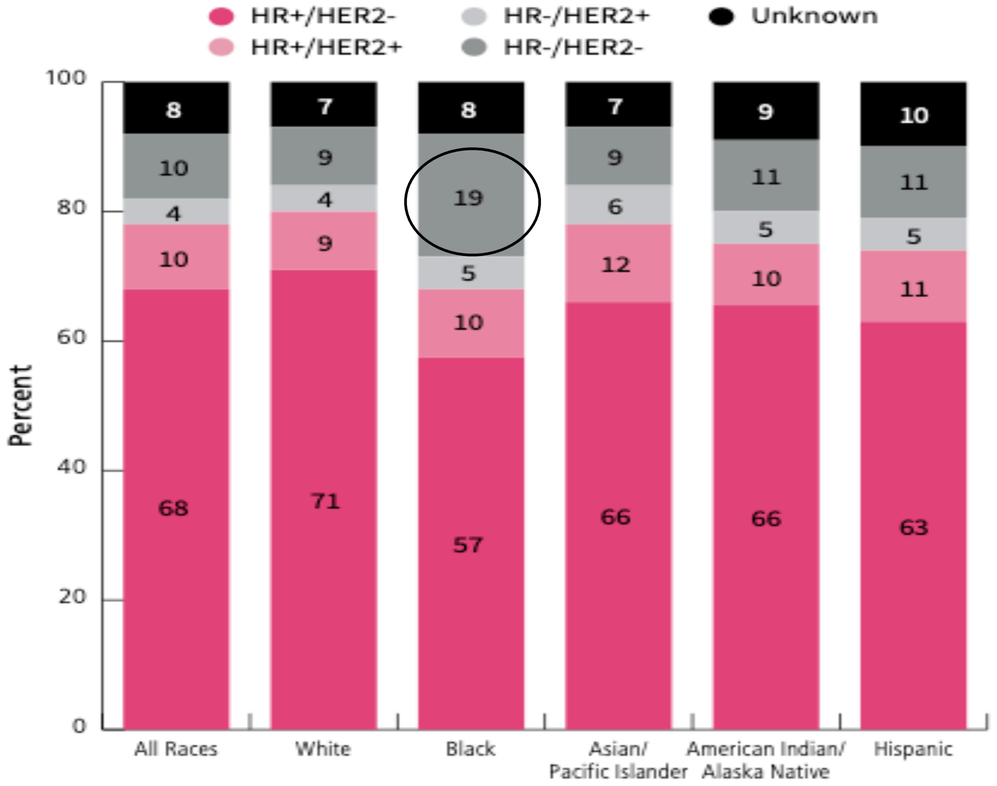
Figure 1. Distribution of Female Breast Cancer Subtypes, US, 2015-2019



HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

Source: North American Association of Central Cancer Registries (NAACCR), 2022.

Figure 4. Distribution of Breast Cancer Subtypes by Race/Ethnicity, Ages 20 and Older, US 2015-2019



HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.
Note: Except for all races, race is exclusive of Hispanic origin. Data for American Indians/Alaska Natives are based on Purchased/Referred Care Delivery Area (PRCDA) counties.

Source: NAACCR, 2022.

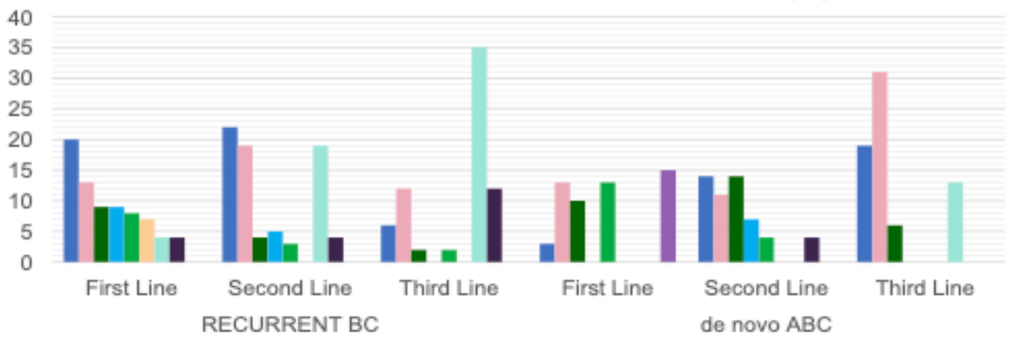
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf

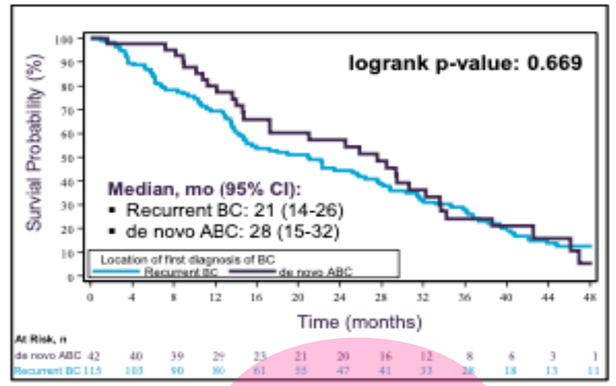
Epidemiology

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)
Age (years) at diagnosis of ABC			
Median (Min;Max)	58 (31;84)	55 (30;87)	57 (30;88)
TNM stage at EBC diagnosis, n (%)			
I	19 (17)	NA	19 (17)
II	57 (50)		57 (50)
III	34 (29)		34 (29)
UK	5 (4)		5 (4)
Time to recurrence, n (%)			
0-12 mo	10 (9)	NA	10 (9)
12-24 mo	45 (39)		45 (39)
24-36 mo	15 (13)		15 (13)
> 36 mo	45 (39)		45 (39)
Time to ABC, mo			
Median (interquartile range)	25 (16;52)	NA	25 (16;52)
Menopausal Status, n (%)			
Postmenopausal	79 (69)	27 (64)	106 (68)
Premenopausal	36 (31)	15 (36)	51 (32)
Family History of BC and/or Ovarian cancer, n (%)			
No	63 (55)	28 (67)	91 (58)
Yes	47 (41)	11 (26)	58 (37)
Unknown	5 (4)	3 (7)	8 (5)
Patients with any Hereditary-risk Genetic test, n (%)			
No	84 (73)	32 (76)	116 (74)
Yes	31 (27)	10 (24)	41 (26)
Most Frequently Mutated Genes only in pts with any genetic test*, n (%)			
BRCA1/2	5/21 (24)	1/7 (14)	6/28 (21)
TP53	6/12 (50)	2/5 (40)	8/17 (47)
Metastatic Lesions, n (%)**			
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)
Nº of different metastatic locations, n (%)			
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	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
n	106	73	52	40	28	16
Pts who reach next line, n (%)	73 (69)	52 (71)	31 (60)	28 (70)	16 (57)	7 (44)
Lost of follow up, n (%)	0	0	0	1 (2)	0	0
Patients ongoing, n (%)	9 (8)	1 (1)	0	4 (10)	3 (11)	0
Deaths, n (%)	24 (23)	20 (28)	21 (40)	7 (8)	9 (32)	9 (56)
Median treatment duration, mo	4	3	2	5	3	3
TTP (mo), median (range)	5 (0-42)	3 (0-23)	3 (0-35)	8 (1-31)	3 (0-22)	4 (0-10)
Median PFS, mo (95% CI)	5 (4-7)	3 (3-4)	3 (2-4)	8 (7-9)	4 (2-5)	4 (1-6)
Median Follow Up, mo (range)		18 (1-61)			19 (2-56)	
Median Survival from ABC, mo (95% CI)		21(14-26)			28(15-32)	

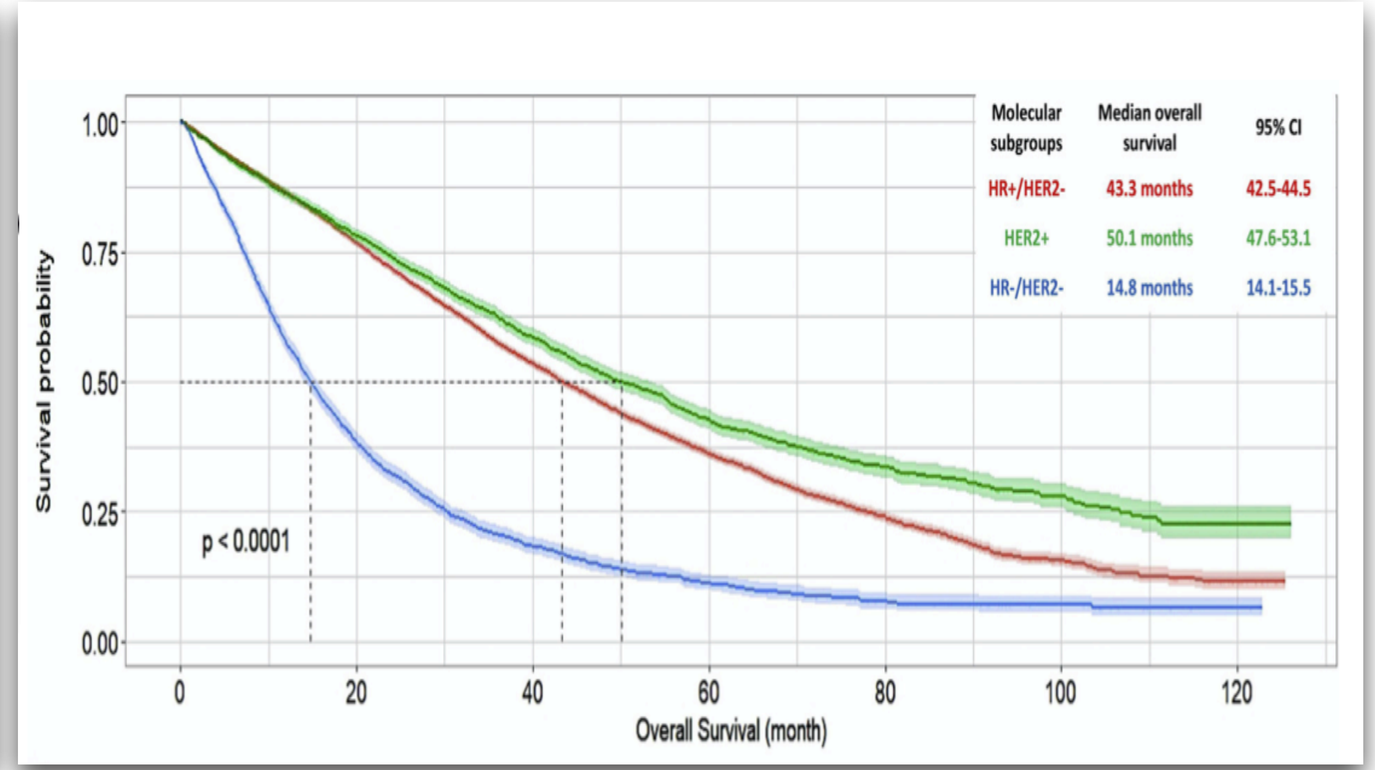
SABCS 2022. Dra. Silvia Antolín

Prognostic

5-Year Relative Survival Percent, Female Breast Subtypes by SEER Combined Summary Stage

Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.1%	31.9%
HR-/HER2-	91.3%	65.8%	12.0%
HR+/HER2+	98.8%	89.3%	46.0%
HR-/HER2+	97.3%	82.8%	38.8%
Unknown	96.1%	76.4%	15.6%
Total	99.1%	86.1%	30.0%

Total 5-year relative survival: TNBC 77.1% (vs 90.6% ALL)

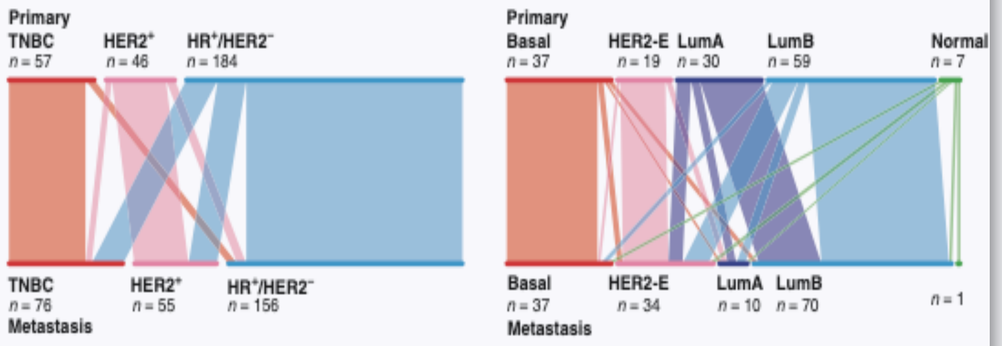


https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf

Caswell-Jin et al ASCO 2022

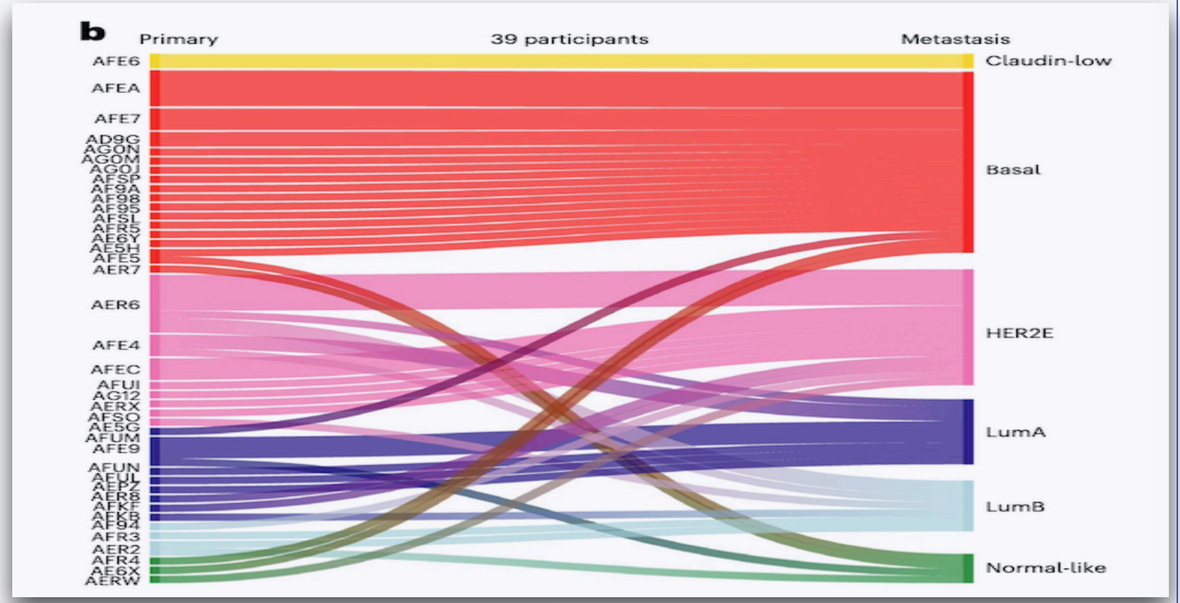
TNBC biology

Subtype (IHC and PAM50_RNAseq) switching @AURORA_EU/BIG



- N=381 pts (19% TNBC @primary tumor) 36% intrinsic subtype switching (total)
- Trend toward higher prevalence of the *HRD signature* in TNBC
- *Closer gene expression profiles in PT and met of TNBC*
  - ↑ median Cancer Cell Fraction for point muts (Δ clonality) between PT vs mets in HR+/HER2− and HER2+ subtypes but not TNBC
  - ↑ median TMB in paired mets vs PT samples in HR+/ HER2− and HER2+ MBC but not in TNBC

Subtype (clinical & molecuclar) by site of mets @AURORA_US



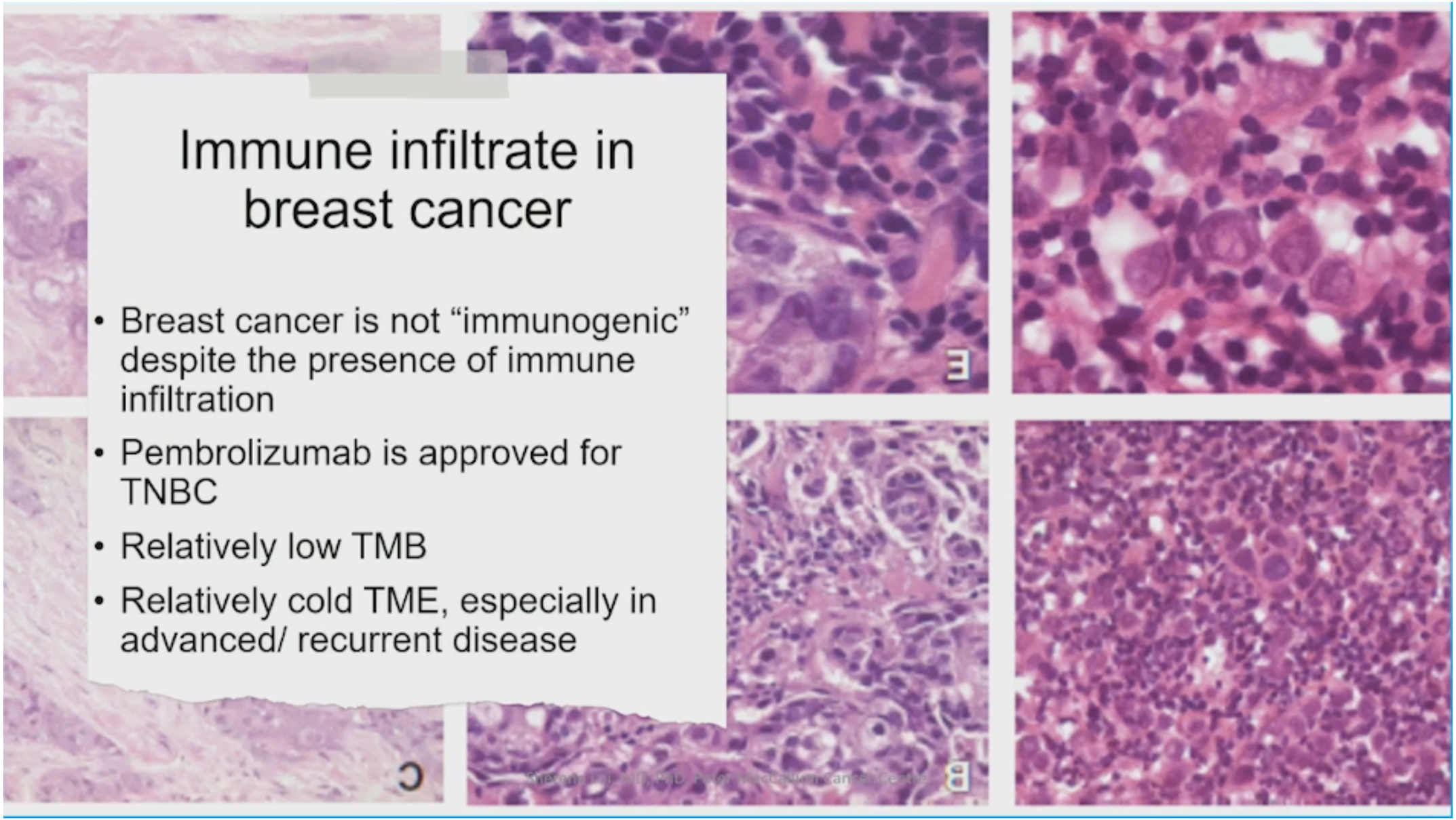
a

	Metastasis						
Primary	Claudin	Basal	HER2E	LumA	LumB	Normal	Participants
Claudin-low	2 (100%)	0	0	0	0	0	1
Basal	0	22 (92%)	0	0	0	2 (8%)	16
HER2E	0	0	12 (63%)	3 (16%)	4 (21%)	0	8
LumA	0	1 (9%)	2 (18%)	6 (51%)	1 (9%)	1 (9%)	8
LumB	0	0	1 (25%)	0	2 (50%)	1 (25%)	3
Normal-like	0	2 (67%)	1 (33%)	0	0	0	3
						Total:	39

Garcia-Recio et al Nature Cancer 2022
Aftimos et al Cancer Discov 2021

Immunotherapy (IO) in aTNBC

Key characteristics of TNBC that enhances ICI responses



Banerji S, et al. Nature. 2012;486(7403):405-409

IMpassion 130

Key eligibility criteria
- Histologically documented metastatic or inoperable, locally advanced TNBC
- No prior therapy for advanced TNBC[a]
  - Prior chemotherapy including taxanes allowed in curative setting if treatment-free interval ≥ 12 mo
- ECOG PS 0-1
- Eligible for taxane monotherapy
- Tumour tissue for PD-L1 testing

(N = 902)

R 1:1 (*Double-blind*)
- Atezolizumab[b] + *nab*-paclitaxel[c]
- Placebo + *nab*-paclitaxel[c]

Treatment until progression or unacceptable toxicity

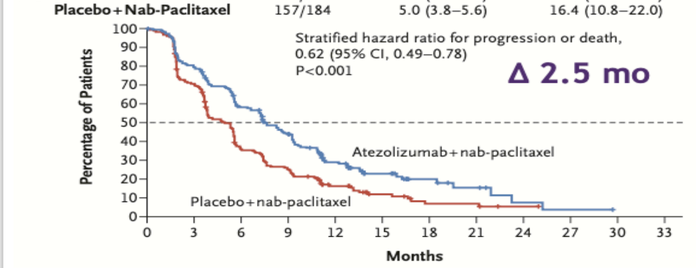
Stratification factors
- Liver metastases (yes vs no)
- Prior taxanes (yes vs no)
- PD-L1 IC status (positive vs negative)[a]

Co-primary endpoints:
- PFS[d] and OS (hierarchically tested in ITT and PD-L1 IC+ populations)

[a] PD-L1 IC ≥ 1% vs < 1% per VENTANA SP142 assay. [b] 840 mg IV on days 1 and 15 (28-day cycle).

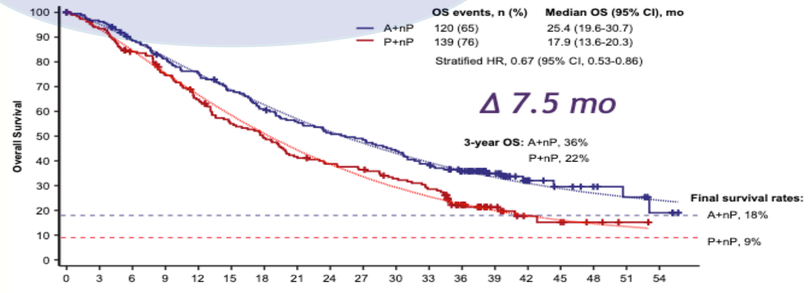
PD-L1 positive (PFS)*

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI) *mo*	1-Yr Rate of Progression-free Survival (95% CI) %
Atezolizumab + Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo + Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



IA2 post-hoc update (PFS) 7.5 vs 5.3 mo (Δ 2.2mo)

PD-L1 positive (OS)



IA2 update (OS) 25 vs 18 mo (Δ 7mo)

- Median 55 yrs; 41% PD-L1+; 27% liver mets; 51% prior-taxane; 63% prior (neo)adj.
- 8.2% vs 15.9% AEs led to discontinuation any drug & 42.2 vs 48.7% G3-4 AEs
- NO compromise of patients' day-to-day functioning or HRQoL or worsening treatment symptoms

Schmid et al NEJM 2018 & Lancet Oncol 2020; Emens et al Ann Oncol 2021; Adams et al Ann Oncol 2020

KEYNOTE-355

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or 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

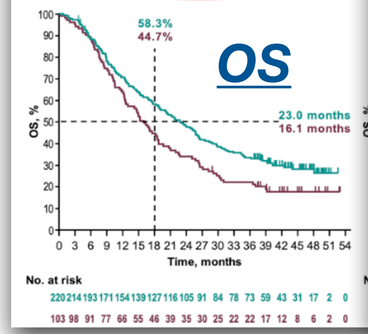
R 2:1
- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

Progressive disease[e]/cessation of study therapy

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

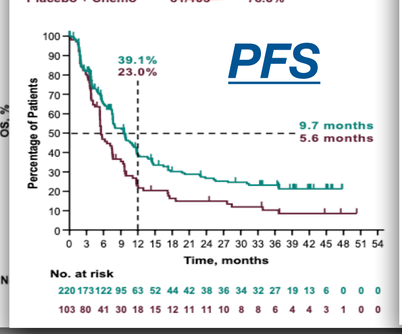
PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		

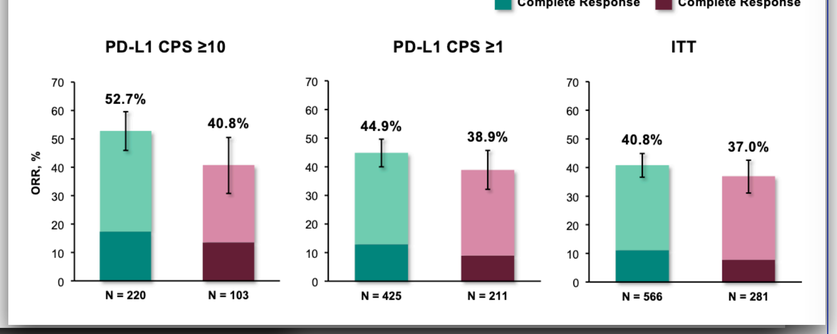


PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



Objective Response Rate



- *Cortes J et al. Lancet 2020;396:1817-28*

TORCHLIGTH STUDY

Key eligibility criteria:

- Histologically confirmed TNBC (ER/PR/HER2 triple negative)
- Initially diagnosed stage IV or recurrent/metastatic TNBC
- At least one measurable lesion as per RECIST v1.1
- ECOG PS of 0-1

N=528

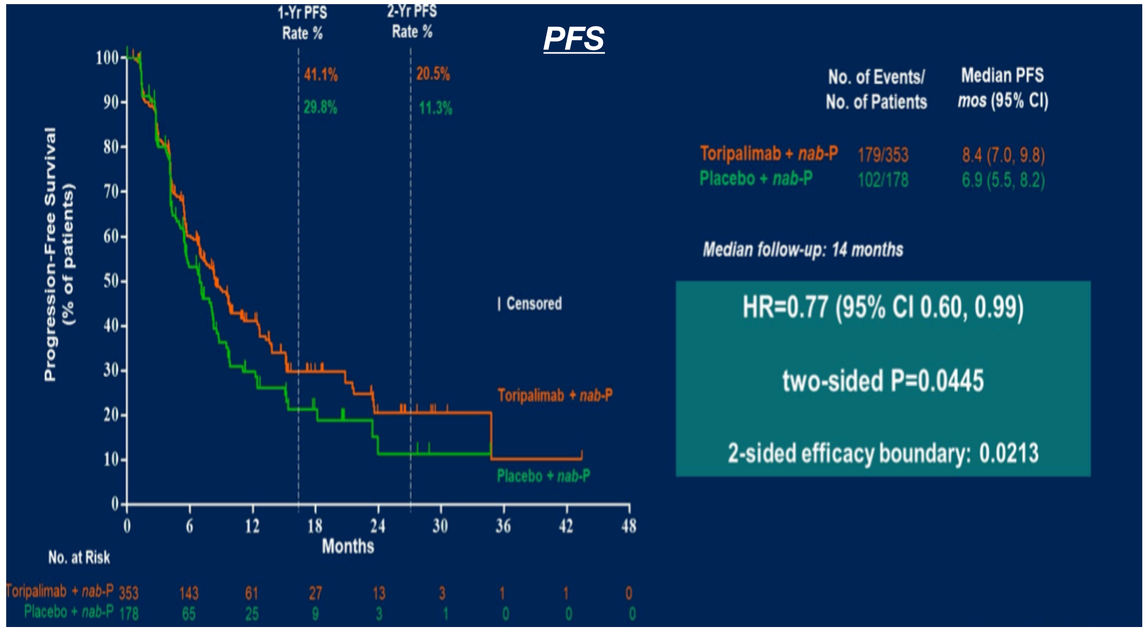
R 2:1

Toripalimab + *nab*-P group:
Toripalimab (240 mg Q3W) plus
nab-paclitaxel (125 mg/m^2, day 1 and day 8, Q3W)

Placebo + *nab*-P group:
Placebo (Q3W) plus
nab-paclitaxel (125 mg/m^2, day 1 and day 8, Q3W)

Treatment was continued until
Disease progression
Or Intolerable toxicity

PFS



	No. of Events/ No. of Patients	Median PFS *mos* (95% CI)
Toripalimab + *nab*-P	179/353	8.4 (7.0, 9.8)
Placebo + *nab*-P	102/178	6.9 (5.5, 8.2)

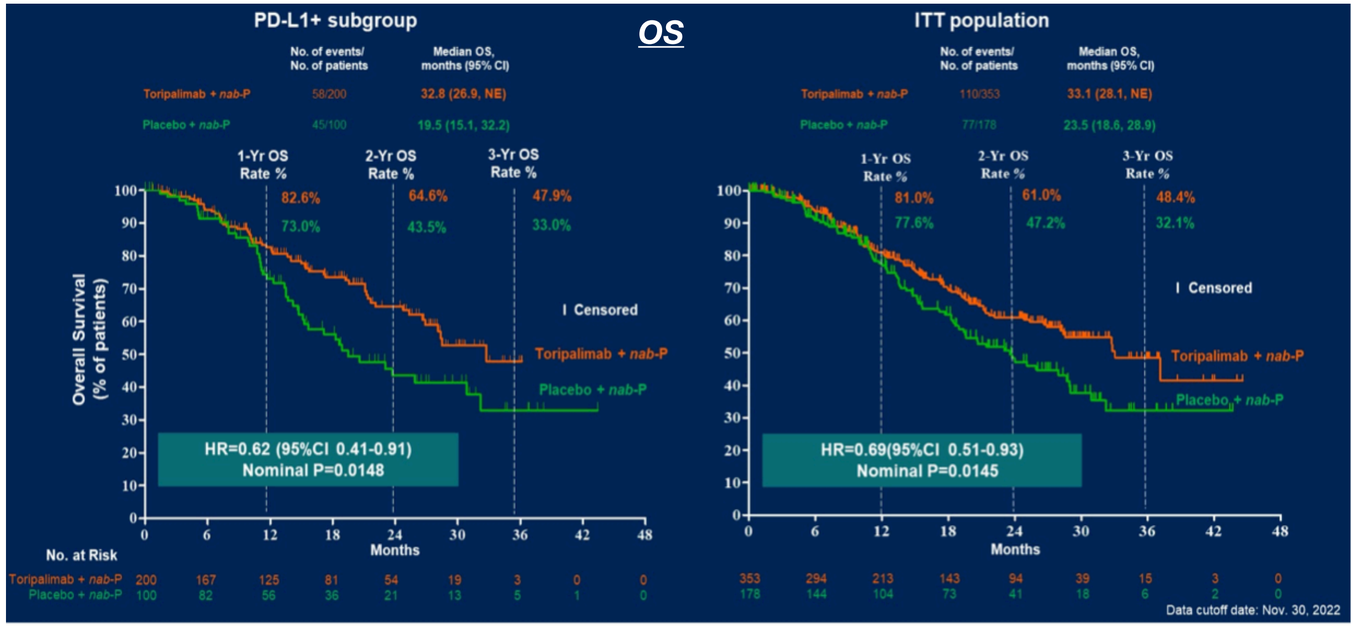
Median follow-up: 14 months

HR=0.77 (95% CI 0.60, 0.99)

two-sided P=0.0445

2-sided efficacy boundary: 0.0213

OS



ASCO 2023

BEGONIA: Phase 1b/2 Platform Study of durvalumab (D) combinations in TNBC

BEGONIA (*NCT03742102*)

Key Eligibility

- Female ≥ 18 yo
- Metastatic or inoperable locally advanced TNBC
- 1L metastatic setting
- ≥ 12 months since prior taxane therapy
- No prior ICI or Topo1-based ADC
- ECOG 0-1
- No history of pneumonitis (Arm 6)

Endpoints

- **Primary:** safety and tolerability
- **Secondary**: ORR, PFS, DoR, OS

- Tumor response evaluated every 6 weeks for first 48 weeks then every 12 weeks
- PD-L1 expression measured SP263 (≥ 10% tumor area positivity)

Arm 6: PD11-08

Unresectable, HR-, HER2 low breast cancer
[IHC2+/ISH-, IHC 1+/ISH-, IHC 1+/ISH untested]

Durvalumab 1120mg q3 weeks

Trastuzumab deruxtecan 5.4mg/kg q3 weeks

Antibody-Drug Conjugate
HER2 antibody + Topo1 inhibitor payload

Arm 7: PD11-09

Unresectable, HR-, HER2- breast cancer

Durvalumab 1120mg q3 weeks

Datopotamab deruxetecan 6mg/kg q3 weeks

Antibody-Drug Conjugate
TROP-2 antibody + Topo1 inhibitor payload

The James
The Ohio State University
Comprehensive Cancer Center

KEYPOINT: *Durvalumab may(?) enhance efficacy, durability of ADCs but does not increase toxicity*

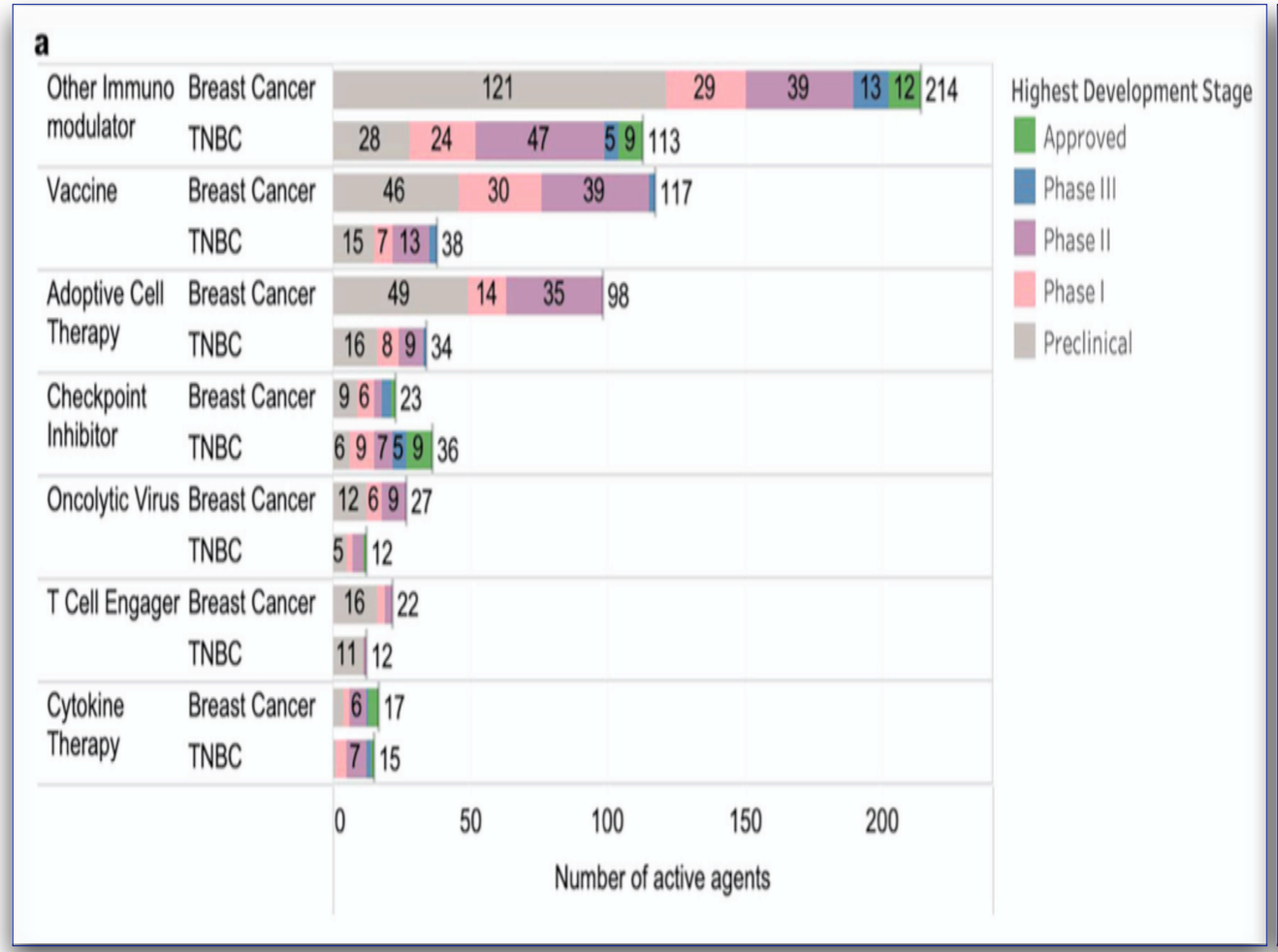
	T-DXd + Durvalumab *PD 11-08* *BEGONIA, Arm 6*	**T-DXd** *DESTINY- Breast04* *Modi et al. NEJM. 2022.*	**Dato-DXd + Durvalumab** *PD 11-09* *BEGONIA, Arm 7*	**Dato-DXd** *TROPION-PanTumor01* *Krop et al. SABCS 2021.*
Prior Tx*	***1L Metastatic*** ***27% no prior tx***	***Median of 3 prior tx*** ***62% had ≥ 3 prior***	***1L Metastatic*** ***41% no prior tx***	***Median of 3 prior tx*** ***68% had ≥ 2 prior***
ORR	**56.9%**	**50%**	**73.6%**	**34%** *52% in Trop2 ADC naïve*
mPFS	***12.6 months*** *(8.3 to not calculated)*	**8.5 months** *(4.3 to 11.7)*	---	---
Toxicity	*GI symptoms, fatigue, neutropenia, alopecia*		*GI symptoms, stomatitis, alopecia, fatigue*	

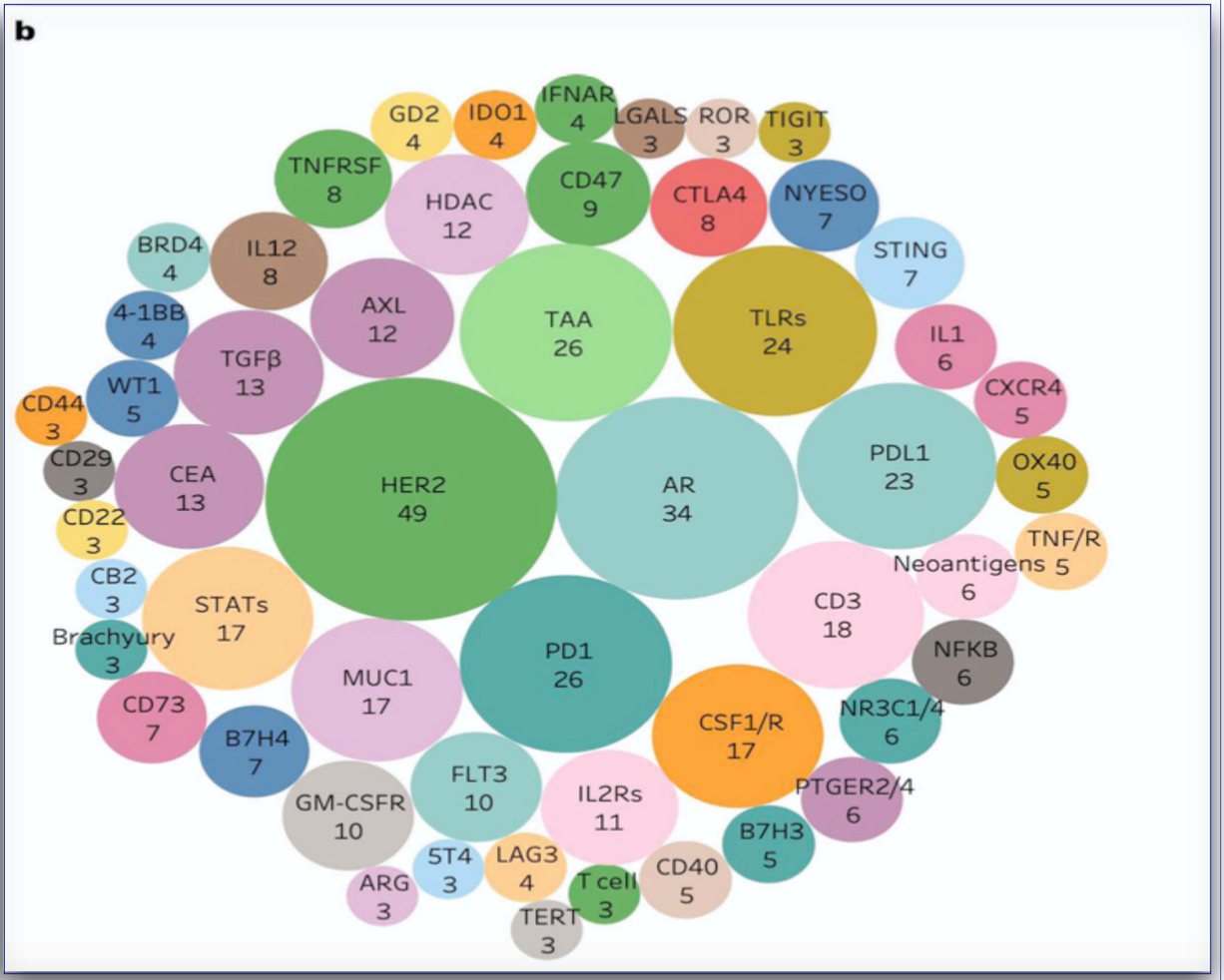
**BEGONIA study was for 1st line, metastatic TNBC, whereas both DESTINY-Breast04 and TROPION were in heavily treated patients*

The James

The Ohio State University
Comprehensive Cancer Center

Immunotherapy (IO): the future





Abdou et al npj Breast Cancer 2022

PD 11-10: KN046 (anti-PD-L1/CTLA-4 bispecific antibody) in combination with nab-paclitaxel in mTNBC (PI: Li)

Key Eligibility (n = 27)

- Metastatic or inoperable locally advanced TNBC
- 1L metastatic setting
- Prior (neo)adjuvant chemotherapy allowed if ≥ 12 months
- ECOG 0-1

Nab-paclitaxel 100mg/m2 on Days 1, 8, 15 of 28 day cycle

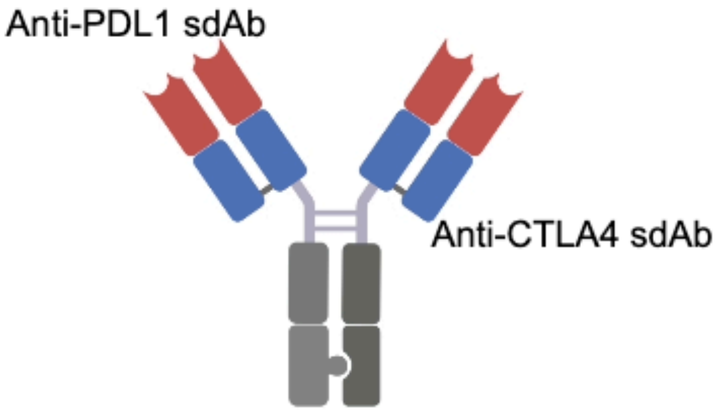
PLUS

DL 1: KN046 **3mg/kg** on Days 1 and 15

OR

DL 2: KN046 **5mg/kg** on Days 1 and 15

KN046



sdAb = single domain antibody

Endpoints

- **Primary:** ORR per IRC
- **Secondary**: PFS,OS, safety and tolerability

- Tumor response evaluated every 8 weeks
- PD-L1 expression measured SP142 (≥ 1% IC)

The James
The Ohio State University
Comprehensive Cancer Center

Figure 3: PFS

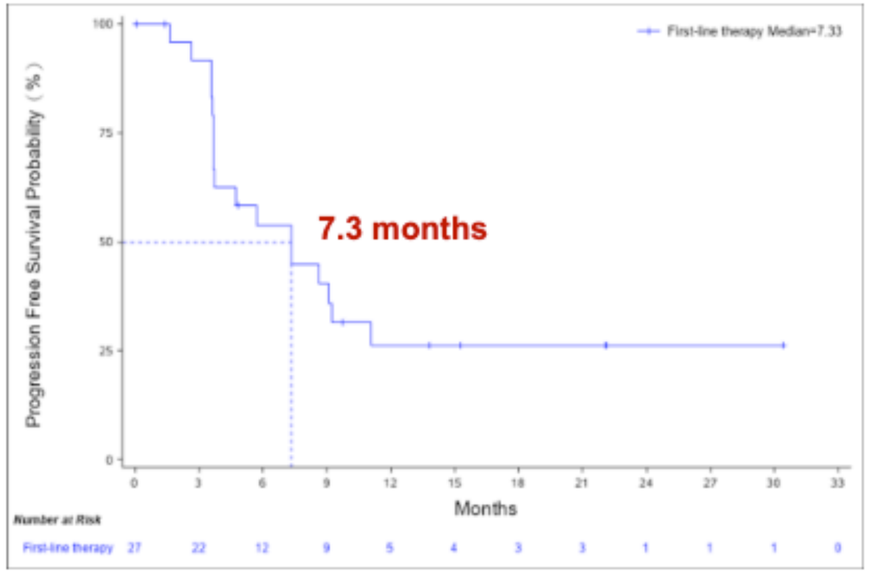
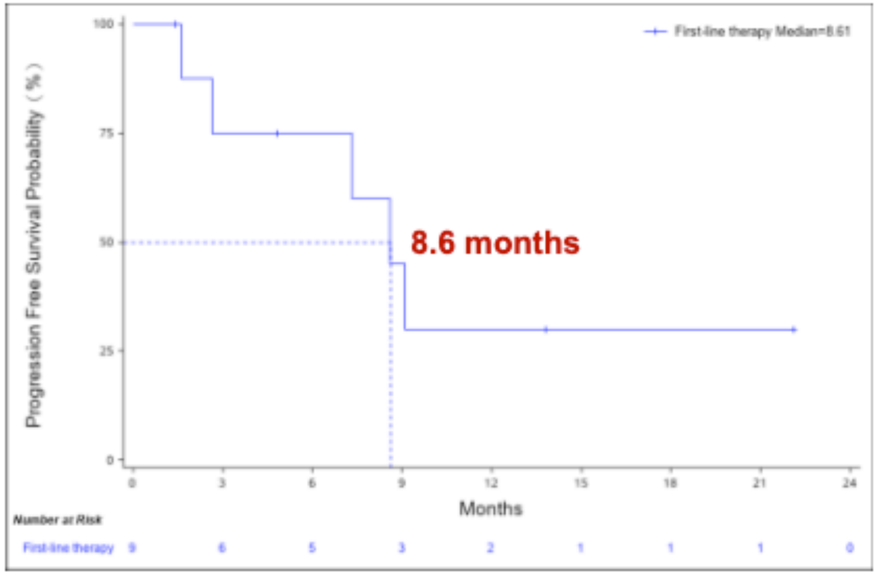
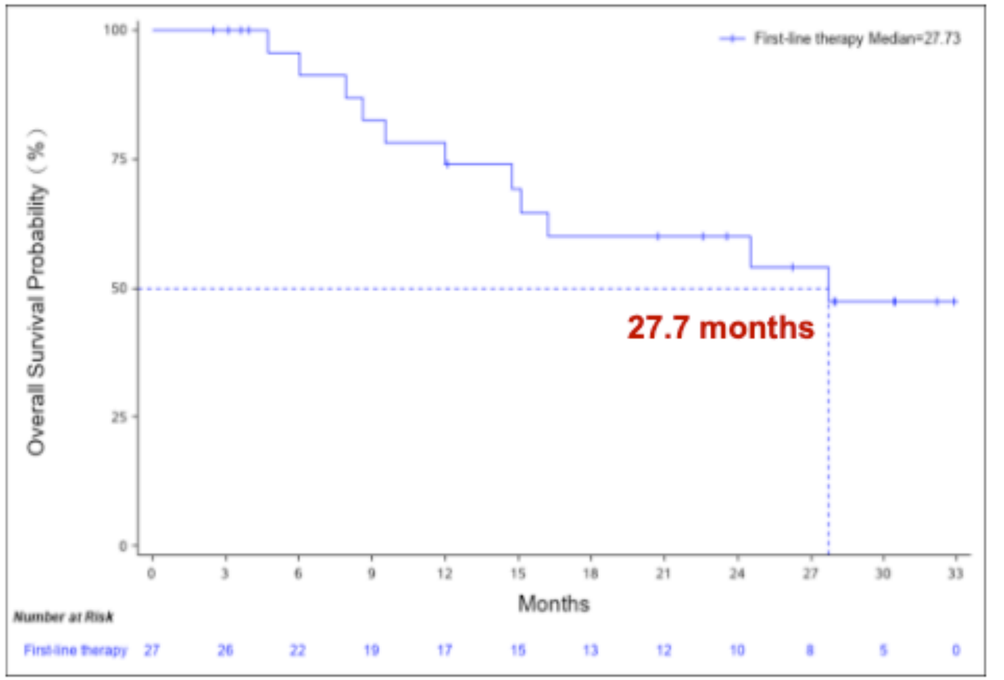


Figure 4: PFS in PD-L1+



- PFS improved in patients with PD-L1+ tumors
- *ORR is 44% with 1 CR and 8 PR per IRC*
- *Preliminary estimate of median overall survival = 27.7 months*

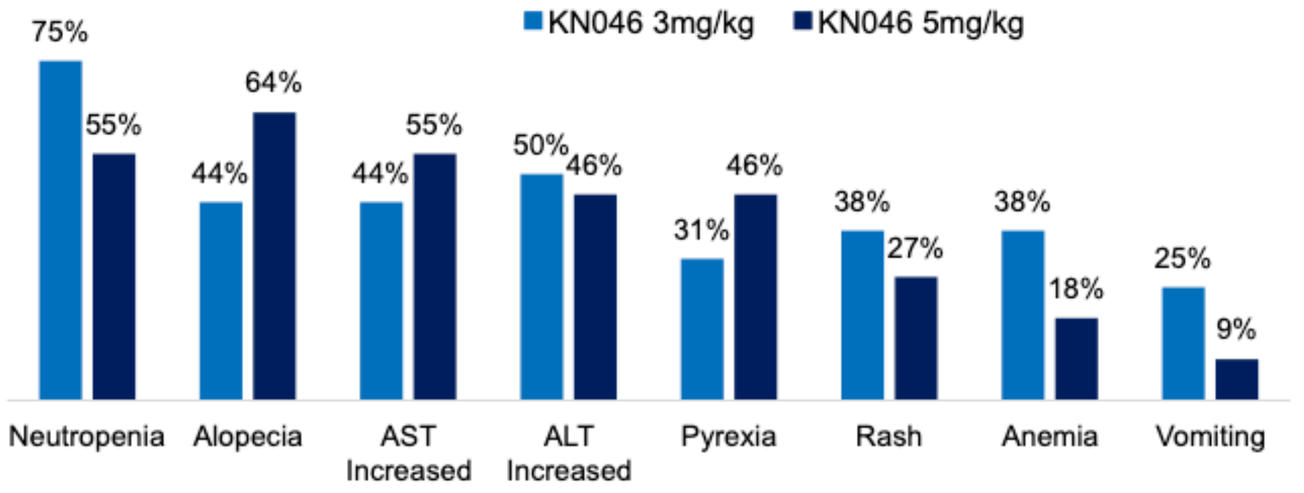


The James
The Ohio State University
Comprehensive Cancer Center

Abbreviated Table 3 and 4: Safety Summary	KN046 3mg/kg	KN046 5mg/kg
Any Grade TRAEs, n (%)	16 (100)	11 (100)
Any Grade ≥ 3 TRAEs	11 (68.8)	7 (63.6)
Related serious AE	4 (25.0)	2 (18.2)
Immune-related AE	8 (50.0)	5 (45.5)
Any Grade ≥ 3 irAE	0	3 (27.3)

AE: Adverse Event; TRAE: treatment Related Adverse Events

Table 4: Commonly Reported AEs: Nab-Paclitaxel + KN046



- irAEs in ~50% but most were low grade with 11% G3+
- Bone marrow suppression, alopecia likely in part due to nab-paclitaxel
  - Neuropathy not reported
- Historically combination therapy has a high toxicity profile
  - Onset within weeks
  - Commonly experience colitis, rash, hepatitis, endocrine, pneumonitis

Wang et al. JAMA Oncol.2021 ; Dearden H et al. Eur J Cancer. 2021

- Considering median PFS 7-8 months
  - Well beyond typical toxicity period
  - Received more than 4 doses of drug

The James
The Ohio State University
Comprehensive Cancer Center

KEYPOINT: *KN046 is a promising bispecific antibody in combination with nab-paclitaxel in 1L mTNBC*

- Improved efficacy over historical estimates for nab-paclitaxel… but not better then standard of care KEYNOTE-355

	KN046 + nab-paclitaxel*	KEYNOTE-355** (Cortes J et al, 2020. Lancet)	
		nab-paclitaxel + Pembrolizumab	nab-paclitaxel only
mPFS in ITT	7.3 months	7.5 months	5.4 months
mPFS in PD-L1+	8.6 months	9.9 months	5.5 months

** PD-L1+ using SP142 ≥ 1% IC; **PD-L1+ using CPS ≥ 10*

- Toxicity is improved over standard dual ICI combination

The James

The Ohio State University Comprehensive Cancer Center

PD 11-11: ALICE – Atezolizumab with Immunogenic Chemotherapy in Patients with Metastatic Triple Negative Breast Cancer (PI: Kyte)

Key Eligibility (n= 59)

- Metastatic or inoperable locally advanced TNBC
- 0-1 prior therapy in metastatic setting
- Prior (neo)adjuvant chemotherapy ≥ 12 months
- Prior ICI excluded
- ECOG 0-1

2:3

Pegylated doxorubicin 20mg/m2 every 4 weeks during week 2
Cyclophosphamide 50mg/day po for weeks 1 and 2
N = 28

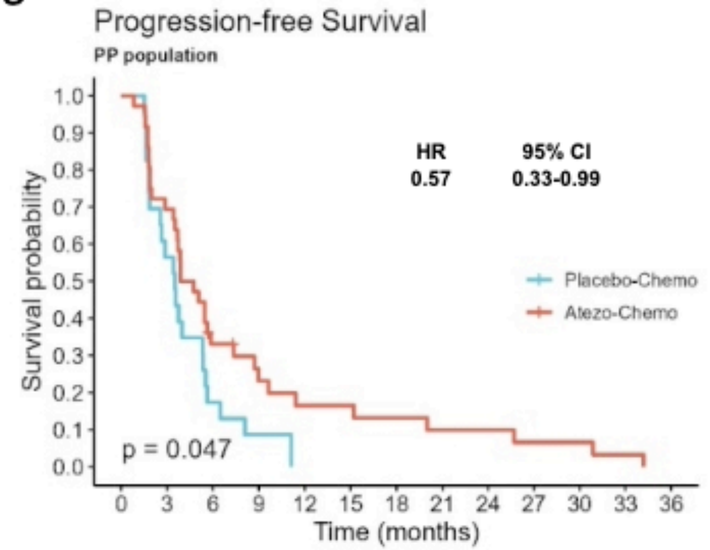
Pegylated doxorubicin 20mg/m2 every 4 weeks during week 2
Cyclophosphamide 50mg/day po for weeks 1 and 2
Atezolizumab 840mg every 4 weeks during week 2
N = 40

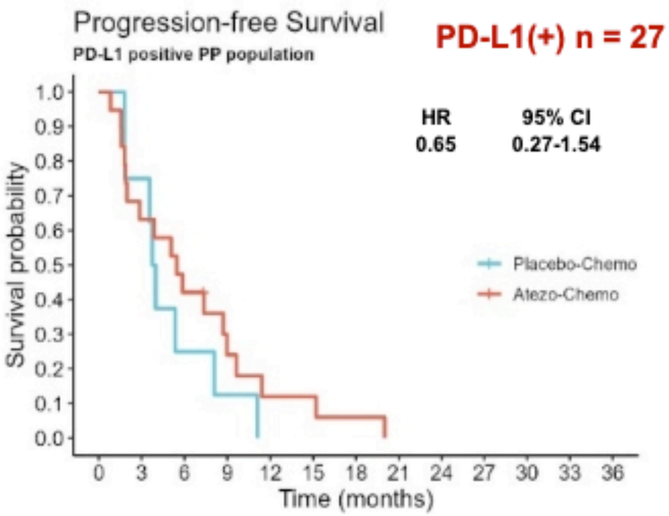
Endpoints

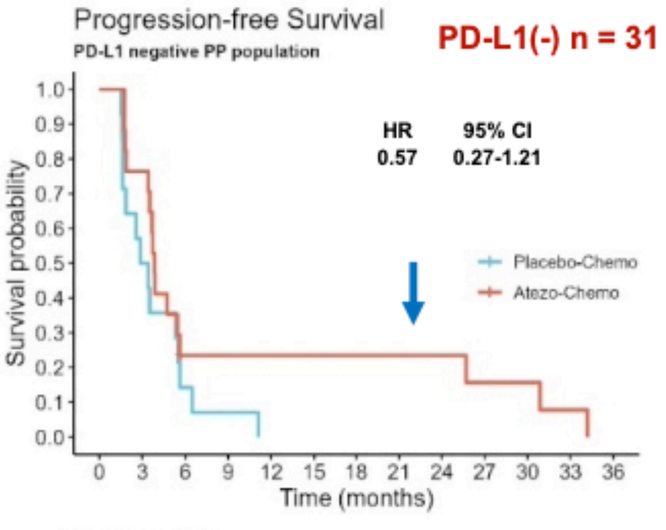
- **Primary:** Safety, PFS
- **Secondary**: ORR, CBR, DR, OS, TMEΔ
- Tumor response evaluated every 8 weeks
- PD-L1 expression measured SP142 (≥ 1% IC)

The James
The Ohio State University
Comprehensive Cancer Center

Figure 2







(PP = received > 3 atezolizumab and > 2 pegylated doxorubicin)

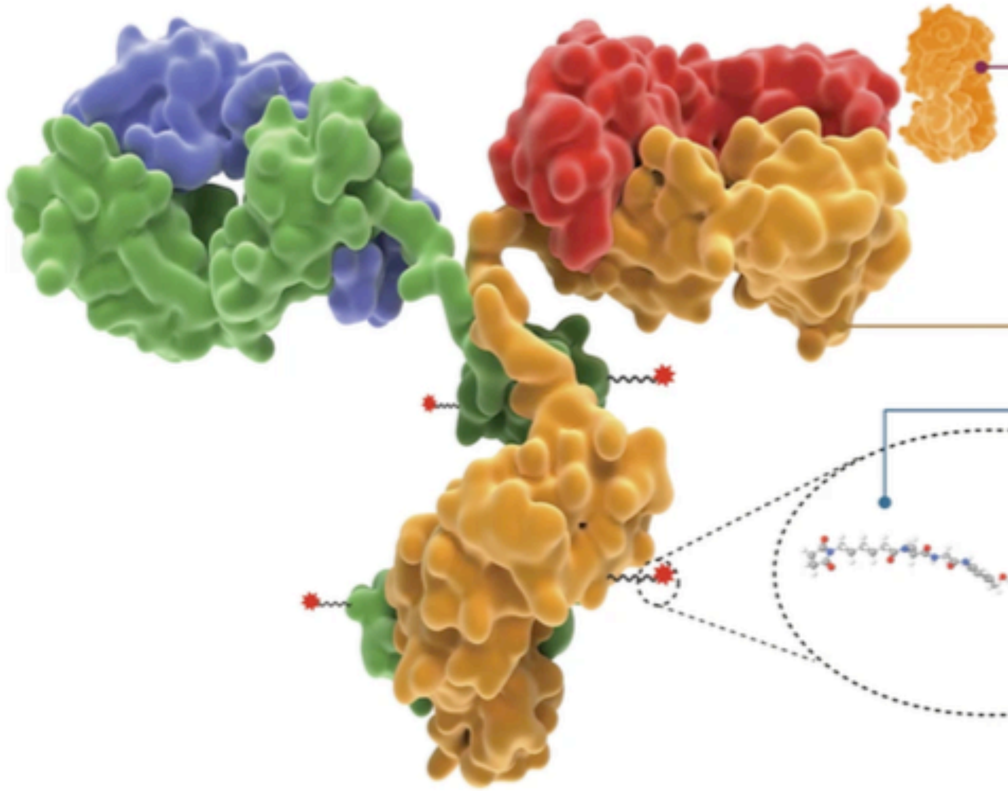
- Addition of immunogenic chemotherapy significantly improved the PFS in the per-protocol (PP) patients
  - ORR = 30.6% in atezolizumab + chemo vs 21.7% placebo + chemo
  - No difference in OS
- Subgroup analysis via PD-L1 status did not show a significant association but numbers were small

The James

The Ohio State University
Comprehensive Cancer Center

Antibody-Drug Conjugates

ADCs- Key Components



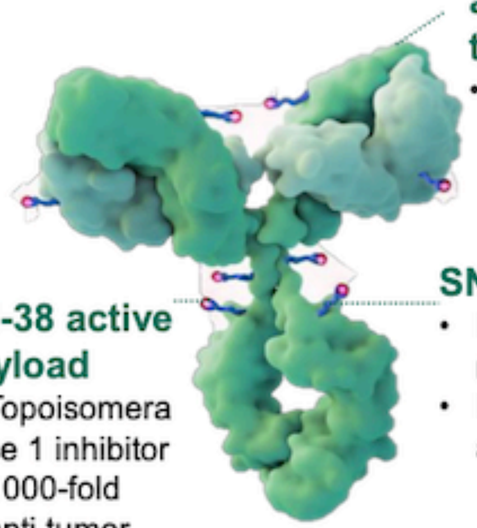
Target antigen	Recognition of target cancer cells
Antibody	Guidance system for cytotoxic drugs
Linker	Bridge between antibody and drugs and to control the release of drugs inside cancer cells
Cytotoxic drug	Warhead for destroying cancer cells

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

Signal Transduction and Targeted Therapy 2022; 7(93)

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

SG Molecular Structure



Humanized Monoclonal antibody targeting Trop-2

- Binds to Trop-2，a Epithelial antigen expressed in multiple solid tumor

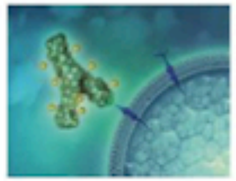
SN-38 linker

- Hydrolysis linker releasing SN-38
- High drug-to-antibody ratio(7.6: 1)

SN-38 active payload

- Topoisomerase 1 inhibitor
- 1000-fold anti tumor activity than Irinotecan

Mechanism of Action

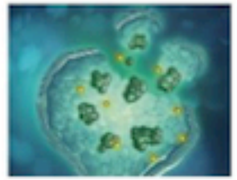


1、Linker

- Antibody from SG specifically recognize and adhere to Trop-2 on tumor cell surface

2、Endocytosis

- ADC undergoing receptor-mediated endocytosis，then enter in lysosomes



3、Attacking

- SN-38 released by acid hydrolysis in low PH environment，killing tumor cells

1. Goldenberg DM, et al. Oncotarget . 2018 Jun 22;9(48): 28989-29006.
2. Zeng P, et al. Sci Rep . 2016 Sep 20;6: 33658.
3. van Rij CM, et al. J Nucl Med. 2011 Oct;52(10): 1601-7.
4. Chen Y, et al. Front Immunol. 2020 May 29;11: 1088.
5. Han C, et al. Gynecol Oncol. 2020 Feb;156(2): 430-438.
6. Varughese J, et al. Cancer. 2011 Jul 15;117(14): 3163-72.
7. Trail PA. Pharmacol Ther. 2018 Jan;181: 126-142.
8. Criscitiello C, et al. J Hematol Oncol. 2021 Jan 28;14(1): 20.

Unique Advantages of SG

1、High specific targeting TROP2

- **Binds to Trop-2**、strong ADCC effect、stable in circulation

2、Uniquely potent payload:

- SN-38 is a **topoisomerase 1 inhibitor which can prevent cross-resistance**
- SN-38 has 1000 times more anti tumor activity than Irinotecan

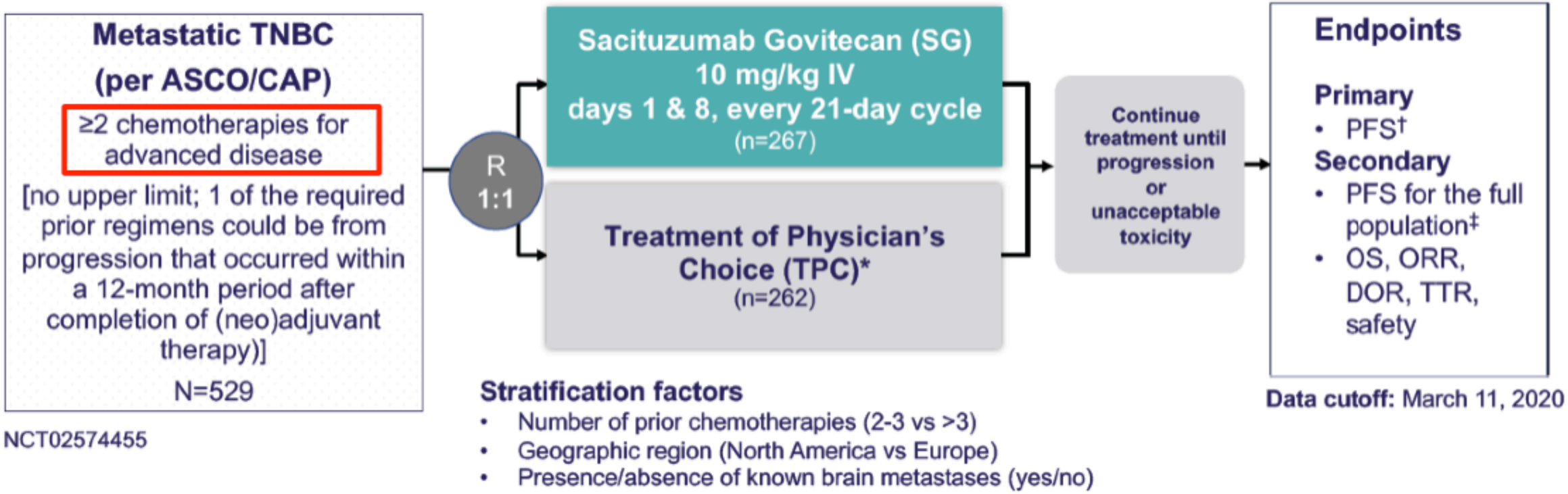
3、Cleavable linker

- stable in circulation，can be **cleaved from target cell in the low pH environment to release SN-38 and induce a strong bystander effect,** killing neighboring negative or low expression cells
- high solubility and low-frequency resistance

4、High drug-to-antibody ratio(7.6: 1)

- Offer adequate doses to kill tumor cells, **even and stable**

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

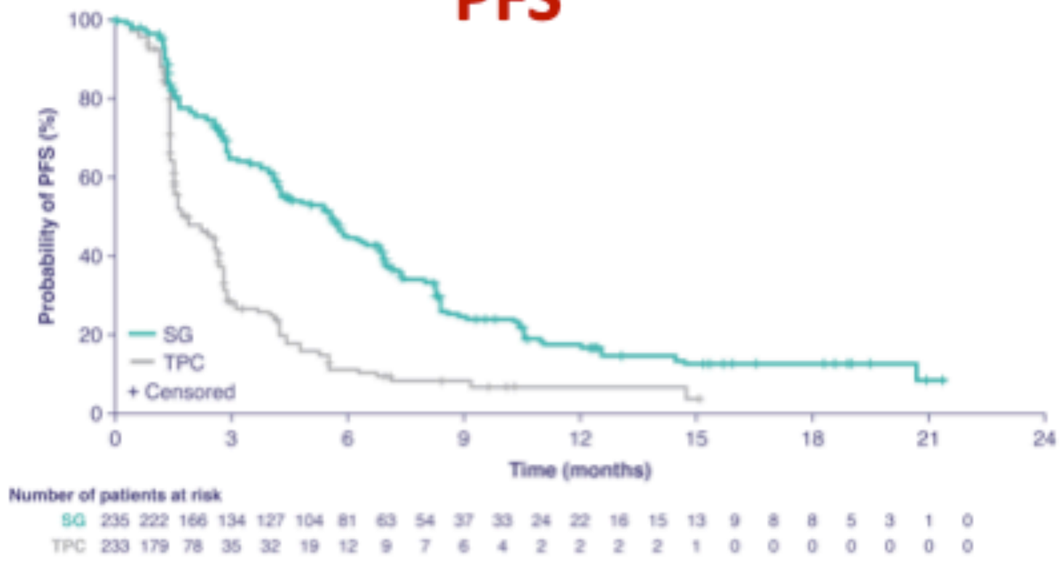


* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

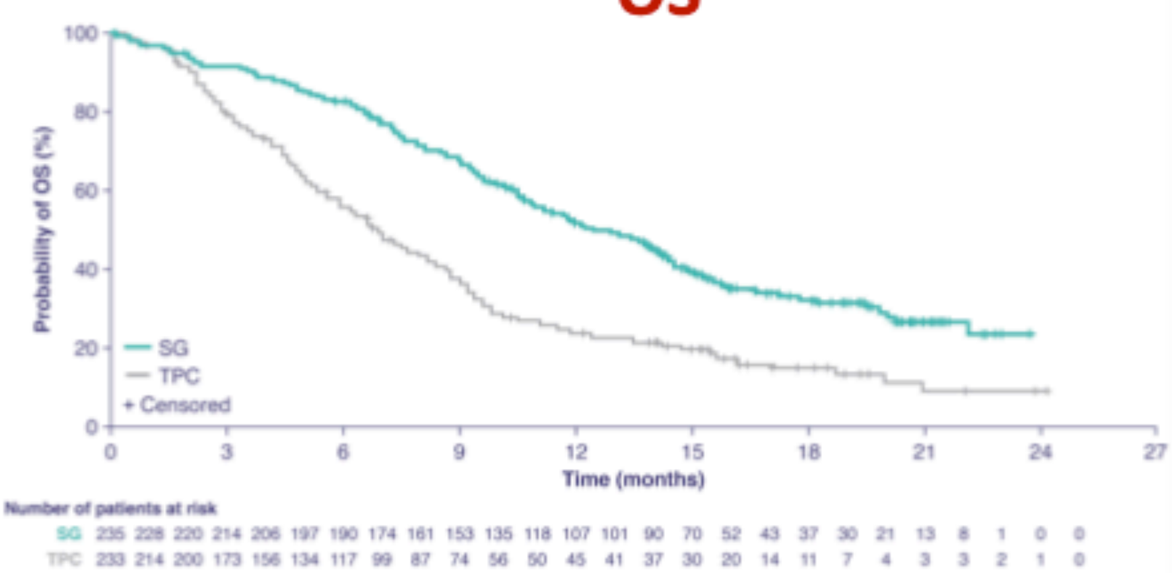
Sacituzumab Govitecan *(SG): PFS and OS*

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**	

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**	

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

A. Bardia, NEJM 2021

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

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

1ªL

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

1L mTNBC PD-L1+
- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

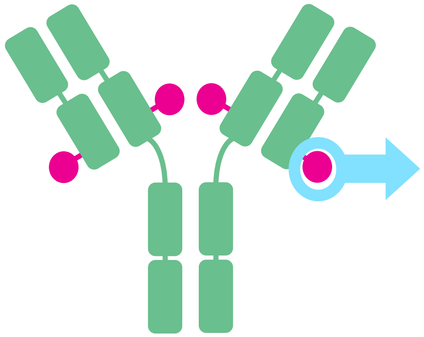
→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

Datopotamab Deruxtecan (Dato-DXd)

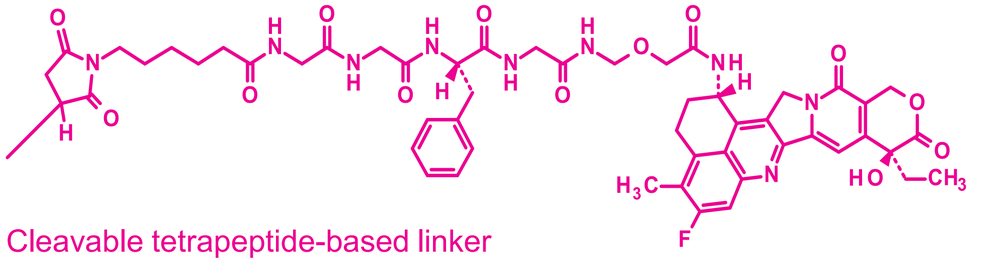
Dato-DXd is an ADC with 3 components[1,2]:

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

Humanized anti-TROP2 IgG1 mAb



Deruxtecan[a,4]



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

- 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: Datopotamab in TNBC Cohort

- Unresectable or metastatic HR+/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Progressed on ≥1 endocrine therapy; previously treated with 1-3 prior lines of chemotherapy in the advanced setting
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed

→

NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

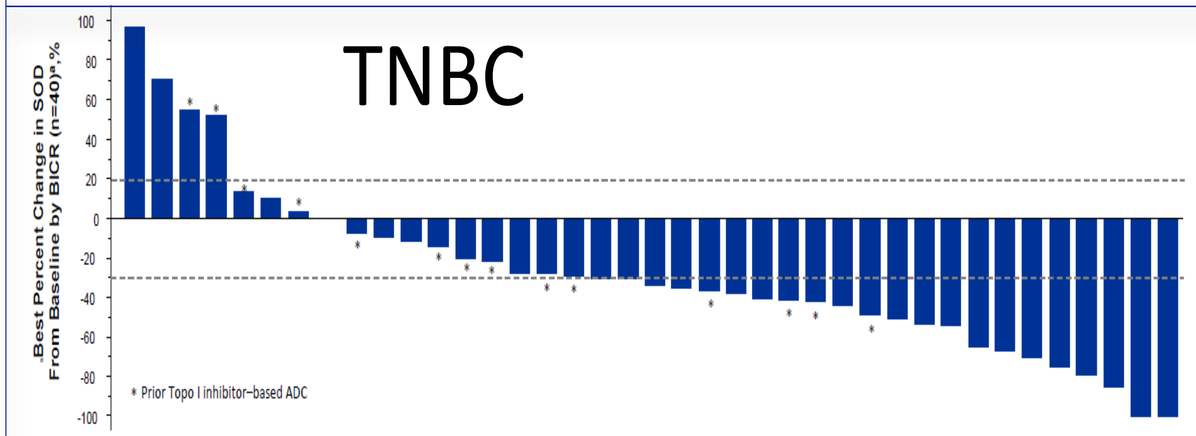
TNBC[c]
8 mg/kg IV Q3W (n=2);
6 mg/kg IV Q3W (n=42)

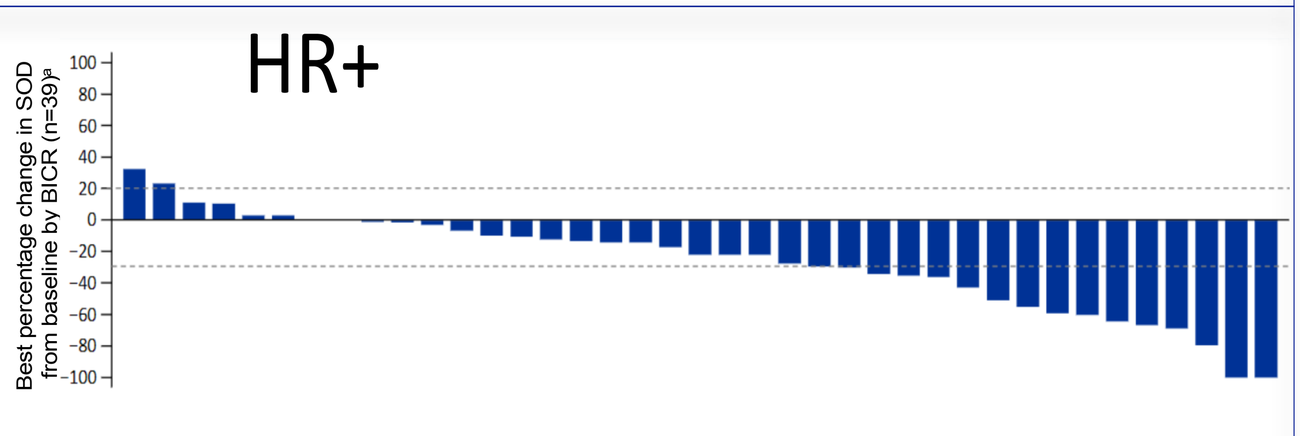
HR+/HER2− breast cancer
6 mg/kg IV Q3W (n=41)

Other tumor types
(SCLC, bladder, gastric, esophageal, CRPC, pancreas)

Primary objectives
- Safety
- Tolerability

Secondary objectives[d]
- Efficacy[e]
- Pharmacokinetics
- Antidrug antibodies





ORR by BICR:
- All patients: 32%
- Topo I inhibitor-naive patients: 44%
- Median PFS: 4.4-7.3 mo

Bardia A, et al. SABCS 2022. Poster Presentation P6-10-03.

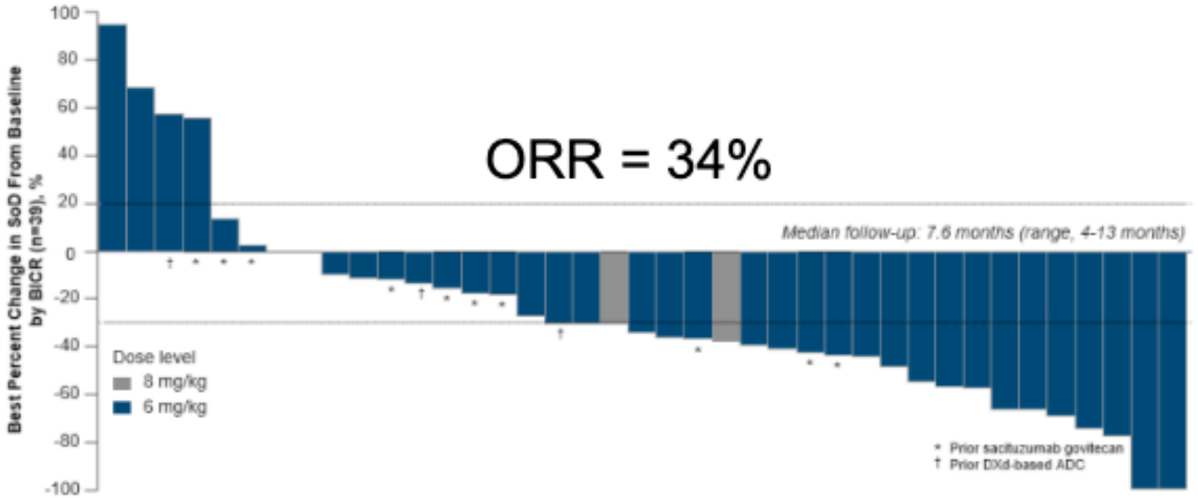
AEs:Most common TEAEs:
stomatitis (73 -83%/grade 3 10%),
nausea (66%), vomiting (39%)

- ORR (all PR): 27%;
- CBR: 44%
- Med PFS 8.3 mo
- 59% alive for >1 year

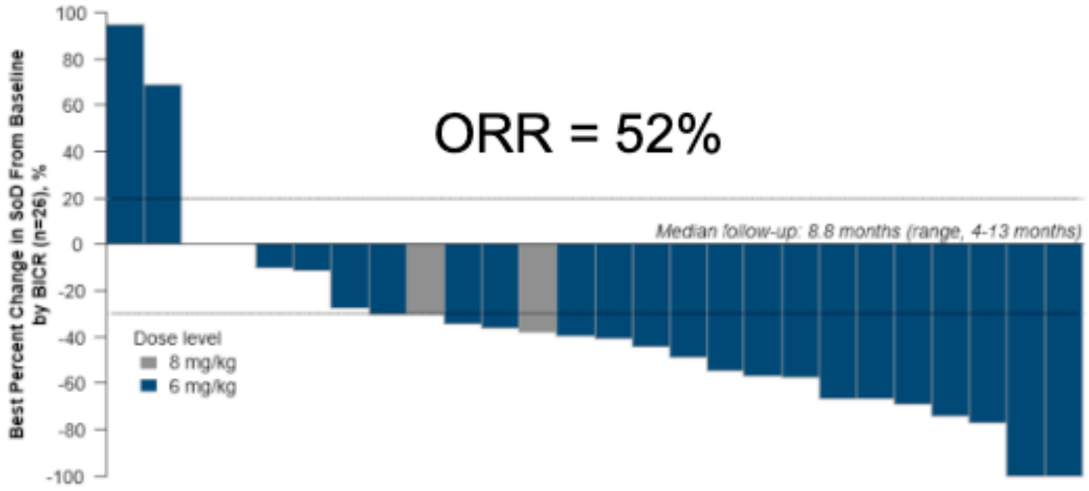
Meric-Bernstam et al, SABCS 2022

TROPION-PanTumor01: **Datopotamab** in TNBC Cohort

All patients N=44



Patients without prior Topo I inhibitor-based ADC N=27



Median prior lines of therapy = 3
Prior Topo1 inhibitor-based ADC= 30%

TROPION-Breast01

NCT05104866

Key Eligibility Criteria

- HR-positive, HER2-negative inoperable/ metastatic breast cancer with disease progression following 1 or 2 lines of chemotherapy (& progressed on, or not suitable for, endocrine therapy)
- Targeted agents (i.e., inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and endocrine therapies do not count as prior lines of chemotherapy
- At least 1 measurable lesion
- FFPE tumor sample
- Adequate organ function

Stratification factors:

- 1 vs. 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US/Canada/EU vs rest of world)
- Previous CDK 4/6 inhibitor use

1:1

Dato-DXd
6mg/kg IV Q3W
N=350

Investigator's Choice of Chemotherapy
(Eribulin, Vinorelbine, Capecitabine or Gemcitabine)
N=350

Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2 IHC

Statistical Considerations:

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses

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.

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

TROPION-Breast02

NCT05374512

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI >12 months)

Dual primary endpoint:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

Dato-DXd

Investigator's choice of chemotherapy

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

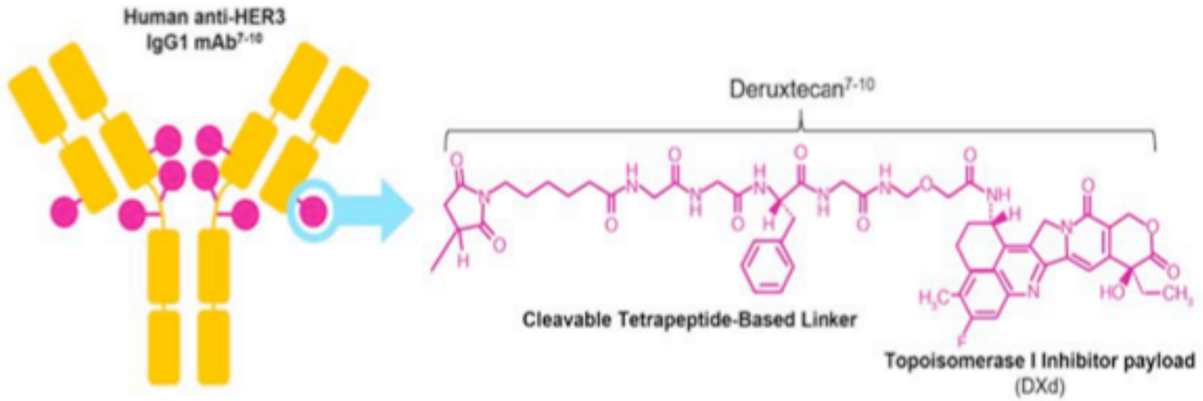
Patritumab Deruxtecan(U3-1402): a HER3-directed ADC

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

Adapted from Ocaña *et al.*, *JNCI*; 2013;105:266–273

Structure of HER3-DXd (Antibody-Drug Conjugate)



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

Krop et al, ASCO 2022

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[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
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.
[a] 95% exact binomial confidence interval (by Clopper-Pearson method).
[b] No patients had a CR.

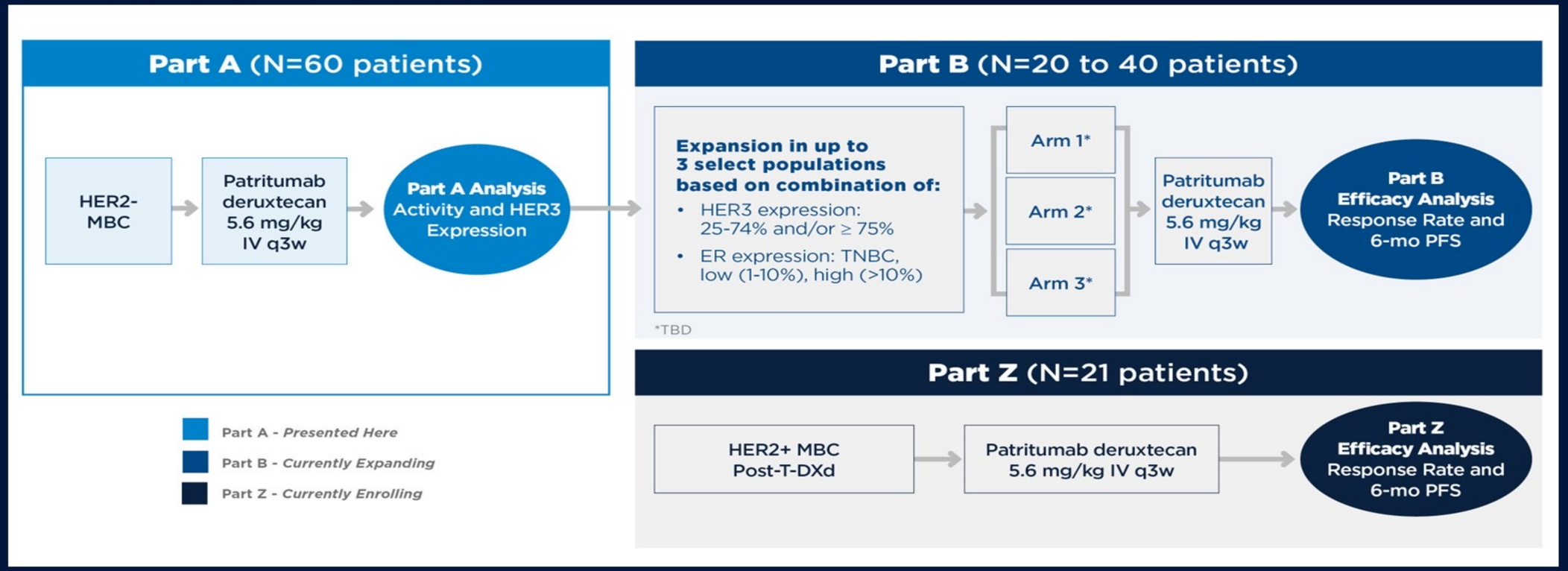
7

Krop et al, ASCO 2022

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

Study Design

- This Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC.
- Here, we present data for Part A.



HER3 expression was not an enrollment criterion for Part A; HER3 expression was retrospectively assessed using immunohistochemistry.

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

Response – Investigator Assessment

	Membrane HER3 ≥75% (N=30)	Membrane HER3 25%- 74% (N=13)	Membrane HER3 <25% (N=4)	Unknown Membrane HER3 Expression* (N=13)	Total (N=60) N (%)
Best Overall Response, n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
Stable disease (SD)	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
Progressive disease (PD)	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
Missing/no post baseline	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR, n (%)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
95% CI	(17.3, 52.8)	(19.2, 74.9)	(6.8, 93.2)	(5.0, 53.8)	(23.1, 48.4)
CBR, n (%)**	**12 (40.0)**	**7 (53.8)**	**2 (50.0)**	**5 (38.5)**	**26 (43.3)**
95% CI	(22.7, 59.4)	(25.1, 80.8)	(6.8, 93.2)	(13.9, 68.4)	(30.6, 56.8)
DoR ≥6 months, n (%)†	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

*HER3 results available for 47 pts. Remaining 13 pts had tissue not available/testing result unevaluable.
**CBR=CR, PR, or SD ≥180 days
†Percentage calculation uses the number of pts who responded as the denominator.

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

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

Data cutoff: September 6, 2022.

Response by HER3 Expression Level and Clinical Subtype

HER3 Membrane Expression ≥75%

	ER+ (N=16)	TNBC (N=11)
ORR, n (%)	6 (37.5)	2 (18.2)
95% CI	(15.2, 64.6)	(2.3, 51.8)
CBR, n (%)	8 (50.0)	2 (18.2)
95% CI	(24.7, 75.3)	(2.3, 51.8)
DoR ≥ 6 months, n (%)	3 (50.0)	1 (50.0)

There are 30 total pts with HER3 ≥75%. 2 pts were ER-/PR+, and 1 pt did not have ER/PR testing results; therefore, they are not included in the table.

HER3 Membrane Expression 25% to 74%

	ER+ (N=5)	TNBC (N=5)
ORR, n (%)	3 (60.0)	1 (20.0)
95% CI	(14.7, 94.7)	(0.5, 71.6)
CBR, n (%)	3 (60.0)	2 (40.0)
95% CI	(14.7, 94.7)	(5.3, 85.3)
DoR ≥ 6 months, n (%)	1 (33.3)	0

There are 13 total pts with HER3 25% to 74%. 2 pts were ER-/PR+, and 1 pt did not have ER/PR testing results; therefore, they are not included in the table.

ORR and CBR were not higher for patients with HER3 expression ≥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)

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

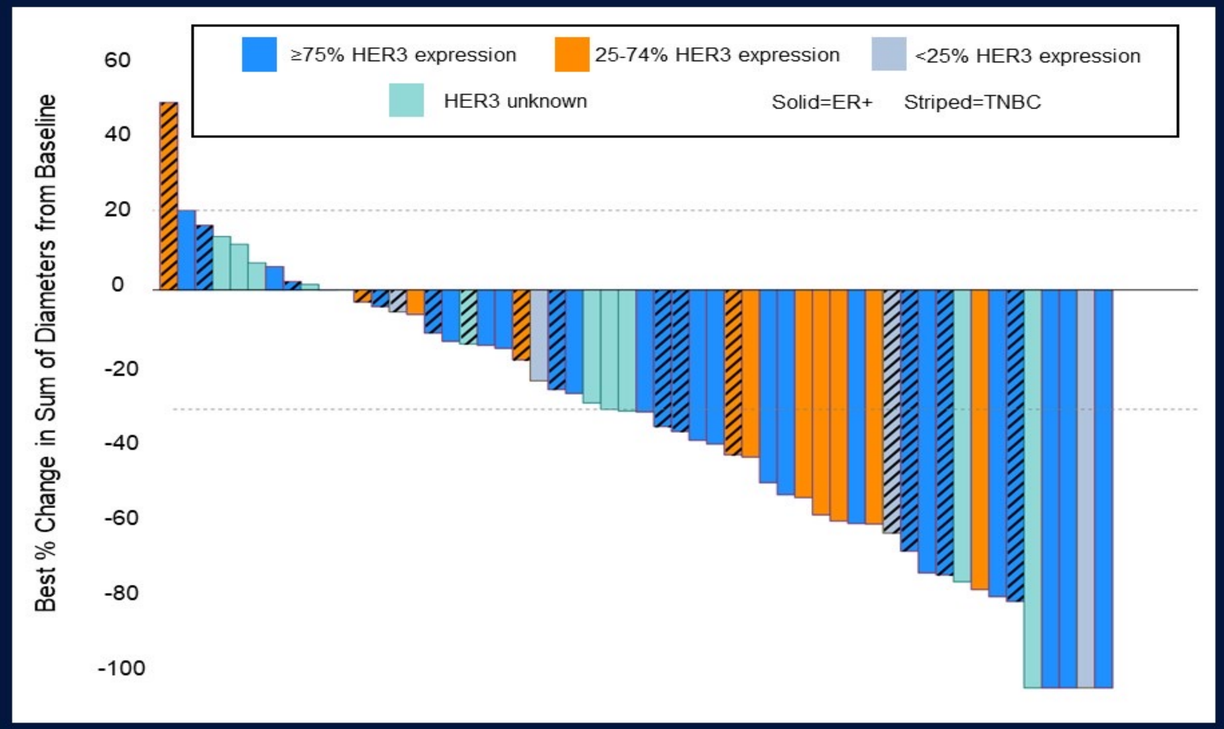
Data cutoff: September 6, 2022.

PRESENTED BY: Erika P. Hamilton, MD

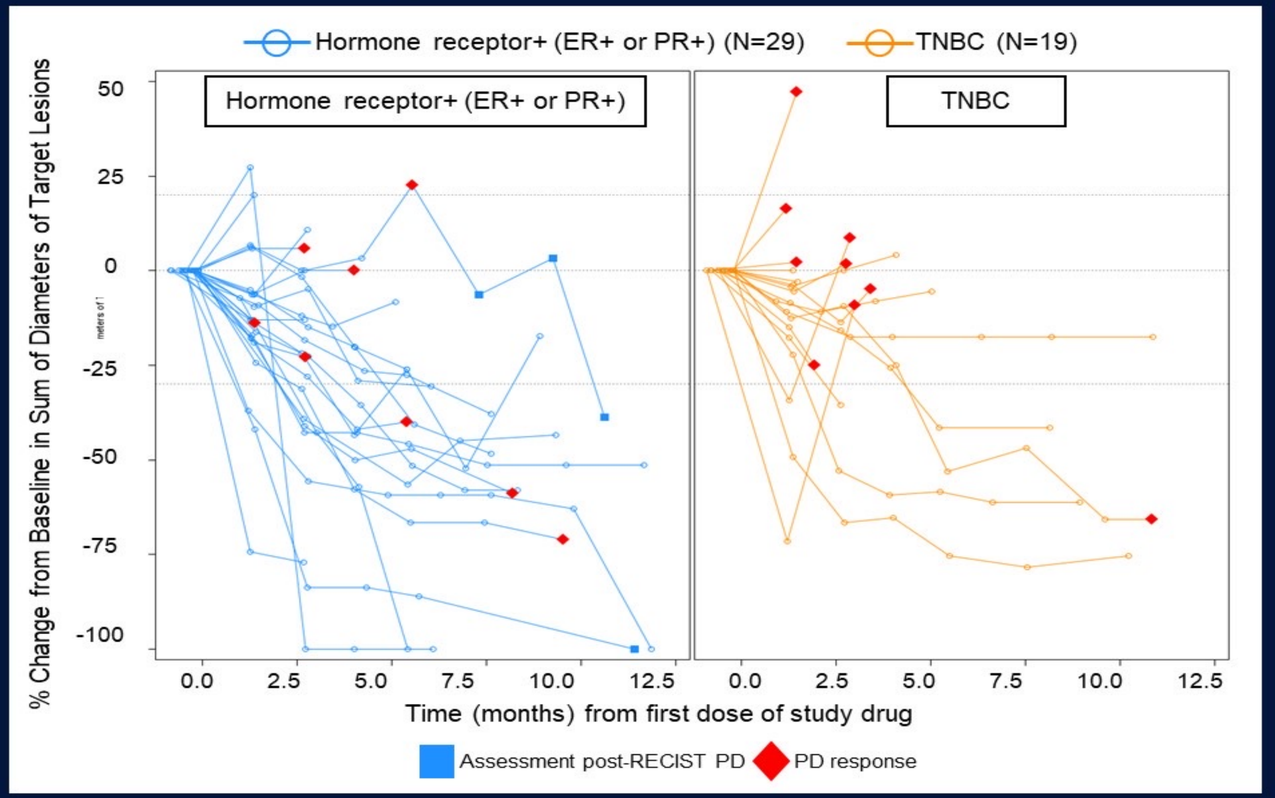
Patritumab Deruxtecan*(U3-1402): a HER3-directed ADC*

Majority of Patients Had Tumor Shrinkage

Best Percent Change in Sum of Diameters from Baseline in Target Lesions

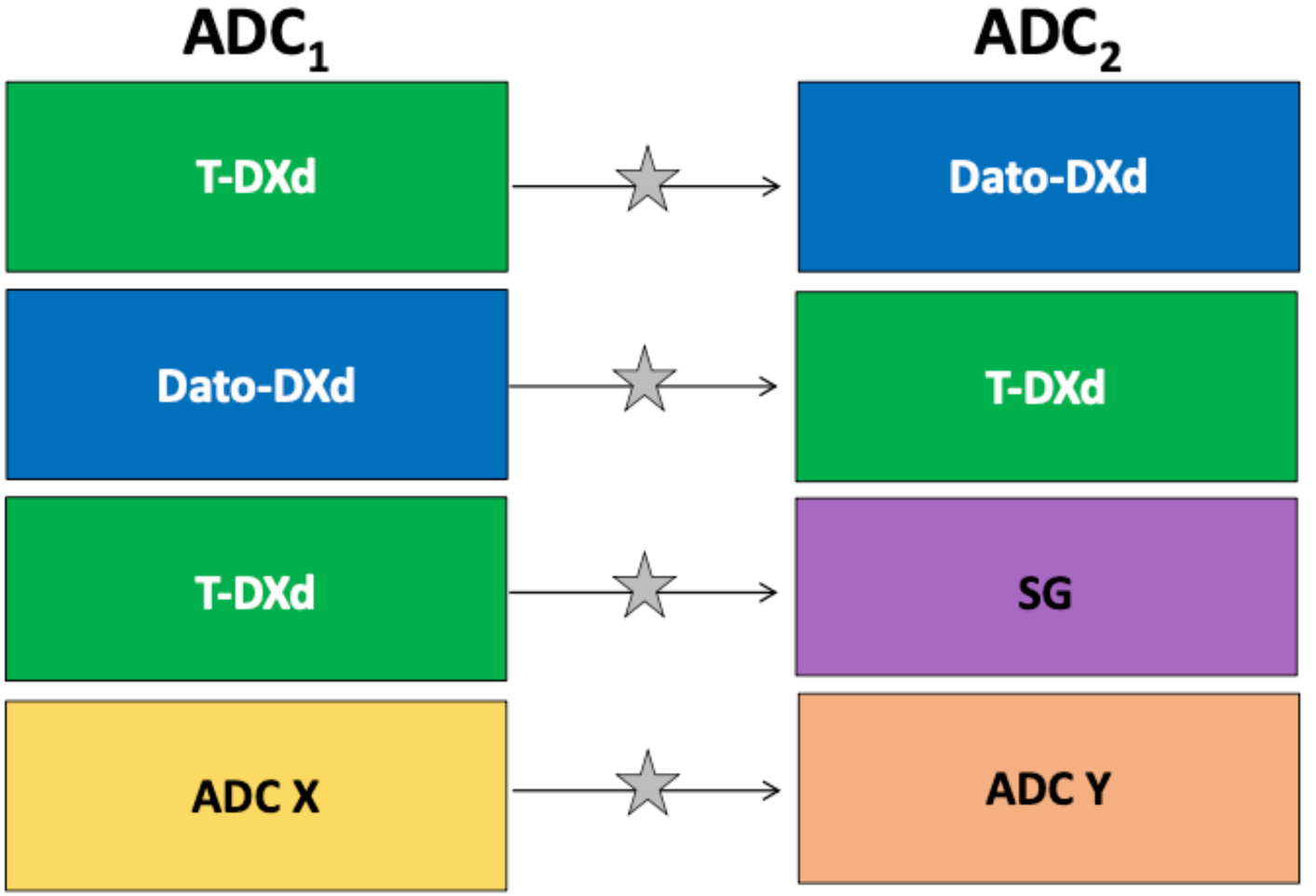


Percent Change from Baseline in Sum of Diameters of Target Lesions HR+ vs TNBC



Data cutoff: September 6, 2022.

Will Need to Understand Sequencing of ADCs



Need comparison and sequencing studies

American Society of Clinical Oncology Annual Meeting, 2023

Mass General Brigham
Mass General Cancer Center

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

CONQUER CANCER® THE ASCO FOUNDATION | MERIT AWARD

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

Harvard Medical School

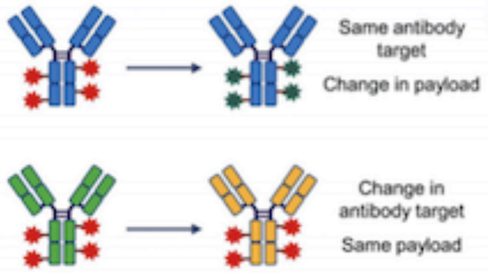
BACKGROUND

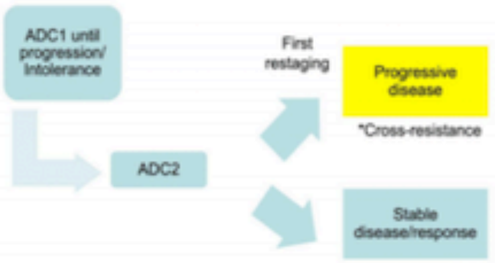
- Antibody-drug conjugates (ADCs) allow antibody-directed delivery of chemotherapy, improving efficacy and toxicity compared to standard chemotherapy.
- The recent approvals of sacituzumab govitecan (SG) for HR+/HER2- and triple negative metastatic breast cancer (MBC) and trastuzumab deruxtecan (T-DXd) 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.



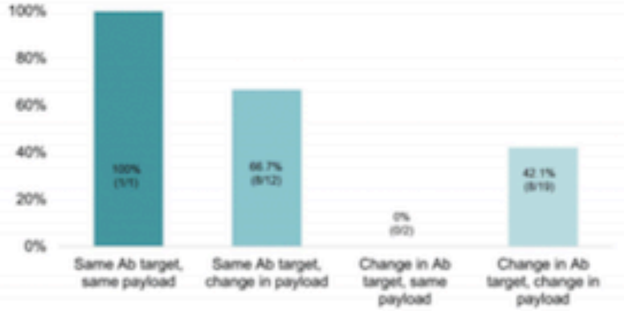


RESULTS

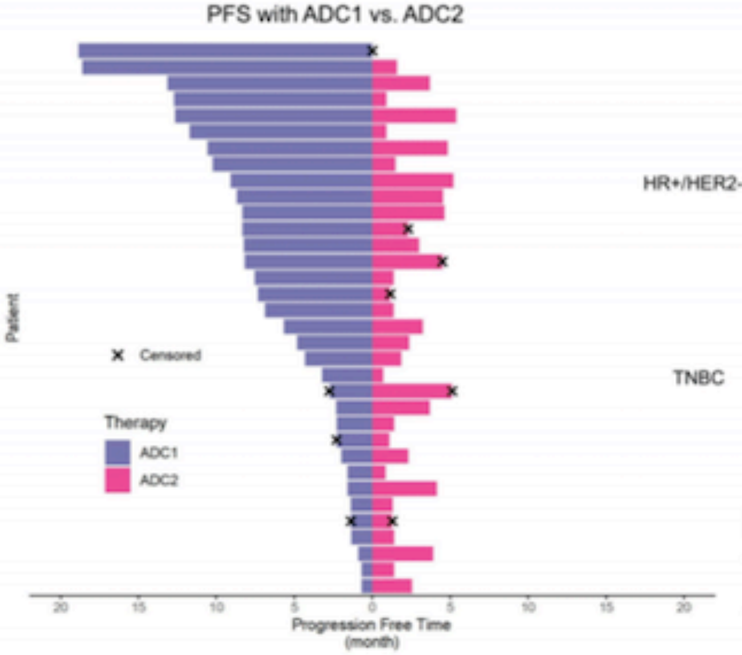
Table 1: Demographics

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%)

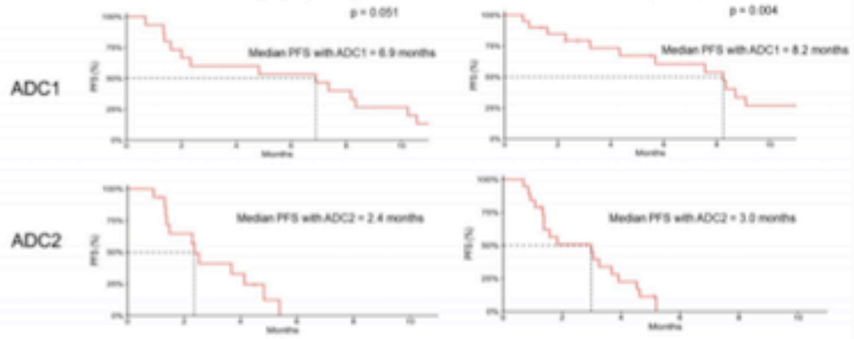
Cross-Resistance with ADC1 vs. ADC2



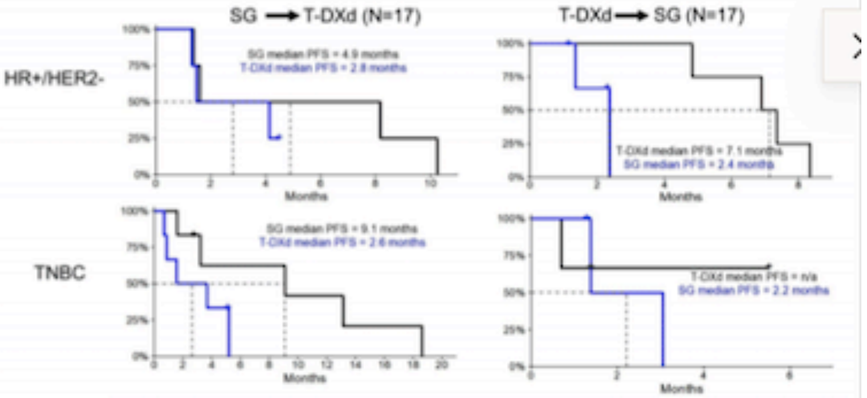
PFS with ADC1 vs. ADC2



PFS with ADC1 vs. ADC2, by Subtype



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

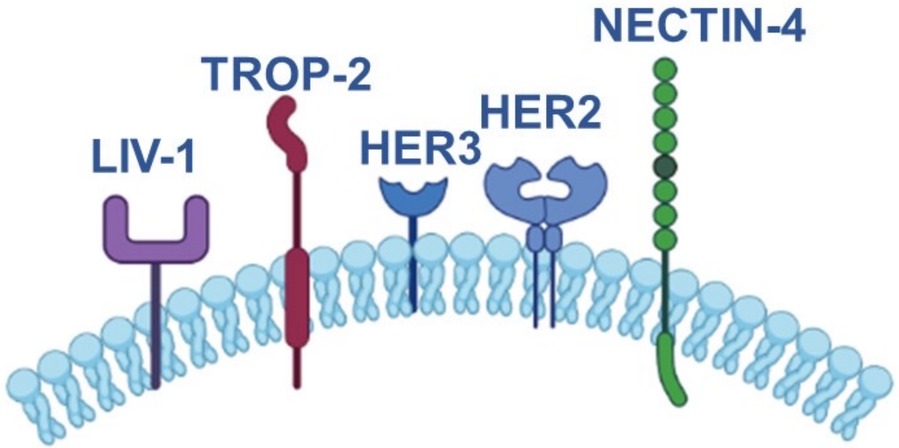


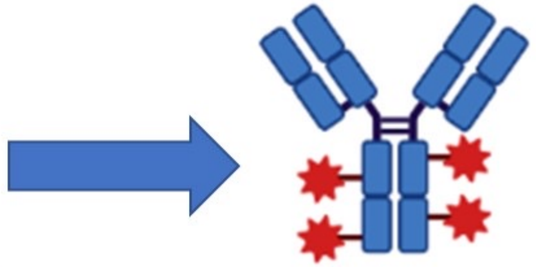
CONCLUSIONS AND FUTURE DIRECTIONS

- 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.

Context:

-The target landscape of ADCs is expanding rapidly





14 APPROVED ADCs

> 140 ADCs in clinical development

-Lower expression of the target is necessary

ADC: Payload potency, optimal DAR, bystander effect

Required target expression is lowering

HER2:< 150,000 – 10^6
TROP2: 250,000

Does TROP-2 expression matter??

In vitro cytotoxic studies

Table 1. Expression of Trop-2 and *in vitro* cytotoxicity of SN-38 and hRS7-SN-38 in several solid tumor lines

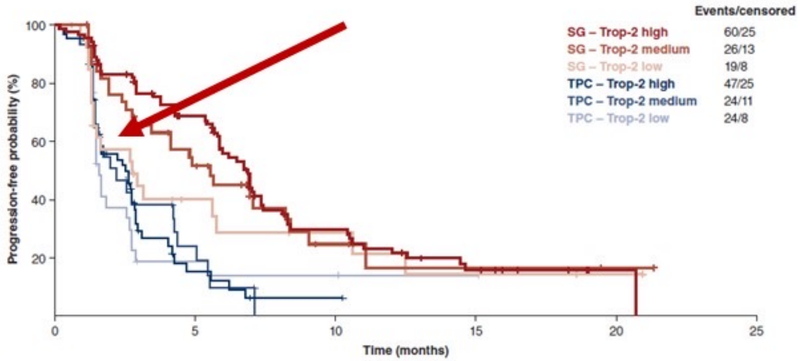
Cell line	Trop-2 expression *via* FACS		Cytotoxicity results				
	Median fluorescence (background)	Percent positive	SN-38	95% CI	hRS7-SN-38[a]	95% CI	ADC/free SN-38 ratio
			IC_{50} (nmol/L)	IC_{50} (nmol/L)	IC_{50} (nmol/L)	IC_{50} (nmol/L)	
Calu-3	282.2 (4.7)	99.6%	7.19	5.77–8.95	9.97	8.12–12.25	1.39
COLO 205	141.5 (4.5)	99.5%	1.02	0.66–1.57	1.95	1.26–3.01	1.91
Capan-1	100.0 (5.0)	94.2%	3.50	2.17–5.65	6.99	5.02–9.72	2.00
PC-3	46.2 (5.5)	73.6%	1.86	1.16–2.99	4.24	2.99–6.01	2.28
SK-MES-1	44.0 (3.5)	91.2%	8.61	6.30–11.76	23.14	17.98–29.76	2.69
BxPC-3	26.4 (3.1)	98.3%	1.44	1.04–2.00	4.03	3.25–4.98	2.80

[a]IC_{50}-value is shown as SN-38 equivalents of hRS7-SN-38.

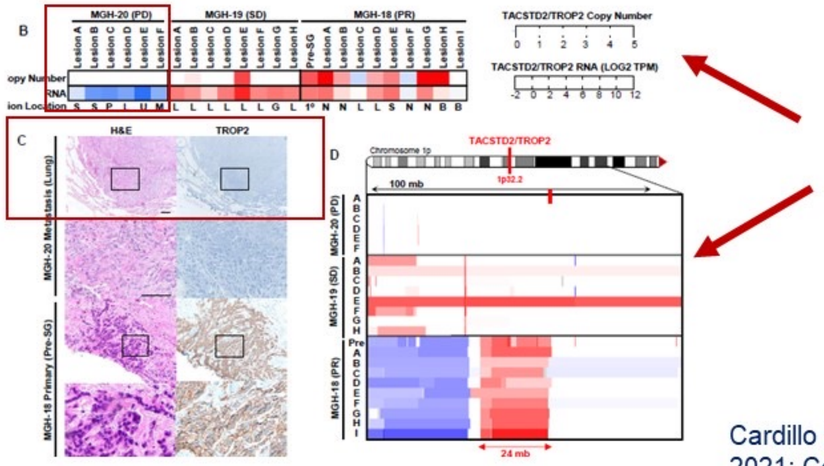
IC50 ADC:free SN-38 was lower in the higher Trop-2-expressing cells

Enhanced ability to <u>internalize</u> the ADC when more antigen is present

Clinical data



mPFS 2.7 mos [95%CI 1.4-5.8 mos] in low TROP-2 H-score (0 to <100), 6.9 months [95% CI 5.8-7.4months] in high TROP-2 H score (>200-300)



ASCENT trial:
Numerically higher efficacy outcomes (mPFS, ORR) in high and medium TROP-2 expression subgroups

Undetectable TROP2 RNA and absence of TROP2 (IHC) were associated to *de novo* resistance to SG

Cardillo et al, Clin Cancer Res 2011; Bardia et al, Ann Oncol 2021; Coates et al, Cancer Discov, 2021

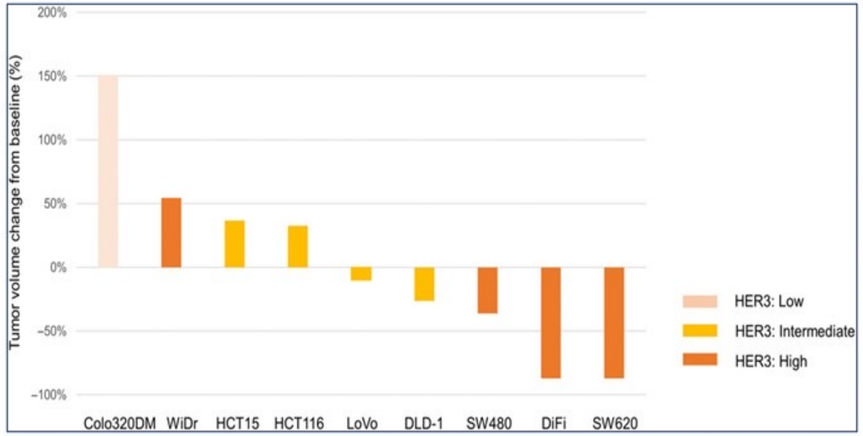
ASCO BIOMARKER TESTING IN ABC: insufficient data to recommend routine testing for TROP-2

Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker tests recommended by the ASCO expert panel			
PIK3CA	Evidence-based	High	Strong
Germline *BRCA1* and *BRCA2*	Evidence-based	High	Strong
PD-L1	Evidence-based	Intermediate	Strong
dMMR/MSI-H	Informal consensus-based	Low	Moderate
TMB	Informal consensus-based	Low	Moderate
NTRK fusions	Informal consensus-based	Low	Moderate
Biomarker tests not recommended by the ASCO expert panel			
ESR1	Evidence-based	Insufficient	Moderate
PALB2	Evidence-based	Low	Moderate
HRD	Informal consensus-based	Low	Moderate
TROP2 expression	Informal consensus-based	Low	Moderate
ctDNA	Informal consensus-based	Low	Moderate
CTCs	Informal consensus-based	Low	Moderate

Lin et al, J Clin Oncol 2022

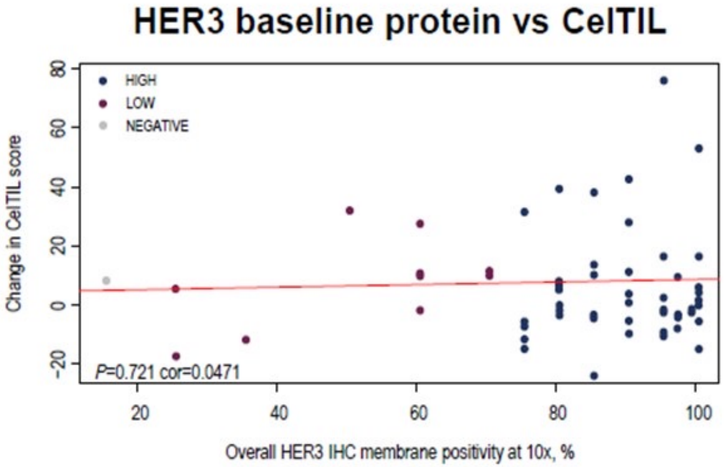
Does HER 3 expression matter??

In vitro models



no antitumor activity in HER3-low expressing tumor xenografts

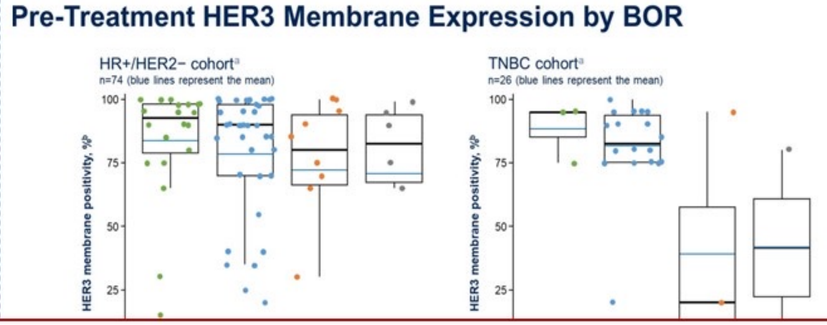
Clinical data



TOT-HER:

- **1/61 HER-3 neg (IHC)**
- **14/71 ERBB3 ULTRALOW**

Weak correlation between ERBB3 and HER3 expression



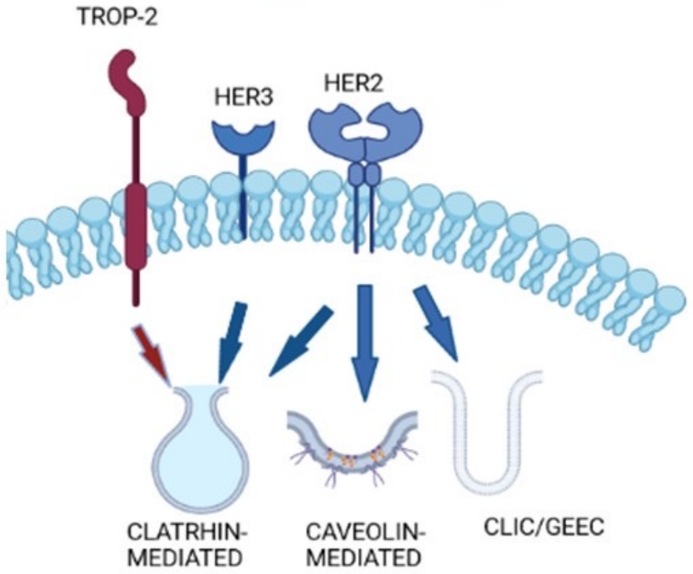
U3-1402-J101:
Only HER3-expressing tumors (≥ 25% membrane positivity 10x)

Activity across a broad range of HER3 membrane expression, but very few patients with HER3-low BC

Koganemaru et al, Mol Cancer Ther 2019; Prat et al, E

Target antigens are entry portals: localization in the tumor cell and endocytosis pathway also affect ADC activity

How efficiently the ADC is internalized also depends on the endocytosis pathways



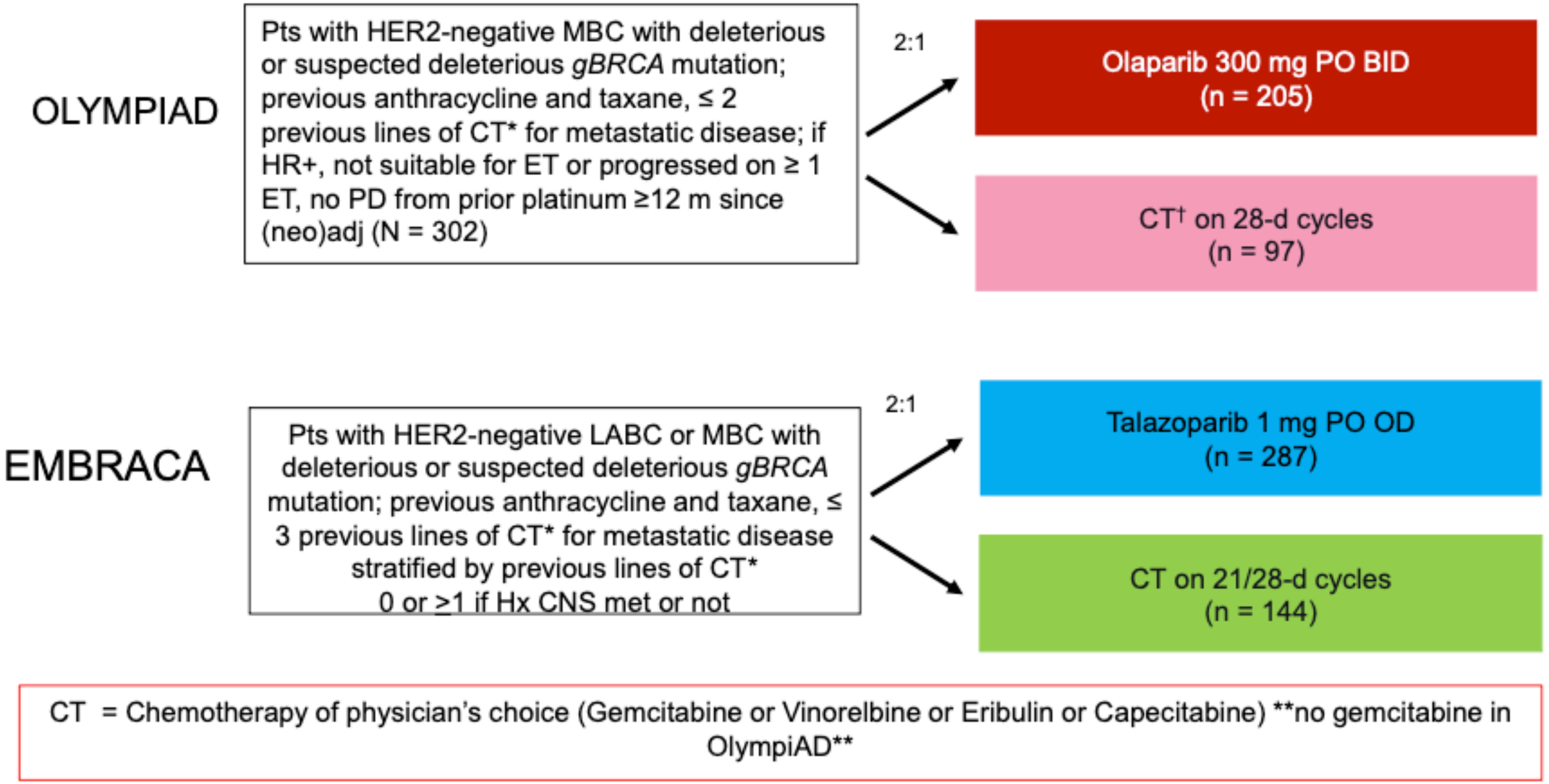
Little is known on how endocytosis processes affect ADC response

Can TARGET INTERNALIZATION be increased? (statins, irreversible pan-HER inhibitors, bispecific/biparatropic)

Ambrogi et al, PLOSOne 2014; Tretorola et al, Oncogene 2013; Pereira et al, Nat Commun 2018; Li et al, Cancer Discovery, 2020; Sung et al, Mol Cancer Ther 2018; Paul et al, Nat Communications 2023; Cheng et al, Antibodies 2020; Liu et al, Cancer Res 2022

PARP inhibitors in aTNBC

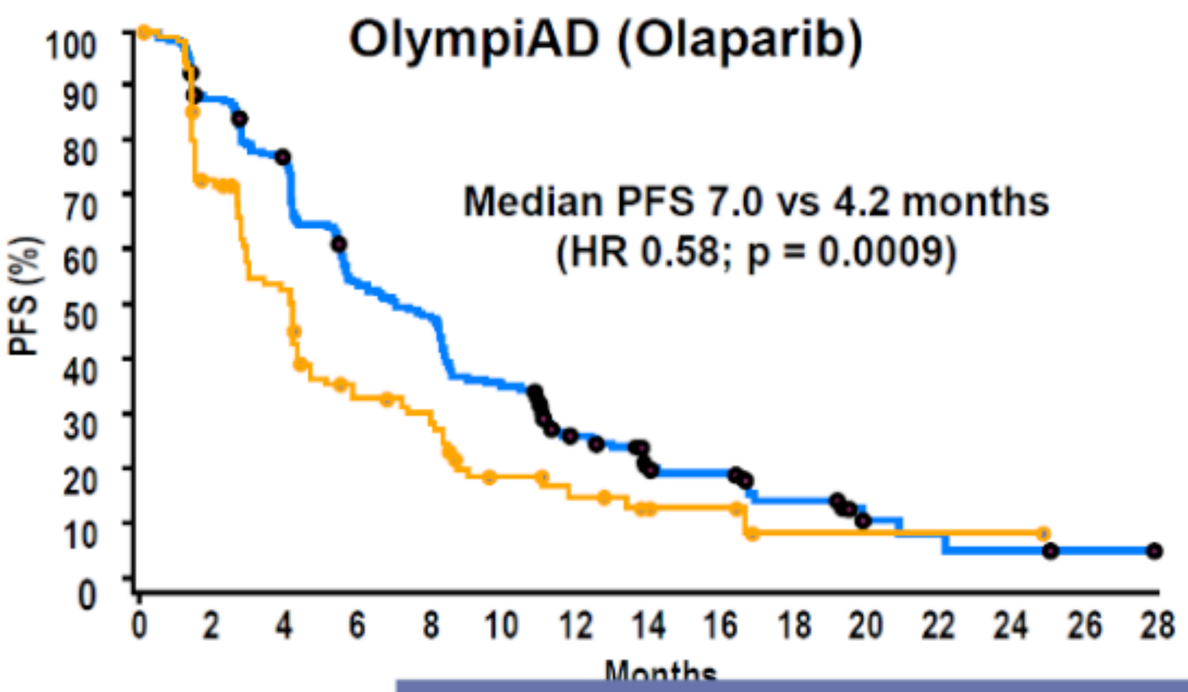
PARP inhibitors in aTNBC

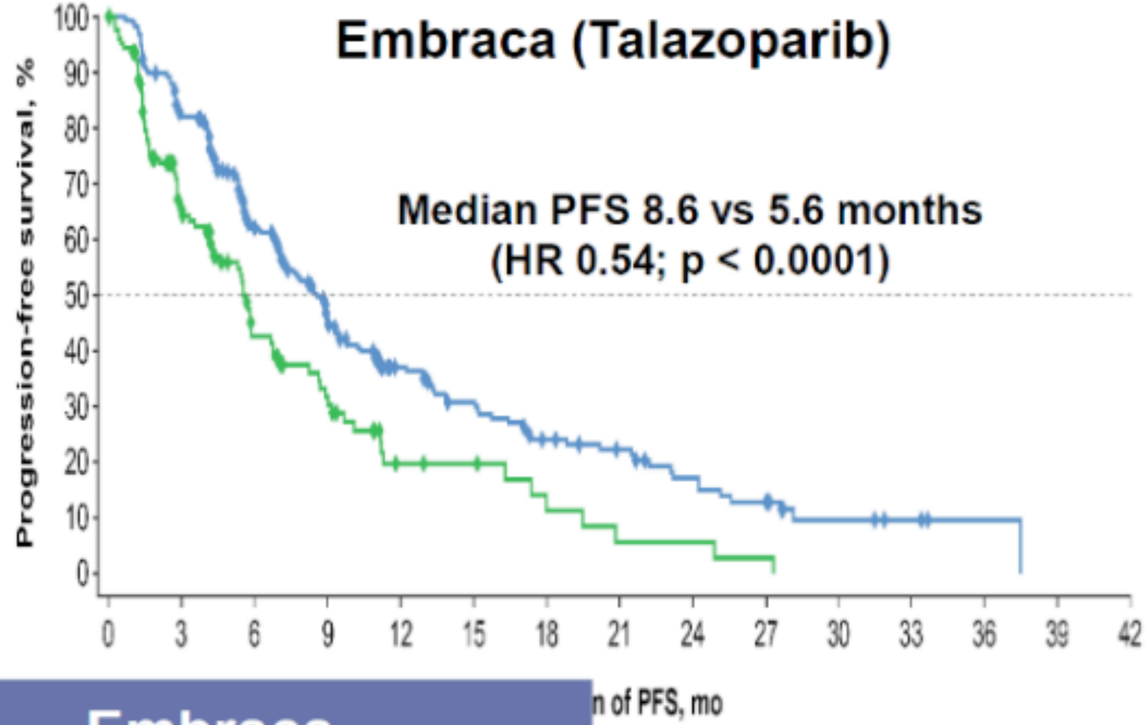


CT = Chemotherapy of physician's choice (Gemcitabine or Vinorelbine or Eribulin or Capecitabine) **no gemcitabine in OlympiAD**

Robson et al NEJM 2017; Robson et al Ann Oncol 2019; Robson et al EJC 2019; Robson et al SABCS 2019 [PD4-03]

PARP inhibitors in aTNBC



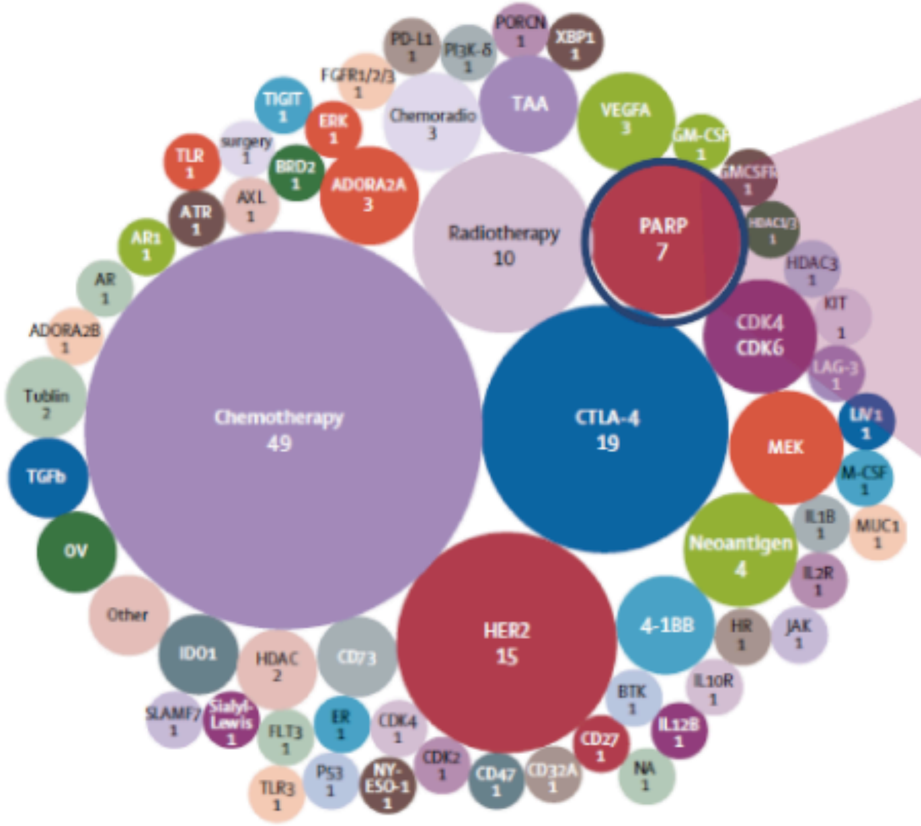


Response rates	Olympia	Embraca
PARPi	60%	62.6%
Chemo	29%	27.2%

Robson M, et al. ASCO 2017, Litton J, et al. SABCS 2017

There are many targeted therapies being investigated in combination with IO

Several trials are investigating PARPi and IO combinations as PARPi has been shown to upregulate PD-L1 expression in breast cancer cells (both BRCA-deficient and BRCA-proficient cells)[1,2]



IO-PARPi combination trials[3]

IO	PARPi	Setting	Phase
Atezolizumab	Olaparib	Locally advanced unresectable and/or metastatic HER- negative breast cancer	II
Durvalumab	Olaparib	- Resectable stage II/III TNBC - Locally advanced or metastatic platinum-treated advanced TNBC - mTNBC - Advanced or metastatic solid tumours - Locally advanced or metastatic ER-positive HER2-negative breast cancer	I/II II (DORA) II I/II (MEDIOLA) II (DOLAF)
Pembrolizumab	Olaparib	Locally advanced TNBC	II/III (KEYLYNK-009)
Pembrolizumab	Niraparib	Advanced mTNBC/OC	II (TOPACIO)
Avelumab	Talazoparib	ABC	I/II (TALAVE)

The number in each bubble indicates the number of active PD-1 and PD-L1 combination trials under investigation

ABC=advanced breast cancer; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; IO=immuno-oncology; OC=ovarian cancer; PARPi=PARP inhibitor; PD-1=programmed cell death-1; PD-L1=programmed death-ligand 1; (m)TNBC=(metastatic) triple-negative breast cancer

1. Esteva F, et al. *Lancet Oncol.* 2019;20:e175–186; 2. Jiao S, *Clin Cancer Res.* 2017;23:3711–20; 3. Peyraud F, Italiano A. *Cancers (Basel).* 2020;12(6):1502

San Antonio Breast Cancer Symposium® - December 6–10, 2022

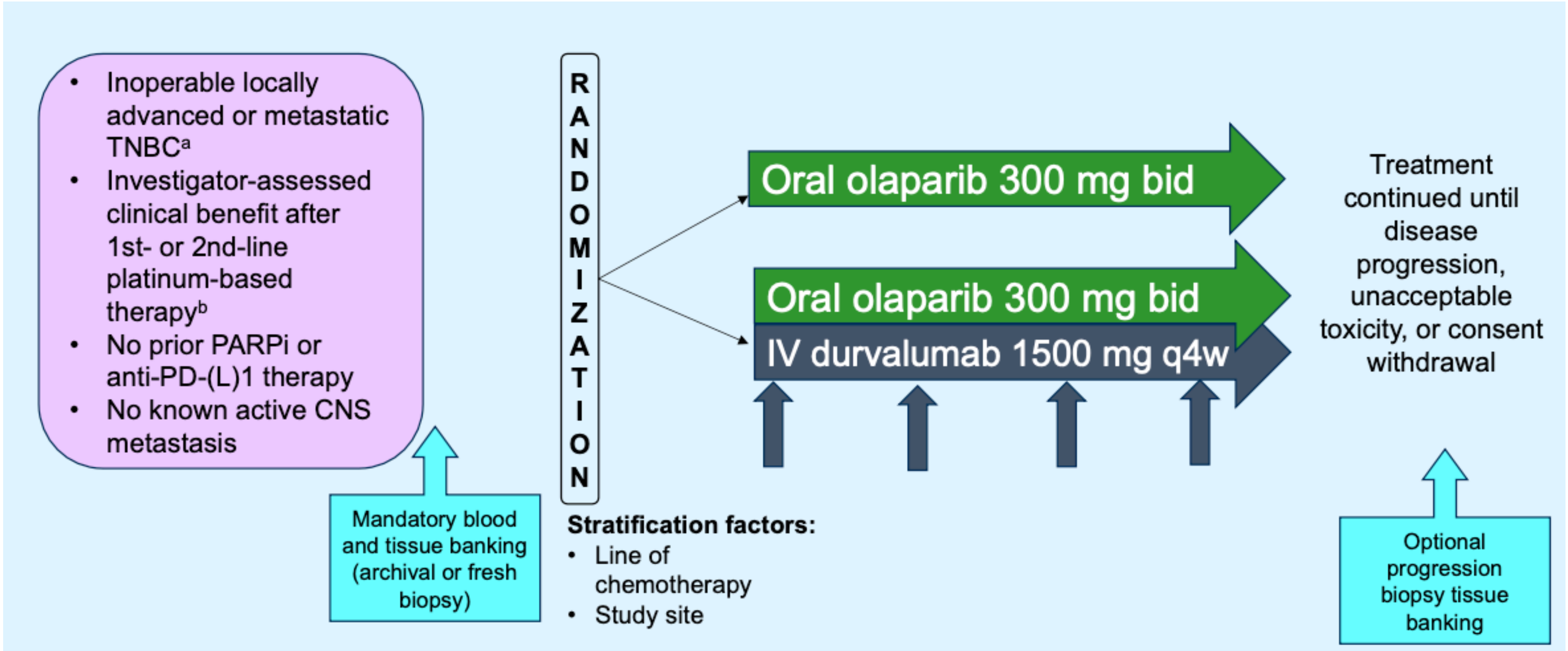
PD-11-12

DORA: A phase II, multicenter, international study of olaparib with or without durvalumab as a chemotherapy-free maintenance strategy in platinum-pretreated advanced triple-negative breast cancer (TNBC)

Sarah L. Sammons,[1,2] Tira J. Tan,[3,4] Young Hyunk Im,[5] Lilin She,[6] Kelly Mundy,[6] Robert Bigelow,[6] Tiffany A. Traina,[7] Carey Anders,[1] Ezequiel Renzulli,[8] Sung-Bae Kim,[9] Rebecca Dent[3,4]

[1]Duke Cancer Institute, Durham, NC, USA; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]National Cancer Centre Singapore, Singapore; [4]Duke-NUS Medical School, Singapore; [5]Samsung Medical Center, Seoul, Korea; [6]Duke Clinical Research Institute, Durham, NC, USA; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Tempus Labs, Inc., Chicago, IL, USA; [8]Asan Medical Center, Seoul, Korea

DORA maintenance trial design



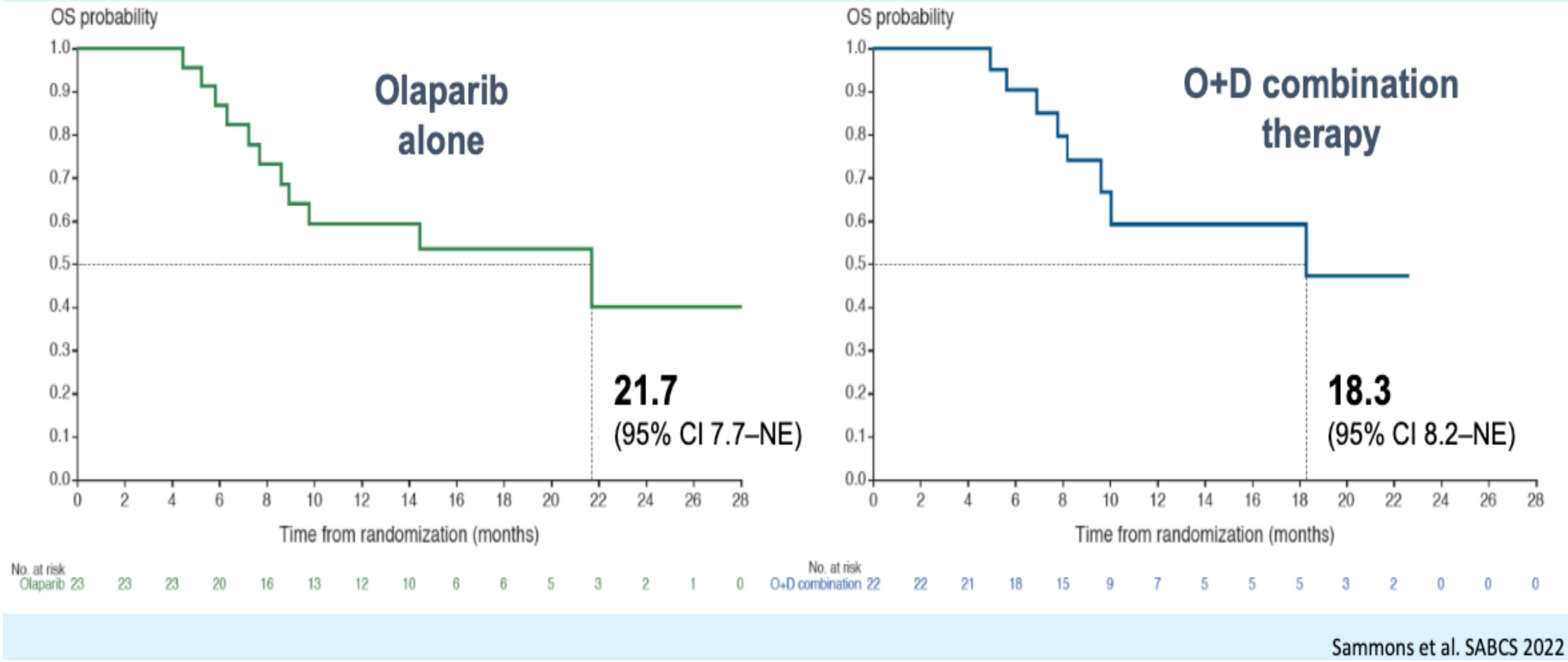
bid = twice daily; IV = intravenous; q4w = every 4 weeks.
[a]Enrollment of known g*BRCA* carriers was limited to 10 patients. [b]At least three 3-weekly cycles or at least six weekly cycles.

Sammons et al. SABCS 2022

Baseline characteristics (ITT population)

Characteristic	Olaparib alone (n=23)	O+D combination (n=22)
Median (range) age, years	48 (35–77)	51.5 (25–72)
Most recent platinum, n (%)		
1st line	18 (78)	19 (86)
2nd line	5 (22)	3 (14)
Prior platinum regimen, n (%)		
Carboplatin	16 (70)	10 (45)
Cisplatin	7 (30)	12 (55)
Single agent	2 (9)	6 (27)
Doublet with taxane	14 (61)	9 (41)
Doublet with gemcitabine	7 (30)	7 (32)
g*BRCA* status, n (%)		
Deleterious mutation	1 (4)[a]	7 (32)[b]
No mutation detected/VUS	13 (57)	6 (27)
Not tested[c]	9 (39)	9 (41)
DFI from initial diagnosis to advanced/mTNBC, n (%)		
De novo	7 (30)	4 (18)
≤1 year	3 (13)	2 (9)
>1 year	13 (57)	16 (73)

EC-DORA: Overall survival



Sammons et al. SABCS 2022

Platinum agents

TNT trial

ER-, PgR-/unknown & HER2- or known *BRCA1/2*
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

Carboplatin (C)
AUC 6 q3w, 6 cycles

On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles

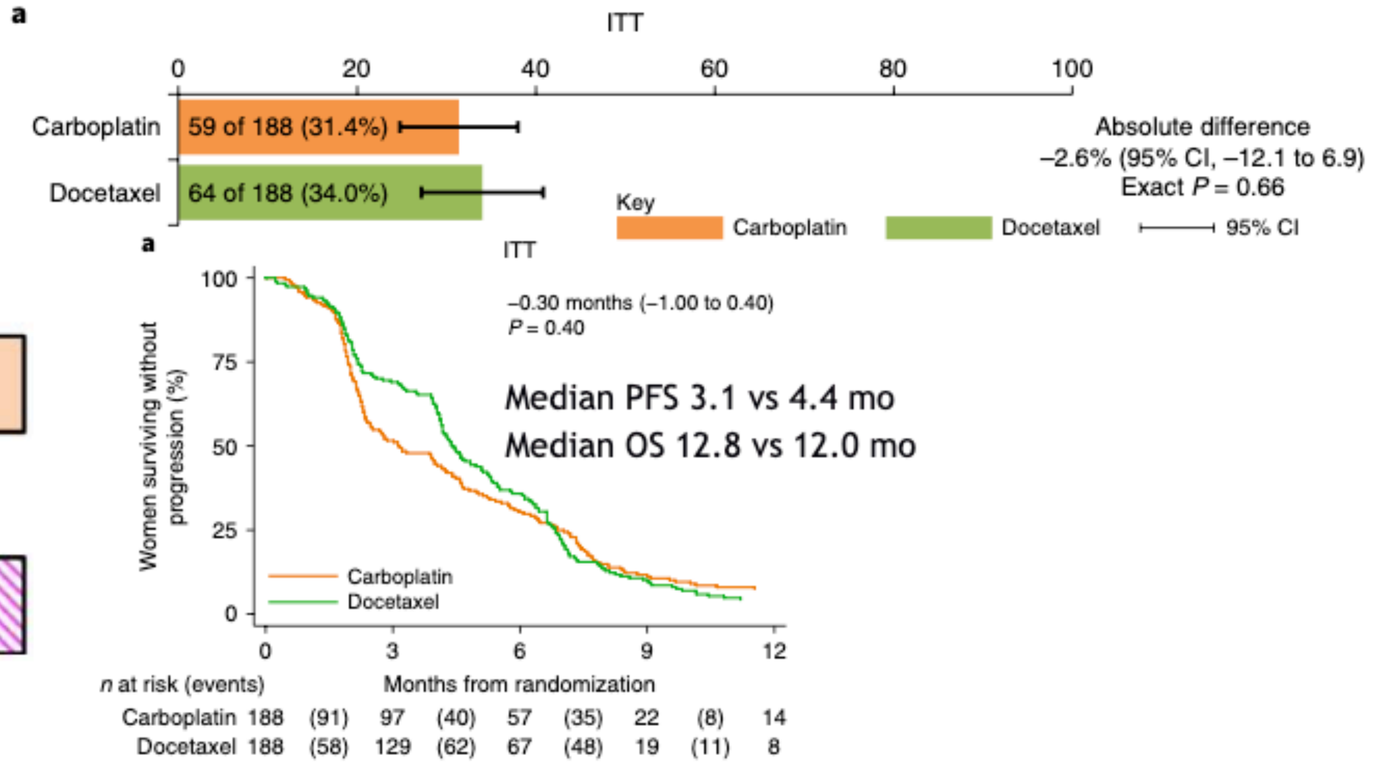
n-376

BRCA1/2 = 9%/12%

Docetaxel (D)
100mg/m² q3w, 6 cycles

On progression, crossover if appropriate

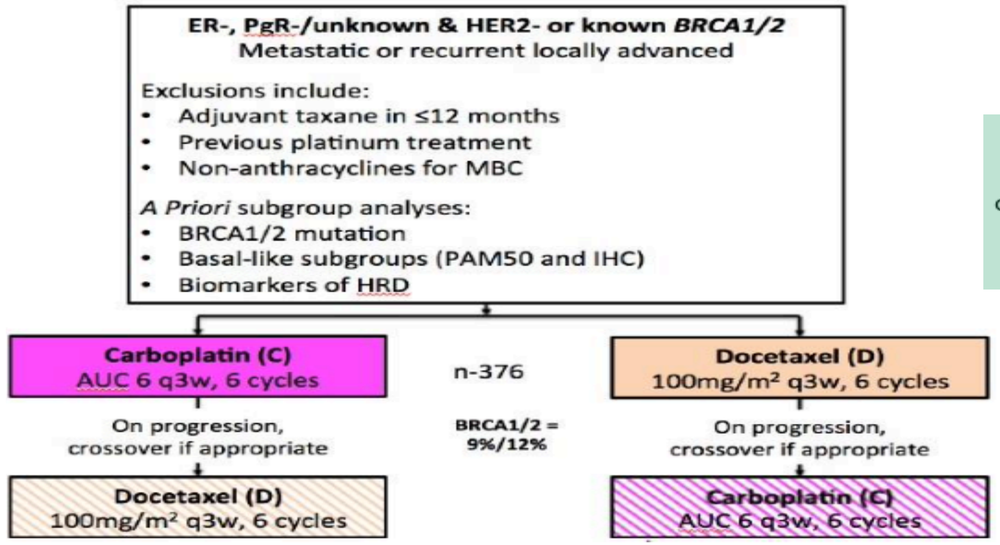
Carboplatin (C)
AUC 6 q3w, 6 cycles



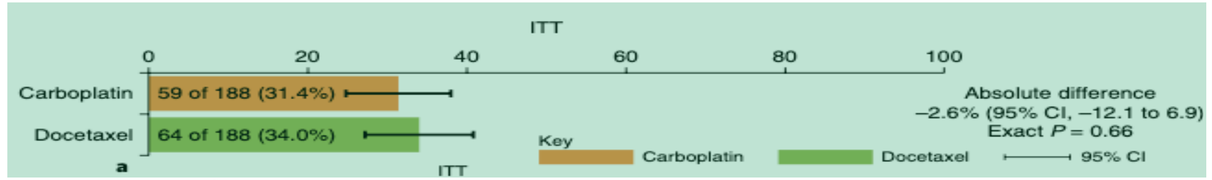
- Median 55 yrs; N=376 pts
- 33.5% previous taxanes; 72.6% gBRCA1/2 wt, 24.2% no prior adj CT
- Overall Carbo not more active than Doce (NS)

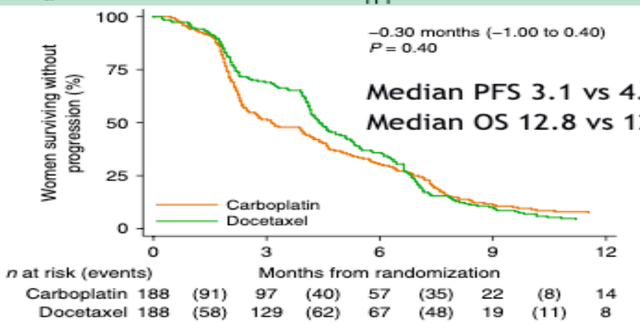
Zhu et al BBA Rev Cancer 2022

TNT trial



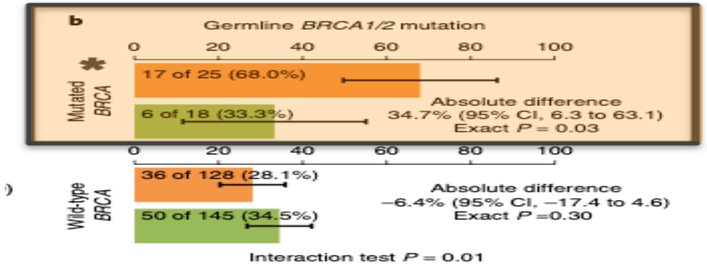
- Median 55 yrs; N=376 pts
- 33.5% previous taxanes; 72.6% gBRCA1/2 wt, 24.2% no prior adj CT

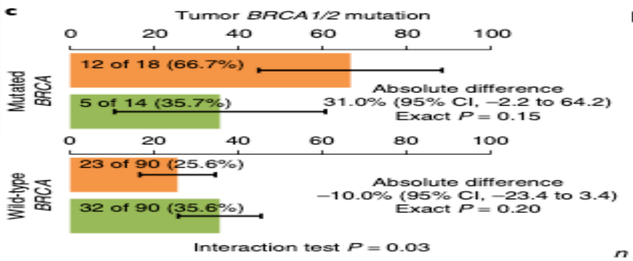


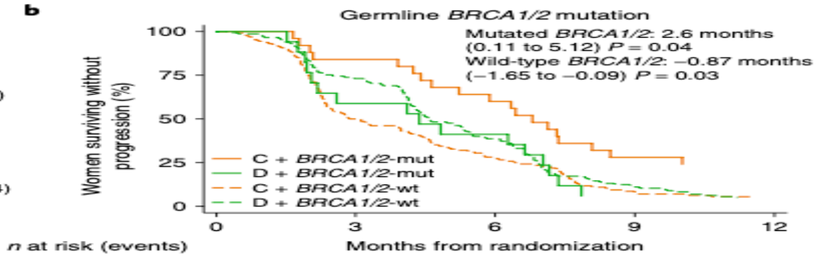


Median PFS 3.1 vs 4.4 mo
Median OS 12.8 vs 12.0 mo

Overall Carbo not more active than Doce (NS)

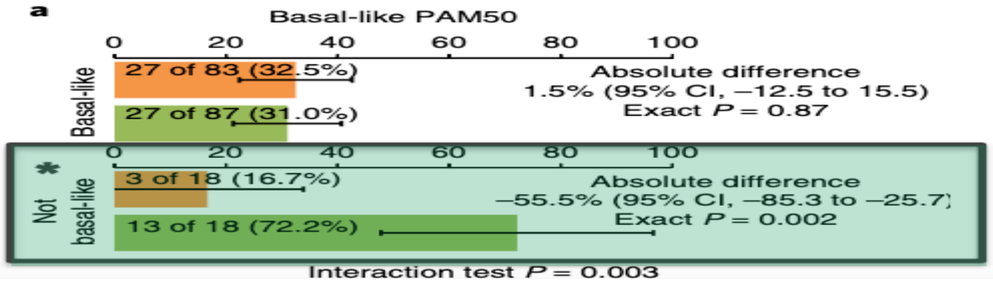






- gBRCA-BC: Carbo ORR 2x vs Doce

Median PFS (gBRCA1/2m) 6.8 vs 4.4 mo (Δ 2.6*)
No OS difference

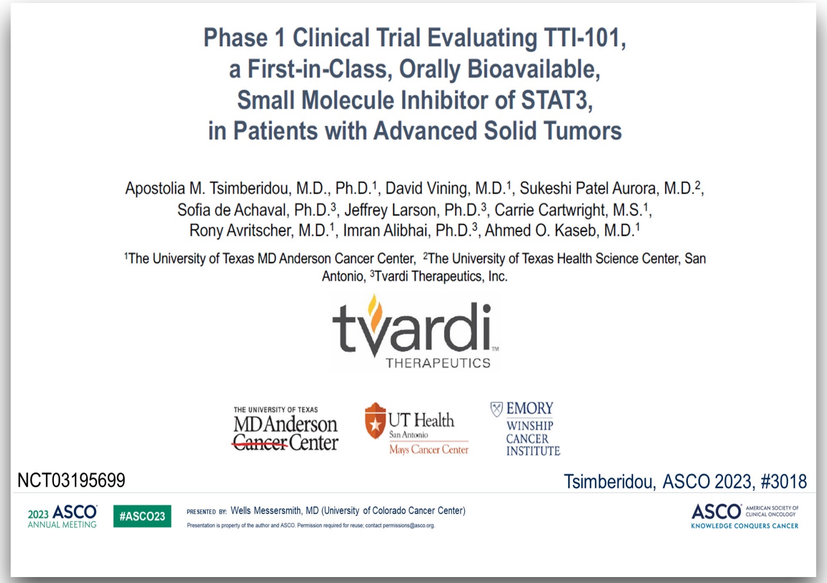


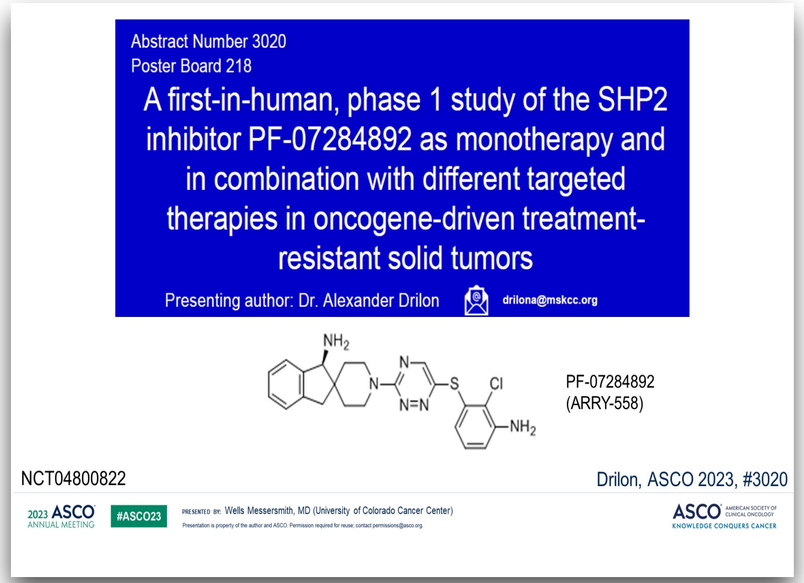
× Benefit not observed for BRCA1 methylation, BRCA1 mRNA-low tumors or Myriad HRD assay high score

Zhu et al BBA Rev Cancer 2022

New molecules

New molecules in advanced solid tumors





Tinengotinib

Small molecule/oral STAT3 inhibitor

SHP2 inhibitor

2023 ASCO ANNUAL MEETING

FUTURE-SUPER: a randomized, subtyping-based umbrella phase II trial for first-line treatment of metastatic triple-negative breast cancer

Zhi-Ming Shao, M.D., Ph.D.

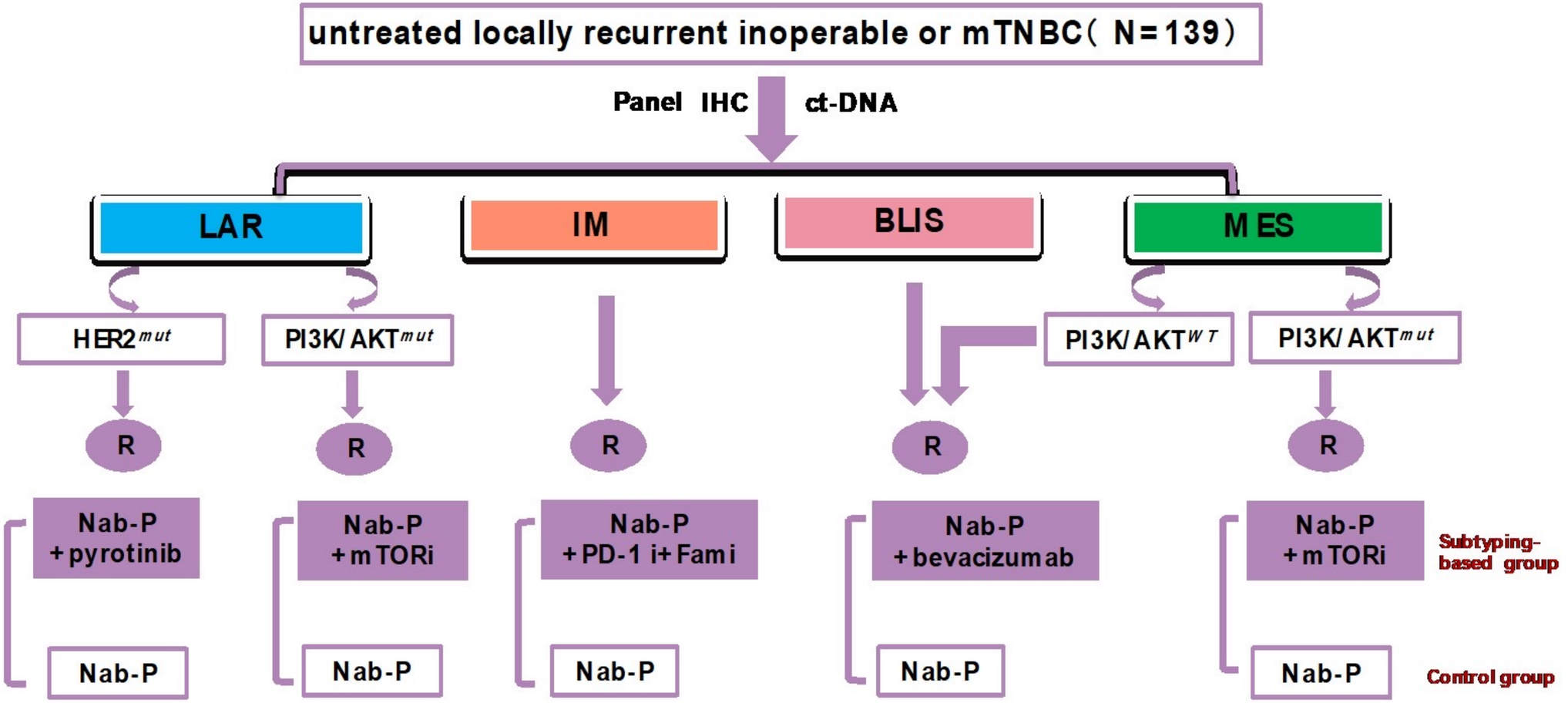
Fudan University Shanghai Cancer Center, Shanghai, China

On behalf of On behalf of Lei Fan, Linxiaoxi Ma, Songyang Wu, Li Chen, Xiyu Liu, Wenjuan Zhang, Xinyi Sui, Ruohong Shui, Wentao Yang, Xin Hu, Yizhou Jiang, Zhonghua Wang, Huajun Li

PRESENTED BY:

FUTURE-SUPER Study Design (NCT04395989)

Goal: To further evaluate the efficacy of subtyping-based therapy in the first-line treatment of mTNBC.

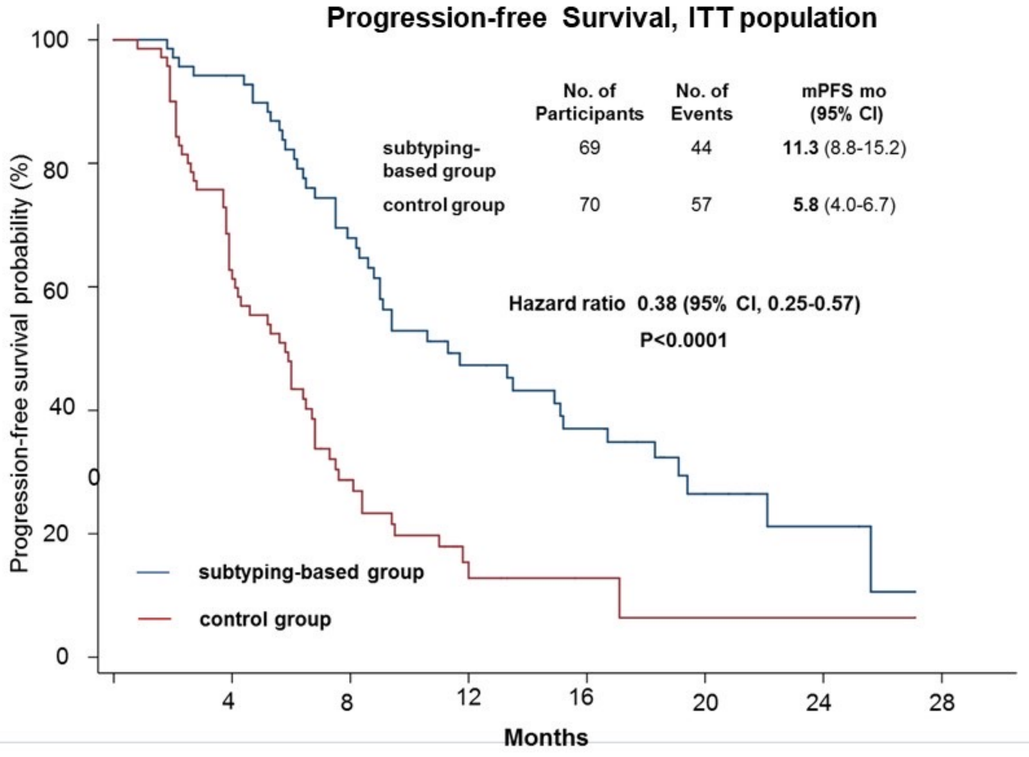


PRESENTED BY: Zhi-Ming Shao @ FUSCC

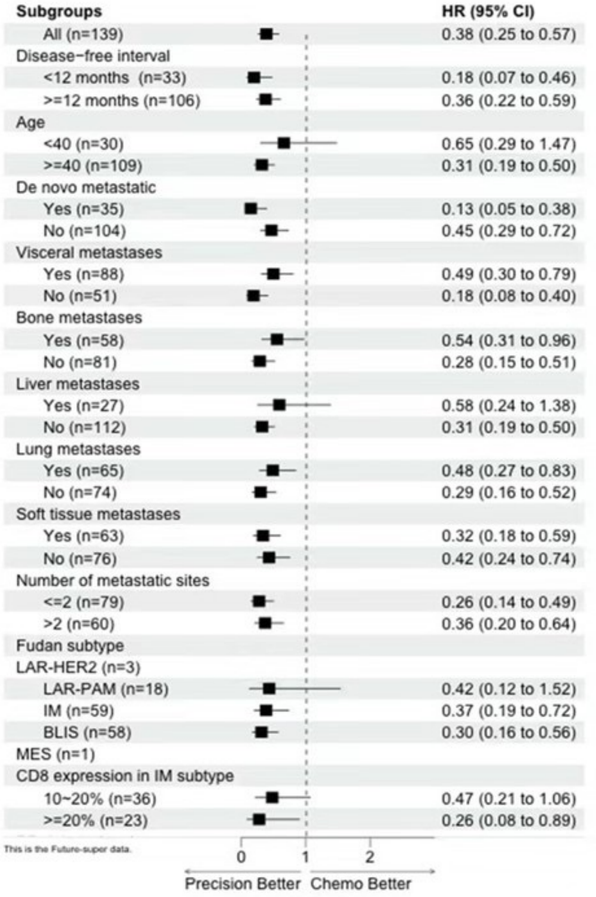
Results Primary Endpoint: mPFS (11.3m vs 5.8m)

- N = 139, F-U = 18.5 mo (range, 3.5 to 30.3),101 (72.7%) events of PFS
- **mPFS: 11.3 mo vs 5.8 mo; HR, 0.38; 95% CI, 0.25 to 0.57; *P* < 0.0001**
- **PFS advantage for the subtype-based group was observed consistently across subgroups**
- OS data were not mature

Kaplan-Meier estimates of progression-free survival.



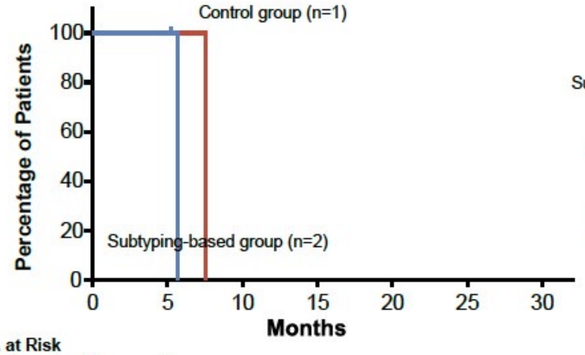
Subgroup analysis of progression-free survival.



PFS by subgroup

- PFS benefits were seen for IM, BLIS, LAR-PI3K/AKT^{mut} subtypes

LAR-HER2^{mut}

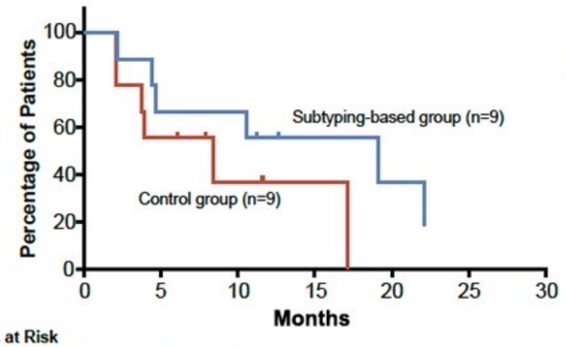


	Median Progression-free Survival (95% CI)
Subtyping-based group	5.7 (NR-NR)
Control group	NR (NR-NR)

median, 5.7 mo vs NR;
HR= NR (95% CI, 0-NR)

No. at Risk						
Subtyping-based group	2	1				
Control group	1	1				

LAR-*PI3K*/AKT^{mut}

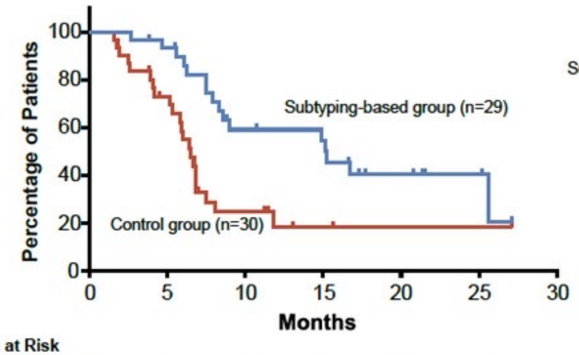


	Median Progression-free Survival (95% CI)
Subtyping-based group	19.1 (2.2-NR)
Control group	8.4 (2.1-NR)

median, 19.1 mo vs 8.4 mo;
HR=0.42; 95% CI, 0.12 to 1.53

No. at Risk					
Subtyping-based group	9	7	6	4	3
Control group	9	5	3	1	0

IM

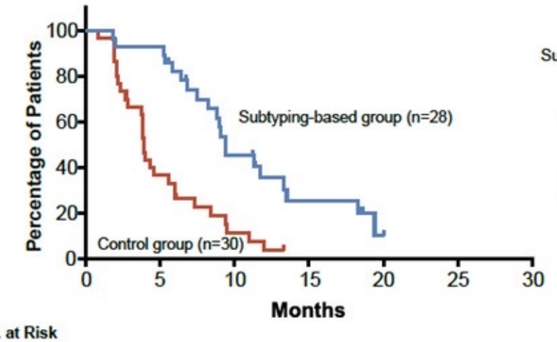


	Median Progression-free Survival (95% CI)
Subtyping-based group	15.1 (8.3-NR)
Control group	6.5 (5.2-7.5)

median, 15.1 mo vs 6.5 mo;
HR=0.37; 95% CI, 0.19 to 0.73

No. at Risk						
Subtyping-based group	29	27	14	12	6	3
Control group	30	20	7	3	2	2

BLIS/MES-*PI3K/AKT*^{WT}



	Median Progression-free Survival (95% CI)
Subtyping-based group	9.4 (7.5-13.3)
Control group	3.9 (2.8-6.0)

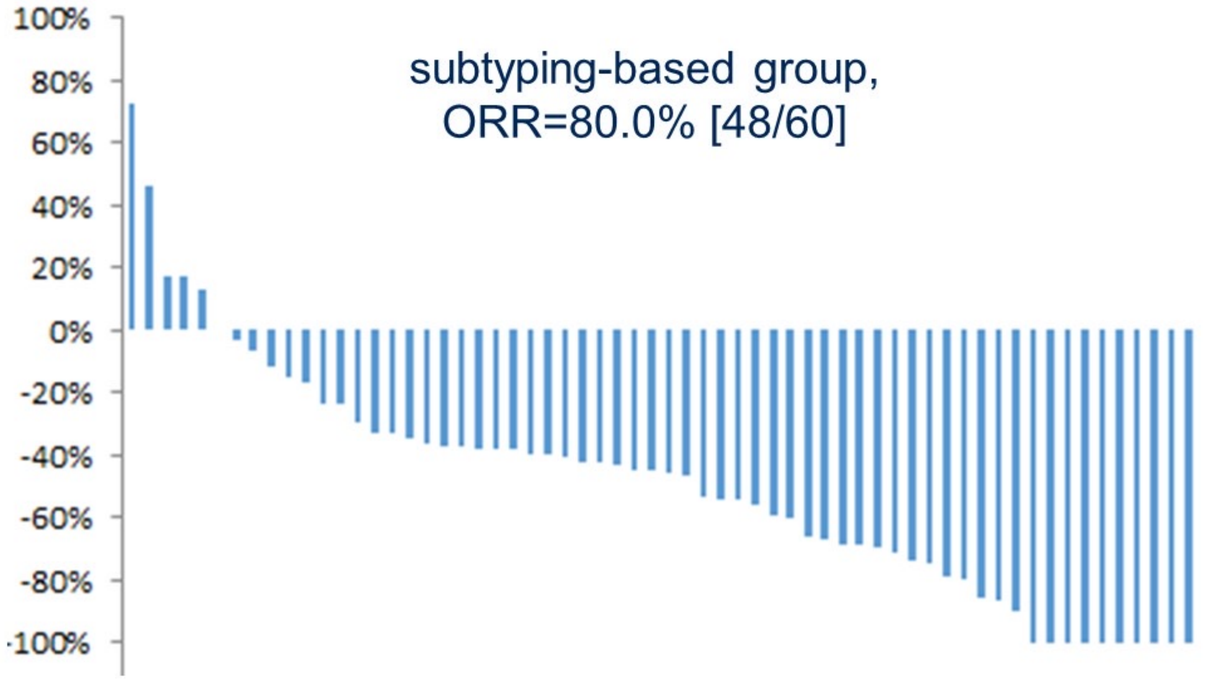
median, 9.4 mo vs 3.9 mo;
HR= 0.41; 95% CI, 0.16 to 0.56

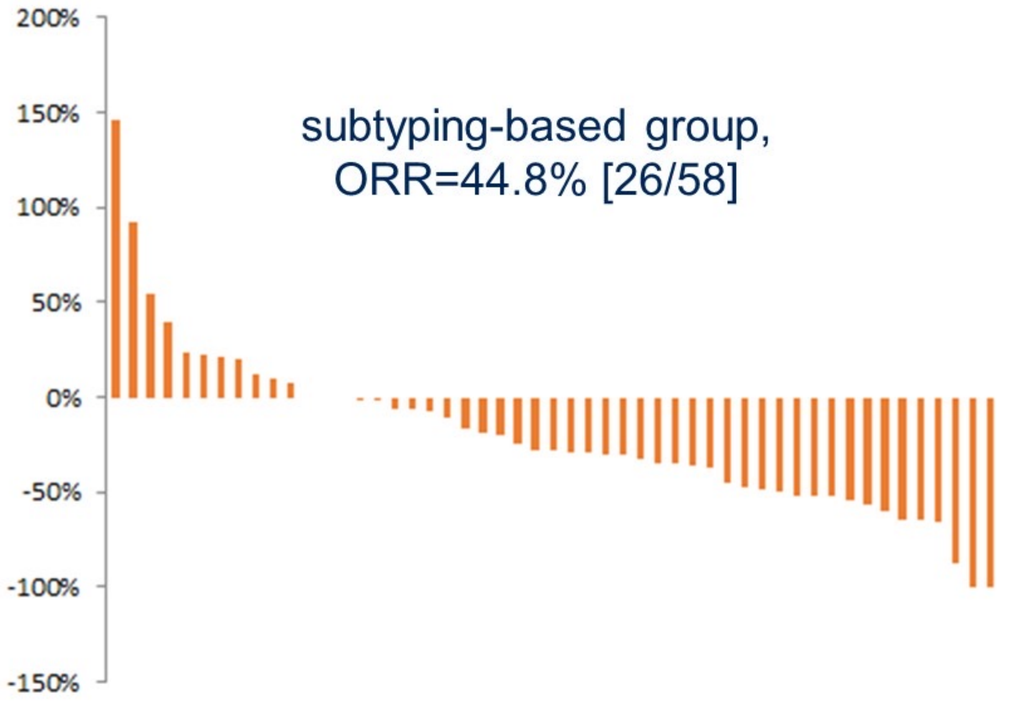
No. at Risk					
Subtyping-based group	29	27	14	12	6
Control group	30	20	7	3	2

Second Primary Endpoint-Objective Response Rate [measurable-disease population]

ORR was higher in the subtyping-based group than in the control group

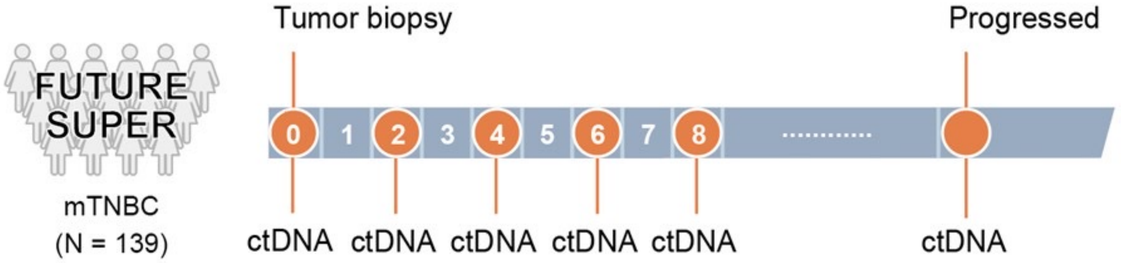
- 80.0% [48/60] vs. 44.8% [26/58]
- odds ratio, 0.20; 95% CI, 0.09 to 0.46

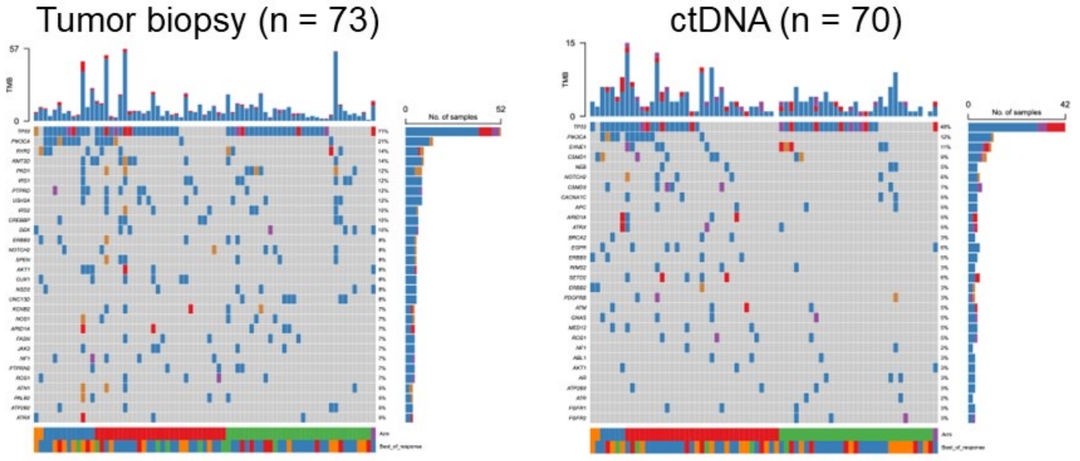


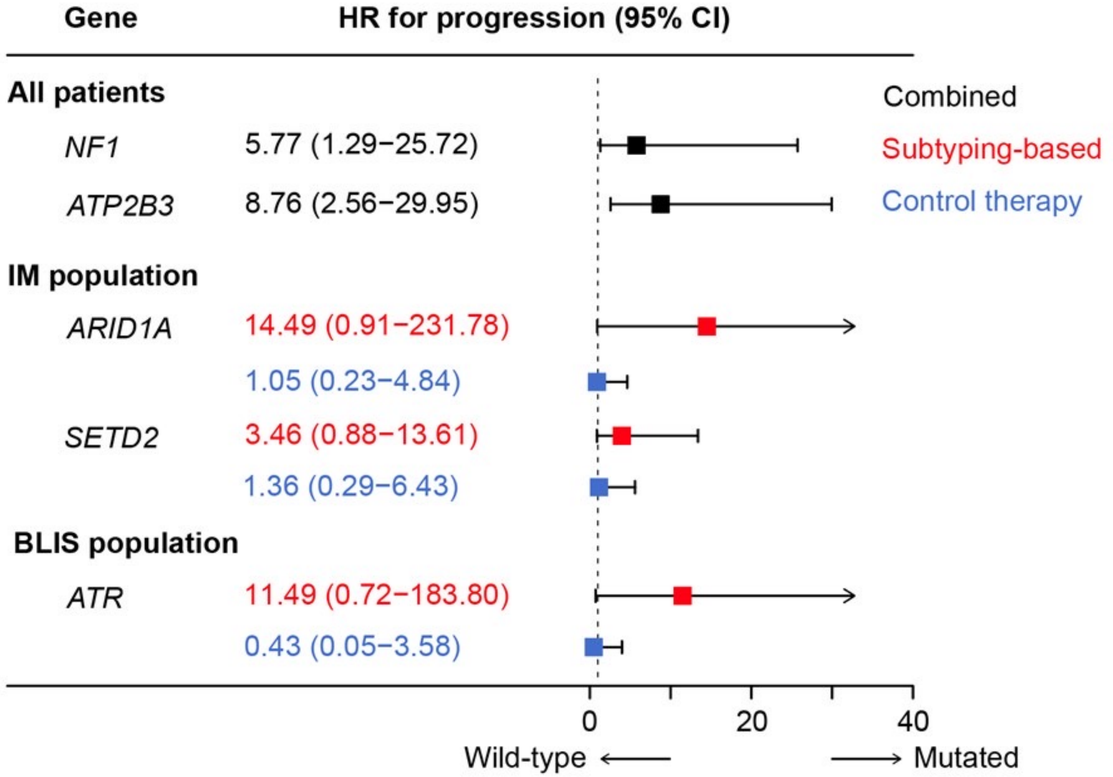


Biomarker analysis

- Frequent mutations detected in **tumor biopsy and ctDNA were highly consistent (~ 81.0%)**
- Pre-treatment *NF1*, *ATP2B3* mutations in ctDNA indicated worse prognosis, while *ARID1A*, *SETD2*, and *ATR* mutations could potentially predict the efficacy of subtyping-based therapy







Therapy sequencing in mTNBC

1st line	Chemotherapy +/- Pembrolizumab
	PARPi if gBRCA1/2 mutation
2nd line +	Sacituzumab govitecan
	PARPi if gBRCA1/2 mutation
	Trastuzumab deruxtecan if HER2 low
	Chemotherapy

Hope Rufo. SABCS 2021

Conclusions

- ***AURORA AMERICANO y EUROPEO*:** tanto el tumor primario como la metástasis del cáncer de mama TRIPLE NEGATIVO, genéticamente tienen un patrón de transcripción génica mucho más parecido frente a los HER2 o LUMINALES.
- ***KEYNOTE-355*** ha establecido el tratamiento estándar de 1º línea en TNBC irresecable o metastásico + PD-L1 (CPS ≥10): Pembrolizumab en combinación con quimioterapia.
- La ***quimioterapia puede ser inmunomodulador:***
  - Inducción de muerte celular inmunogénica, vías moleculares, regulación positiva de PD-L1
  - Reducción de la inmunosupresión
- La quimioterapia sigue siendo el tratamiento de referencia del TNBC, aunque queda por aclarar el ***uso óptimo de los agentes basados en platino:***
  - Las pacientes con mutación germinal en BRCA1-2 son las que obtienen mayor beneficio.
- ***SACITUZUMAB GOVITECAN*** se ha establecido como una opción de tratamiento estándar en cáncer de mama TN irresecable o metastásico (CMTNm) tras dos o más tratamientos sistémicos previos, incluido al menos uno de ellos para la enfermedad avanzada.
- Se ha observado actividad clínica de **patritumab deruxtecan** en un amplio rango de niveles de expresión de membrana de HER3 en pacientes con cáncer de mama con metástasis ER+ y TN muy pretratados.
- La optimización del ***uso secuencial de los conjugados de fármacos y anticuerpos (ADC)*** es un área de necesidad insatisfecha y de creciente importancia clínica.
- Necesitamos conocer los ***niveles de TARGET EXPRESSION del tumor:***
  - HER2: SI
  - TROP-2: Preferible.
  - HER-3: Todavía no está claro
- El ***tratamiento de precisión*** basado en la subtipificación, en primera línea de TNBC avanzado, ha demostrado profundos beneficios clínicos y ha delineado una dirección para una mayor exploración.

Muchas gracias