Sequencing Therapy for Metastatic Triple Negative Breast Cancer: Immunotherapy, PARP Inhibitors, and Antibody- Drug Conjugates

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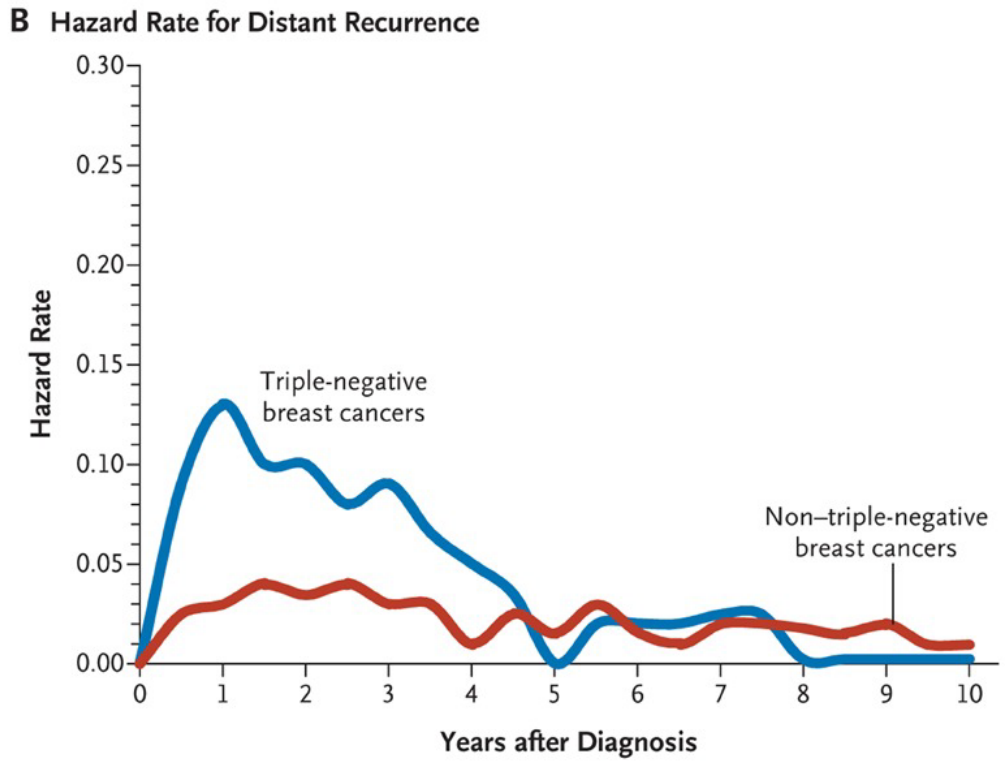
Disclosures

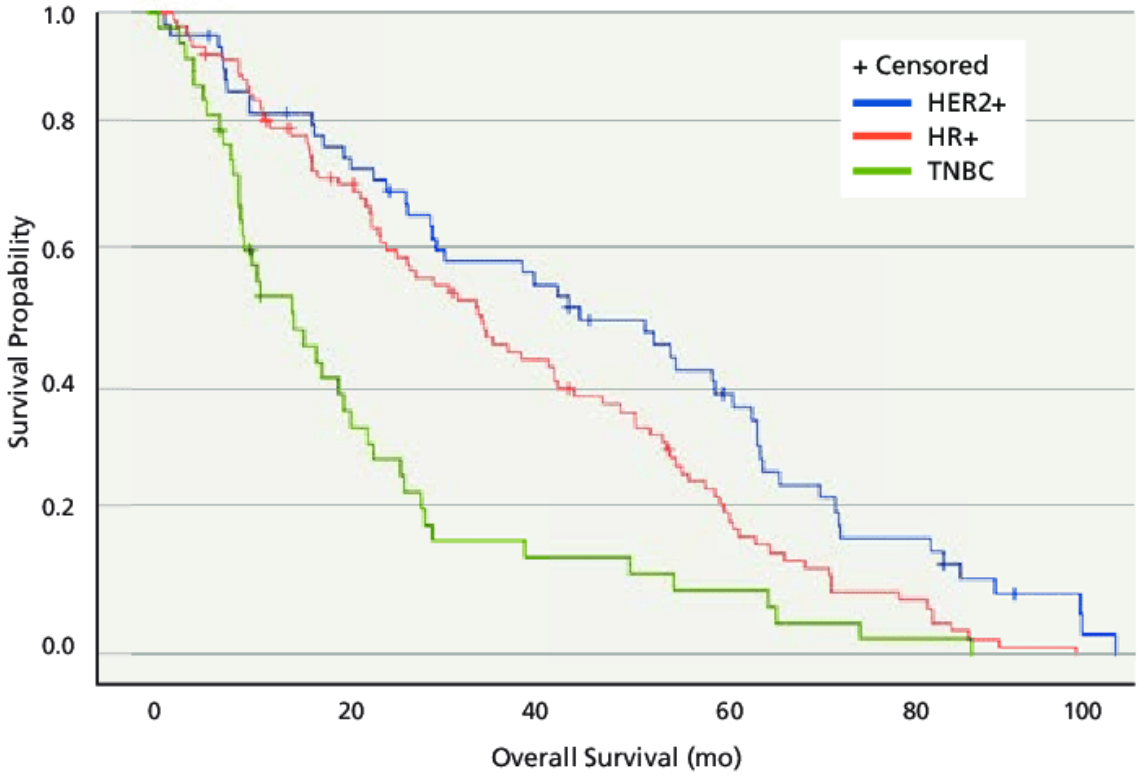
None

TNBC: Increased recurrence and Poor survival

Majority of Recurrences in first 4 years



Metastatic Breast cancer Survival by Subtype

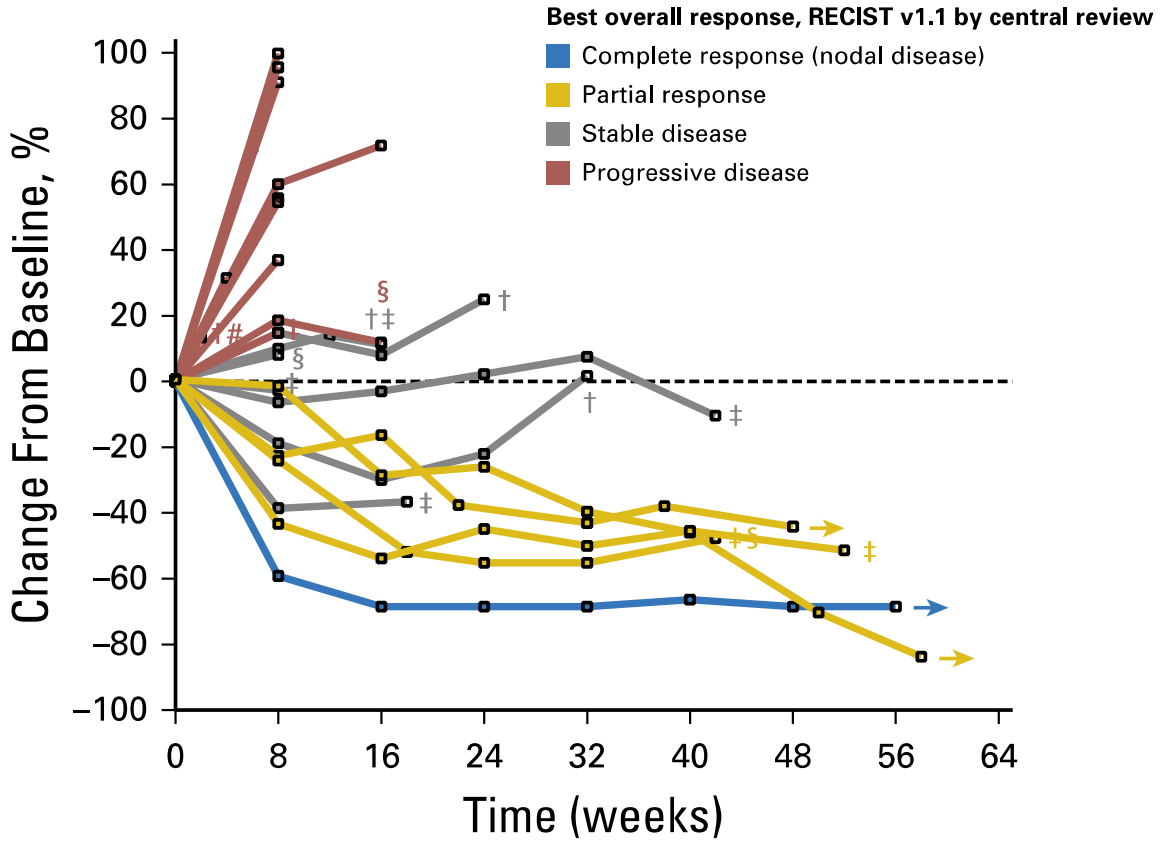


Foulkes WD et al. N Engl J Med. 2010 Nov 11;363(20):1938-48.
Seah DS, et al. J Natl Compr Canc Netw. 2014 Jan;12(1):71-80.

Pembrolizumab in Metastatic TNBC: Limited Monotherapy Response, but Durable

Pembrolizumab monotherapy Response Rates

Study	N	% ORR-PD-L1+
KN-012/1L+	27	18.5
KN-086- B/1L	84	21.4
KN-086-A/2L+	170	5.7

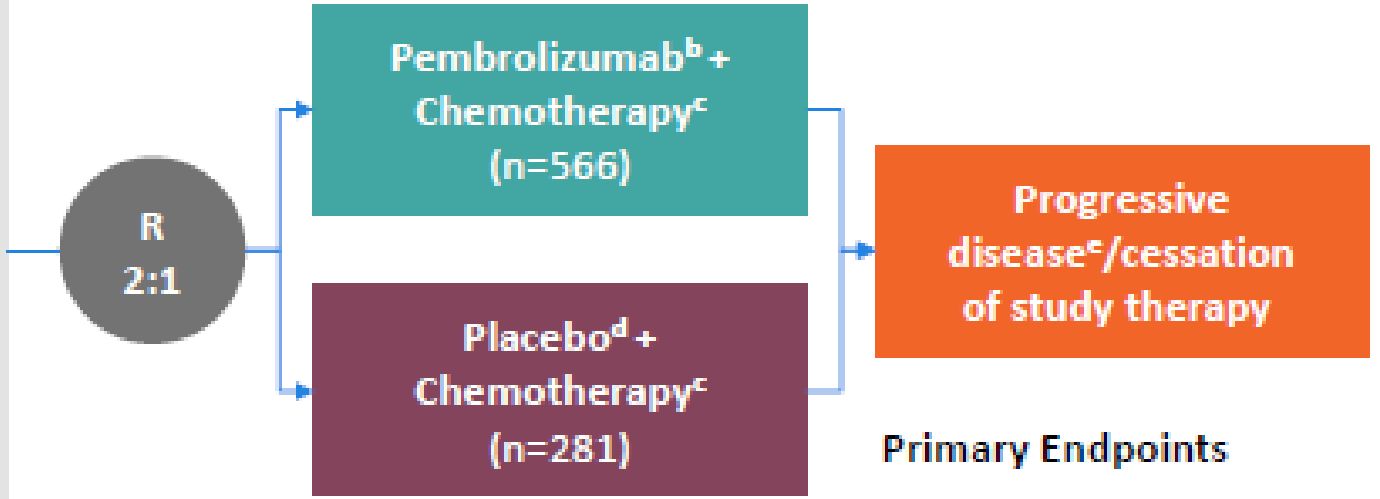


Nanda. J Clin Oncol. 2016;34:2460. Adams. Ann Onc. 2019;30:405. Adams. Ann Oncol. 2019;30:397.

KEYNOTE -355: Chemotherapy +/- Pembrolizumab in Advanced TNBC

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 PS 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systematic steroids
- No active CNS metastases
- No active autoimmune disease



Primary Endpoints

- PFS in PD-L1-positive population (CPS ≥10 and CPS ≥1) and ITT population
- OS in PD-L1-positive population (CPS ≥10 and CPS ≥1) and ITT population

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)

Baseline Characteristics, ITT

Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastasis	167 (29.5)	84 (29.9)
<12 months	126 (22.3)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

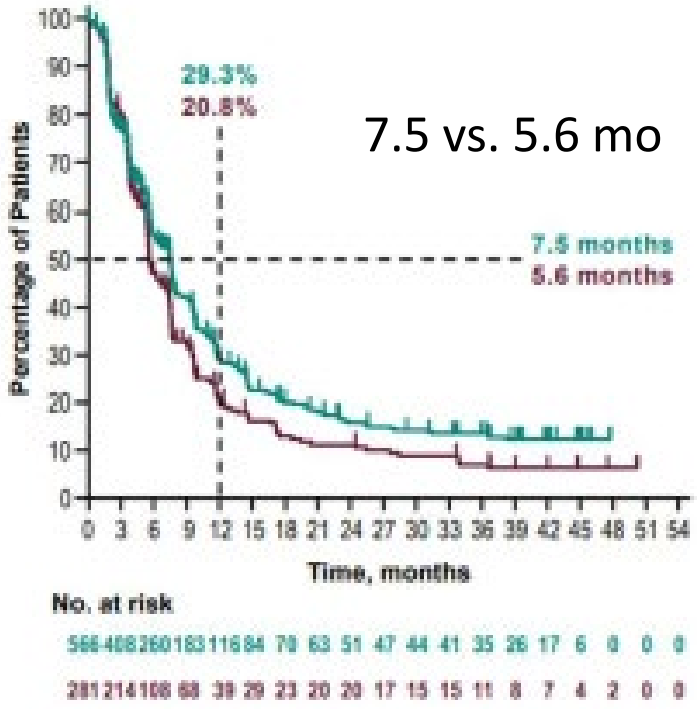
Data cutoff date: December 11, 2019.

Cortes J et al. ASCO 2020. Abstract 1000.

KN-355: Pembrolizumab Improved PFS in PD-L1 CPS ≥10

ITT

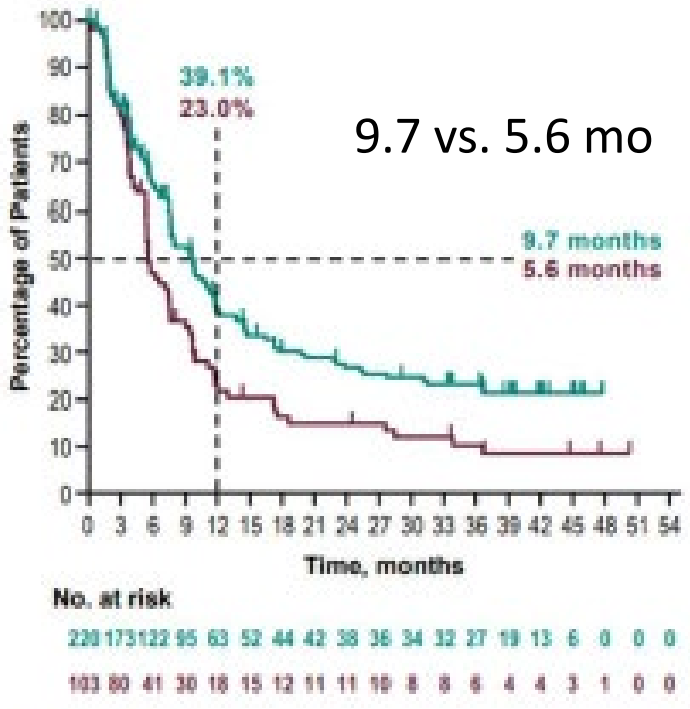
	n/N	Events	HR (95% CI)
Pembro + Chemo	406/566	71.7%	0.82 (0.70-0.98)
Placebo + Chemo	217/281	77.2%	



7.5 vs. 5.6 mo

PD-L1 CPS ≥10

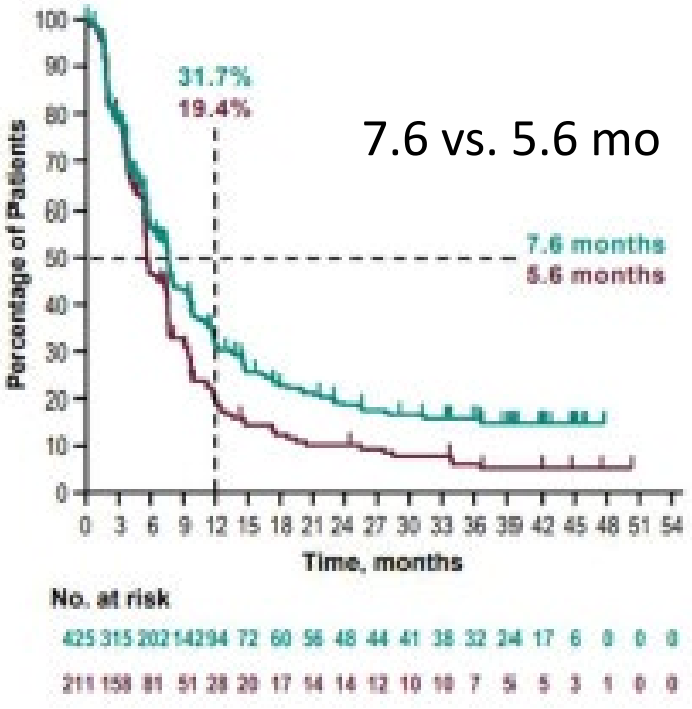
	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



9.7 vs. 5.6 mo

PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)
Pembro + Chemo	299/425	70.4%	0.75 (0.62-0.91)
Placebo + Chemo	166/211	78.7%	



7.6 vs. 5.6 mo

Data cutoff: June 15, 2021

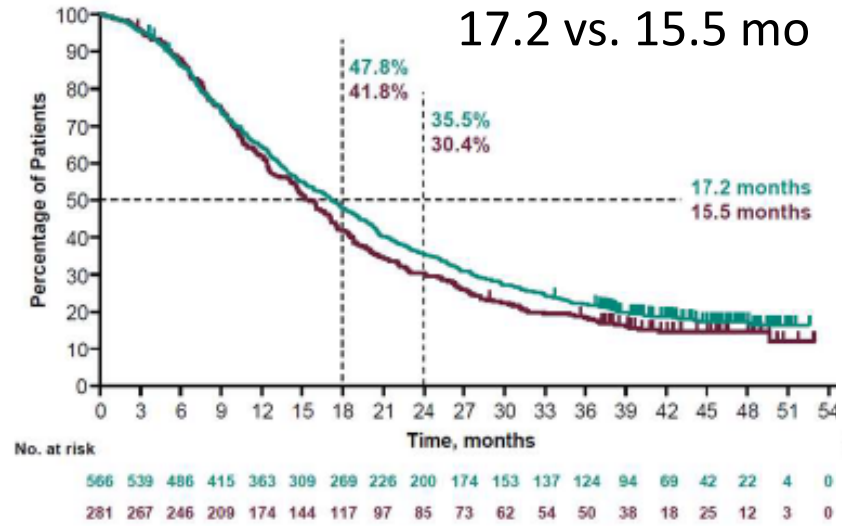
Rugo et al. ESMO 2021

KN-355: Pembrolizumab Improved OS in PD-L1 CPS ≥10

ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)
Placebo + Chemo	238/281	84.7%	

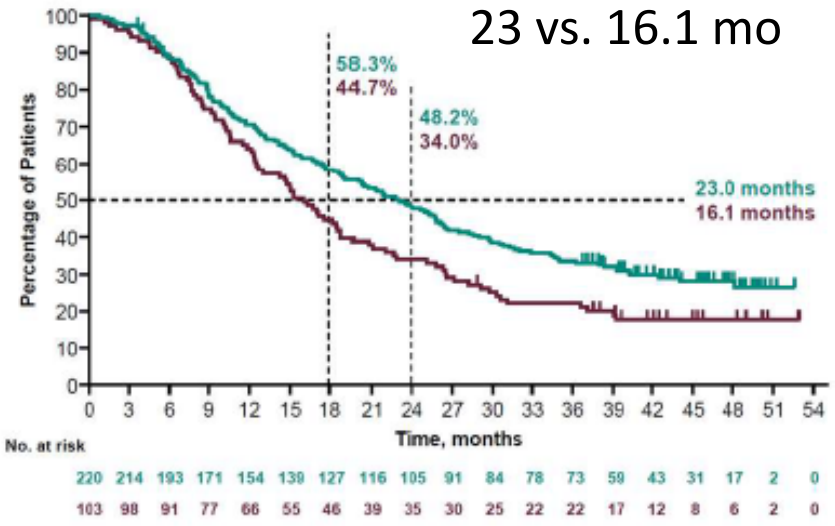
17.2 vs. 15.5 mo



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%		

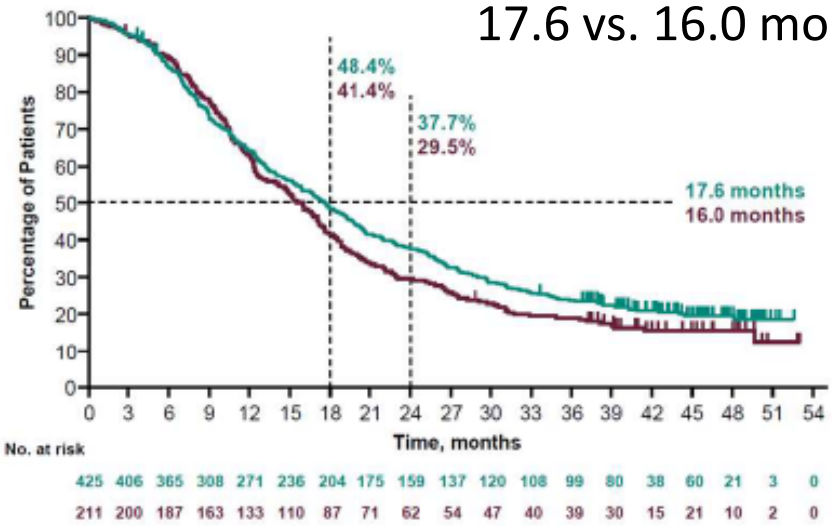
23 vs. 16.1 mo



PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[a]
Placebo + Chemo	177/211	83.9%		

17.6 vs. 16.0 mo

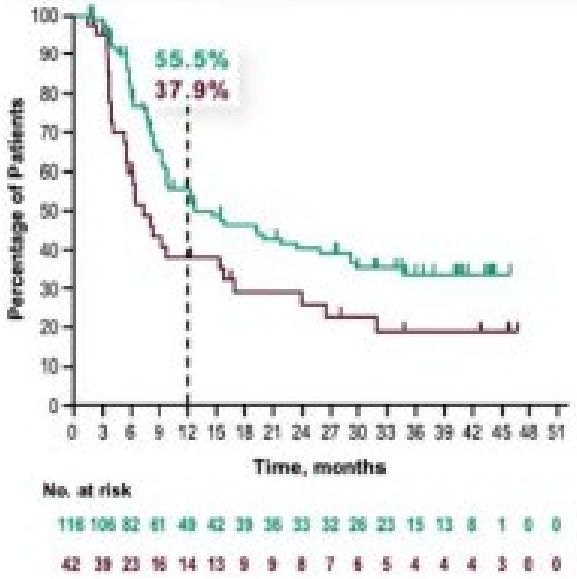


Rugo et al. ESMO 2021

KN-355 Duration of Response and Overall Survival by PD-L1 CPS

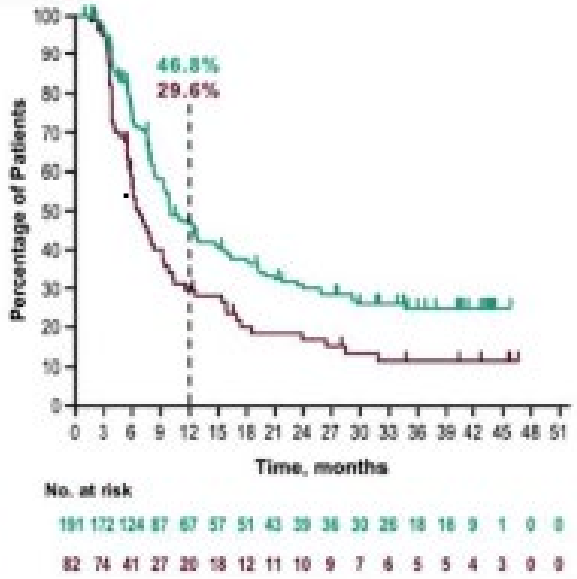
PD-L1 CPS ≥10

Duration of Response	Median, mo (range)
Pembro + Chemo	12.8 (1.6+ to 45.9+)
Placebo + Chemo	7.3 (1.5 to 46.6+)



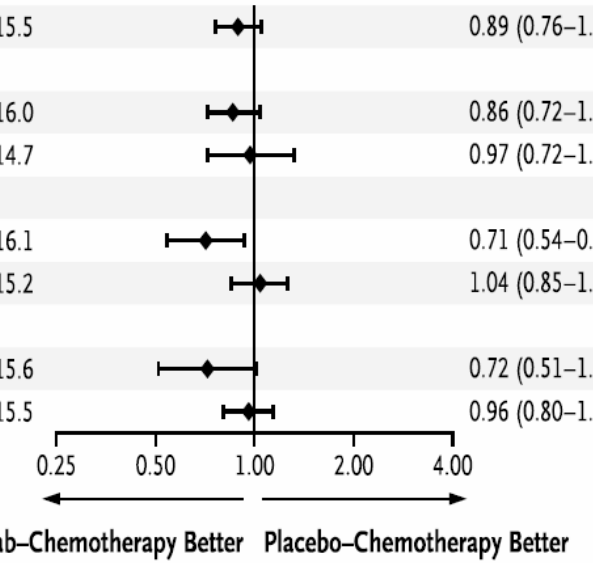
PD-L1 CPS ≥1

Duration of Response	Median, mo (range)
Pembro + Chemo	10.1 (1.0+ to 45.9+)
ebo + Chemo	6.8 (1.5 to 46.6+)



Rugo et al, ESMO LBA16 ESMO 2021.

Subgroup	No. of Patients	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)

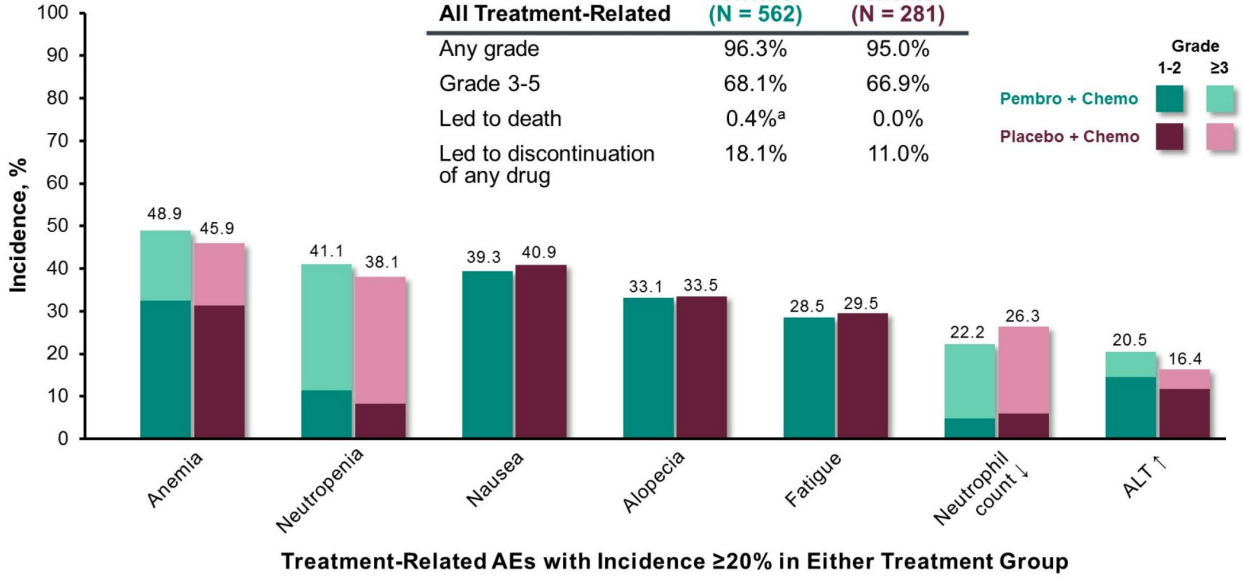


Cortes J, et al. *N EnglJ Med*. 2022;387:217-226

KN-355 Adverse Events

Treatment-Related AEs

All Treatment-Related	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	96.3%	95.0%
Grade 3-5	68.1%	66.9%
Led to death	0.4%[a]	0.0%
Led to discontinuation of any drug	18.1%	11.0%

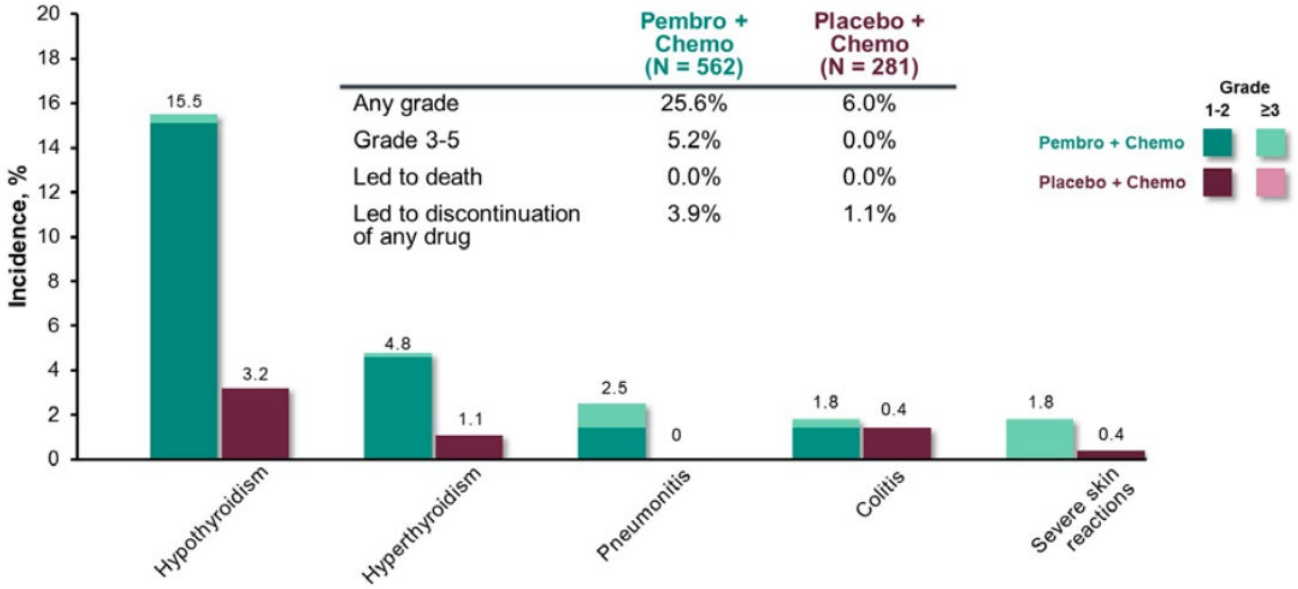


Treatment-Related AEs with Incidence ≥20% in Either Treatment Group

[a]1 patient from acute kidney injury and 1 patient from pneumonia. Data cutoff date: December 11, 2019.

Immune-Mediated AEs

	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%



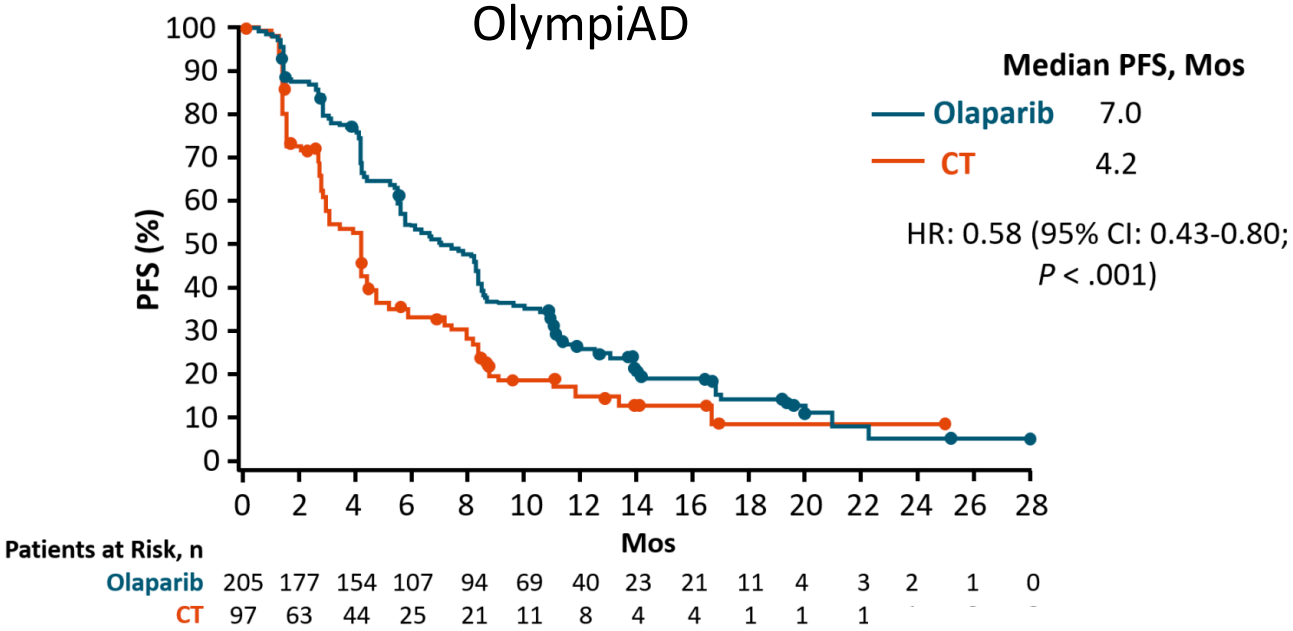
Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group[a]

[a]Based on a list of terms prespecified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included. Data cutoff date: December 11, 2019.

Cortes J et al. ASCO 2020. Abstract 1000.
Lancet. 2020;396 (10265): 1817-1828

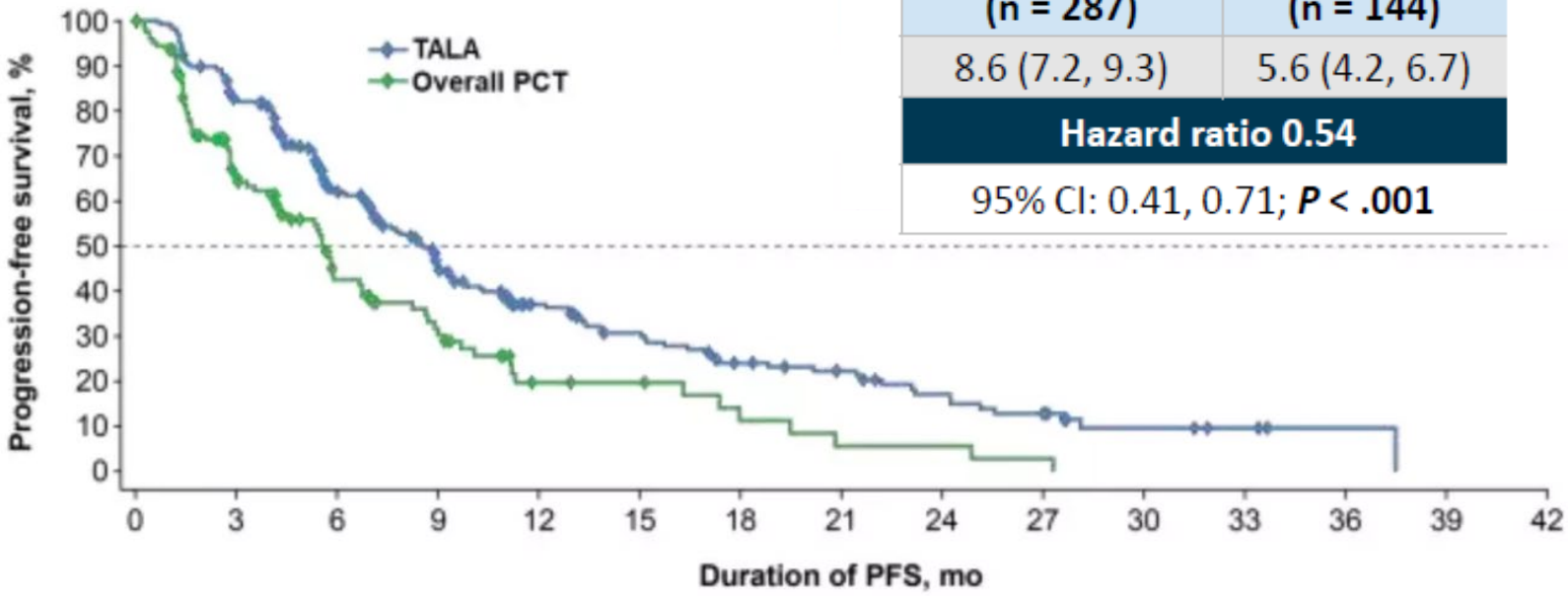
PARP Inhibitors Improve PFS in BRCAmut Metastatic Breast Cancer

OlympiAD



EMBRCA

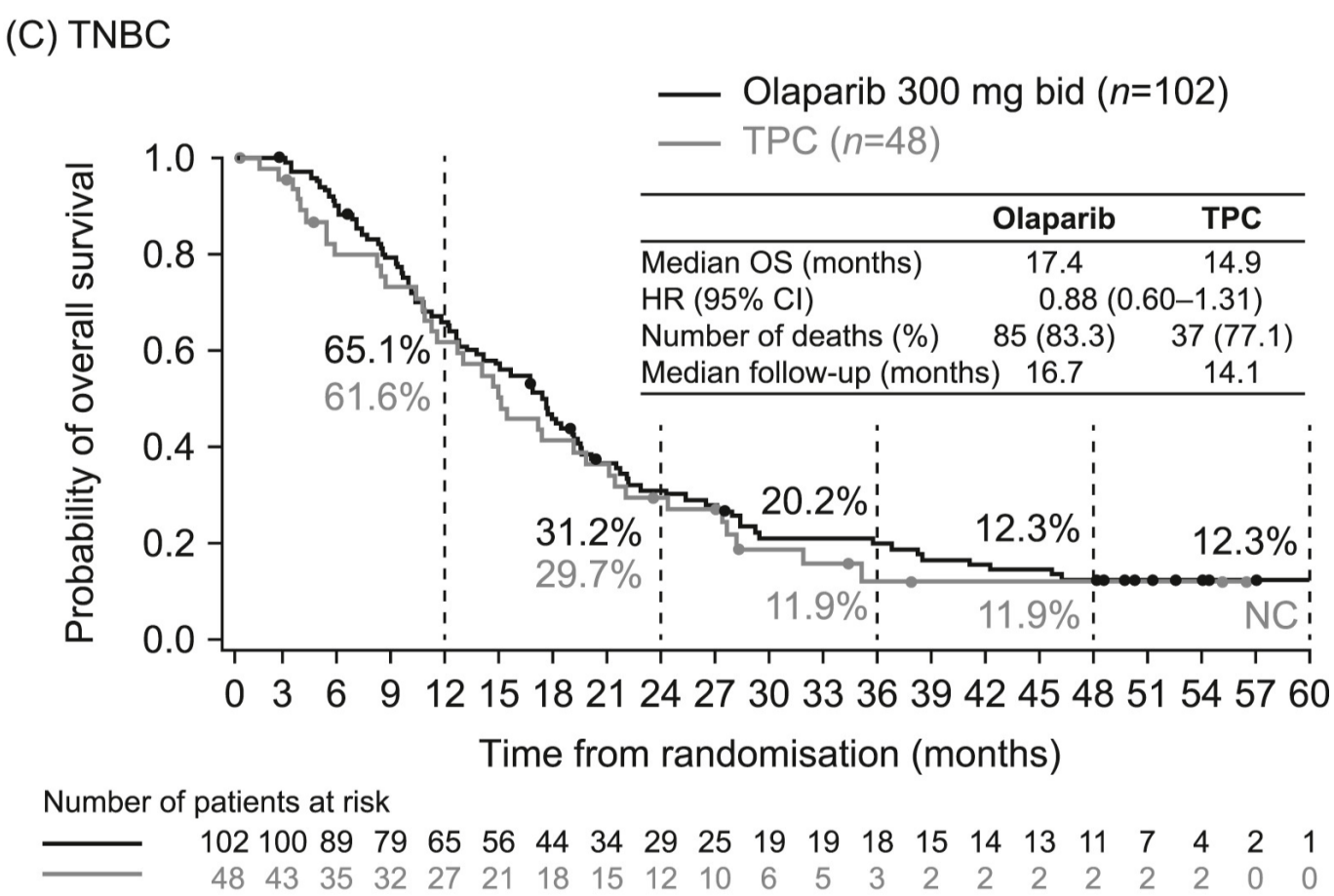
Talazoparib (n = 287)	Overall PCT (n = 144)
8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio 0.54	
95% CI: 0.41, 0.71; ***P* < .001**	

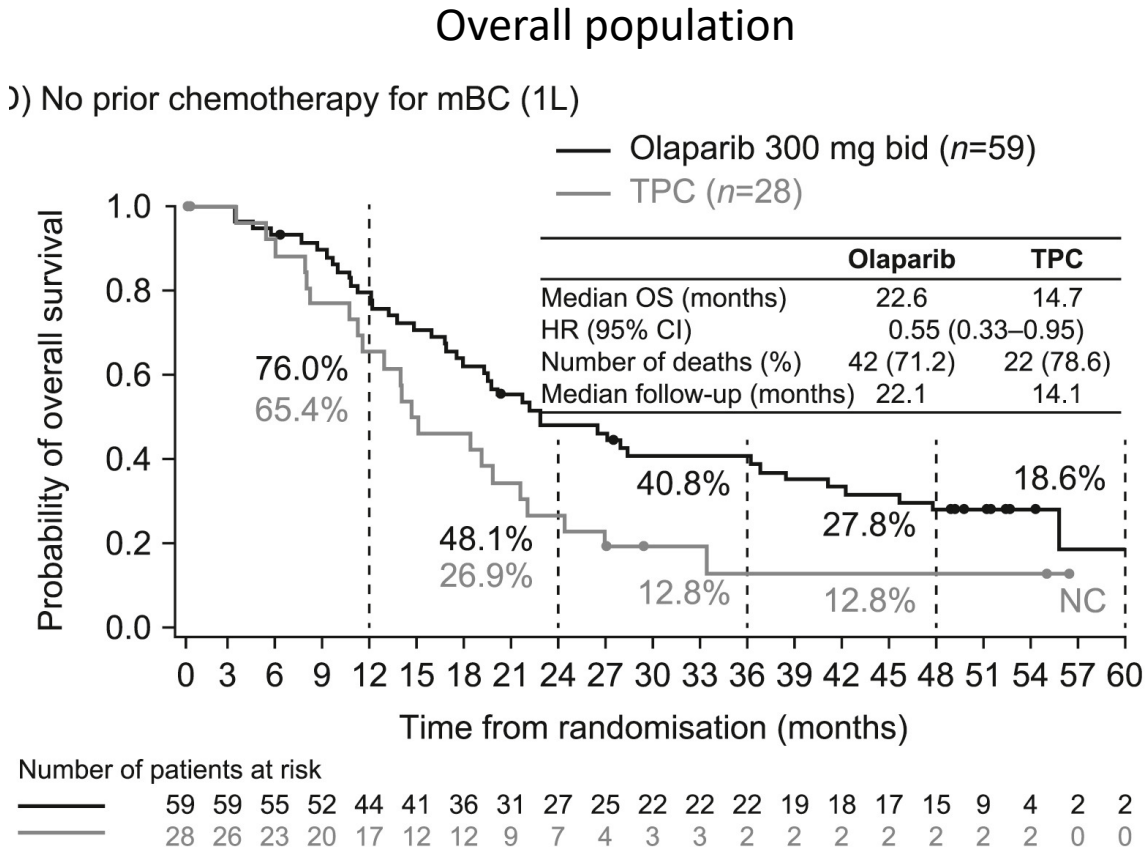


Robson M et al. *NEJM*. 2017;377(6):523-533 Litton JK et al. *NEJM*.2018;379(8):753-763.

PARP Inhibitors: OlympiAD Overall Survival

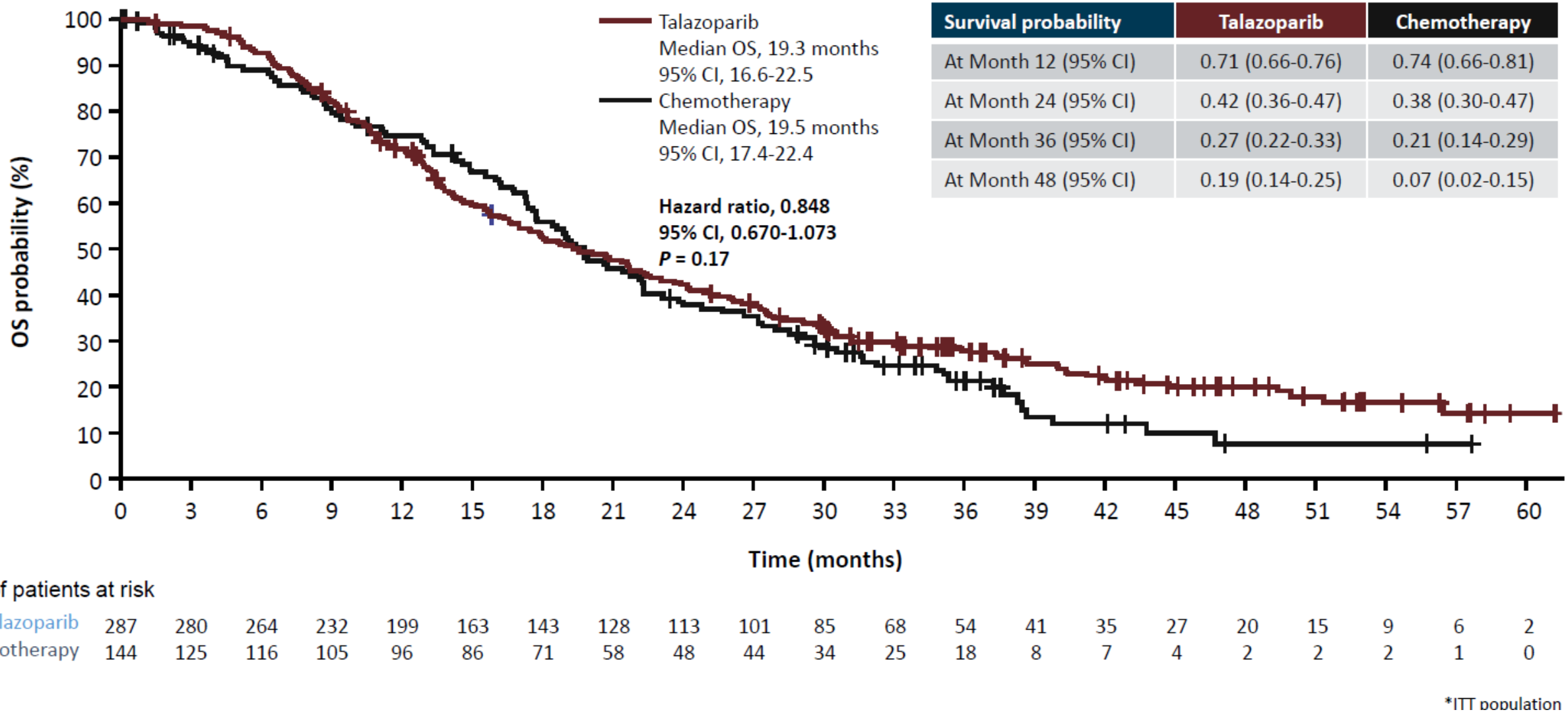
Overall, 8.8% on Olaparib vs. no patients in TPC at 3 yrs





Robson ME, et al. Eur J Cancer. 2023 May;184:39-47.

EMBRACA: Final OS



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
At Month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
At Month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
At Month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

Number of patients at risk

Talazoparib	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
Chemotherapy	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

*ITT population

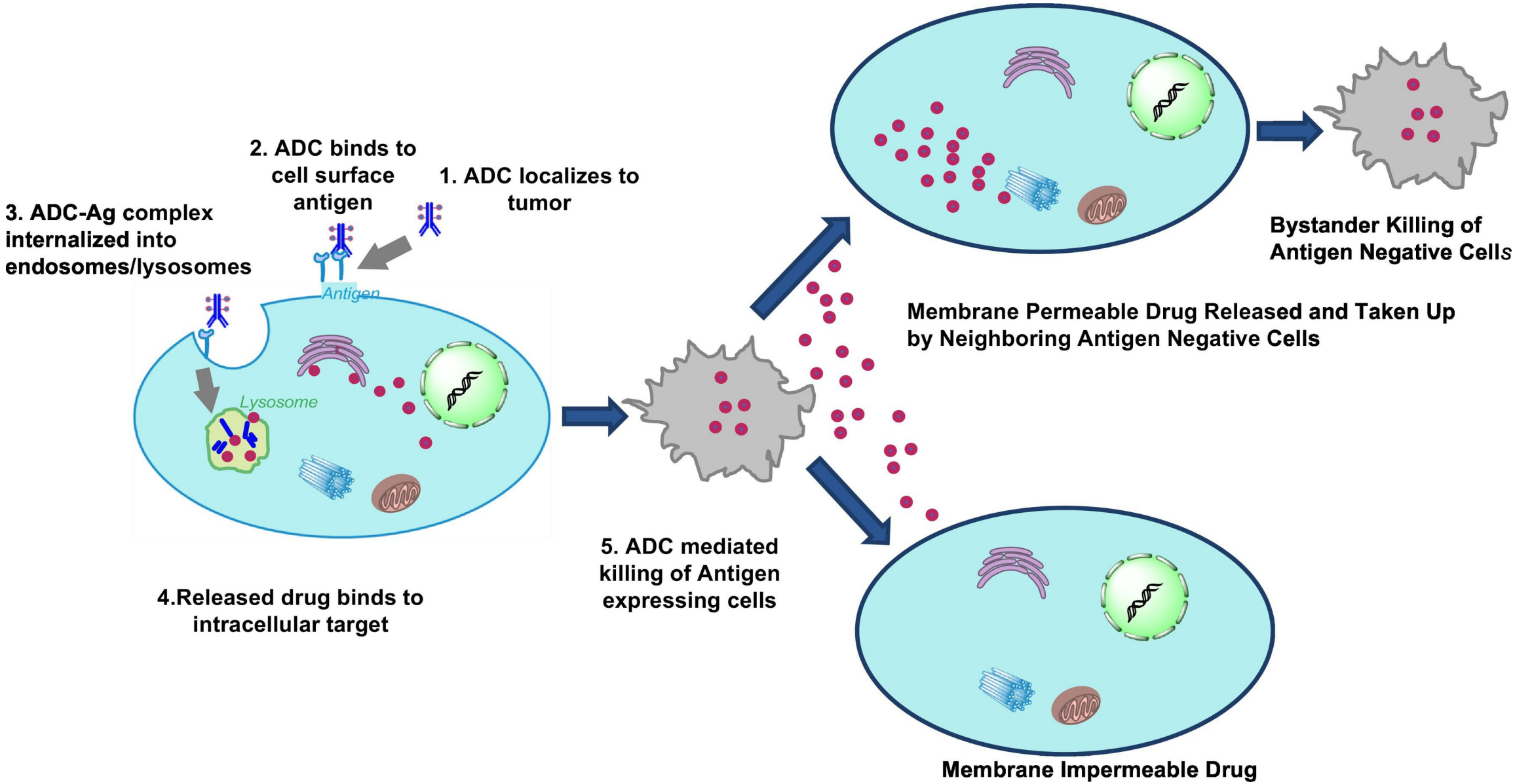
Litton JK, et al. *Ann Oncol*. 2020;31:1526-1535.
Litton JK, et al. AACR 2020. Abstract CT017.

Combining Immunotherapy with PARP Inhibitors

Trial	Treatment	N	ORR (%)	DOR (mo)	PFS (mo)
KN-086-A/2L+	Pembrolizumab	170	5.7 PD-L1+	NR (1.2-21.5+)	2
OlympiAD (≤2L)	Olaparib	205	60	6.4	7
EMBRCA (≤3L)	Talazoparib	287	63	5.4	8.6
MEDIOLA (≤2L)	Olaparib + Durvalumab	30	63	9.2	8.2
TOPACIO (≤2L)	Niraparib + Pembrolizumab	15	47	NR (0.7-25)	8.3

Adams et al. Ann Oncol. 2019;30:397
Robson M, et al. *N EnglJ Med*. 2017;377:523-533.
Litton JK, et al. *N EnglJ Med.* 2018;379:753-763.
DomchekS. et al. *Ann Oncol.* 2019;30(suppl_5):v475-v532; DomchekSM, et al. *Lancet Oncol.* 2020;21:1155-1164.
Vinayak s, et al. *JAMA Oncol.* 2019;5:1132-1140.

Cancer Specific Antibody drug conjugate (ADC)



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

ASCENT: Sacituzumab in Refractory mTNBC

Trop-2 expressed in ~85-90% all breast cancer subtypes

Target Antigen: TROP2

mAb isotype: IgG1

Linker type: cleavable

Payload (class): SN-38, active metabolite of irinotecan (Camptothecin)
Payload action: Topoisomerase-1 inhibitor

DAR: 8

Metastatic TNBC
(per ASCO/CAP)
≥2 chemotherapies for advanced disease
[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]
N=529

NCT02574455

R 1:1

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

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

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS†

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

Data cutoff: March 11, 2020

Stratification factors
- Number of prior chemotherapies (2-3 vs >3) **-median 4**
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

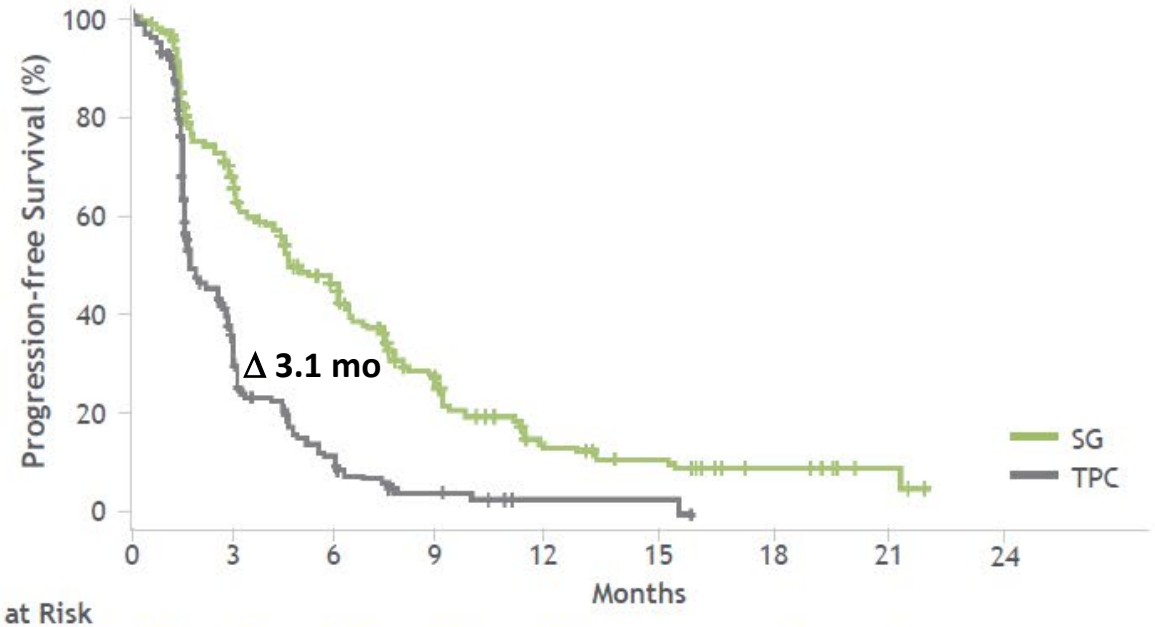
* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Corti C et al. Cancers. 2021; 13 (12):2898

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

ASCENT: Sacituzumab Improves PFS and OS

Progression Free Survival



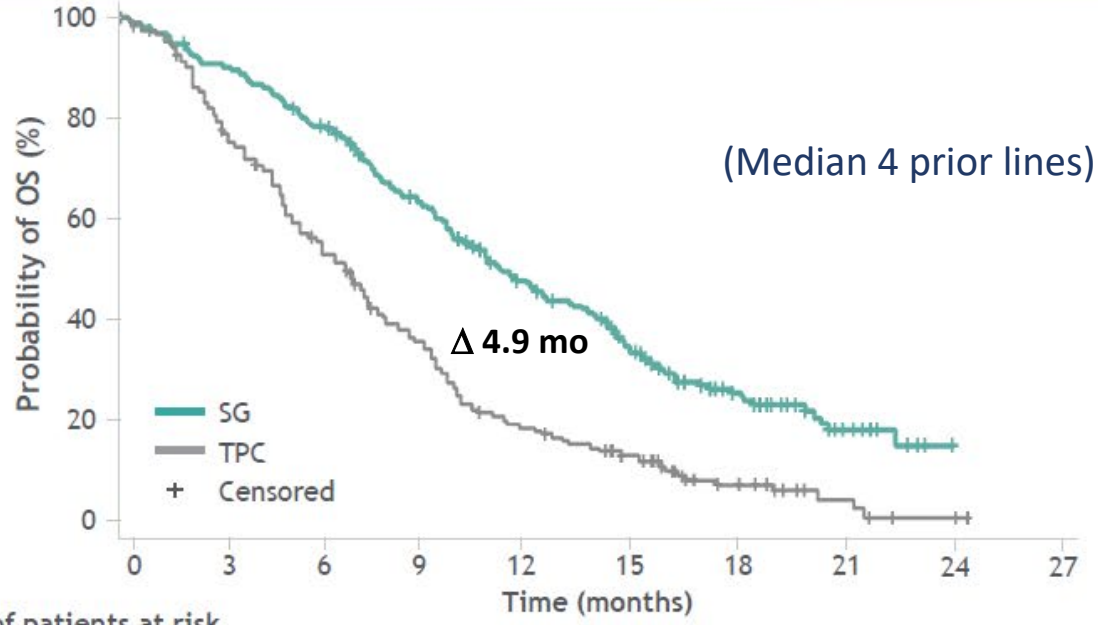
No. at Risk

SG	267	145	82	38	23	14	8	1
TPC	262	41	13	6	2	1	0	0

	SG (n=267)	TPC (n=262)
Median PFS –mo (95% CI)	4.8 (4.1-5.8)	1.7 (1.5-2.5)
HR (95% CI)	0.43 (0.35-0.54)	

Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

Overall Survival



(Median 4 prior lines)

No. of patients at risk

SG	267	260	250	242	232	219	208	189	174	164	145	127	116	109	98	76	56	46	39	31	21	13	8	1	0	0
TPC	262	239	222	192	174	150	132	113	97	84	64	58	52	46	42	34	24	17	14	9	6	5	3	2	1	0

	SG (n=267)	TPC (n=262)
Median OS –mo (95% CI)	11.8 (10.5-13.8)	6.9 (5.9-7.7)
HR (95% CI)	0.51 (0.41-0.62)	

Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

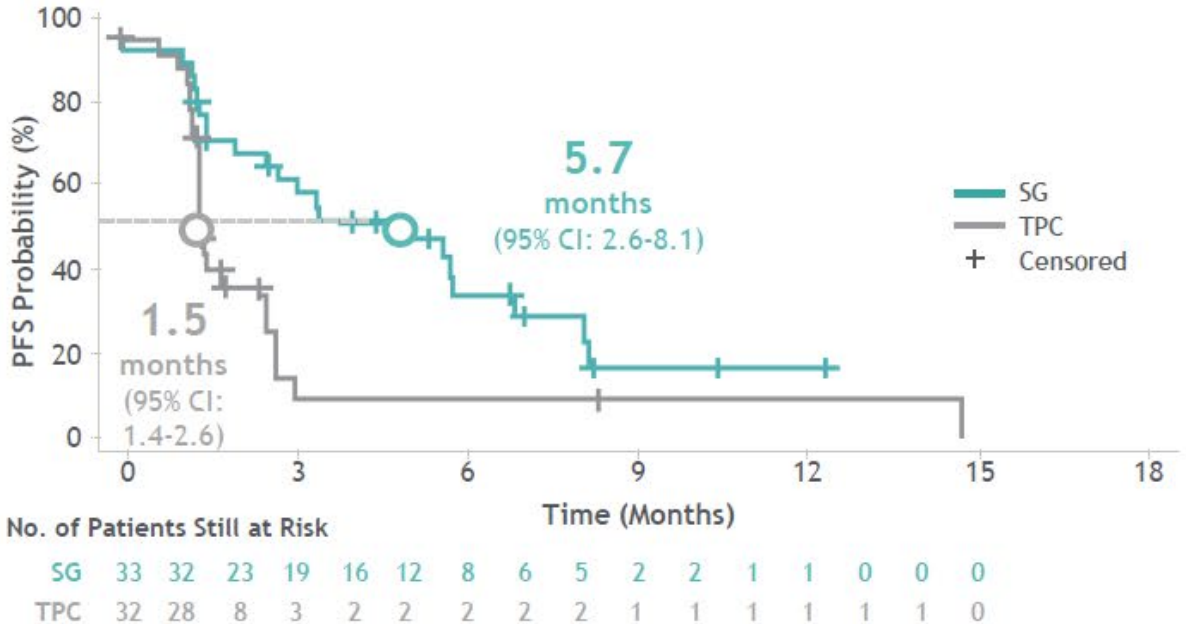
PFS and OS Benefits with Sacituzumab seen across Trop 2 expression subgroups and especially in high/medium expressers

Bardia A, et al. *N Engl J Med* 2021;384:1529-41.

Bardia A et al. Ann Oncol. 2021;32(9):1148-1156

Subgroup Analysis: PFS and OS in the 2L Metastatic Setting in the BMNeg Population

Progression Free Survival

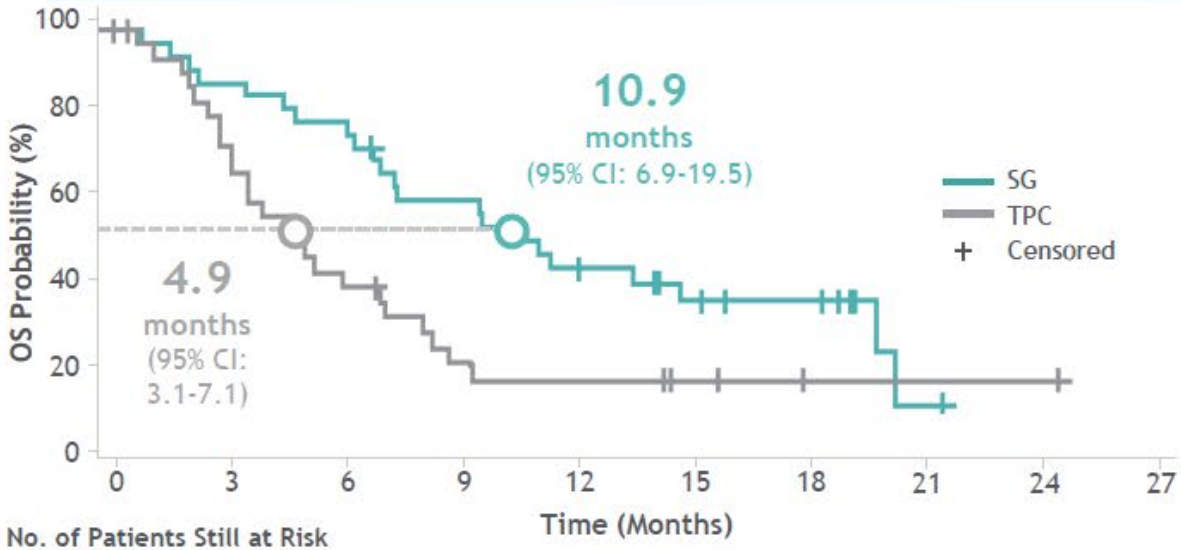


No. of Patients Still at Risk

SG	33	32	23	19	16	12	8	6	5	2	2	1	1	0	0	0
TPC	32	28	8	3	2	2	2	2	2	1	1	1	1	1	1	0

BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS—mo (95% CI)	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

Overall Survival



No. of Patients Still at Risk

SG	33	32	31	29	28	26	26	21	19	19	17	15	13	13	11	9	7	7	7	4	2	1	0	0	0	0
TPC	32	29	27	22	17	14	12	10	8	6	5	5	5	5	5	3	2	2	1	1	1	1	1	1	1	0

	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	0.51 (0.28-0.91)	

Patients treated with SG vs. TPC demonstrated improved mPFS of 5.7 vs 1.5 months and mOS of 10.9 vs 4.9 months

Assessed by independent central review in the brain metastasis-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received 1 line of therapy in the metastatic setting, prior to study enrollment.

Carey, LA et al. NPJ Breast cancer 2022;8 (1): 72

ASCENT: Adverse Events

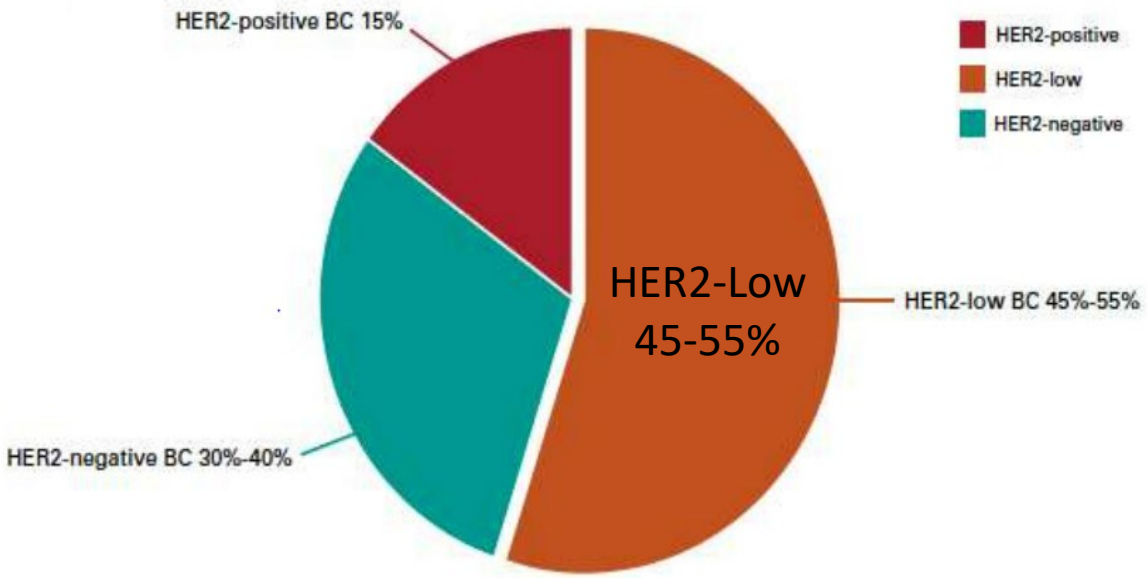
TRAEs (All Grade >20%, Grade 3/4 >5% of Patients)

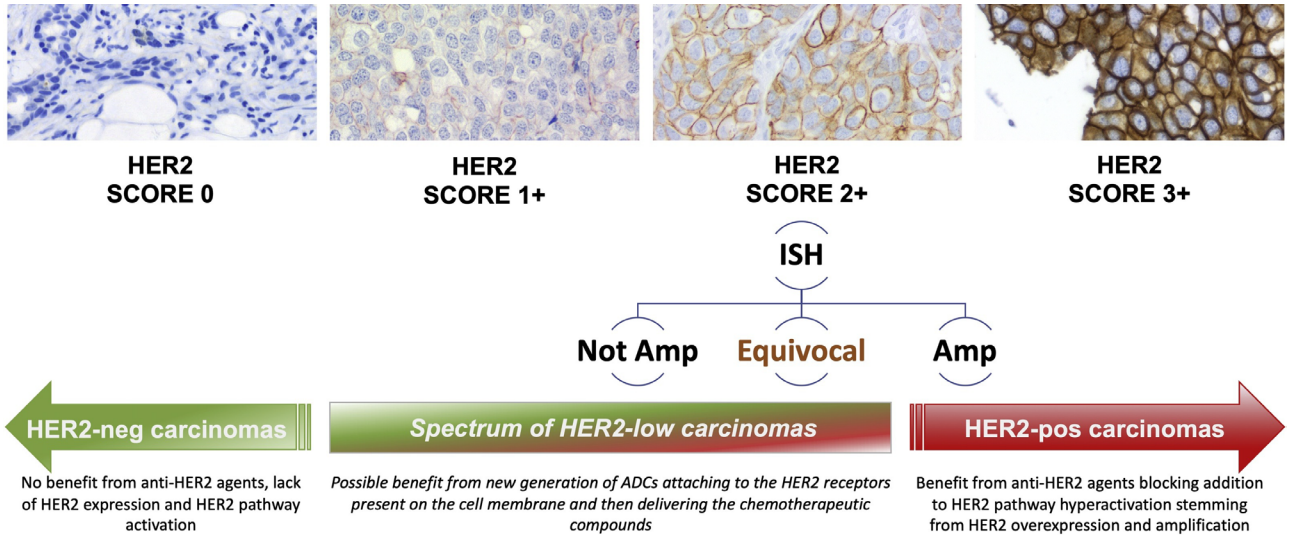
		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**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

Dose interruptions[1]	61%	33%
Dose reductions[2]	22%	26%
Treatment discontinuation[2]	4.7%	5.4%

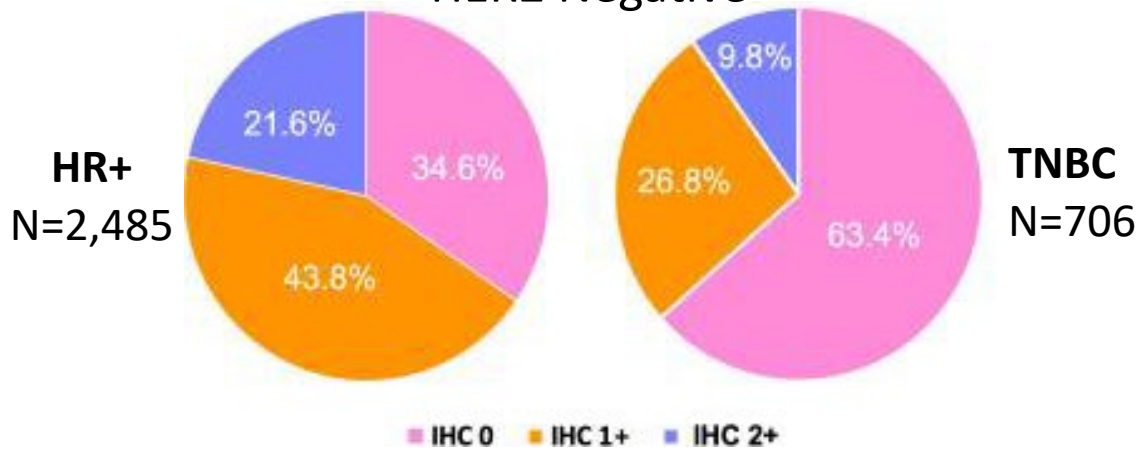
Fewer dose modifications and discontinuations due to AEs were observed in SG vs. TPC patients

Prevalence by HER2 expression





HER2 Negative



HER2 Low Disease

- 65% HR+ vs. 37% TNBC
- Change through disease course

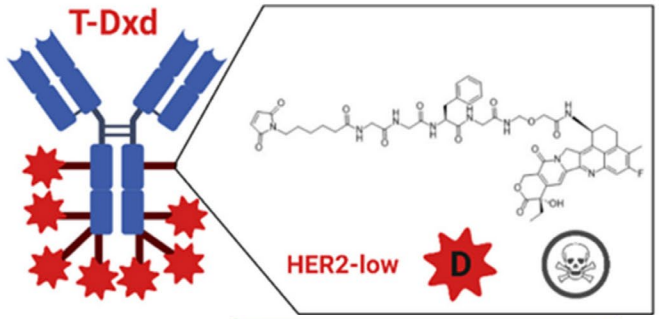
(Primary vs. Recurrent, Pre vs. Post neoadjuvant)

- Clinically and Prognostically similar to Her2 0

Tarantino P et al. J Clin Oncol. 2020;38(17):1951-1962 Schettni F, et al. NPJ Breast Cancer 2021; 7 (1): 1
Marchiò C, Annaratone L et al. Semin Cancer Biol. 2021 Jul;72:123-135 Viale, G et al. J Clin Oncol. 2022; 40(16):1087

DESTINY-Breast-04

T-DXd in HER2-low Advanced Breast Cancer



Target Antigen: HER2 (trastuzumab vehicle)

mAb isotype: IgG1

Linker type: cleavable

Payload (class): Dxd (Camptothecin)

Payload action: Topoisomerase-1 inhibitor

DAR: 8

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

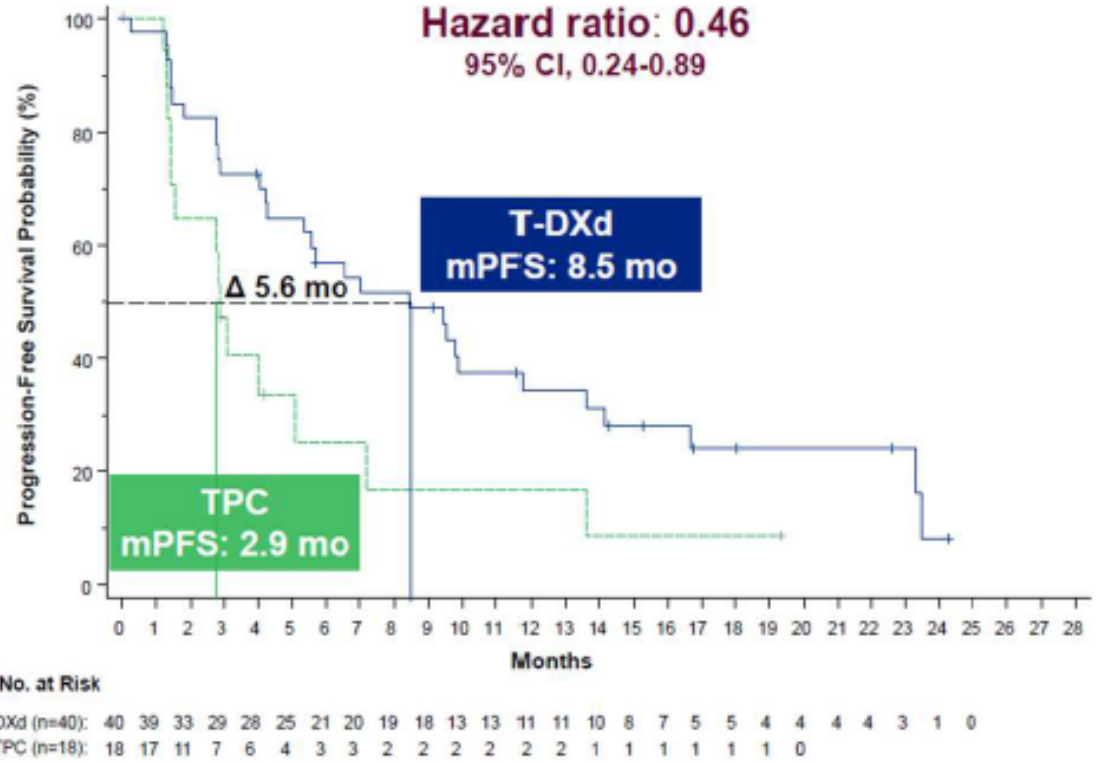
Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy (38.9-45.1% with 2 prior chemo)
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

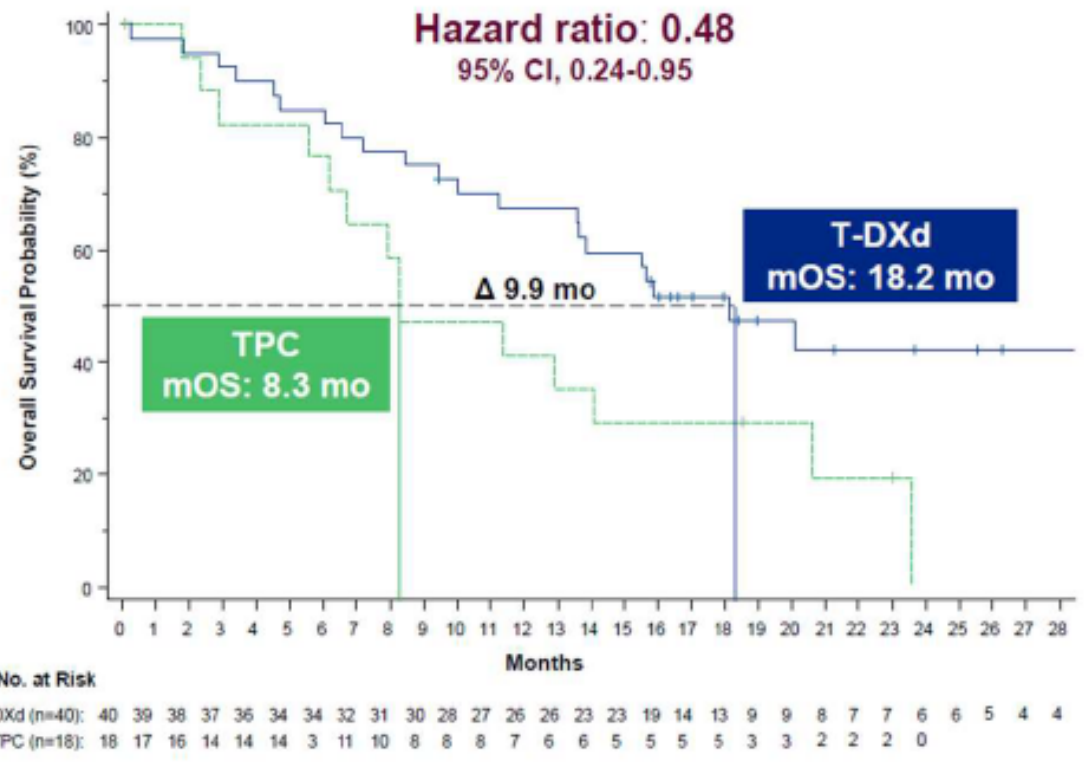
Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022. Corti C et al. Cancers. 2021; 13 (12):2898

DESTINY-Breast-04

T-DXd in HR-HER2-low Advanced Breast Cancer





PFS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median PFS, months	8.5	2.9
HR (95% CI)	0.46 (0.24-0.89)	

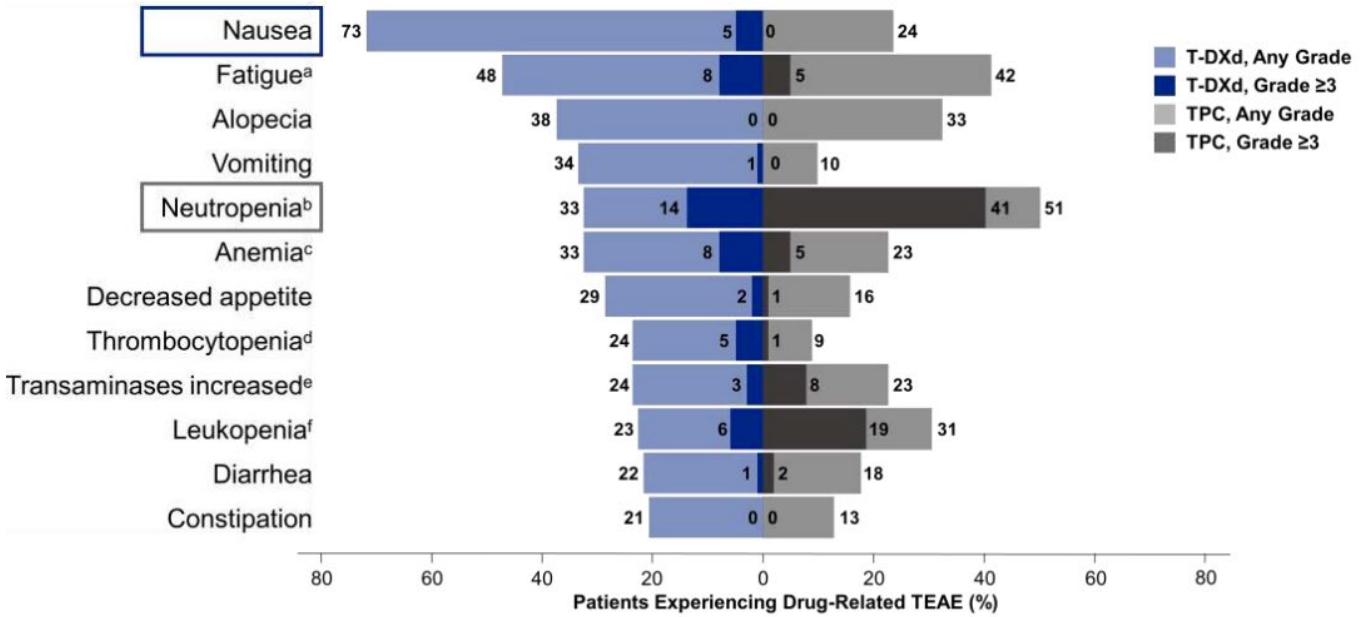
OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

Modi S, et al. ASCO 2022. Abstract LBA3; Modi S, et al. New Engl J Med. 2022 Jun 5

DESTINY-BREAST-04

Safety Analysis

Drug-Related TEAEs in >20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell cour decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

		Safety analysis set[a]	
n (%)	**Median treatment duration** T-DXd: 8.2 months (range, 0.2-33.3) TPC: 3.5 months (range, 0.3-17.6)	**T-DXd (n = 371)**	**TPC (n = 172)**
Total patient-years of exposure, years[b]		283.55	63.59
TEAEs		369 (99)	169 (98)
Grade ≥3		195 (53)	116 (67)
Serious TEAEs		103 (28)	43 (25)
TEAEs associated with dose discontinuations		60 (16)	14 (8)
TEAEs associated with dose interruptions		143 (39)	72 (42)
TEAEs associated with dose reductions		84 (23)	66 (38)
TEAEs associated with deaths		14 (4)	5 (3)

AEs of Special Interest, n (%)			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Adjudicated as drug-related ILD/pneumonitis[a]		**T-DXd (n=371)**	**13 (3.5)**	**24 (6.5)**	**5 (1.3)**	**0**	**3 (0.8)**	**45 (12.1)**
		TPC (n=172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction[b]	Ejection fraction decreased	T-DXd (n=371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
		TPC (n=172)	0	0	0	0	0	0
	Cardiac failure[c]	T-DXd (n=371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
		TPC (n=172)	0	0	0	0	0	0

- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

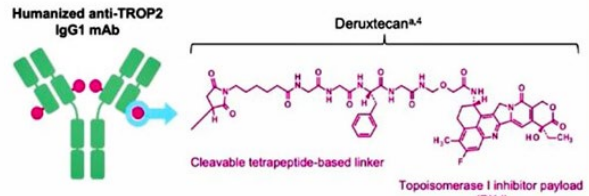
Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

TROPION-PanTumor01 (NCT03401385)

Phase 1 Study in Relapsed/Refractory Metastatic Solid Tumor

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

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



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

Figure 1. Structure of Dato-DXd, source: Daiichi Sankyo

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

→ NSCLC[b] (0.27 to 10 mg/kg IV Q3W)

→ **TNBC[c] 8 mg/kg (n=2); 6 mg/kg (n=42)**
Median 3 prior lines

→ HR+/HER2− breast cancer[d]

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

Primary objectives

- Safety
- Tolerability

Secondary objectives[e]

- Efficacy[f]
- Pharmacokinetics
- Antidrug antibodies

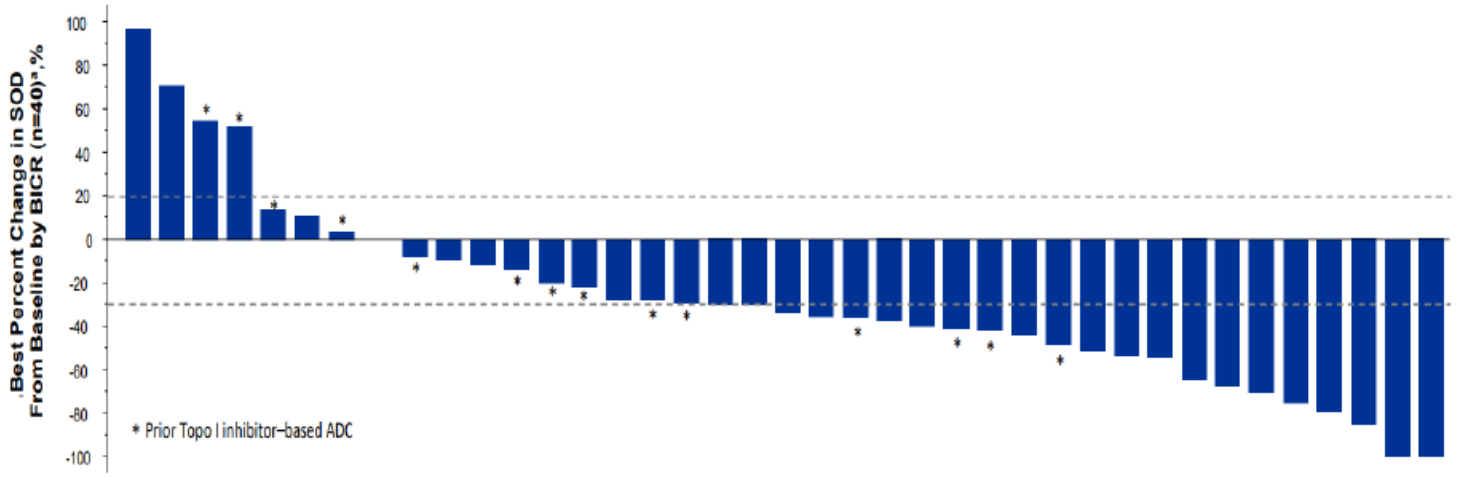
Data cutoff: July 30, 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Results from the NSCLC cohort have been previously reported.[1,2] [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Enrollment in the HR+/HER2− cohort is now complete and data will be forthcoming. [e] Exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST 1.1.

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

Krop I, et al. SABCS 2021. Abstract GS1-05.

TROPION-PANTumor01: Dato-DXd for refractory mTNBC



[a] Postbaseline tumor assessments were not available for 1 patient at data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.

Prior treatment included Sacituzumab govitecan (same AB, different payload, n=11; trastuzumab deruxtecan (different AB, same payload, n=2; patritumab deruxtecan (HER3 AB, same payload), n=1.

PFS	Median (95% CI), mo	Events n/N (%)
All patients	4.4 (3.0-7.3)	29/44 (66)

OS	Median (95% CI), mo	Events n/N (%)
All patients	13.5 (10.1-16.3)	28/44 (64)

Patients, n (%)*	All TNBC patients (n=44)	Topo I inhibitor–naive patients with measurable disease at BL n=27
Objective response rate	14 (32)	12 (44)
Complete response	1 (2)	1 (4)
Partial response	13 (30)	11 (41)
Non-CR / non-PD	3 (7)	0
Stable disease	18 (41)	10 (37)
Not evaluable	1 (2)	1 (4)
Disease control rate	35 (80)	22 (81)
Clinical benefit rate[b]	17 (39)	13 (48)
Progressive disease	8 (18)	4 (15)
Duration of response, median (95% CI)	16.8 (5.6–NE)	16.8 (5.6–NE)

- In the overall TNBC cohort (n=44), an ORR by BICR of 32% and DCR by BICR of 80% were observed
- In patients who were treatment-naïve to topoisomerase I inhibitor-based ADC therapies (n=27), an ORR by BICR of 44% and DCR by BICR of 81% were observed 32% (n=14) had prior Topo 1 inhibitor based ADC
- Mean DoR was 16.8 months in both groups

Data cutoff: July 22, 2022.

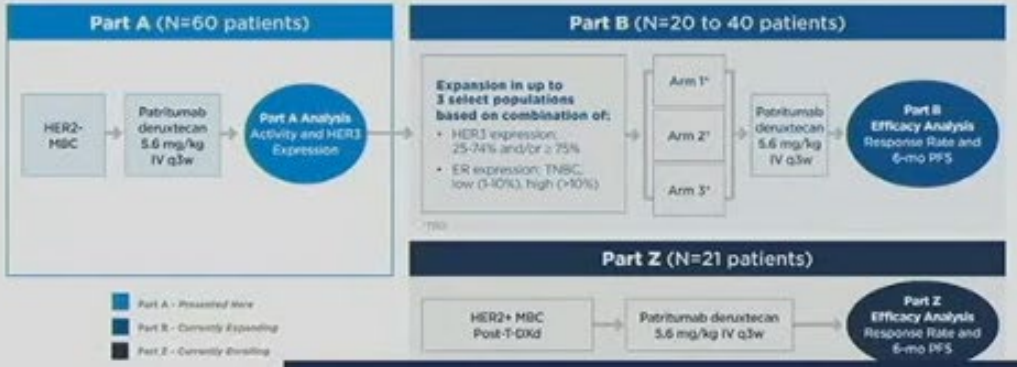
*Postbaseline tumor assessments were not available for 1 patient at data cut-off. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD. bCR + PR + SD for ≥6 months..

Bardia A et al. Presented at: SABCS; Dec 6-10, 2022; San Antonio, TX. Poster P6-10-03.

Patritumab deruxtecan (HER3-DXd) with 35% ORR

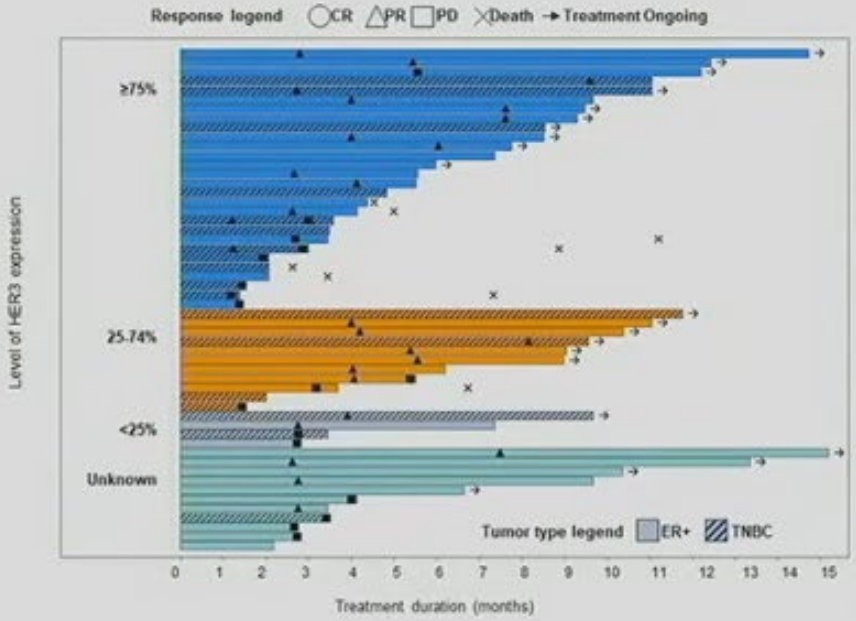
BRE354: Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC (Part A)

≈ 40% TNBC
4 (8.5%) HER3 IHC < 25%



Median prior lines of systemic therapies for ABC: 3 [1-9]

≈8.3 % of patients: prior SG



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 evaluable/awaiting result unevaluable.
**CBR=CR, PR, or SD ≥180 days
†Percentage calculation uses the number of pts who responded as the denominator.

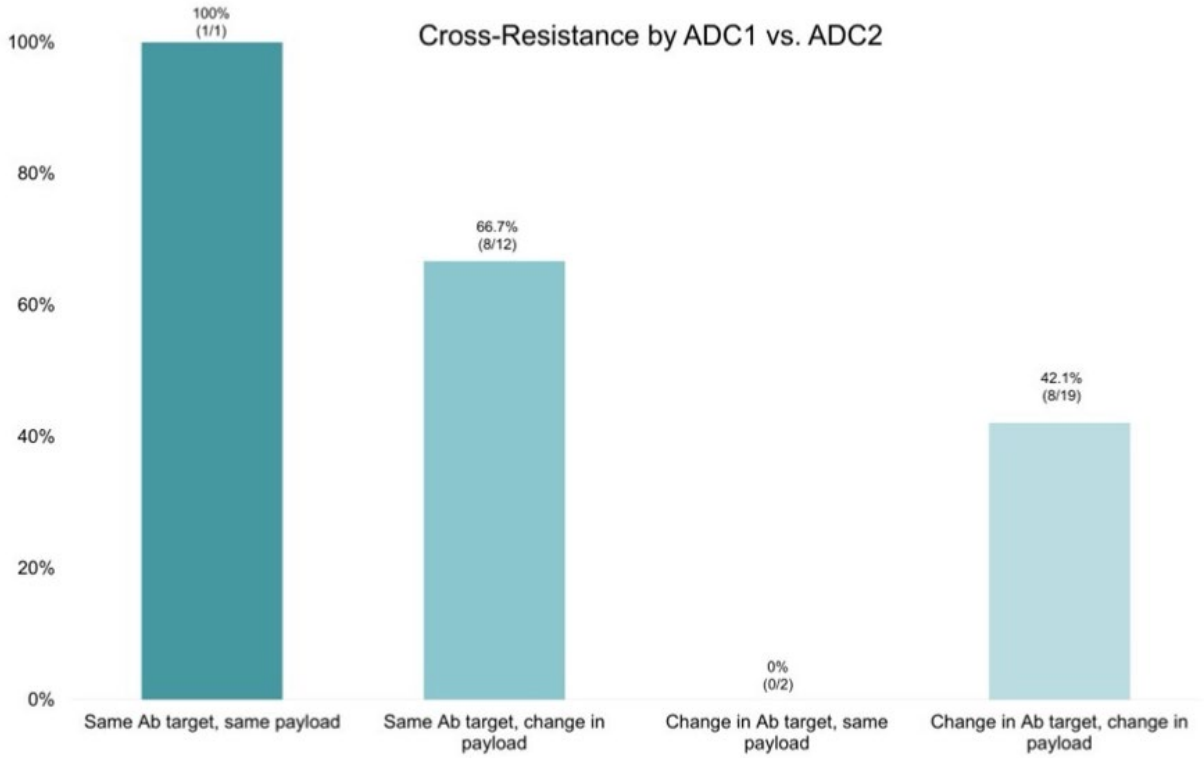
Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

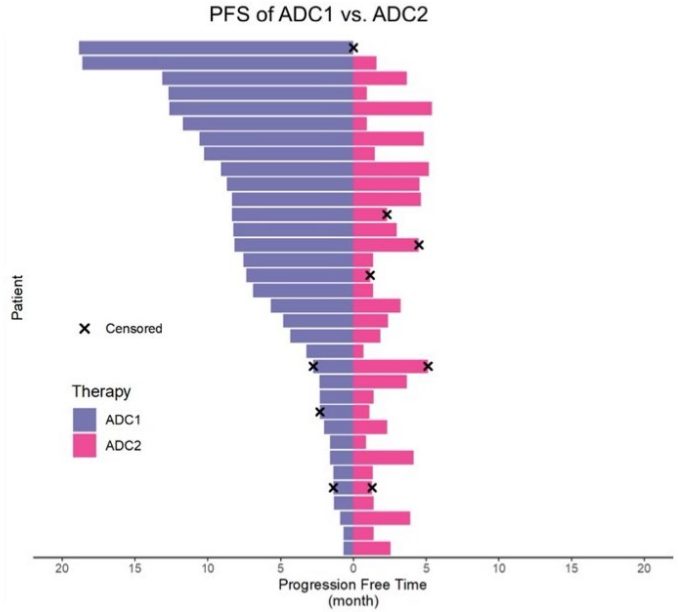
Activity irrespective of HER3 expression

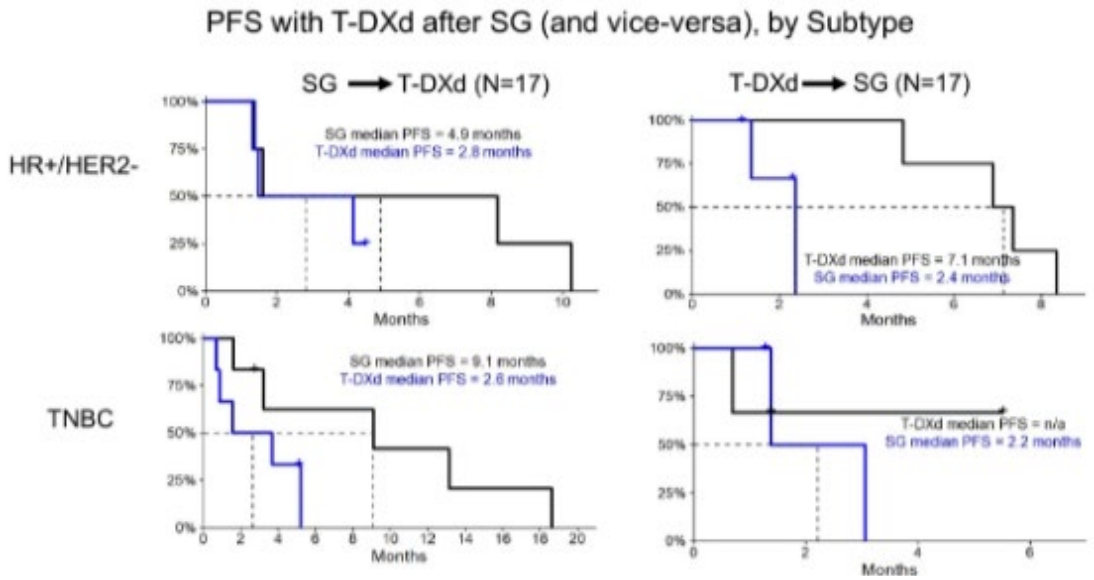
Hamilton et al, ASCO 2023, abs 1004

Presented by Barbara Pistilli, ASCO 2023

Sequencing Antibody Drug Conjugates (ADCs)







- 35 patients: ER+/Her2- and TNBC (n=20, 57%) patients in a single academic institution
- For TNBC subgroup, median PFS for ADC1 was 8.2 mo and median PFS for ADC2 was 3 mo
- Suggests that changing antibody target may lessen cross resistance

Abelman, R et al. Abs 1022.ASCO 2023

Future Directions

ASCENT-04

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
- ≥6 months since treatment in the curative setting
- Prior anti-PD-(L)1 agent allowed in the curative setting

R 1:1

N=440
(≤25% *de novo*)

SG + Pembrolizumab[a]
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
TPC
Gem+carbo: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
Paclitaxel: 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles
Nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles
Pembro: 200 mg IV on day 1 of 21-day cycles

Treated until BICR-verified progression or unacceptable toxicity

Crossover to SG allowed after BICR-verified progression

Long-term follow-up

Stratification Factors:

- *De novo* vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region (US/CAN/Western Europe vs RoW)
- Prior exposure to anti-PD-(L)1 therapy

DESTINY-BREAST06

POPULATION

- Advanced/metastatic HR+ BC
- HER2 IHC 0+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

Prior lines of ET in metastatic setting:

- 2 prior lines OR
- 1 prior line and primary ET resistance*

Stratification factors:

- Prior CDK4/6i
- HER2 IHC 2+ v. 1+ v. >0<1+
- Prior taxane in non-metastatic setting

- First subject in: July 2020
- 791 patients enrolled
- 310 sites open

TREATMENT

R 1:1

n=425 **T-DXd**

n=425 **Investigator's choice chemotherapy** (capecitabine, paclitaxel, nab-paclitaxel)

- Treatment continues until progressive disease or toxicity
- HER2 IHC 0+ defined by tumour membrane expression characterised as faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumour cells

TRADE-DXd

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

Allocation 1:1 to T-DXd or Dato-DXd as ADC_1

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR

ADC_1

T-DXd 0-1 prior lines → HR+ (Arm A), HR- (Arm B) → Crossover to ADC_2 at progression → Dato-DXd 1-2 prior lines → HR+ (Arm E), HR- (Arm F) → Treat until progression or unacceptable toxicity

Dato-DXd 0-1 prior lines → HR+ (Arm C), HR- (Arm D) → Crossover to ADC_2 at progression → T-DXd 1-2 prior lines → HR+ (Arm G), HR- (Arm H) → Treat until progression or unacceptable toxicity

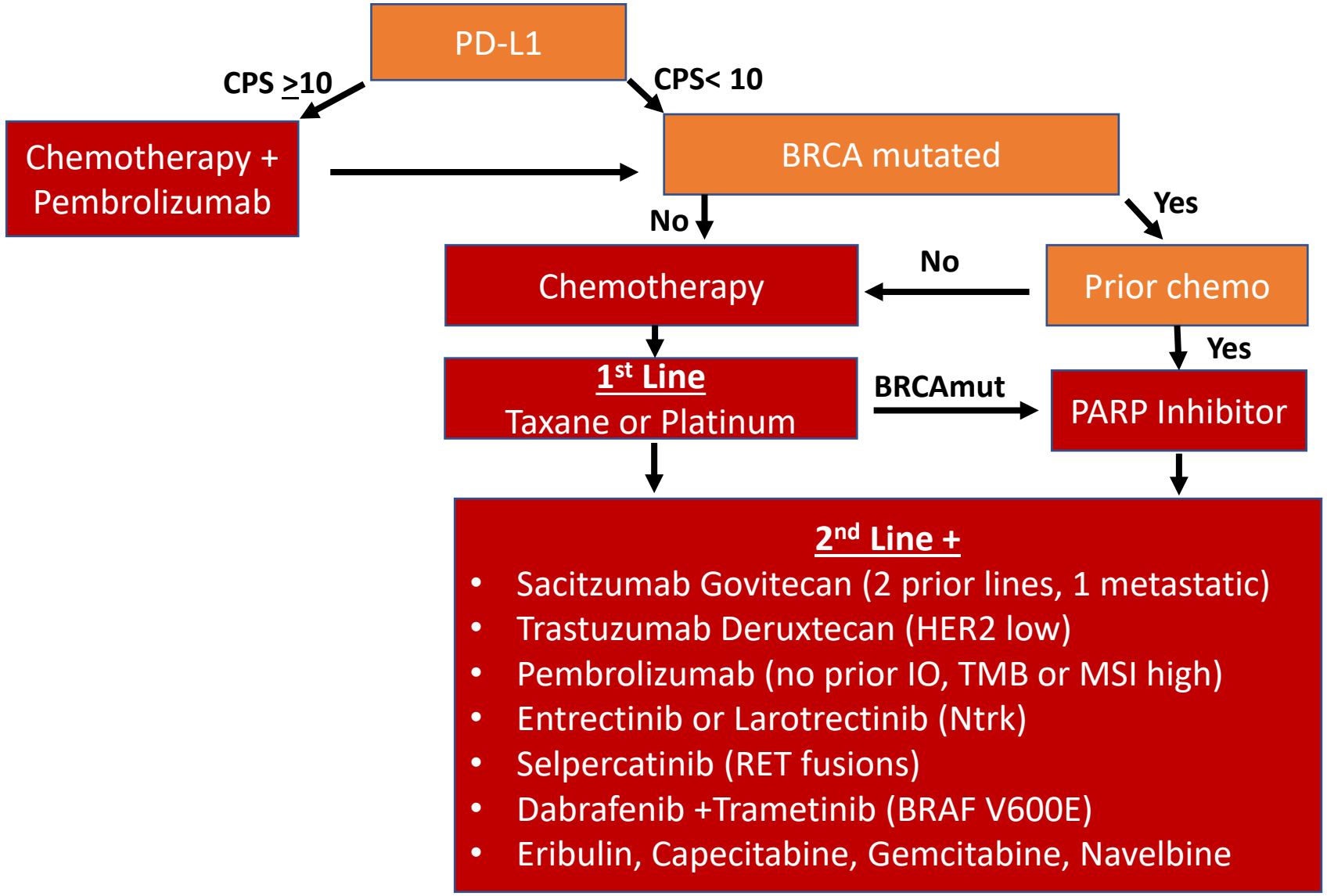
ADC_2

Baseline Pre-ADC_1 Biopsy; Post-C2 On-ADC_1 Biopsy; Baseline Pre-ADC_2 Biopsy; Optional Post-ADC_2 Biopsy

★ Tumor assessments + Blood collection q9w

*Patients who received T-DXd/Dato-DXd as ADC_1 off-study allowed to enroll on ADC_2 cohorts.

Metastatic TNBC: Choosing a Therapy



Thank you

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center